Chemistry and Heterocyclization of Thiosemicarbazones

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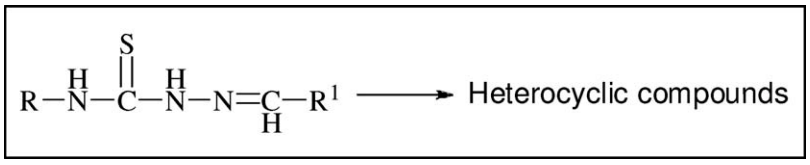
Received April 9, 2010
DOI 10.1002/jhet.677
Published online 18 October 2011 in Wiley Online Library (wileyonlinelibrary.com).



The review summarizes the literatures dealing with the synthesis of thiosemicarbazone derivatives, chemical reactions and their applications in the synthesis of important heterocyclic as well as fused heterocyclic compounds

J. Heterocyclic Chem., **49**, 21 (2012).

Contents

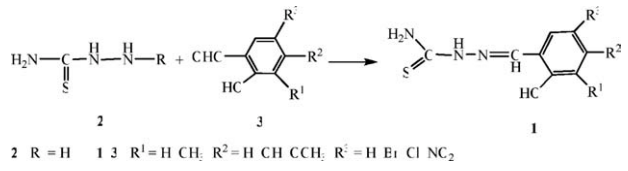
1. INTRODUCTION

Thiosemicarbazones have been a subject of interest in recent decades due to their various applications in industry and analytical chemistry [1,2]. Thiosemicarbazones are a class of compounds showing promise in the treatment of many diseases, cancer in particular, and their development is still in progress [3–10]. Thiosemicarbazones [11–15] and their metal complexes are widely known as having a broad range of biological applications, and medicinal properties, including antiviral, antimalarial, antifungal, and antitumor activity [16–31].

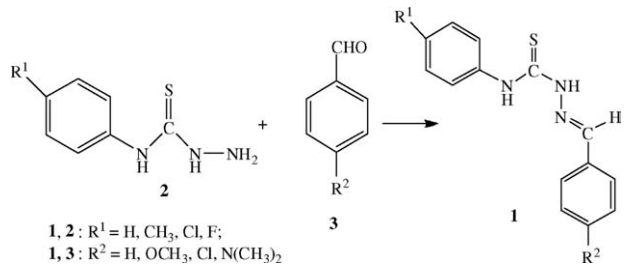
2. SYNTHESIS OF SUBSTITUTED THIOSEMICARBAZONES

2.1. Preparation of thiosemicarbazones from aromatic aldehydes. The desired thiosemicarbazones 1 were obtained by heating thiosemicarbazide **2** with

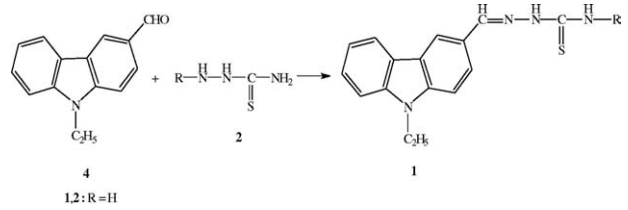
appropriate aldehydes **3** at 50–60°C with continuous stirring in the presence of few drops of *p*-toluenesulfonic acid as catalyst [32].



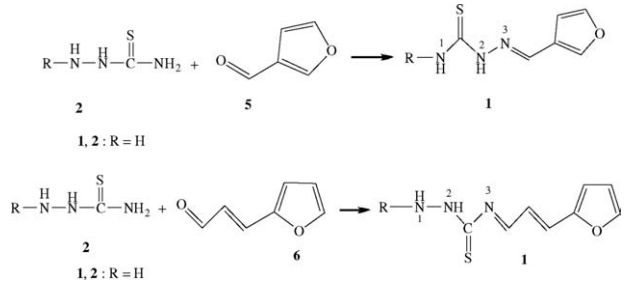
Condensation of (4-substituted phenyl) thiosemicarbazide **2** with aldehydes **3** afforded the corresponding thiosemicarbazones **1** [33,34].



2.2. Preparation of thiosemicarbazones from heterocyclic aldehydes. *2.2.1. From carbazole derivatives.* Refluxing of *N*-ethylcarbazolecarboxaldehyde **4** with thiosemicarbazide **2** in ethanol gave **1** as pale-yellow crystals [35].



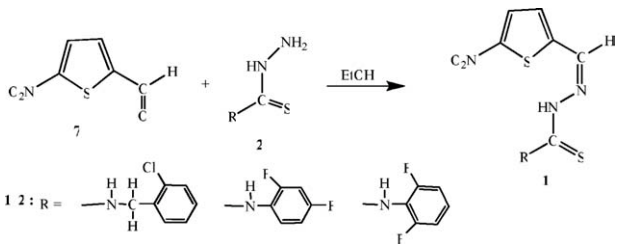
2.2.2. From 3-furaldehyde and 3-(2-furyl)prop-2-enal. Reaction of thiosemicarbazide **2** with 3-furanyldehyde **5** and 3-(2-furyl)prop-2-enal **6**, respectively, gave *N*-(3-furanyl)thiosemicarbazone (**1**, 3FTSC) and *N*-3-(2-furanyl)prop-2-enal thiosemicarbazone (**1**, FATSC) as shown below.



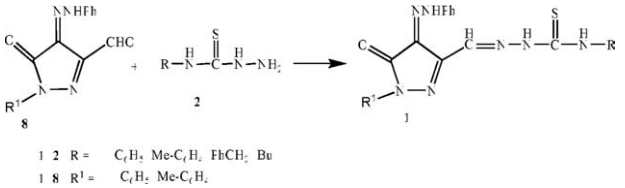
The sulfur atom and N^3 of the hydrazone are in trans-configuration relative to the C^1—N^2 bond, and this molecular configuration is determined by the presence of the intramolecular hydrogen bond N^1—H^2...N^3 [36].

The IR spectra of (FATSC and 3FTSC are very similar and are consistent with their assigned structures. The bands appearing around 1355 and 752 cm^{-1} are assigned to ν (C—S) vibration [37,38], whereas those in the 3270–3440 cm^{-1} region are attributed to the symmetrical and asymmetrical stretching modes [39]. On the other hand, the strong band observed at 1600 cm^{-1} is assigned to ν (C—N) frequencies.

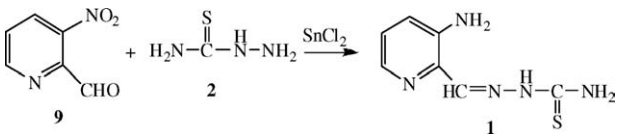
2.2.3. From 5-nitrothiophene-2-carboxaldehyde. Condensation of **2** with 5-nitrothiophene-2-carboxaldehyde **7** in ethanol at 25°C for 3 h afforded 5-nitrothiophene-2-carboxaldehyde thiosemicarbazones **1** in 63–71% yield [40].



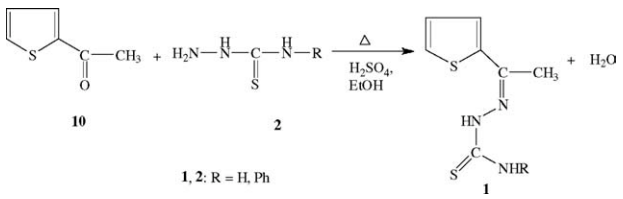
2.2.4. From pyrazolecarboxaldehydes. The pyrazolecarboxaldehyde thiosemicarbazones **1** were prepared by condensing pyrazolecarboxaldehyde **8** with thiosemicarbazide derivatives **2** [41].



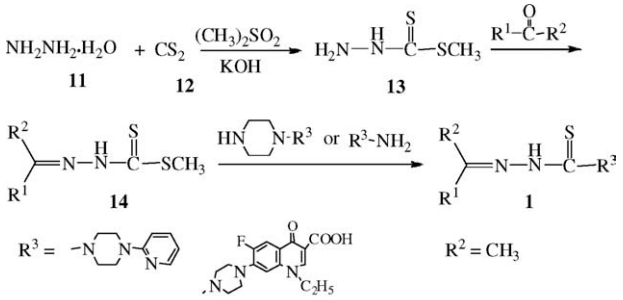
2.2.5. From 3-nitropicolinaldehyde. The direct reaction of 3-nitropiconaldehyde **9** with thiosemicarbazide **2** in the presence of $SnCl_2$ gave thiosemicarbazone **1** [42].



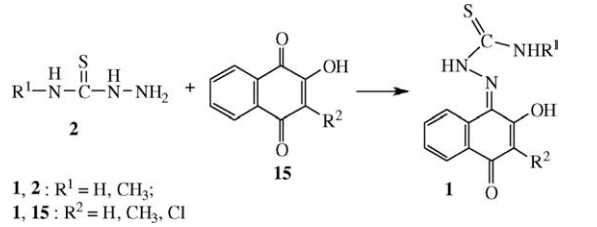
2.3. Preparation of substituted thiosemicarbazones from aromatic and heterocyclic ketones. Compounds 1 (R = H, R = Ph) were prepared by reacting (i) thiosemicarbazide and (ii) 4-phenylthiosemicarbazide **2** with 1-(thiophen-2-yl)ethanone **10** in ethanol followed by the addition of sulfuric acid [43–45].



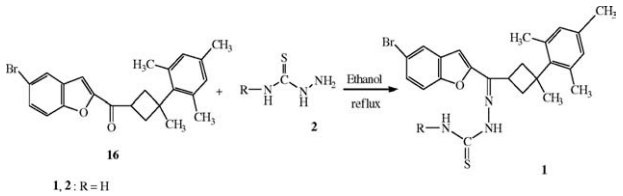
Different derivatives of thiosemicarbazones were synthesized via three steps starting from hydrazine hydrate **11** and carbon disulfide [46].



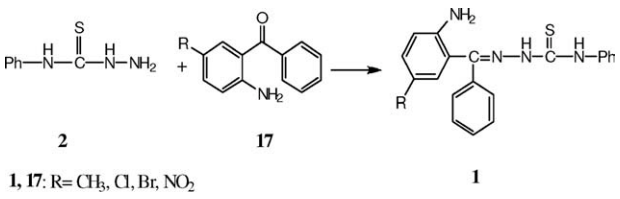
Refluxing thiosemicarbazides **2** with substituted 1,4-naphthoquinone **15** afforded quinonethiosemicarbazone derivatives **1** [47].



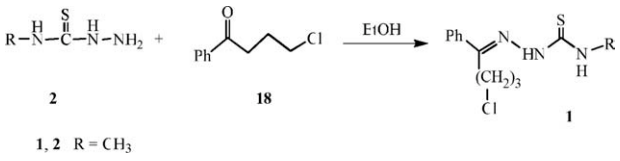
Reaction of (5-bromobenzofuran-2-yl)(3-methyl-3-mesitylcyclobutyl)ketone **16** with thiosemicarbazide **2** (R = H) in dry ethanol and the presence of *p*-toluenesulfonic acid for 8 h afforded the corresponding thiosemicarbazone **1** as shown below [48].



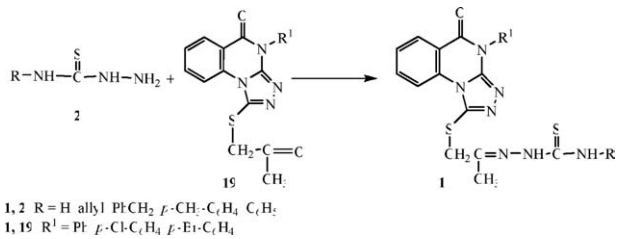
Reaction of phenylthiosemicarbazide **2** with 2-aminobenzophenone **17** likewise gave the expected thiosemicarbazone **1** [49].



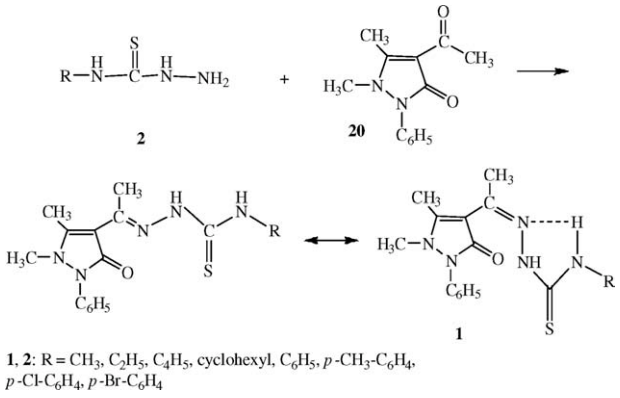
Condensation of substituted thiosemicarbazide **2** with 4-chlorobutyrophenone **18** in ethanol gave the corresponding thiosemicarbazone **1** [50].



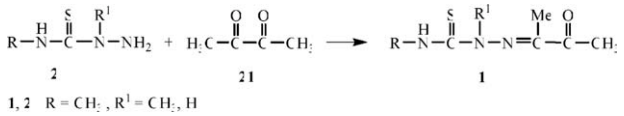
Substituted thiosemicarbazides **2** reacted with 4-substitued-1-(2-oxopropyl)thio[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-ones **19** to give thiosemicarbazone derivatives **1** [51].



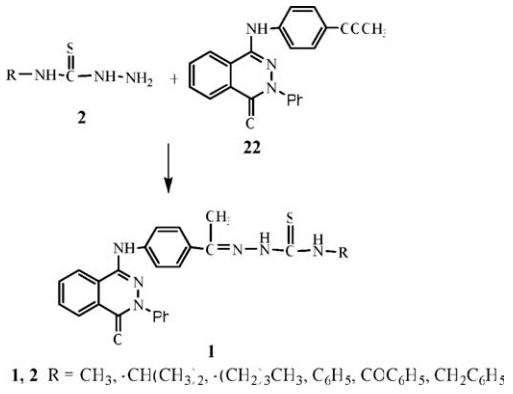
Substituted thiosemicarbazides **2** were condensed with 4-acetylantipyrine **20** to produce 4-acetylantipyrine-4-alkyl- (or phenyl)-3-thiosemicarbazones **1** [52].



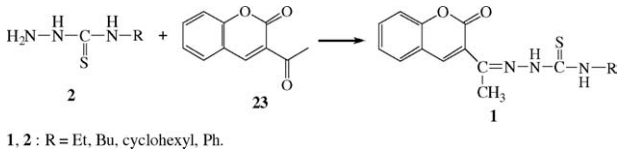
The reaction of substituted thiosemicarbazides **2** with diketones such as butane-2,3-dione **21** afforded thiosemicarbazones **1** [53].



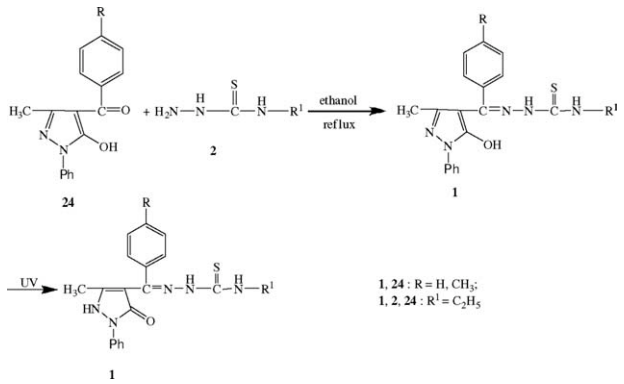
The reaction of substituted thiosemicarbazides **2** with 4-(*p*-acetylanilino)-2-phenylphthalazin-1-one 22 afforded 2-(1-(4-(4-oxo-3phenyl-3,4-dihydrophethalazin-1-ylamino)-phenyl)ethylidene-*N*-substituted hydrazinecarbothioamide derivatives **1** [54,55].



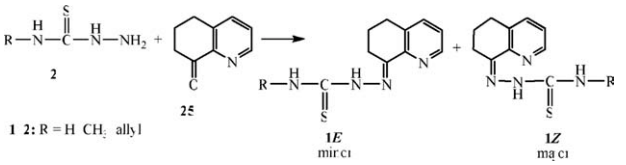
Condensation of 3-acetylcoumarin **23** with thiosemicarbazides **2** in ethyl alcohol afforded thiosemicarbazones **1** in 75–99% yield [56].



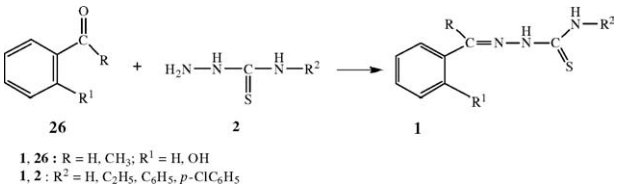
1-Phenyl-3-methyl-4-(4-methylbenzoyl)-5-pyrazolone-4-substituted thiosemicarbazone **1** was prepared by direct condensation of 1-phenyl-3-methyl-4-benzoyl-5-hydroxy-pyrazole **24** with thiosemicarbazide **2** in ethanol [57–58].



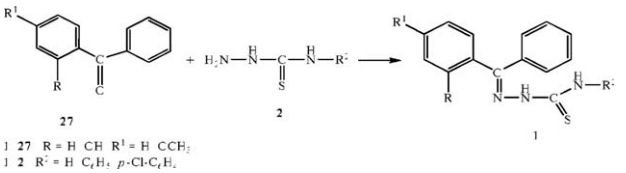
The reaction of substituted thiosemicarbazides **2** with 5,6-dihydro-8(7*H*)-quinoline **25** afforded two isomers. The major one was 5,6-dihydro-8(7*H*)-quinoline thiosemicarbazone (1 *Z*), and the minor one was (1 *E*) [59].



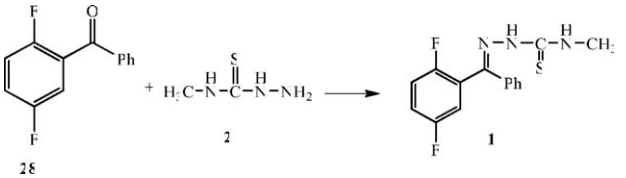
The thiosemicarbazones **1** were prepared by mixing equimolar amounts of the ketone **26** with substituted thiosemicarbazides **2** [60].



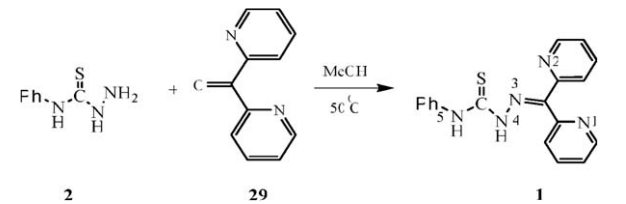
Also, mixing equimolar amounts of **2** with benzophenone **27** in ethanol gave thiosemicarbazones **1** [60].



Reaction of 2,5-diflourobenzophenone **28** with **2** gave thiosemicarbazone **1** [61].

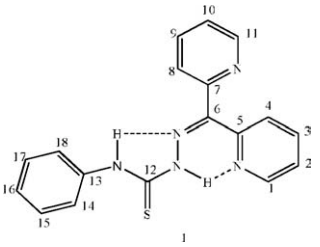


Refluxing **2** with di-2-pyridyl ketone **29** in methanolic solution gave **1** [62].



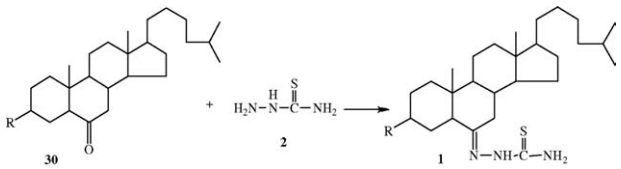
The ^{1}H-NMR spectrum of compound **1** showed a sharp singlet, which integrates as singlet at $\delta = 14.55$

ppm was assigned to N^4-hydrogen, while another singlet at $\delta = 9.55$ ppm was assigned to the N^5-hydrogen. The downfield shifts of these protons are assigned to their hydrogen-bonding interactions with adjacent nitrogen atom N^1 and N^3. Hydrogen-bonding decreases the electron density around the proton, and, thus, moves the proton absorption to the lower field. Two doublets at $\delta = 8.84$ and 8.67 ppm were assigned to the C(1)H and C(11)H protons, respectively.



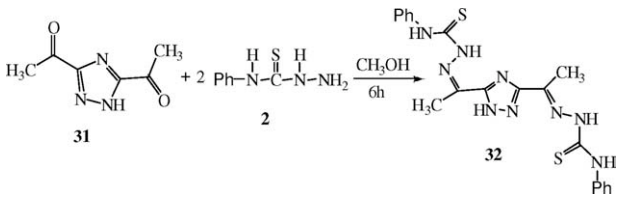
1

The reaction of 3β-substituted-5α-cholestan-6-one **30** with thiosemicarbazide **2** in ethanol gave 3-substituted thiosemicarbazones **1** [63].

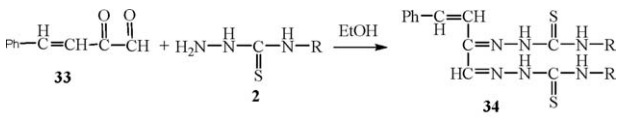


1, 30 : R = CH_3COO, H, Cl

2.4. Preparation of bis(thiosemicarbazones). Bis(4-phenylthiosemicarbazone) **32** was prepared by refluxing 3,5-diacetyl-1,2,4-triazole **31** and 4-phenyl-thiosemicarbazide **2** in methanol [64].

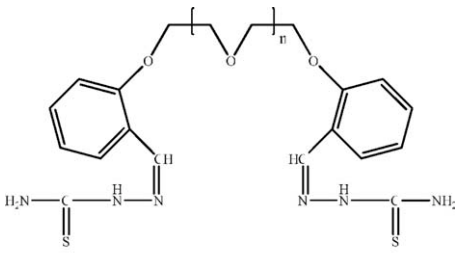


Also, reactions of substituted thiosemicarbazides **2** with ketoaldehyde **33** in boiling ethanol gave 4-phenyl-2-oxo-3-butenol-1,2-bis(substituted thiocarbamoyl)hydrazones **34** [65].



2, 34 : R = CH_3, allyl, *p*-Br-C_6H_4, *p*-Cl-C_6H_4

Reaction of appropriate dialdehyde with thiosemicarbazide **2** afforded bis(thiosemicarbazones) **35** [66].



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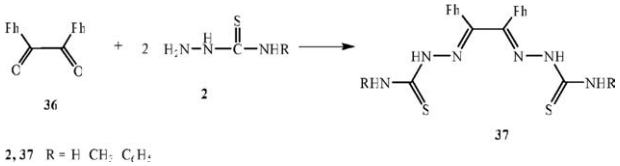
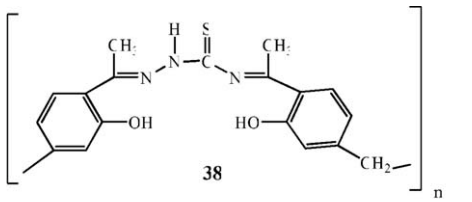
(r = 0, 1, 2)

Benzil bis(thiosemicarbazone) **37** was prepared by refluxing benzil **36** and thiosemicarbazide **2** in methanol [67].



2, 37 R = H, CH_3, C_6H_5

2.5. Synthesis of Schiff's base polymer of thiosemicarbazones. Poly-5,5′-methylenebis(2-hydroxyacetophenone)thiosemicarbazone (PHATS, **38**), and 6,6′-methylenebis(2-hydroxynaphthaldehyde)thiosemicarbazone (PHNTS, **39**) were prepared by polycondensation of 5,5′-methylenebis-(2-hydroxyacetophenone) (MHA) and 6,6′-methylenebis-(2-hydroxynaphthaldehyde) (MHN) with thiosemicarbazide **2** [68].



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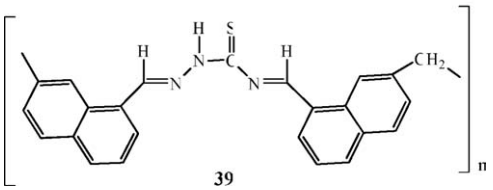

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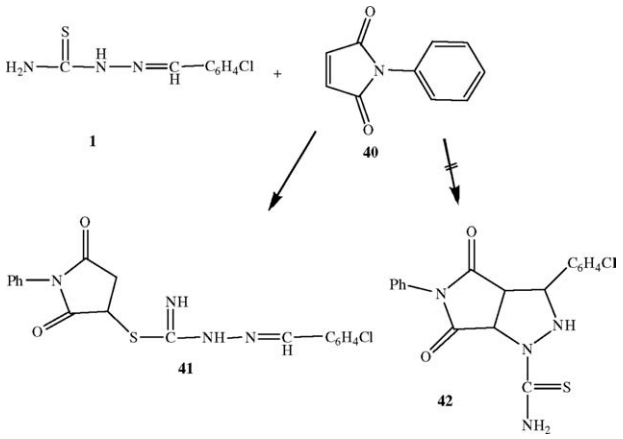
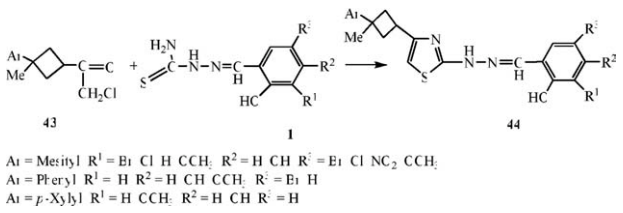
3. REACTIONS OF THIOSEMICARBAZONES

3.1. Synthesis of pyrrolidine derivatives. Addition of **1** to *N*-phenylmaleimide **40** gave S-(*N*-phenyl-2,5-dioxo-3-pyrrolidinyl)isothiosemicarbazone **41** rather than pyrrolidino[3,4-d]-1-thiocarboxamido-2,6-pyrazolidine-dione **42** based on NMR spectral data [69].

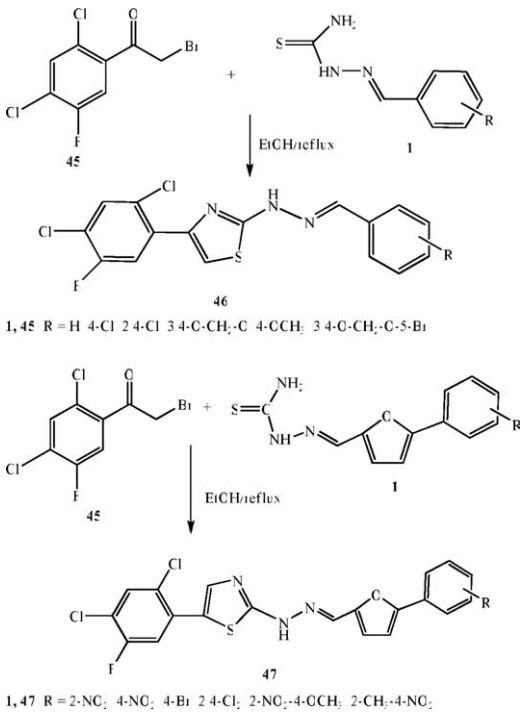


3.2. Synthesis of thiazole, thiazoline and thiazolidine derivatives. Thiosemicarbazones reacted with cyclization reagents, such as ethyl chloroacetate, ethyl-2-chloroacetoacetate and 2-bromoacetophenone to give substituted thi-azolidinone and thiazoline derivatives [70]. Aldehyde thiosemicarbazones are also appropriate substrates for the preparation of five- or six-membered heterocyclic rings that contain two heteroatoms on treatment them with oxidizing reagents or other cyclization reagents [71–73].

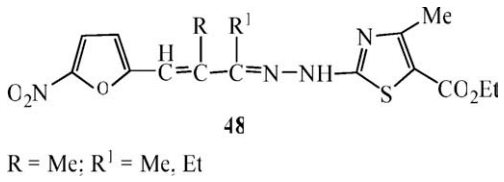
Appropriate thiosemicarbazones was reacted with α-chloroketone **43** to convert it into hydrazides that underwent cyclization to 2,4-disubstituted thiazoles **44** [32].



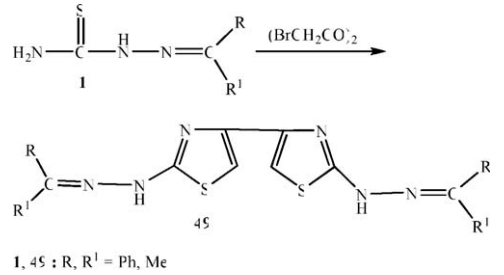
Reaction of araldehyde and 5-aryl-2-furfuraldehyde thiosemicarbazones **1** with 2,4-dichloro-5-flurophenacyl bromides **45** gave 2-acyl substituted-4-(2,4-dichloro-5-fluorophenyl)thiazoles **46** and **47**, respectively [74].



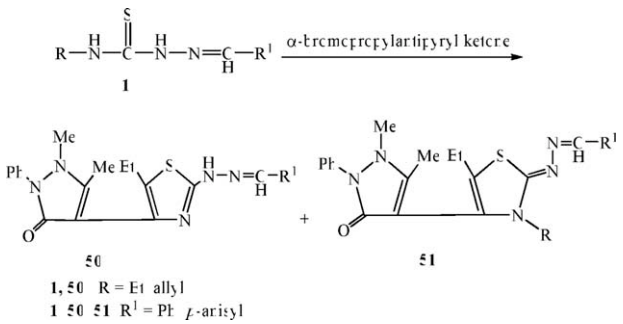
4-Methyl-5-carbethoxy-2-hydrazinothiazoles **48** have been synthesized by the reaction of 2-chloroacetoacetate with thiosemicarbazones of ethyl(5-nitro-2-furyl)vinyl ketone [75].



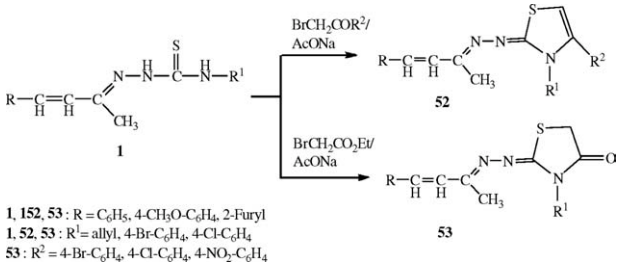
The reaction of thiosemicarbazone **1** with 1,4-dibromodiacetyl afforded 2,2′-bis(disubstituted-methylene)hydrazinyl-4,4′-bithiazoles **49** [76].



Cyclocondensation of thiosemicarbazones **1** with α-bromopropylantipyryl ketone gave antipyrylthiazolyl and antipyrylthiazolonyl hydrazones **50** and **51**, respectively [77].

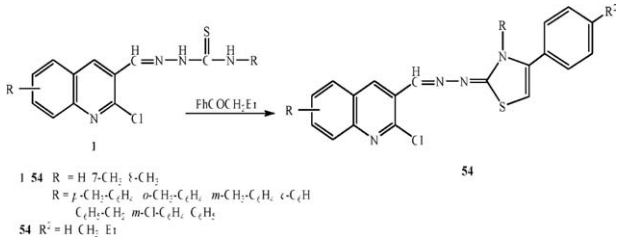


4-Substituted-3-buten-2-one-thiosemicarbazones **1** cyclized into the corresponding thiazolines **52** and thiazolidinones **53** by treatment with phenacyl bromide derivatives and with ethyl bromoacetate/sodium acetate under Hantzsch conditions, respectively [78].

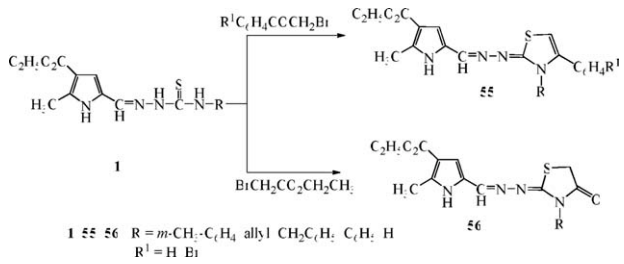


Other thiazoline derivatives were obtained when thiosemicarbazones **1** were treated with phenacyl bromide and sodium acetate, or when thiosemicarbazones **1** were treated with ethyl bromoacetate [79].

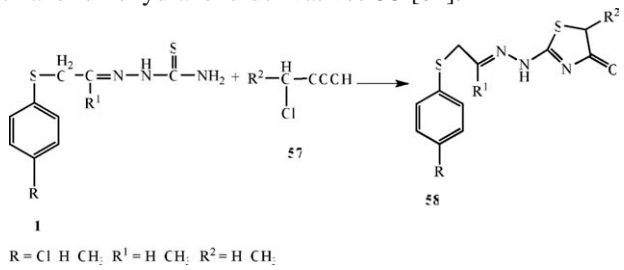
Cyclization of thiosemicarbazones **1** with phenacyl bromide gave at series of 2-chloroqunolin-3-carbaldehyde(2,3-dehydrothiazol-2-ylidene)hydrazones **54** [78].



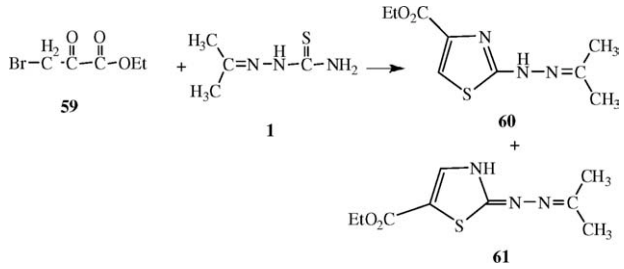
Compounds **1** reacted with phenacyl bromide derivatives to give substituted-3-(ethoxycarbonyl)-2-methylpyrrole-5-carboxaldehyde(3,4-disubstituted-2,3-dihydrothiazo-2-ylidene)hydrazones **55** [80]. On the other hand, **1** reacted with ethyl bromoacetate to yield 3-(ethoxycarbonyl)-2-methylpyrrole-5-carboxaldehyde(3-substituted thiazolidin-4-one-2-yilidene)hydrazones **56** [80].



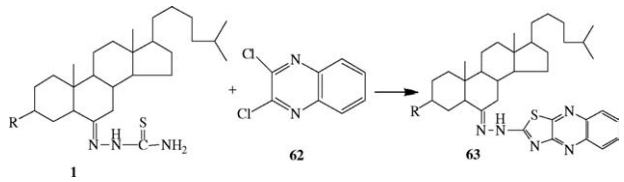
Cyclization of **1** with chloroacetic acid **57** generated thiazolidinehydrazone derivatives **58** [81].



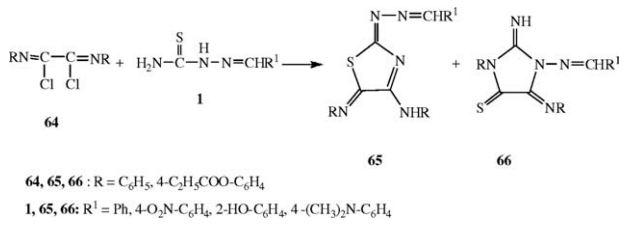
Reactions of ethyl-3-bromo-2-oxopropanoate **59** with thiosemicarbazones **1** gave thiazoles **60** and **61** [82].



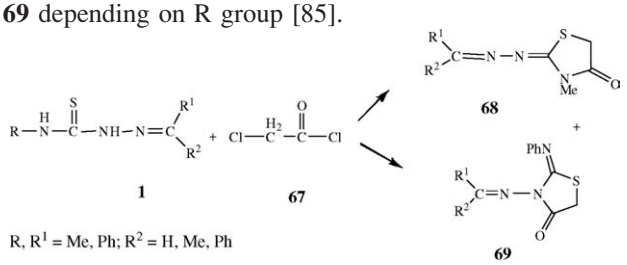
Refluxing of an equimolar ratio of thiosemicarbazones **1** and 2,3-dichloro quinoxaline **62** in dry ethanol afforded thiazolo[4,5-*b*]quinoxaline-2-yl-hydrazone derivatives **63** [83].



Aryl substituted oxalic bisimidochlorides **64** reacted with thiosemicarbazones **1** to give substituted thiazole-4-amines **65** and substituted imidazolidine-4-thiones **66** [84].

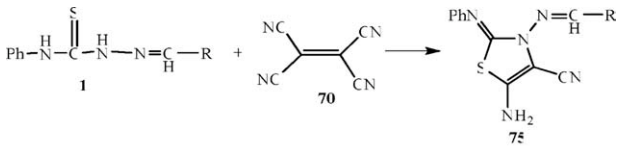


Cyclocondensation of **1** with **67** gave either hydrazinothiazolidinones **68** or alkylidene aminothiazolidinones **69** depending on R group [85].



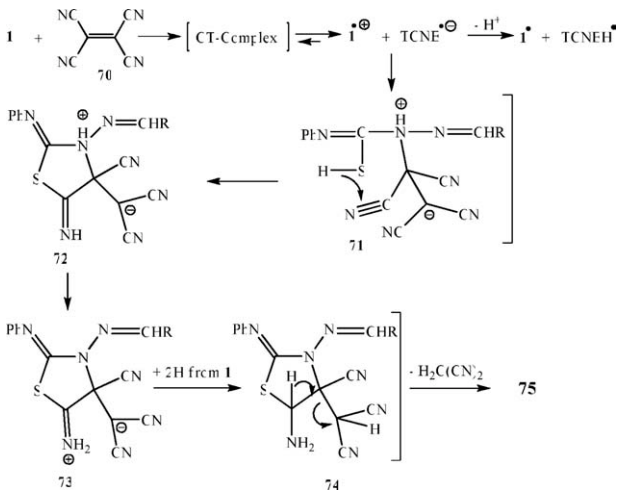
R, R^1 = Me, Ph; R^2 = H, Me, Ph

2-Substituted ylidene-*N*-phenylhydrazinecarbothioamides **1a–e** reacted with ethenetetracarbonitrile **70** in ethyl acetate to give thiazole derivatives **75** [86].

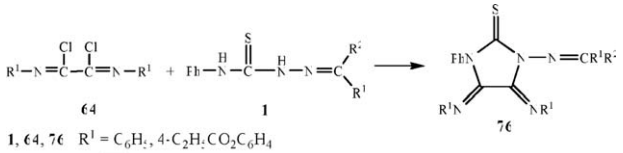


1,75: R = C_6H_5; Cl-C_6H_4-*p*; CH_3O-C_6H_4-*p*; HO-C_6H_4-*o*; $(CH_3)_2N$-C_6H_4-*p*

The reaction presumably occurs *via* the initial adduct **71**, and subsequently proceeds *via* the mechanism shown below [86].



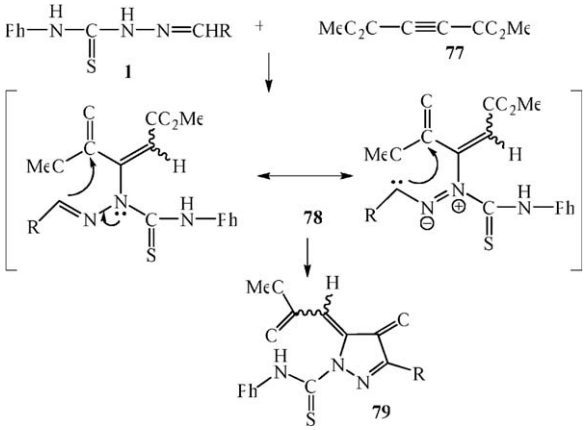
3.3. Synthesis of pyrazole derivatives. Aryl substituted oxalic bis-imidochlorides **64** were reacted with thiosemicarbazones **1** to give pyrazole derivatives **76** [84].



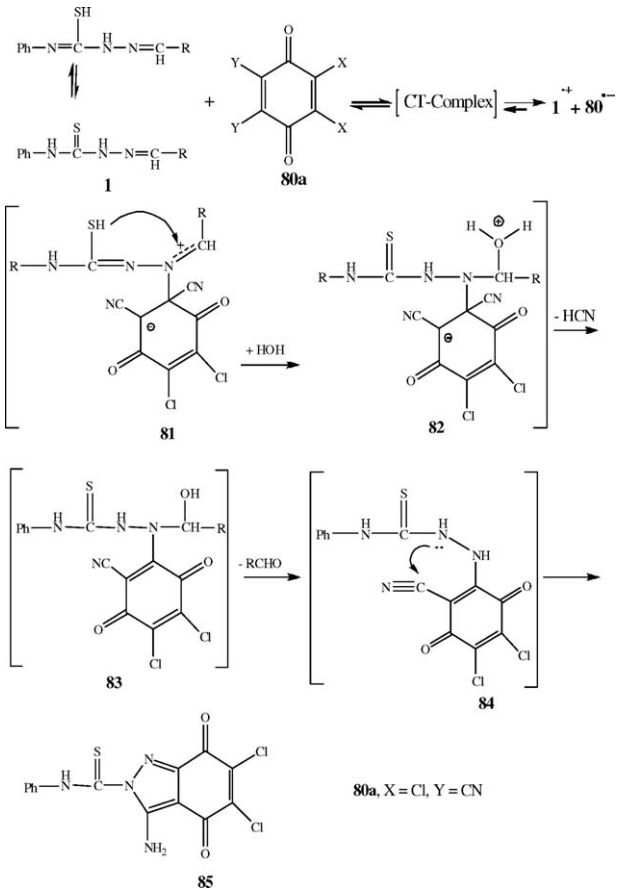
1, 64, 76 R^1 = C_6H_5, 4-$C_2H_5CO_2C_6H_4$

1, 76 R^2 =  ; X = O_2N, CN, Cl, H, OCH_3, $N(CH_3)_2$

The reaction of **1** with dimethyl but-2-ynedioate **77** under reflux in methanol yielded the corresponding methyl-2-(4-oxo-3-substituted-1-(phenylcarbamothioyl-pyrazol-5-ylidene)acetate **79** [87].



3.4. Synthesis of indazole and benzindazole derivatives. Reaction of **1** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone **80** was carried out in the methylene chloride to afford indazole derivative **85** [88].

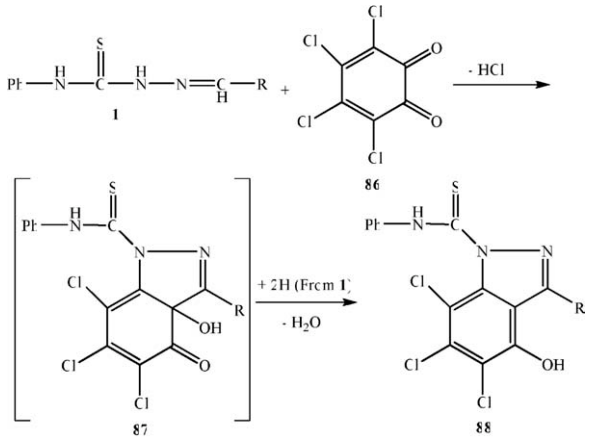


80a, X = Cl, Y = CN

The formation of the product **85** may be rationalized *via* hydrolysis of **81** and elimination of HCN and benzaldehyde followed by cyclization to afford the indazole derivative **85**. Thus, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

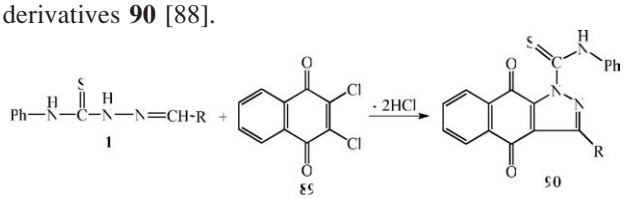
80 may act either as a mediator or as a building block in heterocyclization of thiosemicarbazones **1** [88].

Reaction of **1** with **86** in methylene chloride followed by chromatography gave indazole derivatives **88** [88].



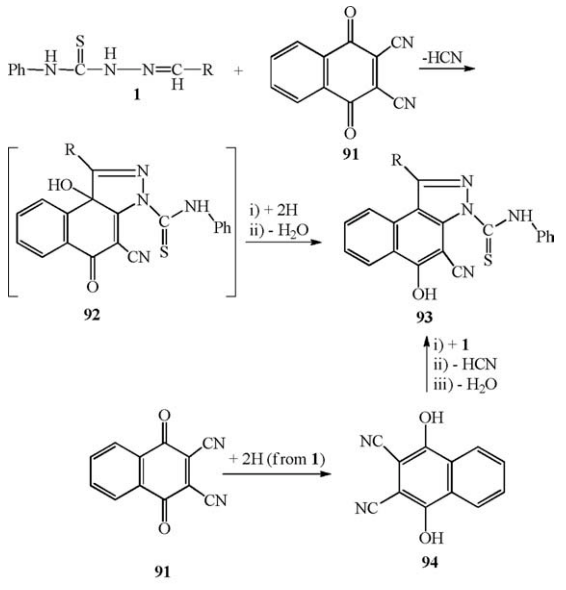
1,88: a, R = C_6H_5; c, R = C_6H_4-*p*-OCH_3; f, R = 2-Thienyl; g, R = 2-Furyl

Reaction of **1** with 2,3-dichloro-1,4-naphthoquinone **89** gave substituted benzoindazole-4,9-diones **90**. Elimination of two molecules of HCl afforded the indazole derivatives **90** [88].



1, 50: R = C_6H_5, C_6H_4-*p*-OCH_3, 2-Thienyl, 2-Furyl

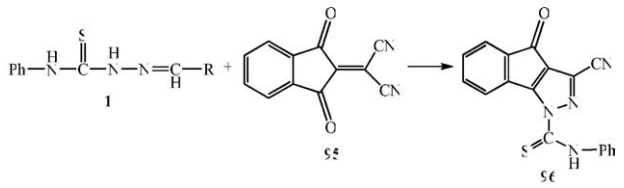
Reaction of **1** with 2,3-dicyano-1,4-naphthoquinone **91** led to formation of 4-cyano-5-hydroxy-*N*-substituted-1-phenylbenzo[*e*]indazole-3-carbothioamides **93** and 2,3-dicyano-1,4-dihydronaphthoquinone **94** [88].



1, 93 : R = C_6H_5, C_6H_4-*p*-OCH_3, 2-Thienyl, 2-Furyl

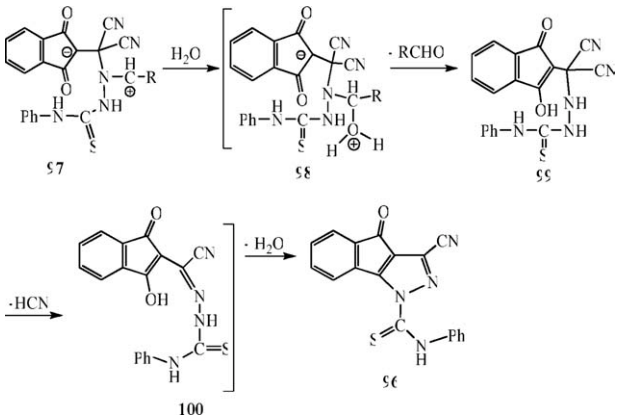
The formation of **93** presumably occurs *via* replacement of one cyano group in the **91** by **1** with intramolecular nucleophilic attack on the carbonyl group to afford **92**. The intermediate **92** presumably abstracts a molecule of hydrogen from **1** followed by dehydration to give the products **93**. Compounds **93** may be also formed *via* the reaction of dihydronaphthoquinone **94** and **1** with elimination of HCN and H_2O [88].

3.5. Synthesis of oxoindenopyrazole derivatives. Reaction of **1** and **95** in warm pyridine in presence air, followed by chromatography, afforded **96** [89].

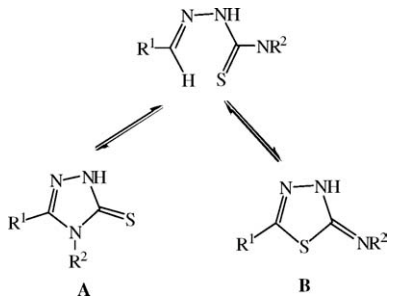


1: R = C_6H_5, Cl-C_6H_4-*p*, CH_2O-C_6H_4-*p*, 2-Thienyl, 2-Furyl

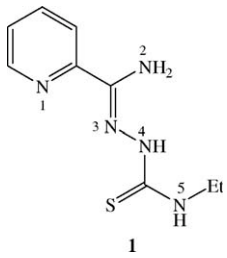
These results suggested that thiosemicarbazones **1** reacted with **95** *via* addition to the C=C double bond of **95**, whose four electron-withdrawing groups facilitate nucleophilic attack to form the intermediates **97**. Hydrolysis of **97** followed by loss of the aldehyde moiety with concomitant elimination of HCN and H_2O afforded the indenopyrazole **96** [89].



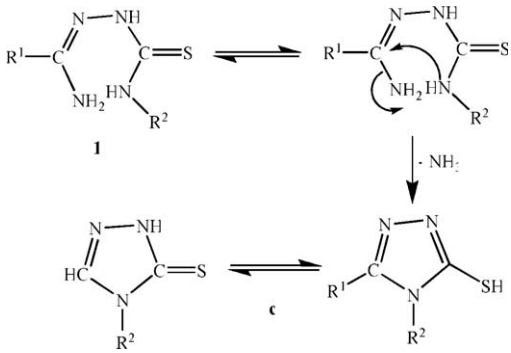
3.6. Synthesis of thiadiazole, oxadiazole and triazole derivatives. Different routes exist; however, thiosemicarbazones are preferred substrates for cyclization to 1,2,4 and 1,3,4-thiadiazole derivatives, typically, in the presence of a metal salt [90–96]. 1,2,4-Triazol-3-thiones, and their thiosemicarbazones, exhibit ring-chain tautomerism in solution, whereas, in the solid state, they are present only in the *thione* form.



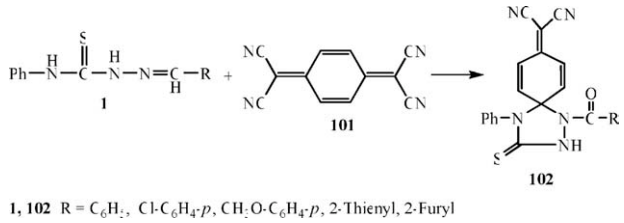
This ring-chain tautomerism depends on the structure of the starting thiosemicarbazones; thus, 1,2,4-triazole and 1,3,4-thiadiazole heterocyclic rings can both formed from 2-pyridine formamide thiosemicarbazone derivatives **1**. In particular, 2-pyridine formamide *N*-4-ethyl-thiosemicarbazone **1** forms a 1,2,4-triazol-3-thione, the presence of a substituent on the N^4 nitrogen atom being a decisive factor for the regiochemistry of the cyclization [97].



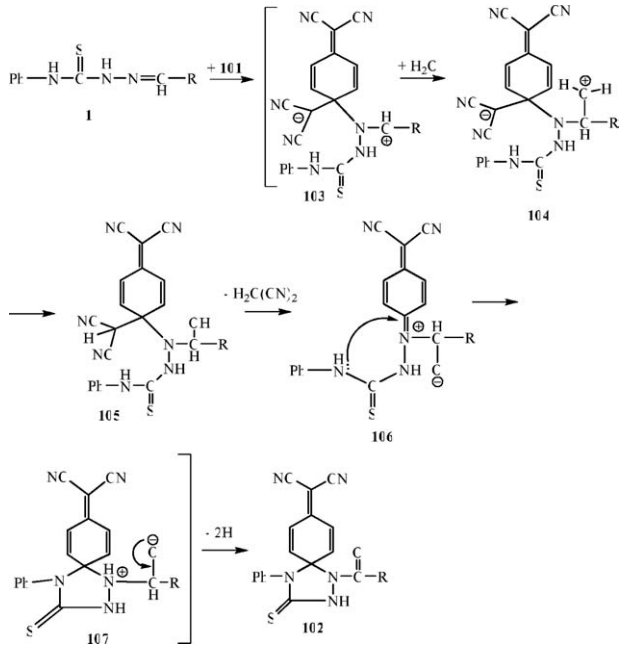
The proposed cyclization mechanism suggests nucleophilic attack of the azomethine carbon by the N^5 thioamide sulfur with concomitant elimination of ammonia.



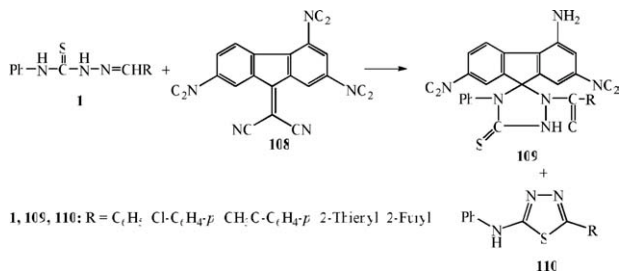
2-Substituted ylidene-*N*-phenylhydrazinecarbothioamides **1** reacted with 7,7′,8,8′-tetracynoquinodimethane **101** in dry pyridine to form spirotriazoles **102**.



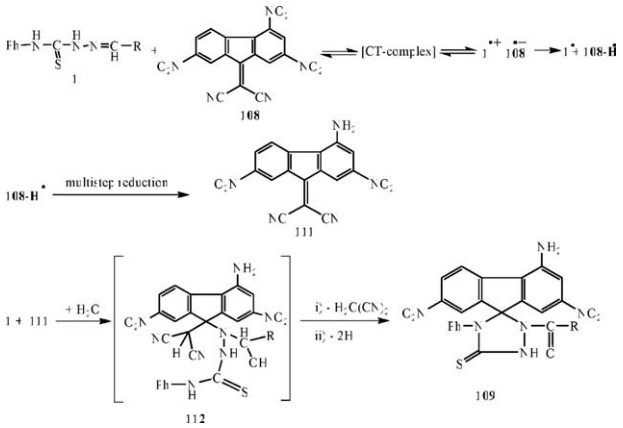
The product's spectroscopic and microanalatycal data suggest that **1** and **101** had combined in presence of water in a 2:1 ratio with subsequent loss of one molecule of malononitrile and two hydrogens [89].



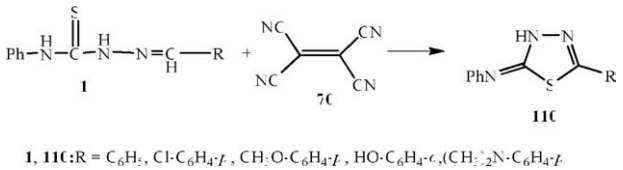
2-Substituted ylidene-*N*-phenylhydrazinecarbothioamides **1** reacted with (2,4,7-trinitro-9*H*-fluoren-9-ylidene)propanedinitrile **108** to give the spirotriazolidine **109** and thiadiazole derivatives **110** [89].



Formation of the spiro compounds **109a-e** can be rationalized as follow:

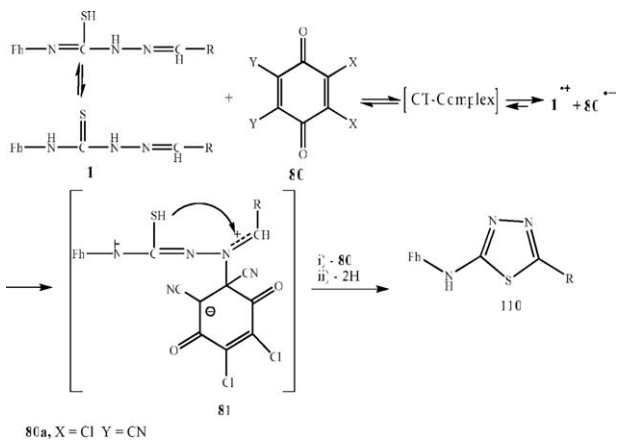


2-Substituted ylidene-*N*-phenylhydrazinecarbothioamides **1** reacted with ethenetetracarbonitrile **70** in ethyl acetate to form thiadiazole derivatives **110** [86].



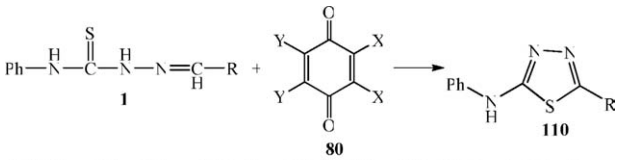
1, 110: R = C_6H_5, Cl-C_6H_4-*p*, CH_3O-C_6H_4-*p*, HO-C_6H_4-*o*, $(CH_3)_2N$-C_6H_4-*p*

Reaction of **1** and **80** in methylene chloride afforded **110**. Formation of **110** can be explained by a process putatively involving assembly and dissociation of a charge transfer complex, recombination of the ion-radical constituents of the complex to form the intermediate **81**, and, finally, expulsion of **80** with loss of two hydrogens [88].



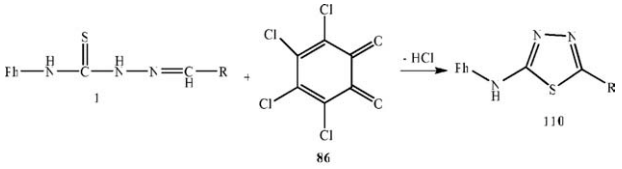
80a, X = Cl Y = CN

The reaction of **1** with **80** was carried out in the methylene chloride at room temperature followed by chromatographic separation to give **110** [88].



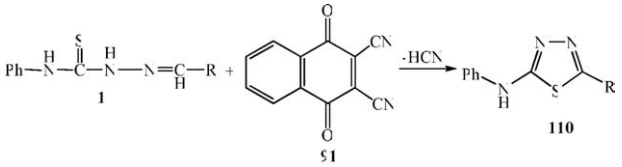
1,110: R = C_6H_5, C_6H_4-*p*-Cl, C_6H_4-*p*-OCH_3, C_6H_4-*o*-OH, 2-Thienyl, 2-Furyl
80b, X= Y= Cl

The reaction of **1** with 3,4,5,6-tetrachloro-1,2-benzoquinone **86** gave thiadiazole derivatives **110** [88].



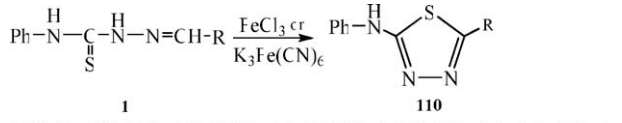
1 110 R = C_6H_5, C_6H_4-*p*-CH_3, 2-Thienyl 2-Furyl

The reaction of **1** with 2,3-dicyano-1,4-naphthoquinone **91** led to the formation of thiadiazoles **110** [88].



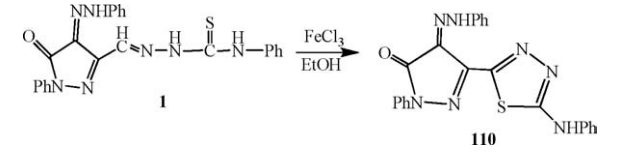
1,110: R = C_6H_5, C_6H_4-*p*-OCH_3, 2-Thienyl, 2-Furyl

5-Substituted 2-anilino-1,3,4-thiadiazoles **110** were prepared by oxidation of thiosemicarbazones with $FeCl_3$ or $K_3Fe(CN)_6$ [98].

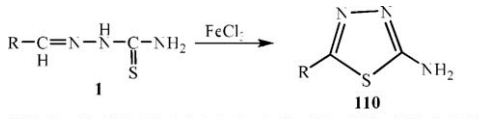


1,110 R = 3-Me-C_6H_4, 3-MeO-C_6H_4, 4-AcNH-C_6H_4, 3,4-Cl_2-C_6H_3, 4-Br-C_6H_4, 2-Furyl

Cyclocondensation of **1** in ethanol containing $FeCl_3$ gave thiadiazole derivatives **110** [41].



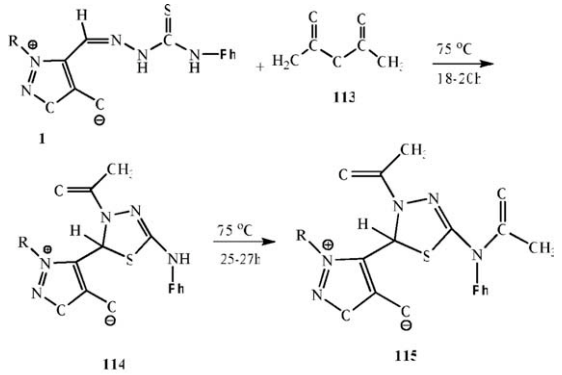
Also substituted 2-amino-1,3,4-thiadiazoles **110** were prepared by oxidation of **1** with $FeCl_3$ in the refluxing ethanol [99].



110 R = Ph-CH=CH, 3,4-(MeO)$_2$-C$_6$H$_3$, 4-Br-C$_6$H$_4$, 4-MeO-C$_6$H$_5$, Ph, 2- and 4-O$_2$N-C$_6$H$_4$

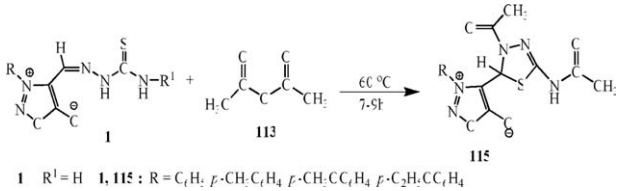
Treatment of 3-aryl-4-formyl-sydnone 4′-phenyl thiosemicarbazones **1** with acetic anhydride **113** in dichloromethane solution, followed by heating in an oil bath for 18–20 h, produced the desired products **114**.

When the reaction of compounds **1** with acetic anhydride was heated for a longer period, the initial products, monoacetyl-substituted thiadiazolines **114** were converted completely to the diacetyl-substituted thiadiazolines **115**.



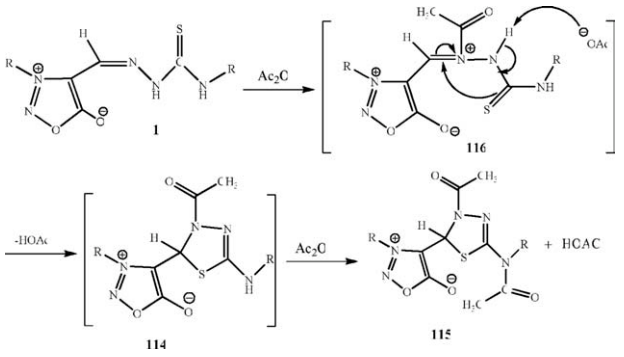
1, 115 : R = C$_6$H$_5$, *p*-CH$_3$C$_6$H$_4$, *p*-CH$_3$CC$_6$H$_4$, *p*-C$_2$H$_5$CC$_6$H$_4$

However, in the second case, treating 3-aryl-4-formyl sydnone 4′-thiosemicarbazones **1** with acetic anhydride without any other solvents, and heating the mixed solution at 60 °C for 7–9 h directly produced the diacetyl-substituted thiadiazolines **115** in good yields [100].

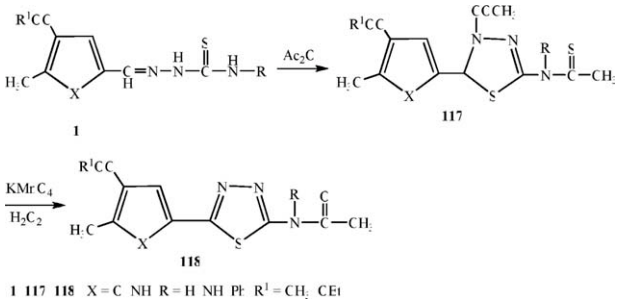


1 R^1 = H **1, 115 :** R = C$_6$H$_5$, *p*-CH$_3$C$_6$H$_4$, *p*-CH$_3$CC$_6$H$_4$, *p*-C$_2$H$_5$CC$_6$H$_4$

In this case, the treatment of **1** with acetic anhydride, no mono acetyl-substituted thiadiazolines can be detected by TLC even at a lower reaction temperature [100].

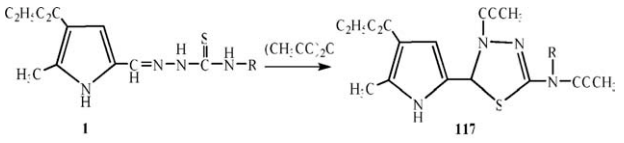


Thiosemicarbazone derivatives **1** reacted with acetic anhydride to give thiadiazoline derivatives **118**. Compounds **118** were synthesized by oxidation of the corresponding thiadiazolines **117** with potassium permanganate in acidic medium [101].



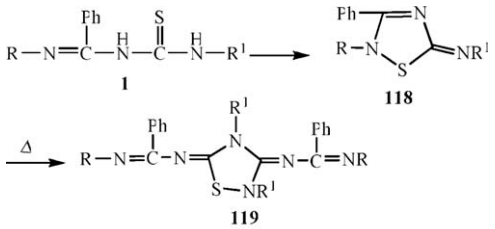
1 117 118 X = C NH R = H NH Ph R^1 = CH$_3$ CEt

Compounds **1** reacted with acetic anhydride under reflux to produce 3-(ethoxycarbonyl)-2-methyl-5-[3-acetyl-5-(*N*-substituted acetamide)-2,3-dihydro-1,2,3-pyrrolyl thiadiazoles **117** [102].



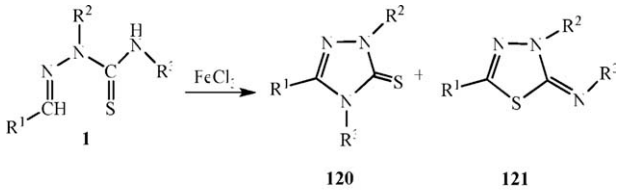
1 117 R = *m*-CH$_3$-C$_6$H$_4$ allyl CH$_2$C$_6$H$_5$ C$_6$H$_5$ H

Cyclization of **1** afforded iminothiadiazolines **118**, which on heating gave **119** [103].



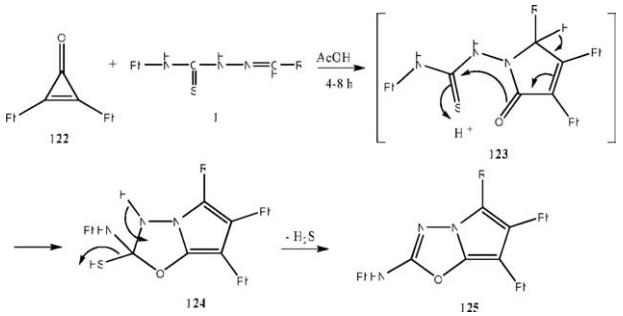
1, 118,119: R = C$_6$H$_5$, 2,6-Me$_2$-C$_6$H$_3$, 4-O$_2$N-C$_6$H$_4$; R^1 = Me, Et, CHMe$_2$, cyclohexyl, CH$_2$-Ph, Ph

Thiosemicarbazones **1** treated with ferric chloride hexahydrate in hot boiling ETOH yielded triazole **120** and thiadiazoline derivatives **121**. The formation of thiadiazoline derivatives was observed only when a strong electron withdrawing group (trifluoromethyl or nitro groups) was present on the phenyl group attached to the carbon nitrogen double bond. Since interconversion between **120** and **121** was not observed under the reaction conditions used, in these compounds, intermolecular nucleophilic attack by nitrogen always predominates over attack by sulfur, because the latter is in the nonreactive C=S form. It is noted in the case of *N*-methyl-substituted aldehyde thiosemicarbazones analogues of **1**, substituents on the phenyl group on to the carbon–nitrogen double bond were able to modify the regiochemistry of the cyclization. The difference behavior between 2-*N*-phenyl and 2-*N*-methyl-thiosemicarbazones suggests that the electronic density on N^2 influences the rates of the two intramolecular attacks differently [104–106].



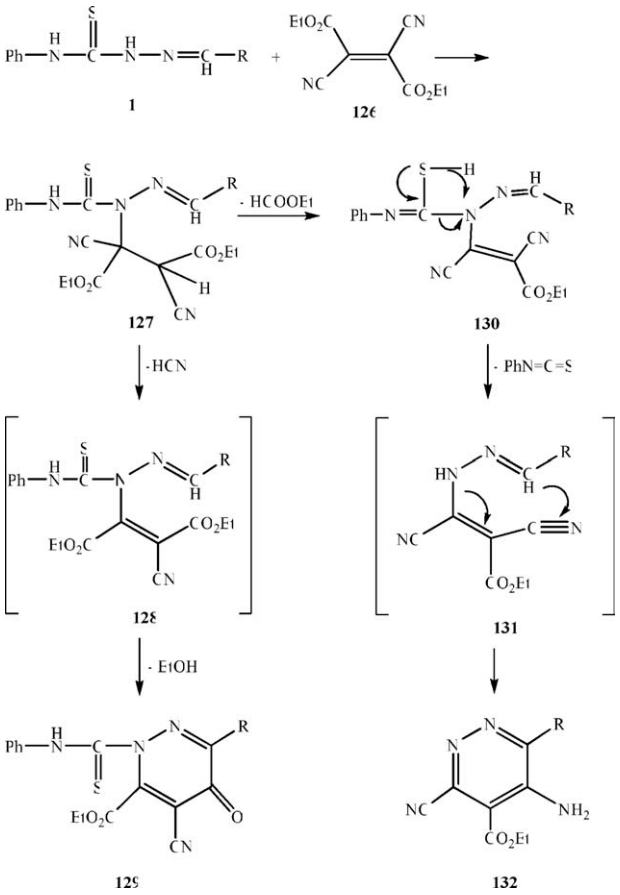
1,120,121: R^1 = *p*-$CH_3OC_6H_4$, *m*-BrC_6H_4, *p*-$CF_3C_6H_4$, *p*-$NO_2C_6H_4$, C_6H_5
R^2 = *p*-$CH_3OC_6H_4$, *p*-ClC_6H_4, *m*-$CH_3C_6H_4$, C_6H_5
R^3 = *p*-$NO_2C_6H_4$, *m*-ClC_6H_4, *p*-ClC_6H_4, *p*-$CH_3OC_6H_4$, C_6H_5

Reaction of 2-substituted ylidene-*N*-phenylhydrazinecarbothioamides **1** with 2,3-diphenylcyclopropenone **122** in acetic acid gave 2,5,6,7-tetrasubstituted pyrrolo[2,1-*b*](1,3,5-oxadiazolyl)-2-amines **125** [107]. The stable final product **125** presumably formed *via* expulsion of a molecule of H_2S from the putative intermediate **124** that formed on aromatization of the pyrrole ring of the thiosemicarbazide adduct **123** [107].

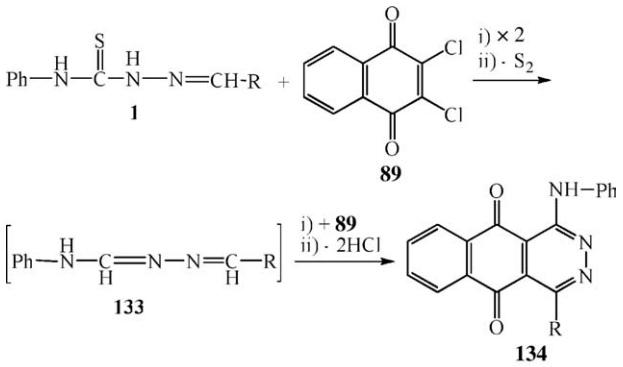


3.7. Synthesis of pyridazine derivatives. 2-Substituted ylidene-*N*-phenylhydrazinecarbothioamides **1** reacted with (*E*) diethyl-2,3-dicyanobutenedioate **126** to give ethyl-4-cyano-6-substituted-5-oxo-2-(phenyl-carbamothioyl)-2-5-dihydropyridazine-3-carboxylates **129** and ethyl-5-amino-3-cyano-6-substituted pyridazine-4-carboxylates **132** [87].

Presumably, intramolecular Michael addition of the NH_2 group of **1** to the carbon–carbon double bond of **126** afforded the open-chain adduct **127**, where upon elimination of HCN and a second molecule of EtOH gave the pyridazine **129**. Similarly, compounds **132** were obtained *via* elimination of one molecule of ethyl formate and another of phenylisothiocyanate from **127** [87].

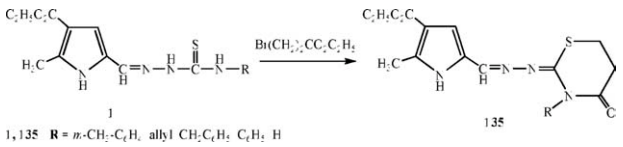


3.8. Synthesis of benzophthalazine derivatives. The reaction of **1** with 2,3-dichloro-1,4-naphthoquinone **89** gave substituted benzophthalazinediones **134**. The reaction of intermediate **133** with **89** followed by elimination of two molecules of HCl afforded the phthalazine derivatives **134** [88].



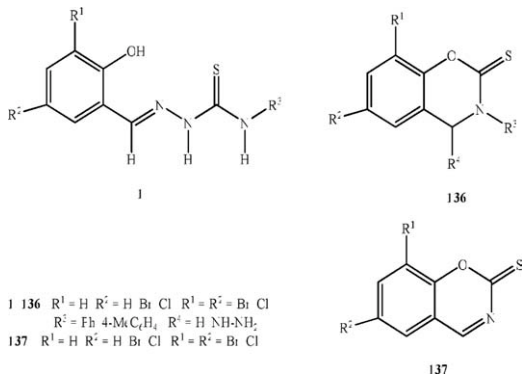
1,139,140: R = C_6H_5, C_6H_4-*p*-OCH_3, 2-Thienyl, 2-Furyl

3.9. Synthesis of thiazine derivatives. Thiosemicarbazones **1** reacted with ethyl-β-bromo-propionate in refluxing ethanol to yield substituted-3-(ethoxycarbonyl)-2-methylpyrrole-5-carboxaldehyde-3-(substituted-5,6-dihydrothiazin-4-one-2-ylidene)hydrazones **135** [108].



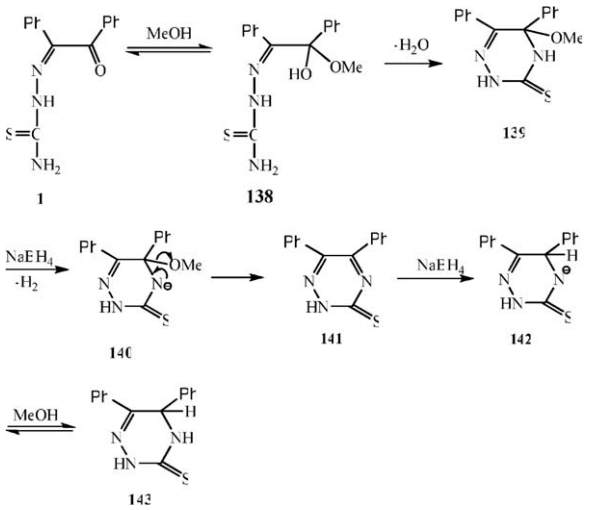
1,135 R = *m*-CH_3-C_6H_4, allyl $CH_2C_6H_5$, C_6H_5, H

3.10. Synthesis of benzoxazine thione derivatives. Cycloisomerization of salicylaldehyde 4-arylthiosemicarbazones **1** yielded 3,4-dihydro-4-hydrazino-2*H*-benz[*e*]-1,3-oxazine-2-thiones **136** (R^4 = H_2NNH), which on reductive dehydrazination furnished 3,4-dihydro-2*H*-benz[*e*]-1,3-oxazine thiones **136** (R^4 = H). Under the same conditions, salicylaldehyde thiosemicarbazones **1** (R^3 = H) underwent cyclodehydrazination to yield 2*H*-benz[*e*]-1,3-oxazine-2-thiones **137** [109].

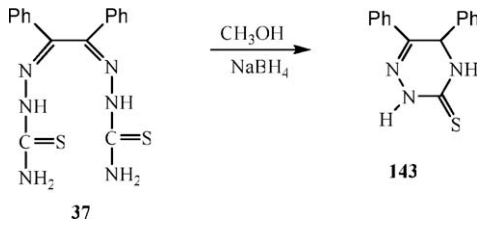


1, 136 R^1 = H R^2 = H, Br, Cl R^1 = R^2 = Br, Cl
R^2 = Ph, 4-MeC_6H_4 R^2 = H, $NH-NH_2$
137 R^1 = H R^2 = H, Br, Cl R^1 = R^2 = Br, Cl

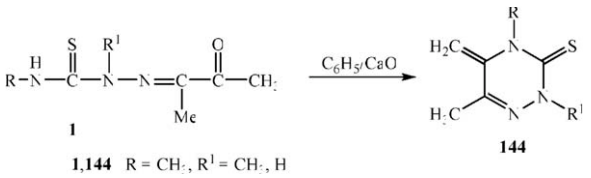
3.11. Synthesis of triazine derivatives. Reaction of **1** with methyl alcohol in the presence of $NaBH_4$ afforded 5,6-diphenyl-4,5-dihydro-2*H*-[1,2,4] triazine-3-thione **143** [108].



The reaction of benzil bis thiosemicarbazone **37** with methyl alcohol in the presence of $NaBH_4$ afforded 5,6-diphenyl-4,5-dihydro-2*H*-[1,2,4]triazine-3-thione **143** [108].

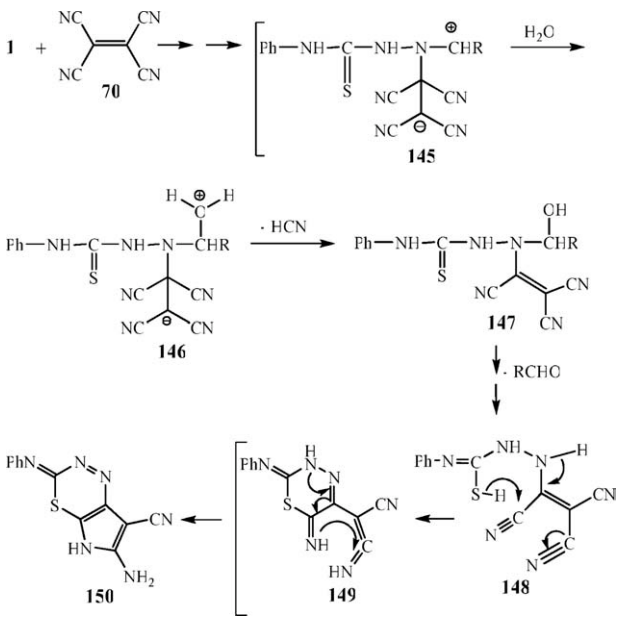


Refluxing thiosemicarbazones **1** in benzene over CaO gave triazine derivatives **144** [109].



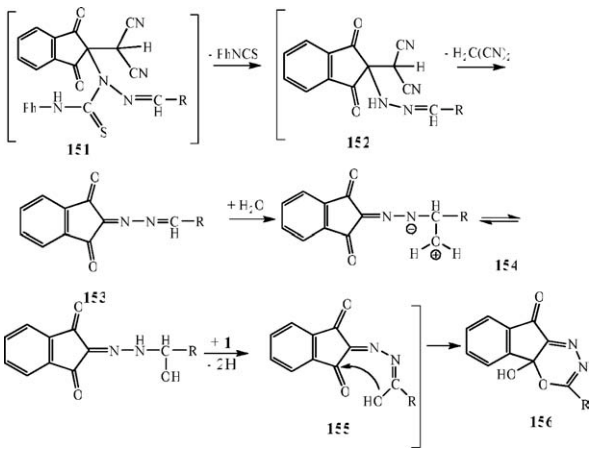
1,144 R = CH_3, R^1 = CH_3, H

3.12. Synthesis of pyrrolothiadiazine derivatives. 2-Substituted ylidene-*N*-phenylhydrazinecarbothioamides **1** reacted with ethenetetracarbonitrile **70** in ethyl acetate to form compound **150**.



The formation of compound **150** can be rationalized *via* nucleophilic attack of the imino group of **1** on **70** followed by hydrolysis and loss a molecule of HCN from **146** to yield the tricyanovinylation product **147,** which cyclized with the release of RCHO from **147** to give **150** [86].

3.13. Synthesis of oxoindnooxadiazine derivatives. Solutions of **1** (1 mmol) each in dry pyridine were added to solution of **95** (2 mmol). The mixtures were gently warmed for 4 h with admission of air. Chromatographic separation of the residue afforded **156**. Thiosemicarbazones **1** reacted with **95** through a nucleophilic attack of **1** to the C=C (double bond) of **95**, where the four electron-withdrawing groups (two nitrile and two carbonyl groups) facilitate this reaction to form the intermediates **151** [89].



Elimination a molecule of Ph-N=C=S from the adduct **151**, followed by another molecule of malononitrile lead to the formation of **153** which in turn undergo hydrolysis followed by dehydrogenation to give **155**, compound **155** exerts its nucleophilic character and attacking C-1 and forming compounds **156** [89].

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