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Thiosemicarbazides in the synthesis of five- and six-membered heterocyclic compounds

G A Gazieva, A N Kravchenko

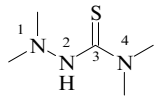
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Abstract. Data on key chemical transformations of thiosemicarbazides resulting in heterocyclic compounds are generalized and described systematically. Methods for the synthesis of five- and six-membered heterocycles with two and three heteroatoms are considered. The bibliography includes 190 references.

I. Introduction

Thiosemicarbazides have attracted great interest for many years as reagents for synthetic organic chemistry. Due to the presence of several reactive centres, these compounds are widely used in the synthesis of nitrogen- and sulfur-containing heterocyclic compounds (thiazoles, pyrazoles, thiadiazoles, triazoles, thiadiazines, triazines, pyrimidines), including fused compounds (thiazolotriazines, pyrazolotriazines, *etc*.). The diversity of heterocycles generated from thiosemicarbazides is associated primarily with the fact that these compounds can exhibit properties of N(1),N(2)-, N(1),N(4)-, N(2),N(4)-, N(1),S-, N(2),S- and N(4),S-dinucleophiles.



Due to the ability of thiosemicarbazide to form complexes with iron, zinc, copper, nickel and other metal cations,[1–3] which play an important role in biological processes, its derivatives have a wide range of biological activities.[3–9] Among these derivatives are compounds exhibiting antitumour,[7–12] antimicrobial,[4,7,8,13,14] antiparasitic,[5–8,15,16] insecticidal,[17] antioxidant and antisclerotic[18] activity.

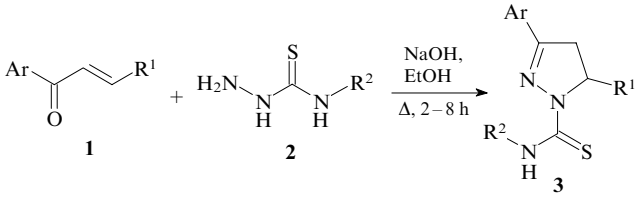
Due to a considerable synthetic potential of thiosemicarbazides combined with the practical value of compounds derived from them, thiosemicarbazides continue to attract interest. This is reflected in a large number of publications over the years. In 2004, the data on the use of cyclization reactions of thiosemicarbazide and its derivatives for the synthesis of 1,2,4-triazoles and thiazoles were summarized in the publication.[19] The chapter devoted to thiosemicarbazides is included in the review,[20] where the data on the condensation reactions of thioamides with acetylenecarboxylic acids are systematically considered. In the last 15 years, the publications concerning this problem were devoted mainly to methods for the synthesis of five- and six-membered rings with two or three heteroatoms. The pathway of these reactions is determined by the type of substitution at the nitrogen or sulfur atoms in thiosemicarbazide, the structures of other reactants and the reaction conditions.

II. Synthesis of five-membered rings with two heteroatoms

1. Pyrazoles

The condensation of thiosemicarbazides with α,β-unsaturated ketones giving 4,5-dihydro-1*H*-pyrazole derivatives is one of reactions most widely used for preparative synthesis. In these reactions, thiosemicarbazides act as N(1),N(2)-dinucleophiles.

For instance, the reactions of 1,3-di(het)arylprop-2-en-1-ones **1** (R^1 = Ar, Het) with amino-substituted thiosemicarbazides **2** under reflux in ethanol[21–34] or methanol[35,36] in the presence of NaOH,[21–27,34–36] KOH[28–31] or AcOH[32]



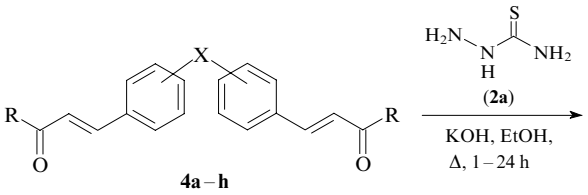
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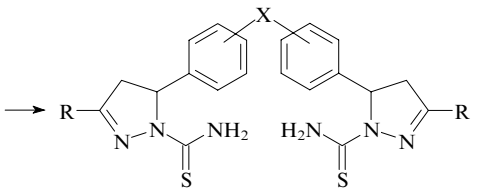
as the catalyst give 1-thiocarbamoyl-substituted 3,5-di(het)-aryl-4,5-dihydro-1*H*-pyrazoles **3** in good or moderate yields.

It was found that some 1-thiocarbamoylpyrazolines exhibit antiinflammatory,[21,22] antimicrobial[23,28,29] or antiviral[25] activity, and some other act as monoamine oxidase (MAO) inhibitors.[30,31] This has stimulated interest in these compounds and resulted in the synthesis of a large number of derivatives containing various substituents at positions 3 and 5 of the pyrazole ring and in the thiocarbamoyl moiety (Table 1).

The reactions of unsubstituted thiosemicarbazide (**2a**) with bis(3-arylprop-2-en-1-ones) **4a**–**h** under reflux in ethanol afford bis(5-aryl-4,5-dihydro-1*H*-pyrazole-1-thiocarboxamides) **5a**–**h**.[37]



4a–**h**



5a–**h**

Compound **5**	X	R	Yield (%)
a	2-O(CH$_2$)$_2$O-2′	Ph	52
b	2-O(CH$_2$)$_2$O-2′	4-ClC$_6$H$_4$	41
c	2-O(CH$_2$)$_2$O-2′	4-FC$_6$H$_4$	43
d	2-O(CH$_2$)$_2$O-2′	4-MeC$_6$H$_4$	56
e	2-O(CH$_2$)$_2$O-2′	2-Th	44
f	4-O(CH$_2$)$_2$O-4′	Ph	45
g	4-O(CH$_2$)$_2$O-4′	4-ClC$_6$H$_4$	29
h	4-O(CH$_2$)$_2$O-4′	4-MeC$_6$H$_4$	25

Isomeric 3(5)-ferrocenyl-1-thiocarbamoyl-4,5-dihydro-1*H*-pyrazoles **6a**–**d** and **7a**–**c** were synthesized by the condensation of thiosemicarbazide (**2a**) with chalcones **8a**–**d** and **9a**–**c**, respectively.[38] The reaction is accompanied

Table 1. 3,5-Di(het)aryl-1-thiocarbamoyl-4,5-dihydro-1*H*-pyrazoles **3**.

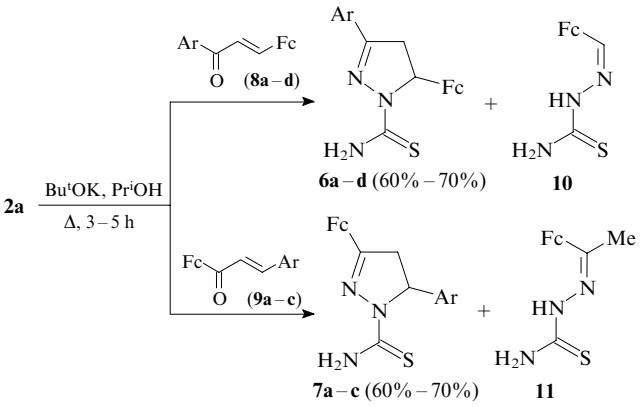
Ar	R^1	R^2	Yield (%)	Ref.
Ph	4-BnOC$_6$H$_4$	H	40	24
	Ph	H	24–68	25, 33
	4-MeC$_6$H$_4$, 2-EtC$_6$H$_4$, 2-Pr^{i}C$_6$H$_4$, 2-ClC$_6$H$_4$, 2,3-Cl$_2$C$_6$H$_3$, 2,4,6-Me$_3$C$_6$H$_2$, 3-Ind	H	11–24	25
	2-HOC$_6$H$_4$, 4-MeOC$_6$H$_4$	H	75–80	29
	3,4-(MeO)$_2$C$_6$H$_3$, 2-Cl-3,4-(MeO)$_2$C$_6$H$_2$	H	77–84	31
	2,3-(OCH$_2$O)C$_6$H$_3$, 2-Th	H	66–72	33
4-FC$_6$H$_4$	4-ClC$_6$H$_4$, 4-MeC$_6$H$_4$, 2-Fu	H	50–57	30
4-ClC$_6$H$_4$	2-Fu, 2-Th	H	74–78	21
	2-Pyr	Me, Et, All, Ph	35–55	22
	4-BnOC$_6$H$_4$	H	50	24
	3,4-(MeO)$_2$C$_6$H$_3$, 2-Cl-3,4-(MeO)$_2$C$_6$H$_2$	H	69–71	31
	2-Th	Me, Et, All, Ph	31–33	36
4-BrC$_6$H$_4$	2-Fu	H	71	21
	4-BnOC$_6$H$_4$	H	45	24
	3,4-(MeO)$_2$C$_6$H$_3$	H	74	31
	2-Cl-3,4-(MeO)$_2$C$_6$H$_2$	H	86	31
4-MeC$_6$H$_4$	2-Fu	H	72	21
	2-Pyr	Me, Et, All, Ph	37–60	22
	4-BnOC$_6$H$_4$	H	56	24
	4-ClC$_6$H$_4$, 4-MeC$_6$H$_4$, 2-Fu	H	52–58	30
	3,4-(MeO)$_2$C$_6$H$_3$, 2-Cl-3,4-(MeO)$_2$C$_6$H$_2$	H	88–94	31
	2-Th	Me, Et, All, Ph	37–60	36
4-MeOC$_6$H$_4$	2-Pyr	Me, Et, All, Ph	32–60	22
	3,4-(MeO)$_2$C$_6$H$_3$, 2-Cl-3,4-(MeO)$_2$C$_6$H$_2$	H	65–82	31
	2-Th	Me, Et, All, Ph	31–48	36
2-HOC$_6$H$_4$	4-HOC$_6$H$_4$	H	60	35
4-MeSO$_2$C$_6$H$_4$	Ph, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-BnOC$_6$H$_4$, 3-BnOC$_6$H$_4$, 4-BnOC$_6$H$_4$	H	39–59	34
2,4-Me$_2$C$_6$H$_3$	Ph	H	–	28
3-MeO-4-HO$_2$CCH$_2$OC$_6$H$_3$	Ph, 2-ClC$_6$H$_4$, 2-HOC$_6$H$_4$, 2-O$_2$NC$_6$H$_4$, 4-FC$_6$H$_4$,4-ClC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-HOC$_6$H$_4$, 4-H$_2$NC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, Bn	H	78–94	32

Table 1 (continued).

Ar	R^1	R^2	Yield (%)	Ref.
2-Th	Ph, 2-Th	H	63 – 66	26
	2-Py, 3-Py, 4-Py	H	–	27
	4-ClC_6H_4, 4-MeC_6H_4, 2-Fu, 2-Th	H	48 – 58	30
5,6,7,8-Tetrahydro-2-naphthyl	Ph	H	–	28
2-Benzofuryl	Ph, 4-ClC_6H_4	H	84 – 86	23

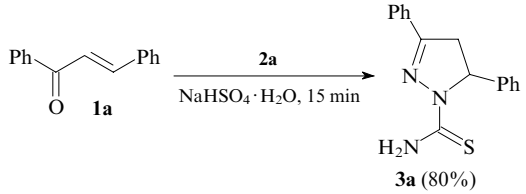
Note. Ind is indolyl, Th is thienyl, Fu is furyl, Pyr is pyrrolyl, All is allyl and Py is pyridyl; a dash indicates that the yield was not reported in the original publication.

by the partial fragmentation of the starting chalcones and the formation of by-products **10** and **11** (yields 8% – 20%).



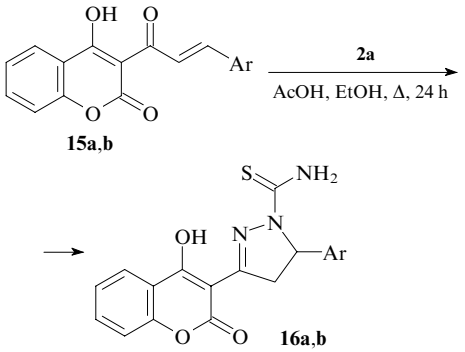
6 – **9**: Ar = Ph (**a**), 4-$MeOC_6H_4$ (**b**), 4-BrC_6H_4 (**c**), Fc (**d**) (Fc is ferrocenyl)

Methods based on mechanically activated solid-state reactions have been extensively developed in recent years. The first example of the cyclization of chalcone **1a** with compound **2a** in the presence of $NaHSO_4 \cdot H_2O$ in a high-speed planetary ball mill was described quite recently.[39] This reaction gives 3,5-diphenyl-4,5-dihydro-1*H*-pyrazole-1-thiocarboxamide (**3a**). Considerable advantages of this method are that the products are formed in good yields, the reaction time is reduced and the reaction proceeds under fairly environmentally friendly conditions.



The condensation of α,β-unsaturated β-furyl-substituted aldehyde **12a** and ketones **12b** – **d** with thiosemicarbazide in propan-2-ol affords thiosemicarbazones **13a** – **d**, which undergo cyclization in the presence of triethylamine to give 5-furyl-4,5-dihydro-1*H*-pyrazole-1-thiocarboxamides (**14a** – **d**). In the presence of base catalysts, compounds **13** form intermediate **A** containing the activated nucleophilic centre at the nitrogen atom N(2), which attacks the β-carbon atom of the conjugated double bond to give pyrazolines **14** (Scheme 1).[40] In the reactions of compounds **12** and **2a** under prolonged heating (15 h) in the presence of catalytic amounts of triethylamine, pyrazolines **14a** – **d** are obtained without isolation of intermediate carbazones **13**.

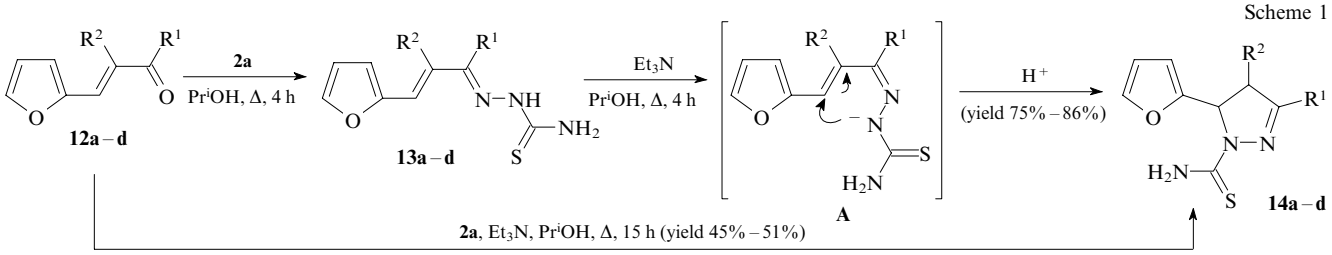
The reaction of thiosemicarbazide with 3-(3-(het)aryl-acryloyl)-4-hydroxycoumarins **15a**,**b** in an acidified ethanolic solution gives 3,5-disubstituted pyrazoline-1-thiocarboxamides **16a**,**b** in 60% and 80% yields, respectively.[41]



15, **16**: Ar = 4-$MeOC_6H_4$ (**a**), 3-Py (**b**)

The cyclization of 2,6-bis(benzylidene)cyclohexanone (**17**) with thiosemicarbazide (**2a**) in ethanol produces *cis*-[(3*R*,3a*R*)-**18**],[42] and/or *trans*-diastereomers [(3*R*,3a*S*)-**18**][21] of 7-benzylidene-3-phenyl-3,3a,4,5,6,7-hexahydro-2*H*-ind-

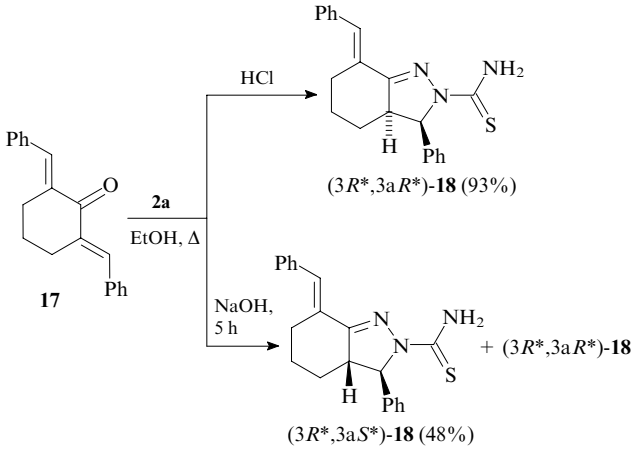
Scheme 1



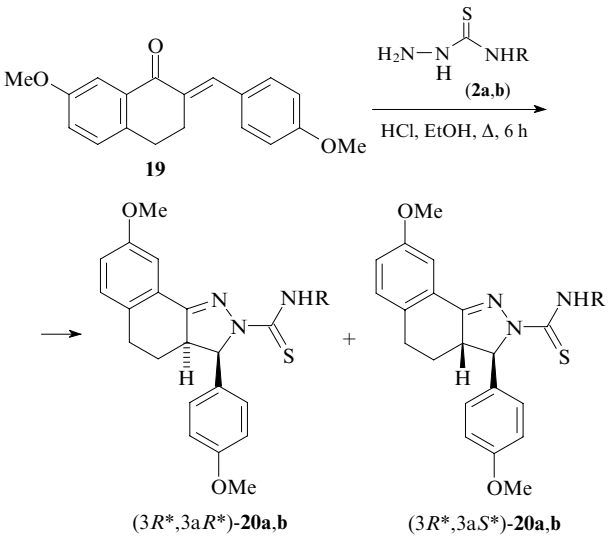
12, **13**: R^1 = H, R^2 = Me (**a**); $R^1 - R^2 = (CH_2)_n$ [*n* = 3 (**b**), 4 (**c**), 5 (**d**)]

azole-2-thiocarboxamide depending on the nature of the catalyst (Scheme 2).

Scheme 2



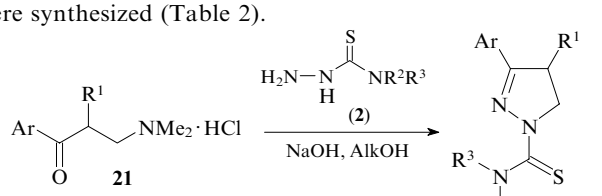
The reactions of thiosemicarbazides with α,β-unsaturated ketone **19** gave diastereomeric (4-methoxyphenyl)-8-methoxy-2*H*-benzo[*g*]indazoles **20a**,**b** having both (3*R*,3a*R*)- and (3*R*,3a*S*)-relative configurations of the chiral atoms.[43] Diastereomers **20a**,**b** were synthesized by refluxing thiosemicarbazides **2a**,**b** with ketone **19** in ethanol in the presence of HCl, and the products were separated by chromatography.



R = H (**a**), Me (**b**)

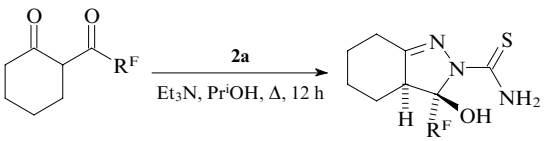
The total yield of the products sharply decreases in the reaction of indazole **20b** (28%) as compared to the reaction with compound **20a** (96%).

Apart from α,β-unsaturated ketones, 1-thiocarbamoyl-4,5-dihydro-1*H*-pyrazoles were synthesized by the reactions of thiosemicarbazides with β-dimethylamino ketones **21**.[44–46] In these reactions, heterocycles are produced in low yields; however, these reactions can be used to synthesize 3-substituted (R^1 = H) or 3,4-disubstituted ($R^1 \neq H$) 1-thiocarbamoylpyrazolines **22**. The reactions are performed by refluxing the reactants in alcohols under an inert atmosphere (nitrogen). The reaction time depends on the thiosemicarbazide used. Unsubstituted thiosemicarbazide **2a** undergoes cyclization with ketones **21** during 1 h,[44] whereas the condensation of N(4)-substituted and N(4),N(4)-disubstituted thiosemicarbazides is completed within 48 and 48–72 h, respectively.[45] A series of 3-aryl-1-thiocarbamoyl-1*H*-pyrazolines having antiparasitic activity were synthesized (Table 2).



Alk = Me, Et

It was shown[47,48] that the condensation of thiosemicarbazide (**2a**) with fluoroalkylated β-diketones affords exclusively 5-fluoroalkyl-substituted 5-hydroxypyrazolines. The reactions with the use of 2-(polyfluoroacyl)cyclohexanones **23a**–**f** produce 3-fluoroalkyl-3-hydroxy-3,3a,4,5,6,7-hexahydro-2*H*-indazole-2-thiocarboxamides **24a**–**f** in 50%–76% yields.[47]



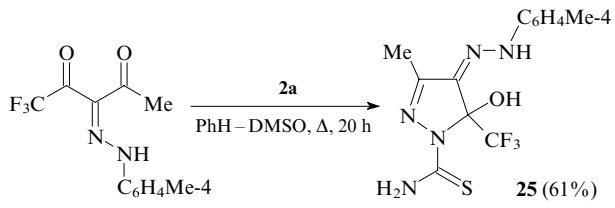
23, **24**: R^F = CF_2H (**a**), CF_3 (**b**), $(CF_2)_2H$ (**c**), n-C_4F_9 (**d**), n-C_6F_{13} (**e**), n-C_8F_{17} (**f**)

3-(*p*-Tolylhydrazono)-1,1,1-trifluoropentane-2,4-dione reacts with thiosemicarbazide to form 5-hydroxy-1-thiocarbamoyl-4-(*p*-tolylhydrazono)-5-(trifluoromethyl)pyrazoline **25**.[48,49]

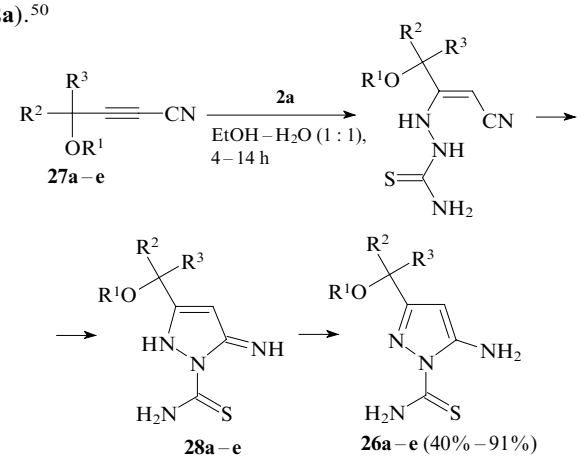
Table 2. 3-Aryl-1-thiocarbamoyl-1*H*-pyrazolines **22**.

Ar	R^1	R^2	R^3	Yield (%)	Ref.
Ph	H, Me	H	H	45–51	45, 46
	Me	Pr^i, Bu^n, Bu^i, cyclo-C_5H_9, cyclo-C_6H_{11}, cyclo-C_8H_{15}, 2-MeC_6H_4, 2-$ClC_6H_4CH_2$	H	18–77	46
	Me	see [a]	see [a]	13	46
3-ClC_6H_4	H, Me	H	H	25–47	44, 45
	H	3-$CF_3C_6H_4$	H	6	44
3-BrC_6H_4	H, Me	H	H	24–62	44, 45
	H	Me, n-C_6H_{13}	H	10–18	44
3-$F_3CC_6H_4$	H, Me	H	H	30–35	44
3,4-$Cl_2C_6H_3$	H, Me	H	H	20–52	44

[a] R^2–R^3 = $(CH_2)_2N(Ph)(CH_2)_2$.



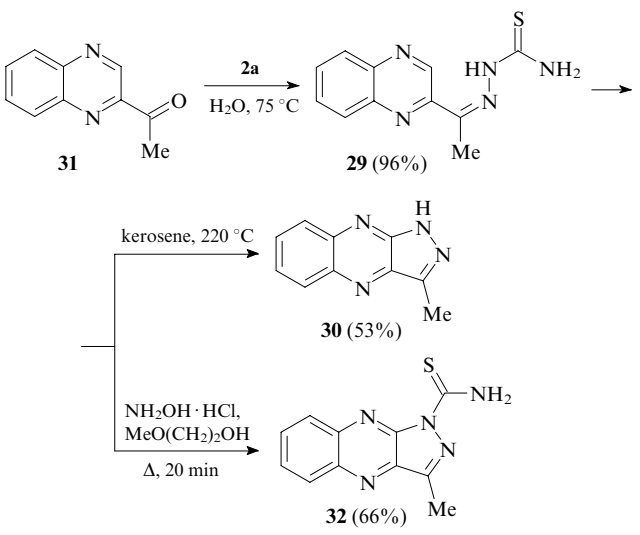
A method was developed for the synthesis of 3-alkyl-5-amino-1-thiocarbamoyl-1*H*-pyrazoles **26a – e** by the cyclization of but-2-ynenitriles **27a – e** with thiosemicarbazide (**2a**).[50]



26 – 28: R^1 = H: R^2 = R^3 = Me (**a**); R^2 = Me, R^3 = Et (**b**); $R^2 – R^3$ = $(CH_2)_4$ (**c**), $(CH_2)_5$ (**d**); R^1 = $Bu^nOCH_2CH_2$, R^2 = R^3 = Me (**e**)

The reaction is regioselective. It was suggested that the hydrazide NH_2 group of thiosemicarbazide adds to the triple bond of alkyne **27** to form a linear intermediate. The latter undergoes cyclization at the cyano group to give iminodihydropyrazole **28** followed by the prototropic shift resulting in the formation of pyrazole **26**.

2-Acetylquinoxaline thiosemicarbazone (**29**) is cyclized at a temperature near the melting point to form thermally more stable 3-methyl-1*H*-pyrazolo[3,4-*b*]quinoxaline (**30**).[51] Based on this fact, a method was proposed for the synthesis of heterocyclic compound **30** starting from compound **2a** and 2-acetylquinoxaline (**31**). A suspension of thiosemicarbazone **29**, which was obtained in the first step, in kerosene was carefully heated to a temperature higher than its decomposition point (195 °C).



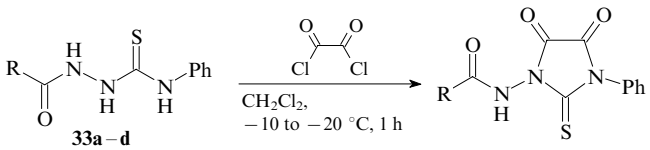
The oxidative cyclization of thiosemicarbazone **29** in the presence of hydroxylamine hydrochloride gives 3-methyl-1-thiocarbamoyl-1*H*-pyrazolo[3,4-*b*]quinoxaline (**32**).[51]

Therefore, methods for the synthesis of pyrazole derivatives based on reactions of thiosemicarbazides with α,β-unsaturated ketones, β-dimethylamino ketones, but-2-ynenitriles and 1,3-diketones are well developed.

2. Imidazoles

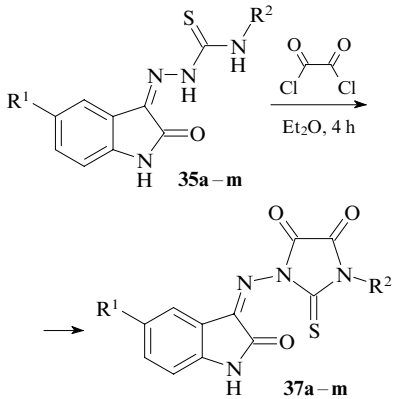
It is convenient to classify methods for the synthesis of 1-amino-2-thioxoimidazolidines according to the nature of the electrophilic reagent used for the cyclization with thiosemicarbazides. In these reactions, the latter act as N(2),N(4)-dinucleophiles. Thiosemicarbazones of aliphatic, aromatic and heterocyclic aldehydes and ketones are widely used as the starting compounds for the synthesis of five-membered heterocycles. These reagents are prepared by the condensation of carbonyl compounds with thiosemicarbazides in alcohols either at elevated[5, 14, 44, 52 – 63] or room temperature[9, 64, 65] under acid catalysis[4, 11, 12, 15, 18, 44, 52, 53, 59 – 65] or under microwave radiation.[11, 61 – 63]

The reactions of 1,4-disubstituted thiosemicarbazides **33a – d** with oxalyl chlorides gave 2-thioxoimidazolidine-4,5-diones **34a – d**.[66]

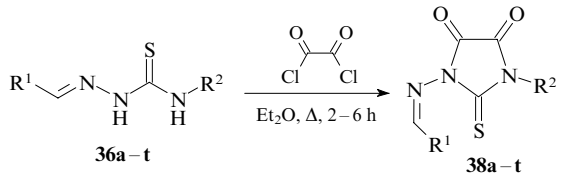


R = Me (**a**), Ph (**b**), 3-Py (**c**), 4-Py (**d**)

The corresponding reactions with thiosemicarbazones **35a – m**[53, 54] and **36a – t**,[55, 67] produce compounds **37a – m** and **38a – t**, respectively. Generally, the cyclization is performed in anhydrous diethyl ether or dichloromethane on cooling to – 10 to – 20°C, at room temperature or under reflux for 1 – 6 h.



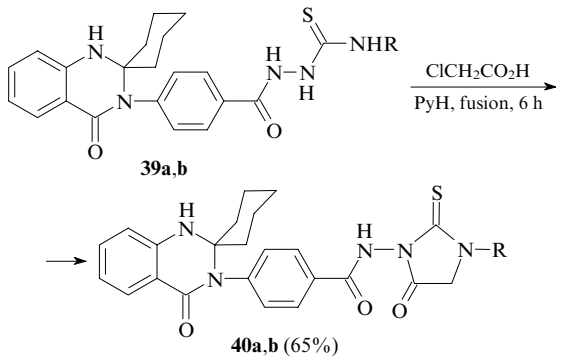
R^1 = H: R^2 = All (**a**, 81%), Bu^n (**b**, 61%), Ph (**c**, 89%), 4-MeC_6H_4 (**d**, 78%), 4-FC_6H_4 (**e**, 83%), 4-BrC_6H_4 (**f**, 84%), 4-$O_2NC_6H_4$ (**g**, 73%); R^1 = Br: R^2 = cyclo-C_6H_{11} (**h**, 94%), Ph (**i**, 93%), 4-MeC_6H_4 (**j**, 95%), 4-BrC_6H_4 (**k**, 91%), 4-ClC_6H_4 (**l**, 18%), 4-FC_6H_4 (**m**, 71%)



36a–t **38a–t**

R^2 = cyclo-C_6H_{11}: R^1 = 2-ClC_6H_4 (**a**, 97%), 3-MeC_6H_4 (**b**, 94%), 4-MeC_6H_4 (**c**, 96%), 2-$O_2NC_6H_4$ (**d**, 98%), 4-$O_2NC_6H_4$ (**e**, 97%), 4-$HO_2CC_6H_4$ (**f**, 96%), 3,4-$Me_2C_6H_3$ (**g**, 96%), 3-MeO-4-HOC_6H_3 (**h**, 94%), 2-HO-5-BrC_6H_3 (**i**, 92%), 5-O_2N-2-Fu (**j**, 93%), 2,3-$(OCH_2O)C_6H_3$ (**k**, 97%); R^2 = 3,4-$(MeO)_2C_6H_3(CH_2)_2$: R^1 = 4-FC_6H_4 (**l**, 18%), 2-ClC_6H_4 (**m**, 33%), 3-ClC_6H_4 (**n**, 43%), 4-ClC_6H_4 (**o**, 27%), 4-BrC_6H_4 (**p**, 16%), 2-HOC_6H_4 (**q**, 6%), 4-$HO_2CC_6H_4$ (**r**, 91%), 2-$O_2NC_6H_4$ (**s**, 13%), 2-Fu (**t**, 58%)

The synthesis of 3-amino-2-thiohydantoin derivatives from thiosemicarbazides is performed with the use of chloroacetic acid or its ester. For example, the condensation of 1-acylthiosemicarbazides **39a**,**b** with chloroacetic acid in the presence of pyridine gives thiohydantoins **40a**,**b**.[68]

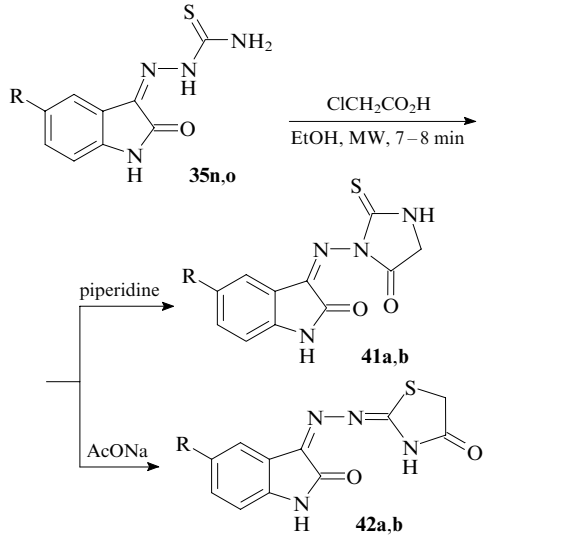


39a,**b**

40a,**b** (65%)

R = Ph (**a**), cyclo-C_6H_{11} (**b**)

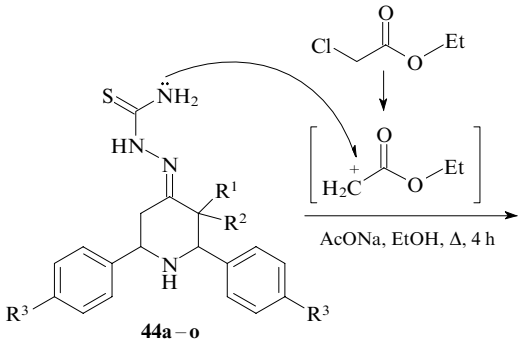
Under microwave (MW) radiation, thiosemicarbazones **35n**,**o** undergo similar cyclization reactions with chloroacetic acid in the presence of bases. In the presence of piperidine, the reactions afford 3-(5-oxo-2-thioxoimidazolidin-1-ylimino)-1,3-dihydro-2*H*-indol-2-ones **41a**,**b**, whereas the reactions in the presence of AcONa give the corresponding 1,3-thiazolidin-4-ones **42a**,**b**.[61] Microwave radiation makes it possible to substantially reduce the reaction time and provides high yields of the target products.



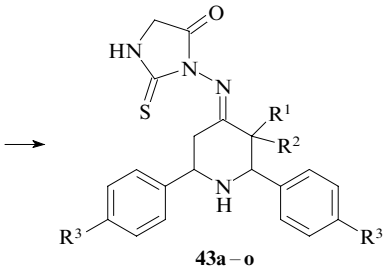
35n,**o** **41a**,**b** **42a**,**b**

Compound		R	Yields (%)	
35	**41**, **42**		**41**	**42**
n	**a**	H	92	90
o	**b**	Br	80	85

A series of 3-piperidinylideneamino-2-thioxoimidazolidin-4-ones **43a–o** exhibiting antimicrobial activity[58] were synthesized from thiosemicarbazones **44a–o** and ethyl chloroacetate. The authors suggested that the electrophilic species that is produced upon the abstraction of the chloride anion from the chloroacetic ester molecule is preferentially attacked by the N(4) atom rather than by the sulfur atom of the thiosemicarbazide moiety.



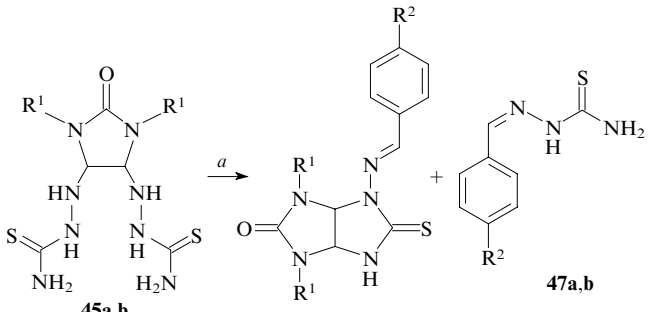
44a–o



43a–o

R^1 = R^2 = H: R^3 = H (**a**, 74%), F (**b**, 78%), Cl (**c**, 67%), Me (**d**, 70%), MeO (**e**, 72%); R^1 = Me, R^2 = H: R^3 = H (**f**, 75%), F (**g**, 78%), Cl (**h**, 75%), Me (**i**, 70%), MeO (**j**, 72%); R^1 = R^2 = Me: R^3 = H (**k**, 76%), F (**l**, 77%), Cl (**m**, 75%), Me (**n**, 71%), MeO (**o**, 72%)

An unusual reaction of 4,5-bis(thiosemicarbazido)-imidazolidin-2-ones **45a**,**b** with aromatic aldehydes giving 5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-ones **46a–d** has been discovered recently.[69] This reaction yields the



45a,**b** **47a**,**b**

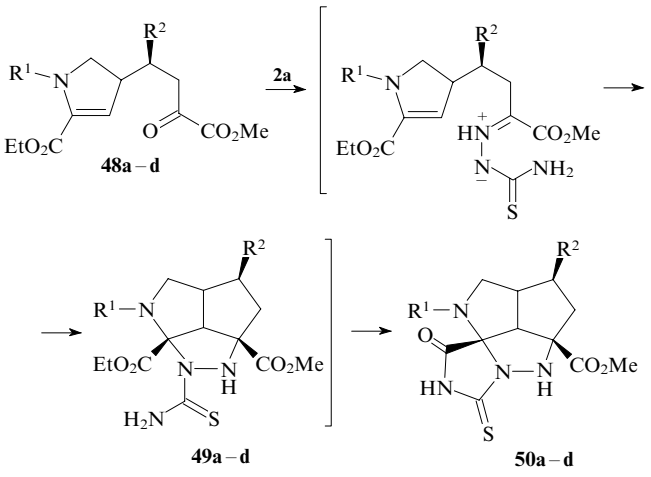
46a–d (20%–58%)

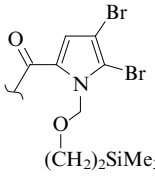
(*a*) , HCl, MeOH, Δ, 1.5 h

R^1 = Me (**45a**, **46a**, **46b**), Et (**45b**, **46c**, **46d**);
R^2 = H (**46a**, **46c**, **47a**), Br (**46b**, **46d**, **47b**);

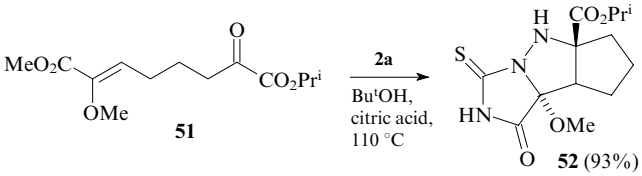
corresponding thiosemicarbazones **47a**,**b** as secondary products.

The intramolecular 1,3-dipolar cycloaddition of azomethines generated *in situ* from unsaturated keto dicarboxylic acid esters **48a–d** and thiosemicarbazide (**2a**) was investigated with the aim of synthesizing precursors of the bisguanidine alkaloids palau'amine and styloguanidine.[70–73] It was shown that the addition is stereoselective and is accompanied by acylation of intermediate **49**, resulting in the formation of tetracyclic compounds **50a–d** containing the fused pyrrole, pyrazoline and imidazolidine rings.



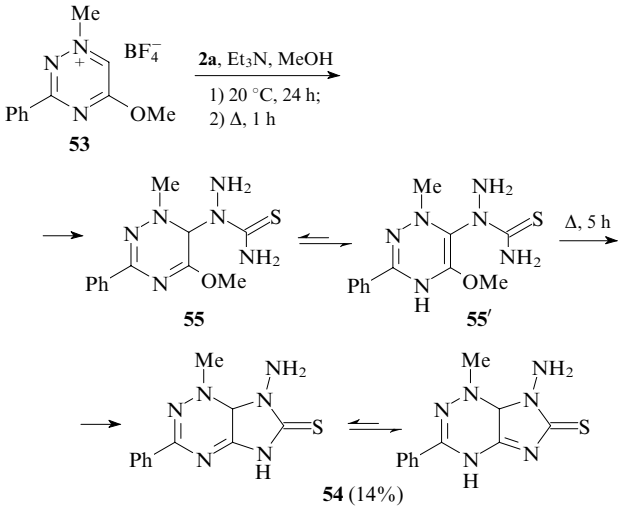
Compounds **48–50**	R^1	R^2	Reaction conditions	Yield (%)	Ref.
a	CO_2Bn	H	AcOH, 70 °C, 24 h	87–95	70, 71
b	$SO_2(CH_2)_2SiMe_3$	H	AcOH, 70 °C, 24 h	89	71
c	$SO_2(CH_2)_2SiMe_3$	$OSiMe_2Bu^t$	AcOH, 70 °C	49–58	71–73
d		$OSiMe_2Bu^t$	EtOH, 110 °C	69–71	71–73

The similar cyclization of compound **51** yields hexahydroimidazo[1,5-*b*]pyrazole **52**.[73]



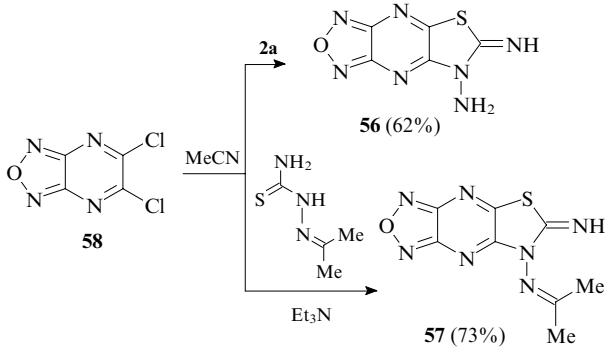
A tandem $A_N - S_N^{ipso}$ process involving the nucleophilic addition of the N(2)H group and the replacement of the good leaving methoxy group by the $N(4)H_2$ group of thiosemicarbazide was observed in the reaction of compound **2a** with the π-deficient heterocyclic compound, *viz*., the 5-methoxy-1-methyl-3-phenyltriazinium cation (**53**).[74] This reaction produced imidazo[4,5-*e*]-1,2,4-triazine-6-thione **54**. Intermediate **55** was isolated 1 h after the beginning of the reaction. This intermediate was in equilibrium with tautomer **55′**. Hence, it was concluded that the nucleophilic attack on position 6 of triazine **53** occurs in the first step, and the replacement of the 5-methoxy group is the final step resulting in the formation of cyclization product **54**.

An analysis of the above-considered publications shows that both conventional methods based on the reactions of thiosemicarbazides with oxalyl chloride and chloroacetic acid or its ethyl ester and new approaches involving tandem addition (including 1,3-dipolar cycloaddition) and substitution reactions are used to synthesize imidazole derivatives.



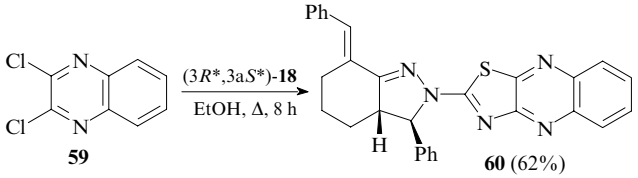
3. 1,3-Thiazoles

A well-known method for the synthesis of fused thiazolopyrazines is based on the nucleophilic substitution of *o*-dichloropyrazines with thiosemicarbazide derivatives acting as N(2),S- or N(4),S-dinucleophiles. For example, furazano[3,4-*b*]-1,3-thiazolo[4,5-*e*]pyrazine-6(7*H*)-imines **56** and **57** were synthesized by the condensation of 5,6-dichlorofurazano[3,4-*b*]pyrazine (**58**) with thiosemicarbazide (**2a**) and acetone thiosemicarbazone, respectively, in acetonitrile.[75]



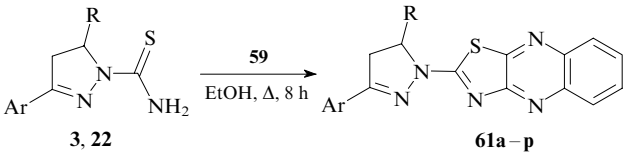
The reaction proceeds stepwise. Hence, both cyclic (**56**, **57**) and linear (with the participation of two nucleophile molecules) substitution products can be formed. In the latter case, the addition of an equimolar amount of a hydrogen chloride acceptor (triethylamine) to the reaction mixture results in the cyclization of the active intermediate produced in the first step.[75]

7-Benzylidene-3-phenyl-3,3a,4,5,6,7-hexahydro-2*H*-indazole-2-thiocarboxamide (**18**) reacts with 2,3-dichloroquinoxaline (**59**) under reflux in ethanol to form 1-(thiazolo[4,5-*b*]quinoxalin-2-yl)pyrazoline **60**.[21]



59 **60** (62%)

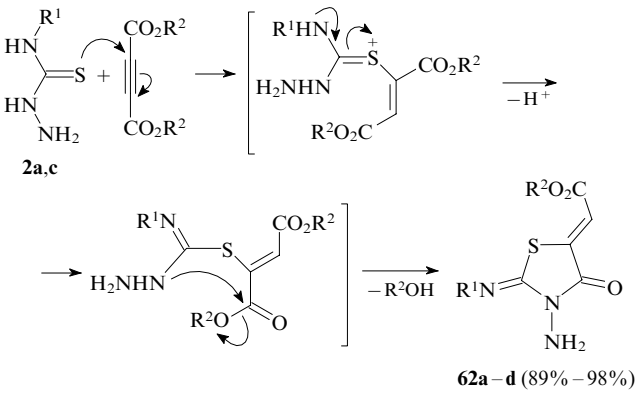
Similar products **61a–p** were synthesized based on 1-thiocarbamoylpyrazolines **3** (R = Me, Ar, Het)[21,25] or **22** ($R^1 = R^2 = R^3 = H$),[45] which were prepared from thiosemicarbazide and α,β-unsaturated or β-dimethylamino-substituted ketones.



3, **22** **61a–p**

Compound **61**	Ar	R	Yield (%)	Ref.
a	Ph	H	70	45
b	Ph	Me	63	45
c	Ph	Ph	43	25
d	Ph	4-MeC_6H_4	22	25
e	Ph	2-EtC_6H_4	18	25
f	Ph	2-$Pr^iC_6H_4$	16	25
g	Ph	2-ClC_6H_4	34	25
h	Ph	2,3-$Cl_2C_6H_3$	22	25
i	Ph	2,4,6-$Me_3C_6H_2$	24	25
j	Ph	3-Ind	49	25
k	4-ClC_6H_4	2-Fu	72	21
l	4-ClC_6H_4	2-Th	75	21
m	2-ClC_6H_4	H	49	45
n	2-ClC_6H_4	Me	41	45
o	2-BrC_6H_4	H	55	45
p	2-BrC_6H_4	Me	46	45

The reaction of thiosemicarbazides **2a**,**c** with acetylenedicarboxylic acid esters in dry dichloromethane at 0 °C gives (3-amino-2-imino-4-oxothiazolidin-5-ylidene)acetic acid esters **62a–d** within a few minutes.[76]

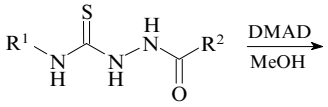


62a–d (89%–98%)

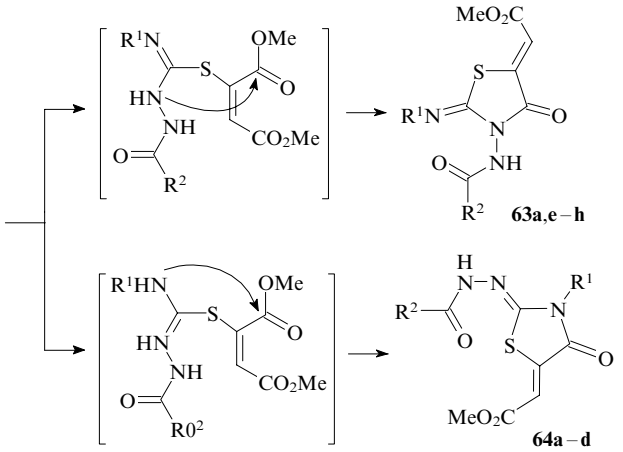
R^1 = H (**2a**): R^2 = Me (**62a**), Et (**62b**); R^1 = Ph (**2c**): R^2 = Me (**62c**), Et (**62d**)

It was hypothesized that the addition occurs through the attack of the sulfur atom of thiosemicarbazides **2** on the C≡C triple bond followed by cyclocondensation of the corresponding intermediates to thiazolones **62** involving the nitrogen atom N(2) of thiosemicarbazide.

The regioselective reaction of 1,4-disubstituted thiosemicarbazides **33a–h** with dimethyl acetylenedicarboxylate (DMAD) was described.[66] Depending on the substituent at the nitrogen atom N(4) of thiosemicarbazide, the reaction gives 3-amino-2-imino-1,3-thiazolidines **63a**,**e–h** or 2-hydrazono-1,3-thiazolidines **64a–d**. Apparently, not only the nitrogen atom N(2) but also the nitrogen atom N(4) can be involved in the cyclocondensation in the second step of the reaction. The yields of compounds **63** are 63%–93%. Along with thiazolidine **63a**, the reaction produces the corresponding minor product **64a**. The yields of thiazolidines **64b–d** are 65%–71%. The reactions are performed at room temperature overnight.

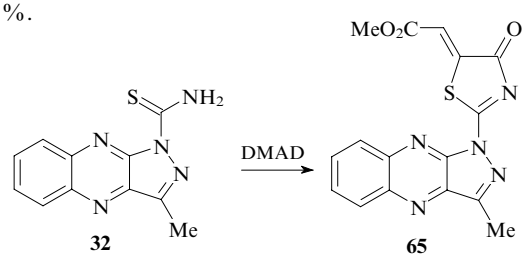


33a–h



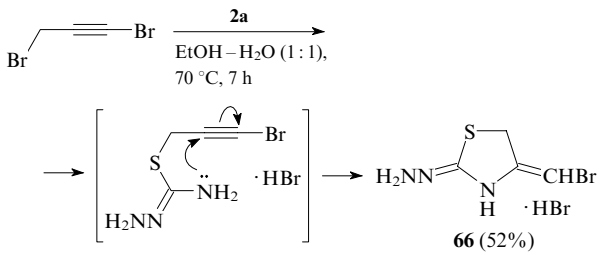
R^1 = Ph: R^2 = Me (**a**), Ph (**b**), 3-Py (**c**), 4-Py (**d**); R^1 is acridin-9-yl: R^2 = Me (**e**), Ph (**f**), 3-Py (**g**), 4-Py (**h**)

The cyclization of 1-thiocarbamoyl-substituted pyrazolo[3,4-*b*]quinoxaline **32** proceeds under more drastic conditions (dioxane, 100 °C, 6 h) compared to thiosemicarbazide.[51] The yield of methyl thiazol-5-ylideneacetate **65** is 40%.



32 **65**

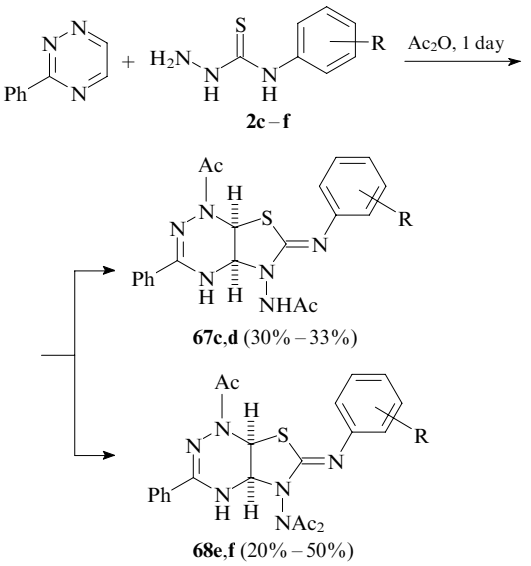
The heterocyclization of 1,3-dibromopropyne with thiosemicarbazide (**2a**) begins with the alkylation at the sulfur atom. The subsequent intramolecular addition of the $N(4)H_2$ group of thiosemicarbazide to the triple bond



66 (52%)

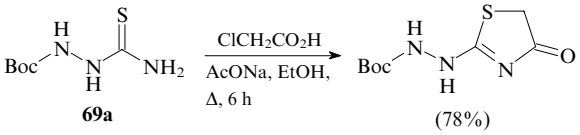
gives rise to (4-bromomethylidene-1,3-thiazolidin-2-ylidene)hydrazine hydrobromide (**66**).[77]

The annulation of the thiazole ring to the triazine moiety resulting in the formation of 1,4,4a,7a-tetrahydrothiazolo[4,5-*e*]-1,2,4-triazines was performed for the first time by successive nucleophilic addition reactions (A_N-A_N) of 4-arylthiosemicarbazides **2c–f** with 3-phenyl-1,2,4-triazine.[78] The addition of thiosemicarbazides **2c**,**d** in acetic anhydride at room temperature affords diacetyl derivatives **67c**,**d**. The cyclization of 4-(3-chlorophenyl)- (**2e**) and 4-(4-tolyl)thiosemicarbazides (**2f**) under the same conditions gives compounds **68e**,**f** containing the *N*,*N*-diacetylated hydrazine moiety.



R = H (**c**), 4-F (**d**), 3-Cl (**e**), 4-Me (**f**)

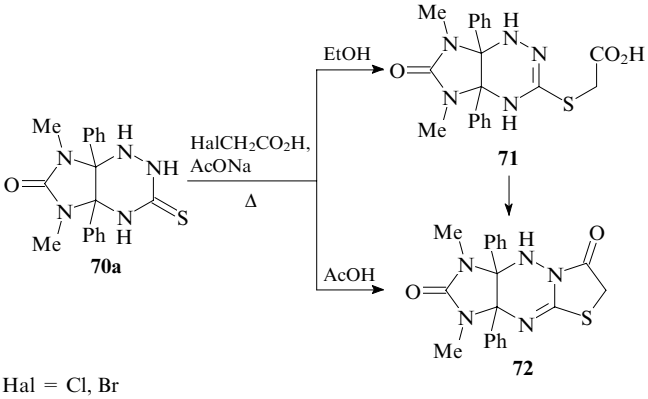
A conventional method for the synthesis of 1,3-thiazoles is based on the condensation of thiosemicarbazide derivatives with α-halocarboxylic acids or their esters. For example, 1-Boc-substituted thiosemicarbazide **69a** reacts with chloroacetic acid under reflux in ethanol in the presence of an equimolar amount of sodium acetate to form the corresponding 1,3-thiazolin-4-one.[16,79]



Boc = CO_2Bu^t

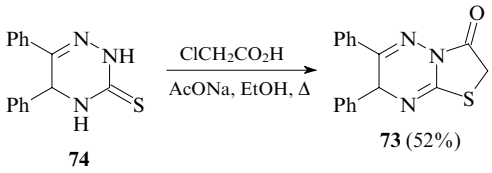
The condensation of chloro- or bromoacetic acid with 5,7-dimethyl-4a,7a-diphenyl-3-thioxoperhydroimidazo[4,5-*e*]-1,2,4-triazin-6-one (**70a**) under similar conditions produces carboxymethylthio derivative **71**, whose cyclization in acetic anhydride gives 1,3-dimethyl-3a,9a-diphenyl-3,3a,9,9a-tetrahydroimidazo[4,5-*e*]-1,3-thiazolo[3,2-*b*]-1,2,4-triazine-2,7(1*H*,6*H*)-dione (**72**) in 83% yield.[80]

The yields of acid **71** are 85% when the reaction is performed for 2 h in the presence of bromoacetic acid and 90% when the reaction is carried out under reflux with chloroacetic acid for 6 h. Thiazolotriazine **72** is generated also by the alkylation of triazinethione **70a** in acetic acid. The reaction time is 1.5 h (yield 75%) and 2.5 h (yield 63%) in the reactions with the use of bromoacetic and chloroacetic acid, respectively.[80]

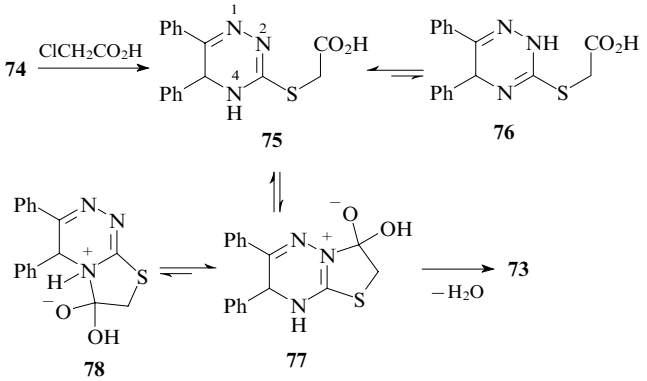


Hal = Cl, Br

The formation of the N(2),S-disubstitution product instead of the N(4),S-disubstitution product, *viz*., 6,7-diphenylthiazolo[3,2-*b*]-1,2,4-triazin-3(2*H*)-one (**73**), in the reaction of 5,6-diphenyl-2,3,4,5-tetrahydro-1,2,4-triazine-3-thione (**74**) with chloroacetic acid was described also in the earlier study.[81]

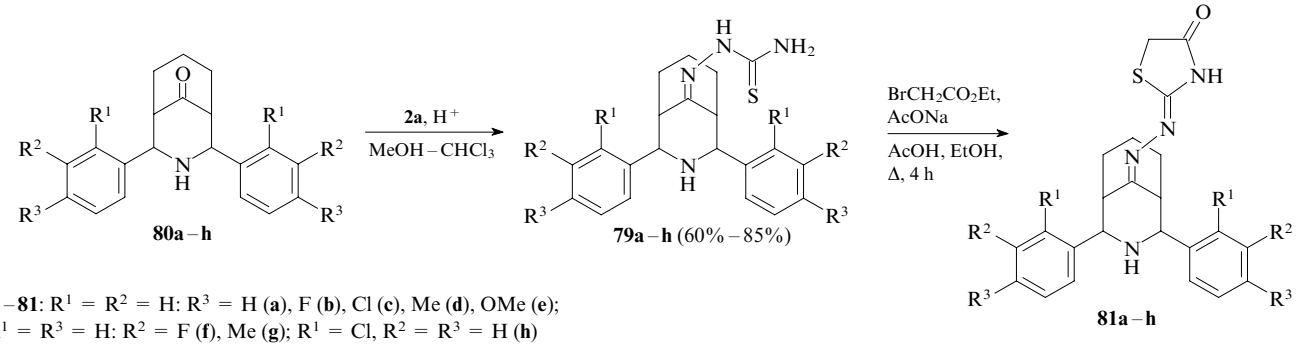


The following reaction mechanism was proposed. The initial formation of tautomer **75** is more probable than the formation of tautomer **76**, because the lone pair in **75** can be delocalized over a more extended system in the molecule. The lone pair on the nitrogen atom N(4) in intermediate **75** is conjugated with the $-C=N(2)-N(1)=CPh$ system, whereas the lone pair on the nitrogen atom N(2) in intermediate **76** can be conjugated with either the $N(1)=CPh$ system or with the $C(3)=N(4)$ group. In tautomer **75**, the sp^2-hybridized pyridine-like atom N(2), being more nucleophilic than the pyrrole-like sp^3-hybridized atom N(4), attacks the carboxyl carbon atom to form intermediate **77**. The latter eliminates a water molecule and is transformed into thiazolotriazine **73**. The attack of the nitrogen atom N(4) giving rise to intermediate **78** seems to be less probable.



Thiosemicarbazones **79a–h**, which were synthesized by the condensation of thiosemicarbazide **2a** with ketones **80a–h**, react with ethyl bromoacetate in ethanol in the

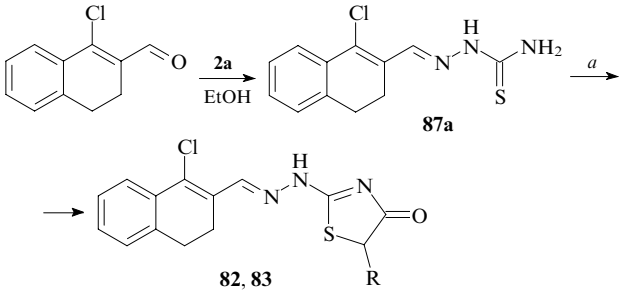
Scheme 3



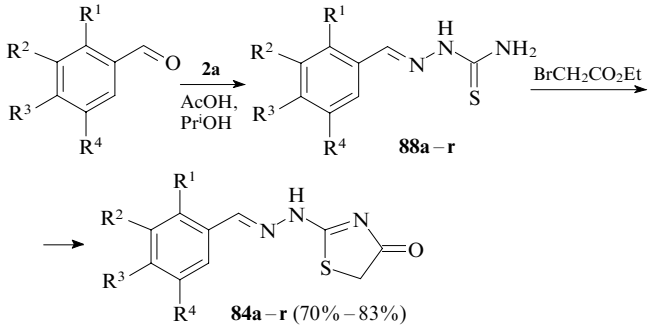
79–**81**: $R^1 = R^2 = H$: $R^3 = H$ (**a**), F (**b**), Cl (**c**), Me (**d**), OMe (**e**); $R^1 = R^3 = H$: $R^2 = F$ (**f**), Me (**g**); $R^1 = Cl$, $R^2 = R^3 = H$ (**h**)

presence of acetic acid and an excess of sodium acetate.[4] This reaction gives 2-[(2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ylidene)hydrazono]-1,3-thiazolidin-4-ones **81a**–**h** (Scheme 3). Sodium acetate and acetic acid create a buffer system maintaining the pH value at 4.5–5.0, which prevents the cleavage of the C=N bond. An excess of AcONa binds hydrogen bromide, and acetic acid acts as a cyclizing agent. The yields of compounds **81a**–**h** are 72%–79%.[4]

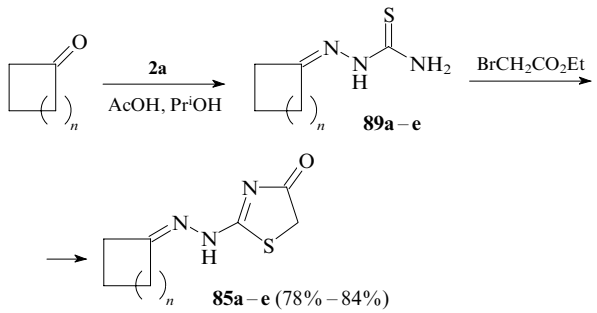
Thiazolones **82**–**86** were synthesized in good yields by the reactions of thiosemicarbazones of 1-chloro-3,4-dihydronaphthalene-2-carbaldehyde (**87a**),[14] aromatic aldehydes (**88a**–**r**), cyclic ketones (**89a**–**e**)[65] and 4-(piperidinosulfonyl)acetophenones (**90a**,**c**).[82] The condensation of these thiosemicarbazones with ethyl bromoacetate or ethyl bromomalonate proceeds under heating in anhydrous alcohols in the presence of an excess of anhydrous sodium acetate.



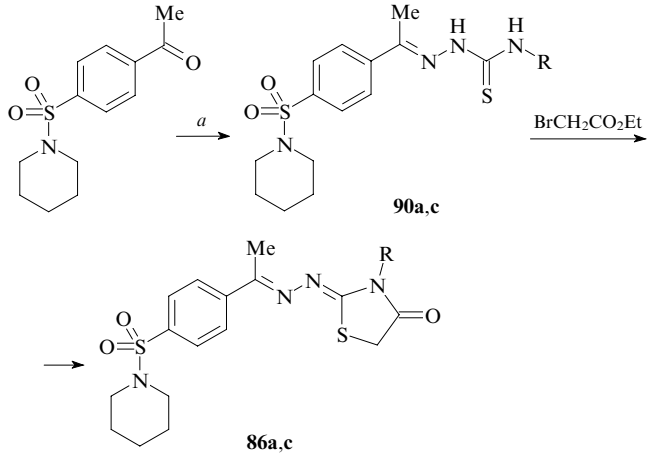
(*a*) $BrCH(CO_2Et)_2$ [R = CO_2Et (**82**, 78%)] or $BrCH_2CO_2Et$ [R = H (**83**, 70%)]



84, **88**: $R^1 = R^2 = R^4 = H$: R^3 = F (**a**), Cl (**b**), Br (**c**), Me (**d**), OMe (**e**), NO_2 (**f**); R^1 = OH, $R^2 = R^3 = H$: R^4 = F (**g**), Cl (**h**), Br (**i**); $R^1 = R^3 = H$: $R^2 = R^4$ = Cl (**j**), Br (**k**); $R^1 = R^3 = R^4 = H$: R^2 = F (**l**), Cl (**m**), Br (**n**), Me (**o**), OMe (**p**), NO_2 (**q**), OH (**r**)

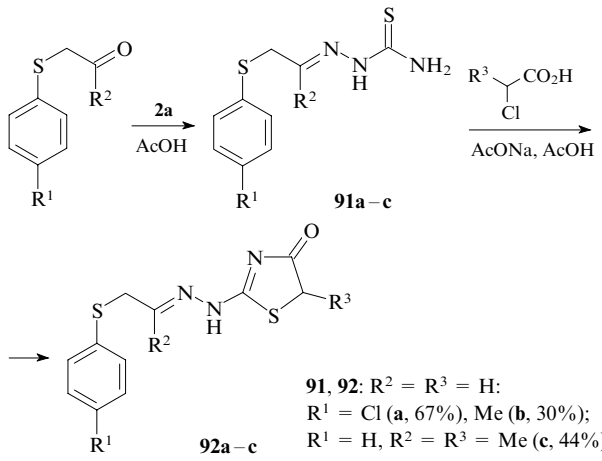


85, **89**: *n* = 1 (**a**), 2 (**b**), 3 (**c**), 4 (**d**), 5 (**e**)



(*a*) $RNHC(S)NHNH_2$ (**2a**,**c**), EtOH, Δ; R = H (**a**, 80%), Ph (**c**, 85%)

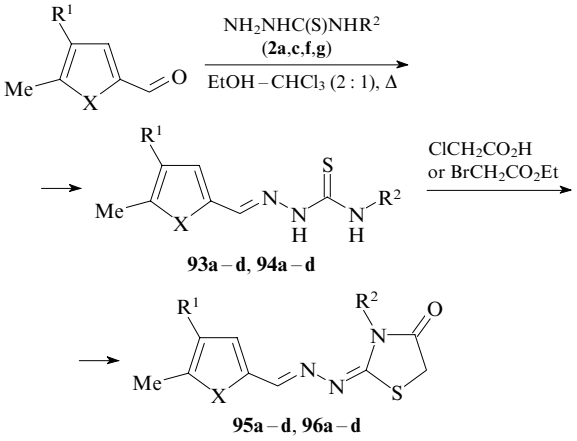
The cyclization of chloroacetic and α-chloropropionic acids with thiosemicarbazones **91a**–**c**, which were synthe-



91, **92**: $R^2 = R^3 = H$:
R^1 = Cl (**a**, 67%), Me (**b**, 30%);
R^1 = H, $R^2 = R^3$ = Me (**c**, 44%)

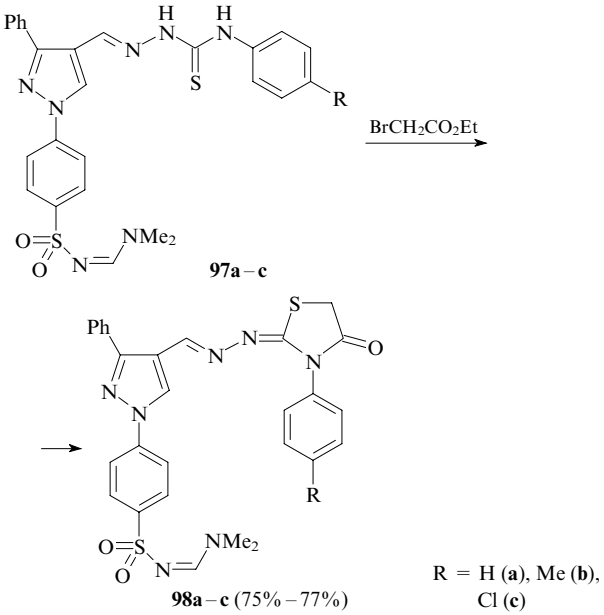
sized from phenylthioacetaldehyde or phenylthiopropan-2-one and thiosemicarbazide (**2a**), affords *N*-(4-oxothiazolin-2-yl)-*N′*-phenylthioethylidene(2-propylidene)hydrazones **92a**–**c**.[16]

Compounds efficient against *Candida albicans* were synthesized by the condensation of furan- (**93a**–**d**) and pyrrole-2-carbaldehyde thiosemicarbazones (**94a**–**d**) with chloroacetic acid. The reactions were performed under reflux for 4–8 h in glacial acetic acid in the presence of an excess of sodium acetate. The similar reaction proceeds with ethyl bromoacetate in anhydrous ethanol. Both methods produce thiazolidin-4-ones **95a**–**d** and **96a**–**d** in 66%–78% yields.[83]



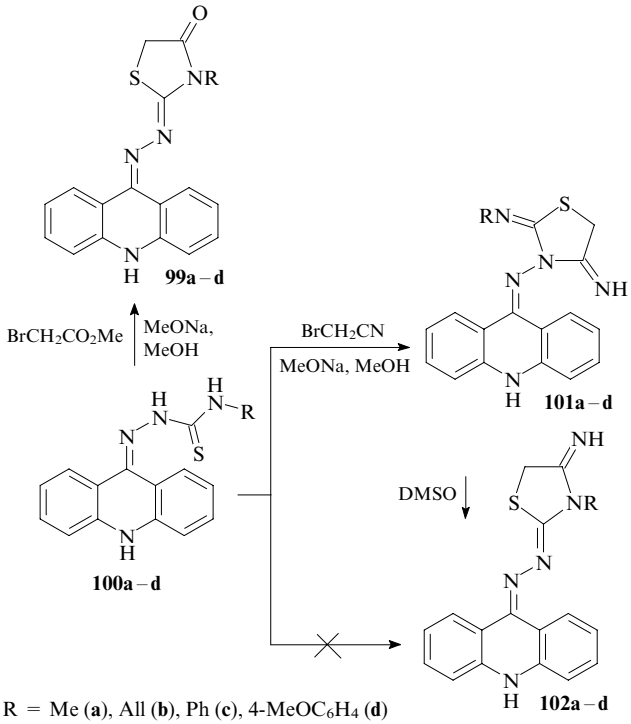
X = O, R^1 = CO_2Et (**93**, **95**); X = NH, R^1 = Ac (**94**, **96**);
R^2 = H (**2a**, **93a**, **94a**, **95a**, **96a**), Ph (**2c**, **93b**, **94b**, **95b**, **96b**),
4-MeC_6H_4 (**2f**, **93c**, **94c**, **95c**, **96c**), 4-ClC_6H_4 (**2g**, **93d**, **94d**, **95d**, **96d**)

The reaction of 1,3-diarylpyrazole-4-carbaldehyde thiosemicarbazones **97a**–**c** with ethyl bromoacetate under reflux in dioxane also produces 1,3-diarylpyrazole-4-carbaldehyde (4-oxo-1,3-thiazolidin-2-ylidene)hydrazones **98a**–**c**.[84]



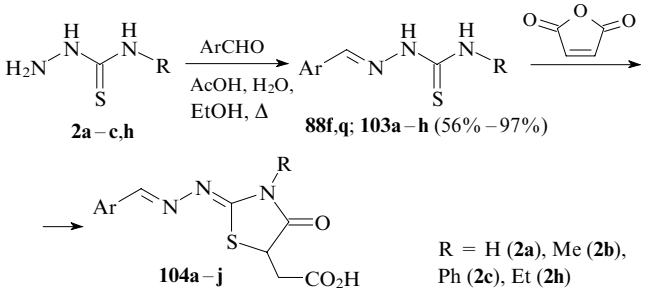
R = H (**a**), Me (**b**), Cl (**c**)

3-Substituted acridin-9(10*H*)-one (4-oxo-1,3-thiazolidin-2-ylidene)hydrazones **99a**–**d** were synthesized by the reaction of methyl bromoacetate with acridin-9(10*H*)-one thiosemicarbazones **100a**–**d** in methanol in the presence of sodium methoxide.[85] The cyclocondensation of compounds **100a**–**d** with bromoacetonitrile under the same conditions affords N^3-acridin-9(10*H*)-ylidene-4-imino-2-[alkyl(aryl)-imino]-1,3-thiazolidines **101a**–**d**, which undergo a spontaneous rearrangement (Dimroth-like rearrangement) in DMSO to form acridin-9(10*H*)-one (4-imino-1,3-thiazolidin-2-ylidene)hydrazones **102a**–**d**.[85]



R = Me (**a**), All (**b**), Ph (**c**), 4-$MeOC_6H_4$ (**d**)

The Michael addition of *o*-, *m*- and *p*-nitrobenzaldehyde thiosemicarbazones **88f**,**q** (R = H) and **103a**–**h** (R ≠ H) was performed with the use of maleic anhydride as the Michael acceptor. The reaction was performed by refluxing the starting compounds in a mixture of anhydrous toluene and DMF and produced thiazolidin-5-ylacetic acids **104a**–**j**.[5]

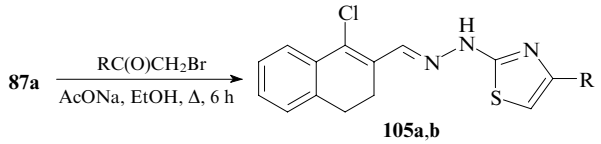


R = H (**2a**), Me (**2b**), Ph (**2c**), Et (**2h**)

Starting thiosemicarbazone	Product **104**	R	Ar	Yield (%)
88f	**a**	H	4-$O_2NC_6H_4$	52
88q	**b**	H	3-$O_2NC_6H_4$	95
103a	**c**	Me	2-$O_2NC_6H_4$	26
103b	**d**	Me	3-$O_2NC_6H_4$	36
103c	**e**	Me	4-$O_2NC_6H_4$	26
103d	**f**	Et	2-$O_2NC_6H_4$	33
103e	**g**	Et	3-$O_2NC_6H_4$	60
103f	**h**	Et	4-$O_2NC_6H_4$	56
103g	**i**	Ph	2-$O_2NC_6H_4$	65
103h	**j**	Ph	3-$O_2NC_6H_4$	50

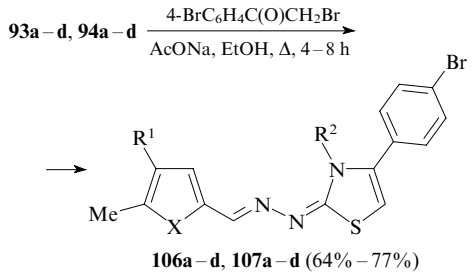
Yet another well-known method for the synthesis of biologically active 1,3-thiazoles is based on the condensation of aldehyde and ketone thiosemicarbazones with α-halo ketone or α,β-halo keto acid derivatives. These reactions are performed in alcohols under reflux [13, 14, 82, 83, 86–88] or at room temperature [64] with the use of sodium acetate,[14, 83, 86, 87] acetic acid [86, 87] or triethylamine.[13]

The cyclization of thiosemicarbazone **87a** with bromoacetone or phenacyl bromide affords 4-methyl(phenyl)-1,3-thiazoles **105a**,**b** [14] exhibiting antimicrobial activity.



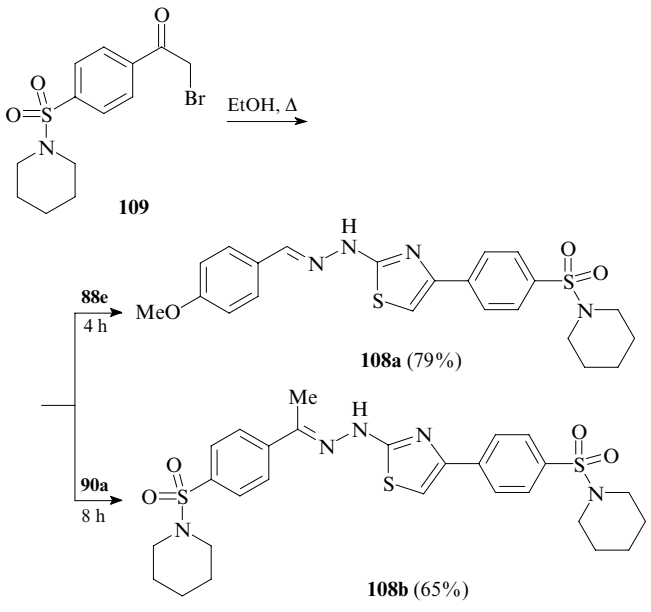
105: R = Me (**a**, 77%), Ph (**b**, 78%)

1,3-Thiazoles **106a**–**d** and **107a**–**d**, which were synthesized from furan- (**93a**–**d**) and pyrrole-2-carbaldehyde thiosemicarbazones (**94a**–**d**), respectively, also have antimicrobial activity.[83]

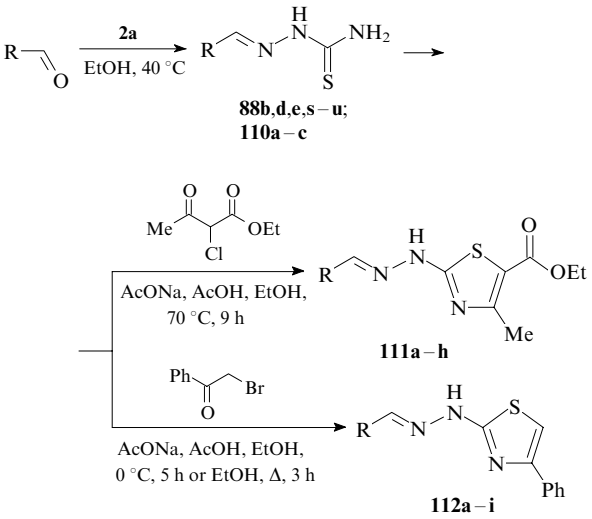


93, **106**: X = O, R^1 = CO_2Et; **94**, **107**: X = NH, R^1 = Ac: R^2 = H (**a**), Ph (**b**), 4-ClC_6H_4 (**c**), 4-MeC_6H_4 (**d**)

4-Substituted benzaldehyde {4-[4-(piperidinylsulfonyl)-phenyl]-1,3-thiazol-2-yl}hydrazones (**108a**,**b**) were synthesized by refluxing thiosemicarbazones **88e** and **90a** in ethanol in the presence of phenacyl bromide **109**.[82]



The similar cyclization of thiosemicarbazones of aromatic (**88**) and heterocyclic aldehydes (**110**) with ethyl 2-chloro-3-oxobutanoate or bromoacetophenone produces substituted 1,3-thiazoles **111** and **112**.[86]



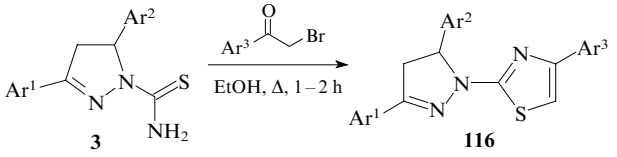
R = Ar (**88**), Het (**110**)

Starting thiosemicarbazone	R	Product **111**	Yield (%)	Product **112**	Yield (%)
88b	4-ClC_6H_4	**a**	77	**a**	77
88d	4-MeC_6H_4	**b**	62	**b**	85
88e	4-$MeOC_6H_4$	**c**	65	**c**	74
88s	Ph	**d**	50	**d**	71
88t	4-NCC_6H_4	**e**	71	**e**	72
88u [a]	2-HO-1-Naph	—	—	**f**	70
110a	2-Fu	**f**	56	**g**	61
110b	2-Th	**g**	70	**h**	71
110c	2-Py	**h**	82	**i**	81

[a] See Ref. 13; Naph is naphthyl.

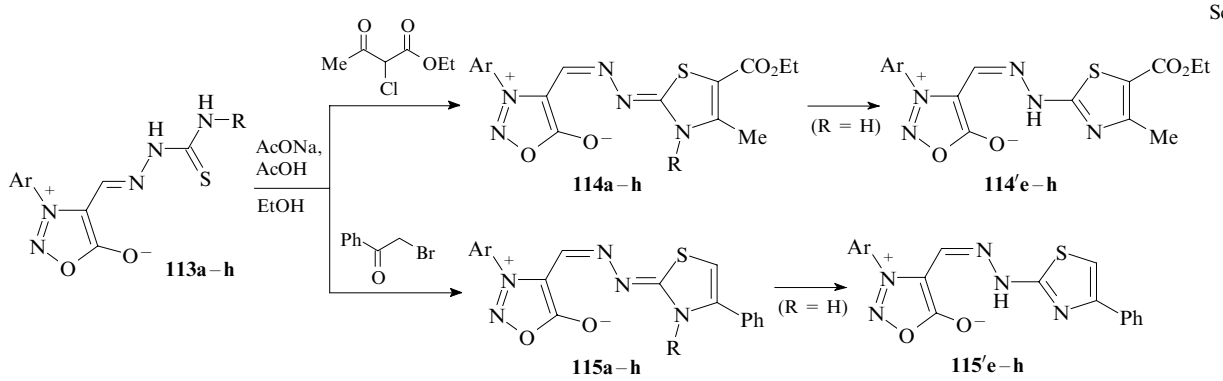
It should be noted that *N*-phenyl-substituted thiosemicarbazones **113a**–**d** react with the above reactants to form 2-imino-1,3-thiazolines **114a**–**d** and **115a**–**d**, whereas in the case of R = H these compounds (derived from thiosemicarbazones **113e**–**h**) exist predominantly in the aminothiazole tautomeric form **114′e**–**h** and **115′e**–**h** (Scheme 4).[86, 87]

A series of 2-(pyrazolin-1-yl)thiazoles **116** were synthesized in good yields from 1-thiocarbamoyl-3,5-di(het)arylpyrazolines **3** under reflux in ethanol in the presence of phenacyl bromides (Table 3).[13, 23, 24]



5-Phenyldiazenyl-1,3-thiazoles **117a**,**b** were synthesized by the reaction of naphthalenecarbaldehyde thiosemicarbazone **88u** with 1-(2-phenylhydrazono)-1-halopropan-2-ones or 2-(2-phenylhydrazono)-2-halo-1-phenylethanones in the presence of an equimolar amount of triethylamine.[13]

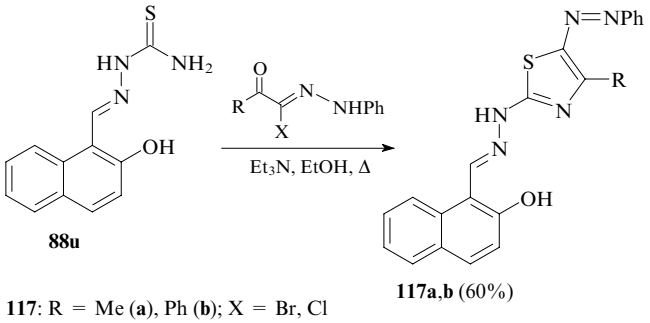
Scheme 4



Compound	Ar	R	Yield (%)	Ref.	Compound	Ar	R	Yield (%)	Ref.
114a	Ph	Ph	47	87	**115a**	Ph	Ph	57	87
114b	4-MeC_6H_4	Ph	40	87	**115b**	4-MeC_6H_4	Ph	48	87
114c	4-$MeOC_6H_4$	Ph	45	87	**115c**	4-$MeOC_6H_4$	Ph	51	87
114d	4-$EtOC_6H_4$	Ph	42	87	**115d**	4-$EtOC_6H_4$	Ph	48	87
114′e	Ph	H	68	86, 87	**115′e**	Ph	H	68	86, 87
114′f	4-MeC_6H_4	H	55	86, 87	**115′f**	4-MeC_6H_4	H	65	86, 87
114′g	4-$MeOC_6H_4$	H	62	86, 87	**115′g**	4-$MeOC_6H_4$	H	80	86, 87
114′h	4-$EtOC_6H_4$	H	73	86, 87	**115′h**	4-$EtOC_6H_4$	H	68	86, 87

Table 3. 4-Aryl-2-[3,5-di(het)aryl-4,5-dihydro-1*H*-pyrazol-1-yl]thiazoles **116**.

Ar^1	Ar^2	Ar^3	Yield (%)	Ref.
Ph	4-$BnOC_6H_4$	4-ClC_6H_4	60	24
	4-$BnOC_6H_4$	4-MeC_6H_4	77	24
4-ClC_6H_4	4-$BnOC_6H_4$	4-ClC_6H_4	71	24
	4-$BnOC_6H_4$	4-MeC_6H_4	79	24
4-MeC_6H_4	4-$BnOC_6H_4$	4-ClC_6H_4	71	24
	4-$BnOC_6H_4$	4-MeC_6H_4	78	24
4-BrC_6H_4	4-$BnOC_6H_4$	4-MeC_6H_4	80	24
	4-$BnOC_6H_4$	4-ClC_6H_4	72	24
2-Naph	Ph	Ph	80	13
	2-Th	Ph	80	13
2-Benzofuryl	Ph	Ph	90	23
	Ph	4-BrC_6H_4	88	23
	4-ClC_6H_4	Ph	90	23
	4-ClC_6H_4	4-BrC_6H_4	82	23

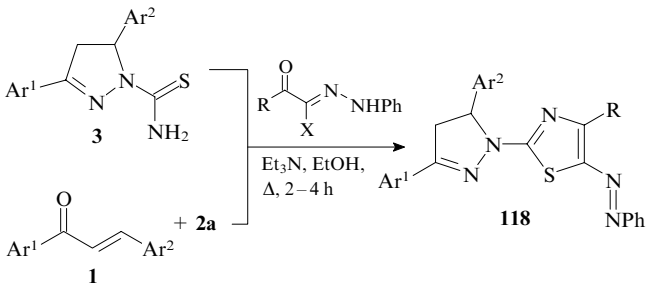


117: R = Me (**a**), Ph (**b**); X = Br, Cl

The same reagents were used in the reactions with 1-thiocarbamoylpyrazolines **3** (R = H) to synthesize compounds **118**.[13, 33] The latter are also formed in the three-component reactions of thiosemicarbazide (**2a**), 1-(2-phenylhydrazono)-1-halopropan-2-ones or 2-(2-phenylhydrazono)-2-halo-1-phenylethanones and chalcones **1** (Table 4).

Table 4. 2-[3,5-Di(het)aryl-4,5-dihydro-1*H*-pyrazol-1-yl]-5-(phenyldiazenyl)-1,3-thiazoles **118**.

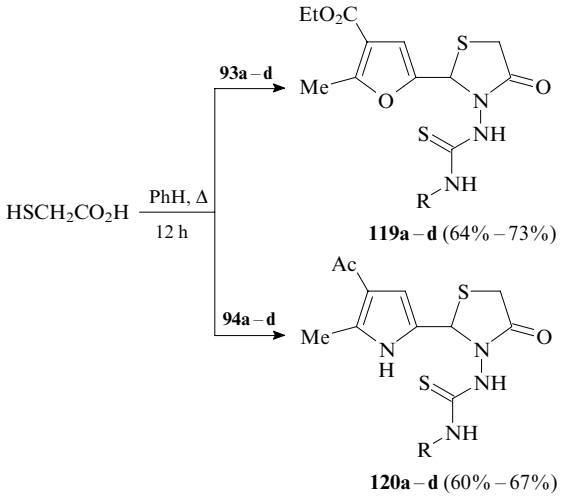
Ar^1	Ar^2	R	Yield (%)	Ref.
Ph	2-Th	Me	82	33
	2-Th	Ph	84	33
	2-Th	2-Th	85	33
	2-Th	2-Naph	78	33
	Ph	Me	79	33
	Ph	Ph	81	33
	Ph	2-Th	80	33
	Ph	2-Naph	69	33
	4-$BnOC_6H_4$	Me	67	33
	4-$BnOC_6H_4$	Ph	69	33
	4-$BnOC_6H_4$	2-Th	72	33
	4-$BnOC_6H_4$	2-Naph	75	33
2-Naph	Ph	Ph	70	13
	Ph	Me	50	13
	2-Th	Ph	70	13
	2-Th	Me	60	13



R = Me, Ph; X = Br, Cl

The cyclization of aromatic and heterocyclic aldehydes thiosemicarbazones with α-bromo ketones occurs also in dioxane [84] or dimethylformamide [51] to give 2,4-disubstituted 1,3-thiazoles.

The distinguishing feature of the condensation of thioglycolic acid with thiosemicarbazones **93a–d** or **94a–d** is the formation of *N*-(2-furyl)- (**119a–d**) and *N*-(pyrrol-2-yl)-4-oxo-1,3-thiazolidin-3-ylthioureas (**120a–d**), whose thiazolidine ring has only one nitrogen atom [N(1)] from the starting thiosemicarbazide.[83]



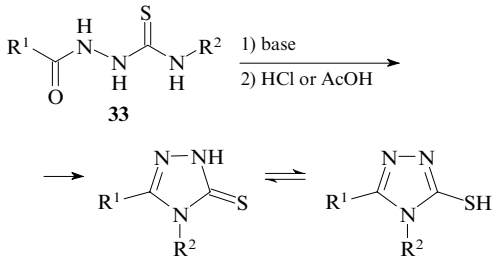
R = H (**a**), Ph (**b**), 4-ClC_6H_4 (**c**), 4-MeC_6H_4 (**d**)

The reactions of thiosemicarbazide derivatives with functionalized acetylenes, α-halocarboxylic acids and α-halo ketones continue to attract interest, which shows that the synthetic potential of these reactions is far from being exhausted, and these reactions would be expected to be developed in the future.

III. Synthesis of five-membered rings with three heteroatoms

1. 1,2,4-Triazoles

2*H*-1,2,4-Triazole-3(4*H*)-thiones (4*H*-1,2,4-triazole-3-thiols) can be synthesized by the cyclization of 1-acylthiosemicarbazides or by the direct reaction of thiosemicarbazides with carboxylic acids and their esters. In these reactions, thiosemicarbazide derivatives act as N(1),N(4)-dinucleophiles. Antimicrobial, antiinflammatory and antihypertensive agents were synthesized from thiosemicarbazides **33** under reflux in aqueous or alcoholic solutions of NaOH,[66,89–100] Na_2CO_3,[101] $NaHCO_3$,[89,102] NaOAlk[91] or Et_3N.[103] Triazole derivatives **121** (Table 5) exist as thiones **121** or their tautomers, thiols **121′**.



The reactions of thiosemicarbazides **2**[104–106] with carboxylic acids are performed under acid catalysis conditions (with excess of the acid that is involved in the reaction),[106,107] whereas the reactions with their esters are carried out in the presence of bases (NaOMe, PyH).[104,105] The reaction with the use of trifluoroacetic acid ester gives, apart from cyclization products **121** (see Table 5), S-alkyl

Table 5. 4,5-Disubstituted-4,5-dihydro-2(4)*H*-triazole-5-thiones **121**.

R^1	R^2	Yield (%)	Ref.
Me	3,4-$F_2C_6H_3$	66	104
Me, Ph	acridin-9-yl	64–71	66
Ph	Ph	89	91
4-FC_6H_4	H, Et, Pr^n, All, Ph	54–89	89
3-ClC_6H_4	Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-BrC_6H_4, 2-BrC_6H_4, 4-IC_6H_4, 2-IC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 2,5-$F_2C_6H_3$, 2,6-$F_2C_6H_3$	65–95	98
4-$MeSO_2C_6H_4$	cyclo-C_6H_{11}, Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4	76–97	101
2-HOC_6H_4, 4-HOC_6H_4, 2-HO-5-ClC_6H_3, 4-$EtOC_6H_4CH_2$	All	68–94	92
4-$ClC_6H_4SO_2(CH_2)_2$, 4-$BrC_6H_4SO_2CH_2$, 4-$MeC_6H_4S(CH_2)_2$, 4-$BrC_6H_4SCH_2$	H, Ph	82–93	91
2-HO-5-(2,4-$F_2C_6H_3$)C_6H_3	Me, Et, All, cyclo-C_6H_{11}, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$	68–91	94
2-Fu, Bn	Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$NO_2C_6H_4$	63–79	93
4-(4-R-Phenyl)-1,3-thiazol-2-ylamino (R = H, Cl, Br, NO_2)	Ph, 2-MeC_6H_4, 4-MeC_6H_4, 2-$MeOC_6H_4$, 4-$MeOC_6H_4$	58–84	100
1-Methyl-5-nitroimidazolin-2-yl	Me, Et	81–80	102
Pyrimidin-2-yl	Me, All	82–84	97
4-Py	Ph, 4-FC_6H_4	60–91	90
Pyrazin-2-yl *N*(4)-oxide	cyclo-C_6H_{11}	43	97
6-Oxo-3-R-4,5-dihydropyridazin-1(4*H*)-yl (R = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-EtC_6H_4, 4-$Bu^iC_6H_4$, 4-PhC_6H_4, 4-ClC_6H_4)	Ph, 4-ClC_6H_4, 4-MeC_6H_4	32–72	99
Quinolin-2-yl	Et, All,[a] Bn, Ph, cyclo-C_6H_{11}	65–70	95
	Me, 4-ClC_6H_4	86–88	97

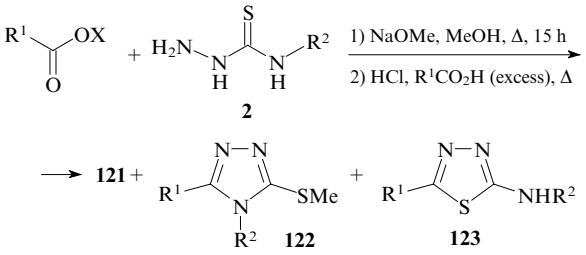
Table 5 (continued).

R^1	R^2	Yield (%)	Ref.
5-R-3-Phenylindol-2-yl (R = Br, Cl, Me)	H	64–70	105
4,5,6,7-Tetrahydro-1-benzothiophen-2-yl, 5-R-2-thiophenyl (R = Ph, 4-MeC_6H_4)	Et	87–98	96
5-Methyl-2-oxobenzo[*d*]oxazol-3(3*H*)-yl	Me, Et, Pr^i, Ph	82–97	103
2-Th, 3-Py, CF_3 (see [b])	4-FC_6H_4	41–63	104
H, Me, CF_3	4-$CF_3OC_6H_4$, 4-$CF_3C_6H_4$	40–71	104
	piperidin-1-yl [c]	70–84	104
Me, CF_3	3-Py	56–67	104
CF_2H	Ph, 3,4-$(MeO)_2C_6H_3$ (see [d])	45	106
CF_3	Ph,[e] 4-MeC_6H_4, 4-FC_6H_4 (see [f]), piperidin-1-yl	50–55	106

[a] In Ref. 97, the yield was 90%; [b] the yield was 22%; in addition, compound **122** was isolated in 32% yield; [c] the yield was 60 %; in addition, compound **122** was isolated in 68% yield; [d] the yield was 35% for a mixture with compound **123**, the ratio **121** : **123** = 10 : 1; [e] the yield was 70% for a mixture with compound **123**, the ratio **121** : **123** = 30 : 1; [f] the yield was 88% for a mixture with compound **123**, the ratio **121** : **123** = 10 : 1.

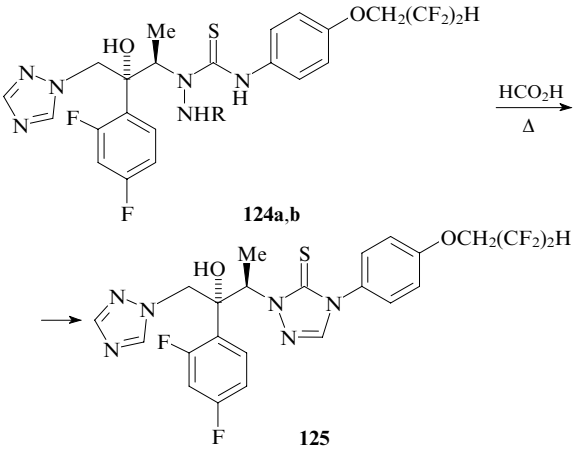
derivatives **122**. Vasil'eva *et al.*[104] hypothesized that compounds **121** are alkylated with methyl trifluoroacetate, which is produced through transesterification of ethyl ester with the solvent (methanol).

In the reactions of thiosemicarbazides with fluoroacetic acids, thiadiazoles **123** were detected as impurities (yields 3%–9%) to triazoles **121**.[106]



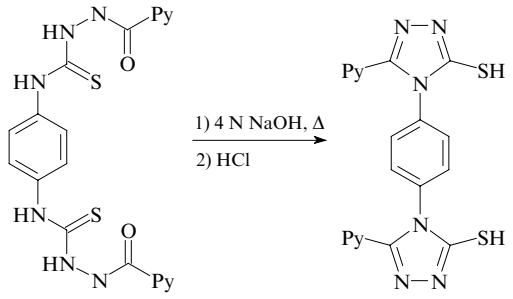
X = H, Et

In the presence of formic acid, 2,4-disubstituted thiosemicarbazides **124a**,**b** undergo cyclization to 2,4-disubstituted triazole **125** in 70% and 50% yields, respectively.[107]



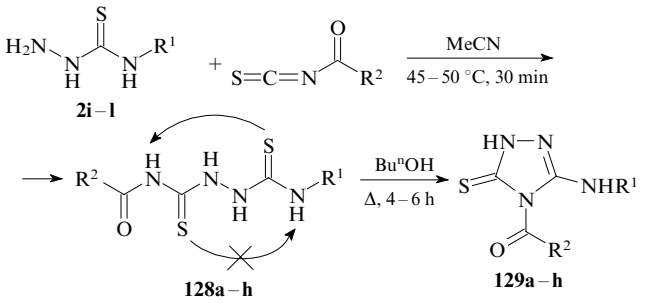
R = H (**a**), Boc (**b**)

The cyclization of phenylenebis(thiosemicarbazides) **126a**–**c** was used to synthesize phenylenebis(1,2,4-triazoles) **127a**–**c** in 87%–90% yields.[108]



Isomers of Py: 2 (**a**), 3 (**b**), 4 (**c**)

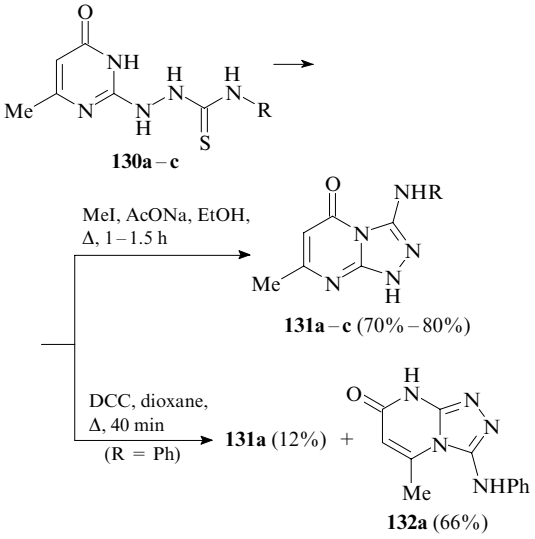
The condensation of thiosemicarbazides **2i**–**l** with aroyl isothiocyanates affords 1,2-bis(thiocarbamoyl)hydrazines **128a**–**h**, which readily undergo cyclization to 5-aryl(arylalkyl)amino-4-aroyl-1,2,4-triazole-3(2*H*)-thiones **129a**–**h**. An alternative cyclization pathway with the participation of the aryl(arylalkyl)amino group was not observed.[109]



Compound **2**	R^1	Compounds **128**, **129**	R^2	Yield of **129**, %
i	9-anthrylmethyl	**a**	4-ClC_6H_4	67
j	2-$MeOC_6H_4$	**b**	2-Th	78
		c	4-$Bu^tC_6H_4$	72
k	Bn	**d**	4-MeC_6H_4	67
		e	4-FC_6H_4	79
		f	4-ClC_6H_4	81
l	$Ph(CH_2)_2$	**g**	3-FC_6H_4	76
		h	4-ClC_6H_4	76

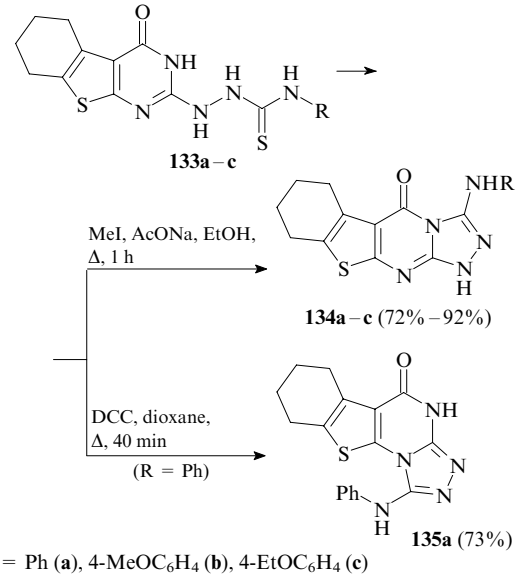
The reaction of 1-(6-oxo-1,6-dihydropyrimidin-2-yl)-4-arylthiosemicarbazides **130a**–**c** with iodomethane in the presence of sodium acetate gave fused 1,2,4-triazoles

131a–c.[110] In the author's opinion, the alkylation of the sulfur atom resulting in the formation of *S*-methyl derivatives occurs as the first reaction step followed by the intramolecular cyclization of these derivatives and elimination of the methanethiol molecule. The use of *N*,*N*′-dicyclohexylcarbodiimide (DCC) for the cyclization of thiosemicarbazide **130a** resulted in the formation of a mixture of regioisomeric fused 1,2,4-triazoles **131a** and **132a**, with the latter predominating.[111]



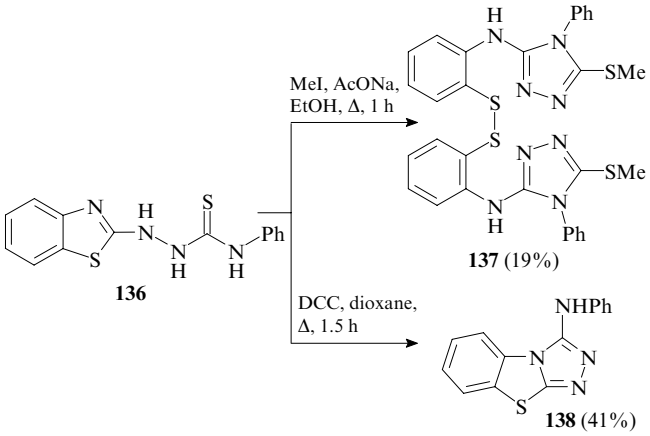
R = Ph (**a**), 4-MeOC$_6$H$_4$ (**b**), 4-EtOC$_6$H$_4$ (**c**)

Similar transformations of thiosemicarbazides **133a–c** containing the fused pyrimidine ring gave the corresponding regioisomeric fused triazoles **134a–c** and **135a**.[112]

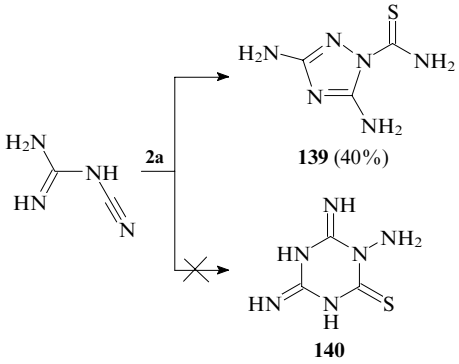


R = Ph (**a**), 4-MeOC$_6$H$_4$ (**b**), 4-EtOC$_6$H$_4$ (**c**)

However, the reaction of benzothiazolylthiosemicarbazide **136** with iodomethane gives bis-product **137** without elimination of methanethiol, whereas the reaction with DCC affords 3-anilino-1,2,4-triazolo[3,4-*b*]-1,3-benzothiazole **138**.[113]



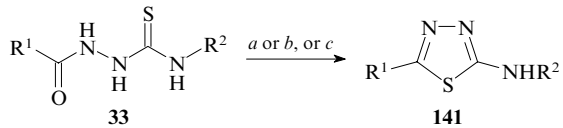
Chernyshev and co-workers[114] found that the reaction of thiosemicarbazide (**2a**) with *N*-cyanoguanidine in concentrated HCl yields 3,5-diamino-1-thiocarbamoyl-1,2,4-triazole (**139**) rather than 1,3,5-triazine **140**, as has been speculated earlier.[115]



As follows from the aforesaid, the reactions of thiosemicarbazides with carboxylic acids and their esters and the cyclization of 1-acylthiosemicarbazides are among the most facile routes to 1,2,4-triazole derivatives due to high yields of the target products, the availability of the reagents and the simplicity of the reactions.

2. 1,3,4-Thiadiazoles

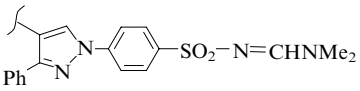
Like 1,2,4-triazole-5-thiones **121** (see Section III.1), 2-amino-1,3,4-thiadiazoles **141** can be synthesized by the cyclization of 1-acylthiosemicarbazides **33** [N(1),S-dinucleophiles] but in an acidic rather than in a basic medium (Table 6).[94–96, 103, 116, 117]



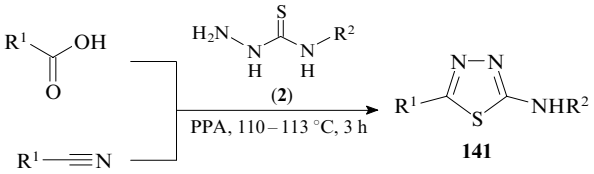
(*a*) H_2SO_4, 0 or 20 °C; (*b*) H_3PO_4, Δ; (*c*) $POCl_3$, Δ

A one-pot method was developed for the synthesis of thiadiazoles **141** (see Table 6) based on the condensation of thiosemicarbazides **2** with carboxylic acids or their nitriles in polyphosphoric acid (PPA).[91, 118]

Table 6. 2,5-Disubstituted-1,3,4-thiadiazoles **141**.

R^1	R^2	Yield (%)	Ref.
4-$ClC_6H_4SO_2(CH_2)_2$, 4-$BrC_6H_4SO_2CH_2$, 4-$MeC_6H_4S(CH_2)_2$, 4-$BrC_6H_4SCH_2$	H, Ph	76 – 95	91
Bn	H	87	91
2-HO-5-(2,4-$F_2C_6H_3$)C_6H_3	Me, Et, All, cyclo-C_6H_{11}, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$	46 – 94	94
Quinolin-2-yl	Et, All, cyclo-C_6H_{11}, Bn, Ph	63 – 67	95
4,5,6,7-Tetrahydro-1-benzothiophen-2-yl, 5-phenyl-2-thienyl	Et	43 – 80	96
5-Methyl-2(3*H*)-oxobenzo[*d*]oxazol-3-yl	Me, Et, Ph	47 – 93	103
$R_nC_6H_{5-n}OCH_2$ (R_n = H, 2-F, 2-Cl, 2-Br, 2-Me, 2-O_2N, 3-F, 3-Cl, 3-Br, 3-Me, 3-O_2N, 4-F, 4-Cl, 4-Br, 4-Me, 4-MeO, 4-O_2N, 2,3-Me_2, 2,4-Me_2, 3-Me-4-Cl)	H	49 – 58	116
Ph, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$O_2NC_6H_4$, 4-Py	Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 4-$NO_2C_6H_4$	38 – 92	117
3-R-Indazol-5(1*H*)-yl (R = H, Me, Et, Ph)	H	53 – 92	118
3-R-Isoquinolin-6-yl (R = H, Me)	H	59 – 76	118
2,3-Dihydrobenzo-1,4-dioxin-6-ylcarbonyl	Bu^t, Ph, 2-MeC_6H_4, 4-MeC_6H_4, 2,6-$Me_2C_6H_3$, 2,6-$Cl_2C_6H_3$	see [a]	119
Me, n-C_7H_{15}, n-C_9H_{19}, n-$C_{11}H_{23}$	H	83 – 93	120
2,4-$(HO)_2C_6H_3$	Me, 4-MeC_6H_4, 4-PhC_6H_4, 3-$CF_3C_6H_4$, 1-Naph	67 – 89	121
	Ph, 4-MeC_6H_4, 4-ClC_6H_4	60 – 63	84
4-$MeOC_6H_4$	H	6, 60	122, 123
Ph, 4-MeC_6H_4, 4-ClC_6H_4, 3-ClC_6H_4	H	62 – 70	123, 124
PhCH=CH	H	60	123
2-Furyl 5-nitro-, 1-methyl-5-nitroimidazol-2-yl, 5-nitro-2-thienyl	H	85 – 90	125

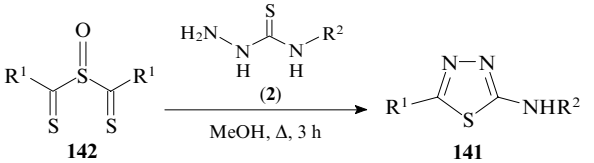
[a] The yields were not reported.



141

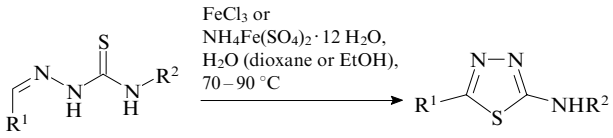
The cyclization reactions of thiosemicarbazide with acids in the presence of $POCl_3$ (Refs 118, 119) and under microwave radiation in the presence of acidic aluminium oxide proceed in a similar way.[120]

1,3,4-Thiadiazoles **141** were synthesized also by the reaction of sulfinylbis[(2,4-dihydroxy)methanethione] (**142**) with thiosemicarbazides **2** (see Table 6).[121]

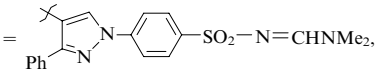


142 **141**

With the aim of preparing 1,3,4-thiadiazole derivatives **141**, the oxidative cyclization of thiosemicarbazones **88** and **97a – c** was investigated using the cyclizing agents $FeCl_3$ (Refs 84 and 122 – 124) or $NH_4Fe(SO_4)_2 \cdot 12\,H_2O$ (Ref. 125).



88, **97a – c** **141**

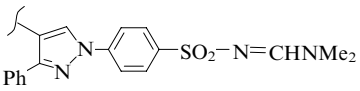
R^1 = Ar, R^2 = H (**88**); R^1 = 

R^2 = 4-XC_6H_4 [X = H (**97a**), Me (**97b**), Cl (**97c**)]

Thiosemicarbazones can also undergo various intramolecular cyclization reactions to form the thiadiazole ring.

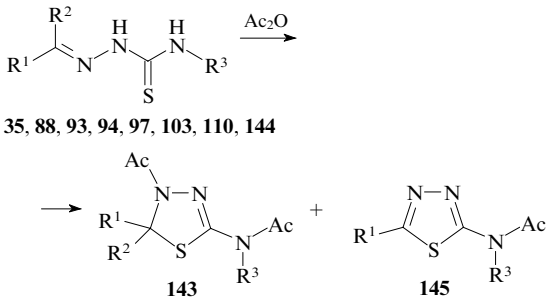
2-Acetylamino-1,3,4-thiadiazolines **143** (Table 7) can be synthesized by heating thiosemicarbazones of various aromatic and heterocyclic aldehydes (**88**, **93**, **94**, **97**, **103**, **110**) and ketones (**35**, **144**) in acetic anhydride; the reaction time varies from 10 – 30 min [126, 127] to 2 – 5 h.[83, 84, 128, 129] It should be noted that the reaction of pyridine-4-carbaldehyde thiosemicarbazone with acetic anhydride at 100 °C for 2 h affords a mixture of 2-acetylamino-4-acetyl-5-(4-pyridyl)-1,3,4-thiadiazoline (**143**) (37%) and 2-acetylamino-5-(4-pyridyl)-1,3,4-thiadiazole (**145**) (25%), whereas the reac-

Table 7. 2-Acetylamino-4-acetyl-4,5-dihydro-1,3,4-thiadiazoles **143**.

R^1	R^2	R^3	Yield (%)	Ref.
Ph	H	H	71	126
4-$MeOC_6H_4$, 4-BrC_6H_4, 4-$NO_2C_6H_4$	H	benzo-1,3-thiazol-2-yl	33–48	127
2-Fu, 2-furyl-5-methyl	H, Me	H	74–78	126
2-Furyl-5-nitro	H	H	72	126
3-Ethoxycarbonyl-5-furyl-2-methyl	H	H, Ph, 4-ClC_6H_4, 4-MeC_6H_4	69–87	83
4-Acetyl-5-methyl-1*H*-pyrrol-2-yl	H	H, Ph, 4-ClC_6H_4, 4-MeC_6H_4	55–68	83
	H	Ph, 4-ClC_6H_4, 4-MeC_6H_4	82–86	84
1*H*-1,2,4-Triazol-1-ylmethyl	4-RC_6H_4 (R = H, Cl, Br, Me, MeO)	H	73–79	128
Benzotriazol-1-ylmethyl	4-RC_6H_4 (R = H, Cl, Br, Me, MeO)	H	74–82	128
4-$MeOC_6H_4$, 2-Py, 3-Py, 4-Py (see [a]), 2-Th, 2-Fu, 3-Ind	H	H	40–98	129

[a] The yield is 37%; 2-acetylamino-5-(4-pyridyl)-1,3,4-thiadiazole **145** (25%) is formed as a by-product.

tion performed at 120 °C for 5 h gives exclusively thiadiazole **145** (63%).[129]

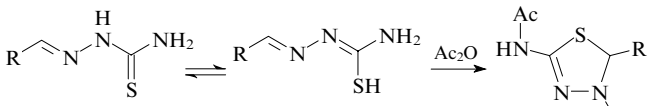


35, **88**, **93**, **94**, **97**, **103**, **110**, **144**

143 **145**

It was noted[126] that thiosemicarbazones, which are 1,5-ambiphiles, contain two terminal nucleophilic centres (the sulfur atom and the amide nitrogen atom) capable of being involved in the cyclization. The reactions of thiosemicarbazones of both aldehydes (**110**) and ketones (**144**) with acetic anhydride produce exclusively 1,3,4-thiadiazolines **143**, which is indicative of the higher nucleophilicity of the sulfur atom. The fact that the acylation of thiosemicarbazones is independent of the nature and structure of the arylidene moiety is, apparently, attributed to the participation of cyclic tautomer **146** in the cyclization. In the authors' opinion, the structure of the latter tautomer is confirmed by the acylation of the nitrogen atom (Scheme 5).

Larina *et al.*[129] hypothesized that thiosemicarbazones **88e** and **110a–f** are involved in the reaction in linear tautomeric form **88′e** and **110′a–f**, respectively. The addition of the SH group to the CH=N bond accompanied by the acetylation of the NH group of the ring and the NH_2 group at position 2 results in the formation of 4-acetyl-2-acetylamino-5-(het)aryl-1,3,4-thiadiazolines **143**.

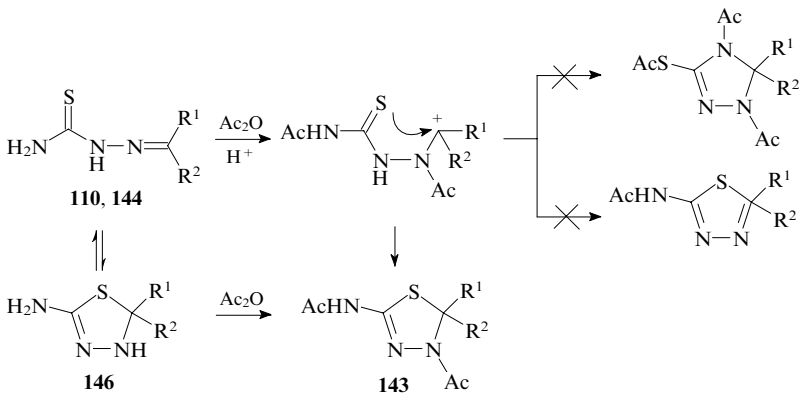


88e, **110a–f** **88′e**, **110′a–f** **143**

88e, **88e′**: R = 4-$MeOC_6H_4$;
110, **110′**: 2-Fu (**a**), 2-Th (**b**), 2-Py (**c**), 3-Py (**d**), 4-Py (**e**), 3-Ind (**f**)

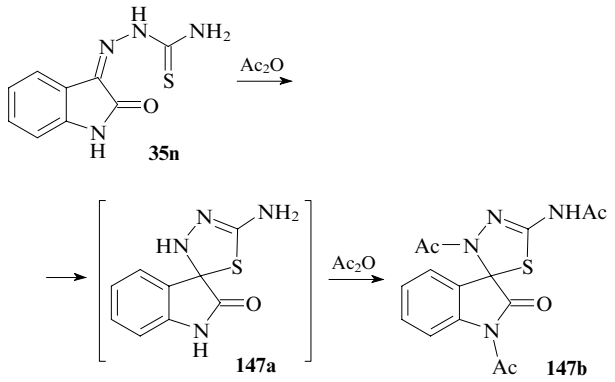
The reaction of isatin thiosemicarbazone **35n** with acetic anhydride at 115–120 °C for 4 h produced spirocyclic intermediate **147a**, and the acetylation of the latter gave 1,3′-diacetyl-5′-acetylaminospiro[indolo-3,2′-1,3,4-thiadiazol]-2(1*H*)-one (**147b**) in 74% yield.[129]

Scheme 5

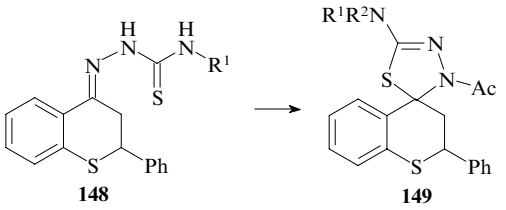


110, **144** **146** **143**

R^1 = H (**110**), Me (**144**); R^2 = Ph, 2-Fu, 2-furyl-5-methyl, 2-furyl-5-nitro



The spirocyclization of thioflavanone thiosemicarbazones **148** to spirothiadiazolines **149** was performed with the use of an acetic anhydride–pyridine or acetic anhydride–$ZnCl_2$ mixture as acetylating and cyclizing agents.[130, 131] The latter reaction gives a mixture of products **149** with $R^2 = H$ and $R^2 = Ac$, which can be separated by chromatography.

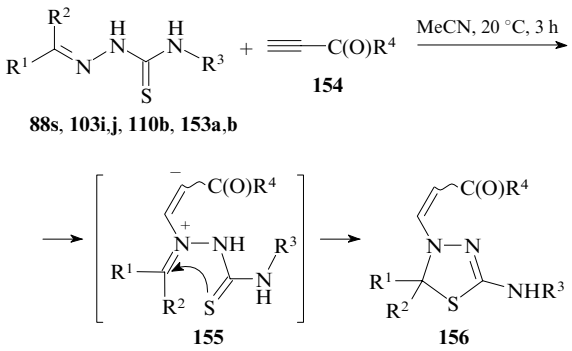


R^1	R^2	Conditions	Yield (%)
H	Ac	Ac_2O, PyH, 100 °C, 3 h	66
Ph	Ac	Ac_2O, PyH, 20 °C, 3 days	75
Ph	Ac	Ac_2O, $ZnCl_2$, 20 °C, 3 days	40
Ph	H	Ac_2O, $ZnCl_2$, 20 °C, 3 days	7

The heterocyclization of thiosemicarbazones of α,β-unsaturated carbonyl compounds **13a–h** was performed in pyridine in the presence of acetic anhydride at 50 °C for 4 h.[40, 132] The reaction is regioselective and is accompanied by the intramolecular nucleophilic attack of the sulfur atom on the carbon atom of the azomethine moiety without the involvement of the C=C double bond. This reaction affords thiadiazolines **150a–h**, unlike the cyclization in propan-2-ol in the presence of triethylamine, which gives pyrazolines **14** (see Ref. 40) (see Section II.1) (Scheme 6).

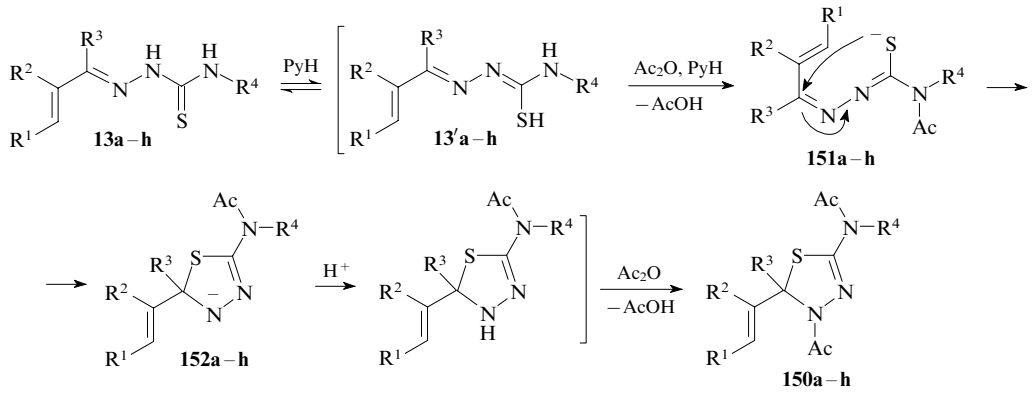
The reaction begins with the tautomeric transformation of the thione form of thiosemicarbazone **13** into thiol **13′** followed by the acylation of the latter at the amino group to form intermediate **151**. Compound **151** contains the activated nucleophilic centre at the sulfur atom and two electrophilic centres, *viz*., the carbon atom of the C=N bond and the β-carbon atom of the conjugated double bond. The attack of the lone pair of the sulfur atom on the C=N bond gives rise to structure **152**, which is stabilized through the addition of a proton. The subsequent acylation affords the final thiadiazoline **150**.

The reactions of thiosemicarbazones **88s**, **103i,j**, **110b** and **153a,b** with acylacetylenes **154** were performed with the aim of designing new antituberculosis agents. In the first step, the addition of the acetylene moiety to the thiosemicarbazone nitrogen atom N(1) gives rise to intermediate **155**, which easily undergoes cyclization to form 3-(2-acylvinyl)-5-amino-2*H*-1,3,4-thiadiazole (**156**) (Table 8).[133, 134]



R^1 = Ph, R^2 = H: R^3 = H (**88s**), Ph (**103i**);
R^1 = 2-Th, R^2 = H: R^3 = H (**110b**), Ph (**103j**);
$R^1–R^2 = (CH_2)_5$: R^3 = H (**153a**), Ph (**153b**); R^4 = 2-Th, Ph

Scheme 6



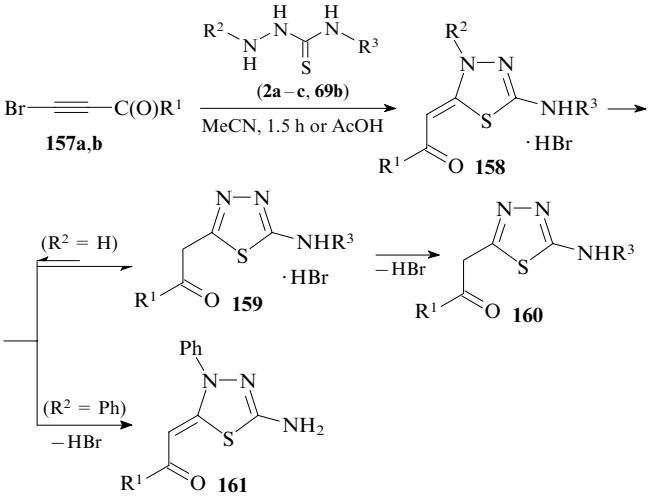
Compound	R^1	R^2	R^3	R^4	Yield of **150** (%)	Compound	R^1	R^2	R^3	R^4	Yield of **150** (%)
a	2-Fu	H	H	Me	63	**e**	2-Fu	H	Me	Ph	49
b	2-Fu	$(CH_2)_3$		H	59	**f**	Ph	$(CH_2)_4$		H	64
c	2-Fu	$(CH_2)_4$		H	62	**g**	2-ClC_6H_4	$(CH_2)_4$		H	51
d	2-Fu	$(CH_2)_5$		H	56	**h**	4-$MeOC_6H_4$	$(CH_2)_4$		H	56

Table 8. 3-(2-Acylvinyl)-5-amino-2-aryl(acylmethyl)-2*H*-1,3,4-thiadiazoles **156**.

R^1	R^2	R^3	R^4	Yield (%)	Ref.
Ph	H	Ph	Ph	97	133, 134
2-Th	H	H	Ph	94	133, 134
2-Th	H	H	2-Th	93	133, 134
$(CH_2)_5$		H	Ph	83	133, 134
$(CH_2)_5$		Ph	Ph	81	133, 134
$(CH_2)_5$		Ph	2-Th	81	133, 134
$(CH_2)_5$		H	2-Th	88	133, 134
$BzCH_2$	H	Ph	Ph	93	135
2-ThC(O)CH_2	H	Ph	2-Th	86	135

The reactions of acylacetylenes **154** with 4-phenylthiosemicarbazide **2c** in a ratio of 2 : 1 in methanol at room temperature produce 3-(2-acylvinyl)-2-acylmethyl-5-phenylamino-2*H*-1,3,4-thiadiazoles **156** ($R^1 = R^4 = BzCH_2$, 2-ThC(O)CH_2; $R^2 = H$, $R^3 = Ph$) in 67% – 78% yields. The higher yields were achieved when performing the reaction at −30 °C (see Table 8).[135]

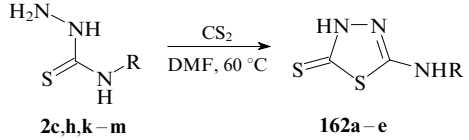
The condensation of 1-acyl-2-bromoacetylenes **157a**,**b** with thiosemicarbazides **2a – c** and **69b** generates 5-amino-2-aroylmethylidene-3*H*-1,3,4-thiadiazole hydrobromides **158**. 3-Unsubstituted thiadiazoles **158** are easily transformed into more stable thiadiazole hydrobromides **159** in 57% – 85% yields.



R^1 = 2-Th (**157a**), Ph (**157b**); R^2 = H: R^3 = H (**2a**), Me (**2b**), Ph (**2c**); R^2 = Ph, R^3 = H (**69b**)

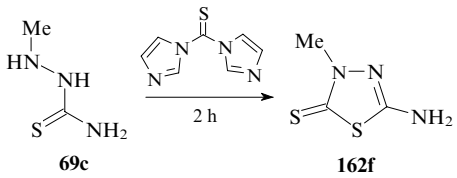
When heated in ethanol or aqueous ethanol (3 : 1) in the presence of triethylamine, hydrobromides **159** are transformed into free bases **160** (yields 71% – 85%).[136] Under these conditions, *N*-phenyl-substituted hydrobromides **158** (R^2 = Ph) form bases **161**.

4-Alkyl(phenyl)thiosemicarbazides **2c**,**h**,**k – m** react with carbon disulfide to give 5-amino-1,3,4-thiadiazole-2(3*H*)-thiones **162a – e** in yields up to 89%.[137]



R = Ph (**2c**, **162a**), Et (**2h**, **162b**), Bn (**2k**, **162c**), $Ph(CH_2)_2$ (**2l**, **162d**), $Ph(CH_2)_4$ (**2m**, **162e**)

5-Amino-3-methyl-1,3,4-thiadiazole-2(3*H*)-thione (**162f**) was synthesized by the reaction of 1,1′-thiocarbonyldiimidazole with thiosemicarbazide **69c** in anhydrous THF under a nitrogen flow.[137]

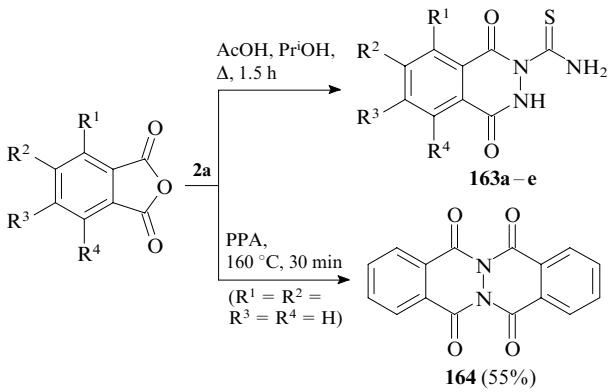


It should be noted that methods for the synthesis of five-membered heterocyclic compounds with two or three heteroatoms are being developed by many research groups in different countries with the aim of testing them for biological activity.

IV. Synthesis of six-membered rings with two heteroatoms

1. Pyridazines

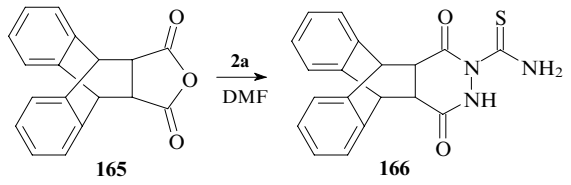
Unlike pyrazoles, pyridazines are rather rarely synthesized directly from thiosemicarbazide, which acts as a N(1),N(2)-dinucleophile in these reactions. The reactions of thiosemicarbazide (**2a**) with phthalic anhydrides[138, 139] in boiling propan-2-ol produce 1,4-dioxo-3,4-dihydrophthalazine-2(1*H*)-carbothioamides (**163a – e**) in good yields (69% – 75%), except for 5-nitro derivative **163e** (yield 37%).[138, 139] The cyclization with phthalic anhydride and 4-substituted thiosemicarbazides under reflux in acetic acid proceeds in a similar way.[140]



163: $R^1 = R^2 = R^3 = R^4$ = H (**a**); $R^1 = R^4$ = H, $R^2 = R^3$ = F (**b**); $R^1 = R^4$ = F, $R^2 = R^3$ = H (**c**); $R^1 = R^2 = R^3$ = H: R^4 = F (**d**), NO_2 (**e**)

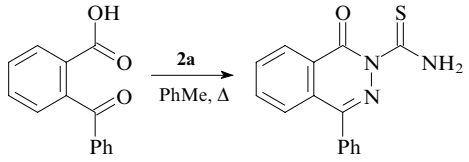
Under more drastic conditions (polyphosphoric acid, 160 °C), the reaction gives phthalazino[2,3-*b*]phthalazine-5,7,12,14-tetraone (**164**) as a result of the condensation of thiosemicarbazide with two phthalic anhydride molecules.[138]

The cyclization of annulated furan-2,5-dione **165** with thiosemicarbazide (**2a**) resulting in the formation of thiocarbamoylphthalazine **166** was described by Khalil *et al.*[141] as one of the steps in the multistep synthesis of 1,3-thiazole derivatives exhibiting antibacterial activity.



165 **166**

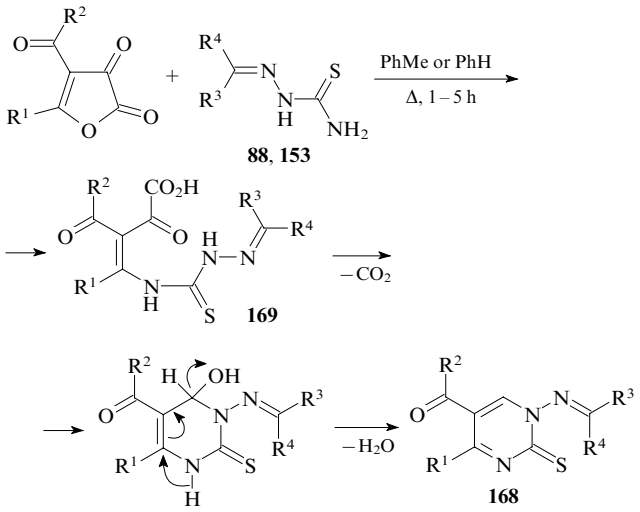
1-Oxo-4-phenylphthalazine-2(1*H*)-carbothioamide (**167**) was synthesized by the condensation of thiosemicarbazide with 2-benzoylbenzoic acid.[142]



167 (88%)

2. Pyrimidines

A method for the synthesis of 1-methylideneaminopyrimidine-2-thiones **168** was developed based on the reaction of thiosemicarbazones **88** and **153** [N(2),N(4)-dinucleophiles] with furan-2,3-diones (Table 9).[143–146]



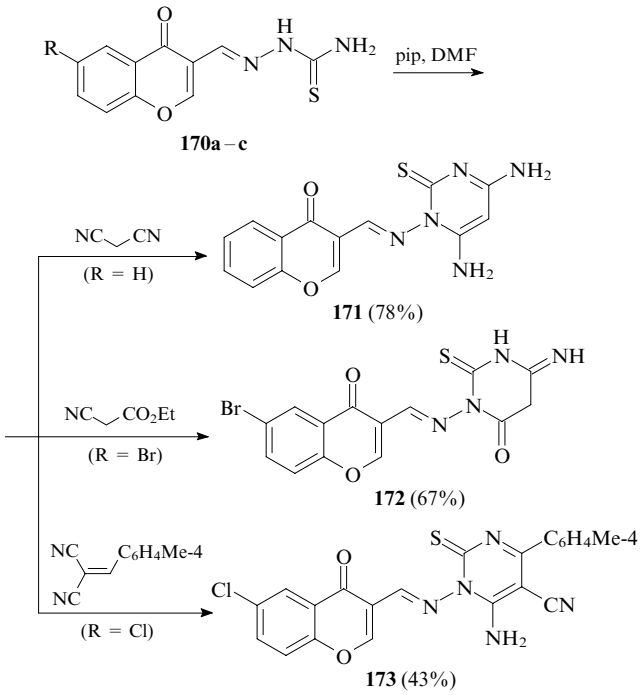
R^4 = H, R^3 = Ar (**88**); R^3 = Alk, R^4 = Ar; R^3–R^4 = cyclo-Alk (**153**)

Table 9. 1-(Methylideneamino)pyrimidine-2-thiones **168**.

R^1	R^2	R^3	R^4	Yield (%)	Ref.
Ph	Ph	H	Ph	35	143
	Ph	Me	Ph	33, 34	143, 144
	Ph	Ph	Ph	60	143
	Ph	Me	Me	34	143
	Ph	$(CH_2)_5$		30	143
	Ph	Me	Et	48	143
	Ph	Me	Bu^i	68	143
	Ph	H	4-ClC_6H_4	45	145
	EtO	H	4-$Me_2NC_6H_4$	40	145
4-$MeOC_6H_4$	4-$MeOC_6H_4$	Me	Ph	45	146
	4-$MeOC_6H_4$	H	4-$MeOC_6H_4$	40	146
	4-$MeOC_6H_4$	H	Ph	55	146
	4-$MeOC_6H_4$	Me	4-$MeOC_6H_4$	33	146

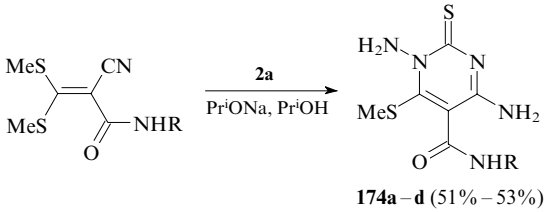
Akcamur *et al.*[143] suggested that the reaction begins with the Michael-like nucleophilic attack of the NH_2 group of thiosemicarbazone on position 5 of the furan ring. The ring opening, the decarboxylation of intermediate α-oxocarboxylic acid **169** followed by the cyclization through the addition of the NH group of the hydrazine moiety to the C=O bond and, finally, the elimination of a water molecule result in the formation of pyrimidinethiones **168**.

The reactions of thiosemicarbazones **170a–c**[147] and thiosemicarbazide **2a**[148] with nitriles under reflux in DMF in the presence of piperidine and in propan-2-ol in the presence of sodium isopropoxide were investigated. The condensation of compound **170a** with malononitrile yields 3-[(4,6-diamino-2-thioxo-2*H*-pyrimidinoimino)-methyl]chromen-4-one (**171**). The reaction of thiosemicarbazone **170b** with ethyl cyanoacetate gives pyrimidinone derivative **172**. Pyrimidinecarbonitrile **173** was synthesized from carbazone **170c** and 4-methylbenzylidenemalononitrile.



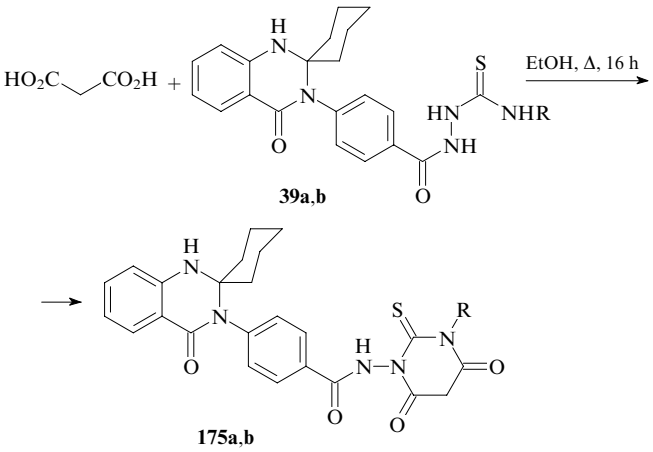
R = H (**a**), Br (**b**), Cl (**c**); pip is piperidine

Thioacetals of α-cyano ketones react with thiosemicarbazide **2a** to form pyrimidinethiones **174a–d**.[148]



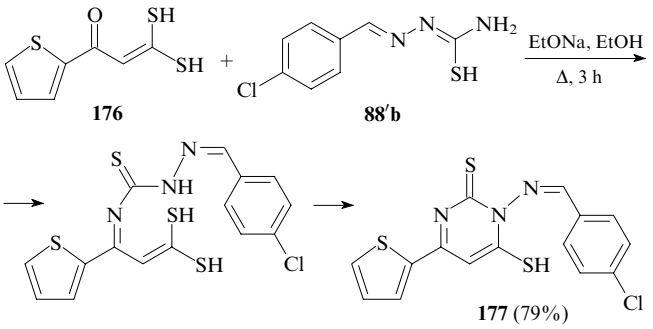
174: R = Ph (**a**), 4-MeC_6H_4 (**b**), 4-ClC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**)

The cyclization of compounds **39a**,**b** with malonic acid under reflux in ethanol gives 4,6-dioxopyrimidine-2-thiones **175a**,**b**.[68]

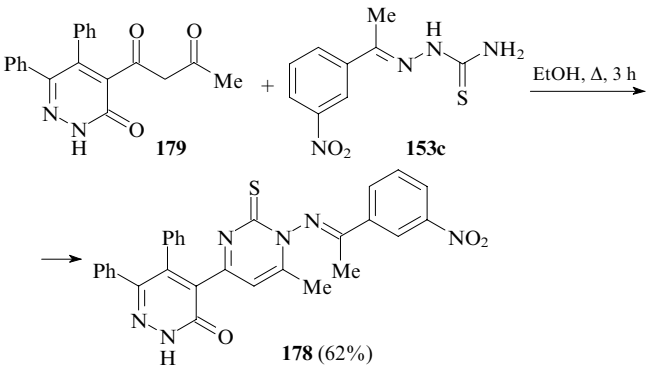


R = Ph (**a**, 73%), cyclo-C_6H_{11} (**b**, 60%)

The reaction of thiosemicarbazone **88′b** with 3,3-disulfanyl-1-(2-thienyl)prop-2-en-1-one (**176**) proceeds only in the presence of a strong base (sodium ethoxide) and gives 6-(2-thienyl)dihydropyrimidine-2,4-thione **177**.[149]



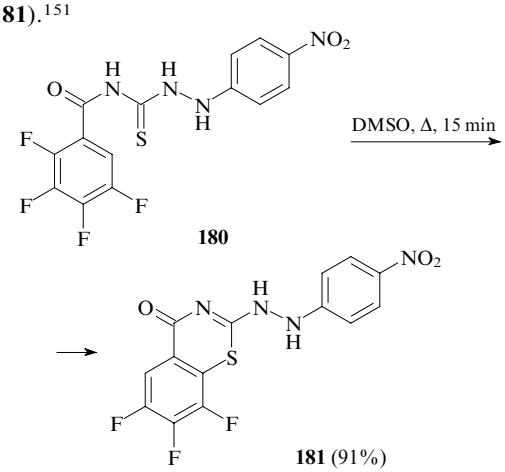
Pyrimidinethione **178** was synthesized in moderate yield from thiosemicarbazone **153c** and pyridazine-containing 1,3-diketone **179**.[150]



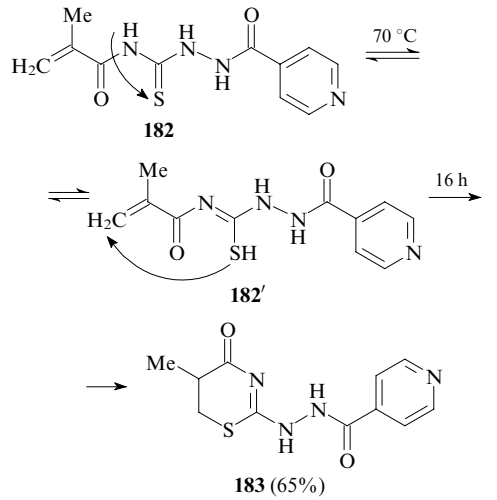
To summarize, condensation reactions of thiosemicarbazides and thiosemicarbazones with furan-2,3-diones, 1,3-dicarboxylic acids and their esters, nitriles, as well as with 1,3-diketones, are widely used for the synthesis of pyrimidine derivatives.

3. 1,3-Thiazines

To synthesize 1,3-thiazines, it is necessary that thiosemicarbazide derivatives behave as N(4),S-dinucleophiles. Due to the presence of reactive groups in substituents at the thiosemicarbazide nitrogen atoms, 4-(4-nitrophenyl)-1-(2,3,4,5-tetrafluorobenzoyl)thiosemicarbazide (**180**) can be subjected to intramolecular cyclization to 2-[2-(4-nitrophenyl)hydrazino]-6,7,8-trifluoro-4*H*-1,3-benzothiazin-4-one (**181**).[151]

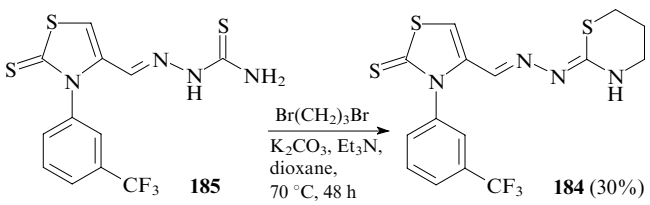


The prolonged heating of 4-methacryloylthiosemicarbazide **182** in propan-2-ol facilitates the formation of 5,6-dihydro-4*H*-1,3-thiazine **183**.[152]

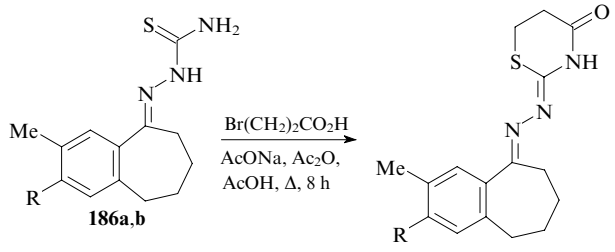


The addition of an equimolar amount of cyclic secondary amine (morpholine, piperidine) or an alkaloid (anabasine, cytisine) gives rise not to the expected addition products at the double bond of the methacryloyl moiety of compound **182** but to thiazine **183** in 82% yield. Apart from an increase in the yield of product **183**, the reaction time substantially decreases and the temperature can be reduced to 30 °C.[153] It was hypothesized that the presence of a base (secondary amine) in the reaction mixture facilitates the formation of the tautomeric thiol form of thiosemicarbazide **182′** necessary for the cyclization.

1,3-Thiazinane **184** was prepared by the alkylation of thiosemicarbazone **185** with 1,3-dibromopropane.[154]



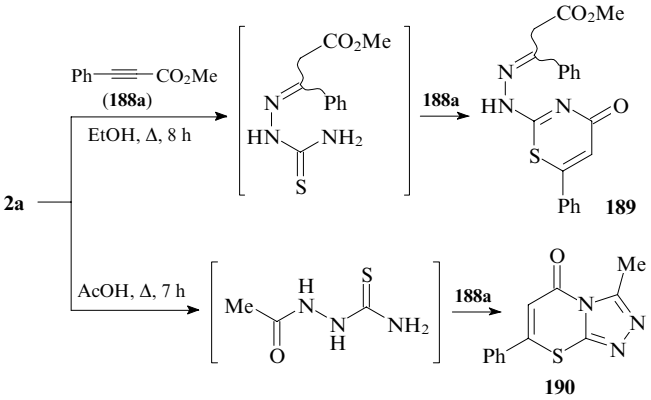
The reactions of derivatives **186a**,**b** with the use 3-bromopropionic acid as the alkylating agent[155] give 1,3-thiazinan-4-ones **187a**,**b**.



186a,b **187a,b**

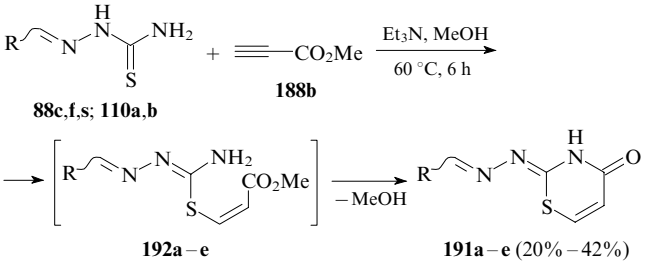
R = H (**a**, 66%), Me (**b**, 68%)

Thiosemicarbazide (**2a**) reacts with two methyl phenylpropiolate molecules (**188a**) under reflux in ethanol to form thiazine **189**. In acetic acid, the condensation with ester **188a** occurs only at the thioamide group to form triazolothiazine **190** due to the acylation of thiosemicarbazide.[156]



189 **190**

Thiosemicarbazones of aromatic (**88**) and heteroaromatic aldehydes (**110**) undergo cyclization with methyl propiolate (**188b**) to give 3*H*-1,3-thiazin-4-one **191a–e**.[157] The reaction proceeds through the formation of intermediate addition products **192a–e**, two of which (compounds **192a,b**) were isolated from the reaction mixture in 23%–35% yields.



88c,f,s; 110a,b **188b** **192a–e** **191a–e** (20%–42%)

R = Ph (**88s**, **191a**, **192a**), 4-BrC$_6$H$_4$ (**88c**, **191b**, **192b**), 4-O$_2$NC$_6$H$_4$ (**88f**, **191c**, **192c**), 2-Fu (**110a**, **191d**, **192d**), 2-Th (**110b**, **191e**, **192e**)

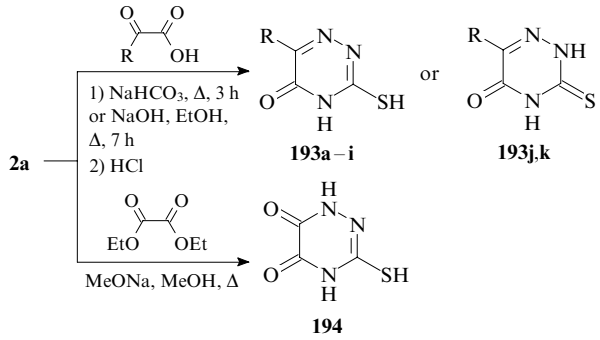
Therefore, the main methods for the synthesis of 1,3-thiazine derivatives are based on the cyclization of functionalized thiosemicarbazides and the reactions of thiosemicarbazides with such electrophiles as 1,3-dibromopropane, bromopropionic acid and acetylenecarboxylic acid esters.

V. Synthesis of six-membered rings with three heteroatoms

1. 1,2,4(1,3,5)-Triazines

The condensation reactions of thiosemicarbazide with α-difunctional compounds afford 3-thioxo(sulfanyl)-1,2,4-triazine or 2-amino-1,3,4-thiadiazine derivatives depending on the role played by thiosemicarbazide [N(1),N(4)- or N(1),S-dinucleophile].

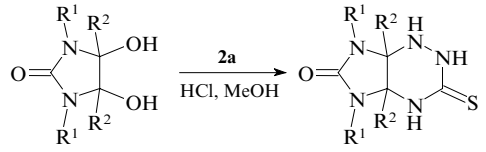
The condensation of α-keto carboxylic acids with thiosemicarbazide (**2a**) in an alkaline medium gives 6-alkyl(aryl)-3-sulfanyl(thioxo)-4,5-dihydro-1,2,4-triazin-5-ones **193a–i** (Ref. 158) or **193j,k** (Ref. 159) in 67%–85% yields. The reaction of thiosemicarbazide with diethyl oxalate produces 3-sulfanyl-1,4,5,6-tetrahydro-1,2,4-triazine-5,6-dione (**194**) in 19% yield.[158]



193a–i **193j,k** **194**

193: R = Me (**a**), Pr^i (**b**), Bu^i (**c**), Bu^t (**d**), Bn (**e**), Ph (**f**), 4-MeOC$_6$H$_4$ (**g**), 2-H$_2$NC$_6$H$_4$ (**h**), 2-furfuryl (**i**), 4-ClC$_6$H$_4$ (**j**), 4-BrC$_6$H$_4$ (**k**)

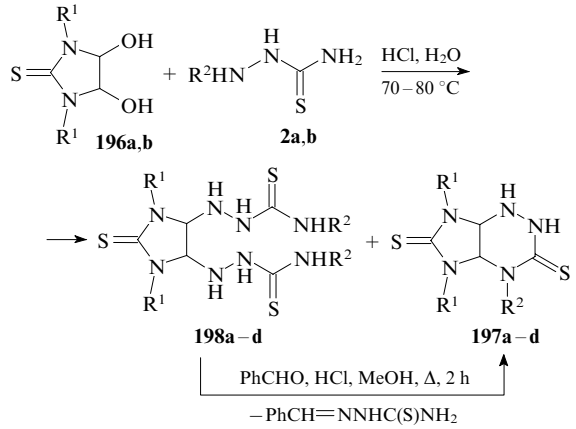
Imidazotriazines **70a–c** were synthesized in high yields by the α-ureidoalkylation of thiosemicarbazide (**2a**) with 4,5-dihydroxyimidazolidin-2-ones (**195a–c**) under acid catalysis conditions.[160, 161]



195a–c **70a–c** (90%–96%)

70, **195**: R^1 = Me: R^2 = Ph (**a**), H (**b**); R^1 = Et, R^2 = H (**c**)

The similar reaction of thiosemicarbazide with 4,5-dihydroxyimidazolidine-2-thiones **196a,b** gives rise to imidazotriazines **197a–d** in low yields (2%–15%). This reaction affords 4,5-disubstituted imidazolidin-2-ones **198a–d** as the major products of α-thioureidoalkylation of thiosemicarbazide.[162, 163]



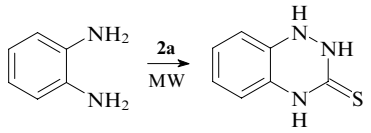
196a,b **2a,b** **198a–d** **197a–d**

R^1 = Me (**196a**), Et (**196b**); R^2 = H (**2a**), Me (**2b**); **197**, **198**: R^2 = H: R^1 = Me (**a**), Et (**b**); R^2 = Me: R^1 = Me (**c**), Et (**d**)

An alternative method for the synthesis of imidazotriazines **197a,b** in higher yields (55%–63%) is based on the

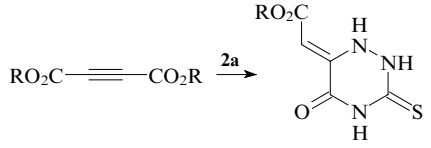
reaction of compounds **198a**,**b** with benzaldehyde in boiling methanol in the presence of HCl.[69] This reaction yields also benzaldehyde thiosemicarbazone.

In recent years, the microwave radiation of reactants in the solid phase has given a new impetus to investigations of numerous well-known reactions. For example, 1,2-dihydrobenzo[*e*]-1,2,4-triazine-3(4*H*)-thione (**199**) was prepared by the microwave-induced solid-state synthesis. The condensation of *o*-phenylenediamine with thiosemicarbazide proceeds within 5–6 min and gives triazine **199** in 70% yield.[164] The method used earlier required prolonged heating (5 h) and gave the product in 48% yield.[165]



199 (70%)

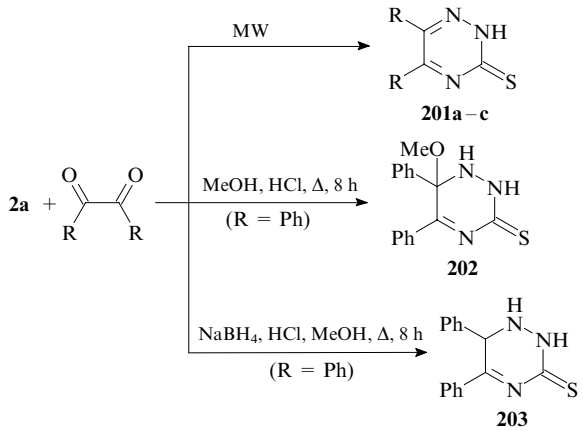
Heravi *et al.*[166] showed that thiosemicarbazide **2a** reacts with acetylenedicarboxylic acid esters to form 6-alkoxycarbonylmethylidene-3-thioxo-1,2,4-triazinan-5(4*H*)-ones (**200a**,**b**) both under solvent-free microwave heating for 9 min and under reflux in MeOH or EtOH for 20–30 min, whereas the reaction of the same reactants in dichloromethane at 0 °C affords 1,3-thiazolidines **63**.[76] The yields of compounds **200a**,**b** in the solid-state reaction are 85%–89%, whereas the reaction under reflux in alcohols are 76%–80%.[166]



200a,**b**

200: R = Me (**a**), Et (**b**)

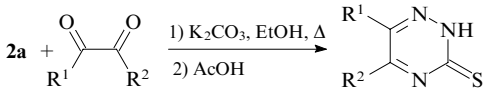
The microwave solid-state synthesis of 3-thioxo-1,2,4-triazines **201a–c** from thiosemicarbazide and α-diketones gives products in 89%–93% yields already within 6–7 min.[166]



201: R = Ph (**a**), Me (**b**), H (**c**).

Thiosemicarbazide (**2a**) reacts with benzil under reflux in methanol to form 5-methoxy derivative **202** in 73% yield. In the presence of $NaBH_4$, the reaction product is reduced to 1,6-dihydro-1,2,4-triazine-3(2*H*)-thione **203** in 95% yield.[167]

The ability of heterocyclic α-diketones **204a–c** to undergo condensation with thiosemicarbazide at ambient and elevated pressure was investigated.[168, 169] The heterocyclization of bis(thienyl) derivative **204a** under ambient pressure is completed within 30 min to give triazine **205a** in 93% yield,[168] whereas the yield of triazine **205b** in the reaction of unsymmetrical diketone **204b** under the same conditions is 74% after 48 h.[169]



204a–c **205a**,**b**

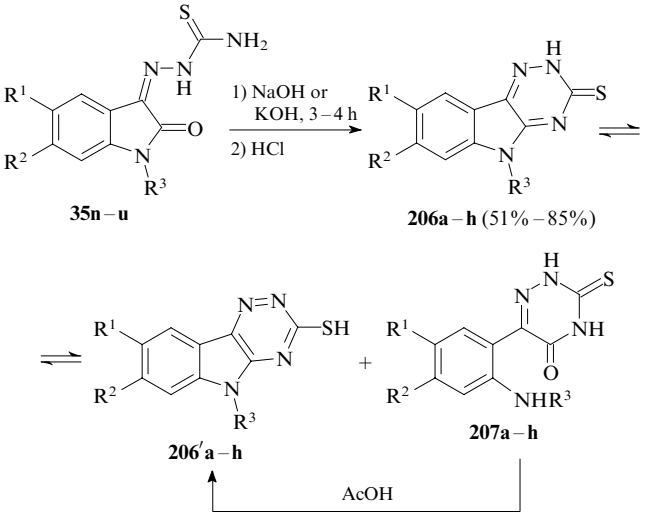
204, **205**: $R^1 = R^2$ = 2,5-dimethyl-3-thienyl (**a**); R^1 = 2,5-dimethyl-3-thienyl, R^2 = 3-Ind (**b**); $R^1 = R^2$ = 3-Ind (**c**)

The high-pressure reaction proceeds more rapidly and gives product **205b** in higher yield:

Pressure /MPa	Time /h	Yield of triazine **205b** (%)
500	2	60
1000	2	78
1000	6	94

Due to the different reactivities of the carbonyl groups in diketone **204b,** only one isomer of triazinethione **205b** was obtained. The condensation of bis(indolyl)ethanedione **204c** with thiosemicarbazide occurs neither at ambient nor at elevated pressure.[169]

One of approaches to the synthesis of fused 1,2,4-triazines is based on the cyclization of isatin thiosemicarbazones. Triazinoindoles **206a–h** were synthesized from compounds **35n–u** under reflux in aqueous alkali.[170–173]



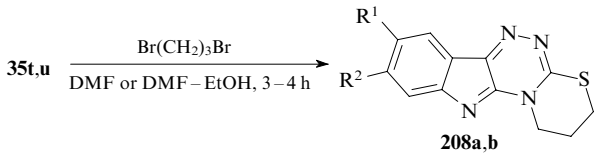
35n–u **206a–h** (51%–85%)

206′a–h **207a–h**

Compound **35**	Compounds **206**, **206′**, **207**	R^1	R^2	R^3	Ref.
n	**a**	H	H	H	170, 171
o	**b**	Br	H	H	170
p	**c**	H	H	Me	170
q	**d**	Me	H	H	170
r	**e**	MeO	H	H	170
s	**f**	NH_2	H	H	170
t	**g**	H	Me	H	172
u	**h**	Pr^i	H	H	173

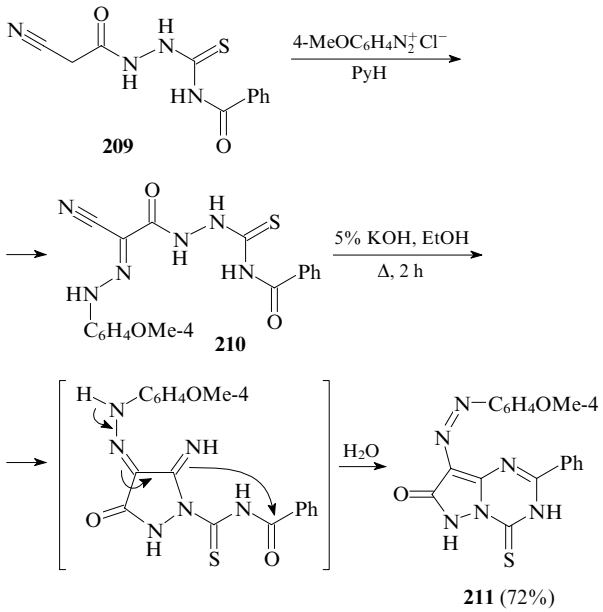
The reaction may be accompanied by the partial opening of the indole ring. The resulting compounds **207a–h** undergo cyclization to triazinoindoles **206a–h** upon heating in acetic acid.[170] Compounds **206** exist predominantly as thiones rather than as thiols **206′**.[170, 172, 173]

Thiazinotriazinoindoles **208a,b** were synthesized by heating thiosemicarbazones **35t,u** (R^3 = H) with 1,3-dibromopropane in DMF.[172, 173]

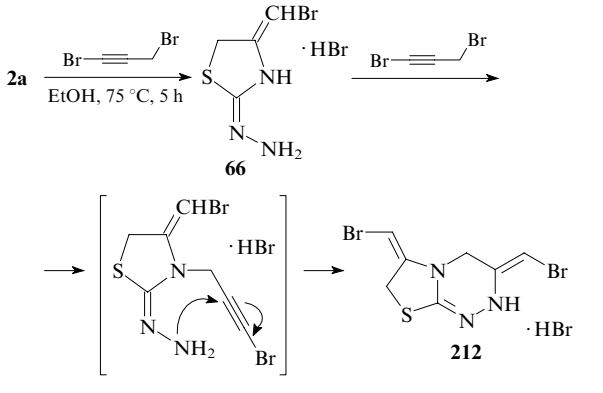


R^1 = H, R^2 = Me (**a**, 35%); R^1 = Pr^i, R^2 = H (**b**, 85%)

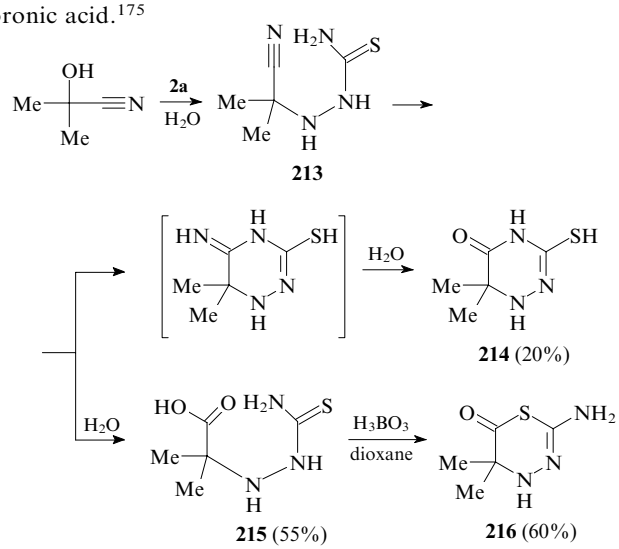
The condensation of 4-benzoyl-1-cyanoacetylthiosemicarbazide **209** with 4-methoxyphenyldiazonium chloride affords (arylhydrazono)acetylthiosemicarbazide **210**, which is subjected to the intramolecular cyclization in the presence of an aqueous KOH solution to form pyrazolo[1,5-*a*]-1,3,5-triazine **211**.[174]



Volkova *et al.*[77] showed that the reaction of thiosemicarbazide (**2a**) with two equivalents of 1,3-dibromopropyne does not stop at the formation of 1,3-thiazolidine **66** and gives thiazolotriazine **212** as a result of condensation with the second 1,3-dibromopropyne molecule.



The reaction of acetone cyanohydrin with thiosemicarbazide in an aqueous medium performed under heating affords 2-methyl-2-thiosemicarbazidopropanoic acid nitrile (**213**). The latter either undergoes cyclization to 5-imino-6,6-dimethyl-3-sulfanyl-1,2,4-triazine, which is hydrolyzed to 6,6-dimethyl-3-sulfanyl-1,2,4-triazin-5-one (**214**) (yield 20%), or is directly hydrolyzed to form 2-methyl-2-thiosemicarbazidopropanoic acid (**215**) (yield 55%). An attempt to perform the cyclization of acid **215** in an aqueous medium failed, and 2-amino-5,5-dimethyl-1,3,4-thiadiazin-6-one (**216**) was obtained after heating in dioxane with boronic acid.[175]

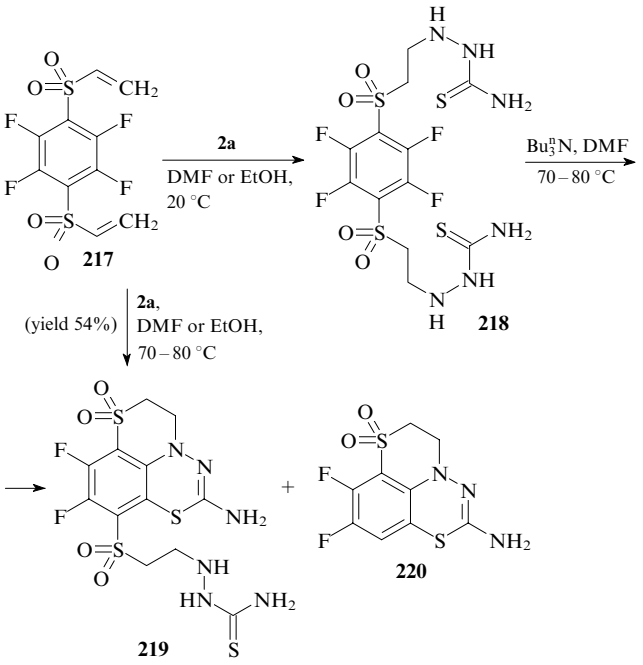


It should be noted that the well-known reactions of thiosemicarbazides with α-dicarbonyl compounds, acetylenedicarboxylic acid esters, producing 1,2,4-triazine derivatives have been further developed in recent years due to the application of microwave-induced solid-state synthesis or high-pressure synthesis.

2. 1,3,4-Thiadiazines

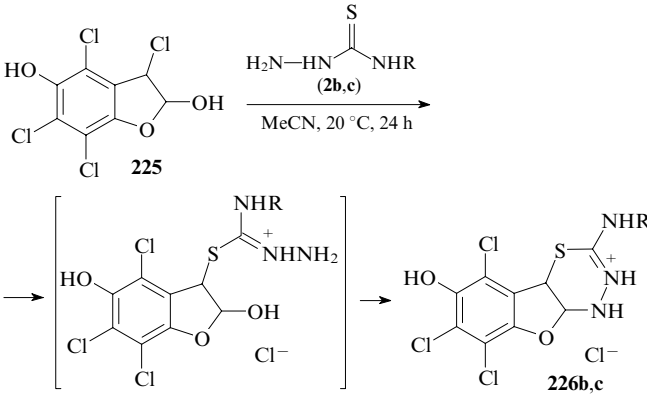
Functionalized polyfluorobenzenes are convenient synthons for the synthesis of fluorine-containing fused thiadiazines. In these reactions, thiosemicarbazide derivatives act as N(1),S-dinucleophiles.

The reaction of 3,6-bis(vinylsulfonyl)-1,2,4,5-tetrafluorobenzene (**217**) with thiosemicarbazide (**2a**) taken in a ratio of 1 : 2 and 1 : 4 in DMF and ethanol at 20 °C and 70–80 °C was investigated.[176] At 20 °C, the reaction with the use of a twofold molar excess of thiosemicarbazide both in DMF and ethanol affords the nucleophilic addition product, *viz.*, 3,6-bis(2-thiosemicarbazidoethylsulfonyl)-1,2,4,5-tetrafluorobenzene (**218**), in 70% and 77% yields, respectively. An increase in the temperature to 75–80 °C and the use of a fourfold excess of thiosemicarbazide results in the formation of fused heterocyclic compound **219** in 54% yield. The formation of benzothiazinothiadiazine **219** begins with the addition of NH_2 groups at position 1 of thiosemicarbazide to both activated double bonds of vinylsulfonylfluorobenzene **217** to give product **218**. This step is followed by the intramolecular replacement of the fluorine atoms by one of thiosemicarbazide moieties (by the NH group in the *ortho* position and by the sulfur atom in the *meta* position). When heated in DMF at 70–80 °C in the presence of a threefold excess of a strong base (Bu^n_3N), compound **218** forms fused heterocyclic compounds **219** and **220** in 81% and 18% yields, respectively.[176–178]



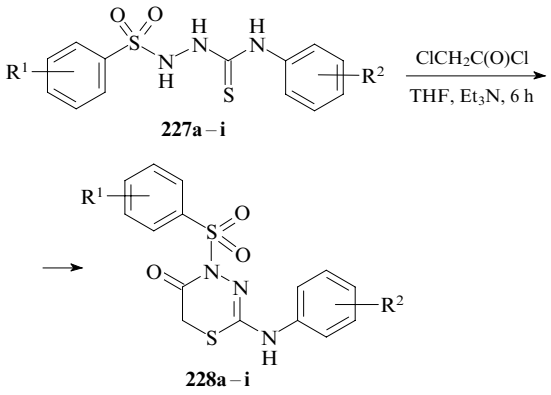
Another example of this type of cyclization was described for 3-thiosemicarbazido-2-polyfluorobenzoyl acrylates **221a**,**b**, which were prepared by the reaction of 2-polyfluorobenzoyl acrylates **222a**,**b** with 4-cyclohexylthiosemicarbazide (**2n**). Under reflux in toluene, acrylates **221a**,**b** form thiadiazinoquinolines **223a**,**b** in 60% and 37% yields, respectively (Scheme 7).[179] In another study,[180] intermediate quinoline **224b** was isolated (yield 79%) in the reaction performed under heating in ethanol and it was transformed into product **223b** in 74% yield.

The cyclization of dihydrobenzofuran **225** with 4-methyl(phenyl)thiosemicarbazides **2b**,**c** produces salts **226b**,**c**.[181]



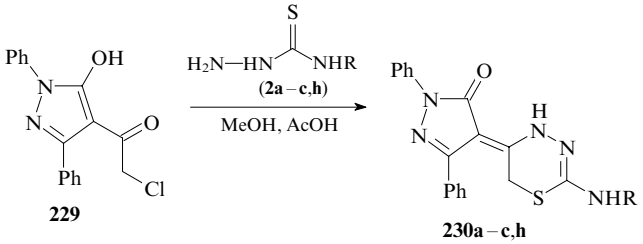
R = Me (**b**, 61%), Ph (**c**, 90%)

The condensation of 1-aryl-4-arylsulfonylthiosemicarbazides **227a**–**i** with chloroacetyl chloride gives 2-arylamino-4-arylsulfonyl-4*H*-1,3,4-thiadiazin-5(6*H*)-ones **228a**–**i**.[182]



Compound	R^1	R^2	Yield (%)
a	4-Me	H	40
b	4-Me	2-Me	89
c	4-Cl	H	86
d	4-Cl	2-Me	82
e	4-Cl	3-Cl	83
f	2-Cl	2-Me	85
g	4-NO_2	H	66
h	4-NO_2	2-Me	80
i	4-NO_2	3-Cl	75

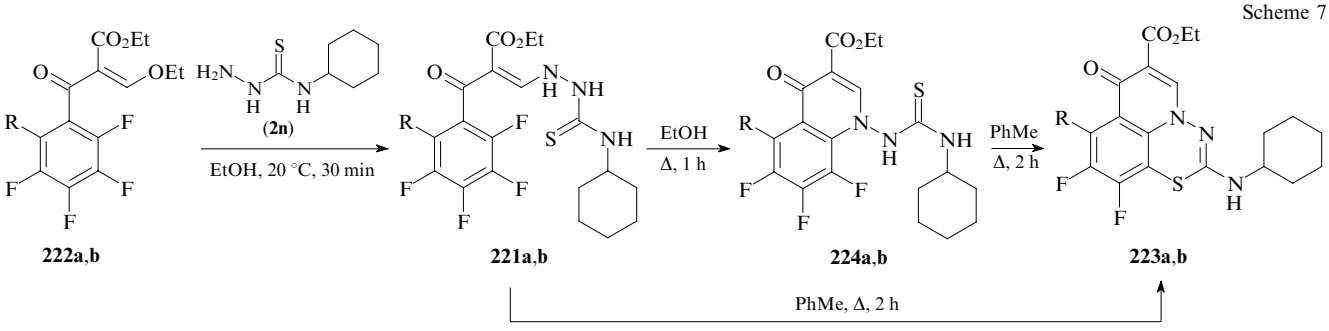
The reaction of thiosemicarbazides with α-halocarbonyl compounds, which was used for the first time by Bose in 1925 for the synthesis of 1,3,4-thiadiazines, is still employed.[183–185] The reaction of 2-chloro-1-(5-hydroxy-1,3-diphenyl-1*H*-pyrazol-4-yl)ethanone (**229**) with thiosemicarbazides **2a**–**c**,**h** performed under heating in methanol gives thiadiazines **230a**–**c**,**h** in high yields (80%–85%).[183]



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

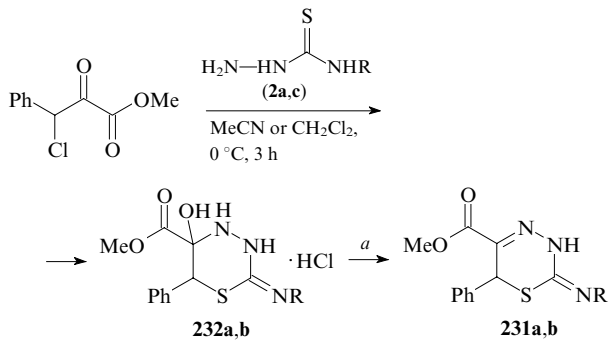
The condensation of methyl 3-chloro-2-oxo-3-phenylpropionate with thiosemicarbazides **2a**,**c** produces 1,3,4-thiadiazines **231a**,**c**. The reaction performed in the absence of an acid or a base made it possible to isolate stable

Scheme 7



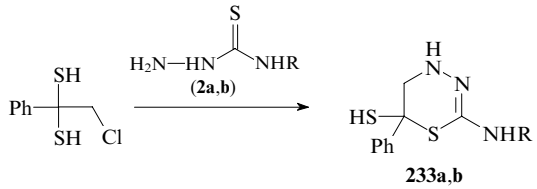
221–**224**: R = H (**a**), F (**b**)

intermediates, *viz*., 5-hydroxy-1,3,4-thiadiazinane-2-imines **232a**,**b**.[184, 185]



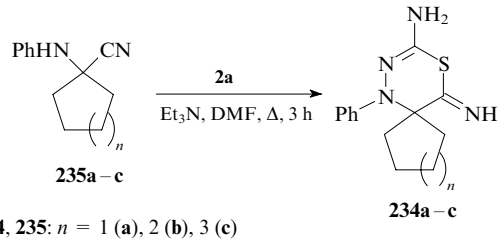
R = H (**a**, 85%), Ph (**b**, 100%); (*a*) 1) CF_3CO_2H, MeCN, 55–60 °C, 1 h; 2) 0.5% $NaHCO_3$, 2 h or 5% $NaHCO_3$

2-Amino-6-phenyl-5,6-dihydro-4*H*-1,3,4-thiadiazine-6-thiols (**233a**,**b**) were synthesized by the reaction of 2-chloro-1-phenylethane-1,1-dithiol with thiosemicarbazides **2a**,**b** in anhydrous methanol at −5 °C.[186]



R = H (**a**, 59%), Me (**b**, 64%)

Spirocyclic cycloalkanethiadiazines **234a**–**c** were synthesized by the condensation of cycloalkanecarbonitriles **235a**–**c** with unsubstituted thiosemicarbazide.[187]

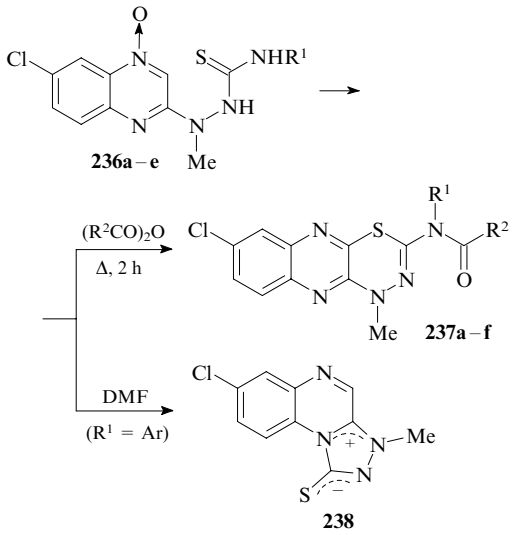


234, **235**: *n* = 1 (**a**), 2 (**b**), 3 (**c**)

The selectivity of the cyclization of 2-(thiosemicarbazido)quinoxaline 4-oxides **236a**–**e** was investigated in a mixture of dioxane and trifluoroacetic anhydride, in acetic anhydride and dimethylformamide. It was found that the reactions of compounds **236a**–**e** with trifluoroacetic anhydride give 4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxalines **237a**–**e**, whereas the cyclization with acetic anhydride proceeds only with methyl derivative **236e** to form thiadiazinoquinoxaline **237f**.[188, 189] Mesoionic triazolo[4,3-*a*]quinoxaline **238** is formed from aryl derivatives **236a**–**c** under reflux in DMF (Scheme 8).[188]

On the whole, the reactions of thiosemicarbazides with fluorobenzenes, derivatives of α-chlorocarboxylic acids and ketones serve as convenient methods for the synthesis of 1,3,4-thiadiazine derivatives. However, these reactions require the careful selection of the reaction conditions (temperature, solvent, catalyst).

Scheme 8



Compound **236**	Compound **237**	R^1	R^2	Yield (%)	
				237	**238**
a	**a**	Ph	CF_3	83	32
b	**b**	4-ClC_6H_4	CF_3	61	63
c	**c**	4-BrC_6H_4	CF_3	53	51
d	**d**	Bn	CF_3	38	
e	**e**	Me	CF_3	88	
	f	Me	Me	81	

* * *

The data presented in this review provide convincing evidence that thiosemicarbazides are unique synthons for the synthesis of various nitrogen- and sulfur-containing heterocyclic compounds. Despite the fact that, due to the presence of several nucleophilic centres, it is difficult to predict the structures of condensation products of new thiosemicarbazide derivatives, the cyclization reactions are generally regioselective. Hence, these reactions can be used for the synthesis of desired compounds. It should be noted that the publications concerning reactions of thiocarbohydrazides, which can be considered as 4-aminothiosemicarbazides containing one more reactive nucleophilic centre, are beyond the scope of the present review, because a large review has been published recently,[190] where the employment of thiocarbohydrazide in the synthesis of heterocyclic compounds is considered.

The chemistry of thiosemicarbazide is far from being exhausted. The prospects of the practical application, primarily, in medicine, give impetus to the development of methods for the synthesis of cyclic thiosemicarbazide derivatives and procedures for their modifications.

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