Chemistry of Heterocyclic Compounds, Vol. 32, Nos. 11-12, 1996

N-AMINOAZOLINTHIONES AND N-AMINOAZINTHIONES. 1. SYNTHESIS* (REVIEW)

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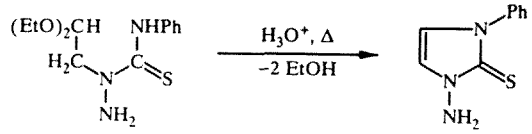
The methods for the synthesis of N-aminoazolinthiones and N-aminoazinthiones are reviewed.

Recently there has been a marked upsurge in interest in the chemistry of N-aminoazoles [1] and N-aminoazinium salts [2] which are valuable synthons in a wide range of reactions, especially cyclization and heterocyclization. Particularly promising in this respect are N-amino derivatives of nitrogen heterocycles which contain a mercapto group in addition to the amine (although compounds discussed in this review have in some cases been named as mercapto derivatives, they all exist in the thione form [3]). Methods for the synthesis of these compounds will be discussed in this review. Their reactivity and physicochemical properties will be examined in the second part of the review. Literature up to the end of 1995 has been covered.

1. N-AMINOIMIDAZOLINTHIONES

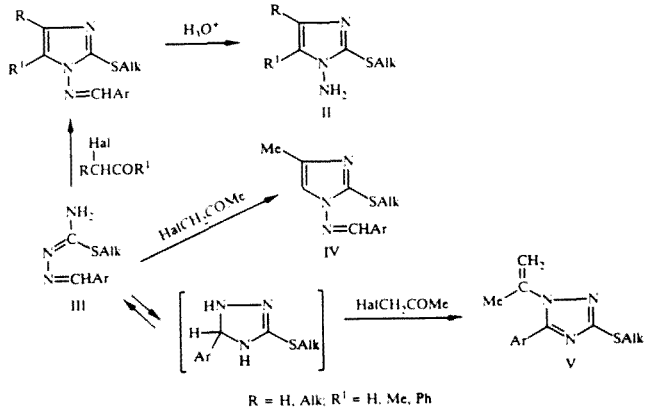
1.1. Syntheses Using Cyclization and Recyclization Reactions

Most of the known methods to prepare α-mercapto-N-aminoimidazoles are based on the cyclization of acyclic compounds or recyclization reactions. The first example, 1-amino-3-phenylimidazolin-2-thione (I), was prepared as long ago as 1894 by the reaction [4]:



I

1-Amino-2-alkylthioimidazoles (II) have been prepared from S-alkylisothiosemicarbazides (III) and α-halogenocarbonyl compounds [5-7]. This reaction is complex with α-halogenoacetones giving mixtures of imidazoles (IV) and 1-isopropenyl-3-alkylthio-1,2,4-triazoles (V). Bromoacetone formed the N-aminoimidazole (IV) predominantly, whereas chloroacetone gave mainly compound V [7].



R = H, Alk; R¹ = H, Me, Ph

*Dedicated to Academician É. Ya. Lukevits on his 60th birthday.

Rostov State University, Rostov-on-Don 344090. Translated from Khimiya Geterotsiklicheskikh Soedinenii, Nos. 11-12, pp. 1494-1509, November-December, 1996. Original article submitted October 16, 1996

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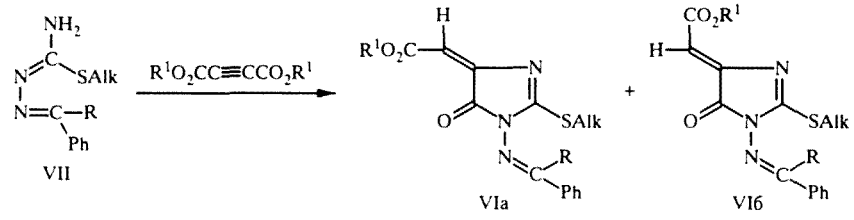
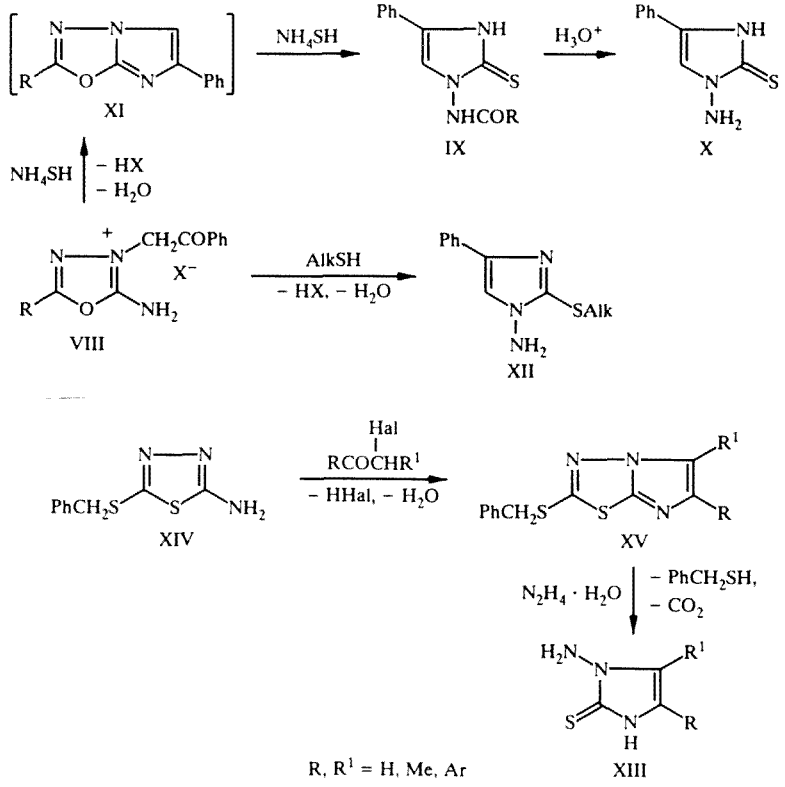
Recently Japanese workers synthesized the stereoisomers of 4(1-R_1-hydroxycarbonyl)methylenimidazoline-4 (VIa,b) by the reaction of compound VII with acetylenedicarboxylates. Only the Z-isomer VIa was isolated when the reaction was carried out in ethanol in the presence of sodium acetate, whereas the main product was the E-isomer VIb in acetonitrile containing a small amount of acetic acid [8]:



R = H, Me, Ph; R^1 = Me, Et

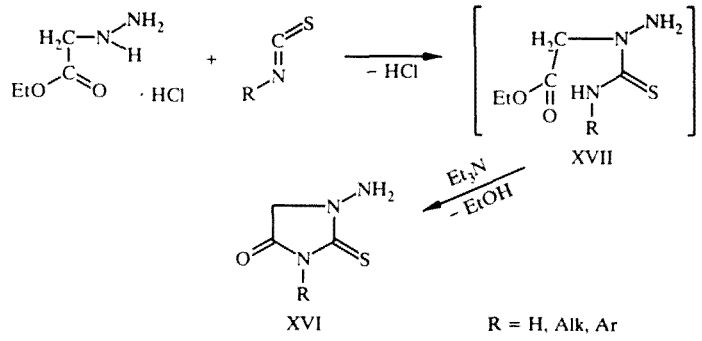
2-Amino-3-phenacyl-1,3,4-oxadiazolium salts (VIII) recyclize to 1-acetamido-4-phenylimidazolin-2-thiones (IX) on heating with ammonium hydrogen sulfide. The aminothiones X can then be obtained by hydrolysis [9]. Presumably the reaction proceeds via the intermediate formation of an imidazo[2,1-*b*]-1,3,4-oxadiazole (XI). 1-Amino-2-alkylthio-4-phenylimidazoles (XII) are obtained if alkanethiols are used in place of NH_4HS [10].



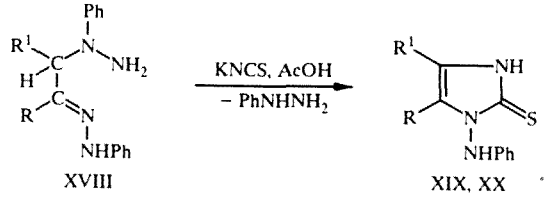
R, R^1 = H, Me, Ar

This reaction is very similar to the synthesis of 1-aminoimidazolin-2-thiones (XIII) developed by Beyer et al in 1963. This synthesis is based on 2-amino-4-benzylthio-1,3,4-thiadiazole (XIV) as starting material. Condensation of XIV with an α-halogenoacetone gave an imidazo[2,1-*b*]-1,3,4-thiadiazole XV which on subsequent heating with hydrazine hydrate gave a thione XIII [11].

Recently 1-aminoimidazolin-4-one-2-thiones (XVI) have been synthesized starting from ethyl hydrazinacetate hydrochloride and isothiocyanates [12, 13]. Apparently the reaction goes via the intermediate XVII, which was isolated in one case (R = Ph). Compounds XVII were converted to the N-aminoimidazolin-2-thiones XVI in 64-85% yield when treated with triethylamine.



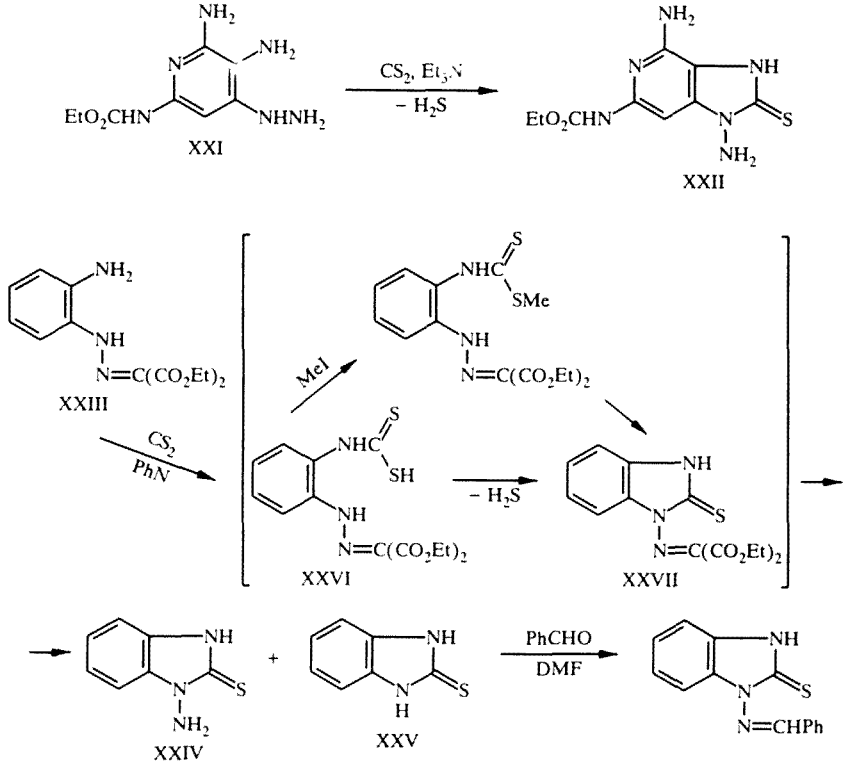
The hydrazones XVIII were converted to the 1-anilinoimidazoline (XIX) or the 1-anilinotetrahydrobenzimidazolin-2-thione (XX) in an analogous manner by reaction with potassium thiocyanate [14].



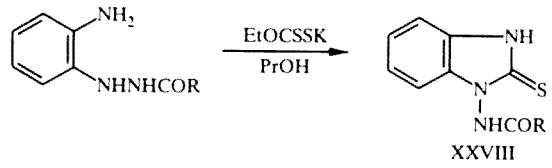
XIX R = Ph, R^1 = Me; XX R, R^1 = $(CH_2)_4$

A derivative of 1-aminoimidazo[4,5-*c*]pyridin-2-thione (XXII) was obtained by condensation of 2,3-diamino-4-hydrazino-6-ethoxycarbonylaminopyridine (XXI) with carbon disulfide [15].

1-Aminobenzimidazolin-2-thione (XXIV) mixed with benzimidazolin-2-thione (XXXV) was obtained when diethyl *o*-aminophenylhydrazonomesoxalate (XXIII) was heated at 80-90°C in pyridine with an excess of carbon disulfide. The yield of the aminothione XXIV was 33% based on compound XXIII, but the yield was increased to 64% when an equimolar amount of methyl iodide was added to the reaction mixture during the cyclization [16].



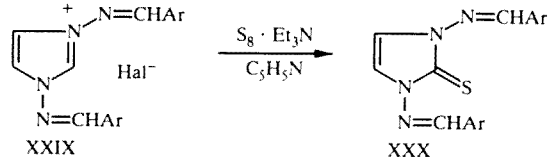
1-Acylaminobenzimidazolin-2-thiones XXVIII were obtained by cyclization of 1-acyl-2-(2-aminophenyl)hydrazines with ethyl xanthate [17].



XXVIII

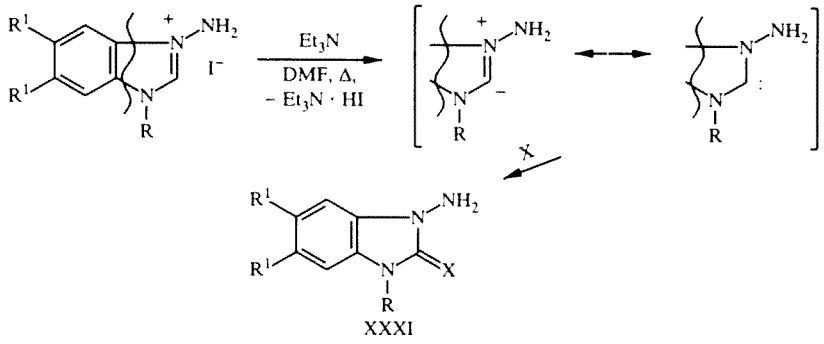
1.2. Direct Introduction of Mercapto Groups into N-Aminoimidazoles

Direct introduction of a mercapto group into the imidazole ring was first done with N-aminoimidazolium salts XXIX [18]. Treatment with sulfur in the presence of triethylamine in pyridine gave the thiones XXX in good yield.



XXIX XXX

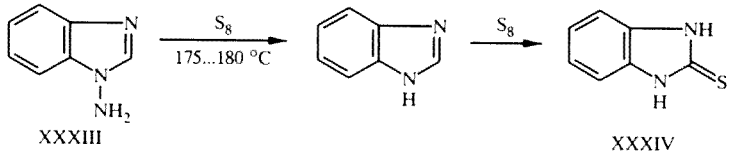
Both amino groups in the starting material were protected. However, this is not necessary for imidazolium salts because the conditions for the thiolation reaction are so mild. For example, 1-amino-3-alkyl-benzimidazolin-2-thiones (XXXI) were prepared in 69-81% yield by thiolation of 1-amino-3-alkylbenzimidazolium iodides in boiling DMF. The corresponding selenones were obtained in 71-80% yield from the analogous reaction with selenium [19, 20]. 1-Amino-3-methyl-perimidin-2-thion (XXXII) was obtained similarly [21]. A carbene mechanism has been proposed for thiolation of these salts since the presence of triethylamine is required.



XXXI XXXII

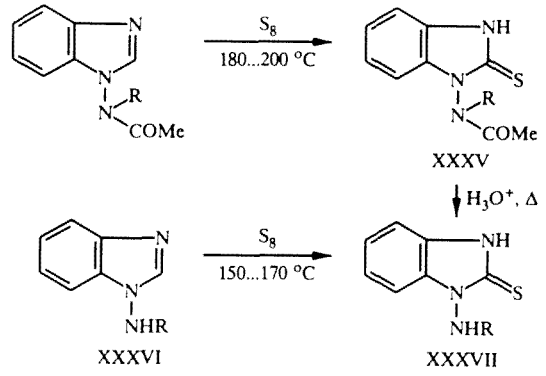
X = S, Se; R = Me, Et; R^1 = H, Me

Protection of the amino group is necessary in thiolations based on 1-aminobenzimidazole. In fact, when the amine (XXXIII) was heated with sulfur it underwent oxidative deamination to give benzimidazole which was then converted to benzimidazolin-2-thione (XXXIV) [16].

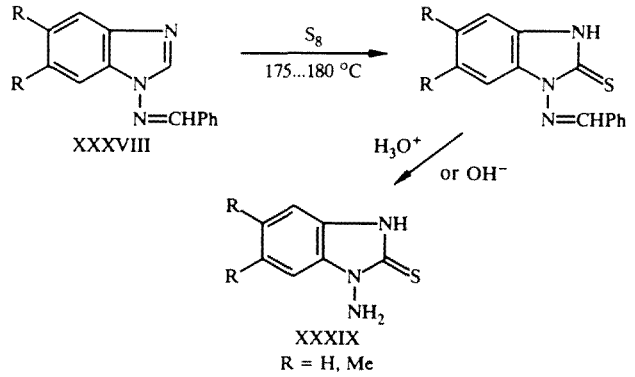


XXXIII XXXIV

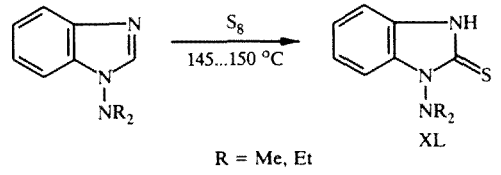
When 1-alkylacetylaminobenzimidazoles were heated with sulfur, 1-(N-alkyl-N-acetylamino)benzimidazolin-2-thiones (XXXV) were obtained in 60-75% yields. The aminothiones XXXVII were obtained analogously in 30-66% yield by thiolation of compounds XXXVI [22].



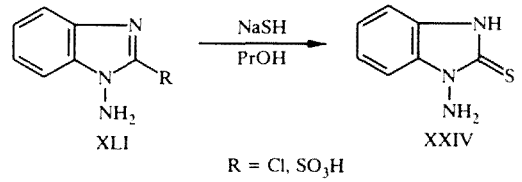
1-(Benzylidenamino)benzimidazoles (XXXVIII) are readily thiolated by fusing with sulfur to give the corresponding thiones in excellent yield. Hydrolysis of the latter gave 1-aminobenzimidazolin-2-thiones XXXIX [23].



1-(Dialkylamino)benzimidazolin-2-thiones (XL) were obtained in 56-73% yields by fusing 1-(dialkylamino)benzimidazoles with sulfur at 145-150°C [22].

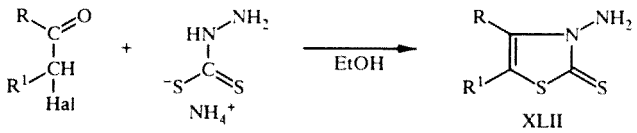


Lithuanian chemists recently suggested a new method for the preparation of 1-aminobenzimidazolin-2-thione (XXIV) based on the nucleophilic replacement of halogen or sulfonic acid groups at position 2 of compound XLI with a thiol group by heating with ammonium hydrogen sulfite [17]. The yield of the aminothione XXXIV was 30-35%.



2. N-AMINOTHIAZOLINTHIONES

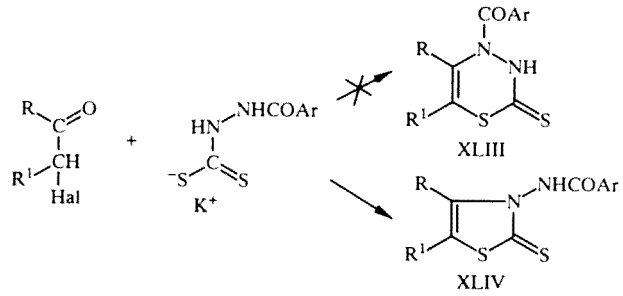
The synthesis of 3-aminothiazolin-2-thiones (XLII) based on the reaction of α-halogenocarbonyls with ammonium dithiacarbazate has been described [24-27]:



XLII

R = Me, Ph; R^1 = H, CO_2Et

Potassium aroyldithiocarbazates have also been used in this reaction [28-30]. Initially the reaction product was said to have the thiadiazine structure XLIII [28] but this was later altered to the correct structure XLIV [29, 30].



XLIII

XLIV

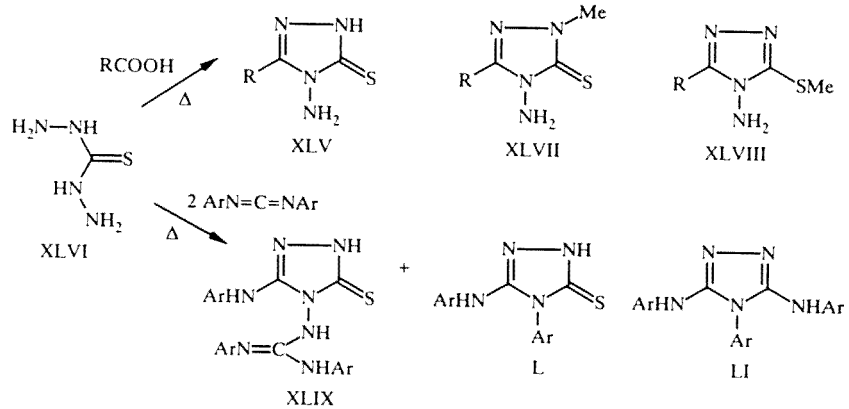
R = Me, Ph; R^1 = H, CO_2Et

3. N-AMINO-1,2,4-TRIAZOLINTHIONES

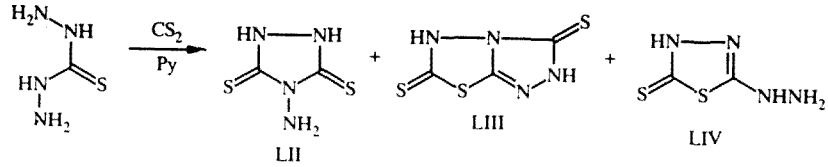
3.1. Synthesis by Cyclization and Recycylization

Stolle first prepared 4-amino-1,2,4-triazolin-3-thione (XLV, R = H) in 1908 by heating the thiocarbohydrazine XLVI with ethyl orthoformate [31]. This result was later confirmed in a number of papers in which amides and esters of aliphatic acids [32], iminophores [34], and dithiocarboxylate salts [35, 36] were used in addition to ortho esters [32, 33]. Currently use of carboxylic acids themselves is preferred [37-41] since they produce improved yields (up to 75-80%) of the aminothiones XLV. 2-Methylthiocarbohydrazide and α-methylisothiocarbohydrazide reacted with carboxylic acids to give the corresponding compounds XLVII and XLVIII [42]. Reaction of thiocarbohydrazide with two equivalents of a diarylcarbodimide gave compounds XLIX in 20-50% yields; a certain amount of compounds L and LI was also formed, depending on the nature of R and the reaction conditions [43].

Reaction of thiocarbohydrazide with carbon disulfide in pyridine gave a mixture of 4-amino-1,2,4-triazolin-3,5-dithione (LII), triazolo[3,4-*b*]-1,3,4-thiadiazolin-2,5-dithione (LIII) and the thiadiazole LIV in yields of 50, 40, and 2% respectively [44, 45]. Only the dithione LII was obtained when potassium xanthate, generated *in situ* from carbon disulfide and ethanolic KOH, was used [46, 47].

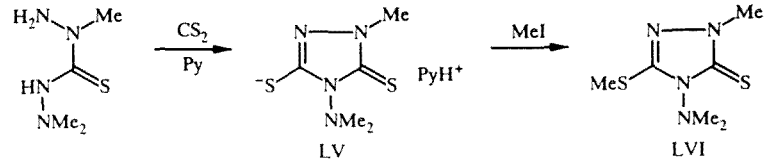


XLV, XLVII, XLVIII R = H, Alk



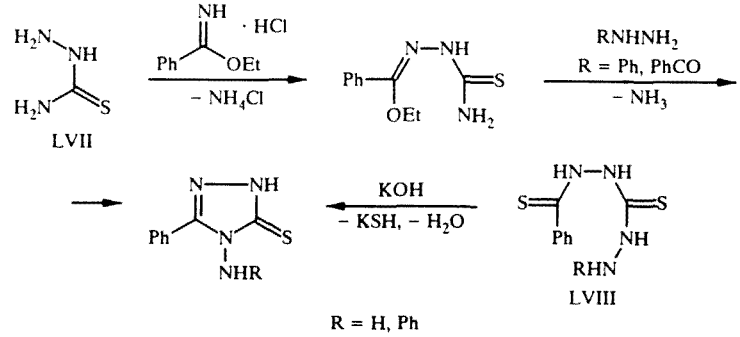
LII LIII LIV

Salt LV was obtained by reaction of trimethylated thiocarbohydrazide with carbon disulfide. Methylation of LV gave LVI [48].



LV LVI

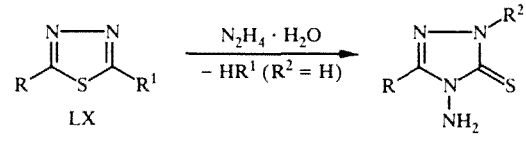
Other methods for the synthesis of 4-amino-1,2,4-triazolin-3-thiones are the two-step cyclization of thiosemicarbazide LVII with imino esters or ortho esters [49] and cyclization of 1-thiobenzoylthiocarbohydrazide LVIII under basic conditions [50].



LVII LVIII

R = H, Ph

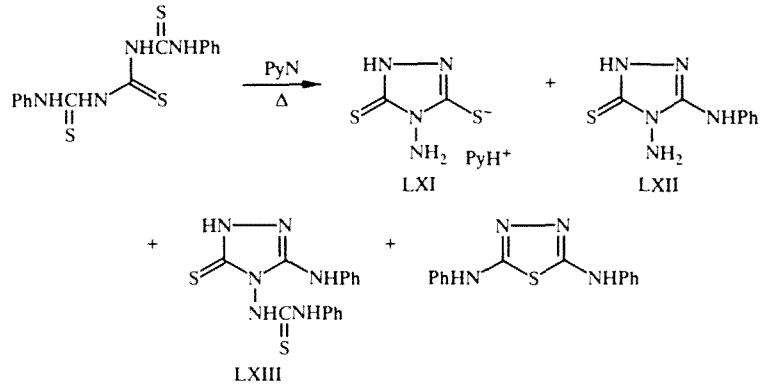
The synthesis of 1-R^2-3-R-4-amino-1,2,4-triazolin-5-thiones (LIX) by recyclization of 1,3,4-thiadiazoles LX with hydrazine has been described [43, 51].



LX LIX

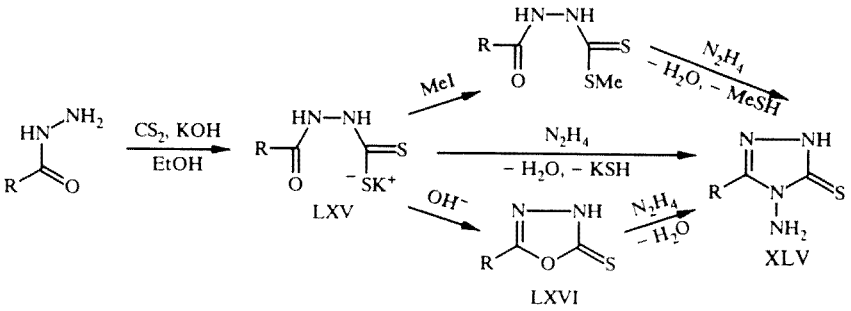
R = H, Alk, NHAr; R^1 = Cl, NH_2, SO_2Alk, SH

When 1,5-di(phenylthiocarbamoyl)thiocarbohydrazide was boiled in pyridine, a mixture of compounds LXI-LXIII was obtained with yields of 44, 33 and 7% respectively [52].



LXI LXII LXIII

4-Amino-1,2,4-thiadiazolin-3-thiones (XLV) are currently most frequently prepared by the Hoggarth method [53]. An acid hydrazide is converted into an acyldithiocarbazate LXV by reaction with carbon disulfide in the presence of KOH. The carbazate is methylated and the methyl ester is cyclized to compound XLV by heating with hydrazine.

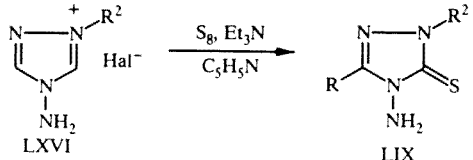


Reid and Heindel showed that compounds XLV can be obtained by cyclizing the dithiocarbazates LXV with hydrazine [54]. They also suggested another modification of the Hoggarth method in which compounds LXV are first converted into 5-R-1,3,4-oxadiazolin-2-thiones (LXVI) under the influence of base, followed by recyclization of the latter by heating with hydrazine. They suggested that the oxadiazoles LXV are formed as intermediates on treatment of the salts LXIV with hydrazine. There is in fact a literature report on the conversion of oxadiazoles LXV to XLVI under the influence of hydrazine [55].

The Hoggarth method and its modifications have been used for the synthesis of a wide range of 5-alkyl- [56-59], 5-aryl- [60-64] and 5-hetaryl derivatives of 4-amino-1,2,4-triazolin-3-thiones [65-67].

3.2. Direct Insertion of Mercapto Groups into the Triazole Ring

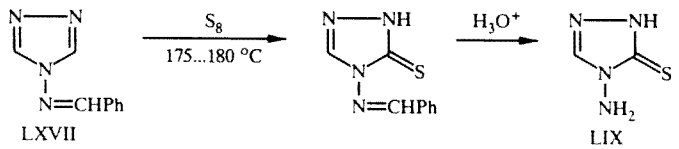
The 4-amino-1,2,4-triazolin-5-thiones LIX were obtained by thiolation of 4-amino-2-alkyl-1,3,4-triazolium salts [68,69].



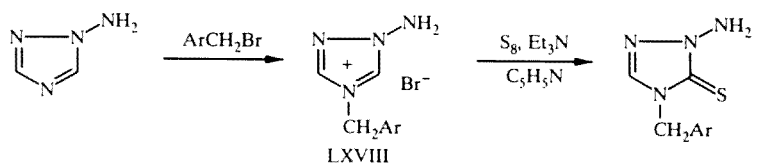
Hal⁻

R^2 = Me, CH_2Ar

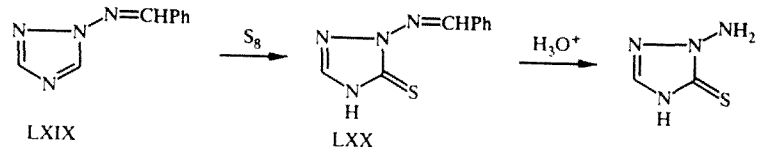
4-Amino-1,2,4-triazolin-3-thione (LIX, R = H) has also been synthesized by thiolation of 4-benzylidenamino-1,2,4-triazole (LXVII) followed by hydrolysis of the benzylidenamino group [23]:



Two methods have been reported for the synthesis of 1-amino-1,2,4-triazolin-5-thiones. In the first, a 1-amino-4-aralkyl-1,2,4-triazolium bromide (LXVIII) is thiolated in pyridine in the presence of triethylamine [70].



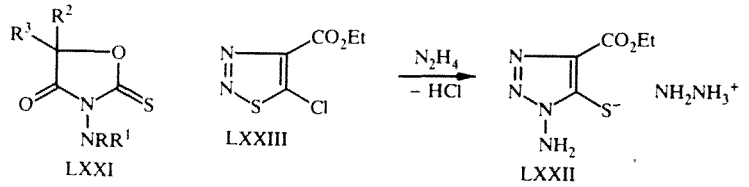
In the second case, the 1-benzylidenamino derivative LXIX was thiolated to give 35% of the thione LXX [23].



LXIX LXX

4. OTHER N-AMINOAZOLINTHIONES

The aminooxazolidinthiones LXXI are mentioned in the patent literature, but no method of synthesis was given [70]. The only mention of a mercapto derivative of N-amino-1,2,3-triazole is the synthesis of compound LXXII by recyclization of 5-chloro-4-ethoxycarbonyl-1,2,3-thiadiazole (LXXIII) [72].



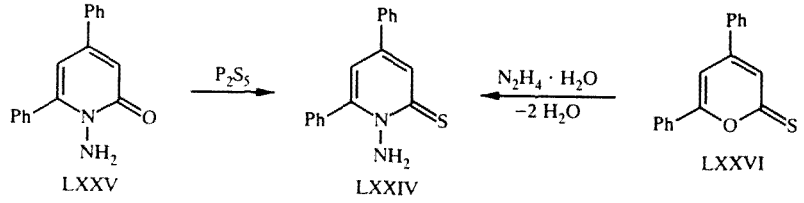
LXXI LXXIII LXXII

R, R^1 = Alk; R^2 = Ph, Het; R^3 = Hal, Me, Ac

5. N-AMINOPYRIDINTHIONES

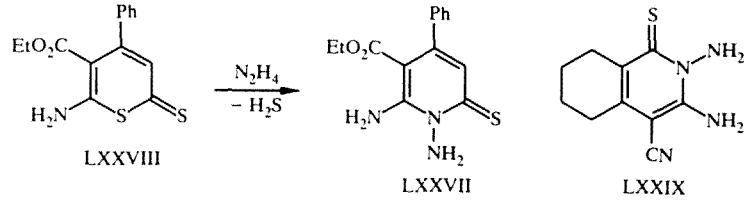
The known methods for the synthesis of α-mercapto derivatives of N-aminoazines include cyclization of noncyclic starting materials, recyclization and replacement of oxo groups by thio groups. In contrast to the N-aminoazolinthiones, no cases of direct thiolation of the heterocyclic ring have been reported for the N-aminoazinthiones.

The most studied of the α-mercapto-N-aminopyridines is 1-amino-4,6-diphenylpyridin-2-thione (LXXIV) which was first synthesized by Molina and his co-workers by two methods: replacement of oxygen by sulfur in the 1-aminopyridone-2 (LXXV) by treatment with P_2S_5 [73] and recyclization of 4,6-diphenylpyran-2-thione (LXXVI) with hydrazine hydrate [74-76]. An attempt to recyclize 4,6-dimethylpyran-2-thione was unsuccessful [77].



LXXV LXXIV LXXVI

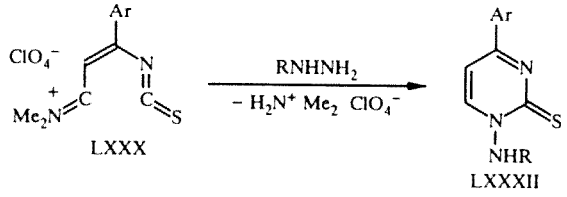
1,6-Diaminopyridin-2-thione LXXVII was synthesized from the thiopyran-2-thione LXXVIII by recyclization with hydrazine hydrate [78, 79]. The amniothione LXXIX was prepared analogously.



LXXVIII LXXVII LXXIX

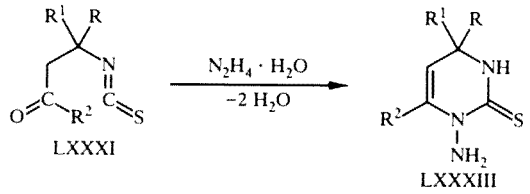
6. N-AMINOPYRIMIDINTHIONES

A general method for the synthesis of 1-amino-pyrimidin-2-thiones is cyclization of isothiocyanates of types LXXX and LXXXI with hydrazine or methylhydrazine. For example, compounds LXXXII [80-82] and LXXXIII [83-86] were prepared in high yield.



LXXX LXXXII

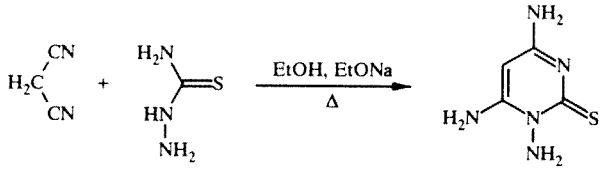
R = H, Alk, Ar, AlkCO, PhCO, EtOCO



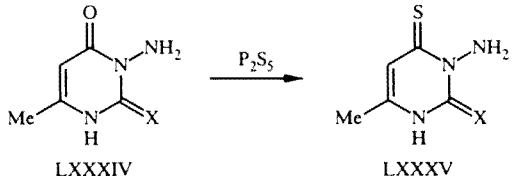
LXXXI LXXXIII

R, R^1, R^2 = H, Me, Ph

Another method for preparing N-aminopyrimidin-2-thiones is the cyclocondensation of thiosemicarbazide with malonitrile [87].



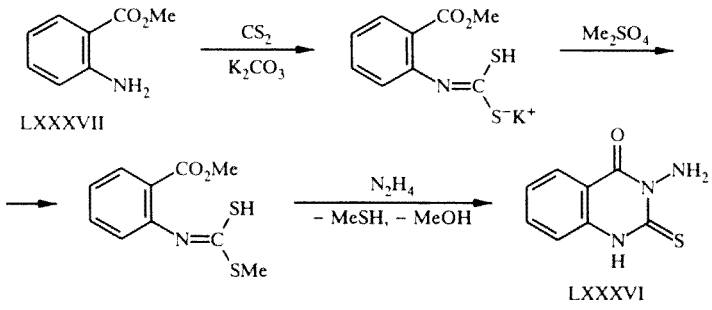
The reaction of 1-amino-4-methyl-pyrimidon-6-one (LXXXIV) with P_2S_5 gave the pyrimidin-6-thione (LXXXV) [88].



LXXXIV LXXXV

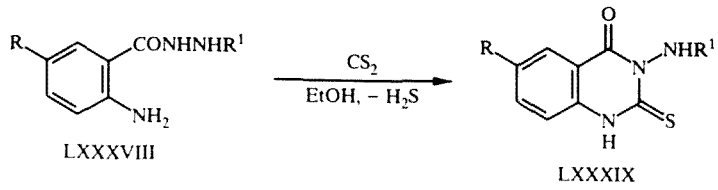
X = O, S

Methyl *o*-aminobenzoate (LXXXVII) was treated successively with carbon disulfide in the presence of potassium carbonate, dimethyl sulfate and hydrazine hydrate to give 3-aminoquinazolin-4-on-2-thione (LXXXVI) (80%) [89].



LXXXVII LXXXVI

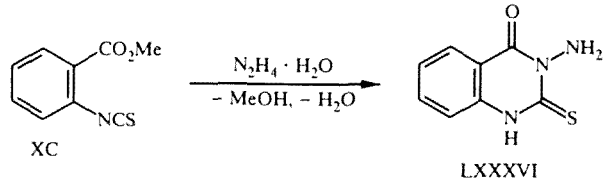
Compounds LXXXIX were prepared from the hydrazides of 5-R-2-aminobenzoic acids (LXXXVIII) and carbon disulfide [90].



LXXXVIII LXXXIX

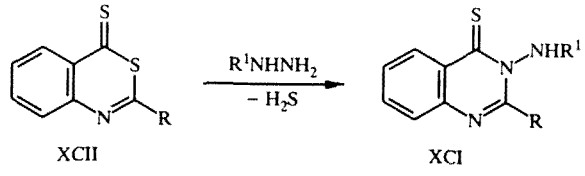
R = H, Cl; R^1 = H, Me

Methyl *o*-isothiocyanatobenzoate (XC) gave 3-aminoquinazolin-4-one-2-thione (LXXXVI) on heating with hydrazine hydrate [91].



XC LXXXVI

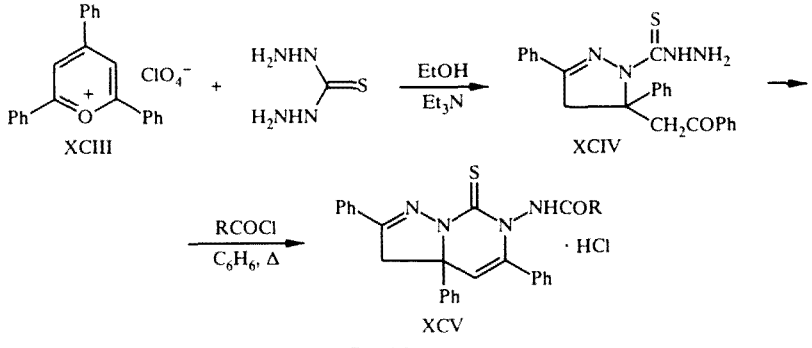
3-Amino-2-R-quinazolin-4-thiones (XCI) were synthesized by recyclization of 2-R-1,3-benzothiazin-4-thiones (XCII) with hydrazine, phenylhydrazine or semicarbazide [92].



XCII XCI

R = Alk, Ar; R^1 = H, Ph, $CONH_2$

The pyrazoline XCIV was prepared by reaction of 2,4,6-triphenylpyrillium perchlorate (XCIII) with thiocarbazide. The pyrazoline was converted to the compounds XCV, isolated as the hydrochlorides, by boiling with acyl chlorides [93].

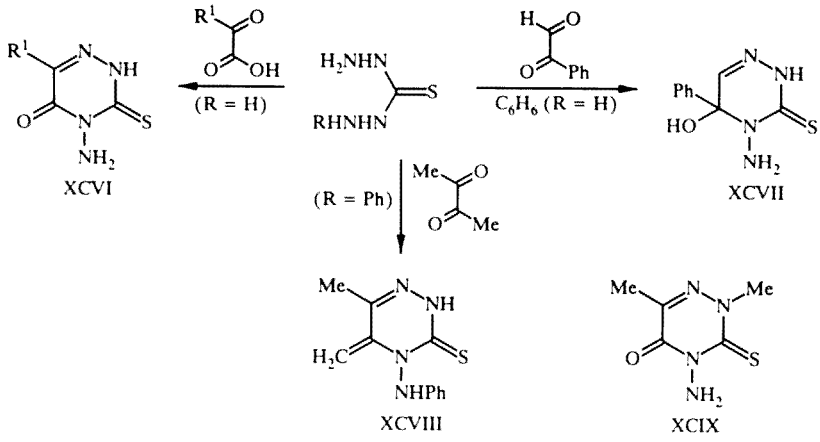


XCIII XCIV XCV

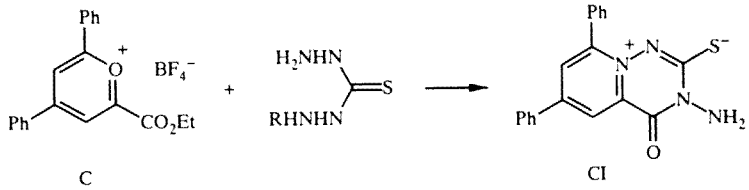
R = Me, Ar

7. N-AMINO-1,2,4-TRIAZINTHIONES

α-Mercapto derivatives of N-amino-1,2,4-triazines were made by condensation of thiocarbohydrazide with dicarbonyls. The reaction with α-keto acids gave 4-amino-6-R-1,2,4-triazin-5-one-3-thiones (XCVI) [94-96] whereas the thione XCVII [97] was obtained from phenylglyoxal in 70% yield. The corresponding thiones XCVIII [97] and XCIX [98] were obtained from 3-phenylthiocarbohydrazide and diacetyl or 2-methylthiocarbohydrazide and pyruvic acid.



When the pyrillium salt C was used as the carbonyl starting material, the mesoionic bicyclic aminothione CI was formed [99].



In conclusion it should be noted that, despite the obvious successes in the synthesis of N-amino-α-mercapto derivatives of azoles and azines, many examples of this class are still unknown. For example not one N-aminopyrazolinthione has been described, and 1-aminoperimidin-2-thiones with free N_3H groups, derivatives of N-aminopyrazine and N-aminopyridazinthiones have yet to be described.

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