Pergamon

Tetrahedron 55 (1999) 7957–8024

TETRAHEDRON

Tetrahedron report number 495

The Chemistry of Thiocyanic Esters

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Received 20 April 1999

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PII: S0040-4020(99)00386-5

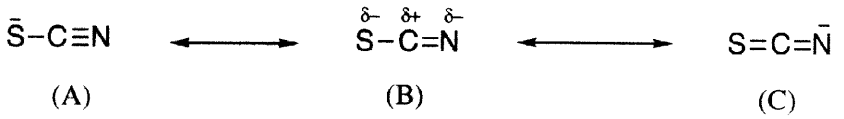
I. Introduction

Much greater attention is being given nowadays to organosulfur compounds. Many of these compounds have found uses which are comparable, and in many cases, superior to their carboxylic analogs. They are used as dyestuffs, lubricants, insecticides, herbicides, disinfectants, germicides and above all, as drugs.[1-17] In spite of these interesting advances, a lot of work remains to be done as several aromatic systems are known but their sulfur analogs remain unknown. The main obstacle in this regard is the scarcity of suitable stable sulfur precursors. Important examples of such precursors are thiocyanic esters which have proven to be valuable tools in the synthesis of a wide variety of organo-sulfur systems. Numerous reports in the literature concerning their applications attest to their growing importance. Although reviews covering the chemistry of cyanates and isothiocyanates,[2-4] the potential biomedical and industrial importance of thiocyanates[5-8] and thiocyanogen addition reactions[9] have appeared, there is no review of the utility of thiocyanic esters in organic synthesis. It is hoped that this survey will provide a useful guide in choosing the right method of preparing the appropriate thiocyanic esters required as precursors in the synthesis of novel organo-sulfur compounds. This review covers the literature up to 1997 and considers the properties, reactions and applications of open-chain thiocyanic esters. Thiocyanogen (**1**), methylene bisthiocyanate (**2**) and alkyl thiocyanic esters **3a-c** are of particular interest in this study due to their frequent appearance in the literature as well as their potential biomedical and industrial importance.

$(SCN)_2$	$CH_2(SCN)_2$	RSCN
1	**2**	**3a**, R = alkyl, aryl **b**, R = $ArCOCH_2$ **c**, R = $R`O_2C\text{-}CH_2$

II. Molecular Structures and Spectral Properties

Organic thiocyanates RSCN are interesting molecules for spectroscopic studies of the electronic properties of the S-C≡N functional group, since no major electronic rearrangement (depending upon the nature of R) is expected to occur in such compounds, whereas the ionic thiocyanate ion $(SCN)^-$ may be considered as the weighted average form (**B**) of the mesomeric structures (**A**) and (**C**).[18-23]



(A) (B) (C)

Infra-red spectroscopic studies[24-37] of thiocyanates showed that the absorption bands of the SCN group lie between 2175 and 2120 cm^{-1} (Tables 1 and 2).

Table 1. Infra-red Absorption Frequencies of the SCN Group in Some Aromatic Compounds.[24-30]

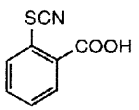
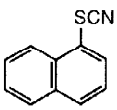
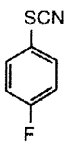
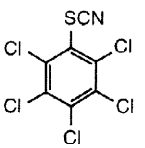
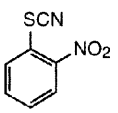
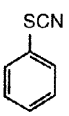
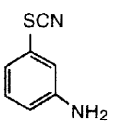
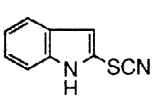
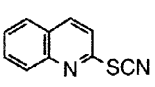
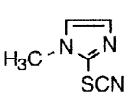
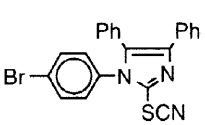
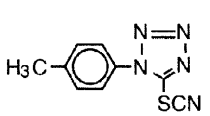
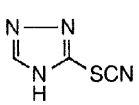
Thiocyanate compd.	ν (cm^{-1})	Thiocyanate compd.	ν (cm^{-1})
	2170 (s)		2156 (m)
	2160 (m)		2156 (m)
	2163 (m)		2158 (s)
	2167 (s)		

Table 2. Infra-red Absorption Frequencies of the SCN Group in Some Heterocyclic Compounds.[24,31-37]

Thiocyanate compd.	ν (cm^{-1})	Thiocyanate compd.	ν (cm^{-1})
	2167 (s)		2163 (s)
	2158 (m)		2175 (w)
	2165 (m)		2178 (w)
	2167 (s)		

Some carbon and nitrogen NMR data have been published for ionic thiocyanates[20,21,38-40] and saturated or aromatic organic thiocyanates.[41-46] From the ^{15}N results (Table 3)[18] it appears that the $(SCN)^-$ ion as well as the SCN functional group are unambiguously identified by their respective chemical shifts which lie in well separated areas, and the high electron density on the nitrogen atom is clearly evident in ^{15}N spectroscopy.[47-50]

Table 3.[18] ^{15}N Chemical Shifts of Vairous Thiocyanato RSCN (**3**) Compounds.

R	^{15}N NMR	R	^{15}N NMR
Me	–105	$-C(Ph)=CH_2$	–97.2
Bu^n	–102.5	$-C(Me)=CHPh$	–97.5
Ph	–97	$-C(SMe)=CHC_5H_{11}$	–97.0[a]
$-CH=CH_2$	–95.6	$-C(Bu^t)=CH_2$	-93.6
$-C(Pr^n)=CH_2$	–93.9	$-C(C_6H_{13})=CH_2$	–93.1

[a] The configuration of the two stereoisomers connot be established unambiguously.

^1H NMR and ^{13}C NMR have also been used to study the chemical shifts of the carbon atoms α and β to the SCN group in the thiocyanic esters (Table 4).[18,51-53] In the vinylic series (Table 5), for pent-1-ene derivatives, the shift of the β-carbon, when compared with that in the alkene, is larger in the thiocyanate. These results suggest that the SCN group has an electron-withdrawing effect on the C=C bond.[21,54,55]

Table 4. ^{13}C and ^1H Chemical Shifts of Vinylic Thiocyanates.

	–SCN				
	$\delta(^{13}C)$	$\delta(^{13}C_\alpha)$	$\delta(^{13}C_\beta)$	$\delta(^1H_\alpha)$	$\delta(^1H_\beta)$
$n\text{-}C_4H_9$	112.1	34.1	32.4	3.01	
$C_\alpha H{=}C_\beta H_2$	108.8	120.3	120.8	6.19	5.73–5.78
$C(Pr^n){=}CH_2$	108.6	135.7	117.3		5.48[a]
$C(Bu^t){=}CH_2$	109.5	146.1	114.0		5.62[a]

[a] For both hydrogens an accidentally equivalent chemical shift is observed.

Table 5.[18] Pent-1-ene Derivatives.

	$\delta(^{13}C_\alpha)$	$\delta(^{13}C_\beta)$	$\delta(^{1}H_\beta)$
$n-C_3H_7-C_\alpha H=C_\beta H_2$	137.6	113.5	4.88–4.94
$n-C_3H_7-C(SCN)=CH_2$	135.7	117.3	5.48

The crystal structure of neutral and protonated methyl thiocyanate[56,57] and phenacyl thiocyanate[58,59] are shown in figures 1 and 2, respectively.

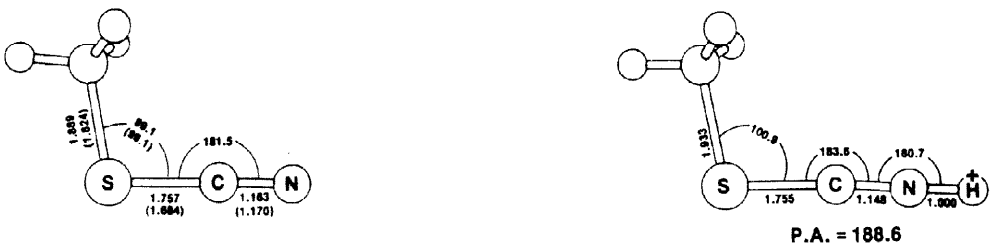


Fig. 1.[56] Calculated structures of neutral and protonated CH_3SCN and their proton affinities. Bond lengths are in Å and proton affinities in Kcal/mol. Experimental structural parameters of CH_3SCN[43] are shown in parentheses.

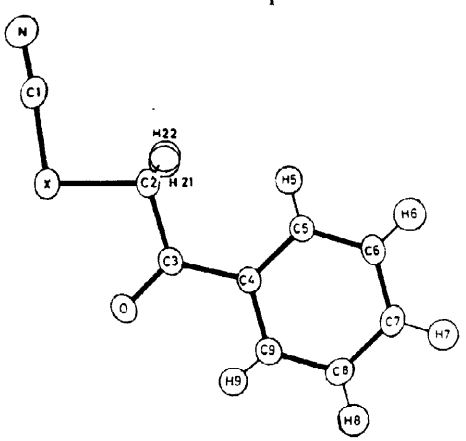
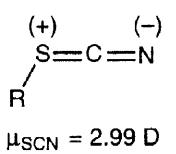


Fig. 2. ORTEP drawing of phenacyl thiocyanate. The sulfur atom, X, the cyano carbon atom, C1, and the methylene carbon atom, C2, are in the plane of the paper.

From the dipole moments of aromatic thiocyanates, the group moments of the triatomic group is estimated as μ_{SCN} = 2.99 D; showing a contribution from a polar structure. No appreciable difference is found between the moments of aromatic and aliphatic compounds.[60,61]



μ_{SCN} = 2.99 D

III. Methods of Preparation

A. General Methods

Several methods have been reported for the synthesis of thiocyanic esters, most of these involve substitution with thiocyanic acid or its salts. Sodium, potassium or ammonium thiocyanate reacts with an organic halide to give an organic thiocyanate.[62-71]

$$RX + KSCN \longrightarrow RSCN + KX$$

i. Preparation of Phenacyl Thiocyanate

The treatment of a phenacyl halide with an alkali metal thiocyanate gave phenacyl thiocyanate, useful in the control of microorganisms such as fungi and bacteria, in 95% yield.[72-77]

$$PhCOCH_2X + KSCN \longrightarrow PhCOCH_2SCN + KX$$

ii. Preparation of Methylene Bisthiocyanate (MBT)

Methylene bisthiocyanate is important because of its antifungal properties. Many patents and papers[76-84] have described its preparation from CH_2Br_2 or CH_2I_2 and an alkali thiocyanate in water in 94% yield.

$$CH_2X_2 + 2\,KSCN \xrightarrow[75^\circ C]{H_2O} CH_2(SCN)_2 + 2\,KX$$

B. Preparation of Thiocyanogen

Free thiocyanogen was first obtained by Söderbäck[85] who reacted iodine with an ethereal suspension of silver thiocyanate.

$$2\,AgSCN + I_2 \rightleftharpoons 2\,AgI + (SCN)_2$$

Like the halogens, thiocyanogen may also be prepared by electrolysis of thiocyanates.[86-91] Interaction of lead tetracetate and thiocyanic acid in ethereal solution presumably takes place in accordance with the following equations.

$$Pb(AcO)_4 + 4\,HSCN \longrightarrow Pb(SCN)_4 + 4\,AcOH$$

$$Pb(SCN)_4 \longrightarrow Pb(SCN)_2 + (SCN)_2$$

Welcher and Cutrufello[92] report a high yielding procedure for the preparation of thiocyanogen by passing gaseous chlorine into a solution of sodium thiocyanate in aqueous toluene at 2-8°C.

C. Direct Replacement of a Hydrogen Atom by a Thiocyanate Group

The direct replacement of a hydrogen atom by a thiocyano group through the use of thiocyanogen, $(SCN)_2$, is commonly termed thiocyanation.

$$RH + (SCN)_2 \longrightarrow RSCN + HSCN$$

This replacement reaction is limited practically to aromatic amines[93-100] and phenols,[101-105] although a few reactive aromatic hydrocarbons such as naphthalenes and anthracenes can also be thiocyanated.[106-109]

$$ArOH + (SCN)_2 \longrightarrow ArOSCN + HSCN$$

$$ArNH_2 + (SCN)_2 \longrightarrow ArN\text{–}SCN + HSCN$$

Thiocyanogen takes part in addition reactions with olefinic and acetylenic systems.[110-117]

$$R_2C{=}CR_2 + (SCN)_2 \longrightarrow R_2C(SCN)\text{–}CR_2(SCN)$$

Thiocyanogen can replace the heavy metal atom of certain organometallic compouds.[118,119]

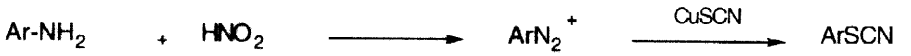
$$R_2Zn + 2\,(SCN)_2 \longrightarrow 2\,RSCN + Zn(SCN)_2$$

$$Ar_2Hg + (SCN)_2 \longrightarrow ArSCN + ArHgSCN$$

$$Ar_3Sb + (SCN)_2 \longrightarrow Ar_3Sb(SCN)_2$$

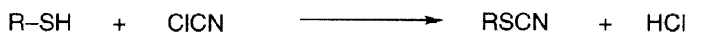
D. Sandmeyer Reaction

This well-known adaptation of the Sandmeyer reaction has been used quite successfully in preparing aromatic thiocyanates. The major restriction is that the initial amine must be able to withstand diazotization without affecting other functional groups which may be present.[120]



E. Condensation of Cyanogen Chloride with Mercaptans

The preparation of alkyl thiocyanates by the reaction of cyanogen chloride with a mercaptan has been used.[121-123]



IV. Chemical Reactions

The combination of a sulfur atom with a cyano group allows the wide use of thiocyanic esters for cyclization reactions proceeding under mild conditions.

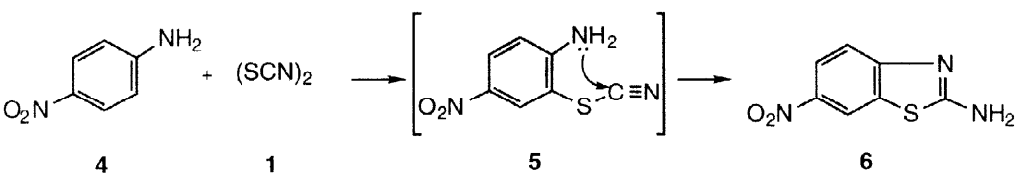
A. Reactions Involving the C≡N Group

Thiocyanates resemble cyanides in undergoing addition reactions to the triple bond which is polarized in the sense

1. Interaction with Amines

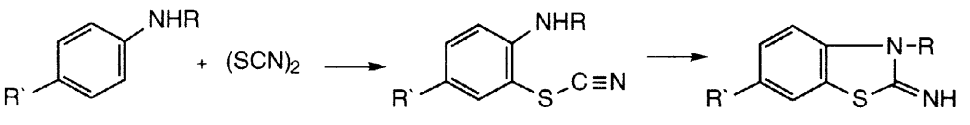
1.1. Interaction of Thiocyanogen with Amines

One of the most successful methods of introducing sulfur into organic compounds is the application of Kaufmann's thiocyanation of aromatic amines. Kaufmann[95,124,125] found that aromatic amines could be thiocyanated at the 4-position with thiocyanogen which is liberated *in situ* by the action of chlorine or bromine on inorganic thiocyanates at low temperatures. 4-Thiocyanoaniline was obtained in this manner from aniline.[95] If the *para* position is blocked, thiocyanation takes place at the ortho-carbon.[124] *p*-Nitroaniline, for example, reacts with ammonium thiocyanate and bromine in glacial acetic acid to yield 2-amino-6-nitrothiazole **6**.[125,126]



4 1 5 6

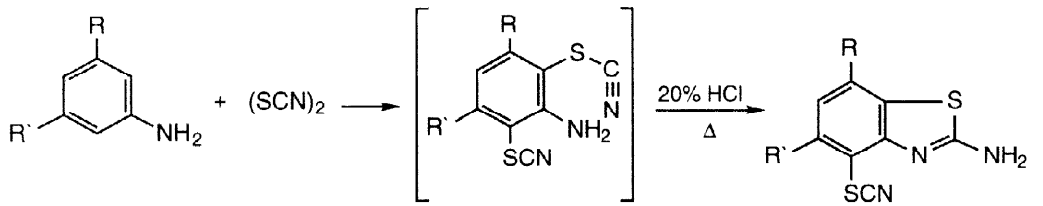
The ease of formation of the thiazole derivative varies with the substituents in the primary products; thiocyanophenetidine rearranges spontaneously, whereas 1-thiocyano-2-naphthylamine rearranges when warmed with ethanolic hydrogen chloride.[99] The ortho-thiocyano derivatives often can be isolated if a low temperature is maintained and if acid is excluded.[10,127-132] The *ortho*-thiocyano derivatives of monoalkylamines rearrange readily into 2-iminobenzothiazolines **9**.[133]



7 **1** **8** **9**

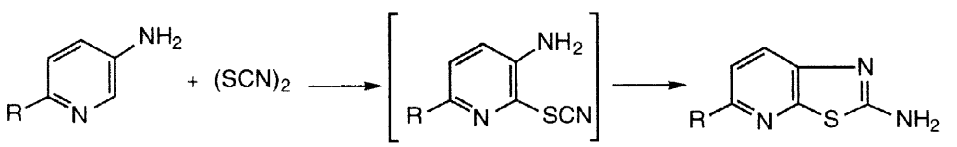
N,N-Dimethylaniline gives N,N-dimethyl-4-thiocyanatoaniline (92% yield)[134,135] and N,N-dimethyl-*p*-toluidine gives N,N-dimethyl-2-thiocyano-*p*-toluidine (21% yield).[134] Diphenylamine and triphenylamine are converted into dithiocyano derivatives, each with two of the phenyl rings substituted in the para position.[136]

An important series of antiparasitic thiocyanatobenzothiazoles **12** can be obtained by treating the appropriate aniline derivative with thiocyanogen.[137]



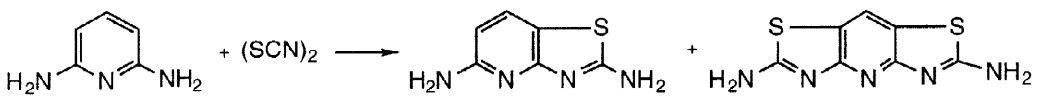
10 **1** **11** **12**

Owing to the directive influence of the ring nitrogen in competition with the amino group, the position of attack by nascent thiocyanogen will depend on the dominating group. 3-Amino-pyridines **13** bearing electron-releasing groups at the 6-position were converted in this way, like aromatic amines, to 2-aminothiazolo[5,4-b]pyridines **15** *via* the 2-thiocyano derivative **14**.[138-140]



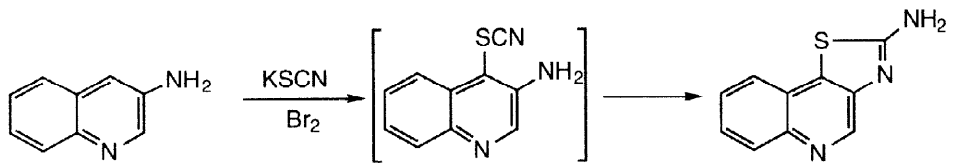
13 **1** **14** **15**

The thiocyanation of 2,6-diaminopyridine was investigated by three groups of workers whose results led to contradictions on the structures, melting points and purity of the products. Yamamoto, Takahashi and Ueda[141-143] obtained a product which they formulated as 2,5-diaminothiazolo[4,5-b]pyridine **17**. Bernstein[144] confirmed these results and obtained, in addition, 2,6-diamino-bisthiazolo[4,5-b:5`,4`-e]pyridine **18**, if two equivalents of the thiocyanating agent were used. Maggiolo,[145] on the other hand, reported that the bisthiazolopyridine compound **18**, is the only product of the reaction.



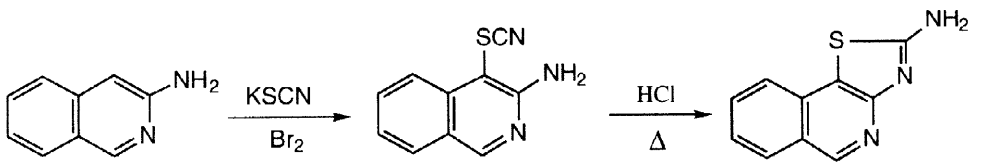
16 **1** **17** **18**

Quinoline,[145] isoquinoline,[146-148] pyrimidine,[149,150] and thiazole[151,152] were successfully thiocyanated with bromine and inorganic thiocyanates in glacial acetic acid. Maggiolo[145] reported the conversion of 3-aminoquinoline **19** to 2-aminothiazolo[4,5-d]quinoline **21** but no physical data nor chemical evidence was presented in favour of the cyclized structure over the thiocyano derivative, **20**, invoked as an intermediate.



19 **20** **21**

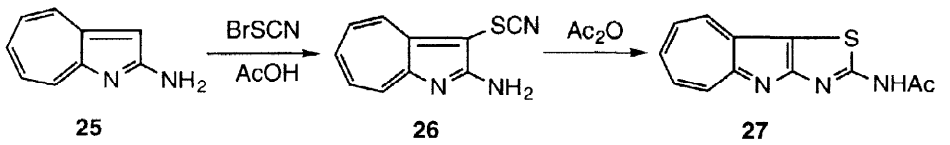
3-Aminoisoquinoline **22**, on the other hand, gave the 4-thiocyano derivative **23** in 56% yield. Cyclization of the latter was achieved by refluxing in aqueous alcoholic HCl.[147]



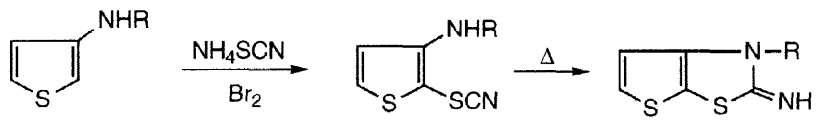
22 **23** **24**

The reaction of 2-amino-1-azaazulene **25** with thiocyanogen bromide, prepared by adding bromine to a solution of potassium thiocyanate in acetic acid, afforded 2-amino-3-thiocyanato-1-

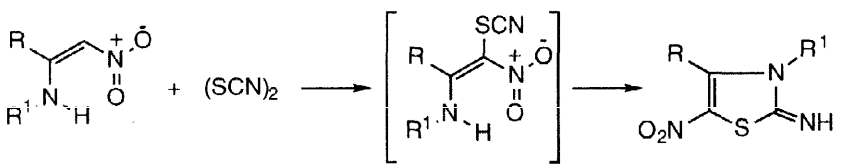
azaazulene **26.** The latter was cyclized by the action of acetic anhydride to give the pyrrolo[2,3-d]-thiazole derivatives **27**.[153]



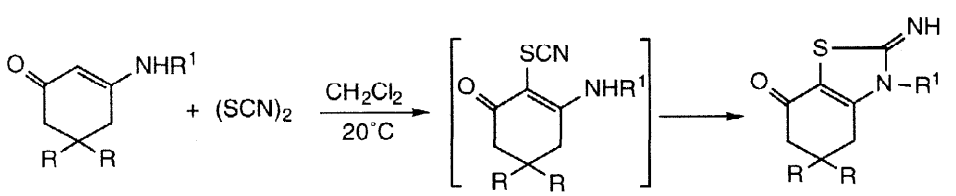
The thieno[3,2-d]thiazole derivatives **30** can be prepared by the thiocyanation of aminothiophenes **28** followed by thermal cyclization.[154-156]



Thiazoline derivatives **33** can be prepared by the reaction of β-nitroenamines **31** with thiocyanogen at 0°C.[157,158]

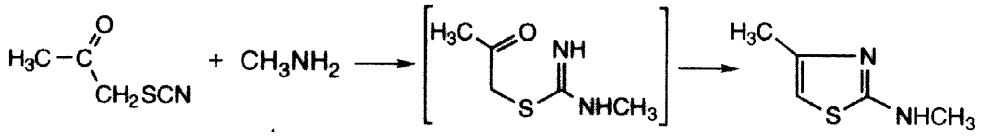


Similarly, the reaction of cyclic α,β-unsaturated β-aminoketones **34** with $(SCN)_2$ at 20°C gives the oxotetrahydrobenzothiazole **36** *via* the intermediate **35**.[159]



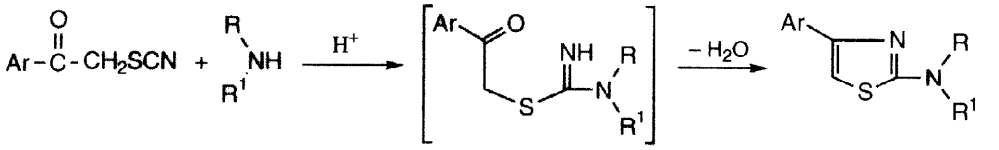
1.2. Interaction of α-Functionalized Thiocyanic Esters with Amines

The action of amines on α-thiocyanatoacetone (**37**) in ether solution gives 4-methyl-2-aminothiazole.[162] For example, methylamine gives in a first step *S*-acetonyl-N-methylisothiourea **38** in 80% yield, which can be cyclized by heating with dilute hydrochloric acid to afford the 4-methyl-2-methylaminothiazole derivative **39**.[160,161]



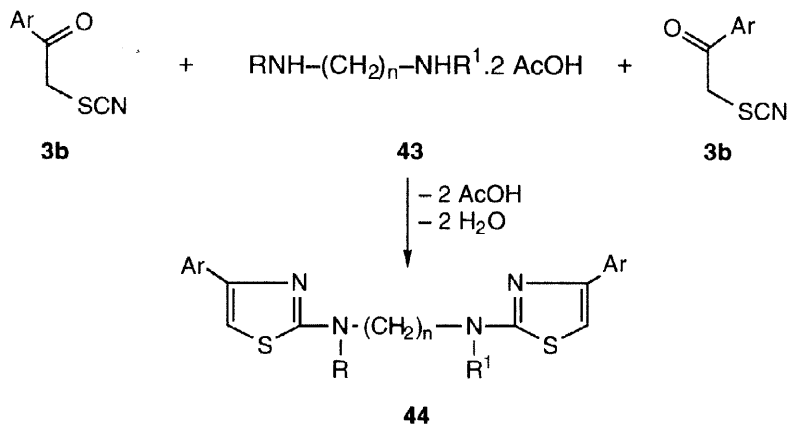
37 38 39

α-Thiocyanatoacetophenones **3b** react with amines in acetic acid with the formation of 1:1 cyclocondensation products **42** *via* intermediates such as **41**.[162-166]



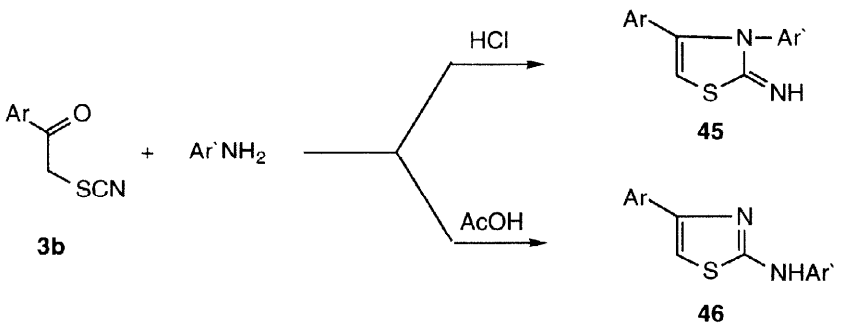
3b 40 41 42

N,N`-Bis(thiazol-2-yl)diaminoalkanes **44** are obtained from the reaction of α-thiocyanatoacetophenones **3b** with N,N`-dialkyldiaminoalkanes **43**.[166]



3b 43 3b 44

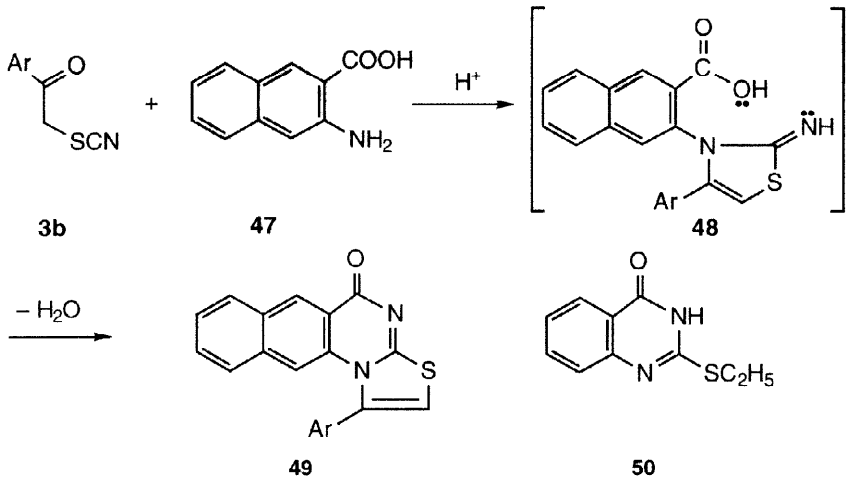
Depending on the reaction medium, α-thiocyanatoacetophenones **3b** react with aromatic amines to give either **45** or **46**.[163,167-169]



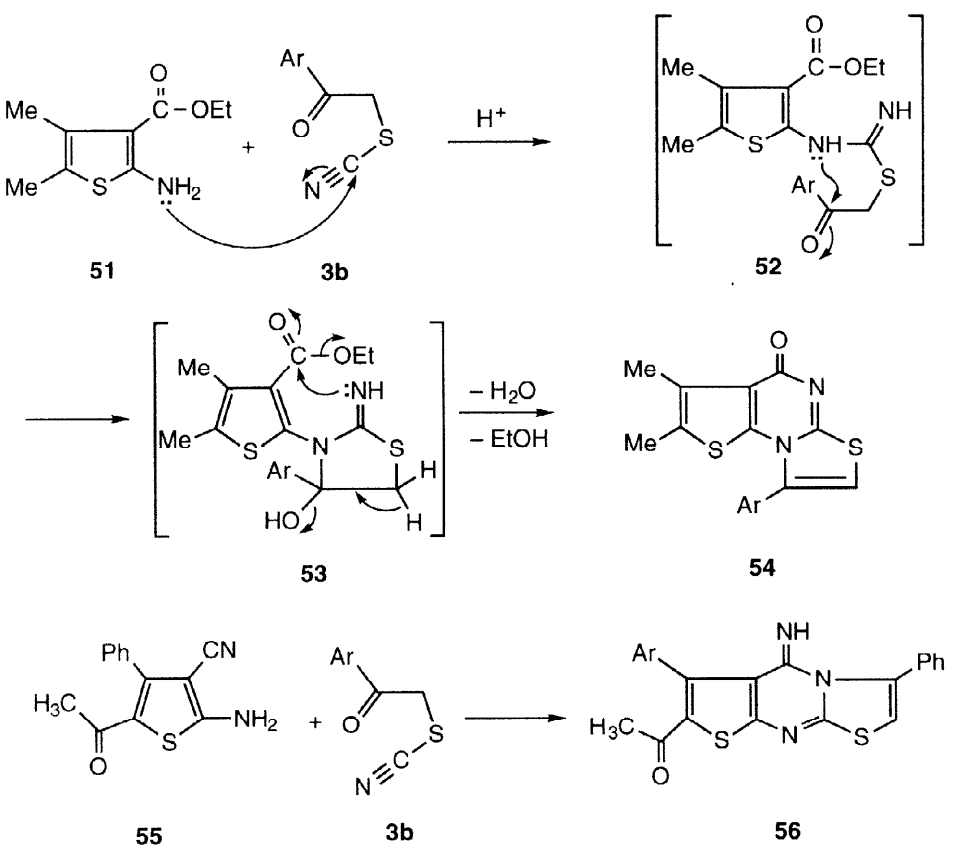
3b 45 46

The benzo[g]thiazolo[3,2-a]quinazoline **49** can be obtained *via* the reaction of 3-amino-2-naphthoic acid hydrochloride **47** with α-thiocyanoketones **3b**. The reaction proceeds *via* the

adduct **48**.[170] Similarly 2-ethylmercapto-4(3H)quinazoline **50** was synthesized *via* the reaction of anthranilic acid with ethyl thiocyanate.[170]

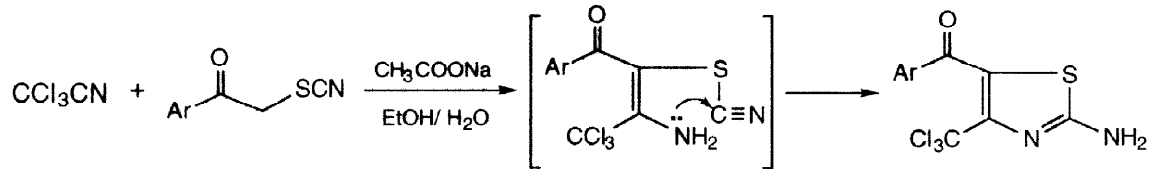


Condensation of **3b** with ethyl thiophene-3-carboxylate **51** furnished thiazolothienopyrimidines **54**. The reaction mechanism is given in Scheme 1.[171-173] Similarly, 2-aminothiophene-3-carbonitrile derivative **55** reacted with **3b** in refluxing ethanol containing HCl to afford the 1:1 adduct **56.**[174]



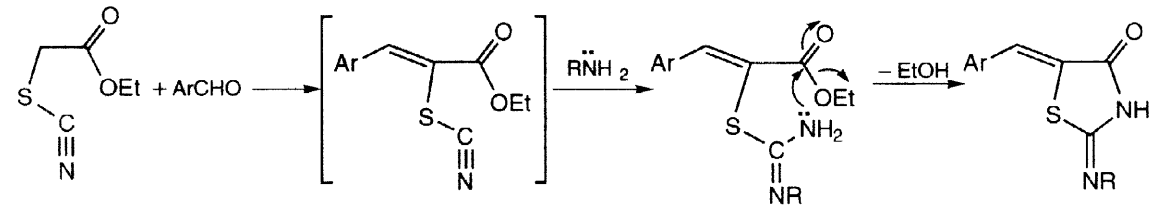
Scheme 1

The reaction of β-keto thiocyanates **3b** with trichloroacetonitrile (TCA) (**57**) in the presence of sodium acetate gives aroylthiazole derivatives **59** *via* the intermediate **58**.[175,176]



57 **3b** **58** **59**

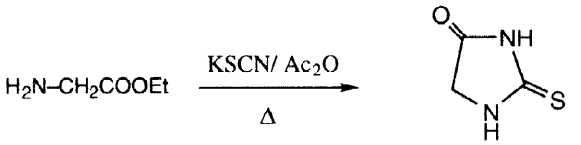
Treatment of ethyl thiocyanoacetate **3c** with aldehydes and an amine or ammonium acetate yield 5-arylidene-2-imino-4-thiazolidinones **63**. The reaction was initiated by condensation of **3c** with the aldehyde to give the intermediate **61**, followed by the addition of amines and cyclization.[177]



3c **60** **61** **62** **63**

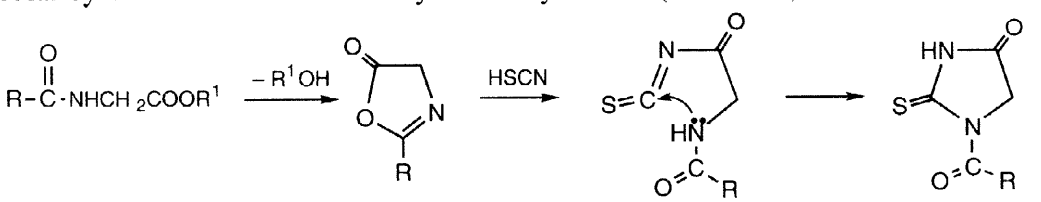
1.3. Interaction of Thiocyanate Anion with Amines

It was reported by Klason,[178] and later confirmed by Johnson,[179] that 2-thiohydantoin **65** is formed when the hydrochloride of glycine ethyl ester **64** and potassium thiocyanate are heated together at 140-150°C, in presence of acetic anhyride.[180]



64 **65**

The mechanism suggested by Johnson and Scott involved the intermediate formation of the cyclic anhydride of the N-acylamino acid followed by the acyl isothiocyanate, which underwent intramolecular cyclisation to form the 1-acyl-2-thiohydantoin (Scheme 2).[181]



66 **67** **68** **69**

Scheme 2

This type of hydantoin synthesis, involving the reaction of ammonium thiocyanate in acetic anhydride solution, has been applied successfully not only to a series of α-amino acids and their N-acyl derivatives (Table 6)[180,182-199] but also to certain peptides.[200]

Table 6.[180,182-199] Various Amino Acids and Derivatives Used in the Reaction with KSCN.

Amino acids	References	Amino acids	References
α-Aminoalanine	182, 183-185	Asparagine	185, 189
β-aminoalanine	186	β-Cyclohexylalanine	183
α-Amino-*n*-butyric acid	183	Cysteine	190
2- Aminoheptanoic acid	183	Glutamic acid	191
1-Aminohexahydrobenzoic acid	187	Glutathione	192
2-Aminooctanoic acid	183	Glycine	193-197
α-Amino-α-phenylacetic acid	188	Hippuric acid	185, 198
α-Amino-*n*-valeric acid	183	Leucine	183
Pyrrolidonecarboxylic acid	185, 199	Isoleucine	183
Tyrosine	185	Methionine	183
Valine	183	Phenylalanine	183, 185

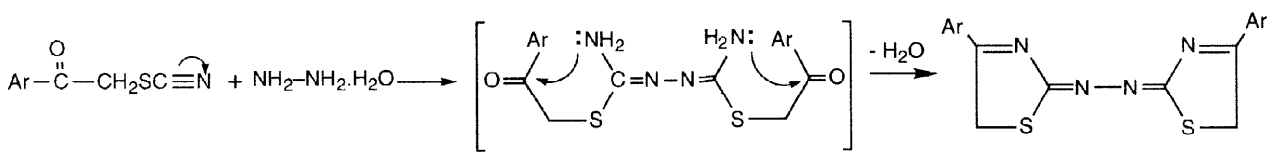
2. Interaction of Thiocyanogen with Hydrazones

N,N-Diphenylhydrazines **70** react with thiocyanogen to give N,N-bis-(*p*-thiocyanophenyl)-hydrazines **71** in 65-75% yields.[93,201-204]

$$(C_6H_5)_2N\text{–}NHR \quad + \; 2\,(SCN)_2 \longrightarrow (p\text{–}NCSC_6H_4)_2N\text{–}NHR \quad + \; 2\,HSCN$$

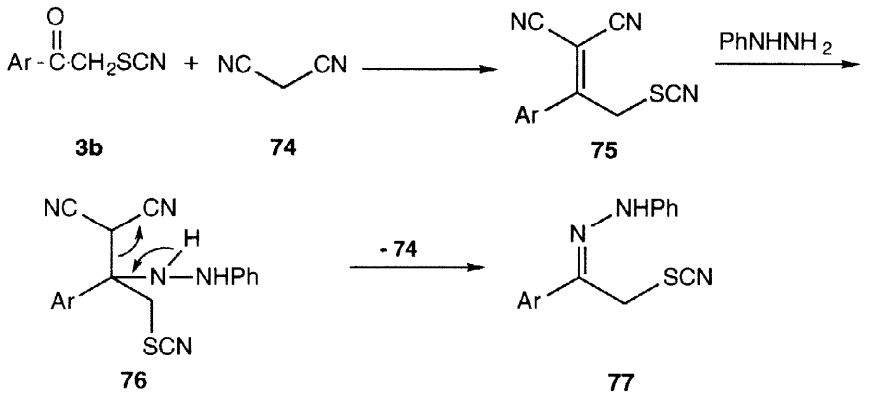
70 **71**

α–Thiocyanatoacetophenones **3b** react with hydrazine hydrate to yield bis(4-aryl-*S*-hydro-thiazol -2-ylidene) **73**. The reaction is assumed to proceed *via* amidines **72**.[205]

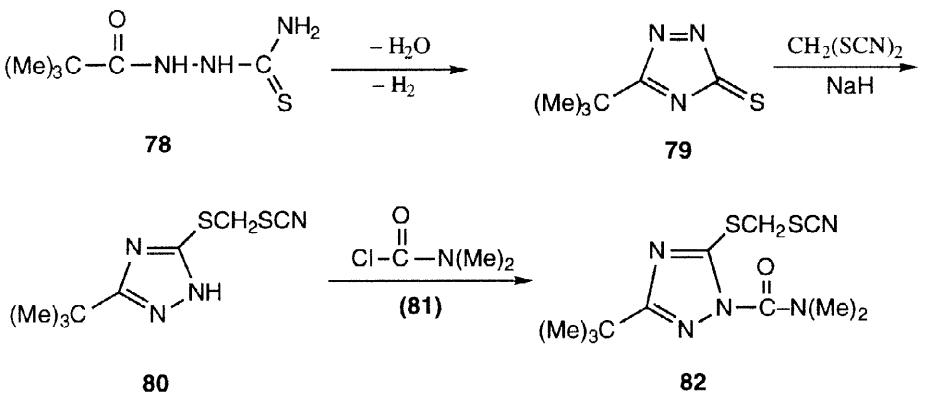


3b **72** **73**

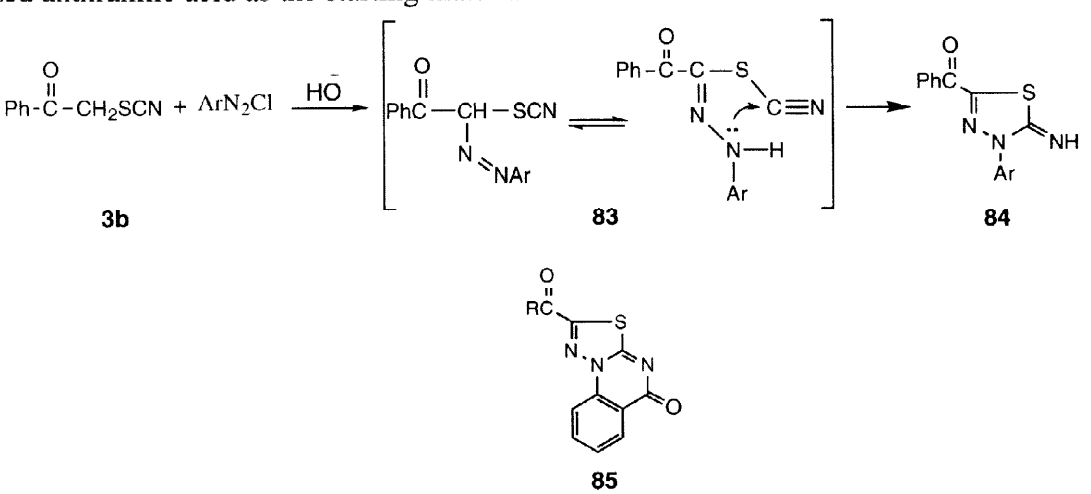
Malononitrile **74** reacts with **3b** to give the Knoevenagel condensate **75** which, in turn, reacts with phenylhydrazine to yield the hydrazone **77**.[205,206]



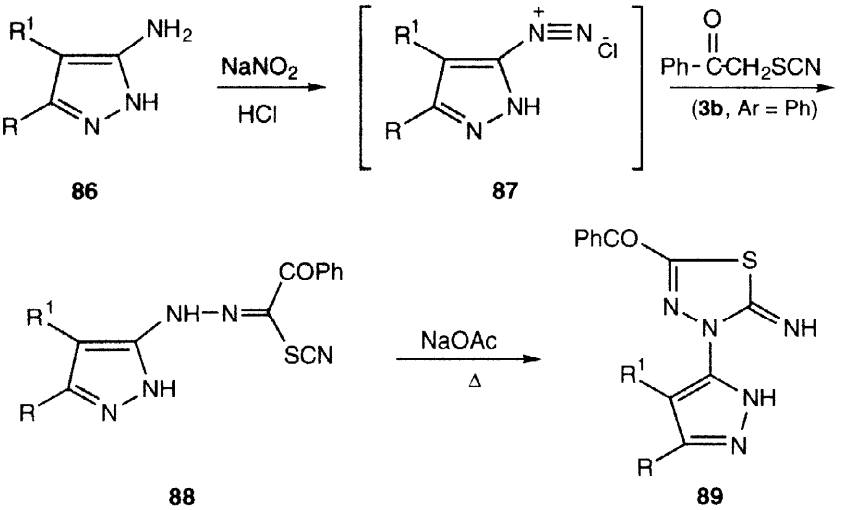
1-Dimethylcarbamoyl-1,2,4-triazole **82**, an important insecticide, was obtained by cyclizing **78** to give triazole-3-thione **79** which was treated with NaH and methylene bisthiocyanate (**2**) to give **80**. The latter condensed with chloro-N,N-dimethylformamide (**81**) to give **82**.[207]



Phenacyl thiocyanate (**3b**, Ar= Ph) couples with aryldiazonium salts in sodium acetate buffered solution of ethanol to give the hydrazones **83**. The latter cyclize readily in the reaction medium to give the thiadiazolines **84**.[208-210] Thiadiazolo[2,3-b]quinazolines **85** were prepared by using diazotized anthranilic acid as the starting material.[211-214]

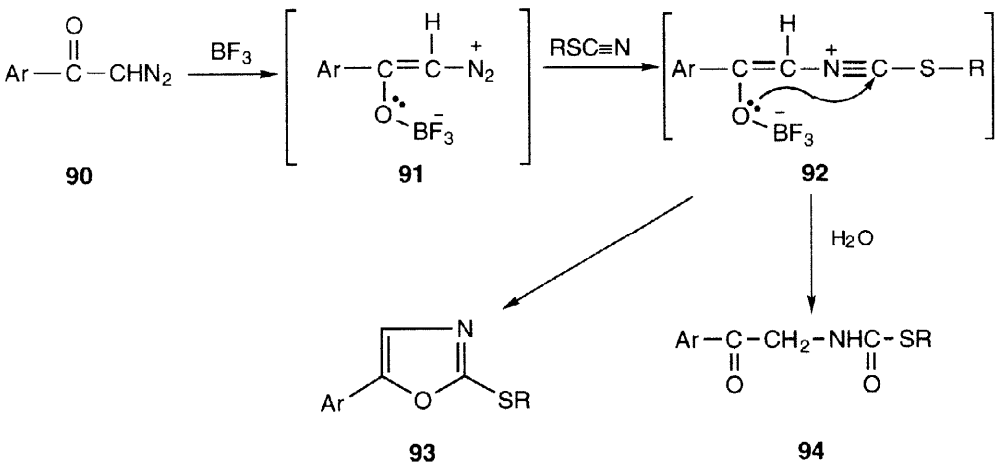


Similarly, the reaction of diazotized aminopyrazoles **87** with phenacyl thiocyanate (**3b**; Ar = Ph) yields the corresponding hydrazone derivatives **88**.[215-217] The latter thermally cyclized in the presence of a weak base to afford **89**.[218]



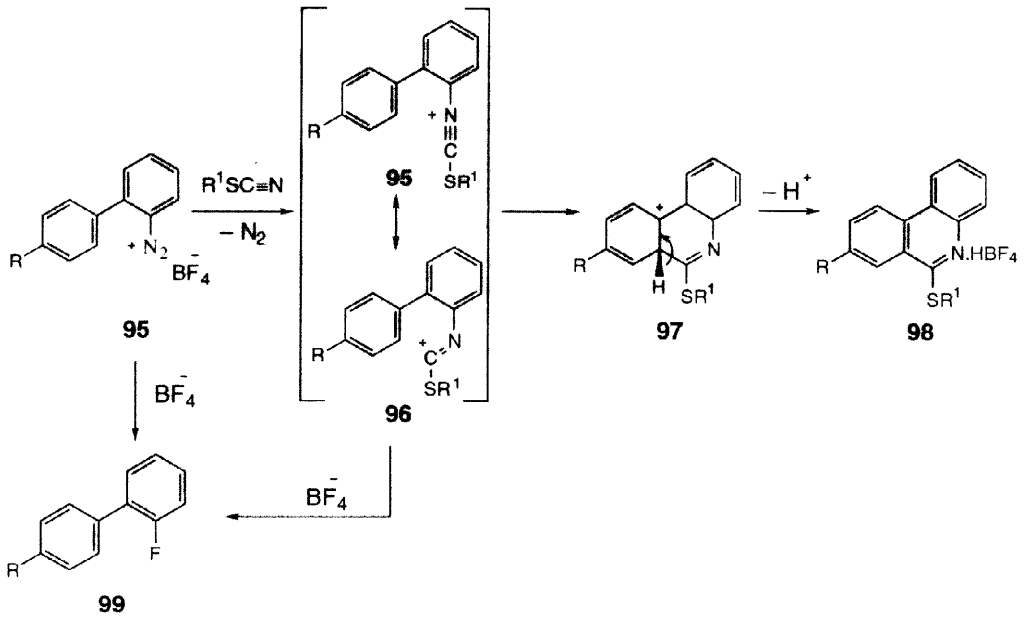
86 **87** **88** **89**

The BF_3-catalyzed decomposition of *p*-substituted-α-diazoacetophenones **90** with excess RSCN gave the 5-aryloxazoles **93**. The reaction, initiated by the attack of BF_3 on the carbonyl oxygen of the diazo ketone to afford the diazonium betaine intermediate **91**, gave the betaine **92** which was attacked at the nitrile nitrogen to extrude nitrogen gas. Cyclization of the betaine produced oxazoles **93**. However, reaction of **92** with water give thiocarbamate **94**.[219]

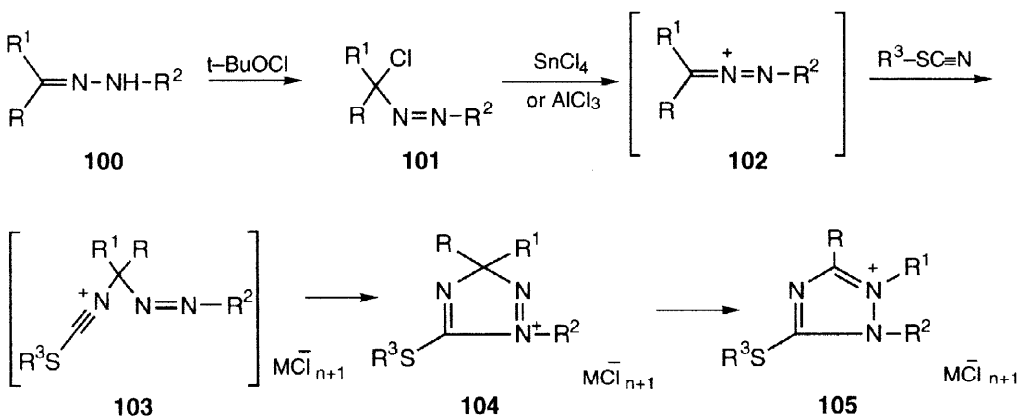


90 **91** **92** **93** **94**

The thermal decomposition of the 2-biphenyldiazonium tetrafluoroborates **95** in anhydrous aliphatic or aromatic thiocyanates leads to the formation of 6-substituted phenanthridines **98** and **99**.[220,221]



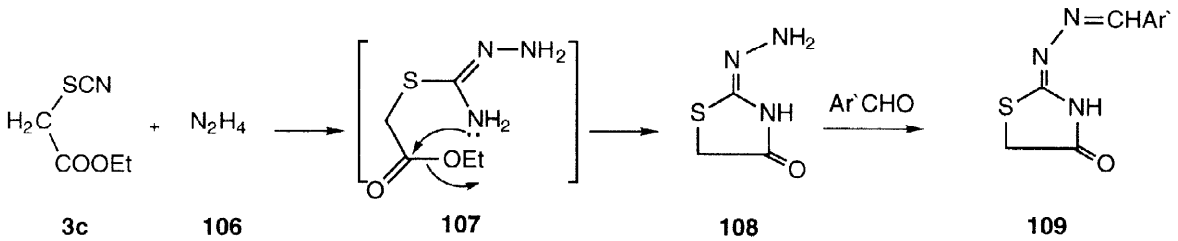
The synthesis of 1,2,4-triazolium salts from the reaction of 1-aza-2-azoniaallene salts with nitriles in the presence of antimony(V) chloride or aluminium (III) chloride was first decribed by Conde et al.,[222] Scheme 3 shows the mechanism proposed by Jochims[223] and Amer.[224] In the first step the aryl- and alkylhydrazones **100** of alkylketones are transformed into 1-chloroalkylazo compounds **101** with tert-butylhypochlorite. Compounds **101** react with Lewis acids to give 1-aza-2-azoniaallene salts **102** as reactive intermediates, which are transformed into 3H-1,2,4-triazolium salts **104** by thiocyanates.[222-224]



Scheme 3

A convenient synthesis of 2-arylidenehydrazono-4-thiazolidinone **109** from ethyl thiocyanoacetate **3c**, and hydrazine hydrate has been reported.[225] Presumably, the reaction proceeds *via* the amidrazone intermediate **107** which cyclizes to give **108.** The condensation of **108** with the

aromatic aldehyde affords the 5-arylidene derivative **109**. The reaction of **109** with ammonium acetate and an aromatic aldehyde gives 5-arylidene-2-imino-4-thiazolidinones.[225]

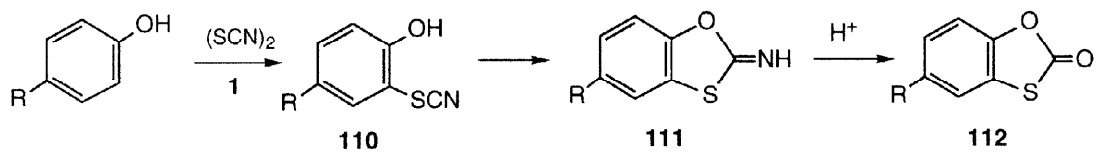


3c **106** **107** **108** **109**

3. Interaction of Thiocyanogen with Hydroxy and Thiol Compounds

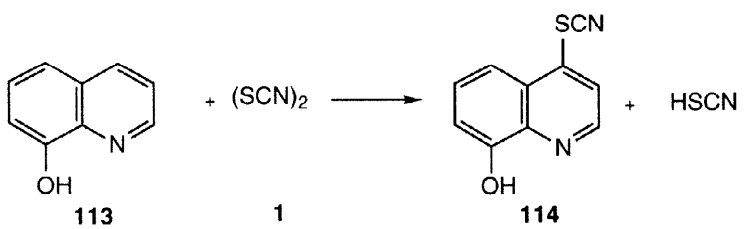
Phenol can be thiocyanated with thiocyanogen to give 4-thiocyanophenol in 69% yield;[101,134] *o*-cresol into 4-thiocyano-*ortho*-cresol in 90% yield,[103] thymol into 4-thiocyanothymol in 95% yield,[103] and α-naphthol into 4-thiocyano-1-naphthol in 83% yield.[104] The point of attack is again the *para* position if free as in amines, or the *ortho* position when the former is blocked, as in the reaction of *p*-cresol and β-naphthol (100% yield).[104]

Ortho-thiocyanophenols rearrange similarly to the corresponding amines to yield 2-imino-benzothioxazoles.[226] The imino group is readily hydrolyzed to a keto group with acid.



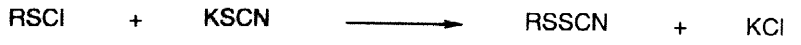
110 **111** **112**

Both 2-hydroxyquinoline and 8-hydroxyquinoline react in the 4-position, *para* to the nitrogen atom.[93]

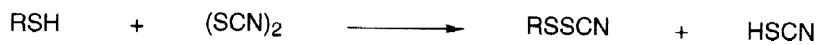


113 **1** **114**

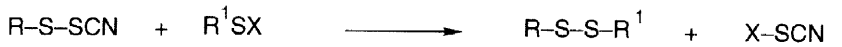
The original studies of the sulfenyl thiocyanates (RSSCN) are recorded in three papers by Lecher and coworkers.[110,227,228] It was suggested that the sulfenyl thiocyanates may be prepared in two ways: **a**) by reaction of a sulfenyl halide with a metal thiocyanate,



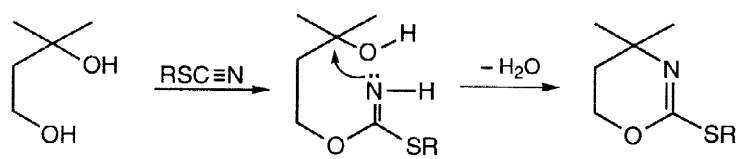
and **b**) by reaction of a thiophenol or mercaptan with thiocyanogen.



The sulfenyl thiocyanate method of disulfide synthesis has been applied by Hiskey et al.,[229-233] to prepare a series of cystine peptides containing various amino acid residues.

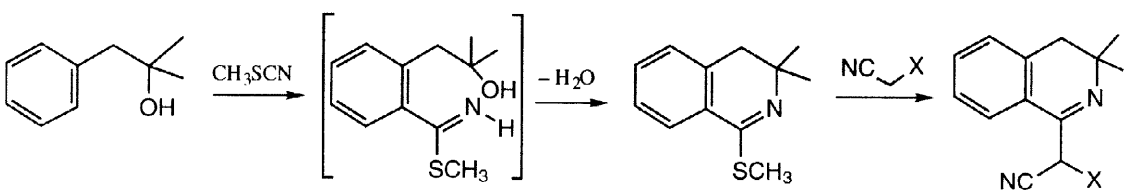


In the presence of concentrated sulfuric acid, 2-methyl-2,4-butanediol **115** reacts with alkyl thiocyanates to give the 1,3-oxazines **117**.[234-236]



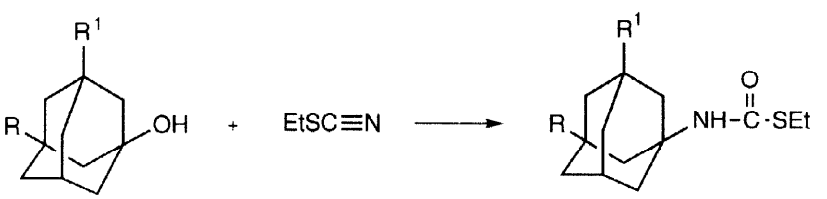
115 **116** **117**

1-Phenyl-2-methylpropan-2-ol **118** reacts exclusively with methyl thiocyanate to give **120**.[237] The latter reacts further with active methylene reagents to give **121**.[237]



118 **119** **120** **121**

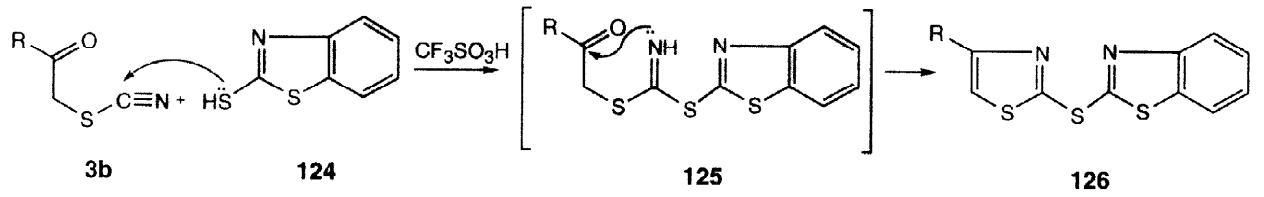
Adamantylthiocarbamates **123** can be prepared in 88% yield by the reaction of ethyl thiocyanate with adamantol derivatives **122** in concentrated H_2SO_4.[238]



122 **123**

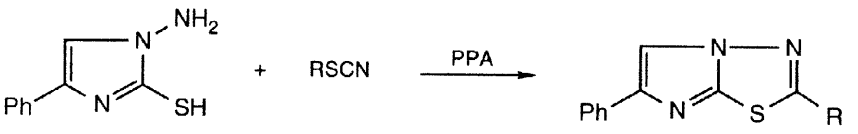
A general method for the synthesis of a wide variety of 2-(4-arylthiazol-2-yl)thiobenzothiazoles **126** from α-thiocyanatoketones **3b** was reported by Teller and Dehne,[239] The reaction

involves the addition of the mercapto group in **124** to the thiocyanate group in **3b** and subsequent cyclization of the adduct **125**.[239]



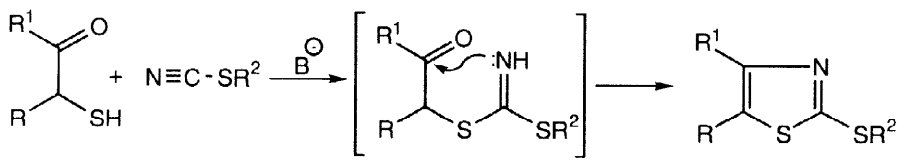
3b **124** **125** **126**

The cyclocondensation of aminoimidazolethiol **127** with thiocyanates in polyphosphoric acid gave 2-(alkylthio)-6-phenylimidazo[2,1-b]-1,3,4-thiadiazoles **128**.[240]



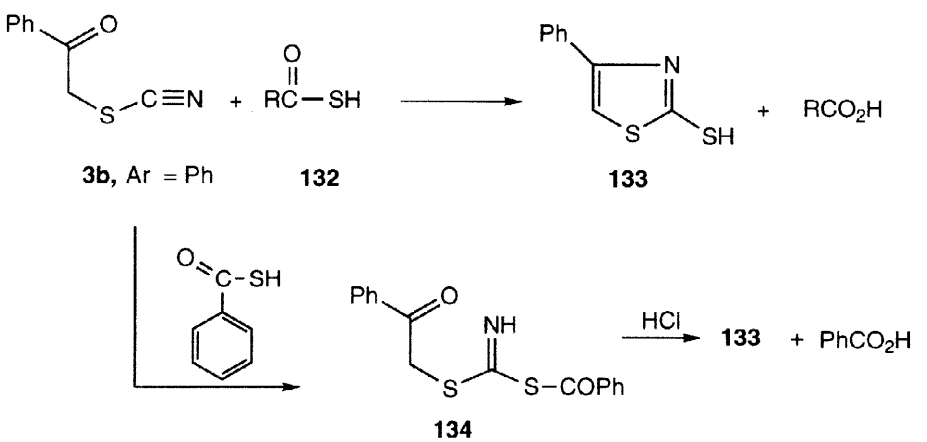
127 **128**

Similarly, α-mercaptoketones **129** and thiocyanates react in the presence of secondary amines or sodium cyanide to give thiazolyl sulfides **131** *via* **130**.[241]



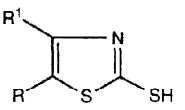
129 **130** **131**

Thioacids **132** react with α-thiocyanatoacetophenone (**3b**, Ar = Ph) to produce 2-mercapto-4-phenylthiazole **133**. With thiobenzoic acid, an acyclic intermediate **134** has been isolated which can be cyclized by heating with dilute acid (Table 7).[242,243]



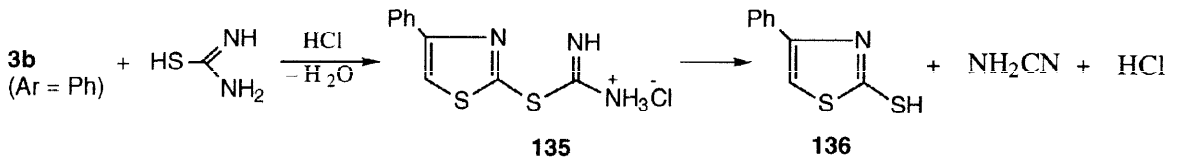
3b, Ar = Ph **132** **133** **134** **133** + $PhCO_2H$

Table 7. 2-Mercaptothiazole Derivatives From α-Thiocyanatoketones and Labile Sulfur.



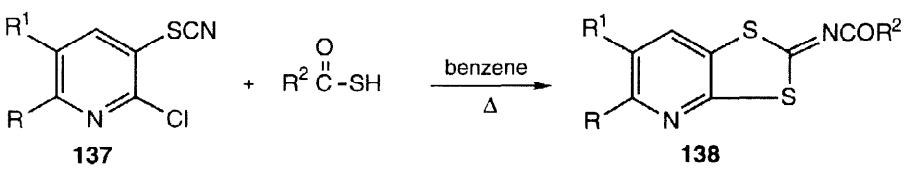
R	R^1	Yield, %	Ref.
H	Me	-	244
H	C_6H_5	79	245
H	p-$CH_3C_6H_4$	85	245
H	p-ClC_6H_4	60	245
H	p-BrC_6H_4	39	245
H	p-$MeOC_6H_4$	75	245
Me	Me	-	244

Alternative methods involving other sulfur compounds such as thiourea, ammonium dithiocarbamate or hydrogen sulfide also lead of course to 2-mercaptothiazoles. Thus thiourea has been used in the synthesis of 4,5-dimethyl- and 4-aryl-2-mercaptothiazoles.[244,245]



135 136

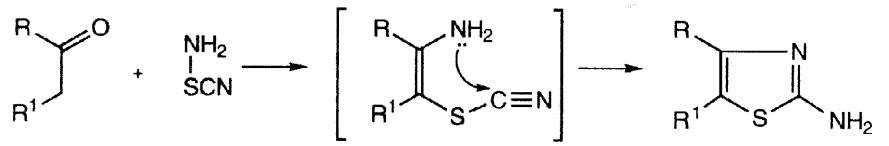
Neighbouring chloro and thiocyanate groups react on heating with a thiocarboxylic acid[246] to form a dithiole ring **138**.



137 138

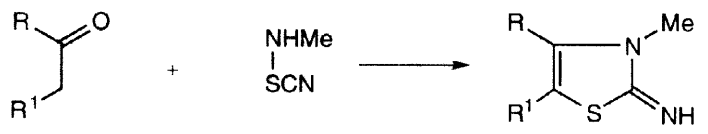
4. Interaction with Active Methylenes and Methylketones

2-Aminothiazoles **142** can be prepared by condensing aminothiocyanogen **140** with a variety of ketones in ether. An enamine intermediate **141** (R = Me; R^1 = COOEt) was isolated.[247,248]



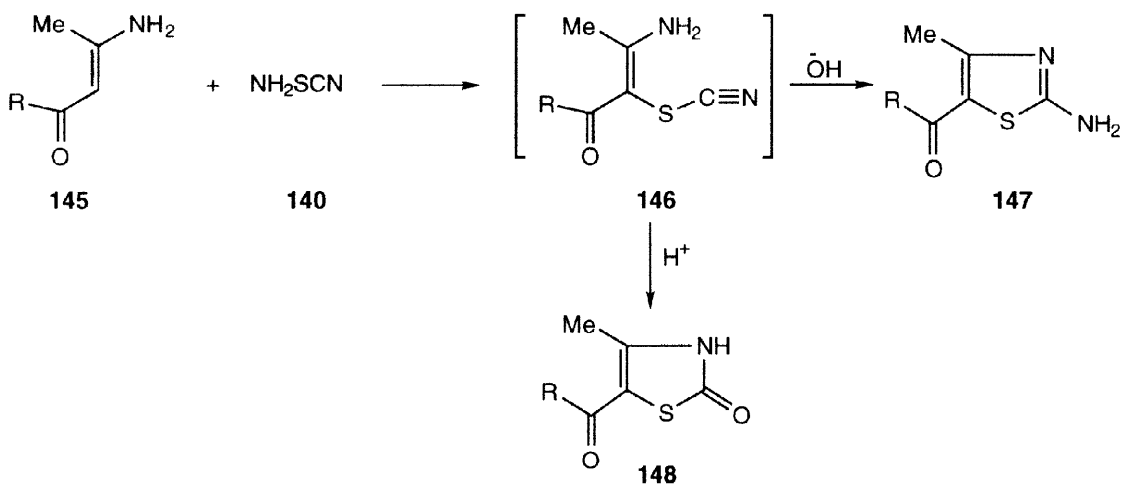
139 **140** **141** **142**

N-Methylthiazolines **144** are accessible from N-methylaminothiocyanogen **143**.[249]



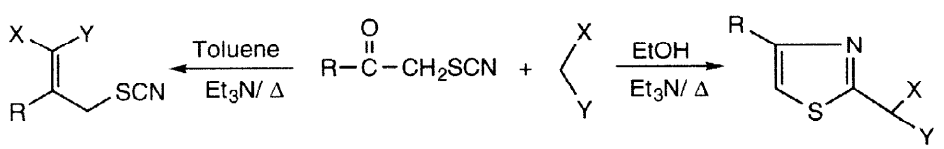
139 **143** **144**

When either β-aminocrotonic esters or enamines **145** are used in the condensation, intermediates **146** are obtained, which cyclize either to 2-aminothiazoles **147** under the influence of alkalis or to thiazolones **148** with acid.[249]



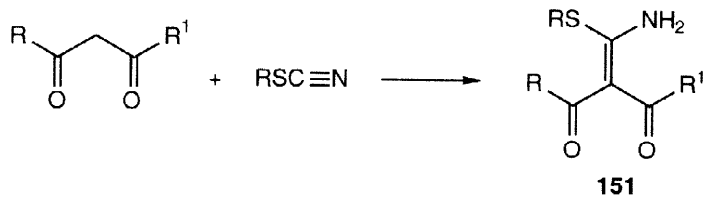
145 **140** **146** **147** **148**

Depending on the solvent of the reaction, α-thiocyanatoketones **3b** react with active methylene reagents to yield either thiazoles **150**[250-252] or Knoevenagel condensate products **149**.[253,254]



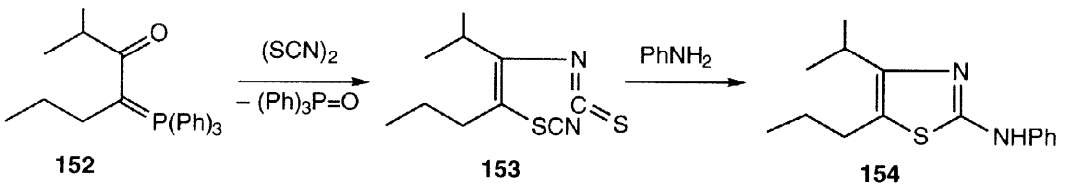
149 **3b** **140** **150**

The reaction of RSCN; R = alkyl or aryl with α-diketo compounds in the presence of Ni bis(acetylacetonate) gives the adduct **151**.[255,256]



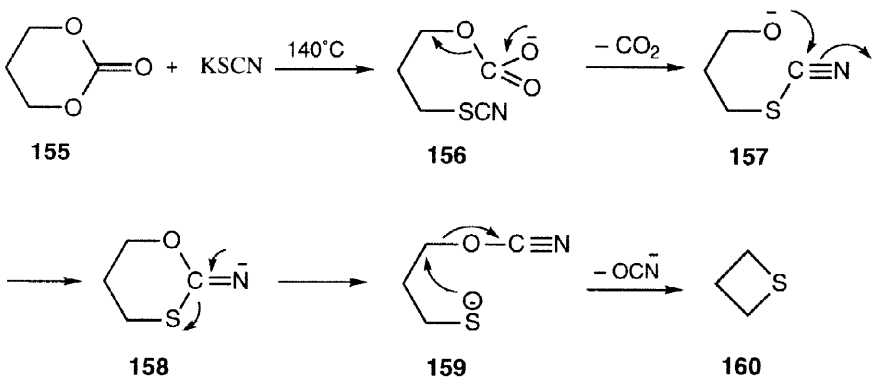
151

Zbiral and Hengstberger[257,258] found that 2-methyl-3-isothiocyanato-4-thiocyanatohept-3-ene **153**, prepared from thiocyanogen and oxoalkylene phosphorane **152**, gave anilino-4-propyl-5-isopropylthiazole **154** by condensation with aniline.



152 153 154

It has been reported that fusion of equimolar quantities of potassium thiocyanate and cyclic carbonate ester **155** resulted in the formation of carbon dioxide and the related thietane **160**.[259-262]



155 156 157 158 159 160

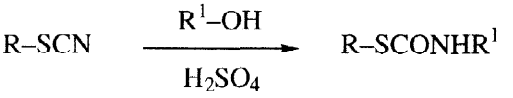
Scheme 4

5. Reaction of Thiocyanates with Mineral Acids

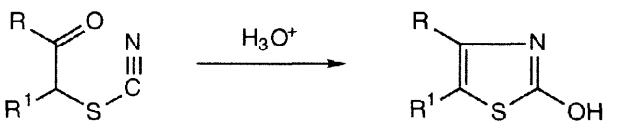
Treatment of thiocyanates with concentrated sulfuric acid at 0-5°C leads to thiocarbamates.[263-266] Schmidt and Kollek[267] have used this method to prepare several N-alkylthiocarbamates containing an odd number of carbon atoms, beginning with C_{13}.

$$R\text{–}SCN \xrightarrow[H_2SO_4]{H_2O} R\text{-}SCONH_2$$

Riemschneider[268-270] and others[271] found that thiocyanates react with alcohols and olefins in the presence of sulfuric acid to give products which, upon hydrolysis, yield N-substituted thiocarbamates.[268-274]



The cyclization of α-thiocyanatoketones **3b** in aqueous acid leads to 2-hydroxythiazoles **161**.[275-293]

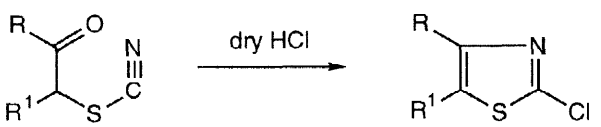


3b **161**

Table 8. 2-Hydroxythiazole Derivatives by Cyclization of α-Thiocyanatoketones in Acidic Media.

R	R^1	Conditions	Yield, %	Ref.
Me	H	$NaHCO_3$, H_2O	42 - 68	275-277
CH_2SCN	H	HOAc, H_2SO_4, H_2O	50	278
Ph	H	HOAc, H_2SO_4	87	279, 280
p-MeC_6H_4	H	HOAc, H_2SO_4	90	279, 280
p-ClC_6H_4	H	HOAc, H_2SO_4	85	279, 281
p-BrC_6H_4	H	HOAc, H_2SO_4	80	279, 281
2,4-$(HO)_2C_6H_3$	H	HOAc, H_2SO_4, H_2O	92.5	282, 283
3,6-$Me(OH)C_6H_3$	H	HOAc, H_2SO_4	70	283
4,6-$Me(OH)C_6H_3$	H	HOAc, H_2SO_4	85	283
Me	Me	HOAc, H_2SO_4	40	284
Me	CO_2Et	HOAc, H_2SO_4	20	285 - 290
Ph	Ph	HOAc, H_2SO_4, H_2O	85	291-293

Treatment of α-thiocyanatoketones at low temperature with dry hydrogen chloride in ether solution gives satisfactory yields of 2-chlorothiazole derivatives **162**.[278-280,283,294]

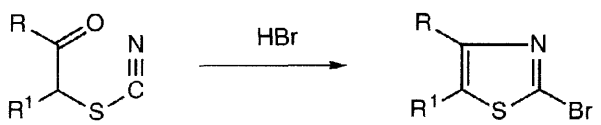


3b **162**

Table 9. 2-Chlorothiazole Derivatives From α-Thiocyanatoketones and Dry HCl Gas in Ethereal Solutions.

R	R^1	Conditions	Yield, %	Ref.
Ph	H	Ether, dry HCl, 0°C	85	279,280
p-MeC_6H_4	H	Ether, dry HCl, 0°C	86	279,280
p-ClC_4H_6	H	Ether, dry HCl, 0°C	84	279,280
p-BrC_6H_4	H	Ether, dry HCl, 0°C	80	279,280
p-$MeOC_6H_4$	H	Ether, dry HCl, 0°C	85	279,280
3,4-$Cl_2C_6H_3$	H	Ether, dry HCl, 0°C	90	283
Me	Me	Ether, dry HCl, 0°C	52	278
Ph	Br	Ether, dry HCl, 0°C	67	294
p-MeC_6H_4	Br	Ether, dry HCl, 0°C	66	294
p-ClC_6H_4	Br	Ether, dry HCl, 0°C	71	294

The same general procedure was applied satisfactorily to the synthesis of 2-bromothiazoles **163** using hydrogen bromide below 0°C.[295,296]

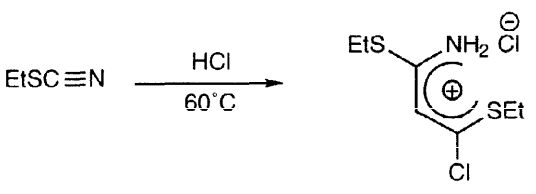


3b **163**

A new synthesis of 2-bromo-4-aminothiazoles **165** has been reported using α-cyanoalkylthiocyanates **164** and hydrogen bromide.[297]

164 **165**

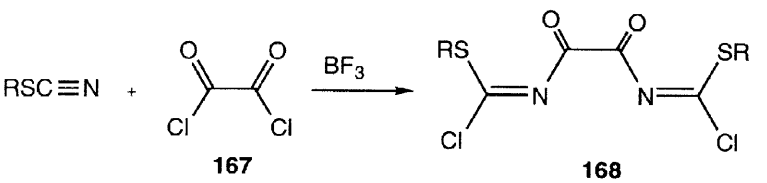
Yanagida et al.,[298] and Hamed[299] reported that the reaction of ethyl thiocyanate with HCl at the higher temperature of 60°C, in a sealed glass tube, afforded a dimeric 2:2 adduct **166**.

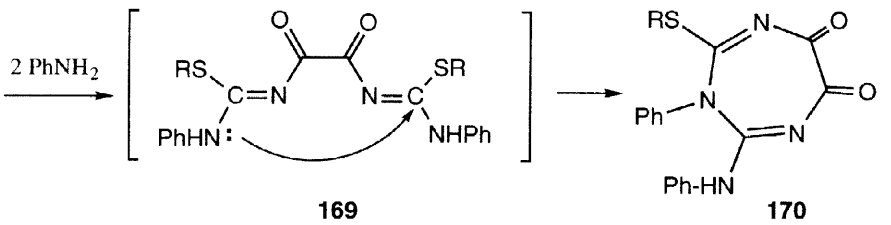


166

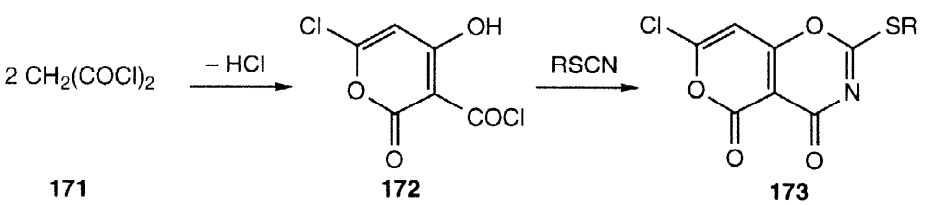
6. Condensation with Acid Chlorides

Alkyl thiocyanates react with oxalyl chloride (**167**) in the presence of BF_3 to give N,N`-bis-(methylthiochloromethylene)oxamides **168**. Interaction of **168** with aniline yields new derivatives of triazepine **170**.[300]

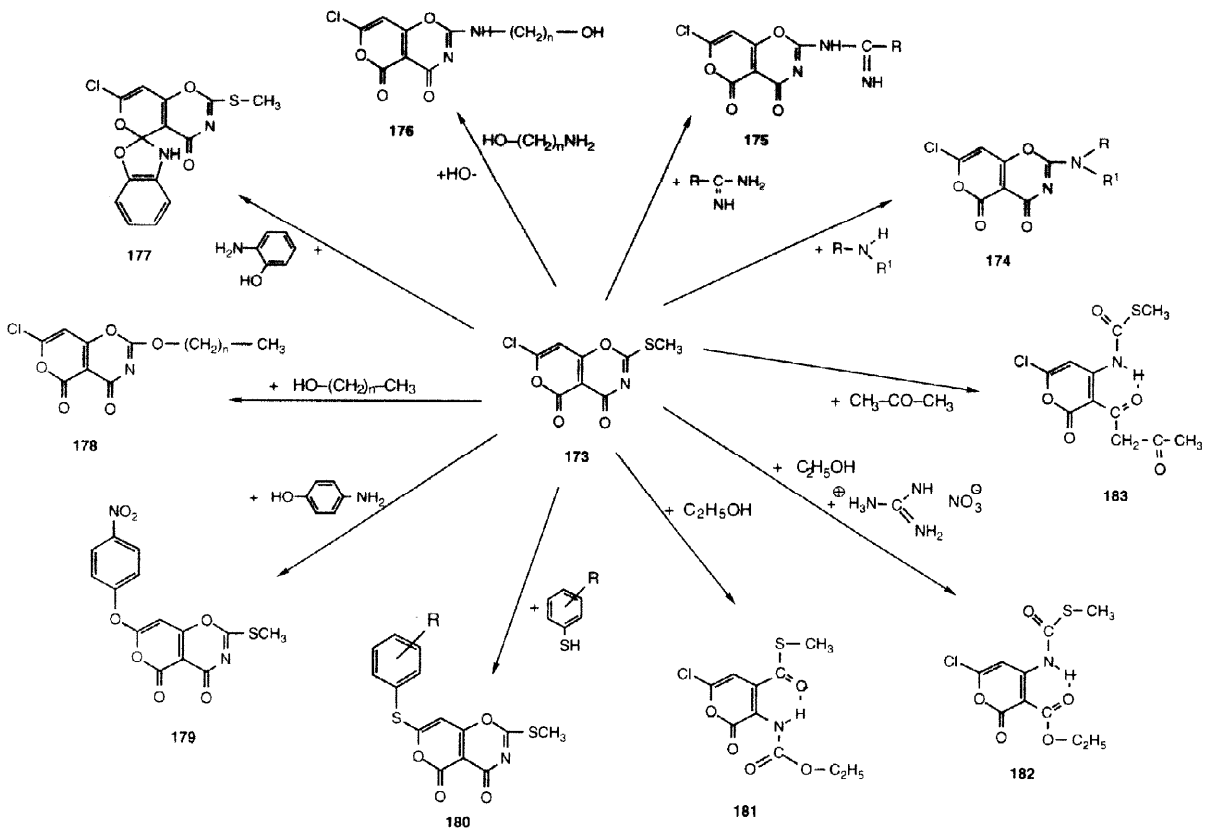




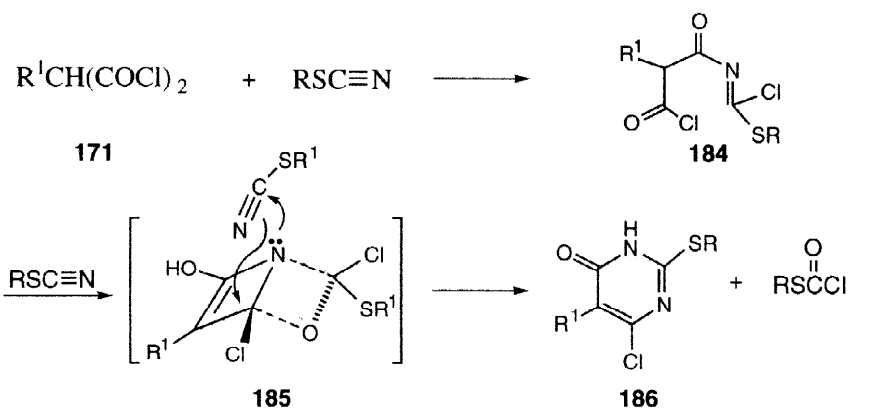
A general synthetic route for pyrano[3,4-e][1,3]oxazine derivatives, such as **173**, using malonyl dichloride (**171**) and organic thiocyanates has been reported by Ried et al.,[301,302] Treatment of **173** with nucleophiles, resulted in displacement of the 2-alkyl(aryl) thiosubstituent, leading to compounds **174-183** (Scheme 5).[301-304]



Alternatively, excess thiocyanates react with malonyl chlorides at room temperature to give the corresponding 4-chloropyrimdine-6-ones **186** with an alkylthio or arylthio group in the 2-position (Scheme 6).[305,306]

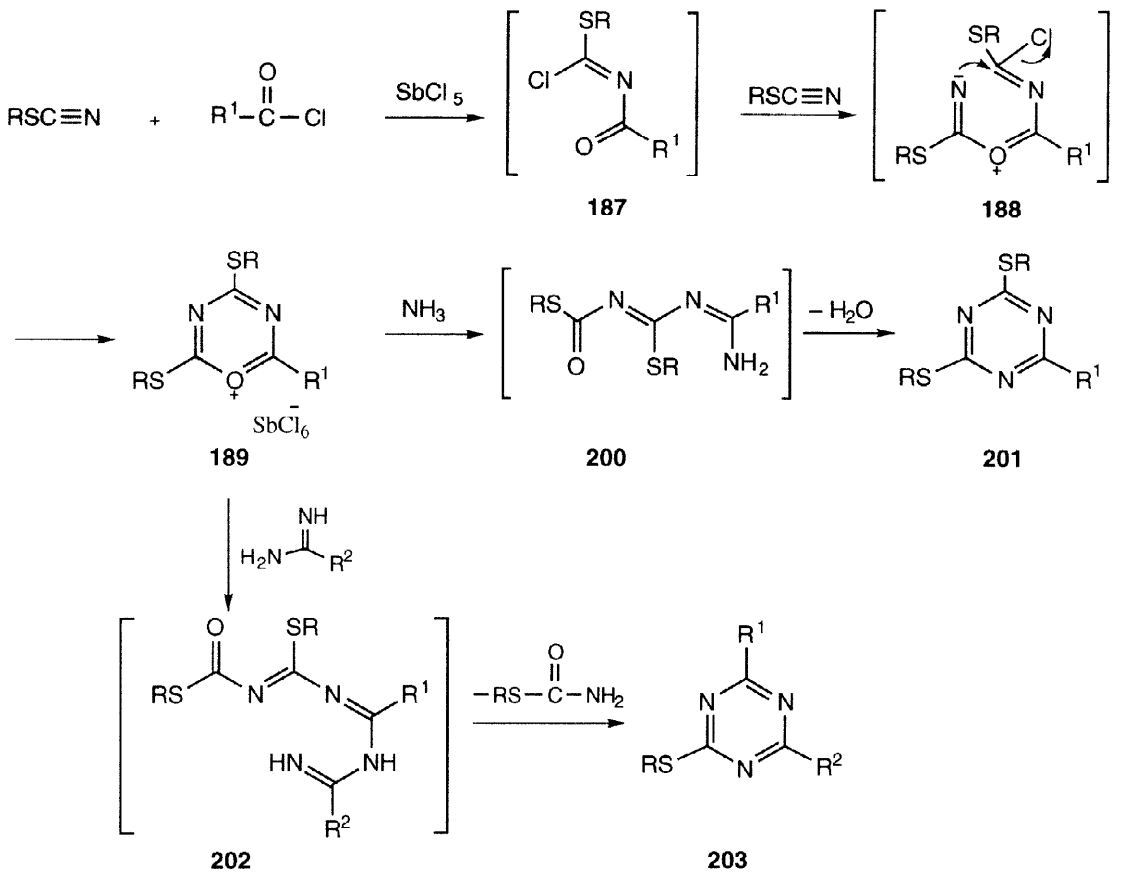


Scheme 5



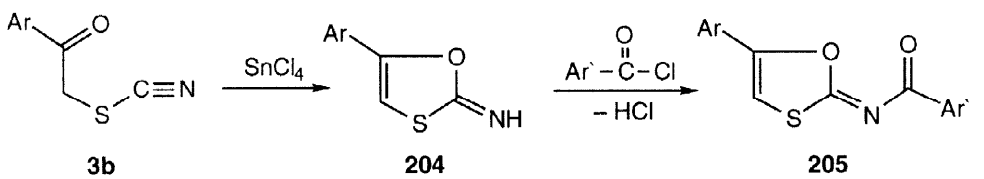
Scheme 6

Herrmann et al.,[307,308] have reported the synthesis of 2-alkyl(aryl)-4,6-bis(alkylthio)-1,3,5-oxadiazinium salts[189,309], important intermediates in organic syntheses, *via* the reaction of acid chlorides with alkyl thiocyanates. These salts can react with ammonia and amidines to give the 1,3,5-triazine derivatives **201** and **203**, respectively (Scheme 7).



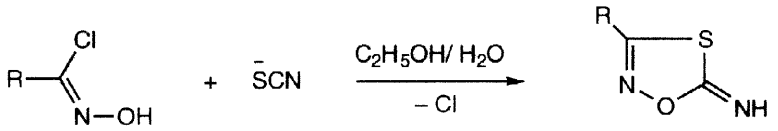
Scheme 7

2-Aroylimino-5-aryl-1,3-oxathiols **205** could be prepared by condensation of α-thiocyanoacetophenones **3b** with aroyl chlorides in the presence of Lewis acids.[310-313]



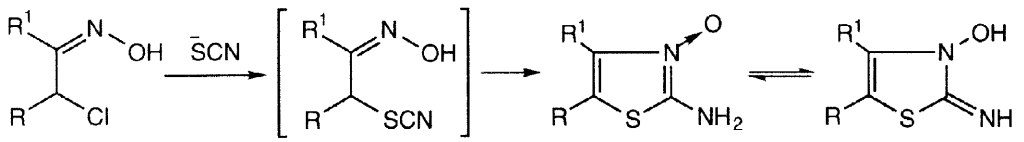
7. Reaction of Halogenated Compounds with Thiocyanate Ion

The reaction of hydroxamic acid chlorides with thiocyanate ions was first described by Musante.[314] The reaction products, which were obtained in nearly quantitative yield, were 1,4,2-oxathiazole derivatives **207**.



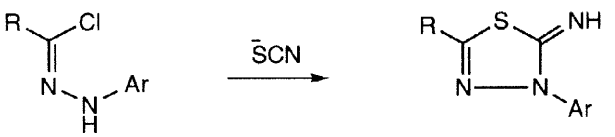
206 207

It should also be mentioned that syntheses with the hydroxamic acid system can be formally seen in the reaction of 2-chlorooximes with thiocyanate ion.[315-317]



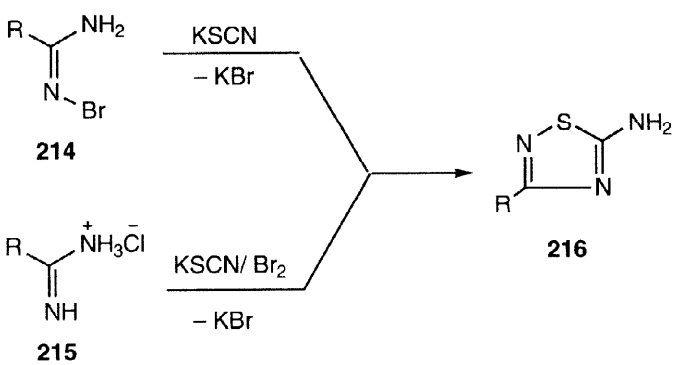
208 209 210 211

A large number of hydrazonyl halides of the general formula **212** have been cyclized using thiocyanate ion, affording the corresponding thiadiazolines **213**.[318-323]



212 213

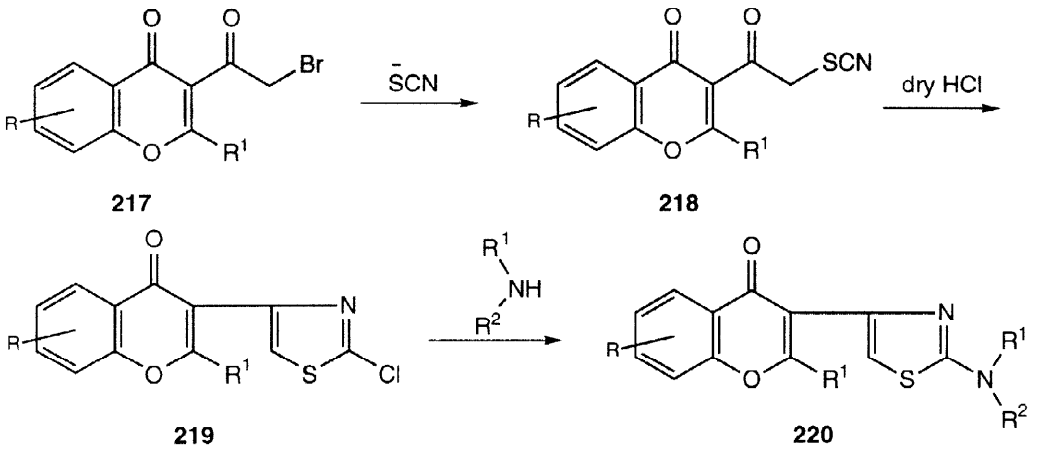
An important class of heterocyclic amines of the type **216** can be prepared from N-halo-amidines **214** and KSCN or from amidine hydrochloride **215** with bromine and KSCN.[324,325]



214 215 216

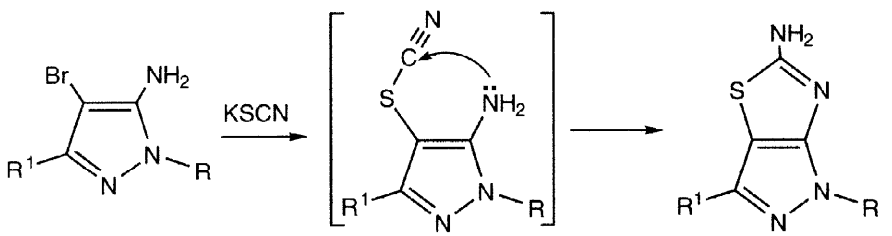
The antiinflammatory chromones **218-220** were synthesised *via* the reaction of α-bromo-acetylchromones **217** with thiocyanate ion to yield 3-thiocyanatoacetylchromones **218**. The latter could be cyclized into **219** on treatment with dry HCl gas in ether. The condensation of **219** with

the appropriate cyclic amines in N-methylpyrrolidone, in the presence of Ag_2O, afforded the corresponding 3-(2-N-substituted aminothiazol-4-yl)chromones **220**.[326-328]



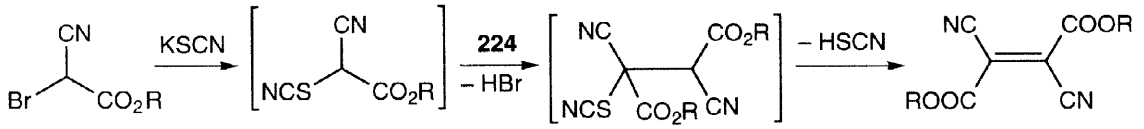
217 **218** **219** **220**

A large number of bromoheterocyclic compounds have been reported to react with the thiocyanate ion to yield the corresponding thiazolo[4,5-c]pyrazole derivatives **223**.[329-333]



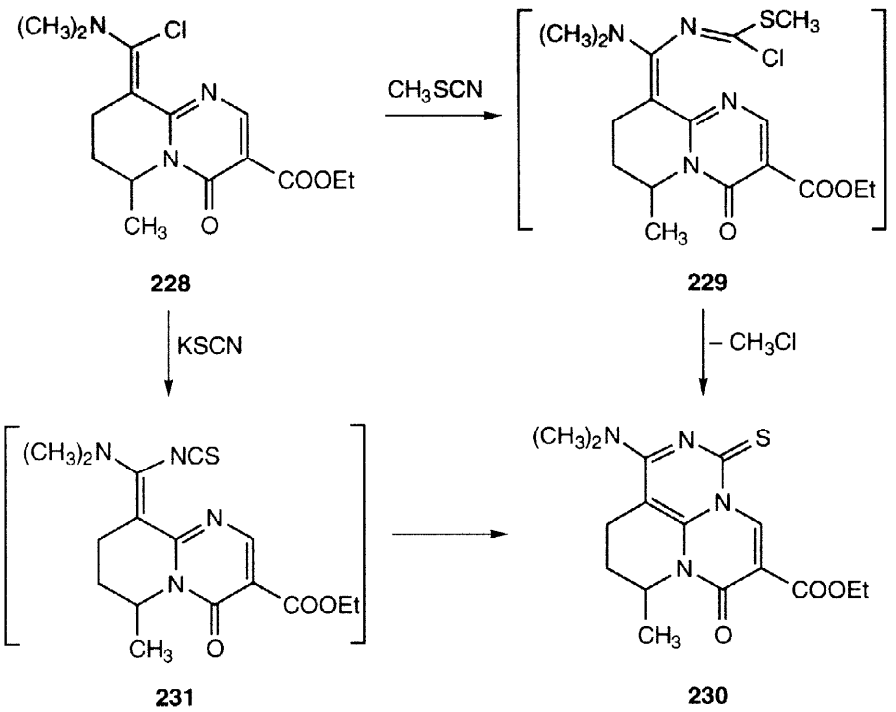
221 **222** **223**

Dialkyl(*E*)-2,3-dicyanobutendioates **227**, potentially useful intermediates for the synthesis of a wide variety of heterocyclic compounds, are prepared by the reaction of alkyl bromocyanoacetates **224** with potassium thiocyanate.[334]



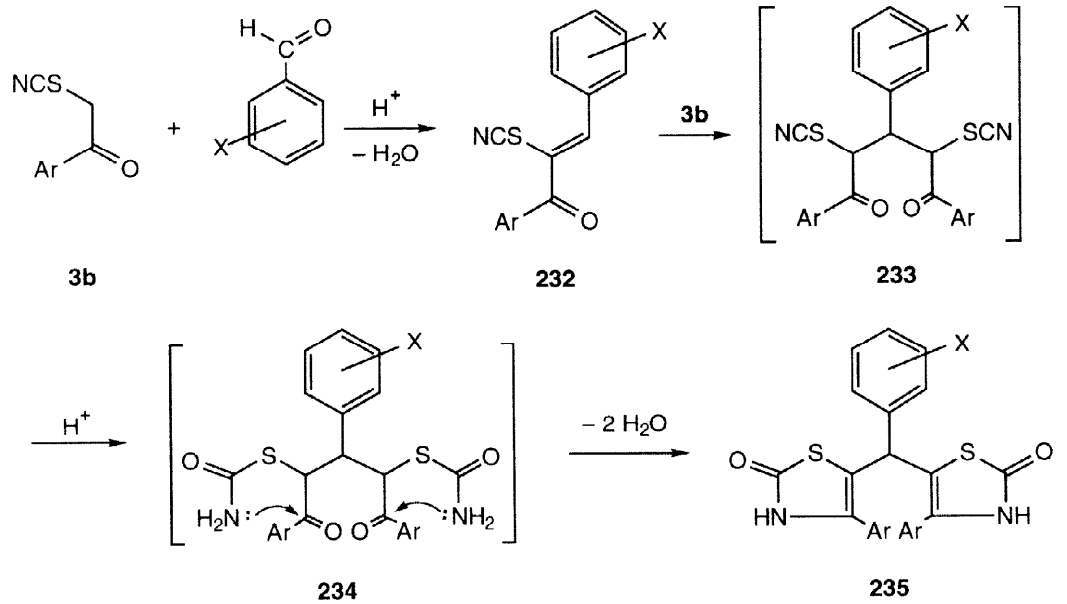
224 **225** **226** **227**

The α-chloroenamine moiety in **228** reacted with methyl thiocyanate to yield the adduct **229** which subsequently cyclized into **230**. Compound **230** also formed on reacting **228** with thiocyanate ion.[335]



8. Condensation with Aldehydes

Teller and Dehne[336] have reported in their patent the synthesis of 5,5`-benzylidene-bis(thiazolin-2-ones) **235** (Table 10).[336] Compounds **235**, useful intermediates in organic synthesis, were prepared by the condensation of α-thiocyanoketones **3b** with aldehydes to yield the arylidene derivatives **232** which, in turn, reacted with another molecule of **3b** to form the intermediate diketones **233**. The latter were readily converted into **235** in acid medium.



The condensation of salicylaldehydes with thiocyanatoacetic esters **3c**, in the presence of K_2CO_3 as catalyst, afforded the corresponding 3-(alkoxycarbonylmethylthio)coumarins **338** in good yields.[337]

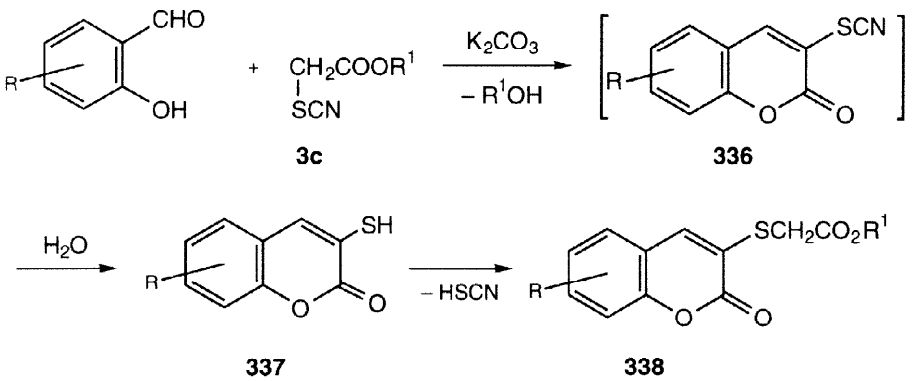
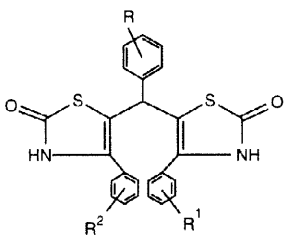
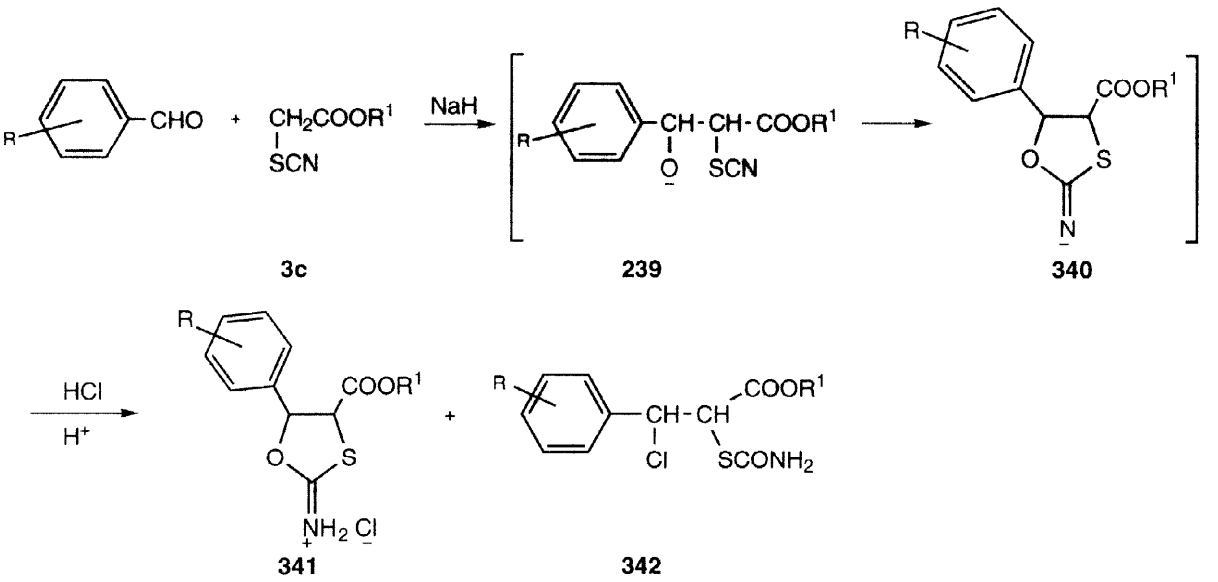


Table 10.[336] 5,5`-Benzylidene-bis(thiazolin-2-ones) from α-Thiocyanato Ketones.

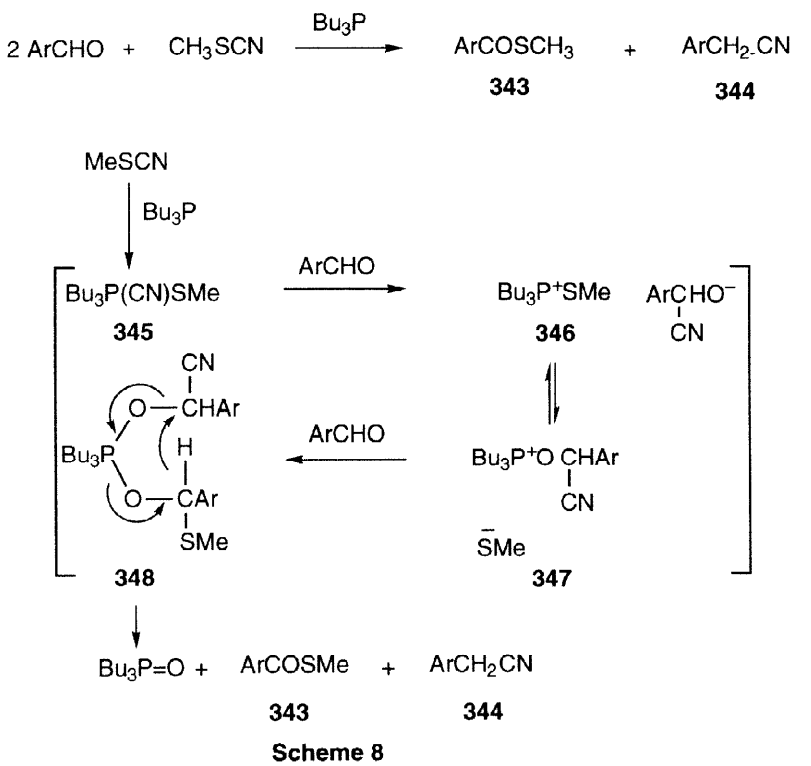


R	R^1	R^2	Yield, %	M.p.°C
H	H	H	77	311-312
H	2-Cl	4-Cl	72	292-293
H	3-NO_2	H	75	280-282
4-Br	H	H	80	294-295
4-Br	4-Br	H	88	314-316
4-Cl	4-Cl	H	82	328-316
4-Cl	4-OH	H	82	328-330
3,4-Cl_2	H	H	68	Z > 320
3,4-Cl_2	2-Cl	4-Cl	84	253-254
4-CH_3	4-CH_3O	H	74	313-315
2,4-$(CH_3)_2$	2-NO_2	H	80	318-319
2,3-$(CH_3)_2$	4-F	H	85	288-289

An equimolar reaction of thiocyanoacetic esters **3c** with aromatic aldehydes in the presence of sodium hydride, followed by treatment with HCl gas, led to a mixture of 4-alkoxycarbonyl-5-aryl-2-imino-1,3-oxathiolane hydrochloride **341** and α-(*S*-carbamoylthio)-β-chlorodihydrocinnamic esters **342**.[338]



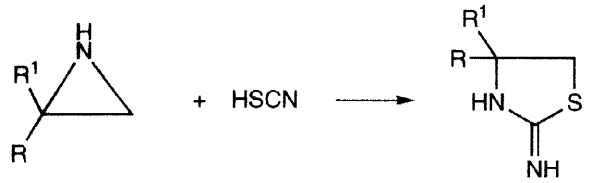
Aryl aldehydes react with methyl thiocyanate in the presence of tributylphosphine to afford *S*-methylthiobenzoates and arylacetonitriles in good yields. This unprecedented reaction is considered to proceed *via* the route shown in Scheme 8.[339]



Scheme 8

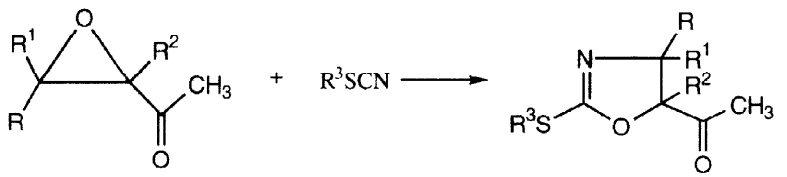
9. Miscellaneous Reactions Involving the C≡N Group

The reaction of aziridines **349** with thiocyanic acid give 2-iminothiazolidines **350**.[340-344]



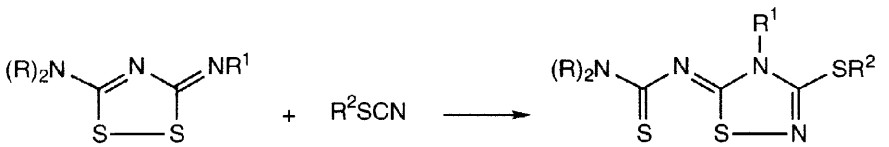
349 350

Oxazolines **352** were prepared by treatment of acetyloxiranes **351** with RSCN in the presence of $BF_3.OEt_2$ or anhydrous $AlCl_3$.[345-348]



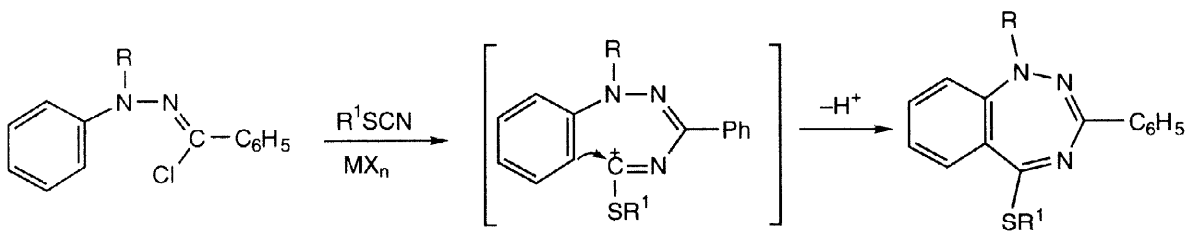
351 352

A series of 5-(thiocarbomylimino)-1,2,4-thiadiazolines **354** were prepared by ring-opening cycloaddition reactions from imino-1,2,4-dithiazoles **353** and different thiocyanates.[349-351]



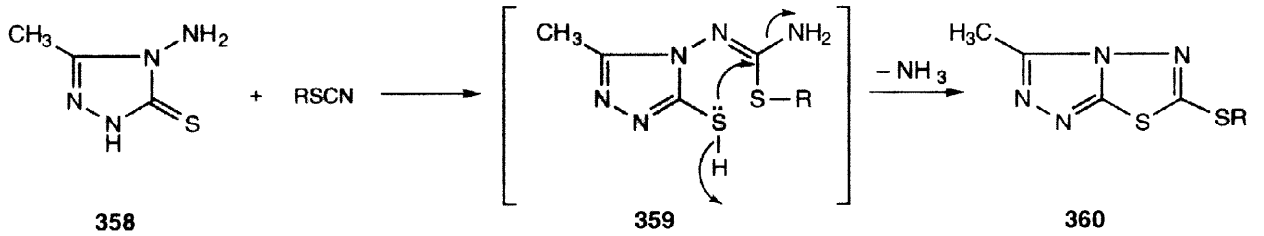
353 354

Benzhydrazonyl chlorides **355** react with thiocyanates in the presence of Lewis acids to give a nitrillium salt **356**. The carbocation in **356** attacks the ortho position of the benzene ring to yield, by intramolecular cyclization, an 1H-1,2,4-benzotriazepines **357**.[352,353]



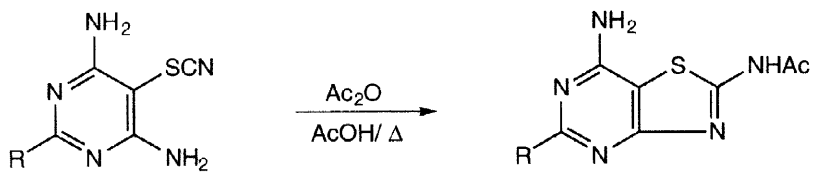
355 356 357

4-Amino-5-methyl-1,2,4-triazole-3-thione **358** reacted with alkyl thiocyanates in polyphosphoric acid to give triazolo[3,4-b][1,3,4]thiadiazoles **360** in ~ 94% yield. The reaction proceeds *via* the intermediate **359**.[354]



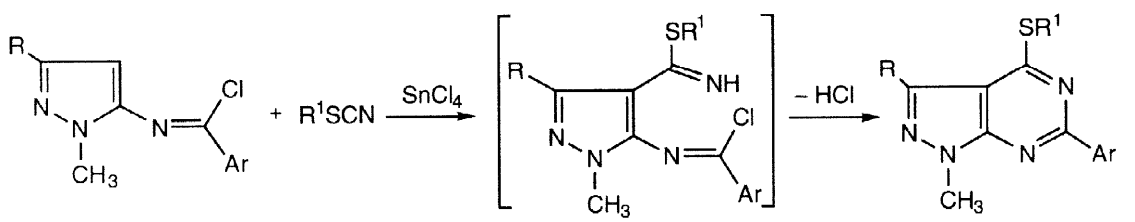
358 359 360

A thiazole ring may be formed from aminothiocyanates **361** by heating in a suitable solvent such as ethanol, but substitution in the parent ring may inhibit cyclization. In such cases, heating in acetic acid sometimes overcomes this problem.[355]



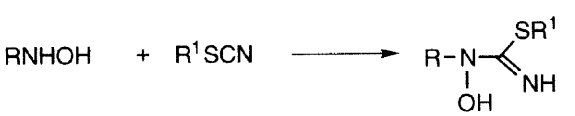
361 362

Pyrazolopyrimidines **365** could be prepared by treating pyrazolylimidoyl chlorides **363** with thiocyanates in the presence of $SnCl_4$.[356]



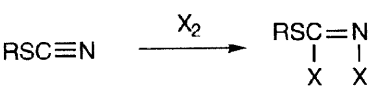
363 364 365

The N-hydroxythioureas **367** were obtained in 80% yield by treating hydroxylamines **366** with alkylthiocyanates.[357]



366 367

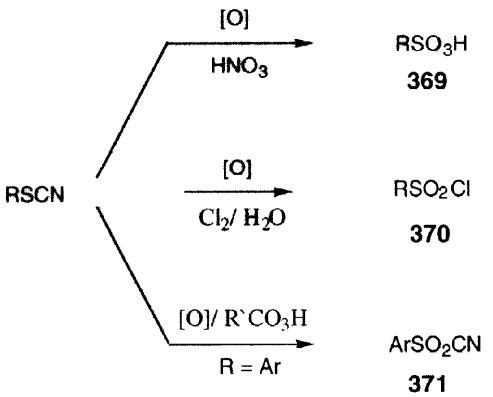
Halogens and interhalogens (ICl and IBr) added to the triple bond of -SC≡N group to give **368**.[358,359]



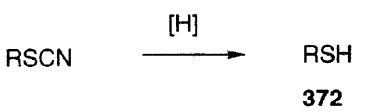
368

B. Reactions Involving S-CN Bond Fission

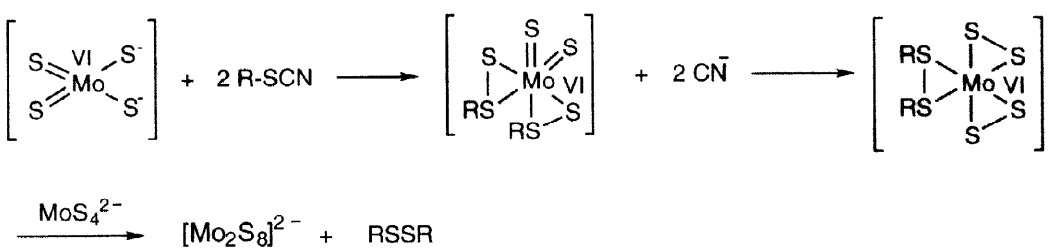
Oxidation of thiocyanates to sulphonic acids with nitric acid or to sulphonyl chlorides with chlorine and water occurs with S-CN bond fission, but oxidation of aryl thiocyanates with peroxy acids gives sulphonyl cyanides.[360]



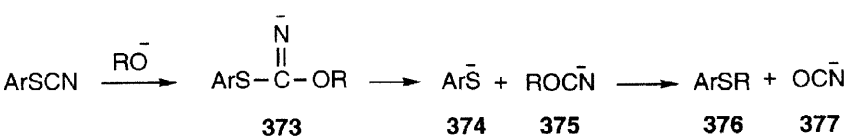
Reduction occurs with a variety of reagents such as zinc and acid, sodium and liquid ammonia, lithium aluminium hydride or sodium borohydride to give thiols in reasonable yields.[361]



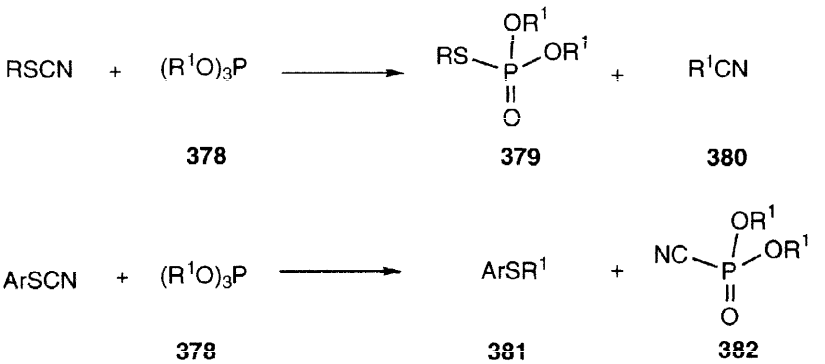
An interesting reductive dimerization of organic thiocyanates using benzyltriethylammonium tetrathiomolybdate [$(PhCH_2NEt_3)_2MoS_4$], led to the formation of the corresponding disulfides.[362-365]



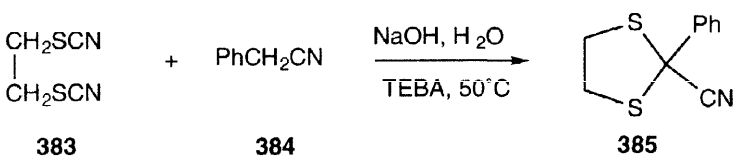
Certain aryl thiocyanates having electron withdrawing groups give alkyl sulphides **376** with alcoholic potassium hydroxide, presumably owing to alkylation of the thiolate ion.[366]



Fission of the S-CN bond can also occur as a result of nucleophilic substitution at sulfur, which should be the preferred position of attack by soft nucleophiles. Trialkyl phosphites **378** react with alkyl thiocyanates to give phosphorothioates **379** by an Arbuzov reaction, but aryl thiocyanates also give the alkyl aryl sulfides **381**, the formation of which is favoured by electron-withdrawing substituents in the aromatic ring.[367]

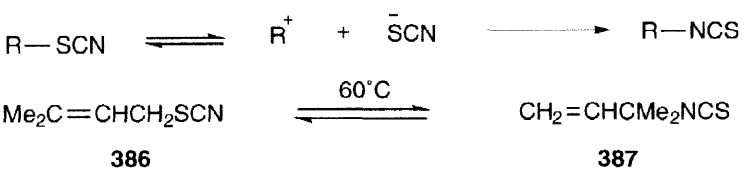


Carbanions are sulfenylated by thiocyanates in good yields, especially in the presence of phase-transfer agents such as triethylbenzylammonium chloride.[368]

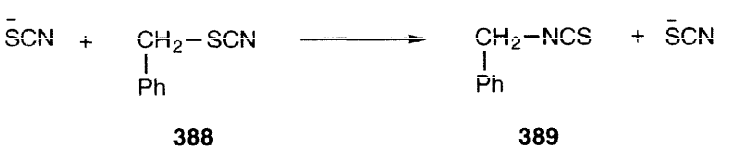


C. Reactions Involving R-S Bond Fission

The most widely studied reaction involving R-S bond fission is the thermal isomerization of thiocyanates to isothiocyanates, which is commonly observed during distillation.[369]

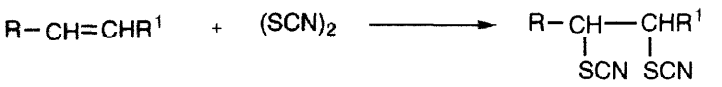


In the presence of thiocyanate ions, rearrangement also occurs by substitution involving the nitrogen atom of the thiocyanate ion, although its nucleophilic reactivity is lower than that of the sulfur.[369-371]

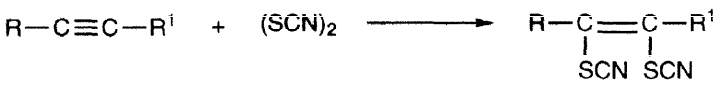


1. Addition of Thiocyanogen to Olefins and Acetylenes

Many patents and papers are devoted to obtaining dithiocyanate compounds by the addition of thiocyanogen to double[372-385] and triple bonds[386-393] for the purpose of producing biologically active compounds and drugs. Thiocyanogen reacts easily with olefins either with or without catalysis. As a rule, the products are dithiocyanates. All the products were prepared by addition of thiocyanogen to the corresponding unsaturated compounds preferably in acetic acid at or below room temperature.[394-399]

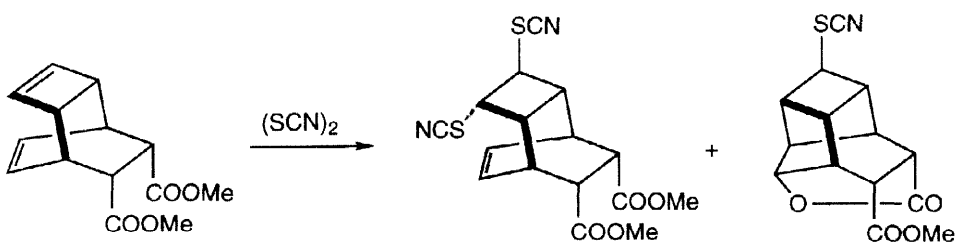


390 **391**



392 **393**

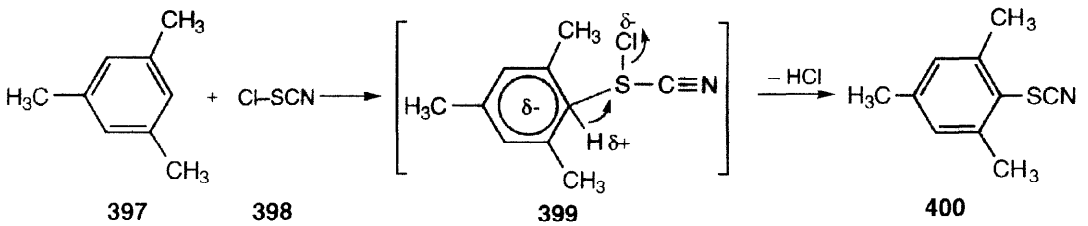
The reaction of dimethyltricyclo[4.2.2.0]deca-3,7-diene-9,10-dicarboxylate **394** with thiocyanogen in acetic acid at room temperature in the presence of a radical inhibitor gave **395** (44%) and **396** (27%).[400]



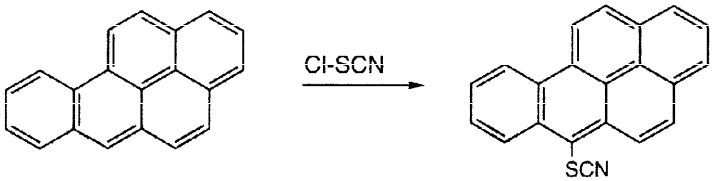
394 **395** **396**

2. Thiocyanation of Aromatic Hydrocarbons

The only aromatic hydrocarbons known to undergo uncatalysed substitution by thiocyanogen are anthracene and some large polycyclic compounds.[401] Söderbäck found that the reactivity of thiocyanogen is greatly enhanced by Friedel Crafts catalysts, which readily led to substitution even in benzene.[402] Without the aid of a catalyst, thiocyanogen chloride (**398**) causes thiocyanation of a wider range of aromatic hydrocarbons than does thiocyanogen under similar conditions.[403-406]

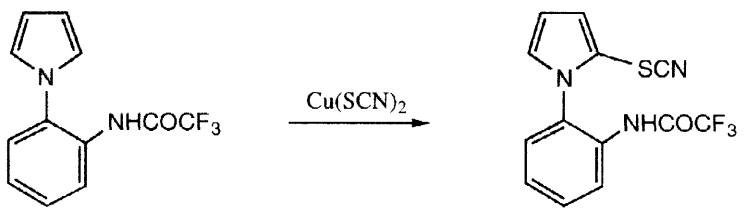


397 398 399 400



401 402

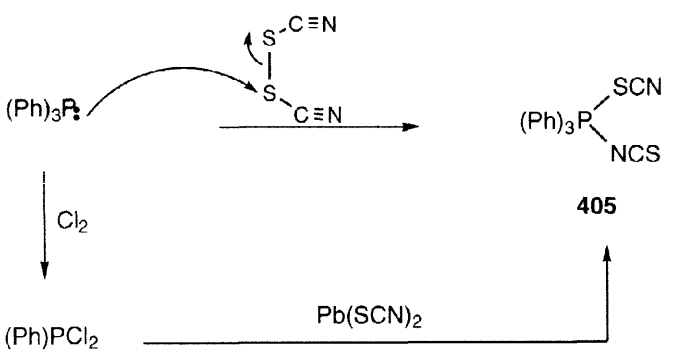
Thiocyanation of the trifluoroacetamidophenylpyrrole derivative **403** with $Cu(SCN)_2$ gave the thiocyanato derivative **404** in 62% yield.[407,408]



403 404

D. Triphenylphosphine-Thiocyanogen (TPPT) in Organic Synthesis

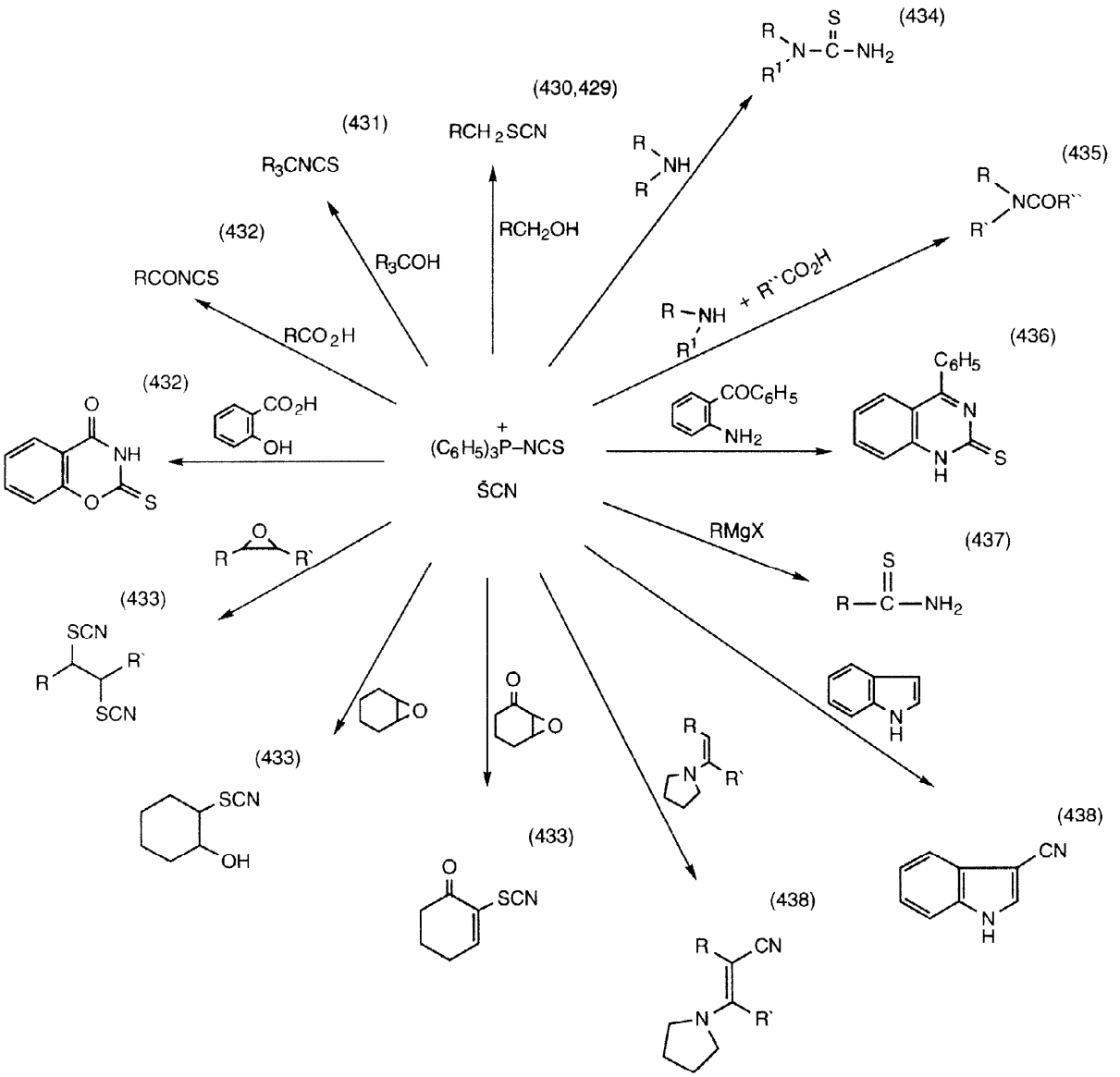
Triphenylphosphine-thiocyanogen (TPPT) (**405**) was prepared by a combination of equimolar amounts of triphenylphosphine and thiocyanogen or by the reaction of triphenylphosphine with chlorine and $Pb(SCN)_2$.[409-428]



405

TPPT reacts easily with nucleophilic reagents for the purpose of producing biologically active compounds and drugs. Scheme 9 summarizes the reaction of TPPT with a variety of nucleophilic

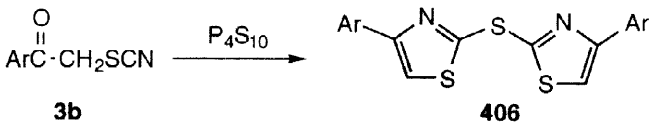
reagents.[409] As observed, the reaction of TPPT with alcohols,[429-431] carboxylic acids[432] and epoxides,[433] proceeds *via* nucleophilic attack on the phosphorus atom of TPPT followed by substitution of the SCN anion on the adjacent carbon to the oxygen atom of the intermediate with elimination of triphenylphosphine oxide. In the case of amines,[434-436] organometallic compounds,[437] indoles[438] and pyrroles,[438] nucleophilic addition to the -N=C=S carbon of TPPT, gives thiocarbamoylated compounds (Scheme 9).



Scheme 9

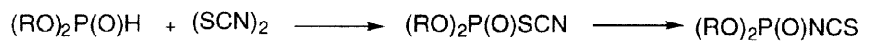
E. Miscellaneous Reactions of Thiocyanic Esters

Bis(4-arylthiazol-2-yl)sulfides **406**,[439] important pesticide intermediates,[440] could be prepared in 90% yield by refluxing α-thiocyanatoacetophenones **3b** with P_4S_{10}.[439,440]



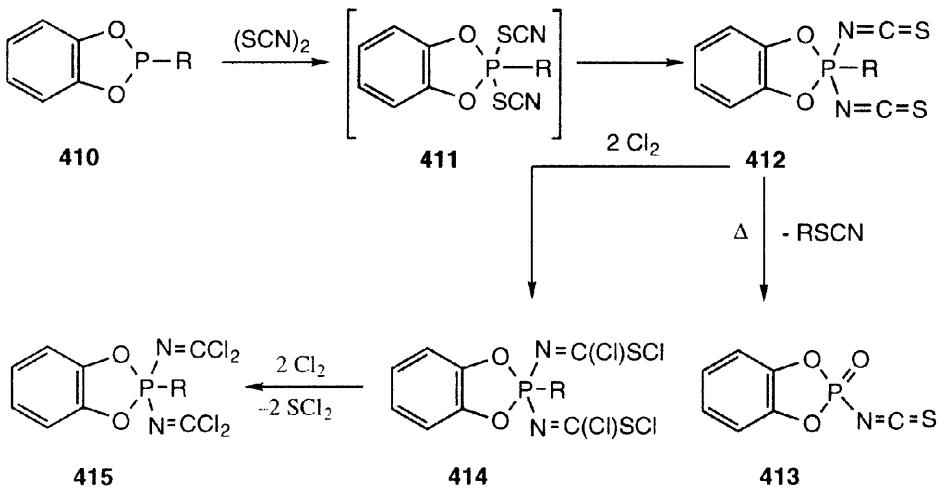
3b **406**

The reaction of thiocyanogen with dialkyl phosphites **407** and related systems lead to isothiocyanidates **409**.[441] Compounds **409** have been reinvestigated by others.[442-445]



407 **1** **408** **409**

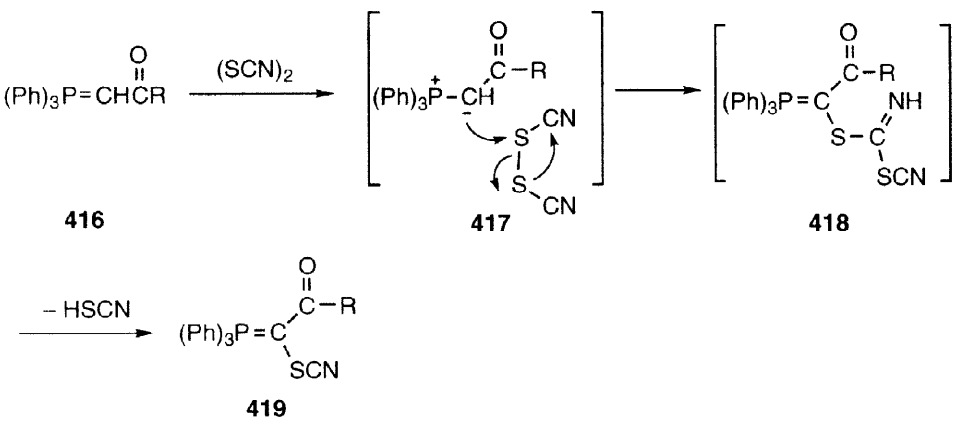
Five-co-ordinate phosphorus systems **414** were prepared by the oxidative addition of thiocyanogen to organic phosphites **410**.[446-449] Warming **412** to 20°C resulted in clean decomposition to give the phosphoroisothiocyanidate **413**. Compound **412** reacted with chlorine to give five co-ordinate structures **414** and **415** (Scheme 10).[446-449]



410 **411** **412** **415** **414** **413**

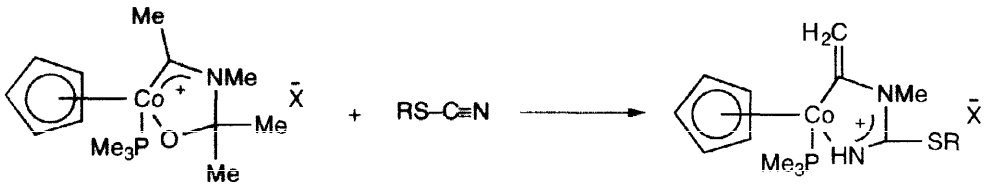
Scheme 10

Triphenyl-β-oxoalkylenphosphoranes **416** react with thiocyanogen to give **419**. Compound **419** proved to be useful as a precursor for thiazole formation.[450-452]



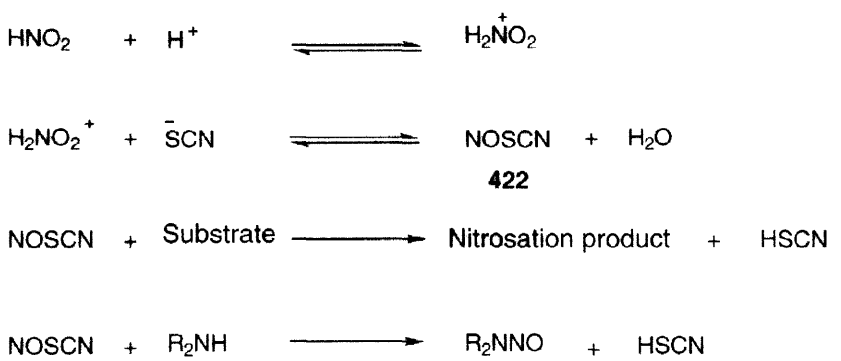
416 **417** **418** **419**

One example of a large number of complexes containing a thiocyanic ester from an organometallic complex is the cycloaddition reactions of organocobalt complex **420** with alkyl thiocyanates.[453-461]



420 **421**

Nitrosyl thiocyanate (**422**), known as a blood-red species, stable only in solution,[462,463] is readily synthesized from nitrous acid and thiocyanic acid, nitrosyl chloride and silver thiocyanate or ethyl nitrite and thiocyanic acid.[136,464] Nitrosyl thiocyanate is a very important agent for the nitrosation of hydroxylamine and its methyl derivatives,[465] aniline derivatives, morpholine,[462] hydrazoic acid,[467] alcohols[462,463] and thiols.[362,462,468]

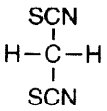
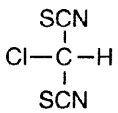
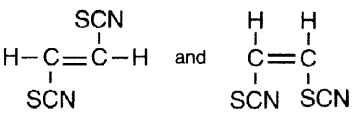
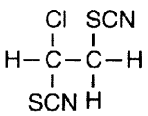


V. Biological Activity

Methylene bisthiocyanate (**2**) exhibits extremely high biological activity as a fungicide,[469-472] antifolate,[473,474] slime control agent,[475,476] microbicidal agent[477-481] and in controlling mollusks.[482]

Wehner[483-486] described the use of methylene bisthiocyanate (MBT), chloromethyl bisthiocyanate (CMBT), vinylene bisthiocyanate (VBT), chloroethylene bisthiocyanate (CEBT) (Table 11) in the control of sulfate-reducing anaerobic bacteria.

Table 11. Structural Formulae of Bisthiocyanates Used.

Methylene bisthiocyanate (MBT)	
Chloromethyl bisthiocyanate (CMBT)	
Vinylene bisthiocyanate (VBT)	
Chloroethylene bisthiocyanate (CEBT)	

The data shown in tables 12-15 explain the biological activity of thiocyanic esters against a wide variety of moulds, syeasts, algae and bacteria.[486-488]

Table 12.[486] Antibacterial Screening Lesis Using the Agar Dilution Technique.

Organism	Inhibitor			
	MBT	CMT	VBT	CEBT
Enterobacter aerogenes	7.5		1.5	4.5
Bacillus mycoides	3.75		2	2
Bacillus subtilis	6.25	15	2	
Clostridium sp. (from oil field H2O)	1.5	11	3.5	3.5
Desulfovibrio sp. (API strain A)	1.5	2.5		2
Escherichia coli	6.25	8		
Mycobacterium smegmatis	4	8	2	
Proteus vulgaris	2.5	4	2	
Pseudomonas aeruginosa	6.25	4	7.5	2.5

Table 13.[486] Agar Dilution Screening Test.

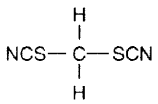
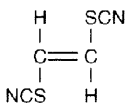
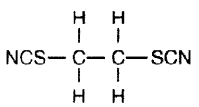
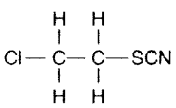
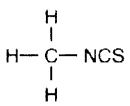
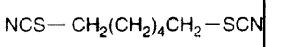
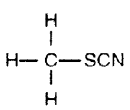
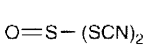
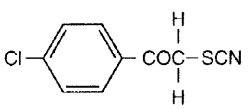
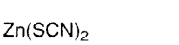
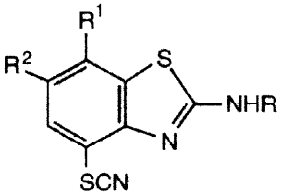
Structure	*Aspergillus flavus*	*Bacillus mycoides*	*Chaetomium globosum*	*Fusarium moniliforme*	*Penicillium citrinum*	*Trichoder maviridae*
	6.25	2.5	2.5	2.5	2.5	2.5
	6.25	2.5	2.5	2.5	2.5	2.5
	> 50	> 50	25	25	> 50	50
	50	> 50	50	50	50	50
	>500	>500	250	250	500	500
	>500	>500	> 125	>500	>500	>500
	>500	>500	125	500	500	500
	>500	>500	>500	>500	>500	>500
	> 50	> 50	25	25	25	> 50
	> 50	> 50	25	50	50	50

Table 14.[488] Inhibitory Effects of Thiocyanic Esters on the Growth of Histoplasma Capsulatum.

Compound	MIC, μg/mL	
	H-7	H-25
n-$BuSO_2CH_2SCN$	15	15
2-Benzothiazolyl-SCH_2-SCN	10 (p5)	5 (p2.5)
$CH_2(SCN)_2$	2.5	2.5

Table 15.[137] Anthelmintic and Antifungal Activity of 2-Amino-4-thiocyanatobenzothiazoles.



R	R^1	R^2	Anthelmintic act.[a] in *vivo*, % reductions				Antifungal act., MIC.[b]		
			A. suum		*H. nana*				
			300 mg/kg	100 mg/kg	300 mg/kg	100 mg/kg	*T. glabrata (VM22)*	*C. tropicalis (VM25)*	*C. krusei (VM-29B)*
H	H	Cl	31	I[e]	75	I[e]	10	>50	30
H	H	C_2H_5	92	69	93	30	>50	>50	>50
H	H	SCH_3	25	I[e]	I[e]	I[e]	>50	>50	>50
H	Cl	F	I[e]	I[e]	94	50	10	30	10
H	CH_3	F	I[e]	I[e]	100	78	>50	>50	>50
H	Cl	Cl	I[e]	I[e]	58	I[e]	<1	40	2
$COCH_3$	Cl	Cl	I[e]	I[e]	100	90[c]	>50	>50	>50
dl-Tetramisole			Toxic	100	Toxic	I[e]			
Bunamidine			Toxic	11	Toxic	100			
Nystatin[d]							≤10	≤10	≤10

[a] Suum infected mice were dosed twice a day for 5 days. *H. nana* infected mice were dosed twice a day for 3 days. [b]Minimal inhibitory concentration against indicated species of yeast (Norwich Pharmacol culture number) in Sabouraud's liquid medium BBL, μg/ml. [c]Dosed at 25 mg/Kg three times b.i.d. [d]Potency = 4162 units/mg. [e]I = Inactive.

VI. Conclusion and Prospects

Thiocyanic esters remain very important precursors for the construction of polyfunctionally substituted sulfur compounds which, otherwise, may be difficult to obtain. Furthermore, the thiocyanation of halogen compounds by thiocyanate anion may lead to the preparation of many diverse compounds. Recently the large number of papers and patents concerning biologically active thiocyanic esters testifies to the enormous potential of these compounds as industrial and antimicrobial agents.[489-506] Finally it is hoped that this review will encourage the exploration of the chemistry of thiocyanic esters.

VII. REFERENCES

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Sherif M. Sherif was born in Cairo, Egypt in 1956. He received both his B.Sc. (Honours, 1977) and Ph.D. (1985) degrees from Cairo University, where he currently holds the rank of Professor of Organic Chemistry (1996-present). He is the co-author of more than 50 scientific publications in the area of heterocyclic chemistry, dipolar cycloaddition, organometallic chemistry, and nucleosides synthesis. He was a UNESCO research fellow at **Tokyo Institute of Technology**, Japan (1987-1988) gaining a Diploma of Advanced Chemical Technology (Organic Chemistry). He conducted a post-doctoral research at Chemistry Department, **Oslo University**, Norway for two years as Royal Norwegian Council for Scientific and Industrial Research (NTNF) Fellow (1991-1993) in the area of Transition metal catalysis cross-coupling techniques for the stereoselective synthesis of optically active β-nucleosides and α-substituted α-amino acids. He has been the recipient of the **Egyptian National Prize for Chemical Sciences** (1996).