Synthesis of heterocyclic compounds based on oxamic acid monothiooxamides and thiohydrazides

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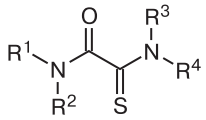
The review integrates and systematizes the key chemical transformations of monothiooxamides and thiohydrazides of oxamic acids and their derivatives, which give rise to various five-, six-, and seven-membered heterocyclic compounds with several heteroatoms.

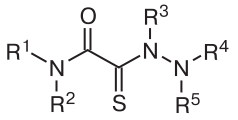
Key words: oxamic acid monothiooxamides and thiohydrazides, chloroacetamides, sulfur, amines, heterocyclic compounds.

Introduction

Oxamic acid monothiooxamides (**A**) and thiohydrazides (**B**), which contain amide, thioamide, and thiohydrazide groups, can undergo a variety of reactions owing to their polyfunctional nature. Compounds with these groups are often used to synthesize products exhibiting various pharmacological activities.[1—10] Study of the synthetic potential of oxamic acid monothiooxamides and thiohydrazides and the effect of interplay between the most proximate groups on the structure and reactivity of compounds are of considerable theoretical and practical interest.



A



B

R^1—R^5 = H, Ar, Het

Previously, we described convenient methods for the preparation of oxamic acid monothiooxamides and thiohydrazides, including optically active products,[11] by the reaction of an amine/elemental sulfur mixture prepared in advance with chloroacetamides under mild conditions, which made these compounds readily accessible.[12] The method offers numerous combinatorial options, since isomeric compounds can be prepared from chloroacetamides obtained from the amine component. It was demonstrated that oxamic acid monothiooxamides and thiohydrazides can be converted to various products, including N- and S-containing heterocycles possessing diverse biological activities.[13—15] The amide moiety was shown to considerably affect the reactivity of the thioamide group in monothiooxamides. Unlike benzothioamides, they easily react with hydroxylamine to give amidoximes, which, in their turn, were used for the preparation of heterocyclic derivatives such as 1,3,4-oxadiazoles, 1,2,4-oxadiazoles, furoxans, and isoxazoles.[16] The reactivity difference between the amide, thioamide, and thiohydrazide groups makes oxamic acid monothiooxamides and thiohydrazides valuable starting compounds also for the synthesis of mixed diheterocycles.[12]

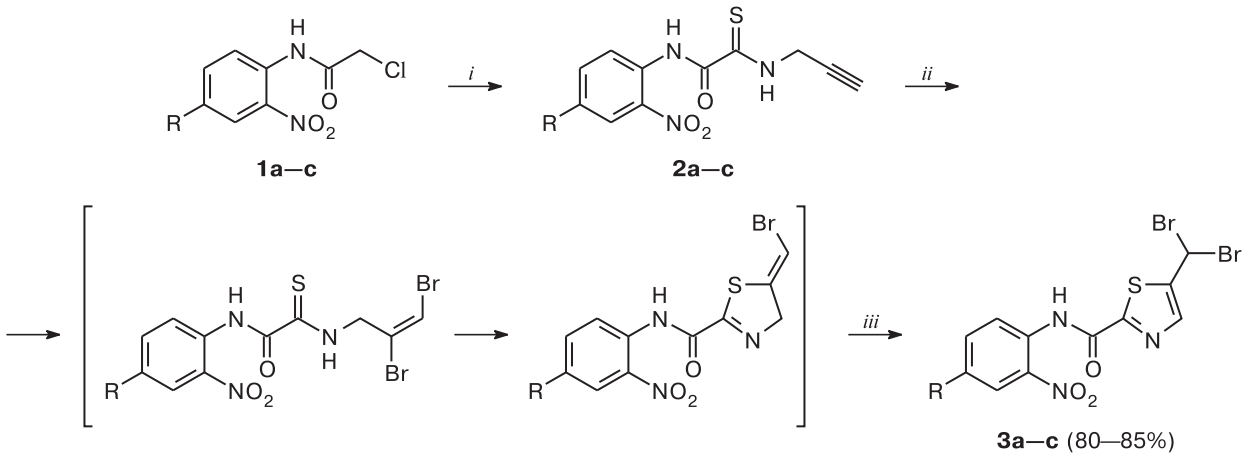
Lately, a large body of information related to the chemistry of oxamic acid monothiooxamides and thiohydrazides has been accumulated, with a considerable part of the data being devoted to the design of heterocycles from these compounds. Previously,[17] we published a brief review disclosing some aspects of the chemistry of oxamic acid thiohydrazides. The present review integrates the comprehensively describes the synthetic potential of oxamic acid monothiooxamides and thiohydrazides whose transformations induced by treatment with diversified reagents provide new synthetic routes to both known and novel bi- and polyheterocyclic systems, in particular, heterocyclic derivatives of natural compounds. In view of their simplicity, these approaches are useful, in particular, for the generation of amine-based combinatorial libraries of potential biologically active compounds of carboxamide-containing heterocycles.

Synthesis of five-membered rings with two heteroatoms

The literature describes monothiooxamide heterocyclization reactions that proceed either with retention of the thiocarbonyl sulfur atom, giving rise to sulfur-containing heterocyclic structures, or with replacement of this atom, resulting in N,O-containing heterocycles.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 6, pp. 1143—1163, June, 2019.
1066-5285/19/6806-1143

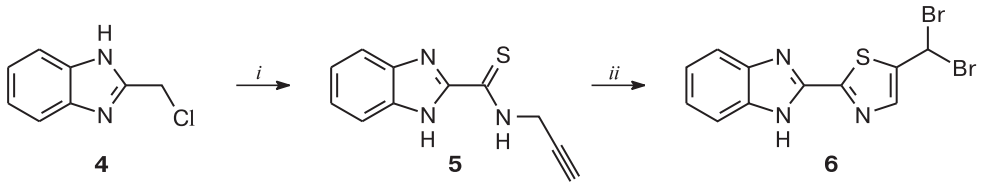
Scheme 1



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

Reagents and conditions: *i*. Propargylamine, S_8, ~20 °C, DMF. *ii*. Br_2, ~20 °C, 2—5 min, 1-*n*-butyl-5-methylimidazolium hexafluorophosphate. *iii*. Br_2.

Scheme 2



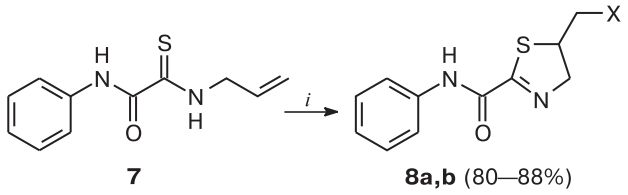
Reagents and conditions: *i*. Propargylamine, S_8, ~20 °C, DMF. *ii*. Br_2, ~20 °C.

The former route is illustrated by the approach to *N*-aryl-5-(dibromomethyl)-1,3-thiazole-2-carboxamides **3a—c** (Scheme 1), which includes the reaction of halogens with monothiooxamides **2a—c** containing a propargyl group. The latter are, in turn, formed upon the reaction of propargylamine and elemental sulfur with 2-chloro-*N*-phenylacetamides **1a—c**. The effect of solvents on the course of the reaction was studied and the best yields of thiazoles **3a—c** (80—85%) were found for the reaction conducted in an ionic liquid, 1-*n*-butyl-5-methylimidazolium hexafluorophosphate.[18]

The method is general and is appropriate for available thioamides containing propargyl groups. It was shown, in particular, that the 2-(chloromethyl)-1*H*-benzimidazole (**4**) is smoothly thiolated at the chloromethyl group and, after bromination in 1-*n*-butyl-5-methylimidazolium hexafluorophosphate, affords 2-[5-(dibromomethyl)-1,3-thiazol-2-yl]-1*H*-benzimidazole (**6**) in 78% yield (Scheme 2).[18]

This approach can also be extended to derivatives containing an ethylene group. For example, the reaction of halogens with monothiooxamide **7** containing an allyl group affords 5-(bromomethyl)-*N*-phenyl-4,5-dihydro-1,3-thiazole-2-carboxamide (**8a**) and 5-(iodomethyl)-*N*-phenyl-4,5-dihydro-1,3-thiazole-2-carboxamide (**8b**) in 80—88% yield (Scheme 3).[18] The reaction in ionic liquids takes place at room temperature and takes 2—5 min, whereas in other solvents, a longer reaction time or more drastic conditions are required.

Scheme 3

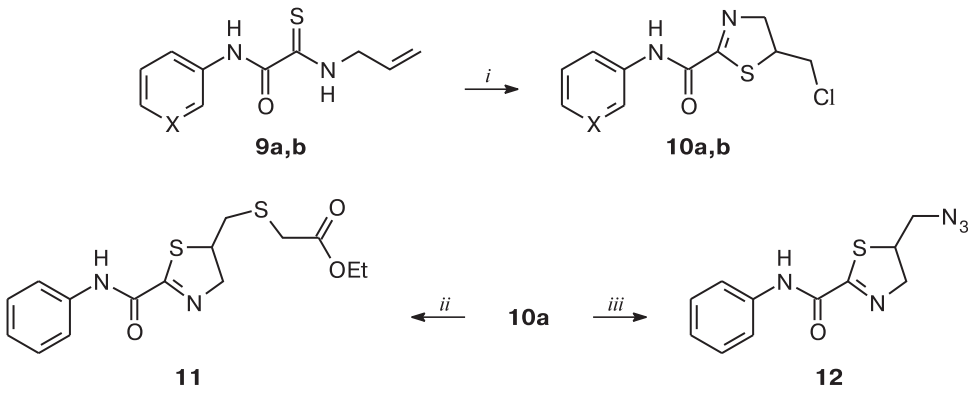


X = Br (**a**), I (**b**)

Reagents and conditions: *i*. X_2, 1-*n*-butyl-5-methylimidazolium hexafluorophosphate or tetrafluoroborate.

The double bond of monothiooxamides **9a**,**b** is also involved in reactions with thionyl chloride proceeding

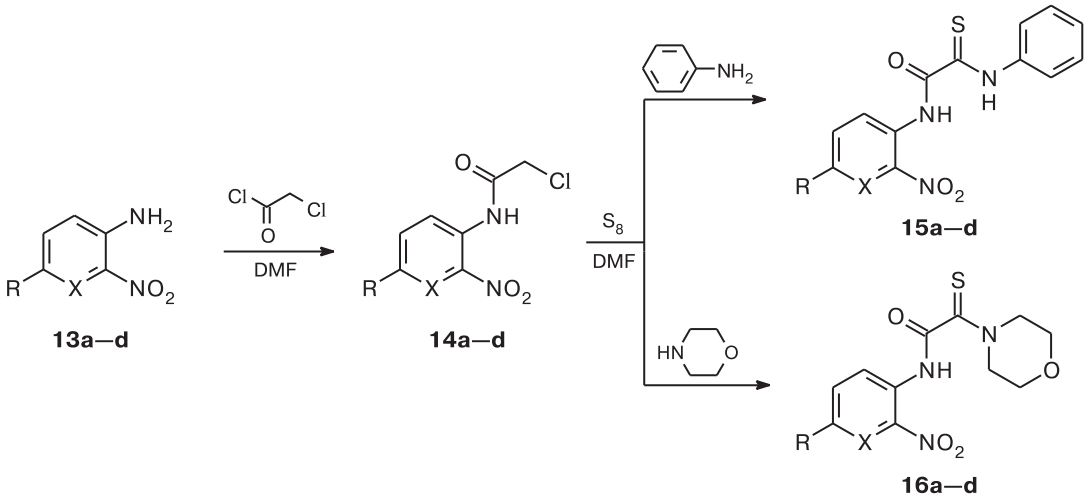
Scheme 4



X = CH (**a**), N (**b**)

Reagents and conditions: *i*. $SOCl_2$, 1-*n*-butyl-5-methylimidazolium hexafluorophosphate. *ii*. $HSCH_2C(=O)OEt$, ТГФ. *iii*. NaN_3, DMF.

Scheme 5



X = CH, R = H (**a**); X = CH, R = Cl (**b**); X = CH, R = Me (**c**); X = N, R = H (**d**)

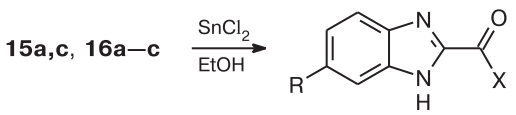
as heterocyclizations giving chloromethyl derivatives **10a**,**b**, which can be converted to sulfide **11** or azide **12** (Scheme 4).[18]

Aminonitroarenes and -pyridines **13a—d** were converted to 2-chloro-*N*-(2-nitrophenyl)acetamides **14a—c** and 2-chloro-*N*-(2-nitropyridin-3-yl)acetamide **14d**, which underwent S-functionalization under the action of pre-prepared solutions of elemental sulfur in amines to afford monothiooxamide derivatives **15a—d** and **16a—d** (Scheme 5),[19] which are employed in the synthesis of carboxamide-containing benzimidazoles. The reaction with morpholine smoothly proceeds at room temperature, while in the case of a weaker base, *e.g.*, aniline, it is necessary to add triethylamine or pyridine (see Scheme 5).[19]

The reduction of the nitro group located in the *ortho*-position to the monothiooxamide moiety of 2-anilino-*N*-(2-nitrophenyl)-2-thioxoacetamides **15a,c** and 2-anilino-*N*-(2-nitropyridin-3-yl)-2-thioxoacetamides **16a—c** is accompanied by heterocyclization to benzimidazoles **17a**,**b** and **18a—c** (Scheme 6).[19] This reaction affects both chalcogen atoms of the monothiooxamide moiety: the carbonyl group is involved in heterocyclization, whereas the thione group is hydrolyzed with the subsequent formation of the amide.

The formation of monothiooxamides followed by heterocyclization involving the thioamide group was described for 2-amino-4,5-difluoroaniline. The reaction of 2-chloro-*N*-(4,5-difluoro-2-nitrophenyl)acetamide (**19**)

Scheme 6



17a,b, 18a—c

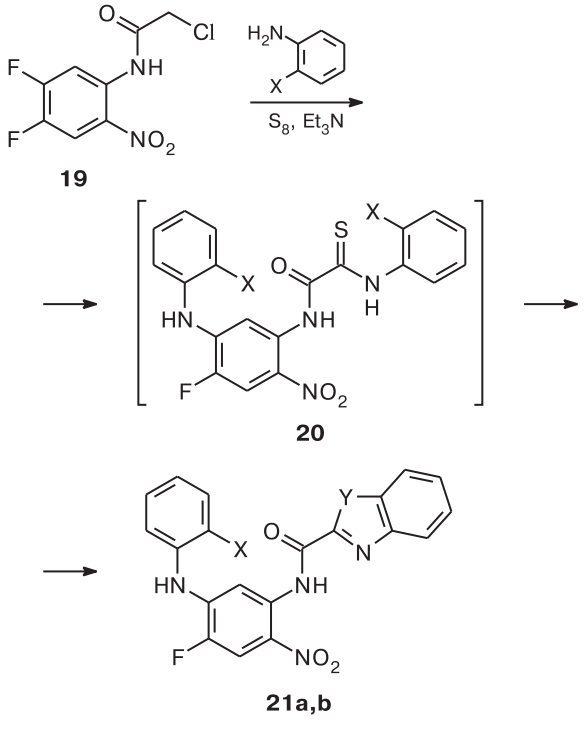
R = H, X = NHPh (**17a**); R = Me, X = NHPh (**17b**);

R = H, X = —N O (**18a**); R = Cl, X = —N O (**18b**);

R = Me, X = —N O (**18c**)

with *o*-phenylenediamine or *o*-aminophenol in the presence of elemental sulfur proceeds *via* the formation of monothiooxamide **20**, which undergoes heterocyclization at the thioamide group, resulting in the formation of benzimidazole **21a** or benzoxazole **21b**, respectively (Scheme 7).[20] The reaction is accompanied by replacement of the fluorine atom in the *para*-position to the nitro group by the aromatic amine residue.

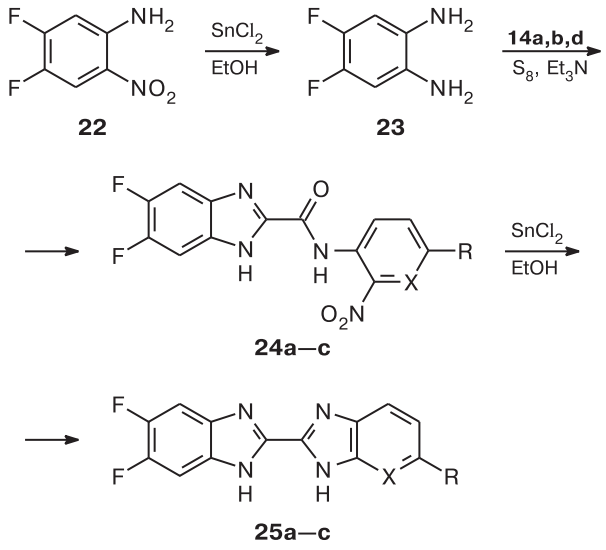
Scheme 7



X = NH_2, Y = NH (**a**); X = OH, Y = O (**b**)

The intramolecular cyclization of imidazoles **24a—c** (Scheme 8),[20] which involves the carbonyl group and is accompanied by nitro group reduction, opens up the way to difluorobis(benzimidazoles) **25a**,**b** and difluorobenzimidazolylimidazo[4,5-*b*]pyridine **25c**.

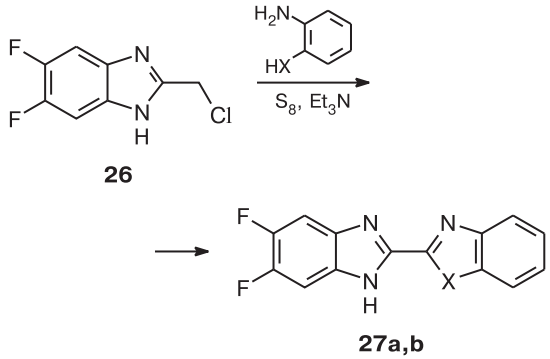
Scheme 8



X = CH, R = H (**a**); X = CH, R = Cl (**b**); X = N, R = H (**c**)

2-(Chloromethyl)-5,6-difluoro-1*H*-benzimidazole **26** was converted to products **27a**,**b** with two different heterocycles directly linked to each other (Scheme 9).[20]

Scheme 9



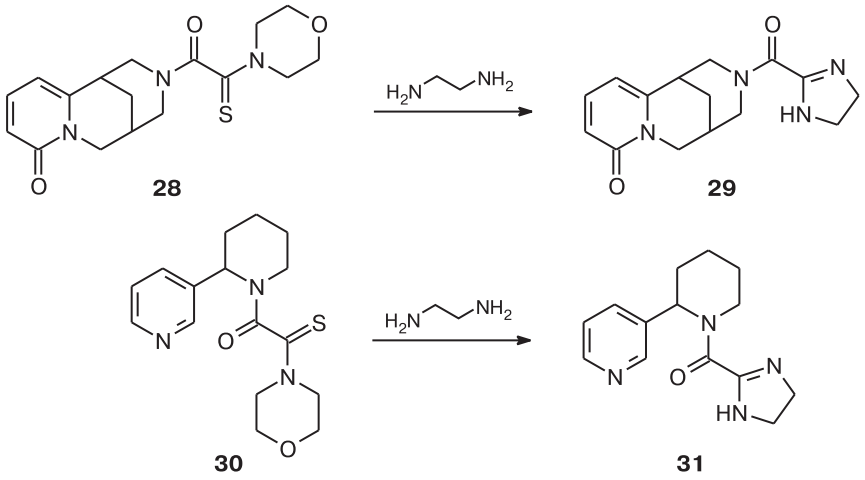
X = NH (**a**), O (**b**)

Monothiooxamides and their transformations have an interesting application in the alkaloid chemistry (Scheme 10). The formation of imidazoline moieties in the reactions of ethylenediamine with monothiooxamides **28** and **30** based on cytisine and anabasine resulted[21] in the synthesis of alkaloid derivatives **29** and **31**.

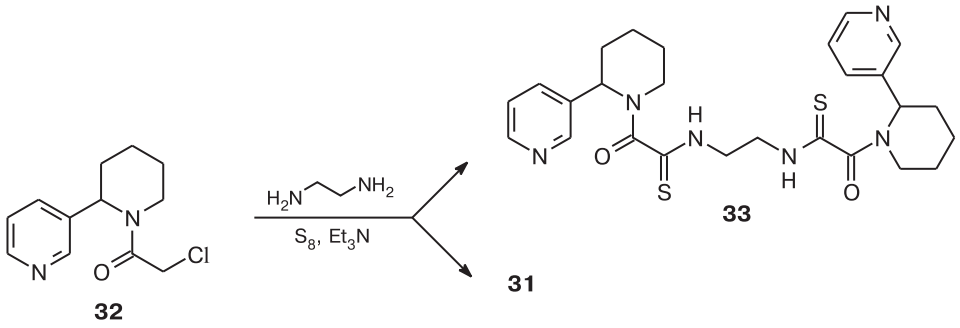
It is noteworthy that the simultaneous action of ethylenediamine and elemental sulfur on chloroacetamide **32** affords bis(thioxoacetamide) **33**, whereas the use of a preprepared solution of elemental sulfur in ethylenediamine gives the above-noted dihydroimidazole **31** (Scheme 11).[21]

The reaction of bromoacetone **34** with alkaloid monothiooxamides **35** and **36** yielded thiazoles **37** and **38**, respectively (Scheme 12).[21]

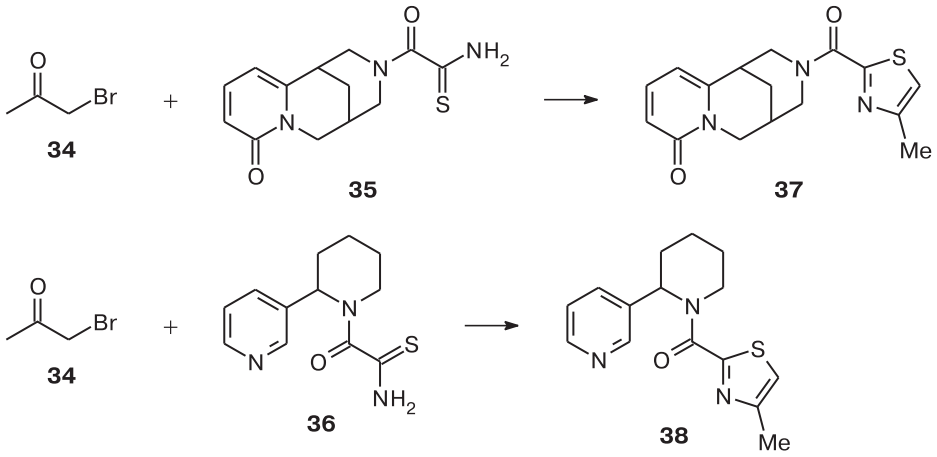
Scheme 10



Scheme 11



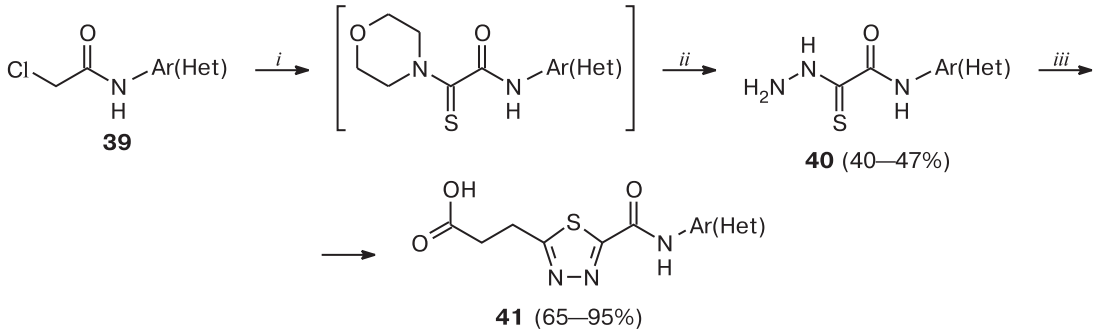
Scheme 12



Synthesis of five-membered rings with three heteroatoms

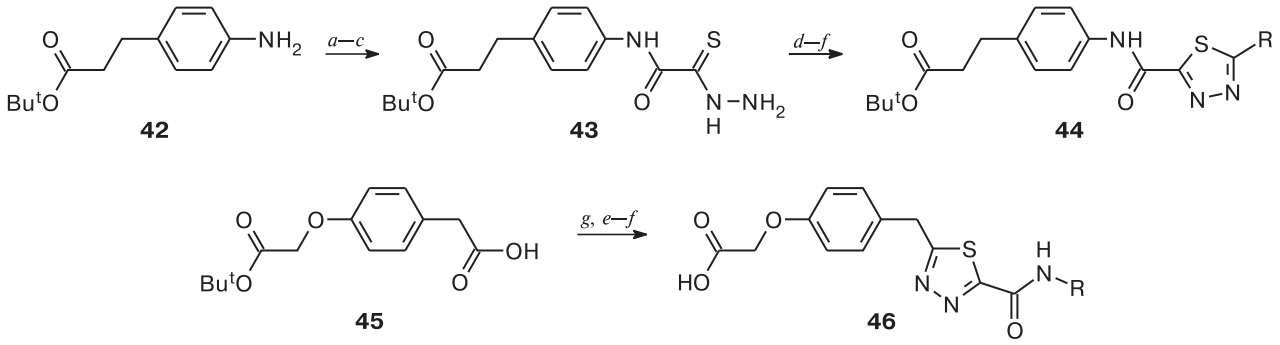
The involvement of oxamic acid thiohydrazides and their derivatives in the heterocyclization represents a route to five-membered rings with three heteroatoms, in particular, thiadiazole derivatives (Schemes 13 and 14).[22–24] For example, 3-(1,3,4-thiadiazol-2-yl)propanoic acids **41**, new free fatty acid receptor 1 (GPR40) agonists, were synthesized by several routes with participation of oxamic acid thiohydrazides (see Scheme 13).

Scheme 13



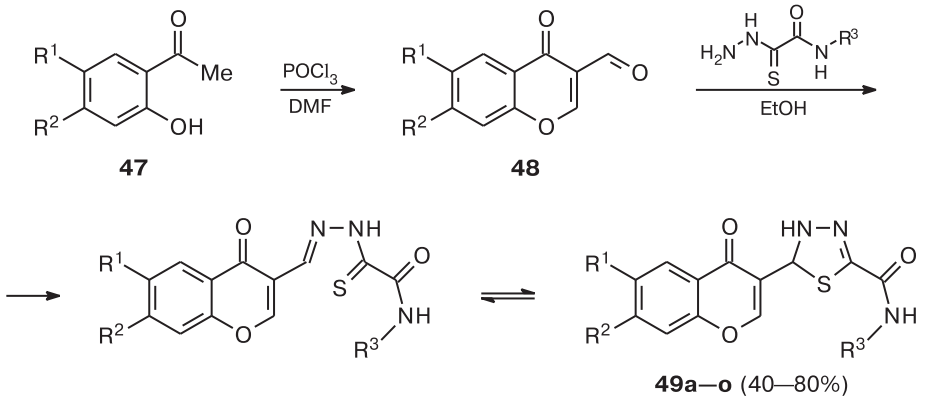
Reagents and conditions: *i*. S_8, morpholine, Et_3N, DMF, ~20 °C. *ii*. N_2H_2. *iii*. Succinic acid anhydride, glacial AcOH, refluxing, 2 h.

Scheme 14



Reagents and conditions: *a*. Chloroacetyl chloride, Et_3N, THF, 0 °C→~20 °C. *b*. S_8, morpholine, Et_3N, DMF, ~20 °C, 16 h. *c*. $N_2H_4 \cdot H_2O$, DMF, ~20 °C, 16 h. *d*. RCOOH, CDI, CH_2Cl_2, ~20 °C, 16 h. *e*. Glacial AcOH, refluxing, 30 min. *f*. 4 *M* solution of HCl in 1,4-dioxane, ~20 °C, 16 h. *g*. $ArNHCOC(S)NHNH_2$.

Scheme 15

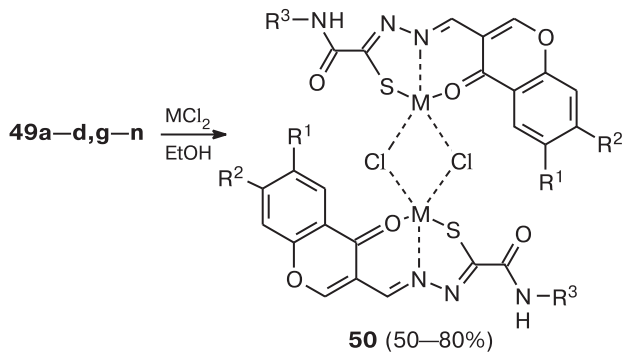


49	R^1	R^2	R^3	**49**	R^1	R^2	R^3	**49**	R^1	R^2	R^3
a	Ph	H	H	**f**	4-FC_6H_4	Br	OH	**k**	4-$MeOC_6H_4$	F	H
b	4-FC_6H_4	H	H	**g**	Ph	F	H	**l**	4-$MeOC_6H_4$	H	H
c	Ph	H	OH	**h**	4-FC_6H_4	F	H	**m**	2,5-$(MeO)_2C_6H_3$	H	H
d	Ph	Br	OH	**i**	4-$MeOC_6H_4$	H	OH	**n**	2,5-$(MeO)_2C_6H_3$	F	H
e	4-FC_6H_4	H	OH	**j**	4-$MeOC_6H_4$	Br	OH	**o**	3,5-$Cl_2C_6H_3$	H	H

Hydrazones obtained from oxamic acid thiohydrazides are widely used to prepare heterocyclic products. Note that these hydrazones exist as open-chain and cyclic tautomers.[25] The isomer ratio strongly depends on the nature of groups in the thiohydrazide moiety of the hydrazones. For example, hydrazones obtained by the reaction of oxamic acid thiohydrazides with formylchromones **48** exist in solutions as cyclic forms **49a—o** (Scheme 15).[26,27]

However, in metal complexes **50**, they occur as open-chain isomers (Scheme 16)[26,27].

Scheme 16



M = Cu, Co, Ni

The reactions of *N*-(aryl)-2-hydrazino-2-thioxoacetamides **51a**,**b** with 2-formylbenzoic acid afford hydrazones that exist as tautomers **52a**,**b** and **53a**,**b** . The intramolecular acylation of one form (**53a**,**b**) was utilized in the synthesis of *N*-aryl-5-oxo-5,9b-dihydro[1,3,4]thiadiazolo-[2,3-*a*]isoindole-2-carboxamides **54a**,**b** (Scheme 17).[28]

The oxidation of open-chain (**55a—c**) and cyclic (**56a—c**) isomers of thiohydrazones gives different products (Scheme 18).[28] On treatment with DDQ, cyclic thiohydrazones **56a—c** are converted to 5-phenyl-1,3,4-thiadiazole-2-carboxamides **57a—c**, whereas hydrazones **55a—c** react with MCPBA to afford 2-hydrazino-2-oxoacetamide hydrazones **58a—c** (see Scheme 18), with the thiocarbonyl group being converted to the carbonyl group.

It was shown that the one-pot reactions of *o*-, *m*-, or *p*-pyridinecarbaldehydes **59** with thiohydrazides **60** comprise the steps of hydrazone **61** formation and cyclization to the dihydrothiazole moiety **62** followed by oxidation with air oxygen to give a thiadiazole ring. These reactions can be conducted without intermediate isolation of hydrazones and thus afford 1,3,4-thiadiazoles **63** starting from any pyridinecarbaldehyde isomer **59** (Scheme 19).[29]

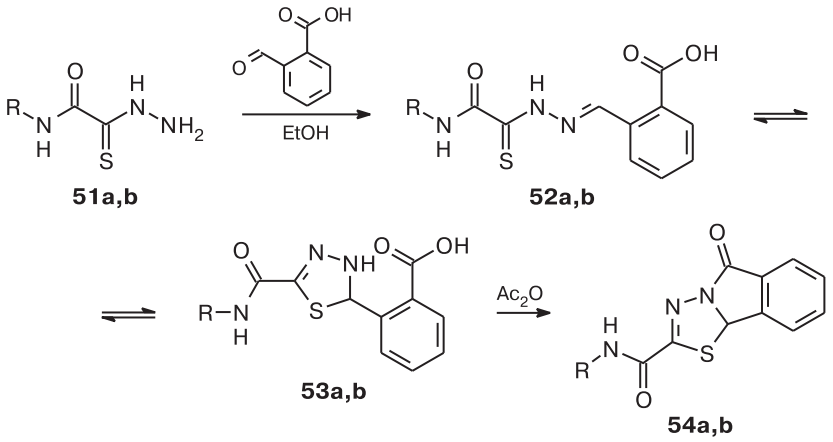
The thiohydrazides of oxamic acids fruitfully serve for the preparation of heterocyclic steroid derivatives (Scheme 20). 16-Hydroxymethylidene-17-oxo androstane **64** and estrone **65** derivatives, which exist in dynamic equilibrium with the keto-aldehyde tautomer, react with oxamic acid thiohydrazides **66a**,**b**, yielding[30] thiohydrazones **67a**,**b** and **68a**,**b**. The reaction is regioselective, and the 17-oxo group is not displaced even when a twofold excess of thiohydrazide is used.

The authors note that just after dissolution, thiohydrazones **67a,b** and **68a,b** exist as thione form **A**; however, the thiol (**B**) and cyclic (**C**) forms are generated very rapidly (Scheme 21).

The last-mentioned forms are relatively stable: they are oxidized to thiadiazolyl-substituted steroids **69a**,**b** and **70a**,**b** in 60—64% yields only when compounds **67a**,**b** and **68a**,**b** are refluxed in dioxane (Scheme 22).[30]

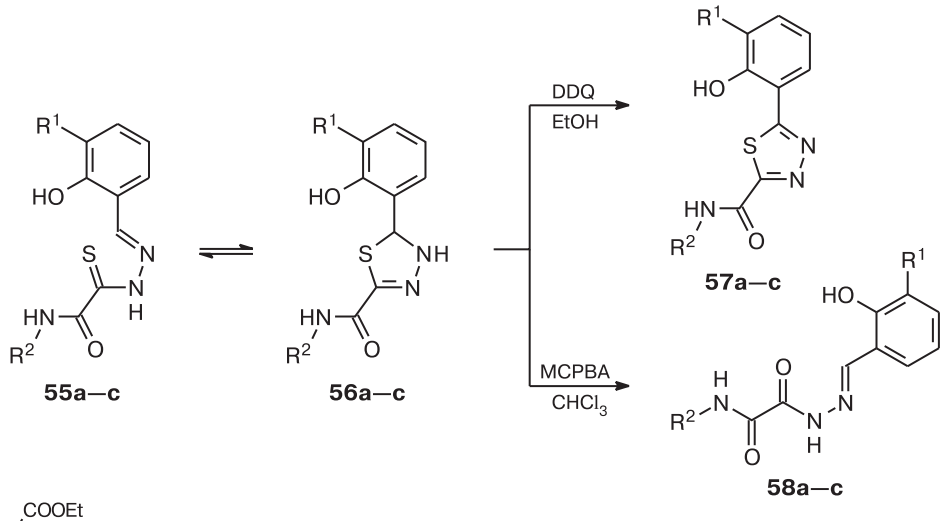
Hydrazone preparation and cyclization to the thiadiazole system can be accomplished in one stage if compounds **64** and **65** are refluxed in acetic acid with appropriate oxamic acid thiohydrazides. In this case, cyclization is accompanied by acylation of the hydroxy group in position 3 of ring A of the steroid molecule and gives acetates **71a**,**b** and **72a**,**b** (Scheme 23).

Scheme 17

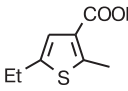


R = 4-FC_6H_4 (**a**), 2-$F_3CC_6H_4$ (**b**)

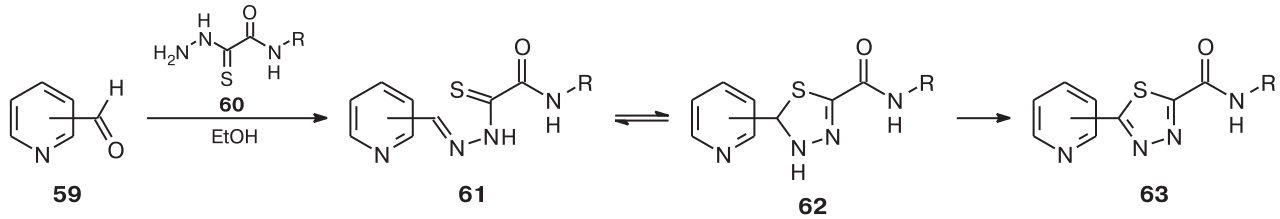
Scheme 18



55a—c 56a—c 57a—c 58a—c

R^1 = H, R^2 =  (**a**); R^1 = H, R^2 = 4-FC_6H_4 (**b**); R^1 = OEt, R^2 = 4-FC_6H_4 (**c**)

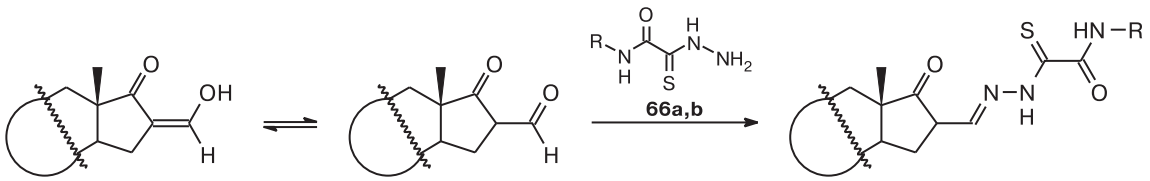
Scheme 19



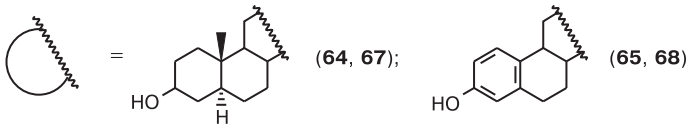
59 61 62 63

R = Ar, Het

Scheme 20

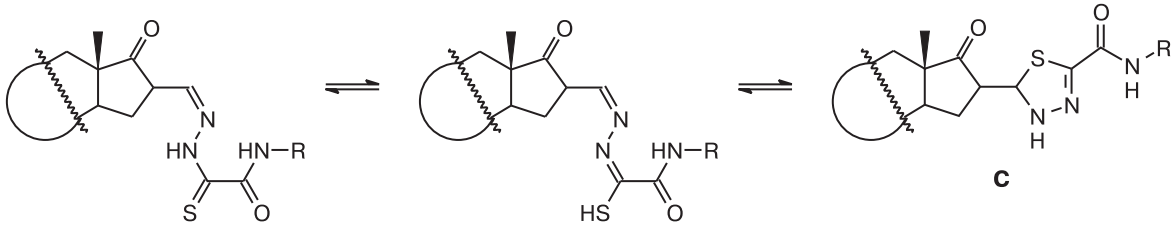


64, **65** **67a,b**, **68a,b**

 (**64**, **67**); (**65**, **68**)

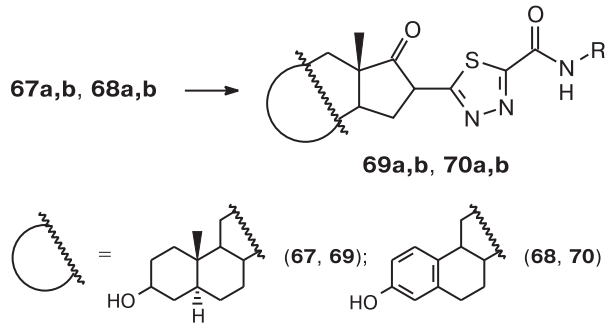
R = 4-$MeOC_6H_4$ (**a**), 4-FC_6H_4 (**b**)

Scheme 21

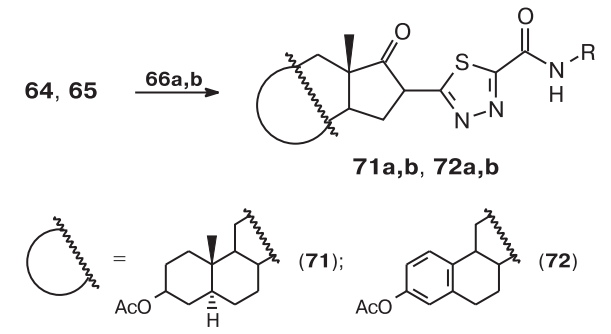


A **B** **C**

Scheme 22



Scheme 23



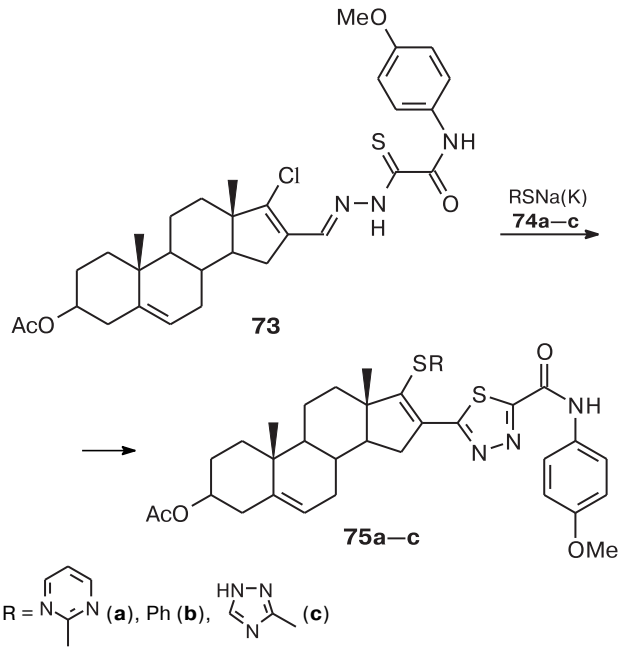
The reaction of hydrazone **73** with alkali metal (hetaryl)arenethiolates **74a—c** gives 17-(hetaryl)arylthio derivatives and is accompanied by cyclization of the thiohydrazone moiety to the 1,3,4-thiadiazole ring, thus giving compounds **75a—c** (Scheme 24).[31]

Modification of oxamic acid thiohydrazide hydrazones extends the range of accessible heterocyclic compounds. The reduction of the azomethine moiety in thiohydrazones increases the number of nuleophilic reaction sites in the molecule and expands the synthetic potential for the design of heterocyclic structures.

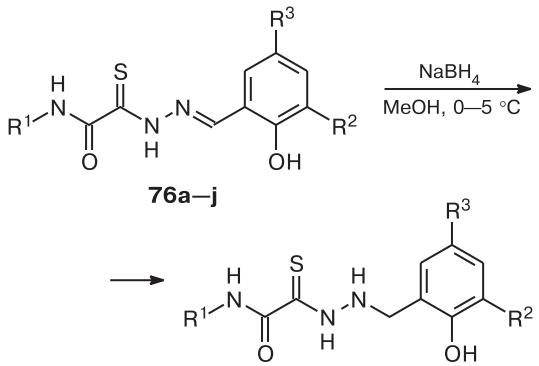
Regioselective reduction of the imine bond in thiohydrazones **76a—j** with sodium borohydride at a temperature close to 0 °C has been carried out; the reaction does not affect the carbonyl or thiocarbonyl group and can be used to prepare *N*-(hetaryl)aryl-2-(2-arylhydrazino)-2-thioxoacetamides **77a—j** (Scheme 25).[13,28]

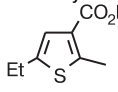
The reaction is sensitive to the structure of oxamic acid thiohydrazide hydrazones. The reduction of compounds **76a—j** was conducted in methanol; however, attempted reactions with thiohydrazones **78a—d** in this solvent yielded complex product mixtures. The successful reduction of compounds **78a—d** to thiohydrazides **79a—d** was accomplished in THF at 0—5 °C (Scheme 26).[28]

Scheme 24



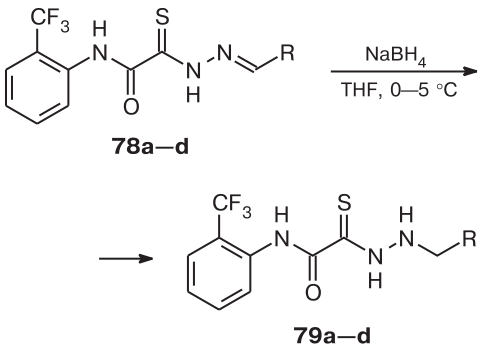
Scheme 25



77	R^1	R^2	R^3	77	R^1	R^2	R^3
a	2-MeC_6H_4	H	H	**f**	2-$F_3CC_6H_4$	OEt	H
b	2-FC_6H_4	OEt	H	**g**	3-$F_3CC_6H_4$	OEt	H
c	3-FC_6H_4	OEt	H	**h**	4-$F_3CC_6H_4$	OEt	H
d	4-FC_6H_4	OEt	H	**i**	Py	H	H
e	4-FC_6H_4	Br	Br	**j**		H	H

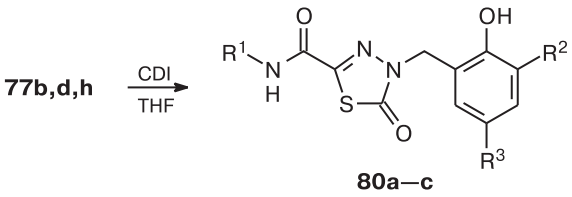
A variety of heterocyclization reactions involving the products of reduction of oxamic acid thiohydrazide hydrazones have been reported.[2,4] It was shown, for example, that *N*-aryl-4-arylmethyl-5-oxo-4,5-dihydro-1,3,4-thiadiazole-2-carboxamides **80a—c** can be prepared from the thiohydrazide moiety of the reduced hydrazone on treatment with carbonyldiimidazole (Scheme 27).[13]

Scheme 26



R = 2-thienyl (**a**), 5-methyl-2-thienyl (**b**), 3-pyridyl (**c**), 4-pyridyl (**d**)

Scheme 27



R^1 = 2-FC_6H_4, R^2 = OEt, R^3 = H (**a**);
R^1 = 4-FC_6H_4, R^2 = OEt, R^3 = H (**b**);
R^1 = 3-$F_3CC_6H_4$, R^2 = OEt, R^3 = H (**c**)

N-Aryl-4-arylmethyl-5-thioxo-4,5-dihydro-1,3,4-thiadiazole-2-carboxamides **81a**—**c**, thio analogues of compounds **80a**—**c**, are obtained by keeping thiohydrazides **77c**,**d**,**g** with carbon disulfide and a 2—3-fold excess of alkali in methanol at room temperature for two days (Scheme 28).[28] The reactions of thiohydrazides **77d**,**f**,**g** with 3-ethoxy-2-hydroxybenzaldehyde in methanol produced the corresponding 4,5-dihydro-1,3,4-thiadiazole-2-carboxamides **82a**—**c** in good yields. Thiohydrazides **77b**,**d**,**f** react with diethyl chlorophosphate in benzene, being converted to phosphorus-containing heterocycles, dihydrothiadiazaphospholane oxides **83a**—**c**, in 60—70% yields.

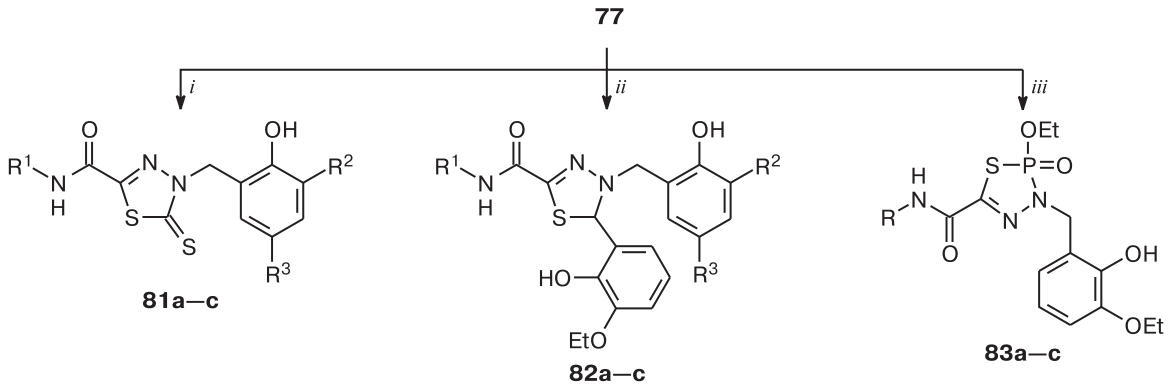
4-Thiazolidinones are widely used in the synthesis of various biologically active molecules,[32—35] a special place among which is occupied by 2-thioxo-1,3-thiazolidin-4-ones (rhodanines), which exhibit antiviral, antibacterial, and antitumor activities. They are also utilized in the therapy of diabetes mellitus (Epalrestat drug) and show high inhibitory activity against the human immunodeficiency virus 1 (HIV-1).

An attempt was made to prepare rhodanines based on oxamic acid thiohydrazides. It turned out, however, that the reaction of oxamic acid thiohydrazides **84a**—**c** with carbon disulfide in the presence of bases cannot be stopped after the formation of the primary dithiocarbamate adduct: both on heating and at −15 °C, cyclization at the thiocarbonyl group takes place, yielding *N*-aryl-5-thioxo-4,5-dihydro-1,3,4-thiadiazole-2-carboxamides **85a**—**c** in 61—70% yields (Scheme 29).[36]

The reaction of oxamic acid thiohydrazides with trithiocarbonyldiglycolic acid did not give rhodanines either: the reaction in diglyme yielded the same thiadiazole-2-thiones **85a**—**c**.

It was assumed that activation of the carboxyl group of trithiocarbonyldiglycolic acid would promote the formation of intermediate amide followed by cyclization to rhodanine. Indeed, the reaction of oxamic acid thiohydrazides **86a—m** with trithiocarbonyldiglycolic acid in anhydrous THF in the presence of DCC or CDI at 0 °C resulted in the formation of 2-[(4-oxo-2-thioxo-1,3-thiazolidin-3-yl)amino]-*N*-(hetaryl)aryl-2-thioxoamides **87a**—**m** in 70—80% yields (Scheme 30).[37]

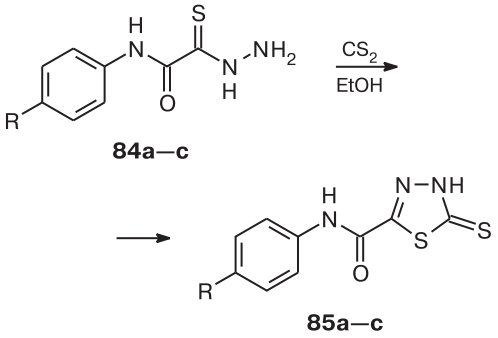
Scheme 28



81: R^1 = 3-FC_6H_4, R^2 = OEt, R^3 = H (**a**); R^1 = 4-FC_6H_4, R^2 = OEt, R^3 = H (**b**); R^1 = 3-$F_3CC_6H_4$, R^2 = OEt, R^3 = H (**c**)
82: R^1 = 4-FC_6H_4, R^2 = OEt, R^3 = H (**a**); R^1 = 2-$F_3CC_6H_4$, R^2 = OEt, R^3 = H (**b**); R^1 = 3-$F_3CC_6H_4$, R^2 = OEt, R^3 = H (**c**)
83: R = 2-FC_6H_4 (**a**), 2-$F_3CC_6H_4$ (**b**), 4-FC_6H_4 (**c**)

Reagents and conditions: *i*. CS_2, KOH/MeOH, 48 h. *ii*. 3-Ethoxy-2-hydroxybenzaldehyde, MeOH, [H^+]. *iii*. $(EtO)_2POCl$, C_6H_6, refluxing.

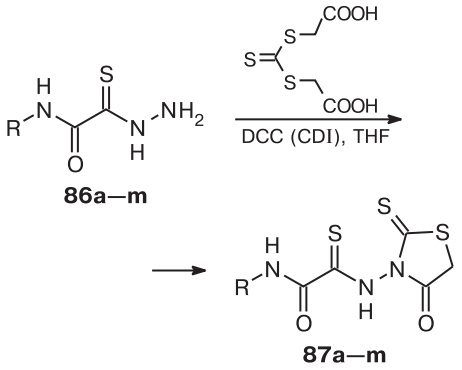
Scheme 29



84a—c **85a—c**

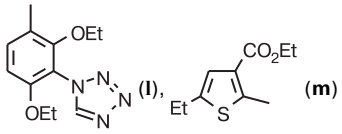
R = H (**a**), Cl (**b**), OMe (**c**)

Scheme 30



86a—m **87a—m**

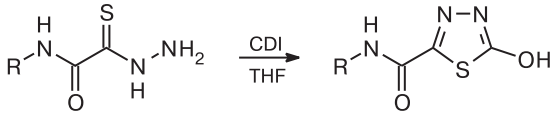
R = Ph (**a**), 4-ClC_6H_4 (**b**), 4-$MeOC_6H_4$ (**c**), 4-FC_6H_4 (**d**), 3-$O_2NC_6H_4$ (**e**), 4-HOC_6H_4 (**f**), 3-$F_3CC_6H_4$ (**g**), 4-$F_3CC_6H_4$ (**h**), 3,5-$(F_3C)_2C_6H_3$ (**i**), 3,4-$(MeO)_2C_6H_3$ (**j**), 3,4,5-$(MeO)_3C_6H_2$ (**k**),



(**l**), (**m**)

In the absence of trithiocarbonyldiglycolic acid, oxamic acid thiohydrazides **88a—e** were converted in THF at room temperature to 5-hydroxy-1,3,4-thiadiazole-2-carboxamides **89a—e** in 85—92% yields (Scheme 31).[36]

Scheme 31

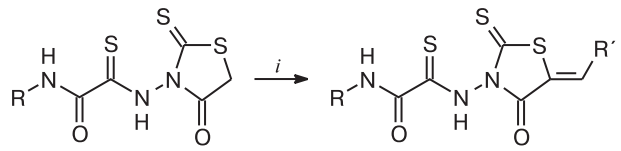


88a—e **89a—e**

R = Ph (**a**), 4-ClC_6H_4 (**b**), 4-$MeOC_6H_4$ (**c**), 4-BrC_6H_4 (**d**), 3-$O_2NC_6H_4$ (**e**)

Since functional derivatives of rhodanine are widely used in the synthesis of biologically active products, much attention is paid to the synthetic potential of rhodanine-based oxamic acid thiohydrazides whose modification markedly expands the range of rhodanine derivatives. 2-Thioxo-1,3-thiazolidin-4-one **90** reacts with aromatic aldehydes in methanol at room temperature in the presence of catalytic amounts of ethylenediammonium diacetate to give, within 30—60 min, 5-arylidenerhodanines **91a—c** in 85—95% yields (Scheme 32).[38,39]

Scheme 32



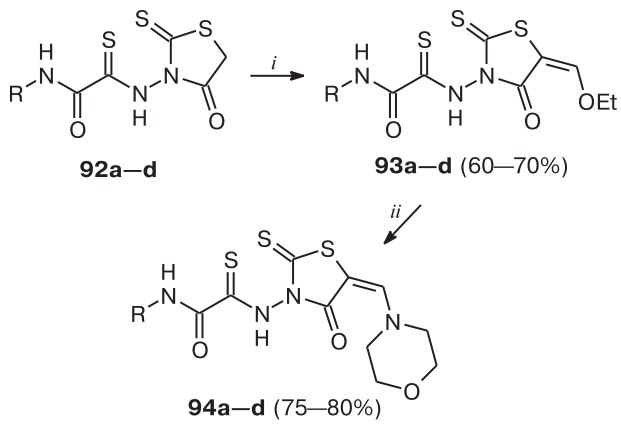
90 **91a—c**

R = 4-ClC_6H_4, R′ = Ph (**a**); R = R′ = 4-ClC_6H_4 (**b**); R = 4-ClC_6H_4, R′ = 5-niitrofuran-2-yl (**c**)

Reagents and conditions: *i*. R′CHO, ethylenediammonium diacetate, MeOH, 30—60 min, ~20 °C.

The reaction of rhodanines **92a—d** with triethyl orthoformate in acetic acid in the presence of sodium acetate (40 °C, 1—1.5 h) affords ethoxymethylenerhodanines **93a—d** in 60—70% yields, which then react with morpholine furnishing the corresponding enamines **94a—d** (Scheme 33).[39]

Scheme 33



92a—d **93a—d** (60—70%)

94a—d (75—80%)

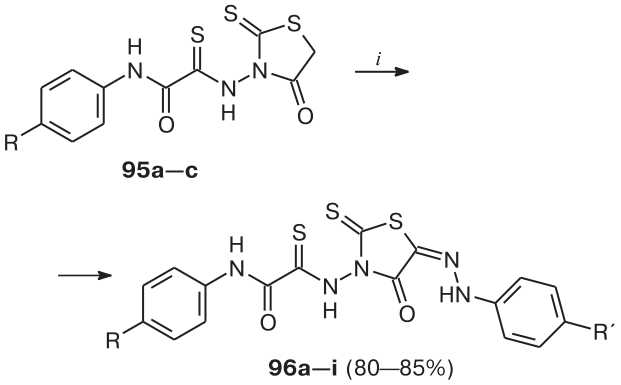
R = Ph (**a**), 4-ClC_6H_4 (**b**), 4-$MeOC_6H_4$ (**c**), 3-$O_2NC_6H_4$ (**d**)

Reagents and conditions: *i*. $HC(OEt)_3$, AcOH, AcONa, 40 °C, 1—1.5 h. *ii*. Morpholine, EtOH.

It is noteworthy that the reaction of rhodanines **93a—d** with morpholine carried out below 40 °C does not affect other reactive groups, in particular, the thioamide group. Higher temperatures induce decomposition of ethoxymethylenerhodanines.

The reaction of 2-thioxo-1,3-thiazolidin-4-ones **95a—c** with diazonium salts in the presence of potassium carbonate and sodium acetate in aqueous ethanol resulted in the synthesis of 5-arylhydrazonorhodanines **96a—i** in 80—85% yields (Scheme 34).[39]

Scheme 34



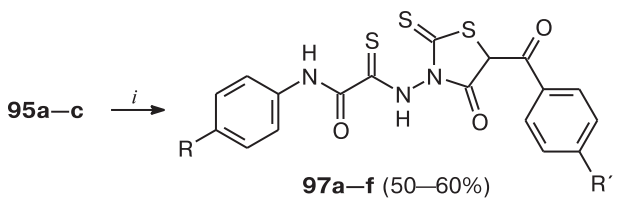
95: R = H (**a**), Cl (**b**), OMe (**c**)

96	R	R′	**96**	R	R′	**96**	R	R′
a	H	H	**d**	Cl	H	**g**	OMe	H
b	H	Br	**e**	Cl	Br	**h**	OMe	Br
c	H	OMe	**f**	Cl	OMe	**i**	OMe	OMe

Reagents and conditions: *i*. R′$C_6H_4N_2Cl$, K_2CO_3, AcONa, $EtOH/H_2O$.

Although rhodanine molecules **95a—c** contain several nucleophilic centers, they are acylated with benzoic acid chlorides on heating in dioxane in the presence of sodium hydroxide to give mainly 5-acylrhodanines **97a—f** in 50—60% yields (Scheme 35).[39]

Scheme 35

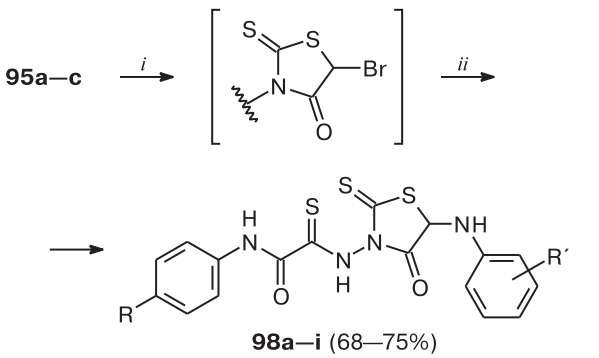


97: R = R′ = H (**a**); R = H, R′ = Cl (**b**); R = Cl, R′ = H (**c**); R = R′ = Cl (**d**); R = OMe, R′ = H (**e**); R = OMe, R′ = Cl (**f**)

Reagents and conditions: *i*. R′$C_6H_4C(=O)Cl$, dioxane, NaOH.

Rhodanines **95a—c** are smoothly brominated in dioxane at room temperature. Since 5-bromorhodanines are fairly labile, they are used for alkylation of anilines without isolation of intermediate bromination products. 5-Arylaminorhodanines **98a—i** are produced in 68—75% yields (Scheme 36).[39]

Scheme 36

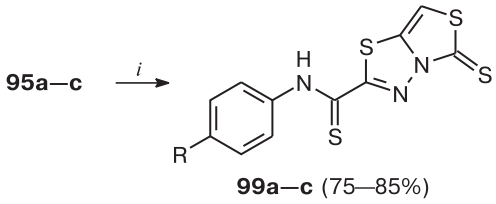


98: R = R′ = H (**a**); R = H, R′ = 3-F (**b**); R = H, R′ = 3,5-Cl_2 (**c**); R = Cl, R′ = H (**d**); R = Cl, R′ = 3-F (**e**); R = Cl, R′ = 3,5-Cl_2 (**f**); R = OMe, R′ = H (**g**); R = OMe, R′ = 3-F (**h**); R = OMe, R′ = 3,5-Cl_2 (**i**)

Reagents and conditions: *i*. Br_2, dioxane. *ii*. R′$C_6H_4NH_2$.

Rhodanines with oxamic acid thiohydrazide moieties were used to prepare fused heterocycles. Refluxing of compounds **95a—c** with the Lawesson reagent or phosphorus pentasulfide in toluene gives *N*-aryl-5-thioxo[1,3]thiazolo[4,3-*b*][1,3,4]thiadiazole-2-carbothioamides **99a—c** in 75—85% yields (Scheme 37).[40]

Scheme 37



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

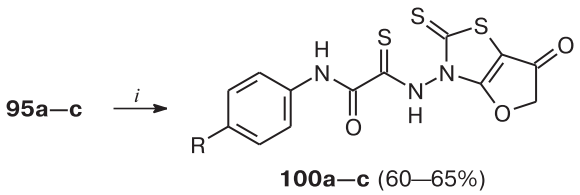
Reagents and conditions: *i*. Lawesson reagent or P_2S_5, toluene.

The condensation of rhodanines **95a—c** with chloroacetic acid in methanol in the presence of sodium methoxide provided the route to 2-thioxo-2,3-dihydrofuro[2,3-*d*][1,3]thiazol-6-ones **100a—c** in 60—65% yields (Scheme 38).[40]

5-Benzylidenerhodanines **101a—c** containing a conjugated carbonyl group react with phenylhydrazine in the presence of sodium acetate, giving rise to tetrahydro-5*H*-pyrazolo[3,4-*d*][1,3]thiazole-5-thiones **102a—c** in 55—65% yields (Scheme 39).[40] In anhydrous ethanol with sodium acetate, the reaction proceeds within 3.5 h, whereas with heating in acetic acid it takes 7 h to achieve the same yield. Note that the reaction conditions do not affect the thioamide groups of the rhodanine ring or the thiohydrazide moiety.

Refluxing of benzylidene rhodanine derivatives **101a—c** with ethyl cyanoacetate in an acetic acid solution of am-

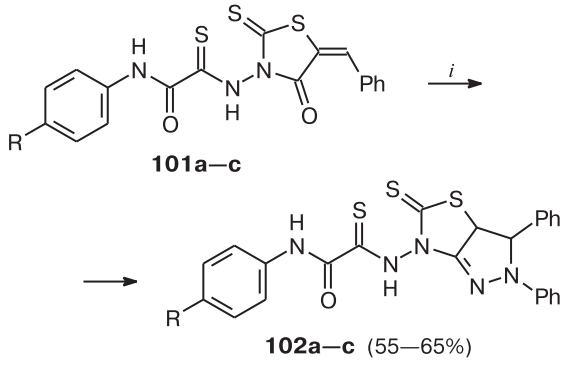
Scheme 38



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

Reagents and conditions: *i*. $ClCH_2COOH$, MeONa, MeOH.

Scheme 39



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

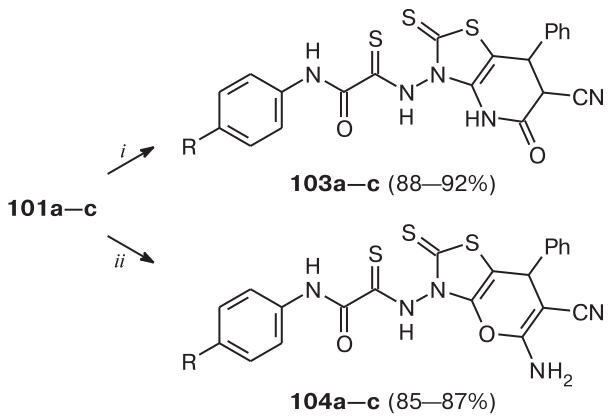
Reagents and conditions: *i*. $PhNHNH_2$, AcONa, EtOH.

monium acetate for 4 h affords[40] substituted 2-thioxothiazolepyridine-6-carbonitriles **103a**—**c** in 50—55% yields. The yields of fused heterocycles **103a**—**c** can be considerably increased by using microwave irradiation. Indeed, by the microwave-assisted reaction of benzylidene rhodanine derivatives **101a**—**c** with ethyl cyanoacetate in an acetic acid solution of ammonium acetate, we obtained substituted thiazolo[4,5-*b*]pyridine-6-carbonitriles **103a**—**c** in 88—92% yields (Scheme 40).[41] Relatively low yields of 3,7-dihydro-2*H*-pyrano[2,3-*d*][1,3]thiazole-2-thiones **104a**—**c** were obtained when benzylidene derivatives **101a**—**c** were heated with malonodinitrile in the presence of triethylamine in DMF for 10 h (25—35%) or in anhydrous ethanol for 3 h (30—35%) (see Scheme 40).

When this reaction was carried out in acetic acid with microwave assistance for 45 min, the yields of 2*H*-pyrano[2,3-*d*][1,3]thiazole-2-thiones **104a**—**c** were[41] 85—87%.

An alternative route to pyranothiazole-2-thiones is to heat hetarylidenemalonodinitriles with rhodanines **105a**—**c** in ethanol in the presence of piperidine. This approach makes it possible to prepare a variety of pyrano[2,3-*d*]-[1,3]thiazoles and increases their yield based on the starting rhodanine. Indeed, 5-nitro-2-furyl- and thienylpyrano[2,3-*d*][1,3]thiazole derivatives **106a**—**f** were synthesized in 55—60% yields (Scheme 41).[40]

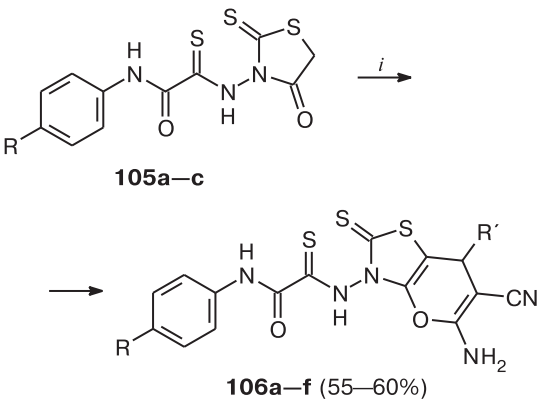
Scheme 40



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

Reagents and conditions: *i*. Ethyl cyanoacetate, $AcONH_4$, AcOH, microwave irradiation. *ii*. Malonodinitrile, $AcONH_4$, AcOH, microwave irradiation.

Scheme 41

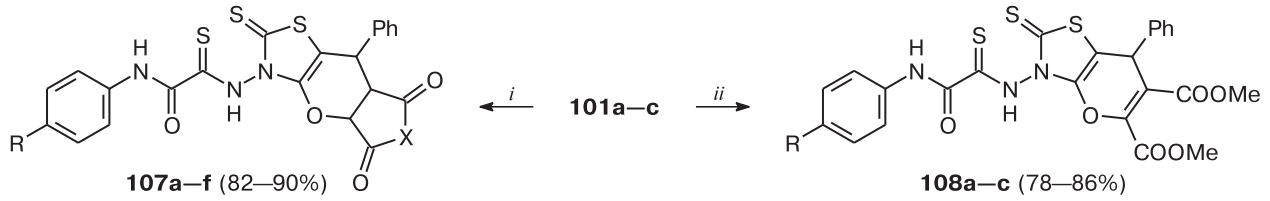


105: R = H (**a**), Cl (**b**), Br (**c**)
106: R = H, R′ = 5-nitrofuran-2-yl (**a**); R = H, R′ = thiophen-2-yl (**b**); R = Cl, R′ = 5-nitrofuran-2-yl (**c**); R = Cl, R′ = thiophen-2-yl (**d**); R = Br, R′ = 5-nitrofuran-2-yl (**e**); R = Br, R′ = thiophen-2-yl (**f**)

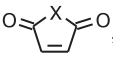
Reagents and conditions: *i*. $R'CH{=}C(CN)_2$, EtOH, piperidine.

The cycloaddition of arylidene rhodanines to dienophiles was accomplished under microwave irradiation. This gave pyrano[2,3-*d*]thiazoles **107a**—**f** and **108a**—**c** in 78—90% yields (Scheme 42).[41] It is worth noting that these compounds cannot be prepared from 5-arylidenerhodanines by known procedures. The reactions were carried out under various conditions at room temperature and at reflux and in various solvents. The cycloaddition also did nor proceed at elevated pressure (from 10 to 150 kbar), no matter whether at room temperature or on heating (40 to 150 °C). In all cases, the starting compounds were recovered; in addition, refluxing in high-boiling solvents led to resinification of the reaction mixture.[41]

Scheme 42



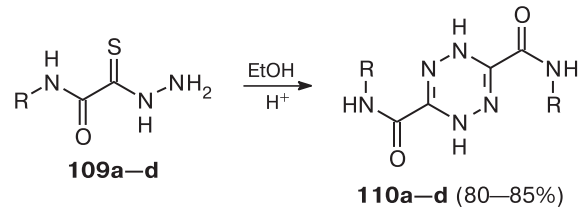
107: R = H, X = O (**a**); R = H, X = NPh (**b**); R = Cl, X = O (**c**); R = Cl, X = NPh (**d**); R = OMe, X = O (**e**); R = OMe, X = NPh (**f**)
108: R = H (**a**), Cl (**b**), OMe (**c**)

Reagents and conditions: *i*.  , AcOH, microwave irradiation. *ii*. MeOOC—C≡C—COOMe, AcOH, microwave irradiation.

Synthesis of six-membered heterocyclic compounds

When thiohydrazides **109a**—**d** are heated in ethanol, *N*,*N*′-diaryl-1,4-dihydro-1,2,4,5-tetrazine-3,6-dicarboxamides **110a**—**d** are formed in good yields (Scheme 43).[28]

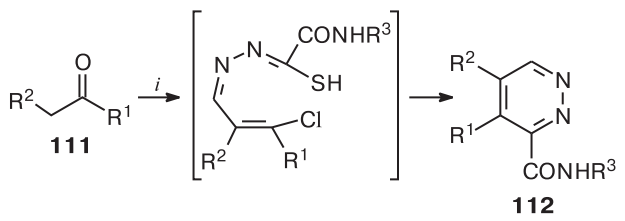
Scheme 43



R = pyridin-2-yl (**a**), 2-MeC_6H_4 (**b**), 3-FC_6H_4 (**c**), 4-FC_6H_4 (**d**)

A new two-step route proposed for the synthesis of pyridazines from ketones includes Vilsmeier—Haack chloroformylation of enolyzable ketones **111** followed by imination with oxamic acid hydrazides to give oxamic acid thiohydrazide hydrazones as sources of the 2,3-diazahexatriene system, which undergoes cascade electrocyclization/aromatization giving functionalized pyridazines **112** in moderate to high yields (32—89%) (Scheme 44).[42—44]

Scheme 44



Reagents and conditions: *i*. 1) Vilsmeier—Haack reaction; 2) $H_2NNHCSCONHR^3$, TsOH (10 mol.%).

It was found that heterocyclization of oxamic acid thiohydrazide hydrazones is accompanied by release of molecular sulfur as a reaction product. Quantum chemical calculations in combination with NMR studies demonstrated that, despite the possibility for cyclization to follow a nucleophilic pathway, the 6π-electrocyclic pathway is much more favorable. Advantages of the method include the ready accessibility of reactants, broad range of reactive substrates, and easy implementation.[42,43]

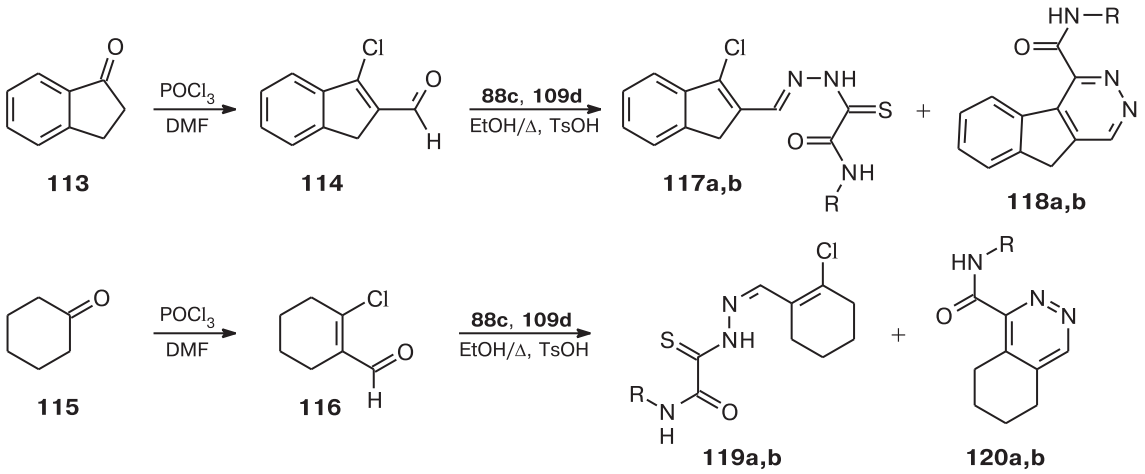
Refluxing of 3-chloro-1*H*-indene-2-carbaldehyde **114** (obtained from indanone **113**) with oxamic acid thiohydrazides **88c** and **109d** in ethanol in the presence of TsOH affords a mixture of thiohydrazone **117a**,**b** and pyridazine **118a**,**b** in 1 : 4 ratio (Scheme 45).[30,44] Similarly, cyclohexanone **115** is converted to chloro aldehyde **116**, which is transformed to thiohydrazone **119a**,**b** and pyridazine **120a**,**b** in 1 : 4 ratio upon refluxing with thiohydrazides **88c** and **109d** in ethanol in the presence of TsOH (see Scheme 45).[30,44]

The approach described above was successfully utilized to obtain steroids containing pyridazine moieties. It was shown that thiohydrazones **121a**,**b** cyclize to pyridazines **122a**,**b** in 92% yield, the reaction being conducted in ethanol in the presence of a catalytic amount of TsOH (Scheme 46).[42]

Refluxing of oxamic acid thiohydrazides in ethanol with formyl androstene and estrone derivatives in the presence of TsOH smoothly produces pyridazines **124a**,**b** in one step (without isolation of intermediate hydrazones) (Scheme 47).[42]

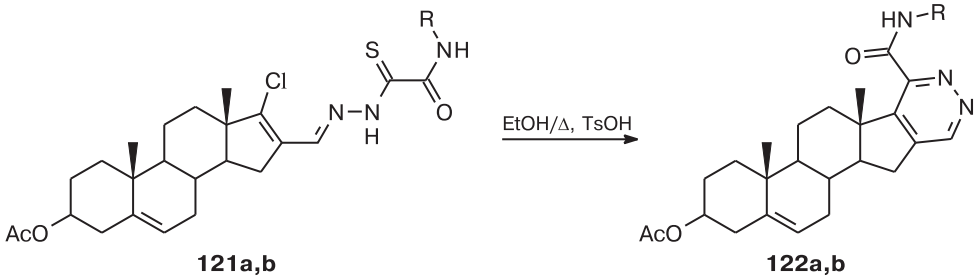
The putative mechanism of cyclization of thiohydrazone **123a** to pyridazine **124a** is depicted[42—44] in Scheme 48. Analysis of 2D NMR spectra demonstrated that thiohydrazone **123a** exists in solutions as a mixture of open-chain thione (*syn*-1) and thiol (*syn*-2) forms and cyclic form (*cycl*). The cyclization takes place for isomer *syn*-2, which ensures the maximum proximity of the C—SH carbon atom and the chlorine atom at C(17). This induces disrotatory 6π-electrocyclization giving heterocycle **125**, which contains both sulfur and chlorine atoms; this is followed by aromatization with the release of elemental sulfur and hydrogen chloride to give the pyridazine ring of compound **124a**. Sulfur was isolated from the reaction medium in a nearly quantitative yield.

Scheme 45



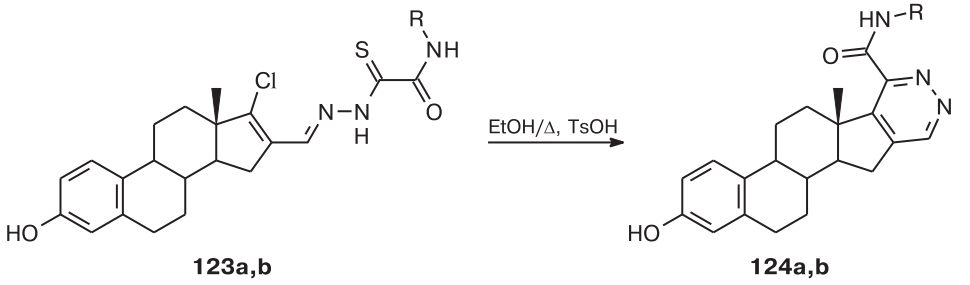
R = 4-FC_6H_4 (**a**), 4-$MeOC_6H_4$ (**b**)

Scheme 46



R = 4-$MeOC_6H_4$ (**a**), 4-ClC_6H_4 (**b**)

Scheme 47

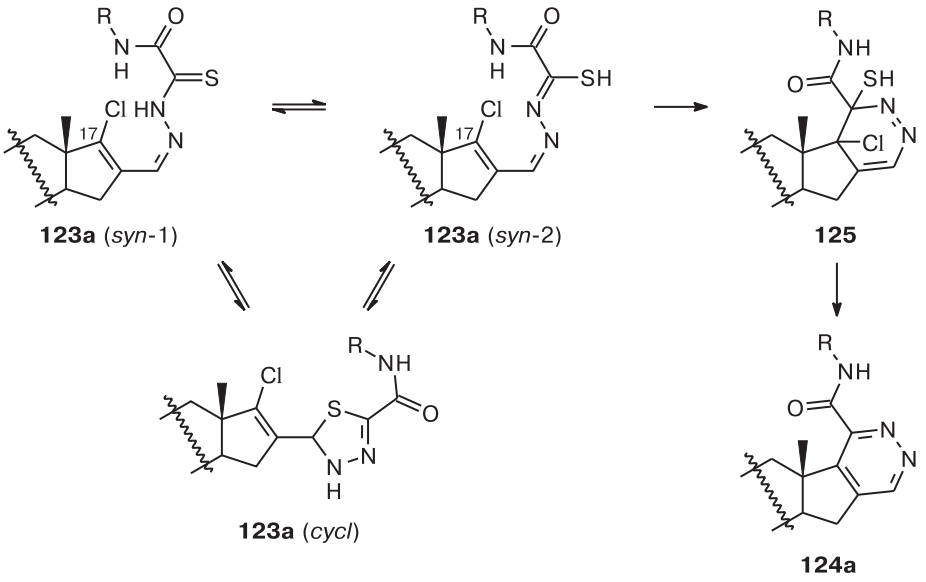


R = 4-$MeOC_6H_4$ (**a**), 4-ClC_6H_4 (**b**)

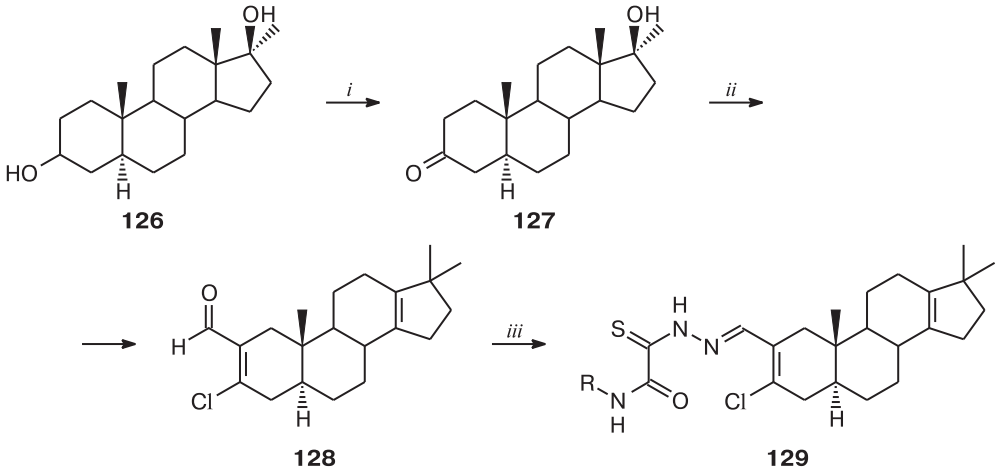
3-Chloro-2-formyl-17α-methyl-5α-androsta-2,16-diene **128** obtained in two steps (**126** → **127** → **128**) reacts with oxamic acid thiohydrazide **88c** in ethanol at 20 °C in the presence of a catalytic amount of TsOH, being converted to thiohydrazone **129** in 75% yield (Scheme 49).[43] Simultaneously, in ring D of the steroid molecule, the Wagner—Meerwein rearrangement takes place, accompanied by migration of the Me group from position 13 to position 17 of the carbon skeleton and double bond formation.

When thiohydrazone **129** is refluxed in ethanol for 2 h in the presence of a catalytic amount of TsOH, pyridazine **130** is formed in 73% yield; this product can also be prepared in on stage (without isolation of intermediate hydr-

Scheme 48



Scheme 49



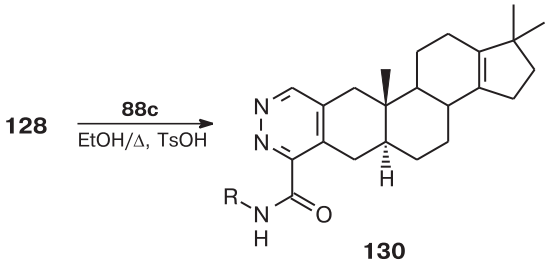
R = 4-$MeOC_6H_4$

Reagents and conditions: *i*. Jones reagents, Me_2CO, propan-2-ol. *ii*. $POCl_3$, DMF, CH_2Cl_2. *iii*. Thiohydrazide **88c**, EtOH, TsOH, 20 °C.

azone) by refluxing formyl derivative **128** with oxamic acid thiohydrazide **88c** in ethanol in the presence of TsOH (Scheme 50).[43]

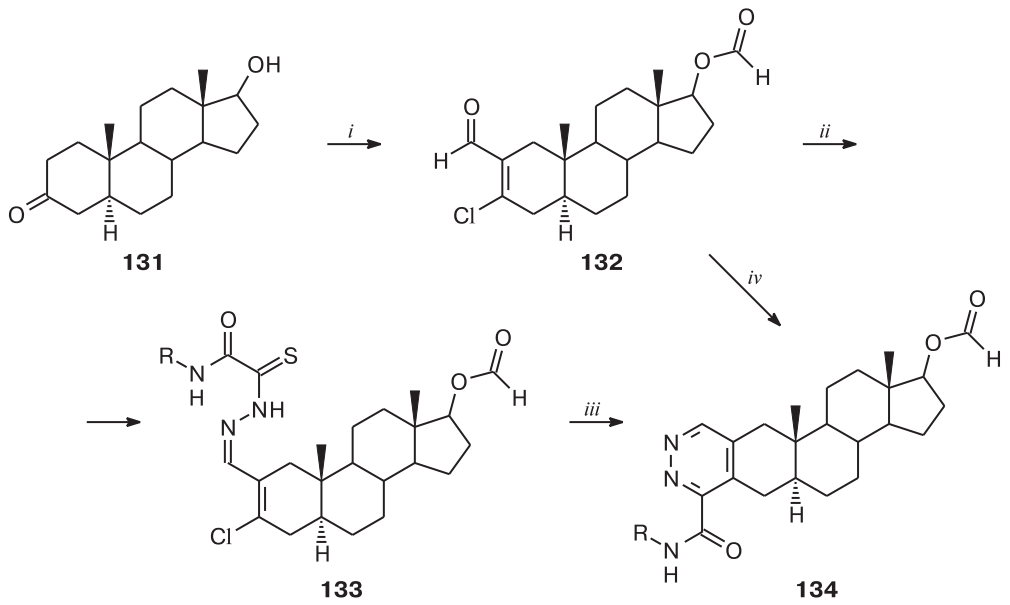
17β-Hydroxy-5α-androstan-3-one **131** was subjected to a similar reaction sequence (Scheme 51).[44] During the synthesis of chloroaldehyde **132**, the 17β-OH-group of compound **131** is formylated to give compound **132**, which reacts with thiohydrazide **88c** to give **133**; the latter is converted to 17β-formyloxy-5α-H-androst-2-ene-[3,2-*d*]-3′-(4-methoxyphenylcarbamoyl)pyridazine **134** in 81% yield.

Scheme 50



R = 4-$MeOC_6H_4$

Scheme 51

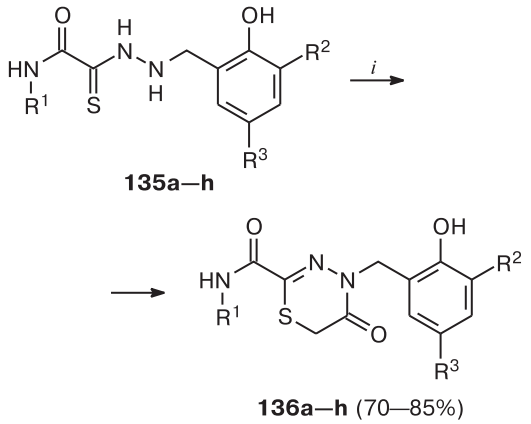


R = 4-$MeOC_6H_4$

Reagents and conditions: *i*. $POCl_3$, DMF, CH_2Cl_2. *ii*. Thiohydrazide **88c**, EtOH, TsOH. *iii*. EtOH, TsOH, Δ. *iv*. Thiohydrazide **88c**, EtOH, TsOH, Δ.

The products of reduction of oxamic acid thiohydrazide hydrazones **135a—h** react with chloroacetic acid in the presence of ammonium acetate, giving rise to *N*-aryl-4-arylmethyl-5-oxo-5,6-dihydro-4*H*-1,3,4-thiadiazine-2-carboxamides **136a—h** (Scheme 52).[14,28]

Scheme 52

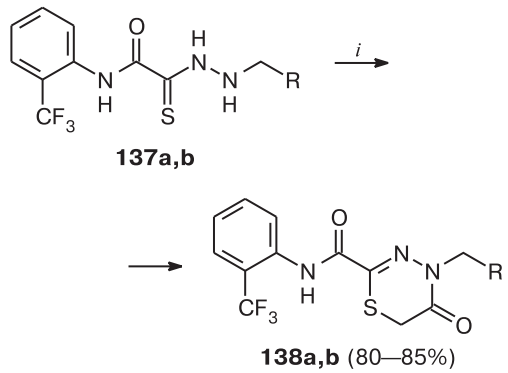


136	R^1	R^2	R^3	**136**	R^1	R^2	R^3
a	4-FC_6H_4	OEt	H	**e**	2-$F_3CC_6H_4$	OEt	H
b	3-FC_6H_4	OEt	H	**f**	3-$F_3CC_6H_4$	OEt	H
c	2-FC_6H_4	OEt	H	**g**	2-$F_3CC_6H_4$	Br	Br
d	4-FC_6H_4	Br	Br	**h**	4-$F_3CC_6H_4$	OEt	H

Reagents and conditions: *i*. $ClCH_2COOH$, $AcONH_4$, Pr^iOH, 2 h, Δ.

The reaction with thiohydrazides **137a**,**b** containing a pyridyl substituent does not require a catalyst: most likely, the pyridine ring itself acts as a base (Scheme 53).[14,28]

Scheme 53

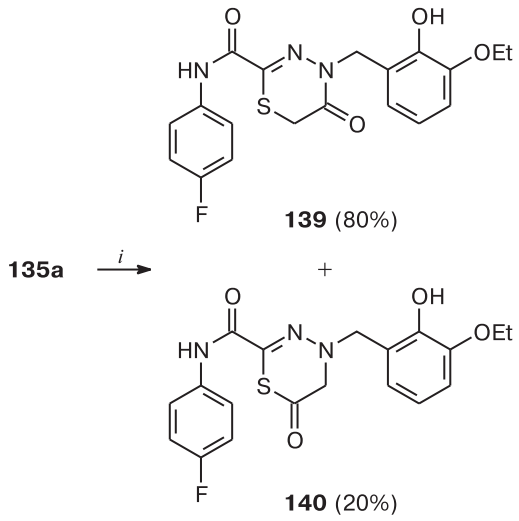


R = 4-pyridyl (**a**), 3-pyridyl (**b**)

Reagents and conditions: *i*. $ClCH_2COOH$, Pr^iOH, Δ.

The use of chloroacetic acid chloride in the reaction with thiohydrazide **135a**, unlike the use of chloroacetic acid, resulted in the formation of two products, thiadiazinone **139** being the predominant one. 6-Oxo-5,6-dihydro-4*H*-1,3,4-thiadiazine-2-carboxamide **140** was isolated as a side product (Scheme 54).[28]

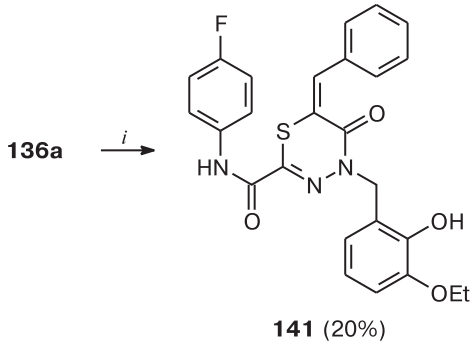
Scheme 54



Reagents and conditions: *i*. $ClCH_2C(=O)Cl$, DMF.

The possibility of modification of the thiadiazinones thus formed involving the ring methylene group was demonstrated. For example, refluxing of thiadiazinone **136a** with benzaldehyde in acetic acid for 8 h yielded the benzylidene condensation product **141** (Scheme 55).[28]

Scheme 55

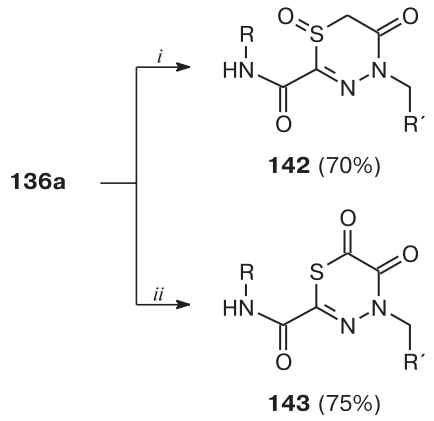


Reagents and conditions: *i*. Benzaldehyde, AcOH, 8 h, Δ.

The oxidation of thiadiazinone **136a** with hydrogen peroxide in acetic acid generates sulfoxide **142** (Scheme 56).[28] The attempts at selective oxidation of the ring methylene group without affecting the thiocarbonyl group did not meet with success: multicomponent product mixtures were obtained. However, 5,6-dioxo-5,6-dihydro-4*H*-1,3,4-thiadiazine-2-carboxamide **143** was still prepared by the reaction of thiohydrazide **136a** with oxalyl chloride in DMF at temperatures around 0 °C (see Scheme 56).[28]

The reaction of compound **136a** with aromatic α-bromo ketones resulted in the synthesis of thiadiazines **144a—c** (Scheme 57).[28]

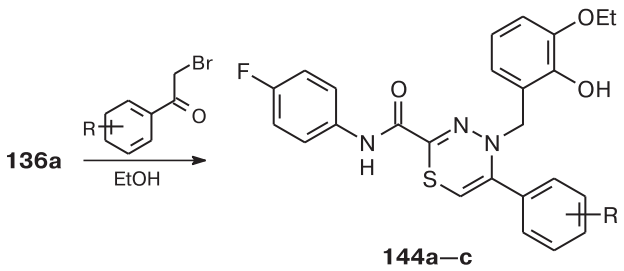
Scheme 56



R = 4-FC_6H_4, R′ = 2-HO-3-$EtOC_6H_3$

Reagents and conditions: *i*. H_2O_2, AcOH. *ii*. Oxalyl chloride, DMF, ~0 °C.

Scheme 57



R = H (**a**), 3-NO_2 (**b**), 4-Cl (**c**)

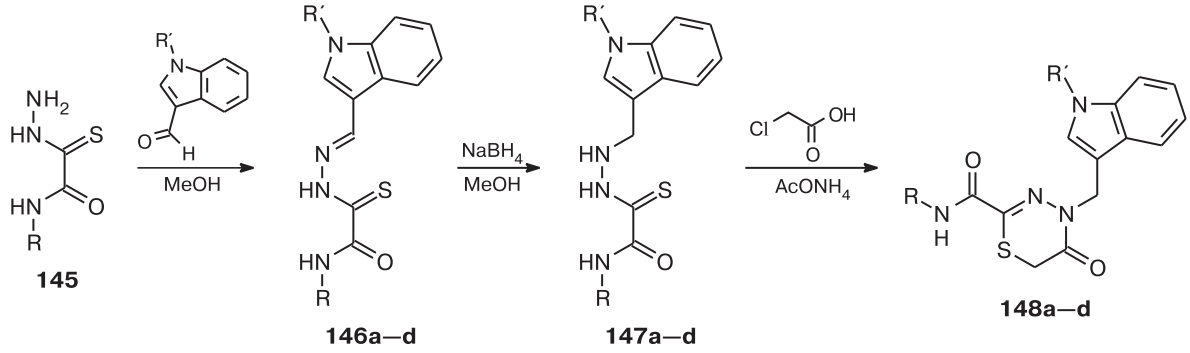
Thiohydrazides **145** were converted to indolecarbaldehyde hydrazones **146a—d**, which were reduced with sodium borohydride in methanol to afford derivatives **147a—d**. Their subsequent alkali-catalyzed reaction with monochloroacetic acid yields indole-containing thiadiazines **148a—d** (Scheme 58).[14]

Synthesis of seven-membered rings with various heteroatoms

Chloroacetamides **149a—c** were shown[19] to react with a mixture of 2,2′-diaminodiphenyl, triethylamine, and elemental sulfur prepared in advance (Scheme 59) to give carbamoyl-containing 5*H*-dibenzo[*d*,*f*][1,3]diazepines **151a—c**. The reaction is likely to proceed *via* monothiooxamides **150a—c**, which are then converted to dibenzodiazepines **151a—c**.

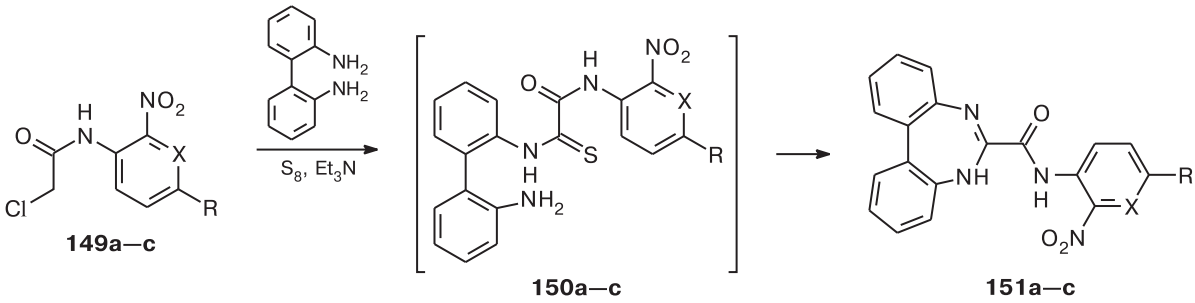
Thiohydrazides **135b**,**c**,**h** react with bromopropionic acid, being thus converted to tetrahydrothiadiazepines **152a—c** (Scheme 60).[14]

Scheme 58



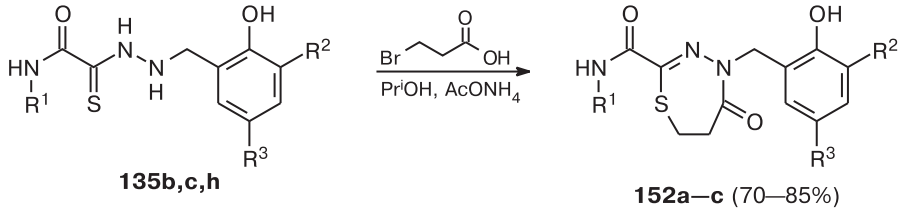
R = 2-$F_3CC_6H_4$, R′ = H (**a**); R = 2-$F_3CC_6H_4$, R′ = Me (**b**); R = 2-MeC_6H_4, R′ = H (**c**); R = 2,4-$F_2C_6H_3$, R′ = H (**d**)

Scheme 59



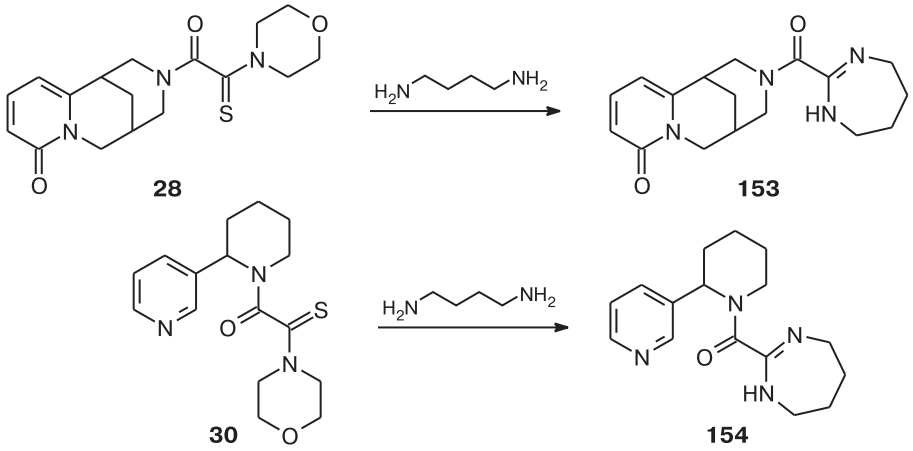
X = CH, R = H (**a**); X = CH, R = Cl (**b**); X = N, R = H (**c**)

Scheme 60



152: R^1 = 2-FC_6H_4, R^2 = OEt, R^3 = H (**a**); R^1 = 3-FC_6H_4, R^2 = OEt, R^3 = H (**b**); R^1 = 4-$F_3CC_6H_4$, R^2 = OEt, R^3 = H (**c**)

Scheme 61



The reaction of alkaloids **28** and **30** containing monothiooxamide moieties with diaminobutane furnishes tetrahydrodiazepines **153** and **154**, respectively (Scheme 61).[21]

Conclusion

The reactions summarized in the review demonstrate good prospects for the application of oxamic acid monothiooxamides and thiohydrazides in the construction of various heterocyclic compounds. The synthetic potential of oxamic acid monothiooxamides and thiohydrazides is comprised of the reactivities of the amide and thioamide groups or thiohydrazide group. There are numerous examples of separate involvement of these groups into generation of heterocyclic molecules.[45—51] However, the effect of the interplay between the most proximate amide and thioamide or thiohydrazide groups on the structure and reactivity of compounds has not been adequately studied. Therefore, the chemical potential of such compounds has not been fully implemented as yet. The preparation of carboxamide-containing thiazoles and their derivatives based on monothiooxamides has been studied most extensively. Oxamic acid monothiooxamides and thiohydrazides were found to have good prospects for the synthesis of other carboxamide-containing heterocycles that are of obvious interest as biologically active compounds, as indicated by published data. However, the synthetic potential of carboxamide groups of these compounds for the synthesis of polycyclic fused heterocyclic products has scarcely been investigated. It is evident that more extensive use of oxamic acid monothiooxamides and thiohydrazides as the starting compounds for the design of various mono- and polyheterocycles is promising for the preparation of new drugs. It is noteworthy that oxamic acid monothiooxamides and thiohydrazides are easily prepared from amines and, hence, it is possible to elaborate approaches to heterocyclic moieties based on quite a broad range of starting compounds, including numerous amine-containing natural products.

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Received September 24, 2018;
in revised form February 13, 2019;
accepted February 28, 2019