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REVIEW

Condensations of Thioamides with Acetylenecarboxylic Acid Derivatives

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Abstract—The review summarizes published data on the reactions of cyclic and acyclic thioamides with derivatives of acetylenecarboxylic acids, which lead to the formation of both acyclic and heterocyclic systems, including thiazolidines and thiazines. Methods for determination of the structure of the condensation products and factors responsible for the reaction direction are discussed.

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From left to right:

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1. INTRODUCTION

Thioamides and their derivatives occupy a specific place among the other N,S-containing compounds used in the synthesis of heterocyclic systems due to their accessibility and the ability to act as difunctional nucleophiles. It should be emphasized that wide application of thioamides in the synthesis of heterocycles would be impossible without a huge number of compounds having two or more electrophilic centers; the use of different electrophilic components makes it possible to vary the size of heterocyclic systems thus obtained and the degree of their saturation. Acetylenecarboxylic acid derivatives are classed with electrophilic reagents whose reactions with thioamides were used for the synthesis of various heterocyclic systems over the past century. Unfortunately, no review articles covering all known reactions of this sort have been published so far. Therefore, the present review was aimed at summarizing and systematizing available published data on the reactions of linear and cyclic thioamides with derivatives of acetylenecarboxylic acids and methods for determination of the product structure, as well as at elucidating factors determining the direction of these reactions.

2. REACTIONS OF ACETYLENECARBOXYLIC ACID DERIVATIVES WITH CARBOTHIOAMIDES

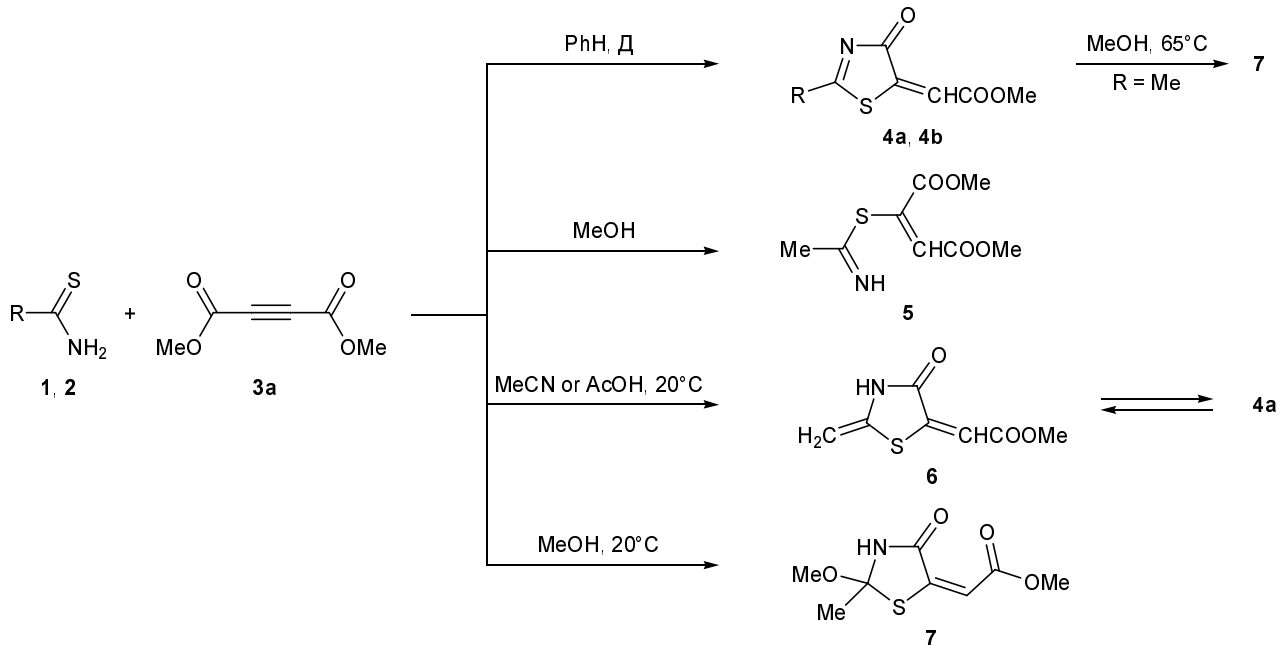
2.1. Aliphatic Carbothioamides

The condensations of thioacetamide (**1**) and phenylthioacetamide (**2**) with dimethyl acetylenedicarboxylate (**3a**) in benzene were reported [1] to give thiazolidinones **4a** and **4b**, respectively, as the only product (Scheme 1). According to Lown and Ma [2], the main product of the reaction of thioacetamide (**1**) with diester **3a** under the same conditions is dimethyl 2-(1-iminoethylsulfanyl)fumarate (**5**) which does not undergo cyclization to thiazolidinone **4a**. Even more unusual conclusion was drawn in [3]: the authors assigned the structure of 2-methylidenethiazolidinone **6** (which is tautomeric to **4a**) to the product of condensation of compounds **1** and **3a** in acetonitrile or acetic acid; on heating in boiling methanol, compound **6** took up a molecule of methanol at the activated C=N bond (due to possible tautomeric transformation **6**↔**4a**) to give 2-methoxy derivative **7**. The latter was also obtained by direct reaction of compounds **1** and **3a** in methanol at room temperature. It should be noted that the ^{1}H and ^{13}C NMR proofs given in [3] for the methoxythiazolidine structure seem to be more convincing than those given in [2] in favor of the open-chain structure (**5**). The ^{13}C NMR spectrum of **7** contained a signal at δ_C 97.0 ppm, typical of the sp^3-hybridized C^2 atom.

Ylidene derivatives were isolated in the reactions of α-(carbamoyl)thioacetamides **8** with diester **3a** [4, 5]. The probability for formation of these compounds was higher than in the reaction with thioacetamide due to greater mobility of the methylene hydrogen atoms in malonic acid derivatives. The reactions of thioamides **8a**, **8b**, **8d**–**8h** [4], and **8c** [5] and (cyano)thioacetamide (**8i**) [4] with **3a** in chloroform gave 2,5-dialkylidenethiazolidin-4-ones **9a**–**9i**, **10b**, and **10i**. From 2-(dimethylcarbamoyl)thioacetamide **8b**, pure isomers (*E*,*Z*)-**9b** and (*Z*,*Z*)-**10b** were isolated; (cyano)thioacetamide (**8i**) gave rise to a mixture of (*E*,*Z*)-**9i** and (*Z*,*Z*)-**10i** which could not be separated; and the reactions of thioamides **8a** and **8c**–**8h** afforded only the corresponding thiazolidines **9a** and **9c**–**9h** (Scheme 2).

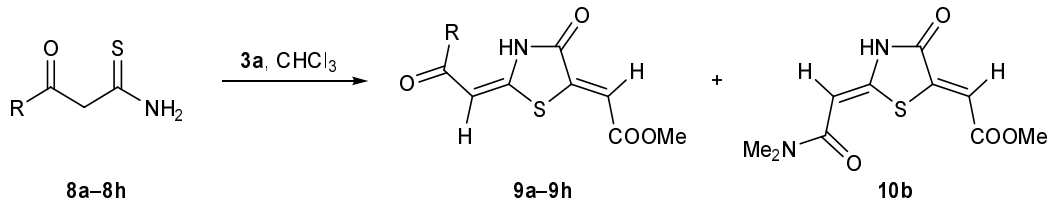
The reaction direction changes in going from acetylenedicarboxylate **3a** to acetylenemonocarboxylates. Thioamides **8a**, **8b**, and **8d**–**8h** and (cyano)thioacetamide (**8i**) failed to react with 2-propynoic acid esters at all [4], while the condensation of thioacetamide (**1**) with methyl 2-propynoate (**11a**) gave only

Scheme 1.

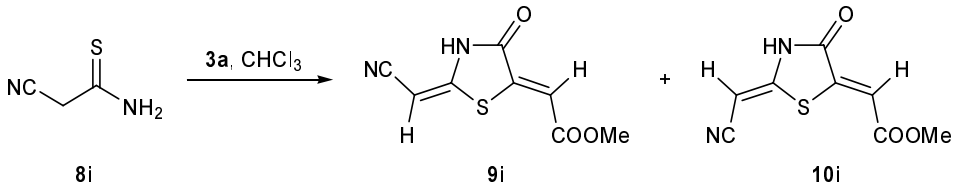


1, **4a**, R = Me; **2**, **4b**, R = $PhCH_2$.

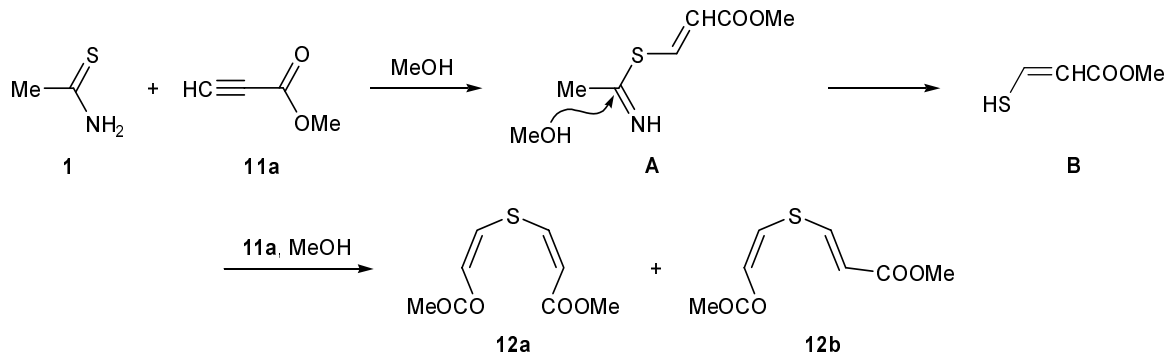
Scheme 2.



R = EtO (**a**), Me_2N (**b**), 4-MeC_6H_4NH (**c**), 2-MeC_6H_4NH (**d**), 2,6-$Cl_2C_6H_3NH$ (**e**), 2-$MeOC_6H_4NH$ (**f**), piperidino (**g**), morpholino (**h**).



Scheme 3.



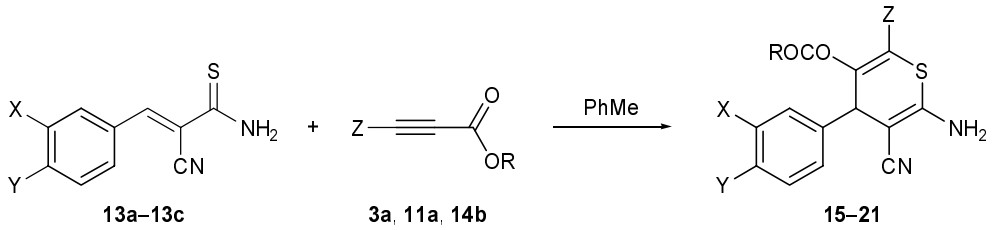
dimethyl (*Z*,*Z*)- and (*Z*,*E*)-4-thiahepta-2,5-dienedioates **12a** and **12b** at a ratio of 1:1 (Scheme 3) [2]. Presumably, thioacetamide (**1**) and ester **11a** form adduct **A** which reacts with methanol to give methyl 3-sulfanylprop-2-enoate **B**, and reaction of the latter with the second molecule of **11a** leads to diesters **12a** and **12b**.

2.2. α,β-Unsaturated Carbothioamides

Reactions of acetylenecarboxylic acid derivatives with thioamides having multiple bonds conjugated with the thioamide moiety should be considered separately, taking into account possible competition between nucleophilic addition of the SH group at the triple bond of the activated acetylenic compound and Diels–Alder reaction of the enethioamide (diene) with acetylene (dienophile). However, Diels–Alder adducts **15**–**21** were isolated only once in the condensation of 2-cyano-3-phenylprop-2-enethioamides **13a**–**13c** with dimethyl acetylenedicarboxylate **3a** and methyl propynoates **11a** and **14b** in boiling toluene [6] (Scheme 4).

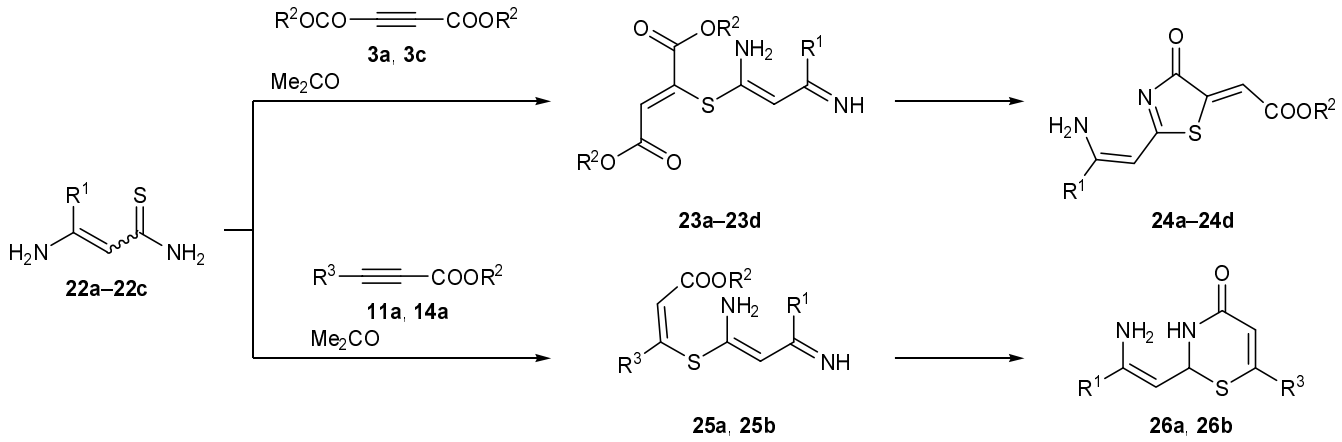
The presence of a conjugated bond system in molecules of enamino thioamides did not alter the usual reaction direction typical of thioamides and acetylenecarboxylic acid esters. Compounds **22a**–**22c** reacted with diester **3a**, acetylenedicarboxylic acid **3c**, and propynoic acid esters **11a** and **14a** in acetone to give thiazolidinones **24a**–**24d** and thiazinones **26a** and **26b**, respectively (Scheme 5) [7]. The condensation is favored by the *trans*-imino configuration of thioamides (**22A**), which is characterized by increased negative charge on the sulfur atom; the molecule of 2-aminocyclopent-1-enecarbothioamide (**27**) is fixed as *cis*-imino isomer, and it does not react with diester **3a**.

Scheme 4.

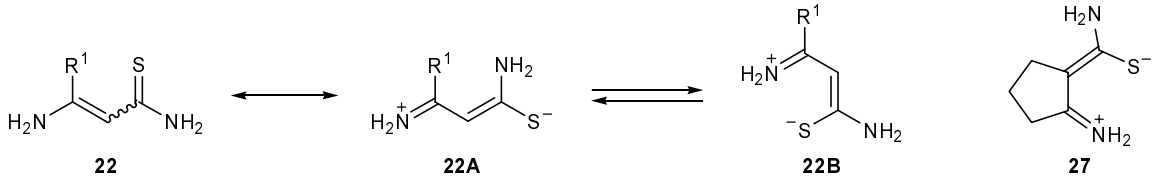


13a, **15**, **16**, **21**, X = NO_2, Y = H; **13b**, **17**, **18**, X = Y = OMe; **13c**, **19**, **20**, X = Y = Cl; **11a**, **15**, **17**, **19**, Z = H; **3a**, **16**, **18**, **20**, Z = COOMe; **14b**, **21**, Z = Ph, R = Et; **3a**, **11a**, **15**–**20**, R = Me.

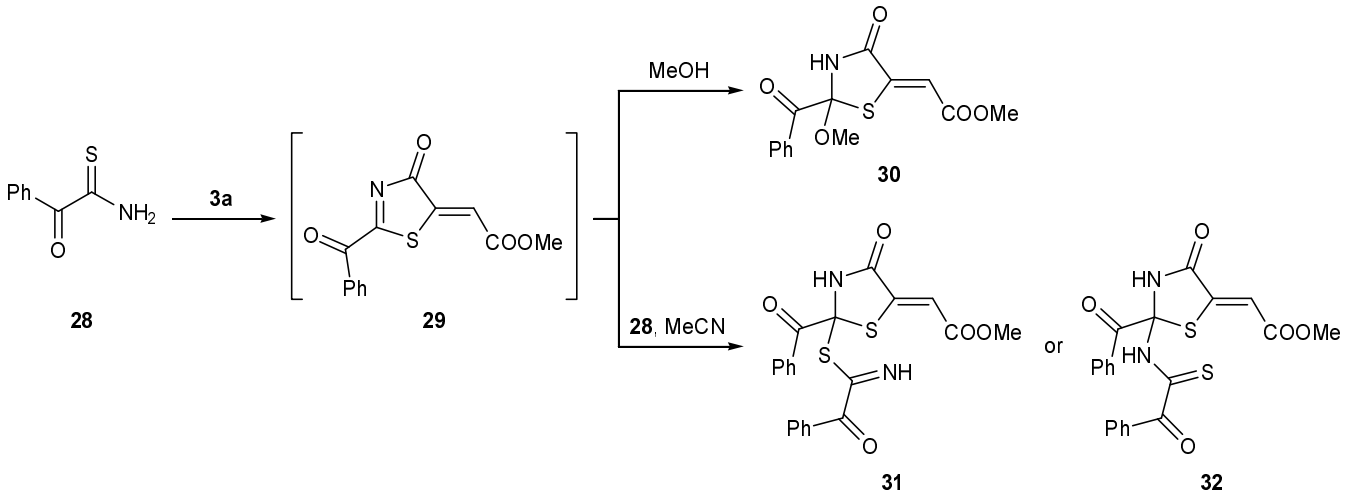
Scheme 5.



22a, **23a**, **23b**, **24a**, **24b**, **25a**, **25b**, **26a**, **26b**, R^1 = Me; **22b**, **23c**, **24c**, R^1 = Ph; **22c**, **23d**, **24d**, R^1 = 4-ClC_6H_4; **3c**, **23a**, **24a**, R^2 = H; **3a**, **11a**, **14a**, **23b**–**23d**, **24b**–**24d**, **25a**, **25b**, **26a**, **26b**, R^2 = Me; **11a**, **25a**, **26a**, R^3 = H; **14a**, **25b**, **26b**, R^3 = Ph.



Scheme 6.

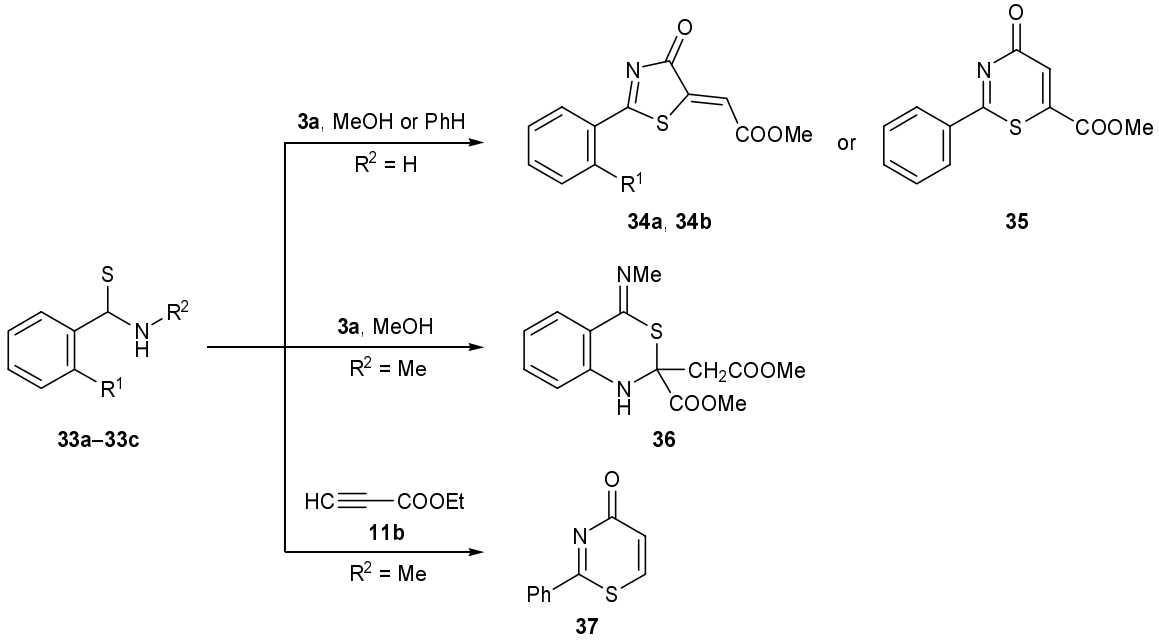


Methoxythiazolidinone **30** was isolated in the condensation of 2-oxo-2-phenylethanethioamide (**28**) with diester **3a** in methanol (Scheme 6) [3], i.e., the reaction direction was the same as with thioacetamide (**1**). When the condensation was carried out in acetonitrile, the primary product, 2-benzoylthiazolidinone **29**, took up the second molecule of thioamide **28** at the activated C=N bond to give methyl 2-[2-benzoyl-2-(1-imino-2-oxo-2-phenylethenylsulfanyl)-4-oxotetrahydro-1,3-thiazol-5-ylidene]acetate (**31**) or its isomer **32** which could not be distinguished [3].

2.3. Aromatic Carbothioamides

Reactions of dimethyl acetylenedicarboxylate (**3a**) with thiobenzamide (**33a**) in benzene [1] or methanol [8] and with 2-aminothiobenzamide (**33b**) in methanol gave thiazolidinones **34a** and **34b**, respectively [1] (Scheme 7). However, according to [2], the only product of the reaction of **33a** with **3a** in methanol was thiazine **35**. Obviously, the product has structure **34a**, while the experimental data in [2] were interpreted erroneously (for unambiguous determination of the

Scheme 7.



33a, **34a**, R^1 = H; **33b**, **33c**, **34b**, R^1 = NH_2; **33a**, **33b**, R^2 = H; **33c**, R^2 = Me.

structure of diester **3a** condensation products with thioamide derivatives, see Section 3). On the other hand, benzothiazine **36** was formed in the reaction of *N*-methylthiobenzamide (**33c**) with disester **3a** [3]; here, the ester moieties in **3a** were not involved in the condensation (Scheme 7).

1,3-Thiazine-4-one **37** was obtained by heating thiobenzamide (**33a**) with ethyl propynoate (**11b**) at 100°C under solvent-free conditions [1], while the reaction of **33a** with methyl propynoate (**11a**) in methanol [2] afforded a mixture of dimethyl (*Z*,*Z*)- and (*E*,*Z*)-4-thiahepta-2,5-dienedioates **12a** and **12b** (Scheme 3).

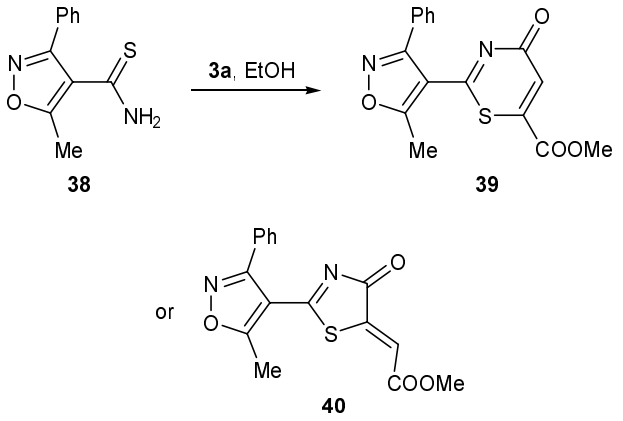
2.4. Heterocyclic Carbothioamides

Heteroaromatic carbothioamides **38** and **41a**–**41h** were reported to react with acetylenecarboxylic acid derivatives with formation of thiazolidines **40**, **43a**, **43b**, and **43e**–**43h** [9] rather than isomeric thiazines **39** and **42** (Schemes 8, 9). The product structure was proved on the basis of the $^2J_{HC}$ and $^3J_{HC}$ coupling constants in the ^{13}C NMR spectra. The presence of an amino group on C^5 in hetarenecarbothioamides **41g** and **41h** did not change the reaction direction, while thioamides **41c**–**41f** having three nitrogen atoms in the heteroring showed reduced reactivity toward **3a**. The corresponding condensation products (compounds **43e** and **43f**) were isolated only in the reactions of *N*-alkyl-1,2,3-triazole-4-carbothioamides **41e** and **41f** with diester **3a** (Scheme 9).

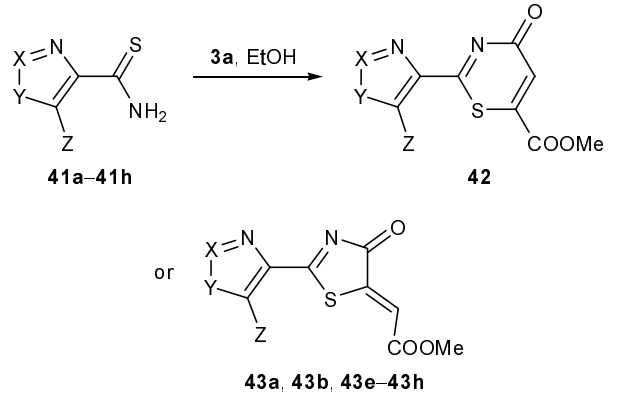
2.5. Carbothioamides Having an Azomethine Ylide Moiety

Pyridinium and isoquinolinium thiocarbamoylazomethine ylides **44a**–**44c** [10] are interesting substrates from the viewpoint of their behavior in reactions with

Scheme 8.

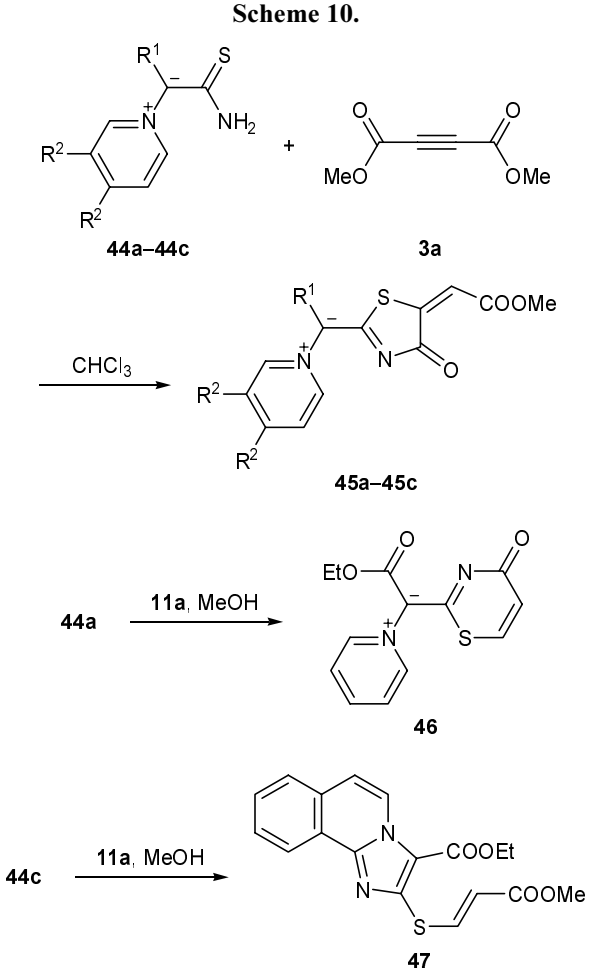


Scheme 9.



X = CH (**a**, **b**, **g**), N (**c**–**f**, **h**); Y = NH (**a**, **b**, **g**), NPh (**c**, **d**), NMe (**e**), NCH_2Ph (**f**), S (**h**); Z = EtS (**a**), $PhCH_2S$ (**b**, **c**), MeS (**d**–**f**), NH_2 (**g**, **h**).

Scheme 10.



44, **45**, R^1 = EtOCO (**a**, **c**), PhNHCO (**b**); R^2 = H (**a**, **b**); R^2R^2 = $(CH{=}CH)_2$ (**c**).

acetylenecarboxylic acid derivatives; the presence in their molecules of several nucleophilic centers could give rise to a variety of reaction pathways. The direction of heterocyclization is determined by the nature of the azinium fragment in the ylide and acetylenic dipolarophile. The reactions of ylides **44a**–**44c** with **3a** in chloroform do not involve the ylide fragment, and the products are compounds **45a**–**45c** (Scheme 10). Ylide **44a** reacted with methyl propynoate (**11a**) to give pyridinium ylide **46** having a thiazine ring, and the condensation of **11a** with isoquinolinium ylide **44c** produced imidazo[1,2-*a*]isoquinoline derivative **47**.

Thus, condensations of thioamides with acetylenedicarboxylic acid ester generally lead to the formation of thiazolidinones and their derivatives. However, 4-thiahepta-2,5-dienedioic acid esters or 1,3-thiazinones are formed in reactions of thioamides with acetylenemonocarboxylates. The formation of 4-thiahepta-2,5-dienedioates is favored by carrying out the reactions in alcohol, while 1,3-thiazinones are obtained in solvents having no nucleophilic groups.

3. REACTIONS OF ACETYLENECARBOXYLIC ACID DERIVATIVES WITH THIOUREA AND ITS DERIVATIVES

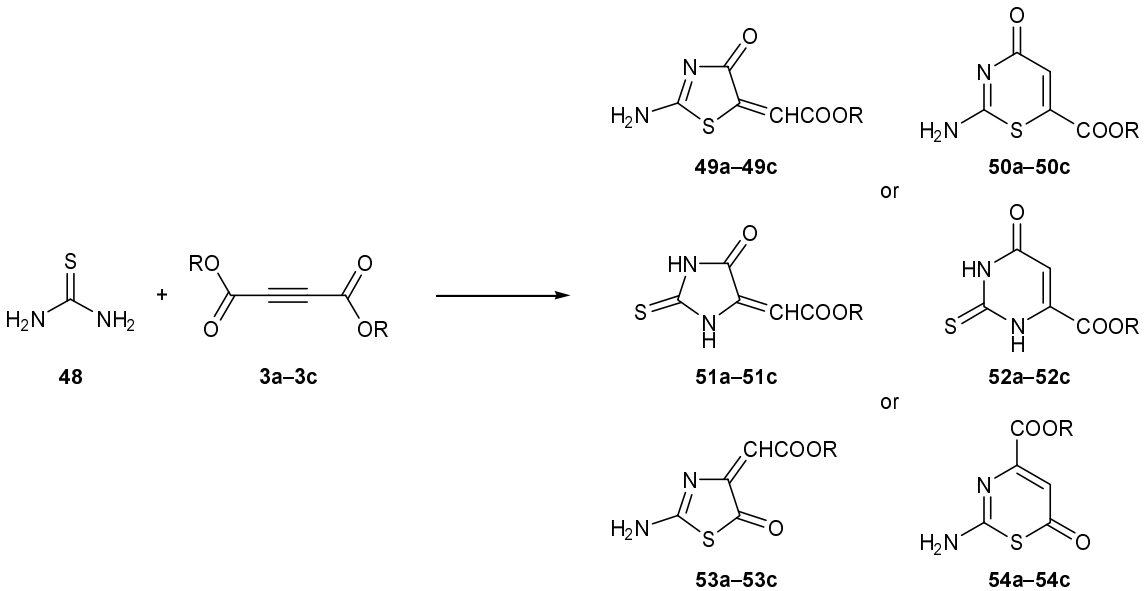
3.1. Unsubstituted Thiourea

Reaction of unsubstituted thiourea (**48**) with acetylenedicarboxylic acid (**3c**) and its methyl and ethyl esters **3a** and **3b** could give rise to five- (compounds **49**, **51**, **53**) and six-membered heterocycles (**50**, **52**, **54**) (Scheme 11). Five-membered heterocycles **49**, **51**, and **53** may be formed as *Z* and *E* isomers with respect to the exocyclic double bond, so that the number of possible reaction products increases to 9. It should be noted that compounds **51**–**54** can readily be identified by the ^{13}C NMR data [11, 12]. However, in most cases these products were not detected. Therefore, derivatives of thiazolidinones **49** and thiazinones **50** will be discussed in more detail in this and next sections.

Thiazolidinones **49a** and **49c** were isolated in the condensation of thiourea (**48**) with acetylenedicarboxylic acid (**3c**) [1, 13] and its dimethyl ester **3a** [1, 13, 14] in methanol and/or ethanol. Compound **49a** was also obtained by reaction of disester **3a** with thiourea in 40% phosphoric acid [15]. When the condensation of **48** with **3a** and **3c** was performed in the presence of hydrochloric or *p*-toluenesulfonic acid, products of addition of the SH group of thiourea at the triple bond were isolated [16]. Despite similar conditions of the condensations of thiourea with diester **3a** in [1, 13, 14] and [16–20] (methanol and/or ethanol), the product was assigned in [16–20] the structure of thiazinone **50a**. According to [16], thiazinones **50a** and **50c** were formed in the condensation of thiourea with diester **3a** in water or with acid **3c** in water and methanol.

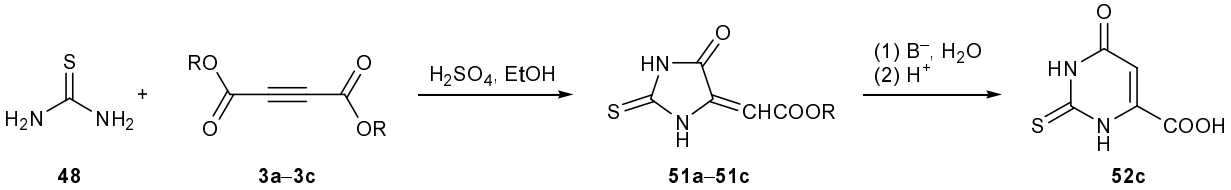
In fact, the products of this reaction, regardless of the conditions, are likely to be the corresponding thiazolidines rather than thiazines (for determination of the

Scheme 11.



R = Me (**a**), Et (**b**), H (**c**).

Scheme 12.



48 3a–3c 51a–51c 52c

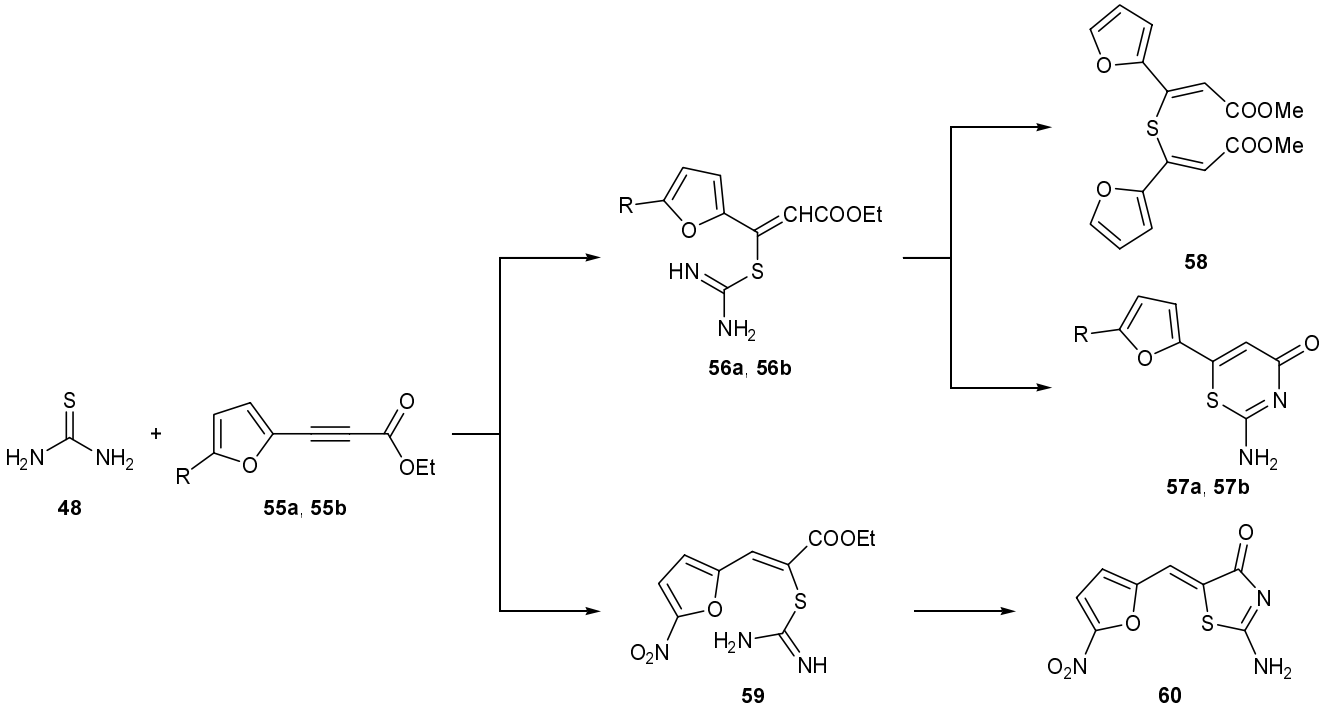
R = Me (**a**), Et (**b**), H (**c**).

structure of products formed by the reaction of thiourea with compound **3a**, see Section 3.4 [21]). Unfortunately, five- (**49a**–**49c**) and six-membered condensation products (**50a**–**50c**) cannot be distinguished by standard ^{1}H and ^{13}C NMR, IR, UV, and mass spectra. Therefore, the data of [22, 23], according to which the reaction of thiourea with acetylenedicarboxylic acid (**3c**) in H_2SO_4 and with esters **3a** and **3b** in water and alcohol gives imidazolidinones **51a**–**51c** (Scheme 12), seem to be doubtful.

Moriyama [22] also reported that condensation products **51a**–**51c** undergo rearrangement into 4-oxo-2-thioxo-1,3-pyrimidine-6-carboxylic acid salt on heating in a solution of sodium hydroxide; the subsequent acidification yields acid **52c** (Scheme 12) [22]. Short et al. [13] reproduced the condensation of thiourea (**48**) with acetylenedicarboxylic acid (**3c**) in sulfuric acid and with ester **3a** in water and methanol and isolated thiazolidinones **49a** and **49c**, respectively (Scheme 11). Heating of acid **49c** and ester **49a** in 2 N NaOH under the conditions described in [22] for the rearrangement of **51a**–**51c** into pyrimidine **52c** (100°C, 2 h) resulted in hydrolytic decomposition of the substrates, and only 15% of **49c** was isolated.

A number of publications reported on reactions of thiourea with acetylenecarboxylic acids having a substituent on C^3 other than carboxy group. Taking into account some similarity between the furan ring fragment and carboxy group, 3-(2-furyl)propynoic acid ester may be regarded as a close analog of diester **3a**. The regio- and stereoselectivity of the condensation of ethyl 3-(2-furyl)- and 3-(5-nitro-2-furyl)propynoates **55a** and **55b** with thiourea were found to depend on both the activating power of the substituent at the triple

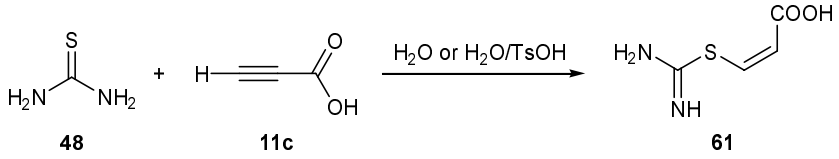
Scheme 13.



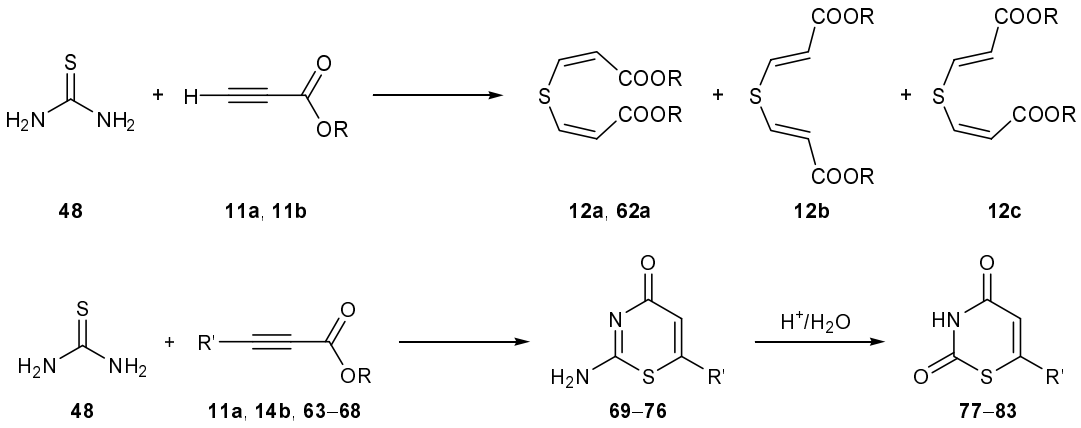
48 55a, 55b 56a, 56b 58 57a, 57b 59 60

R = H (**a**), O_2N (**b**).

Scheme 14.



Scheme 15.



11a, **12a**–**12c**, **64**, R = Me; **11b**, **14b**, **62a**, **63**, **65**–**68**, R = Et; **11a**, **69**, R' = H; **63**, **70**, **77**, R' = Me; **64**, **71**, **78**, R' = $ClCH_2$; **14b**, **72**, **79**, R' = Ph; **65**, **73**, **80**, R' = 4-MeC_6H_4; **66**, **74**, **81**, R' = 4-$MeOC_6H_4$; **67**, **75**, **82**, R' = 4-ClC_6H_4; **68**, **76**, **83**, R' = 2-ClC_6H_4.

bond and solvent polarity (acetone, methanol, ethanolic HCl) [24]. In the molecule of ethyl 3-(2-furyl)propynoate (**55a**), the ester group is a stronger acceptor than the 2-furyl group; therefore thiourea adds exclusively at the β-position, regardless of the solvent polarity. Primary β-adduct **56a** is converted mainly into 2-amino-6-(2-furyl)-4*H*-1,3-thiazin-4-one (**57a**) and diethyl 3,3-di(2-furyl)-4-thiahepta-2,5-dienedioate (**58**) (Scheme 13). 5-Nitro-2-furyl and ethoxycarbonyl groups are comparable in their activating effect on the triple C≡C bond, and the ratio of β- and α-adducts **56b** and **59** in reactions with nucleophiles depends on the solvent: polar solvents favor formation of the β-adduct. β-Adduct **56b** was isolated as hydrochloride when the condensation was carried out in a mixture of ethanol with hydrochloric acid.

It was very difficult to effect cyclization of **56b** in water at pH 2; the reaction was accompanied by decomposition of the furan ring, and it resulted in formation of a mixture of polymeric products and only a small amount of 1,3-thiazine **57b**. α-Adduct **59** derived from thiourea and ethyl 3-(5-nitro-2-furyl)-propynoate (**55b**) readily underwent ring closure to 2-amino-5-(5-nitro-2-furfurylidene)-4,5-dihydro-1,3-thiazol-4-one (**60**) in aprotic medium (Scheme 13).

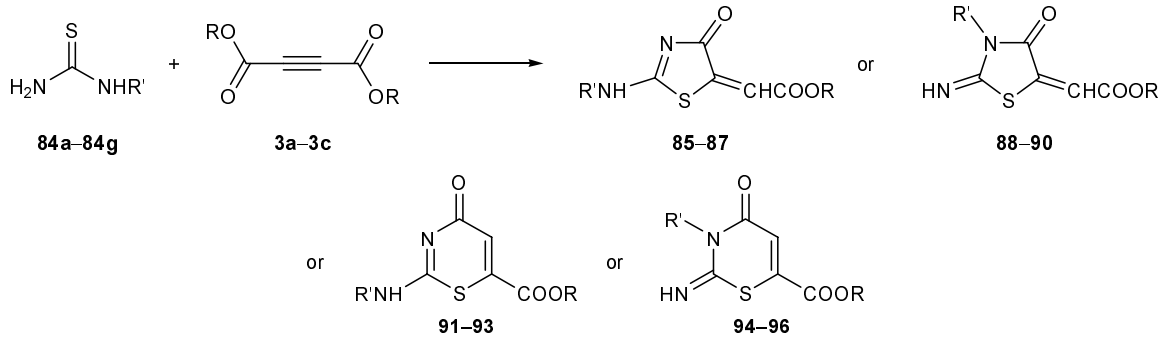
The reaction of thiourea **48** with propynoic acid (**11c**) in water gave compound **61** via addition of the SH group at the triple bond of **11c** [16] (Scheme 14). Dallas et al. [25] isolated three isomeric dimethyl 4-thiahepta-2,5-dienedioates, (*Z*,*Z*)-**12a**, (*Z*,*E*)-**12b**, and (*E*,*E*)-**12c**, in the reaction of thiourea (**48**) with methyl propynoate (**11a**) in methanol, while Kataev et al. [16] obtained a mixture of (*Z*,*Z*)-**12a**, (*Z*,*E*)-**12b**, and thiazinone **69** in the same reaction (Scheme 15). The condensation of **48** with ethyl propynoate (**11b**) afforded only (*Z*,*Z*)-4-thiahepta-2,5-dienedioate (**62a**) [18].

Presumably, substituted propynoates such as **14b** [26, 27], **64** [28], **14b**, **63**, and **65**–**68** [18] should be used and their reactions with thiourea should be carried out in solvents possessing no nucleophilic properties (e.g., in acetone) [26, 27] to obtain heterocyclic systems. It should be noted that hydrolysis of 1,3-thiazinones **70**–**76** may be regarded as a convenient method for the synthesis of 6-substituted thiauracils **77**–**83** (Scheme 15) [18, 26, 28].

3.2. N-Monosubstituted Thioureas

Apart from the ring size in the products, reactions of monosubstituted thioureas **84a**–**84h** with acetylenedicarboxylic acid, its esters, and furylpropynoates involve another regioselectivity problem which arises from nonequivalence of the nucleophilic centers in N-substituted thiourea molecules (Scheme 16). The

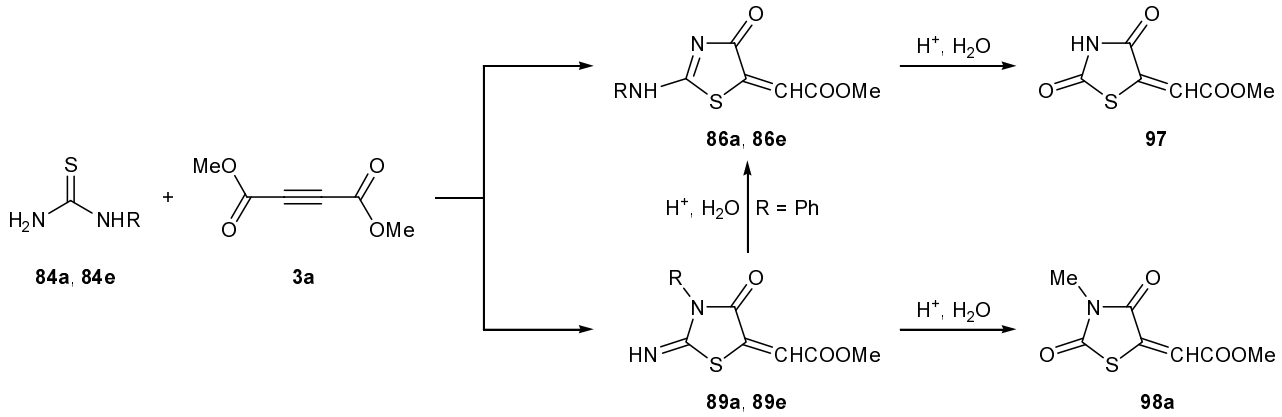
Scheme 16.



84a–84g **3a–3c** **85–87** **88–90** **91–93** **94–96**

3c, **85**, **88**, **91**, **94**, R = H; **3a**, **86**, **89**, **92**, **95**, R = Me; **3b**, **87**, **90**, **93**, **96**, R = Et; R' = Me (**a**), Et (**b**), Pr (**c**), *i*-Pr (**d**), Ph (**e**), 2-$MeOC_6H_4$ (**f**); $PhCH_2$ (**g**), 4,6-dimethylpyrimidin-2-yl (**h**).

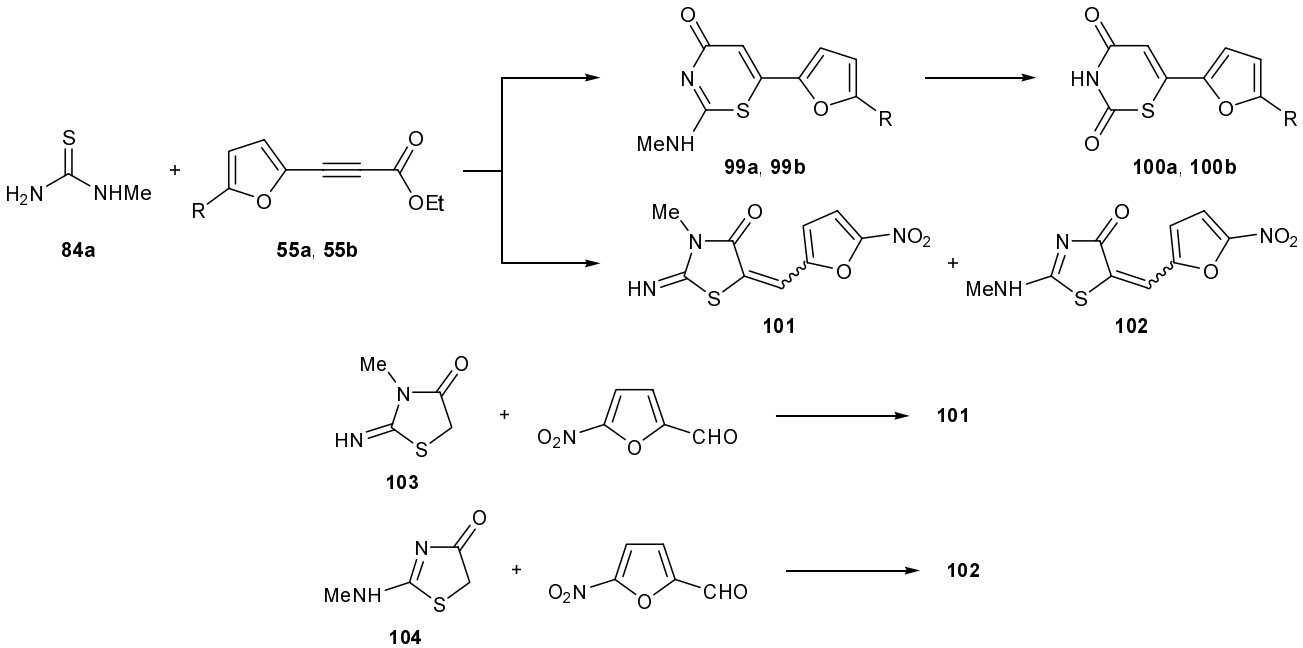
Scheme 17.



84a, **84e** **3a** **86a**, **86e** **97** **89a**, **89e** **98a**

R = Me (**a**), Ph (**e**).

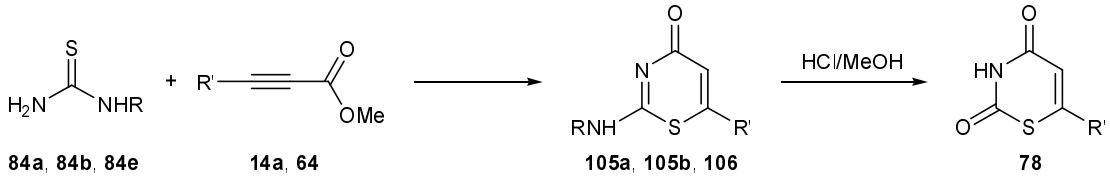
Scheme 18.



84a **55a**, **55b** **99a**, **99b** **100a**, **100b** **101** **102** **103** **104**

R = H (**a**), O_2N (**b**).

Scheme 19.



84a, **84b**, **84e** **14a**, **64** **105a**, **105b**, **106** **78**

84a, **105a**, R = Me; **84b**, **105b**, R = Et; **84e**, **106**, R = Ph; **64**, **105a**, **105b**, **78**, R' = $ClCH_2$; **14a**, **106**, R' = Ph.

formation of both five-membered thiazolidine (compounds **85e**, **85g**, **86e**, **86g** [1], and **87h** [29]) and six-membered 1,3-thiazine systems (**92a**, **92e**, and **92f** [19]) was reported. Moreover, the condensation can take both pathways simultaneously, resulting in the formation of equimolar mixtures of thiazines **92a**/**95a** and **92b**/**95b** [17]. Mixtures **86a**/**89a** and **86e**/**89e**, isomers **89a** and **89e** prevailing, were isolated in the reactions of dimethyl acetylenedicarboxylate (**3a**) with *N*-methyl- and *N*-phenylthioureas **84a** and **84e**, respectively [14]. The structure of thiazolidine **89a** was later proved by the X-ray diffraction data [30].

Unlike 3-methylthiazolidinone **89a**, its phenyl-substituted analog **89e** undergoes rearrangement into isomer **86e** in the presence of aqueous acid; this follows from the fact that acid hydrolysis of a mixture of thiazolidinones **86e** and **89e** gives compound **97** as the only product [14] (Scheme 17).

The reactions of *N*-methylthiourea (**84a**) with ethyl 3-(2-furyl)propynoate (**55a**) in solvents with different polarities and of ethyl 3-(5-nitro-2-furyl)propynoate (**55b**) in polar solvents (methanol or ethanol containing HCl, i.e., under conditions favoring formation of the corresponding β-adduct and its cyclic derivatives) gave only isomers **99a** and **99b**, and hydrolysis of the latter afforded 6-furylthiazinediones **100a** and **100b** [24] (Scheme 18). Both isomers **101** and **102** (the latter prevailing) were formed in the reaction of ethyl 3-(5-nitro-2-furyl)propynoate **55b** with *N*-methylthiourea (**84a**) in aprotic solvents (acetone). Their structure was proved by independent synthesis (Scheme 18). The direction of the reaction between *N*-phenylthiourea (**84e**) with methyl propynoate (**11a**) was the same as in the reaction of **11a** with unsubstituted thiourea (**48**); the condensation in methanol gave a mixture of isomeric dimethyl 4-thiahepta-2,5-dienedioates **12a**–**12c** (Scheme 15) [25].

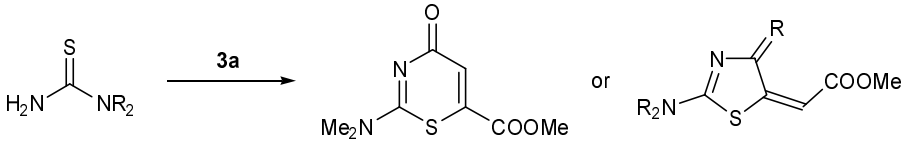
Monosubstituted thioureas **84a**, **84b**, and **84e** reacted with β-substituted acetylenemonocarboxylic acid esters to produce thiazine systems (Scheme 19). The reactions of **84a** and **84b** with methyl 4-chlorobut-2-ynoate (**64**) in alcohol gave thiazines **105a** and **105b**, respectively [22]. Thiazinedione **78** having no methyl group on the nitrogen was obtained by acid hydrolysis of **105a**. Dallas et al. [25] reported on the formation of 2-methylaminothiazine **106** from methyl 3-phenylpropynoate (**14a**) and thiourea **84e**.

3.3. N,N-Disubstituted Thioureas

N,*N*-Dimethylthiourea (**107a**) [17] and *N*,*N*-diphenylthiourea (**107b**) [1] react with diester **3a** in a way similar to unsubstituted thiourea, and the products are 2-(dimethylamino)thiazinone **108** [17] and 2-(diphenylamino)thiazolidinone **109b** [1] (Scheme 20). The structure of compound **109c** was proved by X-ray analysis [31, 32] and ^{13}C NMR spectroscopy [21].

Chemical transformations leading to 1,3-thiazine derivatives **112a** and **112b** were described in [33] (Scheme 21). In the first stage, compound **3a** acts as a dipolarophile, so that dithiazolethiones **110a** and **110b** give rise to dimethyl 2-[(aminocarbothioyl)-imino]-2,3-dihydro-1,3-dithiole- and *N*-phenylthiazole-4,5-dicarboxylates **111a** and **111b** which then react with the second molecule of **3a**, yielding 1,3-thiazines **112a** and **112b** (Scheme 21).

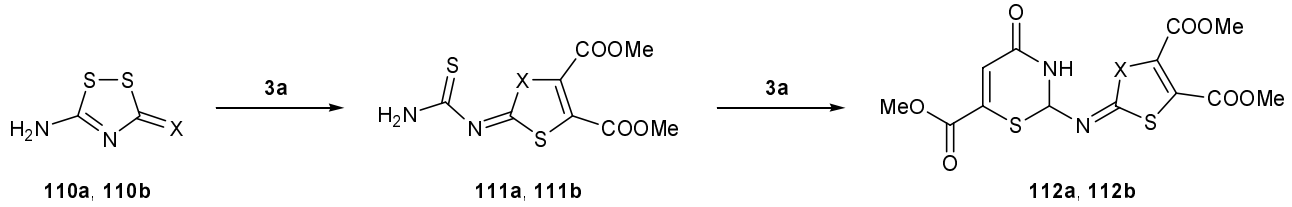
Scheme 20.



107a–**107c** **108** **109b**, **109c**

R = Me (**a**), Ph (**b**); R_2N = piperidino (**c**).

Scheme 21.



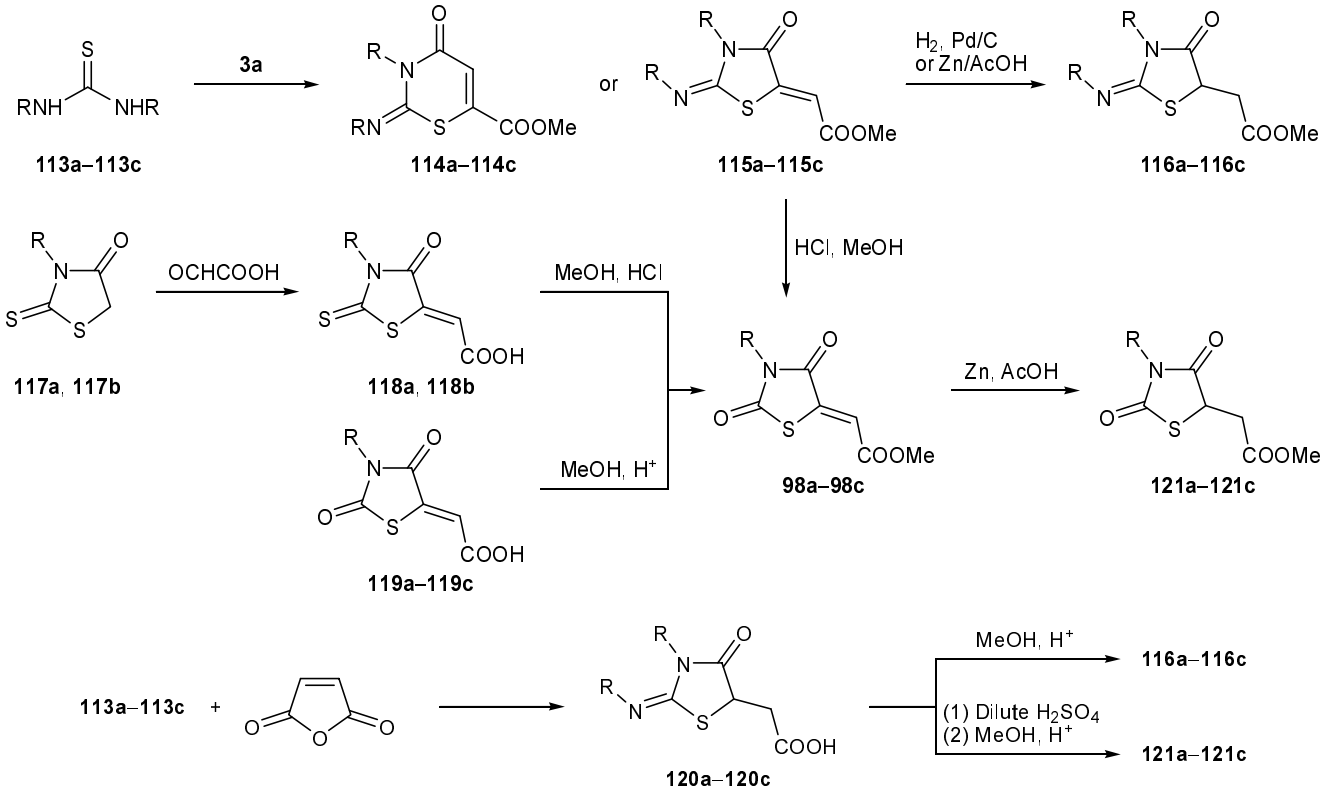
X = S (**a**), NPh (**b**).

3.4. N,N′-Disubstituted Thioureas

Reactions of *N*,*N*′-disubstituted thioureas with dimethyl acetylenedicarboxylate (**3a**) were reported to produce both five- [1, 14, 21], and six-membered heterocyclic systems [2, 19]. Like *N*-monosubstituted thioureas, unsymmetrical *N*,*N*′-disubstituted thioureas with different groups R and R' on the nitrogen atoms possess two nonequivalent nucleophilic centers, so that their reactions could give rise to regioisomeric products. Hiroshi [14] tried to determine the ring size of the products formed by reactions of symmetric *N*,*N*′-disubstituted thioureas (R = R') with diester **3a** on the basis of their chemical transformations and high-resolution mass spectra (Scheme 22). The results seem to be quite convincing. To exclude possible rearrangement of thiazines **114** into thiazolidines **115**, the latter were hydrogenated to compounds **116** which cannot be formed via rearrangement of tetrahydrothiazines **122** (Scheme 23).

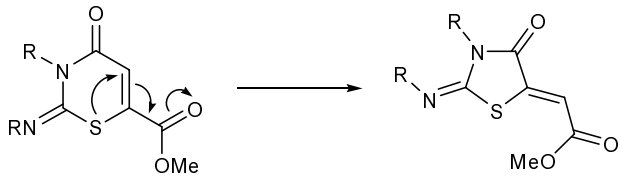
Vögelí et al. [21] were the first to apply ^{13}C NMR spectroscopy, including analysis of the coupling constants $^{2}J_{HC}$ and $^{3}J_{HC}$, to structure determination of the condensation products of substituted thioureas with acetylenecarboxylic acid derivatives. Using compounds **123** and **124** as model structures (which were synthesized by condensation of 3-methyl-2-methylimino-1,3-thiazolidin-4-one with benzaldehyde and by

Scheme 22.

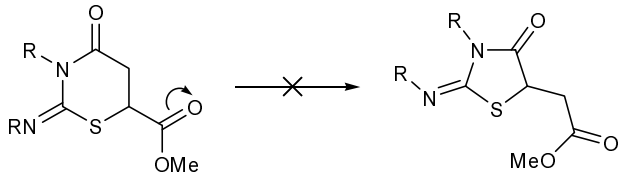


R = Me (**a**), $PhCH_2$ (**b**), Ph (**c**).

Scheme 23.

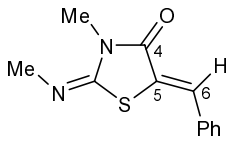


114 **115a–115c**

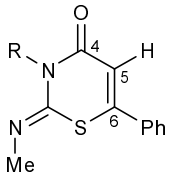


122 **116a–116c**

reaction of *N*,*N*′-dimethylthiourea with ethyl 3-phenylpropynoate, respectively), the authors found that the vicinal coupling constants $^{3}J(C^{4},6\text{-H})$ are equal to ~5 Hz (**123**) and that the geminal coupling constants $^{2}J(C^{4},5\text{-H})$ are equal to ~1 Hz (**124**). These values are fully consistent with the known dependences of $^{n}J_{HC}$ upon both *n* (the number of bonds between the interacting ^{13}C and ^{1}H nuclei) and hybridization of the carbon atom ($^{2}J_{HC}$) or the torsion angle HCCC ($^{3}J_{HC}$) [34].



123

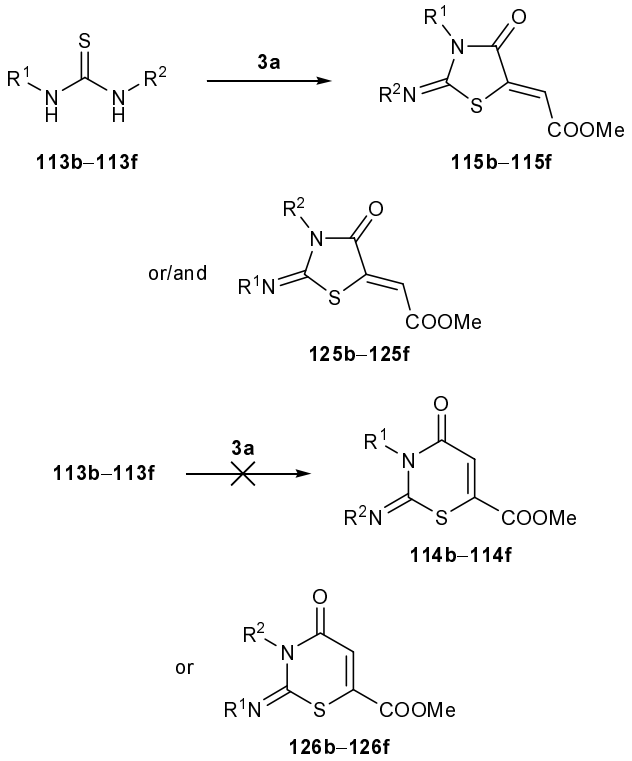


124

If the coupling constant for the "vinylic" proton and endocyclic carbon atom in a condensation product of thiourea with **3a** is about ~5 Hz (vicinal coupling), this product has a five-membered ring; if the coupling constant approaches a value of 1 Hz (geminal coupling), the product should be assigned six-membered thiazine structure. Signals from the exo- and endocyclic carbonyl carbon atoms are unambiguously assigned on the basis of their multiplicity. The condensation products of thioureas **113b**–**113f** with diester **3a** were thiazolidinones **115b**–**115f** (Scheme 24), for the coupling constants $^{3}J_{HC}$ between the endocyclic carbon atom and vinylic proton in the ^{13}C NMR spectra of these compounds ranged from 5 to 6 Hz [21].

Furthermore, the same authors found that the multiplicity of the signal from the lactam carbonyl carbon atom indicates which of the nitrogen atoms in the initial thiourea undergoes acylation, i.e., which isomer (**115** or **125**) is formed from unsymmetrically substituted thioureas. The $^{3}J_{C=O,HC}$ values also show that the exocyclic double C=C bond in molecules **115b**–**115e** has *Z* configuration.

Scheme 24.



113b–113f **115b–115f**

125b–125f

114b–114f

126b–126f

$R^{1} = R^{2} = PhCH_{2}$ (**b**), Ph (**c**); $R^{1}R^{2} = (CH_{2})_{2}$ (**d**); $R^{1} = PhCH_{2}$, R^{2} = Ph (**e**); R^{1} = Me, R^{2} = 4-$BrC_{6}H_{4}$ (**f**).

Thus the above data on the reactions of various thiourea derivatives with acetylenecarboxylic acids and their esters clearly indicate that the product structure is determined mainly by the nature of the electrophilic component (i.e., by the substituent in the β-position of acetylenecarboxylic acid derivative) rather than by the reaction conditions or nucleophile nature. In fact, acetylenedicarboxylic and 3-(5-nitro-2-furyl)-propynoic acid derivatives give rise to the corresponding thiazolidinones, while thiazine systems are obtained from acetylenemonocarboxylic acid derivatives.

4. REACTIONS OF ACETYLENECARBOXYLIC ACID DERIVATIVES WITH THIOSEMICARBAZIDE AND SUBSTITUTED THIOSEMICARBAZIDES

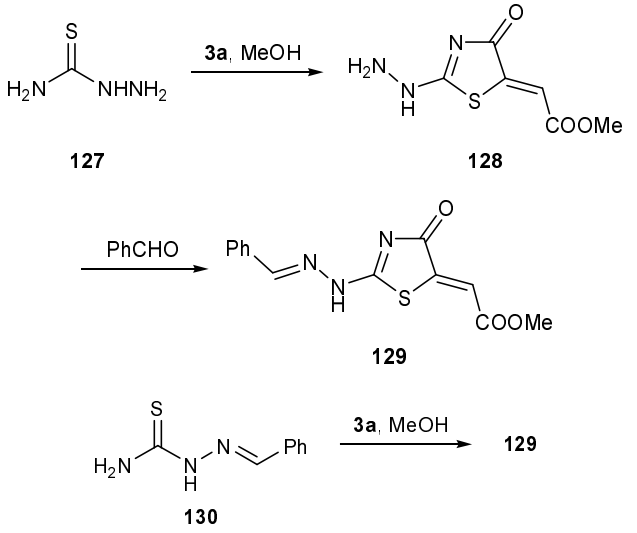
Unlike thioureas, the molecule of thiosemicarbazide contains four nucleophilic centers; therefore, the number of possible products which could be formed

by reactions of thiosemicarbazide derivatives with acetylenemono- and acetylenedicarboxylic acid esters increases.

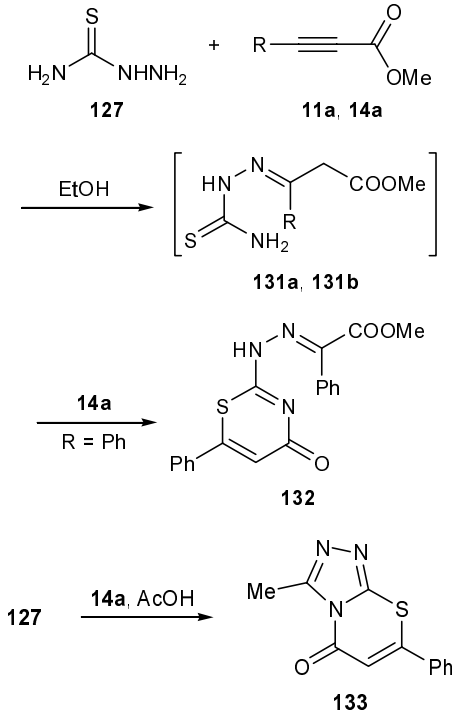
4.1. Unsubstituted Thiosemicarbazide

Hydrazinothiazolidinone **128** was obtained by heating unsubstituted thiosemicarbazide (**127**) with diester **3a** in methanol. Compound **128** reacted with benzaldehyde to give hydrazone **129** which was also synthesized by reaction of benzaldehyde thiosemicarbazone (**130**) with compound **3a** in methanol [8] (Scheme 25).

Scheme 25.



Scheme 26.



11a, **131a**, R = H; **14a**, **131b**, R = Ph.

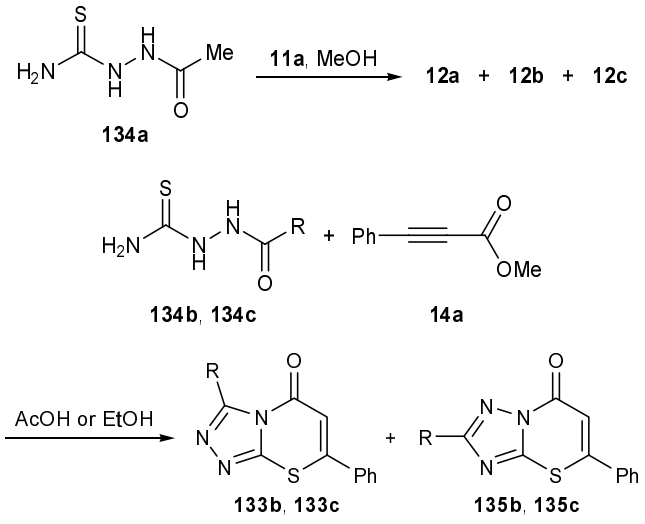
Unlike diester **3a**, the reaction of methyl 3-phenylpropynoate (**14a**) with **127** in alcohol or acetic acid resulted in the formation of hydrazonothiazine **132** and triazolothiazine **133** (Scheme 26) [35]. Presumably, thiazine **132** was formed via reaction of **14a** with thiosemicarbazone **131b** derived from methyl 3-oxo-4-phenylbutanoic acid; analogous thiosemicarbazone **131a** was isolated in the reaction of **127** with methyl propynoate (**11a**) in methanol [2].

4.2. Monosubstituted Thiosemicarbazides

As far as we know, reactions of 1-substituted thiosemicarbazides with acetylenedicarboxylic acid or its esters were not reported as yet. On the other hand, there are published data on reactions of 1-acylthiosemicarbazides with propynoic acid esters. The cyclization of 1-(perfluoroacyl)thiosemicarbazides **134b** and **134c** with methyl 3-phenylpropynoate (**14a**) in acetic acid or alcohol (Scheme 27) led to mixtures of isomeric triazolothiazines **133b**/**135b** and **133c**/**135c** [36]. However, a mixture of dimethyl (*Z*,*Z*)- and (*Z*,*E*)-4-thiahepta-2,5-dienedioates **12a** and **12b** was isolated in the reaction of 1-acetylthiosemicarbazide (**134a**) with ester **11a** in methanol [2], while Dallas et al. [25] isolated all three isomeric esters **12a**–**12c** in the same reaction (Scheme 15).

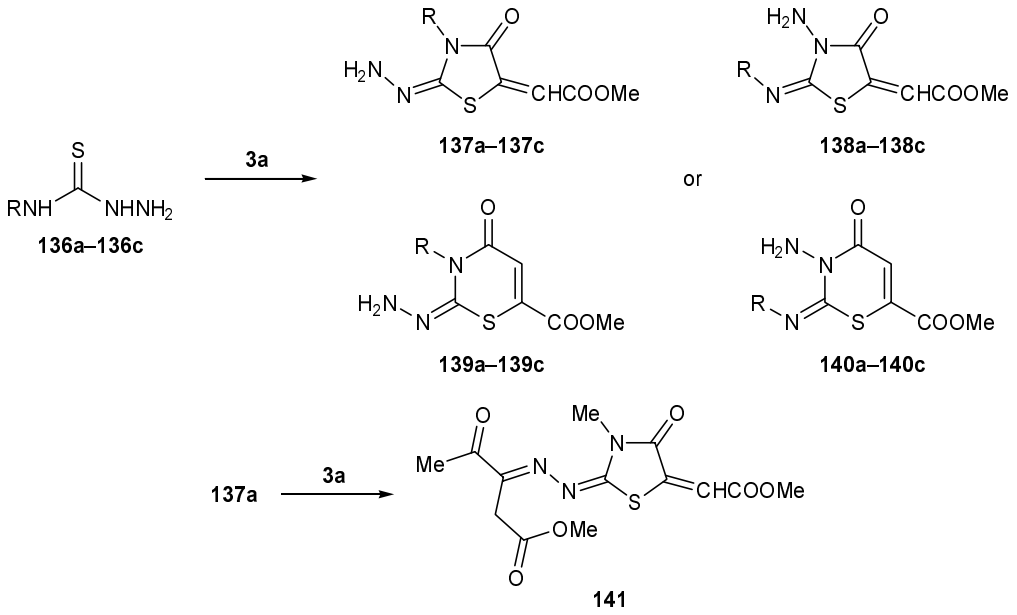
4-Substituted thiosemicarbazides **136** could react with diester **3a** to give two five- (**137**, **138**) and two

Scheme 27.



R = CF_3 (**b**), C_6F_{13} (**c**).

Scheme 28.



R = Me (**a**), Ph (**b**), CH_2=$CHCH_2$ (**c**).

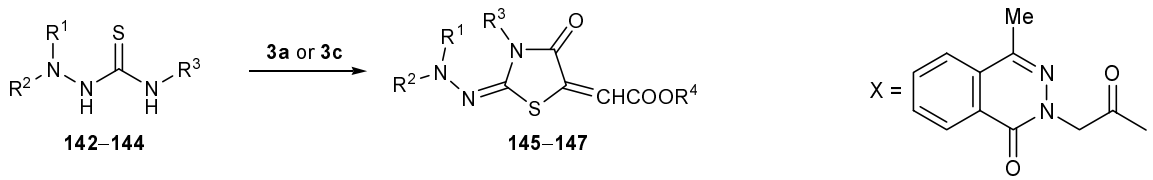
six-membered heterocycles (**139**, **140**) (Scheme 28). 1,3-Thiazines **140a**–**140c** were obtained by reaction of thiosemicarbazides **136a**–**136c** with compound **3a** in methanol [2]. The major products of the reactions of 4-substituted thiosemicarbazides **136a** and **136b** [37] or **136a**–**136c** [38] with dimethyl acetylenedicarboxylate (**3a**) were assigned the structure of thiazolidinones **138a**–**138c**; this assignment seems to be quite probable, taking into account convincing proofs given in [38]. Thiazolidinone **137a** formed via cyclization at N^4 was not isolated as individual substance [37], but it was trapped as hydrazone **141**.

4.3. Disubstituted Thiosemicarbazides

As with monoalkyl or monoaryl derivatives, reactions of 1,1- and 1,4-disubstituted thiosemicarbazides **142** and **143** with ester **3a** may involve both N^2 and N^4 to give five- or six-membered heterocycles. According to [38, 39], the reactions of 1,1- and 1,4-dialkyl(aryl)-thiosemicarbazides with compounds **3a** and **3c** in methanol give exclusively the cyclization products at N^4, thiazolidines **145** and **146** (Scheme 29) [38, 39]. Vas'kevich et al. [40] found that the reactions of 1,4-disubstituted thiosemicarbazides **148**–**150** with compound **3a** in methanol and dioxane take different pathways. In methanol, the final stage is intramolecular acylation in adduct **C** with formation of thiazolidines **151**–**153** (Scheme 30). Dioxane is an aprotic solvent which is more basic than methanol, and the reaction involves repeated nucleophilic addition of the N^1 atom at the activated double C=C bond in intermediate **C**; as a result, dihydrothiadiazoles **154**–**156** are obtained. The presence of a donor substituent in the *para*-position of the benzene ring on N^4 in thiosemicarbazides **149a** and **149b** appreciably increases the nucleophilicity of that nitrogen atom, thus favoring acylation to give thiazolidines **152a** and **152b** together with dihydrothiadiazoles **155a** and **155b** (Scheme 30).

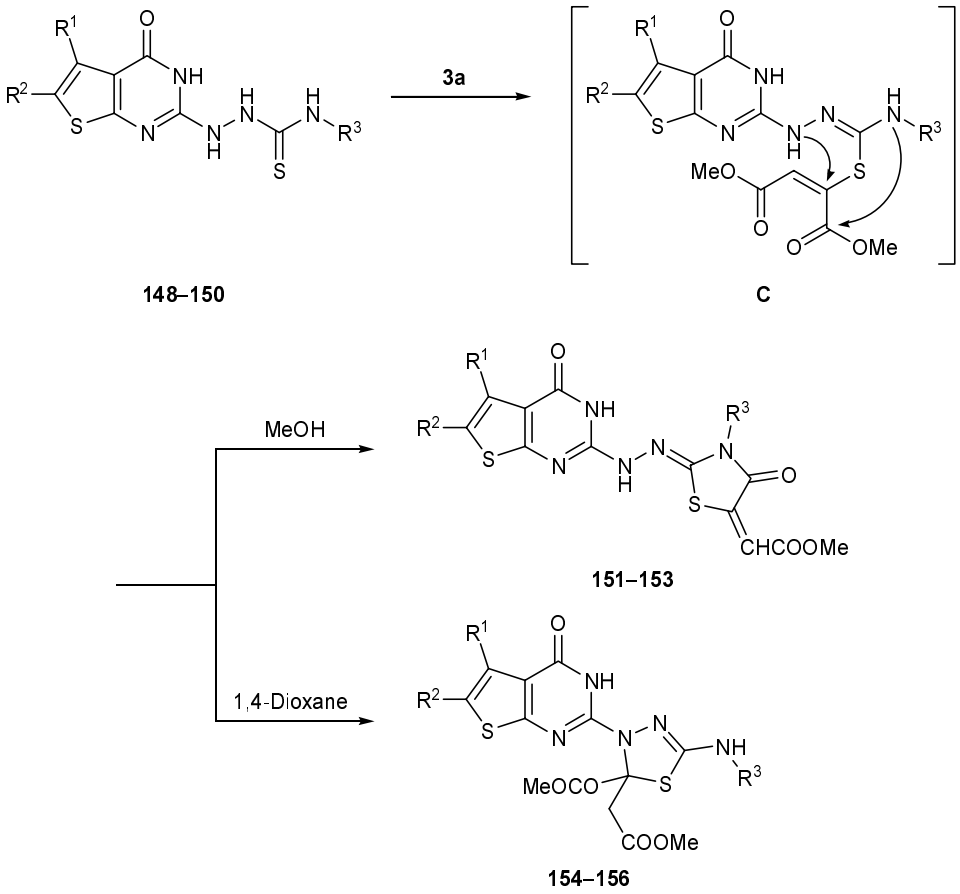
Although 2,4-disubstituted thiosemicarbazides **157** lack hydrogen atoms on N^2 and N^4, they nevertheless react with ester **3a** in boiling acetic acid [38]. Prob-

Scheme 29.



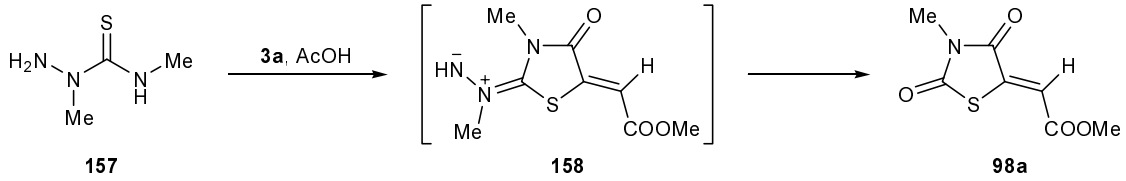
R^1 = Alk, Ar, X; R^2, R^3 = H, Alk, Ar; R^4 = H, Me.

Scheme 30.



$R^1R^2 = (CH_2)_4$ (**a**); $R^1 = R^2 = Me$ (**b**); **148**, **151**, **154**, R^3 = Ph; **149**, **152**, **155**, R^3 = 4-$MeOC_6H_4$; **150**, **153**, **156**, R^3 = 4-$EtOCOC_6H_4$.

Scheme 31.



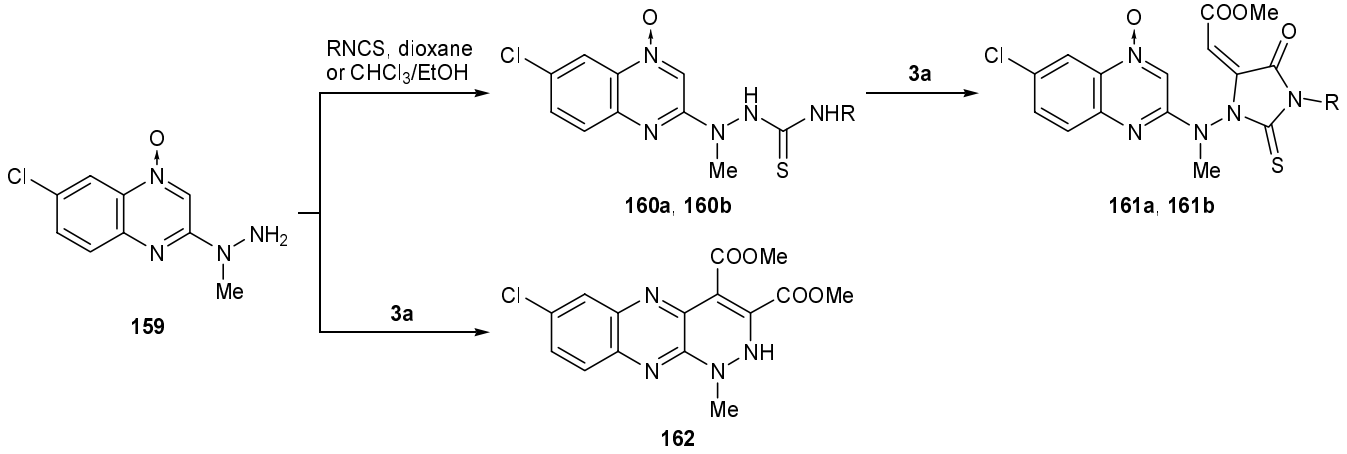
ably, initially formed zwitterionic intermediate **158** undergoes hydrolysis to thiazolidinone **98a** in acid medium (Scheme 31).

4.4. Trisubstituted Thiosemicarbazides

Thiazolidinones **147** were obtained by reaction of 1,1,4-trisubstituted thiosemicarbazides **144** with compounds **3a** and **3c** as a result of acylation of the N^4 atom (Scheme 29) [38]. However, the condensation of analogous thiosemicarbazide derivatives **160a** and **160b** with an equimolar amount of diester **3a** in alcohol gave unexpected products **161a** and **161b** [41] (Scheme 32), i.e., neither thiazolidinones nor 1,3-dipolar cycloaddition products were formed, in contrast to the reaction with **159**. The structure of compounds **161** as imidazolidine-2-thione derivatives was confirmed by measuring the nuclear Overhauser effect on protons of the N–CH_3 and $COOCH_3$ groups, 3-H in the quinoxaline ring, and protons at the exocyclic double bond (HC=C), as well as by the $^{13}C\{^1H\}$ NMR spectra recorded with selective long-range decoupling.

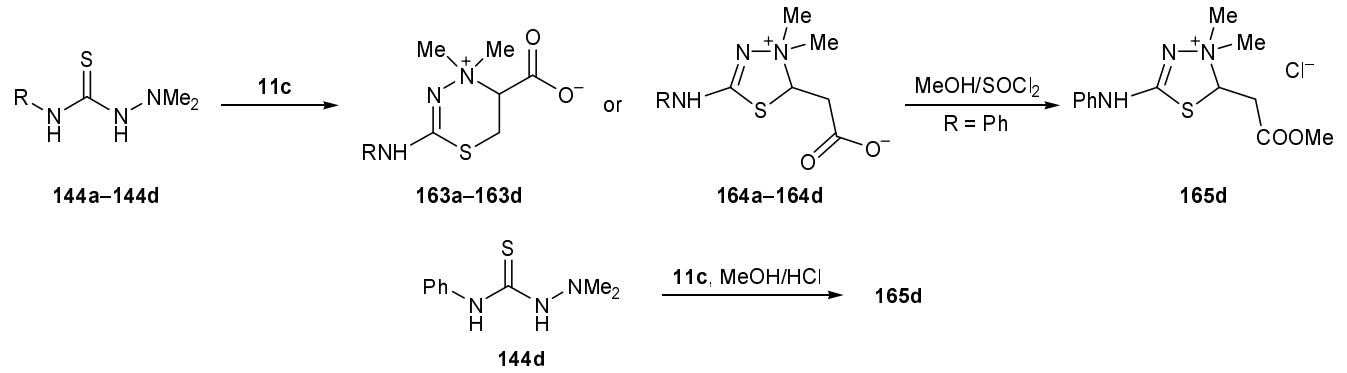
1,1,4-Trialkyl(aryl)thiosemicarbazides **144a**–**144d** reacted with propynoic acid (**11c**) in water, aqueous ethanol, and acetic acid in a way different from that observed in the reaction of 1,1,4-trisubstituted thio-

Scheme 32.



R = Me (**a**), Ph (**b**).

Scheme 33.



R^1 = H (**a**), Me (**b**), $PhCH_2$ (**c**), Ph (**d**).

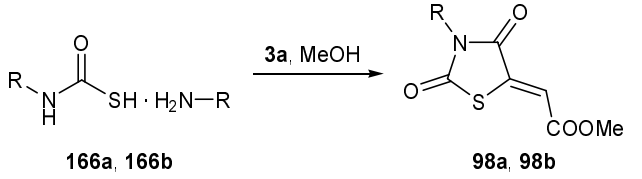
semicarbazides with acetylenedicarboxylic acid (**3c**) (Scheme 29), and the products were betaines **164a**–**164d** (Scheme 33) [42]. The structure of the products was proved by X-ray analysis of ester **165d** derived from **164d**. Thus, alternative formation of thiadiazine derivatives **163** was ruled out.

We can conclude that the structure of condensation products obtained from thiosemicarbazides and acetylenecarboxylic acid derivatives depends the nature of both acetylenic compound (as with thioureas) and nucleophilic agent. 4-Alkylthiosemicarbazides react with dimethyl acetylenedicarboxylate (**3a**) with formation of thiazolidines via condensation at the N^2 atom, while di- and trialkylthiosemicarbazides (regardless of the position of the substituents) give rise to five-membered products as a result of acylation at N^4. The direction of condensation of unsubstituted thiosemicarbazide with methyl propynoate (**11a**) is the same as in the reactions of other thioamides (the products are isomeric dimethyl 4-thiahepta-2,5-dienedioates **12**), and its reaction with methyl 3-phenylpropynoate leads to thiazine derivatives.

5. REACTIONS OF ACETYLENECARBOXYLIC ACID DERIVATIVES WITH ALKYLTHIOCARBAMATES

The only reported example of reactions of alkylammonium alkylthiocarbamates with acetylenecarboxylic acid derivatives is the reactions of methylammo-

Scheme 34.



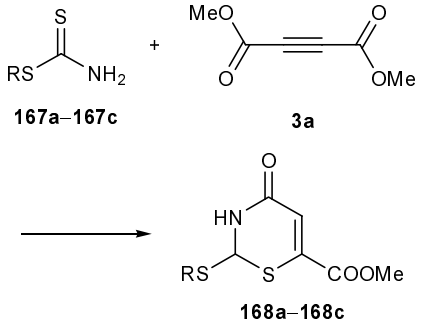
R = Me (**a**), $PhCH_2$ (**b**).

nium methylthiocarbamate (**166a**) and benzylammonium benzylthiocarbamate (**166b**) with diester **3a** in methanol at 18–25°C, which give thiazolidine-2,4-diones **98a** and **98b** (Scheme 34); i.e., alkylthiocarbamates behave similarly to thioureas.

6. REACTIONS OF ACETYLENECARBOXYLIC ACID DERIVATIVES WITH *S*-ALKYL DITHIOCARBAMATES

Adjon et al. [43] were the only to report on the reactions of *S*-alkyl dithiocarbamates **167a**–**167c** with ester **3a**, which resulted in formation of thiazinones **168a**–**168c** as the only products (Scheme 35).

Scheme 35.



R = Me (**a**), Et (**b**), $PhCH_2$ (**c**).

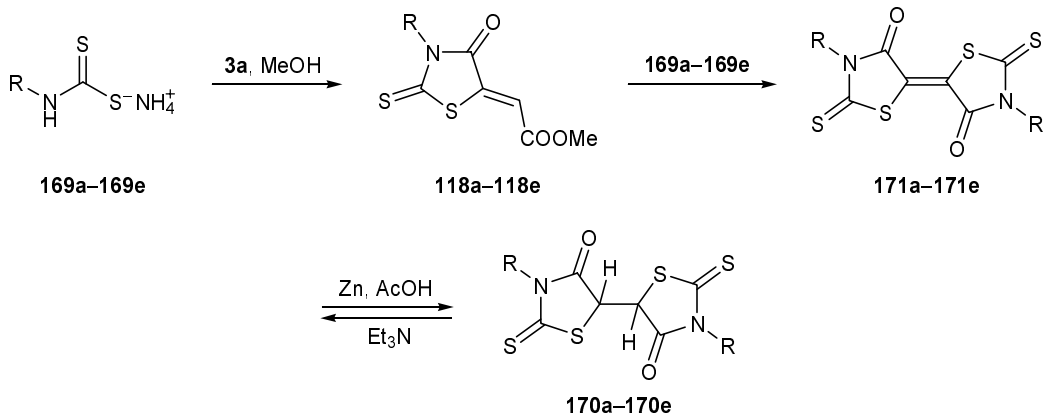
7. REACTIONS OF ACETYLENECARBOXYLIC ACID DERIVATIVES WITH AMMONIUM ALKYL(ARYL)DITHIOCARBAMATES

Reactions of ammonium alkyl- and aryldithiocarbamates with acetylenecarboxylic acid derivatives were studied in [26, 37, 44, 45]. 3,3'-Dialkyl-2,2'-dithioxo-5,5'-bi(1,3-thiazolidin-5-ylidene)-4,4'-diones **171a**–**171e** were obtained by addition of compound **3a** to solutions of ammonium dithiocarbamates **169a**–**169e** [37]; the subsequent reduction of **171a**–**171e** with zinc in acetic acid gave bithiazolidines **170a**–**170e** which can readily be oxidized back to compounds **171a**–**171e** in the presence of a catalytic amount of triethylamine (Scheme 36).

When these reactions were carried out by slowly adding ammonium alkyldithiocarbamate **169a**–**169e** to a solution of **3a** in methanol (i.e., maintaining excess **3a**), the only products were 2-thioxothiazolidin-4-ones **118a**–**118e**. The latter were converted into compounds **171a**–**171e** upon addition of excess salt **169a**–**169e**. Presumably, the observed difference in the behavior of thioureas, alkylthiocarbamates, and alkyldithiocarbamates originates from the higher nucleophilicity of the thioamide fragment in the latter; as a result, the reaction does not stop at the stage of formation of adduct **118** which is a weaker electrophile than **3a**.

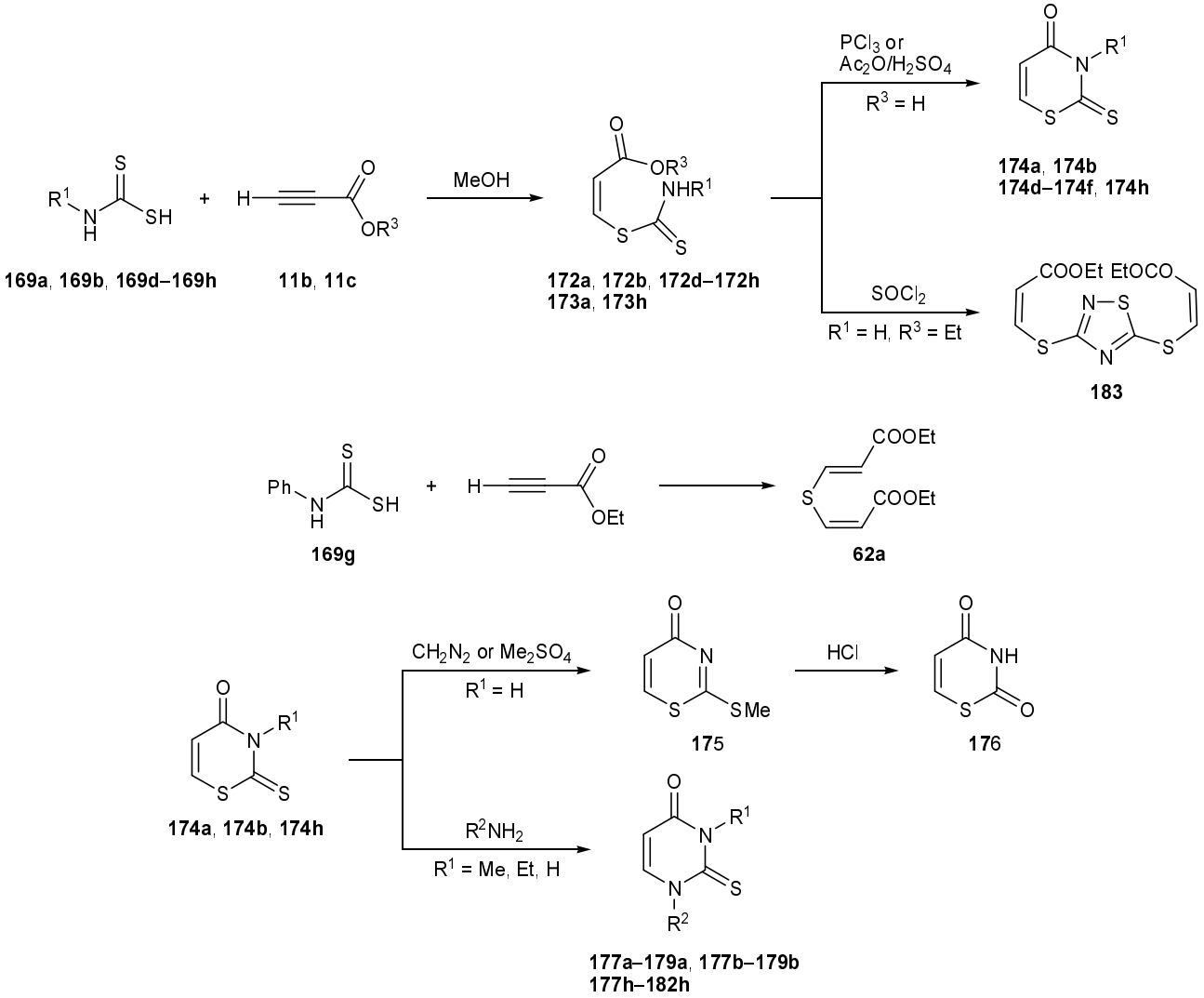
Adducts **172a**, **172b**, **172d**–**172h**, **173a**, and **173h** can be isolated in the reactions of ammonium dithiocarbamate **169h** and alkylcarbamodithioic acids **169a**, **169b**, and **169d**–**169g** with propynoic acid (**11c**) and its esters [26, 44, 45] (Scheme 37). β-Sulfanylacrylic acid derivatives **172** thus formed readily undergo cyclization to 2-thioxo-1,3-thiazin-4-ones **174** in the presence of phosphorus trichloride [44] or in acetic anhydride containing traces of sulfuric acid [26, 45] (phosphorus trichloride cannot be used for the cyclization of **172h**). Cyclization products **174a**, **174b**, and **174h** were used as initial compounds in the regioselective synthesis of thiouracils **177**–**179** (**a, b**) and **177h**–**182h** [45], as well as in the preparation of 1,3-thiazine-

Scheme 36.



R = Me (**a**), Et (**b**), Pr (**c**), Bu (**d**), $PhCH_2$ (**e**).

Scheme 37.



R^1 = Me (**a**), Et (**b**), Pr (**d**), Bu (**e**), $PhCH_2$ (**f**), Ph (**g**), H (**h**); **177**, R^2 = H; **178**, R^2 = Me; **179**, R^2 = Et; **180**, R^2 = $PhCH_2$; **181**, R^2 = $HOCOCH_2$; **182**, R^2 = PhNH; **11c**, **172a**, **172b**, **172d–172h**, R^3 = H; **11b**, **173a**, **173h**, R^3 = Et.

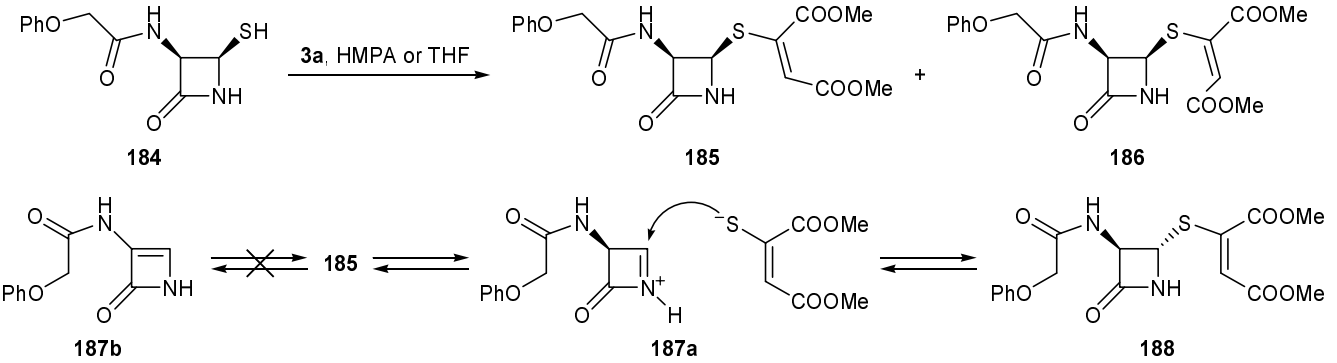
2,4-dione **176** [26] (Scheme 37). On the other hand, it was quite difficult to find conditions for the cyclization of ethyl esters **173a** and **173h** [26]. The only product obtained by heating compound **173h** in boiling SO_2Cl_2 was thiadiazole **183** (Scheme 37).

We can conclude that dithiocarbonic acid derivatives exhibit enhanced reactivity toward dimethyl acetylenedicarboxylate (the resulting thiazolidinones are capable of reacting further to give bis-adducts) and reduced reactivity toward acetylenemonocarboxylic acids and their esters (thiazine ring is formed only under severe conditions from the acids while cyclization of dithiocarbamate adducts with acetylenic esters does not occur at all).

8. REACTIONS OF ACETYLENECARBOXYLIC ACID DERIVATIVES WITH HETARENETHIOLS

Heterocyclic thiols in which the C–SH group is neighboring to a ring nitrogen atom may be regarded as derivatives of cyclic thioamides. However, in most cases the properties of these compounds differ from the properties of acyclic thioamides. The differences are associated first with the ring size and hence steric strain arising from deviations of the bond angles from their standard values. Second, many cyclic thioamides are heteroaromatic compounds, and the aromatic system affects the basicity and nucleophilicity of the nitrogen and sulfur atoms in the thioamide fragment. Taking into account the above stated, we believed it

Scheme 38.



reasonable to discuss reactions of cyclic thioamides with acetylenecarboxylic acid derivatives in a separate section. It should also be emphasized that these compounds can exist in both thione and thiol forms; however, problems of the thione–thiol tautomerism fall beyond the scope of the present review, and the term *hetarenethiols* is used in the further treatment only conventionally. The discussed structures are referred to as thiol or thione as they were given in the corresponding literature.

8.1. Four-Membered Heterocyclic Thiols

4-Sulfanylazetidin-2-one **184** belongs to the smallest heterocyclic system for which condensation with diester **3a** was reported [46]. The reaction in anhydrous HMPA gave a mixture of *cis* and *trans* isomers **185** and **188** via addition of the SH group across the triple bond of ester **3a**; in THF, a mixture of *cis*-adducts **185** (*E*) and **186** (*Z*) was obtained (Scheme 38).

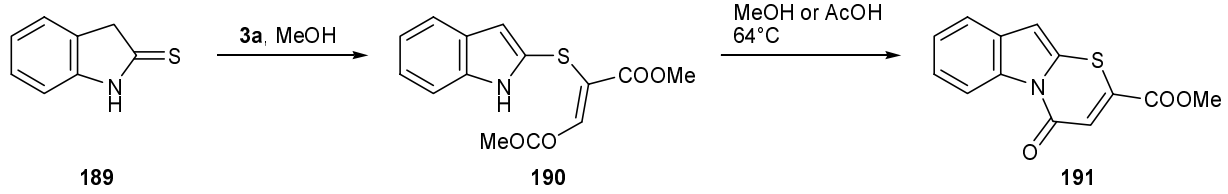
8.2. Five-Membered Heterocyclic Thiols

8.2.1. Five-membered heterocyclic thiols with one heteroatom. To our knowledge, condensations of 2-sulfanylpyrroles with compound **3a** and other acetylenecarboxylic acids were not studied, and only a single publication [3] is available on the reaction of 2,3-dihydro-1*H*-indole-2-thione **189** with dimethyl acetylenedicarboxylate (**3a**) in methanol; the reaction gave dimethyl 2-(1*H*-indol-2-ylsulfanyl)fumarate (**190**) and thiazinoindole **191**. Compound **190** undergoes heterocyclization to **191** on heating in boiling methanol or acetic acid but does not in acetonitrile or dioxane (Scheme 39).

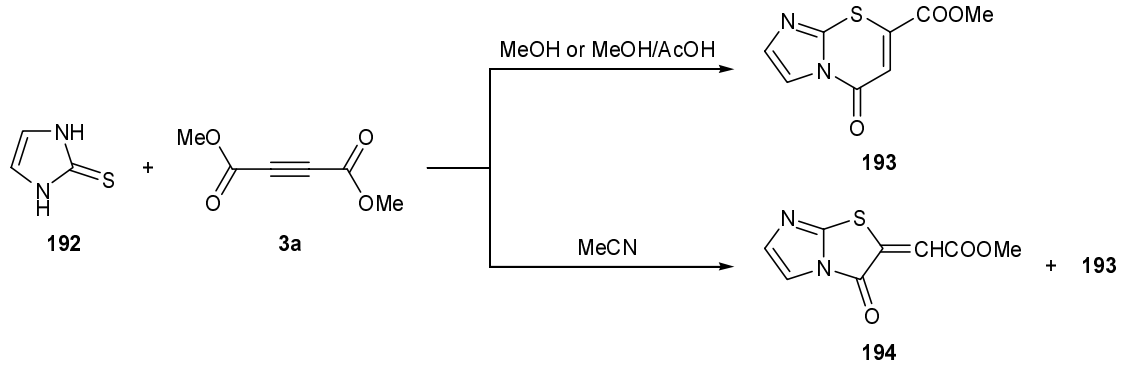
8.2.2. Five-membered heterocyclic thiols with two heteroatoms. The reactions of imidazolidine-2-thione (**113d**) with acetylenecarboxylic acid derivatives were discussed together with those of *N*,*N*′-disubstituted thioureas (see Section 3.4) due to similarity in their structure and properties. Therefore, only reactions of unsaturated hetarenethiols are considered below.

2,3-Dihydro-1*H*-imidazole-2-thione (**192**) reacted with compound **3a** in methanol or methanol–acetic acid to give imidazolothiazine **193** [3], while in boiling acetonitrile a mixture of isomeric imidazolothiazine **193** and imidazolothiazolidine **194** at a ratio of 2:1 was isolated (Scheme 40). Thiazine and thiazolidine systems were also obtained by condensation of benzimidazole-2-thione **195** with acetylenedicarboxylic acid (**3c**) and its esters **3a** and **3b** (Scheme 41). The reaction of **195** with dimethyl and diethyl acetylenedicarboxylates **3a** and **3b** in acetic acid [47] led to exclusive formation of benzimidazothiazolylideneacetates **196a** and **196b**, respectively, and the condensation with acetylenedicarboxylic acid (**3c**) in ethyl acetate stopped at the stage of addition of the SH group of **195** at the triple bond. 2-(Benzimidazol-2-yl)sulfanylfumaric acid (**198c**) thus formed underwent cyclization to compound **196c** on heating in dilute hydrochloric acid. Thiazolidinecarboxylic acid **196c** was also obtained by acid hydrolysis of esters **196a** and

Scheme 39.

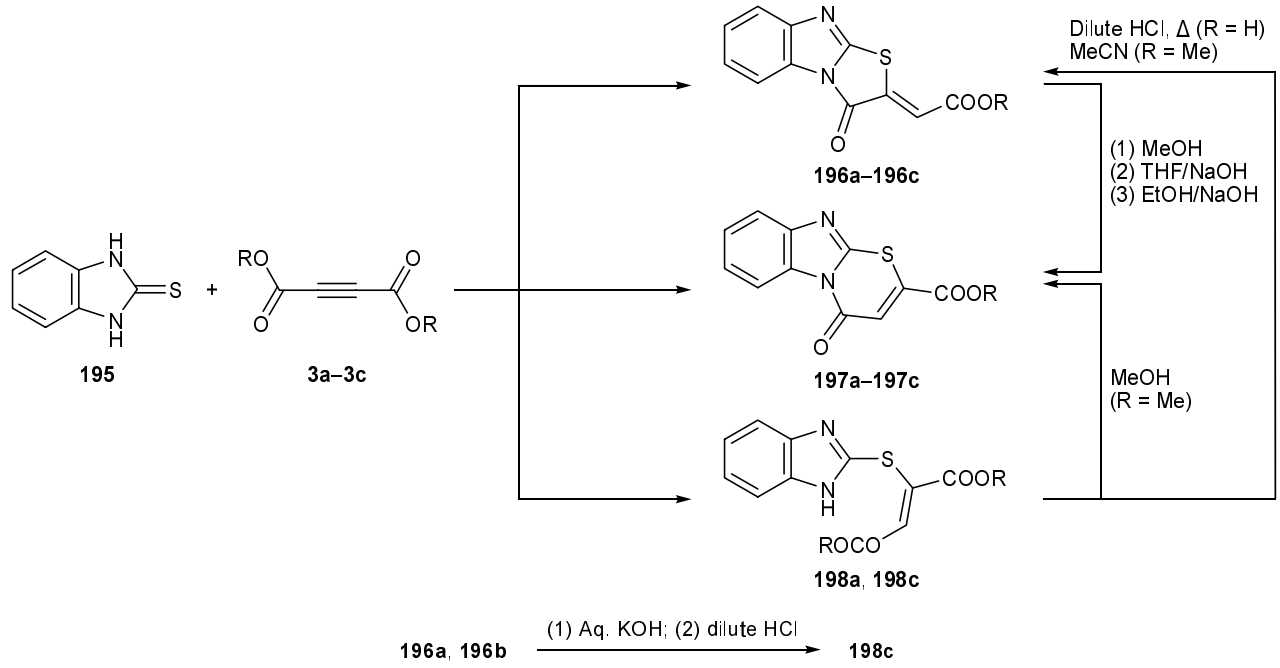


Scheme 40.



192 3a 193 194

Scheme 41.



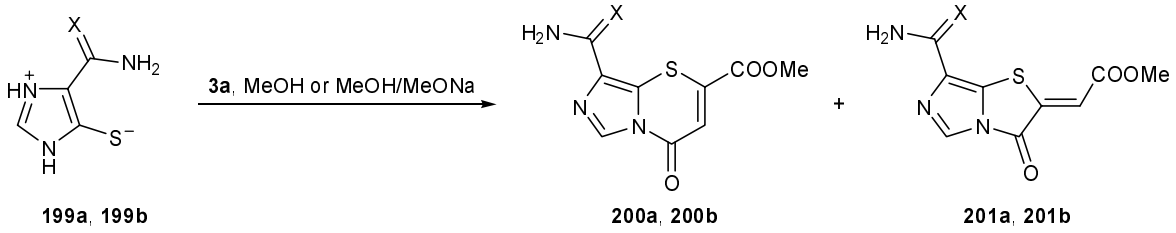
195 3a–3c 196a–196c 197a–197c 198a, 198c

196a, 196b → 198c

R = Me (**a**), Et (**b**), H (**c**).

196b, whereas alkaline hydrolysis of the latter resulted in opening of the thiazolidine ring with formation (after acidification) of 2-(benzimidazol-2-ylsulfanyl)-fumaric acid **198c** [47]. Mixtures of isomers **196a** and **197a** at ratios of 2:1 and 1:1 were isolated when the reaction of benzimidazole-2-thione **195** with diester (**3a**) was carried out in methanol and acetic acid, respectively [48, 49], and the condensation of **195** with diethyl acetylenedicarboxylate in alcohol or acetic acid gave a mixture of isomers **196b** and **197b** [49]. The structure of **196a** was proved by the X-ray diffraction data [48], as well as by analysis of the coupling constants $^{2}J_{HC}$ and $^{3}J_{HC}$ in the ^{13}C NMR spectra (compounds **196a**, **196b**, **197a**, and **197b**) [49]. Benzimidazothiazinecarboxylate **197a** was isolated as the only product in the reaction of **3a** with benzimidazolethione **195** in anhydrous methanol [3]. The reaction in acetonitrile gave thiazolidine **196a**, and in aqueous acetonitrile, adduct **198a** which underwent cyclization to thiazolidinone **196a** on heating and to thiazine **197a** in boiling methanol. Acheson and Reid [3] also succeeded in revealing rearrangements of thiazolidine **196a** into thiazine **197a** (in boiling methanol), ester **197b** (on heating in ethanolic sodium hydroxide), and acid **197c** (in boiling aqueous tetrahydrofuran in the presence of NaOH). No expansion of five-membered ring to six-membered was observed in acid medium (a mixture of methanol with acetic acid), and the melting points of compounds **196a**–**196c** and **197a**–**197c** isolated by different authors [3, 47–49] coincided.

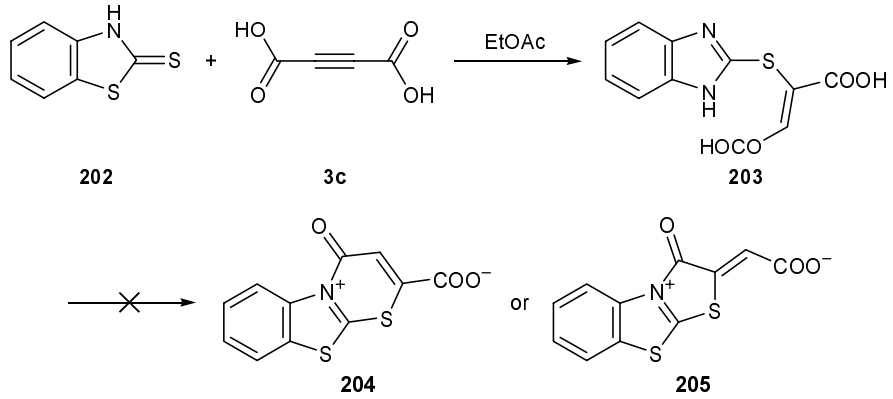
Scheme 42.



199a, **199b** **200a**, **200b** **201a**, **201b**

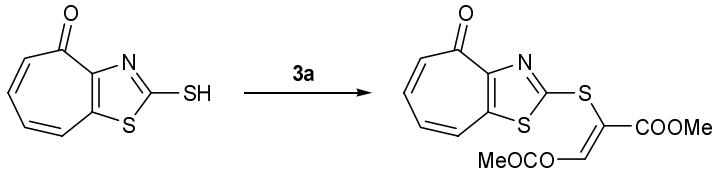
X = O (**a**), S (**b**).

Scheme 43.



202 **3c** **203** **204** **205**

Scheme 44.



206 **207**

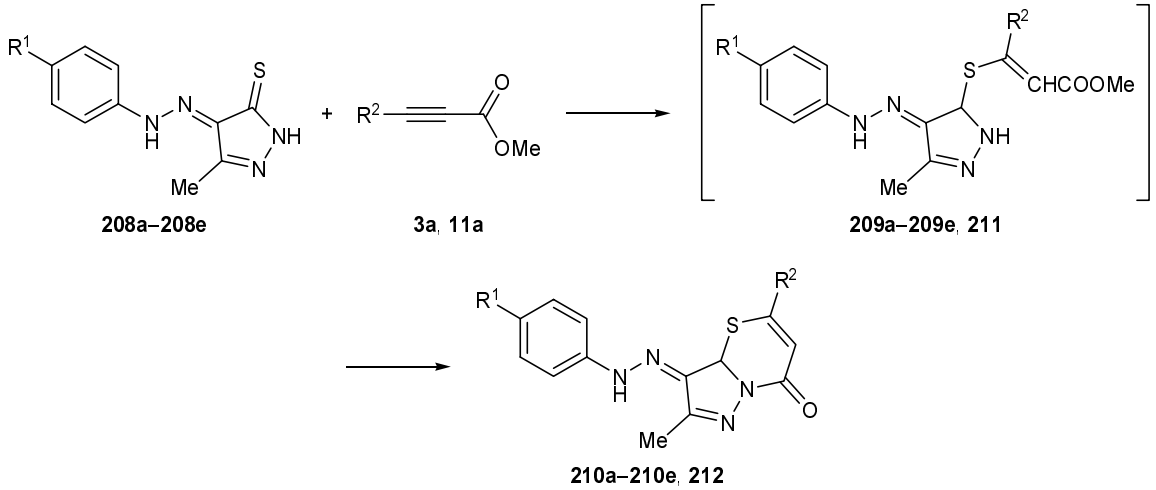
In the condensation of 5-sulfanylimidazole-4-carboxamide (**199a**) with dimethyl acetylenedicarboxylate (**3a**) in methanol, the only isolated product was imidazolothiazinone **200a** [50], while under basic conditions (MeOH/MeONa) a mixture of imidazolothiazinone **200a** and imidazolothiazolidinone **201a** at a ratio of 7:3 was obtained. Unlike compound **199a**, its thio analog **199b** reacted with diester **3a** to give a mixture of isomers **200b** and **201b** at a ratio of 9:1, regardless of the conditions (Scheme 42).

The reaction of benzothiazole-2-thione (**202**) (which is a thia analog of **195**) with acetylenedicarboxylic acid stopped at the stage of formation of adduct **203** [47], and no intramolecular heterocyclization to zwitterionic product **204** or **205** occurred (Scheme 43). Likewise, adduct **207** was isolated in the reaction of 2-sulfanyl-4*H*-cyclohepta[*d*]thiazol-4-one (**206**) with diester **3a** [51] (Scheme 44).

Some reactions of pyrazolethiones with acetylenedicarboxylic acid derivatives were reported. Pyrazolothiazines **210a**–**210e** were the only products formed in the reactions of 4-arylhydrazonopyrazole-5-thiones **208a**–**208e** with compound **3a** in methanol in the presence of triethylamine [50] (Scheme 45). It should be noted that 5-sulfanylimidazole-4-carboxamide (**199a**) failed to react with ester **11a** (Scheme 42), while the reaction of 4-arylhydrazonopyrazole-5-thione **208d** with the same ester smoothly afforded 1,3-thiazinone derivative **212** [50] (Scheme 45).

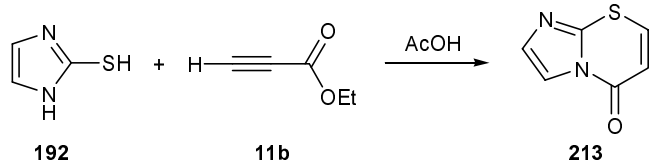
Other five-membered hetarenethiols react with propynoic acid derivatives via addition of the SH group at the triple bond; the subsequent heterocyclization of the adducts thus formed yields exclusively thiazine systems. For example, the reaction of imidazole-2-thiol (**192**) with ethyl propynoate in boiling acetic acid gave imidazolothiazinone **213** [52] (Scheme 46).

Scheme 45.

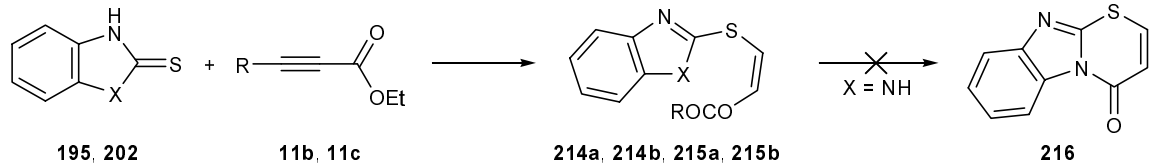


208–**210**, R^1 = H (**a**), Me (**b**), MeO (**c**), Cl (**d**), EtOCO (**e**); R^2 = MeOCO; **211**, **212**, R^1 = Cl, R^2 = H; **3a**, R^2 = MeOCO; **11a**, R^2 = H.

Scheme 46.

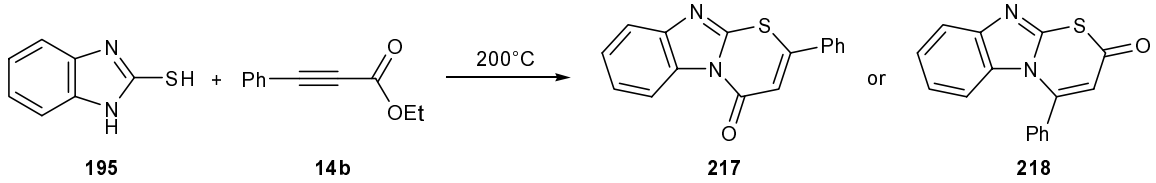


Scheme 47.



195, **214**, X = NH; **202**, **215**, X = S; **11c**, **214a**, **215a**, R = H; **11b**, **214b**, **215b**, R = Et.

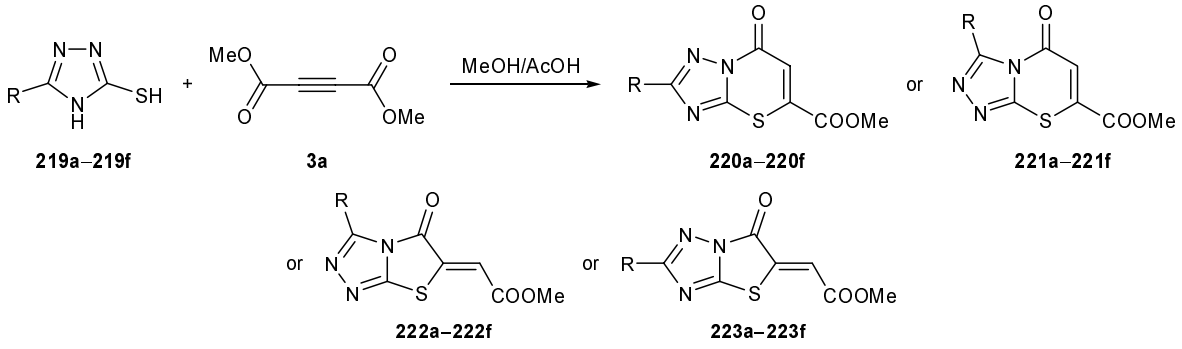
Scheme 48.



The reactions of benzimidazole-2-thione (**195**) and benzothiazole-2-thione (**202**) with propynoic acid and its ethyl ester in anhydrous ethanol or ethyl acetate led to addition products **214a**, **214b**, **215a**, and **215b** [47] (Scheme 47), and even compound **214b** did not undergo cyclization to thiazine **216**. Ethyl 3-phenylpropynoate (**14b**) reacted with benzimidazole-2-thione (**195**) on heating at 200°C (12 h) without a solvent to give 2-phenyl-4*H*-[1,3]thiazino[3,2-*a*]benzimidazol-4-one (**217**) [53] (Scheme 48). Previously, Al-Jallo and Muniem [54] erroneously assigned the structure of 4-phenyl-2*H*-[1,3]thiazino[3,2-*a*]benzimidazol-2-one (**218**) to the product obtained under the same conditions.

8.2.3. Five-membered heterocyclic thiols with three heteroatoms. Reactions of acetylenecarboxylic acid derivatives with 1,2,4-triazole-3-thiols were extensively studied. The number of isomeric products which could be formed in the reaction with dimethyl acetylenedicarboxylate (**3a**) is determined not only by

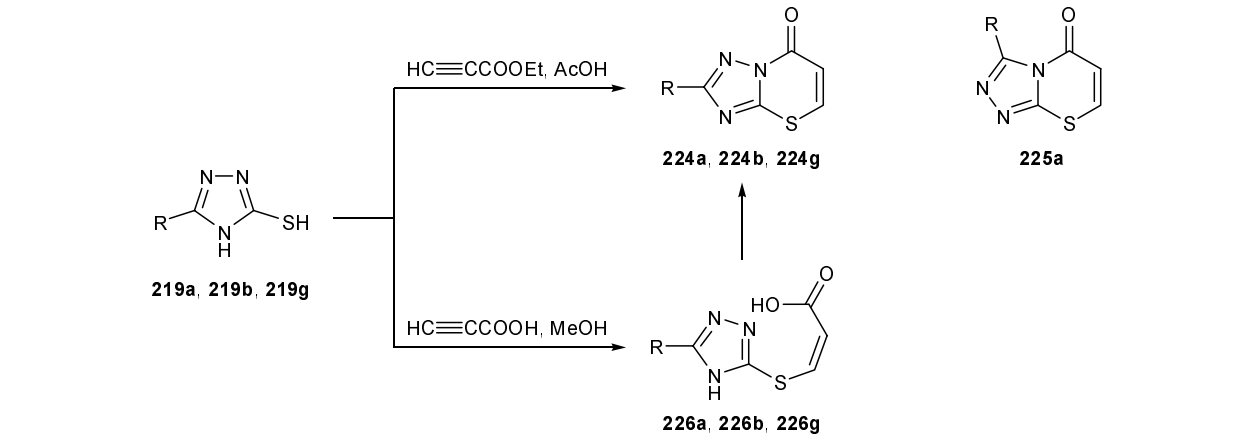
Scheme 49.



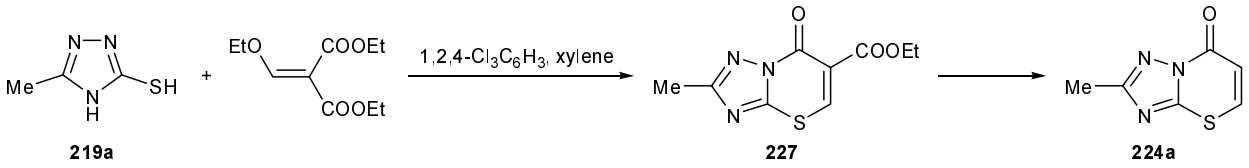
219a–219f **3a** **220a–220f** **221a–221f** **222a–222f** **223a–223f**

R = Me (**a**), Ph (**b**), 4-FC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**), 4-$O_2NC_6H_4$ (**e**), 2,4-$Cl_2C_6H_3$ (**f**).

Scheme 50.



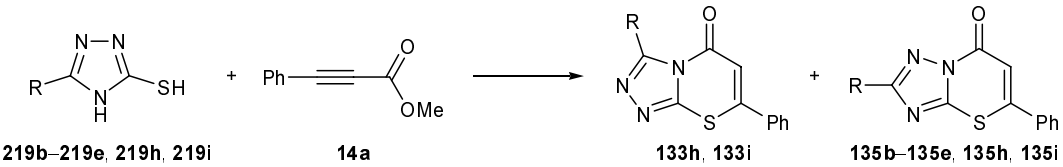
219a, **219b**, **219g** **224a**, **224b**, **224g** **225a** **226a**, **226b**, **226g**



219a **227** **224a**

R = Me (**a**), Ph (**b**), H (**g**).

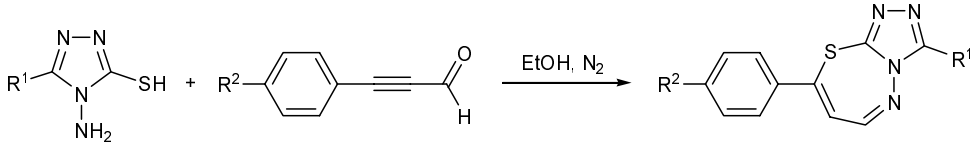
Scheme 51.



219b–219e, **219h**, **219i** **14a** **133h**, **133i** **135b–135e**, **135h**, **135i**

R = Ph (**b**), 4-FC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**), 4-$O_2NC_6H_4$ (**e**), CF_3 (**h**), C_6F_{13} (**i**).

Scheme 52.



227a–227f **228**, **229** **230a–230f**, **231a**, **231e**

R^1 = Ph (**a**), cyclohexyl (**b**), 4-FC_6H_4 (**c**), 2-BrC_6H_4 (**d**), $PhCH_2$ (**e**), 4-$Me_2NC_6H_4$ (**f**); **228**, **230**, R^2 = H; **229**, **231**, R^2 = Br.

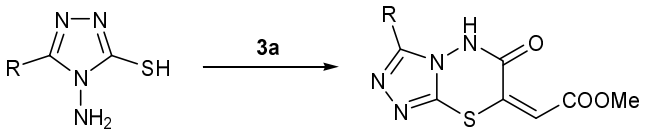
their ring size but also by the possibility for intramolecular cyclization to occur at the N^2 or N^4 atom. Triazolothiazines **220a**–**220f** or **221a**–**221f** were isolated in the reactions of triazolethiols **219a** [55, 56], **219b** [56–58], **219c**–**219e** [58], and **219f** [59] with compound **3a** in methanol in the presence of a catalytic amount of acetic acid [57, 59] or without it [55, 56, 58] (Scheme 49).

It was presumed [55, 56] that the process involves the N^4 atom of the triazole ring to give products **221a**, and **221b**, while the authors of [57–59] believed that the cyclization occurred with participation of N^2 to form triazolothiazines **220b** and **220c**. The X-ray diffraction data for the condensation products derived from triazolethiols **219a** [60] and **219b** [58] and compound **3a** unambiguously showed that the cyclization involved the N^2 atom of the triazole ring with formation of triazolothiazinones **220a** and **220b**, respectively. *trans*-Addition of 1,2,4-triazole-3-thiols **219a**, **219b**, and **219g** to propynoic acid gave compounds **226a**, **226b**, and **226g**, which underwent cyclization to triazolothiazines **224a**, **224b**, and **224g** [61] in concentrated sulfuric acid. Compound **224a** was also synthesized by reaction of triazolethiol **219a** with ethyl propynoate in boiling acetic acid [52] (Scheme 50). The formation of triazolothiazine **224a** rather than its isomer **225a** was proved by X-ray analysis of the minor product isolated in the condensation of 5-methyl-1,2,4-triazole-5-thiol (**219a**) with diethyl ethoxymethylidenemalonate, followed by hydrolysis and decarboxylation of triazolothiazine **227** [52]; the spectral and chromatographic parameters of this product were identical to those of **224a**.

5-Aryl-1,2,4-triazole-3-thiols **219b**–**219e** reacted with methyl 3-phenylpropynoate (**14a**) in methanol to give compounds **135b**–**135e** [58], while the reactions of the same ester with perfluoroalkyltriazolethiols **219h** and **219i** in methanol, methanolic sodium methoxide, and acetic acid resulted in formation of mixtures of isomeric triazolothiazines **133h**/**135h** and **133i**/**135i** [36] (Scheme 51).

Unusual products, triazolothiadiazepines **230** and **231**, could be obtained by reaction of 5-substituted 4-amino-1,2,4-triazole-3-thiols with acetylenecarboxylic acid derivatives. However, such a reaction was reported in only one publication [62] where 3-phenylpropynal derivatives **228** and **229** were used as acetylenic component (Scheme 52). The reaction products of ester **3a** with 5-substituted 4-amino-1,2,4-triazole-3-thiols **227a** [57], **227g** [63], **227h** [64], and **227i**–**227k** [65] were assigned the structure of triazolothiadiazines **232a**, and **232g**–**232k** (Scheme 53).

Scheme 53.



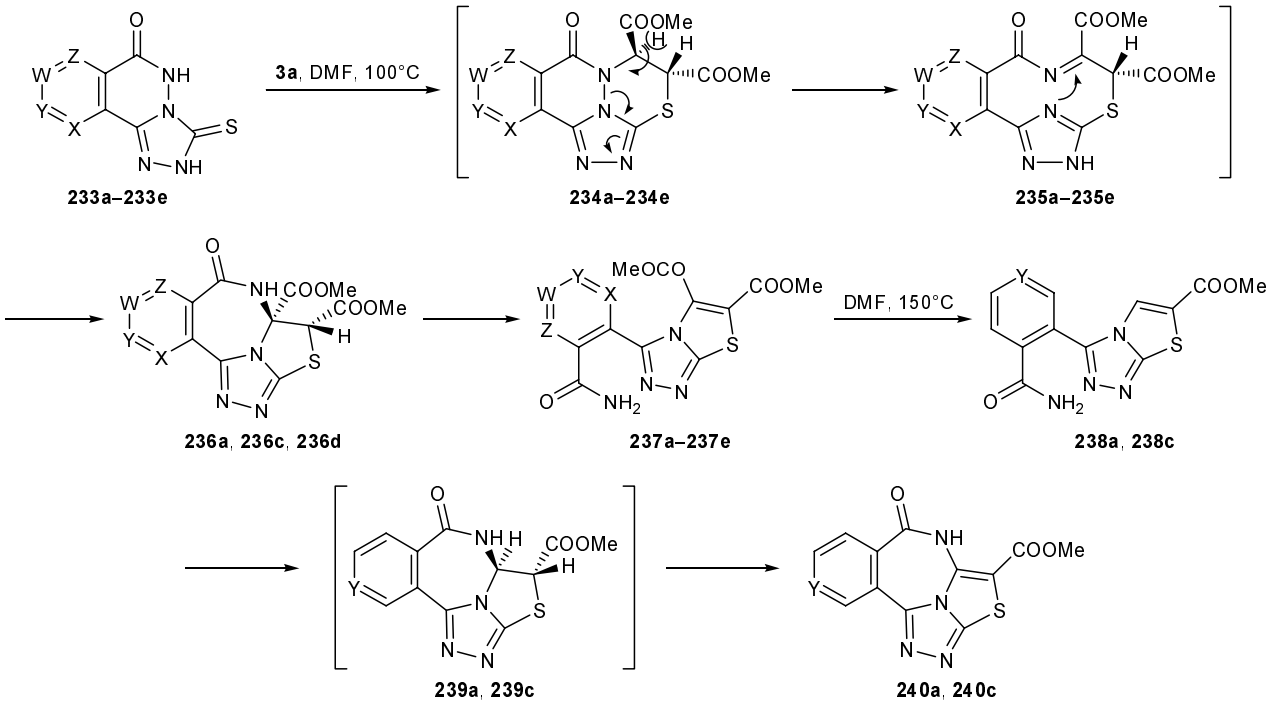
227a, **227g**–**227k** **232a**, **232g**–**232k**

R = Ph (**a**), 2,4-$Cl_2C_6H_3$ (**g**), Me (**h**), $PhOCH_2$ (**i**), 2,3,4-$Cl_3C_6H_2CH_2O$ (**j**), 2,3,4-$Me_3C_6H_2CH_2O$ (**k**).

It might be expected that the condensation of **3a** with tricyclic compounds **233a**–**233e** will follow the same pattern, for the latter contain an *N*-amino-1,2,4-triazole-5-thiol fragment. However, Simó et al. [66] found that the ester groups of **3a** are not involved in this reaction and that the addition of the SH and NH groups at the triple bond is followed by rearrangement of the initially formed pyridazine ring to give different products, depending on the cyclization conditions. The products obtained in the reaction performed at 100°C were assigned the structure of *cis*-diazepines **236a**, **236c**, and **236d** and thiazolotriazoles **237b** and **237e** (Scheme 54). Raising the temperature to 150°C changed the reaction direction: a mixture of compounds **237a** and **240a** at a ratio of 1:6 was obtained from thioxotriazolophthalazinone **233a**; pyridotriazolopyridazinones **233b**, **233d**, and **233e** gave rise to thiazole derivatives **237b**, **237d**, and **237e** in good yields; and the reaction of pyridotriazolopyridazinone **233c** resulted in formation of a mixture of bis- and monomethoxycarbonyl derivatives **237c** and **240c** at a ratio of 7:5 (Scheme 54).

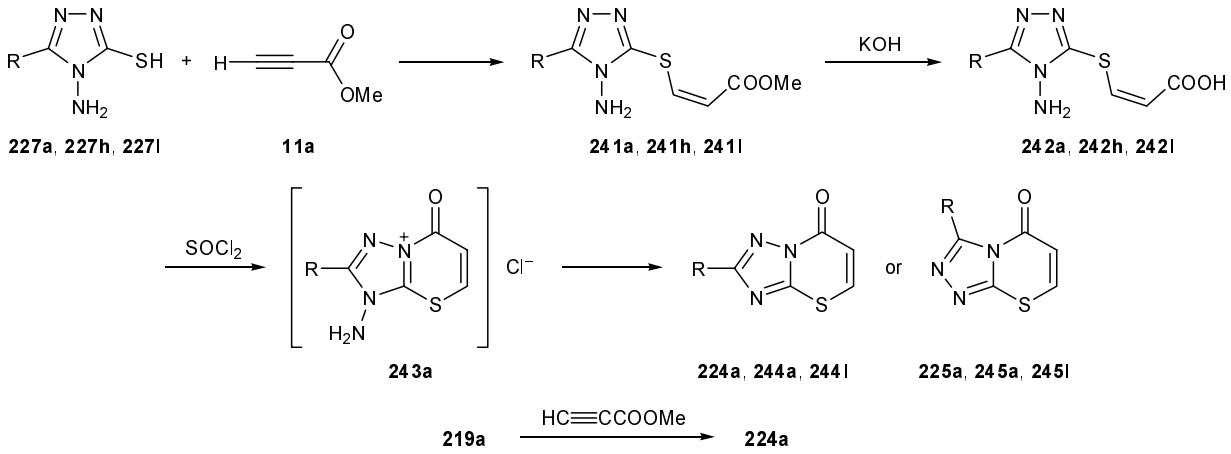
Heindel and Reid [67] isolated methyl β-(1,2,4-triazol-3-ylsulfanyl)acrylates **241a**, **241h**, and **241l** in the condensation of methyl propynoate (**11a**) with 3-substituted 4-amino-1,2,4-triazole-3(4*H*)-thiones **227a**, **227h**, and **227h**, respectively, in boiling anhydrous methanol (Scheme 55). Acrylates **241a**, **241h**, and **241l** failed to undergo cyclization to the corresponding triazolothiadiazepines. No cyclization with participation of the exocyclic amino group occurred even when acrylic acid derivatives **242a**, **242h**, and **242l** (obtained by hydrolysis of esters **241a**, **241h**, and **241l**) were heated with thionyl chloride. The isolated products were triazolothiazines **224a**, **244l**, and water-soluble salt **243a**, the latter being converted into triazolothiazine **244a** on heating. Triazolothiazine **224a** was also synthesized independently from 5-methyl-4*H*-1,2,4-triazole-3-thiole **219a** and methyl propynoate.

Scheme 54.



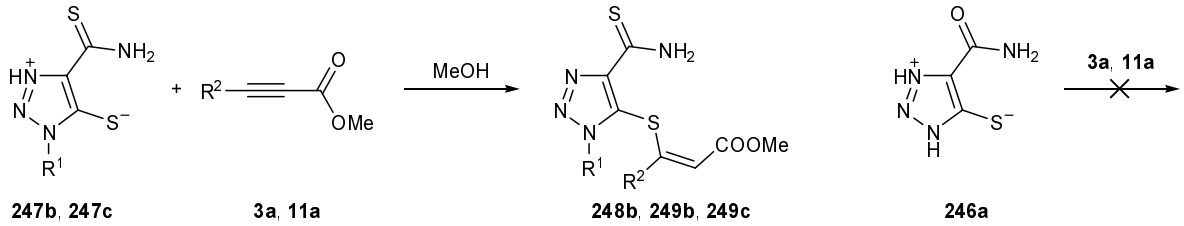
X = Y = W = Z = CH (**a**); X = N, Y = W = Z = CH (**b**); Y = N, X = W = Z = CH (**c**); W = N, X = Y = Z = CH (**d**); Z = N, X = Y = W = CH (**e**).

Scheme 55.



227, **241**–**245**, R = Ph (**a**), Me (**h**), *t*-Bu (**l**); **224a**, **225a**, R = Me.

Scheme 56.



R^1 = H (**a**), Me (**b**), Ph (**c**); **11a**, **248**, R^2 = H; **3a**, **249**, R^2 = MeOCO; **246**, X = O; **247**, X = S.

According to [50], 5-sulfanyl-1,2,3-triazole-4-carboxamide **246a** having no substituent on the N^1 atom reacts neither with diester **3a** nor with methyl propynoate. The reactions of its analogs **247b** and **247c** with an alkyl or aryl group on N^1 and carbothioamide group instead of carboxamide gave only products **248b**, **249b**, and **249c** as a result of addition of the SH group at the triple bond of acetylenecarboxylic acid derivatives **3a** and **11a** (Scheme 56).

The higher reactivity of thiol group toward acetylenic reagents is likely to originate from the fact that aminotriazolethiols exist as zwitterionic species with the negative charge localized on the sulfur atom.

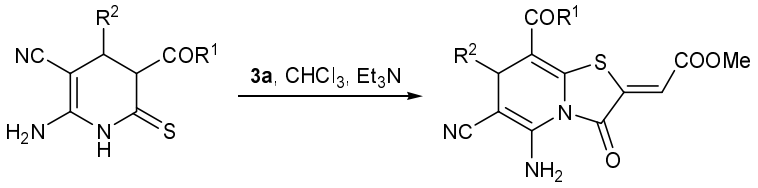
8.3. Six-Membered Heterocyclic Thiols

8.3.1. Six-membered heterocyclic thiols with one heteroatom. Bakulev et al. [50] were the only to report on the condensation of pyridine derivatives with dimethyl acetylenedicarboxylate (**3a**). The authors found that 3,4-dihydropyridine-2(1*H*)-thiones **250a**–**250c** react with ester **3a** to give thiazolopyridines **251a**–**251c** (Scheme 57).

8.3.2. Six-membered heterocyclic thiols with two heteroatoms. Reactions of 2-thioxopyrimidin-4-ones with ester **3a** do not always follow the general scheme assumed for the condensation of hetarenethiols with acetylenecarboxylic acid derivatives. For example, no expected product **253** or **254** was obtained from 6-methyl-2-thiouracil **252** [68] (Scheme 58), but compound **255** or **256** was isolated. On the basis of the NMR and UV spectral data, the product was assigned the structure of dimethyl thiazolopyrimidinedicarboxylate **255** as 1:1 adduct of **252** and **3a**. The reaction of 2-thioxotetrahydroquinazolin-4-one **257** with ester **3a** in methanol was similar to that described above, but a greater variety of products was obtained. When the reaction was carried out in boiling methanol, four main products were isolated: thiazoloquinazolinedicarboxylates **258**–**260**, compound **261** resulting from addition of one molecule of thione **257** to two molecules of **3a**, and dimethyl fumarate (**262**) (Scheme 59) [69]. The structure of compounds **258**–**260** was proved by ^{13}C NMR spectroscopy and X-ray analysis, and the ^1H and ^{13}C NMR data were sufficient to determine the structure of **261** as tetramethyl 2,2'-(1,2,3,4-tetrahydro-4-oxo-2-thioxoquinazoline-1,3-diyl)difumarate.

Cycloalkane- or cycloalkene-fused 5,6-dihydro-2-thioxopyrimidin-4-ones **263**–**266** reacted with dimethyl acetylenedicarboxylate (**3a**) in methanol according to the usual scheme to give 1,3-thiazino[3,2-*b*]pyrimidinones **267**–**270** [70, 71] (Scheme 60). Initially, formation of six condensation products **D**–**I** was believed to be possible; analysis of the spectral data simplified the problem and reduced the number of possible products to 2 (**G** and **I**); these isomers are

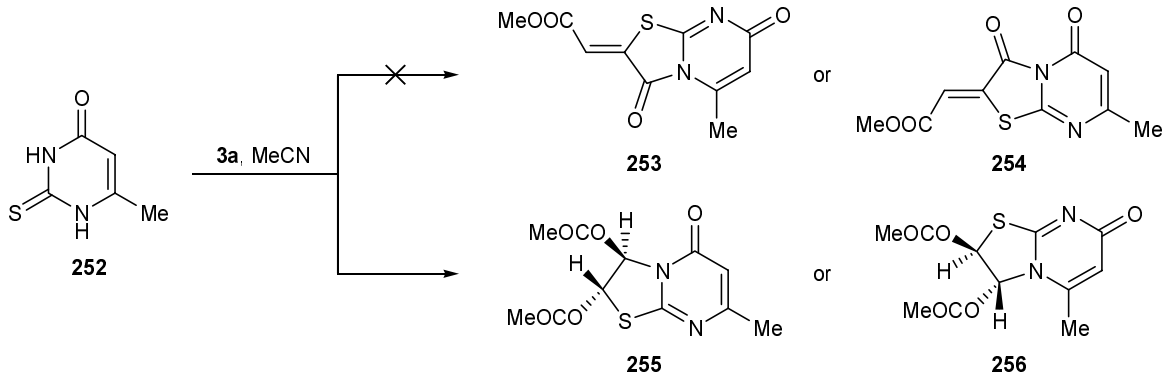
Scheme 57.



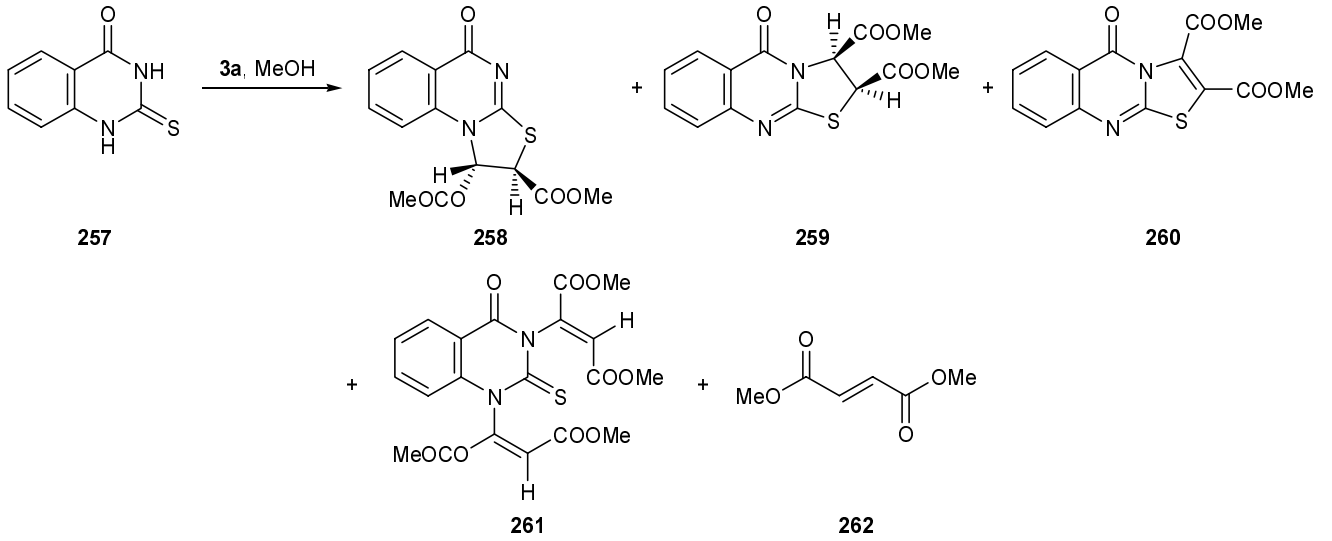
250a–250c **251a–251c**

R^1 = NH_2 (**a**, **b**), EtO (**c**); R^2 = Ph (**a**), 2-thienyl (**b**, **c**).

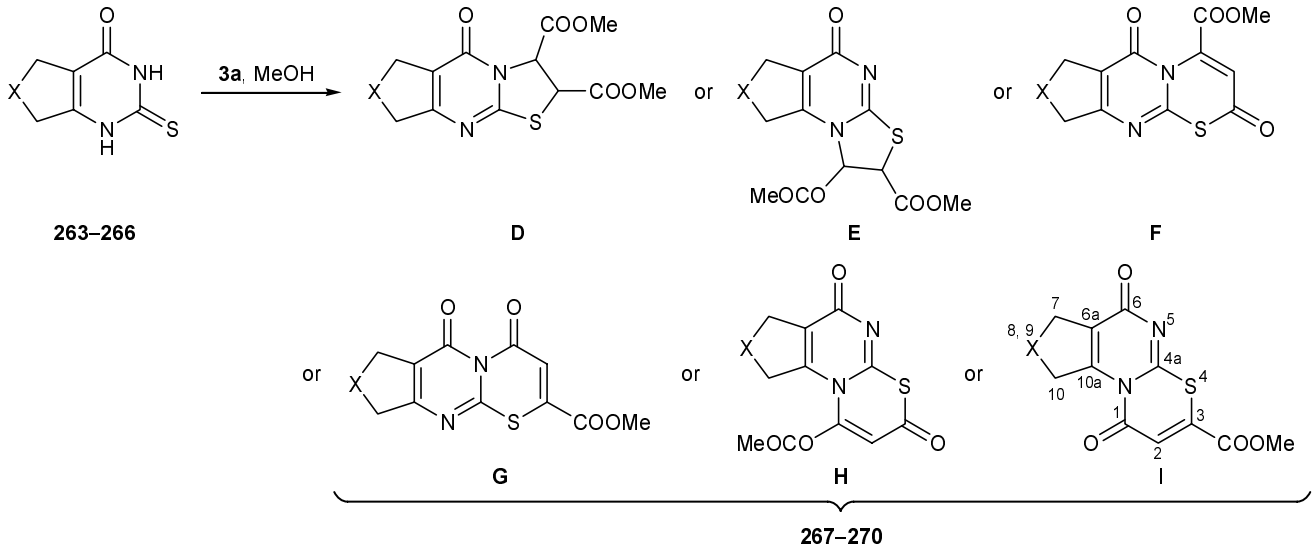
Scheme 58.



Scheme 59.



Scheme 60.



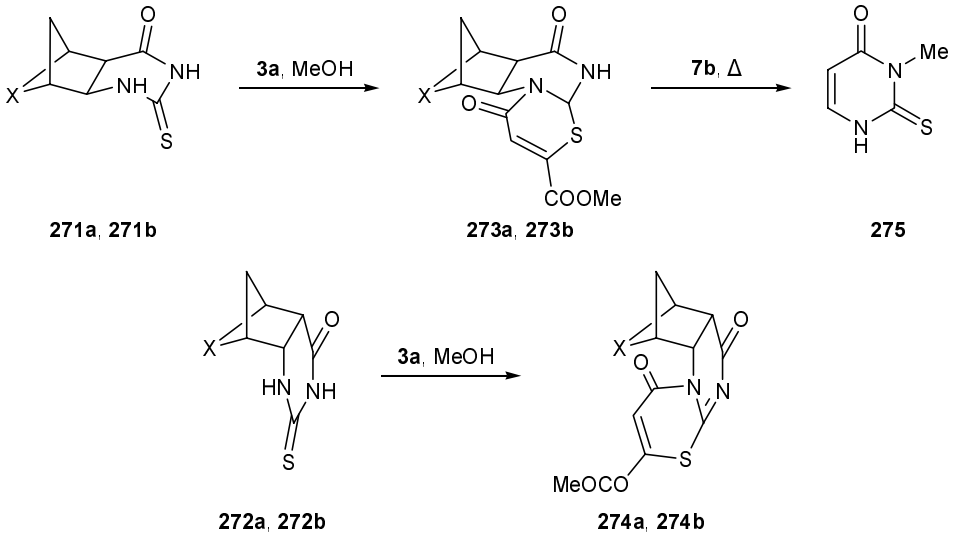
263, **267**, X = CH_2; **264**, **268**, X = CH=CH; **265**, **266**, **269**, **270**, X = CH_2CH_2; *cis* (**263**, **265**, **267**, **269**), *trans* (**264**, **266**, **268**, **270**).

formed via acylation of N^3 or N^1, respectively, by the ester group of **3a**. Unambiguous choice between isomeric structures **G** and **I** in favor of **I** was made on the basis of the ^{13}C NMR spectra recorded without decoupling from protons. It should be emphasized this method for structure determination is convenient for products obtained from acetylenecarboxylic acid derivatives and hetarenethiols having two or more structurally nonequivalent nitrogen atoms in the ring.

Stajer et al. [71] reported on the reactions of di-*exo* and di-*endo* norbornane- and norbornene-fused thioxopyrimidinones **271** and **272** with dimethyl acetylenedicarboxylate (**3a**), which led to fused [1,3]thiazinopyrimidines **273** and **274** (Scheme 61). On heating to the melting point, di-*exo*-norbornene derivative **273b** underwent intramolecular retro-Diels–Alder reaction to give 3-methyl-2-thioxotetrahydropyrimidin-4-one (**275**). The mode of ring junction (*exo* or *endo*) in compounds **273a**, **273b**, **274a**, and **274b** was determined on the basis of the NOE and DNOE measurements, and the HMBC data were used to determine which nitrogen atom in the pyrimidine was involved in the cyclization [71].

Bicyclic *N*-aminopyrimidinethiols **276**–**279** reacted with ester **3a** in methanol, yielding thiazinoquinazolidinones **281**–**284** [72] (Scheme 62). The reaction

Scheme 61.

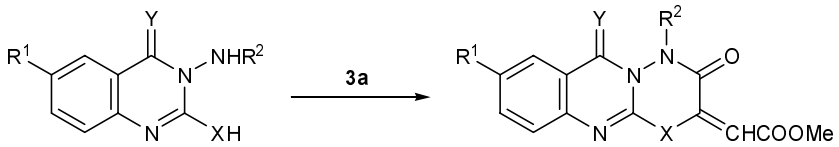


271a, **271b** **273a**, **273b** **275**

272a, **272b** **274a**, **274b**

X = CH_2CH_2 (**a**), CH=CH (**b**).

Scheme 62.



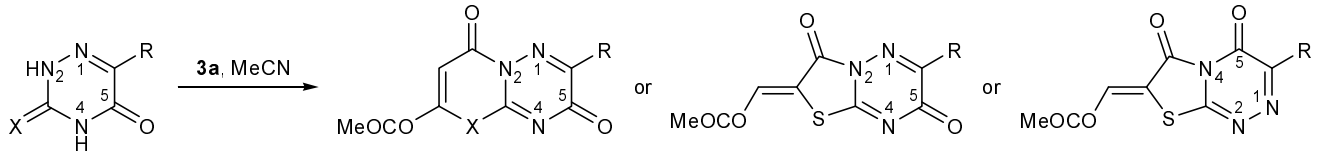
276–280 **281–285**

276, **277**, **280–282**, **285**, R^1 = H; **278**, **279**, **283**, **284**, R^1 = Cl; **276**, **278**, **280**, **281**, **283**, **285**, R^2 = H; **277**, **279**, **282**, **284**, R^2 = Me; **276–279**, **281–284**, X = S; Y = O; **280**, **285**, X = Se, Y = NH.

direction did not change when the sulfur atom was replaced by selenium: in the reaction with selenoxopyrimidine **280**, selenadiazinoquinazolidine **285** was isolated [73]. It should be noted that no thia(or selena)diazepine systems were formed in the reactions of thiols **276–279** and selenol **280** with compound **3a** (as with *N*-aminotriazolethiols **227**).

8.3.3. Six-membered heterocyclic thiols with three heteroatoms. The reaction of 6-methyl-3-thioxo-1,2,4-triazin-5-one (**286b**) with dimethyl acetylenedicarboxylate (**3a**) in acetonitrile gave thiazinotriazine **288b** [74], while the product obtained in a similar reaction in methanol was assigned the structure of thiazololotriazine **290b** with *Z* configuration of the exocyclic double bond [75] (Scheme 63). Obviously, the condensation products of triazinethiols **286a–286d** and compound **3a** are thiazolidinone derivatives **290a–290d**, for the formation of just thiazolidine rather than thiazine ring was proved by the ^{13}C NMR data (using $^2J_{HC}$ and $^3J_{HC}$ values) [75]. The formation of thiazolotriazines **290a–290d** (via reaction at N^2 of the triazine ring) rather than **291a–291d** (via condensation at N^4) also followed from the chemical shifts of C^5 in the ^{13}C NMR spectra of the products: the signal from C^5

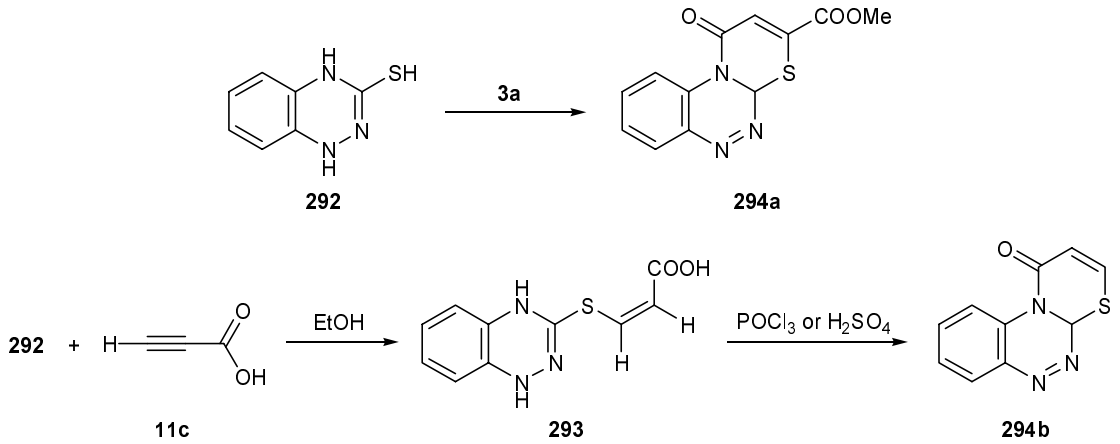
Scheme 63.



286a–286d
287a–287c **288b**, **289a–289c** **290a–290d** **291a–291d**

R = H (**a**), Me (**b**), $PhCH_2$ (**c**), Ph (**d**); **286**, **288**, **290**, **291**, X = S; **287**, **289**, X = Se.

Scheme 64.



adjacent to the pyridine-type nitrogen atom is located in a weaker field (δ_C 159–161 ppm) than that of the C^5 atom linked to the pyrrole-type nitrogen (δ_C 148–152 ppm). Seleno analogs **287a**–**287c** gave rise to the corresponding selenazinotriazines **289a**–**289c** [76] (Scheme 63).

In the condensation of benzotriazinethiole **292** with ester **3a** tricyclic compound **294a** was formed [77] (Scheme 64). The same thiol reacted with propynoic acid (**11c**) to give product **293** via *trans*-addition of the SH group of **292** at the triple bond of **11c**; no cyclization of compound **293** occurred on heating in high-boiling solvents or treatment with bases [78]. Thiazinobenzotriazine **294b** was isolated only when acid **293** was heated in boiling phosphoryl chloride or in sulfuric acid at 50°C (Scheme 64).

At first glance, cyclic thioamides give rise to a wider variety of pathways in the reactions with acetylenecarboxylic acids and their esters, as compared to acyclic analogs. Nevertheless, the reactivity of acetylenedicarboxylic acid and its esters toward various thioamides is characterized by the following general relations. In all cases, the process involves nucleophilic addition of the SH group at the triple bond and intramolecular acylation of the nitrogen by one of the carboxy group. Acylation of acyclic thioamides leads to thiazolidine systems, whereas in the reactions with hetarenethiols, depending on the cyclic thioamide structure, both thiazolidine and thiazine rings can be formed. The formation of thiazine ring is favored by the presence of one or three nitrogen atoms in the five-membered ring of the thioamide, whereas mixtures of five- and six-membered condensation products are usually formed from the imidazole-2-thione system. By contrast, condensation of dimethyl acetylenedicarboxylate with six-membered hetarenethiols having a conjugated bond system and one or three nitrogen atoms in the ring leads to thiazolidinone derivatives. Reactions of 1,3-diazine-2-thiols fused to a cycloalkane ring and containing no conjugated bond system result mainly in thiazine ring closure. The reaction mechanism of unsaturated 2-thioxopyrimidin-4-ones with dimethyl acetylenedicarboxylate falls out from the general scheme; in this case, double nucleophilic addition at the triple bond occurs with formation of dimethyl thiazolopyrimidinedicarboxylates.

Presumably, the formation of both thiazolidine and thiazine ring systems in the condensation of hetarenethiols with acetylenedicarboxylic acid esters is determined by the hardness of cyclic nucleophiles and additional strains appearing in the resulting bi- and tricyclic systems. However, there no factors hampering formation of thiazolidine systems as a more favorable direction in the reactions with acyclic thioamides.

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