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# CYCLOACYLATION OF THIOAMIDES AND THEIR DERIVATIVES BY COMPOUNDS CONTAINING AN ACTIVATED MULTIPLE BOND (REVIEW)

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*The cycloacylation reactions of thioamides and their derivatives containing an activated multiple bond are analyzed and summarized.*

**Keywords:** dithiocarbamates, 1,3-thiazin-4-ones, thiazolidin-4-ones, thioamides, thioureas, thiosemicarbazides, thiosemicarbazones, multiple bond, cycloacylation.

The cycloacylation of thioamides and their derivatives containing an activated multiple bond is an accessible and convenient method for the synthesis of five- and six-membered sulfur- and nitrogen-containing heterocycles – primarily 4H-1,3-thiazin-4-ones [1] and thiazolidin-4-ones [2], and also 2-thioxopiperidines [3], thiopyran-4-ones [4], and pyrimidin-4-ones [5]. Heterocyclic compounds of these types exhibit a wide spectrum of biological activity and have extensive practical applications [1, 2, 6].

This group of reactions is also of interest from the theoretical standpoint since they make it possible to study, analyze, and predict the relationships between the reactivity of substrates containing the ambident NH─C═S group and their structure, reaction conditions, and the nature of substituents at the heteroatoms. Therefore, in spite of the fact that the first papers on this subject were published 50 of more years ago [7, 8] synthetic investigations in the field are continuing to this day [9-12].

Nevertheless, no reviews have been published on this subject. It should be mentioned that certain methods for the cycloacylation of thioamides by derivatives of unsaturated carboxylic acids were analyzed in reviews on the synthesis of 1,3-thiazines [1] and thiazolidin-4-ones [2, 13], reactions of N-aminoazolinethiones and N-aminoazinethiones [14], thioamides [15-17], and carbon suboxide [18]. However, the information on this subject in these publications has not been coordinated and is not exhaustive.

New publications on the cycloacylation of thioamides, in which the range of both reagents and substrates has been extended, have appeared recently. Modern physical methods of establishing the structure of the synthesized products were used, and this made it possible to prove their structure unequivocally.

For this reason we attempted to fill the gap and to analyze the information concerning the cycloacylation of acyclic and cyclic thioamides by compounds containing an activated multiple bond. This reviews covers papers not examined in [1, 2, 13-18] and also papers that have appeared more recently.

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## 1. CYCLOACYLATION OF THIOAMIDES AND THEIR DERIVATIVES BY COMPOUNDS CONTAINING AN ACTIVATED TRIPLE BOND

Reactions of this group were analyzed quite comprehensively in the recently published review [17]. We nevertheless consider it necessary to present the following information.

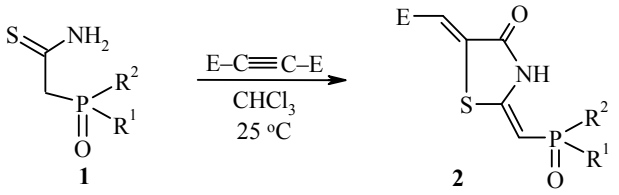
As known, reagents suitable for the cycloacylation of thioamides are acetylenedicarboxylic and 3-R-propiolic acids (R = H, Alk, Ar) and also their acid chlorides, esters, and nitriles. A special feature of the reactions of 3-R-propiolic acids and their derivatives with thioamides is the selectivity and predictability, since they are as a rule realized exclusively by a [3+3] cyclocondensation scheme, leading to the formation of 1,3-thiazin-4-ones [17].

Acetylenedicarboxylic acid and its esters are ambident dielectrophiles, leading to the following relationships: 1) Depending on the structure of the substrate and the reaction conditions, the reactions with compounds containing a thioamide fragment can take place according to [3+3], [2+3], [2+4], and [4+1] cycloaddition schemes [17]; 2) It is frequently impossible to identify the products of these transformations unambiguously by such trivial (by today's standards) methods of investigation as $^{1}$H NMR and IR spectroscopy; 3) Investigation of these reactions makes increased demands on the methods of determining the structure of the synthesized compounds. It should be mentioned that the most accurate, informative, and reliable physical methods capable of identifying unambiguously the structure of the products of such transformations are $^{13}$C NMR spectroscopy (with and without suppression of C–H spin–spin coupling) [17, 19, 20] and X-ray crystallographic analysis [21, 22].

As far as the scheme of the investigated reactions is concerned it can be concluded on the basis of experimental data [17] that the first stage is clearly addition of the activated triple bond of the reagent at the thioxo group of the substrate, followed by intramolecular attack by the carbonyl group at the N atom of the thioamide fragment. It should be noted that the products from S-acylation were not synthesized in any of the papers [17], and this is probably explained by their lower stability compared with the N-acyl derivatives [23].

### 1.1. Reactions with Acetylenedicarboxylic Ester

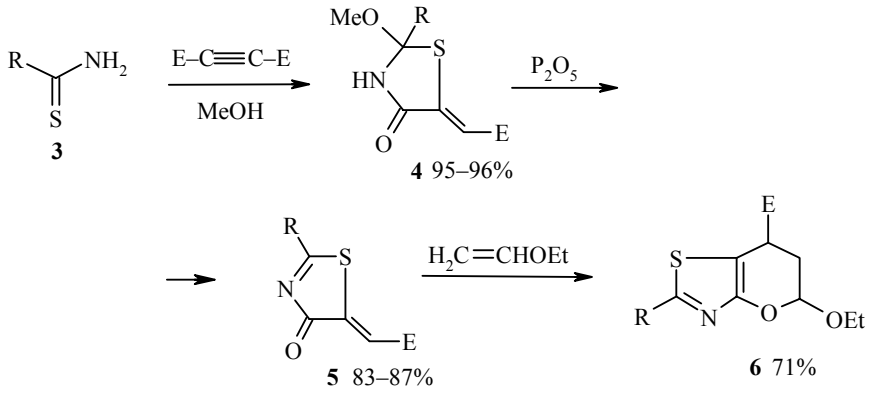
It was shown recently [9] that the reaction of dimethyl acetylenedicarboxylate (DMAD) with thioamides (**1**) is a convenient method for the synthesis of phosphorylated thiazolidin-4-ones (**2**) with an *E*,*Z*-structure.




**1** **2** 75–80%

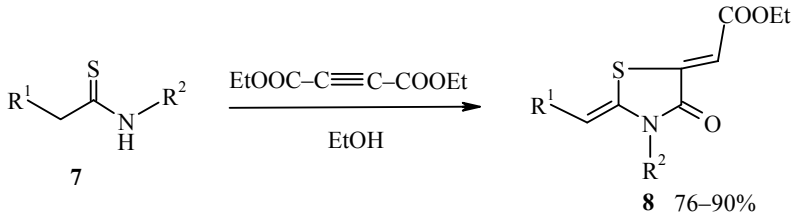
$R^1$, $R^2$ = OEt, Ph, E = $CO_2Me$

The reactions of DMAD with thioamides **3** containing polyfluoroalkyl substituents [11, 24] differ from the cycloacylation of the unfluorinated substrates. On account of the strong electron-withdrawing effect of the polyfluoroalkyl groups 2-methoxy-2-R-5-methoxycarbonylmethylenethiazolidin-4-ones **4** and not thiazolidin-4-ones are formed in this reaction. Their derivatives **5** react readily with dienophiles (vinyl ethyl ether) and 1,3-dienes (isoprene and 2,3-dimethyl-1,3-butadiene), being converted into 5H-pyrano[2,3-*d*]thiazolines **6** and 4-oxo-1-thia-3-azaspiro[4,5]deca-2,8-dienes [24].



R = $CF_3$, $H(CF_2)_4$; E = $CO_2Me$

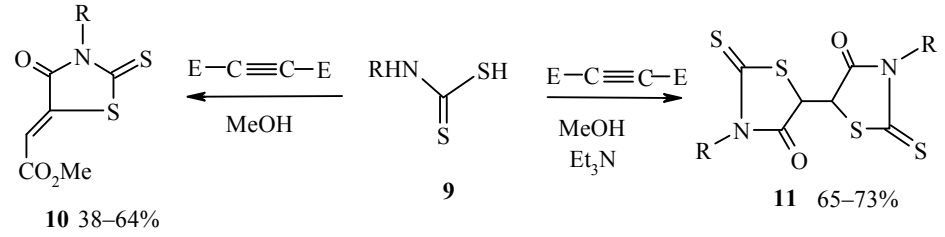
In [25, 26] it was established that the thioamides **7** containing an active methylene group react smoothly with acetylenedicarboxylate ester. The reaction is selective with the formation of 2-($R^1$-methylene)-5-ethoxycarbonylmethylene-3-$R^2$-1,3-thiazolidin-4-ones **8**. Their structure was proved unequivocally by means of the $^{13}C$ NMR spectra, recorded with and without suppression of C–H spin–spin coupling:



$R^1$ = MeCO, PhCO, $PhSO_2$; $R^2$ = Me, Ph, 4-$FC_6H_4$

The reactions of compounds containing an activated triple bond with dithiocarbamates differ somewhat from the analogous cyclocondensations with thioamides and thioureas, and this is explained by the high nucleophilicity of the dithiocarbamates.

H. Nagase [27] investigated the reaction of DMAD with dithiocarbamic acid **9** and found that thiazolidin-4-ones **10** were formed when the reagents were in an equimolar ratio and di(thiazolidin-4-ones) **11** were formed when there was an excess of the dithiocarbamate:

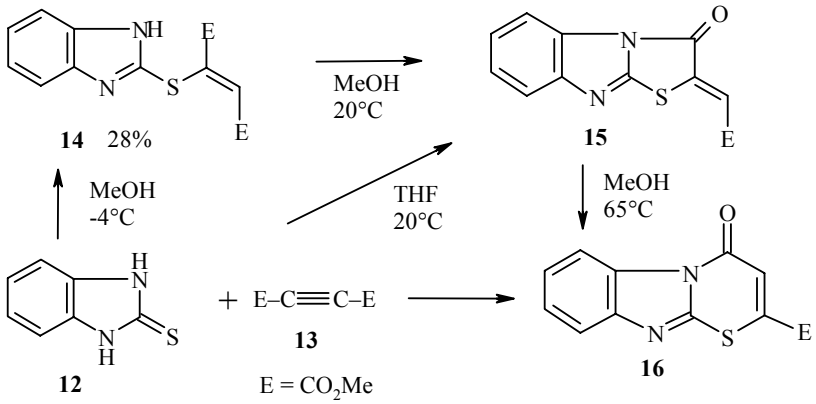


R = Me, Et, Pr, Ph, *n*-Bu, $PhCH_2$; E = $CO_2Me$

The same author showed that compounds **10** can be used as dienophiles in the Diels-Alder reaction [28] and can also enter into reaction with *o*-aminothiophenol, forming (3-oxo-4H-1,4-benzothiazin-2-yl)thiazolidinones [29].

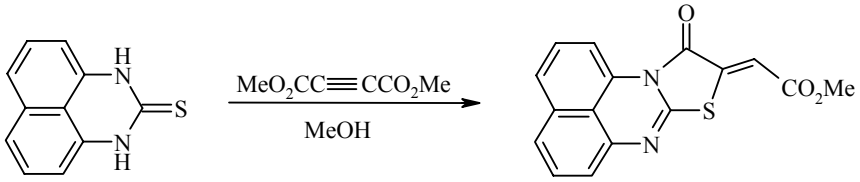
Cyclic thioamides can react with acetylenedicarboxylic ester with the formation of two bicycles – derivatives of thiazol-4-one and 1,3-thiazin-4-one. These products can be identified by $^{13}C$ NMR spectroscopy [17] or chemical transformations [30].

Extremely interesting is the reaction of benzimidazolin-2-thione **12** with acetylenedicarboxylic ester **13**, which depending on the nature of the employed solvent and the temperature can take place in two directions [30]. It was established that a mixture of thiazolo[3,2-*a*]benzimidazole **15** and [1,3]thiazolo[3,2-*a*]benzimidazole **16** in a ratio of ~2:1 is formed with an overall yield of 62% in the case of condensation at 20°C in THF whereas only the thiazinone **16** is formed with a yield of 96% on boiling in methanol.



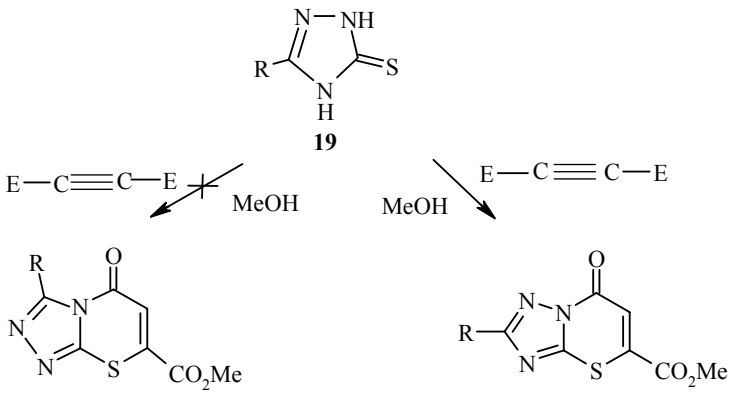

J. J. Wade also isolated the 2-(benzimidazolyl-2-thio)fumarate **14** from the reaction mixture and showed that it was an intermediate product during the production of the thiazolidinone **15** [30]. The same investigator separated compounds **15** and **16** by chromatography and then characterized them by $^{1}H$ NMR, IR, and mass spectroscopy. It was also found that the thiazolidinone **15** was a metastable compound – it is transformed into the thiazinone **16** after prolonged boiling (17 h) in methanol or after keeping in a methanol solution of sodium methoxide for several minutes. The structure of the reaction products was confirmed by an alternative synthesis [30].

The reaction of DMAD with 2-thioxoperimidine **17** makes it possible to obtain a preparative yield of 2-methoxycarbonylmethylene-1H-perimido[2,1-*b*]thiazolidin-3-one (**18**), the structure of which was proved by the $^{1}H$ NMR, IR, and UV spectra [31].




**17** **18** 77%

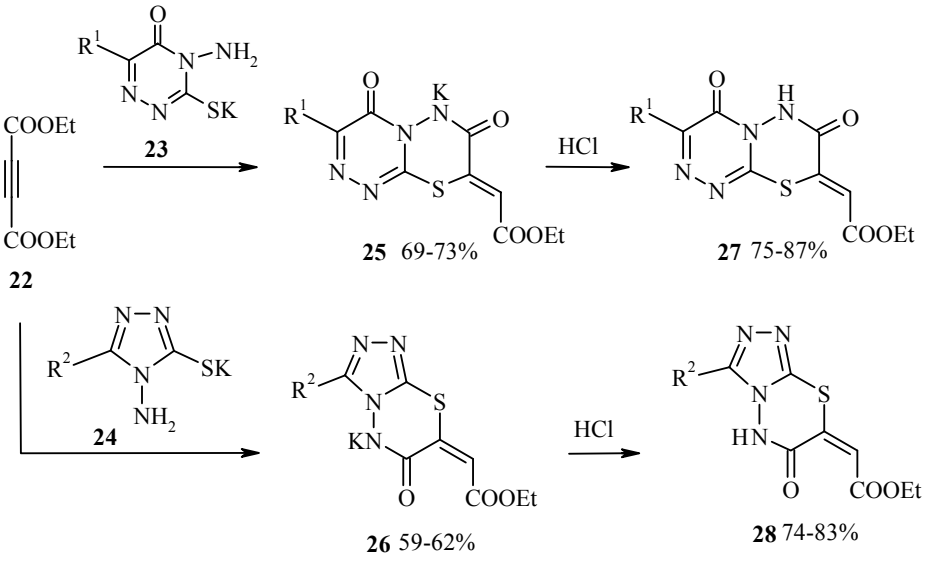
In the opinion of Indian researchers [32], the products from the condensation of 4,5-dihydro-1H-1,2,4-triazole-5-thiones **19** with DMAD in methanol are 5-methoxycarbonyl-2-phenyl-7H-[1,2,4]triazolo[5,1-*b*]-[1,3]thiazin-7-ones **21**, whereas the authors of [33, 34] suggest that these compounds have the structure of 7-methoxycarbonyl-3-phenyl[1,2,4]triazolo[3,4-*b*][1,3]thiazin-5-ones **20**.




R = H, Me, Ph, 4-$FC_6H_4$, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$; E = $CO_2Me$

In [22] it was shown unambiguously by X-ray crystallographic analysis that [1,2,4]triazolo[5,1-*b*]-[1,3]thiazin-7-ones **21** are produced in this reaction.

4-Amino-6-R-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazin-5-ones and 4-amino-3-R-4,5-dihydro-1H-1,2,4-triazole-5-thiones react with acetylenedicarboxylic ester only in the form of the thiolates **23** and **24** [35]. Here 8-ethoxycarbonylmethylene-3-R-7,8-dihydro-4H,6H-[1,2,4]triazino[3,4-*b*][1,3,4]thiadiazine-4,7-diones **27** and 7-ethoxycarbonylmethylene-3-R-6-oxo-6,7-dihydro-5H-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines **28** were isolated after acidification of the reaction mixture.



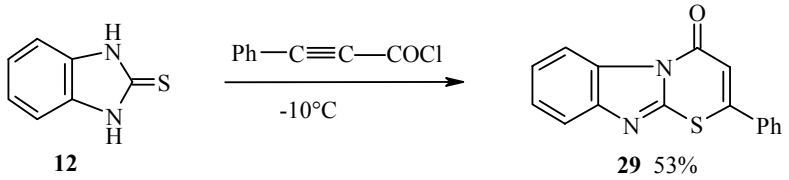

$R^1$ = *t*-Bu, Ph; $R^2$ = $PhCH_2$, $PhOCH_2$

The low reactivity of 4-amino-6-3-thioxo-R-2,3,4,5-tetrahydro-1,2,4-triazin-5-ones and 4-amino-3-R-4,5-dihydro-1H-1,2,4-triazole-5-thiones is probably explained by the fact that they exist exclusively in the thione form [36].

Thus, derivatives of thiazolidin-4-one are as a rule formed in the reactions of acetylenedicarboxylic ester with acyclic thioamides, whereas the thermodynamically more stable derivatives of 1,3-thiazin-4-one are formed in its reaction with cyclic ureas.

### 1.2. Cyclocondensation with Derivatives of 3-R-Propiolic Acids

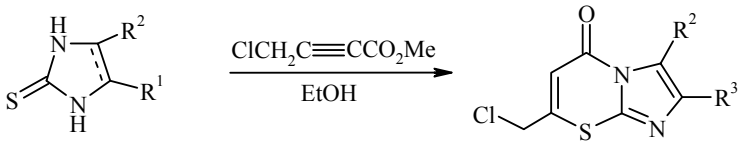
2-Phenyl-4H-[1,3]thiazino[3,2-*a*]benzimidazol-4-one **29** was synthesized by the reaction of propioloyl chloride with benzimidazoline-2-thione **12** in pyridine at -10°C [37].




**12** **29** 53%

However, 3-phenyl-2-propinoyl chloride is a thermally unstable reagent [38], and this significantly reduces its synthetic value.

According to data in [39], methyl 4-chlorotetrolate condenses with imidazoline-2-thione and benzimidazoline-2-thione **30** forming 5H-imidazo[2,1-*b*][1,3]thiazin-5-ones **31**.

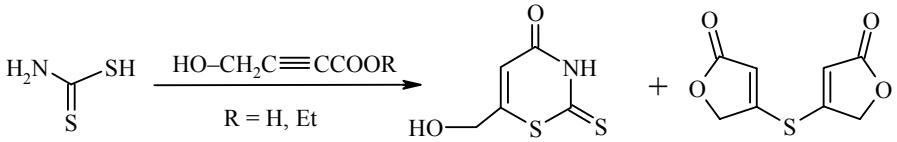



**30** **31** 11–21%

$R^1 = R^2 = H, CO_2Et, R^1 + R^2 = CH{=}CH{-}CH{=}CH$

However, the low yields of the products (11-21%) do not make it possible to use the heterocycles **31** as "synthesis blocks" for further transformations.

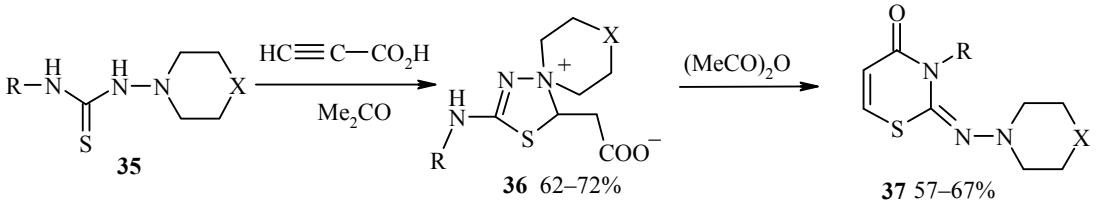
The products from the reaction of dithiocarbamic acid (**32**) with γ-hydroxytetrolic acid (ethyl γ-hydroxytetrolate) in aqueous solution at -5°C are 6-hydroxymethyl-2-thioxo-2,3-dihydro-1,3-thiazin-4-one **33** and the thiodilactone **34** [40].




**32** **33** 6–64% **34**

A special feature of thiosemicarbazide and its derivatives is the presence of four reaction centers, the selectivity of which in reactions with cycloacylating reagents is as a rule affected significantly both by the structure of the substrates and by the nature of the employed solvent.

Thiosemicarbazides **35** react with propiolic acid in an unusual way [41]:

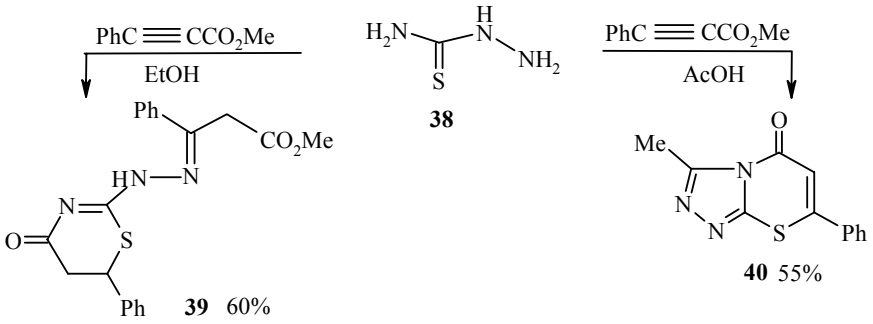



**35** **36** 62–72% **37** 57–67%

R = $CH_2CH{=}CH_2$, Ph; X = $CH_2$, $(CH_2)_2$, O

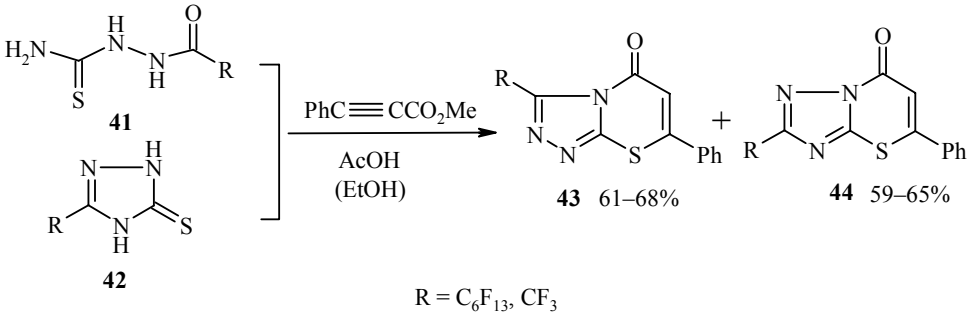
The intermediate products of this reaction are zwitterionic compounds **36**, which recyclize to 2,3-dihydro-4H-thiazin-4-ones **37** under the influence of a dehydrating agent.

The direction of the reaction of thiosemicarbazide **38** with methyl 3-phenylpropiolate also depends on the nature of the solvent – methyl 3-[(4-oxo-6-phenyl-4H-1,3-thiazin-2-yl)hydrazono]-3-phenylpropionate **39** is formed in ethanol and 3-methyl-7-phenyl-5H-[1,2,4]triazolo[3,4-*b*][1,3]thiazin-5-one **40** in acetic acid [10]:




However, the authors [10] did not consider the possibility of the formation of the isomeric product 2-methyl-5-phenyl[1,2,4]triazolo[5,1-*b*][1,3]thiazin-7-one in the reaction in acetic acid. Since the structure of the regioisomers can only be resolved by X-ray diffraction, the question of the structure of compound **40** remains open.

In [42] it was shown that the products from the reaction of 3-R-1,2,4-triazoline-5-thione **42** and 3-trifluoroacetyl(perfluorohexanoyl)thiosemicarbazide **41** with methyl 3-phenylpropiolate in acetic acid (ethanol) are mixtures of two isomeric bicycles – 3-R-7-phenyl-5H-[1,2,4]triazolo[3,4-*b*][1,3]thiazin-5-ones (**43**) and 2-R-5-phenyl[1,2,4]triazolo[5,1-*b*][1,3]thiazin-7-ones **44**, which are obtained with overall yields of 70-80% in a ratio of 10:1. Since the structure of compounds **43** and **44** cannot be identified unambiguously by the data from the IR, $^{1}$H and $^{13}$C NMR, and mass spectra, the structure of the isomers given by the authors [42] is provisional until the results from X-ray diffraction analysis are obtained. It should be noted that in the overwhelming majority of cases the reactions of 1,2,4-triazole derivatives with electrophilic reagents take place selectively at the N-1 position of the triazole ring, as confirmed by the data from X-ray crystallographic analysis [21, 22, 43].




## 2. CYCLOACYLATION OF THIOAMIDES AND THEIR DERIVATIVES BY COMPOUNDS CONTAINING AN ACTIVATED DOUBLE BOND

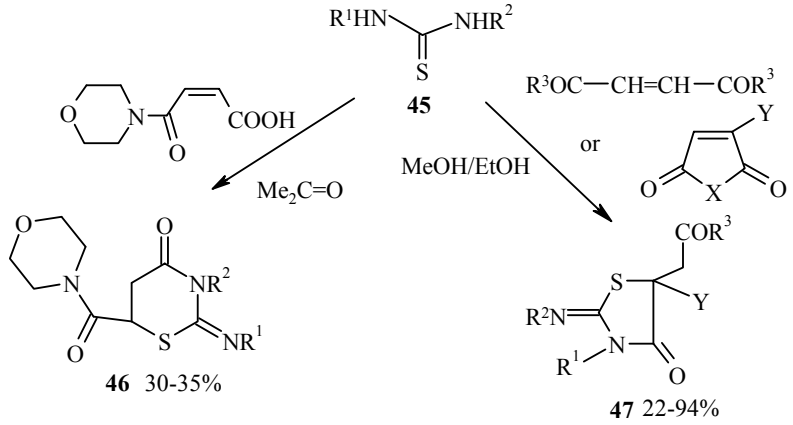
In contrast to the reactions described above, this group of cyclocondensations is distinguished by the large assortment of reagents. Maleic anhydride and maleimides, 2-R$^{1}$-3-R$^{2}$-propenoic and 3-aroylacrylic acids, α-unsaturated nitriles, carbon suboxide, ketene, diketene, 2,3-diphenylcyclopropenone, 2-chlorocarbonyl-2-arylketenes, and ethyl [(aryl)hydrazono]chloroacetates have been used as reagents.

The transformations can take place by different mechanisms and according to [3+3], [3+2], and [4+2] condensation schemes. Depending on the structure of the cycloacylating agent, the first stage can be both addition of its activated double bond at the thioxo group of the substrate [44, 45] and N-acylation of the substrate [46-48]. The products from S-acylation of compounds containing a thioamide group are formed much more rarely, and they are less stable than the N-acylation products. Nevertheless, an S,N-transacylation mechanism [49, 50], in which the intermediates are S-acyldithiocarbamates, is realized during the cycloacylation of dithiocarbamates.

### 2.1. Reactions with Maleic Anhydride and its Derivatives

Reactions with maleic anhydride and its derivatives were investigated vigorously in 1900-2005, and this was reflected in the reviews [2, 13] and papers [51-55]. Cycloacylation with maleic anhydride and maleamides takes place by [3+2] and [3+3] condensations.

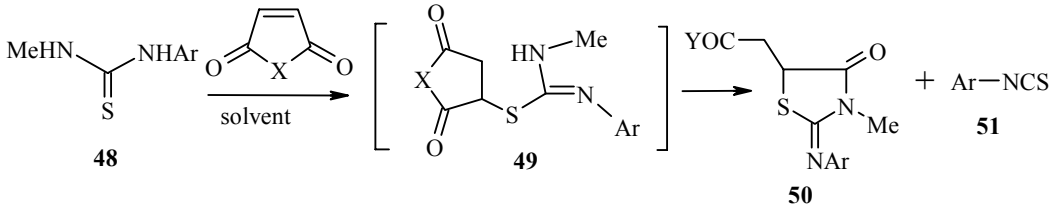
In [51] 2-imino-4-oxothiazolidine-5-acetic acids and their esters and amides were obtained by the reaction of N-$R^1$-N′-$R^2$-thioureas **45** and fumaric (maleic) acid, diethyl maleate, and N-alkylmaleimides:




$R^1$ = H, Me, $CH_2$=CH–$CH_2$, *n*-Bu, Ph; $R^2$ = H, Me, *i*-$C_3H_7$, cyclohexyl, *n*-Bu, Ph, 4-$PhOC_6H_4$, 2,4-$Me_2C_6H_3$, 3-$CF_3C_6H_4$, 2-F-3-$MeC_6H_3$; $R^3$ = OH, OEt, MeN, *n*-BuNH, *n*-$C_8H_{17}NH$, *n*-$C_{10}H_{21}NH$, *n*-$C_{12}H_{25}NH$, PhNH; X = O, *n*-BuN, *n*-$C_8H_{17}N$, *n*-$C_{10}H_{21}N$, *n*-$C_{12}H_{25}N$; Y = H, Br

4-Oxothiazolidine-5-acetic acids **47** are also formed during the fusion of N-aryl-3-oxobutanethioamides [52] and thioureas [53] with (bromo)maleic anhydride, whereas the products from the cycloacylation of thiourea with the morpholide of maleic acid are 1,3-thiazin-4-ones **46** (53).

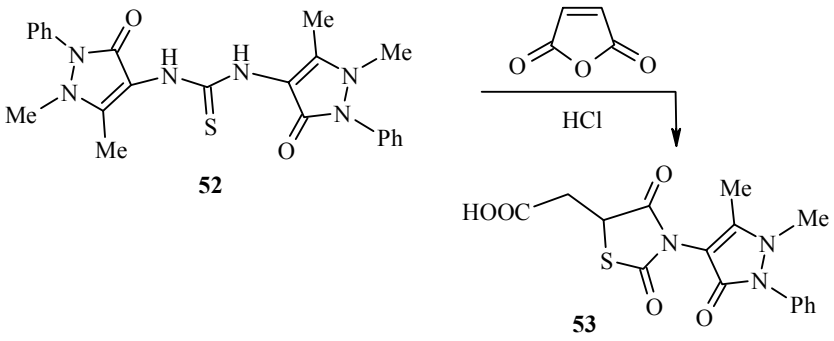
In [54] the reaction of maleic anhydride and N-R-maleimides with N-methyl-N'-arylthioureas **48**, in which 2-imino-4-oxothiazolidine-5-acetic acids **50** are obtained, was studied in great detail. If high-boiling solvents (toluene, xylene) are used pyrolysis of the initial thioureas **48** and the formation of aryl isothiocyanates **51** are also observed.




Ar = Ph, 2,4-$Me_2C_6H_3$, 3-$CF_3C_6H_4$, 4-$PhOC_6H_4$, 2-F-3-$MeC_6H_3$, 3,4-3,4-methylenedioxyphenyl; X = O; NMe, NPh; Y = OH, NHMe, NHPh

The condensation was conducted in the absence of additives of basic character, and the acylation of the N-methyl-N'-arylthioureas therefore took place selectively at the more basic group. The authors [54] suggest that the first stage of the reaction is addition of the thioxo group of the substrate at the activated double bond of the maleic anhydride (maleimide). The structure of the thiazolidine-5-acetic acids **50** was proved both by the $^1$H NMR spectra and by data from X-ray crystallographic analysis.

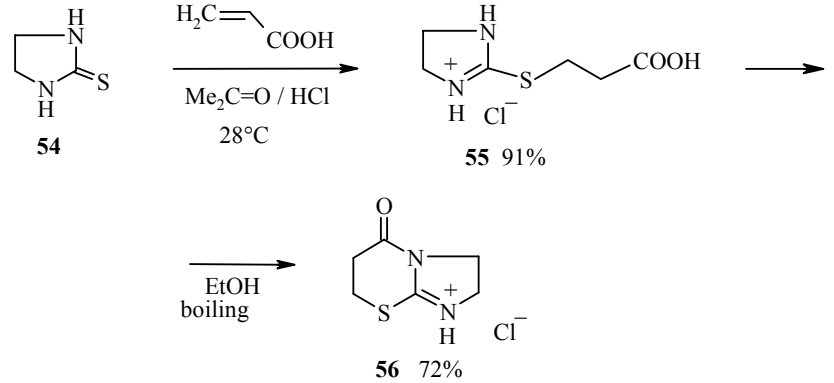
Concentrated hydrochloric acid can also be used as solvent for condensations of such a type [55]. It was possible to synthesize 5-carboxymethyl-3-(4-antipyryl)thiazolidine-2,4-dione **53** from diantipyrylthiourea **52** by this method.



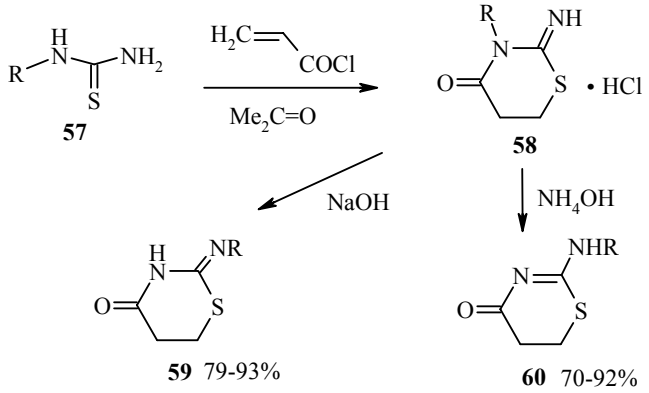

## 2.2. Cyclizations with 2-R-Propenoic Acids and Their Esters and Acid Chlorides

The cycloacylation of thioamides with acrylic acid and acryloyl chloride, which takes place by a [3+3] condensation, is one of the most accessible methods for the synthesis of derivatives of 5,6-dihydro-4H-1,3-thiazin-4-one.

In [45] it was shown that the first stage of such condensations is attack by the activated double bond of the reagent on the thioxo group of the substrate **54**, accompanied by the formation of 2-(imidazolinyl)thiopropionic acid **55**. When heated the latter is converted smoothly into 2,3,6,7-tetrahydro-5H-imidazo[2,1-*b*]-1,3-thiazin-5-one **56**.



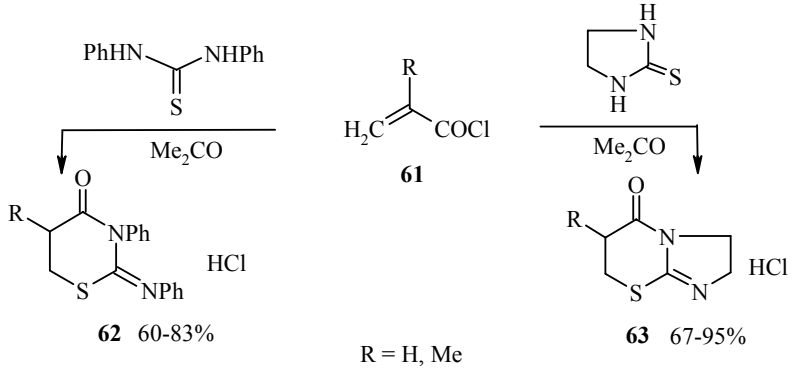

In [56-58] it was established that the products from the cycloacylation of N-R-thioureas **57** with acryloyl chloride in acetone at 0-5°C are the hydrochlorides of 2-imino-3-R-2,3,5,6-tetrahydro-1,3-thiazin-4-ones **58**. With bases the latter undergo a Dimroth rearrangement to 2-(R-imino)-5,6-dihydro-4H-1,3-thiazin-4-ones **59** and 2-R-amino-2,3,5,6-tetrahydro-4H-1,3-thiazin-4-ones **60** [56, 58].



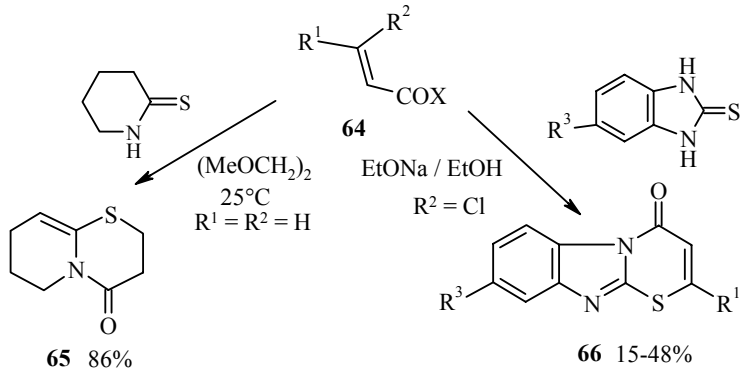

However, the structure of the compounds **58-60**, extremely close in structure, was only proved by UV, $^1$H NMR, and IR spectroscopy [56, 57].

The reaction of acryloyl chloride with N-phenylthiourea in dioxane and with thiourea in acetic acid was also investigated in [59, 60]. It was shown by $^1$H NMR and IR spectroscopy that the products of these reactions are the hydrochlorides of 2-imino-3-R-2,3,5,6-tetrahydrothiazin-4-one **58**.

In the case of the cyclocondensation of N,N′-diphenylthioureas and imidazolidine-2-thione with 2-R-acryloyl chlorides **61** the hydrochlorides of 5-R-3-phenyl-2-phenylimino-2,3,5,6-tetrahydro-4H-1,3-thiazin-4-ones **62** and 6-R-2,3,6,7-tetrahydro-5H-imidazo[2,1-*b*]-1,3-thiazin-5-ones **63** respectively are formed [61].

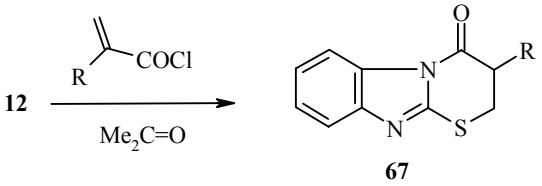



A. Padwa and coworkers realized the condensation of acryloyl chloride **64** ($R^1 = R^2 = H$) with 2-thioxo-piperidine in 1,2-dimethoxyethane and isolated tetrahydro-2H-pyrido[2,1-*b*][1,3]thiazin-4-one **65** with a preparative yield [62].



4H-[1,3]-Thiazino[3,2-*a*]benzimidazol-4-ones **66** were obtained in the reaction of *cis*-3-chloroacrylic acid [63] or ethyl *cis*-3-chlorocrotonate [64] with 6-$R^3$-benzimidazoline-2-thiones. In the first case the reaction was conducted in xylene, and in the second in ethanol in the presence of sodium ethoxide, but the low yields did not make it possible to use these methods for preparative purposes.

A convenient method for the synthesis of 2-R-2,3-dihydro-4H-[1,3]thiazino[3,2-*a*]benzimidazol-4-ones **67** is the reaction of 2-R-propenoyl chlorides (R = H, Me, Et) with benzimidazoline-2-thione **12** in acetone [65, 66]. The yields of the products **67** here range from 53% to quantitative.

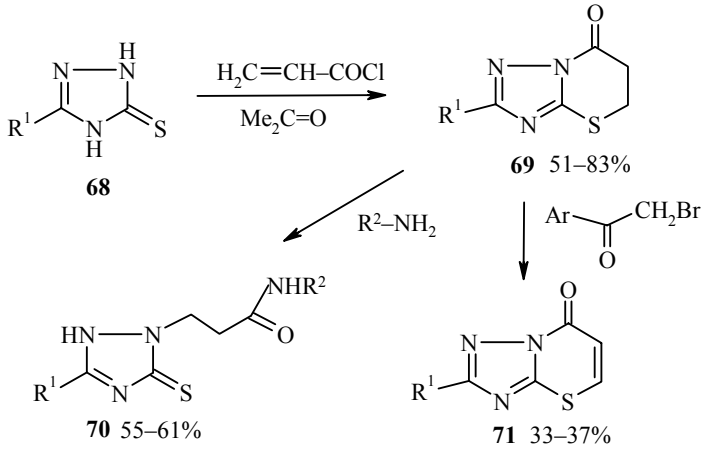



**67**

R = H, Me

[1,3]-Thiazino[3,2-*a*]benzimidazol-4-ones **67** were also synthesized from 6-R-benzimidazoline-2-thiones by a two-stage method, involving the production of β-(6-R-benzimidazol-2-ylthio)propionic acids and their subsequent dehydration with acetic anhydride [67, 68] or dicyclohexylcarbodiimide [69].

In [70] it was demonstrated that the reaction of acryloyl chloride with 3-R-4,5-dihydro-1H-1,2,4-triazole-5-thiones **68** provides a preparative method for the synthesis of 2-$R^1$-5-$R^2$-5,6-dihydro-7H-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-7-ones **69**.




**68**

**69** 51–83%

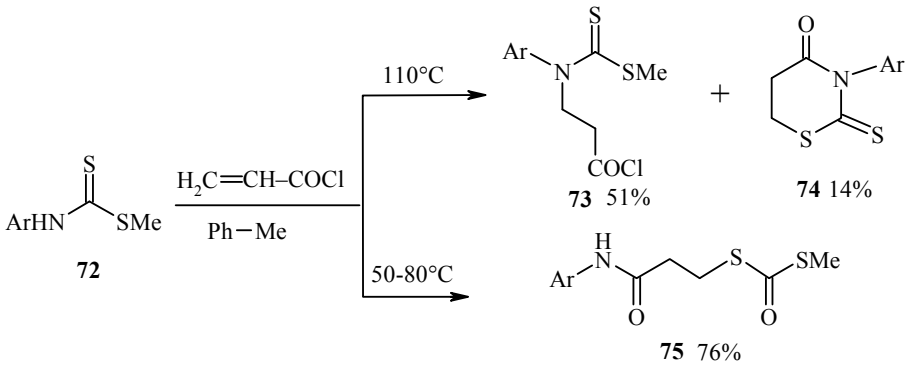
**70** 55–61%

**71** 33–37%

$R^1$ = H, Ph, 4-$FC_6H_4$, 4-$MeOC_6H_4$, 1-1-naphthyl, 1-1-adamantyl, $Ph_2CH$, 4-$O_2NC_6H_4$;
$R^2$ = Ph, $PhCH_2$; Ar = Ph, 4-$ClC_6H_4$

It was established by the same authors that triazolo[5,1-*b*][1,3]thiazin-7-ones **69** undergo S,N-rearrangement when heated with aniline (benzylamine), being converted into 3-(3-aryl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)propanamides **70** [71], and are dehydrated when fused with α-halo ketones [72]. The last method, in contrast to [73, 74], makes it possible to synthesize triazolo[5,1-*b*][1,3]thiazin-7-ones **71** without the use of expensive and difficultly obtainable compounds.

In [75] it was found that the acyclic compounds **73** and **75** and the cyclic compound **74** are formed in the reaction of S-methyl-N-aryldithiocarbamates **72** with acryloyl chloride depending on the temperature conditions.

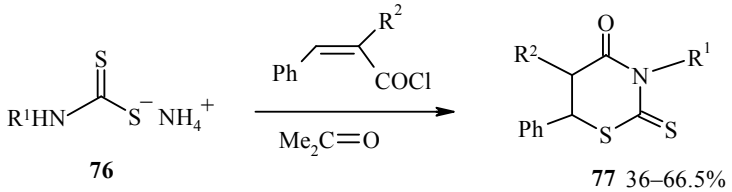



Ar = Ph, 4-$MeOC_6H_4$, 3-$MeC_6H_4$, 4-$MeC_6H_4$

## 2.3. Reactions with 3-Aryl-2-propenoyl Chlorides

Earlier [2, 8, 13] it was reported that 3-aryl-2-propenoic acids and their esters react with thioamides according to a [3+3] condensation scheme under very mild conditions, and this has a negative effect on the yields of the desired products. As a result of their higher reactivity aryl-2-propenoyl chlorides are suitable reagents for the cycloacylation both of dithiocarbamates [49, 50, 76] and of thioamides with various structures [4, 47, 48, 77]. Unlike acryloyl chloride, 3-aryl-2-propenoyl chlorides do not polymerize when heated and in the presence of bases. Moreover, with their use it is possible to synthesize 5,6-dihydro-1,3-thiazin-4-ones containing various aryl substituents at position 6 of the thiazine ring. Such an approach extends to boundaries of the method and is of considerable importance in the production of biologically active compounds.

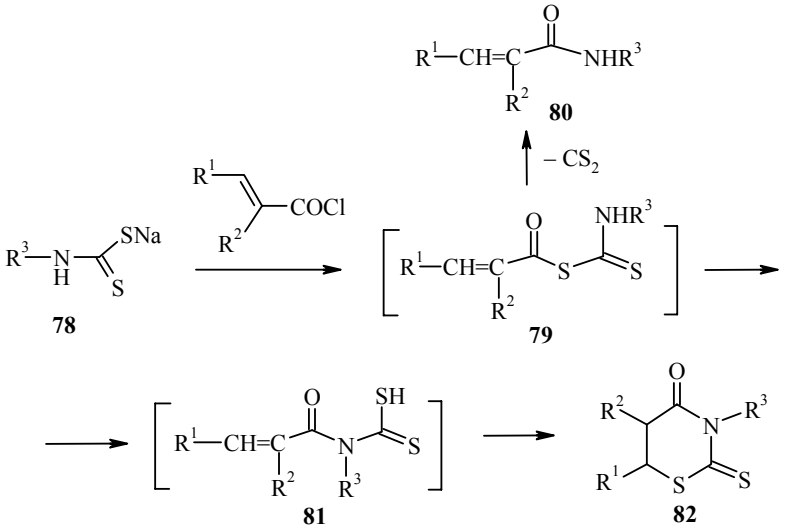
In the patent [76] the condensation of the dithiocarbamates **76** with 3-phenyl-2-R-propenoyl chloride in acetone (or diethyl ether) in the range of -15-0°C was proposed as a preparative method for the synthesis of 2,3,5,6-tetrahydro-4H-1,3-thiazin-4-ones **77**, which have been patented as ingredients of cosmetic products.




$R^1$ = $PhCH_2CH_2$, 4-$ClC_6H_4CH_2$; $R^2$ = H, Ph

The reaction of the salts of dithiocarbamic acid **78** with the chlorides of α,β-unsaturated acids was studied in greater detail in [49, 50].

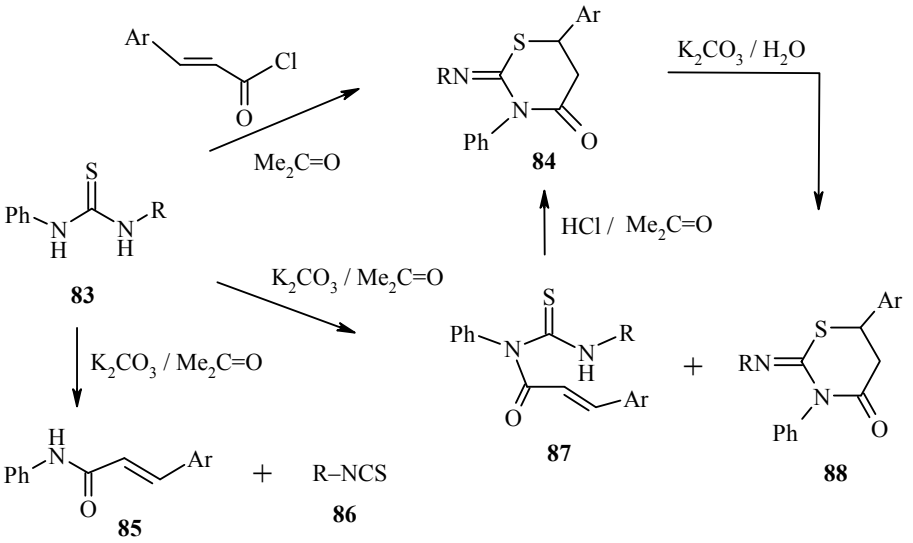
The reaction was conducted in a mixture of acetone and water [49] in the range of −5 to +3°C or in diethyl ether at −10°C [50]. It was noticed [49] that the addition of acid to the reaction mixture retards the cyclization, whereas the presence of bases accelerates it. It was suggested [49, 50] that the first stage of the process is the formation of S-acyl dithiocarbamates **79**. After this, depending on the nature of the substituents in the dithiocarbamate and the acid chloride and also on the reaction conditions, either hydrogen sulfide is eliminated and the amides of propenoic acids **80** are produced or S,N-transacylation occurs and the products cyclize immediately to 2,3,5,6-tetrahydro-4H-1,3-thiazin-4-ones **82**. The yields of the 1,3-thiazin-4-ones **82** vary between moderate (28%) and quantitative (91%) [49, 50].



$R^1$ = Ph, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 2-$O_2NC_6H_4$, 2- furyl, H; $R^2$ = H, Ph; $R^3$ = H, Me, Et, *n*-Pr, *n*-Bu, Ph, $PhCH_2$, $PhCH_2CH_2$, 4-$HOC_6H_4$, 4-$MeOC_6H_4$, 4-$ClC_6H_4$

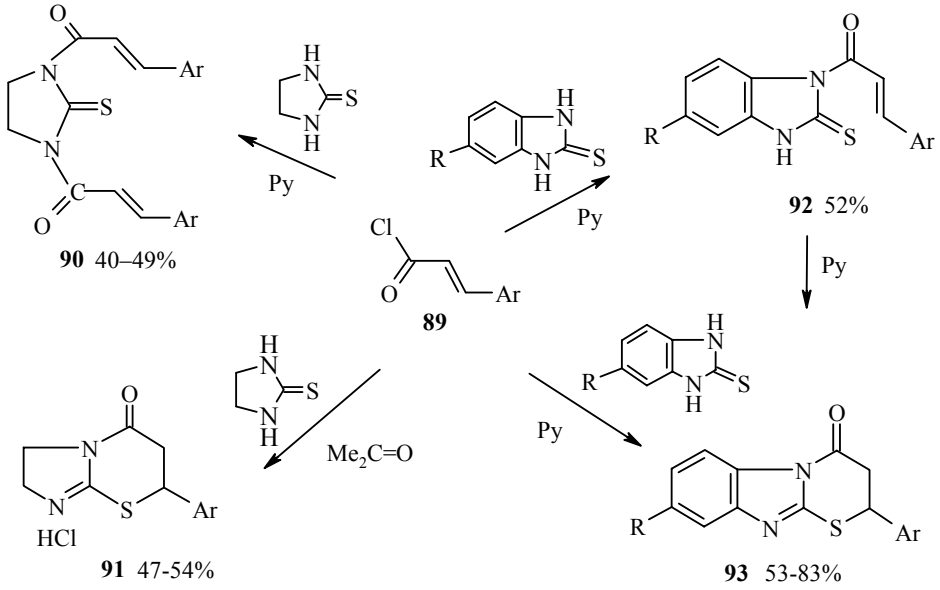
The cycloacylation of N-R-N'-phenylthioureas **83** by 3-aryl-2-propenoyl chlorides was studied in [77]. A feature of this reaction is the possibility of the formation both of 2,3,5,6-tetrahydro-4H-1,3-thiazin-4-ones and of 1,2,3,5,6-pentahydro-2-thioxo-4H-pyrimidin-4-ones and, in the case of the reaction with unsymmetrical N-phenylurea **83**, probably the formation of two 4H-1,3-thiazin-4-ones and two 2-thioxo-4H-pyrimidin-4-ones. It was discovered that the direction of this condensation depends on the presence of a base ($K_2CO_3$) in the reaction medium.

In the absence of the base the reaction products are the hydrochlorides of 2,3,5,6-tetrahydro-4H-1,3-thiazin-4-ones **84**, whereas in the presence of $K_2CO_3$ a mixture of products from N-acylation **87**, cycloacylation **88**, and degradation **85** and **86** is obtained. It should be noted that in the case of cycloacylation of the unsymmetrical N-phenylthiourea **83** the reaction takes place at the more acidic N atom.



R = H, Ph; Ar = Ph, 2- thienyl

In [47, 48] a single-stage method was developed for the production of 2-aryl-2,3-dihydro-4H-[1,3]-thiazino[3,2-*a*]benzimidazol-4-ones **93**, involving the reaction of 5-R-benzimidazoline-2-thiones with 3-aryl-2-propenoyl chlorides **89** in pyridine. When 3-aryl-2-propenoyl chlorides containing substituents (MeO, Cl) at the *ortho* position, which hinder cyclization, were used it was possible to isolate the intermediate N-acylation products **92** from the reaction solution.

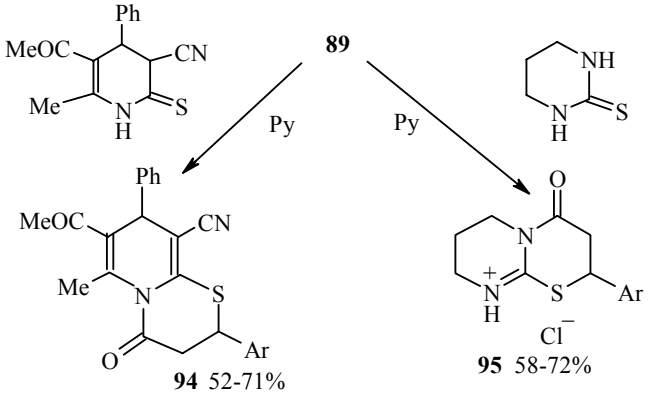



R = H, EtO; Ar = Ph, 4-$MeOC_6H_4$, 2-$MeOC_6H_4$, 4-$FC_6H_4$, 3-$O_2NC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$, 2- thienyl, 2- furyl, 1-(3,4- methylenedioxy)phenyl

The direction of condensation of chlorides **89** with 2-imidazolidine-2-thione depends substantially on the basicity of the employed solvent; in pyridine only the N-acylation product **90** is formed, whereas in acetone heterocyclization takes place smoothly with the formation of the hydrochlorides of 7-aryl-2,3,6,7-tetrahydro-5H-imidazo[2,1-*b*]-1,3-thiazin-5-ones **91** [47].

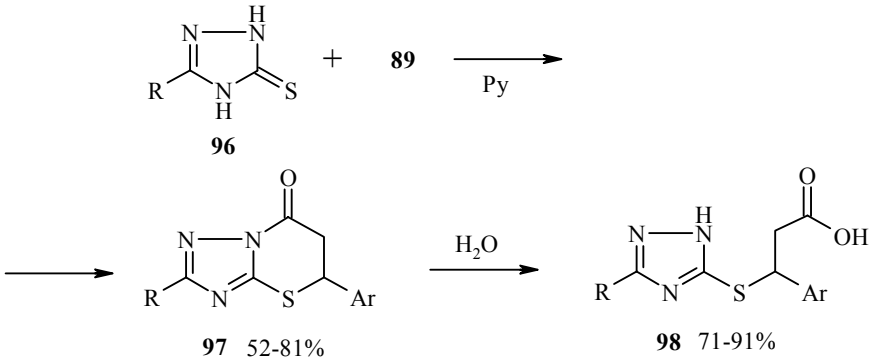
It is necessary to mention the high herbicidal activity of 2-aryl-2,3-dihydro-4H-[1,3]thiazino[3,2-*a*]-benzimidazol-4-ones **93** [78].

Methods have also been developed for the synthesis of 2-aryl-2,3,6,7,8-pentahydro-4H-pyrimido[2,1-*b*]-1,3-thiazin-4-ones **95** [79] and 7-acetyl-2,8-diaryl-9-cyano-6-methyl-3,4-dihydro-2H,8H-pyrido[2,1-*b*]-[1,3]thiazin-4-ones **94** [80], involving the reaction of 1H-3,4,5,6-tetrahydropyrimidine-2-thione and 5-acetyl-3-cyano-6-methyl-4-phenyl-1,4-dihydropyrimidine-2(3H)-thione with 3-aryl-2-propenoyl chlorides **89** in pyridine.



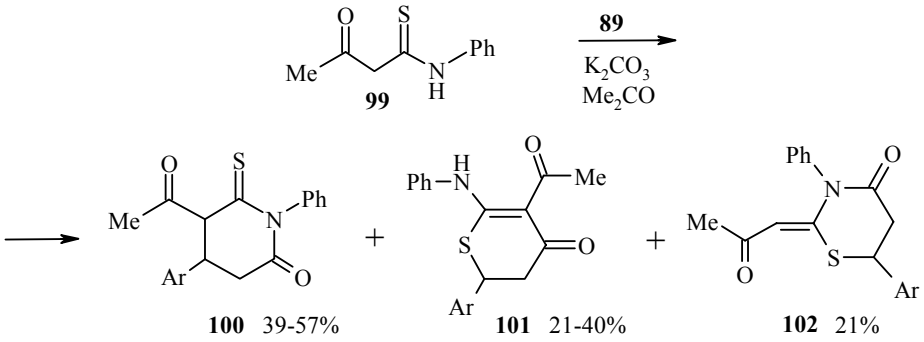

Ar = Ph, 4-$MeOC_6H_4$, 3-$O_2NC_6H_4$

2-R-5-Aryl-5,6-dihydro-7H-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-7-ones **97** were obtained similarly [81, 82]. However, the amide bond in these compounds is weak, as a result of which they are readily hydrolyzed by water to the corresponding 3-aryl-3-(5-thio-1H-1,2,4-triazol-5-yl)propionic acids **98** [82].




R = H, Ph, 4-$FC_6H_4$, 1- naphthyl, 1- adamantyl, diphenylmethyl;
Ar = Ph, 4-$MeOC_6H_4$, 4-$FC_6H_4$, 3-$O_2NC_6H_4$, 2- thienyl, 2- furyl

If a compound containing an active methylene group – N-phenyl-3-oxobutanethioamide (**99**) – is used as substrate, the reaction takes place nonselectively with the formation of three groups of compounds, i.e., thioxopiperidin-2-ones **100**, 2,3-dihydro-4H-thiopyran-4-ones **101**, and 5,6-dihydro-4H-1,3-thiazin-4-ones **102** [4, 83].



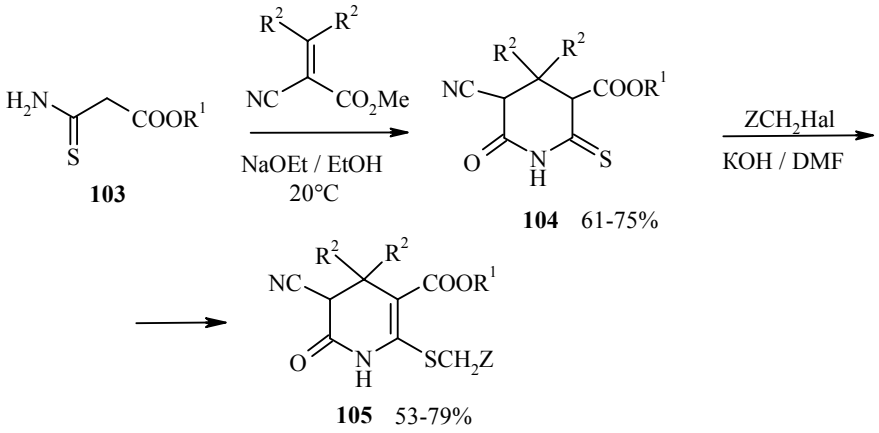

Ar= Ph , 4-$MeOC_6H_4$, 3-$O_2NC_6H_4$, 2- thienyl

The type of heterocycles, their ratio, and the yields depend on the nature of the substituents present in the phenyl ring of the initial 3-aryl-2-propenoyl chlorides. It was also shown [4, 83] that the thioxopiperidin-2-ones **100** are prospective starting materials for the synthesis of condensed heterocycles – 6H-thieno[2,3-*b*]-pyridin-6-ones and pyrazolo[3,4-*b*]pyridin-6-ones.

By the cycloacylation of phenylsulfonyl-N-R-thioacetamides with 3-aryl-2-propenoyl chlorides it is possible to synthesize exclusively derivatives of 1,3-thiazin-4-one [25]. This can probably be explained by the reduced acidity and, accordingly, by the low reactivity of the active methylene group in the phenylsulfonyl-N-R-thioacetamides [84].

Methyl 2-cyano-2-cyclohexylideneacetate [3] and 2-R-4-arylidene-5-oxazolidones [44], structurally similar to the derivatives of 3-aryl-2-propenoic acids, have also been used as cyclizing agent.

The reaction of ethoxy(methoxy)carbonylacetamide **103** with methyl 2-cyano-2-cyclohexylideneacetate, which was conducted in anhydrous ethanol in the presence of sodium ethoxide, was studied in [3].

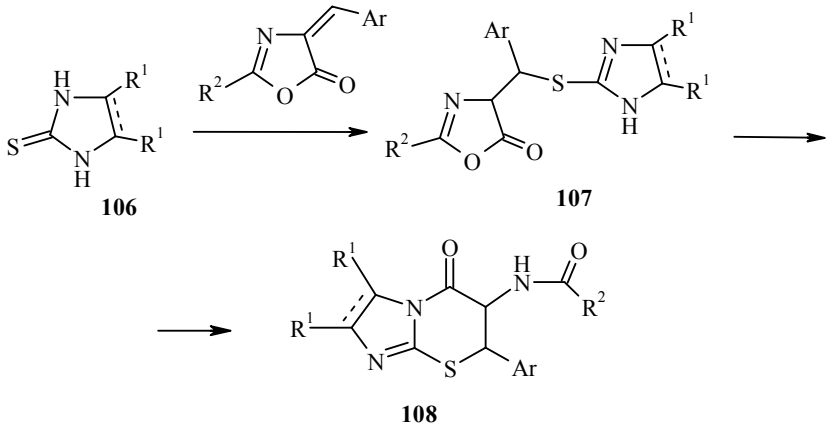



**103** **104** 61-75% **105** 53-79%

$R^1$ = Me, Et; $R^2+R^2$ = $(CH_2)_5$; Z = H, PhNHCO, 4-$BrC_6H_4NHCO$, PhCO; Hal = Cl, Br, I

The products of this reaction are 6-oxo-4-spirocyclohexane-5-cyano-3-ethoxy(methoxy)carbonyl-piperidine-2-thiones **104**, which are alkylated in an alkaline medium with the formation of the piperidones **105**.

In reaction with benzimidazoline-2-thione and imidazolidine-2-thione **106** 2-R-4-arylidene-5-oxazolones undergo recyclization to 4H-[1,3]thiazino[ 3,2-*a*]imidazol-4-ones **108** [44]. The authors of [44] found that this reaction takes place through the adducts **107** and showed that compounds **108** have fungicidal activity.



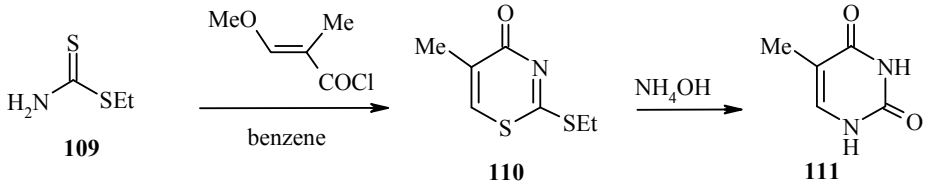
**106** **107** **108**

$R^1$ = H, $R^1 + R^1$ = CH=CH–CH=CH; $R^2$ = Me, Ph; Ar = Ph, 3(4)-$O_2NC_6H_4$, 4-$Me_2NC_6H$

## 2.4. Cyclizations with Acid Chlorides and Esters of 3-Alkoxy-2-R-propenoic Acids

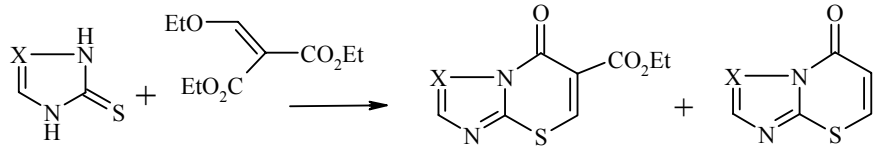
The alkoxyl group in the acid chlorides (esters) of 3-alkoxy-2-R-propenoic acids is a good nucleofuge. Nevertheless, only three papers on the cycloacylation of thioamides and their derivatives by these reagents are known.

The reaction of S-ethyl dithiocarbamate **109** with 3-methoxy-2-methyl-propenoyl chloride was covered in [5]. It was found that the product of this condensation was 2-ethylthio-5-methyl-1,2-thiazin-4-one **110**, which isomerized to 5-methylpyrimidine-2,4-dione **111** under the influence of an aqueous solution of ammonia.




**109** **110** **111**

The cyclocondensation of the azolethiones **112** with diethyl ethoxymethylenemalonate (**113**) was investigated in [21]. The low reactivity of this compound was noted, and in order to increase it the reaction was conducted in high-boiling solvents – in 1,2,4-trichlorobenzene and xylene – during 24 h. The cyclization is complicated by a side process – decarboxylation, leading to the formation of two products **114** and **115** [21]. The structure of [1,2,4]triazolo[5,1-*b*][1,3]thiazin-7-one **115** (X = N) was proved by X-ray crystallographic analysis and also by an alternative synthesis by the reaction of the corresponding thione **112** with ethyl propiolate in acetic acid.

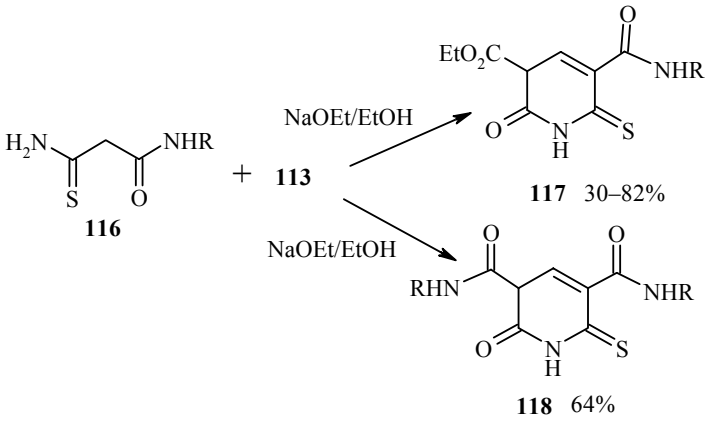



**112** **113** **114** **115**

29-58%

X = N, CH

Recently it was shown [12] that in an alkaline medium diethyl ethoxymethylenemalonate **113** reacts with 2-thiocarbamoyl-N-arylacetamides **116** in two concurrent directions with the formation of 1,2-dihydropyridine-6-thiones **117** and **118**, the yields of which depend on the excess of the thioamide **115**.




**116** **113** **117** 30–82%

NaOEt/EtOH

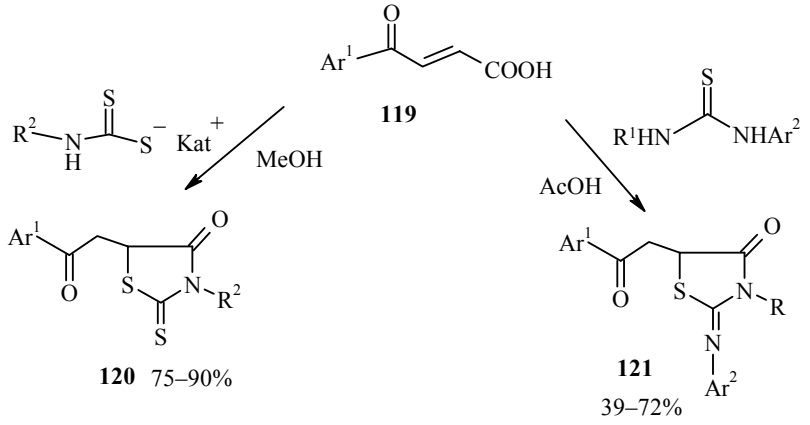
**118** 64%

R = H, Ph, 2-MeOC$_6$H$_4$, 2-MeC$_6$H$_4$, 3-MeC$_6$H$_4$

## 2.5. Cyclocondensations with 3-Aroylacrylic Acids

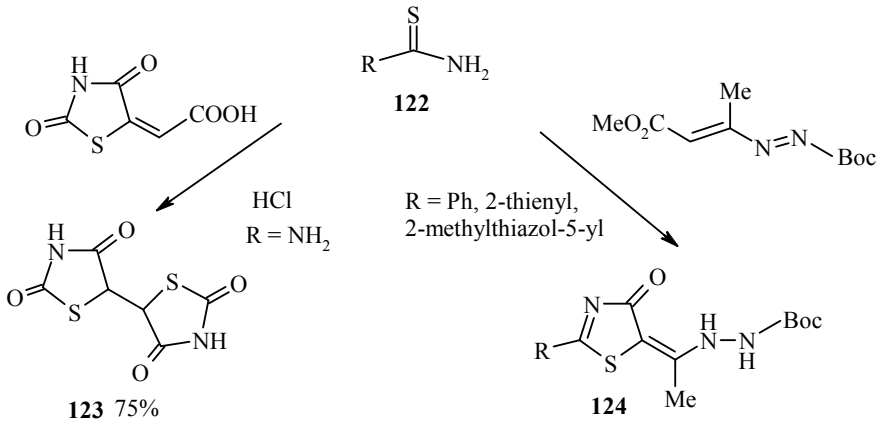
3-Aroyl-3-acrylic acids, unlike 3-R-propioloic and 2-R$^1$-3-R$^2$-propenoic acids and their esters and acid chlorides, react with compounds containing a thioamide fragment exclusively by a [3+3] cycloaddition mechanism. This is explained by the effect of the oxygen of the aroyl group, which reduces the electron density at the C-2 atom, thereby activating it for nucleophilic attack.

3-Aroyl-2-acrylic acids **119** react with thioureas when boiled in acetic acid [85, 86]. The reaction takes place regioselectively with the formation of thiazolidin-4-ones (**121**), which are the products from acylation at the more basic amino group. 3-Aroyl-2-acrylic acids react with dithiocarbamates in a similar way at 20°C in methanol [87-89]. The products of this condensation are 5-aroylmethyl-2-thioxothiazolidin-4-ones **120**.




$Ar^1$ = Ph, 2-$MeC_6H_4$, 2-$BrC_6H_4$, 2-$ClC_6H_4$, 4-$ClC_6H_4$, 2,5-$Cl_2C_6H_3$, 2,5-$Br_2C_6H_3$, 2-HO-5-Br-$C_6H_3$, 2- naphthyl; $Ar^2$ = Ph, 4-$MeOC_6H_4$, 2-$HOC_6H_4$; $R^1$ = H, $CH_2$=$CHCH_2$; $R^2$ = 4-$MeC_6H_4$, $PhCH_2$, H; Kat = Na, $NH_4$, $NH_3CH_2Ph$

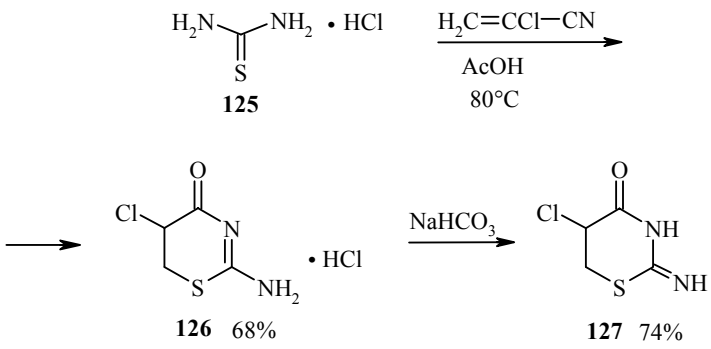
The reaction of the cyclic analog of 3-aroylacrylic acids – 5-(carboxymethylene)thiazolidine-2,4-dione – with thiourea **122** in concentrated hydrochloric acid leads to the formation of 5-(2,4-dioxo-5-thiazolidinyl)thiazolidine-2,4-dione **123** [90].



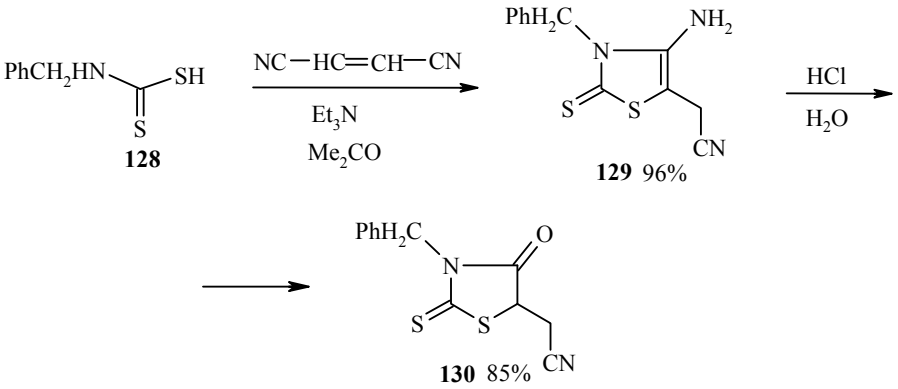

2-Thiazolin-4-ones **124**, used as "synthesis blocks" for the production of biologically active compounds, were obtained in a similar way by the reaction of *tert*-butyl (3-methoxy-1-methyl-3-oxo-1-propenyl)diazenecarboxylate with arylthioamides (**122**) [91].

### 2.6. Reactions with α-Unsaturated Nitriles

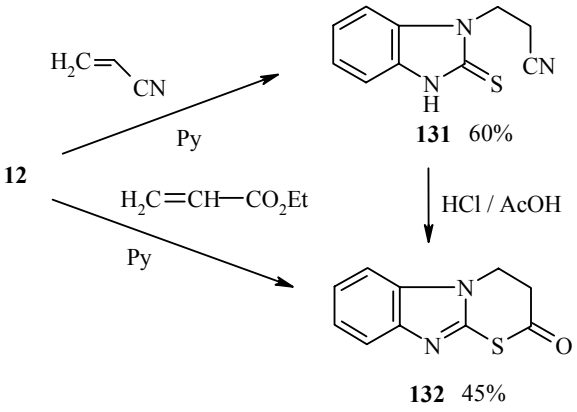
2-Chloroacrylonitrile reacts readily with thiourea hydrochloride **125** by a [3+3]condensation mechanism with the formation of the hydrochloride **126**. The latter is converted by treatment with an aqueous solution of $NaHCO_3$ into 5-chloro-2-imino-4H-5,6-dihydro-1,3-thiazin-4-one **127** [192].




In [93] it was shown that the reaction of fumaro(maleo)dinitrile with the dithiocarbamate **128** followed by hydrolysis of the intermediate product **129** provides a preparative two-stage method for the synthesis of 2-thioxothiazolidin-4-one **130**.




An example of N-cyanoethylation is found in [94], in which the reaction of benzimidazoline-2-thione **12** with acrylonitrile was realized in aqueous pyridine and the cyclization of the adduct **131** was realized in hydrochloric–acetic acid solution. [1,3]-Thiazino[3,2-*a*]benzimidazol-2-one **132** was also obtained by a single-stage method – by cyclocondensation of thione **12** with ethyl acrylate in aqueous pyridine. It should be mentioned that the structure of compound **132** was only demonstrated by the data from the IR spectrum and elemental analysis.

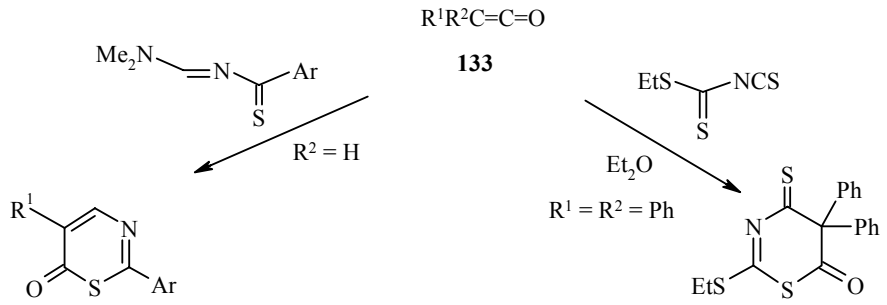


Very close to the reactions examined above are the condensations of 2-cyano-1-phenylacetylene and tertiary cyanoacetylene alcohols with cyclic thioamides (1,2,4-triazoline-4-thione, imidazolidine-2-thione, and benzimidazolidine-2-thione), the products of which are 1,3-thiazine 4-imine [95-100]. However, hydrolysis of the latter to 1,3-thiazin-4-ones was not realized in these papers.

### 2.7. Cyclizations with 2-$R^1$-2-$R^2$-Ketene

A special feature of this reagent is the ability to react with thioamides by a [4+2] cyclocondensation mechanism, realized as cycloacylation at the S atom of the substrate with the formation of derivatives of 1,3-thiazin-6-one.

The reaction of phenylketene **133** with N,N-dimethyl-N′-thioaroylformamidines takes place according to a [4+2] scheme. The structure of the reaction products – 1,3-thiazin-6-ones **134** – was proved by the data from $^1$H NMR spectroscopy and elemental analysis [101].




**134** 18–53% **135** 37%

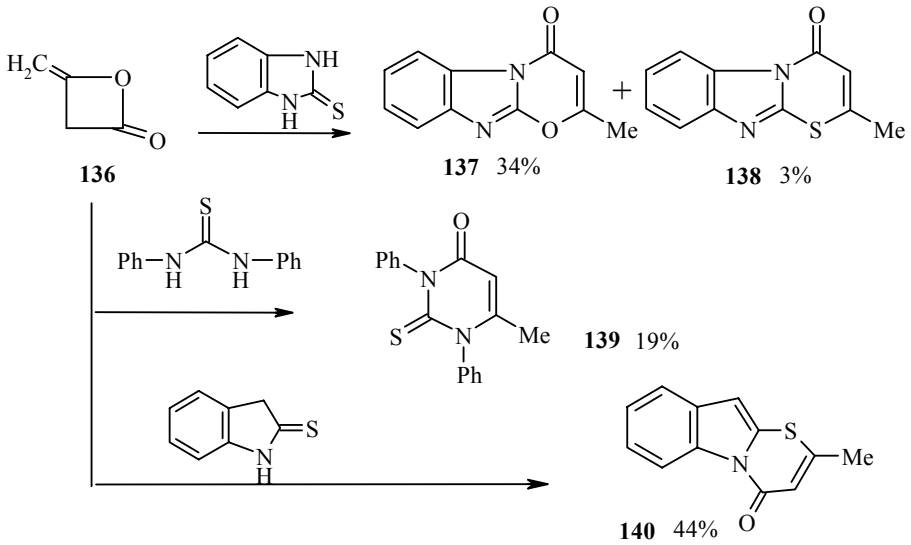
$R^1$ = Ph; $R^2$ = H, Ph; Ar = Ph, 4-$MeC_6H_4$, 4-$MeOC_6H_4$

The reaction of 2,2-diphenylketene **133** with (ethylthio)thiocarbonyl isothiocyanate leads to the production of 2-ethylthio-5,5-diphenyl-4-thioxo-5,6-dihydro-1,3-thiazine **135** [102].

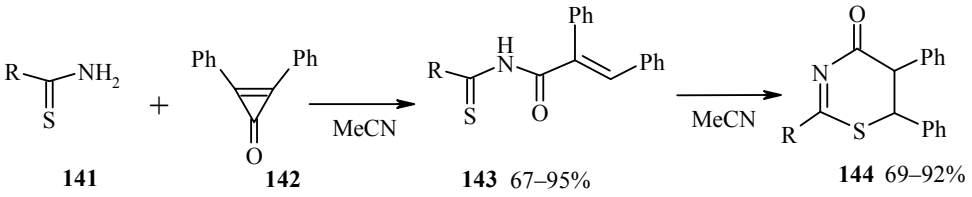
### 2.8. Cycloacylation with Diketene, 2-Aryl-2-chlorocarbonylketenes, 2,3-Diphenylcyclopropenone, and Carbon Suboxide

Reagents of this group have the ability to react with thioamides and their derivatives according to a [3+3] cyclocondensation scheme.

The condensation of the diketene **136** with acyclic and cyclic thioureas was studied in [103]. It was found that two products **137** and **138**, of which 4H-[1,3]oxazino[3,2-*a*]benzimidazol-4-one **137** predominates, are formed in the reaction of diketene with benzimidazoline-2-thione. The reaction of the diketene **136** with N,N′-diphenylthiourea and 2-thioxoindoline takes place selectively as N-acylation and leads to the production of 2-thioxo-1,3-diphenyluracil (**139**) and 4H-[1,3]thiazino[3,2-*a*]indol-4-one **140**.

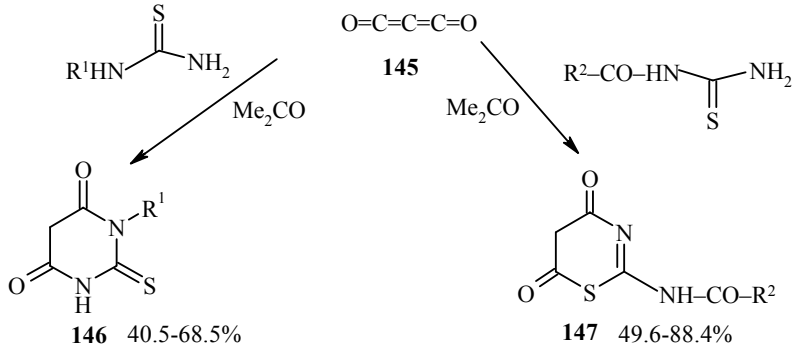


With 2,3-diphenylcyclopropenone **142** the thioamides **141** form N-(2,3-diphenylpropenoyl)thioamides **143**, which undergo cyclization to 1,3-thiazin-4-ones **144** when heated [46]:



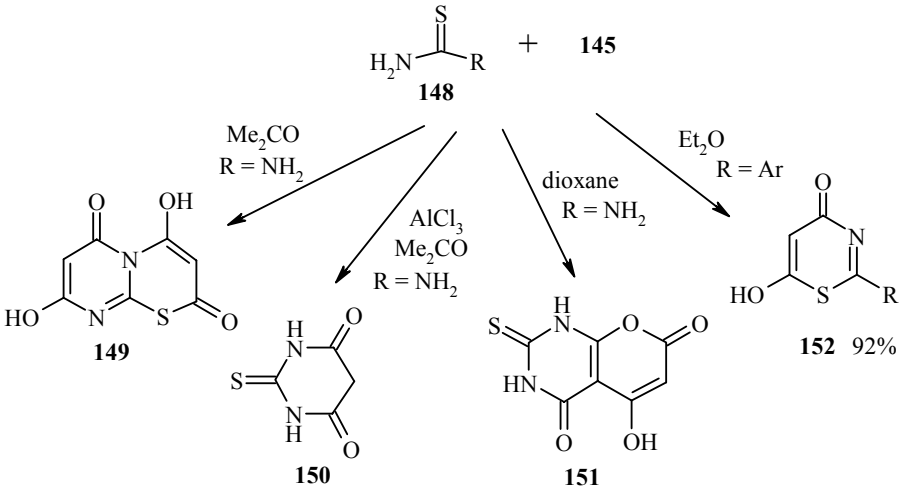
R = Me, $PhCH_2$, Ph

The reactions of carbon suboxide **145** with N-arylthioureas and N-aroylthioureas were studied in detail in [104]. Derivatives of thiobarbaric acid **146** were obtained in the first case, and 1,3-thiazine-4,6-diones **147** in the second. In all probability the presence of the aryl group in the N-aroylthioureas reduces the electron density at the N atom attached to this group, leading to the formation of products from S-acylation **147**.



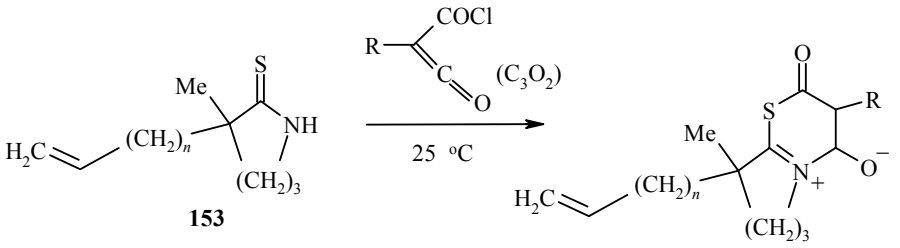
$R^1$, $R^2$ = Ph, 4-$MeC_6H_4$, 4-$MeOC_6H_4$, 4-$ClC_6H_4$

The reaction of carbon suboxide **145** with thiobenzamides leads to the formation of 2-aryl-6-hydroxy-1,3-thiazin-4-ones **152**, whereas the direction of the reaction with thiourea depends on the nature of the solvent and the added catalysts [105]. The products of these transformations are thiobarbituric acid (**150**), 2H,6H-pyrimido[2,1-*b*][1,3]thiazine-2,6-dione **149**, and 7H-pyrano[2,3-*d*]pyrimidine-4,7-dione **151**.




$R = NH_2$, Ph, $4\text{-}ClC_6H_4$

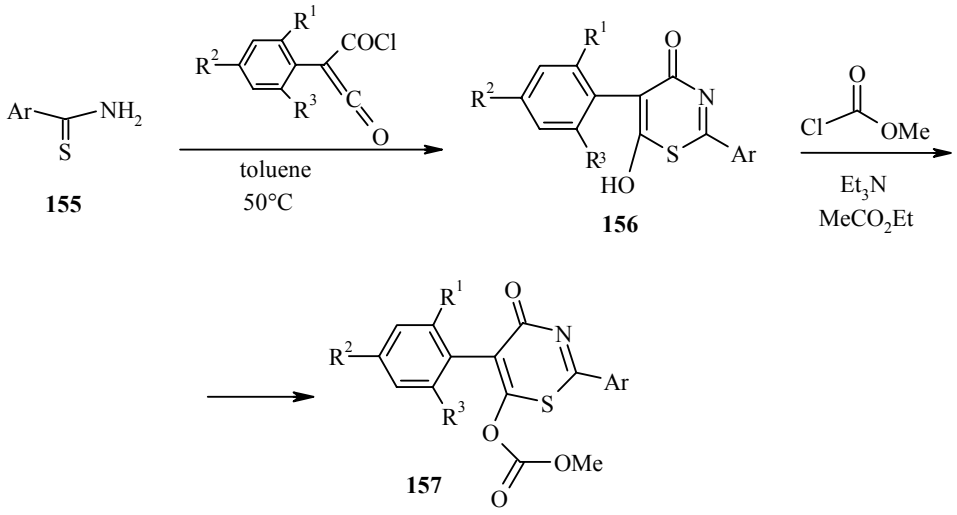
2-Chlorocarbonyl-2-R-ketene and carbon suboxide react readily with 3-(2-R-1-buten-4-yl)-3-methyl-2-thioxopiperidine **153** in dichloromethane (benzene) [106] with the formation of 1,3-thiazinium betaines **154**. The latter were used as starting materials for intramolecular 1,4-dipolar cycloaddition in order to produce trinuclear framework compounds [106].




R = H, Ph; *n* = 2, 3

Data on the reaction of 2-aryl-2-chlorocarbonylketenes with arylthioamides **155** were given in the patent [107]. It was established that the products of this reaction were 5-aryl-6-hydroxy-4H-1,3-thiazin-4-ones **156**.

The synthesized 1,3-thiazin-4-ones **156** and also the products from their O-acylation **157** have a wide spectrum of pesticidal activity (herbicidal, insecticidal, acaricidal) [107].



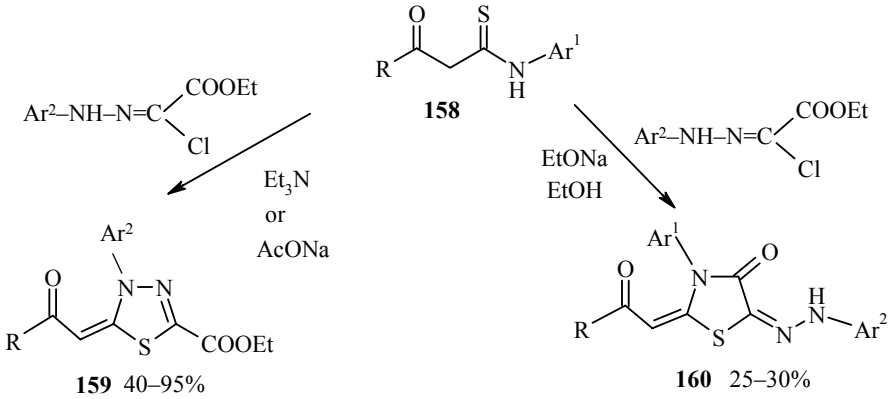

**155** **156** **157**

$R^1$ = Me,Cl; $R^2$ = H, Cl, Me; $R^3$ = H, Me; Ar = Me, $CHMe_2$, 2-$ClC_6H_4CH_2$, 3,4-$Cl_2C_6H_3CH_2$, 4-$FC_6H_4$, 2-$FC_6H_4$, 3-Cl-4-$FC_6H_3$, 2,6-$Cl_2C_6H_3$, 2,4-$Cl_2C_6H_3$, 3,4-$Cl_2C_6H_3$, 3-$CF_3C_6H_4$, 4-$CF_3C_6H_4$, 3-$MeC_6H_4$, 4-$MeC_6H_4$, 2,6-$F_2C_6H_3$, PhO

## 2.9. Condensations with Ethyl[(aryl)hydrazono]chloroacetamides

It is known that the esters of [(aryl)hydrazono]chloroacetic acids exhibit dual reactivity and can react both with dipolarophiles and with dinucleophiles [108, 109]. Thioamides can also be used as dinucleophiles [110, 111]. The direction of these cyclocondensations, realized by a [3+2] scheme, depends on the strength of the bases [110, 111], the structure of the initial substrate, and the nature of the substituents at the phenyl end of the reagents [111].

The products of the reaction of N-Ar-3-oxo-3-R-propanethioamides **158** with the esters of [(aryl)hydrazono]chloroacetic acids in the presence of triethylamine (sodium acetate) are 3-aryl-2-ethoxycarbonyl-5-(2-oxo-2-R-ethylidene)-1,3,4-thiadiazolines **159**, whereas 3-aryl-5-arylhydrazono-2-(2-oxo-2-R-ethylidene)thiazolin-4-ones **160** are obtained in the presence of sodium ethoxide [110].



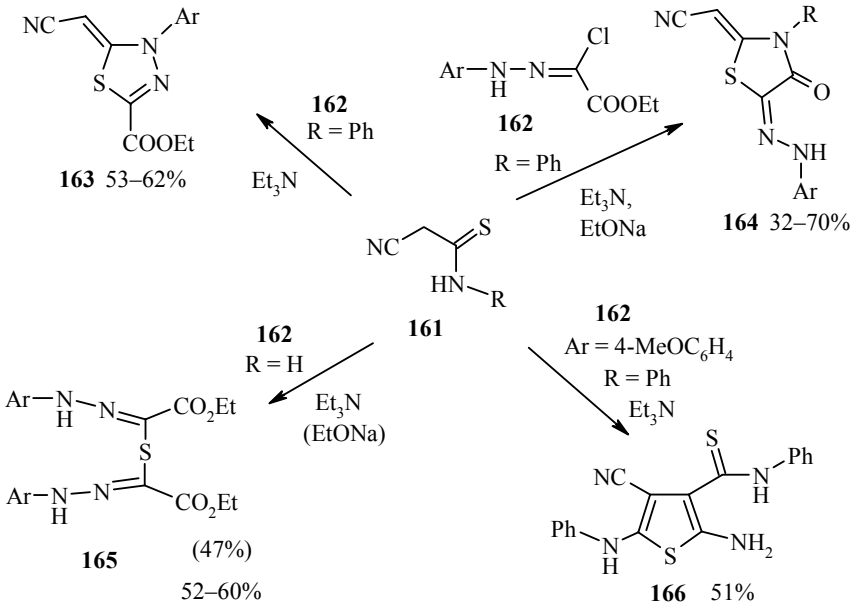

**158**

**159** 40–95%

**160** 25–30%

$Ar^1$ = Ph, 4-$MeOC_6H_4$; R = Me, Ph, 4-$MeC_6H_4$; $Ar^2$ = Ph, 4-$MeOC_6H_4$, 4-$ClC_6H_4$

Apart from the strength of the base the direction of the reaction of N-R-2-cyanothioacetamides **161** with the esters of [(aryl)hydrazono]chloroacetic acids **162** is also affected by the structure of the thioamide and the nature of the substituents in the phenyl ring of the esters **162** [111].




R = Ph, H; Ar = Ph, 3-$MeC_6H_4$, 4-$FC_6H_4$, 3-$CF_3C_6H_4$, 4-$CHF_2SO_2C_6H_4$, 4-$MeOC_6H_4$

This cyclocondensation leads to the formation of 3-aryl-2-cyanomethylene-5-ethoxycarbonyl-1,3,4-thiadiazoles **163**, 5-arylhydrazono-2-cyanomethylene-3-phenylnethiazolidin-4-ones **164**, and di(ethoxycarbonyl-[(aryl)hydrazono]methyl) sulfides **165**. If such a low-reactivity reagent as ethyl [(4-methoxyphenyl)-hydrazono]chloroacetate is used self-condensation of N-phenyl-2-cyanothioacetamide **161** to 5-amino-3-cyano-2-phenylamino-4-(phenylaminothiocarbonyl)thiophene **166** occurs.

Thus, the cycloacylation of thioamides by derivatives of unsaturated carboxylic acids is an important method for the production of five- and six-membered heterocycles. As far as the relationships of these processes are concerned it can be concluded on the basis of analysis of the information presented above that the cycloacylation of thioamides in most cases takes place with the formation of products containing an amide group and endocyclic sulfur. Products containing the O═C─S group are isolated much more rarely, and moreover in most cases they are unstable. In the case of such ambident substrates as thioamides containing an active methylene group the structure of the products depends on the basicity of the reaction medium; in the absence of bases the active methylene group is not the reaction center, whereas in an alkaline medium N,C-cycloacylation, affecting the methylene group, occurs. The products are heterocycles containing exocyclic (thione) sulfur.

To judge from the number of publications this direction of research continues to develop successfully. Methods of synthesis are improving and being perfected, and new approaches are appearing. The range of heterocyclic systems on which this development can be realized is being extended. However, with a few exceptions the chemical characteristics of the synthesized heterocycles (e.g., recyclization transformations and their use as synthesis blocks) have been studied little and await an investigator.

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