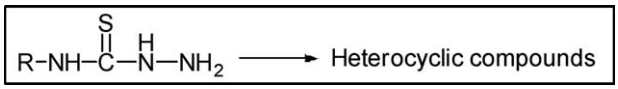
Alaa A. Hassan* and Ahmed M. Shawky

Chemistry Department, Faculty of Science, Minia University, El-Minia, Egypt
*E-mail: alaahassan2001@yahoo.com
Received March 7, 2010
DOI 10.1002/jhet.553
Published online 15 March 2011 in Wiley Online Library (wileyonlinelibrary.com).



This review summarizes the preparation of substituted thiosemicarbazides with their application with synthesis of important linear and heterocyclic compounds.

J. Heterocyclic Chem., **48**, 495 (2011).

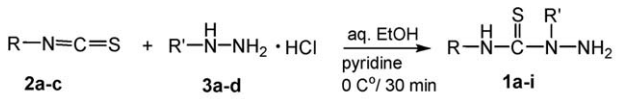
Contents

1. INTRODUCTION

Finding new methodologies for the synthesis of a family of biologically potent compounds by using building blocks with multifunctional groups is a key issue for drug discovery. Thiosemicarbazides appear to be ideal candidates for the development of such processes, as they are the core feature in families of compounds known to display biological activities, *e.g.*, pyrazoles [1], 1,2,4-triazoles [1–5], 1,3,4-oxadiazoles [3,4], 1,3,4-thiadiazoles [1,4,5], 1,3-thiazoles [6], 1,2,4-triazepine [7], 1,3,4-thiadiazine [8], and 1,3,4-thiadiazepine [9].

2. METHODS OF PREPARATION

2.1. From hydrazines and isothiocyanates. The general method for preparation of 2,4-disubstituted thiosemicarbazides **1a–i** is the reaction between substituted isothiocyanates **2a–c** and the appropriate hydrazine hydrochloride **3a–c** in aqueous ethanol and in presence of pyridine [10].



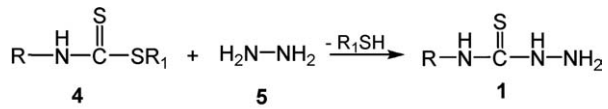
2a-c 3a-d 1a-i

2: **a**, R = C_6H_5; ,**b**, R = $C_6H_5CH_2$; **c**, R = CH_2=CH-CH_2

3: **a**, R' = C_6H_5; **b**, R' = 4-CH_3-C_6H_4; **c**, R' = 4-Cl-C_6H_4

1: **a**, R = R'= C_6H_5; **b**, R = C_6H_5, R' = 4-CH_3-C_6H_4; **c**, R = C_6H_5, R' = 4-Cl-C_6H_4; **d**, R = $C_6H_5CH_2$, R' = C_6H_5; **e**, R = CH_2=CH-CH_2, R' = C_6H_5; **f**, R = $C_6H_5CH_2$, R' = 4-CH_3-C_6H_4; **g**, R = C_6H_5, R' = H; **h**, R = $C_6H_5CH_2$, R' = H; **i**, R = CH_2=CH-CH_2, R' = H

2.2. Hydrazinolysis of *N*-alkyl dithiocarbamates. 4-Substituted thiosemicarbazides **1** were prepared by hydrazinolysis of *N*-alkyl dithiocarbamates **4**. The yields are comparable to those obtained in the reactions between hydrazines and isothiocyanates so that an *S*-alkyl and *N*-alkyl dithiocarbamate can be used instead of an isothiocyanate to prepare 4-substituted thiosemicarbazides [11–13].

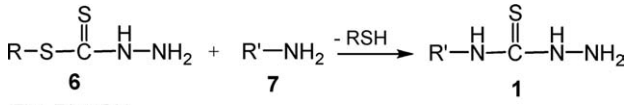


4 5 1

3: R = R_1 = CH_3
R = R_1 = C_2H_5

1: R = CH_3
R = C_2H_5

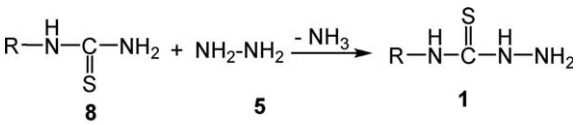
2.3. Aminolysis *of S*-alkyl dithiocarbazate. Aminolysis of *S*-methyl dithiocarbazate **6** also afforded the corresponding 4-methyl thiosemicarbazide **1** [14].



6 7 1

R = R' = CH_3

2.4. Hydrazinolysis of thioureas. Some attempts to prepare thiosemicarbazides by hydrazinolysis of thioureas derivatives **8** were carried out [15,16].

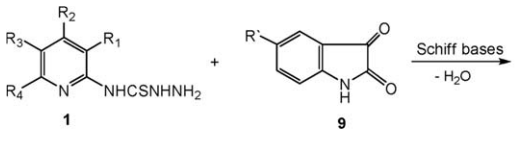


8 5 1

1, 8: R = CH_3; C_2H_5; C_6H_5

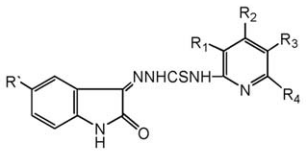
3. REACTIONS OF SUBSTITUTED THIOSEMICARBAZIDES

3.1. Synthesis of thiosemicarbazones. The reaction of 4-(substituted pyridin-2-yl)thiosemi-carbazides **1** with 5-halogenated isatin derivatives **9** afforded the corresponding Schiff bases **10** through the condensation of the keto group of isatin with various thiosemicarbazides [17].



1 9

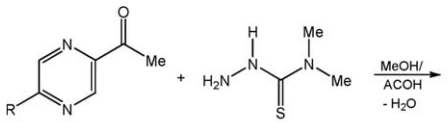
R' = F, Cl, Br



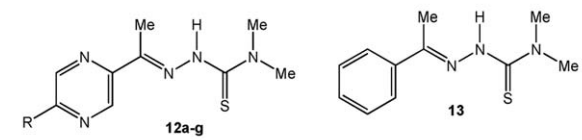
10a-o

a, R' = F; R_1 = R_2 = R_3 = R_4 = H
b, R' = F; R_1 = R_2 = R_4 = H; R_3 = Cl
c, R' = F; R_1 = CH_3; R_2 = R_3 = R_4 = H
d, R' = F; R_1 = H; R_2 = CH_3; R_3 = R_4 = H
e, R' = F; R_1 = R_2 = R_3 = H; R_4 = CH_3
f, R' = Cl; R_1 = R_2 = R_3 = R_4 = H
h, R '= Cl; R_1 = CH_3; R_2 = R_3 = R_4 = H
g, R' = Cl; R_1 = R_2 = R_4 = H; R_3 = Cl
i, R' = Cl; R_1 = H; R_2 = CH_3; R_3 = R_4 = H
j, R' = Cl; R_1 = R_2 = R_3 = H; R_4 = CH_3
k, R' = Br; R_1 = R_2 = R_3 = R_4 = H
l, R' = Br; R_1 = R_2 = R_4 = H; R_3 = Cl
m, R` = Br; R_1 = CH_3; R_2 = R_3 = R_4 = H
n, R' = Br; R_1 = H; R_2 = CH_3; R_3 = R_4 = H
o, R' = Br; R_1 = R_2 = R_3 = H; R_4 = CH_3

The reaction of acetylpyrazines **11a–g** with *N,N*-dimethylthiosemicarbazide **1** yielded the final thiosemicarbazones **12a–g** [18,19]. Analogous acetophenone *N,N*-dimethylthiosemicarbazone **13** was prepared for comparison in the same synthetic way [20–22].



11a-g 1

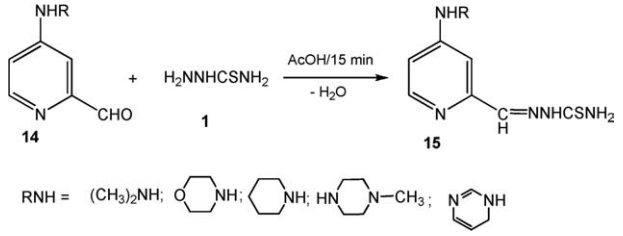


12a-g 13

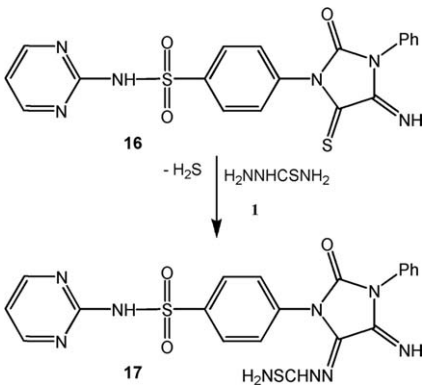
R:**a** = H; **b** = propyl; **c** = isopropyl; **d** = butyl; **e** = *tert*-butyl; **f** = pentyl; **g** = hexyl

A series of 4-substituted-2-formylpyridine thiosemicarbazones **15** has been synthesized through the reaction

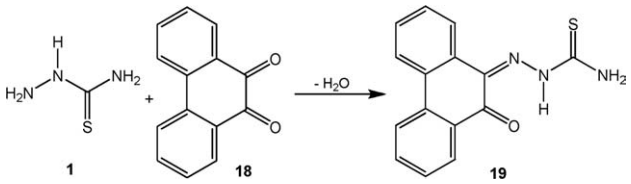
of thiosemicarbazide **1** with 4-substituted pyridine-2-carboxaldehyde **14** in AcOH [18].



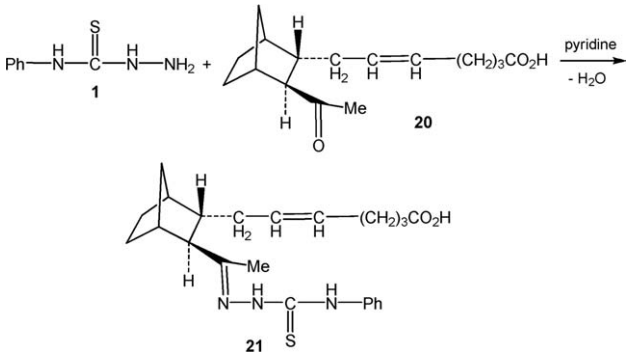
Thiosemicarbazone derivative **17** was produced by treatment of compound **16** with thiosemicarbazide **1** under reflux in absolute ethanol, via elimination of hydrogen sulfide [19].



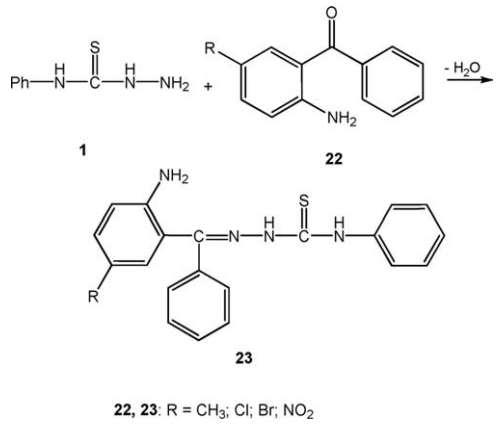
Reaction of thiosemicarbazide **1** with phenanthraquinone **18** afforded phenanthraquinone monothiosemicarbazone **19** [23].



4-Phenyl thiosemicarbazide **1** reacted with **20** in pyridine to give (Z)7-[3-α-[1-[[(phenylamino)thioxomethyl]-hydrazono]ethyl]bicyclo[2.2.1]heptyl]heptenoic acid **21** [24].

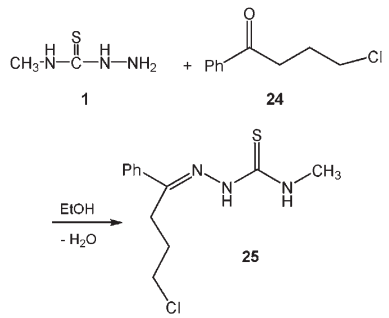


Reaction of phenyl thiosemicarbazide **1** with the corresponding 2-aminobenzophenone derivatives **22** afforded 4-phenylthiosemicarbazones of 5-substituted-2-aminobenzophenone **23** [25].

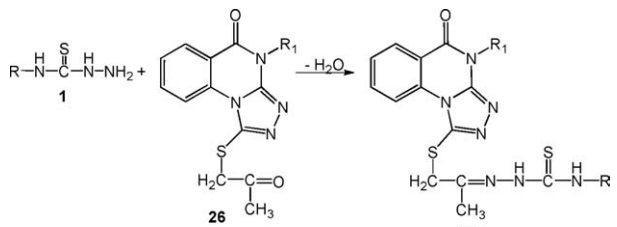


22, 23: R = CH_3; Cl; Br; NO_2

Reaction of substituted thiosemicarbazide **1** with 4-chloro-1-phenylbutan-1-one **24** in ethanol produced 2-(4-chloro-1-arylbutylidene)hydrazinecarbothioamide derivative **25** [26].

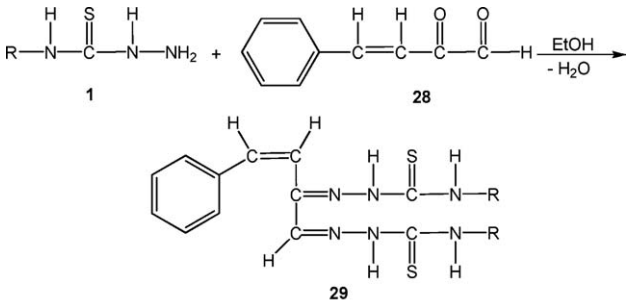


Substituted thiosemicarbazides **1** reacted with 4-phenyl-1-(2-oxopropyl)thio[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones **26** to give thiosemicarbazone derivatives **27** [27].



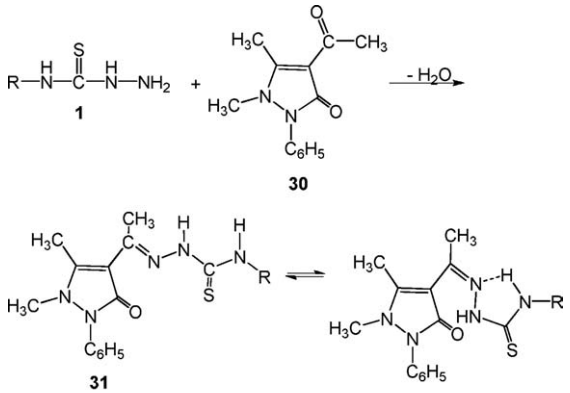
1,27: R = H; allyl; $PhCH_2$; *p*-CH_3-C_6H_4; C_6H_5
26,27: R_1 = Ph; *p*-Cl-C_6H_4; *p*-Br-C_6H_4

Also, reaction of substituted thiosemicarbazides **1** with ketoaldehyde **28** in boiling ethanol gave 1,2-bis-(substituted thiocarbamoyl)hydrazones **29**, which have anticancer, antimicrobial, and antifungal agents [28].



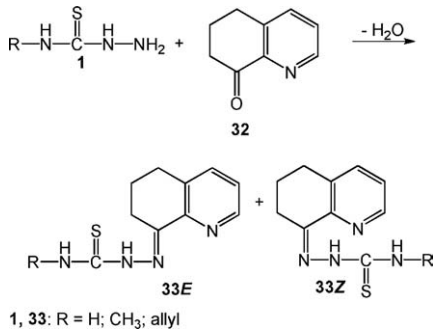
1, 29: R = CH_3; allyl; *p*-Br-C_6H_4; *p*-Cl-C_6H_4

Substituted thiosemicarbazides **1** were condensed with 4-acetylantipyrine **30** to produce the corresponding thiosemicarbazones **31** [29].



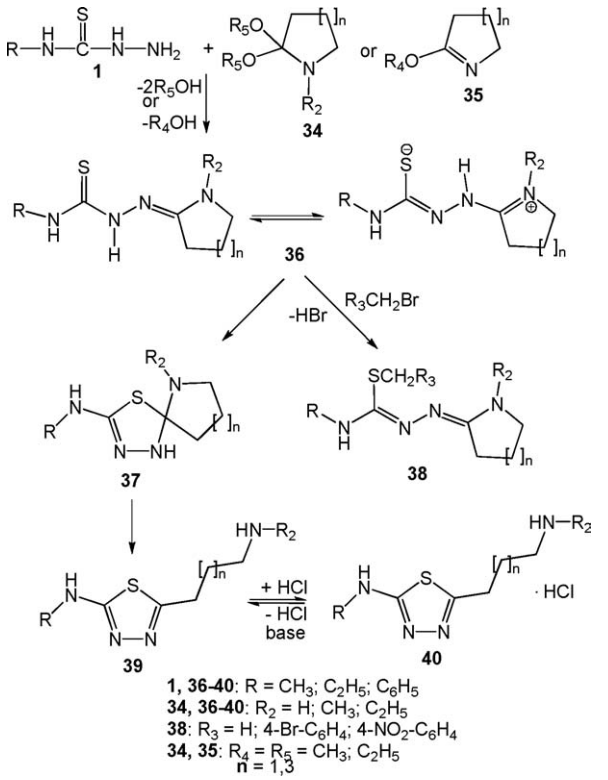
1,31: R = CH_3; C_2H_5; C_4H_9; cyclohexyl; C_6H_5; *p*-CH_3-C_6H_4; *p*-Cl-C_6H_4; *p*-Br-C_6H_4

The reaction of substituted thiosemicarbazides **1** with 5,6-dihydro-8(*7H*)-quinolinone **32** afforded two isomers, the major product was (*Z*) 5,6-dihydro-8(*7H*)-quniolinone thiosemicarbazones **33***Z* and the minor is **33***E* [30].



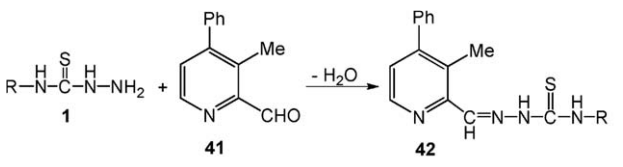
1, 33: R = H; CH_3; allyl

Thiosemicarbazides **1** reacted with lactam acetal **34** or lactim ether **35** by condensation to give unusual ziwitterionic tautomers **36** of lactamthioacylhydrazones, these compounds form **37**, **38**, and **39** in neutral solution. In acidic medium, **36** gave 2-(α-amino alkyl)-1,3,4-thiadiazole salt **40**. Also, alkylation of zwitterionic thioacylamidrazones **36** gave 5-alkylation product **38** [31].



1, 36-40: R = CH_3; C_2H_5; C_6H_5
34, 36-40: R_2 = H; CH_3; C_2H_5
38: R_3 = H; 4-Br-C_6H_4; 4-NO_2-C_6H_4
34, 35: R_4 = R_5 = CH_3; C_2H_5
n = 1,3

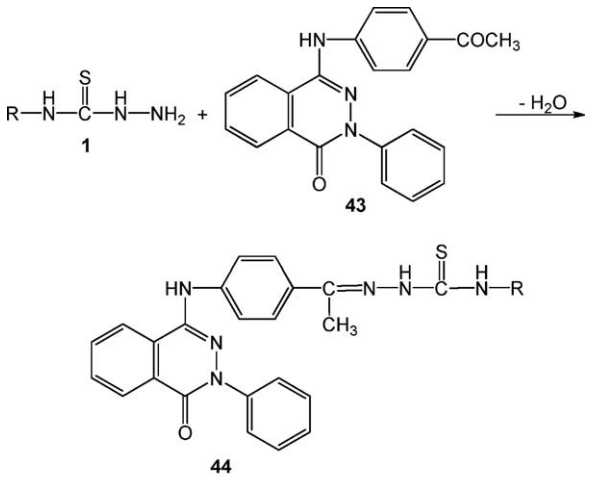
Reaction of substituted thiosemicarbazides **1** with 2-formyl-3-methyl-4-phenylpyridine **41** in ethanol at room temperature afforded the corresponding thiosemicarbazones **42**, which have antitumor activity in animals [32].



1, 42; R = H; CH_3; C_6H_5; allyl; $-CH_2CH_2C_6H_5$; $-(CH_2)_3N(CH_3)_2$; $C_6H_4N(CH_3)_2$

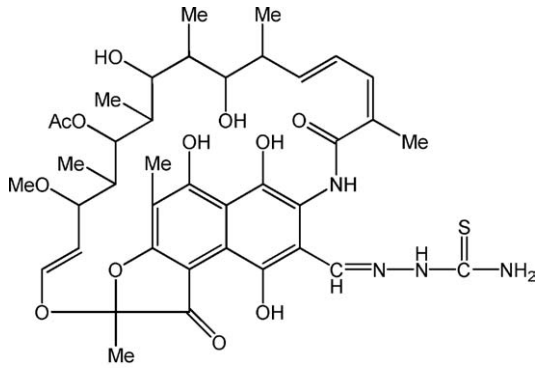
The reaction of substituted thiosemicarbazides **1** with 4-(*p*-acetylanilino)-2-phenylphthalazin-1-one **43** afforded 4-*p*[ω-(4-substituted thiosemicarbazono)-α-ethyl]anilinophthalizin-1-one derivatives **44** [33]. Compound **44** inhibit the growth of microorganisms through poisoning

of sulfahydryl groups of specific enzymes responsible for nucleic acids biosynthesis [34,35].

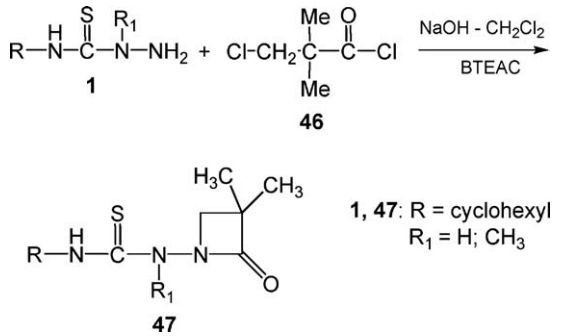


1,**44**: R = CH_3; -$CH(CH_3)_2$; -$(CH_2)_3CH_3$; C_6H_5; COC_6H_5; -$CH_2C_6H_5$

The reaction of thiosemicarbazides **1** with 3-formylrifamycin SV gave thiosemicarbazone **45**, which exhibited bacterial activity [36].

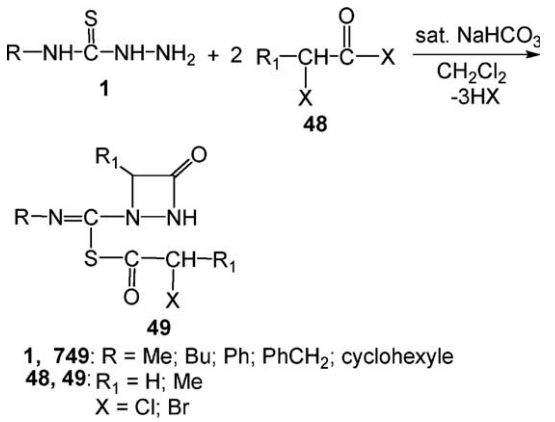


3.2. Synthesis of azetidine derivatives. Reaction of 4-cyclohexylthiosemicarbazide **1** with 3-chloro-2,2-dimethylpropanoyl chloride **46** in 5% aqueous NaOH/CH_2Cl_2 in presence of benzyltriethylammonium chloride (BTEAC) gave azitidinone derivatives **47** [37,38].



1, 47: R = cyclohexyl
R_1 = H; CH_3

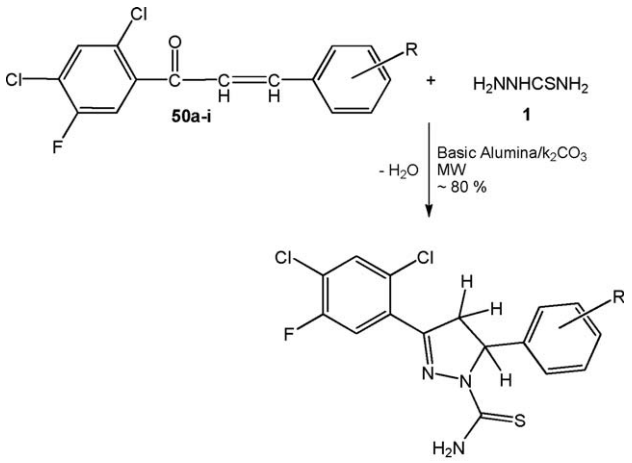
The reaction of substituted thiosemicarbazides **1** with α-haloacylhalides **48** in saturated aqueous $NaHCO_3$/CH_2Cl_2 afforded 4-substituted-4-aza-2-azetidinone **49** [37,38].



1, 749: R = Me; Bu; Ph; $PhCH_2$; cyclohexyle
48, 49: R_1 = H; Me
X = Cl; Br

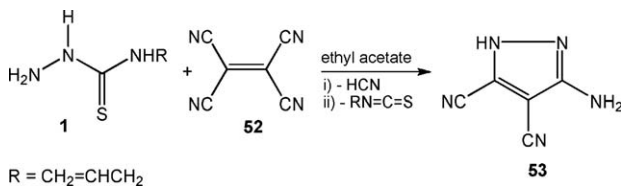
3.3. Synthesis of pyrazole derivatives.

3.3.1. From chalcones. The new fluorine-containing 1-thiocarbamoyl-3,5-diphenyl-2-pyrazoline **51a–i** have been synthesized in 80–85% yield by a microwave-promoted solvent-free condensation of 2,4-dichloro-5-fluoro chalcones **50a–i** with thiosemicarbazide over potassium carbonate [39].



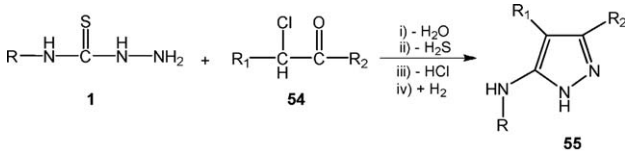
50,51: **a**, R = H; **b**, R = 2-NO_2; **c**, R = 3-NO_2; **d**, R = 2-Cl; **e**, R = 4-Cl; **f**, R = 4-$N(CH_3)_2$; **g**, R = 3,4,5-$(OCH_3)_3$; **h**, R = 3-OC_2H_5; **i**, R = 4-OCH_3

3.3.2. From ethenetetracarbonitrile. Thiosemicarbazides **1** reacted with ethenetetracarbonitrile (TCNE) **52** in ethyl acetate with admission of air to afford a mixture of different compounds among of them 3-amino-1*H*-pyrazole-4,5-dicarbonitrile **53** [40].



R = CH_2=$CHCH_2$

3.3.3. From α-haloketones. Pyrazole derivatives **55** were prepared by reaction between substituted thiosemicarbazides **1** and the derivatives of haloketones **54** [41].



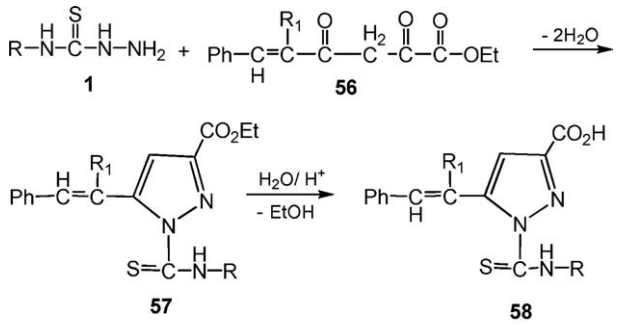
1, **54**, **55**

1,55: R = C_6H_5; Cl-C_6H_4; 3-Cl-4-F-C_6H_3

54,55: R_1 = CH_3; -$COOC_2H_5$; -COOH

R_2 = $COOC_2H_5$; COOH; H

3.3.4. From diketoesters and diesters. Condensation reaction of thiosemicarbazides **1** with diketoesters **56** afforded new substituted 1-thiocarbamoyl derivatives of 3,5-disubstituted pyrazoles **57**, which were readily hydrolyzed to their corresponding acid derivatives **58** [42].

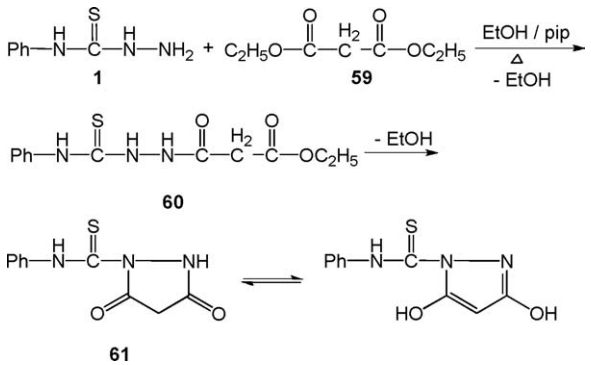


1, **56**, **57**, **58**

1,57,58: R = C_6H_5; cyclohexyl; $(CH_2)_3CH_3$; allyl; $C_6H_5CH_2$

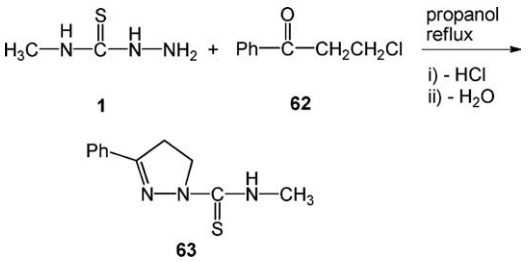
56-58: R_1 = H; CH_3; C_6H_5

Also, **1** reacted with diethyl malonate **59** in refluxed ethanolic/piperidine solution to give intermediate **60** followed by cyclization with loss a molecule of ethanol to form diketopyrazole **61**, which exists in tautomeric form of 3,5-dihydroxy-1-thiocarbanilidopyrazole [43].



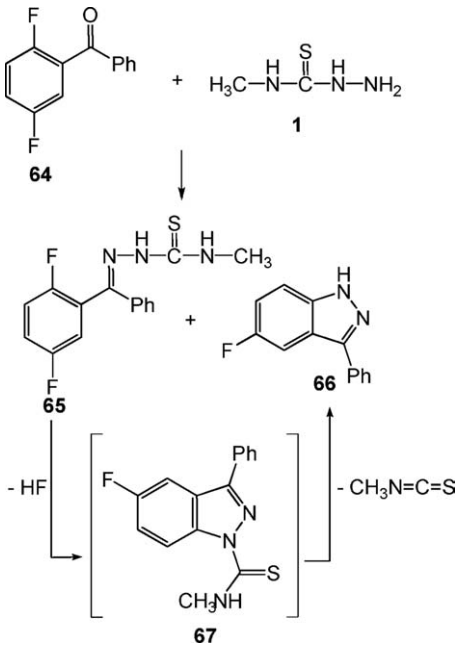
1, **59**, **60**, **61**

3.3.5. From β-haloketones. Reaction of **1** with 3-chloro-1-phenylpropan-1-one **62** in boiling propanol afforded 4,5-dihydro-3-phenyl-1*H*-pyrazole-1-carbothioamides **63** [42] or by mild condition with stirring in ethanol at room temperature [44].



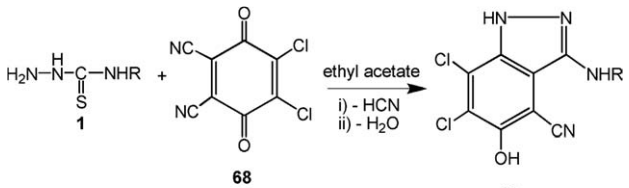
1, **62**, **63**

3.4. Synthesis of indazole derivatives. Reaction of 2,5-diflourobenzophenone **64** and methyl thiosemicarbazide **1** gave a mixture of thiosemicarbazone **65** and indazole **66** [45]. Also, treatment of **65** with sodium hydride in dimethylformamide (DMF) gave **66** through intermediate **67** [45].



64, **1**, **65**, **66**, **67**

4-Substituted thiosemicarbazides **1** reacted with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) **68** in ethyl acetate ultimately gave indazole derivatives **69a–c** through the formation of CT-complexes [46].



1, **68**, **69a-c**

a, R = Ph

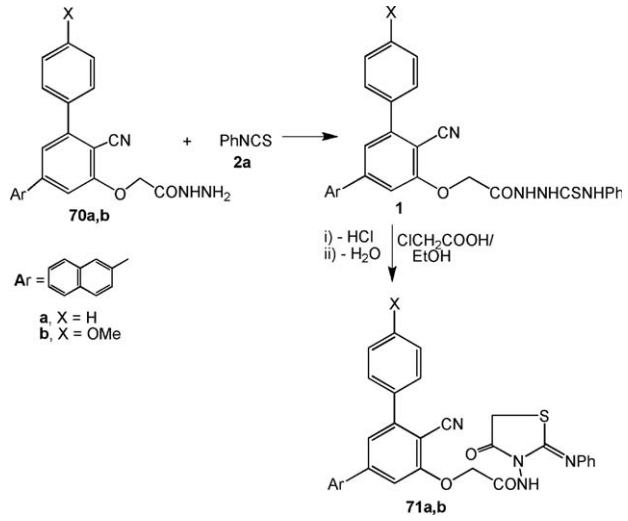
b, R = $PhCH_2$

c, R = CH_2=$CHCH_2$

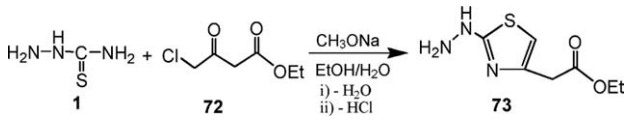
3.5. Synthesis of thiazole, thiazoline, thiazolidinone, and thiazolidine derivatives.

3.5.1. From phenylisothiocyanate. The reaction of compounds **70a,b** with phenylisothio-cynate **2a** in dry dioxane

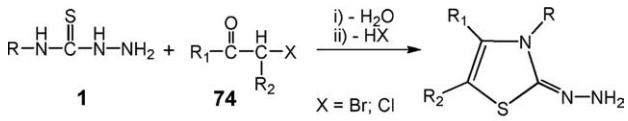
yielded the corresponding thiosemicarbazide derivatives **1**, which were cyclized with chloroacetic acid in ethanol to produce the corresponding thiazolidinone derivatives **71a,b** [47].



3.5.2. From γ-haloketo-esters. Thiosemicarbazide condensed with γ-haloketo-esters such as ethyl 4-chloroacetoacetate **72** in presence of $CH_3ONa/EtOH/H_2O$ to give ethyl-2-hydrazino-thiazole-4-acetate **73** [48].



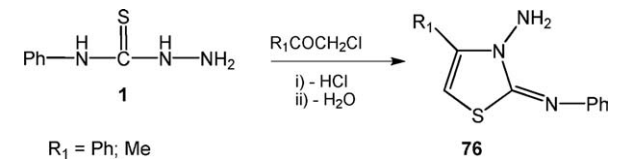
3.5.3. From α-haloketones. Substituted thiosemicarbazides **1** reacted with α-haloketones **74** and forming thiazole derivatives **75** [49].



1,75: R = allyl; $(CH_3)_2$-CH-CH_2

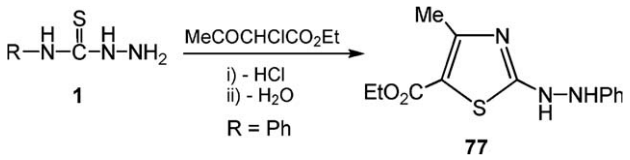
74, 75: R_1 = C_6H_5; *p*-CH_3-C_6H_4; *p*-Br-C_6H_4; *p*-Cl-C_6H_4
R_2 = H; CH_3

4-Phenyl thiosemicarbazide **1** reacts with α-haloketones and yield 3-amino-2-phenylimino-4-substituted-Δ^4-thiazolines **76** [50]. An extension of this approach was reported earlier [51].

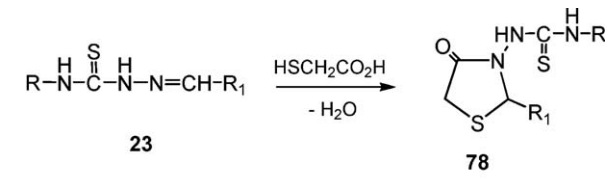


R_1 = Ph; Me

3.5.4. From α-haloesters, α-haloacids, and thioglycollic acid. α-Haloesters also behave in an identical manner; 5-carbethoxy-4-methyl-2-hydrazinothiazole **77** was reported to be formed on reacting thiosemicarbazide **1** with ethyl α-chloroacetoacetate at 50–70°C [52]. Similar treatment of thiosemicarbazide with ethylbromo-acetoacetate and subsequent saponification yields 2-(1,2-disubstituted) hydrazino-4-methylthiazole-5-carboxylic acid [53]. With substituted thiosemicarbazide **1**, 2-phenylhydrazino-4-methyl-5-carbethoxythiazole was reported to be formed [54].

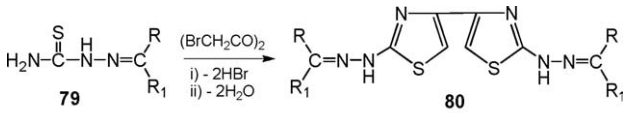


It was observed that on heating thiosemicarbazide derivatives **1** with α-chloroacetic acid, cyclocondensation occurs yielding a thiazolidine derivatives [55]. However, when 4-phenylthiosemicarbazide was treated with chloroacetic acid, 2-hydrazono-3-phenyl-thiazolidin-4-one was reported to be formed [56]. On the other hand, Yadav *et al*. observed the effects of thioglycollic acid on 4-aryl thiosemicarbazones **23** to furnish thiazolidine derivatives **78** [57].



23,78: R = *p*-$MeOC_6H_4$; *o*-MeC_6H_4
R_1 = D-Glucopentyl

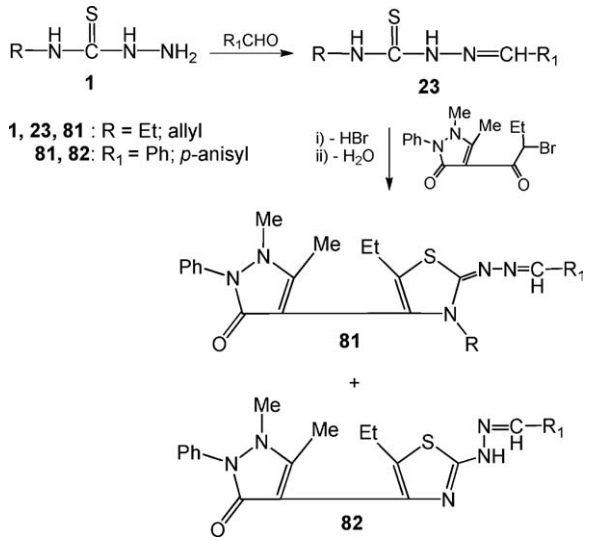
It has been reported that α-haloketoesters on reaction with thiosemicarbazides afforded thiadiazine or thiazole or the corresponding carboxylic acid depending upon the acidity of the medium [58]. With α,β-dichloroether, a thiazole derivatives were found to be formed [54]. Just as thiosemicarbazides, the nature of the substituent at 4-position plays a critical role in the reaction of thiosemicarbazones with chloroacetyl chloride [59]. A hydrazino bisthiazolyl derivatives **80** were obtained by the reaction of thiosemicarbazone **79** with 1,4-dibromodiacetyl.



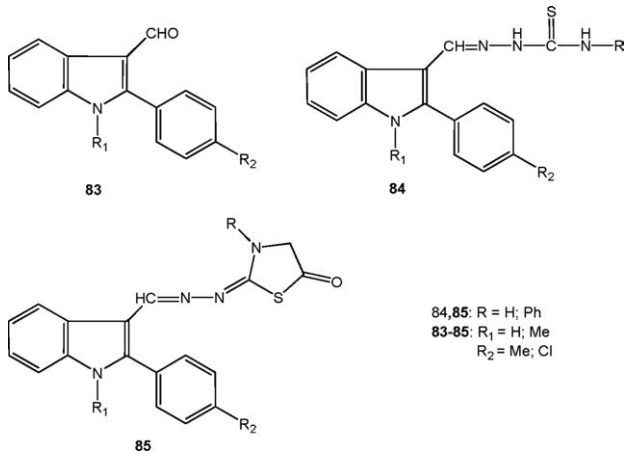
79, 80: R, R_1 = Ph; Me

3.5.5. From aldehydes, ketones, and tetrachloro-dihydrobenzofurandiol. Reaction of substituted thiosemicarbazide derivatives **1** with aldehydes gave thiosemicarbazone

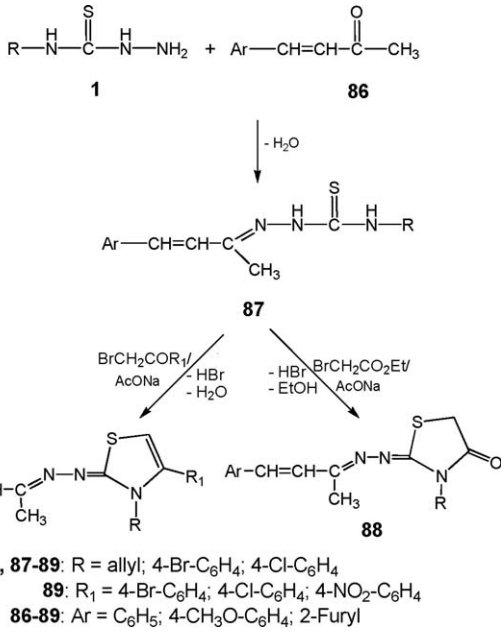
derivatives **23**, followed by cyclocondensation with α-bromopropyl-antipyryl ketone to yield antipyrylthiazolyl and antipyrylthiazolonyl hydrazones **81** and **82**, respectively [60].



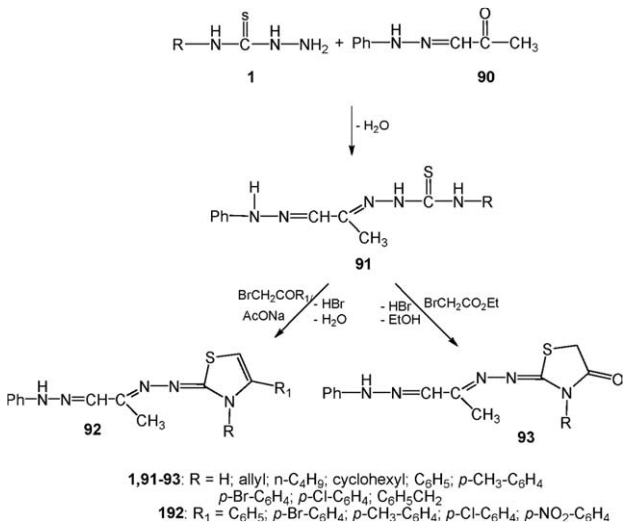
In the same way, condensation of indolecarboxaldehyde **83** with substituted thiosemicarbazides **1** gave thiosemicarbazone **84**, which cyclized with α-chloroacetic acid to give thiazoline derivatives **85** [61].



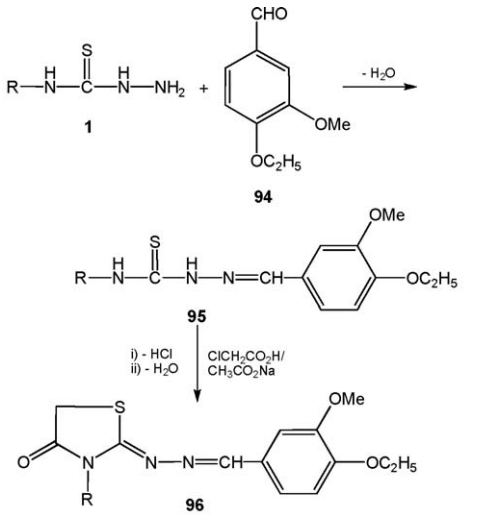
Condensation of substituted thiosemicarbazides **1** with 4-aryl-3-buten-2-ones **86** gave 4-substituted-3-buten-2-one-2-thiosemicarbazones **87**, which cyclized into the corresponding thiazolines **88** and thiazolidinones **89** by treatment with ethyl bromoacetate/sodium acetate or with phenacyl bromide derivatives under Hantzsch's reaction condition, respectively [62].



Substituted thiosemicarbazides **1** reacted with hydrazone **90** to yield thiosemicarbazones **91**, the latter reacted or treated with selected phenacyl bromide derivatives and sodium acetate to give the corresponding thiazolines **92**. Also, when thiosemicarbazones **91** reacted with ethyl bromoacetate, thiazolidinones **93** were prepared [63].

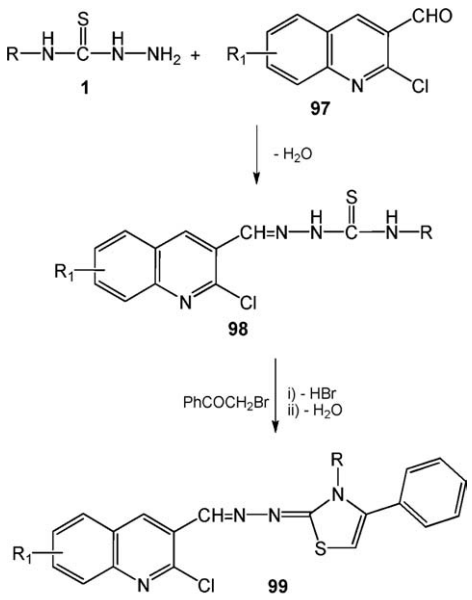


4-Ethoxy-3-methoxybenzaldehyde **94** reacted with substituted thiosemicarbazides **1** to give 1-(4-ethoxy-3-methoxy)phenyl-4-aryl-3-thiosemicarbazones **95**, which cyclized with monochloroacetic acid in the presence of sodium acetate to form the corresponding 3-aryl-4-oxo-thiazoline-2-yl(4-ethoxy-3-methoxy)phenylhydrazones **96** [64].



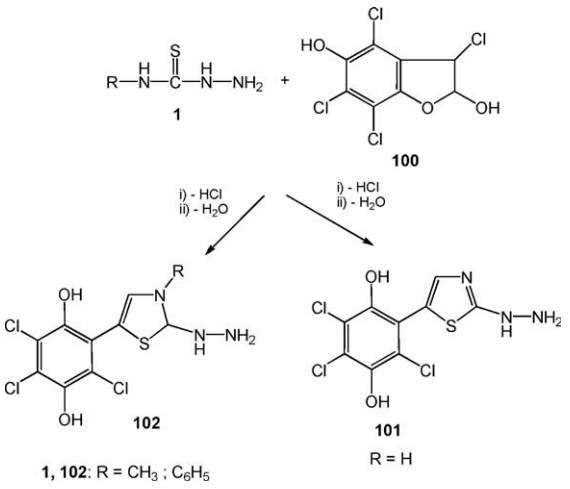
1, **95**, **96**: R = C_6H_5; 2-Me-C_6H_4; 3-Me-C_6H_4; 4-Me-C_6H_4; 2-MeO-C_6H_4; 3-MeO-C_6H_4; 4-MeO-C_6H_4; 4-EtO-C_6H_4; 4-C_3H_7O-C_6H_4; 4-Cl-C_6H_4; C_6H_{11}

2-Haloquinolin-3-carbaldehyde derivatives **97** reacted with substituted thiosemicarbazides **1** to give 2-chloroquinolin-3-carbaldehydethiocarbamoyl hydrazones **98**, which undergo cyclization with phenacyl bromide and gave series of 2-chloroquinolin-3-carbaldehyde-(2,3-dehydrothiazol-2-yilidene)hydrazones **99** [65].



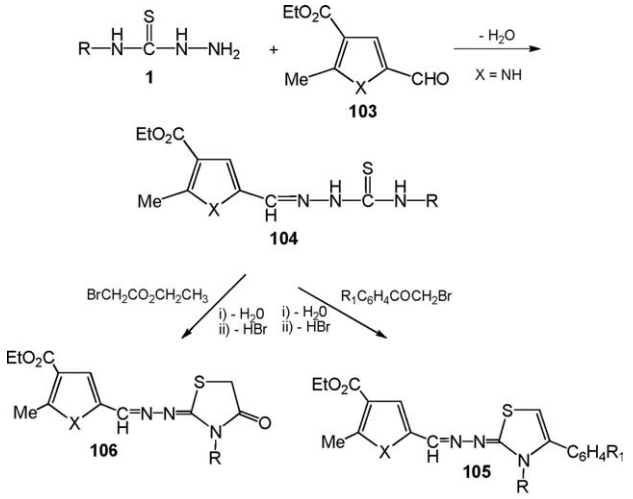
1,98,99: R = *p*-CH_3-C_6H_4; *o*-CH_3-C_6H_4; *m*-CH_3-C_6H_4 *c*-C_6H_{11}; C_6H_5-CH_2; *m*-Cl-C_6H_4; C_6H_5
97-9: R_1 = H; 7-CH_3; 8-CH_3

Reaction of substituted thiosemicarbazides **1** with tetrachlorodihydrobenzofurandiol **100** afforded the derivatives of thiazole **101** and thiazolines **102** [66].



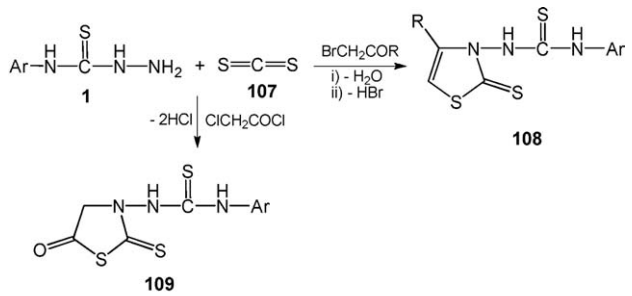
1, 102: R = CH_3 ; C_6H_5

Substituted thiosemicarbazides **1** reacted with pyrrole derivatives **103** to give the carbazone **104**, which reacted with phenacyl bromide derivatives and affording substituted-3-(ethoxycarbonyl)-2-methylpyrrole-5-carbo-xaldehyde(3,4-disubstituted-2,3-dihydrothiazol-2-ylid-ene)hydrazones **105** [67]. On other hand, **104** reacted with ethylbromoacetate and afforded 3-(ethoxycarbonyl)-2-methylpyrrol-5-carboxaldehyde(3-substituted-thiazolidin-4-one-2-yilidene)hydrazones **106** [67].



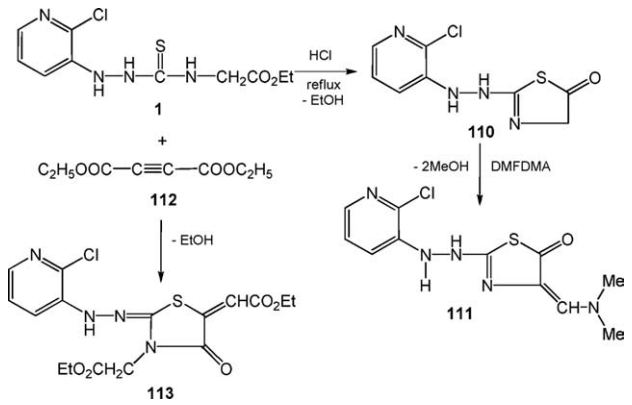
1, 104-106: R = *m*-CH_3-C_6H_4; allyl; $CH_2C_6H_5$; C_6H_5 ; H
105: R_1 = H; Br

3.5.6. By reaction with carbon disulfide and α-halo ketones. Reaction of 4-aryl-thiosemicarbazides **1** with carbon disulfide **107** in alkaline medium affords the nonisolable sulfide salts, which reacted with α-Br-CH_2-CO-R, and Cl-CH_2CO-Cl to give substituted 2,3-dihydrothiazoles **108** and thiazolidines **109**, respectively [68].

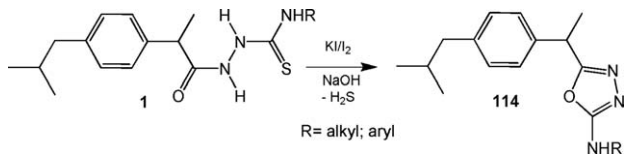


1,108,109: Ar = C_6H_5; 4-Cl-C_6H_4; 4-CH_3-C_6H_4; 4-CH_3O-C_6H_4
108: R = C_6H_5; OEt

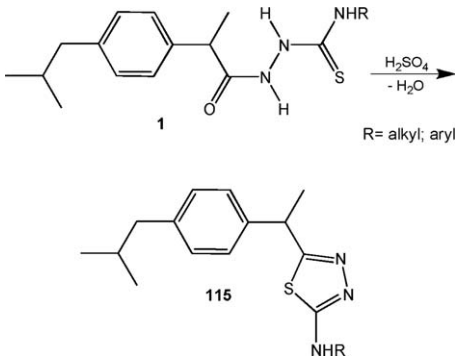
Heating thiosemicarbazide derivatives **1** in aqueous hydrochloric acid, cyclization of the side chain took place to give 1-(2-chloro-pyridyl-3)-2-(5-oxothiazolinyl-2)-hydrazine **110** [69]. Methylation of **110** with *N,N*-dimethyl-formamidedimethylacetal (DMFDMA) gave 1-[methyl-(2-chloropyridyl-3)]-2-(4-dimethylamino-methyl-idene-5-oxo-thiazolinyl-2)hydrazine **111** [69]. Also, **1** reacted with diethyl acetylenedicarboxylate (**112**) to give 2-(2-chloropyridyl-3)hydrazono-3-ethoxy-carbonylmethyl-5-ethyoxycarbonylmethylidine-4-thiazolidone (**113**) [69].



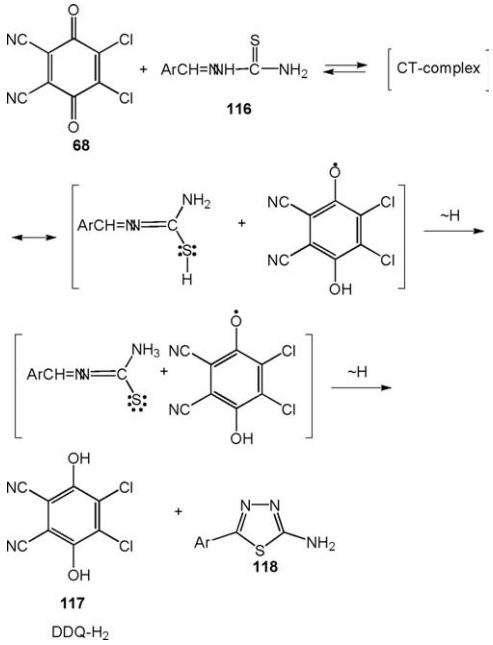
3.6. Synthesis of oxadiazoles. Thiosemicarbazides **1** were oxidatively cyclized to 2-alkyl/arylamino-5-substituted-1,3,4-oxadiazoles **114** by elimination of H_2S using iodine and potassium iodide in ethanolic sodium hydroxide [70].



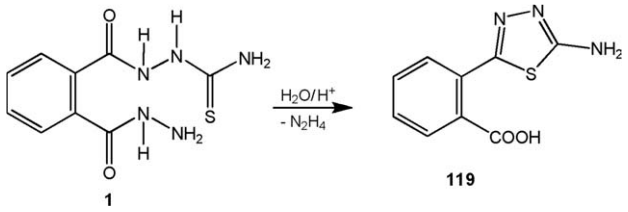
3.7. Synthesis of thiadiazoles. 2-Alkyl/arylamino-5-substituted-1,3,4-thiadiazoles **115** were obtained by cyclization of the thiosemicarbazide derivatives **1** by treating with cold concentrated sulfuric acid [70].



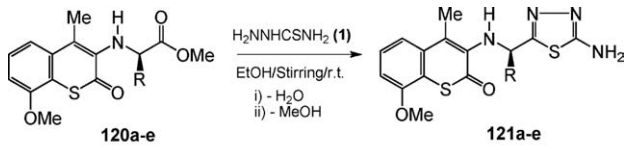
Mixing of two fold molar amounts of DDQ **68** (electron acceptor) with one mole of thiosemicarbazone derivatives **116** (electron donors) in ethyl acetate gives a blue color, which changes gradually to brown with the formation of a solid product. This behavior is explained as being due to an initial formation of unstable CT-complexes followed by a chemical reaction which yields dichlorodicyanohydr-quinone (DDQ-H_2) **117** and 3-amino-thiadiazoles **118** [71].



In the presence of acid, thiosemicarbazide derivative **1** cyclizes, originating *o*-(2-amino-1,3,4-thiadiazol-5-yl)benzoic acid **119** in 90% yield [72].

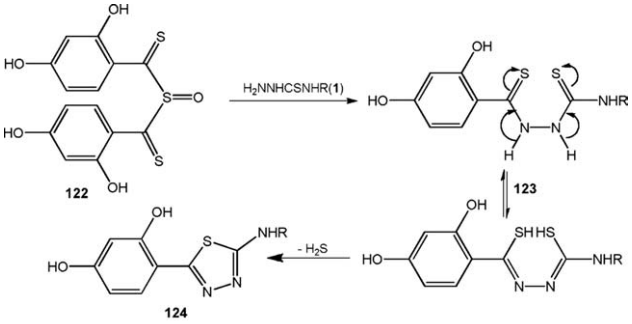


Thiosemicarbazide **1**, upon reaction with compounds **120a–e** in ethanol, produced a series of required thiadiazole derivatives **121a–e** in good yields [73].



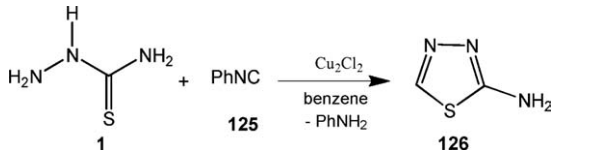
120,121a-e = **a**, H; **b**, CH; **c**, $PhCH_2$; **d**, 2-indolyl; **e**, *p*-hydroxyl benzyl

N-Substituted 2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles **124** were prepared by the reaction of sulfinyl bis(2,4-dihydroxythiobenzoyl) (STB) **122** with 4-substituted thiosemicarbazides **1** [74].

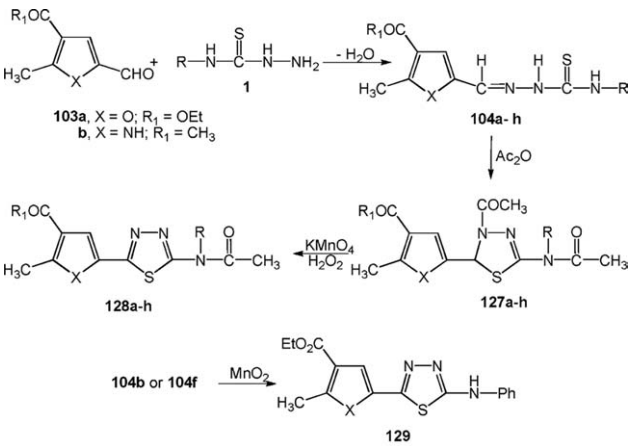


R = C_6H_5; cylohexyl; $CH_3(CH_2)CH_2$; 2-$C_2H_5C_6H_4$-

Reaction between thiosemicarbazide **1** with phenylisocyanide **125** in refluxing benzene with copper (I) chloride as catalyst gave only 2-amino-1,3,4-thiadiazole **126** [75].



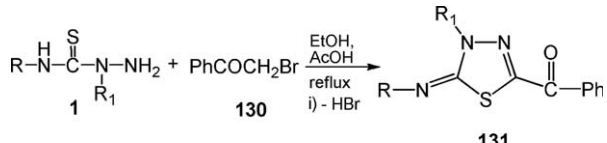
Reactions of thiosemicarbazide **1** with 3-substituted-2-methyl-5-furancarboxaldehyde **103a** and 3-substituted-2-methyl-5-pyrrolecarboxaldehyde **103b** afforded 5-thiosemicarbazone derivatives **104a–h**, which cyclized with acetic anhydride affording thiadiazoline derivatives **127a–h**.



104,127,128a: X = O; R = H; R_1 = OEt
b: X = O; R = Ph ; R_1= OEt
c: X = O; R = H; R_1 = CH_3
d: X = O; R = Ph; R_1 = CH_3
e: X = NH; R = H; R_1 = OEt
f: X = NH; R = NH ; R_1 = OEt
g: X = NH ; R = H; R_1 = CH_3
h: X = NH; R = Ph; R_1 = CH_3

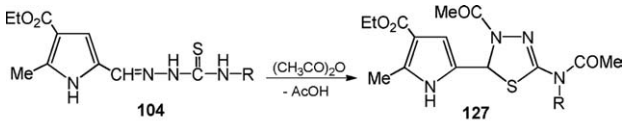
Thiadiazole derivatives **128a–h** were synthesized on oxidation of the corresponding thiadiazolines **127a–h** with potassium permanganate in acidic medium [76]. On the other hand, oxidative cyclization of 4-phenylthiosemicarbazone derivatives **104b, 104f** with manganese dioxide afforded the corresponding 1,3,4-thiadiazole derivatives **129** [76].

On treatment of **1** with 2-bromo-1-phenylethan-1-one **130** in ethanol at room temperature, the thiosemicarbazone intermediates were not isolated and 2,3-dihydo-1,3,4-thiadiazole **131** was obtained [44].



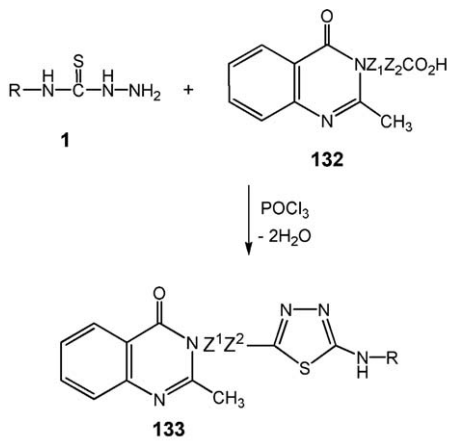
1, 131: R = Ph
R_1 = CH_3

Compound **104** reacted with acetic anhydride under reflux to produce 3-(ethoxy-carbonyl)-2-methyl-5-[3-acetyl-5-(*N*-substitutedacetamide)-2,3-dihydro-1,2,3-thiadiazol-2-yl]pyrroles **127** [66].



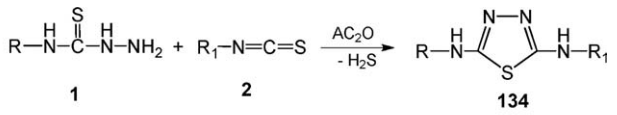
104, 127: R = *m*-CH_3-C_6H_4; allyl; $CH_2C_6H_5$; C_6H_5; H

Compounds **1** reacted with carboxylic acids **132** in presence of $POCl_3$ to give the thiadiazole derivatives **133** [77].



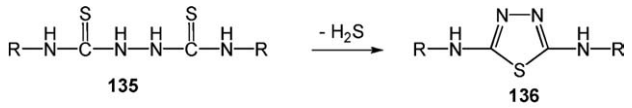
1, 133: R = Bu; $PhCH_2$; C_6H_5; *p*-Cl-C_6H_4 ; *p*-CH_3-C_6H_4
132,133: Z_1 = dirict bond, NH
Z_2 = *p*-phenylene, CH_2

Cyclization of substituted thiosemicarbazides **1** with substituted isothiocyanates **2** in presence of AC_2O gave diaminothiadiazoles **134** [78].



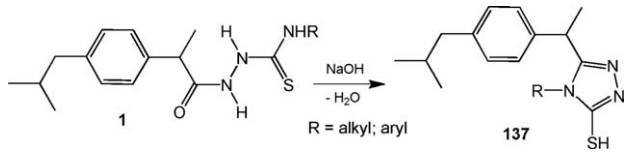
2,134: R_1 = CH_3; allyl; 4-F-C_6H_4; C_6H_5; $CH_2CMe=CH_2$; $CH_2CH=CHMe$; $CH=CHCH_2Cl$
1,134: R = C_2H_5; CH_3; $CH=CHCH_2Cl$; allyl

2,5-Diphenylamino-1,3,4-thiadiazoles **136** were prepared from 1,6-diaryl-2,5-dithiobiurea **133** (thiosemicarbazide derivatives) via thermal cyclization with evolution of hydrogensulphide [79,80].

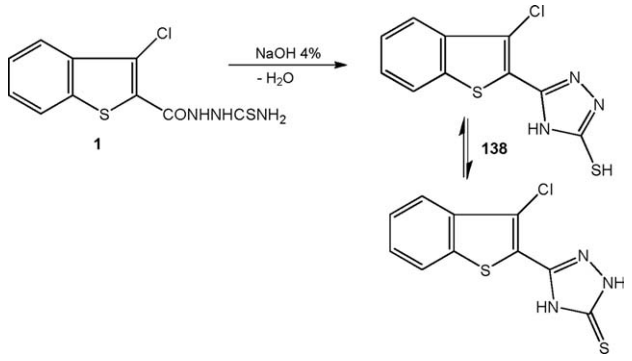


135, 136: R = C_6H_5; *p*-CH_3O-C_6H_4; *p*-CH_3-C_6H_4; *p*-Cl-C_6H_4; *p*-C_2H_5O-C_6H_4; n-C_4H_9; CH_3

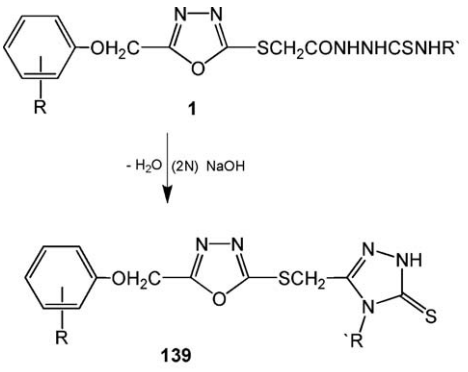
3.8. Synthesis of triazole, triazoline, and triazolidine derivatives. On heating thiosemicarbazides **1** with NaOH in ethanol underwent smooth cyclization through dehydration to afford 5-substituted-4-alkyl/aryl-3-mercapto-*4H*-1,2,4-triazoles **137** [80].



Thiosemicarbazides **1** upon ring closure with NaOH gave 5-(3-chloro-1-benzothien-2-yl)-*4H*-1,2,4-triazole-3-thiol derivative **138**, which exist in a tautomeric thiol-thione equilibrium as indicated by IR spectra [81].

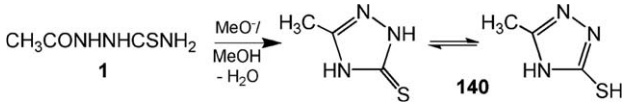


N^1-[5-(substituted phenoxymethyl)-1,3,4-oxadiazolyl-2-thioacetyl]-N^4-arylthiosemicarbazide derivatives **1** were cyclized with (2*N*) NaOH to give the corresponding triazole derivatives **139** in good yields [82].

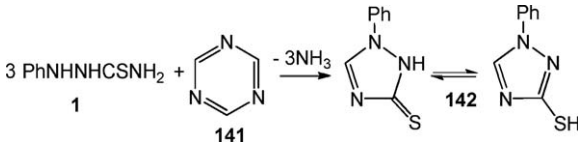


1,139: R = 4-CH_3; 4-chloro
R' = C_6H_5-, $C_6H_5CH_2$-, 3-Cl-C_6H_4, 2-CH_3O-C_6H_4

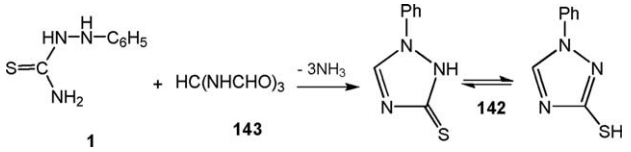
Substituted thiosemicarbazide **1** was also used as an initial substance to prepare 3-substituted-1,2,4-triazoline-5-thione. Thus, 1-acetylthiosemicarbazide **1** may cyclize with sodium methoxide in methanol to 3-methyl-1,2,4-triazoline-5-thione **140** [83].



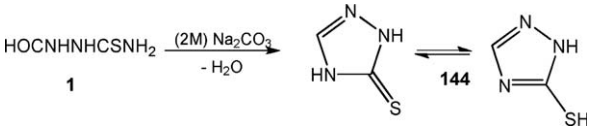
Cyclization of 1-phenylthiosemicarbazide **1** with s-triazine **141** led to 2-phenyl-1,2,4-triazoline-5-thione **142** in 80% yield [84].



A better yield (93%) of 2-phenyl-1,2,4-triazoline-5-thione **142** was prepared by means of a shortened method of direct cyclization of 1-phenylthiosemicarbazide **1** with triformylaminomethane **143** [85].

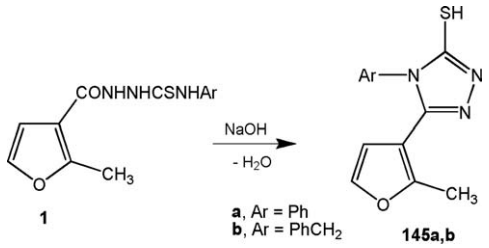


1,2,4-Triazoline-5-thione **144** can be obtained by cyclization of 1-formylthiosemi-carbazide **1** in 2.0*M* solution of sodium carbonate [86].

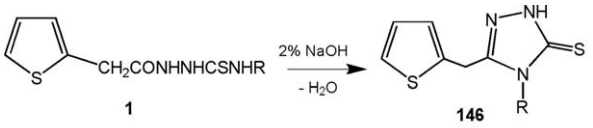


Heating of substituted thiosemicarbazides **1** in an aqueous sodium hydroxide solution afforded the

corresponding 3,4-disubstituted-1,2,4-triazole-5-thiol derivatives **145a,b** in good yields [87].

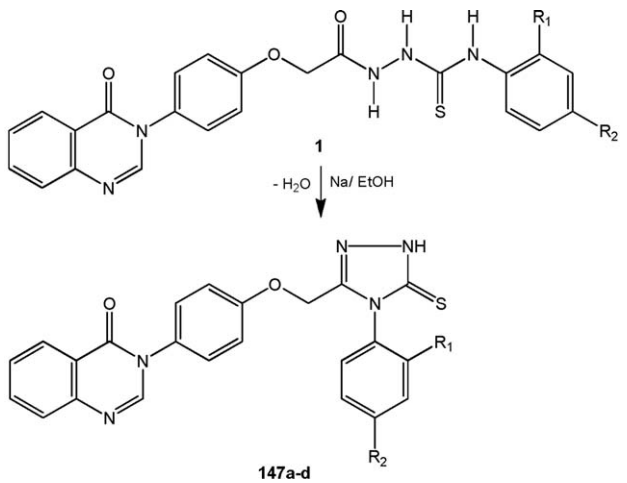


Substituted thiosemicarbazides **1** were subjected to cyclization in 2% of sodium hydroxide solution giving suitable 4-substituted-3-(thiophene-2-yl methyl)-Δ^2-1,2,4-triazoline-5-thione derivatives **146** [88].

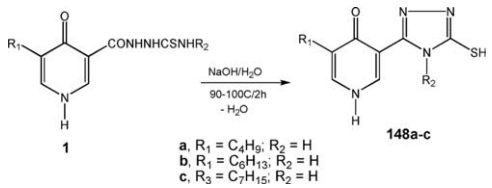


1,146: R= C_2H_5-; $CH_2C_6H_5$-; 4-CH_3-C_6H_4-; 4-CH_3O-C_6H_4-; 4-Br-C_6H_4-; 4-Cl-C_6H_4-

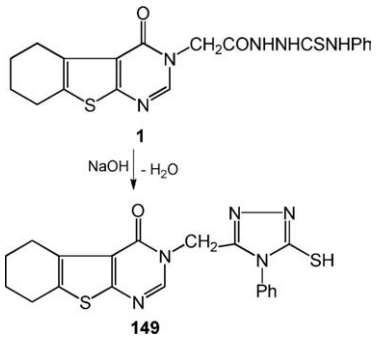
Thiosemicarbazide derivatives **1** on cyclization with sodium metal in ethanol gave 3-[4-(4-substituted phenyl-5-thioxo-4,5-dihydro-*1H*-[1,2,4]triazol-3-yl methoxy)-2-phenyl-*3H*-quinazolin-4-one derivatives **147a–d** in 56–65% yields [89].



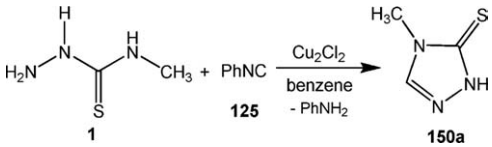
1-Acyl-4-substituted thiosemicarbazides **1** can be cyclized with base-catalysts to give 3-mercapto-*4H*-1,2,4-triazoles **148** [90].



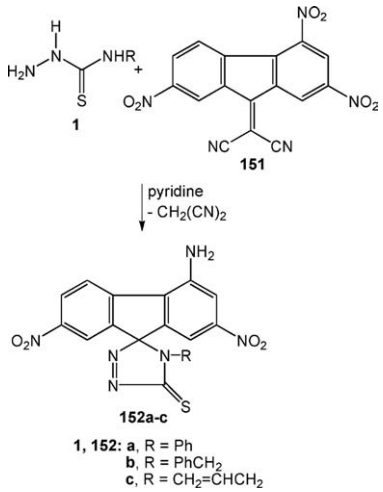
Cyclodehydration of thiosemicarbazide derivative **1** with sodium hydroxide resulted in the formation of *N*-phenyl mercaptotriazole derivative **149** in 65% yield [91].



Reaction between 4-methylthiosemicarbazide **1** with phenylisocyanide **125** in refluxing benzene with copper (I) chloride as catalyst gave almost exclusively 2,4-dihydro-4-methyl-3H-1,2,4-triazole-3-thione **150a** [75].

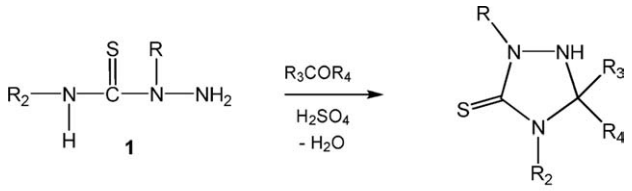


4-Substituted thiosemicarbazides **1** reacted with (2,4,7-trinitro-9*H*-fluoren-9-ylidene)propanedinitrile (DTF) **151** in pyridine with admission of air to form spiro[fluorene-9,3′-triazole] derivatives **152a–c** [92].



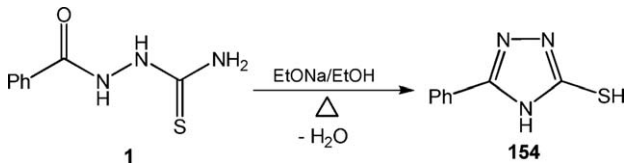
Cyclocondensation of substituted thiosemicarbazide derivatives with ketones in the presence of a catalytic amount of sulfuric acid is known to afford

triazolidinethione derivatives [93,94]. Thus, the reaction of thiosemicarbazides **1** with ketones afforded 4-alkenyl-1-aryl-3,3-disubstituted-1,2,4-triazolidine-5-thiones **153** [95].

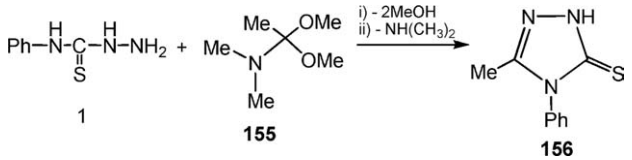


1, 153: R = C_6H_5; R_2 = $CH_2C(Me)=CH_2$
153: R_3 = Me, Et, Ph; R_4 = Me

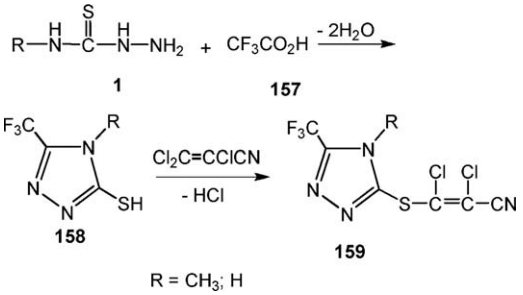
Heating of substituted thiosemicarbazide **1** in ethanol in presence of sodium ethoxide gave the corresponding 4*H*-5-mercapto-3-phenyl-1,2,4-triazole **154** in good yield [96].



Ring cyclization of the desired thiosemicarbazides **1** with dimethylacetamide dimethylacetal **155** [97] led to the corresponding triazoles **156** in good yields [98].

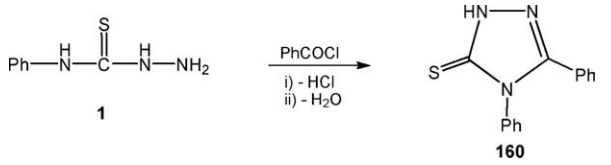


Substituted thiosemicarbazides **1** reacted with trifluoroacetic acid **157** to give the triazole derivatives **158**, which can be alkylated by reaction with 1,1,2-trichloro-2-cyanoethylene to give 4-substituted-5-trifluromethyl-3-(1,2-dichloro-2-cyanovinylthio)-1,2,4-triazoles **159** [99].

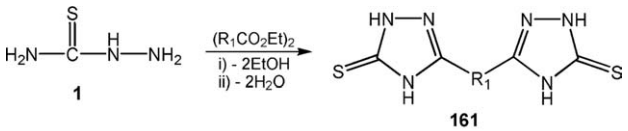


R = CH_3; H

4-Phenylthiosemicarbazide **1** on treatment with benzoyl chloride in boiling pyridine or alkali was reported to undergo *in situ* benzoylation and cyclization resulting in the formation of 4-phenyl-3-phenyl-Δ^2-1,2,4-triazoline-5-thione **160** [100].

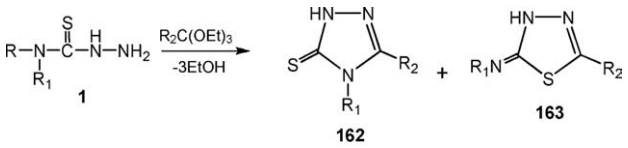


Reactions of aliphatic and aromatic esters with 4-alkyl/aryl thiosemicarbazides in the presence of sodium alkoxide afforded 1,2,4-triazoline-5-thiones [101]. Accordingly, 1,2,4-triazoline-5-thione was prepared by the reaction of thiosemicarbazide with ethyl formate in the presence of sodium methoxide [102]. With 1-benzyl/phenylthiosemicarbazide, 2-substituted triazole was formed [103,104]. The base catalyzed condensation of thiosemicarbazide **1** with alkyl or aryl dicarboxylic acid esters like diethyl malonate, diethyl tartrate afforded compounds containing two 1,2,4-triazoline-5-thione moieties linked through the 3-position by an alkyl chain **161** [103,104].



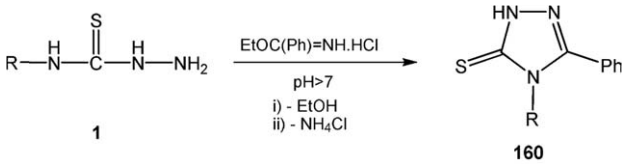
161: R_1 = -CH_2-; $C_2H_4O_2$

Similarly, 4-phenyl thiosemicarbazide on refluxing with ethyl orthoacetate in xylene, the product formed was 3-methyl-4-phenyl-Δ^2-1,2,4-triazoline-5-thione [105]. It has been reported that on heating a mixture of appropriately substituted thiosemicarbazides **1** and orthoesters, both 1,2,4-triazoline-5-thiones **162** and iminothiadiazole derivatives **163** [106,107] or in some cases just triazolinethiones alone were formed [108,109].



1: R, R_1 = H; Me
162,163: R_1 = H; Me
R_2 = H; Me; Ph

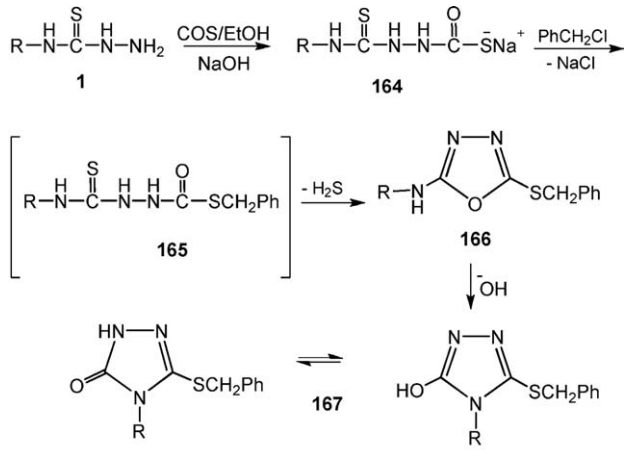
4-Phenyl thiosemicarbazide **1** reacted with ethylphenylimidate hydrochloride at pH > 7 and resulted in the formation of 3,4-bis(phenyl)-Δ^2-1,2,4-triazoline-5-thione **160** [110].



1, 160: R = Ph

Reaction of substituted thiosemicarbazides **1** with carboxysulphide in ethanol in the presence of sodium

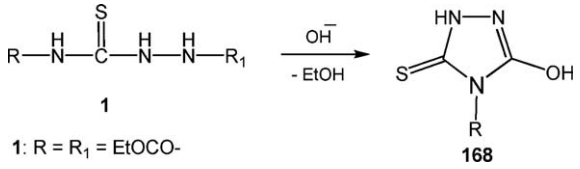
hydroxide gave β-(*N*-alkyl/arylthiocarbamyl)thiosemicarbazinates **164** [11].



1,**164-167**: R = *p*-CH_3-C_6H_4; C_6H_5; *p*-Cl-C_6H_4; *p*-CH_3-O-C_6H_4 ; CH_3

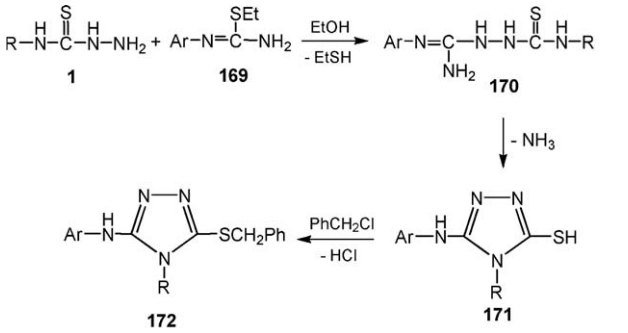
Benzylation of **164** gave 5-alkyl/arylamino-2-benzylmercapto-1,3,4-oxadiazoles **166**, which on refluxing in ethanolic sodium hydroxide afforded 4-aryl-3-benzylmercapto-1,2,4-triazolin-5-one **167** [111].

An attempted synthesis of thiosemicarbazide by Ohshiro *et al*. [112] resulted in its cyclization to the triazolinethione. Also, a similar reaction was reported by Elmoghayar *et al*. [113]; diacyl and diaroyl derivatives also are known to undergo cyclization under alkaline conditions [114–116]. The ring closure of 4-benzoyl-1-carbamoyl/ethoxycarbonylthiosemicarbazide in alkaline medium has been demonstrated independently by Kurzer *et al*. [116,117]. In continuation, Kurzer *et al*. depicted the formation of 3-hydroxy-Δ^2-1,2,4-triazoline-5-thione **168** from 1,4-diethoxycarbonyl thiosemi-carbazide **1** under alkaline condition [118].



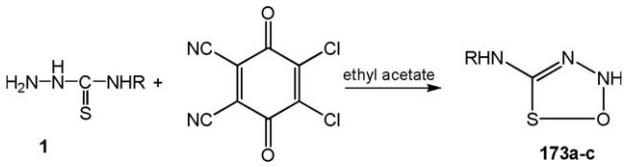
1: R = R_1 = EtOCO-

Reaction of substituted thiosemicarbazides **1** with 1-aryl-2-*S*-ethylisothiourea **169** in ethanol gave 3-mercapto-4-phenyl-5-phenylamino-1,2,4-triazole **171** through thiosemicarbazone derivatives **170**. When **171** treated with benzylchloride and alkali, it yielded triazole derivatives **172** [80].



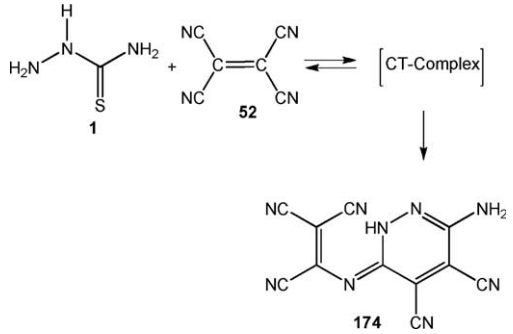
1, **170-172** : R = C_6H_5; *p*-CH_3O-C_6H_4; *p*-Cl-C_6H_4; *p*-CH_3-C_6H_4, *p*-C_2H_5-C_6H_4; *n*-C_4H_9; CH_3
169-172: Ar = C_6H_5; *p*-Cl-C_6H_4; *p*-CH_3-C_6H_4; *p*-C_2H_5O-C_6H_4; *p*-CH_3O-C_6H_4

3.9. Synthesis of oxathiadiazoles. 4-Substituted thiosemicarbazides **1** reacted with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) **68** in ethyl acetate ultimately gave oxathiadiazole derivatives **173a–c** through the formation of CT-complex [46].

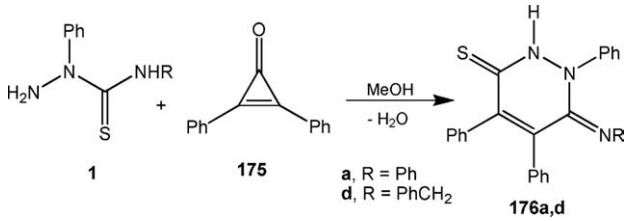


a; R = Ph
b; R = $PhCH_2$
c; R = CH_2=$CHCH_2$

3.10. Synthesis of pyridazines. Reaction of thiosemicarbazide with tetracyanoethylene (TCNE) **52** in ethyl acetate at room temperature gave the pyridazine derivative **174** through the formation of CT-complex [71].

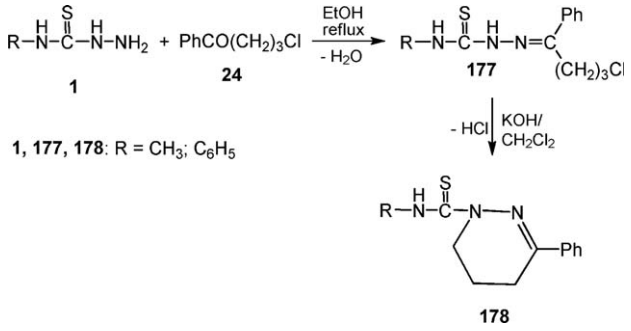


The reaction of 2,4-disubstituted thiosemicarbazides **1** with 2,3-diphenylcyclopropenone **175** in MeOH afforded pyridazine derivatives **176a,d** [119].



1 175 176a,d

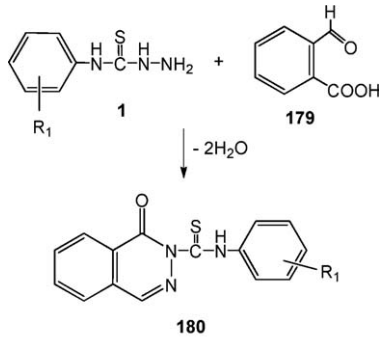
Thiosimicarbazides **1** react with 4-chloro-1-phenylbutan-1-one **24** in ethanol at room temperature, the corresponding thiosemicarbazones intermediate **177** formed then readily cyclized to pyridazino-thiocarboxamide **178** by treatment with potassium hydroxide in dichloromethane in presence of a catalytic amount of benzyltriethylammoniumchloride at room temperature [44].



1 24 177 178

1, 177, 178: R = CH_3; C_6H_5

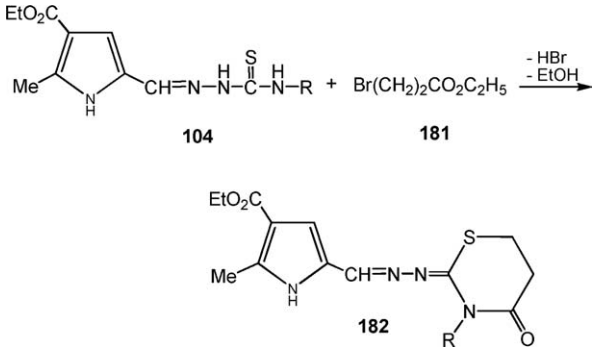
Refluxing substituted thiosemicarbazides **1** with cyclohexanone in ethanol gave cyclohexanone-4-alkyl thiosemicarbazones [120]. On the other hand, substituted thiosemicarbazides **1** reacted with 2-carboxybenzaldehyde **179** in acetic acid to give 1-(substituted) thioanilido-8-keto-3-substituted benzopyridazines **180** [121].



1 179 180

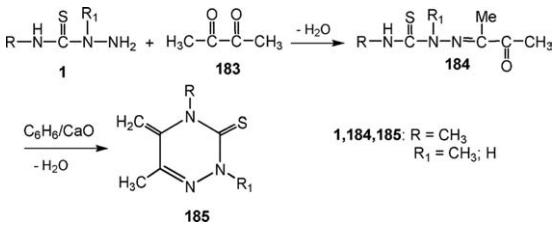
1,203 R_1 = H; 4-Cl; 2-CH_3; 3-CH_3; 4-CH_3

3.11. Synthesis of thiazine derivatives. Substituted thiosemicarbazbides **1** reacted with (3-ethoxycarbonyl)-2-methyl pyrrole-5-carboxaldehyde **103** to yield 3-(ethoxycarbonyl)-2-methylpyrrole-5-carbox-aldehyde(-thiocarbonyl)hydrazones **104** [67]. **104** Reacted with ethyl 3-bromo-propanoate **181** in refluxing ethanol to yield substituted-3-(ethoxycarbonyl)-2-methyl-pyrrole-5-carboxaldehyde-3-substituted-5,6-dihydrothiazin-4-one-2-ylidene)hydrazones **182** [67].



104 181 182

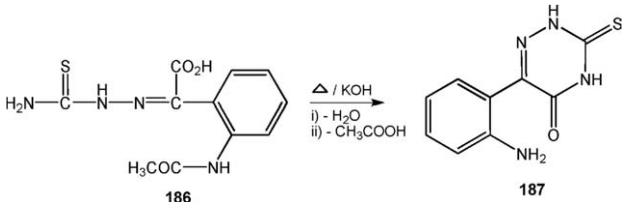
3.12. Synthesis of triazines.. The reaction of thiosemicarbazides **1** with diketones, such as **183**, gave thiosemicarbazones **184**, which when refluxed in benzene over CaO gave triazine derivatives **185** [122].



1 183 184 185

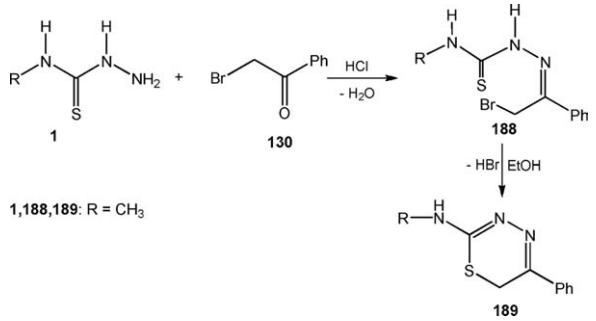
1,184,185: R = CH_3
R_1 = CH_3; H

Thiosemicarbazone derivatives **186** when heated with aqueous KOH it gave triazinone derivatives **187** [123].



186 187

3.13. Synthesis of thiadiazines.. The reaction of substituted thiosemicarbazides **1** with 2-bromo-1-phenylethan-1-one **130** in 2.0*M* hydrochloric acid initially provide the corresponding thiosemicarbazones **188**, followed by cyclization to 2-amino-5-aryl-*6H*-1,3,4-thiadiazines **189** upon boiling in ethanol [44].

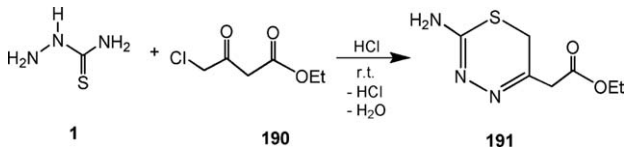


1 130 188 189

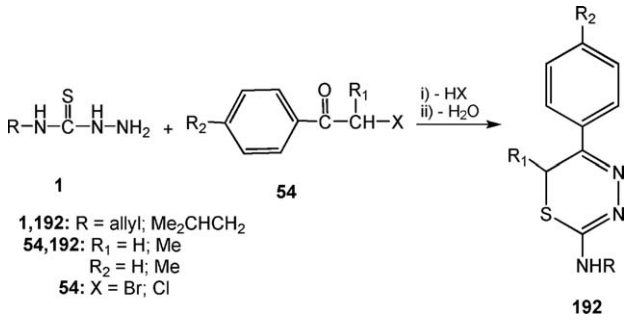
1,188,189: R = CH_3

Thiosemicarbazide condensed with γ-haloketoesters such as ethyl-4-chloroacetoacetate **190** in acidic medium

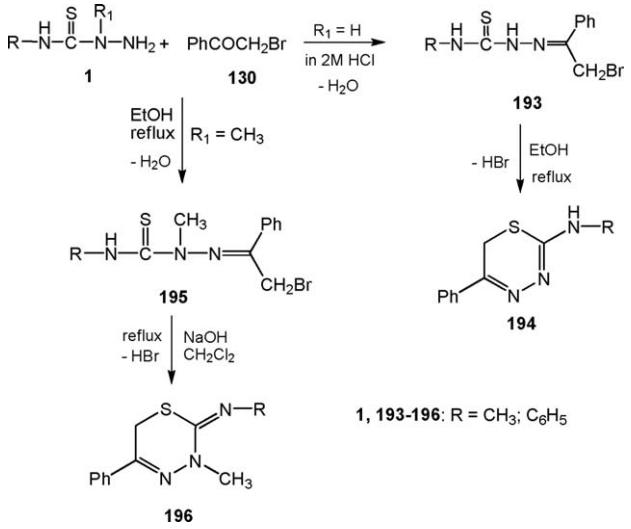
(HCl) at room temperature to give ethyl-2-amino-6*H*-1,3,4-thiadiazine-5-acetate hydrochloride **191** [48].



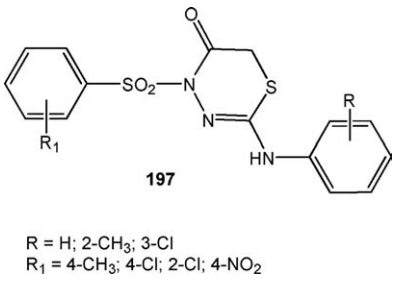
Substituted thiosemicarbazides **1** reacted with α-haloketones **54** to give 1,3,4-thiadiazine derivatives **192** [49,124–128].



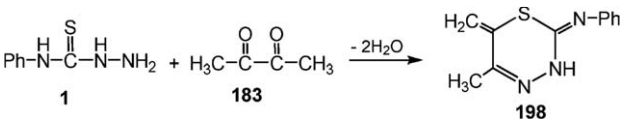
On the reaction between substituted thiosemecarbazides **1** (R_1 = H) and 2-bromo-1-phenylethan-1-one **130** in warm 2.0*M* of HCl, the corresponding thiosemecarbazones **193** were formed followed by cyclization to 1,3,4 thiadiazines **194** [129]. On the other hand, disubstituted thiosemicarbazide **1** (R_1 = CH_3) reacted with bromo-1-phenylethan-1-one **130** in ethanol at room temperature in absence of acid catalyst to give thiosemicarbazones **194**, which cyclized in alkaline medium to 5-phenyl-2,3-dihydro-6*H*-1,3,4 thiadiazines **195** [44].



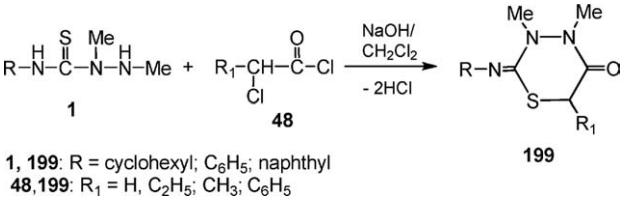
When chloroacetylchloride reacted with sulfonyl derivatives of **1**, substituted 1,3,4-thiadiazinone **197** was formed [130].



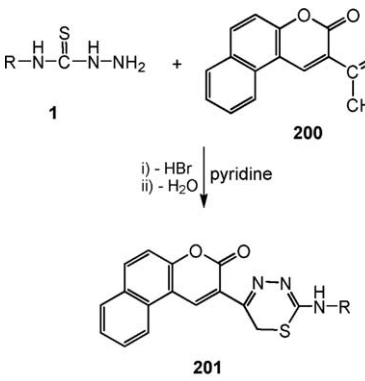
4-Phenylthiosemicarbazide **1** reacted with diketone **183** in methanol for one day to give thiadiazine derivative **198** [122].



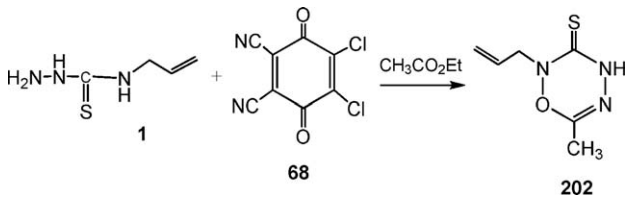
1,2-Dichloro-2-substituted ethan-1-one **48** also reacted with 1-substituted-2,3-dimethylthiosemicarbazides **1** in aqueous base to form 2-imino-1,2,3-tetrahydro-3,4-dimethyl-1,3,4-thiadiazin-5-ones **199** [37,38].



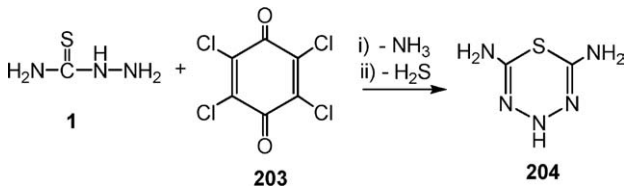
Reaction of substituted thiosemicarbazides **1** with 3-(bromoacetyl)coumarine **200** in the presence of pyridine gave the thiadiazine derivatives **201** [131].



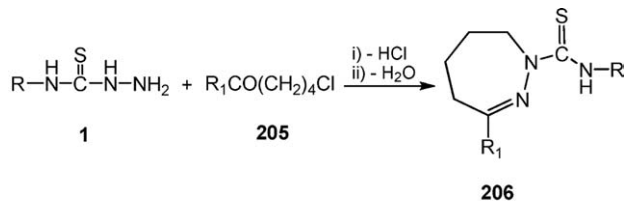
3.14. Synthesis of oxatriazines. 4-Allyl thiosemicarbazide **1** reacted with 2,3-dichloro-5,6-dicyano-1,4-benzo-quinone (DDQ) **68** in ethyl acetate ultimately gave oxatriazine derivative **202** through the formation of CT-complex [46].



3.15. Synthesis of thiatriazene derivative. Mixing two fold molar excess of 2,3,5,6-tetrachloro-1,4-benzoquinone (CHL-*p*) **203** with one mol of thiosemicarbazide **1** lead to the formation of an initial CTC followed by immediate chemical reaction, which was completed after a few days, and besides diaminothiatriazine **204** was isolated [71].



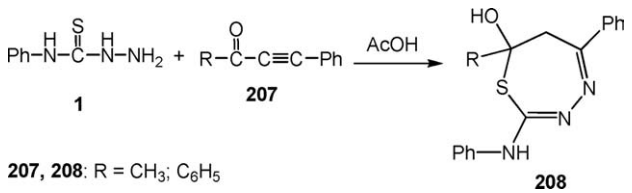
3.16. Synthesis of diazepines. The reaction of substituted thiosemicarbazides **1** with 5-chloro-1-substituted pentan-1-one **205** [97] yielded derivatives of tetrahydro-1,2-diazepine ring system **206** [98].



1,206: R = CH_3; C_2H_5; C_6H_5
205,2206: R_1 = C_6H_5; 4-CH_3-C_6H_4; 4-CH_3O-C_6H_4; 4-Cl-C_6H_4

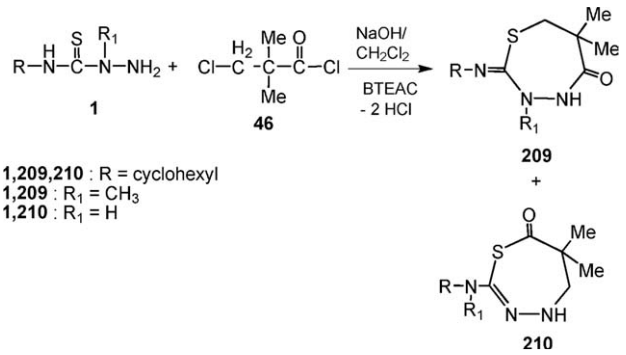
3.17. Synthesis of thiadiazepines.

3.17.1. From acetylene derivatives. Reaction of 4-phenylthiosemicarbazides **1** with acetylene derivatives **207** in presence of acetic acid afforded thiadiazepines **208** [132].



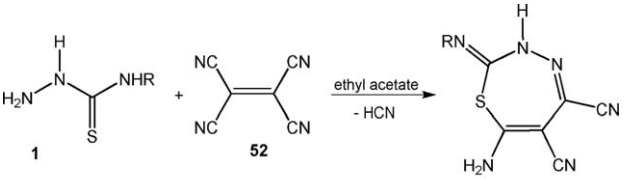
207, 208: R = CH_3; C_6H_5

3.17.2. From β-chloroacylhalide. Reaction of 4-cyclohexylthiosemicarbazides **1** with 3-chloro-2,2-dimethylpropanoyl chloride **46** in 5% aqueous NaOH/CH_2Cl_2 in presence of benzyltriethyl-ammonium chloride (BTEAC) gave 1,3,4-thiadiazepine derivatives **209** and **210** [37,38].



1,209,210 : R = cyclohexyl
1,209 : R_1 = CH_3
1,210 : R_1 = H

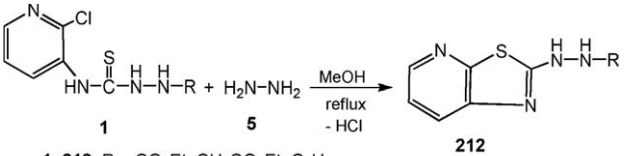
3.17.3. From ethenetetracarbonitrile. Thiosemicarbazides **1** reacted with TCNE **52** in ethyl acetate with admission of air to afford a mixture of different compounds among of them thiadiazepine derivatives **211a,b** [40].



a, R = Ph
b, R = $PhCH_2$

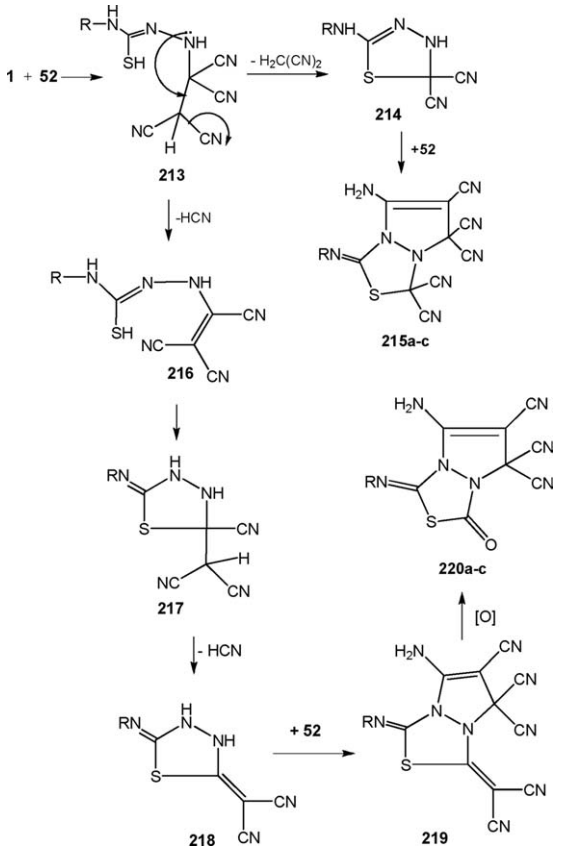
3.18. Synthesis of some fused heterocylic systems.

3.18.1. Thiazolopyridines. When pyridine derivatives of **1** was refluxed with hydrazine hydrate **5** in methanol, 2-aminothiazolo[5,4-*b*]pyridine **212** was formed [69].

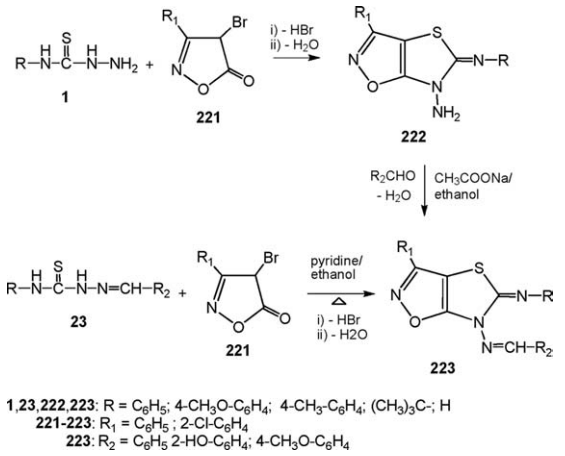


1, 212: R = CO_2Et; CH_2CO_2Et; C_6H_5

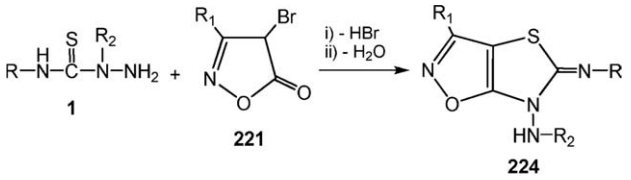
3.18.2. Pyrazolothiadiazoles. Thiosemicarbazides **1** reacted with TCNE **52** in ethyl acetate with admission of air to afford a mixture of different compounds among of them pyrazolo[1,2-*c*]thiadiazole derivatives **215a–c** and **220a–c** [40]. The mechanism of the reaction is suggested to proceed as the following:



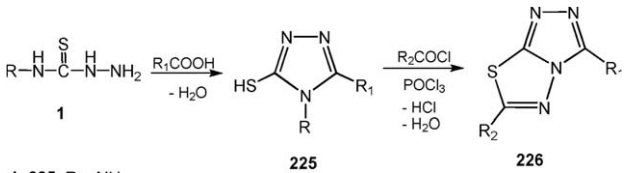
3.18.3. Thiazoloisoxazoles. Substituted thiosemicarbazides **1** reacted with heterocyclic haloketones such as 4-bromo-3-substituted-(4*H*)-isoxazol-5-ones **221** in refluxing ethanol in presence of pyridine to afford 6-amino-5-alkyl/arylimino-3-substituted-thiazolo[5,4-*d*]isoxazoles **222**, which reacted with aldehydes in presence of sodium acetate to afford Schiff's bases **223** which can be prepared by interaction between thiosemicarbazone **23** with **221** [133].



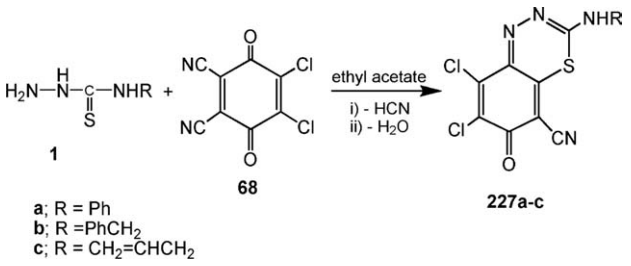
Substituted thiosemicarbazides **1** and **221** under similar conditions gave 6-anilino- 5-arylimino-3-substituted thiazolo[5,4-*d*]isoxazoles **224** [133].



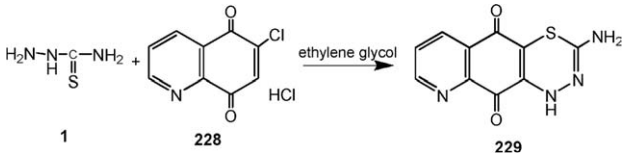
3.18.4. Triazolothiadizoles. The condensation of substituted thiosemicarbazides **1** with aliphatic and aromatic carboxylic acids led to one of the choicest methods for the preparation of 3-alkyl/aryl-4-amino-Δ^2-1,2,4-triazoline-5-thiones [108,134–137]. Reaction of **1** with carboxylic acids at their melting points afforded 5-substituted-4-amino-3-mercapto-1,2,4-triazole **225**, which easily reacted with carboxylic acids or acid chlorides and affording the 1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole ring system **226** [138].



3.18.5. Benzothiadiazines. 4-Substituted thiosemicarbazides **1** reacted with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) **61** in ethyl acetate ultimately gave benzothiadiazine derivatives **227a–c** through the formation of CT-complexes [46].

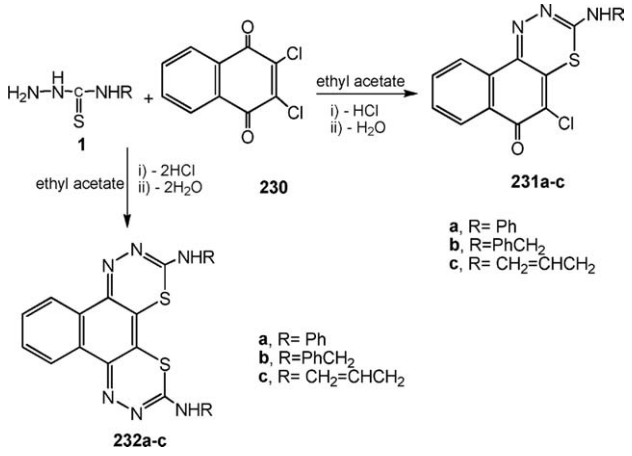


Reaction of thiosemicarbazides **1** with 6-chloroquinolin-5,8-dione hydrochloride **228** in ethylene glycol gave thiadiazino[6,5-g]quinoline-5,10-dione **229** which showed remarkable biological activity [139].

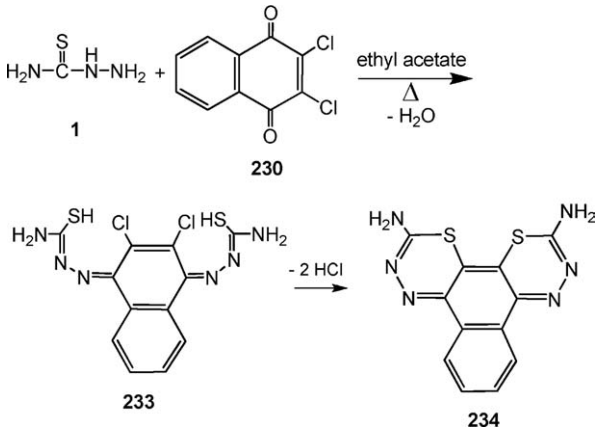


Mixing equimolar amounts of 4-substituted thiosemicarbazides **1** with 2,3-dichloro-1,4-naphtho-quinone

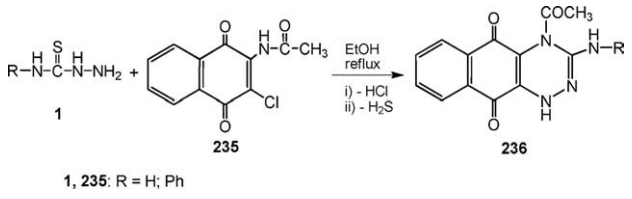
(DCHNQ) **230** in ethyl acetate led to the formation of thiadiazine derivatives **231a–c** and **232a–c** [46].



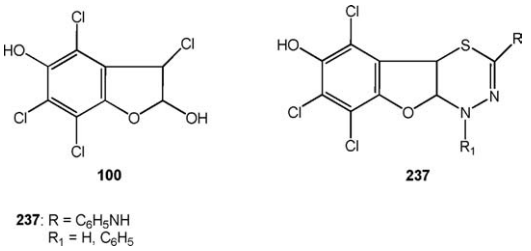
By heating equimolar amounts of thiosemicarbazide **1** and 2,3-dichloro-1,4-naphthoquinone (DCHNQ, **230**) in ethyl acetate yielded the thiadiazine derivatives **234** [71].



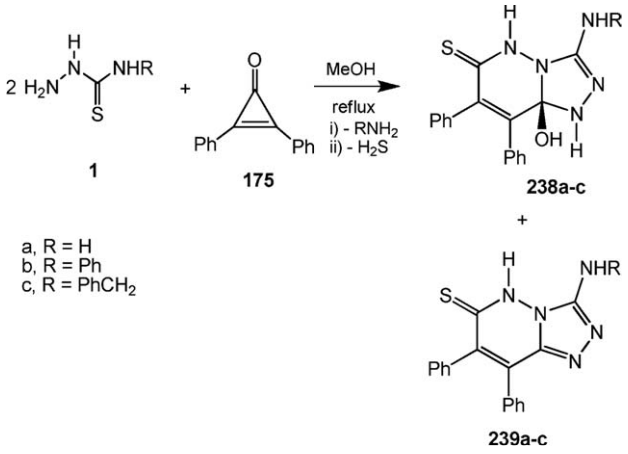
3.18.6. Naphthotriazines. The reaction of substituted thiosemicarbazides **1** with 2-acetamido-3-chloro-1,4-naphthoquione **235** in ethanol under reflux gave naphtho[2,3-*e*]-1,2,4-triazine-5,10-diones **236** [140].



3.18.7. Benzofurothiadiazines. Reaction of substituted thiosemicarbazides with tetrachlorodihdrobenzofurandiol **100** gave benzofuro-1,3,4-thiadiazines **237** [141].



3.18.8. Triazolopyridazines. Thiosemicarbazide **1** reacted with 2,3-diphenylcyclo-propenone **175** in MeOH afforded triazolopyridazine derivatives **238a–c** and **239a–c** [119,142].



REFERENCES AND NOTES

[1] Zelenin, K. N.; Solod, O. V.; Alekseev, V. V.; Pekhk, T. I.; Kuznetsova, O. B.; Terent'ev, P. B.; Kalandarishvili, G. Chem Heterocycl Compd 1990, 26, 1051.

[2] Chernyshev, V. M.; Kosov, A. E.; Gladkov, E. S.; Shishkina, S. V.; Taranushich, V. A.; Desenko, S. M.; Shishkin, O. V. Russ Chem Bull Int Ed 2006, 55, 388.

[3] El-Essawy, F. A.; Khattab, A. F.; Abdel-Rahman, A. A.-H. Monatsh Chem 2007, 138, 777.

[4] Hovsepian, T. R.; Dilanian, E. R.; Engoyan, A. P.; Melik-Ohanjanian, R. G. Chem Heterocycl Compd 2004, 40, 1194.

[5] Öztür, Ö. F. Trans Metal Chem 2007, 32, 224.

[6] Çapan, G.; Ulusoy, N.; Ergenç, N.; Kiraz, M. Monatsh Chem 1999, 130, 1399.

[7] Neidlein, R.; Ober, W.-D. Monatsh Chem 1976, 107, 1252.

[8] Shagun, L. G.; Ermolyuk, L. P.; Sarapulova, G. I.; Dorofeev, I. A.; Voronkov, M. G. Chem Heterocycl Compd 2005, 41, 946.

[9] Fathalla, W.; Pazdera, P. International Conference on Synthetic Organic Chemistry (ECSOC-11), Switzerland, November 1–30, 2007. Available at: http://www.usc.es/congresos/-ecsoc/11/ECSOC11.htm.

[10] Noto, R.; Lo Meo, P.; Gruttadauria, M.; Werber, G. J Heterocycl Chem 1999, 36, 667.

[11] Schultz, O. E.; Barthold, E. Arch Pharm (Weinheim) 1952, 585, 267.

[12] Hodgkins, J. E.; Ehlinger, M. G. J Org Chem 1956, 21, 404.

[13] Hodgkins, J. E.; Recves, W. P.; Liu, U. T. G. J Am Chem Soc 1961, 83, 2532.

[14] Jensen, K. A.; Barcaro, H. R.; Buchardt, O.; Olsen, G. G.; Pedersen, C.; Toft, J. Acta Chem Scand 1961, 15, 1109.

[15] Busch, M.; Ulmer, T. Chem Ber 1902, 35, 1710.

[16] Raiford, L. C.; Daddow, W. T. J Am Chem Soc 1931, 53, 1552.

[17] Aanandhi, V. M.; George, S.; Vaidhyalingam, V. Arkivoc 2008, (xi), 187.

[18] Agrawal, K. C.; Booth, B. A.; Denuzzo, S. M.; Sartolli, A. C. J Med Chem 1976, 19, 1209.

[19] El-Gaby, M. S. A.; El-Sherief, A. M. S.; Atalla, A. A.; El-Adasy, A. A. A. J Chin Chem Soc 2004, 15, 327.

[20] Easmon, J.; Heinisch, G.; Holzer, W.; Rosenwirth, B. J Med Chem 1992, 35, 2188.

[21] Jampilek, J.; Opletalova, V.; Pour, M.; Kunes, J.; Silva, L.; Buchta, V.; Richardson, D. R.; kalinowski, D. S.; Al-Hallak, L.; Honcova, D. Book of abstract of the Joint Meeting 2006, Marburg (Germany), October 4–7, C-76, 2006.

[22] Jampilek, J.; Opletalova, V.; Donhal, J. 10th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-10), Switzerland, November 1–30, 2006. Available at: http://www.usc.es/congresos/ecsoc/10/ECSOC10.htm

[23] Singh, A. K.; Trikha, K. C.; Singh, R. P.; Katyal, M. Talanta 1975, 22, 551.

[24] Garland, R. B.; Miyano, M. U. S. US 4,973,604 (Cl. 514–562, A61k31/ 195) (1990), Appl 283,669 (1988), 24 pp; Chem Abstr 1991, 115, 114058y.

[25] Dvorkin, A. A.; Gifeisman, T. Sh.; Simonov, Yu. A.; Andronati, S. A.; Pavlovskii, V. I.; Yavorskii, A. S.; Ssr, D. A. N.; Geol, S. B. Khim Biol Nauki 1987, 11, 35; Chem Abstr 1989, 111, 133738d.

[26] Commons, T. J.; Masial, C. L.; Christman, S.; USA U. S. US 6,008,362 (Cl. 546–331; C07D211/70) (1999), Us Appl 49,654,16; Chem Abstr 2000, 132, 49788w.

[27] Omar, A. M. M. E.; Shams El-Dine, S. A.; Labouta, I. M.; El-Tombary, A. Alex J Pharm Sci 1988, 2, 176.

[28] Omar, A. M. M. E.; Chaaban, I.; Hassan, A. M. M.; Ismail, K. A. A.; Abou-Shleib, H. Alex J Pharm Sci 1987, 1, 17.

[29] Salman, A.; Ates, Ö.; Cesur, N.; Ötük, G. Arch Pharm (Weinheim) 1991, 324, 55.

[30] Lemke, T. L.; Shak, T. W.; Cates, L. A.; Smith, L. K. J Med Chem 1977, 20, 1351.

[31] Radics, U.; Liebscher, J.; Ziemer, B.; Rybakov, V. Chem Ber 1942, 125, 1389.

[32] Rahman, M. F. Indian J Chem 1980, 19B, 828.

[33] Kassem, E. M.; Kamel, M. M.; El-Zahar, M. Pharmazie 1990, 45, 215.

[34] Varma, R.; Gupta, K.; Amar, N.; Misra, V.; Indian J Microbiol 1964, 4, 63; Chem Abstr 1966, 64, 13124j.

[35] Kamel, M. M. Pharmazie 1982, 37, 147.

[36] Cricchio, R.; Cietto, G.; Rossi, E.; Aridi, V. Farmaco Ed Sci 1973, 30, 695; Chem Abstr 1975, 83, 192973c.

[37] Okawara, T.; Kato, R.; Yamaski, T.; Yasuda, N.; Furukawa, M. Heterocycles 1986, 24, 4.

[38] Okawara, T.; Kato, R.; Yasuda, N.; Yamasaki, T.; Furukawa, M. J Chem Res (S) 1987, 254.

[39] Patel, V. M.; Desai, L. R. Arkivoc 2004, (i), 123.

[40] Hassan, A. A.; Mohamed, N. K.; Shawky, A. M.; Döpp, D. Arkivoc 2003, (i), 118.

[41] Rádl, S. Collect Czech Chem Commun 1992, 57, 656.

[42] Mokhtar, H. M.; Faid-Allah, H. M. Pharmazie 1987, 42, 7.

[43] Abdel Sayed, N. I. Egypt J Chem 1999, 42, 175.

[44] Tomita, Y.; Kabashima, S.; Okawara, T.; Yamasaki, T.; Furukawa, M. J Heterocycl Chem 1990, 27, 707.

[45] Jones, W. D., Jr.; Kane, J. M.; Still, A. D. J Heterocycl Chem 1983, 20, 1359.

[46] Hassan, A. A.; Ibrahim, Y. R.; Shawky, A. M. J Sulfur Chem 2007, 28, 211.

[47] Mohamed, S. F.; Youssef, M. M.; Amr, A. E.; Kotob, E. R. Sci Pharm 2008, 76, 279.

[48] Campaigne, E.; Selby, T. P. J Heterocycl Chem 1978, 15, 401.

[49] Pfeiffer, W. D.; Dilk, E.; Bulka, E. Z Chem 1977, 17, 218; Chem Abstr 1977, 87, 135147v.

[50] Beyer, H.; Hohn, H.; Lassig, W. Chem Ber 1952, 85, 1132.

[51] Mohareb, R. M.; Shams, H. Z.; Yehia, M. E. Phosphorus Sulfur Silicon Relat Elem 1992, 72, 93.

[52] Beyer, H.; Wolter, G. Chem Ber 1956, 89, 1652.

[53] Gautam, C.; Sikka, L. J Indian Chem Soc 1998, 75, 427.

[54] Beyer, H.; Henseke, G. Chem Ber 1950, 83, 247.

[55] El-Ablak, F. Z.; Etman, H. A.; Metwally, M. A.; Am, F. A. Pharmazie 1995, 50, 222.

[56] Mohareb, R. M.; Shams, H. Z.; Aziz, S. I. Sulfur Lett 1991, 13, 101.

[57] Yadav, L. D. S.; Singh, S. Indian J Chem 2001, 40B, 440.

[58] Mamedov, V. A.; Krokhina, L. V.; Berdnikov, E. A.; Levin, Y. A. Khim Geterotsikl Soedin 1996, 9, 1266; Chem Abstr 1997, 126, 89345g.

[59] Kabashima, S.; Tomita, Y.; Okawara, T.; Yamasaki, T.; Furukawa, M. Heterocycles 1990, 31, 2139.

[60] Amal, H.; Ates, O.; Salman, A. Doga Seric 1980, 4, 13; Chem Abstr 1982, 96, 52232d.

[61] Cortes, E.; Martinez, R.; Gutierrez, G.; Martha, B. J Heterocycl Chem 1991, 28, 1413.

[62] Omar, A. M. M. E.; Ahmed, I. C.; Aboul Wafa, O. M.; Hassan, A. M.; Abou-Shleib, H.; Ismail, K. A. Alex J Pharm Sci 1989, 3, 211.

[63] Omar, A. M. M. E.; Ahmed, I. C.; Hassan, A. M.; Aboul Wafa, O. M.; Abou-Shleib, H.; Ismail, K. A. Alex J Pharm Sci 1990, 4, 182.

[64] Dimri, A. K.; Parmar, S. S. J Heterocycl Chem 1978, 15, 335.

[65] Farghally, A. M.; Habib, N. S.; Hazzaa, A. A. B.; El-Sayed, O. A. J Pharm Belg 1985, 40, 360.

[66] Karlivan, G. A.; Valter, R. E.; Batse, A. E.; Gulbis, Y. V. Khim Geterotsikl Soedin 1996, 10, 1424; Chem Abstr 1997, 126, 89301q.

[67] Mokhtar, H. M.; El-Sayed, O. A.; El-Sabaeny, A. H. Bull Pharm Sci, Assiut University 1995, 18, 59.

[68] Mohareb, R. M.; Sherif, S. M. J Heteroatom Chem 1997, 8, 77.

[69] Koren, B.; Stanovnik, B.; Tišler, M. Monatsh Chem 1988, 119, 333.

[70] Amir, M.; Kumar, S. Acta Pharm 2007, 57, 31.

[71] Hassan, A. A.; Ibrahim, Y. R.; Semida, A. A.; Mourad, A. E. Liebigs Ann Chem 1994, 989.

[72] Hejsek, M.; Wiedermannova, I. Acta Univ Polacki Fac Rer Nat Chemica 2001, 40, 15.

[73] Prasanna, B.; Chandramouli, G. V. P. Phosphorus Sulfur Silicon 2004, 179 2059.

[74] Matysiak, J.; Niewiadomy, A. Synth Commun 2006, 36, 1621.

[75] Treppendahl, S.; Jakobsen, P. Acta Chem Scand 1977, 32B, 264.

[76] Hassan, S. Y.; Faidallah, H. M.; El-Massry, A. M.; Al Hazia, M. A.; El-Sadek, M. M. J Saudi Chem Soc 1999, 3, 171.

[77] Khalil, M. A.; Habib, N. S. Farmaco Ed Sci 1987, 42, 973; Chem Abstr 1988, 109, 210994x.

[78] Shen, T. Y.; Clark, R. L.; Robert, L.; Pessolano, A. A. S African 7503,527 (Cl. C07D) (1976), US Appl. 491,205 (1947); 26 pp; Chem Abstr 1977, 86, 72662r.

[79] Hassan, A. A.; Mourad, A. E.; El-Shiab, K. M.; Abou-Zied, A. H.; Döpp, D. Heteroatom Chem 2003, 14, 535.

[80] Joshua, C. P.; Annie, V. J Indian Chem Soc 1990, 67, 759.

[81] (a) Sharba, A. H. K.; Al-Bayati, R. H.; Aouad, M.; Rezki, N. Molecules 2005, 10, 1161; (b) Henichart, J.; Houssin, R.; Lablanche, B. J Heterocycl Chem 1977, 14, 615.

[82] Sengupta, A. K.; Garg, M. Def Sci 1981, 31, 91.

[83] Wohl, A.; Marckwald, W. Chem Ber 1889, 22, 576.

[84] Grudmann, C. J.; Kreutzberber, A. J Am Chem Soc 1957, 79, 2839.

[85] Dobosz, M. Ann UMCS Lublin sectio AA 34; 1979, 18, 163.

[86] Orient, J.; Martinova, O.; Hedlicka, J.; Pochalik, J Czech 1978, CS200, 559; Chem Abstr 1983, 99, 139946a.

[87] Shehata, I. A. Saudi Pharm J 2003, 11, 87.

[88] Wujec, M.; pitucha, M.; Dobosz, M.; Kosikowska, U.; Malm, A. Acta Pharm 2004, 54, 251.

[89] Havalder, F. H.; Patili, A. R. E J Chem 2008, 5, 347.

[90] Balogh, M.; Hermecz, I.; Meszaros, Z.; Pusztay, L. J Heterocycl Chem 1980, 17, 175.

[91] Ghorab, M. M.; Abdel-Hamide, S. G. Phosphorus Sulfur Silicon 1995, 106, 9.

[92] Hassan, A. A.; Ibrahim, Y. R.; Shawky, A. M.; Döpp, D. J Heterocycl Chem 2006, 43, 849.

[93] Sandstrom, J. Acta Chem Scand 1960, 14, 1037.

[94] Korzycka, L.; Glowka, M.; Janicka, J. J Polym Chem 1998, 72, 73; Chem Abstr 1998, 128, 217332f.

[95] Schulze, K.; Richter, C.; Ludwig, R.; Klatt, K. Z Chem 1988, 28, 288; Chem Abstr 1989, 110, 154304d.

[96] Creangă, A. A.; Bercean, V. N.; Badea, V.; Ledeti, I.; Csunderlik, C. Chem Bull ''POLITEHNICA'' Univ (Timişora) 2008, 53, 1.

[97] Pesson, M.; Antoine, M. C. R. Acad Sci Paris 1961, 253, 285.

[98] De Rosa, M. Bioorg Med Chem Lett 2006, 16, 4444.

[99] Aoyagi, E. I. U. S. US 4,477,459 (Cl. 424–269, Ao1n43164) (1984), Appl 518,340 (1983); Chem Abstr 1985, 102, 95652a.

[100] Fromm, P.; Kappeler, R.; Feniger, M.; Krauss, P.; Schwanenfeld, M.; Wetternik, L. Ann 1926, 447, 294.

[101] Pesson, M.; Polmanss, G.; Dupin, S. Comput Rend 1959, 248, 1677; Chem Abstr 1959, 53, 21904h.

[102] Willems, J. F.; Vandenberghe, A. Bull Soc Chim Belg 1966, 75, 358.

[103] Boots, S. G.; Cheng, C. C. J Heterocycl Chem 1967, 4, 272.

[104] Kovalev, E. G.; Postovskii, I. Y. Khim Geterotsikl Soedin 1968, 4, 740; Chem Abstr 1969, 70, 37729r.

[105] Reynolds, G. A.; Van Allan, J. A. J Org Chem 1959, 24, 1478.

[106] Ainsworth, C. J Am Chem Soc 1956, 78, 1973.

[107] Coburn, R. A.; Bhooshan, B.; Glennon, R. A. J Org Chem 1973, 38, 3947.

[108] Kroeger, C. F.; Beyer, H.; Busse, G.; Justus Liebigs Ann Chem 1960, 637, 135.

[109] Kanaoka, M. J Pharm Soc (Jpn) 1955, 75, 1149; Chem Abstr 1956, 50, 5647a.

[110] Weidinger, H.; Kranz, J. Chem Ber 1963, 96, 1059.

[111] Chande, M. S.; Karnikt, A. V.; Inamdar, A. N.; Damle, S. D. Indian J Chem 1991, 30B, 430.

[112] Ohshiro, Y.; Ando, N.; Komatsu, M.; Agawa, T. Synthesis 1985, 3, 276.

[113] Elmoghayar, M. R. H.; Elghandour, A. H. H. E. Monatsh Chem 1986, 117, 201.

[114] Wojahn, H. Arch Pharm (Weinheim) 1952, 285, 122.

[115] Hoggarth, E. J Chem Soc 1950, 614.

[116] Kurzer, F.; Hanks, D. R. Chem Ind (London) 1966, 1143; Chem Abstr 1967, 66, 115651t.

[117] Kurzer, F.; Hanks, D. R. J Chem Soc 1967, 746.

[118] Kurzer, F.; Secker, J. L. J Heterocycl Chem 1989, 26, 355.

[119] Aly, A. A.; Hassan, A. A.; Gomaa, M. A.-M.; El-Sheref, E. M. Arkivoc 2007, (xiv), 1.

[120] Zhao, W.; Zhao, M. Huaxue Shiji 1999, 21, 40; Chem Abstr 1999, 130, 223003g.

[121] Chaturuedi, B.; Tiwari, N.; Nizamuddin, K. Indian J Pharm Sci 1988, 50, 316; Chem Abstr 1989, 111, 70577c.

[122] Zelenin, K. N.; Alekssev, V. V.; Pehk, T.; Kuznetsou, O. B. Khim Geterotsikl Soedin 1989, 9, 1288; Chem Abstr 1990, 112, 216883u.

[123] Tomchin, A. B.; Krylova, I. M. Zh Org Khim 1986, 22, 2420; Chem Abstr 1987, 107, 175824b.

[124] Jones, W. D., Jr.; Miller, F. P. Ger Offen 3,031,703 (Cl. C07D285/16) (1981); Chem Abstr 1981, 95, 81033z.

[125] Miller, F. P.; Jones, W. D. Belg 884,990 (Cl. C07D) (1980); Chem Abstr 1981, 95, 62276q.

[126] Merrell, R. Inc Neth Appl Nl 8006,206 (Cl. C07D285/16) (1982); Chem Abstr 1982, 97, 216243g.

[127] Jones, W. D.; Miller, F. P. Belg 884,991 (Cl. C07D) (1980); Chem Abstr 1981, 95, 115618m.

[128] Jones, W. D., Jr.; Miller, F. P. U.S. Us 4,309,426 (Cl. 424–246; A61K31/54) (1982); Chem Abstr 1982, 96, 181317j.

[129] Busby, R. E.; Domineg, T. W. J Chem Soc Perkin Trans 1980, 2, 890.

[130] Jia, G.; Li, Z. J Heteroatom Chem 1997, 8, 71.

[131] Veerabhadraiah, U.; Rao, R. V.; Rao, P. T. V. J Indian Chem Soc 1990, 67, 81.

[132] Nakhmanovisch, A. S.; Glotova, T. E.; Khim Geterotsikl Soadin 1996, 1, 130; Chem Abstr 1996, 125, 167933t.

[133] Chande, M. S.; Joshi, R. M. Indian J Chem 1997, 36B, 403.

[134] Patil, S. A.; Badiger, B. M.; Kudari, S. M.; Kulkarni, V. H. J Indian Chem Soc 1984, 61, 713.

[135] Prasad, A. R.; Rao, A. N.; Ramalingam, T.; Sattur, P. B. Indian Drugs 1988, 25, 301; Chem Abstr 1988, 109, 47837n.

[136] Potts, K. T.; Huseby, R. M. J Org Chem 1966, 31, 3528.

[137] Kroeger, C. F.; Tenor, E.; Beyer, H. Justus Liebigs Ann Chem 1961, 643, 128.

[138] Invidiata, F. P.; Furno, G.; Lampronti, I.; Simoni, D. J Heterocycl Chem 1997, 34, 1255.

[139] Yanni, A. S.; Collect Czech Chem Commun 1991, 56, 1919.

[140] Fandy, R. F.; Atta, A. H.; Hammam, A. S.; Afinidad 1997, 54, 401; Chem Abstr 1998, 128, 22885f.

[141] Karlivan, G. A.; Valter, R. E.; Batse, A. E.; Gulbis, Y. V. Khim Geterotsikl Soedin 1996, 4, 463; Chem Abstr 1996, 125, 167926t.

[142] Aly, A. A.; Brown, A. B.; El-Emary, T. I.; Ewas, A. M. M.; Ramadan, M. Arkivoc 2009, I, 150.