Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926081

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To cite this Article Sharma, Satyavan(1989) 'Isothiocyanates in Heterocyclic Synthesis', Journal of Sulfur Chemistry, 8: 5, 327 — 454
To link to this Article: DOI: 10.1080/01961778908046181
URL: http://dx.doi.org/10.1080/01961778908046181

Sulfur Reports
Volume 8(5), 1989, pp. 327–469
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ISOTHIOCYANATES IN HETEROCYCLIC SYNTHESIS*

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(Received December 18, 1987)

A brief introduction of the chemical structure and physico-chemical properties of various synthetic and naturally occurring isothiocyanates is presented. The different methods used to prepare alkyl, aryl, 1-alkenyl, carbonyl, thiocarbonyl, 1-aminoalkyl, aminophosphoryl and silyl isothiocyanates are systematically described. The use of the above isothiocyanates in the synthesis of thiazetidines, thiophenes, imidazoles, thiazoles, oxazoles, isothiazoles, oxathiolanes, dithiolanes, dioxolanes, triazoles, thiadiazoles, oxadiazoles, tetrazoles, thiatriazoles, pyridines, thiopyrans, oxazines, thiazines, pyrimidines, triazines, thiadiazines, oxadiazines, triazepines, benzimidazoles, benzothiazoles, quinazolones and various bicyclic and polyheterocyclic compounds with ring nitrogen and/or sulfur are reviewed.

Key words: Isothiocyanates, non-benzoheterocycles, benzoheterocycles, polyheterocycles.

CONTENTS

*Communication No. 4186 from the Central Drug Research Institute, Lucknow 226 001 (India).

1. INTRODUCTION

Although isothiocyanates belong to the highly reactive organosulfur synthons which have been known to organic chemists for over a century, their synthetic utility remained unexplored till the introduction of electronic concepts in organic chemistry. Before the beginning of the early fifties the use of isothiocyanates was mainly confined to the synthesis of a small group of open-chain and cyclic molecules. However, soon it was recognised that an isothiocyanate may serve as a versatile building block to prepare a wide class of nitrogen, sulfur and oxygen heterocycles and organometallic compounds of academic, pharmaceutical and industrial interest. The high electrophilicity and nucleophilicity associated with the carbon and sulfur atoms, respectively, of the isothiocyanates and their extended π electron system make them unique precursors of a large variety of target molecules. The ability of isothiocyanates to undergo cycloaddition reactions further helps to generate additional interesting heterocycles.

The literature covering the chemical and physico-chemical aspects of isothiocyanates is exceedingly voluminous and cannot be reviewed in the limited space of this article. The main aim of the present article is to provide comprehensive coverage of the use of isothiocyanates to construct various heterocycles. No attempt has been made to compile all the literature falling within the scope of this review, instead emphasis has been laid on all those publications which would help to present a broader perspective of isothiocyanates in heterocyclic syntheses. Readers interested in the historical development and the general physical, chemical or synthetic aspects of isothiocyanates may consult some publications which have appeared since 1923.[1-19]

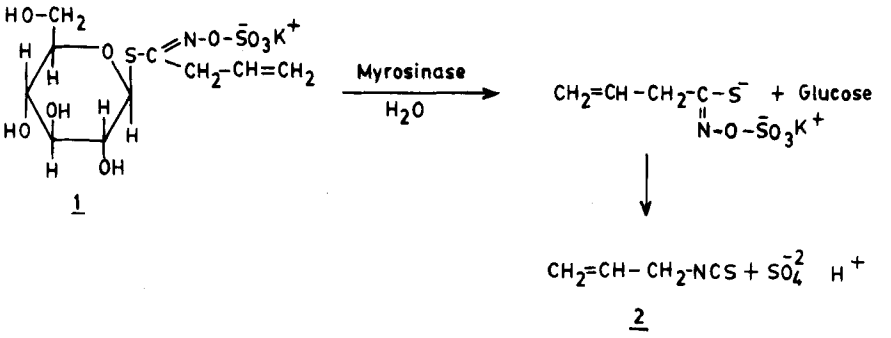
2. SOME BASIC CONSIDERATIONS

The isothiocyanates (R–NCS) are the esters of isothiocyanic acid (H–NCS), a very strong acid which is a colourless gas at room temperature with a high tendency to undergo polymerisation. In solution, isothiocyanic acid forms a tautomeric equilibrium with thiocyanic acid (HSCN). The isothiocyanates may also be regarded as the sulfur analogues of isocyanates (R–NCO), as isomeric with thiocyanates (R-SCN) and as isoelectronic with thioketenes ($R_2C=C=S$).

Generally the simple aliphatic and aromatic isothiocyanates are colourless liquids possessing a pungent or irritating odour and sharp taste. Several isothiocyanates have been isolated from the roots and seeds of various plants. The major constituent, for example, of the ordinary mustard oil obtained by steam distillation of the powdered seeds of black mustard (*Brassica nigra*) or the roots of horse radish (*Cochlearia armoracea*) is allyl isothiocyanate ($CH_2=CH-CH_2-NCS$). Obviously, some workers prefer to call the isothiocyanates 'mustard oils'. The other minor isothiocyanates isolated from horse radish and black mustard are β-phenylethyl isothiocyanate ($C_6H_5CH_2-CH_2-NCS$), 3-butenyl isothiocyanate ($CH_2=CH-CH_2-CH_2-NCS$) and benzyl isothiocyanate ($C_6H_5CH_2-NCS$).[14,16,19,20] In addition to horse radish and black mustard, isothiocyanates have also been reported as present in undetectable amounts in healthy intact plants.[14]

In the plants, the isothiocyanates arise by the breakdown of glucosinolates produced

by all the plants of the family *Cruciferae* that have been investigated so far. Thus, the most predominantly occurring mustard oil, allyl isothiocyanate **2**, is obtained from the β-glucoside sinigrin (glucosinolate, **1**) by the action of the enzyme mirosinase after damage to the plant (Scheme 1). The other naturally occurring isothiocyanates and their corresponding glucosinolates have been reviewed by Kjær[4,21,22] and Ettlinger and Kjær[23] where a systematic description of the biosynthesis, degradation, structure and analytical aspects of the glucosinolates may also be found.

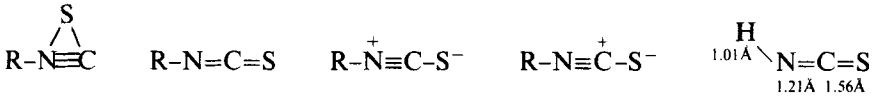


1 **2**

Scheme 1

The structure of the isothiocyanates and their physical and chemical properties have been a matter of detailed investigation since Dadieu and Kohlrausch[24,25] who suggested a cyclic structure **3** for the -NCS group in 1930. The voluminous literature accumulated on the physico-chemical aspects of isothiocyanates is beyond the scope of the present article. However, mention of some basic data relevant in governing the heterocycle-forming potential of isothiocyanates must be made here.

It has now been well established that isothiocyanates possess a linear structure[26] represented either by the formulae **4a**[27] or **4b**.[28-30] It is also possible to represent the structure of the -NCS group[31] by a hybrid of the mesomeric structures **4a** and **5**. The microwave spectral analysis[32] of gaseous isothiocyanic acid has shown this compound to possess the molecular structure **6** wherein the C=S bond is very short similar to that found in the thioketene group. This would suggest that the structure **4b** may not contribute much to the resonance of the -NCS group.



3 **4a** **4b** **5** **6**

Microwave spectroscopy has also been used to determine the bond lengths and bond angles of some isothiocyanates.[32,33] Thus, the bond lengths and bond angles[32] in H-NCS were found to be C=S, 1.56 Å; C=N, 1.21 Å; N-H, 1.01 Å and ∠ H-N-C, 130.15° while D-NCS exhibited D-N, 1.003 Å and ∠ D-N-C, 132.16°. These values are quite close to the calculated bond lengths based on the double-bond radii of Cordy[34] and the single-bond radii of Schomaker and Stevenson[35] which are as follows: C=S, 1.61 Å; C=N, 1.27 Å and N-H, 1.03 Å. The bond lengths and bond angles determined by microwave

spectroscopy in methyl isothiocyanate[33] are: H–C, 1.09 Å; C–N, 1.47 Å; N–C, 1.22 Å; C–S, 1.56 Å; ∠ H–C–N, 109°; ∠ C–N–C, 142° and ∠ N–C–S, 180°.

The dipole moments of the isothiocyanates have also been determined by several workers[28,36–38] and provide insight into the polar character and structure of the isothiocyanates. The dipole moment data clearly indicate that the -NCS group has an electron-accepting character with the negative end of the dipole at the sulfur atom. The dipole moment μ (D) values of some alkyl and aryl isothiocyanates in benzene are given below:

R–NCS		Ar–NCS	
R	*μ (D)*	*Ar*	*μ (D)*
CH_3	3.18	C_6H_5	2.91
C_2H_5	3.31	4-C_6H_4Cl	1.55
t-C_4H_9	3.73	3-C_6H_4Cl	2.59
CH_2=CH–CH_2	3.30	3-C_6H_4NCS	2.78
		4-C_6H_4NCS	0

The dipole moment studies have also helped to determine the conformation of the isothiocyanate function. Thus the dipole moments of various 4-substituted cinnamoyl isothiocyanates recorded in benzene at 20 °C indicate that the acyl isothiocyanate group possesses a *Z* conformation.[39] However, the -CO–NCS group of cinnamoyl isothiocyanates (C_6H_5–CH=CH–CO–NCS) does not lie in a plane, but forms a dihedral angle of 53° around -CO–C=N bond. A value of 3.43 D with an angle of 25° was obtained for the ethylenic bond relative to the group moment of the -CO–NCS group.[39]

The infra-red spectra of simple alkyl and substituted phenyl isothiocyanates are characterised by the appearance of a strong, often dispersed and split band in the region 2100–2000 cm^{-1} which is due to the -N=C=S stretching vibration. However, the carbonyl isothiocyanates (-CO–NCS) such as acetyl, benzoyl and ethoxycarbonyl isothiocyanate exhibit infrared absorption around 1930–1990 cm^{-1}. The ultraviolet spectra of alkyl isothiocyanates are marked by a singlet absorption in the region 244–248 nm ($\varepsilon \sim 10^3$) while the aromatic isothiocyanates show absorption at higher wavelengths. For example, phenyl isothiocyanate exhibits a strong band at 280 nm ($\log \varepsilon = 40.5$). Acyl and thioacyl isothiocyanates display their u.v. absorptions at still higher wavelengths.

Simple alkyl and aryl isothiocyanates are usually stable[2] but the more reactive acyl and sulfonyl isothiocyanates (R–CO–NCS and R–SO_2–NCS) are less stable.[6,18] However, the thioacyl isothiocyanates (R–CS–NCS) are deep red and unstable liquids or solids.[40–43] The phosphoryl isothiocyanates (R_2PO–NCS) are usually stable liquids but decompose thermally to form alkyl thiocyanates and metaphosphoric acid esters.[10,17]

3. PREPARATION OF ISOTHIOCYANATES

Several methods have been developed to prepare different isothiocyanates the majority of which use either salts of thiocyanic acid, carbon disulfide or thiophosgene as the sulfur source. Specific methods have also been developed not only to obtain alkyl, aryl or acyl isothiocyanates but also some particular isothiocyanates needed in the chemistry of organosulfur compounds.[3,14,16]

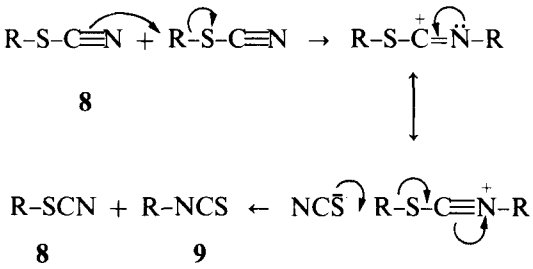
3.1 *Alkyl and Aryl Isothiocyanates*

Method A: From organylhalides and thiocyanates This is one of the oldest methods to prepare alkyl or aralkyl isothiocyanates which involves the reaction of a halide (**7**) with a metal or ammonium salt of thiocyanic acid to form the corresponding thiocyanate **8** which thermally rearranges to give the corresponding alkyl or aralkyl isothiocyanate **9**.[2,44-48] However, this process is not the method of choice for preparing alkyl and aryl isothiocyanates.

$$\underset{\mathbf{7}}{R\text{-}X} + {}^{-}SCN \rightarrow \underset{\mathbf{8}}{R\text{-}SCN} \rightarrow \underset{\mathbf{9}}{R\text{-}NCS}$$

Thus, under normal reaction conditions, the reaction of an alkyl or aralkyl halide **7** with ammonium, lead or alkali metal thiocyanates (rhodanides) may form a mixture of the corresponding thiocyanate **8** or isothiocyanate **9** the ratio of which depends on the nature and the reactivity of the halide and the reaction conditions. However, since the isothiocyanates are thermally more stable than the thiocyanates, it is usually possible to isolate pure isothiocyanates **9** by heating either **8** or a mixture of **8** and **9** at elevated temperatures, especially in the presence of cadmium iodide,[49] zinc chloride[50] or a strong acid.[51,52]

The isomerisation of **8** to **9** may proceed by several mechanisms.[53-55] However, on the basis of kinetic studies, it has been assumed that the reaction takes place with a bimolecular mechanism (S_N2) requiring a polar solvent and steric access to the carbon atom.[53] The α-carbon atom of one molecule forms a bond with the nitrogen atom of another molecule, followed by nucleophilic substitution by the thiocyanate ion to give the isothiocyanate.



Thus, reaction of chloromethyl methyl ether (**10a**),[56,57] diphenylmethyl bromide (**10b**)[58] or triphenylmethyl chloride (**10c**)[59] with potassium thiocyanate gives high yields of the corresponding isothiocyanates (**11a–c**).

$$\underset{\mathbf{10a},\ R = CH_2OCH_3,\ X = Cl}{R\text{-}X} + KSCN \rightarrow \underset{\mathbf{11a},\ R = CH_2OCH_3}{R\text{-}NCS}$$

10b, R = $CHPh_2$; X = Br — **11b**, R = $CHPh_2$

R = CPh_3; X = Cl — **11c**, R = CPh_3

t-Butyl thiocyanate **12a**, obtained by treating *t*-butyl chloride with ammonium thiocyanate, rearranges quantitatively in the presence of zinc chloride to form *t*-butyl iso-

thiocyanate **13a**.[50,60] Similarly, methyl thiocyanate **12b**[61] and the related thiocyanates **12c, d**[56,57,62-64] also isomerise to yield the corresponding alkyl isothiocyanates (**13b–d**).

$$\text{R–SCN} \rightarrow \text{R–NCS}$$

12a, R =	*t*-Bu	**13a**, R =	t-Bu
b, R =	CH_3	**b**, R =	CH_3
c, R =	CH_2OR^1	**c**, R =	CH_2OR^1
d, R =	CH_2SR^1	**d**, R =	CH_2SR^1

In a comparative study of the reactivity of various thiocyanates towards alkyl halides it was found that the reaction of isopropyl iodide **14a** with the thiocyanic acid salts of potassium, silver(I) and mercury(II) gives a mixture of *n*-propyl thiocyanate **15** and isopropyl isothiocyanate **16a** in the ratios 97:3, 80:20 and 25:75, respectively.[65] However, treatment of *n*-butyl bromide **14b** with mercuric thiocyanate yielded 20% of butyl isothiocyanate **16b** while a similar reaction with *t*-butyl bromide **14c** afforded 96% of *t*-butyl isothiocyanate **16c**.[65] The reason for the high selectivity of the mercuric salt has been attributed to its ability to form a direct Hg–S bond making the nitrogen atom sterically more accessible for substitution. A similar situation pertains in the case of thallium(II) thiocyanate.[66]

$$\text{R–X} \xrightarrow[\text{M = K, Ag, Hg}]{\text{MSCN}} \underset{\textbf{15}}{\textit{n}\text{-Pr–SCN}} + \text{R–NCS}$$

14a, R =	*i*-Pr, X = I	**16a**, R =	*i*-Pr
b, R =	*n*-Bu, X = Br	**b**, R =	*n*-Bu
c, R =	*t*-Bu, X = Br	**c**, R =	*t*-Bu

Allyl isothiocyanate **2**, the main constituent of black mustard and horse radish oil, may be prepared by isomerisation of allyl thiocyanate **18** at 90 °C. The latter is obtained conveniently by treating allyl chloride **17** either with a mixture of sodium cyanide and sulfur[67] or sodium thiocyanate in a saturated solution of sodium chloride.[68]

$$\underset{\textbf{17}}{CH_2{=}CH{-}CH_2{-}Cl} \xrightarrow[\text{or NaSCN}]{\text{NaCN, S}_8} \underset{\textbf{18}}{CH_2{=}CH{-}CH_2{-}SCN}$$

$$\downarrow$$

$$\underset{\textbf{2}}{CH_2{=}CH{-}CH_2{-}NCS}$$

Rapid distillation of γ-methylallyl thiocyanate **19** causes its 100% isomerisation with allyl rearrangement to α-methylallyl isothiocyanate **20**.[69] However, no such allyl rearrangement occurs when cinnamyl thiocyanate **21** is heated and instead of the anticipated α-phenylallyl isothiocyanate **23**, cinnamyl isothiocyanate **22** is obtained.[70]

$$CH_3—CH=CH—CH_2—SCN \rightarrow CH_2=CH—\underset{\displaystyle CH_3}{\underset{|}{CH}}—NCS$$

19 **20**

$$C_6H_5—CH=CH—CH_2—SCN \rightarrow C_6H_5—CH=CH—CH_2—NCS$$

21 **22**

$$C_6H_5—\underset{\displaystyle NCS}{\underset{|}{CH}}—CH=CH_2$$

Alkylene diisothiocyanates may also be prepared by the thiocyanate method. Thus, reaction of 1,4-dichlorobutane **24** with ammonium thiocyanate gives the desired 1,4-diisothiocyanatobutane **25**.[71]

$$Cl—CH_2CH_2CH_2CH_2—Cl \xrightarrow{NH_4SCN} SCN—CH_2CH_2CH_2CH_2—NCS$$

24 **25**

Treatment of acyl(chloromethyl)amines **26a** with potassium thiocyanate gives acylaminomethylisothiocyanates **27a**.[72,73] Similarly, alkyl(chloromethyl)nitramine **26b** reacts with silver thiocyanate in ether to form alkyl(nitroamino)methyl isothiocyanate **27b**.[74]

$$R^1—\underset{\displaystyle R}{\underset{|}{N}}—CH_2—Cl \xrightarrow[\text{or AgSCN}]{KSCN} R^1—\underset{\displaystyle R}{\underset{|}{N}}—CH_2—NCS$$

26a, R = H, R^1 = CO—alkyl **27a, b**

b, R = NO_2, R^1 = alkyl

When dichloromethyl methyl ether and the corresponding sulfide **28a, b** are treated with silver thiocyanate, both halogen atoms are substituted by SCN groups and the corresponding diisothiocyanates are formed.[75,76] However, when KSCN is allowed to react with perfluoroisobutene **30**, only one fluorine atoms is substituted with formation of 1,3,3,3-tetrafluoro-2-trifluoromethyl-1-propenyl isothiocyanate **31**.

$$CH_3—X—CHCl_2 + 2\,AgSCN \rightarrow CH_3—X—CH(NCS)_2$$

28a, X = O **29**

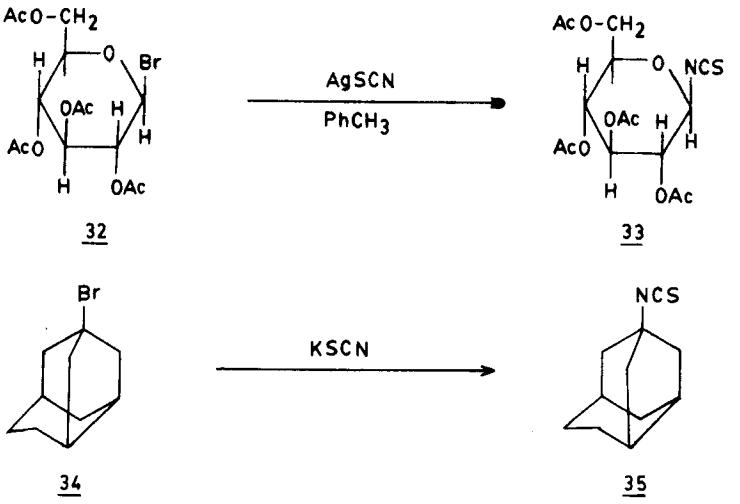
b, X = S

$$F_3C—\underset{\displaystyle CF_3}{\underset{|}{C}}=CF_2 + KSCN \rightarrow F_3C—\underset{\displaystyle CF_3}{\underset{|}{C}}=CF—NCS$$

30 **31** (66%)

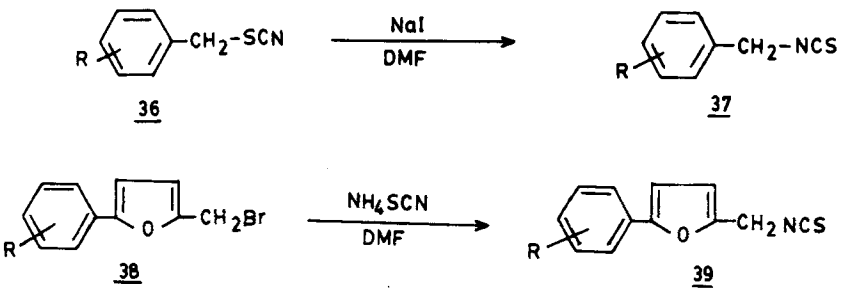
Reaction of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl bromide **32** with AgSCN[78] or $Pb(SCN)_2$[79] in refluxing toluene affords 1-(2,3,4,6-tetraacetyl-β-D-glucosyl) isothiocyan-

ate **33**. Similarly, 1-bromoadamantane **34** gives 1-isothiocyanatoadamantane **35** when treated with potassium thiocyanate in refluxing DMF for 5 hours[80] (Scheme 2).



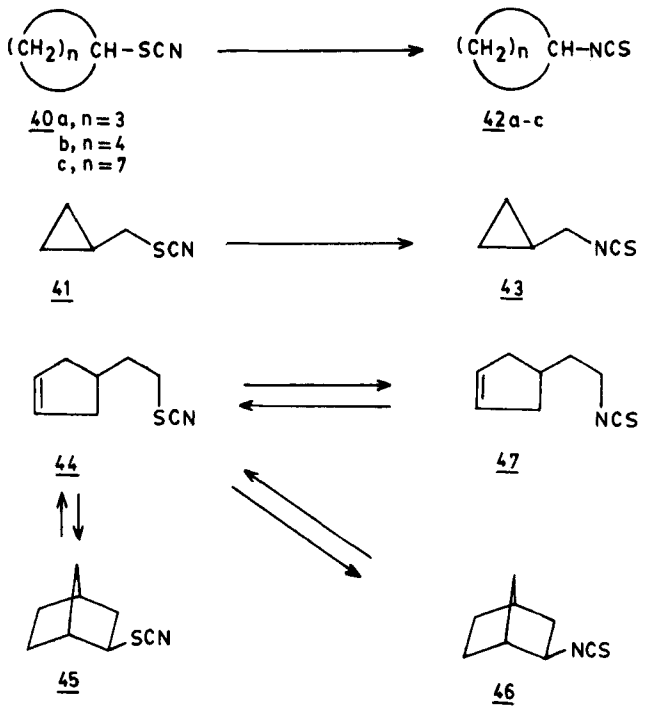
Scheme 2

A number of substituted benzyl isothiocyanates **37** have been prepared in high yields by isomerising the corresponding thiocyanates **36** in refluxing DMF or DMSO in the presence of sodium iodide.[81] Similarly, when a mixture of a 5-aryl-2-furfuryl bromide **38** and ammonium thiocyanate is heated in *N*,*N*-dimethylformamide, the corresponding isothiocyanate **39** is obtained[82] (Scheme 3).



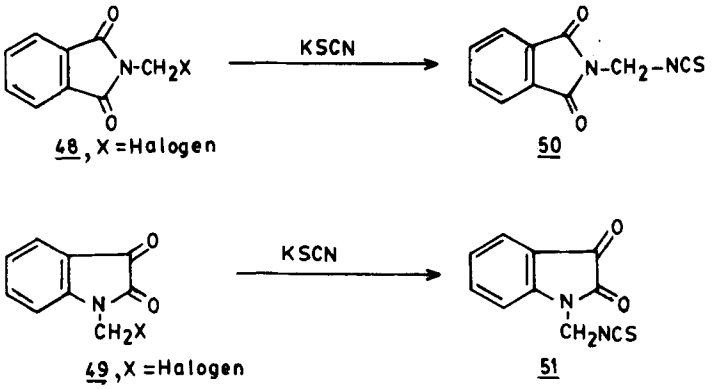
Scheme 3

A number of cycloalkyl isothiocyanates (**42a–c** and **43**) have been prepared by isomerising the corresponding thiocyanates **40a–c** and **41**, respectively.[83a] However, the isomerisation of 2-(cyclopent-3-enyl)ethyl thiocyanate **44** gives rise to a mixture of *exo*-2-norbornyl thiocyanate **45**, *exo*-2-norbornyl isothiocyanate **46** and 2-(cyclopent-3-enyl)ethyl isothiocyanate **47**[83b] (Scheme 4). Recently, Gonda *et al.*[84] have prepared 1-isothiocyanato-1,2,3-triphenyl-2-cyclopropene by treating 1,2,3-triphenylcyclopropyl carbanion with KSCN in acetonitrile.



Scheme 4

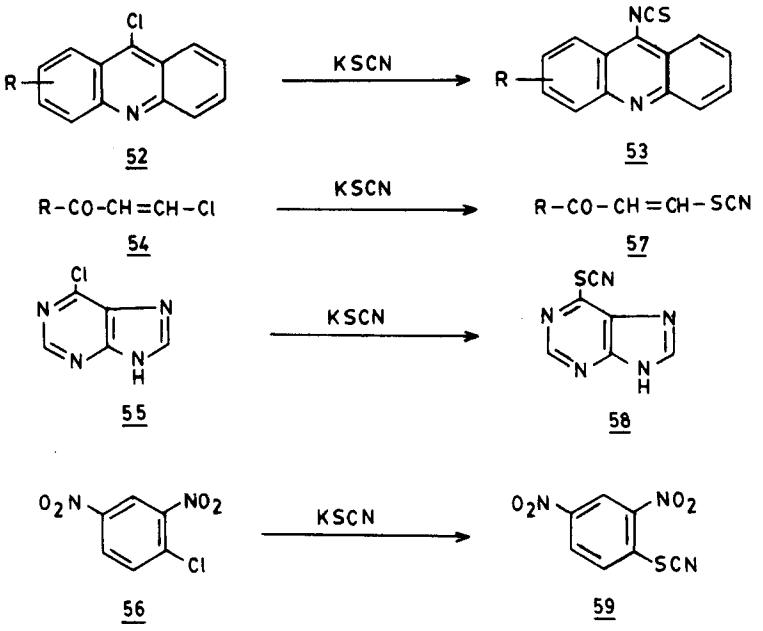
The above reaction has also been extended to the synthesis of the *N*-isothiocyanatomethyl derivatives **50** and **51** of phthalimide and isatin involving the reaction of the corresponding halo compounds **48** and **49** with alkali metal thiocyanates or silver thiocyanate[85] (Scheme 5).



Scheme 5

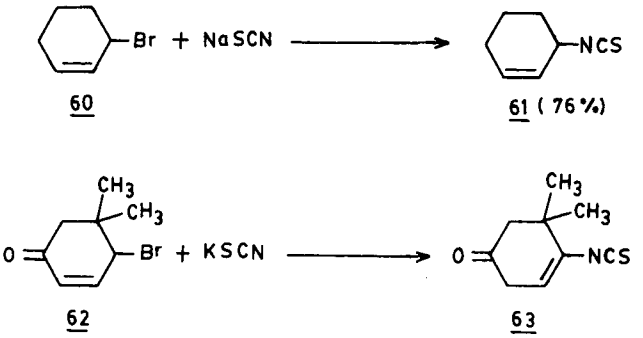
A similar isomerisation is observed when 9-chloroacridine **52** is treated with AgSCN or $Pb(SCN)_2$ in non-polar solvents or with KSCN in DMF to yield 9-isothiocyanatoa-

cridine **53**.[86,87] However, no such conversion is achieved in the reaction of **54–56** with KSCN since the end products isolated were the thiocyanates **57–59** and not the isothiocyanates[47,88–91] (Scheme 6).



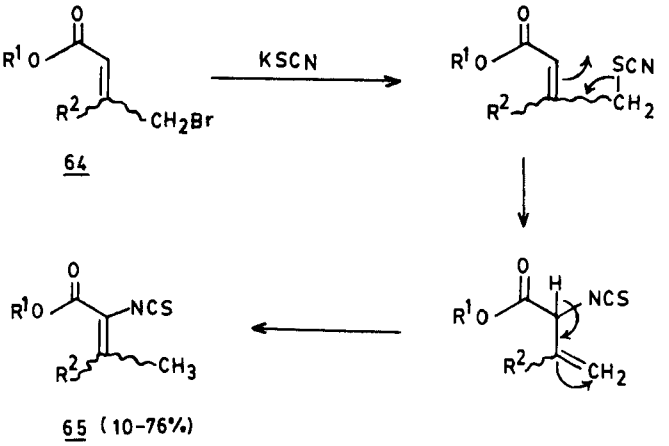
Scheme 6

A number of unsaturated alkyl isothiocyanates have also been prepared with the thiocyanate method. Thus, reaction of 3-bromocyclohexene **60** with sodium thiocyanate yields 3-isothiocyanatocyclohexene **61** at room temperature.[92] A similar reaction occurs when **62** is treated with KSCN, but the end product obtained is the rearranged compound 6,6-dimethyl-1-isothiocyanato-4-oxocyclohexene **63**[93] (Scheme 7).



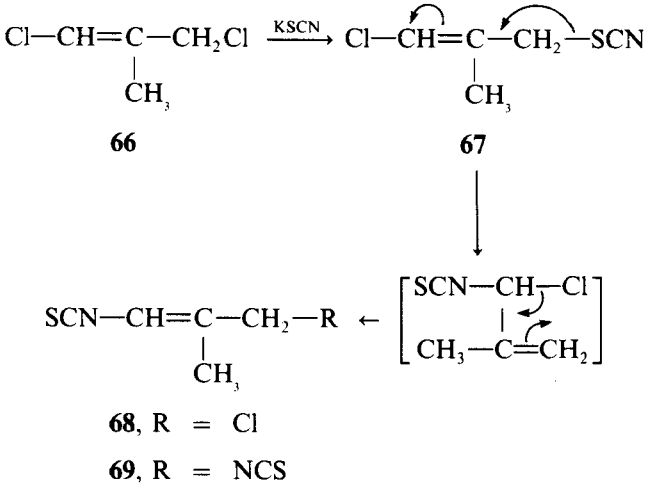
Scheme 7

Migration of the thiocyanate was also observed when 3-alkoxy-2-alkenyl bromides **64** were treated with KSCN to afford 2-isothiocyanato-2-alkenyl esters **65**[93] (Scheme 8).



Scheme 8

A somewhat similar rearrangement occurs when γ-chloromethallyl thiocyanate **67**, obtained by condensing the dichloride **66** with KSCN, is heated to form γ-chloromethallyl isothiocyanate **68** which may be further allowed to react with ammonium thiocyanate to give the diisothiocyanate **69**[94] (Cf. Scheme 8, isothiocyanate migration).



Method B: From thiocyanic acid In this method, thiocyanic acid, generated *in situ* by treatment of KSCN with an acid, is allowed to add to an alkene. Thus, addition of thiocyanic acid (H–SCN), generated *in situ* by treating NaSCN with 73% H_2SO_4, to diisobutylene **70** afforded *t*-octyl isothiocyanate **71** in 66% yield.[95] Similarly, when thiocyanic acid was allowed to add to 2-methylpropene **72** at room temperature, a mixture of *t*-butyl thiocyanate **73** (62%) and *t*-butyl isothiocyanate **74** (32%) was obtained. By heating the mixture of **73** and **74**, pure **74** was obtained.[96]

$$(CH_3)_3C{-}CH{=}C(CH_3)_2 \xrightarrow[H_2SO_4]{NaSCN} (CH_3)_3C{-}CH_2{-}C(CH_3)_2(NCS)$$

70 → **71**

$$(CH_3)_2C{=}CH_2 + HSCN \rightarrow (CH_3)_3C{-}SCN + (CH_3)_3C{-}NCS$$

72 + HSCN → **73** + **74**

Following the above method, a series of β-isothiocyanatoketones **76** have been prepared by *in situ* addition of thiocyanic acid to α,β-unsaturated ketones **75**.[97] Thiocyanic acid also adds to isonitriles to form α-iminoalkyl isothiocyanates **77**.[98]

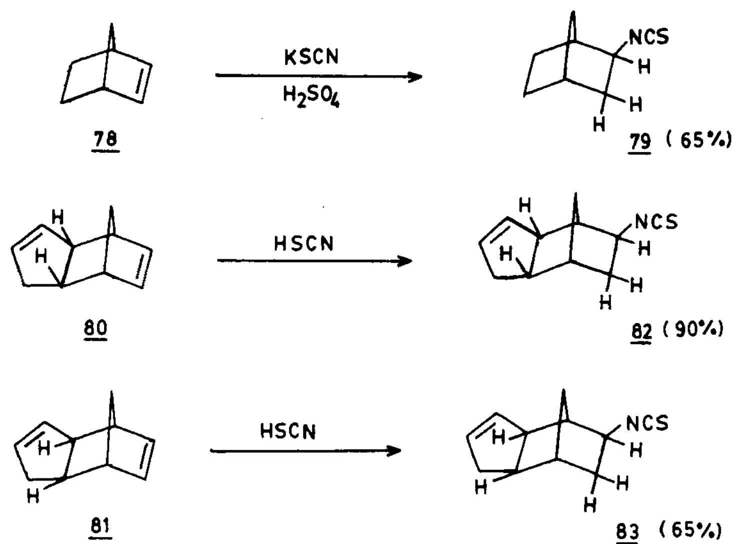
$$CH_3CO{-}C(R){=}CHR^1 \xrightarrow[H^+]{KSCN} CH_3CO{-}CH(R){-}CH(R^1){-}NCS$$

75, R = H, CH_3; R^1 = H, CH_3, C_6H_5 → **76**

$$R{-}\overset{+}{N}{\equiv}C^- + HSCN \rightarrow R{-}N{=}CH{-}NCS$$

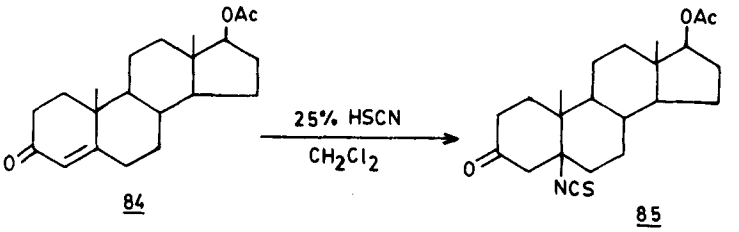
77

This method can also be successfully used to prepare cyclic isothiocyanates. Thus, reaction of norbornene **78**, with thiocyanic acid *in situ* gives rise to *exo*-2-norbornyl isothiocyanate **79** in 65% yield.[99] Similarly, reaction of *endo*- and *exo*-dicyclopentadiene (**80, 81**) with thiocyanic acid results in the formation of *exo*-5-isothiocyanato-5,6-dihydro-*endo*-dicyclopentadiene **82** and *exo*-5-isothiocyanato-5,6-dihydro-*exo*-dicyclopentadiene **83**, respectively[100,101] (Scheme 9).



Scheme 9

5-Isothiocyanatoandrostan-17β-ol-3-one **85** may be prepared conveniently by addition of thiocyanic acid to testosteryl acetate **84** in dichloromethane in a nitrogen atmosphere[102,103] (Scheme 10).



84 85

Scheme 10

Method C: From Carbon Disulfide Primary alkyl- and arylamines readily react with carbon disulfide in the presence of alkali or ammonia in an organic or aqueous medium to form salts of dithiocarbamic acids **86**.[104-106] Aliphatic amines, being stronger bases than aromatic amines, react with carbon disulfide in the absence of a base to give alkylammonium dithiocarbamates.[107]

$$R{-}NH_2 + CS_2 \xrightarrow{\text{base}} R{-}NH{-}CS{-}S^- \; M^+$$

86, M = K, Na, NH_4

$$2\,R{-}NH_2 + CS_2 \rightarrow R{-}NH{-}CS{-}S^- \; \overset{+}{N}H_3{-}R$$

87

The above salts **86** and **87** may be decomposed with a variety of reagents as illustrated below

Method C-1: Decomposition by heavy-metal salts When the salts of dithiocarbamic acids (**86**, **87**) are heated with heavy-metal salts such as lead nitrate,[108-111] lead acetate,[112] copper sulphate,[113] zinc sulphate,[110] ferric chloride,[115] mercury salts[113,116] or with copper wool[114] in an aqueous medium, unstable heavy-metal dithiocarbamates are generated which spontaneously decompose to give isothiocyanates **88** and the corresponding metal sulfides.

$$R{-}NH{-}CS{-}\bar{S} \; M^+ \xrightarrow{Pb(NO_3)_2} R{-}NCS + PbS + MNO_3 + HNO_3$$

86, **87** **88**

By the above method also various labelled isothiocyanates have been prepared .[14,121]

$$\text{(a)}\quad R{-}NH_2 + {}^{14}CS_2 \rightarrow [R{-}NH{-}{}^{14}CS{-}SH] \xrightarrow{Pb(NO_3)_2}$$

$$R{-}N^{14}CS + PbS + 2\,HNO_3$$

$$\text{(b)}\quad R{-}NH_2 + C^{35}S_2 \rightarrow [R{-}NH{-}C^{35}S{-}{}^{35}SH]$$

$$\xrightarrow{Pb(NO_3)_2} R{-}NC^{35}S + Pb^{35}S + 2\,HNO_3$$

$$\text{(c)}\quad 2\,Ph{-}NCS + 2\,NH_4^{35}SH \rightarrow 2[Ph{-}NH{-}C^{35}S{-}SNH_4]$$

$$\xrightarrow{Ph(NO_3)_2} Ph{-}NCS + Ph{-}NC^{35}S + PbS + Pb^{35}S + 2\,NH_4NO_3$$

In a slight modification this method may be successfully extended to prepare isothiocyanates **89** with an amino function.[118]

$$R_2N{-}CH_2CH_2{-}NH_2 + CS_2 \rightarrow R_2\overset{+}{N}H{-}CH_2{-}CH_2{-}NH{-}CS{-}\overset{-}{S}$$

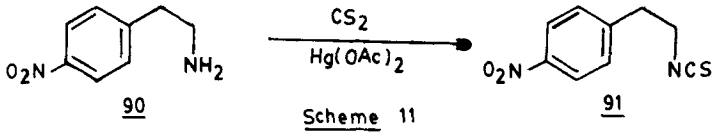
$$\downarrow HgCl_2$$

$$[R_2\overset{+}{N}H{-}CH_2{-}CH_2{-}NH{-}CS{-}\overset{-}{S}\ Hg^{2+}\ Cl^-]$$

$$\downarrow 2\,Et_3N$$

$$R_2N{-}CH_2CH_2{-}NCS + HgS + 2\,Et_3N{\cdot}HCl$$

In another example involving the decomposition of dithiocarbamic acid by a heavy-metal salt to obtain the corresponding isothiocyanate, reaction of 2-(4-nitrophenyl)ethylamine **90** with carbon disulfide offords the corresponding dithiocarbamic acid which is then heated with mercuric acetate *in situ* to yield 2-(4-nitrophenyl)ethyl isothiocyanate **91**[119,120] (Scheme 11).



90 91

Scheme 11

Method C-2: Decomposition by activated chloro compounds The aliphatic and aromatic dithiocarbamates **86** can be conveniently decomposed with compounds containing active chloro groups to give high yields of the corresponding isothiocyanates. The chlorine-containing compounds used to decompose **86** are alkyl chloroformates, phosgene, sodium hypochlorite and $POCl_3$.

Decomposition of **86** with methyl chloroformate[121] or ethyl chloroformate[122-127] produces alkyl and aryl isothiocyanates in high yields (Kaluza reaction). The reaction proceeds via formation of the unstable intermediate, the alkoxycarbonyldithiocarbamate **92** which spontaneously decomposes to form the corresponding isothiocyanate. Bases like triethylamine and alkali are known to increase the rate of decomposition of alkoxycarbonyldithiocarbamates.[128-131] The Kaluza reaction works well with aliphatic and simple aromatic amines. The presence of electron-withdrawing groups in the aromatic ring prevents the formation of dithiocarbamates **86** and no isothiocyanates are obtained.[3]

$$R{-}NH{-}CS{-}\overset{-}{S}\ M^+ + ClCOOEt \xrightarrow[-MCl]{}$$

86

$$R{-}N(H){-}C(=S){-}S{-}C(=O){-}OEt \rightarrow R{-}NCS + COS + EtOH$$

$$\downarrow Et_3N \qquad\qquad \uparrow$$

$$[R{-}N{=}C(S^-){-}S{-}COOEt \leftrightharpoons R{-}\overset{-}{N}{-}C(=S){-}S{-}COOEt]\,Et_3\overset{+}{N}H$$

An improved Kaluza synthesis of isothiocyanates involves the reaction of the amine hydrochloride **92** with a mixture of carbon disulfide and triethylamine at low temperature. The generated dithiocarbamate is treated *in situ* with ethyl chloroformate to give the carbethoxy dithiocarbamate **93** which decomposes at room temperature to afford the corresponding isothiocyanate **94** in high yield.[132]

$$CH_3OOC—CH_2—CH_2—NH_2\cdot HCl + CS_2 \xrightarrow[-12°C]{Et_3N}$$

92

$$CH_3OOC—CH_2—CH_2—NH—CS—S^- \xrightarrow{ClCOOEt}$$

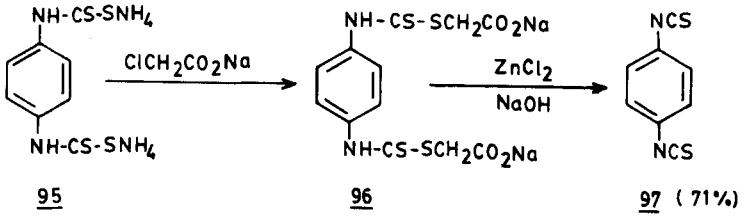
$$CH_3OOC—CH_2—CH_2—NH—CS—S—COOEt \xrightarrow[RT]{\Delta}$$

93

$$CH_3OOC—CH_2—CH_2—NCS$$

94 (81%)

Substitution of the alkyl chloroformates by sodium chloroacetate in the above reaction has been used to prepare some aryl isothiocyanates. Thus reaction of ammonium *p*-phenylene dithiocarbamate **95**, obtained by treating *p*-phenylenediamine with carbon disulfide and ammonium hydroxide, with sodium chloroacetate gave **96** which was decomposed in a weakly basic medium (pH 7) in the presence of $ZnCl_2$ to form *p*-phenylene diisothiocyanate **97**,[133] an effective antitapeworm drug for man and domestic animals[134,135] (Scheme 12).



Scheme 12

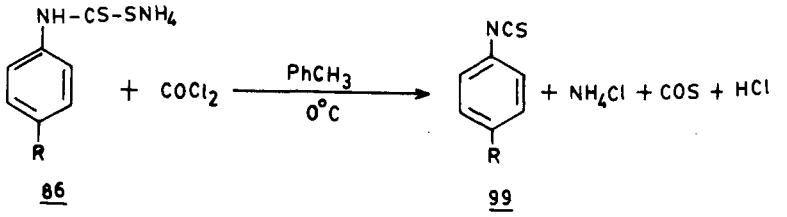
At this point it may also be added that *S*-alkyl derivatives **98** of dithiocarbamic acids **86**, obtained by treating the latter with methyl or ethyl iodide, also decompose thermally[136–139] or under basic[140] conditions or in the presence of metal salts[141] to give excellent yields of alkyl and slightly lower yields of aryl isothiocyanates.

$$R—NH—CS—SR^1 \rightarrow R—NCS + R^1—SH$$

98, R = alkyl, aryl

R^1 = CH_3, C_2H_5

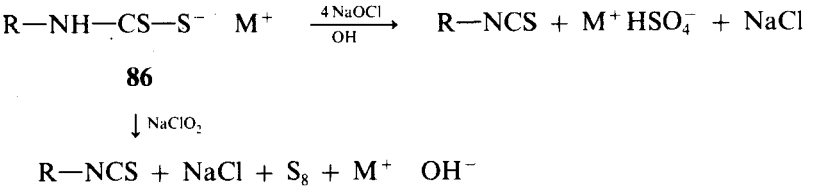
Some aromatic isothiocyanates **99** may also be prepared conveniently by decomposing **86** with phosgene. The method works well with phenyl or with aryl with an electron-donating group in the 4-position. However, it fails to give aryl isothiocyanates with electron-withdrawing groups like NO_2 or Br in the 4-position[142–146] (Scheme 13).



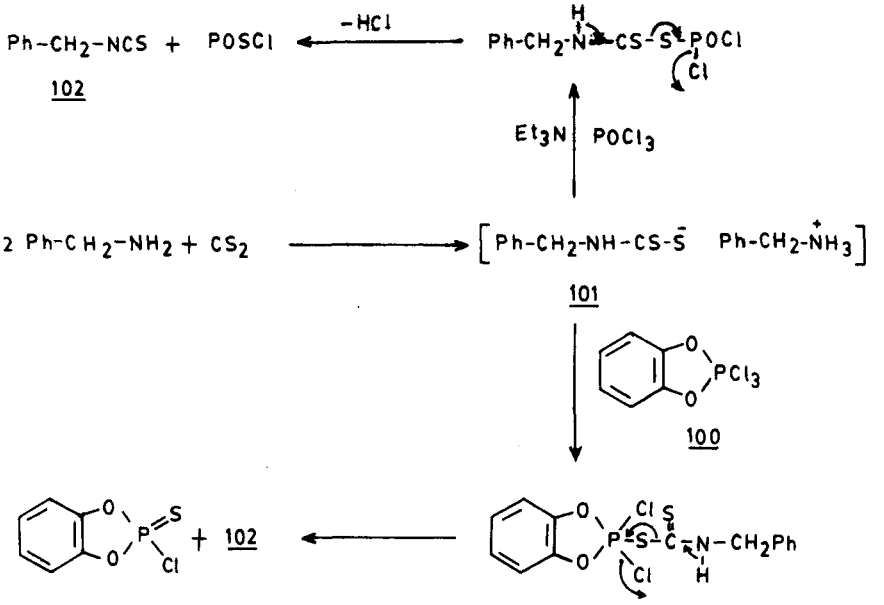
86 99

Scheme 13

Aliphatic and aromatic isothiocyanates have also been prepared by oxidative decomposition of the corresponding dithiocarbamates **86** with sodium hypochlorite in an alkaline medium[147,148] or with sodium chlorite.[149,150]

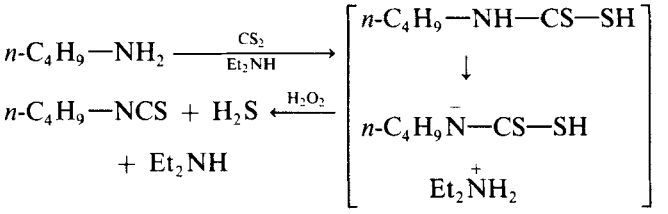


The decomposition of dithiocarbamates can also be achieved with $POCl_3$ or pyrocatechol phosphorotrichloridate **100** in the presence of triethylamine to form the corresponding isothiocyanates.[151-153] Typically, when benzylammonium dithiocarbamate **101** is decomposed with **100**, benzyl isothiocyanate **102** is obtained in 84% yield. Decomposition of **101** with $POCl_3$ also affords **102**, but in lower yields than the above method[152] (Scheme 14).

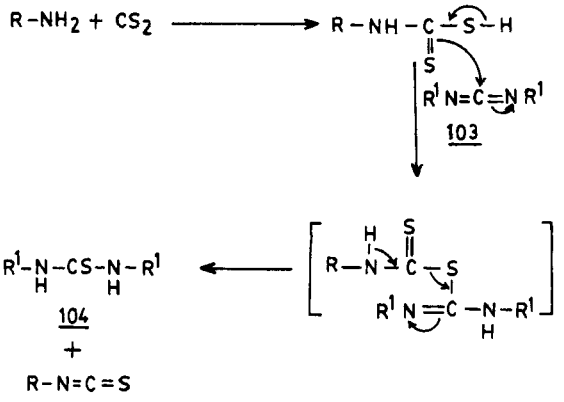


Scheme 14

Method C-3: Decomposition by hydrogen peroxide Some isothiocyanates have been prepared by oxidative decomposition of a mixture of primary amine and carbon disulfide with 30% H_2O_2 in the presence of a secondary amine. The reaction proceeds exothermally giving rise to the formation of an isothiocyanate.[154,155]

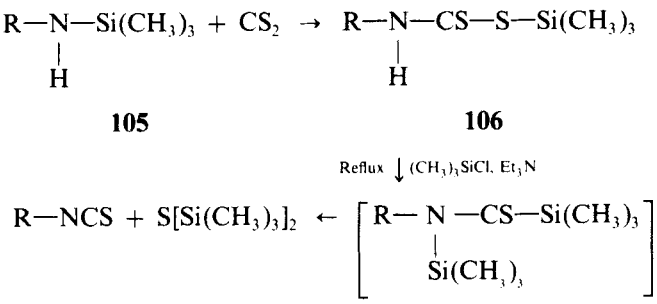


Method C-4: Decomposition with carbodiimides Both alkyl and aryl dithiocarbamic acids, obtained by treating the corresponding primary amines with CS_2, react with carbodiimides **103** in a suitable organic solvent at $-10\,°C$ to form isothiocyanates. For the preparation of aliphatic isothiocyanates diethyl ether and tetrahydrofuran have proved to be good solvents.[156–158] In the case of aromatic amines, symmetric diarylthioureas are also formed along with dicyclohexylthiourea **104** and aryl isothiocyanates. The formation of diarylthioureas may be avoided by using pyridine or triethylamine; consequently high yields of aryl isothiocyanates are obtained.[159] Compound **104** results due to the obvious reaction of dicyclohexyl carbodiimide **103**, (R = C_6H_{11}-*c*) with dithiocarbamic acid (Scheme 15).



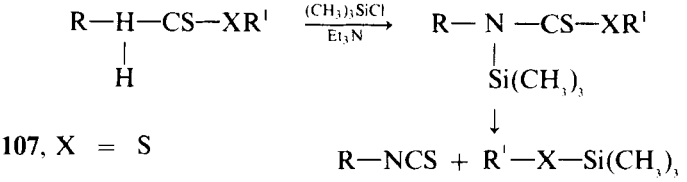
Scheme 15

Method C-5: Decomposition with trimethylsilyl chloride *N*-Silylated primary aliphatic amines **105** react with carbon disulfide at -5 to $0\,°C$ to form silylated esters of dithiocarbamic acid **106** which, being unstable above $0\,°C$, decompose with trimethylsilyl chloride in the presence of triethylamine to form isothiocyanates.[160]



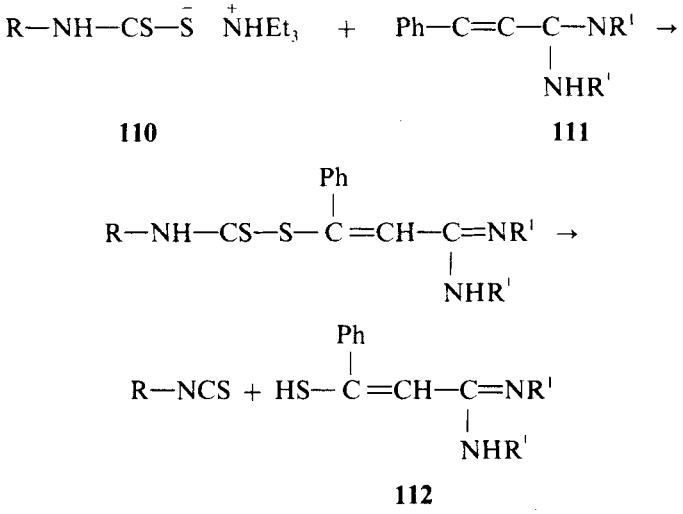
105 **106**

Similarly, alkyl and aryl esters of dithiocarbamic acids **107**, thiocarbamic acids **108** and aroyl dithiocarbamic acids **109** may be decomposed by action of trimethylsilyl chloride to furnish the corresponding isothiocyanates.[161,162]



107, X = S
108, X = O
109, X = S—CO

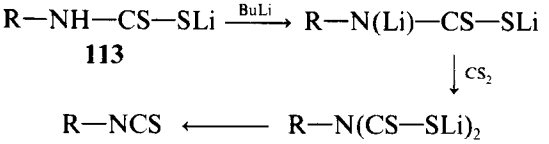
Method C-6: Other methods of decomposition A number of other reagents have also been used to decompose dithiocarbamates. Thus, triethylammonium dithiocarbamates **110** decompose under mild conditions in the presence of *N,N'*-disubstituted propiolamides **111** to form the corresponding isothiocyanates and *β*-mercaptocinnamamidines **112** as by-product.[163]



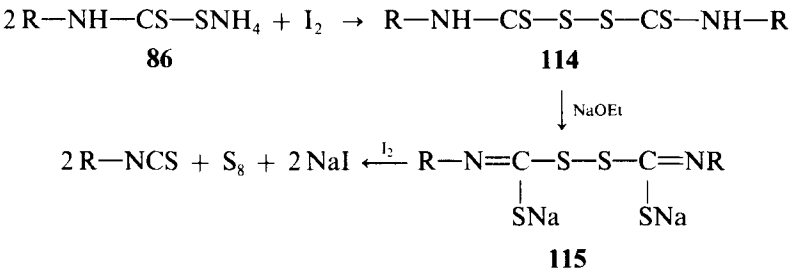
110 **111**

112

Aliphatic and aromatic isothiocyanates can be prepared in 71–99% yield by decomposing the corresponding lithium dithiocarbamates **113** by successive reaction of the latter with butyllithium and carbon disulfide.[164]



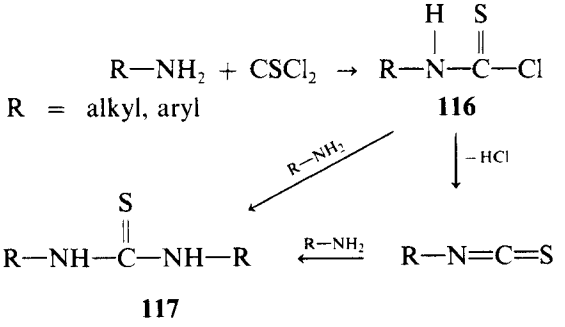
An earlier method to decompose dithiocarbamates **86** uses iodine which oxidises the former at low temperatures to form thiuram disulfides **114** as the intermediate product. Reaction of **114** with sodium ethoxide gives the sodium salt **115** which is oxidised with iodine to form the corresponding isothiocyanate.[165–167]



Some other reagents such as aryl cyanates,[168] cyanogen chloride,[169] cyanuric chloride,[170] chloramine T,[171] 2-chloropyridinium salts[172] and acrylonitrile[173] have also been used to decompose dithiocarbamates to the corresponding isothiocyanates.

Method D: From Thiophosgene The reaction of thiophosgene with primary amines is the simplest and most convenient method which has been widely used to prepare a variety of alkyl, aryl and heteroaryl isothiocyanates in high yields.[174–176] Thiophosgene also reacts with other substrates to form isothiocyanates which may be described as follows.

Method D-1: From primary amines and thiophosgene Alkyl and aryl amines react readily with thiophosgene to form thiocarbamoyl chlorides **116** which, being unstable, undergo facile dehydrohalogenation upon heating to give isothiocyanates.[177–182] The intermediate **116** may also react with excess amine to afford a thiourea **117** as by-product.[183–185] The formation of **117** can be avoided by using a small excess of thiophosgene.



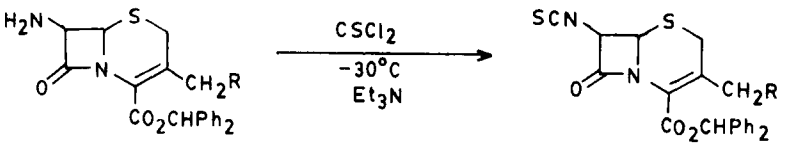
A general procedure to prepare isothiocyanates involves treatment of a solution of the appropriate primary amine in chloroform, dichloromethane, benzene, toluene, acetone, dioxan or tetrahydrofuran with a solution of thiophosgene in the same solvent in the presence or absence of a base ($CaCO_3$, Na_2CO_3, $NaHCO_3$, triethylamine, etc.) at low or elevated temperatures.[186-190] A solution of the desired amine in water or dilute HCl may also be treated with thiophosgene dissolved in a water-immiscible solvent like chloroform or benzene to get a good yield of the isothiocyanate.[191-193] Using the above procedure a wide variety of isothiocyanates with an alkyl,[194-202] aralkyl,[203-215] aryl[216-273] or heteroaryl[274-295] residue have been prepared. The examples below broadly illustrate the scope of the thiophosgene method.

Reaction of octadecylamine **118a** with thiophosgene in toluene gives octadecyl isothiocyanate **119a** in 88% yield.[296] Similarly, the synthesis of carbethoxymethyl isothiocyanate **119b** may be achieved in 50–60% yield by treating a suspension of carbethoxymethylamine hydrochloride **118b** with thiophosgene at 110–115 °C in toluene.[297] 2-Methylpropanamide **118c** also reacts with thiophosgene to give the corresponding isothiocyanate **119c**.[197]

$$R{-}NH_2 + CSCl_2 \longrightarrow R{-}NCS$$

118a, R	= $(CH_2)_{17}CH_3$	**119a**, R	= $(CH_2)_{17}CH_3$
b, R	= $CH_2{-}COOEt$	**b**, R	= $CH_2{-}COOEt$
c, R	= $COCH(CH_3)_2$	**c**, R	= $COCH(CH_3)_2$

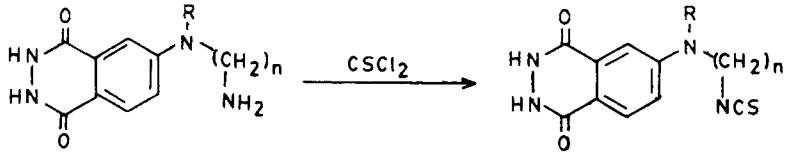
Matsuo and coworkers[298] have prepared a few 7-isothiocyanatocephalosporins **121** by reaction of the corresponding 7-aminocephalosporins **120** with thiophosgene at −30 °C in the presence of triethylamine (Scheme 16).



120 121

Scheme 16

Aralkyl isothiocyanates with a functionalised heterocyclic moiety can also be prepared by the thiophosgene method. Thus, reaction of 11 wt. parts of the amine **122** in 50 parts 1 M sodium carbonate with thiophosgene at room temperatures yields the corresponding isothiocyanate of isoluminol **123**[299] (Scheme 17).

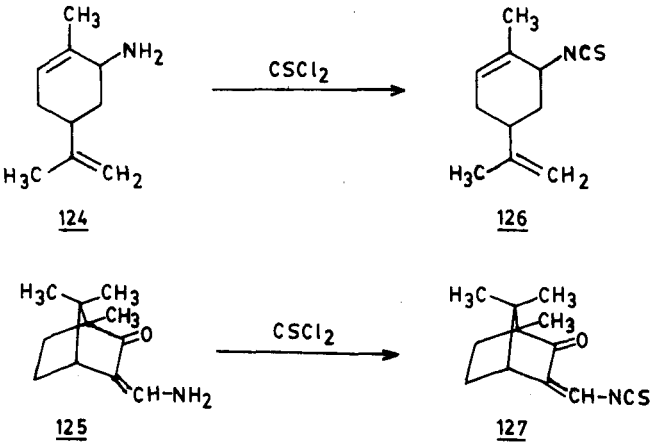


122 R = alkyl
n = 1-8

123

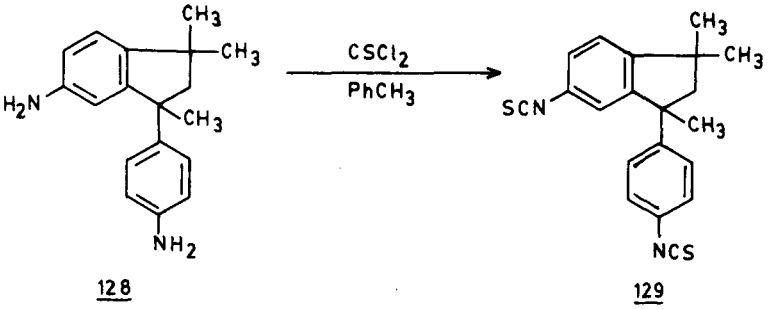
Scheme 17

Thiophosgene reacts preferentially at the nitrogen centre of an aliphatic or aromatic primary amine containing a carbon-carbon double bond to form the corresponding isothiocyanate.[300-307] Typically, 6-amino-4-isopropenyl-1-methylcyclohexene **124** and 3-aminomethylene-DL-camphor **125** react with thiophosgene to form 4-isopropenyl-6-isothiocyanato-1-methylcyclohexene **126** and 3-isothiocyanatomethylene-DL-camphor **127**, respectively[301] (Scheme 18).



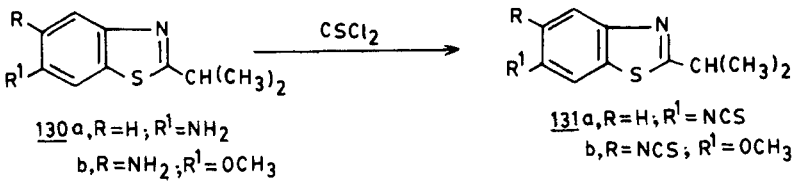
Scheme 18

Several aryl and heteroaryl isothiocyanates have been conveniently prepared by this method. Thus, treatment of 1-(4-aminophenyl)-1,3,3-trimethyl-6-aminoindan **128** with excess thiophosgene in toluene gives 1-(4-isothiocyanatophenyl)-1,3,3-trimethyl-6-isothiocyanatoindan **129** which may further react with compounds containing active hydrogens to form various polymers[308] (Scheme 19).



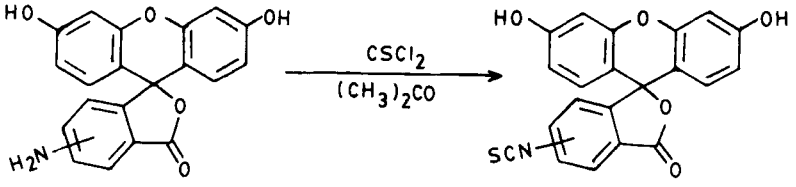
Scheme 19

A number of 5(6)-isothiocyanatobenzimidazoles[309,310] and substituted benzothiazoles with isothiocyanato groups at the 5- and/or 6-position[311-315] have been synthesized possessing marked antiparasitic activity. In a typical example, reaction of 6-amino- and 5-amino-6-methoxy-2-isopropylbenzothiazole **130a,b** with thiophosgene gave the corresponding isothiocyanates **131a,b** of which **131a** was active against tapeworms and a number of bacteria and fungi[313] while **131b** killed ovine liver fluke, *Fasciola hepatica*, at an oral dose of 25 mg/kg[314] (Scheme 20).



Scheme 20

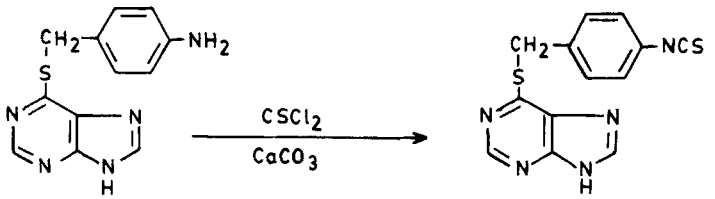
Thiophosgene may also be made to react preferentially with primary amines in the presence of other reactive groups to give synthetically useful isothiocyanates. Thus, for example, the synthesis of isomeric 5- and 6-isothiocyanatofluoresceins **133** may be conveniently achieved by treating the corrsponding amines **132** with thiophosgene[316] (Scheme 21).



132 133

Scheme 21

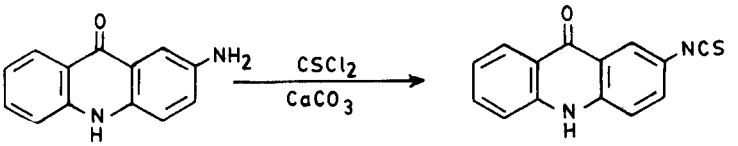
Wagner and coworkers[317,318] have prepared a number of isothiocyanatopurines and -uracils. Typically, treatment of 6-(4-aminobenzylthio)purine **134** with thiophosgene in dioxan in the presence of calcium carbonate leads to the selective formation of 6-(4-isothiocyanatobenzylthio)-purine **135**[317] (Scheme 22).



134 135

Scheme 22

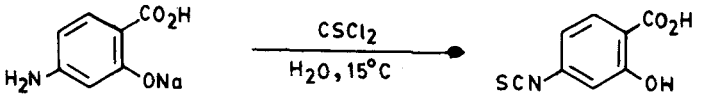
A series of isothiocyanates derived from benzophenones, fluorenones, acridines and acridones has been prepared.[319] Thus, 2-isothiocyanato-9-acridone **137** may be obtained in 54% yield by reaction of 2-amino-9-acridone **136** with thiophosgene (Scheme 23).



136 137

Scheme 23

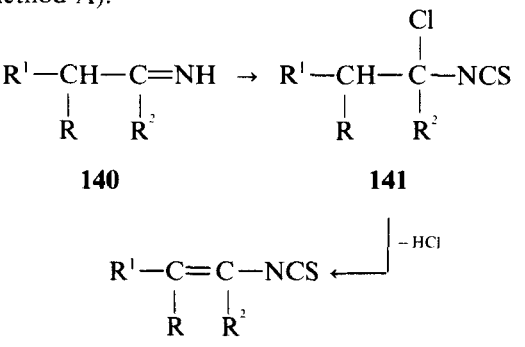
5-Isothiocyanatosalicylic acid **139** has been prepared conveniently by treating the aqueous solution of the alkaline salt of 5-aminosalicylic acid **138** with thiophosgene[320,321] (Scheme 24).



138 **139**

Scheme 24

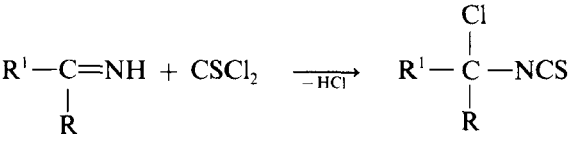
Method D-2: From secondary amines and thiophosgene The reaction of thiophosgene with secondary amines is not a method of choice for generating isothiocyanates. However, some ketimines **140** having an α-hydrogen react with thiophosgene to form α-chloroalkyl isothiocyanates **141** as the intermediate product which undergoes dehydrohalogenation to give the corresponding α-alkenyl isothiocyanate **142** in good yield[322,323] (see also Sect. 3.2, method A).



140 **141**

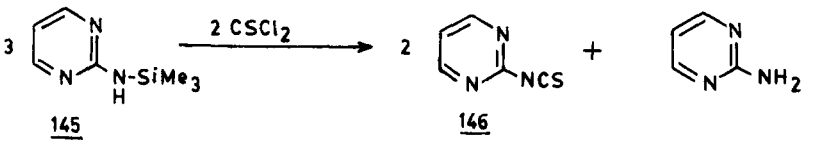
142 (60–75%)

The ketimines **143**, having no α-hydrogen, also react with thiophosgene at 100–130 °C to yield the α-chloroalkyl isothiocyanates **145**.[322,324]



143 **144** (40–80%)

Reaction of 2-(trimethylsilylamino)pyrimidine **145** with thiophosgene in absolute ether at -60 °C in a nitrogen atmosphere gives 2-isothiocyanatopyrimidine **146**[325] (Scheme 25).

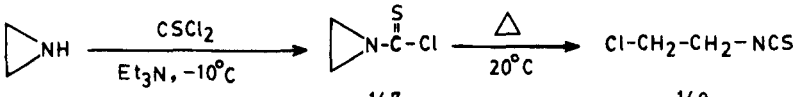


145 **146**

Scheme 25

A number of heterocyclic isothiocyanates have been prepared by treating the corresponding amines with thiophosgene in an ether-water medium in the presence of sodium bicarbonate. These include 2-pyridyl, 4,6-dimethyl-2-pyridyl, 4,6-dimethyl-2-pyrimidyl, 4-methyl-2-thiazolyl, and 1-phenyl-2,3-dimethyl-4-pyrazol-5-onyl isothiocyanate.[187]

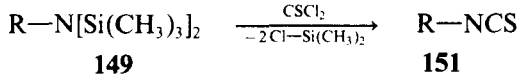
Reaction of ethylenimine with thiophosgene at $-10-0\,^{\circ}C$ in the presence of triethylamine gives *N*-(chlorothiocarbonyl)ethyleneimine **147** which undergoes intramolecular ring opening at 20 °C to form 2-chloroethyl isothiocyanate **148**[326] (Scheme 26).



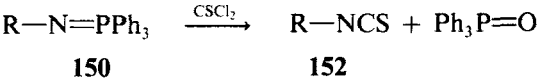
147 148

Scheme 26

Method D-3: From tertiary amines and thiophosgene *N*-Silylated and -phosphonylated tertiary amines **149** and **150** may be allowed to react with thiophosgene to yield the corresponding isothiocyanates **151** and **152**, respectively.[327,328]

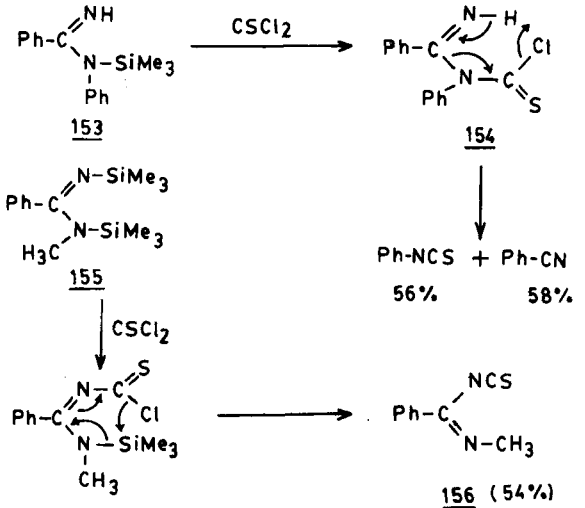


149 **151**



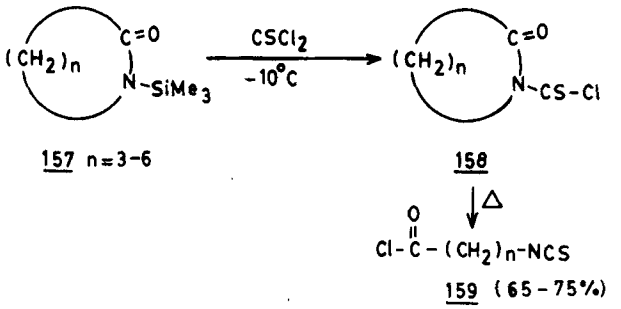
150 **152**

Reaction of *N*-trimethylsilyl-*N*-phenylbenzamidine **153** with thiophosgene proceeds with initial attack of thiophosgene on the N–Si bond to give the intermediate thiocarbamoyl chloride **154** which undergoes synchronous intramolecular decomposition leading to the formation of phenylisothiocyanate, benzonitrile and amidine hydrochloride.[329] A similar reaction occurs when *N*,*N*′-bis(trimethylsilyl)-*N*-methylbenzamidine **155** is treated with thiophosgene to afford *N*-methylbenzimidoyl isothiocyanate **156**[330] (Scheme 27).



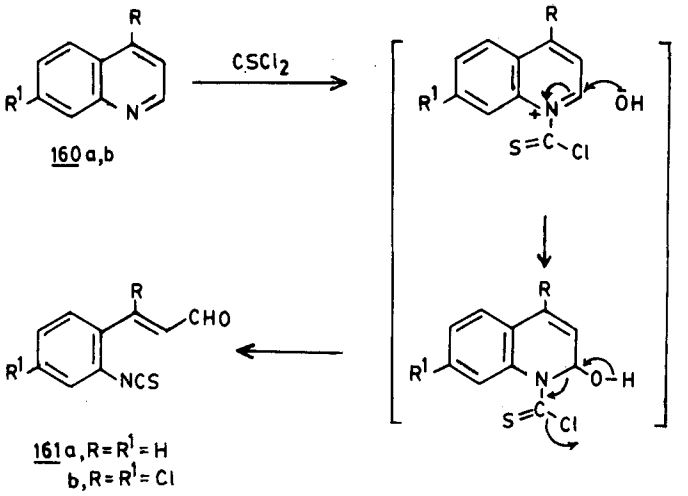
Scheme 27

A number of long-chain aliphatic isothiocyanato acid chlorides **159** have been prepared by heating *N*-(chlorothiocarbonyl)lactams **158** which, in turn, were obtained by the action of thiophosgene on *N*-(trimethylsilyl)lactams **157** at $-10\,^{\circ}C$[331] (Scheme 28).



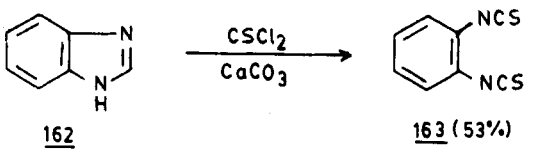
Scheme 28

Reaction of quinoline **160a** with thiophosgene in the presence of aqueous potassium cyanide causes heterocyclic ring cleavage with formation of a small quantity of 2-isothiocyanato-*E*-cinnamaldehyde **161a** along with 3-oxoimidazo[1,5-*a*]quinoline as by-product.[332-334] However, treatment of 4,7-dichloroquinolime **160b** with thiophosgene in the presence of barium carbonate gave a 58% yield of *β*,4-dichloro-2-(isothiocyanato)-cinnamaldehyde **161b**. Other 4- and 6-monosubstituted quinolines behave in a similar manner when allowed to react with thiophosgene[335,336] (Scheme 29).



Scheme 29

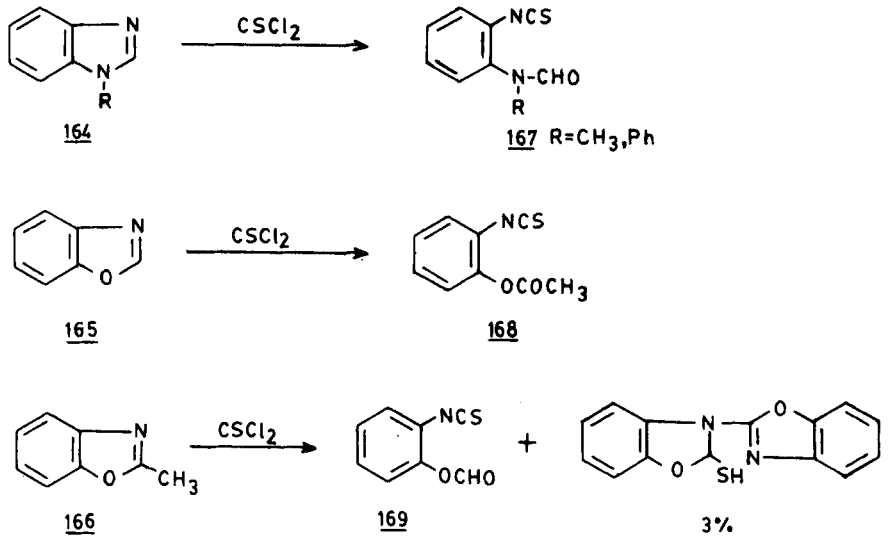
An improved method to prepare *o*-phenylene diisothiocyanate **163** involves reaction of benzimidazole **162** with thiophosgene.[337] Compound **163** was prepared earlier as a by-product by reaction of *o*-phenylenediamine with thiophosgene in 10% yield[338] (Scheme 30).



162 163 (53%)

Scheme 30

1-Substituted benzimidazoles **164**, benzoxazole **165** and 2-methylbenzoxazole **166** also react with thiophosgene under ring cleavage to form the 2-substituted phenylisothiocyanates **167–169**, respectively, in 63–72% yield[339] (Scheme 31).



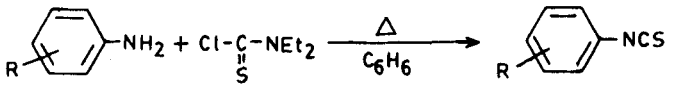
164 167 R=CH3,Ph

165 168

166 169 3%

Scheme 31

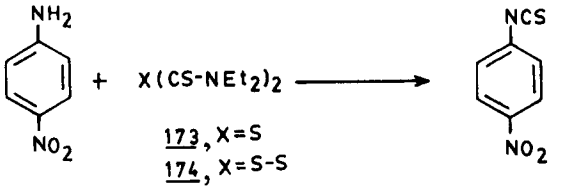
Method E: From Thiocarbonyl Compounds Two thiocarbonyl compounds, *N,N*-diethylthiocarbamoyl chloride **171**[340] and thiocarbonyldiimidazole[341,342] have been used in place of the toxic thiophosgene to prepare isothiocyanates. Thus, when an aromatic amine **170** is heated with *N,N*-diethylthiocarbamoyl chloride **171** in an inert solvent such as benzene, toluene or 1,2-dichloroethene a good yield of the corresponding isothiocyanate **172** is obtained[340] (Scheme 32).



170 171 172

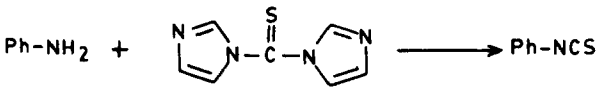
Scheme 32

In a slight modification, *N,N*-diethylthiocarbamoyl chloride **171** may be replaced by bis(diethylthiocarbamoyl) sulfide **173** or disulfide **174** in the above reaction to obtain the corresponding isothiocyanates[343] (Scheme 33).



Scheme 33

Aryl isothiocyanates may also be conveniently prepared by treating the appropriate arylamines with *N,N'*-thiocarbonyldiimidazole **175**[344] (Scheme 34).



175

Scheme 34

Method F: By Decomposition of Thioureas Diarylthioureas **176** can be decomposed with hot mineral acids to aryl isothiocyanates and arylamines.[345] Frequently used acids are hydrochloric,[346-348] sulfuric[349,350] and phosphoric acid.[345] Using this method, cyclohexyl isothiocyanate has been prepared by heating dicyclohexylthiourea with phosphoric acid.[351]

$$Ph—NH—CS—NH—Ph \xrightarrow{HCl} Ph—NCS + Ph—NH_2 \cdot HCl$$

When unsymmetrical thioureas are decomposed, both possible isothiocyanates are formed.[352] For example, *N*-(4-chlorophenyl)-*N'*-phenylthiourea, when heated with HCl, yields a mixture of 4-chlorophenyl and phenyl isothiocyanate which may be separated by fractional distillation.[352]

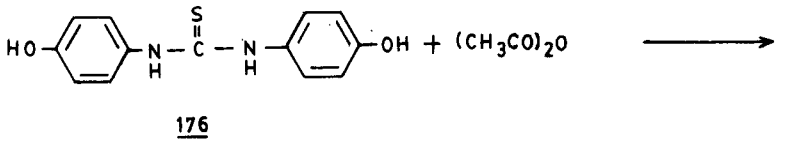
$$C_6H_5—NH—CS—NH—C_6H_4Cl—4 + HCl \rightarrow C_6H_5—NCS + 4—ClC_6H_4—NCS$$

The cleavage of diaryl thioureas can be also be accomplished with acetic anhydride; the end products are aryl isothiocyanates and acetanilides.[353-356]

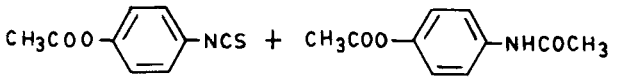
$$PhNH—CS—NHPh + (CH_3CO)_2O \rightarrow Ph—NCS + Ph—NHCOCH_3$$

Using the above method it was possible to prepare 4-acetoxyphenyl isothiocyanate **177** by cleavage of 4,4'-dihydroxydiphenylthiourea **176** with acetic acid anhydride[357] (Scheme 35).

Reaction of diphenylthiourea with diketene also affords a mixture of phenylisothiocyanate, acetoacetanilide and diphenylurea.[358] 4-Benzylthiosemicarbazide **178** may be



176



177

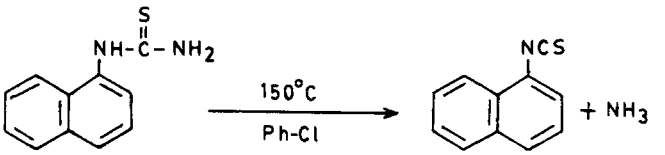
Scheme 35

decomposed in acetic acid in the presence of $FeCl_3$ at 50 °C to form benzyl isothiocyanate **179**.[359]

$$PhCH_2—NH—CS—NH—NH_2 \xrightarrow{FeCl_3} PhCH_2—NCS$$

178 **179**

Decomposition of *N*-arylthioureas such as *N*-naphthylthiourea **180** may be achieved by prolonged heating at 150 °C in chlorobenzene to obtain 1-naphthyl isothiocyanate **181** in high yield[360] (Scheme 36).



180 181 (91.5%)

Scheme 36

Pyrolysis of *N*-acyl-*N'*-arylthioureas **182**, obtained from the corresponding *N*-arylthioureas, also leads to the formation of aryl isothiocyanates.[361] Pyrolysis of thioureas may also be carried out in the presence of polychlorosilanes to give high yields of the isothiocyanates.[362]

$$Ar—NH—CS—NH—COR \rightarrow Ar—NCS + R—CONH_2$$

182

In another method, symmetrical thioureas are treated with butyllithium in the presence of carbon disulfide to form two moles of the aryl isothiocyanate per mole of the *N,N'*-diaryl- or dialkylthiourea used.[363]

$$R—NH—CS—NH—R \xrightarrow[CS_2]{BuLi} 2\,R—NCS$$

Method G: By Sulfuration of Compounds with NC Groups A number of compounds containing an NC function may be sulfurated to form isothiocyanates which is illustrated below.

Method G-1: Sulfuration of Isocyanides Sulfuration of aryl isocyanides such as *o*-biphenylyl isocyanide **183** with elemental sulfur in refluxing benzene for 64 hrs gives *o*-biphenylyl isothiocyanate **184** in excellent yield.[364]

$$o\text{-Ph}-C_6H_4-\overset{+}{N}\equiv\overset{-}{C} + 1/8\,S_8 \xrightarrow[\text{reflux}]{\text{benzene}} o\text{-Ph}-C_6H_4-NCS$$

183 **184** (97.6%)

Replacement of sulfur by chlorocarbonyl sulfenyl chloride in the above reaction also gives isothiocyanate. Thus, reaction of cyclohexyl isocyanide **185** with chlorocarbonyl sulfenyl chloride **186** proceeds with the formation of the intermediate **187** which loses phosgene to give cyclohexyl isothiocyanate **188**.[365]

$$C_6H_{11}-\overset{+}{N}\equiv\overset{+}{C} + Cl-CO-SCl \rightarrow$$

185 **186**

$$C_6H_{11}-N=\underset{\displaystyle Cl}{\underset{|}{C}}-S-COCl \xrightarrow{-COCl_2} C_6H_{11}-NCS$$

187 **188**

Reversible exchange of sulfur takes place when an aromatic isonitrile is treated with an aromatic isothiocyanate.[364] Similarly, reaction of an isonitrile with a thiol causes radical addition of the thiol to form either a thioformimidate **189** or an isothiocyanate.[366]

$$R-\overset{+}{N}\equiv\overset{-}{C} + Ar-NCS \rightleftharpoons R-NCS + Ar-\overset{+}{N}\equiv\overset{-}{C}$$

$$R-\overset{+}{N}\equiv\overset{-}{C} + R^1-SH \rightarrow R^1-S-CH=NR \text{ or } R-NCS$$

189

Method G-2: Sulfuration of Dichloromethyleneimines Dichloromethyleneimines (carbonimidoyl chlorides, **190**) may be sulfurated with sodium sulfide[367] or ammonium sulfide[368] in acetone or an acetone-water mixture at 20 °C to give isothiocyanates. Reaction of **191** with hexamethyldisilthiane **192** also affords the corresponding isothiocyanate in high yield.[369]

$$R-N=CCl_2 + Na_2S \xrightarrow{20\,^\circ C} R-NCS$$

190

$$Ph-N=CCl_2 + (Me_3Si)_2S \xrightarrow{170\,^\circ C} Ph-NCS$$

191 **192** 91%

Treatment of dichloromethyleneimines **190** with P_2S_5 in boiling toluene, xylene or chlorobenzene also yields the corresponding isothiocyanates.[370]

$$R{-}N{=}CCl_2 + P_2S_5 \xrightarrow{\text{xylene}} R{-}NCS$$

190

Reaction of *N*-1,2-(dichloroethyl)dichloromethyleneimine **191** with P_2S_5 in toluene at 80–90 °C affords 1,2-dichloroethyl isothiocyanate **192**.[371]

$$Cl{-}CH_2{-}\underset{\displaystyle Cl}{\underset{|}{CH}}{-}N{=}CCl_2 + P_2S_5 \xrightarrow[\text{toluene}]{\Delta} Cl{-}CH_2{-}\underset{\displaystyle Cl}{\underset{|}{CH}}{-}NCS$$

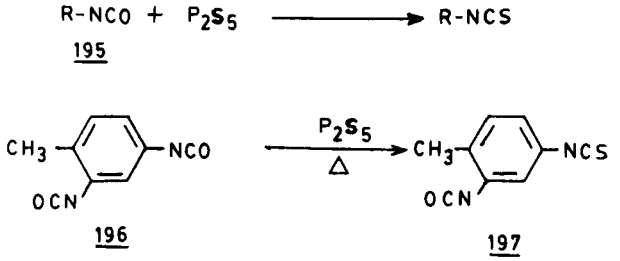
191 **192** (87%)

Difluoromethyleneimines such as **193** may also be sulfurated with P_2S_5 to form pentafluoroethyl isothiocyanate **194**.[372]

$$F_3C{-}CF_2{-}N{=}CF_2 + P_2S_5 \rightarrow F_3C{-}CF_2{-}NCS$$

193 **194**

Method G-3: Sulfuration of Isocyanates The sulfuration of isocyanates **195** may be carried out either with P_2S_5 or carbon disulfide[2,373,374] to yield the desired isothiocyanate. However, when 1-methyl-2,4-(diisocyanato)-benzene **196** is treated with P_2S_5 at 150–180 °C only one isocyanate group is sulfurated and 1-methyl-2-isocyanato-4-isothiocyanatobenzene **197**[2] is formed (Scheme 37).



Scheme 37

Isocyanates may also be sulfurated with *O,O*-diethyl dithiophosphate **198**. Typically, reaction of *n*-butyl isocyanate with **198** in an inert solvent at 20–25 °C leads to the formation of an intermediate, *O,O*-diethyl-*S*-(butylaminocarbonyl)-dithiophosphate **199** which can be decomposed by heating at 125–30 °C to yield *n*-butyl isothiocyanate.[375]

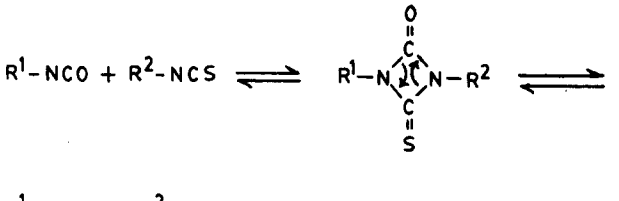
$$n\text{-}C_4H_9{-}NCO + HS{-}PS(OEt)_2 \xrightarrow{20\text{–}25\,^\circ C}$$

198

$$n\text{-}C_4H_9{-}NH{-}CO{-}S{-}PS(OEt)_2 \xrightarrow{125\text{–}130\,^\circ C} n\text{-}C_4H_9{-}NCS$$

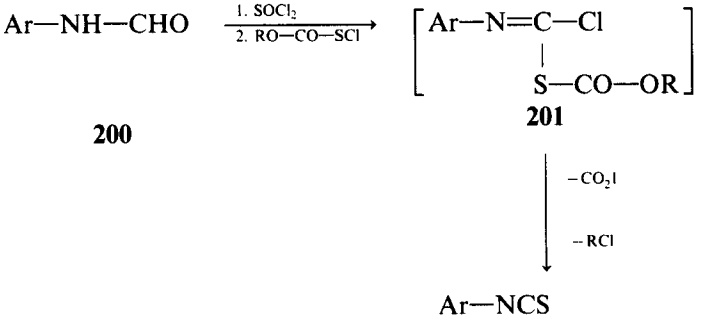
199 73.5%

When an isocyanate is allowed to react with an isothiocyanate, oxygen-sulfur exchange takes place to give a mixture of isothiocyanates and isocyanates with different substituents[376-378] (Scheme 38).

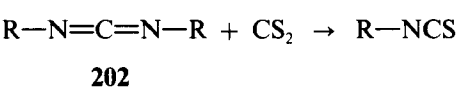


Scheme 38

Method G-4: Sulfuration of Formamides Kuehle and Hartmann[379,380] have developed a useful method to convert alkyl- and arylformamides to the corresponding isothiocyanates. The reaction involves successive treatment of the formamide **200** with thionyl chloride and alkoxycarbonyl sulfenyl chloride to form the intermediate **201** which loses CO_2 and alkyl chloride to give the corresponding isothiocyanate.

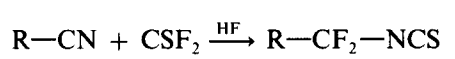


Method H: By Introduction of a Thiocarbonyl Group at a Nitrogen Function The thiocarbonyl group may be inserted across an N=C, N=P, N=S or N=O bond by treatment with carbon disulfide. Thus, when carbodiimides **202** are treated with carbon disulfide at higher temperatures, isothiocyanates are formed.[381]



202

Reaction of nitriles with thiocarbonyl difluoride in dry HF yields 1,1-difluoroalkyl isothiocyanates **203**.[382]



203

Reaction of phosphinimines **204**,[328,383] phosphoramidate anions **205**[384] or thiophosphinamidate anions **206**[385] with carbon disulfide yields the corresponding isothiocyanates.

$$R{-}N{=}P(Ph)_3 + CS_2 \rightarrow R{-}NCS + SP(Ph)_3$$

204

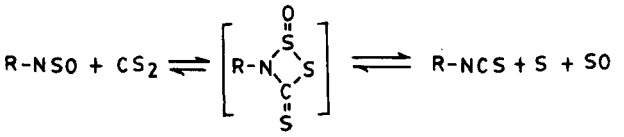
$$R{-}\bar{N}{-}PO(OEt)_2 + CS_2 \rightarrow R{-}NCS + \bar{S}PO(OEt)_2$$

205

$$R{-}\bar{N}{-}PS(Ph)_2 + CS_2 \rightarrow R{-}NCS + \bar{S}PS(Ph)_2$$

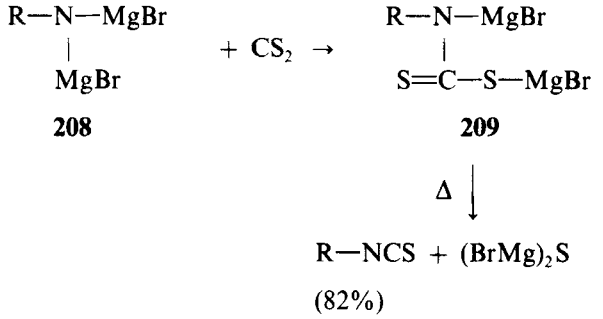
206

Aromatic *N*-sulfinylamines **207** also react with CS_2 at 200 °C in a pressure reactor to give quantitative yields of the isothiocyanate[386] (Scheme 39).

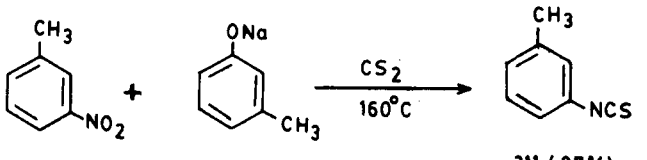


Scheme 39

Some bis-(bromomagnesio)amines **208** have also been shown to react with carbon disulfide to form the intermediate **209** which rearranges to give the corresponding isothiocyanate.[387]



Insertion of thiocarbonyl takes place across the N=O bond when a nitro compound is heated with CS_2 in an autoclave. For example, when a mixture of *m*-nitrotoluene **210** and sodium 3-methylphenoxide is heated at 160 °C in an autoclave with excess CS_2, *m*-tolyl isothiocyanate **211** is obtained in 87% yield[388,389] (Scheme 40).



Scheme 40

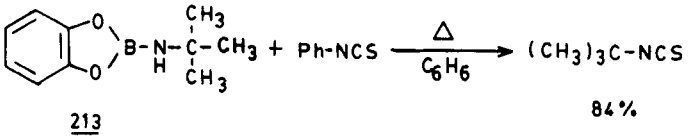
Method I: Miscellaneous Preparations Aryl- and *t*-alkylformaldimines **212** undergo sulfuration when heated with elemental sulfur under pressure to form the corresponding isothiocyanates.[390]

$$R{-}N{=}CH_2 + S_8 \xrightarrow{120\text{–}130\,^\circ C} R{-}NCS$$

212

R = aryl, alkyl

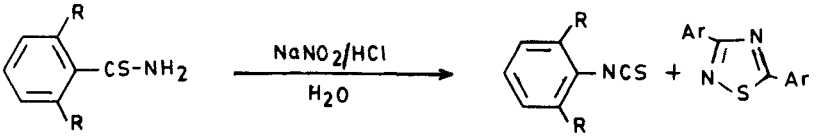
Treatment of 2-*t*-butylamino-1,3,2-benzodioxaborole **213** with phenyl isothiocyanate leads to an exchange reaction and formation of *t*-butyl isothiocyanate in high yield[391] (Scheme 41).



213

Scheme 41

Oxidation of 2,6-dihalothiobenzamides **214** with dilute HNO_2 leads to a mixture of 2,6-dihalophenyl isothiocyanates **215** and 3,5-diaryl-1,2,4-thiadiazoles[392,393] (Scheme 42).

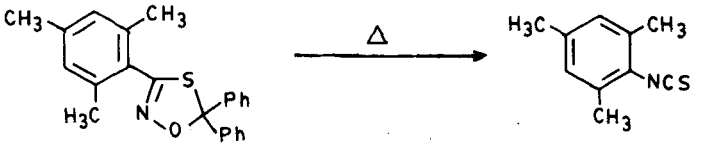


214 R=Cl, Br

215 (32%)

Scheme 42

When 3-mesityl-5,5-diphenyl-1,4,2-oxathiazole **216** is heated 20–30 °C above its melting point until the blue colour disappears, an 87% yield of mesityl isothiocyanate **217** is obtained[394] (Scheme 43).

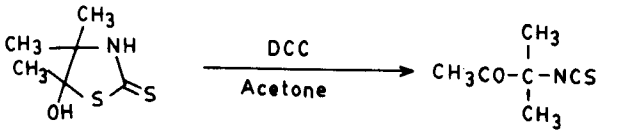


216

217 (87%)

Scheme 43

Reaction of 5-hydroxy-4,4,5-trimethylthiazolidine-2-thione **218** with DCC in acetone at room temperature gives an excellent yield of 3-isothiocyanato-3-methyl-2-butane **219**[395] (Scheme 44).



218 219 (93%)

Scheme 44

1-Ethoxy-2-bromoethyl isothiocyanate **221** may be conveniently prepared by treating 1,1-diethoxy-2-bromoethane **220** with tetra(isothiocyanato)silane.[396]

$$Br—CH_2—CH(OEt)_2 + Si(NCS)_4 \xrightarrow[\Delta]{\text{benzene}}$$

220

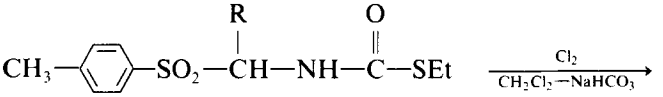
$$Br—CH_2—\underset{\displaystyle OEt}{\underset{|}{CH}}—NCS$$

221 (61%)

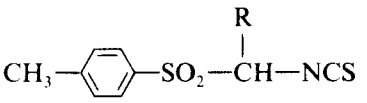
When an aqueous solution (40%) of methylamine is treated with a mixture of CS_2 and cyanamide, methyl isothiocyanate is obtained in 55.7% yield.[397]

$$CH_3NH_2 + CS_2 + H_2N—CN \rightarrow CH_3—NCS$$

S-Ethyl-*N*-[1-(4-methylphenylsulfonyl)alkyl]thiocarbamates **222** react with chlorine in a heterogeneous mixture of dichloromethane and aqueous $NaHCO_3$ to afford 1-(4-methylphenylsulfonyl)-alkyl isothiocyanates **223** in good yield.[398]



222, R = H, Et, Bz

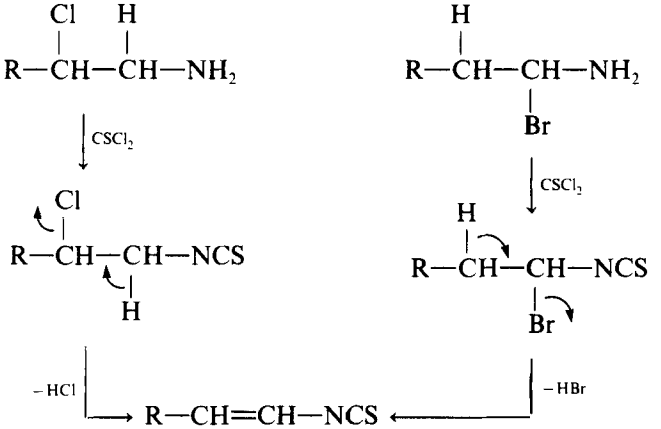


223 (67%)

3.2 1-Alkenyl Isothiocyanates

1-Alkenyl isothiocyanates, where the NCS group is directly bound to a carbon-carbon double bond, serve as versatile synthons in heterocyclic syntheses. Unfortunately, they cannot be prepared by conventional methods due to the nonreactivity or instability of the alkenylamines which ought to be used as starting materials. Special methods, therefore, have been developed to synthesize 1-alkenyl isothiocyanates which are described below.

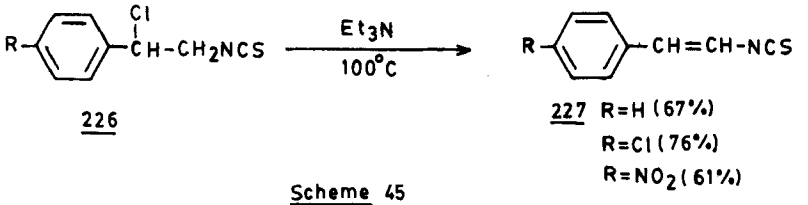
Method A: By Dehydrohalogenation of Isothiocyanates This is the most widely used method to prepare 1-alkenyl isothiocyanates. The method consists of preparing an α- or β-haloalkyl isothiocyanate by action of thiophosgene on an α- or β-haloalkylamine. The resulting isothiocyanate is then subjected to dehydrohalogenation in the presence of a base to form a 1-alkenyl isothiocyanate.



Thus, vinyl isothiocyanate **225** has been prepared by dehydrobromination of 1-isothiocyanato-2-bromoethane **224** in the presence of triethylamine.[399]

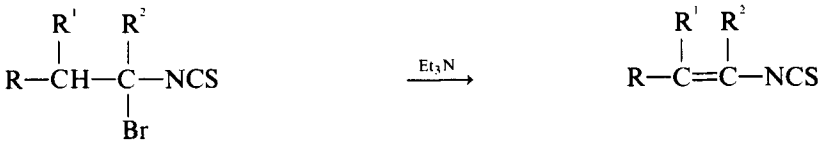
$$\underset{\textbf{224}}{Br{-}CH_2CH_2{-}NCS} \xrightarrow[40\text{-}50\,^{\circ}C]{Et_3N\text{—Ether}} \underset{\textbf{225}\ (63\%)}{CH_2{=}CH{-}NCS}$$

Similarly, dehydrohalogenation of 2-chloro-2-phenylethyl isothiocyanate **226** gives a mixture of *cis*- and *trans*-β-styryl isothiocyanate **227**[400,401] (Scheme 45).



Scheme 45

A number of alkenyl isothiocyanates **229** have been prepared by dehydrobromination of α-bromoalkyl isothiocyanates **228** in the presence of triethylamine.[402]



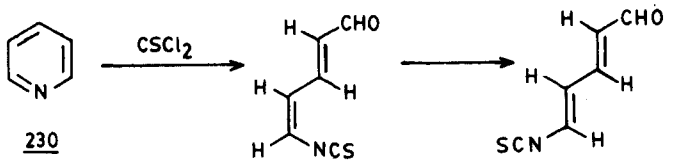
228, R = H, CH_3

R^1 = H, CH_3, $-(CH_2)_4-$

R^2 = H, CH_3, $COOCH_3$

229 (63–92%)

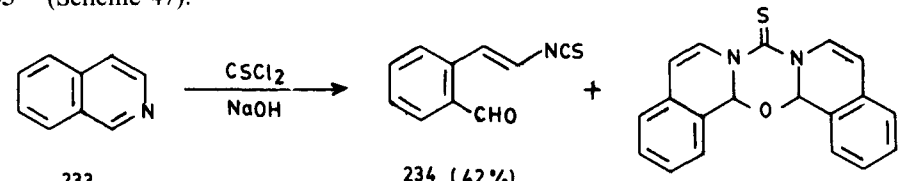
Method B: By Cleavage of Nitrogen Heterocycles Reaction of pyridine **230** with thiophosgene causes ring scission and yields 2-(E)-4-(Z)-5-isothiocyanato-2,4-pentadienal **231** which may be further isomerised to the (E,E)-isomer **232**.[403,404] (Scheme 46).



230 231 (8%) 232 (6%)

Scheme 46

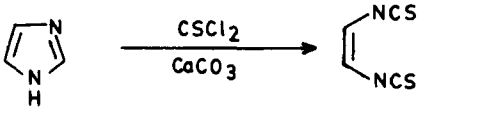
Isoquinoline **233** also reacts with thiophosgene in the presence of dilute NaOH to give *cis-o*-(2-isothiocyanatovinyl)benzaldehyde **234** along with the pentacyclic by-product **235**[403] (Scheme 47).



233 234 (42%) 235 (32%)

Scheme 47

When imidazole **236** is allowed to react with thiophosgene in dichloromethane and aqueous acetonitrile in the presence of $CaCO_3$ in a nitrogen atmosphere at 5 °C, a solution of *cis*-vinylene diisothiocyanate **237** is obtained which may be stored in a refrigerator for a long time[405] (Scheme 48).



236 237 (46%)

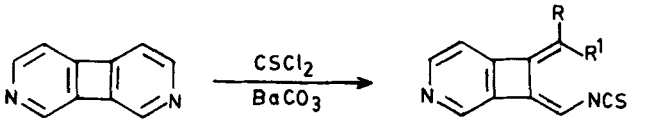
Scheme 48

Treatment of 2-methyloxazole **238** with thiophosgene leads to a facile ring cleavage and the formation of 2-acetoxyvinyl isothiocyanate **239** in 60% yield[406] (Scheme 49).

238 239 (60%)

Scheme 49

2,7-Dizabiphenylene **240** also undergoes ring opening when treated with thiophosgene at 0 °C in the presence of barium carbonate in aqueous methylene chloride to form cyclobutapyridine **241** which readily isomerises to give the isothiocyanate **242** in 60% yield[407] (Scheme 50).

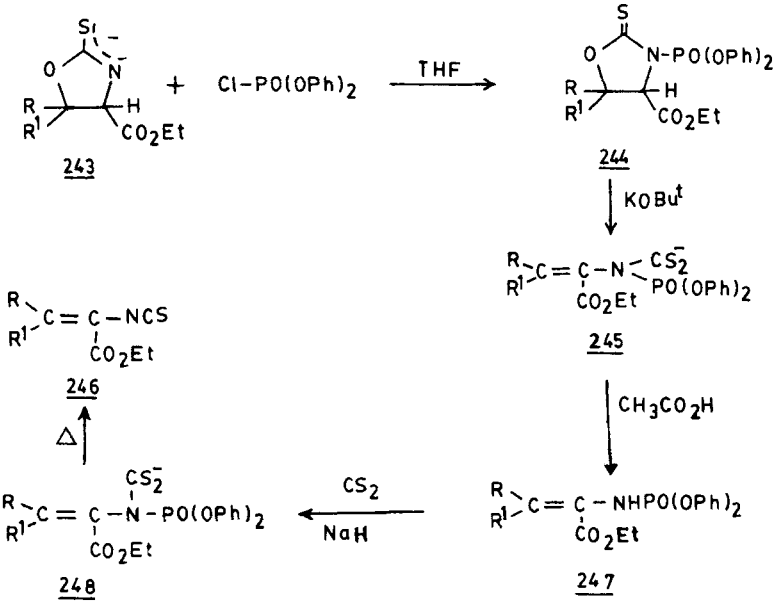


240

241 R=H, R¹=CHO
242 R=CHO, R¹=H

Scheme 50

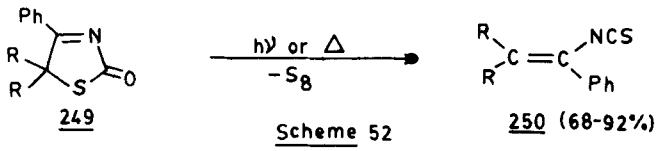
Phosphorylation of the anion of oxazolidine-2-thiones **243** with diphenylphosphoryl chloride at 20–30 °C in THF gave **244** which was decomposed with potassium *t*-butoxide to *N*-phosphoryl-*N*-vinylthiocarbamates (**245**) and then to the isothiocyanates **246**.[408,409] Compounds **245** may also be converted to α-(diphenoxyphosphorylamino)acrylic acid esters **247** by treatment with glacial acetic acid at −60 °C. The latter when treated with carbon disulfide and sodium hydride afford *N*-phosphoryldithiocarbamates **248** which decompose at 20–40 °C to form the isothiocyanates **246**[408,409] (Scheme 51).



243 244 245 246 247 248

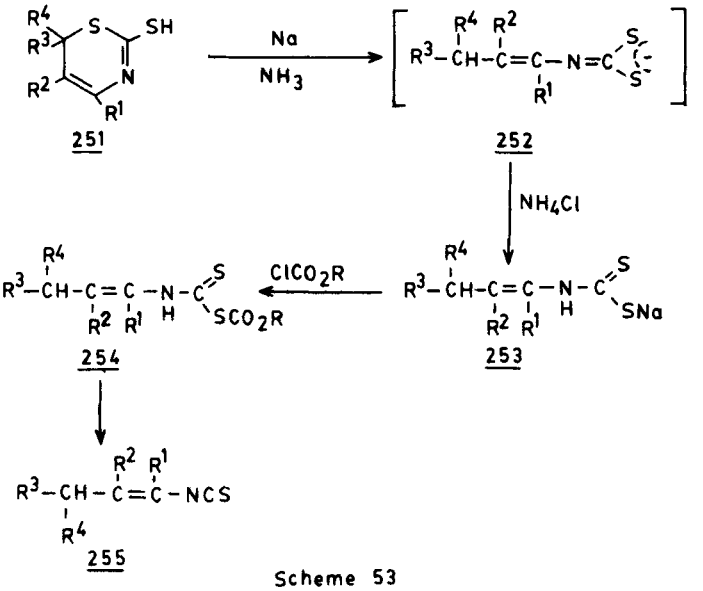
Scheme 51

Photolytically, thermally or trimethyl phosphite induced ring cleavage of 2-thioxo-2,5-dihydro-1,3-thiazoles **249** causes elimination of sulfur and formation of 1-alkenyl isothiocyanates **250**[410] (Scheme 52).



249 Scheme 52 250 (68-92%)

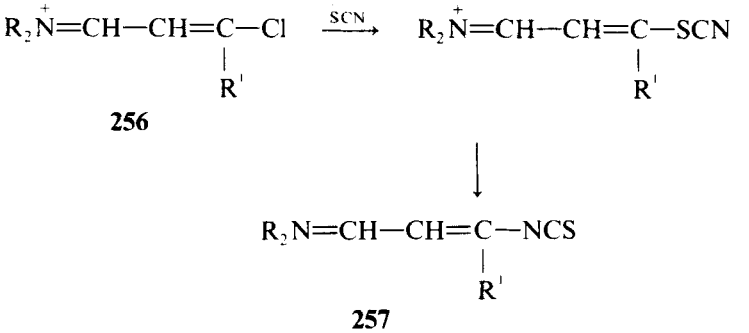
Reaction of 2-mercapto-6*H*-1,3-thiazines **251** with sodium in liquid NH_3 causes ring opening to form the disodium dithiocarbamates **252** which when treated with one mole of NH_4Cl give rise to the monosodium dithiocarbamates **253**. The latter are then allowed to react with alkyl chloroformates to afford *N*-(1-alkenyl)-*S*-(alkoxycarbonyl)dithiocarbamates **254** which on heating give the 1-alkenyl isothiocyanates **255**[411] (Scheme 53).



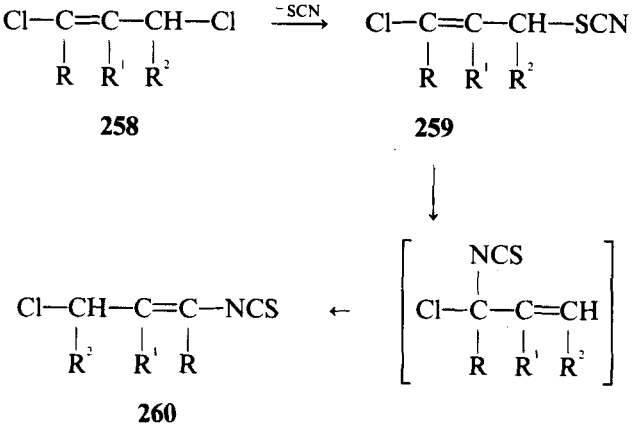
Scheme 53

Method C: By reaction of 1-chloroalkenes with KSCN The synthesis of some 1-alkenyl isothiocyanates (**61, 63** and **65**)[93] by reaction of 1-chloroalkenes and alkyl chlorides KSCN has been described in Sect. 3.2 (method A).

Activated 1-chloroalkenes such as 3-chloroallyliminium salts **256** react with thiocyanates to give 3-isothiocyanatoallyliminium salts **257**.[412,413]



When 3-chloroallyl chlorides **258** are allowed to react with thiocyanates, only one of the chloro groups is substituted to form 3-chloroallyl thiocyanates **259** which may be isolated and isomerised to give 3-chloroallyl isothiocyanates **260**.[414,415]



Method D: Miscellaneous Preparations Sulfuration of *N*-vinyldichloromethyleneimine **261** with P_2S_5 gives an 80% yield of vinyl isothiocyanate **262**.[416]

$$CH_2{=}CH{-}N{=}CCl_2 + P_2S_5 \rightarrow CH_2{=}CH{-}NCS$$

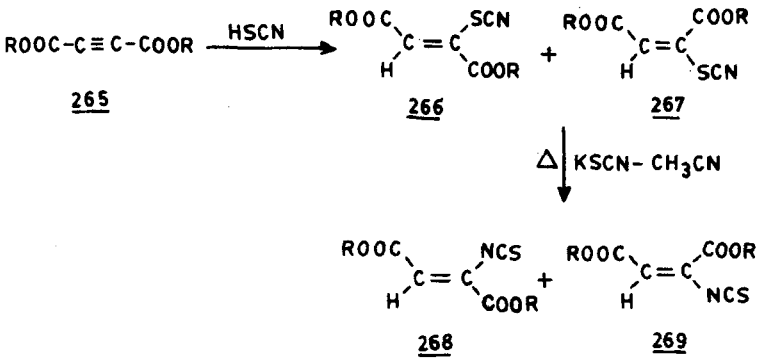
261 **262** (80%)

However, when vinylmercury thiocyanate **263** is heated at 100–120 °C, a mixture of vinyl thiocyanate **264** and vinyl isothiocyanate **262** is obtained.[417]

$$CH_2{=}CH{-}Hg{-}SCN \xrightarrow{\Delta} CH_2{=}CH{-}SCN + CH_2{=}CH{-}NCS$$

263 **264** (60%) **262** (30%)

Addition of thiocyanic acid to dialkyl acetylenedicarboxylates **265** gives a mixture of dialkyl thiocyanatomaleates and -fumarates **266** and **267**. This mixture is then refluxed in acetonitrile in the presence of a catalytic amount of KSCN to form dialkyl isothiocyanatomaleates and -fumarates **268** and **269**, respectively[418] (Scheme 54).



Scheme 54

3.3 Acyl Isothiocyanates

Acyl and alkoxycarbonyl isothiocyanates designated by the general formulas RCO-NCS and ROOC-NCS, respectively, are highly reactive organic synthons which have been widely used to prepare a variety of organic molecules. Consequently the chemistry of carbonyl isothiocyanates has been extensively reviewed.[6,7,9,15,18,419] Although some of the carbonyl isothiocyanates are unstable and tend to dimerise or polymerise at room temperature, they can be easily prepared and stored at low temperatures.[14]

Method A: From acyl chlorides and thiocyanates In this most commonly used method an appropriate acyl chloride is treated with lead(II) thiocyanate [$Pb(SCN)_2$] in benzene or toluene or with sodium, potassium or ammonium thiocyanate (MSCN; M = Na, K or NH_4) in solvents like acetone, acetonitrile or ethyl acetate to give 31–97% yields of the corresponding acyl isothiocyanates.[420–441]

$$R{-}CO{-}Cl \quad + \quad MSCN \rightarrow R{-}CO{-}NCS$$

R = alkyl, aryl

Typically, benzoyl isothiocyanate **271** may be prepared in 46–62% yield by treating benzoyl chloride **270** with KSCN in acetone.[405] When **270** was treated with freshly prepared lead thiocyanate [$Pb(SCN)_2$] **271** was obtained in 85% yield.[437] An elegant method to prepare **271** involves reaction of **270** with trimethylsilyl isothiocyanate at 160–200 °C and a 98% yield of the desired product is obtained.[442]

$$Ph{-}CO{-}Cl + (CH_3)_3Si{-}NCS \rightarrow Ph{-}CO{-}NCS$$

270 **271**

Similarly, reaction of acetyl chloride **272a** and fluoroacetyl chloride **272b** with $Pb(SCN)_2$ in refluxing benzene gave acetyl and fluoroacetyl isothiocyanate (**273a,b**), respectively, in good yields.[437,443]

$$R{-}CH_2CO{-}Cl + Pb(SCN)_2 \xrightarrow{\text{benzene}} R{-}CH_2CO{-}NCS$$

272a, R = H **273a**, R = H

b, R = F **b**, R = F

The acid chlorides may also be allowed to react with potassium thiocyanate under phase transfer conditions to furnish good yields of acyl isothiocyanates.[444]

$$R{-}COCl + KSCN \xrightarrow[C_6H_6-H_2O]{n\text{-}Bu_4\overset{+}{N}\,Br^-} R{-}CO{-}NCS$$

A convenient, mild and stereoselective method to obtain acyl isothiocyanates involves treatment of an acid with isothiocyanatophosphonium salt **275**, prepared by oxidative addition of thiocyanogen to triphenylphosphine **274**.[445]

$$Ph_3P + (SCN)_2 \rightarrow Ph_3\overset{+}{P}{-}NCS \quad SCN^-$$

274 **275**

$$\downarrow \text{RCOOH}$$

$$R{-}CO{-}NCS + Ph_3PO \leftarrow R{-}CO{-}O{-}\overset{+}{P}Ph_3 \quad SCN^-$$

Alkyl(aryl)oxycarbonyl isothiocyanates **277** have also been prepared by condensing the corresponding acyl chlorides **276** with thiocyanates.[446-450]

$$\underset{\mathbf{276}}{\text{ClCOOR}} + \text{KSCN} \rightarrow \underset{\mathbf{277}}{\text{SCN—COOR}}$$

Typically, ethoxycarbonyl isothiocyanate **279a** has been prepared by treating ethyl chloroformate **278a** with KSCN in 65–73% yield.[451-454] Similarly, phenoxycarbonyl isothiocyanate **279b** may be obtained in 60–80% yield by reaction of phenyl chloroformate **278b** with potassium thiocyanate in ethyl acetate.[455]

$$\underset{\mathbf{278a},\ \text{R} = \text{Et}}{\text{ROOC—Cl}} + \text{KSCN} \rightarrow \underset{\mathbf{279a},\ \text{R} = \text{Et}}{\text{ROOC—NCS}}$$

$$\mathbf{b},\ \text{R} = \text{Ph} \qquad\qquad \mathbf{b},\ \text{R} = \text{Ph}$$

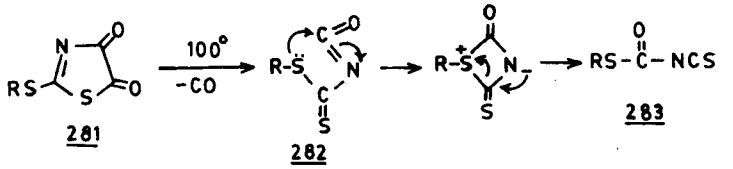
The method involving reaction of acyl chlorides with thiocyanates has also been used to prepare carbamoyl isothiocyanates **280a**,[456-460] (organylthio)carbonyl isothiocyanates **280b**[446] and halocarbonyl isothiocyanates **280c**.[461-463]

$$\text{R—CO—Cl} + \text{KSCN} \rightarrow \underset{\mathbf{280a},\ \text{R} = \text{NR}_2}{\text{R—CO—NCS}}$$

$$\mathbf{b},\ \text{R} = \text{SR}$$

$$\mathbf{c},\ \text{R} = \text{halogen}$$

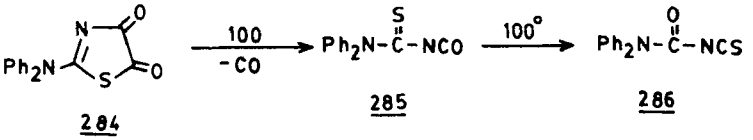
Method B: By Heterocyclic Ring Cleavage When 2-[alkyl(aryl)thio]thiazoline-4,5-diones **281** are heated, carbon monoxide is eliminated and [alkyl(aryl)thio]thiocarbonyl isocyanates **282** are formed. The latter rapidly rearrange to give [alkyl(aryl)-thio]-carbonyl isothiocyanates **283**[457,464,465] (Scheme 55).



281 **282** **283**

Scheme 55

Similarly, pyrolysis of 2-(*N*,*N*-diphenylamino)thiazoline-4,5-dione **284** gives rise to *N*,*N*-diphenylthiocarbamoyl isocyanate **285** which rearranges to *N*,*N*-diphenyl-carbamoyl isothiocyanate **286** when heated at 100 °C[457] (Scheme 56).



284 **285** **286**

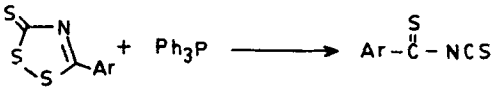
Scheme 56

3.4 Thioacyl Isothiocyanates

Like carbonyl isothiocyanates, the thiocarbonyl isothiocyanates **289** can also be prepared by treating the corresponding thioacyl chloride **287** with thiocyanates to yield thioacyl thiocyanates **288** which may be stored at −20 °C. At higher temperatures **288** isomerise to give **289**.[466,467]

$$\underset{\mathbf{287}}{Ar{-}CS{-}Cl} \rightarrow \underset{\mathbf{288}}{Ar{-}CS{-}SCN} \xrightarrow{\Delta} \underset{\mathbf{289}}{Ar{-}CS{-}NCS}$$

Treatment of 3-thioxo-3*H*-1,2,4-dithiazoles **290** with triphenylphosphine causes elimination of sulfur resulting in the formation of the thioacyl isothiocyanates **289**[467](Scheme 57).



Scheme 57

A number of thiocarbamoyl isothiocyanates **291a**,[468-470] [alkyl(aryl)thio]-thiocarbonyl isothiocyanates **291b**[471] and halothiocarbonyl isothiocyanates **291c**[472] have also been synthesized by treating the corresponding thioacyl chlorides with thiocyanates.

$$R{-}CS{-}Cl + KSCN \rightarrow R{-}CS{-}NCS$$

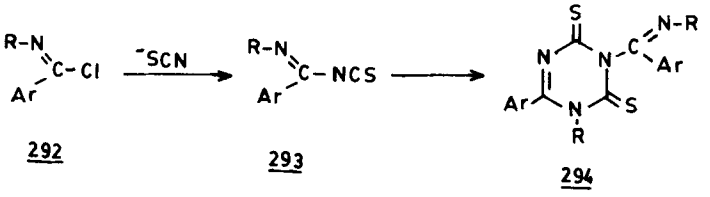
291a, R = NR_2

b, R = SR

c, R = halogen

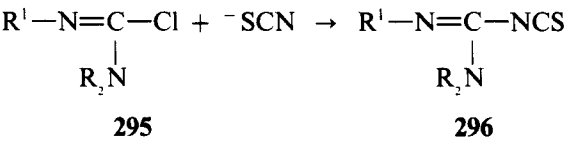
3.5 1-Iminoalkyl Isothiocyanates

Reaction of imidocarbonyl chlorides **292** with thiocyanates affords 1-iminoalkyl isothiocyanates **293** which are highly prone to dimerisation to **294**[473-479] (Scheme 58).



Scheme 58

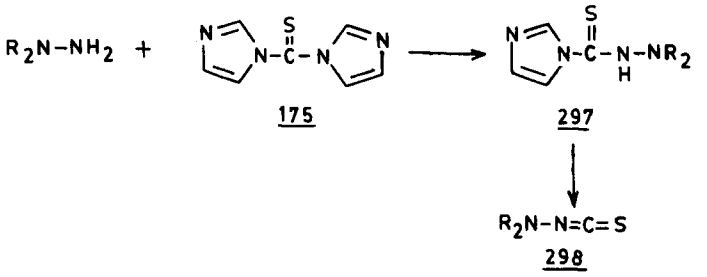
The closely related formamidinoyl isothiocyanates **296** may also be prepared by treating the corresponding chlorides **295** with thiocyanate.[480]



295 **296**

3.6 Amino Isothiocyanates

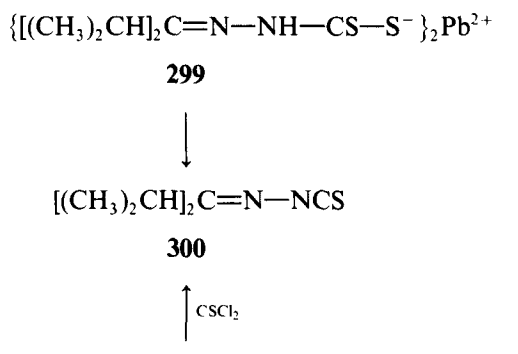
The amino isothiocyanates **298** are usually unstable compounds, but can be conveniently prepared by thermal decomposition of 1-(hydrazinothiocarbonyl)imidazoles **297**, obtained by treating *N,N*-disubstituted hydrazines with *N,N'*-thiocarbonyldiimidazole **175**[481-483] (Scheme 59).



175 **297** **298**

Scheme 59

Thermal decomposition of the lead salt of dithiocarbono-2-(1-isopropyl-2-methylpropylidene)hydrazine **299** gives the unstable (1-isopropyl-2-methylpropylidenamino) isothiocyanate **300**.[484] The latter is also prepared by the action of thiophosgene on the triethylammonium salt of **299**.[485]



299 **300** **299**

Reaction of trimethylammonioacetohydrazide chloride (**301**, Girard reagent T) with thiophosgene in the presence of hydrochloric acid below 25 °C affords the amino isothiocyanate **302**.[486]

$$(CH_3)_3\overset{+}{N}—CH_2—CO—NH—NH_2\ \ Cl^- \xrightarrow[HCl]{CSCl_2}$$

301

$$(CH_3)_3\overset{+}{N}—CH_2—CO—NH—N=C=S\ \ Cl^-$$

302

3.7 Sulfonyl Isothiocyanates

A few sulfonyl isothiocyanates have been prepared by reaction of sulfonyl chlorides with thiocyanate. Thus, treatment of benzenesulfonyl chloride **303** with thiocyanate in refluxing benzene yields benzenesulfonyl isothiocyanate **304**.[487] Similarly, ethoxysulfonyl chloride **305** reacts with lead(II) thiocyanate in benzene to afford ethoxysulfonyl isothiocyanate **306**.[488]

$$Ph—SO_2—Cl + {}^-SCN \xrightarrow[\Delta]{\text{benzene}} Ph—SO_2—NCS$$

303 **304** (57%)

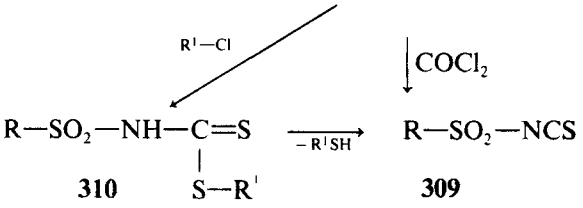
$$EtO—SO_2—Cl + Pb(SCN)_2 \xrightarrow[\text{benzene}]{\Delta} EtO—SO_2—NCS$$

305 **306** (40%)

Sulfonamines **307** also serve as useful substrates for the preparation of sulfonyl isothiocyanates. Thus, reaction of **307** with carbon disulfide gives the sulfonyliminodithiocarbamates **308** which may be treated with phosgene, $SOCl_2$, $POCl_3$ or alkyl chloroformates to yield sulfonyl isothiocyanates **309**.[489-491] Alternatively, **308** can also be alkylated to the *S*-alkyl derivative **310** which on thermolysis forms alkanethiol and **309**.[492-495]

$$R—SO_2—NH_2 \xrightarrow[KOH]{CS_2} R—SO_2—N=C(SK)—SK$$

307 **308**



310 **309**

Benzenesulfonyl isothiocyanate **304** may also be prepared by treating benzenesulfonamide **311** with thiophosgene at temperatures below 0 °C.[496a]

$$Ph—SO_2NH_2 + CSCl_2 \rightarrow Ph—SO_2—NCS$$

311 **304**

3.8 Phosphoryl Isothiocyanates

In general, phosphoryl isothiocyanates are prepared by treatment of the corresponding phosphoryl chlorides with thiocyanates.[496b] The methods to prepare a variety of isothiocyanates of this class such as disubstituted isothiocyanatophosphine oxides [$R_2PO(NCS)$], diisothiocyanatophosphine oxides [$RPO(NCS)_2$], triisothiocyanatophosphine oxides [$OP(NCS)_3$], isothiocyanatophosphine sulfides [$R_2PS(NCS)$], diisothiocyanatophosphine sulfides [$RPS(NCS)_2$], triisothiocyanatophosphine sulfide [$SP(NCS)_3$], isothiocyanatophosphines (R_2P-NCS), diisothiocyanatophosphines [$RP(NCS)_2$] and triisothiocyanatophosphine [$P(NCS)_3$] have been reviewed.[7,10,14]

$$R_2POCl + KSCN \rightarrow R_2PO(NCS)$$

A convenient and stereoselective method to prepare isothiocyanatophosphine oxides and isothiocyanatothiophosphine sulfides **313a, b** involves reaction of the isothiocyanatophosphonium salts **275** with the hydroxy compounds **312a, b**.[445]

$$\underset{\textbf{312a, X = O}\\ \textbf{b, X = S}}{R_2PX(OH)} + \underset{\textbf{275}}{Ph_3\overset{+}{P}-NCS} \xrightarrow[-H^+]{} R_2PX(\overset{+}{O}PPh_3)SCN^- \rightarrow \underset{\textbf{313a, X = O}\\ \textbf{b, X = S}}{Ph_3PO + R_2PX(NCS)}$$

Reaction of triethoxyphosphine **314** with powderised KSCN in acetonitrile in the presence of trimethylamine hydrochloride at 35–40 °C affords a 60% yield of diethyl isothiocyanatophosphonate **315**.[497]

$$\underset{\textbf{314}}{(EtO)_3P} + KSCN \xrightarrow[CH_3CN]{(CH_3)_3N\cdot HCl} \underset{\textbf{315}\ (60\%)}{(EtO)_2PO(NCS)}$$

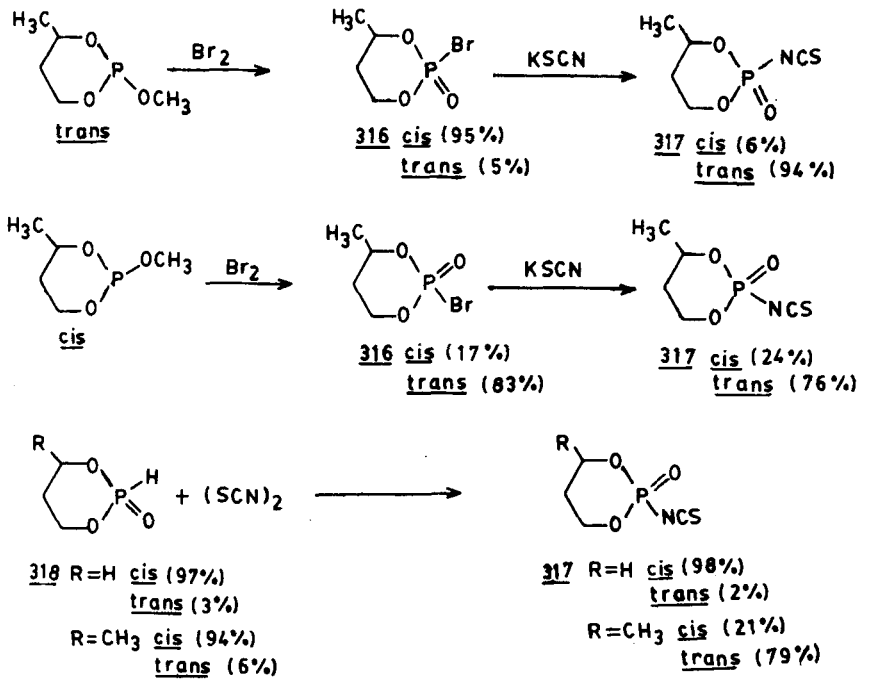
Lopusinski and coworkers[498] have prepared *cis*- and *trans*-2-isothiocyanato-2-oxo-4-methyl-1,3,2-dioxaphosphorinans **317** by treating 2-bromo-2-oxo-4-methyl-1,3,2-dioxaphosphorinans **316** with KSCN. Reaction of thiocyanogen with the 1,3,2-dioxaphosphorinans **318** also gives *cis*- and *trans*-**317** (Scheme 60).

Reaction of diethyl selenophosphites **319** with thiocyanogen in benzene affords a 55% yield of *O,O*-diethyl (isothiocyanato)selenophosphate **320**.[499]

$$\underset{\textbf{319}}{(EtO)_2PH{=}Se} + (SCN)_2 \rightarrow \underset{\textbf{320}}{(EtO)_2P{=}Se(NCS)}$$

Chlorophosphates **321** may be allowed to react with trimethylsilyl isocyanide to give a variety of isothiocyanatophosphine oxides and sulfides of the general formula **322**.[500]

$$\underset{\textbf{321, R = Me, EtO, Ph}\\ \text{n = 1–3}\\ \text{X = O, S}}{R_{3-n}{-}P(X)Cl_n} + Me_3SiNC \rightarrow \underset{\textbf{322}}{R_{3-n}{-}PX(NCS)_n}$$



Scheme 60

Sulfuration of the dichloromethyleneimine **323** with bis(trimethylsilyl) sulfide **324** gives 2-(difluorophosphoryl)-vinyl isothiocyanate **325**.[501]

$$F_2P(O)—CH=CH—N=CCl_2 + [(CH_3)_3Si]_2S \rightarrow$$

323 **324**

$$F_2P(O)—CH=CH—N=C=S$$

325 (82%)

3.9 Silyl Isothiocyanates

In general, silyl isothiocyanates are prepared by treating a halosilane with AgSCN or $Hg(SCN)_2$ in benzene or hexane, or NH_4SCN or KSCN dissolved in acetonitrile.[502-510] For example, trimethylsilyl chloride **326** reacts with silver thiocyanate in refluxing benzene to give a 71% yield of trimethylsilyl isothiocyanate **327**.[503,504] Similarly, treatment of tetrachlorosilane **328** with ammonium thiocyanate in a carbon tetrachloride-acetonitrile mixture leads to the formation of tetrakis-(isothiocyanato)-silane **329**.[505]

$$(CH_3)_3SiCl + AgSCN \rightarrow (CH_3)_3Si—NCS$$

326 **327** (71%)

$$SiCl_4 + NH_4SCN \rightarrow Si(NCS)_4$$

328 **329** (87%)

Besides halide ions other groups such as a sulphate or thiolate, or atoms like nitrogen and hydrogen bound to silicon, may also be replaced by thiocyanate to give the corresponding silyl isothiocyanates.[511-514] Typically, reaction of cyclohexylsilane **330** with silver thiocyanate in carbon tetrachloride gives a 41% yield of cyclohexylsilyl isothiocyanate **331** along with small amounts of cyclohexyltriisothiocyanatosilane **332**. The latter may be obtained in 91% yield by heating one mole of **330** with three moles of silver thiocyanate.[514]

$$\underset{\textbf{330}}{\textit{cyclo}\text{-}C_6H_{11}SiH_3} + AgSCN \rightarrow$$

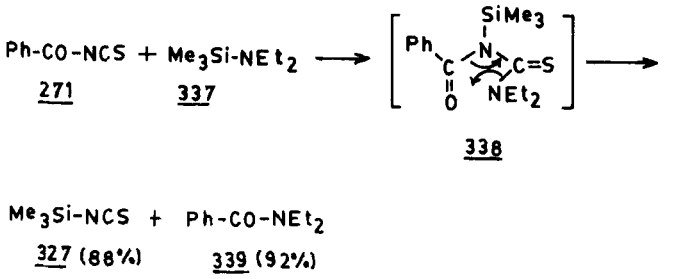
$$\underset{\textbf{331}}{\textit{cyclo}\text{-}C_6H_{11}SiH_2NCS} + \underset{\textbf{332}}{\textit{cyclo}\text{-}C_6H_{11}Si(NCS)_3}$$

Sulfuration of silyl isocyanates **333a,b** has been used to prepare trimethylsilyl and triphenylsilyl isothiocyanate **334a,b**.[515,516] Similarly, dimethyl-phenylsilyl isocyanate **335**, when heated with sulfur, gives a 57% yield of dimethyl-phenylsilyl isothiocyanate **336** which can also be obtained in 60% yield by treating **335** with silver thiocyanate.[517]

$$\underset{\textbf{333a, R = CH}_3}{\underset{\textbf{b, R = Ph}}{R_3Si{-}NC}} + S_8 \rightarrow \underset{\textbf{334a, R = CH}_3}{\underset{\textbf{b, R = Ph}}{R_3Si{-}NCS}}$$

$$\underset{\textbf{335}}{(CH_3)_2C_6H_5Si{-}NC} + S_8 \rightarrow \underset{\textbf{336}}{(CH_3)_2C_6H_5Si{-}NCS}$$

Thermal decomposition of the 1:1 adduct **338**, obtained from benzoyl isothiocyanate **271** and (trimethylsilyl)diethylamine **337**, gives trimethylsilyl isothiocyanate **327** and *N,N*-diethylbenzamide **339**[518] (Scheme 61).



Scheme 61

The synthesis of trimethylsilyl isothiocyanate **327** may also be achieved by treating bis(trimethylsilyl) sulphate **340** with potassium thiocyanate[519] in *N*-methylpyrrolidine.

$$\underset{\textbf{340}}{(Me_3SiO)_2SO_2} + KSCN \rightarrow \underset{\textbf{327 (94\%)}}{Me_3Si{-}NCS}$$

Some isothiocyanates with more remote trimethylsilyl groups have also been prepared. For example, reaction of the dithiocarbamic esters **341** with trimethylsilyl chloride in the presence of triethylamine gives ω-isothiocyanatocarboxylic acid trimethylsilyl esters **342**.[520]

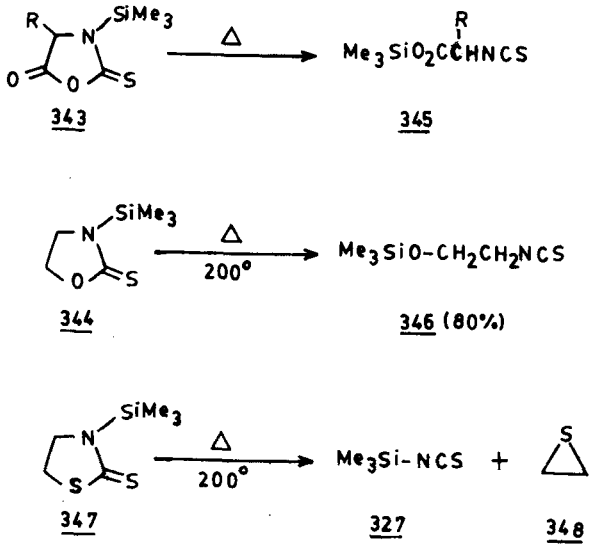
$$HOOC{-}(CH_2)_n{-}NH{-}CS{-}SEt + (CH_3)_3Si{-}Cl \rightarrow$$

341

$$(CH_3)_3Si{-}OOC{-}(CH_2)_n{-}NCS$$

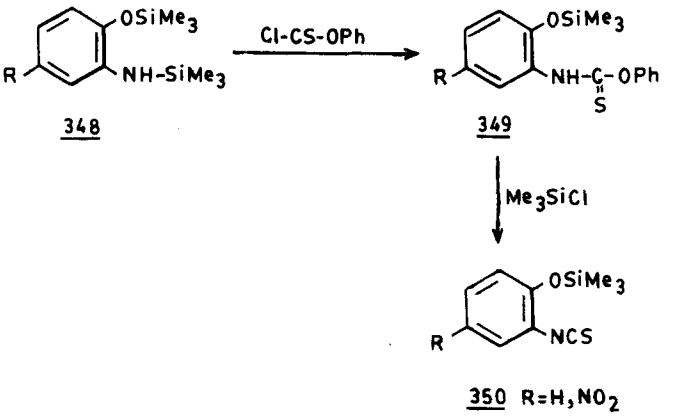
342, n = 1–3

N-Silylated cyclic derivatives also serve as convenient precursors for silylated isothiocyanates.[520–522] Thus, *N*-silylated 1,3-oxazolidine-2-thione-5-ones **343** and the 1,3-oxazolidine-2-thione **344** may be cleaved to form the silylated isothocyanates **345** and **346**, respectively. However, on thermolysis of *N*-(trimethylsilyl)thiazolidine-2-thione **347**, instead of the expected 2-(trimethylsilylthio)ethyl isothiocyanate, a rapidly polymerising mixture of trimethylsilyl isothiocyanate **327** and ethylene sulfide **348** is obtained (Scheme 62).



Scheme 62

Reaction of *N*-[2-(trimethylsiloxy)phenyl]thiocarbamic acid phenyl ester **349**, obtained by condensing *N*,*O*-bis(trimethylsilyl)-2-aminophenols **348** with *O*-phenyl chlorothioformate in boiling dry toluene, with trimethylsilyl chloride affords the 2-trimethylsiloxyphenyl isothiocyanates **350**[520] (Scheme 63).

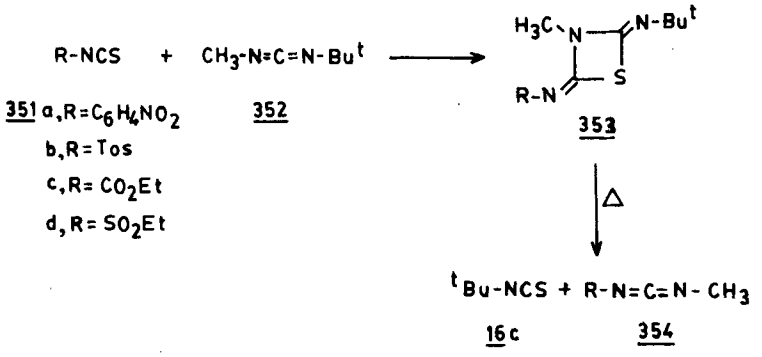


Scheme 63

4. SYNTHESIS OF FOUR-MEMBERED HETEROCYCLES

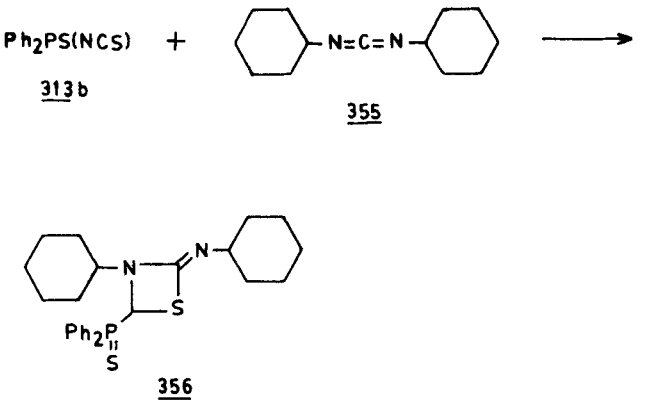
Isothiocyanates can enter into [2 + 2] cycloadditions with their C=N or C=S bonds when treated with compounds containing C=C moieties. The products formed are usually thietanes or thiazetidines.[523]

Reactive isothiocyanates such as 4-nitrophenyl, tosyl, and ethoxycarbonyl isothiocyanate or sulfonyl isothiocyanates **351a–d** react with carbodiimides like methyl-*t*-butylcarbodiimide **352** to form [2 + 2] cycloadducts, **353**[524,525] which have been characterised as 1,3-diazetidines.[526] These heterocycles gives negative Feigl tests for C=S groups (a drop of reagent, prepared by dissolving 3 g sodium azide in 100 ml 0.1 N iodine in water, is mixed with a drop of test compound in water or an organic solvent. Brisk evolution of nitrogen bubbles shows the presence of a C=S or C–SH group in the compound; see "Qualitative Analysis by Sport Tests" by F. Feigl, Elsevier Publishing Co., Amsterdam, 1947), and decomposes thermally to give *t*-butyl isothiocyanate **16c** and the carbodiimide **354**[525,526] (Scheme 64).



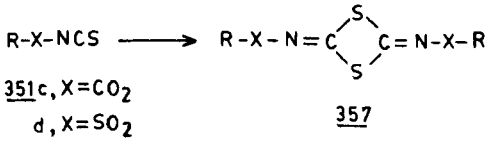
Scheme 64

Diphenylthiophosphinyl isothiocyanate **313b**, R = Ph also reacts with dicyclohexylcarbodiimide **355** to give the [2 + 2] cycloadduct **356** in quantitative yield[526] (Scheme 65).



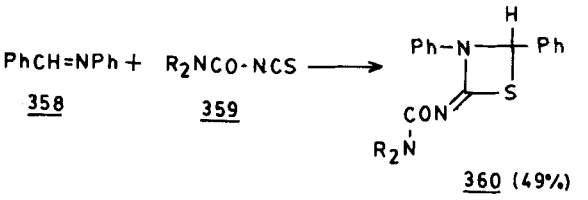
Scheme 65

Alkoxycarbonyl and sulfonyl isothiocyanates **351c,d** smoothly dimerise through their C=S bonds to yield 2,4-bis(carbonyl/sulfonylimino)-1,3-dithietanes **357**[527] (Scheme 66).



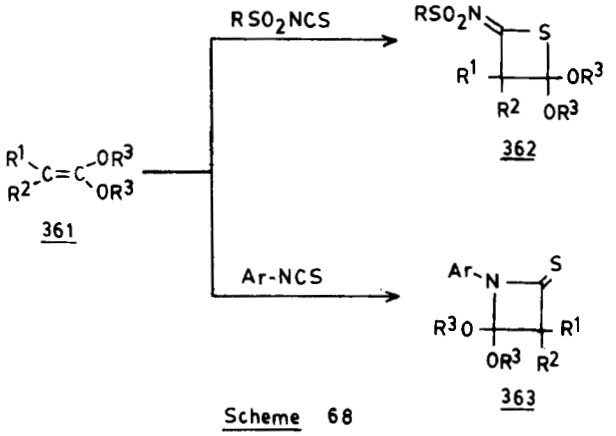
Scheme 66

The Schiff's base **358** reacts with carbamoyl isothiocyanates **359** to give the cycloadducts **360** in 49% yield[528] (Scheme 67).



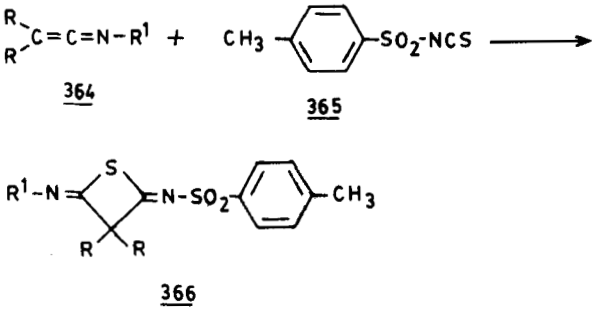
Scheme 67

The ketene acetals **361** may be made to undergo [2 + 2] cycloadditions with sulfonyl isothiocyanates and aryl isothiocyanates to afford 2-iminothietanes **362** and azetidine-2-thiones **363**, respectively[529] (Scheme 68).



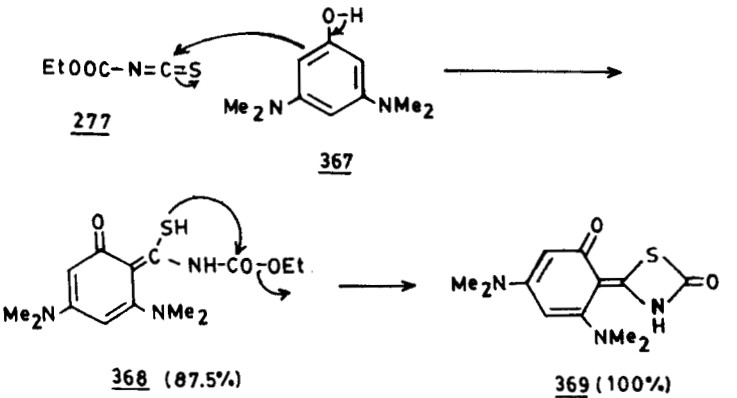
Scheme 68

The ketimines (**364**) also react with 4-methylphenylsulfonyl isothiocyanate **365** to give [2 + 2] cycloaddition products, the (diimino)thietanes **366**[530] (Scheme 69).



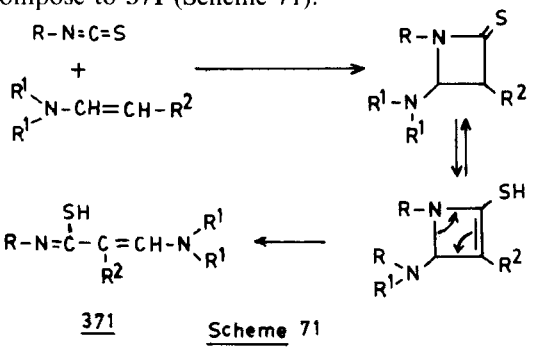
Scheme 69

3,5-Bis(N_1 N-dimethylamino)phenol **367** may be allowed to react with ethoxycarbonyl isothiocyanate **277**, (R = Et) to give a high yield of **368** which, when heated at its melting point, undergoes thermal ring closure to form the 1,3-thiazetidin-2-one **369**[531] (Scheme 70).



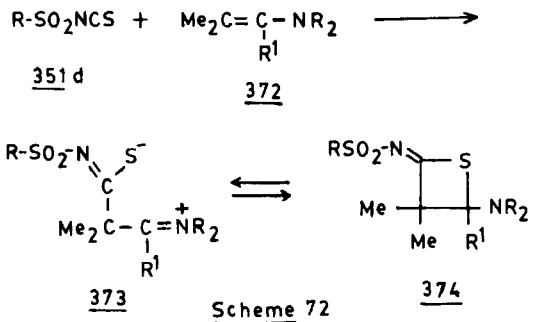
Scheme 70

Cases of [2 + 2] cycloadditions involving the C=N bond of isothiocyanates and other π-electron systems have also been studied.[532-534] Azetidines **370** are usually formed which, being unstable, decompose to **371** (Scheme 71).



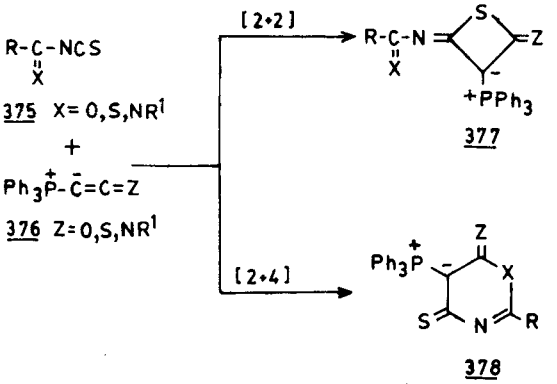
371 Scheme 71

However, sulfonyl isothiocyanates **351d** react with β,β-disubstituted enamines **372** to form crystalline 1:1 adducts **373** which are in equilibrium with the iminothietanes **374** in non-polar solvents[14,535] (Scheme 72).



351d **372** **373** Scheme 72 **374**

Acyl, thioacyl and imidoyl isothiocyanates **375** react with phosphacumulenylidenes **376** to give two products, namely the thietanes **377** and the six-membered nitrogen heterocycles **378** as a result of [2 + 2] and [2 + 4] cycloadditions, respectively[536] (Scheme 73).



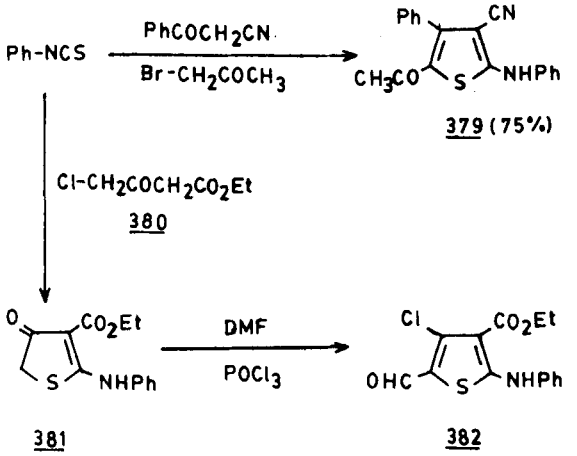
375 X = O, S, NR^1 + **376** Z = O, S, NR^1 **377** **378**

Scheme 73

5. SYNTHESIS OF FIVE-MEMBERED HETEROCYCLES

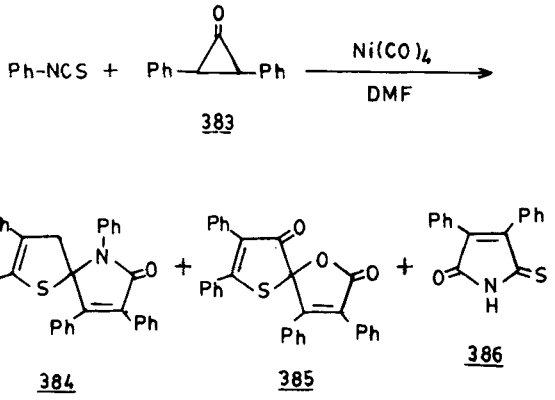
5.1 Thiophenes

Phenyl isothiocyanate reacts with a mixture of benzoylacetonitrile and bromoacetone in the presence of NaH in DMF to form 2-acetyl-5-phenylamino-4-cyano-3-phenylthiophene **379**.[537] Phenyl isothiocyanate may also be treated with ethyl chloroacetoacetate **380** to give the thiophenone **381** which when subjected to Vilsmeier-Haack conditions affords thiophene **382**[538] (Scheme 74).



Scheme 74

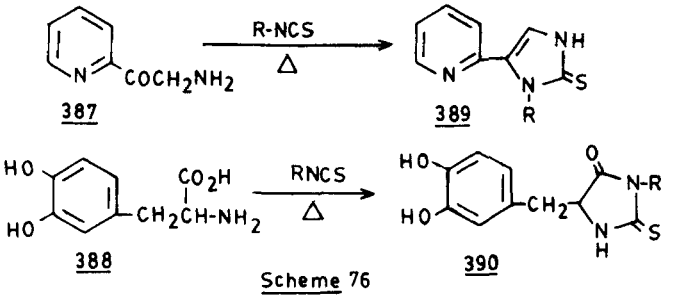
Treatment of phenyl isothiocyanate or benzoyl isothiocyanate with 2,3-diphenylcyclopropenone **383** in the presence of nickel tetracarbonyl in DMF at 65–70 °C affords a mixture of the pyrrolidin-2-one-5-spiro-5′-thiolen-4-one **384** (major product) and thiolen-2-one-5-spiro-5′-thiolen-4-one **385** (minor product). Sometimes traces of the pyrrolidonethione **386** are also formed in the above reaction[539] (Scheme 75).



Scheme 75

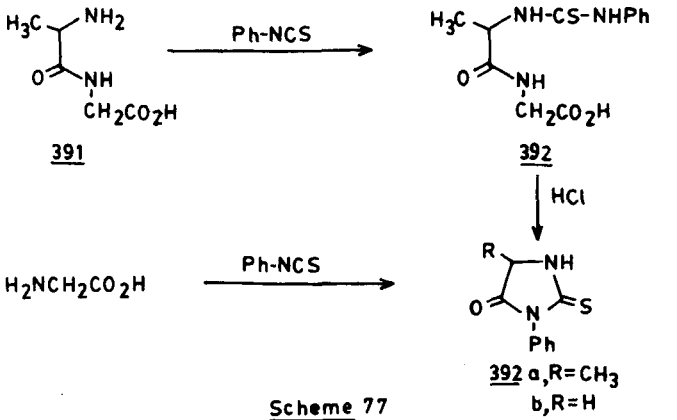
5.2 Imidazoles

Cyclisation of 2-pyridyl aminomethyl ketone **387** and of L-dopa **388** with R-NCS gives appreciable yields of 3-(2-pyridyl)imidazole-2-thione **389**[540] and the 2-thiohydantoins **390**,[541] respectively (Scheme 76).



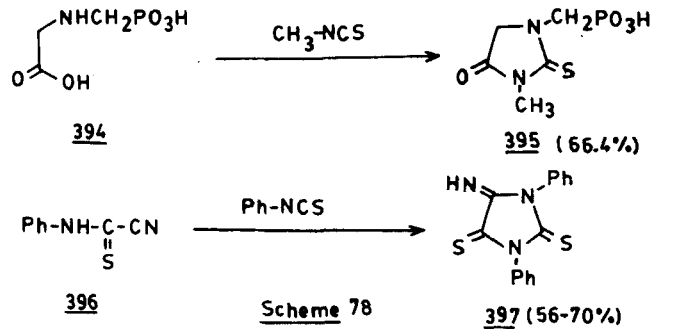
Scheme 76

Condensation of DL-alanylglycine **391** with phenyl isothiocyanate in a pyridine-water (1:1) mixture at pH 9 gives the thiourea **392** which cyclises in the presence of HCl to form 5-methyl-3-phenyl-2-thiohydantoin **393a**.[542,543a] Similarly, glycine may be treated with phenyl isothiocyanate to yield **393b**[543b] (Scheme 77).



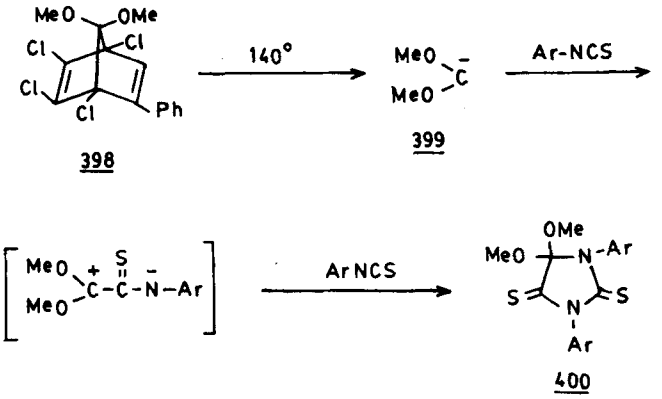
Scheme 77

Similarly, reaction of the acid **394** with methyl isothiocyanate gives the imidazolidinedionyl phosphonic acid **395**[544] while 5-imino-1,3-diphenyl-4-thioxo-2-imidazolidinethione **397** has been obtained by cyclising **396** with phenyl isothiocyanate[545] (Scheme 78).



Scheme 78

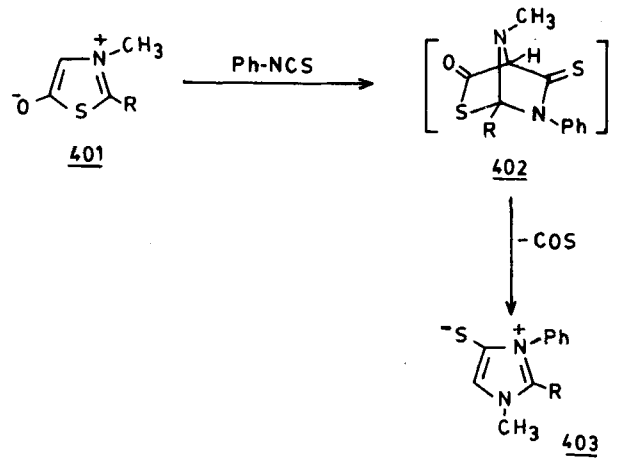
Dimethoxycarbene **399**, obtained by thermal decomposition of 1,2,3,4-tetrachloro-7,7-dimethoxy-5-phenylbicyclo[2.2.1]hepta-2,5-diene **398**, reacts with excess aryl isothiocyanates to yield the corresponding 5,5-dimethoxydithiohydantoins **400**[546] (Scheme 79).



398 399 400

Scheme 79

The 1,3-dipolar anhydro-2-aryl-5-hydroxy-3-methylthiazolium hydroxide **401** smoothly reacts with phenyl isothiocyanate in hot benzene to give the [3 + 2] cycloadduct **402** which decomposes to form anhydro-2-aryl-4-mercapto-1-methyl-3-phenylimidazolium hydroxide **403**[547] (Scheme 80).

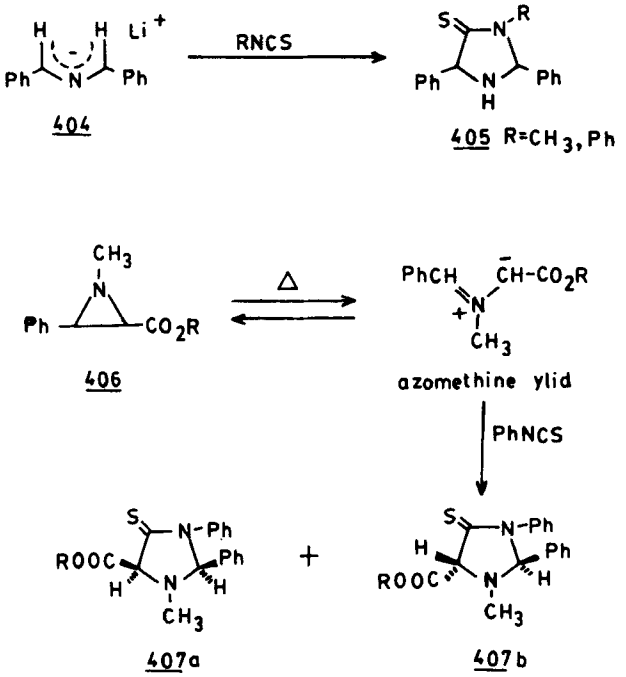


401 402 403

Scheme 80

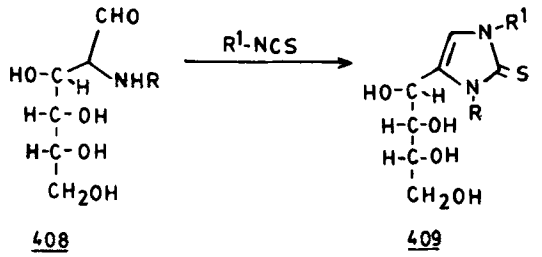
The lithium complex **404** may be treated with phenyl isothiocyanate or methyl isothiocyanate to furnish 46–59% yields of imidazolidines **405**.[548] The aryl isothiocyana-

tes cause an insertion reaction when they react with 2-alkoxycarbonyl aziridines **406** leading to the formation of the epimeric thioimidazolidones **407a,b**[549] (Scheme 81).



Scheme 81

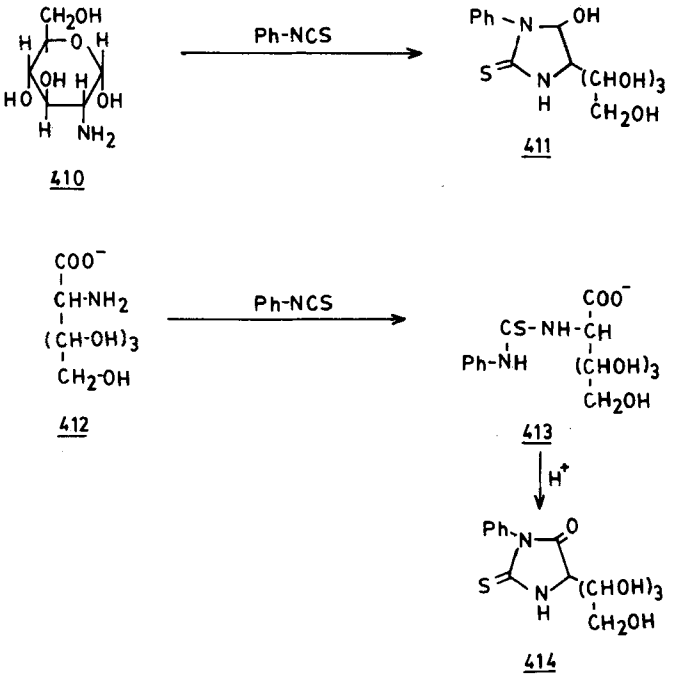
Some *C*-nucleosides **409** have been prepared by treating 1-alkylamino-1-deoxy-D-*arabino*-hexuloses **408** with methyl or phenyl isothiocyanate in methanol or ethanol[550] (Scheme 82).



Scheme 82

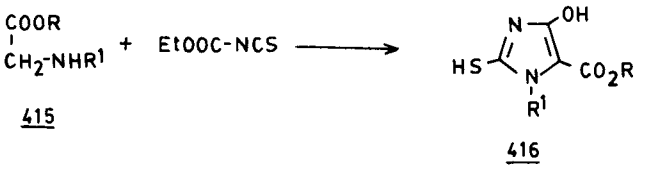
Glucosamine **410** reacts with phenyl isothiocyanate to give 4-hydroxy-3-phenyl-5-tetrahydroxybutylimidazolidenethione **411** resulting from the spontaneous cyclisation of the addition product. However, the addition product **413**, obtained by treating

2-aminogluconic acid **412** with phenyl isothiocyanate requires an acidic medium to give the 3,5-disubstituted thiohydantoin **414**[551] (Scheme 83).



Scheme 83

Reaction of *N*-alkylaminoacetates **415** with ethoxycarbonyl isothiocyanate leads to the formation of 1,5-disubstituted 4-hydroxy-2-mercaptoimidazoles **416**[552] (Scheme 84).

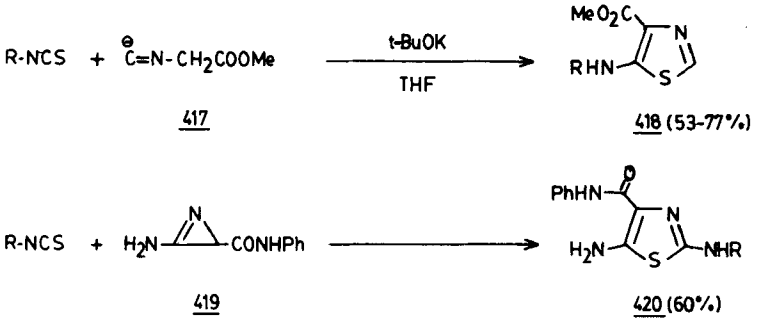


Scheme 84

5.3 Thiazoles

A convenient synthesis of the methyl 5-amino-1,3-thiazole-4-carboxylates **418** involves reaction of alkyl or aryl isothiocyanates with methyl α-isocyanoacetate **417** in THF in the presence of potassium *t*-butoxide.[553] 2-Amino-3-(phenylcarbamoyl)azirine **419** also

reacts with alkyl/aryl isothiocyanates to afford the 5-amino-2-organylamino-4-(phenylcarbamoyl)thiazoles **420**[554] (Scheme 85).

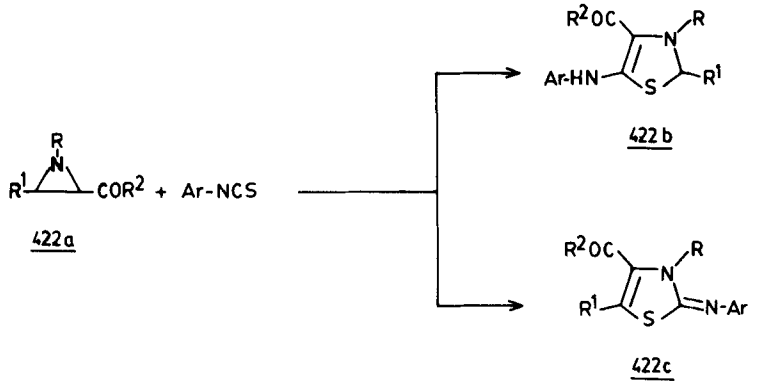


Scheme 85

Treatment of the 2,3-disubstituted azirines **421** with benzoyl isothiocyanate leads to a [2 + 2] cycloaddition to form 2-benzamido-4,5-disubstituted-1,3-thiazoles **422**[555a] (Scheme 86).

Scheme 86

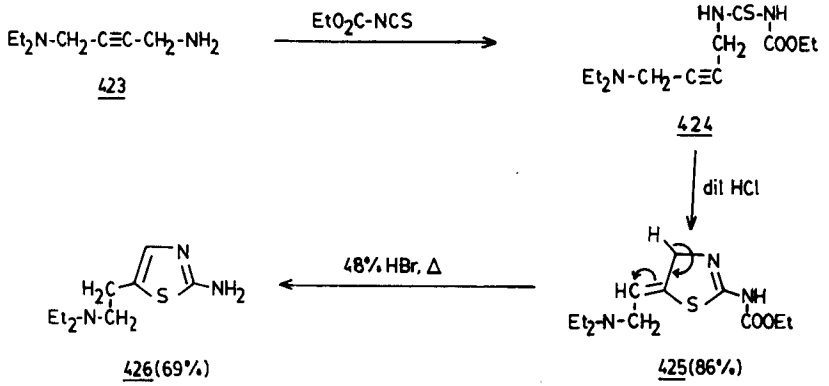
It is also possible to isolate two isomeric thiazolines **422b,c** when the aziridine **422a** is allowed to react with aryl isothiocyanates[555b,c] (Scheme 87).



Scheme 87

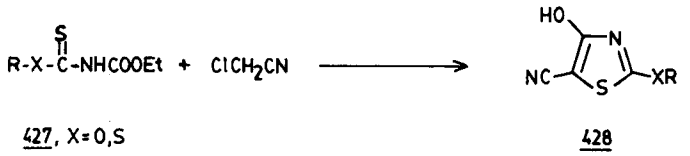
Various alkenylamines are known to react with ethoxycarbonyl isothiocyanate to form thiazolidines.[556-559] Thus, condensation of *N,N*-diethyl-2-butyne-1,4-diamine **423**

with ethoxycarbonyl isothiocyanate gives an adduct **424** which undergoes facile cyclisation in the presence of acids to yield 2-amino-5-[2-(*N*,*N*-diethylamino)ethyl]thiazole **426**[559] (Scheme 88).



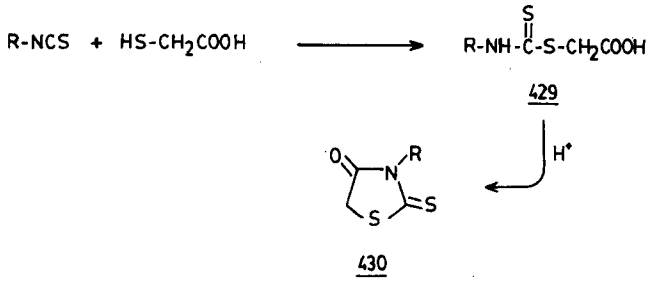
Scheme 88

Another convenient method to obtain 2,4,5-trisubstituted thiazoles **428** employs the reaction of the adducts **427**, obtained from ethoxycarbonyl isothiocyanate **279a** and alcohols or thiols, with chloroacetonitrile[560] (Scheme 89).



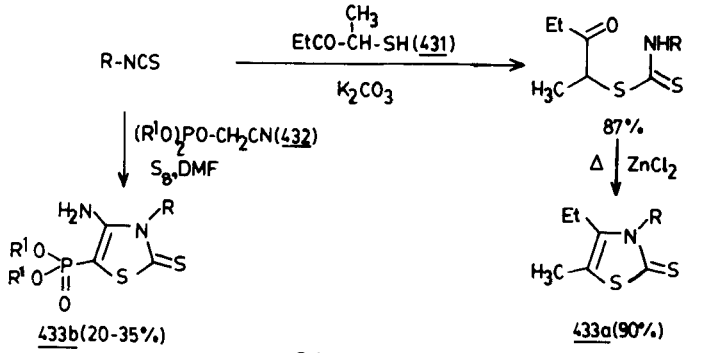
Scheme 89

The adducts **429**, obtained by condensing an isothiocyanate with a mercapto acid, also cyclise in acidic media to form 3-substituted rhodanines **430**[561,562] (Scheme 90).



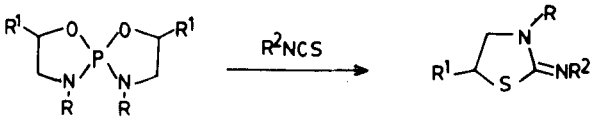
Scheme 90

The synthesis of various 3,4,5-trisubstituted thiazoline-2-thiones **433a,b** may be carried out by treating alkyl/aryl isothiocyanates either with a mercapto ketone **431**[563] or alkyl cyanides **432** in the presence of sulfur[564] (Scheme 91).



Scheme 91

A number of 2-iminothiazolidines **435** have been prepared by treating alkyl/aryl isothiocyanates with phosphorus-containing derivatives of ethanolamine such as the spiroxaazaphospholidines **434**[565,566] (Scheme 92).

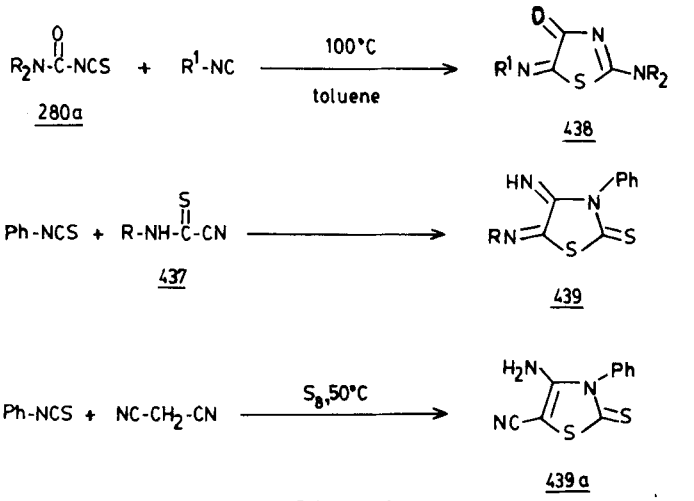


434

Scheme 92

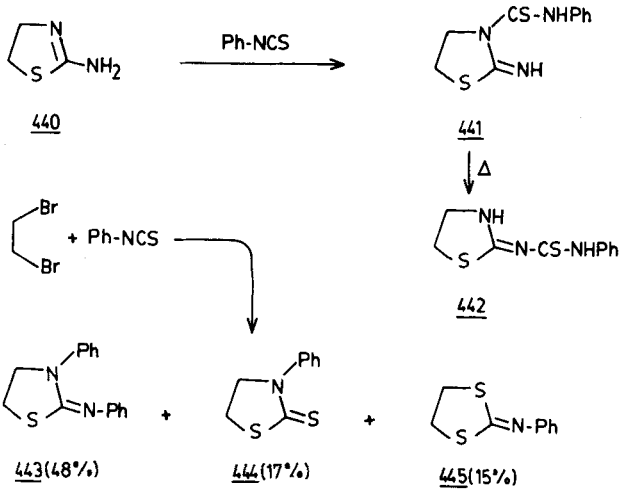
435

5-Iminothiazolidines **438**, **439** can also be prepared by treating the isocyanides **436**[528] or the cyanothioformamides **437**[567a] with carbamoyl isothiocyanates **280a** and phenyl isothiocyanate, respectively. Phenyl isothiocyanate also reacts with malononitrile in the presence of sulfur to form the 4-aminothiazoline **439a**[567b] (Scheme 93).



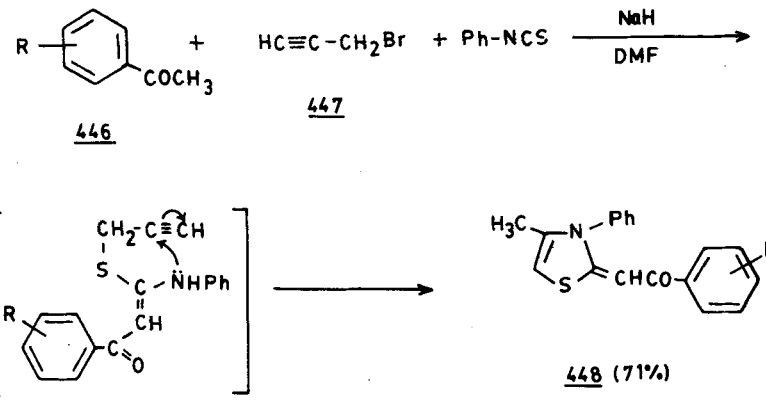
Scheme 93

Reaction of 2-aminothiazoline **440** with phenyl isothiocyanate gives the corresponding thiourea **441** which rearranges thermally to afford 2-(*N*-phenylthiocarbamoyl)iminothiazoline **442**.[568] However, phenyl isothiocyanate reacts with 1,2-dibromoethane to give a mixture of 3-phenyl-2-phenylimino-1,3-thiazolidine **443**, 3-phenyl-1,3-thiazolidine-2-thione **444** and 2-phenylimino-1,3-dithiolane **445**[569] (Scheme 94).



Scheme 94

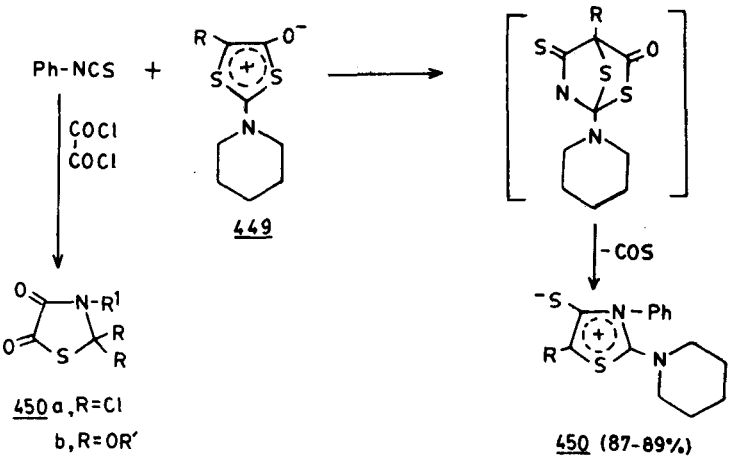
A facile and one-step synthesis of 3-alkyl/aryl-4-methyl-2-(substituted methylene)-2,3-dihydro-1,3-thiazoles **448** has been reported by reaction of acetophenones **446** with phenyl isothiocyanate and propargyl bromide **447** in the presence of sodium hydride[570] (Scheme 95).



Scheme 95

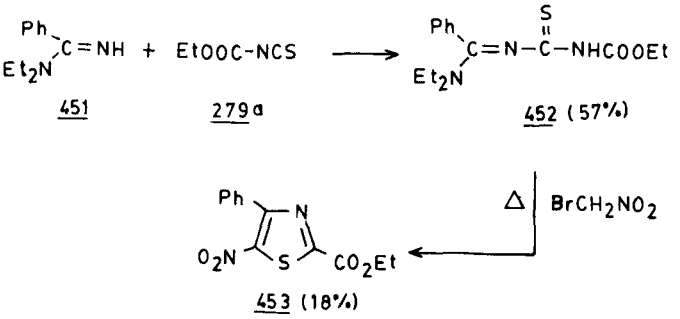
The 1,3-dithiolium-4-olates **449** also react with phenyl isothiocyanate to form the mesoionic 1,3-thiazolium-4-thiolates **450** in excellent yields.[571a] The synthesis of 3-alkyl/

aryl-2,2-dichlorothiazolidine-4,5-diones **450a** has been achieved by treating alkyl/aryl isothiocyanates with oxalyl chloride which may be easily converted into **450b** by the action of an alcohol[571b] (Scheme 96).



Scheme 96

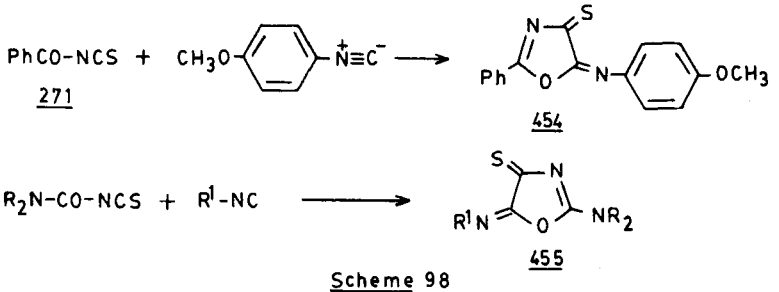
Treatment of *N,N*-diethylbenzamidine **451** with ethoxycarbonyl isothiocyanate **279a** gives a 1:1 adduct **452** which may be cyclised with bromonitromethane to give the substituted thiazole **453**[572] (Scheme 97).



Scheme 97

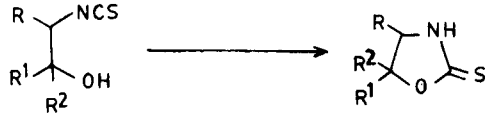
5.4 Oxazoles

Activated isothiocyanates such as benzoyl isothiocyanate **271** or carbamoyl isothiocyanates **280a** undergo [4 + 1] cycloaddition with isonitriles to form 2-substituted 5-iminooxazoline-4-thiones (**454** and **455**), respectively[528] (Scheme 98).



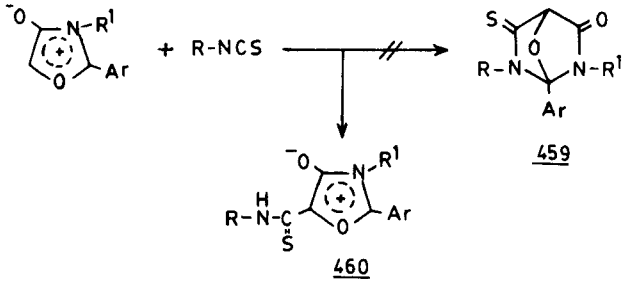
Scheme 98

Naturally occurring isothiocyanates **456** with a β-hydroxyl group undergo spontaneous ring closure to form the oxazolidine-2-thiones **457**[14] (Scheme 99).



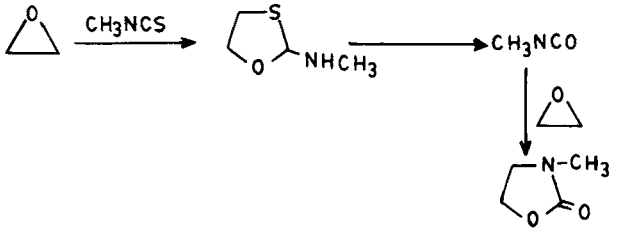
Scheme 99

It has been reported earlier that mesoionic compounds **458** react with phenyl isothiocyanate or benzoyl isothiocyanate to yield a 1:1 adduct **459**.[573,574] However, later it was established that the reaction product of **458** and R-NCS is not **459**, but the thioacylated mesoionic derivative **460**[575] (Scheme 100).



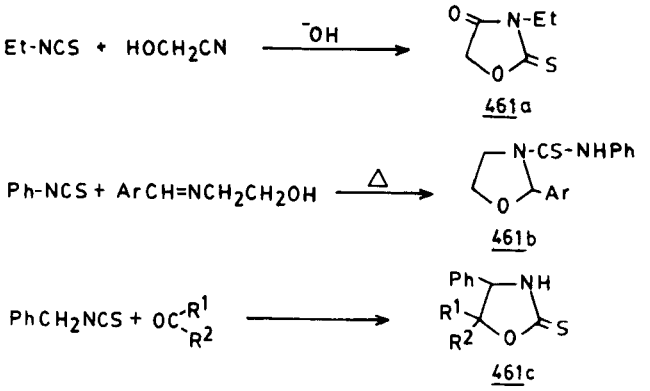
Scheme 100

Etlis and coworkers[576] have shown that the main cycloadduct formed by reaction of methyl isothiocyanate with ethylene oxide is the oxazolidone **461** which may arise probably by a mechanism shown in Scheme 101.



Scheme 101

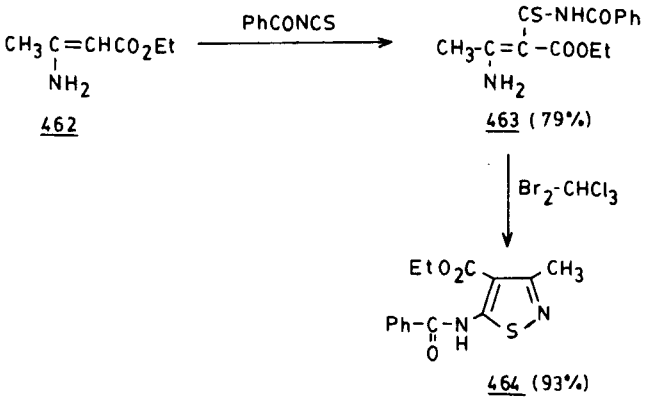
Various oxazolidines **461a–c** have been prepared by treating an alkyl/aryl isothiocyanate with an alcohol[577a,b] or a ketone[577c] (Scheme 101a).



Scheme 101a

5.5 Isothiazoles

Reaction of an enamine such as ethyl β-aminocrotonate **462** with an alkyl, aryl, acyl or sulfonyl isothiocyanate gives an α-acyl-β-aminothiocrotonamide **463** which may be cyclised in the presence of bromine in cold chloroform to form a 5-substituted 4-carbethoxy-3-methylisothiazole **464**[578–581] (Scheme 102).

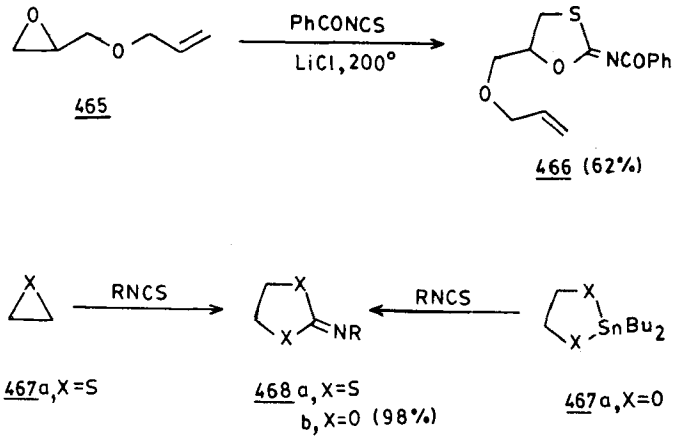


Scheme 102

5.6 Oxathiolanes, dithiolanes and dioxolanes

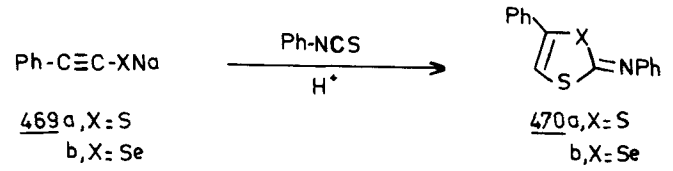
Benzoyl isothiocyanate **271** reacts at its C=S bond with 1-allyloxy-2,3-epoxypropane **465** in the presence of lithium chloride to give 2-benzoylimino-5-allyloxymethyl-1,3-oxathiolane **466**.[582] Alkyl isothiocyanates also cycloadd to ethylene sulfide **467a** giving

rise to 2-imino-1,3-dithiolanes **468a**.[583a] 2-Phenylimino-1,3-dioxolane **468b** has been obtained by treating PhNCS with 2,2-dibutyl-1,3,2-dioxastannolane **467a**[583b] (Scheme 103).



Scheme 103

Reaction of phenyl isothiocyanate with sodium phenylethynyl thiolate **469a** in the presence of acetonitrile as proton donor at room temperature affords 2-phenylimino-4-phenyl-1,3-dithiolane **470a**. Similarly, the selenium-containing acetylene **469b** reacts with phenyl isothiocyanate to give the selenathiolane **470b**[584a] (Scheme 104). Acyl isothiocyanates also react in a similar manner to give **470**.[584b]

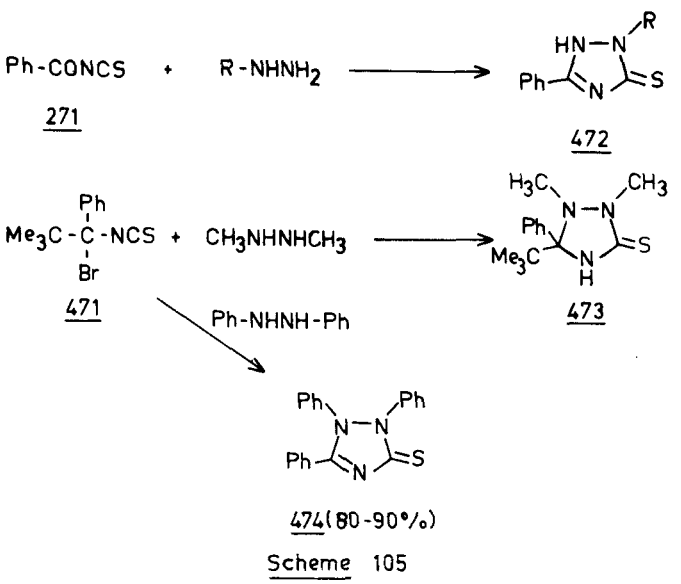


Scheme 104

5.7 Triazoles

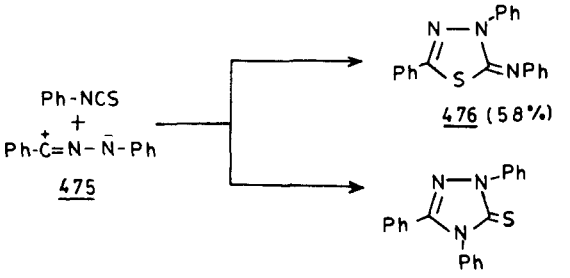
Hydrazines or their derivatives serve as key intermediates in the preparation of various triazolines and triazines. Thus, reaction of benzoyl isothiocyanate **271** and of 1-bromo-1-*t*-butyl-1-phenylmethyl isothiocyanate **471** with mono- and dialkylhydrazines gave 1-alkyl-3-phenyl-Δ^3-1,2,4-triazoline-5-thiones **472**[585] and 5-*t*-butyl-1,2-dimethyl-5-phenyl-1,2,4-triazoline-3-thione **473**,[586] respectively. However, treatment of **271** with *N*,*N*′-diphenylhydrazine affords a high yield of the triazoline **474**[587] (Scheme 105).

Huisgen[588] has shown that diphenylnitrileimine **475** obtained by thermolysis of 2,5-diphenyltetrazole, reacts with phenyl isothiocyanate in a [3 + 2] manner where both the



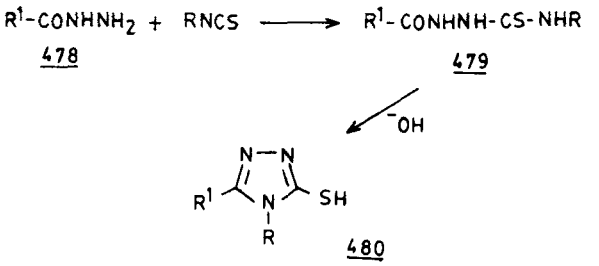
Scheme 105

C=S and the C=N bond of the -NCS group take part in the cycloaddition to form a mixture of 3,5-diphenyl-2-phenylimino-2,3-dihydro-1,3,4-thiadiazole **476** and 1,3,4-triphenyl-1,2,4-triazole-5-thione **477** (Scheme 106).



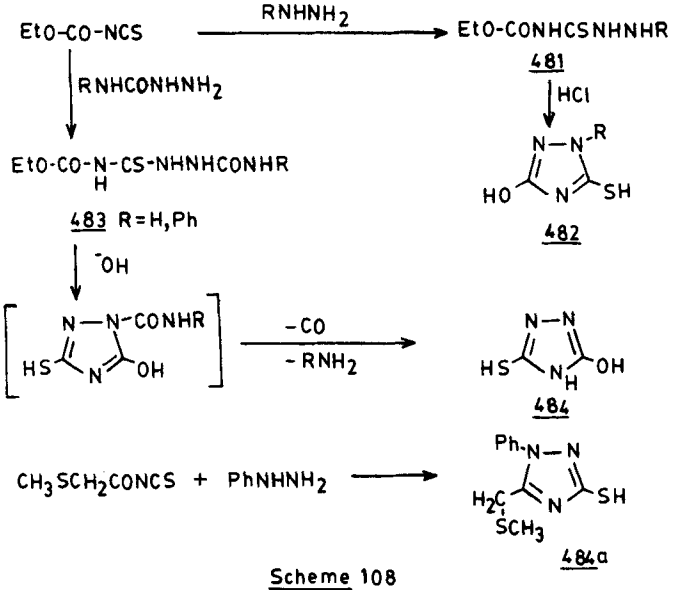
Scheme 106

The most widely used method for the preparation of various triazoles **480** involves the cyclisation of the thiosemicarbazides **479**, obtained from hydrazides **478** and R-NCS, in the presence of a base[589-596] or under thermal conditions[597] (Scheme 107).



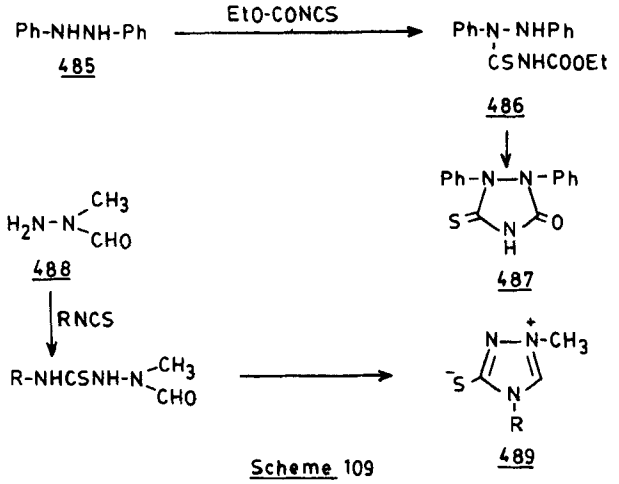
Scheme 107

It is also possible to cyclise the adduct **481**, obtained from a monosubstituted hydrazine and ethoxycarbonyl isothiocyanate, in the presence of HCl to give a 1-substituted 3-hydroxy-1,2,4-triazole-5-thiol **482**.[598] However, the monoadduct **483**, prepared by treatment of ethoxycarbonyl isothiocyanate with a semicarbazide, is cyclised in the presence of alkali to form 3-hydroxy-5-mercapto-1,2,4-triazole **484**.[599a] Acyl isothiocyanates also react with phenyl hydrazine to give **484a**[599b] (Scheme 108).



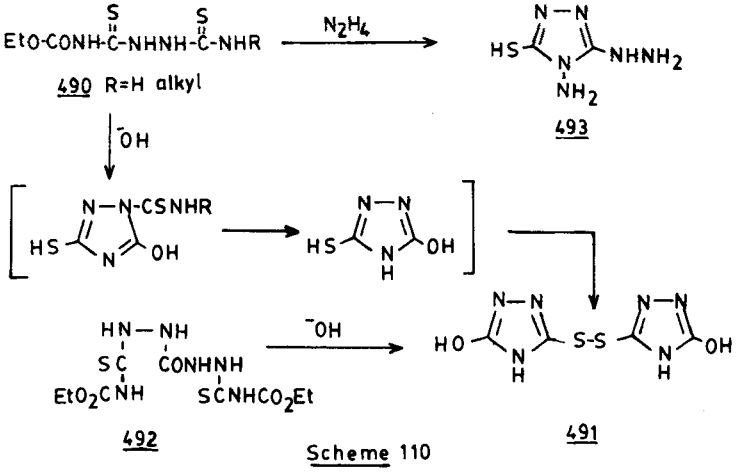
Scheme 108

N,N'-Diphenylhydrazine **485** also reacts with ethoxycarbonyl isothiocyanate **279a** to form the corresponding 4-acylthiosemicarbazide **486** which spontaneously eliminates ethanol during crystallisation and cyclises to yield 1,2-diphenyl-5-thioxo-1,2,4-triazolidin-3-one **487**.[600] However, 1-formyl-1-methylhydrazine **488** gives the mesoionic 1,2,4-triazole **489** when treated with an isothiocyanate[14] (Scheme 109).



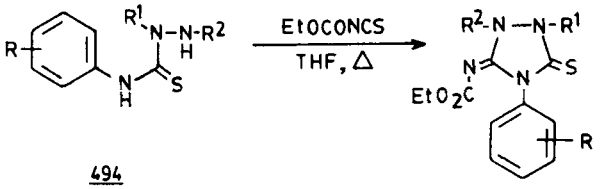
Scheme 109

The monoadduct **490**, obtained by treating ethoxycarbonyl isothiocyanate with thiosemicarbazide, undergoes ring closure in the presence of alkali to form **484** which further oxidises to give the disulfide **491**.[599] The latter may also be obtained by cyclisation of the diadduct **492** in the presence of aqueous alkali.[601] The monoadduct **490** may also be treated with hydrazine to afford a 45% yield of 4-amino-3-hydrazino-5-mercapto-1,2,4-triazole **493**[599] (Scheme 110).



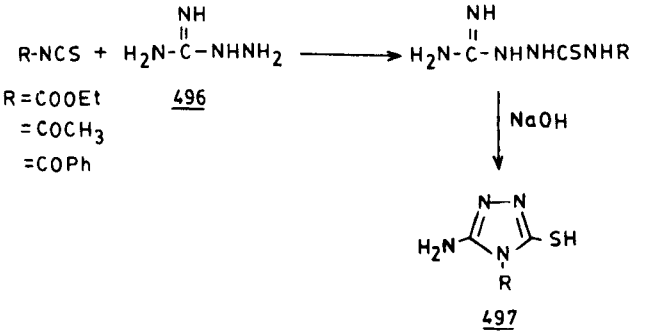
Scheme 110

Reaction of 1,3,4-trisubstituted thiosemicarbazides **494** with ethoxycarbonyl isothiocyanate gives rise to the 1,2,4-triazolidine-3-thiones **495**[602] (Scheme 111).



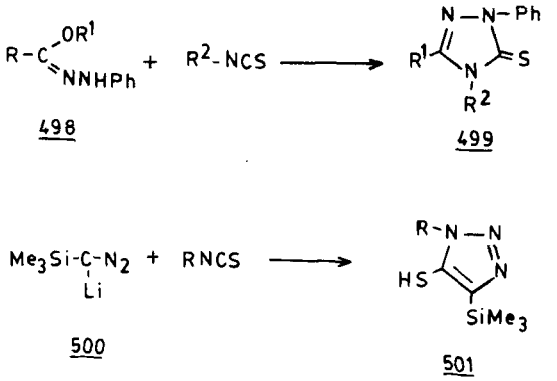
Scheme 111

Cyclocondensation of salts of aminoguanidine **496** with ethoxycarbonyl, acetyl, or benzoyl isothiocyanate leads to the formation of 3-amino-5-mercapto-1,2,4-triazoles **497**[603,604] (Scheme 112).



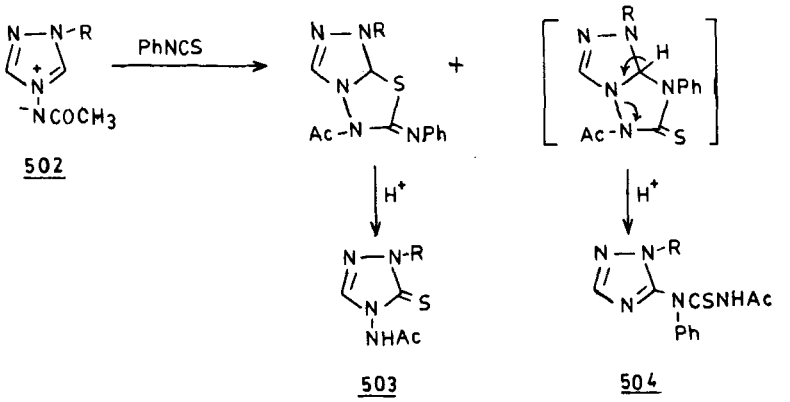
Scheme 112

Reaction of the hydrazonates **498** with isothiocyanates yields the triazolethiones **499**[605] while 1-substituted 4-(trimethylsilyl)-1,2,3-triazole-5-thiones **501** were obtained by treating lithio-(trimethylsilyl)diazomethane **500** with isothiocyanates[606] (Scheme 113).



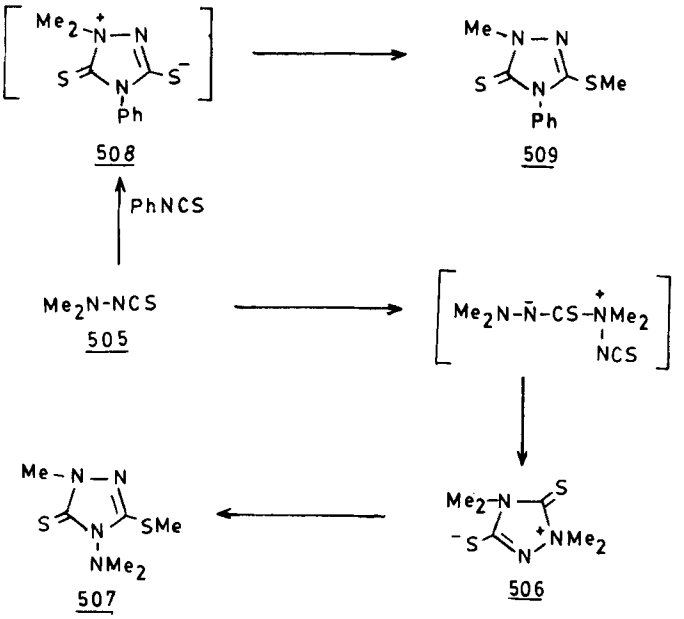
Scheme 113

Treatment of the betaine **502** with aryl isothiocyanates gives a mixture of two triazoles such as **503** and **504** by a mechanism presented in Scheme 114.[607a]



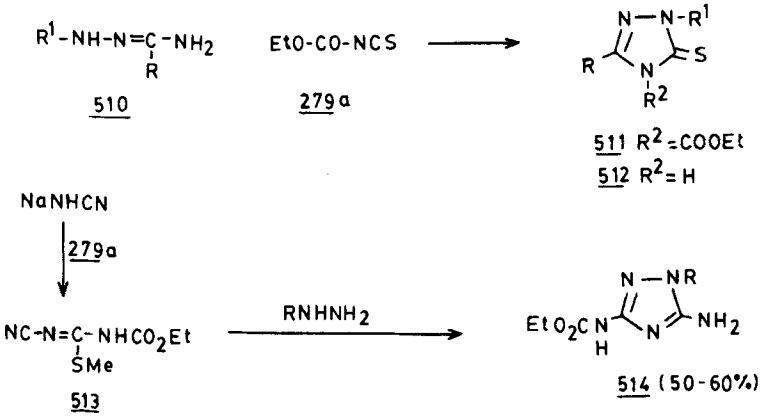
Scheme 114

Dimerisation of *N*-(isothiocyanato)dimethylamine **505** at room temperature leads to a stable and crystalline dimer **506** which rearranges in solution to give the triazole-5-thione **507**.[607b] Treatment of **505** with phenyl isothiocyanate gives a 1,3-cycloadduct **508** which, being thermally unstable, isomerises by migration of the methyl group to form the triazoline-5-thione **509**[14] (Scheme 115).



Scheme 115

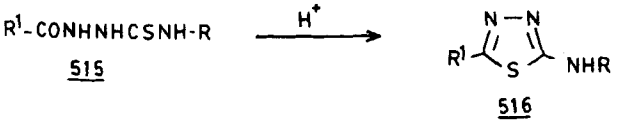
Reaction of 1-substituted amidrazones **510** with **279a** leads to the formation of a mixture of 1,2,4-triazoline-5-thiones **511** and **512** as major and minor products, respectively.[608] Various substituted 1,2,4-triazines **514** have been prepared by treating monosubstituted hydrazines with 1-carbethoxy-3-cyano-*S*-methylisothiourea **513**, obtained by treating **279a** with cyanamide[609] (Scheme 116).



Scheme 116

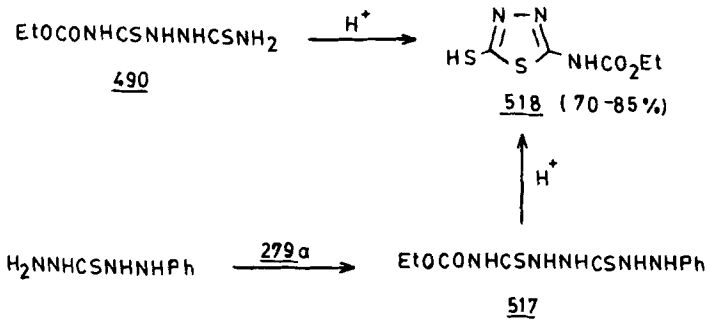
5.8 Thiadiazoles

A convenient method for the synthesis of thiadiazoles **516** involves cyclisation of **515**, obtained by treatment of hydrazides **478** with R-NCS, in the presence of an acid[589,591,594,610-612] (Scheme 117).



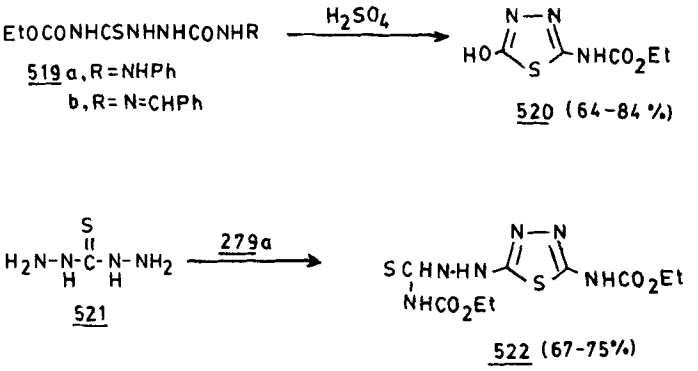
Scheme 117

The adducts **490** and **517** are also cyclised in the presence of an acid to form 2-(*N*-ethoxycarbonylamino)-5-mercapto-1,3,4-thiadiazole **518**[599,601] (Scheme 118).



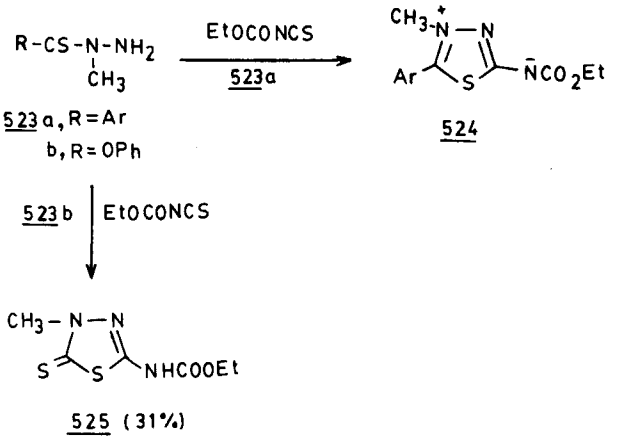
Scheme 118

The monoadducts **519a,b** are cyclised in the presence of H_2SO_4 to give the thiadiazole **520**[601] while carbohydrazide **521** reacts with ethoxycarbonyl isothiocyanate to form **522** in high yield[601] (Scheme 119).



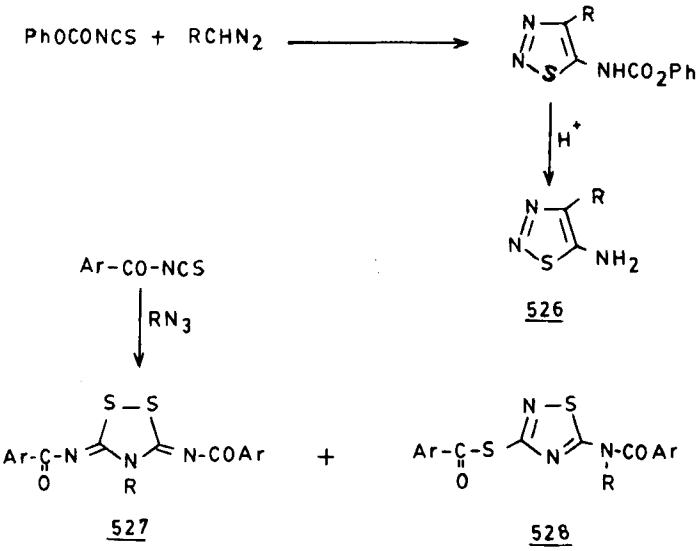
Scheme 119

Reaction of *N*-methylthiobenzhydrazides **523a** with ethoxycarbonyl isothiocyanate **279a** gives the mesoionic 1,3,4-thiadiazoles **524** while **523b** reacts with **279a** to form the 1,3,4-thiadiazolidine-2-thione **525**[613,614] (Scheme 120).



Scheme 120

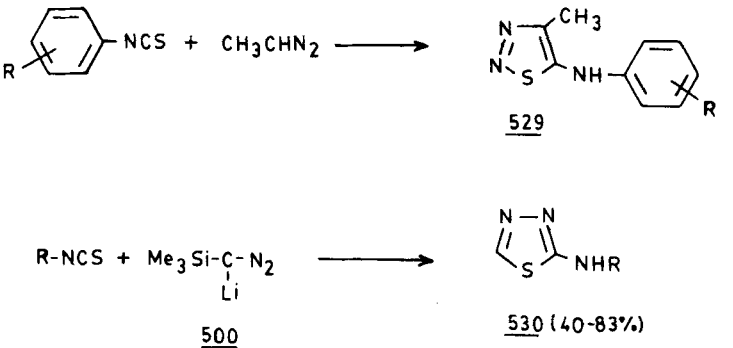
5-Amino-1,2,3-thiadiazoles **526** have been prepared by treating acyl isothiocyanates with diazomethane.[9,615] However, reaction of azides with acyl isothiocyanates leads to the formation of a mixture of 1,2,4-dithiazolidenes **527** and 1,2,4-thiadiazoles **528** with the latter as the major product[616] (Scheme 121).



Scheme 121

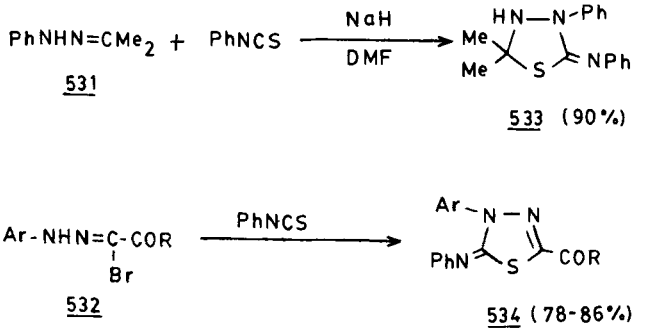
Alkyl, aryl, acyl and several other isothiocyanates are also subject to heterocyclisation when treated with diazomethane.[617-621] Thus, reaction of alkyl/aryl isothiocyanates with

diazomethane and lithiotrimethylsilyldiazomethane **500** yields 5-arylamino-4-methyl-1,2,3-thiadiazoles **529**[617] and 2-substituted 1,3,4-thiadiazoles **530**,[622] respectively (Scheme 122).



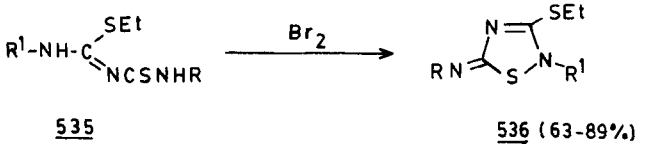
Scheme 122

Cyclisation of the hydrazones **531** and **532** with phenyl isothiocyanate affords the thiadiazolidines **533**[623] and **534**,[624] respectively (Scheme 123).



Scheme 123

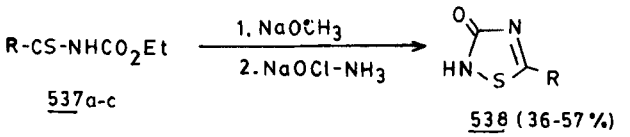
Oxidative cyclisation of the 1-organyl-2-ethyl-5-aryl-2-isodithiobiurets **535**, generated from the appropriate isothiocyanates with bromine or iodine gave high yields of the thiadiazolidines **536**[625] (Scheme 124).



Scheme 124

Reaction of ethoxycarbonyl isothiocyanate **279a** with ethanol, 4-chlorobenzyl alcohol and dimethylamine gives the adducts **537a–c** which on treatment with chloramine afford the 3-hydroxy-1,2,4-thiadiazoles **538a–c**[626] (Scheme 125). However, *N*-ethoxycarbonylt-

hioureas (RNHCS-NHCOOEt; R = H, CH_3), obtained by reaction of **279a** with ethanolic ammonia or methylamine, react with bromine in chloroform to form a complex mixture of 1,2,4-thiazolines.[627]



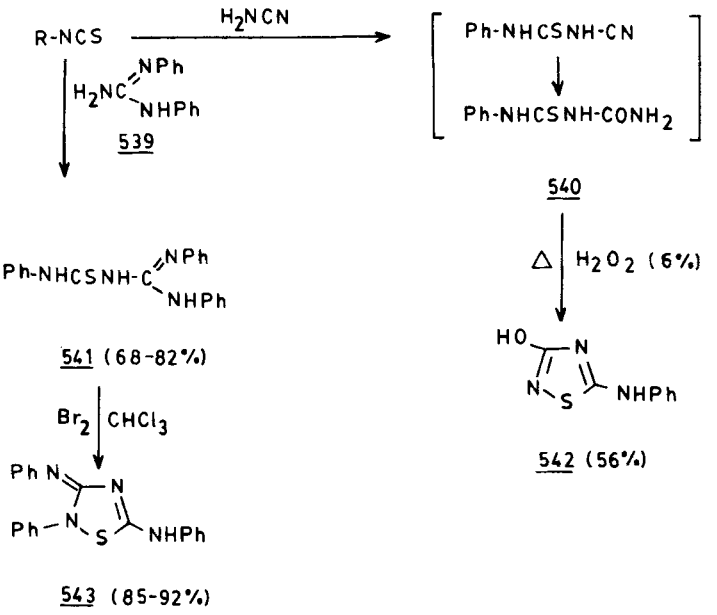
537a-c

538 (36-57%)

537, 538 a, R = OEt
b, R = $OCH_2C_6H_4Cl$
c, R = NMe_2

Scheme 125

Kurzer *et al.*[628,629] have treated phenyl isothiocyanate with cyanamide or *N,N'*-diphenylguanidine **539** to obtain the thioureas **540** and **541**, respectively, which may be cyclised under oxidative conditions to afford the 1,2,4-thiadiazoles **542** and **543** (Scheme 126).

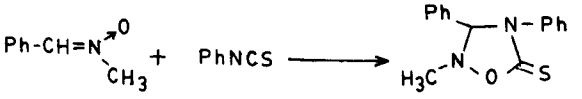


Scheme 126

5.9 Oxadiazoles

Isothiocyanates can enter into [1 + 3] cycloadditions with nitrones (azomethine oxides), usually at their C=N bonds, to form 1,2,4-oxadiazolidine-5-thiones.[630-637] Thus, for example, *C*-phenyl-*N*-methylnitrone **544** reacts with phenyl isothiocyanate to give the

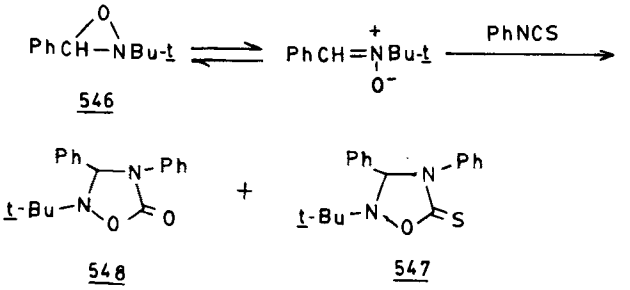
stable 1,2,4-oxadiazolidine-5-thione **545**. Cycloadducts such as **545** with a hydrogen at C-3 can undergo thermal decomposition to yield amidines and carbonyl sulfide[631] (Scheme 127).



544 **545**

Scheme 127

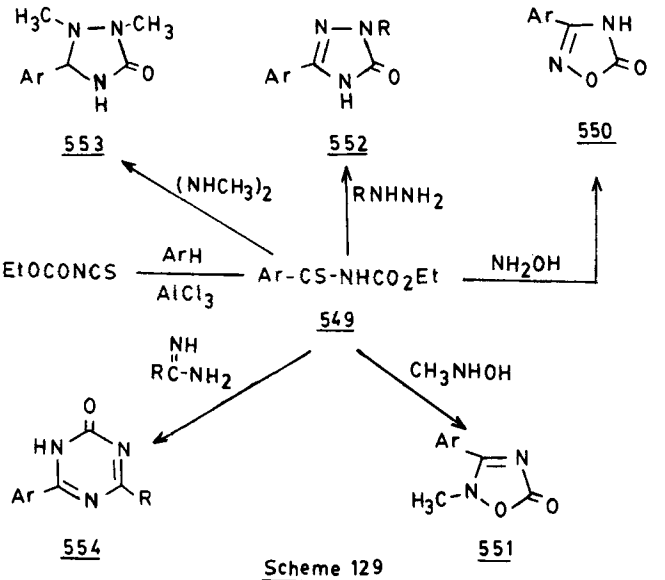
2-*t*-Butyloxaziridine **546** also reacts with phenyl isothiocyanate to give two 1:1 cycloadducts, *i.e.* the oxadiazolidines **547** and **548** as major and minor products, respectively[638] (Scheme 128).



546 **548** **547**

Scheme 128

Various aromatic compounds are known to react with ethoxycarbonyl isothiocyanate in the presence of aluminium chloride to form *N*-(ethoxycarbonyl)thioamides **549** which may be used to prepare 1,2,4-oxadiazolones (**550**, **551**), 1,2,4-triazolones (**552**, **553**) and 1,3,5-triazinones (**554**) as shown in Scheme 129.[639,640]

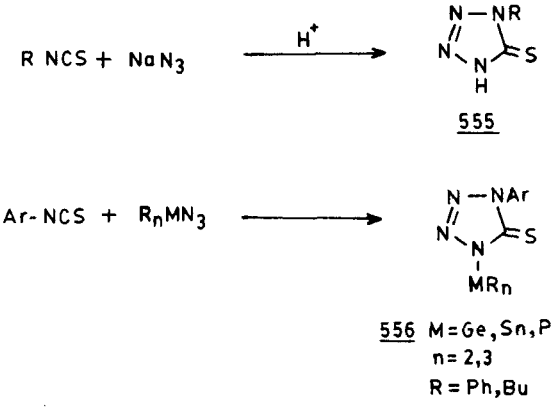


553 **552** **550** **549** **554** **551**

Scheme 129

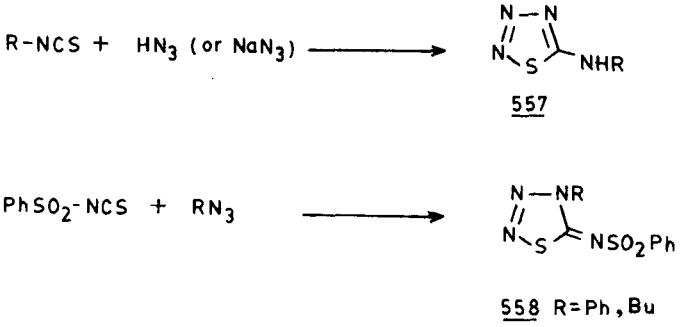
5.10 Tetrazoles and Thiatriazoles

Isothiocyanates may react with azides at their C=N or C=S bonds forming tetrazoles and thiatriazoles, respectively. Thus reaction of alkyl and aryl isothiocyanates with sodium azide gives 1-substituted tetrazoline-5-thiones **555**.[641-646] Similarly, 1,2-cycloaddition of aryl isothiocyanates to Ph_3MN_3 (M = Ge, Sn, Pb)[647,648] or Bu_2MN_3 (M = Ga, Tl)[649] yields the corresponding organometal substituted tetrazoles **556** (Scheme 130).



Scheme 130

Alkyl and aryl isothiocyanates undergo [1 + 2] cycloaddition to hydrazoic acid or sodium azide via their C=S bond to form 5-substituted 1,2,3,4-thiatrazoles **557**.[650,651] The arylsulfonyl isothiocyanates also react with butyl or benzyl azide at their C=S bonds to yield 1,2,3,4-thiatriazoles such as **558**[652] (Scheme 131).

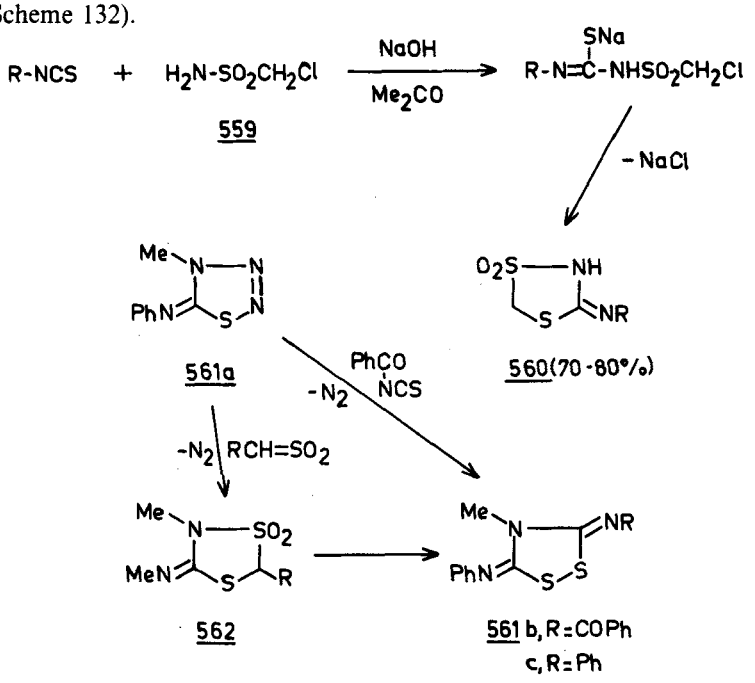


Scheme 131

5.11 Miscellaneous Five-Membered Heterocycles

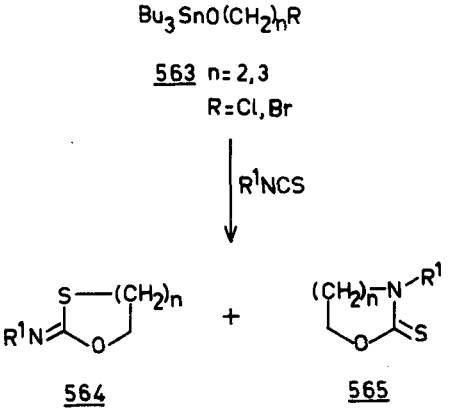
The synthesis of 5-substituted imino-1,3,4-dithiazolidine 3,3-dioxides **560** has been carried out by treating chloromethanesulfonamide **559** with R-NCS in a basic medium.[653] Heterocumulenes such as RCONCS also react with 4-methyl-5-(phenylimino)-1,2,3,4-thiatriazoline **561a** in a bimolcular cycloaddition-elimination reaction to

give **561b**. Alternatively, reaction of the sultam **562** with phenyl isothiocyanate also gives **561c**[654] (Scheme 132).



Scheme 132

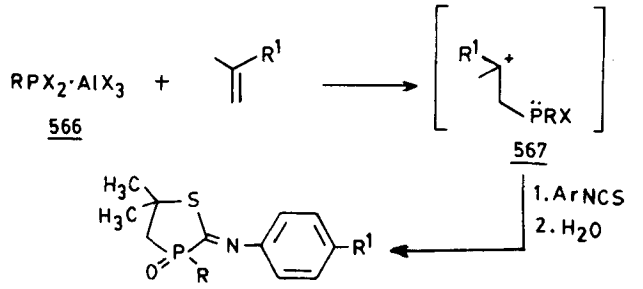
Reaction of tri-*n*-butylstannyloxy-ω-haloalkanes **563** with alkyl and aryl isothiocyanates yields a mixture of **564** and **565**, the ratio of which depends on the alkane chain length, the substituents attached to it and the solvent used[655] (Scheme 133).



Scheme 133

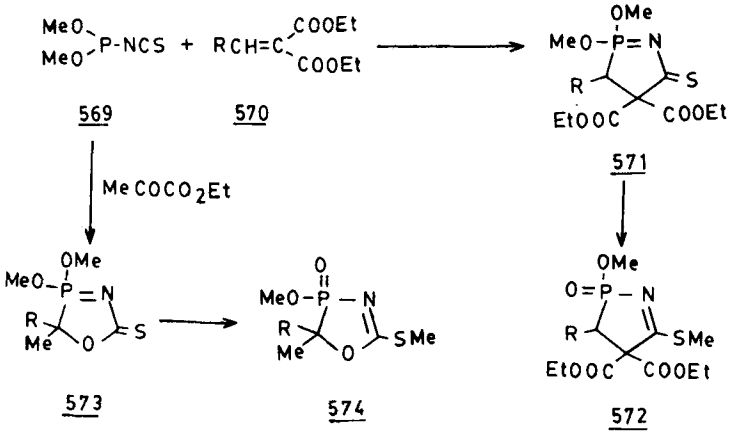
A large number of phosphorus heterocycles have been synthesized using isothiocyanates.[656] Thus reaction of the complex **566** with isobutylene gave a carbonium ion **567**

which could be trapped by adding an aryl isothiocyanate to the reaction mixture yielding the iminothiophospholane **568**[657] (Scheme 134).



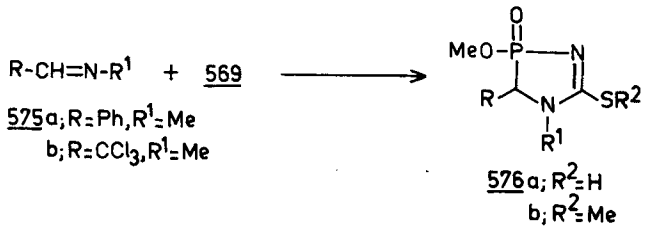
Scheme 134

Dimethoxyisothiocyanatophosphine **569** reacts with methylene- and ethylidene-malonate **570** to form azaphospholines **571** which are stabilized to **572** due to their imide amide rearrangement.[658] Similarly, ethyl pyruvate may be treated with **569** to yield 2-substituted 3-methoxy-3-oxo-5-methylthio-Δ^4-1,4,3-λ^5-oxazaphospholines **574** formed by *S*-alkylation of the intermediate **573**[659,660] (Scheme 135).



Scheme 135

Treatment of **569** with *N*-(benzylidene)methylamine or *N*-(trichloroethylidene)aniline (**575a,b**) leads to the formation of the 1,5-disubstituted 4-alkoxy-4-oxo-Δ^2-1,3,4-λ^5-diazaphospholines **576a,b**[661] (Scheme 136).

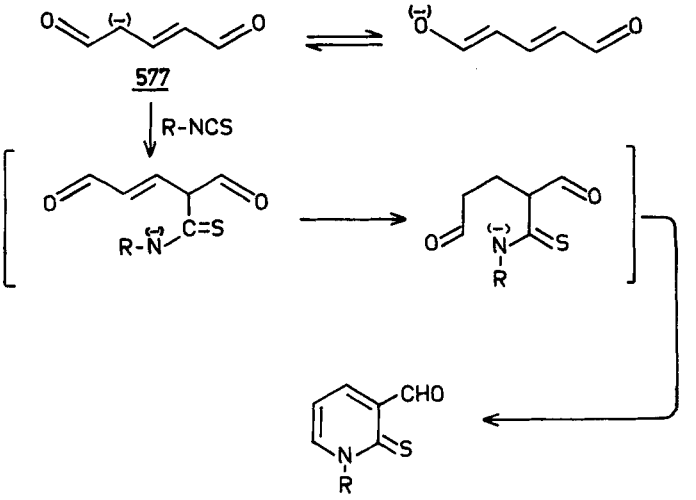


Scheme 136

6. SIX-MEMBERED HETEROCYCLES

6.1 Pyridines and Thiopyrans

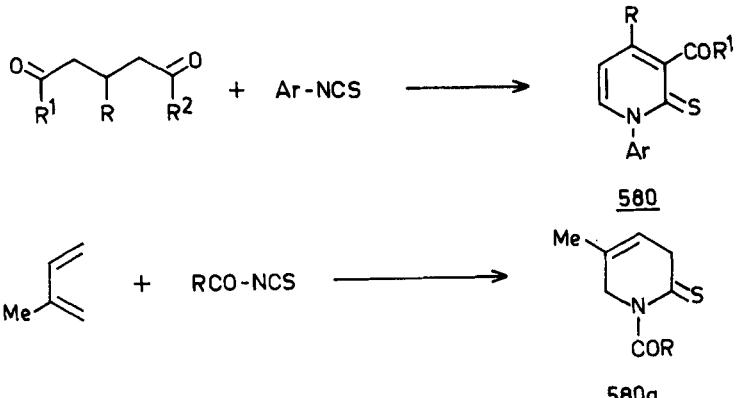
Becher and coworkers[662-669] have developed various methods to prepare different pyridine derivatives. Thus, reaction of glutaconedialdehyde anion **577** with alkyl and aryl isothiocyanates in DMF or DMSO at room temperature gave 1-substituted 3-formyl-2*H*-pyridine-2-thiones **578** in 30–98% yield[662-664] (Scheme 137).



578 (30-98%)

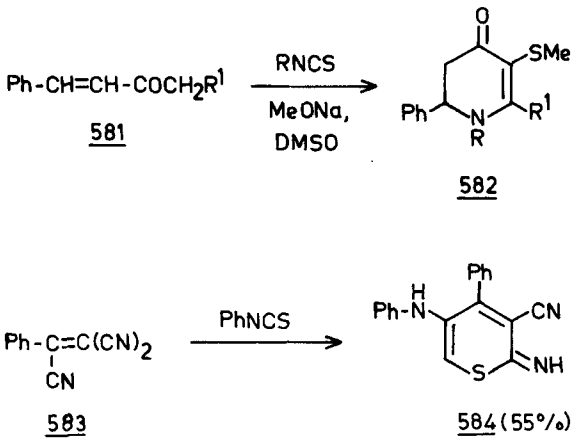
Scheme 137

Replacement of **577** by diketones **579** in the above scheme leads to the formation of 1-aryl-3-acyl/aroylpyridine-2-thiones **580** in high yield.[665,666a] Arbuzov and Zobova[666b] have reported diene syntheses with acyl isothiocyanates and butadiene, isoprene, cyclopentadiene or 2,3-dimethyl-1,3-butadiene yielding the 1,2,3,6-tetrahydropyridines **580a** (Scheme 138). Various styryl ketones **581** also react with isothiocyanates in the



Scheme 138

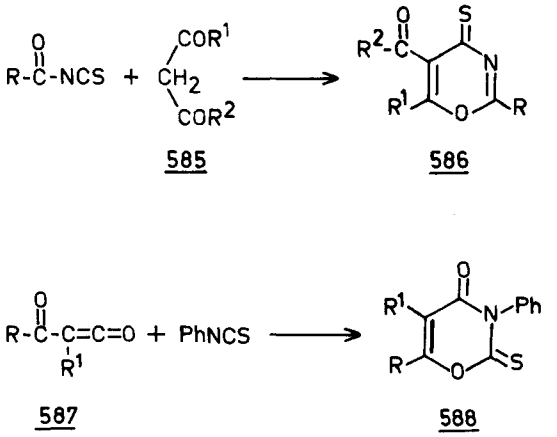
presence of sodium methoxide in DMSO to form 2,3-dihydro-6-methylthio-4-(1*H*)-pyridines (**582**).[668] The thiopyran **584** is prepared by treating the cyano compound **583** with phenyl isothiocyanate[669] (Scheme 139).



Scheme 139

6.2 Oxazines

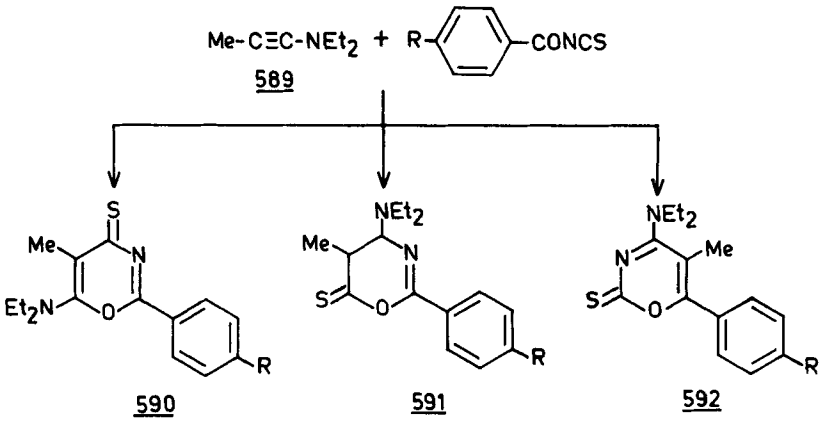
Acyl isothiocyanates react with 1,3-diketones **585** to give 2,6-disubstituted 5-acyl-4*H*-1,3-oxazine-4-thiones **586**.[670,671] However, 1,3-oxazin-4-one-2-thiones **588** may be obtained by cycloaddition of phenyl isothiocyanate to acetylketenes **578**[672] (Scheme 140).



Scheme 140

Cycloaddition of benzoyl isothiocyanate to electron-rich allenes such as **589** leads to the formation of a mixture of three oxazines (**590–592**) as the result of three concurrent

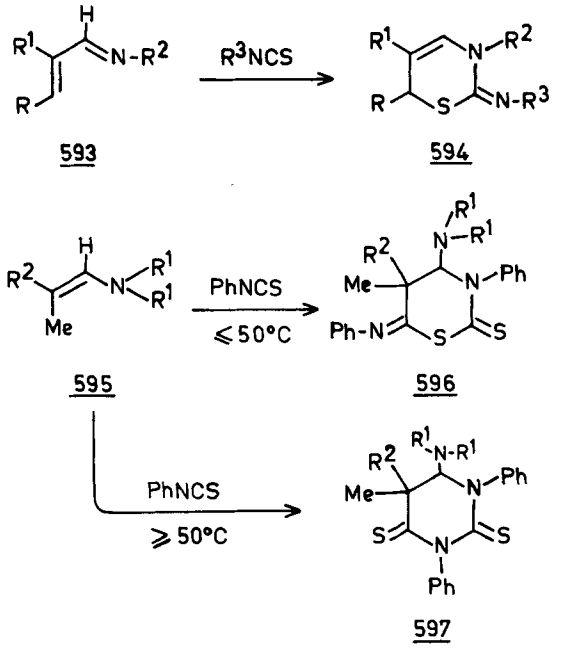
processes, viz., [4 + 2], [2 + 2], and [1 + 2] additions involving the alkyne triple bond and different sites of benzoyl isothiocyanate[673] (Scheme 141).



Scheme 141

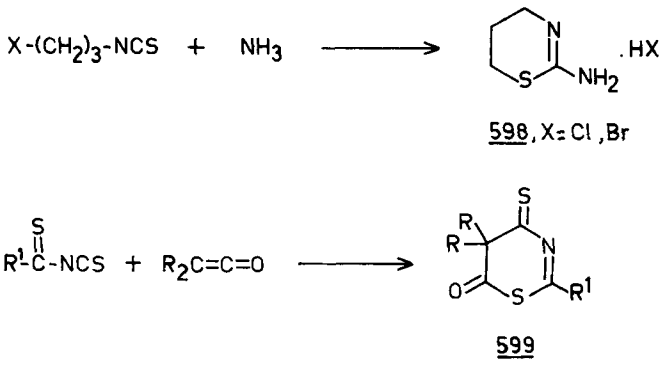
6.3 Thiazines

A novel synthesis of 6-substituted 2-imino-6*H*-2,3-dihydro-1,3-thiazines **594** involves reaction of the imines **593** with aryl isothiocyanates.[674,675] Aryl isothiocyanates also react with enamines **595** to form two types of 2:1 cycloadducts, **596** and **597**, depending upon the reaction temperature[676] (Scheme 142).



Scheme 142

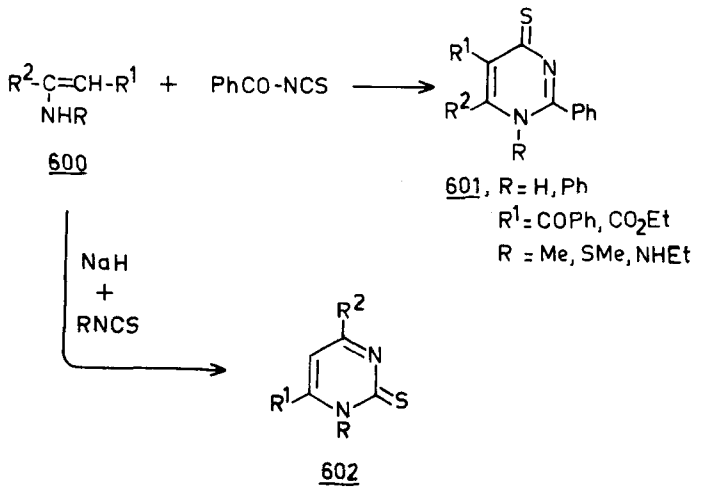
3-Halopropyl isothiocyanates may react with ammonia to give 2-amino-5,6-dihydro-4*H*-1,3-thiazine **598**.[677] Similarly, thioacyl isothiocyanates undergo cycloaddition with ketenes to form the 2,5,5-trisubstituted 4-thioxo-5,6-dihydro-4*H*-1,3-thiazin-2-ones **599** (Scheme 143).[467,471]



Scheme 143

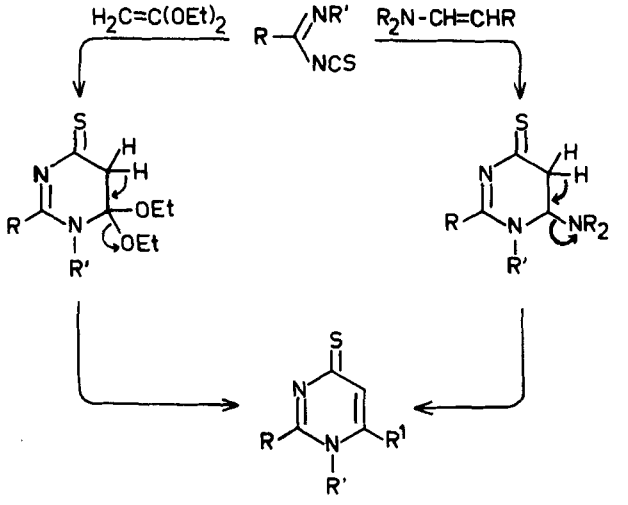
6.4 Pyrimidines

Enamines have been used as key intermediates to prepare various pyrimidines by reaction with isothiocyanates. Thus, acyl isothiocyanates react with different enamines **600** to give the pyrimidinethiones **601**.[532,678,679] However, **600** may undergo cyclisation with aryl isothiocyanates in the presence of sodium hydride in DMF at low temperatures to give the pyrimidine-2-thiones **602**[680] (Scheme 144).



Scheme 144

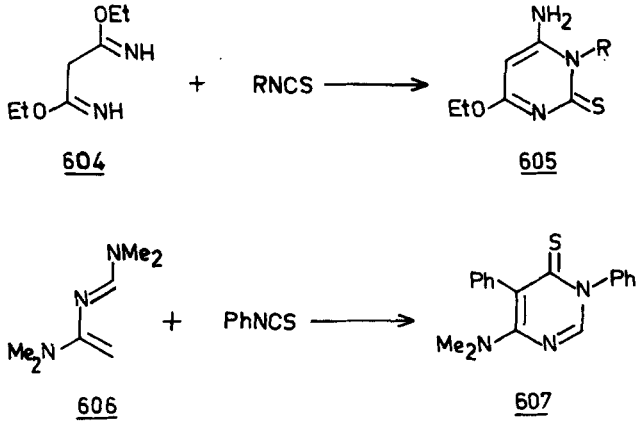
Imidoyl isothiocyanates also react with enamines ($R_2N-CH=CHR$) or ketene diethylacetal [$CH_2=C(OEt)_2$] to give a 1:4-cycloadduct which loses amine or alcohol respectively to afford a 1,4-dihydropyrimidine-4-thione **603**[471] (Scheme 145).



603, R^1 = H, OEt

Scheme 145

Cyclisation of diethyl malonodiimidate **604** with isothiocyanates gives the 4-aminopyrimidine-2-thiones **605** in 30–56% yield[681] (Scheme 146). 1,3-Bis-(*N*,*N*-dimethylamino)-2-aza-1,3-butadiene **606** also undergoes cycloaddition with Ph-NCS to give a 36% yield of the pyrimidinethione **607**.[682]



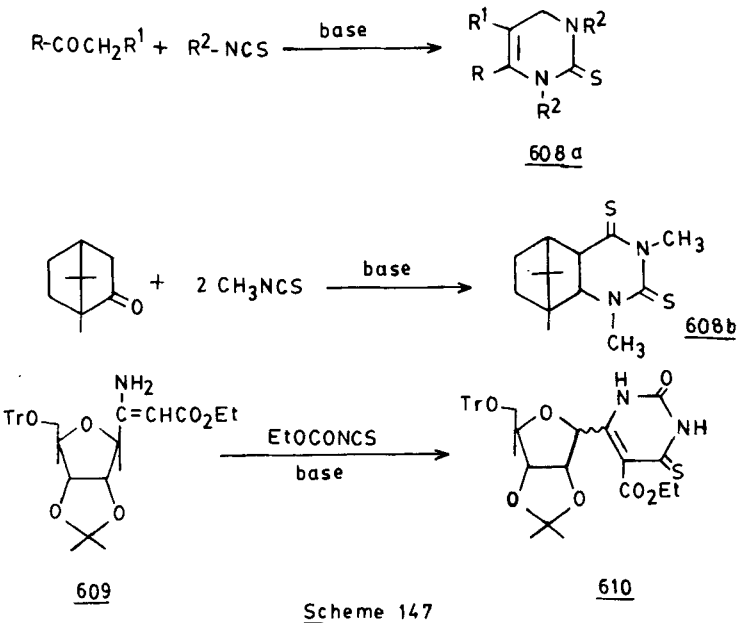
604 **605**

606 **607**

Scheme 146

Various tetrahydropyrimidines **608a**, **b** have been prepared by cycloaddition reactions of alkyl and aryl isothiocyanates with ketones having at least one α-hydrogen, in a basic medium.[683] Another cyclisation is observed when the enamine **609** is treated with

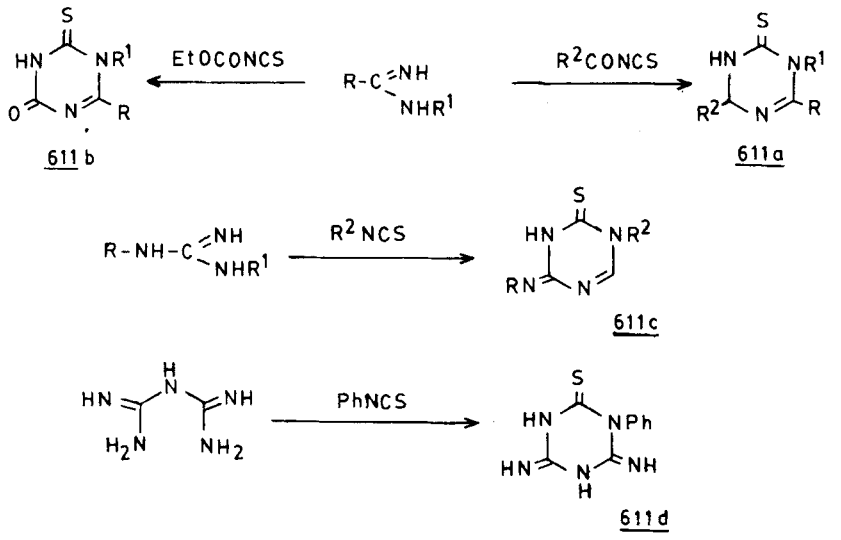
ethoxycarbonyl isothiocyanate to give the desired thiourea which cyclises in the presence of base to give the 5-ethoxycarbonyl-4-thiouracil *C*-nucleoside **610**[684] (Scheme 147).



Scheme 147

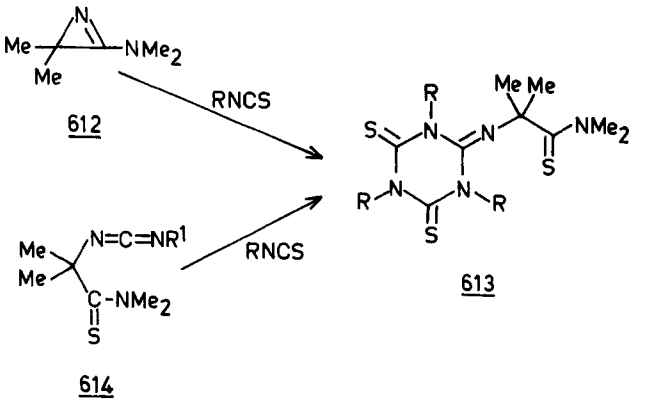
6.5 Triazines

The reaction of acyl isothiocyanates with amidines and guanidines has been widely used to prepare various triazinethiones.[685-690] Amidines[685-687] and guanidines[688-690] react with acyl and aryl isothiocyanates to afford triazine-2-thiones **611a–d** (Scheme 148).



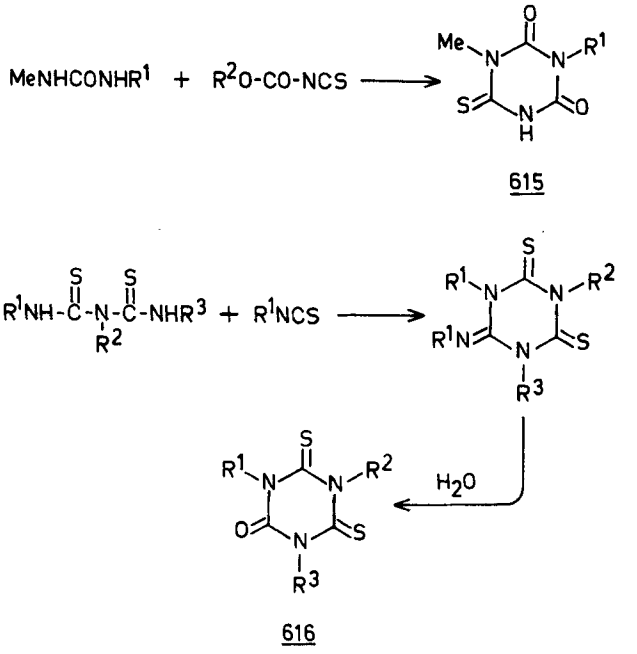
Scheme 148

Cyclic amidines such as the azirines **612** also react with alkyl isothiocyanates to give the triazine-2,4-dithiones **613** as a result of a [3 + 1] cycloaddition.[691] The latter may also be obtained by treating alkyl isothiocyanates with the carbodiimides **614**[691] (Scheme 149).



Scheme 149

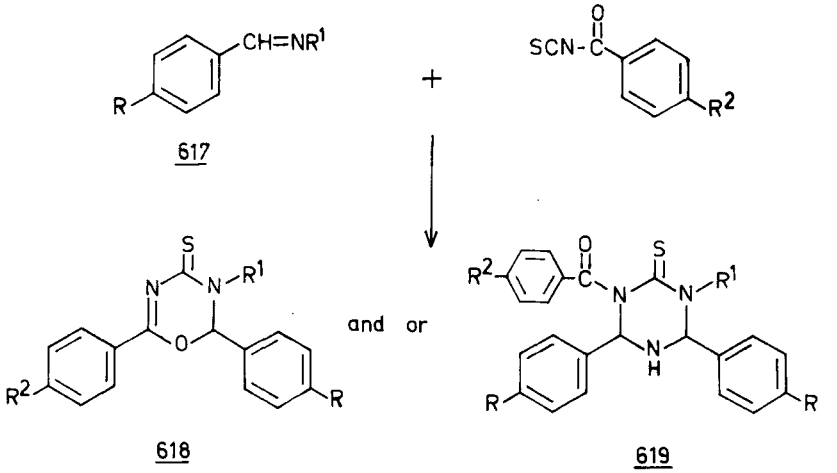
Both ureas and thioureas may be used to generate various substituted triazines (**615**, **616**) by reaction with isothiocyanates under different conditions[692,693] (Scheme 150).



Scheme 150

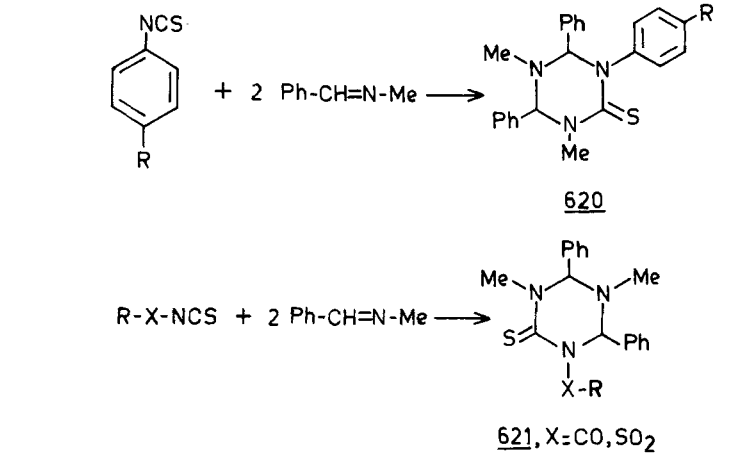
The azomethines **617** also react with aryl and acyl isothiocyanates to afford substituted triazinethiones via [4 + 2] cycloaddition.[694-696] Thus 4-substituted *N*-benzylide-

neamines **617** react with aroyl isothiocyanates to give either the 1:1 adduct, a 1,3,5-oxadiazine **618** or the 2:1 adduct, a triazine **619** or a mixture of both.[694,695] The triazines **619** are usually formed with aroyl isothiocyanates having strongly electron-withdrawing substituents at the benzene ring[694] (Scheme 151).



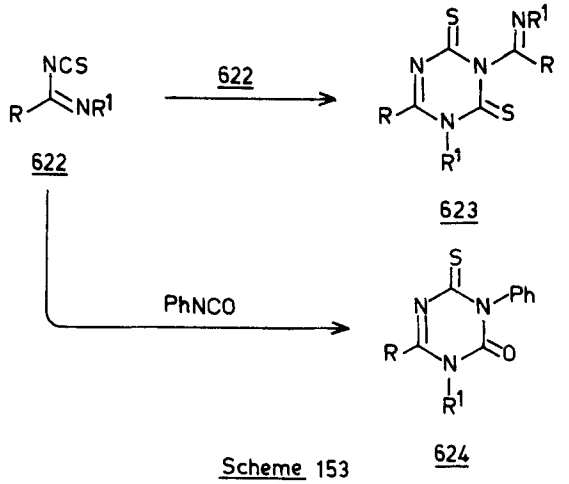
Scheme 151

It is also possible to get exclusive formation of triazines in the reaction of azomethines with isothiocyanates. Thus aryl isothiocyanates react with azomethines to give solely 2:1 adducts, the hexahydro-*s*-triazinethiones **620**.[696] Similarly, acyl and sulfonyl isothiocyanates also undergo 2:1 cycloaddition with two molecules of *N*-benzylidenemethylamine to form **621**[458,520] (Scheme 152).



Scheme 152

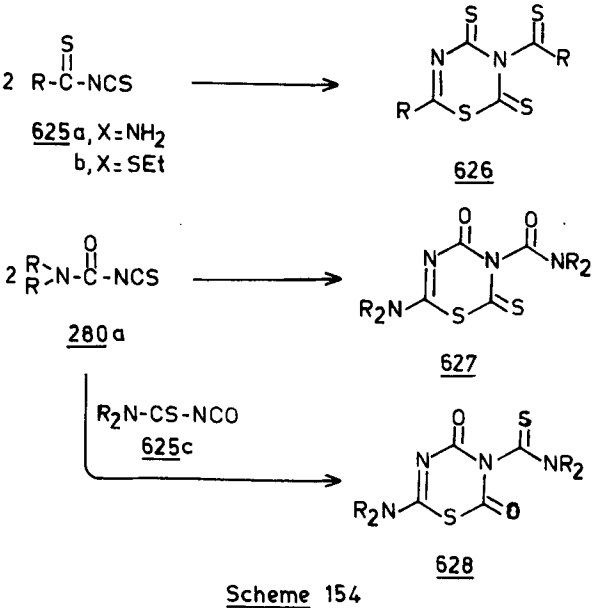
Dimerisation of imidoyl isothiocyanates **622** or their reaction with phenyl isothiocyanate afford tetrahydro-*s*-triazinethiones **623** and **624**[475] (Scheme 153).



Scheme 153

6.6 Thiadiazines

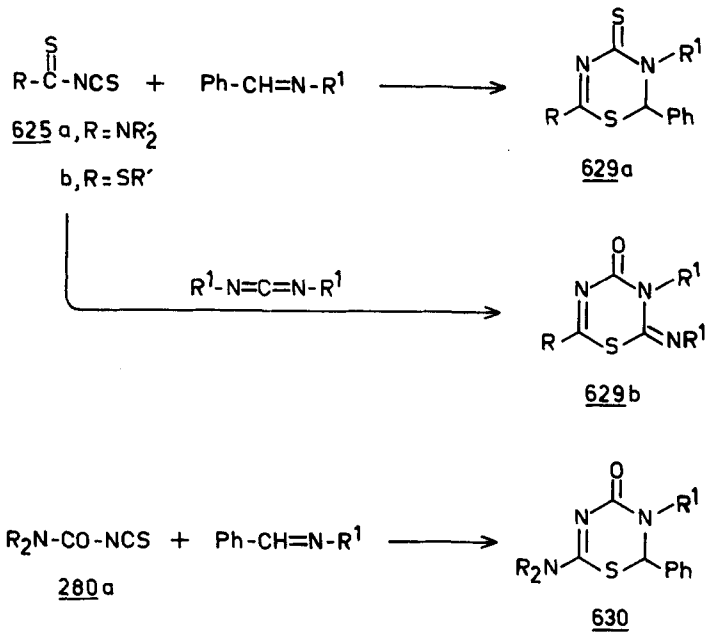
Thiocarbamoyl isothiocyanates **625a** and ethyl isothiocyanatodithioformate **625b** are known to dimerise to form the thiadiazines **626**.[9,460,471] Dimerisation of *N,N*-dialkylcarbamoyl isothiocyanates **280a** or their reaction with thiocarbamoyl isocyanates **625c** also gives the substituted thiadiazines **627** and **628**, respectively[459,528] (Scheme 154).



Scheme 154

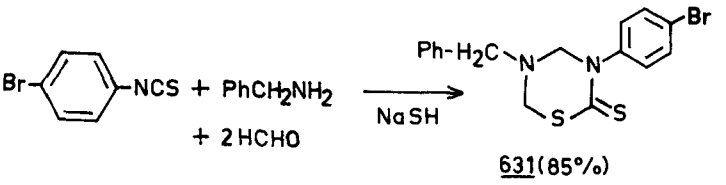
Thiocarbamoyl isothiocyanates **625a** and thioacyl isothiocyanates **625b** may also be allowed to react with azomethines or carbodiimides to yield the 1,3,5-thiadiazine-4-

thiones **629a,b**.[469,471,697] Carbamoyl isothiocyanates **280a** can also be treated with azomethines to afford the thiadiazinones **630**[528] (Scheme 155).



Scheme 155

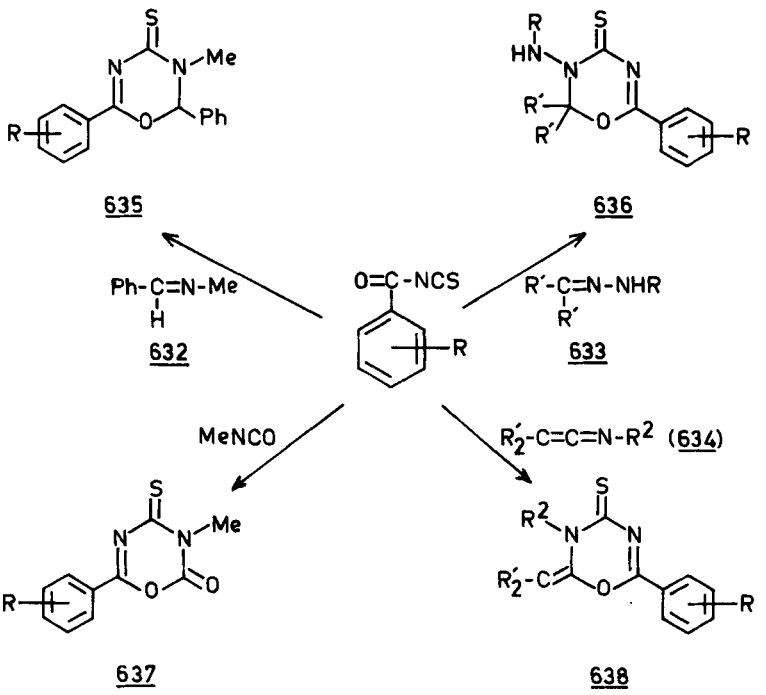
5-Benzyl-3-(4-bromophenyl)tetrahydro-1,3,5-thiadiazine-2-thione **631** has been prepared in 85% yield by treating 4-bromophenyl isothiocyanate with benzylamine in the presence of formaldehyde and NaSH at room temperature[698] (Scheme 156).



Scheme 156

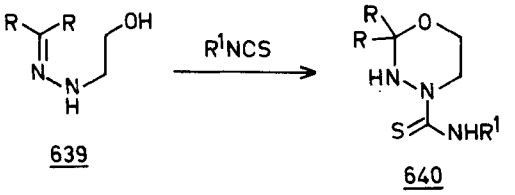
6.7 Oxadiazines

Benzoyl isothiocyanate may be allowed to react with the azomethines **632**,[694,696] hydrazones **633**,[698] an isocyanate[699] or ketimines **634**[530] to yield the oxadiazines **635–638**, respectively (Scheme 157).



Scheme 157

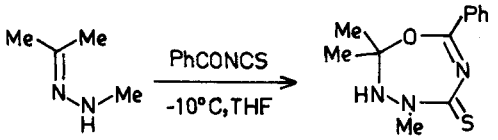
Cyclisation of hydrazones **639** with isothiocyanates affords the 4-(thiocarbamoyl)-3,4,5,6-tetrahydro-1,3,4-oxadiazines **640**[700] (Scheme 158).



Scheme 158

7. SEVEN-MEMBERED HETEROCYCLES

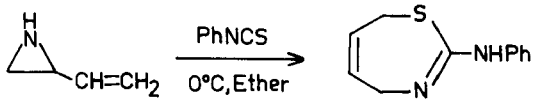
Reaction of 1-isopropylidene-2-methylhydrazine **641** with benzoyl isothiocyanate in THF at -10 °C gives 2,3,4,5-tetrahydro-2,2,4-trimethyl-7-phenyl-1,3,4,6-oxatriazepine-5-thione **642**[701] in 75% yield (Scheme 159).



641 642 (75%)

Scheme 159

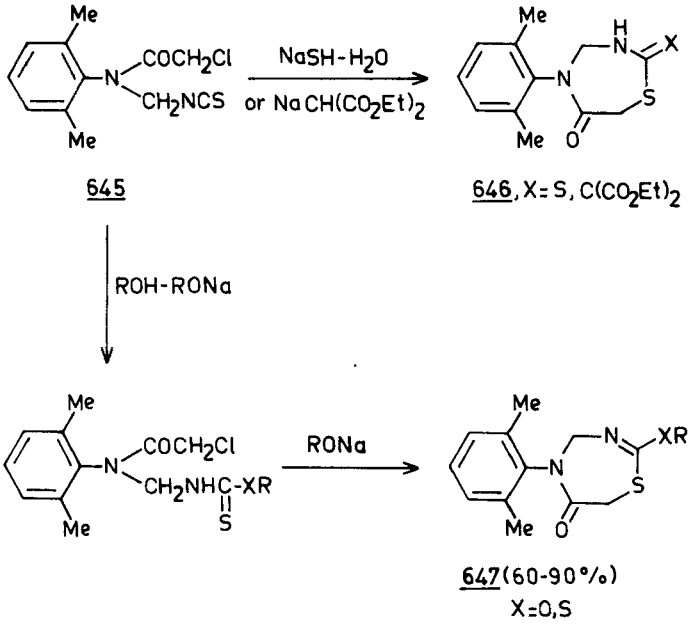
2-Vinylaziridine **643** also reacts with phenyl isothiocyanate at 0 °C to give 2-phenylamino-4,7-dihydro-1,3-thiazepine **644**[702] (Scheme 160).



643 644 (59%)

Scheme 160

The bifunctional isothiocyanate **645** may be cyclised with NaSH or diethyl sodiomalonate and alcohol-sodium methoxide to yield the 1,3,5-thiazepines **646** and **647**, respectively[703] (Scheme 161).



645 646, X = S, $C(CO_2Et)_2$

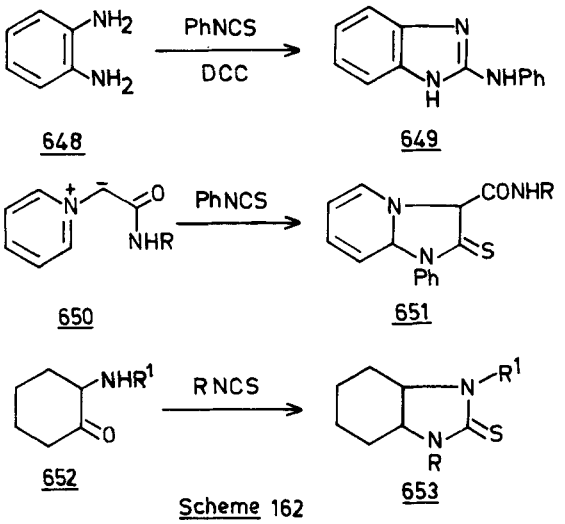
647 (60-90%)
X = O, S

Scheme 161

8. BENZOHETEROCYCLES

8.1 Benzimidazoles and Related Compounds

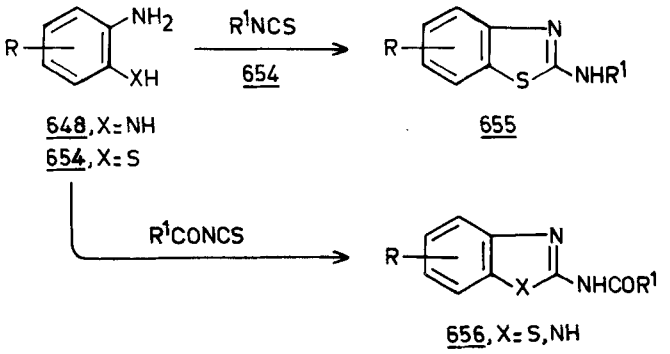
Reaction of *o*-phenylenediamine **648** with phenyl isothiocyanate in refluxing benzene in the presence of dicyclohexylcarbodiimide (DCC) affords a high yield of 2-(phenylamino)benzimidazole **649**.[704] The imidazopyridines **651** may be obtained by cycloaddition of phenyl isothiocyanate to the pyridinium ylides **650**.[705] The aminocyclohexanone oximes **652** also undergo cyclocondensation to form 4,5,6,7-tetrahydrobenzimidazoline-2-thiones **653** when treated with isothiocyanates[706] (Scheme 162).



Scheme 162

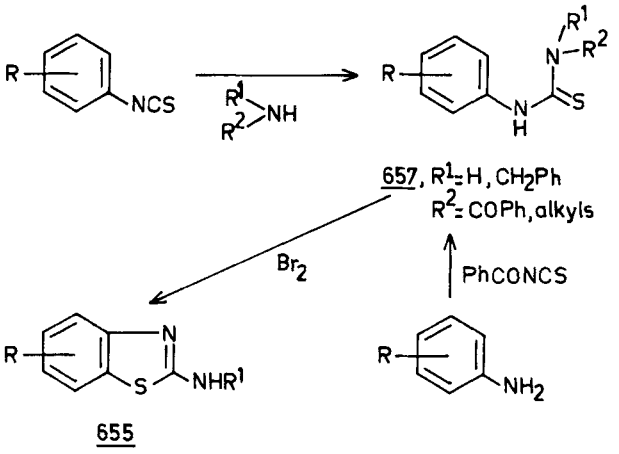
8.2 Benzothiazoles

Reaction of the *o*-aminothiophenols **654** with alkyl/aryl isothiocyanates in refluxing benzene or xylenes gives the 2-aminobenzothiazoles **655**[707-709] while 2-(acylamino)-benzothiazoles and -benzimidazoles **656** have been obtained by cyclising **648** or **654** with acyl isothiocyanates[710] (Scheme 163).



Scheme 163

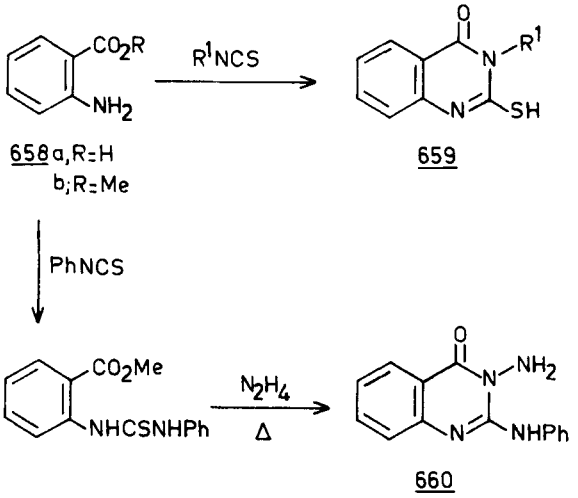
Alternatively, *N*-arylthioureas **657**, obtained by condensing an amine with an isothiocyanate, may be treated with bromine in chloroform to yield the 2-aminobenzothiazoles **655**[711,712] (Scheme 164).



Scheme 164

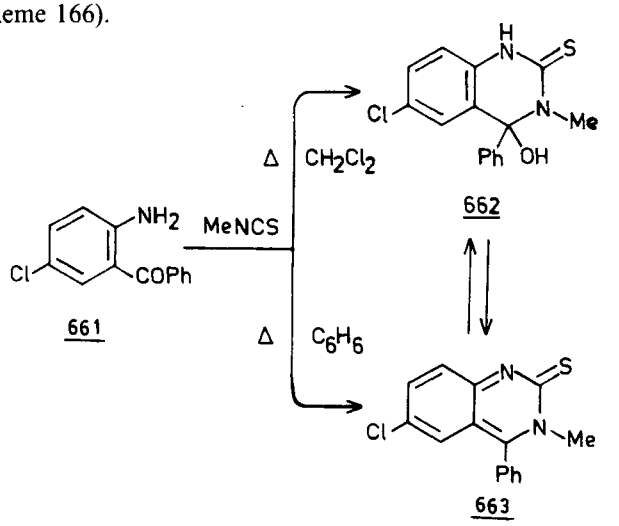
8.3 Quinazolones

Reaction of 2-aminobenzoic acids (anthranilic acids, **658a**) with alkyl and aryl isothiocyanates gives the desired thioureas which cyclise spontaneously in acidic medium to give the corresponding 3,4-dihydroquinazolin-4-ones **659** in high yields.[713–718] Methyl anthranilate **658b** also undergoes a similar reaction with isothiocyanates to form **659**.[719] 2,3-Diamino-3,4-dihydroquinazolin-4-ones **660** may be prepared by successive reaction of **658b** with phenyl isothiocyanate and hydrazine hydrate[720] (Scheme 165).



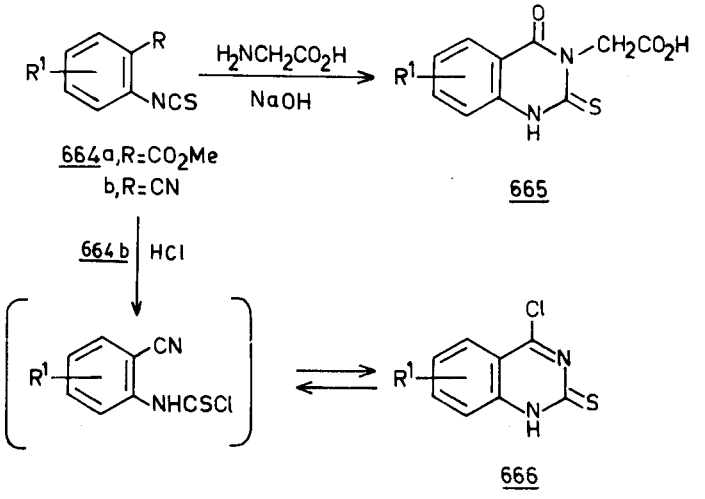
Scheme 165

By treating 2-amino-5-chlorobenzophenone **661** with methyl isothiocyanate, two quinazoline-2-thiones (**662** and **663**) are formed depending on the reaction temperature[721] (Scheme 166).



Scheme 166

A convenient method to prepare the quinazoline-2-thiones **665** and **666** involves treating 2-methoxycarbonyl or 2-cyanophenyl isothiocyanate (**664a,b**) with glycine and HCl or HBr, respectively[722,723] (Scheme 167).

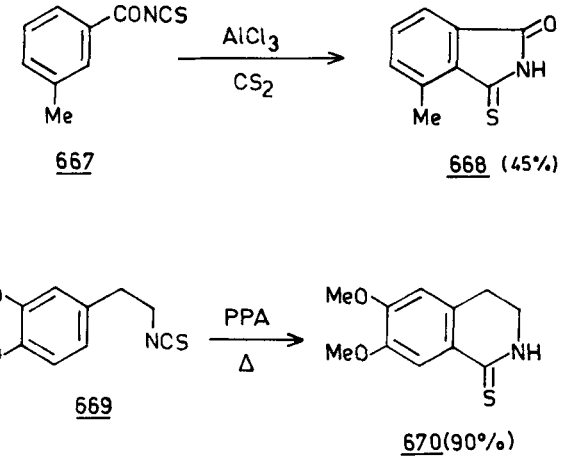


Scheme 167

8.4 Other Benzoheterocycles

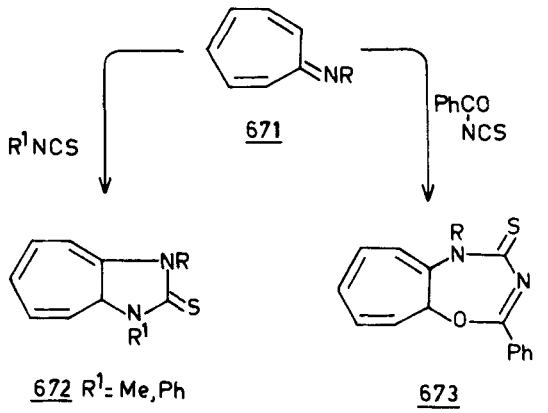
2-Thio-3-methylphthalimide **668** may be prepared by refluxing 3-methylbenzoyl isothiocyanate **667** in carbon disulfide in the presence of aluminium chloride.[724] Similarly,

2-(2,3-dimethoxyphenyl)ethyl isothiocyanate **669** cyclises in the presence of polyphosphoric acid to give 6,7-dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-thione **670**[725] (Scheme 168).



Scheme 168

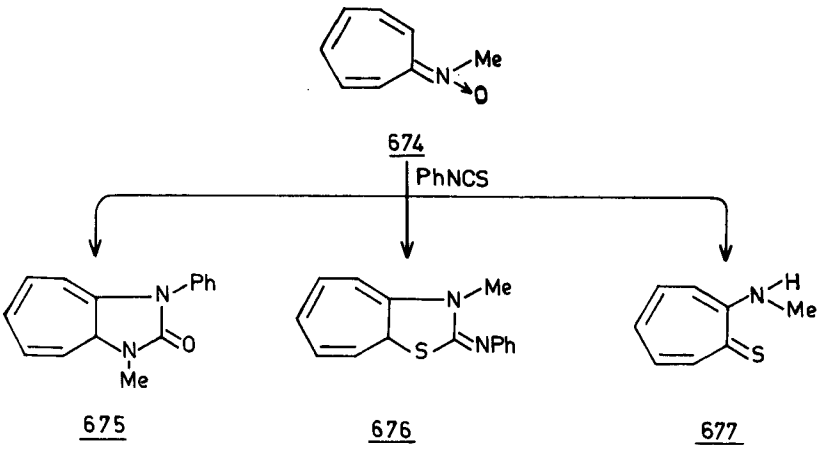
Reaction of 8-azaheptafulvenes **671** with methyl or phenyl isothiocyanate yields the cyclohept[*d*]imidazoles **672** while benzoyl isothiocyanate reacts with **671** to form the cycloadduct cycloheptenoxadiazepinethione **673**[726] (Scheme 169).



Scheme 169

The *N*-oxide of **671** (**674**) also undergoes cycloaddition when treated with phenyl isothiocyanate resulting in the formation of a mixture of **675**–**677**, the proportion of

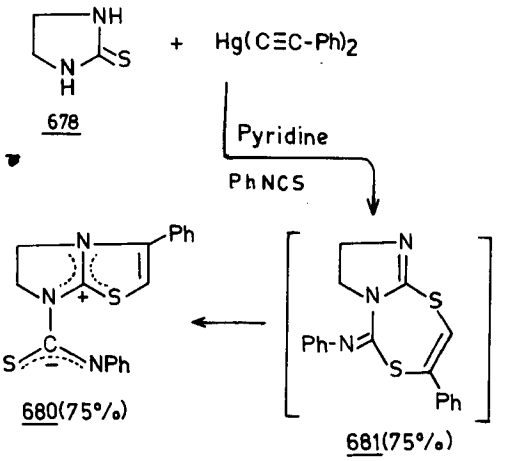
which depends on the nature of the substituents present in the 4-position of phenyl isothiocyanate[727] (Scheme 170).



Scheme 170

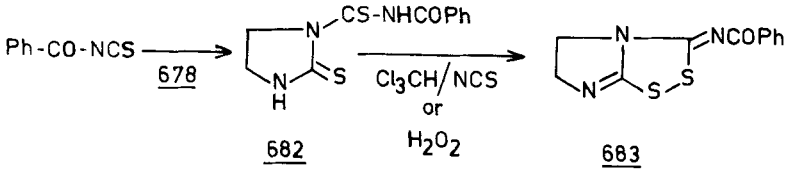
9. NON-BENZO BICYCLIC HETEROCYCLES

Treatment of imidazoline-2-thione **678** with mercury bis(phenylacetylide) **679** and phenyl isothiocyanate in pyridine affords either 3-phenyl-7-phenyl(thiocarbamoyl)-5,6-dihydroimidazolium betain **680**[728] which is probably formed via the intermediate 5-phenylimino-3-phenyl-5*H*-7,8-dihydroimidazo[2,1-*b*][1,5,3]dithiazepine **681**[729] (Scheme 171).



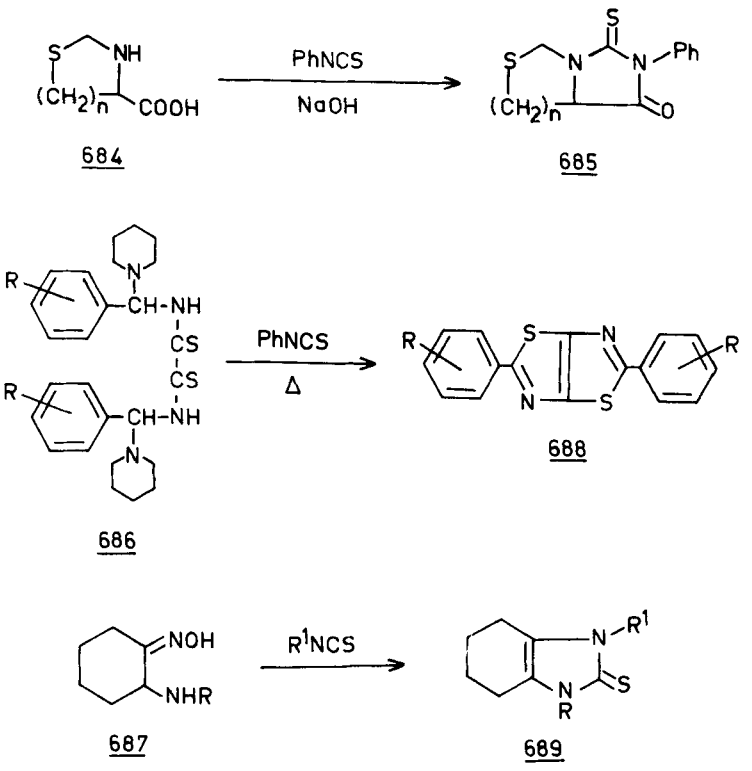
Scheme 171

Reaction of **678** with benzoyl isothiocyanate gives the thiourea **682** in 56% yield which may be oxidised with *N*-chlorosuccinimide or hydrogen peroxide to yield 3-benzoylimino-5,6-dihydro-3*H*-{imidazo[2,1-*c*][1,2,4]dithiazole} **683**[730] (Scheme 172).



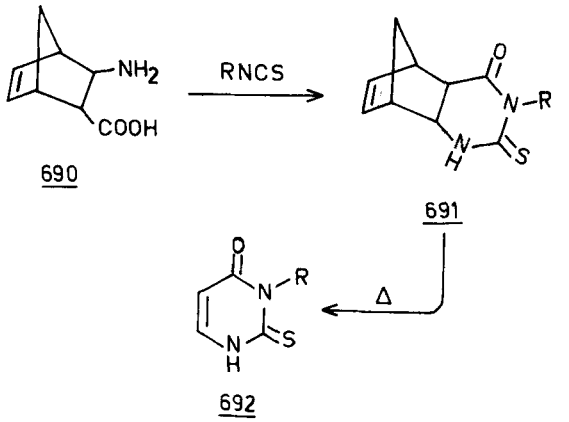
Scheme 172

α-Aminocarboxylic acid derivatives **684** may be cyclised with phenyl isothiocyanate to form **685** in high yields.[731] 2,5-Disubstituted thiazolo[5,4-*d*]thiazoles **688**[732] and 4,5,6,7-tetrahydrobenzimidazoline-2-thiones **689**[733] have also been prepared by cyclocondensation of **686** and **687**, respectively, with isothiocyanates (Scheme 173).



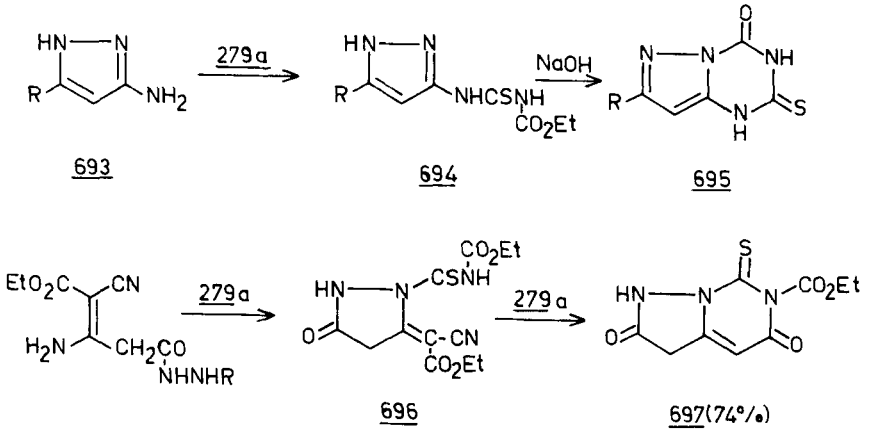
Scheme 173

β-Amino carboxylic acids such as the *endo*- and *exo*-norbornenes **690** also react with alkyl and aryl isothiocyanates to form condensed pyrimidines **691** which, on thermolysis, undergo a retro-Diels-Alder reaction to give the thiouracils **692**[734] (Scheme 174).



Scheme 174

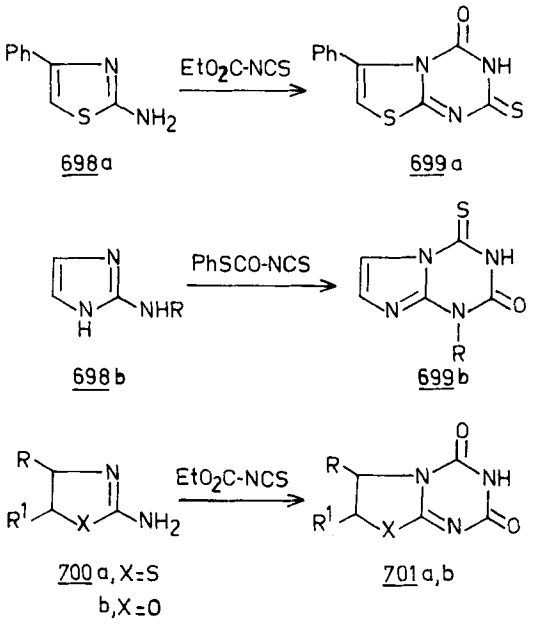
Various amino substituted heterocycles with an amino group α to a ring nitrogen react with isothiocyanates to form the corresponding thioureas which may be isolable or undergo spontaneous ring closure in the presence of base to afford a variety of fused heterocycles.[735-742] Thus, 3-aminopyrazoles **693** react with ethoxycarbonyl isothiocyanate **279a** to form the corresponding thioureas **694** which on treatment with alkali cyclise into pyrazolo[1,5-*a*]-1,3,5-triazines **695**.[735-737] A somewhat similar cyclisation occurs to give **697** when 3-[cyano(ethoxycarbonyl)methylene]-1-(ethoxycarbonylaminothiocarbonyl)-5-oxopyrazolidine **696** is treated with **279a**[738] (Scheme 175).



Scheme 175

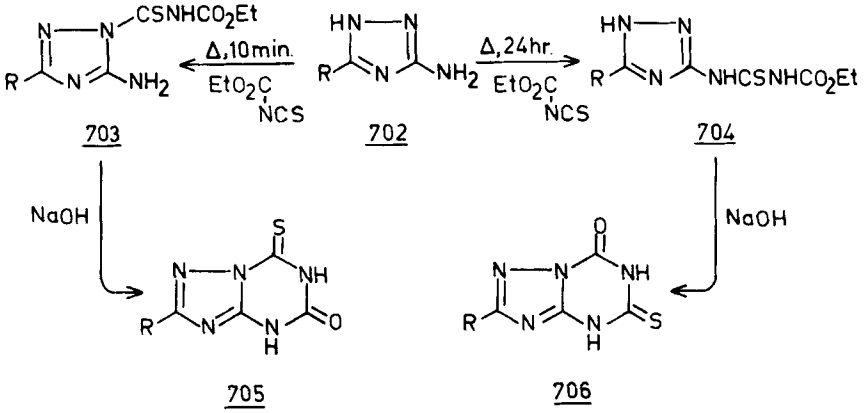
Reaction of the 2-aminothiazoles and 2-aminoimidazoles **698a,b** with ethoxycarbonyl isothiocyanate or *S*-phenyl isothiocyanatothioformate (PhS-CO-NCS), respectively,

affords the thiazolo[3,2-*a*]- and imidazo[1,3-*a*]-1,3,5-triazines **699a,b**.[739,740] Similarly, 2-aminothiazolines and -oxazolines **700a,b** form the 1,3,5-triazines **701a,b** when treated with ethoxycarbonyl isothiocyanate[741,742] (Scheme 176).



Scheme 176

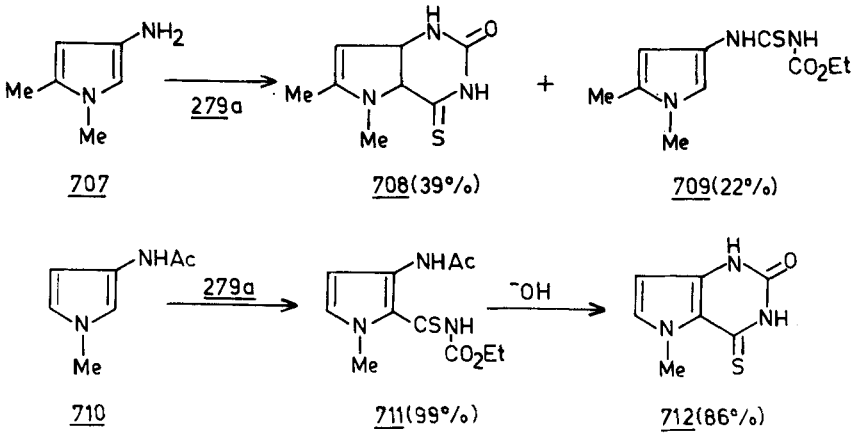
Treatment of the 3-amino-1,2,4-triazoles **702** with ethoxycarbonyl isothiocyanate gives two types of thioureas (**703** and **704**), depending upon the reaction conditions. Both of these thioureas may be cyclised with base to give the isomeric triazolotriazines **705** and **706**, respectively[743] (Scheme 177).



Scheme 177

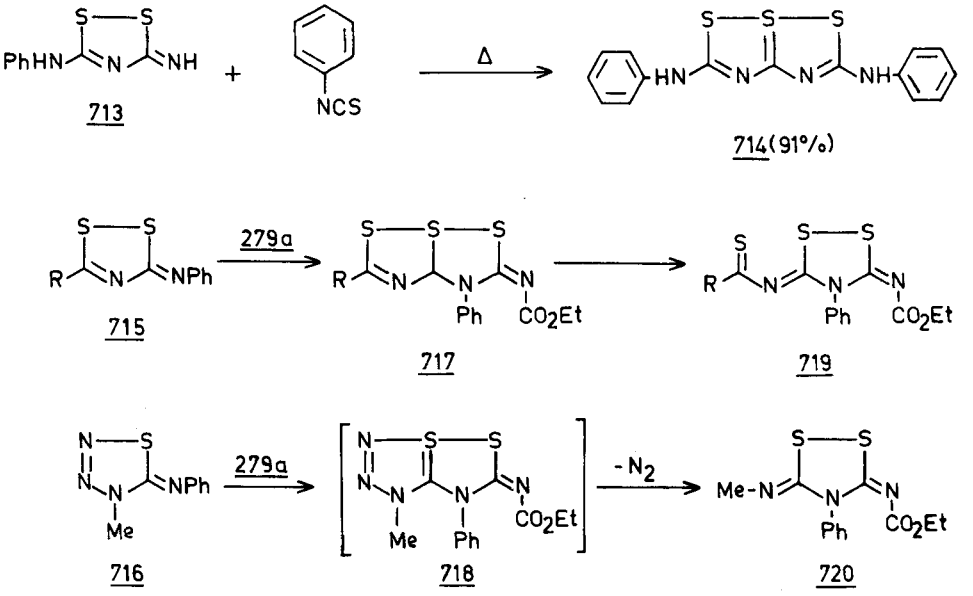
3-Amino-1,5-dimethylpyrrole **707** reacts with **279a** in THF to give a mixture of the bicycloheterocycle **708** and the thiourea **709**. However 3-acetylamino-1-methylpyrrole

710, when treated with ethoxycarbonyl isothiocyanate **279a**, gives the 3-acetylamino-1-methyl-2-(*N*-ethoxycarbonyl)thiocarboxamidopyrrole **711** which cyclises in the presence of base to form the pyrrolo[3,2-*d*]pyrimidine **712**[744] (Scheme 178).



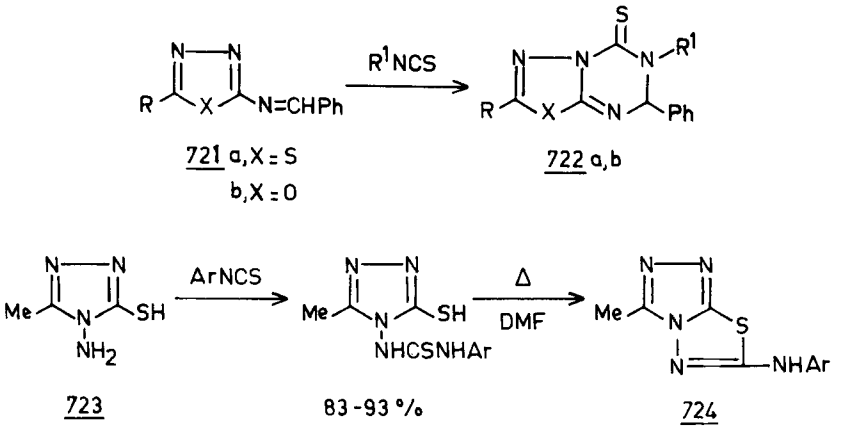
Scheme 178

Iminoheterocycles also react with reactive isothiocyanates to form different new heterocycles. Thus, treatment of phenylthiouret **713** with phenyl isothiocyanate at 140–150 °C affords the 1,2,4-dithiazole **714** in high yield.[745] However, later it was shown that reaction of the *N*-(phenylimino)heterocycles **715** and **716** with ethoxycarbonyl isothiocyanate gives rise to the 1,2,4-dithiazolidines **719** and **720** via initial formation of the bicyclic intermediates **717** and **718**, respectively[746–748] (Scheme 179).



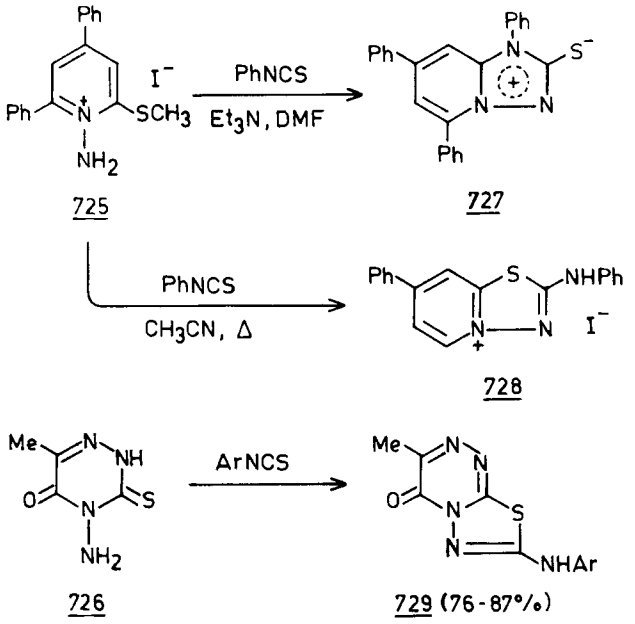
Scheme 179

2-(Benzylideneimino)thiadiazoles and -oxadiazoles **721a,b** may be allowed to react with aryl isothiocyanates to yield the 1,3,4-thia(oxa)diazolo[3,2-*a*]-*s*-triazine-5-(6*H*,7*H*)thiones **722a,b**.[749,750] 1-Amino-2-thioxotriazoline **723** can also be used to prepare the bicyclic compound **724** by reaction with aryl isothiocyanates[751] (Scheme 180).



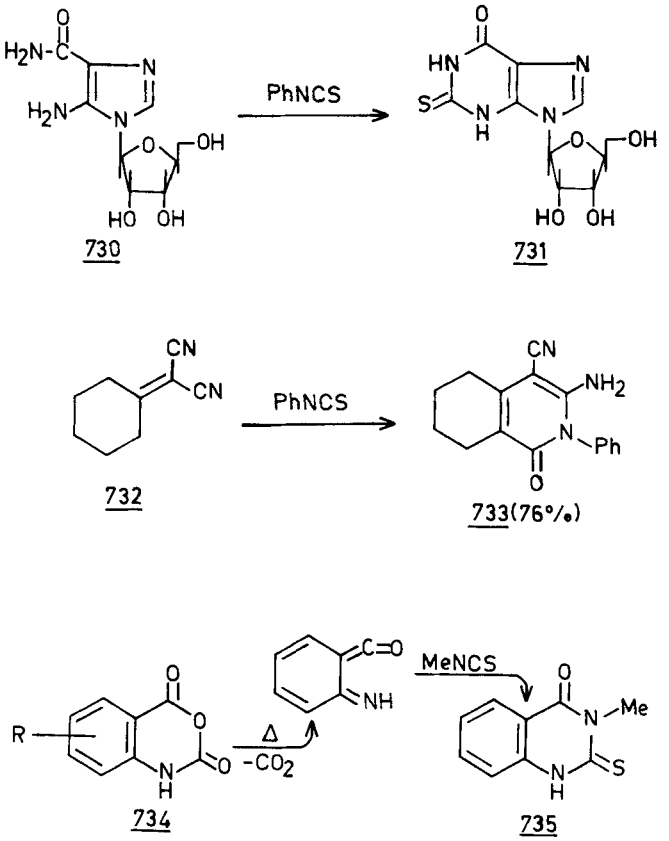
Scheme 180

Molina and coworkers[752-754] have treated 1-amino-2-methylthio-4,6-diphenylpyridinium iodide **725** and 1-aminotetrahydrotriazine **726** with aryl isothiocyanates to obtain various bicyclic nitrogen heterocycles **727–729** as shown in Scheme 181.



Scheme 181

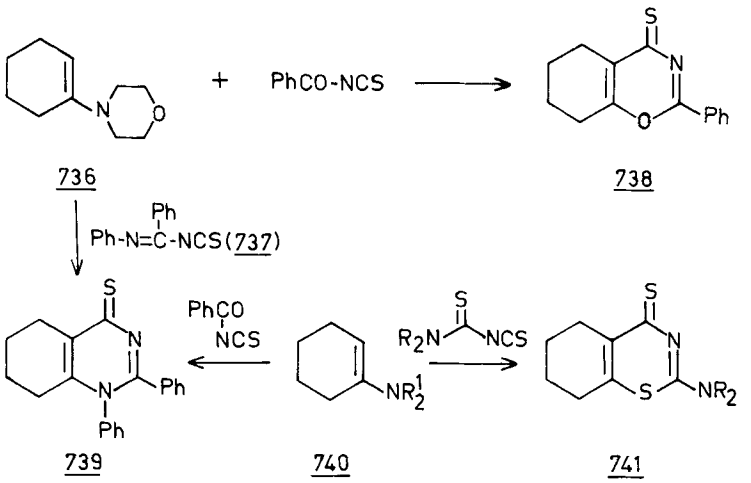
Phenyl isothiocyanate reacts with 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide **730** to yield 2-mercaptoinosine **731**.[755] A novel cyclisation occurs when cyclohexylidenemalononitrile **732** is treated with phenyl isothiocyanate, yielding the tetrahydroisoquinoline derivative **733**.[756] However, the tetrahydroquinazolone **735** has been obtained by treating isatoic anhydride **734** with methyl isothiocyanate[757] (Scheme 182).



Scheme 182

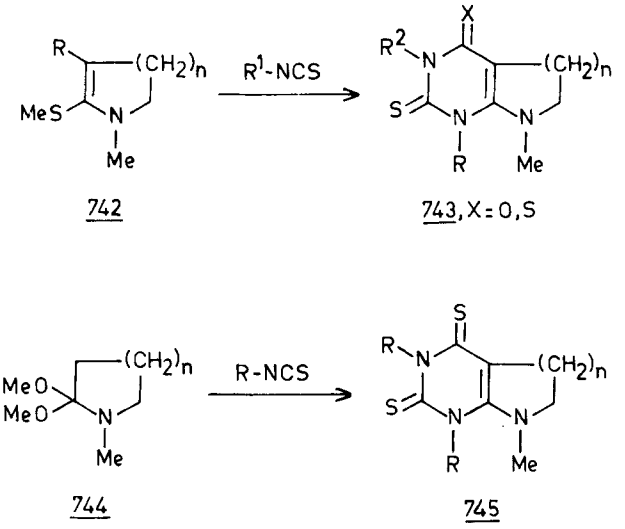
Enamines react with various isothiocyanates to afford different heterocycles. Thus, reaction of 1-morpholinocyclohexene **736** with benzoyl isothiocyanate **271** or *N*-phenylbenzimidoyl isothiocyanate **737** gives a tetrahydro-1,3-oxazine and a quinazolene (**738** and **739**), respectively.[758,759] Alternatively, **739** may also be prepared by treating 1-phenylaminocyclohexene (**740**) with benzoyl isothiocyanate.[758] Replacement of benzoyl

isothiocyanate by thiocarbamoyl isothiocyanates in the above reaction has been found to yield 2-aminotetrahydrobenzothiazin-4-ones **741**[467] (Scheme 183).



Scheme 183

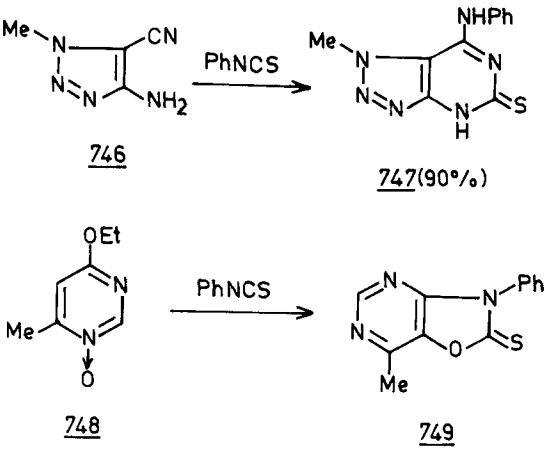
Ketene *N,S*-acetals **742**, representing activated lactams, react with aryl isothiocyanates to form the pyrimidine derivatives **743**.[760,761] The lactam acetals **744** also react with aryl isothiocyanates to afford the azacycloalkano[2,3-*d*]pyrimidines **745**[762] (Scheme 184).



Scheme 184

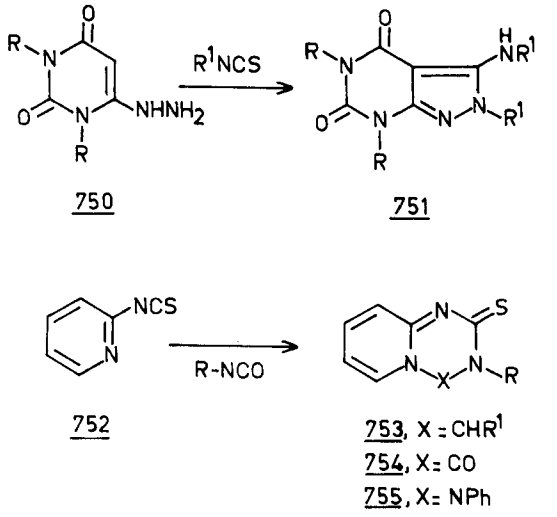
Treatment of 4-amino-5-cyano-1-methyl-1,2,3-triazole **746** with phenyl isothiocyanate yields 6-anilino-7-methyl-8-azapurine-2-thione **747** quantitatively.[763] Phenyl isoth-

iocyanate also reacts with 4-ethoxy-6-methylpyrimidine *N*-oxide **748** to form the unusual product **749**[764] (Scheme 185).



Scheme 185

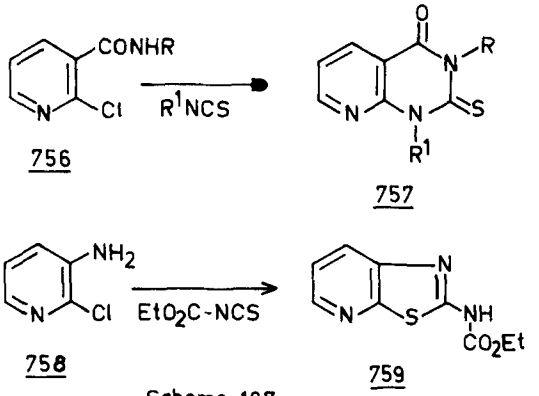
The 6-hydrazinouracils **750** undergo cyclocondensation to form the 3-alkyl/acylaminopyrazolo[3,4-*d*]pyrimidines **751** when treated with alkyl/acyl isothiocyanates.[765,766] A [4 + 2] cycloaddition takes place when 2-pyridyl isothiocyanate **752** is treated with an isocyanate resulting in the formation of the mixture **753–755**[767] (Scheme 186).



Scheme 186

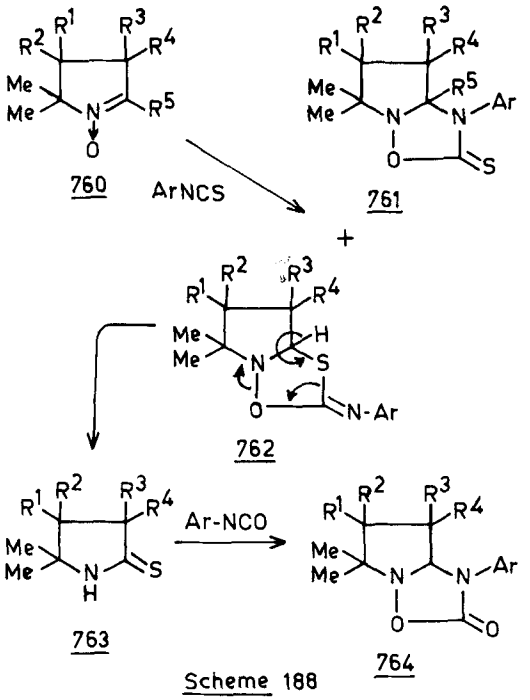
2-Chloropyridine-3-carboxamide **756** reacts with isothiocyanates to form the pyridopyrimidinethiones **757**[768] while the thiazolo[5,4-*b*]pyridine **759** is obtained by treat-

ment of 3-amino-2-chloropyridine **758** with ethoxycarbonyl isothiocyanate[769] (Scheme 187).



Scheme 187

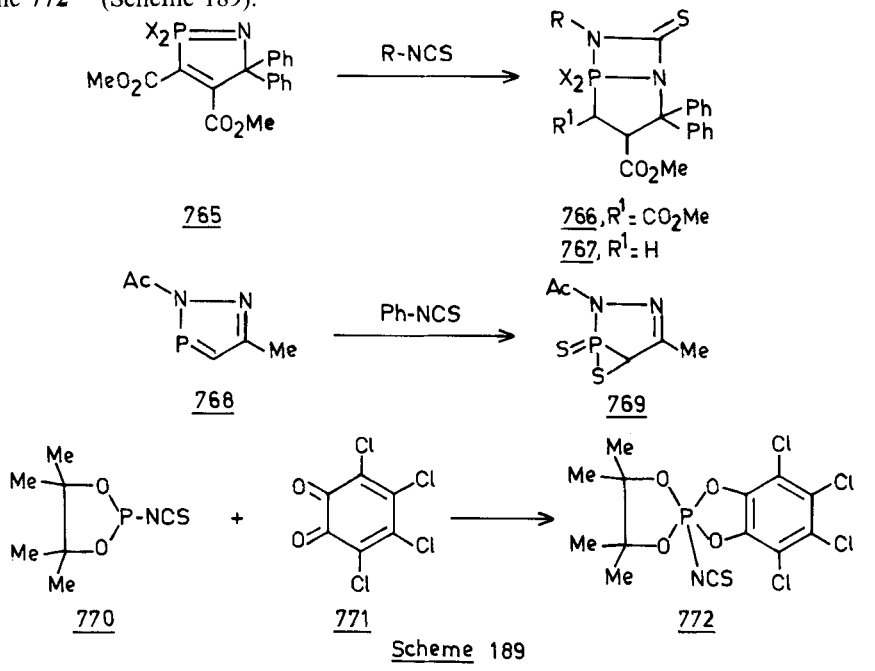
Reaction of 1-pyrroline 1-oxides **760** with aryl isothiocyanates affords either the 4-aryl-2-oxa-1,4-diazabicyclo[3.3.0]octane-3-thiones **761** or a mixture of **761** and the C=S adduct **762** which decomposes to the thiolactam **763** and an aryl isocyanate. The last two products may react to yield the 4-aryl-1,4-diazabicyclo[3.3.0]octan-2-ones **764**[631,634] (Scheme 188).



Scheme 188

Cycloaddition of isothiocyanates to azaphospholanes **765** gave the bicyclic phosphorus heterocycles **766** and **767**.[770] Reaction of 2-acetyl-5-methyl-1,2,3-diazaphosphole **768** with phenyl isothiocyanate affords **769**.[771] Treatment of *o*-chloranil **771** with the

2-isothiocyanato-1,3,2-dioxaphospholane **770** leads to the formation of the spirophosphorane **772**[772] (Scheme 189).

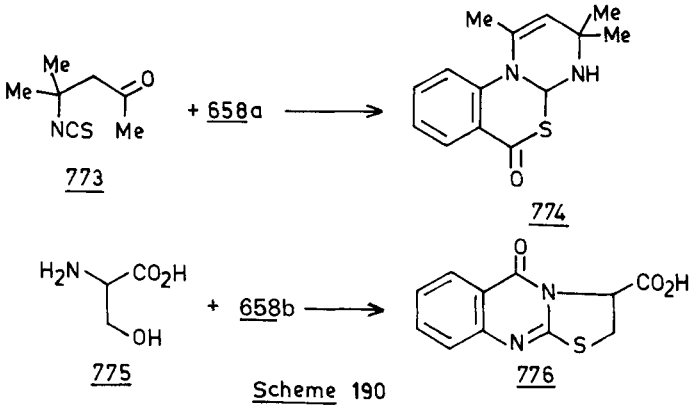


Scheme 189

10. POLYCYCLIC HETEROCYCLES

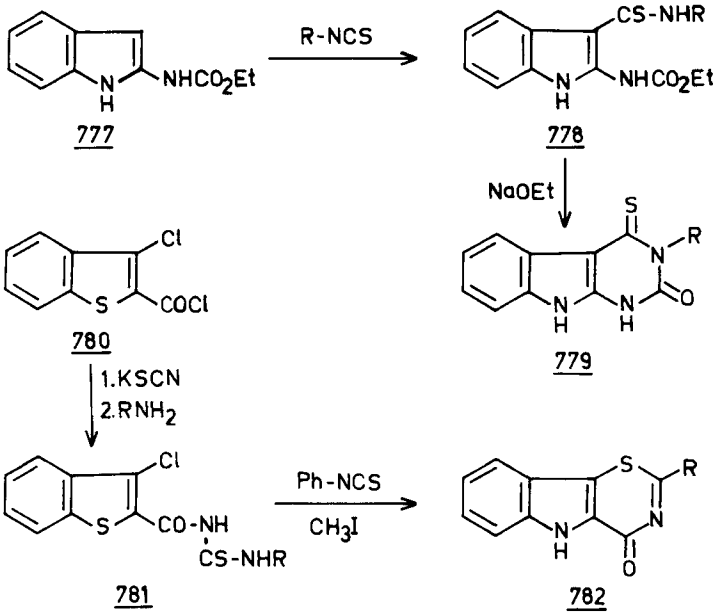
Polycyclic heterocycles are accessible by essentially the same chemistry as described in the synthesis of bicyclic benzo- and nonbenzoheterocycles (Sect. 8 and 9). The present section will, therefore, be restricted to the synthesis of representative polyheterocycles via isothiocyanate-induced cyclisations.

Reaction of anthranilic acid **658a** with 4-methyl-4-isothiocyanato-2-pentanone **773** gives the 3*H*,6*H*-pyrimido[1,2-*a*][3,1]benzothiazin-6-one **774** in 95% yield[773] while methyl anthranilate **658b** reacts with serine **775** with double cyclisation to form **776**[722] (Scheme 190).



Scheme 190

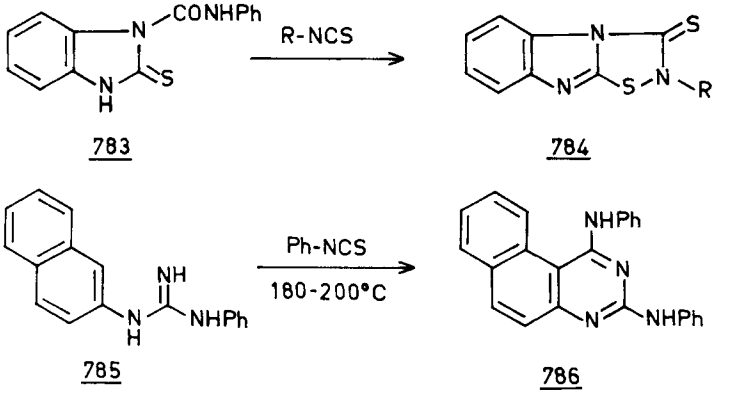
Condensation of 2-(carbethoxyamino)indole **777** with alkyl/aryl isothiocyanates gives the addition products **778** which may be cyclised in the presence of sodium ethoxide to yield the pyrimido[4,5-*b*]indoles **779**.[774] A thiourea **781**, obtained by successive treatment of 3-chlorobenzo[*b*]thiophene-2-carbonyl chloride **780** with potassium thiocyanate and an amine, can also be cyclised in the presence of phenyl isothiocyanate and methyl iodide to yield a mixture of the thiophene heterocycle **782** and an isothiourea[775] (Scheme 191).



777 778 779 780 781 782

Scheme 191

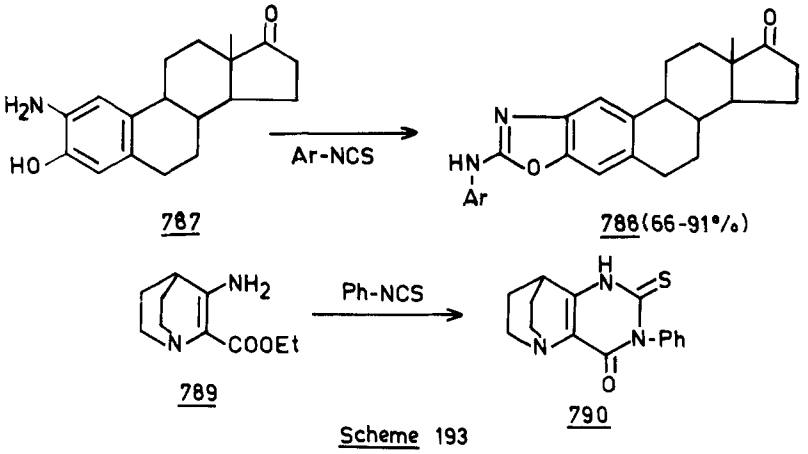
Condensation of 1-substituted benzimidazole-2-thiones **783** with isothiocyanates leads to the formation of the benzimidazolo[1,2-*d*][1,2,4]thiadiazolines **784**.[776] Cyclisation of *N*-naphthyl-*N*″-phenylguanidine **785** with phenyl isothiocyanate at higher temperatures also affords 2,4-bis(phenylamino)-5,6-benzoquinazoline **786**[776a] (Scheme 192).



783 784 785 786

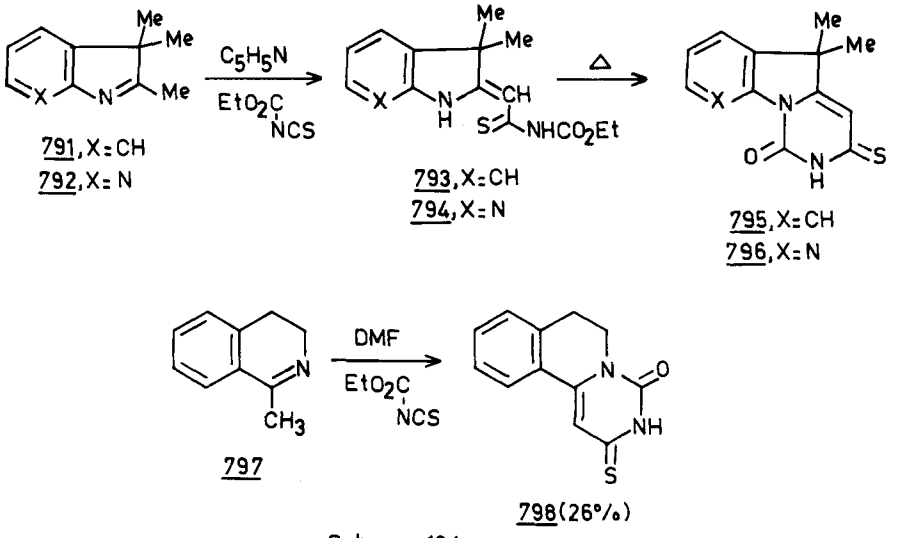
Scheme 192

2′-Organylamino-17-oxoestra-1(10),4-dieno[2,3-*d*]oxazoles **788** may be prepared conveniently and in high yield by treating 2-aminoestrone **787** with aryl isothiocyanates in the presence of DCC.[777] Reaction of 2-ethoxycarbonyl-3-amino-2,3-dehydroquinuclidine **789** with phenyl isothiocyanates gives the tricyclic quinazolone-containing heterocycle **790**[778] (Scheme 193).



Scheme 193

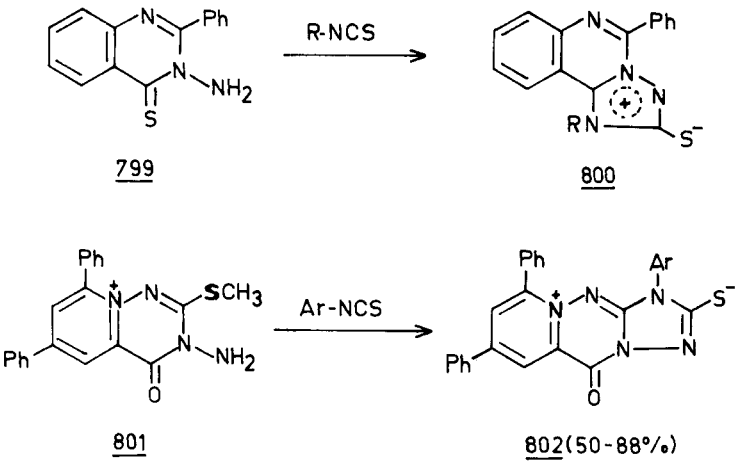
When 2,3,3-trimethylindolenine **791** and its 7-aza analog **792** are refluxed with ethoxycarbonyl isothiocyanate in pyridine or toluene formation of the tricyclic products **795** and **796** takes place, presumably by cyclisation of the intermediate thiocarbamates **793** and **794**, resepctively.[779-781] A similar cyclisation takes place when 1-methyl-3,4-dihydroisoquinoline **797** is treated with ethoxycarbonyl isothiocyanate in DMF in the presence of triethylamine at room temperature to yield **798**[781] (Scheme 194).



Scheme 194

Reaction of 3-amino-2-phenylquinazolone-4-thione **799** with isothiocyanates gives the 1,3,4-triazolo[3,2-*c*]quinazolines **800**[782] while cyclisation of the dihydropyridotriazi-

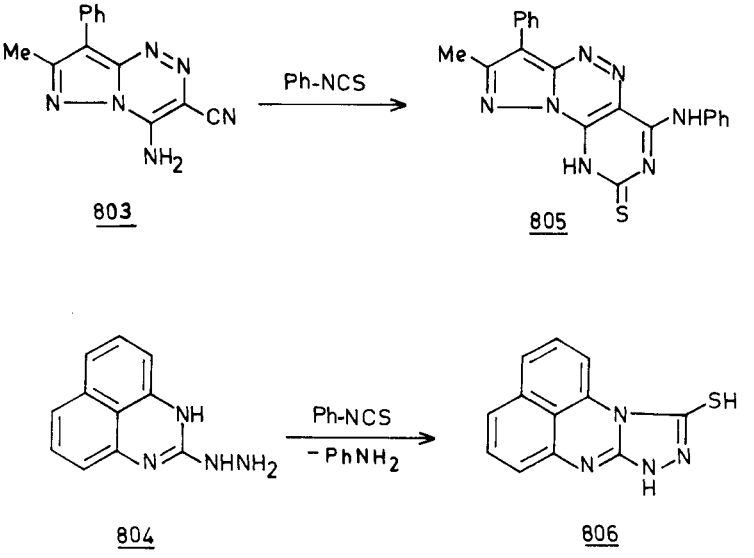
nium cation **801** with aryl isothiocyanates leads to the synthesis of the pyridotriazinotriazoles **802**[783] (Scheme 195).



799 800 801 802(50-88%)

Scheme 195

The aminoheterocycles **803** and **804** undergo smooth cyclisation to form the polycyclic nitrogen heterocycles **805** and **806**, respectively, when treated with phenyl isothiocyanate[784,785] (Scheme 196).

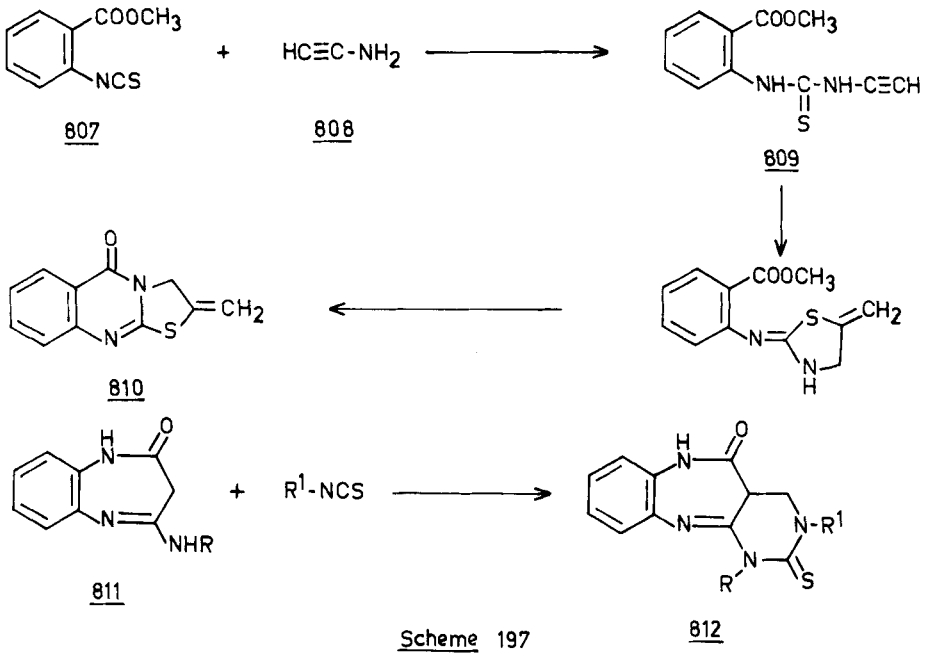


803 805 804 806

Scheme 196

Condensation of methyl 2-isothiocyanatobenzoate **807** with propargylamine **808** gives the desired thiourea **809** which may finally be cyclised to 2-methylene-5-oxo-5*H*-1,3-

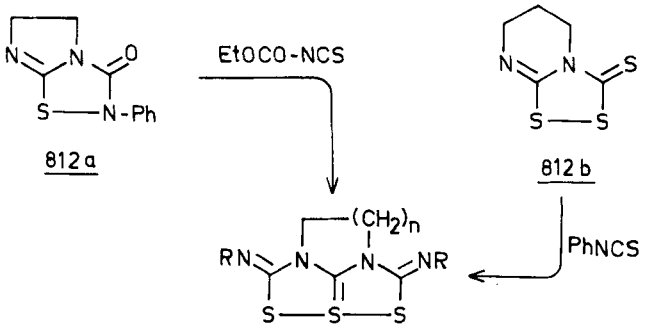
thiazolo[2,3-*b*]quinazol-4-one **810**.[786] Aminobenzodiazepinones **811** also react with DMF and an isothiocyanate to give 1*H*-pyrimido[4,5-*d*][1,5]benzodiazepines **812**[787] (Scheme 197).



807 808 809 810 811 812

Scheme 197

Reaction of imidazodithiazoles and pyrimidinodithiazoles **812a,b** with ethoxycarbonyl isothiocyanate and phenyl isothiocyanate leads to the formation of the novel heteropentalenes **813a,b**[788,789] (Scheme 198).



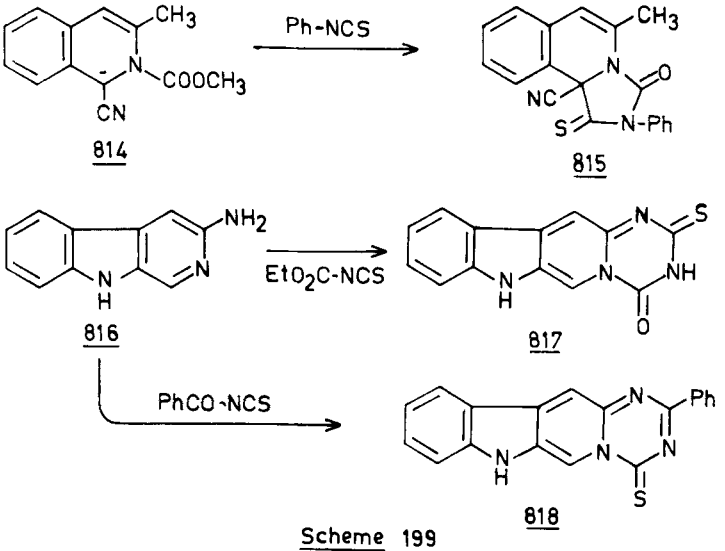
812a 812b

813a, R = COOEt; n = 1
b, R = Ph; n = 2

Scheme 198

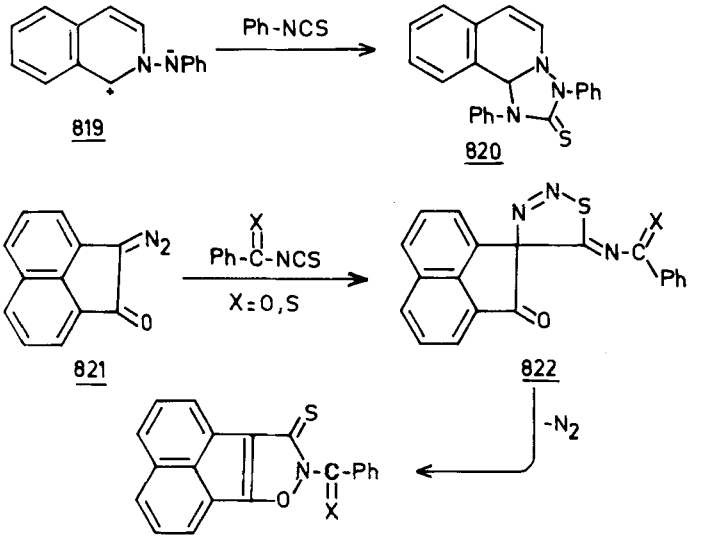
A new synthesis of imidazo[5,1-*a*]isoquinolines **815** has been reported by reaction of the anion **814** of *N*-methoxycarbonyl-3-methyl-1,2-dihydroisoquinoline-1-carbonitrile with phenyl isothiocyanate.[790] It was also possible to prepare the triazinopyridoin-

dolethiones **817** and **818** by cyclisation of 3-amino-9*H*-pyrido[3,4-*b*]indole **816** with ethoxycarbonyl and benzoyl isothiocyanate, respectively[791] (Scheme 199).



Scheme 199

Azomethineimines such as isoquinoline-*N*-phenylimine **819** exhibit high reactivity towards isothiocyanates and cyclise to form 1:1 adducts such as **820**.[792] *β*-Keto diazo compounds such as **821** also react with benzoyl or thiobenzoyl isothiocyanate to give the corresponding thiadiazoline derivatives **822** which eliminate nitrogen and recyclise to form 8-benzoyl- or -thiobenzoylacenaphtho[1,2]-Δ^4-isoxazoline-9-thione **823**[793] (Scheme 200).



Scheme 200

11. CONCLUSION

The present review clearly demonstrates the great synthetic versatility of alkyl, aryl, acyl and other isothiocyanates in organic and organometallic chemistry. The fact that several good and convenient methods are now available to prepare various isothiocyanates on a laboratory scale further increases the potential of this class of reagents in the construction of a diversified array of organic heterocycles. Consequently, many classes of five- and six-membered nitrogen and sulfur heterocycles, either carrying various substituents or fused with benzo or non-benzo nuclei to interesting polyheterocycles, have been synthesized from isothiocyanates which is undoubtedly a landmark in organosulfur chemistry.

Although a large variety of organic heterocycles have been synthesized with isothiocyanates as the cyclising agent, the synthetic applicability of these reagents has been marred by the lack of proper chemotherapeutic evaluation of the compounds surveyed in the present article. The author is of the view that the compounds prepared by isothiocyanate heterocyclisations have a promising potential in medicinal chemistry. Thus these five- and six-membered heterocycles and their corresponding fused benzo-derivatives deserve a broader biological evaluation, especially in the area of chemotherapy of parasitic diseases. The small-ring compounds such as three-membered sulfur heterocycles and polyheterocycles may find use in cancer chemotherapy and should be evaluated for their anticancer activity. Thus, a proper blend of synthesis and biological screening would not only lead to the fruitful use of these organosulfur compounds, but will also add new dimensions to the chemistry of isothiocyanates.

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