HALOALKYL ISOTHIOCYANATES, USEFUL AND VERSATILE REAGENTS IN HETEROCYCLIC CHEMISTRY[§]

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Abstract - This review deals with the preparations and reactions of haloalkyl isothiocyanates, which constitute useful and versatile tools in the synthesis of heterocycles.

CONTENTS

[§]Dedicated to Professor Masatomo Hamana on the occasion of his 75th birthday.

1. INTRODUCTION

Heterocumulenes are versatile and important reagents in organic synthesis.[1] Isocyanates and isothiocyanates have enabled a wide variety of useful and often novel synthetic transformations, especially in the construction of heterocyclic structures.[2] These heteroallenes are in general easily available substances and can undergo diverse reactions, which convert these compounds in attractive synthons. Nevertheless, many conceivable applications are seriously hampered by their inherent toxicity. The Bhopal tragedy caused by methyl isocyanate,[3] among other substances, was a sadly famous incident and a severe warning for the industrial use of these compounds. However, in a micro and preparative scale they can be employed in a rapid and safe manner. Haloalkyliso(thio)cyanates are indeed hazardous compounds and they are considered to be cancer suspect agents. They should be handled with care owing to their potential mutagenicity. The chemistry of haloalkyl isocyanates has been recently reviewed[4] and many of them are commercially available substances. However, the corresponding thio derivatives have received less attention. Haloalkyl isothiocyanates are bifunctional compounds with enhanced reactivity due to both isothiocyanate and halogen groups. The present survey will emphasize the preparation and synthetic applications of these compounds.

2. SYNTHESIS OF HALOALKYL ISOTHIOCYANATES

2.1. Reaction of Nitrogen Compounds with Sulfur Reagents

A general method for the preparation of haloalkyl isothiocyanates is the reaction of the corresponding haloalkylamines with thiophosgene. Thus, ω-haloalkyl isothiocyanates[5-9] were easily obtained by this procedure. The reaction can be performed in chloroform-triethylamine or in a heterogeneous phase of chloroform-water.

$$\underset{\mathbf{1}}{X(CH_2)_nNH_2} + Cl_2CS \xrightarrow[CHCl_3 / H_2O / Na_2CO_3]{CHCl_3 / N(C_2H_5)_3 \text{ or}} \underset{\mathbf{2}}{X(CH_2)_nNCS}$$

n = 2-6, 8, 10

X = F, Cl, Br, I

Likewise, a series of 2-aryl-2-haloethylamines (**3**) were treated with thiophosgene to afford the corresponding 2-chloroethyl isothiocyanates (**4**),[7] which were further dehydrohalogenated to give substituted 2-arylethenyl isothiocyanates.

$$\underset{\mathbf{3}}{4\text{-}RC_6H_4CHClCH_2NH_2} \xrightarrow{Cl_2CS} \underset{\mathbf{4}}{4\text{-}RC_6H_4CHClCH_2NCS}$$

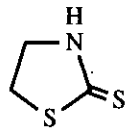
R = H, CH_3, CH_3O, Br, NO_2

A related process involves the reaction of haloamines with carbon disulfide.[10,11] Thus, ω-fluoroalkyl isothiocyanates (**6**) were prepared by treatment of **5** with carbon disulfide and ethyl chloroformate in the presence of base.[10] Curiously, the reaction of 2-chloroethylamine with carbon disulfide gave no isothiocyanate, instead the thiazolidine-2-thione[5] (**8**) was obtained.

$$F(CH_2)_nNH_2 + CS_2 + ClCO_2C_2H_5 \xrightarrow{NaOH} F(CH_2)_nNCS$$

5 **6**

$$ClCH_2CH_2NH_2 + CS_2 \longrightarrow$$

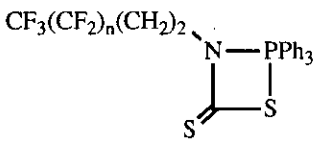


7 **8**

Some polyfluoroalkyl isothiocyanates have been synthesized by condensation of azides with triphenylphosphine. The resulting iminophosphoranes were treated with carbon disulfide to give isothiocyanates (**12**), *via* the cycloreversion of the four-membered ring intermediate (**11**).[12]

$$CF_3(CF_2)_n(CH_2)_2N_3 \xrightarrow{PPh_3} CF_3(CF_2)_n(CH_2)_2N{=}PPh_3 \xrightarrow{CS_2}$$

9 **10**



$$\xrightarrow{-Ph_3PS} CF_3(CF_2)_n(CH_2)_2NCS$$

11 n = 0-14 **12**

α-Chloroalkyl isothiocyanates (**14**) can be also obtained by reaction of ketimines (**13**) with thiophosgene.[13a] However in the presence of β-hydrogens, α-alkenyl isothiocyanates (**16**) were formed by further dehydrohalogenation.[13b]

$$RR^1C{=}NH + Cl_2CS \xrightarrow[\Delta]{PhCH_3} RR^1ClCNCS$$

13 **14**

R, R^1 = $^tC_4H_9$, Ph, 1-$C_{10}H_7$

$$RR^1CHCR^2{=}NH + Cl_2CS \xrightarrow[\Delta]{PhCH_3} RR^1C{=}CR^2NCS$$

15 **16**

R, R^1 = H, alkyl, aryl, halo

R^2 = H, alkyl, aryl, perhalomethyl

Carbonimidoyl dichlorides have also proved to be effective substrates for the synthesis of haloalkyl isothiocyanates, by treatment with several sulfur reagents. Thus, **17** reacts with phosphorus (V) sulfide to afford the 1,2-dichloroethyl isothiocyanate (**18**) in high yield.[14,15]

$$ClCH_2CHClN{=}CCl_2 + P_4S_{10} \xrightarrow{PhCH_3} ClCH_2CHClNCS$$

17 **18** (87%)

The perfluoro-2-azapropene (**19**) was converted into the trifluoromethyl isothiocyanate (**20**) by treatment with phosphorus (V) sulfide,[16] $(EtO)_2PS_2K$,[17a] hydrogen sulfide,[17b] or thioacetic acid.[18] In this case the reaction

must proceed *via* the unstable addition product (**21**), which eliminates acetyl fluoride and hydrogen fluoride. Analogously, perchloro-2-azapropene was transformed into trichloromethyl isothiocyanate.[15]

$$\underset{\mathbf{19}}{CF_3N{=}CF_2} \xrightarrow[\text{or } H_2S,\ \Delta]{P_4S_{10} \text{ or } (C_2H_5O)_2PS_2K} \underset{\mathbf{20}}{CF_3NCS} \xleftarrow{82\%} \underset{\mathbf{21}}{[CF_3NHCF_2SCOCH_3]} \xleftarrow[20^\circ C]{CH_3COSH} \mathbf{19}$$

Treatment of **22** with bis(trimethylsilyl) sulfide yields 2-(isothiocyanatoalkenyl) fluorophosphoranes (**23**).[19]

$$\underset{\mathbf{22}}{F_2P(O)CH{=}CRN{=}CCl_2} \xrightarrow{(CH_3)_3SiSSi(CH_3)_3} \underset{\mathbf{23}}{F_2P(O)CH{=}CRNCS}$$

R = H, Me

Likewise, 1,1-difluoroethyl isothiocyanate (**24**) may be obtained by treating acetonitrile with fluorothiophosgene catalyzed with hydrogen fluoride.[20]

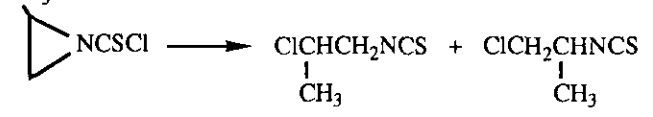
$$CH_3CN \xrightarrow[0\text{-}80^\circ C]{CSF_2 \,/\, HF\ (cat.)} \underset{\mathbf{24}}{CH_3CF_2NCS}$$

2.2 Ring-Opening of Heterocycles

Besides amines, aziridines react with thiophosgene to give unstable (1-aziridine)thiocarbonyl chlorides, which in turn furnished haloalkyl isothiocyanates in moderate yields (45-52%).[21,22]

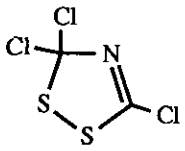
25 **26** **27** (52%)

The thiocarbonyl chloride intermediate (**26**) can be obtained as a thermolabile material and characterized at reduced temperature (-10℃) by nmr and ir spectrometry.[21] Nevertheless, isomerization to 2-chloroethyl isothiocyanate was complete at room temperature in 18-20 h. With unsymmetrically substituted aziridines, [1-(2-methylaziridine)]thiocarbonyl chloride (**28**), almost equimolecular mixture of regioisomers are obtained.



28 **29** (55-60%) **30** (40-45%)

Other heterocycles can be also converted into haloalkyl isothiocyanates. The 1,2,4-dithiazole derivative (**31**) when treated with $Hg(SCF_3)_2$ gave the perfluoroalkyl isothiocyanate **32**.[23]



31

+ $Hg(SCF_3)_2$ ⟶ CF_3-S-S-CF_2NCS

32

2.3 Nucleophilic Substitution Reactions. Isomerization of Thiocyanates

Syntheses of haloalkyl isothiocyanates often involve the usual nucleophilic substitution with thiocyanic acid or its salts. Aryl difluoromethyl isothiocyanates (**34**) are obtained by an exchange reaction of aryl difluorobromomethanes (**33**) with silver thiocyanate.[24]

$$ArCF_2Br \xrightarrow[20°C]{AgSCN} ArCF_2NCS$$

33 **34**

Ar = C_6H_5 (34%), 4-ClC_6H_4 (43%), 4-$^tC_4H_9C_6H_4$ (43%)

Similarly, highly functionalized haloalkyl isothiocyanates may be also prepared by treating *N*-haloalkyl amides[25,26] (**35**) or ureas,[27,28] and α-haloethers[29] (**37**) with thiocyanates. Not only halogen atoms, but also alkoxy groups can be displaced by silicon thiocyanate, such as in haloalkyl acetals[30] (**39**).

$$RCONHCHClCHCl_2 + NaSCN \xrightarrow{CH_3CN} RCONHCH(NCS)CHCl_2$$

35 **36**

R = C_6H_5, 4-$CH_3C_6H_4$, 4-ClC_6H_4

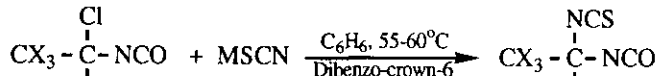
$$ClCH_2CHClOC_2H_5 \xrightarrow{NH_4SCN} ClCH_2CH(NCS)OC_2H_5$$

37 **38** (93%)

$$BrCH_2CH(OC_2H_5)_2 \xrightarrow[7.5\ h]{Si(NCS)_4,\ C_6H_6} BrCH_2CH(NCS)OC_2H_5$$

39 **40** (61%)

Likewise, the haloalkyl isocyanates (**41**) were treated with potassium or ammonium thiocyanate in the presence of dibenzo-18-crown-6 to give the highly functionalized 1-isothiocyanatoalkyl isocyanates (**42**) in moderate yields (61-67%).[31]



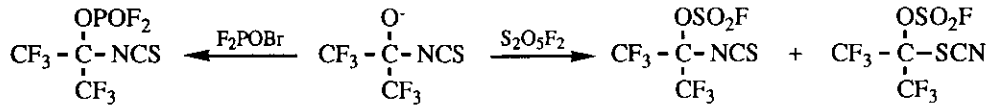
41

M = NH_4, K
R = H; X = Cl
R = C_6H_5, 4-$CH_3C_6H_4$; X = F

42

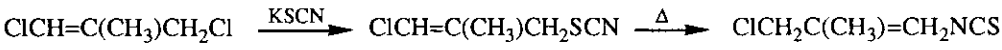
A mixture of 2-thiocyanato and 2-isothiocyanato-2-*O*-fluorosulfatohexafluoropropane (**44** and **45**) was obtained

by addition of NaSCN to hexafluoroacetone and further reaction with pyrosulfuryl fluoride.[32] In the presence of phosphorus (V) oxide bromide difluoride, the isothiocyanate (**46**) was exclusively obtained.



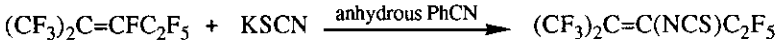
46 **43** **44** **45**

Polyhaloalkenes react smoothly with potassium thiocyanate to give haloalkenyl isothiocyanates.[11,33-35] The reaction proceeds *via* the kinetically formed thiocyanates (**48**), which are converted by thermolytic rearrangement into the thermodynamically more stable isothiocyanates (**49**).



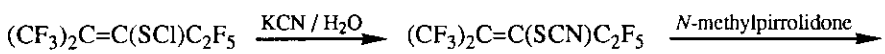
47 **48** (60%) **49** (50%)

Analogously, perfluoroalkenyl isothiocyanates are prepared[36] by reaction of perfluoroalkenes with potassium thiocyanate.

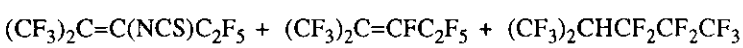


50 **51**

An alternative synthesis of perfluoroalkenyl isothiocyanates was also performed by treatment of RSCl with aqueous potassium cyanide, and further isomerization to the corresponding isothiocyanates with *N*-methylpirrolidone.[36]

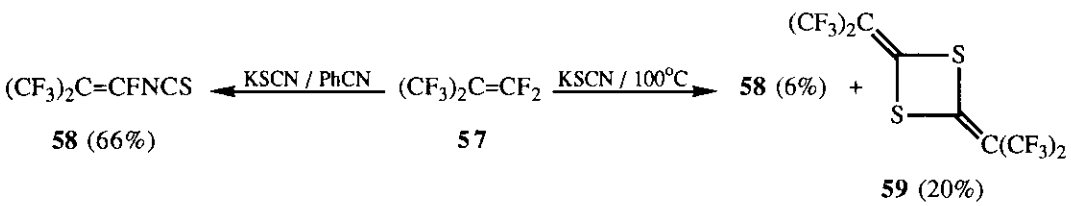


52 **53**



54 (62%) **55** (10%) **56** (28%)

In some cases, heterocyclic compounds can be also isolated.[17] The perfluoroolefin (**57**) when treated with potassium thiocyanate in PhCN afforded the isothiocyanate (**58**), whereas at 100℃ gave bis[bis(trifluoromethyl)-methylene]-1,3-dithiethane (**59**) and a small amount of the isothiocyanate (**58**).



58 (66%) **57** **58** (6%) **59** (20%)

Likewise, polyhaloazoalkenes (**60**) can be converted into the corresponding isothiocyanates by treatment with

thiocyanates under mild conditions.[37]

$$RN{=}CClCCl_3 \xrightarrow[acetone]{NaSCN} RN{=}C(NCS)CCl_3$$

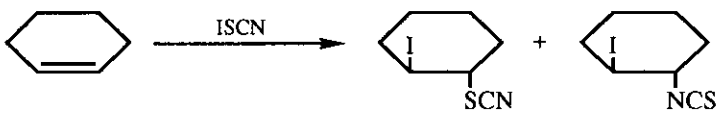
60 **61**

R = CH_3, C_2H_5, C_6H_{11}, C_6H_5

Transformation of 3-chloropropyl isothiocyanate into 3-iodopropyl isothiocyanate by halogen exchange with sodium iodide has been also reported.[38]

2.4 Addition of XSCN to Alkenes

Alkenes react with iodine (I) thiocyanate to give *vicinal* iodothiocyanates and iodoisothiocyanates.[39] The reagent is prepared *in situ* by treatment of ICl with potassium or thallium thiocyanate, or by treating iodine with KSCN in chloroform or a chloroform-sulfolane mixture. Thus, reaction of ICl with KSCN in $CHCl_3$-sulfolane at 0℃ followed by addition of cyclohexene gave 67% *trans*-1-iodo-2-thiocyanatocyclohexane (**62**) and 1% *trans*-1-iodo-2-isothiocyanatocyclohexane (**63**). Treatment with iodine-KSCN in the same solvent mixture at 0℃ in the dark gave **62** in 96% yield, whereas use of TlSCN gave **62** in 15% yield and **63** in 60% yield. When chloroform alone was used as solvent with TlSCN, **62** in 25% yield and **63** in 53% yield were obtained. Therefore, simple variation of the metal thiocyanate allows formation of either the iodothiocyanate or the iodoisothiocyanate as the major product.



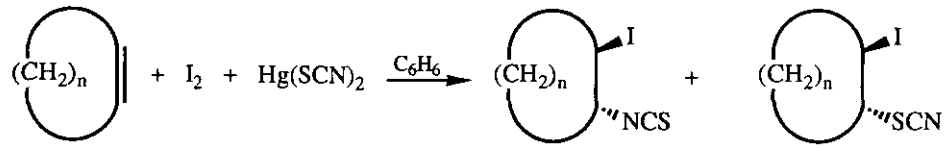
62 **63**

The authors have suggested that the enhanced yield of iodoisothiocyanate from TlSCN is presumably due to retention of thallium-sulfur bonding, which results in increased availability of nucleophilic nitrogen in the potential ambident anion, as postulated for the iodocarboxylation of alkenes.[40]

This interesting electrophilic addition to alkenes can be also carried out under phase-transfer conditions.[41] Moreover, the rate of addition of iodine thiocyanate is accelerated using water as a second phase and further increased by addition of phase-transfer catalysts, such as Adogen 464 or 18-crown-6.

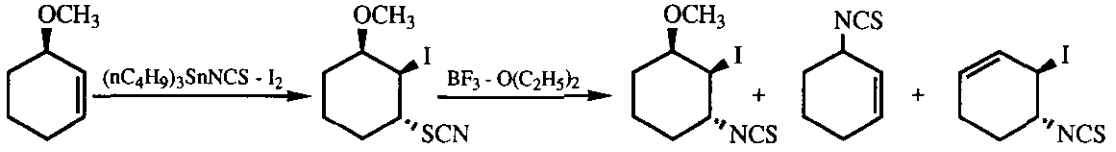
Further studies[42,43] have indicated that the ratio of the products varies with the reagents used to generate the ISCN, the conditions employed, and the nature of the alkene. A radical mechanism must be discarded, since treatment of cyclohexene with iodine-KSCN gave the same results when the reaction was performed in the presence of the free-radical inhibitor galvinoxyl, indicating an ionic pathway. The products are consistent with the intermediacy of an iodonium ion for cyclohexene as well as for 5α-androst-2-ene, and an open or asymmetric cation for α-arylalkenes. Although the method provides mixtures of iodothiocyanates and iodoisothiocyanates, reaction of boron trifluoride-etherate with the formed iodothiocyanate effects isomerization to the iodoisothiocyanate. The same authors have also found that the addition of iodine-thiocyanogen to alkenes can occur under ionic and radical conditions.[44] Thus, addition to alkenes in the dark proceeds by a regioselective ionic pathway to give mainly *vic*-iodoisothiocyanates, whereas under uv irradiation radical reactions afford *vic*-

iodothiocyanates as the major products. The addition of iodine-$Hg(SCN)_2$ to alkenes gave a mixture of *vic*-iodoisothiocyanate and *vic*-iodothiocyanate, the former being predominant.[45] Identical results were obtained by using AgSCN or TlSCN, albeit the yield and the selectivity were slightly lower. The use of KSCN in place of $Hg(SCN)_2$ resulted mainly in the formation of β-iodothiocyanates.



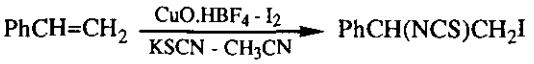
64 n = 0, 1, 2 **65** (major) **66** (minor)

The combination of isothiocyanatotributylstannane-iodine is a more effective reagent than iodine-KSCN, giving moderate yields of iodothiocyanato adducts when reacted with alkenes in dichloromethane.[46] A catalytic amount of the isothiocyanatotributylstannane led to low yields of adducts. Likewise, the use of *N*-iodosuccinimide instead of iodine led also to a lower yield of the adduct. On the other hand, the reaction under uv irradiation gave no iodothiocyanate.



67 **68** (43%) **69** (36%) **70** (8%) **71** (4%)

The reaction of an alkene with a mixture of iodine-$CuO.HBF_4$ and an excess of nucleophile, provides the corresponding *trans*-1,2-iodofunctionalized product stereoselectively.[47] Reaction with KSCN as nucleophile in acetonitrile affords the *vic*-iodoisothiocyanate. The Markovnikov regioisomer was exclusively obtained with styrene and 2-methylpent-1-ene, but monosubstituted alkenes gave an equimolecular mixture of two regioisomers. The authors have also proposed a mechanism involving a cyclic iodonium ion intermediate.



72 **73** (42%)

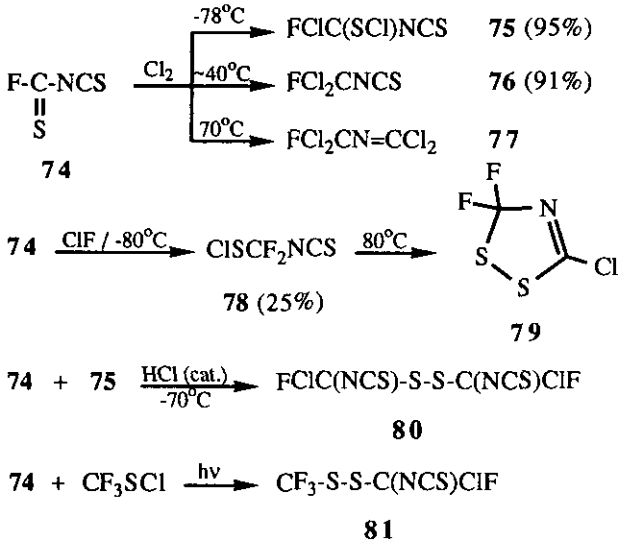
Addition to alkenes has been also carried out with chlorine (I) thiocyanate. Again, *trans* adducts and Markovnikov regioisomers were mainly obtained.[48]

Iodothiocyanates can isomerize into more thermodynamically stable iodoisothiocyanates, although attempted isomerization of 2-iodoethyl thiocyanate with BF_3-etherate gave only a trace of the 2-iodoethyl isothiocyanate.[42,43,46] However, this transformation for 1,1-dichloroalkyl thiocyanates, $RCCl_2SCN$, has not been observed.[49]

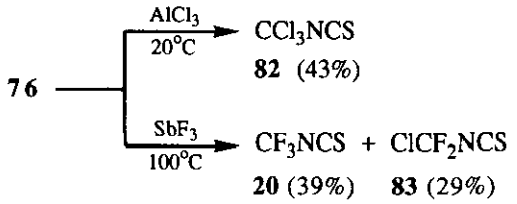
2.5 Halogenation of Saturated and Unsaturated Isothiocyanates

Halogenation procedures constitute an expeditious methodology to obtain a wide variety of haloalkyl

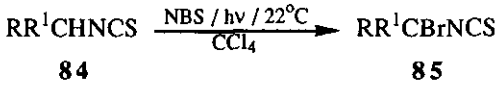
isothiocyanates. Thus, several fluorochloromethyl isothiocyanates are obtained from fluoromethylthiocarbonyl isothiocyanate (**74**) with chlorine or chlorofluoride at different temperatures.[23]



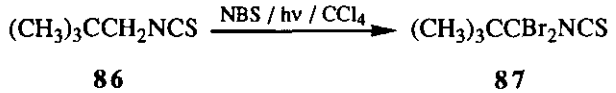
Likewise, the isothiocyanate (**76**) may be converted into other perhalomethyl isothiocyanates by treatment with aluminium chloride or antimony (III) fluoride,[23,50,51] as indicates below.



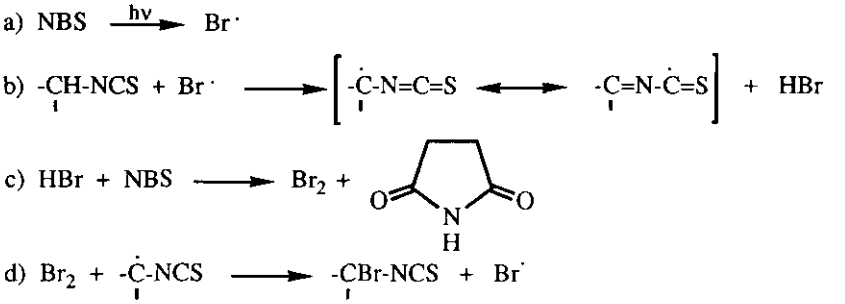
Chlorination of α-alkenyl isothiocyanates provides dichloroalkyl isothiocyanates in good yield.[52] Similarly, addition of bromine to allyl isothiocyanates results in 2,3-dibromopropyl isothiocyanates in high yield.[35a,53,54] Secondary isothiocyanates and activated primary isothiocyanates with an electron-withdrawing group, react with NBS under uv irradiation to form α-brominated isothiocyanates in excellent yields.[55]



The unactivated primary isothiocyanates give α,α-dibromoisothiocyanates, and methyl isothiocyanate did not react by this procedure.

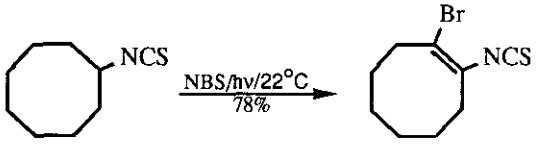


For α-bromination of isothiocyanates with NBS the so-called Goldfinger mechanism[56] was suggested, wherein the formed radical is stabilized by the NCS group (Scheme 1).



Scheme 1

In the presence of β-hydrogens, some α-bromoisothiocyanates eliminate HBr to give β-bromo- and β,β-dibromoalkenyl isothiocyanates.

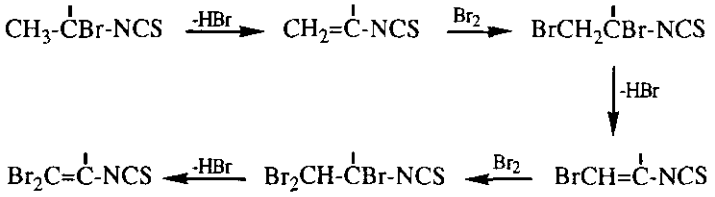


88 **89**

$CH_3CHPh\text{-}NCS \xrightarrow{NBS/h\nu/22^\circ C} CBr_2{=}CPh\text{-}NCS$

90 **91**

These compounds are formed through the corresponding alkenyl isothiocyanates by bromination-dehydrobromination reaction. The Scheme 2 highlights this process.



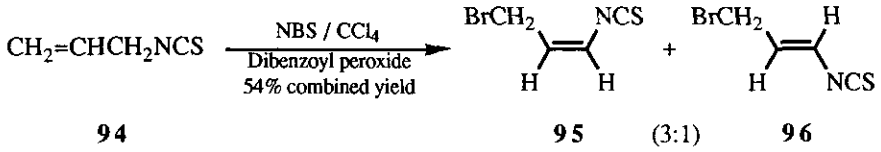
Scheme 2

2-Isothiocyanato-2-butenoates (**92**) have been successfully brominated with NBS to give γ-bromo-α-isothiocyanatoacrylic esters (**93**).[57]

$CH_3CPh{=}C(NCS)CO_2R \xrightarrow{NBS} BrCH_2CPh{=}C(NCS)CO_2R$

92 R = CH_3 (89%), R = C_2H_5 (92%) **93**

A further study[58] on the radical bromination of allyl isothiocyanate indicates that *cis*- (**95**) and *trans*-3-bromo-1-propenyl isothiocyanates (**96**) are obtained in the ratio 3:1, from which the pure *trans* isomer was isolated by freezing out.



94 **95** (3:1) **96**

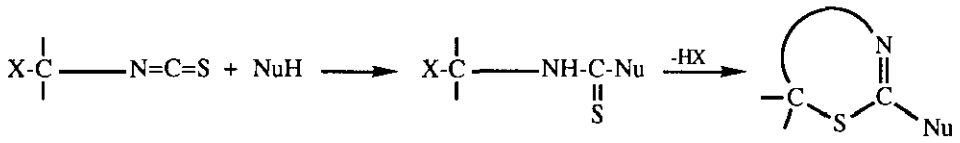
3. REACTIONS OF HALOALKYL ISOTHIOCYANATES

Haloalkyl isothiocyanates are bifunctional compounds due to the presence of two active electrophilic centers.

The presence of halogen atoms in places other than α-position does not affect the reactivity of the isothiocyanato group, although some anomalous reactivities have been also reported (see sections 3.1 and 3.5.1). In contrast, α-haloalkyl isothiocyanates display enhanced reactivity of the isothiocyanato group and the α-halogen atoms, due to their mutual influence. Thus, hard nucleophiles attack the α-carbon atom with substitution of halide, whereas soft nucleophiles add to the carbon atom of the isothiocyanato group.

Unlike α-haloalkyl isocyanates, R_2CX-N=C=O, which undergo anionotropic rearrangement with the iminocarbonyl halide form, R_2C=N-CXO, α-haloalkyl isothiocyanates exist only in the isothiocyanato form.

Additions of nucleophiles on the isothiocyanato group allow formation of either unsaturated compounds by β-dehydrohalogenation, or heterocycles by cyclodehydrohalogenation (Scheme 3).



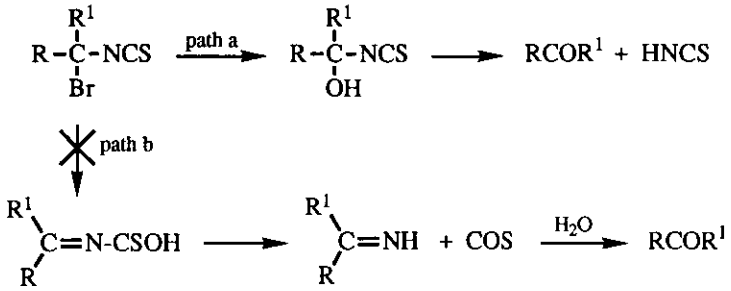
Scheme 3

The diastereomerically pure *erythro*- and *threo*-1-chloro-1-phenyl-2-isothiocyanatopropanes, among other compounds, have been prepared and further used to determine the stereochemical course of these reactions.[7d] One should note that these processes occur in a stereospecific fashion with several nucleophiles.

γ-Haloalkenyl isothiocyanates give mainly γ-substituted products. On the other hand, the bielectrophilic haloalkyl isothiocyanates can also react with bifunctional nucleophiles to give a wide variety of heterocycles, and it will be outlined in further sections.

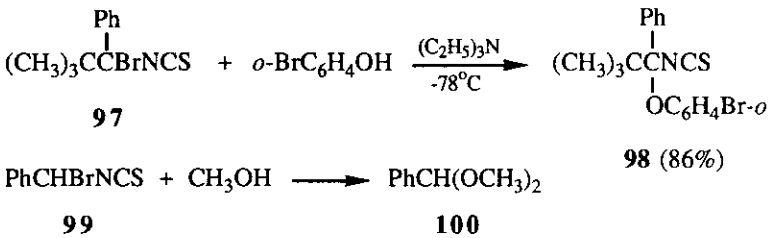
3.1. Reaction with Oxygen Nucleophiles

The hydrolysis of α-bromoalkyl isothiocyanates leads to carbonyl compounds[55b] (Scheme 4).



Scheme 4

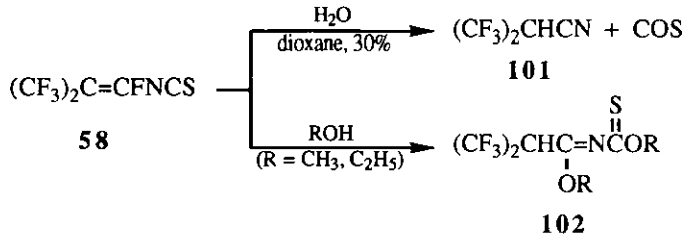
The reaction takes place by attack of water (hard nucleophile) to give the corresponding halogen substitution (path a). The alternative addition to isothiocyanato group (path b) must be discarded, since the reaction with alcohols gives rise α-alkoxy isothiocyanates (**98**). The reaction of **99** with methanol afforded the dimethyl acetal **100**.



97 **98** (86%)

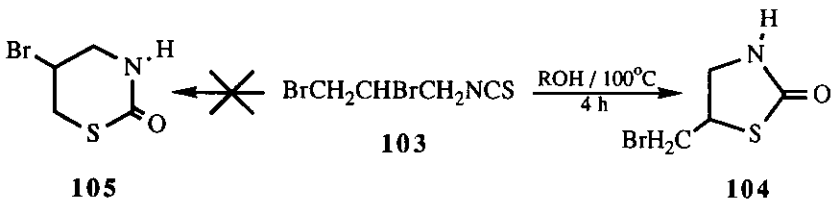
99 **100**

In contrast, α-fluoroalkenyl isothiocyanates add water to give nitriles. By cautious hydrolysis the corresponding amide can be isolated. Perfluoroalkenyl isothiocyanates react with alcohols to afford addition-substitution products (**102**).[33]



58 **101** **102**

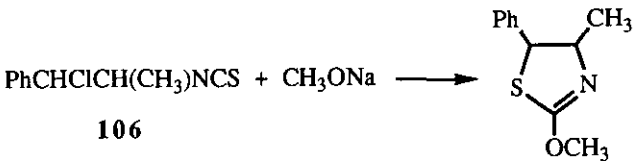
β-Haloalkyl isothiocyanates react with alcohols to produce thiazolidin-2-ones in moderate to good yields.[59,60] The formation of five-membered rings is more favorable than that of six-membered rings.[54] Thus, 2,3-dibromopropyl isothiocyanate gives exclusively the thiazolidine (**104**).



105 **103** **104**

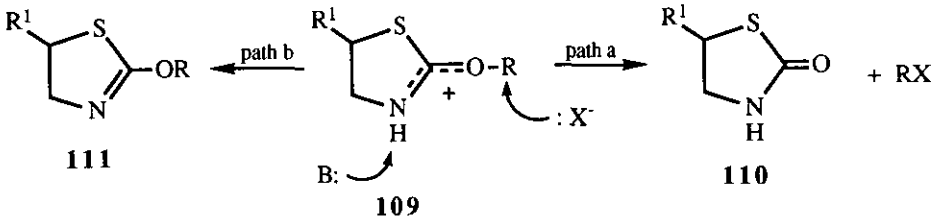
ROH	**104** (%)
CH_3OH	53
C_3H_7OH	39
C_5H_5OH	55
i-C_5H_5OH	47

The reaction of haloalkyl isothiocyanates with a sodium alkoxide or with alcohols in the presence of an organic base gives rise 2-alkoxy-2-thiazolines.[29,61]



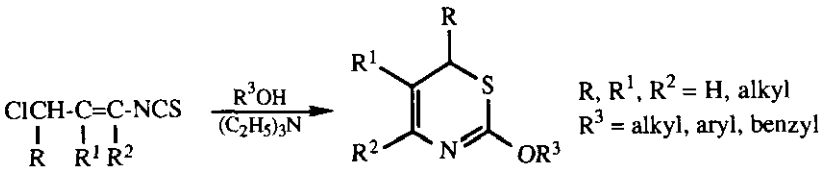
106 **107**

The formation of products should occur from **108**, $R^1CHXCH_2NHCSOR$, *via* the intermediate (**109**). Without base, the halide ion forces the elimination of alkyl halide (path a). In the presence of base, the alkoxy thiazoline (**111**) is generated by deprotonation.



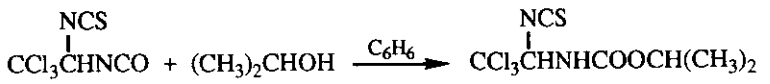
111 **109** **110**

γ-Isothiocyanatoallyl chlorides react with alcohols in the presence of triethylamine to provide 2-alkoxy-6*H*-1,3-thiazines, among other addition-substitution products.[62]



112 **113**

Alcohols add selectively to the isocyanate group of *gem*-isothiocyanatoalkyl isocyanates, which is in agreement with the greater reactivity of this functional group.[31]

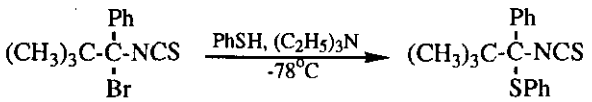


114 **115**

Curiously, neither α- nor β-naphthol reacted with 5-fluoropentyl and 6-fluorohexyl isothiocyanates.[10]

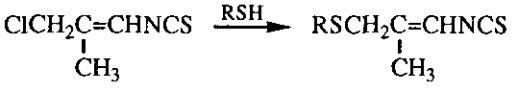
3.2. Reaction with Sulfur and Selenium Nucleophiles

The reactions of α-haloalkyl isothiocyanates with thiols in the presence of triethylamine give rise to α-thioalkyl (aryl) isothiocyanates.[55b,c]



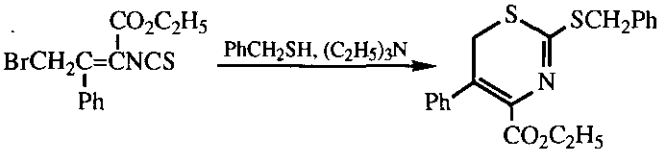
97 **116** (90%)

γ-Haloalkenyl isothiocyanates (**117**) display a similar behavior[34c,57] to give the corresponding substitution products (**118**), although they can also undergo addition to the isothiocyanate group and further cyclization to afford the 6*H*-1,3-thiazine-4-carboxylate (**119**).



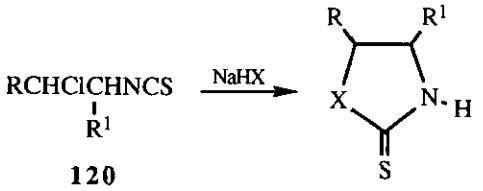
117 **118**

R = C_2H_5, n-C_4H_9, $PhCH_2$, Ph



93 **119**

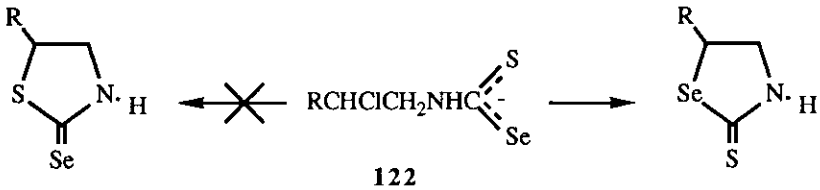
β-Haloalkyl isothiocyanates react with hydrogen sulfide anion to form thiazolidine-2-thiones[7c,d,63,64] (**121**, X=S). These compounds are effective *S*-transfer reagents for the conversion of oxiranes in thiiranes.[64] Analogously, 1,3-selenazolidine-2-thiones (**121**, X=Se) are generated by treatment with sodium hydrogen selenide.[7c,63] These syntheses proceed stereospecifically[7d] with high yields (75-95%).



X = S; R = H, aryl; R^1 = H
X = S; R, R^1 = C_2H_5, n-C_3H_7, -$(CH_2)_4$-
X = Se; R = H, CH_3, aryl; R^1 = H

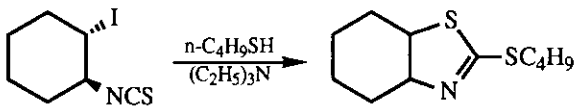
120 **121**

The products (**121**) arise from the corresponding dithio- or selenothiocarbamate salts, which upon acid treatment undergo an intramolecular S_N2 cyclization. The selenothiocarbamate intermediate (**122**) could also lead to thiazolidine-2-selenones (**123**), though selenazolidine-2-thiones (**124**) were exclusively formed due to the higher nucleophilicity of selenium.



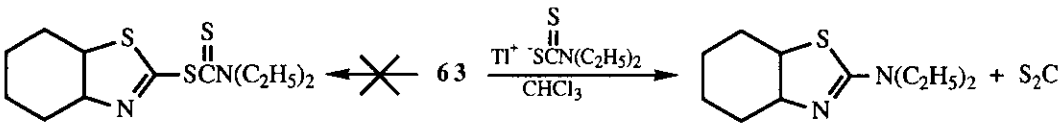
123 **122** **124**

β-Haloalkyl isothiocyanate, **63**, reacts with n-butanethiol to give 7% of **125** in the absence of base and 72% with triethylamine.[61,64,65]



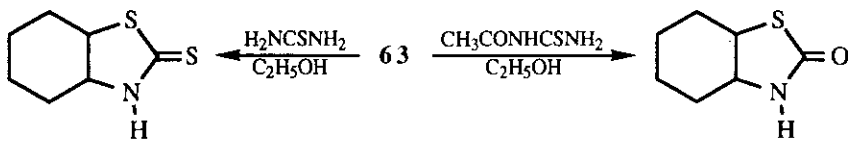
63 **125** (72%)

The reaction of **63** with the thallium salt of *N,N*-diethyl dithiocarbamate gave no the expected adduct (**126**), but instead the *N,N*-diethylamino-2-thiazoline (**127**) was obtained by expulsion of carbon disulfide.



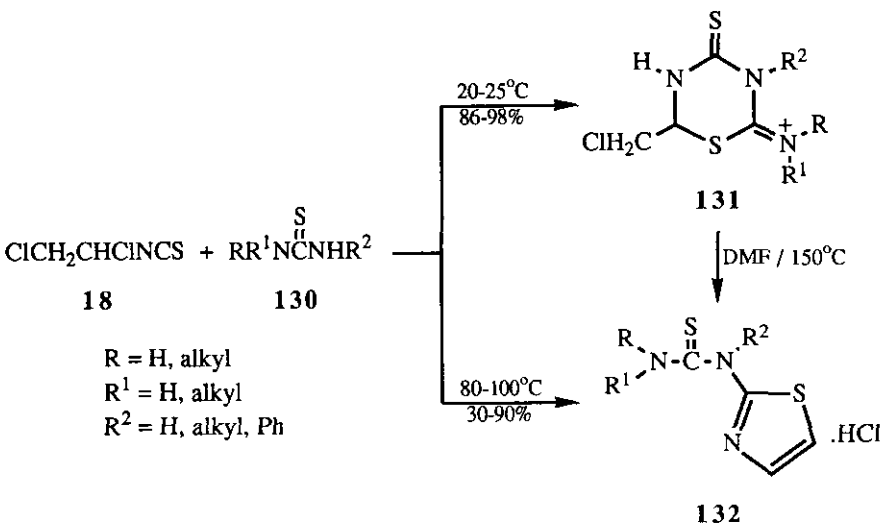
126 **127** (86%)

Treatment of **63** with thiourea in ethanol or sulfolane and aqueous sodium hydroxide gives rise to a mixture of products, which contained mainly the starting material and a small amount of the thiazolidine-2-thione (**128**). Reaction with *N*-acetyl thiourea in ethanol affords the thiazolidin-2-one (**129**) by solvent attack. In addition, attempts to convert **63** into **128** with ethyl dithiocarbonate anion, EtOCSS$^-$, were unsuccessful and **63** was essentially recovered.



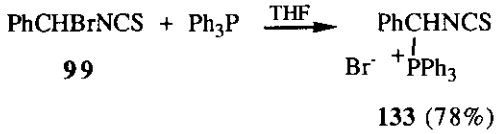
128 (<7%) **129** (62%)

In contrast, the reaction between 1,2-dichloroethyl isothiocyanate (**18**) and thiourea or substituted thioureas (**130**) provides tetrahydro-1,3,5-thiadiazine derivatives (**131**) or *N*-(thiazol-2-yl)thioureas (**132**) depending on the reaction conditions.[14]

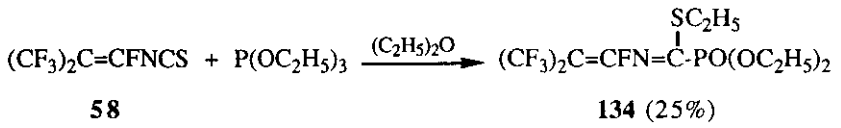


3.3. Reaction with Phosphorus Nucleophiles

Unlike α-haloalkyl isocyanates,[4] reactions of their corresponding thiocounterparts with phosphorus nucleophiles are relatively scarce. A few examples with phosphines and phosphites in Arbuzov-type reactions have been reported. Thus, the α-bromoisothiocyanate (**99**) reacts with triphenylphosphine to afford the phosphonium salt **133**.[55b]



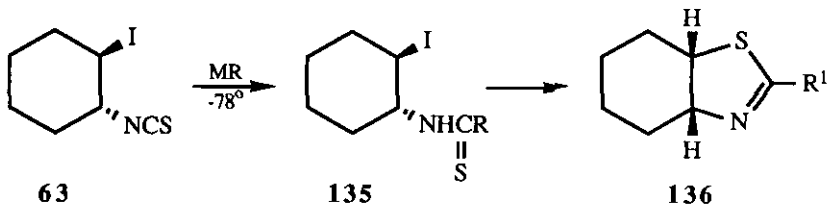
The perfluoroalkenyl isothiocyanate (**58**) gives the ketimine derivative (**134**) in low yield, upon treatment with triethyl phosphite.[33]



3.4. Reaction with Carbon Nucleophiles

Haloalkyl isothiocyanates (**63**) react with some carbon nucleophiles to give thioamides (**135**), although cyclization into 2-substituted 2-thiazolines (**136**) can be easily effected.[30b,38,65,66] Moreover, 2-thiazolines may be formed directly from the starting isothiocyanates, which are markedly influenced by the nature of nucleophile and the solvent mixture.

Reactions of *trans*-1-iodo-2-isothiocyanatocyclohexane with carbon nucleophiles are summarized in Table I.[38]



63 **135** **136**

Table I

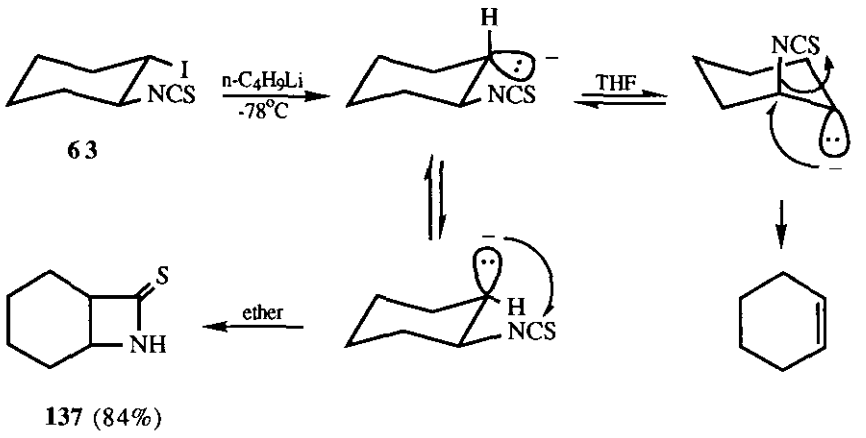
MR	R^1	**135** (%)	**136** (%)
KCN	CN	100	100
4-$CH_3OC_6H_4C{\equiv}CLi$	4-$CH_3OC_6H_4C{\equiv}C$	64	73
4-$CH_3OC_6H_4C{\equiv}CMgBr$	4-$CH_3OC_6H_4C{\equiv}C$	73[a]	73[a]
$PhC{\equiv}CLi$	$PhC{\equiv}C$	—[b]	68
$(CH_3)_3SiC{\equiv}CLi$	$HC{\equiv}C$	100	41
PhLi	Ph	100	80
CH_3MgI	CH_3	—[c]	70
C_2H_5MgI	C_2H_5	—[c]	72
n-C_4H_9MgBr	n-C_4H_9	—[c]	83
n-C_4H_9MgI	n-C_4H_9	—[c]	61

[a]Four-fold molar excess of Grignard reagent. [b]Not determined. [c]Not observed

No product could be isolated when the iodoisothiocyanate (**63**) was treated with ethynyllithium. In order to stabilize the product, the ethynyl group was introduced in a protected form as trimethylsilylethynyllithium. Reaction of the latter with **63** gave the adduct (**135**), which underwent both cyclization and cleavage of the trimethylsilyl group to give **136**.

Reactions of simple alkyl Grignard reagents with **63** afforded the 2-substituted 2-thiazolines (**136**) in one step. The use of an excess of Grignard reagent did not result in further alkylation of the 2-thiazolines. The reaction of **63** with *n*-butylmagnesium bromide was faster than that with *n*-butylmagnesium iodide, giving better overall yield of **136**.

The use of *n*-butyllithium as nucleophile was also examined.[38] Curiously, treatment of **63** with *n*-butyllithium in ether at -78℃ afforded *cis*-7-azabicyclo[4.2.0]octane-8-thione (**137**) rather than the expected product (**136**, R^1 = *n*-Bu). This procedure constitutes a novel, although not general, method for the synthesis of thioxo-β-lactams. It is assumed that reaction of **63** with *n*-butyllithium in ether gives a carbanion which undergoes inversion at the anionic center. This conformation would favor intramolecular nucleophilic attack to give **137**. When a more basic solvent such as tetrahydrofuran is employed, elimination takes place. This process can be envisaged through conformational inversion of the carbanion, which leads to an *anti*-periplanar disposition between the isothiocyanate group and the anionic lone pair (Scheme 5).



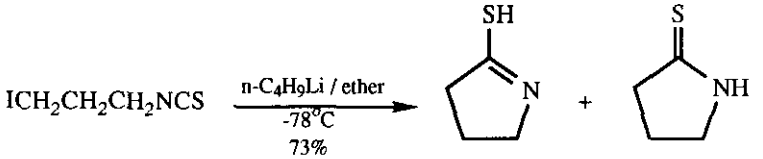
63

137 (84%)

Scheme 5

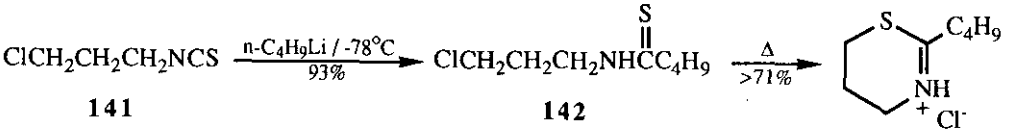
A further study with other *vic*-iodoisothiocyanates evidenced the conformational requirements in the above reactions. Thus, relatively rigid substrates with *trans*-diaxial substituents favor elimination, whereas conformationally mobile isothiocyanates favor a preferential thioxo-β-lactam formation.

A similar behavior was found in the reaction of 3-iodopropyl isothiocyanate (**138**) with *n*-butyllithium. A tautomeric (7:3) mixture of 4,5-dihydro-2-mercapto-1-pyrroline (**139**) and the 2-thioxopyrrolidine (**140**) was obtained.



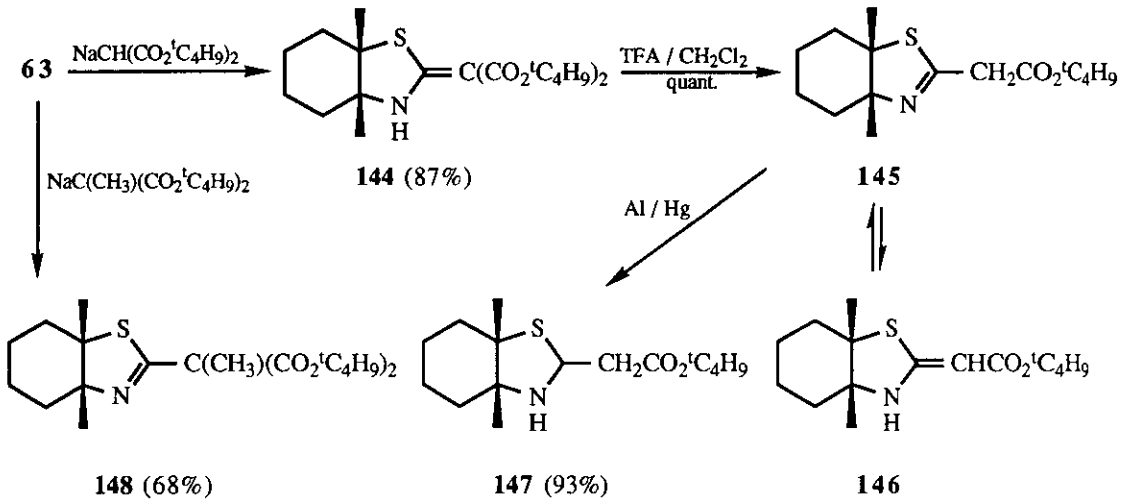
138 **139** **140**

However, no metal-halogen exchange was detected in the reaction of 3-chloropropyl isothiocyanate (**141**) with *n*-butyllithium. In this case, the *n*-butyl carbanion attacked the NCS group to give *N*-(3-chloropropyl)thiopentamide (**142**) which, on heating, gave 2-butyl-5,6-dihydro-4*H*-1,3-thiazinium chloride (**143**)[38].

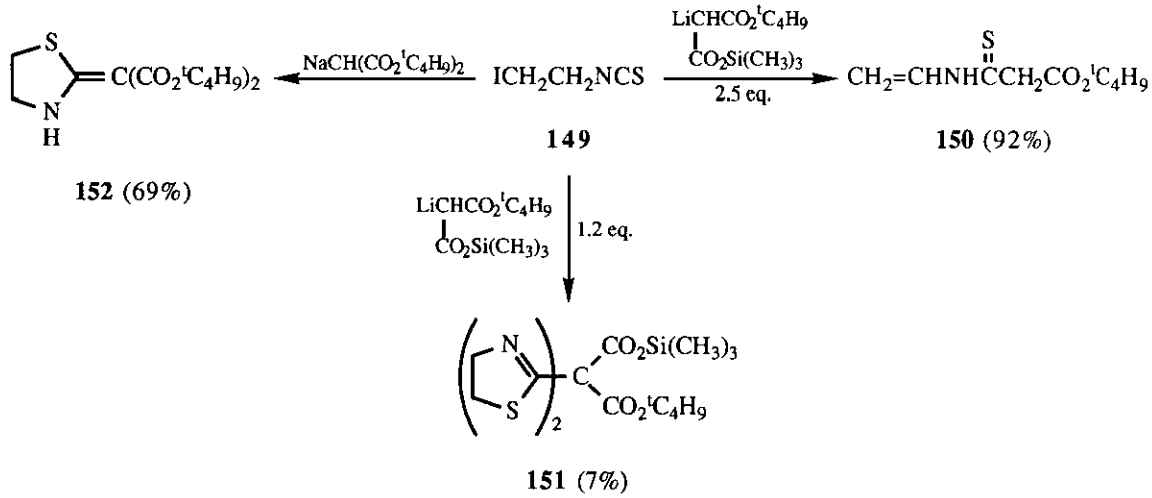


141 **142** **143**

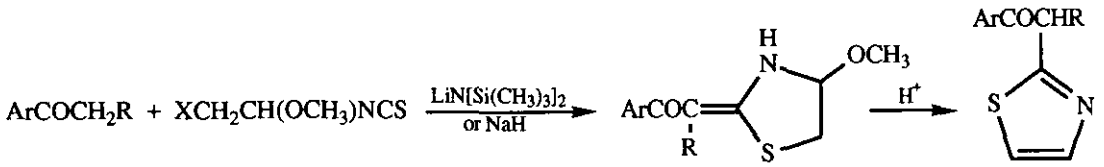
Treatment of *vic*-iodoisothiocyanates (*e.g.* **63**) with dialkyl sodiomalonates gave the corresponding dialkyl 2-(thiazolidin-2-ylene)malonates (**144**) in high yields. Cleavage of the dialkyl esters with trifluoroacetic acid was accompanied by concomitant decarboxylation to afford a tautomeric mixture of **145** and **146**. Further reduction of these mixtures with aluminium amalgam gave thiazolidines (**147**), which are suitable starting materials for the synthesis of penam and other polycyclic β-lactams.[66] In addition, reaction of **63** with di-*tert*-butylsodium 2-methylmalonate afforded the 2-(thiazolin-2-yl)methylmalonate (**148**).



In a related research on this topic, the authors have studied[66] the reaction of 2-iodoethyl isothiocyanate (**149**) with several carbanions. Treatment of **149** with 2.5 equiv. of the lithium salt of *tert*-butyl trimethylsilylmalonate gave the unstable thioenamide (**150**). Use of 1.2 equiv. of the same reagent in a less basic solvent afforded a product mixture, in which the bis-adduct (**151**) could be isolated. Finally, cyclization of **149** into the desired thiazolidine (**152**) was successfully achieved by employing the corresponding sodium malonate. Neither *tert*-butyl lithioacetate, nor potassium *tert*-butyl sodiomalonate, nor *tert*-butoxycarbonyl methylmagnesium bromide effected cyclization of *vic*-iodoisothiocyanates.



Carbon nucleophiles derived from ketones also add to haloalkyl isothiocyanates.[30b] The carbanion generated from **153** with lithium hexamethyldisilazide or sodium hydride in tetrahydrofuran, reacts with 2-chloro- or 2-bromo-1-methoxyethyl isothiocyanate (**154**) to give the corresponding 4-methoxythiazolidine (**155**). A further elimination gave the thiazole derivative (**156**), which exists as a tautomeric mixture with its thiazoline form.



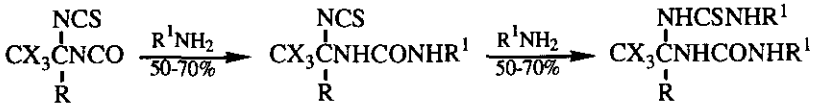
153 **154** **155** **156**

R = H, $CO_2C_2H_5$ X = Cl, Br

3.5. Reaction with Nitrogen Nucleophiles

3.5.1. Reaction with Amines

Reaction of haloalkyl isothiocyanates with amines was described as early as the beginning of the 20th century.[35a,53] The reaction with tertiary amines leads to dehydrohalogenation (see section 3.7), whereas primary and secondary amines add to the NCS group to form the corresponding thioureas.[25-27,67-72] The isocyanate group shows a greater reactivity than the isothiocyanate group. Thus, the *gem*-isothiocyanatoalkyl isocyanate (**42**) reacts with amines to give the urea (**157**). With an excess of amine, the thiourea derivative (**158**) may be also formed.[31]



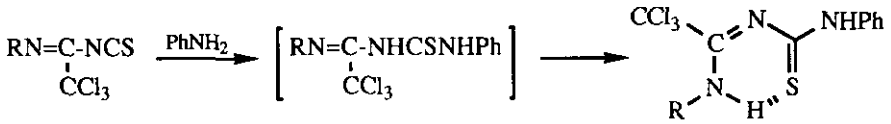
42 **157** **158**

X = F, Cl
R = H, aryl

R^1 = aryl, cyclohexyl

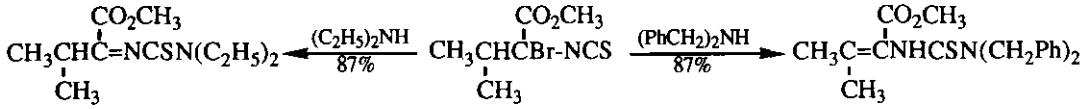
Surprisingly, 5-fluoropentyl and 6-fluorohexyl isothiocyanates failed to react with aniline and anhydrous ammonia.[10]

Imidoyl thioureas (**159**) tautomerize into **160**, which are stabilized by an intramolecular hydrogen bridge.[37]



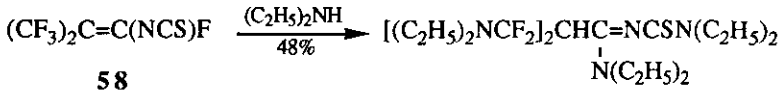
61 **159** ***160***

Other unsaturated thioureas are generated[55b,c] by reaction of α-bromo- or α,α-dibromoalkyl isothiocyanates with amines in diethyl ether at low temperatures (-78℃). Thus, **161** produces the alkyliden thiourea (**162**) or the vinyl thiourea (**163**).



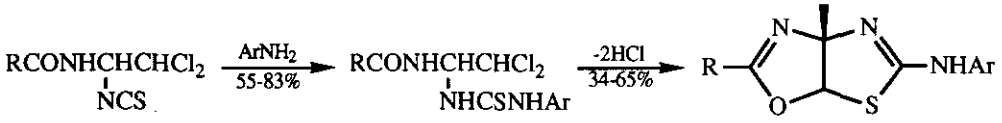
162 **161** **163**

The perfluorovinyl isothiocyanate (**58**) reacts with diethylamine to afford the imidoyl thiourea (**164**), by simultaneous addition, substitution, and isomerization processes.[33]



58 **164**

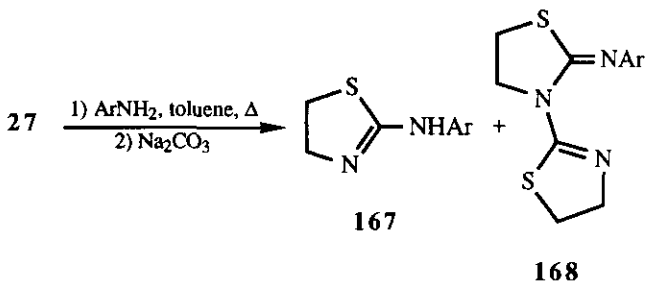
Some haloalkyl isothiocyanates react with ammonia and primary or secondary amines to give heterocyclic compounds in one-step.[6,8,60,65,67,73-87] β-Haloalkyl isothiocyanates afford 2-amino-2-thiazoline derivatives, which can be aromatized to the corresponding thiazoles[86] or, with the appropriate functionalization, they can undergo a double cyclization process. Thus, **36** gives rise thiazoloxazoles (**166**).[26]



36 **165** **166**

An interesting feature has been observed in the reaction of 2-chloroethyl isothiocyanate (**27**) with aromatic amines, which produces a mixture of 2-arylamino-2-thiazolines (**167**) and the bis-adducts (**168**).[88]

The data in Table II reveal that electron-releasing substituents on the aryl ring result in the preferential formation of **167**, while electron-withdrawing groups favor the *N*-thiazolinyl-2-iminothiazolidines (**168**). Reaction with 2-aminopyridine gave no 2-amino-2-thiazoline (**167**).

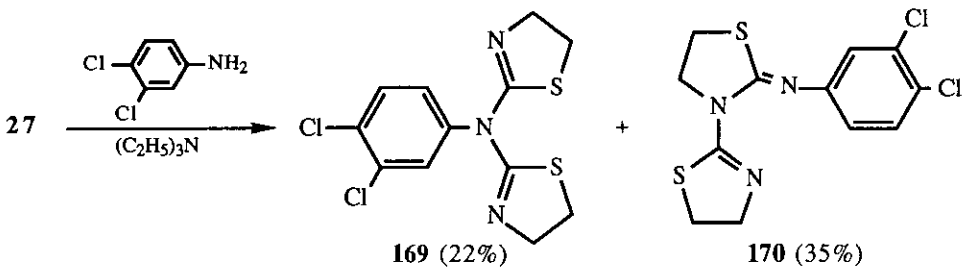


167 **168**

Table II

Ar	**167**(%)	**168**(%)
4-$CH_3C_6H_4$	79	9
3-BrC_6H_4	66	9
3,4-$Cl_2C_6H_3$	38	30
	23	44
	0	73

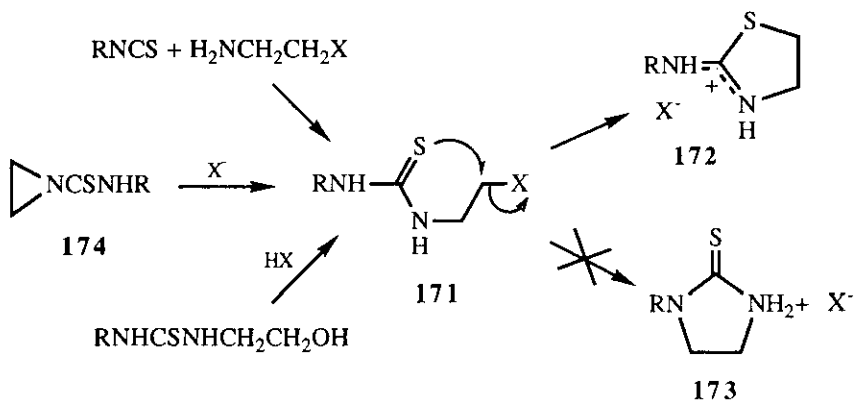
Reaction of 3,4-dichloroaniline with **27** in the presence of triethylamine provides two bis-adducts (**169**) and (**170**).



169 (22%) **170** (35%)

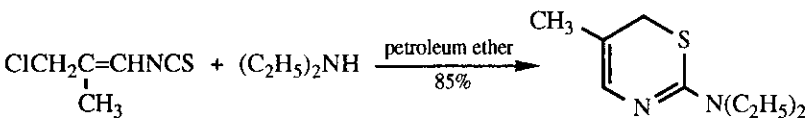
These reactions must occur *via* the corresponding haloethyl thioureas (**171**), which may be also generated by reaction of 2-haloethyl amines with isothiocyanates,[84,85,87] by treatment of 2-hydroxyethyl thioureas or allyl thioureas with hydrogen halide, or halide promoted opening of carbamoylaziridines (**174**)[89] (Scheme 6).

The intermediates (**171**) undergo S_Ni reactions to give rise **172**, because of the greater nucleophilicity of the sulfur atom. The reaction occurs in a stereospecific fashion,[7d] and it can be interpreted in terms of the HSAB concept. Curiously, the formation of imidazolidine-2-thiones (**173**) has been also proposed in two cases,[90-92] although further reinvestigations[87,93,94] have confirmed the structure of 2-amino-2-thiazoline in the first one.[90,91]



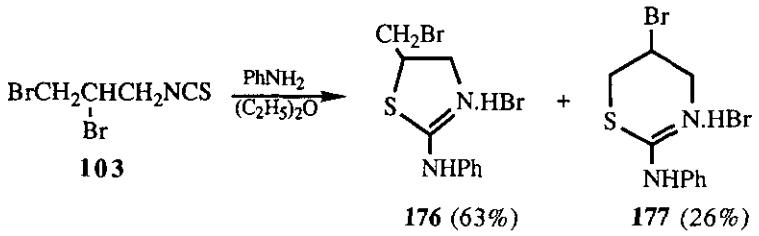
Scheme 6

Analogously, γ-haloalkyl isothiocyanates can be converted into 2-amino-4*H*,5*H*,6*H*-1,3-thiazines,[6] and γ-alkenyl isothiocyanate derivatives (**49**) are transformed into 2-amino-6*H*-1,3-thiazines (**175**).[34a,62]



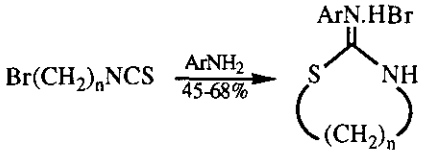
49 **175**

The reaction of β,γ-dihalopropyl isothiocyanates with amines leads to a preferential formation of five-membered rings.[95,96]



103 **176** (63%) **177** (26%)

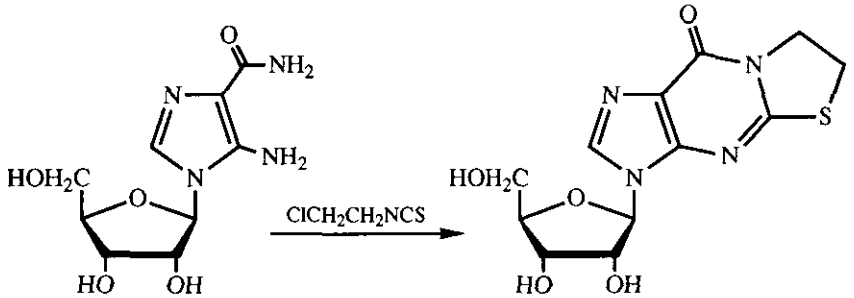
Finally, the reaction between ω-bromoalkyl isothiocyanates and aromatic amines serves as a general method for the synthesis of 2-arylimino-1,3-thiaazacycloalkanes (**178**). Thus, thiazepine (n = 4), thiazocine (n = 5), thiazonine (n = 6), thiaazacycloundecane (n = 8), and thiaazacyclotridecane (n = 10) derivatives were prepared in moderate yields.[8]



178, n = 4, 5, 6, 8, 10

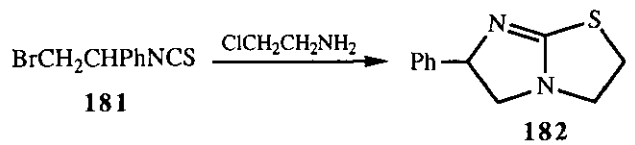
3.5.2. Double Cyclization with β-Functionalized Amines

Haloalkyl isothiocyanates can react with amines containing reactive groups in the β-position taking place a double cyclization process, which leads to a fused system.[97-100] Thus, the *N*-nucleoside (**180**) was prepared[100] in one-pot *via* cyclization of 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (**179**) with 2-chloroethyl isothiocyanate.



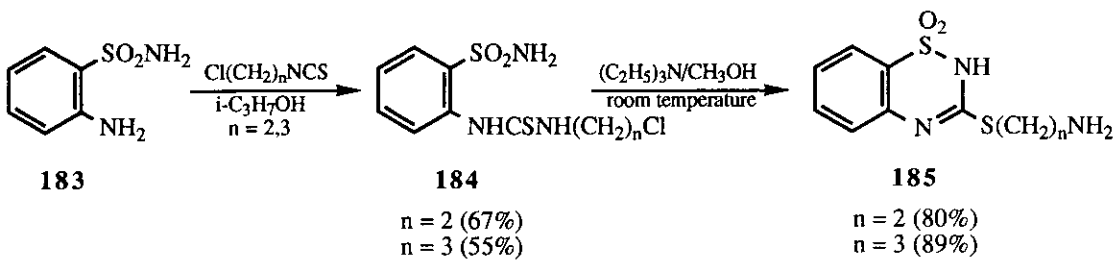
179 **180**

Addition of 2-chloroethylamine to the isothiocyanate (**181**) provides fused heterocycles, namely tetramisoles (**182**).[101]



181 **182**

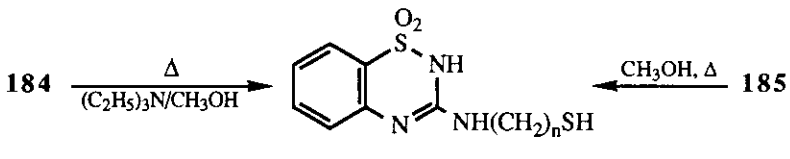
Reaction of 2-aminobenzenesulfonamide (**183**) with 2-chloroethyl or 3-chloropropyl isothiocyanate leads to construction of the 2*H*-1,2,4-benzothiadiazine 1,1-dioxide ring system bearing a side chain at C-3 capable of forming a further fusion component.[102]



183 **184** **185**

n = 2 (67%)
n = 3 (55%)

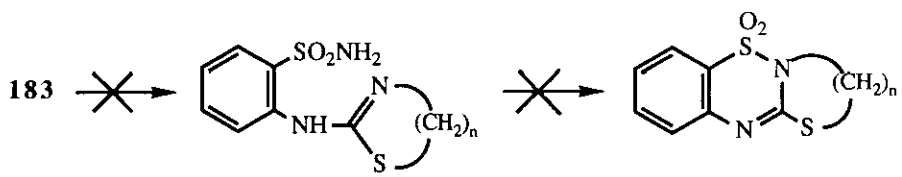
n = 2 (80%)
n = 3 (89%)



186

n = 2 (95%)
n = 3 (77%)

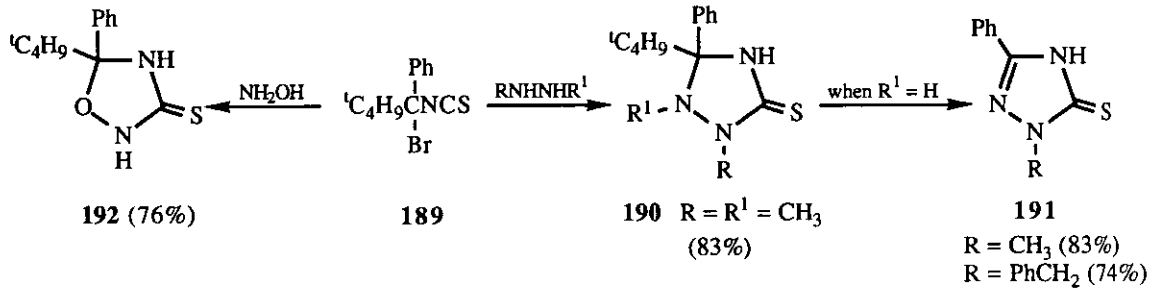
Nevertheless, the expected compound (**187**) could not be obtained, and therefore the logical final product (**188**) was also rejected.



187 **188**

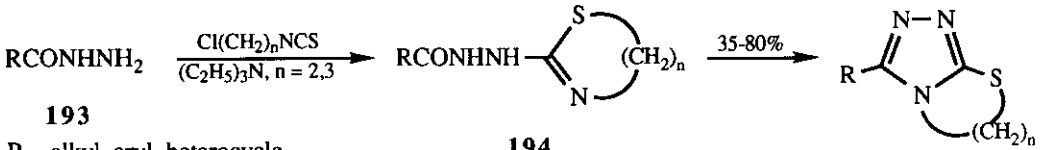
3.5.3. Reaction with Bifunctional Nucleophiles

The reaction of α-haloalkyl isothiocyanates with bifunctional nucleophiles gives heterocycles by addition and substitution to the two electrophilic centers.[55b,c] Addition of mono- and 1,2-disubstituted hydrazines to **189** forms 5*H*-1,2,4-triazolin- (**190**) and 1,2,4-triazolidin-3-thione (**191**) derivatives, respectively. Treatment with hydroxylamine affords the 1,2,4-oxadiazolidin-3-thione (**192**).



192 (76%) **189** **190** $R = R^1 = CH_3$ (83%) **191** $R = CH_3$ (83%), $R = PhCH_2$ (74%)

Aryl- and acylhydrazines,[102-106] ureas,[14] thioureas[14] (see also section 3.2), and guanidines[107] react with ω-haloalkyl isothiocyanates to substitute the hydrogen of the NH group by 2-thiazoline or 2-thiazine rings.

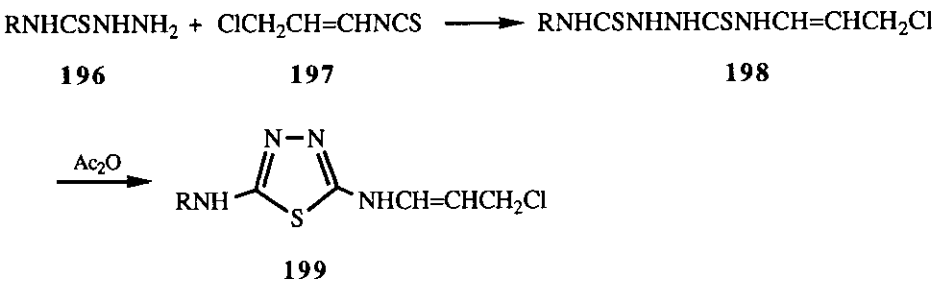


193
R = alkyl, aryl, heterocycle

194

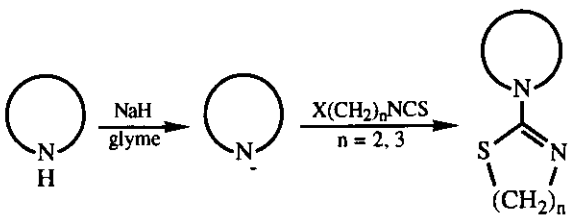
195

The γ-chloropropenyl isothiocyanate (**197**) reacts with thiosemicarbazides to give an adduct (**198**), which cyclizes to 1,3,4-thiadiazoles (**199**) by treatment with acetic anhydride.[108]



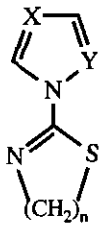
3.5.4. Reaction with Heterocyclic NH Groups

A comprehensive literature has been reported on this topic. In general treatment of heterocyclic NH groups with sodium hydride in glyme forms a heterocyclic anion, which is further attacked by haloalkyl isothiocyanates to produce 2-thiazoline or 2-thiazine derivatives (Scheme 7).

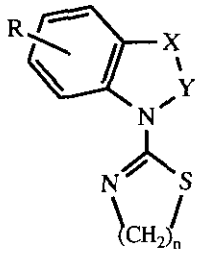


Scheme 7

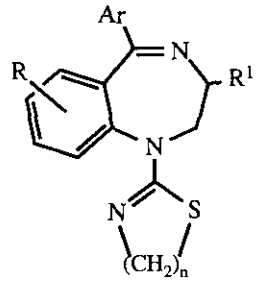
Thus, pyrazole (**200**),[109,110] imidazole (**201**),[110] 1,2,4-triazole (**202**),[111] fused benzoheterocycles (**203**),[110,112] (**204**),[113] (**205**),[110,114] (**206**),[110,115-120] (**207**),[110,121,122] (**208**),[76,123,124] (**209**),[125] benzodiazepines (**210**),[126] as well as other heterocyclic rings[110,126,127] underwent this derivatization.



200 X = CH, Y = N
201 X = N, Y = CH
202 X = Y = N



203 X = Y = CH
204 X = CH, Y = N
205 X = Y = N
206 X = N, Y = C-NH_2
207 X = N, Y = C-R^1, R^1 = H, Ar, SCH_3
208 X = NR, Y = CO, CS
209 X = Y = CH_2

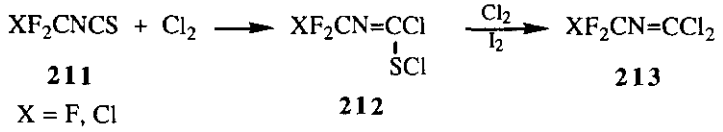


210

3.6. Halogenation

As was pointed out previously (section 2.5), halogenation of isothiocyanates constitutes a good procedure for the synthesis of haloalkyl isothiocyanates. These compounds can be converted into other polyhaloalkyl derivatives by further halogenation. This feature is particularly important, since polyhalogenated compounds represent an ongoing research area.

Trifluoromethyl and chlorodifluoromethyl isothiocyanates (**211**) add chlorine to the thiocarbonyl group to give intermediates (**212**), which in the presence of iodine afford the polyhaloazaalkenes (**213**).[23b] Other haloalkyl isothiocyanates react with chlorine to give the corresponding polyhalogenated products in high yields.[5,52]



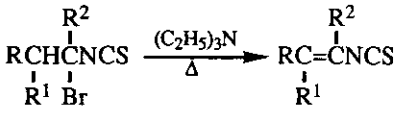
211 X = F, Cl

212

213

3.7. Dehydrohalogenation

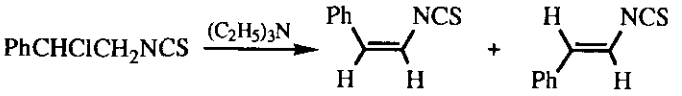
Some α-haloalkyl isothiocyanates (**214**) with hydrogen atoms in the β-position, spontaneously evolve hydrogen halide to give the α-alkenyl isothiocyanates (**215**).[55a] Dehydrohalogenation can be also achieved by treatment with a base, such as triethylamine.[55b]



214 **215**

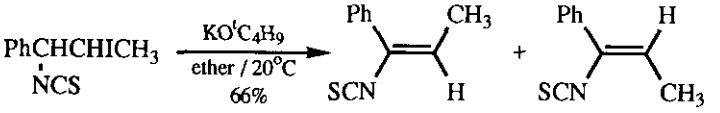
R	R^1	R^2	**215** (%)
H	H	CH_3	65
H	$-(CH_2)_4-$		83
CH_3	CH_3	CO_2CH_3	83

Thus, the simple vinyl isothiocyanate is easily obtained from 2-bromoethyl isothiocyanate with triethylamine.[9,128] When 2-aryl-2-chloroethyl isothiocyanates (**216**) are used as starting materials, diastereomeric mixtures of 2-aryl-2-vinyl isothiocyanates (**217**) and (**218**) are obtained with the *trans* form prevailing.[7a,b]



216 **217** (1:4) **218**

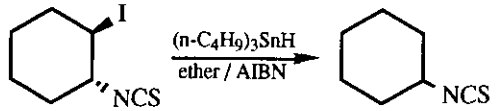
Elimination of hydrogen iodide has been also performed by treating the *vic*-iodoisothiocyanates (**219**) with potassium *tert*-butoxide under mild conditions.[60]



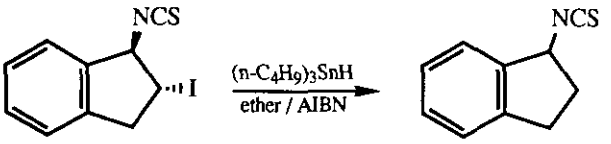
219 **220** (~1:1) **221**

3.8. Dehalogenation

Elimination of halogens is a representative reaction of haloalkyl isothiocyanates. Treatment of *vic*-iodoisothiocyanates (**63**) with tri-*n*-butyltin hydride effected selective reduction to the corresponding isothiocyanates (**222**) in high yields.[60]



63 **222** (81%)



223 **224** (76%)

Likewise, γ-bromoalkyl isothiocyanates (**93**) have been dehalogenated quantitatively in the presence of potassium iron tetracarbonyl hydride.[57]

$$BrCH_2CPh{=}C(CO_2C_2H_5)NCS \xrightarrow[CH_3OCH_2CH_2OCH_3\,/\,30^\circ\,/\,3\,h]{KHFe(CO)_4} CH_3CPh{=}C(CO_2C_2H_5)NCS$$

93 **92**

α-Bromoalkyl isothiocyanates (**85**) react also with thiocyanates to produce *gem*-diisothiocyanates (**225**) in moderate to good yields.[55b]

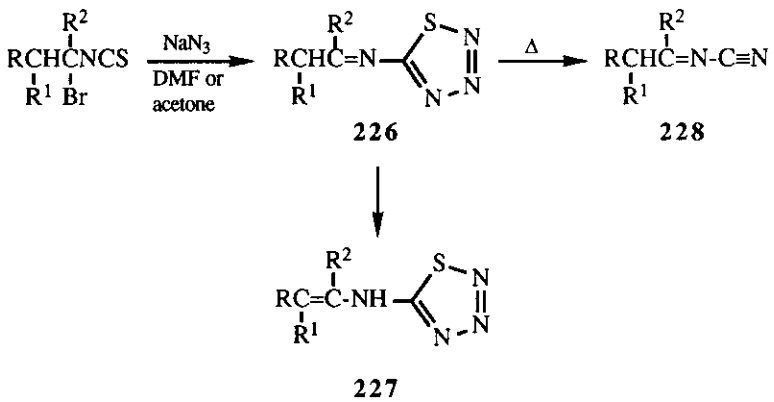
$$RR^1CBrNCS \xrightarrow{SCN^-} RR^1C(NCS)_2$$

85 **225**

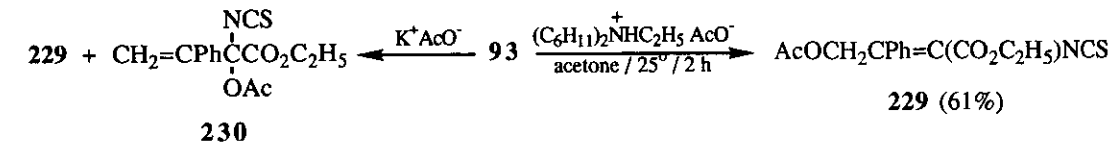
R	R^1	**225** (%)
CH_3	CH_3	76
	$-(CH_2)_5-$	57
$^iC_3H_7$	CO_2CH_3	88
$^tC_4H_9$	Ph	94

3.9. Reaction with Inorganic Salts

α-Bromoalkyl isothiocyanates, when treated with sodium azide in DMF or acetone, cyclize to produce 5-alkylidenaminothiotriazoles (**226**). These compounds may undergo tautomerization to give **227**, or thermal decomposition into alkylidencyanamides (**228**).[55b]

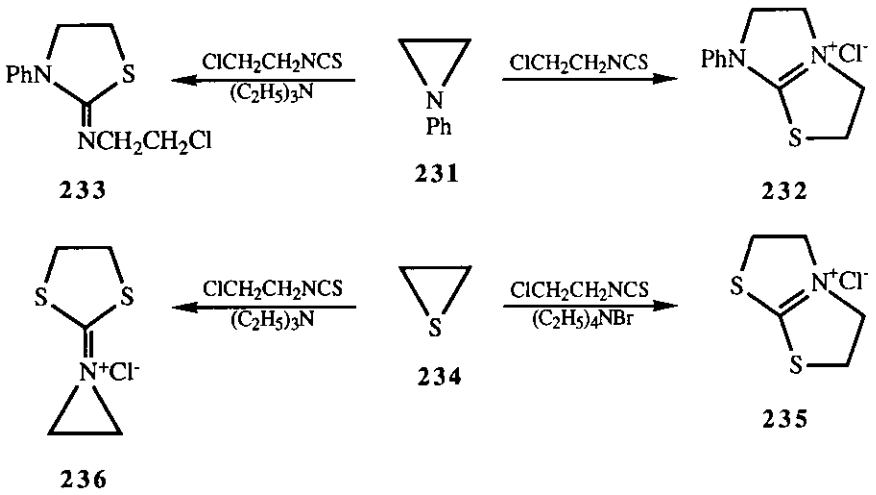


The γ-bromoalkyl isothiocyanate (**93**) exchanges the bromine atom by treating with dicyclohexylethylammonium acetate or potassium acetate at room temperature to give **229** or **230**.[57]

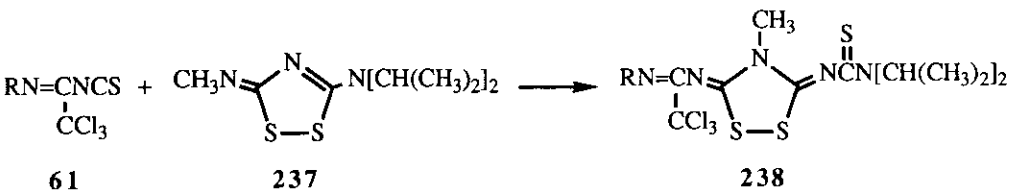


3.10. Reaction Involving Heterocyclic Rings

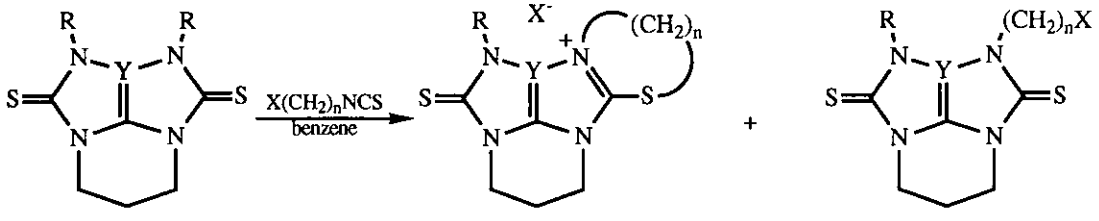
Aziridines (**231**) and thiiranes (**234**) react with haloalkyl isothiocyanates with ring-expansion to give other heterocycles (**232**, **233**, **235**, **236**).[129] The structure of these products depends upon the presence or absence of triethylamine.



The condensation of **61** with the 1,2,4-dithiazoline derivative (**237**) affords the 1,2,4-dithiazolidine (**238**) by ring cleavage-cyclization reactions.[130]

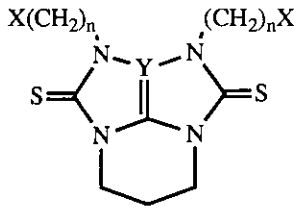


Tetraazapentalene derivatives (**239**) react with ω-bromoalkyl isothiocyanates to give exclusively the fused-cyclic system (**240**) as bromide in good yield. However, reaction of **239** (R = CH_3) with ω-chloroalkyl isothiocyanates provides a mixture of **240** as chloride, as well as the mono- and di-*N*-chloroalkyl tetraazapentalenes (**241**) and (**242**).[131]



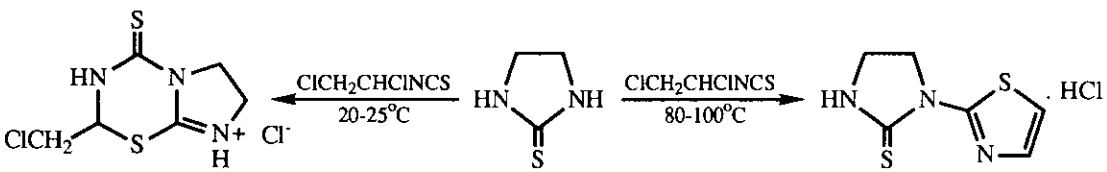
239 240 241

R = CH_3, allyl
X = Cl, Br
Y = S, Se
n = 2, 3



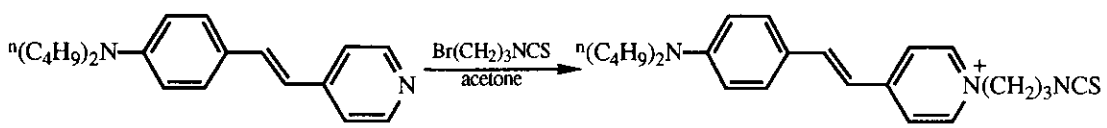
242

Reaction between 1,2-dichloroethyl isothiocyanate and imidazolidine-2-thione produces **244** or **245** depending on temperature conditions.[14] A similar behavior has been already described for acyclic thioureas (see section 3.2).



245 243 244

In a synthetic approach to a number of aminostyrylpyridinium dyes and their heterocyclic analogues, which are of interest as electronic probes for membrane potential, compound (**246**) was condensed with 3-bromopropyl isothiocyanate to give the γ-isothiocyanatoalkyl pyridinium bromide (**247**).[132]

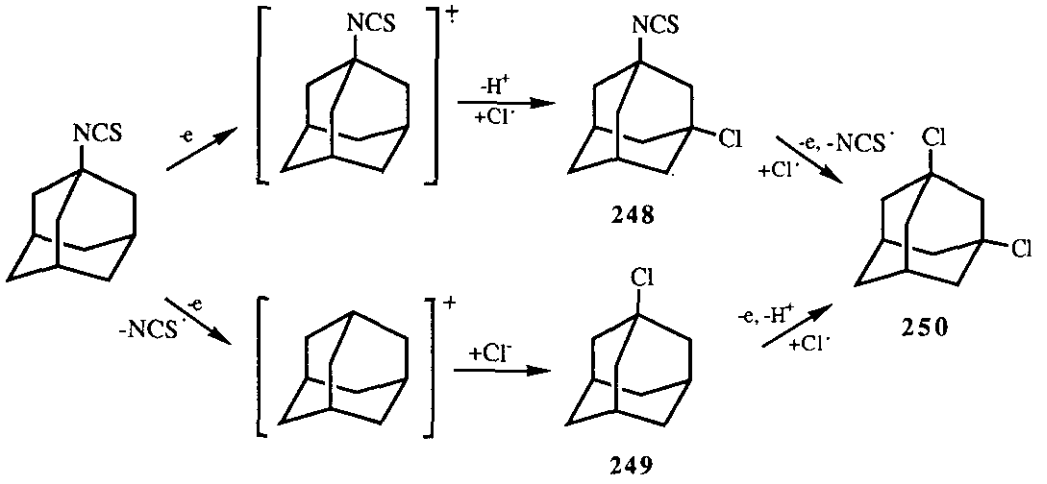


246 247 (60%)

3.11. Electrochemical Oxidation

Anodic oxidation of primary and secondary alkyl isothiocyanates in dichloromethane gives two isomers of five-membered heterocyclic products. However, tertiary alkyl isothiocyanates did not yield cyclic products, but instead underwent chlorination to substitute a hydrogen or NCS group by chlorine.[133] Thus, the oxidation of 1-

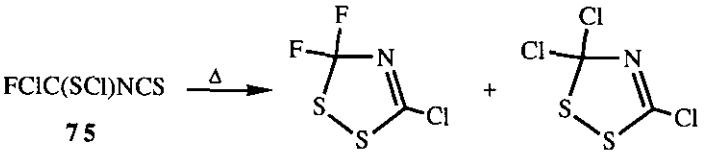
adamantyl isothiocyanate is outlined in the Scheme 8. Monochlorination products (**248** and **249**) were formed when ~1 Faraday/mol was consumed, whereas 1,3-dichloroadamantane (**250**) was the major product when ~2 F/mol was used.



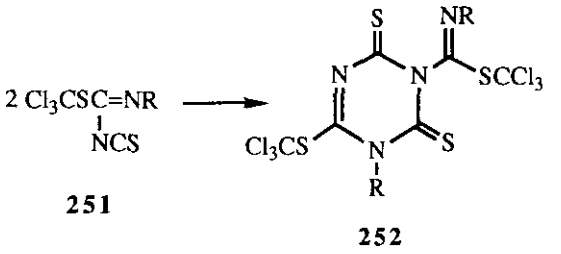
Scheme 8

3.12. Miscellaneous Reactions

Many synthetic processes can be carried out with the versatile haloalkyl isothiocyanates, which explore their potential reactivity. The thermolysis of some haloalkyl isothiocyanates(**75**) produces mixtures of heterocycles(**79**) and (**31**).[23b]

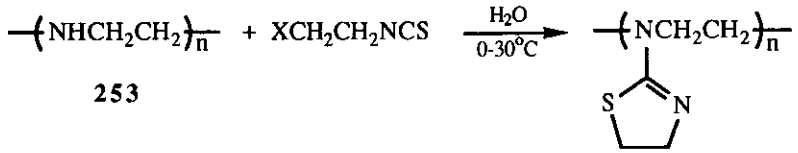


Dimerization reactions have been also reported for the synthesis of heterocyclic structures.[37]



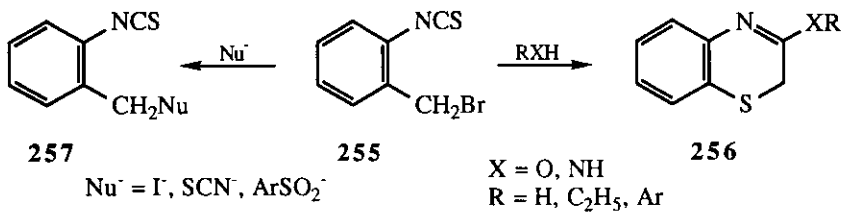
Syntheses of poly[*N*-(2-thiazolin-2-yl)]ethylenimines (**254**) have been described by reaction of poly-

ethylenimines (**253**) with 2-haloethyl isothiocyanates in water under mild conditions.[134]



253 **254**

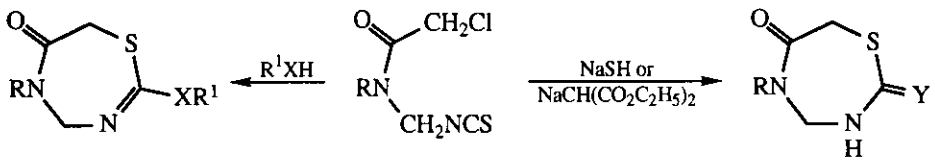
Likewise, 3-bromopropyl isothiocyanate has been added to some relevant biological substances, such as leucine, insulin or albumen.[135] Other isothiocyanates, which cannot be considered strictly as haloalkyl isothiocyanates exhibit a similar behavior. 2-Bromomethylphenyl isothiocyanate (**255**)[136] and *N*-alkyl(aryl)-*N*-isothiocyanatomethyl carboxamides (**258**)[137] provide heterocycles upon treatment with several nucleophiles.



257 **255** **256**

$Nu^- = I^-, SCN^-, ArSO_2^-$

X = O, NH
R = H, C_2H_5, Ar



260 **258** **259**

X = O, S
$R^1 = CH_3, {}^iC_3H_7$

Y = S, $C(CO_2C_2H_5)_2$

Finally, the chemistry of haloacyl isothiocyanates lies beyond the scope of this review, and it has not been discussed here.

4. CONCLUDING REMARKS

Haloalkyl isothiocyanates have been widely employed for the synthesis of heterocycles. Thus far, the addition-cyclization approach has been exploited to a large extent. Nevertheless, other synthetic transformations have been less documented and particularly cycloaddition, photochemical, and electrochemical reactions among others, await to be systematically studied. Likewise, the enhanced reactivity of these compounds and the possibility of further desulfurization would provide a rapid access to many organic molecules. It is hoped that this report will stimulate more interest in the development and applications of these compounds.

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