Chemistry of Heterocyclic Compounds, Vol. 33, No. 9, 1997

SYNTHESIS AND PROPERTIES OF N-AMINOAZOLINETHIONES AND N-AMINOAZINETHIONES. 2.* REACTIONS

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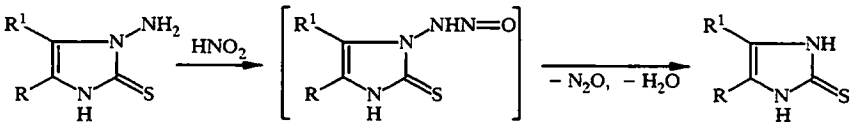
Literature data on the reactivity of α-mercapto derivatives of N-aminoazoles and N-aminoazines are reviewed.

Data on the methods of synthesis of N-aminoazolinethiones and N-aminoazinethiones were systematically discussed in the first part of this review [1]. The sequel contains information on the chemical properties of these compounds, particularly pertaining to all types of heterocyclization involving the amino and mercapto groups.

1. ELIMINATION OF N-AMINO AND MERCAPTO GROUPS

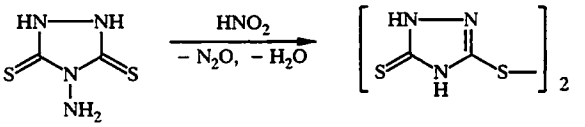
The basic method for the elimination of N-amino groups in heterocyclic aminothiones is treatment with nitrous acid. It is suggested that during these reactions, which usually occur with good yield, an unstable N-nitrosoamine of type I is formed, which decomposes with the evolution of nitrous oxide [2]. For example, the 1-aminoimidazoline-2-thiones II were converted into imidazolinethiones III [3]. Deamination of 4-amino-1,2,4-triazoline-3-thiones [4-6], 3,5-dialkylthio-4-amino-1,2,4-triazoles [7] and 1-amino-5-benzoyl-4-phenyl-pyrimidine-2-thiones [8] occur in an analogous manner:



II I III

R, R[1] = H, Me, Ar

In a number of cases oxidation of the mercapto group accompanied elimination of the amino group on treatment with nitrous acid. For example, 4-amino-1,2,4-triazoline-3,5-dithione (IV) was converted to the disulfide V in 95% yield [9]. The formation of similar disulfides was also observed for 3-aminothiazoline-2-thiones [10-12], 4-amino-5-anilino-1,2,4-triazoline-3-thiones [13] and 1,6-diamino-4-phenyl-5-ethoxycarbonylpyridine-2-thione [14]:



IV V

Deamination can also occur with hydrazones. When thiones VI were heated above their melting points the corresponding nitrile was eliminated to give compounds VII in 90-98% yield [15].

*For Part 1 see [1].

Rostov State University, Rostov-on-Don 344090. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1155-1181, September, 1997. Original article submitted March 11, 1997.

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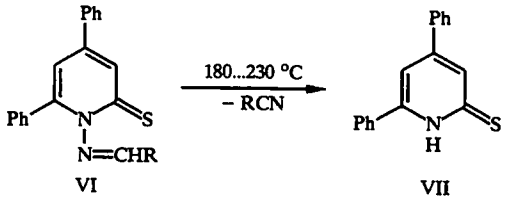
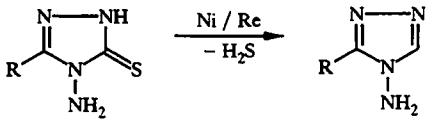


VI VII

R = Ar, PhCH=CH

As the following example shows it is possible to eliminate the mercapto group selectively [16, 17]:

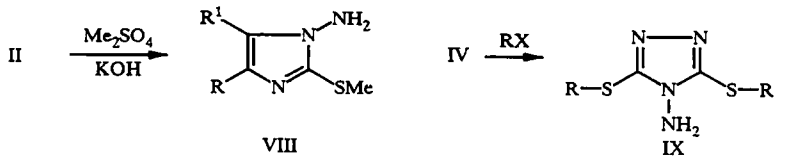


R = Ar, Het

However 1-amino-4,5-dialkylimidazoline-2-thione lost both the sulfur atom and the amino group under these conditions [3].

2. ALKYLATION

Alkylation of N-aminoazolin- and N-amioazinethiones occurs exclusively at the sulfur atom. In this respect they do not differ from other heterocyclic thiones [18]. For example the aminothiones II react with methyl iodide or dimethyl sulfate in the presence of base to give the methylthio derivatives VIII [3, 19]. 4-Amino-1,2,4-triazoline-3-thiones [6, 15, 20-23], 1-aminobenzimidazoline-2-thiones [24], and 4-amino-1,2,4-triazine-3-thiones [25, 26] were alkylated analogously. The dithione IV was alkylated with alkyl halides in neutral media at both sulfur atoms to give the 3,5-bis(alkylthio) derivatives IX [7, 9].

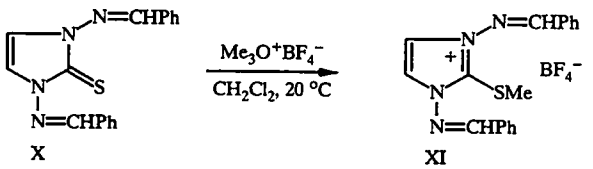


VIII IX

R, R^1 = H, Me, Ar

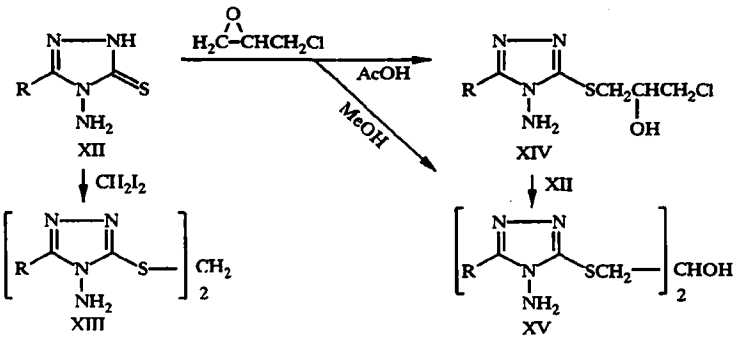
R = Me, CH_2Ph, CH_2CO_2H;
X = Cl, I

Treatment of 1,3-dibenzylideneaminoimidazoline-2-thione (X) with trimethyloxonium tetrafluoroborate gave the salt XI [27]. 3-Alkyl-1-aminobenzimidazoline-2-thiones(selenones) [28, 29], 3-amino-4-phenylthiazoline-2-thiones [30], 4-alkyl-1-amino-1,2,4-triazoline-5-thiones [31], 1-alkyl-4-amino-1,2,4-triazoline-5-thiones [32], 1-aminopyridine-2-thiones [33] and 1-aminopyrimidine-2-thiones [34] were methylated similarly:



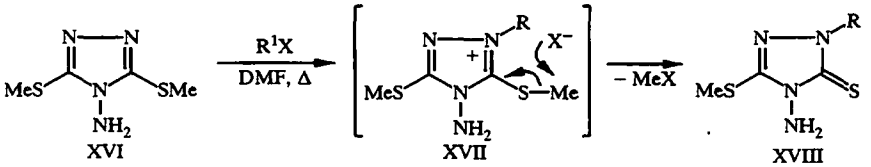
X XI

The aminothiones XII reacted with diiodomethane to give compounds XIII [22]. Compounds XIV or XV were formed on reaction with epichlorhydrin, depending on the conditions. The latter can also be obtained by reaction of 4-amino-3-(2-hydroxy-3-chloropropyl)thio-1,2,4-triazole (XIV) with the thione XII [35].



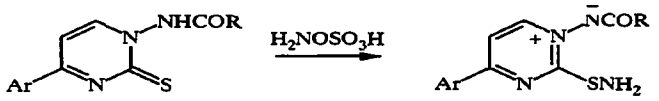
R = H, NH_2, Ar

P. Molina and his co-workers found that alkylation of 4-amino-3,5-dimethylthio-1,2,4-triazole (XVI) gave the salts XVII which were demethylated to the thiones XVIII [36]. The N-amino group was not affected. In one case the salt XVII (R = Me, X = I) was isolated but not characterized.



R = Me, CH_2COPh, CH_2CO_2Et; X = Br, I

One example is known of the electrophilic amination of the sulfur atom in aminothiones with hydroxylamine-O-sulfuric acid [37]:

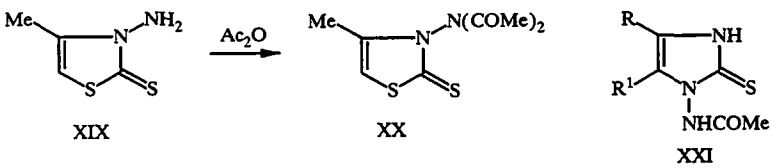


R = Alk, Ph, NH_2, NHPh

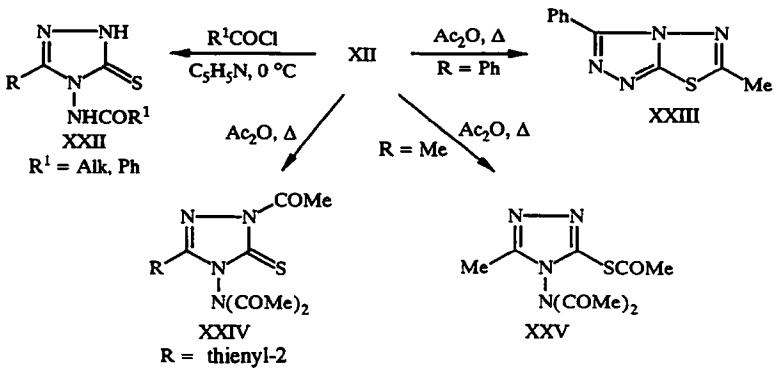
3. ACYLATION

In contrast to alkylation, acylation of aminothiones in most cases occurs at the N-amino group. For example, when compound XIX was heated with acetic anhydride compound XX was formed [12]. Boiling 1-amino-4-oxo-3-phenylimidazolidine-2-thiones [38] and 4-amino-1,3-dimethyl-1,2,4-triazoline-2-thiones [5] with excess acetic anhydride also gave the diacetylamino derivatives. The monoacetylamino derivatives XXI [3] were obtained in high yield by treatment of 1-aminoimidazoline-2-thiones with acetic anhydride at room temperature.

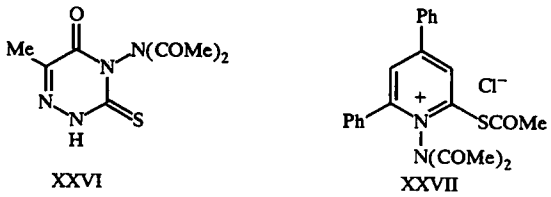
The aminothiones XII reacted with an equimolar amount of an acyl chloride in pyridine to give compounds XXII [22, 39, 40]. An interesting observation is that 2-methyl-5-phenyl-1,2,4-triazolo[3,4-*b*]1,3,4-triazole (XXIII) was obtained when 5-phenyl-1,2,4-triazolinethione (XII, R = Ph) was boiled with excess acetic anhydride [39]. Under the same conditions but with R = thienyl-2-triazole XII formed the triacetyl derivative XXIV [40] while the triazole (XII, R = Me) gave compound XXV in 30% yield [4].



R, R^1 = H, Me, Ar, CO_2Et



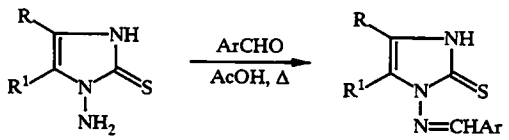
The diacetylamino derivative XXVI was obtained when 4-amino-6-methyl-1,2,4-triazin-5-one-3-thione was treated with an excess of acetyl chloride in pyridine [41]. Acylation of 1-amino-4,6-diphenylpyridine-2-thione with excess of acetyl chloride occurred at both the amino group and the sulfur atom to give the chloride XXVII [33].



XXVI XXVII

4. REACTIONS WITH ALDEHYDES

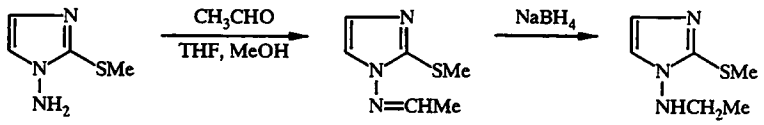
The corresponding hydrazones were formed when aminothiones reacted with aldehydes. The reaction occurs most readily in acetic acid. For example, the 1-arylideneaminoimidazoles XXVIII were obtained from the 1-aminoimidazoline-2-thiones II under these conditions [3]. Hydrazones based on 3-aminothiazolidine-2-thiones [11, 42], 4-amino-1,2,4-triazoline-3-thiones [43-47], 1-amino-1,2,4-triazoline-5-thione [48], 1-aminopyridine-2-thione [15, 49] and 4-amino-1,2,4-triazine-3-thione [41] were obtained similarly. Using 1-aminoimidazoline-4-one-2-thione as an example it has been shown that formation of similar hydrazones is possible with acetone [38]:



II XXVIII

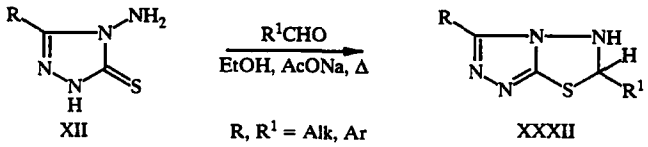
R, R¹ = H, Me, Ar, CO_2Et

1-Amino-2-methylthioimidazole XXIX reacted with acetaldehyde to give the hydrazone XXX which gave 1-ethylamino-2-methyl-thioimidazole XXXI on reduction with sodium tetrahydroborate [51]:

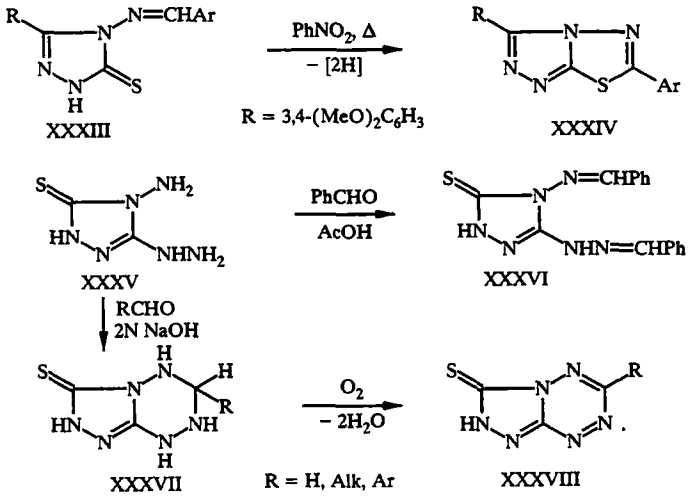


XXIX XXX XXXI

The bicyclic compounds XXXII were obtained in 65-80% yield when the aminothiones XII were treated with aldehydes in the presence of bases [52-55]. This is evidently the result of nucleophilic addition of the sulfur of the SH group at the C=N bond of the intermediate hydrazone.



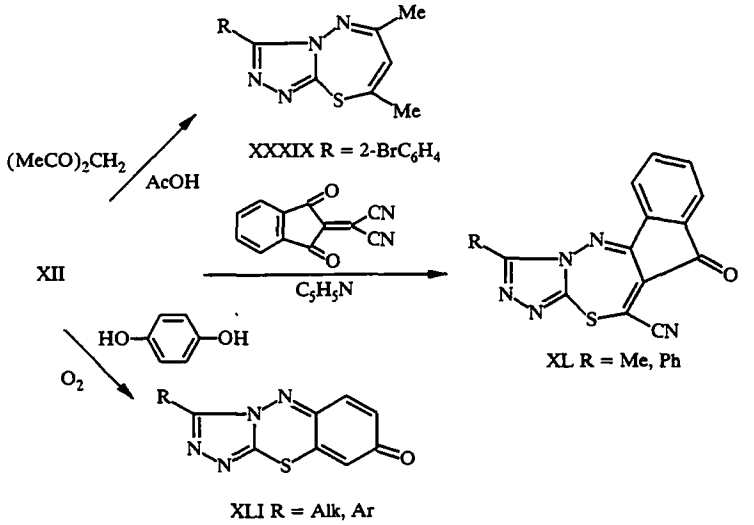
The azomethines XXXIII obtained from 4-amino-3-R-1,2,4-triazoline-5-thiones with the corresponding aldehydes were converted quantitatively to the compounds XXXIV on heating in nitrobenzene [56].

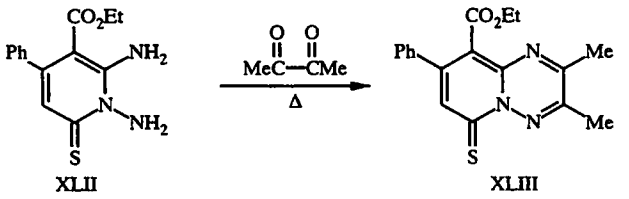


Interaction of 4-amino-5-hydrazino-1,2,4-triazoline-3-thione XXXV with benzaldehyde in acetic acid [57] or in alcohol in the presence of HCl [58] gave the bishydrazone XXXVI. Compound XXXV reacted with aldehydes in alkaline media to give the unstable tetrazine XXXVII which oxidized very rapidly in air to the bright red compound XXXVIII [59]. This reaction has been proposed as a qualitative test for aldehydes since compound XXXV does not react with ketones, esters or other carbonyl compounds under these conditions. It is interesting that the sulfur atom does not participate in the cyclization. This shows indirectly that compound XXXV initially forms a monohydrazone at the hydrazino group which then ring closes at the amino group.

5. REACTIONS WITH DICARBONYL COMPOUNDS

The aminothiones XII react with acetylacetone to give the 1,3,4-thiadiazepines XXXIX [61]. Compound XL is formed with 2-(dicyanomethylidene)-1,3-indandione [62]. 1,2,4-Triazolo[3,4-*b*]benzothiadiazoles XLI [63] were obtained from hydroquinone and the aminothiones XII. One can suppose that *p*-benzoquinones are formed *in situ* in these reactions.

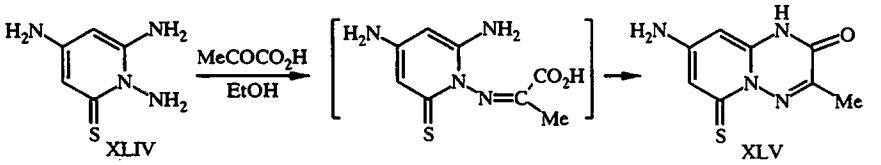




XLII XLIII

Pyrido[1,2-*b*]triazine XLIII was formed in 65% yield from heating 1,6-diaminopyridine-2-thione XLII with diacetyl [14].

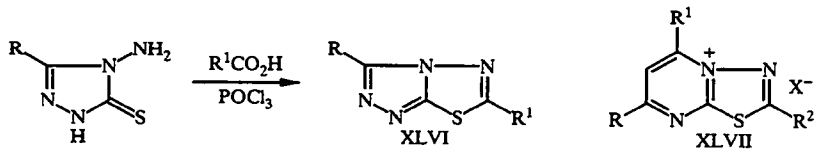
Condensation of the triaminothione XLIV with pyrotartaric acid gave compound XLV, again with participation of the amino group alone [64].



XLIV XLV

6. REACTIONS WITH CARBOXYLIC ACIDS AND THEIR DERIVATIVES

The characteristics of the aminothiones are probably most clearly seen in their reactions with carboxylic acids and their derivatives, leading to condensed 1,3,4-thiadiazoles. For example, compound XII reacts with carboxylic acids in the presence of $POCl_3$ to give 1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazoles XLVI [65-71] in 40-77% yields. 1-Aminopyrimidine-2-thiones [72] and 4-amino-1,2,4-triazine-3-thiones [73] react similarly to give the salts XLVII and XLVII. In preparing compounds XLVI the acid chlorides [52, 74], the acid nitriles [55], and in the case of a compound XLVII, the half acid chloride [34, 75] were used. Cyclocondensation of 1-aminopyrimidine-2-thione with the Willsmeier reagent ($HCONMe_2-POCl_3$) gave the salts XLVII (R = H) [76]. Compounds XLIX, L, and XLVI can also be obtained by heating N-acylamino-α-mercapto derivatives of imidazoles [3], thiazoles [77] and 1,2,4-triazoles [35, 78, 79] with $POCl_3$ or conc. H_2SO_4.



XII

XLVI

R, R^1 = H, Alk, Ar, Het

XLVII

R, R^2 = Alk, Ar
R^1 = H, NH_2
X = Cl, H_2SO_4

XLVIII

R = Me, Ph
R^1 = Alk, Ar

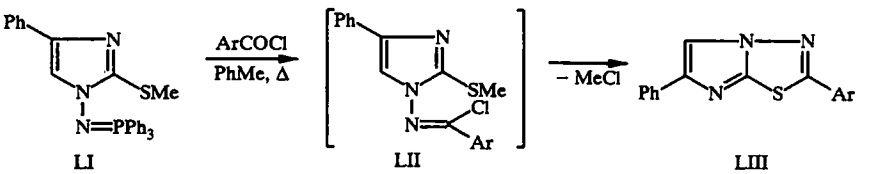
XLIX

R, R^1 = H, Me, Ar, CO_2Et

L

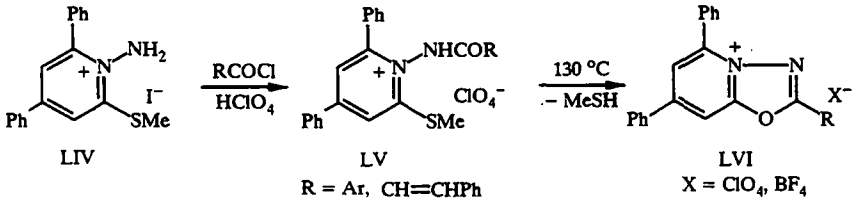
R = H, Me; R^1 = Me, Ph
X = Cl, H_2SO_4

Interaction of the iminophosphorane LI with aroyl chlorides goes via the intermediates LII, some of which were isolated. Further cyclization gave the imidazo[2,1-*b*]-1,3,4-thiadiazoles LIII [80]:



LI LII LIII

The 1-aminopyridinium salt LIV reacts with acyl chlorides to give the acylation products LV which are converted into the oxazolo[3,2-*a*]pyridines LVI apparently by nucleophilic displacement of the SMe group by the carbonyl oxygen atom [81]:

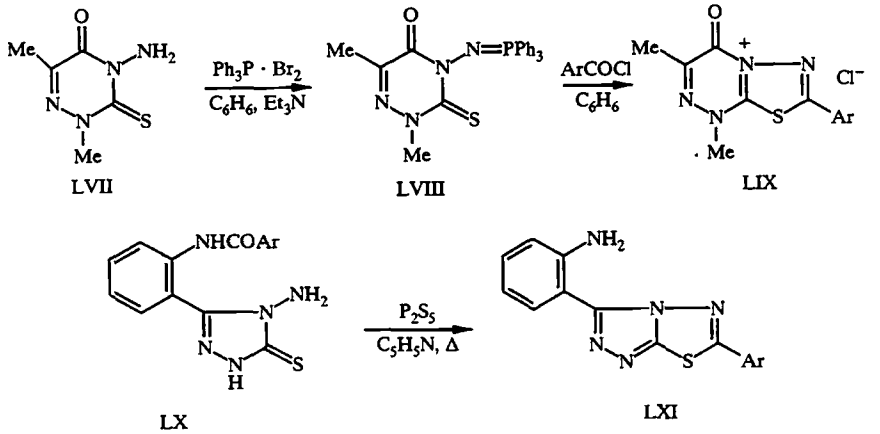


LIV LV LVI

R = Ar, CH=CHPh X = ClO_4, BF_4

Thiadiazolo[2,3-*c*]-1,2,4-triazine chlorides LIX were obtained by treatment of the amines LVII with $Ph_3P \cdot Br_2$ and subsequent reaction of the aminophosphoranes formed LVIII with aroyl chlorides [80].

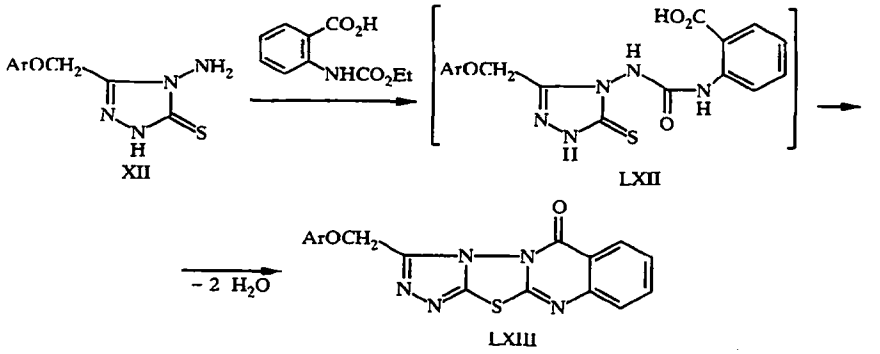
When 5-(*o*-aroylaminophenyl)-4-amino-1,2,4-triazoline-3-thione was heated with P_2S_5, transacylation occurred followed by ring closure of the thiadiazole ring to give compounds LXI (61-80% yields) [82].



LVII LVIII LIX

LX LXI

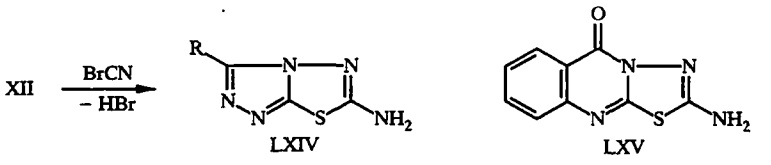
Aryloxymethyl substituted aminothiones XII react with *o*-(ethoxycarbonylamino)benzoic acid to give the tetracyclic compound LXIII, probably via the intermediate LXII [83]:



XII LXII

LXIII

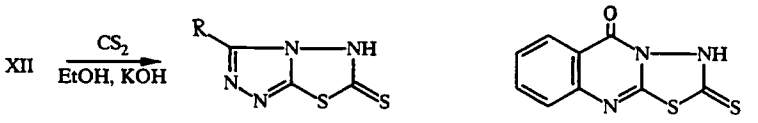
Treatment of alkyl- and arylaminothiones XII [84-86] and 3-aminoquinazoline-2-thione [87] with cyanogen bromide gave the corresponding amines LXIV and LXV.



LXIV LXV

R = Alk, Ar

The triazoles XII react with carbon disulfide in alcoholic alkali to give the thiones LXVI (60-70% yield) [78, 79, 84, 88, 89]. Compound LXVII was prepared analogously from 3-amino-quinazoline-2-thione [87].

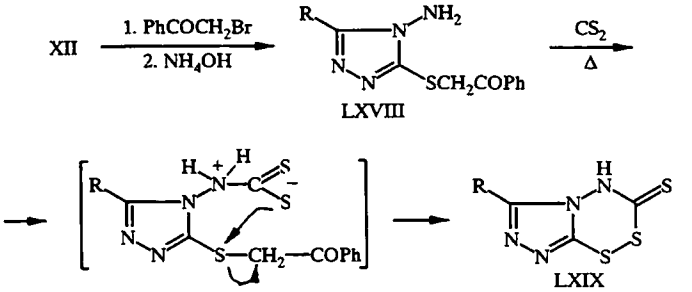


LXVI

R = Alk, Ar, Het

LXVII

The cyclocondensation of 4-amino-3-phenacylthio-1,2,4-triazoles LXVIII with carbon disulfide occurred quite differently to give the 1,2-dithia-4,5-diazine-3-thiones LXIX as the final products [90]:

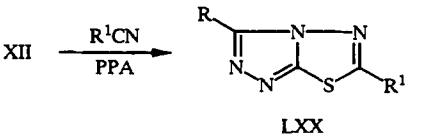


LXVIII

LXIX

R = Ar, CH_2Ar

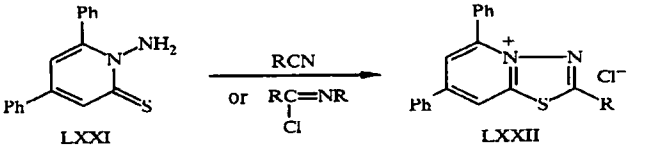
Compounds LXX were formed from the reaction of the aminothiones XII with aromatic nitriles [91]:



LXX

R = Me, Et; R^1 = Ar, CH_2CO_2Et

Reaction of the aminothione LXXI with nitriles [81, 92] or imidoyl chlorides [93] gave the salts LXXII.



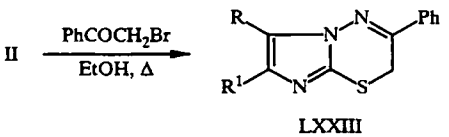
LXXI

LXXII

R = Me, CH_2Cl, Ar

7. REACTIONS WITH α- AND β-HALOGENOCARBONYL COMPOUNDS

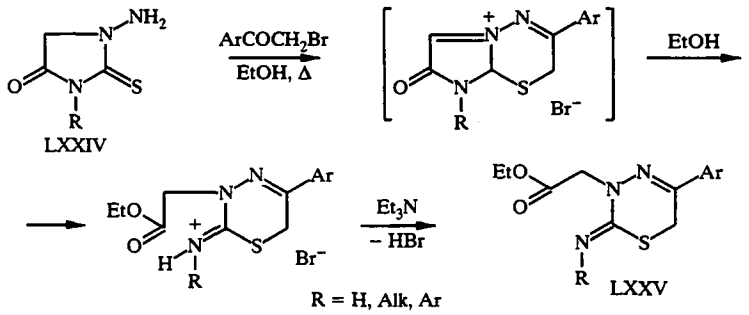
The aminothiones II react with α-halogenocarbonyl compounds to give the condensed 1,3,4-thiadiazines, for example [3, 94]:



LXXIII

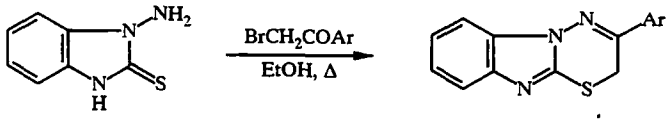
R, R^1 = H, Me, Ph, CO_2Et

In the case of the imidazoline-2-thiones LXXIV the triazines LXXV were obtained by ring opening of the imidazole ring [95]:



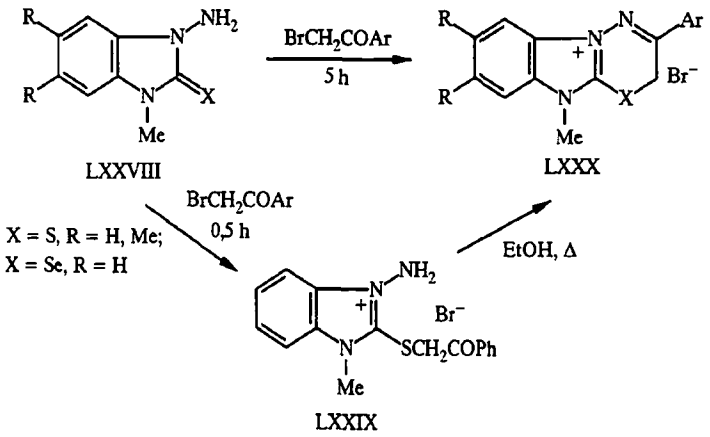
LXXIV LXXV

Interaction of 1-amino-benzimidazoline-2-thione LXXVI with aryl(bromomethyl)ketones gave the thiadiazines LXXVII [24].



LXXVI LXXVII

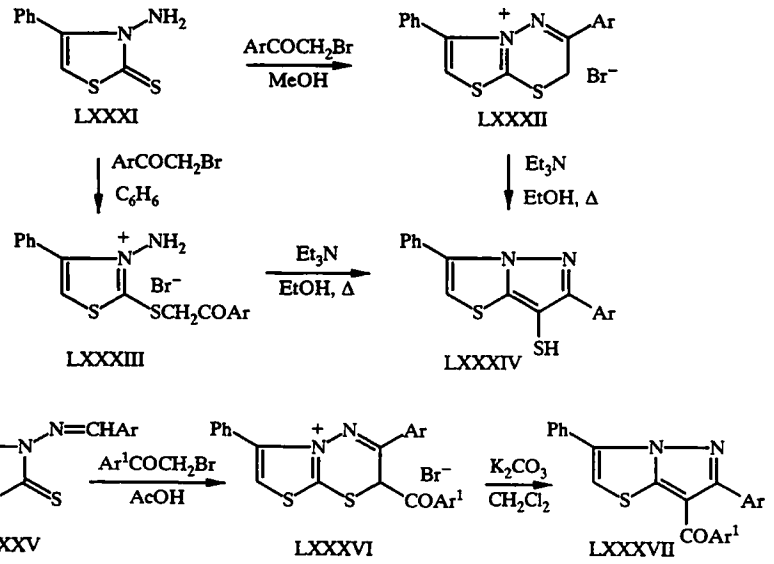
A series of 1,3,4-thia(seleno)diazino[3,2-*a*]benzimidazolium bromides LXXX were obtained by heating 1-amino-3-methylbenzimidazoline-2-thione(selenones) LXXVIII with phenacyl bromide and its derivatives in alcohol. Using phenacyl bromide it was established that the intermediately formed salts LXXIX could be isolated if the reaction time was reduced [96].



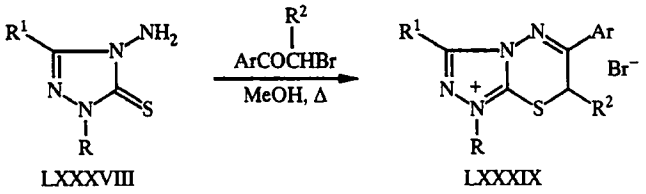
LXXVIII LXXX LXXIX

Treatment of 3-amino-4-phenylthiadiazoline-2-thione (LXXXI) with phenacyl bromides in methanol gave the 1,2,4-thiadiazines LXXXII. In benzene the reaction stops at the formation of the S-alkylation product LXXXIII. Heating the salts LXXXII with triethylamine lead to ring contraction of the thiadiazine ring to give pyrazolo[5,1-*b*]thiazoles LXXXIV. The same product can be obtained under the same conditions from the salts LXXXIII [97].

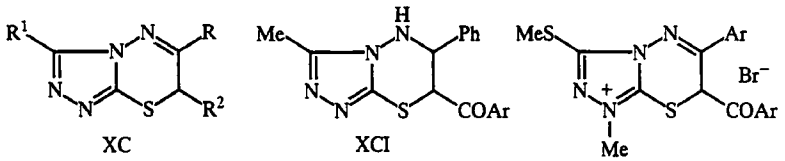
N-Arylideneaminoazolinethiones, e.g., LXXXV, also react with α-halogenoketones but both the sulfur atom and the azomethine group react to give the salts LXXXVI which are converted in mild conditions in high yield to the pyrazolo[5,1-*b*]thiazoles LXXXVII [42].



4-Aminoderivatives of 1,2,4-trizoline-3-thione [31, 97-106] and 1,2,4-triazoline-5-thiones LXXXVIII [32, 107] react with α-halogenoketones to give 1,3,4-thiadiazines LXXXIX and XC. 4-Arylideneamino-1,2,4-triazoline-3-thiones [46] and 4-arylideneamino-1-methyl-1,2,4-triazoline-5-thione form compounds XCI and XCII.

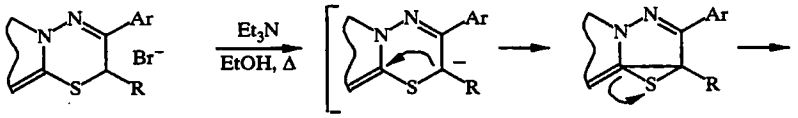


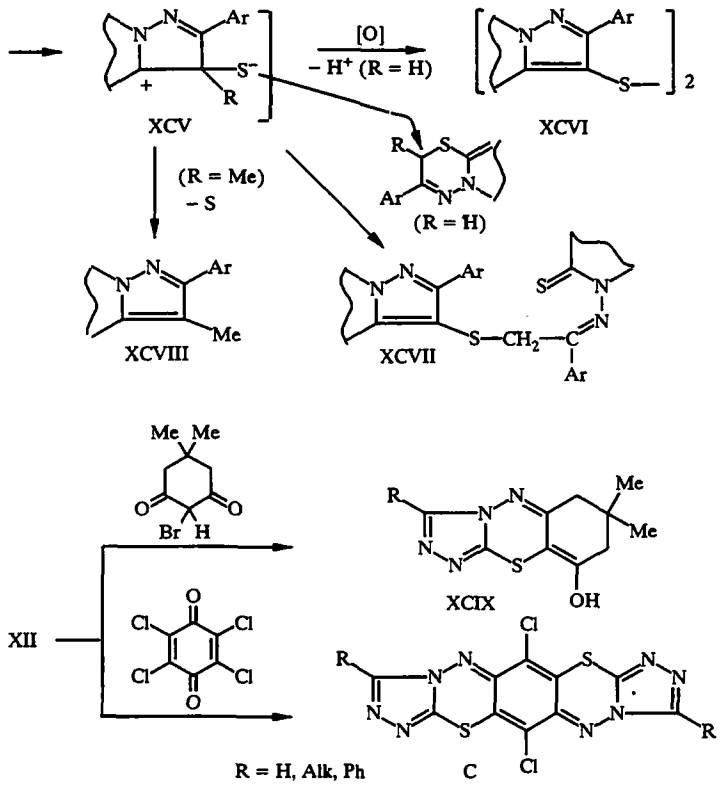
R = Me, CH_2Ar; R^1 = H, Me, SMe; R^2 = H, Me



R, R^1, R^2 = H, Alk, Ar, Het, CH_2CO_2Et

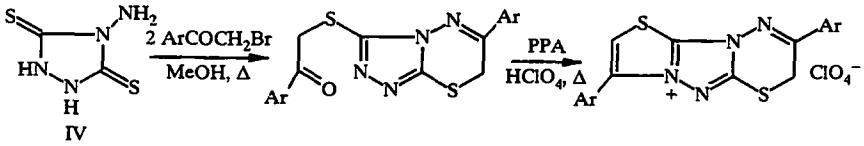
Salts LXXX and LXXXIX, which do not have alkyl substituents at position 2 of the thiadiazine ring, are both converted into a mixture of compounds XCVI and XCVII on heating with triethylamine. The C-anion XCIII formed predominantly via the intermediate XCIV is converted to the S-anion XCV. The latter may be stabilized via two routes: oxidative dimerization to the disulfide XCVI or attack by the S-anion XCV at position 2 of the starting material with opening of the thiadiazine ring to give compound XCVII. Salts LXXX and LXXXIX with methyl groups at position 2 are converted into the pyrazolo[5,1-*c*]-1,2,4-triazoles XCVII under the same conditions. It is proposed that the S-anion XCV, which contains the poor methyl leaving group, is stabilized by extrusion of the sulfur atom [96, 107].



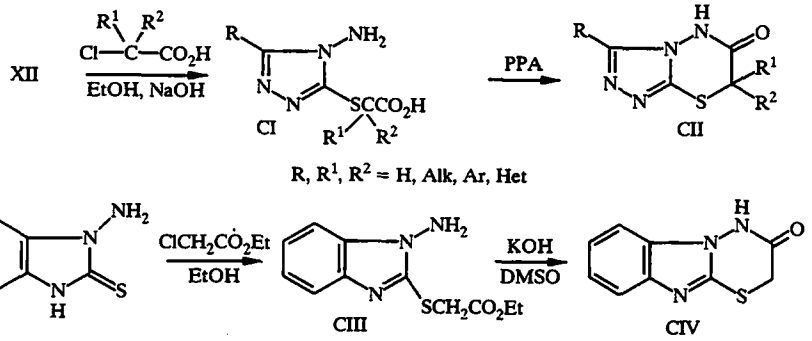


The reactions of 4-amino-1,2,4-triazoline-3-thiones XII with such α-halogenoketones as 5-bromo- and 5-bromo-5-nitrobarbituric acids [108], 1-bromo-4,4-dimethylcyclohexan-2,6-dione [109], tetrachloro(fluoro)-*p*-benzoquinone and 2,3-dichloro-1,4-naphthoquinone [61]. Polycyclic systems of the types XCIX or C were formed.

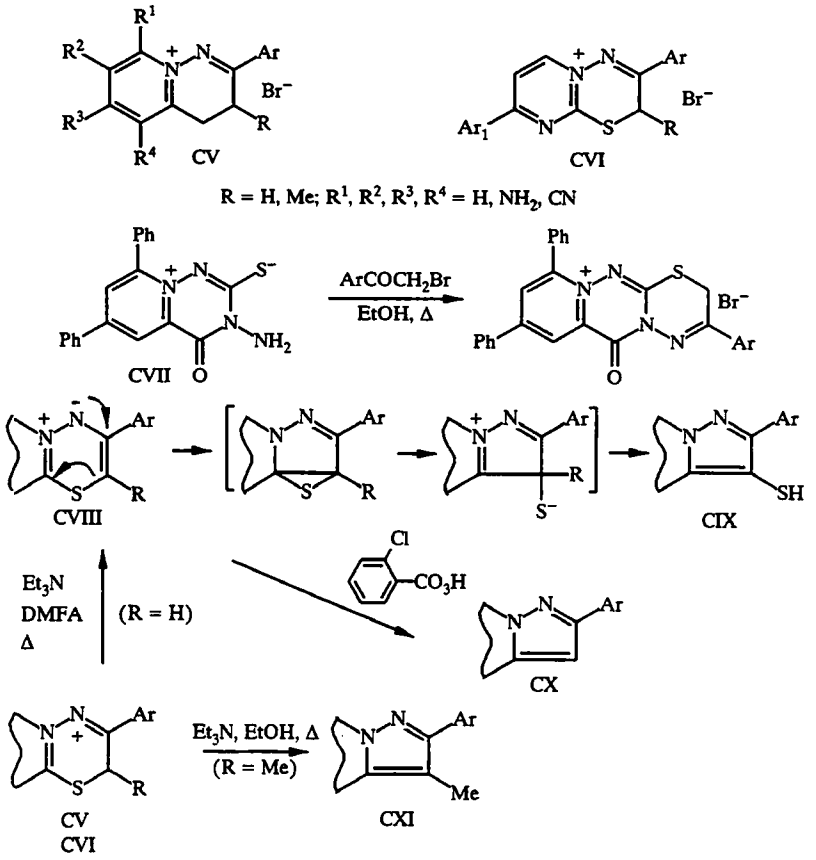
The dithione IV reacts with two moles of α-bromoketones as follows [110]:



α-Halogenocarboxylic acids [54, 111] or their esters [81, 112] react with the aminothione XII to give the sulfides CI which cyclize to the triazolo[3,4-*b*]-1,3,4-triazine-6-ones CII on treatment with sodium ethoxide or on heating with polyphosphoric acid. The sulfide CIII obtained from 1-aminobenzimidazole-2-thione and ethyl chloroacetate is converted into the thiadiazine CIV by treatment with KOH in DMSO [24].

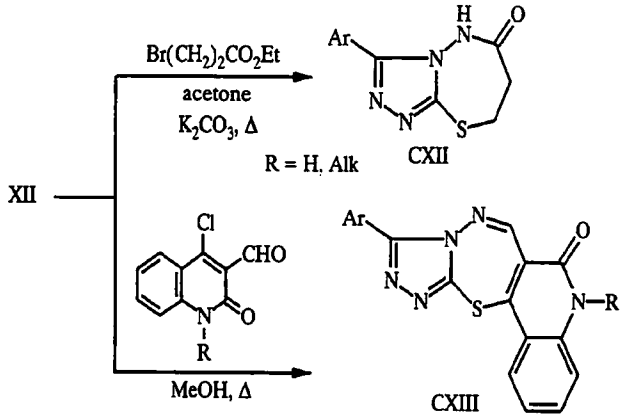


Derivatives of 1-aminopyridine-2-thione [33, 113, 114] and 1-aminopyrimidine-2-thione [115] react with α-halogenoketones to give the salts CV and CVI. The mesoionic compounds CVII underwent a similar reaction [116].

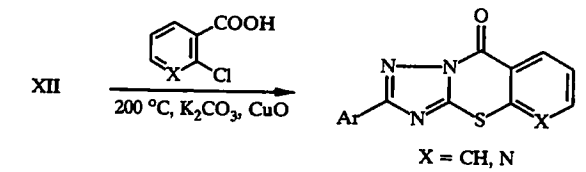


Treatment of compounds CV and CVI with triethylamine led to contraction of the thiadiazine ring to give the corresponding pyrazoloazines. The first step is formation of the mesoionic intermediate CVIII which is converted into the pyrazolo[1,5-*a*]pyridines CIX [113, 115]. In some cases the betaines CVIII were isolated and characterized [114]. Extrusion of sulfur with formation of the pyrazoles CX occurred when the betaines were treated with *m*-chloroperbenzoic acid. Sulfur extrusion to give the pyrazoles CXI also occurred when the 2-methyl substituted thiadiazines CV were treated with triethylamine [113].

Reaction of the aminothiones XII with β-halogenocarbonyl compounds (ethyl 2-bromopropionic acid [117], 2-chloro-3-formylquinoline [118] or 4-chloro-3-formylquinolinones [119]) gave 1,3,4-thiadiazepines of types CXII and CXIII.

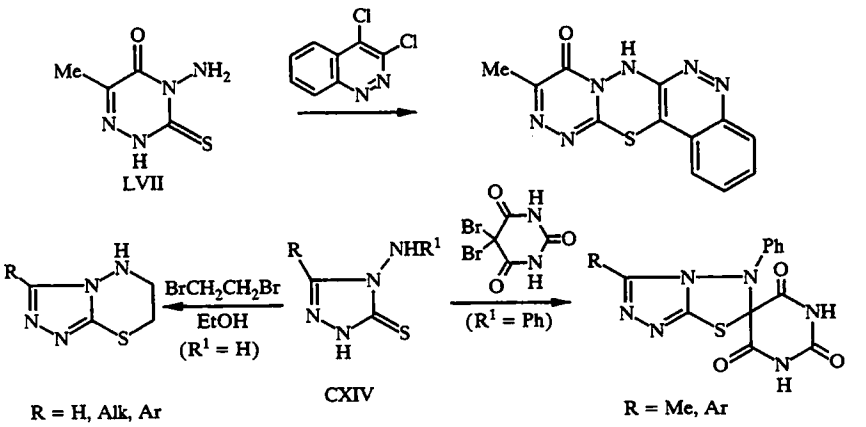


Cyclization accompanied by elimination of N-amino groups occurred on fusing the amniothiones XII with 2-chlorobenzoic or 2-chloronicotinic acids [120].



8. REACTIONS WITH DIHALIDES

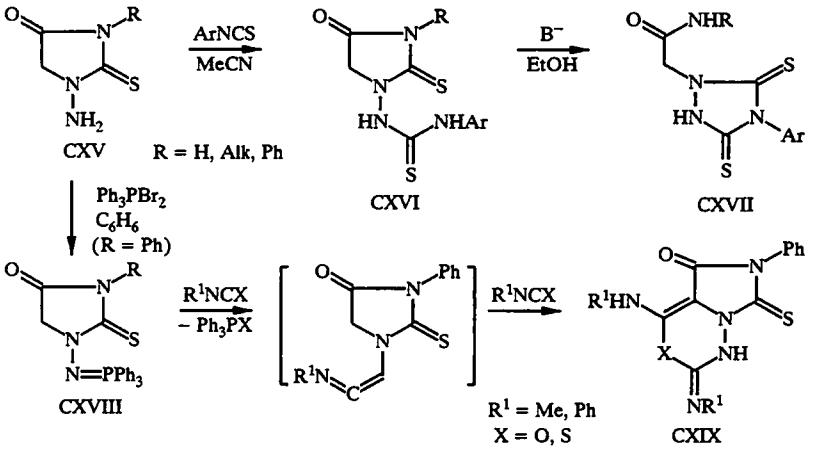
The following conversions exemplify reactions with 3,4-dichloroquinoline [121], dibromoethane [109], 5,5-dibromobarbituric acid [122] and 4,4-dibromopyrazoline-5-thione [122].



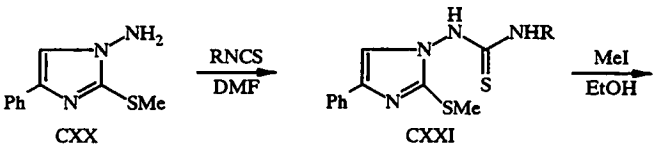
9. REACTIONS WITH ISOCYANATES, ISOTHIOCYANATES, AND THIOCYANATES

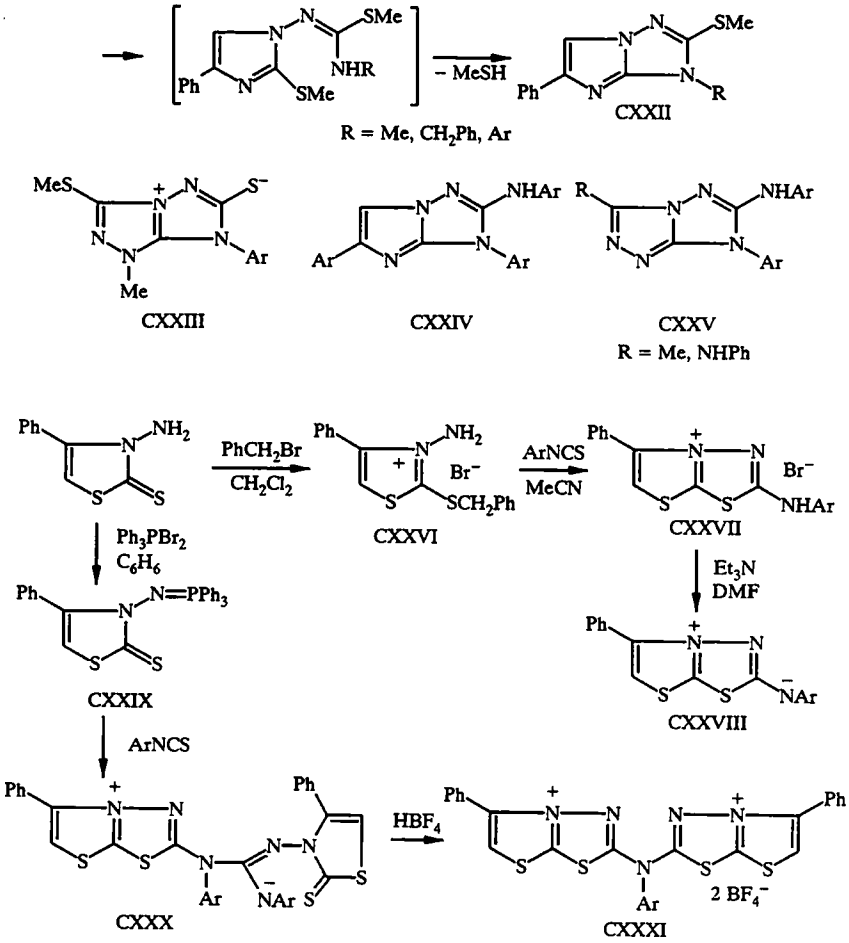
Phenyl isocyanate and phenyl isothiocyanate add to the amino group of 1-aminoimidazoline-2-thiones to give the N-ureido and N-thioureido derivatives respectively in 70-76% yield [3].

The thioureides CXVI was also obtained from the aminothiones CXV. The thioureides cyclized to the triazoles CXVII on treatment with base [95]. Treatment of the iminophosphorane CXVIII with isocyanates of isothiocyanates gave imidazo[1,5-*d*]-1,3,4-oxa(thia)diazines CXIX [123].



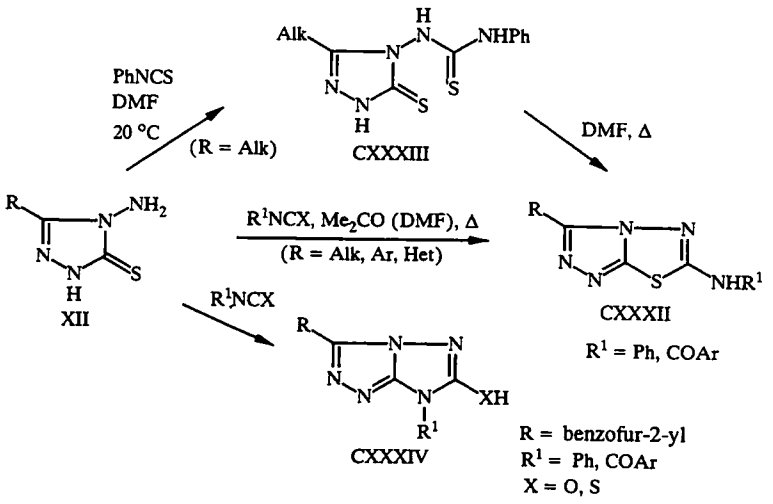
Treatment of 1-amino-2-methylthioimidazole CXX with isothiocyanates gave the thioureides CXXI which cyclized to the imidazo[2,1-*b*]-1,2,4-triazoles CXXII on methylation with methyl iodide [124]. The mesoionic 1,2,4-triazolo[4,3-*b*]-1,2,4-triazoles CXXIII [125, 126] were synthesized from 4-amino-1-methyl-3,5-dimethylthio-1,2,4-triazolium iodide and isothiocyanates. Compounds CXXIV and CXXV were obtained by the reaction of diarylcarbodiimides with 1-amino-5-aryl-2-methylthioimidazoles [126] and 4-amino-5-R-3-methylthio-1,2,4-triazoles [6, 127] respectively.



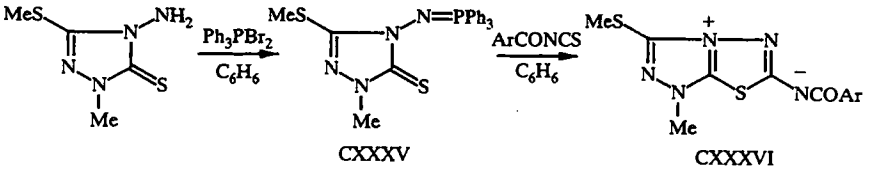


As the example of compound CXXVI shows, N-aminoazolium salts also react with isothiocyanates. The reaction occurs in the presence of triethylamine to give 1,3,4-thiadiazolium bromides CXXVII which are converted to the mesoionic compounds CXXVIII by bases [42]. Compounds CXXX, which were obtained analogously from the iminophosphorane CXXIX, cyclized further to the salts CXXXI [128, 129].

The amniothiones XII react with isothiocyanates in boiling acetone or DMF to give 1,3,4-thiadiazoles CXXXII [130, 131]. The thioureides CXXXIII were obtained in 80-85% yield when the reaction was carried out in DMF at room temperature. The thioureides were converted into compounds CXXXII on boiling in DMF [78, 79]. According to [53] the thiazole XII (R = benzofur-2-yl) reacts differently to its analogs (R = Alk, Ar, pyridyl-2) and reacts with isocyanates and isothiocyanates to give the 1,2,4-triazolo[4,3-*b*]-1,2,4-triazoles CXXXIV.

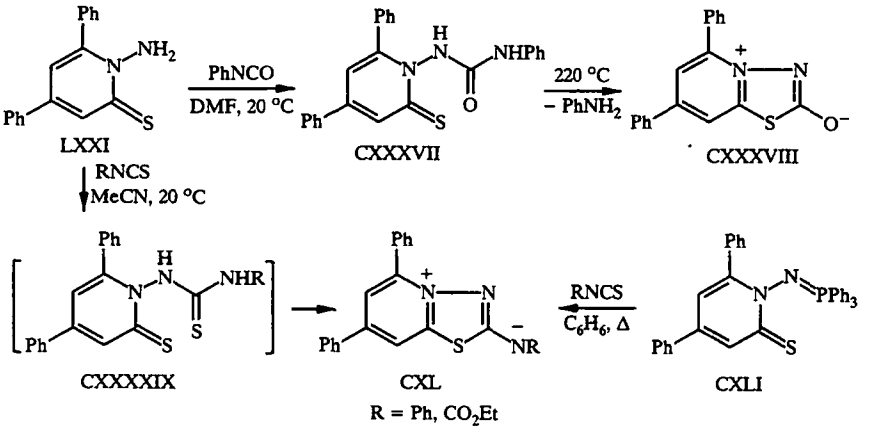


The mesoionic triazolo[3,4-*b*]-1,3,4-thiadiazoles CXXXVI were prepared by reaction of the iminophosphoranes CXXXV with isothiocyanates.



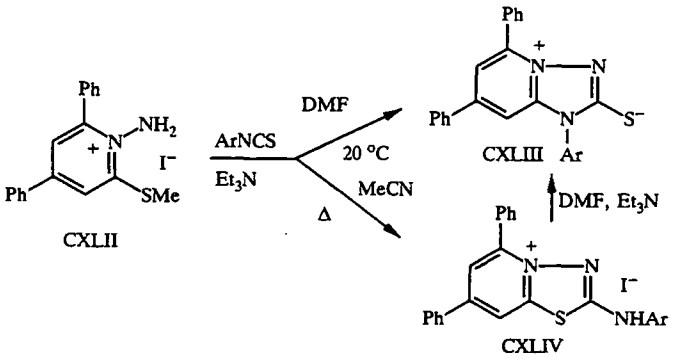
CXXXV CXXXVI

1-Amino-4,6-diphenylpyridine-2-thione LXXI [133], like 1-aminopyrimidine-2-thione [8] react with phenyl isocyanate to give the ureide CXXXVII. Thermolysis of the latter led to cyclization to the thiadiazolo[3,2-*a*]pyridine CXXXVIII. The thiadiazoles CXL were obtained in 65-79% yield the reaction of the aminothione LXXI with isothiocyanates. It is proposed that reactive derivatives of thiourea CXXXIX are formed as intermediates and these cyclize to the thiadiazole. Compounds CXL were also synthesized by the reaction of aryl isothiocyanates with the iminophosphorane CXLI [133].



LXXI CXXXVII CXXXVIII CXXXXIX CXL CXLI

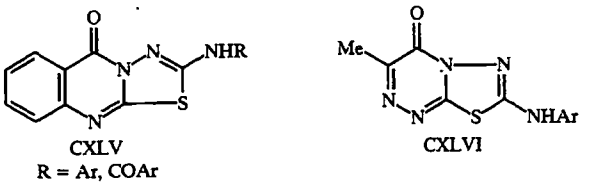
R = Ph, CO_2Et



CXLII CXLIII CXLIV

The pyridinium salt CXLII reacts with aryl isothiocyanates to give 1,2,4-triazolo[2,3-*a*]pyridines CXLIII or 1,3,4-thiadiazolo[3,2-*a*]pyridines CXLIV, depending on the reaction conditions. The latter are converted into compounds CXLIII in quantitative yield when heated with triethylamine in DMF [134, 135].

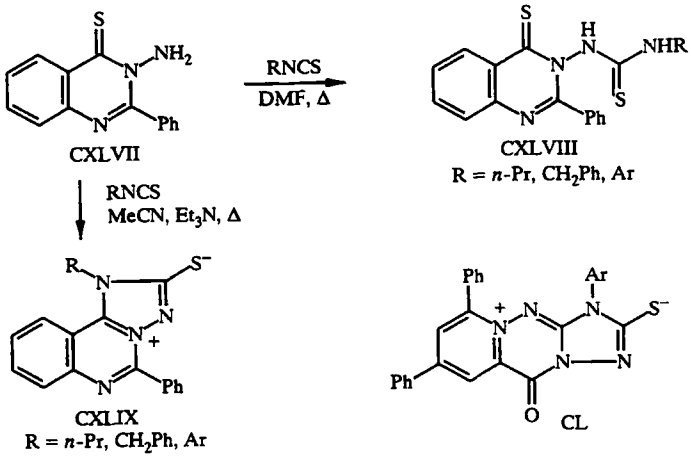
1,3,4-Thiadiazolo[2,3-*b*]quinazolinones CXLV [87] and 1,3,4-thiadiazolo[2,3-*e*]-1,2,4-triazinones CXLVI [136] were synthesized from the corresponding N-aminothiones and aryl isothiocyanates.



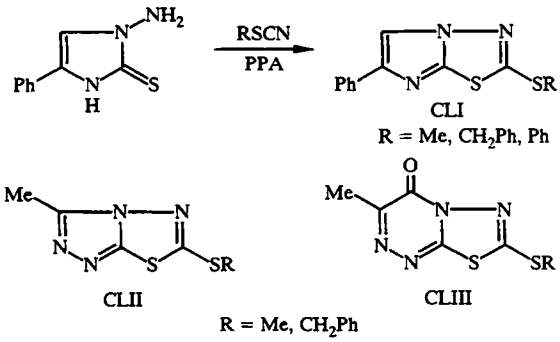
CXLV CXLVI

R = Ar, COAr

Despite the structural similarities between 1-amino-4,6-diphenylpyridine-2-thione and 3-amino-quinazoline-4-thione CXLVII, they differ somewhat in their reactions with isothiocyanates. For example, the thione CXLVII gives thiourea derivatives CXLVIII or mesoionic 1,2,4-triazolo[3,2-*c*]quinazolines CXLIX [137] depending on the conditions. Compounds were also obtained in a similar way from the reaction of isothiocyanates with 3-amino-4-oxo-pyrido[2,1-*f*]1,2,4-triazinium-2-thiolate [116].

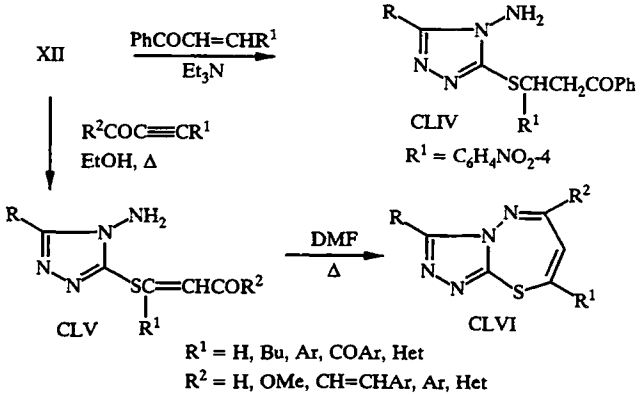


The 1,3,4-thiadiazoles CLI, CLII and CLIII were formed respectively from the reactions of thiocyanates with imidazoline-2-thione [138], 1,2,4-triazoline-3-thione [139] and 1,2,4-triazine-3-thione [140].

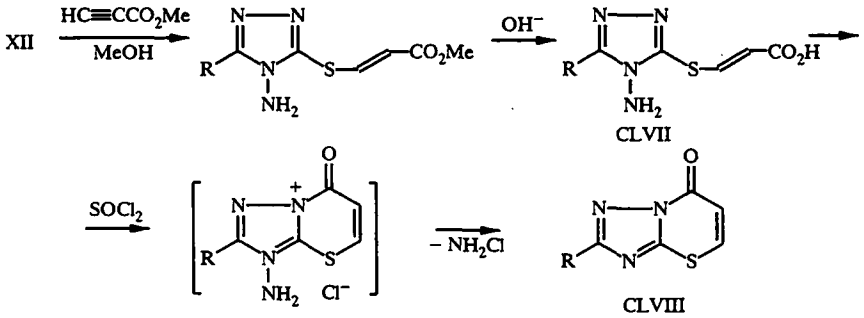


10. REACTIONS WITH DERIVATIVES OF ETHYLENE AND ACETYLENE

4-Amino-1,2,4-triazoline-3-thiones XII react with propenones [141] and propynones [141-144] to give products of addition at the mercapto group, CLIV and CLV. The latter cyclize to 1,3,4-thiadiazepines CLVI on heating in DMF.

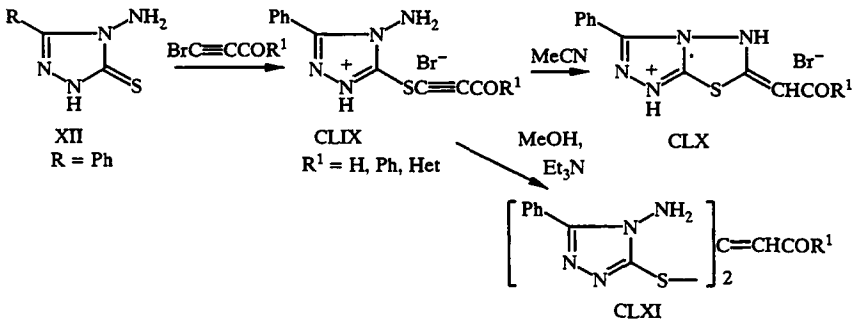


2-(1,2,4-Triazolyl-3-thio)vinylacetic acids CLVII, obtained from the aminothiones XII and methyl propargylate, cyclizes differently. They cyclize to compounds CLVIII on treatment with thionyl chloride [142].

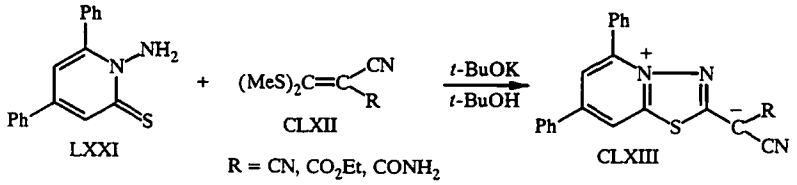


R = Me, *t*-Bu, Ph

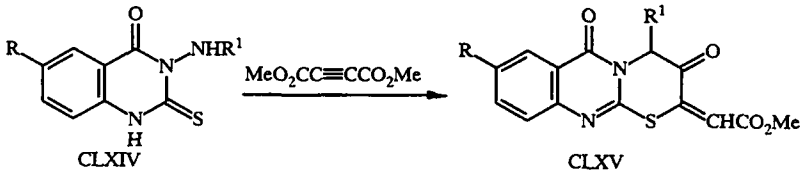
The reactions of the aminothiones XII with 1-bromo-2-acylacetylenes have been investigated [143]. It has been suggested that the salts CLIX are formed first and they are then converted into compounds CLX or CLXI depending on the conditions:



1-Aminopyridine-2-thione LXXI reacted with ethylene derivatives CLXII to give 1,3,4-thiadiazolo[3,2-*a*]pyridines CLXIII in 58-71% yields [145].

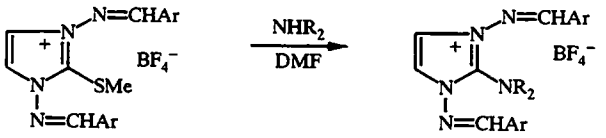


1,3,4-Thiadiazines CLXV were formed by the reaction of 3-aminoquinazoline-2-thiones CLXIV with dimethyl acetylenedicarboxylate [146].



11. NUCLEOPHILIC DISPLACEMENT OF METHYLTHIO GROUPS

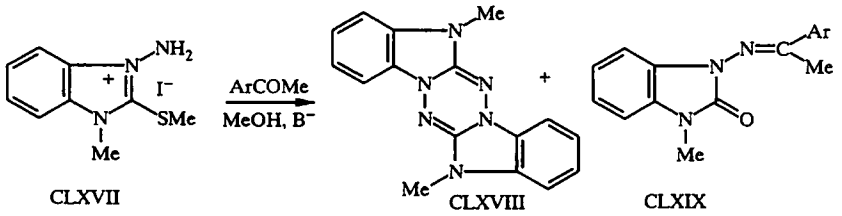
Methylthio groups in N-aminoazoles and N-aminoazines, either as the free bases or as their salts, are readily displaced by a variety of nucleophiles. For example the imidazolium salts XI react with ammonia or dimethylamine to give the 2-amino derivatives CLXVI [27].



XI CLXVI

R = H, Me

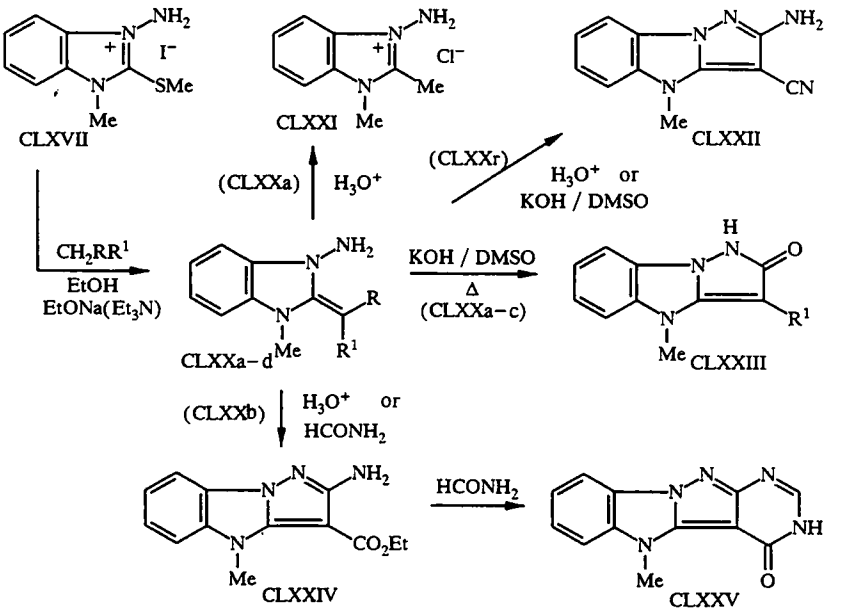
The salt CLXVII reacts with arylmethylketones in the presence of sodium methoxide or trimethylamine to give a mixture of the tetrazine CLXVIII and the hydrazone CLXIX which shows that the ketones are not converted into their carbanions under these conditions [29].



CLXVII CLXVIII CLXIX

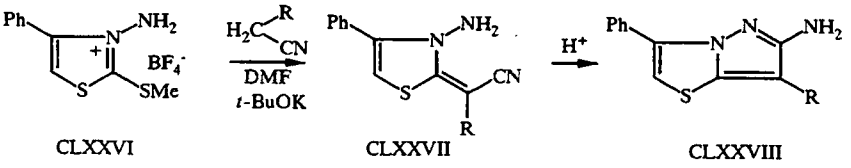
Ar = Ph, $C_6H_4NO_2$-4

The situation is quite different when stronger CH acids are used: diethyl malonate, malonodinitrile, ethyl cyanoacetate and ethyl nitroacetate. In this case the salt CLXVII forms derivatives of 1-amino-3-methyl-2-methylenebenzimidazoline, CLXXa-d in excellent yield. On boiling the diester CLXXa in dilute hydrochloric acid the ethoxycarbonyl groups are hydrolyzed with subsequent decarboxylation to give 1-amino-2,3-dimethylbenzimidazolium chloride, CLXXI. Under these conditions the cyanoether CLXXb cyclizes on account of the nitrile group to give the aminopyrazole CLXXIV. This reaction occurs on boiling in formamide in the absence of acid. However, in this case a 42% yield of the tetracyclic compound CLXXV is also obtained, which may be the result of cyclization of the aminopyrazole CLXXIV under the influence of formamide. Conversion of the dinitrile CLXXd into the aminopyrazole CLXXII takes place both in acid media and in the DMSO-KOH system. It is interesting that the use of the KOH-DMSO with the methylene bases CLXXa-c completely changes the direction of the cyclizations: they now occur with participation of the ethoxycarbonyl groups to give the pyrazole CLXXIII [29].



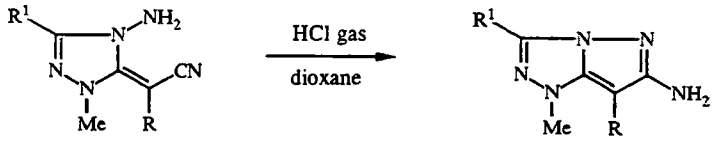
CLXX a R = R^1 = CO_2Et; b R = CO_2Et, R^1 = CN;
c R = CO_2Et, R^1 = NO_2; d R = R^1 = CN

3-Amino-4-phenyl-2-methylthiothiazolium tetrafluoroborate (CLXXVI) reacts with C-nucleophiles to give the methylene bases CLXXVII which cyclize in acid media to pyrazolo[5,1-*b*]thiazoles CLXXVIII [97]. The compounds CLXXIX followed by the pyrazolotriazoles CLXXX were obtained analogously from 4-amino-1-methylthio-3-R-1,2,4-triazoles.



CLXXVI CLXXVII CLXXVIII

R = CN, CO_2Et, CO_2Me

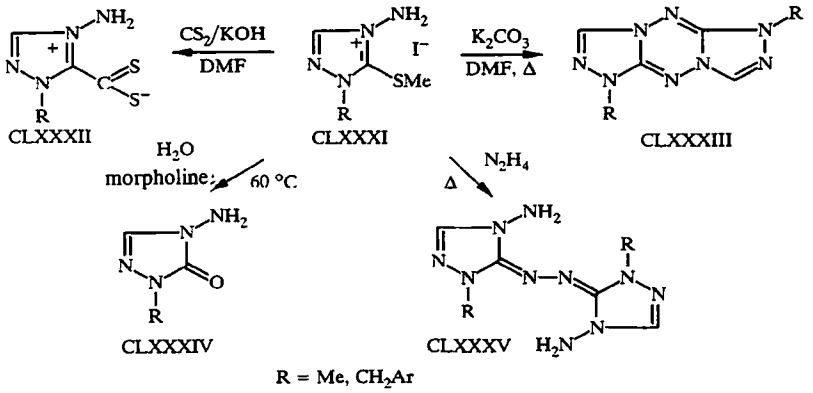


CLXXIX CLXXX

R = CN, CO_2Alk, $CONH_2$, $CONHNH_2$

R^1 = Me, SMe

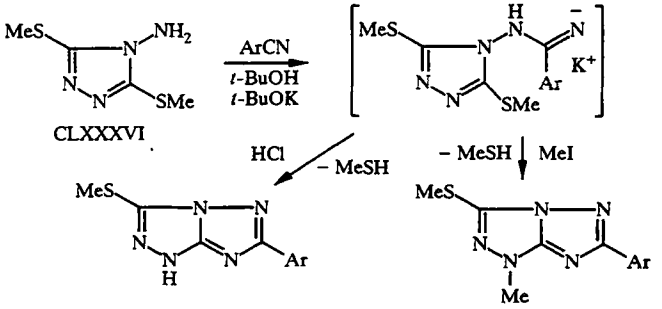
The 1,2,4-triazolium salts CLXXXI reacted with carbon disulfide in the presence of KOH to give the dithiocarbazates CLXXXII. When the same salts were heated in DMF in the presence of K_2CO_3 they underwent cyclodimerization to the tetrazines CLXXXIII [32]. When the salts CLXXXI were heated with water in the presence of morpholine [48] or with hydrazine [32] compounds CLXXXIV and CLXXXV were formed respectively.



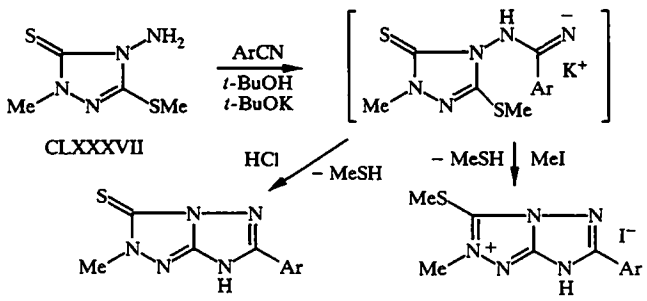
CLXXXII CLXXXI CLXXXIII CLXXXIV CLXXXV

R = Me, CH_2Ar

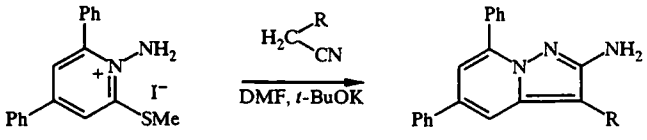
The corresponding 1,2,4-triazolo[4,3-*b*]-1,2-4-triazoles were formed in excellent yields when derivatives of 4-amino-3-methylthio-1,2,4-triazole CLXXXVI or CLXXXVII reacted with aromatic nitriles [148, 149].



CLXXXVI

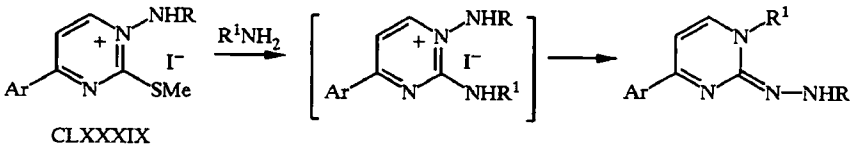


The 1-aminopyridinium salt CXLII reacted with CH acids to give the pyrazolo[1,5-*a*]pyridines CLXXXVIII. The intermediate products of the displacement of the methylthio groups were not isolated in these cases [150, 151].



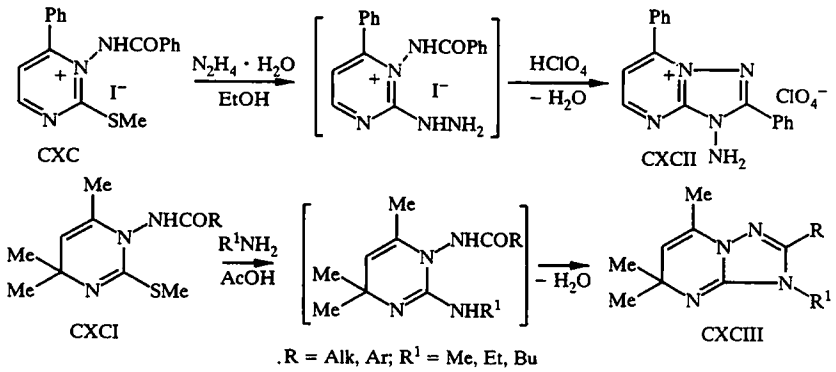
R = CN, COMe, CO_2Me, CO_2Et

Interaction of the pyrimidinium salts CLXXXIX with primary amines or hydrazines was accompanied by the Dimroth rearrangement [152].



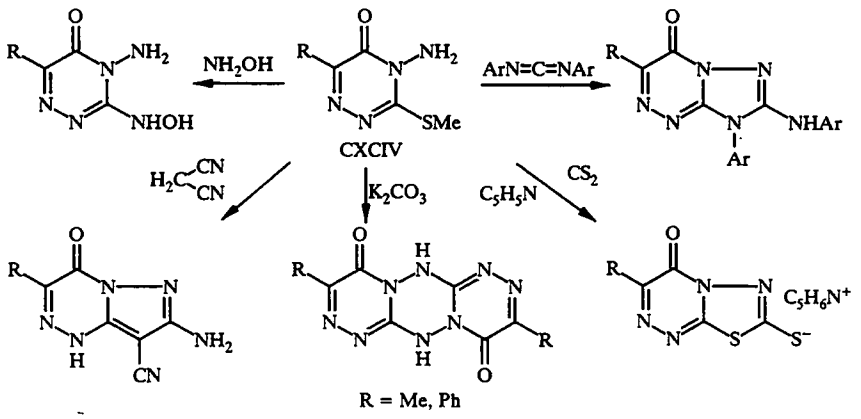
R = CH_2Ph, Ar; R^1 = Alk, NH_2, NHMe

The 1-benzoylamino-2-methylthiopyrimidinium salt CXC [153], like the substituted pyrimidines CXCI [154], reacted with primary amines or hydrazines to give the derivatives of 1,2,4-triazolo[1,5-*a*]pyrimidine CXCII and CXCIII respectively.

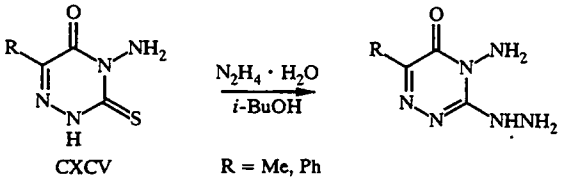


.R = Alk, Ar; R^1 = Me, Et, Bu

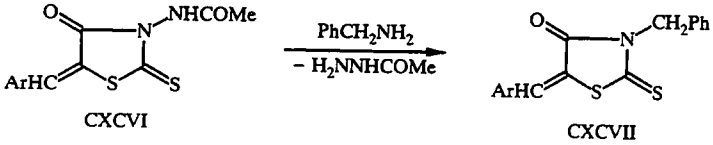
Displacement of the methylthio group is possible in neutral heterocycles. For example, 4-amino-3-methylthio-1,3,4-triazines CXCIV reacted with hydroxylamine [155], dicarbodiimides [127, 156], malonodinitrile [155], carbon disulfide [72, 157] or underwent cyclodimerization [155].



The reaction of the aminothiones CXCV with hydrazine hydrate is an example of nucleophilic displacement of an unsubstituted mercapto group [158].



Heating 3-acetamido-5-arylidenethiazolidine-4-one-2-thiones (CXCVI) with benzylamine gave products of recyclization CXCVII [159].



Apparently the first step in the reaction is nucleophilic attack by the benzylamine nitrogen at position 2 of the thiazole ring.

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