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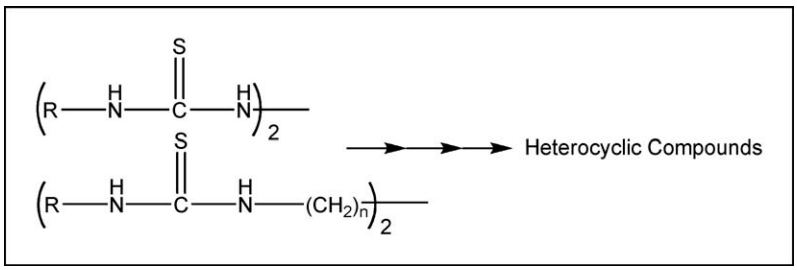


This review summarizes published data on the behavior and reactions of dithiobiurea and thioureidoalkylthiourea derivatives, which lead to the formation of heterocyclic systems, including methods of preparation in addition to synthesis of imidazolidine, thiazole, thioazolidine, triazolidine, thiadiazine, and spiro compounds.

J. Heterocyclic Chem., **47**, 764 (2010).

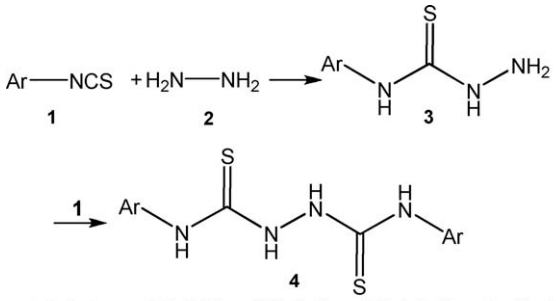
Contents **Page**

1. INTRODUCTION

In recent years, there has been increasing interest in the synthesis of heterocyclic compounds by cyclization of appropriate linear compounds [1–15]. Organosulfur compounds play an important role in modern organic synthesis, not only because they constitute a particularly useful class of synthons [16] but also because they are of great biological interest [17–23] such as fungicidal [24], bactericidal [25–27], insecticidal [28], and antitumor agents for thioureidoalkanethiourea [29–32]. Symmetrical and unsymmetrical 2,5-dithiobiureas have been utilized widely in the synthesis of heterocylic compounds and are considered as very good complexing agents for a variety of materials in the synthesis of complexes [33–39]. Substituted-2,5-dithiobiureas and their derivatives are versatile compounds, which have been extensively used in the preparation of heterocyclic ring systems. Also, oxidation of *S*-alkylisodithiobiureas resulted in the formation of thiadiazole derivatives [40], but oxidation of 1,5-diaryl-2-*S*-alkylisodithiobiuretes led to the formation of benzothiazolylisothiouereas [41]. Alkylation of 1-substituted-2,5-dithiobiureas by refluxing with appropriate alkyl halide in ethanol led to the formation of thiadiazole derivatives [42].

On the other hand, symmetrical 2,5-dithiobiureas underwent cyclization in the presence of alkali to form the corresponding 1,2,4-triazolidine-3,5-thione [43,44], and, therefore, the substituted dithiobiureas and their

Scheme 1



derivatives act as a key for the synthesis of many organic heterocyclic ring systems.

2. SYNTHESIS OF DITHIOBIUREAS AND THEIR DERIVATIVES

The reaction of aryl isothiocyanates **1** with hydrazine (**2**) in great excess and at low temperature in ethanol readily gave 4-arylthiosemicarbazides **3**, which reacted further with another molecule of **1** to give *N*,*N*′-di(arylthioformyl)hydrazines **4** (Scheme 1) [45].

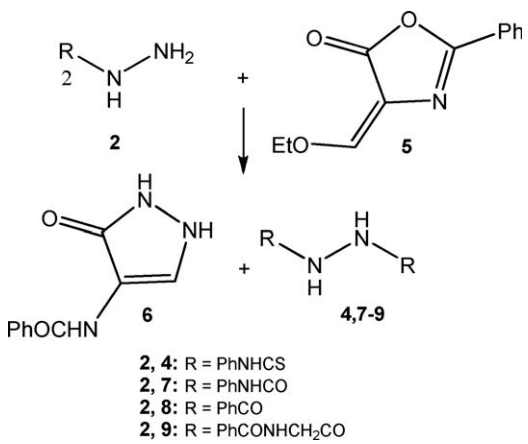
When oxazolone **5** was heated with two equivalents of appropriate hydrazine derivatives **2** in dioxane for 0.5–2 h, the products **6**, **4**, and **7–9** were separated (Scheme 2) [46].

Ammoniumthiocyanate **10** was added to a solution of dilute H_2SO_4, and thiosemicarbazide **3** to afford 2,5-dithiobiurea **4** in 52% yield (Scheme 3) [47].

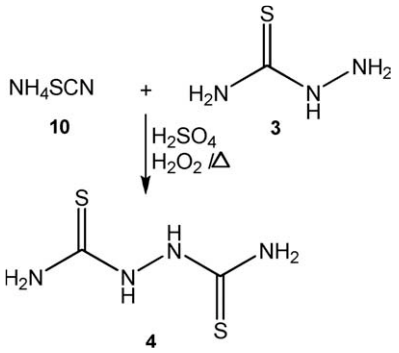
Egri [48,49] reported the synthesis of substituted dithiobiureas by treating RNH_2 and $R'NH_2$ with $CSCl_2$ and then with hydrazine hydrate (Figure 1).

Heating naphtho[1,2-*d*]oxazole-2(1*H*)-thione **12** (which was prepared by heating a mixture of 1-imino-2-hyroxynaphthalene hydrochloride **11** and phenyl isothiocyanate **1** in boiling ethanol) with hydrazine hydrate **2** in

Scheme 2



Scheme 3



ethanol did not give the expected product, 2-hydrazinonaphth[1,2-*d*]oxazole **13**, but the obtained product contained sulfur. This indicates that the reaction of **12** with hydrazine hydrate as nucleophile led to cleavage of the oxazolinethione ring and formation of 3-amino-1,3-dihydro-2*H*-naphth[1,2-*d*]imidazole-2-thione **14** or 4-(2-hydroxy-naphthaien-1-yl)thiosemicarbazide **15**. The spectral data are in agreement with the structure of thiosemicarbazide **15**, which reacted with the appropriate aryl isothiocyanate at room temperature to afford the derivatives of **4** (Scheme 4) [50].

1,2-Bis(thiocarbamoyl)hydrazine **4** was prepared by treating 4-substituted thiosemicarbazide **3** with allyl isothiocyanate **1** (Scheme 5) [51].

1,1-Bis(β-hydroxyethyl)thiocarbohydrazide **16** was heated with isothiocyantes **1** in ethanol to give dithiobiurea derivatives **4** (Scheme 6) [52].

When benzhydryl isothiocyanate was allowed to react with excess of hydrazine, a good yield of 4-benzhydrylthiosemicarbazide was obtained. Equivalent amounts of these reactants, however, gave a dithiobiurea **4** as the major product (Figure 2) [53].

Unsaturated 1,6-disbstituted-2,5-dithiobiureas **4** was obtained from the reaction of substituted isothiocyanates **1** with 4-substituted thiosemicarbazides **3** (Scheme 7) [54].

The reaction of thiocarbohydrazide **17** with 2*M* equivalents of benzaldehyde results in the formation of the monobenzylidene derivatives **18**, which further reacted with isobutyl isothiocyanate and triethylamine in

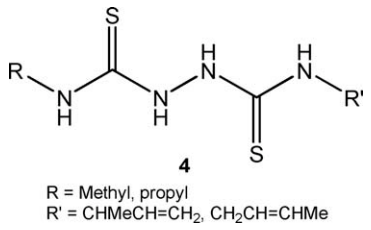
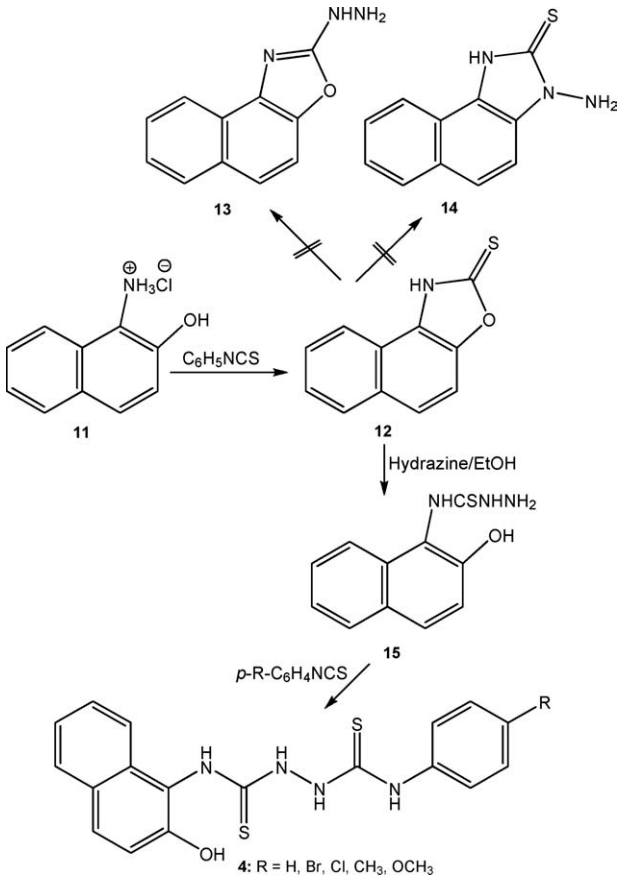


Figure 1. Substituted dithiobiureas from primary amines.

Scheme 4

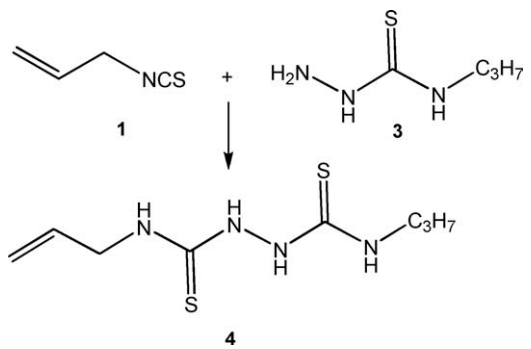


dimethylformamide (DMF) to gave 1-benzylidene-5-(*N*-isobutylthiocarbamoyl)-thiocarbohydrazide **4** (Scheme 8) [55].

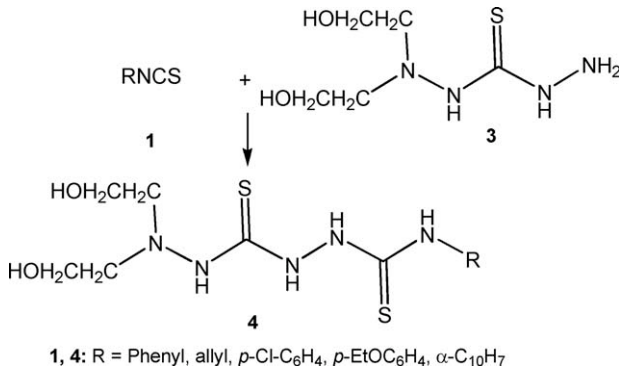
Refluxing phenyl thiosemocarbazide with appropriate isothiocyanates in absolute ethanol gave dithiobiurea derivatives **4** (Figure 3) [56].

The reductive debenzylation of 5-*S*-benzyliso-1-aryl-2-thiohydrazodicarbonamides **19** afforded **4** (Scheme 9) [57,58].

Scheme 5



Scheme 6



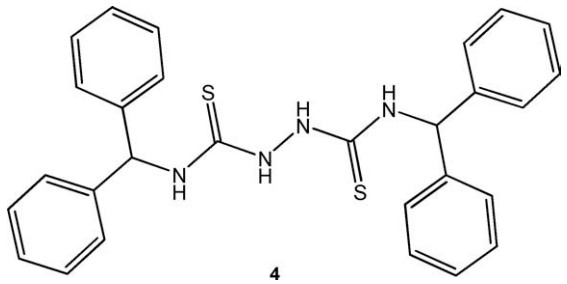


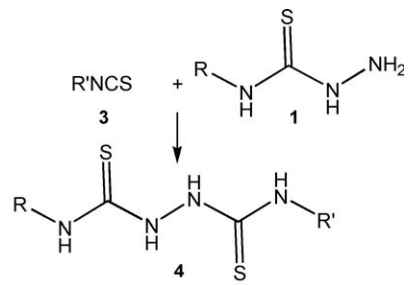
Figure 2. Dithiobiurea from benzhydryl isothiocyanate.

The reduction of 6-substituted amino-3-amino-1,2,4,5-dithiadiazines **20** under similar conditions of the above reaction gave **4** in good yields (Scheme 10) [57,58].

Thioureidoalkanethiourea derivatives **21** (n = 2–4, 6, 7) were prepared from the reaction of diamines with isothiocyanates (Figure 4) [59].

When α-mannosyl isothiocyanate **1** was reacted with diamines **22** (n = 2, 6), **21** was formed after deacetylation with sodium methanolate in methanol [24] (Scheme 11).

Scheme 7



Scheme 8

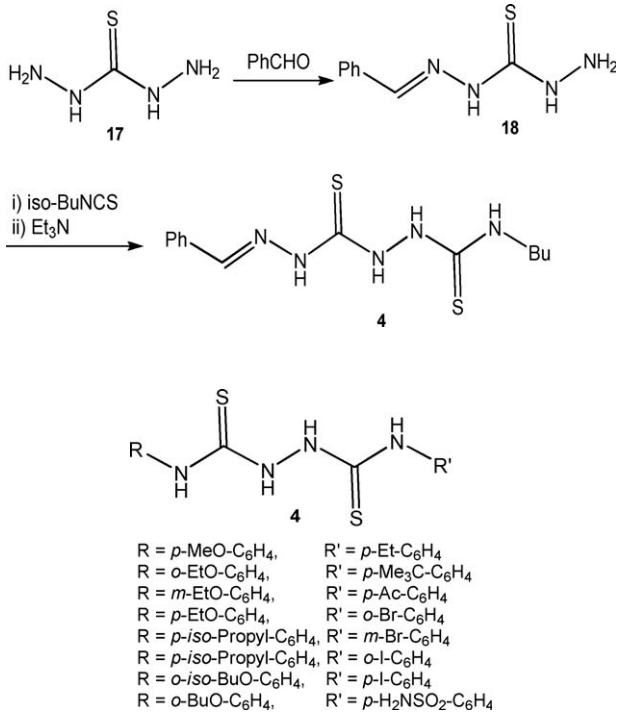
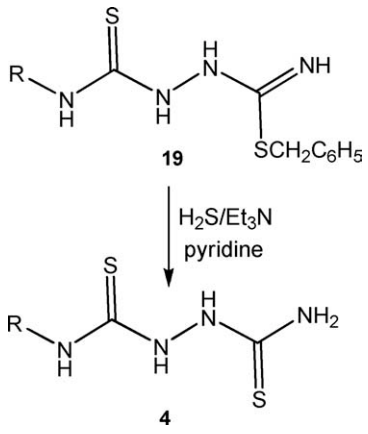
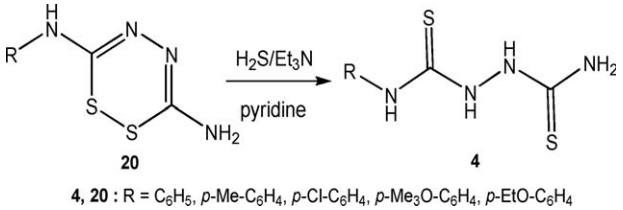


Figure 3. Dithiobiurea derivatives from phenyl thiosemicarbazide.

Scheme 9



Scheme 10



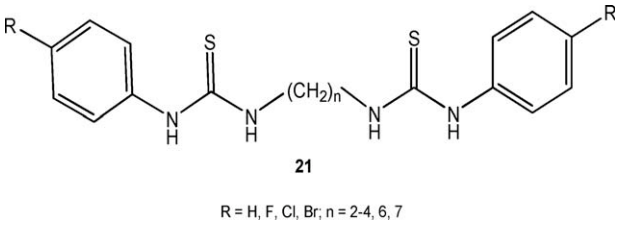
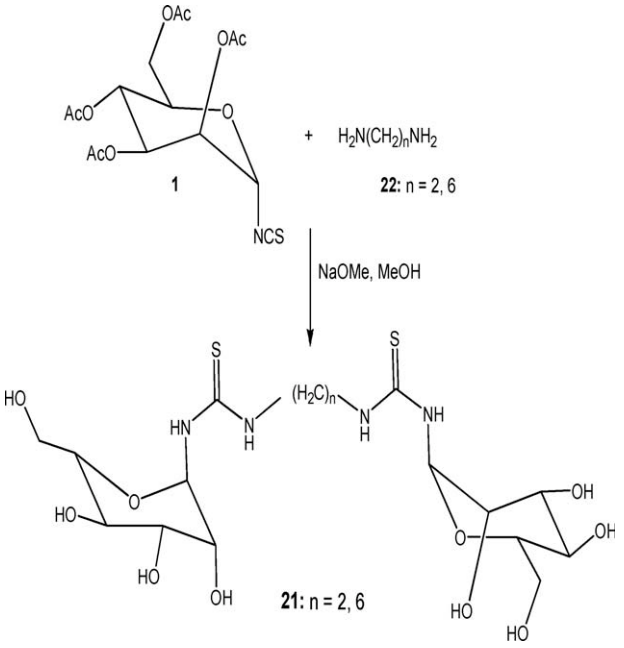


Figure 4. Thioureidoalkanethiourea derivatives from diamines.

Scheme 11



Page and Roy [26] reported that, when *p*-amino-phenyl 2,3,4,6-tetra-*o*-acetyl-α-D-mannopyranoside **23** was dissolved in dichloromethane containing diisopropylethylamine (DIPEA) and thiophosgene, compound **1** was formed, which when added to a solution of diamine in dichloromethane containing a catalytic amount of DIPEA, derivatives of compounds **21** were formed (Scheme 12).

1,6-Bis(allylthioureido)alkanes **21** were prepared by treating of diamine (1,2-diaminoethane, 1,3-di-amino-propane, 1,4-diaminobutane, 1,5-diaminopentane, and 1,6-diaminohexane) with allyl isothio-cyanate (Figure 5) [60].

Disubstituted thioureidothioureas **21** were obtained from ethylenediamine **22** and isothiocyanates **1** (Scheme 13) [61].

Compound **21** was obtained by refluxing ethylenediamine **22** with EtOH, NaOH, and phenyl isothiocyanate, while when HCl was added to the solution, NaCl was precipitated together with imidazoline derivatives **24** (Scheme 14) [62].

Scheme 12

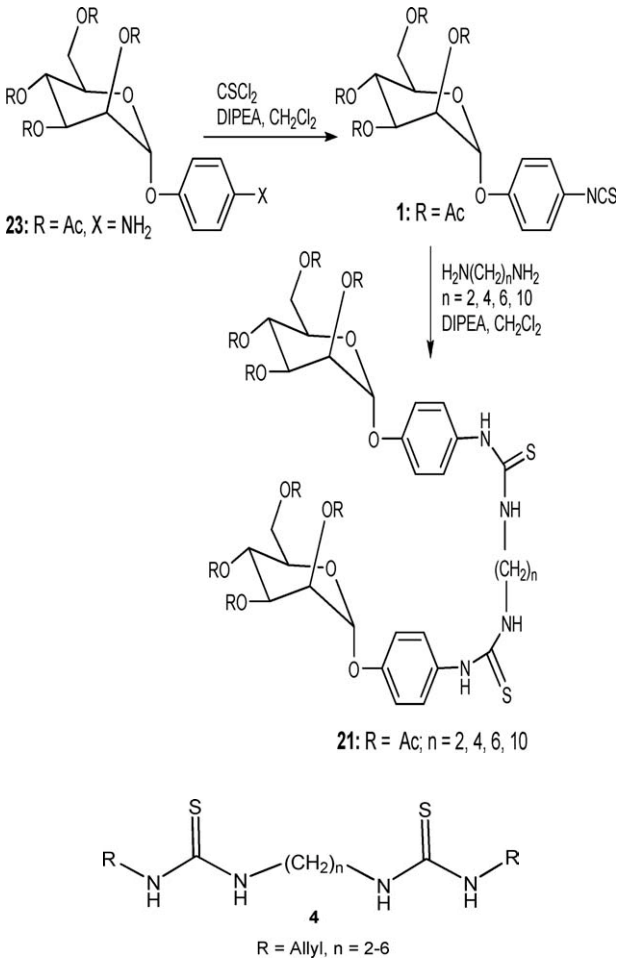
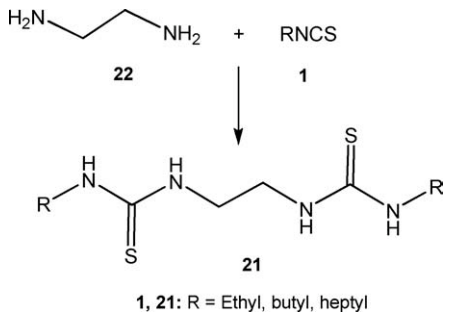


Figure 5. 1,6-Bis(allylthioureido)alkanes from different diamines.

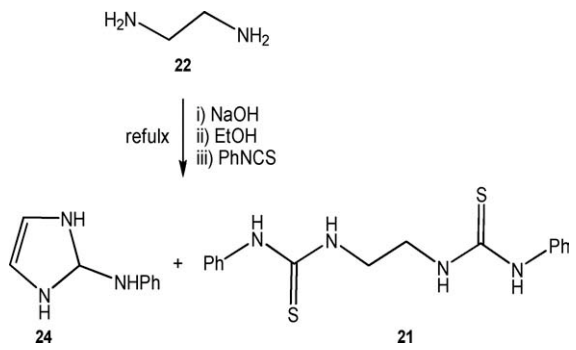
Ethylenediaryldithiocarboamides **21** were prepared by the action of 2 mol of isothiocyanates **1** with ethylenediamine **22** and boiling with concentrated HCl or KOH (Scheme 15) [63].

Ethylene diisothiocyanate **25** gave **21** and imidazolidine derivatives **26** when reacted with a nucleophilie (aniline or marpholine) (Scheme 16) [64].

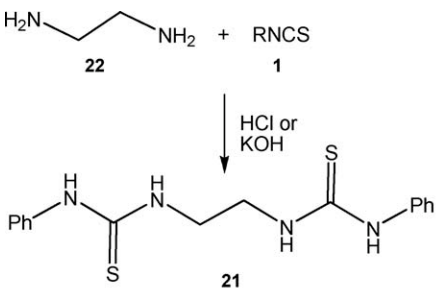
Scheme 13



Scheme 14



Scheme 15

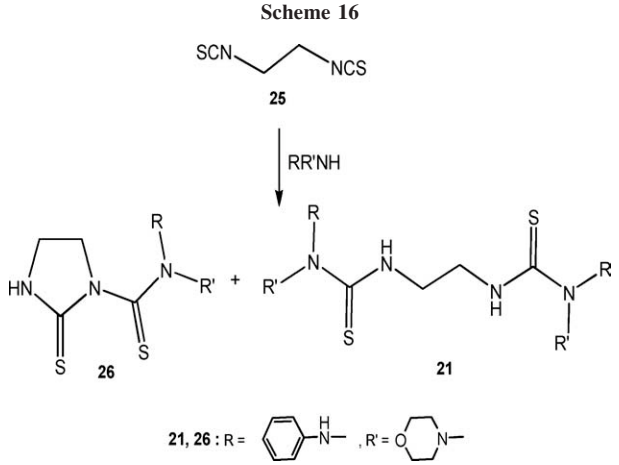


Also, trimethylene diisothiocyanate **27** and tetramethylene diisothiocyanate **28** gave linear mono-addition derivatives **29** and bis-adducts **21** when reacted with aniline or morpholine (Scheme 17) [64].

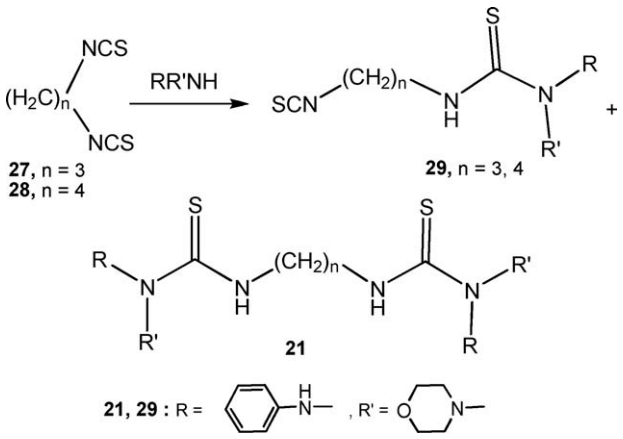
3. REACTIONS OF DITHIOBIUREAS AND THIOUREIDOALKYLTHIOUREAS

3.1. Synthesis of imidazolidine derivatives. The reaction of thioureidoethyl- and propylthioureas **21** with mercury bis(phenyl acetylide) **30** afforded corresponding

Scheme 16



Scheme 17



cyclic symmetrical mercaptides **31** and **32**. The thermal decomposition of **31** led to the formation of imidazolidines **35** (Scheme 18) [65].

4-Chloro-*N*′-(4,5-dihydro-1*H*-imidazo-2-yl)-benzene-1,2-diamine **36** was prepared by addition of ethylenediamine **22** to the corresponding 4-chloro-2-nitrophenylisothiocyanate **1** (Figure 6) [66].

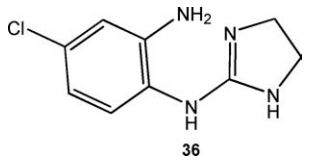
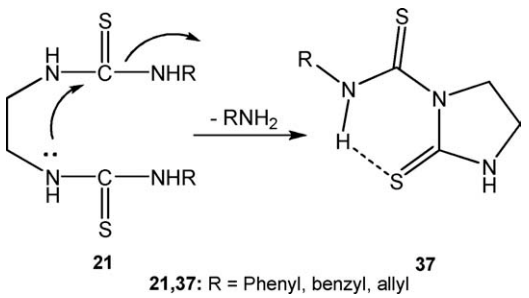


Figure 6. Substituted imidazoylbenzendiamine from ethylenediamine.

Scheme 19



Hassan *et al*. [67] reported that imidazolidine **37** can be formed on heating or microwave irradiation of thioureidoethylthiourea derivatives **21** (Scheme 19).

3.2. Synthesis of thiazole, thiazolidine, and thiazolium derivatives. 2,5-Dithiobiurea **4** reacted with methylphenylchloropyruvate exclusively as thiourea (Hantzsch reaction) forming dimethyl 2,2′-(hydrazine-1,2-diyl)-bis(5-phenylthiazol-4-carboxylate) **38** (Figure 7) [68].

It has been reported that bis(*N*-phenyl)thiourea **4** was cyclized to thiazolidine-4-one **39** when reacted with monochloroacetic acid in the presence of EtOH/AcONa (Scheme 20) [69].

Symmetrical azines of 3-allylthiazolidine-4-one **39** can be obtained by treating allyldithiourea **4** with acid derivatives **40** under reflux in alcohol in the presence of AcOK (Scheme 21) [70].

Trisubstituted thiazoles **42** can be obtained by heating a mixture of **4** and **41** (Scheme 22) [71].

Reaction of ethylenediamine **22** with allyl isothiocyanate **1** followed by treating by aq. HCl gave bisthiazoline **43** (Figure 8) [72].

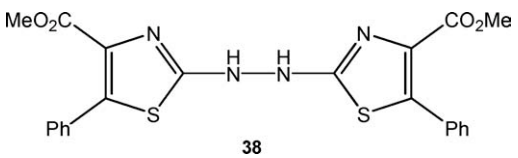
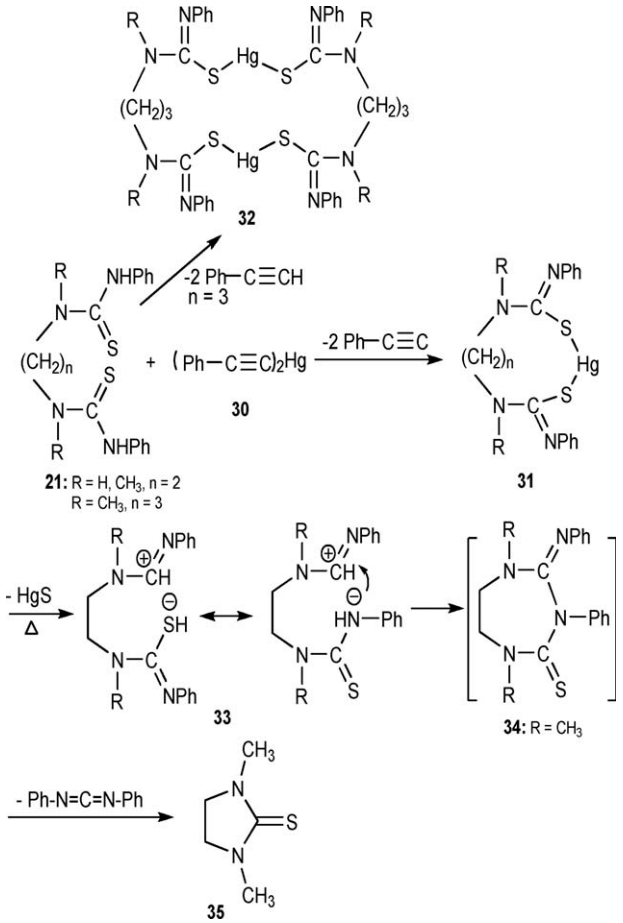
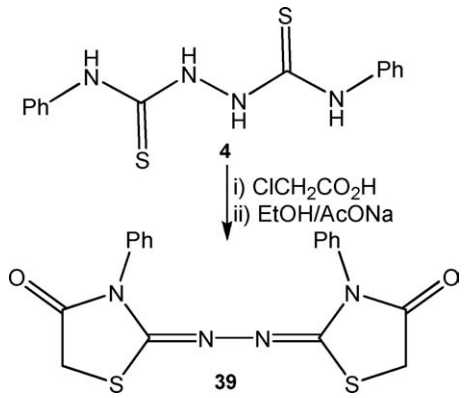


Figure 7. (Hydrazine-1,2-diyl)-bis(5-phenylthiazol-4-carboxylate) from dithiobiurea.

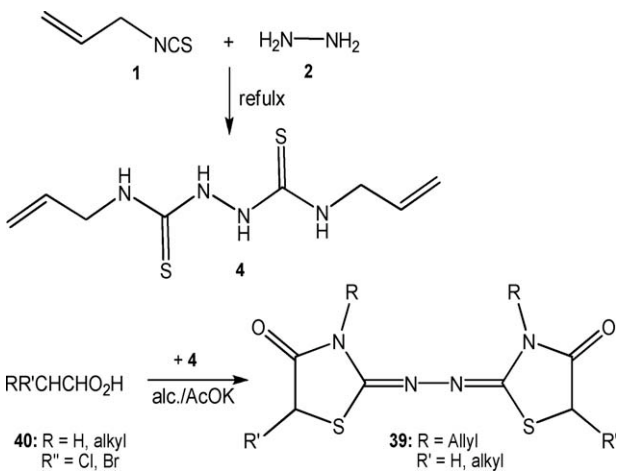
Scheme 18



Scheme 20



Scheme 21



Symmetrical bisthiazolidine **44** was obtained by heating *N*,*N*′-ethane-1,2-diylbis(thiourea) **21** with α-chloroacetic acid in butanol (Scheme 23) [73].

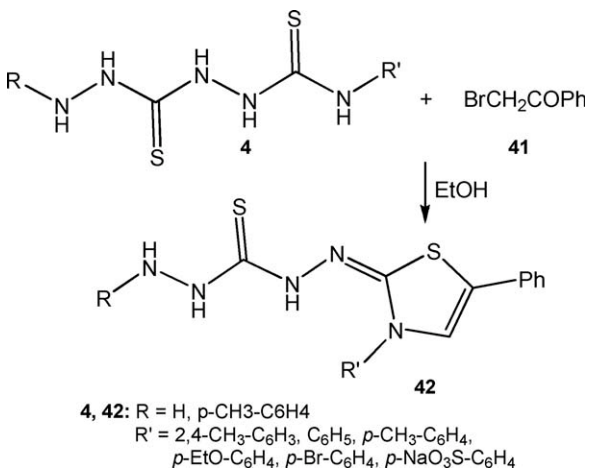
3.3. Synthesis of thiadiazole derivatives. 2-Amino-5-mercapto-1,3,4-thiadiazole **45** was obtained *via* cyclization of 2,5-dithiobiurea **4** in refluxing HCl (Scheme 24) [74].

Also, oxidation of 1-substituted-4-*S*-alkyl(aryl)-2,4-isodithiobiuretes **46** afforded 3-alkylmercapto-5-arylamino-1,2,4-thiadiazoles **47** (Scheme 25) [40].

On heating 1-substituted-5-*S*-alkyl(aryl)isodi-thiobiureas **48** in ethanol or water in the presence of hydrochloric acid, 5-alkylmercapto-2-substituted amino-1,3,4-thiadiazoles **49** were obtained (Scheme 26) [42].

On the other hand, alkylation of 1-substituted-2,5-dithiobiureas **4** with alkyl halide in ethanol gave substituted-1,3,4-thiadiazoles **49** (Scheme 27) [42].

Scheme 22



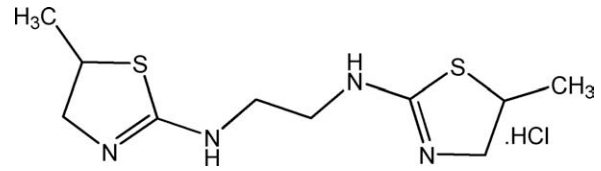
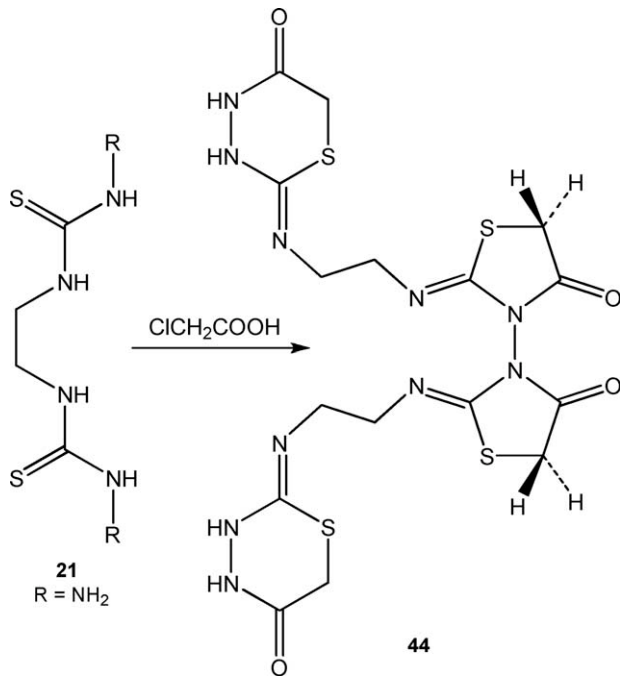
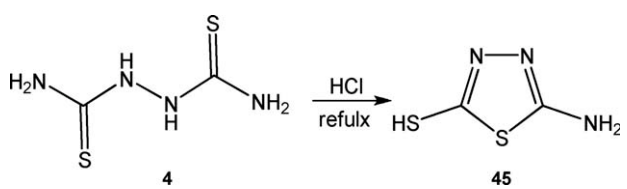


Figure 8. Bisthiazoline from ethylenediamine.

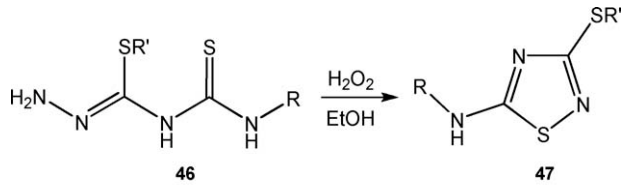
Scheme 23



Scheme 24

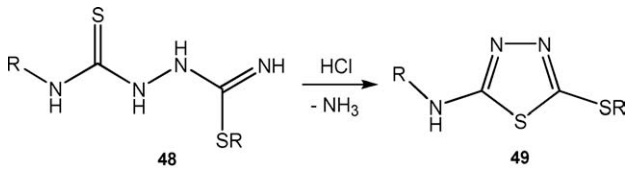


Scheme 25



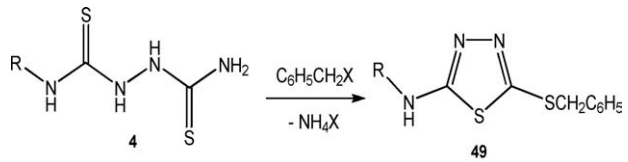
46, 47: R = Phenyl, benzyl, R' = phenyl, methyl

Scheme 26



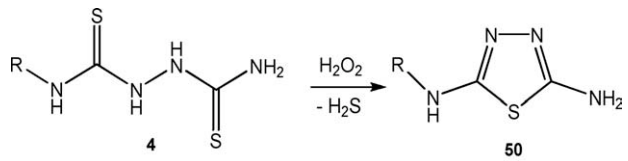
48, 49: R = Benzyl, ethyl, methyl

Scheme 27



4, 49: R = C_6H_5, CH_3, C_2H_5, *p*-Me-C_6H_4

Scheme 28

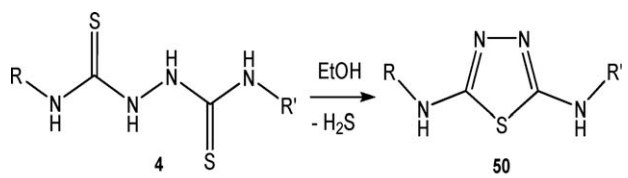


4, 50: R = C_6H_5, CH_3, C_2H_5, *p*-Me-C_6H_4

Oxidation of substituted-2,5-biueras **4** with either hydrogen peroxide or iodine in warm ethanolic medium afforded 2-amino-5-substituted amino-1,3,4-thiadiazoles **50** (Scheme 28) [42].

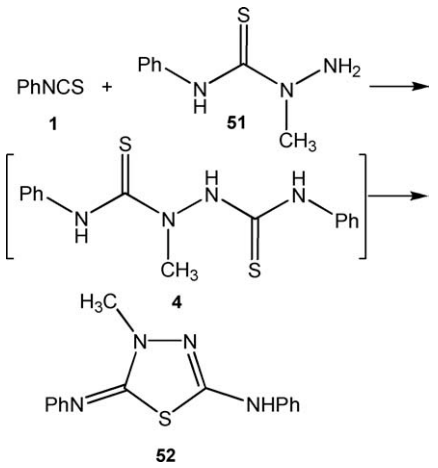
Thiadiazole derivatives **50** can be obtained by cyclization of compounds **4** in an alkaline medium with evolution of hydrogen sulfide (Scheme 29) [75].

Scheme 29

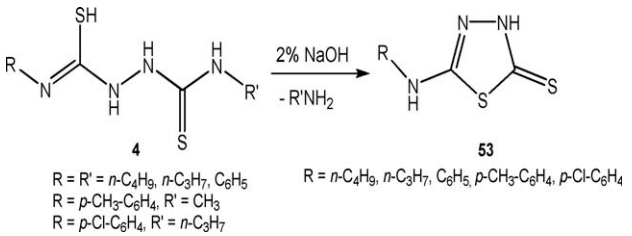


4, 50: R = R' = C_6H_5, *p*-Me-C_6H_4, *p*-Cl-C_6H_4, *p*-EtO-C_6H_4, *p*-MeO-C_6H_4

Scheme 30



Scheme 31



4

R = R' = *n*-C_4H_9, *n*-C_3H_7, C_6H_5
R = *p*-CH_3-C_6H_4, R' = CH_3
R = *p*-Cl-C_6H_4, R' = *n*-C_3H_7

53

R = *n*-C_4H_9, *n*-C_3H_7, C_6H_5, *p*-CH_3-C_6H_4, *p*-Cl-C_6H_4

2,4-Disubstituted thiosemicarbazide **51** was allowed to react with phenyl isothiocyanate **1** to give dithiobiurea **4** as an intermediate, followed by cyclization with elimination of hydrogen sulfide to give 5-anilino-3-methyl-2-phenylimino-2,3-dihydro-1,3,4-thiadiazole **52** (Scheme 30) [76].

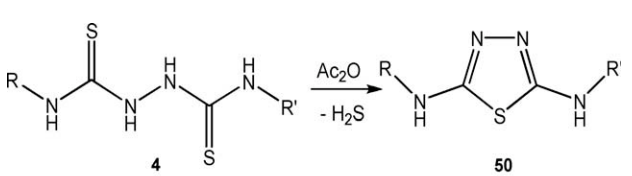
Alkali-catalyzed thermal cyclization of 1-alkyl and 1,6-dialkyl-2,5-dithiobiureas **4** gave 2-alkyl amino-Δ^2-1,3,4-thiadiazoline-5-thiones **53** (Scheme 31) [77].

On the other hand, oxidative cyclization of 1,6-disubstituted-2,5-dithiobiueras **4** was occurred in the presence of Ac_2O to produce the corresponding thiadiazoles **50** (Scheme 32) [78,79].

When 2,5-dithiobiurea **4** treated with Me_2SO_4 and hypophosphorous acid in H_2O; the reaction underwent formation of 2-amino-5-(methylthio)-1,3,4-thiadiazole **49** (Scheme 33) [80].

Wegner [81] has reported the synthesis of substituted thiadiazoles **54** by the reaction of substituted amine with

Scheme 32



4, 50: R = C_2H_5, R' = CH_2=CH-CH_2, *p*-F-C_6H_4, C_6H_5, CH_2=C(CH_3)-CH_2

Scheme 33

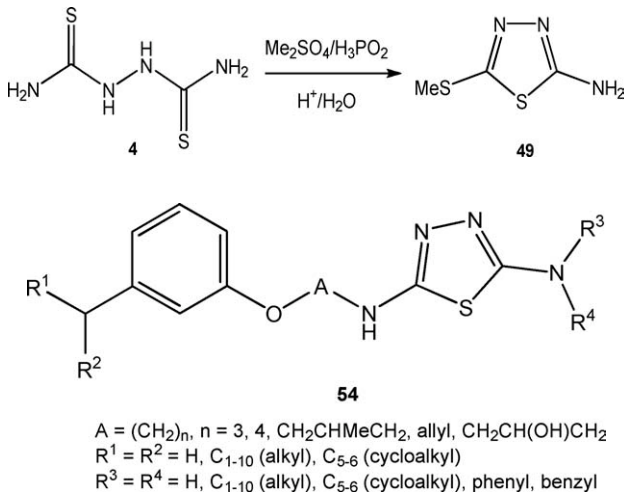


Figure 9. Substituted thiazoles from hydrazinecarbothioamide.

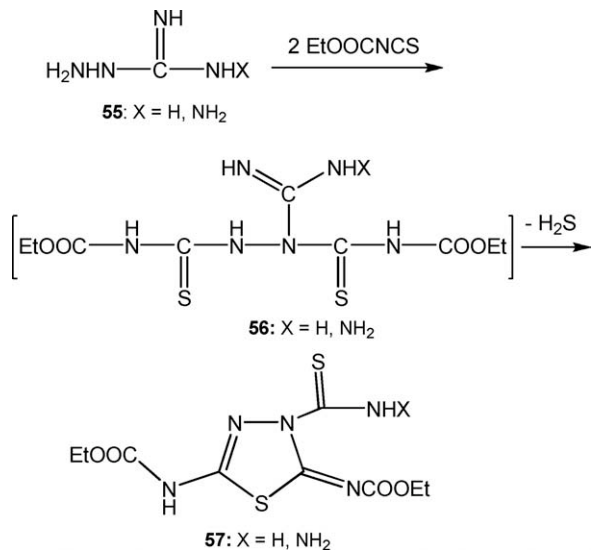
$ClCS_2Ph$, and the resulting product was allowed to react with hydrazine hydrate to form substituted hydrazinecarbothioamide **4**, which further reacted with phenyl isothiocyanate dichloride (Figure 9).

The interaction of guanidine derivatives **55** and ethoxycarbonyl isothiocyanate under mild conditions afforded the thiadiazole derivatives **57** (Scheme 34) [82].

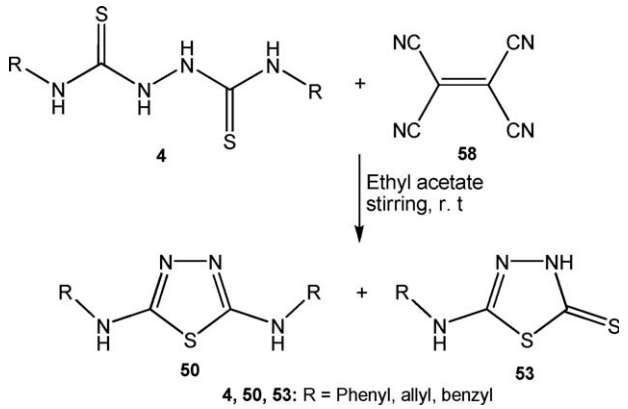
Addition of two equivalents of ethenetetracarbonitrile **58** to a solution of 1,6-disubstituted-2,5-dithiobiureas **4** in ethyl acetate at room temperature led to the formation of thiadiazole derivatives **50** and **53** as side products (Scheme 35) [83].

A phase transfer catalytic oxidation of hydrazinedicarbothioamide leads to a red colored solid **59**, the reduction of **59** with hydrazine or other reductants trans-

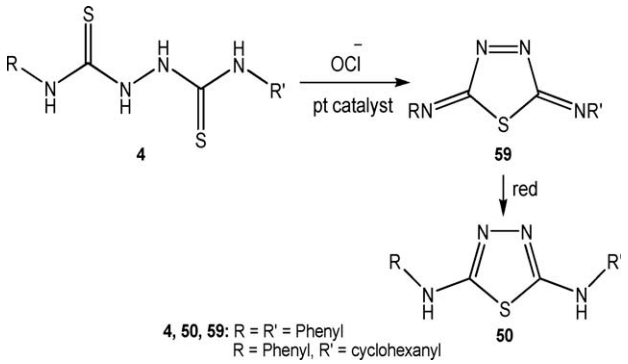
Scheme 34



Scheme 35



Scheme 36



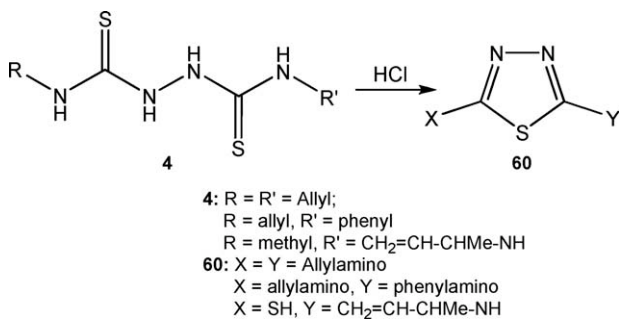
formed it into colorless compound, 2,5-diphenylamino-1,3,4-thiadiazole **50** (Scheme 36) [84].

Cyclization of symmetrical and unsymmetrical 1,6-bis(substituted)-2,5-dithiobiureas **4** in acid media gave 1,3,4-thiadiazoles **60** (Scheme 37) [85].

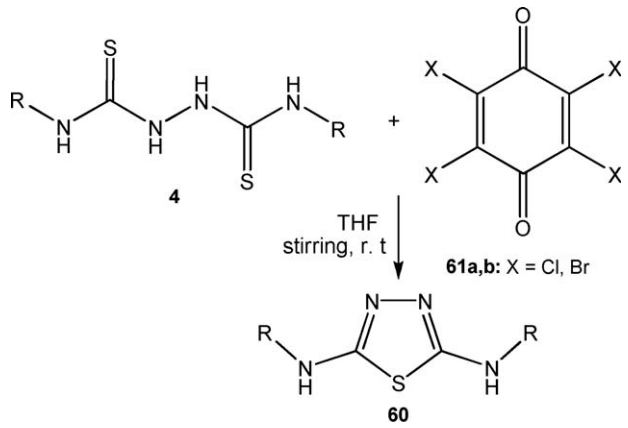
On adding tetrahydrofuran (THF) solution of 1,6-disubstituted-2,5-dithiobiureas **4** to a solution of chloranil or bromanil **61a,b** in the same solvent lead to the formation of thiadiazole derivatives **50** as a side product (Scheme 38) [86].

On the other hand, the addition of THF solution of 1-substituted-2,5-dithiobiureas **4** to a solutions of

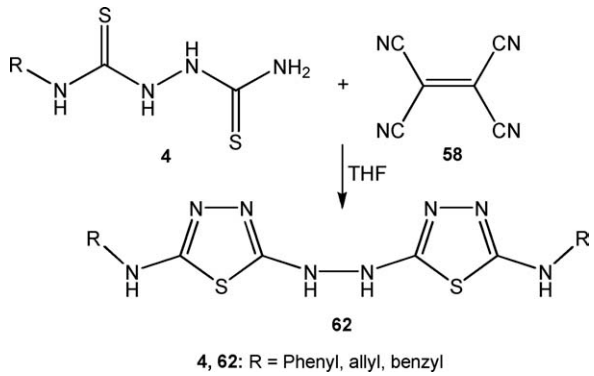
Scheme 37



Scheme 38



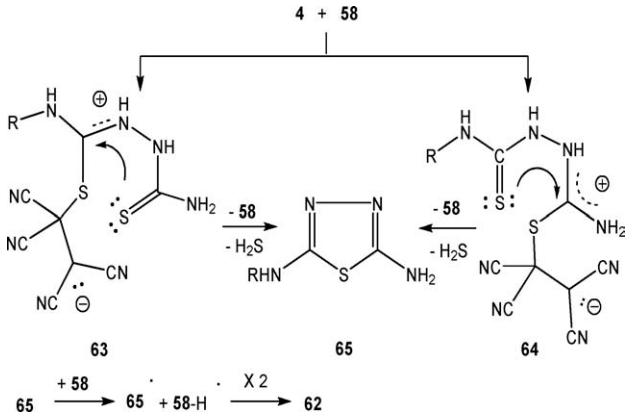
Scheme 39



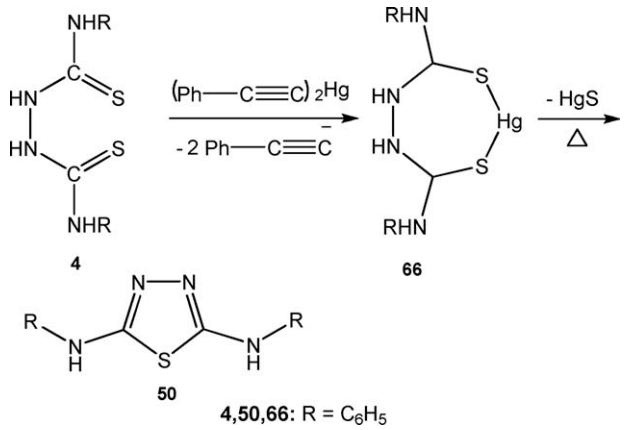
ethenetetracarbonitrile **58** in the same solvent lead to the formation of 1,2-bis[5-(substituted amino)-1,3,4-thiadiazole-2-yl)hydrazines **62** (Scheme 39) [87].

Scheme 40 showed the mechanism of formation of thiadiazole and bisthiadiazole derivatives from **4** by using ethnetetracarbonitrile **58**, which reacted as a mediator.

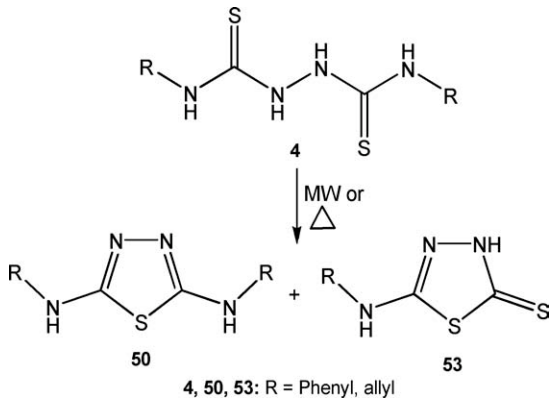
Scheme 40



Scheme 41



Scheme 42



Diphenylhydrazine-1,2-dicarbothioamide **4** reacted with mercury bis(phenyl acetylide) **30** to give the intermediate **66**, which under thermal decomposition afforded the thiadiazole derivatives **50** (Scheme 41) [88].

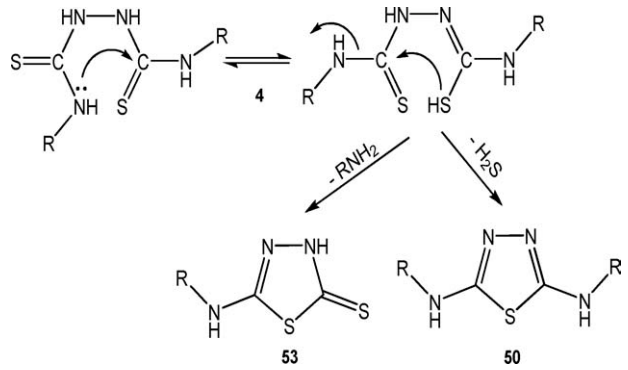
Microwave (MW) and thermal heterocyclization of *N*,*N*′-disubstituted hydrazinecarbothioamide **4** results in formation of 2,5-disubstituted amino[1,3,4]thiadi-azoles **50** and 5-substituted amino[1,3,4]thiadi-azole-2-thiones **53** (Scheme 42) [67].

A mechanism for the formation of thermal or MW irradiation for 1,6-disubstituted hydrazinecarbothio-amide **4** as shown in Scheme 43 [67].

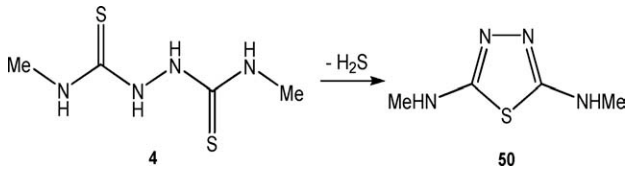
Thiadiazole derivatives **50** was prepared by cyclization of 1,6-dimethyl-2,5-dithiobiurea **4**, which was obtained by the reaction of methyl isothiocyanate with methylthiosemicarbazide (Scheme 44) [89].

1,6-Di(2-pyridyl)hydrazodithiocarbonamide **4** can be obtained from 2-pyridyl isothiocyanate and 2-pyridylthiosemicarbazide, which thermally cyclized to 2,5-di(2-pyridylamino)-1,3,4-thiadiazole **50** (Scheme 45) [90].

Scheme 43



Scheme 44



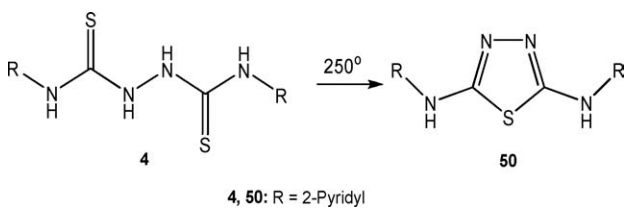
In case of the reaction of **4** with methyl iodide in the absence of the base, 5-acylamino-2-anilinidene-3-methyl-1,3,4-thiadiazoline **68** and 2-acylamino-5-methyl-thio-1,3,4-thidiazole **70** were formed (Scheme 46).

This reaction is presumed to be initiated by *S*- and *N*-methylation to form the intermediate **69**, followed by cyclization through the attack of SH group on C=N with elimination of dimethylaniline to afford **70**. On the other hand, **4** ($R^2 = CH_3$) was merely methylated on the sulfur atom, followed by elimination of CH_3SH to give **68** [91].

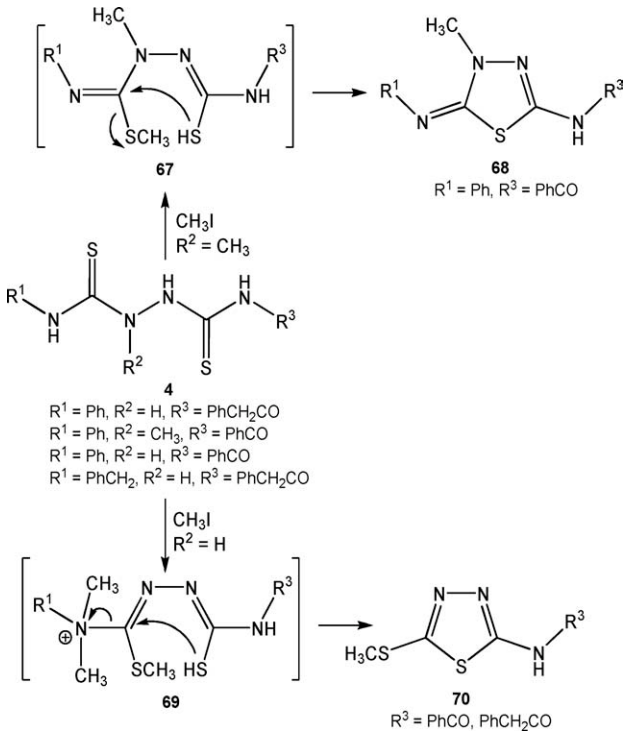
The reaction of trifluoroacetic acid with dithiobiurea **4** (R = CH_3) afforded 1,3,4-thiadi-azolineimine **71** and 1,3,4-thiadiazoline-2-thione **72** with loss of hydrogen sulfide and methylamine, respectively. On the other hand, dithiobiurea **4** (R = Ph) underwent ring closure with elimination of hydrogen sulfide and gave 1,3,4-thiadiazolineimine **71** as the only product. The different cyclization behavior of **4** (R = CH_3 and R = Ph) under acidic conditions appears to be caused in the different basicity of the R—NH moiety (Scheme 47) [92].

The reaction of ''nonalkylated'' carbothiohydrazide derivatives **73** with substituted isothiocyanates **1** at room

Scheme 45

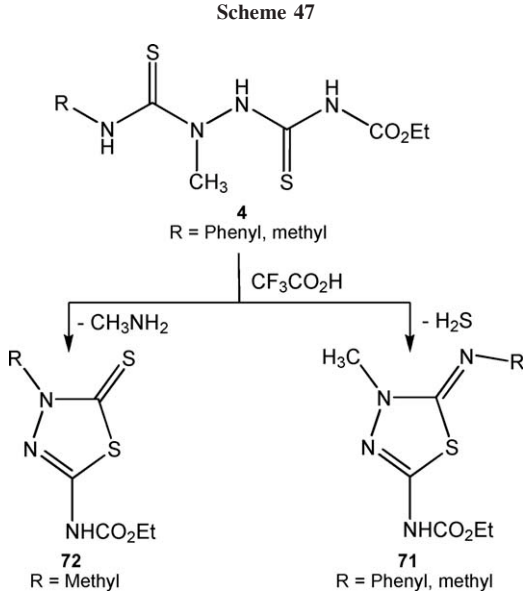


Scheme 46

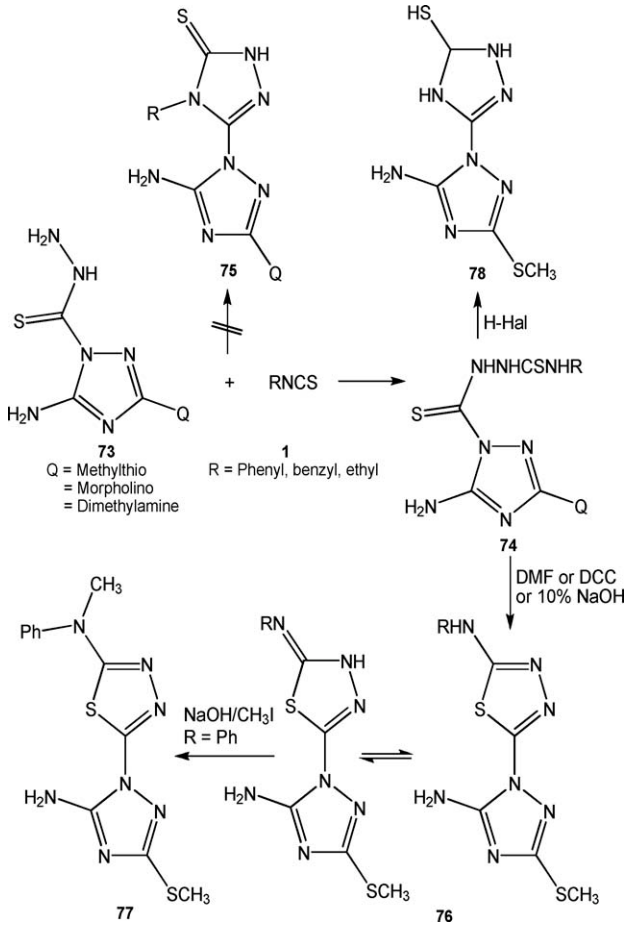


temperature in methanol or (Scheme 48) DMF as a solvent led to the thermally unstable thiocarbamoyl derivatives **74** and not **75** [93]. These were cyclized either in boiling DMF, or by reaction with dicyclohexyl carbodiimide (DCC), or by heating in 10 % sodium hydroxide to **76** and **78**. Compound **76** was changed to **77** after *N*-methylation. The alkylation of the ''nonalkylated'' derivatives **74** with methyl iodide and benzyl bromide in

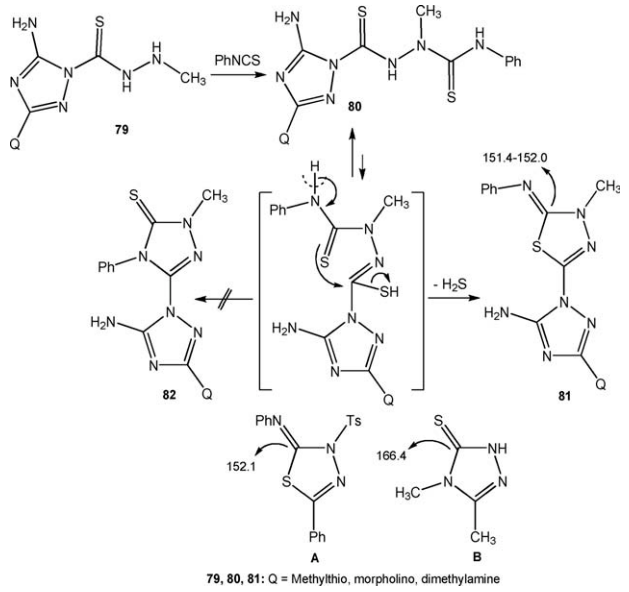
Scheme 47



Scheme 48



Scheme 49



either methanol or DMF afforded the corresponding **78** [94].

The reaction of **79** with phenyl isothiocyanate **1** afforded the expected phenylthiocarbomoyl derivatives **80** (Scheme 49).

The thermally unstable derivatives **80** could by easily cyclized probably through their tautomeric form to the thiadiazoles **81** by their short heating in DMF. It should be mentioned that the loss of H_2S from derivatives **79** may, in principal, also lead to the formation of derivatives **82**, thus, the structure of derivatives **81** formed had to be confirmed [94]. The decision between structure **81**, **82** made possible the comparison of the chemical shifts of the thiadiazole carbon atoms 5 of derivatives **81** (δ C5 = 151.4–152.0 ppm) with those of corresponding carbon atoms of model compounds **A**, **B** (δ C5 = 152.1 and 166.4 ppm, respectively) to prove structure **81** unequivocally.

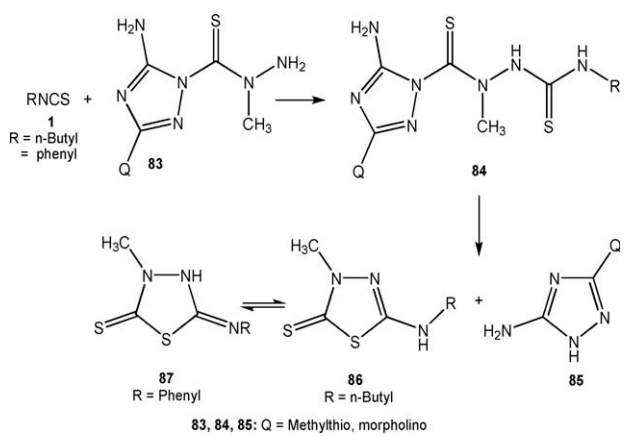
From the reaction of **83** and butyl- or phenyl-isothiocyanate instead of the corresponding thiocarbomoyl derivatives **84**, 2,3-dihydro-3-methyl-5-(*n*-butylamino)-1,3,4-thiadiazole-2-thione **86** or 2,3,4,5-tetrahydro-3-methyl-5-phenylimino-1,3,4-thiadiazole-2-thione **87**, respectively, were isolated besides 5-amino-3-(methylthio and merpholine)-1*H*-1,2,4-triazoles **85** (Scheme 50) [94].

3.4. Synthesis of triazole, triazoline, and triazolidine derivatives. Symmetrically substituted-2,5-dithiobiureas **4** lost ammonia or amine in the presence of alkali, giving 1,2,4-triazolidine-3,5-dithione derivatives **88** (Scheme 51) [43].

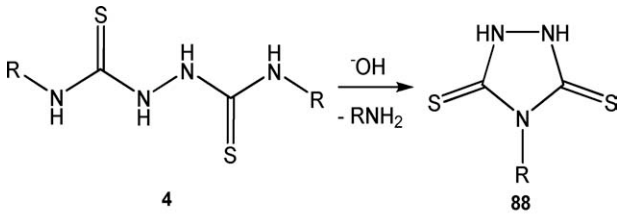
1,6-Dimethyl-2,5-dithiobiurea **4** cyclized under either strong or weak basic conditions to produce compound **88** as the major product and in minor amount of compound 4-methyl-5-methylamino-1,2,4-triazoline-3-thione **89** was also obtained (Scheme 52) [95].

When 1-alkyl-2,5-dithiobiureas **4** were refluxed with sodium methoxide in methanol, the reaction directly

Scheme 50

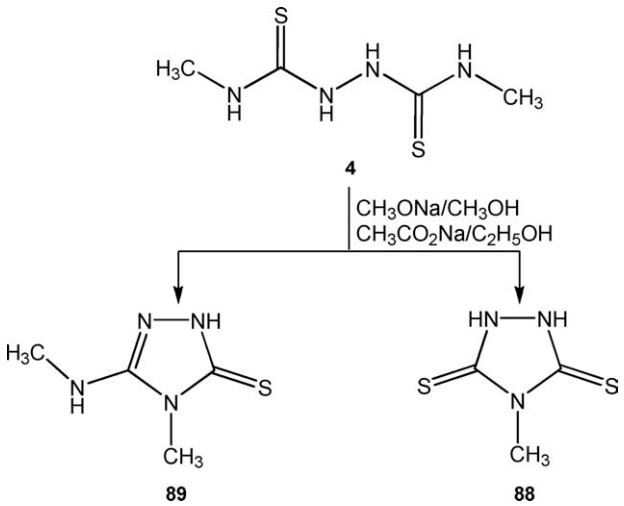


Scheme 51



4, 88: R = n-Butyl, benzyl, methyl

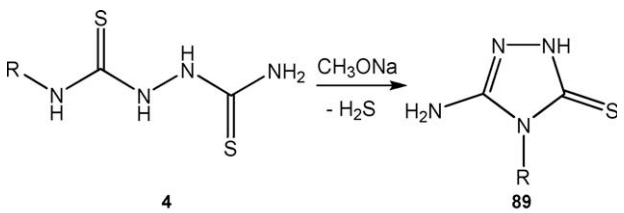
Scheme 52



produced 4-alkyl-5-amino-1,2,4-triazoline-3-thiones **89** (Scheme 53) [95].

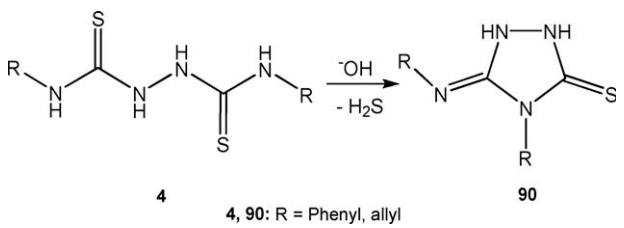
Similarly, cyclization of substituted-2,5-dithiobiueras **4** in alkaline medium took place with the elimination of H_2S to give the 1,2,4-triazoles **90** (Scheme 54) [95].

Scheme 53



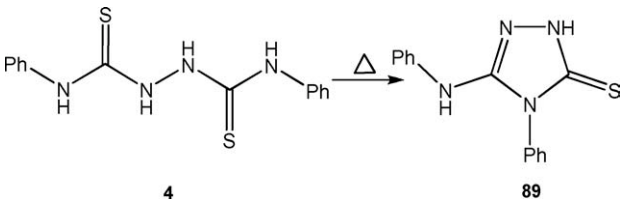
4, 89: R = *n*-Butyl, benzyl, methyl

Scheme 54

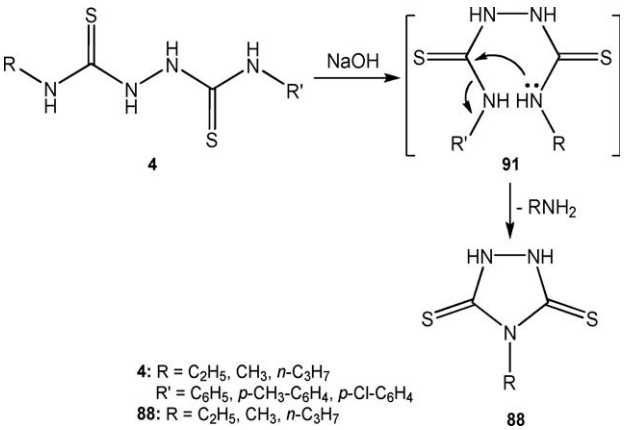


4, 90: R = Phenyl, allyl

Scheme 55



Scheme 56



4: R = C_2H_5, CH_3, *n*-C_3H_7
R' = C_6H_5, *p*-CH_3-C_6H_4, *p*-Cl-C_6H_4
88: R = C_2H_5, CH_3, *n*-C_3H_7

On the other hand, 1,6-diphenyl-2,5-dithiobiurea **4** was heated in the presence of alkali afforded 4-phenyl-3-phenyl amino-Δ^2-1,2,4-triazoline-5-thione **89** (Scheme 55) [44].

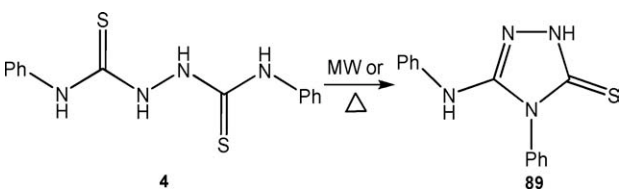
In a different manner, alkali-catalyzed thermal cyclization of 1-alkyl-6-aryl-2,5-dithiobiureas **4** led to the formation of 4-alkyl-1,2,4-triazolidine-3,5-dithiones **88** (Scheme 56) [96,97].

MW and thermal heterocyclization of *N,N′*-disubstituted hydrazinecarbothioamide **4** results in formation of 4-phenyl-5-phenylamino[1,2,4]triazole-3-thione **89** (Scheme 57) [67].

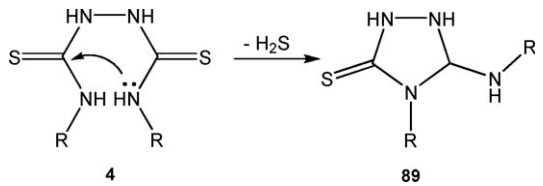
A mechanism for the formation of thermal or MW irradiation for 1,6-disubstituted hydrazinecarbothio-amide **4** to produce 4-phenyl-5-phenylamino[1,2,4]-triazole-3-thione **89** [67] as shown in Scheme 58.

The action of alkali or hydrazine on **4** produced moderate yields 3-amino-5-mercapto-1,2,3-triazole **92** or 4-

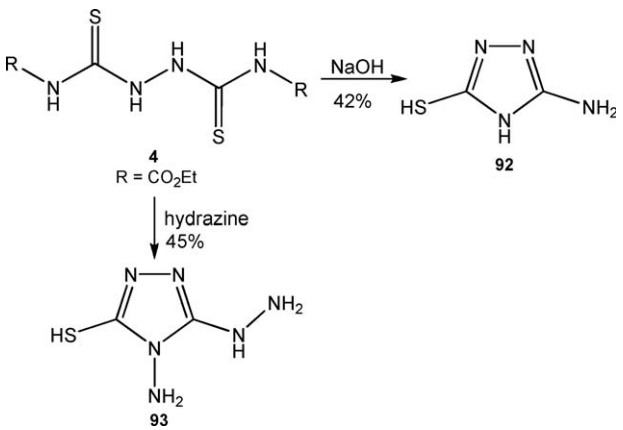
Scheme 57



Scheme 58



Scheme 59



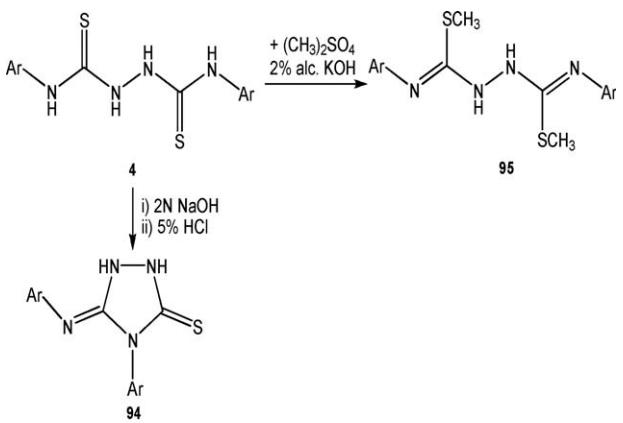
amino-3-hydrazino-5-mercapto-1,2,4-triazole **93** (Scheme 59) [82].

Dubenko *et al*. [98] reported the formation of 4-alkyl/aryl-1,2,4-triazolidine-3,5-dithiones **94**, during alkali-catalyzed thermal cyclization of 1,6-dialkyl/aryl-2,5-dithiobiureas **4**. Treatment of **4** with alcohol/KOH in presence $(CH_3)_2SO_4$ gave **95** (Scheme 60).

Triazolidines **88** and **94** can be obtained by cyclization of **4** with aqueous NaOH (Scheme 61) [99].

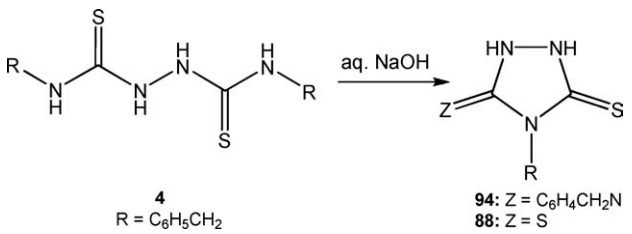
Framm and co-workers [44] reported that when 1,6-diphenyl-2,5-dithiobiurea **4** was heated in the presence

Scheme 60



4, 94, 95: Ar = *p*-Me-C_6H_4, *o*-Cl-C_6H_4, *p*-Cl-C_6H_4, *p*-Et-C_6H_4, *o*-MeO-C_6H_4, *p*-MeO-C_6H_4, *m*-Cl-C_6H_4, *o*-I-C_6H_4, Me_2-C_6H_3

Scheme 61



of alkali, the sole product obtained was 4-phenyl-3-phenylamino-Δ^2-1,2,4-triazoline-5-thione **96** (Figure 10).

Alkali catalyzed thermal cyclization of 1,6-dialkyl-2,5-dithiobiureas **4** (R = R' = alkyl) results in the formation of 4-alkyl-1,2,4-triazolidine-3,5-dithiones **88** (alkyl = Me or Et) and 2-alkylamino-Δ^2-1,3,4-thidiazoline-5-thione **52** (alkyl = *n*-Pr or *n*-Bu) (Scheme 62).

The anions **97** and **98**, respectively, formed from **4** carry a negative charge on the nitrogen and sulfur atoms and these can undergo cyclization by nucleophilic attack on the carbon atom at the other end, displacing

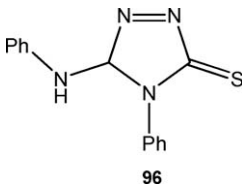
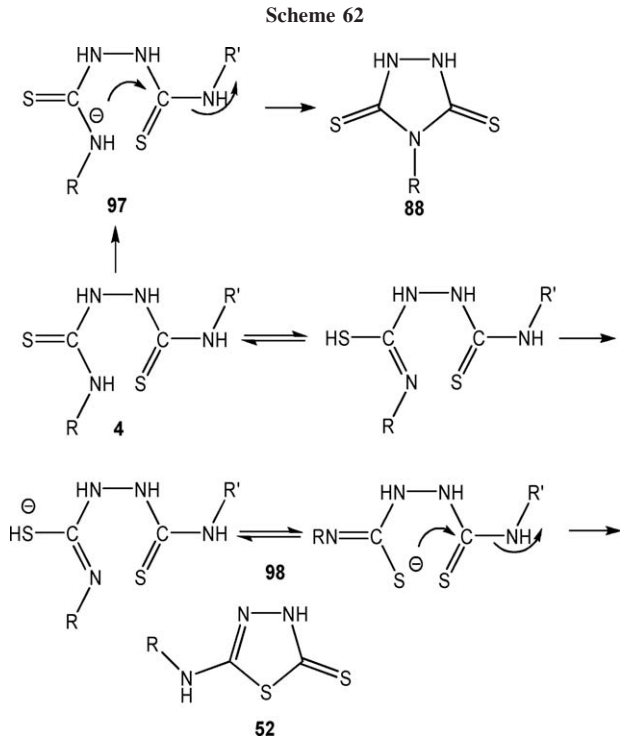
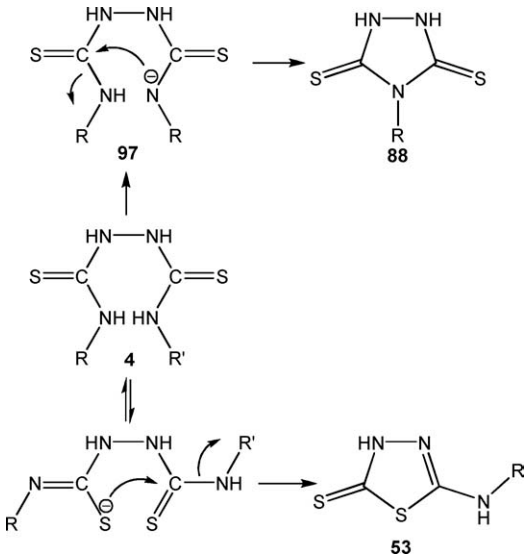


Figure 10. Triazolinethione from dithiobiurea.

Scheme 62

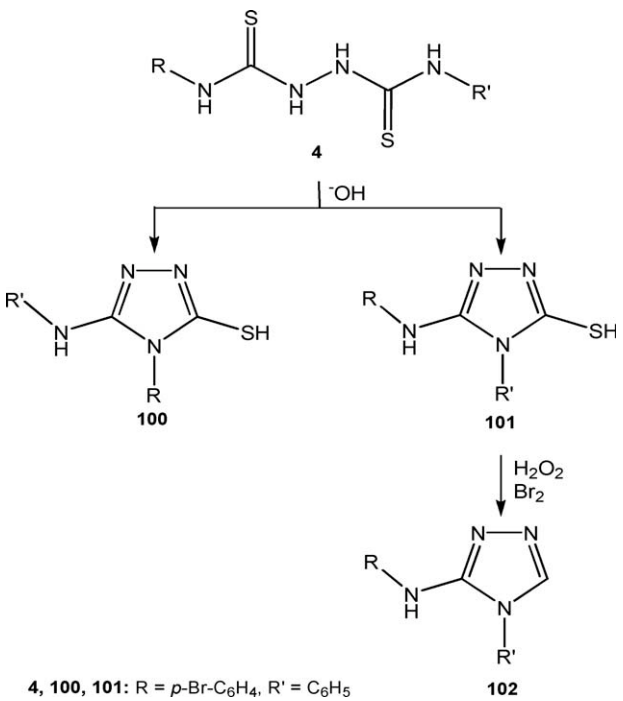


Scheme 63



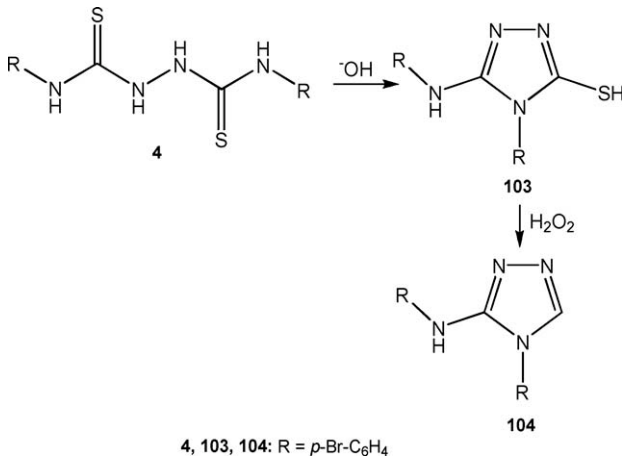
alkylamine. The formation of the different products during cyclization can be explained on the basis of the electronic and steric effects of the alkyl groups. When the alkyl groups are methyl or ethyl the electronic effect of the alkyl group is the major factor governing the mode of cyclization and the attack by the nitrogen atom carrying the alkyl substituent always occurs resulting in the formation of 4-ethyl/methyl-1,2,4-triazolidine-3,5-dithiones **88**. While going from methyl, ethyl, *n*-propyl to *n*-butyl, the inductive effect increase in the order

Scheme 64



4, 100, 101: R = *p*-Br-C_6H_4, R' = C_6H_5

Scheme 65

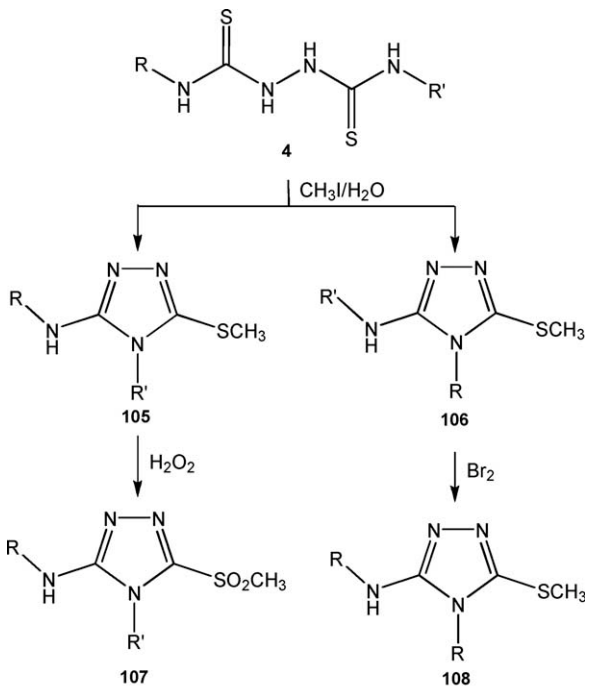


4, 103, 104: R = *p*-Br-C_6H_4

given. However, the steric effect of the alkyl group also increases and it exerts some influence on the mode of cyclization as follows [77].

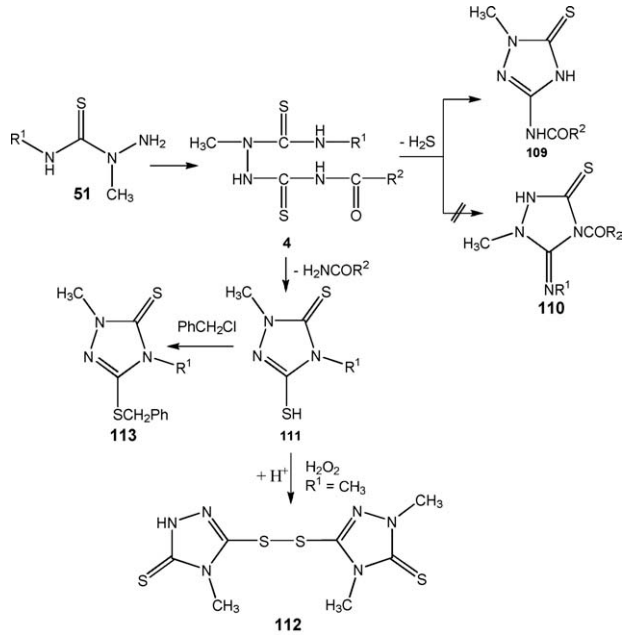
In view of the different modes of cyclization observed with alkyl substituted derivatives, a few 1-alkyl-6-aryl-2,5-dithiobiureas **4** (R = alkyl, R' = aryl) were also subjected to this cyclization reaction. The aryl groups chosen were; phenyl, 4-methylphenyl, *p*-chlorophenyl, and *p*-anisyl. When the alkyl group was methyl or ethyl, two products were obtained; one of the products was identified as 2-arylamino-Δ^2-1,3,4-thiadiazolidine-5-thiones **53**, the other product was identified as 4-ethyl/

Scheme 66



4, 105-108: R = *p*-Br-C_6H_4, R' = C_6H_5

Scheme 67



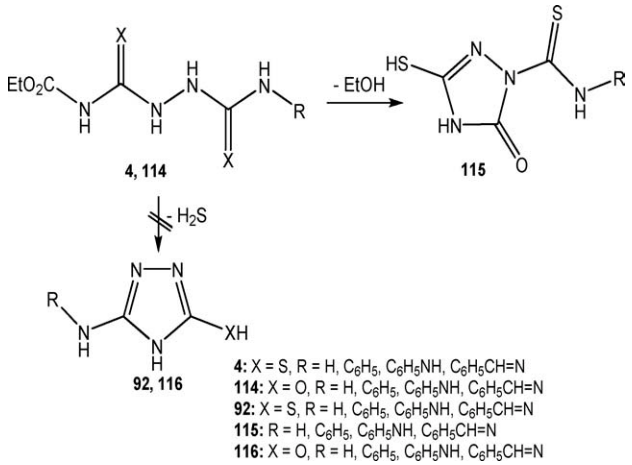
4,109 : R^1 = Methallyl, phenyl, R^2 = Ethoxy, phenyl

methyl-1,2,4-triazoline-3,5-dithione **88** [77]. When the alkyl group was *n*-propyl or *n*-butyl, the sole product obtained was characterized as 2-arylamino-Δ^2-1,3,4-thiadiazolidine-5-thion **53**. It was presumably formed by the elimination of alkylamine (Scheme 63).

Simiti and Marie [100] studied the behavior of symmetrical and asymmetrical *p*-bromodianilide of *N,N′*-bisthiocarbonic acid **4** toward —OH and CH_3I/—OH. The isomeric triazole **100** and **101** were formed from **4** in NaOH. Oxidation of **101** by H_2O_2 gave **102** (Scheme 64).

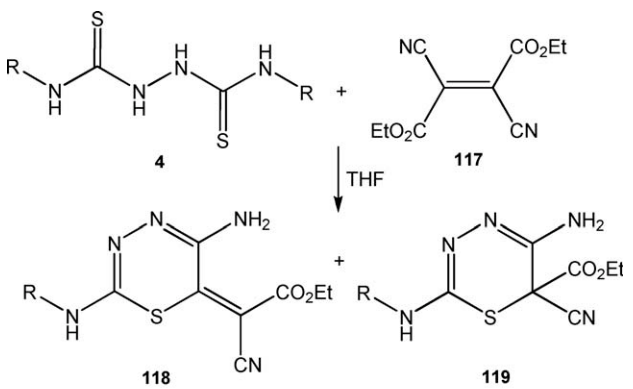
On the other hand, the action of NaOH on symmetrical **4** gave **103**, which oxidized by H_2O_2 to give **104** (Scheme 65) [100].

Scheme 68



4: X = S, R = H, C_6H_5, C_6H_5NH, C_6H_5CH=N
114: X = O, R = H, C_6H_5, C_6H_5NH, C_6H_5CH=N
92: X = S, R = H, C_6H_5, C_6H_5NH, C_6H_5CH=N
115: R = H, C_6H_5, C_6H_5NH, C_6H_5CH=N
116: X = O, R = H, C_6H_5, C_6H_5NH, C_6H_5CH=N

Scheme 69

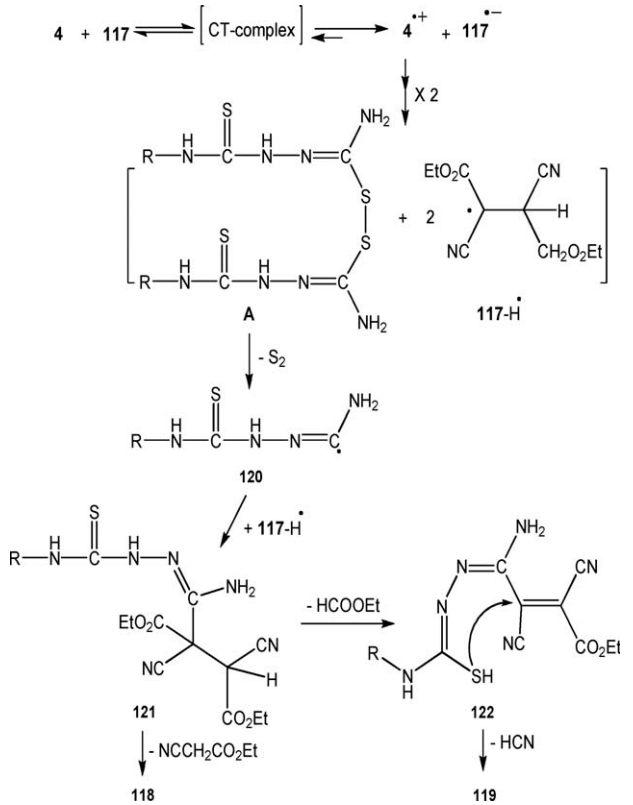


4,118,119: R = Phenyl, allyl, benzyl

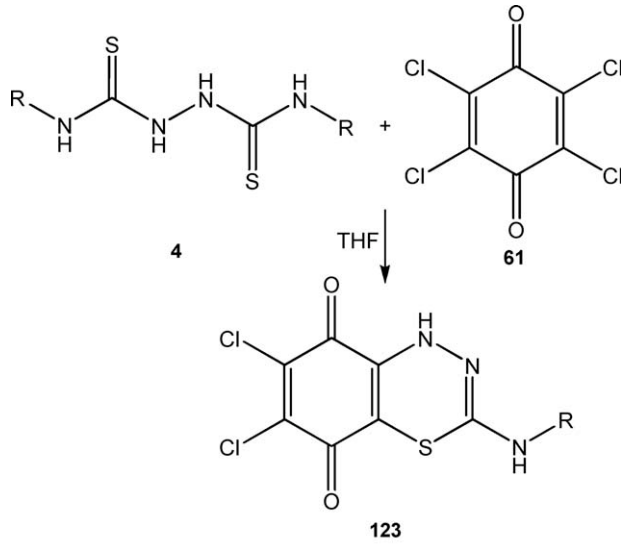
Also the action of NaOH and MeI, respectively, on **4** gave **105** and **106**. Oxidation of **105** by H_2O_2 gave **107**, while bromonation of **106** gave **108** (Scheme 66) [100].

2,4-Disubstituted thiosemicarbazides **51** reacted with acyl isothiocyanates to give dithiobiureas **4**, which cyclized to 1,2,4-triazoline-3-thiones **109** (not **110**) and 5-mercapto-1,2,4-triazoline-3-thiones **111** by the action of sodium ethanolate (Scheme 67).

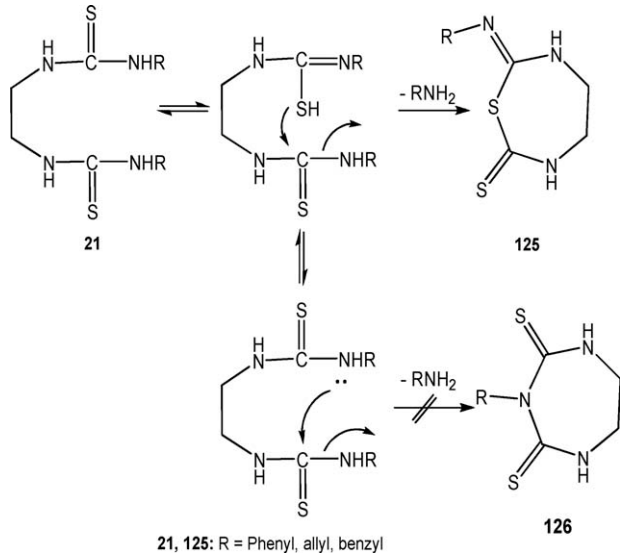
Scheme 70



Scheme 71



Scheme 73



Compound **111** was converted to the more stable *S*-benzyl derivatives **113**. However, **111** were oxidized by hydrogen peroxide to disulfide **112** [92].

Cyclization of dithiobiurea and thiobiurea derivatives involving the usual loss of hydrogen sulfide or H_2O and did not convert compounds of type **4** and **114** into **92** or **116**, but occurs in fact with elimination of ethanol and formation of 1*H*-(thio)amide-1,2,4-triazoles **115** (Scheme 68) [101–103].

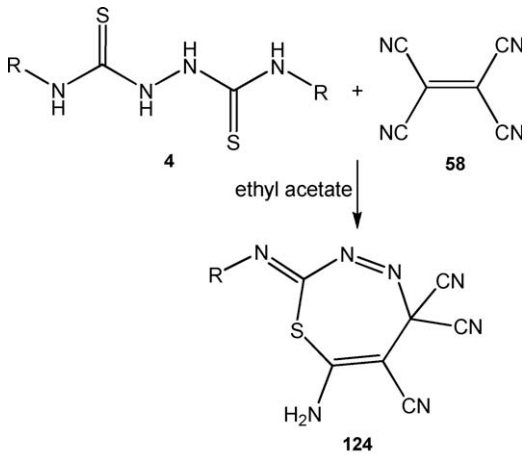
3.5. Synthesis of thiadiazine derivatives. 1-Substituted hydrazinecarbothioamide **4** reacted with ditheyl (*E*)-2,3-dicyanobutenedioate **117** in THF at room temperature to give ethyl (*Z*)-2-[-2-amino-2-(substituted amino)-6*H*-1,3,4-thiadiazine]-2-cyanoacetate **118** and ethyl 5amino-6-cyano-2-(substituted amino-6*H*-1,2,4-thiadiazine-6-carboxylate **119** (Scheme 69) [87].

A rationalization for the formation of thiadiazines compounds is given in Scheme 70 [87].

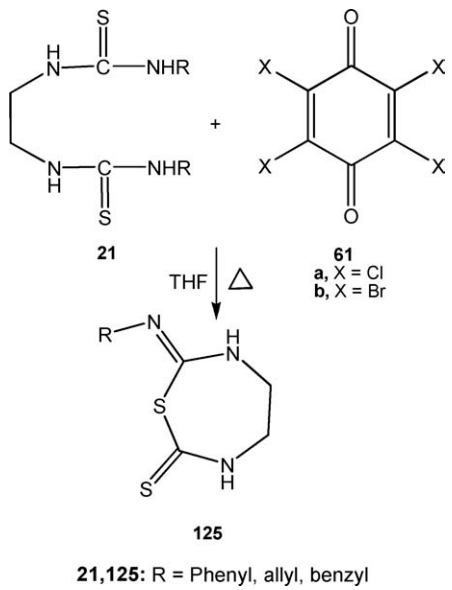
The interaction between 1,6-disubstituted hydrazinearbothioamides **4** and chloranil **61** in THF led to the formation of 3-substituted amino-6,7-dichloro-1*H*-benzo[*e*][1,3,4]thiadiazine-5,8-diones **123** (Scheme 71) [86].

3.6. Synthesis of thiadiazepine and thiadiazepane derivatives. Addition of two equivalents of ethenetetracarbonitrile **58** to 1,6-disubstituted-2,5-dithiobiureas **4** in ethyl acetate lead to the formation of 7-amino-2-

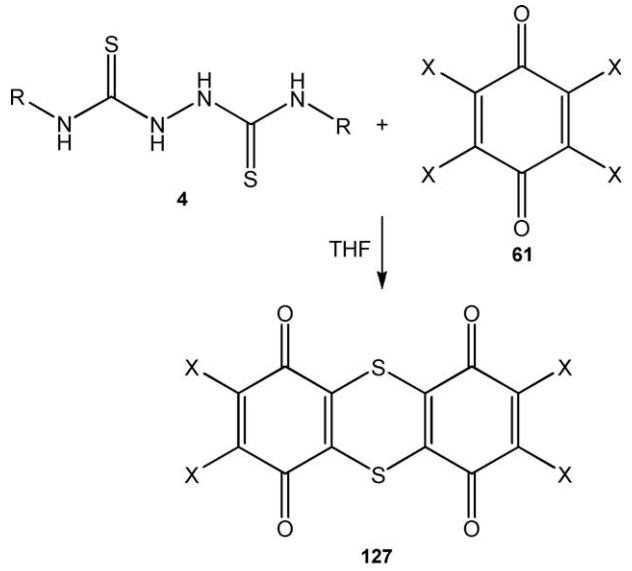
Scheme 72



Scheme 74



Scheme 75



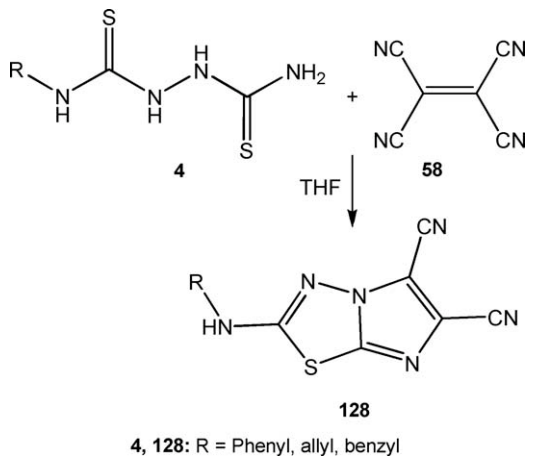
substituted imino-2*H*-[1,3,4]thiadiazepine-5,5,6-tri-carbonitriles **124** (Scheme 72) [83].

1,3,6-Thiadiazepane-2-thione **125** can be obtained on heating or microwave irradiation of thioureido-thioureas **21** [67]. The formation of **125** can be explained by nucleophilic attack of SH on C═S with elimination of a molecule of amine. The alternative structure **126** could be ruled out on the basis of spectral data of **125** (Scheme 73).

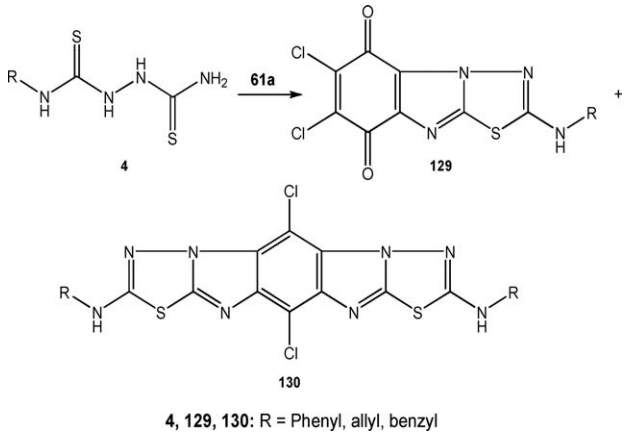
Also, 1,3,6-thiadiazepane-2-thione **125** was formed *via* interaction between thioureidothioureas **21** with chloranile or bromanile **61a,b** in boiling THF (Scheme 74) [86].

3.7. Synthesis of thiantherne derivatives. On adding 1,6-disubstituted-2,5-dithiobiureas **4** to chloranil or bromanil **61a,b**, 2,3,7,8-tetrahalothia-anthrene derivatives **127** were formed (Scheme 75) [86].

Scheme 76



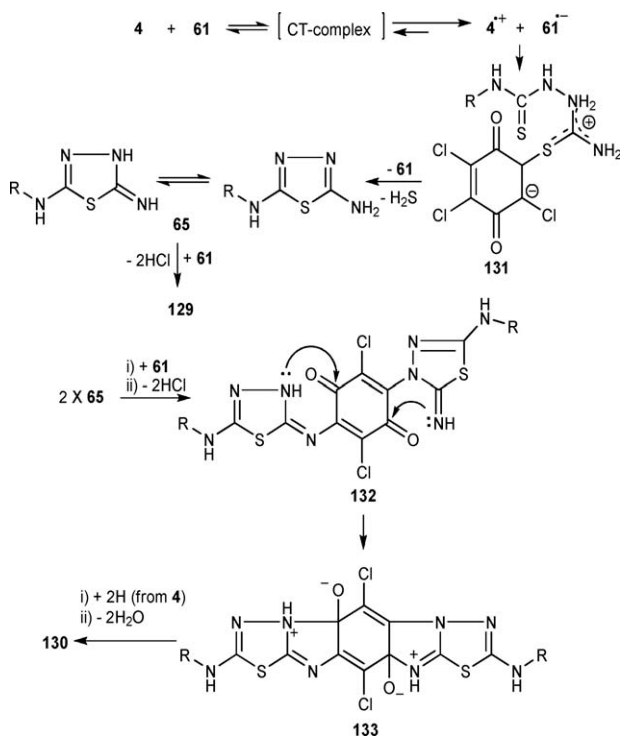
Scheme 77



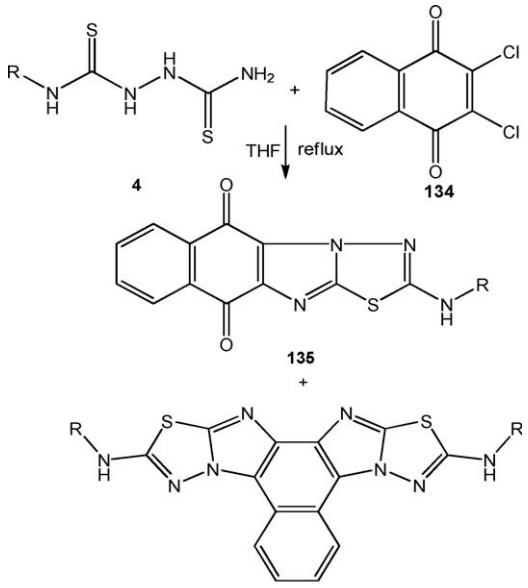
3.8. Synthesis of imidazothiadiazole derivatives. 2-(Substituted amino)imidazo[2,1-*b*][1,3,4]thiadi-azole-5,6-dicarbonitriles **128** were formed during the interaction between 1-substituted-2,5-dithiobiureas **4** with ethenete-tracarbonitrile **58** (Scheme 76) [87].

On the other hand, the reaction of chloranil **61a** with 1-substituted-2,5-dithiobiureas **4**, 2-substituted amino-6,7-dichlorobenzo[4,5]imidazo[2,1-*b*][1,3,4]-thiadiazole-5,8-diones **129** and 5,11-dichloro-2,8-disubstituted

Scheme 78



Scheme 79



4,135,136: R = Phenyl, allyl, benzyl

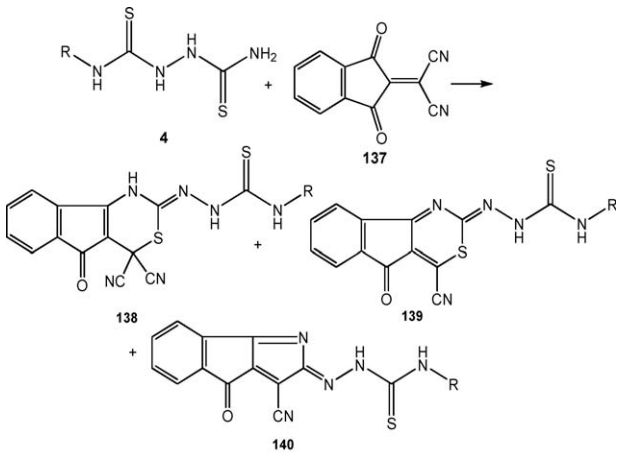
aminobenzo[21,3-*d*:6,5-*d*']bis(imidazo-[2,1-*b*][1,3,4]thiadiazoles) **130** were formed (Scheme 77) [104].

The formation of products **129** and **130** as in Scheme 78 [104]:

Also, the reaction between 1-substituted-2,5-dithiobiureas **4** and 2,3-dichloro-1,4-naphthoquinone **134** gave 2-substituted aminonaphtho[4,5]imidazo-[2,1-*b*][1,3,4] thiadiazole-5,10-diones **135** and 2,11-disubstituted aminonaphtho[1,2-*d*:4,3-*d*']bis-(imidazo[2,1-*b*][1,3,4]thidiazoles) **136** (Scheme 79) [104].

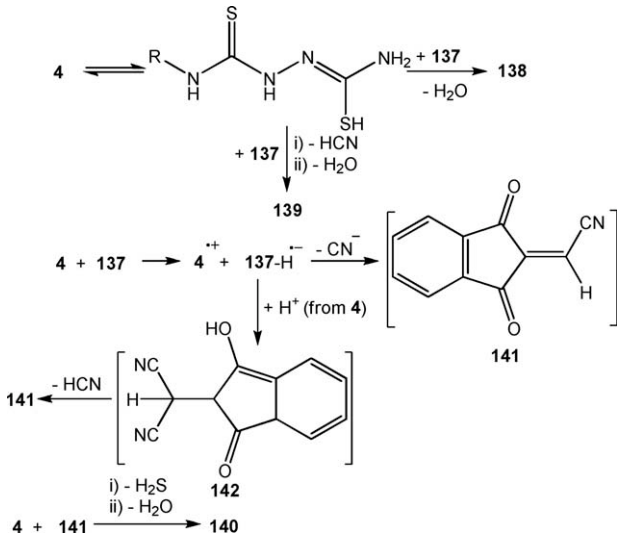
3.9. Synthesis of oxoindenothiazine and oxoindenopyrrole derivatives. (1,3-Dioxo-2,3-dihydro-1*H*-inden-2ylidene)-propanedinitrile **137** reacted with 1-substi-

Scheme 80



4,138,140: R = Phenyl, allyl, benzyl

Scheme 81

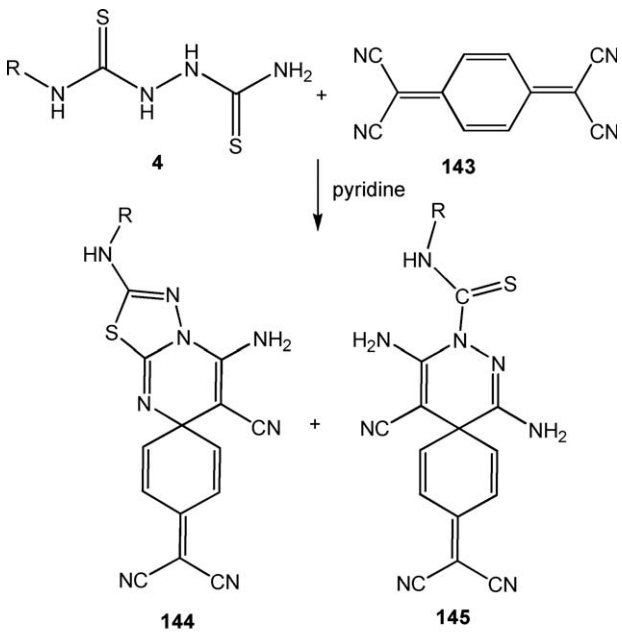


tuted-2,5-dithiobiureas **4** in ethyl acetate to give *N*-substituted-2(4,4-dicyano-5-oxoindeno[1,2-*d*][1,3]thiazin-2-(1*H*,4*H*,5*H*)-ylidene)hydrazinecarbothioamides **138**, *N*-substituted-2(4-cyano-5-oxoindeno-[1,2-*d*][1,3]-thiazin-2-(5*H*)-ylidene)hydrazinecarbothioamides **139** and *N*-substituted-2(3-cyano-4-oxoindeno[1,2-*b*]pyrrol-2-(4*H*)-ylidene)hydrazinecarbothioamides **140** (Scheme 80) [104].

A rationalization for the formation of products **138**–**140** is shown in Scheme 81 [104].

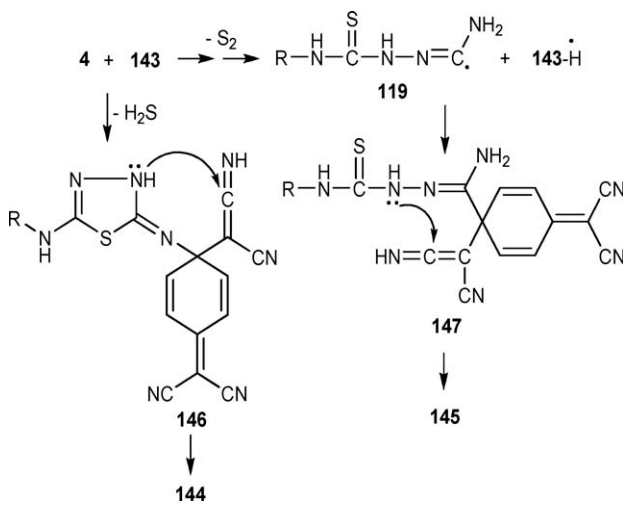
3.10. Synthesis of spiro compounds. The reaction of 1-substituted-2,5-dithiobiureas **4** with 7,7′,8,8′-

Scheme 82



4,144,145: R = Phenyl, allyl, benzyl

Scheme 83



tetracyanoquinodimethane **143** in dry pyridine lead to the formation of {5-amino-6-cyano-2-(substituted amino)spiro[1,3,4]thiadiazolo[3,2-*a*]-pyrimidine-7,1′-cyclohexa[2,5]diene-4′-ylidene}malononitriles **144** and 1,4-diamino-5-cyano-9-(dicyanomethylene)-*N*-substituted-2,3-diazospiro-[5,5′]undeca-1,4,7,10-tetraene-9-thioamides **145** (Scheme 82) [87].

The formation of compounds **144** and **145** can be rationalized by the following mechanism (Scheme 83) [87].

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