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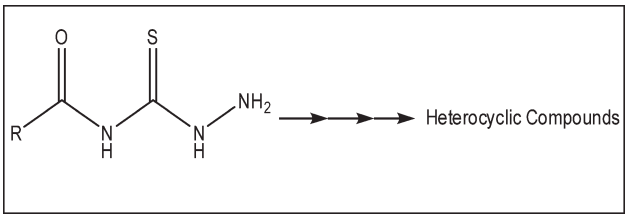


The review summarizes published data on the behavior and reactions of acylthiosemicarbazides and their derivatives, which lead to the formation of heterocyclic systems, including methods of preparation in addition to synthesis of pyrrole, thiazole, thiadiazole, thiadiazolidine, and triazole derivatives as well as fused heterocyclic compounds.

J. Heterocyclic Chem., **49**, 38 (2012).

Contents

1. INTRODUCTION

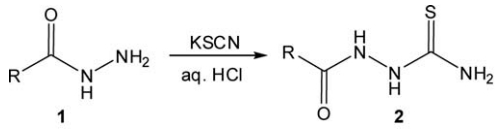
Thiosemicarbazide and its derivatives are a class of very important organic compounds that were found to be associated with various biological activities [1–15], such as antifungal [16,17], anti-inflammatory, anti-HIV [18,19], and of herbicidal activities [20].

Recent studies have shown that some compounds can be used as corrosion inhibitors of steal [21,22], and some can be used as semiconductors [23], and others used in the metal complexes [24–36]. On the other hand, the cyclized products were also intensively studied because of their biological and other properties [37–40].

Thiosemicarbazides are versatile compounds, which have been extensively used in the synthesis of different heterocyclic ring systems [37–40]. Several authors developed a new simple and efficient procedure for preparation of thiosemicarbazide derivatives [32,40]. Recently, different successful approaches have been reported for synthesis of thiazine, thiadiazole, thiadiazine, thiadiazepine, oxathiadiazole, and indazole, as well as pyridazine derivatives from thiosemicarbazides [41–52].

2. SYNTHESIS OF ACYLTHIOSEMICARBAZIDES

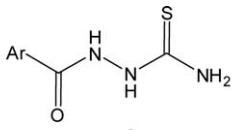
Several authors [53–56] were interested to synthesis of acylthiosemicarbazides **2**, because they were found to be associated with various biological activities. The reaction of acylhydrazide (**1**) with KSCN in aq. HCl under microwave irradiation gave 1-acylthiosemicarbazides **2** [57].



R = C_6H_5, *p*-CH_3-C_6H_4, *p*-CH_3O-C_6H_4, *p*-Cl-C_6H_4, 3-pyridyl

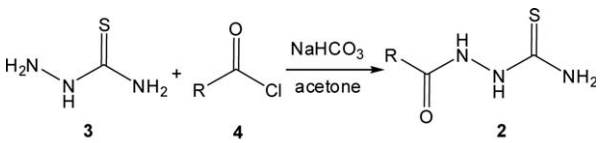
Treatment of thiosemicarbazide (**3**) with acyl halides in aprotic polar solvent afforded compound **2**, thus, EtCOCl was gradually added to a mixture of **3** and *N*,*N*-dimethylacetamide to give $EtCONHNHCSNH_2$ **2** [58].

$ArCONHNH_2$ in EtOH was saturated with dry HCl, the salt dissolved in EtOH and reacted with NH_4SCN, the mixture was heated to give **2** [59,60].



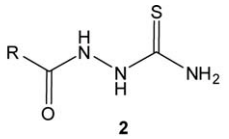
Ar = C_6H_5, *p*-HO-C_6H_4, *p*-EtO-C_6H_4, *p*-C_3H_7-C_6H_4, *p*-*iso*-C_3H_7-C_6H_4, *p*-BuO-C_6H_4, *p*-*iso*-BuO-C_6H_4, *p*-*sec*-BUO-C_6H_4, *p*-n-$C_6H_{13}O$-C_6H_4, *p*-$C_6H_5CH_2$-C_6H_4, *p*-NO_2-C_6H_4

Equivalent amounts of thiosemicarbazide (**3**) and RCOCl **4** in acetone were treated with $NaHCO_3$ to give acylthiosemicarbazides **2** [61,62].



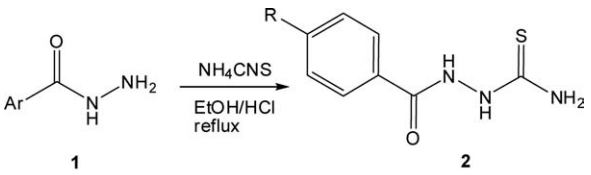
2,4: R = Me, Et, n-C_3H_7, ph, $phCH_2$, *p*-O_2N-C_6H_4

Heating acylhydrazide **1** in HCl with KSCN gave acylthiosemicarbazides **2** [63].



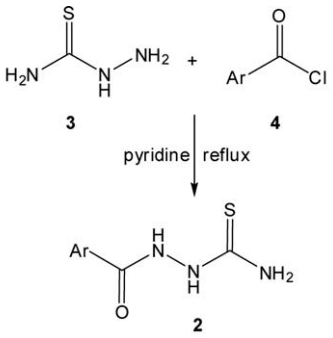
R = Me, Ph, $PhCH_2$, *o*-HO-C_6H_4,*p*-HO-C_6H_4, *p*-O_2N-C_6H_4, $PhCH_2NHNH_2$

Refluxing substituted benzoyl chloride with hydrazine and then with ammonium thiocyanate in ethanol in the presence of hydrochloric acid led to the formation of acylthiosemicarbazides **2** [64].



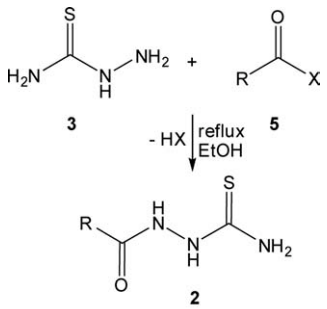
R = H, *p*-CH_3O, *p*-NO_2, 4-(*p*-NO_2-C_6H_4NH), 4-(*p*-Cl-C_6H_4NH), 4-(*p*-CH_3O-C_6H_5), 4-*iso*-C_3H_7, 2-CH_3O-4-CH_3, 2,4-$(CH_3)_2$

Also, acylthiosemicarbazides **2** were obtained *via* interaction between thiosemicarbazide (**3**) and substituted acid chloride **4** in pyridine [65].



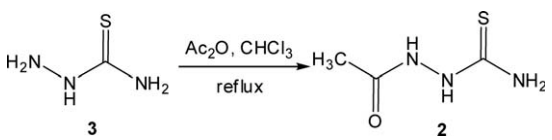
2,4: Ar = C_6H_5, 4-N_2O-C_6H_4, 3-pyridiyl, 4-pyridiyl

On the other hand, acylthiosemicatbazides **2** were prepared by the reaction of thiosemicarbazide (**3**) with aliphatic carboxylic acids **5** [66].

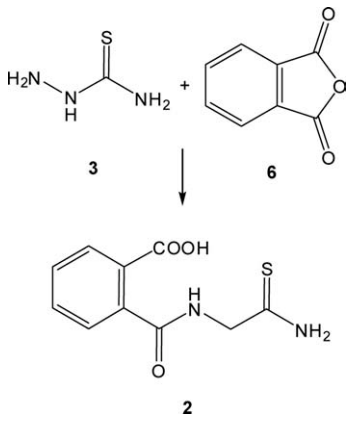


2,5: R = H, CH_3, C_2H_5, X = OH

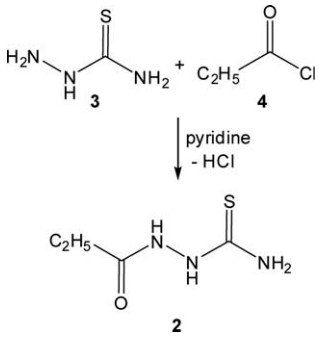
Refluxing equimolar amounts of thiosemicarbazide (**3**) and acetic anhydride in chloroform gave 1-acetylthiosemicarbazide (**2**) [67,68].



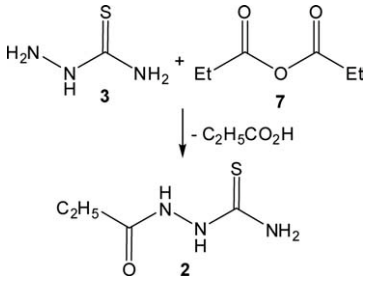
Phthalic anhydride (**6**) reacted with thiosemicarbazide (**3**) in presence of glacial acetic acid to give *N*-thioureidophthalamic acid (**2**) [69].



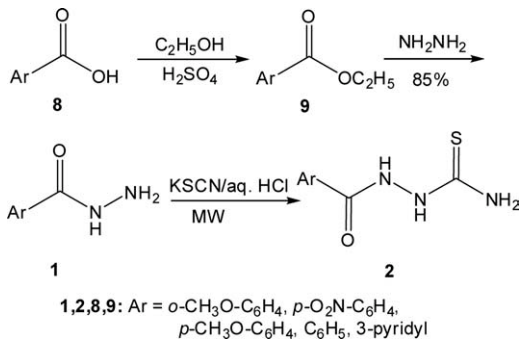
Reaction of thiosemicarbazide (**3**) with propionyl chloride (**4**) in the presence of pyridine gave **2** [70].



2-Propionylhydrazinecarbothioamide (**2**) was also prepared by the reaction of thiosemicarbazide (**3**) with propanoic anhydrides (**7**) [71].



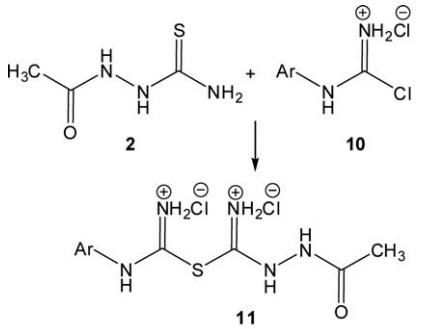
1-Aroylthiosemicarbazides **2** were also synthesized by microwave irradiation of aromatic carboxylic acids **8** with ethanol in presence of sulfuric acid, hydrazine hydrate, and KSCN *via* the formation of compounds **9** and aroylhydrazine derivatives **1** [72].



1,2,8,9: Ar = *o*-CH_3O-C_6H_4, *p*-O_2N-C_6H_4, *p*-CH_3O-C_6H_4, C_6H_5, 3-pyridyl

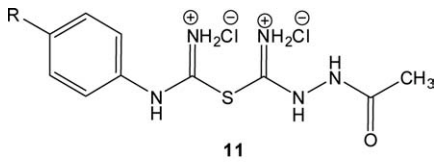
3. CHEMISTRY OF ACYLTHIOSEMICARBAZIDES

3.1. Synthesis of thioformamidine and hydrazonoyl sulfide derivatives. α-Chloroarylformamdine hydrochlorides **10** reacted with 1-acetylthiosemicarbazide **2** in acetone to give thio-bisformamidine derivatives **11** [73].



10,11: Ar = C_6H_5, 4-CH_3-C_6H_4, 4-Cl-C_6H_4, 3-CH_3-C_6H_4, 2-CH_3-C_6H_4, 3-CH_3O-C_6H_4, 4-C_2H_5-C_6H_4, 3-Cl-C_6H_4, 2,6-$(CH_3)_2$-C_6H_3

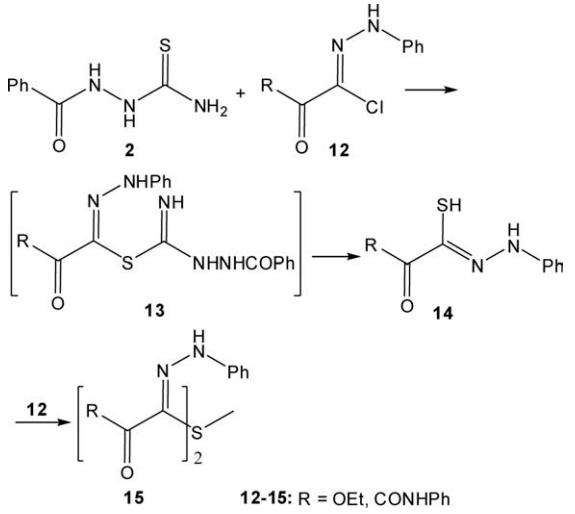
The interaction of various aryl amidine chlorides with thiourea, allylthiourea, thiosemicarbazide and acetylthiosemicarbazide in acetone at 0–5°C, afforded thio-bisformamidine derivatives for example compounds **11** [73,74].



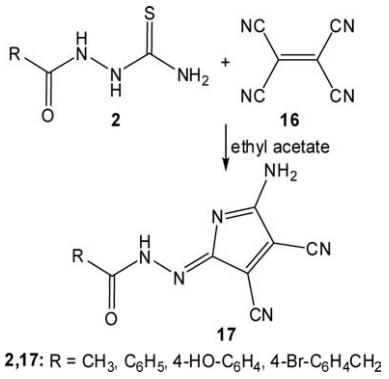
R = H, CH_3O, C_2H_5O

Hydrazonoyl chlorides **12** reacted with benzoyl thiosemicarbazide (**2**) in ethanol/or triethylamine to give two products. The first product was assigned as a

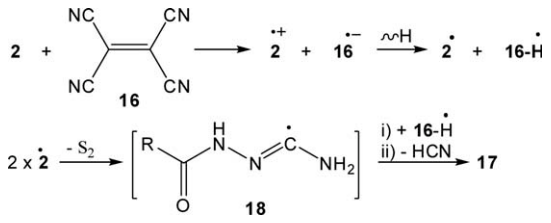
C-substituted-*N*-phenylhydrazonoyl sulfide **14**, where the second product as a *C*-substituted-*N*-phenylhydrazonoyl bissulfide **15** [75,76].



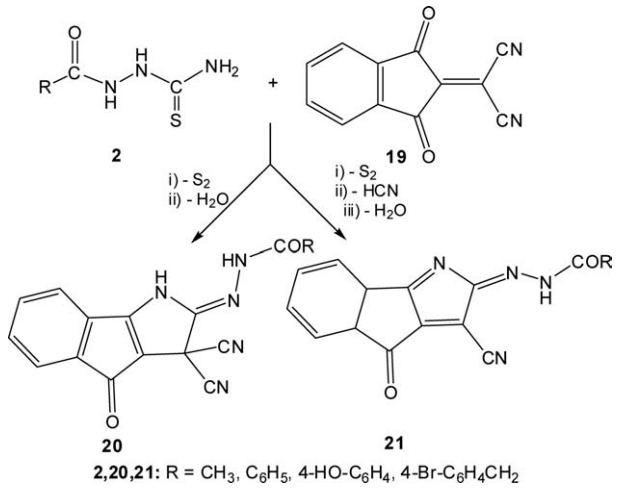
3.2. Synthesis of pyrrole derivatives. *N*′-2-(5-Amino-3,4-dicyano-2*H*-pyrrol-2-ylidene)-2-substituted hydrazide **17** was obtained *via* interaction between 1-acylthiosemicarbazides **2** with ethenetetracarbonitrile (TCNE, **16**) in ethyl acetate [77].



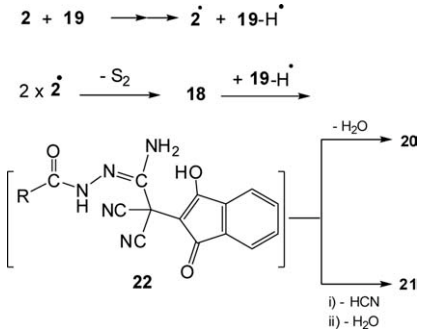
Compound **17** can be rationalized by the following mechanism [77].



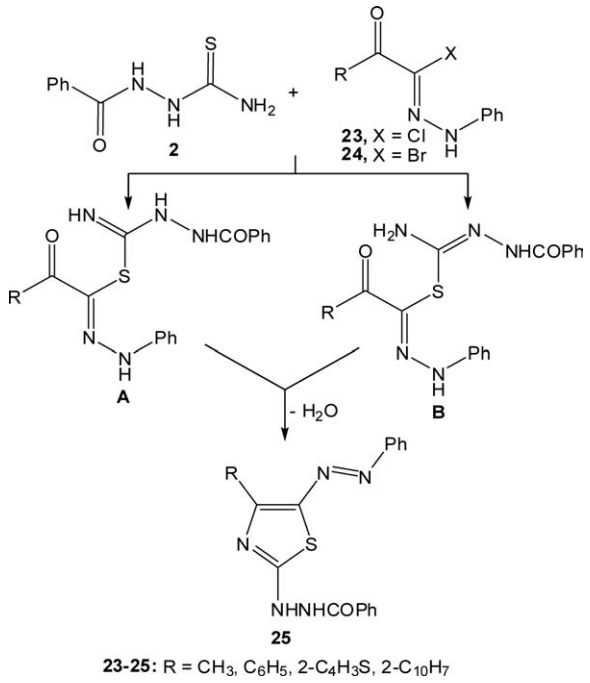
Also, the treatment of acylthiosemicarbazides **2** with two molar equivalents of (1,3-dioxo-2,3-dihydro-1*H*-inden-2-ylidene)propanedinitrile (CNIND, **19**), in ethyl acetate at room temperature, forms the derivatives of oxoindenopyrrolylidenehydrazides **20** and **21** [78].



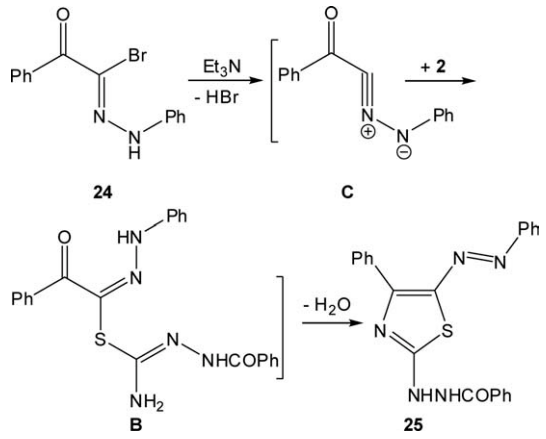
The derivatives of oxoindenopyrrolylidenehydrazide **20** can be obtained during the reaction of CNIND **19** with **2** in ethyl acetate by elimination of a molecule of sulfur to form intermediate **22**, which loss H_2O to form compounds **20**, whereas *N*′-(3-cyano-4-oxoindeno[1,2-*b*]pyrrol-2(4*H*)-ylidene) substituted hydrazides **21** were obtained by reacting **2** and **19** with elimination a molecule of sulfur, a molecule of hydrogen cyanide, and a molecule of H_2O [78].



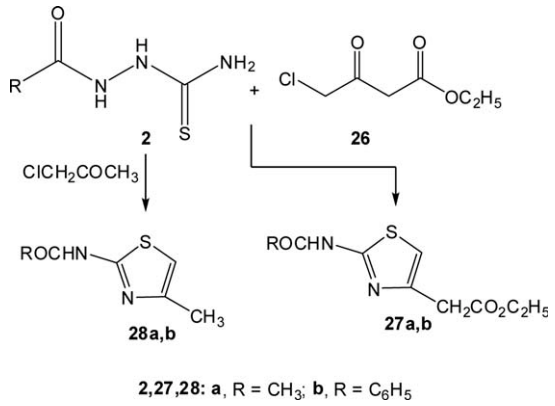
3.3. Synthesis of thiazole derivatives. By contrast, α-ketohydrazonoyl halides **23**, **24** reacted with benzoylthiosemicarbazide (**2**) in ethanolic triethyl-amine to give, in each case, one product which was assigned as 5-phenylazothiazoles **25**. The reaction is believed to take place *via* formation of an intermediate (**A**, **B**), which readily loses one molecule of water to afford **25** [76].



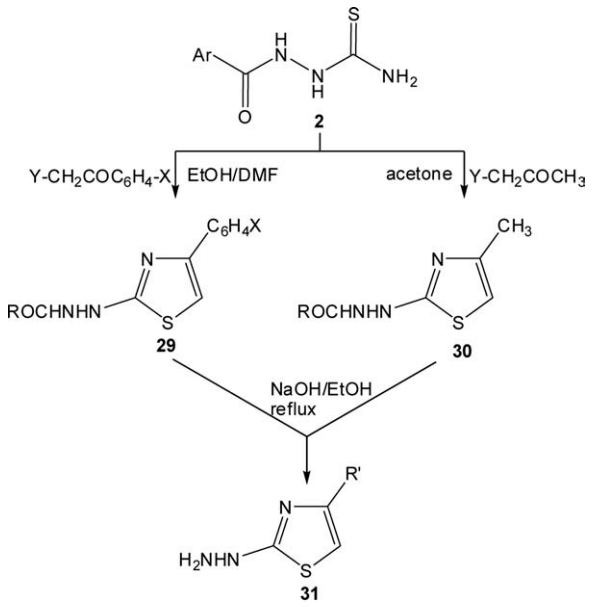
Hydrazonoyl bromide **24** reacted with benzoyl-thiosemicarbazide (**2**) to give *N*′-(4-phenyl-5-(phenyl-diazenyl)thiazol-2-yl)benzohydrazide **25** [79].



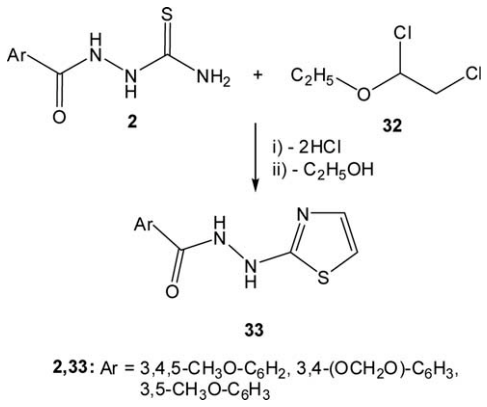
Campaigne and Selby [80] reported that a number of thiazole acetic esters were obtained in a good yield by reacting ethyl 4-chloroacetoacetate (**26**) with thiosemicarbazones and acylthiosemicarbazides [80]. Cyclization of 1-acetylthiosemicarbazide **2a** and 1-benzoylthiosemicarbazide **2b** with ethyl 4-chloroacetoacetate (**26**) gave ethyl-2-(2-acetamidothiazol-4-yl) acetate (**27a**) and ethyl-2-(2-benzamidothiazol-4-yl) acetate (**27b**), whereas **2a,b** was cyclized with chloroacetone to give 4-methyl thiazole derivatives **28a,b** [81].



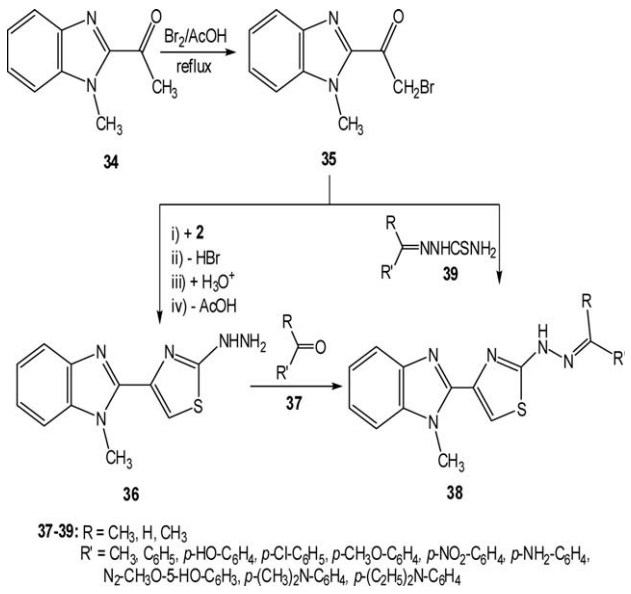
1-Alkoxybenzoyl-2-thiazolylhydrazines **29** and **30** [82] were prepared by the reaction of alkoxybenzoylthiosemicarbazides **2** [83] and the appropriate α-halogenoketone (phenacyl bromides or chloro acetone). Alkaline hydrolysis of hydrazides **29** and **30** gave 2-thiazolylhydrazines **31** [84,85], in addition to alkoxybenzoic acid derivatives [73].



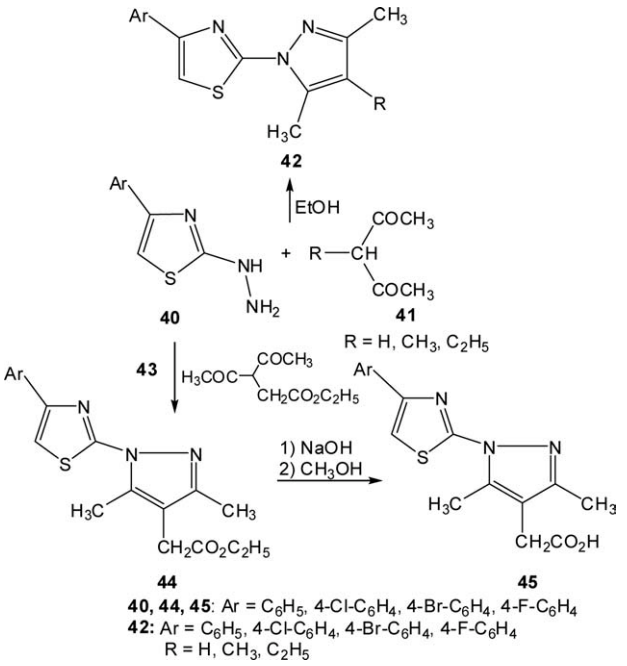
On the other hand, thiazole derivatives **33** were formed by refluxing alkoxy benzoylthiosemicarbazide (**2**) with (1,2-dichloroethyl)ethylether (**32**)[82,83,86–94].



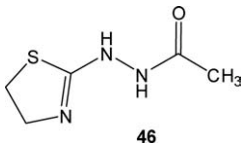
1-Methyl-2-(2-hydrazino-4-thiazolyl)benzimidazole **36** was synthesized by condensation of compound **35** with 1-acetylthiosemicarbazide (**2**). Compound **38** was synthesized by reaction of **36** with the ketones **37** or condensation of **35** directly with thiosemicarbazones **39** [95–97].



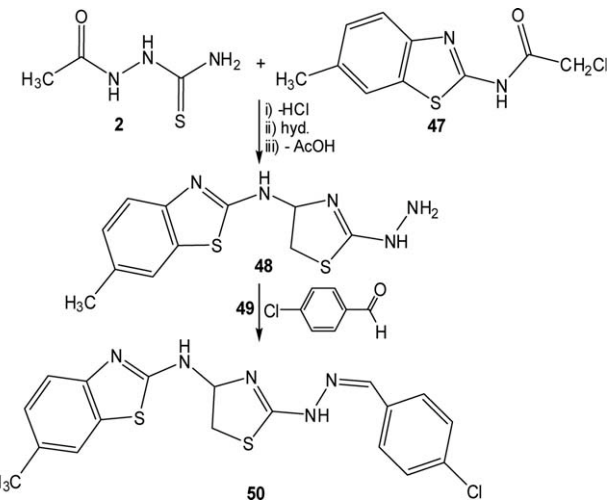
2-Hydrazino-4-arylthiazoles **40** were prepared by the condensation of appropriate phenacyl bromide with **2** followed by acid hydrolysis with dil. HCl. Refluxing **40** with 3-substituted pentane-2,4-diones **41** in ethanol with little acetic acid afforded pyrazolothiazoles **42**, whereas on condensation with 3-carboethoxymethylpentane-2,4-dione **43** gave compound **44**, alkaline hydrolysis of **44** gave **45** [98,99].



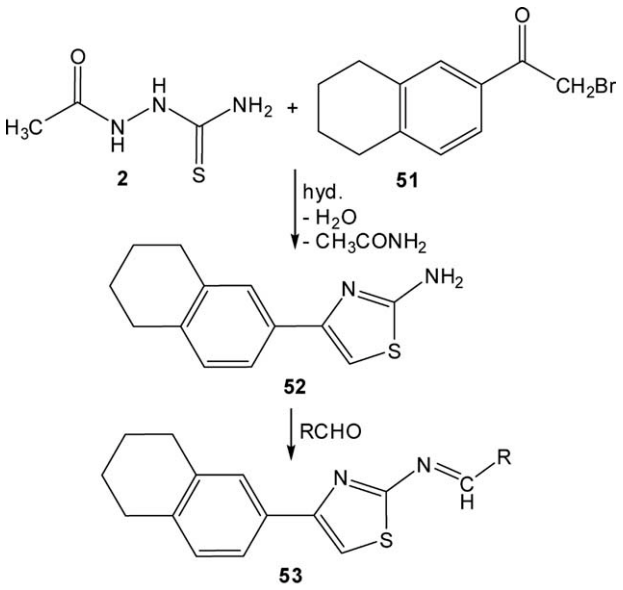
Cyclization of 1-acetylthiosemicarbazide (**2**) with $BrCH_2CH_2NH_2.HBr$ in *iso*-propyl alcohol gave *N*′-(4,5-dihydrothiazol-2-yl)acetohydrazide (**46**) with eliminating a molecule of NH_4Cl [100].



Fathalla et al. [101], reported the reaction of 6-methyl-2-chloroacetamidobenzothiazole (**47**) with **2** followed by hydrolysis to yield hydrazinothiazole derivatives **48**, which in turn reacted with *p*-chlorobenzaldehyde (**49**) to give (Z)-*N*-(2-(2-(4-chlorobenzylidene)hydrazinyl)-4,5-dihydrothiazol-4-yl)-6-methylbenzo[*d*]thiazol-2-amine **50**.

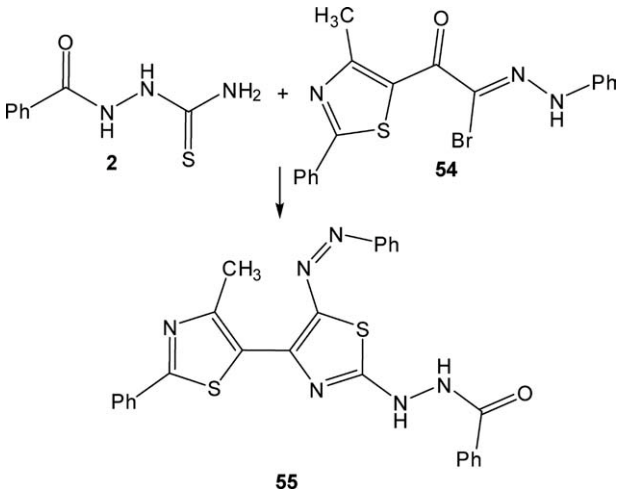


Also, the reaction of bromoacetyltetralin (**51**) with acylthiosemicarbazide (**2**) gave 4-(5,6,7,8-tetrahydronaphthalen-2-yl)thiazol-2-amine (**52**) (during the elimination of H_2O, HBr, and CH_3CONH_2 after hydrolysis). **52** Reacted with aromatic aldehydes to give thiazole derivatives **53** [102].

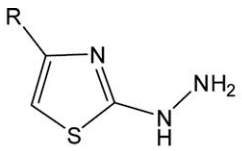


R = C_6H_5, 4-CH_3-C_6H_4, 4-CH_3O-C_6H_4, 2-pyridyl, 2-thienyl

Hydrazonoyl bromide derivative **54** was reacted with benzoylthiosemicarbazide (**2**) to give 5-arylazothiazole derivatives **55** [103].

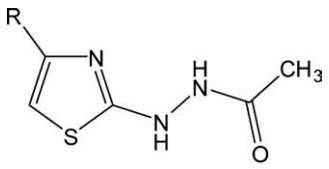


Thiazole derivatives **31** were prepared by heating 1-acetylthiosemicarbazide **2** with the corresponding phenacyl halides followed by hydrolysis [104].



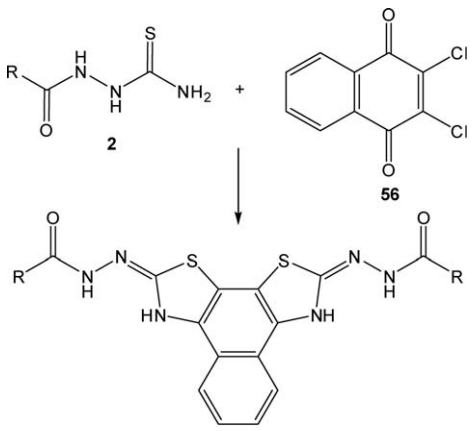
R = C_6H_5, 3,4-HO-C_6H_4, 2,3,4-HO-C_6H_2
2,5-HO-C_6H_3, 3,5-HO-C_6H_3

2,4-Disubstituted thiazoles **33** were obtained during the reaction of $RCOCH_2Cl$ with 1-acetylthiosemicarbazide (**2**) [105,106].



R = 3,4-$(HO)_2$-C_6H_3,
2,5-$(HO)_2$-C_6H_3,
2,3,4-$(HO)_3$-C_6H_2

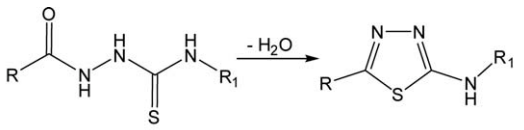
Naphthobisthiazole **57** can be obtained by refluxing 1-acylthiosemicarbazides **2** with 2,3-dichloro-1,4-naphthoquinone (DCHNQ, **56**) in ethyl acetate. Compounds **57** were formed from reaction of one molecule of (DCHNQ, **56**) and two molecules of **2** by loss of two molecules of HCl and another two molecules of H_2O after abstracting a molecule of H_2 [107].



2,57: R = CH_3, C_6H_5, 4-HO-C_6H_4, 4-Br-$C_6H_4CH_2$

3.4. Synthesis of thiadiazole and thiadiazoline derivatives. 1-Acylthiosemicarbazides **2** were cyclized with dehydrating reagents to thiadiazole derivatives **58**.

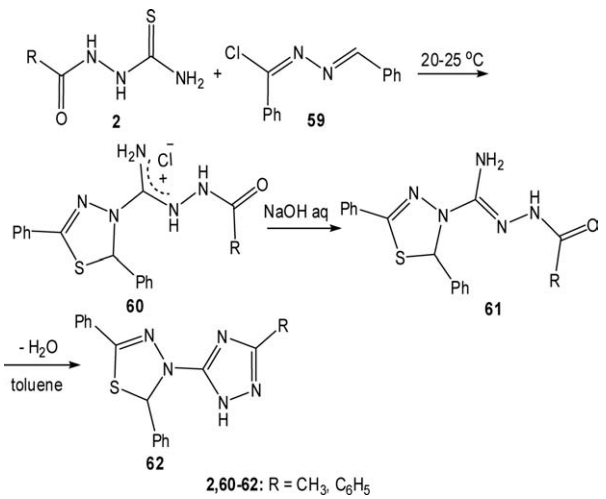
Common reagents for this cyclization such as neat sulfuric acid, neat polyphosphoric acid or mixtures [108,109], and phosphorus halides have been used when R is alkyl but the reaction fails when R is aryl [110,111]. In contrast, Kress and Costantino [112] reported that these procedures require a large molar excess of acid, water, and base. So the following treatment report a convenient and general cyclization where R = alkyl or aryl. Thus, treatment of **2** with methanesulfonic acid in refluxing toluene for 4–6 hr afforded good yields of the thiadiazolines **58** [112].



2 **58**

2,58: R = *p*-CF_3-C_6H_4, *p*-Cl-C_6H_4, $C_6H_2CH_2$, $(C_6H_5)_2CH$, $(CH_3)_3C$
R_1 = H, CH_3

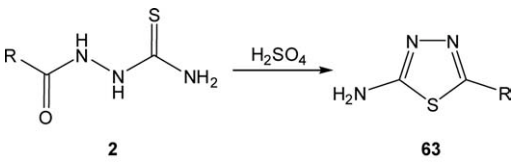
When 1-acetyl- and benzoylthiosemicarbazides **2** [64,113] were separately treated with chlorodiazo-butadiene derivative **59**, at ambient temperature, hydrochlorides **60** were formed, which were readily converted into the corresponding bases 4-substituted-Δ^2-1,2,3-thiadiazoline **61** [114,115], whereas 4-triazole-3-yl-Δ^2-1,3,4-thiadiazolines **62** was obtained during dehydration of **61** by refluxing with toluene.



2 **59** **60** **61** **62**

2,60-62: R = CH_3, C_6H_5

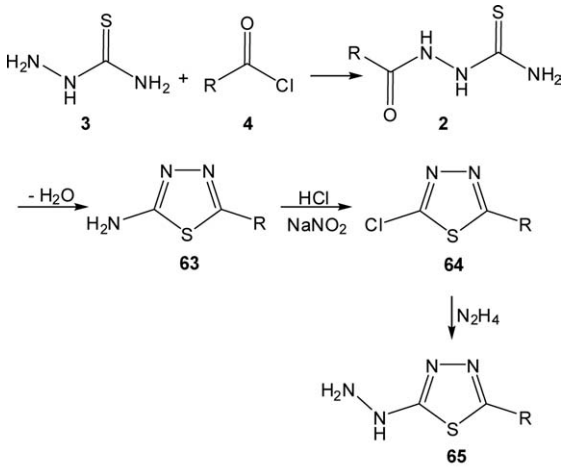
Treating 1-acylthiosemicarbazides **2** with concentrated H_2SO_4 pouring into water and neutralizing with NH_4OH or Na_2CO_3 afforded 5-substituted-2-amino-1,3,4-thiadiazoles **63** [62,63,116,117].



2 **63**

2,63: R = CH_3, C_2H_5, C_3H_7, C_6H_5, $C_6H_4CH_2$, *p*-O_2N-C_6H_4, *p*-HO-C_6H_4, cyclohexyl, 3-pyridyl, 4-pyridyl

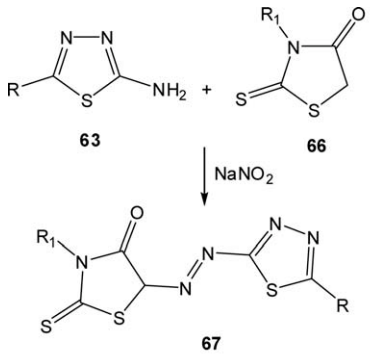
1,3,4-Thiadiazoles **65** were prepared *via* the acylation of thiosemicarbazide followed by dehydration to afford thiadiazoles **63** [112]. Thiadiazoles **63** could be transformed into **64** and subsequent hydrazinolysis of **64** under mild condensations provided thiadiazoles **65** [118,119].



3 **4** **2** **63** **64** **65**

2,4,63-65: R = CH_3, C_2H_5, C_6H_5, n-C_3H_7C, *iso*-C_4H_9

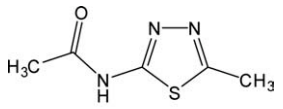
Cyclodehydration of acylthiosemicarbazides **2** gave thiadiazoles **63**, which were reacted with 3-aryl-2-thioxo-thiazolidin-4-one **66** to give 3-substituted-5-[(5-substituted-1,3,4-thiadiazol-2-yl)diazenyl]-2-thioxothia-zolidin-4-one **67** [120].



63 **66** **67**

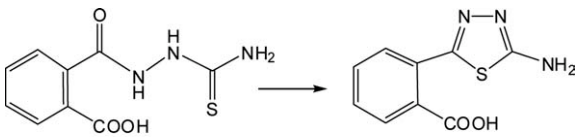
63,66,67: R = C_6H_5, $C_6H_5CH_2$, 2-CH_3-C_6H_4, 3-CH_3-C_6H_4, 4-CH_3-C_6H_4
R_1 = C_6H_5, 2-CH_3-C_6H_4, 4-CH_3-C_6H_4, 4-CH_3O-C_6H_4

Refluxing thiosemicarbazide (**3**) omitted with AcCl followed by elimination of H_2O gave 2-acetamido-5-methyl-1,3,4-thiadiazole (**68**) [121].



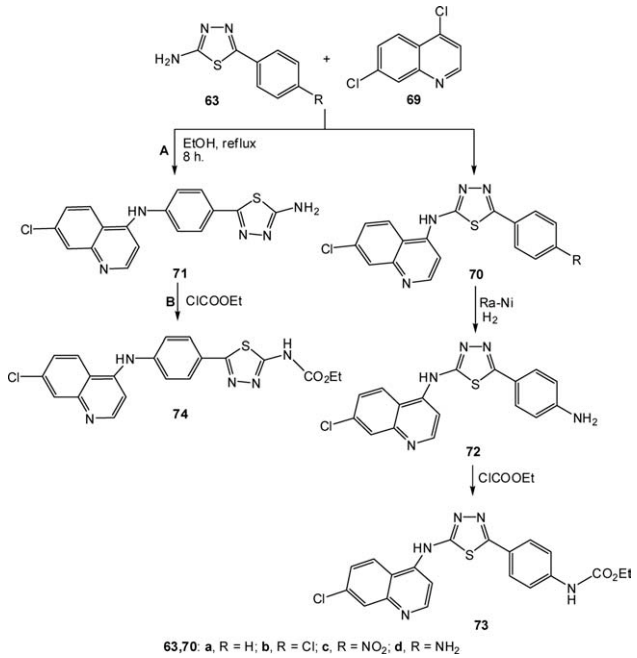
68

o-(2-Amino-1,3,4-thiadiazol-5-yl)benzoic acid (**63**) can be obtained by refluxing of *N*-thiouridophthalonic acid (**2**) in polyphosphoric acid or acetic acid [69].



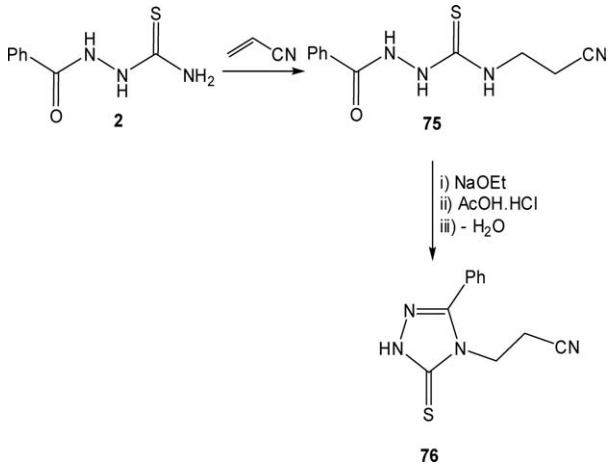
2 **63**

The reaction of 2-amino-5-(4-substituted phenyl)-1,3,4-thiadiazoles **63** with 4,7-dichloroquinoline (**69**) yielded thiadiazoles **70**. Among these thiadiazoles, the nitro derivative **70c** was hydrogenated over Raney-nickel to give 5-(4-aminophenyl)-*N*-(7-chloroquinolin-4-yl)-1,3,4-thiadiazol-2-amine (**72**). Acylation of **72** with ethyl chloroformate yielded 2-(7-chloro-4-quinolinylamino)-5-(*p*-carbethoxyaminophenyl)-1,3,4-thiadiazole (**73**). On the other hand, hydrogenation of **63c** in the presence of Raney-nickel yielded the corresponding amino compound **63d**, which transformed to 5-[4-(7-chloroquinolin-4-ylamino)phenyl]-1,3,4-thiadiazol-2-amine (**71**) and ethyl 5-(4-(7-chloroquinolin-4-ylamino)phenyl)-1,3,4-thiadiaz-ol-2-ylcarbamate **74** by reaction with **69** *via* steps **A** and **B** [122].



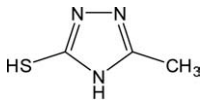
63,70: **a**, R = H; **b**, R = Cl; **c**, R = NO_2; **d**, R = NH_2

3.5. Synthesis of triazole and triazoline derivatives. 1,2,4-Triazoline-5-thione derivative **76** could be synthesized independently *via* cyclization of 1-benzoyl-4-β-acyanoethyl thiosemicarbazide (**75**), which was prepared *via* cyanoethylation of 1-benzoyl thiosemicarbazide (**2**) [123].



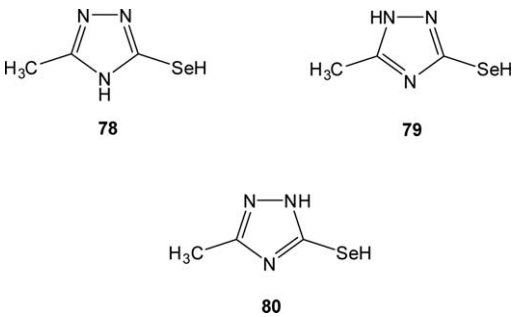
2 **75** **76**

Pyrolysis of 1-acetylthiosemicarbazide (**2**) gave 5-methyl-4*H*-1,2,4-triazole-3-thiol (**77**) as a major product. A free radical mechanism has been suggested to account for the products [124].



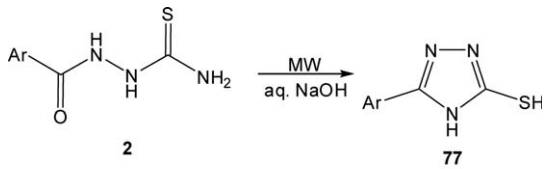
77

1,2,4-Triazole-3-selenols **78–80** were prepared by the treatment of acetyl thiosemicarbazide (**2**) with aq. Na_2Se at pH = 7.8 and acidification with AcOH at pH = 4 [125].



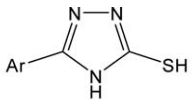
78 **79** **80**

On the other hand, 5-aryl-1,2,4-triazoline-3-thiol **77** was obtained *via* microwave irradiation of acylthiosemicarbazides **2** in aq. NaOH for several minutes [126].



2,77: Ar = C_6H_5, subst-C_6H_5, 3-pyridyl

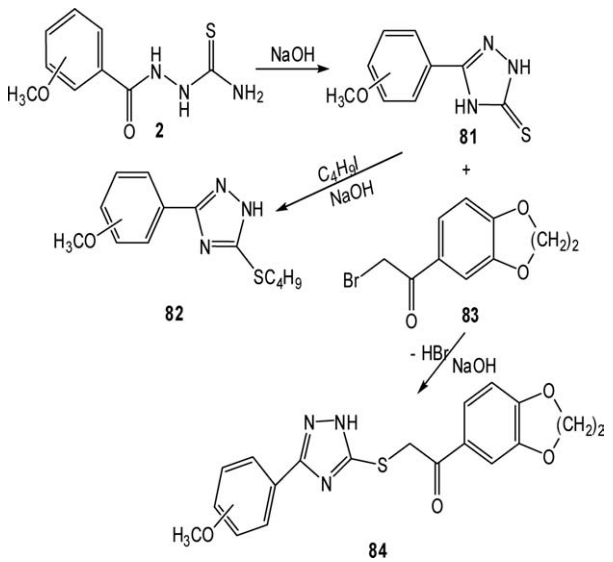
Also, triazole derivatives **77** were prepared by the reaction of appropriate acylthiosemicarbazides **2** and KOH in ethanol under reflux, followed by acidification with acetic acid [127].



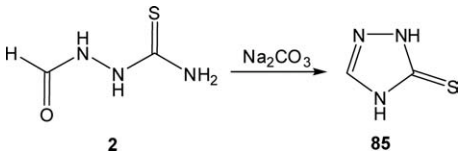
77

Ar = *p*-CH_3-C_6H_4, *p*-CH_3O-C_6H_4, *p*-Cl-C_6H_4, *m*-Br-C_6H_4

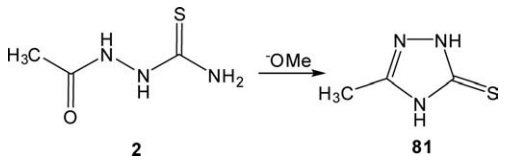
New *S*-alkylated 5-(butylthio)-3-substituted phenyl-1*H*-1,2,4-triazoles **82** and 1-(2,3-dihydrobenzo[*b*][1,4]-dioxin-6-yl)-2-(3-substituted phenyl-1*H*-1,2,4-triazol-5-ylthio)-ethanones **84** were synthesized by alkylation of 1,2,4-triazole-5-thiones **81** with iodobutane or with 2-bromo-1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)ethanone (**83**) [128].



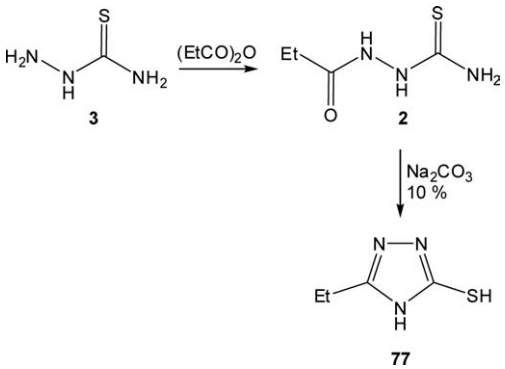
1,2,4-Trizoline-5-thione (**85**) can be obtained by cyclization of 1-formylthiosemicarbazide **2** in a 2*M* sodium carbonate solution [129].



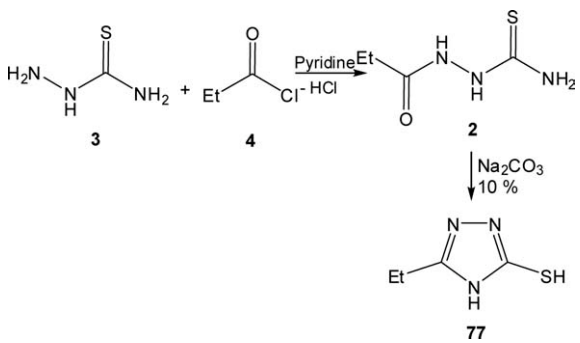
1-Acetylthiosemicarbazide (**2**) cyclized with sodium methoxide in methanol to 3-methyl-1,2,4-triazoline-5-thione (**81**) [130]. Alternatively, the cyclization can be affected by heating to about 185°C [131,132].



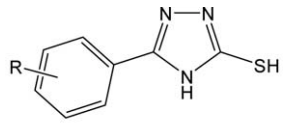
Another route to the acylthiosemicarbazides **2** was offered by the reaction of thiosemicarbazide **3** with aliphatic anhydrides [71], one mole of propionic anhydride, reacted with **3** to give 1-propionyl thiosemicarbazide, which cyclized into 3-ethyl-1,2,4-triazoline-5-thiol (**77**) [71].



On the other hand, 5-ethyl-4*H*-1,2,4-triazole-3-thiol (**77**) can be obtained during the reaction of thiosemicarbazide **3** with appropriately substituted acid chlorides in the presence of pyridine [19,133].



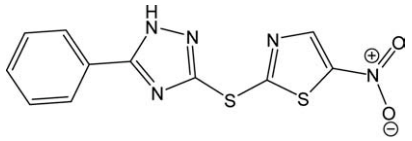
Also, triazole derivatives **77** were also obtained by the cyclization of acylthiosemicarbazides **2** on treating 4-substituted benzoyl chloride with thiosemicarbazide (**3**) and elimination a molecule of HCl and H_2O from **2** to give triazoles **77** [134].



77

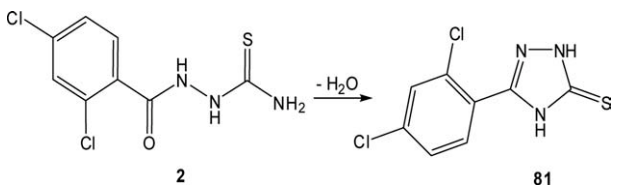
R = H, 4-OH, 4-OCH_3, 4-Cl, 3,4-$(Cl)_2$

However, nitrothiazolylmercaptotriazole **86** can be obtained by the treatment of 3-phenyl-5-thione-1,2,4-triazole (in MeOH) with 2-bromo-5-nitrothiazole in presence of NaOMe [135].



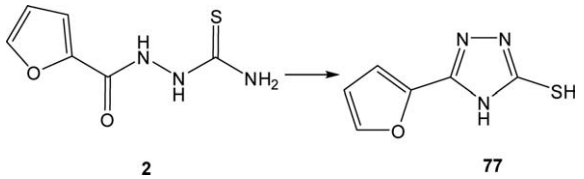
86

Goswami *et al*. [136] reported that oxidative cyclization of 1-(2,4-dichlorobenzoyl)thiosemicarbazide (**2**) gave 3-(2,4-dichlrophenyl)-1*H*-1,2,4-triazol-5-thione (**81**) [137].



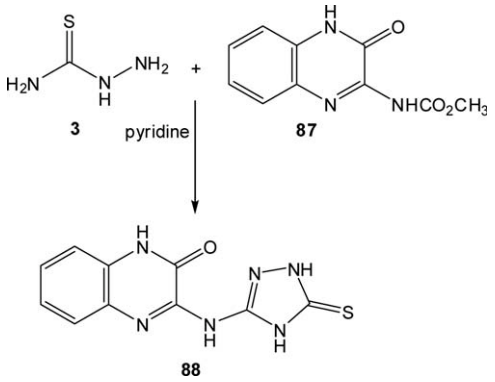
2 **81**

5-Furan-2-yl-4*H*-1,2,4-triazole-3-thiol (**77**) was prepared by the reaction of the appropriate 2-furoyl-thiosemicarbazide (**2**) and potassium hydroxide in ethanol for 3 hr under reflux, followed by acidification with acetic acid [138,139].



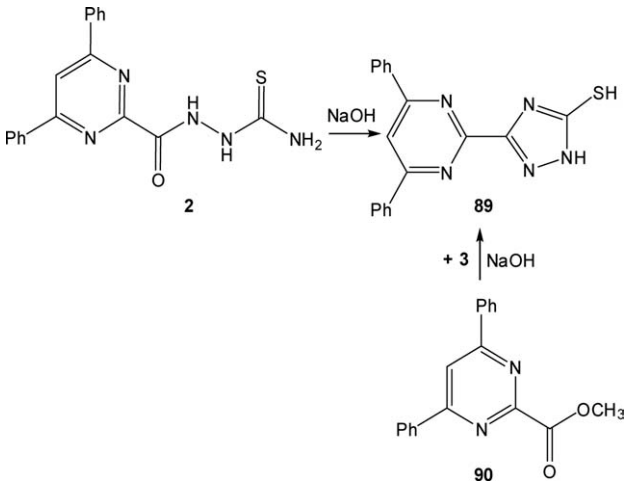
2 **77**

Condensation of methyl 3-oxo-3,4-dihydroquinoxalin-2-ylcarbamate (**87**) with thioesemicarbazide in boiling pyridine *via* initial nucleophilic attack of the amino group to ester carbonyl without attack at the carbonyl of the quinoxaline ring followed by cyclization to give 3-(5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-ylamino)quinoxalin-2(1*H*)-one (**88**) [140,141].



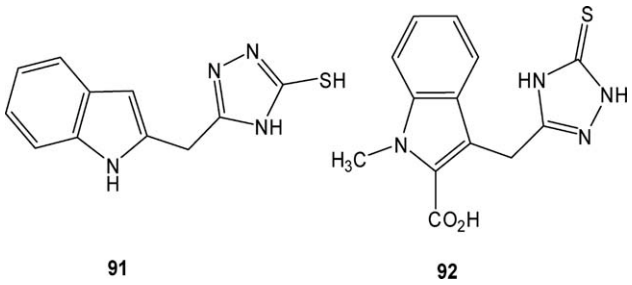
3 **87** **88**

5-(4,6-Diphenylpyrimidin-2-yl)-1,2,4-triazolin-3-thiole **89** [142] could be prepared either by base-catalyzed cyclization of acylthiosemicarbazide **2** or by the reaction of methyl pyrimidine-2-carboxylate **90** with thiosemicarbazide **3** in presence of NaOH.



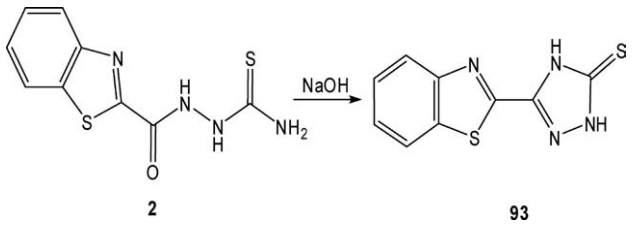
2 **89** **90**

Similarly, triazoles **91** and **92** were obtained by the cyclization of the corresponding thiosemicarbazides in alkaline medium [143,144].



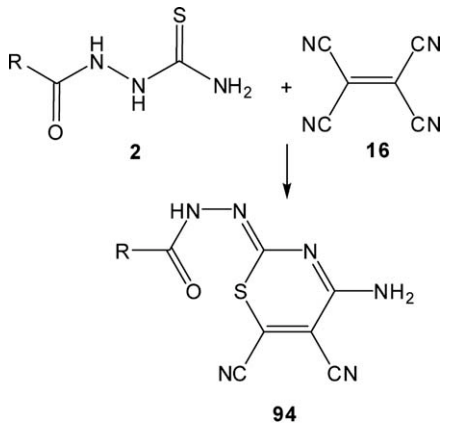
91 92

Also, heating of 1-(2-benzothiazolylcarbonyl)thiosemi-carbazide (**2**) with sodium hydroxide, followed by intramolecular cyclization gave 3-(benzo[*d*]thiazol-2-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (**93**) [145].



2 93

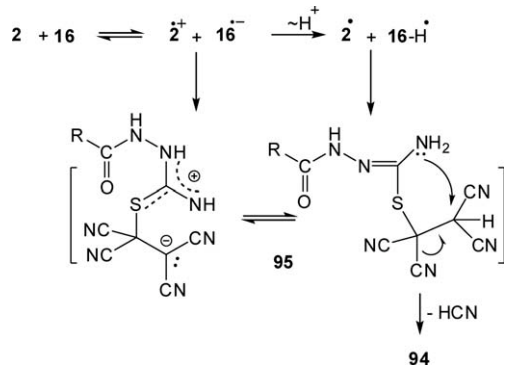
3.6. Synthesis of thiazine derivatives. 1-Acylthiosemicarbazides **2** reacted with TCNE (**16**) in ethyl acetate to give N′-(4-amino-5,6-dicyano-2H-1,3-thiazin-2-ylidene) substituted hydrazides **94** [77].



2 16 94

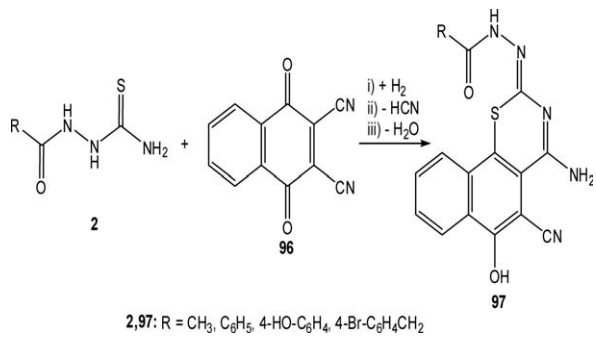
2,97: R = CH_3, C_6H_5, 4-HO-C_6H_4, 4-Br-C_6H_4

The formation of compound **94** can be rationalized as following [77].



95 94

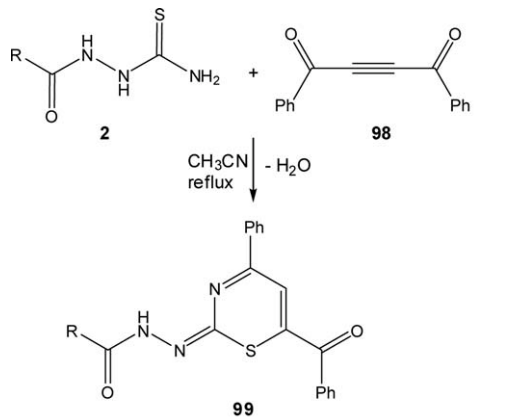
Addition of 1-acylthiosemicarbazides **2** to 2,3-dicyano-1,4-naphthoquinone (**96**), resulted in an initial formation of CTC followed by the formation of naphthothiazine derivatives **97** [107].



2 96 97

2,97: R = CH_3, C_6H_5, 4-HO-C_6H_4, 4-Br-$C_6H_4CH_2$

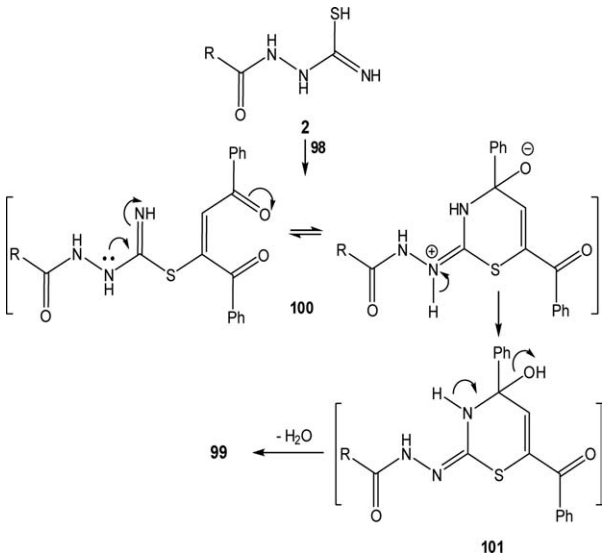
On the other hand, refluxing equivalent amount of 1-acylthiosemicarbazides **2** with 1,4-diphenylbut-2-yne-1,4-dione (**98**) in acetonitrile lead to the formation of 1,3-thiazin-2-ylidene-substituted hydrazides **99** [146].



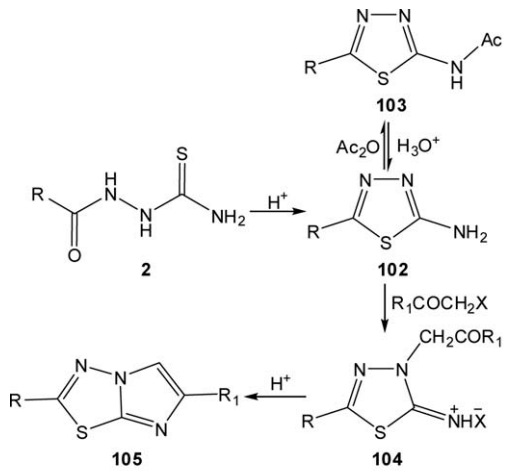
2 98 99

2,99: R = C_6H_5, 4-HO-C_6H_4, 4-CH_3O-C_6H_5, 4-Br-C_6H_5,CH_3

The formation of thiazine derivatives **99** can be rationalized as shown [146].

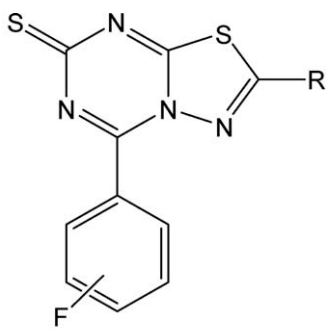


3.7. Synthesis of fused heterocyclic systems containing 1,3,4-thiadiazole ring. 1-Acylthiosemicarbazides **2**, under the action of concentrated H_2SO_4, was converted to aminothiadiazoles **102**. *N*-Acetyl derivatives **103** was obtained by the action of acetic anhydraide on compound **102**, whereas imidazo[2,1-*b*][1,3,4]thiadiazoles **105** was formed by the condensation of **102** with α-haloketones *via* intermediate **104** [147].



2,102,103: R = 2-Phenylthiazol-4-yl, 4-methyl-2-phenylthiazol-5-yl
105: R = 2-Phenylthiazol-4-yl, 4-methyl-2-phenylthiazol-5-yl
R_1 = Methyl, phenyl
X = Cl, Br

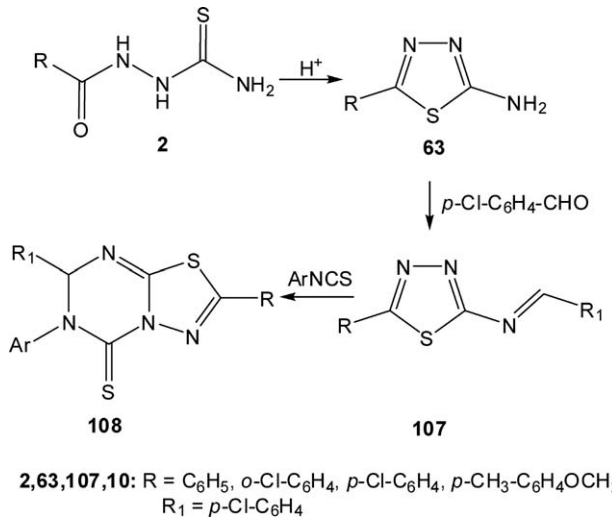
Also, thiadiazolotriazine derivatives **106** were prepared by the cyclodehydration of the appropriate **2**, reaction of the resulting aminothiadiazoles with aromatic acid chlorides and NH_4SCN, followed by cyclodehydration [148].



106

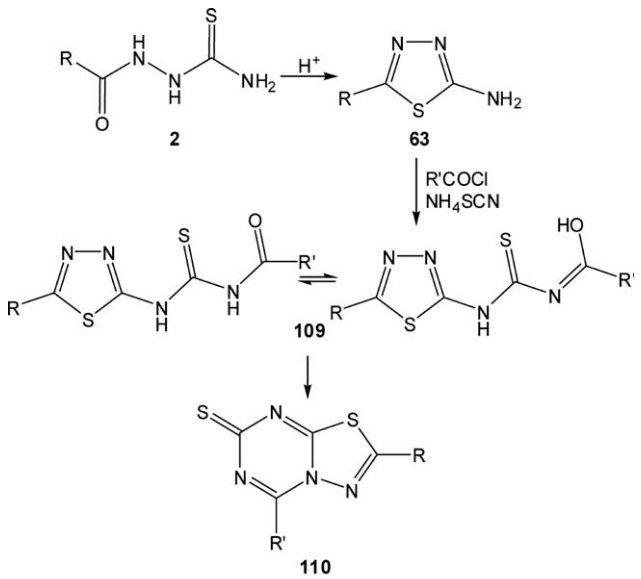
R = C_6H_5, *p*-Cl-C_6H_4, $C_6H_5OCH_2$
F = *o*-F-C_6H_4, *p*-F-C_6H_4

It has been reported that cycloaddition of 5-aryl/aryloxymethyl-2-benzylideneamino-1,3,4-thiadiazole derivatives **107** to arylisothiocyanate afforded **108** [149–152], and **107** was prepared by the reaction of thiadiazole **63** with *p*-chlorobenzaldehyde.



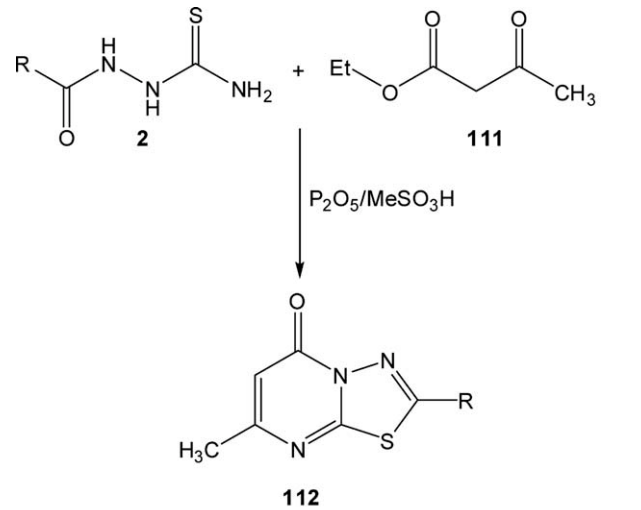
2,63,107,10: R = C_6H_5, *o*-Cl-C_6H_4, *p*-Cl-C_6H_4, *p*-CH_3-$C_6H_4OCH_2$
R_1 = *p*-Cl-C_6H_4

Also Singh et al. [153] reported that, 1-acyl thiosemicarbazide **2** on cyclodehydration with conc. H_2SO_4 gave the corresponding compound **63,** which on treatment with acylchlorides and NH_4SCN in acetone followed by the cyclization of the resultant *N*-acyl-*N*′-(5-aralkyl/aryl-1,3,4-thiadiazol-2-yl)thioureas **109** with $PCl_5/POCl_3$ gave the corresponding thiadiazolotriazine derivatives **110**, which have herbicidal activity [154,155].



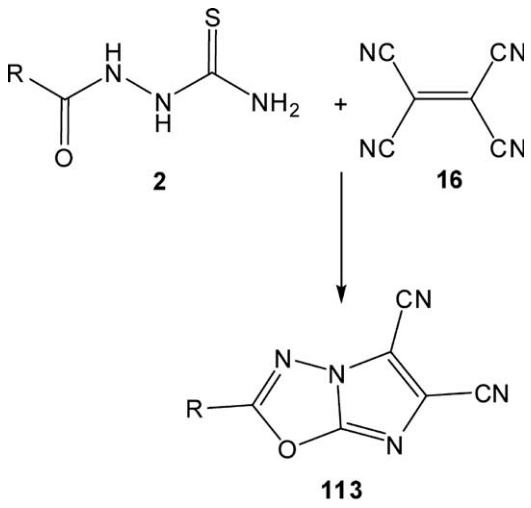
2,63,109,110: R = $C_6H_5CH_2$, C_6H_5, *o*-Cl-C_6H_4, *o*-CH_3-C_6H_4, *m*-CH_3-C_6H_4
R' = C_6H_5, *p*-Cl-C_6H_4, *p*-Cl-$C_6H_4OCH_2$

On the other hand, heating mixture of acylthiosemicarbazides **2** and ethyl acetoacetate (**111**) with P_2O_5/CH_3SO_3H (CH_3SO_3H = methanesulfonic acid) gave thiadiazolopyrimidine derivatives **112** [156–159].



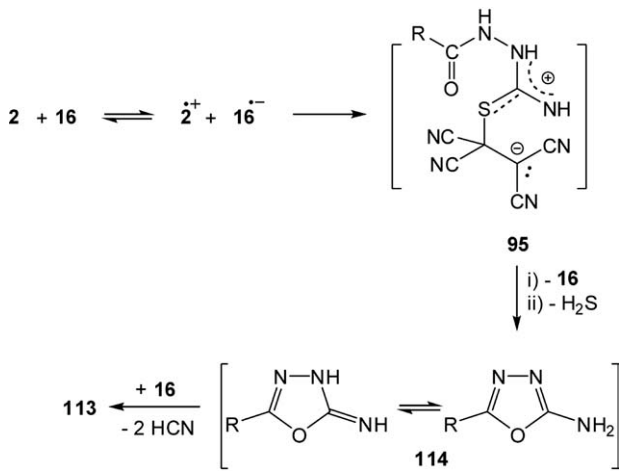
2,112: R = H, CH_3, C_6H_5, *o*-CH_3O-C_6H_4, *p*-CH_3O-C_6H_4, *o*-Cl-C_6H_4, *m*-Cl-C_6H_4, *p*-Cl-C_6H_4, *m*-O_2N-C_6H_4, *p*-CH_3-C_6H_4

3.8. Synthesis of fused heterocyclic systems containing 1,3,4-oxadiazole ring. 1-Acylthiosemicarbazides **2** is reacted with TCNE (**16**) in ethyl acetate to give 2-subsituted imidazo[2,1-*b*]oxadiazole-5,6-dicarbonitrile **113** [77].

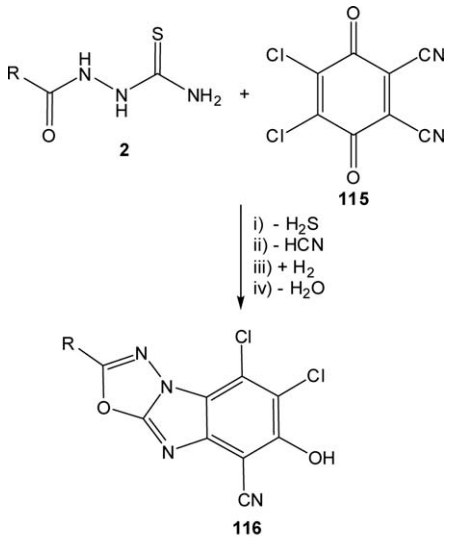


2,113: R = CH_3, C_6H_5, 4-HO-C_6H_4, 4-Br-C_6H_4

Rationales for the formation of products **113** are presented as shown. Compounds **113** were formed from **2** and **16** after the loss of H_2S and two molecules of HCN *via* intermediates **95** and **114** [77].

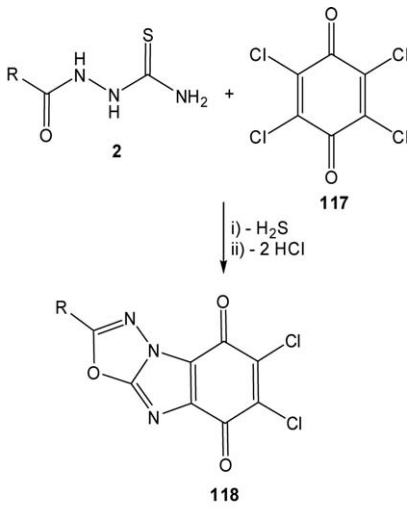


1-Acylthiosemicarbazides **2** reacted with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (**115**) in ethyl acetate at room temperature resulted in the formation of unstable charge-transfer complexes followed by chemical reaction to give benzimidazoxadiazoles **116** [107].



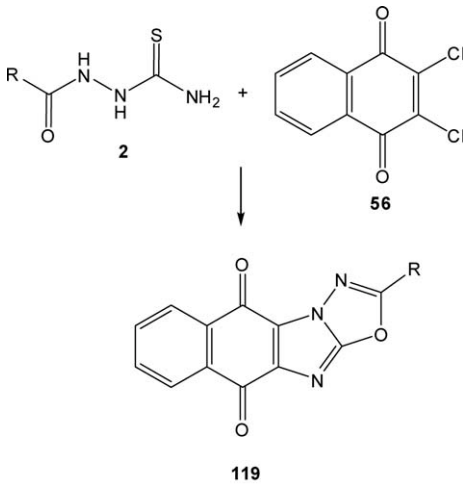
2,116: R = CH_3, C_6H_5, 4-HO-C_6H_4, 4-Br-$C_6H_4CH_2$

On the other hand, mixing of two-fold molar excess of 2,3,5,6-tetrachloro-1,4-benzoquinone (**CHL-*p***, **117**) with one molecule of 1-acylthiosemicarbazides **2** lead to the formation of an initial charge transfer complexes (CTC) followed by the formation of benzimidazoxadiazolediones **118** [107].



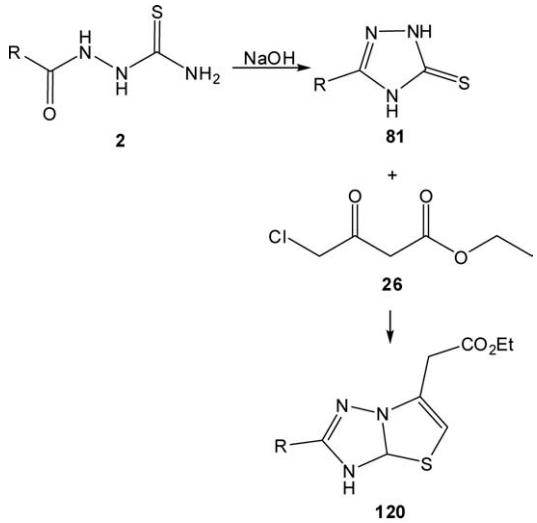
2,118: R = CH_3, C_6H_5, 4-HO-C_6H_4, 4-Br-$C_6H_4CH_2$

Naphthoimidazoxadiazole **119** can be obtained by refluxing 1-acylthiosemicarbazides **2** with 2,3-dichloro-1,4-naphthoquinone (DCHNQ, **56**) in ethyl acetate, during the elimination of one molecule of H_2S and two molecules of HCl [107].



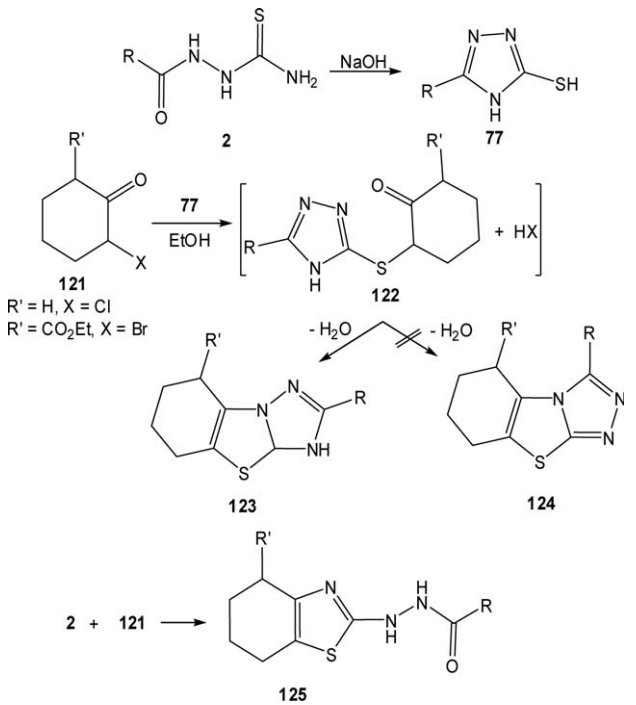
2,119: R = CH_3, C_6H_5, 4-HO-C_6H_4, 4-Br-$C_6H_4CH_2$

3.9. Synthesis of fused heterocyclic systems containing 1,2,4-triazole ring. Cyclization of benzoylthiosemicarbazide derivatives **2** [114] in sodium hydroxide afforded 1,2,4-triazoline-5-thione derivatives **81** [80], which was refluxed with ethyl 4-chloro-3-oxo-butyrate (**26**) to give thiazolotriazole derivatives **120** [160,161].



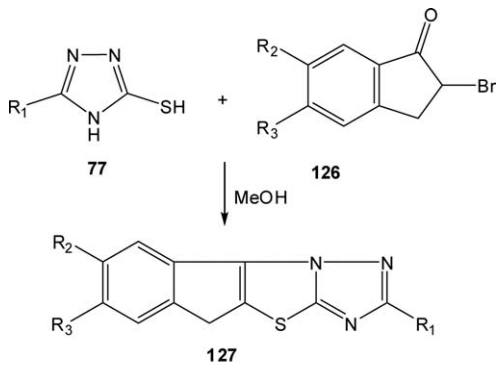
2,81,120: R = C_6H_5, *o*-Cl-C_6H_4, *p*-Cl-C_6H_4,

Cyclization of acylthiosemicarbazides **2** under alkaline conditions gave 3-thiol-5-aryl-1,3,4-triazoles **77**, which reacted with 2-halocyclohexanones **121** in ethanol to give compounds **123** *via* intermediate **122** rather than **124** [54–56,162–166]. On the other hand, compounds **125** were formed during the reaction of **2** with **121**.



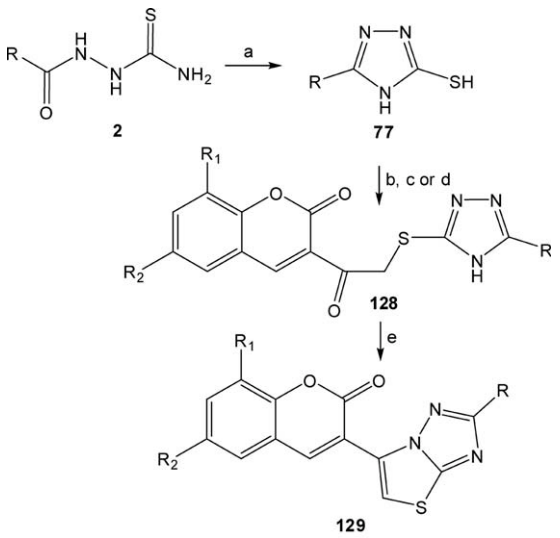
2,77,125: R = C_6H_5, *o*-CH_3-C_6H_4, *p*-CH_3O-C_6H_4, *p*-Cl-C_6H_4, *p*-CH_3-C_6H_4, *o*-CH_3-C_6H_4
121,125: R' = H, $CO_2C_2H_5$

2-Aryl-6,7-dialkoxyindeno[1,2:4,5]thiazolo[3,2-*b*]triazoles **127** [167] were synthesized by the reaction of 2-bromoindanones **126** [168] in the presence of dry methanol, and **77** was obtained by the cyclization of aroyl thiosemicarbazides **2** with KOH [169].



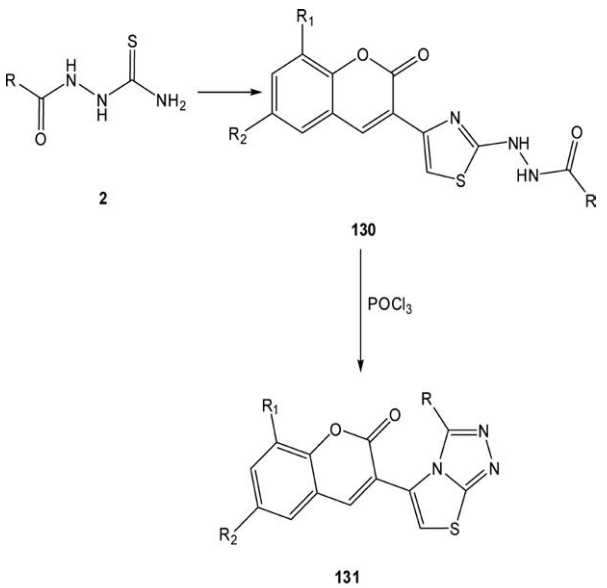
77,127: R_1 = 4-MeO-C_6H_4, $C_6H_5CH_2$, C_6H_5, o-Cl-C_6H_4
126,127: R_2 = OMe, OEt
R_3 = OMe, OEt

Condensation of 3-methyl or ethyl-5-thiol-triazoles **77** with either 3-(2-bromoacetyl)coumarins in acetic acid or *via* direct reaction with substituted 3-acetyl coumarins in carbon tetrachloride or dioxane under photohalogenation and using bromine in the presence of chloro-(*N*,*N*″-ethylenebisaminobenzamide)lanthanum (II) or samarium (III) as catalyst, gave uncyclized ketone **128**, which was cyclized using polyphosphoric acid (PPA) to give **129** [170–175].

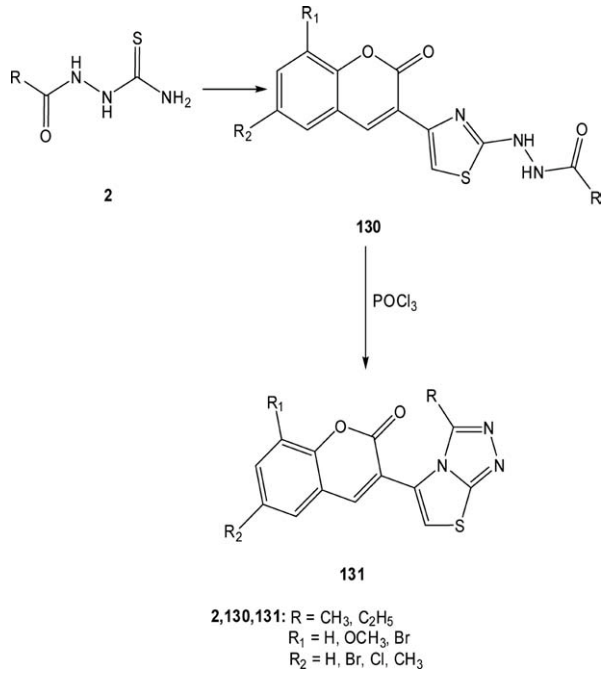


2,77,128,129: R = CH_3, C_2H_5
a, 4% NaOH
b, Br_2, CCl_4 or dioxane, [Ln(EBAB)Cl_3]
c, Disubst- 3-acetylcoumarine
d, Disubst- 3-(2-bromoacetyl)coumarine EtOH, AcOH
e, PPA

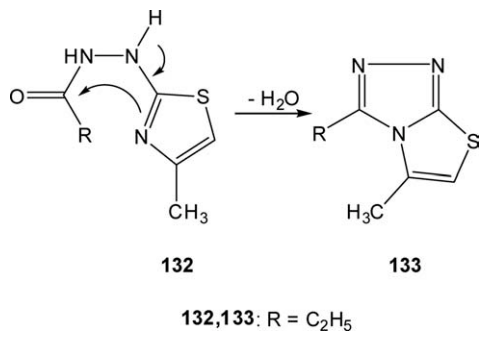
Condensation of 1-acylthiosemicarbazides **2** with disubstituted-3-(2-bromoacetyl)coumarines in the presence of bromine in dry carbon tetrachloride or dioxane using lanthanum catalyst or when reacted with disubstituted 3-acetylcoumarine in absolute ethanol yielded 2-acetylhydrazino-4-coumarinylthiazole **130**. Subsequent treatment of **130** with $POCl_3$ induced facile cyclization to give **131** [175].



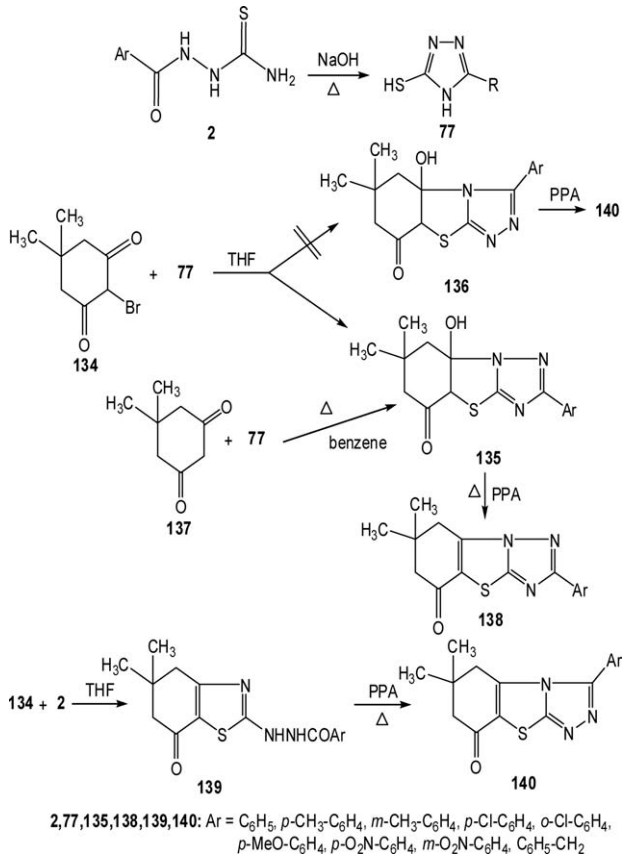
2,130,131: R = CH_3, C_2H_5
R_1 = H, OCH_3, Br
R_2 = H, Br, Cl, CH_3



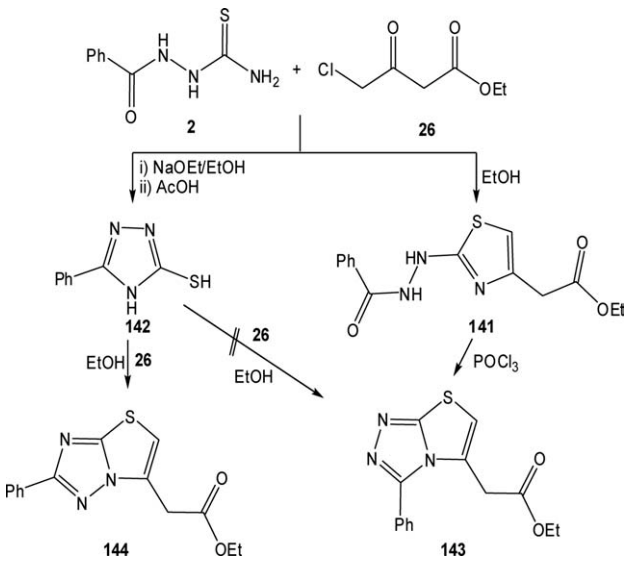
A mixture of 1-acetylthiosemicarbazide (**2**), chloroacetone and ethanol was heated under reflux to give **132**, which on treatment with ammonium acetate in refluxing EtOH converted to thiazolotriazole derivatives **133** [84].



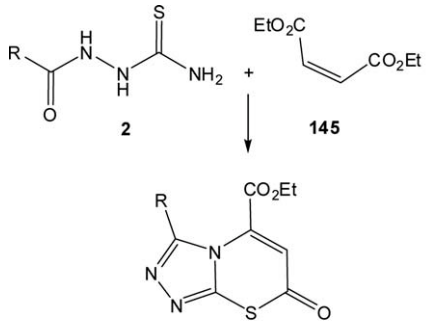
Khazi and Mahajanshetti [176] reported that condensation of 3-thiol-1,3,4-triazoles **77** and 2-bromodimedone derivatives **134** in THF/or benzene gave **135** [177]. Compounds **135** were also obtained by heating a mixture of dimedone **137** and **77** in benzene containing a trace of benzoylperoxide. Thermal dehydration of **135** in PPA/or ethanol yielded the corresponding **138**. Formation of **136** during the reaction of **134** with **77** was ruled out by an unambiguous synthesis of **140** from reaction of **2** with **134** in THF *via* formation of **139**, which was heated with PPA to give **140**.



Refluxing 1-benzoylthiosemicarbazide (**2**) and 4-chloroacetoacetate (**26**) in ethanol afforded thiazole derivatives **141**. Thiazolyltriazole derivatives **143** were formed during the reaction of **141** with $POCl_3$ in xylene. The corresponding structural isomer **144** was obtained by reacting **142** with **26** in ethanol [178,179].

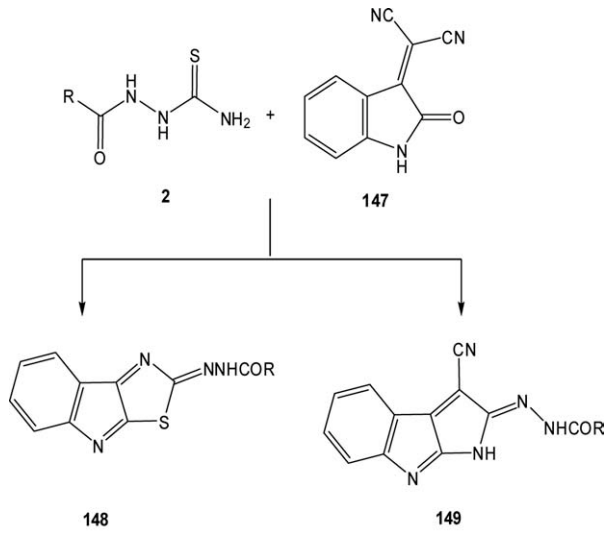


Also, the interaction between 1-acylthiosemicarbazides **2** and diethyl maleate (**145**) in refluxing glacial acetic acid gave [1,2,4]triazolo[3,4-*b*][1,3]thiazine-5-carboxylates **146** [180].



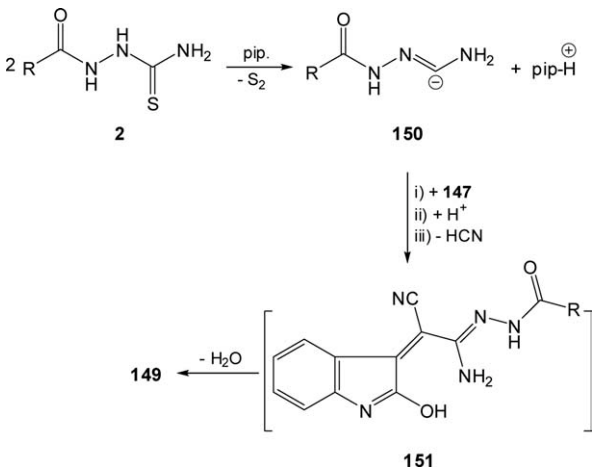
2,146: R = CH_3, C_6H_5, 4-HO-C_6H_4, 4-Br-$C_6H_4CH_2$

3.10. Synthesis of fused indoles. Substituted thiazoloindolidene **148** and substituted pyrroloindolidene **149** can be obtained by refluxing one mole of 1-acylthiosemicarbazides **2** with two equivalents of 3-(dicyanomethylene)-2-indolone (**147**) in ethanol/piperidene [78].

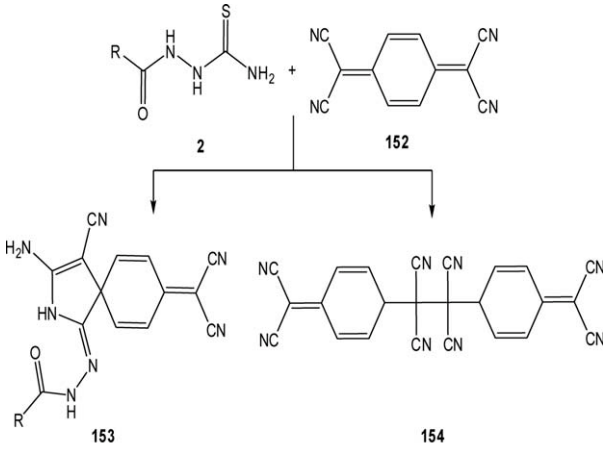


2,148,149: R = CH_3, C_6H_5, 4-HO-C_6H_4, 4-Br-$C_6H_4CH_2$

Compounds **148** could be formed during reaction of **2** with **147** and elimination of a molecule of malononitrile and a molecule of water, whereas **149** were formed *via* dimerization of **2** with loss of a molecule of sulfur and the reaction with **147** *via* eliminating one molecule of hydrogen cyanide and one molecule of water [78].

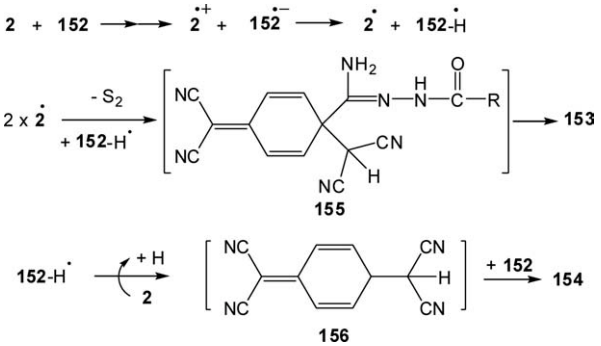


3.11. Synthesis of spiro-compounds. On the other hand, a pyridine solution of 7,7,8,8-tetracyanoquinodimethane (TCNQ, **152**) and 1-acylthiosemicarbazides **2** in a molar ratio of 2:1 were kept at 100°C for 2 h with admission of air to give spiro-compounds **153** in addition to compound **154** [78].

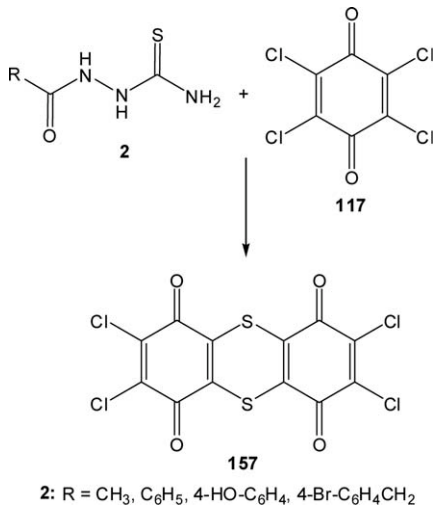


2,153: R = CH_3, C_6H_5, 4-HO-C_6H_4, 4-Br-$C_6H_4CH_2$

The formation of the spiro-compounds can be rationalized by the following mechanism [78].



3.12. Synthesis of thianthrenetetraone. Mixing twofold molar excess of 2,3,5,6-tetrachloro-1,4-benzoquinone **117** with one mole of acylthiosemicarbazides **2** leads to the formation of an initial CTC followed by formation of products 2,3,7,8-tetrachlorothianthrene-1,4,6,9-tetraone **157** [107].



2: R = CH_3, C_6H_5, 4-HO-C_6H_4, 4-Br-$C_6H_4CH_2$

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