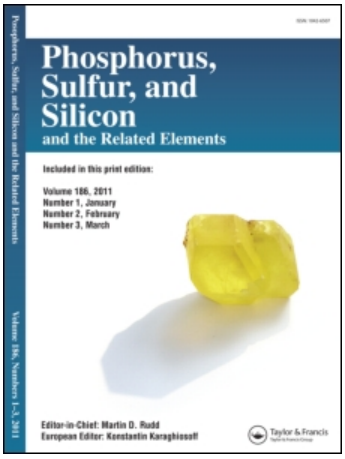

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THE CHEMISTRY OF 3-AMINOTHIOACRYLAMIDES; PART II: 3-AMINOTHIOACRYLAMIDES AS USEFUL SYNTHONS IN ORGANIC SYNTHESIS

Jürgen Liebscher[a]; Berhanu Abegaz[b]; Alexander Knoll[a]
[a] Sektion Chemie, Humboldt-Universität zu Berlin, Berlin, German Democratic Republic [b] Department of Chemistry, Addis Ababa University, Addis Ababa, Ethiopia

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THE CHEMISTRY OF 3-AMINOTHIOACRYLAMIDES; PART II: 3-AMINOTHIOACRYLAMIDES AS USEFUL SYNTHONS IN ORGANIC SYNTHESIS

JÜRGEN LIEBSCHER,*[a] BERHANU ABEGAZ,[b]
ALEXANDER KNOLL[a]

[a] *Sektion Chemie, Humboldt-Universität zu Berlin, Hessische Str. 1-2, DDR-1040 Berlin, German Democratic Republic*
[b] *Department of Chemistry, Addis Ababa University, P.O. Box 1176, Addis Ababa, Ethiopia*

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3-Aminothioacrylamides are a class of organic sulfur containing compounds that are easily available and exhibit polyfunctional reaction behaviour. 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.

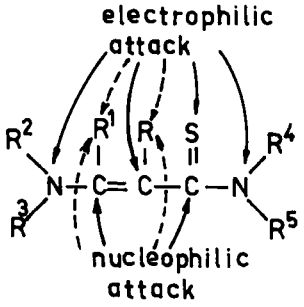
Keywords: 3-aminothioacrylamides, heterocyclic synthesis, cyclisation, sulfur compounds.

1. INTRODUCTION

It has been shown, in the first part of this publication,[1] that 3-aminothioacrylamides with various substitution patterns can be prepared with relative ease. Hence this class of compounds could serve as useful starting materials for further synthetic applications.

Besides the reactive centers typical for thioamides (that is electrophilic properties at the thiocarbonyl carbon atom and nucleophilic at thiocarbonyl sulfur and nitrogen atoms) 3-amino-thioacrylamides have an additional electrophilic carbon atom at position 3, and further nucleophilic positions at the enamine carbon atom (position 2) and at the amino nitrogen atom connected to position 3 (see Scheme 1). Furthermore it is possible that active sites may be found in the substituents R and R^1 as well as in the amino substituents. Due to this exceptionally polyfunctional reaction behaviour, 3-aminothioacrylamides have a wide synthetic potential.

This publication gives a review on the application of 3-amino-thioacrylamide systems in the preparation of open chain and especially heterocyclic compounds. The review is organized according to synthetic aspects. Products derived by mere reaction at one of the substituents R, R^1, R^3, R^4 and R^5 are not included. Intramolecular cyclisations in which the intermediate 3-aminothioacrylamide systems were not isolated have been considered in the previous publication.[1]

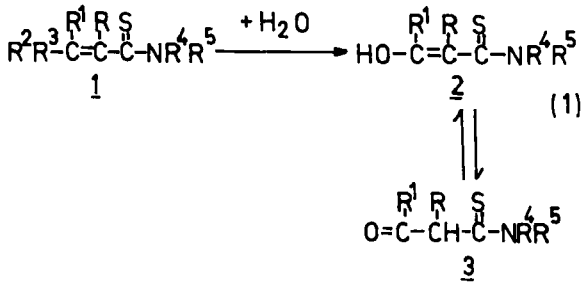


Scheme 1

2 SYNTHESIS OF OPEN CHAIN PRODUCTS

2.1. Substitution Reactions by Nucleophiles

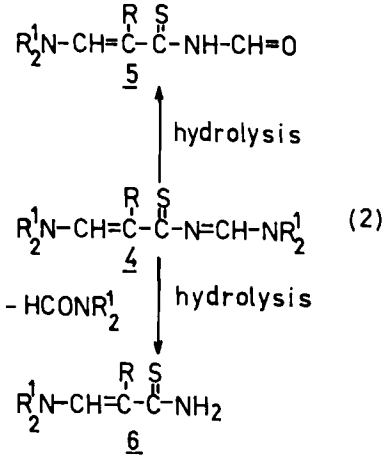
According to Scheme 1, there are two sites for nucleophilic attack at positions 1 and 3 of 3-aminothioacrylamides. In reactions with simple nucleophiles, usually only substitutions of the 3-amino group are obtained. For example 3-hydroxythioacrylamides **2** or their tautomers **3** are formed by mild acidic hydrolysis regardless of the nature of the substituents R^2 and R^3 (1).[2-16] Under



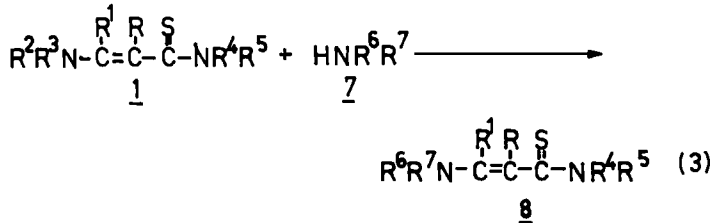
more strongly acidic conditions cleavage of the C—C-bond between positions 1 and 2 may take place in addition to the nucleophilic substitution (1).[15,16] Some 3-aminothioacrylamides bearing an acetyl group at position 2 (R = COMe) may also loose the acetylsubstituent during the hydrolysis (1) leading to products with no substituents at the position **2** (R = H).[10] A simple hydrolysis according to equation (1) is observed for compounds **1** possessing an acyl group ($R^1 = R^2 = Ph$; $R = R^3 = R^5 = H$; $R^4 = COC_6H_5$)[17] or an aminothiocarbonyl group [$RR^1 = (CH_2)_4$; NR^2R^3 = pyrrolidino; $R^5 = Et$; $R^4 = CSNHEt$][15] at the thioamide nitrogen atom.

On the other hand, the enamine structure is retained if (3-aminothioacryloyl)-formamidines **4** are subjected to hydrolytic conditions. Depending on both the reaction conditions and the substituent R, either (3-aminothioacryloyl)-formamides **5** or 3-aminothioacrylamides **6** are formed by substitution of the NR_2^1 and loss of formamide groups, respectively.[18]

Since 3-aminothioacrylamides **6** cannot be synthesised by direct iminoformylation of thioacetamides (see part I),[18,19] the hydrolytic cleavage (2) provides the only access to these compounds.

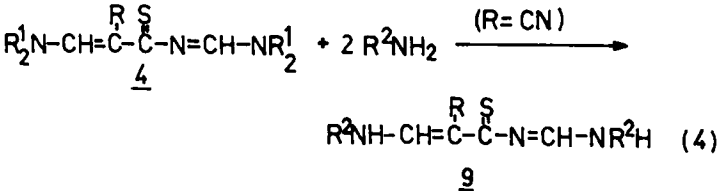


The amino group attached to position 3 of the thioacrylamides **1** (R^2, R^3 = alkyl)[20] or (R^2 = aryl; R^3 = H)[21] can also be selectively substituted by primary aliphatic and aromatic[20–22] or by secondary aromatic amines (3).[20]

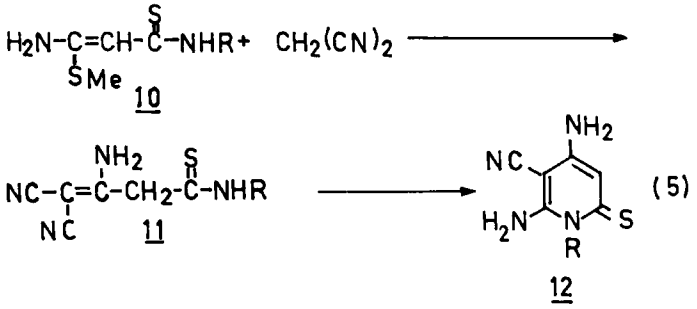


The interaction of hydrazines **7** (R^6 = NHR; R^7 = H)[20] or glycinates **7** (R^6 = $CH_2COOalkyl$; R^7 = H)[23] with thioamides **1** also gives the corresponding substitution products **8**, which are intermediates in the synthesis of pyrazoles and pyrroles (see Section 3.4.).

When 3-aminothioacrylamides **1** (R^4 = COOEt; R^5 = H)[24,25] or *o*-(morpholinothiocarbonylamino)-thiobenzmorpholide[26] are reacted with primary amines or ammonia, in addition to the substitution (3) (and without the isolation of corresponding substitution products) a cyclisation to pyrimidinthiones takes place (see also Section 3.9.). The same is true for the reaction of arylsubstituted (3-aminothioacryloyl)-formamidines **4** (R = aryl) with primary amines and hydrazines (see Section 3.9). Cyanosubstituted compounds **4** (R = CN), however, can be transformed to the open chain disubstitution products **9** (4).[27,28]

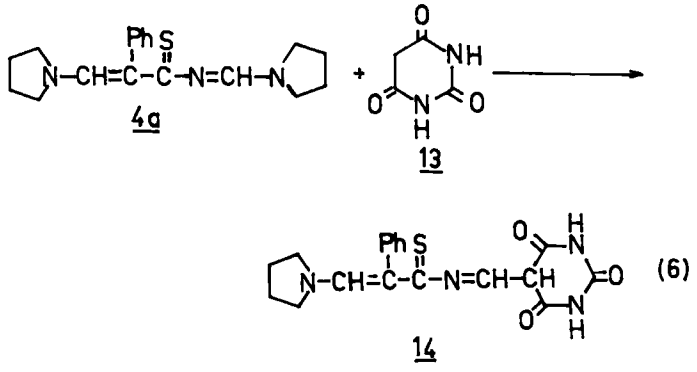


An attack at the 3-position of 3-aminothioacrylamides is also possible by C-nucleophiles. When malononitrile[29–32] or cyanoacetate[31] are employed, however, no corresponding substitution products can be isolated since cyclisation takes place giving rise to pyrimidine[29–32] or thiopyrylium systems[30,32,33] (see Section 3.5). The 3-methylmercapto substituted 3-aminothioacrylamides **10** act in a different way and an open chain intermediate can be isolated the 3-methylmercapto being substituted rather than the 3-amino group (5).[34] An open



(5)

chain monosubstitution product **14** with an intact 3-aminothioacrylamide skeleton is formed in the reaction (6) of (3-aminothioacryloyl)-formamidine **4a** with barbituric acid. The attack of the CH-acidic reagent, however, occurs at the amidine carbon atom.[18]

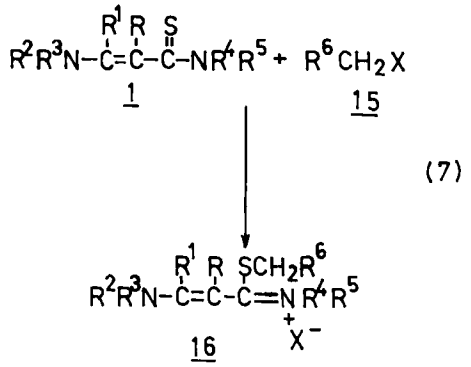


(6)

2.2. *Reactions with Electrophiles*

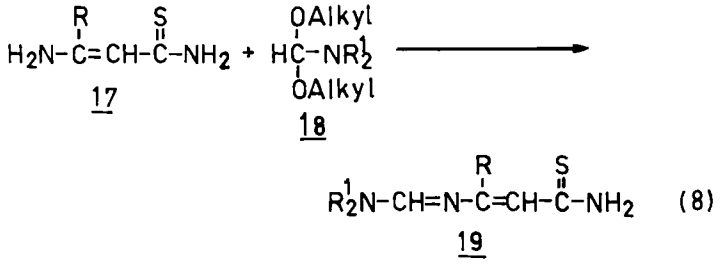
Although only a few examples are given here, the reaction of 3-aminothioacrylamides with electrophiles is frequently used in the synthesis of several heterocyclic systems (see section 3.1–3.3, 3.5–3.8). The interaction of 3-aminothioacrylamides with alkylating reagents gives rise to an alkylation of the thiocarbonyl sulfur atom.[20,35–38]

When the resulting isothioamide systems **16** possess acidic CH_2-groups (R^6 electronwithdrawing) subsequent cyclisation to thiophenes can easily occur (see Section 3.5). Simple S-alkylations are occasionally used to perform a smoother substitution of the S atom of the 3-aminothioacrylamides by nucleophiles[39] especially in cyclisation reactions.[20,23,40] No S-iminoformylation products are



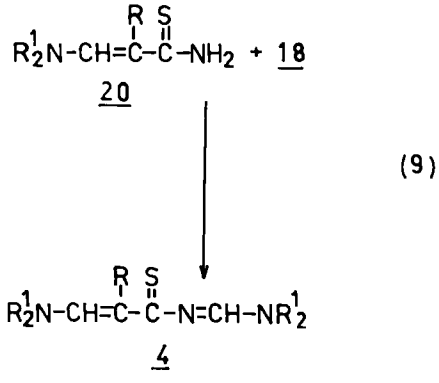
(7)

isolated when 3-aminothioacrylamides are reacted with activated formamide derivatives, such as formamide chlorides **21** or formamide acetals **18**. N-unsubstituted reactands **17** react with formamide acetales at the amino group connected to position 3 (formation of **19**)[41] and the N-substituted 3-aminothioacrylamides **20** are iminoformylated at the thioamide nitrogen atom



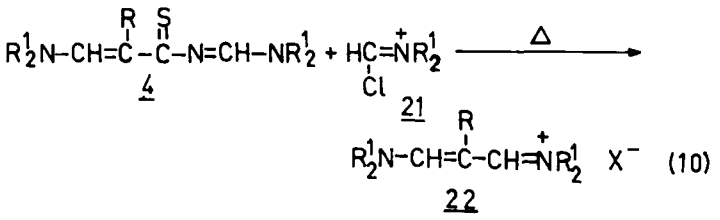
(8)

(formation of **4**).[19] Attempts to synthesise (3-aminothioacryloyl)-formamidines having different terminal amino groups by the reaction (9) failed in most cases. Usually reactions of 3-aminothioacrylamides **20** with formamide acetales possessing differently substituted amino groups than NR_2^1 (in **18**) result in the formation of transamination products **4**.[18]



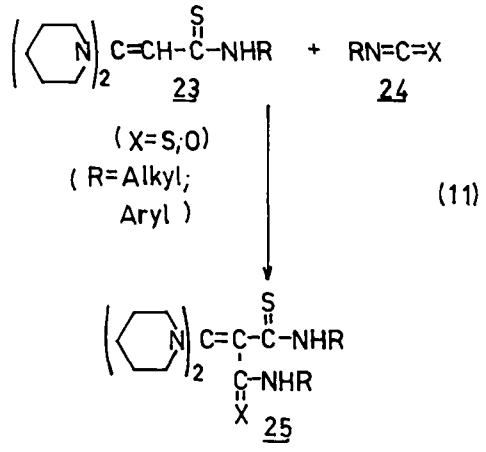
(9)

(3-Aminothioacryloyl)-formamidines **4** lack a free amino group. Therefore, in reactions with formamide chlorides **21** the enamine carbon at position 2 is attacked with C—C-bond cleavage between position 1 and 2 thus giving rise to formation of trimethinium salts **22**.[42]



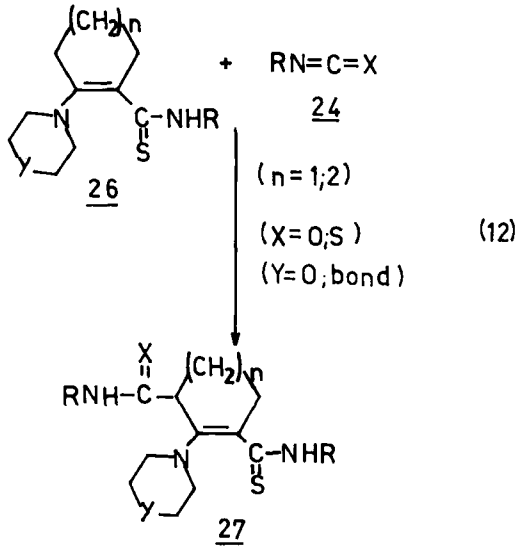
(10)

3-Aminothioacrylamides can react with isocyanates or isothiocyanates in different ways. In reactions with these heterocumulens **24** 3,3-dipiperidino substituted compounds **23** are attacked at the enamine carbon atom yielding malonamide derivatives **25** (11).[43]



(11)

Due to the absence of H at the 2-position the attack of heterocumulens at cyclic 3-aminothioacrylamides **26** takes place at the CH-acidic methylene group attached to position 3. Sometimes this substitution (12) is accompanied by an

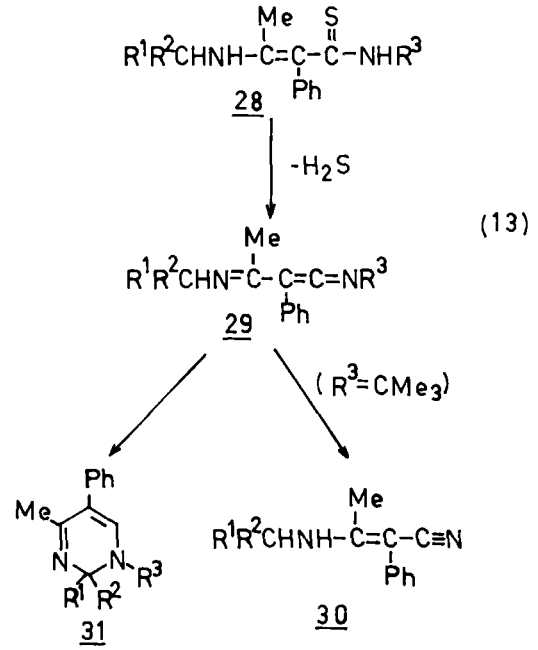


(12)

exchange of the original aminothiocarbonyl group CSNHR by the reacting heterocumulen **24**.[13] Cyclisations to pyrimidine systems can also occur in reactions of 3-aminothioacrylamides with isocyanates or isothiocyanates[13,44] (see Section 3.6).

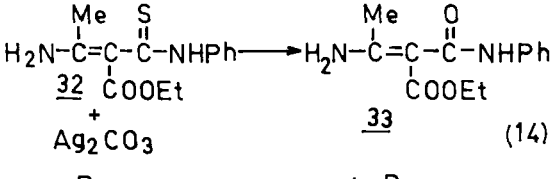
2.3. *Desulfurization Reactions*

The sulfur atom of 3-aminothioacrylamides can be removed either by elimination or by substitution reactions. Such reactions are important for the synthesis of other derivatives of 3-aminoacrylic acids. The H_2S-elimination from compounds **28** for example gives the corresponding keteneimines **29** which can further be modified to 3-aminoacrylonitriles **30** or pyrimidine systems **31**.[45]



(13)

As has been shown with several examples **32**, **34** and **36** the sulfur atom of 3-aminothioacrylamides can be substituted by oxygen using classical desulfurizing reagents Ag_2CO_3 or H_2O_2 to give 3-aminoacrylamides **33**,[46] **35**[35] or **37**.[47]



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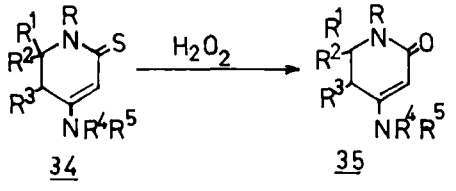

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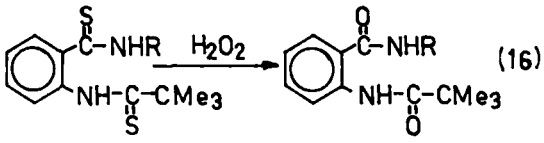
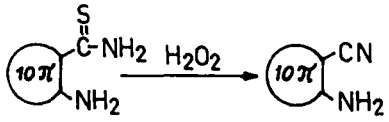


(16)

36 37

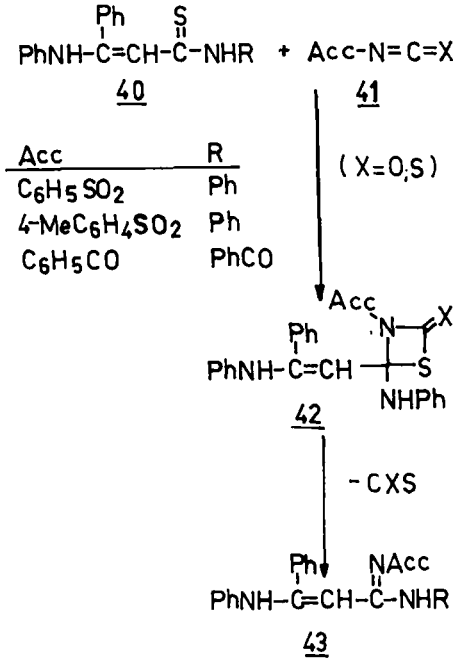


(17)

38 39

The desulfurization with H_2O_2 may also lead to *o*-aminonitriles **39**[49] of the naphthalene or quinoline series. The most common reaction of 3-aminothioacrylamides with oxidising reagents is, however, the oxidative ring closure to isothiazole compounds and not desulfurization (see Section 3.7).

Desulfurization can also be accompanied by the introduction of an iminofunction when the reagents are heterocumulenes **41** substituted by an electron withdrawing substituent. In such cases 3-aminoacrylamidines **43** are formed via intermediate cycloadducts **42**.[17,50]

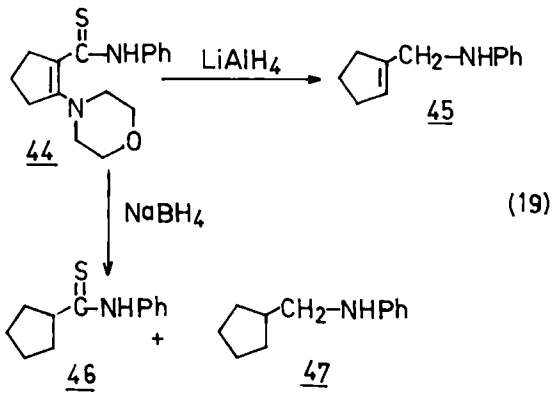


Acc	R
$C_6H_5SO_2$	Ph
4-$MeC_6H_4SO_2$	Ph
C_6H_5CO	PhCO

(18)

40 41 42 43

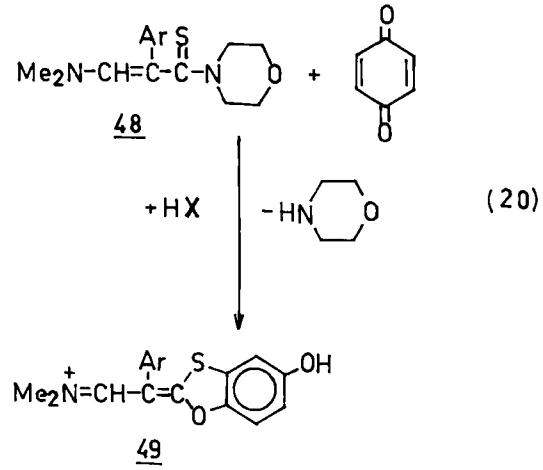
Finally reduction of the cyclic 3-aminothioacrylamide **44** by means of complex hydrides is to be mentioned. These reductions cause a degradation of the thioacrylamide skeleton. $NaBH_4$ reduction partly results in the S-containing product **46**.[51]



3 SYNTHESES OF HETEROCYCLIC COMPOUNDS

3.1 Application as C—S-Synthon

If a 3-aminothioacrylamide is to react as a C—S-synthon in the synthesis of heterocycles the reactand needs both electrophilic and nucleophilic properties. Usually the problem arises that the electrophilic C-atom at position 3 competes for the nucleophilic site in the reactand. Hence 3-aminothioacrylamides are difficult to apply as C—S-synthon. The only heterocyclic synthesis known so far is the reaction of 3-aminothioacrylamides **48** with benzoquinone giving rise to benzoxathiolium salts **49** and morpholine as byproduct.[52] Probably the primary attack of the quinone occurs at the thiocarbonyl-S-atom. The subsequent cyclisation is then achieved by the nucleophilic attack at the thiocarbonyl-C-atom rather than at position 3.

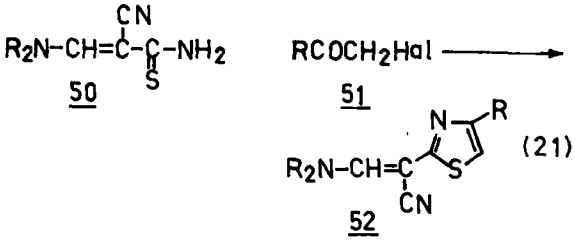


3.2. Application as N—C—S-Synthon

According to the reactivity pattern shown above (see Scheme 1) 3-aminothioacrylamides can act as N—C—S-synthons if they are reacted with

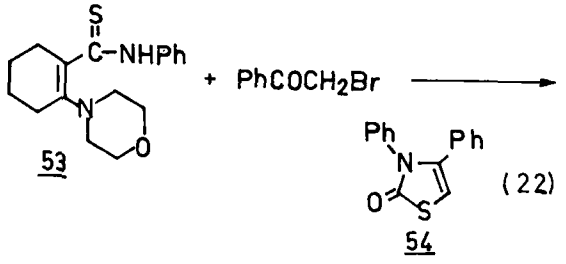
bifunctional electrophiles attacking both, the thioamide-S and the thioamide-N-atom. As a precondition in the amino group at position 1 at least one H-atom is necessary.

The interaction of 3-aminothioacrylamides **50** with α-haloketones **51** gives aminovinylthiazoles **52** in a Hantzsch-like synthesis (21).[53] The formation (22) of



(21)

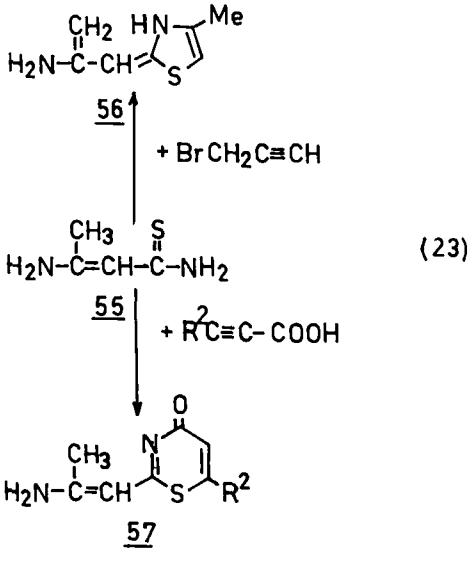
the thiazolinon **54** is a special case of the reaction of a 3-aminothioacrylamide as a N—C—S-synthon. The substrate **53** only acts as a thiocarboxylic acid derivative since a C—C-bond scission takes place and morpholino-cyclohexene is eliminated[54] (for a similar case see Reference[131]).



(22)

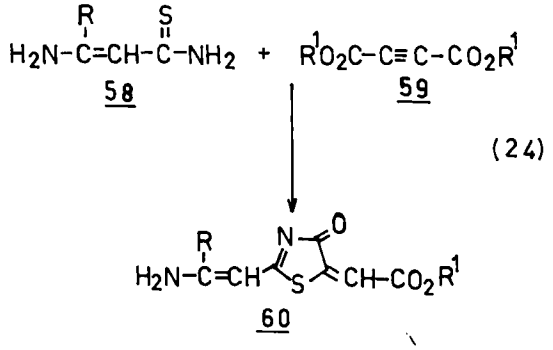
Sometimes reactions of 3-aminothioacrylamides having an H-atom at the thioamide amino group with phenacyl bromides do not end up with thiazoles but with thiophenes[54] (see Section 3.5).

In the synthesis (23) of the thiazoline-derivative **56** from the 3-



(23)

aminothioacrylamide **55**, propargyl bromide could be used as a C_2-building block instead of a corresponding α-haloaldehyde.[55]

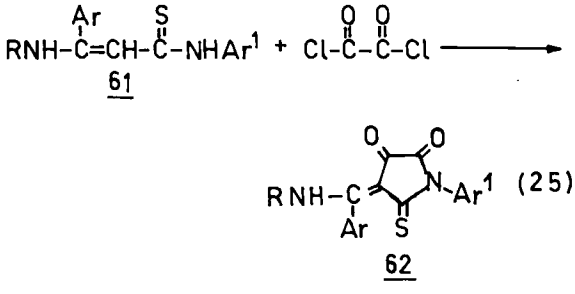


(24)

Alkynes possessing an α-carbonyl group can also be employed as bifunctional electrophiles in the transformation of 3-aminothioacrylamides to heterocycles. The application of acetylene dicarboxylates gives the thiazole systems **60** (24) while the use of propiolic acid leads to the 6-membered thiazinones **57** (23).[55]

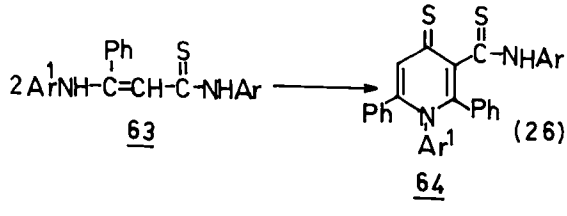
3.3. Application as C—C—N-Synthon

3-Aminothioacrylamides have rarely been used as C—C—N-synthons. In the reaction of compounds **61** [R = CH_2CH_2N = C(Me)Ar] with oxalyl chloride an electrophilic attack occurs at both, the thioamide amino group and the enamine C-atom at position 2 (25) to give thiazolidinones **62**.[56]



(25)

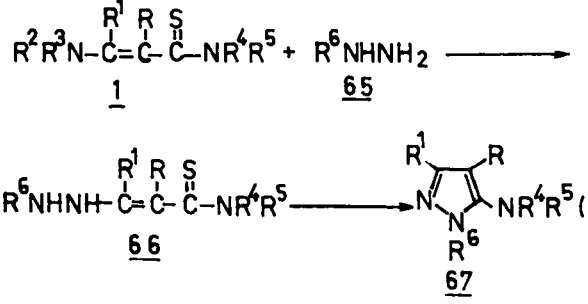
In the formation of pyrimidinthiones **64**[57] by self condensation (26) of 3-aminothioacrylamides **63** one molecule of the reactand acts as a C—C—N-synthon while the other acts as a 1,3-bifunctional electrophilic C_3-building block. Again the electrophilic attack occurs at position 2.



(26)

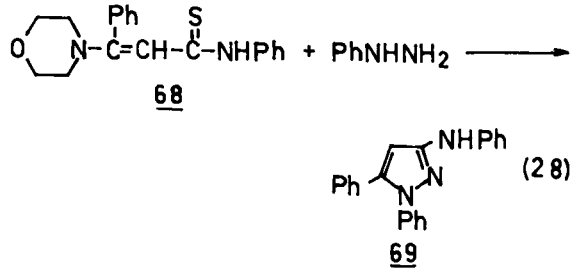
3.4. *Application as C_3-Synthon*

3-Aminothioacrylamides are heteroanalogues of β-ketoamides and hence would be expected to provide C_3-building blocks in their reaction with bifunctional nucleophiles to give heterocycles. As could be seen in reactions with simple nucleophiles (see Section 2.1) the primary site of nucleophilic attack is assumed at position 3. The subsequent nucleophilic attack at position 1 gives rise to the substitution of the thiocarbonyl-S-atom rather than the amino group. Hence 3-aminothioacrylamides are superior to β-functionalised acrylamides in so far as amino substituted heterocycles can be synthesised which are difficult to attain by other routes. For example pyrazoles **67** containing a mono ($R^5 = H$; R^4 = aryl,[10,40,58] alkyl,[58,59] allyl[40] or benzoyl[58]) or disubstituted amino group (NR^4R^5 = morpholino[20]) can be synthesised from 3-aminothioacrylamides **1** (NR^2R^3 = dialkylamino, morpholino or pyrrolidino) and hydrazines **65** ($R^6 = H$[10,20,40,58,59] or aryl[10,20]). The substituent R can represent H,[58,59] alkyl,[59] aryl,[20] acetyl[10] or nitro[40] or R,R^1 can be $(CH_2)_n$.[58] R^1 may be H,[20,52], phenyl,[58,59] methyl[10] or dimethylamino.[40]

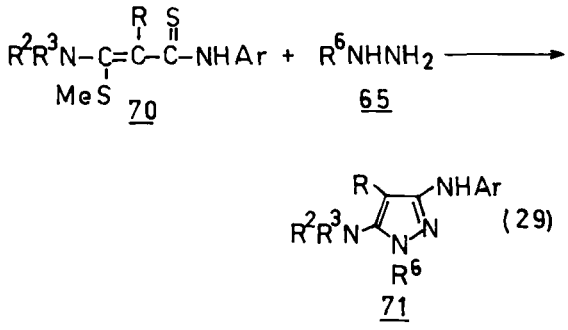


In order to increase the leaving tendency of the thiocarbonyl-S-atom, 3-aminothioacrylamides **1**[40] or the intermediate 3-hydrazinothioacrylamides **66**[20] were S-alkylated sometimes. Usually the yields achieved are high. But with 2-acetyl[10] or 2-cyano substituted[130] 3-aminothioacrylamides **1** (R = COMe or CN) there is a competing formation of pyrazoles by the nucleophilic attack at position 3 and the carbonyl or cyano-C-atom rather than the thiocarbonyl-C-atom.[10]

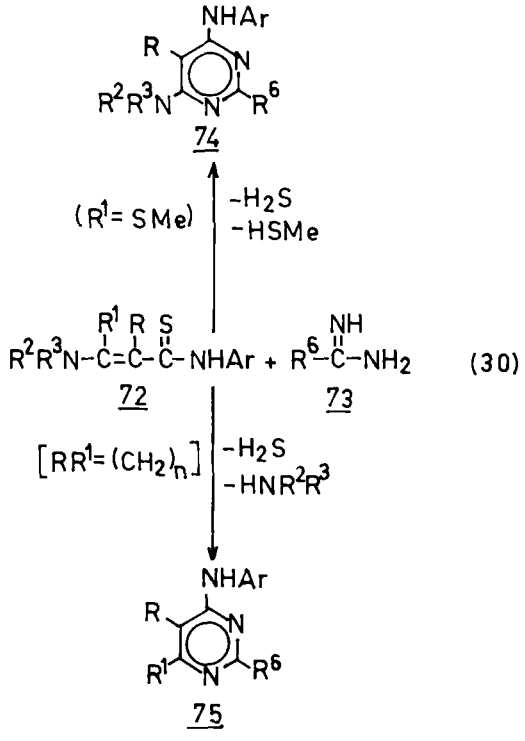
In contrast to reaction (27) there is one case reported where instead of the pyrazoles **67** isomeric products **69** are formed (28).[58]



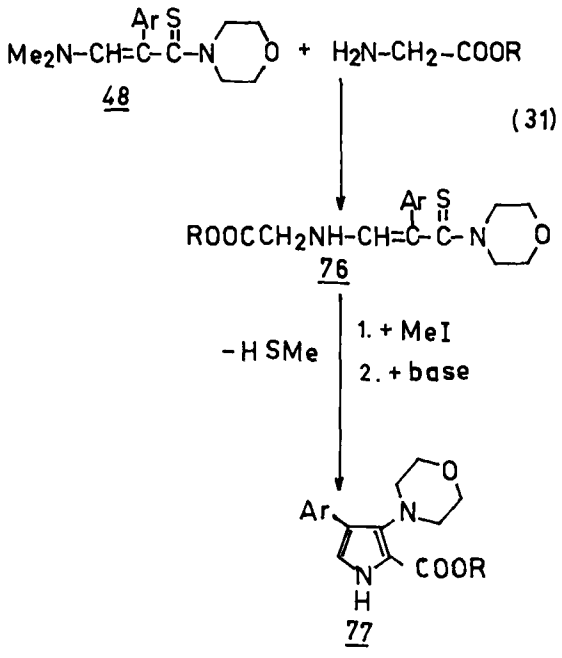
Methylmercapto substituted 3-aminothioacrylamides **70** react with hydrazines by substitution of the methylmercapto group to give 2,5-diaminopyrazoles **71** [R = H, $R^2 = R^3 = Me$[60] or $R/R^2 = (CH_2)_n$, $R^3 = Me$[61]] (29).



A similar behaviour is observed when 3-aminothioacrylamides react as C_3-synthons with amidines in order to synthesise aminopyridines. Methyl mercaptan is eliminated giving rise to the formation of 4,6-diaminopyrimidines **74** (R = H, $R^2 = R^3 = Me$[60]; $R/R^2 = (CH_2)_2$, $R^3 = Me$[61]) if $R^1 = SMe$. Otherwise the amino group at position 3 leaves the molecule and 4-aminopyrimidines **75** ($R^6 = Ph$)[58] are obtained (30).

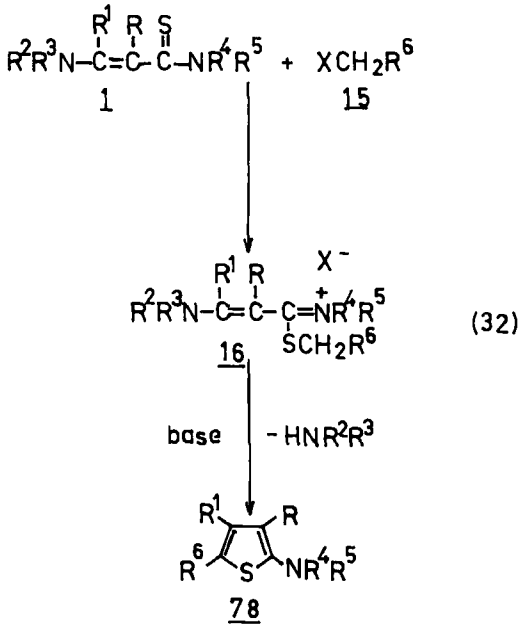


3-Aminothioacrylamides **48** can also be applied as C_3-synthons in the synthesis of pyrroles when glycinates are used as 1,2-bifunctional nucleophiles. In the first step of this reaction (31) the substitution products **76** are formed, which after S-methylation and subsequent deprotonation of the methylene group by base give the pyrrol-2-carboxlic acids **77**[23] while methyl mercaptan is eliminated.



3.5. *Application as C_3—S-synthon*

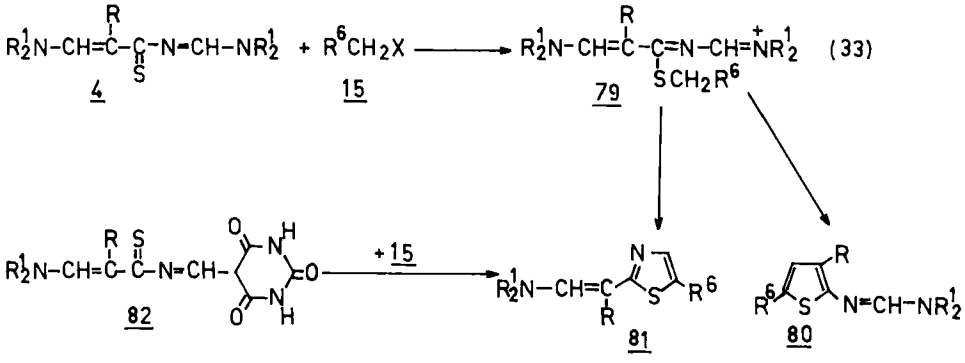
According to Section 2.2 reaction (7) the S-alkylation of 3-aminothioacrylamides takes place at the thiocarbonyl-S-atom. A subsequent, usually base catalysed, cyclisation (32) of the resulting 1-methylmercaptotrimethinium salts **16** by nucleophilic attack of the deprotonated methylene group at position 3 is possible



as long as R^6 represents an electron withdrawing substituent such as acyl[25,38,54,62–70], nitro[38,71] or 4-nitrobenzyl.[38] Thiophenes **78** are formed when the amino group at position 3 ($NR^2R^3 = NH_2$[25,54,63,65,68,71] NH-alkyl[62] or $Nalkyl_2$ which can also be bridged[38,54,62,64,66,67,69–71]) is eliminated. The starting 3-aminothioacrylamides **1** act as a C_3-synthon for the thiophene ring.

In most cases isolation of the intermediate S-alkylation products **16** is avoided. Synthesis (32) provides a convenient way to N-mono- and N-disubstituted 2-aminothiophenes **78** with a wide variety of substituents ($R^5 = H$, R^4 = alkyl,[25,62,67,71] aryl[25,54,62,63,67,68,71], allyl,[62,67] acyl,[25,54,65] or alkoxycarbonyl[69,70] and NR^4R^5 = morpholino[38,64,66] or alkoxycarbonyl[69,70] and NR^4R^5 = morpholino[38,64,66] or piperidino[38]) (see also an older review[72]). In addition to bridged systems $R/R^1 = (CH_2)_3$[54] the substituents R may be H,[66] alkyl,[38,69] aryl,[38,64] acyl,[25,69,71] alkoxycarbonyl[25,54,63,65,68,69,71] or nitro[62,67,71] and R^1 H,[38,64,66,69,70] alkyl[25,54,63,65,68,69,71] or styryl.[69]

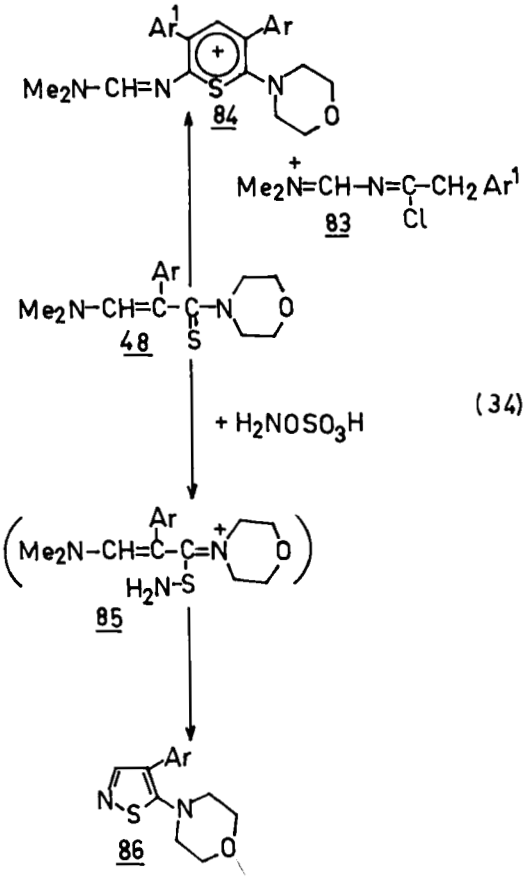
Formation (22) of the thiazole **54** from the 3-aminothioacrylamide **53** and phenacyl bromide by C—C-bond scission mentioned in Section 3.2 is an exception. But the reaction of (3-aminothioacryloyl)-formamidines **4** with halomethylene compounds **15** as a rule either give thiophenes **80** in analogy to reaction (32) or thiazoles **81** (33). In the latter case cyclisation of the intermediate **79** takes place by attack of the deprotonated CH_2-group at the formamidine-C-atom. The formation (33) of 2-formamidinothiophenes **80** or the 2-(β-aminovinyl)-thiazoles **81** is usually regioselective. The regioselectivity is governed mainly by the type of substituent R and to a certain extend by the reaction conditions.[73]



As was shown in one example (R = Ph, NR_2^1 = pyrrolidino, $R^6 = 4\text{-}BrC_6H_4$)[18] 2-(β-aminovinyl)thiazoles **81** can also be synthesised starting from chloromethylene compounds **15** and the condensation products **82** of (3-aminothioacryloyl)-formamidines **4** and barbituric acid.

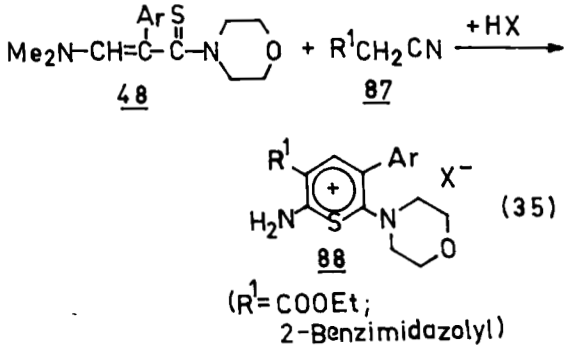
With arylacetimidoylchlorides **83** 3-aminothioacrylamides **48** react similar to methyl halides **15**. After a primary electrophilic S-iminoacylation of the thiocarbonyl S-atom a Knoevenagel-like intramolecular condensation occurs giving rise to 2,6-di-aminothiopyrylium salts **84**[33] (34).

3-Aminothioacrylamides **48** can also react as C_3-S-synthons with hydroxylamine-*O*-sulfonic acid. The primary attack probably occurs at the

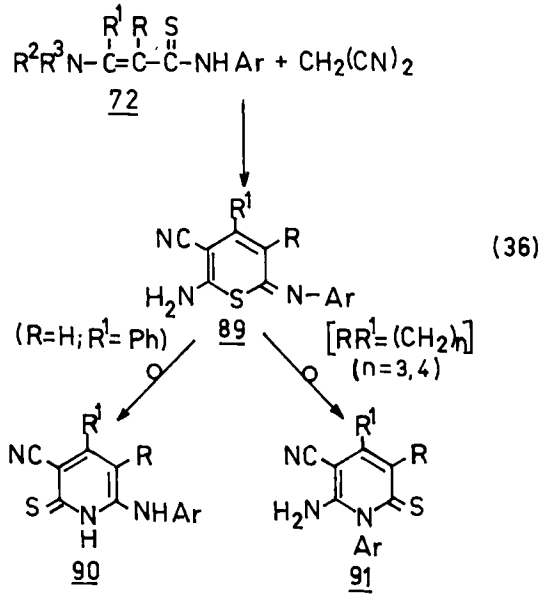


(34)

thiocarbonyl-S-atom leading to the intermediate salts **85** to give 5-morpholinoisothiazoles **86**[74] as products (34). The reverse reaction sequence is likely in reactions (35), (36) of 3-aminothioacrylamides with CH-acidic acetonitriles or malonic acid derivatives. In the first step a nucleophilic attack of the deprotonated CH_2-group at position 3 should take place followed by a Thorpe-like nitrile cyclisation to thiopyranimines. These heterocycles can be isolated either as 2,6-diaminothiopyrylium salts **88**[33] or as uncharged compounds **89**.[30,32]



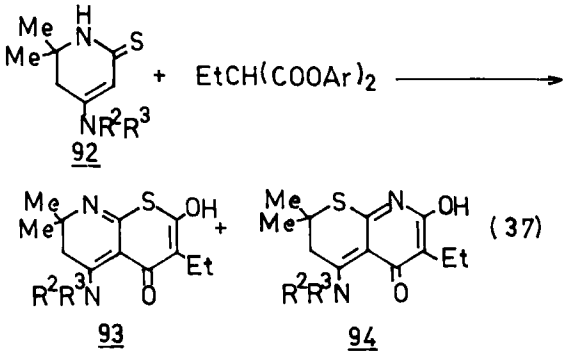
(35)



(36)

The latter easily undergoe Dimroth-rearrangement to 6-aminopyridin-2-thiones **90**[32] or **91**.[30] The reactands are not found as C_3—S but as C_3—N-fragments in the rearranged heterocyclic rings **90** and **91**. Sometimes these rearrangements are so fast that no thiopyranimines can be isolated (see Section 3.6).

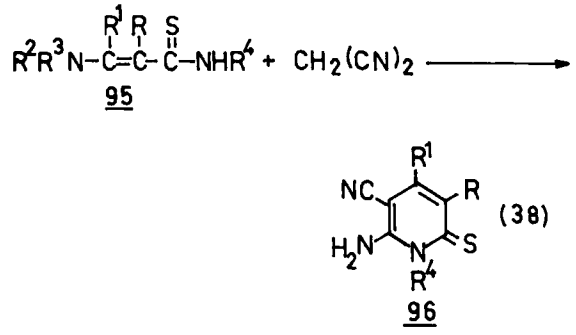
In reactions of cyclic 3-aminothioacrylamides **92** with activated malonates the expected thiopyran systems **93**[5] are obtained together with Dimroth-rearranged products **94**[75] (37).



(37)

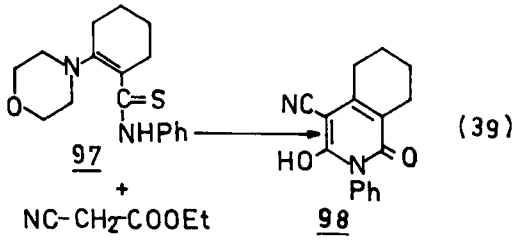
3.6. Application as C_3—N-Synthon

It has been shown in the above chapter that 3-aminothioacrylamides can be transformed into pyridinthiones by their reaction with malononitrile via thiopyranimines (36). Further pyridinthiones **96** [R = Ph, H; R^1 = H, Et or $RR^1 = (CH_2)_n$; R^4 = aryl] have been synthesised directly, starting from 3-aminothioacrylamides as C_3—N-synthons (38) i.e. without observation of intermediate thiopyranimines.[29,31]



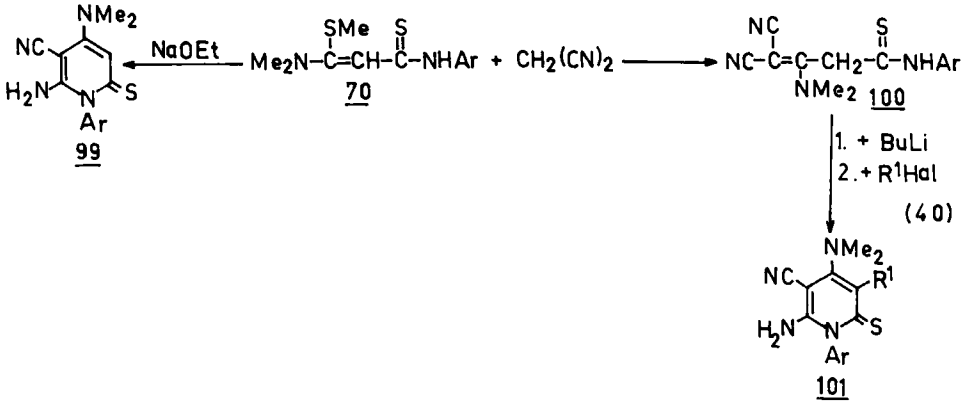
95 96 (38)

If cyanoacetate is used as C_2-synthon, the cyclisation runs via the carbethoxy group rather than the cyano group (39). 6-Hydroxy-2-pyridone **98** is obtained by subsequent hydrolysis of the thiocarbonyl group.[31]



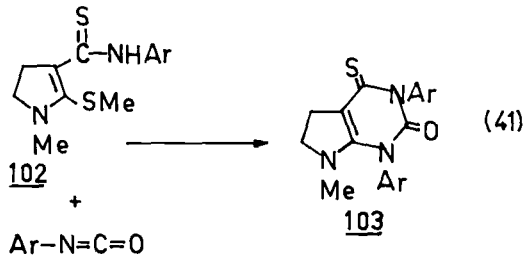
97 + NC-CH$_2$-COOEt 98 (39)

In reactions of 3-methylmercapto substituted 3-aminothioacrylamides **70** with malononitrile the methyl mercaptan is eliminated prior to the dimethylamino group giving 4-dimethylamino-pyridin-2-thiones **99** (40).[34] It is possible to isolate the open chain condensation products **100** under mild conditions. These can be subsequently cyclised by strong base while alkylation can also be achieved affording products **101** (40).[34]



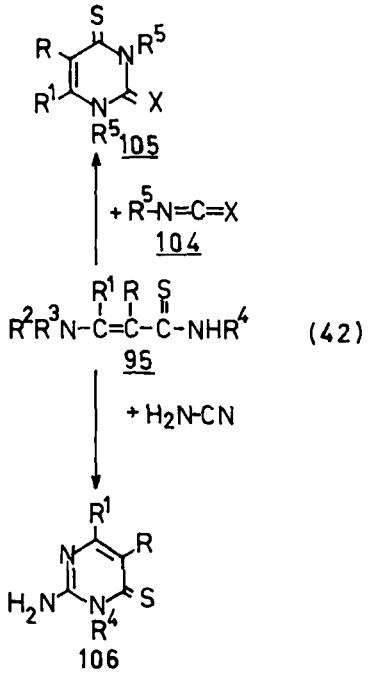
99 70 100 101 (40)

Cyclic 3-methylmercapto substituted 3-aminothioacrylamides **102** can also be employed as C_3—N-synthons in the synthesis of pyrimidines when isocyanates are used as reactands. This reaction (41) probably proceeds via thioureas which recyclise by elimination of methyl mercaptan to give pyrimidine-4-thiones **103**.[76]



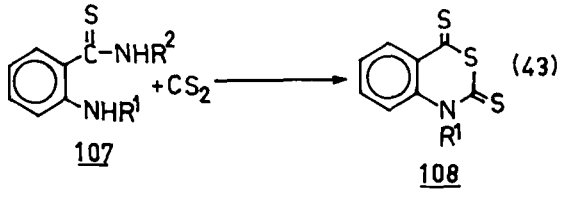
(41)

When 3-aminothioacrylamides **95** lacking an additional leaving group at position 3 are reacted with isocyanates[13,44] or isothiocyanates[54] the amino group NR^2R^3 is substituted and thiouracil compounds **105** are formed (42).



(42)

Amino substituted pyrimidin-4-thiones **106** can be obtained in a reaction (42) of 3-aminothioacrylamides **95** with cyanamide[29] resembling reaction (38).



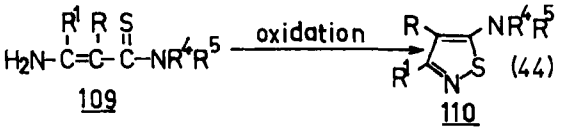
(43)

Differing from reactions (38)–(42) the 3-aminothioacrylamide skeleton can also serve as a C_3—N-synthon if not the amino group at position 3 but rather at position 1 is substituted. In this way thiazinthiones **108** are formed when

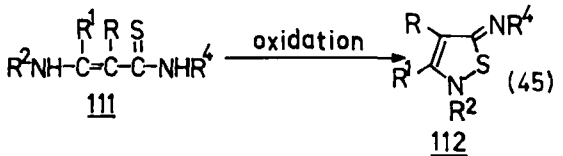
thioanthranilo amides **107** are reacted with CS_2 (43)[77] (for the formation of pyrimidinthiones see Section 3.8).

3.7. *Application as N—C_3—S-Synthon*

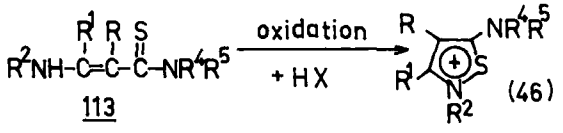
3-Aminothioacrylamides are frequently used as N—C_3—S-synthons in the synthesis of isothiazoles. In order to synthesise such heterocycles, thioacrylamides having at least one H-atom at the 3-amino group, are treated with oxidising agents, such as Cl_2,[30] Br_2[20,45,78,80–86], I_2,[82–85,87–90] chloramine,[91] chloramine-T,[85] H_2O_2,[20,49,85,90,92–103] SO_2Cl_2,[48,84,104], bromonitromethane[71] or concentrated sulfuric acid.[105,106] Depending on the degree of substitution at both aminosubstituents of the starting materials **109**,**111**,**113** and to a certain extent also on the pH, oxidative cyclisation can furnish three different types of isothiazole systems **110**, **112** or **114**.



109 **110**



111 **112**



113 **114**

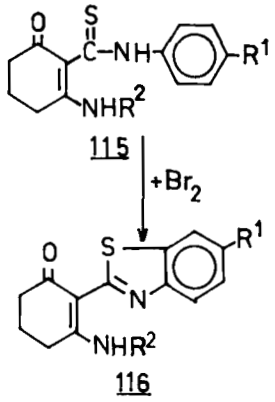
When the 3-amino group is unsubstituted (**109**) isothiazoles **110**[30,49,71,78,83–85,87–103,105–109] are obtained, R being H,[85,87–89,91,97] alkyl,[85,107] acyl[71,84] alkoxycarbonyl,[3,83–85] aminocarbonyl,[83] cyano[84,92,93,96] or nitroso[98] and R^1 being H,[107] alkyl,[30,71,83–85,87,89,91,94,98,103,109] aryl,[83,85,88] dimethylamino,[92] methylmercapto,[93,98] alkoxy[96,97,103] or $R^1C=CR$ is a phenyl ring,[101,105] a heterocyclic ring,[49,78,90,95,99,100,102,106,108] or a cycloalkenyl.[107] Usually the amino group of the isothiazoles **110** is unsubstituted,[49,78,85,87–97,99,100,103,105,106,108,109], but it can also be mono[30,71,83–85,98,99,106] or disubstituted.[101,107] When both amino groups of 3-aminothioacrylamides **111** are monosubstituted (R^2 = alkyl,[80–82,110,111], aryl[79,80] or bridged with R,[81,86,104] R^4 = alkyl,[45,82] aryl,[81,110] acyl[80,82,86,104,110] or ethoxycarbonyl[81,86]) oxidative cyclisation results in 5-iminoisothiazoles **112** (45).[45,80–82,86,104,110–112] The substituents R are H,[82] phenyl,[45] benzoyl,[80] alkoxycarbonyl,[82,111], nitro[80,81,86] or chloro[104] and R^1 alkyl,[45,82,111] substituted amino[80,81] or methylmercapto.[80] Furthermore isothiazoles **112** where R and R^1 are bridged[81,104,110,112] have also been prepared.

Finally, the oxidation of N,N-disubstituted 3-aminothioacrylamides **113** (NR^4R^5 = diethylamino,[48] morpholino[20]) as well as of N-aryl substituted com-

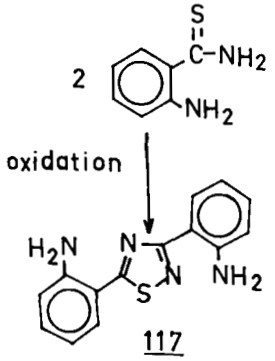
pounds **113** ($R^5 = H$; R^4 = phenyl[85]) result in 5-aminoisothiazolium salts **114** (R = aryl; $R^1 = H$[20]; R = COOEt, R^1 = Me;[85] $R^1C = CR$ = pyridine[48]).

In addition to isothazoles there are some special cases in which also nitriles by formal oxidative elimination of H_2S are formed[49] (see Section 2.3).

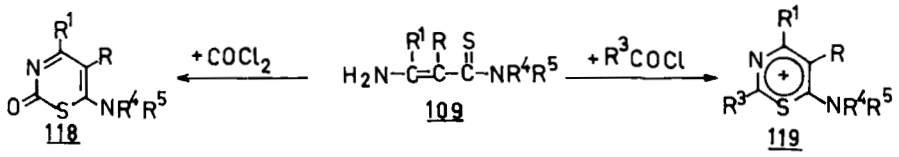
Instead of yielding isothiazoles the oxidation of the 1-aryl-substituted 3-aminothioacrylamide **115** gives benzothiazoles **116** (47) where the reactand is not found as a N—C_3—S-skeleton in the heterocyclic ring.[110]



There has also been reported[113] a thiadiazole as oxidation products of thioanthranilic acid. In this case (48) the 3-aminothioacrylamide system has reacted like a normal primary thioamide[79] which is not further functionalised.

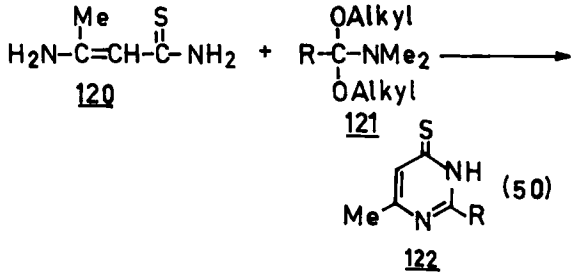


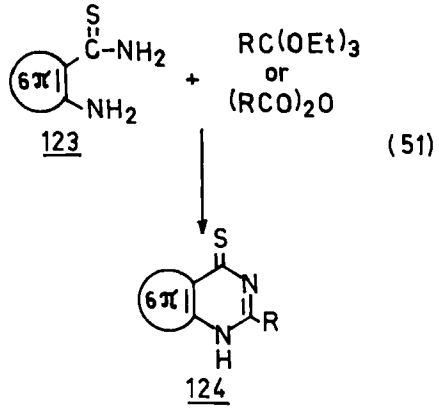
Furthermore 3-aminothioacrylamides **109** can be used too as N—C_3—S-synthons in the synthesis of 6-membered heterocycles, such as thiazinones **118** or thiazinium salts **119**[107] (49), if they are reacted with phosgene or acyl chlorides. Again, there is an electrophilic attack at the thiocarbonyl sulfur and at the 3-aminogroup. In a similar way the reaction of 3-aminothioacrylamides **1** ($RR^1 = (CH_2)_n$, $R^2 = R^4 = H$, R^3 = Ph, R^4 = aryl) with 1,2-dibromoethane results in 1,4-thiazepine derivatives.[131]

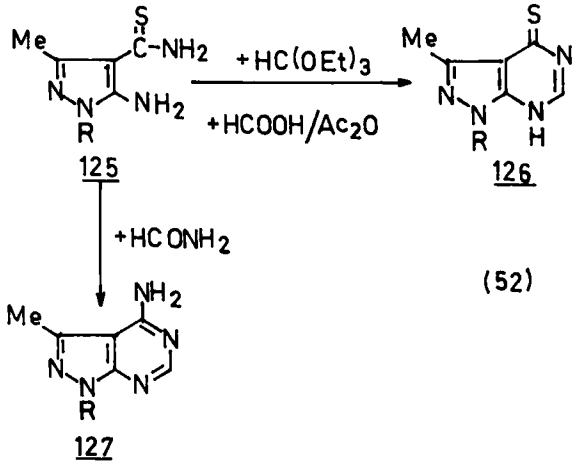


3.8. *Application as N—C_3—N-Synthon*

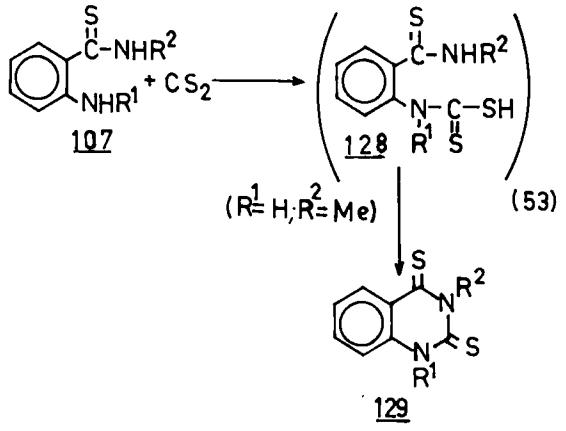
3-Aminothioacrylamide compounds with unsubstituted or mono-substituted amino groups at both position 1 and 3 can act as N—C_3—N-synthons in reactions with suitable electrophiles. 3-Aminothiocrotonamide **120**, for example, reacts with amide acetals **121** (R = H, Me) as a C-building block to give pyrimidinthiones **122** (50).[41] Sometimes additional S-methylation of the products **122** was found. Similar to reaction (50) condensed pyrimidinthiones **124**[114–116] (51) and **126**[117] (52) can be synthesised starting from *o*-aminothiobenzamide **123**,[114,115] 4-aminopyridine-5-thiocarboxamide **123**[116] or pyrazoles **125**[117] respectively and orthoformates, formic acid/acetic anhydride or acidic anhydrides.





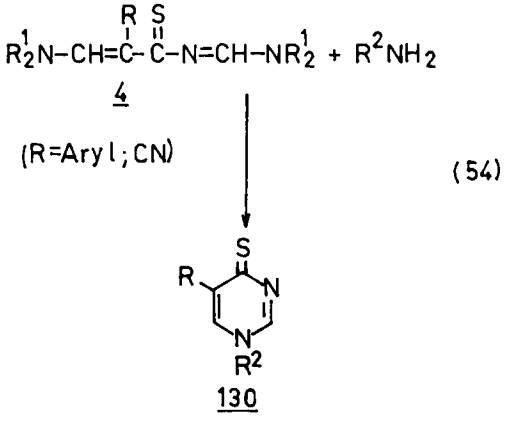


On the other hand, the same pyrazolecarboxamides **125** form condensed aminopyrimidines **127** in reactions with formamide.[117] If CS_2 is applied as C_1-synthon in reactions with *o*-aminothiobenzamides as N—C_3—N-building blocks benzopyrimidindithiones **129**[77] are afforded (53) (see Section 3.6 for the formation of benzothiazinthiones). The primary attack is presumably at the *o*-amino group.

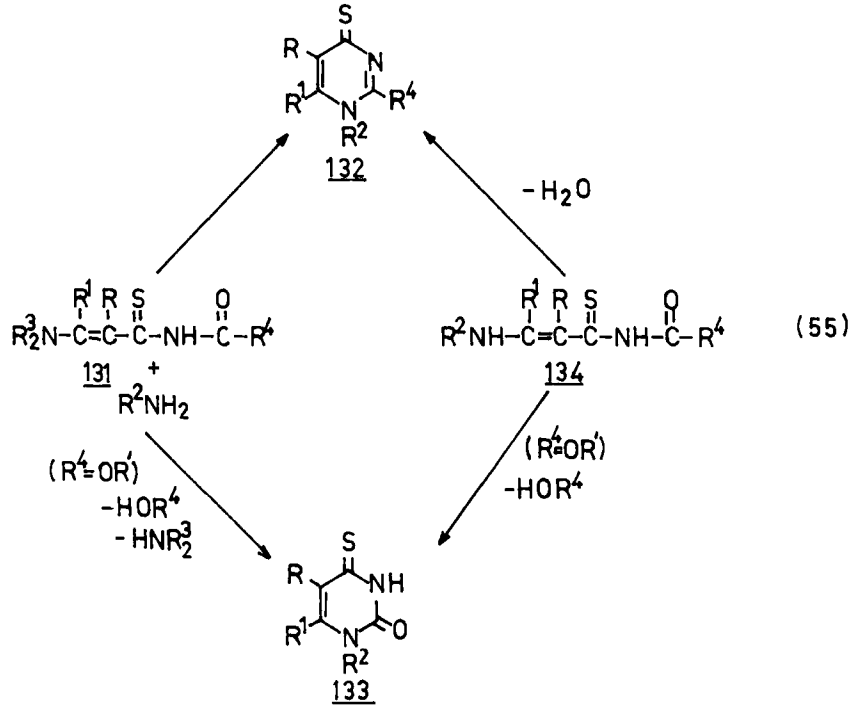


3.9. *Application as C_3—N—C, N—C_3—N—C, C_3—N—C—N, C_3—N—C—S-Synthon*

Application of 3-aminothioacrylamide systems as bifunctional electrophilic C—N—C_3 building blocks is only possible if the basic skeleton is extended by an additional electrophilic C-atom. This can be found in (3-aminothioacryloyl)-formamidines **4** which are attacked by ammonia or primary amines (R^2 = H, alkyl, aryl) or hydrazines (R^2 = NHR) at position 3 and at the amidine-C-atom. Pyrimidin-4-thiones **130**[27,28] are formed because both terminal amino groups are eliminated (54). If R is a cyano group either pyrimidinthiones **130** (R = CN) (54) or open chain disubstitution products **9** (4) (see Section 2.1) may be formed depending on the structure of the amine R^2NH_2.

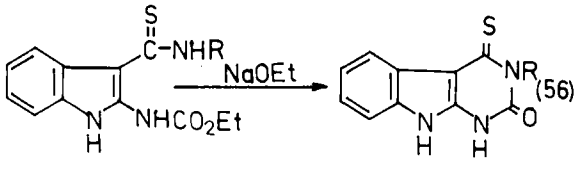


In a comparable way (3-aminothioacryloyl)-amides **131** can act as C_3—N—S-synthons for pyrimidinthiones **132**[118,119] or monothiouracils **133**[119] if R^4 = alkoxy (55). The corresponding mono-substitution products **134** have been proved to be intermediates.[118] In order to synthesise pyrimidinthiones **132**[17,50,80,84,86,118,120–125] or monothiouracils **133**[84,122,123] it is more convenient to start with 3-aminothioacryloylamides **134** (R^4 = alkyl,[118,122,124] aryl,[17,50,80,84,86,118,120–125] styryl,[124] or furyl[122]) or 3-aminothioacryloylurethanes **134** (R^4 = O-alkyl,[122] O-aryl[84,123]) already possessing a secondary amino group R^2NH suitable to undergo an intramolecular cyclisation. In these cases the reactants **134** act as N—C_3—N—C-synthon.

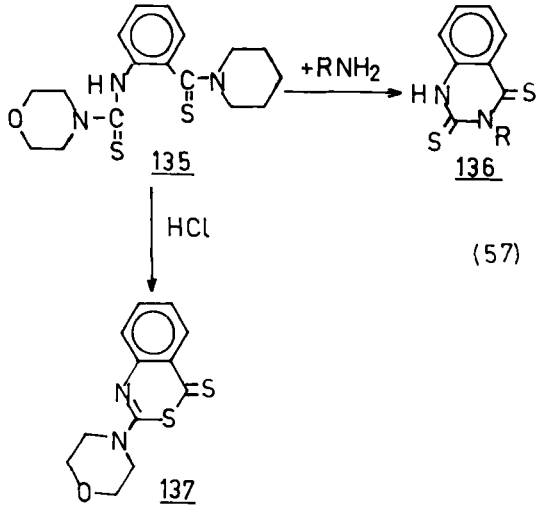


(55)

The following substitution patterns have been performed in the pyrimidinthiones **132**: R = H,[17,124] phenyl,[118] acyl,[80,84,122–124] ethoxycarbonyl,[84,121–124] anilinocarbonyl,[50] cyano[122,124] or nitro;[86,120] R^1 = H,[118,123] alkyl,[84,121–124] aryl,[17,50,124] methylmercapto,[80] substituted amino[80] or diethoxymethyl,[124]; RR^1 = alkylene;[118,125]; R^1R^2 = alkylene[120] or S-ethylene;[86] R^2 = H,[84,121–124] alkyl[80,123] or aryl.[17,50,80,121,123,125] The intramolecular cyclisation (56) represents an example of the application of an 3-aminthioacrylamide system as N—C_3—N—C-synthon, where the thioamide-N-atom is the nucleophilic site.[132]

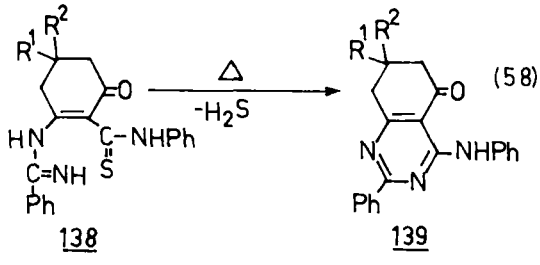


Anthranilothioamides **135** possess an additional thiocarbonyl-C-atom attached to the amino group at position 3 of the thioacrylamide skeleton. Hence, compounds **135** can react as a 1,5-bifunctional electrophilic C_3—N—C-synthon with primary amines furnishing pyrimidindithiones **136**[26] (57). On the other hand, thioanthraniloamide **135** acts as C_3—N—C—S-synthon when reacted with HCl. A benzothiazinthione **136**[26] is formed by intramolecular attack of the thiourea-S-atom at the thioamide-C-atom morpholine being eliminated (57).



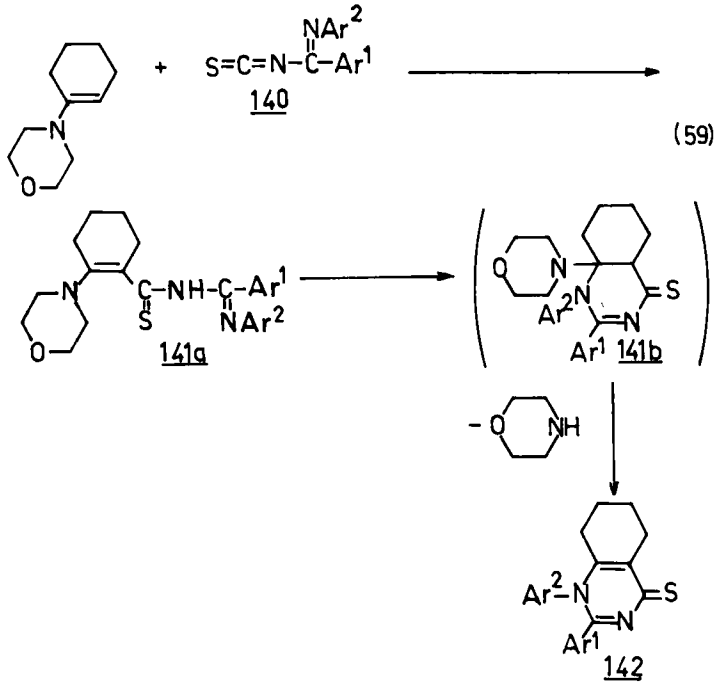
(57)

The 3-amidinothioacrylamides **138** can be used as C_3—N—C—N-synthons if their terminal amidine-N-atom has an H-atom. On heating, this imino group attacks the thiocarbonyl—C-atom yielding 4-aminopyrimidines **139**[126] (58). It is noteworthy that the 1-amino group is not eliminated as in reaction (56) but H_2S.



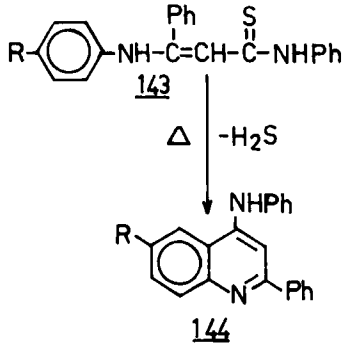
(58)

Probably the adducts of morpholinocyclohexene to isothiocyanates **140** are not of cyclic structures **141b** but rather open chain bridged 3-morpholinothioacryloylguanidines **141a** (see also part I[1]). Hence the subsequent formation of pyrimidinthiones **142**[127] has to be considered as a further example for the application of a 3-aminothioacrylamide derivative as C_3—N—C—N-synthon.

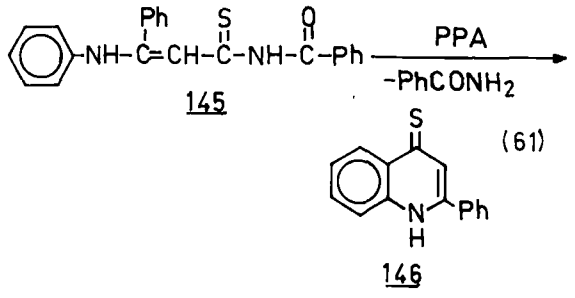


3.10. *Application as C_3—N—C_2-Synthon*

The *o*-C-atom of 3-aminothioacrylamides **143** or **145** entails an additional nucleophilic site to the 3-aminothioacrylamide skeleton. This *o*—C-atom can attack the thiocarbonyl-C-atom giving rise to the formation of quinolines. In these cases, reactants **143** and **145** serve as C_3—N—C_3-synthons for the quinoline ring. Cyclisation of compounds **143** to 4-aminoquinolines **144**[8] can be achieved by heating (60). They can also be synthesised directly from a corresponding enamine and phenylisothiocyanate at higher temperatures without isolation of the intermediate 3-aminothioacrylamides **143**.[8,128]



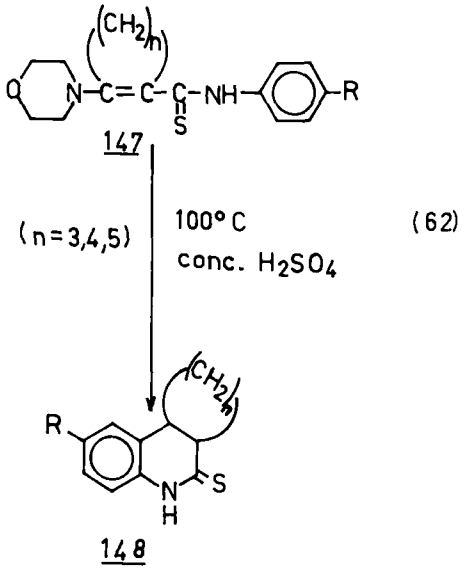
Surprisingly the anilinothioacryloylamide **145** neither forms a pyrimidinthione as has been shown in Section 3.9 nor cyclises according to equation (59) to give an



(61)

aminoquinoline. When reactand **145** is heated with polyphosphoric acid benzamide is eliminated and quinolinthione **146**[17] is obtained (61).

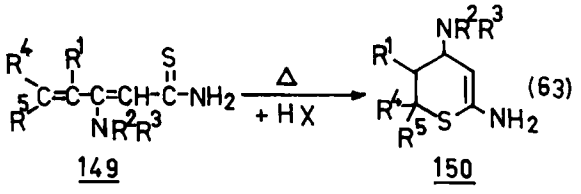
Thioacrylanilides **147** do not possess an arylaminosubstituent at position 3. In this case the *o*—C-atom of the 1-arylamino group can serve as a nucleophilic site and quinolin-2-thiones **148**[16] are formed by nucleophilic attack at position 3 of the thioacrylamide skeleton (62).



(62)

3.11. Application as C_5—S-Synthon

Cyclisation (63) of 3-vinyl substituted compounds **149** represents a special case of a reaction of 3-aminothioacrylamides. The terminal C-atom of the conjugated π-system has to be considered as vinylogues thioamide—C-atom. On heating in acidic medium this electrophilic site attacks the thio-carbonyl-S-atom affording dihydrothiopyranimines **150** (63).[129] Hence 3-aminothioacrylamides **149** have served as C_5—S-synthons.



(63)

4. SUMMARY

3-Aminothioacrylamides can readily be prepared with a large variety of substituents (see Part I). They are usually stable and can easily be handled. Their high synthetic potential is further extended by additional functional groups attached to the basic 3-aminothioacrylamide system (see Section 3.9–3.11). 3-Aminothioacrylamide compounds have been widely used in the synthesis of organic sulfur compounds, especially of heterocycles. In other cases the thiocarbonyl-S-atom is a good leaving group leading to sulfur free products. Most of the products obtained from 3-aminothioacrylamides have not been synthesised otherwise.

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