Thioamides as Useful Synthons in the Synthesis of Heterocycles

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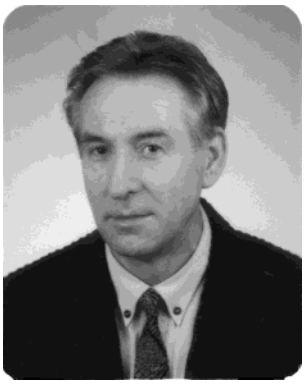
I. Introduction

More than 100 years have passed since the first synthesis and structural recognition of thioamides. Due to the great practical and synthetic applicability of that class of carboxylic acid derivatives, their significance and impact on the development of chemistry are continuously growing. Some thioamides are known today as biologically active compounds, either plant protection agents or drugs, while others are used as flotation and vulcanization agents, as additives to lubricating oils and greases, and as interesting ligands in coordination chemistry. Although comprehensive reviews of the chemistry of thioamides have been published in the past,[1] a vast amount of information has accumulated since that time, in particular during the last 20 years. Many interesting papers which have appeared lately report on functionalization of thioamides and their use in organic synthesis, including regio- and stereoselective heterocyclization reactions. In particular, this concerns the thioamides which have another reactive center in the molecule and therefore may serve as convenient building blocks.

Thioamides are most often prepared by simple thionation of the corresponding amides with the aid of phosphorus pentasulfide or the Lawesson reagent.[1,2] The practical use of this method is limited by the availability of the starting amide. Other methods for thioamide synthesis have been reviewed previously.[1,3,4] Recently, a direct synthesis of thioamides in the reaction related to the Friedel−Crafts



Tadeusz Stefan Jagodziński graduated from Technical University of Szczecin, Poland, in 1972 with a M.S. in chemical technology. In 1977 he received his Ph.D. degree in organic chemistry from Lomonosov State University in Moscow, Russia; his doctoral thesis, "Synthesis of condensed heterocycles from indolylurethanes", was completed under the supervision of Prof. A. N. Kost. From 1977 to 1991, he conducted research on thioamide chemistry and taught organic chemistry at Technical University of Szczecin. He received his habilitation degree in 1991 from Warsaw University of Technology for research on synthesis, reactions, and properties of the thioamide derivatives of benzene and some five-membered heterocycles. In 1994, he was appointed associate professor at the Department of Organic Chemistry, Technical University of Szczecin. Since 1991, he has been the head of this department. His current research interests concern the development of new methods for the synthesis of heterocyclic compounds from thioamide synthons.

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synthesis, namely by reacting isothiocyanates with aromatic[5,6] and heteroaromatic[7,8] compounds in the presence of Lewis acids, has been developed. Its practical usefulness prompted us to study the reaction mechanism[7] and, in particular, to attempt to explain the increased reactivity of isothiocyanates in a medium containing Lewis acids. An alternative method has been developed for the synthesis of thioamides from heteroaromatic substrates which are known to be unstable in strong acid media; such heteroaromatics must be converted into their metal derivatives prior to the reaction with isothiocyanates.[1,9−11]

The chemical and physical properties of thioamides are determined by the two active centers. One of them is associated with the nitrogen atom with the unshared pair of electrons, and the other one is localized on the thiocarbonyl group. The inductive and conjugation effects of the introduced substituents face in thioamides the mesomeric effect due to delocalization of π electrons and lability of the unshared electron pairs on the nitrogen and sulfur atoms. A distinct barrier to rotation about the formally single carbon−nitrogen bond and, consequently, *cis*(*Z*)/*trans*(*E*) isomerism are therefore observed in these systems.[1] Some thioamides may also reveal *s-cis*/*s-trans* isomerism arising from restricted rotation of the thioamide group about the carbon−carbon bond.[10,12,13]

II. Synthesis of Heterocyclic Compounds Using the Thioamide Group as a Single Building Unit

A. Reactions with Dielectrophiles

Two nucleophilic centers in thioamides are localized on the heteroatoms (sulfur and nitrogen). A potential third center appears in the thioamides having a hydrogen atom on the α carbon. An electrophilic center is associated with the thiocarbonyl carbon atom (Figure 1).

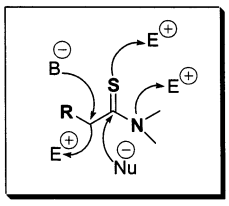


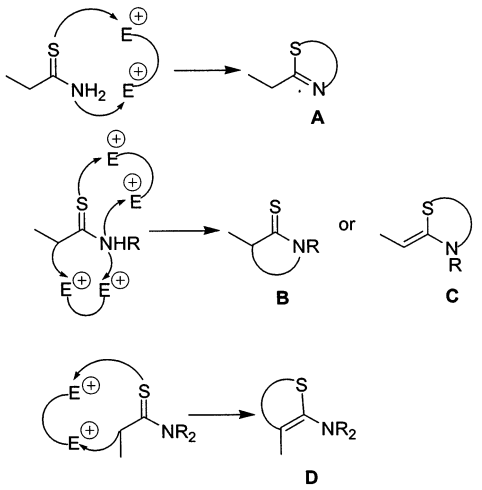
Figure 1.

Due to the presence of those active centers, the reactions of thioamides with dielectrophilic reagents may lead, depending on the structure of the starting thioamide, the nature of the dielectrophile, and the reaction conditions, to the formation of different heterocyclic compounds (structures **A**−**D**, Scheme 1).

A.1. Reactions with Alkyl Dihalides, Alkenyl Dihalides, and Halocarbonyl Derivatives

The heterocyclization reactions of thioamides with dielectrophiles reviewed in the following paragraphs proceed entirely within the thioamide group, although the α carbon atom may sometimes participate in the reaction. The respective reaction variants are

Scheme 1



shown in Scheme 1. Some of the examples presented below refer to functionalized thioamides, but, as a general rule, this additional functional group does not take part in the heterocyclization.

Alkylation of primary and secondary thioamides with alkyl 1,2-, 1,3-, and 1,4-dihalides is one of the earliest and simplest heterocyclization reactions known. Only the nitrogen and sulfur atoms of the thioamide group are alkylated, with the formation of the type A compounds. Although they have been known for a long time,[1] these alkylation reactions are occasionally used today in the synthesis of Δ^2-thiazolines[1,14] (**1**, $n = 1$), 5,6-dihydro-4*H*-1,3-thiazines[1] (**1**, $n = 2$), and thiazole **2**[1,15] and benzothiazepine **3**[1] derivatives (Figure 2).

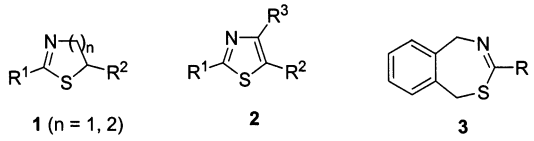
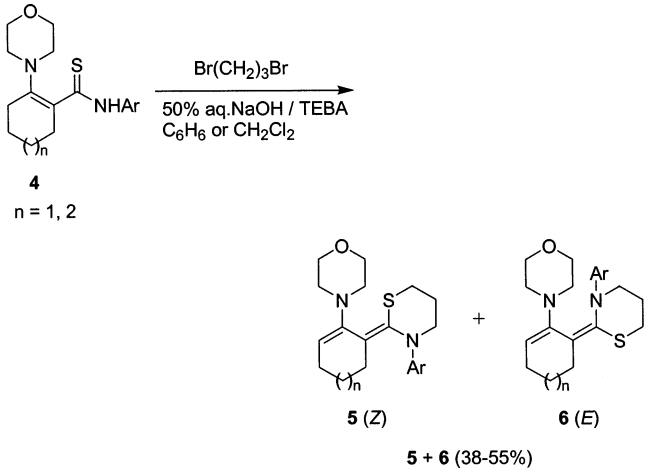


Figure 2.

N,S-Alkylation of thioamides with alkyl dihalides may be also realized in a two-phase system composed of a 50% aqueous solution of sodium hydroxide and benzene or dichloromethane as an organic phase, and benzyltriethylammonium chloride (TEBA) as a cata-

Scheme 2



lyst.[16,17] For example, thioanilides **4** react in such a system with 1,3-dibromopropane to give isomeric 3-aryl-1,3-thiazines **5** and **6** (Scheme 2).[16]

Thioanilides derived from enamines or cyclic ketones reacted under analogous conditions with 1,2-dibromoethane, yielding thiazolidine derivatives **7**−**10** of *Z* configuration (Figure 3).[16,17] The alkylation

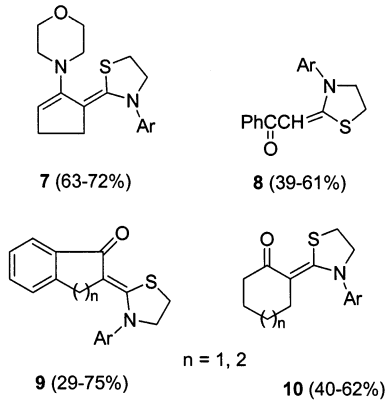
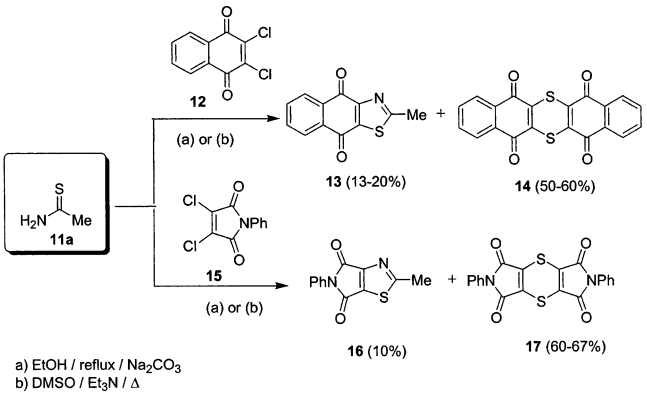


Figure 3.

invariably occurred exclusively at the nitrogen and sulfur atoms, furnishing heterocyclic compounds in moderate to good yields.

Quinone and maleimide derivatives are often used as reactive dienophiles in cycloaddition reactions. There are also known reactions of primary thioamides with dichloro compounds in which the vinyl chlorine atoms readily undergo a nucleophilic substitution.[18−21] For instance, 2,3-dichloro-1,4-naphthoquinone **12** and 2,3-dichloro-*N*-phenylmaleimide **15** react with thioacetamide **11a** to give mixtures of condensed thiazoles **13** and **16** and thianthrenes **14** and **17** (Scheme 3).[19,20]

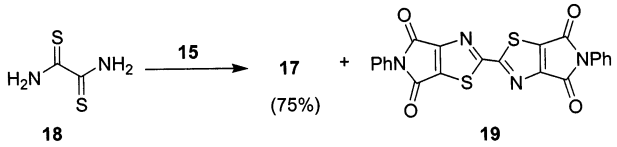
Scheme 3



When 2,3-dichloro-*N*-phenylmaleimide **15** was treated with dithiooxalic acid diamide **18**, the same 1,4-dithiine derivative **17** was obtained in 75% yield; the bisthiazole **19** was also present in the reaction mixture, although attempts to isolate it were unsuccessful (Scheme 4).[21] There are numerous examples of analogous reactions with thiourea and its *N*-substituted derivatives.[18−21]

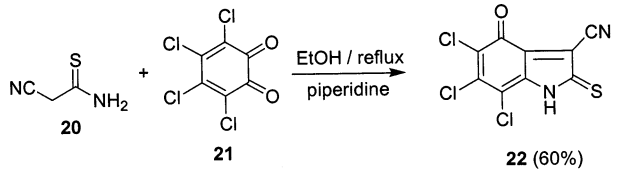
The reaction of primary thioamides with 3,4,5,6-tetrachloro-1,2-benzoquinone **21** takes a different course. Thus, **21** reacts with cyanothioacetamide **20** in the presence of a base to give the bicyclic system

Scheme 4



22 (Scheme 5).[22] This heterocyclization proceeds as the nucleophilic substitution−condensation with par-

Scheme 5

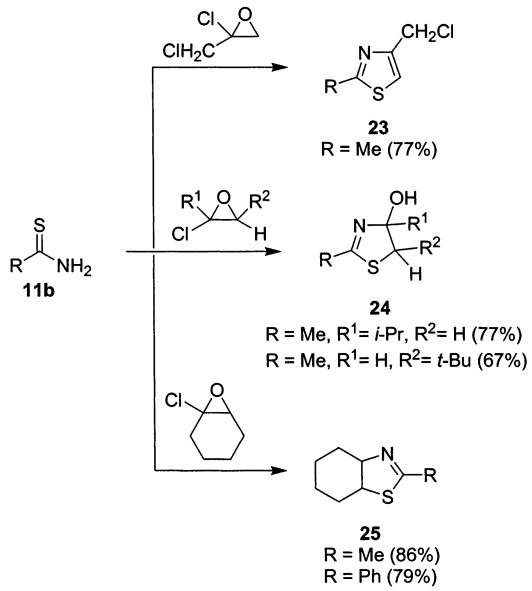


ticipation of both the nitrogen atom and the active methylene group of cyanothioacetamide and both the chlorine atom and the carbonyl group of **21**.

Since the thiazole ring is present in the structures of many biologically active compounds, methods for its synthesis still hold the interest of chemists. One of the oldest methods, as popular today as ever, involves the reaction of primary thioamides with α-halocarbonyl compounds (Hantzsch reaction).[1,23] A wide range of variously substituted thiazoles **2**, such as those bearing ester,[24−32] carboxy,[33] aminoalkyl,[34] and methyl-triphenylphosphonium[35] functions and aryl,[36,37] aryl-alkylamino,[38] and aryl-heterocyclic[39,40] substituents, can be obtained in the reactions of thioamides derived from aliphatic, aromatic, and heterocyclic acids with appropriately functionalized carbonyl compounds. The most important methods for the synthesis of 1,3-thiazoles **2** (Figure 2), including those starting with thioamides, have been reviewed by Liebscher in a comprehensive monograph.[23]

Thiazole derivatives can also be synthesized in the reactions of thioamides with 2-chlorooxiranes, which are isomeric with α-chlorocarbonyl compounds. Depending on the structure of the starting 2-chloro-

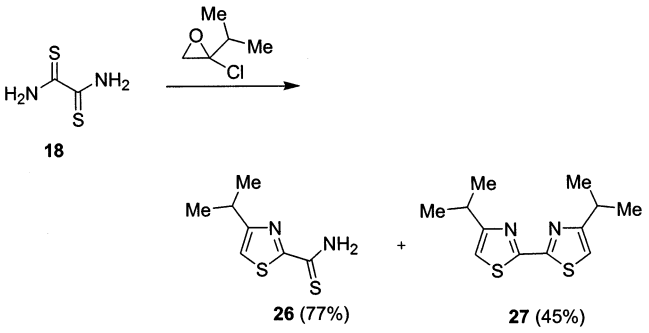
Scheme 6



oxirane, derivatives of thiazole **23**, 4,5-dihydrothiazole **24**, or tetrahydrobenzothiazole **25** are obtained (Scheme 6).[41]

In the reaction with dithiooxalic acid diamide **18**, the ratio of the starting materials determines whether thiazole-2-carbothioamide **26** or 2,2′-bisthiazole **27** is isolated in good yield (Scheme 7). 2-Chlorooxiranes

Scheme 7



react with thiourea derivatives in a similar way.[41]

A few new thiazole derivatives with potential biological activity were prepared with the use of 3-bromolactams as the α-halocarboxylic substrates. Thus, Uchikawa obtained biheterocyclic thiazole-derived systems **28** in the reaction of thiobenzamides with 3-bromolactame in refluxing ethanol; the yields were, however, rather low (Figure 4).[34,42]

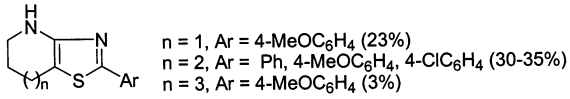
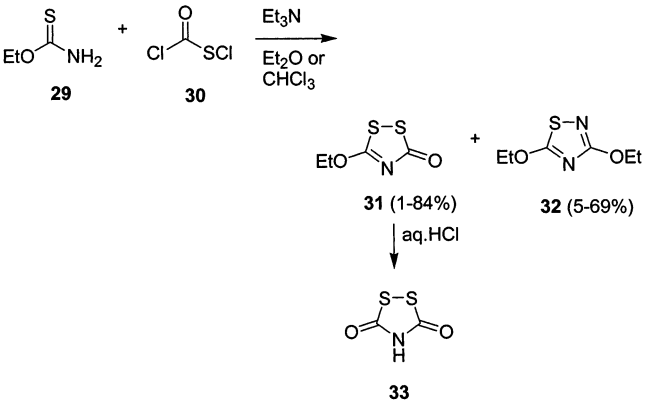


Figure 4.

Solvent effects are particularly conspicuous in the reactions of primary thioamides with (chlorocarbonyl)sulfenyl chloride **30**.[43] Reaction of *O*-ethyl thiocarbamate **29** with **30** gives 3-ethoxy-1,2,4-dithiazolin-5-one **31** and 3,5-diethoxy-1,2,4-thiadiazole **32**, the relative amounts of **31** and **32** formed depending very much on the solvent (e.g., diethyl ether favors **31**, while chloroform favors **32**) (Scheme 8). Compound

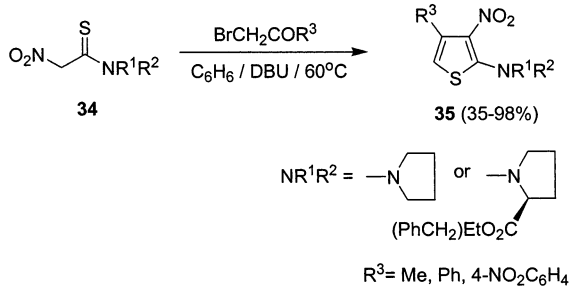
Scheme 8



31 was converted into 1,2,4-dithiazolidine-3,5-dione **33**, a highly effective sulfurization agent.[43]

In contradistinction to the reactions of primary and secondary thioamides, the nitrogen atom cannot take part in heterocyclization of tertiary thioamides. However, if a tertiary thioamide has an active methylene group, it is capable of yielding 2-aminothiophene derivatives in the reaction with α-halocarbonyl compounds.[44,45] For example, nitrothioacetamides **34** react in the presence of a base with α-bromoketones to give 2-amino-3-nitrothiophenes **35** (Scheme 9).[45]

Scheme 9



Tricyclic thiophene derivatives **36** and **37** were synthesized from appropriate thiolactams and α-halocarbonyl compounds by Hart[46] and Meyers,[47] respectively (Figure 5). Both of the thioamide hetero-

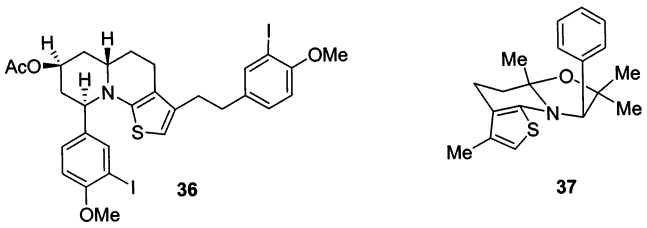
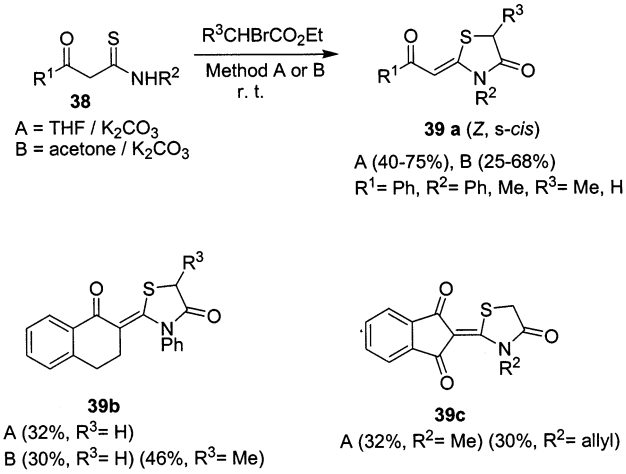


Figure 5.

atoms are also active in the reaction of secondary β-keto thioamides **38** with α-bromoesters. When the reaction is carried out at room temperature in anhydrous THF or acetone in the presence of anhydrous potassium carbonate, it gives the derivatives of (*Z*)-*s*-*cis*-2-acylmethylenethiazolin-4-one **39a**−**c** (Scheme 10).[48] Rather unexpectedly, the indandione-

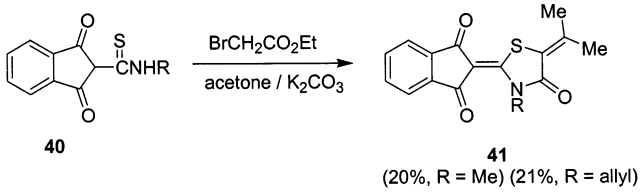
Scheme 10



derived thioamides **40** react with ethyl bromoacetate in acetone to yield the corresponding 5-isopropylidene

derivatives **41** only (Scheme 11);[48] that means that the initially formed thiazolone reacts also with

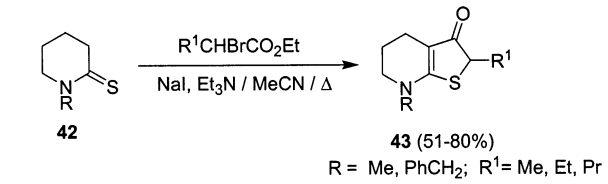
Scheme 11



acetone. Under analogous conditions, **38** and **40** failed to cyclize in the reaction with ethyl 2-bromopropionate; only *S*-alkylation of the thioamides was noted. With **39a**−**c**, which readily condense with aromatic aldehydes, acetone proved to be an inert solvent.[48]

α-Bromoesters were also reported to react with *N*-substituted piperidine-2-thiones **42** to form thieno-[2,3-*b*]pyridin-3-ones **43** (Scheme 12).[49]

Scheme 12

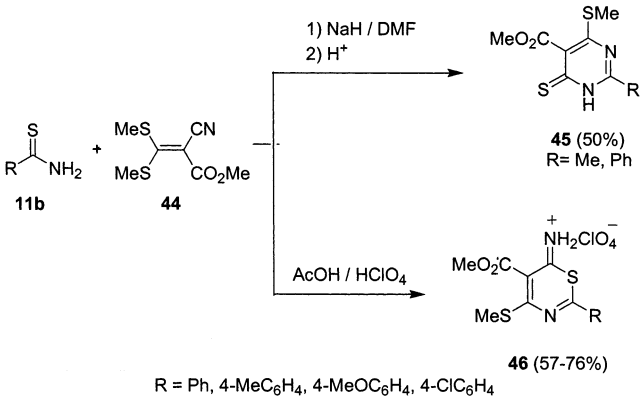


B. Reactions Involving an Activated Unsaturated Bond

B.1. Addition–Cyclization Reactions

The sulfur and nitrogen atoms of primary thioamides stand high enough in the order of nucleophilicity to induce heterocyclization reactions of thioamides with activated alkenes. Thus, in the reaction **11b**,**c** with the ketene dithioacetal **44**, derivatives of pyrimidine-6-thione **45** are formed (Scheme 13),[50] and

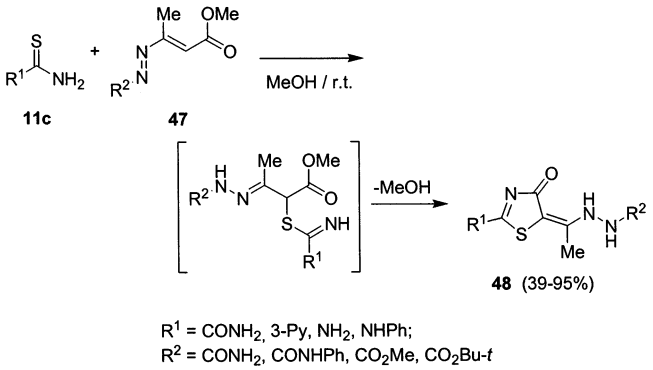
Scheme 13



in the reaction with methoxycarbonylazaalkenes **47**, derivatives of thiazolin-4-one **48** (Scheme 14)[51] are formed. The reactions follow the two-step addition−cyclization mechanism.

Derivatives of 6-imino-6*H*-1,3-triazine **46** were isolated in the reactions carried out in a highly acidic medium (a mixture of acetic acid with anhydrous perchloric acid).[52] These labile compounds are intermediates in the reaction of thioamides with ketene-

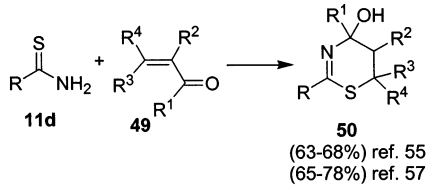
Scheme 14



dithioacetal. Pyrimidine-6-thiones **45** were also obtained in an analogous reaction of thioamides with methoxymethylene compounds.[53,54]

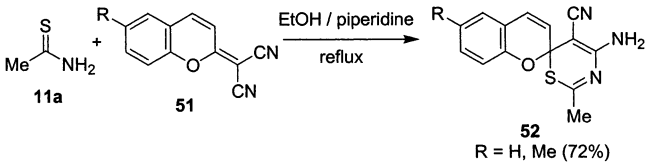
Similarly, vinyl ketones **49** readily react with primary thiomides **11d** to yield thiazine derivatives **50** (Scheme 15).[55−57]

Scheme 15



The formation of spiroheterocyclic compounds **52** was noted in the reaction of thioacetamide **11a** with heterocyclic dienophiles such as 2-chromenylidenemalonodinitrile **51** (Scheme 16).[58] Irrespective of

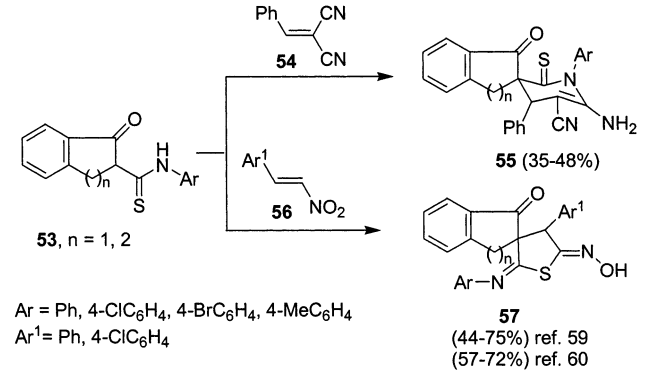
Scheme 16



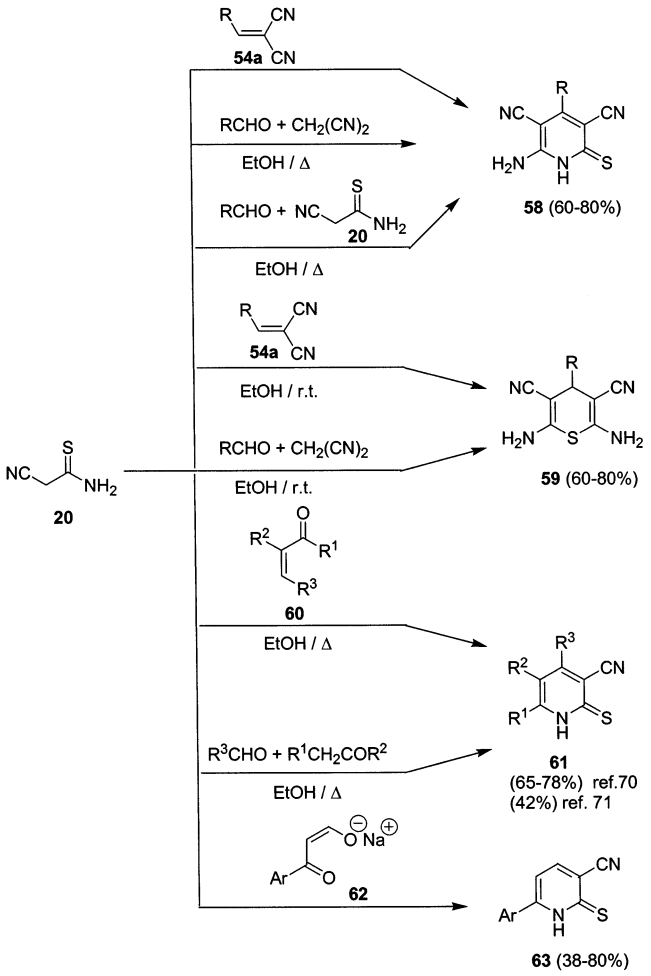
whether the reactions are base-[1,55] or acid-catalyzed,[1,56] both of the thioamide heteroatoms are engaged.

Different spiroheterocyclic systems, **55** and **57**, are formed in the two-step reactions of secondary thioamides **53** with arylidenemalononitriles **54** and nitroalkenes **56** (Scheme 17).[59,60]

Scheme 17



Scheme 18



The thioamides having active α hydrogen atoms, such as 2-cyanothioacetamide **20**, undergo addition−cyclization reactions with *gem*-dicyanoalkenes. Thus, derivatives of pyridine-2-thione **58** were obtained in the base-catalyzed reactions of 2-cyanothioacetamide **20** with alkylidene- and arylidenemalonodinitriles **54a** (Scheme 18).[61,62] In situ generation of the alkylidene- and arylidenemalonodinitriles is often practiced in these reactions.[63,64] Depending on the reaction temperature, the addition−cyclization reactions involve either the nitrogen or the sulfur atom of the thioamide group and one of the cyano groups of the olefinic dinitrile.

Pyridine-2-thiones **58** are also formed in the reaction of 2 mol of 2-cyanothioacetamide **20** with 1 mol of the appropriate aldehyde (Scheme 18).[65,66] However, if this reaction is carried out at room temperature, 4*H*-thiopyranes **59** are obtained instead and, in contradistinction to the reactions described earlier, the heterocyclization takes place via the sulfur atom.[67−69]

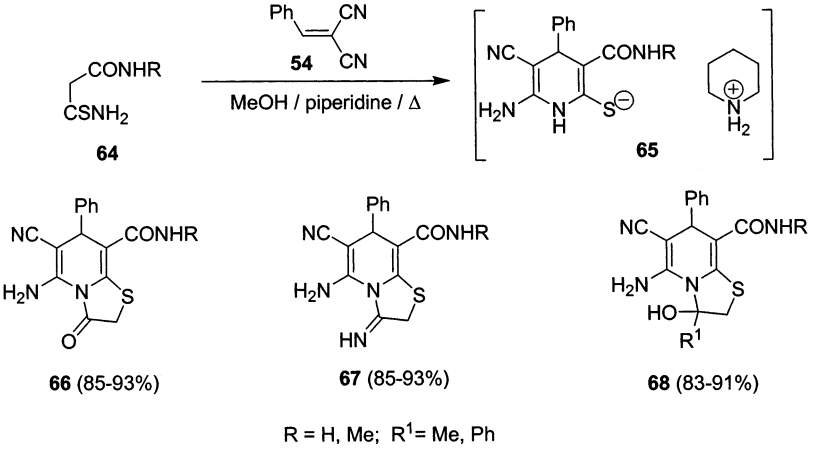
With the alkylidene derivatives of ketones[70,71] (**60**, R^2 = H, alkyl) and β-ketoamides[72,73] (**60**, R^2 = CONHR), 2-cyanothioacetamide **20** yields 2-thiopyridones **61**; the formation of hydrogenated thiopyridones or pyridines was also encountered.[72,73] Reactions of **20** with β-keto aldehydes **62** afforded similar products **63** (Scheme 18).[74]

Similar reactions have been reported by Dubur et al.,[75] who reacted thiocarbamoylacetamide **64** with benzylidenemalononitrile **54**; 1,4-dihydropyridine-2-thiolate **65**, which was formed here as an intermediate, served as the substrate in the synthesis of various bicyclic heterocycles, **66**−**68** (Scheme 19).

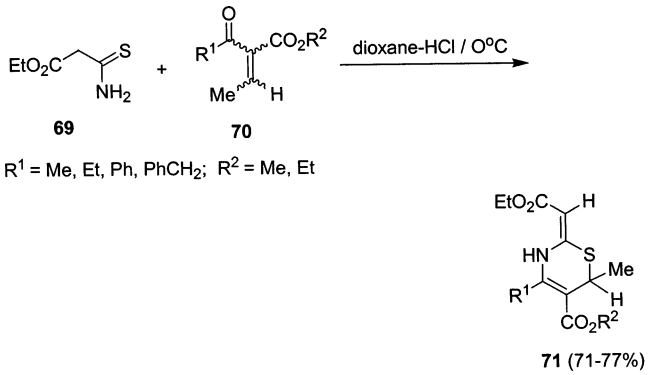
Cyclocondensation reactions may be also catalyzed by acids. Thus, condensation of ethoxycarbonylthioacetamide **69** with α,β-unsaturated keto esters **70** using anhydrous hydrogen chloride in 1,4-dioxane gave dihydrothiazines **71** in yields of 71−77% (Scheme 20).[76] Photolytic transformations of **71** were also investigated.[76]

An analogous reaction of thioamide with α,β-unsaturated ketone was used in the search for a method for the synthesis of an extremely labile γ-lactam with structural similarity to a cephalosporin antibiotic. Young and co-workers[77] prepared the thiazine allyl ester **73** by condensation of ethoxycarbonylthioacetamide **69** with allyl 2-oxo-3-methyl-but-3-enoate **72**. This was converted into the γ-lactam allyl ester **74** with the aid of oxalyl chloride (Scheme 21).[77] Heteroannulation of thioamides can be also effected with the aid of epoxyphosphonates.[78−80] The cyclocondensation proceeds with regioselective conjunction of the thioamides (bis-nucleophile) to the carbonyl group and the adjacent oxirane carbon of the epoxide precursor. Thus, reaction of the thiocarboxamides **11e** with cyclohexyl phosphonate **75** in boiling ethanol afforded satisfactory yields of the

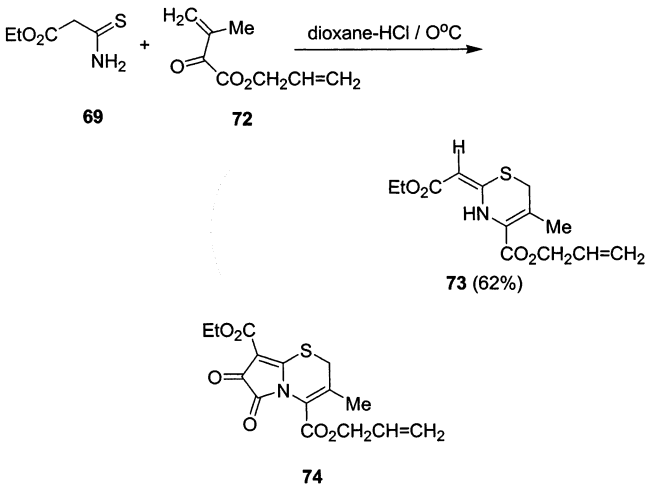
Scheme 19



Scheme 20



Scheme 21



desired bicyclic annulation products **77**.[80] An intermediate cyclization product **76** was isolated after a short reaction time. Reaction of the corresponding cyclopentylphosphonate **78** with thiobenzamide **11e** (R = Ph) yielded the cyclopentathiazole derivative **79** as a single isomer (Scheme 22).[80] In earlier investigations, similar cyclocondensations of thioamides with dialkyl (3-acyloxiranyl)phosphonates **80**[78] and dialkyl (3-acyloxiranylmethyl)phosphonates **81**[79] were achieved by Öhler and co-workers (Scheme 22).

Also known are reactions in which the unsaturated carbonyl substrate is formed in situ in the reaction mixture. The 2-diazo-1,3-diketones **82** react with thioamides **11f** via the acyl ketenes **84**, resulting from Wolff rearrangement,[81,82] to give 1,3-oxazine-4-ones **86**. However, by increasing the electrophilicity of the diazo compounds or the nucleophility of the thioamides, 5-acylthiazoles **85** are obtained. These are derived from the diketocarbene intermediates **83** (Scheme 23).[83]

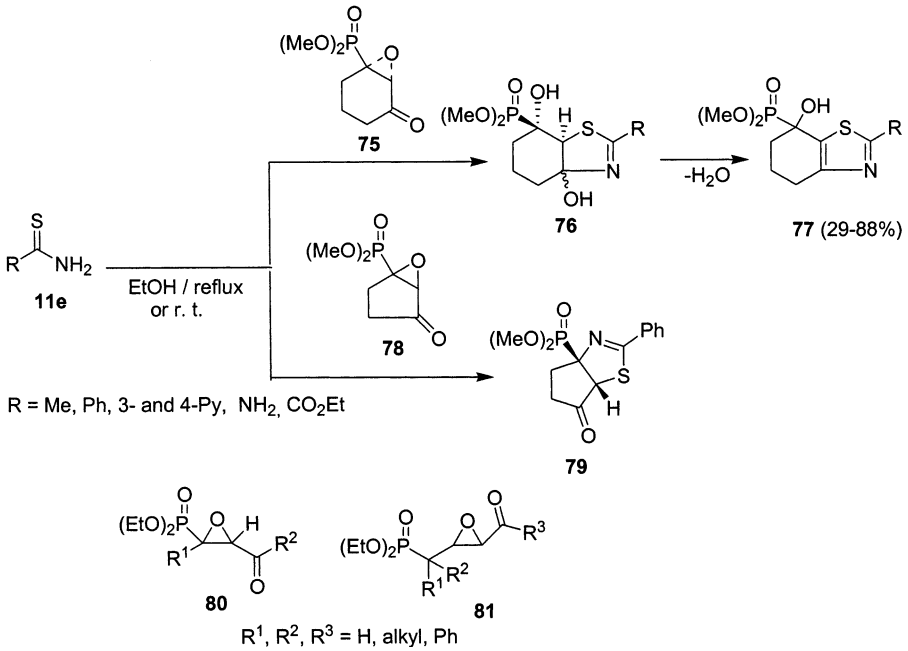
B.2. Cycloaddition Reactions

As in other thiocarbonyl compounds, the thiocarbonyl group of thioamides may react in the cycloaddition reactions as a dienophile. For example, the reaction of thioamides **87** with nitrileimines generated from **88**, which proceeds according to the [3 + 2] cycloaddition mechanism, is known to give 1,3,4-thiadiazoles **89** (Scheme 24).[84,85] The formation of spiroheterocyclic compounds was noted in the analogous reaction of pyrimidine-2-thiones with nitrileimines.[86] A similar reaction of *N*,*N*-dimethylthioformamide **90** with the dienes **91** followed the [2 + 4] mechanism to yield thiopyrans **92** (Scheme 25).[87]

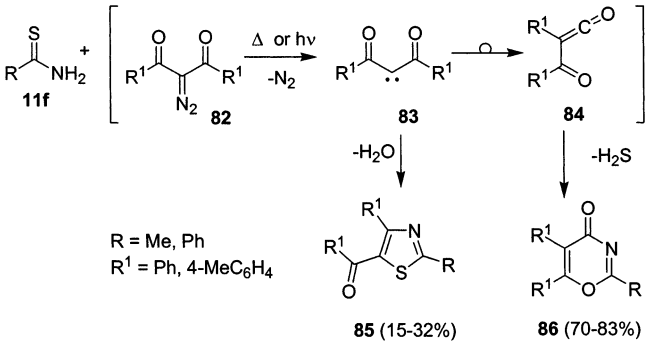
The photochemical reaction of primary thioamides **11g** with furans **94**, used for the preparation of the derivatives of 2-aryl-4-formyl(acetyl)pyrroles **96**, may serve as another illustrative example of the thioamide cycloaddition reactions.[88] This conversion involves a [2 + 2] cycloaddition of furans **94** to the C=N bond of the imine form of thioamide **93** and a subsequent rearrangement of the intermediate **95** to the pyrrole derivatives **96** (Scheme 26).

An analogous [2 + 2] cycloaddition is known to be active in the synthesis of β-lactam **99** from *S*-alkylated thioamide **97** and a diene-ketene. Reaction of **97** with the diene-ketene photochemically gener-

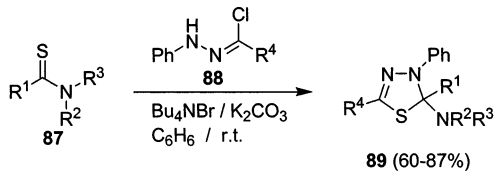
Scheme 22



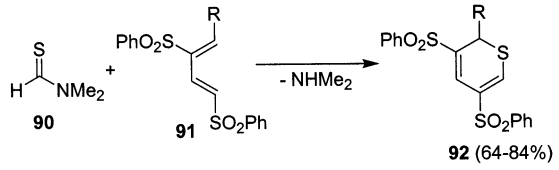
Scheme 23



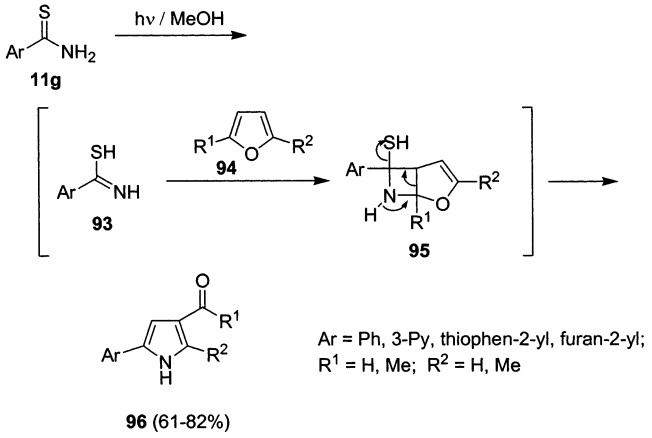
Scheme 24



Scheme 25

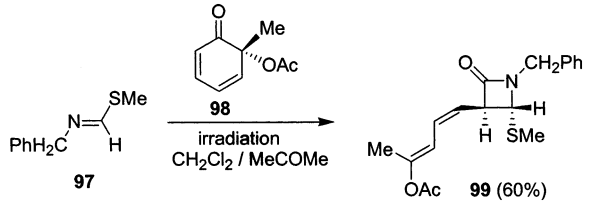


Scheme 26



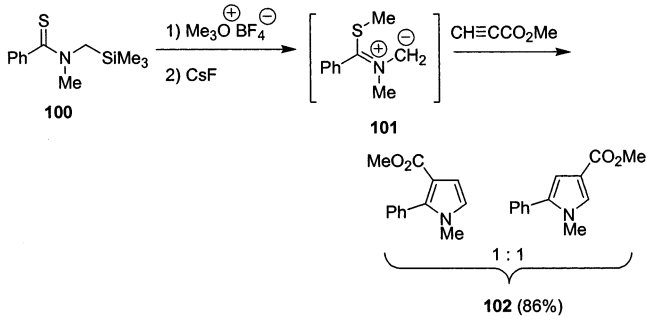
ated from *rac*-**98** results exclusively in the trans-configured product *rac*-**99** (Scheme 27).[89]

Scheme 27



Thioamides may be also useful in generating reactive 1,3-dipolar compounds for further cycloaddition reactions. Thus, when thioamide **100** is *S*-alkylated and next desilylated with cesium fluoride, the azomethine ylides **101** formed react with esters of propiolic acid according to the [3 + 2] cycloaddition mechanism to give derivatives of pyrrole **102** (Scheme 28).[90]

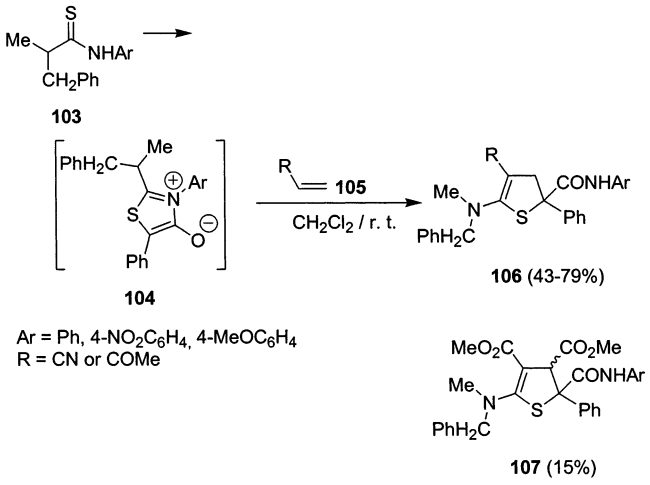
Scheme 28



Similar reactions of azomethine ylides with dipolarophiles and with acrylic and propiolic esters have been reported earlier.[91]

Mesoionic compounds have been known for many years and have been extensively utilized as substrates for 1,3- and 1,4-dipolar cycloadditions. They are easily prepared by cyclocondensation of an appropriate thioamide with a substituted malonyl dichloride derivative, with (chlorocarbonylphenyl)-ketene α-(tosylhydrazono)phenylacetylchloride, or with carbon suboxide.[92−99] They react with a variety of dienophiles to give heterocyclic compounds including annulated polycyclic systems. Thus, dihydrothiophenes **106** can be obtained by a general protocol involving the reaction of 2-aminothioisomünchnones **104** with electron-deficient alkenes **105**.[99] The overall process can be interpreted as a sequential [3 + 2] cycloaddition/ring-opening cyclization process. When **104** was treated with acrylonitrile **105** (R = CN) or methyl vinyl ketone **105** (R = COMe), the corresponding dihydrothiophenes **106** were regiospecifically formed as the sole products.[99] Mesoionic compounds **104** were also found to react with dimethyl maleate to afford the dihydrothiophene **107**, albeit in lower yields (Scheme 29).[99]

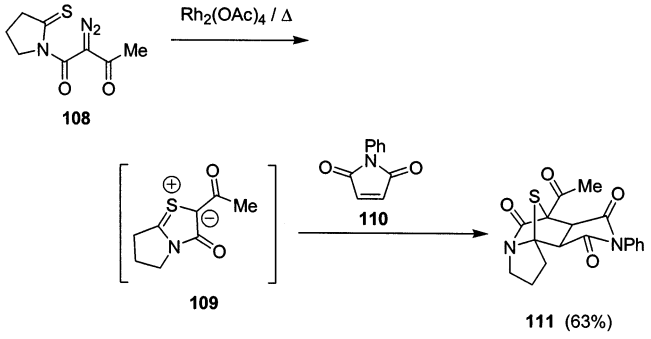
Scheme 29



Padwa and co-workers[93] used diazo derivatives of thioamides **108** as precursors of thioisomünchnone

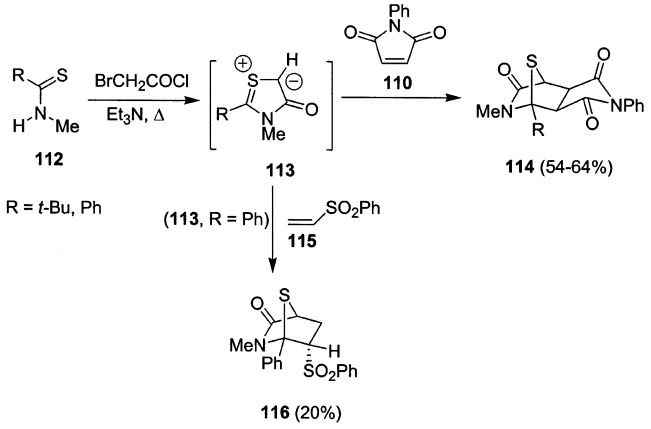
109. For example, in the reaction with rhodium tetraacetate, **108** is converted into **109**, which, when treated with *N*-phenylmaleimide **110**, gives the cycloadduct **111** (Scheme 30).[93]

Scheme 30



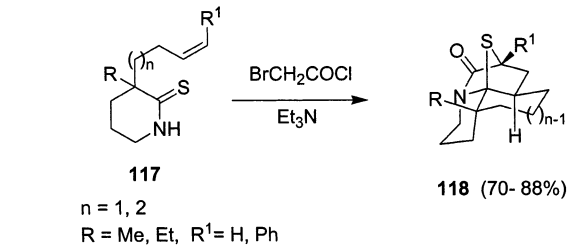
In other reactions, sequential treatment of thioamides **112** with bromoacetyl chloride and triethylamine in the presence of 1 equiv of *N*-phenylmaleimide **110** afforded cycloadducts **114**. These compounds are derived by dipolar cycloaddition of the mesoionic species **113** with the added dipolarophile. Cycloaddition of thioisomünchnone **113** with an unsymmetrical dipolarophile, such as phenyl vinyl sulfone **115**, afforded the cycloadduct **116** (Scheme 31).[93] When an alkene chain is present in the starting

Scheme 31



thioamide **117**, the reactions of thioisomünchnone cycloaddition may also proceed according to an intramolecular mechanism. Polycyclic heterocycles, such as compound **118**, are formed in these reactions (Scheme 32).[93]

Scheme 32



Several papers concerning 1,4-dipolar cyclization with the use of cross-conjugated heteroaromatic betaines have been published by Padwa over the past decade.[93−98] Six-membered mesoionic compounds with the 1,3-thiazine core **123** are formed in the reactions of an appropriate thioamide **119** with methyl malonyl dichloride **120**, with (chlorocarbonyl)phenyl ketene **121**, and with carbon suboxide **122**.[93−98] These cross-conjugated heteroaromatic betaines **123** undergo regio- and diastereospecific 1,4-dipolar cycloaddition with electron-rich and electron-deficient π-bonds to produce 1,4-cycloadducts **127**−**130**, containing a carbonyl−sulfide bridge. In certain cases, the initially formed cycloadduct can be induced to lose carbonyl sulfide on further heating. Illustrative examples of certain reactions are shown in Scheme 33.[94]

The thiazine betaines **132**, **135**, and **138** may undergo an intramolecular 1,4-dipolar cycloaddition with the formation of aza-, diaza-, and polyazaheterocyclic systems.[95−98] This takes place when the starting thioamide, prior to the conversion into betaine, contains in its structure an alkene or alkyne chain. Selected examples of such intramolecular cycloadditions are shown in Scheme 34.

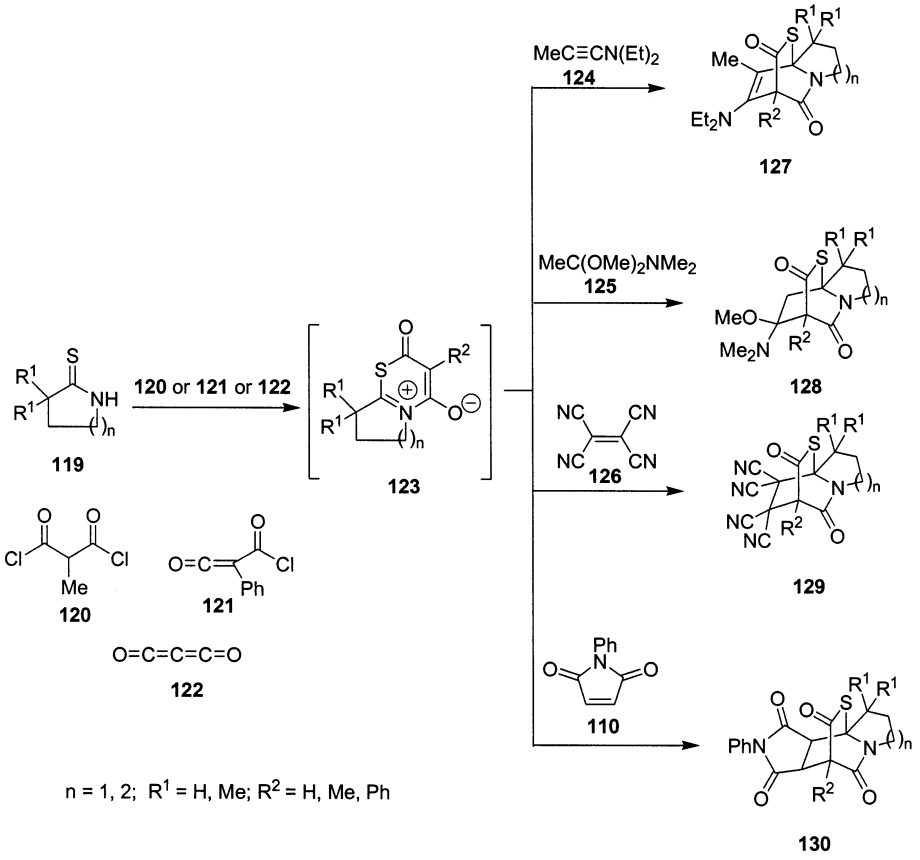
An interesting method for the synthesis of the derivatives of pyrrole, **145**, **149**, **150**, and of imidazole, **148**, has been advanced by Katritzky.[100] Thus, lithiation of *N*-(benzotriazol-1-ylmethyl)thioamide **140**, followed by *S*-methylation with methyl iodide, gives the corresponding *S*-methylthioimidate **141**, which undergoes [2 + 3] cycloaddition reactions with α,β-unsaturated esters, ketones, and nitriles **142**. Subsequent elimination of the benzotriazole and thiomethyl group yields 2,3,4-trisubstituted pyrroles **145**. When 4-vinylpyridine **143** and 2-vinylpyridine **144** were used, the 2-phenyl-3-(pyridin-4-yl)pyrroles **149** and 2-phenyl-3-(pyridin-2-yl)pyrroles **150** were obtained (Scheme 35).[100] Lithiation of **141** followed by reactions with imines **146** gives 4,5-dihydroimidazoles **147**, which upon further treatment with zinc bromide or direct refluxing in toluene are converted into 1,2,5-trisubstituted imidazoles **148** in good yields (Scheme 35).

The reactions of *N*-phenylmaleimide **110** with primary and secondary thioamides in refluxing dioxane are known to give products of greater complexity.[101] With thiobenzamide and *p*-toluamide **11h**, for example, they give **151** together with 4-hydroxythiazoles **152** (Scheme 36).[101] The yields of the two products **151** and **152** depend mostly on the proportion of the substrates and to a lesser extent on the reaction time. A decrease in the yield of **152** and a marked increase in that of **151** were observed with an excess of the maleimide substrate.

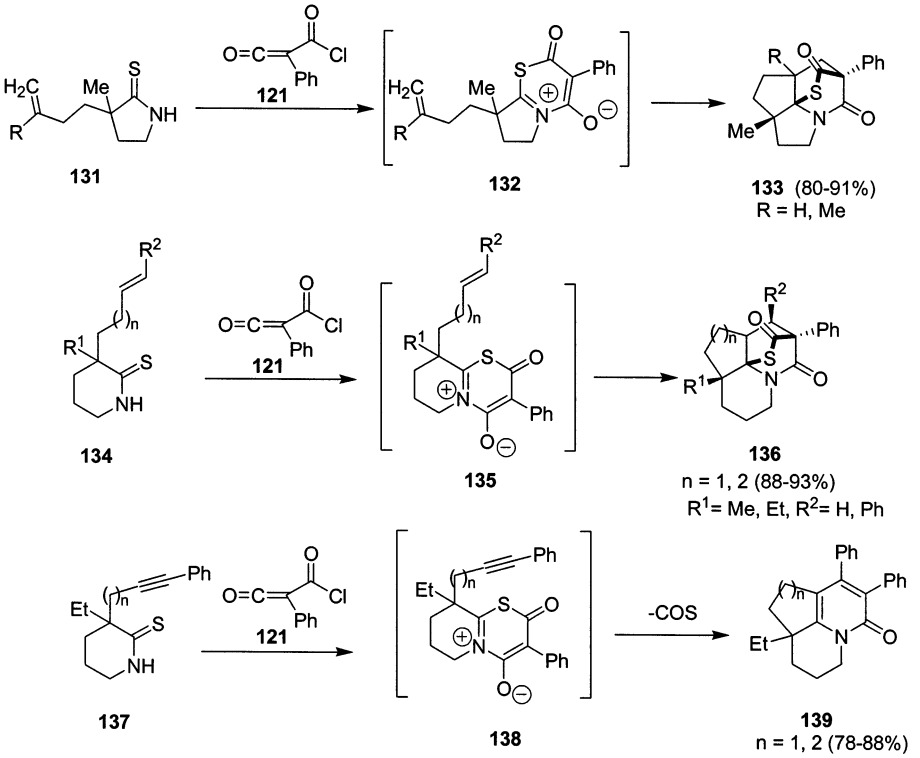
However, only the addition product **154** was obtained when a similar reaction of secondary thioamides, such as thioacetanilide **153** with *N*-phenylmaleimide **110**, was carried out with no acid added to the reaction medium (Scheme 37).[101]

Polycyclic indole systems can be obtained in the reaction of primary arylthioamides with 2-furan- and 2-thiopheneacrylic acids.[102] Photolysis of thiobenzamide **11i** (Ar = Ph) and 4-pyridinecarbothioamide **11i** (Ar = 4-pyridyl) with heterocyclic derivatives of

Scheme 33

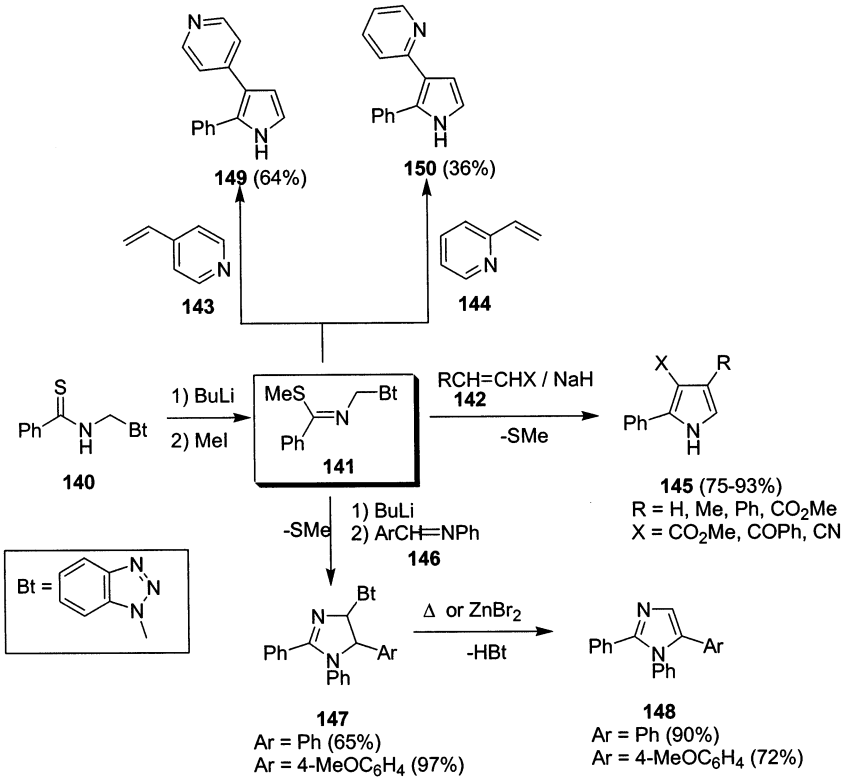


Scheme 34

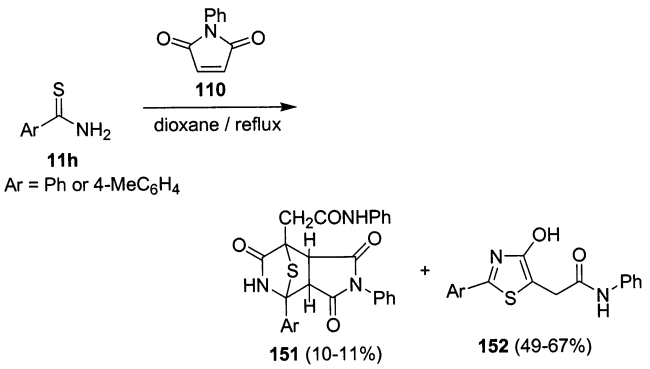


acrylic acid **155** in benzene gives tetracyclic derivatives of indole **156**; disubstituted derivatives of 1,3-dihydropyrrol-2-ones **157** are formed as byproducts (Scheme 36).[102] An analogous reaction of the thioamides derived from furoic acid **11i** (Ar = 2-furyl) and thiophene-2-carboxylic acid **11i** (Ar = 2-thienyl) gives only the corresponding derivatives of pyrrolin-2-one **157**. In the presence of iodine, the 2,3-diaryl-

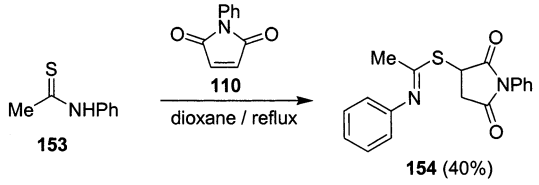
Scheme 35



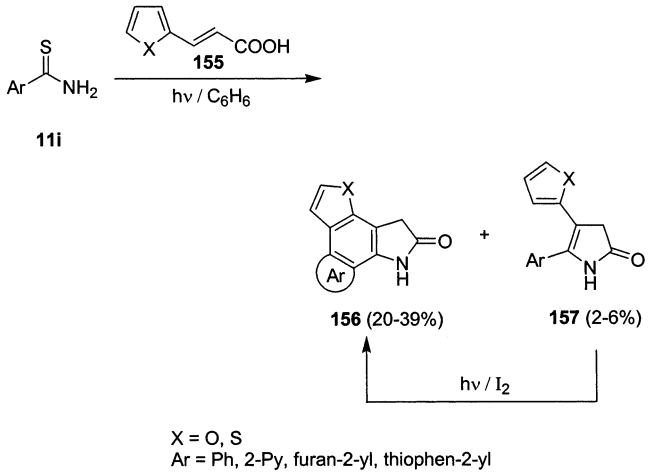
Scheme 36



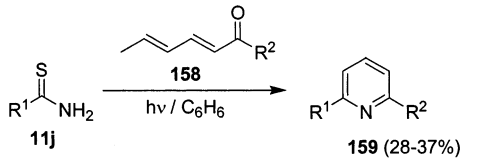
Scheme 37



Scheme 38



Scheme 39



2-pyrrolin-5-ones **157** derived from six-membered arenecarbothioamides **11i** (Ar = Ph and 2-pyridyl) were readily converted in good yields by photolysis into the tetracyclic indoles **156**. This was not the case with the five-membered arenecarbothioamides, which failed to yield the tetracyclic structures (Scheme 38).[102]

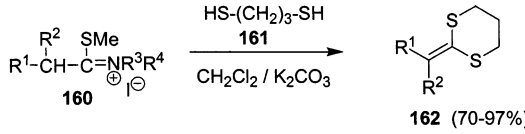
Moderate yields of 2,6-disubstituted and 2-substituted derivatives of pyridine **159** were also obtained in a complex photoreaction of arenecarbothioamides **11j** with diene-conjugated carbonyl compounds **158** in benzene (Scheme 39).[103]

C. Reactions with Nucleophiles

To increase the reactivity of thioamides toward nucleophilic reagents and to block the sulfur atom in the heterocyclization process, *S*-alkylation is often employed. However, both the nitrogen and sulfur atoms of the thioamide undergo substitution in the reaction with dinucleophilic compounds. Thus, ketene

thioketals **162** can be obtained in the reaction of **160** with dimercaptan **161** (Scheme 40),[104] tetrahydro-

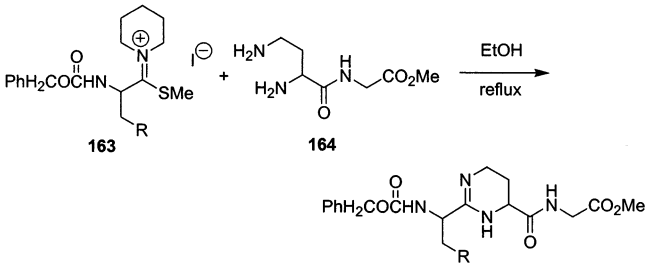
Scheme 40



R^1 = Me, Ph, CH_2Ph, $CH_2=CH(CH_2)_7$-, $CH_3(CH_2)_4$-, $Ph(CH_2Ph)CH$-, *t*-$BuOCOCH_2$-, $Me_2NCOCH_2(Ph)CH$-; R^2 = H, Me, $R^3 = R^4$ = Me, R^3R^4 = -$(CH_2)_3$-

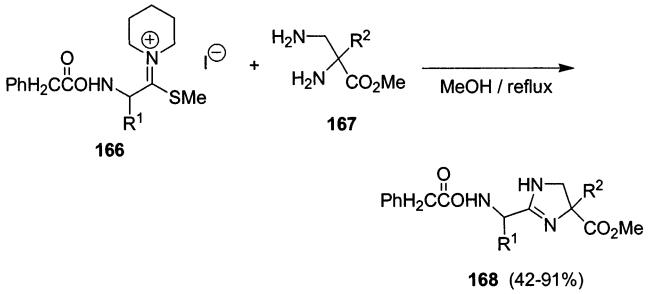
pyrimidines **165** in the reaction of **163** with diamine **164** (Scheme 41),[105] and imidazolines **168** in the reaction of **166** with diamines **167** (Scheme 42).[106]

Scheme 41



R = $PhCH_2O$- and $PhCH_2OC_6H_4$-

Scheme 42



R^1 = $PhCH_2$, indole-3-CH_2, $PhCH_2OCO$-NH-$(CH_2)_4$-
R^2 = $Me(CH_2)_3$-, $PhCH_2$, $PhCH_2OCO$-NH-$(CH_2)_4$-

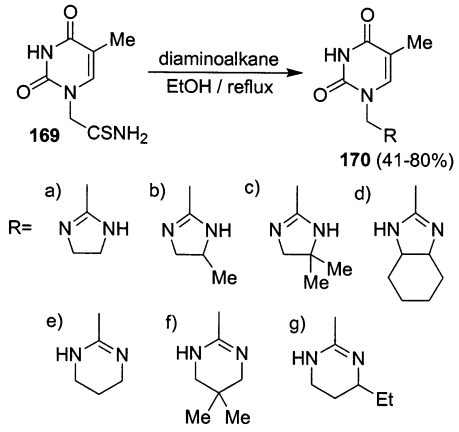
S-Alkylation of thioamides is unnecessary in some instances; 1-[(thiocarbamoyl)methyl]thymine **169** yields amidinomethylthymines **170** when refluxed with appropriate diaminoalkanes in ethanol (Scheme 43).[107]

With dinucleophiles having two distinct nucleophilic groups, e.g., with *o*-aminophenol **172** (X = O) and *o*-aminothiophenol **172** (X = S), derivatives of benzoxazole **173** (X = O) and benzothiazole **173** (X = S) are formed, respectively, whereas 2-aminoethanol **174** (X = O) and 2-aminoethanethiol **174** (X = S) give rise to the formation of Δ^2-oxazoline **175** (X = O) and Δ^2-thiazoline **175** (X = S) derivatives, respectively (Scheme 44).[108]

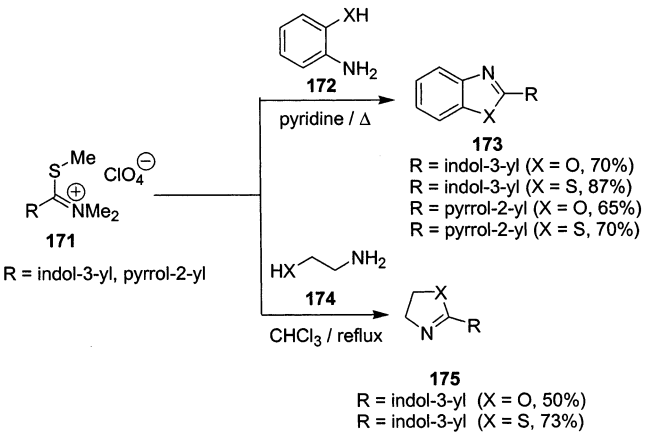
1,3-Oxazine derivatives **178** are formed in the reaction of *S*-methyl thiouronium salts **176** with the derivatives of propanolamine **177** (Scheme 45).[109]

The reaction of *S*-methyl thiouronium salts **179** with amidrazones **180** was carried out at room

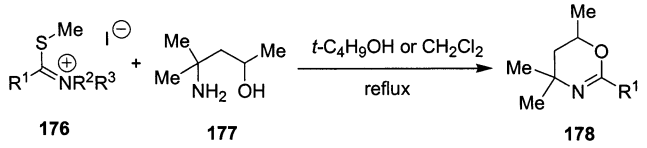
Scheme 43



Scheme 44



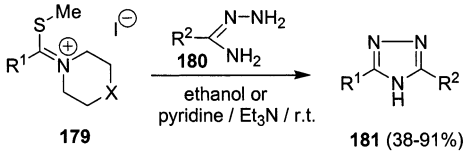
Scheme 45



R^1 = Pr, CH_2Ph, $Ph(CH_2)_2$-, $CH_2=CH(CH_2)_8$-, $Me(CH_2)_4CH(Me)$-, $Me(CH_2)_3CH(Me)$-, $Me(CH_2)_3CH(Ph)$-, *t*-$BuO_2CCH_2CH(Me)CH_2$-; R^2 = H or Me; R^3 = Me; R^2R^3 = -$(CH_2)_4$-

temperature in both neutral (anhydrous ethanol) and basic (a mixture of pyridine and triethylamine) media. In both cases, the same compounds, 3,5-disubstituted derivatives of 1,2,4-triazole **181**, were obtained (Scheme 46).[110]

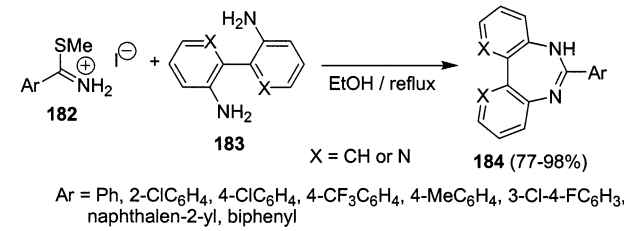
Scheme 46



X = O, CH_2
R^1 = Me, Ph, 4-BrC_6H_4, 4-$NO_2C_6H_4$ 4-OHC_6H_4, 2-OHC_6H_4, 3-ClC_6H_4;
R^2 = Me, 2-Py

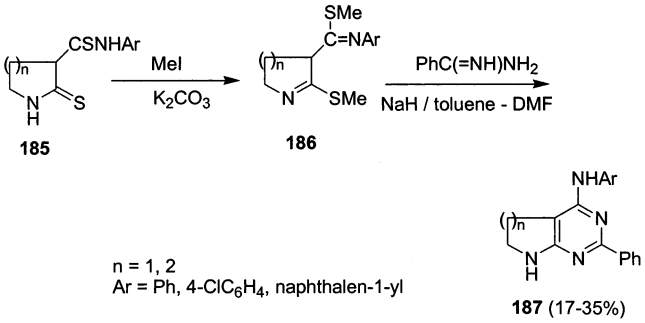
Good yields of annelated 1,3-diazepine derivatives **184** are obtained in a similar reaction of *S*-methylthiobenzimidate hydriodide **182** with 2,2′-diamino-

Scheme 47



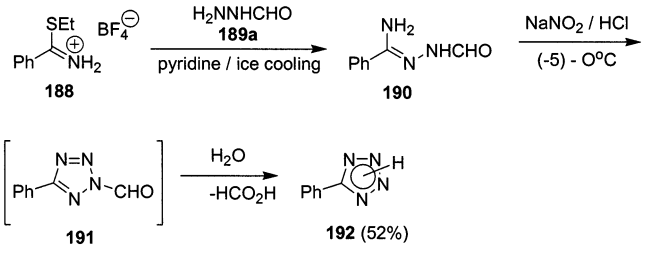
biphenyl or 3,3′-diamino-2,2′-bipyridine **183** in refluxing ethanol (Scheme 47).[111] Similar reactions of *S*-methylated bisthioamides are also known.[112] Methylation of bisthioamides **185** with methyl iodide gave the dithioimidates **186**, which are regarded as 1,3-bis-electrophilic reagents. Compounds **186**, without purification, were allowed to react with benzamidine hydrochloride as a dinucleophile in the presence of NaH to afford the azacycloalka[2,3-*d*]-pyrimidine **187** in moderate yields (Scheme 48).[112]

Scheme 48



Most reactions of *S*-alkylated nonfunctionalized thioamides with mononucleophilic compounds give acyclic amidrazones.[1] Also known are reactions in which the amidrazone **190**, prepared from the thiobenzimidate **188** and formylhydrazine **189a**, is converted by nitrous acid into the 5-substituted tetrazole **192** (Scheme 49);[113] the unstable 2-formyltetrazole

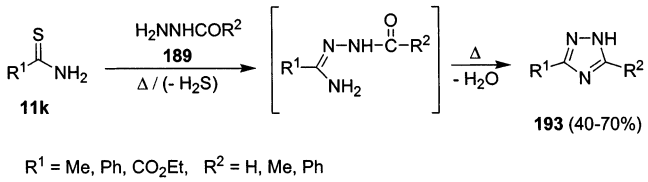
Scheme 49



intermediate **191** readily loses the formyl substituent and therefore is not isolated. However, in the tetrazole syntheses via amidrazones, *O*-alkylated amides, not *S*-alkylated thioamides, are preferred as the substrates, although the latter may be used if more convenient.[113]

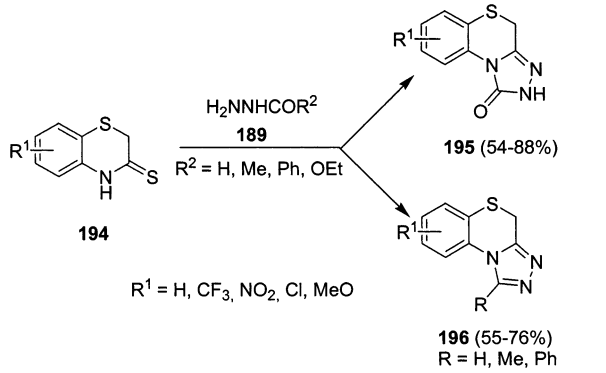
Reactions are also known in which the carbonyl group of the nucleophilic reagent participates in cyclization. For example, primary thioamides **11k** react with formylhydrazine **189a** (R^2 = H) to give 1,2,4-triazole derivatives **193** (R^2 = H) in good yields (Scheme 50).[114,115] Nucleophilic substitution of the

Scheme 50



thioamide sulfur atom with the formation of an amidrazone is invariably the first step of those reactions. Earlier *S*-alkylation of the thioamide is often unnecessary since, as in the reaction with acetylhydrazine **189b** (R^2 = Me), yielding **193**, simple use of a high-boiling solvent makes the reaction proceed.[116] Cyclic thioamides behave analogously. Thus, the reaction of a cyclic thioamide **194** with carboethoxyhydrazine **189b** (R^2 = OEt) gives rise to the formation of triazolone compounds **195**, whereas tricyclic 1,3,4-triazole compounds **196** are formed with formylhydrazine **189a** (R^2 = H) and benzoylhydrazine **189b** (R^2 = Ph) (Scheme 51).[117,118]

Scheme 51



Analogous condensation−cyclization reactions of primary aromatic thioamides with anthranilic acid were reported by Walther[119] and Pawlewski[120] a century ago. Recently, the same reaction path was used to obtain several new derivatives of quinazolin-4-(3*H*)-one **197**.[121−123] All of these reactions require high-temperature conditions (135−140 °C) (Figure 6).

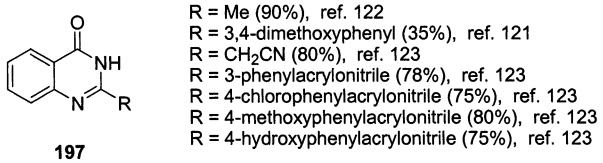
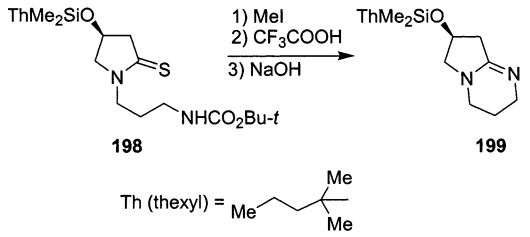


Figure 6.

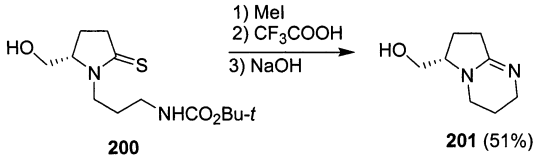
The synthesis of enantiopure analogues of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) **199** and **201** from the thioamides **198** and **200** may serve as another interesting example of nucleophilic substitution at the thioamide sulfur atom (Schemes 52 and 53).[124] The crucial step here is the intramolecular cyclization, which proceeds through a nucleophilic attack of the amine group on the *S*-alkylated thiocarbonyl function.

The same method has been used for the syntheses of the hydroxyethyl-substituted amidine **202** and of

Scheme 52



Scheme 53



the diastereoisomeric amidines **203** and **204** with a secondary hydroxy function (Figure 7).[125] In these reactions, however, the intramolecular heterocyclizations engage an additional functional group of the thioamide.

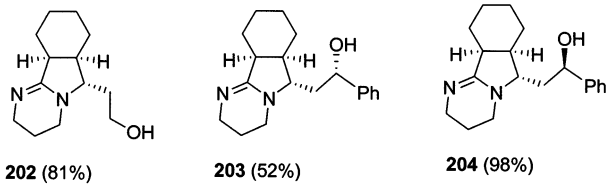


Figure 7.

D. Reactions of Ketene *S,N*-Acetals with Electrophiles

S-Alkylation of tertiary thioamides having α,α hydrogen atom(s) gives rise to the formation of ketene *S,N*-acetals **205** and **206** (Figure 8), also known as

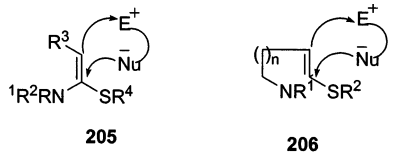
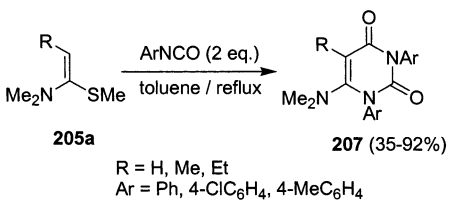


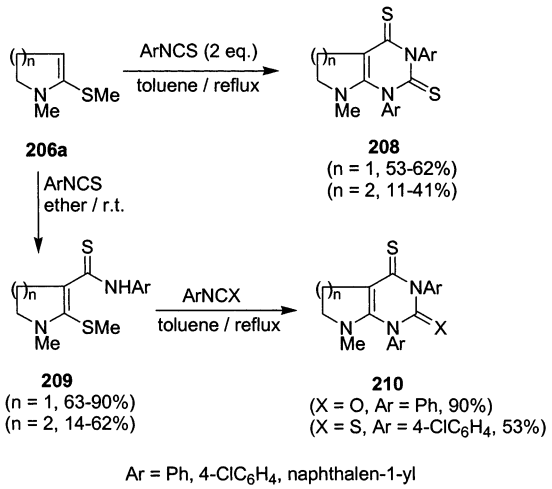
Figure 8.

alkylthio derivatives of enamines.[126−129] These compounds readily react with electrophilic agents. Moreover, an intramolecular heterocyclization with elimination of the *S*-alkyl group may occur when a nucleophilic center is also present in the reacting compound (Figure 8). Thus, high yields of pyrimidine-2,4-diones **207** (Scheme 54) or azacycloalkano[2,3-*d*]-

Scheme 54



Scheme 55



pyrimidines **208** (Scheme 55) were obtained in the reaction of the ketene *S,N*-acetals **205a** and **206a** with 2 mol of an aryl isocyanate or an aryl isothiocyanate in refluxing toluene.[129] However, if the reaction between **206a** and an aryl isothiocyanate is carried out at room temperature in diethyl ether, it is possible to isolate the primary products **209** and to obtain in that way new thioamides preserving much of the framework of the starting one (Scheme 55).[126,129,130] In the reaction with another molecule of aryl isocyanate or aryl isothiocyanate, compounds **209** undergo cyclization to yield the uracil derivatives **210** (Scheme 55).[126,129]

The thioamide **209** can also react as an 1,3-dicarbonyl compound. Reactions of **209** with amidines, hydrazine, and phenylhydrazine are known which yield pyrimidine and pyrazole derivatives.[127,129]

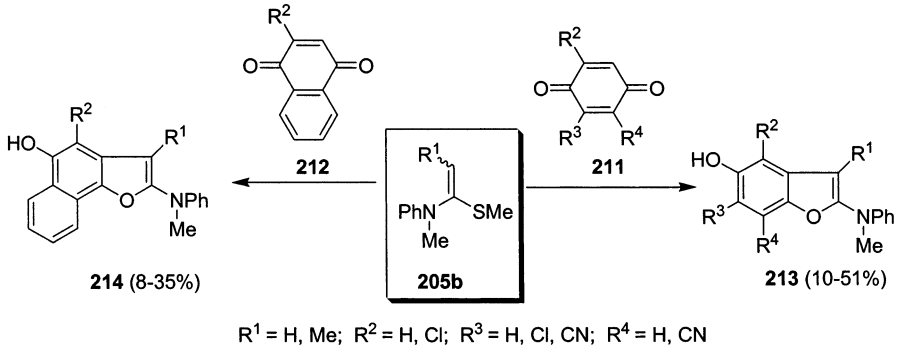
Owing to the universal reactivity of the ketene *S,N*-acetals such as **205** and **206**, some of these compounds were used in cycloaddition reactions.[128] For example, annelation of **205b** with 1,4-quinones **211** and 1,4-naphthoquinones under reflux in several kinds of solvents proceeded to give the selectively demethanethiolated 2-aminobenzofurans **213** and naphtho[1,2-*b*]furans **214**, respectively (Scheme 56).[128] Studies on the effect of the solvent revealed that the highest yields were obtained in refluxing toluene or THF.

The same authors reported on the conversion of **213** and **214** into oxepines in the reaction with acetylenedicarboxylate (DMAD) in refluxing dioxane.[128]

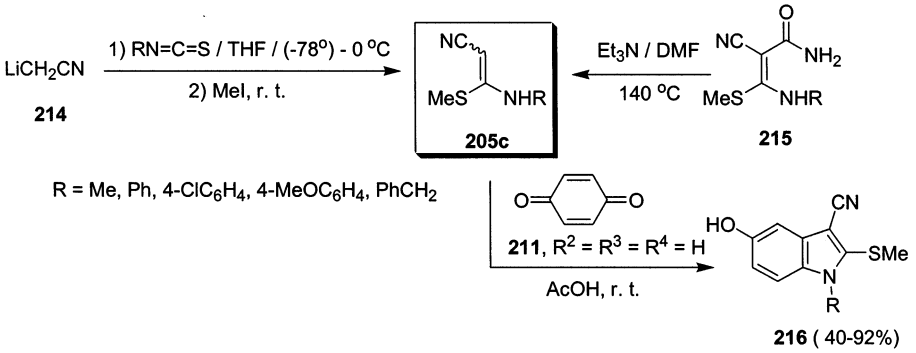
α-Methylthio-*β*-cyanoenamines **205c** were found to be useful starting compounds for synthesis of *N*-substituted 5-hydroxyindoles **216**. The *β*-cyanoenamines **205c** were prepared by two procedures: (a) the reaction of acetonitrile lithium anion **214** with appropriate isothiocyanates followed by methylation and (b) decarboxyimidation of 3-arylamino-2-cyano-3-methylthio-acrylamides **215** (Scheme 57).[131]

Compounds **205c** (a mixture of *E*-, *Z*-, and imino forms) also react with 1,4-benzoquinone **211** (R^2 = R^3 = R^4 = H) to afford *N*-substituted 3-cyano-5-hydroxy-2-(methylthio)indoles **216** (Scheme 57).[131]

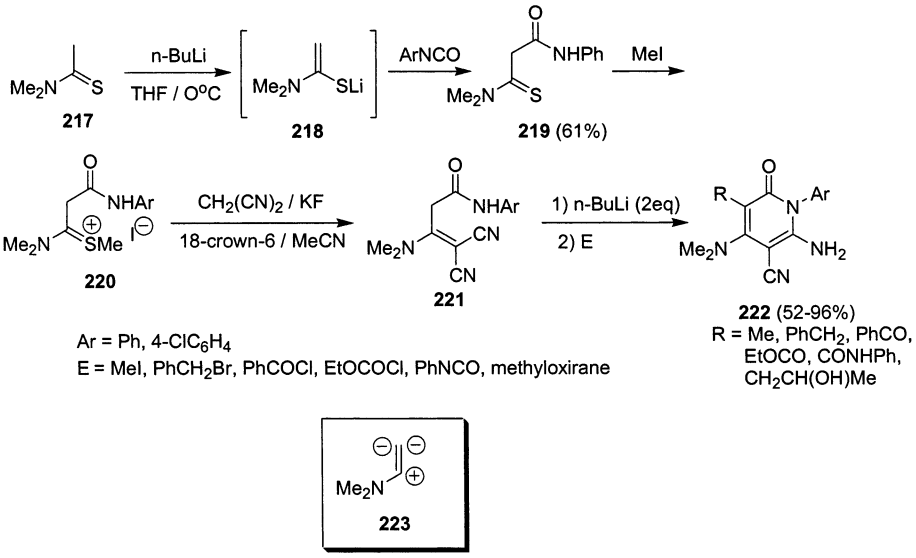
Scheme 56



Scheme 57



Scheme 58

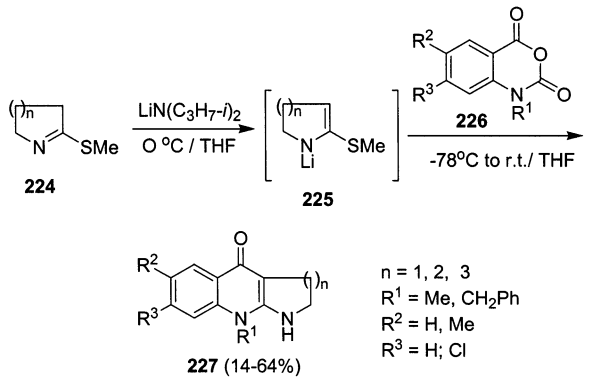


E. Reactions of Lithioketene *S,N*-Acetals and Lithiated Thiolactams

The lithioketene *S,N*-acetal **218**, generated from[58] reaction of *N,N*-dimethylthioacetamide **217** with *n*-butyllithium, reacts with aryl isocyanates at −78 to 0 °C to afford the monothiodiamides **219**. The formation of thioiminium salts **220** with methyl iodide, followed by nucleophilic attack with malonitrile in the presence of 18-crown-6 as a catalyst and potassium fluoride as a base, in acetonitrile at room temperature, gave enaminonitriles **221** in good yields. Reaction of compounds **221** with 2 equiv of *n*-butyllithium gives the corresponding bislithioketene *O,N*-acetals, which react with a variety of electrophiles to afford multifunctionalized 2-pyridones **222** (Scheme 58).[132] In these synthetic sequences, *N,N*-dimethylthioacetamide **217** is synthetically equivalent to the synthon **223**.

In other reactions, 2 equiv of lithiated enamines **225**, generated from cyclic thioimidates **224** by treatment with lithium diisopropylamide, react with *N*-alkylisatoic anhydrides **226** to afford azacycloalkane-[2,3-*b*]quinolin-4-ones **227** (Scheme 59).[133]

Scheme 59



III. Synthesis of Heterocycles from Thioamides Containing an Additional Functional Group

As shown in the examples referred to earlier, the reactivity centers in thioamides and their *S*-alkylated analogues are capable of entering into various intermolecular reactions, leading to the formation of heterocyclic systems. Many more heterocycles can be obtained when the thioamide contains another reactive functional group which can participate in the heterocyclization process. Since such thioamides are rather readily available, the range of synthetic applications of the thioamide substrates gets much wider.

A. Reactions of Unsaturated Thioamides

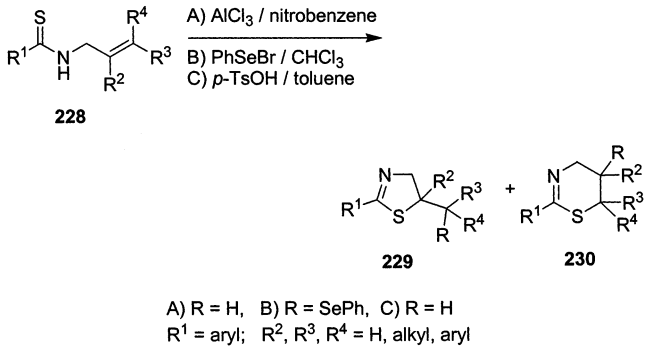
The electrophilic cyclization of olefins with the formation of a new carbon−heteroatom bond (in most cases nitrogen, oxygen, and sulfur) is an important reaction in the regio- and stereoselective syntheses of heterocyclic systems including natural products. In several interesting papers that appeared recently, *N*-alkenylthioamides as well as thioamides derived from γ,δ- and δ,ϵ-unsaturated carboxylic acids were used as the olefinic substrates.

A.1. Reactions of N-Alkenylothioamides

N-Allylthioamides **228** heated in nitrobenzene in the presence of a Lewis acid (zinc chloride, boron trifluoride, or aluminum chloride) cyclize to give the appropriate derivatives of Δ^2-thiazolines **229** and Δ^2-thiazines **230**.[1,134] According to the authors of that study, the Markovnikov rule determines the proportion of the products formed (Scheme 60, variant A). The heterocyclizations of **228** with phenylselenyl bromide (Scheme 60, variant B) and with *p*-toluenesulfonic acid in boiling toluene (Scheme 60, variant C) reveal a higher regioselectivity.[134]

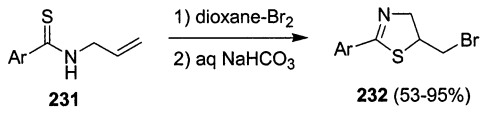
However, the heterocyclization of unsaturated thioamides is most frequently initiated by bromine or iodine. There are also reports on the use of the crystalline bromine−dioxane complex.[135−137] The *N*-allythioamides **231** derived from benzene and thiophene, readily available from reaction of the appropriate aromatic compounds and allyl isothiocyanate under Friedel−Crafts reaction conditions, are

Scheme 60



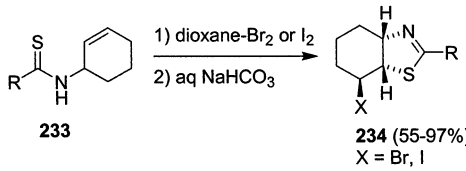
cyclized by this complex to yield exclusively the derivatives of Δ^2-thiazoline **232** (Scheme 61).[135] A

Scheme 61



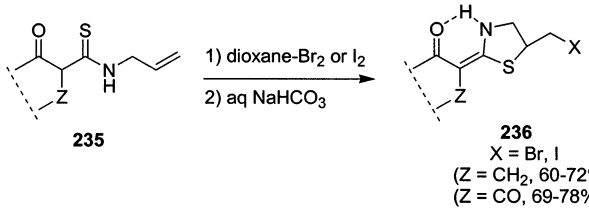
similar cyclization of *N*-(2-cyclohexenyl)thioamides **233** is highly stereoselective. It gives only one diastereoisomeric product, namely (3a*RS*,7*SR*,7a*RS*)-7-bromo-3a,4,5,6,7,7a-hexahydrobenzotriazole **234** (Scheme 62).[136]

Scheme 62



N-Allylthioamides derived from cyclic ketones and diketones are cyclized with the aid of the bromine−dioxane complex or iodine to the corresponding 4,5-dihydrothiazoles **236** (Scheme 63), which may exist

Scheme 63

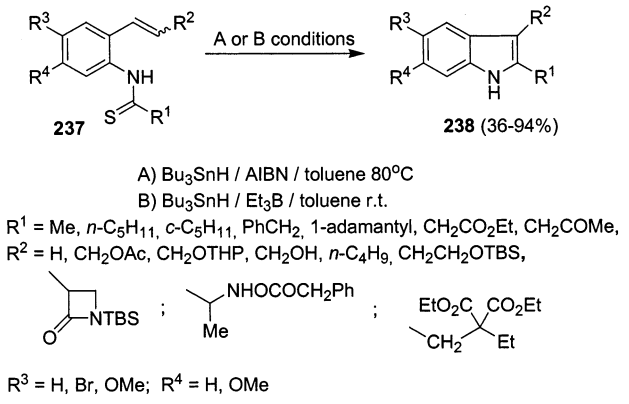


in different tautomeric forms.[137] NMR spectroscopy with the use of the deuterium effect was helpful in the investigation of the tautomeric equilibria in both the thioamides **235** and the thiazoles **236**.[137]

An interesting method for the free-radical cyclization of 2-alkenylthioanilides **237** was developed by

Fukuyama et al.[138] Thus, treatment of **237** with tri-*n*-butylstannane and α,α′-azobisisobutyronitrile (AIBN) in toluene at 80 °C for 5 min resulted in the clean formation of the 2,3-disubstituted indoles **238** (Scheme 64). When triethylborane was used as the

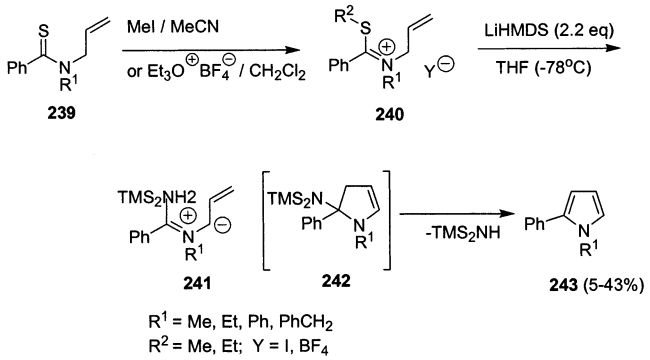
Scheme 64



radical initiator, a similar reaction occurred at room temperature within 5−45 min to afford **238** in 36−94% yield. The rate of the triethylborane-initiated reaction was found to depend on the geometry of the olefin. Moreover, the authors proposed the reaction mechanism and presented novel methods for the synthesis of the starting 2-alkenylthioanilides **237**.[138]

Tertiary *N*-allylthioamides **239**, when reacted with methyl iodide in acetonitrile or with triethyloxonium tetrafluoroborate in methylene chloride, give thioimidinium salts **240**. When treated with 1,4-diazacicyclo[2,2,2]octane (DABCO), tetramethylethylenediamine (TMEDA), or triethylamine, compounds **240** are converted into the corresponding amides.[139] However, reaction of **240** with 2.2 equiv of lithium hexamethyldisilylamide (LiHMDS) affords the corresponding pyrroles **243** in 17−43% yields as well as the dealkylation products, i.e., thioamides, in 10−30% yields. According to the original mechanistic proposal (Scheme 65), the salts **240** are deprotonated

Scheme 65



to give the zwitterionic structures **241**, which undergo an 1,5-dipolar cyclization with the formation of dihydropyrroles **242** and, subsequently, pyrroles **243**.[139] Activation of thioamides with Lewis acids instead of alkylating agents was also reported.[139]

A.2. Reaction of α,β-, γ,δ-, and δ,ϵ-Unsaturated Thioamides and Thioimidates

The thioamide derivatives of α,β- γ,δ- and δ,ϵ-unsaturated acids are very useful synthons in the heterocyclization reactions. Moreover, they readily undergo transformation reactions. Thus, α,β-unsaturated thioamides add on various heteronucleophiles in the 1,4-addition reaction.[140,141] Compounds **246** were obtained from the cinnamic acid-derived thioamides **244**, whereas α,β-unsaturated thiolactams **245** yielded cyclic compounds **247**, mostly as the trans-addition products (Figure 9).[140]

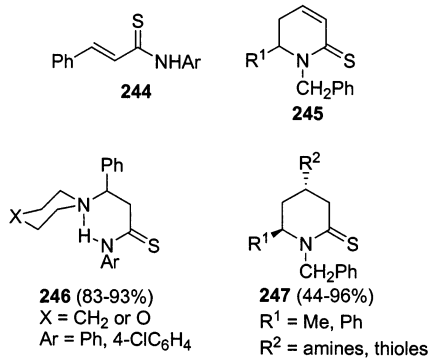
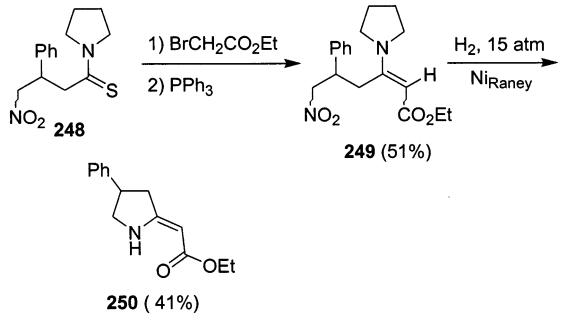


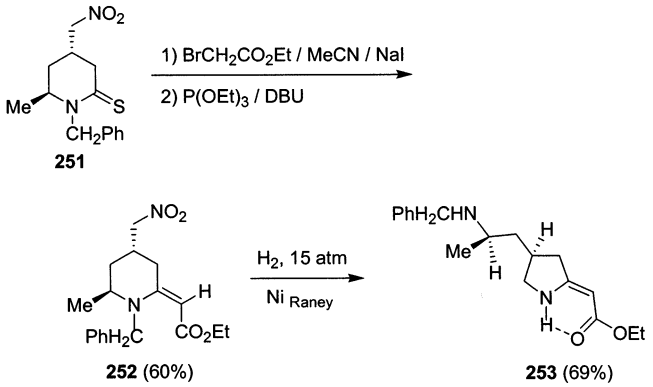
Figure 9.

Compounds **248** and **251**, obtained in the reactions of **244** (NHAr = pyrrolidine) and **245** (R^1 = Me) with nitromethane, react with ethyl bromoacetate to give the corresponding *S*-alkylated products, which rearrange to enamino esters **249** and **252**, respectively, when treated with a phosphine (Schemes 66 and 67). This is a recent example of the Eschenmoser reaction.[142,143] Hydrogenation of **249** and **252** under 15 atm in the presence of Raney nickel results in

Scheme 66



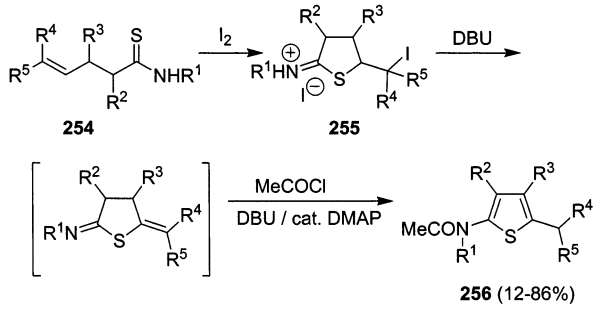
Scheme 67



rearrangement to the esters of (*Z*)-α-(tetrahydro-2-pyrrolidene)acetic acid, **250** and **253**, respectively (Schemes 66 and 67).[144]

γ,δ-Unsaturated thioamides may be used in the synthesis of the derivatives of thiophene and pyrrole.[129,145] For instance, the iodine-induced cyclization of **254** proceeds as a regio- (5-exo-trigonal) and chemoselective (the formation of a sulfur−carbon bond) reaction.[146] It yields iminothiolactones **255**, which are converted in a two-step process of dehydroiodination and *N*-acetylation, into acetamidothiophenes **256**.[129,145] Polysubstituted 2-aminothiophenes were thus obtained in one pot (Scheme 68).

Scheme 68



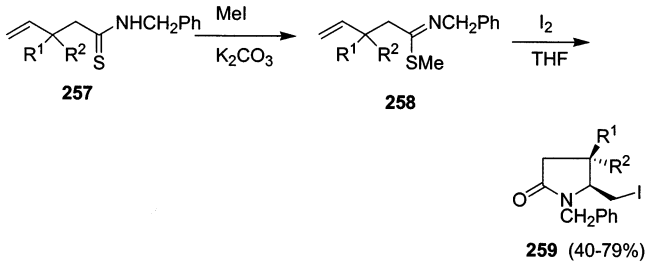
254 **255** **256** (12-86%)

R^1 = Ph, $PhCH_2$; R^2 = H, Me, *c*-C_6H_{11}, $PhSO_2$, PhNHCO;
R^1R^2 = -$(CH_2)_n$-, n = 3, 4, 5; R^3 and R^4 = H, Me; R^5 = H, Me, Ph

The same authors also developed original methods for the transformation of simple secondary thioamides into their γ,δ-unsaturated analogues.[145]

Cyclization of γ,δ-unsaturated thioamides **257** and **260** was investigated first by Takahata et al.[146] from the point of view of 1,2-allylic[147,148] and 1,3-homoallylic[149] asymmetric induction. The ultimate products, γ-lactams, were used by these authors for the synthesis of several biologically active compounds. The asymmetric synthesis of 4,5-disubstituted lactams **259** proceeds as a regio- and stereoselective ring closure in the iodine-induced lactamization of γ,δ-unsaturated thioamides **258** (Scheme 69). In the case

Scheme 69



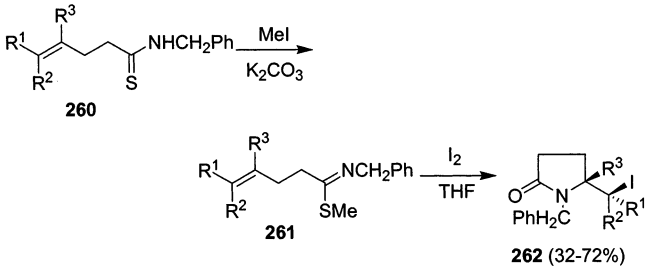
257 **258** **259** (40-79%)

R^1 = OH, OTBS, OMOM, NHBoc, Me, Ph, *n*-Pr, *i*-Pr
R^2 = H, Me

of thioamides **257** (R^1 = OH; OMOM, OTBS, and NHBoc), bearing polar substituents in the allylic position, 4,5-disubstituted γ-lactams are formed mostly as the 4,5-cis-diastereoisomers (Scheme 69).[147] A reversed selectivity (4,5-trans products) was observed with large allylic substituents (**257**, R^1 = Ph, *n*-propyl, and isopropyl; R^2 = H; Scheme 67).[147]

Thioimidates **261** and **263**, bearing substituents at the olefinic bond, undergo regio- and diastereoselective iodine-induced cyclization to provide γ-lactams **262** and **264** as single isomers, respectively (Schemes 70 and 71).[146,147] However, iodolactamization of 5,5-disubstituted thioimidate **261** (R^1 = R^2 = Me; R^3 = H) does not proceed.

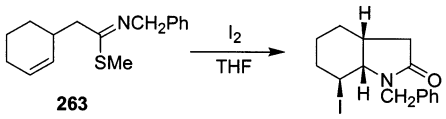
Scheme 70



260 **261** **262** (32-72%)

R^1 = H, Me, Ph; R^2 and R^3 = H or Me

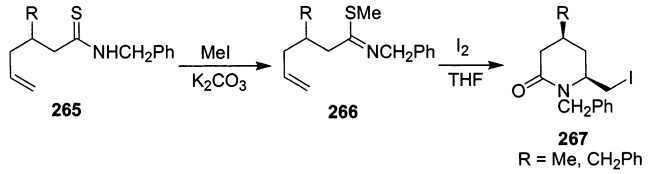
Scheme 71



263 **264** (63%)

The same synthetic procedure was applied next in the investigation of the iodolactamization reactions of β-substituted δ,ϵ-unsaturated thioimides **266**, which provided 4,6-cis-disubstituted δ-lactams **267** (Scheme 72).[150] The stereochemistry of this cyclization process was also studied.

Scheme 72



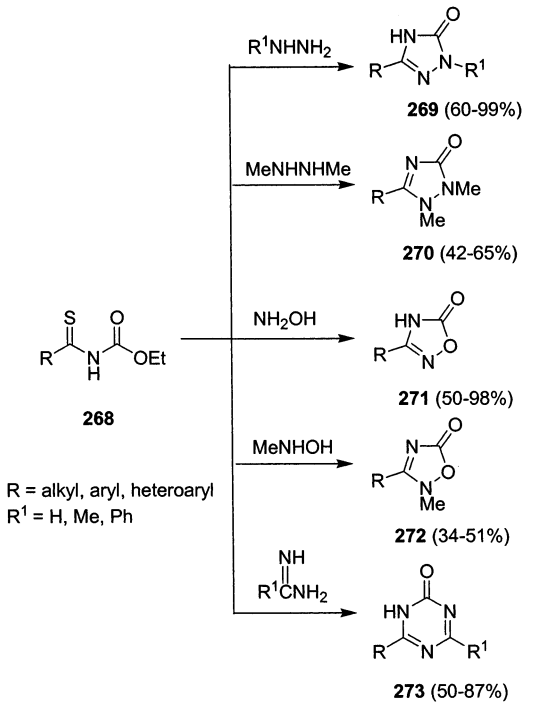
265 **266** **267**
R = Me, CH_2Ph

B. Heterocyclization of Thioamides Having a Carbonyl Group

B.1. Reaction of Thioamides with an Ester Function

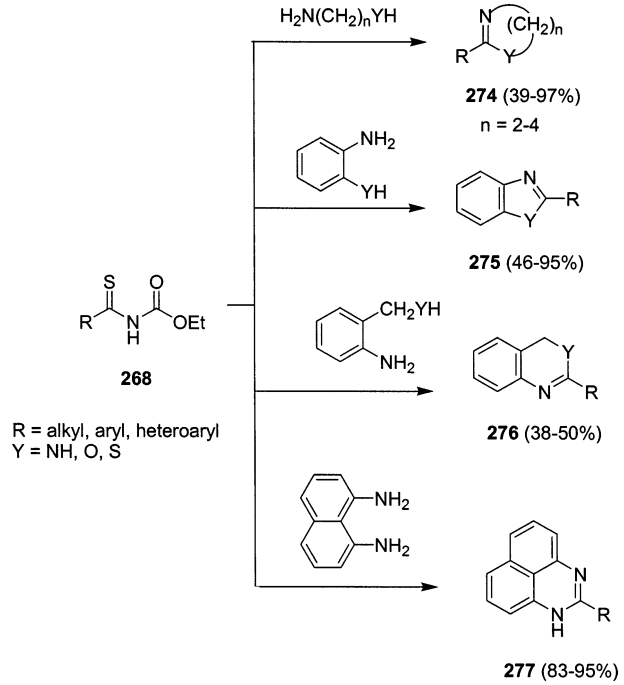
N-Ethoxycarbonylthioamides **268** have proved to be versatile starting materials for the preparation of a wide variety of heterocyclic compounds.[151,152] With nucleophilic reagents, the heterocyclization reactions occur with elimination, depending on the structure of the nucleophile, of a molecule of ethanol or urethane. Thus, the reactions of *N*-ethoxycarbonylthioamides **268** with hydrazines, hydroxylamines, and amidines lead to 1,2,4-triazolones **269** and **270**, 1,2,4-oxadiazolones **271** and **272**, and 1,3,5-triazinones **273**, respectively (Scheme 73).[151] In contrast, the reactions of *N*-ethoxycarbonylthioamides **268** with 1,2-, 1,3-, and 1,4-dinucleophilic reagents follow to form various other heterocyclic compounds: 4,5-dihydroimidazoles **274** (Y = NH, *n* = 2), -oxazoles **274** (Y = O, *n* = 2), and -thiazoles **274** (Y = S, *n* = 2); 1,4,5,6-tetrahydropyrimidines **274** (Y = NH, *n* = 3);

Scheme 73



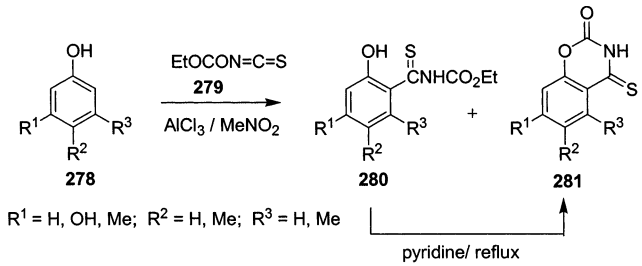
5,6-dihydro-1*H*-oxazines **274** (Y= O, $n = 3$); 4,5,6,7-tetrahydro-1*H*-1,3-diazepines **274** (Y = NH, $n = 4$); benzimidazoles **275** (Y = NH), benzoxazoles **275** (Y = O), benzothiazoles **275** (Y = S); and 3,4-dihydroquinazolines **276** (Y = NH), 4*H*-1,3-benzoxazines **276** (Y = O), and perimidines **277** (Scheme 74).[151]

Scheme 74



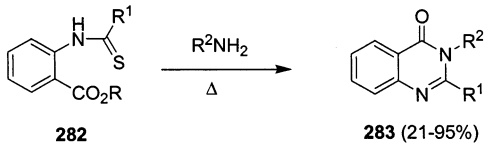
Ethoxycarbonyl isothiocyanate **279** reacts, in the presence of aluminum chloride in nitromethane, with ortho-unsubstituted phenols **278** to form the appropriately substituted *o*-hydroxy-*N*-ethoxycarbonylthiobenzamides **280**, which cyclize under the reaction conditions to 1,3-benzoxazine-4-thiones **281**.[6] If a mixture of **280** and **281** is obtained in this reaction, the cyclization may be completed by heating the mixture in pyridine (Scheme 75). Analogous reactions

Scheme 75



were effected with 2-naphthol.[6] The alkoxycarbonyl group may take part in the heterocyclization process, even if it is not directly attached to the nitrogen atom. *N*-(2-Ethoxycarbonylphenyl)thioamides **282** have been found by Papadopoulos[153,154] to react with nucleophilic reagents to form 4(3*H*)-quinazolinone derivatives **283** (Scheme 76); both the thiocarbonyl and the ester groups here are engaged in the heterocyclization.

Scheme 76

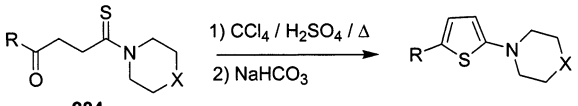


R = Me, Et; R^1 = 4-MeOC$_6$H$_4$, pyrrol-2-yl;
R^2 = H, *n*-Bu, PhCH$_2$, NH$_2$, NHMe, NHPh,
OH, CH$_2$CH$_2$OH, CH$_2$CH$_2$NH$_2$, CH$_2$CH$_2$NHCONHPh,
CH$_2$CH$_2$NHCOMe, Ph, 2-MeC$_6$H$_4$, 2-OHC$_6$H$_4$

B.2. Reaction of Oxothioamides

Heterocyclization of oxothioamides may be catalyzed by strong acids as well as by bases. Thus, 4-oxothioamides **284**, when heated in carbon tetrachloride in the presence of concentrated sulfuric acid, have been found to give the derivatives of 2-aminothiophene **285** (Scheme 77).[155] 3-Hydroxy-substi-

Scheme 77

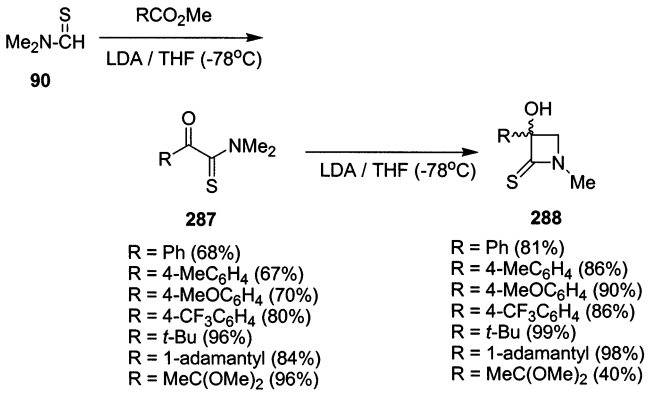


X = O, CH$_2$
R = Ph, 4-MeC$_6$H$_4$, thiophen-2-yl, *n*-C$_5$H$_{11}$

tuted *β*-thiolactams **288** can be obtained in the LDA-induced intramolecular heterocyclization of *N*,*N*-dimethyl-2-oxothioamides **287**, which are available in the reaction of the lithium derivative of *N*,*N*-dimethylthioformamide **90** with esters of carboxylic acids. In the preparation of **288**, there is no need to isolate and purify **287**.[156] Scheme 78 gives yields in the conversion of esters into *β*-thiolactams. Further transformations of *β*-thiolactams into chiral systems have been reported previously.[157]

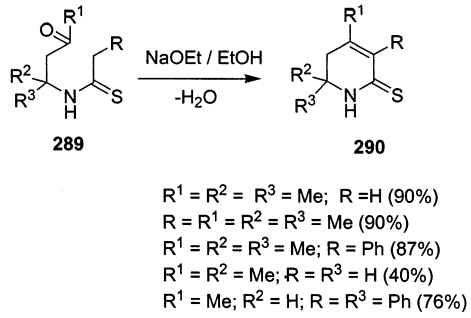
Strong bases can also catalyze cyclization of thioamides with an oxoalkyl group attached to the

Scheme 78



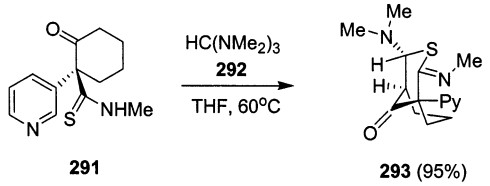
nitrogen atom. For example, *N*-3-oxothioamides **289** cyclize in an ethanolic solution of sodium ethoxide to afford good yields of the derivatives of 5,6-dihydropyridine-2-thione **290** (Scheme 79).[158]

Scheme 79



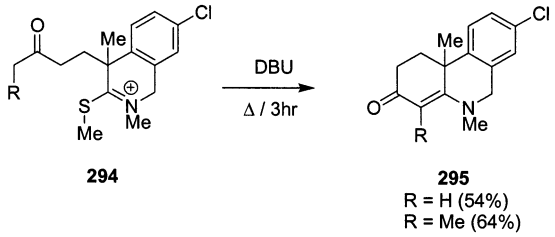
In some cases, such as in that of tris(dimethylamino)methane, the basic cyclization catalyst may also serve as a reaction substrate. Thus, 2-oxo-1-pyridin-3-ylcyclohexanecarbothioic acid methylamide **291** reacts with tris(dimethylamino)methane **292** to yield a [3.3.1]-bicyclic compound of the type **293** (Scheme 80). The acidity of the hydrogen atoms α with respect

Scheme 80



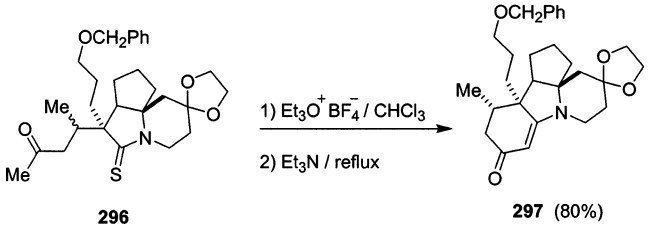
to the carbonyl group is the most important factor here.[159] The starting **291** is a precursor of biologically active compounds. Its synthesis and some transformations have been published by Hart separately.[160,161] Cyclization may also be effected by the attack of an enol anion on the *S*-methylated thioamide group. The final step in the synthesis of the *N*-methylphenanthridin-3-one derivatives **295** involves intramolecular cyclization of the activated thioiminium ion **294** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Scheme 81).[162] Analogous reactions have been recently described by Guarna.[163] The same cyclization method was applied previously by Heathcock[164] in a multistep total synthesis of a *Daphniphyllum* alkaloid. Treatment of a chloroform solution of **296** with

Scheme 81



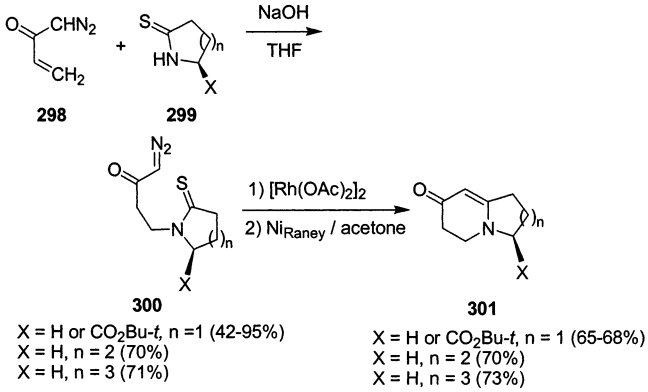
triethyloxonium tetrafluoroborate gave a polar material (presumably an *S*-ethylthioiminium salt), which was immediately treated with triethylamine. Although **296** was a 5:1 mixture of diastereoisomers at the methyl-bearing stereocenter, the tetracyclic vinylogous amide **297** was obtained as a single stereoisomer (Scheme 82).[164] When carbonyl and diazo

Scheme 82



groups are present in the fragment attached to the thioamide nitrogen atom, the so-called aza-Robinson annelation may occur. In a tandem reaction, Michael addition of a diazo-substituted α,β-unsaturated ketone **298** to thiolactam **299** is followed by azaheterocyclization of the thus-formed *N*-ketoazaalkyl-thioamide **300** with the aid of the rhodium(II) acetate dimer; bicyclic compound **301** is the final product of these reactions (Scheme 83).[165] Similar transforma-

Scheme 83



tions underlie the strategy in the synthesis of several natural products.[166,167]

N-Benzoylthioamides derived from cyclic β-diketones **302** readily undergo condensation with thiourea, malononitrile, and aniline and subsequent intramolecular heterocyclization to yield the derivatives of partially hydrogenated quinazolin-5-one **303**, 4-thioxoisoquinolin-5-one **304**, and 4-thioxoquinazolin-5-one **305**, respectively (Figure 10).[168] Refluxing thioamide **302** in xylene in the presence of triethylamine afforded oxazine **306** as the product of cyclodehydration (Figure 10).

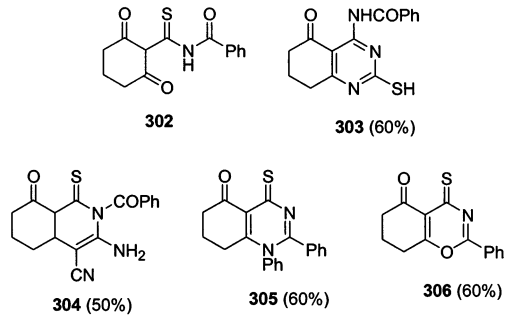


Figure 10.

Acyl thioformanilides **307**[169−171] have two possible sites for nucleophilic attack. As found by Lu et al.,[172] compounds **307** condense with dinucleophiles as if they were 1,2-dicarbonyl compounds. It is interesting to note that compounds **308** were obtained from **307** and *o*-phenylenediamine in refluxing pyridine or ethanol, while compounds **309** were formed in methanol at room temperature. The reaction with semicarbazide gave semicarbazones (condensation at the carbonyl group), which were cyclized in refluxing pyridine to give 1,2,4-triazines **310**. It was also found that **307** condensed with aminoguanidine hydrochloride to yield **311** (Figure 11).[172]

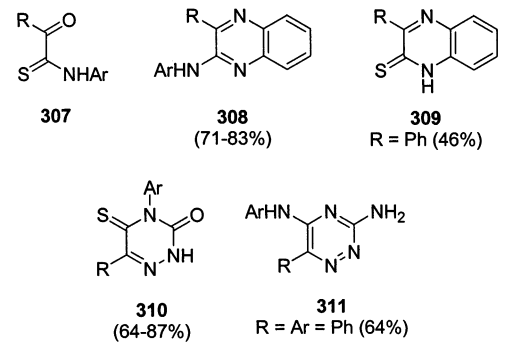
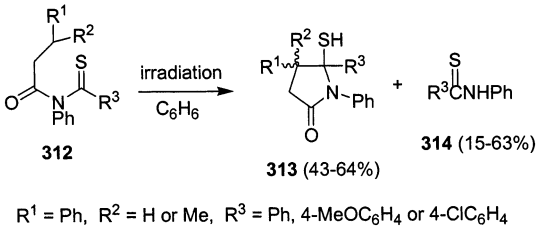


Figure 11.

N-Oxoalkylthioamides **312** may be also cyclized in photochemical conditions. Thus, irradiation of a solution of **312** in benzene gave rise to the formation of the derivatives of 5-mercaptopyrrolidin-2-one **313** (Scheme 84).[173] Thioanilide **314** is a side product of

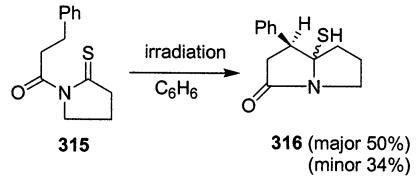
Scheme 84



this reaction. Generally, the photochemical reactions of acyclic monothioamides in solution entails hydrogen abstraction by the thiocarbonyl sulfur atom from the β, γ, and δ positions, and their regioselectivity depends on the substituents on the nitrogen atom and the acyl group.[174−177]

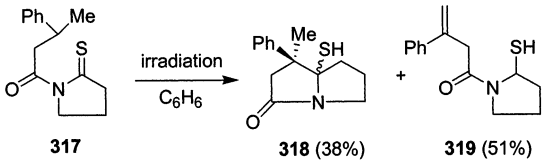
Photochemical reactions of semicyclic *N*-oxoalkylthioamides lead in most cases to the formation of more complex mixtures of products. However, irradiation of the semicyclic monothioamide **315** gave the bicyclic lactam, 5-mercapto-4-phenyl-1-azabicyclo-[3.3.0]octan-2-one **316** (Scheme 85).[173]

Scheme 85



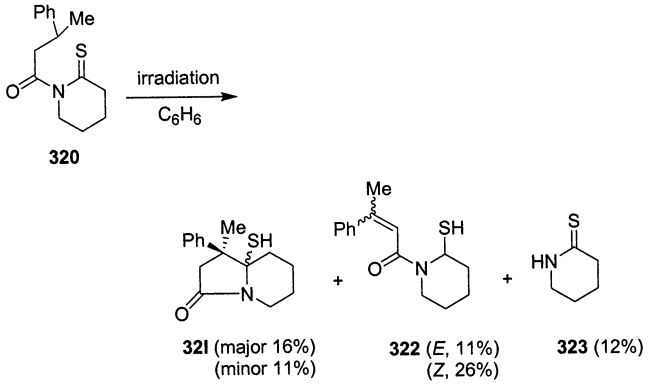
With thioamide **317**, both lactam **318** (one isomer isolated) and 1-(3-phenyl-3-enoyl)-pyrrolidine-2-thiol **319** were obtained (Scheme 86).[173] When the six-

Scheme 86



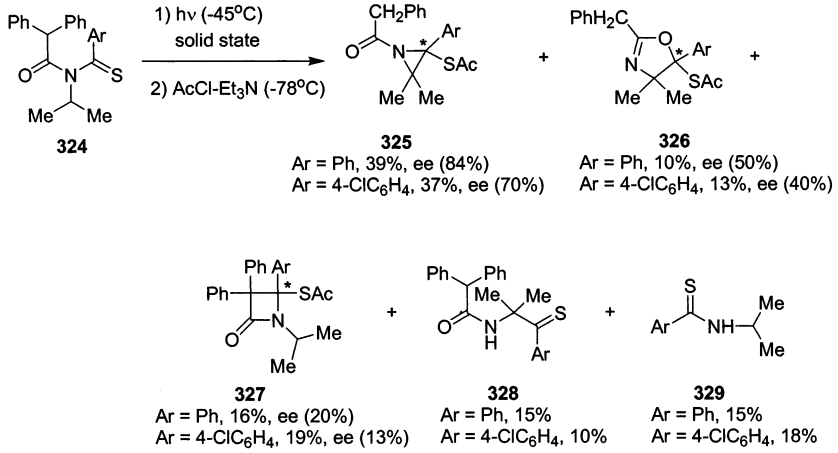
membered semicyclic monothioamide **320** was irradiated under the same conditions, an α,β-unsaturated amide, 1-(β-methylcinnamoyl)pyrrolidine-2-thiol **322**, was obtained as the main product, accompanied by bicyclic lactam **321** and thiolactame **323** (Scheme 87).[173] Photochemical reactions of *N*-oxoalkythio-

Scheme 87

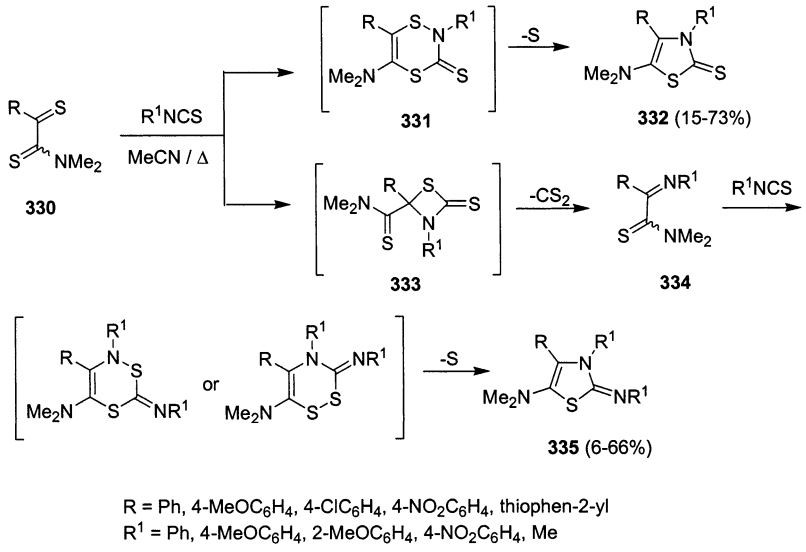


amides may also proceed in the solid state. These are unique in that their regio- and stereoselectivities, and even their product selectivities, differ from those observed when the same substrates are reacted in solution. Irradiation of *N*-oxoalkylthioamide **324** gave several heterocyclic compounds **325**−**329**; because of poor stability, the optically active compounds **325**−**327** were isolated as the acetyl derivatives (Scheme 88).[178] Because of the multiplicity of products, this reaction was of little preparative value. As far as the sulfur analogues of oxothioamides, i.e., thioxothioamides, are concerned, Marchand and Morel reported recently on the cycloaddition of α-thioxothioamides **330** to aryl isothiocyanates, phenyl isocyanate, and

Scheme 88

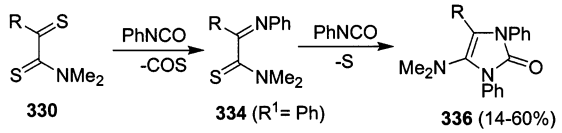


Scheme 89



an aliphatic (methyl) isothiocyanate.[179] Two products, namely 2,3-dihydro-2-thioxothiazole **332** and 2-iminothiazole **335**, were obtained in the reaction of **330** with isothiocyanates. The product ratios depended mainly on the nature of the starting isothiocyanate. The results were explained on the basis of [4 + 2] and [2 + 2] additions to the C=N bond of the heterocumulene, followed by ring contraction of the 2,3-dihydro-1,4,2-dithiazine **331** (sulfur extrusion) or cycloconversion of the 2-thiothiazetidine **333** (elimination of carbon disulfide) (Scheme 89). An independent synthesis of α-iminothioamides **334** proved that they are intermediates in the formation of **335**. Only one compound, 5-aminoimidazol-2-one **336**, is produced in the reaction of α-thioxothioamide **330** with phenyl isothiocyanate (Scheme 90). The reaction proceeds also with the intermediate formation of α-iminothioamide **334** (R^1 = Ph).[179]

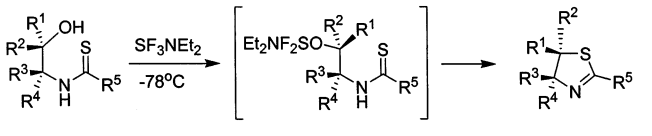
Scheme 90



C. Heterocyclization of Thioamides Having a Hydroxy Group

Intramolecular nucleophilic substitution of the hydroxy group with sulfur transforms *N*-(*β*-hydroxy)-thioamides into Δ^2-thiazolines. The reaction is used in the synthesis of natural products derived from thiazoline. Lafargue applied diethylaminosulfur trifluoride (SF_3NEt_2, DAST) to effect heterocyclization of *β*-hydroxythioamides **337** to thiazolines **338**. The cyclization is totally diastereoselective, with inversion of configuration at C-2 of **337** (Scheme 91).[180] Wipf et al.[181−183] have developed a method which made it possible to dehydratate *N*-(*β*-hydroxy)thioamides without epimerization. In one of the steps of the synthesis of optically active peptides with the Δ^2-thiazoline ring, they cyclized *β*-hydroxythioamides **340** with use of the Burgess reagent ($MeO_2CNSO_2NEt_3$) and the Mitsunobu reagent [PPh_3 + diisopropyl azodicarboxylate (DIAD)]. In general, a simple and stereoselective method for direct conversion of oxazolines **339** into thiazolines **341** and **342** via the hydrothioamide intermediates **340** was presented in these papers. An illustrative example of such conversions follows (Scheme 92).[182] Ino and Murabayashi[184] used the same method recently in order to effect cycliza-

Scheme 91



tion of thioamide **343** in their total synthesis of yersiniabactin, a siderophore from cultures of the *Yersina enterocolitica* bacteria. Chirality at the readily racemizable C-9 carbon was preserved during cyclization of β-hydroxythioamide by means of the Burgess reagent, leading to thiazoline **344** (Scheme 93).[184]

According to another recent report, *N*-(2-hydroxyalkyl)-2-phosphonoethanethioamides **345** readily cyclized under the conditions of the Mitsunobu reaction [Ph_3P + diethyl azodicarboxylate (DEAD)] to yield phosphonothiazolines **346**. With enantiopure aminoethanols (easily accessible from amino acids), this method was applied to the synthesis of phosphonylated chiral thiazolines **346**, which were potential new ligands for asymmetric catalysis (Scheme 94).[185]

The Mitsunobu reagents have also been used for heterocyclization of *N*-benzylthioamides **347**, derived from γ-hydroxycarboxylic acids. A mixture of thiolactam **348** and the 2-iminotetrahydrothiophene derivative **349** was formed in this reaction (Scheme 95).[186] When the starting γ-hydroxythioamide **347** was *S*-alkylated and the thioimidinium salt formed was heated in a 10% hydrochloric acid, *O*-nucleophilic substitution took place on the thiocarbonyl carbon atom, with the formation of lactone **350**. Hydrolysis of the thioamide C−N bond occurred as the result of the accompanying transformations (Scheme 96).[186]

Recently, the Mitsunobu method was used in similar heterocyclizations of some *N*-(2-hydroxyethyl)thioureas.[187,188]

D. Reactions of 3-Aminothioacrylamides

3-Aminothioacrylamides are a class of readily available organic sulfur-containing compounds which exhibit polyfunctional reaction behavior. They can be used widely in the synthesis of a variety of heterocyclic and open-chain compounds. The synthetic utility of 3-aminothioacrylamides can be further extended if additional functionalities are incorporated. Heterocyclization reactions using 3-aminoacrylthioamides as universal synthons were reviewed previously.[189] Therefore, the following presents only more recent synthetic studies.

Liebscher and Rolfs developed a simple and efficient method for the synthesis of 3-aminothioacrylamides. It involves the reaction of tertiary thioacetamides with trismorpholinomethane or triethyl orthoformate in the presence of morpholine or pyrrolidine.[190−193]

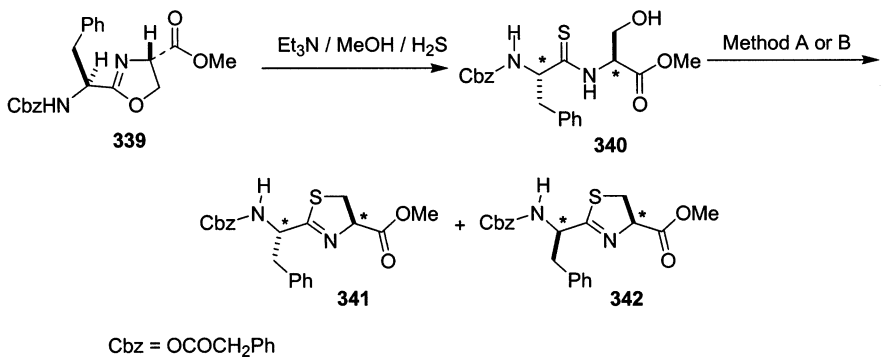
The synthesis of 3-aminopyrroles **355** is shown in Scheme 97. Its first step is the substitution reaction of 3-aminothioacrylamides **351** with derivatives of glycine **352**. Subsequent oxidation of the intermediates **353** by iodine or bromine (for technical use, hydrogen peroxide) or an anodic process provides 5-aminoisothiazolium salts **354**, which can be isolated or directly transformed into 3-aminopyrroles **355** by elimination of sulfur.[194] A 1,3-thiazine could possibly be involved in the ring transformation.[195] The mechanism of the synthesis of 3-aminopyrroles from substituted 2-methyl-1,2-thiazolinium salts was presented previously.[196] When hydrazine or hydroxylamine was used in place of the glycine esters, 3-aminopyrazoles **357** and 5-amino-1,2-oxazoles **358**, respectively, were obtained (Scheme 98).[197]

Isothiazole derivatives **360** were obtained in the reaction of 3-aminothioacrylamides **359** with hydroxylamino-*O*-sulfonic acid in the presence of triethylamine (Scheme 99).[198]

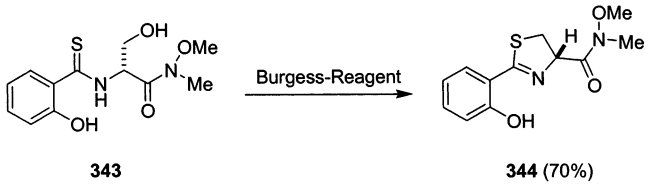
Under the conditions of the Vilsmeier−Haack reaction, some thioamides can undergo self-condensation. Thus, arylthioacetomorpholides **361**, in the presence of *N*,*N*-disubstituted amides **362** and phosphoryl chloride, self-condense to give 2-aryl-3-benzyl-3-morpholinothioacrylamides **363**, which are next converted into the four-membered-ring vinamidinium salts **366** or 2,4-dimorpholino-3,5-diarylthiophenes **365** (Scheme 100).[199]

Hartmann and co-workers[200] reported recently on the synthesis of 2-amino-5-thiophenecarboxylates **369** from 3-aminothioacrylamides **367**. Thus, *N*,*N*-disubstituted thioacrylamides **367** were allowed to react

Scheme 92

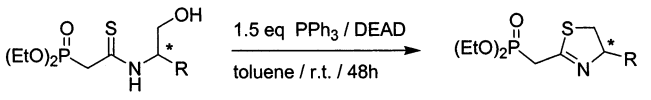


Scheme 93



343 **344** (70%)

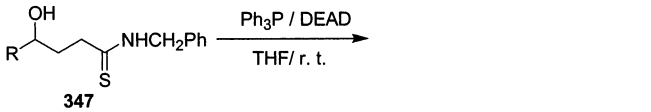
Scheme 94



345 **346** (51-78%)

R = H, Et, *i*-Pr, Ph, $PhCH_2$

Scheme 95

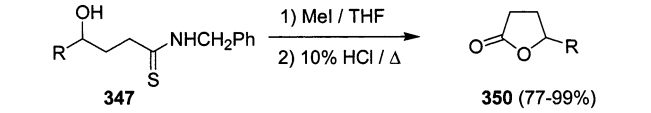


347

348
R = Me (42%)
R = Et (40%)
R = Ph (47%)

349
R = Me (32%)
R = Et (23%)
R = Ph (23%)

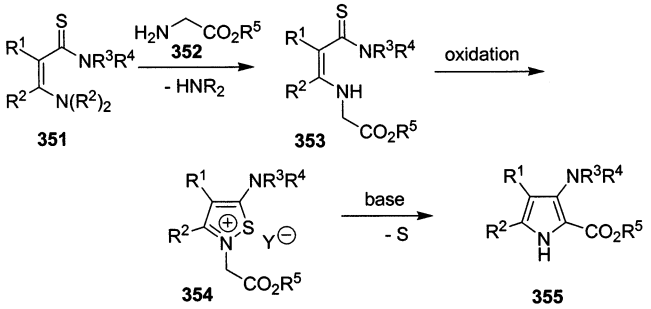
Scheme 96



347 **350** (77-99%)

R = Me, Et, Ph, *n*-butyl, *n*-pentyl, *n*-hexyl, *n*-octyl

Scheme 97



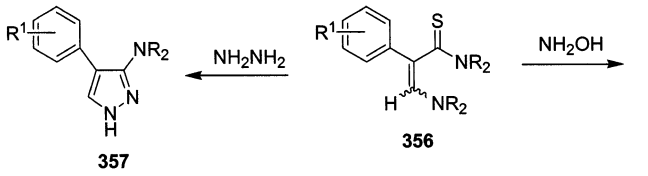
351 **353** **354** **355**

R^1 = Ph, 4-ClC_6H_4, CO_2Et; R^2 = H, Me
NR^3R^4= $N(CH_2CH_2)_2O$, $N(CH_2)_4$, NHPh, $N(CH_2CH_2)CHCO_2Et$, $N(CH_2CH_2)$N-2-furoyl,
R^5 = Me, Et, *i*-Bu

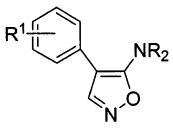
with alkyl haloacetates to yield the *N*,*N*-disubstituted 1-amino-1-[(alkoxycarbonyl)methylthio]propeniminum salts **368**, which were cyclized in situ in the reaction with sodium methoxide to give the 2-dialkylamino-5-thiophenecarboxylate derivatives **369** (Scheme 101).[200] An analogous reaction of **367** with halomethyl ketones gives rise to the formation of 2-amino-5-acylthiophenes.[201]

On the other hand, when 3-aminothioacrylamides **370** were reacted with 2,2-dicyanoethenyl- and 1,2,2-tricyanoethenyl-substituted bromomethylalkanes, bromomethyl benzenes, thiophenes, and furans **371** and **372**, a series of 5-dicyanoethenyl- and 5-tricyanoethenyl-substituted 2-aminothiophenes **373** and their (hetero)benzologous analogues **374** was obtained (Scheme 102).[202]

Scheme 98

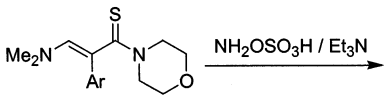


357 **356**

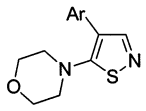


358

Scheme 99

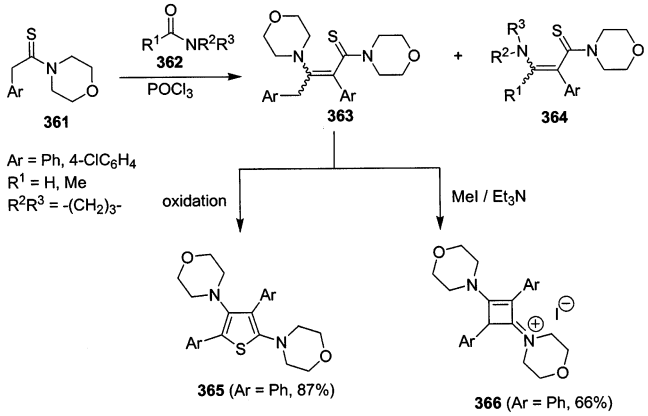


359



360 (46-67%)
Ar = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$

Scheme 100

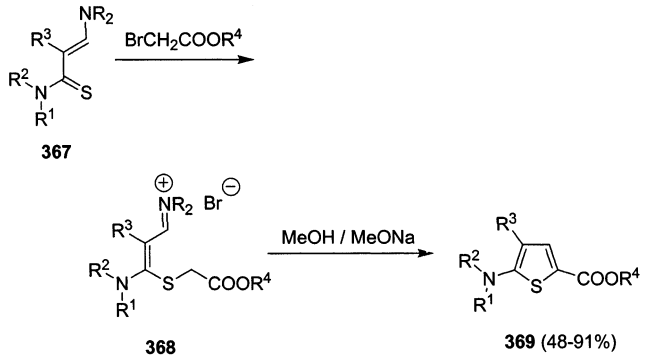


361 **363** **364**

Ar = Ph, 4-ClC_6H_4
R^1 = H, Me
R^2R^3 = -$(CH_2)_3$-

365 (Ar = Ph, 87%) **366** (Ar = Ph, 66%)

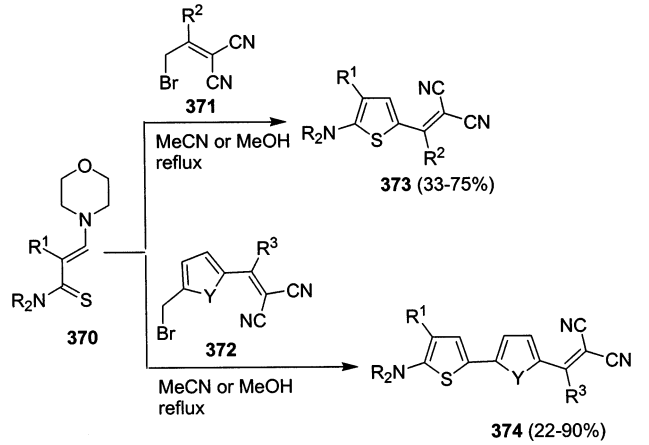
Scheme 101



367 **368** **369** (48-91%)

NR_2 = NMe_2, $N(CH_2CH_2)_2O$; R^1R^2 = -$CH_2CH_2OCH_2CH_2$-, -$(CH_2)_4$-, Me, Et
R^3 = H, Ph, CN; R^4 = Me, Et

Scheme 102

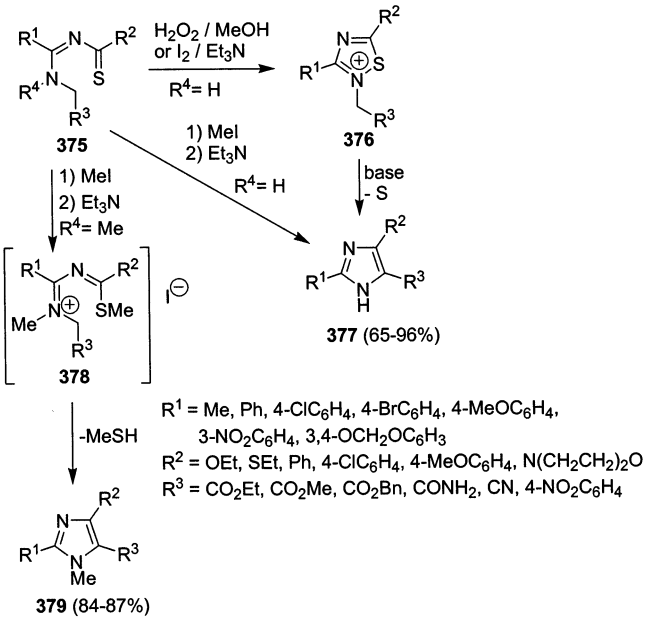


NR_2 = $N(CH_2CH_2)_2O$, NMe_2, NEt_2, NPh_2
R^1 = H, Ph; R^2 = Me, Ph; R^3 = H, CN;
Y = -CH=CH-, S, O

E. Reactions of Thiocarbonylamidines

Thiocarbonylamidines **375** may be regarded as a specific variety of thioamides (Scheme 103). In contradistinction to the typical thioamides, they have two nitrogen atoms, of which the thioamide one is sp^2-hybridized. Compounds **375**, with R^4 = H, cyclize to 1,2,4-thiadiazolium salts **376** when oxidized with hydrogen peroxide in methanol or with iodine in the presence of triethylamine. Ring transformation/desulfurization of **376** results in the formation of imidazoles **377**.[203]

Scheme 103

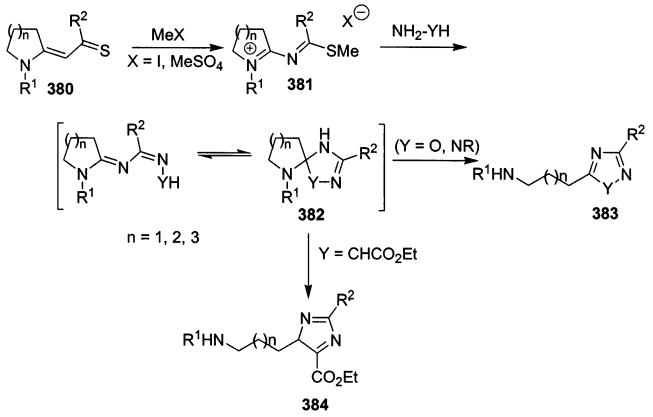


R^1 = Me, Ph, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, 3-$NO_2C_6H_4$, 3,4-$OCH_2OC_6H_3$
R^2 = OEt, SEt, Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, $N(CH_2CH_2)_2O$
R^3 = CO_2Et, CO_2Me, CO_2Bn, $CONH_2$, CN, 4-$NO_2C_6H_4$

Oxidative conversion of *N*′,*N*′-disubstituted *N*-(thiocarbonyl)amidines **375** (R^4 = Me) to 1,2,4-thiadiazolium salts **376** is, of course, not possible. To gain access to 1-substituted imidazoles **379**, amidines **375** were *S*-methylated with methyl iodide in the presence of triethylamine. The expected intermediate *N*-imidoylisothioimidates **378** were instantly losing the methylthiol group, to afford imidazoles **379** in the reaction mixture (Scheme 103).[203]

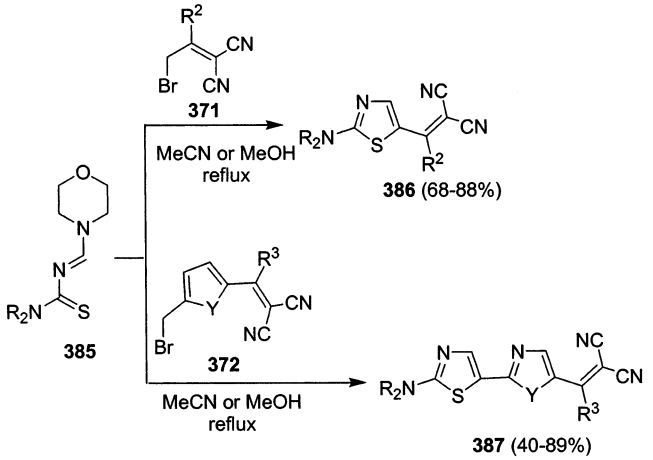
The ring−chain reactions of thioacylamidines with binucleophilic compounds result in the formation of ω-aminoalkyl derivatives of heterocyclic compounds, including analogues of histamine. The *S*-alkylated thioacylamidines **380** react with 1,2-binucleophiles as the C−N−C synthons to afford the ω-aminoalkyl derivatives of 1,2,4-triazole **383** (Y = NR), 1,2,4-oxadiazole **383** (Y = O), and imidazole **384** (Scheme 104).[204−206] According to the postulated mechanism,

Scheme 104



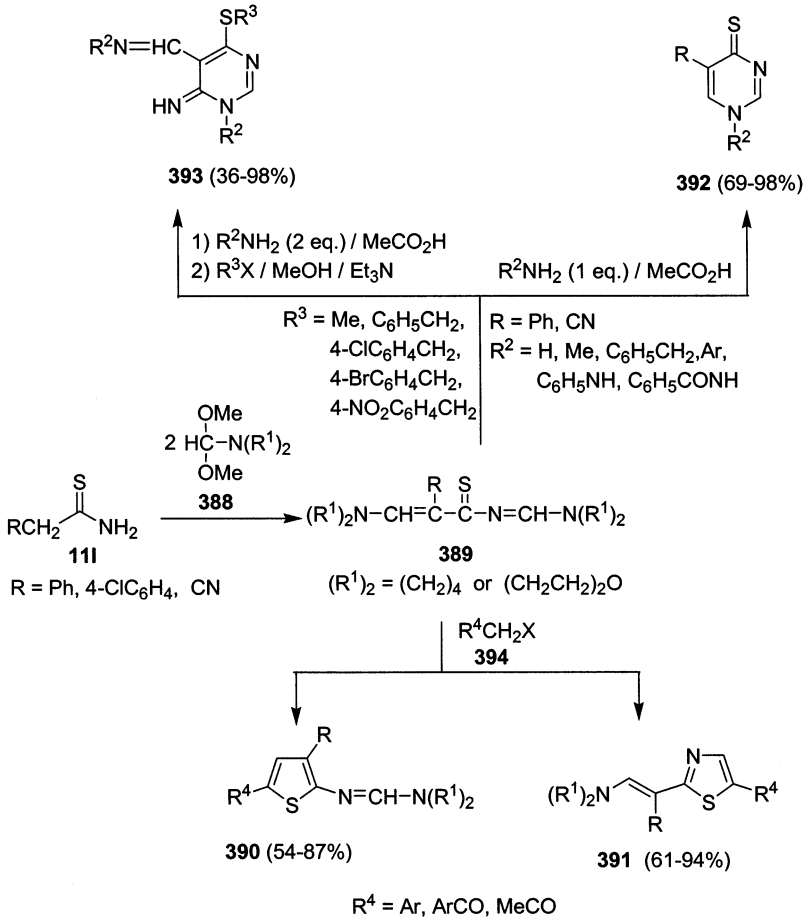
the reactions proceed via the spiroheterocyclic intermediate **382**. This ring−chain transformation sequence is known as the ANSARO ring transformation (addition of nucleophile, spiro annulation, ring opening). Several examples of similar transformations were reviewed previously by Liebscher.[205] Thioacylamidines **385** react with 2,2-dicyanoethenyl- and 1,2,2-tricyanoethenyl-substituted bromoalkanes, bromomethylbenzenes, thiophenes, and furans **371** and **372** in a way similar to the reaction with 3-aminothioacrylamides **370**. Cyanoethenyl derivatives of thiazole **386** or their (hetero)benzologous analogues **387** are the products of these reactions (Scheme 105).[202]

Scheme 105



NR_2 = $N(CH_2CH_2)_2O$, NMe_2, NEt_2, NPh_2
R^2 = Me, Ph; R^3 = H, CN
Y = - CH=CH-, S, O

Scheme 106

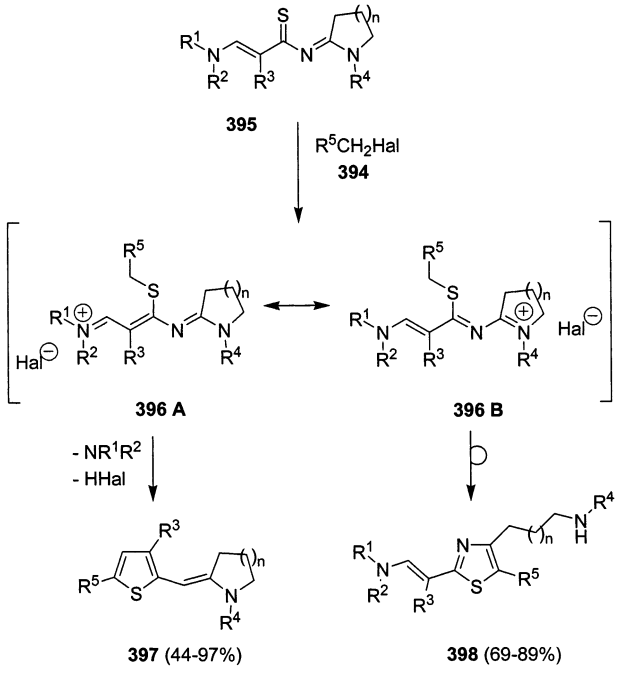


F. Reactions of *N*-(3-Aminothioacryloyl)formamidines

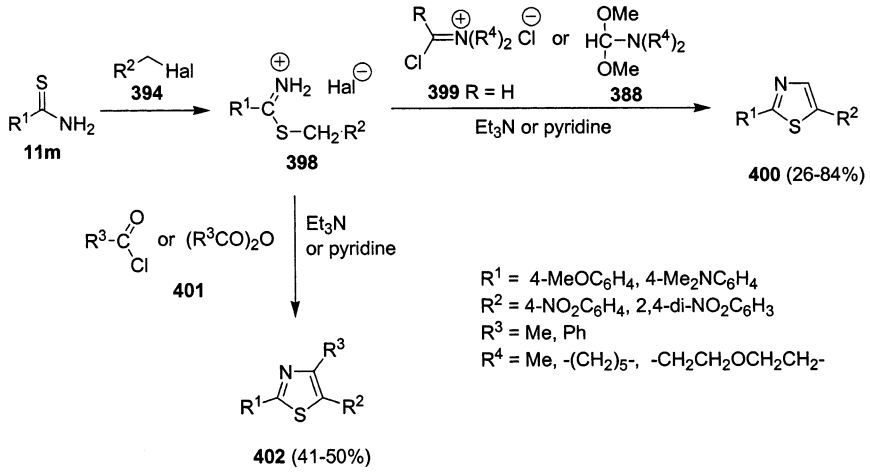
Heterocyclization of thioamides containing both 3-aminothioacrylamide and thioacylamidine fragments was investigated by Liebscher and Knoll.[207−209] They reported on bisiminoformylation of thioacetamides and thiourea, accomplished by their reaction with formamide acetals. The resulting *N*-(3-aminothioacryloyl)formamidines **389** are polyfunctional compounds which can be used as starting materials in the synthesis of heterocycles. The interaction of **389** with methyl halides having an electron-withdrawing group, **394**, or a base gives rise to the formation of 2-formamidinothiophenes **390** or 2-aminovinylthiazole **391**, respectively (Scheme 106). Compounds **389** are also capable of reacting with primary amines to give either 4(1*H*)-pyrimidinethiones **392** or 6(1*H*)-pyrimidinimines **393** (Scheme 106).[207−209]

N-(3-Aminothioacryloyl)lactam imines **395** consist of both a 3-aminothioacrylamide moiety and an *N*-thioacyllactam imine unit. The two separated substructures are known to react with acidic methyl halides **394** to give 2-aminothiophenes **397** by regular cyclization[210,212] or 4-aminoalkyl-1,3-thiazoles **398** by ring−chain transformation,[211,212] respectively (Scheme 107).

Scheme 107



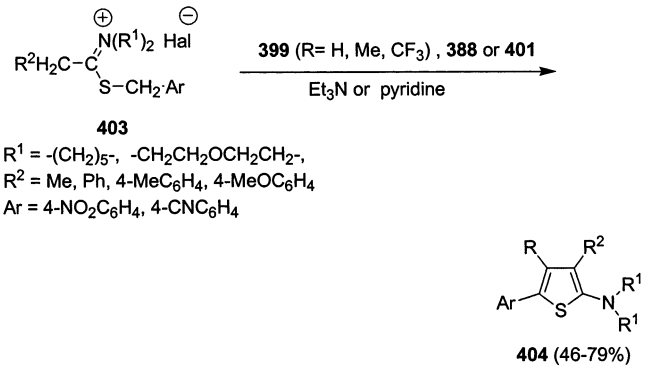
Scheme 108



IV. Miscellaneous Reactions

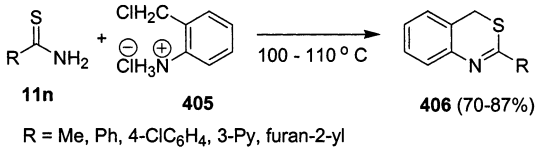
The reaction of mercaptomethyleniminium salts **398**, possessing electron-withdrawing aryl substituents R^2, with formamide chlorides **399** or acetals **388** in the presence of a base gives rise to the formation of 2,5-disubstituted thiazoles **400**. If other acid derivatives **401** instead of **399** or **388** are employed in this reaction, 2,4,5-trisubstituted thiazoles **402** are obtained (Scheme 108).[213] Thioureas react in a similar way.[213] On the other hand, the reaction of *N*,*N*-disubstituted isothiuronium salts **403** with formamide chlorides **399** or other acid derivatives, such as substituted formamide acetals **388** or acid anhydrides **401**, in the presence of a base gives rise to the formation of 2-aminothiophene derivatives **404** (Scheme 109).[214]

Scheme 109



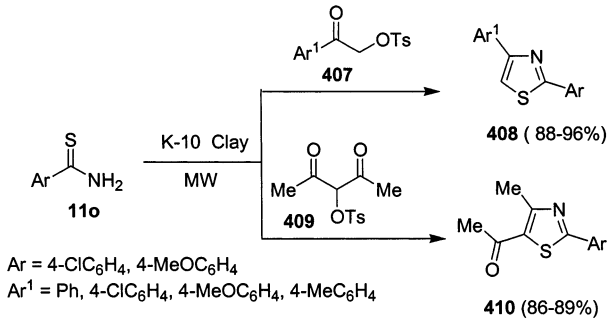
Certain reactions of thiobenzamides with electrophilic reagents can take place in a melt or in a solid state. For instance, fusion of *o*-aminobenzyl chloride hydrochloride **405** with different thiocarboxamides **11n** affords the 4*H*-3,1-benzothiazine derivatives **406** in good yield (Scheme 110).[215]

Scheme 110



Varma and co-workers[216] describe expeditious syntheses of 1,3-thiazoles **408** from the readily accessible α-tosyloxyketones **407** and mineral oxides in processes that are accelerated by exposure to microwaves. Compounds **408** are readily obtained from thioamides **11o** and α-tosyloxyketones **407** in the presence of montmorillonite K-10 clay. In the case of diketone, as exemplified by the reaction of 3-tosyloxypentane-2,4-dione **409** with thioamides **11o**, the formation of 5-acetyl-4-methyl-2-aryl-1,3-thiazole derivatives **410** can be realized in excellent yields (Scheme 111).[216]

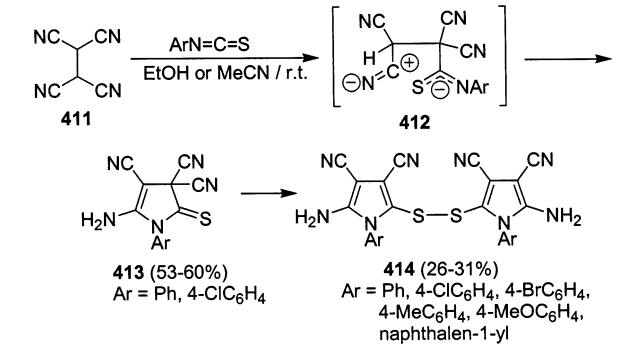
Scheme 111



Thioamides also may act as reactive intermediates in the synthesis of heterocyclic compounds. For instance, this is the case with the thioamide intermediates having some additional reactive centers capable of instant cyclization with the thioamide group.

The reaction of 1,1,2,2-tetracyanoethane **411** with aromatic isothiocyanates, carried out in ethanol or acetonitrile in the presence of triethylamine, gives bis(2-amino-1-aryl-3,4-dicyano-4,5-dihydro-5-thiones) **414** (Scheme 112).[217] Thioamide **412** is here the primary reaction product, which cyclizes to yield 4,5-dihydro-5-thione **413**. This cyclization occurs with participation of the vicinal cyano group. When an analogous reaction is carried out in an isopropanol−water 2:1 mixture, that is, in a medium of much lower basicity, isolation of the intermediate cyclization product **413** becomes possible. Aliphatic isothiocyanates do not react in a similar way; since only decomposition of the reaction mixture was observed.

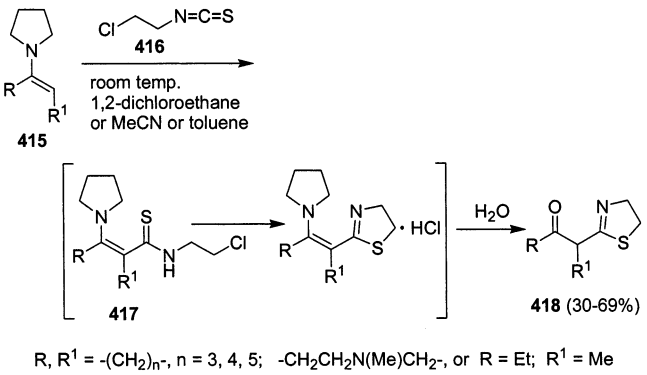
Scheme 112



The mechanism of the cyclization was investigated and described in detail.[217]

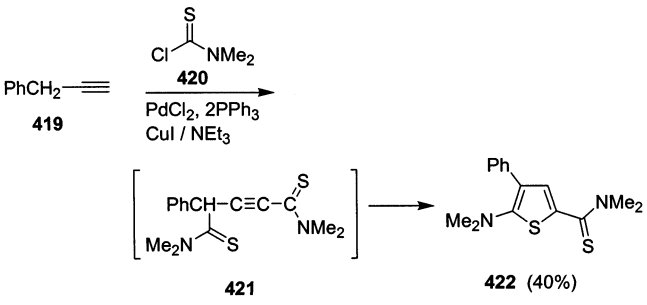
The thioamide **417** is also an intermediate in the reaction of enamines with 2-chloroethyl isothiocyanate. Pyrrolidine-derived enamines **415** react with 2-chloroethyl isothiocyanate **416** to give, after hydrolysis, 2-(*β*-oxo)-2-thiazolines **418** in fair to good yields (Scheme 113).[218] Similarly, in the palladium

Scheme 113



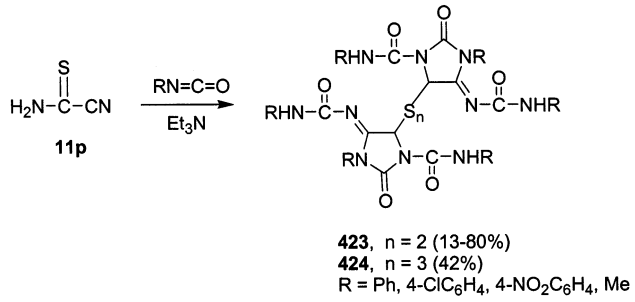
chloride-catalyzed reaction of benzylacetylene **419** with *N*,*N*-dimethylthiocarbamoyl chloride **420**, dithioamide **421** is first formed as an active intermediate which spontaneously cyclizes to give the derivatives of 2-thiophenecarbothioamide **422** (Scheme 114).[219]

Scheme 114



Other heterocyclizations utilizing isothiocyanates, in which thioamides are formed as the active intermediates, have been described by Mukerjee and Ashare.[220] Recently, the reaction of cyanothioformamide **11p** with isocyanates has been reported by Ketcham and co-workers.[221] Thus, **11p** reacts with aryl isocyanates to give bis[3-aryl-1-(arylcarbamoyl)-2-oxo-4-(arylcarbamoylimino)imidazolidin-5-yl] disulfides **423**. Reaction with methyl isocyanate gives the related trisul-

Scheme 115



fide **424**, along with the disulfide **423** (Scheme 115). The mechanism of this multistep reaction was proposed.

Even if it is not engaged directly in the heterocyclization process, the thioamide group can significantly affect the course of this reaction. There are known reactions of resorcinol-derived thioamides **425** with citral, resulting in the formation of cannabicitran **426** and its open-chain isomers **427** (Figure 12);[222,223] these reactions proceed at high tempera-

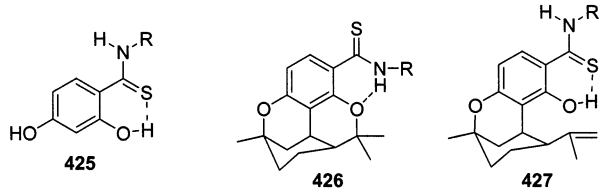


Figure 12.

tures in the presence of 2,4,6-collidine. The multistep mechanism of this reaction, including among others condensation and Diels−Alder cyclization, has been discussed in detail.[222]

V. Concluding Remarks

The material included in this review covers only the most interesting reactions of thioamides, the reactions which exemplify the universal applicability of these compounds as useful building blocks in organic synthesis. Its selection, by necessity, reflects the author's point of view and therefore may be considered to be somewhat subjective. However, it should be remembered that the scope of the presented reactions can be vastly expanded by additional functionalization of the basic thioamide structure. The synthetic importance of such polyfunctional thioamides can hardly be overestimated.

VI. Acknowledgments

I would like to express my thanks to Professor Jerzy Lange (Warsaw University of Technology) for helpful discussions and assistance in preparation of the manuscript.

VII. References

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