The Chemistry of Cyanates and their Thio Derivatives
Edited by Saul Patai

The chemistry of cyanates and their thio derivatives

Part 2

Edited by

SAUL PATAI

The Hebrew University, Jerusalem

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Foreword

The present volume, "The Chemistry of Cyanates and their Thio Derivatives" includes material on cyanates, isocyanates, thiocyanates and isothiocyanates as well as on isocyanate dihalides and on selenocyanates and related compounds. The volume is organized on the same general lines as the other volumes of "The Chemistry of Functional Groups" series, and which are described in the "Preface to the Series" appearing on the following pages.

For once, all the chapters included in the original plan of the volume materialized. Hence omissions, if any, this time are solely the responsibility of the Editor.

The chapters have been commissioned for this volume in the Spring of 1974, and were mostly delivered between March and August 1975. In most cases the literature coverage of the chapters is therefore roughly up to the Spring of 1975.

Jerusalem, June 1976 SAUL PATAI

The Chemistry of Functional Groups Preface to the series

The series 'The Chemistry of Functional Groups' is planned to cover in each volume all aspects of the chemistry of one of the important functional groups in organic chemistry. The emphasis is laid on the functional group treated and on the effects which it exerts on the chemical and physical properties, primarily in the immediate vicinity of the group in question, and secondarily on the behaviour of the whole molecule. For instance, the volume *The Chemistry of the Ether Linkage* deals with reactions in which the C—O—C group is involved, as well as with the effects of the C—O—C group on the reactions of alkyl or aryl groups connected to the ether oxygen. It is the purpose of the volume to give a complete coverage of all properties and reactions of ethers in as far as these depend on the presence of the ether group but the primary subject matter is not the whole molecule, but the C—O—C functional group.

A further restriction in the treatment of the various functional groups in these volumes is that material included in easily and generally available secondary or tertiary sources, such as Chemical Reviews, Quarterly Reviews, Organic Reactions, various 'Advances' and 'Progress' series as well as textbooks (i.e. in books which are usually found in the chemical libraries of universities and research institutes) should not, as a rule, be repeated in detail, unless it is necessary for the balanced treatment of the subject. Therefore each of the authors is asked *not* to give an encyclopaedic coverage of his subject, but to concentrate on the most important recent developments and mainly on material that has not been adequately covered by reviews or other secondary sources by the time of writing of the chapter, and to address himself to a reader who is assumed to be at a fairly advanced post-graduate level.

With these restrictions, it is realized that no plan can be devised for a volume that would give a *complete* coverage of the subject with *no* overlap between chapters, while at the same time preserving the readability of the text. The Editor set himself the goal of attaining *reasonable* coverage with *moderate* overlap, with a minimum of cross-references between the chapters of each volume. In this manner, sufficient freedom is given to each author to produce readable quasi-monographic chapters.

The general plan of each volume includes the following main sections:

(a) An introductory chapter dealing with the general and theoretical aspects of the group.

(b) One or more chapters dealing with the formation of the functional group in question, either from groups present in the molecule, or by introducing the new group directly or indirectly.

(c) Chapters describing the characterization and characteristics of the functional groups, i.e., a chapter dealing with qualitative and quantitative methods of determination including chemical and physical methods, ultraviolet, infrared, nuclear magnetic resonance and mass spectra; a chapter dealing with activating and directive effects exerted by the group and/or a chapter on the basicity, acidity or complex-forming ability of the group (if applicable).

(d) Chapters on the reactions, transformations and rearrangements which the functional group can undergo, either alone or in conjunction with other reagents.

(e) Special topics which do not fit any of the above sections, such as photochemistry, radiation chemistry, biochemical formations and reactions. Depending on the nature of each functional group treated, these special topics may include short monographs on related functional groups on which no separate volume is planned (e.g. a chapter on 'Thioketones' is included in the volume *The Chemistry of the Carbonyl Group*, and a chapter on 'Ketenes' is included in the volume *The Chemistry of Alkenes*). In other cases, certain compounds, though containing only the functional group of the title, may have special features so as to be best treated in a separate chapter, as e.g. 'Polyethers' in *The Chemistry of the Ether Linkage*, or 'Tetraaminoethylenes' in *The Chemistry of the Amino Group*.

This plan entails that the breadth, depth and thought-provoking nature of each chapter will differ with the views and inclinations of the author and the presentation will necessarily be somewhat uneven. Moreover, a serious problem is caused by authors who deliver their manuscript late or not at all. In order to overcome this problem at least to some extent, it was decided to publish certain volumes in several parts, without giving consideration to the originally planned logical order of the chapters. If after the appearance of the originally planned parts of a volume it is found that either owing to non-delivery of chapters, or to new developments in the subject, sufficient material has accumulated for publication of a supplementary volume, containing material on related functional groups, this will be done as soon as possible.

The overall plan of the volumes in the series 'The Chemistry of Functional Groups' includes the titles listed below:

The Chemistry of Alkenes (two volumes)
The Chemistry of the Carbonyl Group (two volumes)
The Chemistry of the Ether Linkage
The Chemistry of the Amino Group
The Chemistry of the Nitro and Nitroso Groups (two parts)
The Chemistry of Carboxylic Acids and Esters
The Chemistry of the Carbon–Nitrogen Double Bond
The Chemistry of the Cyano Group
The Chemistry of Amides
The Chemistry of the Hydroxyl Group (two parts)
The Chemistry of the Azido Group
The Chemistry of Acyl Halides
The Chemistry of the Carbon–Halogen Bond (two parts)
The Chemistry of Quinonoid Compounds (two parts)
The Chemistry of the Thiol Group (two parts)
The Chemistry of Amidines and Imidates
The Chemistry of the Hydrazo, Azo and Azoxy Groups (two parts)
The Chemistry of Cyanates and their Thio Derivatives (two parts)
Supplement A: The Chemistry of Double-Bonded Functional Groups (two parts)

Titles in press:
The Chemistry of the Diazonium and Diazo Groups
The Chemistry of the Carbon–Carbon Triple Bond
Supplement B: The Chemistry of Acid Derivatives

Future volumes planned include:
The Chemistry of Cumulenes and Heterocumulenes
The Chemistry of Organometallic Compounds
The Chemistry of Sulphur-containing Compounds
Supplement C: The Chemistry of Triple-Bonded Functional Groups
Supplement D: The Chemistry of Halides and Pseudo-halides
Supplement E: The Chemistry of $-NH_2$, $-OH$, and $-SH$ Groups and their Derivatives

Advice or criticism regarding the plan and execution of this series will be welcomed by the Editor.

The publication of this series would never have started, let alone continued, without the support of many persons. First and foremost among these is Dr. Arnold Weissberger, whose reassurance and trust

encouraged me to tackle this task, and who continues to help and advise me. The efficient and patient cooperation of several staff-members of the Publisher also rendered me invaluable aid (but unfortunately their code of ethics does not allow me to thank them by name). Many of my friends and colleagues in Israel and overseas helped me in the solution of various major and minor matters, and my thanks are due to all of them, especially to Professor Z. Rappoport. Carrying out such a long-range project would be quite impossible without the non-professional but none the less essential participation and partnership of my wife.

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CHAPTER 17

Syntheses and preparative applications of isocyanates

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I. INTRODUCTION

Isocyanates are esters of isocyanic acid, and the first member of this class of compounds was synthesized by Wurtz in 1848. Shortly thereafter several prominent nineteenth century scientists, such as Hofmann and Curtius, systematically investigated the chemistry of isocyanates. Although many of the standard reactions of isocyanates were discovered in the early investigations, it took almost a century until it was recognized by Bayer and his coworkers in 1937 that diisocyanates are ideally suited for preparing polymers by a simple polyaddition reaction. The pioneering work on polyurethanes, the polymers derived from diisocyanates and diols, was conducted at the laboratory of I. G. Farbenindustrie in Leverkusen, Germany, and after a long delay caused by the Second World War, rapid growth of the polyurethane market was observed. The anticipated production of polyurethanes in the U.S. by 1976 is over 2 billion pounds. While the majority of polymers are based on a narrow range of chemical intermediates, polyurethanes can be made from numerous types of raw materials, making possible the manufacture of polymers with an extremely broad range of properties.

Approximately 90% of the total world production of di- and polyisocyanates is accounted for by two products, tolylene diisocyanate (TDI) and diphenylmethane diisocyanate (MDI). The U.S. market value of the two diisocyanates is in excess of 200 million dollars annually. Numerous polyester and polyether based diols are used in the manufacture of polyurethane products. This versatility allows formulation of products ranging from hard rigid foams to soft thermoplastic elastomers.

Some of the basic aromatic diisocyanates are converted on a commercial scale into derived products containing residual isocyanate groups. For example, tolylene diisocyanate is trimerized and sold as a solvent solution, and hexamethylene diisocyanate is converted into a substituted biuret.

Reaction with a deficient amount of a diol produces non-volatile carbamates containing terminal isocyanate groups (prepolymers).

Monoisocyanates are also produced in commercial quantities as intermediates for the manufacture of derived end products. The isocyanate derivatives, mainly carbamates and ureas, are used in the production of herbicides and crop protection agents. Long chain aliphatic monoisocyanates are used for surface treatment of textiles and *n*-butyl isocyanate and *p*-toluenesulphonyl isocyanate are used in the manufacture of antidiabetic drugs.

The reactivity of isocyanates has generated considerable interest in synthetic organic chemistry. While new examples of addition to active-hydrogen-containing substrates are constantly uncovered, considerable research in recent years has been conducted in the area of cycloaddition reactions of isocyanates. For example reactions with C=N double bond containing substrates are used for convenient interconversions of isocyanates (exchange of R groups). The so-called insertion reactions of isocyanates, i.e. reaction with activated single bonds, are used to prepare novel adducts.

Stable isocyanates, having the isocyanate group attached to elements other than carbon, have become available in recent years, and silicon, phosphorus and sulphur isocyanates are important chemical intermediates. An increase in reactivity of these isocyanates toward nucleophilic addition reactions is usually observed. For example arenesulphonyl isocyanates react rapidly at room temperature with water to produce arenesulphonamides and carbon dioxide gas. We have utilized this reaction for rapid drying of organic solvents. The hydrogen atom of the NH group in sulphonyl carbamates is acidic, and therefore water-soluble salts can be formed on neutralization with inorganic or organic bases. This fact can be utilized for the solubilization of polymers in aqueous systems.

In summary, isocyanates are a fascinating class of compounds which have found wide-ranging applications in organic and polymer chemistry. Their commercial success is unparalleled in the short history of the plastics industry.

II. SYNTHESIS OF ISOCYANATES

A. Alkyl and Aryl Isocyanates

1. Phosgenation of amines, imines, carbamates and ureas

The phosgenation of arylamines to produce isocyanates was first reported by Hentschel in 1884[1], and several years later Gattermann[2]

extended this reaction to aliphatic amine hydrochlorides. The initial reaction of amines with excess phosgene gives carbamoyl chlorides (**1**), which, upon heating above 50 °C, eliminate hydrogen chloride to yield the isocyanates (**2**).

$$2\ RNH_2 + COCl_2 \longrightarrow RNHCOCl + RNH_2 \cdot HCl \qquad (1)$$

$$RNHCOCl \longrightarrow RN{=}C{=}O + HCl \qquad (2)$$

The by-product, amine hydrochloride, is converted at elevated temperature with excess phosgene to isocyanate as the sole reaction product. In order to prevent reaction of the generated isocyanate with starting amine to produce 1,3-disubstituted ureas, several methods are used. The 'free base' phosgenation involves addition of the amine, dissolved in an inert diluent, to excess phosgene collected in the same diluent. The diluent is necessary because of formation of a slurry of the solid carbamoyl chloride and amine hydrochloride. The reaction mixture is slowly heated above the decomposition temperature of the carbamoyl chloride (50–70 °C) and the amine hydrochloride is converted with excess phosgene above 100 °C, usually at the reflux temperature of the solvent. The appearance of a clear solution signals the end of the reaction. However long-chain alkyl amine hydrochlorides are quite soluble and infrared techniques are used to monitor the progress of reaction.

In an alternative procedure the free amine is first treated with hydrogen chloride or carbon dioxide to form a slurry of the corresponding amine salts, which are subsequently phosgenated above 100 °C. This method has the disadvantage that the gaseous phosgene reacts only very slowly with the suspended amine salt. While less basic amine hydrochlorides, which are appreciably dissociated above 100 °C into free amine and hydrogen chloride, are converted quite rapidly, exceedingly long reaction times are required for aliphatic diamine dihydrochlorides. ω-Chloroalkylene isocyanates are by-products, especially if the reaction is conducted above 150 °C[3,4]. Since the monofunctional isocyanates are difficult to remove by fractional distillation their formation has to be minimized in order to produce a polymer grade diisocyanate.

In a recently-reported new method we have converted the amine first with thionyl chloride to the corresponding *N*-sulphinylamine (**3**) and in the subsequent phosgenation of **3** the isocyanate is formed in high yield[5]. In this reaction step the thionyl chloride is regenerated. This method has the advantage that the amine hydrochloride is rapidly converted with

thionyl chloride, and that the phosgenation of the soluble *N*-sulphinylamines (**3**) proceeds rapidly in the presence of a catalytic amount of pyridine or *N*,*N*-dimethylformamide. In the absence of the catalyst no reaction occurs.

$$RNH_2 + SOCl_2 \longrightarrow RN{=}S{=}O + 2\,HCl$$

(**3**)

$$RN{=}S{=}O + COCl_2 \longrightarrow RN{=}C{=}O + SOCl_2$$

The solvents most commonly used in phosgenation reactions include benzene, toluene, xylenes, halobenzenes, halonaphthalenes and, occasionally, more-polar solvents such as acetates, dioxane, nitrobenzene and dimethyl sulphone are used. The highly polar solvents, such as dimethylsulphoxide (DMSO), *N*,*N*-dimethylformamide (DMF) and hexamethylphosphoramide (HMPA) are not suitable as diluents because of rapid reaction with phosgene. Recently the use of an aqueous organic solvent system in the presence of sodium hydroxide to neutralize the hydrogen chloride, has been described[6]. However this modification is not advantageous from a commercial point of view because the generated hydrogen chloride is usually collected and sold as a by-product while sodium chloride is difficult to discard.

The reaction of amine hydrochlorides with phosgene is reported as being catalysed by tertiary amines[7], metal halides[8] and boron trifluoride[9]. The value of these catalysts is limited because they also catalyse the cyclotrimerization of isocyanates. The Lewis acid catalysts would also tend to catalyse the electrophilic reaction of the isocyanato group with the solvent. Better catalysts for the phosgenation of aromatic amine hydrochlorides are tetramethylurea, tetramethylphenylguanidine and *N*,*N*-dimethylformamide[10]. In these cases the effective catalysts are iminium chlorides, which are generated by the rapid reaction of the catalysts with phosgene[11].

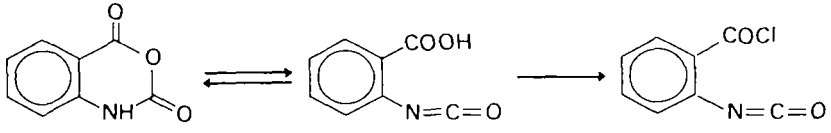
The aliphatic or aromatic structure can be substituted by a variety of groups which are non-reactive with phosgene (halo, cyano, nitro, alkoxy carboalkoxy, etc.)[12]. However ether cleavage has been observed in the phosgenation of short chain ether and thioether group containing alkyl amines[4].

If the aliphatic or aromatic moiety contains groups which react with phosgene, clean conversion of the attached groups often occurs also. For example, phosgenation of a variety of aminoalkylcarboxylic acids (**4**) in dioxane produced the corresponding isocyanatoalkylcarboxylic acid chlorides (**5**) in fair-to-good yield[13].

$$H_2N(CH_2)_nCOOH \xrightarrow{COCl_2} OCN(CH_2)_nCOCl$$

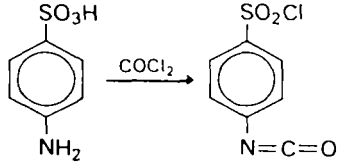
(4) (5)

Likewise aromatic aminocarboxylic acids are converted to isocyanatoaryl carboxylic acid chlorides provided the substituents are not *ortho* to each other. The reaction is considerably facilitated if a catalytic amount of *N*,*N*-dimethylformamide is used. Isatoic anhydride (**6**) is in equilibrium with 2-isocyanatobenzoic acid (**7**) and therefore phosgenation to the corresponding carboxylic acid chloride (**8**) is readily accomplished, again using *N*,*N*-dimethylformamide as the catalyst[14].



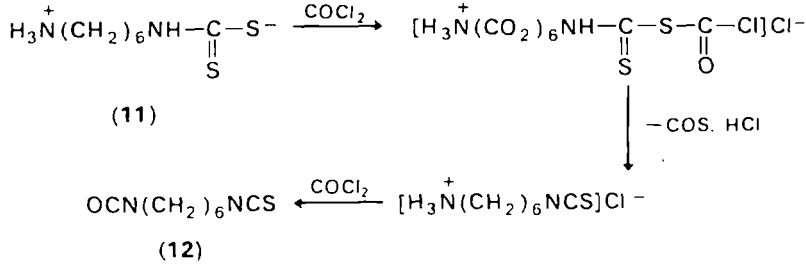
(6) (7) (8)

Arenesulphonic acids are also readily converted to isocyanatoarenesulphonyl chlorides. For example sulphanilic acid (**9**) affords isocyanatobenzenesulphonyl chloride (**10**) in high yield[15].



(9) (10)

Isothiocyanatoalkyl isocyanates are obtained from the phosgenation of a mixture of alkylenediamines and carbon disulphide. For example, hexamethylenediamine adds carbon disulphide to produce the thiocarbamate **11**, which upon reaction with phosgene yields 6-isothiocyanatohexamethylene isocyanate (**12**)[16].



(11) (12)

Sometimes a more reactive group can be converted selectively with phosgene, thereby producing an isocyanate having an attached group which could undergo further reaction with either the isocyanato group or phosgene. 2,4,6-Tribromo-*m*-phenylenediamine can be phosgenated selectively, giving 2,4,6-tribromo-3-aminophenyl isocyanate as the main product[17].

Likewise 2,6-disubstituted aminophenols are readily converted into the corresponding substituted isocyanatophenols[18]. Surprisingly even the unsubstituted *m*- and *p*-aminophenol can be selectively phosgenated to the corresponding isocyanatophenols[19]. Upon attempted isolation of the unsubstituted isocyanatophenol from the solvent, homopolymerization is observed. The monomeric isocyanatophenol can be regenerated upon heating of the homopolymer[19]. If aminophenols are phosgenated for prolonged periods of time above 100 °C, preferentially in the presence of *N*,*N*-dimethylformamide as the catalyst, isocyanatoaryl chloroformates are obtained[20]. In Table 1 the reaction products obtained in the phosgenation of reactive group containing substrates, are listed.

TABLE 1. Reaction products obtained in the phosgenation of substrates containing reactive groups

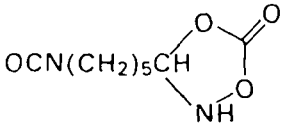
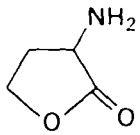
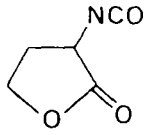
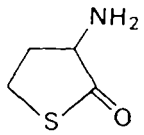
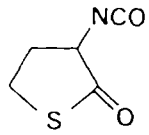
Substrate	Product	Reference
$H_2N(CH_2)_nCOOH$	$OCN(CH_2)_nCOCl$	13
$H_2N(CH_2)_5CONHOH$		45
	$OCN(CH_2)_5NCO$	46
$H_3\overset{+}{N}(CH_2)_nNHCSS^-$	$OCN(CH_2)_nNCS$	16
		21
		32

TABLE I (*cont.*). Reaction products obtained in the phosgenation of substrates containing reactive groups

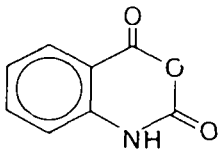
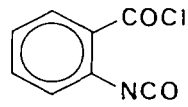
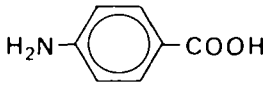
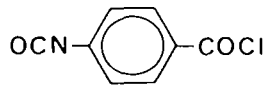
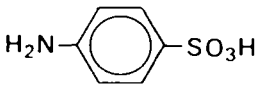
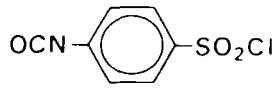
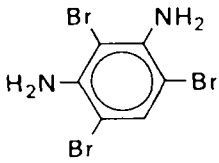
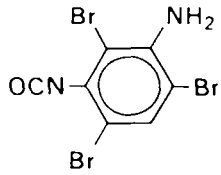
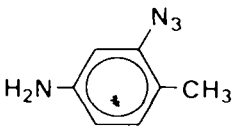
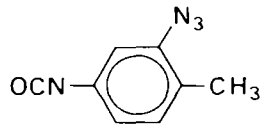
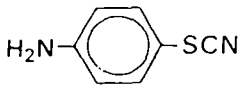
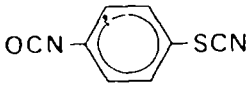
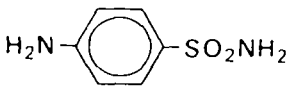
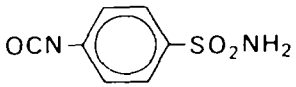
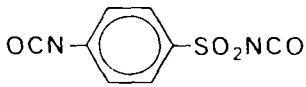
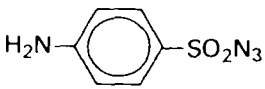
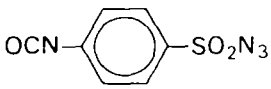
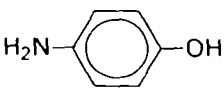
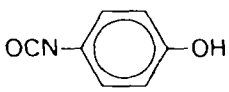
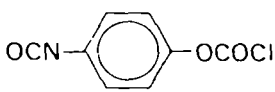
Substrate	Product	Reference
		14
		13
		15
		17
		22

TABLE 1 (*cont.*). Reaction products obtained in the phosgenation of substrates containing reactive groups

Substrate	Product	Reference
		53
		23
		
		24
		19
		20

The phosgenation of secondary amines yields secondary carbamoyl chlorides, which are stable compounds. However some secondary carbamoyl chlorides can be readily converted to isocyanates. For example, *t*-butylalkylcarbamoyl chlorides (**13**) are thermolysed above 120°C to produce an isocyanate, isobutylene and hydrogen chloride[25].

$$(CH_3)_3CN(COCl)R \xrightarrow{\Delta} RNCO + (CH_3)_2C{=}CH_2 + HCl$$

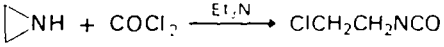
(**13**)

Also 4-isocyanatobenzylphenylcarbamoyl chloride (**14**) reacts with hydrogen chloride at elevated temperatures to produce phenyl (**15**) and 4-chloromethylphenyl isocyanate (**16**)[26].

$$4\text{-}OCNC_6H_4CH_2NC_6H_5(COCl) \xrightarrow{HCl} C_6H_5NCO + 4\text{-}ClCH_2C_6H_4NCO$$

(**14**) (**15**) (**16**)

The phosgenation of aziridines, using triethylamine as hydrogen chloride acceptor, gives fair-to-good yields of 2-chloroalkyl isocyanates. For example from ethylene imine (**17**), 2-chloroethyl isocyanate (**18**) is obtained in 53% yield[27].



(**17**) (**18**)

Silylamines are also converted into isocyanates on treatment with phosgene. For example reaction of $Me_3SiNHMe$ with phosgene below room temperature gives a mixture of methyl isocyanate and trimethylchlorosilane[28]. Also reaction of the secondary silylamine[29] **19** and the tertiary silylamine[30] **20** with phosgene produces the corresponding isocyanates.

$$Bu_3Sn(CH_2)_3NHSiMe_3 \xrightarrow{COCl_2} Bu_3Sn(CH_2)_3NCO + Me_3SiCl + HCl$$

(**19**)

$$Et_3Ge(CH_2)_3N(SiMe_3)_2 \xrightarrow{COCl_2} Et_3Ge(CH_2)_3NCO + 2\ Me_3SiCl$$

(**20**)

Reaction of phosgene or oxalyl chloride with diarylimines produces tautomeric mixtures of *N*-chlorocarbonyl ketimines **21** and isocyanates **22**[31].

$$Ph_2C{=}NH + COCl_2 \longrightarrow \underset{(21)}{Ph_2C{=}NCOCl} \rightleftharpoons \underset{(22)}{Ph_2C(Cl)NCO}$$

Similar tautomeric mixtures are obtained in the reaction of the same imines with carbonyl fluoride[31].

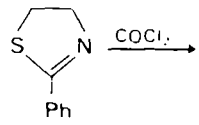
If one of the substituents is a secondary alkyl group, elimination of hydrogen chloride occurs, and the isolated product is a 1-alkenyl isocyanate (**23**)[33].

$$Me_2CHC(C_6H_5){=}NH + COCl_2 \longrightarrow \underset{(23)}{Me_2C{=}C(C_6H_5)NCO}$$

The imine intermediate **24**, which is formed on reduction of an aliphatic nitrile, can be trapped with phosgene to produce the *N*-chlorocarbonyl imine **25**, which is reduced under the reaction conditions to the isocyanate **26**[34].

$$RCN \xrightarrow{H_2} \underset{(24)}{RCH{=}NH} \xrightarrow{COCl_2} \underset{(25)}{RCH{=}NCOCl} \xrightarrow[-HCl]{H_2} \underset{(26)}{RCH_2NCO}$$

Phosgenation of cyclic lactim ethers[35] or thioethers[36] produces linear isocyanate esters. For example reaction of **27** with phosgene gives δ-β-isocyanatoethyl thiocarboxylate (**28**)[36].



(**27**)

$$\xrightarrow{COCl_2} \underset{(28)}{PhCOSCH_2CH_2NCO}$$

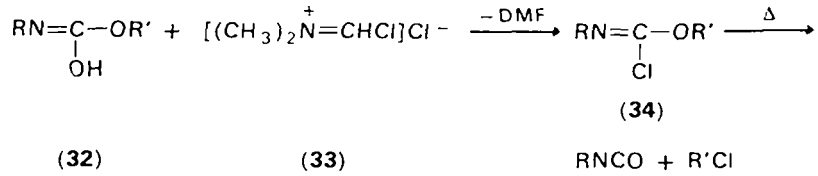
Oxalyl chloride has been used to convert the perhaloimine **29** into the α-haloisocyanate (**30**), which on dechlorination with zinc gives the perfluorovinyl isocyanate **31**[37].

$$\underset{(29)}{CF_2Cl(CF_3)C{=}NH} \xrightarrow{(COCl)_2} \underset{(30)}{CF_2Cl(CF_3)\underset{Cl}{C}NCO} \xrightarrow{Zn} \underset{(31)}{CF_2{=}\underset{CF_3}{C}NCO}$$

The phosgenation of alkyl carbamates is another useful method to synthesize alkyl isocyanates. Although carbamates are usually produced from alcohols and isocyanates, several methods are known for producing carbamates directly from olefins, ketones or aldehydes.

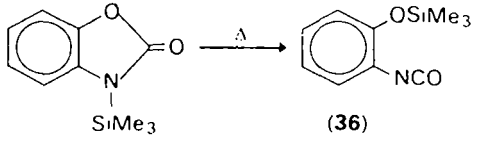
The conversion of carbamates to isocyanates proceeds readily using phosgene and a catalytic amount of *N*,*N*-dimethylformamide[38]. In the

absence of the catalyst no reaction has been observed. The reaction most likely proceeds by initial attack on the enol form of the carbamate **32** by chlorodimethylformiminium chloride (**33**) with formation of the imidochloroformate (**34**) and regeneration of the catalyst. The thermolysis of **34** to produce isocyanates and alkyl halides is a well-known reaction.



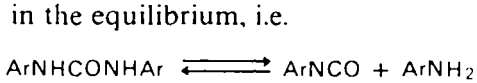
(**32**) (**33**) (**34**)

The conversion of carbamates or *N*-chlorocarbamates can also be accomplished using phosphorus pentachloride[39], catechol phosphorus trichloride[40] and trimethylsilyl chloride[41]. The latter method is especially useful, and it has been extended to convert heterocyclic carbamates into isocyanates[42]. For example, thermolysis of silylated benzoxazolones (**35**) produces the corresponding isocyanates (**36**)[42].

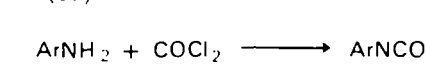


(**35**) (**36**)

Of the derivatives of carbonic acid, ureas were the first to be converted to isocyanates by means of phosgene. Hentschel[1] had already described the formation of phenyl isocyanate in the phosgenation of *N*,*N*-diphenylurea. However since *N*,*N*-diarylureas (**37**) are dissociated appreciably at elevated temperature, the reaction proceeds via phosgenation of the amine generated in the equilibrium, i.e.



(**37**)



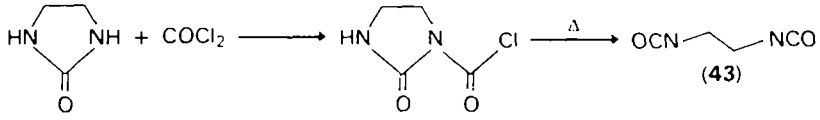
In contrast alkylureas undergo a facile reaction with phosgene. The attack of *N*,*N'*-dialkylureas (**38**) could occur on the oxygen or on the nitrogen to produce *N*,*N'*-dialkylchloroformamidine hydrochlorides (**39**) and allophanoyl chlorides (**40**), respectively[43]. The latter can be dehydrochlorinated at elevated temperature to produce 2 moles of isocyanate and hydrogen chloride.

$$\underset{(38)}{RNHCONHR} + COCl_2 \longrightarrow \underset{(39)}{RNHCCl{=}\overset{+}{N}HR]Cl^-} + \underset{(40)}{RNHCON(COCl)R}$$

(R = Alkyl)

$$RNHCON(COCl)R \xrightarrow{\Delta} 2\,RNCO + HCl$$

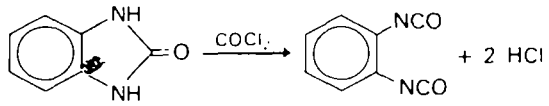
The structural feature of the starting *N,N'*-dialkylurea determines the distribution of **39** and **40**[43]. In primary alkyl-substituted ureas predominantly **40** is formed, while secondary and tertiary alkyl-substituted ureas produce preferentially **39**. Cyclic five and six-membered ring alkylureas are readily converted to aliphatic diisocyanates by this method. For example phosgenation of ethylene urea (**41**) yields the cyclic allophanoyl chloride (**42**) which is readily dehydrochlorinated using a tertiary amine at room temperature or by thermolysis at elevated temperature, in the presence of $FeCl_3$ as the catalyst, to produce ethylene diisocyanate (**43**)[43].



(41) (42) (43)

Since ethylene diisocyanate cannot be synthesized by direct phosgenation of ethylenediamine, this method provides an attractive alternative route to **43** because the starting **41** is readily prepared from ethylenediamine and carbon dioxide.

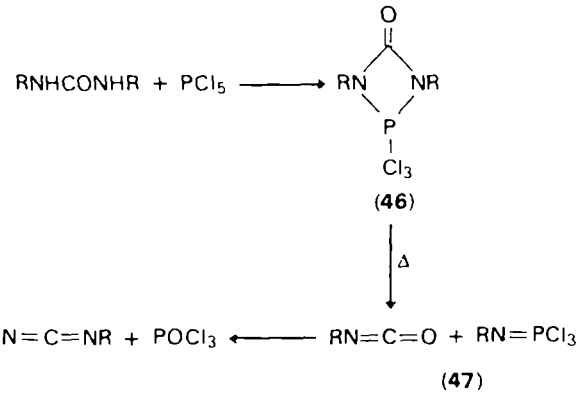
In a similar manner, benzimidazolones (**44**) can be converted into *o*-diisocyanates (**45**) on prolonged phosgenation at elevated temperature[44].



(44) (45)

N-Alkylureas have been converted to isocyanates using boron trifluoride[47] or nitrous acid[48] to complex or destroy the by-product ammonia. Treatment of 1-aryl-3-dialkylureas with HCl and CO_2 gives a mixture of phenyl isocyanate and dialkylamine hydrochloride[49].

In the reaction of *N,N*-dialkylureas and *N*-alkyl-*N*-arylureas with phosphorous pentachloride *N*-attack is also observed with formation of the four-membered ring 1,2,4-phosphadiazetidin-3-ones (**46**). Thermolysis of **46** produces isocyanate and phosphazene (**47**), but the facile reaction of the generated isocyanate with **47** leads to the formation of a carbodiimide rather than the isocyanate[50].



Likewise *N*-arenesulphonyl-*N'*-alkylureas (**48**) are very readily phosgenated to yield a mixture of arenesulphonyl isocyanate (**49**) and alkyl isocyanate[51].

$$\underset{\textbf{(48)}}{RSO_2NHCONHR} + COCl_2 \longrightarrow \underset{\textbf{(49)}}{RSO_2NCO} + RNCO$$

The reaction proceeds via the unstable allophanoyl chlorides as evidenced by the fact that the dissociation product, arenesulphonamide, can not be phosgenated under the reaction conditions. The rapid rate of phosgenation of **48** has been utilized in the conversion of arenesulphonamides to arenesulphonyl isocyanates in the presence of a catalytic amount of an alkyl or aryl isocyanate[51] (see Section II.C.10). Since the ureas (**48**) can be obtained in quantitative yield by reacting **49** with alkyl amines and alkylenediamines, rapid phosgenation of the 'masked' amines and diamines is assured. In contrast, phosgenation of the highly insoluble alkylenediamine dihydrochlorides proceeds only slowly and long reaction times are necessary[4]. Alkoxyalkylamines are also readily converted by this method into alkoxy isocyanates, thus avoiding the ether cleavage which occurs in the direct phosgenation of alkoxyalkylamines[52]. The required sulphonyl isocyanate is regenerated in the phosgenation and can be re-used in a consecutive reaction. The overall reaction proceeds as follows:

$$\underset{\textbf{(49)}}{RNH_2} + \underset{\textbf{(49)}}{RSO_2NCO} \longrightarrow \underset{\textbf{(48)}}{RNHCONHSO_2R}$$

$$\underset{\textbf{(48)}}{RNHCONHSO_2R} \xrightarrow{COCl_2} RNCO + \underset{\textbf{(49)}}{RSO_2NCO}$$

The reaction of **48** with phosphorous pentachloride also produces an alkyl isocyanate: the by-product arenesulphonylphosphazene does not

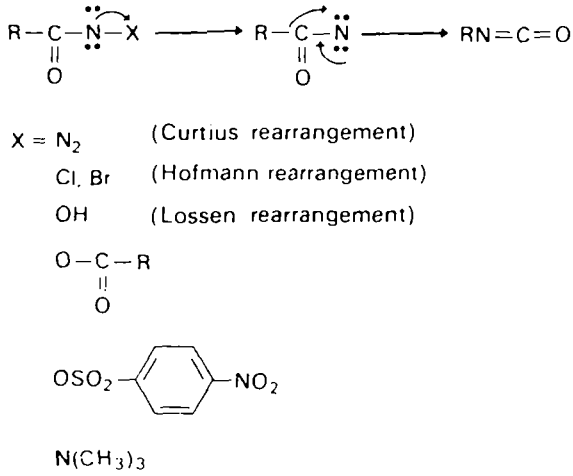
react with the isocyanate[50]. *N,N'*-Dialkylureas (**38**) can be converted to a mixture of isocyanate and *N*-sulphinylamine upon reaction with thionyl chloride[52].

Instead of phosgene diaryl carbonates can also be used to prepare isocyanates. For example, reaction of aromatic amines and aliphatic diamines with diphenyl carbonate produces aryl and alkylene diisocyanates[54]. Also addition of gaseous methylamine[55] or phenyl methylcarbamate[56] to molten diphenyl carbonate produces methyl isocyanate in 86–88% yield.

$$MeNH_2 + (PhO)_2C{=}O \longrightarrow MeN{=}C{=}O + 2\ PhOH$$

2. Formation of alkyl and aryl isocyanates via nitrene intermediates

A group of rearrangements which could formally involve acyl or aroyl nitrenes as common intermediates has been used to synthesize isocyanates in the laboratory. The general outline is shown in Scheme 1.



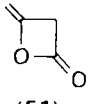
SCHEME 1.

The carbonyl azide (**50**) precursors were first synthesized by Curtius in 1890[57], and Curtius and his students have studied the thermal decomposition of **50**, which produces isocyanates and nitrogen, extensively. A summary of the classical work related to the Curtius rearrangement

appeared in 1946[58]. The starting carbonyl azides (**50**) are best prepared from carboxylic acid chlorides and sodium azide or from carboxylic acid hydrazides and nitrous acid, and the fragmentation can be conducted thermally or photolytically. The Curtius rearrangement is a good laboratory method for preparing isocyanates, but the handling of the sensitive **50** can be hazardous, especially in larger scale reactions.

$$\underset{\textbf{(50)}}{RCON_3} \xrightarrow{\Delta \text{ or } h\nu} RN{=}C{=}O + N_2$$

A recent modification of this reaction involves the reaction of carboxylic acid chlorides with trimethylsilyl azide[59]. Also anhydrides[60,61] and lactones[61] can be reacted with trimethylsilyl azide to give isocyanates. For example ketene dimer **51** reacts with trimethylsilyl azide to give a mixture of the two unsaturated isocyanates **52** and **53**[61].



(51)

$$+ Me_3SiN_3 \longrightarrow \underset{\textbf{(52)}}{CH_2{=}C(OSiMe_3)CH_2NCO} + \underset{\textbf{(53)}}{CH_3{-}C(OSiMe_3){=}CHNCO}$$

Esters react similarly with trimethylsilyl azide to give isocyanates[61].

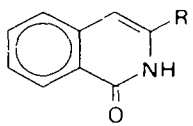
Reaction of the carboxylic acid fluoride (**54**) with sodium azide also gives the expected isocyanate (**55**)[37].

$$\underset{\textbf{(54)}}{CF_2(CF_2){-}CFCOF} + NaN_3 \longrightarrow \underset{\textbf{(55)}}{CF_2(CF_2){-}CFNCO}$$

The Curtius reaction can be used to synthesize isocyanates containing groups which are reactive with phosgene. For example heterocyclic isocyanates are obtained by this method[62]. A detailed procedure for the synthesis of substituted arylene diisocyanates has appeared recently[63].

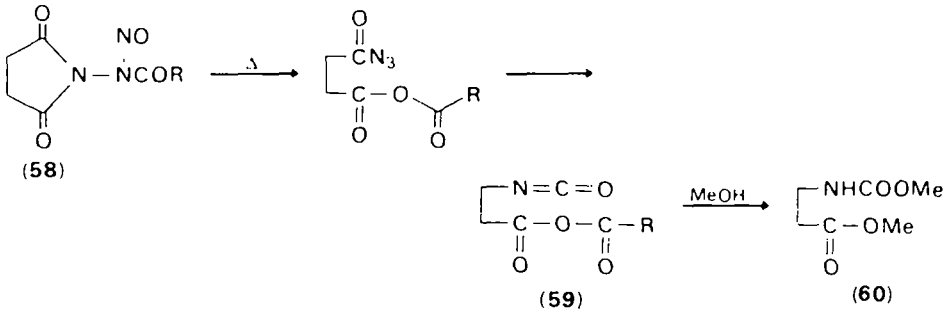
Styryl isocyanates (**56**) can also be obtained by the Curtius reaction, but at elevated temperatures they rearrange to give isocarbostyryls (**57**) in excellent yields[64].

$$PhCH{=}C(R)CON_3 \xrightarrow{-N_2} \underset{\textbf{(56)}}{PhCH{=}C(R)NCO} \xrightarrow{\Delta}$$



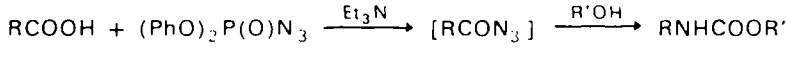
(57)

N-Nitroso-*N*-succinimidylamides (**58**) upon heating produce isocyanates **59**, which are trapped as the carbamates **60**[65].



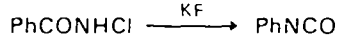
(**58**) (**59**) (**60**)

A simple one-step conversion of carboxylic acids to urethanes has been achieved by heating an equimolar mixture of a carboxylic acid with diphenylphosphorazidate (**61**) and triethylamine in alcohol[66]



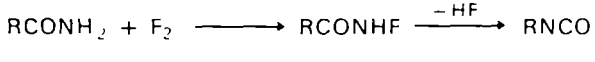
(**61**)

The Hofmann rearrangement is usually conducted in an aqueous system, and the generated isocyanates undergo secondary reactions. However by using *t*-butyl hypochlorite instead of sodium hypobromite isocyanates can be generated in inert solvents. Potassium fluoride has recently been used to convert *N*-chlorobenzamide **62** to phenyl isocyanate[67].



(**62**)

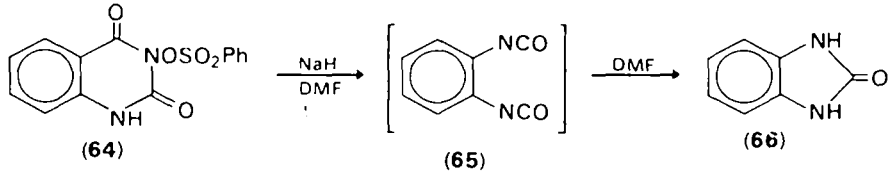
Fluorination of cyclohexylamide (**63**) with elementary fluorine in acetonitrile gives a low yield of cyclohexyl isocyanate[68]



(**63**)

The Lossen rearrangement also has found some utility for the synthesis of isocyanates. Pyrolysis of several benzhydroxamic chlorides at 180 °C gave aryl isocyanates in moderate yields[69]. Reaction of hydroxamic acids with the pyridine/SO_3 complex produces crystalline water-soluble salts which, on treatment with tertiary amines, produce aliphatic isocyanates in good yields[70]. Isocyanates are also obtained by thermal

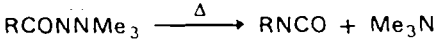
decomposition of acetates of hydroxamic acids[71]. The proton of the cyclic hydroxamic acid ester **64** can be removed with sodium hydride in DMF, and benzimidazolone **66** has been isolated. The latter is formed by interaction of the *o*-diisocyanate **65** with DMF[881].



(64) (65) (66)

Benzimidazolone can be converted into **65** by prolonged phosgenation at elevated temperatures[44].

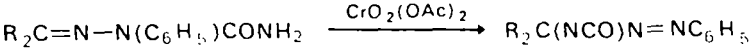
Heating of aminimides also produces isocyanates by a mechanism similar to the Curtius rearrangement. A variety of aliphatic isocyanates are thus obtained in high yield on heating of trimethylamine-acylimides **67**[72]



(67)

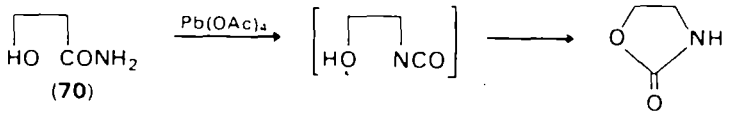
The tertiary amine leaving group has to be modified to synthesize aromatic isocyanates, because trimethylamine causes trimerization of aryl isocyanates. However, heating of dimethylphenyl amine–aroylimide produces aryl isocyanates[73].

The carbonyl nitrene intermediates can also be obtained by oxidation of primary carboxylic acid amides with lead tetraacetate[74]. For example oxidation of 2-phenylsemicarbazones (**68**) with lead tetraacetate or chromyl acetate in chloroform produces phenylazomethyl isocyanates (**69**)[75]



(68) (69)

Lead tetraacetate in pyridine oxidizes β-hydroxy primary amides (**70**) to 2-oxazolidinones (**71**) in high yields[76].



(70) (71)

The direct conversion of amino and nitro compounds with carbon monoxide to produce isocyanates has received considerable attention in recent years. The reaction probably proceeds via the nitrene as the reactive intermediate, and trapping of the nitrene by the excess carbon monoxide produces the isocyanate. For example Hardy and Benett[77] obtained phenyl isocyanate in the reaction of nitrobenzene (**72**) with carbon monoxide at high pressure and high temperature in the presence of rhodium on carbon and ferric chloride.

$$C_6H_5NO_2 + 3\,CO \longrightarrow C_6H_5NCO + 2\,CO_2$$

(**72**)

Up to 72% of 4-chlorophenyl isocyanate was obtained from 4-chloronitrobenzene and carbon monoxide in the presence of palladium chloride as the catalyst[78]. In numerous recently-issued patents conversion of 2,4-dinitrotoluene to tolylene 2,4-diisocyanate has also been claimed. A variety of noble metal catalysts is disclosed and the more soluble complexes stabilized by ligands, such as triphenylphosphine, allow reaction at lower pressure. Similarly carbonylation of amines to isocyanates, using equivalent amounts of palladium dichloride as the oxidizing agent, has been described[79]. Moderate yields of monoisocyanates and a low yield of tolylene diisocyanate were obtained. Tolylene diisocyanate was also obtained from the corresponding diamine, carbon monoxide and oxygen in the presence of nickel tetracarbonyl[80].

The above methods could be of economical significance but difficulty in catalyst recovery and slow reaction rates, even at the high pressures used, renders these processes impractical.

The intermediacy of nitrene is further indicated by the fact that aryl azides (**73**), a conventional source of arylnitrenes, undergo reaction with carbon monoxide under pressure, in the absence of catalysts, to yield isocyanates[81].

$$RN_3 + CO \longrightarrow RNCO + CO_2 \qquad (R = \text{Aryl})$$

(**73**)

Azo compounds could be intermediates in some of the above reactions as evidenced by the fact that lower pressures produced azo compounds as by-products[79], and conversion of the perfluoroalkyl derivative **74** to the corresponding isocyanate under similar conditions[82].

$$CF_3N{=}NCF_3 + 2\,CO \longrightarrow CF_3NCO$$

(**74**)

3. Formation of alkyl and aryl isocyanates by thermal processes

The 1:1 adducts obtained by the addition of an active hydrogen compound to an isocyanate are thermally labile to a certain degree. Usually the reversal of this reaction is of limited synthetic interest because the adducts are most readily prepared from the corresponding isocyanate.

Carbamates, the 1:1 adducts of alcohols and phenols with isocyanates, eliminate alcohol at elevated temperatures. The dissociation temperatures of various carbamates are shown in Table 2[83]. Heating of carbamates in the presence of phosphorous pentoxide also produces isocyanates[84].

TABLE 2. Dissociation temperatures of carbamates RNHCOOR'

R	R'	Temperature (°C)
Aryl	Aryl	120
Alkyl	Aryl	180
Alkyl[a]	$4\text{-}O_2NC_6H_4$	130
Aryl	Alkyl	200
Alkyl	Alkyl	250

[a] Hexamethylene diisocyanate adduct.

With carbamates derived from tertiary alcohols at elevated temperatures, fragmentation to the corresponding olefin, amine and carbon dioxide is observed. Generally the eliminations are catalysed by the same catalysts which are used in the carbamate formation. Since the adducts of the more acidic phenols dissociate at lower temperatures, they have been used for the preparation of 'masked' isocyanates. For example isocyanate-terminated prepolymers are reacted with phenols and the obtained stable oligomeric carbamates are heated with a hydroxy-terminated polyester or polyether to form the final polyurethane coating. This reaction is initiated by the elimination of phenol, thereby releasing the reactive isocyanate group.

The carbonate, derived from catechol, has been used to synthesize low-boiling aliphatic monoisocyanates. For example, reaction of this carbamate with ethylamine yields a carbamate which on gentle heating to 250°C eliminates ethyl isocyanate, which is removed from the equilibrium by distillation[4]. The dissociation of alkyl or arylthiocarbamates also produces isocyanates[85], while heating of alkyl allophanates and alkyl thioallophanates (the 2:1 adducts of isocyanates to alcohols and mercaptans, respectively) gives rise to the formation of two equivalents of isocyanates[86]. The allophanates and thioallophanates (**74**) can be

prepared from the corresponding allophanoyl chlorides (**75**) and sodium alcoholates or sodium mercaptides, respectively[86]

$$\underset{(75)}{RNHCON(COCl)R} + R'XH \longrightarrow \underset{(74)}{RNHCON(COXR')R} \xrightarrow{\Delta} 2\,RNCO + R'XH$$

X = O, S

Dissociation of *N*-silylcarbamates (**76**), prepared by reaction of carbamates with trimethylsilylacetamide, produces isocyanates at relatively low temperatures (50–70 °C)[41]. The advantage of this method is the fact that the generated aryloxysilane does not recombine with the isocyanate.

$$\underset{(76)}{RN(SiMe_3)COOC_6H_5} \xrightarrow{\Delta} RNCO + C_6H_5OSiMe_3$$

Thermolysis of silylcarbamates (**77**), obtained by reacting silylamines with carbon dioxide, followed by *N*-silylation similarly gives alkyl isocyanates[87].

$$RNHSiMe_3 \xrightarrow{CO_2} RNHCOOSiMe_3 \xrightarrow{Me_3SiCl} \underset{(77)}{RN(SiMe_3)COOSiMe_3} \xrightarrow{\Delta} RNCO + \tfrac{1}{2}(Me_3Si)_2O$$

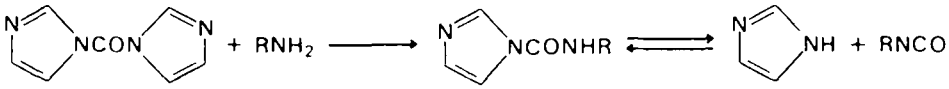
Reaction of some olefins with ethyl carbamate or ethyl *N*-chlorocarbamate produces *N*-substituted carbamates, which upon reaction with a high boiling diisocyanate generate the lower boiling isocyanate, which is constantly removed from the reaction mixture by distillation[88].

Di- and tri-substituted ureas dissociate on heating into isocyanates and amines. For example methyl isocyanate is readily prepared via pyrolysis of 1,1-diphenyl-3-methylurea (**78**). The urea **78** can be obtained from diphenylcarbamoyl chloride (**79**) and methylamine[4,98].

$$Ph_2NH + COCl_2 \longrightarrow \underset{(79)}{Ph_2NCOCl} \xrightarrow{MeNH_2} \underset{(78)}{Ph_2NCONHMe} \xrightarrow{\Delta} Ph_2NH + MeNCO\uparrow$$

Low boiling aliphatic isocyanates are also obtained upon heating of *N,N'*-dialkylureas with diphenylcarbonate[89].

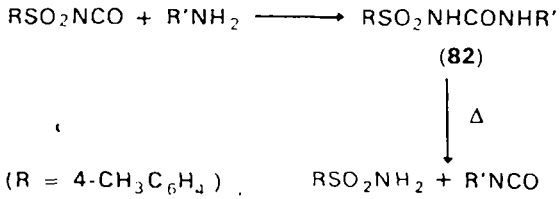
Enureas (i.e., ureas having double bonds in conjugation to the NHCONH group) dissociate more readily than *N,N'*-diarylureas. For example imidazolyl substituted ureas (**80**), prepared via reaction of *N,N'*-carbonyldiimidazole (**81**) with primary amines, dissociate exceedingly readily to the corresponding isocyanate and imidazole[90].



(**81**) (**80**)

The chloroform solution of urea **80** (R = C_6H_5) at room temperature shows dissociation to the extent of 16·1%[90].

Some lower alkyl isocyanates are quite unstable and upon long storage trimerization is observed because it is quite difficult to remove traces of hydrogen chloride, which can catalyse this reaction. We have developed an interesting method to generate thermally the required isocyanates simply by heating the corresponding tosylurea (**82**) in a distillation apparatus[91]. The tosylureas **82** are prepared in quantitative yield from tosyl isocyanate and primary amines, and the crystalline urea derivatives can be stored indefinitely. Phosgenation of the *p*-toluenesulphonamide, produced in the elimination reaction, regenerates the required tosyl isocyanate.

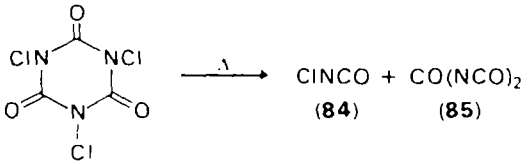


Pyrolysis of acetoacetamides at approximately 500 °C also yields mono- and diisocyanates[92].

The insertion products, obtained by addition of isocyanates to reactive single bonds, also dissociate at elevated temperature to reform the starting isocyanate or to form new isocyanates via an exchange process[93]. However these reactions are of limited preparative use because trimerization occurs simultaneously.

Other pyrolysis procedures involve the thermolysis of homopolymers of isocyanates and thermolysis of certain heterocyclic compounds. The isocyanate trimers (isocyanurates) can be pyrolysed at 600–800 °C to give

monomeric isocyanates[94]. This method has been used to synthesize chloro isocyanate (**84**) and carbonyl diisocyanate (**85**) from *N*,*N*',*N*''-trichloroisocyanurate (**83**)[95].



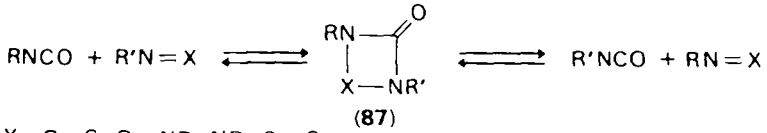
(**83**)

The formation of **85** is due to disproportionation of **84** which also results in formation of NCl_3.

Dimeric isocyanates (**86**) also dissociate upon heating to regenerate the monomeric isocyanates, but the aryluretidinones **86** (R = Aryl) are again best prepared from aryl isocyanates. Alkyluretidinones **86** (R = Alkyl) are only occasionally obtained on attempted oligomerization of alkyl isocyanates.

(**86**)

The 2 + 2 cycloaddition of isocyanates to a number of double bonded substrates produces four-membered ring 1:1 adducts. Fragmentation of these adducts **87** results in the starting materials as well as a new set of compounds, and removal of the lowest boiling fragment can shift the equilibria to give a new isocyanate.



(**87**)

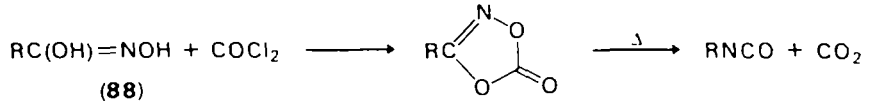
X = C = S, C = NR, NR, S = O

It is not necessary to isolate the four-membered ring adducts **87**. For example heating of a lower-boiling isothiocyanate with an aryl isocyanate[96], or diisocyanate[97] gives rise to the formation of the lower boiling isocyanate, which is removed from the equilibrium by distillation. A similar exchange reaction occurs with *N*-sulphinylamines and isocyanates[99], and carbodiimides and isocyanates[100].

Likewise 2 + 2 cycloadducts derived from azobenzene and diphenylketene[101], and nitrosobenzene and diphenylketeniminines dissociate on heating to give aryl isocyanates[102].

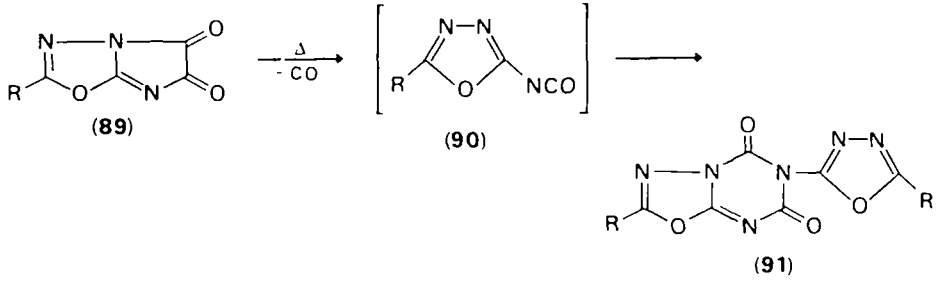
Heating of C=N double bond containing substrates (imines, amidines, guanidines, etc.) with isocyanates also leads to an exchange reaction[103].

A wide variety of other heterocyclic compounds also produce isocyanates on heating (Scheme 2). The generated by-product is usually a volatile gas. Several of the Type I heterocycles (Scheme 2) are readily synthesized from hydroxamic acids (**88**) and carbonyl chloride (phosgene), thionyl chloride and thiophosgene, respectively, and pyrolysis of the heterocycles produces isocyanates in excellent yields[104].

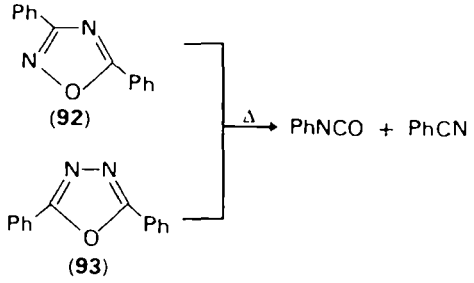


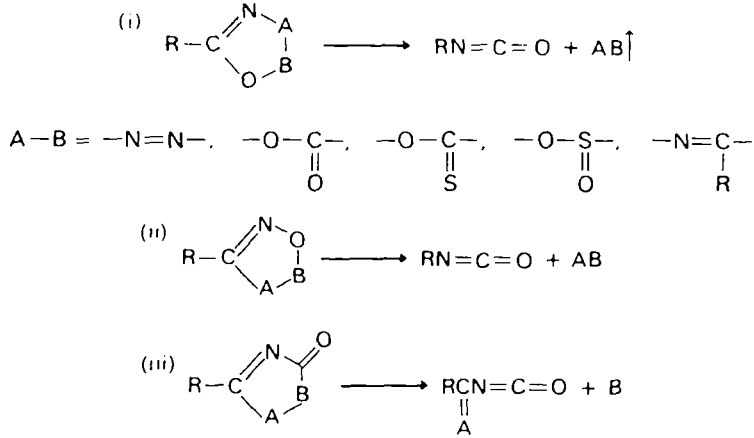
This method has also been used to synthesize diisocyanates[105] and methoxymethyl isocyanate[106].

Heating of the heterocycle **89** in *o*-dichlorobenzene produces an intermediate heterocyclic isocyanate, **90**, which rapidly dimerizes to produce the isolated **91**[107]



Heating of 3,5-diphenyl-1,2,4-oxadiazole (**92**) and 2,5-diphenyl-1,3,4-oxadiazole (**93**) produces phenylisocyanate and benzonitrile[108]. Pyrolysis

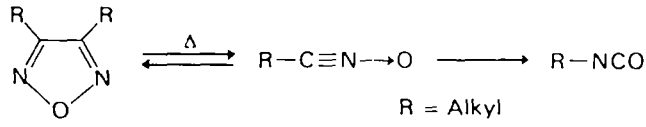




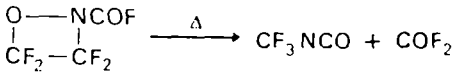
SCHEME 2.

of 5-(2-alkenyloxy)-1,2,3,4-thiatriazoles produces 2-alkenyl isocyanates[114].

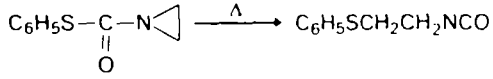
Mono- and di-isocyanates can readily be prepared in good yields on heating furazan *N*-oxides (furoxanes) above 200 °C. The reactions were shown to proceed via thermally generated nitrile oxides which rearrange to isocyanates[883].



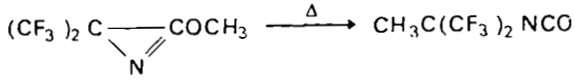
Pyrolysis of perfluoro-2-fluoroformyl-1,2-oxazetidine (**94**) at 400°C yields trifluoromethyl isocyanate (**95**) and carbonyl fluoride (**96**)[109]



Also certain three-membered ring N-heterocycles, on heating, can produce isocyanates. For example acylaziridines such as **97** yield β-substituted ethyl isocyanates[110].

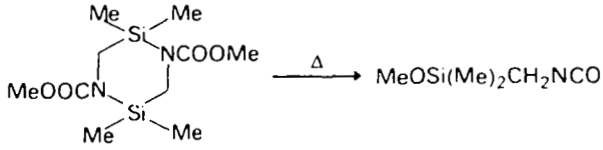


Also heating of the unsaturated three-membered ring N-heterocycle **98** produces the fluoroalkyl isocyanate **99**[111].



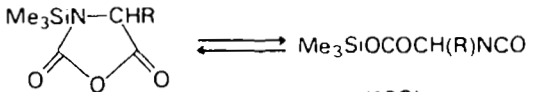
(**98**) (**99**)

Five, six and seven-membered ring Si–N heterocycles, such as **100**, pyrolyse at 200 °C to produce alkyl isocyanates containing silicon[112].



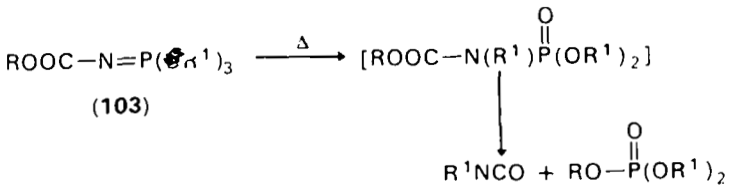
(**10**

N-Trimethylsilyloxazolidinediones-2,5 (**101**) are in equilibrium with *α-isocyanatocarboxylic acid trimethylsilyl esters* (**102**)[113].



(**101**) (**102**)

Heating of phosphorimidates **103** to 200 °C results in the formation of alkyl isocyanate and trialkyl phosphate[115]. Likewise, heating of phosphoramidate anions with carbon dioxide produces alkyl isocyanates[116].



(**103**)

4. Reaction of organic halides and sulphates with salts of cyanic acid

The reaction of organic sulphates with potassium cyanate was the method used by Wurtz in 1848 to synthesize the first organic isocyanate[117]. For example ethyl isocyanate can be obtained in 95% yield by heating diethyl sulphate (**104**) with potassium cyanate[117].

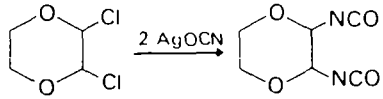
$$(EtO)_2SO_2 + KOCN \longrightarrow EtNCO$$

(104)

A similarly high yield was obtained from ethyl bromide and potassium cyanate in dimethyl sulphone as solvent[118]. The reaction of alkyl phosphates[119] and alkyl *p*-toluenesulphonates[120] with potassium cyanate also produces alkyl isocyanates. It is sometimes advantageous to conduct this reaction in a mixed solvent. For example methoxymethyl chloride reacts in a mixture of xylene and *N*,*N*-dimethylformamide with sodium cyanate to give methoxymethyl isocyanate in good yield[121]. Unsaturated isocyanates were prepared from the corresponding bromides and silver cyanate in diethyl ether[122].

The use of highly polar solvents in the absence of a cosolvent leads to exclusive formation of isocyanate trimers (isocyanurates)[123]. If alcohols are added, the corresponding carbamates are obtained in high yields[124].

Diisocyanates were also obtained in the reaction of dihalides and silver cyanate. For example reaction of the α,α-dihaloalkylether (**105**) with silver cyanate in diethyl ether produces the diisocyanate **106** in good yield[125].



(105) (106)

Polyurethanes are prepared by reacting dihalides, such as 1,4-dichloro-2-butene, with sodium cyanate in glycols[126].

Reaction of carbonyl fluoride with potassium cyanate in a eutectic melt of LiCl and KCl at 400 °C gives a mixture of carbonyl diisocyanate (**107**) and fluorocarbonyl isocyanate (**108**)[127].

$$COF_2 + KOCN \longrightarrow OC(NCO)_2 + FCONCO$$

(107) (108)

Also from chloroalkyl silanes upon reaction with potassium cyanate the corresponding isocyanates are obtained[128]. Likewise chloromethyl siloxanes and chloromethyl phosphates produce isocyanates upon reaction with silver cyanate[129].

Polymeric cyano isocyanate has been obtained in the reaction of cyanogen chloride with silver cyanate[130]. The monomeric cyano isocyanate can be generated in the pyrolysis of the polymer under vacuum, and the monomer is a liquid at liquid nitrogen temperature.

5. Reaction of olefins, aldehydes and imines with isocyanic acid

The addition of isocyanic acid to olefins affords aliphatic isocyanates in relatively good yields. However isocyanic acid is not stable and has to be generated *in situ* by pyrolysis of cyanuric acid (trimeric cyanic acid), urea or carbamates. For example heating of a mixture of isocyanic acid and *m*-[131] or *p*-diisopropenylbenzene[132] gives mixtures of mono and diisocyanates. Other substrates used include isobutylene[132], isoprene[132], styrene[132], α-methylstyrene (**109**)[132], norbornene[133] and vinyl ethers[134].

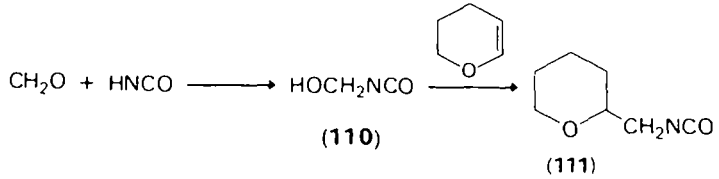
$$C_6H_5C(CH_3)=CH_2 + HNCO \longrightarrow C_6H_5C(CH_3)_2NCO$$

(**109**)

In contrast, reaction of olefins with isocyanic acid in the presence of *t*-butyl hypochlorite gives β-chloroalkylisocyanates[135]. β-Chloroalkylisocyanates are also obtained by reacting olefins with isocyanic acid and chlorine in the presence of iodoaryl compounds[136].

$$RCH=CH_2 + HNCO + BuOCl \longrightarrow RCHClCH_2NCO$$

Certain aldehydes and ketones also react with isocyanic acid at low temperatures to give α-hydroxy isocyanates. If the hydroxy group is scavenged with dihydropyran an ether isocyanate is produced[137]. For example reaction of formaldehyde with isocyanic acid gives the α-hydroxyalkylisocyanate, **110**, which immediately reacts with dihydropyran to produce 2-isocyanatomethyltetrahydropyran **111**[137].



(**110**) (**111**)

Addition of isocyanic acid to pentafluoroguanidine gives a 1:1 adduct, **112**, which on further fluorination produces tris(difluoroamino)methyl isocyanate (**113**)[138].

$$(F_2N)_2C=NF + HNCO \longrightarrow (F_2N)_2C(NCO)NHF \xrightarrow{F_2} (F_2N)_3CNCO$$

(**112**) (**113**)

Also reaction of halogenated aromatic and aliphatic hydrocarbons with isocyanic acid in the vapour phase in the presence of nickel oxide or cupric chloride on pumice, affords isocyanates in low yield[139]. Vapour-phase reaction of primary amines with isocyanic acid in the presence of

hydrogen chloride gives mixtures of isocyanates and carbamoyl chlorides[140].

6. Miscellaneous methods

Carbonimidoyl dichlorides (isocyanide dichlorides) which are available by a variety of synthetic procedures not involving isocyanates as starting materials, are readily hydrolysed to produce isocyanates. The hydrolysis can be conducted with methanesulphonic acid[141], phosphoryl chloride and water[141], anhydrides[142] or formic acid[143].

$$RN{=}CCl_2 + HCOOH \longrightarrow RNCO + CO + 2\,HCl$$

Trifluoromethylcarbonimidoyl difluoride (**114**) can be hydrolysed with water to give trifluoromethyl isocyanate (**115**)[144].

$$\underset{\textbf{(114)}}{CF_3N{=}CF_2} + H_2O \longrightarrow \underset{\textbf{(115)}}{CF_3NCO} + 2\,HF$$

If the carbonimidoyl dichloride is generated in the presence of a carboxyl group an intramolecular reaction occurs to produce the corresponding α-chloro-β-isocyanatocarboxylic acid chloride (**116**) in low yield[141].

$$CH_3CH{=}CHCOOH \xrightarrow[ClCN]{Cl_2} [CH_3\underset{\displaystyle N{=}CCl_2}{\underset{|}{C}}HCH(Cl)COOH] \xrightarrow{-HCl} CH_3\underset{\displaystyle NCO}{\underset{|}{C}}HCH(Cl)COCl$$

(116)

Reaction of isobutylene with sulphur trioxide and cyanogen chloride produces the isocyanate **118** via the cyclic intermediate **117** in 50% yield[141]. If chlorosulphonic acid is used instead of sulphur trioxide the same isocyanate is obtained[141].

$$(CH_3)_2C{=}CH_2 + SO_3 + ClCN \longrightarrow \underset{\textbf{(117)}}{\left[\begin{array}{l} CH_3 \quad CH_3 \\ \diagdown\ \diagup \\ N \\ \| \\ Cl\diagup\ \diagdown O\diagup\ \diagdown SO_2 \end{array}\right]} \longrightarrow \underset{\textbf{(118)}}{(CH_3)_2C(NCO)CH_2SO_2Cl}$$

Trifluoromethyl isocyanate is obtained in the reaction of the carbonimidoyl dichloride **119** (the chlorination product of methyl isocyanate) with hydrogen fluoride[145]

$$ClCON{=}CCl_2 + HF \longrightarrow CF_3NCO$$

(119)

Alkylation of ClCN with alkyl chlorides in the presence of $FeCl_3$ gives carbonimidoyl dichloride complexes (**120**) which are converted to isocyanates using ZnO or salts of carboxylic acids[146].

$$ClCN + (CH_3)_2CHCl \longrightarrow [(CH_3)_2CHN{=}CCl_2]_3(FeCl_3)_2$$

(120)

$$\downarrow ZnO$$

$$(CH_3)_2CHNCO$$

Chloroformimidates (**121**) on thermolysis[147] or treatment with base[148] also produce isocyanates.

$$RN{=}CCl_2 \xrightarrow{NaOR} RN{=}C(Cl)OR \xrightarrow{\Delta} RNCO + RCl$$

(121)

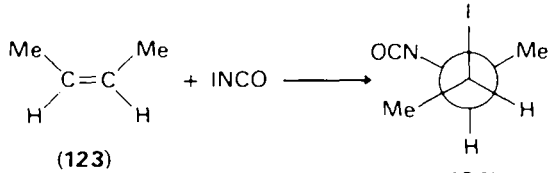
Isocyanates are also obtained in the reaction of nitriles with phosgene or carbonyl fluoride. For example reaction of acetonitrile with carbonyl fluoride gives α,α-difluoroethyl isocyanate (**122**)[149].

$$CH_3CN + COCF_2 \longrightarrow [CH_3C(F){=}NCOF] \longrightarrow CH_3CF_2NCO$$

(122)

Similarly trifluoroacetonitrile on reaction with carbonyl fluoride in the presence of CSF at 200–300°C gives perfluoroethyl isocyanate in 18% conversion[150].

Addition of iodine isocyanate to olefins yields β-iodo alkyl isocyanates[151]. The addition is stereospecific, the iodine and isocyanate functions being introduced *trans* to each other. For example from *cis*-2-butene (**123**) the *threo*-3-iodo-2-butyl isocyanate (**124**) is obtained exclusively[152].



(123) (124)

Two classes of compounds which are isomeric to isocyanates (nitrile oxides and cyanates) can be rearranged to produce isocyanates. For example sterically hindered nitrile oxides (**125**) are readily converted into isocyanates upon heating[153].

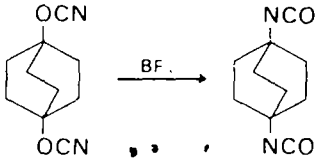
$$\underset{\textbf{(125)}}{RC{\equiv}N{\rightarrow}O} \xrightarrow{\Delta} RN{=}C{=}O$$

The steric hindrance is necessary because otherwise nitrile oxides undergo dimerization rather than rearrangement.

Aryl nitrile oxides, obtained in the reaction of NOCl with toluene or benzyl chloride, rearrange also to give phenyl isocyanate[154]. Primary aliphatic cyanates are also known to rearrange readily to give isocyanates[155]. Another example of this rearrangement involves the formation of perfluoroisopropyl isocyanate (**126**) from perfluoro acetone[156].

$$(CF_3)_2CO + KF \longrightarrow (CF_3)_2C(F)OK \xrightarrow{ClCN} [(CF_3)_2CFOCN] \longrightarrow \underset{\textbf{(126)}}{(CF_3)_2CFNCO}$$

Also tertiary bridgehead dicyanates such as **127** rearrange in the presence of a catalytic amount of boron trifluoride to give the diisocyanate, **128**[157].



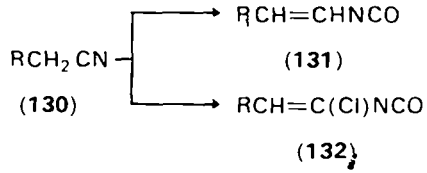
(127) (128)

Isonitriles (**129**) are readily oxidized to produce isocyanates. The oxidizing agents used include dimethyl sulphoxide[158], mercuric oxide[159], pyridine *N*-oxide[160], nitrile oxides[161], nitric oxide[162] and ozone[163].

$$\underset{\textbf{(129)}}{RNC} \xrightarrow{[O]} RNCO$$

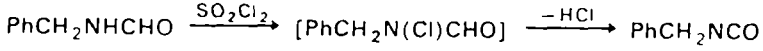
Also isothiocyanates can be oxidized to give isocyanates using mercuric oxide as oxidizing agent[164].

Nitriles have also been converted into isocyanates. For example α,β-unsaturated isocyanates (**131**) can be obtained in moderate yields (27–50%) by reacting aliphatic nitriles (R = alkyl) having α-hydrogen atoms (**130**) with phosgene in the presence of hydrogen chloride[165]. If this reaction is conducted with sterically hindered aryl acetonitriles (R = aryl groups with substituents in the 2 and 6 position), α-chlorostyryl isocyanates (**132**) are obtained[166].



Also reaction of enaminonitriles with phosgene gives isocyanates in moderate to good yields[167].

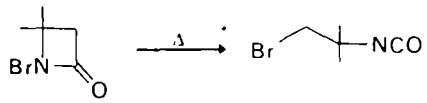
Oxidation of monosubstituted formamides is another method of producing isocyanates. Arylformamides are intermediates in the carbonylation of amines to isocyanates (see Section II.A.2). Recently it was shown that phenylformamide can be oxidized to phenyl isocyanate in low yield (~20%) using a Pd/Ni catalyst[168]. A high yield of benzyl isocyanate (**134**) can be obtained in the oxidation of benzylformamide (**133**) with sulphuryl chloride[169].



(**133**) (**134**)

Elimination of hydrogen halide from *N*-halo formamides to give mono and diisocyanates has also been conducted using a tertiary amine as acceptor[170]. Reaction of formamidothiophenes with phosgene in the presence of triethylamine gives isocyanatothiophenes[171].

Rearrangement of *N*-halo-2-azetidinones produces β-halo alkyl isocyanates. The reaction is conducted at 50 °C and peroxides are used as initiators. The presence of an olefin as a co-catalyst is necessary, and the obtained yields are high in the case of the *N*-bromo-2-azetidinones (**135**)[172].



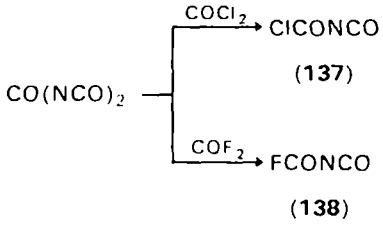
(**135**)

Adducts of phosgene to carbodiimides **136** are in equilibrium with isocyanates and carbonimidoyl dichlorides at elevated temperatures[173].

$$RN(COCl)C(Cl)=NF \rightleftharpoons RNCO + RN=CCl_2$$

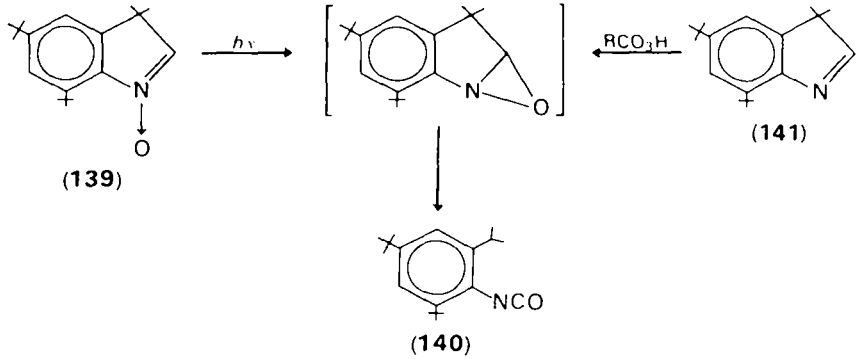
(136)

Reaction of phosgene or carbonyl fluoride with carbonyl diisocyanate gives the corresponding halocarbonyl isocyanates **137** and **138**, respectively, in high yields[127]



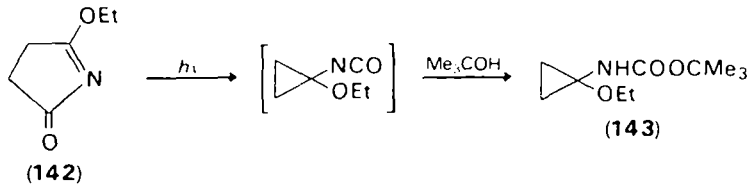
(137) (138)

Isocyanates can also be generated in the photolysis of special C=N double-bond-containing heterocycles. For example photolysis of 5,7-di-*t*-butyl-3,3-dimethyl-3*H*-indole-1-oxide (**139**) gives 2-isopropyl-4,6-di-*t*-butylphenyl isocyanate (**140**). The same isocyanate is also obtained in moderate yield through the oxidation of 5,7-di-*t*-butyl-3,3-dimethyl-3*H*-indole (**141**) with peracid[174].



(139) (141) (140)

Photolysis of 2-ethoxypyrrolin-5-one (**142**) in *t*-butanol results in a 70% yield of *N*-(ethoxycyclopropyl)carbamate (**143**)[175].

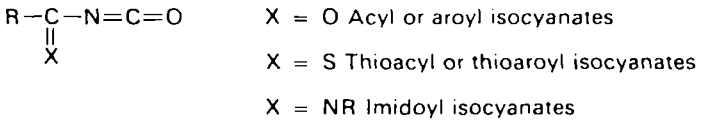


(142) (143)

Isocyanates can also be generated in electrochemical processes. For example treatment of a methanolic solution of potassium cyanate and anisol with an electric current produces methyl *N*-anisylcarbamate[176].

B. Acyl, Thioacyl and Imidoyl Isocyanates

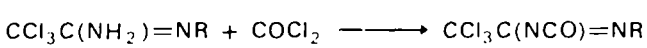
In this class of isocyanates the cumulative double bond system N=C=O is directly attached to a carbon atom double-bonded to oxygen, sulphur or nitrogen:



The neighbouring groups stabilize the developing negative charge in the transition state of nucleophilic reactions and therefore these isocyanates are considerably more reactive than aryl isocyanates. Furthermore stabilization by 2 + 4 cycloaddition to form dimeric species can occur and, in fact, in the case of thioacyl isocyanates, only the dimers are stable.

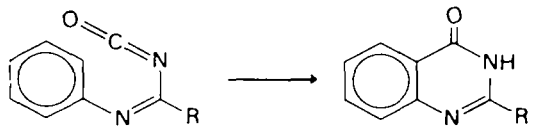
Since the synthesis of acyl and thioacyl isocyanates is discussed in a separate chapter of this volume, only the synthesis of imidoyl isocyanates is treated in this section.

Imidoyl isocyanates were postulated as intermediates in chemical transformations as early as 1936[177], but only recently were stable imidoyl isocyanates synthesized by phosgenation of certain amidines. For example reaction of trihaloalkylamidines **142** with phosgene produced the corresponding imidoyl isocyanates **143** in good yield[178].



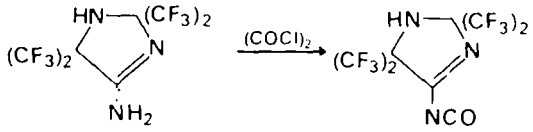
(142) **(143)**

Attempts to prepare the corresponding *N*-phenyl derivatives **144** by a variety of methods resulted in formation of the intramolecular 2 + 4 cycloadduct **145**[178].



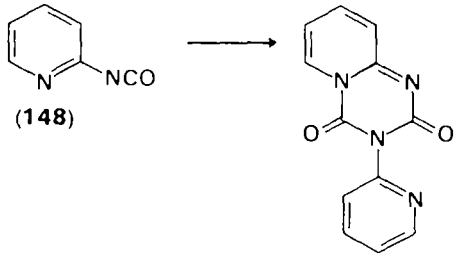
(144) **(145)**

The cyclic perhalo imidoyl isocyanates **147** are obtained in the reaction of the corresponding cyclic amidine **146** with oxalyl chloride[179].



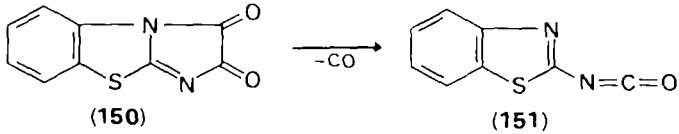
(146) (147)

Isocyanates derived from *N*-heterocyclic α-amines are imidoyl isocyanates. For example 2-isocyanatopyridine **148** can be generated by phosgenation or thermolysis of the corresponding phenylcarbamate, but only its cyclodimer **149** can be isolated[180].



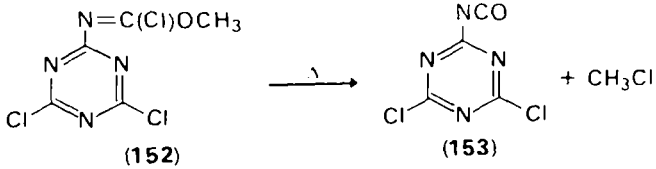
(148) (149)

Dimeric species were also obtained from 2-aminothiazole and 2-aminobenzthiazole. The imidoyl isocyanate **151** was also generated by thermolysis of the bicyclic derivative, **150**, obtained from 2-aminobenzthiazole and oxalyl chloride.



(150) (151)

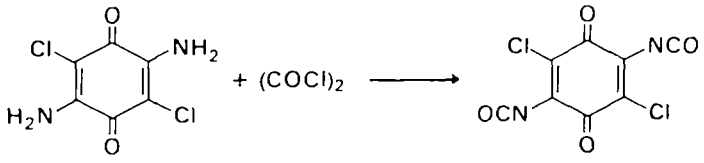
Recently the synthesis of 2,6-diisocyanatopyridine was reported[181], however it is not stable and homopolymerization occurs on standing. 2,4-Dichloro-6-isocyanato-1,3,5-triazine (**153**) has been obtained upon pyrolysis of the chloroimidate **152**[182]



(152) (153)

Stable heterocyclic isocyanates were also obtained from aminoperchloropyridines, pyrimidines, pyrazines and triazines and oxalyl chloride[183].

Diaminodichloro-1,4-benzoquinone **154** has also been converted into the corresponding diisocyanate **155** using oxalyl chloride[183].



(154) (155)

C. Inorganic Isocyanates

In this category isocyanates are discussed in which the NCO group is not attached to carbon. Ionic species such as salts of isocyanic acid are not included. Also isocyanato complexes of transition metals do not fall within the scope of this chapter. The main groups of the periodic system have been used in order to present a consistent picture and the elements under discussion are summarized in Scheme 3.

Inorganic isocyanates

Main group	Element
3	Boron
4	Silicon, germanium, tin, lead
5	Nitrogen, phosphorus, arsenic, antimony
6	Oxygen, sulphur
7	Chlorine, bromine, iodine

SCHEME 3

The standard method of synthesis of inorganic isocyanates consists of reaction of the corresponding halides with a cyanate salt. However other methods have been used frequently, especially in the synthesis of phosphorus and sulphur isocyanates. The inorganic isocyanates are considerably more reactive than isocyanates in which the NCO group is attached to carbon. For example nitrogen and oxygen isocyanates are not known in the monomeric form, and halogen isocyanates are rather unstable. Even iodine isocyanate can be handled only in solution. Silicon, phosphorus and hexavalent sulphur isocyanates are stable for prolonged periods of time, but the lower valent sulphur isocyanates are also rather

unstable. Often perhalo alkyl substitution enhances the stability, as has been observed for the divalent sulphur isocyanates. The hydrolytic sensitivity of the carbamate linkage attached to the inorganic elements renders some of the synthesized isocyanates rather useless for polymer applications, but exceptions are sulphonyl carbamates which are quite stable. Iodine isocyanate is mainly being used for addition reactions to olefins and the derived carbamates are stable.

1. Boron isocyanates

The reaction of boron tribromide with silver cyanate produces boron tricyanate rather than the triisocyanate[184]. However in the reaction of dimethylbromoborane (**156**) with silver cyanate the corresponding isocyanate **157** was obtained in 90% yield[185].

$$(CH_3)_2BBr + AgOCN \longrightarrow (CH_3)_2BNCO$$

(**156**) (**157**)

Many boron isocyanates have been synthesized by this method and the compounds obtained are moderately stable at room temperature[186].

Difluoroisocyanatoborane (**159**) is supposed to be generated in the reaction of silyl isocyanate (**158**) with boron trifluoride, but the compound undergoes rapid decomposition at room temperature[187].

$$H_3SiNCO + BF_3 \longrightarrow H_3SiF + F_2BNCO$$

(**158**) (**159**)

2. Silicon isocyanates

The classical method of synthesis of silicon isocyanates is the reaction of silicon halides with silver cyanate[188]. Instead of silver cyanate, lead dicyanate or alkali cyanates can also be used, but the yields are usually lower[189]. Reasonably good yields of silicon isocyanates are obtained when the reaction of silicon chlorides with potassium cyanate is conducted in liquid sulphur dioxide[190], and silicon isocyanates are also obtained in the reaction of silicon halides with isocyanic acid[191].

Alkoxysilicon isocyanates are produced in the reaction of silicon tetraisocyanate with alcohols[192], while fluorosilicon isocyanates are obtained on reaction of silicon tetraisocyanate with antimony trifluoride[193]. Thermolysis of silicon ureas also gives rise to the formation of silicon

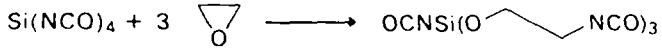
isocyanates. For example heating of the silicon urea **160** to 250–300°C gives trimethylsilicon isocyanate **161**[194].

$$\underset{(160)}{Me_3SiNHCONPh_2} \xrightarrow{\Delta} \underset{(161)}{Me_3SiNCO} + Ph_2NH$$

Reaction of trimethylsilicon chloride **162** with chloro isocyanate or tri-*n*-propyltin isocyanate[202] gives rise to the formation of trimethylsilicon isocyanate, **163**[195].

$$\underset{(162)}{Me_3SiCl} + ClNCO \longrightarrow \underset{(163)}{Me_3SiNCO} + Cl_2$$

Reaction of silicon tetraisocyanate (**164**) with ethylene oxide at 100°C gives the tetraisocyanate **165**[196]



(164) (165)

3. Germanium isocyanates

Germanium tetraisocyanate[197], trimethylgermanium isocyanate[198] and GeH_3NCO[199] have been synthesized by reacting the corresponding halides with silver cyanate.

4. Tin isocyanates

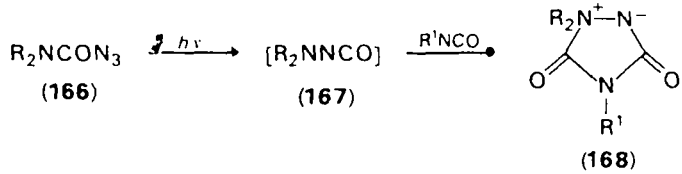
Several tin isocyanates have also been synthesized by reaction of the corresponding halides with silver cyanate[200]. In the synthesis of the tin isocyanates moisture has to be rigorously excluded, otherwise crystalline hydrates are isolated. Triaryltin isocyanates are also obtained in the reaction of triaryltin iodides with lead cyanate[201]. Reaction of ethyl carbamate with trialkyltin methoxide also produces trialkyltin isocyanates in good yields[202]

5. Lead isocyanates

Only trimethyllead isocyanate has been obtained in low yield by the standard halide/silver cyanate procedure[203].

6. Nitrogen isocyanates

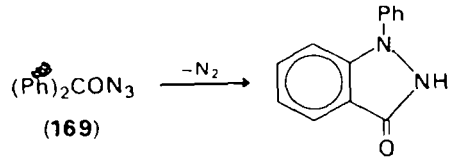
Isocyanates having the NCO group attached directly to nitrogen are not stable in the monomeric form. Dialkylamino isocyanates can be generated as transient intermediates by the photo-Curtius rearrangement of carbamoyl azides[204], by treatment of *N,N*-dialkylaminophosphoramidate anions with CO_2[205], and by reaction of *N,N*-dimethyl-*N'*-dimethylaminoformamidine with phenyl isocyanate[206]. For example photolysis of dialkylcarbamoyl azides (**166**) produces the monomeric dialkylamino isocyanates (**167**), which can be trapped with other isocyanates to form the cycloadducts **168**[207]. Thermolysis of the cycloadducts occurs on heating to 60 °C when R^1 = *t*-butyl, and this method has been used to generate the dialkylamino isocyanates for trapping with other reagents[208]



(166) (167) (168)

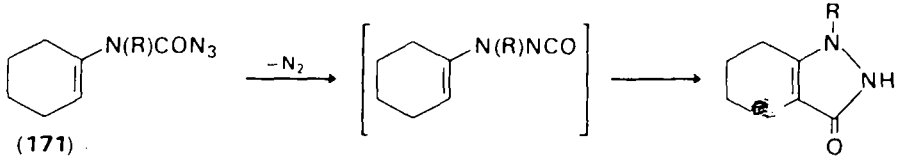
In the absence of substrates which add to **167** the isocyanate forms a dimer with structure **168** ($R^1 = NR_2$).

Arylcarbamoyl azides upon photolysis or thermolysis also produce the corresponding arylamino isocyanates which undergo intramolecular cycloaddition to give indazolone derivatives. For example, heating of diphenylcarbamoyl azide **169** in xylene yields 1-phenylindazolone (**170**)[209].



(169) (170)

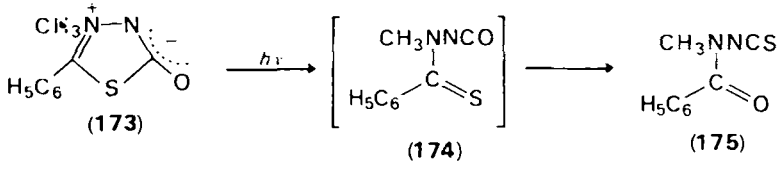
Substituted 4,5,6,7-tetrahydro-3-indazolidinones (**172**) are obtained in the thermolysis of carbamoyl azides (**171**)[210].



(171) (172)

The intermediate isocyanates can be trapped if the reaction is conducted in the presence of alcohols or amines[211]. A review article related to the synthesis and reactions of carbamoyl azides has appeared recently[212].

Amino isocyanates are also generated in the photolysis of mesoionic heterocycles. For example in the photolysis of **173** the isocyanate **174** is formed as a transient intermediate which rearranges rapidly to give the amino isothiocyanate (**175**)[213].



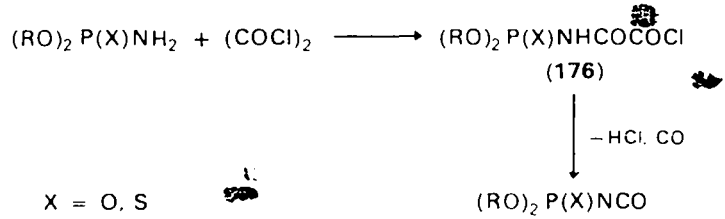
(**173**) (**174**) (**175**)

7. Phosphorus isocyanates

The isocyanates derived from trivalent and pentavalent phosphorus derivatives are well known. A variety of methods of synthesis of phosphorus isocyanates is reported and the isocyanato group directly attached to phosphorus is quite reactive. A review article related to the synthesis and reactions of phosphorus isocyanates has appeared recently[214].

The reaction of phosphorus amides with phosgene often results in the cleavage of the P–N bond with formation of a P–Cl bond. However moderate yields of phosphorus isocyanates can be obtained in the direct phosgenation of $(EtO)_2P(O)NH_2$, $(MeO)_2P(S)NH_2$ and $(ArO)_2P(S)NH_2$ in the presence of pyridine[215]. Instead of the free amide the sodium salt of the corresponding amide or urea can be used[216].

Pentavalent phosphorus isocyanates are also obtained in the reaction of the amides with oxalyl chloride, and in one case (R = Aryl, X = O) the thermolabile intermediate **176** could be isolated[215,217].



The most general method of synthesis of phosphorus isocyanates involves the reaction of phosphorus halides with sodium, potassium or silver

cyanate. For example reaction of phosphorus trichloride with silver cyanate gave isocyanates by stepwise replacement of the chloro groups[218]. Alkyl and aryldihalophosphines are similarly converted to the corresponding diisocyanates[219], and phosphoryl trichloride and thiophosphoryl trichloride have been converted to triisocyanates[220]. Phosphonic acid dichlorides[221], phosphinic acid chlorides[221,222] and tetraiodobiphosphine[223] react in a similar manner with silver cyanate to give the corresponding mono, di and tetra isocyanates, respectively. Halophosphoric acid esters are converted to isocyanates in good yields by conducting the displacement reaction with sodium cyanate in acetonitrile[224]. In the mixed halides RP(O)ClF only the chloro group is displaced by sodium cyanate[225]. Also methylphosphonic acid azidoisocyanate can be obtained by reaction of $MeP(O)ClN_3$ with sodium cyanate[226]. Mono and diisocyanates of alkylthiophosphonic acids are obtained in the reaction of $RPCl_2$ with sodium cyanate in acetonitrile, followed by reaction with $PSCl_3$[227]. Tetramethylphosphordiamidic isocyanate $(Me_2N)_2P(O)NCO$ was also synthesized by reacting $(Me_2N)_2P(O)Cl$ with silver cyanate in benzene[228].

The reaction of alkoxydichlorophosphines with cyanic acid in the presence of pyridine produces diisocyanates. For example $C_6H_5OP(NCO)_2$ was obtained in 61% yield upon reaction of $C_6H_5OPCl_2$ with isocyanic acid[229].

Reaction of phosphorylureas **177** with thionyl chloride produces phosphoryl isocyanates and alkylsulphinylamines[230].

$$R_2P(O)NHCONHR' + SOCl_2 \longrightarrow R_2P(O)NCO + R'NSO$$

(177)

Thermolysis of alkoxycarbonyliminophosphorans to produce isocyanates was discovered by Kirsanov in 1954[231]. For example, reaction of carbamates (**178**) with phosphorus pentachloride produces trichlorophosphazenes (**179**), which eliminate alkyl halide quite readily to produce the isocyanate **180**.

$$ROCONH_2 + PCl_5 \longrightarrow [ROCON{=}PCl_3] \longrightarrow Cl_2P(O)NCO + RCl$$

(178) **(179)** **(180)**

A revised procedure for the synthesis of **180** has appeared recently[232]. *N*-Chloroimino carbonates **181** have also been used to produce isocyanates as shown in the following reaction sequences[233]:

$$(RO)_2C{=}NCl + X_2PCl \longrightarrow [(RO)_2C{=}NPX_2Cl]Cl$$

(181)

$$[(RO)_2C{=}NPX_2Cl]Cl \xrightarrow{-RCl} ROCON{=}PX_2Cl$$

$$ROCON{=}PX_2Cl \longrightarrow X_2P(O)NCO + RCl$$

S = Alkyl, aryl, ArO, Cl

Also thermolysis of alkyl and arylphosphoryl carbamates (**182**) can be used to synthesize phosphoryl isocyanates[234]. The generated alcohol or phenol has to be removed in order to prevent recombination.

$$(RO)_2P(O)NHCOOR' \xrightarrow{\Delta} (RO)_2P(O)NCO + R'OH$$

(182)

The transfer reaction of phosphites with phosphorus triisocyanate yields mixtures of substituted isocyanates[235].

$$(RO)_3P + P(NCO)_3 \longrightarrow ROP(NCO)_2 + (RO)_2PNCO$$

Likewise tetraisocyanatosilane undergoes transesterification with POF_3 to yield difluorophosphoryl isocyanate **183**[236].

$$Si(NCO)_4 + POF_3 \longrightarrow F_2P(O)NCO$$

(183)

Carbonimidoyl dichlorides (**184**) are also readily converted to phosphoryl isocyanates (**185**) on treatment with formic acid[237].

$$RP(O)ClN{=}CCl_2 + HCOOH \longrightarrow RP(O)ClNCO + 2\,HCl + CO$$

(184) (185)

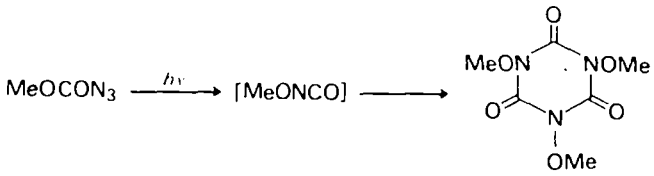
8. Arsenic and antimony isocyanates

Reaction of arsenic trichloride or antimony trichloride with silver cyanate gives a mixture of the corresponding non-volatile tricyanate and the triisocyanate[220]. At elevated temperatures the triisocyanates isomerize to the tricyanates. Antimony triisocyanate has also been obtained in the reaction of phosphonic diisocyanates with SbF_3[238].

9. Oxygen isocyanates

Phosgenation of *O*-benzylhydroxylamine gave only the corresponding trimer (1,3,5-tribenzyloxyisocyanurate)[239]. The same compound was

obtained when Staab and Benz used the mild imidazole method to produce the monomeric benzyloxy isocyanate[240]. 1,3,5-Trimethoxy and 1,3,5-triethoxyisocyanurate were obtained in the reaction of the corresponding diethyl *N*-alkoxyphosphoramidate anions with carbon dioxide[241]. Even room temperature photolysis of methyl azidoformates gave only the corresponding triisocyanurate derivative (**186**) indicating that monomeric methoxy isocyanate, produced by the rearrangement of methoxycarbonyl nitrene, is not stable at room temperature[242].



(**186**)

10. Sulphur isocyanates

Stable isocyanates having the NCO group attached directly to sulphur are well known, and derivatives derived from di, tetra, and hexavalent sulphur have been synthesized. Review articles related to the synthesis and reaction of sulphonyl isocyanates have appeared recently[243,244]. Trifluoromethylsulphur isocyanate (**188**), the first monomeric divalent sulphur isocyanate, was synthesized by Emeleus and Haas in 1963[245]. Their synthesis consists of reacting the corresponding sulphur chloride (**187**) with silver cyanate, and as a by-product the dimer **189** is obtained.

$$CF_3SCl + AgOCN \longrightarrow CF_3SNCO + (CF_3)_2NCONCO$$

(**187**) (**188**) (**189**)

In a similar manner dichlorofluoro- and difluorochlorosulphur isocyanate can be prepared, but these isocyanates slowly dimerize on standing[246]. Pentafluorobenzenesulphenyl isocyanate can only be obtained as a polymeric solid[247], but $F_3SCClFSNCO$[248], $ClCOSNCO$[249], $FCOSNCO$[249], and $Cl_3C(S)SNCO$[250] have been isolated as monomeric isocyanates.

Sulphinyl chlorides also react with silver cyanate to give sulphinyl isocyanates. In this manner CCl_3SONCO[251], $4\text{-}CH_3C_6H_4SONCO$[252], CF_3SONCO[253] and $n\text{-}C_4F_9SONCO$[253] are obtained.

Hexavalent sulphur isocyanates are considerably more stable than the

lower valent isocyanates. The direct phosgenation of arenesulphonamides occurs at high temperature, and simultaneous cleavage of the S—N bond is observed[254,255]. The use of nitrobenzene as solvent for the phosgenation of arenesulphonamides has been reported also[256]. However best results are obtained if the phosgenation of the arenesulphonamide is conducted in the presence of an alkyl isocyanate. Rapid reaction occurs at approximately 100 °C the corresponding sulphonyl urea (**190**) being the intermediate[51].

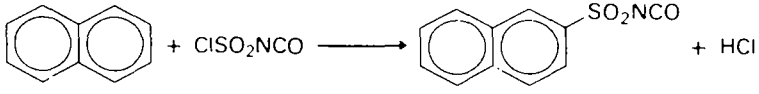
$$RSO_2NH_2 + COCl_2 \xrightarrow{R'NCO} [RSO_2NHCONHR'] \longrightarrow RSO_2NCO + R'NCO$$

(**190**)

In this manner arenesulphonyl isocyanates can be synthesized free of chloride by-products. Instead of phosgene, arenesulphonamides can also be reacted with carbonyldiimadazole to give an adduct, which on heating in the presence of P_2O_5 yields arenesulphonyl isocyanates[257].

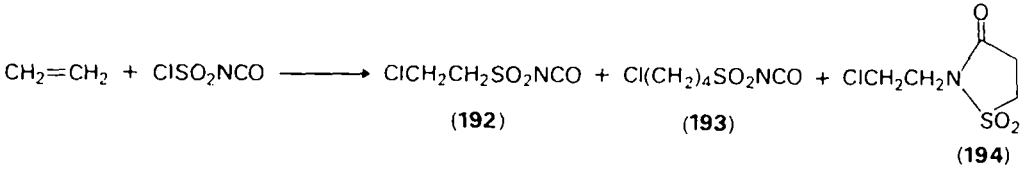
Reaction of arenesulphonamides with excess oxalyl chloride also produces the corresponding sulphonyl isocyanates[258]. Perfluoroalkanesulphonyl isocyanates are also obtained in the reaction of the corresponding sulphonamide with chlorosulphonyl isocyanate in refluxing sulpholane[259].

Chlorosulphonyl isocyanate has been used also to synthesize arenesulphonyl isocyanates. For example electrophilic reaction of chlorosulphonyl isocyanate with naphthalene at 150 °C in the absence of a catalyst gives a 55% yield of 2-naphthalenesulphonyl isocyanate (**191**)[260].



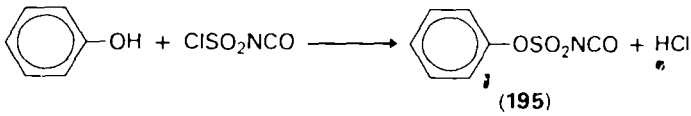
(**191**)

Free-radical-catalysed addition of chlorosulphonyl isocyanate to olefins yields a mixture of telomeric chloroalkylsulphonyl isocyanates[261]. For example, addition of chlorosulphonyl isocyanate to ethylene yields 2-chloroethylsulphonyl isocyanate (**192**), 4-chlorobutylsulphonyl isocyanate (**193**) and the heterocyclic adduct **194**[261].



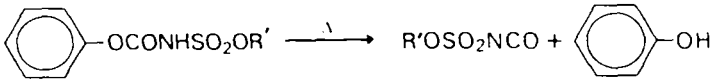
(192) (193) (194)

Reaction of phenols with chlorosulphonyl isocyanate in refluxing toluene produces aryloxysulphonyl isocyanates (**195**) in good yields[262].



(195)

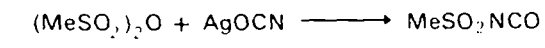
Thermal decomposition of carbamates (**196**) derived from chlorosulphonyl isocyanate and phenol, followed by reaction with an alcohol produces alkoxysulphonyl isocyanates (**197**)[263].



(196) (197)

Also arenesulphonylcarbamates undergo thermolysis in the presence of P_2O_5 to give the corresponding arenesulphonyl isocyanates[264]. The required carbamates can be obtained by reacting the sodium salt of the corresponding sulphonamide with alkyl chloroformates. Arenesulphonyl isocyanates are also obtained in the pyrolysis of thiocarbamates $RSO_2NHCOSMe$[265].

Reaction of arenesulphonyl chlorides with silver cyanate produces arenesulphonyl isocyanates[266]. Sulphonyl diisocyanate can be obtained similarly from chlorosulphonyl isocyanate and silver cyanate[267]. Methanesulphonyl isocyanate (**199**) was also obtained in 38% yield in the reaction of methanesulphonic anhydride (**198**) with silver cyanate[268].



(198) (199)

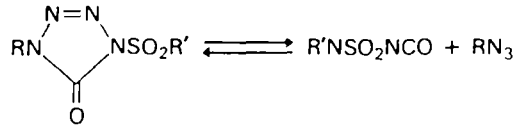
Reaction of 1,3-arenesulphonylphenylurea with thionyl chloride also yields arenesulphonyl isocyanates and phenyl sulphinylamine[230].

Alkanesulphonyl isocyanates are readily prepared by thermolysis of trimethylsilylated sulphonyl carbamates (**200**)[269].

$$RSO_2N(SiMe_3)COOEt \xrightarrow{\Delta} RSO_2NCO + Me_3SiOEt$$

(**200**)

Thermolysis of certain tetrazolin-5-ones (**201**) also gives rise to the formation of arenesulphonyl isocyanates, but since tetrazolin-5-ones are best produced by cycloaddition of arenesulphonyl isocyanates to azides, this method is of no preparative significance[270].



(**201**)

The reaction of cyanogen chloride with sulphur trioxide produces a mixture of chlorosulphonyl isocyanate and chloropyrosulphuryl isocyanate (**202**)[271].

$$ClCN + SO_3 \longrightarrow ClSO_2NCO + ClS_2O_5NCO$$

(**202**)

In contrast, reaction of cyanogen bromide with sulphur trioxide gives a mixture of sulphonyl diisocyanate (**203**) and pyrosulphuryl diisocyanate (**204**)[272].

$$BrCN + SO_3 \longrightarrow SO_2(NCO)_2 + S_2O_5(NCO)_2$$

(**203**) (**204**)

Sulphonyl diisocyanate is also formed (besides chlorine and SO_2) on heating chlorosulphonyl isocyanate to 200–500 C, preferentially in presence of catalysts[273].

A small amount of chlorosulphonyl isocyanate is obtained in the reaction of urea with chlorosulphonic acid[274], and fluorosulphonyl isocyanate can be obtained from sulphonyl diisocyanate and fluorosulphonic acid[275]. However the best method of synthesis of fluorosulphonyl isocyanate involves fluorination of chlorosulphonyl isocyanate[276]. Pyrosulphuryl isocyanate has also been obtained from potassium cyanate and sulphur trioxide[277].

Hydrolysis of the carbonimidoyl dichloride derivative **205** with water produced the sulphur isocyanate **206**[278].

$$SF_5N{=}CCl_2 + H_2O \longrightarrow SF_5NCO$$

(205) (206)

11. Halogen isocyanates

In 1929 Birkenbach and Linhard[279] obtained monomeric iodo isocyanate upon reaction of iodine with silver cyanate in diethyl ether. In contrast only dimeric species $X_2NCONCO$ were isolated even at $-80\,^{\circ}C$ when this reaction was extended to chlorine and bromine[280]. In 1966 Nachbaur and Gottardi reported the synthesis of monomeric chloro isocyanate by pyrolysis of its cyclic trimer, *N*-trichloroisocyanuric acid[281].

The melting point of monomeric chloro isocyanate is $-98{\cdot}5$ C, and spectral data and derived reaction products verify the proposed structure. In the liquid phase chloro isocyanate undergoes rapid dimerization[282], and on attempted distillation extensive decomposition occurs. In contrast iodo isocyanate is relatively stable in ethereal solution, and the isocyanate is usually reacted *in situ*. For example the stereospecific addition of iodo isocyanate to a wide variety of olefins has been well investigated[151]. The preparation and stability of iodo isocyanate solutions has been described in detail by Rosen and Swern[283].

III. REACTIONS OF ISOCYANATES

A. General

The polarization of the isocyanate group in the manner indicated

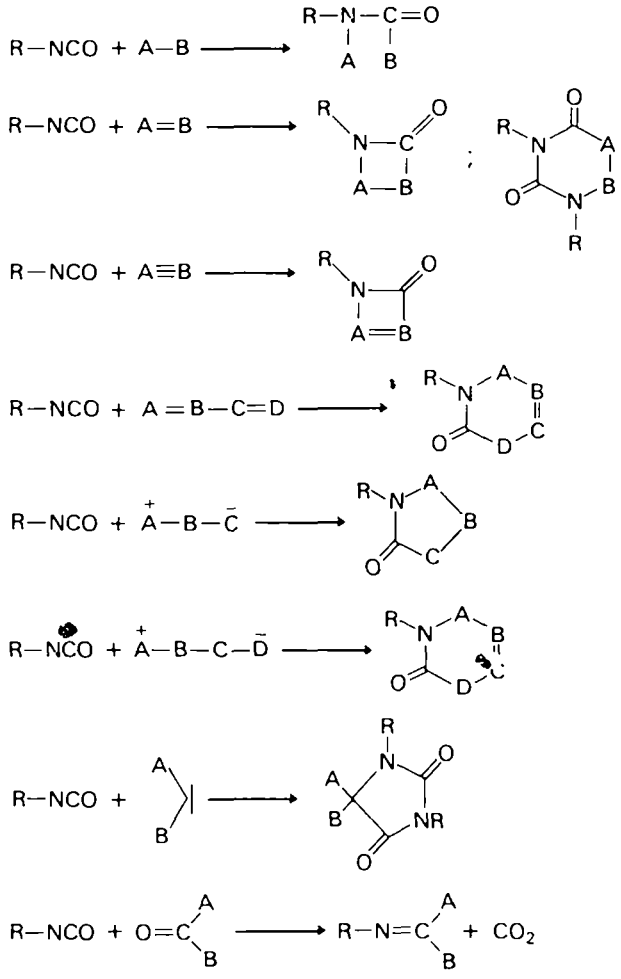
$$R{-}\bar{\underline{N}}{-}\overset{+}{C}{=}O \longleftrightarrow R{-}N{=}C{=}O \longleftrightarrow R{-}N{=}\overset{+}{C}{-}\bar{\underline{O}}|$$

clearly shows the electrophilic character of the central carbon atom. Consequently most reactions are initiated by an attack of isocyanates on electron-rich centres. Electron-withdrawing groups in R or directly linked to the isocyanate moiety increase the reactivity of the NCO group.

Most of the chemistry of isocyanates is based on reactions of the C=N bond of the O=C=N moiety with substrates A—B, A=B, A≡B, A=B—C=D as well as 1,3- and 1,4-dipolar compounds, resulting in the formation of widely differing acyclic and cyclic reaction products. New types of reactions and application of known ones to new substrates are reported continuously. Very often initially-formed reaction products are further modified by action of excess isocyanate or substrate. A number of typical reactions of isocyanates are summarized in Scheme 4 below.

Reactions which take place under participation of the R—N or C=O bonds of isocyanates are known too. In addition isocyanates are known to react with each other, forming dimers, trimers and polymers.

The reaction of alcohols with isocyanates to give carbamates (urethanes) and its application to polyfunctional alcohols and isocyanates is the basis of the polyurethane industry. Other reactions such as the formation of ureas, oxazolines, imides and carbodiimides and the oligomerization of isocyanates are also of importance in industrial applications. The continued search for new and potentially useful reactions of isocyanates is certainly one of the main reasons for the steady increase in the amount of information about the chemistry of isocyanates.



SCHEME 4.

The large amount of material related to synthetic reactions involving isocyanates together with the space limitations of this book allow for only a limited coverage of the area. The chemistry of acyl and thioacyl isocyanates is excluded. Occasional mention of reactions of these compounds is limited to cases where a distinction between alkyl, aryl and other isocyanates must be emphasized.

Strict adherence to the arrangement chosen for the description of the reactions of isocyanates is sometimes not possible. Certain transformations, belonging to different sections but leading to related products or involving similar intermediates, are occasionally treated under one heading with the intention of conveying to the reader the various aspects of a particular type of reactions.

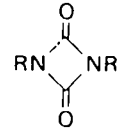
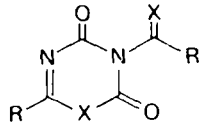
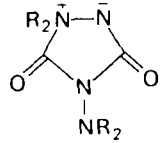
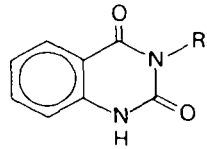
B. Reactions of Isocyanates Across Their C=N Bond

1. Oligomerization and polymerization of isocyanates

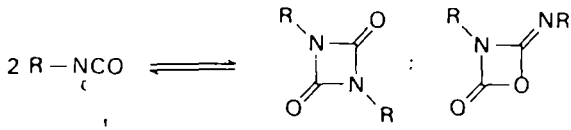
a. *Dimerization.* The dimerizations of isocyanates are not uniform reactions in regard to the nature of the products formed. They depend rather upon the reactivity and structure of the starting materials. Aryl isocyanates dimerize generally under crosswise addition to the C=N bonds of the NCO group. Acyl, thioacyl and imino isocyanates give dimers under the inclusion of adjunct C=X groups (X = O, S, NR) in the ring formation. Amino isocyanates and halo isocyanates give still other types of dimers (see Scheme 5).

Hoffman observed that phenyl isocyanate is readily dimerized in presence of triethyl phosphine as catalyst[284]. Other trialkyl phosphines and aryldialkylphosphines, dialkylcarbamoyl diethyl phosphite, tris-dialkylcarbamoyl phosphites, hexaalkyl phosphortriamides, and bis-*N*-dialkyl phosphoramidous acid ethyl ester[355], as well as a number of amines (pyridines, 1,2-dimethylimidazole[285], *N,N,N',N'*-tetramethyl-*N''*-phenyl guanidine[286]) were later shown to catalyse the dimerization of aryl isocyanates as well[93]. Structure determination on the well-crystallizing aryl isocyanate dimers by X-ray diffraction[361] revealed their existence in the symmetric 1,3-diazetidinedione and not the equally possible imino-oxazetidinone form. The role of the catalyst in the oligomerization and polymerization of isocyanates has been discussed extensively[93] and it is assumed that polar intermediates of various chain length are formed from catalyst and isocyanate. Attack by the catalyst on the central carbon atom of the isocyanate moiety is believed to be the initial reaction step.

Dimers of isocyanates

Monomer	Type of Reaction	Product
RNCO R = Aryl, alkyl, R'S	[2 + 2] cycloaddition	
RCNCO ‖ X R = Aryl X = O, S, NR	[2 + 4] cycloaddition	
R_2N-NCO R = Alkyl	[2 + 3] cycloaddition	
XNCO X = Cl, Br	X-N insertion	$X_2NCONCO$
$RNCO(AlCl_3)$ R = Aryl	[2 + 4] cycloaddition with H shift	

SCHEME 5.

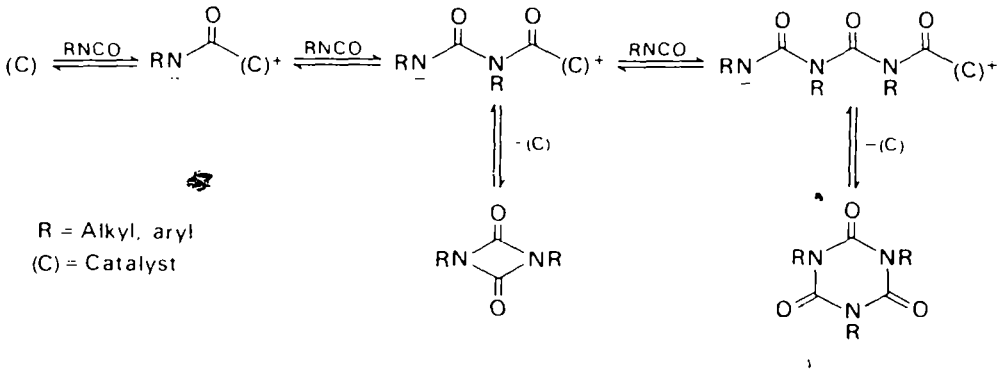


Very reactive isocyanates, such as sulphonyl isocyanates, form only polar 1:1 adducts with amine catalysts, which do not further oligomerize[243].

It is a curious phenomenon that simple alkyl isocyanates do not dimerize but rather trimerize to isocyanurates under comparable reaction conditions. It has recently been claimed, however, that butyl and cyclohexyl isocyanates and also hexamethylene diisocyanate can be cyclodimerized in less than 1 % yield on heating in presence of tributylphosphine or other catalysts[287]. We were able to cyclodimerize a number of benzyl isocyanates in reasonable yield in the presence of 1,2-dimethylimidazole[285]. By-products in these reactions are the corresponding tribenzyl isocyanurates. Infrared spectroscopic monitoring of the reactions revealed

slow conversion of the initially formed dimers into trimers. Catalysed trimerizations of other aliphatic isocyanates could be shown to proceed in some cases via formation of dimers as intermediates. A related but slow conversion of phenyl isocyanate to triphenyl isocyanurate via 1,3-diphenyl-1,3-diazetidinedione was observed in presence of a guanidine catalyst[286]. Trialkylphosphines, which have been regarded as highly specific dimerization catalysts for aryl isocyanates, were recently shown to catalyse the conversion of dimer into trimer on prolonged standing of the reaction mixtures[288]. Pyridines and other basic catalysts have an even lower degree of specificity because at elevated temperature trimerization competes with dimerization. Mixtures of dimers and trimers of aryl isocyanates are also obtained with sodium perbenzoate in dimethylformamide[288], organosilyl sulphides[27] and trimethylsilyldiphenylphosphine[289].

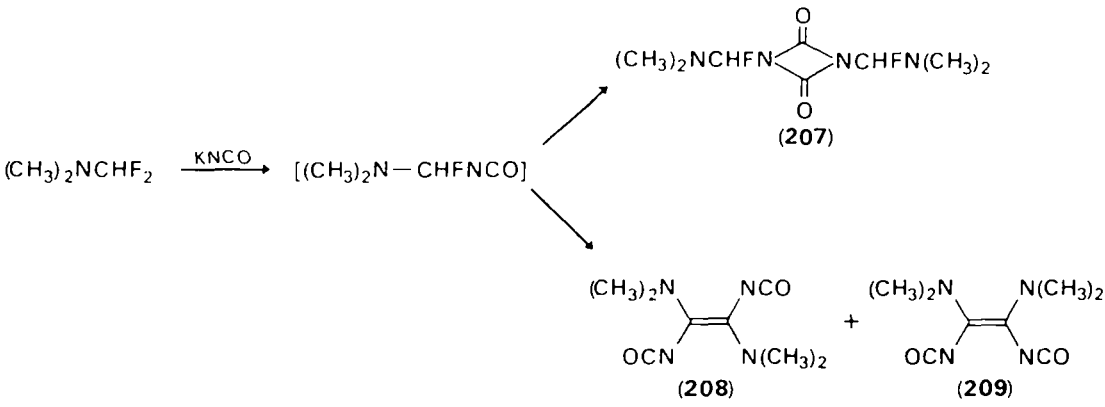
The graduai disappearance of the dimers and appearance of trimers in these catalysed oligomerizations of alkyl and aryl isocyanates can be explained by the assumption of equilibria between dimer and polar intermediates formed from dimer and catalyst. The latter are able to react further with excess isocyanate to give trimer. It is, however, not possible so far to predict the formation of a certain product (dimer or trimer) with a certain catalyst. Factors such as charge stabilization in the polar intermediates and their lifetime or steric requirements might be of importance too.



Phenyl isocyanate is also dimerized when heated under pressure. 1,3-Diphenyl-1,3-diazetidine-2,4-dione is obtained in over 90% yield at 16 kilobars at a temperature range of 175–225 °C, while higher temperatures and pressures lead to formation of by-products[357].

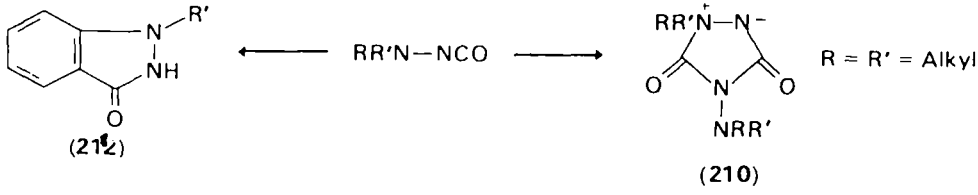
Certain isocyanates are known to dimerize even without a catalyst.

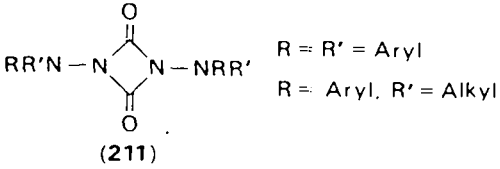
Thus dimethylamino fluoromethyl isocyanate, in which the dimethylamino group is possibly acting as catalyst, dimerizes to give **207** when synthesized from potassium cyanate and dimethylaminodifluoromethane: 1,2-bisdimethylamino-1,2-diisocyanatoethylenes **208** and **209** are formed as by-products[289]



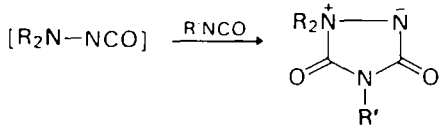
1,3-Bistrifluoromethylsulphenyl-1,3-diazetidinedione is obtained on dimerizing the corresponding sulphenylisocyanate at room or elevated temperature[246,290].

The dimerization of dialkylamino isocyanates, formed as transient intermediates in a number of reactions, does not lead to formation of 1,3-diazetidinediones but rather 1,2,4-triazolidine-3,5-dione-1,2-ylides **210**[204–208]. This behaviour is in contrast to that of *N*,*N*-diarylamino and arylalkylamino isocyanates which are claimed to give 1,3-diazetidinediones (**211**) and varying amounts of 1-phenylindazolone (**212**)[209] (see also p. 39).



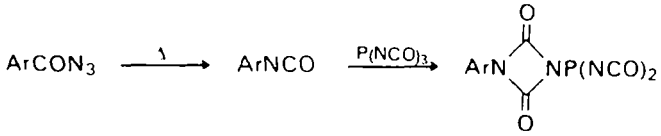


Mixed dimers **210a** are obtained on intercepting the dialkylamino isocyanates with alkyl or aryl isocyanates[205,208,364].



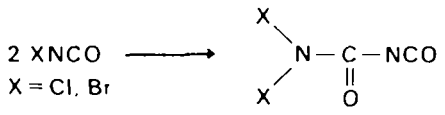
(210a)

Formation of mixed dimers of two different aryl isocyanates or aryl and alkylisocyanates has not been observed to date. The latter (as well as 1,3-dialkyldiazetidinediones) have been prepared from *N*-aryl-*N'*-alkyl-allophanyl chlorides on treatment with base[291–294]. [2 + 2] Adducts, **213**, with diazetidine-dione structure are obtained in very good yield on heating triisocyanatophosphine with aroyl azides[295].



(213)

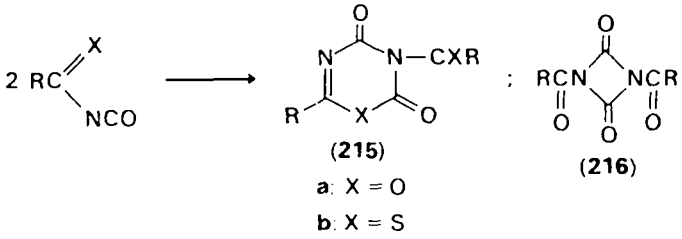
A different type of oligomerization is the dimerization of *N*-haloisocyanates. *N*-Chloro and bromo isocyanate dimerize rapidly to give *N,N*-dihalo carbamoyl isocyanates (**214**)[279,280,282].



(214)

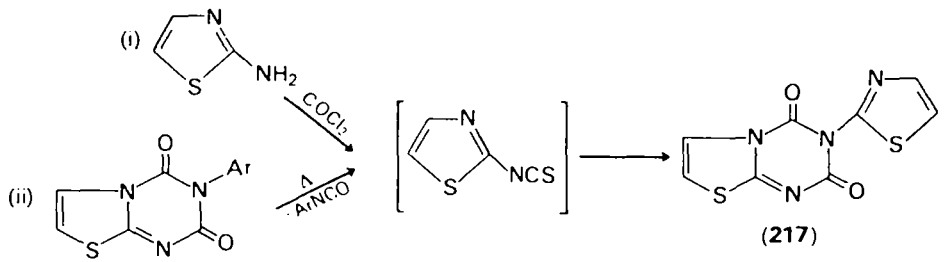
Two different structural formulas have been suggested for dimers derived from acyl isocyanates. Neidlein claims that the dimer of the pyridine-catalysed dimerization of benzoyl isocyanate has the 1,3-diazetidine-2,4-dione structure [illegible][296]. Subsequent investigation into the catalysed di- and trimerization of aroyl isocyanates in presence of amines, amine oxides and stannic chloride at room or elevated temperature revealed the formation of a number of different products[297,298]. The

dimers formed in these reactions are believed to be 1,3,5-oxadiazine derivatives (**215a**) produced in a [2 + 4] cycloaddition from two isocyanate molecules acting as diene and dienophile. These structure assignments are in agreement with related dimers of thioacyl isocyanates which were found to be 1,3,5-thiadiazine derivatives (**215b**)[299,300].

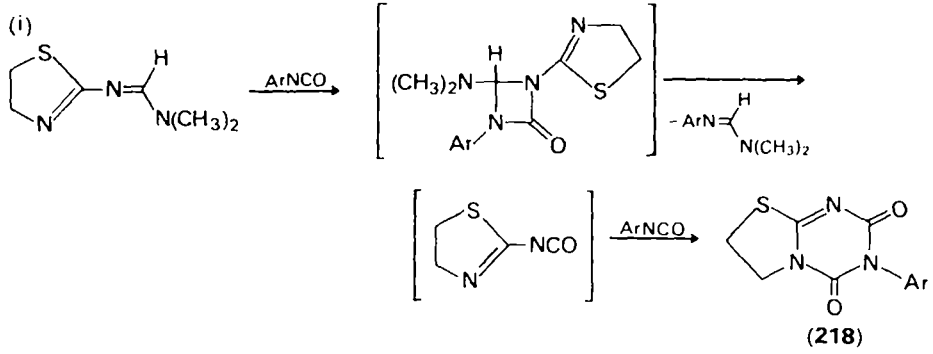


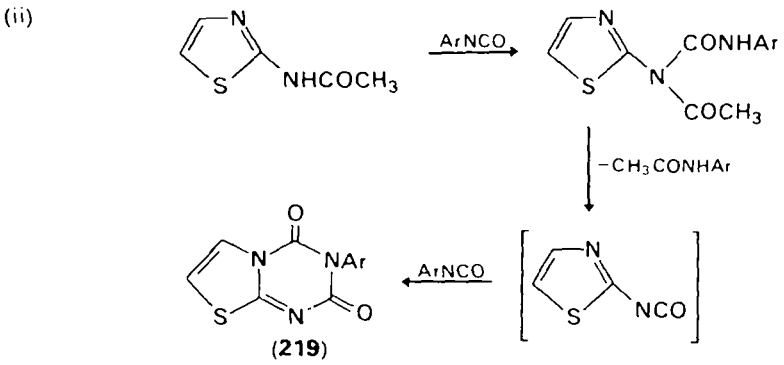
A number of isocyanates bearing an imino group adjacent to the NCO moiety are not stable in the monomeric form and dimerize in a [2 + 4] cycloaddition with incorporation of the imino group into the ring giving 1,3,5-triazine derivatives. When such imino isocyanates, in which the imino group can be part of a heteroaromatic ring, are generated in presence of excess arylisocyanate, mixed dimers with related structure are formed. A few examples of cyclodimerizations of imino isocyanates, including their path of generation, are shown below.

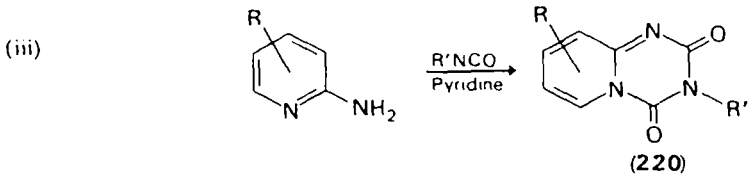
Imino isocyanate dimers[180,302]: (see also Section II.B).



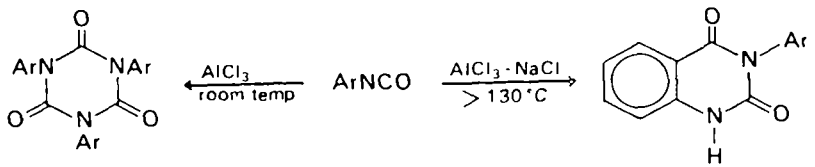
Imino isocyanate–aryl isocyanate co-dimers[301–303,356].







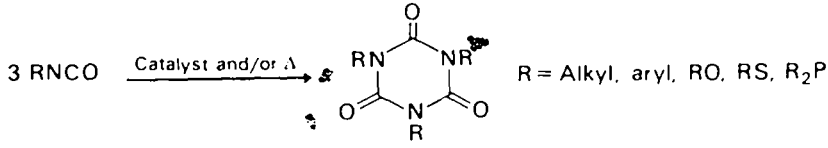
A different type of dimerization of aryl isocyanate takes place in the presence of Lewis acids. Treatment of phenyl isocyanate with aluminium chloride at room temperature gives rise to formation of isocyanate trimers (isocyanurates); at temperatures of 130–135 °C and in presence of aluminium chloride–sodium chloride mixtures high yields of 3-phenyl-2,4-dioxotetrahydroquinazoline (**221**) obtained instead[362]. Other quinazoline derivatives can be obtained with substituted arylisocyanates[363].



(221)

In this reaction, which can formally be regarded as a [2 + 4] cycloaddition with successive proton shift, the aryl isocyanate acts as both diene and dienophilic component.

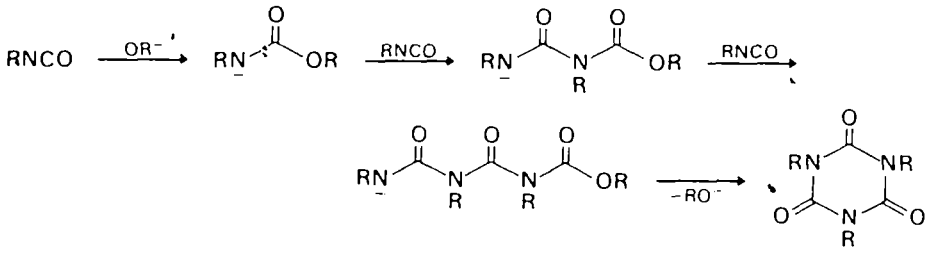
b. *Trimerization.* Like isocyanic acid, alkyl, aryl and some other isocyanates trimerize on heating or in presence of catalysts to 1,3,5-trisubstituted hexahydro-*s*-triazinetriones (isocyanurates). Only highly hindered isocyanates, such as *t*-butyl and *t*-octyl isocyanate, fail to undergo trimerization.



Numerous catalysts, such as lithium oxide, sodium and potassium alkoxides, sodium formate, carbonate, benzoate and borohydride, potassium and calcium acetate, alkali soaps, lead hydrides, lead salts, metal alkoxides and metal naphthenates in general, tertiary amines, *N*,*N*-dimethylformamide, and Friedel–Craft type compounds, are reported to cause trimerization. Among these, alkali metal alkoxides are most effective and are widely used. More recently a growing number of metal organic compounds of groups IVa, IVb, Va and IIb elements have been suggested as trimerization catalysts[123]. The usually-slow trimerization of isocyanates in presence of tertiary amines can be dramatically increased by adding olefin oxides, carbonyl-group-containing compounds, alkyleneimines or alkylene carbonate as co-catalysts[304–309].

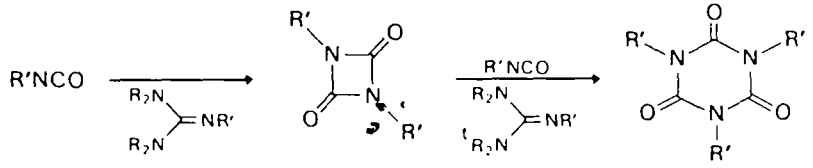
Trialkylphosphines or arylalkyl phosphines which are known to be excellent dimerization catalysts for aromatic isocyanates trimerize aliphatic isocyanates. A compilation of catalysts as well as experimental details for several trimerizations can be found in recent reviews[93,123].

The common step in all the catalysed trimerizations is the activation of the C=N double bond of the isocyanate group. The example below shows the catalytic action of the alkoxide anion which causes formation of carbamate and allophanate intermediates:
Alkoxide catalysis:



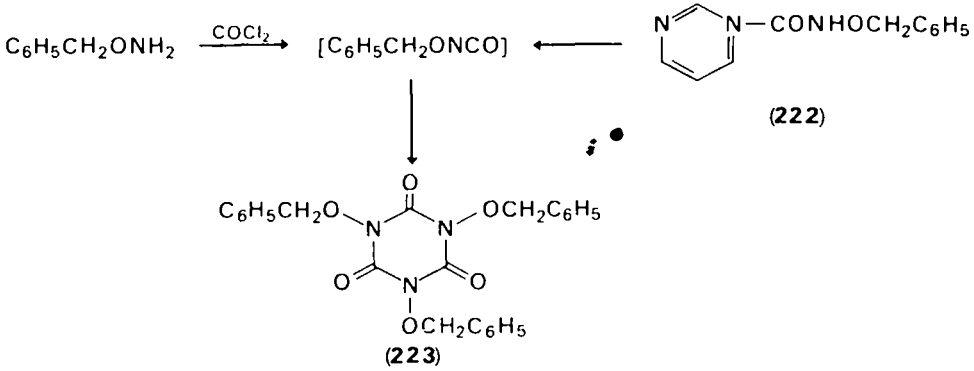
Related oligomerization steps must be involved with other catalysts, of which a detailed discussion can be found elsewhere[93].

Since some catalysts initiate dimerization and trimerization (as well as polymerization) under certain conditions, equilibria between monomeric isocyanate/catalyst, dimer/catalyst and trimer/catalyst must exist. Triphenylisocyanate is obtained in 77% yield from phenyl isocyanate in presence of catalytic amounts of a penta-substituted guanidine. On interrupting the reaction after only a short time, 1,3-diphenyldiazetidine-2,4-dione can be isolated[286].



Application of certain basic catalysts in the trimerization of aryl isocyanates can lead to formation of carbodiimides instead of the expected isocyanurates, or mixtures of both, especially with sterically hindered aromatic isocyanates (2,6-diethylphenyl isocyanate) and bulky alkali alkoxides such as potassium or lithium *t*-butoxide[100]. Interaction of the formed carbodiimide with isocyanate to cyclic 1:1 adducts[100,310] or, under certain conditions, 1:2 adducts[311,312] is likely and leads to complicated reaction mixtures.

While certain isocyanates, such as the highly sterically hindered *t*-butyl isocyanate and sulphonyl isocyanates, are so far not known to trimerize, others are not stable or only stable to a limited extent in the monomeric form. Attempts to prepare alkoxy isocyanates produced only the isocyanurates in each instance. Thus phosgenation of *O*-benzylhydroxylamine or thermolysing **222** leads to formation of the trimer **223**[239,240].



(222)

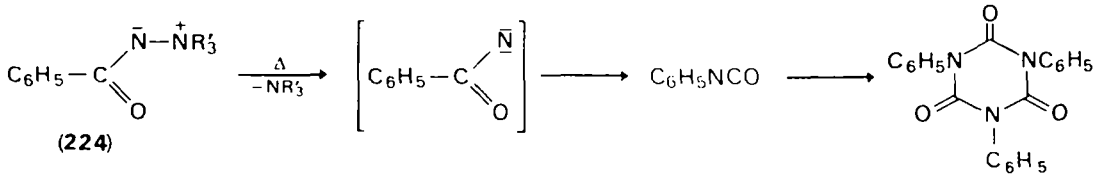
(223)

Other trialkoxy isocyanurates are obtained from *N*-alkoxy phosphoramidate anion and carbon dioxide[241] or photolysis of methyl azidoformate[242].

Trialkyltin isocyanate trimerizes to tris(trialkyltin)isocyanurates during preparation from trialkyltin oxide and isocyanic acid[313], and diphenyl phosphinic isocyanate[314] as well as phenyl diisocyanatophosphine[315] trimerize slowly on standing.

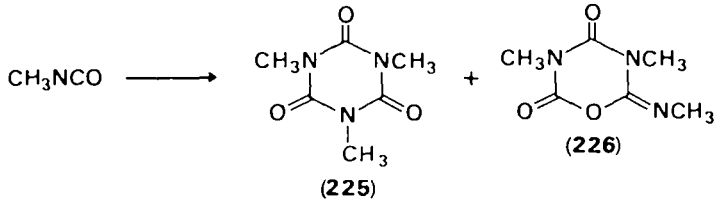
Alkylation of alkali cyanates with alkyl halides in hot dimethylformamide or other highly polar solvents causes formation of 1,3,5-trialkyl isocyanurates in high yield besides the monomeric isocyanates[316–318].

During thermal decomposition of trialkylamine-benzamide (**224**) a trialkylamine and phenyl isocyanate are formed. The latter readily trimerizes to triphenyl isocyanurate[319,320,72].



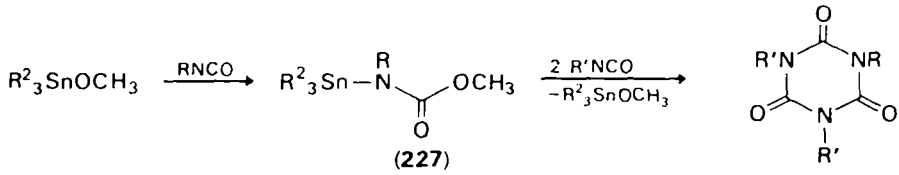
(224)

The behaviour of methyl isocyanate which forms two different products during the trialkylphosphine-catalysed trimerization is unusual. Besides the expected triazine (**225**) 3,5-dimethyl-2-methylimino-4,6-dioxohexahydro-1,3,5-oxdiazine (**226**) is obtained also[321]

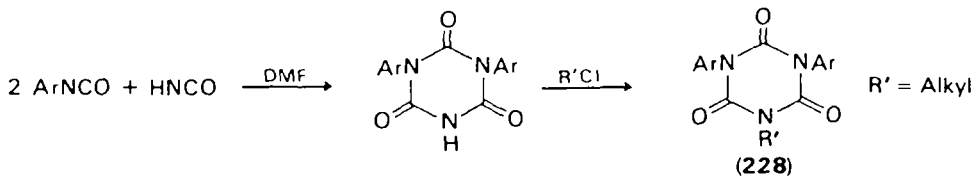


The co-trimerization of different isocyanates to isocyanurates has been attempted in different ways. Random formation of all possible trimers is observed in simple base-catalysed co-trimerization of two different aromatic and aliphatic isocyanates[322]. The reactions can be somewhat influenced by using an excess of one component.

Heating of a 2:1 mixture of aryl isocyanates with different degrees of reactivity, such as 4-nitrophenyl isocyanate and *p*-tolyl isocyanate, is claimed to lead cleanly to co-trimers[323]. The systematic stepwise formation of isocyanurates from two different aliphatic or aromatic isocyanates was shown to be possible with certain organotin catalysts[324–327]. Trialkyltin methoxide and isocyanates give an isolable carbamate **227** formed by insertion of the isocyanate into the Sn–O bond. Application of a different isocyanate for the formation of the isocyanurate via an allophanate leads cleanly to 2:1 co-trimers.

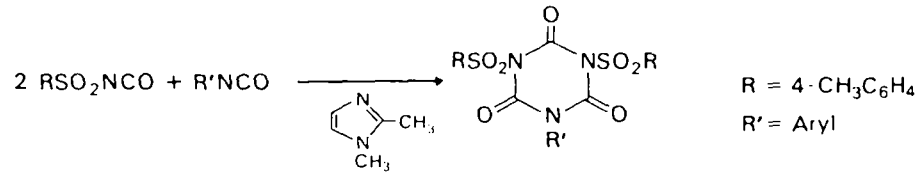


Co-trimerizations between isocyanic acid (alkali cyanates) and aryl isocyanates (or their dimers) in *N,N*-dimethylformamide give cyclic 1:2 adducts in excellent yield. Carrying out the reactions in presence of an alkyl halide leads to *N,N'*-diaryl-*N''*-alkyl isocyanurates **228**[328–330].

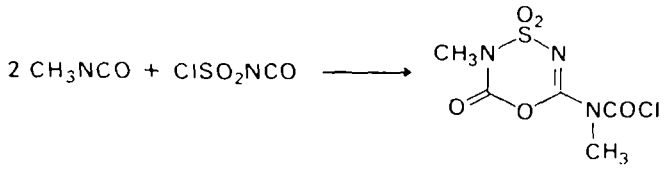


(228)

It has recently been found that even *p*-tolylsulphonyl isocyanate can be co-trimerized with aryl isocyanates to 2:1 adducts in presence of 1,2-dimethylimidazole[876]. Isocyanurates containing only one arenesulphonyl isocyanate as building block have been synthesized via different routes[876,331-333]

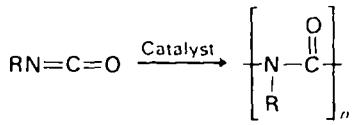


A rather unusual 2:1 cycloadduct, **229**, is obtained on reacting methyl isocyanate with chlorosulphonyl isocyanate in presence of stannic chloride[334]



(299)

c. *Polymerization.* Alkyl and aryl isocyanates have been shown to polymerize in the presence of anionic and basic catalysts and also photochemically. The reactions are generally conducted in highly polar solvents such as *N*,*N*-dimethylformamide and at temperatures below −40 °C, since higher temperatures cause formation of considerable amounts of trimeric isocyanates (isocyanurates). Shashoua and coworkers[335,336], who effected this low temperature polymerization of a number of alkyl and aryl isocyanates in presence of sodium cyanide, sodium ketyl, sodium naphthalene, sodium in *N*,*N*-dimethylformamide, or *N*-methyl acetamide, called the products *N*-substituted 1-nylons (**230**).



(230)

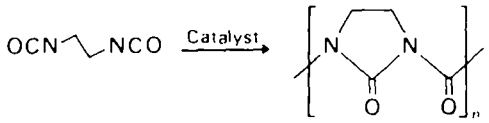
It was later found by Natta and coworkers[337] that alkyl lithium and sodium catalysts and Friedel-Craft catalysts promote the polymerization too. Polymers obtained from *n*-butyl and phenyl isocyanate are crystalline. Boron trifluoride etherate[338] and tris-isobutyl aluminium[339] as well as organic bases like hexamethylene tetramines[340] and $(CH_3)_2$-$N(CH_2)_2N(CH_3)_2$[341] have been used as catalysts for the homopolymerization or copolymerization[342] of isocyanates. The polymerization has also been induced by radiation[343] and electrochemically[344]. Recently it was shown by Iwakura and coworkers that even aqueous bases can effect the homopolymerization of phenyl isocyanate provided that the reaction is conducted at $-50\,°C$[345]. A *N*,*N*-dimethyl formamide solution of lithium azide is supposed to cause polymerization of phenyl isocyanate above room temperature[346].

Molecules containing more than one isocyanato group have also been homopolymerized under related conditions[358,359]. An optically active polyisocyanate is obtained from D-β-phenylpropyl isocyanate[360].

The homopolymers melt around 180–250 °C usually with decomposition. Treatment of polyisocyanate solutions in dimethylformamide with di-*n*-butylamine effects depolymerization with formation of the corresponding trimer and urea, the latter compound arising from the reaction of the monomer with the amine[347].

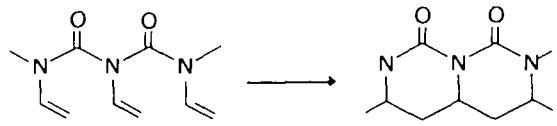
Structure determinations of homopolymeric alkyl and aryl isocyanate revealed that the macromolecules have a stiff, rod-like structure[348–350].

Heterocyclic polymers are obtained from α,ω-polymethylene diisocyanates such as 1,2-diisocyanatoethane[351].



Vinyl isocyanate has also been selectively polymerized to give the 1-nylon homopolymer **231**, which on treatment with azoisobutyronitrile and ultraviolet light at room temperature gave the ladder polymer **232**[352].

The same polymer can be obtained from vinyl isocyanate directly on γ-irradiation[353,354].



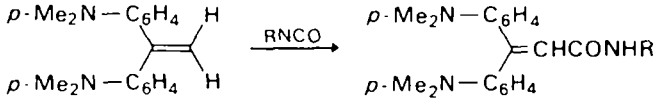
(231) (232)

2. Cycloadditions

a. [2 + 2] *Cycloadditions*

(i) With C=C bonds. Reactions of olefins, as well as other systems with C=C double bonds (such as allenes and ketene derivatives), and isocyanates are numerous and have been studied in great detail; many of these reactions are of significant synthetic value, especially for the preparation of β-lactams and carboxylic acid amides.

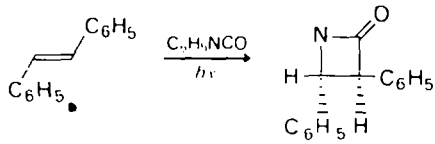
Alkyl and aryl substituted olefins and dienes. Aryl isocyanates react only occasionally with olefins. *p*-Nitrophenyl isocyanate and the phenylogous ketene aminal α,α′-bis-*p*-dimethylaminophenyl ethylene give a substitution product **233**[365].



(**233**) R = $C_6H_4NO_2$

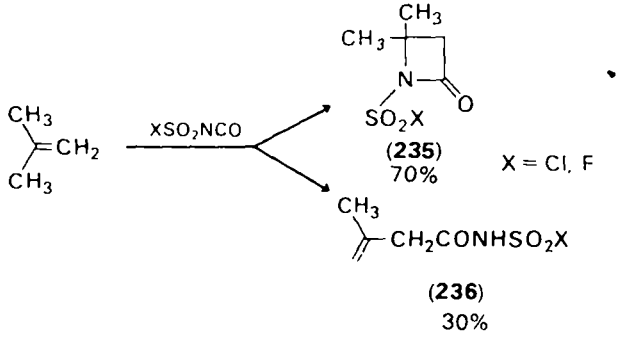
Formation of a 1,4-dipolar intermediate is likely in this reaction, since such a species could be isolated in the analogous reaction with CSI[366].

Irradiation of *trans*-stilbene in phenyl isocyanate was shown to give 45% of *trans*-1,3,4-triphenylazetidinone-2, **234**, besides 20% of stilbene dimers[367].

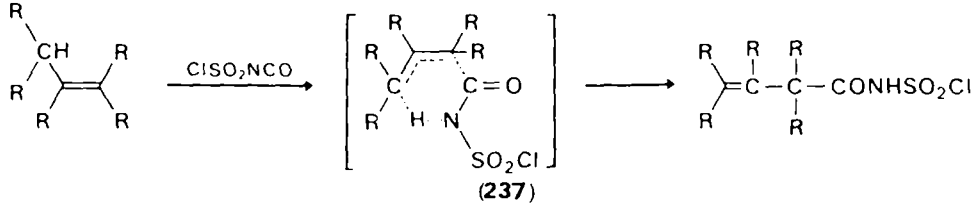


(**234**)

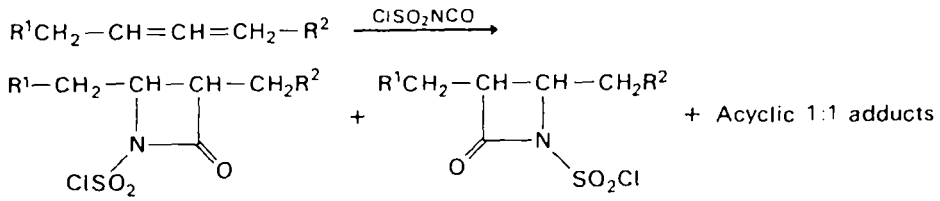
The generally more reactive sulphonyl isocyanates add to a variety of olefins, giving substitution products or β-lactams[368]. Very often both reactions take place at the same time, as is shown with isobutene and halosulphonyl isocyanate[369].



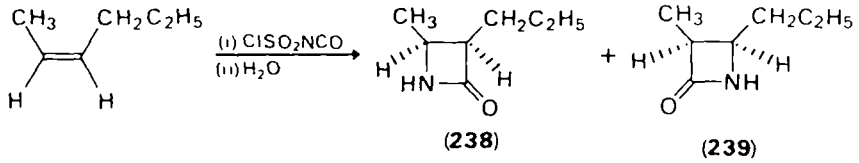
Other sulphonyl isocyanates give similar products with a number of related olefins[370]. The acyclic 1:1 adducts of type **236** are probably being formed as secondary products from the cyclic [2 + 2] adducts, like **235**, since it could be shown in certain cases that initially-formed β-lactams are transformed into acyclic β,γ-unsaturated carboxylic acid amides[370,371]. Alternative mechanisms such as equilibria between cycloadduct and 1,4-dipolar intermediates with successive proton migration and/or concerted addition–elimination involving a cyclic transition state, **237**, have been suggested also[372,373].



Mixtures of structurally isomeric cycloadducts (and also small amounts of acyclic 1:1 adduct) are obtained from unsymmetrically substituted olefins[374]:

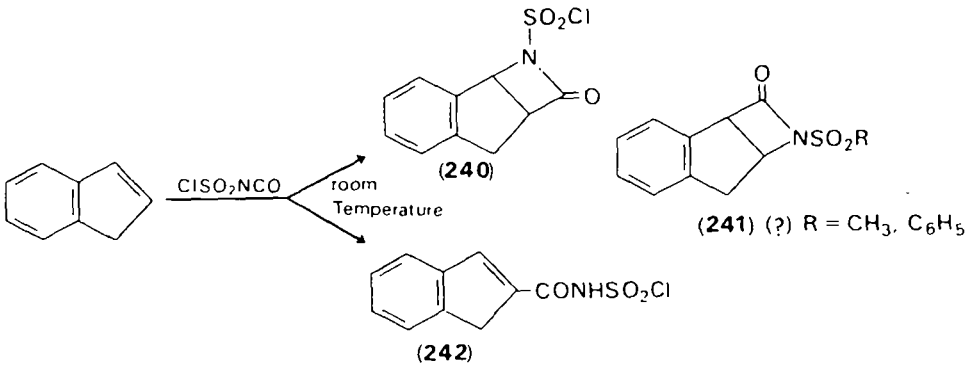


It was found that these cycloadditions proceed with conservation of the stereochemistry on the olefin[372,374]. Thus *trans*-butene-2 gives *trans*-3,4-dimethyl-azetidine-2-one and *cis*-hexene-2 yields a mixture of the structurally-different *cis* isomers **238** and **239**[374].



(238) **(239)**

The reaction of indene and CSI (chlorosulphonyl isocyanate) yields two different products depending on the conditions. Cycloaddition to the unstable **240** is observed at room temperature[375,833] (a structurally different adduct **241** with reverse isocyanate addition has been suggested for benzenesulphonyl and methanesulphonyl isocyanate[376]), while heating of the components resulted in the formation of **242**[369].

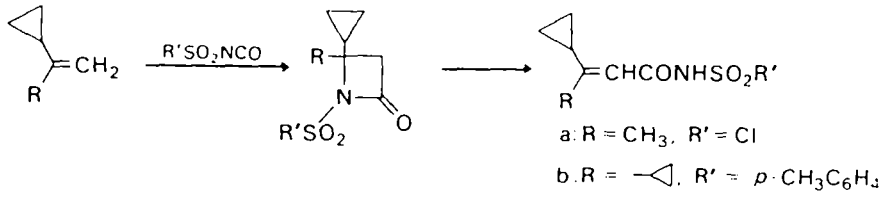


(240)

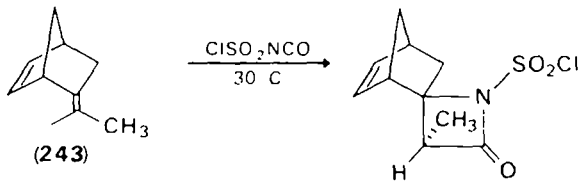
(241) (?) R = CH_3, C_6H_5

(242)

The successive formation of cycloadduct and acyclic substitution products can also be observed in reactions of cyclopropyl ethylenes with sulphonyl-isocyanates as shown below[377,378].

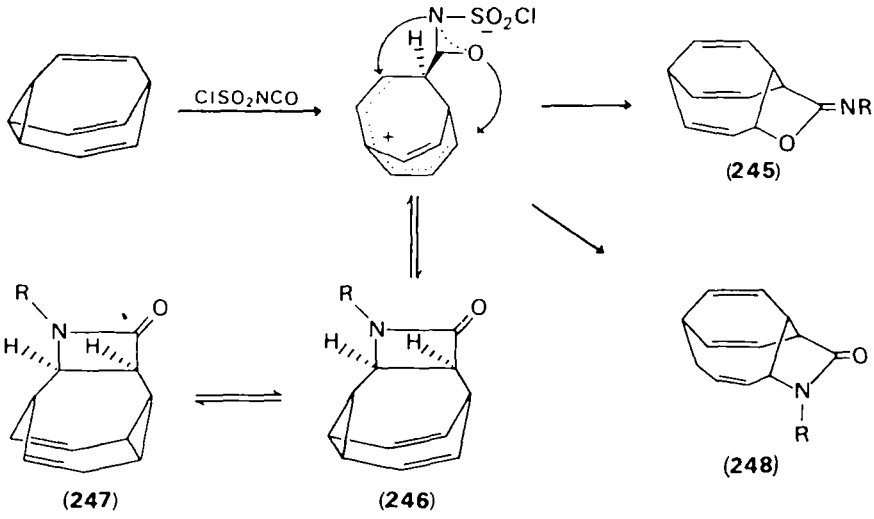


The behaviour of CSI (chlorosulphonyl isocyanate) toward 5-ethylidene-bicyclo[2.2.1]hept-2-ene (**243**) is rather unusual. [2 + 2]-Cycloaddition takes place, giving a β-lactam, 1-chlorosulphonyl-3-methyl-2-azetidinone-4-spiro-5'-bicyclo[2.2.1]hept-2'-ene (**244**) in high yield[379]. Attack of the isocyanate occurred exclusively at the exocyclic and not, as expected, at the norbornenyl double bond.

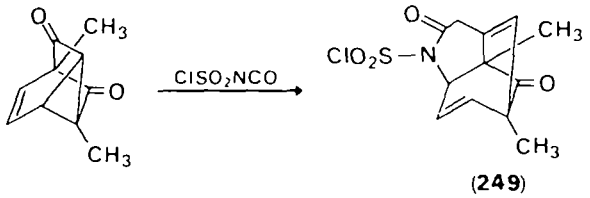


(**243**) (**244**)

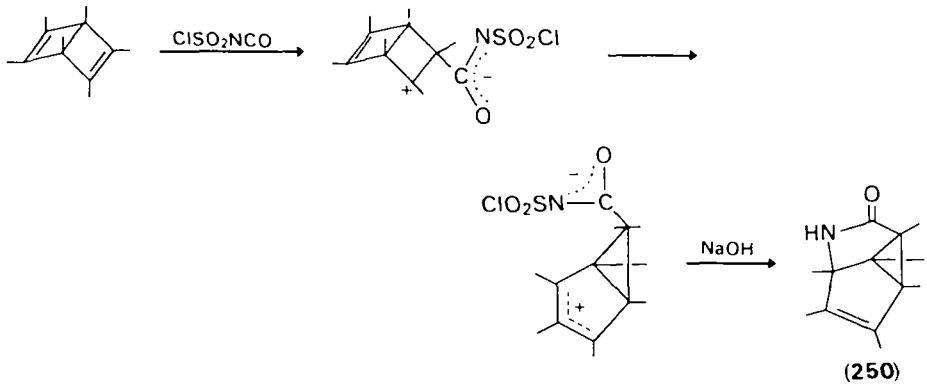
The reaction of bullvalene with CSI yields a temperature dependent mixture of products[380]. Equivalent amounts of the reagents yield the lactone **245**, the valence isomeric β-lactam **246** and **247** and lactam **248** when reacted at 0 °C (isolated after hydrolysis). This ratio can be changed by raising the reaction temperature, resulting in an almost complete disappearance of the β-lactam **246** and **247**. An initially formed dipolar intermediate, in which the positive charge is delocalized over part of the molecule, is likely to be responsible for the observed 1,2- and 1,6-cyclizations.



1,6-Addition is exclusively observed in the reaction of 5,7-dimethyl-8-methylene-tricyclo[3,2,1,$0^{2,7}$]oct-3-en-6-one with CSI leading to adduct **249** in 70–75% yield[381].

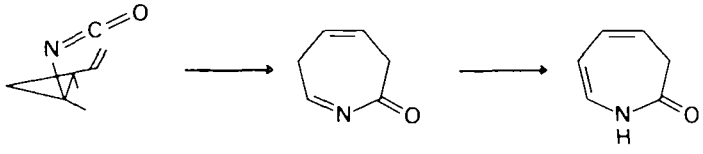


Treatment of hexamethyl Dewar benzene with the same isocyanate at low temperature causes also extensive rearrangements in the molecule via several dipolar intermediates, resulting in the formation of a 1:1 adduct, isolated after hydrolytic removal of the chlorosulphonyl group as lactam **250**[382].



(250)

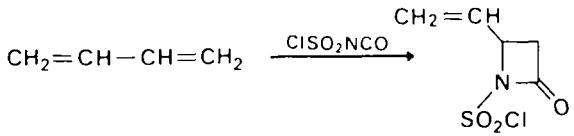
Some isocyanate–olefin reactions are known to proceed intramolecularly and are connected with additional changes in the molecules[383–385]. The formation of **251**, observed during preparation of *cis*-2-vinylcyclopropyl isocyanate from the corresponding azide, is explained by a Cope rearrangement, followed by double bond shift[383]. The same product is obtained from the *trans*-isocyanate on heating to 350 °C.



(251)

Exo-Δ^2-norcarenyl 7-isocyanate failed to undergo a similar Cope rearrangement on heating to 195 °C[386].

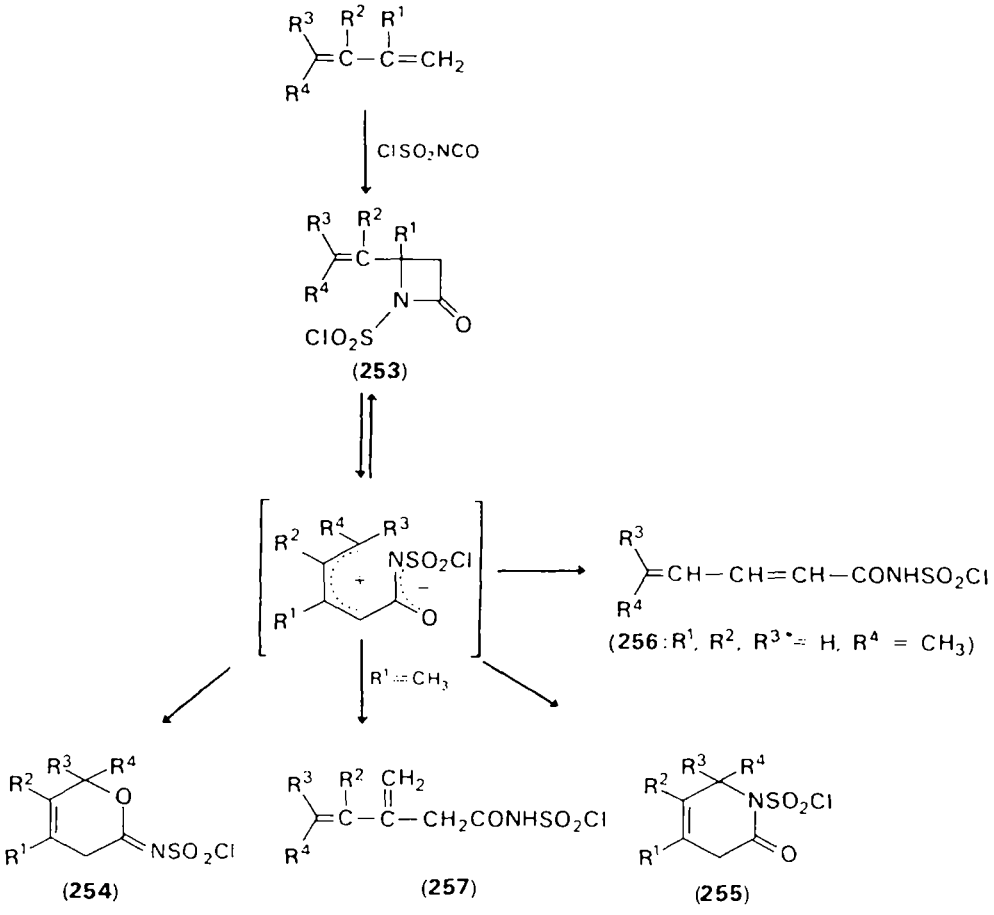
Equally complex is the behaviour of sulphonyl isocyanates towards 1,3-dienes. Butadiene and CSI yield predominantly the β-lactam *N*-sulphochloride **252** and only a little unsaturated carboxylic acid amide-*N*-sulphochloride[387,388].



(252)

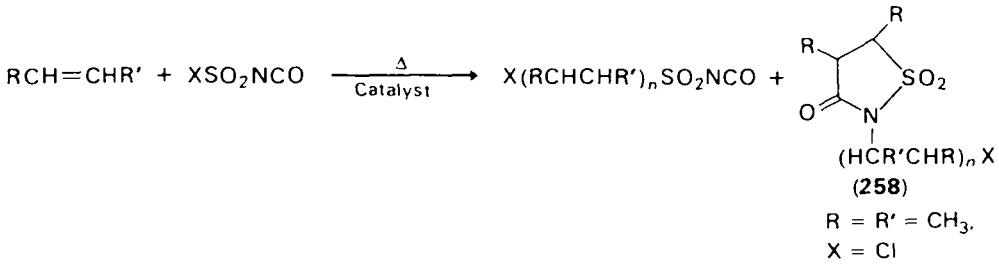
Different products are, however, obtained on reacting other 1,3-dienes with sulphonyl isocyanates. Thus mixing molar amounts of isoprene with CSI at low temperature yields a [2 + 2] cycloadduct **253** which rearranges

at room temperature via a 1,6-dipole giving a Δ^3-dihydropyrone, **254** ($R^1 = CH_3$; R^2, R^3, $R^4 = H$)[389,390]. (In another paper the isomeric dihydropyridone formula **255** was suggested for the rearranged 1:1 adduct[391].) Other 1,3-dienes behave similarly or give mixtures of [2 + 2] cycloadducts **254** and **255** with ring closure taking place either across the C=O or C=N bond of the isocyanate group. It was observed that dienes with the general formula $CH_2{=}CR^1{-}CR^2{=}CR^3R^4$ in which R^3 and R^4 represent hydrogen and R^1 and R^2 aryl and/or alkyl groups, react with isocyanates preferentially under formation of 3,6-dihydro pyrones. Successive exchange of the R^3, R^4 hydrogens by alkyl or aryl groups leads increasingly to formation of δ-lactam and unsaturated amides, possibly due to an increased stabilization of the 1,6-dipole. The scheme below



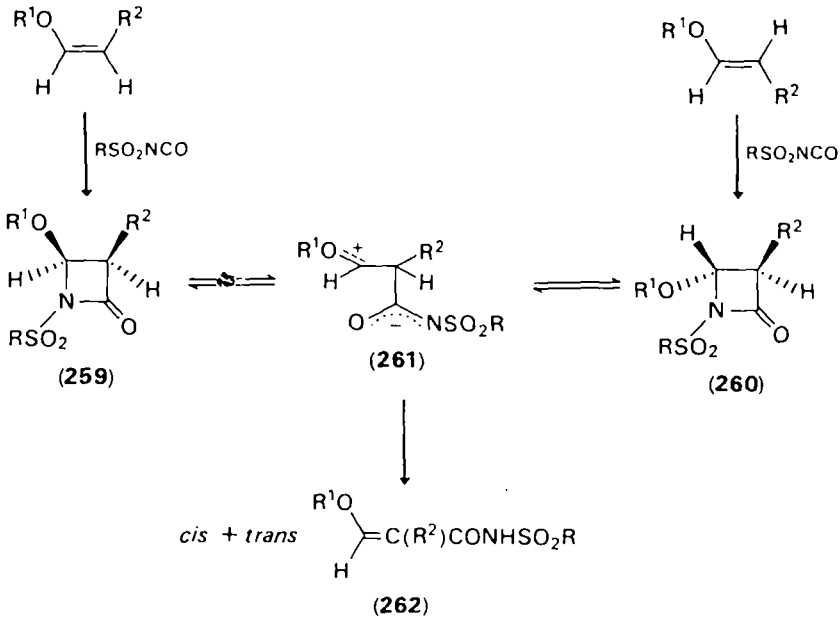
summarizes all the products observed in reactions of simple 1,3-dienes with chlorosulphonyl isocyanate.

Alkenes, cycloalkenes and bicycloalkenes are claimed to react with halogen sulphonyl isocyanates in the presence of catalytic amounts of free radical catalysts (azobisisobutyronitrile) with insertion into the X–S bond (X = Cl, Br), giving β-haloalkyl sulphonyl isocyanates and higher oligomers as well as cyclic products like **258**[392].

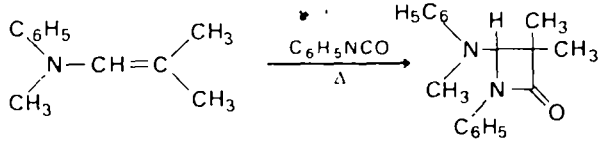


Olefins with electron donating groups. Reactions involving isocyanates and electron rich olefins (enamines, vinyl ethers, ketene acetals, tetramethoxy and tetraamino olefins) have been studied extensively in the past 10 years and results on enamines[393] and vinyl ether[394] have been summarized in recent reviews. These reviews should be consulted for detailed information. More literature is given in Reference 93.

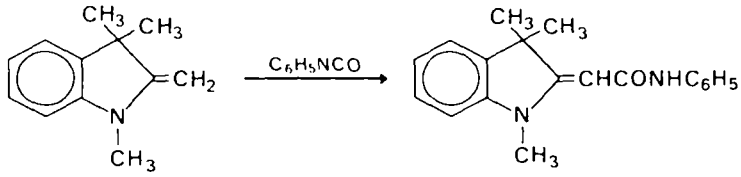
The reactions of alkyl vinyl ethers and *p*-toluenesulphonyl isocyanate give 4-alkoxy-azetidinones-2 in stereospecific (and stereoselective) processes[373,395–397]. Isomerization of initially formed *cis*- or *trans*-adducts **259** and **260** into mixtures of both isomers are believed to proceed via a 1,4-dipolar intermediate **261** which is also responsible for irreversible rearrangement of the [2 + 2] cycloadducts into *cis* and *trans*-β-alkoxy-acryl amides **262**. This implies that the initial *cis* addition leading to the azetidinones is a one-step multicentre process, while the rearrangement to acryl amides and the isomerization has to proceed via a zwitterionic intermediate. Certain arylthiovinyl ethers were also shown to react at low temperatures stereospecifically with CSI to 2-arylthio-azetidinones-2 while others give pyrimidine derivatives[398]. Vinyl esters were found to give similar [2 + 2] cycloadducts with CSI[399].



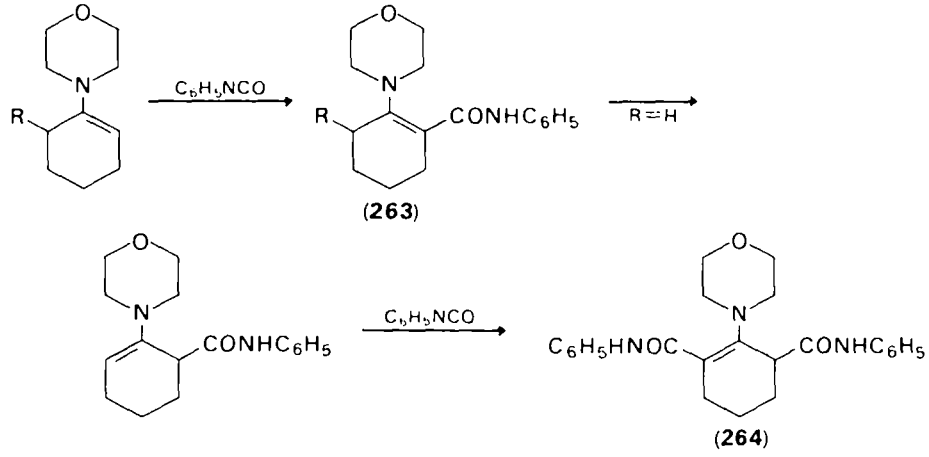
Enamines react readily with isocyanates, giving electrophilic addition or substitution products. The formation of cycloadducts in a molar ratio of 1:1 is only observed when the β-carbon atom is fully alkylated[400,401], but [2 + 4] cycloadducts (enamine–isocyanate ratio 1:2) have also been obtained in certain cases[402].



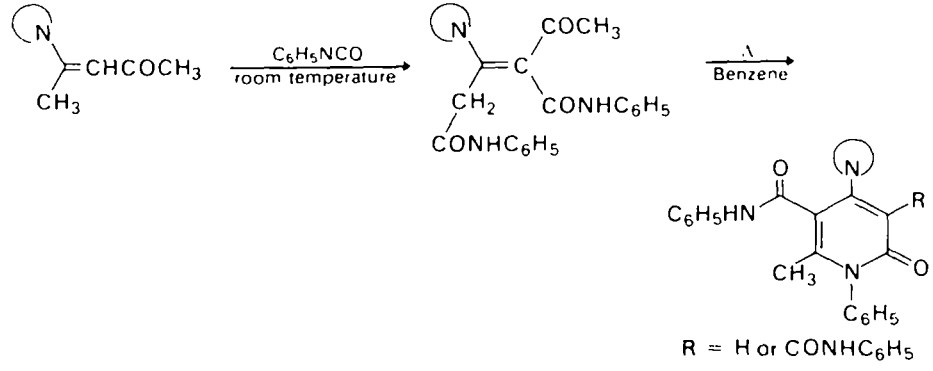
More common, however, are substitution reactions on enamines with one or no substituents on the β-carbon. The adducts, such as the one derived from Fischer's base (1,3,3-trimethyl-2-methylene-indolene) shown below[403], are obtained in high yield with aliphatic and aromatic isocyanates.



Reactions of isocyanates with enamines derived from ketones may lead to acyclic 1:1 and 2:1 adducts such as **263** and **264**[404,405]. Mixed adducts (with aryl isocyanate and isothiocyanate) have been prepared this way[406].

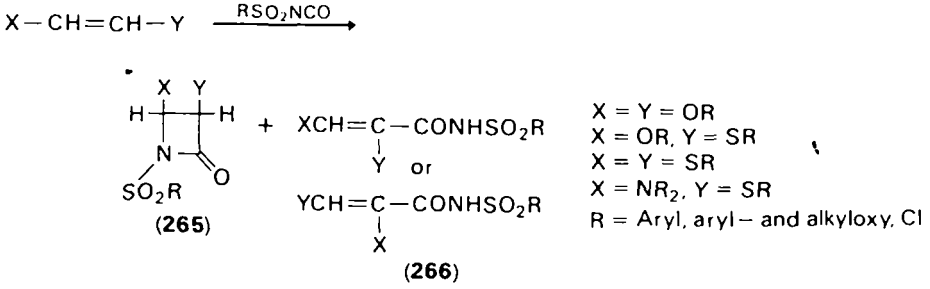


Secondary reactions of initially formed 1:1 or 2:1 adducts under more stringent conditions have also been observed; below is given one example in which heterocycles have been synthesized from acyclic 2:1 adducts[407].

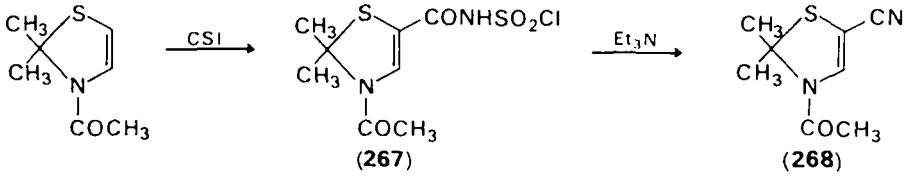


P and N containing six-membered heterocycles have been obtained similarly[408].

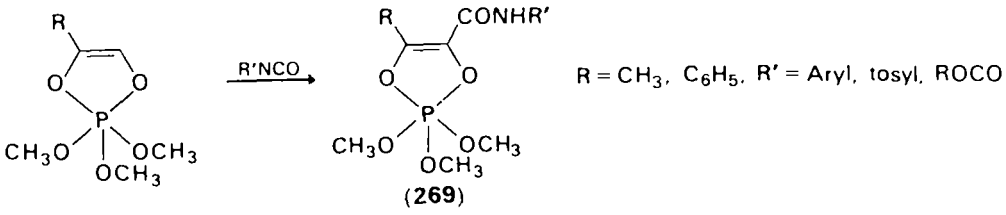
A number of sulphonyl isocyanates have also been reacted with α,β-disubstituted olefins leading to [2 + 2] cycloadducts (β-lactams) and acrylamides[409,410].



The substitution products of type **266** with R = Cl have been shown to be excellent starting materials for the synthesis of nitriles[411,412]. Thus by treating the adduct **267** obtained from CSI and 2,2-dimethyl-3-acetyl-Δ^4-thiazoline with triethylamine, the nitrile **268** is obtained in 70–80% yield[411].



Aryl, acyl and sulphonyl isocyanates were also shown to react readily with 2,2,2-trialkoxy-1,3,2-dioxaphospholenes, giving the carbamoyl phospholenes, **269**, in high yield[413].



Aryl and arenesulphonyl isocyanates add also to cyclic and acyclic trimethylsilyl enol ethers, giving substitution products at the β-carbon or [2 + 2] cycloadducts[414].

Ketene-*N*,*N*-, *N*,*S*-, *N*,*O*- and -*S*,*S*-acetals were found to react readily with alkyl, aryl and especially sulphonyl isocyanates in a molar ratio of 1:1 and 1:2 depending on the number of protons present on the β-carbon. All adducts obtained were found to be substituted acrylamides or alkylidene malonamides[415-418].

X = Y = NR_2, R = H[415, 422]

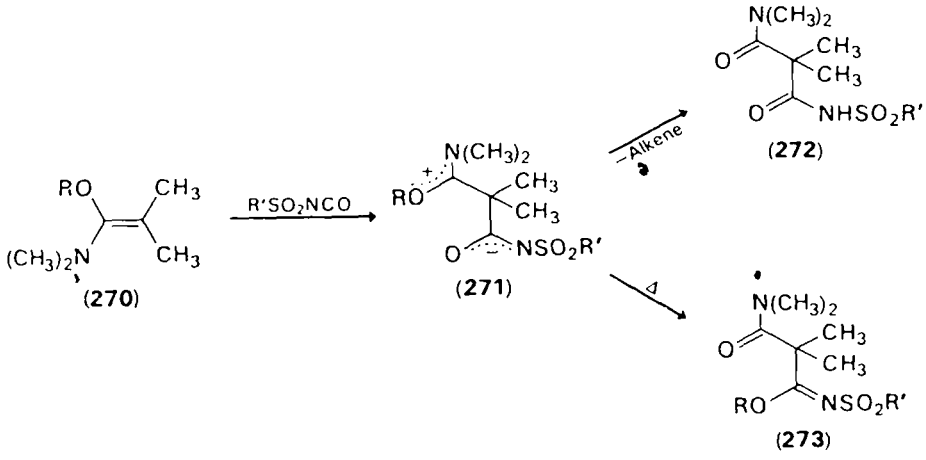
X = Y = SR, R = H[416]

X = Y = SR, R = C_6H_5[417]

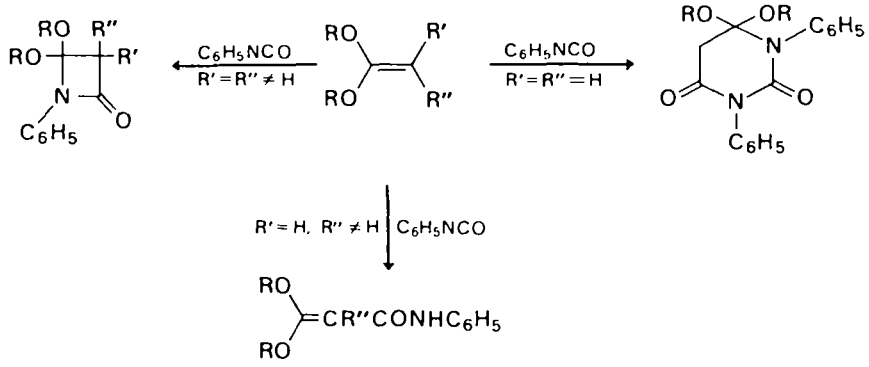
X = SR, Y = NR_2, R = $C(=S^{418})SR$ alkyl[419]

X = CR, Y = NR_2, R = H[422]

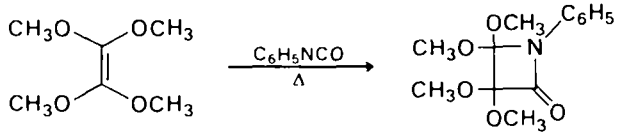
Reactions between the ketene-*O*,*N*-acetals **270** (without protons at the β-carbon) and sulphonyl isocyanates lead to formation of stable 1,4-dipoles **271** which were shown to rearrange to **273** or to eliminate alkene, giving **272**[420].



The nature of the products formed in reactions of ketene-*O,O*-diethyl acetals and phenyl isocyanate depends on the degree of substitution on the β-carbon of the acetals: β-disubstituted ketene acetals give [2 + 2] cycloadducts; [2 + 4] cycloadducts with pyrimidine structure are obtained with unsubstituted ketene acetals. Monosubstituted acetals yield acrylanilides[421a–c,422].



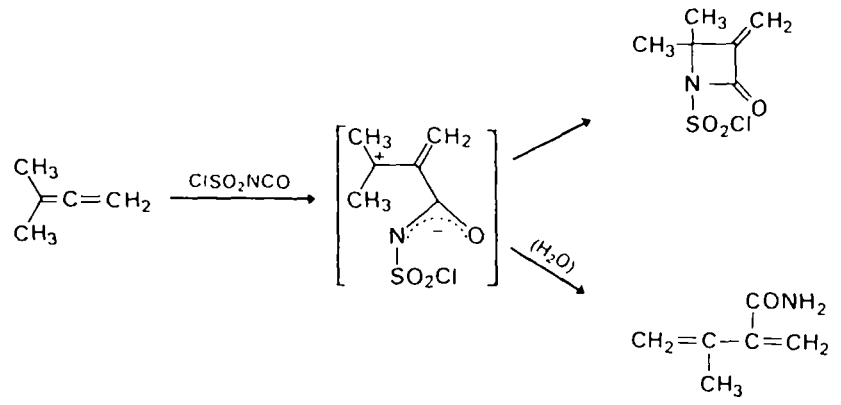
Tetramethoxyethylene and phenyl isocyanate react at elevated temperature to 3,3,4,4-tetramethoxy-1-phenyl azetidinone-2 (**274**) in very good yield[423].



(**274**)

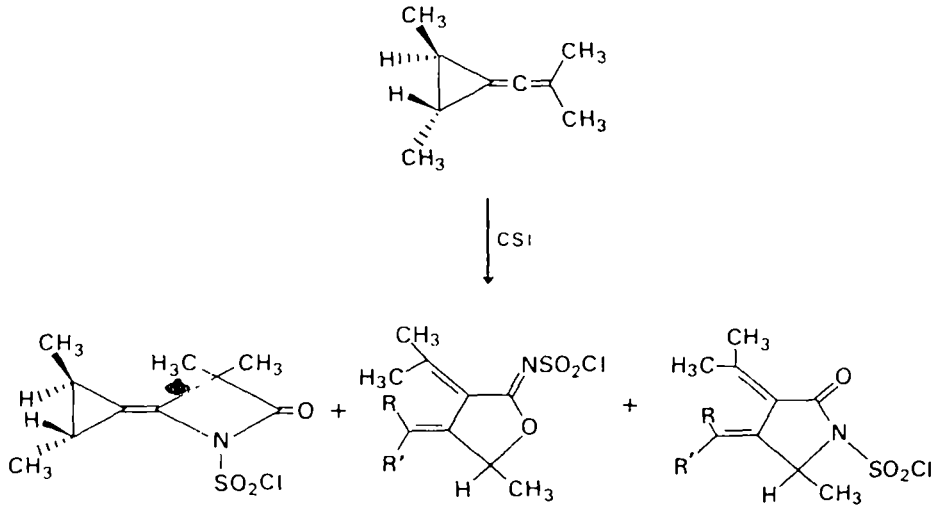
Tetraaminoethylenes behave like heterocarbene precursors and react with isocyanates under cleavage of the C=C double bond (a description of reactions of this type can be found in Section III.B.2.e).

Allenes, ketenes and ketenimines. Addition of CSI and *p*-toluenesulphonyl isocyanate to variously alkylated allenes leads to formation of both *N*-chlorosulphonyl-β-lactams ([2 + 2] cycloadducts) and, after work-up with water, 2-carbamoyl-1,3-butadienes[424–426]. The reactions proceed in a stepwise fashion via dipolar intermediates which either cyclize to β-lactams or are stabilized by proton transfer as is shown below for 3-methyl-1,2-butadiene[424].



Reactions of substituted isobutenylidene cyclopropanes with CSI have been studied in detail and were shown to lead in all cases to complicated product mixtures[427–429]. The mechanism of these reactions involving various dipolar intermediates (partially formed under opening of the cyclopropyl ring) as well as configurational aspects were studied.

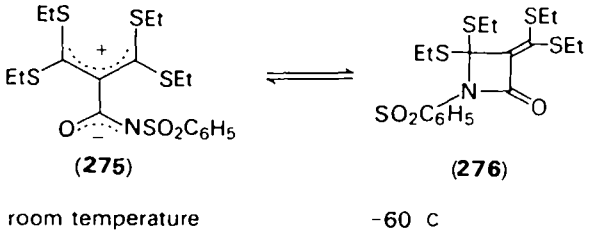
The products obtained from *trans*-2,3-dimethylisobutenylidene cyclopropane are shown below[429]



a: R=H, R′=CH$_3$

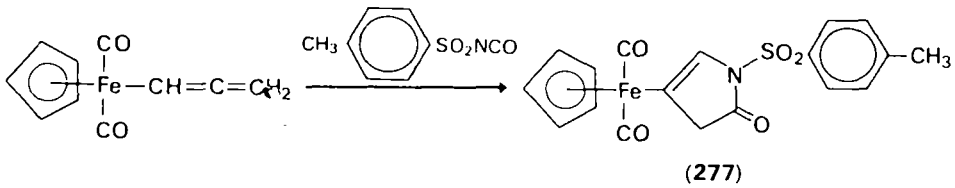
b: R=CH$_3$, R′=H

The electron-rich tetrakis(ethylthio)allene reacts with phenylsulphonyl isocyanate, giving a 1:1 adduct which exists at low temperature in the β-lactam form (**276**) and at room temperature in the resonance-stabilized dipolar form **275**[430].

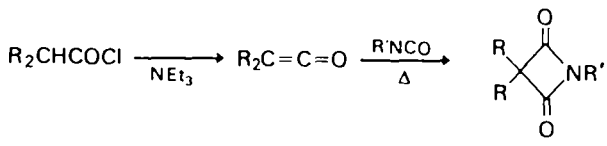


An allene with electron-donating and -withdrawing substituents on opposing ends of the molecule was shown to give a cyclic [2 + 2] adduct with phenyl isocyanate[431].

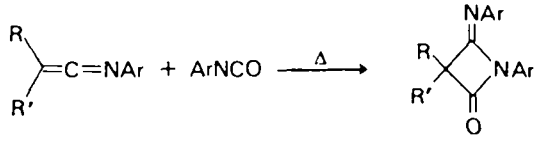
The cycloadduct formed from dicarbonyl (*pentahaptocyclopentadienyl*) (allenyl) iron and toluenesulphonyl isocyanate at room temperature was found to be the butenolactam **277**[432].



Ketenes and derivatives undergo [2 + 2] cyclization reactions with alkyl, aryl and sulphonyl isocyanates. This type of reaction was first investigated by Staudinger and coworkers, who reacted diphenylketene with phenyl isocyanate at high temperature and obtained *N*-phenyl diphenylmalonimide[433]. Many other malonimides were prepared similarly[434-437]. It has occasionally been found advantageous to use carboxylic acid chlorides as precursors of ketenes and carry out the reactions in presence of isocyanate and trialkylamine as the HCl acceptor[438].

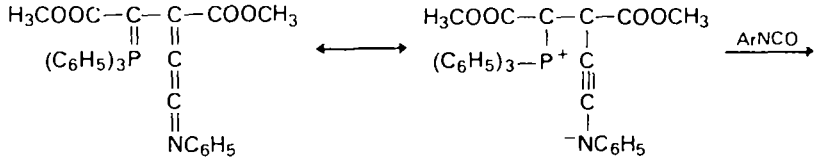


Thermal reactions between aryl isocyanates and *N*-aryl ketenimine give excellent yields of 4-iminoazetidine-2-ones (**278**); with CSI, however, a [2 + 4] cycloadduct with 2 moles ketenimine as building block is obtained[439]

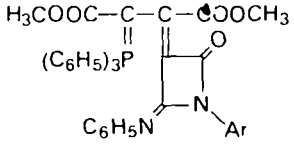


(**278**)

The resonance-stabilized *N*-phenyl alkylidine ketenimine, **278a**, reacts with 3,4-dichlorophenyl isocyanate to the [2 + 2] cycloadduct **278b**[865].



(**278a**)

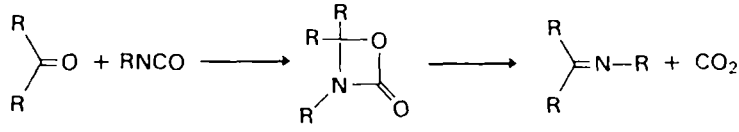


(**278b**)

Ar = 3,4-dichlorophenyl

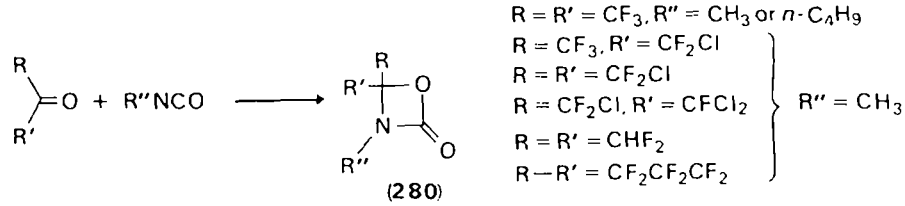
(ii) With C=O bonds. Reactions of isocyanates with carbonyl-group-containing compounds are numerous but primary reaction products can

only occasionally be isolated. [2 + 2] Cycloadducts **279** with 1,3-oxazetidine structure are believed to be formed initially, and these decompose immediately to imines and carbon dioxide.



(279)

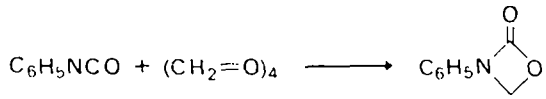
Only recently have stable 1:1 adducts been isolated. Thus heating ketones bearing strongly electron-withdrawing substituents (such as in hexafluoroacetone and other perhalogenated ketones) with alkyl isocyanates gives low to moderate yields of 1,3-oxazetidinones **280**[440,441]. Aromatic isocyanates and CSI failed to react. Boron trifluoride was found to catalyse the cycloadditions.



(280)

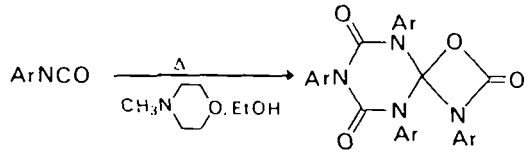
Cyclic 2:1 and 1:2 adducts are obtained as major products besides **280** when methyl isocyanate and hexafluoroacetone are heated for about 8 h at 100 °C in the presence of a caesium fluoride[440].

On reacting phenyl isocyanate with 1,3,5,7-tetroxocane (tetrameric formaldehyde) in the presence of boron trifluoride etherate as catalyst at 0 °C, a low yield of 3-phenyl-1,3-oxazolidinone (**281**) is obtained[442].



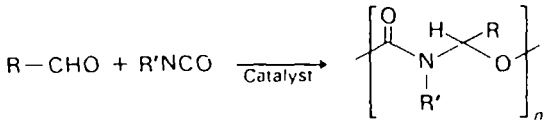
(281)

4-Chlorophenyl and 3,4-dichlorophenyl isocyanate are claimed to tetramerize on heating with small amounts of ethanol and *N*-methylmorpholine[443]. The initially-formed 1,3,5-triaryl isocyanurate is supposed to add another molecule of aryl isocyanate across one of the carbonyl groups to give **282**.



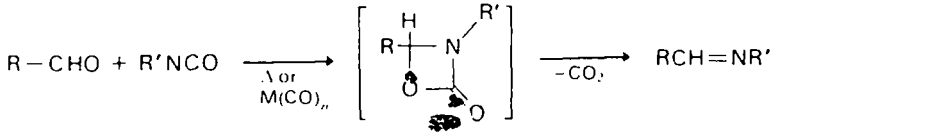
(**282**)

Aliphatic aldehydes and aliphatic or aromatic isocyanates are also known to form acyclic polymeric adducts with a molar ratio of 1:1, 2:1, 3:1 and 1:3. Anionic catalysts such as sodium cyanide, naphthalene or fluorene sodium and butyllithium as well as low reaction temperatures are required in order to obtain good yields of the polycarbamates **283**[444–447].



(**283**)

The tendency of cyclic [2 + 2] adducts derived from isocyanates and carbonyl compounds to decompose readily into carbon dioxide and imines has preparative value. Heating of aryl isocyanates with benzaldehyde, furfural and 2-formyl thiophene gives low to good yields of the corresponding *N*-arylated Schiff bases[448]. The reactions can be catalysed by adding metal carbonyls of Co, W, Fe, Mo and Cr[449]

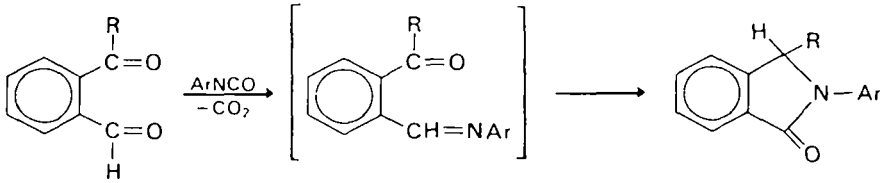


R = Aryl, furfuryl, thienyl, styryl, $CH_3-CH=CH-$

R' = C_6H_5

Benzophenones and aryl isocyanates react similarly[450]. 1,2-Diphenylcyclopropenone and 4-pyrones react already at room temperature with sulphonyl and acyl isocyanates to give the corresponding imino cyclopropenes and pyrones respectively in good to excellent yield[451,452].

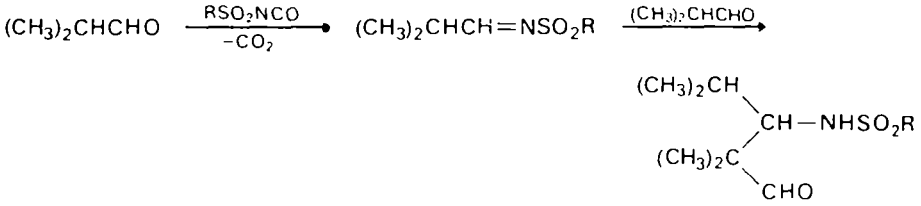
On heating phthalaldehyde with aryl isocyanates at 170 °C, *N*-arylphthalimidines **284** are obtained in excellent yield in a reaction which involves an intramolecular redox process[453]. *O*-Benzoylbenzaldehyde behaves similarly[454].



(284)

R = H, C_6H_5

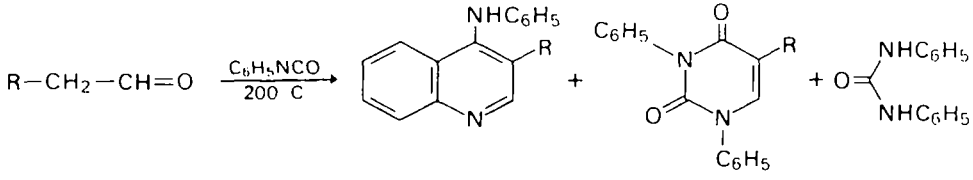
Sulphonylimines are obtained on reacting sulphonyl isocyanates with a variety of aromatic and aliphatic aldehydes[455,255]. A reaction of *p*-toluene sulphonyl isocyanate and isobutyraldehyde at room temperature took an unexpected course in that two molecules of aldehyde were incorporated into the product **(285)**[255].



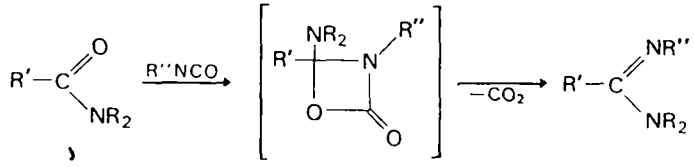
(285)

R = *p*-$CH_3C_6H_4$

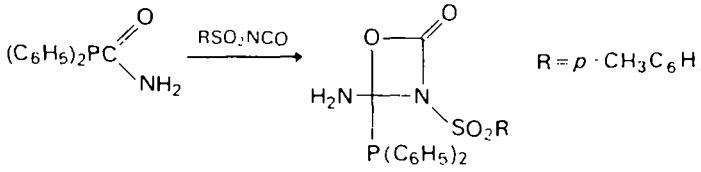
Aliphatic aldehydes and ketones having CH_2 groups adjacent to the carbonyl group yield uracils and quinolines on heating with aromatic aldehydes to 200 °C[882].



N,*N*-Disubstituted formamides and other *N*-disubstituted carboxamides have in many instances been converted into *N*-persubstituted amidines on heating with isocyanates[457-461]. Aryl isocyanates and benzoylisocyanates require heating for the amidine formation[462]; cooling and dilution are necessary, however, in similar reactions with sulphonyl isocyanates[463].

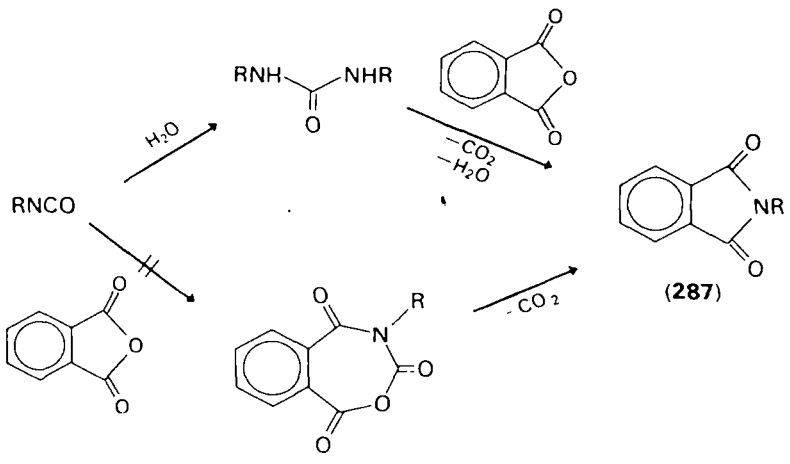


N-Monosubstituted carboxylic acid amides have also been transformed into *N*,*N*'-disubstituted amidines by the same method[472,856]. *N*,*N*'-Tetramethyl-*N*''-phenylguanidine has been prepared from tetramethyl urea and phenylisocyanate[471]. In the reaction of carbamoyl diphenylphosphine with *p*-toluenesulphonyl isocyanate the cycloadduct 4-amino-4-diphenylphosphinyl-3-*p*-tolylsulphonyl-1,3-oxazetidinone (**286**) has been obtained in very low yield[464].



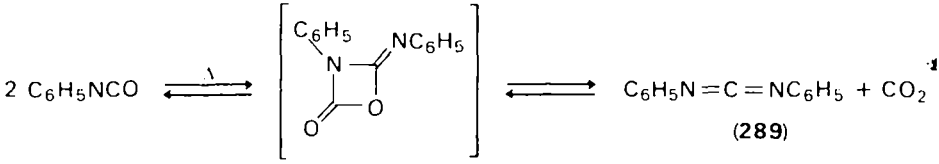
(**286**)

The reaction of carboxylic acid anhydrides with isocyanates, giving imides and carbon dioxide, has been well investigated. Both aliphatic and aromatic isocyanates have been heated with aliphatic or aromatic acid anhydrides to give the imides[465]. Recent investigations into the reaction of phthalic anhydride with phenyl isocyanate revealed that the formation of *N*-phenylphthalimide (**287**) in hot pyridine is dependent on the presence of a proton source (H_2O, primary or secondary amines)[466]. Almost no imide is formed on heating in dry pyridine; adding one equivalent of water to the reaction mixture leads to formation of 97% of **287** within 2 hours, indicating that *N*,*N*'-diphenylurea and not a seven-membered cyclic intermediate (**288**) as had been suggested earlier[467], is involved in this transformation.



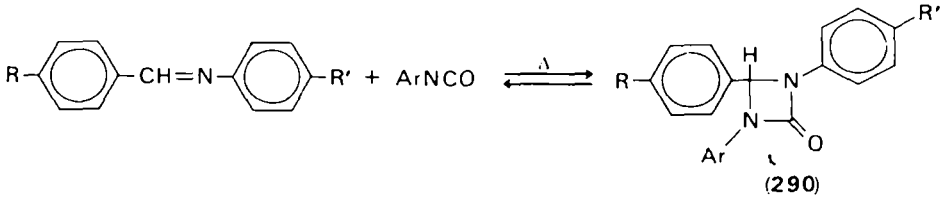
The $Co_2(CO)_8$ catalysed reactions of carboxylic acid anhydrides with phenyl isocyanate which give imides in high yield[468] seem to be entirely different in their mechanism.

The long-known, uncatalysed, thermal formation of carbodiimides from isocyanates[469] must involve asymmetric isocyanate dimers as intermediates. It has recently been shown that prolonged heating of phenyl isocyanate alone does not lead to *N,N'*-diphenylcarbodiimide (**289**). Passing a slow stream of nitrogen through the reaction mixture, however, removes the carbon dioxide and **289** is formed[470]. Catalysed carbodiimide formations involve a different mechanism and are discussed in Section C.



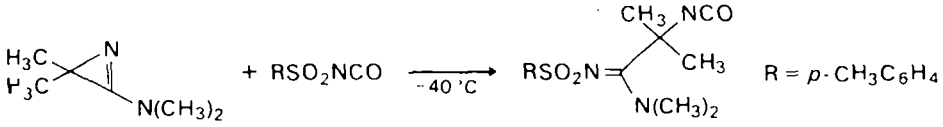
(iii) With C=N bonds. Isocyanates and compounds containing C=N double bonds are known to give, in some cases, cyclic 1:1 adducts with diazetidinone structure. More common, however, is the formation of cyclic 1:2 and 2:1 adducts. It is so far not possible to predict with certainty the nature of the product of imine isocyanate reactions.

Heating of aryl isocyanates with benzaldehyde anils derived from benzaldehydes having electron-donating groups in the *para* position leads to 1,2,3-triaryl-1,3-diazetidine-4-ones (**290**) in yields of 5–85%[450].

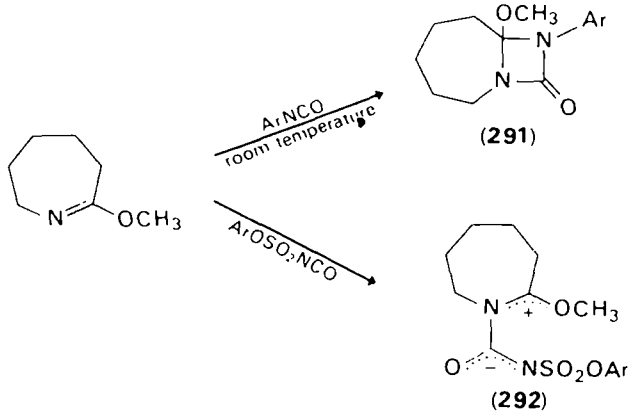


(290)

The reactions are thermal equilibria and are shifted toward the starting materials at elevated temperature. Scrambling of substituents takes place when imines ArCH=NR are heated with isocyanates Ar'N=C=O. This is sometimes observed at room temperature and below. A case where no [2 + 2] cycloadduct formation is observed is shown below[473-475].

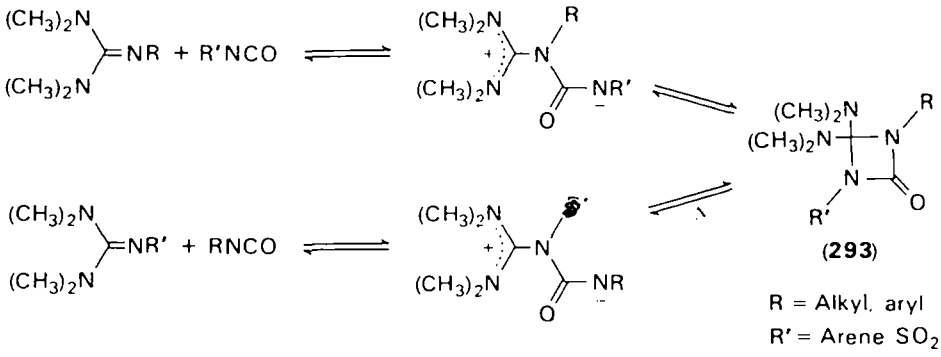


Reacting ε-caprolactim methyl ether with equimolar amounts of aryl isocyanates at room temperature yields 1,3-diazetidinones (**291**)[476], while higher reaction temperatures lead to entirely different products[477,478]. The corresponding 1:1 adduct of ε-caprolactim methyl ether and aryloxy sulphonyl isocyanates was found to exist in the zwitterionic form **292**[479].

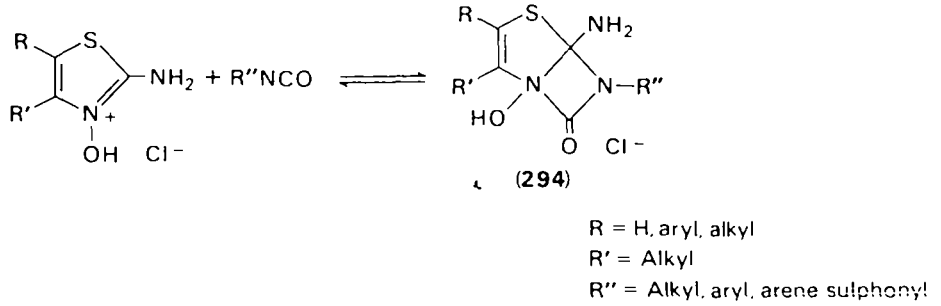


The formation of 1:1 adducts from arenesulphonyl isocyanates and *N*-persubstituted guanidines has been reported too, but it seems to be

unlikely that these compounds exist in the proposed 1,3-diazetidinone form[480]. Scrambling of substituents is observed in the thermal decomposition of the adduct of *N,N'*-tetramethyl-*N''*-*n*-butyl guanidine and *p*-tosyl isocyanate, indicating at least the temporary existence of a cyclic intermediate **293**.



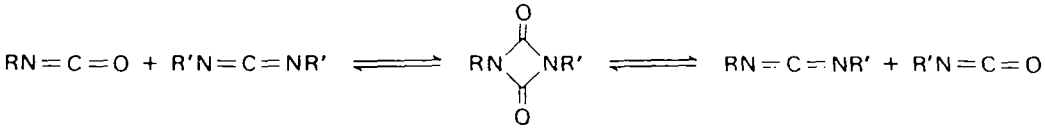
Cyclic [2 + 2] adducts are claimed to be formed in moderate to good yield from 2-amino-3-hydroxythiazolium chloride and alkyl or aryl isocyanates[481]. Structure determination of the 4-oxo-diazetidino[2,3-*b*]-thiazolium chlorides (**294**) is based mainly on spectral evidence.



1,3-Disubstituted 1,3-diazetidine-2,4-diones, the cyclodimers of aryl and alkyl isocyanates, are of course also products of an addition of isocyanates to CN double bonds. A description of these compounds is found in Section III.B.1.a.

The addition of isocyanates to one C=N double bond of carbodiimide to give imino-1,3-diazetidinones (**295**) is a well investigated reaction. The

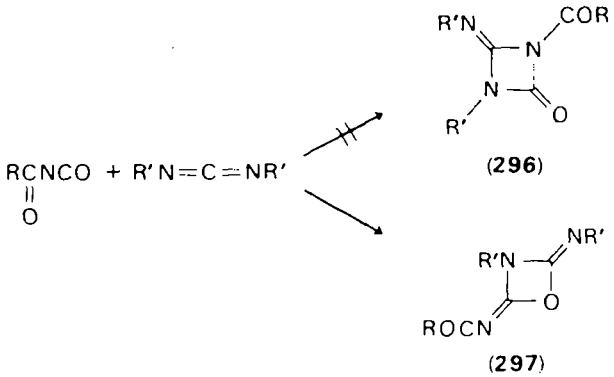
[2 + 2] cycloadditions can be carried out in the presence of catalysts (cuprous and cupric salts)[482] or by heating the reactants in absence of solvents[100,310]; very reactive aryl isocyanates such as *p*-nitrophenyl isocyanate form adducts with diarylcarbodiimides even at room temperature[877]. Excess of either isocyanate or carbodiimide in the reaction mixture does not lead to formation of 2:1 cycloadducts provided acidic catalysts are absent[312]. The adducts are thermally labile and dissociate on heating above the melting point with reversal of the mode of formation or fragmentation into a new pair of isocyanate and carbodiimide[10,100]



(295)

N-Triethylgermyl-*N'*-phenylcarbodiimide and phenyl isocyanate give also a stable diazetidinone[483].

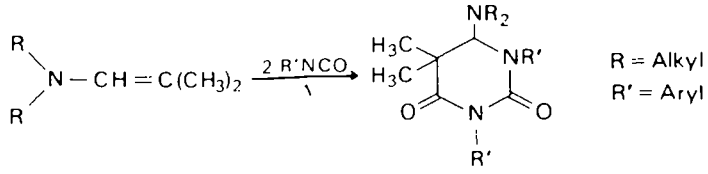
The cyclic [2 + 2] adducts derived from benzoyl isocyanates and dialkyl or diaryl carbodiimides previously believed to be imino-1,3-diazetidinone **296**[296] were recently shown by fragmentation experiments to be 2,4-diimino-1,3-oxazetidines **297**[484].



Reactions between dialkyl carbodiimides and arenesulphonyl isocyanates lead to 1,4-dipolar 1:1 adducts in the first reaction step; subsequent addition of more isocyanate, however, gives cyclic 1:2 adducts[485,486].

b. [2 + 4] *Cycloadditions*

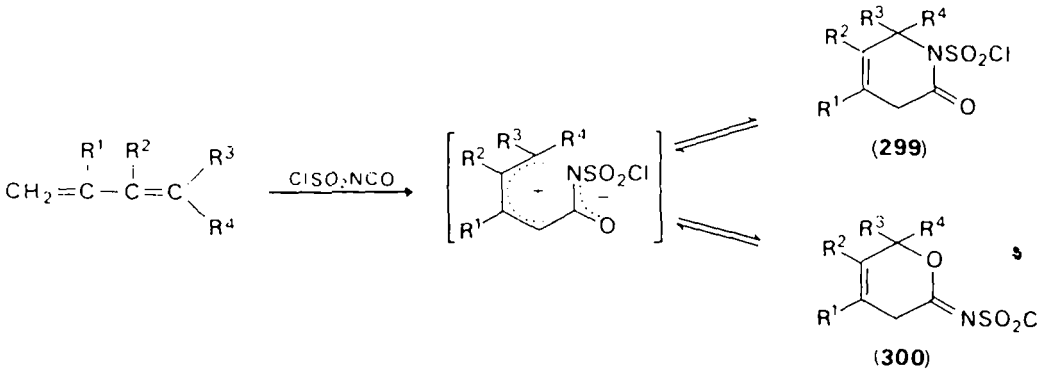
(i) With olefins, 1,3-dienes and heterodienes and cumulenes. The formation of cyclic addition products from olefins, 1,3-dienes (hetero)-cumulenes and other conjugated double bond systems on the one hand and isocyanates on the other has been observed occasionally. Many of these [2 + 4] cycloadditions are believed to proceed in a stepwise fashion via dipolar intermediates. A detailed discussion on the mechanism of these reactions has appeared recently[487]. In the case of olefins, adducts with a molar ratio of 1:2 and 2:1 (isocyanate: C=C component) can be obtained, often independently of the molar ratio of the reactants. On reacting β-disubstituted enamines with aryl isocyanate at elevated temperatures amino hydrouracils (**298**) are obtained in good yield[412].



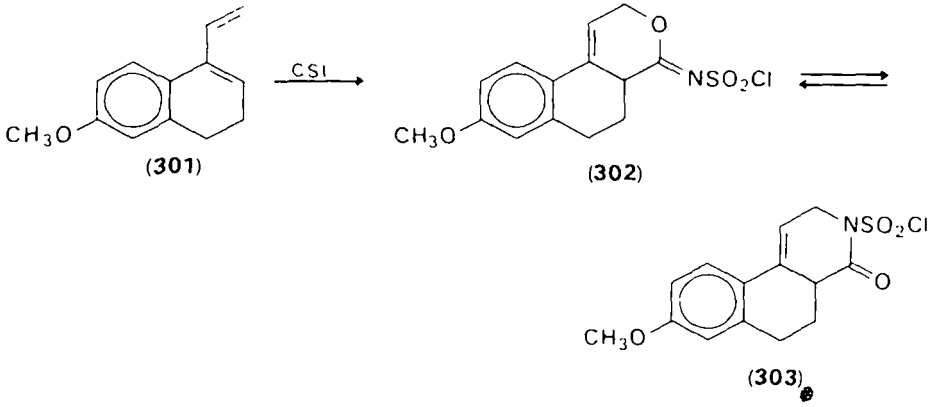
(**298**)

Ketene diethyl acetal is also claimed to give a [2 + 4] cycloadduct with 2 moles of phenyl isocyanate[421a]. *cis*-β-Methylthiostyrene reacts with CSI (followed by hydrolysis) giving cycloadducts with a molar ratio of 1:2 (pyrimidines) and 2:1 (pyridone derivatives), while 1-(phenylthio)-1-propene gives only a 1:2 cycloadduct (dihydrouracil) as major product[489].

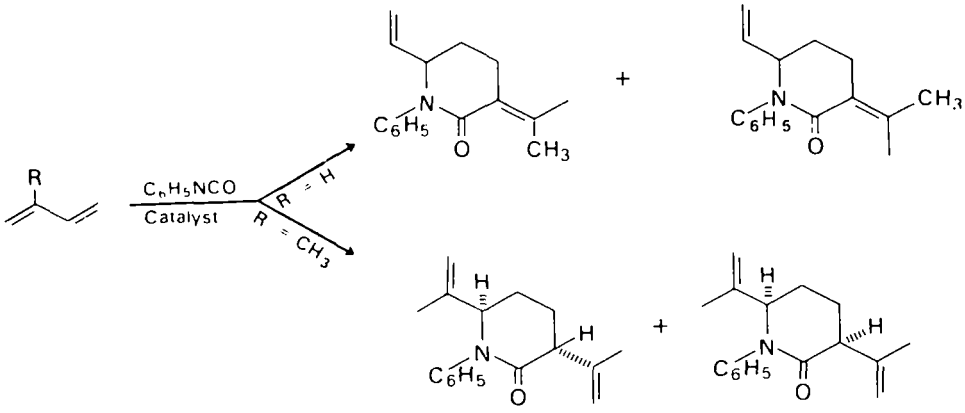
1,3-Dienes give [2 + 2] and also [2 + 4] cycloadducts with sulphonyl isocyanates in dependence on the nature of the substituents on the diene system. Dienes with the general formula $CH_2=CR^1-CR^2=CR^3R^4$ were shown to react either across the C=O or C=N bond of the isocyanate to give 3,6-dihydropyridones (**299**) or 3,6-dihydropyrones (**300**) in a ratio influenced by the substituents R^1–R^4: if R^3 and R^4 are hydrogen and R^1 and R^2 aryl and/or alkyl groups, pyrones are preferentially obtained; exchange of R^3, R^4 hydrogens by alkyl or aryl groups leads increasingly to pyridone formation[389]. A 1,6-dipole is probably the common intermediate.



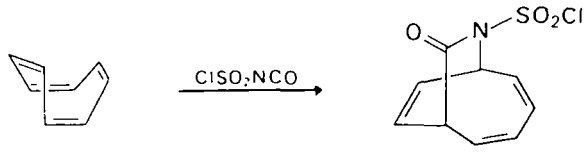
On reacting the 1-vinyldihydronaphthalene (**301**) with CSI at low temperature, a [2 + 4] cycloadduct, **302**, is obtained which is slowly converted into the isomeric adduct, **303**[491]. This interconversion is best explained with a 1,6-dipolar transition state. Acid-catalysed shift of the cyclic double bond to conjugated lactams was observed in this and other cases also[391].



Entirely different reactions take place between 1,3-dienes and phenyl isocyanate in the presence of palladium–triphenylphosphine complexes[492]. Thus heating of isoprene or butadiene with phenyl isocyanate in benzene in the presence of catalytic amounts of bis(triphenylphosphine) (maleic anhydride) palladium leads to mixtures of two isomeric 2:1 cycloadducts (diene:isocyanate) identified as 3-alkylidene-6-vinyl- and 3,6-divinyl-2-piperidones respectively.



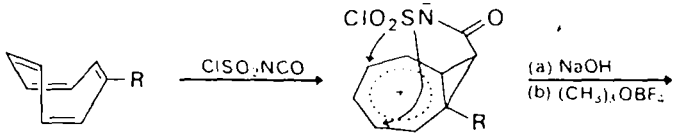
Cyclooctatetraene was shown to react with chlorosulphonyl isocyanate in a [2 + 4] fashion, giving the lactam, **304**, in high yield[493,494].

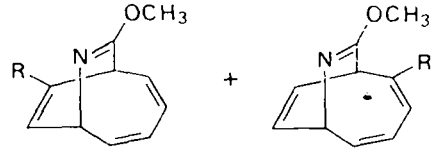


(304)

Monosubstituted cyclooctatetraenes react similarly and yield mixtures of two isomeric [2 + 4] cycloadducts, **305** and **306**, in varying ratios. The involvement of dipolar intermediates (homotropylium cations) is likely and explains the ring closure at $C_{(3)}$ and $C_{(5)}$, as well as the different product ratios observed for differently substituted starting materials. The adducts are not isolated as such but are transformed into imino ethers by action of sodium hydroxide and trimethyl oxonium fluoroborate[493]. Benzocyclooctatetraene also undergoes a cycloaddition reaction with chlorosulphonyl isocyanate yielding mostly one isomer with a structural formula similar to **306**[493].

Intramolecular cycloaddition of an isocyanate and 1,3-diene is observed during the thermal generation of 1,3-pentadienyl isocyanate from sorboyl chloride and trimethylsilyl azide[861]. The isocyanate slowly cyclized on heating in *o*-dichlorobenzene, giving 3-methyl-2(1*H*)-pyridine in 17% yield.

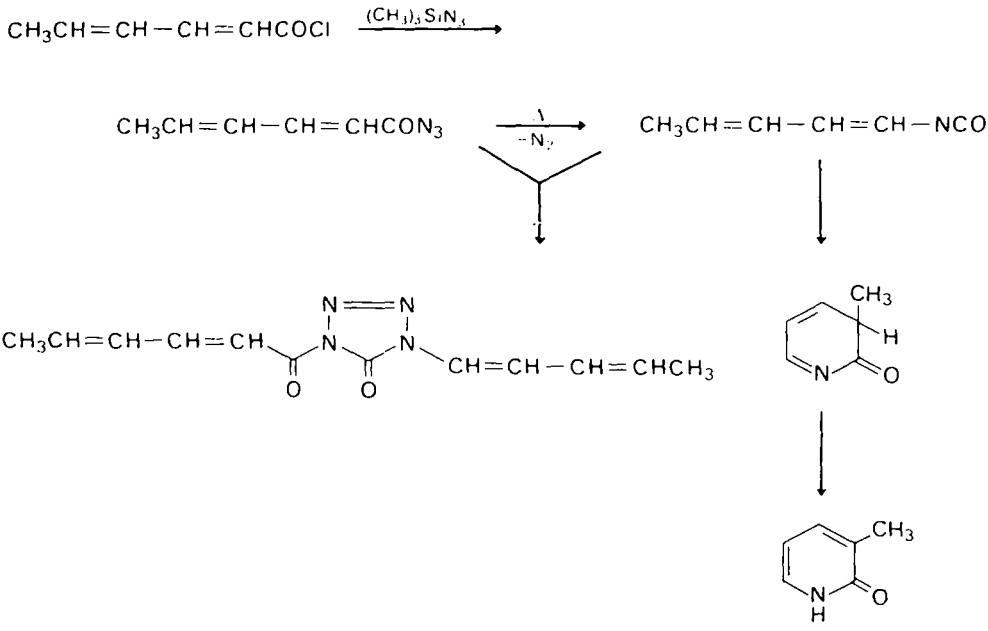




(305) (306)

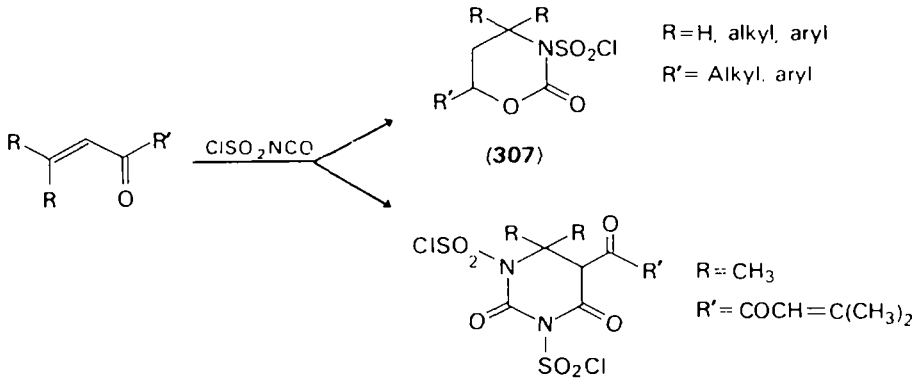
R		
CH_3	65%	35%
OCH_3	17%	83%
C_6H_5	80%	20%
p-$CH_3OC_6H_4$	45%	55%

Generating the isocyanate at a lower temperature causes interception of the isocyanate by sorboyl azide and formation of a tetrazolinone[861].



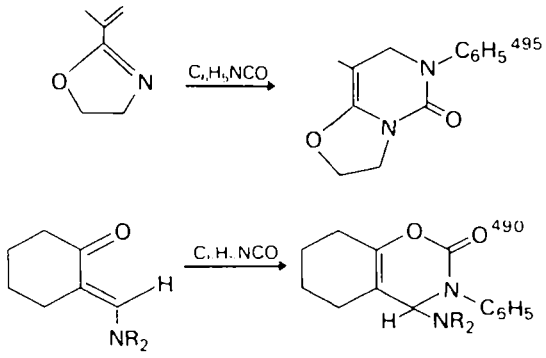
Compounds containing two double bonds such as C=C, C=O or C=N in conjugation may undergo cycloaddition reactions with isocyanates with participation of one or both double bonds.

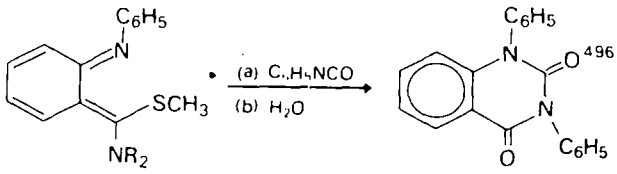
Phoron, which contains three double bonds, reacts with 2 moles CSI at 0–10°C only with addition to one C=C bond, giving barbituric acid derivatives, **308**[488]. On the other hand a number of vinyl ketones and distyryl ketone were shown to undergo [2 + 4] cycloaddition with participation of the C=C and C=O double bonds affording 1,3-oxazine-2-ones (**307**)[488].



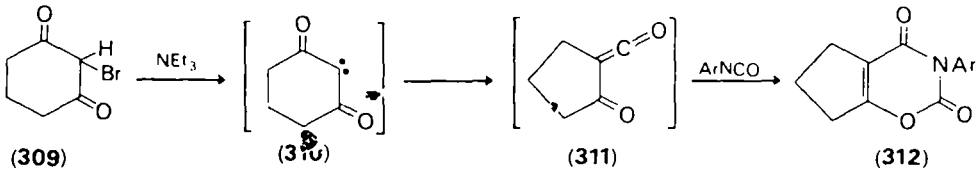
Perfluoro methacryloyl fluoride was shown to react with cyclohexyl isocyanate affording a 3,4-dihydro-2*H*-oxazinone besides other products[437].

Other cases in which heterodienes react with isocyanates in a molar ratio of 1:1 are shown below.





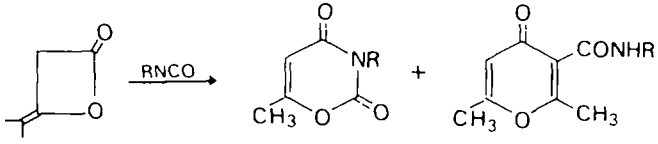
Treatment of bromodione **309** with triethylamine leads to the dioxocarbene **310** which undergoes Wolff rearrangement, giving a ketoketene **311**; the latter can be intercepted with aryl isocyanates to **312**[497]



(309) (310) (311) (312)

Other ketoketenes were shown to react similarly[498 500,880].

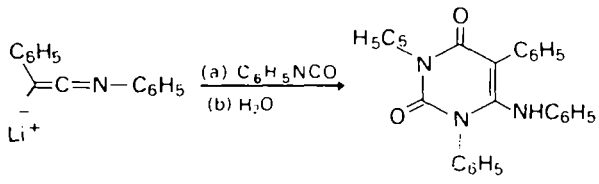
Diketene reacts with cyanic acid and aryl isocyanates in the presence of acidic catalysts (*p*-toluenesulphonic acid, BF_3-etherate, $SnCl_4$) to yield 3,4-dihydro-2,4-dioxo-6-methyl-2*H*-1,3-oxazines (**313**) and 3-carbamoyl-2,6-dimethyl-4-pyrones (**314**)[501].



(313) (314)

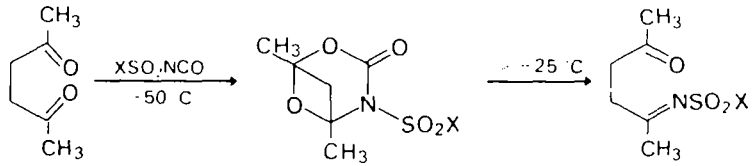
R = Aryl, H R = Aryl

Reaction of lithium (*N*-phenyl)phenylketenimine (obtained on fragmentation of 1,4-diphenyl-1,2,3-triazolyl lithium) with phenyl isocyanate produces 6-anilino-1,3,5-triphenyl uracil[502].



Phosphoranylidene substituted pyrimidinetriones are obtained from aryl isocyanates and phosphoranylidene ketenes[503].

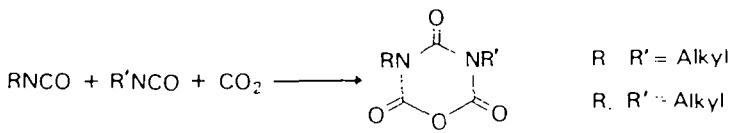
A rather unusual [2 + 4] cycloaddition has been observed in the reaction of 2,5-hexanedione and chloro and fluoro sulphonyl isocyanate[488]. Both ketonic carbonyl groups take part in the formation of a bicyclic 1:1 adduct **315** at −50°C. Heating of **315** to −25°C or higher results in loss of carbon dioxide and formation of azomethine, **316**.



(315) **(316)**

X = Cl, F

(ii) With C=O compounds. The formation of 1,3,5-oxadiazine derivatives from isocyanates and carbonyl group containing compounds has been observed occasionally. Methyl isocyanate was shown to react with carbon dioxide in the presence of triethylphosphine as catalyst to give 3,5-dimethyl-1,3,5-oxadiazine-2,4,6-trione[321] (**317**, R, R′ = CH_3). Similar reactions were carried out with other aliphatic isocyanates and catalysts (phosphines, arsines, triphenylarsinoxide)[504–506]. Mixtures of two different isocyanates were also employed in these reactions.

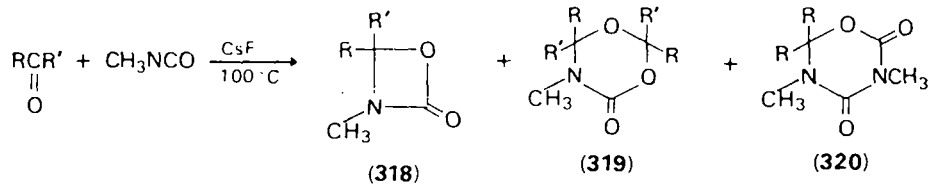


(317)

R R′ = Alkyl

R, R′ = Alkyl

Cycloadducts **319** and **320** with 2:1 or 1:2 molar composition have been obtained along with a 1:1 cycloadduct (oxazetidinone) **318** in the caesium-fluoride-catalysed reaction of halogenated acetones with methyl isocyanate[440].

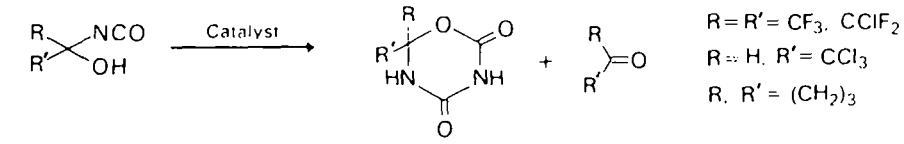


R = R' = CF_3, CHF_2

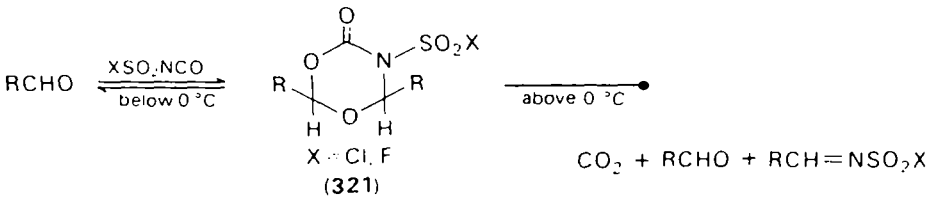
R = CF_3, R' = CF_2Cl

R, R' = $(CF_2)_3$

Compounds with a related structure, which can be formally regarded as cycloadducts of isocyanic acid and aliphatic halogenated aldehydes or ketones, are obtained from substituted hydroxymethyl isocyanates on standing or on treatment with water or pyridine[137,507].



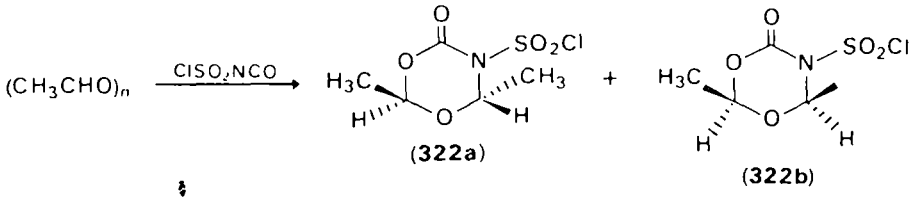
The behaviour of halogen sulphonyl isocyanates towards a wide variety of carbonyl-group-containing compounds has been thoroughly investigated[488]. Aromatic aldehydes and pivalaldehyde form cyclic 2:1 adducts (**321**) (1,3,5-dioxazine-6-ones) with chloro and fluorosulphonyl isocyanates in good yield at −20 and −60 °C in suitable solvents. Heating of these adducts to room temperature and above leads to dissociation and eventually formation of azomethines.



Similar reactions with acetaldehyde, butyraldehyde, and isobutyraldehyde lead primarily to trimerization of the aldehydes and the cyclic acetals

obtained add only slowly to sulphonyl isocyanates, giving related 2:1 adducts.

Tetrameric acetaldehyde and paraldehyde add CSI giving a mixture of isomeric 2:1 adducts, **322a** and **b** at low temperatures.

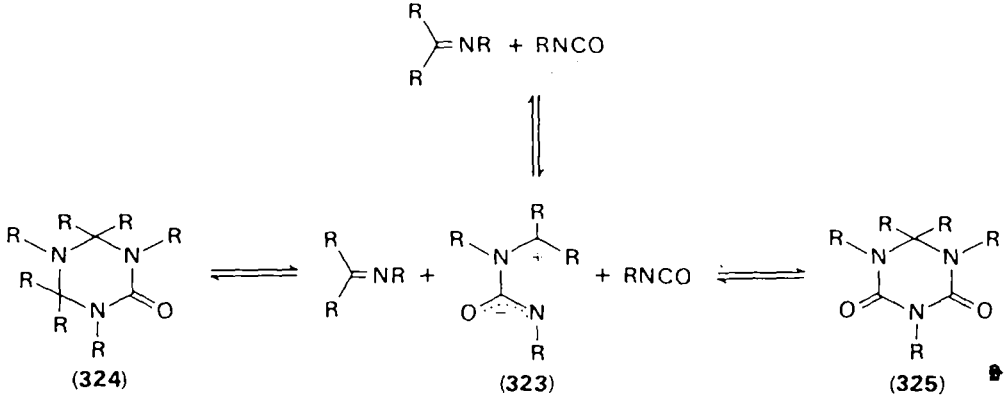


Oligomers of formaldehyde, *s*-trioxane and 1,3,5,7-tetroxocane, as well as methaldehyde (trimeric acetaldehyde), react with the same isocyanate to give either cyclic 2:1- or 4:1-adducts at $-20\,^{\circ}C$ in liquid sulphur dioxide. The composition of the products can be influenced by choosing the appropriate molar ratio for the transformations. All these reactions are believed to involve dipolar intermediates of various chain lengths.

The behaviour of ketones towards halogen sulphonyl isocyanates is different. Diarylketones, like benzophenone and Michler's Ketone, give only azomethines at room temperature and above. Ketones with α-hydrogens and β-dicarbonyl compounds react under CH or OH insertion (see Section III.B.3.a and c). Vinyl ketones and 2,5-hexanedione behave like heterodienes in reactions with sulphonyl isocyanates (see Section III.B.2.a.i)[488].

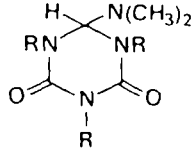
(iii) *With C=N bonds.* Imines and isocyanates are also known to form cycloadducts with a molar ratio of 2:1 in which either one of the two reactants can be the dominating component. A recent review article describes the synthesis of such 2:1 and 1:2 adducts (hexahydro-*s*-triazines) in detail[123]; reaction mechanisms responsible for the formation of these compounds are discussed elsewhere[487,508,509]. The ease with which adducts are formed from imines and isocyanates depends largely upon the electron density on the N atom of the imine and the electrophilicity of the central carbon of the isocyanate. Most reactive are therefore the per-substituted guanidines and amidines on one side and isocyanates bearing electron-withdrawing substituents (*p*-nitrophenyl, acyl, sulphonyl) on the other. Reactions between these groups of compounds are generally exothermic and require diluents. Steric factors are only of secondary importance and are normally limited to influencing the nature of the product, not the reaction itself. The [2 + 4] cycloadditions described here proceed

via formation of 1,4-dipolar intermediates, **323**. Addition of a second molecule of isocyanate or imine leads to the adduct **324** or **325**.

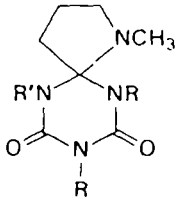


(324) **(323)** **(325)**

Many differently substituted hexahydro-*s*-triazines derived from one molecule of imine and two molecules of isocyanate have been synthesized by reacting benzaldehyde and benzophenone anils, amidines and guanidines with alkyl, aryl and sulphonyl isocyanates:

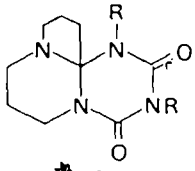


R = Alkyl, aryl[510-513]

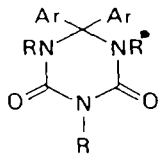


R = Aryl, R' = alkyl, aryl[510,514]

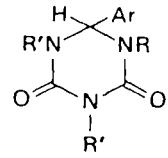
R = Alkyl, R' = alkyl, aryl[510-515]



R = Aryl[510]

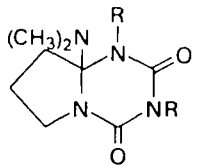


R = Aryl[450]

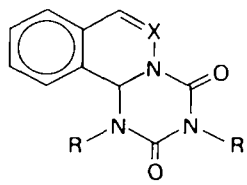


R = Aryl, alkyl, R' = SO_2R[479, 516, 517]

R = Alkyl, R' = aryl[518, 519]

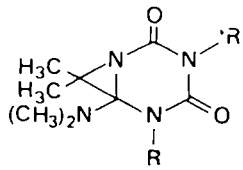


R = Aryl[510]



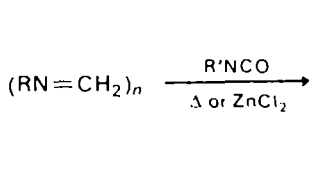
R = C_6H_5, X = CH[518]

R = C_6H_5, X = N[877]



R = C_6H_5[475]

The formation of 2:1 adducts with imine as dominating component is less common. Monomeric or oligomeric *N*-alkyl and aryl formaldimines generally give adducts of type **326** with aryl and alkyl isocyanates on heating or in the presence of zinc chloride as catalyst[877,520–523].



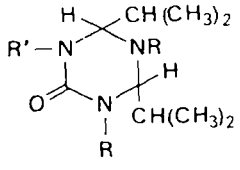
(**326**)

R = Alkyl, R' = alkyl, aryl[520, 521]

R = Alkyl, R' = SO_2R''[479]

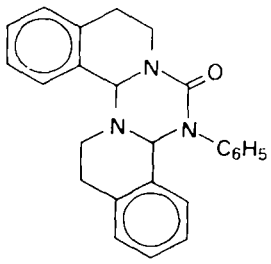
R = Aryl, R' = aryl[877,522]

The mechanism responsible for the formation of adducts **326** from oligomeric, especially trimeric, formaldimines is not well understood in all aspects and it is questionable whether a cyclization mechanism as proposed is operative. It could be shown that higher adducts composed of three molecules of formaldimine and two molecules of isocyanate are occasionally involved as intermediates[521]. Reports on the synthesis of adducts of type **326** with other imines are scarce. *N*-(2-Methylpropylidene)alkylamines react with chlorophenyl isocyanate at room temperature to the cyclic 2:1 adducts **327**[524]. A similar adduct **328** is obtained from 3,4-dihydro isoquinoline and phenyl isocyanate[518]; *N*-benzylidene amines give adducts **329** with sulphonyl isocyanates[479].

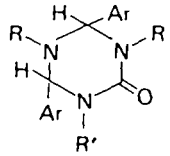


(327)

R = Alkyl, R' = aryl



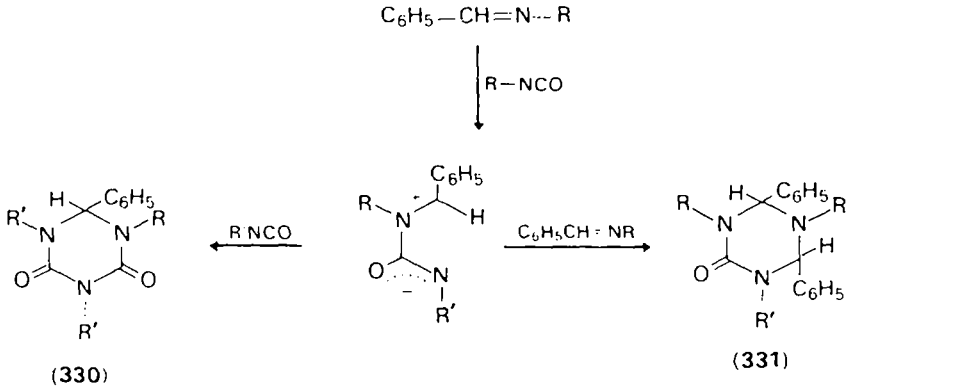
(328)



(329)

R=Alkyl, R' = $SO_2CH{=}CHR$

Attempts to influence the composition of 2:1 cycloadducts by adding an excess of one component to the reaction mixture are successful in only a few cases. Thus reacting *N*-benzylidenealkylamines with phenyl isocyanate or vinylsulphonyl isocyanate in a ratio of 1:2 and 2:1 gives either **330** or **331**[518,479].



(330)

a: R = C_2H_5, R' = C_6H_5

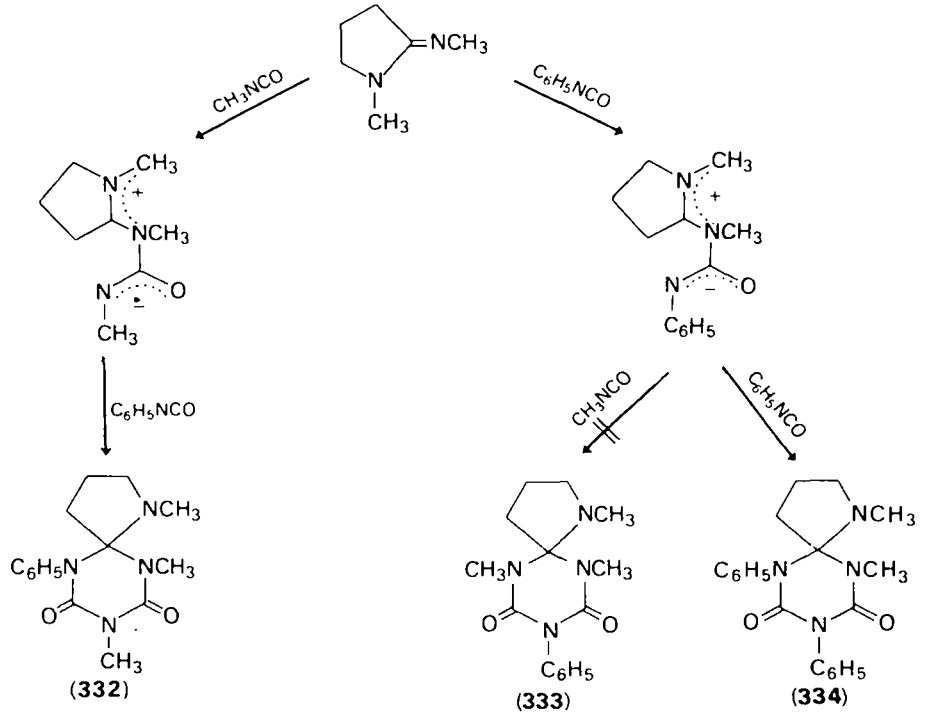
b: R = C_6H_5, R' = $SO_2CH{=}CH_2$

(331)

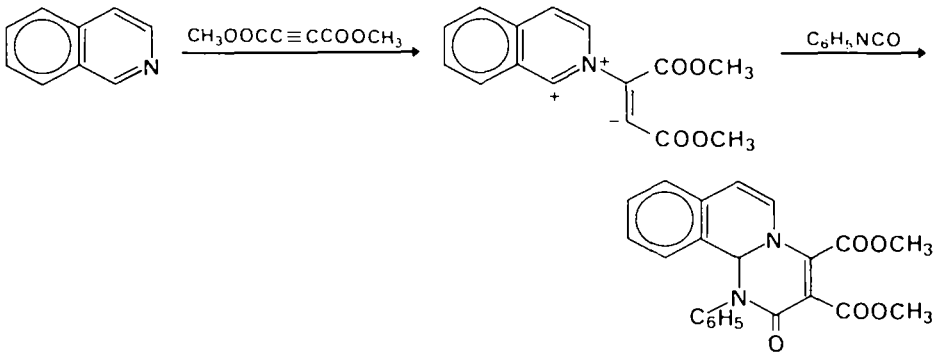
a: R = C_2H_5, R' = C_6H_5

b: R = C_6H_5, R' = $SO_2CH{=}CH_2$

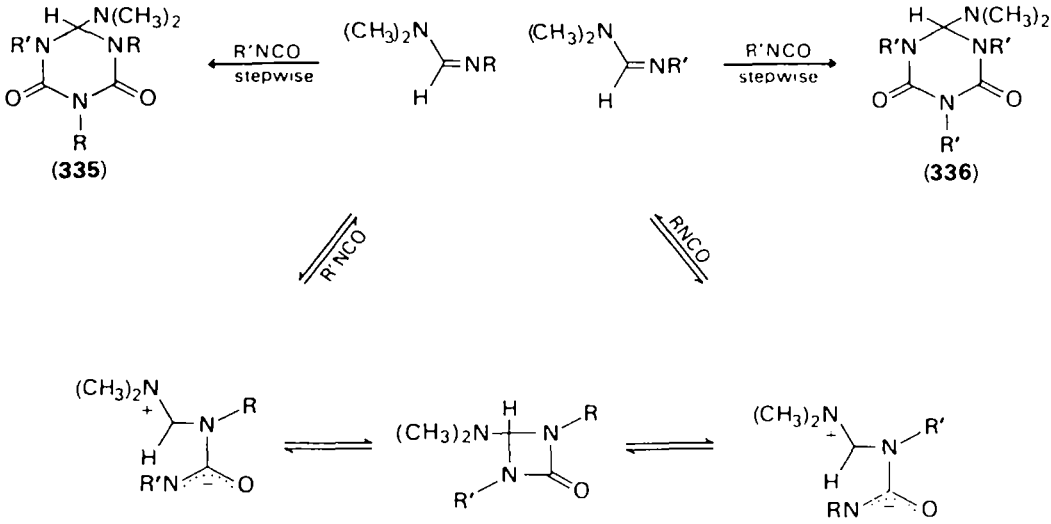
Proof for the formation of dipolar intermediates of type **323** as shown above was obtained through stepwise synthesis of 2:1 adducts with two different isocyanates. RNCO and R'NCO, as building blocks[286,515]. 1-Methyl-2-methyl-iminopyrroline reacts with methyl isocyanate and phenyl isocyanate in that sequence to give the cycloadduct **332**. If this reaction is carried out with phenyl isocyanate in the first step, no interception of the dipole with methyl isocyanate is possible under the reaction conditions and **334** is obtained instead of **333**[515].



A similar set of reactions is observed between *N,N'*-tetramethyl-*N''*-phenylguanidine and phenyl and methyl isocyanate[286]. Another three-component reaction in which phenyl isocyanate acts as interceptor of the 1,4-dipole takes place between isoquinoline and dimethyl acetylenedicarboxylate[518].

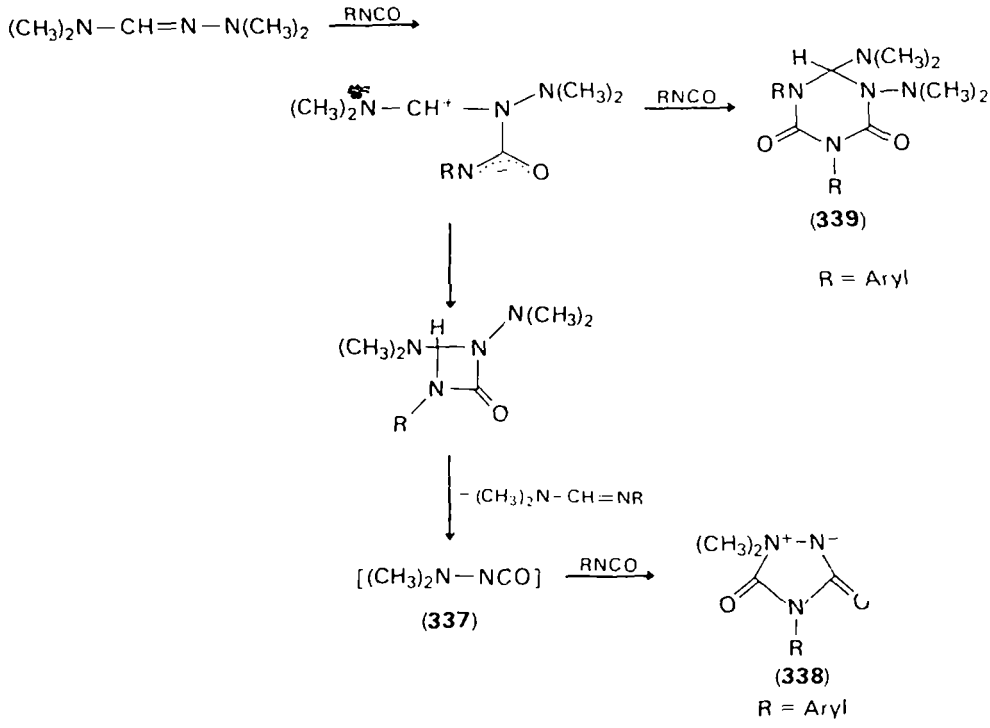


Since all steps in the [2 + 2 + 2] adduct formation are equilibria, scrambling of substituents on the 2:1 adducts might occur, especially if one component is used in large excess. The reaction of *N*,*N*-dimethyl-*N'*-aryl formamidine with methyl isocyanate leads to a mixture of two differently substituted hexahydro-*s*-triazines **335** and **336**[511]. Exchange of the *N*-substituents on the formamidine can well be explained with the formation and reversed ring scission of a cyclic 1:1 adduct (1,3-diazetidinone) as shown below.

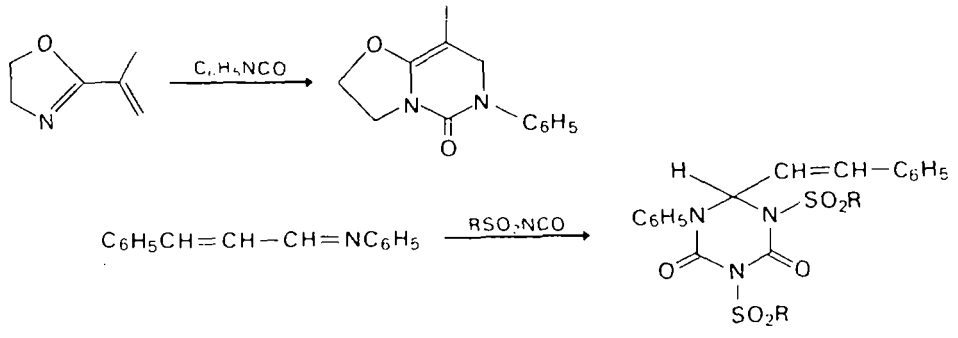


(335) **(336)**

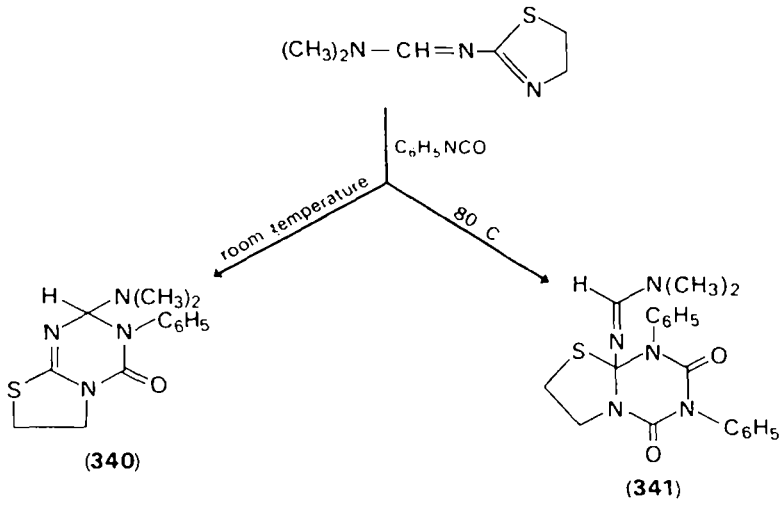
On reacting *N*,*N*-dimethyl-*N'*-(dimethylamino)formamidine with a number of aryl isocyanates triazolidinium betaines (**338**) are obtained as products of an initial cycloaddition of the isocyanate to the amidine C=N bond, followed by ring scission and formation of dimethylamino isocyanate (**337**). Excess aryl isocyanate will add to **337** in a [2 + 3] cycloaddition to give **338**[209]. Other chloro- and trifluoromethyl substituted aryl isocyanates reacted with the same formamidine to give [2 + 4] cycloadducts, **339**[209].



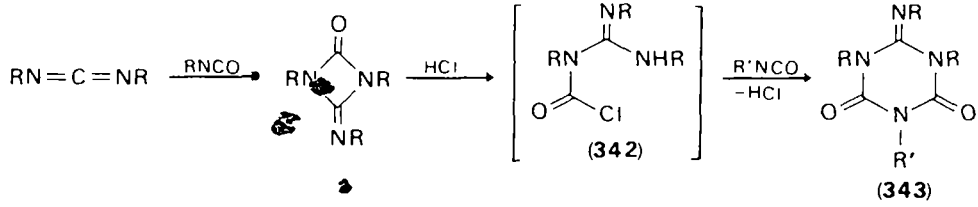
Compounds containing a double bond (C=C or C=N) adjacent to the C=N bond may or may not behave like heterodienes as illustrated by the reaction of 2-isopropenyl-Δ^2-oxazoline with phenyl isocyanate[495] and *trans*-cinnamaldehyde anil with *p*-toluenesulphonyl isocyanate[877].



The heterodiene *N,N*-dimethyl-*N'*-(2-thiazoline-2-yl)formamidine can react both ways and undergoes two different cycloadditions with phenyl isocyanate as shown below[301].



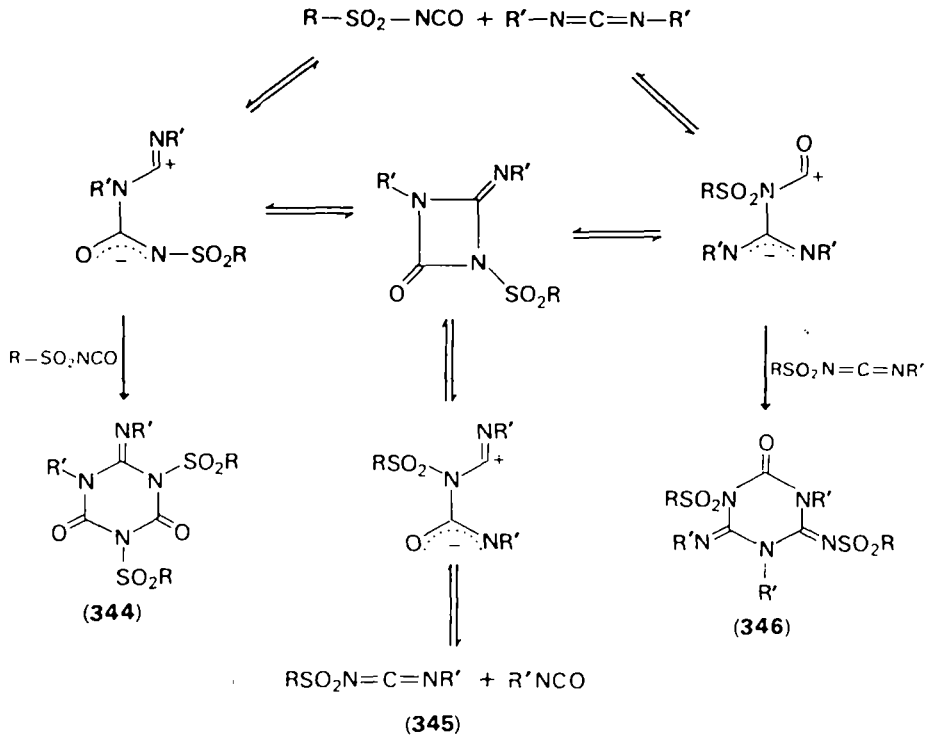
2:1 Adducts with an *s*-triazine structure are also formed from carbodiimides and isocyanates. Aryl isocyanates and *N,N'*-diaryl carbodiimides give only [2 + 2] cycloadducts on reacting at room or elevated temperature[100,310]; transformation of these adducts with excess isocyanate into [2 + 4] adducts in the presence of hydrogen chloride as catalyst is possible[312]. Since ring closure with a



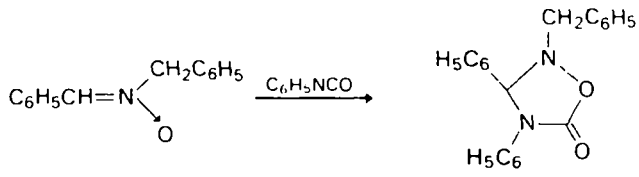
different isocyanate R'NCO in the second step gives exclusively the iminohexahydro-*s*-triazine dione (**343**) and none of the other isomers, the intermediate formation of an acyclic HCl adduct **342** seems likely.

N,N'-Bis(trimethylsilyl)carbodiimide reacts with phenyl isocyanate without catalyst, giving an iminohexahydro-*s*-triazinedione[483].

Arenesulphonyl isocyanates and *N*,*N*'-dialkyl carbodiimides give exclusively [2 + 2 + 2] adducts, but scrambling of *N*-substituents occurs during the reaction and mixtures of **344** and **346** are obtained[485,486]. Formation of the 2:1 adduct **346** derived from two carbodiimides and sulphonyl isocyanate can best be explained with equilibria between different polar 1:1 intermediates which lead to formation of an asymmetric carbodiimide **345**.

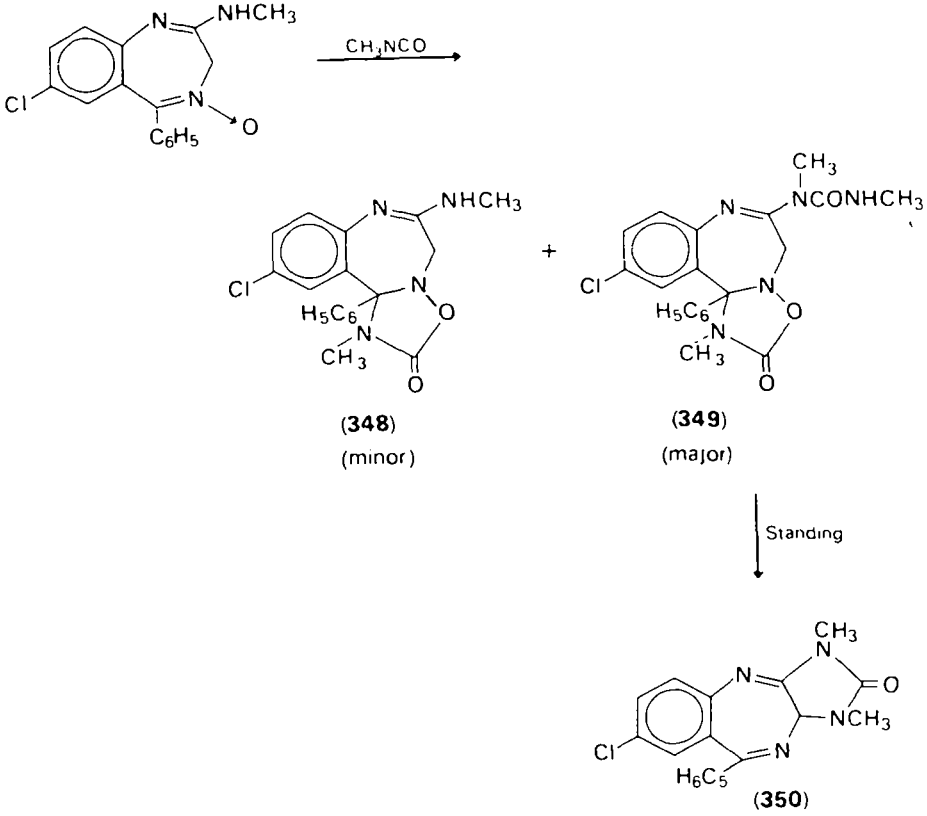


c. [2 + 3] *Cycloadditions*. Cycloaddition reactions between isocyanates and 1,3-dipolar compounds have been used extensively to synthesize a variety of heterocyclic compounds. A comprehensive review article describing the many reactions of isocyanates with 1,3-dipoles has been published recently[525]. *N*-Oxides of imines or heteroaromatic amines give cycloadducts with a number of aryl isocyanates. Thus reacting *C*-phenyl-*N*-benzyl nitrone with phenyl isocyanate yields the 1,2,4-oxadiazolidine-5-one, **347**[526,527]. Other nitrones derived from cyclic or acyclic imines give all similar adducts with 1,2,4-oxadiazoline-5-one structure[528–532].



(347)

The reaction of 7-chloro-2(methylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide with methyl isocyanate gives initially a mixture of the two expected products **348** and **349**. The acyclic urea derivative, however, proved to be unstable and rearranged in a base-catalysed reaction giving the cyclic urea **350**[533].

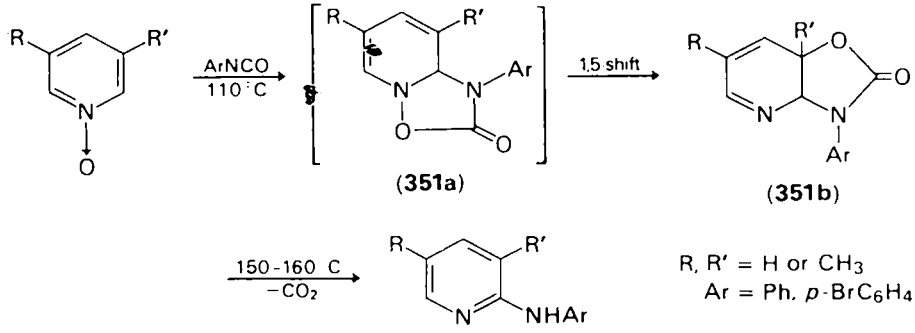


(348)
(minor)

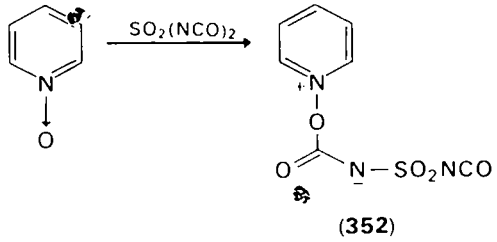
(349)
(major)

(350)

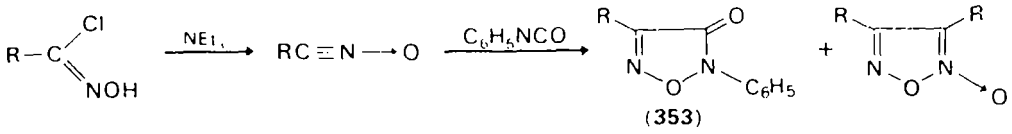
N-Oxides of pyridine, isoquinoline and phenanthridine and other heteroaromatic amines react with phenyl isocyanate at 110°C with evolution of carbon dioxide to give heteroaromatic amines having anilino groups adjacent to the nitrogen[530,534–536]. It is believed that these reactions involve the formation of [2 + 3] cycloadducts as labile intermediates. Such [2 + 3] adducts can indeed be obtained in the reaction of 3-picoline oxide with phenyl isocyanate at 100–110°C[537]. The 1,2-dihydropyridines (**351a**) were recently shown to be formed only as short-lived intermediates which rapidly undergo 1,5-sigmatropic shift giving the more stable 2,3-dihydro compounds **351b**[878]. Higher reaction temperatures lead directly to the 2-amino-picolines.



The related reaction of pyridine-*N*-oxide with sulphonyl diisocyanate does not lead to a [2 + 3] cycloadduct; an acyclic dipolar 1:1 adduct **352** is obtained instead[538].

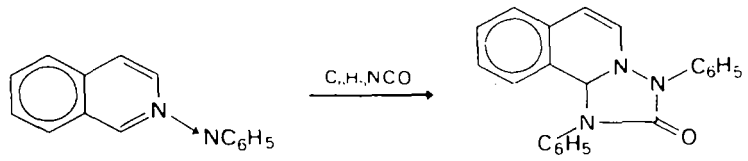


Nitrile oxides have only recently been shown to give cycloadducts with aryl isocyanates[539]. On generating aromatic nitrile oxides from aryl hydroxamyl chloride with triethylamine or sodium hydroxide as base in the presence of phenyl isocyanate, 2,4-diaryl-1,2,5-oxadiazole-3-ones (**353**) are formed in addition to the nitrile oxide dimers (furoxanes).



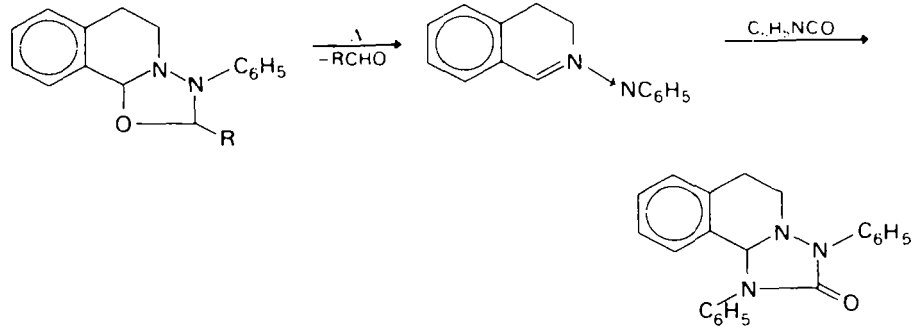
(353)

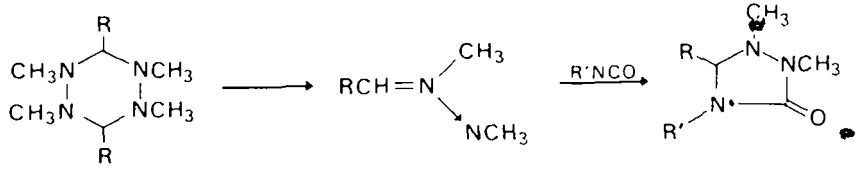
Azomethine imines and aromatic nitrile imines, the nitrogen analogues of *N*-oxides and nitrile oxides, are also known to add to isocyanates under formation of five-membered ring heterocycles. Thus by reacting isoquinoline *N*-phenylimine with phenyl isocyanate at room temperature, high yields of the adduct **354** are obtained[540].



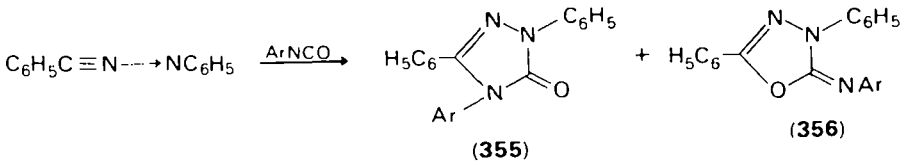
(354)

A number of other cyclic and acyclic azomethine imines give related cycloadducts[541,542,868]. Certain azomethine imines have to be generated from other cycloadducts and reacted *in situ* with excess isocyanate as shown by the following two examples[543,544].



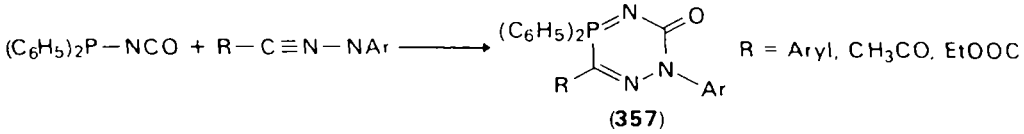


Aromatic nitrile imines, generated by thermolysis from 2,5-diphenyltetrazole or by dehydrochlorination of carboxylic acid hydrazide chlorides, add readily to aryl isocyanates[540,545]. Benzonitrile-*N*-phenylimine and aryl isocyanates give mixtures of adducts **355** and **356** formed by addition across the C=N or C=O bond of the isocyanate.



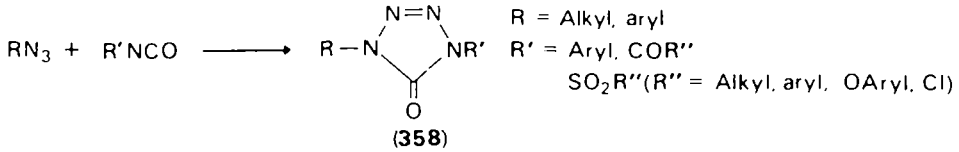
(355) **(356)**

In the reaction of diphenyl phosphinous isocyanate with nitrile *N*-arylimines both components behave like 1,3-dipoles and adducts of type **357** are obtained[546].



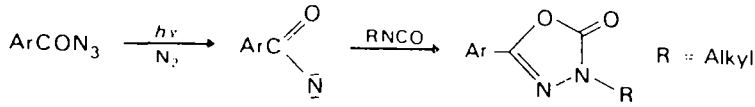
(357)

The behaviour of azides towards isocyanates is more complex. Heating of alkylazides with aryl isocyanates for an extended period (40 h to 23 days) leads to formation of 1-alkyl-4-aryl-Δ^2-tetrazoline-5-ones (**358**) in excellent yield; acyl and sulphonyl isocyanates react with alkyl and aryl azides more readily to give similar adducts[547,874].



(358)

Monosubstituted Δ^2-tetrazoline-5-ones are obtained on reacting aluminium azide with aryl isocyanates in tetrahydrofuran[548]. Photochemical reactions of aroyl azides with alkyl isocyanates take a different course. Loss of nitrogen leads to formation of aroyl nitrenes which intercept isocyanates to give [2 + 3] cycloadducts **359**[549,550].

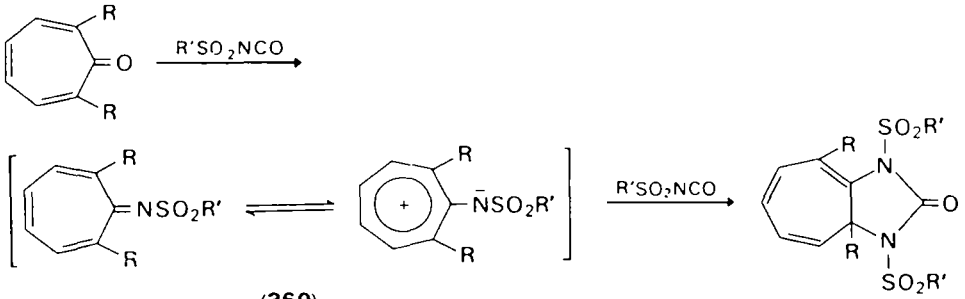


(359)

Thermal and photochemical reactions of azidoformates in the presence of isocyanates are again different (see Section III.B.2.f). They lead to complicated reaction mixtures[550].

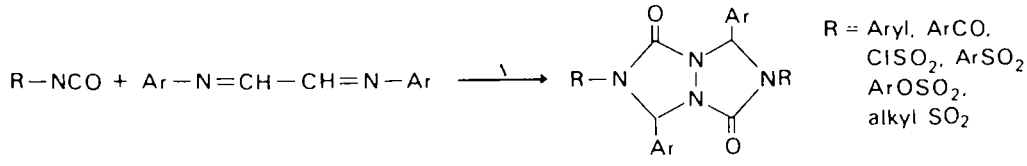
Dimerizations of *N*,*N*-dialkylamino isocyanates, formed from carbamoyl azides (described in the sections on the synthesis and dimerization of isocyanates) are also [2 + 3] cycloaddition reactions[204-208].

Certain compounds containing C=N double bonds in conjugation with other double bonds behave like 1,3-dipoles in reactions with isocyanates. Thus treating tropone or 2,7-diphenyltropone with arenesulphonyl isocyanates leads initially to formulation of imines, **360**, which with excess isocyanate give imidazolones, **361**[551,552].



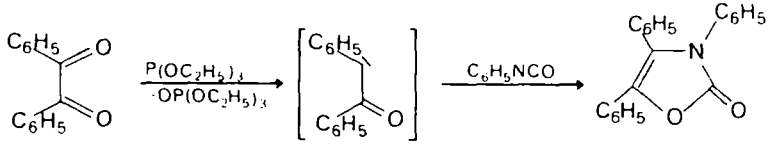
(360) (361)

A number of arenecarboxaldehyde azines react readily on heating with aryl, acyl and sulphonyl isocyanates in a double 1,3-dipolar cycloaddition ('criss-cross' addition) involving both C=N double bonds, affording tetrahydro-triazolo-triazoles (**362**)[479,516,553-555].



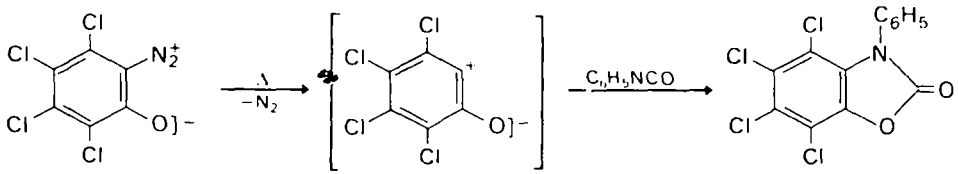
(362)

A ketocarbene is possibly formed in the reactions of benzil with triethyl phosphite in the presence of anhydrous $CuSO_4$ since 3,4,5-triphenyl-4-oxazoline-2-one (**363**) is obtained in presence of phenyl isocyanate[556]. (For different cyclization reactions involving 1,2-dicarbonyl compounds, aryl isocyanates and trimethyl phosphite, see Section III.B.2.f.)



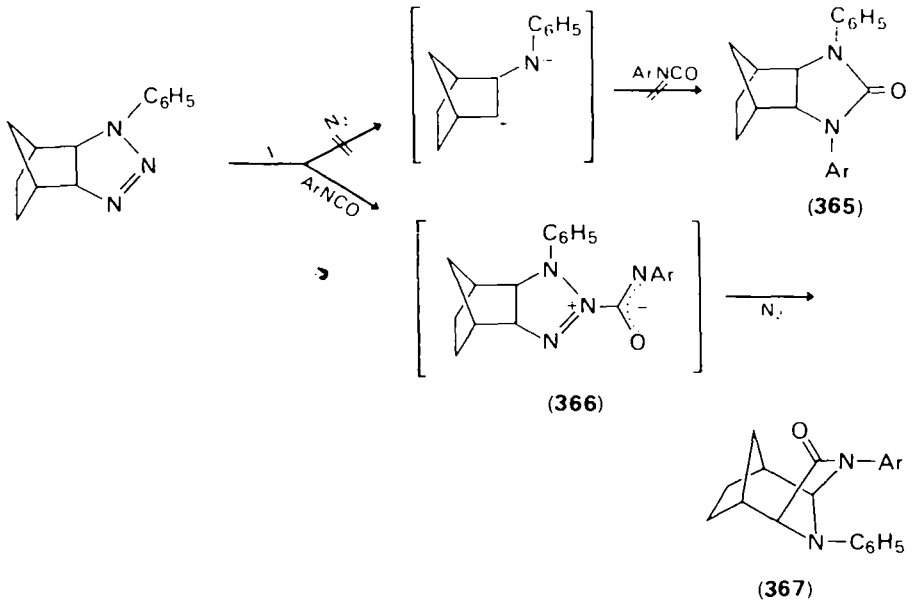
(**363**)

On heating 3,4,5,6-tetrachlorophenyl-2-diazo-1-oxide in presence of phenyl isocyanate, nitrogen is evolved and a benzoxazolone (**364**) is obtained[557]. The ketocarbene intermediate formed on nitrogen elimination reacts like a 1,3-dipolar compound.

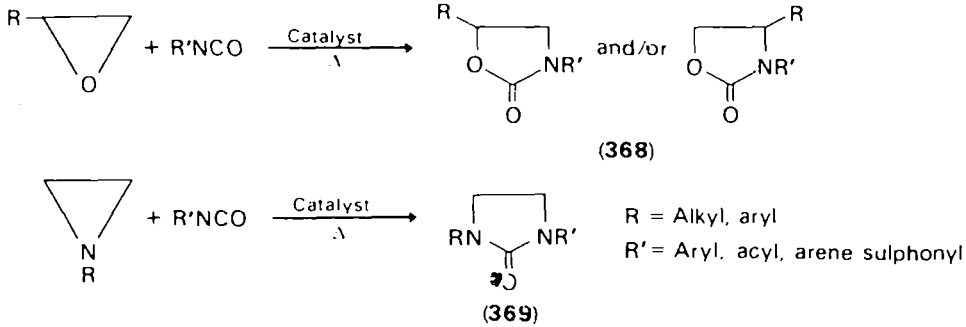


(**364**)

A similar mechanism was postulated for the adduct formation during thermal decomposition of exo-3-phenyl-3,4,5-triazatricyclo[5,2,1,$0^{2,6}$]-dec-4-ene in presence of aryl isocyanates giving imidazolone derivatives **365**[540,558]. It was later shown, however, that actually the reaction takes a different course and adducts **367** are obtained instead, possibly via **366**[559–561].



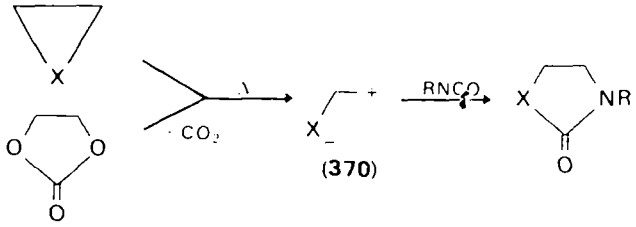
Epoxides and aziridines are known to react readily at elevated temperature with alkyl, aryl, acyl and sulphonyl isocyanates, mostly in presence of soluble lithium salt–phosphine oxide adducts as catalysts, to give 2-oxazolidinones (**368**) and imidazolidinones (**369**) respectively[106,562-568]. Unsymmetrically-substituted 1,2-epoxides were shown to give mixtures of isomeric oxazolidinones in several cases[563]. Application to bis-epoxides and diisocyanates gives



polyoxazolidinones[565]. The reactions can formally be regarded as interceptions of thermally-generated 1,3-dipolar intermediates (**370**) by

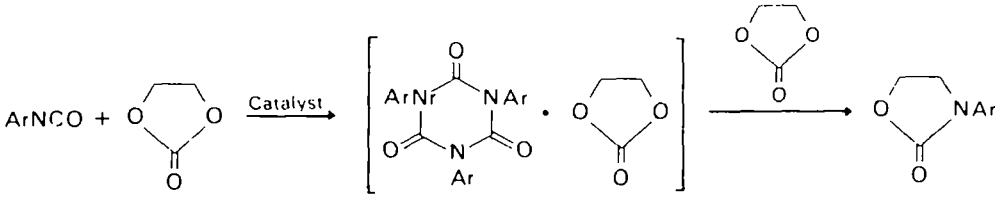
isocyanate. Other studies indicate, however, that direct reactions between isocyanates and epoxides do not take place unless catalysts initiate epoxide ring opening[570] or the isocyanate is transformed into urethane prior to reaction with epoxides[566,571].

Similar dipolar intermediates are possibly formed in the thermal decomposition of alkylene carbonates[540], which also yield oxazolidinones in presence of isocyanates[572]. Yields in all these reactions involving alkylene oxides,



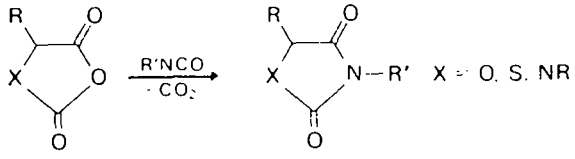
(370)

carbonates and aziridines are high. Catalysts added to accelerate the transformation often cause trimerization of isocyanates. 1:1 Adducts (**371**) of triaryl isocyanurate and ethylene carbonate can be obtained in presence of *N*-methylmorpholine, which on further treatment with ethylene carbonate are converted into oxazolidinones[573].

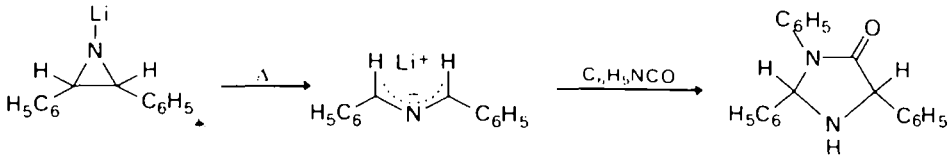


(371)

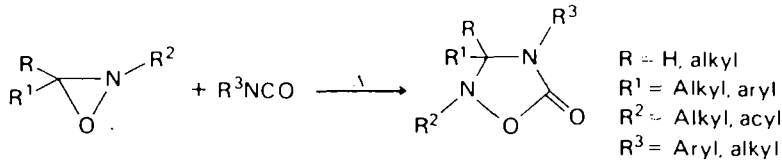
Carbonates of α-hydroxy carboxylic, α-mercapto carboxylic and α-*N*-substituted amino acids react also with isocyanates under expulsion of carbon dioxide to give oxa- and thiazolidine-2,4-dione, and imidazolidine-2,4-diones[574].



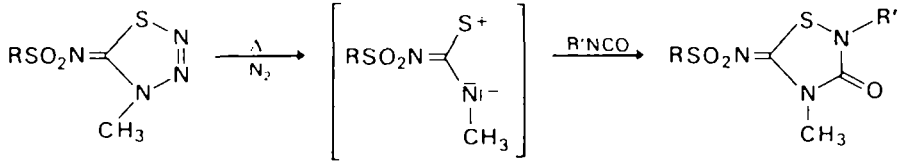
Interception of *trans, trans*-1,3-diphenyl-2-azaallyl lithium, prepared by thermal ring cleavage from *N*-lithio-2,3-diphenylaziridine, with phenyl isocyanate at low temperature gives 2,3,5-triphenylimidazoline-4-one in a 1,3-anionic cycloaddition reaction[575].



N-Substituted oxaziridines have also been shown recently to react with alkyl and aryl isocyanates at elevated temperatures to give 1,2,4-oxadiazolidine-5-ones in good to very good yield[576,577].



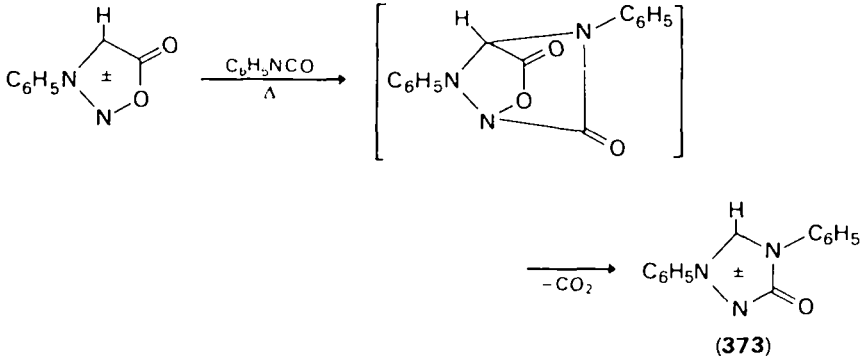
The reaction of 1,2,3-triethyldiaziridine with phenyl isocyanate in refluxing benzene leads to a complex mixture of products[578]. The thermal decomposition of 4-methyl-5-arylsulphonylimino-4,5-dihydro-1,2,3,4-thiatriazole leads to formation of a 1,3-dipolar intermediate **372**, which can be intercepted by aryl and arenesulphonyl isocyanates to give 4-methyl-3-oxo-5-sulphonylimino-1,2,3-thiadiazolidines[862].



(372)

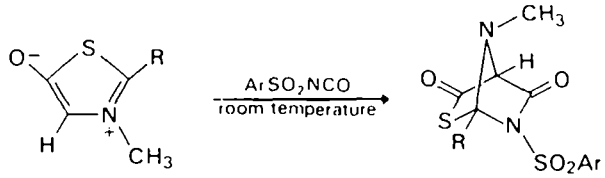
R = CH_3, aryl
R' = Aryl, arenesulphonyl

When 3-phenylsydnone is heated with phenyl isocyanate, carbon dioxide is generated and a new mesoionic compound, 1,4-diphenyl-1,2,4-diazolone (**373**) is obtained in very good yield, possibly via a labile [2 + 3] cycloadduct[579].

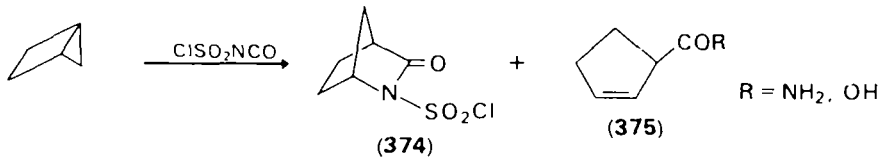


(373)

Other mesoionic compounds, anhydro-2,4-disubstituted 5-hydroxy-3-methylthiazolium hydroxide, react with activated isocyanates (sulphonyl and aroyl isocyanates) at room temperature to give stable 1 : 1 cycloadducts in good yield[860].



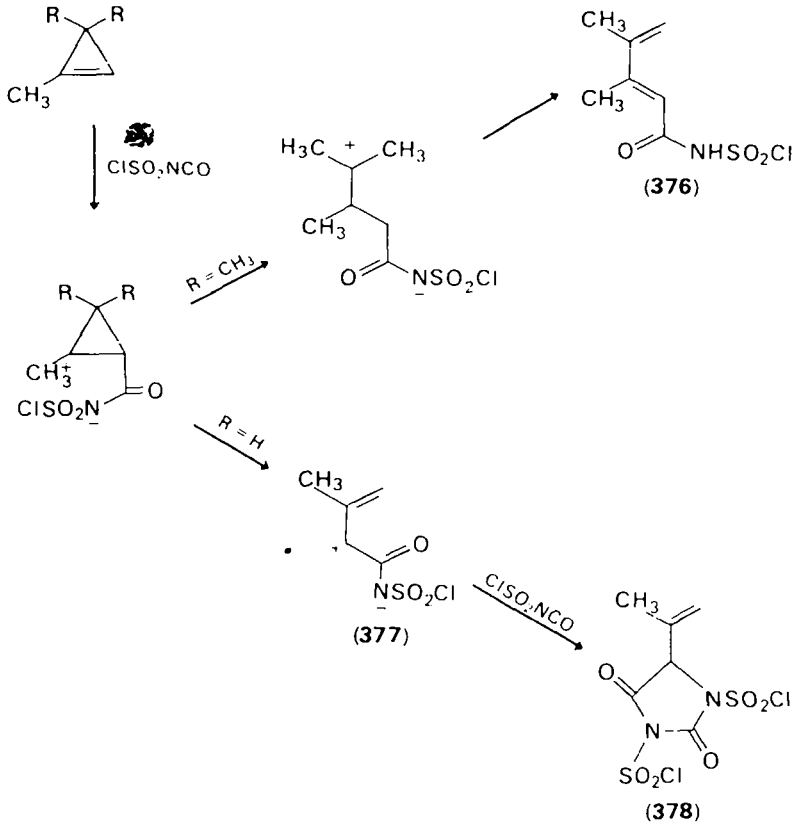
Some reactions involving isocyanates and aliphatic three-membered ring compounds proceed by ring cleavage and extensive skeletal rearrangements. Reacting bicyclo[2,1,0]pentane with CSI in appropriate solvents at room temperature and below leads to a mixture of **374** and (after aqueous work-up) **375**[580].



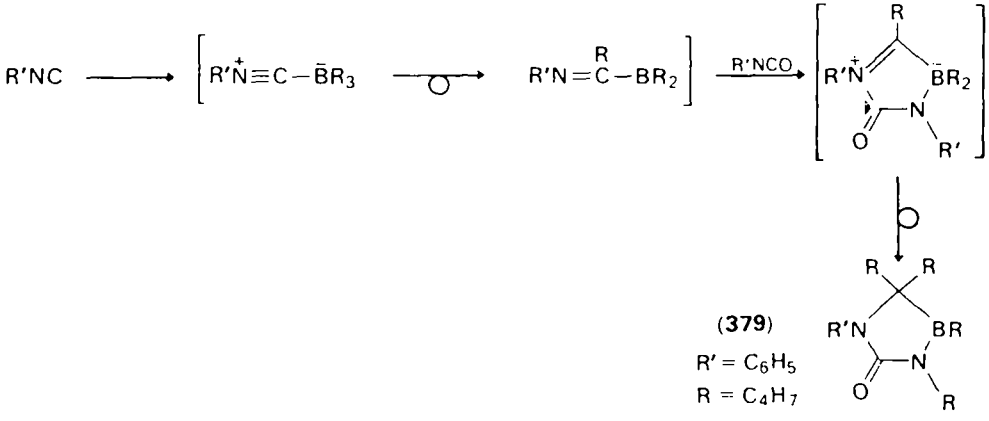
(374) (375)

Two structurally different products are obtained on treating substituted cyclopropenes with CSI[581]. 1,3,3-Trimethylcyclopropene and the isocyanate give, at low temperature, an acyclic product (**376**) while a similar reaction with 1-methylcyclopropene gave a cyclic 1:2 adduct (**378**). The latter product is believed to arise from a 1,3-dipolar intermediate **377** while **376** is formed via a different mechanism.

1,3-Dipolar adducts, which rearrange to α-iminoboranes are formed on reacting trialkylboranes with isonitriles in inert solvents. These

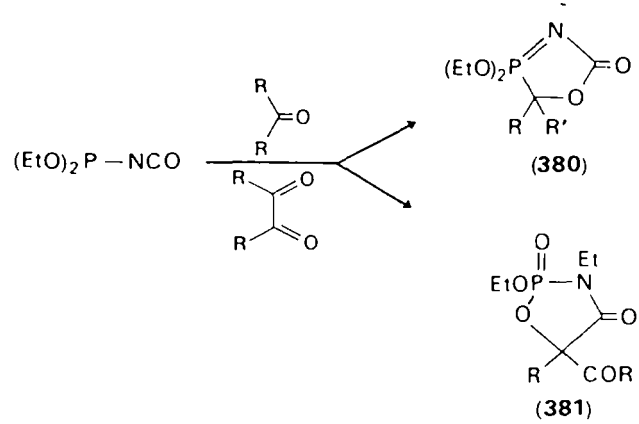


intermediates can be intercepted by phenyl isocyanate, affording 1,4-diaza-2-boracyclopentanones **379** after further alkyl migration[582].

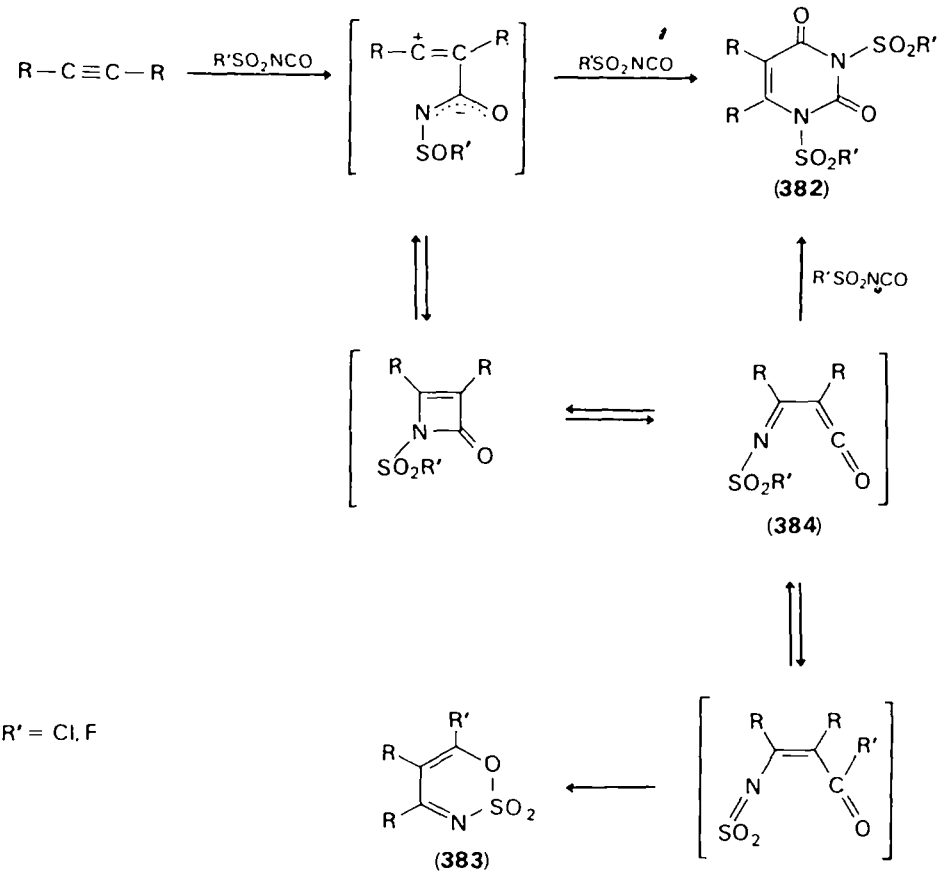


Reactions of electron-rich olefins with isocyanates leading to formation of 1,3,6,9-tetraaza-spiro[4,4]nonanes are also believed to involve 1,3-dipolar intermediates. They are described in Section III.B.2.e.

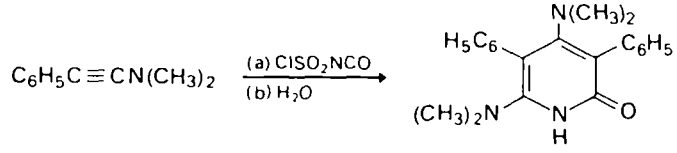
The behaviour of isocyanato phosphonites towards carbonyl-group-containing compounds is exceptional. The trivalent P-compounds react with aldehydes, α-diketones, phenyl glyoxal and esters of α-keto acids like 1,3-dipoles[583–585]. Adducts **380** could be isolated with aldehydes in low yield[583]. Isomeric 1:1 adducts (**381**) are, however, obtained with other carbonyl compounds in which an alkyl group of the phosphonites has migrated to the adjacent nitrogen[584,585]. Bicyclic adducts are obtained as a result of alkyl migration in similar reactions with alkylene isocyanato phosphonites and α-diketones[585].



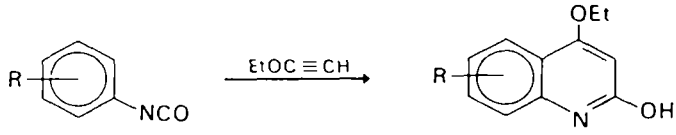
d. *Cycloadducts with acetylenes.* Reactions between isocyanates and compounds containing C≡C triple bonds have been investigated in recent years, resulting in the discovery of a number of interesting cyclization reactions. Two structurally different types of cycloadducts are obtained on reacting fluoro or chlorosulphonyl isocyanate with alkyl, aryl, and aryl alkyl substituted acetylenes at ambient temperatures[586–589]. Cycloadducts **382** derived from acetylenes and isocyanate in a molar ratio of 1:2 are preferentially formed with fluorosulphonyl isocyanate[586,587,590]. 1:1 Cycloadducts which were identified by X-ray analysis to be 6-halo-1,2,3-oxathiazine-2,2-dioxides (**383**) are obtained mainly with CSI and their formation can best be explained with the reaction steps in the following scheme[586,587,590]. The formation of the 2:1 adducts **383** is possible in a stepwise cycloaddition reaction via a 1,4-dipolar intermediate, although an alternative mechanism via the iminoketene intermediate **384** would explain the formation of both products (see below).



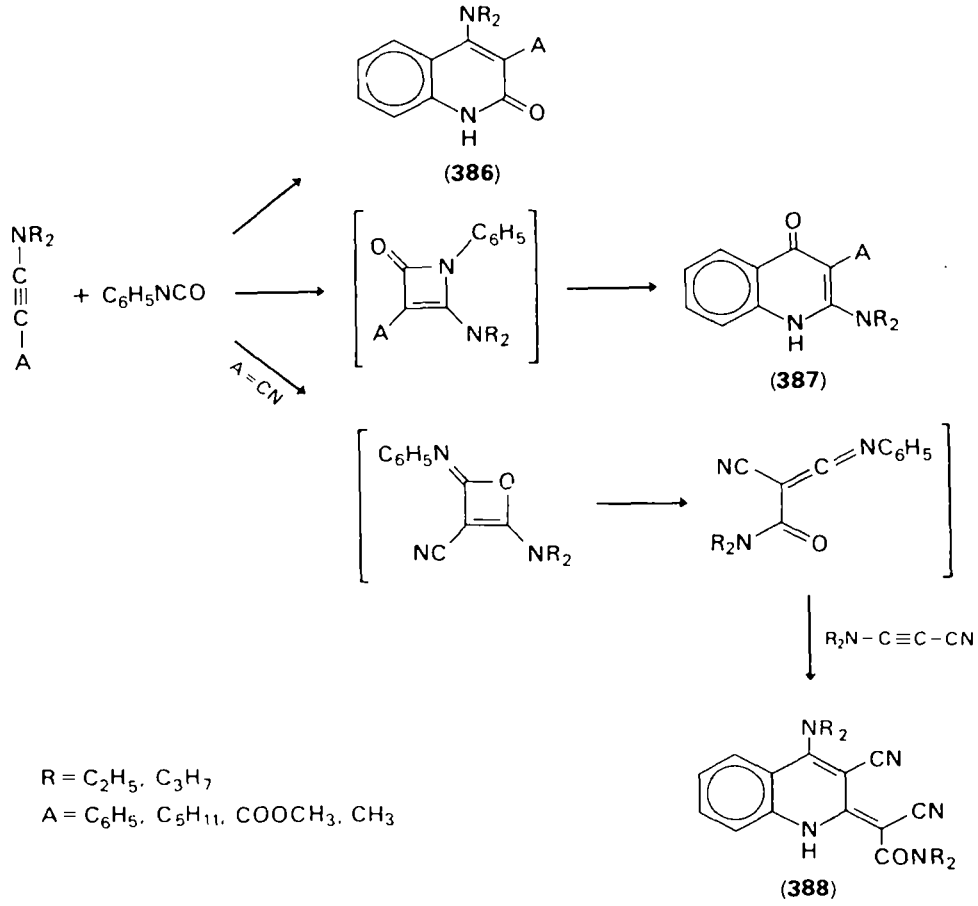
Similar 1,2,3-oxathiazine-2,2-dioxides are obtained on reacting CSI with 1-methylthio-2-phenyl- and 1-methyl-2-(*p*-tolythio)acetylene[591]. The behaviour of the same isocyanate towards 1-dimethylamino-2-phenylacetylene, however, is entirely different, giving rise to formation of the pyridone **385**[591].



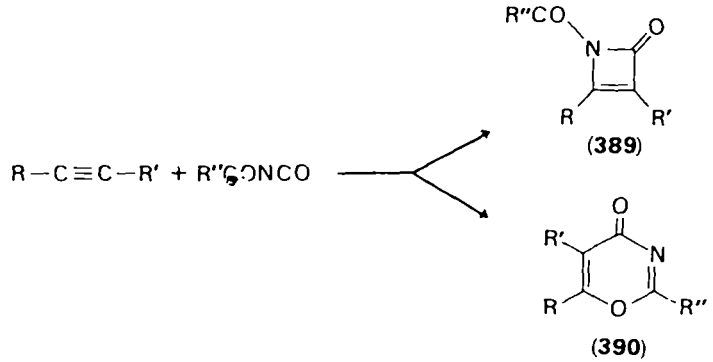
The reaction of ethoxyacetylene with a number of aryl isocyanates is claimed to proceed in a [2 + 4] fashion in which the isocyanate acts as the heterodiene[592,593].



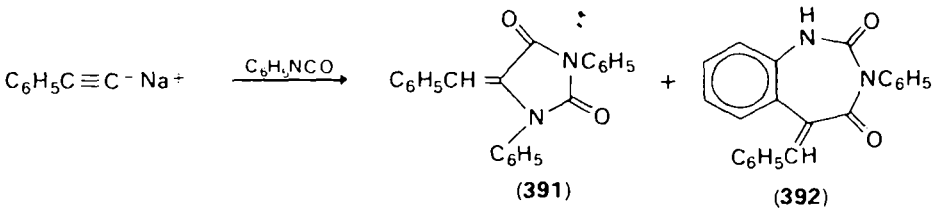
The reactions of aryl isocyanates with aminoacetylenes (ynamines) give other kinds of cycloadducts. On mixing phenyl isocyanate with ynamines in appropriate solvents, 4-amino-2-quinolones (**386**) and 2-amino-4-quinolones (**387**) are formed[594,595]. A [2 + 4] cycloaddition accounts for the formation of **386**, while the isomeric adducts **387** are the result of an initial [2 + 2] cycloaddition followed by ring scission at the C—N bond (to give an iminoketene) and recyclization. A third type of product is



obtained on reacting cyanoynamines with phenyl isocyanate[596]. It is believed that the 1:1 adduct resulting from an initial addition of the C=O group of the isocyanate across the triple bond of the ynamine, isomerizes to a ketenimine which reacts with more ynamine in a [2 + 4] cyclo addition to give the product **388**. Acylisocyanates were found to react with substituted acetylenes and ynamines in [2 + 2] or [2 + 4] cycloadditions, giving either azetine-4-ones **389** or 1,3-oxazine-4-ones **390**[597-600].

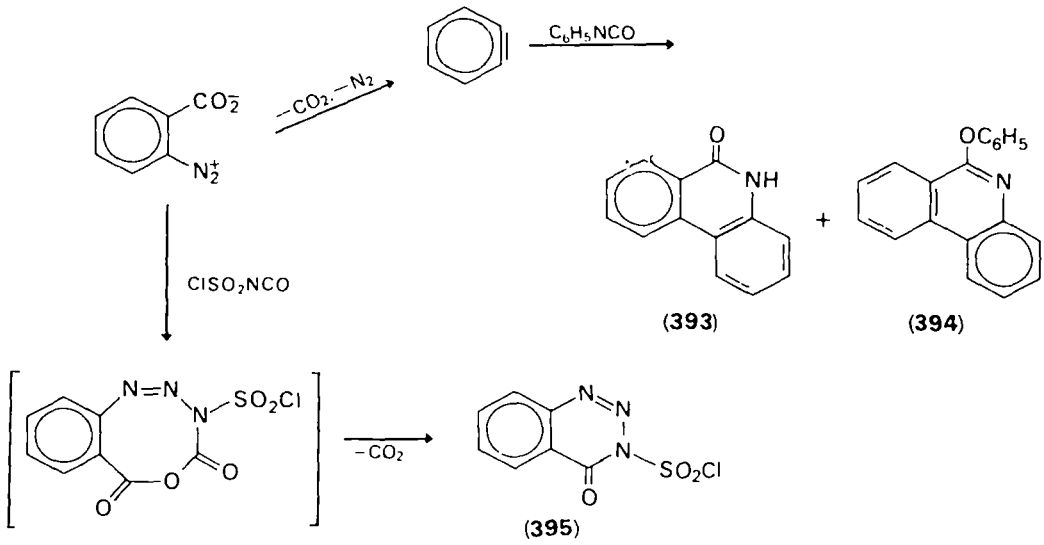


On reacting sodium phenylacetylide with phenyl isocyanate in ether, a hydantoin, **391**, is formed besides an isomeric 1:2 adduct believed to be **392**[601].

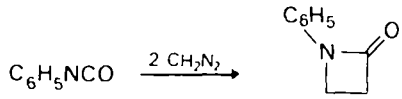


The same hydantoin **391** is obtained in high yield besides varying amounts of 2,5-diphenylcyclopentadienone iron tricarbonyl on reacting phenylacetylene with phenyl isocyanate in presence of iron pentacarbonyl[602].

Two attempts to add isocyanates across the triple bond of benzyne failed. Reacting phenyl isocyanate with diazotized anthranilic acid leads to formation of phenanthridinone (**393**) and 9-phenoxyphenanthridine (**394**) in low yield[603]. Chlorosulphonyl isocyanate and the same benzyne precursor gave a 1,2,3-benzotriazine-4-one (**395**) in high yield believed to be formed via an eight-membered heterocycle[588].

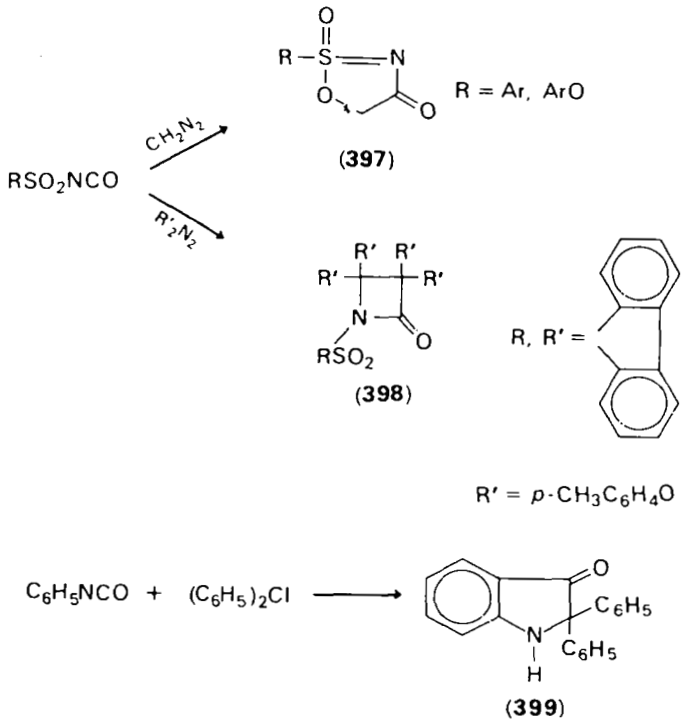


e. *Cycloadducts with carbenes and carbene precursors.* The simplest case of a cycloaddition between an isocyanate and a bivalent carbon is the reaction between 2 moles of diazomethane and phenyl isocyanate, giving the β-lactam **396**[604].

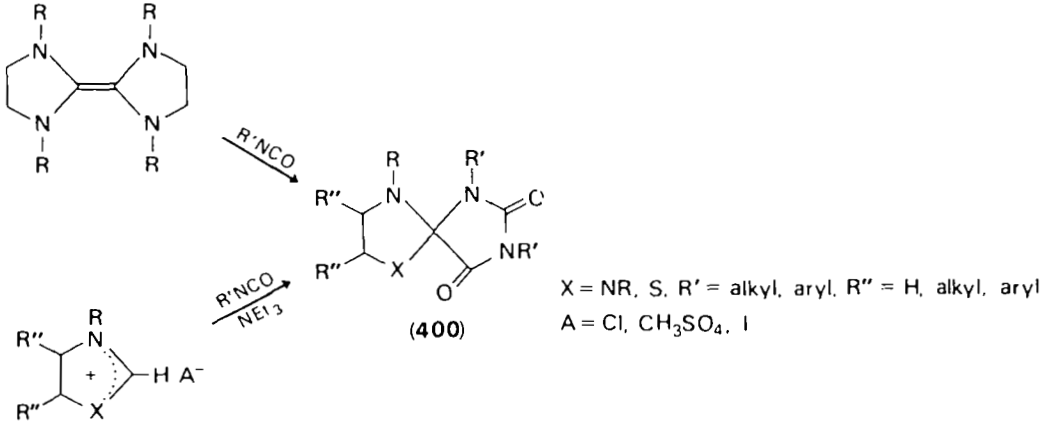


(396)

A similar type of product is obtained on reacting diazofluorene with arenesulphonyl isocyanate at low temperature[605]. The same isocyanate gives, however, a 1,2,3,-oxathiazole-4-one-2-oxide (**397**) when reacted with diazomethane in diethyl ether at −25°C[605]. Another type of cycloaddition was observed in the reaction of phenyl isocyanate with the photochemically generated diphenylcarbene, which gives 2,2-diphenylindoxyl (**399**) probably via an α-lactam as intermediate[606]. The reactions of certain electron-rich olefins with isocyanates can be regarded as cycloadditions involving carbenes. Thus reacting aryl or alkyl isocyanates with *N,N'*-disubstituted diimidazolinylidene-2 in a molar ratio of 4:1 leads to cleavage of the C=C double bond and formation of 1,3,6,9-tetraazaspiro[4,4]nonanes (**400**)[607-608]. These products are also accessible via a different route. 1,3-Diphenylimidazolium chloride or *N*-substituted

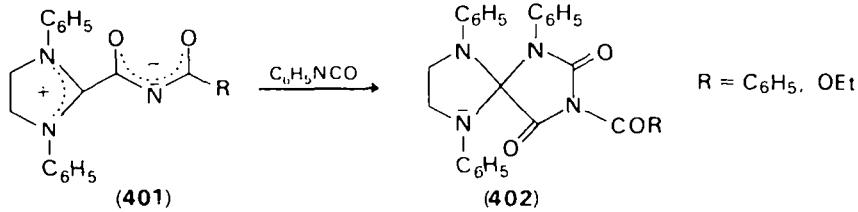


thiazolium methosulphates behave also like nucleophilic carbenes when treated with triethylamine and form similar parabanic acid derivatives



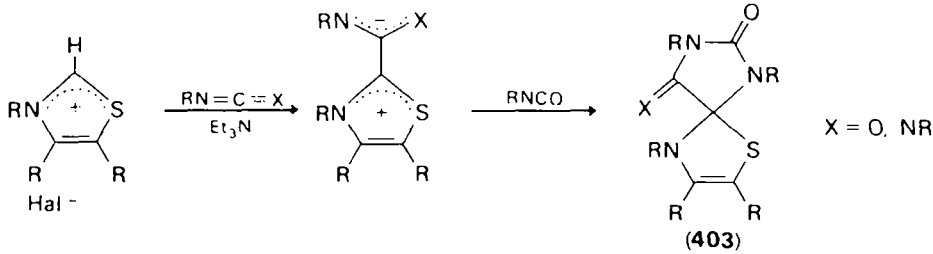
with aryl or alkenyl isocyanates[609]. Stable 1.4-dipoles, **401**, are obtained on reacting 1,1',3,3'-tetraphenyl-2,2'-diimidazolinylidene with acyliso-

cyanates; they can be intercepted with phenyl isocyanate as dipolarophile to give related tetraazaspiro[4.4]nones (**402**)[610].



(**401**) (**402**)

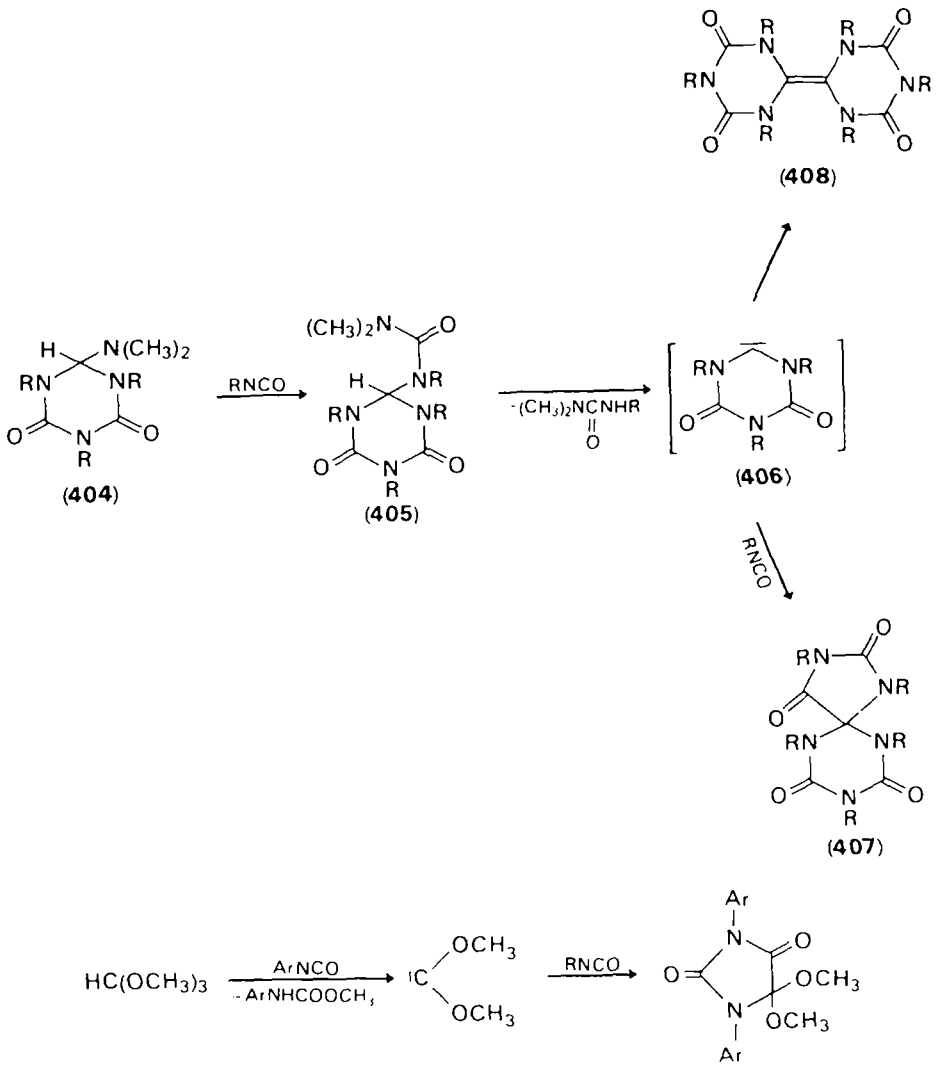
A number of 3,4,5-trisubstituted thiazolium and thiazolidinium halides react in presence of triethylamine with isocyanates or carbodiimide and isocyanates in a stepwise fashion with formation of 1-thia-4,6,8-triaza-spiro-[4.4]-none-2-enes (**403**) or hydrogenated species in good yields[611–613].



(**403**)

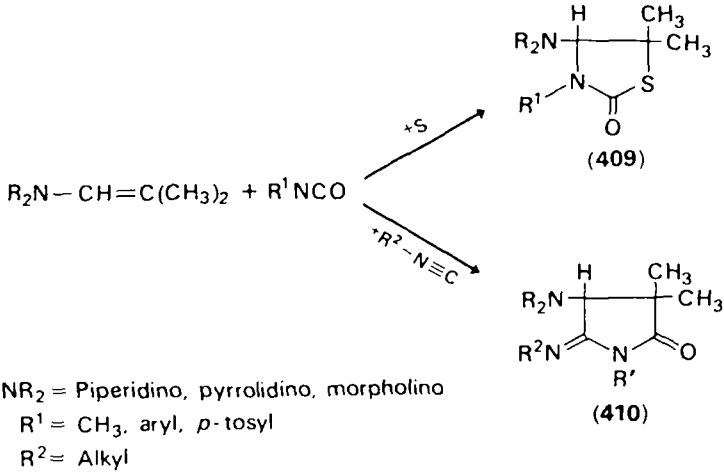
Reactions of 2-dialkylamino-1,3,5-triaryl-4,6-dioxohexahydro-*s*-triazines (**404**) with excess aryl isocyanates are related. Thermal elimination of *N*,*N'*-trisubstituted urea from the initially formed ureido-*s*-triazines (**405**) leads to a heterocarbene, **406**, which is either intercepted by excess isocyanate, giving a pentaazaspiro[4.5]-decanetetraone (**407**) or, in absence of isocyanate, a bis-*s*-triazine tetraone (**408**)[512,513,614,615]. The reactions of trimethyl orthoformate with aryl isocyanates leading to parabanic acid *O*,*O*-acetals probably proceed via dimethoxycarbene as intermediate[616,751].

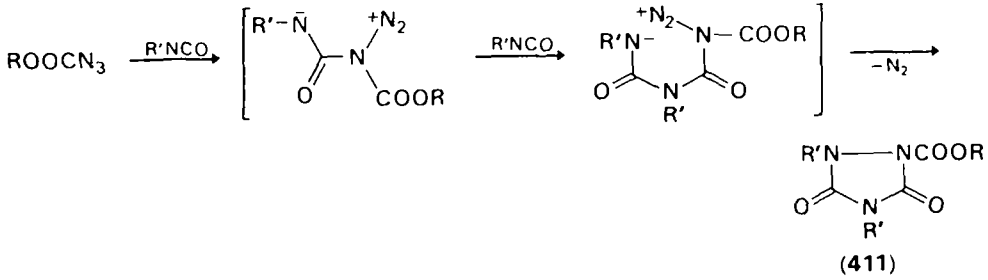
f. *Miscellaneous cyclizations.* Formation of [2 + 2 + 1] cycloadducts has been observed on reacting α-amino-alkenes with isocyanates and sulphur or isonitriles in highly polar, non-protic solvents[617–620]. The amino olefins are first reacted with sulphur or isonitrile, followed by addition of aryl or alkyl isocyanate. The structure of the obtained 1,3-thiazolidine-2-ones (**409**) and iminopyrrolidinones (**410**) indicates a stepwise addition sequence.



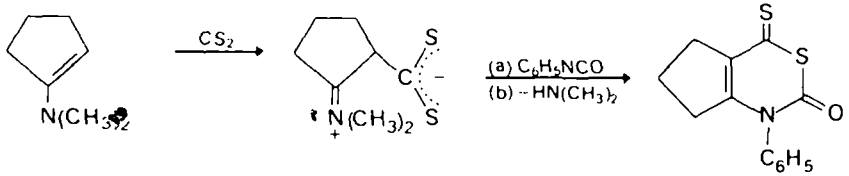
The formation of 1.4-dialkyl-2-ethoxycarbonyl urazoles (**411**) in the thermal and photochemical reaction of azido alkyl formates in presence of alkyl isocyanate can only formally be regarded as a [2 + 2 + 1] cycloaddition.

It is suggested by the authors that **411** is formed -among five other reaction products- via an initial nucleophilic attack of the N_γ of the azide on the isocyanate carbonyl with successive reaction steps as outlined below[550].



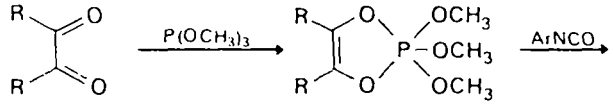


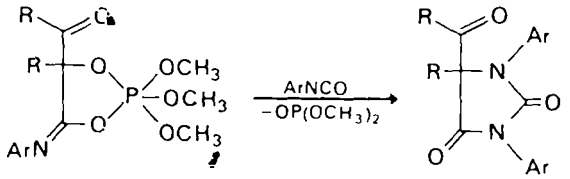
Enamines react with carbon disulphide at low temperatures to give deeply coloured 1,4-dipoles which can be intercepted with aryl isocyanates with formation of 1,3-thiazines[621].



Isocyanates react with 1,2-dicarbonyl compounds and trimethyl phosphite with formation of 5-acyl hydantoins **412** and trimethyl phosphate in good yields[622-624]. The indicated products are obtained via initial formation of 2,2,2-trimethoxy-2,2-dihydro-1,3,2-dioxaphospholenes from $P(OCH_3)_3$ and the dicarbonyl compounds. Attack of isocyanate

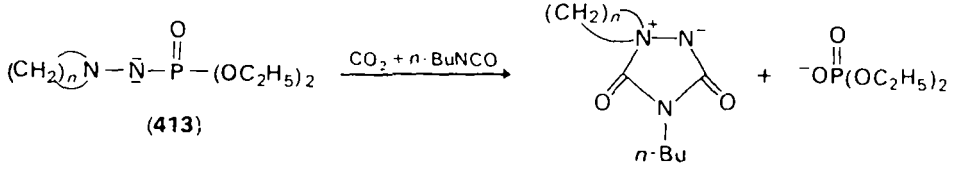
leads to another intermediate which is finally converted to the hydantoins with excess isocyanates.





(412)

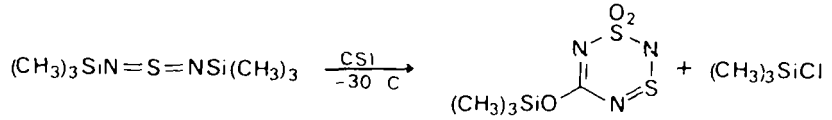
On treating the anion of certain diethyl *N*-alkylaminophosphoramidates (**413**) with carbon dioxide in the presence of *n*-butyl isocyanate, spiro nitrogen ylides are formed[625].



(413)

(414)

Cycloaddition reactions of isocyanates and compounds having S=O and S=N bonds have also been observed. On reacting *N*,*N'*-bis(trimethylsilyl)sulphur diimide with equimolar amounts of CSI, a 1,3,2,4,6-dithiatriazine-1,1-dioxide (**415**) is obtained in low yield[626].

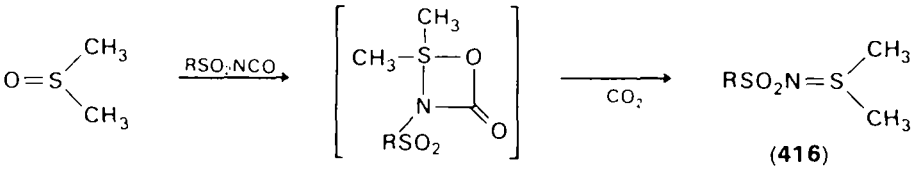


(415)

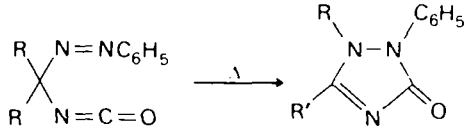
Formation of 1:1-cycloadducts with so-far unknown structure has been observed during mixing of halogen sulphonyl isocyanates as well as sulphonyl diisocyanate with S_4N_4 in inert solvents[873].

Sulphonyl isocyanates react readily also with dimethylsulphoxide to dimethyl sulphimines (**416**) and carbon dioxide[538,255]. CH insertion

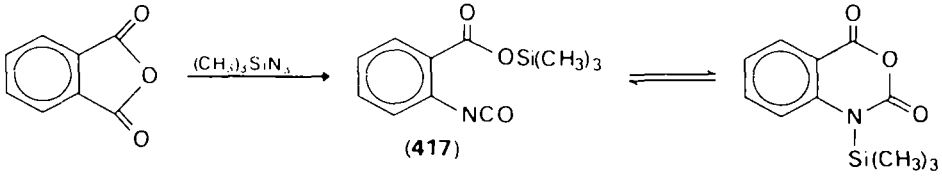
on the methyl group takes place, however, on treating the sodium salt of DMSO (and sulphones) with aryl isocyanates[628].



Bond shift and alkyl or aryl group migration together with cyclization takes place during brief heating of phenylazomethyl isocyanates at 140 °C, resulting in the formation of Δ^3-1,2,4-triazoline-5-ones[629].



Cyclic carboxylic acid anhydrides react with trimethylsilyl axide, giving rise to vigorous evolution of nitrogen and formation of *N*-trimethylsilyl-*N*-carboxanhydride isocyanates (**417**) which cyclize to 1,3-oxazine diones with simultaneous migration of the trimethylsilyl group to the ring nitrogen[863]. The corresponding reaction of phthalic anhydride is shown below.



3. Insertion reactions

a. *Reactions with OH- and SH-group-containing compounds.* Alkyl and aryl isocyanates react with water resulting in the formation of *N,N'*-disubstituted areas. Addition of 1 mole water to isocyanate produces the labile carbamic acid, which loses carbon dioxide giving a primary amine capable of adding another mole of isocyanate. This sequence is generally not observed in the hydrolysis of sulphonyl isocyanates. The reactions stop at the amine stage since the generated sulphonamides are not basic enough to react with another mole of isocyanate[243]. Therefore the behaviour of fluorosulphonyl isocyanate, which was shown to form

N,N'-bis-fluorosulphuryl urea upon mild hydrolysis[630], is exceptional. Industrially the most important reaction

$$RNCO \xrightarrow{H_2O} [RNHCOOH] \xrightarrow[-CO_2]{} RNH_2 \xrightarrow{RNCO} RNHCONHR$$

$$RSO_2NCO \xrightarrow{H_2O} RSO_2NH_2 + CO_2$$

of isocyanates is their addition to alcohols and conversion to carbamates (urethanes), since application to diisocyanates and diols produces polymeric urethanes of widely varying qualities and characteristics. The development of this chemistry and recognition of its industrial potential was pioneered by Bayer. A detailed description of the urethane formation including polymeric materials can be found elsewhere[631-633,857].

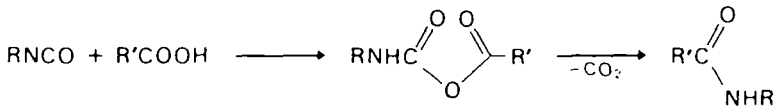
$$RNCN + R'OH \underset{(Catalyst)}{\rightleftharpoons} RNHCOOR'$$

The reactions, which are simple additions, are reversible and RNCO and R'OH can be regenerated on heating.

The reactions of thioalcohols and thiophenols with isocyanates are much slower than those of the corresponding alcohols and proceed even in presence of mild base catalysts (triethylamine) at moderate temperature at very slow rate[870,871]. Rapid formation of mixtures of thiocarbamates and thioallophanates is, however, observed in presence of alkoxide as catalyst[871]

$$RSH \xrightarrow{CH_3NCO} CH_3NHCOSR \xrightarrow{CH_3NCO} CH_3NHCONH(CH_3)COSR$$

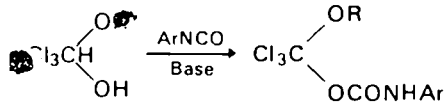
A different type of reaction is involved in carboxylic acid–isocyanate interactions, which irreversibly yield carboxamides and carbon dioxide via formation of a mixed anhydride[631,634,635]. Amines are recommended as catalysts in these reactions[634].



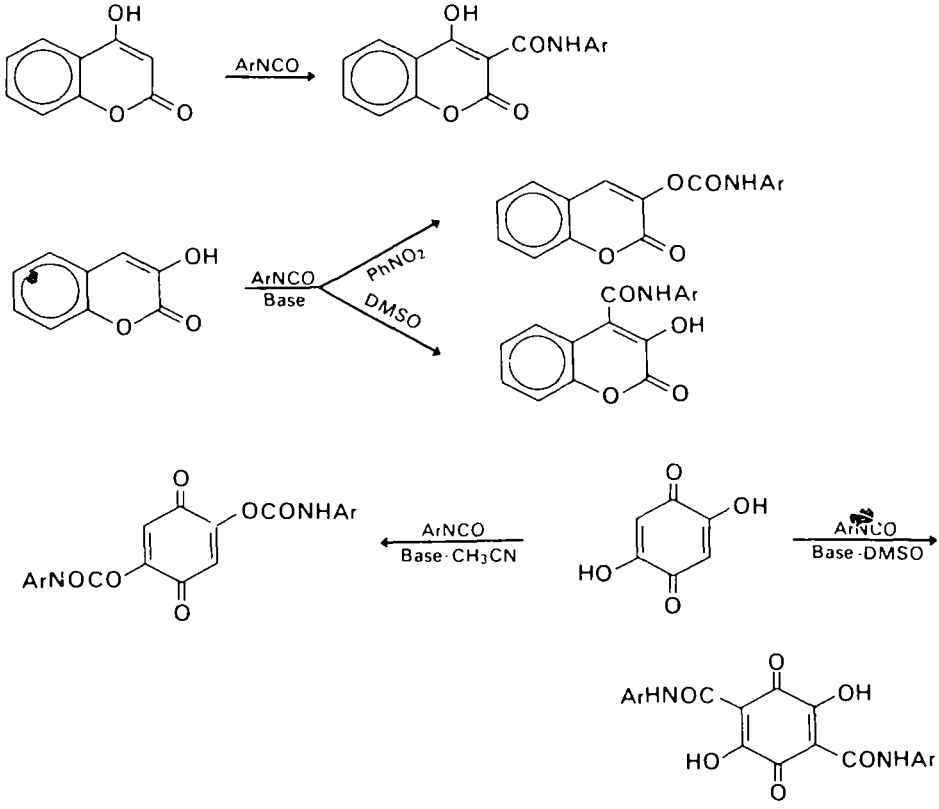
Quaternized amino acids were also shown to react readily with aryl isocyanates to the corresponding amides[636].

N,N-Disubstituted hydroxylamines[637] and oximes[638,639], (*N*-hydroxyimino)dichloromethane[640] or hemiacetals of chloral[641] react also with

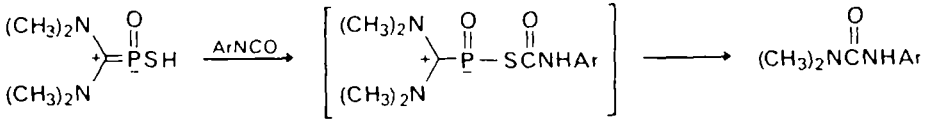
isocyanate to give carbamates. Hydroperoxides, such as *t*-butyl hydroperoxide, give peroxicarbamates[642].



Reactions of isocyanates with OH-group bearing compounds can sometimes take an unexpected course. Thus treating 4-hydroxy coumarins with aryl isocyanates leads to 3-(*N*-aryl)carbamoyl-4-hydroxycoumarins[643]. Carbamates are, however, formed on heating 3-hydroxycoumarin in nitrobenzene with isocyanates in presence of base[644]. CH instead of OH attack is observed between these two reactants on conducting the reactions in dimethyl sulphoxide[644]. A similar solvent-dependent orientation of the isocyanate attack was observed in reactions of aryl isocyanates with 2,5-dihydroxy-1,4-benzoquinone which lead to carbamates or 3,6-bis(*N*-arylcarboxamides)[879].

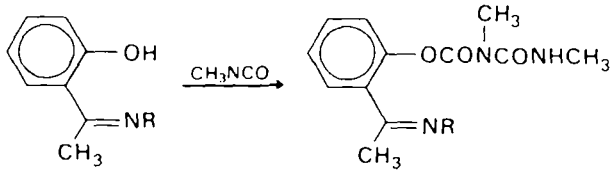


No thiocarbamate but rather a *N,N,N'*-trisubstituted urea is obtained on treating aryl isocyanates with certain dimethylamido thiolophosphoric acids[645]. Unstable intermediates like **418** are believed to be involved in these reactions. *O,O*-Diethylthiolophosphoric acid is known to give thiocarbamates with alkyl and aryl isocyanates at low temperature[646].



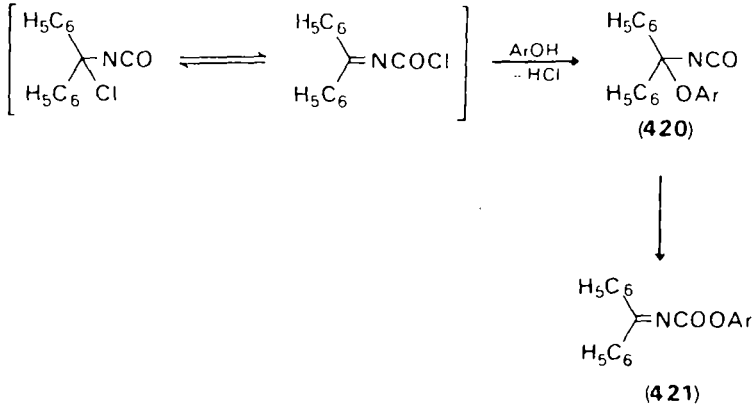
(418)

The behaviour of methyl isocyanate toward 2-(1-iminoethyl)phenols is exceptional, leading to formation of allophanates **419** instead of the expected carbamates[647].



(419)

α-Chloro-α-diphenylmethyl isocyanates react with phenols with elimination of HCl giving an unstable α-phenoxy isocyanate (**420**) which is spontaneously converted to the isomeric **421**[648].

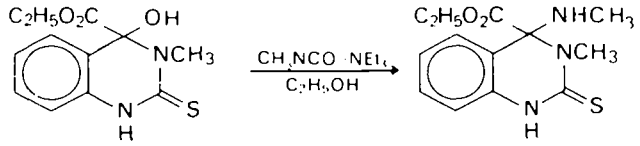


(420)

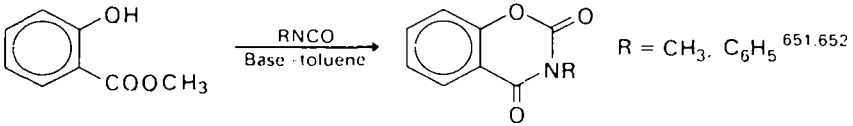
(421)

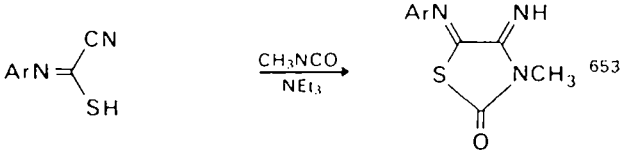
Certain carbamates, obtained by reacting hydroxyl-group-containing benzoxazines and quinazolines with alkyl or aryl isocyanate, were shown to be easily converted into the corresponding amines on treatment with

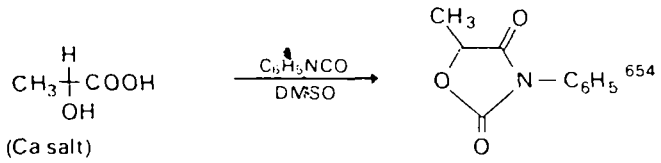
triethylamine or water; primary and secondary amines were also shown to replace the carbamoyl group[649,650]. An example is shown below[650].

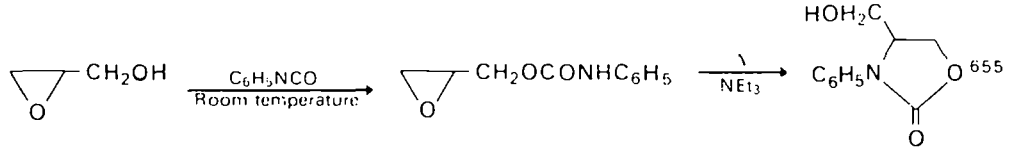


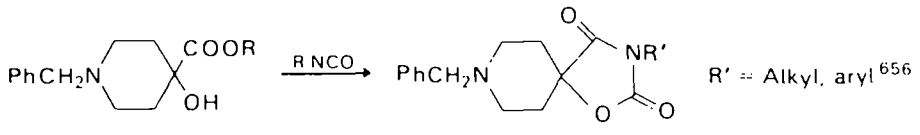
Many reactions of isocyanates with substrates containing OH or SH groups are known, in which the originally formed carbamates and thiocarbamates are further modified by interaction with adjacent substituents. Heterocyclic compounds are often formed in processes which are catalysed or thermally initiated. A number of examples are given below.

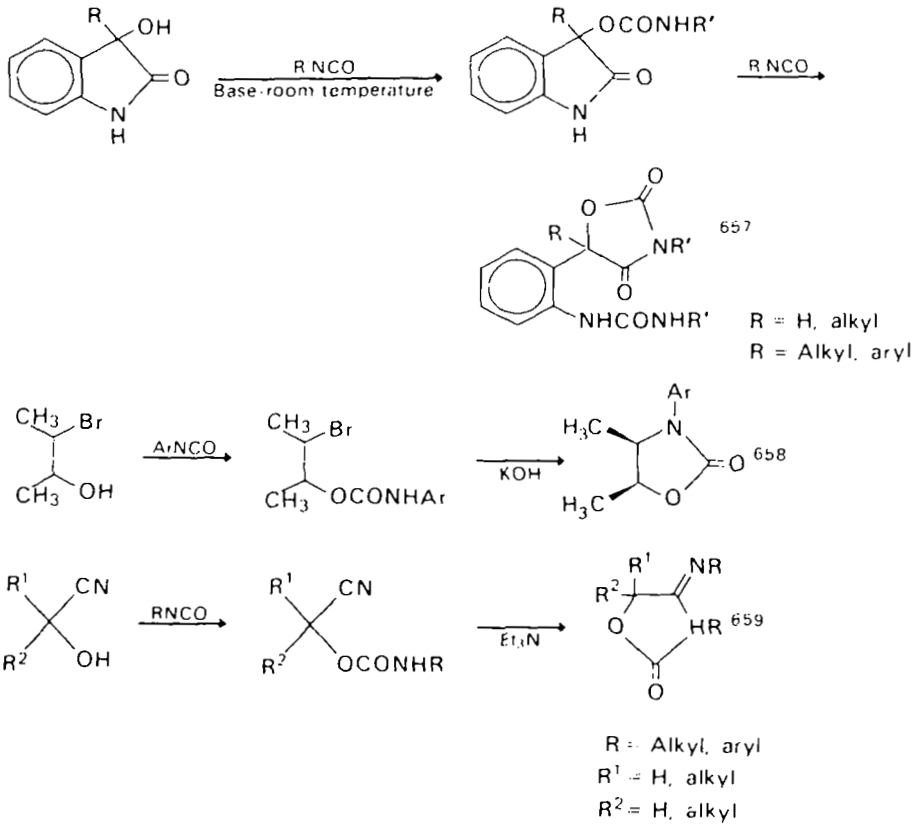




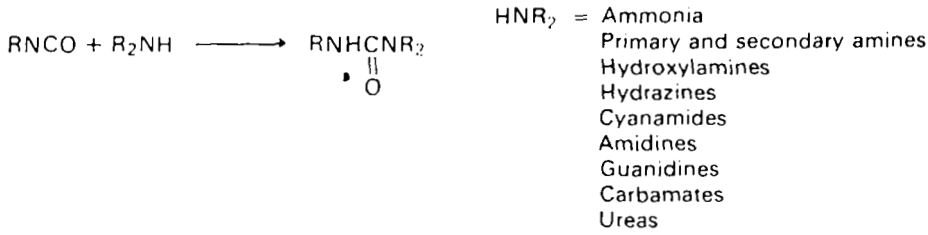






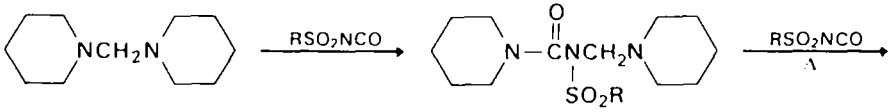


b. *Reactions with amines.* Reactions of isocyanates with compounds bearing NH_2 or NH groups lead generally to the formation of ureas. The scope, kinetics, solvent dependence and catalysis of these isocyanate transformations have been studied in detail and are described elsewhere[631,660].

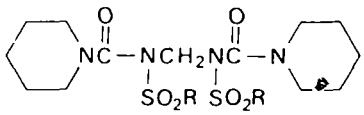


A detailed description of these generally well-known reactions is omitted. Instead a selection of reactions involving more complex, unexpected and less known transformations with amines is given.

Tertiary amines also react with isocyanates, occasionally with formation of labile dipolar 1:1 adducts[538], but generally under oligomerization of the isocyanates (see Section III.B.1.a and b). Formaldehyde-*N*,*N*-acetals react with aryl and sulphonyl isocyanates with insertion into a C—N bond and formation of ureas **422**[91,661]; excess isocyanate and elevated reaction temperatures can lead to insertion into both C—N bonds, giving **423**[91].



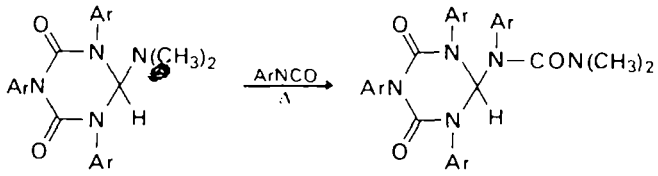
(422)



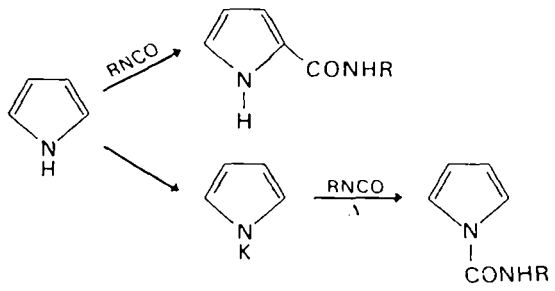
(423)

This reaction is related to the formation of hexahydro-*s*-triazine derivatives from oligomeric formaldimines and isocyanates (see Section III.B.2.6.iii).

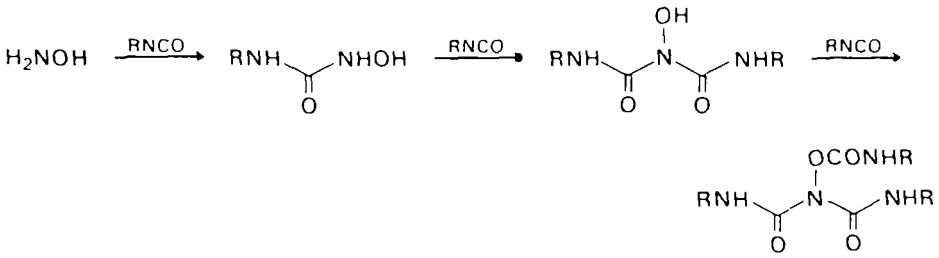
Tris-aminomethane derivatives react with aryl isocyanates at elevated temperatures with insertion into a C—N bond and formation of ureas[512,513].



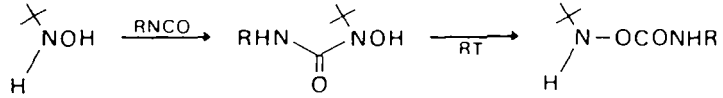
Not all compounds having free NH or NH_2 groups available can be converted into ureas or related products by action of isocyanates. Isocyanates and pyrrole, indole or carbazol undergo substitution reactions on the aromatic nucleus[662,663]. Only conversion of pyrrole into the potassium salt assures urea formation with alkyl and aryl isocyanates[664,665]. Hydroxylamine, which has both OH and NH_2 available for reaction with isocyanates, adds isocyanates exclusively at the amino group, giving 1-phenyl-3-hydroxyurea and 1,5-diphenyl-3-hydroxybiuret[666,667] and



only excess isocyanate attacks the hydroxy group[667,668]. *N*-Alkyl and aryl hydroxylamines also react first with the remaining NH proton[867].

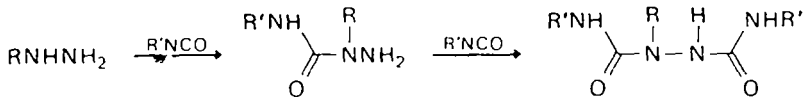


N-Hydroxyl ureas, **424**, obtained on treatment of *N*-isopropyl and *t*-butyl hydroxylamine with alkyl isocyanates, rearrange at room temperature to the corresponding *O*-carbamoyl hydroxylamines **425**[669]. Other *N*-alkyl (CH_3, cyclohexyl) and aryl hydroxylamines failed to undergo this rearrangement.

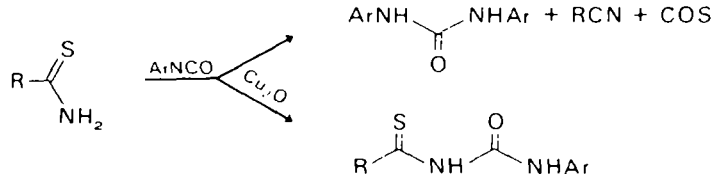


(424) **(425)**

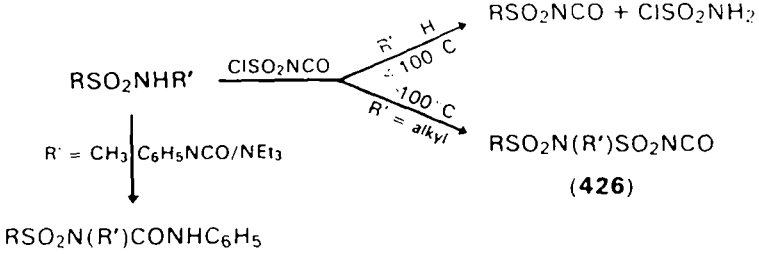
Stepwise addition of isocyanates to monoalkylated hydrazines leads initially to urea formation at the alkylated amino group and only a second mole of isocyanate attacks the NH_2 group[670,671].



Carboxamides are known to react readily with alkyl and aryl isocyanates, giving acyl ureas[672]. Similar reactions with thiocarboxamides and aryl isocyanates require the presence of Cu(I) oxide[673], since symmetrical diaryl ureas and other products are obtained otherwise[674].

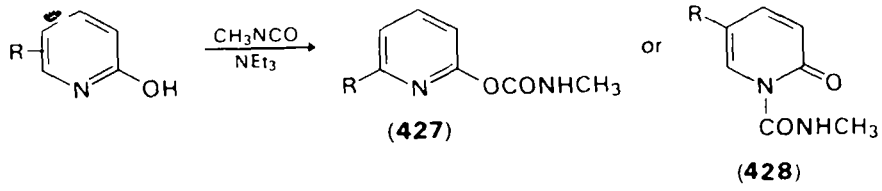


Sulphonamides react with CSI at the $ClSO_2$ group with retention of the isocyanate group. Aryl and alkyl sulphonyl isocyanates are obtained besides chlorosulphonamide on reacting aryl and alkyl sulphonamides with CSI below 100 °C[675]. *N*-Alkylated sulphonamides again react differently above 100 °C giving sulphonyl isocyanates **426**[676]. Sulphonylureas are formed, on the other hand, on refluxing sulphonamides with phenyl isocyanate in toluene in presence of triethylamine[677] or reacting alkali salts of sulphonamides with isocyanates[678].

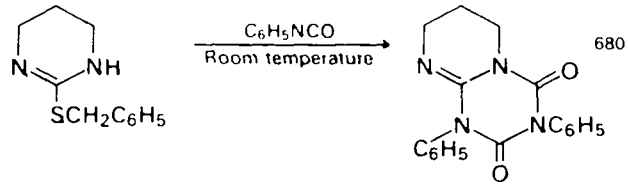


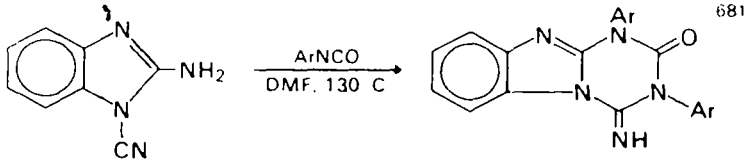
N,*N*-Dialkyl and diarylsulphamides react with CSI at room temperature in a similar fashion giving *N*-chlorosulphonyl-*N'*-(dialkyl- and diarylsulphamoyl) ureas in generally excellent yield[872].

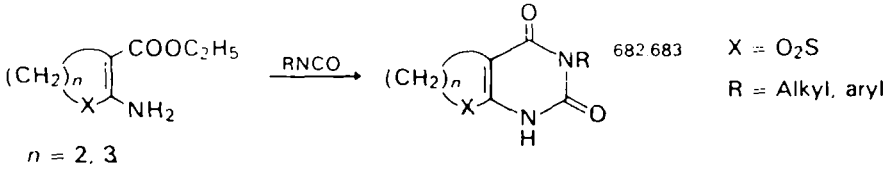
Substituted pyridine-2-ols were shown to react with methyl isocyanate (in dependence on the position and nature of the substituent) either in the amide or imide form, giving **427** or **428**[679]

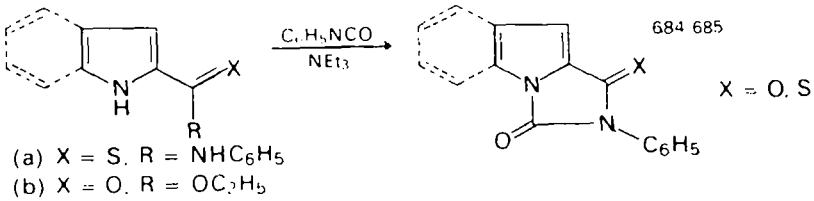


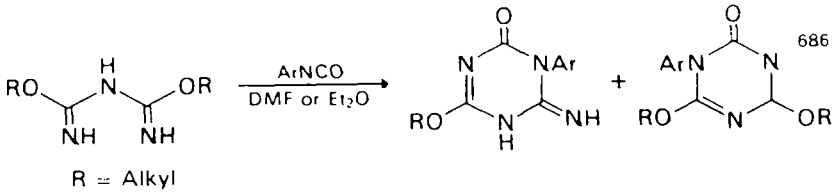
A number of isocyanate–amine (imine) interactions were shown to lead to a variety of heterocyclic compounds most often resulting from secondary ring closures of initially-formed acyclic adducts. Some examples are listed below.

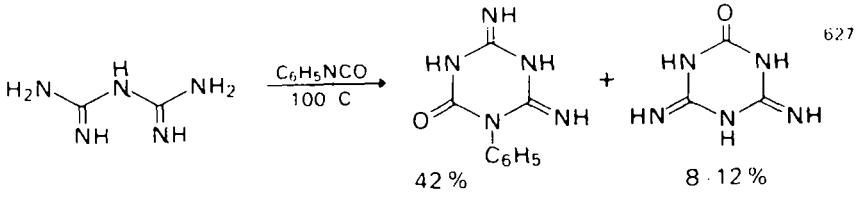


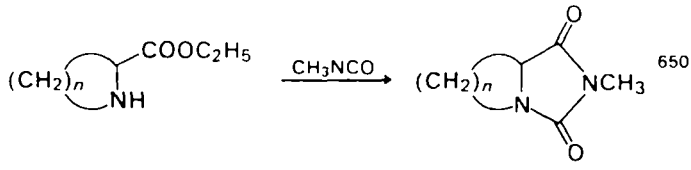


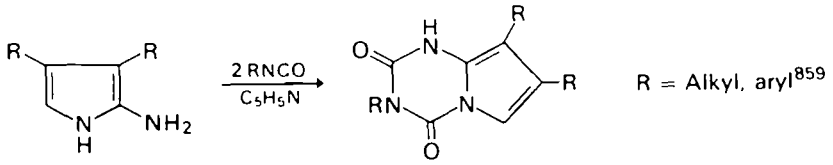


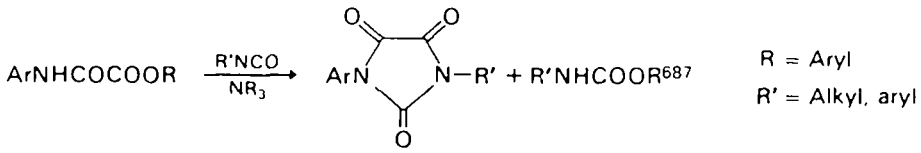


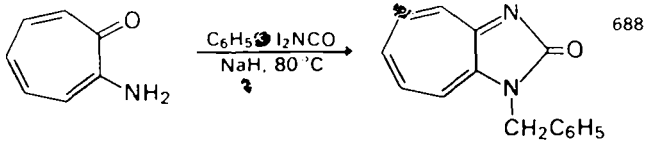


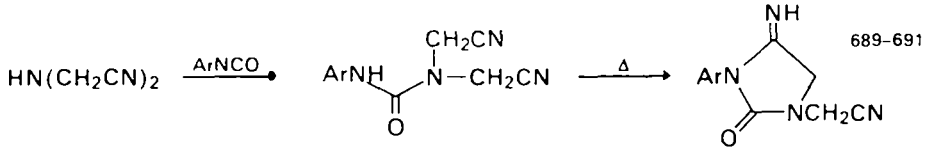


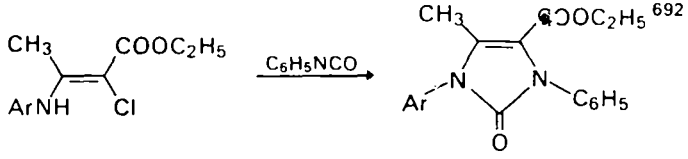

COOC2H5
(CH2)n
NH
CH3NCO
(CH2)n
NCH3
650
n = 3, 4

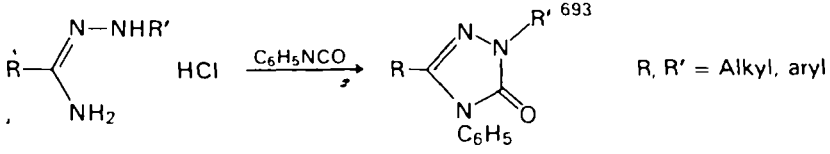

R
R
N
H
NH2
2 RNCO
C5H5N
H
N
R
O
RN
N
R
O
R = Alkyl, aryl859

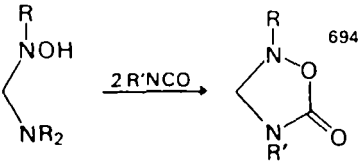

ArNHCOCOOR
R'NCO
NR3
O
O
ArN
N—R' + R'NHCOOR687
O
R = Aryl
R' = Alkyl, aryl

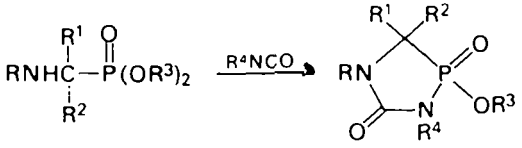

O
NH2
C6H5I2NCO
NaH, 80 °C
N
O
N
CH2C6H5
688

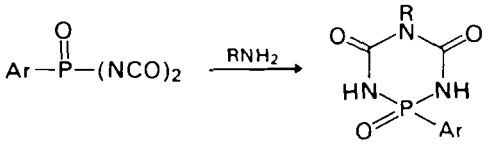

HN(CH2CN)2
ArNCO
CH2CN
ArNH
N—CH2CN
O
Δ
NH
ArN
NCH2CN
O
689-691


CH3
COOC2H5
ArNH
Cl
C6H5NCO
CH3
COOC2H5
692
Ar
N
N
C6H5
O

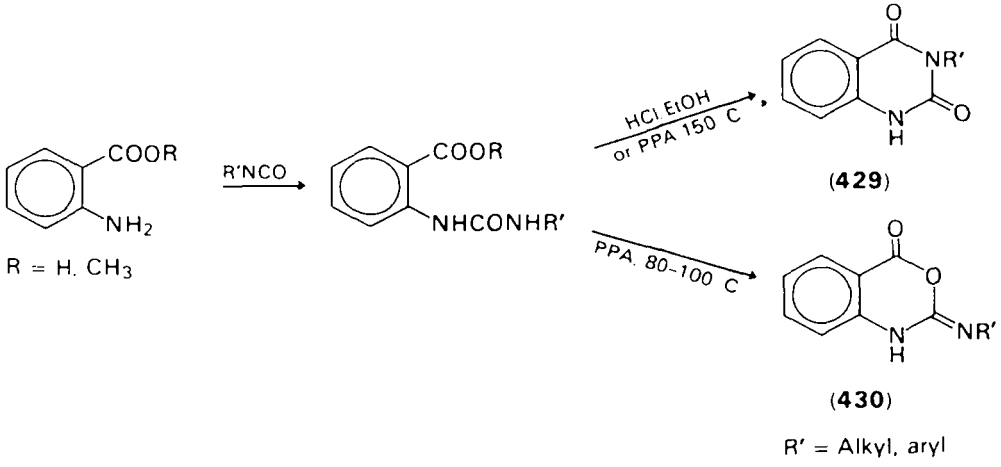

N—NHR'
R
NH2
HCl
C6H5NCO
R'
693
R
N
N
N
O
C6H5
R, R' = Alkyl, aryl



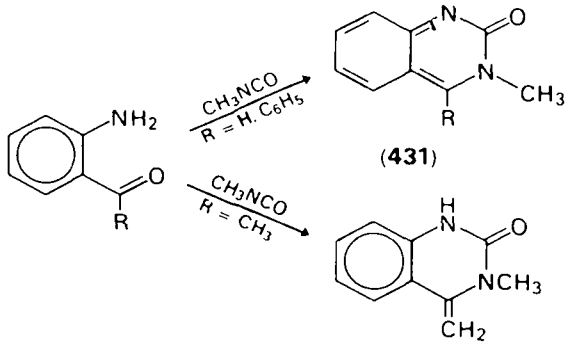




Anthranilic acid and alkyl anthranilates give carbanilides on reacting with alkyl and aryl isocyanates. Treatment of these ureas with acidic catalysts (concentrated HCl) leads to cyclization under participation of the adjacent COOR group, giving quinazolinediones, **429**[697–699]. Isomeric benzoxazine-4-ones (**430**) are obtained on conducting the cyclizations with polyphosphoric acid below 100 °C; higher temperatures and longer reaction times yield **429** here also[700]. Ethyl *N*-hydroxyanthranilate was also shown to yield tetrahydroquinazolines with isocyanates[864].



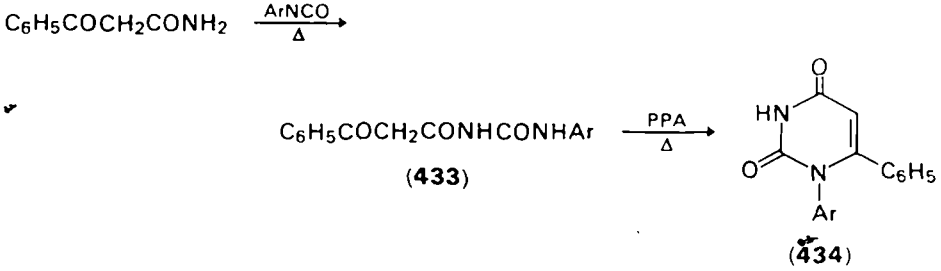
o-Aminobenzaldehyde and *o*-aminobenzophenone react also with isocyanates with formation of cyclic products, quinazolones (**431**), which are derivatives of 1,2-benzoquinones[701,702]. A methylenequinazolinone **432** is obtained, however, on treating *o*-aminoacetophenone with methyl isocyanate[703].



(**431**)

(**432**)

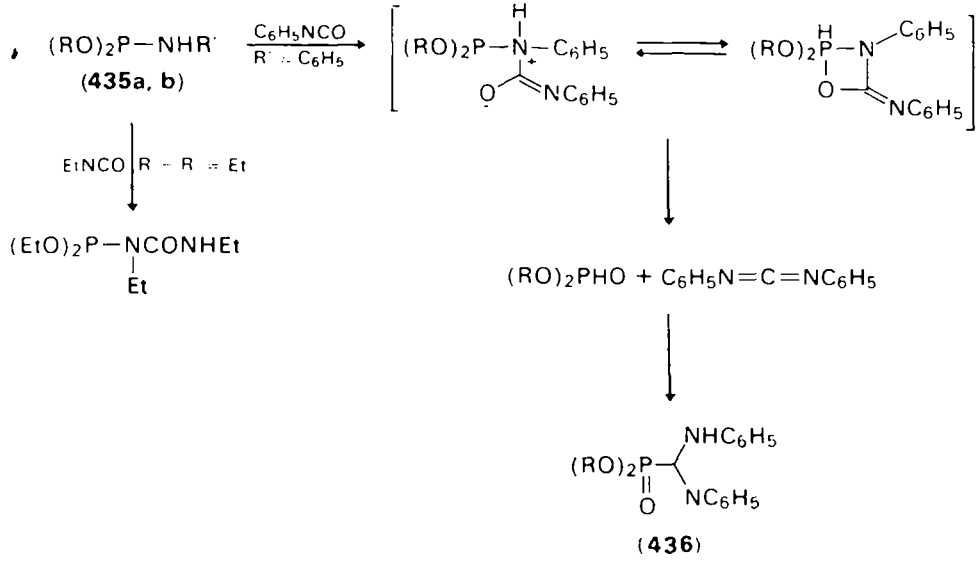
Benzoyl acetamide reacts with *in situ* generated aryl isocyanates (from the corresponding aroyl azides) on heating, giving *N*-aryl-*N*-benzoylacetylureas (**433**) which are readily converted by action of PPA into 1,6-diaryluracils **434**[704].



(**433**)

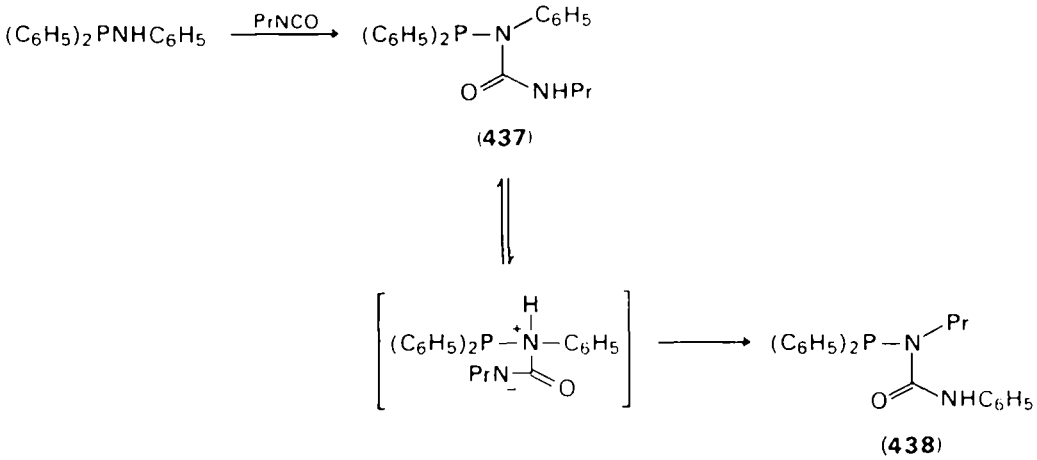
(**434**)

A P(III) → P(V) oxidation giving **436** is observed during the reaction of phenyl isocyanate with the *N*-phenylphosphinous amide **435a**, believed to involve the steps shown below[705].



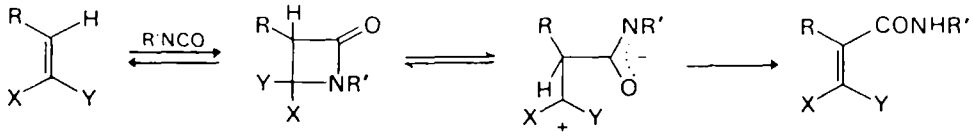
The reaction does not seem to be general, since the *N*-alkyl phosphinous amide **435b** (R ≠ R′ = Et) gives a NH insertion product instead[706].

Still another possibility for the reaction of R_2PNHR type compounds was observed with propyl isocyanate and diphenyl *N*-phenyl phosphinous amide which gave a mixture of **437** and **438**[782].

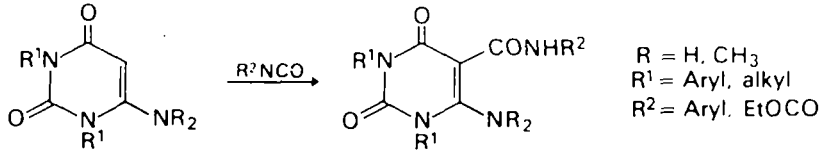


The behaviour of compounds containing SiNH bonds towards aryl isocyanates under various conditions has also been studied in detail. Generally complex product mixtures were obtained[707].

c. *Insertion into C—H bonds.* Olefins and aromatic as well as aliphatic compounds having a CH or CH_2 group were shown to react in a number of cases with isocyanates producing N-substituted carboxylic acid amides. Substitution reactions (acylations) on olefins, especially those bearing electron-donating groups, have been studied thoroughly in connection with [2 + 2] cycloaddition reactions and are treated in Section III.B.a.i. It was found that many insertions into olefinic C—H bonds are the result of irreversible isomerizations of initially formed 1,4-dipolar intermediates or cycloadducts[394,396].



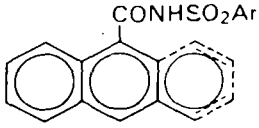
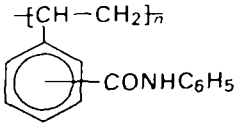
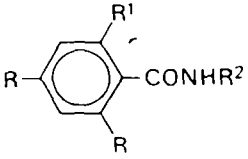
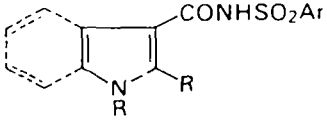
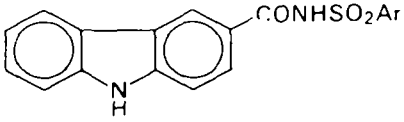
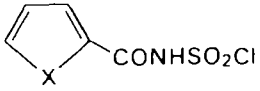
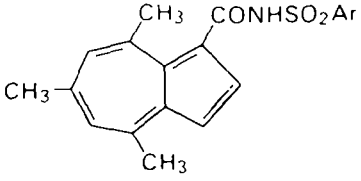
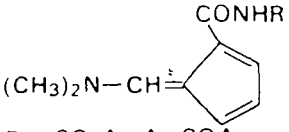
Some other insertions of isocyanates into olefinic C—H bonds are not likely to involve the intermediacy of [2 + 2] cycloadducts as shown in the equation above. Reactions of 4-amino uracils[456,708] with isocyanates might be more related to electrophilic substitutions on aromatic compounds.



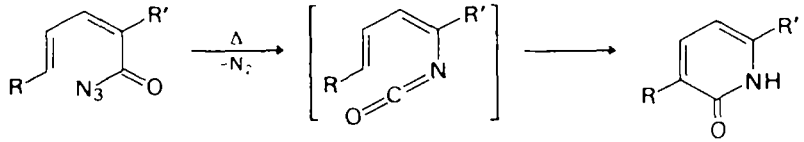
The factors governing the acylation of aromatic compounds by isocyanates are very much similar to those of other acylations: electron-donating groups on the aromatic nucleus on the one side, and electron-withdrawing groups adjacent to the NCO group of the isocyanate enhance the reactivity of both components. Lewis acids such as aluminium chloride have been applied successfully as catalysts[709,710]. *N*-Substituted carboxylic acid amides are obtained in each case. Application of the highly reactive sulphonyl isocyanates yields *N*-sulphonated carboxamides which can readily be converted into the free carboxylic acids or esters of these acids[662].

Several examples of acylations of aromatic and heteroaromatic compounds by isocyanates are listed below.

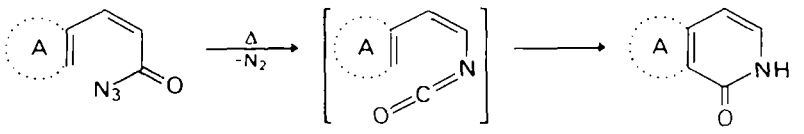
$$ArH + RNCO \xrightarrow{Catalyst} ArCONHAr$$

Product				Catalyst	Reference
p-$XC_6H_4CONHSO_2NHAr$					
X = H, Cl, CH_3, OCH_3				$AlCl_3$, HBF_4, HPF_6	709, 710
X = R_2N					662
				$AlCl_3$	709
				$AlCl_3$	711
	R	R^1	R^2		
	$N(CH_3)_2$	H	Ar, SO_2Ar	—	713, 713
	OCH_3	H	SO_2Cl	—	712
	OCH_3	OCH_3	SO_2Cl, SO_2Ar	—	712
				—	662
				—	662
 X = O, S				—	369
				—	712
 R = SO_2Ar, Ar, COAr				—	712

Other carboxamidations involving aromatic compounds have been shown to take place photochemically or during the thermal generation of certain isocyanates from carbonyl azides. Carboxamidations resulting in the formation of substituted or condensed pyridones have been observed during thermolysis of certain acryloyl azides substituted in β-position by vinylidene radicals, aryl or hetaryl rings[869,714].

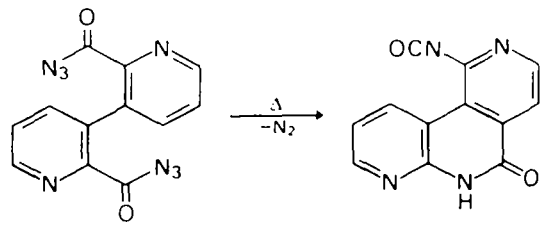


R = Alkyl, aryl, hetaryl
R' = H, aryl



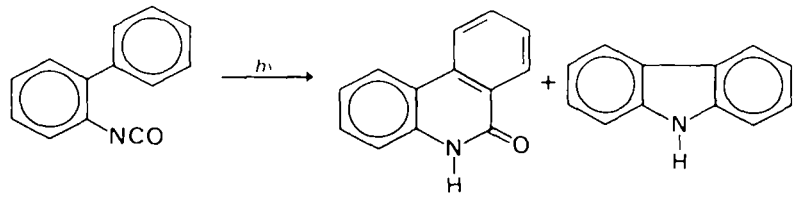
A = Aromatic or heterocyclic ring

Heating of the bis-acyl azide of 3,3'-bipyridine to 60-65 °C yields quantitatively 1-isocyanatopyrido[2,3-*h*]-2,6-naphthyridine-5-one (**439**)[714].

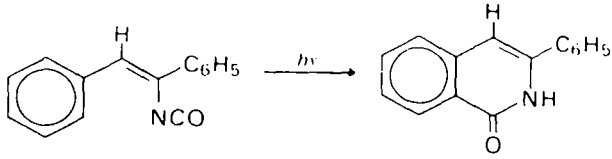


(**439**)

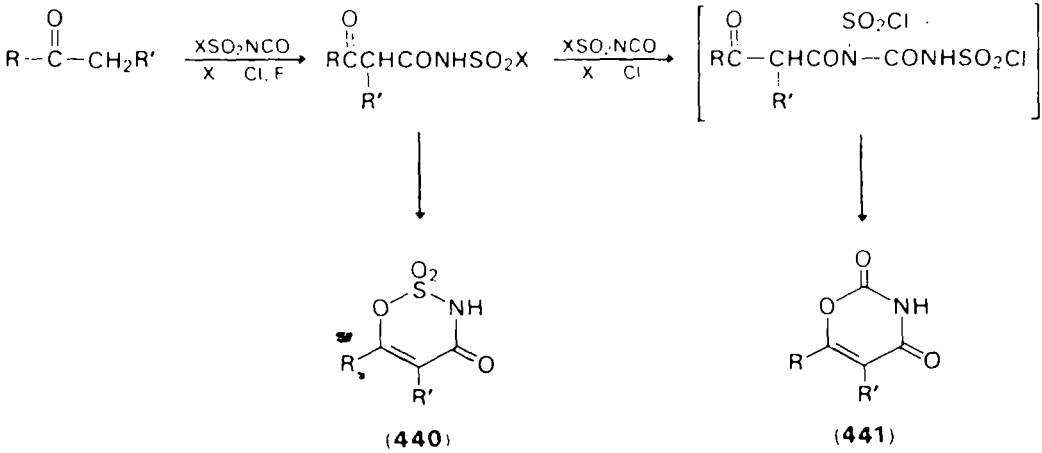
Ring closure takes place also during photolysis of 2-biphenyl isocyanate leading to a mixture of phenanthridone and carbazole[715].



A related ring closure with formation of 3-phenyl isocarbostyril is observed during irradiation of β-styryl isocyanate[716].

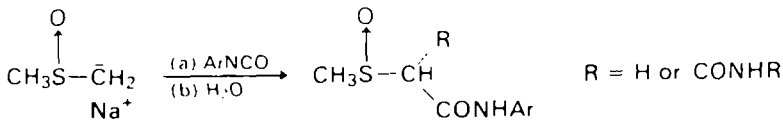


A large number of CH insertion reactions have been carried out on compounds having a RCH_2CO- group in which R is preferentially, but not necessarily, an electron-withdrawing substituent. Fluoro and aryloxy sulphonyl isocyanate react with alkylated and arylated ketones[488]. Other ketones react with chloro and fluoro sulphonyl isocyanate at room temperature (in dependence on the solvent used) to give, after work-up with aqueous bisulphite, 1,2,3-oxathiazines (**440**) or 1,3-oxazines (**441**) as a result of secondary reactions of initially formed adducts[717].



(**440**) (**441**)

The carbanions of dimethyl sulphoxide and dimethyl sulphone add 1 or 2 moles of aryl isocyanates, giving β-mono or diamido sulphoxides and sulphones[628].



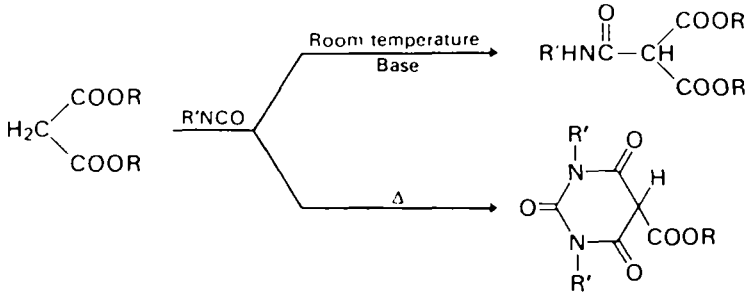
α-Aryl sulphonylacetophenone and *p*-tolylsulphonylacetone were shown to react similarly with aryl isocyanates[718].

$$ArSO_2CH_2COR \xrightarrow{ArNCO} ArSO_2\underset{\displaystyle COR}{\underset{|}{C}}HCONHAr$$

R = CH_3, C_6H_5

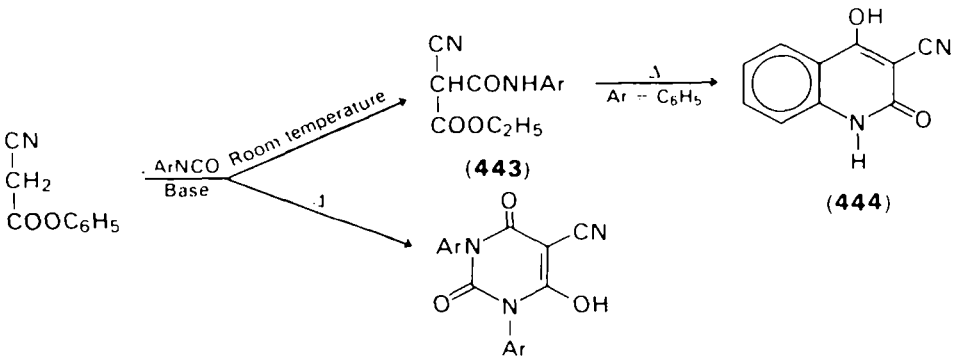
Inorganic isocyanates, such as $P(NCO)_3$ or $OP(NCO)_3$, react with acetophenone also by CH insertion in refluxing toluene[719].

Dialkyl malonates react with phenyl and methyl isocyanate in presence of triethylamine or alkali to give dialkyl carbamoyl malonates[729,721]. Heating the reaction mixtures leads to consumption of 2 moles of isocyanate and formation of 1,3-disubstituted barbituric acid-5-carboxylates (**442**)[721].



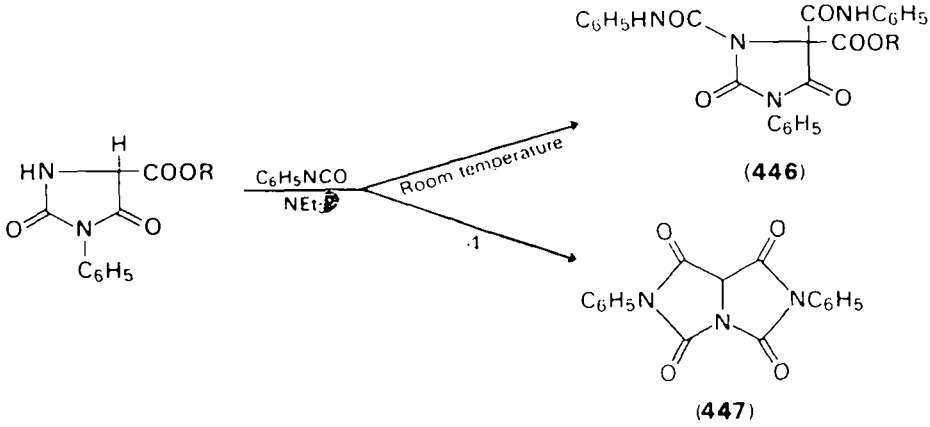
(**442**)

Reaction conditions influence the nature of products in reactions of ethyl cyanoacetate with phenyl isocyanate. Thus heating of phenyl- or *p*-chlorophenyl isocyanate with ethyl cyanoacetate in pyridine yields 5-cyano barbiturates (**445**)[722]. On carrying out the reactions at room

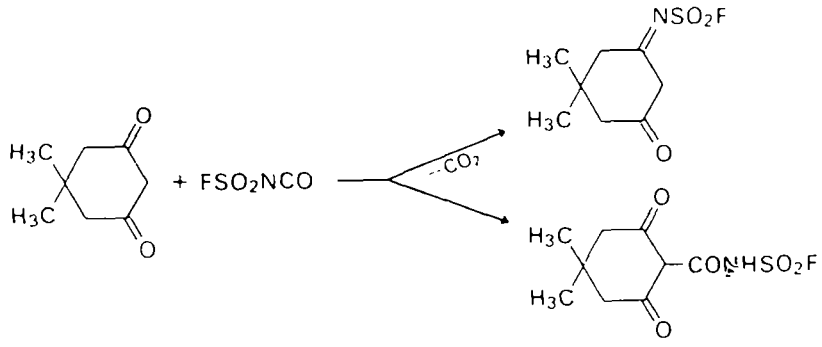


temperature, ethyl cyanmalonanilic acids (**443**) are obtained, which on heating (Ar = C_6H_5) cyclize to 3-cyano-4-hydroxycarbostyril (**444**)[723].

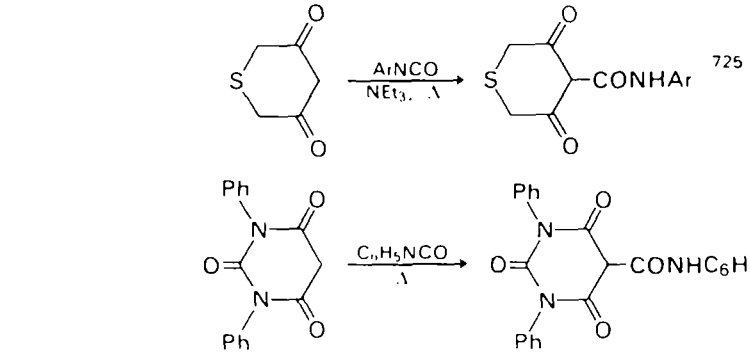
Alkyl hydantoin carboxylates, prepared from alkyl aminomalonate hydrochloride and aryl isocyanates, react with phenyl isocyanate at room temperature in presence of triethylamine by CH and NH insertion and formation of **446**[724]. Heating a mixture of the same reactants leads to an imidazolo[1,5-c]imidazole (**447**)[724].

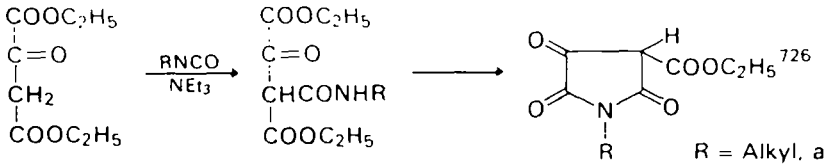


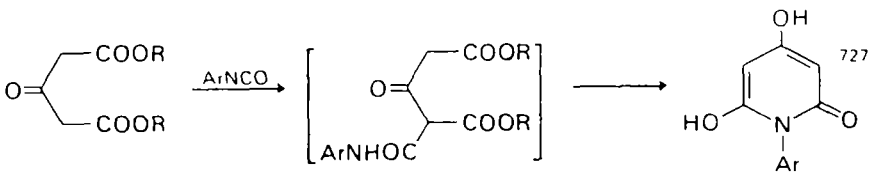
A mixture of products resulting from CH and C=O attack is obtained in the reaction of dimedone with fluorosulphonyl isocyanate[488].

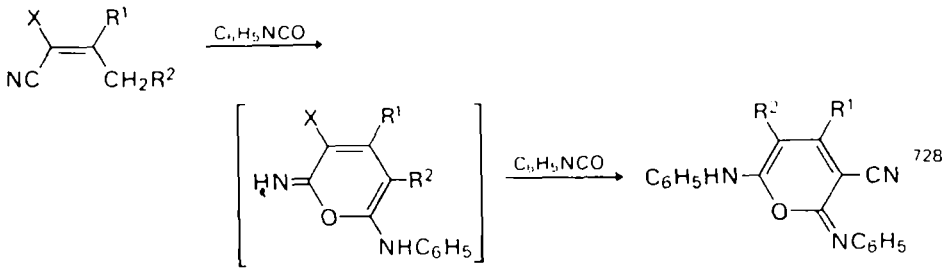


Other reactions of compounds of the general formula RCH_2COR with isocyanates are shown below:







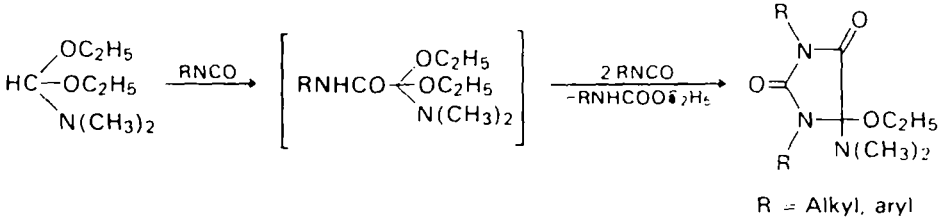


X = CN, $COOC_2H_5$

R^1, R^2 = $(CH_2)_4$

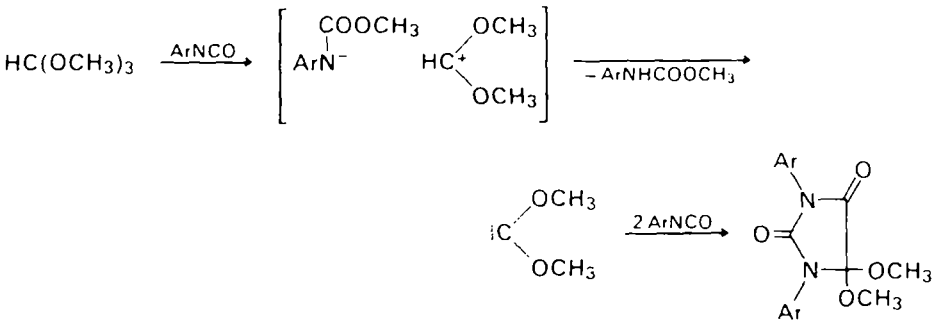
R^1 = C_6H_5, R^2 = CH_3

The formation of parabanic acid *O.N*-acetals from dimethyl formamide dialkylacetals and alkyl as well as aryl isocyanates is also explained with initial insertion of isocyanates into the CH bond of the orthoformic acid derivative[729].

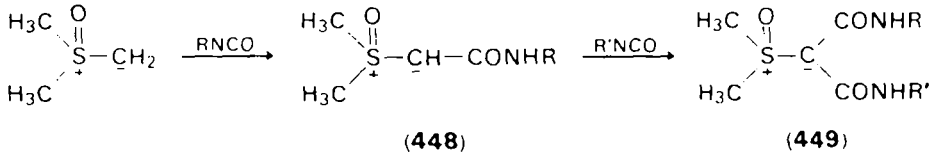


R = Alkyl, aryl

The validity of the proposed mechanism is questionable, however, since orthoformates and trisaminomethane derivatives were shown to react with isocyanates under insertion into a C—OR or C—NR_2 bond[616,512,513,730]. An example is shown below:

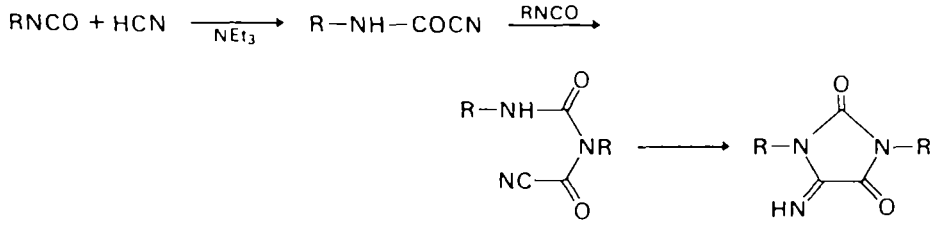


Dimethyloxosulphonium methylide was shown to react readily with 1 or 2 moles of aliphatic or aromatic isocyanate to dimethyl-oxo-sulphonium-[(bis)-carbamoyl-methylides] **448** and **449**[731]. Other sulphur and phosphorus ylides react similarly[732,733].

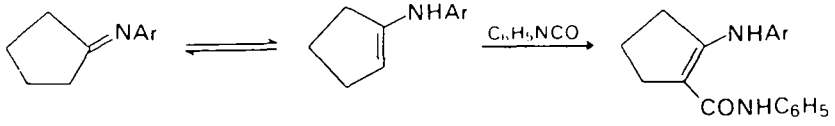


(448) **(449)**

Hydrogen cyanide adds to aliphatic and even better to aromatic isocyanates in presence of tertiary amines and highly polar solvents (DMSO, dimethylacetamide) at low temperatures with final formation of 1,3-imidazolidines[734].

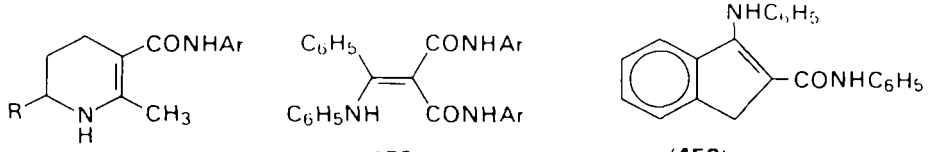


Not all reactions taking place between N-substituted imines and isocyanates lead to formation of cyclic adducts. Imines having a $R-CH_2$ or CH_3 group attached to the carbon atom of the C=N group are known often to behave like tautomeric enamines and react with isocyanates under CH insertion[735]. Thus, treating cyclopentanone anils with phenyl isocyanate gives 1-anilinocyclopentene-2-carboxanilides (**450**)[558].



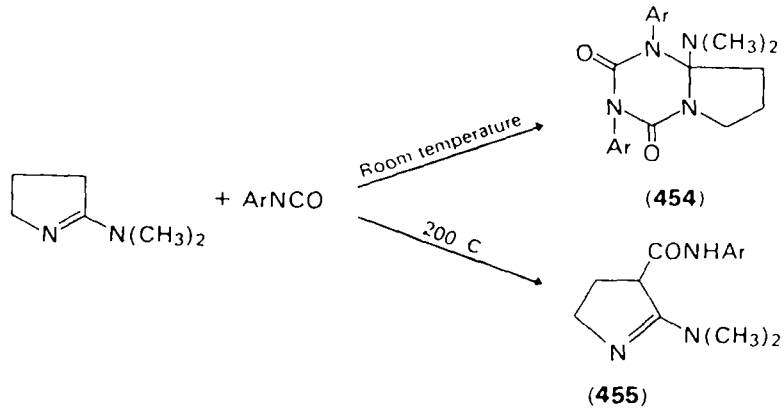
(**450**)

2-Methyl- and 2,6-dimethyl-Δ^1-piperidine also reacts with 1 mole isocyanate with C-substitution giving **451** (R = H, CH_3)[737]. Acetophenone anil reacts with aryl isocyanates twice at the methyl group with substitution to aroyl malonic acid dianilides (**452**)[738], and α-indanone anil reacts with phenyl isocyanate to give an acyclic 1:1 adduct **453**.[739]

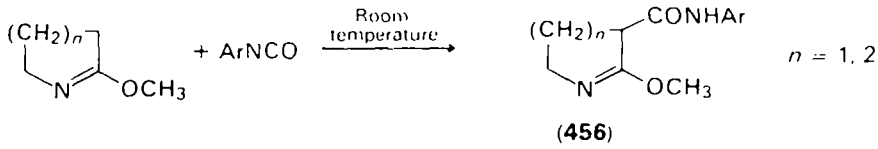


(**451**) (**452**) (**453**)

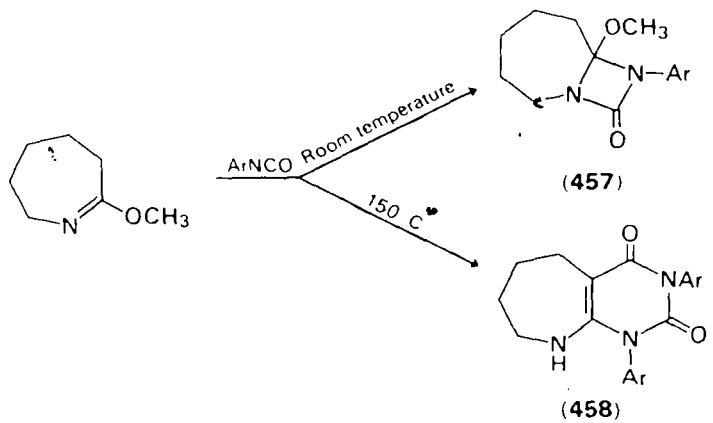
N-Aryliminoacetoacetic acid anilides react similarly[740]. 2-Dimethylamino-Δ^1-pyrroline, which gives cyclic 2:1 adducts **454** on reacting with aryl isocyanates at room temperature[510], yields 3-arylcarbamoyl-2-dimethylaminopyrrolines (**455**) on heating, without solvent, to 200–210 °C[515].



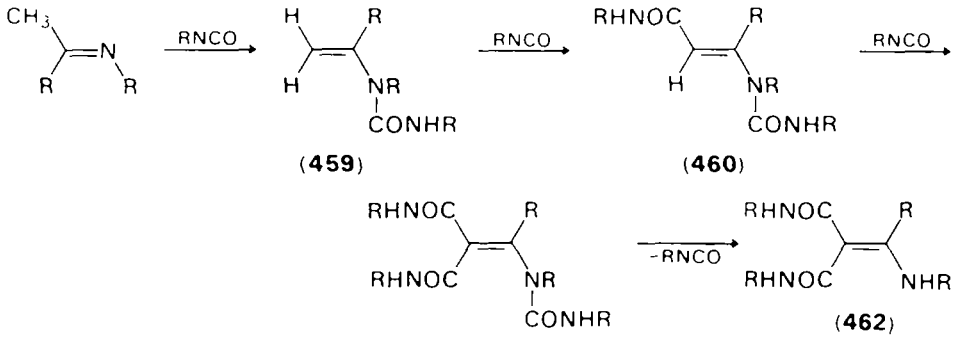
Comparable reactions of 2-methoxy-Δ^1-pyrroline and 3,4,5,6-tetrahydropyridine with aryl isocyanates give, even at room temperature, the corresponding 3-arylcarbamoyl compounds **456** and no cycloadducts[478].



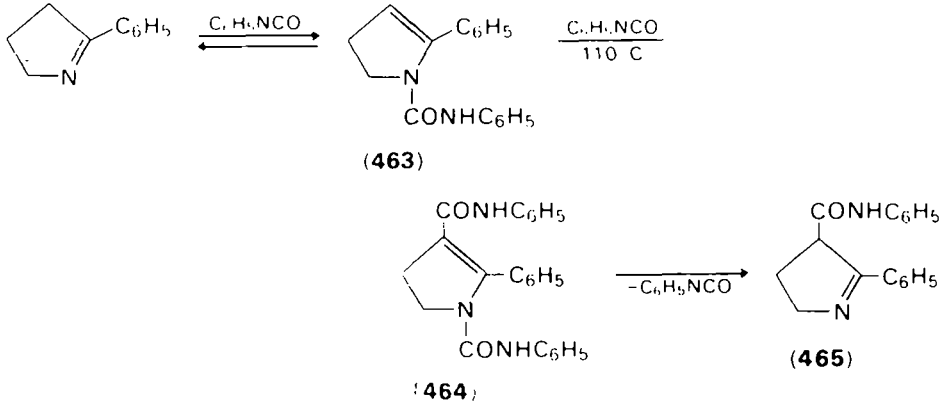
This is surprising, since it was found earlier that ε-caprolactim ether gives cyclic 1:1 adducts **457** with aryl isocyanates at room temperature[476]. At elevated temperatures pyrimido azepines (**458**) are obtained instead[477].



Other reactions of structurally similar imines often proceed via initial attack of the isocyanate on the nitrogen atom followed by proton shift, and en-ureas **459** are formed in the first reaction step. Compounds of this type react with more isocyanate under substitution on the newly formed C=C double bond, giving **460** or **461**. The latter two adducts are able to loose the originally-introduced isocyanate molecule due to the reduced basicity of the

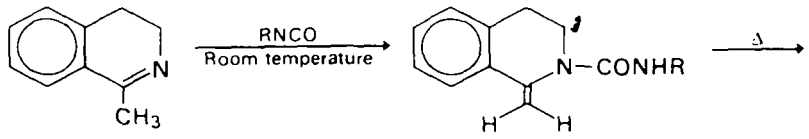


nitrogen atom, thus erasing the evidence for an initial N attack of the isocyanate. Examples of all these proposed reaction intermediates have been synthesized. 2-Phenyl-Δ^1-pyrroline and phenyl isocyanate give three different products, **463**, **464** and **465**, depending on the reaction conditions[74].

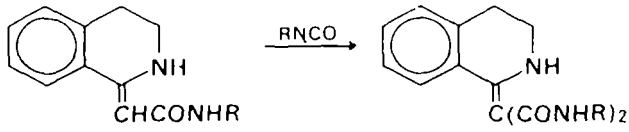


Only en-ureas are obtained on reacting *N*-alkyl-*N*-cyclohexylidene-amines with alkyl or aryl isocyanates in the molar ratio of 1:1[524,743].

1-Methyl-3,4-dihydro-isoquinoline and aryl isocyanates give labile en-ureas (**466**) at room temperature. 1:1- and 1:2-adducts with newly formed C—C bonds are obtained at elevated temperature[744,745].

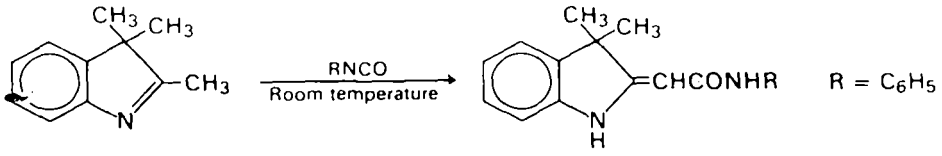


(**466**)



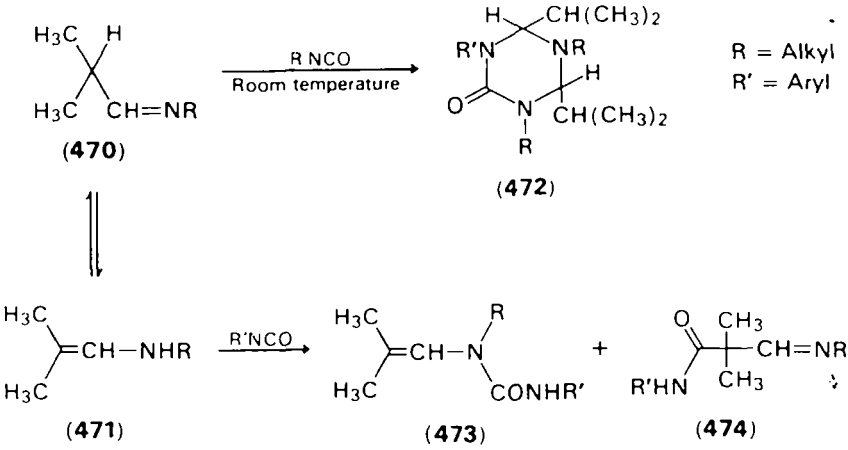
(**467**) (**468**)

2,3,3-Trimethyl indolenine was shown to react with phenyl isocyanate to give 3,3-dimethyl-phenylcarbamoyl methylene-2,3-dihydro-indole **469** in high yield[736].

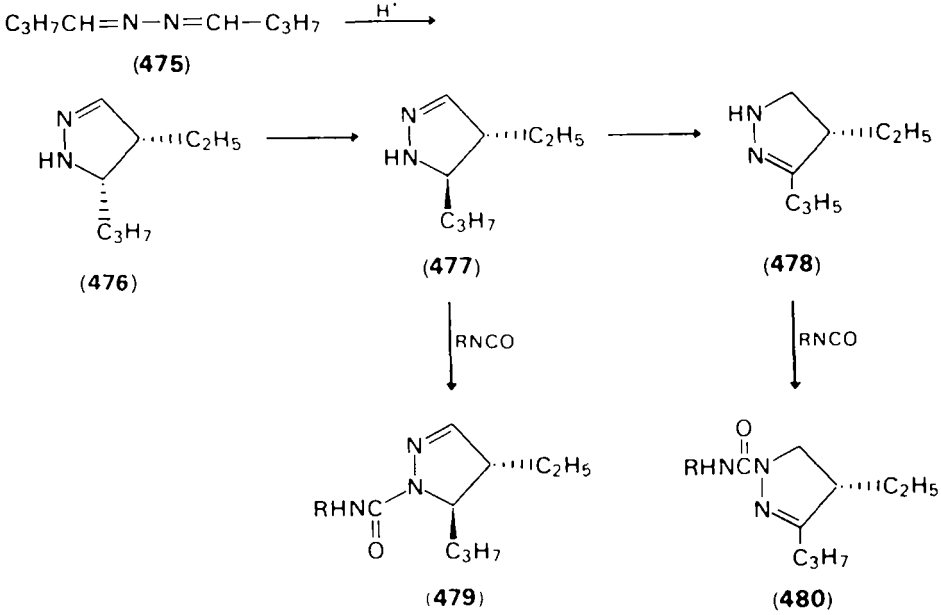


(**469**)

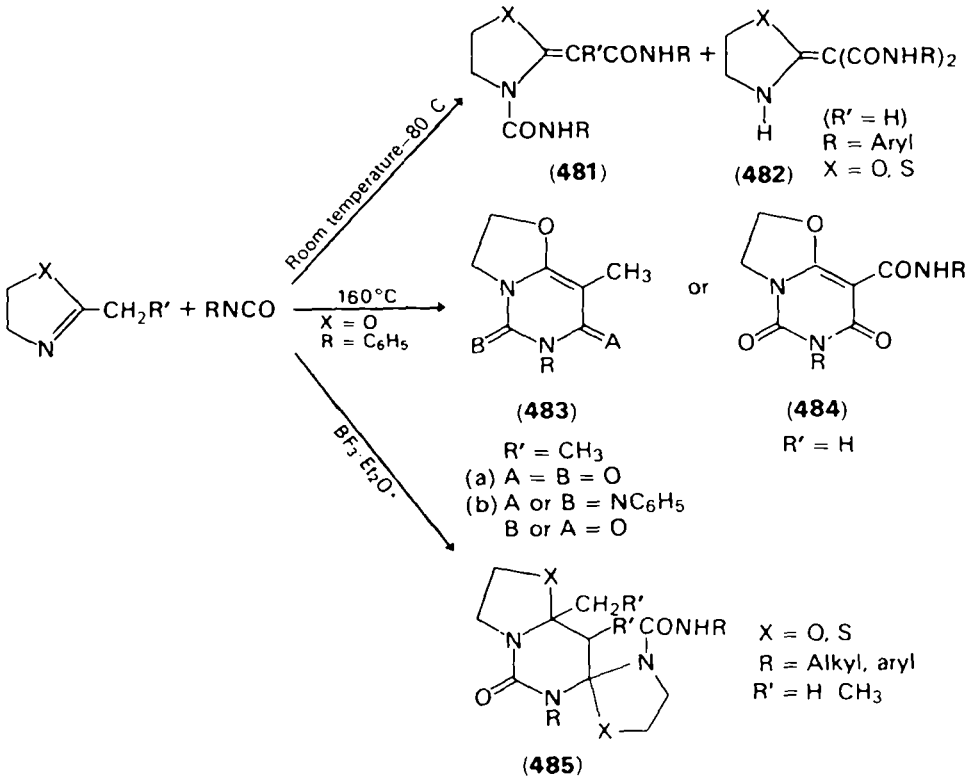
The behaviour of *N*-(2-methylpropylidene)alkyl amines (**470**) towards aryl isocyanates is more complex[524]. Cyclic 1:2 adducts **472** with *s*-triazine structure are obtained at room temperature. Higher reaction temperatures lead to acyclic 1:1 adducts, en-ureas (**473**), and carbanilides (**474**), which are probably formed from the tautomeric enamine **471**.



The reaction of butyraldazine **475** with phenyl or benzyl isocyanate in presence of acid (picric acid) is entirely different in its course. The isocyanate attack is preceded by an acid-promoted proton shift in **475** followed by cyclization to the *cis*- and *trans*-pyrazolines **476** and **477** as well as the isomeric **478**. Insertion of isocyanate into the N–H bond of **477** and **478** gives rise to the 1:1 adducts **479** and **480**[742].

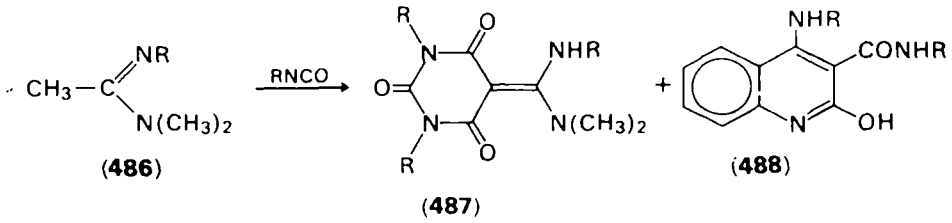


Many different products are obtained on reacting 2-alkyl-Δ^2-oxazolines and -thiazolines with alkyl, aryl and benzoyl isocyanates. Acyclic 2:1 adducts **481** and **482** in which the isocyanate is linked to a carbon or nitrogen (ketene-*O*(*S*),*N*-acetals, en-ureas) are formed at room, or only slightly elevated, temperature[746,747,555]. Oxazolopyrimidines **483** and **484** are, however, obtained on heating 2-methyl- or 2-ethyl-Δ^2-oxazoline with phenyl isocyanate to 160 °C[877]. Still different adducts with a molar ratio of 2:2 are obtained in the presence of catalytic amounts of boron trifluoride etherate at room temperature. Similar adducts are formed also with methyl isocyanate in absence of the catalyst[748].



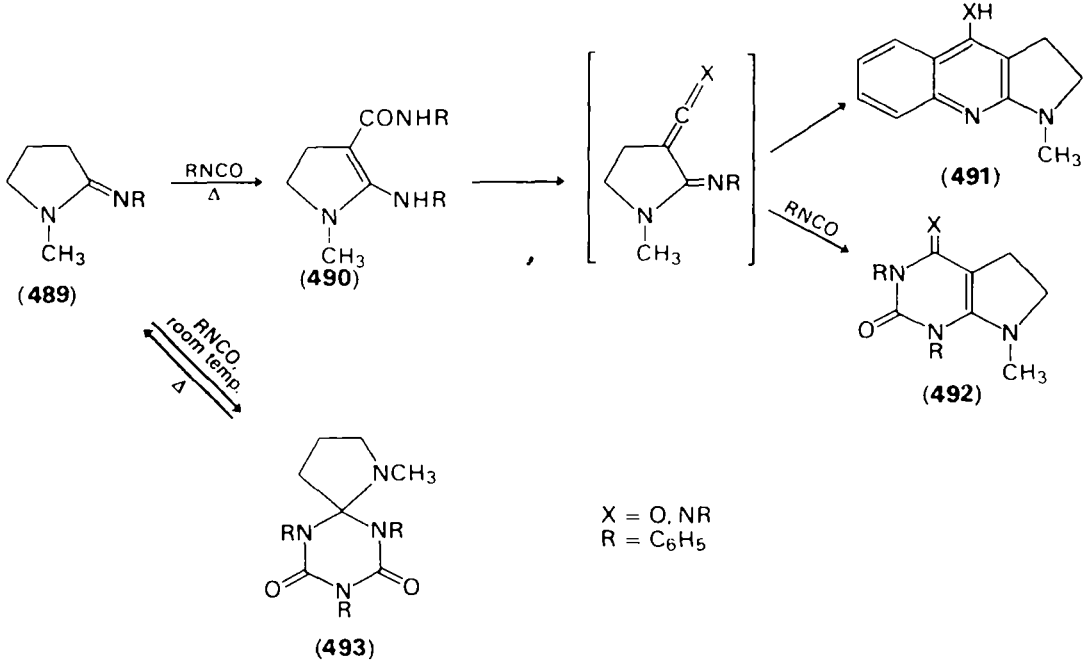
Even more complicated are the reactions of *N*,*N*-dimethyl-*N'*-phenyl-acetamide **486**[708] and 1-methyl-2-phenyliminopyrrolidine **489**[514,749] with aryl isocyanates. A 5-diamino methylene-1,3-diphenyl barbituric acid (**487**) is obtained on reacting *N*,*N*-dimethyl-*N'*-phenylacetamidine with phenyl isocyanate at elevated temperature[708]. A by-product of

unknown structure formed in these reactions could very well be the quinoline carboxanilide, **488**.



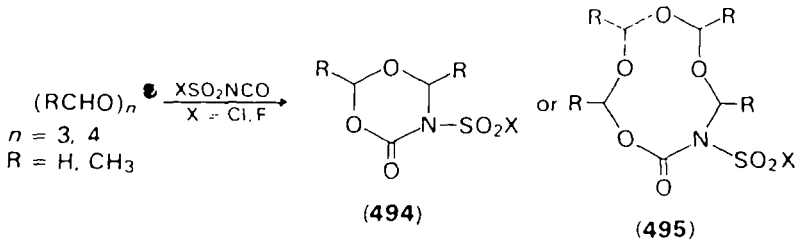
(**486**) (**487**) (**488**)

Heating of *N*-methylpyrrolidinone with excess phenyl isocyanate to 140 °C initially produces **489**. This amidine and phenyl isocyanate react further to give 1-methyl-2-phenylamino-2-pyrrolino-3-carboxanilide (**490**), the key intermediate, from which two differently substituted pyrrolo-[2,3-*b*]pyrimidines (**492**) and pyrrolo[2,3-*b*]quinolines (**491**) are obtained in inter- and intramolecular [2 + 4] cycloaddition reactions.

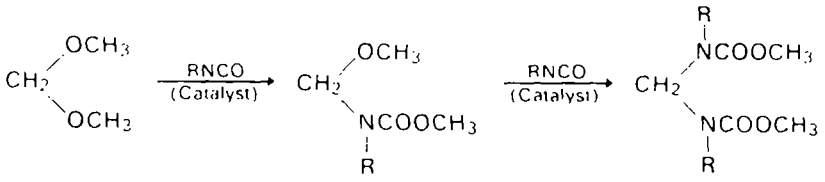


Mixing the amidine **489** at room temperature with phenyl isocyanate gives a cyclic 2:1 adduct **493** in almost quantitative yield[514].

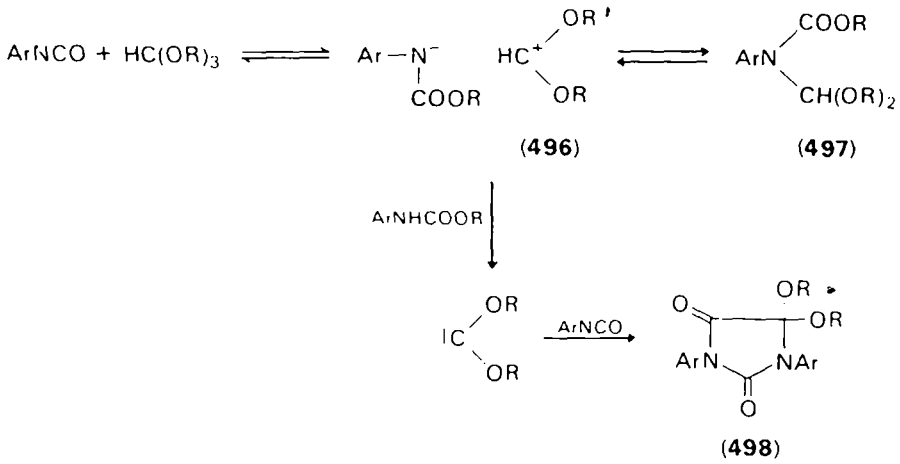
d. *Insertion into COC and C–halogen bonds.* Isocyanates are able to insert into COC bonds resulting in the formation of carbamates. Several of these reactions, which can best be described by the general equation $R_3COR + R'NCO \rightarrow R_3CN(R')COOR$, have been treated in Section III.B.2.b.ii. Oligomeric aliphatic aldehydes (formaldehyde, acetaldehyde) which have the general formula $[RCH{-}O]_n$, react readily with fluoro and chlorosulphonyl isocyanate at low temperature to adducts **494** or **495**[488].



Similarly, methylal reacts with chlorosulphonyl isocyanate or alkyl and aryl isocyanates in presence of Lewis acids (BF_3, $ZnCl_2$, $AlCl_3$) with formation of carbamates[308,750]. Double insertion into both COR bonds is observed on

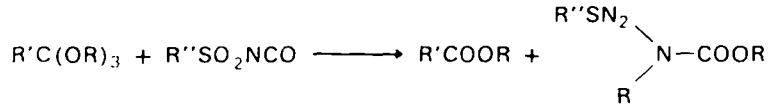


increasing the quantity of acid catalyst[730]. Thioketals were found to react similarly. Orthoformates also form 1:1 adducts (**497**) with aryl and alkyl isocyanates when heated to 30–70 °C in presence of Lewis acids[730]. Refluxing aryl isocyanates with excess triethyl orthoformate, however, leads to 1,3-diaryl-5,5-diethoxy(3*H*,5*H*)imidazolediones **498**[751]. The latter reactions are related to the formation of *O*,*N*-acetals of 1,3-disubstituted parabanic acids from isocyanates and dimethyl formamide diethyl acetal[752]. It is likely that both types of products are formed via a common intermediate **496** as shown below[616].

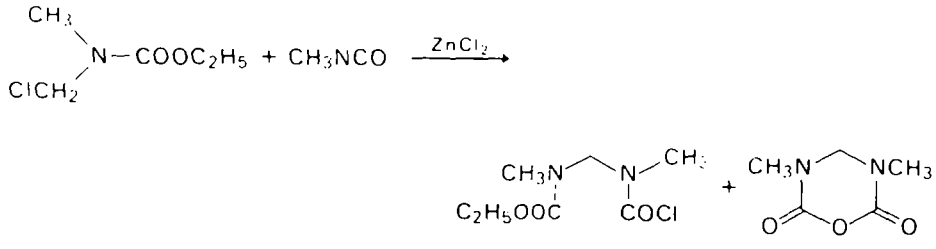


(496) (497) (498)

Sulphonyl isocyanates and ortho esters of formic, acetic and benzoic acid react in a third mode and afford mixtures of *N*-(chloro or aryl)-sulphonyl-*N*-alkyl urethanes and esters of carboxylic acids[730].

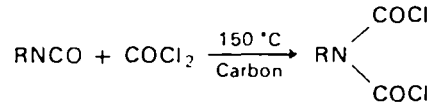


The insertion of isocyanates into C–halogen bonds affording carbamoyl halides has been observed occasionally and all known examples indicate that catalysts are required for these additions. Thus ethyl *N*-methyl-*N*-chloromethyl carbamate reacts with methyl isocyanate in the presence of small amounts of zinc chloride to yield a mixture of **499** and a cyclic anhydride of methylene-bis(*N*-methylcarbamic acid), **500**. Other carbamoyl chlorides are prepared similarly[753].

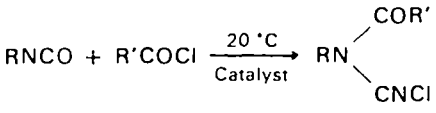


(499) (500)

Lewis acids or elemental carbon are also catalysts in reactions of carboxylic acid halides with isocyanates[754,755]. Examples are shown below.



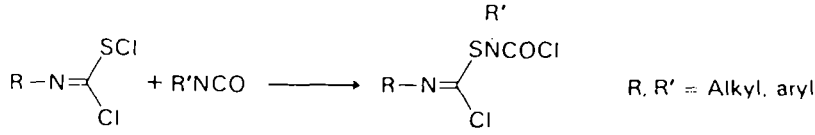
R = CH_3, C_2H_5, C_3H_7, C_3H_5



Catalysts: $SnCl_4$, $SnCl_2$, $SbCl_5$, $TiCl_4$, $ZnCl_2$, etc.

R = Alkyl, alkenyl
R′ = Alkyl, alkenyl, aralkyl

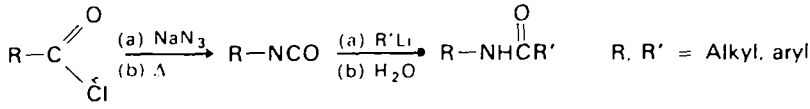
N-Aryl and alkyl-*S*-chloroisothiocarbamoyl chlorides, however, react with isocyanates by insertion into the SCl and not the CCl bond as shown below[756].



R, R′ = Alkyl, aryl

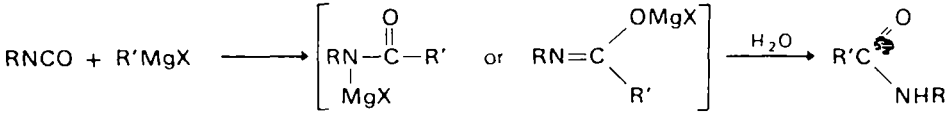
e. *Insertions involving metal organic compounds.*

(i) Group I, IIa, IIb and IIIa elements. Organolithium compounds have recently been shown to react readily with thermally generated (from the corresponding acylazides) isocyanates to give, after work-up with water, excellent yields of *N*-substituted amides[757].

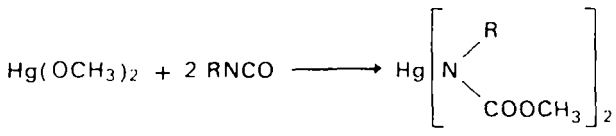


R, R′ = Alkyl, aryl

Alkyl and aryl magnesium halides react similarly with phenyl and furyl isocyanate, giving the corresponding substituted carboxylic acid amides[758-761,875]. Two types of intermediates have been considered as being formed in these reactions and none could be ruled out[762].

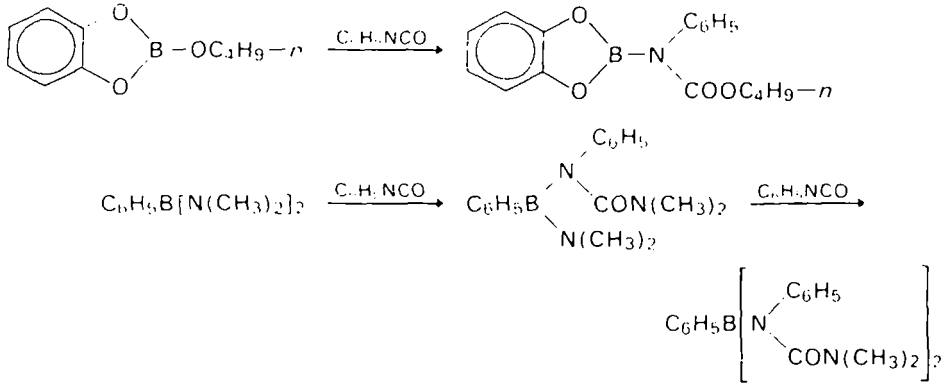


Organozinc compounds behave like Grignard compounds and undergo similar reactions[763]. Insertion of isocyanates into $HgOCH_3$ bonds takes place readily, giving carbamates such as **501**[764].

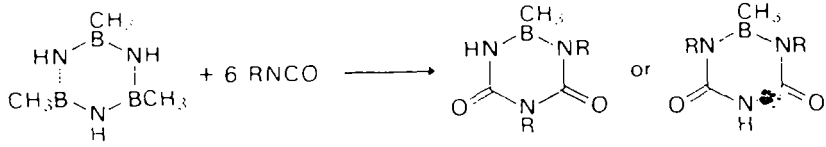


(501)

Triphenylborane and phenyl isocyanate give benzanilide on heating in xylene followed by work-up with water[765–766]. The insertion of isocyanates into BOR bonds is not common and has only been observed in the reaction of phenyl isocyanate with 2-*n*-butoxy-1,3,2-benzodioxaborole[767]. Tri-*n*-butoxy borane failed to react with the same isocyanate on refluxing. Insertions into $B—NR_2$ bonds, however, take place readily and have been observed with mono-, di- and triaminoboranes[767–770]. Bis(dimethylamino)phenylborane reacts smoothly with 1 mole phenyl isocyanate while the second exchange can be effected only under forcing conditions[768].

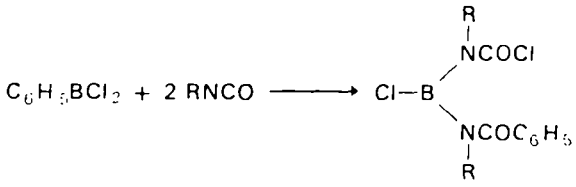


Trimethyl borazine reacts with isocyanate not on the available NH groups but rather through cleavage of the B-N bonds of the ring, yielding 2:1 cycloadducts **502** or **503** derived from isocyanate and the hypothetical $CH_3B{=}NH$[768]. In contrast, tris-*B*-(diethylamino)borazine reacts with isocyanate with insertion into the exocyclic $B—NEt_2$ bonds[768].

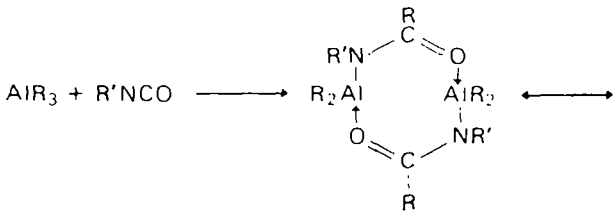


(502) (503)

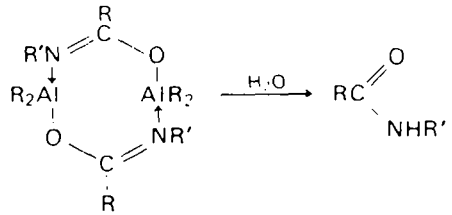
Boron halides or arylchloroboranes react also with isocyanates[766]. All three BCl bonds are available for insertion in BCl_3; no reaction, however, was observed with BF_3. Phenyl dichloroborane reacts with 2 moles of isocyanate with insertion into a BCl and B—C bond[766].



Organoaluminium compounds of the general type AlR_3 with R = alkyl behave like Grignard compounds in reactions with alkyl and aryl isocyanates, yielding carboxylic acid amides upon hydrolysis of the reaction mixtures[771-773]. The initial adducts formed in these reactions were shown to be dimeric and are best represented by the cyclic structures **504a** and **504b**[774].

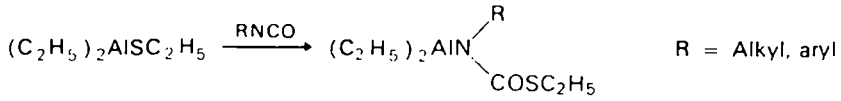


(**504a**)



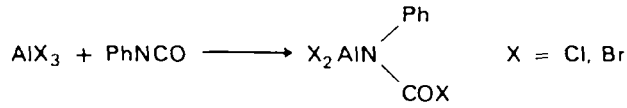
(**504b**)

Alkyl aluminium chlorides could be applied in these reactions as well[771,774]. Diethylaluminium ethyl thiolate or dimethylamide react with equimolar amounts of alkyl and aryl isocyanate with preferred Al—SR and Al—NR_2 bond cleavage yielding 1:1 adducts like **505**[775].



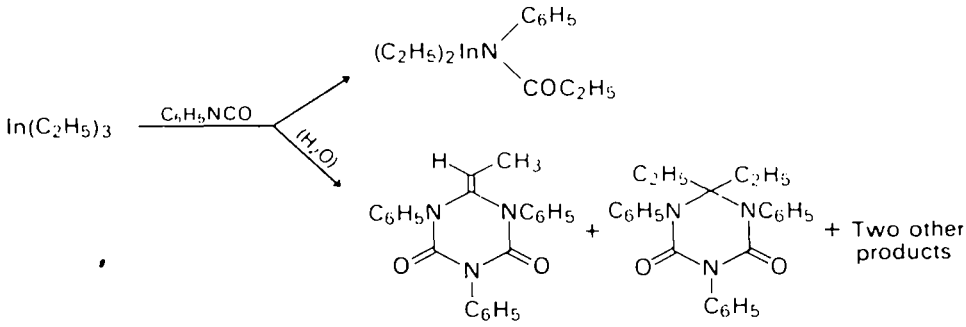
(505)

Reactions between aluminium halides and isocyanates have also been studied. Various structural formulas have been suggested for 1:1 adducts of phenyl isocyanate and $AlCl_3$[325,362,363], but from evidence provided by later investigations on $AlBr_3$·RNCO adducts it is believed that all these adducts have to be formulated as Al–X insertion products **506**[774].



(506)

Triethylindium was shown to give a 1:1 adduct with equimolar amounts of phenyl isocyanate; with excess isocyanate, however, 2,4-dioxo-6-ethylidene- and 2,4-dioxo-6,6-diethyl-1,3,5-triphenyl hexahydro-*s*-triazine **507** and **508** are obtained besides *N*,*N*′,*N*″-triphenylbiuret and *N*-phenylpropionamide[776,777]. The product ratio can be influenced by varying the isocyanate–$InEt_3$ ratio. The product formation in this unusual reaction is partially explained by the occurrence of Et_2InOH as intermediate.



(507) **(508)**

(ii) Group IVa and IVb elements. Organotin compounds are by far the most intensively studied metal organic compounds in isocyanate

chemistry. Both Sn(II) and Sn(IV) compounds have been found to react readily with isocyanates.

Tin(II) dimethoxide was shown to exchange both methoxy groups on reacting with phenyl isocyanate, giving a bis(methyl *N*-phenylcarbamate)-tin(II) **509**[778].

$$Sn(OCH_3)_2 + 2\,C_6H_5NCO \longrightarrow Sn(NCOOCH_3)_2 \quad (C_6H_5)$$

(509)

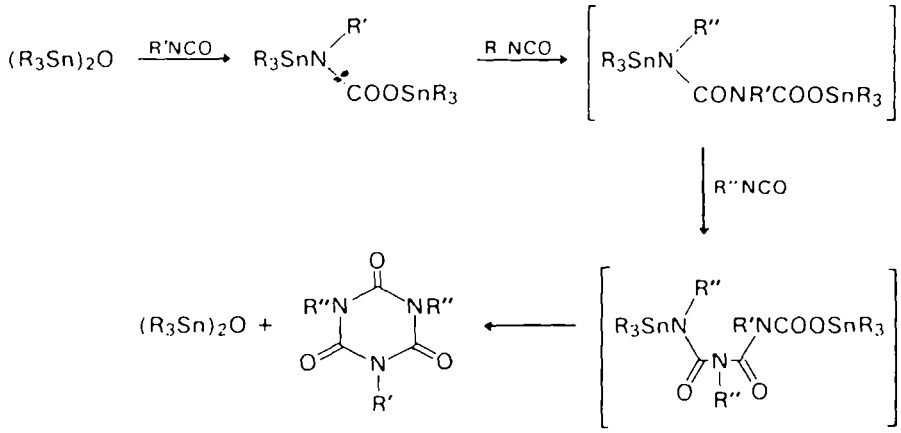
Reactions involving Sn(IV) compounds deal mostly with insertions into SnOR and SnOSn bonds, and have been investigated in connection with catalysed oligomerizations of isocyanates (see Section III.B.1.a and b). Two typical reactions are shown below[779,780].

$$R_3SnOCH_3 \xrightarrow{R'NCO} (C_2H_5O)_3SnN(R')COOCH_3$$

$$R_3SnOSnR_3 \xrightarrow{R'NCO} R_3SnN(R')COOSnR_3$$

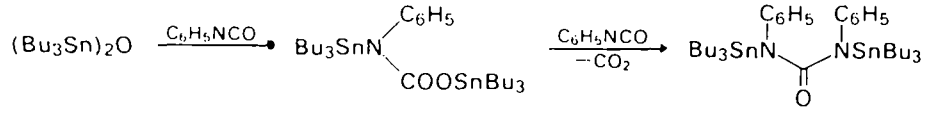
R = Alkyl
R' = Alkyl, aryl

On treating bis-tributyltin oxide with excess, or stepwise, with two different isocyanates, isocyanurates are obtained via repeated insertion of isocyanate into SnO and SnN bonds as shown below[781].

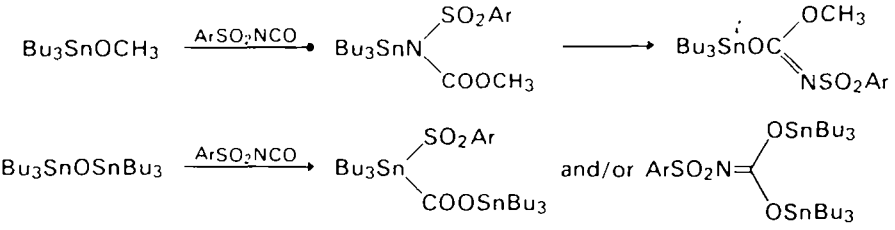


Depending on the structure of the isocyanates used in these trimerizations, insertions might take a different course and urea derivatives are obtained

as a result of two successive SnO bond insertions[732,783]. Insertions into GeOGe and GeOSn bonds have also been investigated[784]:

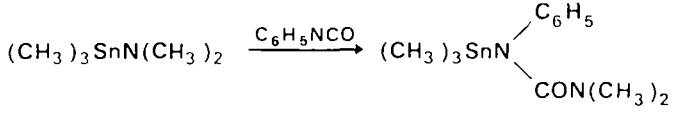


Insertion and isomerizations are observed on reacting tributyl tin methoxide or bis-tributyltin oxide with arenesulphonyl isocyanates[785,786].

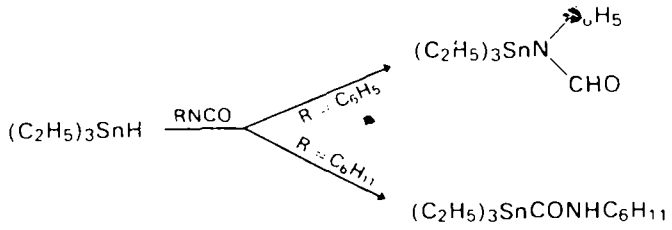


Triphenyltin *t*-butyl peroxide is also capable of undergoing reactions with alkyl isocyanates, giving *t*-butyl *N*-alkyl-*N*-triphenyl stannylperoxycarbamates[787].

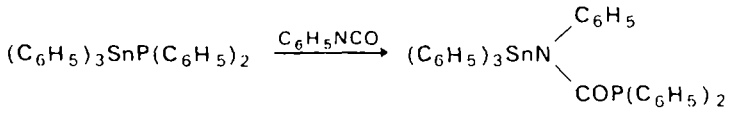
Reactions of isocyanates with compounds containing Sn–N bonds are very similar to SnO insertions[788].



Insertions into SnH bonds have also been observed and are not uniform with regard to the structure of the products obtained as is shown below[789–791]



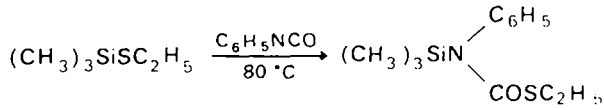
Stannylphosphines were shown to react with phenyl isocyanate, breaking the Sn–P bond and giving **510** in good yield[792].



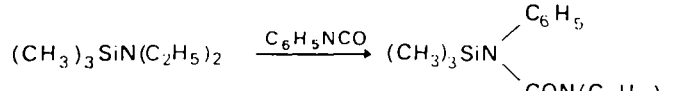
(510)

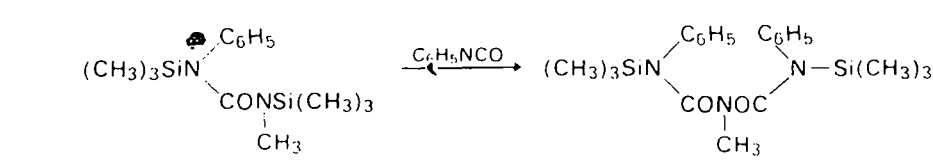
Reactions of isocyanates with silicone compounds having Si–S, Si–N, Si–OR, Si–P, Si–C and Si–H bonds have been investigated and resemble in many instances those of tin compounds.

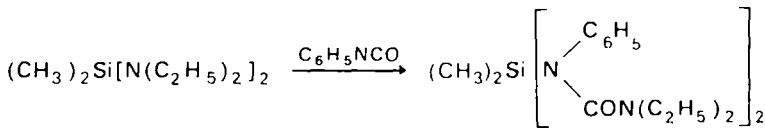
β-Halogen alkoxy trimethyl silanes react only at elevated temperature (170–200 °C) with phenyl isocyanates with insertion into the SiO bond; initially formed adducts, however, react with excess isocyanate, giving rise to formation of complex reaction mixtures containing *N,N'*-diphenyl carbodiimide, triphenyl isocyanurate as well as a cyclic 2:1 adduct of phenyl isocyanate and *N,N'*-diphenyl carbodiimide but no defined product of a SiO insertion[793]. This is different from Si–SR compounds which readily yield silyl thiocarbamates and isocyanate trimers[794].



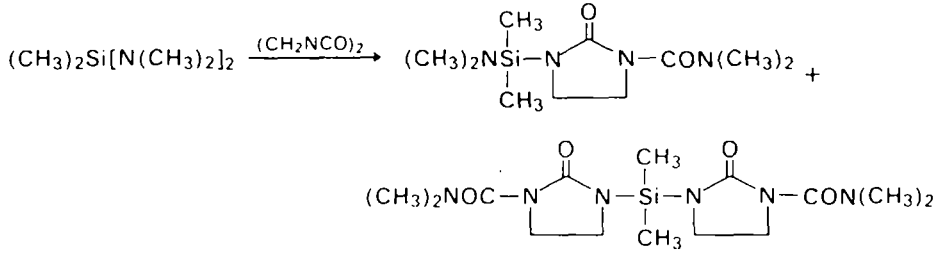
Even more reactive are compounds with Si–N bonds, and insertions of isocyanates are exothermic[795–798].



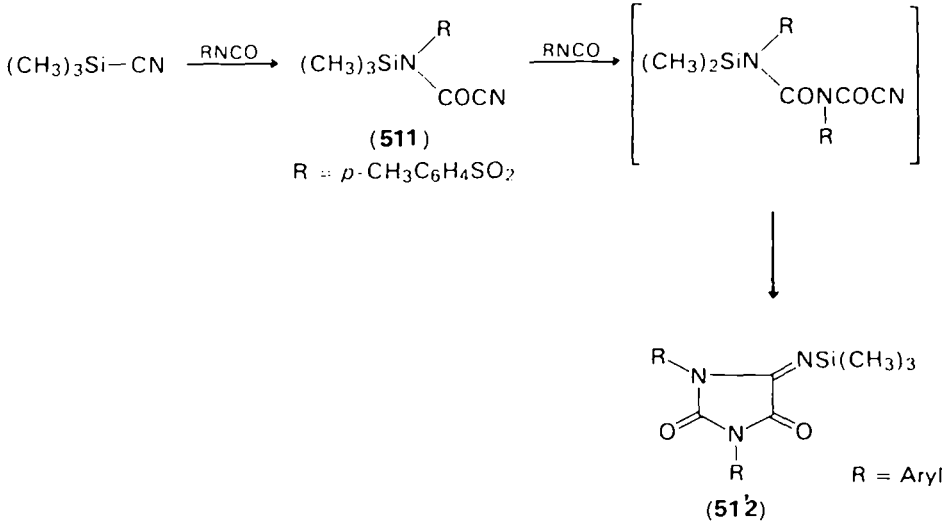




Cyclization to *N*-silylimidazolidinones is observed during the reaction of dimethyl bis(dimethylamino)silane with ethylene diisocyanate[799].

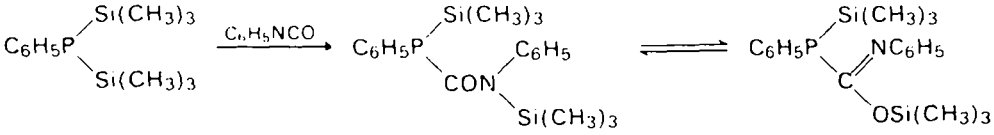


Trimethylsilyl cyanide reacts with aryl and *p*-tosyl isocyanate initially with insertion into the Si–CN bond, giving **511**. Only with sulphonyl isocyanate, however, is it possible to isolate a 1:1 adduct; uncatalysed addition of another mole of isocyanate is observed in all other cases, ultimately leading to *N*,*N*′-disubstituted 5-trimethylsilylimino imidazolidinedione **512**[800].



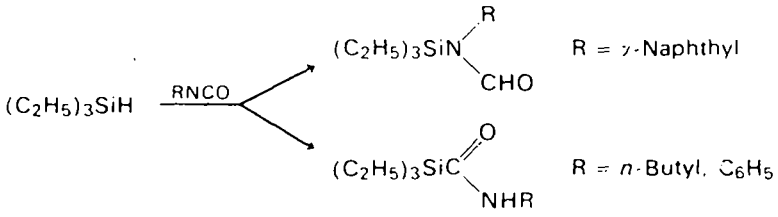
Reactions of compounds having Si–P bonds have also been studied. Very often isocyanate oligomerization was observed exclusively, together with carbodiimide formation. In the case of phenyl-bis(trimethylsilyl)-phosphine, however, acyclic 1:1 adducts resulting from a Si–P bond

insertion could be isolated. These initially-formed adducts isomerize readily, giving mixtures of **513** and **514**[801].

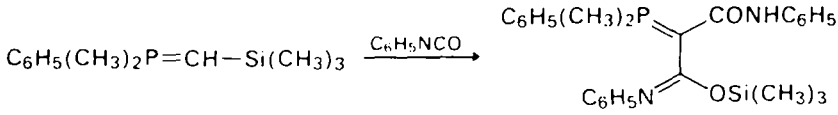


(513) **(514)**

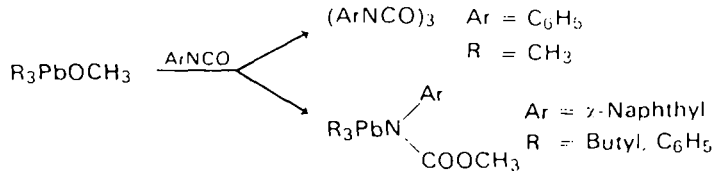
Two different pathways have been observed in reactions of triethylsilane with alkyl and aryl isocyanates in presence of palladium catalysts at 80 °C. While silyl formamides are formed with α-naphthyl isocyanate, similar reactions with phenyl and *n*-butyl isocyanate lead to Si–C bond formation giving carbamoyl silanes[802]. Related reactions are observed with organotin hydrides.



(Trimethylsilylmethylene)dimethylphenyl phosphorane reacts with phenyl isocyanate at −35 °C in ether, giving a 1:2 adduct, formed by insertion into the CH and C–Si bonds, involving also a $Si(CH_3)_3$ migration[858].

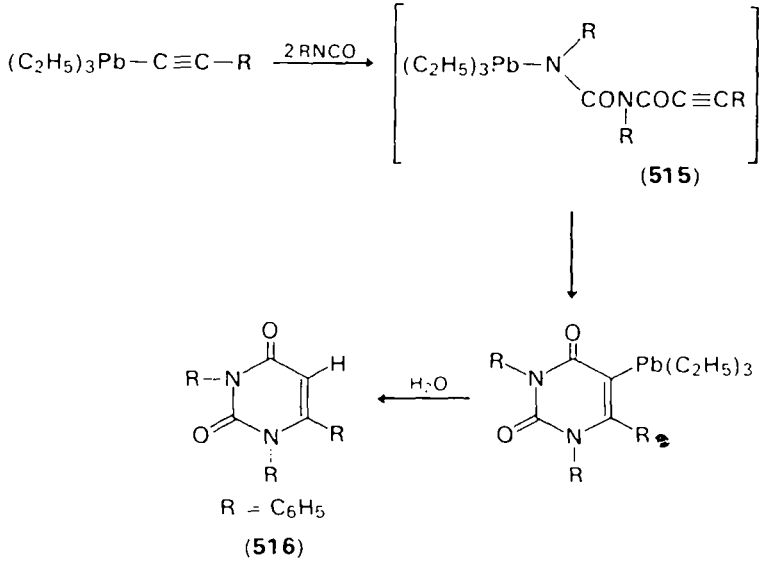


Insertion reactions involving lead compounds are also known, and are similar to reactions of compounds of other group IVa elements. Insertion into a Pb–OR bond takes place on treating triphenyl or tributyl lead methoxide with α-naphthyl isocyanate[803]. Spontaneous trimerization of phenyl isocyanate, however, is observed in the presence of trimethyl lead methoxide[804].

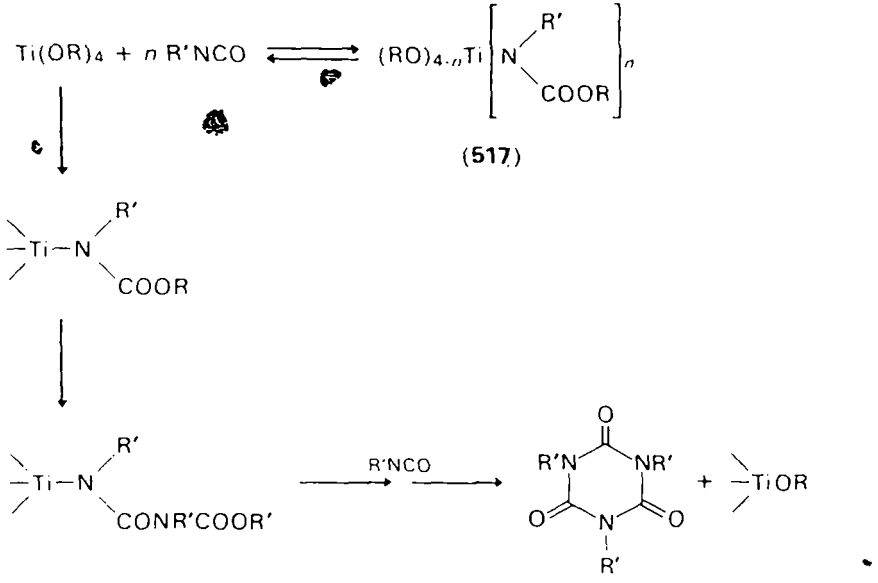


On careful addition of phenyl or cyclohexyl isocyanate to tributyl plumbyl-*N*-diethylamine, a 1:1 insertion product is formed. Reverse addition, however, leads, even with traces of the plumbyl amine, to trimerization of the isocyanate[805].

Triethyl phenylethynyl lead reacts exothermically with phenyl isocyanate. Two moles of the isocyanate are inserted into the Pb–ethynyl bond giving a linear adduct **515**. Cyclization of the latter and hydrolysis yields 1,3,5-triphenyl-uracil **516**[806].



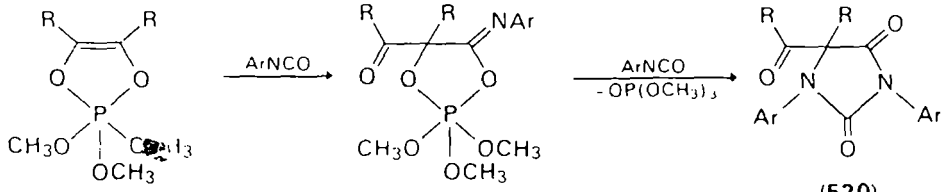
Reactions of titanium compounds with isocyanates have also been explored[807,808]. Ready insertion of both alkyl and aryl isocyanates into Ti–OR bonds is observed at low temperatures. Titanium tetraalkoxide reacts reversibly with 4 moles of isocyanate, giving tetracarbamates with the general formula **517**. On standing at room temperature, slow conversion into isocyanate trimers was observed and titanium alkoxide was reformed, indicating the following processes:



(517)

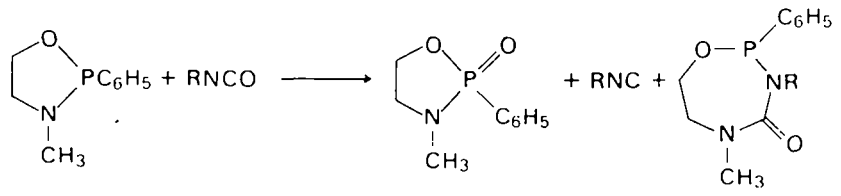
(iii). Group Va elements. A number of reactions involving phosphorus compounds and isocyanates are described in Section C, leading very often to the formation of carbodiimides. Other phosphorus-containing compounds are known to be excellent catalysts for the oligomerization of isocyanates[795,809,810].

A large number of phosphorus compounds react readily with isocyanates with insertion into a P–R bond. Isocyanate insertion into P–H or P–N bonds, resulting in the formation of amides and ureas (see equations below) is observed with both P(III) and P(V) compounds. However, reactions of trivalent P compounds lead occasionally to unexpected products. Treating 2,2,2-trimethoxy-2,2-dihydro-1,3,2-dioxaphospholenes (**518**) with aryl isocyanates leads to formation of 4-aryliminodioxaphospholanes **519**[624]. The latter can be further converted with excess isocyanate into hydantoins (**520**) and trimethyl phosphate.



(518) (519) (520)

The conversion of isocyanates into isonitriles on treatment with 2-phenyl-1,3,2-oxazaphospholidine as described in Section C is accompanied by formation of an insertion product **521**[811].



(**521**)

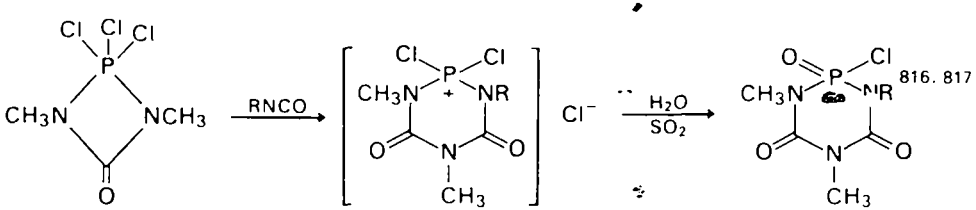
Reactions of phosphorus-containing compounds with isocyanates:

$$(RO)_2PHO \xrightarrow[NEt_3]{RNCO} (RO)_2P(=O)CONHR \quad 812$$

$$[(CH_3)_2N]_2PHO \xrightarrow{C_6H_5NCO} (CH_3)_2NC(=O)NHC_6H_5 + \text{Resinous material from P-containing component} \quad 813$$

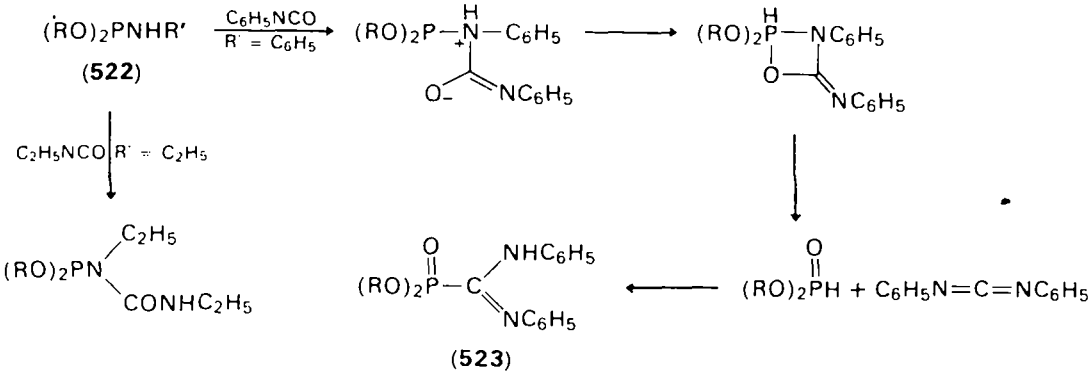
$$[(CH_3)_2N]_2PR \xrightarrow{R'NCO} RP[NCON(CH_3)_2]_2 \quad \begin{matrix} \text{a: } R = CH_3,\ R' = C_2H_5 \quad 814 \\ \text{b: } R = C_6H_5,\ R' = p\text{-}CH_3C_6H_4SO_2 \quad 815 \end{matrix}$$

$$[(CH_3)_2N]_2POC_2H_5 \xrightarrow{p\text{-}CH_3C_6H_4SO_2NCO} (CH_3)_2NP(OC_2H_5)-N(SO_2C_6H_4CH_3\text{-}p)(CON(CH_3)_2) \quad 814$$



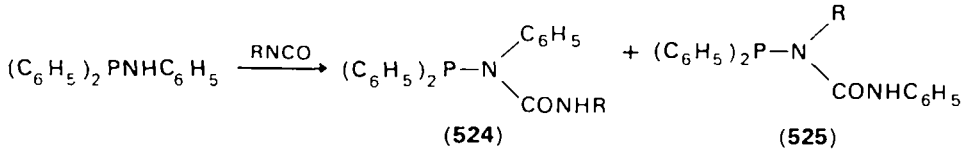
Most phosphorus compounds having $P-NR_2$ linkages react with isocyanate with insertion into the P–N bond or oligomerization of the isocyanates. P–N compounds derived from primary amines, however, behave differently and can give different products depending on the structure of the reactants (see also Section III.B.3.b). When dialkyl-*N*-phenylphosphoramidites (**522**) are treated with phenyl isocyanate,

diesters of *N,N'*-diphenylamidinophosphonic acid (**523**) are obtained, believed to be formed via the following pathway[706,782]:



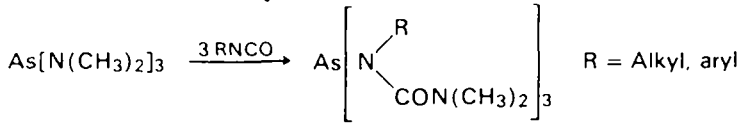
(**523**)

This reaction is, however, not common, since diethyl-*N*-ethylphosphoramidite reacts with ethyl isocyanate only under NH insertion[782]. Another possibility of interaction is encountered between alkyl as well as aryl isocyanates and *N*-phenyl diphenylphosphinous amide, yielding a mixture of **524** and **525**[782]. Similar reactions are described with silylamines[796].



(**524**) (**525**)

Both alkyl and aryl isocyanates were shown to insert readily into As–N bonds, giving tris-ureas **526** in high yield[795,814].



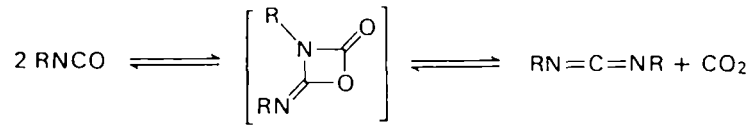
(**526**)

Other reactions of phosphine and arsine oxides with isocyanates are described in Section C.

C. Reactions of Isocyanates Across Their C=O Bond

Reactions of isocyanates on their C=O group are less common. The thermal formation of carbodiimides from isocyanates has been reported

for several examples in which asymmetric isocyanate dimers (**527**) are believed to be intermediates.

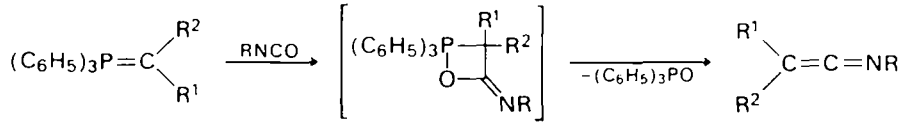


(**527**)

It is not entirely certain whether a truly uncatalysed carbodiimide formation from isocyanates exists at all.

Compounds of group V elements (P, As, Sb), which readily undergo reactions with isocyanates across their carbonyl group.

The phosphonium ylids **528** were shown to react with alkyl and aryl isocyanate possibly via a four-membered ring transition state, giving triphenyl phosphine oxide and the ketenimines **529**[569,818].

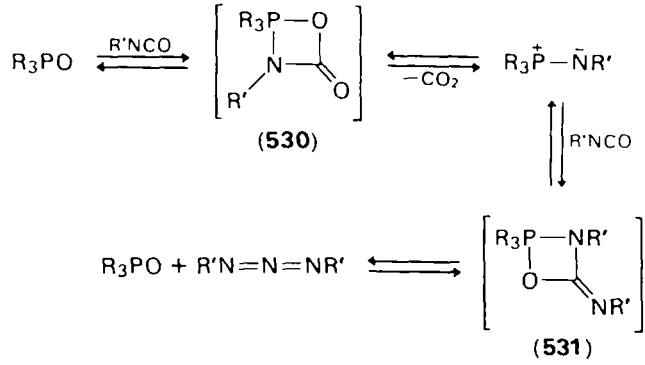


(**528**) (**529**)

A polar adduct is claimed to be formed from dimethyl methylene triphenyl phosphorane and phenyl isocyanate[819], and unsubstituted methylene phosphoranes react with isocyanates preferentially by CH insertion[819].

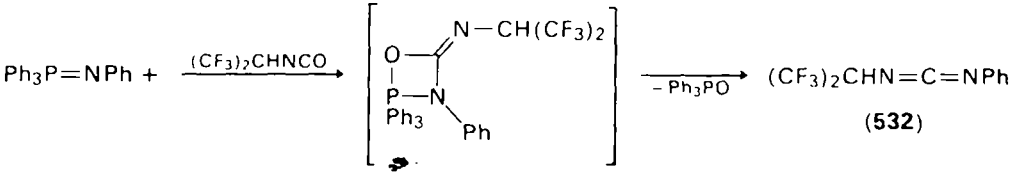
More important are reactions of isocyanates with phosphine imines; the latter are readily formed from tertiary phosphines and azides[569]. Phosphine imines react with isocyanates to form carbodiimides and phosphine oxide[820]. A number of other phosphine oxides were later found to react rapidly with isocyanates, giving phosphinimines, which with excess isocyanate form carbodiimide and regenerate the phosphine oxides[470,821–832]. In a study involving five different phosphine oxides and independently prepared *N*-phenylphosphine imines, it was found that the phosphin imines react 10^5–10^7 times faster with phenyl isocyanate than the corresponding phosphine oxides[833]. Since the phosphine oxide is constantly regenerated, catalytic amounts are sufficient for the conversion of isocyanates into carbodiimides. Cyclic phosphine oxides such as 1-alkyl- and aryl-3-phospholene-1-oxides are outstanding catalysts for the carbodiimide preparation[470], but 1,3,2-diazaphospholidine-2-oxides[824,834], 1,3,2-diazaphosphorine-2-oxides[824], phosphetane 1-oxides[835] and acyclic phosphine oxides as well as others were shown to

catalyse the reaction too. Alkyl as well as aryl isocyanates have been converted into carbodiimides:

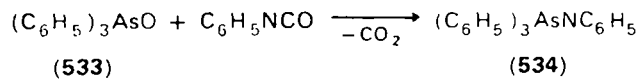


benzoyl isocyanate reacts differently and gives, in addition to unidentified products, benzonitrile and carbon dioxide[470]. Sulphonyl isocyanates react readily with cyclic or acyclic phosphine oxides, giving *N*-sulphonyl phosphin imines, which can not be further transformed into *N,N'*-bis-sulphonyl carbodiimides[836,837].

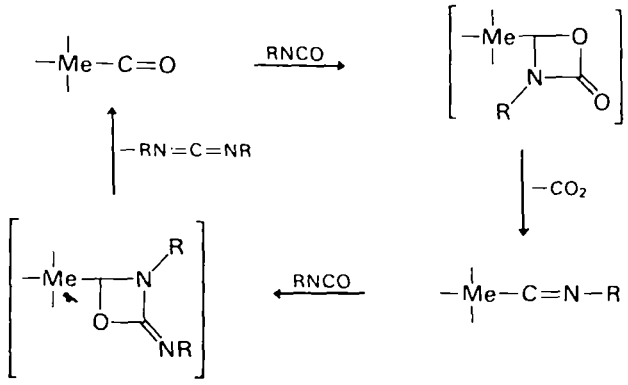
The preparation of carbodiimides having two different *N*-substituents is possible in certain cases. Thus reacting *N*-phenyl-triphenylphosphinimine at −78 °C with α-hydroperfluoroisopropyl isocyanate gives the carbodiimide **532** in good yield[838,839].



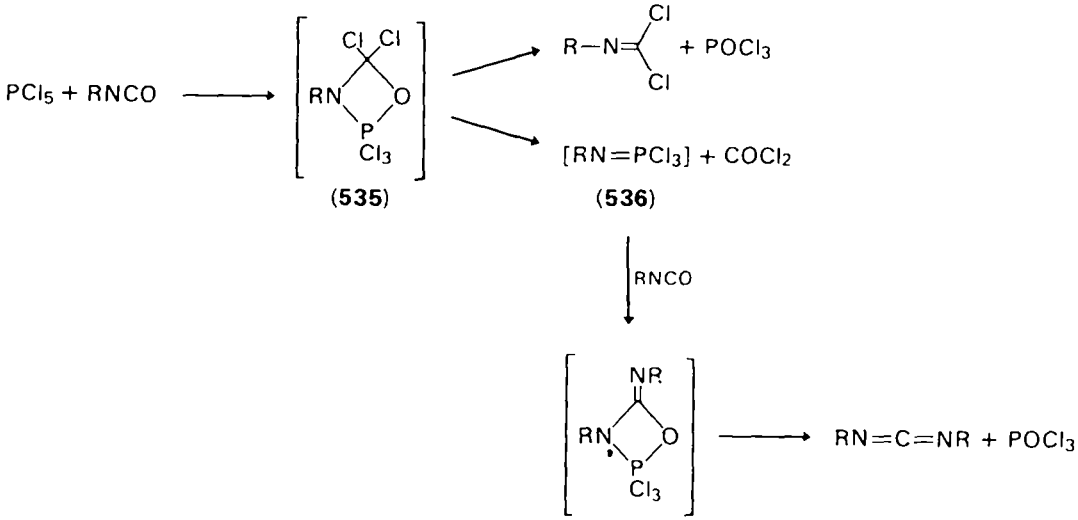
Other compounds of group V elements with metal–oxygen bonds such as triphenylarsine oxide **533** or triphenylstibine oxide are also carbodiimide catalysts[822]. Molar amounts of **533** and aryl isocyanate give high yields of triphenylarsine imines **534**[840]



The conversion of aryl isocyanates into carbodiimides in the presence of catalytic amounts of iron, tungsten and molybdenum carbonyls is likely to proceed via formation of isonitrile–metal complexes, as outlined below[841].

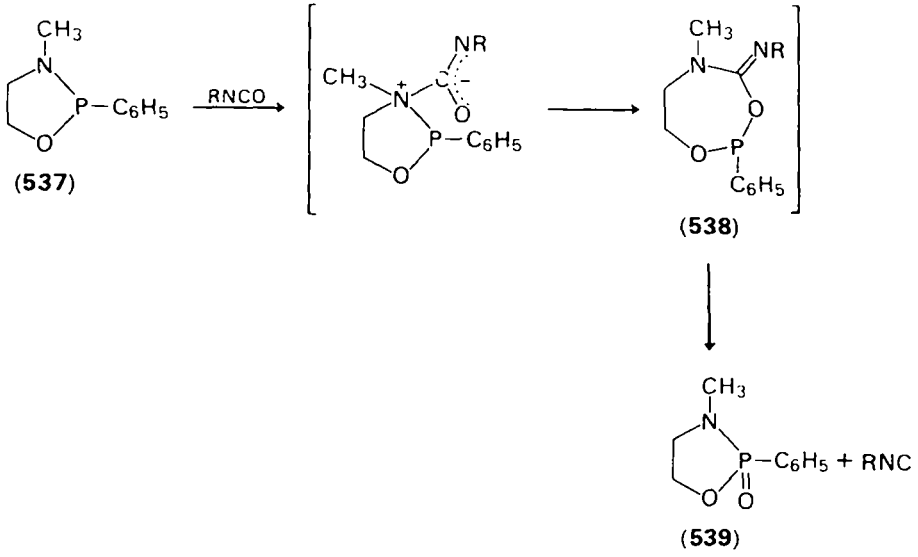


Heating of aryl isocyanates with phosphorus pentachloride produces aryl isocyanide dichlorides, phosphorus oxychloride, diaryl carbodiimide and phosgene[842,843]. It is believed that a cyclic 1:1 adduct **535** is responsible for the formation of these products. *N*-Substituted trichlorophosphinimine (**536**), a likely intermediate, is converted with excess isocyanate into carbodiimide and $POCl_3$.



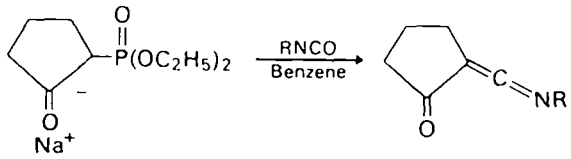
Trivalent phosphorus compounds are used as deoxygenating agents of isocyanates leading to formation of isonitriles and pentavalent phosphorus compounds[811,844]. When 2-phenyl-3-methyl-1,3,2-oxaphospholidine (**537**) is reacted with aryl or alkyl isocyanates at a low temperature, isonitriles are obtained in good yield in addition to small amounts of

3-substituted perhydro-2-phenyl-5-methyl-1,3,5,2-oxadiazaphosphine-4-one. The formation of the isonitrile is believed to involve an intermediate, **538**, which collapses to give product and **539**[811,844,845].



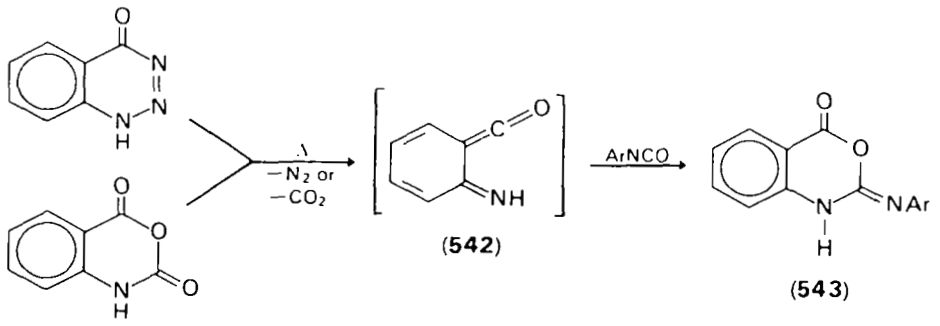
(537) (538) (539)

Ketenimines (**541**) are obtained in high yield on reacting α-(*O,O*-diethylphosphono)-γ-butyrolactone carbanion **540** with alkyl isocyanates in warm benzene[846].



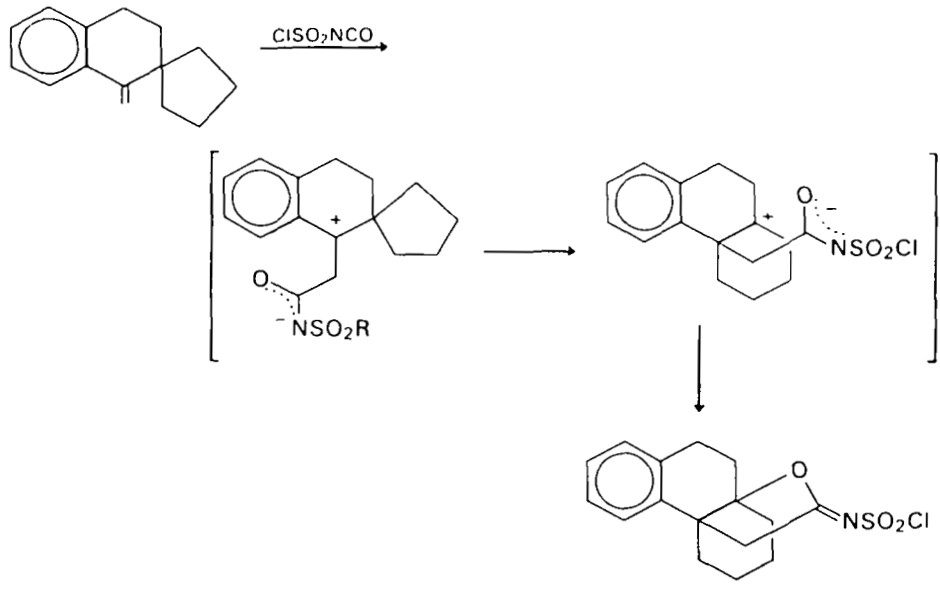
(540) (541)

2-Aryliminobenz-3,1-oxazine-4-ones (**543**) are formed during the thermal decomposition of benzotriazinone and isatoic anhydride in presence of aryl isocyanates[847,848]. The reactions are believed to involve formation of iminoketene, **542**. The obtained phenyl isocyanate adduct, **543**, can be rearranged into 3-phenylquinazoline-2,4-dione. 2,2-Tetramethylene-1-methylene 1,2,3,4-tetrahydronaphthalene reacts with CSI at low temperature to give quantitatively 4a, 10a-[2'-*N*-chlorosulphonylimino-3'-oxapropano]1,2,3,4,4a,9,10,10a-octahydrophenanthrene (**544**) in a reaction accompanied by a Wagner-Meerwein rearrangement in the dipolar stage[849].



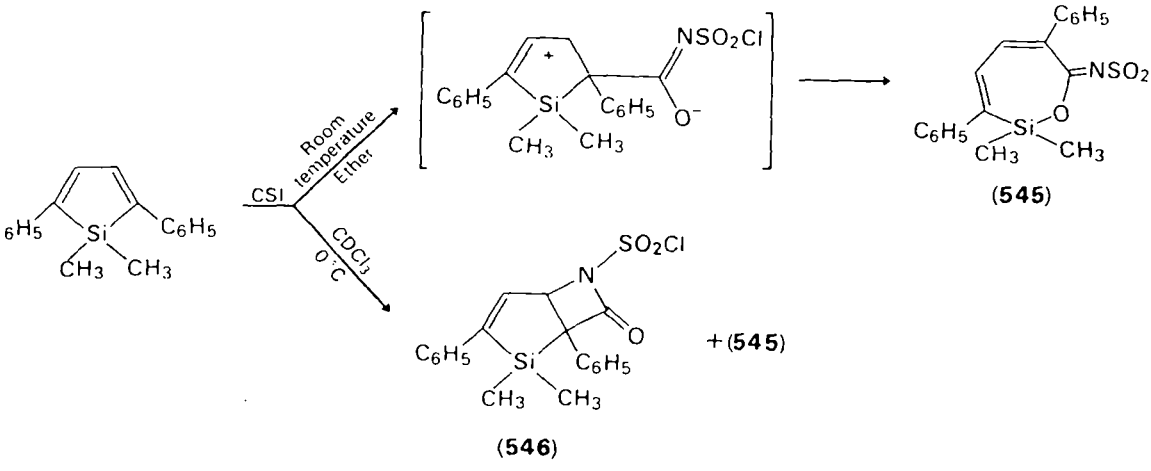
(542)

(543)



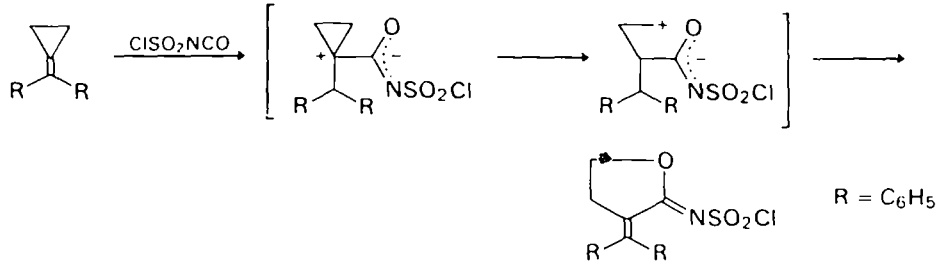
(544)

Two different addition products have been obtained from 1,1-dimethyl-2,5-diphenyl-1-silacyclopenta-2,4-diene and CSI. Mixing the components in ether at room temperature produced **545** in good yield[866]. The reaction is likely to proceed via a dipolar intermediate which rearranges to **545** via silicon migration to oxygen. Mixtures of **545** and **546** are obtained, however, on carrying out the reaction at 0°C in $CDCl_3$[866]. On reacting CSI with diphenyl methylene cyclopropane at room temperature, α-diphenylmethylene-*N*-chlorosulphonylimino-γ-butyrolactone (**547**) is formed in high yield[850]. Possible dipolar intermediates in this [2 + 3] cycloaddition reaction are shown below.



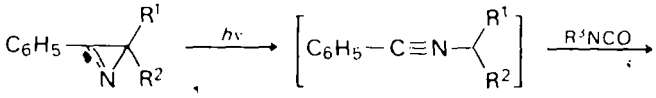
(545)

(546)



(547)

A related 1,3-dipolar cycloaddition is used for the preparation of oxazolines from 3-phenyl-2*H*-azirines. Irradiation of the latter in solution leads to benzonitrile methylene ylids (**548**) which can be intercepted by heterocumulenes such as aryl isocyanates, giving oxazolines (**549**) in good yield[851].

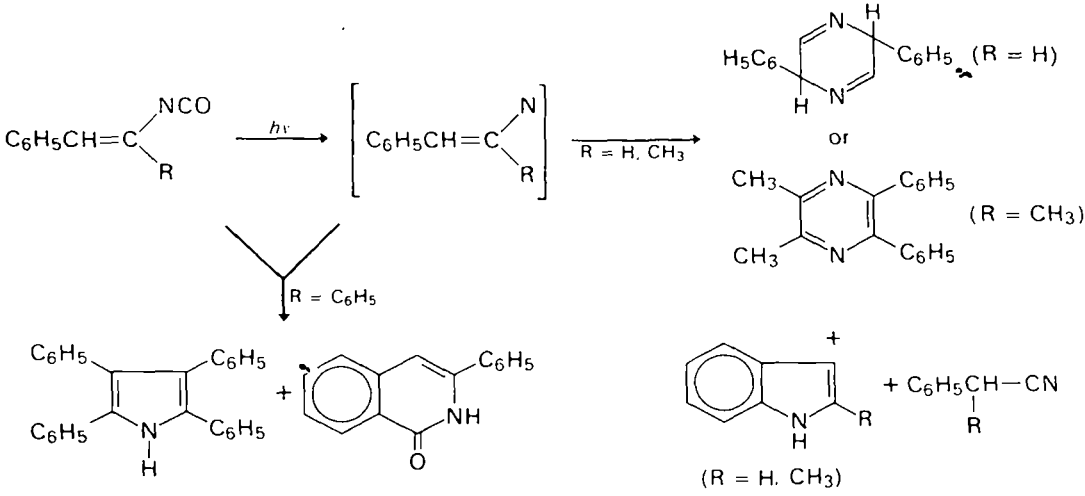


(548)

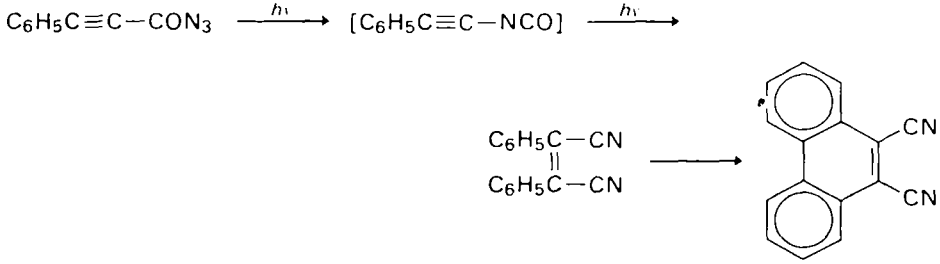
R^1 = H, alkyl; R^2 = Alkyl, aryl; R^3 = Aryl

(549)

Phenyl isocyanate has been shown to dimerize to 1,3-diphenyldiazetidinedione on irradiation with ultraviolet light[852]. Extensive polymerization and evolution of carbon monoxide is observed when several β-styryl isocyanates are irradiated[716,853,854]. The styryl nitrenes produced in these decarbonylations undergo further reactions resulting in the formation of a number of products which are shown below.



Decarbonylation takes place also on irradiating phenylethynyl isocyanate generated from phenylpropionyl azide, resulting in the formation of α,β-dicyanostilbene. The latter is photochemically transformed into 9,10-dicyanophenanthrene[855].



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The Chemistry of Cyanates and their Thio Derivatives
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CHAPTER 18

Syntheses and preparative applications of thiocyanates

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1. INTRODUCTION

This chapter deals with the syntheses and preparative applications of organic thiocyanates (**1**).

$$\underset{(1)}{R-S-C\equiv N} \qquad \underset{(2)}{R-N=C=S}$$

Discussion is limited to thiocyanates in which the functional group is covalently bonded to carbon, nitrogen or sulphur.

Organic thiocyanates are readily prepared by a wide range of methods which often show a striking parallel with those used for making the corresponding halides, thus reflecting the marked pseudohalide character of the thiocyanato group[1]. The most common by-product of the reactions, often occurring in substantial amounts, is the corresponding and thermodynamically more-stable isothiocyanate (**2**), which may be formed either in the primary reaction or in a secondary isomerization reaction. In many investigations this has not been appreciated or has been disregarded, and so the interpretation of such work often needs to be viewed with caution and re-appraised in the light of current knowledge. Physical methods, e.g. i.r.[2] and n.m.r.[3] spectroscopy, now permit rapid detection of isothiocyanato by-products, which may be readily removed, if necessary, by chemical or chromatographic methods[4]. Isothiocyanates are the subject of a separate chapter, and consequently discussion in this chapter will be confined to the circumstances under which they arise in the synthesis and reaction of thiocyanates.

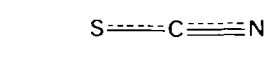
Thiocyanates undergo a rich variety of reactions due to the ability of the thiocyanato functional group in **1** to react either as a pseudohalide group or as a sulphenyl cyanide group. This dichotomy of behaviour provides attractive routes to many types of compounds, particularly S- and S-heterocycles of marked physiological activity. In this context, it should also be noted that many thiocyanates show toxic effects, mainly dermatitis, which vary considerably in different individuals, and so due precautions should be exercised in all handling of these compounds.

Previous reviews of the syntheses and preparative applications of organic thiocyanates include those by Kaufman (1941)[5], Wood (1946)[6], Bacon (1961)[7], Reid (1965)[8], and Knoke, Kottke and Pohloudek-Fabini (1973)[9]. The last two publications[8,9] are particularly comprehensive accounts, with Reid's article[8] also tabulating physical data for, and reviewing the physiological activity and commercial applications of, a wide range of organic thiocyanates. This review, therefore, will concentrate

on recent developments in synthetic methods, preparative applications, theories, and reaction mechanisms, with adequate reference to the earlier work where appropriate. In particular, results of mechanistic studies on the reactions of thiocyanogen with organic compounds are emphasized in order to rationalize the extensive, but often confused, literature on such reactions.

II. PREPARATION OF THIOCYANATES BY REACTION OF ISOTHIOCYANIC ACID OR ITS SALTS WITH ORGANIC COMPOUNDS

The reaction of isothiocyanic acid (HNCS) or its salts with organic compounds is one of the most widely used methods of thiocyanate synthesis[8,9]. As in the corresponding reactions of hydrogen halides or their salts, isothiocyanic acid[8] behaves as an electrophilic reagent and its salts as nucleophilic reagents. The thiocyanato anion, however, differs from halide anions in that it is an ambident[10] nucleophile due to the resonance $\overset{\frown}{S}{-}C{\equiv}N \leftrightarrow S{=}C{=}\overline{N}$, which results in the hybrid structure and charge distribution shown in **3**[11].



(3)

Consequently, kinetically-controlled reactions of the thiocyanato anion with organic compounds may lead either to thiocyanates (**1**) via nucleophilic attack by the sulphur atom, isothiocyanates (**2**) via nucleophilic attack by the nitrogen atom, or mixtures of **1** and **2**. In common with other ambident species[12], the reactivity ratio (relative nucleophilicity) k_S/k_N[13] of the two ends, S and N, of the thiocyanato anion **3** may depend on the interplay of various factors, e.g. solvent or medium, counter-ion, catalyst, concentration, temperature, leaving group, and structure of the organic compound.

In heavy-metal thiocyanates, the thiocyanato group may be S-bonded or N-bonded to the metal atom as in $Hg(SCN)_2$ and $Cu(NCS)_2$ respectively[14]. Not surprisingly, the behaviour of these thiocyanates with organic compounds may be quite different to that of the ionic alkali metal thiocyanates, and some successful exploitations of this difference are described below. Cupric thiocyanate occupies a special position since it can also act as a source of thiocyanogen on being heated[5,6].

A. Halides

The archetypal method of preparing alkyl and aralkyl thiocyanates, and the one on which most mechanistic studies have been made, is the reaction of the corresponding halides with metal thiocyanates in suitable solvents[7,8,9] (equation 1).

$$RHal + [SCN]^- \longrightarrow RSCN + Hal^- \quad (1)$$

Traditionally, solutions of sodium, potassium or ammonium thiocyanate in water, ethanol or acetone are used[4]. Glycols[15] and liquid sulphur dioxide[16] have also been used as solvents. However, dipolar aprotic solvents such as dimethylformamide, diethylformamide, dimethyl sulphoxide and tetramethylene sulphoxide[17] have been shown to be superior since they reduce reaction times, lower temperatures, and improve yields. This has been attributed[18] to the formation of onium-type intermediates (**4**) which react more rapidly than the original halide with the thiocyanato anion (equation 2).

$$RX + HCONMe_2 \rightleftharpoons \underset{(4)}{R-\overset{+}{O}=\overset{H}{\overset{|}{C}}-NMe_2} + X^- \xrightarrow{[SCN]^-} RSCN + HCONMe_2 \quad (2)$$

Intermediates of type **4** have been isolated and shown to undergo inversion of configuration on treatment with metal thiocyanates[19]. Good results have also been obtained using the technique of phase-transfer catalysis[19a].

As in other nucleophilic displacement reactions, the reactivity of the organic halide in equation (1) follows the sequence Hal = I > Br > Cl ≫ F, thus permitting selective displacement in dihalides[17] (equation 3).

$$F(CH_2)_4Br + KSCN \xrightarrow[30\ C]{DMF} F(CH_2)_4SCN + KBr \quad (3)$$

Usually the only by-product of reaction (1) is the corresponding isothiocyanate, RNCS. Bacon and coworkers have shown that the amount of isothiocyanate increases in the order of primary < secondary ≪ tertiary halides, and in the order of alkyl < aryl < polycyclic aryl substituents on the carbon atom at which substitution occurs[20,21,22]. This may occur through secondary, thermodynamically-controlled isomerization processes (see Section VI.B), but recent studies by Fava[13], Okano[23], and their coworkers have shown that it may also occur in kinetically-controlled S_N2 and S_N1 reactions.

Under S_N2 conditions, the competing kinetically-controlled reactions of

the S and N ends of the thiocyanato nucleophile are as shown in equations (4a) and (4b) respectively.

$$RX + [SCN]^- \xrightarrow{k_S} RSCN + X^- \quad (4a)$$

$$RX + [SCN]^- \xrightarrow{k_N} RNCS + X^- \quad (4b)$$

The overall rate of reaction follows the expected order of primary > secondary > tertiary halide, while the relative rate ratio, k_S/k_N, as measured by the resulting kinetically-controlled isomer distribution, decreases in the same order[23]. Some typical results are shown in Table 1.

TABLE 1. Reaction of RBr with KSCN in DMF[23]

R in RBr	k_S/k_N
n-Bu	99
$PhCH_2$	49
i-Pr	49
PhCHMe	32
c-C_6H_{11}	24
t-Bu	0·92[a]

[a] Some isomerization may have occurred.

This increasing tendency for isothiocyanate formation as the halide structure changes from primary to secondary to tertiary may be rationalized on the basis of the Hard and Soft Acids and Bases (HSAB) principle[24], which states that hard acids prefer to coordinate to hard bases while soft acids prefer to coordinate to soft bases. In these systems, the thiocyanato nucleophile **3** is the base, with the more polarizable, less electronegative sulphur atom being the softer atom and the nitrogen atom the harder one; the organic halide is the acid, with the degree of hardness of the attached carbon atom increasing with increasing electrophilic character, i.e. in the order primary < secondary < tertiary. Thus primary halides (soft acids) prefer to react with the soft sulphur atom of **3** giving thiocyanates predominantly, whereas secondary and tertiary halides (increasingly harder acids) give increasing amounts of isothiocyanates by their greater tendency to react with the harder nitrogen atom.

Fava and coworkers[13] have shown that, for S_N2 attack on benzylic carbon, the relative nucleophilicity of the two ends of **3** is dependent on both temperature and solvent. For example, at 70 °C in methyl ethyl ketone and acetonitrile, the k_S/k_N values are 1000 and 725 respectively; at

100 °C the corresponding values are 650 and 460, i.e. isothiocyanate formation is favoured by increasing temperature.

Under S_N1 conditions, the competing kinetically-controlled reactions of the sulphur and nitrogen ends of **3** are as shown in equations (5a) and (5b) respectively.

$$R^+ + [SCN]^- \xrightarrow{k_S} RSCN \quad (5a)$$

$$R^+ + [SCN]^- \xrightarrow{k_N} RNCS \quad (5b)$$

In the few investigations reported, values of k_S/k_N ranging from 2 to 9 have been obtained for R = *t*-butyl[25] and 4,4'-dimethylbenzhydryl[26] in various solvents. In the related metal-catalysed S_N1 reactions of heavy-metal thiocyanates, e.g. mercuric thiocyanate, with alkyl bromides, the observed reactivity order is *n*-BuBr: *i*-BuBr: *t*-BuBr = 1:10:10^4 at 65 °C in *n*-hexane and much lower k_S/k_N values are obtained in a range of solvents[23]. Some typical results are shown in Table 2.

TABLE 2. Reaction of RBr with $Hg(SCN)_2$ in di-*n*-butyl ether[23]

R in RBr	k_S/k_N
n-Bu	3·7
$PhCH_2$	1·8
c-C_6H_{11}	0·37
i-Pr	0·18
t-Bu	0·04
PhCHMe	0·01

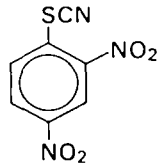
The smaller k_S/k_N ratios obtained in S_N1 reactions (cf. Table 1), and the decreasing k_S/k_N ratio as the halide structure changes from primary to secondary to tertiary, are both consistent with the HSAB principle, since the carbon atom of carbonium ions is harder than the polarized carbon atom of halides in S_N2 reactions, and carbonium ions increase in hardness in the order primary < secondary < tertiary[24]. The increased preference for isothiocyanate formation in the metal-catalysed S_N1 reactions has been attributed[23] to the formation of the sulphur-bonded $[BrHg(SCN)_2]^-$ counter-ion (**5**), which reacts preferentially via the sterically favourable and more electronegative nitrogen atom (equation 6).

$$RBr + Hg(SCN)_2 \xrightarrow{\text{slow}} R^+ + [BrHg(SCN)_2]^- \xrightarrow{\text{fast}}$$

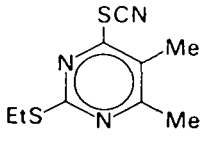
(5)

$$\rightarrow \underset{\text{(major)}}{RNCS} + RSCN + BrHgSCN \qquad (6)$$

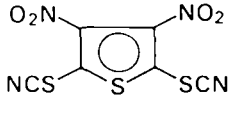
Other types of organic halides which have been thiocyanated by treatment with a metal thiocyanate, but usually not examined in the same detail as described above, include vicinal[17] and geminal[15] dihalides, haloketones[27], haloesters[28], acyl[29,30] and thioacyl halides[30], aryloxyalkyl[31] and carbanilinoalkyl[32] halides, halosulphides[33], tetrahydrofurfuryl halides[34], haloanilides[35] and halo-polymers[36]. Allylic halides react readily, but may undergo ready isomerization[37]. Aryl, heteroaromatic, and vinyl halides are unreactive unless activated by suitable electron-withdrawing substituents. Thus compounds **5**[38], **7**[39], **8**[40], **9**[41], **10**[42], and **11**[43] are readily prepared from the corresponding halide by treatment with an alkali-metal thiocyanate.



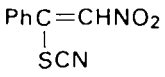
(6)



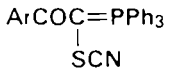
(7)



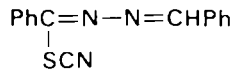
(8)



(9)



(10)



(11)

Sulphenyl halides similarly yield the corresponding sulphenyl thiocyanates, RSSCN[44].

B. Esters

The thiocyanato anion displaces the sulphonate anion from alkyl and aryl sulphonates under S_N2 conditions (equation 7).

$$ROSO_2R^1 + [SCN]^- \longrightarrow RSCN + \bar{O}SO_2R^1 \qquad (7)$$

(R^1 = 4-MeC_6H_4, 4-BrC_6H_4, Me, etc.)

The same range of solvents as described in Section II.A may be used in the

preparation of, e.g. acyclic dithiocyanates[45] and allylic[46], cycloalkyl[47], norbornyl[48], steroidal[49], and polysaccharide[50] thiocyanates; in the latter case the reaction serves to distinguish primary hydroxyl groups from secondary ones. Although no detailed studies have been made, the k_S/k_N ratios follow the general trends outlined in Section II.A[47,48]. Dialkyl sulphates, $(RO)_2SO_2$, behave in essentially the same way[51].

Normally, the carboxylate anion is not displaced from carboxylic acid esters, but small-ring lactones[52] may react to give the corresponding thiocyanate by a ring-opening reaction (equation 8).

$$\begin{array}{l} CH_2-CH_2 \\ | \quad\quad | \\ O-\!\!-CO \end{array} + [SCN]^- \longrightarrow NCSCH_2CH_2CO_2^- \qquad (8)$$

Recently, benzoate esters have been shown to give thiocyanates by an S_N2 process on fusion with a metal thiocyanate mixture[53] (equation 9).

$$ArCO_2R + KSCN/NaSCN \xrightarrow{\text{fuse}} RSCN + ArCO_2^- \qquad (9)$$

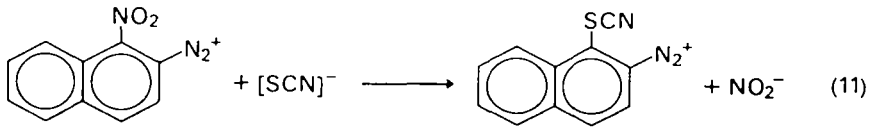
As expected from these reaction conditions, the corresponding isothiocyanates are also formed.

C. Diazonium Salts

Reaction of metal thiocyanates with diazotized primary aromatic amines is the traditional method[9,54] of preparing aryl and heteroaromatic thiocyanates (equation 10a); the corresponding isothiocyanate may also be formed in a competing kinetically-controlled reaction (equation 10b)

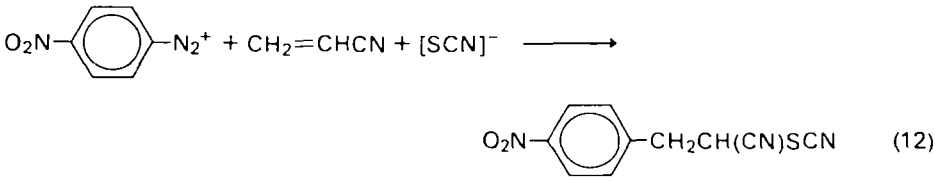
$$ArN_2^+ + [SCN]^- \begin{cases} \xrightarrow{k_S} ArSCN & (10a) \\ \xrightarrow{k_N} ArNCS & (10b) \end{cases}$$

In uncatalysed reactions of benzene diazonium tetrafluoroborate, the k_S/k_N ratio was found[55] to be 2·4 ± 0·5 at 40 °C in aqueous solution. More commonly, the reaction is carried out under Sandmeyer-type conditions which appear to increase both the yield and the k_S/k_N ratio. The catalysts usually employed are cuprous thiocyanate[9,54] and ferric thiocyanate[56], and the increased k_S/k_N ratio may be due to the formation of N-bonded complexes, e.g. $K_3Cu(NCS)_4$, which would react preferentially via the sterically-favourable sulphur atom to give the thiocyanate. It should be noted that the activating effect of the diazonium grouping may lead to the displacement of another group in the molecule (equation 11)[57].



(11)

Recently it has been shown[58] that the Meerwein arylation reaction may be applied to the synthesis of thiocyanates (equation 12).

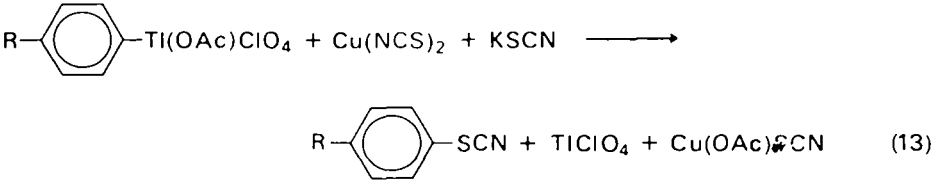


(12)

Diazotization of *t*-butyl amine in the presence of thiocyanate ions leads to formation of *t*-butyl thiocyanate and *t*-butyl isothiocyanate, with $k_S/k_N = 1{\cdot}9$[25].

D. Thallium Compounds

The versatility of organo-thallium(III) compounds in synthetic work has recently been demonstrated further by their conversion into alkyl and aryl thiocyanates by treatment with metal thiocyanates. Thus arylthallium acetate perchlorates react with a mixture of cupric and potassium thiocyanate in dioxane to yield the corresponding aryl thiocyanate[59] (equation 13).

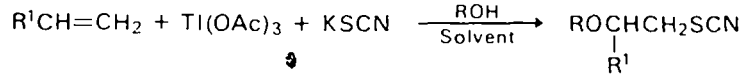


(13)

Photolysis of the readily available arylthallium bis-trifluoroacetates in aqueous potassium thiocyanate solution also leads to aryl thiocyanates[60] (equation 14).

(14)

A convenient method[61] of preparing vicinal alkoxythiocyanates from alkenes, thallium triacetate and a metal thiocyanate is shown in equation (15).

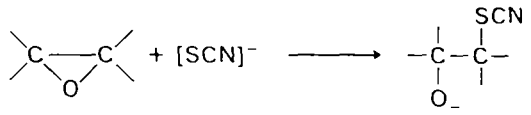


(15)

The reaction proceeds via oxythallation, replacement of an acetate ion with a thiocyanate ion, and dethallation, successively.

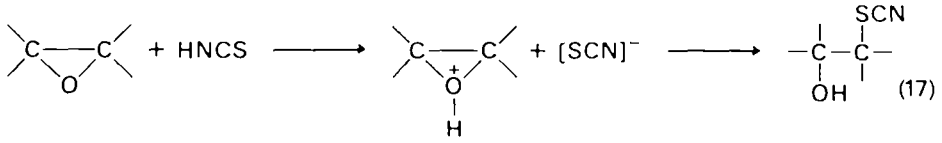
E. Epoxides, Aziridines, and Oxaziridines

The thiocyanato anion readily attacks epoxides, opening the ring in an S_N2 reaction, and giving vicinal thiocyanatoalkoxides[62] (equation 16)



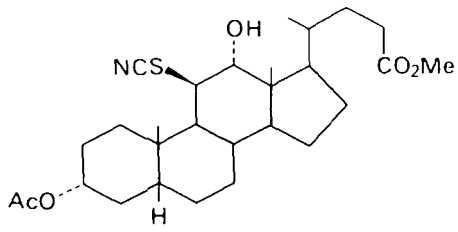
(16)

This alkoxide is rapidly converted into an episulphide (see Section VII.B.2.d). Under acid conditions, or by using a solution of isothiocyanic acid in ether or chloroform, the corresponding hydroxythiocyanate may be obtained[63] (equation 17).



(17)

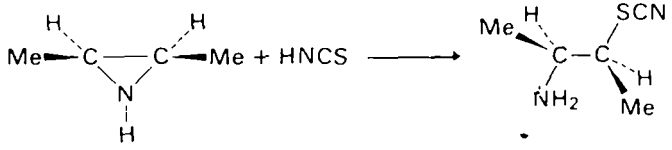
The *trans*-stereospecificity of this reaction has been confirmed in a variety of alicyclic[63] and steroidal[64] systems. In the latter case, addition is *trans*-diaxial; thus, methyl 3α-acetoxy-11α,12α-epoxycholanate gives compound **12**[64].



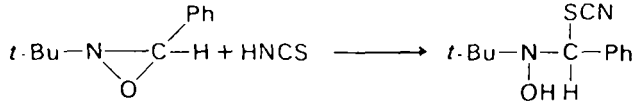
(12)

No isothiocyanate formation has been reported in these reactions, in keeping with the high k_S/k_N ratio expected for S_N2 reactions on the basis of the HSAB principle (see Section II.A).

This reaction has been applied similarly to aziridines[65] (equation 18) and oxaziridines[66] (equation 19), and the mechanism and stereochemistry discussed.



(18)



(19)

F. Alkenes

Isothiocyanic acid behaves as an electrophilic reagent towards alkenes under heterolytic conditions, adding across electron-rich double bonds in the same manner as the hydrogen halides. The additions are regiospecific, yielding the Markownikoff-orientated products. However, the products are either mixtures of thiocyanates and isothiocyanates, or isothiocyanates exclusively[67–70]. The reactions of 2-methylpropene[67] and styrene[68] are shown in equations (20) and (21) respectively.

$$Me_2C{=}CH_2 + HNCS \xrightarrow{Et_2O} t\text{-BuSCN} + t\text{-BuNCS} \quad (20)$$

$$PhCH{=}CH_2 + HNCS \xrightarrow{H_2O} PhCH(NCS)CH_3 \quad (21)$$

These results are consistent with the formation of a carbonium ion intermediate which reacts with the ambident thiocyanato anion (see equation 5) to give isothiocyanates preferentially according to the HSAB principles discussed in Section II.A. In the reaction shown in equation (20), the value of k_S/k_N for the *t*-butyl carbonium ion is 0·51. Comparison of this value with the values of 2 to 9 obtained in other solvents[25], and the value of 0·04 obtained in the metal-catalysed reaction of *t*-butyl bromide in di-*n*-butyl ether[23] (see Section II.A), shows clearly the effect of solvent and complex formation on the ambident reactivity of the thiocyanato anion.

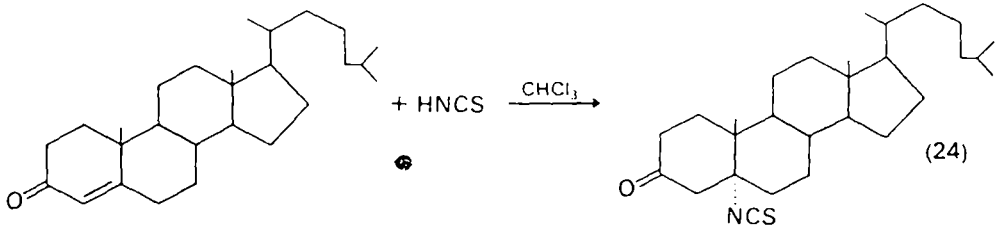
Attempts to add isothiocyanic acid homolytically to alkenes were unsuccessful[67].

G. α,β-Unsaturated Carbonyl Compounds

Isothiocyanic acid adds regiospecifically across the conjugated double bond of α,β-unsaturated carbonyl compounds yielding either thiocyanates, isothiocyanates or mixtures of the two according to the degree of substitution in the substrates. Typical reactions of α,β-unsaturated esters[68], acyclic ketones[71,72], and steroidal ketones[73,74] are shown in equations (22), (23), and (24) respectively.

$$CH_2{=}CHCO_2Me + HNCS \xrightarrow{H_2O} NCSCH_2CH_2CO_2Me \qquad (22)$$

$$R^1R^2C{=}CHCOR^3 + HNCS \xrightarrow{H_2O} R^1R^2C(NCS)CH_2COR^3 \qquad (23)$$

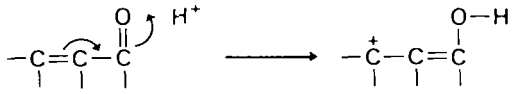


(24)

Addition to other steroidal ketones is non-stereospecific and gives both thiocyanato and isothiocyanato derivatives, with the latter predominating[74].

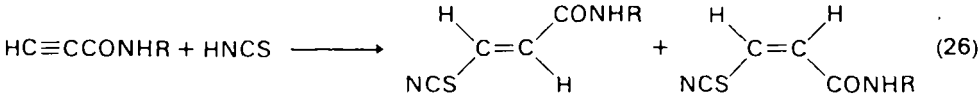
These results are consistent with carbonium ion formation as in equation (25), and with k_S/k_N ratios being determined by the HSAB

behaviour of primary, secondary and tertiary carbonium ions (see Section II.A).



(25)

Addition to propiolamides is regiospecific and *trans*-stereoselective, and yields the thiocyanato products exclusively[75] (equation 26), suggesting that primary vinylic carbonium ions, like the corresponding alkyl carbonium ions (see Table 2), prefer to react as soft acids on the HSAB principle.



(26)

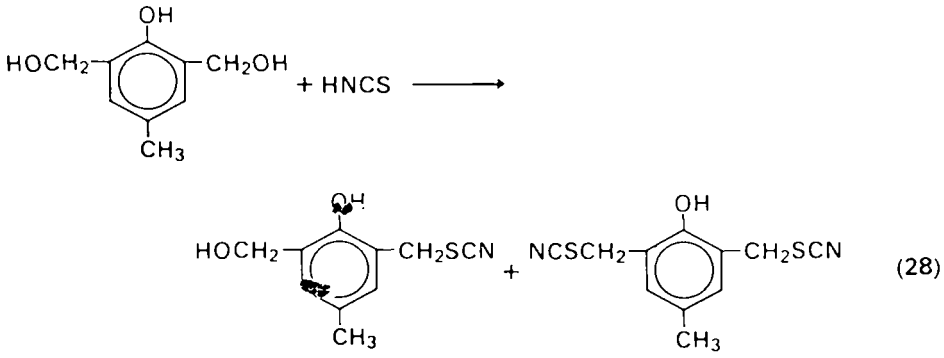
H. Miscellaneous Compounds

Isothiocyanic acid shows normal behaviour with nitrogenous bases, forming salts, some of which may be used for characterization purposes. Examples include quinolines[76], alkaloids[77], azines[78], and hydrazines[79].

Diazoketones react with isothiocyanic acid to form thiocyanatoketones[80] (equation 27).

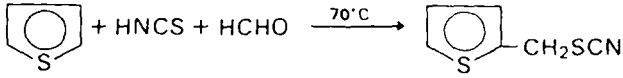
$$RCOCHN_2 + HNCS \longrightarrow RCOCH_2SCN + N_2 \qquad (27)$$

Alcohols react with isothiocyanic acid, probably via carbonium ion intermediates, to form thiocyanates, but the reaction has not been studied in depth. An example[81] is shown in equation (28).



(28)

Direct thiocyanomethylation of thiophen has recently been accomplished[16] (equation 29).



(29)

Some isothiocyanate is also formed in the reaction, but may be an isomerization product.

Valeryl peroxide, on treatment with cupric thiocyanate under mild conditions, gives a quantitative yield of *n*-butyl thiocyanate[82] (equation 30).

$$(n\text{-}BuCO_2)_2 + Cu(NCS)_2 \xrightarrow[0\,^\circ C]{MeCN} n\text{-}BuSCN + n\text{-}BuCO_2^- + CO_2 \qquad (30)$$

III. PREPARATION OF THIOCYANATES BY REACTION OF THIOCYANOGEN OR RELATED REAGENTS WITH ORGANIC COMPOUNDS

Thiocyanogen, $(SCN)_2$, and its halides, i.e. thiocyanogen chloride, bromide and iodide (XSCN: X = Cl, Br and I respectively), are pseudohalogen analogues of the halogens and interhalogens respectively. Following Soderback's pioneering work on thiocyanogen[83,84], these reagents have been widely used in the preparation of organic thiocyanates in essentially the same ways as the halogens, i.e. by addition and substitution reactions. Recent work has confirmed the halogen analogy by showing that the reactions may take place by either heterolytic or homolytic mechanisms. In this survey, the reactions of thiocyanogen and related reagents with organic compounds are accordingly interpreted in terms of heterolytic and homolytic reactions.

A. Thiocyanogen

Thiocyanogen is readily prepared in solution by a wide variety of methods[6], the customary laboratory ones being the reaction between bromine and an excess of (a) lead thiocyanate suspended in a dry, inert solvent, or (b) an alkali-metal thiocyanate dissolved in acetic acid (equation 31; M = metal).

$$2\,MSCN + Br_2 \longrightarrow (SCN)_2 + 2\,MBr \qquad (31)$$

The infrared[85] and Raman[86] spectra of the solutions show that thiocyanogen has the disulphide structure **13**.

$$N{\equiv}C{-}S{-}S{-}C{\equiv}N$$

(13)

Thiocyanogen is used in syntheses in essentially the same way as the halogens, with the exception that certain precautions must be observed owing to the relative instability of the reagent[6].

1. Heterolytic reactions

Under heterolytic conditions, thiocyanogen behaves as an electrophile, which undergoes heterolytic S–S bond fission. Due to the polarization $S^{\delta+}{-}C{\equiv}N^{\delta-}$ within each thiocyanato group, electrophilic attack on a nucleophile X: occurs via a sulphur atom of the thiocyanogen molecule and thus leads, via kinetic control of reaction, to the initial attachment of a thiocyanato group rather than an isothiocyanato group (equation 32).

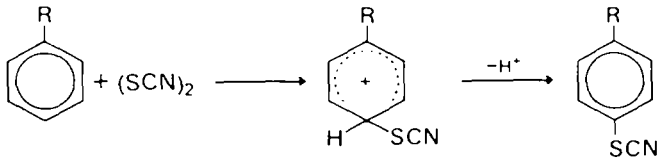
$$X: \curvearrowright \underset{\curvearrowright SCN}{SCN} \longrightarrow X^{+}{-}SCN + [SCN]^{-} \qquad (32)$$

In its heterolytic reactivity, thiocyanogen is intermediate between bromine and iodine[5,6], and thus its reactions are confined to electron-rich organic compounds with readily available π- or p-electrons. However, its reactivity is considerably enhanced by the use of typical Friedel–Crafts catalysts[87] which presumably increase the polarization of the S–S bond in **13**. Although only a few systems have been investigated, the results clearly indicate that the catalytic process could be used advantageously in cases where the less reactive molecular reagent fails.

Traditionally, these heterolytic reactions have been carried out in diffuse daylight or in darkness at 0–20 °C[5,6]. Such conditions, although satisfactory for the reactions of thiocyanogen with many organic compounds, have sometimes resulted in conflicting reports of reaction rates or products, or both. Recent work has shown that these anomalous results may be due to the incursion of a homolytic reaction (see Section III.A.2), which can, however, be completely suppressed by the addition of a radical inhibitor.

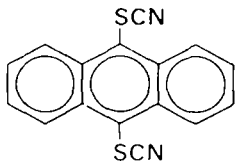
a. *Aromatic compounds.* Thiocyanogen reacts with aromatic compounds that are highly susceptible to electrophilic substitution with the

formation of aryl thiocyanates. No detailed mechanistic studies have been reported, but from the many qualitative observations[5-9] that electron-donating substituents increase, and electron-withdrawing substituents decrease, the reaction rate, and from the finding that the reaction with various phenols is bimolecular[88], the S_E2 mechanism in equation (33) seems to be appropriate.



(33)

Hydrocarbons of the benzene and naphthalene series do not react with thiocyanogen under heterolytic conditions[5-9] unless a Friedel–Crafts catalyst is added[87]. However, polynuclear hydrocarbons[89] react readily, and anthracene[89] and azulene[90] are sufficiently reactive to give the dithiocyanato derivatives **14** and **15** respectively.



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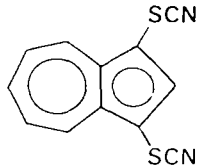
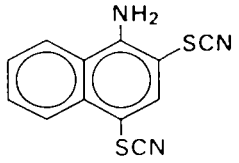


(15)

Primary, secondary, and tertiary amines of the benzene, naphthalene and anthracene series react readily and give high yields of product[5-9,91-93]. Thiocyanation occurs *para* to the amino group (equation 33; R = NH_2 etc.), or *ortho* if the *para* position is occupied; in the latter case, the rates and yields are generally lower, probably due to the steric requirements of the bulky thiocyanogen molecule, and cyclization to benzothiazoles or benzothiazolines commonly occurs (see Section VII.B.2). Di- and trisubstitution can be achieved if sufficient activating groups or rings are present; thus 1-naphthylamine[6] and 1,3,5-triaminobenzene[94] yield compounds **16** and **17** respectively.



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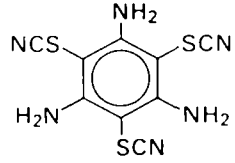
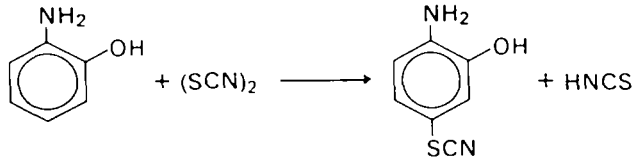


(17)

Thiocyanation of arylamines still proceeds if an electron-withdrawing group is present, but if two or more such groups are present, the reaction may be prevented[92]. Acylation of the amino group also prevents reaction[6].

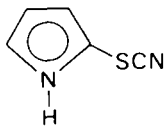
Phenols of the benzene, naphthalene, and anthracene series behave similarly[5–9,93,95,96], but are not so reactive as the analogous amines. Thus, in aminophenols, the amino group controls the orientation of attack[97] (equation 34).



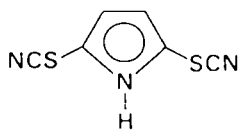
(34)

The presence of one or more electron-withdrawing groups, or alkylation of the hydroxyl group, slows down the reaction or may prevent it altogether[98]. However, improved yields may be obtained by the use of a Friedel–Crafts catalyst[87].

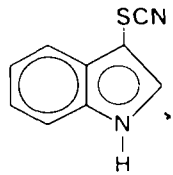
b. *Heteroaromatic compounds.* The common heteroaromatic compounds show the expected reactivities towards thiocyanogen. Thus, pyrrole readily yields the mono- or di-thiocyanato products **18** and **19** respectively[99], and indole gives compound **20** under very mild conditions[100].



(18)

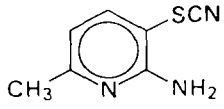


(19)



(20)

Thiophen gives a low yield of 2-thiocyanatothiophen with thiocyanogen[101], but good yields when the reaction is catalysed by aluminium trihalides[87,102], and 2,5-dithiocyanato derivative may also be prepared by this method[87]. Pyridines and pyrimidines react only when there are at least two electron-donating groups present in the ring; quinolines require at least one such group in the hetero-ring for reaction to occur[103–105]. For example, compounds **21** and **22** are readily prepared from the corresponding heterocycle and thiocyanogen under mild conditions.



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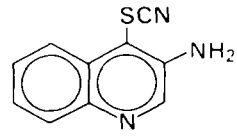
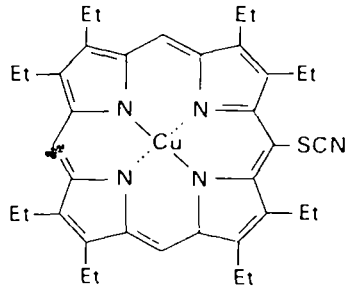


(22)

Other heterocycles which react with thiocyanogen include acridines[106], barbituric acids[107], carbazoles[108], imidazoles[109], indazoles[110], phenothiazines[111], pyrazolidines[112], pyrazolopyridines[113], quinazolones[114], tetrazoles[115], thiazoles[116], thiadiazoles[117], and triazoles[118].

c. *Metal complexes.* Metal complexes with a pseudo-aromatic ring are also readily thiocyanated. Thus copper complexes of porphyrins[119] yield *meso*-thiocyanates such as **23**, and metal acetylacetones[120–123] yield products of the type **24** [M = Al(III), Be(II), Cr(III), Co(III), Fe(III), Mn(III), Pd(II), Rh(III)], in which each of the ligands is thiocyanated.



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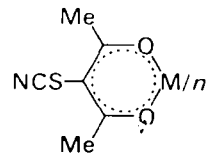
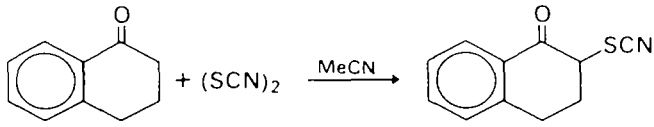


(24)

d. *Activated methylene compounds.* Compounds with activated methylene groups[5-9], e.g. ethyl acetoacetate[6], indandiones[124], and α-tetralone[125] (equation 35), react with thiocyanogen under, presumably, heterolytic conditions. The reaction probably proceeds via the enol tautomer in the manner well established for halogenation.



(35)

e. *Aliphatic amines.* Primary and secondary aliphatic amines yield the corresponding *N*-thiocyanato-amines (**25**) when treated with thiocyanogen[5-9,126] (equation 36).

$$2\ RR'NH + (SCN)_2 \xrightarrow{Et_2O} \underset{(25)}{RR'NSCN} + RR'NH_2^+[SCN]^- \qquad (36)$$

O,N-Disubstituted hydroxylamines react similarly[5-9].

f. *Sulphur compounds.* Thiocyanogen also forms *S*-thiocyanates with appropriate sulphur compounds[5-9]. Thus alkyl and aryl thiols[127] and thio-ethers[128] yield sulphenyl thiocyanates (**26**) (equation 37; X = H, trityl, benzhydryl, 2-tetrahydropyranyl, isobutyloxymethyl). Thio-acids react similarly[129].

$$RSX + (SCN)_2 \longrightarrow \underset{(26)}{RSSCN} + XSCN \qquad (37)$$

Sulphonyl thiocyanates (**27**) are readily prepared from thiocyanogen and sulphinates[130] (equation 38).

$$ArSO_2Na + (SCN)_2 \xrightarrow[0\ C]{CH_2Cl_2} \underset{(27)}{ArSO_2SCN} + NaSCN \qquad (38)$$

g. *Organo-metallic compounds.* Organo-mercury compounds react with thiocyanogen to give the corresponding thiocyanate[5-9] (equation 39; R = phenyl[83], ferrocenyl[131], 2-thienyl[132]).

$$R_2Hg + (SCN)_2 \longrightarrow RSCN + RHgSCN \quad (39)$$

Organo-zinc compounds behave similarly[83], but the yields are low. Benzylmagnesium chloride reacts with thiocyanogen to give *o*-thiocyanatotoluene; an intermediate cyclic complex has been postulated to account for this unexpected result[133].

h. *Alkenes.* Traditionally[5,6], thiocyanogen has been reported to react with alkenes by addition, yielding the corresponding α,β-dithiocyanates (equation 40; X = SCN)

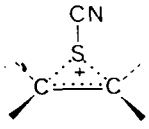
$$\text{>C=C<} + (SCN)_2 \longrightarrow -\overset{|}{\underset{X}{C}}-\overset{|}{\underset{SCN}{C}}- \quad (40)$$

Recent work has shown that this reaction, which is also important from an analytical viewpoint[134], is more complicated than indicated by equation 40, and can occur by both heterolytic and homolytic mechanisms (see Section III.A.2.b).

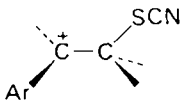
Under heterolytic conditions in benzene, thiocyanogen reacts slowly with electron-rich alkenes to yield α,β-dithiocyanates (equation 40; X = SCN) and the corresponding α-isothiocyanato-β-thiocyanates (equation 40; X = NCS) in various proportions[135]. The additions to alkyl alkenes and cycloalkenes are *trans*-stereospecific, and, in the case of the isothiocyanato-thiocyanates of unsymmetrical alkenes, non-regiospecific. In contrast, additions to alkenes with α-aryl substituents are *trans*-stereoselective and regiospecific. Some examples of these are shown in Table 3[135].

In acetic acid solvent, reactions are considerably faster, and the corresponding α-acetoxy-β-thiocyanates (equation 40; X = OAc) are also formed[135,136]. No addition occurs with alkenes containing electron-withdrawing substituents.

For aliphatic alkenes, a two-step, kinetically-controlled heterolytic addition involving (a) initial electrophilic attack of the alkene by thiocyanogen with the formation of a cyano-sulphonium ion (**28**), and (b) subsequent *trans*-diaxial opening of the sulphonium ring at either of the ring carbon atoms by the ambident thiocyanato anion **3** or by solvent molecules



(**28**)



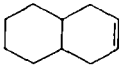
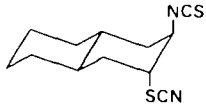
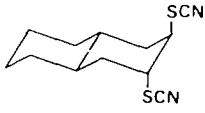
(**29**)

in acetic acid, has been postulated[135] to account for the observed *trans*-stereospecificity and non-regiospecificity of these reactions.

For the aryl alkenes, a similar mechanism, but with the formation of the more stable of the two possible open thiocyanato-carbonium ions (**29**), accounts for the observed non-stereospecificity and regiospecificity of these reactions. The observed preference for *trans*-addition is ascribed to steric control of reaction by the bulky thiocyanato group of the carbonium ion **29**[135].

The k_S/k_N ratios of these reactions (see Table 3) show the same range of values as those for other carbonium ion reactions (see Table 2), and are likewise consistent with the HSAB principles outlined in Section II.A.

TABLE 3. Heterolytic addition[a] of thiocyanogen to alkenes in benzene[135]

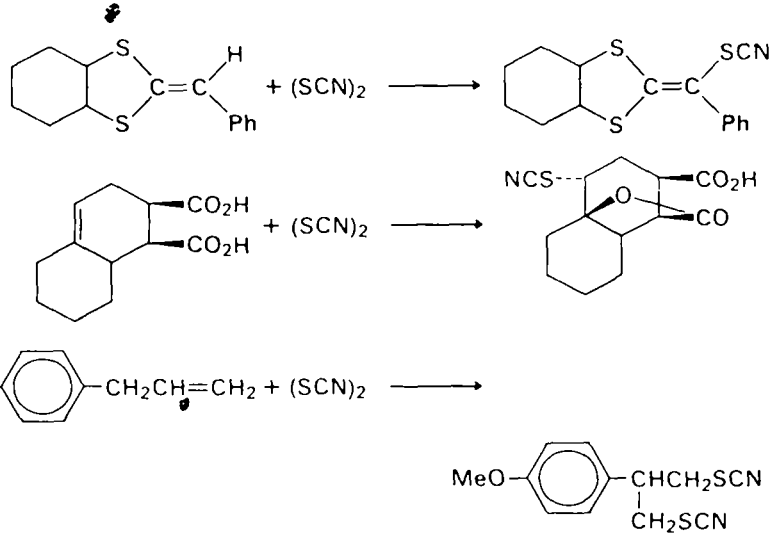
Alkene	Reaction time (h)	Products	Yield (%)	k_S/k_N
$Me_2C{=}CMe_2$	1	$Me_2C(NCS)C(SCN)Me_2$	60	0·50
		$Me_2C(SCN)C(SCN)Me_2$	30	
cis-*i*-PrCH=CHPr-*i*	168	*threo*-*i*-PrCH(NCS)CH(SCN)Pr-*i*	30	0·50
		(±)-*i*-PrCH(SCN)CH(SCN)Pr-*i*	15	
n-BuCH=CH_2	168	*n*-BuCH(NCS)CH_2SCN	27	1·5
		n-BuCH(SCN)CH_2NCS		
		n-BuCH(SCN)CH_2SCN	42	
	168		5	2·0
			10	
PhCH=CH_2	24	PhCH(NCS)CH_2SCN	22	2·0
		PhCH(SCN)CH_2SCN	44	
trans-PhCH=CHMe	168	*threo*-PhCH(NCS)CH(SCN)Me	2	0·66
		erythro-PhCH(NCS)CH(SCN)Me	10	
		threo-PhCH(SCN)CH(SCN)Me	2	
		erythro-PhCH(SCN)CH(SCN)Me	6	

[a] At room temperature in darkness and with added radical inhibitor.

Apart from those listed in previous reviews[5–9], many other alkenes[136,137], cycloalkenes[138–140], dienes[137,140], enols[141], enals[141], enones[141], enoic acids[137,141–143] and esters[136,142], unsaturated

carbohydrates[144], and ketene thioacetals[145] have been thiocyanated using thiocyanogen in the dark or, presumably, in diffuse light. Relative[141,146,147] and absolute[142] reaction rates have been measured under the same conditions.

Although the concurrent formation of isothiocyanato-thiocyanates has not been detected or reported in all but a few[136,137,144] of these thiocyanations, the reactions probably occur through the heterolytic mechanism described above, or an extension of it. Thus the products of the reactions shown in equations (41)[145], (42)[148], and (43)[149] are best explained respectively in terms of addition–elimination, neighbouring group participation, and rearrangement variations of the basic heterolytic mechanism.



It must be emphasized, however, that competing, or even dominant, homolytic reactions cannot be ruled out under these conditions (see Section III.A.2.b), and, since the reports of isolation and identification of products are often too incomplete to make an informed choice of mechanisms on the basis of the products, many reactions, particularly those involving rate data, may need to be reassessed under strictly heterolytic conditions. Similar comments apply to these reactions when used in the determination of the 'thiocyanogen number' of alkenes[134]. This is a notoriously fickle estimation, and the lack of reproducibility, which has been ascribed to many factors (including the latitude of the laboratory in which the determination is carried out), may be due, at least in part, to the incursion of a radical process.

The low yields and relatively large amounts of isothiocyanato-thiocyanates shown in Table 3 may be considerably altered by the addition of catalytic amounts of metals[150] (see Table 4). These results may be explained by (a) reaction of thiocyanogen with the metal to give N-bonded

TABLE 4. Effect of metals[a] on the heterolytic addition of thiocyanogen to cyclohexene[150]

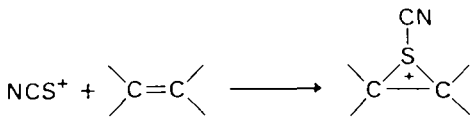
Solvent	Metal	Yield (%)			k_S/k_N[b]
					
C_6H_6	—	7	5	—	1·4
	Fe	17	4	—	4·2
	Zn	32	4	—	8·0
	Sn	47	2	—	23·5
CCl_4	—	2	2	—	1·0
	Fe	4	2	—	2·0
	Zn	7	2	—	3·5
	Sn	4	3	—	1·3
AcOH	—	27	11	10	2·5
	Fe	38	5	9	7·6
	Zn	51	0	13	>51
	Sn	26	8	14	3·2

[a] 5% based on the thiocyanogen concentration.
[b] Based on the *trans*-dithiocyanate/*trans*-isothiocyanato-thiocyanate product ratio.

metal thiocyanates[14] (equation 44) which polarize or ionize the remaining reagent molecules by acting as Friedel–Crafts catalysts (equation 45), thus speeding up electrophilic attack on the alkene (equation 46), and (b) preferential attack of the carbonium ion at the sterically more accessible sulphur atom in the complex counter-ion (equation 47).

$$M + n(SCN)_2 \longrightarrow M(NCS)_{2n} \quad (44)$$

$$NCS{-}SCN + M(NCS)_{2n} \longrightarrow NCS^+ + [M(NCS)_{2n+1}]^- \quad (45)$$



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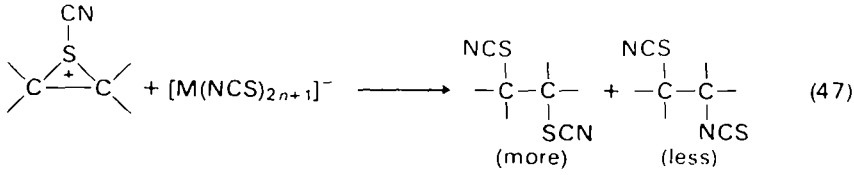
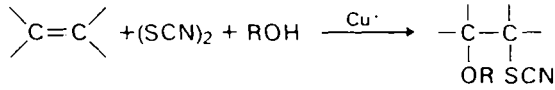


(47)

Friedel–Crafts catalysis by copper(I) salts has likewise been postulated in the direct alkoxythiocyanation of alkenes[151] (equation 48).

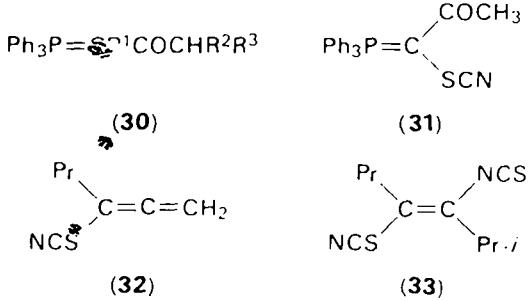


(48)

Vinyl acetates, alkyl vinyl ethers, and α,β-unsaturated aldehydes also react, the products being obtained in the form of dialkyl acetals.

i. *Alkynes.* The general comments made in the previous section apply to the literature reports on the reaction of thiocyanogen with alkynes. Thus the reported ready addition to mono- and di-substituted alkynes[5–9] in darkness or diffuse light has been shown to be due to the incursion of a homolytic reaction (see Section III.A.2.d); when carried out under strictly heterolytic conditions, e.g. in the presence of a radical inhibitor, the additions are considerably slower than to the corresponding alkenes (in keeping with heterolytic additions of the halogens), and the yields are consequently extremely small[152]. By analogy with their effect on additions to alkenes (see previous section), Friedel–Crafts catalysts should prove useful in these cases.

j. *Phosphoranes.* Triphenyl-β-oxoalkylenephosphoranes (**30**) react readily with thiocyanogen giving various products.



Thus, the unsubstituted compound **30** ($R^1 = R^2 = R^3 = H$) gave the phosphorane derivative **31**, whereas the substituted phosphoranes **30** (R^1 = Pr, $R^2 = R^3 = H$) and **30** (R^1 = Pr, $R^2 = R^3$ = Me) gave the

allenic thiocyanate (**32**) and the *trans*-α-isothiocyanato-β-thiocyanato-alkene (**33**) respectively. A heterolytic mechanism involving electrophilic attack by thiocyanogen on the P=C bond has been suggested[153].

2. Homolytic reactions

The S–S bond of thiocyanogen (**13**) is readily broken homolytically[154], giving resonance-stabilized thiocyanato radicals (**34a**) ↔ (**34b**) to which the canonical form (**34a**) makes the main contribution[155].

$$\dot{S}-C\equiv N \longleftrightarrow S=C=\dot{N}$$

(**34a**) (**34b**)

This homolysis is readily effected not only by ultraviolet light from mercury-vapour lamps, but also by sunlight or even diffuse light. Furthermore, in the dark, radicals from the breakdown of peroxides, present in the reactants or formed *in situ* by the action of atmospheric oxygen, can also effect homolysis[156] (equation 49).

$$R^{\bullet} + (SCN)_2 \longrightarrow RSCN + [SCN]^{\bullet} \qquad (49)$$

Thiocyanogen can thus act as a source of thiocyanato radicals under very mild conditions.

Bacon and Guy and their coworkers have shown that thiocyanato radicals can initiate radical chain reactions in essentially the same way as the halogens, i.e. by substitution and addition. In these reactions the thiocyanato radical behaves as an electrophilic, or acceptor, radical, which is considerably less reactive than the corresponding halogen atoms (see Table 5). Reaction is thus restricted to systems highly susceptible to radical attack, e.g. benzylic and allylic hydrogen atoms, and π-electron systems.

TABLE 5. Electron affinities of various radicals[157]

Radical	$Cl^{\bullet}$	$Br^{\bullet}$	$I^{\bullet}$	$[SCN]^{\bullet}$
Electron affinity (kJ mol^{-1})	365	344	311	220

a. *Aralkanes.* When irradiated with ultraviolet light, thiocyanogen reacts with primary α-hydrogen atoms of aralkyl hydrocarbons yielding the corresponding thiocyanates[22] (equation 50; R = R^1 = H).

$$ArCHR^1R^2 + (SCN)_2 \xrightarrow{h\nu} ArC(SCN)R^1R^2 + HNCS \qquad (50)$$

The mechanism suggested involves a radical-chain reaction of the type well-known for photohalogenation (equations 51 and 52).

$$ArCHR^1R^2 + [SCN]^{\bullet} \longrightarrow Ar\dot{C}R^1R^2 + HNCS \quad (51)$$

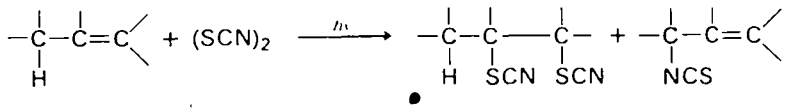
$$Ar\dot{C}R^1R^2 + (SCN)_2 \longrightarrow ArC(SCN)R^1R^2 + [SCN]^{\bullet} \quad (52)$$

Formation of the thiocyanate, rather than the isothiocyanate, in reaction (52) may be attributed to kinetically-controlled S_H2 attack of the nucleophilic, or donor, aralkyl radical on the position of lowest electron density in the thiocyanogen molecule, i.e. the sulphur atom. This is also consistent with the HSAB principles outlined in Section II.A.

Reaction with secondary α-hydrogen atoms proceeds similarly, but reaction with tertiary α-hydrogen atoms leads to mixtures of the corresponding thiocyanates and isothiocyanates, or exclusively to isothiocyanates[22]. This may occur through secondary, thermodynamically-controlled isomerization reactions (see Section VI.B). However, if it is a kinetically-controlled reaction, then the increased tendency to form isothiocyanate may be explained on the HSAB basis (see Section II.A), if the hardness of radicals follows the same order as carbonium ions, i.e. primary < secondary < tertiary, and thus increases the tendency of tertiary radicals to attack the nitrogen atoms of the thiocyanogen molecule. Alternatively, the main factor may be a steric one, with primary, secondary, and tertiary radicals finding it progressively more difficult to attack the central sulphur atoms of the bulky thiocyanogen molecule.

b. *Alkenes.* The stimulus which sunlight or irradiation from a lamp has on the reaction of thiocyanogen with alkenes was noticed as early as 1925[84]. However, this observation was not exploited until recently, when it was shown that such reactions are homolytic, differing significantly from the heterolytic reactions described in Section III.A.1.h. in their rates, stereochemistry and the nature of the products[154,156,158].

Under the influence of ultraviolet light[154,156,158] or peroxide initiators[154,156,159] thiocyanogen reacts rapidly with alkenes to yield either α,β-dithiocyanates or allylic isothiocyanates or mixtures of the two, the relative amounts of each depending on the structure of the alkene (equation 53).

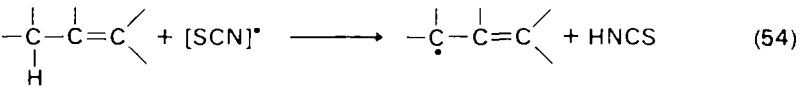


(53)

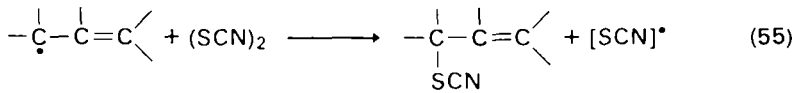
Apart from 3-methylbut-1-ene, which yields both products, acyclic terminal alkenes of the type $RCH=CH_2$ and $R^1R^2C=CH_2$ yield the dithiocyanates exclusively. In contrast, the reaction with alkenes of the

type RCH=CHR is dependent on the nature of the substituents R. Reaction may lead to (a) complete and non-stereospecific addition, e.g. *cis*- and *trans*-but-2-ene (R = Me) give identical mixtures of (±)- and *meso*-MeCH(SCN)CH(SCN)Me exclusively; (b) a combination of non-stereospecific addition, allylic substitution and *cis–trans* isomerization, e.g. *cis*- and *trans*-hex-3-ene (R = Et) give identical mixtures of (±)- and *meso*-EtCH(SCN)CH(SCN)Et and *trans*-MeCH(NCS)CH=CHEt (c) a combination of allylic substitution (with subsequent allylic rearrangement) and *cis–trans* isomerization, e.g. *cis*- and *trans*-2,5-dimethylhex-3-ene (R = *i*-Pr) give identical mixtures of *trans*-$Me_2C(NCS)CH{=}CHPr$-*i* and $Me_2C{=}CHCH(NCS)Pr$-*i*; and (d) *cis–trans* isomerization exclusively, e.g. *cis*- and *trans*-dichloroethylene (R = Cl) each give the equilibrium mixture of the alkenes. In the cyclohexene series, addition and allylic substitution generally occur together; the addition, however, is stereospecifically *trans*, e.g. cyclohexene gives *trans*-1,2-dithiocyanatocyclohexane and 3-isothiocyanatocyclohexene, and *trans*-Δ^2-octalin gives 2*a*,3*a*-dithiocyanato-*trans*-decalin and 3-isothiocyanato-*trans*-Δ^1-octalin. The position of substituents can alter the addition:substitution ratio markedly; e.g. the ratios for 4-methyl-, 3-methyl-, and 1-methyl-cyclohexene are 1:1·7, 1:23 and 1:3·8 respectively[158]. No addition occurs to sterically hindered alkenes, although allylic substitution may occur, as in the case of cholesterol[160].

These results have been rationalized[154,158] in terms of two competing radical-chain reactions similar to those involved in homolytic halogenation of alkenes. Radical attack at the susceptible allylic hydrogen atom leads to an allylic thiocyanate (**35**) (equations 54 and 55). Compound **35** may be isolated under favourable conditions but normally undergoes spontaneous isomerization to an isothiocyanate (see Section VI.B.2).



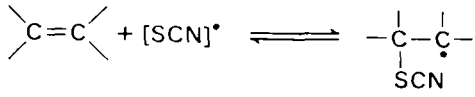
(54)



(55)

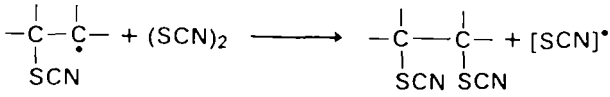
(35)

Radical attack at the double bond occurs via the two kinetically-controlled reactions shown in equations (56) and (57).



(56)

(36)



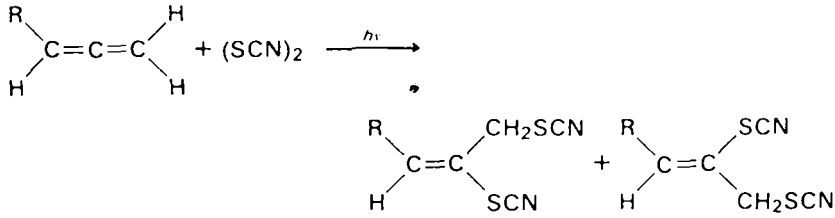
(57)

The reversible addition of the thiocyanato radical in (56) accounts for the *cis–trans* isomerizations observed in both starting materials and products, while the open radical **36** accounts for the stereochemical results obtained in the acyclic systems.

The stereospecific additions observed in the cyclohexene systems are attributed to conformational effects in the intermediate cyclohexyl radical and the steric requirements of the bulky thiocyanogen molecule in the transfer step (equation 57). This steric requirement is clearly larger than that of the thiocyanato anion (**3**) in the corresponding heterolytic additions (see Section III.A.1.h), and is responsible for the marked difference in reactivity of thiocyanogen towards hindered alkenes, e.g. 2,5-dimethylhex-3-ene (see above and Table 3), under homolytic and heterolytic conditions.

Isothiocyanato-thiocyanates have been observed in only a few cases. Thus, *cis*- and *trans*-stilbene each yield identical mixtures not only of the expected *meso*- and (±)-dithiocyanates but also the *threo*- and *erythro*-α-isothiocyanato-β-thiocyanate, the k_S/k_N ratio being 5. These results are consistent with either the HSAB or the steric hindrance theories outlined in Section III.A.2.a.

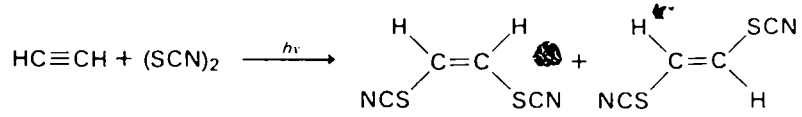
c. *Allenes.* A similar homolytic mechanism accounts for the photoaddition of thiocyanogen to allenes[161], which gives mixtures of 2,3-dithiocyanatopropenes as products (equation 58).



(58)

d. *Alkynes.* Equimolar amounts of thiocyanogen and acetylene react readily under the influence of light[84,152] or peroxides[162] yielding a

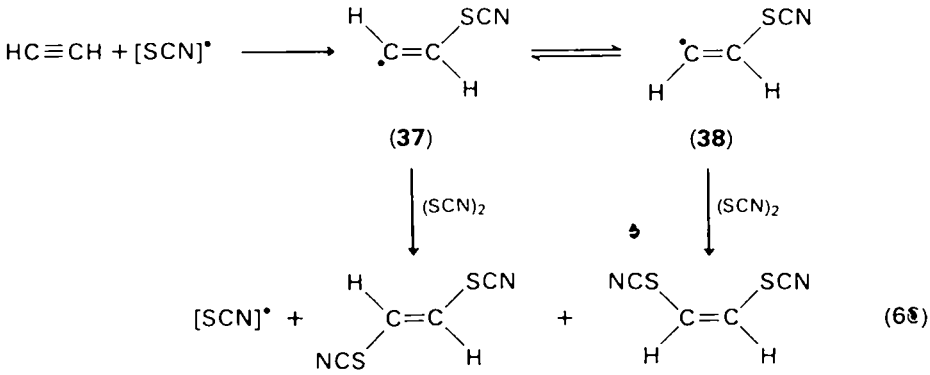
mixture of *cis*- and *trans*-dithiocyanatoethylene in the ratio 5:95[152] (equation 59).



(59)

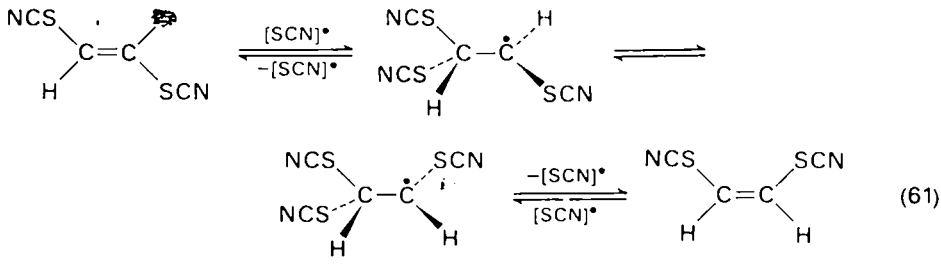
With excess reagent and prolonged irradiation, no further addition occurs, but the product ratio reaches an equilibrium value of *cis*:*trans* = 20:80[84,152]. The same equilibrium mixture can be achieved by irradiation of either isomer in the presence of a trace of thiocyanogen.

The homolytic mechanism proposed[152] is shown in equation (60).



(60)

In the pair of equilibrating vinyl radicals **37** and **38**, S_H2 displacement on thiocyanogen is sterically favoured for isomer **37**, thus leading to preferential, kinetically-controlled formation of the *trans*-dithiocyanate. Subsequent reversible addition of thiocyanato radicals to the alkenic products leads, via *trans*–*cis* isomerization, to the equilibrium mixture (equation 61).



(61)

Similar results have been obtained with mono- and di-substituted alkyl and aryl alkynes, but, due to the additional steric effects of the substituents on the corresponding pairs of vinyl radicals, the ratios of the *cis*- and *trans*-dithiocyanato products differ considerably[152].

B. Thiocyanogen Chloride

Thiocyanogen chloride is prepared rapidly and practically quantitatively by mixing equimolar amounts of thiocyanogen and chlorine in dry, inert organic solvents[163] (equation 62).

$$Cl_2 + (SCN)_2 \longrightarrow 2\,ClSCN \tag{62}$$

A useful alternative method[164] is shown in equation (63).

$$2\,Cl_2 + Pb(SCN)_2 \xrightarrow{AcOH} 2\,ClSCN + PbCl_2 \tag{63}$$

The infrared[165] and ultraviolet spectra[166] of the solutions show that the reagent has the structure Cl—S—C≡N, and that it is not detectably in equilibrium with chlorine and thiocyanogen.

Thiocyanogen chloride resembles thiocyanogen in its reactions with organic compounds, but shows marked differences in reactivity which make it a valuable complementary thiocyanating agent.

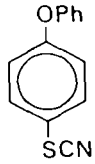
1. Heterolytic reactions

Under heterolytic conditions, thiocyanogen chloride is a stronger electrophilic thiocyanating agent than thiocyanogen (see Section III.A.1) due to polarization of the Cl–S bond in the manner $Cl^{\delta-}—^{\delta+}SCN$. Its reactivity is comparable with that of iodine chloride.

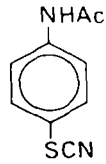
a. Aromatic compounds. In aromatic substitution processes thiocyanogen chloride yields aryl thiocyanates exclusively according to equation (64).

$$ArH + ClSCN \longrightarrow ArSCN + HCl \tag{64}$$

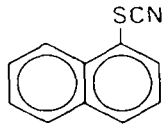
It reacts readily with mononuclear aryl ethers and anilides[164], naphthalene, alkyl naphthalenes, and alkyl benzenes containing two or more alkyl groups[20,21], which are unreactive towards thiocyanogen. The products **39**, **40**, **41**, and **42** are obtained in good yield from diphenyl ether, acetanilide, naphthalene and *m*-xylene respectively.



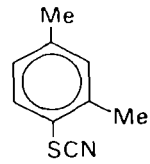
(39)



(40)



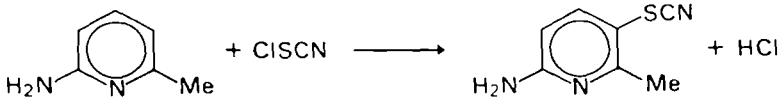
(41)



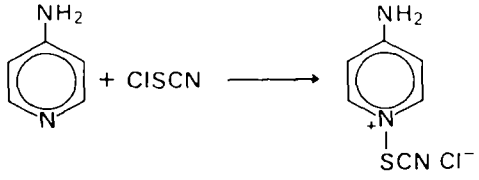
(42)

The reagent is less reactive, however, than thiocyanogen activated by a Friedel–Crafts catalyst[87], since thiocyanogen chloride does not attack benzene or toluene.

b. *Heteroaromatic compounds.* Thiocyanogen chloride reacts rapidly with pyrrole and thiophen in acetic acid to give the corresponding 2,5-dithiocyanates in good yield, but no further substitution occurs with excess reagent. Pyridines and quinolines with electron-donating substituents can react in two ways, giving either nuclear thiocyanates (equation 65) or ionic *N*-thiocyanato chlorides[67] (equation 66).



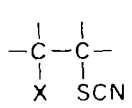
(65)



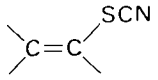
(66)

The stability of the ionic products varies widely and, in general, is less than that of the corresponding compounds of iodine chloride.

c. *Alkenes.* Thiocyanogen chloride reacts readily with alkyl[168] and aryl[169] alkenes under heterolytic conditions in acetic acid solvent to yield α-chloro-β-thiocyanates (**43**; X = Cl), α-acetoxy-β-thiocyanates (**43**; X = OAc) and, in appropriate cases, vinyl thiocyanates (**44**).



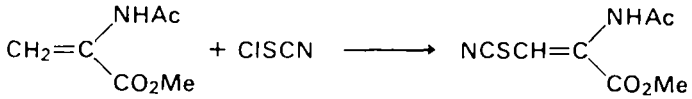
(43)



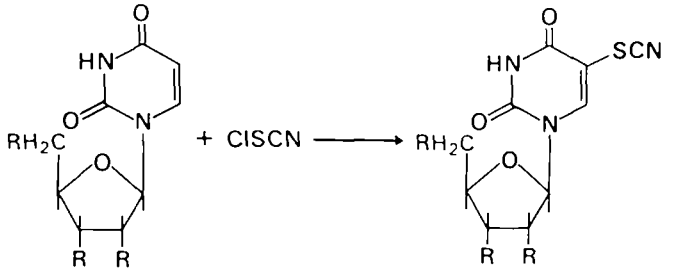
(44)

Again, the reaction rates are considerably greater than those of the corresponding additions of thiocyanogen, but otherwise the general features of the reactions are very similar, e.g. the additions to alkyl alkenes are *trans*-stereospecific[168] and non-regiospecific[170], the additions to aryl alkenes are *trans*-stereoselective[169] and regiospecific yielding the Markownikoff-oriented products exclusively[170], the reaction rate increases with increasing solvating power of the solvent, and one or more electron-withdrawing groups on the alkene prevent reaction. Consequently, these reactions of thiocyanogen chloride have also been interpreted in terms of the cyano-sulphonium ion (**28**) for alkyl alkenes, and the open carbonium ion (**29**) for aryl alkenes. Ion-pairing has been postulated to account for the different ratios of products obtained from *cis*- and *trans*-stilbene[169].

Thiocyanogen chloride also reacts with acrylic acid derivatives[171] and pyrimidine nucleosides[172] to yield the corresponding Markownikoff-oriented vinyl thiocyanates (equations 67 and 68 respectively).

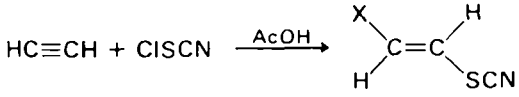


(67)



(68)

d. *Alkynes.* Heterolytic addition of thiocyanogen chloride to alkynes is considerably slower than to alkenes (cf. thiocyanogen) and yields the corresponding vinyl products; no further addition occurs with excess reagent. The addition to acetylene is *trans*-stereospecific (equation 69; X = Cl, OAc), whereas that to phenylacetylene is non-stereospecific but regiospecific[173] (equation 70; X = Cl, OAc).



(69)

$$PhC{\equiv}CH + ClSCN \xrightarrow{AcOH} \underset{Ph}{\overset{X}{\diagdown}}C{=}C\underset{SCN}{\overset{H}{\diagup}} + \underset{Ph}{\overset{X}{\diagdown}}C{=}C\underset{H}{\overset{SCN}{\diagup}} \qquad (70)$$

2. Homolytic reactions

Thiocyanogen chloride readily undergoes homolytic fission of the Cl–S bond either on irradiation (equation 71) or on attack by a radical[154] (equation 72).

$$ClSCN \xrightarrow{h\nu} Cl^{\bullet} + [SCN]^{\bullet} \qquad (71)$$

$$R^{\bullet} + ClSCN \longrightarrow RSCN + Cl^{\bullet} \qquad (72)$$

In the reaction shown in equation (71), ultraviolet light is normally used, but, as with thiocyanogen (see Section III.A.2.b), diffuse daylight is sufficient to cause the homolysis, and thus thiocyanogen chloride can act as a source of chlorine atoms and thiocyanato radicals under mild conditions[21]. Although the chlorine atom is the more reactive species (see Table 5), each of the radicals produced in (71) is capable of initiating chain reactions. However, in the reaction shown in equation (72), S_H2 attack by the donor radical $R^{\bullet}$ occurs exclusively on the electron-deficient sulphur of the thiocyanogen chloride molecule, thus giving a thiocyanato product and a chlorine atom as the sole chain carrier.

a. *Aralkanes.* Thiocyanogen chloride reacts with primary α-hydrogen atoms of aralkyl hydrocarbons on irradiation, yielding α-thiocyanato products exclusively[20,21] (equation 73; $R^1 = R^2 = H$).

$$ArCHR^1R^2 + ClSCN \xrightarrow{h\nu} ArC(SCN)R^1R^2 + HCl \qquad (73)$$

The suggested mechanism is shown in equations (74) and (75).

$$ArCHR^1R^2 + Cl^{\bullet} \longrightarrow Ar\dot{C}R^1R^2 + HCl \qquad (74)$$

$$Ar\dot{C}R^1R^2 + ClSCN \longrightarrow ArC(SCN)R^1R^2 + Cl^{\bullet} \qquad (75)$$

The reactions are generally faster and give higher yields than the corresponding reactions of thiocyanogen (see Section III.A.2.a); thus 1-methylnaphthalene gives a 78% yield of 1-thiocyanatomethylnaphthalene in 1·5 h with thiocyanogen chloride, and a 50% yield in 3 h with thiocyanogen[21]. This may be due to the relative reactivity of thiocyanato radicals and chlorine atoms in reactions (51) and (74) respectively, or to the relative steric effects of thiocyanogen and thiocyanogen chloride in the transfer steps (52) and (75) respectively.

Aralkanes with secondary α-hydrogen atoms also yield thiocyanates, but those with tertiary α-hydrogen atoms yield mixtures of the corresponding thiocyanates and isothiocyanates, or isothiocyanates exclusively. This behaviour may be rationalized in the same way as for thiocyanogen.

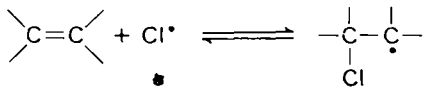
b. *Alkenes.* Alkenes unreactive towards thiocyanogen chloride under heterolytic conditions, e.g. vinylidene chloride, *cis*- and *trans*-dichloroethylene, cinnamic acid and methyl acrylate, add the reagent readily when irradiation is used, and yield α-chloro-β-thiocyanates[173]. The addition is predominantly anti-Markownikoff, e.g. vinylidene chloride reacts according to equation (76); it is also non-stereospecific, e.g. *trans*-cinnamic acid reacts according to equation (77).

$$CH_2{=}CCl_2 + ClSCN \xrightarrow{h\nu} \underset{(93\%)}{ClCH_2CCl_2SCN} + \underset{(7\%)}{CCl_3CH_2SCN} \qquad (76)$$

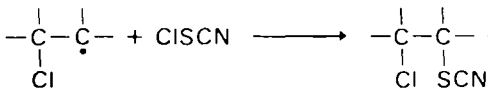
$$\textit{trans}\text{-}PhCH{=}CHCO_2H + ClSCN \xrightarrow{h\nu} \textit{threo}\text{- and }\textit{erythro}\text{-}PhCH(SCN)CHClCO_2H \qquad (77)$$

trans-Dithiocyanatoethylene is isomerized to the equilibrium mixture of *cis*- and *trans*-dithiocyanatoethylene.

These results may be rationalized in terms of the mechanism shown in equations (78) and (79),



(78)



(79)

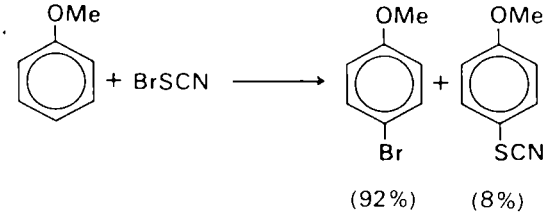
with the preferential anti-Markownikoff addition occurring via the more stable of the two possible open chloroalkyl radicals in (78). The greater reactivity of thiocyanogen chloride over that of thiocyanogen (see Section III.A.2.b) in homolytic addition reactions is attributable to the relative steric effects in the transfer steps (57) and (79).

C. Thiocyanogen Bromide

Thiocyanogen bromide has the polarized structure $\overset{\delta-}{Br}{-}\overset{\delta+}{SCN}$[165,174] but its value as an electrophilic thiocyanating agent is severely limited by its dissociation in organic solvents[165] (equation 80).

$$2\,BrSCN \rightleftharpoons Br_2 + (SCN)_2 \qquad (80)$$

Bromine is the most reactive component in the system, and thus heterolytic substitution reactions of thiocyanogen bromide with organic compounds produce mixtures of brominated and thiocyanated products with the former predominating, as illustrated in equation (81)[174].



(81)

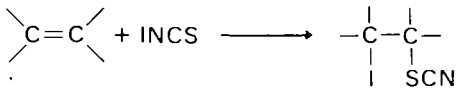
No homolytic work has been reported, but clearly similar difficulties would be encountered.

D. Iodine Thiocyanate

On the basis of its infrared spectrum[165] and the relative electronegativities[1] of the iodo and thiocyanato groups, the most likely structure for iodine thiocyanate is $\overset{\delta+}{I}-\overset{\delta-}{N}CS$. It is even more extensively dissociated in organic solvents (equation 82) than thiocyanogen bromide[165].

$$2\,INCS \rightleftharpoons I_2 + (SCN)_2 \qquad (82)$$

The most reactive component in the equilibrium (82) appears to depend on the type of reaction involved[175]. In aromatic substitution reactions the most reactive component appears to be thiocyanogen (see Section III.A.1.a) since, with arylamines and phenols, the products are either aryl thiocyanates or mixtures of aryl thiocyanates and iodides, with the former predominating[176]. On the other hand, alkenes appear to react preferentially with iodine thiocyanate, giving labile addition products which are stated to be α-iodo-β-thiocyanates[177] (equation 83). Alkynes behave similarly[178].



(83)

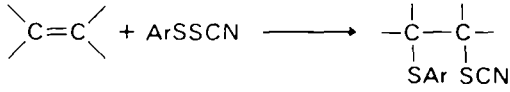
However, the possibility of concurrent formation of the corresponding

isothiocyanate (cf. thiocyanogen additions in Section III.A.1.h) has not been excluded by, for example, spectral examination of the products.

The kinetics and activation parameters of the addition reactions have been measured for a large range of alkenes, and indicate an electrophilic addition; the addition rates to substituted styrenes show good correlation with the Hammett equation, while those for acyclic aliphatic alkenes correlate with the Taft equation[179].

E. Aryl Sulphenyl and Sulphonyl Thiocyanates

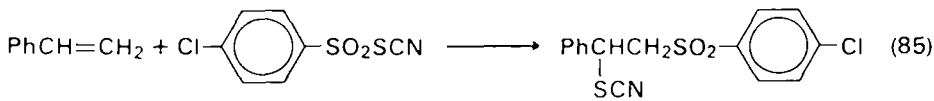
Aryl sulphenyl thiocyanates are stated to react smoothly with alkenes to give the corresponding α-arylthio-β-thiocyanates[44] (equation 84); spectral confirmation of the thiocyanato structure is, however, lacking.



(84)

The mechanism of the reaction has not been established, but the observation that the addition is *trans*-stereospecific suggests, by analogy with thiocyanogen (see Section III.A.1.h), that it is a heterolytic one.

The corresponding sulphonyl thiocyanates add to alkenes and alkynes in the presence of a radical initiator to give α-thiocyanato-β-sulphones[130]. The orientation of addition to styrene (equation 85) suggests that sulphonyl radicals, rather than thiocyanato radicals, are the chain carriers (cf. thiocyanogen chloride in Section III.B.2.b) in this homolytic addition reaction.



(85)

(45)

The interesting observation was also made that compound **45** reacts with diazomethane by insertion to give $4\text{-}ClC_6H_4SO_2CH_2SCN$[130].

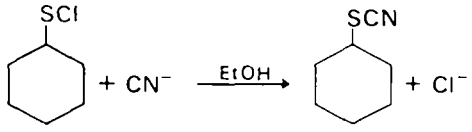
IV. PREPARATION OF THIOCYANATES BY CYANATION OF ORGANO-SULPHUR COMPOUNDS

In these reactions, thiocyanates are synthesized by cyanation of appropriate organo-sulphur compounds, i.e. by the formation of the S–CN bond. The most common cyanating agents are the cyanide ion and the cyanogen halides; more recently, 2-nitro-5-thiocyanatobenzoic acid has been used, particularly in biological systems. The obvious advantage of this method is the avoidance of simultaneous formation of the corresponding isothiocyanates (see Sections II and III), although subsequent isomerization may still take place in some cases (see Section VI.B).

These reactions have been comprehensively reviewed recently[9], and so only a brief account is given below.

A. Cyanide Ion

Cyanide ion reacts with organo-sulphur compounds containing stable leaving groups with the formation of thiocyanates by nucleophilic displacement on sulphur. The method has been applied to sulphenyl halides[121,180] (equation 86), sulphenyl thiocyanates[181] (equation 87), thiosulphates[182] (equation 88), and disulphides[183,184] (equation 89).



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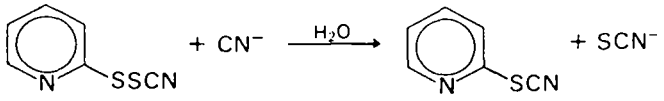

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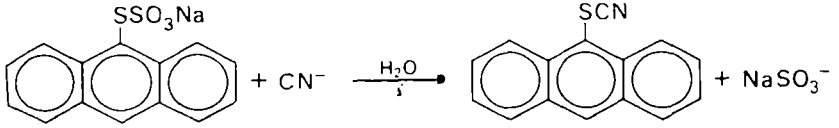
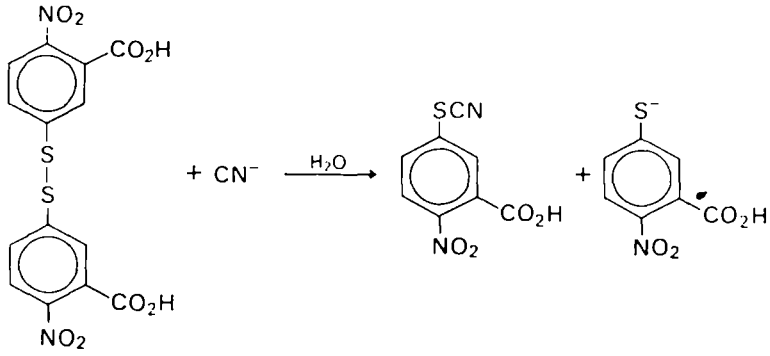


(88)

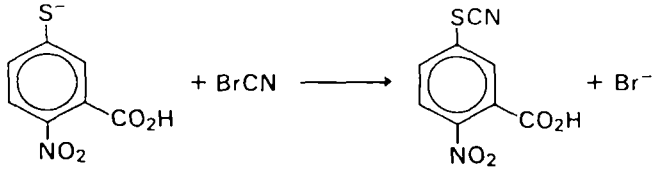


(89)

(45)

B. Cyanogen Halides

Organo-sulphur compounds can displace the halide ion from cyanogen chloride, bromide, or iodide with the formation of the corresponding thiocyanate. The method has been applied to thiols in either acidic[185] or alkaline[186] solutions. A recent example is shown in equation (90)[183]; by applying reactions (89) and (90) successively, an almost quantitative yield of **46** may be obtained from the disulphide **45**[183].



(90)

(46)

Metal thiolates may also be used[67,181]; thus *t*-butyl thiocyanate is formed on reaction of the lead thiolate with cyanogen chloride[67], and acetylenic thiocyanates have recently been prepared in the two-step reaction shown in equation (91)[187].

$$RC{\equiv}CLi \xrightarrow[\text{(b) ClCN}]{\text{(a) S}} RC{\equiv}CSCN + LiCl \qquad (91)$$

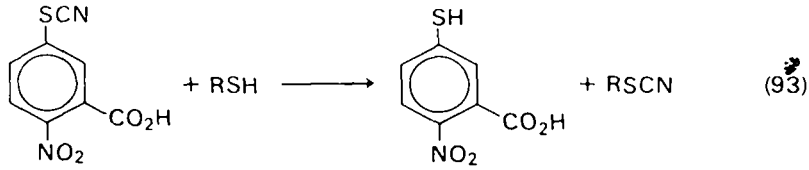
Cyanogen bromide also cleaves sulphides according to equation (92).

$$RSR + BrCN \longrightarrow RSCN + RBr \qquad (92)$$

The factors controlling the cleavage of unsymmetrical sulphides have been discussed[188].

C. 2-Nitro-5-thiocyanatobenzoic Acid

2-Nitro-5-thiocyanatobenzoic acid (**46**) is a remarkably mild and selective cyanating agent for thiols[189] (equation 93). Its reactivity is due to the ease of displacement of the 4-nitrothiophenolate anion, which is a very good leaving group with respect to sulphur nucleophiles.



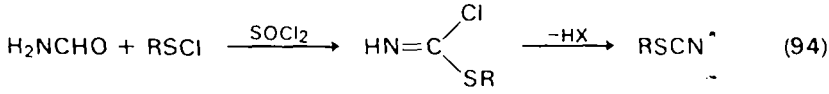
(93)

(**46**)

V. PREPARATION OF THIOCYANATES BY MISCELLANEOUS METHODS

In this section, some miscellaneous methods of preparing thiocyanates are briefly described. Some appear to be of general application, while others are limited in scope. In all cases, the primary products are exclusively thiocyanates.

A wide range of thiocyanates has been prepared from the corresponding sulphenyl chlorides and formamide in the presence of thionyl chloride[190] (equation 94).

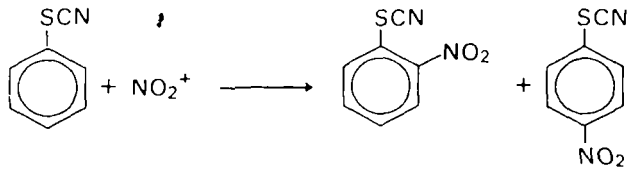


(94)

In an unexpected reaction, an equally wide range of thiocyanates may be prepared by reaction of sulphonyl halides with cyanide ion in an inert solvent[191] (equation 95).

(95)

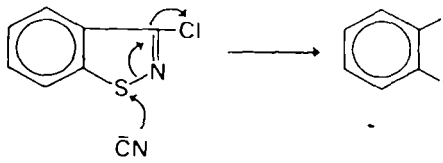
The thiocyanato group has an *ortho/para* directing effect in electrophilic aromatic substitutions[192]. Thus, nitration of phenyl thiocyanate proceeds according to equation (96), with an *ortho/para* ratio of 1/4.



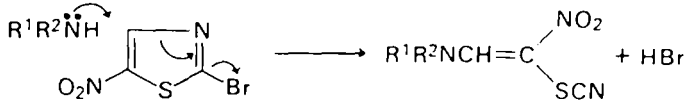
(96)

The *para*-directing effect of the thiocyanato group is considerably larger than that of the chloro, bromo, or methyl groups, and this difference has been exploited in the preparation of disubstituted aryl thiocyanates[192].

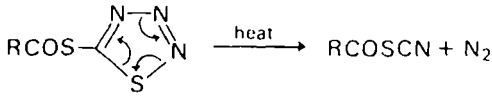
Thiocyanates may also be produced by ring cleavage of appropriate thiazole derivatives. Thus, 3-chloro-1,2-benzisothiazole[193], 2-bromo-5-nitro-thiazole[194], and 5-acylthio-1,2,3,4-thiatriazoles[195] react according to equations (97), (98) and (99) respectively.



(97)



(98)



(99)

VI. PSEUDOHALIDE REACTIONS OF THIOCYANATES

In many of their reactions, organic thiocyanates behave in essentially the same way as the corresponding halides, i.e. as pseudohalides. The most common pseudohalide reactions are those which involve fission of the R–SCN bond. In most reactions of this type the products and mechanisms are the same as for the halides, but thiocyanates show one important reaction which is not available to halides, i.e. isomerization.

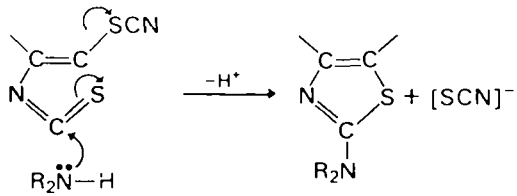
A. Substitution Reactions

Organic thiocyanates undergo S_N1 and S_N2 reactions readily, the overall reactions being as shown in equation (100).

$$X^- + RSCN \longrightarrow RX + [SCN]^- \quad (100)$$

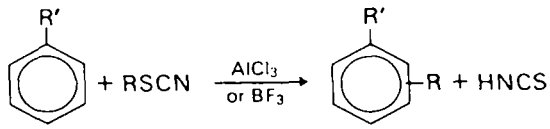
S_N2 reactions are generally confined to weak nucleophiles, e.g. ethanol[21], thiourea[21], thiocyanate[13], and azide[196], since stronger nucleophiles, e.g. alkalies, alkoxides, and amines preferentially attack the carbon atom of the thiocyanato group (see Section VII.A.3). S_N1 solvolyses promoted by ferric chloride[89] or silver nitrate[197] in alcoholic solutions are used as diagnostic tests for labile thiocyanates. Further S_N1 reactions of thiocyanates are discussed in Section VI.B.1.a which deals with isomerization.

Intramolecular displacement of the thiocyanato group occurs when *trans*-α-isothiocyanato-β-thiocyanatoalkenes are treated with amines, and leads to 2-aminothiazoles as shown in equation (101)[153].



(101)

Friedel–Crafts alkylation of substituted benzenes by alkyl thiocyanates (equation 102) is another example of heterolytic fission of the R–SCN bond[198].



(102)

Sulphenyl thiocyanates undergo RS–SCN bond fission on treatment with thiols, and the method has been developed as a synthesis of unsymmetrical disulphides[127,128] (equation 103).

$$RSSCN + R'SH \longrightarrow RSSR' + HNCS \quad (103)$$

The thiocyanato group may also be removed from carbon atoms by metals, e.g. copper in the Ullmann reaction[199], and Raney nickel[144,200].

B. Isomerization Reactions

The most common reaction involving fission of the R–SCN bond in thiocyanates is the isomerization to the isothiocyanate shown in equation (104).

$$R{-}SCN \rightleftharpoons R{-}NCS \qquad (104)$$

The concomitant kinetically-controlled formation of the isothiocyanate in the preparation of some thiocyanates has been discussed in Sections II and III. In this thermodynamically-controlled formation of isothiocyanate, the driving force for the rearrangement is the greater R–N bond strength. Generally, the isomerization is practically complete for the vast majority of substrates and conditions, although in a few cases it is possible to establish the presence at equilibrium of small, or even considerable, amounts of thiocyanate. There are three principal pathways for isomerization; these have been thoroughly reviewed by Fava[201] and Spurlock[202], and so only a brief account is presented here.

1. Dissociation–recombination

Isomerization by this pathway involves either heterolytic or homolytic dissociation of the R–SCN bond followed by recombination of the intermediate species.

a. *Carbonium ion intermediates.* The ease of isomerization of alkyl and aralkyl thiocyanates increases in the order primary < secondary < tertiary thiocyanates and is favoured by the presence of aryl groups on the carbon atom to which the thiocyanato group is attached[20,21,22], or by the addition of a catalyst such as zinc chloride[201]. Thus, in the alkyl series, while primary thiocyanates cannot be isomerized at all, secondary thiocyanates can be isomerized by heating in the presence of zinc chloride, and tertiary thiocyanates can be isomerized readily at room temperature in the presence of zinc chloride. In the aralkyl series no zinc chloride catalyst is required, and the ease of isomerization ranges from that of benzyl thiocyanate, which isomerizes at 250 °C, to that of triphenylmethyl thiocyanate which is so labile that it has never been isolated, even under mild conditions[201].

There is clearly a close parallel between the ease of isomerization (either uncatalysed or catalysed by zinc chloride) and the stability of the carbonium ion derived from the parent thiocyanate. Kinetic studies also show that the isomerization reaction is first-order, that the rate of isomerization increases with increasing solvent polarity, and that it is of the same order of magnitude as for the solvolytic reactions of the corresponding halides[203]. Furthermore, isomerization occurs with 100% retention of configuration[196].

These results have been interpreted in terms of the ionization–recombination mechanism shown in equation (105)[196,203,204].

$$R{-}SCN \rightleftharpoons \underset{(47)}{\{R^+[SCN]^-\}} \rightleftharpoons \underset{(48)}{R^+ + [SCN]^-} \qquad (105)$$

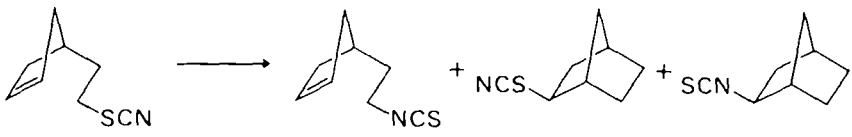
$$\{R^+[SCN]^-\} \longrightarrow R{-}NCS$$

The important feature of equation (105) is that it is the ion pair **47**, and not the free carbonium ion **48**, through which isomerization takes place[204]; collapse of **47** to the isothiocyanate is more likely to occur on the same side of the plane, as defined by the carbonium ion in **47**, from which the thiocyanato ion departed, and thus lead to the observed retention of configuration. The equilibrium fraction of thiocyanate in these thermal isomerizations is generally low. Thus, in alkyl thiocyanate–isothiocyanate isomerizations no thiocyanate is detectable at equilibrium, and in the benzhydryl thiocyanate–isothiocyanate isomerization the amount of thiocyanate at equilibrium in cyclohexane is less than 1%; in acetonitrile the figure is 2·3%[201]. However, in the furfuryl thiocyanate–isothiocyanate equilibrium (equation 106), substantial amounts (11–20%) of the thiocyanate are present; again polar solvents permit larger fractions of the thiocyanate at equilibrium than do non-polar solvents[205].

(106)

It has been suggested that the furan ring, being more polarizable, i.e. softer on the HSAB principle (see Section II.A), than the benzene rings of aralkyl thiocyanates and the σ-bonds of alkyl thiocyanates, shows a greater preference for the soft sulphur atom of the thiocyanato anion[205]. The stabilization of the thiocyanate in more polar media is in agreement with the greater polarity of thiocyanates with respect to isothiocyanates, as shown by their respective dipole moments[201].

Spurlock and coworkers have investigated the isomerization of cyclic and bicyclic thiocyanates, in which anchimeric assistance by σ or π electrons causes the additional complication of skeletal equilibration as illustrated in equation (107), and have discussed the results in terms of ion-pair behaviour[47,202,206].



(107)

Some acyl thiocyanates, RCOSCN, may also isomerize by this ionization mechanism[195].

b. *Radical intermediates.* Parks and Spurlock[207] have recently shown that photo-isomerization of thiocyanates to isothiocyanates can proceed under relatively mild conditions. Thus, ultraviolet irradiation of benzyl thiocyanate in an oxygen-free organic solvent for a few hours at 25 °C produces an equilibrium mixture consisting of 96–99% benzyl isothiocyanate (equation 108).

$$PhCH_2SCN \underset{}{\overset{h\nu}{\rightleftharpoons}} PhCH_2NCS \qquad (108)$$

These ratios were verified as stationary states in each solvent by approach from either isomer, and were shown to be independent of the effects of methoxy, methyl, chloro, and trifluoromethyl substituents in the *para* position.

The mechanism suggested involves photo-induced homolytic dissociation of the R–SCN and R–NCS bonds in thiocyanates and isothiocyanates respectively, followed by recombination of the benzyl and the ambident thiocyanato radicals (see Section III.A.2) in the solvent cage **49** to give the isothiocyanate preferentially[207] (equation 109).

$$PhCH_2SCN \rightleftharpoons \{ Ph\dot{C}H_2[SCN]^{\bullet} \} \rightleftharpoons PhCH_2NCS \qquad (109)$$

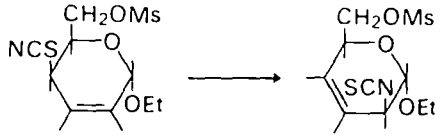
(49)

2. Sigmatropic rearrangement

Allylic thiocyanates isomerize thermally with much greater ease than other systems, e.g. benzyl, of comparable electron-releasing ability. Thus, 3-thiocyanatocyclohexene undergoes isomerization to 3-isothiocyanatocyclohexene at 32 °C, with a half-life of 2 hours[37]. The first-order isomerization rates, unlike those of the alkyl and aralkyl thiocyanates (see Section VI.B.1.a), are only marginally influenced by changes in solvent polarity and electronic effects of substituents. Furthermore, the carbon skeleton undergoes an allylic rearrangement during the isomerization[201]. Thus, crotyl thiocyanate yields α-methylallyl isothiocyanate (equation

110), and heating the allylic thiocyanato-pyranoside (**50**) leads stereospecifically and regiospecifically to the allylic isothiocyanate, **51**[46] (equation 111).

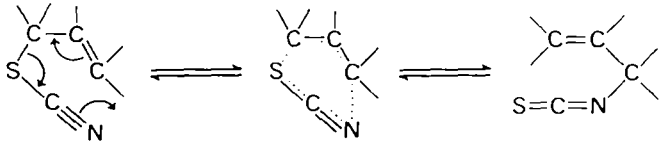
$$CH_3CH{=}CHCH_2SCN \longrightarrow CH_3\underset{\displaystyle NCS}{\underset{|}{C}}HCH{=}CH_2 \qquad (110)$$



(111)

(**50**)

These results have been interpreted[201] in terms of the suprafacial [3, 3] sigmatropic rearrangement[46] and cyclic transition state **52** shown in equation (112).



(112)

(**52**)

As in the isomerization of alkyl and aralkyl thiocyanates, the amount of thiocyanate present at equilibrium is usually small, and is greater in solvents of high polarity. However, where the rearrangement produces a less stable carbon skeleton, the equilibrium fraction of thiocyanate may become sizeable or even unity. Thus, cinnamyl thiocyanate does not undergo allylic rearrangement at all, due to the loss of delocalization energy outweighing the energy gain accompanying isomerization[201] (equation 113).

$$PhCH{=}CHCH_2SCN \not\longrightarrow Ph\underset{\displaystyle NCS}{\underset{|}{C}}HCH{=}CH_2 \qquad (113)$$

3. Direct displacement by thiocyanato ion

In the presence of substantial amounts of thiocyanato ions (**3**), organic thiocyanates may be isomerized in an S_N2 reaction involving direct

nucleophilic displacement of the 'organic' thiocyanato group by the N end of the 'inorganic' thiocyanato ion[13] (equation 114).

$$[SCN]^- + R{-}SCN \longrightarrow SCN{-}R + [SCN]^- \quad (114)$$

For the reasons outlined in Section II.A on the basis of the HSAB principle, the extent of this reaction increases as the structure of the halide changes from primary to secondary to tertiary, and becomes relatively more important than the concomitant reaction involving the S end of the 'inorganic' thiocyanato ion.

This mechanism may be exploited in the synthesis of those isothiocyanates in which the nature of the organic moiety precludes isomerization via the ionization mechanism (see Section VI.B.1.a). Thus, 4-nitrobenzyl isothiocyanate is obtained in moderate yield by heating 4-nitrobenzyl thiocyanate with potassium thiocyanate in acetone[13].

Spurlock[202] has suggested that acyl thiocyanates[195] may also isomerize in an addition–elimination variation of this mechanism (equation 115).

$$RCOSCN + [SCN]^- \longrightarrow R{-}\underset{\displaystyle NCS}{\overset{\displaystyle O^-}{\underset{|}{\overset{|}{C}}}}{-}SCN \longrightarrow R{-}\underset{\displaystyle NCS}{\overset{\displaystyle O}{\underset{|}{\overset{\|}{C}}}} + [SCN]^- \quad (115)$$

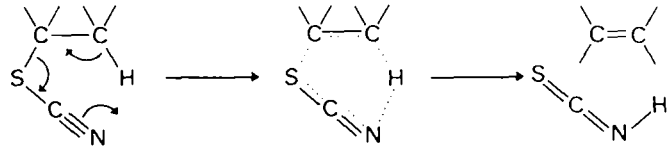
C. Elimination Reactions

Relatively few examples are known of thiocyanates undergoing 1,2-elimination of isothiocyanic acid with the formation of alkenes, but they illustrate the pseudohalide analogy well (cf. Section VII.A.5). Thus, isopropyl thiocyanate yields propene, presumably by the E2 mechanism shown in equation (116), on treatment with potassium *t*-butoxide in dimethyl sulphoxide, the rate of elimination being considerably slower than for the corresponding dehydrobromination[208].

$$t\text{-}BuO^- \cdots H{-}CH_2{-}\underset{\displaystyle H}{\overset{\displaystyle Me}{\underset{|}{\overset{|}{C}}}}{-}SCN \longrightarrow t\text{-}BuOH + CH_2{=}CHMe + [SCN]^- \quad (116)$$

In α-halo-β-thiocyanates, hydrogen halide rather than isothiocyanic acid is eliminated on treatment with bases[170,209].

Gas-phase pyrolysis of thiocyanates occurs readily, and leads to alkenes in a highly concerted, unimolecular reaction proceeding through the six-centred transition state **53**[210] (equation 117).



(117)

(53)

The same mechanism probably applies to the spontaneous decomposition of certain aralkyl thiocyanates to alkenes and isothiocyanic acid on standing at room temperature[22].

D. Addition Reactions

Addition reactions involving fission of the R–SCN bond are exemplified by the heterolytic and homolytic additions of aryl sulphenyl thiocyanates[44] (ArSSCN) and aryl sulphonyl thiocyanates[130] ($ArSO_2SCN$) respectively. These have been discussed as methods of preparing thiocyanates in Section III.E and are illustrated in equations (84) and (85).

E. Oxidation Reactions

Oxidation of alkyl and aryl thiocyanates by peracids leads to the corresponding sulphonyl cyanides[211] (equation 118).

$$RSCN + R'CO_3H \longrightarrow RSO_2CN + R'CO_2H \qquad (118)$$

This may be compared with the peracid oxidation of aryl iodides to iodoxy compounds (RIO_2).

VII. SULPHENYL CYANIDE REACTIONS OF THIOCYANATES

In these reactions, organic thiocyanates show behaviour due to their sulphenyl cyanide structure, i.e. RS–CN. This involves either fission of the RS–CN bond or addition reactions of the RSC≡N bond; in each case the reaction may be intermolecular or intramolecular.

A. Fission of the RS–CN Bond

1. Oxidation reactions

Vigorous oxidation of thiocyanates is a convenient way for preparing the corresponding sulphonic acids (equation 119) (cf. Section VI.E).

$$RSCN + [O] \xrightarrow{H_2O} RSO_3H \qquad (119)$$

Nitric acid is the usual oxidizing agent[212], but the oxidation may also be effected by alkaline hypochlorite, sodium hypoiodite, hydrogen peroxide, or by electrolytic means[8]. Caution should be exercised in treating a thiocyanate with a peroxide, since such mixtures have been known to explode[7].

Oxidation with aqueous chlorine yields the sulphonyl chloride, often in good yield[213] (equation 120).

$$RSCN + 3\,Cl_2 + 2\,H_2O \longrightarrow RSO_2Cl + ClCN + 4\,HCl \qquad (120)$$

2. Reduction reactions

Reduction of an organic thiocyanate produces the corresponding thiol (equation 121).

$$RSCN + [H] \longrightarrow RSH \qquad (121)$$

The reaction may be effected by tin and hydrochloric acid[8], lithium aluminium hydride[214], sodium in liquid ammonia[215], sodium sulphide[216], or dithiothreitol[172].

This reaction is valuable in the synthesis of thiols, e.g. the biologically active 5-mercaptopyrimidine nucleosides[172] or the mercapto analogue of compound **23**, which are difficult or tedious to prepare by other methods.

3. Nucleophilic displacement reactions

Nucleophilic displacement reactions on the RS–CN structure may take place either on the carbon atom (equation 122) or on the sulphur atom[217] (equation 123).

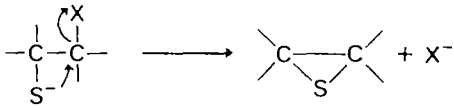
$$X^- \curvearrowright C(=N) \curvearrowright SR \longrightarrow XCN + RS^- \qquad (122)$$

$$X^- \curvearrowright S(R) \curvearrowright CN \longrightarrow XSR + CN^- \qquad (123)$$

The most commonly encountered fission reaction of S–CN bonds, in both the alkyl and the aryl series, is in the conversion of thiocyanates into disulphides by treatment with alkaline reagents, e.g. aqueous or alcoholic solutions of alkali-metal hydroxides or alkoxides, sodium carbonate, amines, and sodium sulphide or hydrosulphide[5,9]. This is readily

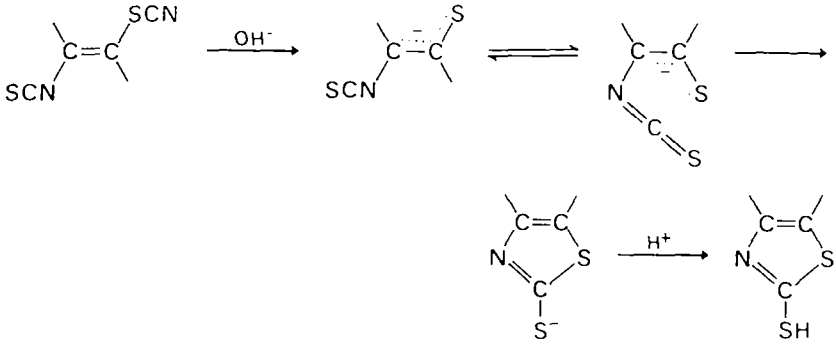
accounted for by a two-stage mechanism, the first of which is the formation of the thiolate anion (equation 122; X = OH, OR etc.), and the second of which is nucleophilic displacement of cyanide ion from the thiocyanate by thiolate ion (equation 123; X = SR).

If the thiolate ion contains a stable anionic group on an adjacent atom, intramolecular displacement takes place readily with the formation of an episulphide (equation 124).



(124)

This has been shown to occur for X = SCN[138,143,218], Cl[143,219], I[220] and OMs[219], and in acyclic[143], alicyclic[138,220], and steroidal[219,220] systems. Recently it has been shown that a similar intramolecular reaction occurs with *trans*-α-isothiocyanato-β-thiocyanato-alkenes, the products being 2-mercaptothiazoles[153] (equation 125).



(125)

Intermolecular reaction with added organic halides[20,90] or alcohols[221] leads to the formation of sulphides (equation 126).

$$RS^- + R'X \longrightarrow RSR' + X^- \qquad (126)$$

Grignard reagents attack either the carbon atom or the sulphur atom of the RS–CN structure according to the reaction conditions[222] (equations 127 and 128).

$$RSCN + R'MgBr \longrightarrow RSR' + MgBrCN \qquad (127)$$

$$RSCN + R'MgBr \xrightarrow{HBr} RSH + R'CN + MgBr_2 \qquad (128)$$

Trialkyl phosphites behave similarly. Thus, aliphatic thiocyanates undergo an Arbuzov-type reaction with trialkyl phosphites yielding alkyl nitriles and the corresponding phosphorothioates, the mechanism involving displacement of the cyanide ion by nucleophilic attack of phosphorus on the sulphur atom[223] (equation 129).

$$(RO)_3P + R'SCN \longrightarrow [(RO)_3\overset{+}{P}SR'\ CN^-] \longrightarrow (RO)_2\overset{O}{\overset{\|}{P}}SR' + RCN \quad (129)$$

In contrast, aromatic thiocyanates react to give aryl alkyl sulphides and phosphorothioates, the mechanism involving displacement of the thiophenoxide ion by nucleophilic attack of phosphorus on the carbon atom[224] (equation 130).

$$(RO)_3P + ArSCN \longrightarrow [(RO)_3\overset{+}{P}CN\ \ ArS^-] \longrightarrow (RO)_2\overset{O}{\overset{\|}{P}}CN + ArSR \quad (130)$$

The difference in behaviour is clearly due to the relative stabilities of the $R'S^-$, CN^-, and ArS^- anions. Similar differences have been observed in the reaction of heterocyclic thiocyanates with diethyl hydrogen phosphite[225].

Nucleophilic attack by cyanide ion occurs uniquely on the sulphur atom, and has been exploited to prepare isotopically-labelled organic thiocyanates[226] (equation 131).

$$^*CN^- + RS{-}CN \longrightarrow RS{-}{}^*CN + CN^- \quad (131)$$

Carbanions behave similarly under conditions of phase-transfer catalysis, yielding sulphides[226a].

4. Homolytic reactions

Cyclohexyl thiocyanate does not undergo photo-isomerization in cyclohexane (see Section VI.B.1.b), but readily affords dicyclohexyl sulphide, dicyclohexyl disulphide and hydrogen cyanide[207]. The proposed mechanism involves homolytic dissociation of the RS–CN bond, followed by radical recombination reactions (equation 132).

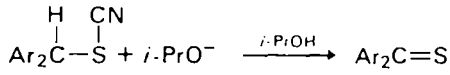
$$C_6H_{11}S{-}CN \xrightarrow{h\nu} C_6H_{11}S^\bullet + {}^\bullet CN$$

$$C_6H_{11}S^\bullet \;\swarrow \qquad C_6H_{11}^\bullet \;\searrow \qquad \swarrow C_6H_{12} \quad (132)$$

$$C_6H_{11}SSC_6H_{11} \qquad C_6H_{11}SC_6H_{11} \qquad C_6H_{11}^\bullet + HCN$$

5. Elimination reactions

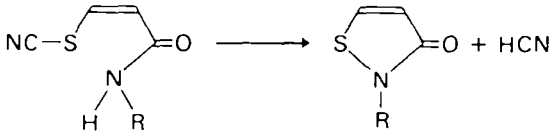
Diphenylmethyl thiocyanates yield thiobenzophenones on treatment with base by a 1,2-elimination of hydrogen cyanide[227] (equation 133) (cf. Section VI.C).



$$Ar_2C(H)(CN)-S + i\text{-}PrO^- \xrightarrow{i\text{-}PrOH} Ar_2C{=}S \qquad (133)$$

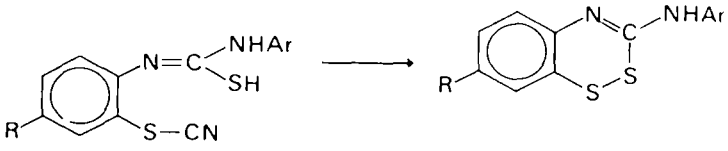
The second-order rate constants fit the Hammett equation, giving a very high ρ value of $+3{\cdot}5$. Optically-active thiocyanates do not racemize during the elimination, and the reaction shows a kinetic isotope effect of $k_H/k_D = 3{\cdot}0$. On the basis of these results, a concerted ElcB-like mechanism has been suggested[227].

In what may be considered to be a 1,5-elimination of hydrogen cyanide, *cis*-3-thiocyanatoacrylamides cyclize to the corresponding 3-isothiazoles[75] (equation 134).



(134)

Similarly, 1,2,4-benzodithiazines are formed by a 1,6-elimination of hydrogen cyanide as shown in equation (135)[228].



(135)

B. Reactions of the RSC≡N Bond

Organic thiocyanates resemble cyanides in undergoing addition reactions at the C≡N bond which is an ambiphilic centre. The orientation of addition is controlled by the polarization $C^{\delta+}{\equiv}N^{\delta-}$, and initial attack may be either by nucleophiles at the carbon atom yielding an imino ion intermediate (**54**, equation 136), or by electrophiles at the nitrogen atom yielding a nitrilium ion intermediate (**55**, equation 137; X = H, R, etc.).

(136)

(54)

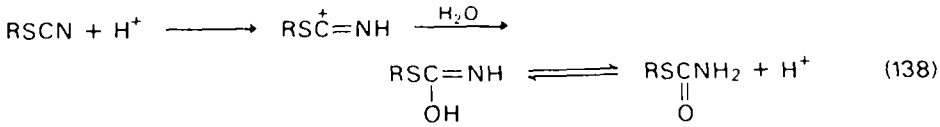
(137)

(55)

These reactions often occur much more readily when they are intramolecular, thus yielding cyclic products. Such cyclization reactions are particularly valuable in the synthesis of heterocycles.

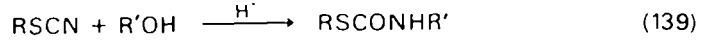
1. Addition reactions

a. *Water and alcohols.* Thiocyanates are readily hydrated to thiocarbamates by treatment with sulphuric acid and then water[229] (equation 138).



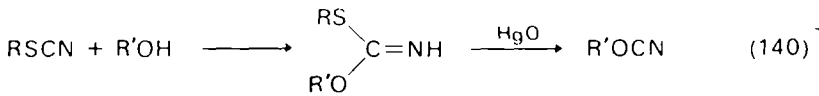
(138)

Alcohols behave similarly, yielding *N*-substituted thiocarbamates[229] (equation 139).



(139)

When the conditions do not favour carbonium ion formation from the alcohol, nucleophilic attack occurs yielding iminothiocarbonates (**56**); if this reaction is carried out in the presence of a thiol-trapping agent, e.g. mercuric oxide, alkyl cyanates are formed in good yields[230] (equation 140).



(140)

(56)

b. *Alkenes.* Alkenes behave similarly to alcohols, yielding *N*-substituted thiocarbamates on treatment with sulphuric acid and then water[229,231] (equation 141).

(141)

c. *Hydrogen sulphide and thio-acids.* Hydrogen sulphide adds to thiocyanates yielding dithiourethanes[232] (equation 142).

$$RSCN + H_2S \longrightarrow RSCSNH_2 \qquad (142)$$

Thio-acids add readily to thiocyanates to give *N*-acyldithiocarbamates[144,233] (equation 143).

$$RSCN + R'COSH \longrightarrow RSCSNHCOR' \qquad (143)$$

This reaction is useful for characterizing thiocyanates and distinguishing them from isothiocyanates, which under similar conditions give *N*-acylamines and carbon disulphide.

d. *Phosphorus pentachloride.* Aromatic thiocyanates are phosphorylated by treatment with phosphorus pentachloride and sulphur dioxide as shown in equation (144)[234].

$$ArSCN + PCl_5 \longrightarrow ArSC(Cl)=\overset{+}{N}PCl_3\ \ddot{P}Cl_6 \xrightarrow{SO_2} ArSC(Cl)=NPOCl_2 \qquad (144)$$

e. *Hydrogen chloride.* Alkyl thiocyanates react with hydrogen chloride in ether yielding thioimidoyl chloride salts (**57**) at 0 °C[235] and dimeric adducts (**58**) at 60 °C[236] (equation 145).

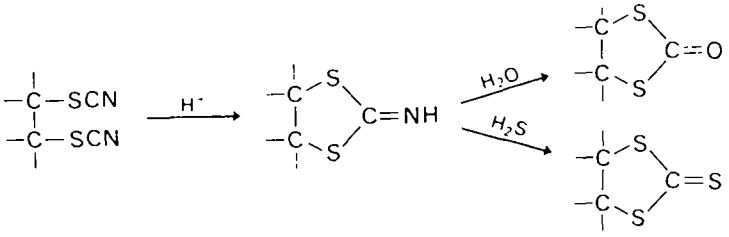
$$RSCN + HCl \longrightarrow RSC(Cl)=\overset{+}{N}H_2\ Cl^- \xrightarrow{RSCN} RS-C(=\overset{+}{N}H_2\ \ddot{C}l)-N=C(Cl)-SR \qquad (145)$$

(**57**)

(**58**)

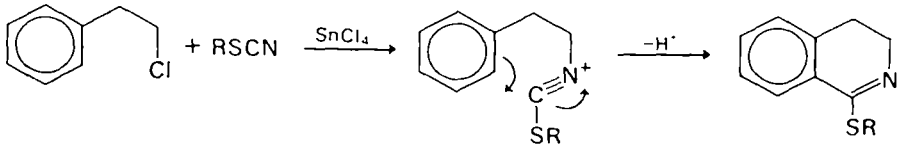
2. Cyclization reactions

a. *S-Heterocycles.* 1,2-Dithiocyanates undergo acid-catalysed cyclization to iminodithiocarbonates, which may be converted into the corresponding di- or tri-thiocarbonates[45,139] (equation 146).



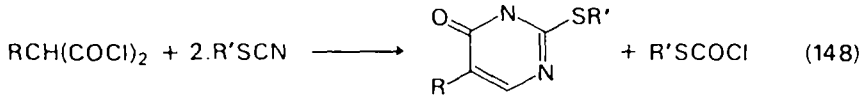
(146)

b. *N-Heterocycles.* In the presence of tin tetrachloride, thiocyanates react with β-chloroethylbenzene forming nitrilium salts which cyclize to 1-thioalkoxy-3,4-dihydroisoquinolines[237] (equation 147).



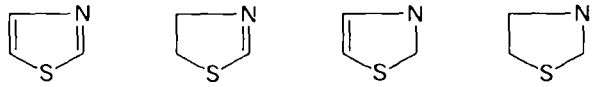
(147)

Thiocyanates react with chloro-, phenyl-, or benzyl-substituted malonyl chlorides to give 4-chloro-pyrimidine-6-ones with an alkyl- or aryl-thio group in the 2-position[238] (equation 148).



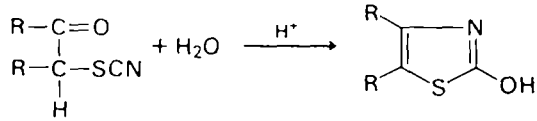
(148)

c. *S,N-Heterocycles.* Thiazoles (**59**), 2-thiazolines (**60**), 4-thiazolines (**61**), and thiazolidines (**62**) are readily prepared from organic thiocyanates by a variety of methods.



(**59**) (**60**) (**61**) (**62**)

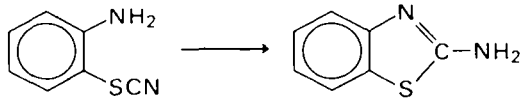
Aliphatic α-thiocyanato ketones react with aqueous acid yielding 2-hydroxythiazoles[27] (equation 149).



(149)

Reaction with hydrogen sulphide[27], hydrogen chloride[27], ammonia[27], diethylamine[64], or aniline[239] gives the corresponding 2-mercapto-, 2-chloro-, 2-amino-, 2-diethylamino-, or 2-anilino-thiazoles.

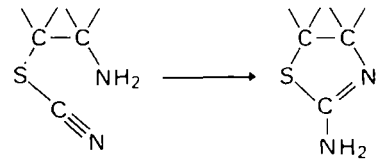
2-Aminobenzothiazoles are readily prepared from *o*-amino aryl thiocyanates[5–9,92,240] (equation 150).



(150)

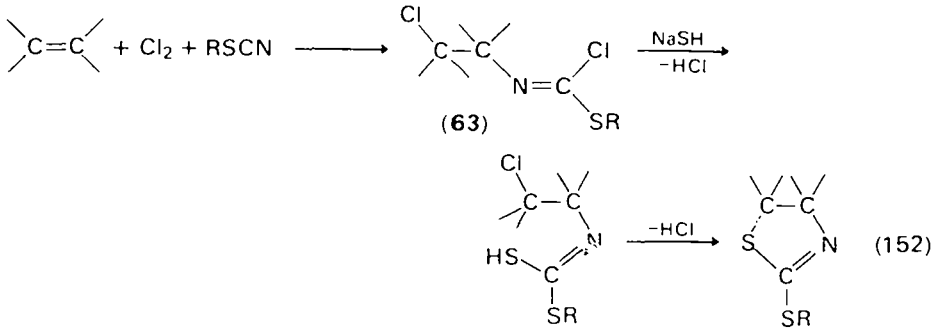
The ease of formation of the thiazole derivative varies with the nature of the thiocyanatoamine, some rearranging spontaneously, whereas others require heating with acid. The reaction has also been used to prepare thiazolo-pyridines[104,105], -quinolines[104], -pyrimidines[103,104,241], -acridines[106], and -indazoles[110]. Bis-[94,242,243] and tris-[94] thiazoles may be prepared from the corresponding thiocyanatoamines.

Aliphatic α-amino-β-thiocyanates cyclize spontaneously to give 2-amino-2-thiazolines[65] (equation 151).



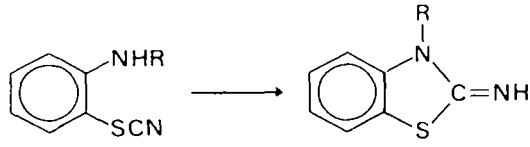
(151)

Chlorination of an alkene in the presence of an alkyl thiocyanate leads stereospecifically to the formation of the *N*-(β-chloroalkyl) imidochloride **63**, which, on treatment with sodium hydrosulphide solution, yields a 2-alkylthio-2-thiazoline[244] (equation 152). The synthesis has the added advantage of being performed as a one-pot process.



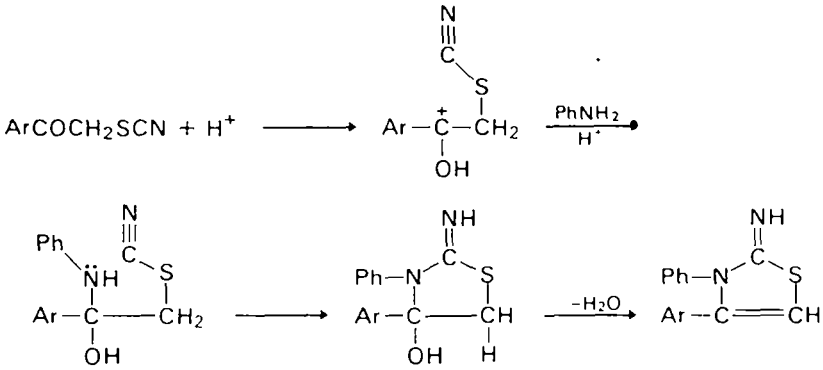
(152)

The *o*-thiocyanato derivatives of secondary aromatic amines rearrange readily to 2-iminobenzothiazolines[5–9] (equation 153).



(153)

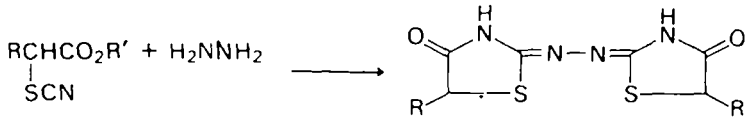
α-Thiocyanatoalkyl aryl ketones, when treated with aniline in the presence of mineral acid, yield 2-imino-4-thiazolines[239] (equation 154).



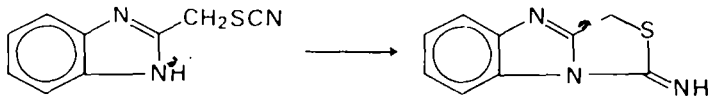
(154)

Thiazolidines may be prepared from α-thiocyanatoanilides[35] (equation 155), α-thiocyanatoesters[28] (equation 156), and 2-thiocyanatomethyl benzimidazole[245] (equation 157).

(155)

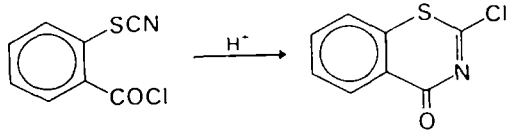


(156)



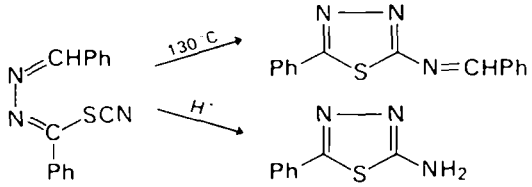
(157)

Cyclization of the thiocyanato group with an *o*-acyl chloride group leads to 1,3-thiazine derivatives in good yield[246] (equation 158).



(158)

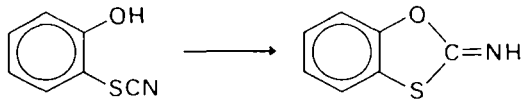
The thiocyanato compound **11** yields 1,3,4-thiadiazole derivatives on cyclization under both thermal and acidic conditions[43] (equation 159).



(159)

(**11**)

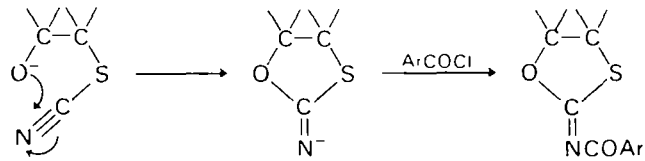
d. *S,O-Heterocycles.* *o*-Thiocyanatophenols rearrange readily to the corresponding 2-iminobenzoxathioles[5-9,247] (equation 160)



(160)

Cyclization is slow in acid solution, but fast in neutral or basic solution, reflecting the relative nucleophilic strengths of the phenolic oxygen atom under these conditions. The imino group may be hydrolysed to a keto group under aqueous conditions.

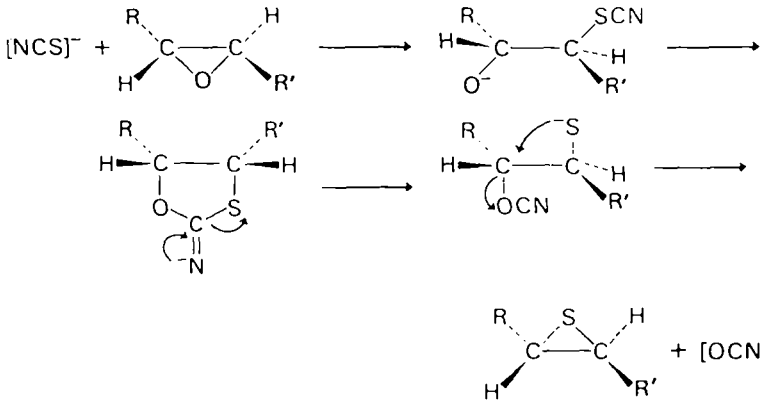
Aliphatic α-hydroxy-β-thiocyanates do not rearrange in this way, but the corresponding alkoxides, with a more powerfully nucleophilic oxygen atom, rearrange rapidly[63] forming the reactive anion **64** which may be trapped as shown in equation (161)[248].



(161)

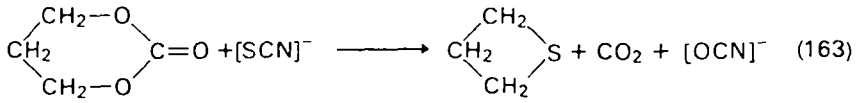
(**64**)

In the absence of the aroyl chloride, however, the anion undergoes C–S bond fission, followed by intramolecular displacement of cyanate ion and formation of an episulphide. This reaction provides an excellent stereospecific synthesis of episulphides from epoxides[62] (equation 162).



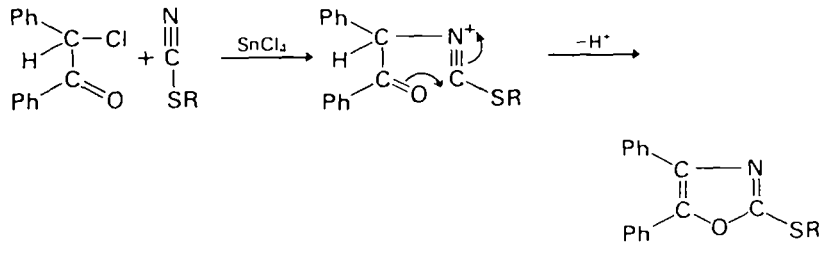
(162)

A similar mechanism has been proposed to account for the formation of thietanes from cyclic carbonate esters and thiocyanate ion[249] (equation 163).

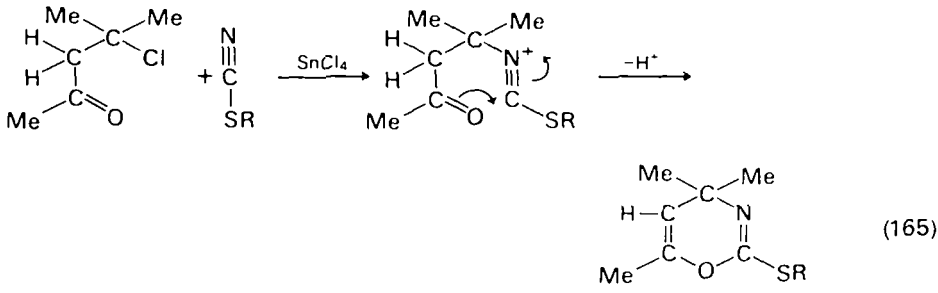


(163)

e. *N,O-Heterocycles.* Thiocyanates may undergo cyclization reactions with suitable oxygen-containing compounds to yield 1,3-oxazoles and 1,3-oxazines[237]. Thus, in the presence of tin tetrachloride, alkyl thiocyanates react with desyl chloride to yield 2-thioalkoxyoxazoles (equation 164), and with 4-chloro-4-methylpentan-2-one to yield 2-thioalkoxy-4*H*-1,3-oxazines (equation 165).

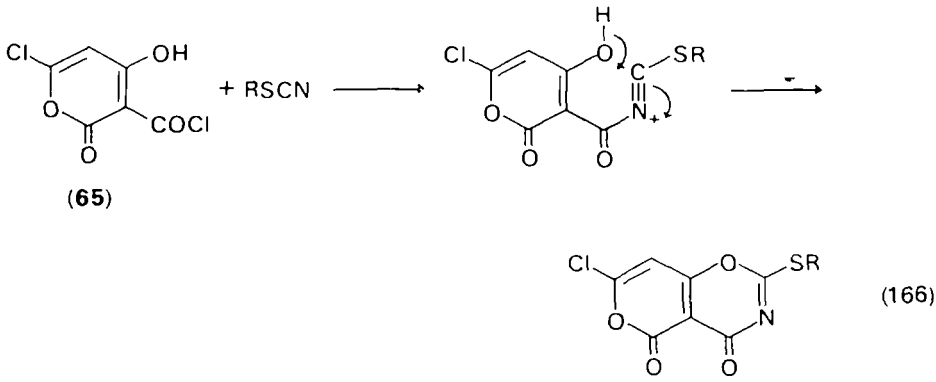


(164)



(165)

Reaction with the self-condensation product (**65**) of malonyl chloride produces a nitrilium salt which undergoes cyclization to a pyrano[3,4-*e*]-[1,3]oxazine-4,5-dione derivative[250] (equation 166).



(166)

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The Chemistry of Cyanates and their Thio Derivatives
Edited by Saul Patai

CHAPTER 19

Selenocyanates and related compounds

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I. INTRODUCTION

Very few reviews exist concerning selenocyanic acid and its derivatives. The preparative aspects of organic derivatives of selenocyanic acid have been reviewed by Rheinboldt[1], who has summarized all the relevant literature. The great majority of general and theoretical data on this subject can be found in the chapters of the recently published comprehensive monograph on organic selenium compounds[2].

Organoselenium compounds are in principle formally similar to those of sulphur. However much fewer compounds of the former are known. The reasons for this are their often difficult obtainability, their sometimes unpleasant or even dangerous handling, as well as the multiplicity of their reaction modes. A notable difference between organosulphur and organoselenium compounds originates in the increasing metallic character of these elements, resulting in an increasingly labile bond to carbon. This is even more noticeable with organotellurium compounds. Hence a great number of organoselenium compounds, as well as some of the starting materials for their preparation, are strongly poisonous. Many have obnoxious odours and cause strong physiological irritation. Their handling should therefore be conducted with the utmost safety precautions.

II. SELENOCYANIC ACID

Selenocyanic acid, HSeCN, is the analogue of thiocyanic acid. A dilute aqueous solution of the former can be prepared by the introduction of hydrogen sulphide into a suspension of lead selenocyanate in water. The anhydrous acid is as yet unknown. Attempts to prepare solutions of selenocyanic acid in organic solvents have been unsuccessful, since these decompose very easily with elimination of elementary selenium.

Of the salts of selenocyanic acid, potassium selenocyanate (**1**) is the most important, it being the most widely used reagent for the introduction of selenium into organic compounds. **1** is very easily obtained by the melting of equimolar quantities of finely pulverized selenium with potassium cyanide (equation 1)

$$KCN + Se \longrightarrow KSeCN \qquad (1)$$

(**1**)

In another procedure **1** is obtained in solution by heating the components in water or alcohol under reflux until all the selenium is dissolved. Filtration and concentration of the solutions precipitates solid **1** which is

purified by recrystallization. Crystalline **1** is hygroscopic but may be kept in well-sealed containers. When exposed to air **1** decomposes easily with elimination of selenium. **1** is soluble in water and a number of organic solvents.

Bosch and his coworkers[3] have investigated the properties of the selenocyanate ion as an analytical reagent. Badu and his coworkers[4] found that the silver/silverselenocyanate electrode is reversible with respect to $SeCN^-$ and is therefore suitable for the potentiometric determination of the latter. The standard potential of the electrode was determined in the same laboratory[5].

Selenoureas result from the reaction of selenocyanate ion with amines[6–9]. For instance, *N*-benzylselenourea (**2**) results from mixing alcoholic solutions of benzylamine hydrochloride and potassium selenocyanate (equation 2).

$$\underset{(1)}{[PhCH_2NH_3]^+Cl^-} + KSeCN \longrightarrow \underset{(2)}{PhCH_2NHCSeNH_2} + KCl \qquad (2)$$

In contrast, all the attempts to obtain selenosemicarbazide by the isomerization of hydrazinoselenocyanate were unsuccessful.

However, if the reactions are conducted under certain conditions in the presence of a carbonyl compound (acetone has proved exceptionally suitable) it is possible to isolate the selenosemicarbazones[10–12]. The following mechanism was postulated[13] for the formation of acetone selenosemicarbazone (**3**) (equations 3–5).

$$2\,MeCOMe + H_2NNH_2 \longrightarrow (Me)_2C{=}NN{=}C(Me)_2 + H_2O \qquad (3)$$

$$(Me)_2C{=}NN{=}C(Me)_2 + H_2O \longrightarrow (Me)_2C{=}NNH_2 + MeCOMe \qquad (4)$$

$$(Me)_2C{=}NNH_2 + HSeCN \longrightarrow \underset{(3)}{(Me)_2C{=}NNHCSeNH_2} \qquad (5)$$

A detailed quantitative study of this reaction has been done[14].

The selenocyanate ion as a ligand has been utilized in many complex compounds. The great number of articles concerning this aspect has been reviewed by Norbury and Sinha[15]. In such complexes the metal atom may be bound to either the nitrogen atom or the selenium atom. The whole selenocyanate ion thus forms a bridging function. Structural assignments can be made by i.r. spectroscopy.

III. ESTERS OF SELENOCYANIC ACIDS

A. Selenocyanates

As mentioned above (see Section II) potassium selenocyanate (**1**) is an important starting material for the introduction of the selenocyanate residue into organic compounds. The reactions consist of the nucleophilic substitution of halogen atoms as well as the diazo function by selenocyanate ion. Owing to the sluggish reactivity of aromatic halides the substitution of halogen is applicable mainly in aliphatic compounds, whereas the substitution of the diazo group is limited to aromatic compounds. Occasionally the selenocyano group is introduced directly, i.e. by the use of dicyanodiselenide $(SeCN)_2$ (**4**). For this purpose the latter need not be isolated and may be formed as an intermediate *in situ*.

1. Preparation

a. *By the exchange of halogen.* The substitution of halogen by selenocyanate is usually achieved by heating the proper halide derivative with potassium selenocyanate (**1**) in ethanol or acetone or another suitable organic solvent. The precipitation of the potassium halide can be used as a measure for the completion of the reaction.

$$RX + KSeCN \longrightarrow RSeCN + KX \qquad (6)$$

Both simple alkyl selenocyanates and alkyl selenocyanates having additional functional groups such as double bonds, carbonyl and carboxyl groups have been prepared by this method[16-24]. It is also possible to prepare by this method haloalkyl selenocyanates. This is achieved by making use of the difference in reactivity of different halogens. Thus 2-chloroethyl selenocyanate (**5**) is prepared by the reaction of 1-bromo-2-chloroethane with potassium selenocyanate (**1**), in acetone (equation 7)[25].

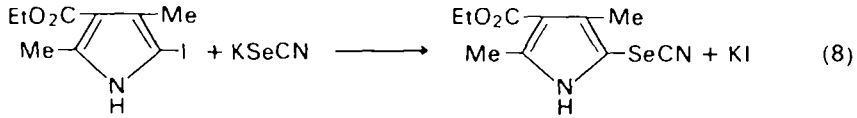
$$\underset{}{ClCH_2CH_2Br} + KSeCN \longrightarrow \underset{(5)}{ClCH_2CH_2SeCN} + KBr \qquad (7)$$

$$(1)$$

As a rule, **1** does not react with aromatic halides. If, however, the aromatic halide is activated by additional suitable substituents, the substitution of the halide by **1** becomes feasible. Thus for instance it is possible to prepare smoothly 2,4-dinitrophenyl selenocyanate by the reaction of 2,4-dinitrochlorobenzene with potassium selenocyanate (**1**) in alcoholic

solution. The positive charge imparted to the ring atoms through the I and M effects of the nitro substituents makes the nucleophilic attack by the $SeCN^-$ ion easier.

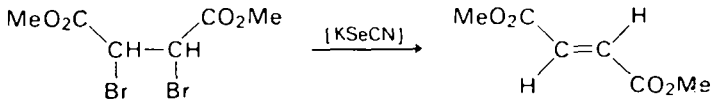
This method is also suitable for the preparation of heterocyclic selenocyanates. Suzuki[26] succeeded in the substitution of the bromide in the 4-position of quinolyl-(1)-oxide with potassium selenocyanate (**1**). In a similar manner Chierici[27] has succeeded in transforming 5-iodo-2,4-dimethyl-3-ethoxycarbonylpyrrole into the corresponding 5-selenocyanato derivative, **6** (equation 8), and the analogous 3-iodo derivative into the 3-selenocyanato derivative[28].



(8)

(**6**)

The substitution of halogen has likewise been applied to the preparation of diselenocyanates[23,29-31]. This however occasionally meets with difficulties. It has been found by van Es[32] that the reaction of vicinal dibromides with potassium selenocyanate (**1**) leads to olefins rather than to the expected selenocyanates. For instance when *meso*-dimethyl 2,3-dibromosuccinate is heated with **1** in dimethylformamide or methanol a 95% yield of dimethyl fumarate (**7**) is obtained (equation 9).

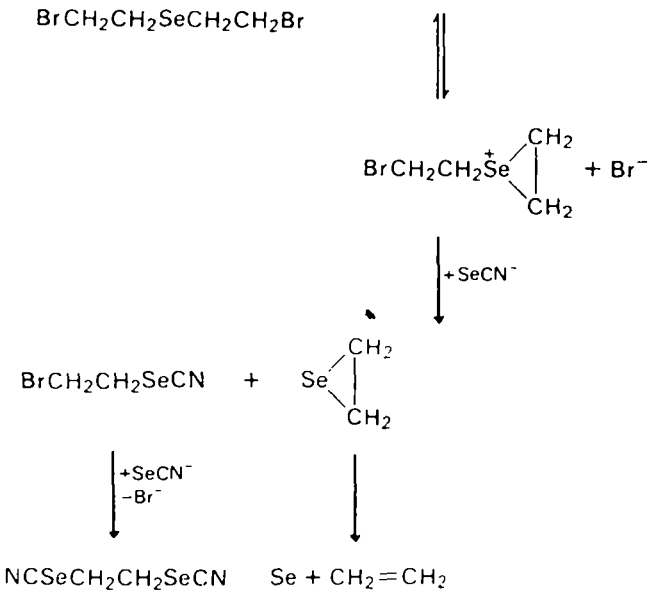


(9)

(**7**)

The reaction of β,β-dibromodiethyl selenide with potassium selenocyanate does not give the expected diselenocyanate. The main product is 1,2-diselenocyanatoethane (**8**) alongside elementary selenium and ethylene. For the reaction path, a mechanism similar to that of the solvolysis of mustard gases going through a cyclic selenonium ion is proposed[33] (Scheme 1).

According to this mechanism the first step in the reaction consists of an intramolecular attack by the nucleophilic selenium on the β-carbon atom. The resulting selenonium ion is subsequently attacked by the selenocyanate ion giving 1-bromo-2-selenocyanatoethane and selenirane. Subsequent reactions of these molecules lead to the observed products.



(8)

SCHEME 1.

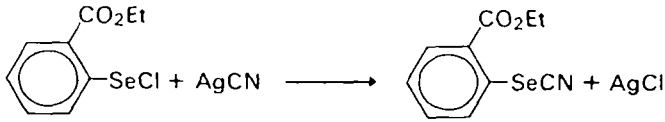
b. *From diazonium salts.* For the preparation of aromatic selenocyanates the reaction of diazonium salts is the most suitable (equation 10).

(10)

This is achieved by the addition of an aqueous solution of alkali selenocyanate to a buffered solution of the diazonium salt. A buffer of pH around 5·5 is essential because free mineral acids cause the selenocyanate ion to decompose with elimination of selenium. It is of interest that this reaction, in contradistinction to the Sandmeyer reaction for the preparation of aryl cyanides or thiocyanates, can be conducted in the absence of catalysts such as copper powder or Cu^{I}-selenocyanate. A large number of selenocyanates is obtained in this manner[34–39].

c. *From selenenyl derivatives.* While, according to the above mentioned methods, the selenocyanate function is introduced as a whole entity, it is also possible to proceed in a stepwise manner by reacting appropriate selenium compounds with cyanide to form the Se–CN bond. Into this class of reactions belong the reactions of silver cyanide and alkali cyanides with selenenyl halides, which have been applied to the preparation of a whole series of selenocyanates[40–44]. For instance, by melting together for a short

period 2-ethoxycarbonylphenylselenenyl chloride with an equivalent quantity of silver cyanide, a 70% yield of 2-ethoxycarbonylphenyl selenocyanate (**9**)[45] is obtained (equation 11).



(11)

(**9**)

Further, the thiocyanate group of selenenyl thiocyanates may be substituted by cyanide on heating the former with potassium cyanide in chloroform, alcohol or glacial acetic acid according to equation (12).

$$ArSeSCN + CN^- \longrightarrow ArSeCN + SCN^- \qquad (12)$$

Selenocyanates may be obtained analogously from alkyl selenenylsulphinates (equation 13)[46].

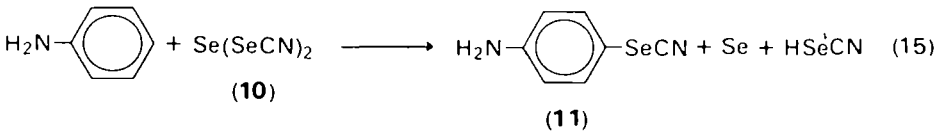
$$ArSeSO_2R + CN^- \longrightarrow ArSeCN + RSO_2^- \qquad (13)$$

Finally it is possible to obtain aromatic selenocyanates simply by heating the corresponding arylselenenyl selenocyanates above their melting points (equation 14).

$$ArSeSeCN \longrightarrow ArSeCN + Se \qquad (14)$$

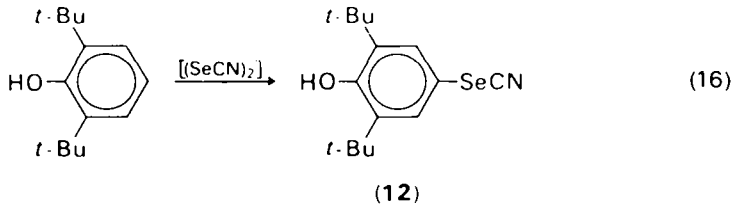
d. *By selenocyanation.* In certain compounds it is possible to introduce the —SeCN function by the direct electrophilic substitution on an aromatic nucleus. An occasionally very useful reagent for this purpose is selenium diselenocyanate (dicyano-triselenide) $Se(SeCN)_2$(**10**). This is prepared by the oxidation of potassium selenocyanate in aqueous solution with chlorine or nitrogen dioxide. **10** is obtained as well defined, relatively stable, yellow to orange crystals, which are easily soluble in many organic solvents. In water or alcohol **10** is hydrolysed. Concerning its reactions **10** may be regarded as the mixed anhydride of the hypothetical acid $Se(OH)_2$ with selenocyanic acid HSeCN.

The reaction of selenium diselenocyanate (**10**) with aniline or substituted anilines by prolonged shaking in ether solution results, at room temperature, in the formation of the appropriately-substituted *p*-aminophenyl selenocyanate. Aniline itself gives **11** (equation 15).



Dicyanodiselenide (selenocyanogen, $(SeCN)_2$,**4**) may similarly be used for the direct introduction of the selenocyanato function into aromatic compounds. **4** is best obtained by the reaction of iodine with silver selenocyanate in anhydrous inert solvents. **4** is a yellow, crystalline, quite-unstable compound which starts decomposing above 20 °C. Traces of humidity cause hydrolysis with elimination of elementary selenium.

Dicyanodiselenide also shows pronounced pseudohalogen characteristics and is thereby a useful reagent for the direct introduction of selenium into organic compounds. For this purpose it is unnecessary to isolate **4**. It is advantageous immediately to use the solution of the reagent for the next step. Thus 1-hydroxy-2,6-di-*t*-butyl-4-selenocyanatobenzene (**12**) was obtained by the dropwise addition of bromine to a mixture of 2,6-di-*t*-butylphenol and potassium selenocyanate in a methanolic solution saturated with KBr (equation 16)[47].

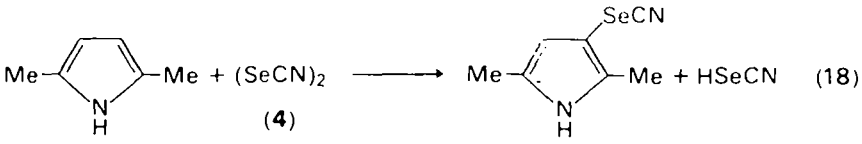


This reaction has been the subject of a detailed study by Agenäs. He showed that it could be applied in a fairly general manner to aromatic amines[48], as well as to heterocycles such as indoles[49,50] pyrroles[51] and indolines[52]. In this procedure first a solution of dicyanodiselenide (**4**) is generally prepared by the oxidation of potassium selenocyanate with bromine in methanol at -70 to -50 °C (equation 17). Then at the same temperature a methanolic solution of the aromatic or heterocyclic compound is added and the mixture is left to warm up slowly to room temperature. Thereby the pseudohalogen **4** substitutes in the appropriate position (equation 18). The simultaneously-formed selenocyanic acid decomposes quantitatively into selenium and hydrogen cyanide according

to equation (19). Finally, the reaction mixture is poured on ice and is appropriately worked-up. In this manner it has been possible to obtain 30% of 2,5-dimethyl-3-selenocyanatopyrrole (**13**) from 2,5-dimethylpyrrole.

$$2\,KSeCN + Br_2 \xrightarrow{-50\,^{\circ}C} (SeCN)_2 + 2\,KBr \qquad (17)$$

(**4**)

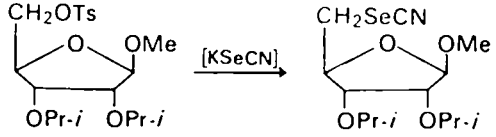


(18)

$$HSeCN \longrightarrow HCN + Se \qquad (19)$$

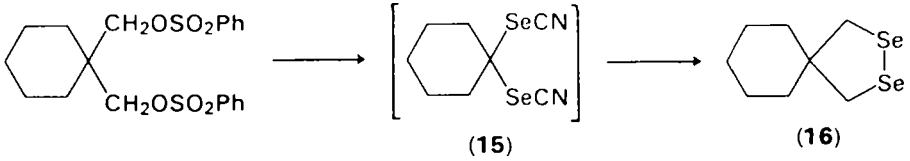
Another appropriate procedure for the preparation of nascent dicyanodiselenide is the anodic oxidation of potassium selenocyanate in aqueous alcohol solution. In the presence of appropriate organic compounds the respective selenocyanates are obtained. Recently this reaction has been studied in more detail[53,54]. It was found that the electrochemical oxidation of $SeCN^-$ on a platinum electrode in acetonitrile with lithium perchlorate as the conducting salt and in the presence of primary, secondary or tertiary aromatic amine, was well suited to the preparation of the respective selenocyanates[55].

e. *By miscellaneous methods.* Besides the halogens, other groups can also be substituted by $SeCN^-$. For instance, the heating of tosylates with potassium selenocyanate in a suitable solvent transforms them smoothly into selenocyanates. Thus *s*-butyl selenocyanate was obtained by the heating in ethanol under reflux, of *s*-butyl *p*-toluenesulphonate, with **1**. Ethyl α-tosyloxypropionate gave analogously ethyl α-selenocyanatopropionate[56]. In both cases inversion at the asymmetric carbon was observed. This reaction has also occasionally been used in carbohydrate chemistry. Thus it is possible to substitute with selenocyanate the tosyl group of methyl-2,3-*O*-diisopropylidene-5-*O*-tosyl-β-D-ribofuranoside by heating them for 15 min in DMF under reflux resulting in methyl-5-deoxy-2,3-*O*-diisopropylidine-5-selenocyanato-β-D-ribofuranoside (**14**, equation 20)[57].



(14) (20)

The attempt to similarly transform the dibenzenesuiphonate of 1,1-bis(hydroxymethyl)cyclohexane into the diselenocyanate by heating at 180°C in ethylene glycol, failed[58]. It rather leads directly to the cyclic diselenide 2,3-diselena-spiro-[4.5]-decane (**16**). The intermediately-formed diselenocyanate (**15**) could not be isolated (equation 21).



(15) (16) (21)

By the heating under reflux of an ethanolic solution of 2,4,5-trinitrotoluene with benzylselenourea, 2,4-dinitro-5-selenocyanatotoluene was obtained[9].

A number of organometallic compounds have served as starting materials for the synthesis of selenocyanates. For instance, the reaction of triphenylbismuth with selenium diselenocyanate (**10**) gives phenyl selenocyanate (**17**, equation 22).

$$(Ph)_3Bi + Se(SeCN)_2 \longrightarrow PhSeCN + (Ph)_2BiSeCN + Se \qquad (22)$$

(10) (17)

Aynsley and his coworkers[59] found that similar selenocyanation is also applicable to organomercury compounds. Diphenylmercury reacted vigorously with **10** in boiling benzene to give an 85% yield of phenyl selenocyanate (**17**) alongside phenylmercury(II) selenocyanate and selenium (equation 23).

$$PhHgPh + Se(SeCN)_2 \longrightarrow PhSeCN + PhHgSeCN + Se \qquad (23)$$

(10) (17) (18)

The methyl analogue of **17** is formed in 43% yield. Both methylmercury(II) selenocyanate and phenylmercury(II) selenocyanate are light sensitive, insoluble in water and thermally unstable.

A corresponding reaction occurs between diphenylmercury and selenium dicyanide (**19**) in benzene solution at room temperature (equation 24). Although the reaction proceeds slowly it gives 80–90% yield of phenyl selenocyanate (**17**) and phenylmercury cyanide.

$$\underset{\textbf{(19)}}{PhHgPh} + Se(CN)_2 \longrightarrow \underset{\textbf{(17)}}{PhSeCN} + PhHgCN \qquad (24)$$

The HgBr function of ferrocenylmercury bromide was substituted in approximately 40% yield by selenocyanate with the aid of copper selenocyanate[60]. The latter is prepared from copper bromide and potassium selenocyanate in acetonitrile and is used without being isolated.

Another procedure leading to selenocyanates is the addition of selenocyanic acid to acetylenes[61].

Dicyanodiselenide (**4**) can, analogously, be added to acetylenes to give diselenocyanato compounds (equation 25). From phenylacetylene **20** is obtained[62].

$$\underset{\textbf{(4)}}{PhC{\equiv}CH + (SeCN)_2} \longrightarrow \underset{\textbf{(20)}}{PhC(SeCN)=CH(SeCN)} \qquad (25)$$

The reaction of potassium selenocyanate with β-propiolactone proceeds with ring-opening to form β-selenocyanatopropionic acid[63]. In a similar manner it is possible to prepare selenocyanatoalkyl sulphonates (**21**) from sultones[64] (equation 26).

$$\underset{\begin{array}{l}|\quad|\\O\text{——}SO_2\end{array}}{CH_2CH_2CH_2} + KSeCN \longrightarrow \underset{\textbf{(21)}}{\begin{array}{l}CH_2CH_2CH_2SO_3K\\|\\SeCN\end{array}} \qquad (26)$$

The reaction of mercury salts with dialkyldiselenides causes the latter to split. Thus the reaction of dimethyl- or diethyl-diselenide with mercury

cyanide gives methyl (**22**) or ethyl (**24**) selenocyanate respectively. Additional products are possibly methylselenenylmercury cyanide (**23**, equation 27) as well as the mercury salt of methylselenol (**25**, equation 28)[64].

$$\underset{}{\text{MeSeSeMe} + \text{Hg(CN)}_2} \longrightarrow \underset{(22)}{\text{MeSeCN}} + \underset{(23)}{\text{MeSeHgCN}} \qquad (27)$$

$$\underset{}{\text{EtSeSeEt} + \text{Hg(CN)}_2} \longrightarrow \underset{(24)}{\text{EtSeCN}} + \underset{(25)}{\text{(EtSe)}_2\text{Hg}} \qquad (28)$$

2. Physical properties

Most selenocyanates are colourless, stable compounds with unpleasant, and in some cases repugnant, odours. They may be distilled without decomposition and are volatile with steam. The aliphatic selenocyanates are mostly liquids with higher boiling points than those of the corresponding alkyl halides. The aromatic selenocyanates are either high-boiling oils or, mostly, crystalline substances with well-defined melting points.

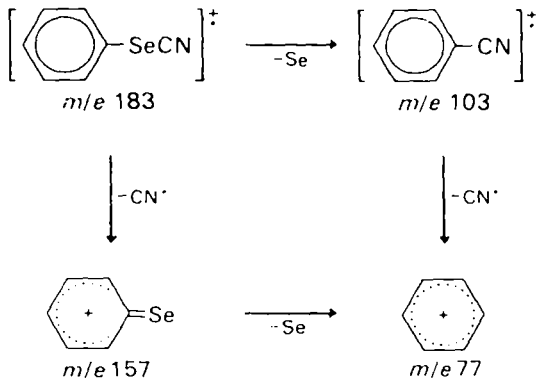
The i.r. spectra of selenocyanates is the subject of a large number of publications. Aynsley and his coworkers[59] have studied the i.r. spectra of methyl selenocyanate and of substituted phenyl selenocyanates and have assigned the absorption bands. Data from a similar study on a series of alkyl selenocyanates have been published by Franklin and coworkers[24]. In the context of a structure–reactivity study of hetero-substituted nitriles, Martin and his coworkers[66–68] reported some i.r. spectra of selenocyanates. For the characterization of selenocyanates and their differentiation from isoselenocyanates the CN stretching band can be used[69,70]. In organic selenocyanates it constitutes a sharp medium–strong band at $2160\ cm^{-1}$.

Very few publications deal with the u.v. spectra of selenocyanates. Cordella and Passerini[71] have measured the spectra of a series of substituted aryl selenocyanates in alcohol and cyclohexane. The spectra have a high intensity band at $\lambda_{max} = 236$ nm and a somewhat less intense band at $\lambda_{max} = 250–270$ nm. This is ascribed to the conjugation between π-electrons of the aromatic ring and the lone electron pairs of the selenium atom. The so-far obtained spectra indicate that there is very little interaction between the phenyl ring and the selenium atom owing to the strong attraction exerted by the CN group on the electrons of the selenium atom.

Agenäs[50] has studied the u.v. spectra of indolyl selenocyanates. These show a good correspondence with those of aryl selenocyanates. The absorption resulting from the conjugation of the heteroaromatic system

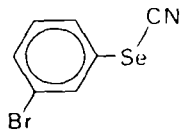
with the selenium atom is in the range of 270–290 nm. Chmutova and Neonilina[72] deal with the u.v. spectra of *p*-substituted phenyl selenocyanates in the context of a study of electronic effects of the SeCN group.

The study of the mass spectra of aromatic selenocyanates was undertaken by Agenäs[73,74]. The data allows the recognition of a unifying mechanism. It shows that the splitting off of the selenocyanate group may proceed in two mutually independent paths, as shown in Scheme 2. The results obtained with indolyl selenocyanates[52,75,76] correspond well with Scheme 2.

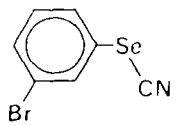


SCHEME 2.

Martin and Brause[77] give evidence for the electron structure of aryl selenocyanates based on dipole moment measurements. Chmutova and coworkers[78] have compared the calculated dipole moments of a series of *o*-, *m*-, and *p*-substituted phenyl selenocyanates with the experimentally observed values. From these it could be shown for instance, that for 3-bromophenyl selenocyanate (**26**) the *anti* form (**26a**) is preponderant and very little exists in the *syn* form (**26b**). The *anti* form is generally preponderant in the *m*- and *o*-substituted compounds. In some of the *o*-substituted phenyl selenocyanates the *syn* form may be completely missing.



(**26a**)



(**26b**)

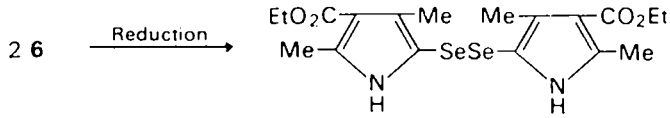
Of n.m.r. studies of selenocyanates very little is known. Studies of ^{13}C n.m.r. measurements on phenyl and *p*-tolyl selenocyanates as well as the $\delta(^{19}F)$ chemical shifts of *p*-fluorophenyl selenocyanate have recently been published[79].

3. Reactions

a. *Reduction.* The reduction of alkyl as well as aryl selenocyanates gives the corresponding selenols (equation 29). Nascent hydrogen, obtained by dissolving zinc in acids, may serve as the reducing agent[27,48,80]. Under

$$\text{RSeCN} \xrightarrow{\text{Reduction}} \text{RSeH} \tag{29}$$

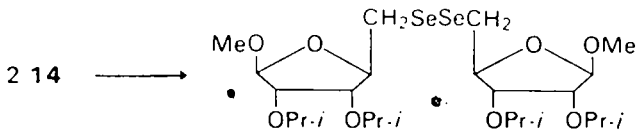
certain conditions it is possible to isolate the intermediate zinc salts $(RSe)_2Zn$, and eventually the diselenides RSeSeR formed by the air oxidation of the selenols. Thus treatment of the 5-selenocyanato derivative **6** with zinc in acetic acid gives bis(2,4-dimethyl-3-ethoxycarbonyl-pyrrolyl)-5,5′-diselenide (**27**, equation 30).



(30)

(**27**)

From the analogous reaction of the 3-selenocyanato derivative the 3,3′-diselenide is formed[28]. *o*-Nitrophenyl selenocyanate is reduced by zinc in alkaline medium to *o*-aminophenylselenol. Other substances which have been found useful as reducing agents are hypophosphorous acid[81], sodium in methanol[82], and alkaline solutions of dithionite as well as alkaline solutions of dextrose. For instance the dissolution of the selenocyanate **14** (see Section III.A.1.e) in methanol containing sodium methoxide, gave 5,5′-diselenobis(methyl-5-deoxy-2,3-*O*-diisopropylidine)-β-D-ribofuranoside (**28**, equation 31). The reactions in alkaline medium, primarily with dextrose



(31)

(**28**)

cannot be unequivocally classified as reductions: they constitute a transition to hydrolysis.

b. *Hydrolysis.* The alkaline hydrolysis of selenocyanates is one of the most important procedures for the preparation of diselenides[16,18,25,35,49,50,52,83,84]. For the as-yet unclarified mechanism of this reaction two hypotheses have been proposed. According to one, seleninic acids are formed as intermediates as in equation (32).

$$RSeCN + H_2O \longrightarrow RSeOH + HCN \quad (32)$$

$$RSeOH + RSeCN \longrightarrow RSeSeR + HCNO \quad (33)$$

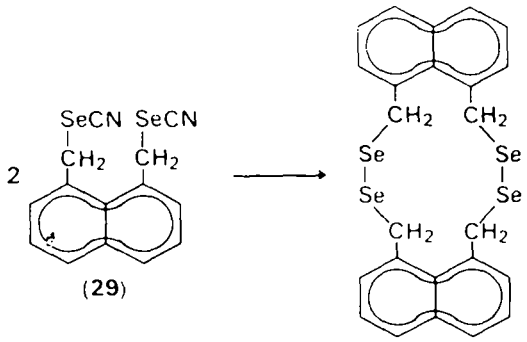
According to the other, the reaction proceeds with selenol intermediates (equation 34).

$$RSeCN + H_2O \longrightarrow RSeH + HCNO \quad (34)$$

$$2RSeH + [O] \longrightarrow RSeSeR + H_2O \quad (35)$$

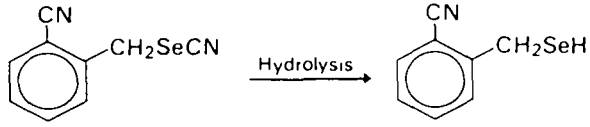
In support of the second hypothesis are the findings that by working with exclusion of atmospheric oxygen selenols can be isolated and that when the hydrolysis is conducted in the presence of alkylating agents, the selenols could be trapped in the form of selenides RSeR'.

A most interesting compound was isolated by Biezais-Zirnis and Fredga[85] from the hydrolysis in methanolic sodium hydroxide, of 1,8-bis(selenocyanatomethyl)-naphthalene (**29**). Instead of the expected naphtho-1,8-diselenepine, the 14-membered ring[85] was obtained.



(29) (30) (36)

The acid hydrolysis of selenocyanates proceeds quite obviously through selenol intermediates, which can, under certain conditions, be isolated[21,81]. For instance the hydrolysis by concentrated sulphuric acid of *o*-cyanobenzyl selenocyanate (**31**) results in *o*-cyanobenzylselenol (**32**, equation 37).



(**31**) (**32**) (37)

Usually, however, the corresponding diselenides are formed by air oxidation. Amongst others, it is possible in this way to transform selenocyanatoalkylcarboxylic acids into the corresponding diselenides; when selenocyanatoacetic acid is heated with hydrochloric acid it is easily converted into the diselenide acid **34** (equation 38).

$$2\,NCSeCH_2CO_2H \longrightarrow HO_2CCH_2SeSeCH_2\,CO_2H \qquad (38)$$

(**33**) (**34**)

Hydrolysis is also applicable to heterocyclic selenocyanates; in this way some indolyldiselenides have been prepared[49,50,52].

c. *Oxidation.* The oxidation of aliphatic and aromatic selenocyanates generally leads to good yields of the corresponding seleninic acids (equation 39). The oxidizing agent mostly used is nitric acid in a large range of concentrations[29,36–38,86–88].

$$RSeCN \xrightarrow{\text{Oxidation}} RSeO_2H \qquad (39)$$

The seleninic acids precipitate as the hydronitrates. With aromatic selenocyanates ring nitration is possible alongside the oxidation. Depending on reaction conditions the former might sometimes be the main reaction[38,86]. Analogously, it is possible to oxidize α,ω-diselenocyanates, with fuming nitric acid, to diseleninic acids[23].

Additional oxidizing agents occasionally used are 40% peracetic acid in glacial acetic acid, 5% potassium permanganate[89,90], and aqueous chlorine.

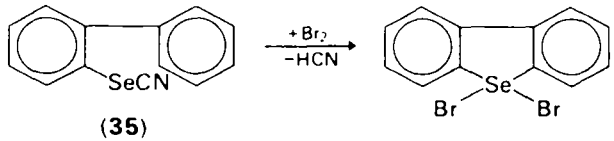
d. *Halogenation.* The reaction of selenocyanates with halogens, especially chlorine and bromine, is dependent upon the ratio of reagents.

When the molar ratio is 1:1 selenenyl halides are formed[34,39,45,91,92], while with an excess of halogen, alkylselenium trihalides are formed[25,34,45] (equation 40).

$$RSeCN \longrightarrow RSeX \longrightarrow RSeX_3 \qquad (40)$$

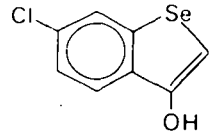
Alkylselenium trichlorides are also formed from the reaction of selenocyanates with sulphuryl chloride[25,93].

e. *Cyclization.* Through the cyclization of suitable selenocyanates it is possible to obtain a series of selenium-containing heterocycles. For instance *o*-selenocyanatobiphenyl (**35**) can easily be transformed with bromine into dibenzoselenophene dibromide (**36**, equation 41).



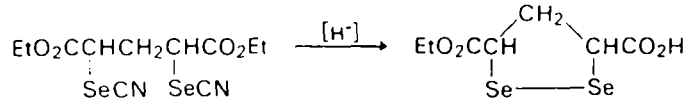
(**35**) (**36**) (41)

The treatment of 2-selenocyanato-4-chloroacetophenone with ammonia in methanol followed by heating for 2 h gives 3-hydroxy-6-chloroselenonaphthene (**37**)[94].



(**37**)

The acid hydrolysis of diethyl α,α'-diselenocyanatoglutarate with sulphuric acid in water/ethanol yielded 15% of the heterocyclic compound (**39**, equation 42)[19].

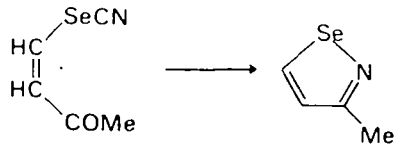


(**38**) (**39**) (42)

The heating at 180 °C of 1,1-bis(selenocyanatomethyl)cyclohexane entails the splitting off of both cyano groups and the formation of **16**[58] (see Section III.A.1.e.) (equation 43).

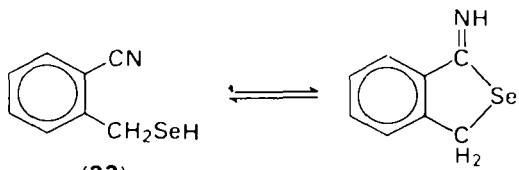
(15) (16) (43)

The cyclization of 3-selenocyanatoacrolein as well as of the corresponding butenone derivative (**40**) in liquid ammonia yields isoselenazole and its 3-methyl analogue (**41**) respectively (equation 44)[61].



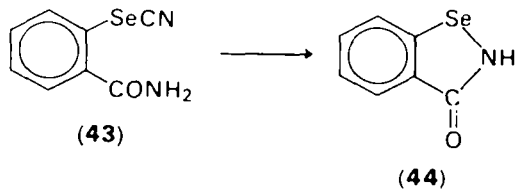
(40) (41) (44)

The selenol (**32**) formed by the hydrolysis of *o*-cyanobenzyl selenocyanate (see Section III.A.3.b) is in equilibrium with its cyclic form: 2-iminoselenanaphthene (1-iminoselenophthalide, **42**[21] (equation 45))[21].



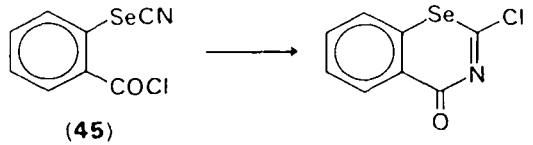
(32) (42) (45)

On melting or heating in glacial acetic acid, 2-selenocyanatobenzamide (**43**) is transformed into benzisoselenazole-3-one[95] (**44**, equation 46).



(43) (44) (46)

The cyclization of 2-selenocyanatobenzoyl chloride with hydrochloric acid at 60°C gives 2-chloro-1,3-benzoselenazine-(4)-one[96] (**46**, equation 47).



(45) (46) (47)

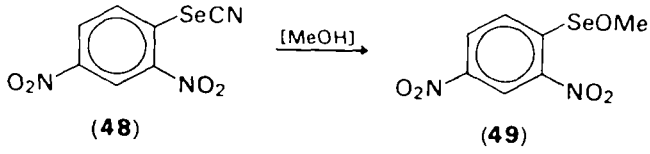
f. *Substitution reactions.* Aryl selenocyanates react vigorously with aryl thiols and give[97], with evolution of hydrocyanic acid, selenide sulphides (thioselenates, thiaselenanes) (equation 48). These compounds are

$$ArSeCN + RSH \longrightarrow ArSeSR + HCN \quad (48)$$

occasionally incorrectly called selenenyl sulphides. For the latter the correct formula is RSeSSeR (see Section III.B). With selenols, diselenides are formed in a similar manner. For instance, the reaction of phenyl selenocyanate with phenylselenol gives diphenyldiselenide (**47**, equation 49).

$$\underset{(17)}{PhSeCN} + PhSeH \longrightarrow \underset{(47)}{PhSeSePh} + HCN \quad (49)$$

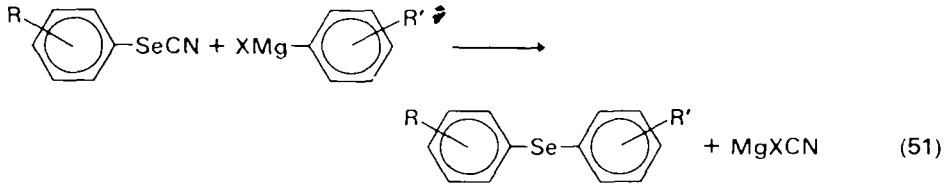
2,4-Dinitrophenyl selenocyanate (**48**) reacts with methanol, in the presence of copper or silver salts and catalytic amounts of pyridine, to give the methyl ester of the corresponding selenenic acid (**49**, equation 50)[98].



(48) (49) (50)

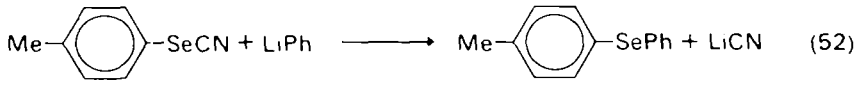
In a similar manner it is possible without difficulty to obtain seleneninates from 2-nitrophenyl, 1-anthraquinolyl, and 4-hydroxy-1-anthraquinolyl selenocyanates.

Unsymmetrical diselenides are formed from the reaction of aryl selenocyanates with Grignard reagents (equation 51).



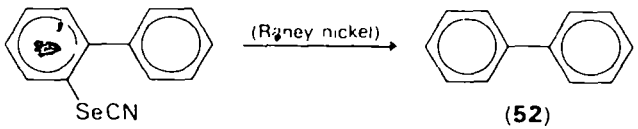
(51)

The same results are achieved by the use of aryllithium compounds instead of arylmagnesium halides[99]. Thus phenyl *p*-tolyl selenide (**51**) is formed in 73% yield from the reaction of phenyllithium with *p*-tolyl selenocyanate (**50**). The phenyllithium is prepared *in situ* from bromobenzene and lithium metal in ether (equation 52).



(50) (51) (52)

The reaction of aryl selenocyanates with Raney nickel leads to deselenation (deselenocyanation) as has been demonstrated in a series of reactions by Wiseman and Gould[100]. For instance the heating of *o*-selenocyanatobiphenyl (**35**) with a twentyfold excess of Raney nickel in ethanol/benzene solution yields 84% of biphenyl (**52**, equation 53).



(35) (52) (53)

B. Selenenyl Selenocyanates

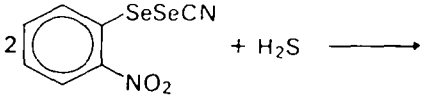
Selenenyl selenocyanates are only formally connected to esters of selenocyanic acid. Concerning their chemical reactions they might rather be regarded as unsymmetrical diselenides. Selenyl selenocyanates may be prepared from selenenyl halides by reacting them with potassium selenocyanate in an inert solvent (equation 54).

$$ArSeBr + KSeCN \longrightarrow ArSeSeCN + KBr \qquad (54)$$

Selenenyl selenocyanates are yellow to orange solid compounds which melt without decomposition. At higher temperatures they decompose with elimination of selenium (see Section III.A.1.c). They are relatively insensitive to hydrolysis by water or alcohol at room temperature. However, treatment with ammonia in ethanol or benzene solution as well as with ethanolic bromine transforms them into symmetrical diselenides. Selenenyl selenocyanates react with thiols to give quantitatively triselenides (equation 55). With hydrogen sulphide the reactions run somewhat

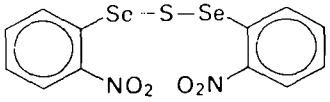
$$2\,ArSeSeCN + 2\,RSH \longrightarrow ArSeSeSeAr + RSSR + Se + 2\,HCN \qquad (55)$$

differently. For instance with *o*-nitrophenylselenenyl selenocyanate the corresponding bis-selenenyl sulphide (**54**) is obtained (equation 56).



(**53**)

$$+ H_2S \longrightarrow$$



(**54**)

$$+ 2\,HCN + 2\,Se \qquad (56)$$

The action of bromine transforms selenenyl selenocyanates into diselenides (equation 57). When an excess of bromine is added selenenyl bromides are formed (equation 58).

$$2\,ArSeSeCN + 2\,Br_2 \longrightarrow ArSeSeAr + Se_2Br_2 + 2\,BrCN \qquad (57)$$

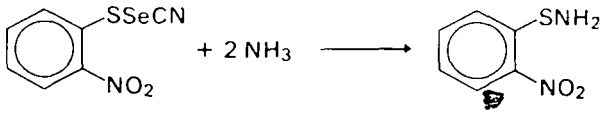
$$2\,ArSeSeCN + 3\,Br_2 \longrightarrow ArSeBr + Se_2Br_2 + 2\,BrCN \qquad (58)$$

C. Sulphenyl Selenocyanates

Sulphenyl selenocyanates may be prepared, by analogy with selenenyl selenocyanates, by the reaction of sulphenyl halides with potassium selenocyanates[101] (equation 59).

$$ArSBr + KSeCN \longrightarrow ArSSeCN + KBr \qquad (59)$$

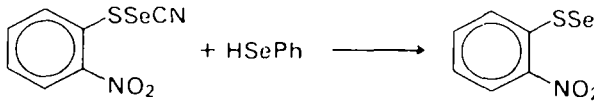
The sulphenyl selenocyanates have no definite melting points. Their reactivity is strongly reminiscent of selenenyl selenocyanate and they can therefore be transformed thermally into disulphides. The latter are also obtained by the action of either ammonia or bromine in ethanolic solution. In contrast when dry ammonia is used sulphenamides are formed, i.e. *o*-nitrophenylsulphenyl selenocyanate (**55**) gives the corresponding sulphenamide (**56**, equation 60).



(60)

(**55**) (**56**)

55 is hydrolysed by water even in the cold. With phenylselenol **55** reacts to give the corresponding selenenyl sulphide (**57**, equation 61).



(61)

(**55**) (**57**)

Sulphenyl selenocyanates give, on reaction with bromine, the corresponding disulphides.

D. Isoselenocyanates ('Seleno mustard oils')

The isoselenocyanates are relatively little known as compared to selenocyanates. Rheinboldt[1], in his detailed review covering the literature up to 1954, remarks that isoselenocyanates are practically unknown since they have never been isolated in the pure state. Soon afterwards, some of the methods which have been known in principle to lead to isoselenocyanates

have been improved to a degree which allowed the isolation of pure isoselenocyanates and the study of their properties. Some data dealing with acyl isoselenocyanates are found in connection with comparisons with the sulphur and oxygen analogues in two review articles dealing with these subjects[102,103].

1. Preparation

Five procedures have been found to be practically applicable to the preparation of isoselenocyanates.

a. *From imidoyl dihalides.* Stolte[104] has attempted already in 1886 to obtain phenyl isoselenocyanate (**58**) by the addition of powdered sodium selenide to an etheric solution of phenylimidoyl dichloride (phenylisocyanyl chloride). He obtained however, a product which was un-

$$PhN{=}CCl_2 + Na_2Se \longrightarrow \underset{(58)}{PhN{=}C{=}Se} + 2\,NaCl \qquad (62)$$

distillable and analytically impure. Since its reaction with ammonia or aniline gave the corresponding substituted selenoureas, it might be implied that at least part of the product was **58**.

Subsequently this procedure has been occasionally reemployed[105–108], but remains limited to the preparation of phenyl and ethyl isoselenocyanates.

b. *By selenation.* Phenyl isoselenocyanate (**58**) was obtained[107] from the reaction of phenyl isocyanate with phosphorus pentasulphide (equation 63).

$$5\,PhN{=}C{=}O + P_2Se_5 \longrightarrow \underset{(58)}{5\,PhN{=}C{=}Se} + P_2O_5 \qquad (63)$$

c. *By isomerization.* The yields of isoselenocyanates obtained by this method are usually unsatisfactory since the equilibrium in the isomerization leads to nearly equal quantities of both isomers[109]. Still it was possible, by heating benzhydrol selenocyanate (**59**) as well as its 4,4'-dimethyl analogue in a closed tube at 120 °C to obtain[20] benzhydryl isoselenocyanate (**60**) and its dimethyl analogue in yields of 40% and 46% respectively (equation 64).

$$\underset{(59)}{(Ph)_2CH{-}Se{-}C{\equiv}N} \overset{(120\,^\circ C)}{\rightleftharpoons} \underset{(60)}{(Ph)_2CH{-}N{=}C{=}Se} \qquad (64)$$

d. *From* N-*substituted diselenocarbamates.* Already Warner[110] has proposed that the formation of selenoureas from carbon diselenide and primary amines proceeds through the intermediacy of the corresponding diselenocarbamates. Attempts by Franklin and Werner[22] to introduce these as starting materials for the preparation of isoselenocyanates were unrewarding and gave, for instance in the case of methyl isoselenocyanate, only poor yields. These studies were again undertaken after a short while by Henriksen[111] who developed them into satisfactory preparative procedures. He succeeded, under certain conditions, in obtaining the alkylammonium salts of *N*-alkyldiselenocarbamates from the reaction of primary amines with carbon diselenide. The presence of an exchangeable proton on the nitrogen atom of the ammonium ion facilitates the splitting-out of HSe^-. By analogy with the formation of isothiocyanates the formation of isoselenocyanates occurs even at room temperature when the ammonium carbamate is successively reacted with an electrophile and a weak base. Thus when isobutylammonium *N*-*i*-butyldiselenocarbamate (**67**) is reacted with tosyl chloride and then with sodium carbonate, a 74% yield of isobutyl isoselenocyanate (**62**) is obtained (equation 65).

$$[i\text{-BuNHCSe}_2]^- i\text{-BuNH}_3^+ \xrightarrow{+\text{TsCl}} i\text{-BuNHCSe}_2\text{Ts} \xrightarrow{+CO_3^{2-}} i\text{-BuN=C=Se} \quad (65)$$

(**61**) (**62**)

e. *By substitution of halogen.* Since selenocyanates are ambident anions they may be alkylated on either selenium or nitrogen. Principally however selenocyanates are formed in alkylation reactions owing to attack by the strongly nucleophilic selenium atom on the respective substrates (see Section III.A.1.a). The reaction of triphenylmethyl chloride with potassium selenocyanate is the sole exception to this behaviour: As shown by Tarantelli and Pecile[69] as well as Pedersen[112], in this case the product is the isoselenocyanate (**63**, equation 66). Some organometallic compounds are also prepared in this manner[113-115].

$$(Ph)_3CX + [SeCN]^- \longrightarrow (Ph)_3CNCSe + X^- \quad (66)$$

(**63**)

The fact that the reaction of SiH_3I with AgSeCN gives SiH_3NCSe[113] has prompted Franklin and Werner[22] to attempt the preparation of methyl isoselenocyanate from silver selenocyanate and methyl iodide. They obtained, however, only methyl selenocyanate.

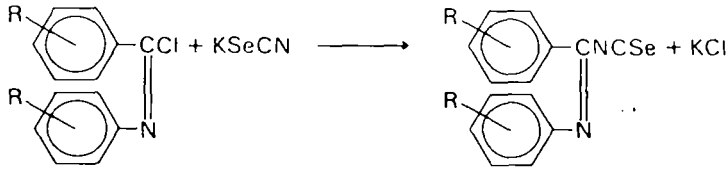
On the other hand, the acylation of selenocyanate ions leads exclusively to acyl isoselenocyanates. Douglass[116] has found that the reaction of

benzoyl chloride with potassium selenocyanate in acetone gave a solution of benzoyl isoselenocyanate (equation 67). Attempts to isolate this sub-

$$PhCOCl + KSeCN \longrightarrow [PhCONCSe] + KCl \quad (67)$$

stance gave only a compound with a probable polymeric structure[70]. The addition of amines or hydrazines to this product in acetone solution gives the corresponding acyl selenourea or acyl selenosemicarbazides[107,116–118] (see Section III.D.3.a.b). This fully justifies the postulated intermediacy of the benzoyl isoselenocyanate. It is similarly possible to obtain solutions of other acylisoselenocyanates[116,119].

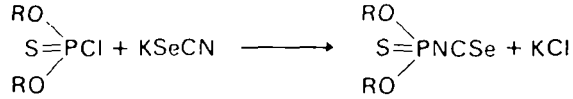
Isoselenocyanates with protected acyl groups (**64**) are obtained[120] from the reaction of *N*-substituted imidoyl dichlorides with potassium selenocyanate (equation 68):



(68)

(**64**)

Gabrio and Barnikow[121] have used dialkylphosphoryl chloride as well as dialkylthiophosphoryl chloride for the synthesis of the corresponding phosphorus-substituted isoselenocyanates (**65**, equation 69).



(69)

(**65**)

f. *From isonitriles.* The so far most useful and most generally applied method for the preparation of isoselenocyanates is the addition of selenium to isonitriles (equation 70). Jensen and Frederiksen[106] were the first to use

$$RN{\equiv}C + Se \longrightarrow RN{=}C{=}Se \quad (70)$$

this procedure for the preparation of phenyl isoselenocyanate (**58**).

Subsequently the method was employed, with only minor modification, to the preparation of a whole series of aromatic[70,107,122–124]

aliphatic[22,107,108,125–127] as well as cycloaliphatic[125–127] isoselenocyanates.

All other experiments to prepare isoselenocyanates in methods analogous to isothiocyanate preparations, as for instance by the action of hydrochloric, phosphoric or acetic acids on symmetrically *N*-substituted selenoureas, have been unsuccessful[128].

2. Physical properties

Isoselenocyanates are mostly solid, well crystallized, colourless substances. The aromatic compounds are remarkably stable and may be stored for years without decomposition. The stability at ambient temperature is strongly dependent on purity. Impurities seem to have autocatalytic influence. Most isoselenocyanates melt without decomposition at relatively low temperatures. They are however, on the whole, considered thermally labile, and decompose on prolonged heating or at high temperatures. Even *in vacuo*, their distillation is possible only with considerable losses. They are volatile with steam; however varying quantities of selenium are eliminated, depending on the isoselenocyanate. Aliphatic isoselenocyanates possess acrid, mostly repugnant, odours, the aromatic compounds have a characteristic not-unpleasant odour, especially in dilute solutions. The vapours have irritating effects on eyes, nose and mucous membranes of the throat. On contact with the skin they occasionally cause eczemas.

Several studies of the i.r. spectra of isoselenocyanates have been published[20,69,70,123,129,130]. A very detailed work by Franklin and coworkers[126] has appeared recently. In contrast to selenocyanates, the isoselenocyanates are marked by a strong wide doublet band in the range of 2000–2200 cm^{-1}. These can be used to distinguish the isoselenocyanates from selenocyanates.

3. Reactivity

The reactivity of isoselenocyanates is determined by the cumulative double bond. In the various canonic formulae of the resonance of the RNCSe molecule, the positive charge is always on the carbon atom.

$$R-N=C=Se \longleftrightarrow R-\bar{N}-\overset{+}{C}=Se \longleftrightarrow R-N=\overset{+}{C}-\bar{Se}$$

Therefore the carbon atom is easily susceptible to attack by nucleophilic reagents. Indeed the isoselenocyanates behave analogously to the isothiocyanates and may be smoothly reacted with, for instance, ammonia, amines and hydrazines. These reactions are also used, sometimes, as chemical evidence for the presence of the isoselenocyanate structure.

a. *Reactions with ammonia and amines.* The nucleophilic addition of

ammonia, primary amines, and secondary amines to isoselenocyanates gives the corresponding selenoureas in good yields [104,105,118,124,125,131–133] (equation 71). Some of these reactions proceed so

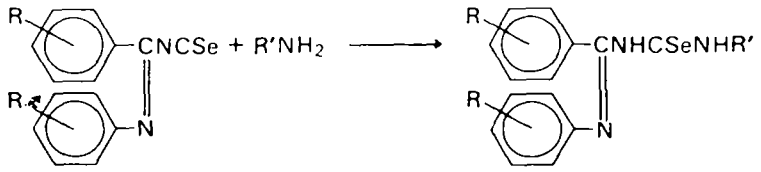
$$RNCSe + HNR^1R^2 \longrightarrow RNHCSeNR^1R^2 \qquad (71)$$

vigorously even at room temperature that the heat released might cause considerable decomposition. In order to obtain higher yields and possibly purer products it is advisable to dilute the components by solvent. In the preparation of selenoureas it is often unnecessary to isolate the isoselenocyanates. It is most advantageous to use the solution in which they are prepared by adding to it an ethanolic solution of ammonia or amine.

In a similar manner it is possible to use the solutions of acyl isoselenocyanates in the reaction with amines or ammonia to obtain the corresponding acylselenoureas[116,118,134]. This method led to the very interesting observation[119] that depending on the nature of the acyl residues a substitution reaction, leading to amides, could occur (equation 72b) alongside the normal reaction leading to acylselenoureas (equation 72a).

$$[RCONCSe] \xrightarrow{+H_2NR'} \begin{cases} \longrightarrow RCONHCSeNHR' & (72a) \\ \longrightarrow RCONHR' + HSeCN & (72b) \end{cases}$$

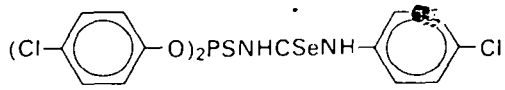
The isoselenocyanates derived from *N*-substituted-imidoylcarbonic acids (**64**) (see Section III.D.1.e) react with aromatic amines to give the correspondingly-substituted selenoureas[120] (**66**, equation 73).



(73)

(**64**) (**66**)

The phosphoric acid derivatives of isoselenocyanates (see Section III.D.1.e) react analogously, i.e. *N*-[di-(*O*-*p*-chlorophenyl)thiophosphoryl]-*N'*-*p*-chlorophenylselenourea (**67**)[121] was obtained in 71% yield from suitable starting materials.



(**67**)

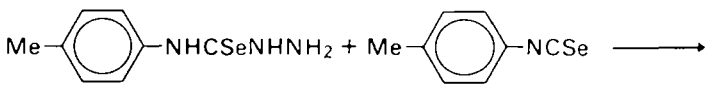
b. *Reactions with hydrazine and substituted hydrazines.* The reactions of isoselenocyanates with hydrazines lead to selenosemicarbazides. Jensen and Frederiksen[106] have obtained, on treating phenyl isoselenocyanate (**58**) with hydrazine hydrate, 4-phenylselenosemicarbazide (**68**, equation 74).

$$\underset{(58)}{PhNCSe} + H_2NNH_2 \longrightarrow \underset{(68)}{PhNHCSeNHNH_2} \qquad (74)$$

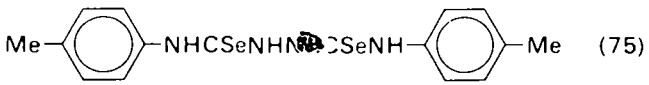
Subsequently a whole series of 4-substituted selenosemicarbazides have been synthesized in good yields by this method[108,112,117,122,135].

By employing monosubstituted hydrazines, disubstituted selenosemicarbazides are formed with substitution at either the 1,4-positions or the 2,4-positions, depending on the hydrazine employed. By analogy with thiosemicarbazides, 2,4-disubstituted selenosemicarbazides result from monoalkylhydrazines[117,127] whereas from monoaryl-substituted selenohydrazines either 1,4-[117,124,135] or 2,4-[136] disubstituted selenosemicarbazides are obtained, depending on reaction conditions. By choosing suitable starting materials this method can lead to additionally-substituted selenosemicarbazides[117,127].

It is interesting to note that under the reaction conditions employed, no formation of bis-selenoureas was observed from the reactions of isoselenocyanates with hydrazine hydrate. The bis-selenoureas can however be prepared by reacting selenosemicarbazides with isoselenocyanates, as could be shown by the synthesis of *N,N'*-di[*N*-*p*-tolylselenocarbamoyl]-hydrazine (**71**) from **69** and **70**[135] (equation 75).



(**69**) (**70**)



(75)

(**71**)

The addition of acylhydrazines to aryl(alkyl) isoselenocyanates runs smoothly. Thus a number of 4-substituted-1-acylselenosemicarbazides (**72**) were prepared[117,124,137] (equation 76) from the corresponding acylhydrazines and isoselenocyanates.

$$RNCSe + H_2NNHCOR' \longrightarrow \underset{(72)}{RNHCSeNHNHCOR'} \qquad (76)$$

1,4-Diacylselenosemicarbazides (**73**) are prepared analogously from the reaction of acyl isoselenocyanates with acylhydrazines[137].

$$RCONHCSeNHNHCOR'$$

(**73**)

c. *Miscellaneous reactions.* Isoselenocyanates show notable stability towards alcohols. The addition of ethanol to cyclohexyl isocyanate (**74**) which occurs upon heating of the components under reflux for 24 h, is the sole example so far published. It gave ethyl *N*-cyclohexyl-selenocarbamate **75** (equation 77) in 49% yield.

$$\underset{(\mathbf{74})}{C_6H_{11}NCSe} + EtOH \longrightarrow \underset{(\mathbf{75})}{C_6H_{11}NHCSeOEt} \qquad (77)$$

The reaction of isoselenocyanates with water at ambient temperatures is very slow, but with even small quantities of very weak acids decomposition with elimination of selenium is immediate. Likewise, they react instantaneously with silver nitrate solutions to form black silver selenide[22]. The reduction of isoselenocyanates with Zn/HCl[22] or $LiAlH_4$[20,69] leads to amines (equation 78):

$$RNCSe \xrightarrow{Reduction} RNH_2 \qquad (78)$$

When triphenylmethyl isoselenocyanate (**63**), is heated in dry acetonitrile, the isoselenocyanate group is quantitatively substituted, resulting in the formation of trityl cyanide[69] (**76**, equation 79).

$$\underset{(\mathbf{63})}{Ph_3CNCSe} \xrightarrow{[CH_3CN]} \underset{(\mathbf{76})}{Ph_3CCN} + Se \qquad (79)$$

Trivalent phosphorus compounds such as triphenylphosphine cause deselenation when reacted with triphenylmethyl isoselenocyanate (**63**). Thus nearly quantitative yields of triphenylmethylisonitrile (**77**) and the corresponding selenophosphorus compound are formed[138] (equation 80). The kinetics of the reaction has been studied in detail.

$$\underset{(\mathbf{63})}{Ph_3CNCSe} + PPh_3 \longrightarrow \underset{(\mathbf{77})}{Ph_3C{-}N^+{\equiv}C^-} + \underset{(\mathbf{78})}{SePPh_3} \qquad (80)$$

IV. TELLUROCYANATES

Very little is known, up to now, about tellurocyanates although the elements of the sixth main group form stable complex ions, such as OCN^-, SCN^- and $SeCN^-$, with the cyanate ion. All attempts to prepare the isologous tellurocyanates through corresponding procedures have been, for many years, unsuccessful[139].

It was known that potassium cyanide in liquid ammonia could dissolve tellurium[140]. However, on concentration of such solutions the sole substances obtained were the starting tellurium and potassium cyanide. This led to the proposition that the tellurocyanate ion exists only in solution. The bonding in the solid state to a relatively small, highly polarizing cation such as alkali metal ions should render it unstable. Starting from these considerations Downs[141] was the first to succeed in preparing a salt of tellurocyanate, by using a large weakly-polarizing cation, namely tetraethylammonium ion. The cyanide of the latter gave, upon reaction with tellurium in dimethylformamide, tetraethylammonium tellurocyanate. Concentration of the solutions brought about the precipitation of pale yellow crystals of the latter which still contained 1 mole of bound solvent, were highly deliquescent, and decomposed on addition of water with elimination of tellurium. Since the compound was very sensitive to atmospheric oxygen no further studies concerning it were conducted.

These views concerning the stability of tellurocyanates obtained further support from the work of Songstad and his coworkers, who have studied the dependence on the nature of the cation of the properties of selenocyanate and thiocyanate ions in acetronitrile solution[142].

They have found that in protic solvents, the small alkali metal ions and other hard Lewis acids associate with the nitrogen atom of the selenocyanate and thiocyanate anions and thereby influence the electron distribution of these ions. In the case of selenocyanates this results in a weakening of the carbon–selenium bond, which is sufficient to impart an electrophilic character to the selenium atom. This reasoning, when applied to tellurocyanates, would imply that hard Lewis acids might facilitate the splitting of the even weaker carbon–tellurium bond. Further, they have found that tetramethylammonium and tetraphenylarsonium thiocyanates as well as selenocyanates were, in contrast to the tetraethylammonium salts, nonhygroscopic and stable. Considering these facts they succeeded in synthesizing two stable salts of tellurocyanate, namely tetramethylammonium and tetraphenylarsonium tellurocyanate[143]. Towards this end they reacted the corresponding cyanides with powdered tellurium in acetonitrile (equation 81).

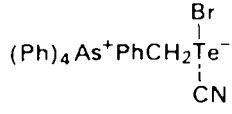
$$[R_4N]^+CN^- + Te \longrightarrow [R_4N]^+TeCN^- \quad (81)$$

Tetraphenylarsonium tellurocyanate shows, when pure, remarkable stability towards atmospheric components as well as towards light. Tetramethylammonium tellurocyanate is somewhat less stable and rapidly decomposes in damp air or by the action of light. Both salts are soluble in aprotic solvents. The positions of their absorption maxima in acetonitrile solution were determined as 2081 cm^{-1} in the i.r. region and in the u.v. range at 247 nm. Their crystal structures have been determined by X-ray diffraction[143].

A more accurate study of the vibrational spectra of tetramethylammonium and tetraphenylarsonium tellurocyanates, with the aid of i.r. and Raman spectroscopy revealed that the tellurocyanate ion possesses three fundamental vibrations. For tetraphenylarsonium tellurocyanate the following assignments have been[144] made: $\nu_1 = 2075\,cm^{-1}$ for the CN bond vibration, $\nu_2 = 458\,cm^{-1}$ for Te–C bond and $\nu_3 = 359\,cm^{-1}$ for TeCN deformation vibration.

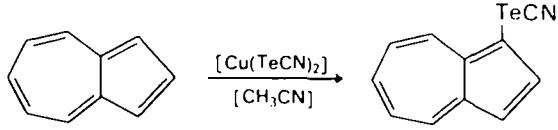
The X-ray–photoelectron spectroscopy of tetraphenylarsonium cyanate, thiocyanate and selenocyanate, as well as tellurocyanate, shows[145] that, contrary to expectations the N–(1s) and C–(1s) bonding energies in the NCX^- ion do not change observably with the change in substituent (X = O,S,Se,Te).

Attempts at alkylation of the tellurocyanate ion were unsuccessful. The reaction of equivalent quantities of benzyl bromide, and tetraphenylarsonium tellurocyanate in acetonitrile led[146] exclusively to an adduct with possibly the structure **79** in high yields.



(79)

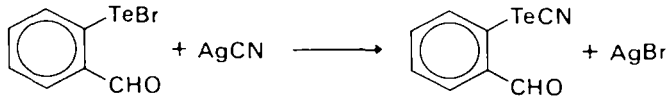
Some, in part contradictory, data were contributed by Nefedov[60]. By heating powdered potassium cyanide and tellurium for 3 hours at 100–250 °C he obtained crude potassium tellurocyanate. The latter, when reacted with azulene in acetonitrile in the presence of copper salts, gave 1-tellurocyanatoazulene (**80**) in 22% yield, in the form of violet crystals m.p. 80–81 °C (equation 82).



(82)

(80)

The only aromatic tellurocyanate so far described[147] is *o*-formylphenyl tellurocyanate (**81**). It is prepared, analogously with selenocyanates by melting an intimate mixture of *o*-formylphenyltellurenyl bromide with silver cyanide (equation 83). The compound is remarkably stable.



(83)

(**81**)

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The Chemistry of Cyanates and their Thio Derivatives
Edited by Saul Patai

CHAPTER 20

Biological formation and reactions of cyanates†

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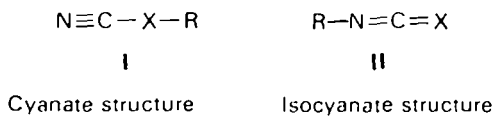
† The term 'cyanate' is used here to denote compounds containing the groupings NCO—, OCN— and NCS—. Compounds containing the grouping SCN— are the subject of another chapter of this Volume; their properties have been included only to the extent required for a clear presentation of the subject discussed.

I. INTRODUCTION

Cyanates, especially the sodium or potassium salt, have long been considered as agents of potential biological interest[1]. This assumption was borne out by their versatile reactivity on the one hand and low toxicity on the other, a combination of properties which is highly desirable if drug application is considered. Schütz and coworkers[2–4] undertook the first systematic studies of the biological properties of cyanates, but almost 20 years had elapsed before a renewal of interest in these compounds, resulting from experience with cyanate-contaminated urea, prompted a new series of investigations.

The formal distinction between cyanate and isocyanate structures, or their corresponding sulphur analogues, is given by structures **I** and **II** below:



I **II**

Cyanate structure Isocyanate structure

(R = H; alkyl; aryl, X = O; S)

Cyanic or thiocyanic acid (**I**, R = H) exists in aqueous solution in equilibrium with the tautomeric isocyanic or isothiocyanic acid (**II**, R = H). Therefore, even though an independent existence in pure form of either N≡C−OH and HN=C=O could be demonstrated[5], this difference in structure is of no consequence in biological media. In this context, the structural difference between organic cyanates and their isomeric isocyanates (**I** and **II**, X = O, R = alkyl or aryl) or organic thiocyanates and their isomeric isothiocyanates (**I** and **II**, X = S, R = alkyl or aryl) is more tangible.

The ionization constant of cyanic acid[6] has been assigned the value of $10^{-3.75}$, which implies that only a negligible fraction, less than 0·001% of the total present, would exist in the non-ionized form at physiological pH (7·2–7·4). Yet, current evidence implicates the non-ionized form as the participant in most biological reactions. More specifically, the reactions of inorganic cyanates are largely those of structure **II** above, almost irrespective of the nature of the group R. For this reason, no distinction will be made

between organic and inorganic cyanates and isocyanates. In fact, however, organic cyanates (I) have seldom been used in biological work, if at all, because of their highly unstable nature and tendency to polymerize to esters of cyanuric acid or isomerize to the corresponding isocyanates.

The case of the thiocyanates and isothiocyanates is different. The biological effects of the inorganic salts are largely those of the thiocyanate ion, NCS^-, but those of the organic thiocyanates and isothiocyanates arise either from these molecules *per se* or from thiocyanate ion that they may eventually generate. In some cases, these effects could be traced to the mere presence of divalent sulphur in the molecule. In view of this, the biological reactions of the thiocyanates and isothiocyanates may not have a common structural denominator.

Most of the biological effects of the inorganic cyanates and organic isocyanates are due to their reactivity as acylating agents. For this reason, the low-boiling, highly reactive, isocyanates are unbearable lachrymators, whilst the less reactive isothiocyanates are only mild irritants that evoke, in low concentration, a rather pleasant spicy effect, reminiscent of mustard. In this respect, these compounds resemble the carbonyl halides which have been reviewed in an earlier volume of this series[7]. Henceforth, the term 'cyanate' will be used to denote the class as a whole, but individual compounds will be referred to according to accepted nomenclature.

Target structures for covalent bond formation with cyanates in biological media are the usual nucleophilic sites in macromolecular structure, such as amino, thiol and hydroxy groups, carboxylate anion, and nitrogen heterocycles such as imidazole and structures incorporating it. The reaction of these with the more reactive cyanate species may be represented by the following general equation:

$$R^1{-}N{=}C{=}O + H{-}X{-}R^2 \longrightarrow R^1{-}NH{-}CO{-}X{-}R^2$$

where R^1 may be H, alkyl or aryl; X may be NH, O, S, COO or NR; and R^2 a carrier molecule or supporting structure. An indication of the occurrence of these reactive functional groups in some important biological systems and their relative nucleophilicities have been given in Reference 7. Their reactions with cyanates and ensuing biological effects are the subject of this presentation.

II. BIOLOGICAL FORMATION OF CYANATES

Cyanate and thiocyanate are formed *in vivo* in the course of detoxification of cyanide. The major and more important pathway, first observed by Lang[8] is conversion to thiocyanate. The reaction is mediated by an enzyme

which was initially called by the trivial name rhodanase, but subsequently given the systematic name thiosulphate sulphur transferase (EC 2.8.1.1). Thiosulphate or even colloidal sulphur are essential cofactors:

$$CN^- + S_2O_3^{2-} \xrightarrow{\text{Rhodanase}} SCN^- + SO_3^{2-}$$

The reaction mediated by rhodanase is practically irreversible, as the equilibrium constant, K, given by

$$K = \frac{[SCN^-][SO_3^{2-}]}{[CN^-][S_2O_3^{2-}]}$$

has a magnitude[9] of 10^{-10}. However, thiocyanate may be reconverted into cyanide by the action of another enzyme, thiosulphate oxidase[10]. This explains the recurrence of toxic symptoms of cyanide poisoning after initial antidotal therapy with thiosulphate.

Rhodanase is located mainly in the mitochondrial fraction of liver cells but has also been found at other sources. It has been isolated in crystalline form[11], has a molecular weight of 37,000 and may use sulphur donors other than thiosulphate, mostly thiosulphonates. The efficacy of these was investigated by Sörbo[9] and is given in Table 1.

TABLE 1. Relative efficacy of sulphur donors as cofactors for rhodanase[a]

Sulphur donor	Relative efficacy
Thiosulphate	100
Benzenethiosulphonate	304
p-Chlorobenzenethiosulphonate	303
p-Bromobenzenethiosulphonate	383
p-Toluenethiosulphonate	329
α-Naphthalenethiosulphonate	113
β-Naphthalenethiosulphonate	132
Ethanethiosulphonate	1054
N-Butanethiosulphonate	1396

[a] Data taken from Sörbo[9]

Sörbo[9], and Westley and Green[12,13] suggested that rhodanase may operate by means of an —S—S— group which acts as a transient sulphur carrier. The following scheme is illustrative:

$$\text{Enzyme}\begin{matrix}|\\S\end{matrix}\!\!\begin{matrix}|\\S\end{matrix} \xrightarrow{S_2O_3^{2-}} \text{Enzyme}\begin{matrix}|\\S^-\end{matrix}\!\!\begin{matrix}|\\S-S_2O_3^-\end{matrix} \xrightarrow{CN} \text{Enzyme}\begin{matrix}|\\S\end{matrix}\!\!\begin{matrix}|\\S\end{matrix} + SO_3^{2-} + SCN^-$$

More recently, Wang and Volini[14] reported on the interdependence of substrate and enzyme conformation in rhodanase catalysis. The enzyme from bovine liver forms ion pairs with the substrate and product anions: thiosulphate, cyanide, sulphite, and thiocyanate. However it may also use such diverse anions as acetate, formate, sulphate, and glycinate for the formation of ion pairs. Binding with thiosulphate leads to a more constrained protein conformation, but relaxation of structure follows release of the product, thiocyanate ion.

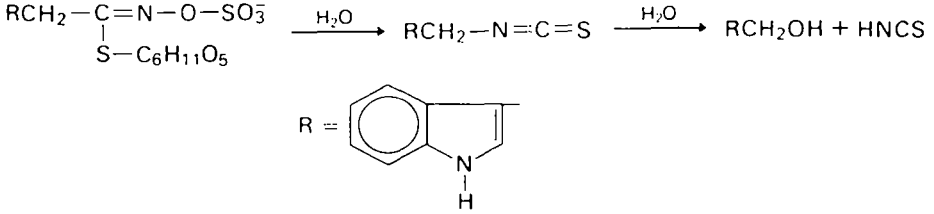
Within certain limits, the rate of cyanide detoxification depends on the rate of sulphur transfer which, in turn, depends on the concentration of sulphur donors. Because these are normally present in tissues in limited amounts, this rate is far too slow for the prevention of cyanide poisoning if intake exceeds detoxification. However, the rate of detoxification may be accelerated considerably by the administration of thiosulphate. For example, it was shown that the LD_{50} of cyanides in dogs could be increased threefold upon treatment with thiosulphate, fivefold upon treatment with nitrite and 18-fold when a combination of both agents was used. Thus, whilst nitrite produces methaemoglobin which competes with cytochrome C, the vulnerable target in cyanide poisoning, for combination with CN^-, added thiosulphate promotes clearance through conversion to a relatively harmless product. This is the basis of the antidotal treatment of cyanide poisoning[15]. Remarkably, further protection against cyanide could be achieved by the administration of the enzyme itself, together with thiosulphate[16], but such usage has not gone beyond the experimental stage because the enzyme is not available as a drug.

Other trans-sulphurase enzymes were also discovered in *E. coli* and rat liver. One of these uses 3-mercaptopyruvate as sulphur donor (EC 2.8.1.2); when cyanide is the acceptor, thiosulphate is formed[17]:

$$HS{-}CH_2COCOO^- + CN^- \longrightarrow CH_3COCOO^- + SCN^-$$

Thiocyanate normally occurs in blood at a concentration which is less than 2 mg per 100 ml and its origin is ascribed to dietary items that contain or generate nitriles[18]. A classical example is the glycoside amygdalin found in bitter almonds and which gives rise, upon hydrolysis, to benzaldehyde, glucose and hydrocyanic acid. High thiocyanate levels were found in communities that consume food containing cyanide, such as cassava which is a staple food in the tropics[19]. The direct intake of thiocyanate rather than cyanide follows the consumption of vegetable products that are particularly rich in what is known as the 'mustard oils' and which consist mainly of organic isothiocyanates. These usually occur as their glycosides, particularly in the brassica plants, an example of which is cabbage[20,21].

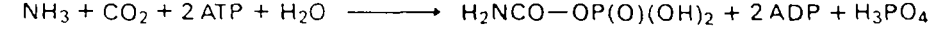
Glucobrassicin contained in 100 g of fresh cabbage leaves may contribute, after hydrolysis, 4 to 31 mg inorganic thiocyanate:



In the related glycoside glucotropaeolin (R = phenyl) hydrolysis leads to benzyl thiocyanate as well as benzyl isothiocyanate. Another rich source of thiocyanate-yielding indole derivatives is woad (*Isatis tinctoria* L.)[21a].

A common source of cyanide and, hence thiocyanate, is cigarette smoking. In a recent study of thiocyanate levels in smokers and non-smokers, Barylko-Pikielna and Pangborn[22] found that this level was roughly proportional to the smoking pattern, but with large individual variations. A rapid increase in salivary thiocyanate occurs immediately upon the smoking of a cigarette, but neither urinary nor salivary SCN^- could serve as an index of a person's exposure to cigarette smoke. Essentially similar conclusions were reached by Ray and Shiller[23] who studied salivary SCN^- levels in smokers and non-smokers among a submarine crew, and by Maehly and Swensson[24] who compared urine CN^- and SCN^- in persons exposed to cyanide either through smoking or as an occupational hazard. A more positive correlation was found by Yacoub and coworkers[25] who reported that SCN^- level in urine was a function of the amount of smoking and correlated, at the same time, with the level of blood carbon monoxide. This variance in results may be partly explained by the observation[26] that large doses of thiocyanate have a faster rate of elimination than 'normal level' thiocyanate and which is due to saturation of thiocyanate-concentrating compartments and the inability of kidneys to reabsorb large amounts of filtered thiocyanate.

With the exception of the detoxification mechanisms discussed above, cyanates are not known to arise as such *in vivo*. However, one may consider the universal carbamylating agent, carbamyl phosphate[27], as cyanate in bound form. The biological formation of carbamyl phosphate is based on the utilization of ammonia and carbon dioxide rather than cyanate and may reflect a pathway of prebiotic evolution:



In ureotelic vertebrates, the reaction is mediated by a carbamate kinase that requires acetyl glutamate as an essential cofactor[28,29]; but the requirements in bacteria may be different. Further reference to carbamyl phosphate as cyanate in bound form will be made in the next section.

III. REACTION OF CYANATES WITH BIOLOGICALLY-IMPORTANT FUNCTIONAL GROUPS

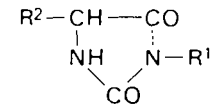
Any consideration of the biological effects of cyanates should be made in the light of their reactions with cell constituents, such as functional polypeptides, proteins, nucleic acids and perhaps lesser molecules if these constitute important substrates or cofactors. Admittedly, not all cyanate reactions reported in the biochemical literature are of immediate biological relevance. For example, there is no proof as yet that cyanates react *in vivo* with *free* amino acids and that such a reaction, if at all possible, has measurable biological consequences. Yet, such reactions are included in this presentation because they provide a general background and offer a clue to possible reactions with prevailing substrates at the cellular level. For the sake of clarity, these reactions are classified in accordance with the nature of nucleophile involved rather than with size or type of substrate. Hence, we shall first proceed by reviewing reactions involving NH_2, OH and SH groups, then describe the overall effect on the supporting macromolecule.

A. Reactions Involving Amino Groups

Cyanates react with primary amino groups to form either *N*-substituted amides of carbamic acid, or ureas; if a vicinal carboxylic acid group is present (as occurs in the α-amino acids or acid hydrolysates of polypeptides that have been treated with a cyanate) then a hydantoin may be formed. In most of the early work with cyanates which had more of an analytical orientation, hydantoins rather than *N*-carbamyl derivatives were the usual end products:

$$R^1{-}NCO + H_2N{-}CHR^2COOH \longrightarrow$$

$$R^1NHCONH{-}CHR^2COOH \xrightarrow{-H_2O}$$



With the inorganic cyanates, R = H; with phenyl isocyanate, a favourite reagent in analytical work, R = Ph. Early documentation of these reactions are the works of Dakin[30] on carbamylamino acids, of Bergmann and coworkers on phenylcarbamyl dipeptides[31], and of Jensen and Evans on phenylcarbamyl-insulin[32]. In a more biological context, the work by Fieser and Creech[33] on the coupling of isocyanates of polycyclic hydrocarbons, some carcinogenic, with amino acids is noteworthy. Subsequently, use of phenylisothiocyanate was advocated by Edman[34] and by Eriksson and Sjosquist[35] in an alternative procedure to the dinitrofluorobenzene method of Sanger[36] for the stepwise determination of terminal amino groups in proteins.

The most comprehensive information on the reaction of cyanates with the amine function of various biological substrates comes from the work of Stark and his collaborators, following a preliminary observation that ribonuclease is slowly inactivated by trace contamination of urea with cyanate[37]. In an early paper on the subject, Stark and Smyth[38] showed that almost all the usual amino acids and a number of representative peptides and proteins could be *N*-carbamylated by mild treatment with KNCO in aqueous phase at pH 8. At this stage, it became clear that the carbamylation of proteins was problematic, presumably on two accounts:

(i) Not all amino groups in a protein molecule are accessible to the reagent unless drastic denaturation and unfolding of tertiary structure is effected by means of urea.

(ii) Not all amino groups are equally reactive towards the reagent; for example, the ε-amino group of lysine residues ($pK_a \sim 10$) appears to be less reactive than a terminal amino group ($pK_a \sim 8{\cdot}5$). This seemed paradoxical in view of the premise[39] adopted by the authors that cyanate and amine are reactive in their ionic forms, i.e. as NCO^- and RNH_3^+ rather than as uncharged species. If that were true, then ε-amino groups of lysine would be expected to be more reactive, whilst in the same investigation glycylglycine (pK_a 8·17) was found to be more reactive than alanine (pK_a 9·69).

In a subsequent and more systematic study, Stark[40] reached the following conclusions:

(i) The logarithm of the second order rate constant, k_i, of the reaction†

$$NCO^- + H_3\overset{+}{N}{-}X{-}COO^- \longrightarrow H_2NCONH{-}X{-}COO^-$$

† In the authors' original notation, k_i is the rate constant of the ionic reaction and k_m is that of the molecular mechanism.

is linearly related to the pK_a value of the amino group involved in the reaction. However, the lower is the pK_a of that amino group, the more reactive would it seem to be (Figure 1, Table 2). An important implication is that at pH ~ 7, the α-amino groups of proteins (pK_a ~ 8) are expected to react with cyanate about 100-times faster than the more basic ε-amino groups (pK_a 10·7). Thus, cyanate may be used as a selective carbamylating agent.

(ii) In view of the above, the reaction of amino groups of proteins with cyanate occurs between the uncharged species and not between their respective ionic forms as formulated above. In support of this contention is the observation that the relative rates of carbamylation in water of a series of ω-amino acids is the same for KNCO and for Et—N=C=O (Figure 2).

These conclusions were confirmed in a latter and independent publication by Smyth[41] who found that the half-life ($t_{1/2}$) of various amino acids and peptides in 0·2 M-NaNCO at pH 6·0 and 30 °C increases with an increase in the pK_a value of the amine involved:

	pK_a	$t_{1/2}$ (min)
Phenylalanine	9·1	145
Leucyleucine	8·3	19
Glycylglycylglycine	7·9	13
Tyrosyltyrosine	7·7	11

Remarkably, the rates of carbamylation increase in the presence of 1 M-formaldehyde. Smyth considers this as further evidence in support of the non-ionic mechanism, since CH_2O is expected to favour the uncharged amine by the following mechanism:

$$R\overset{+}{N}H_3 \xrightleftharpoons{H^+} R\ddot{N}H_2 \xrightleftharpoons{CH_2O} R\ddot{N}H{-}CH_2OH$$

Recently, Garner and collaborators[42] suggested application of cyanate reaction kinetic data for the determination of the pK_a values of α-amino groups in peptides and proteins. The technique was applied to glycylglycine, L-valyl-L-leucyl-L-seryl-L-glutamylglycine and to the main component ferrimyoglobins from a number of maritime mammalia.

B. Reactions Involving Thiols

Cyanate reacts rapidly with thiol groups in cysteine, gluthathione and denatured, reduced proteins, yielding the corresponding *S*-carbamyl

TABLE 2. Apparent specific rate constants for the reaction of amino acids and peptides, as zwitterions, with cyanate at 30°C[a]

RNH_2	pK_a	KNCO(mol/l)	$k \times 10^3$(l mol^{-1}min^{-1})
Tetraglycine	7·75	0·2	275,279
Triglycine	7·91	0·2	213,200
Glycylglycine	8·17	0·2	129
		0·4	150
Threonine	9·12	0·2	33·5
		0·4	31·0
Glycine	9·60	0·2	20·2
		0·4	21·6
Alanine	9·69	0·2	8·42
		0·8	8·13
		1·0	8·56
β-Alanine	10·19	0·8	5·59
		1·0	5·74
ε-Aminocaproic acid	10·75	1·0	2·04
		2·0	1·98

[a] Reprinted with permission from Stark, *Biochemistry*, **4**, 1030 (1965). Copyright by the American Chemical Society.

derivatives. These are stable in solution at pH ~ 5 but regenerate free thiol and cyanate at pH 8, hence, hydroxyl anion may be involved in the retrograde reaction. In view of this assumption, Stark[43] formulated the overall reaction as follows:

$$RS^- + HNCO + H_2O \underset{k_D}{\overset{k_F}{\rightleftharpoons}} RSCONH_2 + OH^-$$

where R represents the cysteinyl residue, $-CH_2CH(NH_2)COOH$ and k_F and k_D are the rate constants of formation and decomposition, respectively. Values of these in the reaction between cysteine and sodium cyanate are given in Table 3. Again, reaction with thiolate anion rather than with thiol requires that cyanate be in the unionized form.

In view of the sensitivity of *S*-carbamylated compounds to hydroxyl ion, these are expected to be short-lived at physiological pH and, therefore, of secondary importance to the more stable *N*-carbamyl derivatives of biologically-important molecules. This statement is, however, subject to the following reservation: *S*-carbamyl derivatives of peptides and proteins could act as intermediates in the carbamylation of other groups, such as amino groups. For example, *S*-carbamylcysteine and triglycine gave, at pH 8, the *N*-carbamyl derivative of the latter[43]. In a more complex system,

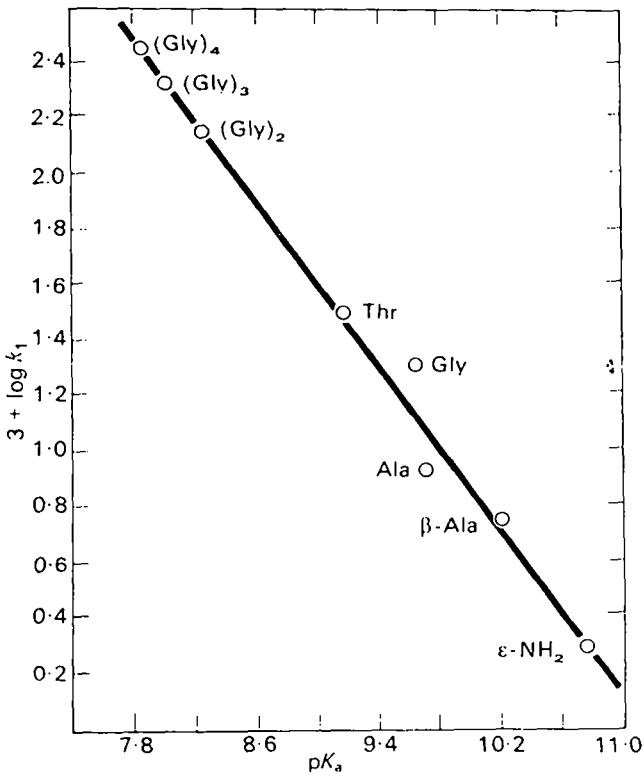


FIGURE 1. Dependence of second-order rate constants of the reaction $R\overset{+}{N}H_3 + NCO^- \rightarrow H_2NCONHR$ on pK_a of amino group in substrate. Data are those in Table 2. Reprinted with permission from Stark, *Biochemistry*, 4, 1030 (1965). Copyright by the American Chemical Society.

the inhibitory effect of *S*-carbamylcysteine on the microorganisms *Lactobacillus arabinosus* and *Streptococcus lactii*[44], at pH 6.8 and 30 °C, could be explained on similar lines. In any case, caution is recommended in the extrapolation of results obtained with small molecules such as cysteine or glutathione to more complex biological systems where reversibility of effect is not a simple direct function of the regeneration of free thiol.

C. Reactions Involving Hydroxyl Groups

Formally, carbamyl phosphate is the addition product of cyanate and orthophosphate. Indeed, Jones, Spector, and Lipmann[45] demonstrated its

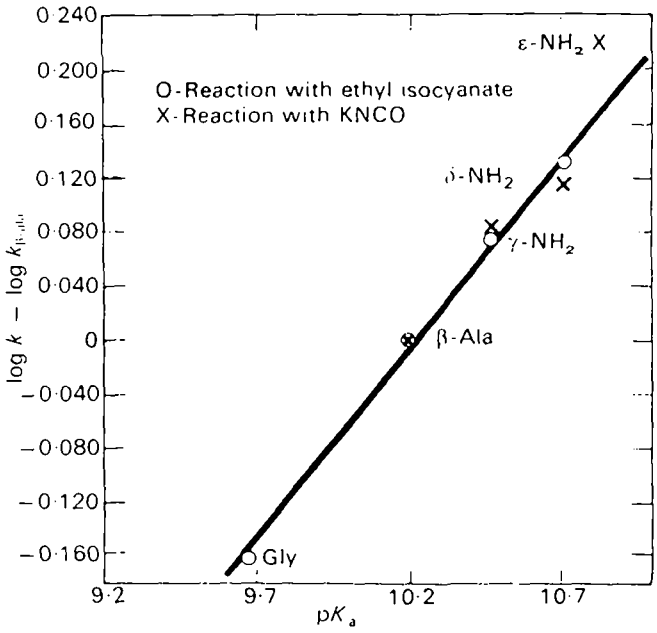


FIGURE 2. Dependence of relative rate constants on pK_a of the amino group in the reaction of γ-aminobutyric, δ-aminovaleric and ε-aminocaproic acids with EtNCO or KNCO at 30 °C in aqueous phase. The reaction is assumed to occur between the uncharged molecules, HNCO or EtNCO and $H_2N(CH_2)_nCOO^-$. Reprinted with permission from Stark, *Biochemistry*, **4**, 1030 (1965). Copyright by the American Chemical Society.

formation in 50% yield from KNCO and KH_2PO_4 in aqueous solution at 30 °C. In living systems, carbamyl phosphate is the universal donor of the carbamyl moiety in the biosynthesis of protein and nucleic acid building blocks[27]. For example, the formation of citrulline, an intermediate in the formation of arginine, proceeds as follows[46]:

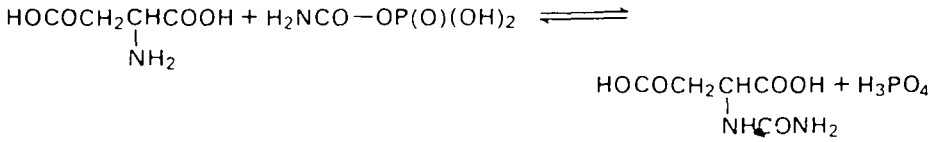
$$H_2N(CH_2)_3\underset{\displaystyle NH_2}{\underset{|}{C}}HCOOH + H_2NCO{-}OP(O)(OH)_2 \rightleftharpoons H_2NCONH(CH_2)_3\underset{\displaystyle NH_2}{\underset{|}{C}}HCOOH + H_3PO_4$$

The reaction is mediated by the enzyme ornithine carbamyl transferase (EC 2.1.3.3). Another important example is the formation of carbamyl-aspartate, an intermediate in the biosynthesis of uridylic acid[47,48]. The reaction is mediated by aspartate transcarbamylase (EC 2.1.3.2):

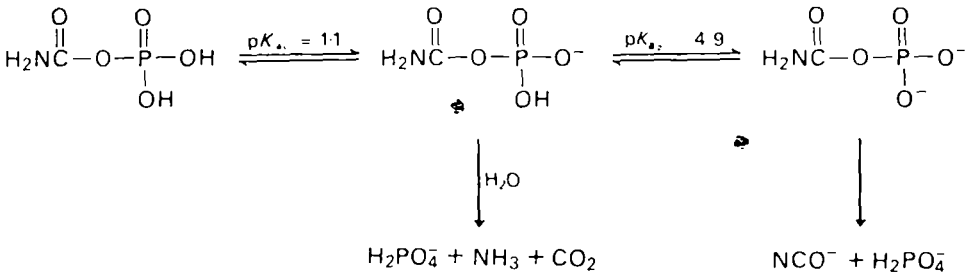
TABLE 3. Rate constants in the reversible reaction of cysteine with cyanate at 25 °C; k_F is related to the forward reaction (formation) and k_D, to the retrograde reaction (decomposition). The rate constant k_F was calculated from *total* concentration of each of cysteine and cyanate and not from that of their respective ionic forms at the corresponding pH[a]

pH	k_F (l mol^{-1} min^{-1})	k_D (l mol^{-1} min^{-1})	k_F/k_D
6·0	4·0	$7{\cdot}9 \times 10^{4}$	$5{\cdot}4 \times 10^{-5}$
7·0	3·7	$7{\cdot}1 \times 10^{4}$	$5{\cdot}0 \times 10^{-5}$
8·0	2·8	$7{\cdot}3 \times 10^{4}$	$3{\cdot}8 \times 10^{-5}$

[a] Reproduced from Stark, *J. Biol. Chem.*, **239**, 1411 (1964) by permission of the American Society of Biological Chemists.



In view of this and more recent evidence on the action of carbamyl phosphate with haemoglobin[49], the question arises whether such reactions *in vivo* do or do not proceed via the transient formation of cyanate. As a model, the non-enzymic hydrolysis of carbamyl phosphate in water does not preclude cyanate formation. The reaction was shown to proceed along two different pathways, depending on the pH[50]. Low pH, i.e. below 4, favours decomposition into phosphate, ammonia and carbon dioxide. Higher pH favours generation of cyanate and phosphate:

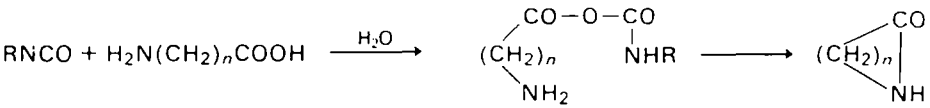


The mechanisms involved were rationalized by Allen and Jones[51].

Thus, generation of cyanate from carbamyl phosphate under physiological conditions has a definite probability and may be illustrated by the non-enzymic carbamylation of haemoglobin and histone[49]. On the other hand,

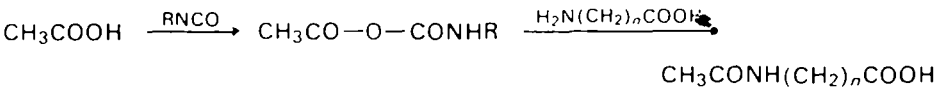
a *single* displacement reaction is suggested by enzyme-mediated carbamylations. For example, ^{32}P-labelled phosphate exchanges with carbamyl phosphate only in the presence of receptor amino acid and specific enzyme[46,52]. In another case[53], cyanate failed to dilute [^{14}C]carbamyl phosphate during citrulline formation from ornithine, mediated by ornithine transcarbamylase (EC 2.1.3.3). Also significant in this context is the biological degradation of carbamyl phosphate which is mediated by the enzyme carbamyl phosphate phosphatase; this reaction is not conducive to cyanate but to NH_3 and CO_2, perhaps in analogy with acid hydrolysis of carbamyl phosphate[54,55]. Indeed, there is plausibility in the view advanced by Stark[40] that carbamyl phosphate may function in the cell by providing a safe means of transport for the otherwise reactive cyanate.

Cyanate was found to react also with carboxylic acids in a reaction which has had as yet no known counterpart *in vivo*. For example, reaction of KNCO or EtNCO with γ-aminobutyric acid or ε-aminocaproic acid led to the formation of 5- or 6-membered lactams, in addition to the expected *N*-carbamyl derivatives[40]:



(R = H, Et; n = 5, 6)

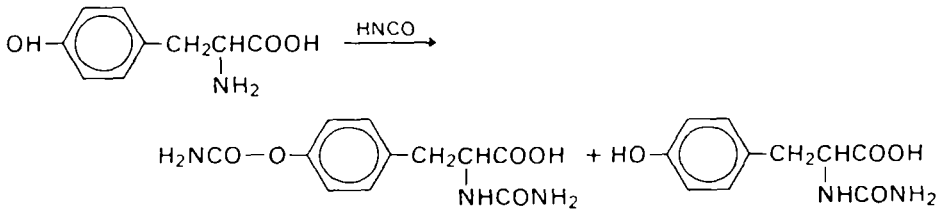
Lactam formation, which depends on the intermediate formation of carbamylcarboxyl anhydrides $RCO{-}O{-}CONH_2$, is favoured at pH 5·3; that of the *N*-carbamyl derivative is favoured at pH 6·8. Remarkably, if acetate is used as buffer in the above reaction, then partial *N*-acetylation of the amino group ensues, indicating the transient formation of a mixed carbamyl–acetyl anhydride, the electrophilic agent in this case:



The hydroxyl group in carbinols and phenols of biological occurrence is also known to incur carbamylation with cyanates, but there have been relatively few studies on this subject whilst some of the earlier reports may require reconsideration in view of latter developments. As a rule, the hydroxyl group in serine and threonine residues has been considered unreactive towards the usual acylating or alkylating agents normally used in protein conjugation or labelling[56]. Even with the more reactive cyanates, such as phenyl isocyanate, formation of *O*-carbamyl derivatives of proteins could not be demonstrated[57]. Stark[40] briefly mentioned that the OH group

in threonine did not react appreciably with potassium cyanate at pH 8. On the other hand, Shaw, Stein, and Moore[58] provided indirect evidence to the effect that the serine-OH group in the catalytic site of chymotrypsin undergoes carbamylation with cyanate, but under the same conditions free serine proved to be unreactive towards the same reagent[59].

The failure to demonstrate the formation of *O*-carbamyl derivatives may be ascribed, at least in some cases, to the lability of these products under the usual working conditions. Indeed, Smyth[41] showed in a careful study that reaction of phenol with excess sodium cyanate led to phenyl carbamate which has a half-life of 2 h in the pH range 6·5–7 at 30 °C, but 30 min at pH 7·4 and 37 °C. Under similar conditions, tyrosine undergoes both *N*- and *O*-carbamylation with sodium cyanate in water, but the reaction with the amino group proceeds five-times as fast as that with the phenol hydroxyl. As a result, the *N*-carbamyl and *N,O*-dicarbamyl derivatives could be isolated, the latter in 65% yield by stepwise alteration of pH from 8 to 6, but not the *O*-carbamyl derivative:

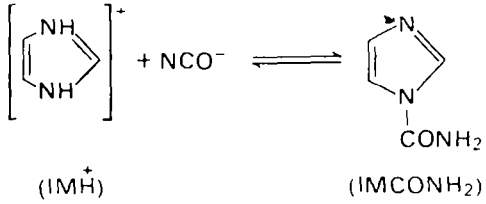


Smyth also showed that *O*-carbamylation occurs in the tyrosine residue in the polypeptide oxytocin[41].

D. Reactions Involving Imidazole

Histidine residue, and hence imidazole, forms an essential part of the active site of many hydrolytic enzymes which are now more commonly referred to as DFP-sensitive enzymes[60] because they are specifically and irreversibly blocked at that site with diisopropyl phosphofluoridate [DFP, $(i\text{-PrO})_2P(O)F$]. The function of the imidazole part is catalysis of acyl transfer from the substrate to the hydroxyl group of serine. Indeed, *N*-acylimidazoles have long been known as good acylating agents[61]. Because a similar function could possibly be performed by carbamylimidazole[62], a detailed study of this agent was carried out by Stark[59]; the conclusions brought here were taken from his work.

At pH near neutrality (7·2 to 8·1) and in the temperature range 20 to 35 °C, imidazolium cyanate exists in equilibrium with carbamylimidazole:



The association constant, K, given by

$$K = \frac{[IMCONH_2]}{[IMH^+][NCO^-]}$$

has a value that depends on the concentration of *free* unprotonated imidazole (Figure 3); hence, unprotonated imidazole catalyses the formation of carbamyl imidazole. The value of K in the presence of 0·08 M-imidazole as free base at 25 °C is 0·25 mol^{-1}, corresponding to $\Delta F°$ = 0·82 kcal/mol, $\Delta H°$ = −2·1 kcal/mol and $\Delta S°$ = −9·9 e.u. at 25 °C.

In the absence of cyanate and free imidazole, the rate at which carbamylimidazole dissociates is independent of pH above 6 but decreases at lower pH. Such behaviour is consistent with a mechanism whereby carbamylimidazolium ion and not carbamylimidazole is attacked by hydroxide anion, in accordance with the following general scheme:

$$\begin{array}{ccc} IMH^+ + NCO^- + H_2O & \rightleftharpoons & IMCONH_2 + H_2O \\ \Downarrow & & \Downarrow \\ IM + HNCO + H_2O & \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} & (IMHCONH_2)^+ + OH^- \end{array}$$

where $k_1 = 10^{2\cdot7}$ l mol^{-1} min^{-1} and $k_{-1} = 10^{9\cdot6}$ l mol^{-1} min^{-1}. The half-life of carbamylimidazole at pH 6 is about 1 min.

Carbamylimidazole proved to be a disappointingly unreactive carbamylating agent towards glycine, threonine and glycylglycine. A small increase in rate observed in the reaction of amino acids with cyanate in presence of imidazole could be due to a small catalytic effect on behalf of unprotonated imidazole itself.

IV. REACTION OF CYANATES WITH INDIVIDUAL PROTEINS

Whilst covalent bond-formation between cyanates and proteins is generally confined to one or more functional groups of the type discussed in the

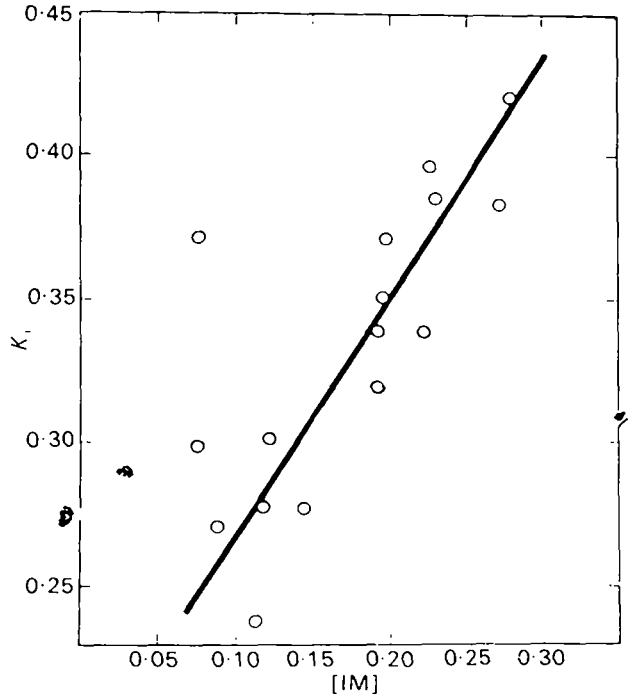


FIGURE 3. Dependence of the association constant, K, in the equilibrium Imidazolium cyanate $\rightleftharpoons$ Carbamylimidazole on the concentration of free, unprotonated imidazole at 25 °C ([IM]). Reprinted with permission from Stark, *Biochemistry*, **4**, 588 (1965). Copyright by the American Chemical Society.

preceding section, the resulting effect on protein structure and function is variable within wide limits. It could be profound and irreversible in one case but almost insignificant in another. In the first place, this effect depends on the nature of the protein itself and the vulnerability of its functional capacity to structural modification. In the second place, the effect depends on the structure of the conjugating moiety which, in the case of isocyanates, is R—NH—CO—. In view of this, the reactions of cyanates with proteins cannot be systematized, at least not in terms of effect on protein function, even though they share a common chemical background. The presentation of these reactions will be made on an individual basis.

A. Haemoglobin

Much of the present knowledge of the reaction of cyanate with haemoglobin has been generated from a concern with sickle-cell anaemia. This haemolytic condition, or 'molecular disease' in the terminology of Pauling

and coworkers[63], is characterized by sickle-shaped red blood cells due to homozygous inheritance of an abnormal haemoglobin (S Hb). It occurs almost exclusively in negroes. In S haemoglobin, valine has substituted glutamic acid as the sixth peptide in the β-chain, causing an alteration of properties with respect to normal haemoglobin (A Hb). The oxygenated form of S Hb is as soluble as that of A Hb, but reduced S Hb is about 1/50th as soluble as reduced A Hb and 1/100th as soluble as its own oxygenated form. Under low O_2 pressure, as occurs in the smaller blood vessels, S Hb forms a semi-solid gel (tactoids), causing sickling of the erythrocytes. These assume a distorted shape and are unable to pass through capillaries.

Cerami and Manning[64] are credited for the first discovery of the anti-sickling properties of cyanate. Cyanate combines with the α-amino group of terminal valine in haemoglobin in an irreversible carbamylation reaction that leads to the incorporation of 1 to 4 carbamyl residues per haemoglobin tetramer. In the case of S Hb, carbamylation and prevention of sickling were found to proceed at the same rate. Globin, the protein moiety of haemoglobin, is composed of four polypeptide chains arranged in the configuration of tetrahedron. These consist of two α-chains of identical composition (141 amino acids) and two β-chains (146 amino acids) also of identical composition. The terminal amino groups in all four chains are those of valine. In a detailed study of the kinetics of carbamylation of these groups with cyanate, Lee and Manning[65] found no difference in reactivity in the various chains of oxyhaemoglobin. These amino groups react 50- to 100-times faster than the ε-amino groups of lysine residues in the same molecule until one carbamyl group has been incorporated per haemoglobin molecule. Likewise, the rate constant for the carbamylation of deoxyhaemoglobin A (normal) was not found to differ from that for deoxyhaemoglobin S, indicating a close similarity in the nucleophilicity of terminal amino groups in normal and pathological haemoglobin. In deoxyhaemoglobin, however, the rates of carbamylation at the α- and β-chains seem to differ. Thus, Manning and coworkers[66] found that the ratio of carbamylation is 1·7:1 in favour of the α-chain in partially deoxygenated blood (40 to 50% O_2 saturation), whereas in fully oxygenated blood the ratio is 1:1. Similar results were reported by Jensen and collaborators[67] who also studied the effects of 2,3-diphosphoroglycerate on sickling and its relationship to oxygenation[67a]. They found that the α-chains reacted at twice the rate in deoxyhaemoglobin as compared to oxyhaemoglobin, whilst β-chain carbamylation was less dependent on oxygenation.

According to Manning and coworkers[68], exposure of human erythrocytes to 10 mM-KNCO for 1 h does not significantly alter cell functions, but the oxygen affinity of carbamylated sickle or normal cells

increases to a level commensurate with the extent of carbamylation. The terminal amino group of valine in haemoglobin is known to fulfil many important functions among which is the transport of carbon dioxide as the carbamino derivative[69]. The high specificity of isocyanic acid, the reactive form of cyanate, towards this amino group has been attributed to the structural similarity between HN=C=O and O=C=O[70]. Indeed, the CO_2-carrying capacity of carbamylated haemoglobin has diminished by about 15%[68].

Kraus and Kraus[71] reported that carbamyl phosphate was found to be more effective than cyanate in the reversion of sickling *in vitro*. This led Carreras-Barnes, Diederich and Grisolia[49] to investigate the comparative effectiveness of these two agents in the carbamylation of haemoglobin in intact erythrocytes. In all instances, the reaction proceeds at a faster rate with cyanate than with carbamyl phosphate but, given enough time, both agents would eventually lead to the incorporation of four carbamyl residues per mole haemoglobin. These and other results are summarized in Table 4.

TABLE 4. Carbamylation of haemoglobin under various conditions[a]

Reagent and conditions	Substrate	mol H_2NCO/ mol Hb	Reference
1 mM-KNCO, 5 h, pH 7, 37 °C	Human sickle RBC	2	64
100 mM-KNCO, 1 h, pH 7, 37 °C	Human sickle RBC	1·5	64
10 mM-KNCO, 1 h, pH 7, 37 °C	Human sickle RBC	0·72	68
10 mM-KNCO, 2 h, pH 7, 20 °C	Intact human RBC	0·4	49
10 mM-KNCO, 2 h, pH 7·8, 20 °C	Intact human RBC	0·25	49
25 mM-KNCO, 1 h, pH 7, 37°C	Intact human RBC	2·5	49
25 mM-KNCO, 4 h, pH 7, 37 °C	Intact human RBC	4	49
25 mM-carbamyl phosphate, 1 h, pH 7, 37 °C	Intact human RBC	1	49
25 mM-carbamyl phosphate, 4 h, pH 7, 37 °C	Intact human RBC	4	49
10 mM-carbamyl phosphate, 30 min, pH 6, 38 °C	A Hb, 25 mg/ml	0·41	49
10 mM-carbamyl phosphate, 30 min, pH 6, 38 °C	S Hb, 25 mg/ml	0·23	49

[a] Abbreviations: RBC = red blood cell; Hb = haemoglobin.

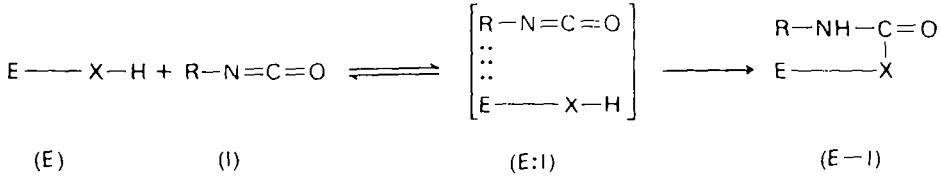
The possible impairment of haemoglobin functions following carbamylation is still a controversial subject. Kilmartin and Rossi-Bernardi[69] found that carbamylation of the α-amino terminal groups in horse haemoglobin

interferes with CO_2 binding. Completely blocked haemoglobin, i.e. carbamylated on all four terminal amino groups, probably binds no CO_2 at all. This should be considered in the light of the fact that direct transport of CO_2 by haemoglobin accounts for 60% of total CO_2 exchanged by the red blood cell during respiration. It remains to be shown that at the rate of carbamylation obtained *in vivo*[70] (one carbamyl group per mole haemoglobin) no deleterious effects really occur.

B. Chymotrypsin and Elastase

Treatment of α-chymotrypsin with 1 M-KNCO at 30°C led to loss of enzymic activity, the rate of inactivation being faster at pH 6·5 than at pH 8·5[58]. A maximum of 11·7 carbamyl groups per mole chymotrypsin (EC 3.4.4.1) could be introduced (in presence of indole) of which five were on the ε-amino, three on terminal α-amino groups and 3·7 acid-labile on groups of undetermined nature. Of these, at least one is a serine-hydroxyl at the active centre, hence inactivation of the enzyme which is not ordinarily sensitive to blockade of amino groups[72].

Reaction with alkyl isocyanate is more specific. Brown and Wold[73] showed that butyl isocyanate inactivates both chymotrypsin and elastase (EC 3.4.4.7) but octyl isocyanate inactivates only the former. In both cases inactivation was due to the carbamylation of serine-hydroxyl at the catalytic centre. As the two enzymes are extensively homologous in their primary amino acid sequence, folded structures and nature of the nucleophilic function at the active site, rationalization of the difference in reactivity towards the two reagents was sought in the topography of the 'binding pocket'. The inactivation process is assumed to proceed through the obligatory formation of an enzyme-inhibitor complex, E:I, in which the nucleophilic group —XH must be properly aligned with the inhibitor electrophile. Following this, interaction between these two groups occurs, leading to the carbamylated enzyme, E–I:



In elastase, the 'binding pocket' cannot ensure a proper alignment of the lengthier octyl isocyanate because of obstruction by valine 216 and

threonine 226. In chymotrypsin, these two positions are occupied by the much smaller glycine. (Figure 4).

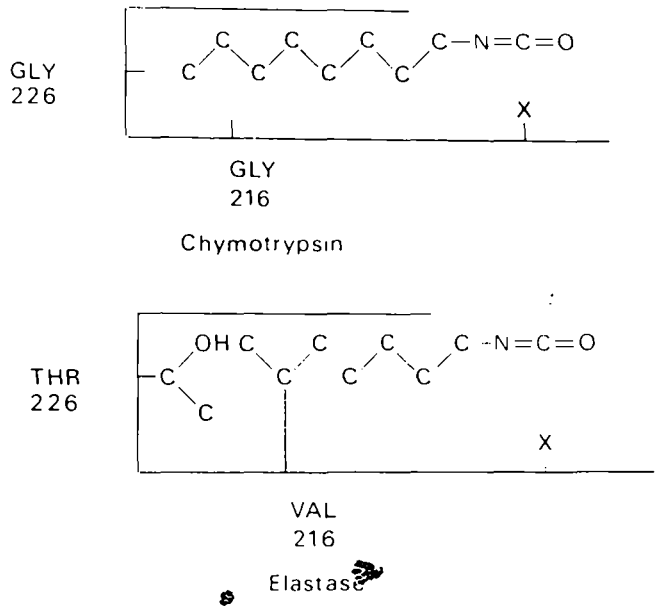


FIGURE 4. Schematic representation of the 'binding pockets' of chymotrypsin and elastase and the possible alignment of alkyl isocyanates in these pockets. Redrawn from Brown and Wold[73].

An opposite case is offered by the cross-linking agent hexamethylene-diisocyanate, $O=C=N-(CH_2)_6-N=C=O$[74]; its reaction with α-chymotrypsin led to the formation of an insoluble product which had retained enzymic activity to the extent of 30%, indicating the formation of intermolecular bridging between ε-amino groups rather than reaction at serine-hydroxyls.

C. Other Peptidohydrolases

In addition to the above examples, other serine enzymes inactivated after treatment with KNCO are *trypsin* (EC 3.4.4.4) and *bilisin* (EC 3.4.4.16)[58]; carbamylation of the active site proceeds simultaneously with reaction at about half the ε-amino groups which are not essential for catalytic activity. The inactivation of *subtilisin* type Novo was studied in more detail by Svendsen[75]. This is an alkaline peptidohydrolase isolated from a strain of *Bacillus subtilis*. Treatment with KNCO led to the carbamylation of ε-amino groups and the terminal amino group of alanine but without

appreciable change in tertiary structure as evidenced by such parameters as sedimentation coefficient, optical rotatory dispersion and pH-dependence pattern of the modified enzyme. Remarkably, treatment of the inactivated enzyme with hydroxylamine restored its catalytic activity without causing the displacement of carbamyl groups from any of the aforementioned amino groups. This is perhaps an indirect implication of serine-hydroxyl as the group involved in inactivation since hydroxylamine is known to displace acyl groups from the active centre of inhibited serine enzymes[76]. In this particular case, the 'active' group was assigned a pK_a of about 7·7.

The carbamylation of two ε-amino groups in *pepsinogen* had no effect on the generation of full pepsin activity[77].

D. Papain

An interesting case is offered by the reaction of activated papain (EC 3.4.4.10) with KNCO[78]. This is a peptidohydrolase that embodies a thiol group at the active centre. Inactivation was shown to proceed rapidly in 0·1 mM-cyanate at pH 6·0 and 20 °C, but activity could be restored slowly by mere dilution of the enzyme–cyanate mixture. The effect was ascribed to the reversible *S*-carbamylation of the essential thiol group of papain. The rate constant of carbamylation varied with substrate concentration (5 to 120 mM-benzoylarginine ethyl ester); at zero substrate concentration it was 9400 l mol^{-1} min^{-1} and at infinite substrate concentration it was 1 500 l mol^{-1} min^{-1} (by extrapolation). Therefore, substrate protection against carbamylation in the complex enzyme substrate is not complete. For comparison, under the same conditions the rate costant of the *S*-carbamylation of free cysteine was found to be 3·4 l mol^{-1} min^{-1}. Thus, the analogous reaction with papain proceeds at a rate 3000-times faster than that with cysteine.

E. Ribonuclease

Stark, Stein, and Moore[37] reported that cyanate inhibited ribonuclease with the formation of both *N*- and *S*-carbamyl derivatives, but selective *S*-carbamylation of the thiol groups in reduced ribonuclease could be achieved by carrying out the reaction with KNCO at pH 6·0 and 25 °C. At this pH, less than 5% of the α-amino groups are expected to react. An interesting case of *N*-carbamylation of ribonuclease without denaturation or loss of activity was reported by Ozawa[74]. Reaction of the enzyme with

the cross-linking agent hexamethylenediisocyanate led to the carbamylation of two ε-amino groups per mole enzyme. Retention of activity, intrinsic viscosity and sedimentation coefficient of the native enzyme indicate formation of an intramolecular bridge between favourably located lysine residues.

F. Phosphatase

Alkaline phosphatase (EC 3.1.3.1) from human or pig kidney was shown to react reversibly with 0·2 M-cyanate[79]. The pH dependence of the reversible reaction suggests that a thiol group is carbamylated at the active centre. Otherwise, prolonged treatment of the enzyme with 0·6 M-cyanate was shown to generate a new enzyme with increased K_m (i.e., lower substrate affinity) and reduced V_{max} (i.e., reduced efficacy). These observations indicate the occurrence of irreversible carbamylations at other sites of the molecule but without blockade of the active centre.

The occasional, and seemingly paradoxical, inactivation of enzymes exposed to high concentrations of urea in the course of isolation and purification procedures is now attributed to the presence of cyanate in this reagent. Thus, enzymic activity of *histidinol phosphate phosphatase* (EC 3.1.3.15) from baker's yeast was subject to temperature-dependent irreversible inhibition by prolonged treatment with 8 M-urea[80]. Another example is the irreversible inactivation of DNA-dependent *RNA polymerase* that was treated with aged urea solutions without prior deionization[81]. Again cyanate, which is in equilibrium with urea, is the inhibitory agent. Inhibition may be due to the carbamylation of cysteine residues of the subunits of this polymerase, since reactivation could be achieved by treatment of the inactivated enzyme with dithiothreitol.

G. β-Galactosidase

Hustad and coworkers[82,83] showed that β-galactosidase (EC 3.2.1.23) could be immobilized on a polyisocyanate polymer without loss of activity. The immobilized enzyme was reasonably stable and retained 65% of its original activity after intermittent use for 118 days. One may infer that in this case bonding of the enzyme to the polymer does not occur at or via the active centre and does not entail extensive conformational changes which would interfere with activity. In this respect, the course of the reaction must be analogous to that reported by Ozawa[74] for a divalent carbamylating agent.

TABLE 5. Effects of cyanates on hormones *in vitro*

Hormone	Conditions	% R.A.[a]	Reference
Insulin	PhNCO	5	32
	1-Naphthyl-NCO	5	32
	PhNCS	?	34, 35
	100 mM-NaNCO, pH 7·4, 1 h, 37 °C	90	58
Oxytocin	NaNCO 40 mM, pH 5, 17 min, 30 °C	50	41
	NaNCO 100 mM, pH 8, 180 min, 30 °C	50	41
Desaminooxytocin	NaNCO 40 mM, pH 6, 2 h, 30 °C	100	41
Desaminodeoxyoxytocin	NaNCO 1 mM, pH 6·5, 2 h, 30 °C	100	41
Adrenocorticotropic hormone	NaNCO 100 mM, pH 7·4, 1 h, 37 °C	86	86
Growth hormone	NaNCO 100 mM, pH 7·4, 1 h, 37 °C	96	86
Thyroid-stimulating hormone	NaNCO 10 mM, pH 7·4, 1 h, 37 °C	7	86
Follicle-stimulating hormone	NaNCO 100 mM, pH 7·4, 1 h, 37 °C	63	86
Luteinizing hormone	NaNCO 10 mM, pH 7·4, 1 h, 37 °C	14	86
Prolactin	NaNCO 100 mM, pH 7·4, 1 h, 37 °C	106	86
Human chorionic gonadotropin	NaNCO 100 mM, pH 7·4, 1 h, 37 °C	101	86
Antidiuretic hormone	NaNCO 10 mM, pH 7·4, 1 h, 37 °C	0	86

[a] R.A. = residual activity

H. Protein and Peptide Hormones

Hormones that consist of polypeptide chains are obvious candidates for reaction with cyanates but the final effects are variable. The biological activity of *thyroid-stimulating hormone* (TSH) was abolished after incubation *in vitro* with NaNCO, but in addition, the product formed proved to be itself inhibitory to the biological activity of native TSH[84]. An analogous case was reported by Smyth[41] who studied the action of cyanate on *oxytocin*, the principal uterus-contracting hormone of the posterior

pituitary. Two types of cyanate-transformed hormones were obtained: *N*-carbamyl oxytocin which had retained only 0·1% of the activity of native oxytocin and *N,O*-dicarbamyloxytocin which could suppress 50% of the effect of oxytocin when applied with the native hormone in the ratio of 25:1. In the dicarbamylated hormone, the location of the *O*-carbamyl group is at the tyrosine residue and, in analogy with *N,O*-dicarbamyltyrosine itself, the *O*-carbamyl group is lost and with it the inhibitory effect of the transformed hormone when this is kept at pH 7·4 and 37 °C for protracted periods of time. As for the *N*-carbamylated hormone, its exceedingly poor biological activity is unexplained. The terminal cysteine-amino group in oxytocin, the site of carbamylation, is not essential for biological activity since the desamino analogue of oxytocin is almost as active. It is surprising, therefore, to find that carbamylation leads to such a loss of activity, unless one assumes concomitant conformational changes or serious steric hindrance in the face of interaction with the receptor. Yet, such a change in conformation could not be substantiated by experiment[85].

Somewhat different results have been reported recently by Graziano and coworkers[86] in a study of the pharmacology of cyanate. These authors confirmed the inactivation of TSH, *luteinizing* (LH) and *anti-diuretic* (ADH) *hormones* when these had been treated *in vitro* with NaNCO, but there was no formation of inhibitory agents such as those reported by the earlier investigators. They ascribed the variance in results to a difference in working conditions which, in the latter case, ought to be conducive to *N*-carbamylation only, but there is no formal proof that this is indeed the case.

It is not clear why *O*- or *S*-carbamylated hormones should be inhibitory rather than simply inactive. Further exploration of the subject is required, particularly in view of Smyth's[41] suggestion that inactive *O*-carbamylated hormones that undergo slow hydrolysis *in vivo* could be exploited for the slow release of active hormone. Some results of hormone modification with cyanates are given in Table 5.

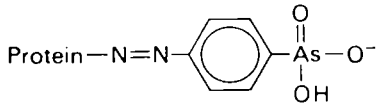
J. Plasma and Immunoproteins

These are the various albumins or globulins which are used as carriers of a desired structure (or hapten) in immunological or diagnostic work. As antigens, they are used to elicit immunological response against a given molecule by coupling or conjugating it with the carrier protein. The isocyanate of the desired molecule and sometimes the isothiocyanate have proved an exceedingly effective means for this operation. In almost all known cases, the reaction occurs at the ε-amino groups of lysine.

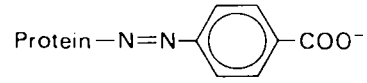
An early example of the application of isocyanates in this respect is the

work of Creech and Franks[87–89] and Fieser and Creech[33] on the coupling of anthracene (**1** and **2**), benzanthracene (**3** and **4**) and 1,2,5,6-dibenzanthracene (**5**) structures to various carrier proteins by use of the corresponding isocyanate derivatives (Figure 5). One of these conjugates, 1,2,5,6-dibenzanthryl-9-carbamidocasein, when used as an antigen in mice, elicited some immunity against the action of dibenzanthracene but was itself mildly carcinogenic. The two effects seem difficult to reconcile. Creech and Peck[90] also studied the coupling of 4-dimethylaminostilbene (**6**), 2'-methyl-4-dimethylaminostilbene (**7**) and 2-acetylaminofluorene (**8**), as their isocyanates, with horse and bovine serum albumins in aqueous dioxane. The number of prosthetic groups introduced per mole protein varied between 13 to 62 and was most probably a function of the extent of unfolding of the tertiary structure since, in most albumins, at least half the number of ε-amino groups of lysine are submerged and, therefore, inaccessible to the reagent. A remarkable feature of the stilbene conjugates was a spontaneous change in their ultraviolet absorption spectra corresponding to rapid conversion from a *trans* to a *cis* stilbene structure.

Chen, Grossberg and Pressman[91] studied the effect of cyanate on the combining capacity of various antibodies with their specific antigens. The authors operated on the premise[92] that specific antibodies directed against a charged group contain a charged group of opposite sign in the combining region. Thus, *anti-p*-azobenzenearsonate (**9**) and *anti-p*-azobenzoate (**10**) antibodies are expected to combine with their respective antigens via a cationic group, most probably an $\varepsilon\text{-}\overset{+}{N}H_3$ group:

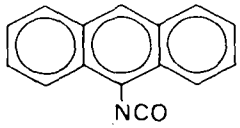


(**9**)



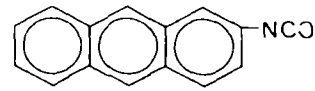
(**10**)

Indeed, carbamylation of anti-*p*-azobenzenearsonate γ-globulins with 1 M-KNCO at pH 8 and 38 °C resulted in the loss of 20 to 30% of their combining sites. This loss in combining capacity could be partially prevented when the carbamylation reaction was carried in the presence of an agent bearing the *p*-azobenzenearsonate group. These observations are considered by the authors as indicative of an attack by cyanate on the combining region. Under similar conditions, the effect of cyanate on the anti-*p*-azobenzoate antibodies led also to a loss of combining capacity. However, the two cases are not equivalent because in the latter case the loss



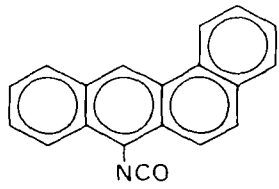
9-Anthryl isocyanate

(1)



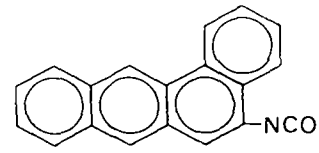
2-Anthryl isocyanate

(2)



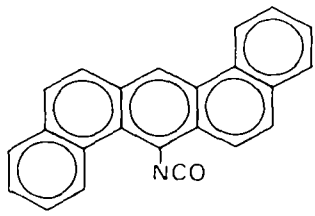
9-(1,2-Benzanthryl) isocyanate

(3)



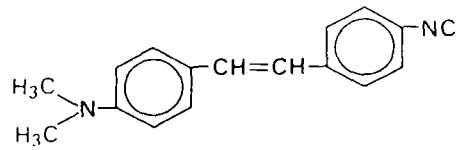
3-(1,2-Benzanthryl) isocyanate

(4)



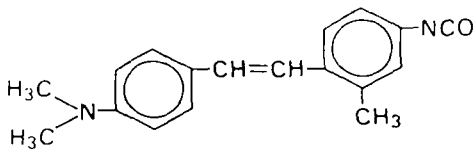
9-(1,2,5,6-Dibenzanthryl) isocyanate

(5)



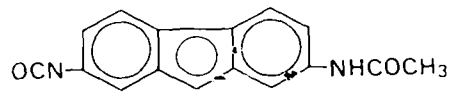
4-Dimethylamino-4'-isocyanatostilbene

(6)



4-Dimethylamino-2'-methyl-4'-isocyanatostilbene

(7)



2-Acetylamino-7-isocyanatofluorene

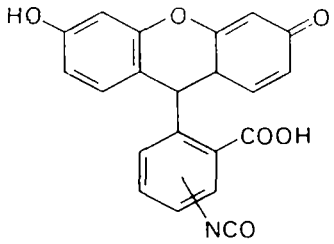
(8)

FIGURE 5. Isocyanates of carcinogenic and structurally-related compounds used for the preparation of protein derivatives[33,87–90].

could not be minimized in the presence of *p*-azobenzoate. Hence, the combining region may not necessarily involve such amino groups as may be carbamylated with cyanate.

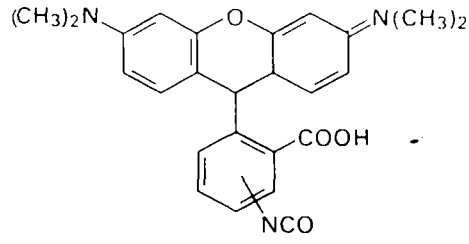
Various 'label' molecules, usually from those that fluoresce strongly under ultraviolet irradiation, have been coupled through their isocyanates

or isothiocyanates to antigens or antibodies and the resulting conjugates have been used as tracers for the location or identification of their combining regions in histochemical investigations. The preparation, purification and characterization of fluorescent protein conjugates have been reviewed recently by Dandliker and Portman[93] so that only brief mention of the more important reagents need be made here. These include the isocyanates and isothiocyanates of fluorescein (**11**) and rhodamine (**12**). Various techniques have been developed in order to ensure optimum labelling and reagent stability. The most common problem encountered in the application of these techniques is protein denaturation with concomitant loss of antigenic specificity following the obligatory use of organic agents, such as acetone or dioxane, as solvents for the otherwise insoluble isocyanate or isothiocyanate.



Fluorescein isocyanate

(**11**)



Rhodamine isocyanate

(**12**)

(The —NCO group may be in position 4 or 5 in the 2-carboxyphenyl entity.)

K. Protein–Cyanate Interactions not Mediated by Covalent Bonding

A number of biochemical effects of cyanates cannot be ascribed to covalent bonding with the target protein. This is particularly true for the less reactive but more *chaotropic* thiocyanate anion which has been studied in a wide variety of biochemical systems. A comprehensive review of these effects is not within the scope of the present chapter, but brief mention of some of the more important effects will be made so that these can be discerned from the covalent-bonding effects.

Thiocyanate ion binds to proteins at sites of opposite charge. McMenamy and coworkers[94] studied the reaction with bovine serum albumin in the pH range 4·5 to 10 and concluded that the binding data could be fitted with two sets of binding constants: $k_1^0 = 700$, $n_1 = 7$ and $k_2^0 = 10$, $n_2 = 90$. This was interpreted as an indication of the existence of

seven preferred sites for SCN^- binding per mole albumin. In a subsequent study[95] it was shown that the binding of SCN^- at these seven primary sites was not affected by modification of protein amino groups with acylating or alkylating agents. In view of the fact that the guanidinium groups are the only ones that are refractory to protein-modification reagents, the authors concluded that SCN^- binding occurs preferentially at arginyl residues.

The use of thiocyanate was also suggested as a means for dissociating protein complexes with other proteins without appreciable denaturation. Unlike cyanate, thiocyanate in a concentration as high as 3 M had no irreversible effects on antigen–antibody binding. DeSaussure and Dandliker[96] showed that antibodies purified in 3 M-SCN^- at neutral pH still retained their ability to combine with their corresponding antigens, but the same concentration of SCN^- would dissolve and dissociate specific precipitates in the equivalence zone.

A number of thiocyanate-induced effects could also be attributed to the reversible SCN^- interaction with anion-binding sites. Examples are the inhibition of rat liver mitochondrial functions which is due to SCN^- binding at the membrane[97] and perhaps the excitatory effects of SCN^- on the spinal chord[98].

The involvement of SCN^- in redox interactions is also on record. Hogg[99] studied the oxidation of reduced nicotinamide nucleotides (NADH) with H_2O_2 and lactoperoxidase, in the presence of SCN^-. In this system, oxidation of thiocyanate appeared to precede that of NADH, but then the oxidized form of thiocyanate would itself oxidize NADH to NAD^+. In cow's milk and human saliva, oxidation of thiocyanate to a bacterial inhibitor is a likely process.

Kidder[100] presented several lines of evidence which tend to implicate cytochrome *c*-SCN^- interaction as the cause of the inhibition of mucosal acid secretion in the stomach. The nature of the reaction, which may not be simple oxidation, has not been established, but the closely related anions OCN^- and NO_2^- elicit similar effects, both *in vivo* and *in vitro*. In this context, we recall that thiocyanate complexes with several metals, notably with ferric ion, so that such a reaction may lie at the root of several enzyme inactivations observed with thiocyanate[101].

V. REACTION OF CYANATES WITH NUCLEIC ACIDS AND THEIR CONSTITUENTS

The reaction of cyanates with nucleic acids or isolated purines, pyrimidines, their nucleosides and nucleotides has so far received limited attention. This

seems surprising in view of the fact that cyanates, which may arise *in vivo*, could possibly react with the genetic components of cell constituents and are, therefore, potentially mutagenic.

Reaction of phenyl isocyanate with adenine[102,103] and cytosine[104] was shown to lead to *N*-phenylcarbamyladenine (**13**) and *N*-phenylcarbamylcytosine (**14**), respectively (Figure 6). Isocytosine and 2- and 4-aminopyrimidines likewise underwent carbamylation at the extranuclear nitrogen. Reaction with guanine[103] led to a monocarbamylated product which was assigned the structure of 2-*N*-phenylcarbamylguanine (**15**) because acid converted it into guanine and xanthine. All these carbamylation reactions were performed at temperatures in excess of 100 °C and, therefore, may not be suitable models for possible analogous reactions *in vivo*. That these working temperatures may have been unnecessarily high was shown by Agarwal and Khorana[104a] who studied the use of phenyl and naphthyl isocyanates for selective blocking of the terminal 3'-hydroxyl group in deoxyribo-oligonucleotides. These agents were found to add quantitatively in dry pyridine and at room temperature to such diverse functional groups as the 3'- and 5'-hydroxyl groups of deoxythymidine (**16**) and the amino groups of deoxyadenosine, deoxycytidine and deoxyguanosine, in addition to the 3'- and 5'-hydroxyl groups of these deoxynucleosides. When the amino groups in these were protected by means of suitable acyl or alkyl groups, then carbamylation occurred only at the hydroxyl groups of deoxyribose.

Reaction with purines and pyrimidines occurs also with their combined forms in deoxyribonucleic acid (DNA). Reaction of phenylisocyanate with DNA, performed at 0 to 4 °C for 10 days on the cetyltrimethylammonium salt of this polymer in dimethylformamide was reported by Jones and Warren[103]. These authors could identify in the acid hydrolysate of the product the *N*-carbamyl derivatives of adenine (**13**), cytosine (**14**) and guanosine (**15**).

VI. ACTION OF CYANATES AT THE CELLULAR LEVEL

An early suggestion by Dustin[105] that sodium cyanate may cause degeneration of cells in mitosis was subsequently disputed by Loveless and Revell[106] and by Dean and Gunz[107] who ascribed the adverse effects observed to general toxicity of the agent rather than a specific anti-mitotic action. The latter authors investigated the effects of injected NaNCO on the bone marrow of rats and concluded, rather surprisingly, that a daily injection of 10 mg per kg caused, after a slight depression, a considerable

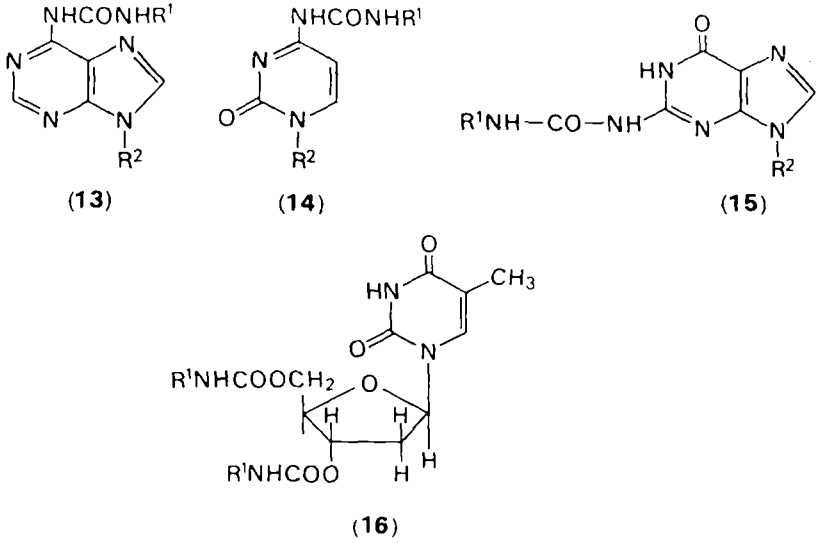
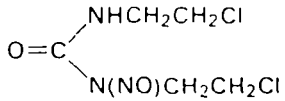


FIGURE 6. Products of the reactions of phenyl isocyanate and naphthyl isocyanate with biological purines and pyrimidines, their deoxynucleosides, or in combination in DNA. From Huber[102], Jones and Warren[103], Dyer, Gluntz, and Tanck[104], and Agarwal and Khorana[104a]. R′ = phenyl or 1-naphthyl; R^2 = H or 2-deoxyribofuranosyl.

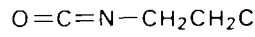
rise in mitotic activity. The number of mitoses in 1500 cells rose from 9 in controls to 23 in cyanate-treated animals. Eventually, continued administration of cyanate resulted in depression which was ascribed to general systemic poisoning. Larger but single doses of cyanate, e.g. 30 mg per kg, reduced the number of mitoses in 1500 nucleated cells to 3; but mitosis was never completely suppressed and returned to its normal rate after 24 hours. Similar conclusions were reached by Skipper and coworkers[108] who found no evidence of leucopenia after injection of large, single doses of KNCO.

With the renewal of interest in cyanates as possible therapeutic agents for the treatment of sickle-cell anaemia, further knowledge on the cellular effects of these drugs became available. Freedman and collaborators[109] reported a prompt inhibition of protein synthesis in both human sickle-cell reticulocytes and rabbit reticulocytes, but the human cells were more sensitive. Cyanate induced conversion of polyribosomes to monoribosomes, a portion of which remained attached to *m*-RNA. Its major effect in the inhibitory process appeared to be on the initiation step of translation, or an early elongation step. Remarkably, cyanate was also found to reduce the concentration of reduced glutathione in treated cells; hence, an involvement of a thiol group in inhibition may be inferred.

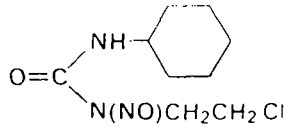
In experimental cancer chemotherapy, the organic isocyanates have been more successful than cyanate salts. Moos and coworkers[110] found that the growth of transplanted Ehrlich ascites tumour in mice could be inhibited by a relatively large number of organic isocyanates provided these be injected in peanut oil; the early failures of these agents in the usual screening tests were ascribed to the use of wrong vehicles, such as saline solution, which promote their rapid decomposition. Some results are shown in Table 6. The authors advanced the view that the anti-tumour properties of 1,3-bis(2-chloroethyl)-1-nitrosourea[111] (**17**) may be due to 2-chloroethyl isocyanate (**18**) which arises from it *in vivo*. Similarly, cyclohexyl isocyanate (**20**) may arise from the carcinostatic 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (**19**)[112], but so far, there has been no direct demonstration of the occurrence of such reactions *in vivo*.



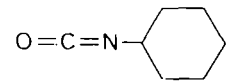
(**17**)



(**18**)



(**19**)



(**20**)

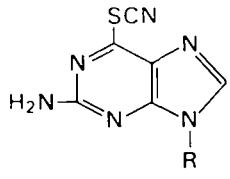
The preparation of several purinyl thiocyanates (thiocyanatopurines) as potential antitumour agents was reported by Saneyoshi and coworkers[113,114]. These were tested against transplanted sarcoma (NF-sarcoma) in mice. The most active members were 6-thiocyanatopurine (**21**), 2-amino-6-thiocyanatopurine (**22**) and their respective nucleosides (Figure 7). These compounds do not owe their antitumour properties to the thiocyanato group *per se*. Rather, their effectiveness is attributed to their probable conversion *in vivo* to the potent antimetabolites 6-mercaptopurine and 2-amino-6-mercaptopurine or to their ability to block the same metabolic pathways as the latter compounds do. In this respect the 6-thiocyanato group is simply fulfilling the role of a latent thiol or a pseudohalogen. Like the corresponding 6-mercaptopurines, the 6-thiocyanatopurines were found to be potent immunosuppressive agents[114a].

TABLE 6. Effects of alkyl and aryl isocyanates on the growth of transplanted Ehrlich ascites tumour cells in mice. Mice were inoculated with 10^6 cells, then treated daily with isocyanate at the indicated dose for 7 consecutive days. The ratio T/C represents the ratio of total packed tumour cell volume in test animals receiving cyanates to that in control animals not receiving therapy. Data compiled from Moos and coworkers[110].

Isocyanate	Dose (mg kg^{-1} day^{-1})	T/C
Allyl	5	0·38
Butyl	10	0·07
Hexamethylene, di	6	0·00
Phenyl	20	0·00
o-Chlorophenyl	30	0·74
m-Chlorophenyl	30	0·37
p-Chlorophenyl	30	0·07
p-Bromophenyl	20	0·17
p-Nitrophenyl	10	1·59
o-Methoxyphenyl	30	0·19
p-Methoxyphenyl	20	0·39
o-Ethoxyphenyl	30	0·00
p-Ethoxyphenyl	20	0·07
o-Tolyl	20	0·56
m-Tolyl	20	0·06
p-Tolyl	20	0·11
1-Naphthyl	40	0·02
1,5-Naphthylene, di	20	1·26

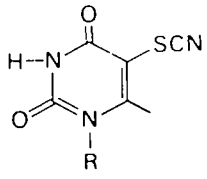
A related case is found in the 5-thiocyanatopyrimidines studied by Witkop and coworkers[115]. Again, the —SCN group in these may be likened to a halogen such as iodine in the potent antiviral agent 5-iodo-2′-deoxyuridine, or, otherwise, it could undergo reduction in biological systems to the corresponding 5-mercaptopyrimidines. Among the pyrimidine derivatives, the only compound that showed significant activity against KB cells or L5178 Y cells was 5-thiocyanato-2′-deoxyuridine (**23**, R = 2-deoxy-β-D-ribofuranosyl) which caused inhibition of growth at a concentration of $9{\cdot}10^{-6}$ M and $8{\cdot}10^{-7}$ M, respectively. This effect, however, could be completely reversed with 10^{-5} M-thymidine. The authors suggest that **23** is reduced *in vivo* to 5-mercapto-2′-deoxyuridine which is subsequently phosphorylated by thymidine kinase (EC 2.7.4.0) to the corresponding 5′-monophosphate, a potent inhibitor of thymidylate synthetase[116]. The use of thiocyanatopurines and pyrimidines may offer

(21)



(22)

(R = H; β-D-ribofuranosyl)



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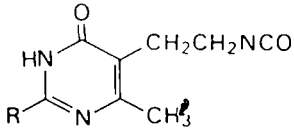


(24)

R = H
β-D-Ribofuranosyl
2′-Deoxy-β-D-ribofuranosyl
β-D-Arabinofuranosyl

R = OH; SH

FIGURE 7. Thiocyanato- and cyanatopyrimidines and purines of potential chemotherapeutic interest. From Saneyoshi and coworkers[113,114,114a], Witkop and coworkers[115], and Morreal, Hall and Eskins[123].

certain advantages over the corresponding mercapto analogues in drug application. But these should be weighed against the hazard incurred following concomitant formation of cyanide ion in the organism which may reach toxic levels. This is a case of the detoxification mechanism in reverse.

An exceptional case of antiviral activity was observed with KNCO which caused a 10-fold reduction in virus infectivity in mice treated with the Aujeszky strain of pseudorabies virus[117]. This activity, however, consisted in the prevention of infection rather than a cure, since it was observed only when the compound had been administered in a prophylactic way. Other viruses, such as herpes simplex and influenza A, were insensitive to pretreatment with cyanate. Free cyanate must be present at the time of infection and appears to prevent pseudorabies penetration in host cells by an unknown mechanism but not to prevent later stages of multiplication[118].

Nakamura[119] studied the ovicidal properties of cyanates on eggs of *Ascaris suila*. Organic isothiocyanates were found more effective in this respect than the corresponding thiocyanates when tests were performed in

saline solution, but the thiocyanates proved more effective in presence of urine and faeces. These findings should be considered in the light of Ortolani's observation[120] that NaSCN itself is capable of interfering with the normal embryonic development of eggs of *Phallusia mamillata* and *Ascida malaca*, the most sensitive period being the end of the neurula stage of the organs differentiation.

Finally, benzyl thiocyanate, like some other sulphur-containing compounds such as disulphiram and dimethyl dithiocarbamate, was found to inhibit the carcinogenic effects of polycyclic hydrocarbons when added to the diet of rats[121].

In contradistinction to the above findings, thiocyanates, isothiocyanates and potential isothiocyanate-forming compounds were found disappointingly poor to non-effective antimicrobial agents *in vivo*[122]. Also ineffective were a number of pyrimidylethyl isocyanates (**24**) which were tested as antagonists of tetrahydrofolic acid on *Streptococcus faecalis*[123].

VII. TOXICOLOGY AND PHARMACOLOGY OF CYANATES

A high order of toxicity in a compound is generally associated with a high degree of specificity for a vital function in an organism. That is, relatively few molecules of the total dose administered are 'wasted' on non-specific interactions with other less vulnerable biological substrates. By the same token, highly reactive molecules that discriminate little among many potential substrates are expected to show a low order of toxicity. Such are the cyanates, at least the inorganic alkali metal salts. Thus, the very noxious nature of the highly unstable free cyanic acid and related molecules incorporating the common X=C=Y structure does not go beyond the limits of strong lachrymation and vesication of exposed parts. Cyanate anion is devoid of these effects.

The toxicity of cyanates should be considered first within the framework of toxicity associated with the X=C=Y structure. The following figures are illustrative:

Allene	$CH_2=C=CH_2$	Toxicity unknown.
Ketene	$CH_2=C=O$	Oral LD_{50} in rat, 1300 mg per kg: lethal breathing concentration to mice, 750 mg per m^3 per min[124].

Carbon dioxide	O=C=O	Practically non-toxic[18].
Isocyanic acid	HN=C=O	Same as cyanate if administered in solution.
Cyanate	$(N{=}C{=}O)^-$	Oral LD_{50} to rat, 1500 mg per kg[70].
Cyanamide	$HN{=}C{=}NH(H_2NC{\equiv}N)$	Oral LD_{50} to rat, 125 mg per kg[124].
Thiocyanic acid	N≡C—SH	Intraperitoneal LD_{50} to mice, 500 mg per kg[124]; this is also the toxic dose for most inorganic thiocyanates, which exist in equilibrium with the isothiocyanates.
Carbon disulphide	S=C=S	Intraperitoneal toxic dose in rat, 400 mg per kg; in rabbit, subcutaneous, 300 mg per kg[124].

However, the above generalization on the low toxicity of cyanates and related compounds is subject to the two following reservations: (i) *Direct* exposure of a highly sensitive structure in a vital organ to the action of these agents entails an apparent rise in toxicity. A classical example of such an organ are the lungs where localized damage of the highly specialized alveolar membrane leads to widespread systemic effects non-commensurate with the dose absorbed. This aspect of inhalation poisoning has been described in more detail for phosgene in an earlier volume of this series[7]. In view of this, inhalation of the more volatile isocyanates may be far more dangerous than oral or parenteral intake. (ii) In substituted isocyanates, RNCO, thiocyanates, RSCN, and isothiocyanates, RNCS, toxicity is also a function of the nature of the substituent R. A classical case is that where R is an ω-fluoroalkyl group that is metabolized to the toxic fluoroacetic acid, FCH_2COOH[125].

With the advent of polyurethane foams in the plastics industry, isocyanates have become an occupational hazard; injury to man may result either through the accidental absorption of a massive dose resulting in acute toxicity, or through prolonged exposure to low concentrations of vapour in air, leading to chronic toxicity or sensitization of subjects. The safety aspects of handling organic isocyanates in industrial plants have been discussed by Corbett[126] and upper air limits for the more common agents have been set by U.S. Occupational Standards (HEW publication, National

Institute of Occupational Safety and Health, 74–134). For tolyl 2,4-diisocyanate, this limit is 140 μg per m^3. Sensitization of workers who had been exposed to this agent was described by Avery and coworkers[127]. In these, asthmatic symptoms developed almost immediately following re-exposure to minute concentrations of agent in air. Surprisingly, most serological tests for the detection of specific antibodies in the sera of these patients were negative, but conjugates of tolyl diisocyanate with human serum albumin produced stimulation of lymphocytes derived from the patients but not from healthy controls.

Data of acute toxicity of representative cyanates are given in Table 7. Most of these have been compiled from the Toxic Substances List[124] which should be consulted for additional information. Others are from the recent work of Cerami and coworkers[70] on the pharmacology of cyanates, and from Pattison[125]. Noteworthy is the percutaneous absorption of cyanates through intact skin and which may be conducive to death.

The chronic toxicity of inorganic cyanate was studied by Cerami and coworkers[70]. The daily intraperitoneal injection of KNCO to mice at the rate of 32 mg per kg, that is one tenth the acute LD_{50}, for a 5-month period, or a daily oral dose to dogs and monkeys of 100 mg per kg for a 15-month period, had no apparent adverse effect on the subjects. The only measurable difference between test and control animals was an increase in oxygen affinity of the blood of animals that received cyanate. Analyses of the haemoglobin of mice kept on such a schedule showed an incorporation of 0·8 to 1·0 carbamyl residue per haemoglobin tetramer, without detectable carbamylation of ε-amino groups. A schedule using a lower daily intake led to a lower rate of carbamylation, whilst one using a higher daily dose, 91 mg per kg, led to weight loss and eventual death. Most of the cyanate administered to mice by intraperitoneal injection (10 μmol) is eliminated as CO_2 (72%) whilst incorporation into erythrocytes accounts for 7% and that into serum proteins for 0·5% only. Toxic doses of cyanate produce marked diuresis and drowsiness in the rat (but not in man), secretions from the eye and nose and terminal convulsions. There is no proof, however, that these symptoms arise from the impairment of oxygen delivery by carbamylated haemoglobin and ensuing hypoxia. An impairment of a function at the level of the nervous system seems more likely.

Bakry, Metcalf and Fukuto[128] studied the insecticidal properties of some organic thiocyanates and isothiocyanates in the house fly, *Musca domestica*. With the exception of *p*-nitrobenzyl thiocyanate, isothiocyanate and *p*-nitrophenyl thiocyanate which were singularly non-toxic, the toxicity of most members by topical application was of the order of 300 to 500 mg per kg. Hence, the level of toxicity on a weight basis in these insects is

TABLE 7. Acute toxicity of cyanates

Compound	Toxic dose (mg/kg)	Species and route of administration
Isocyanic acid		
Na salt	310[a]	ip, rat
	260[a]	ip, mouse
	1500[a]	oral, rate
K salt	841[a]	oral, mouse
	320[a]	ip, mouse
	100[b]	ip, mouse
Methyl ester	2 ppm[c]	inhal., man
	63 ppm, 4 h[c]	inhal., rat
	71[a]	oral, rat
	220[a]	pc, rabbit
2-Chloroethyl ester	1000 mg/m^3, 10 min[c]	inhal., mouse
1,6-Hexamethylene ester	1570 mg/m^3[c]	inhal., mouse
	710[a]	oral, rat
	570[a]	pc, rabbit
Phenyl ester	940[a]	oral, rat
4-Chlorophenyl ester	53[a]	inhal., mouse
	530[a]	oral, mouse
2,4-Tolylene ester	0·5 ppm[c]	inhal., man
	14 ppm, 4 h	inhal., rat
	10 ppm, 4 h	inhal., mouse
	13 ppm, 4 h	inhal., guinea pig
Thiocyanic acid	500[a]	ip, mouse
Ammonium salt	500[a]	ip, mouse
Guanidine salt (1:1)	300[b]	ip, mouse
Potassium salt	80[b]	oral, man
	854[a]	oral, rat
Sodium salt	764[a]	oral, rat
	500[b]	ip, mouse
	484[a]	iv, mouse
Methyl ester	8·5[b]	oral, cat
Amyl ester	75[b]	ip, mouse
Dodecyl ester	1250[a]	oral, rat
2-Fluoroethyl ester	15[a]	ip, mouse
3-Fluoropropyl ester	18[a]	ip, mouse
4-Fluorobutyl ester	2·6[a]	ip, mouse
5-Fluoroamyl ester	30[a]	ip, mouse
6-Fluorohexyl ester	5[a]	ip, mouse
4-Chlorobutyl ester	15[a]	ip, mouse
5-Chloropentyl ester	24[a]	ip, mouse
Trichloromethyl ester	5[a]	iv, mouse
	3[a]	iv, rabbit
2-(2-Butoxyethoxy)ethyl ester	90[a]	oral, rat
	250[a]	pc, rat

TABLE 7. Acute toxicity of cyanates (*continued*)

Compound	Toxic dose (mg/kg)	Species and route of administration
	100[b]	oral, cat
	35[a]	oral, rabbit
	150[a]	pc, rabbit
p-Aminophenyl ester	240[a]	oral, rat
	160[b]	pc, rabbit
2,4-Dinitrophenyl ester	1000[a]	oral, dog
2-Pyridyl ester	500[b]	oral, rat
Isothiocyanic acid		
Methyl ester	305[a]	oral, rat
Allyl ester	339[a]	oral, rat
	4[b]	ip, mouse
5-Fluoroamyl ester	67[a]	ip, mouse
6-Fluorohexyl ester	11·2[a]	ip, mouse
Phenyl ester	400[a]	oral, mouse
	100[b]	ip, mouse
p-Bromophenyl ester	400[a]	oral, rat
1-Naphthyl ester	245[a]	oral, mouse
p-*N*-Dodecyloxyphenyl ester	100[b]	ip, mouse

[a] LD_{50}; [b] minimum reported lethal dose; [c] lethal or toxic concentration.
ip = intraperitoneal; iv = intravenous; pc = percutaneous; sc = subcutaneous; inhal. = inhalation. Most data compiled from the Toxic Substances List[124].

comparable to that in mammals by the oral route. The LD_{50}, in μg per g, for the parent compounds was as follows: $PhCH_2SCN$, 500; $PhCH_2NCS$, 330; PhSCN, 365. In the aliphatic series, the most toxic member was $C_{12}H_{25}SCN$, with an LD_{50} of 225; a shorter hydrocarbon chain as in the octyl or butyl analogues gave less toxic compounds. In addition, benzyl thiocyanates were synergistic with carbaryl, an organic carbamate insecticide, suggesting inhibition of enzymes responsible for the *in vivo* detoxification of carbamates. These are oxidases that incorporate molecular oxygen into the substrate at the *N*-methyl group or aromatic ring, through the mediation of a metal–protein complex, usually copper or iron, producing hydroxyl radicals. Conceivably, such an effect could be induced by thiocyanate ion, the eventual hydrolysis product of these organic thiocyanates. In the authors' view, however, the intact organothiocyanate molecule is essential for both toxicity and synergistic activity. Indeed, isothiocyanates which are expected to yield the same hydrolysis products as the corresponding thiocyanates exerted no synergistic effect.

Inorganic thiocyanate has a completely different pharmacology than inorganic cyanate; its properties reside in the SCN^- ion *per se*, which is not

a carbamylating agent, at least not under conditions prevailing *in vivo*. In fact, SCN^- is handled by the body as if it were a halide ion; it is slowly cumulative, its ultimate concentration being an inverse function of total halogen-ion turnover. This may explain its role as *ionic inhibitor* of the uptake of iodide by the thyroid gland and, hence, its goitrogenic effect in experimental animals[129], patients treated with potassium thiocyanate for hypertension[130], and subjects used to the consumption of thiocyanate-rich diet, especially when iodide intake itself is low[131]. That the function of thiocyanate as ionic inhibitor of the uptake of iodide is not a specific property is shown by the goitrogenic action of such anions as ClO_4^- and BF_4^- which are even more effective in this respect[132,133]. In the normal thyroid gland, the concentration of iodide is about 20-times higher than that in the plasma[134]. Administration of thiocyanate abolishes this gradient and accumulated iodide is discharged from the gland. Surprisingly however, SCN^- itself does not accumulate in the thyroid gland, as one would expect. When thiocyanate labelled with ^{35}S was used, radioactive sulphur was found to accumulate in the gland in the form of sulphate[135].

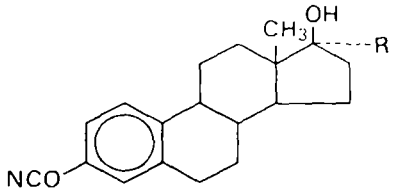
The antihypertensive properties of thiocyanate may well also dwell on an ionic mechanism which is still poorly understood. Sodium or potassium thiocyanate were administered orally to patients suffering from hypertension[130] but its use has been discontinued following toxic reactions elicited by the build-up of excessive plasma levels of the drug. In these reactions, central nervous system toxicity constitutes the most important hazard so that mental aberration should be expected in cases of thiocyanate intoxication. In such cases, elimination of excess thiocyanate could be achieved by the administration of large amounts of chloride[136].

VIII. CONCLUDING NOTES

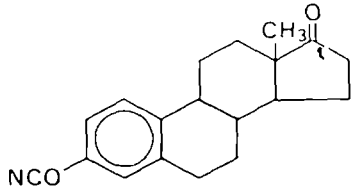
To date, the anti-sickling action of the inorganic cyanates overshadows in importance all other current applications of these agents in biology or medicine. At the same time, the development of sodium or potassium cyanate as a life-long drug for continuous use by patients will require comprehensive knowledge of biological effects in almost all fundamental processes of human life. One would, therefore, anticipate a growing body of investigations with these agents at all levels of biological organization.

The organic cyanates have so far had only limited attention as potential drugs. This may seem unwarranted in view of the unique property of the cyanato or isocyanato group of providing a compact 'anchor' in molecules destined to exert a protracted effect at the site of action. An example of these are hormones. Indeed, a number of efforts in this particular field are already

on record, such as the work of Onken and coworkers[137,138] on cyanate derivatives of sex hormones related to oestradiol:



(**25**: R = H)
(**26**: R = C≡CH)



(**27**)

Oestrone cyanate (**27**) has reached the stage of clinical trials[139,140]. It is active when administered orally, the endometrial proliferation dose being 6 mg in women with secondary amenorrhea. The exact contribution of the 3-cyanato group in the overall activity of these agents has not been elucidated. Remarkably, compounds **25**–**27** are among the very few *cyanates* rather than isocyanates ever used in biomedical research, but the possibility of isomerization should be borne in mind.

Another example is the work of Herzog and collaborators[141] on the preparation of 4-thiocyanato and 4-isothiocyanato derivatives of 3-oxo-$\Delta^{4,6}$-steroids related to progestin, but the biological activity of these agents has not been reported.

The judicious use of cyanates in such problematic fields is still optional so that further application of these agents in biomedical sciences may be forthcoming. Thus, one would expect to see more cyanates among specific enzyme inhibitors or irreversible blocking agents of the various receptors. Water-soluble cyanates, like the closely related water-soluble organic carbodiimides, a synthetic feat in its own right, should be of much convenience in enzymological or pharmacological studies. Admittedly, a major difficulty in such projects and often a deterring factor is the highly reactive nature of the 'cyanate' function which tends to make any cyanate derivative both unstable and non-specific. The control of these properties may prove to be a formidable task but, at the same time, also a stimulating challenge to the medicinal chemist.

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The Chemistry of Cyanates and their Thio Derivatives
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CHAPTER 21

Syntheses and reactions of isocyanide dihalides

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I. INTRODUCTION

The first member of the class of compounds discussed in this chapter was prepared about one hundred years ago by Sell and Zierold[1]. In spite of the fact that numerous derivatives have been synthesized since then, the nomenclature is still very much in doubt. We are using isocyanide dihalide in this chapter, while *Chemical Abstracts* uses the term imidocarbonyl dihalides, and since the isocyanide dihalides are derivatives of the hypothetical carbonimide acid $HN{=}C(OH)_2$, probably carbonimidoyl dihalides would be the more appropriate name. Other names frequently encountered include isonitrile dihalides, carbylamine dihalides, dichloromethyleneamines, carbonyl dichloride imides and iminophosgenes. In fact, isocyanide dihalides are more closely related in their chemistry to phosgene than to isocyanides.

Two summaries of the methods used in the synthesis of isocyanide dihalides have appeared recently[2,3], and their general chemistry has been reviewed also[2,4]. Therefore emphasis on new methods is stressed in this chapter and the general methods of synthesis as well as reactions are only treated briefly. Numerous nucleophilic reactions of isocyanide dichlorides have been investigated[4], and the fact that the two geminal chloride atoms can react selectively in succession allows the synthesis of a wide variety of carbonic acid derivatives. Utility of some of the derivatives as agricultural chemicals is indicated and phenylisocyanide dichloride was used as a war gas in the closing months of World War I.

The utilization of the phosgene dimethylimmonium salts in organic synthesis[5] is another example of the enormous versatility of 'phosgene imide derivatives'.

II. SYNTHESIS OF ISOCYANIDE DIHALIDES

A. *Alkyl and Aryl Isocyanide Dihalides*

1. Addition of halogen to isocyanides

The synthesis of isocyanide dihalides by addition of halogen to isocyanides proceeds in chloroform solution at room temperature[6]. In the aliphatic series it is sometimes advantageous to conduct the reaction in diethyl ether, using sulphuryl chloride as the chlorinating agent. However in long chain aliphatic isocyanides preferential chlorination of the aliphatic chain has been observed[7]. In contrast isocyanides containing tertiary amino groups at the end of the aliphatic side chain readily add chlorine to the isonitrile group to give the corresponding isocyanide dichlorides in 62–64% yield[8].

$$Me_2N(CH_2)_3NC + Cl_2 \longrightarrow Me_2N(CH_2)_3N{=}CCl_2$$

Addition of bromine or iodine to phenyl isocyanide gives rise to the formation of the corresponding dihalides[6,9].

2. Halogenation of isothiocyanates

The chlorination of phenyl isothiocyanate is the classical method of synthesis of phenyl isocyanide dichloride[1]. If this reaction is conducted in carbon tetrachloride below 3 °C, yields of 85–90% are obtained[10]. In the aliphatic series also good yields are obtainable. However it is advantageous to treat the crude reaction mixture with aqueous sodium sulphite and sodium carbonate to remove impurities which may cause decomposition during vacuum distillation[11].

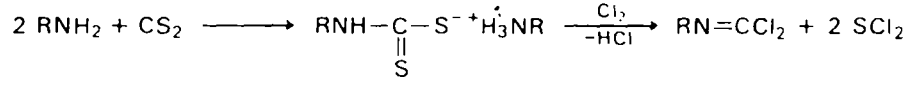
The mechanism of the chlorination of isothiocyanates involves formation of a 1-(chlorothio)formimidoyl chloride intermediate **1**, which upon further chlorination gives a mixture of the isocyanide dichloride **2** and sulphur dichloride[12].

$$RN{=}C{=}S \xrightarrow{Cl_2} \underset{\displaystyle Cl}{\overset{\displaystyle |}{RN{=}C{-}SCl}} \xrightarrow{Cl_2} RN{=}CCl_2 + SCl_2$$

(1) (2)

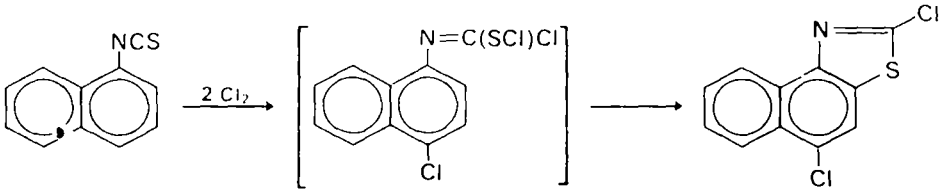
The chlorination of isothiocyanates is a general procedure and excellent yields are reported for a wide variety of aliphatic and aromatic isocyanide dichlorides[2,3]. Also aliphatic isothiocyanates with ether[3] or ester[13]

groups attached to the alkyl chain are readily converted to alkyl isocyanide dichlorides using this method, and recently fluorochloromethyl isocyanide dichlorides were synthesized analogously[14]. Since isothiocyanates are obtained by oxidation of *N*-monosubstituted thiocarbamates **3**, these compounds have also been used as starting materials for isocyanide dichlorides, because the chlorine oxidizes **3** to generate the isothiocyanate *in situ*[15].



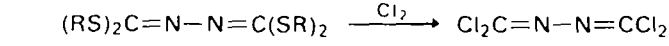
(3)

However 1-naphthyl isothiocyanate does not produce the corresponding isocyanide dichloride, because the (chlorothio)formimidoyl chloride intermediate **4** cyclizes to produce the [1,2-*d*]thiazole derivative **5**[16].



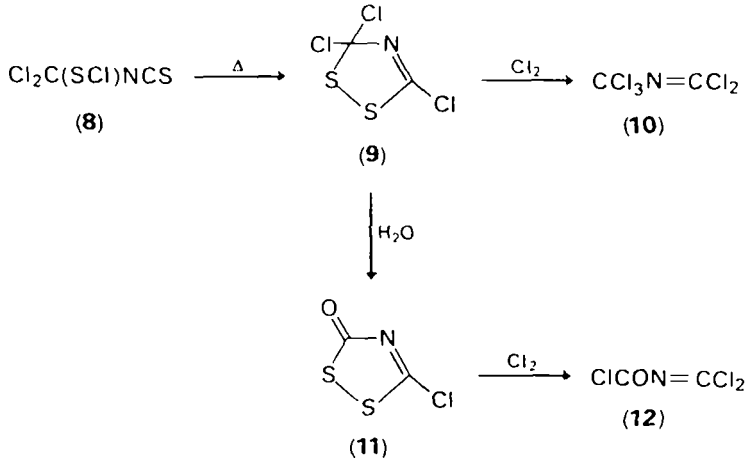
(4) (5)

Chlorination of masked isothiocyanates, such as **6**, **9** and **11** also produces isocyanide dichlorides. Thus chlorination of the thioalkyl derivative **6** gives rise to the formation of diisocyanogen tetrachloride (**7**) in 67–70% yield[17].



(6) (7)

Chlorination of 1,2,4-dithiazoles also produces isocyanide dichlorides[14]. For example thermolysis of **8**, obtained in the chlorination of FCCS:NCS, gives rise to the formation of 3,5,5-trichloro-1,2,4-dithiazole (**9**), which upon further chlorination yields trichloromethyl isocyanide dichloride (**10**). Hydrolysis of **9** produces 3-chloro-5-oxo-1,2,4-dithiazole (**11**), and its chlorination produces chlorocarbonyl isocyanide dichloride (**12**)[14].



Isocyanide difluorides can also be obtained from isothiocyanates. Thus heating of isothiocyanates with mercuric fluoride produces isocyanide difluorides[18].

$$RNCS + HgF_2 \longrightarrow RN{=}CF_2 + HgS$$

3. Halogenation of isocyanates and carbamoyl chlorides

Aliphatic isocyanide dichlorides are obtained in good yield upon reaction of aliphatic isocyanates with phosphorus pentachloride[19,20].

$$RNCO + PCl_5 \longrightarrow RN{=}CCl_2 + POCl_3$$

Aromatic isocyanates react differently[20,21], and acyl and aroyl isocyanates also fail to yield the corresponding isocyanide dichlorides[22]. The latter undergo preferential reaction on the C=O group attached to the isocyanate function to give chloroimidoyl-*N*-carbonyl chlorides (**13**) which are in equilibrium with the isomeric isocyanates **14** when R = alkyl[22].

$$RCONCO + PCl_5 \longrightarrow \underset{\displaystyle Cl}{\overset{\displaystyle |}{RC{=}NCOCl}} \rightleftharpoons RCCl_2NCO$$

(**13**) (**14**)

Chlorination of chloromethyl isocyanate (**15**) yields chlorocarbonyl isocyanide dichloride (**16**)[23].

$$ClCH_2NCO + Cl_2 \longrightarrow ClCON{=}CCl_2$$

(15) (16)

Aliphatic secondary carbamoyl chlorides also produce isocyanide dichlorides on high temperature chlorination, provided one of the alkyl groups is a methyl group[24]. The methyl group, after perchlorination, generates the $N{=}CCl_2$ group with elimination of phosgene.

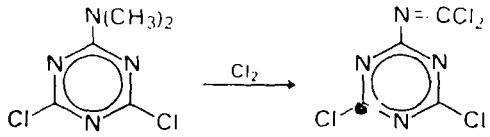
$$(CH_3)_2NCOCl + 6\,Cl_2 \longrightarrow CCl_3N{=}CCl_2 + COCl_2 + 6\,HCl$$

A similar reaction is observed when bis(trifluoromethyl)carbamoyl fluoride (**17**) is heated at 490–575 C; the isolated reaction products are trifluoromethyl isocyanide difluoride (**18**) and carbonyl fluoride (**19**)[25].

$$(CF_3)_2NCOF \xrightarrow{\Delta} CF_3N{=}CF_2 + COF_2$$

(17) (18) (19)

Chlorination of 2-dimethylamino-4,6-dichloro-1,3,5-triazine (**20**) produces mainly the triazinyl isocyanide dichloride **21** (tetrameric cyanogen chloride)[26].

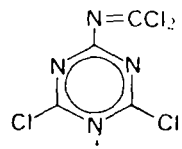


(20) (21)

In a similar manner pentameric and hexameric cyanogen chloride are obtained in the exhaustive chlorination of 2,4-bis(dimethylamino)-6-chloro and 2,4,6-tris(dimethylamino)-1,3,5-triazine, respectively. On attempted synthesis of *N*-cyanoisocyanide dichloride (**22**), its dimer **21** was obtained[17].

$$(MeS)_2C{=}NCN \xrightarrow{Cl_2} [Cl_2C{=}NCN] \longrightarrow$$

(22)



(21)

4. Halogenation of imidoyl chlorides

Reaction of formamides with thionyl chloride generates the imidoyl chlorides, **23**, which are chlorinated with sulphuryl chloride to give isocyanide dichlorides in good yields[3]. In this manner a great number of aromatic isocyanide dichlorides are synthesized simply by adding the corresponding arylformamide to one equivalent of sulphuryl chloride dissolved in excess thionyl chloride at 15–20 °C

$$ArNHCHO + SOCl_2 \longrightarrow \underset{(23)}{ArNH^+{=}CHCl]Cl^-} + SO_2$$

$$\underset{(23)}{ArNH^+{=}CHCl]Cl^-} + SO_2Cl_2 \longrightarrow ArN{=}CCl_2 + 2\,HCl + SO_2$$

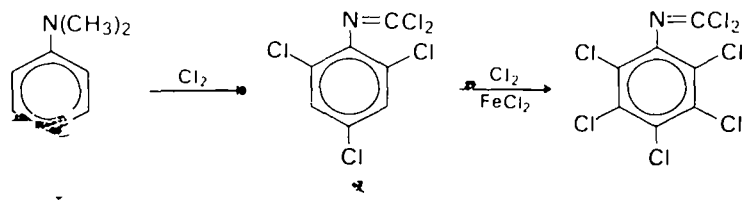
Aliphatic formamides react similarly, but the reaction has to be conducted stepwise, i.e. the initial conversion to **23** has to be completed prior to the addition of the sulphuryl chloride.

The reaction of phenylthioformamide (**24**) with bromine yields 4-bromophenyl isocyanide dibromide (**25**), most likely by a similar mechanism[27].

$$\underset{(24)}{C_6H_5NHCHS} + Br_2 \longrightarrow \underset{(25)}{4\,BrC_6H_4N{=}CBr_2}$$

5. Halogenation of amines

High temperature chlorination of tertiary amines containing two methyl groups attached to nitrogen gives rise to the formation of isocyanide dichlorides. However this reaction is difficult to control and higher halogenated derivatives are usually obtained[28].



Also chlorination of *N.N.N′,N′*-tetramethylethylenediamine (**26**) gives rise to the formation of the perchlorinated bis-isocyanide dichloride **27**[28].

$$(CH_3)_2NCH_2CH_2N(CH_3)_2 \xrightarrow{Cl_2} Cl_2C{=}NCCl_2CCl_2N{=}CCl_2$$

(26) **(27)**

One example of chlorination of a secondary amine to the corresponding isocyanide dichloride has also been reported. Reaction of bis(trifluoromethyl)amine **28** with phosphorus trichloride produces trifluoromethylisocyanide dichloride (**29**)[29].

$$(CF_3)_2NH + PCl_3 \longrightarrow CF_3N{=}CCl_2$$

(28) **(29)**

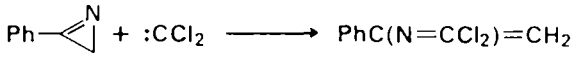
Heating of **28** with sulphur produces trifluoromethyl isocyanide difluoride[30].

6. From dichlorocarbene

Addition of dichlorocarbene, generated from phenyl(bromodichloromethyl)mercury, to aliphatic carbodiimides produces the corresponding isocyanide dichlorides in good yields[31].

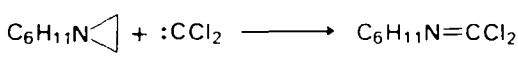
$$PhHgCCl_2Br + RN{=}C{=}NR \longrightarrow RN{=}CCl_2 + RNC + PhHgBr$$

Isocyanide dichlorides are also obtained in the reaction of azirines with dichlorocarbenes[32,33] For example 2-phenylazirine affords the styrylisocyanide dichloride **30**[34].



(30)

Cyclohexylaziridines (**31**) are also attacked by dichlorocarbene to give 30–40% of cyclohexyl isocyanide dichloride (**32**).[35]



(31) **(32)**

Long chain aliphatic isocyanide dichlorides are obtained from the corresponding azides and dichlorocarbene. For example stirring of *n*-octyl azide (**33**) in pentane at 0 °C in the presence of excess potassium

t-butoxide in chloroform affords *n*-octyl isocyanide dichloride (**34**) in 89% yield[36].

$$n\text{-}C_8H_{17}N_3 + :CCl_2 \longrightarrow n\text{-}C_8H_{17}N{=}CCl_2 + N_2$$

(**33**) (**34**)

7. From cyanogen chloride

Cyanogen chloride is an exceedingly useful starting material for isocyanide dichlorides. For example, reaction of chlorine with cyanogen chloride in the presence of charcoal produces *N*-chloro isocyanide dichloride (**35**) in over 95% yield[37].

$$ClCN + Cl_2 \longrightarrow ClN{=}CCl_2$$

(**35**)

In contrast, reaction of cyanogen chloride with ClF produces *N*-dichlorochlorodifluoromethyl amine (**36**) exclusively[38]. Heating of **36** above 100 °C produces *N*-chloroisocyanide difluoride **37**[38].

$$ClCN + 2\,ClF \longrightarrow ClF_2C{-}NCl_2 \xrightarrow{\Delta} ClN{=}CF_2$$

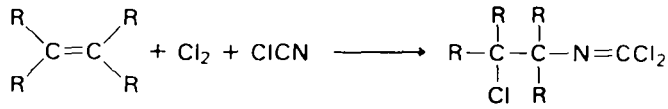
(**36**) (**37**)

Reaction of cyanogen chloride with phosgene over carbon at 130–180 °C and 45–75 atm produces a mixture of *N*-chlorocarbonyl isocyanide dichloride (**38**) and carbonyl bis(isocyanide dichloride) **39**[39].

$$ClCN + COCl_2 \xrightarrow{C} ClCON{=}CCl_2 + CO(N{=}CCl_2)_2$$

(**38**) (**39**)

Chlorination of olefins in the presence of cyanogen chloride gives rise to the formation of chloroalkyl isocyanide dichlorides[40,41]



The yields obtained are in the order of 20–90%. The higher yields were obtained from butadiene or vinyl chloride. In the case of vinyl chloride,

Lewis acids such as $FeCl_3$ are required to catalyse the reaction. In the addition to 2-chloropropene, simultaneous elimination of hydrogen chloride is observed to produce 1-chloroisopropenyl isocyanide dichloride (**40**)[41].

$$CH_2{=}C(Cl)CH_3 \xrightarrow[ClCN]{Cl_2} \left[ClCH_2\overset{\displaystyle CH_3}{\overset{|}{\underset{\displaystyle Cl}{\underset{|}{C}}}}{-}N{=}CCl_2 \right] \xrightarrow{-HCl} ClCH{=}C(CH_3)N{=}CCl_2$$

(**40**)

If this reaction is extended to an α,β-unsaturated carboxylic acid the initial adducts undergo an intramolecular reaction to produce α-chloro-β-isocyanato carboxylic acid chlorides **41**[41].

$$CH_3CH{=}CHCOOH \xrightarrow[ClCN]{Cl_2} [CH_3CH(N{=}CCl_2)CH(Cl)COOH] \xrightarrow{-HCl} CH_3CH(NCO)CH(Cl)COCl$$

(**41**)

A similar reaction occurs when isobutylene is treated with cyanogen chloride and chlorosulphonic acid, the isolated reaction product being the isocyanate **42**[41].

$$(CH_3)_2C{=}CH_2 \xrightarrow[ClSO_3H]{ClCN} [(CH_3)_2C(N{=}CCl_2)CH_2SO_3H] \xrightarrow{-HCl} (CH_3)_2C(NCO)CH_2SO_2Cl$$

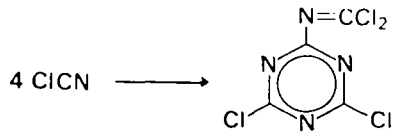
(**42**)

The addition of cyanogen chloride to *N*-chloro-bis(trifluoromethyl)amine in the presence of light produces the isocyanide dichloride derivative **43**[42].

$$(CF_3)_2NCl + ClCN \xrightarrow{h\nu} (CF_3)_2N{-}N{=}CCl_2$$

(**43**)

Tetramerization of cyanogen chloride produces 2,4-dichloro-1,3,5-triazine-6-isocyanide dichloride (**44**) in high yield[43].



(**44**)

8. Miscellaneous methods

Reaction of nitrogen trichloride with carbon tetrachloride in the presence of aluminium chloride gives rise to the formation of trichloromethyl isocyanide dichloride **45**, dichloromethyl-bis(isocyanide dichloride) (**46**), chloromethyl-tris(isocyanide dichloride) (**47**), and cyanuric chloride (**48**)[44].

$$Cl_3N + CCl_4 \xrightarrow{AlCl_3} CCl_3N{=}CCl_2 + Cl_2C(N{=}CCl_2)_2 + ClC(N{=}CCl_2)_3 + (ClCN)_3$$

(**45**) (**46**) (**47**) (**48**)

The same products (**45**, **46**, **47**) are also obtained in the reaction of *N*-chloroisocyanide dichloride with carbon tetrachloride in the presence of aluminium chloride[45]. If chloroform is used in this reaction a mixture of chloromethyl-bis(isocyanide dichloride) and methylene-bis(isocyanide dichloride) is obtained[45].

Reaction of the sodium salt of tricyanomethane with carbon tetrachloride in the presence of aluminium chloride also gives the isocyanide dichloride derivative **49** in low yield[46].

$$NaC(CN)_3 + CCl_4 \xrightarrow{AlCl_3} (NC)_2C{=}C(Cl)N{=}CCl_2$$

(**49**)

Reaction of carbon tetrachloride with nitriles, such as trichloroacetonitrile, in the presence of aluminium chloride produces isocyanide dichlorides **50** (R = Cl, CN, CH_2Cl)[47].

$$RCCl_2CN + CCl_4 \xrightarrow{AlCl_3} RCCl_2CCl_2N{=}CCl_2$$

(50)

Trichloromethyl isocyanide dichloride (**51**) reacts with anhydrides in the presence of $FeCl_3$ to give *N*-chlorocarbonyl isocyanide dichloride (**52**) in excellent yield[48].

$$CCl_3N{=}CCl_2 + (RCO)_2O \xrightarrow{FeCl_3} ClCON{=}CCl_2 + 2\ RCOCl$$

(51) **(52)**

The isocyanide dichloride derivative **52** is also produced in the reaction of **51** with chloral in the presence of $FeCl_3$[49].

Reaction of *N*-chloroisocyanide difluoride (**53**) with tetrafluoroethylene gives a 75% yield of chlorotetrafluoroethyl isocyanide difluoride (**54**)[50].

$$ClN{=}CF_2 + C_2F_4 \longrightarrow ClCF_2CF_2N{=}CF_2$$

(53) **(54)**

Reaction of the perhalogenated amine **55** with iron pentacarbonyl gives a 43% yield of the *N*-fluoroisocyanide dihalide **56**[51].

$$CCl_2FNF_2 \xrightarrow{Fe(CO)_5} FN{=}C(F)Cl$$

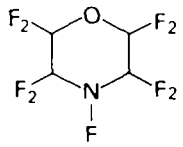
(55) **(56)**

In a similar manner *N*-fluoroisocyanide difluoride and *N*-fluoroisocyanide dichloride are obtained[51]. The thermolysis of trichloronitrosomethane (**57**) gives rise to the formation of trichloromethylisocyanide dichloride (**58**)[52].

$$3\ CCl_3NO \xrightarrow{\Delta} CCl_3N{=}CCl_2 + CCl_3NO_2 + NOCl$$

(57) **(58)**

Pyrolysis of perfluorotriethylamine affords pentafluoroethyl isocyanide difluoride[53]. In a similar manner perfluoro morpholine (**59**) on thermolysis produces pentafluoroethyl isocyanide difluoride (**60**)[54].

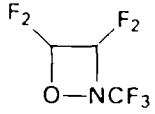


(59)

$$\xrightarrow{\Delta} CF_3CF_2N{=}CF_2 + CF_3CF{=}NCF_3$$

(60)

The oxazetidine derivative, **61**, produced in the cycloaddition reaction of trifluoronitrosomethane and tetrafluoroethylene, on thermolysis or photolysis yields trifluoromethyl isocyanide difluoride (**62**)[55].



(61)

$$\xrightarrow{\Delta} CF_3N{=}CF_2 + COF_2$$

(62)

Thermolysis of the fluoroalkyl azide **63** gives rise to the formation of tetrafluoroethyl isocyanide difluoride (**64**)[56].

$$CF_3CHFCF_2N_3 \xrightarrow{\Delta} CF_3CHFN{=}CF_2 + N_2$$

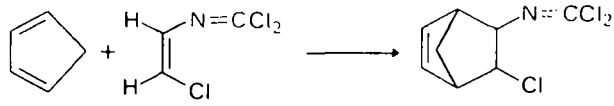
(63) (64)

Reaction of isocyanide dichlorides with hydrogen fluoride produces the corresponding trifluoromethylamine, which eliminates hydrogen fluoride on heating in the presence of potassium fluoride to yield the corresponding isocyanide difluoride[57].

$$RN{=}CCl_2 + 3\,HF \longrightarrow RNHCF_3 \longrightarrow RN{=}CF_2$$

In contrast, reaction of trichloromethyl isocyanide dichloride with sodium fluoride in sulpholane results in step-wise displacement of chloride on the methyl group to give a mixture of fluorodichloromethyl, difluorochloromethyl and trifluoromethyl isocyanide dichloride[58].

Cyclic unsaturated isocyanide dichlorides (**66**) are obtained in the Diels Alder reaction of the unsaturated isocyanide dichloride, **65**, with butadiene or cyclopentadiene[59].



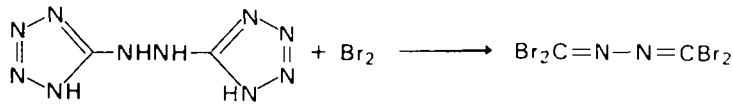
(65) (66)

Unsaturated isocyanide dichlorides are obtained by either dehydrochlorination of the addition products of chlorine and cyanogen chloride to olefins (see Section II.A.8) or by dechlorination of haloalkyl isocyanide dichlorides, such as **67**, with iron or zinc[60].

$$CH_2ClCHClN{=}CCl_2 \xrightarrow{Fe} CH_2{=}CHN{=}CCl_2$$

(67)

Isocyanogen tetrabromide (**69**) is readily obtained in the bromination of the hydrazotetrazole derivative **68**[61].



(68) (69)

B. Acyl and Aroyl Isocyanide Dihalides

1. Halogenation of isothiocyanates

Chlorination of aroyl isothiocyanates for prolonged periods of time at low temperature produces aroyl isocyanide dichlorides **70** (R = aryl) in good yields[62].

$$RCONCS \xrightarrow{Cl_2} RCON{=}CCl_2$$

(70)

Acyl isocyanide dichlorides (**70**, R = alkyl) are best synthesized by chlorination of the corresponding isothiocyanates in the presence of a catalytic amount of titanium tetrachloride[63]. The required acyl or aroyl-isothiocyanates are readily obtained by reacting carboxylic acid chlorides with trimethylsilyl isothiocyanate (**71**)[64].

$$RCOCl + Me_3SiNCS \longrightarrow RCONCS + Me_3SiCl$$

(71)

Chlorination of *N*-aroyldithiocarbamates or diethylaroyliminodithiocarbamates also produces aroyl isocyanide dichlorides[65].

2. From acyl chlorides and cyanogen chloride

Several acyl chlorides are readily converted into acyl isocyanide dichlorides on reaction with cyanogen chloride (see also Section II.A.8). For example reaction of chloroacetyl chloride with cyanogen chloride gives isocyanide dichloride **72** in good yield[66].

$$ClCH_2COCl + ClCN \longrightarrow ClCH_2CON{=}CCl_2$$

(72)

Similarly reaction of phosgene with cyanogen chloride gives a mixture of *N*-chlorocarbonyl isocyanide dichloride and carbonyl-bis(isocyanide dichloride)[39]. *N*-Chlorocarbonyl isocyanide dichloride is also obtained in the chlorination of methyl isocyanate[26].

The lower acyl isocyanide dichlorides dissociate on long standing into acyl chlorides and cyanogen chloride.

C. Sulphenyl Isocyanide Dichlorides

1. Halogenation of isothiocyanates

Chlorination of dithiocyanogen (**73**) in ethyl bromide produces chlorosulphenyl isocyanide dichloride (**74**)[67]. The same compound was also obtained in the chlorination of trimethylsilyl isothiocyanate (**75**)[3].

$$(SCN)_2 \xrightarrow{Cl_2} ClS{-}N{=}CCl_2 \xleftarrow{Cl_2} (CH_3)_3SiNCS$$

(73) (74) (75)

2. From sulphenyl halides and cyanogen chloride

Addition of sulphenyl chloride to cyanogen chloride also produces **74**. addition of a second mole of cyanogen chloride produces the bis(isocyanide dichloride) **76**[68].

$$SCl_2 \xrightarrow{ClCN} ClS{-}N{=}CCl_2 \xrightarrow{ClCN} Cl_2C{=}N{-}S{-}N{=}CCl_2$$

(74) (76)

This reaction is a general reaction and a variety of perhaloalkyl sulphenyl chlorides are readily converted into the corresponding sulphenylisocyanide dichlorides on heating with cyanogen chloride under pressure (60–120 °C) in the presence of charcoal[69,70]

3. Miscellaneous methods

Reaction of chlorosulphenylisocyanide dichloride with thiocarbonyl halides in the presence of light produces the novel isocyanide dichlorides **77** (X = Cl or F)[70].

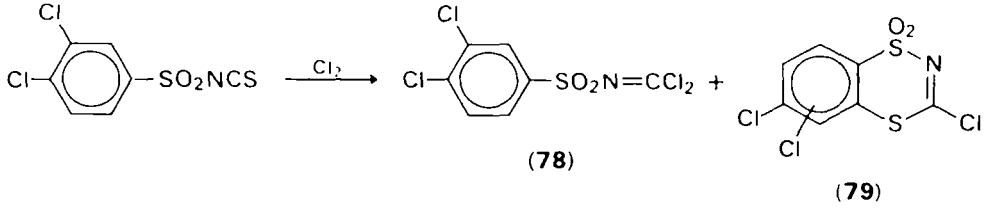
$$ClSN{=}CCl_2 + X{-}\underset{\underset{S}{\|}}{C}{-}F \xrightarrow{h\nu} F{-}\overset{\overset{Cl}{|}}{\underset{\underset{X}{|}}{C}}{-}S{-}S{-}N{=}CCl_2$$

(77)

D. Sulphonyl Isocyanide Dihalides

1. Halogenation of isothiocyanates

The chlorination of arenesulphonyl isothiocyanates in diethyl ether produces the corresponding arenesulphonyl isocyanide dichlorides[71]. However the reaction does not proceed as smoothly as that of aryl isothiocyanates. For example chlorination of 3,4-dichlorobenzenesulphonyl isothiocyanate produces a mixture of the desired isocyanide dichloride (**78**) and the heterocycle **79**[72].



(78) (79)

2. Chlorination of *S,S*-dialkyl-*N*-sulphonyldithiocarbonimides

S,S-Dialkyl-*N*-sulphonyldithiocarbonimides (**80**) react rapidly with chlorine to give sulphonyl isocyanide dichlorides in excellent yields[73,74].

$$\underset{\textbf{(80)}}{RSO_2N{=}C(SR')_2} \xrightarrow{Cl_2} RSO_2N{=}CCl_2 + 2\,R'SCl$$

In a similar manner sulphonylisocyanide dichlorides are obtained in the chlorination of dithiocarbamate salts **81**[75].

$$\underset{\textbf{(81)}}{RSO_2N{=}C(SK)_2} \xrightarrow{Cl_2} RSO_2N{=}CCl_2 + 2\,SCl_2 + 2\,KCl$$

3. Miscellaneous methods

The reaction of the urea derivative **82** with phosphorus pentachloride affords the sulphonyl isocyanide dichloride **83**[76].

$$\underset{\textbf{(82)}}{FSO_2NHCON(CH_3)_2} + PCl_5 \longrightarrow \underset{\textbf{(83)}}{(CH_3)_2NSO_2N{=}CCl_2}$$

E. Phosphoryl Isocyanide Dihalides

1. Halogenation of isothiocyanates

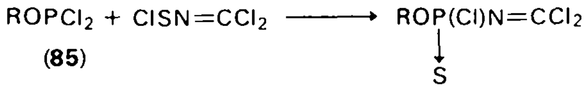
Isothiocyanato groups attached to phosphorus are also readily converted to the corresponding isocyanide dichlorides (**84**) using chlorine[77,78].

$$\underset{\displaystyle\underset{O}{\downarrow}}{(RO)_2P{-}NCS} + 2\,Cl_2 \longrightarrow \underset{\displaystyle\underset{O}{\downarrow}}{(RO)_2P{-}N{=}CCl_2}$$

(84)

2. Miscellaneous methods

Reaction of chlorosulphenylisocyanide dichloride with phosphorus halides (**85**) gives rise to the formation of thiophosphoric acid derivatives **86**[79].



(**85**) (**86**)

F. Dichloroformaldoxime Derivatives

Dichloroformaldoxime (**87**) can be obtained in 44–70% yield by reduction of trichloronitrosomethane[80].

$$CCl_3NO + H_2S \longrightarrow Cl_2C{=}NOH + HCl + S$$

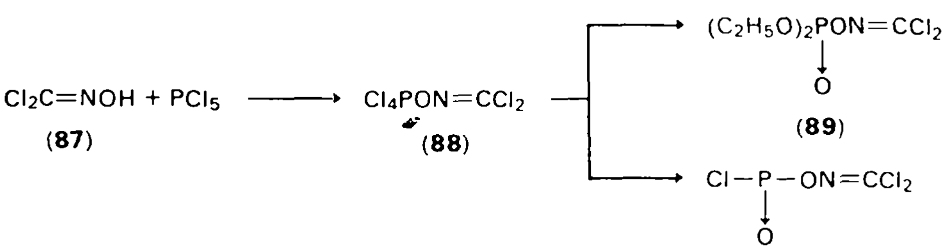
(**87**)

Dichloroformaldoxime as well as the dibromo and the diiodo derivative are also obtained by halogenation of mercuric or sodium fulminate[81].

Reaction of **87** with isocyanates produces the carbamates **88** in good yields[82].

$$\underset{(\mathbf{87})}{Cl_2C{=}NOH} + RNCO \longrightarrow \underset{(\mathbf{88})}{Cl_2C{=}NOCONHR}$$

Reaction of **87** with phosphorus pentachloride produces the pentavalent phosphorus compound **88**, which on treatment with ethanol gives **89** and on reduction with sulphur dioxide gives **90**[83].



(**87**) (**88**) (**89**) (**90**)

Reaction of halonitrosoalkanes with dialkyl phosphites also produces dichloroformaldoxime derivatives. For example passing chlorodifluoronitrosomethane into dimethyl phosphite gives a 20% yield of **91**[84].

$$ClF_2CNO + (CH_3O)_2PHO \longrightarrow (CH_3O)_2P(O)-ON=CF_2$$

(91)

Other halonitrosoalkanes were reacted with a wide variety of phosphorus compounds to yield the corresponding isocyanide dihalides[85].

Reaction of dichloroformaldoxime with the perfluoro compound **92** produces the isocyanide dichloride **93**[86].

$$Cl_2C=NOH + (F_2N)_2C=NF \longrightarrow (F_2N)_2C(NHF)-ON=CCl_2$$

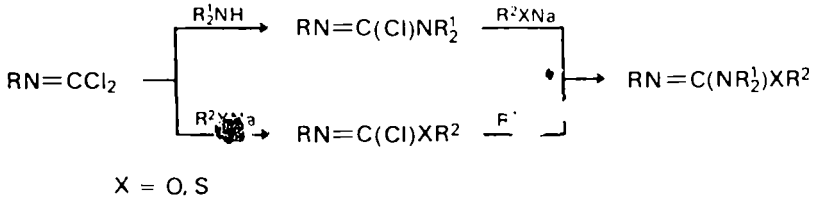
(92) **(93)**

III. REACTIONS OF ISOCYANIDE DIHALIDES

A. Nucleophilic Displacement Reactions

1. Formation of linear reaction products

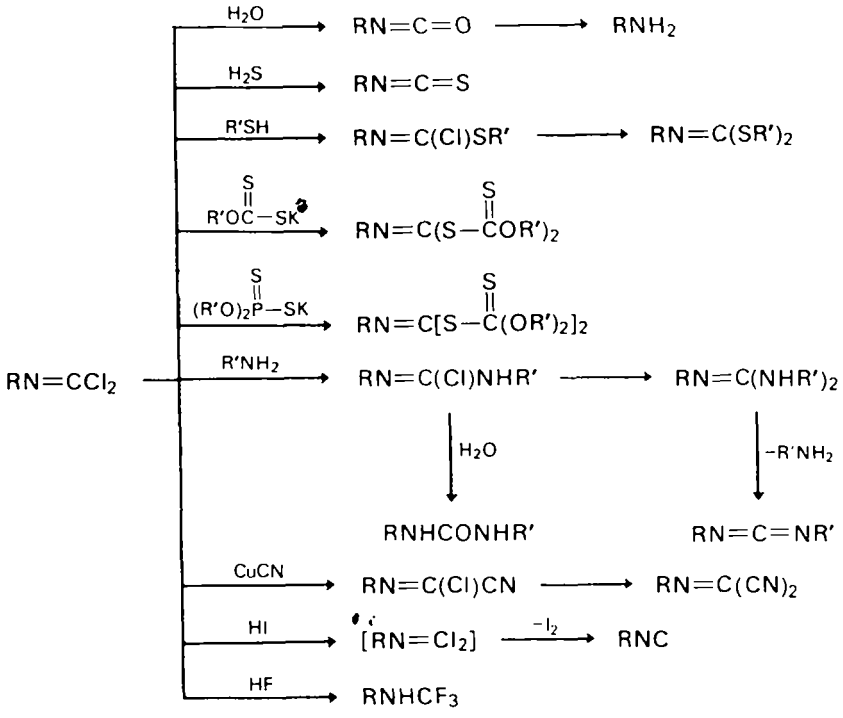
The most important reactions of isocyanide dihalides involve nucleophilic displacement on both halide groups. These reactions have been investigated extensively, and reviews have appeared recently[2-4]. The reactivity of the chloro groups in isocyanide dichlorides is in the order of alkyl < aryl < acylisocyanide dichlorides, the reactivity of the latter approaching that of carboxylic acid chlorides. After substitution of one of the chloro groups the reactivity of the remaining chloro group is considerably reduced, thereby allowing a selective displacement on both chloro groups. The selective displacement reactions can be conducted without isolation of the intermediate monosubstituted imidoyl chloride. For example, reaction of an isocyanide dichloride with an amine and an alkoxide or mercaptide can be conducted either by first reacting the isocyanide dichloride with the amine to the corresponding chloroformamidine intermediate, followed by reaction with the alkoxide, or by reversing the reaction sequence (see Scheme 1).



SCHEME 1.

A general summary of the nucleophilic reactions of isocyanide dichlorides with a wide variety of nucleophiles is shown in Table 1. For pertinent literature references see the review articles[2,4].

TABLE 1. Nucleophilic displacement reactions of isocyanide dichlorides



The conversion of isocyanide dichlorides to isocyanates is best conducted with formic acid, phosphoryl chloride, chlorosulphonic acid or methylsulphonic acid[87]. Hydrolysis with aqueous acid leads to the formation of the corresponding amines by further hydrolysis of the generated isocyanate. Isocyanide dihalides are also converted to isothiocyanates.

However this method is of limited value because isocyanide dichlorides are best synthesized by chlorination of isothiocyanates. One recent method of synthesis of isothiocyanates involves reaction of arylisocyanide dichlorides with thioacetamide in DMF[88].

Monosubstituted thiocarbamic acid *O*-aryl esters (**94**) are readily obtained by reacting isocyanide dichlorides with a phenol in the presence of base, followed by reaction with hydrogen sulphide[89].

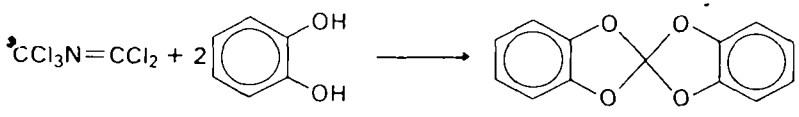
$$RN{=}CCl_2 + R'OH \xrightarrow{:B} RN{=}C(Cl)OR' \xrightarrow{H_2S} RNHCSOR'$$

(**94**)

Isocyanide dichlorides also undergo rapid reaction with sodium malonate or sodium cyanoacetate to mono and disubstituted products[90].

$$RN{=}CCl_2 + 2\,NaCH(COOR)_2 \longrightarrow RN{=}C[CH(COOR)_2]_2$$

Reaction of isocyanide dichlorides with phenols also produces orthocarbonates[91]. For example reaction of trichloromethyl isocyanide dichloride with catechol gives the orthocarbonate **95**[92].

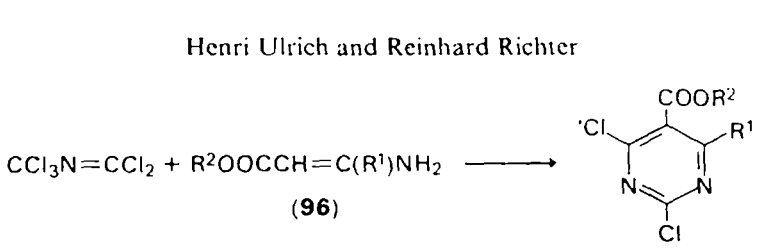


(**95**)

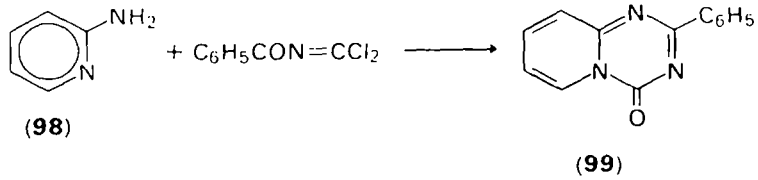
2. Formation of heterocyclic reaction products

Isocyanide dichlorides are widely used to synthesize heterocyclic compounds by nucleophilic displacement reactions. The pertinent reactions leading to cyclic systems are summarized in Tables 2 and 3. In addition a great variety of five-membered ring heterocycles derived from *o*-disubstituted benzene derivatives have also been reported[2-4].

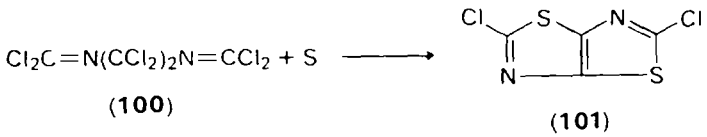
Several special isocyanide dichlorides are used to form different types of heterocycles. In trichloromethyl isocyanide dichloride chloro groups attached to the carbon atom of the methyl group are also utilized in the formation of six-membered ring heterocycles[102]. For example, acrylates (**96**) on reaction with trichloromethyl isocyanide dichloride produce 2,4-dichloropyrimidine-5-carboxylates (**97**)[102].



Benzoylisocyanide dichloride on reaction with amidines provides 1,3,5-triazine derivatives[105]. For example, reaction of 2-aminopyridine (**98**) with benzoylisocyanide dichloride gives the triazine derivative **99**[103].



Reaction of the bis-isocyanide dichloride **100** with elementary sulphur at 240–280 °C gives 2,5-dichlorothiazolo[4,5-*d*]thiazole (**101**)[104].



Pyrolysis of the isocyanide dichloride **102** gives a 70–75% yield of the heterocycle **103**[105].

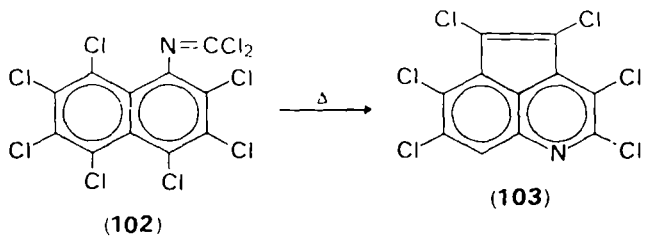


TABLE 2. Formation of four- and five-membered ring heterocycles from isocyanide dichlorides

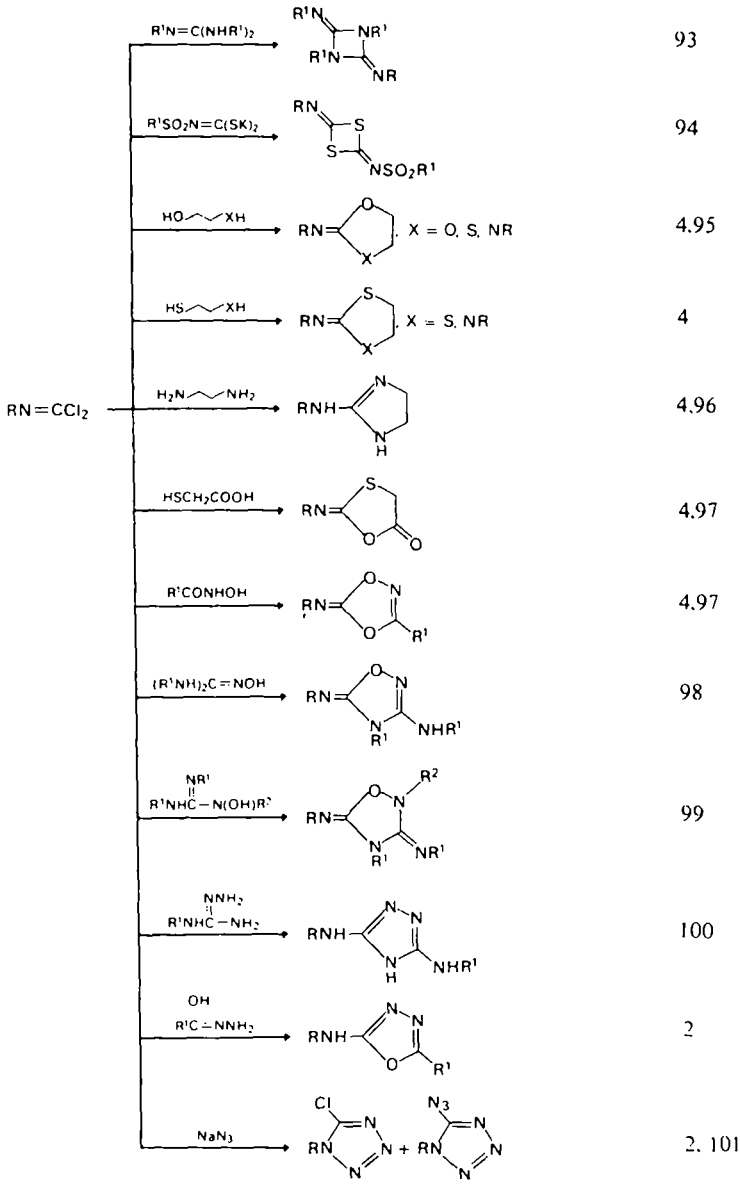
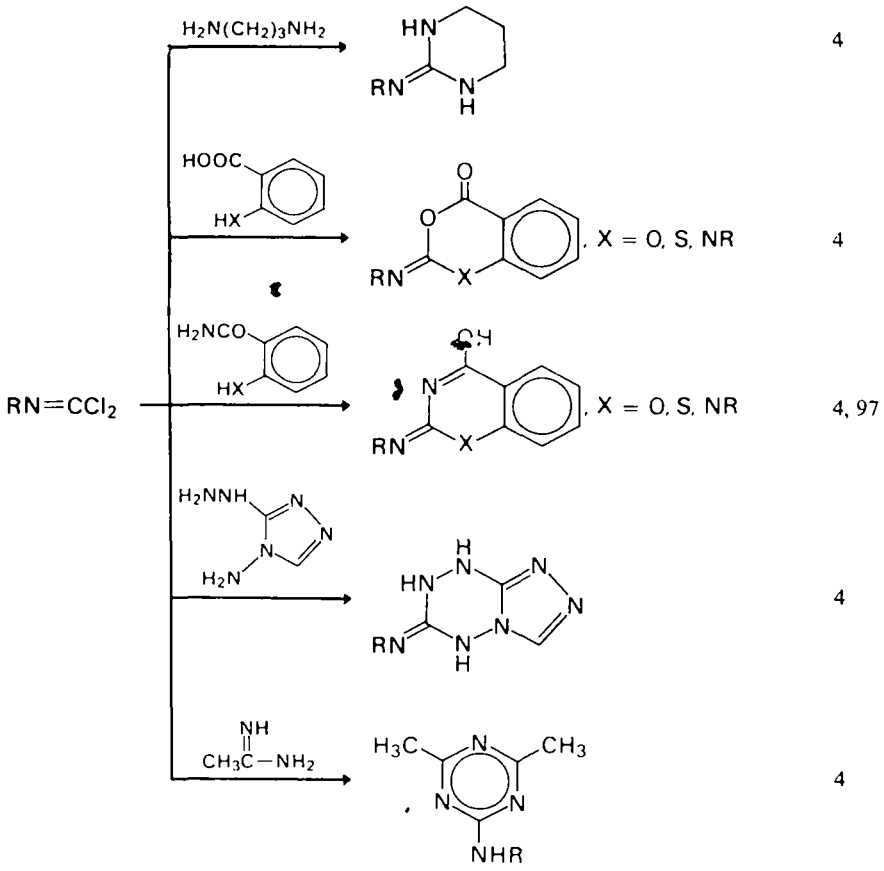
	References
	93, 94, 4.95, 4, 4.96, 4.97, 4.97, 98, 99, 100, 2, 2, 101

TABLE 3. Formation of six-membered ring heterocycles from isocyanide dichlorides



References
4
4
4, 97
4
4

3. Nucleophilic reactions of isocyanide difluorides

The nucleophilic reactions of isocyanide difluorides are similar to those of isocyanide dichlorides. However competition of fluoro groups attached to the carbon of the methyl group is sometimes encountered. For example, reaction of trifluoromethyl isocyanide difluoride with methanol gives **104**[106].

$$CF_3N{=}CF_2 + CH_3OH \longrightarrow CH_3OCF_2N{=}C(F)OCH_3$$

(104)

B. Electrophilic Reactions

1. Friedel–Crafts reaction

The Friedel–Crafts reaction of isocyanide dichlorides with benzene in the presence of aluminium chloride produces imidoyl chlorides, which are hydrolysed to give benzamides **105**[2,4].

$$RN{=}CCl_2 + C_6H_6 \xrightarrow{AlCl_3} RNHCOC_6H_5$$

(105)

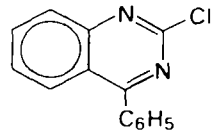
From pentachlorophenyl isocyanide dichloride and benzene in the presence of aluminium chloride the imine **106** is obtained[2,4].

$$C_6Cl_5N{=}CCl_2 + C_6H_6 \xrightarrow{AlCl_3} C_6Cl_5N{=}C(C_6H_5)_2$$

(106)

Reaction of phenylisocyanide dichloride with benzonitrile in the presence of aluminium chloride produces the heterocycle **107**[2,4].

$$C_6H_5N{=}CCl_2 + C_6H_5CN \xrightarrow{AlCl_3}$$

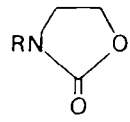


(107)

2. Other electrophilic reactions

The reaction of isocyanide dichloride with ethylene oxide in the presence of zinc chloride gives 2-oxazolidinone derivatives (**108**)[2,4].

$$RN{=}CCl_2 + \text{(epoxide)} \longrightarrow$$



(108)

C. Addition to the C=N Bond

1. Addition of hydrogen halides and carbonyl fluoride

The reaction of isocyanide dichlorides with hydrogen fluoride results in replacement of the chloro groups by fluorine and addition of hydrogen fluoride to the C=N bond (see Table 1). Addition of hydrogen chloride to trifluoromethyl isocyanide difluoride gives rise to the formation of pentafluorochlorodimethylamine[2].

Addition of carbonyl fluoride to trifluoromethyl isocyanide difluoride gives the carbamoyl fluoride (**109**)[2].

$$CF_3N{=}CF_2 + COF_2 \longrightarrow (CF_3)_2NCOF$$

(**109**)

2. Addition of carbenes

Isocyanide dichlorides readily undergo addition of dichlorocarbene to the C=N bond to give tetrachloroaziridines **110**[107].

$$RN{=}CCl_2 + C_6H_5HgCCl_2Br \longrightarrow \underset{\displaystyle Cl\ Cl}{\overset{\displaystyle Cl}{RN\!<\!\!\diagup\!\!\diagdown\!\!>\!Cl}} + PhHgBr$$

(**110**)

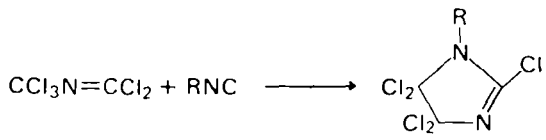
In a similar manner chlorofluorocarbene has been added to phenyl isocyanide dichlorides to give a 74% yield of 1-phenyl-2,2,3-trichloro-3-fluoroaziridine[108].

Treatment of trifluoromethyl isocyanide difluoride with diazomethane produces 1-trifluoromethyl-2,2-difluoroaziridine[4].

$$CF_3N{=}CF_2 + CH_2N_2 \xrightarrow{-N_2} \underset{\displaystyle CH_2}{CF_3N{-}CF_2}$$

3. Other addition reactions

Reaction of isonitriles with trichloromethyl isocyanide dichloride produces chloroimidazolines **111**[109].



(111)

The dimerization of trifluoromethyl isocyanide difluoride also occurs by addition across the C=N bond[2].

D. Miscellaneous Reactions

1. Reaction with phosphorus compounds

The α-elimination of chloro groups from isocyanide dichlorides to give isocyanides is best conducted with triphenylphosphine[4].

$$RN{=}CCl_2 + Ph_3P \longrightarrow RNC + Ph_3PCl_2$$

In contrast, trialkylphosphites undergo the Michaelis–Arbuzov reaction with isocyanide dichlorides to give phosphonates (**112**)[2,4,110].

$$RN{=}CCl_2 + 2\,(R'O)_3P \longrightarrow RN{=}C[\underset{\displaystyle O}{\overset{\displaystyle \downarrow}{P}}(OR')_2]_2 + 2\,R'Cl$$

(112)

Addition of three equivalents of methylenetriphenylphosphorane (**113**) to one equivalent of isocyanide dichlorides produces keteneiminylidene-triphenylphosphoranes **114**[111].

$$RN{=}CCl_2 + Ph_3P{=}CH_2 \longrightarrow RN{=}C{=}C{=}PPh_3$$

(113) (114)

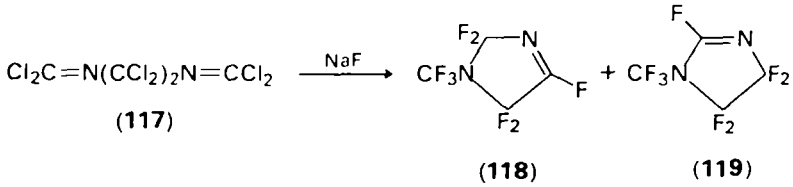
2. Reaction with alkali fluorides

Displacement of the chloro groups by sodium fluoride has already been discussed in the preparation of isocyanide difluorides (see Section II.A.8). However these reactions can also be used to prepare highly fluorinated

amines. For example, reaction of isocyanide dichlorides **115** with sodium fluoride in sulfolane at 120–150 °C gives the imines **116**[112].

$$\underset{\textbf{(115)}}{RR'CClN{=}CCl_2} \xrightarrow{NaF} \underset{\textbf{(116)}}{RR'C{=}NCF_3}$$

Reaction of the bis(isocyanide dichloride) **117** with sodium fluoride in sulfolane gives a mixture of 1-trifluoromethylpentafluorodihydroimidazoles **118** and **119**[113].

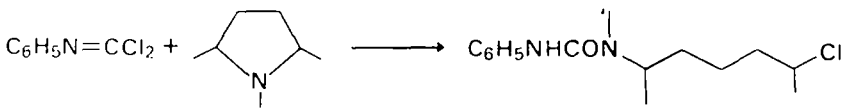


(117) **(118)** **(119)**

If trifluoromethyl isocyanide difluoride is treated with sodium fluoride and carboxylic acids in acetonitrile the corresponding *N*-(trifluoromethyl)-carboxamides are obtained[114].

3. Other reactions

Isocyanide dichlorides react with tertiary amines similarly to phosgene to give hygroscopic salts which undergo dealkylation to produce chloroformamidines[115]. In the case of cyclic tertiary amines ring-opening occurs under mild conditions to give urea derivatives derived from secondary amines. This reaction is similar to the von Braun degradation of tertiary amines. For example, reaction of phenyl isocyanide dichloride with 1,2,5-trimethylpyrrolidine gives the urea **120**[115].



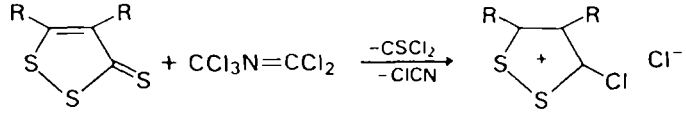
(120)

Nitrilium salts **121** are obtained from isocyanide dichlorides with antimony pentachloride[116].

$$RN{=}CCl_2 \xrightarrow{SbCl_5} [RN{=}\overset{+}{C}{-}Cl]SbCl_6^-$$

(121)

Trichloromethyl isocyanide dichloride reacts with the 1,2-dithia-3-thione **122** to give 3-chloro-1,2-dithiolium chlorides (**123**)[117].



(122) **(123)**

Isocyanide dichlorides have also been used to prepare antidiabetic arenesulphonylureas, either by reaction of *p*-toluenesulphonylisocyanide dichloride with *n*-butylamine, or by reaction of *n*-butyl isocyanide dichloride with *p*-toluenesulphonamide[118].

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The Chemistry of Cyanates and their Thio Derivatives
Edited by Saul Patai

CHAPTER 22

The chemistry of the —NCS group

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I. INTRODUCTION

Up to now, only a limited number of compilatory papers on isothiocyanates have been published. Moreover these papers dealt with more or less specialized problems. A more complex investigation of isothiocyanates gave the materials of the Ist and IInd International Symposium on isothiocyanates organized in Czechoslovakia in 1964 and 1969.

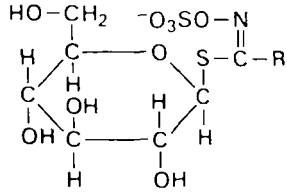
It goes without saying that our knowledge of isothiocyanates has progressed rapidly both in the chemistry of isothiocyanates and in specialized fields such as the knowledge of interesting biological effects of naturally-occurring and synthetic isothiocyanates.

The aim of this chapter is to give information on the present state of knowledge of methods of preparation, chemical structure, reactions and reactivities of isothiocyanates and, at least in part, also about the chemical–biological interactions of isothiocyanates.

II. NATURALLY OCCURRING ISOTHIOCYANATES AND THEIR PRECURSORS

In the past century many sulphur compounds of plant origin attracted attention by their pungency or irritant properties and by their ability to prevent the spoilage of food and fermentation of fruit juices. Two of these substances were revealed to be allyl isothiocyanate and benzyl isothiocyanate. These discoveries mark the beginning of the chemistry of isothiocyanates. Isothiocyanates are present in an undetectable amount in

healthy intact plants. They are present as progenitors and form together with a molecule of glucose and sulphate heteroglycosides called glucosinolates (**1**).



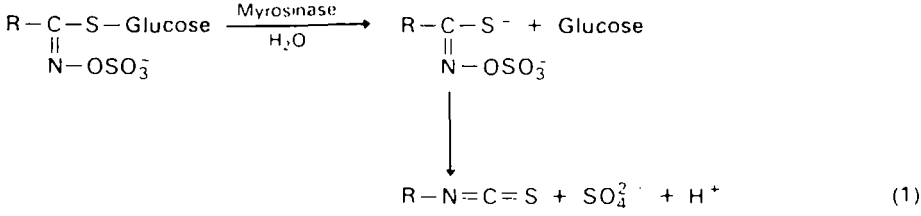
(**1**)

Glucosinolates are produced by plants in families of dicotyledonous angiosperms. They are produced by all species of the large family Cruciferae that have been studied thus far. Glucosinolates represent, besides naturally-occurring unsaturated sulphides, sulphoxides, sulphones, derivatives of thiophene and sulphur-containing alkaloids, one of the most extensive and most widely studied groups of sulphur organic compounds of plant origin. Glucosinolates are present diffusely in the parenchymal tissues of plants, although their content in various parts of the plant is different. The type of the glucosinolate present in the plant is genetically determined. Although its content depends on the vegetation season and conditions of cultivation, it is primarily related to the supply of sulphur. Some plants have only one type of glucosinolate, others contain a larger number.

The present state of knowledge of the biosynthesis, degradation, structure, analytical determination of glucosinolates and relations to systematic botany has been presented in excellent and comprehensive reviews of Kjaer[1-4], and Ettlinger and Kjaer[5]. For the sake of completeness of this chapter we shall briefly review this topic, primarily from the aspect of isothiocyanates.

A. The Origin of Isothiocyanates

Isothiocyanates, along with the by-products glucose and sulphate ion are released from glucosinolates after damage to plants by the action of the enzyme myrosinase (thioglucoside glucohydrolase EC 3.2.3.1, equation 1). This enzyme occurs in all plants which produce glucosinolates.



(1)

After isothiocyanates are formed by the action of myrosinase on glucosinolates in an injured plant, they can be isolated by extraction with organic solvents or by steam distillation. Some glucosinolates produce nitriles[5] or oxazolidinethiones[6]. In other cases the isothiocyanate may subsequently undergo further degradation reactions as, for example, 4-hydroxybenzyl isothiocyanate which is hydrolysed to 4-hydroxybenzyl alcohol and SCN^- ion. In an aqueous medium allyl isothiocyanate is in a concentration equilibrium with allyl thiocyanate, due to an isomerization reaction.

Naturally-occurring isothiocyanates may be identified and quantitatively determined by gas chromatography directly[7,8,9]. Paper or thin layer chromatography may also be used if they are converted to their corresponding thiourea derivatives with ammonia[10]. In addition, treatment of isothiocyanates with thioglycolic acid followed by acidic cyclization produces *N*-substituted rhodanines which are amenable to paper, thin layer and gas chromatography[9,11].

B. Nomenclature and Structure of Glucosinolates

Owing to their ability to produce isothiocyanates, glucosinolates are also called 'mustard oil glucosides'. In the last century individual glucosinolates were given trivial names such as sinigrin, sinalbin and progoitrin. Later the names were formed from the name of the botanic species of the producing plant from which the glucosinolate had first been isolated and the prefix gluco-, e.g. glucobrassicin, a glucosinolate isolated from Brassica plants. According to current chemical nomenclature the name of glucosinolate consists of two parts: the name of the radical (R —) side chain of the structure **1** and the ending -glucosinolate, e.g. benzyl-glucosinolate.

According to the comprehensive review of Ettlinger and Kjaer[5] natural glucosinolates can be divided into the following groups:

(i). Aliphatic glucosinolates containing a C-methyl group, or derived from diacids:
  (a) alkyl, alkenyl, hydroxyalkenyl and acyloxyalkenyl compounds: CH_3—, C_2H_5—, $(CH_3)_2CH$—, $HOCH_2CH(CH_3)$—, $C_6H_5COOC_2H_5CH(CH_3)$—, $(CH_3)_2C(OH)CH_2$—, $HOCH_2CH(C_2H_5)$—, $C_6H_5COOCH_2CH(C_2H_5)$—, $CH_3CH(C_2H_5)CH_2$—, $CH_3C(C_2H_5)(OH)CH_2$—, $CH_3C(CH_2)CH_2CH_2$—
  (b) Ketoalkyl compounds: $C_2H_5CO(CH_2)_4$—, $CH_3(CH_2)_2CO(CH_2)_3$—, $CH_3(CH_2)_2CO(CH_2)_4$—.
  (c) Derivatives of diacids: $CH_3OCO(CH_2)_3$—.

(ii). ω-Methylthioalkylglucosinolates and derivatives:
$CH_3S(CH_2)_3$—, $CH_3SO(CH_2)_3$—, $CH_3SO_2(CH_2)_3$—,
$CH_2{=}CHCH_2$—, $C_6H_5COO(CH_2)_3$—, $CH_3S(CH_2)_4$—,
$CH_3SO(CH_2)_4$—, $CH_3SO_2(CH_2)_4$—,
$CH_3SCH{=}CH(CH_2)_2$—, $CH_3SOCH{=}CH(CH_2)_2$—,
$CH_2{=}CH(CH_2)_2$—, $CH_2{=}CHCH(OH)CH_2$—,
$CH_3S(CH_2)_5$—, $CH_3SO(CH_2)_5$—,
$CH_2{=}CH(CH_2)_3$—, $CH_2{=}CHCH_2CH(OH)CH_2$—,
$CH_3S(CH_2)_6$—, $CH_3SO(CH_2)_6$—, $CH_3SO(CH_2)_7$—,
$CH_3SO(CH_2)_8$—, $CH_3SO(CH_2)_9$—, $CH_3SO(CH_2)_{10}$—.

(iii). Arylmethylglucosinolates:
$C_6H_5CH_2$—, $HOC_6H_5CH_2$— (*para*), $CH_3OC_6H_4CH_2$— (*para*),
$HOC_6H_4CH_2$— (*meta*), $CH_3OC_6H_4CH_2$— (*meta*),
$(CH_3O)_2C_6H_3CH_2$— (*meta*, *para*), 3-indolylmethyl-, *N*-methoxy-3-indolylmethyl-.

(iv). 2-Arylethylglucosinolates and derivatives:
$C_6H_5CH_2CH_2$—, $C_6H_5CH(OH)CH_2$—.

Currently other new glucosinolates[12–15] as well as their absolute configurations are known.

C. Biosynthesis of Glucosinolates

The structural similarity of many aglucons and α-amino acids led to the assumption that glucosinolates are synthesized from amino acids (Table 1). By means of precursors labelled specifically with the nuclides ^{14}C, ^{35}S and ^{15}N this assumption was confirmed[16,17]. Currently this research area is well surveyed by an extensive original literature and comprehensive reviews[18,19,5].

Briefly, the biosynthesis of glucosinolates is as follows: The carbon chain of the decarboxylated amino acid is incorporated into the side chain of the glucosinolate. The carbon of the thiohydroximate group of the glucosinolate originates from the methyl group of acetic acid and/or the acetyl coenzyme A. Here again the carboxyl group is not utilized (equation 2).

$$\overset{3\ 2\ 1}{C_6H_5CH_2CHCOOH}\ (NH_2) + \overset{2'\ 1'}{CH_3COOH} \longrightarrow \overset{3\ 2\ 2'}{C_6H_5CH_2CH_2C}(=N\text{-}OSO_3^-)\text{-}SG1 \qquad (2)$$

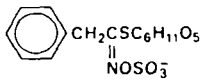
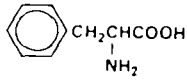
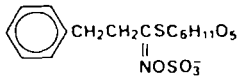
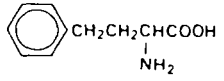
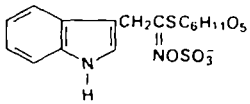
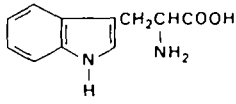
The fate of the sulphur of the sulphate group and that of the thioglucoside sulphur is more obvious on account of the mutual interconversion of the atoms of the inorganic with the organically bound sulphur. A few hours after

the addition of [^{35}S]sulphate to the medium, 80–90% of the total amount incorporated into the glucosinolate appeared in the sulphate group. In the course of several days, however, the relative proportion of the radionuclide in the thioglucoside sulphur amounted to up to one third of the incorporated radioactivity[20,21].

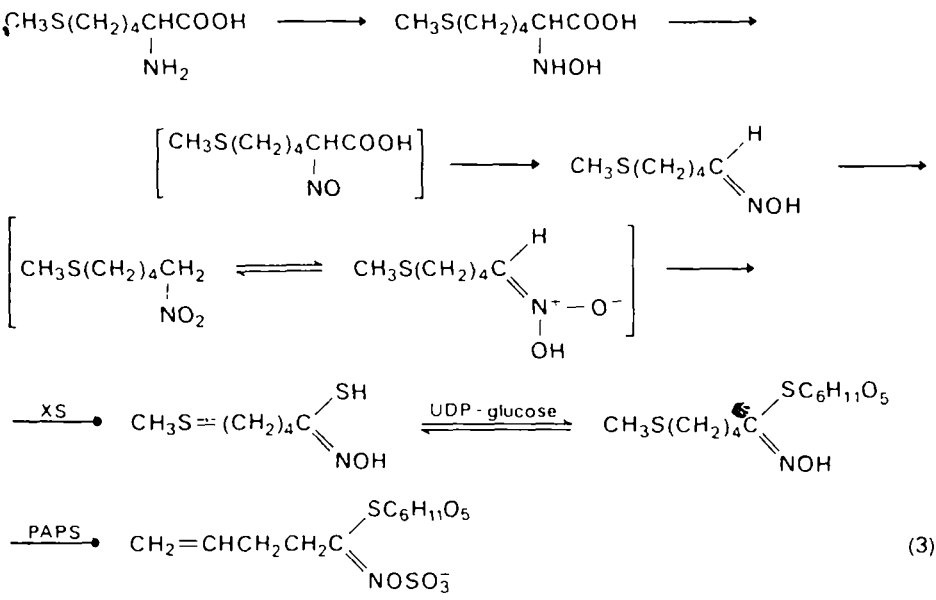
If the sulphur amino acids [^{35}S]methionine and [^{35}S]cysteine[22,23] were used as the sulphur source, then more than 90% of the total amount incorporated appeared in the thioglucoside group.

On the basis of these tracer experiments it was concluded that the major part of known glucosinolates can be derived from a relatively small number of amino acids and their derivatives, as illustrated in Table 1.

TABLE 1. Relation between amino acids and glucosinolates

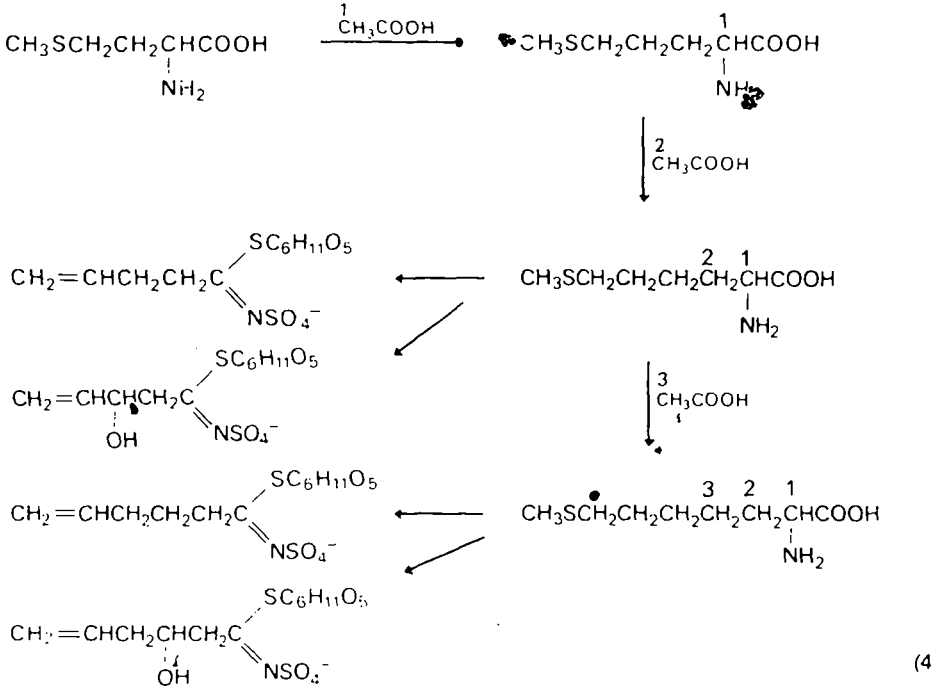
Glucosinolate	Precursor amino acid
$(CH_3)_2CH-C(=NOSO_3^-)-S-C_6H_{11}O_5$	$(CH_3)_2CHCH(NH_2)COOH$
Isopropylglucosinolate	Valine
	
Benzylglucosinolate	Phenylalanine
	
Phenylethylglucosinolate	2-Amino-4-phenylbutyric acid
	
2-Indolylglucosinolate	Tryptophane
$CH_2{=}CHCH_2CSC_6H_{11}O_5$ (NOSO$_3^-$)	$CH_3SCH_2CH_2CH(NH_2)COOH$
Allylglucosinolate	Methionine

A proposed pathway for the biosynthesis of 3-butenyl-glucosinolate in *Brassica napus* is shown in equations (3) and (4). During biosynthesis of



(3)

PAPS = 3-phosphoadenosine-5′-phosphosulphate.



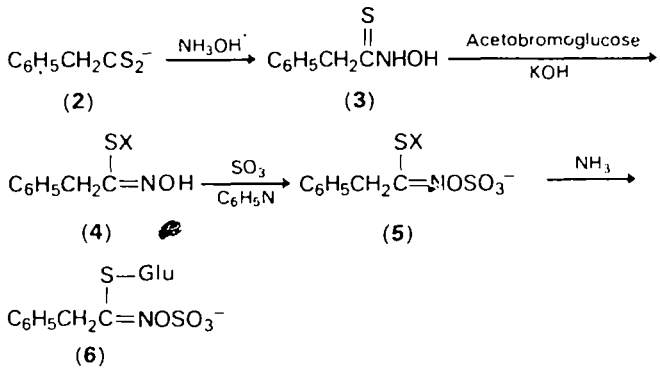
(4)

alkenyl glucosinolates the aliphatic chain is shortened by the elimination of the terminal methylthio group. The chain may be lengthened by using the methyl group of acetate, thus permitting the biosynthesis of the known variety of alkenyl glucosinolates. The proposed pathways for the biosynthesis of the major glucosinolates in *Brassica napus* are shown in equation (4)[24–28].

Inasmuch as glucosinolates formed in plants are derived from amino acids it is apparent that there can be no plant-derived isothiocyanates which have an aromatic group directly bonded to the $^-$NCS moiety. At the same time it indicates that, in contrast to synthetic isothiocyanates, the number of isothiocyanates of natural origin is limited. Currently more than 50 of these substances are known which can be formed from the number of amino acids and their derivatives available to the plants during their metabolism.

D. Synthesis of Glucosinolates

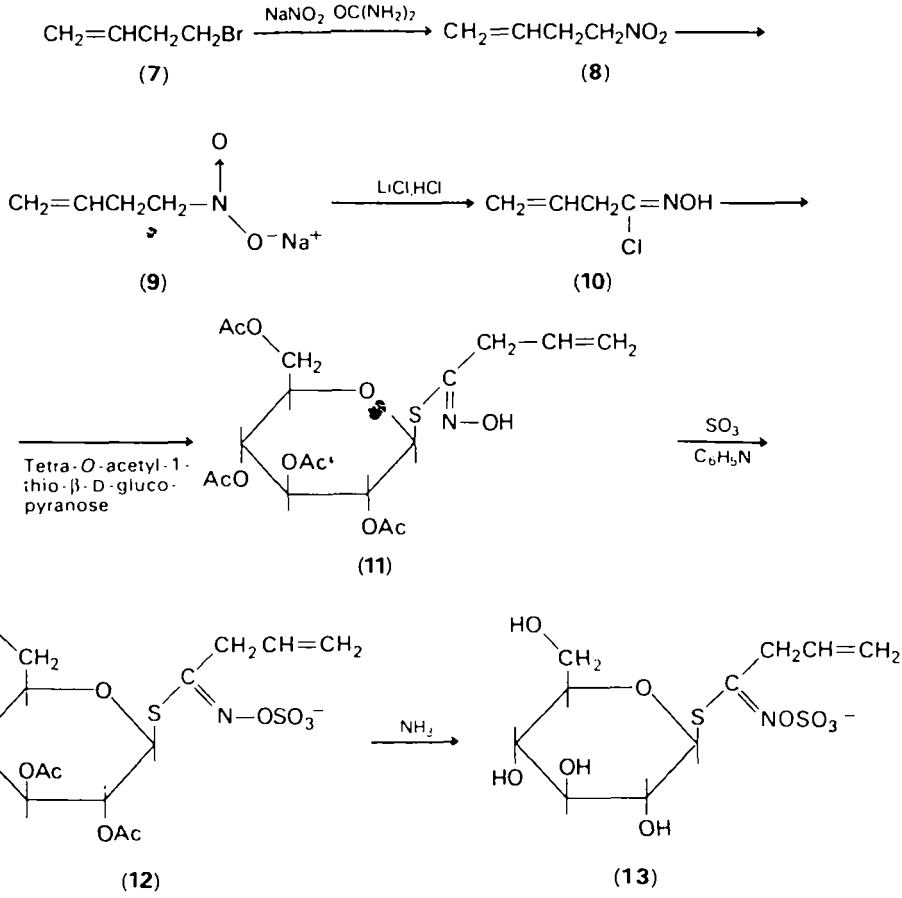
Ettlinger and Lunden[29] in 1957 synthesized the first naturally-occurring glucosinolate. Enzymic hydrolysis of their product yields benzyl isothiocyanate. These authors started with magnesium dithiophenylacetate (**2**) which in reaction with hydroxylamine hydrochloride produced phenylacetothiohydroxamic acid (**3**). After **3** had reacted with KOH and acetobromoglucose, *s*-β-D-1-(tetraacetyl glucopyranosyl) phenylacetothiohydroximic acid (**4**) was obtained. Sulphonation of **4** with pyridine–sulphur trioxide furnished the tetraacetylglucotropeolate ion, **5**. Deacetylation with ammonia yielded glucotropeolate (**6**).



X = Tetraacetyl-β-D-1-glucopyranosyl

In this manner a series of other aryl, aralkyl and alkylglucosinolates have been synthesized[30].

Another method of glucosinolate synthesis was published by Benn and Ettlinger[31] who prepared synthetic allylglucosinolate identical with natural sinigrin. This method achieved formation of the β-thioglucoside linkage by the reaction of tetra-*O*-acetyl-1-thio-β-D-glucopyranose with unsaturated hydroxamoyl chloride. 4-Bromo-1-butene (**7**) on treatment with sodium nitrite and urea furnished 4-nitro-1-butene (**8**). Its Na salt (**9**) on treatment with hydrochloric acid and lithium chloride yielded 3-butenohydroxamoyl chloride (**10**) which was condensed with tetra-*O*-acetyl-1-thio-β-D-glucopyranose. The resulting *S*-(tetra-*O*-acetyl-β-D-glucopyranosyl-3)-butenoisothiohydroximic acid (**11**) was sulphonated in pyridine with pyridine–sulphur trioxide complex, followed by treatment with potassium bicarbonate giving potassium *O*-tetraacetylallylglucosinolate (**12**). Deacetylation of **12** with MeOH–NH_3 yielded allyl-glucosinolate (**13**) which was identical with samples isolated from natural sources.



Using this same method Kjaer and Jensen[32] prepared 3-butenylglucosinolate with 5-bromo-1-pentene its 2-hydroxy derivative[30]. Fundamentally this procedure is applicable for all other alkenylglucosinolates.

E. The Biological Importance of Glucosinolates

Several theories have been advanced to explain the function of glucosinolates in the producing plant. Experiments showing that isothiocyanates have an antimicrobial effect gave rise to the hypothesis that they might be important for the protection of plants against insects and microorganisms. Previous experiments showed, however, that there was no correlation between the glucosinolate content, myrosinase activity and resistance to, for example, clubroot *Plasmodiphora brassicae*[33]. However, any protective effect for the plant would not be preventive but perhaps merely curative, since the isothiocyanate is liberated from the glucosinolate solely in damaged cells.

It has also been proposed that glucosinolates might serve as a reserve of aminonitrogen and sulphur in the cell. The basis for this hypothesis is that in some parts of the plant, such as in seeds, a high content of glucosinolates was found (in *Sinapsis alba* 7·91–10·12% dry matter)[34]; the structure of glucosinolates is derived from *d*-amino acids, the content of glucosinolates increases almost 20-fold in an excess of sulphur supply compared with their content in plants grown under sulphur deficiency. It was proved, however, that they were synthesized in small amounts even when an acute S deficiency inhibited the protein synthesis[35]. The biological importance of glucosinolates has as yet not been unequivocally defined.

III. SYNTHETIC ISOTHIOCYANATES

A. Methods of Preparation

At present many methods are available for the preparation of isothiocyanates but none of them are generally applicable. The choice of method for the preparation of the isothiocyanate will depend on the starting compound which is suitable for the required type of isothiocyanate. Organohalides with a reactive halogen, or primary amines serve most frequently as the starting substances. In the case of organohalides a substitution reaction with inorganic thiocyanates is followed by rearrangements of the resulting thiocyanates into corresponding isothiocyanates. From primary amines, isothiocyanates can be obtained either directly by the action of some sulphur compounds (e.g., thiophosgene,

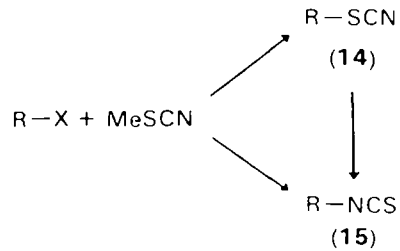
dithiocarbamoyl chloride, trichloromethyl sulphide, etc.) or by converting them into suitable intermediates (dithiocarbamates, dithiocarbazates, thioureas, etc.) which are then decomposed to isothiocyanates by reaction with various agents.

In this section we shall try to present all the possible ways of preparation of isothiocyanates. We shall deal at greater length with methods that can be used in normal chemical laboratories and which are more generally applicable. The methods of synthesis will be classified according to starting compounds and reagents. Isothiocyanates with the NCS group bound to double C=C bonds or to the nitrogen atom form a separate group. For the sake of completeness we shall also refer to those methods of preparation which have more theoretical than practical significance, or rather, that can be applied only in specific cases.

Up to now several excellent reviews have been published referring to the chemistry of isothiocyanates including their synthesis[36–39]. The latter two include results in the field of synthesis, properties and reactions of acyl, sulphonyl and phosphoryl isothiocyanates published up to 1970.

1. Reaction of thiocyanic acid or its salts with various reagents

a. *With organohalides.* The oldest methods for preparing alkyl and acyl isothiocyanates include the thiocyanate method[40,41]. The halides are treated with the salts of thiocyanic acid and, depending on the reactivity of the halides and the reaction conditions, either thiocyanates (**14**) or isothiocyanates (**15**) are formed directly (equation 5).



(5)

Alkyl and aralkyl halides yield preferentially thiocyanates which, depending on the structure of the organic residue, rearrange themselves more or less readily into the corresponding isothiocyanates. Acyl isothiocyanates primarily form isothiocyanates direct.

The first comprehensive paper concerned with the isomerization of organic thiocyanates into isothiocyanates was published by Renson in 1960[42]. According to Renson, organohalides can react either by the mechanism S_N2 or S_N1. The S_N2 mechanism gives rise to thiocyanate which

may later isomerize into isothiocyanate. With respect to the S_N1 mechanism, the author assumes the possibility of a direct formation of isothiocyanate without the formation of the thiocyanate intermediate. The mechanism of isomerization of thiocyanates into isothiocyanates is also discussed in other papers[43–49].

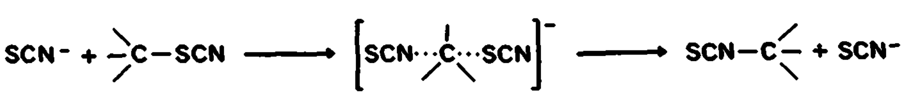
Kinetic studies as well as reactions with labelled compounds have furnished evidence that isomerization of thiocyanates into isothiocyanates may occur by way of several mechanisms[45–50], according to the nature of the organic residue. Primary and secondary alkyl halides react with KSCN forming thiocyanates which partly decompose at a higher temperature, yielding at the same time only a negligible amount of the isomerization product[45,51,52]. In the case of methyl thiocyanate, a rearrangement into methyl isothiocyanate was observed in a sealed tube at 180 °C[53]. On the basis of kinetic studies, Smith and Emerson[45] assume, for the above types of compounds, a bimolecular mechanism of isomerization (equation 6). The suggested mechanism requires a polar medium and a steric access on the carbon atom

(6)

The above S_N2 mechanism assumes bonding of α-carbon of one molecule to nitrogen of the other molecule, followed by substitution with the thiocyanate ion.

In agreement with the mechanism mentioned it was found that butyl thiocyanate isomerizes less readily than methyl thiocyanate (steric effects). The solvent has a marked effect in the case of methyl thiocyanate which does not yield even a trace of methyl isothiocyanate in cyclohexane at 200 °C. The presence of metal salts, such as CdI_2[54,55] or $ZnCl_2$[56,57], and of strong acids[58,59] has a catalytic effect. The catalytic effect of salts on the isomerization of thiocyanates can be explained in both bimolecular and monomolecular ionization mechanisms by the fact that they help to maintain the ionization of thiocyanate by the formation of a complex or by some similar association[45].

Fava and coworkers[48] have proved that primary thiocyanates which show no tendency to ionization can isomerize to isothiocyanates by the catalytic effect of alkaline thiocyanates via the ambident thiocyanate ion (**16**) by a direct nucleophilic substitution of the thiocyanate (equation 7).



(**16**) (7)

The mechanism mentioned was studied in the isomerization of benzyl thiocyanate in the presence of alkaline thiocyanates.

Benzyl thiocyanate is the substrate which is readily subject to bimolecular substitution but does not undergo rapid ionization. Under these conditions the thiocyanate can isomerize mainly through direct nucleophilic substitution via the nitrogen atom of the thiocyanate ion. Besides the exchange reaction between the ionic and 'organic' SCN group (equation 7) isomerization of the organic thiocyanate may take place alongside. In fact, measurement of the rate of isomerization of the benzyl thiocyanate at 110 °C in methyl ethyl ketone, as a function of NaSCN concentration in the presence of a sufficient amount of sodium perchlorate to ensure a constant concentration of the total electrolyte, revealed that under such conditions the mechanism of ionization does not assert itself. Isomerization occurs by bimolecular reaction at which one molecule of the organic thiocyanate reacts with one molecule of the ionic thiocyanate. By comparing the rate of isomerization due to the exchange via the N end of SCN^- (equation 7) with the rate of isotopic exchange, i.e. the rate of the nucleophilic substitution of the thiocyanate realized by the S end of the SCN ion (equation 8), it was possible to determine the ratio of reactivity k_S/k_N of the ambident ion SCN^-.

$$-NC^{35}S + \diagdown\!\!\!\!\diagup C-SCN \rightleftharpoons NC^{35}S-C\diagdown\!\!\!\!\diagup + SCN^- \qquad (8)$$

The kinetic results indicate that the isotopic exchange is much more rapid than isomerization which does not contribute to the rate of exchange in the temperature range of 50–70 °C. The ratio of the rate of exchange to the rate of isomerization, k_{ex}/k_{is}, gives directly the ratio of reactivities (of relative nucleophilicity), k_S/k_N, of the ambident nucleophile SCN^- towards the benzyl carbon in the benzyl thiocyanate. The activation energy of isomerization is about 4 kcal/mol higher than at the exchange reaction. In the experimental temperature range used by the authors (50–115 °C) the ratio was between 10^2–10^3. It is assumed that the given ratio of k_S/k_N will be similar also for other substitutions on the primary carbon. In this case $\approx 0{\cdot}1$ % isothiocyanate may be expected after the nucleophilic substitution of primary thiocyanates. The experiments have shown that in these substitutions which are kinetically controlled thiocyanate is formed almost exclusively. Relative reactivity increases with the electrophilic nature of the reaction centre in favour of the more basic nitrogen atom which forms a stronger bond with the carbon than the more polarized sulphur atom. For these types of rearrangements dipolar aprotic solvents and electron accepting substituents are suitable. For this reason the catalytic effect of

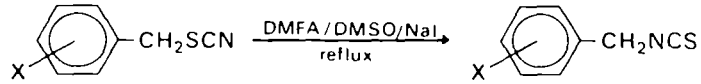
alkaline thiocyanates can be used to advantage in the preparation of isothiocyanates from those substrates which yield thiocyanates unable to isomerize via ionization, or for which other routine methods of preparation are unsuitable. As an example, by heating the *p*-nitrobenzyl thiocyanate with KSCN in acetone one can obtain relatively good yields of the corresponding isothiocyanate.

For thiocyanates that are able to form more stable carbonium ions[45,60,61] the ionizing mechanism S_N1 is assumed at which the rate of rearrangement corresponds to a reaction of the first order (equation 9).

$$R{-}SCN \rightleftharpoons R^{+} + SCN^{-} \longrightarrow R{-}NCS \qquad (9)$$

The rate of isomerization is substantially accelerated by a polar medium, by the catalytic effect of electrophilic agents ($ZnCl_2$, CdI_2) and by the introduction of electron donor substituents into the organic molecule.

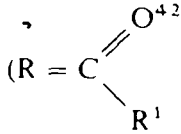
Substituted benzyl isothiocyanates (**18**) can be prepared in good yields by isomerization of the corresponding thiocyanates (**17**) in dimethyl sulphoxide or in dimethylformamide in the presence of NaI[58] (equation 10)



(**17**) (**18**) ~ 80% (10)

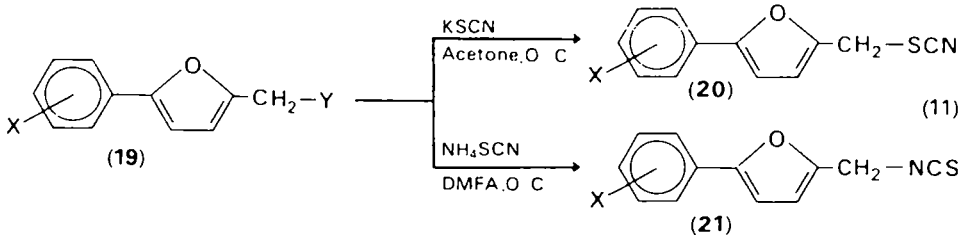
t-Butyl thiocyanate is rearranged quantitatively in the presence of $ZnCl_2$ after stirring for 96 hours and distillation to *t*-butyl isothiocyanate[56]. In contrast to methyl thiocyanate[53], thiocyanates of the type $R{-}CH_2SCN$[61-65] ($R = OR^1$ or SR^1) isomerize relatively easily to the corresponding isothiocyanates. The carbonium ions formed can apparently be effectively stabilized by the mutual interaction of the vacant orbital of the carbonium ion with the orbital of the electron pairs of oxygen or sulphur. At synthesis one proceeds from the corresponding halogen derivative which when heated for several hours with KSCN in petroleum ether or ligroin changes to isothiocyanate.

Similarly, halogen derivatives (RCH_2X) with electron-accepting substituents that are unable to delocalize the positive charge of the transiently formed carbonium ion, yield the corresponding thiocyanates



($R = C$, R^1 = OH[62], OAlk, C_6H_5, C_4H_3S[63], H[66], CH_3[67], NH_2[68], CN[69]).

In many cases it depends on reaction conditions whether thiocyanate or isothiocyanate is formed. Thus for example, 5-(*X*-phenyl)-2-furfuryl bromides (**19**) yield, with alkaline thiocyanates in acetone at a temperature near 0°C, the corresponding thiocyanates (**20**), while by heating in dimethylformamide isothiocyanates (**21**) are formed[70] (equation 11).



(19) (20) (21) (11)

Similarly, diphenylmethyl bromide and KSCN in ether at a low temperature yield thiocyanate, but in benzene at higher temperature diphenylmethyl isothiocyanate[71] is formed. *N*-Isothiocyanatomethyl derivatives of phthalimide and isatin[72], as well as (isochroman-1-yl)isothiocyanate[73], are formed by treatment of the corresponding halogen derivatives with alkaline thiocyanates or silver thiocyanate. Triphenylmethyl chloride reacts with KSCN in acetone, forming the isothiocyanate (90% yield) even at room temperature[74]. Thiocyanates are produced at these reactions probably by the S_N2 mechanism.

The ionic mechanism of isomerization of organic thiocyanates was studied in detail by Fava and coworkers[47]. On the basis of the kinetics of isomerization and exchange reaction of 4,4'-dimethylbenzhydryl isothiocyanate in acetonitrile solution containing $Na^{35}SCN$, they found that the 'organic' SCN group is not in equilibrium with the thiocyanate ion in the solution. As a result, substrates which give benzhydryl or less stable ions cannot isomerize by simple dissociation (equation 9), but an intermediate state, is formed (probably an intimate ion pair **22**), through which isomerization takes place (equation 12).

$$R{-}SCN \underset{k_S}{\overset{k_\cdot}{\rightleftharpoons}} \underset{(22)}{R^+SCN^-} \xrightarrow{k_N} R{-}NCS \qquad (12)$$

The exchange reaction is more sensitive to the salt effect than the isomerization reaction, indicating the higher degree of substrate ionization. In an exchange reaction with ^{35}SCN ion the labelled product is distributed between thiocyanate and isothiocyanate in an approximate ratio of 5:1. This means that the ion intermediate returns from the ion into the covalent state five-times more frequently by way of the S end than the N end of the ^{35}SCN

group ($k_S/k_N = 5$). On the assumption that the intimate ion pair is the precursor of the ion species participating in the exchange, the rate of ionization exceeds the rate of isomerization six-fold. From the ratio of the specific rate of exchange, k_{ex}, and ionization, k_i, it is possible to calculate the fraction of the intimate ion pairs which are subject to dissociation according to the following relation $k_{ex}k_N/k_i(k_S + k_N)$ = fraction of intimate ion pairs.

This fraction amounted to 5·4 % in the case of the benzhydryl thiocyanate. This means that of 100 intimate ion pairs, about five are subject to further ionization and 95 return to the covalent state. Of the latter $\frac{5}{6}$ (about 79) form again thiocyanate and $\frac{1}{6}$ (about 16) isothiocyanate.

The mechanism of isomerization taking place via the intimate ion pair can be illustrated in a simple way as follows (equation 13):

$$\text{R—SCN} \underset{k_S}{\overset{k_i}{\rightleftharpoons}} \text{R}^+\text{SCN}^- \underset{k_{ass}}{\overset{k_{dis}}{\rightleftharpoons}} \text{R}^+ + \text{SCN}^- \qquad (13)$$

$$\text{R}^+\text{SCN}^- \xrightarrow{k_N} \text{R—NCS}$$

It is interesting to compare the ratio between the reactivity of S and N atoms of the ambident ion SCN^- in the mechanisms S_N1 (reaction with carbonium ion) and S_N2 (reaction with the substrate having a partial positive charge on the carbon atom). Whereas in the case of the S_N2 reaction the ratio k_S/k_N for benzyl thiocyanate was 10^3 and for isopropyl thiocyanate 10^2 in the case of benzhydryl thiocyanate (S_N1) it was only 5. From the above it is clear that with increasing electrophilicity of the reaction centre, the reactivity of the more basic nitrogen atom which forms a stronger bond (C—N = 72·8 kcal/mol) than the more nucleophilic atom of sulphur (C—S = 65 kcal/mol) increases.

For further elucidation of the ionic mechanism, stereochemical studies with an optically active (−)-4-chlorobenzhydryl thiocyanate were performed[49]. By thermal isomerization of the laevorotatory thiocyanate (**23**) in various solvents (acetonitrile, acetone, dioxan and benzene) dextrorotatory isothiocyanate (**24**) was obtained (equation 14)

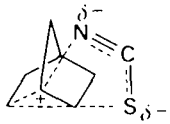
$$\underset{\textbf{(23)}}{(-)\text{-R—SCN}} \longrightarrow \underset{\textbf{(24)}}{(+)\text{-—NCS}} \qquad (14)$$

R = 4-Chlorobenzhydryl

By correlating the configurations of the two isomers the authors found that isomerization took place with complete retention of the configuration.

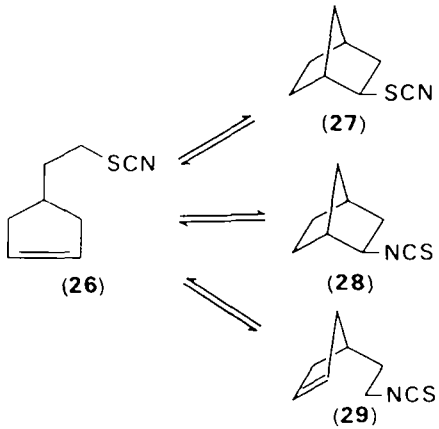
This finding is in agreement with the notion about the mechanism of the intimate ion pairs (12). If the ion pair is the primary intermediate and isomerization occurs via the N atom of the ambident ion it is more likely that a new bond will be formed from the same side of the plane, determined by the carbonium ion, from which the thiocyanate ion has split off.

The mechanism of isomerization of exo-2-norbornyl thiocyanate and 2-(Δ^3-cyclopentenyl)ethyl thiocyanate in various solvents was studied by Spurlock and coworkers[75–77]. The best solvents were DMFA and acetonitrile and the best catalyst boron trifluoride. On the basis of kinetic measurements and the catalytic effect of the salts they proved that isomerization is a reaction of the first order. Experiments with ^{35}S-labelled thiocyanate confirmed the mechanism proposed by Fava and coworkers (equation 13). Isomerization of the optically active (−)-exo-2-norbornyl thiocyanate yielded exclusively racemic isothiocyanate which precludes the simultaneous participation of a concerted mechanism via the transition state[75] **25**.

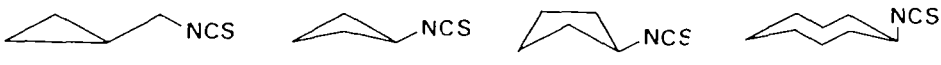


(25)

At the isomerization of 2-(Δ^3-cyclopentenyl)ethyl thiocyanate (**26**) a mixture of *exo*-2-norbornyl thiocyanate (**27**), *exo*-2-norbornyl isothiocyanate (**28**) and 2-(Δ^3-cyclopentenyl)ethyl isothiocyanate (**29**) is formed[76].



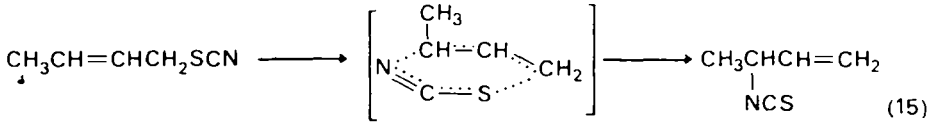
Cyclopropylmethyl (**30**), cyclobutyl (**31**), cyclopentyl (**32**) and cyclooctyl isothiocyanates[77](**33**) were prepared in a similar manner from the corresponding thiocyanates.



(30) (31) (32) (33)

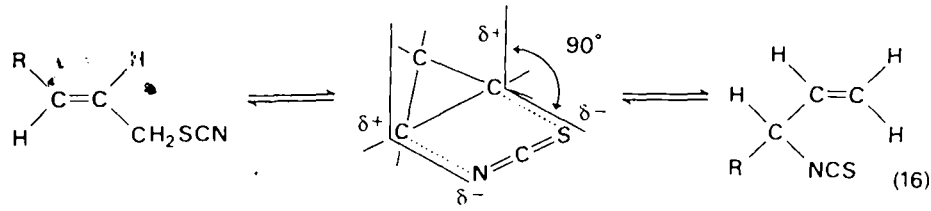
The mechanism via the intimate ion pair was proved also by the isomerization of benzyl and *p*-bromobenzyl thiocyanate catalysed by quaternary ammonium salts (laurylpyridinium bromide and benzylhexamethylenetetraammonium chloride) without a solvent[78]. Isomerization takes place irreversibly according to a reaction of the first order (after completion of the reaction no thiocyanate was detected in the reaction mixture).

Characteristic for allyl thiocyanates is an intramolecular mechanism of isomerization combined with allyl rearrangement[43–45,60,79,80]. Exact evidence of this was provided by Mumm and Richter[44] on crotyl thiocyanate which does not isomerize to crotyl isothiocyanate but to α-methylallyl isothiocyanate (**34**, equation 15).



(34) (15)

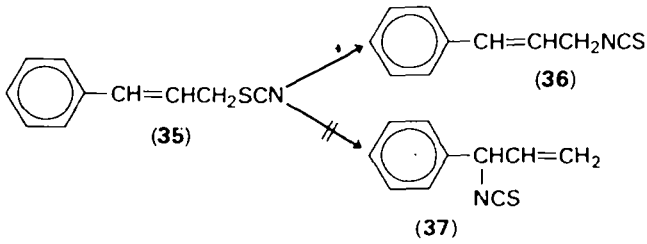
Since this isomerization gives rise to a less stable C-skeleton (the CH_3 group of α-methylallyl isothiocyanate is excluded from hyperconjugation) reaction takes place only up to a certain equilibrium[81] (equation 16).



(16)

In kinetically controlled isomerizations of allyl thiocyanates[45,81] an intramolecular mechanism is indicated also by only a slight effect of solvents and substituents.

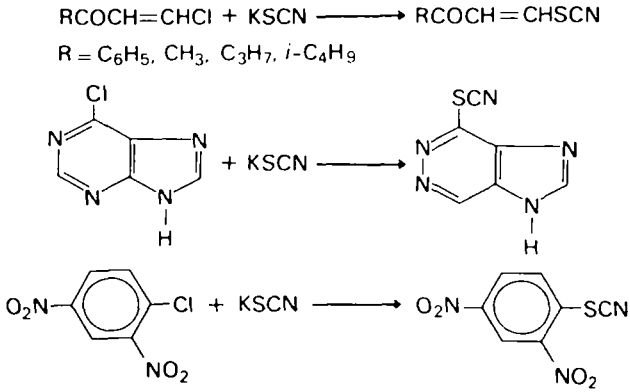
Cinnamyl thiocyanate (**35**) isomerizes without allyl rearrangement and instead of the anticipated α-phenylallyl isothiocyanate (**37**) cinnamyl isothiocyanate(**36**) is formed[82] (equation 17).



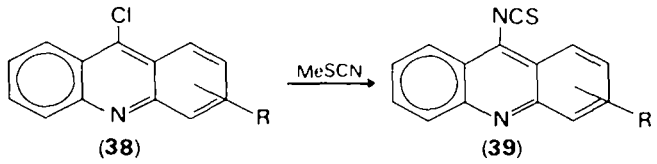
(17)

A study of the kinetics of the above isomerization shows that this takes place at a much slower rate than in the case of allyl thiocyanate. Reaction is of the first order, it exhibits a marked solvent effect and is sensitive to the influence of catalysts of the $ZnCl_2$ type. Hence it can be assumed that the mechanism of isomerization of cinnamyl thiocyanate is of an ionic nature (probably via ion pairs). An intramolecular isomerization would produce an energetically disadvantageous non-conjugated 2-phenylallyl system[45].

Halides of the vinyl and aromatic type (with the halogen bound to the sp^2 carbon) usually react by forming organic thiocyanates which do not rearrange to isothiocyanates[42,83-86].



An exception is 9-chloroacridine (**38**) and some of its derivatives which react with the thiocyanates of heavy metals [AgSCN, $Pb(SCN)_2$] in non-polar solvents and with KSCN in DMFA giving rise to the corresponding isothiocyanates (**39**) in good yields[87,88] (equation 18).



(18)

R = Hal, CH_3, RO, NO_2

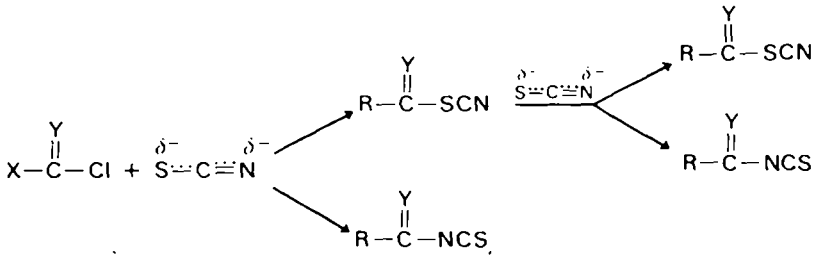
In both cases a bimolecular mechanism of reaction is assumed. Isothiocyanate is formed either directly or by isomerization of the transiently formed thiocyanate. A successful course of reaction requires a highly electrophilic carbon in the reaction centre which in the case of acridines is due to the electron acceptor effect of heteronitrogen.

Carbonyl and phosphoryl isothiocyanates represent a separate group of compounds in which the NCS group is conjugated via the carbon or phosphorus atom with another heteroatom (O, S, N). From the aspect of chemical behaviour and methods of preparation we may assign to this group of compounds also the isothiocyanates of phosphines and sulphonyl isothiocyanates. Isothiocyanates of the above type are characterized by a higher reactivity than alkyl or aryl isothiocyanates which makes them suitable starting material for the preparation of the most varied organic compounds.

Currently there are already many studies dealing with their synthesis and properties. An exhaustive literary review covering this field up to 1969 was presented by Lozinsky and coworkers[39]. Papers by Ulrich[89] and Goerdeler[90] are also concerned with sulphonyl isothiocyanates and acyl isothiocyanates.

The classification as well as some literary data on the preparation and properties of the basic types of these compounds are presented in Tables 2 and 3.

Isothiocyanates summarized in Table 2 are derived from the corresponding halides by substitution reaction with the salts of isothiocyanic acid. The reaction frequently gives rise first to organic thiocyanate which at a later stage isomerizes to isothiocyanate (equation 19).



(19)

X = R, RO, RS, R_2N Y = O, S, NR

Presumably the reaction may take place via the mechanism S_N2 as well as S_N1[39-42]. Thiocyanate was not formed in the case of imidoyl isothiocyanates[118] and formamidinoyl isothiocyanates[122]. On this basis, some authors assume that the corresponding isothiocyanates may be

TABLE 2. Classification of carbonyl, thiocarbonyl and azacarbonyl isothiocyanates

$$X-\overset{\overset{Y}{\|}}{C}-N=C=S \quad (Y = O, S, NR')$$

Isothiocyanates	Structural formula	Reference	Isothiocyanates	Structural formula	Reference
Acyl	$R-\overset{\overset{O}{\|}}{C}-NCS$	91–100	Alkyl(aryl) mercaptothiocarbonyl	$R-S-\overset{\overset{S}{\|}}{C}-NCS$	116
Carbamoyl	$R_2N-\overset{\overset{O}{\|}}{C}-NCS$	101–105	Halogenthiocarbonyl	$Hal-\overset{\overset{S}{\|}}{C}-NCS$	127
Alkyl(aryl) oxycarbonyl	$R-O-\overset{\overset{O}{\|}}{C}-NCS$	106–110	Azaacyl (imidoyl ITC)	$R-\overset{\overset{NR'}{\|}}{C}-NCS$	117–120
Alkyl(aryl) mercaptocarbonyl	$R-S-\overset{\overset{O}{\|}}{C}-NCS$	106	Azacarbamoyl (formamidinoyl ITC)	$R_2N-\overset{\overset{NR'}{\|}}{C}-NCS$	121–123
Halogen carbonyl	$Hal-\overset{\overset{O}{\|}}{C}-NCS$	124–126	Alkyl(aryl) oxyazacarbonyl	$R-O-\overset{\overset{NR'}{\|}}{C}-NCS$	*a*
Thioacyl	$R-\overset{\overset{S}{\|}}{C}-NCS$	111,112			
Thiocarbamoyl	$R_2N-\overset{\overset{S}{\|}}{C}-NCS$	113–115	Alkyl(aryl) mercaptoazacarbonyl	$R-S-\overset{\overset{NR'}{\|}}{C}-NCS$	*a*
Alkyl(aryl) oxythiocarbonyl	$R-O-\overset{\overset{S}{\|}}{C}-NCS$	*a*	Halogenazacarbonyl	$Hal-\overset{\overset{NR'}{\|}}{C}-NCS$	*a*

[a] Not hitherto described in literature; ITC = isothiocyanates

TABLE 3. Classification of phosphoryl isothiocyanates

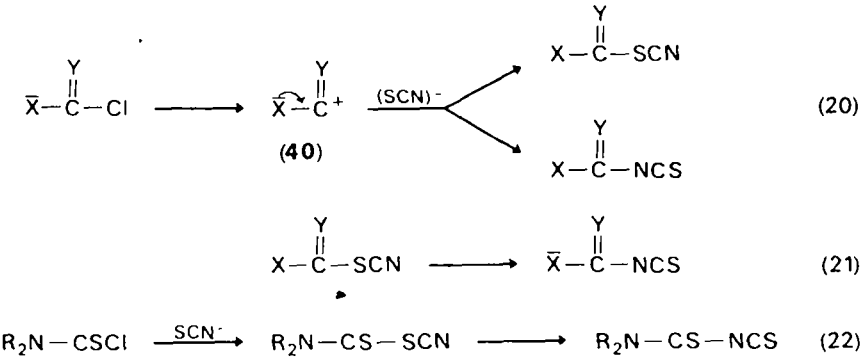
$$X_2P(Y)_n—NCS \quad (Y = O, S; n = 1 \text{ or } 0)$$

Compound	Structural formula	X	Reference
Isothiocyanatophosphates	X_2PNCS	Hal, alkyl, alkoxy, dimethylamino	128–132, 153
Diisothiocyanatophosphates	$XP(NCS)_3$	Hal, alkyl, aryl, alkoxy	129, 133, 135–137
Triisothiocyanatophosphate	$P(NCS)_3$	—	138
Isothiocyanatothiophosphates	X_2PNCS	Hal, alkoxy, dimethylamino, diphenyl	129, 139, 15, 132, 134
Diisothiocyanatothiophosphate	$XP(NCS)_2$	Hal, aryl	139, 135, 140
Triisothiocyanatophosphate	$P(NCS)_3$		135
Isothiocyanatophosphines	X_2PNCS	Hal, aryl	140, 141
Diisothiocyanatophosphines	$XP(NCS)_2$	Alkyl, aryl	140, 142
Triisothiocyanatophosphine	$P(NCS)_3$	—	143

produced from halides by a direct attack of the nitrogen atom of the thiocyanate anion in a thermodynamically controlled reaction[39,42,122].

It appears, however, that those halides whose substituents are able to stabilize the formation of the intermediary carbonium ion (**40**, X = RO, RS, R_2N) react preferentially by the monomolecular mechanism S_N1 (equations 20 and 21).

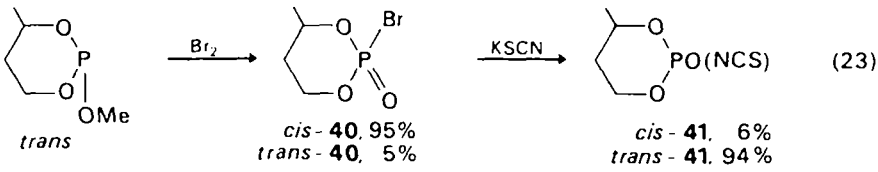
Thus, for example, a study of the reaction between thiocarbamoyl chloride and alkaline thiocyanates provided evidence that both reaction steps are of the first order[90,144] (equation 22).

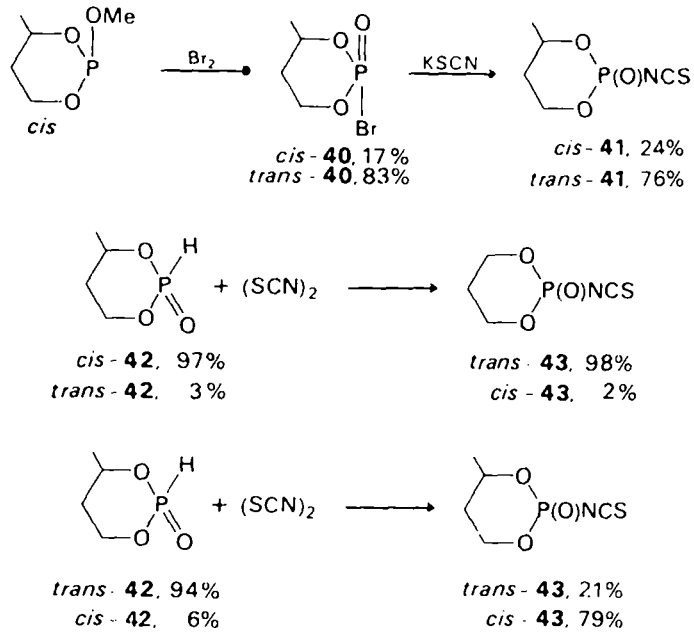


In contrast to acyl isothiocyanates the other types of carbonyl isothiocyanates (Table 2) are fairly unstable. Some derivatives could be isolated only at low temperatures[112] and aryloxycarbonyl isothiocyanates[110] have as yet not been isolated. On standing many of these easily dimerize, polymerize or undergo further transformations[111,116–118,122]. For the preparation of thioacyl and thiocarbamoyl isothiocyanates the ester of acetic acid appears to be the most suitable solvent and NaSCN[114–150] the best reagent. Other types of carbonyl isothiocyanates can be advantageously prepared in acetonitrile or acetone using NaSCN, KSCN or NH_4SCN[102,110,117,122]. In the case of acyl isothiocyanates good yields are also obtained in non-polar solvents with the thiocyanates of heavy metals [$Pb(SCN)_2$[93,96,99,145,146] AgSCN[147]].

The phosphoryl isothiocyanates (Table 3) are usually prepared in polar solvents (acetone[133,148,149], acetonitrile[150–153]), using alkaline thiocyanates. In some cases it is of advantage to work without solvents[131–132] or in liquid sulphur dioxide[135,154].

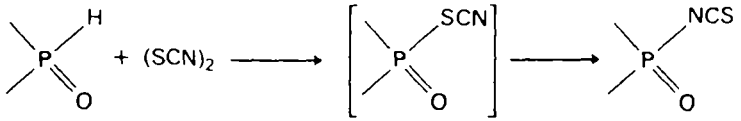
Recently Lopusinski and coworkers[155] prepared *cis*- and *trans*-2-isothiocyano-2-oxo-4-methyl-1,3,2-dioxaphosphorinans (**41**) from the corresponding 2-bromo-2-oxo-4-methyl-1,3,2-dioxaphosphorinans (**40**) by nucleophilic exchange with potassium thiocyanate (equation 23) and by the action of free thiocyanates on the corresponding 2-hydro-2-oxo-4-methyl-1,3,2-dioxaphosphorinans (**42**, equation 24).





(24)

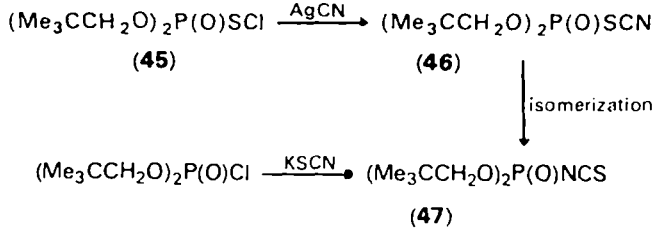
The configuration at phosphorus in the isomeric isothiocyanates has been established by chemical correlations and confirmed by i.r. and n.m.r. data. The authors assumed that in reaction (23) phosphoroisothiocyanates are formed directly without the intermediacy of phosphorothiocyanates. The 'hard' phosphoryl centre is most likely to form a new bond with nitrogen which is the 'harder' nucleophilic site in the ambident thiocyanate ion. The reaction of **40** with potassium thiocyanate proceeds with inversion of configuration at phosphorus. Facile epimerization of the *cis*-2-isothiocyano-2-oxo-4-methyl-1,3,2-dioxaphosphorinan into the more thermodynamically stable *trans* isomer was explained in terms of nucleophilic catalysis by the SCN^- anion. The reaction of the 2-hydro-2-oxo-4-methyl-1,3,2-dioxaphosphorinans (**42**, equation 24) with free thiocyanogen occurs with the formation of a transient phosphorylthiocyano intermediate (**44**, equation 25)[156].



(25)

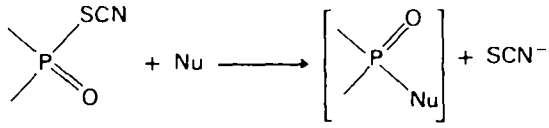
(**44**)

Evidence for the intermediate formation of phosphorothiocyanates leading to the isomeric phosphoroisothiocyanates was given only recently by Lopusinski and coworkers[157]. In the reaction of dineopentoxyoxophosphoranesulphenyl chloride (**45**) with silver cyanide, phosphorothiocyanate (**46**) is formed, which isomerizes very quickly at room temperature to the corresponding isothiocyanate (**47**). The compound (**47**) can be obtained readily in an independent way by direct condensation of the dineopentoxyphosphorochloride with potassium thiocyanate (equation 26).



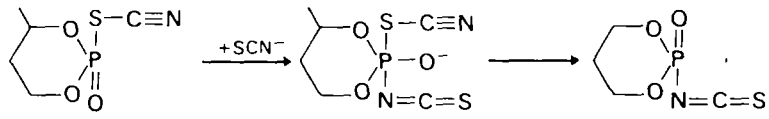
(26)

The results of the stereochemical study of thiocyano–isothiocyano rearrangement of the *cis*- and *trans*-2-thiocyano-2-oxo-4-methyl-1,3,2-dioxaphosphorinans (**48**) allow the authors to suggest an S_N2 (P) type mechanism[156]. They noted, significantly, that the isomerization is strongly dependent upon the concentration of SCN^- anions in the reaction medium. The isomerization is also strongly promoted by the presence of nucleophiles such as H_2O, R_3N, $P(OR)_3$, $P(S)O^-$. All of these compounds may act as a source of SCN^- ions (equation 27).



(27)

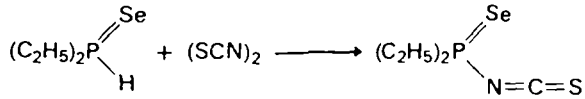
The induction period in epimerization can be ascribed to a delay in forming a minimum concentration of SCN^- anions required for an S_N2 (P) mechanism (equation 28).



(28)

(**48**)

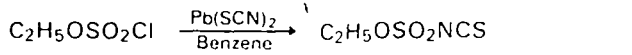
Diethyl selenophosphite (**49**) reacts with thiocyanogen in benzene solution to give *O,O*-diethyl phosphoro(isothiocyano)selenoate (**50**) in 55% yield[158] (equation 29).



(29)

(**49**) (**50**)

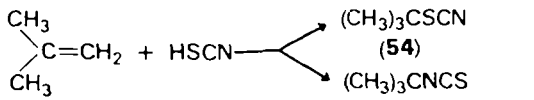
Isothiocyanato phosphines are most frequently prepared in non-polar solvents by reaction of the phosphor halides with thiocyanates of heavy metals[140–143]. The corresponding sulphur analogues are prepared in a similar manner[132,135,139,140]. Ethoxysulphonyl isothiocyanate[159] (**51**) is the only isothiocyanate of sulphonic acid which has thus far been prepared with this method (equation 30).



(30)

(**51**)

b. *With unsaturated compounds.* In some specific cases it is expedient to employ for the preparation of isothiocyanates an addition of thiocyanic acid on unsaturated hydrocarbons *in situ*. This method was first used for the preparation of *t*-butyl isothiocyanate employing the addition of thiocyanic acid on 2-methylpropene[160](**52**). At room temperature a mixture of isothiocyanate (**53**) 62% and thiocyanate (**54**) 32% was formed. The pure isothiocyanate was obtained by isomerization (equation 31).

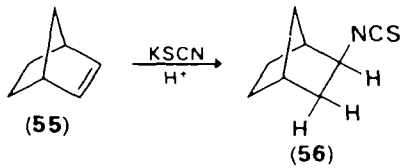


(31)

(**52**) (**54**) (**53**)

Excellent yields were obtained at the preparation of 1,1,3,3-tetramethylbutyl isothiocyanate where the mixture of diisobutylene and NaSCN was treated with diluted sulphuric acid in cold[37].

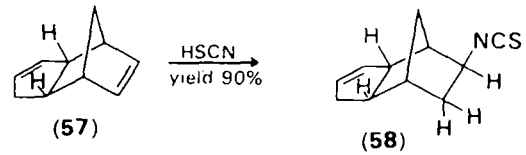
The method was successfully applied also to unsaturated polycyclic systems. Diveley and coworkers also studied the stereochemical course of the synthesis of isothiocyanates of the norbornyl type[161]. They found that the thiocyanic acid reacts *in situ* with norbornene (**55**) giving rise to *exo*-2-norbornyl isothiocyanate (**56**) with a 65% yield (equation 32).



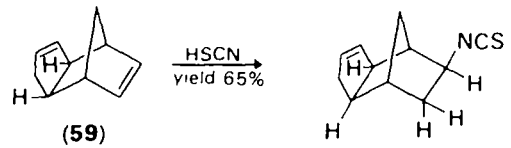
(32)

(**55**) (**56**)

The reaction is carried out by treating the mixture of norbornene and KSCN with diluted H_2SO_4 in benzene at a temperature of 30–40 °C. Evidence of the *exo* position of the isothiocyanate group was provided by its conversion to the known *exo*-2-norbonyl amine as well as by the reaction of norbornene with deuterated thiocyanic acid (DNCS) and by n.m.r. analysis of the product obtained. In contrast to the earlier results[162,163] concerning dicyclopentadienes they found that these react with HNCS by *cis-exo* addition without isomerization of the cyclic system. From *endo*-dicyclopentadiene (**57**) they obtained *exo*-5-isothiocyano-5,6-dihydro-*endo*-dicyclopentadiene (**58**), and from *exo*-dicyclopentadiene (**59**) *exo*-5-isothiocyano-dihydro-*exo*-di-cyclopentadiene (**60**, equations 33 and 34).

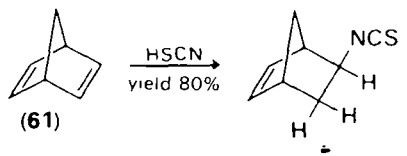


(57) (58) (33)



(59) (60) (34)

Endo- and *exo*-5-chloronorbornenes also react with HSCN without isomerization of the cyclic system (the chlorine atoms in their original *endo*- or *exo*- positions) and so does norbornadiene (**61**, equation 35).

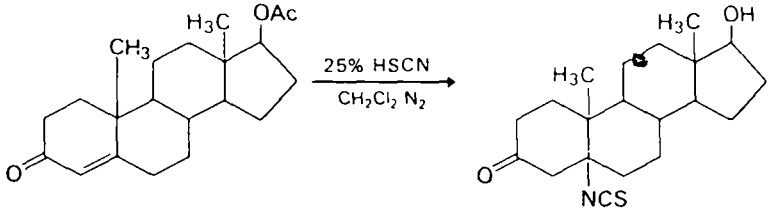


(61) (35)

5,6-Dehydro-*exo*-2-norbornyl isothiocyanate

The addition of thiocyanic acid is of great importance also for the synthesis of biologically interesting steroid isothiocyanates. The literature describes the preparation of the series of isothiocyanate derivatives of androstane by the action of thiocyanic acid on the corresponding steroids.

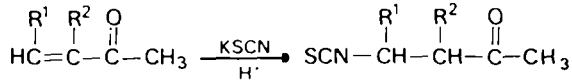
which contain in their skeleton a double bond conjugated with the carbonyl group[164,165] (equation 36).



(36)

Testosteryl acetate — 5-Isothiocyanatoandrostan-17β-ol-3-one

Unkovskij and coworkers studied the reactions of α,β-unsaturated acyclic ketones (**62**) with thiocyanic acid *in situ* and obtained the corresponding β-isothiocyanate ketones (**63**) in 75% yield[166] (equation 37).



(37)

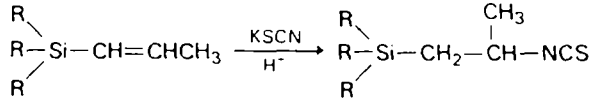
(**62**) (**63**)

R^1 = H, CH_3, C_6H_5

R^2 = H, CH_3

2-Isothiocyanato-2-methylpentan-4-one[167] had already been prepared earlier from mesityl oxide under the same conditions. β-Thiocyanato-ketones which were to be expected due to the existence of two tautomer forms of HSCN were not produced. The authors assume that this may be ascribed to the isomerization on highly polar and thus fairly unstable thiocyanate derivatives which may arise as the primary products of addition.

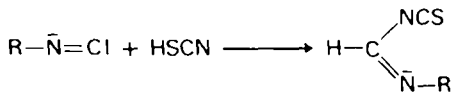
Using a similar method, β-isothiocyanatomethyl-trialkylsilanes were also prepared[168] (**64**, equation 38).



(38)

(**64**)

By the addition of thiocyanic acid to isonitriles α-iminoalkyl isothiocyanates are formed[169] (**65**, equation 39).

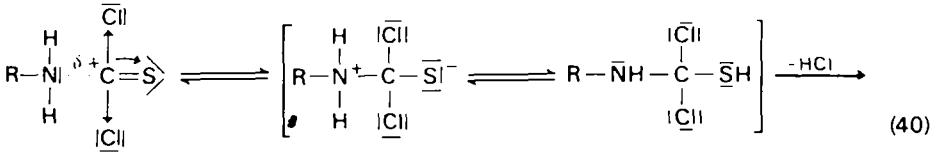


(39)

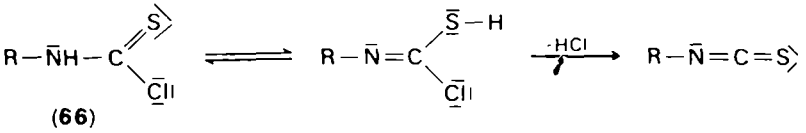
(**65**)

2. Reactions of amines with sulphur compounds

a. *Thiophosgene.* The most generally used method for the preparation of isothiocyanates is based on the direct treatment of the primary amine[170] with thiophosgene. The first product of the reaction is an unstable thiocarbamoyl chloride (**66**) which splits off hydrogen chloride easily yielding isothiocyanate[171]. The course of the reaction can be illustrated by the following addition–elimination mechanism (equation 40).

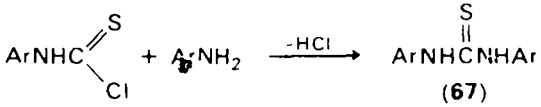


(40)



(66)

In the case of aromatic amines, especially with electron-accepting substituents, *N,N'*-disubstituted thioureas (**67**) may be formed as by-products[172] (equation 41).



(41)

The formation of thioureas can be prevented by the use of a small excess of thiophosgene. Since isothiocyanates as well as thiophosgene are relatively insensitive to water they can also be prepared in an aqueous medium[173]. Not only free amines but also their salts, particularly hydrochlorides, react with thiophosgene to produce isothiocyanates[174].

Reaction with free amines is most frequently performed in such way that a chloroform[175], dichloroethane[176] or toluene[177] solution of amine is added to the water emulsion of thiophosgene. Hydrogen chloride released in the course of the reaction combines with the strongly basic amine hydrochloride which is very difficult to hydrolyse in water and thus complicates the reaction of thiophosgene with the amine. For this reason bases are frequently added to the reaction mixture for the binding of hydrochloride, e.g. calcium carbonate[176], sodium carbonate and sodium bicarbonate[178,179], or triethylamine[180]. It is not advisable to use strong base for this purpose since isothiocyanates are easily hydrolysed in an alkaline medium.

During the preparation of isothiocyanates from the hydrochlorides of primary amines, an aqueous solution of amine hydrochloride is used, preserving similar reaction conditions as employed with free amines[176]. The addition of $CaCO_3$ or alkali carbonates keeps the reaction mixture neutral and assists in the slight hydrolysis of hydrochloride. This modified thiophosgene method is used primarily for the preparation of aliphatic isothiocyanates and for amines that are sensitive to atmospheric carbon dioxide and oxidation (amines of the benzyl type, some diamines, etc.).

The thiophosgene method, thanks to its versatility and mild reaction conditions, is being used in the synthesis of isothiocyanates of very varied structures. In our laboratory alone more than 350 isothiocyanates of the following types have been prepared using this method:

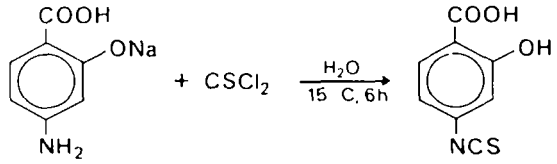
(i) Isothiocyanates with one aromatic ring: substituted phenyl isothiocyanates[181-183], isothiocyanates of phenylalkylsulphides and sulphones[184,185], isothiocyanates of sulphonamides[186], substituted benzyl isothiocyanates[187], aryl and arylmethyl diisothiocyanates[188], substituted β-phenylethyl isothiocyanates[189] and α-substituted 4-tolyl isothiocyanates[190].

(ii) Isothiocyanates with two aromatic rings connected with a bridge, isothiocyanates of diphenylmethane[191], diphenylamine[192], diphenyloxide[193], diphenylsulphide, diphenyl sulphone[194], diphenyl ketone[195], stilbene[196], azobenzene[197,198] and chalcone[199,200].

(iii) Isothiocyanates with multiple ring systems: isothiocyanates of anthracene, chrysene and pyrene[201], biphenyl[202], naphthalene[203,204], phenanthrene[203] and terphenyl[205,206].

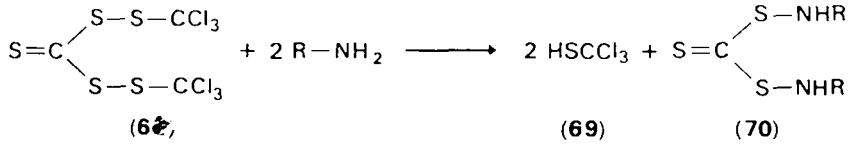
(iv) Isothiocyanates with heterocyclic rings: isothiocyanates of acridine and benzacridine[207,208], isothiocyanates of purine[209,210], benzothiazole[211], benzotriazole[212] and ferrocene[213].

In some cases the thiophosgene method was modified. Thus for example, the preparation of fluorescein isothiocyanate was carried out by treatment of the corresponding amine with the thiophosgene in dry acetone[214]. For the preparation of isothiocyanates derived from amino acid esters the reaction is performed in ether or toluene[215]. Isothiocyanates of the benzyl type are advantageously prepared in a nitrogen atmosphere whereby the free bases are released from the corresponding amino hydrochlorides by the gradual addition of diluted alkali. These react immediately with thiophosgene and the isothiocyanate formed passes into the chloroform layer[187,188,203]. Isothiocyanates from aromatic amines containing the carboxyl group or sulpho group are prepared by treating aqueous solutions of their alkaline salts[216,217] with thiophosgene (equation 42).



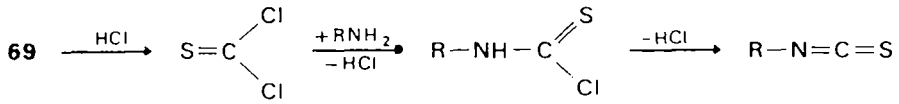
(42)

Another modification of the thiophosgene method utilizes the reaction of the bistrichloromethyl ester of pentathio-dipercarbonic acid (**68**) with primary amines[218]. The reaction can be demonstrated by the equation (43):

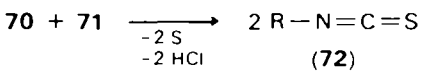


(68) (69) (70)

(43)



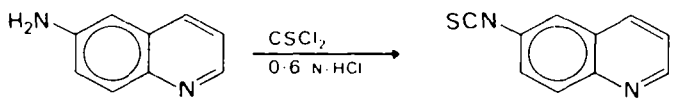
(71) (72)



(72)

Reaction is carried out in a water medium. One mole of the reagent (**68**) suffices for three moles of amine. **68** is a stable, slightly volatile and slightly toxic liquid, and is prepared from trichloromethanesulphenyl chloride and excess of sodium trithiocarbonate[219]. It is suitable for the synthesis of aromatic and aliphatic isothiocyanates.

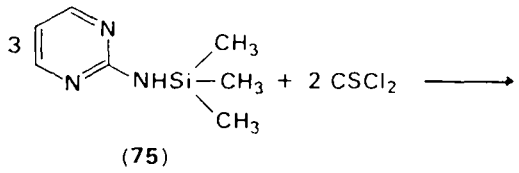
The thiophosgene method meets with difficulties in the case of some heterocyclic amines, e.g. 9-amino-acridine[207], 4,6-diaminoquinoline[220], aminopyridines and 4-aminoantipyrine[221]. If the amino group is on the benzene ring of aminoquinoline (**73**) it reacts readily with thiophosgene, giving rise to the corresponding isothiocyanate[222] (**74**, equation 44).



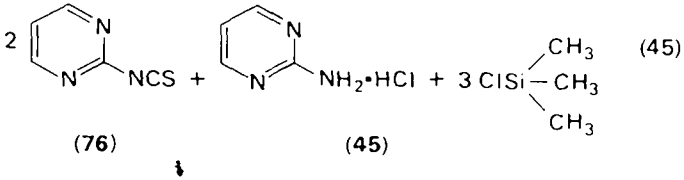
(73) (74)

(44)

It was possible to prepare 2-pyrimidinyl isothiocyanate (**76**) by treating 2-trimethylsilylaminopyrimidine (**75**) with thiophosgene in absolute ether under nitrogen at −60 °C[223] (equation 45).



(75)



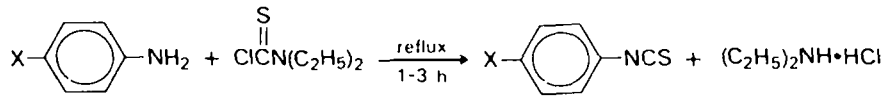
(76) (45) (45)

The following compounds were prepared from other heterocyclic isothiocyanates in a water–ether medium by treating the corresponding amines with thiophosgene in the presence of $NaHCO_3$: 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 isothiocyanates[224].

Amines capable of forming strong intramolecular bonds also do not react with thiophosgene (4-aminoacridine[207], 2-aminoazobenzene[225]). The latter reacts with thiophosgene if a methyl group is introduced in position 3 which prevents the amino group from forming a hydrogen bond[225]. The synthesis of 4-hydroxyisothiocyanate and 9,10-diisothiocyanatoanthracene[188] gave negative results. Aromatic *ortho* diamines and *ortho* aminophenols react with thiophosgene yielding five-member heterocyclic compounds[175]. The reaction of amines with thiophosgene is inhibited by electron-withdrawing substituents[172,216] which decrease the electron density on the amino nitrogen. Steric hindrance by substituents at *ortho* positions is also inhibitory[172].

This is the simplest and most universal method for the preparation of isothiocyanates. It gives high yield and is suitable for the preparation of aliphatic as well as aromatic isothiocyanates. Its importance has increased due to the fact that thiophosgene has become a commercially available reagent. Some authors object to its unpleasant odour and toxicity.

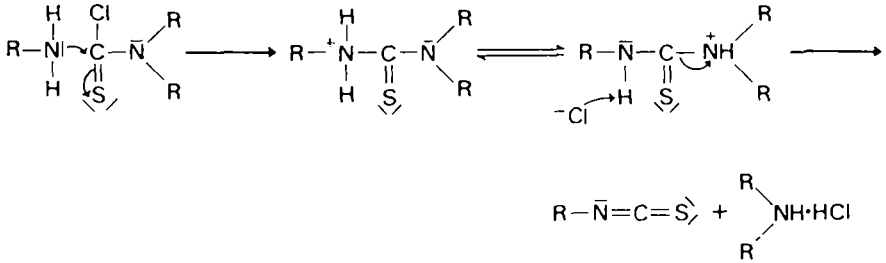
b. *Thiocarbamoyl derivatives.* Sayigh and coworkers[226] have proposed *N,N*-diethylthiocarbamoyl chloride as a new reagent which could replace the toxic thiophosgene. It is universally accessible and is suitable for the preparation of aromatic isothiocyanates with electron-withdrawing substituents. It is a one-step method and consists in the heating of the aromatic amine with *N,N*-diethylthiocarbamoyl chloride (77) in an inert solvent such as chlorobenzene, benzene, toluene or ethylene dichloride (equation 46).



(77) (46)

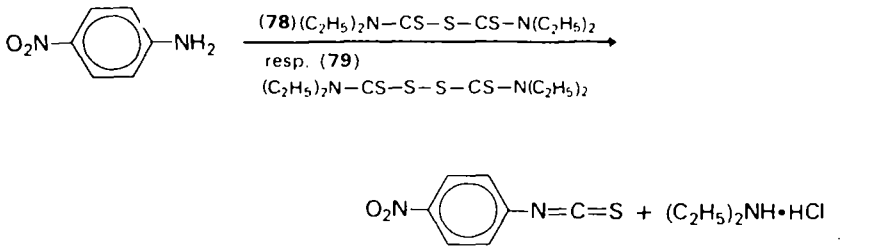
X = NO_2, CN, CH_3CO, C_2H_5OOC, Cl

The yields decrease with the increasing basicity of amines. The limiting pK_a value of the reaction medium is 4·6. Under these conditions phenyl isothiocyanate is formed from aniline in trace amounts only. Reaction probably takes place via the mechanism S_N2 (equation 47).



(47)

Marquard modified the above method by using, instead of diethylthiocarbamoyl chloride, bis-diethylthiocarbamoyl sulphide (**78**) or disulphide[227] (**79**, equation 48).



(48)

The reaction is performed in dry chlorobenzene saturated with hydrogen chloride. Besides isothiocyanate, diethylamino hydrochloride was isolated as a by-product. In the absence of hydrogen chloride, reaction does not take place. The anticipated intermediate (*N*,*N'*-diethyl-*N*(*p*-nitrophenyl)-thiourea) could not be isolated. Higher yields were obtained by using bis-diethylthiocarbamoyl disulphide (tetraethylthiuram disulphide).

3. Decomposition of dithiocarbamic acid and its salts or esters

a. *Decomposition by heavy metal salts.* Synthesis takes place in two steps. In the first step the corresponding salts of dithiocarbamic acid (**80**) are prepared by the action of carbon disulphide and alkali[228,229] or ammonia[230] on the aqueous or organic (alcohol, methylene chloride, toluene, etc.) solution of the primary amine (equation 49). Aliphatic amines react with carbon disulphide in the absence of other bases, yielding alkylammonium dithiocarbamates[231] (**81**, equation 50).

$$R-NH_2 + CS_2 + NaOH \longrightarrow R-NH-\overset{\overset{S}{\|}}{C}-\bar{S}\overset{+}{N}a + H_2O \qquad (49)$$

(**80**)

$$2\,R-NH_2 + CS_2 \longrightarrow R-NH-\overset{\overset{S}{\|}}{C}-\bar{S}\overset{+}{N}H_3-R + H_2O \qquad (50)$$

(**81**)

Obviously amines whose basicity is so low that they do not form dithiocarbamates cannot be used (e.g., nitranilines).

In the second step, heating of alkaline dithiocarbamates with heavy metal salts in an aqueous medium produces unstable heavy metal dithiocarbamates which decompose easily into isothiocyanates and metal sulphides (equation 51).

$$R-NH-CS-\bar{S}\overset{+}{N}H_4 + Pb(NO_3)_2 \longrightarrow R-NCS + PbS + NH_4NO_3 + HNO_3 \qquad (51)$$

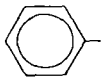
For the decomposition of dithiocarbamates, mercury salts[232,233], lead nitrate[234–236], cupric sulphate[232], ferric chloride[237], etc. were used.

Loose and Weddige[232] prepared isothiocyanates derived from esters of amino acid, i.e. glycine, DL-α-alanine, DL-phenylalanine and DL-valine by decomposing dithiocarbamates with mercury chloride in anhydrous acetone in the presence of triethyl amine. McElhinney[238] used this modification of the dithiocarbamate method for the preparation of aliphatic isothiocyanates with basic substituents (equation 52).

$$R_2N(CH_2)_2NH_2 + CS_2 \longrightarrow R_2\overset{+}{N}H(CH_2)_2NHCSS^- \xrightarrow{HgCl_2} \quad (52)$$

$$[R_2\overset{+}{N}H(CH_2)_2NHCSS^-Hg^+Cl]\,Cl^- \xrightarrow{2\ Et_3N} R_2N(CH_2)_2NCS + HgS + 2\ Et_3N{\cdot}HCl$$

b. *Decomposition by chlorine-containing compounds.* Some aromatic isothiocyanates are advantageously prepared by the decomposition of dithiocarbamates with phosgene[239] (equation 53).



$$\xrightarrow[0\ C]{Toluene} R-NCS + NH_4Cl + COS + HCl \quad (53)$$

The phosgene method failed to succeed in the preparation of some isothiocyanates with electron-withdrawing substituents (4-bromophenyl isothiocyanate, nitrophenyl isothiocyanates, etc.). It furnished in very good yields 4-hydroxyphenyl isothiocyanate which we did not manage to prepare by the thiophosgene method.

The decomposition of dithiocarbamates with ethyl[240-243] or methyl[244] chloroformate produces aliphatic isothiocyanates in very good yields. Reaction takes place via the unstable carbethoxydithiocarbamate (**82**) which decomposes into isothiocyanate, carbonylsulphide and ethanol. Bases, like, alkali and triethylamine, have a catalytic effect on the decomposition of carbethoxydithiocarbamate[245-247] (equation 54).

$$RNHCSS^-\overset{+}{N}H_4 + ClCOOC_2H_5 \xrightarrow{-NH_4Cl} RNHC(=S)SCOOC_2H_5 \longrightarrow$$

(**82**)

(54)

$$\xrightarrow[H^-]{Et_3N} \left[RN=C(S^-)SCOOC_2H_5 \longleftrightarrow R\bar{N}-C(=S)SCOOC_2H_5\right] \longrightarrow$$

$$RNCS + C_2H_5OCOS^-[COS + C_2H_5OH]$$

Aliphatic and aromatic isothiocyanates can be also prepared by the oxidative decomposition of dithiocarbamates by sodium hypochlorite in an alkaline medium[248,249] (equation 55).

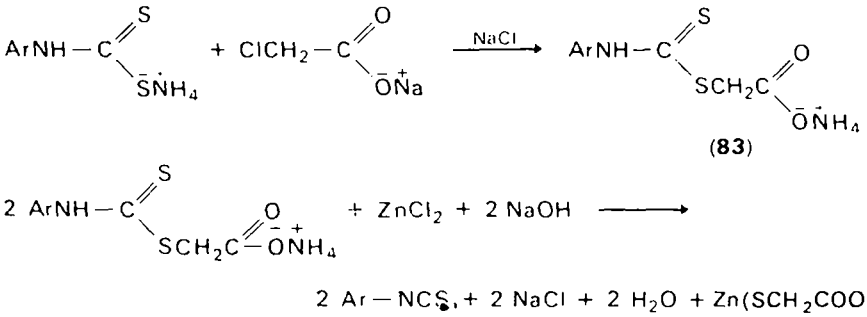
$$RNHCSS^-\overset{+}{N}H_4 + 4\ NaOCl + NaOH \longrightarrow$$

$$R-NCS + Na_2SO_4 + 3\ NaCl + NH_4Cl + H_2O \quad (55)$$

Using this method some aliphatic isothiocyanates such as 2-dimethylaminoethyl isothiocyanate, 3-diethylaminopropyl isothiocyanate and 3-dimethylaminopropyl isothiocyanate were prepared in 80% yield. Some

aromatic isothiocyanates with electron-donor substituents were prepared even in 90% yields[250], e.g. alkoxyphenyl and dimethylaminophenyl isothiocyanates.

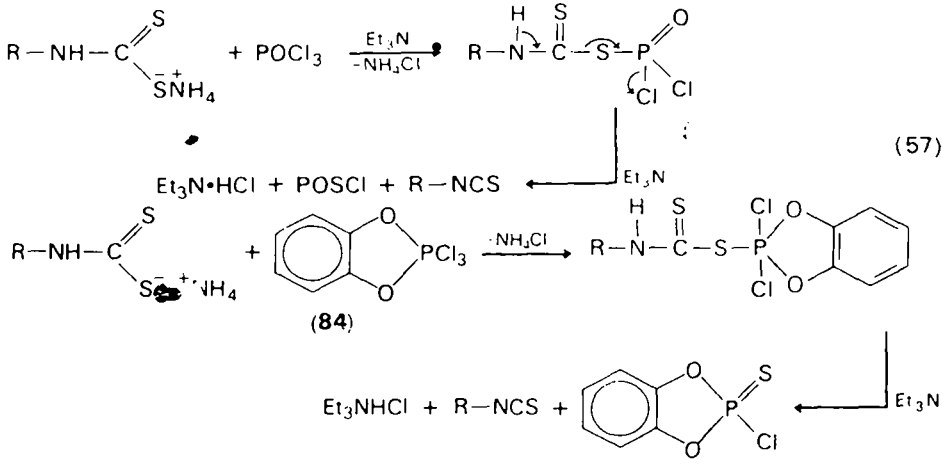
Van den Kerk and coworkers[251] used for the preparation of aromatic isothiocyanates the decomposition of dithiocarbamate with the salts of α-halogen fatty acids. Reaction took place in two steps. In the first step ammonium (*S*-carboxyalkyi)phenyldithiocarbamate (**83**) was formed which decomposed to isothiocyanate in a weakly basic medium in the presence of $ZnCl_2$ (equation 56)



(56)

For example the following aromatic isothiocyanates were prepared using this method: alkoxyphenyl isothiocyanates, halogenphenyl isothiocyanates and *p*-phenylenediisothiocyanate (60–70% yields).

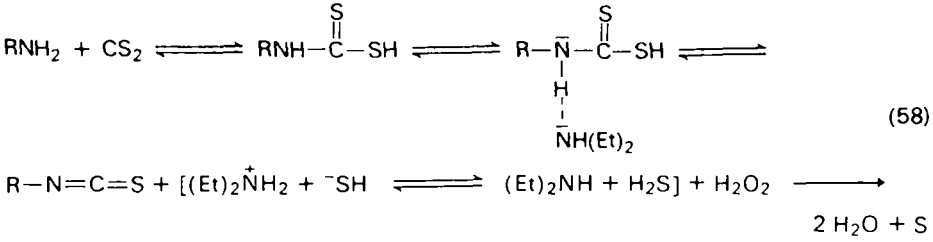
Dithiocarbamates can be also decomposed by means of phosphorus oxychloride or phosphorus *o*-phenylenedioxitrichloride[252,253] (**84**). Dithiocarbamate is suspended in ether or benzene and the decomposition is carried out with cooling in the presence of triethylamine (equation 57).



(57)

84 was prepared by the treatment of pyrocatechol with PCl_5 in benzene[254].

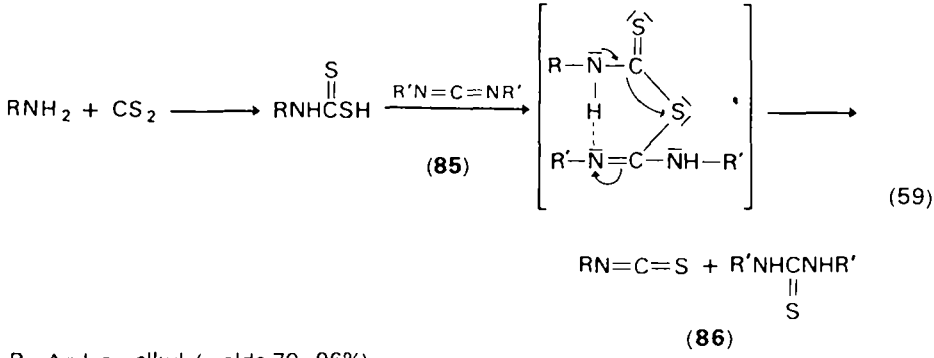
c. *Decomposition by hydrogen peroxide.* Treatment of a mixture of primary amine and carbon disulphide with hydrogen peroxide in the presence of secondary aliphatic amine produces a rapid exothermic reaction which gives isothiocyanates[255] (equation 58).



(58)

This one-step reaction is suitable only for the preparation of aliphatic isothiocyanates. Thioureas are produced as by-products.

d. *Decompositions involving carbodiimides.* Primary amines react with carbon disulphide and dicyclohexyl carbodiimides (**85**) in a suitable organic solvent at temperatures below 0 °C, forming isothiocyanate and 1,3-dicyclohexylthioureas (**86**). For the preparation of aliphatic isothiocyanates ether or tetrahydrofuran[256] proved to be a good solvent. Aromatic amines react under identical conditions only with a one-half molar equivalent of carbodiimide yielding, quantitatively, symmetrical diaryl dithioureas. If, however, the reaction is carried out in pyridine, and in some cases in the presence of the molar equivalent of triethylamine, then isothiocyanates are also formed from aromatic primary amines in very good yields[257] (equation 59).



(59)

R = Aryl or alkyl (yields 70–96%)

R′ = Cyclohexyl

The carbodiimide method can be used for the preparation of aromatic as well as aliphatic isothiocyanates under very mild conditions. By this method were prepared, for example, 9-fluorenyl, benzhydryl, phenyl, isobutyl, 3-pyridyl, 1-naphthyl, 2-naphthyl and other isothiocyanates. 4-Nitroaniline and *o*-phenylendiamine produces under these conditions 1,2,3,-tris(4-nitrophenyl) guanidine and benzimidazolinthione, respectively[257].

e. *Decompositions involving organosilicon compounds.* *N*-Silylated primary aliphatic amines (**87**) react with carbon disulphide giving rise to silylesters of dithiocarbamic acid (**88**) which are unstable above 0 °C and decompose into isothiocyanates[258]. The decomposition is carried out with trimethylsilyl chloride in the presence of triethylamine (equations 60 and 61).

$$\underset{\textbf{(87)}}{RNHSi(CH_3)_3} + CS_2 \xrightarrow{0\,^{\circ}C} \underset{\textbf{(88)}}{RNHC(=S)SSi(CH_3)_3} \qquad (60)$$

$$\textbf{88} + (CH_3)_3SiCl + Et_3N \xrightarrow[Et_3N\cdot HCl]{Reflux} \left[RNC(=S)SSi(CH_3)_3 \;\; Si(CH_3)_3 \right] \longrightarrow$$

$$R{-}NCS + [(CH_3)_3Si]_2S \qquad (61)$$

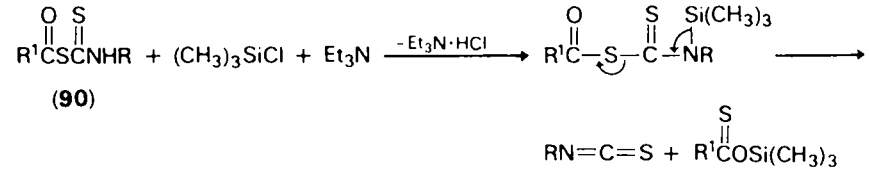
In parallel with isothiocyanates, the corresponding thioureas may also arise. Higher basicity of amine, an excess of carbon disulphide and low temperature are favourable for the formation of isothiocyanate. The reaction is suitable for the preparation of isothiocyanates from amino alcohols and amino acids whereby the hydrogens of the hydroxyl groups are protected by the easily removable silyl group.

O-Alkyl(aryl)esters of thiocarbamic acid (**89**) are similarly decomposed by the action of trimethylsilyl chloride[259] (equation 62).

$$\underset{\textbf{(89)}}{RNHC(=S)OR'} + Si(CH_3)_3Cl + Et_3N \xrightarrow{-Et_3N\cdot HCl} R{-}\overset{|}{N}(Si(CH_3)_3){-}C(=S)OR' \longrightarrow$$

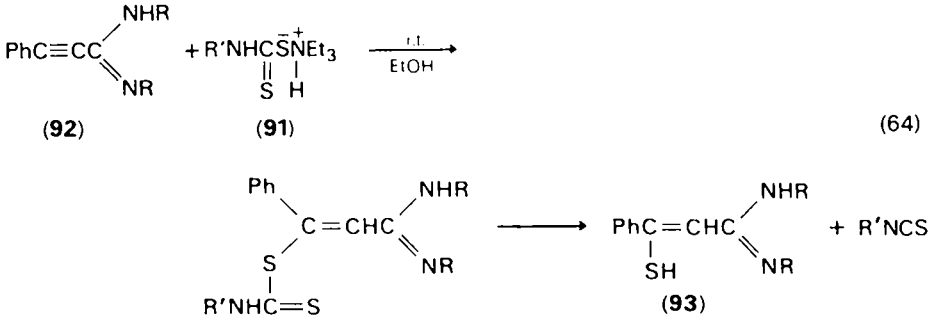
$$RNCS + (CH_3)_3SiOR' \qquad (62)$$

Trimethylsilyl chloride is also used in the presence of triethylamine for the decomposition of *N*-methylaroyldithiocarbamates (**90**) occurring during the reaction of acyl chlorides with dithiocarbamates[259] (equation 63).



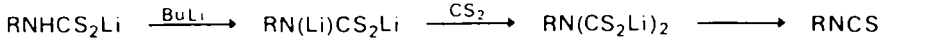
(63)

f. *Other methods of decomposition.* Recently two new modifications of the dithiocarbamate method were published. Fujita and coworkers[260] obtained isothiocyanates in good yields under mild conditions by decomposing triethylammonium *N*-substituted dithiocarbamates (**91**) with *N,N'*-disubstituted propiolamidines (**92**). β-Mercaptocinnamamidines (**93**) are produced as by-products (equation 64).



(64)

The second modification published by Sakai and coworkers[261] is based on the reaction of lithium dithiocarbamate with butyl lithium and carbon disulphide (equation 65).



(65)

The reaction is carried out in TMF under dry nitrogen at 0 °C. Aliphatic and aromatic isothiocyanates were prepared in high yields (71–99 %) using this method.

Of the older, now rarely used, methods the decomposition of dithiocarbamates with iodine via thiuramdisulphide should be

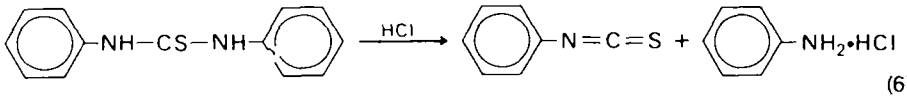
mentioned[262,263]. Dithiocarbamate is first oxidized with an alcoholic solution of iodine at a low temperature to thiuramdisulphide (**94**). Its sodium salt (**95**) obtained in an alcoholic solution of sodium ethoxide is subsequently oxidized to the corresponding isothiocyanate (equation 66).

$$2\ RNHCS\overset{-}{S}\overset{+}{N}H_4 + I_2 \longrightarrow \underset{(94)}{RNHCS-S-CSNHR} \xrightarrow{2\ NaOC_2H_5} \underset{(95)}{RN{=}C(SNa)-S-S-C(SNa){=}NR} \xrightarrow{I_2} 2\ RNCS + S_2 + 2\ NaI \qquad (66)$$

Besides the above mentioned methods the literature refers also to the use of chlorcyanogen[264] and chloramine T[265].

4. Decomposition of thioureas

Aromatic amines can be prepared by the decomposition of *sym*-diarylthioureas with acids or their anhydrides. The most frequently used acids are hydrochloric acid[266–268], sulphuric acid[269,270] and phosphoric acid. The salt of the corresponding arylamine is formed as by-product[271] (equation 67).



(67)

In addition to aromatic isothiocyanates, cyclohexyl isothiocyanate[272] was prepared by the treatment of dicyclohexylthiourea with phosphoric acid. Of carboxylic anhydrides, acetic anhydride[273–275] is the best. This method of decomposition was used also in the synthesis of arylazophenyl isothiocyanates (**96**) from asymmetric thioureas[276] (equation 68).

$$PhN_2C_6H_4NH_2 + C_6H_5NCS \longrightarrow PhN_2C_6H_4NHCSNHC_6H_5 \xrightarrow[AcOH]{Ac_2O} \underset{(96)}{PhN_2C_6H_4NCS} + C_6H_5NHCOCH_3 + CH_3COOH \qquad (68)$$

Isothiocyanates are obtained also by the decomposition of *N*-monoarylthioureas during prolonged heating in chlorobenzene[277]. 1-Naphthyl- and 2-naphthyl isothiocyanate can be prepared in good yields.

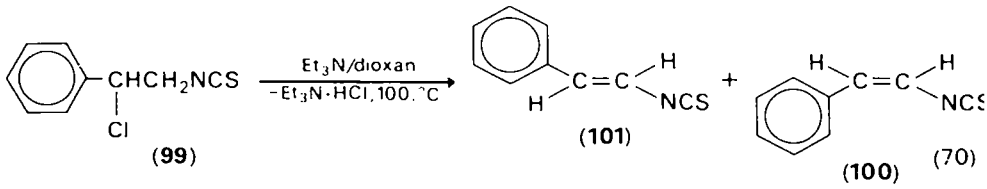
5. Isothiocyanates with the NCS group in conjunction with a multiple bond

Isothiocyanates with the NCS group bound directly to a carbon–carbon double bond cannot be prepared by routine methods. The cause lies in the non-reactivity or instability of the starting compounds, that is of the corresponding organo halides or amines. Nevertheless there exist currently several methods for their preparation.

The first mention of the preparation of this type of isothiocyanates appeared in the patent literature in 1956. Jones and Zimmerman[278] had prepared, by means of dehydrohalogenation of 1-isothiocyanato-2-bromoethane (**97**), vinyl isothiocyanate (**98**) which showed a tendency to polymerization (equation 69).

$$\underset{\textbf{(97)}}{BrCH_2CH_2NCS} \xrightarrow[40\text{–}50\ C]{Et_3N/ether} \underset{\textbf{(98)}}{CH_2{=}CH{-}NCS} \qquad (69)$$

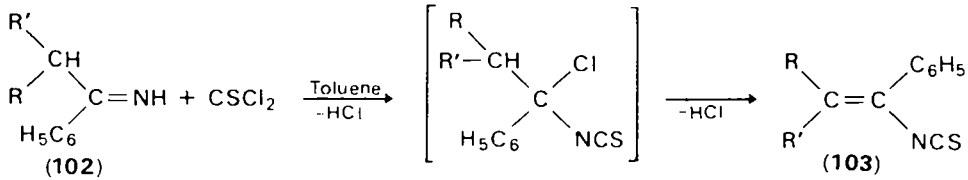
In a similar manner *cis*-(**100**) and *trans*-β-styryl isothiocyanate[279] (**101**) were prepared from 1-phenyl-1-chloroethylisothiocyanate (**99**, equation 70).



(70)

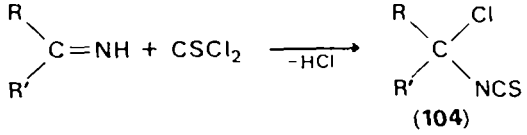
Reaction is performed by heating the reaction mixture for 36 h under nitrogen in a sealed tube. The two isomers (**100** and **101**) are formed in a ratio of 1:4 respectively.

Ketimines (**102**) with β-hydrogen atoms react in the cold with thiophosgene giving α-alkenyl isothiocyanates **103** whereby α-chloralkyl isothiocyanates[280] are probably produced as intermediates (equation 71).



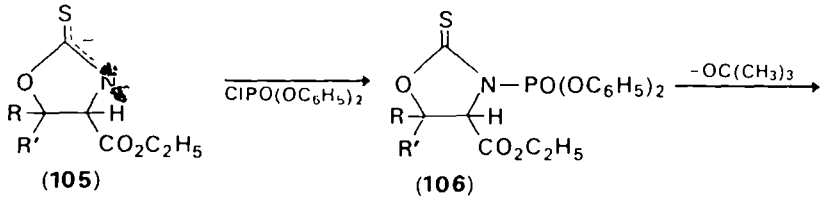
R = CH_3, H,
R' = CH_3, n-C_3H_7, i-C_3H_7 (71)

By heating of ketimines not containing the β-hydrogen atom with thiophosgene in toluene α-chloralkyl isothiocyanates arise (**104**, equation 72).

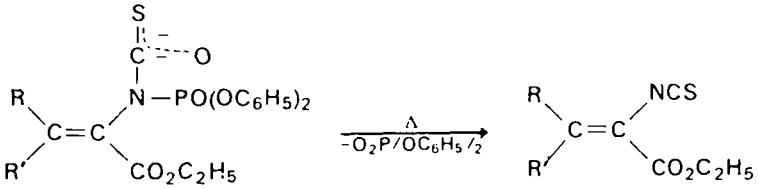


(**104**) (72)

Into this group of compounds may be included also β-substituted esters of α-isothiocyanatoacrylic acid[281]. These are prepared from the anions of oxazolidine-2-thiones (**105**) which are phosphorylated at 20–30 °C in tetrahydrofuran with the diphenylester chloride of phosphoric acid. The phosphorylated product (**106**) is decomposed with potassium *t*-butoxide to *N*-phosphoryl-*N*-vinyl-thiocarbamate (**107**) and further to diphenylphosphate and isothiocyanate (**108**, equation 73)[281].



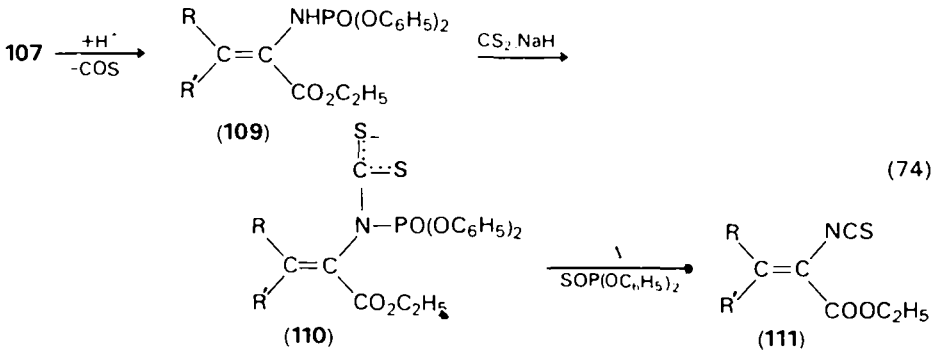
(**105**) (**106**) (73)



(**107**) (**108**)

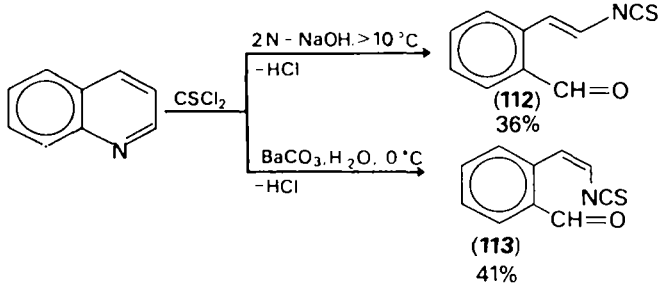
The starting compound can be readily prepared by basic condensation of the ethyl ester of isothiocyanatoacetic acid with carbonyl compounds[282].

For β-monosubstituted and β-arylsubstituted α-isothiocyanatoacrylesters which are sensitive to alkoxide the synthesis must be modified. The compound **107** is first converted at −60 °C with glacial acetic acid to α-(diphenoxyphosphorylamino)acrylic ester (**109**). This when treated with carbon disulphide and sodium hydride yields *N*-phosphoryldithiocarbamate (**110**) which decomposes at 20–40 °C to isothiocyanate (**111**) and *O*, *O'*-diphenylthiophosphate (equation 74).



(74)

Isothiocyanates with the NCS group bound to the dienal conjugated system were prepared for the first time by Hull[283]. By treating quinoline in methylene chloride with thiophosgene and diluted alkali, crystalline *o*-isothiocyano-*trans*-cinnamaldehyde (**112**) was obtained. The use of barium carbonate instead of sodium hydroxide produces an oily *cis* isomer (**113**, equation 75).

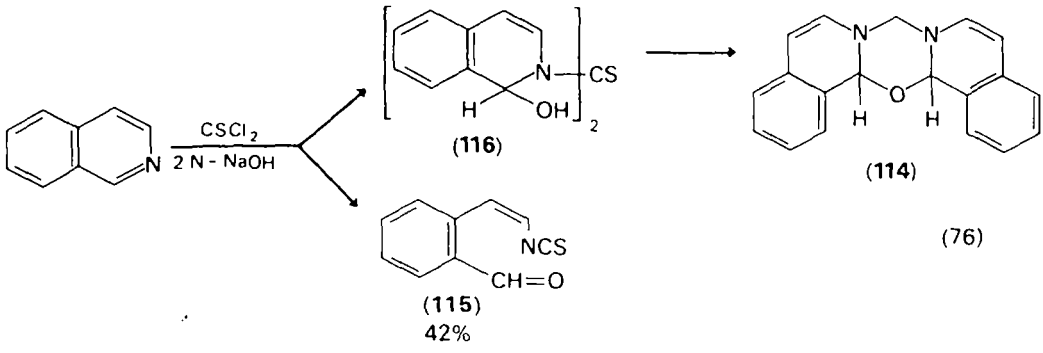


(75)

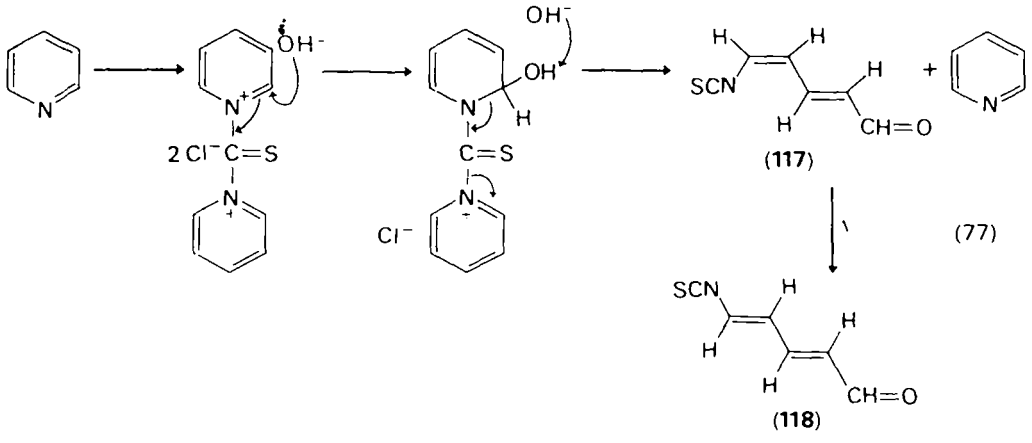
The *cis* isomer is not stable and within 3 days isomerizes entirely to a *trans* derivative.

The reaction of thiophosgene and 2 N-sodium hydroxide with isoquinoline in methylene chloride at a temperature of 5–10 °C yields two products, i.e. crystalline 15*B*,16*a*-dihydro-8*H*-diisoquinolino[1,2-*b*:2',1'-*e*]-[1,3,5]oxadiazine-8-thione (**114**) and *cis*-*o*-isothiocyanatovinylbenzaldehyde (**115**). The pentacyclic derivative is probably formed by dehydration of the derivative **116** (equation 76).

The greatest attention was devoted to the reaction of thiophosgene with pyridine which yields, in the presence of barium carbonate, a mixture of two stereoisomer products, i.e. 5-isothiocyanatopenta-*trans*-2,*cis*-4 dienal (**117**, controlled kinetically) and 5-isothiocyanato-*trans*-2,*trans*-4-dienal (**118**, controlled thermodynamically). The reaction probably takes place by the following mechanism[284] (equation 77).



(76)



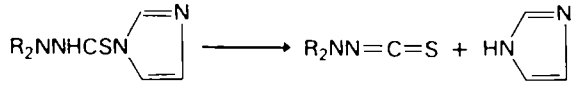
(77)

The raw product is a mixture of both isomers. The *trans, cis* isomer (melting point 59–61 C) is extracted with cold ether and the *trans, trans* product (m.p. 84–85 °C) is crystallized from cyclohexane.

Isothiocyanates of this group represent a heterodiene system in which the NCS group is conjugated with double bonds. Because they are highly reactive in addition and cycloaddition reactions, they are important intermediates of the various organic compounds.

6. *N*-Isothiocyanatoamines and *N*-isothiocyanatoimines

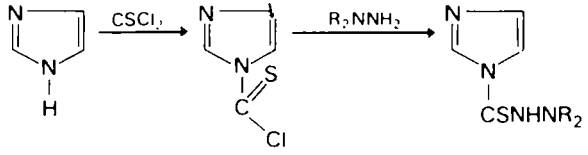
These isothiocyanates represent a new interesting group of compounds that have been studied by Anthoni and coworkers[285-288]. Dialkylamino-isothiocyanates (**120**) were the first to be synthesized by pyrolysis of *N,N*-dialkylthiocarbazolyl imidazole (**119**) in a high vacuum[285,287] (equation 78).



(119) (120) (78)

R = CH_3, C_2H_5, C_3H_7, i-C_3H_7

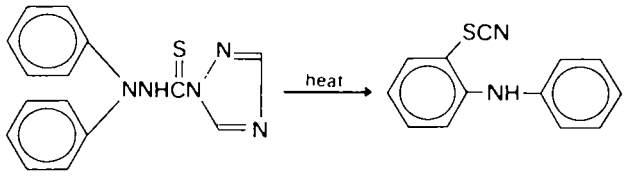
N,N-Dialkylthiocarbazoyl imidazoles (**122**) are prepared by the treatment of imidazole with thiophosgene in dry benzene; the thiocarbamoyl chloride (**121**) formed is subsequently reacted with dialkylhydrazine[288,289] (equation 79).



(121) (122) (79)

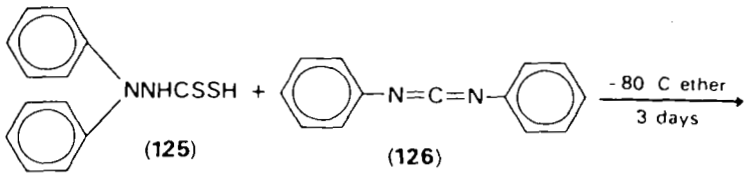
The isothiocyanates formed easily undergo dimerization[288]. Whereas *N*-isothiocyanatodimethylamine and its diethyl and dipropyl derivatives are stable only at −80 °C and dimerize entirely within one minute at room temperature, *N*-isothiocyanatodiisopropylamine requires several hours for dimerization at room temperature[288]. The relatively high stability of this monomer is attributed to steric effects.

The preparation of *N*-isothiocyanatodiphenylamine by thermolysis of 1-(*N,N*-diphenylthiocarbazoyl)-1,2,4-triazole (**123**) was not successful and 2-thiocyanatodiphenylamine (**124**) was always isolated as the resultant product[286] (equation 80).



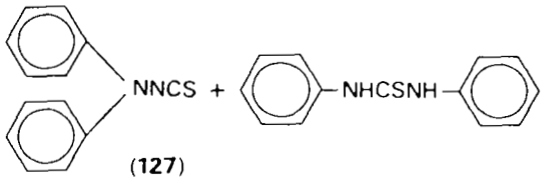
(123) (124) (80)

In order to prevent the possibility of intramolecular rearrangement, a low-temperature method of preparation was devised, based on the reaction of dithiocarbazic acid (**125**) with dicyclohexylcarbodiimide (**126**) at very low temperatures[286] (equation 81).



(125) (126)

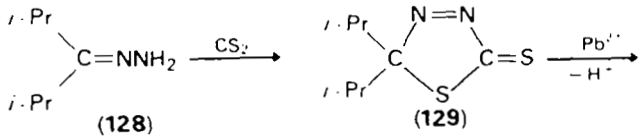
(81)



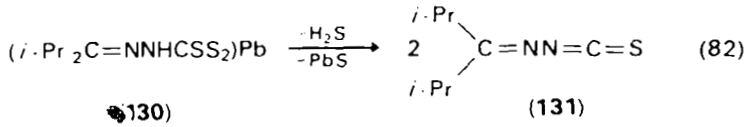
(127)

The formation of *N*-isothiocyanatodiphenylamine (**127**) in the solution was proved by infrared spectroscopy (ν_{NCS} = 1956 cm^{-1}). However, all attempts at its isolation failed due to its immediate isomerization to thiocyanate at higher temperatures.

N-Isothiocyanatoimines were prepared by the thermal degradation of lead bis[3-(diisopropylmethylene)dithiocarbazate](**130**)[290], equation (82).



(128) (129)



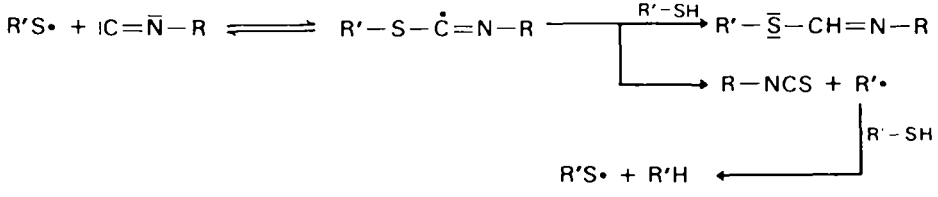
(82)

(130) (131)

5,5-Diisopropyl-1,3,4-thiadiazolidine-2-thione (**129**) is prepared from diisopropylketohydrazone (**128**) and carbon disulphide according to Heugebaert and Willems[291]. Treatment of thiadiazolidine (**129**) with an equimolar amount of lead acetate in a water–methanol medium leads to the opening of the ring with the formation of dithiocarbazate (**130**) which is then decomposed thermally at 120 °C. The resulting isothiocyanate (**131**) is a reddish-yellow oil which dimerizes within 15 minutes at room temperature. It can, however, be stored in liquid air under nitrogen. It is relatively stable also if dissolved in an inert solvent, like chloroform or carbon tetrachloride.

7. Other methods

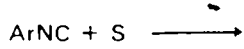
Isonitriles, too, may serve as starting substances for the preparation of isothiocyanates. In this respect several papers have been published recently. Shegusa and coworkers[292] studied the reaction of isonitriles with mercaptans which produces isothiocyanates, probably by the radical mechanism (equation 83).



(83)

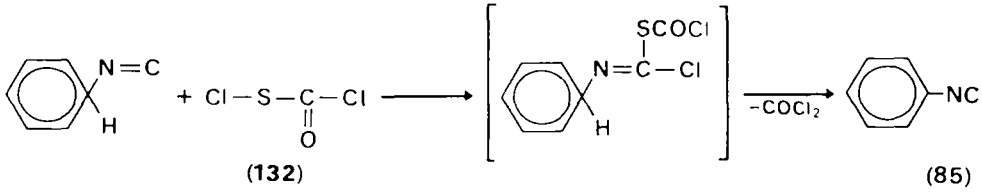
Isobutylmercaptan and cadmium acetate proved to be the best catalysts.

Aromatic isothiocyanates can be prepared from the corresponding aryl isonitriles by heating with sulphur in benzene[293] (equation 84).



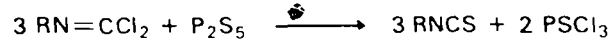
(84)

Reaction of isonitriles with chlorocarbonylsulphenyl chloride (**132**) yields isothiocyanates with the elimination of phosgene[294] (equation 85).



(**132**) (85)

Kuhle and coworkers obtained isothiocyanates in good yields from isonitrile dichlorides (**133**) by treatment with sodium sulphide or phosphorus pentasulphide[295] (equation 86).

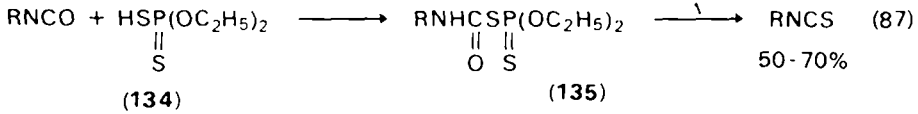


(**133**) (86)

Ottmann and Kober[296] prepared aromatic isothiocyanates directly from the corresponding nitro compounds by treatment with carbon disulphide or carbonyl sulphide at higher temperature and pressure in the presence of basic catalysts. Thiophenolates proved to be the best catalysts, for they substantially reduced the formation of anilines as by-products. Substituted phenyl isothiocyanates were thus prepared in good yields (50–88 %). This

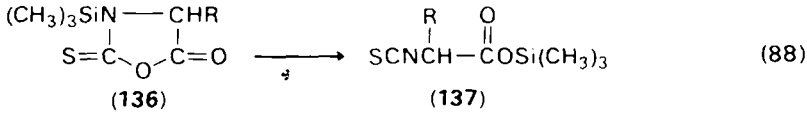
method is not suitable for the preparation of aliphatic isothiocyanates. The mechanism of reaction is not mentioned.

Aromatic and aliphatic mono-and diisothiocyanates can be obtained by exchange reaction of the corresponding isocyanates with *O,O*-diethyldithiophosphate (**134**) via *O,O*-diethyl-*S*-alkyl(aryl)carbamoyl dithiophosphates (**135**)[297]. At higher temperatures these decompose to isothiocyanate, a mixture of sulphur-containing esters of phosphorus acid and a small amount of different unidentifiable products (equation 87).



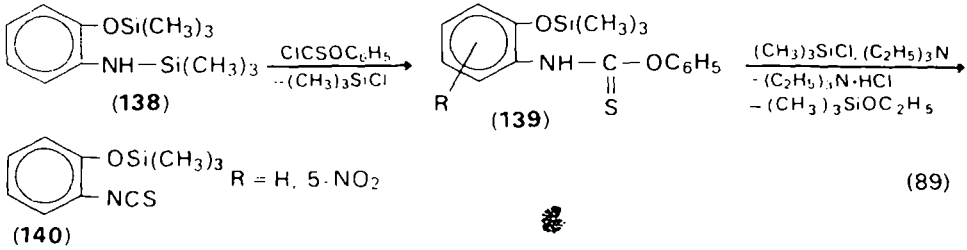
(87)

The decomposition of *N*-silylated cyclic derivatives of carbamic acid to isothiocyanates or isocyanates was studied by Kricheldorf and coworkers[298-301]. They found that, whereas *N*-silylated oxazolidine-2-thione-5-ones (**136**) rearrange rapidly and irreversibly to isothiocyanates (**137**) already at 0 °C (equation 88) the corresponding thiazolidine-2,5-diones do not rearrange[298-300].



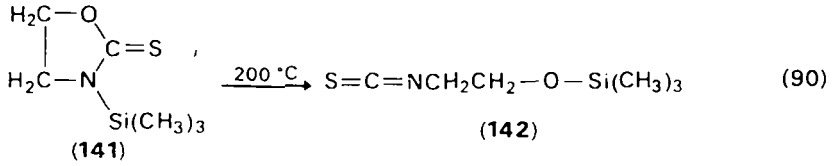
(88)

By treating *N,O*-bis(trimethylsilyl)-2-aminophenols (**138**) with *O*-phenyl chlorothioformate in dry toluene with boiling, and by the subsequent treatment of the obtained *N*-(2-trimethylsiloxyphenyl)thiocarbamic acid phenylester (**139**) with trimethylsilyl chloride and triethylamine, the above authors prepared 2-trimethylsiloxyphenyl isothiocyanates[301] (**140**, equation 89).



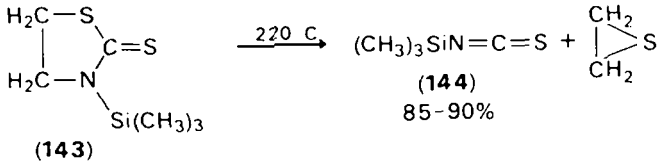
(89)

N-Trimethylsilyloxazolidine-2-thione (**141**) furnishes by thermolysis at 200 °C trimethylsiloxyethyl isothiocyanate (**142**) in up to 89% yields[301] (equation 90).



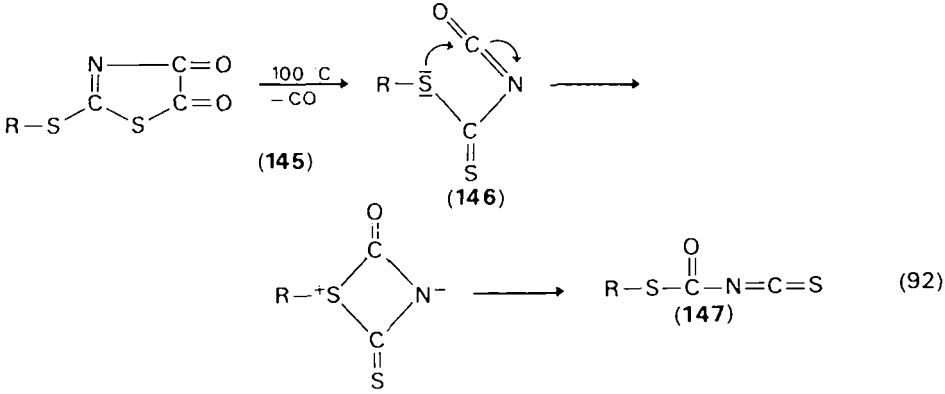
(141) (142) (90)

In the case of *N*-trimethylsilylthiazolidine-2-thione (**143**) instead of the expected trimethylsilylthioethyl isothiocyanate, rapidly polymerizing trimethylsilyl isothiocyanate (**144**) and ethylenesulphide were obtained (equation 91).



(143) (144) 85–90% (91)

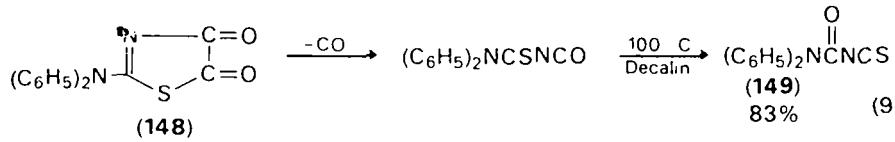
2-Alkyl(aryl)mercaptothiazoline-4,5-diones (**145**) split off carbon monoxide on heating giving alkyl(aryl)mercaptothiocarbonyl isothiocyanates (**146**) which rapidly rearrange to alkyl(aryl)mercaptocarbonyl isothiocyanates[302] (**147**, equation 92).



(145) (146) (147) (92)

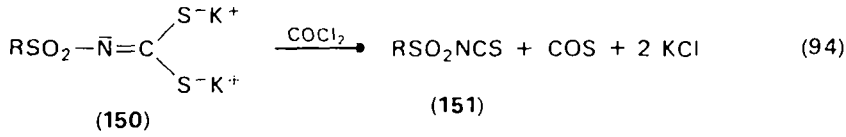
R = C_6H_5, $C_6H_5CH_2$—, CH_3—

In the manner diphenylcarbamoyl isothiocyanate (**149**) was prepared as colourless crystals[101] from diphenylaminothiazoline-4,5-dione (**148**, equation 93).



(148) (149) 83% (93)

Sulphonyl isothiocyanates (**151**) can be prepared in good yields by reaction of dipotassium salt of sulphonyliminodithiocarbonic acid (**150**) with phosgene[303,304], sulphuryl chloride[304] or thionyl chloride[304] in an organic solvent (benzene, chlorobenzene, methylene chloride, equation 94).



(94)

(150) (151)

R = $CH_3C_6H_4$—, $C_6H_5CH_2$—, C_6H_5—

Ottenbrite[305], using thermal cleavage of the corresponding *S*-methyldithiocarbamates at 180–200 °C, prepared trisubstituted aryl isothiocyanates.

Some methods have more of a theoretical significance and are rarely used for the preparation of isothiocyanates. For example, treatment of diazonium salts[306] with inorganic thiocyanates, heating of methylaniline with sulphur[307] under pressure, exchange reaction of *N*-sulphinylamines[308] and isocyanates[309,121] with isothiocyanates, and others.

B. Preparation and Use of Nuclide-labelled Isothiocyanates

In principle the molecule of the isothiocyanate R—NCS can be labelled with nuclides on the functional group of —NCS, or on the skeleton of the molecule R — or on both sites of the molecule. For practical reasons labelling is most frequently done with ^{14}C or with ^{35}S. The chief advantage of the latter lies in the fact that high specific radioactivity can be achieved, theoretically up to 1·500 Ci/milliatom. A certain drawback is that the labelled compounds must for long-term use—due to a shorter half-life —be prepared from fresh nuclide at intervals of several months. This problem is avoided by labelling with the nuclide ^{14}C provided that the labelled compounds are sufficiently resistant to self-radiolysis. However, the theoretical maximum achievable specific radioactivity is merely 64 mCi/milliatom of carbon. In practice the achieved specific radioactivity is, of course, lower; for ^{14}C it is about 60 % of the theoretical value. Sulphur can be prepared as carrier free. Labelling with nitrogen atoms is virtually limited to the stable ^{15}N. The radionuclide ^{13}N, due to its short half-life of 10 minutes, can perhaps be used in special cases.

Labelling on the skeleton R — may be universally performed by means of the radionuclides ^{14}C, ^{3}H or the stable nuclide ^{2}H.

1. Preparation by chemical synthesis

Of hitherto known methods for the preparation of isothiocyanates the most frequent methods for the preparation of the labelled substances start from the corresponding amine and the labelled $CSCl_2$, the dithiocarbamate method starting from the amine and the labelled CS_2, the decomposition of labelled thioureas and the method of isomerization of thiocyanates RSCN.

A reliable method of preparation of [^{14}C]isothiocyanates or [^{35}S]isothiocyanates is the reaction of the corresponding primary amine with thiophosgene $C^{35}SCl_2$ or $^{14}CSCl_2$ (equations 95 and 96).

$$RNH_2 + {}^{14}CSCl_2 \longrightarrow RN^{14}CS + 2\ HCl \qquad (95)$$

$$RNH_2 + C^{35}SCl_2 \longrightarrow RNC^{35}S + 2\ HCl \qquad (96)$$

The radiochemical yield of the reaction is identical with the yield of the pure product, given by stoichiometry of the reaction and the losses in the process of isolation and purification of the labelled product. Thiophosgene $C^{35}SCl_2$ can easily be prepared by the isotopic exchange reaction (equation 97) or by synthesis.

$$C^{32}SCl_2 + {}^{35}S \rightleftharpoons C^{35}SCl_2 + {}^{32}S \qquad (97)$$

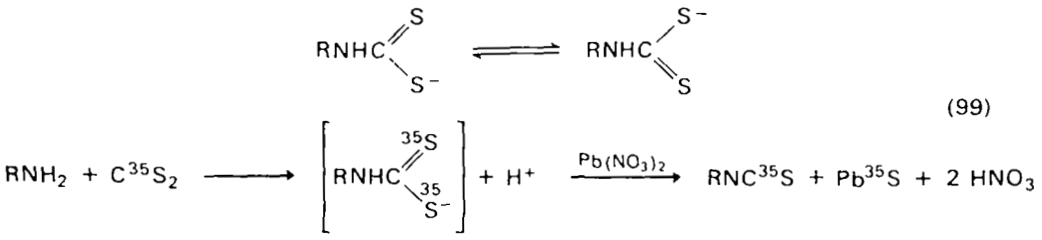
In this manner [4-^{131}I]iodophenyl [^{35}S]isothiocyanate was prepared starting from [4-^{131}I]iodoaniline and [^{35}S]thiophosgene[310].

The method of direct thiophosgenation was used for the preparation of D-glucosyl [^{14}C]isothiocyanate[311].

A frequently used method for preparation of labelled isothiocyanates starts from an amine and labelled CS_2. However, there are differences in radiochemical yield from the reaction when $^{14}CS_2$ or $C^{35}S_2$ is used. Starting from $^{14}CS_2$ all the radioactivity of the reacted carbon disulphide passes into the molecule of the isothiocyanate (equation 98).

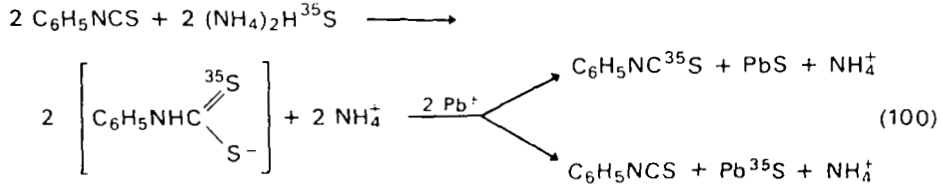
$$RNH_2 + {}^{14}CS_2 \longrightarrow \left[RNH\ {}^{14}C(=S)(S^-) \right] + H^+ \xrightarrow{Pb(NO_3)_2} RN^{14}CS + PbS + 2\ HNO_3 \qquad (98)$$

Because both sulphur atoms in the molecule of the dithiocarbamate are equal, use of $C^{35}S_2$ results in one half of the labelled sulphur atoms appearing in the isothiocyanate and the other half in the split-off sulphide, i.e. the maximum theoretical radiochemical yield will be 50 % (equation 99).



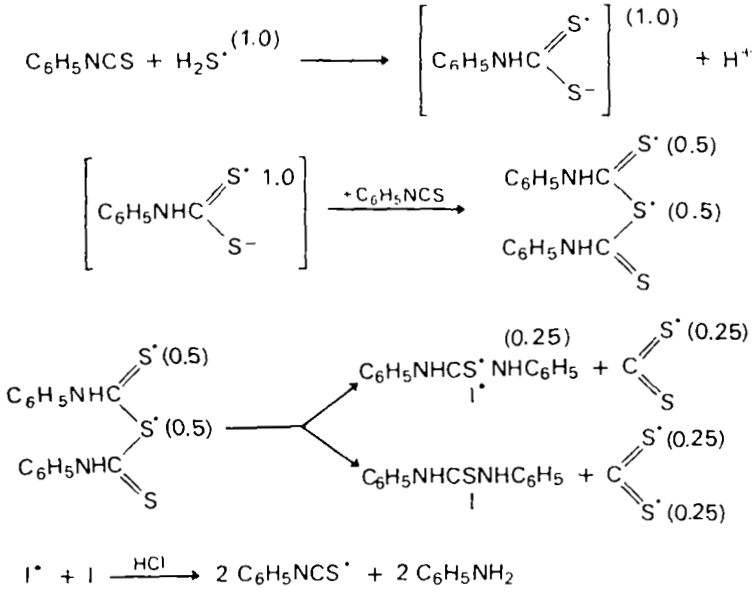
(99)

Similarly, a 50% radiochemical yield in relation to the radionuclide is achieved by preparing the dithiocarbamate from equimolar amounts of isothiocyanate and hydrosulphide, $H^{35}S^-$ (equation 100).



(100)

An even smaller radiochemical yield (25%) can be expected if the labelling is done by reaction of the isothiocyanate and the labelled H_2S in an organic solvent leading to the formation of thioureas and carbon disulphide (equation 101)[312].



(101)

Labelled *N*-monosubstituted dithiocarbamate can also be prepared, by reaction of the isothiocyanate with $Na^{35}SH$ [313] as well as by isotopic exchange reaction between dithiocarbamate and elementary sulphur-^{35}, and by exchange reaction between dithiocarbamate and $NaH^{35}S$ [314]. The reaction of isothiocyanate with hydrosulphide takes place at a sufficient rate also at laboratory temperature[315]. The rate constant is given by the nature of the substituent R and the concentration of the reacting form of HS^-; thus it is a linear function of pH.

The exchange between the elementary sulphur-35 and the aliphatic *N*-monosubstituted dithiocarbamate can be also performed at laboratory temperature; with methyldithiocarbamate, for example, the reaction is completed after 3–5 hours[314] (equation 102).

$$CH_3NHCS^- + {}^{35}S \rightleftharpoons CH_3NHC^{35}SS^- + S \qquad (102)$$

Otto[316] has studied in greater detail the kinetics of this exchange in the series of *N*-disubstituted dithiocarbamates as well as the influence of temperature and solvents.

The labelling of *N*-methyldithiocarbamate by exchange reaction with hydrosulphide ions at laboratory temperature is slow, requiring a reaction time of 3 hours for the completion of the reaction at 100 °C[314] (equation 103).

$$CH_3NHCSS^- + Na^{35}SH \rightleftharpoons CH_3NHC^{35}SS^- + NaSH \qquad (103)$$

Labelled isothiocyanate can be obtained also by the reaction of amine with the labelled ammonium thiocyanate and the decomposition of the thioureas formed[317].

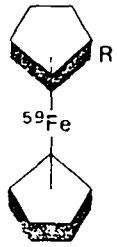
The dithiocarbamate method was used for the preparation of, for example, 4-dimethylaminophenyl [^{35}S]isothiocyanate[318] and fluorescein [^{35}S]isothiocyanate[319]. In the latter the specific radioactivity was three orders higher than that attained by other authors[320] at the preparation of fluorescein isothiocyanate labelled uniformly with the isotope ^{14}C in xanthene benzene rings.

Mann[321] had prepared [^{59}Fe]ferrocenylmethyl isothiocyanate (155) with the procedure known from inactive synthesis, starting from [^{59}Fe]-ferric chloride. $^{59}FeCl_3$ was reduced with electrolytic iron powder in diluted hydrochloric acid to $^{59}FeCl_2$ and the anhydrous product by the reaction with freshly depolymerized cyclopentadiene and diethylamine gave **152**. Through the reaction of (**152**) with *N*,*N*,*N*′,*N*′-tetramethylmethylenediamine and methyl iodide in the presence of methanol

N,*N*-dimethylaminomethylferrocene methiodide (**153**) was prepared. The following two procedures were used:

(i) From potassium phthalimide and **153**, ferrocenylmethylamine (**154**) was prepared which, by reaction with thiophosgene, furnished ferrocenylmethyl isothiocyanate (**155**).

(ii) A bisulphide adduct of formyl [^{59}Fe]ferrocene was prepared and this was converted by reaction with hydroxylamine to formylferrocene oxime (**156**). By reduction of **156** with lithium aluminium hydride, ferrocenylmethylamine (**154**) was prepared which, as in the foregoing procedure, gave **155** on reaction with thiophosgene.



(**152**) R = H
(**153**) R = $I^-(CH_3)_3\overset{+}{N}CH_2$
(**154**) R = NH_2CH_2
(**155**) R = $SCN{=}CH_2$
(**156**) R = $HON{=}CH$

2. Preparation via isotope exchange reaction

It is known that organically bound sulphur can participate in the direct exchange with elementary sulphur, the nature of the bond being decisive for the rate of exchange. These observations were reviewed in 1961[332]. In the series of sulphur compounds with thione sulphur, the rate of the exchange reaction with elementary sulphur decreases in the sequence given by equation (104).

$$C_2H_5OC(=S)S^- > (C_2H_5)_2NC(=S)S^- > CH_3C(=S)OH \gg \text{>C=S} \qquad (104)$$

According to Mikluchin and coworkers[323-326] the exchange takes place in such way that the sulphur is bound to the double bond of the =C=S group forming the cyclic product, the decomposition of which leads to the exchange of sulphur atoms (equation 105).

$$\text{>}\overset{\delta+}{C}{=}\overset{\delta-}{S} + {}^{\bullet}S_n \longrightarrow \text{>}C(S{-}{}^{\bullet}S)({}^{\bullet}S{-}{}^{\bullet}S_{n-2}) \longrightarrow \text{>C=}{}^{\bullet}S + S{}^{\bullet}S_{n-1} \qquad (105)$$

The exchange is more rapid the more polarized is the bond =C=S. Isothiocyanates require temperatures up to 180 °C for labelling by exchange reaction. It may be assumed that the extreme mesomeric structure with a negative charge on the sulphur atom participates in the exchange reaction (see Section V). The exchange can be carried out without a solvent in those isothiocyanates that are liquid at the exchange temperature, or with the use of a suitable inert solvent having an adequate boiling point such as xylene and decahydronaphthalene. It was found, however, that the exchange was faster with a solvent than without one, and that it was more rapid the lower the analytical concentration of sulphur in the reaction mixture[327]. The duration of the exchange can be several hours and, for example in the case of aromatic isothiocyanates, the reaction can be carried to equilibrium at 180 °C with very slight thermal decomposition, i.e. with a good yield of labelled substances. At normally obtainable specific activities of sulphur-35 of 200 mCi/mmol and the molar ratio of the isothiocyanate:sulphur = 1:1, a specific radioactivity of 100 mCi/mmol and a radiochemical yield of 40–50% can be achieved.

For the removal of elementary sulphur from the reaction mixture, fractional distillation of the isothiocyanate was used[328,329]; however the trapping of the sulphur in the column of activated copper appeared to be more convenient[328]. For the simultaneous removal of sulphur and the products of thermal decomposition it is of advantage to use a combined column composed of layers of activated copper, charcoal and activated alumina[329,330].

The ability of the thiocyanate ion ^-SCN to participate in the exchange reaction with aliphatic thiocyanates[331,61] with a half-life of several tens of minutes at 130 °C in cyclohexane (equation 106) and the ability of thiocyanates to isomerize to the corresponding isothiocyanates (equation 107) can be applied to the preparation of labelled isothiocyanates.

$$RSCN + {}^{35}SCN^- \underset{}{\overset{k_{ex.}}{\rightleftharpoons}} R^{35}SCN + SCN^- \qquad (106)$$

$$R^{35}SCN \xrightarrow{k_i} RNC^{35}S \qquad (107)$$

Isomerization of isothiocyanates is an irreversible reaction and once formed, the isothiocyanate participates no more in the exchange reaction with $^{35}SCN^-$ ion. The labelled $K^{35}SCN$ can be prepared by reaction of KCN with the sulphur-35 in ethanol[333]. $NH_4{}^{35}SCN$ arises also by isomerization of [^{35}S]thiourea in an ethanol–xylene mixture (1:1) at a temperature of 120 °C[334].

3. Labelling with isotopes of hydrogen

Tritium-labelled isothiocyanates can be prepared by incorporating tritium into a suitable intermediate for isothiocyanate synthesis such as an amine, or in some cases directly into the isothiocyanate molecule by one of the generally applicable methods of tritiation of organic compounds. For reviews see the following[335,336]:

(i) Labelling by catalytic exchange consists of heating together the compounds to be labelled, a hydrogen-transfer catalyst and the tritiated agent, such as T_2O or tritiated acids, in a suitable solvent.
(ii) Irradiation of compounds with tritium gas using the Wilzbach method[337] or the catalytic gas exposure method[338].
(iii) Hydrogenation of unsaturated compounds with tritium gas, or catalysed halogen–tritium replacement. With this method the highest molar specific activity can be achieved.
(iv) Reduction with tritiated metal hydrides.

The above methods, with the exception of the Wilzbach method, are also suitable for the preparation of deuterated isothiocyanates if a deuterated agent instead of the tritiated agent is used.

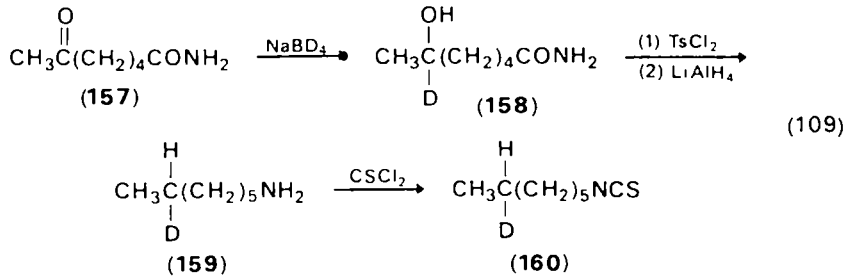
The original Yavorsky method of titration of aromatic hydrocarbons with a boron trifluoride complex of tritiated phosphoric acid[339] has also been elaborated for the tritiation of aromatic isothiocyanates[340]. At the preparation of the tritiated agent one starts from tritiated water, phosphorus pentoxide and BF_3 (equation 108).

$$3\ {}^3H_2O + P_2O_5 \longrightarrow 2\ {}^3H_3PO_4$$

$$^3H_3PO_4 + BF_3 \longrightarrow {}^3H_3PO_4{\cdot}BF_3 \qquad (108)$$

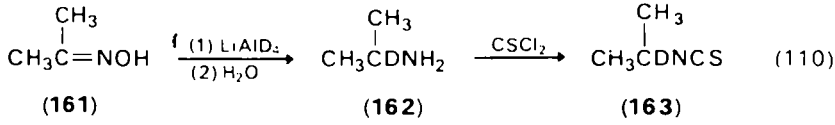
The tritiation is performed at 80 °C in a heterogeneous system by mixing the aromatic isothiocyanate which is dissolved in paraffin or cycloparaffin hydrocarbons, such as cyclohexane, with a layer of $^3H_3PO_4{\cdot}BF_3$. The method is suited particularly to the preparation of tritiated mono- and polynuclear aromatic isothiocyanates.

Isothiocyanates specifically labelled with deuterium are most frequently prepared for the study of their mass spectra. Bach and coworkers[341] prepared 6-*d*-heptyl isothiocyanate (**160**) according to the equation (109).



(109)

The same authors[341] prepared 2-*d*-propyl isothiocyanate (**163**) from acetoxime (**161**) according to the sequence shown in equation (110).



(110)

Isothiocyanic acid, DNCS, was prepared by mixing dry potassium thiocyanate and potassium deuterium sulphate and heating the mixture under vacuum at about 200 °C. The yellow gas was collected at 80 K, and purified by trap-to-trap distillation[342].

4. Preparation of ^{35}S-labelled isothiocyanates by hot-recoil reaction

Dazantiev and coworkers[343] prepared methyl [^{35}S]isothiocyanate by irradiation of an equimolar mixture of methyl isothiocyanate and $CHCl_3$ in a silica ampoule with neutrons ($1-3 \times 10^{11}$ n cm^{-2} sec^{-1}) at 50 °C. After 20–30 hours, 10–15 % of the induced radioactivity was in the form of labelled isothiocyanate with a specific radioactivity of 20 μCi/g. Experiments with irradiation of pure methyl isothiocyanate without $CHCl_3$ showed that the reaction in equation (111) was negligible and that in the given case the reaction according to equation (112) predominated. For the theory and details of the procedure of hot recoil synthesis see References 344 and 345.

$$^{34}S\ (n,\gamma)^{35}S \tag{111}$$

$$^{35}Cl\ (n, p)^{35}S \tag{112}$$

In view of the large amount of decay products and the low specific radioactivity achieved with methods of direct irradiation of organic compounds, this method is apparently not suited for wider application.

5. Labelling by biosynthesis

With the application of suitable labelled precursors of glucosinolate synthesis to the cultivation medium it is possible to isolate labelled glucosinolates from plants, and from these by enzymic splitting through myrosinase, to isolate the corresponding labelled isothiocyanates. As stated in Section II about biosynthesis of glucosinolates, the amino acids are incorporated into the molecule of glucosinolates as a whole after loss of the carboxyl group, so that when using [^{14}C]amino acids R—NCS isothiocyanates labelled on the skeleton R are obtained[24–28]. Amino acid precursors are incorporated in the corresponding glucosinolates with an effectiveness of 25–50 %. When using amino acids labelled with the stable nuclide ^{15}N on the α-amino group the nuclide will appear in the NCS group of the isothiocyanate, but in that case a greater dilution must be expected due to the possible metabolic interconversion of amino acids and keto acids by transamination or oxidative deamination and thus a lower yield calculated for the starting nuclide.

If amino acids, specifically labelled on the COOH group, are used as precursors then no labelled isothiocyanate is obtained because of the decarboxylation reaction taking place during biosynthesis.

[^{35}S] Sulphate is incorporated in glucosinolates with an efficiency of 50 % whereby [^{35}S]glucosinolates are obtained. However, the nuclide is incorporated in a different ratio in the thioglucoside and in the sulphate-bound sulphur. By the action of myrosinase the sulphate group splits off and only the thioglucoside-bound sulphur remains incorporated in the —NCS group. In the first phases of cultivation of the plant in the presence of [^{35}S]sulphate the radionuclide is incorporated almost exclusively in the sulphate group of the glucosinolate and appears only after several days in the thioglucoside group. In view of the simple chemical structure of currently known natural isothiocyanates and the facility of their chemical synthesis, a biosynthetic approach to the use of nuclides is meaningful only in the study of biosynthesis and metabolism of glucosinolates and of their decay products.

6. The uses of labelled isothiocyanates

Isothiocyanates labelled with radionuclides have been used, in many tracer studies in complicated biological systems in pharmacology and biochemistry, as starting compounds, as analytical reagents in protein chemistry and in structural organic chemistry. Here we shall mention at least a few examples. Isothiocyanates labelled with ^{35}S were successfully used for

an autoradiographic study of their distribution in slices of animal tissue after local application on skin and for measuring the rate of resorption (4-bromophenyl [^{35}S]isothiocyanate)[346,347] and after intra-muscular injection (allyl [^{35}S]isothiocyanate)[348]. Penetration of 4-chlorobenzyl [^{35}S]isothiocyanate into animal skin was also studied[349]. Labelled anthelmintic *p*-phenylene diisothiocyanate was used for the study of the interaction of the drug with low molecular and high molecular components of blood[350]. Organ distribution of cancerostatic β-naphthyl [^{35}S]isothiocyanate was studied in rats after intraperitoneal administration[317,351]. 4-Bromophenyl [^{35}S]isothiocyanate was used for the study of kinetics of retention in microbial and animal cells, subcellular distribution and reaction with cell components[352,353].

In the Edman degradation protein sequencing technique, labelled phenyl isothiocyanate is employed for enhancing the sensitivity of the method. For the same purpose, tritium-labelled phenyl isothiocyanate[354], as well as phenyl [^{35}S]isothiocyanate[355], was used in conjunction with isotopic dilution analysis. [^{59}Fe]Ferrocenylmethyl isothiocyanate served as tag by direct reaction with ε-amino groups of lysine in a glutamic acid–lysine–tyrosine copolymer[321].

Deuterated isothiocyanates were used for the study of their mass spectra[341]. Deuterated isothiocyanic acid, DNCS, and isocyanic acid, DNCO, were prepared and studied in the ultraviolet[342] and infrared regions[356] of the spectrum.

C. The Preparation and Use of Macromolecular Polyisothiocyanates

The advance in the chemistry of macromolecular polyisothiocyanates has begun only in the past 10 years owing to the interest in immobilized enzymes and antigens and macromolecular insoluble reagents[357–360].

Macromolecular polyisothiocyanates are either water insoluble compounds and of a suitable micro-spatial arrangement (fibrillar, microporous, gels, glass-like, rubbery, thin membranes) or they are oil or water soluble compounds in which NCS groups are bound to the macromolecular skeleton in a specific sequence of alternating monomer subunits. In accordance with the nature of the basic polymer skeleton these substances may belong, for example, to the group of silylated inorganic glasses, polysaccharides or polypeptides as well as synthetic polymers based on styrene, acrylamide and other polymers and copolymers and cross-linked materials.

For the preparation of macromolecular polyisothiocyanates essentially two procedures can be adopted:

(i) Polymerization of suitable low molecular isothiocyanates, preserving a certain number of free NCS groups. The reaction can be performed as homopolymerization or copolymerization which permits a greater variation in physical and physicochemical properties of the resultant product.

(ii) Formation of the NCS group on the existing polymer, e.g. with bifunctional agents or by direct modification of a certain group to NCS group with methods used in the preparation of other isothiocyanate. In this case the most frequent problem is the preparation of a polyamine of adequate physicochemical properties.

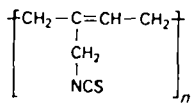
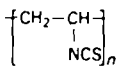
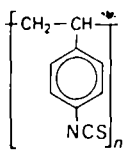
A survey of the most known macromolecular polyisothiocyanates, method of their preparation and application are presented in Table 4.

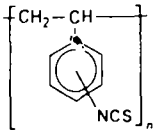
Polyisothiocyanates are regarded as supports for immobilization of enzymes via the reaction of NCO groups with NH_2 groups of proteins giving rise to corresponding disubstituted ureas[380,381,384,385]. However, due to the analogy between the reactivity of low molecular isocyanates and isothiocyanates it may be expected that polymeric polyisocyanates will be less stable in a water medium than macromolecular polyisothiocyanates because of the faster addition of OH^- ions.

IV. SYNTHETIC PRODUCERS OF ISOTHIOCYANATES

Some synthetic precursors yield isothiocyanates spontaneously at laboratory temperatures in aqueous solution or in a solution of organic solvents. Thus they resemble in behaviour aglucones which are formed by enzymic hydrolysis of glucosinolates which may be decomposed also to isothiocyanate. On the basis of this analogy with natural substances Martin[386] introduced in 1962 for synthetic compounds which, by spontaneous decomposition give isothiocyanate, the German term 'synthetische Senfölbildner' which appeared in the English literature as 'synthetic producers of isothiocyanates', or 'mustard oil formers'[387]. In the original work of Martin[386], salts of *N*-monosubstituted dithiocarbamic acids, *O*-esters of *N*-monosubstituted thiocarbamic acids and 3,5-disubstituted tetrahydro-1,3,5-thiadiazine-2-thiones, were considered as synthetic producers of isothiocyanates. Though these substances had been known since the second half of the last century, interest in them was revived

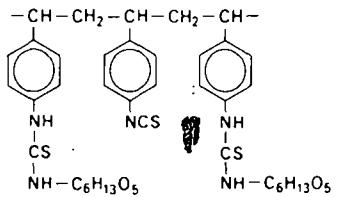
TABLE 4. Macromolecular polyisothiocyanates

Structure	Starting compounds and synthetic route	Utilization
	(i) Polymerization of 2-chloromethyl-butadiene with subsequent treatment of the polymer with excess of ammonium thiocyanate and re-arrangement of polythiocyanate to polyisothiocyanate[361]	Water soluble poly-isothiocyanates used as binders for paper and rayon[361]
	(ii) Polymerization of 2-methylene-3-butenyl isothiocyanate[361]	
	(i) Polymerization of vinyl isothiocyanate; also copolymeriz-ation with acrylamide, acrylonitrile, vinylidene chloride, vinylacetate and styrene[362]	Improving dyeing pro-perties of fibres[362]
	(ii) Polyvinylamine reacted with thiophosgene[363]	Immobilization of papain[363]
	(i) Polymerization of *p*-vinylphenyl isothiocyanate[364]	Soluble in *N*,*N*-dimethylformamide. Pre-paration of thiourea poly-meric derivatives[364]
	(ii) Thiophosgenation of poly-4-aminostyrene[363]	Immobilization of papain[363]
	(iii) Polystyrene beads cross-linked with divinylbenzene, converted to amine by nitration and reduction, followed by the reaction with carbon disulphide and decomposition to isothiocyanate with ethylchloroformate[365]	Insoluble Edman reagent analogous to phenyl isothiocyanate[365]



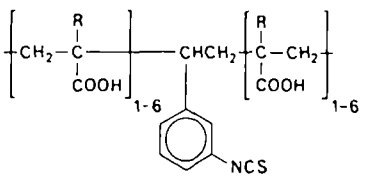
Polymerization of *o*-, *m*-, or *p*-vinylphenyl isothiocyanate; also copolymerization with vinylbenzene[366]

Insoluble glasslike polymers[366]



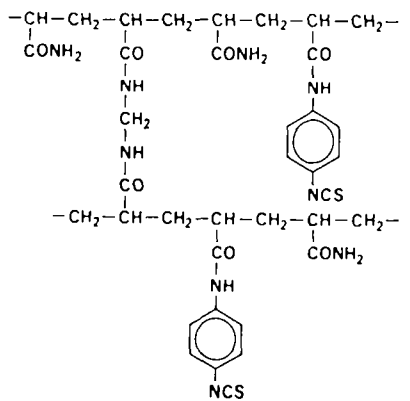
Reaction of polystyrene-NCS with calculated amount of glucosaminol[367]

Insoluble Edman reagent with reduced hydrophobicity[367]



Copolymerization of methacrylic or acrylic acid and isothiocyanatostyrene[368,369,363]

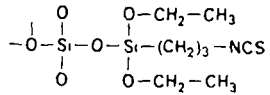
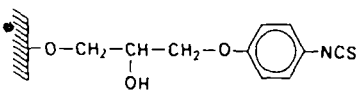
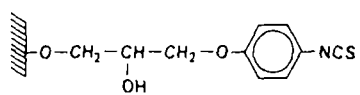
Immobilization of papain[363]

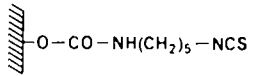
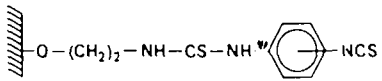


Copolymerization of acrylamides and reaction of free aromatic amino group with thiophosgene[370]

Immobilization of α- and β-amylase[370,371,372]

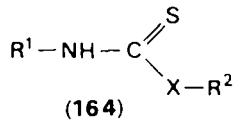
TABLE 4 (*continued*)

Structure	Starting compounds and synthetic route	Utilization
	Silylation of porous silica glass with 3-aminopropyltriethoxysilane and following reaction of free primary amino groups with thiophosgene[373,374]	Immobilization of trypsin[374,375], peroxydase[375], papain[374], glucoamylase[375], glucose oxidase[376]
	Oxidation of the Ni-screen surface with O_2 at 700°C, silanization with aminopropyltriethoxysilane and reaction of amino group with thiophosgene[377]	Immobilization of glucose oxidase[377]
	Cellulose treated with 1,2-epoxy-3-(*p*-nitrophenoxy) propane. Corresponding 2-hydroxy-3-(*p*-nitrophenoxy)propyl ether of cellulose reduced with titanous chloride in HCl. Resulting *p*-aminophenoxy group reacted with thiophosgene[378,379]	Immobilization of α- and β-amylase[378,379]
	Cross-linked dextran treated analogously as in the case of cellulose[380]	Immobilization of trypsin, chymotrypsin and β-amylase[380]. Binding of amino acids, peptides and proteins[381]

	Reaction of OH groups of cellulose with NCO groups of 1-isocyanato-5-isothiocyanato pentane in dry organic solvents[382,383]	Reaction with low molecular amino and thiol compounds and proteins[382,383]
	Reaction of aminoethylether of cellulose with diisothiocyanate[382,383]	Reaction with low molecular amino and thiol compounds and proteins[382,383]

not only by purely scientific endeavours but also by experience of their antibacterial, antifungal, antialgal and antiworm effect and by the need for new soil fungicides and soil sterilants as well as by the shortage of suitable antibiotics having a low toxicity and a wide antimicrobial, or antifungal spectrum.

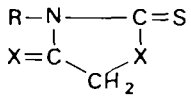
Synthetic producers of isothiocyanates are compounds which contain in the molecule the grouping nitrogen–carbon–sulphur from which an —N=C=S grouping may be formed by hydrolysis. This requirement can be met almost universally by the grouping of bonds given by the general formula **164**, i.e. thione bound sulphur and acidic hydrogen bound to



(164)

nitrogen, or structures derived from the linear structure **164** by forming a 5- and/or 6-member, 3-substituted, 2-thione heterocyclic moiety (**165**, **166**).

According to these criteria the following groups of compounds are involved: *N*-monosubstituted monothiocarbamic acid salts (**167**), *N*-monosubstituted monothiocarbamic acid esters (**168**), *N*-monosubstituted dithiocarbamic acid salts (**169**), *N*-monosubstituted dithiocarbamic acid esters (**170**), *N*-monosubstituted (**171**) and *N*,*N*'-disubstituted thioureas (**172**), *N*-substituted thioamides (**173**), 3-or 3,5-substituted rhodanines (**174**), 3-, or 3,5-substituted thiohydantoins (**175**), 3,5-disubstituted tetrahydro-1,3,5-thiadiazine-2-thiones (**176**).



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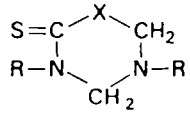


(166)

$R^1-NH-CO-S^-M^+$

(167)

$R^1-NH-CS-O-R^2$

(168)

$R^1-NH-CS-S^-M^+$

(169)

$R^1-NH-CS-S-R^2$

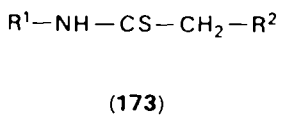
(170)

$R^1-NH-CS-NH_2$

(171)

$R^1-NH-CS-NH-R^2$

(172)



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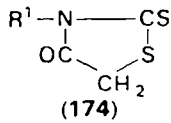

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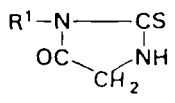

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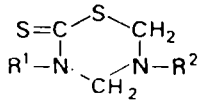
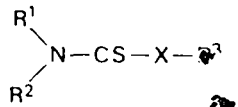


(176)

We shall now deal with the current situation regarding the decomposition of synthetic producers of isothiocyanates under defined conditions, particularly in aqueous solutions of a defined pH with a view to a possible ionization equilibrium and apparent (k_{obs}) as well as the real rate constant (k) of decomposition. In all these compounds the rate of decomposition primarily depends on, besides the actual stability of the molecule, the equilibrium of ionization taking place on the nitrogen and thione-bound sulphur. These determine not only the values k_{obs} but also the type of decomposition, that is the pH of the reaction mixture determines also the terminal products of decomposition in the reaction mixture.

The strictly chemical orientation of this monograph and of the whole series *The Chemistry of Functional Groups* does not permit a wider discussion about the antimicrobial effects of these compounds, their antimicrobial spectrum, cytotoxicity and toxicity in experimental animals. Therefore, for individual structural groups at least, references to papers concerned with this problem are given. Generally it should be noted for the whole of this group of compounds that the mechanism of their biological effect need not be uniform under all circumstances. Apart from the compounds with the already mentioned grouping of bondings (**164**) and their cyclization products, where the formation of a biologically effective isothiocyanate in the cultivation medium or after penetration of the compound into the cell is assumed, the corresponding *N*-disubstituted analogues, as *N*-disubstituted dithiocarbamates (**177**) are equally characterized by a high antimicrobial effect.



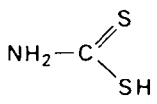
(177)

In these, however, according to present knowledge the formation of isothiocyanate cannot be expected. *N*-Monosubstituted and

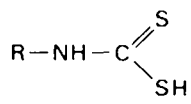
N-disubstituted dithiocarbamates, and esters of *N*-monosubstituted and *N*-disubstituted dithiocarbamic acids, are also characterized by a high antimicrobial effect[388-392]. The question whether in *N*-monosubstituted derivatives it is an 'isothiocyanate' or 'non-isothiocyanate' mechanism of biological effect can usually be decided by comparing the relative biological effect of corresponding *N*-mono-and *N*-disubstituted derivatives, their antimicrobial spectra and by a more detailed biochemical study.

A. N-*Monosubstituted Dithiocarbamates*

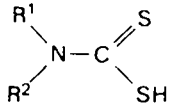
Isothiocyanates are formed only from the *N*-substituted derivatives (**179**) of three possible dithiocarbamic acids (**178–180**).



(**178**)



(**179**)



(**180**)

Free dithiocarbamic acid (**178**) can be prepared by releasing it from its ammonium salts by means of concentrated HCl at 0 °C. It is practically insoluble in non-polar organic solvents and its thermodynamic dissociation constant at 20 °C is $K_a = 1{\cdot}13 \pm 0{\cdot}03 \times 10^{-3}$[393]. By thermal decomposition in the temperature interval from 20 to 100 °C it decomposes into ammonium thiocyanate in two steps (equation 113)[393,394].

$$2\ NH_2CSSH \longrightarrow (NH_2CSS)NH_4 + CS_2$$
$$(NH_2CSS)NH_4 \longrightarrow NH_4SCN + H_2S \qquad (113)$$

Alkali metal salts of dithiocarbamic acid decompose at 100–120 °C and form corresponding alkali metal thiocyanates (stability: $M = Cs^+ > Rb^+ \gg K^+$)[395].

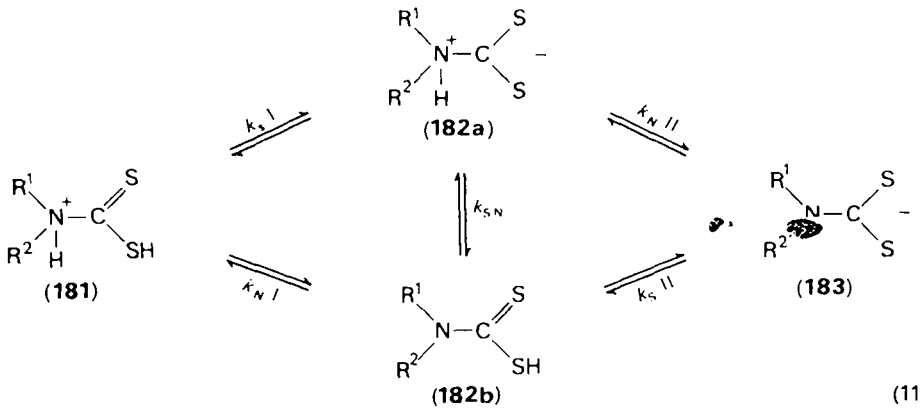
N-Monosubstituted dithiocarbamates are formed by the reaction of hydrosulphide ion with isothiocyanates (equation 114). A reverse reaction is one of the current methods of preparation of isothiocyanates (see Section III). *N*-Monosubstituted dithiocarbamates also originate in the reaction between primary amines and carbon disulphide. A reverse reaction, an acid decomposition leads to primary amines and CS_2 (equation 115).

These reactions are, therefore, reversible and the reaction rates k_1 and k_{-1} (equation 114 and 115) as well as the equilibrium states are determined by the dissociation constants of dithiocarbamates which depend on the character of the substituent R.

$$R{-}NCS + NaHS \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R{-}NHCSS^-Na^+ \quad (114)$$

$$R{-}NH_2 + CS_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R{-}NHCSSH \quad (115)$$

The dissociation constants of dithiocarbamates had already been studied 1957[396] and at present several laboratories work on this problem. Zahradnik[397] on the basis of a polarographic study of the rate of decomposition of the series *N*-mono-and *N*-dialkyldithiocarbamates has determined that the apparent rate constants of the decomposition of *N*-monosubstituted dithiocarbamates in acid medium follow the shape of dissociation curve corresponding to the transfer of a single proton. The ascertained points of inflexion of the functions $k_{obs} = f(pH)$, corresponding to the pK_a values of *N*-alkyl and *N*-dialkyl dithiocarbamates, were found to lie in the pK_{II} range from 2 to 4. On the basis of his observation that dithiocarbamates are stable in alkaline solution and on the assumption that a further ionization stage is to be expected in an acidic medium, Zahradnik[397] proposed the scheme shown in equation (116) for the description of ionization equilibria. He found out that structure **182** was the decomposing form in an acid medium, but from direct experimental data it was not possible to decide whether it was structure **182a** or **182b**. In an alkaline medium *N*-dialkyldithiocarbamates are very stable[398].



(116)

On the basis of the changes in ultraviolet absorption spectra and the kinetic measurements of the decomposition of a series of *N*-monosubstituted dithiocarbamates, Takami and coworkers[399] made a further detailed study of ionization equilibria. From the change in two known ultraviolet absorption bands of water-soluble dithiocarbamates at 250 and 290 nm, they ascertained the ionization equilibrium over a wide

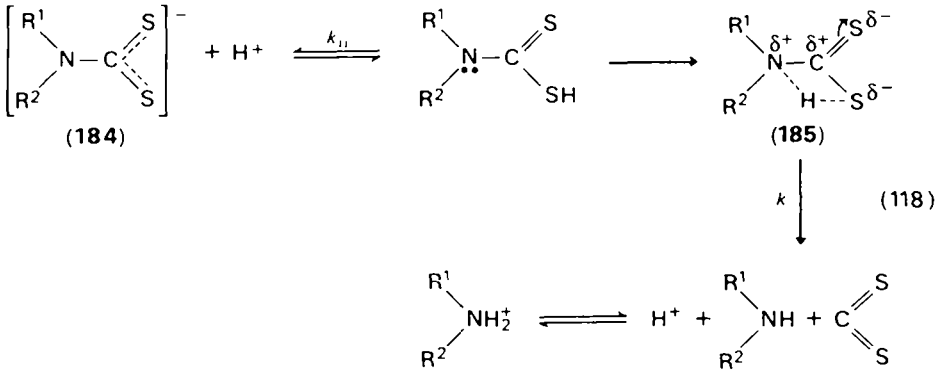
concentration range of alkaline hydroxide (0·001–1·5 M) and determined the pK_a values[400]. The Brönsted plot of pK'_{III} versus pK_a of the corresponding starting amine showed a linear relationship according to equation (117).

$$pK'_{III} = 0{\cdot}49.\ pK_a + 12{\cdot}41 \qquad (r = 0{\cdot}994) \tag{117}$$

It is the ionization stage which was already assumed by Wronski[401] on the basis of kinetic measurements of the decomposition of *N*-ethyl dithiocarbamic and *N*-phenyl dithiocarbamic acids in alkaline solutions (0·4–3·0 N-NaOH).

According to Jorris and coworkers[402] the following steps come into consideration in the acid decomposition of dithiocarbamates (equation 118):

(i) Protonation of one of the sulphur atoms of the anion (**184**).
(ii) Formation of an intramolecular hydrogen bond between this sulphur atom and the nitrogen atom in **185**.
(iii) Cleavage of the N—C bond aided by repulsion between the fractional positive charges in the acid molecule.
(iv) Protonation of the released amine.



From the kinetic measurements of the rate of decomposition of *N*-alkyl substituted dithiocarbamates [ethyl-, benzyl-, (4-amino-2-methyl-5-pyrimidinyl)-methyl-] at different pH values in weakly acidic solutions, Takami and coworkers[399,403] calculated the pK'_{II} values of the acid base equilibrium.

As in the previous case, there also exists the Brönsted plot of pK'_{II} against pK_a of the corresponding amine with equal slope as it is in the case of strong alkaline equilibria (equation 119).

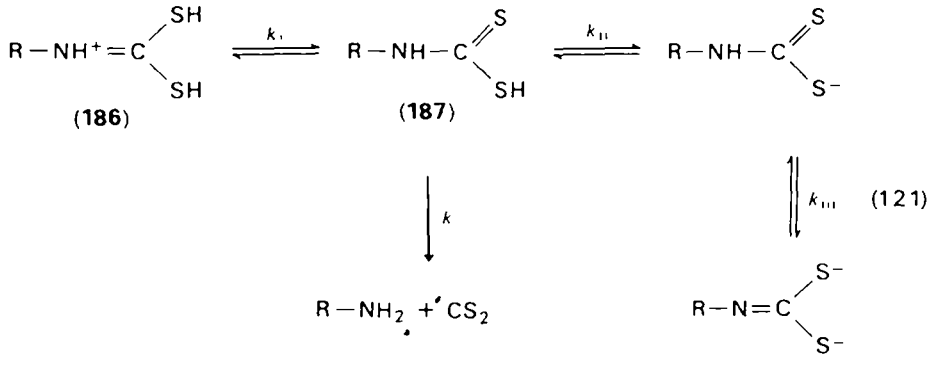
$$pK'_{II} = 0{\cdot}53.\ pK_a - 2{\cdot}60 \tag{119}$$

For the rate of acid decomposition the following relationship was determined (equation 120):

$$\log k = -0{\cdot}37\,\mathrm{p}K_a + 2{\cdot}30 \qquad (120)$$

However, in strongly acidic solutions (as in concentrated sulphuric acid) with the Hammett's acidity function H_0 ranging from -3 to -5, the observed values of the pseudo first-order rate constants of decomposition of *N*-substituted dithiocarbamic acids decrease again.

The fact that a plot of $\log k_{obs}$ versus the Hammett's acidity function H_0 fits in with a dissociation curve indicates the existence of a further ionization equilibrium in a strongly acidic medium, the dissociation constant of which is K_1. The rate constants of the decomposition in a strongly acidic medium are in good agreement with the rate constants determined for the reaction in a weakly acidic solution. Hence the authors came to the conclusion that the decomposing form was **187** and not **186**. These equilibria are expressed by equation (121) and graphically represented by the summary graph (Figure 1).



(121)

With the decomposition of dithiocarbamates, besides well defined acid–base relationships given by the electronic effects, other factors such as the steric influences of substituents and the dielectric constant of the medium, also manifest themselves to a large extent. With the volume of the substituent the rate constant k of decomposition increases in the following order: methyl < dimethyl < di-*n*-butyl < di-*n*-propyl < diethyl < di-isopropyl[404,402]; for disubstituted cyclic derivatives it increases in the order: pyrrolidine < hexamethyleneimine < piperidine[406]. The size of the substituents determines the extent to which solvation reduces the fractional positive charges in the acid molecule (see equation 118).

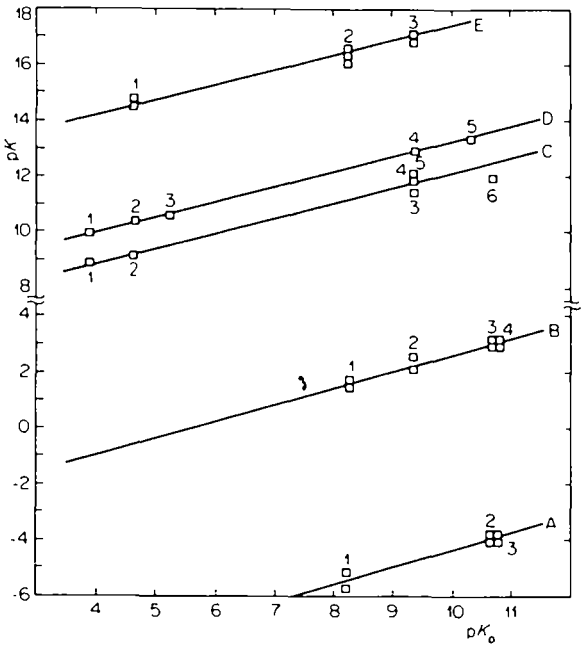


FIGURE 1. Brønsted plot of pK values of N-substituted dithiocarbamic acids (A, B, E), their esters (C), and N-substituted monothiocarbamic acid O-esters (D) vs pK_a values of corresponding amines RNH_2

(A) pK_I (25 °C) values for equation (121). 1, R = (4-amino-2-methyl-5-pyrimidinyl) methyl; 2, R = methyl; 3, R = ethyl (according to Takami and coworkers[403]).

(B) pK_{II} (25 °C) values for equation (121). 1; R = (4-amino-2-methyl-5-pyrimidinyl) methyl; 2, R = benzyl; 3, R = methyl; 4, R = ethyl (according to Takami and coworkers[403]).

(C) pK_I (25 °C) values for equation (133). 1, R^1 = 4-bromophenyl, R^2 = β-hydroxyethyl; 2, R^1 = phenyl, R^2 = β-hydroxyethyl; 3, R^1 = benzyl, R^2 = β-hydroxyethyl; 4, R^1 = benzyl, R^2 = n-propyl; 5, R^1 = benzyl, R^2 = carboxymethyl (according to Drobnica and coworkers[315]); 6, R^1 = methyl, R^2 = methyl (according to Takami and coworkers[419]).

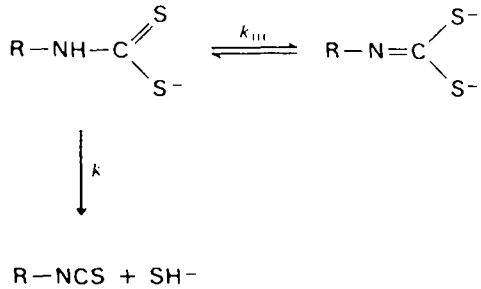
(D) pK_I (25 °C) values for equation (134). 1, R^1 = 4-bromophenyl; 2, R^1 = phenyl; 3, R^1 = 4-ethoxyphenyl; 4, R^1 = benzyl; 5, R^1 = n-butyl, R^2 = ethyl (according to Augustín and Drobnica[405]).

(E) pK_{III} (25 °C) values for equation (121). 1, R = phenyl; 2, R = (4-amino-2-methyl-5-pyrimidinyl)methyl; 3, R = benzyl (according to Takami and coworkers[399,400]).

With decreasing value of the dielectric constant in the water–acid systems, by the addition of methanol for instance, the stability of the dithiocarbamate molecule diminishes because of a decrease in the dipolar character and the reduced ability of the solvent to reduce the repulsive forces between the like charges in a molecule of dithiocarbamate[402].

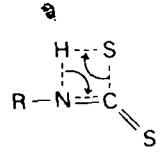
1. Decomposition of *N*-monosubstituted dithiocarbamates leading to the formation of isothiocyanates

Takami and coworkers[407] studied the decomposition of the methyl and phenyl *N*-substituted dithiocarbamates over a wide pH range from a weakly acid region (pH 4·5–6·5) to alkaline and up to the region of alkalinities of 15 M-KOH at temperatures up to 80 °C as well as the decomposition of ethyl, propyl and benzyl derivatives in 0·1 N-NaOH. His results expressed as plots of the logarithm of the observed first-order rate constants $\log k_{obs}$, versus pH or H_0 show that the rate decreases with pH, becoming independent of pH in the middle pH region 9–14 for the phenyl derivative and in the range pH 8 to H_0 17 for the methyl derivative. In more basic solutions a decrease in the values of k_{obs} has been observed in both cases. Decomposition, therefore, proceeds according to equation (122).



(122)

On the basis of these results the authors[407] assume that the formation of isothiocyanate passes through a transition state (**187**) as a unimolecular decomposition. The S—C σ-bond of dithiocarbamate, having an electron attracting group, should be looser than one having an electron-donating group.



(**187**)

In mild acid, neutral or weakly alkaline media, a reaction giving amine and isothiocyanate as well as the corresponding reverse reaction leading to resynthesis can, therefore, come into force. In this case overall rate of decomposition by both the mechanisms mentioned, can be expressed by equation (123)[408].

$$k_{\Sigma} = \left[\frac{[H^+]}{\frac{[H^+]^2}{K_I} + [H^+] + K_{II}} \cdot k_{-1} + \frac{[H^+]}{K_{III} + [H^+]} \cdot k_2 \right] \cdot [DTC] \qquad (123)$$

DTC = Dithiocarbamate

It is known that dithiocarbamates can undergo oxidation in the presence of a mild oxidant, such as $FeCl_3$[409] or during aeration[410]. Oxidation by air was observed in a strongly acid medium[403,411] and in a weakly acid region (pH 4–6), as well as in a weakly alkaline region[412]. At the same time it was observed that at pH 9·5 the rate of decomposition of *N*-methyl dithiocarbamate was dependent on oxygen content of the solution [413].

N-Methyl and *N*-ethyl dithiocarbamate were rapidly oxidized in 10% H_2SO_4 in presence of air and formed the corresponding *N*,*N*'-dialkyl thiuramdisulphides (**188**)[403]. In sufficiently deaerated samples the decomposition in an acid solution affords amine and carbon disulphide exclusively.

$$2\,R{-}NH{-}CS{-}SH \xrightarrow{O_2} \underset{(188)}{R{-}NH{-}CS{-}S{-}S{-}SC{-}NH{-}R} \qquad (124)$$

N,*N*-Disubstituted thiuram disulphides arising in an alkaline medium (equation 124) decompose to the corresponding isothiocyanates. According to Reference 412, on decomposition of *N*-substituted dithiocarbamates in the presence of air, it is necessary to add the rate of oxidative decomposition (equation 125) to the rate of the base-catalysed decomposition. This reaction is assumed to proceed according to equation (126).

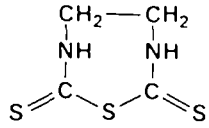
$$v_{Ox} = k_{Ox}[RNHCSS^-]^n [O_2]^m \qquad (125)$$

$$2\,R{-}NH{-}C(=S){-}S^- \rightleftharpoons R{-}NH{-}C(=S){-}S{-}S{-}C(=S){-}NH{-}R + 2\,e^- \qquad (126)$$

$$\downarrow \tfrac{1}{2}\,O_2$$

$$2\,R{-}NCS + H_2O + 2\,S$$

Thorn and Ludwig[410] have, however, shown that oxidation of *N*-monosubstituted dithiocarbamates can lead to the formation of further products. On the aeration of disodium ethylenebisdithiocarbamate they revealed the formation of ethylenethiuramonosulphide (**189**), the corresponding polymeric analogue, and elemental sulphur.



(189)

N-Monosubstituted dithiocarbamates can form complexes with heavy metals at high pH. These complexes subsequently decompose to metal sulphide and isothiocyanate[414] (equation 127).

(127)

2. Consecutive reactions in the decomposition of dithiocarbamates

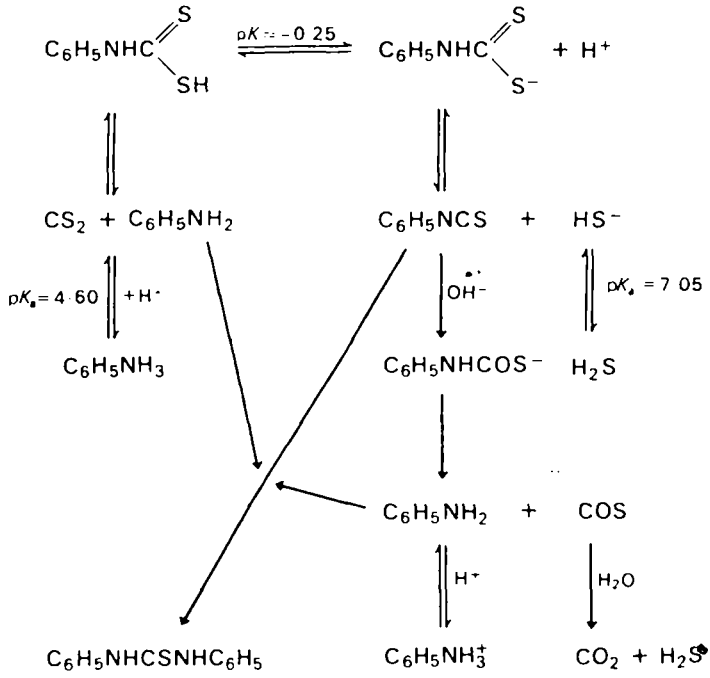
During the base-catalysed decomposition of *N*-substituted dithiocarbamates in a weakly alkaline water solution, i.e. in the region of the formation of isothiocyanates, some reactions can appear which cause the maximum yield of isothiocyanate to be less than stoichiometric. The reasons may be:

(i) The reaction is in equilibrium;
(ii) The isothiocyanate arising continues to react further with OH^- ions (see Section VI) and is transformed into monothiocarbamate which in a weakly alkaline medium gives amine and carbonyl sulphide; the latter decomposes into carbon dioxide and hydrogen sulphide;
(iii) The amine formed as above or in a partial acid decomposition of dithiocarbamate, can further produce *N*,*N*′-disubstituted thiourea.

The entire scheme is expressed by equation (128). Depending on the pH value and the character of the substituent R which determines the p*K* value and reactivity, the individual reaction will take place in various stages.

As a consequence of the above mentioned wide variety in possible reactions of dithiocarbamates and consecutive reactions in water system, the mechanism of their antimicrobial activity has not yet been clearly determined. It is ascribed to three possible reaction mechanisms:

(i) The formation of a biologically effective isothiocyanate.
(ii) The influencing of the redox potential of the cell and the formation of mixed disulphides.
(iii) The chelate effects causing the bonding of bivalent ions, essential for the catalytic function of enzymes.



(128)

B. N-*Monosubstituted Monothiocarbamates*

These compounds (**190**) are formed by a reaction of isothiocyanates with OH^- ions (equation 129). The reaction is irreversible.

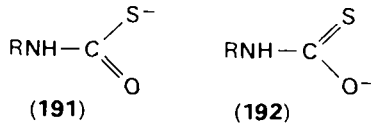
$$R-NCS + OH^- \longrightarrow R-NH-CO-S^- \qquad (129)$$

(**190**)

By the decomposition of **190** in an acid, neutral and weakly alkaline medium, amine and carbonyl sulphide are formed, and the latter further

decomposes to carbon disulphide and hydrogen sulphide. In strongly alkaline solutions monothiocarbamates are stable. The rate of decomposition of 5×10^{-3} M solutions of **190** (where R = phenyl, alkyl or aralkyl) in 0·1 N-NaOH at 25 °C was less than 1 % after 24 hours[415,327]. At higher temperatures decomposition takes place even in an alkaline medium. The half-life of the decomposition of *N*-phenyl monothiocarbamate in 2 N-NaOH at 60 °C is approx. 40 min[401].

Unlike in dithiocarbamate, where both the atoms of sulphur are equivalent, in monothiocarbamates there exists equilibrium of forms **191** and **192**, which is almost entirely shifted to the side of the structure **191** owing



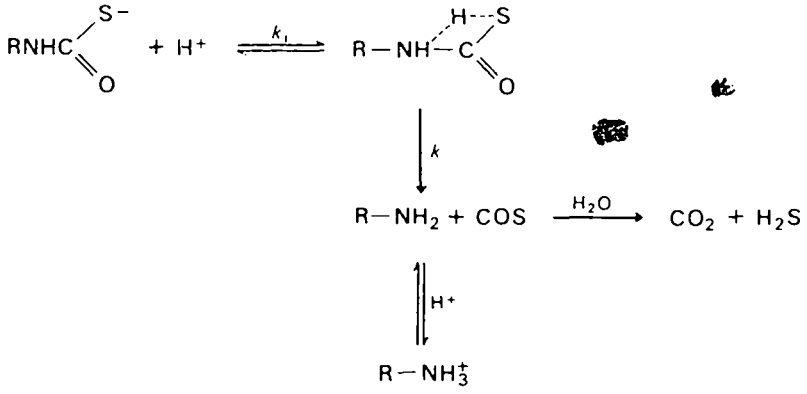
(191) **(192)**

to the unreadiness of the sulphur atoms to form double bonds. The formation of isothiocyanates, can however, be expected only for the structure with thione sulphur. On account of the considerable stability of monothiocarbamates the resulting isothiocyanate could react with OH^- ions and convert back to monothiocarbamate. The formation of isothiocyanate has not, however, been proved even in an alkaline medium containing a surplus of thiol compounds functioning as trapping agents for isothiocyanate formed[327].

Spectrophotometric study of the rate of decomposition of monothiocarbamates in the pH region 6·0–7·6, where R = substituted phenyls, has demonstrated that a molecule which has received a proton is subjected to decomposition[415,327]. On account of the high rate of decomposition it was not possible directly to measure the values of k_{obs} in the pH region where they would not depend on pH, and would therefore represent the rate constants of decomposition of the protonated form, dependent only on the nature of the substituent R. For the series of 4-phenylsubstituted monothiocarbamates, it was found that the values of $\log k_{obs}/H^+$, which were numerically equal to the ratio k/K_1, and the values of the corresponding amine RNH_2 followed the linear Brönstedt's plot (equation 130).

$$\frac{k_{obs}}{[H^+]} = 0{\cdot}36, \qquad pK_a + 5{\cdot}90 \tag{130}$$

On the basis of these facts it is possible to propose a reaction pathway for the decomposition of monothiocarbamates in an acid, neutral, or weakly alkaline medium (equation 131).



(131)

C. Esters of N-Monosubstituted Dithiocarbamic Acids

Besides other ways of preparation, the esters of *N*-monosubstituted dithiocarbamic acids, or dithiourethanes (**193**), may be formed by the reaction of isothiocyanates with thiols. Under favourable conditions they can be split again into isothiocyanate (equation 132).

(132)

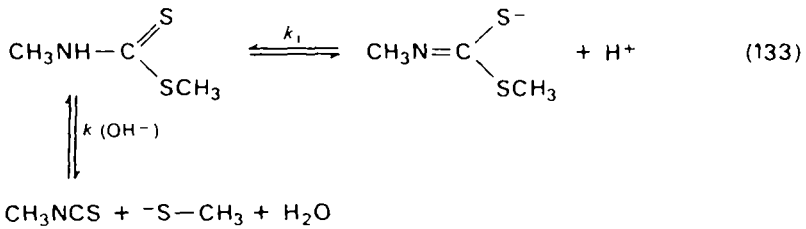
(**193**)

The decomposition of **193** in organic solvents was studied by Garraway[416]. For compounds of the type $X—C_6H_4NHCS—S—(CH_2)_2COOH$ the rate of decomposition in absolute methanol at 26 °C decreased with increasing basicity of the corresponding amine $R'NH_2$ according to the character of the substituent X (4-NO_2 > 2,4-diCl > 4-Cl > H), the *N*-methylderivative was stable in solution. From this fact the author concluded that the instability was caused by the labile nature of the hydrogen attached to the nitrogen atom.

It was known earlier that esters of monosubstituted dithiocarbamic acids decomposed in an alkaline medium and that their stability depends on the character of the substituents R^1 and R^2[417]. The knowledge of the quantitative relationships concerning the decomposition of these compounds was obtained by the study of systems with defined pH values[327]. In the series of compounds **193** where R^1 and R^2 represented benzyl, propyl; benzyl, benzyl; benzyl, phenyl; 4-methoxyphenyl, propyl; phenyl, propyl; 4-bromophenyl, propyl; and phenyl, benzyl it was revealed by means of

ultraviolet spectra that the decomposition gave the corresponding isothiocyanate R^1—NCS. The values of the rate constants of decomposition, k_{obs}, increased with alkalinity of the medium, i.e. the dependence showed in all cases the form of dissociation curve depending on pH which confirmed that the reaction was preceded by the release of one proton. Because of a high rate of decomposition it was not possible to find out either the point of inflexion or the value of k_{max} even in a single case. However in a reaction mixture of isothiocyanate containing at least 100-fold excess of thiol, the equilibrium of the reaction (**132**) is shifted to the side of the formation of the addition product **193**, even in an alkaline pH region, and pK_1 values can be determined spectrophotometrically[418]. The observed pK_1 values are shown in Figure 1. For details see Section V.

Alkyl esters of *N*-alkyl substituted dithiocarbamates (**193**), which are stable in neutral solutions and show the highest stability even in alkaline solution, was considered as another mechanism for the formation of isothiocyanates. Takami and coworkers[419] found that the value of k_{obs} of the decomposition of methylester of *N*-methyldithiocarbamic acid in an alkaline medium decreased with increasing concentration of NaOH in the range from 0·01 to 1·0 N-NaOH. For this reason they consider the mechanism shown by equation (133) to be highly probable.

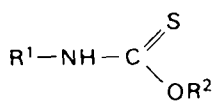


(133)

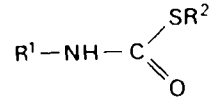
The experimental values $K_1 = 10^{-2}$ and the second-order rate constant at 25 °C $k = 1{\cdot}21 \times 10^{-1}$ l mol^{-1} min^{-1} were determined spectrophotometrically.

D. Esters of N-Monosubstituted Monothiocarbamic Acids

Monothiocarbamates may yield both thione (**194**) and thiol esters (**195**).



(**194**)



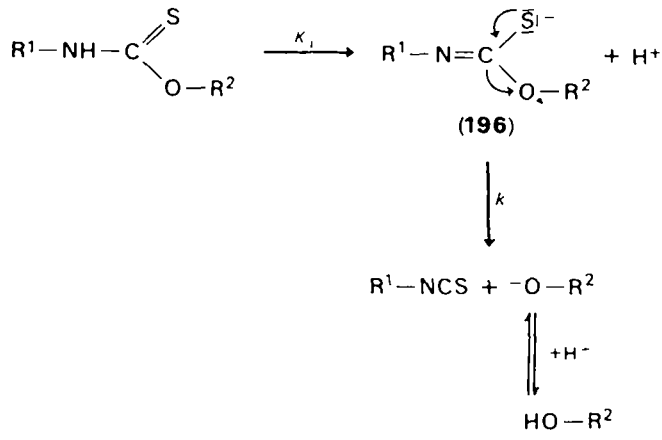
(**195**)

Thionurethanes or thiocarbamates (**194**) are formed, in addition to other ways, by the reaction of isothiocyanates with alcohols or alkoxide ion (see Section V) and according to the nature of the substituents R^1 and R^2 they are either stable substances or substances that readily undergo a reverse reaction and yield isothiocyanate and thiol. *N*-Alkyl-*O*-alkyl derivatives form stable, well defined, Ag salts from which it is possible to displace free thiourethane with hydrogen sulphide[420]. The silver salts of *N*-aryl-*O*-aryl thiourethanes are unstable. At room temperature and in the presence of water they rapidly decompose into isothiocyanate and phenol[421]. *O*-Alkyl esters are relatively stable substances. *O*-Phenyl esters dissolved in organic solvents decompose to isothiocyanate and phenol even at room temperature. The rate of decomposition increases with the dielectric constant of the solvent used[422]. It was established that the rate of decomposition in 50% methanol depends on the substituent R^1 and increases in the order: *i*-propyl < cyclohexyl < phenylethyl < phenyl < 4-chlorophenyl < 4-nitrophenyl[422]. Analogously with the esters of dithiocarbamic acids, the esters of monothiocarbamic acids also undergo acid–base equilibria in water solutions. A direct spectrophotometric determination of K_1 (equation 134) is possible only for *N*-alkyl, or *N*-aryl-*O*-alkylthiourethanes (**194**) which are stable in alkaline solutions. The pK_1 values of acid–base equilibrium fulfil the Brönsted equation as is obvious in Figure 1 (curve D).

N-Alkyl and *N*-aryl-*O*-aryl thiourethanes (**194**) undergo rapid decomposition in neutral and weak alkaline media and give alkyl or aryl isothiocyanates and phenol. The logarithmic values of the observed decomposition rate constants, k_{obs}, increase linearly with the pH value of solution, which indicates that the deprotonated molecule decomposes (equation 134). On account of the high rate of decomposition, however, the values k_{obs} have not been measured yet in that pH region where all molecules are in anion form.

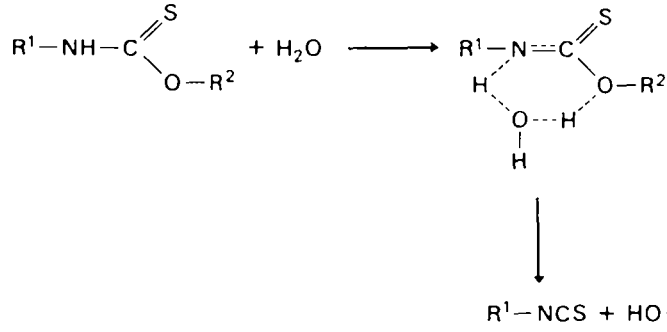
According to the present state of knowledge, it can be assumed that a splitting of **196** into isothiocyanate for substances where R^2 represents a good leaving group, such as phenyl in neutral and alkaline solutions, will go via E1cB elimination of phenol from anion **196**, while the apparent rate of decomposition k_{obs} will be determined by the preceding ionization equilibrium with constant K_1 and the stability of anion.

In substances **194** where R^2 represents a poor leaving group such as alkyl, anion **196** is highly stable even in alkaline solutions. This anion forms well-defined salts with silver ions, from which free thiourethane can be displaced with hydrogen sulphide[420]. Compounds **194** where R^2 is phenyl also form salts with silver ions, but these decompose spontaneously to isothiocyanate[421].



(134)

In weakly acidic solutions where k_{obs} is not a function of concentration of hydrogen ions, or in polar organic solvents, it is necessary to assume that decomposition proceeds via solvolysis according to the following mechanism (equation 135) which was also assumed for the decomposition of carbamate esters[423].



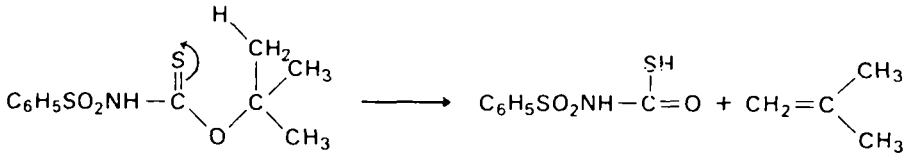
(135)

This is confirmed by the fact that the analogous esters of dithiocarbamic acids (**193**) are much more stable in aqueous solutions if they are present in a non-ionized form as well as in non-polar organic solvents, which, as well as for other reasons, is due to the inability of sulphur to form hydrogen bonds.

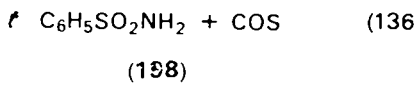
For substances **196** in strongly acid solutions a further ionization stage is expected involving the protonization of nitrogen, the constant pK being in the H_0 region from -2 to -6.

Thionurethanes having a reactive functional group on the substituent R^2 can, as well as splitting reactions, undergo intermolecular reactions. For instance thionurethane (**197**) formed by the reaction between benzenesulphonyl isothiocyanate and *t*-butanol immediately decomposes

and gives sulphonamide (**198**), carbonylsulphide and 2-methylpropene (equation 136)[424].



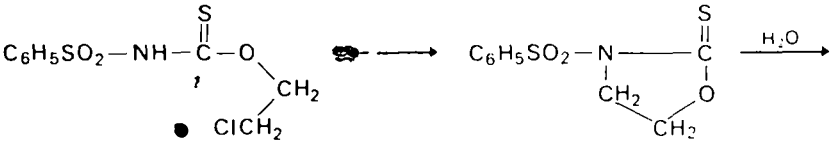
(**197**)



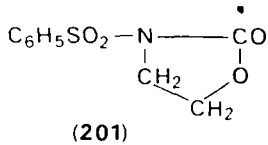
(136)

(**198**)

Thionurethane (**199**) formed by the reaction between benzenesulphonyl isothiocyanate and 2-chloroethanol can undergo a subsequent cyclization to yield **200** which in turn yields **201** after hydrolysis[424].



(**199**) (**200**)



(**201**)

By the decomposition of thiolurethanes (**195**) primary amines R^1NH_2 and carbonyl sulphide are formed. The latter decomposes to carbon dioxide and hydrogen sulphide in an aqueous solution. At the same time, however, it was possible to trap the isocyanate R—NCO in the form of *N,N'*-disubstituted urea in the reaction mixture[425].

Thionocarbamates (**194**) can isomerize into thiolcarbamates (**195**) under certain conditions. Alkyl esters undergo a smooth rearrangement when heated in a non-polar solvent in the presence of an acid catalyst such as boron fluoride etherate or *p*-toluenesulphonic acid[426]. Aryl thionocarbamates undergo a similar rearrangement when heated simply with or without solvent in the absence of an acid catalyst[427,428]. This thermal rearrangement proceeds intramolecularly through a four-membered cyclic transition state[429]. *N*-Monosubstituted thionocarbamates undergo.

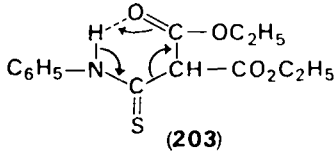
besides the rearrangement, a dissociation in presence of catalysts and the corresponding isothiocyanates and alcohols are formed[430].

E. N-*Substituted Thioamides*

N-Substituted thioamides (**202**) can be formed by the reaction between isothiocyanate and a Grignard reagent[431] (equation 137). The carbon–carbon bond is formed so that, in general, the substances are very stable, but as these substances contain a dissociable hydrogen on the nitrogen atom as do the esters of monothio- and dithiocarbamic acids, they can function as synthetic producers of isothiocyanates under certain conditions. For instance, thioamides derived from phenyl isothiocyanate and the diethyl ester of malonic acid (**203**), can provide phenyl isothiocyanate as well as other products during vacuum distillation. It is assumed that this reaction obeys the following reaction mechanism (equation 138)[432]:

$$C_6H_5NCS + RCH_2MgI \xrightarrow[-Mg(OH)I]{H_2O} C_6H_5NHC(=S)CH_2R \qquad (137)$$

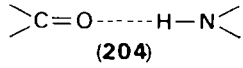
(202)



(203)

$$\xrightarrow{} C_6H_5NCS + CH_2(CO_2C_2H_5)_2 \qquad (138)$$

Isothiocyanate and nickel(II) sulphide may also be obtained by a few hours' boiling of Ni chelate of thioamide in methanol or benzene. This thermal *cis* elimination is facilitated by formation of a hydrogen bonded **204** structure shown in **205**.



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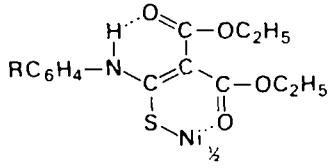
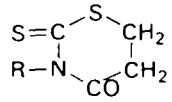


(205)

F. 3-Substituted Tetrahydro-4-oxo-2-thiothiazines

Substances **206** can be prepared by the cyclization of β-(*N*-methylthiocarbamoylthio) propionic acid carried out by refluxing with phosphorus trichloride[416].



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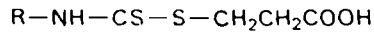
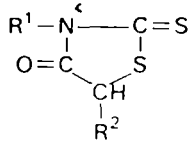


(207)

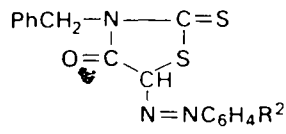
3-Aryl-substituted derivatives of **206** decompose rapidly in absolute ethanol at room temperature to give aryl isothiocyanate. However as stated by Garraway[416], there exists no evidence indicating the formation of β-(*N*-arylthiocarbamoylthio) propionic acids (**207**) as intermediates. As a matter of fact, these compounds undergo a rather slow decomposition to yield aryl isothiocyanates. As for the decomposition of *N*-alkyl-substituted derivatives, the situation is different. For instance, the 3-methyl derivative underwent a ring fission in absolute ethanol and, by comparing the ultraviolet absorption spectra, it was found that the corresponding derivative **207** was the final product. However, in aqueous alkaline solutions the intermediate formed must participate in an ionization equilibrium through the hydrogen atom attached to nitrogen and the decomposition will go on to form isothiocyanate (see Section IV.C).

G. N-Substituted Rhodanines

Rhodanines (**208**) represent a well studied group of substances, the synthesis, structure and properties of which have been described in original papers[433-444] and reviews[445,446]. The formation of rhodanines as final



(208)

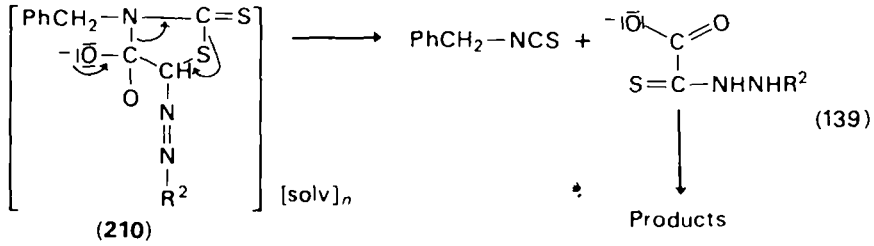


(209)

products of the reactions between acids is discussed in Section VI of this chapter. 3-Substituted rhodanines are usually regarded as substances with antimicrobial activity attributed to the formation of isothiocyanates.

Talukdar[442] studied the p*K* values and kinetics of alkaline hydrolysis of 3-benzyl-5-azorhodanines (**209**). According to the character of the substituents R^2 the p*K* values in a buffered system in the presence of 40% methanol at 25 °C varied from 7·2 to 8·1, but the plot of the p*K* values against

the Hammett's (σ) or Taft's (σ_R) constants of substituents showed a break at about $\sigma = 0{\cdot}4$. According to kinetic studies by this author[443] the decomposition proceeds via solvated anion **210** to the transition complex, and the participation of a solvent molecule in this process causes a fission of the rhodanine ring (equation 139).



(210) (139)

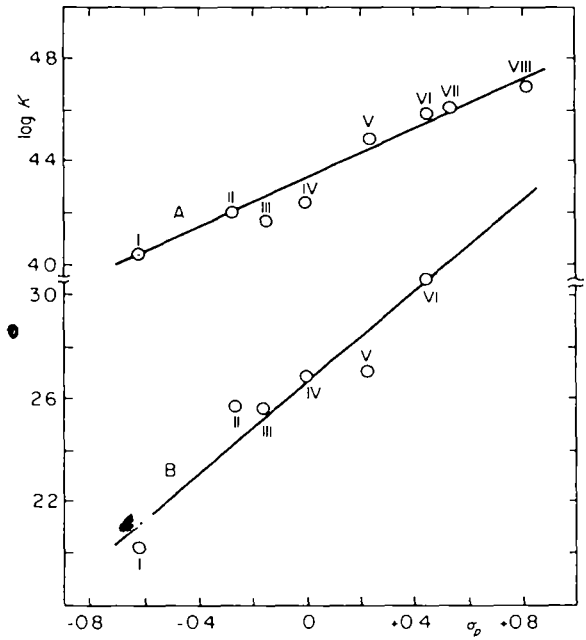


FIGURE 2. (A). Relationship between rate constants k of the splitting of heterocyclic moiety of *N*-substituted 2-thiohydantoins (**216**, R^2 = H) and Hammett constants σ_p of the substituents R—C_6H_4—: 0·1 M-borate buffer pH 9·8, 25 °C. I, 4-dimethylaminophenyl; II, 4-methoxyphenyl; III, 4-methylphenyl; IV, phenyl; V, 4-bromophenyl; VI, acetylphenyl; VII, 4-carbethoxyphenyl; VIII, 4-nitrophenyl; r = 0·94, ρ = 0·871 (according to Knoppová and coworkers[451]).

(B). Relationship between rate constants of formation of isothiocyanates from *N*-substituted rhodanines (**208**, R^2 = H) and Hammett constants σ_p of the substituents R—C_6H_4—: 0·1 M-McIlvaine buffer, pH 8·4 at 25°C. Substituents I–VI as in the previous case: r = 0·97, ρ = 1·85 (according to Knoppová and Drobnica[440]).

3-Arylsubstituted rhodanines (**208**) where R^2 is hydrogen, decompose in buffered systems at pH values exceeding 7·4 to give isothiocyanate and thioglycollic acid without any observable formation of *N*-substituted thiocarbamoylmercaptoacetic acids as intermediary products. The rate constant of this decomposition depends on the concentration of OH^- ions. It has been found[440,446] that a relationship with the values $r = 0{\cdot}97$, $\rho = 1{\cdot}85$ and $n = 8$ exists between the values of the Hammett's σ_p constants of the substituents RC_6H_4 and the logarithms of the rate constants k (min^{-1}) at pH 8·4 and 25 °C (Figure 2).

On the other hand, 3-alkyl-substituted rhodanines in a neutral or mild alkaline medium decompose to produce the corresponding thiocarbamoylmercaptoacetic acids (**211**).

$$R^1{-}NH{-}CS{-}S{-}CH_2{-}COOH$$

(**211**)

Subsequently these substances can split into isothiocyanates, but the rate of splitting of the heterocyclic moiety is an order of magnitude lower than the rate of splitting of rhodanines into isothiocyanates and thiol.

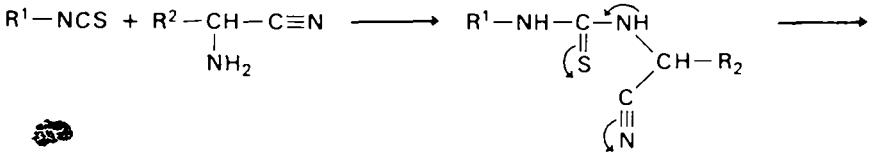
H. N-*Substituted Thiohydantoins*

The structure, preparation and properties of thiohydantoins are described in reviews[447-449]. 3- and 3,5-Substituted 2-thiohydantoins are formed in the reaction between isothiocyanates and the amino group of amino acids followed by cyclization of substituted thioureido acids.

Furthermore, isothiocyanates can afford 3,5-disubstituted thiohydantoins by the reaction with α-aminonitriles (**212**) via thioureidonitrile (**213**) which cyclizes immediately to form 2,5-diaminothiazol (**214**). By boiling with hydrochloric acid this substance affords 3,5-disubstituted-2-thiohydantoin (**216**) probably via thioureido acid (**215**)[449,450].

3-Substituted-2-thiohydantoins decompose in slightly alkaline solutions by opening the heterocyclic ring to give the corresponding thioureido acids (**215**). These substances as other *N,N*-disubstituted thioureas are quite stable in slightly acid, neutral, and slightly alkaline solutions.

The rate of decyclization of thiohydantoins was found to be a function of the concentration of OH^- ions. It may be assumed that OH^- ion attacks the electron-deficient carbon atom of the carbonyl groups in the thiohydantoin ring (equation 140)[446,451]. A similar mechanism of the opening of heterocyclic ring was also suggested for the decomposition of 3-substituted azorhodanines[442]. A correlation with the values $r = 0{\cdot}94$, $\rho = 0{\cdot}871$, $n = 6$



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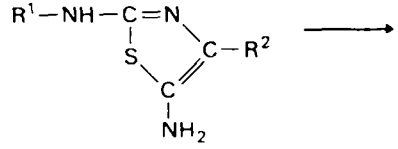

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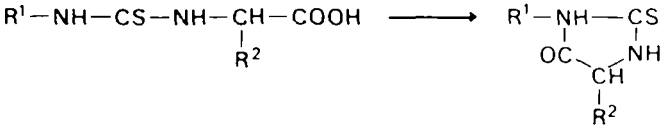

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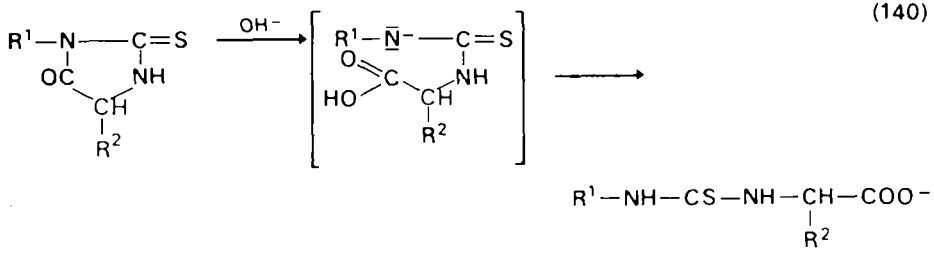
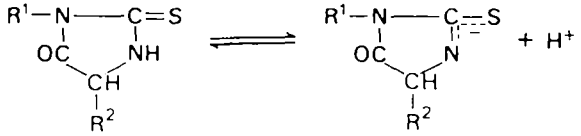
was found to exist between the Hammett's σ_p constants for the substituents $R—C_6H_4$ in position 3 of thiohydantoin ring and the logarithms of the rate constants k (min^{-1}) at pH 9·77 and 25 °C[446].



(140)

Thiohydantoins are able to ionize in alkaline solutions according to equation (141)[452].

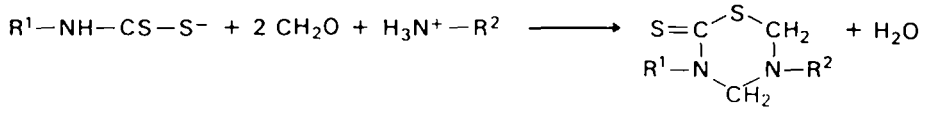


(141)

Owing to the above-mentioned stability of thioureido acids resulting from opening of the thiohydantoin ring under mild conditions, thiohydantoins are not considered to be synthetic producers of isothiocyanates in this sense of the word.

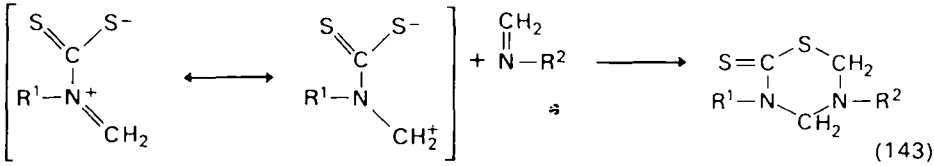
I. 3,5-Disubstituted Tetrahydro-1,3,5-thiadiazine-2-thiones

These substances have been known since 1848[453] but their correct structure was only confirmed as late as 1944[454]. They occur in the reaction of *N*-monosubstituted dithiocarbamate with formaldehyde and primary amines (equation 142). There are several modifications of this reaction[454–457].



(217) (142)

Several working teams[455–459] were concerned with the synthesis and physico-chemical properties of thiadiazines. The biological activity of these substances has also been thoroughly studied[455,460–466]. According to Huisgen[467] the formation of thiadiazines may be regarded as a 1,4-dipolar cycloaddition (equation 143).

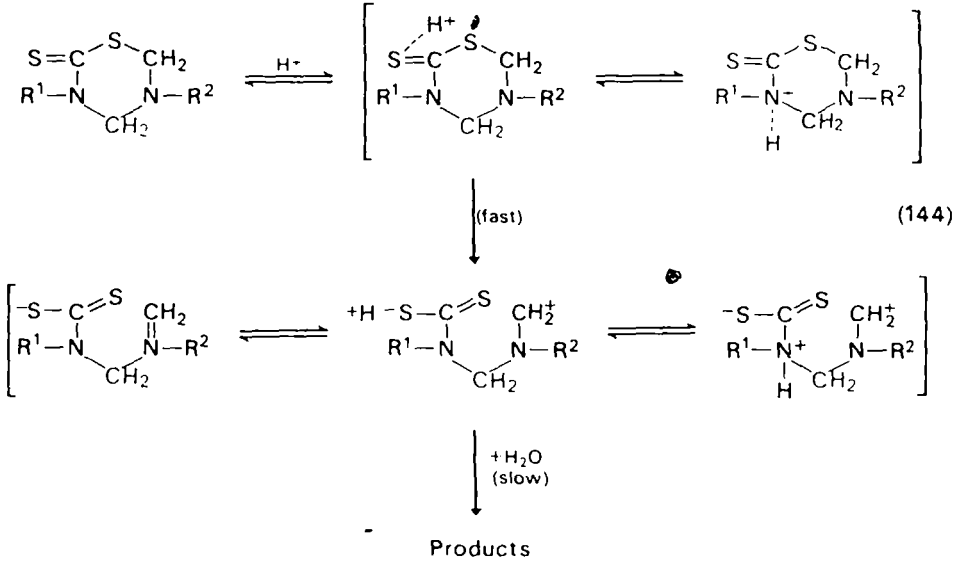


(143)

By analogy with other producers of isothiocyanates, the final products of thiadiazine decomposition depend on the pH value of the reaction mixture. The final products of the cleavage in an acid medium are primary amines, carbon disulphide and formaldehyde. This is used for the analytical determination of thiadiazines which is based on the estimation either of amine or carbon disulphide released.

The kinetics of the decomposition of thiadiazines in an acid medium were studied by Talukdar[468]. He revealed a linear relationship between the rate of decomposition k_{obs} and hydrogen ion concentration as well as a change in the character of this relationship which appeared if the pH value of the reaction medium passed from the acid to the neutral region. The acid decomposition of thiadiazines is supposed to follow the mechanism given by equation (144).

It has been proved by many authors that isothiocyanates are formed as reaction products by the cleavage of thiadiazines. For the decomposition of thiadiazines in a neutral or alkaline medium Talukdar and coworkers assume a direct formation of isothiocyanate due to a decay of the structure formed by the addition of OH^- ions to thiadiazine[468]. Detailed study has.



(144)

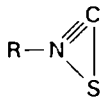
however, demonstrated that the decomposition of thiadiazine in an alkaline medium affords *N*-monosubstituted dithiocarbamates[327,466]. The rate of formation of dithiocarbamates was a linear function of the concentration of OH^- ions. In the pH region from 10 to 14 the formation of isothiocyanate was not observed and the presence of monothiocarbamate which ought to arise from isothiocyanate in such an alkaline medium was not proved either. In a slightly alkaline or neutral medium the decomposition of thiadiazines proceeds in two stages which may be distinguished on the corresponding kinetic curves. The first one is the opening of the thiadiazine ring leading to dithiocarbamate and the second one is the decomposition of dithiocarbamate to isothiocyanate. The mechanism depicting the opening of thiadiazine ring after the addition of OH^- ions and the decomposition giving dithiocarbamate has not been unambiguously cleared up yet.

V. STRUCTURE OF THE —NCS GROUP

A. Introduction

During the development of the chemistry of isothiocyanates there were great changes in the views on the structure of the NCS group.

As early as in 1930, on the basis of the Raman spectra of isothiocyanates, Dadieu and Kohlrausch[469,470] suggested a cyclic structure with triple bond (**218**) for the NCS group.



(218)

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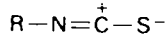
(220)

They deduced from the position of the band in the region 2000–2200 cm^{-1} that a triple bond was present. This idea is in contradiction with the modern concepts of organic chemistry. Earlier, Perschke[471] confirmed the linear structure of the NCS group, but he was not able to decide whether the NCS group contained a system of cumulated double bonds (**219**) or had an ionic structure with a triple bond (**220**). On the basis of the study of dipole moments and Raman spectra of some aromatic isothiocyanates Bergmann and Tschudnowski[472] rejected the cyclic structure and proposed a linear structure (**220**). Starting from the study of Raman spectra other authors[473,474] have assumed a considerable contribution by the mesomeric structure (**220**) to the real structure of isothiocyanates. Goubeau and Gott[475] are of a different opinion. They deduced from the Raman spectra of alkyl isothiocyanates and alkyl thiocyanates that cumulated double bonds (**219**) occur in the structure of isothiocyanates. Linnet and Thompson[476] calculated the force constants of individual bonds in the NCS group and assume that the real structure is a hybrid of mesomeric structures (**221** and **219**).



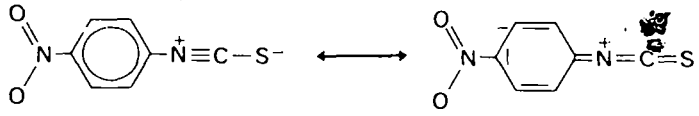
(221)

From the data obtained from the microwave spectrum of methyl isothiocyanate, Beard and Dailey[477] calculated the following bond lengths and bond angles: H—C, 1·09 Å; C—N, 1·47 Å; N—C, 1·22 Å; C—S, 1·56 Å; N—C—N, ∡ 109°; C—N—C, ∡ 142°; N—C—S, ∡ 180°.

Dousmanis and coworkers[478] applied microwave spectroscopy to the determination of the bond lengths and bond angles of isothiocyanic acid and its deuterated analogue—HNCS: C—S, 1·5609 Å; N—C, 1·21658 Å; H—N—C, ∡ 130° 15′; DNCS: D—N, 1·003 Å; D—N—C ∡ 132° 16′.

Williams[479] analysed the infrared spectrum of phenyl isothiocyanate in the region 650–3000 cm^{-1} and considered structure **220** to be the most probable. By comparing the infrared spectra of thiocyanates and isothiocyanates, Lieber and coworkers[480] have come to the conclusion that the prevailing structure of isothiocyanates is the mesomeric structure **220**. For aryl isothiocyanates with a strong electron-withdrawing substituent,

they also propose a contribution from the mesomeric dipolar structure possessing a longer cumulated system (**222**) to the isothiocyanate structure



(**220a**) (**222**)

In one of the fundamental papers on the infrared spectra of isothiocyanates, Ham and Willis[481] discuss the structure of the NCS group in connection with the analysis of vibration frequencies of methyl isothiocyanate. They disapprove structure **220** suggested by Hibben and assume that cumulated double bonds (structure **219**) occur in the NCS group.

The ultraviolet and infrared spectra of aliphatic and aromatic isothiocyanates were studied by Svátek and coworkers[482]. On the basis of the analysis of Raman and infrared spectra they assumed an electron distribution approximating dipolar structure **220** to be present in the NCS group and attribute the absorption in ultraviolet region to the allowed N → V transition which gives rise to cumulated multiple bonds (**219**). They explain the shift of the absorption bond ν_{NCS} from 2100 cm^{-1} to 2054 cm^{-1}, observed with phenyl isothiocyanate, by a conjugation effect which reduces the contribution of the hybrid with triple bond in a molecule of isothiocyanate and favours structure **222**.

B. Polar Character of the NCS Group

1. Substituent constants

The substituent constants are very important for a quantitative evaluation of induction and mesomeric effects of the NCS group. From earlier information about the structure of the NCS group it has not been clear whether this group is able to enter into mesomeric interaction with conjugated systems. A very limited amount of interaction between this group and aromatic carbon residues was inferred from the values of half-wave potentials of polynuclear isothiocyanates[483] as well as slight differences in the π electron densities on skeleton carbons calculated for phenyl, 1-naphthyl and 2-naphthyl isothiocyanates[484].

By using the dissociation constants of the isothiocyanate derivative of benzoic acid and dimethylaniline, Kristian and coworkers[485] determined the Hammett constants σ_m and σ_p for the NCS group (Table 5). The

TABLE 5. pK_a Values of derivatives of benzoic acid and dimethylaniline and the Hammett constants of the isothiocyanate group[485]

Substance	Medium	pK_a^a of derivatives			$\sigma_{m(NCS)}$	$\sigma_{p(NCS)}$
		H	*m*-NCS	*p*-NCS		
Benzoic acid	A	5·23	4·9	4·9	0·32	0·32
	B	6·63	5·81	5·99	0·49	0·38
Dimethylaniline	A	4·8	3·1	3·1	1·7	1·7
	B	3·4	2·6	2·7	0·8	0·7
	C	4·35	3·20	3·20	0·34	0·34

[a] The pK_a values were determined spectrophotometrically in medium A and potentiometrically in B and C. A: 50% methanol-50% water, 20 ± 2 °C, ρ = 1·085 ± 0·062[488]; B: 80% methylcellosolve 20% water, 25 °C, ρ = 1·68 ± 0·05[488]; C: 50% ethanol 50% water, 20 °C, ρ = 3·369 ± 0·042[488]. The accuracy of the determination of pK_a values of benzoic acid and dimethylaniline (potentiometric) is ±0·05; in other cases ±0·1 pK_a units.

difference between the values of σ_m and σ_p, found potentiometrically, evidently represents the ability of the carboxylic group exhibiting the −M effect to produce to a certain extent a more marked mesomeric interaction in the NCS group than in other systems studied.

Furthermore, these authors proved, by comparing the pK_a values of the isothiocyanate derivatives of acridine with the pK_a values of non-substituted acridine and some of its derivatives, that the NCS group showed an electron-withdrawing character which could be ascribed to its induction effect. Antoš and coworkers[489] determined the Hammett constants σ_p for the NCS group by correlating these constants with the vibration frequencies of the hydroxyl and carbonyl groups of phenols, benzoic acids and acetophenones (from the correlation with phenols $\sigma_{p(NCS)} = +0·34 \pm 0·07$, benzoic acids $\sigma_{p(NCS)} = 0·48 \pm 0·15$, and acetophenones $\sigma_{p(NCS)} = 0·32 \pm 0·13$). In the range of experimental error these results are in good agreement with the preceding data and confirm the electron accepting character of the NCS group.

For the determination of inductive effects we usually use the values of dissociation constants of the derivatives of bicyclo[2.2.2]octane carboxylic acid[490], α-substituted *para*- and *meta*-toluyl acids[491], and the esters of α-substituted acetic acid[492] as well as the chemical shifts of the ^{19}F n.m.r. spectra of *meta* substituted fluorobenzenes[493]. (The last method was subjected to criticism recently[494] and is not likely to be used in future.) By using the σ_I values obtained, it is then possible to calculate σ_M by subtracting the share of induction from the total value σ_p. Kristián and coworkers[190] used the infrared spectroscopic method for the determination of the inductive effect of the NCS group. They chose the α-substituted

4-nitrotoluenes as model compounds and assumed that the substituents bonded to the aromatic ring through the methylene group would influence the electronic structure of the nitro group only by their inductive effect. This assumption was confirmed by the ultraviolet spectra of the investigated derivatives, the substituents of which did not affect the position of absorption maxima. They estimated the inductive effect of the NCS group from the linear correlation between ν (as NO_2) and σ_I while they used the corrected values of the empirical constants ($\sigma_{I(NCS)} = +0{\cdot}71 \pm 0{\cdot}19$; $r = 0{\cdot}998$, $\rho = 10{\cdot}84 \pm 0{\cdot}80$). These authors calculated the mesomeric effect from the experimental values of $\sigma_{I(NCS)}$ (obtained spectrophotometrically) and $\sigma_{p(NCS)}$ (obtained potentiometrically). The results show that the NCS group is characterized by a medium +M effect. $\sigma_M = -0{\cdot}33$. By introducing convenient coefficients into the Taft equations Exner[495] calculated from the values of σ_m and σ_p for the NCS group that $\sigma_I = 0{\cdot}54$.

2. Electron transfer effects

Further information about the structure and properties of the NCS group was obtained from the correlation between spectral or polarographic values and the Hammett constants. Rao and Venkataraghavan[496] investigated the dependence of the positions and intensities of vibration frequencies of different groups, including the NCS group, on the Hammett σ, Brown σ^+ and Taft σ^* constants. They found that the relationships ν versus σ and log A versus σ were linear. By correlating the values of log A and σ for different series of compounds they determined the relationship between the sign of the constant ρ and the polar character of a group. These relationships exhibit positive values of the constant ρ for compounds with an electron-donating substituent (e.g., phenols, anilines) and negative values for compounds with an electron-withdrawing substituent (e.g., nitro compounds, nitriles). At the same time the magnitude of the value of ρ is a measure of the intensity of the effect of a group. The slope decreases with increasing electron-accepting character of the group. The authors assign mesomeric structures **220** and **222** to isothiocyanates and conclude that for electron-withdrawing substituents, structure **222** is effective because the intensity of the bond of the NCS group increases with the electron-accepting effect of the substituents (the dipole moment of the bond increases). According to these authors the positive value obtained for the series of *meta*- and *para*-substituted phenyl isothiocyanates indicates the electron-donating character of the NCS group. Kristián and coworkers[181,497] investigated the vibrational frequencies and integrated intensities of the absorption band of the NCS group present in 23 *meta*- and *para*-substituted phenyl isothiocyanates, which were dissolved in solvents of

different polarities for the purpose of studying the structure of the NCS group. They correlated the measured values of $\nu_{as(NCS)}$ and $\log A$ with the Hammett σ_m or σ'' constants. It was not possible to draw unambiguous conclusions from the results thus obtained. A good correlation between $\nu_{as(NCS)}$ and the constants σ'' as well as the shift of the frequencies $\nu_{as(NCS)}$ consistent with the character of substituents indicated a slight mesomeric interaction between the NCS group and substituents and could be regarded as a manifestation of mesomeric structure with triple bond (**220**). On the other hand, the dependence of the integrated intensities $\log A$ (NCS) on σ_m and σ'' in carbon tetrachloride and chloroform was linear with a positive value for the slope ρ, suggesting an electron-donating character for the NCS group and the manifestation of structure **222**[66].

Antoš and coworkers have published several papers dealing with the transfer of the electron effects of substituents through different conjugated systems of isothiocyanates. The transfer coefficients π' calculated according to Jaffe[486] from spectral and polarographic data for different series of compounds are presented in Table 6 and Table 7. The series of substituted phenyl isothiocyanates (benzene system) with reaction constant $\rho^* = -54{\cdot}89$ (Table 6) or $\rho^*_{\pi,R} = +0{\cdot}22$ (Table 7) and coefficient $\pi' = 1$ was used as a reference standard. From the tabulated values it follows that the induction and mesomeric effects if the substituents in conjugated systems are considerably hindered. The lowest values of transfer were found for 4'-substituted 4-isothiocyanatobenzophenones ($\pi' = 0{\cdot}27$, Table 6) and diphenylsulphones ($\pi' = 0{\cdot}03$, Table 7).

3. Dipole moments and electronic interactions

The results of the study of the dipole moments of isothiocyanates provide important information on the structure and polar character of the NCS group. The values of the dipole moments of isothiocyanates unambiguously indicate the electron-accepting character of the NCS group with the negative end of dipole at the sulphur atom (Table 8). The problem of the structure and spatial arrangement of aromatic isothiocyanates is treated in a paper by Antoš and coworkers[501]. On the basis of the zero value of the dipole moment of *p*-phenylene diisothiocyanate they assume a possible coaxial arrangement of the NCS group with respect to the axis of the benzene ring with the C—N—C angle close to 180° as well as the manifestation of mesomeric structures **220** and **222**. On the other hand, the value of the C—N—C angle (163°) calculated from the experimental value of the dipole moment of *p*-chlorophenyl isothiocyanate represents the mean of the value (142°) suggested for this angle by Hamm and Willis, and the value (180°) from the

TABLE 6. Electron transfer effects of substituents through different conjugated systems of isothiocyanates expressed in terms of the constant ρ and coefficient of electron transfer π, the values of which were obtained from the correlation between $\nu_{as(NCS)}$ and the Hammett constants $\sigma(\rho^* =$ reaction constant of benzene system).

No.	System	Number of investigated derivatives	Reaction constant ρ	Correlation coefficient, r	π' (ρ/ρ^*)	Reference
1	Benzene	23	−54·89	−0·979	1	181
2	Stilbene	8	−23·7	0·95	0·43	196
3	Biphenyl	11	−20·11	−0·992	0·37	202
4	Azobenzene	8	−19·77	0·97	0·36	198
5	Diphenyl sulphide	7	−19·77	−0·951	0·36	194
6	Diphenylmethane	6	−18·60	−0·989	0·33	191
7	Diphenyl oxide	6	−15·8	0·968	0·28	193
8	Benzophenone	6	−14·8	0·92	0·27	195

TABLE 7. Electron transfer effects of substituents through different conjugated systems expressed in terms of the reaction constant $\rho_{\pi,R}$ and coefficient of electron transfer π', the values of which were obtained from polarographic data. (The isothiocyanate group occurs in the *para* position with respect to other substituents; ρ^* = reaction constant of benzene system.)

No.	System	Number of investigated derivatives	$\rho_{\pi,R}$ [V]	π' $\rho_{\pi,R}/\rho^+_{\pi,R}$	Correlation coefficient, r	Reference
1	Benzene	10	+0·22	1	0·96	499
2	Biphenyl	7	+0·07	0·32	—	202
3	Stilbene	8	+0·065	0·30	0·989	500
4	Diphenyl sulphide	6	+0·052	0·24	0·995	500
5	Diphenyl sulphide	6	+0·048	0·22	0·932	500
6	Diphenylmethane	6	+0·042	0·19	0·940	500
7	Diphenyl sulphone	7	+0·007	0·03	0·571	500

TABLE 8. Dipole moments of isothiocyanates

No.	R	μ(D) Benzene	Reference	No.	R	μ(D) Benzene	Reference
1	Methyl	3·18	512	7	4-Bromophenyl	1·54	472
2	Ethyl	3·31	512	8	3-Chlorophenyl	2·59	501
3	Allyl	3·30	512	9	4-Chlorophenyl	1·55	472
4	*t*-Butyl	3·73	501	10	4-Nitrophenyl	1·23	501
5	Phenyl	2·91	513	11	3-Isothiocyanatophenyl	2·78	501
6	4-Tolyl	3·32	472	12	4-Isothiocyanatophenyl	0	501

preceding statement. The differences between the experimental and calculated values of the dipole moments of substituted phenyl isothiocyanates ($\Delta\mu = 0{\cdot}09 - 0{\cdot}16$ D) do not indicate any notable mesomeric interaction between the NCS group and the aromatic ring.

It follows from the character of the NCS group that it is not possible to perform the electrophilic substitution reactions of phenyl isothiocyanates without attacking the reactive NCS group. By using the values of the dipole moments of phenyl isothiocyanate and *t*-butyl isothiocyanate and the method of Ri and Eyring[502] they calculated the values of charge distribution on individual atoms for phenyl isothiocyanate as well as the theoretical yields of nitration (Figure 3). The values presented in Figure 3 show that the

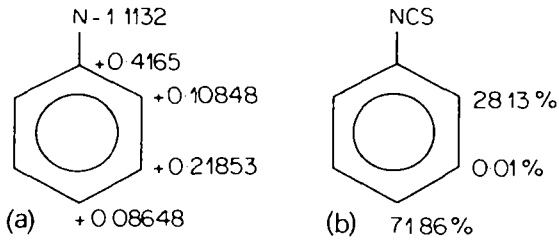


FIGURE 3. Values of electron charge and theoretical yields of nitration of phenyl isothiocyanate calculated by the method of Ri and Eyring. (a) Distribution of electron densities on individual atoms. (b) Theoretical yields of nitration.

NCS group has an effect on the aromatic ring which is analogous to that of halogens and exhibits +M and −I effects.

Suchár and Kristián[503] studied the dipole moments of 4-substituted phenyl isoselenocyanates and *t*-butyl isoselenocyanate and compared the results with the results obtained with the corresponding sulphur and oxygen analogues.

It is interesting that the magnitude of the dipole moments of these heterocumulenes does not depend on the electronegativity of their terminal heteroatom and increases in the order $\mu_{NCO} < \mu_{NCS} < \mu_{NCSe}$ (Table 9). The authors assume that the cause of this phenomenon is the change of the C=X bond lengths (X = Se, S, O) and bond moments as well as the change of polar character of this double bond due to the decreased π-bond interaction between the 2pπ, 3pπ, and 4pπ orbitals of the heteroatom and the 2pπ orbital of the carbon atom. As the changes in the dipole moments of heterocumulenes may also be related with a different mesomeric interaction between the —N=C=X groups (X = O, S, Se) and the aromatic ring, the authors tried to solve this problem by determining the geometry of these

TABLE 9. Experimental values of dipole moments (in debyes) and calculated C—N—C bond angles of heterocumulenes 4-$ClC_6H_4N{=}C{=}X$

X	μ_{exp}	$\mu_{C_6H_5-NCX}$	$\Theta°$	∢C—N—C
Se	2·04	3·41	23	154
S	1·51	2·91	18	159
O	0·84	2·28	14	163

groups and calculating the dipole moments of their limit mesomeric structures. They applied the graphical method of van Woerden and Having[504] to the calculation of the C—N—C angle of the NCS group of phenyl isothiocyanate and determined the group moment of the NCS group (μ_{NCS} = 2·91 D) and the C—N—C bond angle (∢C—N—C = 164°). For isocyanates and isoselenocyanates the calculation was carried out only on the basis of the values of the 4-chlorophenyl derivative (Table 9). The example of isothiocyanates shows that the values obtained by both the methods are in good agreement (∢C—N—C = 164°, 159°). The calculation of dipole moments of the limit mesomeric NCO, NCS, and NCSe structures bonded to the aromatic ring was performed graphically by using vectorial addition of bond moments (Table 10). On the basis of a comparison of the

TABLE 10. Calculated values of dipole moments (in debyes) of mesomeric structures

X	—N=C=X (A)	$-\dot{N}\equiv C-X^{\cdot}$ (B)	$-N=\overset{+}{C}-X^{-}$ (C)
O	1·00	0·59	5·80
S	1·06	11·72	7·90
Se	--	12·57	8·80

experimental values of the dipole moments of heterocumulenes with the calculated values of their mesomeric structures they assume that structure B contributes only slightly to the real structure of heterocumulenes which may best be expressed by limit structures A and C. Moreover, the authors of that study made an attempt to estimate the mesomeric interaction of those heterocumulenes from the differences between the dipole moments of corresponding aromatic and aliphatic compounds (Table 11). The mesomeric moments μ_M indicate that the mesomeric effect of the NCX groups increases in the order NCO < NCSe < NCS. They assumed that this order is in relation to the magnitude of positive charge on the carbon atom of these groups, i.e. the larger the electron defect on the central atom of

TABLE 11. Experimental dipole moments (in debyes) of aromatic and aliphatic isoselenocyanates, isothiocyanates, isocyanates and values of mesomeric moment μ_M

X	C_6H_5X	$(CH_3)_3CX$	C_2H_5X	μ_M
NCO	2·28	—	2·81	−0·53
NCS	2·91	3·73	3·64	−0·82
				(−0·73)
NCSe	3·41	4·03	—	−0·66

heterocumulenes, the more difficult is their π-bond interaction with aromatic rings. The reactivity of these groups in nucleophilic addition reactions increases in the order NCS < NCSe ≪ NCO which is in agreement with the above mentioned results[505].

In another paper Dzurilla and coworkers[506] were concerned with the study of the dipole moments of cinnamoyl isothiocyanate for the purpose of determining the conformation of the acyl isothiocyanate group. They calculated the dipole moments of the *Z* and *E* conformations of 4-substituted cinnamoyl isothiocyanates by vectorial addition of their bond moments (Table 12, Figure 4). At the first sight, it is obvious from the tabulated values

TABLE 12. Dipole moments of 4-substituted cinnamoyl isothiocyanates in benzene at 20°C[506]

No.	Compound	μ_{exp} (D)	μ_{calc} (D) *Z*	*E*
1	Cinnamoyl isothiocyanate	3·40	3·77	1·02
2	4-Methylcinnamoyl isothiocyanate	3·87	4·15	1·30
3	4-Chlorocinnamoyl isothiocyanate	2·12	2·20	1·10
4	4-Bromocinnamoyl isothiocyanate	2·16	2·42	1·00
5	4-Cyanocinnamoyl isothiocyanate	1·61	0·75	3·34

that the dipole moments measured correspond to the dipole moments calculated for the *Z* conformation. They also confirmed this assumption by the graphical method according to Exner[507] (Figure 5). It follows from this figure that the acyl isothiocyanate group of cinnamoyl isothiocyanates occurring in the *Z* conformation is not planar but forms a dihedral O=C—C=N angle of 53°. Furthermore, they obtained the value of 3·43 D with the angle of 25° with respect to the ethylene bond for the group moment of the CONCS group.

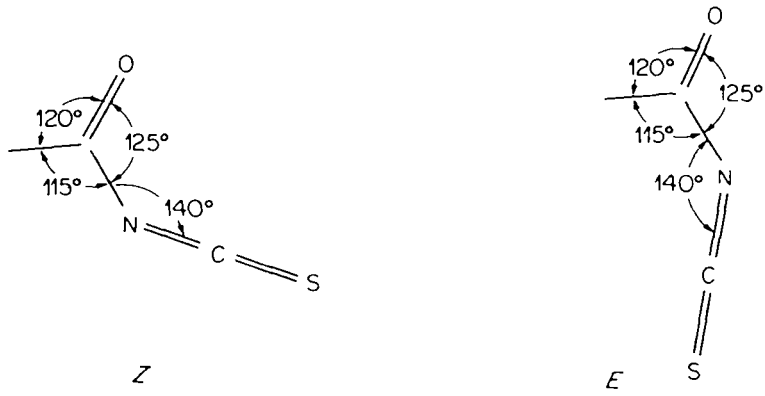


FIGURE 4. Conformational isomers of cinnamoyl isothiocyanates: *Z* conformer, *E* conformer.

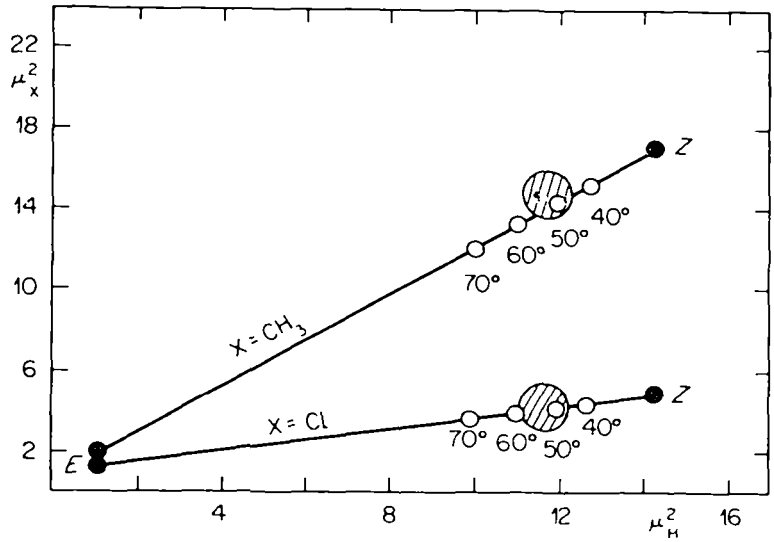


FIGURE 5. Graphical comparison of the calculated and experimental dipole moments of cinnamoyl, 4-methylcinnamoyl and 4-chlorocinnamoyl isothiocyanates. The abscissa represents μ_H^2 for the unsubstituted compound, and on the ordinate axis the μ_X^2 values for 4-substituted derivatives are given. The calculated values for the *E* and *Z* conformers are denoted by empty circles (for the angle 140°) while the experimental value is hatched.

Martvoň[192] investigated the dipole moments of the isothiocyanates of stilbene, azobenzene, diphenyl ether, and diphenylamine with the aim of verifying the possible interactions between the NCS group and these

conjugated systems. He found, from the differences between the values of experimental and calculated dipole moments, that the NCS group in combination with a strong withdrawing substituent (NO_2) exhibited the +M effect to a greater extent than it did in the case of non-substituted derivatives (Table 13).

TABLE 13. Dipole moments of the isothiocyanates of stilbene, azobenzene, diphenyl oxide and diphenylamine measured in benzene at 20 °C[192]

No.	Compound	μ_{exp} (D)	μ_{calc} (D)	$\Delta\mu$
1	4-Isothiocyanatostilbene	3·12	2·9	+0·12
2	4-Isothiocyanatobenzene	2·84	2·9	−0·03
3	4-Isothiocyanatodiphenyloxide	2·97	2·39	+0·56
4	4-Isothiocyanatodiphenylamine	4·44	2·67	+1·8
5	4′-Nitro-4-isothiocyanatostilbene	2·07	1·45	+0·62
6	4′-Nitro-4-isothiocyanatoazobenzene	1·98	1·37	+0.61
7	4′-Nitro-4-isothiocyanatodiphenyl-oxide	3·30	2·67	+0·56
8	4′-Nitro-4-isothiocyanatodiphenyl-amine	4·10	2·8	+1·3

C. Theoretical Calculations and X-Ray Analysis

Zabrodin and coworkers[508] calculated the electronic structures of methyl and phenyl isothiocyanate by using the SCF method in the Parr–Pariser–Pople approximation. Their calculations are based on the assumption that isothiocyanates represent a cumulated system of multiple bonds with a non-delocalized pair of electrons on nitrogen which occurs in an orbital near to sp^2. Such compounds can contain two orthogonal systems of conjugated bonds. One system consists of a π_x nitrogen electron, π_x carbon electron, and π_x^2 sulphur electrons while the other system contains a π_y sulphur electron, π_y carbon electron, and π_y^2 electrons of the free electron pair of nitrogen. The z-axis is oriented in the direction of the NCS group which is linear. For the calculation of the molecules of CH_3NCS and C_6H_5NCS they used the following bond lengths and bond angles: C—N, 1·47 Å; N—C, 1·22 Å; C—S, 1·56 Å; ∠C—N—C, 142°. They assumed that these values were equal for both the molecules while the benzene ring and the NCS group were situated in the same plane, i.e. the yz plane. Later, Zabrodin[509] corrected the calculation for phenyl isothiocyanate in the sense that he considered the angle between the nitrogen bonds to be equal to 180° while

the free electron pair of nitrogen occupied the π orbital. He came to this conclusion on the basis of the results of the determination of the dipole moment of substituted phenyl isothiocyanates according to which the value of the C—N—C angle is near to 180°. Then either of the π-systems of the CNC group can enter into a conjugation with the π electron system of the benzene ring. Since the angle between the nitrogen bonds is, nevertheless, smaller than 180°, Zabrodin assumes that the structure in which the π_x electron system of the NCS group, including the free electron pair of a sulphur atom, enters into conjugation with benzene ring must be the more probable. Schematically, the π electron structure of phenyl isothiocyanate according to Zabrodin and coworkers, may be represented as in Figure 6.

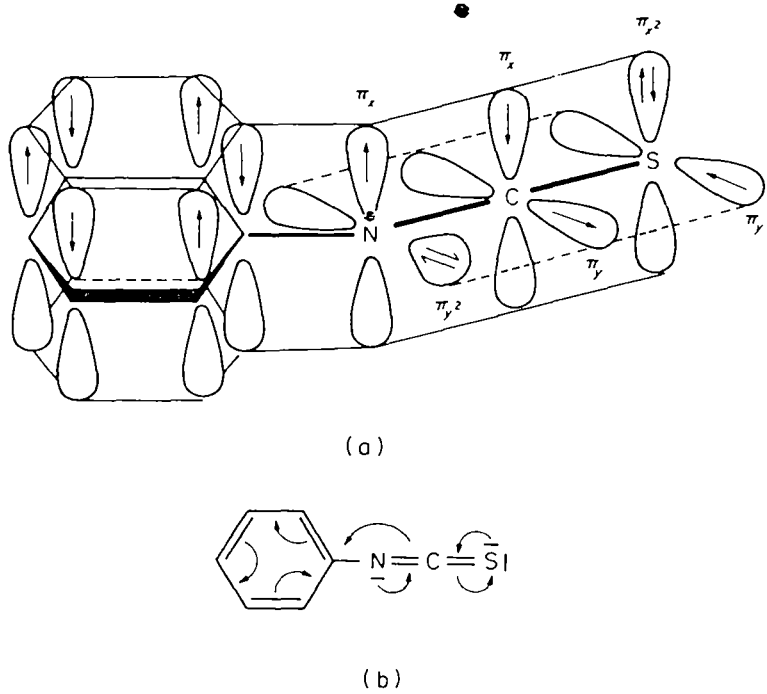
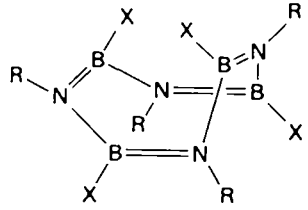


FIGURE 6. Electronic structure of phenyl isothiocyanate. (a) Model of atomic orbitals of two conjugated systems π_x and π_y of the NCS group situated in the yz plane. ∡C—N—C 180°. (b) Illustration of π-electron interactions.

The distribution of the π electron charge in methyl and phenyl isothiocyanate (Table 6) is characterized by considerable negative charge on the atoms of nitrogen and sulphur and positive charge on the carbon atom. The differences in the magnitude of negative charge on the atom of nitrogen and sulphur in methyl and phenyl isothiocyanate are connected with a

possible mesomeric interaction between the π electrons of the NCS group and the aromatic ring. A high electron deficiency of the carbon atom is responsible for its high reactivity in nucleophilic addition reactions. Analogous results concerning the distribution of the π electrons in the NCS group were also achieved by using the simple HMO method for phenyl, 1-naphthyl and 2-naphthyl isothiocyanate as well as β-styryl isothio cyanate[279].

Clarke and Powell[510] determined the crystal and molecular structure of tetra-B-isothiocyanate-tetra-*N*-butylazocine (**223**).



X = NCS
R = *t*-Butyl

(223)

They have found that this molecule contains an eight-membered ring with alternating nitrogen and boron atoms and multiple bonds. Furthermore, the data given in Table 14 show that the NCS group is interacting with the

TABLE 14. Calculated values of the π electron charge and π-bond orders of the NCS group of methyl and phenyl isothiocyanate[508,509]

Substance	Atomic charges			π bond orders	
	Q_N	Q_C	Q_S	π_{NC}	π_{CS}
CH_3NCS[a]	−0·251	+0·338	−0·087	1·212	1·438
C_6H_5NCS[b]	−0·112	+0·320	−0·176	1·495	1·377

[a] The value of the C—N—C angle used for calculation was 142°.

[b] The value of the C—N—C angle used for calculation was 180°.

double B=N bond of the ring. The exocyclic B—N bond (1·431 Å) should correspond to the bond order of 1·39. It is, therefore, shorter than the assumed simple bond. The B—N—C angle (176·42°) is considerably greater when compared with the corresponding angle in a molecule of methyl isothiocyanate (142°) which cannot be in mesomeric interaction with carbon residues. The N—C bond (1·172 Å) is also much shorter than it is in methyl isothiocyanate (1·22 Å). Besides, Table 15 gives the results of X-ray analysis

TABLE 15. Interatomic distances (Å) and C—N—C or B—N—C angles (degrees) of the NCS group calculated for some isothiocyanates

Compound	C—N resp. B—N	N—C	C—S	C—N—C B—N—C	Reference
Methyl isothiocyanate[a]	1·47	1·22	1·56	142	477
4-Bromophenyl isothiocyanate[b]	1·434	1·240	1·627	155·33	511
Tetra-*B*-isothiocyanatotetra-*N*-*t*-butylborazocine[b]	1·431	1·172	1·560	176·42	510

[a] Determined from microwave spectra.
[b] Determined from X-ray analysis.

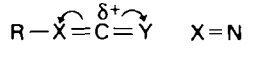
of crystalline 4-bromophenyl isothiocyanate obtained by Ulicky[511]. He has found that the NCS group is in a plane with the benzene ring with respect to the line connecting the atom of bromine, the C_1 and C_4 carbons of the benzene ring and the nitrogen of the NCS group. The C—N—C bond angle (155·33°) and the C—N bond length (1·434) again indicate a possible mesomeric interaction between the NCS group and the aromatic ring though it is less marked than in the case of borazocine derivatives (**223**, Table 15). On the basis of the measured values of the interatomic N—C and C—S distances which are mean values of the double and triple bond for N—C and of the double and single bond for C—S the author supposes that a molecule of 4-bromophenyl isothiocyanate is a resonance hybrid with the mesomeric structures containing a triple $-\overset{+}{N}\equiv C-S^-$ bond or cumulated —N=C=S bonds.

The isothiocyanate group is a medium strong electron-withdrawing substituent with a negative inductive effect and a positive mesomeric effect. From the view-point of directing effect it may be included among *o.p*-orienting substituents. The distribution of the π electron densities on the NCS group is characterized by a negative charge on the atoms of nitrogen and sulphur and a positive charge on the carbon atom. The nucleophilic addition reactions on carbon and cycloaddition reactions on the multiple C=N and C=S bonds are typical reactions of the NCS group. The NCS group itself is linear. The value of the C—N—S bond (140–180°) depends on the character of the carbon residue and thence on the hybridization of the

nitrogen atom in the NCS group. In the molecules of acyl isothiocyanates the acyl isothiocyanate group occurs in the *Z* conformation with the dihedral O=C—N=C angle equal to 53°. The structure of the isothiocyanate group may be expressed only by the limit mesomeric formulae, the contributions of which to the real structure of the molecule are dependent on the structure of the whole molecule.

VI. REACTIONS OF ISOTHIOCYANATES

The foregoing information, as well as the best known reactions of isothiocyanates with different nucleophilic agents, indicate a strong electrophilic character of the NCS group. The electron-withdrawing strength of the carbon atom in the NCS group is most important for these reactions by analogy with the carbon atom in the functional group of isothiocyanates and other typical C-heterocumulenes of structure **224**. The



(224)

presence of such carbon atoms makes reactions of the type Ad_N possible. On the other hand, the mechanism of cycloadditions is different. The NCS group reacts with convenient agents to form 1,2-, 1,3-, and 1,4-cycloadducts. For isothiocyanates it may be assumed that one of the polar resonance structures of the NCS group (equation 145) is effective at the moment of chemical reaction.

$$R-N^{-}-C^{+}=S \longleftrightarrow R-N=C=S \longleftrightarrow R-N=C^{+}-S^{-} \qquad (145)$$

Which of the polar structures is effective depends on the reagent, medium, catalyst, and without doubt, on the radical R to which the NCS group is bound. For the rate of cycloadditions the steric effect of the substituent is of great importance while its electric effect is significant for nucleophilic additions.

Even on the basis of earlier empirical knowledge aryl isothiocyanates were considered to be more reactive than alkyl isothiocyanates, both these types of compounds being still less reactive than analogous isocyanates or carbodiimides. The preparations of acyl, sulphonyl, fluorophosphoryl, thiophosphoryl, aroyl, thioaroyl, imidoyl, carbamoyl, thiocarbamoyl, and other types of isothiocyanates, as well as experience gained in the utilization of these substances for the preparation of new compounds, played an important part in revealing large differences in the reactivity of different

types of isothiocyanates and possibilities in their application as well. This especially concerns the cycloadditions of isothiocyanates more intensively studied in the last decade. The essential problems of the mechanism of these reactions are open to further research. Nevertheless, even simple and long known additions of isothiocyanates have hitherto been applied and explained mostly in an empirical way.

A. Nucleophilic Additions

The most important reactions of this type can be generalized by a common scheme (equation 146) according to which the compounds containing a labile hydrogen, which is able to add in the form of a proton to nitrogen, can react with isothiocyanates while the electronegative residue links with the carbon of the NCS group.

$$R-\bar{N}CS + H-X \longrightarrow R-\bar{N}H-C(=S)-X \qquad (146)$$

According to this reaction scheme it is possible to describe the reactions of isothiocyanates with simple nucleophilic agents such as hydroxyl ions, alcoholates, ammonia, amines, hydroxylamine, hydrazines, alkali sulphides and thiols as well as additions of β-dicarboxylic compounds, carboxylic and thiocarboxylic acids and other compounds. These reactions are described briefly in some earlier surveys[514,36] containing numerous citations of original papers. However, the real evidence in support of a nucleophilic character of important additions of isocyanates results from the research carried out in the last 15 years.

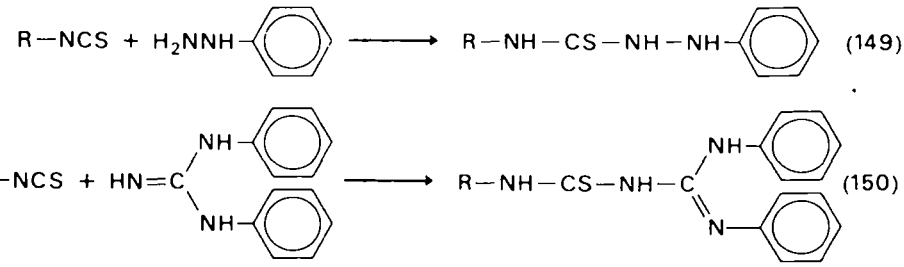
1. Addition of nitrogen bases

The additions of nitrogen bases are utilized to a great extent and therefore they represent the best known reactions of isothiocyanates. By the action of ammonia and primary or secondary amines the corresponding *N*-monosubstituted or even *N,N,N'*-trisubstituted thioureas arise.

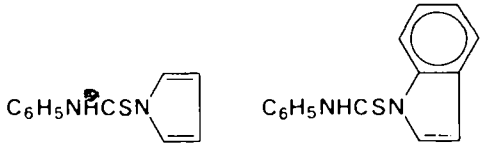
These reactions are also used for the quantitative determination of isothiocyanates or amines[515,516]. In a similar way isothiocyanates react with hydroxylamine (equation 147), hydrazine (equation 148) and its derivatives (equations 149 and 150)[517,518,542] including hydrazides, thiohydrazides, and sulphonohydrazides.

$$R-NCS + H_2NOH \longrightarrow R-NH-CS-NH-OH \qquad (147)$$

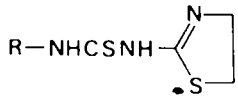
$$2\,R-NCS + H_2NNH_2 \longrightarrow R-NH-CS-NH-NH-CS-NH-R \qquad (148)$$



The reactions between isothiocyanates and heterocyclic compounds with one or more atoms of nitrogen have been relatively less investigated. This fact may be explained mostly by the low reactivity of corresponding amino compounds, their tautomerism, steric and other factors. Of course, this does not hold for strongly basic compounds such as imidazole, which reacts with isothiocyanates easily. Pyrrole reacts with phenyl isothiocyanate to give 2-pyrrole thiocarbanilide (**225**). An analogous product, **226**, is formed in the reaction with indolyl magnesium chloride[519,520].

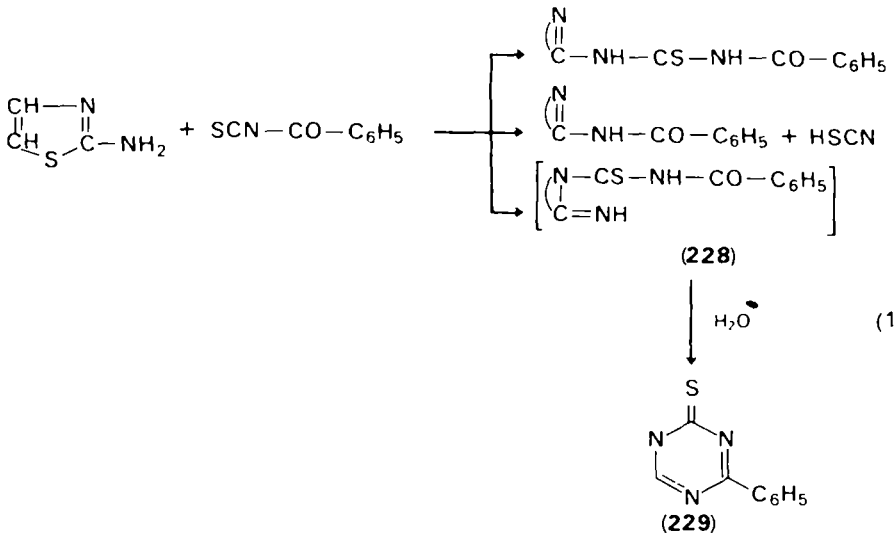


(**225**) (**226**)



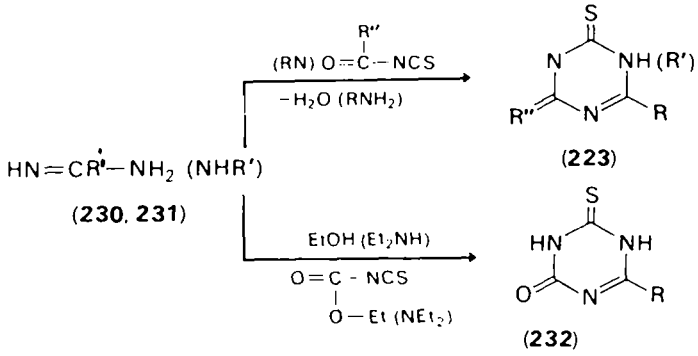
(**227**)

Amino-*N*-heterocycles as ambident amidine systems can react with isothiocyanates through the exo- or endocyclic nitrogen atom[521]. For the reaction of 2-amino-2-thiazoline with isothiocyanates only product **227** was determined[522]. However, the question as to whether the possible reaction with the endocyclic nitrogen atom[523] should be taken into consideration for the more reactive acyl isothiocyanates is still under discussion. On the other hand, owing to the presence of two electrophilic centres in the molecule, acyl isothiocyanates can react with amines to give acyl thioureas and the corresponding amides[524,525,109,526,145]. On the basis of these facts it is possible to explain the formation of at least three identifiable products of the reaction between benzoyl isothiocyanate and 2-amino-thiazole (equation 151) or other amino-*N*-heterocycles[523].



The formation of thiourea **228** as an intermediate is due to the addition of the endocyclic nitrogen atom to the more electrophilic centre of benzoyl isothiocyanate. The subsequent cyclization involving the abstraction of water affords cyclic product **229**. This method of ring closure is analogous to the formation of heterocycles and other products of the reaction between amino compounds and acyl isothiocyanates[527,528], described subsequently (equation 152).

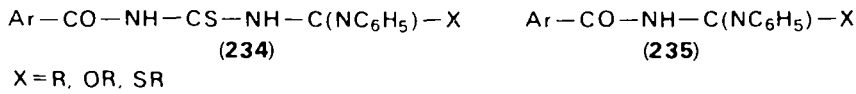
On the basis of earlier studies[529,530] Goerdeler and coworkers investigated in more detail the possibility of preparing triazine thiones by treatment of amidines and amidinoids of types **230** and **231** with acyl isothiocyanates[531,90]. According to the type of isothiocyanate used, triazine thiones of general formula **232** or **233** were prepared (equation 152). As a rule, the intermediates cannot be isolated in the above case.



(152)

R = Alkyl, aryl, RO, RS, R_2N

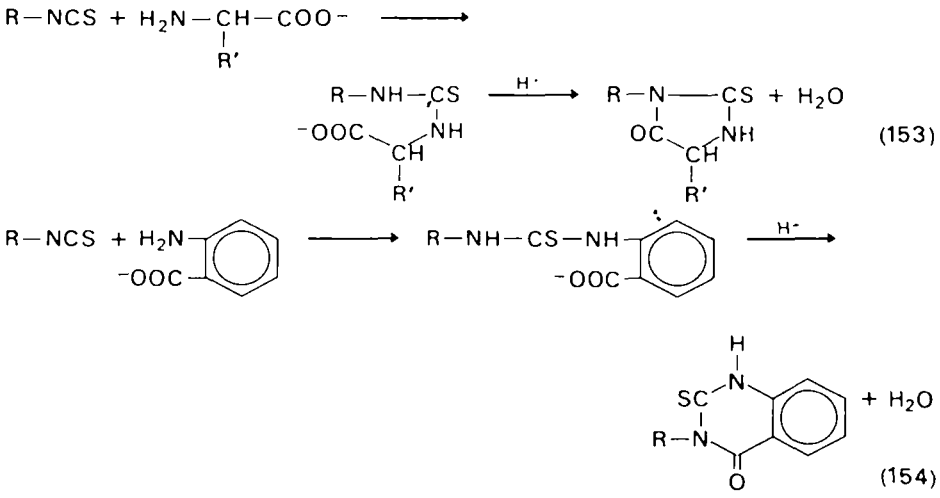
The reaction of aroyl isothiocyanates (and ethoxycarbonyl isothiocyanates also) with *N*-phenylamidino compounds usually affords a mixture of *N*-phenyltriazine thiones and *N*-imidoyl-*N'*-aroyl thioureas **234** (1 : 1 adducts). Triazines originate in the reaction of the *N*-substituted amidines while thioureas are formed by addition to the NH groups of the bases. The latter reaction is the more general one[119]. Furthermore, there is a characteristic side reaction which results in the formation of acyl amidines (**235**) and HSCN.



(234) **(235)**

X = R, OR, SR

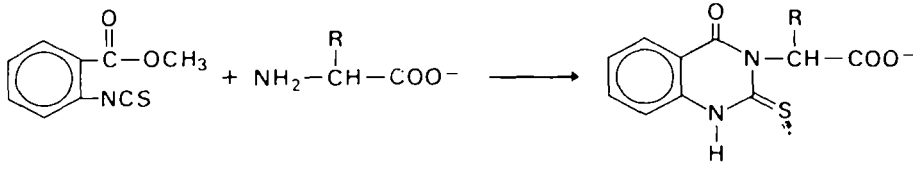
Adducts **234** with suitable groups can be cyclized by treatment in alkali[119]. Other types of heterocyclic compounds may be prepared by the reaction of isothiocyanates with nitrogen bases containing carboxyl or hydroxyl groups in the molecule. This mainly concerns the preparation of the substituted 3-phenyl-2-thiohydantoins described a long time ago[532–536]. The reaction between phenyl isothiocyanate and α-amino acids affords the phenyl thiocarbamoyl amino acid derivatives which cyclize in an acid medium to yield the corresponding 3-phenyl-2-thiohydantoin derivatives (equation 153). The reaction with 2-aminobenzoic acid is analogous (equation 154). The kinetic study of these reactions with different alkyl and aryl isothiocyanates made it possible to define the reaction conditions under which isothiocyanates give, quantitatively, the corresponding addition products and after the cyclization of these products the corresponding thiohydantoins[537].

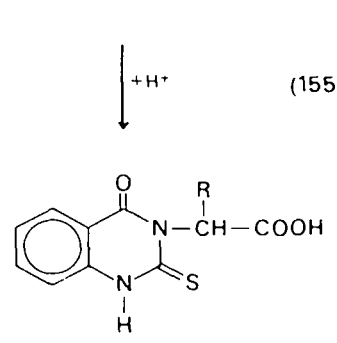


(153)

(154)

The reaction between α-amino acids and 2-carbomethoxyphenyl isothiocyanate in alkaline medium yields tetrahydroquinazoline derivatives (equation 155). In contrast to the foregoing reactions, the carbomethoxy groups (carbon atom of the carbonyl groups) and not the carboxyl group (which is transformed into a non-dissociated form after acidifying) take part in cyclization. If the reaction involves serin (equation 156) or serin-phosphoric acid, a five-membered heterocycle arises after acidifying[538].





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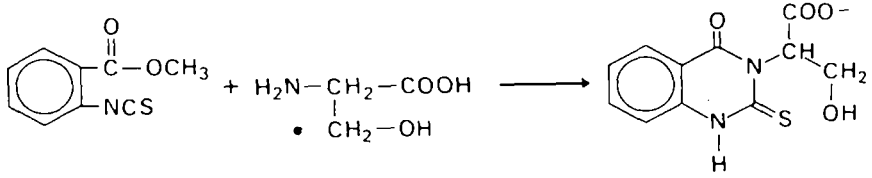
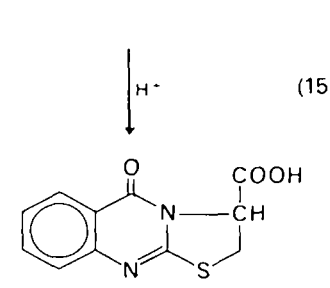
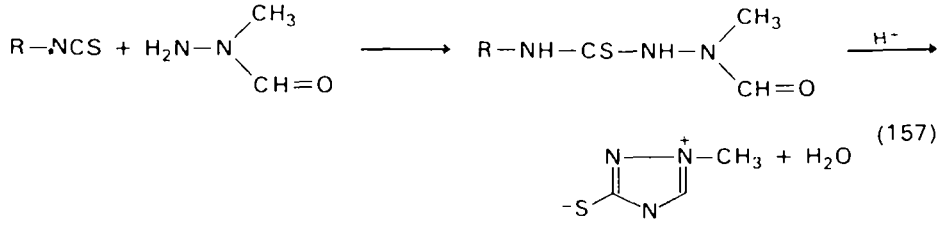




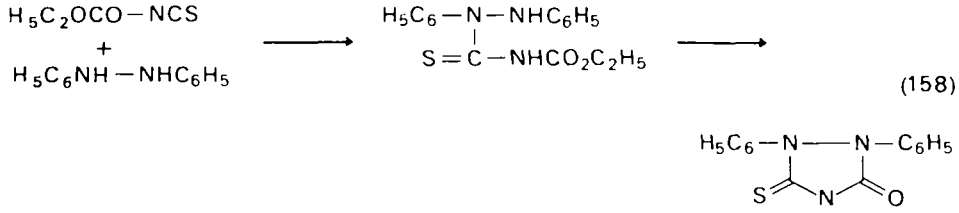
(156)

The reaction between isothiocyanates and 1-formyl-1-methyl hydrazine, followed by cyclization of the addition product, yields mesoionic 1,2,4-triazole derivatives (equation 157).



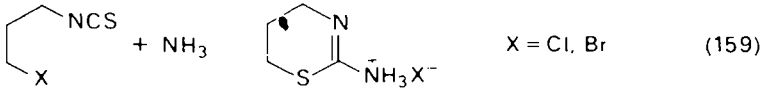
(157)

Another example of the use of acyl isothiocyanates in the preparation of heterocyclic compounds is their reaction with hydrazobenzene. The corresponding 4-acyl thiosemicarbazides, which split off ethanol spontaneously and cyclize during crystallization to give the 1,2-diphenyl substituted 5-thioxo-1,2,4-triazolidine-3-ones[540], are formed in that reaction (equation 158).



(158)

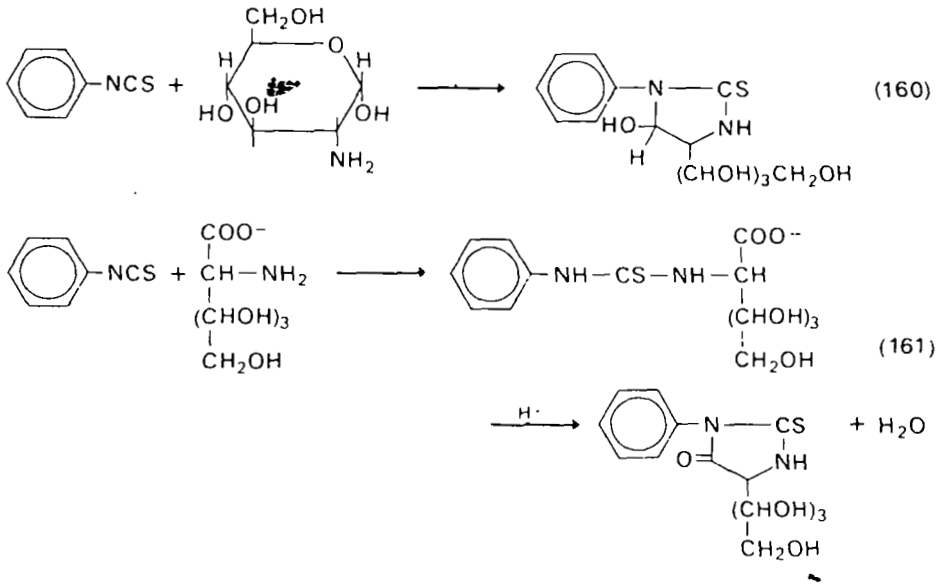
By using the reaction between the 3-halogen substituted propyl isothiocyanates and ammonia in methanol, the 2-amino-5,6-dihydro-4*H*-1,3-thiazines were prepared (equation 159)[180].



(159)

In general, it is assumed that amino sugars such as glucosamine, galactosamine, ribosamine, etc., react to yield the corresponding thiocarbamoyl derivatives. Nevertheless, Scott presented evidence in his, regrettably, rarely cited paper[541] that in contrast to the mentioned amino sugars, glucosamine reacts under the same conditions with phenyl isothiocyanate to give 4-hydroxy-3-phenyl-5-tetrahydroxybutylimidazolidenethione, i.e. the addition product cyclizes spontaneously (equation 160). Cyclization of the addition product of phenyl isothiocyanate with 2-aminogluconic acid is accomplished only in acid medium yielding the 3,5-disubstituted thiohydantoin[541] (equation 161).

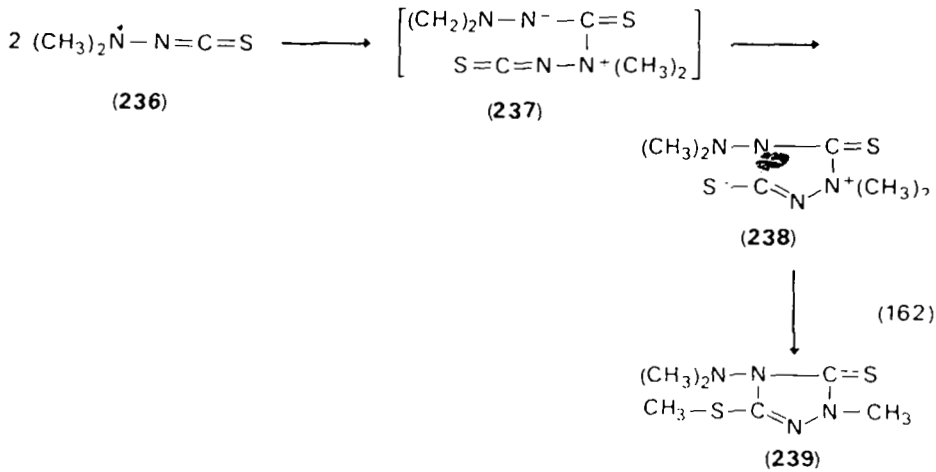
In general, *N*-isothiocyanatoamines represent a class of highly unstable isothiocyanates which dimerize on standing[543]. *N*-Isothiocyanatodimethylamine **236** dimerizes at room temperature in less than one minute[288].



(160)

(161)

The first step in the dimerization consists of a nucleophilic attack by the nitrogen atom of the dimethylamino group upon the carbon atom of the NCS group[543] (equation 162). The dimer formed (**237**) has not been isolated in the pure state but it has a transient existence in solution. The next step is a cyclization involving nucleophilic attack of the negatively charged atom upon the free NCS groups. The dipolar pentane-insoluble dimer **238** thus formed is stable in the crystalline state, but rearranges in solution to pentane-soluble dimer **239** by migration of a methyl group from nitrogen to sulphur. The properties of substance **239** are discussed in References 288 and 544.



(162)

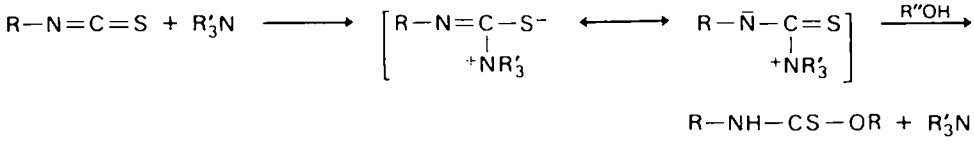
2. Addition of hydroxyl and thiol groups

Alcohols react with isothiocyanates to give monothiourethanes (equation 163). Hofmann directed attention to these reactions in 1869[545]. These reactions proceed very slowly in the cold, but by keeping the alcoholic solutions of isothiocyanates at boiling point under reflux, the time of the reaction can be reduced to a few hours[546,420,547,548]. According to Göckeritz and Pohloudek-Fabini[549] the corresponding monothiourethanes arise in 40 or even 80% yield after 2 hours reflux of the solutions of aromatic isothiocyanates in aliphatic alcohols. On the other hand, phenols react with isothiocyanates slowly even at 180°C (equation 164) and the yields are low because the resulting phenyl esters of *N*-alkyl or *N*-aryl carbamic acids are unstable[421]. Very reactive *N*-isothiocyanatoamines, too, react slowly with phenol[550].

$$R{-}NCS + HO{-}R' \longrightarrow R{-}NH{-}CS{-}O{-}R' \qquad (163)$$

(164)

The reactions of isothiocyanates with alcohols can be accelerated by an admixture of catalytic amounts of triethylamine[551,552], diethylamine or pyridine[553,554]. It can be explained by the formation of an intermediary complex of these nitrogen bases with isothiocyanates[552,553,555] (equation 165), i.e. by the assumption of base-catalysed addition of the alcohol to isothiocyanates.



(165)

In contrast to alcohols, alcoholates react easily with isothiocyanates even in the cold[548,556–560]. As early as in 1909, Rašdestvenskij[561] called attention to this fact. These reactions proved to be of wide application in the preparation of monothiocarbamates and at the same time, they served as evidence of the high nucleophilicity of alkoxide $(RO)^-$ ions as well as of the activity of these ions in nucleophilic attack of the NCS group.

By using the reaction of different types of isothiocyanates with aliphatic alcohols, pyridine and chinoline alcohols, 1,3- up to 1,10-diols and other compounds containing a hydroxyl group, several pharmaceutically

interesting thiourethanes were prepared. The methods of preparation of these substances are dealt with in a comprehensive survey[555]. Thiourethanes as synthetic precursors of isothiocyanates are treated in Section IV of this chapter.

Isothiocyanates react with thiols to yield the *S*-esters of *N*-monosubstituted dithiocarbamic acids (equation 166).

$$R{-}NCS + HS{-}R' \longrightarrow R{-}NH{-}CS{-}S{-}R' \qquad (166)$$

According to earlier papers[546,562,563] it was not recommended to use this method of preparation because the arising dithiocarbamic acids decompose easily to give the original components. The choice of more convenient reaction conditions resulted in good yields[555,564–567]. On the basis of the study of the kinetics and mechanism of the reactions of alkyl and aryl isothiocyanates with thiols in buffered systems, it was possible to define the conditions under which alkyl and aryl isothiocyanates react quantitatively with thiols, i.e. with the strongly nucleophilic RS^- form of these substances[568,569].

By the method put forward by Garraway, 3-substituted rhodanines (**241**) may be prepared in two steps using the reaction between isothiocyanates and mercaptoacetate[570]. The addition products formed in the first step are *N*-substituted thiocarbamoyl mercaptoacetates (**240**) which are difficult to isolate. In the second step these substances split off water and cyclize to give **241** in acid medium (equation 167). Provided 2-mercaptopropionate takes part in the reaction, addition products **242** are not proven to cyclize even in a strongly acid medium[571]. The formation of the corresponding thiazines **244** is achieved only after isolation and heating of **243** in acetic anhydride (equation 168). The kinetic investigations as well as the products of the reactions between alkyl or aryl isothiocyanates and mercaptoacetate have provided evidence that under suitable reaction conditions it is possible to achieve either a direct and quantitative conversion of isothiocyanates into products **241** (without any observable formation of **240**), or a quantitative conversion to species **240** which, however, demand an acid medium to cyclize into products **241**. Under the same conditions, 2-mercaptopropionate affords merely **242** or **243**, i.e. the addition product[568,569,440].

$$R{-}NCS + HS{-}CH_2{-}COO^- \longrightarrow \underset{\textbf{(240)}}{R{-}NH{-}CS{-}S{-}CH_2{-}COO^-} \xrightarrow{H^+} \underset{\textbf{(241)}}{\begin{array}{l} RN{-}CS \\ \quad | \quad | \\ OC{-}S \end{array}} + H_2O \qquad (167)$$

$$R{-}NCS + HS{-}CH_2CH_2COO^- \longrightarrow \underset{(242)}{R{-}NH{-}CS{-}S{-}CH_2CH_2COO^-} \xrightarrow{H^+} \underset{(168)}{R{-}NH{-}CS{-}S{-}CH_2CH_2COOH}$$

$$\xrightarrow{\Delta Q} \underset{(244)}{\text{cyclic thiazolidinone}} + H_2O$$

The reaction between 2-aminothiophenol and phenyl isothiocyanate was described by Hofmann[572]. He found that on heating the reaction mixture, evolution of hydrogen sulphide took place and 2-anilinobenzothiazole (**246**) was formed. A more detailed investigation of this reaction[573,543] revealed that the first step involved the formation of *S*-(2-aminophenyl) phenyl dithiocarbamate, **245** (attack on the SH group in preference to the NH_2 group) which, on heating, yielded product **246** (equation 169).

$$C_6H_5{-}NCS + \underset{H_2N}{\overset{HS}{\text{C}_6\text{H}_4}} \longrightarrow \underset{(245)}{\overset{S{-}CS{-}NH{-}C_6H_5}{\text{C}_6\text{H}_4}\text{-}NH_2} \xrightarrow{\Delta Q} \underset{(246)}{\text{benzothiazole-}C{-}NH{-}C_6H_5} + H_2S \qquad (169)$$

One of the preparation methods for the *N*-monosubstituted alkyl or aryl dithiocarbamates known and used for a long time is based on the reaction between isothiocyanates and alkali sulphides, e.g. potassium sulphide (equation 170). In this case, too, the HS^- ions represent the reactive form[569]. The products are relatively stable in an alkaline medium. They decompose into the original reaction components in weakly alkaline solutions while in neutral or acid medium they split to form the corresponding amine and hydrogen sulphide (see Section IV). Just on the basis of these facts it is possible to account for the earlier finding that isothiocyanates reacting with hydrogen sulphide afford the *N*,*N*-disubstituted thioureas (equation 171). The formation of that product under given reaction conditions is preceded by an addition reaction giving unstable dithiocarbamate which decomposes

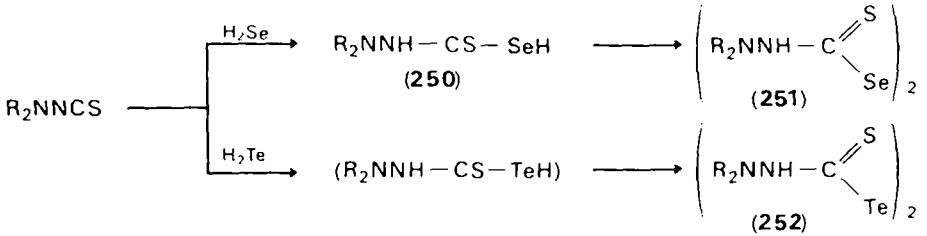
into hydrogen sulphide and the corresponding amine. This amine reacts with isothiocyanate to give the *N,N*-disubstituted thiourea.

$$R{-}NCS + HSK \longrightarrow R{-}NH{-}CS{-}SK \quad (170)$$

$$2\ R{-}NCS + H_2S \longrightarrow R{-}NH{-}CS{-}NH{-}R + CS_2 \quad (171)$$

According to Anthoni and coworkers[543,574] the reaction between *N*-isothiocyanatodialkyl amines and hydrogen sulphide is expected to give dithiocarbazic acids (**248**) which are of stable compounds. However, these cannot be isolated but react with **247** and are immediately transformed into bis(*N,N*-dialkylthiocarbazoyl) sulphides (equation 172). This conclusion is based on analogous reactions to **247** and authentic dithiocarbazic acids. It is remarkable that this reaction proceeds at room temperature while the same reaction involving phenyl isothiocyanate demands a temperature of about 200 °C[575].

$$\underset{(247)}{R_2NNCS} + H_2S \longrightarrow \underset{(248)}{[R_2NNH{-}CS{-}SH]} \xrightarrow{R_2N{-}NCS} \underset{(249)}{(R_2NNHCS)_2S} \quad (172)$$

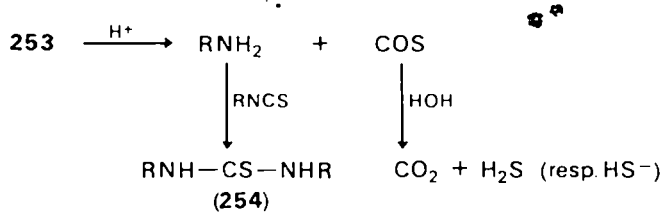


(173)

In contrast to the reaction with hydrogen sulphide, the reaction of **247** with hydrogen selenide results in the formation of selenothiocarbazic acid (**250**) which can be isolated[576]. However, it is very rapidly oxidized in ethanolic solution to give the corresponding bis(*N,N*-dialkylthiocarbazoyl) diselenide (**251**, equation 173). If this reaction is carried out with hydrogen telluride, only **252** is isolated[543]. In aqueous solutions of alkali hydroxides, isothiocyanates form *N*-monosubstituted thiocarbamates **253** (equation 174) which are stable only in strongly alkaline solutions provided R stands for alkyl or aryl[514,36].

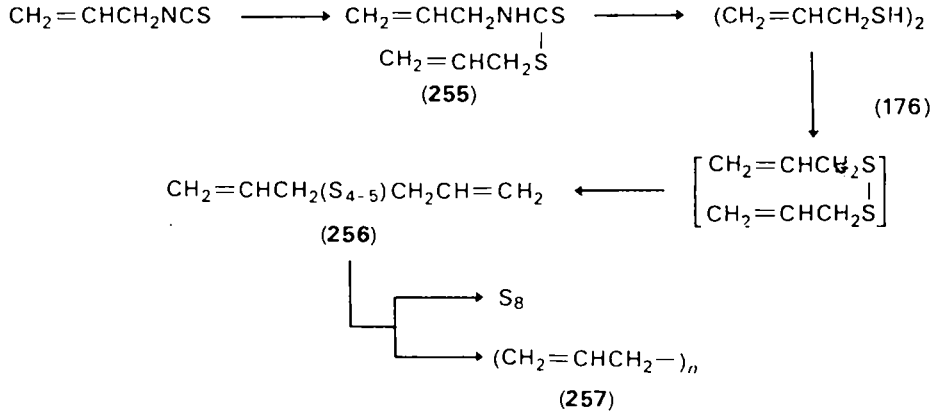
$$\underset{(253)}{RNH{-}CS{-}O^-} \quad (174)$$

Since substances **253** are of no practical importance, there is not much information on their chemical and physicochemical properties. Simple alkyl and aryl isothiocyanates are stable in aqueous solutions and the fact that distillation with water vapour is used for the purification of many derivatives confirms this. However that does not apply to acyl isothiocyanates[577] or highly unstable *N*-isothiocyanatoamines[543]. On the other hand, it is possible to draw a general conclusion that isothiocyanates are subjected to hydrolysis in aqueous solutions mainly as a result of their reaction with OH^- ions. Moreover, the formation of other compounds may be explained by assuming the formation of thiocarbamates and their subsequent decomposition into amine and carbonyl sulphide or H_2S and CO_2 (equation 175).



(175)

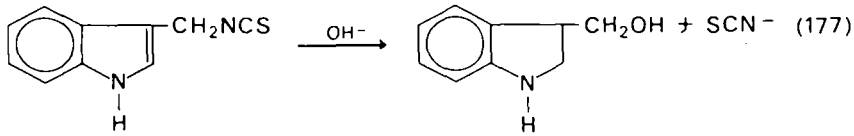
For instance, that applies to relatively stable thioureas (**254**) which arise in the reaction between the residual isothiocyanate and its decomposition product, i.e. amine. Equally, hydrogen sulphide (especially HS^- ions) can react with the residual isothiocyanate to give the corresponding dithiocarbamate which is responsible for the formation of other products. Kawakishi and Namiki investigated thoroughly the decomposition products of alkyl isothiocyanate in aqueous solution[578]. Besides allylamine and dialkyl thiourea, substances **255**, **256** and **257** arise as products of consecutive decomposition (equation 176).



(176)

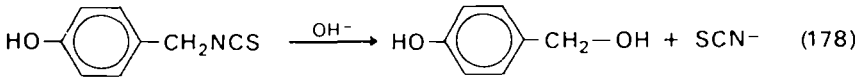
The formation of product **255** can be explained for the derivatives of the allyl type on the basis of the isothiocyanate–thiocyanate isomerization. Allyl thiocyanate formed probably decomposes to give among other products allyl mercaptan which reacts with allyl isothiocyanate to yield product **255**. This fact also indicates that the above mentioned isomerization reaction manifests itself significantly even in an aqueous medium.

Depending on the structure of the isothiocyanates, other types of hydrolysis products can arise in aqueous solution. As to the so-called naturally occurring isothiocyanates, it is worth mentioning the extremely unstable 3-indolyl-methyl isothiocyanate **258**[579,580] as well as 4-hydroxybenzyl isothiocyanate **259**[582,583] which decomposes into the corresponding alcohol and SCN^- ion (equations 177 and 178). In contrast to substance **259**, benzyl isothiocyanate and many of its synthetic derivatives are relatively stable in water.



(177)

(258)

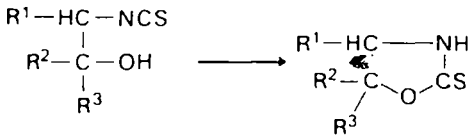


(178)

(259)

As to the synthetic isothiocyanates, we refer to acyl thiocyanates, the hydrolysis of which results in a decomposition giving the SCN^- ions as described earlier[577]. For other types of isothiocyanates having two electrophilic centres in the molecule other possibilities for the attack of OH^- ions have to be taken into consideration.

Naturally occurring isothiocyanates with a β-hydroxyl group undergo spontaneous intramolecular cyclization to give 2-oxozolidinethiones (equation 179).



(179)

3. Addition of carboxylic and thiocarboxylic acids

Even in earlier papers it has been stated that the addition of carboxylic[584,585] and thiocarboxylic acids[586,587] to isothiocyanates, followed by additional elimination of COS or CS_2, gives acyl amines. In these reactions primary adducts **260** (equation 180) or **261** (equation 181) are formed.

$$\mathrm{RCO{-}OH + SCNR' \longrightarrow [RCO{-}O{-}CS{-}NHR'] \longrightarrow \underset{\textbf{(260)}}{} \; COS + RCONHR' \qquad (180)}$$

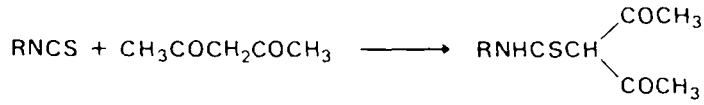
$$\mathrm{RCO{-}SH + SCNR' \longrightarrow RCO{-}S{-}CS{-}NHR' \longrightarrow \underset{\textbf{(261)}}{} \; CS_2 + RCONHR' \qquad (181)}$$

The reaction between isothiocyanates and carboxylic acids demands temperatures above 130 °C[588–590]. Compounds **260** cannot be isolated[591,300]. According to Kricheldorf thiocarboxylic acids react with isothiocyanates faster than do the corresponding carboxylic acids. The primary reaction products are carboxylic thiocarbamic acid thioanhydrides which can be isolated only in certain cases at low temperatures[592]. The higher nucleophilicity of the thiocarboxylate ion may explain the great difference between the reactivity of thiocarboxylic and carboxylic acids[590,592].

The reaction of α,ω-dithiocarboxylic acids with diisocyanates or diisothiocyanates leads to poly[thiocarbonylimino-(6-oxohexamethylenes)] (polythioanhydrides), or at higher temperatures to polyamides of the nylon type. By heating the trimethylsilyl ester of 6-isothiocyanatohexanethioic acid with alcohols or phenols above 200 °C, nylon-6 (m.w up to 10 000)[592] may be obtained. The polyaddition or polycondensation of ω-isocyanato- or ω-isothiocyanatocarboxylic acids is described in papers[590,593].

4. Addition of carbon bases

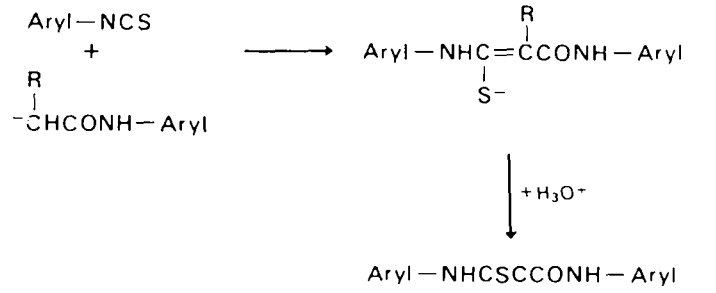
The reactions of this type comprise the additions of acetylacetone[594] (equation 182), ethyl acetoacetate, and ethyl malonate (equation 183) to isothiocyanates described some time ago. The last two compounds undergo addition in the form of their alkali salts[595].



(182)

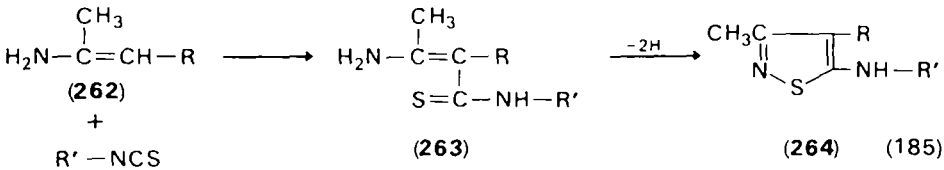
(183)

The *N*-aryl substituted amides of malonic and acetoacetic acid react with aryl isothiocyanates in the presence of alcoholate to yield thioamides. The addition involves a participation of the active methylene group of amides[596] (equation 184).



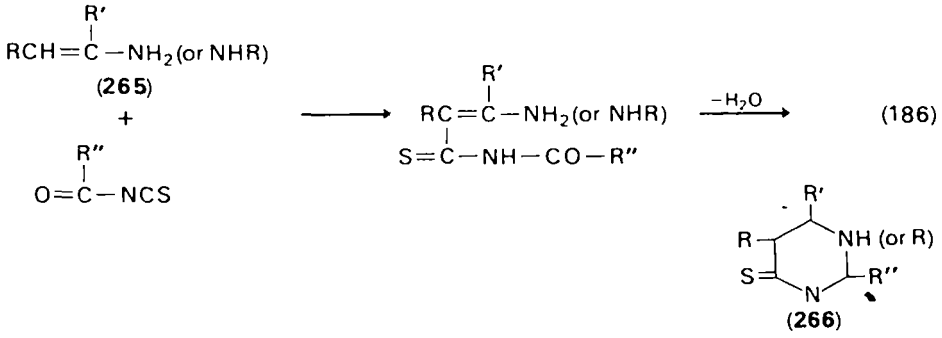
(184)

Similarly, those primary and secondary enamines and imines able to tautomerize can react with isothiocyanates through the methylene group to form the 1:1 C-adducts. For instance, the addition of alkyl, aryl, acyl or sulphonyl isothiocyanates to enamines of the type of the esters of β-aminocrotonic acid (**262**) affords the corresponding α-acyl-β-aminothiocrotonamides **263** which are subjected to dehydrogenation and cyclize to give isothiazole **264** (equation 185)[597,598].



(185)

The adducts of enamines and acyl isothiocyanates are usually capable of undergoing polycondensation. Starting from primary (or secondary) enamines of type **265** and acyl isothiocyanates it is possible to prepare different pyrimidine thiones **266** (equation 186) and 4-thiouracils **267** (equation 187)[90,597,599-601].



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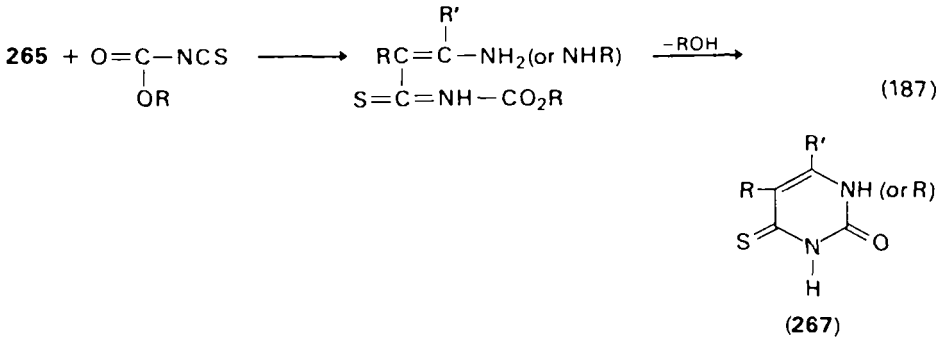
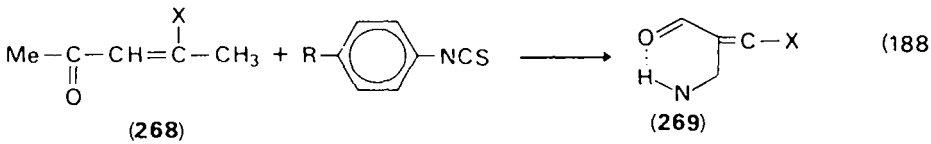


(187)

The compounds of type **266** and **267** may also be synthesized by the reaction of primary amines or ammonia with the addition compounds consisting of acyl or ethoxycarbonyl isothiocyanates and tertiary enamines[602].

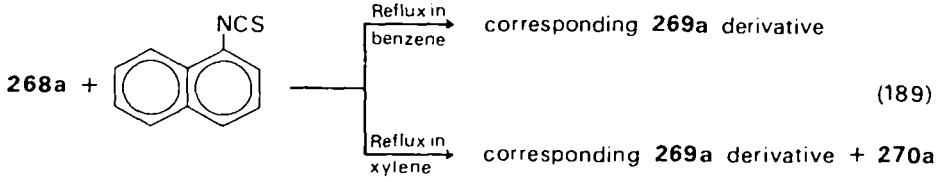
By investigating the reaction of enaminoketones of the type of 4-(1-piperidyl)- and 4-(1-pyrrolidinyl)-3-pentene-2-ones (structures **268a** and **268b**) with phenyl isothiocyanates the presence of the corresponding 3-phenylthiocarbamoyl derivatives **269a** and **269b** as 1 : 1 adducts was also revealed (equation 188). The reaction with 1-naphthyl isothiocyanate gives 3-naphthylthiocarbamoyl and 2-thiopyridone derivatives **270a** and **270b** depending on reaction conditions[604] (equation 189 and 190).



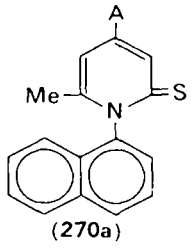
(188)

a: X = piperidyl

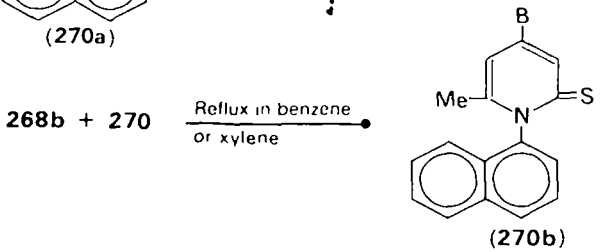
b: X = pyrrolidinyl



(189)



(270a)

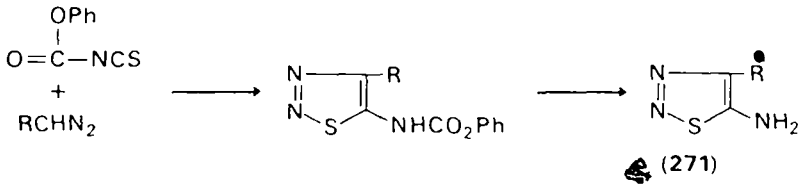


(190)

(270b)

In contrast to phenyl isocyanate, phenyl isothiocyanates react with compounds **268a** and **268b** to give 3,5-diphenylcarbamoyl-2-pyridone and/or its 3-phenylcarbamoyl derivatives depending on reaction conditions[603,604].

By analogy with the reaction between diazomethane and phenyl isothiocyanates described earlier[605], acyl isothiocyanates were used for the preparation of 5-amino-1,2,3-thiadiazoles[606-608]. The hydrolytic elimination of the acyl group, proceeding after addition of isothiocyanate in two steps, made it possible to produce the primary amines (**271**), hitherto unknown[90] (equation 191).

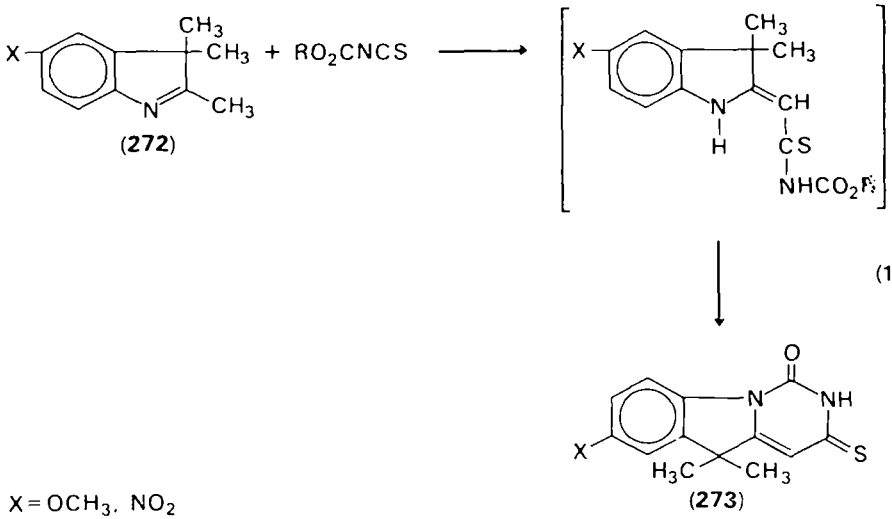


(191)

(271)

Phenoxycarbonyl isothiocyanate is particularly suitable for this method because the hydrolysis proceeds even under very mild conditions (compounds **271** are sensitive to alkali). The reaction of acyl isothiocyanates with diazoalkones is considered to be a (2 + 3) cycloaddition[90].

5-Methoxy- and 5-nitro-2,3,3,-trimethylindolenines (**272**) react with 'dielectric' isothiocyanates to give the pyrimido[3,4-*a*]indoles (**273**, equation 192). Furthermore, 1-methyl-3,4-dihydroisoquinoline condenses with 'dielectric' isothiocyanates to the pyrimido[6,1-*a*]isoquinolines, hitherto unknown in this state of saturation[724].



X = OCH_3, NO_2

B. Cycloadditions[90,608-612]

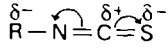
Cycloadditions of heterocumulenes including isothiocyanates are treated in a comprehensive monograph by Ulrich[612] who used the literature up to 1965. Another general review on the 1,3-cycloadditions of isocyanates and isothiocyanates comprising the literature published till 1973 was written by van Loock[613].

In this chapter we are going to give a survey of the most important type of cycloadditions in the course of which two new σ bonds are formed between the components to the detriment of the π bonds. We shall not be concerned with the cycloadditions involving a simple bond or giving unstable cycloadducts which immediately isomerize and form linear adducts. These types of cycloadditions are described in detail in the monograph by Ulrich[612].

1. [2+2] Cycloadditions

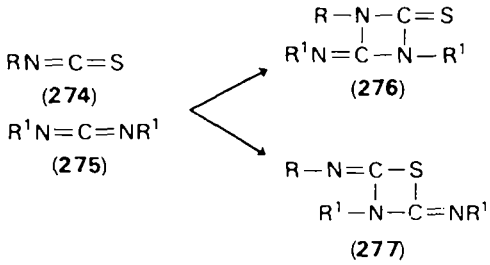
Isothiocyanates can enter into [2 + 2] cycloadditions either through the C=S bond or through the C=N bond which is in agreement with electron

polarization of their NCS group containing fractional negative charges on the atoms of nitrogen and sulphur[52,192,509].



A higher nucleophilicity of the atom of sulphur as well as a decreased 2π–3π interaction of its bonding electrons in comparison with nitrogen enhances the polarity of the C=S bond and thus its dipolarophilic activity in 1,2-cycloadditions. From the view-point of reaction mechanism, the 1,2-cycloadditions of isothiocyanates can follow either a concerted mechanism or a two-step mechanism. Isothiocyanates fulfil the condition of preserving the symmetry of orbitals in the cycloadditions with multiple bonds, provided these cycloadditions proceed as thermally permitted $\pi_s^2 + \pi_a^2$ pericyclic reactions[611,614]. Some authors are inclined to give credit to the two-step mechanism according to which cycloaddition proceeds through a zwitterion intermediate (1,4-dipole)[615,616].

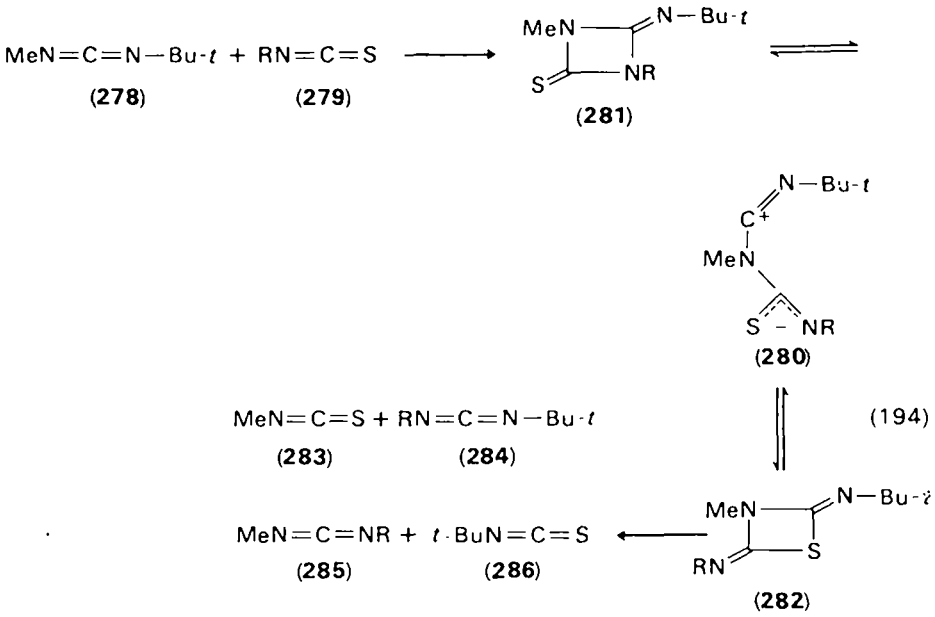
a. *Additions on the C=S bond of isothiocyanates.* By means of the C=S bond, isothiocyanates react with compounds containing double C=N bonds in a molecule to give stable [2 + 2] cycloadducts of the 1,3-thiazetidine type[615,104]. The greatest attention was concentrated upon the reactions between isothiocyanate and carbodiimides. Ulrich and coworkers[612,617,618] found that the reactive isothiocyanates, such as *p*-nitrophenyl and alkyl- or arylsulphonyl isothiocyanates (**274**), reacted quickly with carbodiimides (**275**) to give cycloadducts even at room temperature, while alkyl and aryl isothiocyanates reacted with carbodiimides very unwillingly. On the basis of analogy with isothiocyanates, the authors ascribed the structure of 1,3-diazetidine (**276**) to the main cycloadduct formed. Since isothiocyanates undergo addition in preference through the C=S double bond, they did not exclude the possible formation of 1,3-thiazetidine (**277**, equation 193).



(193)

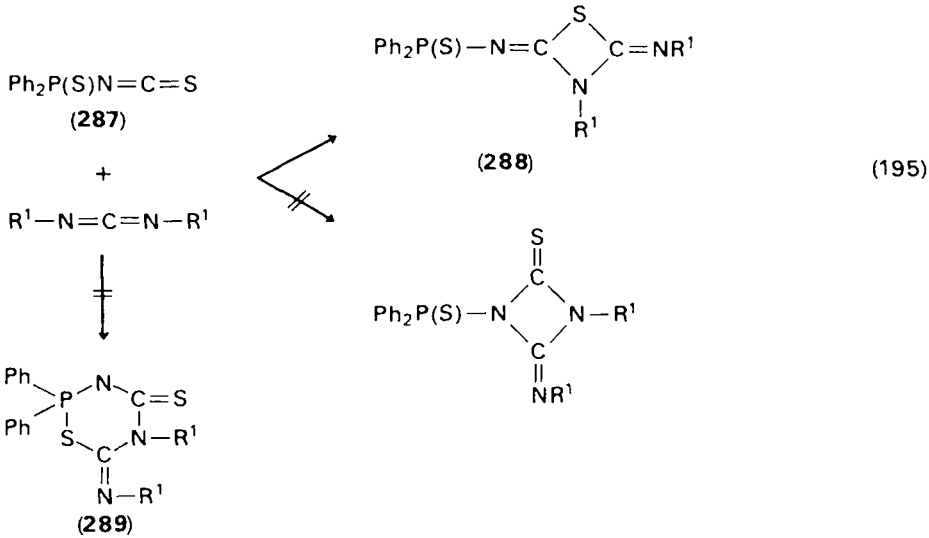
R = 4-$NO_2C_6H_4$, CH_3SO_2, 4-$CH_3C_6H_4SO_2$
R^1 = *i*-C_3H_7, C_6H_{11}, C_6H_5, 2-$CH_3C_6H_4$

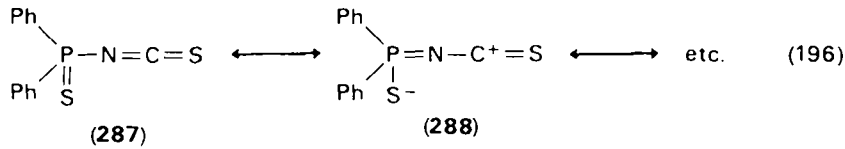
The structure of the cycloadduct was proposed by Ulrich and coworkers[625] and confirmed by Ojima and coworkers[619]. The first authors applied fragmentation of the [2 + 2] cycloadduct of methyl-*t*-butylcarbodiimide (**278**) with 4-nitrophenyl and tosyl isothiocyanate or ethyl isothiocyanatoformate (R—NCS, **279**) to prove the structure. They assumed that the cycloaddition would go exclusively through the sterically less protected C=N bond of carbodiimide.



From the fragmentation of the cycloadduct formed it is possible to determine which of the possible isomeric structures **281** or **282** of the molecule is present. Only *t*-butyl isothiocyanate was isolated from the cycloadducts formed by thermolysis (160 °C) on the basis of which the structure of 1,3-thiazetidine derivative (**282**) was confirmed. Moreover, the authors assumed that the cycloaddition followed a two-step mechanism while the 1,4-dipole (**280**) arising in the first stage of the reaction between carbodiimide and heterocumulene was cyclized into a thermodynamically stable product (equation 194). Further, they investigated the reactions between diphenylphosphinothionyl isothiocyanate (**287**) or *p*-toluenesulphonyl isothiocyanate and carbodiimides. They found that both isothiocyanates reacted with dicyclohexyl- and diisopropyl carbodiimides and afforded solely 1,3-thiazetidine derivatives (**288**) almost in quantitative yields (equation 195). Though the 1,4-dipolar mesomeric structure (**288**,

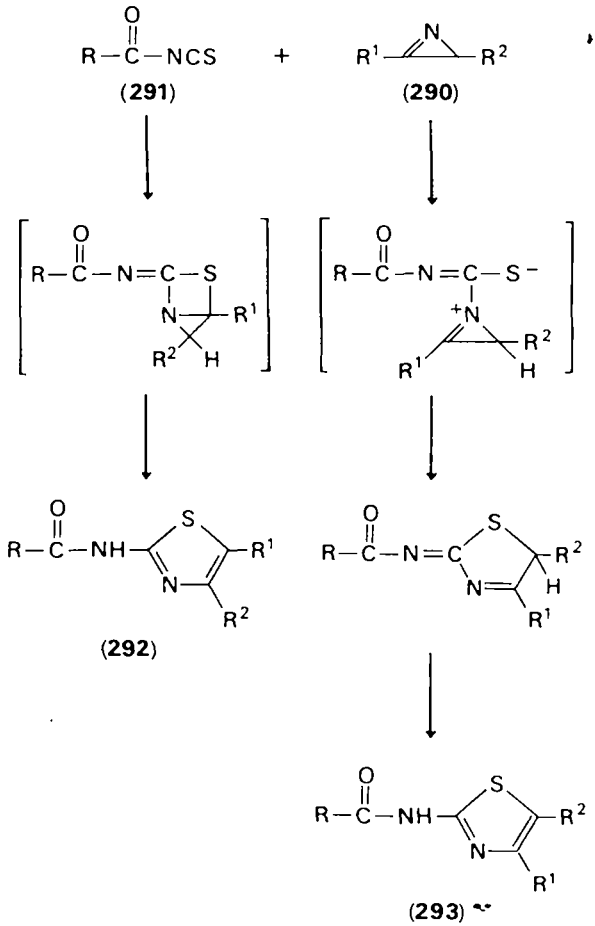
equation 196) is, to a great degree, operative in derivative **289**, no formation of 1,4-cycloadduct was observed.





Nair and Kim[616] investigated the [4 + 2] and [2 + 2] cycloadditions of 1-azirines to heterocumulenes. In contrast to thiobenzoyl isothiocyanates and benzoyl isothiocyanates, which afforded only cycloadducts of the thermal [4 + 2] cycloadditions with 1-azirines (**290**), benzoyl isothiocyanate (**291**) reacted with the above dipolarophiles and gave the [2 + 2] cycloadducts. On the basis of mass spectra and ^{1}H and ^{13}C n.m.r. spectra of the resulting cycloadducts these authors proved that the cycloaddition was regiospecific and involved the C=S bond of the isothiocyanate group, the resulting products being 4,5-disubstituted 2-benzamido-1,3-thiazoles. From the view point of regiospecificity two isomeric products may theoretically arise, each of them through different mechanisms.

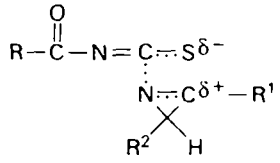
While the formation of compound **292** satisfies the conditions of orbital symmetry for the $[\pi_2^2 + \pi_a^2]$ cycloadditions, compound **293** can arise only via nucleophilic attack by the nitrogen atom of the three-membered azirine ring on the carbon atom of the NCS group and by a cleavage of the 1,3-bond of the adduct formed which is succeeded by a cyclization with 1,5-sigmatropic



(197)

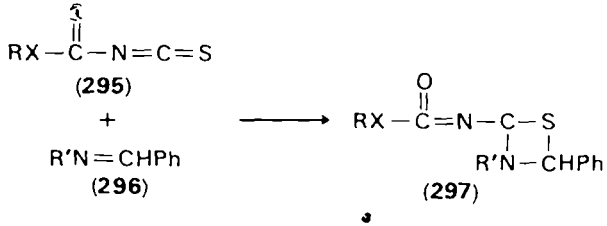
292, 293, **a**: $R^1 = Ph$; $R^2 = Ph$
b: $R^1 = Ph$; $R^2 = CH_3$
c: $R^1 = Ph$; $R^2 = H$

rearrangement of the hydrogen atom. The analysis of ^1H n.m.r. spectra of the cycloadduct $R^1 = Ph$ and $R^2 = H$ has confirmed that only thiazol regiostereoisomer (**292c**) is formed in this cycloaddition. Because of great differences in the yields of product **292c**, depending on the polarity of solvents as well as differences in the pathway of cycloadditions of aroiobenzoyl isothiocyanate and benzoyl isocyanate as compared with benzoyl isothiocyanate, the authors suggest a transition state of dipolar character (**294**) for cycloadduct **292**.



(294)

Among reactions involving the C=S bond of the isothiocyanate group it is worth mentioning the [2 + 2] cycloadditions of alkoxycarbonyl and mercaptocarbonyl isothiocyanates (**295**) with azoimines (**296**) which provide the corresponding 3,4-disubstituted 1,3-thiazetidines (**297**)[90,104] (equation 198).



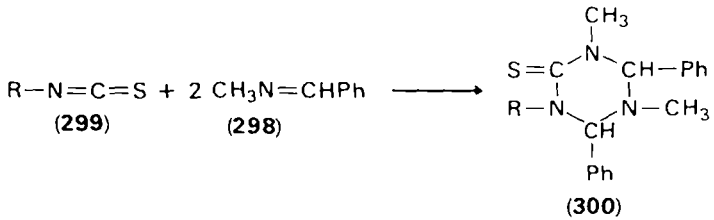
(295) + (296) → (297)

R′ = *i*-Pr, cyclohexyl, Ph

R = CH_3(X=S), C_2H_5(X=O)

1,3-Thiazetidines also arise in the reaction of tosyl isothiocyanate with *p*-methoxybenzylidene aniline, benzylidene aniline and benzylidene α- or β-naphthylamine. Ethoxy carbonyl isothiocyanate and *N*-phenyl-benzimidoyl isothiocyanate do not react with benzylidene aniline[104].

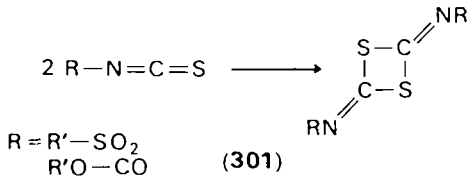
The reaction between azomethines with non-voluminous substituents on nitrogen, e.g. benzylidene methylamine (**298**) and carbonyl isothiocyanates (**299**), provides the 1:2 adducts with a six-membered triazine ring (**300**[301], equation 199).



(299) (298) (300) (199)

R = $CONPh_2$, CO_2Et, COSMe

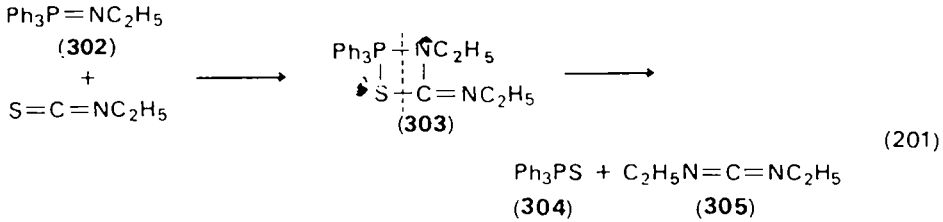
Sulphonyl and alkoxycarbonyl isothiocyanates dimerize easily through the C=S bond, the outcome being a formation of four-membered heterocycles of the 1,3-dithiethane type (**301**[629,90], equation 200).



(200)

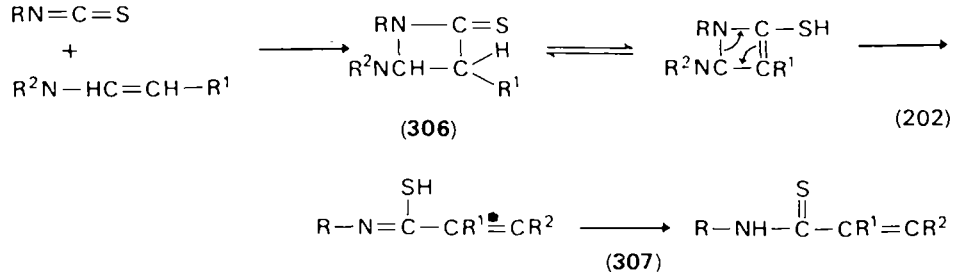
(301)

The reaction between ethyl isothiocyanate and **302**, the pathway of which is similar to the mechanism of the Wittig reaction, has been known for a long time[621]. The unstable four-membered cycloadduct (**303**) is cleaved during the reaction while triphenylphosphine sulphide (**304**) and diethylcarbodiimide (**305**) are formed (equation 201):



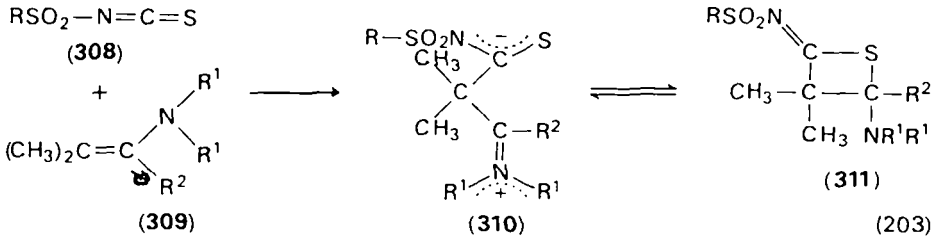
(201)

b. *Additions on the C=N bond of isothiocyanates.* Isothiocyanates only enter into cycloadditions involving the C=C bonds of nucleophilic olefins[599,622,623] (enamines, β-amino- and β-diaminocrotonates, indolyl esters, keteneaminates, etc.[612]). The cycloaddition is likely to proceed analogously with isocyanates through the C=N bond of the isothiocyanate group, and the unstable azetidine ring (**306**) yields **307** (equation 202).



(202)

When sulphonylisothiocyanates (**308**) are reacted with β,β-disubstituted enamines (**309**) crystalline 1:1 adducts are formed[624]. The spectroscopic data are consistent with the dipolar structure **310**. In non-polar solvents an equilibrium exists between **310** and the imidothietanes[36] (**311**, equation 203).



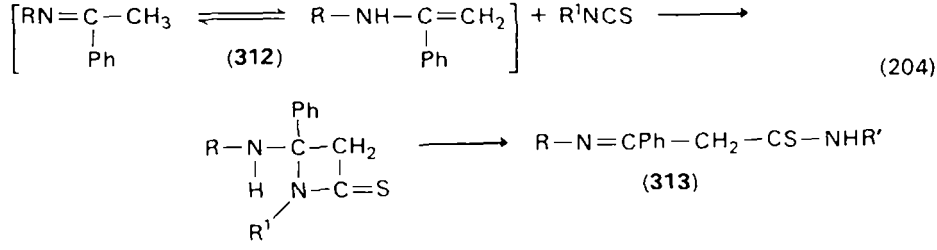
(308) (309) (310) (311) (203)

R = 4-Tolyl, C_6H_5, CH_3, $N(CH_3)_2$, C_2H_5O

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

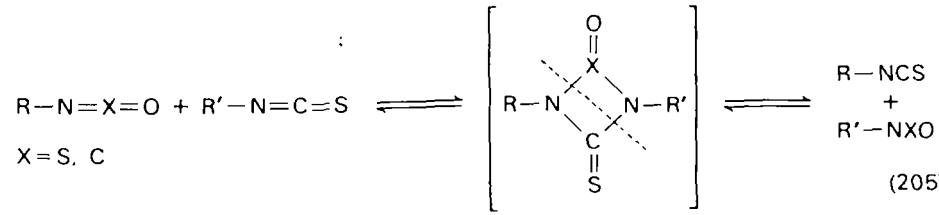
R^2 = H, CH_3, C_3H_7, C_6H_5

The cycloadditions of isothiocyanates with azomethines derived from aryl–alkyl ketones (**312**) giving linear adducts (**313**)[625,612] are quite analogous (equation 204).



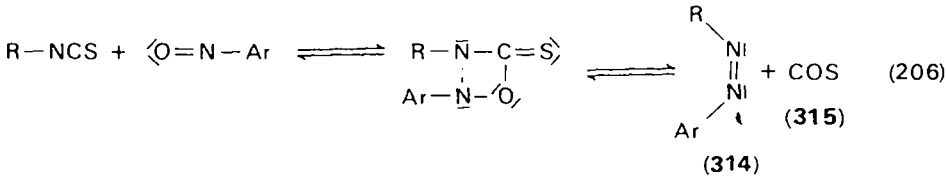
(312) (313) (204)

The exchange reactions between heterocumulenes R—N=X=Y (X = C, S and Y = O, S), for which four-membered rings of dimers may be assumed merely on the basis of the resulting reaction products[308,309,121,626] (equation 205), are also to be included into this kind of cycloaddition. The reaction is of practical importance for the preparation of systems with C=N bonds or for the preparation of heterocumulenes by simple transfer of the substituents R and R'.



X = S, C (205)

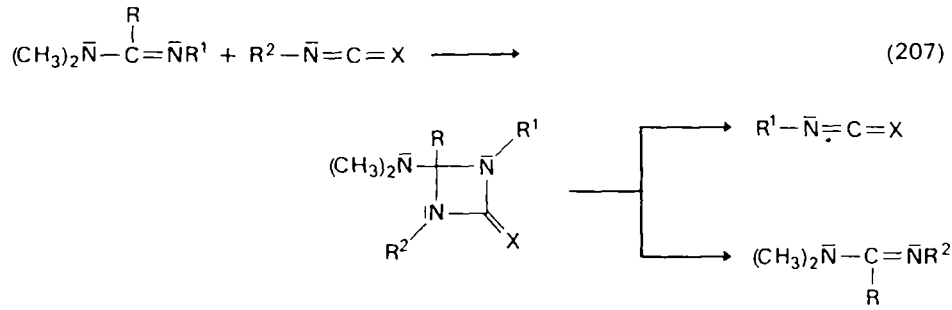
An analogous course is also shown by the reaction between isothiocyanates and nitroso compounds[627] in which azo compounds (**314**) and carbonyl sulphide (**315**) arise (equation 206).



(206)

(**314**) (**315**)

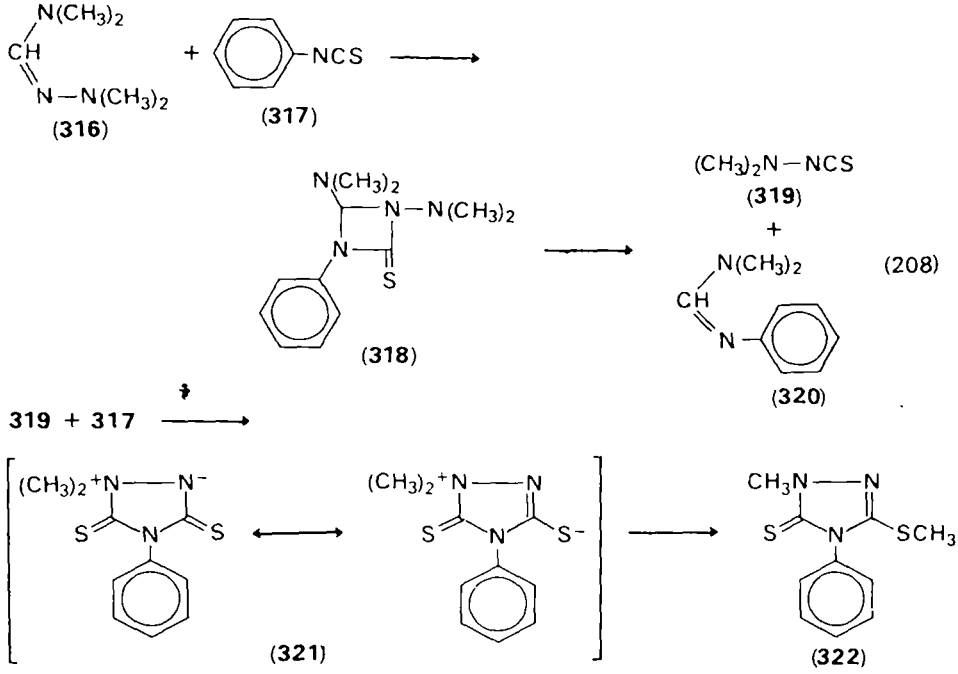
Amidines and guanidines react with *p*-toluenesulphonyl isocyanate and 4-nitrophenyl isothiocyanate even at room temperature to form 1,1-cycloadducts of the diazetidine type. These cycloadducts can sometimes be isolated but they frequently disproportionate even at room temperature to give the starting substances while the substituents R^1 and R^2[628] exchange their positions (equation 207).



(207)

X = O	X = S
R = $(CH_3)_2N$, H	R = $(CH_3)_2N$
R^1 = *n*-C_4H_9, C_6H_5	R^1 = *n*-C_4H_9
R^2 = 4-$CH_3C_6H_4SO_2$	R^2 = 4-$O_2NC_6H_4$

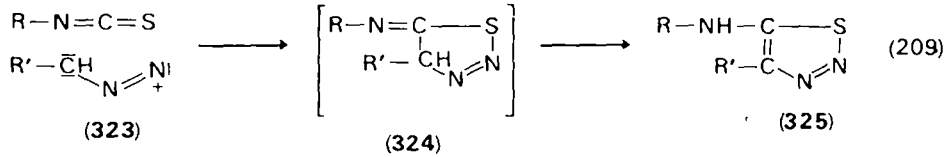
Phenyl isothiocyanate (**317**) reacts with *N*,*N*-dimethyl-*N'*-dimethylaminoformamidine (**316**) and gives the unstable [2 + 2] cycloadducts (**318**) which decompose afterwards to give dimethylaminoisothiocyanate (**319**) and *N*,*N'*-dimethyl-*N'*-phenylformamidine (**320**). The dimethylaminoisothiocyanate (**319**) formed by decomposition gives, with another molecule of phenyl isothiocyanate (**317**), a 1,3-cycloadduct (**321**) which is thermally unstable and isomerizes by rearrangement of methyl group to 1-methyl-3-methylthio-4-phenyl-1,2,4-triazol-2-in-5-thione (**322**, equation 208).



2. [3+2] Cycloadditions

Isothiocyanates may react with some 1,3-dipoles through the double C=S bond[629], with others through the double C=N bond[630], or via both these double bonds to yield a mixture of cycloadducts[631].

a. *Cycloadditions of 1,3-dipoles with unsaturated sextet structure.* The cycloadditions of diazo compounds (**323**) with isothiocyanates giving iminothiadiazolines (**324**) which immediately rearrange into the 5-substituted 1,2,3-thiadiazoles[632,633] (**325**, equation 209), belong to the best known reactions of 1,3-dipoles of that type.



The most diverse types of isothiocyanates, e.g. alkyl[629,634], aryl[634–636,159], acyl[629,634,159,606,108], carbalkoxy[629,159], imidoyl[118], carbamoyl[102], sulphonylalkoxy[159], and dialkyl and diaryl phosphinoyl[637] isothiocyanates undergo this cycloaddition. Diazoalkanes[629,632–634,108],

phenyldiazomethane[635,108], the esters of diazoacetic acid[929,636,108], ω-diazoacetophenone[629,159,108] and diazoacetamide[108] were used as diazo components.

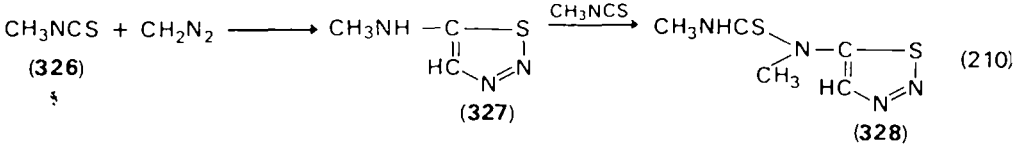
The reactivity of isothiocyanates increases with the electrophilicity of the carbon of the isothiocyanate group which is enhanced by electron-withdrawing groups in the order[629] R < Ar < RO_2C < ArCO.

The ability of diazo compounds to react decreases through the effect of electron-withdrawing substituents[629,108] in the order CH_2N_2, $C_2H_4N_2$ > $C_6H_5CHN_2$ > NH_2—$COCHN_2$ > $C_2H_5O_2C$—CHN_2 > C_6H_5—$COCHN_2$.

For instance, diazo esters react with isothiocyanates only after boiling for several hours in absolute dioxane, while diazomethane dissolved in ether adds to isothiocyanates even in the cold[629]. The cycloaddition of diazo compounds to acyl isothiocyanates may also be carried out by preparing the corresponding isothiocyanate *in situ* in the presence of a diazo compound[108].

For the formation of thiadiazoles a two-step ionic mechanism was originally proposed[633,636]. On the basis of kinetic studies of the effect of substituents in diazo compounds and polarity of solvent on the rate of that reaction, Martin and Mucke[629] have proved unambiguously that thiadiazoles arise in a one-step concerted process by way of a 1,3-dipolar cycloaddition.

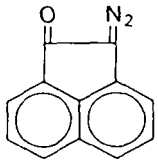
Methyl isothiocyanate (**326**) reacts only with excess diazomethane while thiadiazole (**327**) arising in the first step reacts immediately with another molecule of isothiocyanate to yield *N.N'*-dimethyl-*N*-[1,2,3-thiadiazolyl-(5)] thiourea (**328**, equation 210).



(210)

The reaction between 2-diazoacetophenone (**329**) and benzoyl or thiobenzoyl isothiocyanate (**330**) giving the corresponding thiadiazoline derivative (**331**, cycloaddition through the C=S double bond) in the first step represents a special case. In the subsequent reaction step this derivative splits off nitrogen and recyclizes to give 8-benzoyl- or 8-thiobenzoyl-acenaphtho-(1,2)-Δ^4-isoxazoline-9-thione (**332**[638], equation 211).

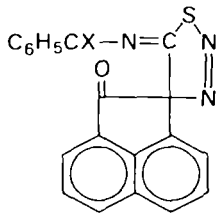
Alkyl and aryl isothiocyanates give cycloadducts with hydrazoic acid via C=S bond while 5-substituted 1,2,3,4-thiatriazoles[639] (**333**) are formed (equation 212).



(329)

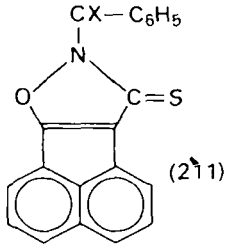
+ $C_6H_5-CX-NCS$ ⟶

(330)



(331)

$-N_2$ ⟶



(332)

(211)

X = O, S

$$RN=C=S + HN_3 \longrightarrow \text{(333)} \qquad (212)$$

R = Alkyl, aryl

Arylsulphonyl isothiocyanates react with butyl azide or benzyl azide through the C=S group of the isothiocyanate groups too, while the corresponding thiatriazolines[640] (**334**, equation 213) are reaction products.

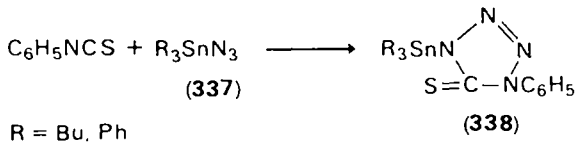
$$C_6H_5SO_2N=C=S + RN_3 \longrightarrow \text{(334)} \qquad (213)$$

R = Bu, Ph

The reaction between natrium azide and isothiocyanates[641–645] became of great importance for the synthesis of 1-substituted tetrazoline-5-thiones (**336**). In contrast to free acid, the cycloaddition of azide ion proceeds via the C=N double bond of the isothiocyanate groups and gives anion **335**, yielding **336** after protonation.

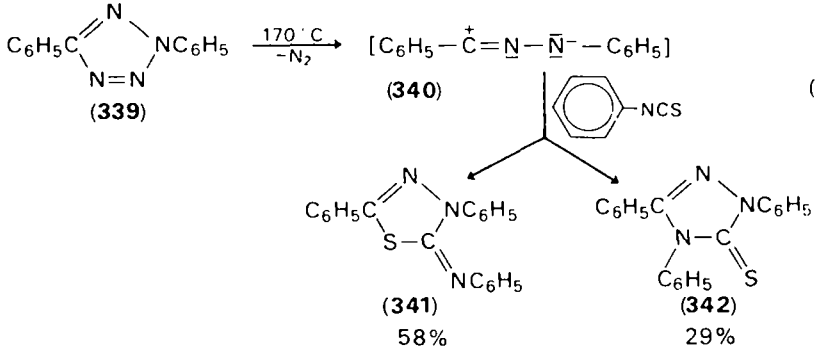
$$RN=C=S + NaN_3 \longrightarrow \text{(335)} \xrightarrow{H^+} \text{(336)} \qquad (214)$$

The addition of tributyl and triphenyl tin azide (**337**) goes through the C=N bond of phenyl isothiocyanate to give cycloadduct **338** (equation 215)[646].



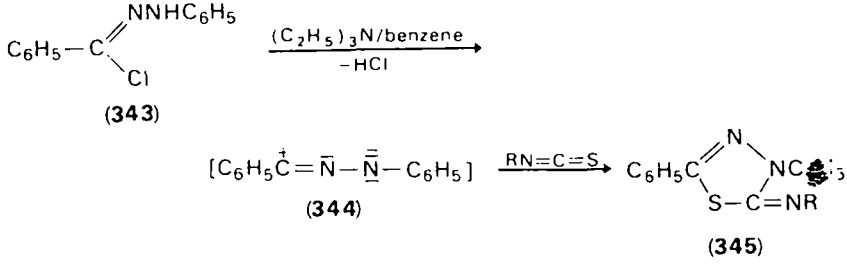
(215)

Nitrile imines belong among other 1,3-dipoles which react with isothiocyanates by the [3 + 2] cycloaddition mechanism. Huisgen and coworkers[608] have found that diphenyl nitrile imine (**340**) arising by thermolysis of 2,5-diphenyltetrazole (**339**) reacts with phenyl isothiocyanate to give 3,5-diphenyl-2-phenylimino-2,3-dihydro-1,3,4-thiadiazole and 1,3,4-triphenyl-1,2,4-triazole-5-thione (**342**). Therefore the cycloaddition involves both the C=S and C=N double bond of the NCS group (equation 216).



(216)

Diphenyl nitrile imine (**334**), prepared *in situ* by splitting of hydrogen chloride from benzoic acid phenylhydrazine chloride (**343**) by triethylamine, adds benzoyl isothiocyanate[631] and imidoyl isothiocyanate[118] solely through the C=S bond of the isothiocyanate group to give the thiadiazole derivative (**345**, equation 217).

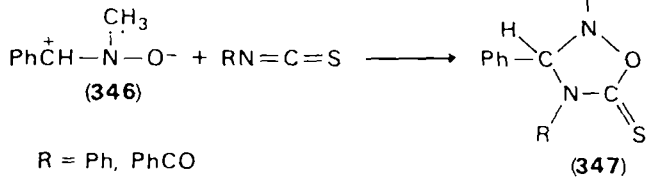


(217)

In contrast to the isothiocyanates already mentioned, diphenyl nitrile imine adds allyl isothiocyanate through the C=C bond, the dipolarophilicity of which is evidently greater than that of the NCS group[631] (the authors give no experimental results).

It is interesting that no cycloadditions of isothiocyanates to nitrile oxides have been revealed up to now though the latter substances represent some of the most studied 1,3-dipoles. Van Loock[613] explains this fact by the low nucleophilic reactivity of the C=N double bond of heterocumulenes with respect to nitrile oxides.

b. *Cycloadditions of 1,3-dipoles with saturated sextet structure.* Isothiocyanates can enter into 1,3-cycloadditions with nitrones (azomethine oxides) either through the C=N or C=S bond[647]. The formation of a particular cycloadduct depends on the structure of the isothiocyanate and steric factors in the molecule of nitrone. For instance, *C*-phenyl-*N*-methylnitrone (**346**) reacts with phenyl isothiocyanate[648] and benzoyl isothiocyanate[647] exclusively through the C=N bond to give 1,2,4-oxadiazolidine-5-thione (**347**, equation 218).

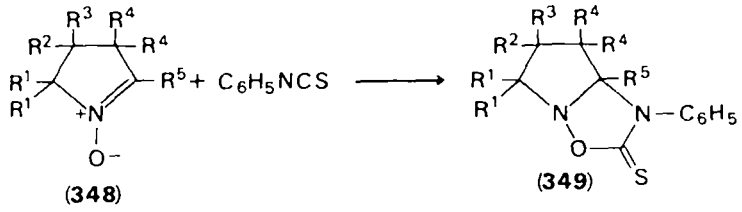


(218)

R = Ph, PhCO

(346) (347)

Cyclic aldo- and ketonitrones react with phenyl isothiocyanate in a similar way. Thus the reaction between methyl substituted 1-pyrroline-1-oxides (**348**) and phenyl isothiocyanate affords the corresponding methyl-substituted 4-phenyl-2-oxa-1,4-diazabicyclo[3.3.0]octane-3-thiones (**349**, equation 218)[647].

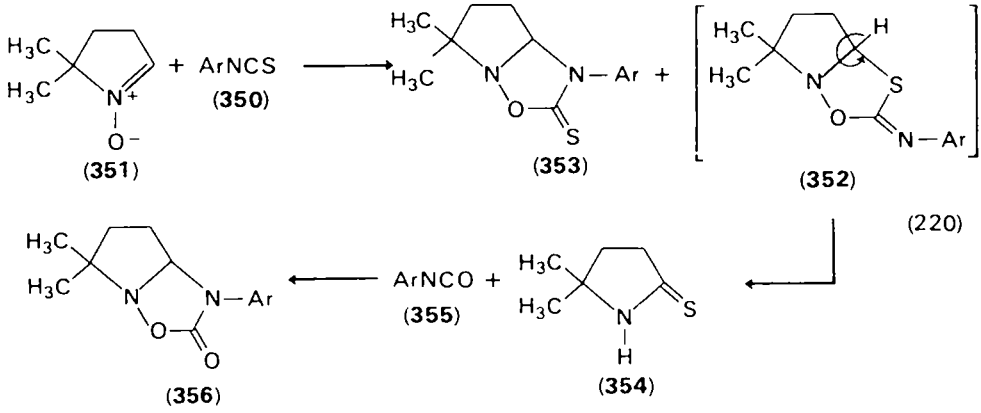


(219)

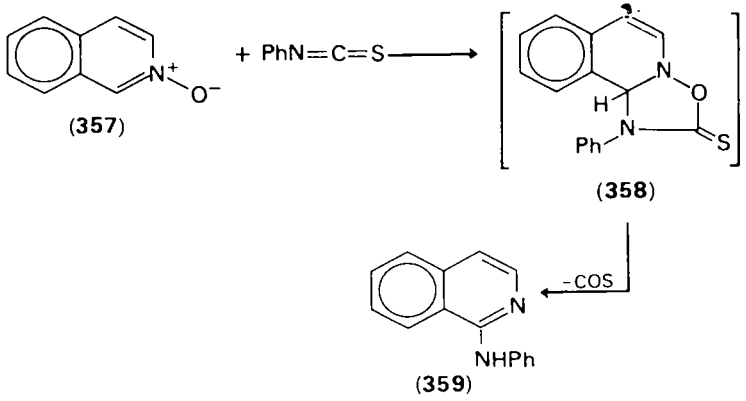
(348) (349)

R^1	R^2	R^3	R^4	R^5
CH_3	H	H	H	H
CH_3	H	H	CH_3	H
H	CH_3	CH_3	H	CH_3
Me	Ph	H	H	CH_3
Me	H	H	H	CH_3

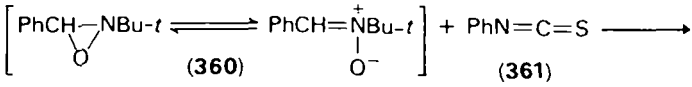
However, substituted phenyl isothiocyanates **350** react with 5,5-dimethyl-1-pyrroline-1-oxide (**351**) to yield both C=S (**352**) and C=N adduct (**353**). The unstable C=S adduct **352** decomposes into thiolactam (**354**) and aryl isocyanate (**355**) which partially react with **351** to give isocyanate adduct **356**[647,649] (equation 220).



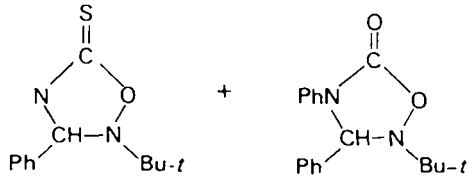
If 3,3,5,5-tetramethyl-pyrroline-1-oxide reacts with aryl or benzoyl isothiocyanates, it affords cycloadducts only through the C=S bond[108]. *N*-Oxides of heteroaromatic compounds, the C=N bond of which is a component of conjugated multiple bonds of the aromatic ring, may be regarded as nitrones. These *N*-oxides (**357**), e.g. the *N*-oxides of isoquinoline[630] and 1-methylbenzimidazole[650], react with isothiocyanates to give unstable cycloadducts (**358**), which split off carbonyl sulphide easily and yield amino derivatives of the corresponding heterocyclic compounds (**359**, equation 221).



Komatsu and coworkers[651] studied the reactions between oxaziridines and phenyl isothiocyanate. They found that only 2-*t*-butyloxaziridine (**360**) reacted with phenyl isothiocyanate (**361**) to give a 1:1 cycloadduct, i.e. oxadiazolidinethione (**362**), in good yield as well as a small amount of oxadiazolidinone (**363**). Because of the steric hindrance of the large *t*-butyl groups this derivative is likely to produce an isomeric nitrone which reacts with isothiocyanate by a 1,3-cycloaddition.

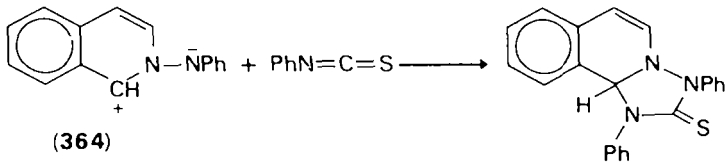


(360) (361)



(362) (363) (222)

Azomethineimines exhibit a high reactivity with respect to isothiocyanates in 1,3-cycloadditions. In contrast to *N*-oxides, they form stable C=N cycloadducts with isothiocyanates. Isoquinoline-*N*-phenylimine (**364**) reacts with phenyl isothiocyanate to give 1:1 adduct **365** (equation 223).

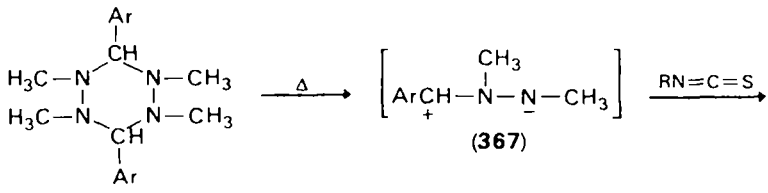


(364) (365) (223)

Azomethine imines (**367**) arising *in situ* by thermolysis of 1,2,4,5-tetrazines (**366**) afford in the presence of isothiocyanates 1,3-cycloadducts of the 1,2,4-triazolidine type (**368**, equation 224)[652].

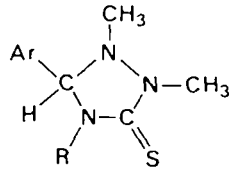
1,3-Dipoles of the azomethienylide system (**369**) may be prepared to advantage *in situ* by thermal decomposition of aziridines[653,654] (equation 225).

A high reactivity of these substances with respect to isothiocyanates manifests itself in the cycloadditions involving the C=S bond of the isothiocyanate group. 1-Cyclohexyl-2-phenyl-4-(*p*-toluoyl)aziridine (**371**) react with *p*-nitrophenyl isothiocyanate (**372**) to give thiazolidine derivative **373** which tautomerizes into 3-cyclohexyl-5-(*p*-nitrophenyl)-amino-2-phenyl-4-(*p*-toluoyl)-4-thiazoline (**374**[655], equation 226).

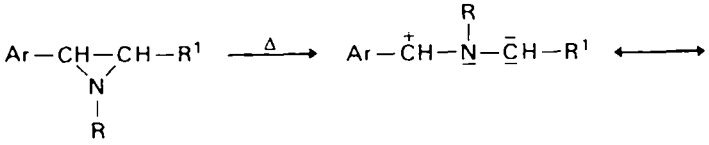


(366) (367)

(224)

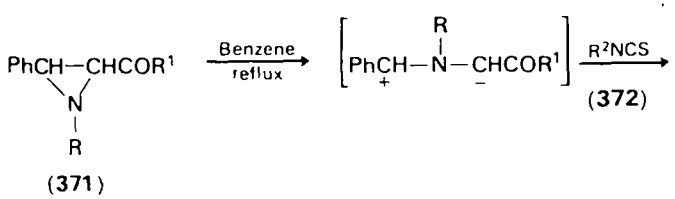


(368)



(369) (370)

(225)

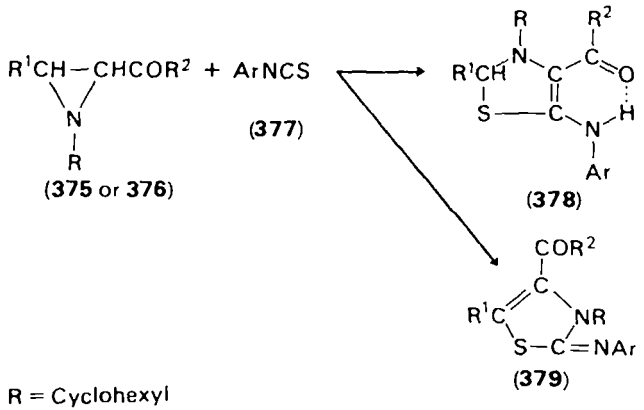


(371) (372) (373) (374)

(226)

R= Cyclohexyl. R^1= p-CH_3—C_6H_4. R^2 = p-NO_2—C_6H_4

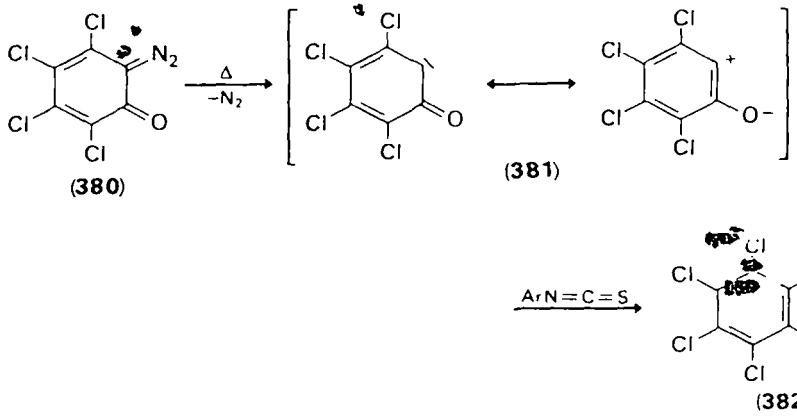
After the reaction between cyclohexyl-2-(*p*-biphenylyl)-3-benzoylaziridine[655] (**375**) or 1-cyclohexyl-2-(2′-thienyl)-3-benzoylaziridine[656] (**376**) and aryl isothiocyanates (**377**) it is possible to isolate two isomeric thiazoline derivatives (**378** and **379**, equation 227).



(227)

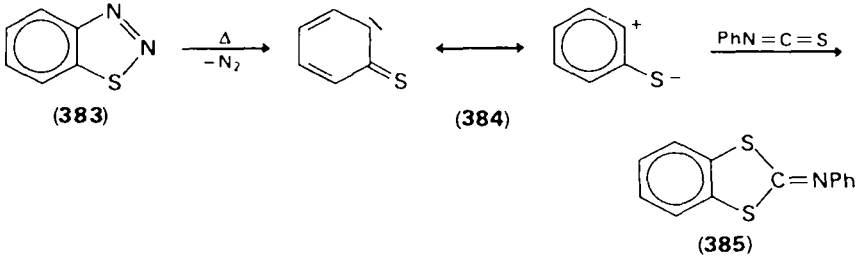
R = Cyclohexyl
R^1 = *p*-Biphenylyl, 2′-thienyl
R^2 = Phenyl

c. *Cycloadditions of other types of* 1,3-*dipoles.* Ketocarbenes containing electron-withdrawing groups are sufficiently stable 1,3-dipoles to enter into cycloadditions with heterocumulenes. Tetrachlorobenzene-*o*-diazooxide (**380**) heated to 130 °C undergoes thermal decomposition into ketocarbenes (**381**) which react in the presence of isothiocyanate through the isothiocyanate C=S double bond to form the 1,3-benzoxathiole derivative **382** (equation 228)[657].



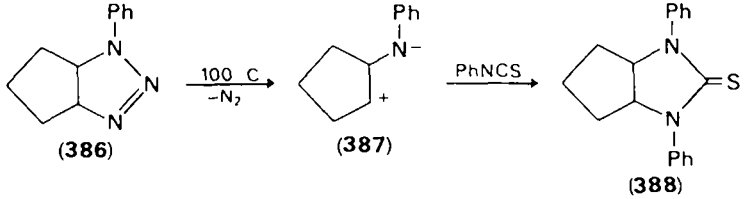
(228)

Thioketocarbenes, too, react with isothiocyanates in an analogous way. Thiocarbene (**384**) produced by thermolysis of 1,2,3-benzothiadiazole (**383**) can react with phenyl isothiocyanate to give 2-phenylimino-1,3-benzodithiole (**385**[658], equation 229).



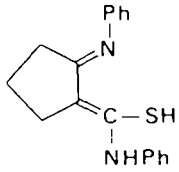
(229)

Huisgen supposed[608] that symmetric cyclic diphenylthiourea was formed in high yield by heating 4-phenyl-2,3,4-triazabicyclo[3.3.0]oct-2-ene (**386**) with phenyl isothiocyanate. The reaction proceeds via the 1,3-dipolar intermediate **387**, the formation of which is followed by 1,3-dipolar cycloaddition (equation 230).

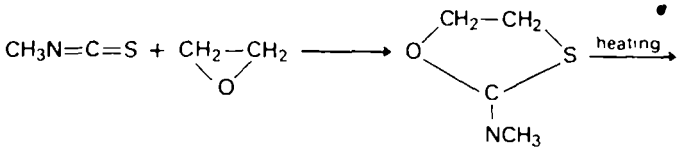


(230)

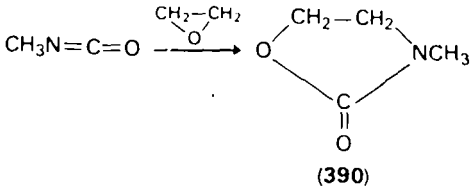
Afterwards Baldwin and coworkers[659] proved on the basis of spectral and chemical data that this reaction followed another mechanism and the final product was not the 1,3-cycloadduct (**388**) but 2-anilinocyclopentenyl-thiocarbanilide (**389**).



Etlis and coworkers were concerned with cycloadditions of alkenoxides[660,661]. The main products of cycloaddition are oxazolidones (**390**) which may arise in different ways according to catalysts and reaction conditions. One of the possible pathways is described by equation (231)[612].

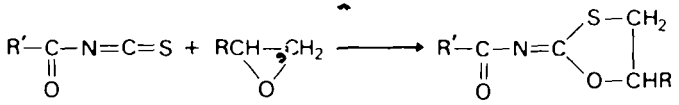


(231)



(390)

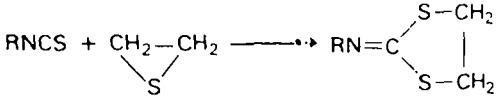
Acyl isothiocyanates (**391**) react with alkylene oxide (**392**) through the C=S double bond of the isothiocyanate group to give 2,5-disubstituted 1,3-oxathiolanes (**393**)[662] (equation 232).



(232)

(391) (392) (393)

The cycloaddition of alkyl isothiocyanates to ethylene sulphide (**394**) yielding the 2-substituted 1,3-dithiolanes[663] (**395**) proceeds in the same way (equation 233).

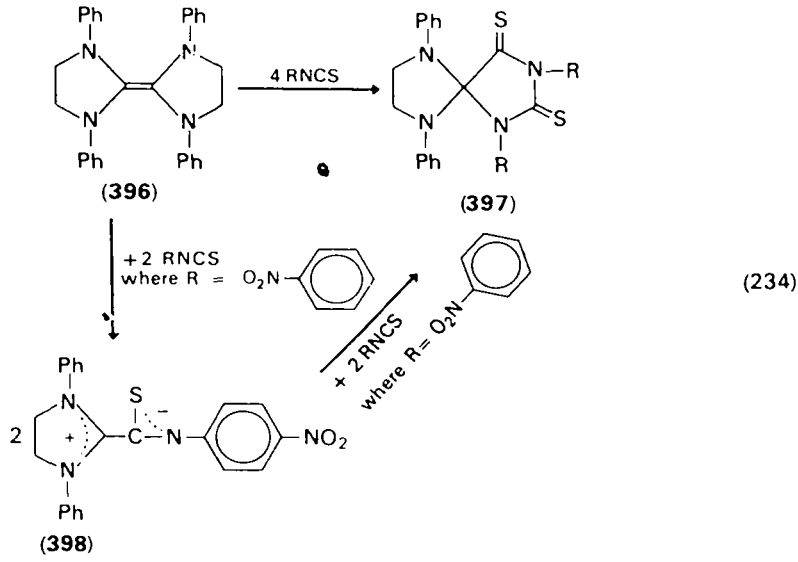


(233)

(394) (395)

Bis(1,4-diphenyl-2-imidazolidinylidene) (**396**) reacts with isothiocyanates in the ratio 4:1 to give 2,4-dithiono-6,9-diphenyl-1,3,6,9-tetraaza-spiro[4.4]nonanes (**397**) in fairly good yields[664]. Provided this reaction was performed with 4-nitrophenyl isothiocyanate in the ratio 2:1, it was possible to isolate a mercapto-*N*-aryl-formimidoyl-imidazate inner salt (**398**) which represents a 1,3-dipolar system stabilized externally. This dipole reacts with another molecule of 4-nitrophenyl isothiocyanate through the C=N double bond of the isothiocyanate group to give product **397**[664] (equation 234).

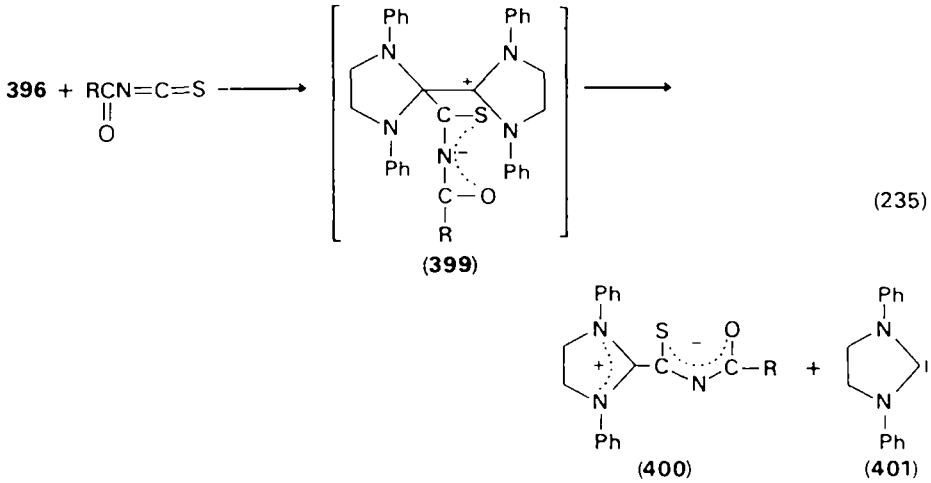
This type of cycloaddition was described for the first time by Winberg and Coffman[665] for bis(1,3-diethyl-2-imidazolidinylidene). Presently Schössler and Regitz[666] heated substance **396** and acyl isothiocyanates in toluene and obtained stable 1,3-dipoles[(2-acylthiocarbamoyl)-1,3-diphenyl-imidazolinium-betaines, **400**] in the crystalline form. In contradiction to earlier authors[665,667] they assumed that only one molecule of



(234)

R = Ph, $PhCH_2$, CH_3, $CH_2{=}CHCH_2$, cyclohexyl, 2-$CH_3C_6H_4$, 4-$NO_2C_6H_4$, 4-$CH_3OC_6H_4$

isothiocyanate entered into reaction and the resulting adduct (**399**) splits into a 1,3-dipole (**400**) and carbene (**401**, equation 235).

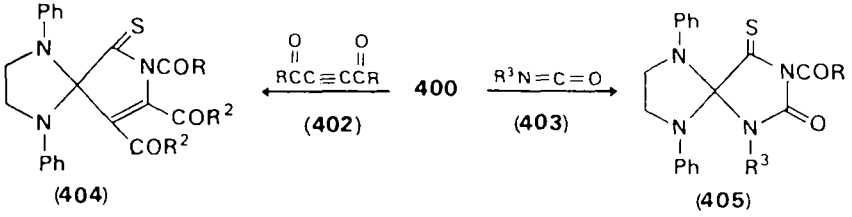


(235)

R = OC_2H_5, Ph, $C_6H_4OCH_3$-*p*, $C_6H_4NO_2$-*p*

The dipoles obtained (**400**) are characterized by [3 + 2] additions to diacylacetylenes (**402**) and isocyanates (**403**). The resulting products of

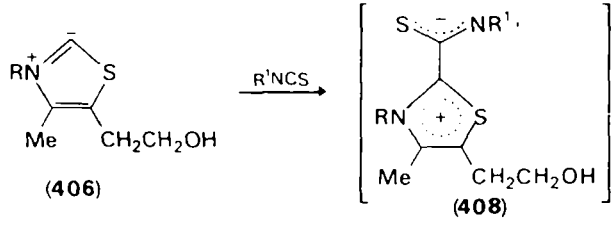
cycloaddition are 1,4,7-triazaspiro[4.4]nonenes (**404**) or 1,4,6,8-tetraazaspiro[4.4]nonanes (**405**, equation 236).



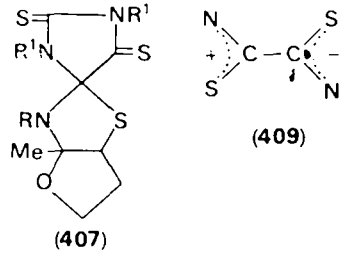
(236)

R^2 = OCH_3, Ph, R^3 = Ph, cyclohexyl.

Takamizawa and coworkers[668] investigated the reactions of thiazolium ylides (**406**) with alkyl isothiocyanates the final products of which were 1:2 cycloadducts containing fused spiro ring systems (**407**). On the basis of analogy with other systems[668,669,670] the authors supposed that this reaction involved the formation of a 1:1 adduct **408**. This 1,3-dipolar intermediate **408** thus formed undergoes subsequent cyclization with another molecule of isothiocyanate to yield a 1:2 cycloadduct **407** (equation 237).



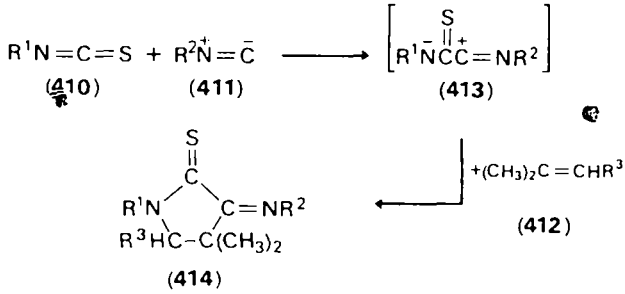
(237)



Later Takamizawa and coworkers[607] confirmed that aryl isothiocyanates reacted with thiamine and related thiazolium ylides to form separable 1:1 adducts containing a new dipolar system (**409**). The distribution of products expressed by the ratio of the 1:1 adduct to the 1:2 adduct depends considerably on the character of substituent in aryl isothiocyanate.

Electron-withdrawing substituents support the formation of the zwitterion (1,3-dipole, **408**) while electron-donating substituents favour the formation of the cycloadduct (**407**).

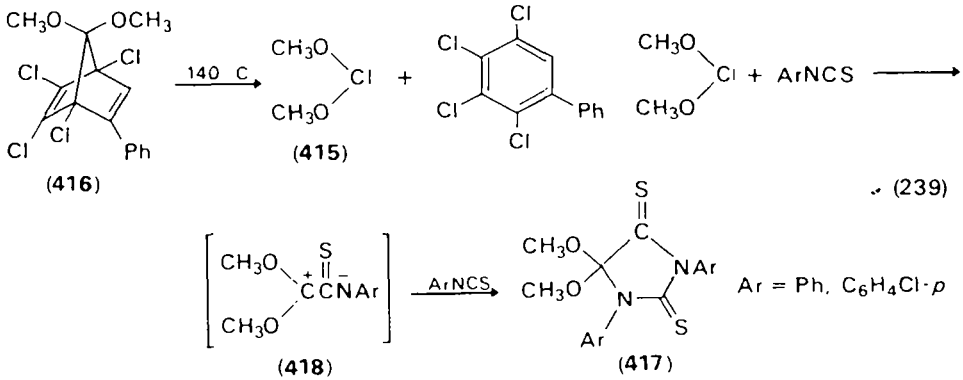
Isothiocyanates (**410**) react with isonitriles (**411**) and enamines (**412**) in polar solvents to yield iminothiopyrrolidines[671] (**414**). Though the authors do not describe the mechanism of this reaction, it may be supposed that by analogy[672] the reaction involves transient formation of the corresponding 1,3-dipole (**413**, equation 238).



(238)

R^1 = Cyclohexyl, 4-nitrophenyl, methyl
R^2 = Cyclohexyl, 4-(3,3′-dimethylazobenzene)
R^3 = *N*-Pyrrolidinyl, *N*-piperidinyl

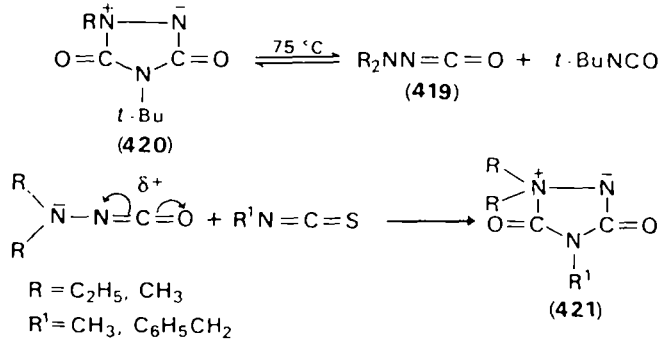
Dimethoxycarbene (**415**) arising by thermal decomposition of 1,2,3,4-tetrachloro-7,7-dimethoxy-5-phenylbicyclo[2.2.1]hepta-2,5-diene (**416**), reacts with excess aryl isothiocyanate to give the corresponding 5,5-dimethoxydithiohydantoins[673] (**417**). In the first reaction step an addition of dimethoxycarbene to aryl isothiocyanate takes place an an externally stabilized 1,3-dipole (**418**) arises. In the second reaction step the 1,3-dipole undergoes cycloaddition through the C=N double bond of another molecule of aryl isothiocyanate to give final product **417** (equation 239).



(239)

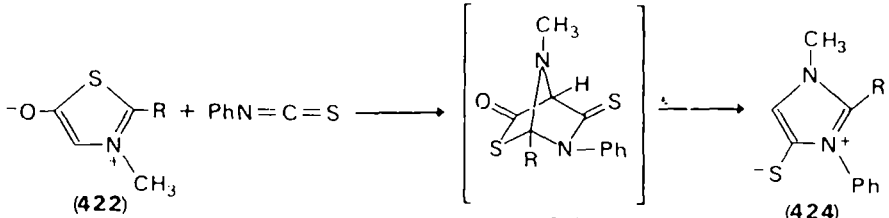
Ar = Ph, C_6H_4Cl-*p*

N,N-Dialkyl aminoisocyanates (**419**) generated from 1,1-dimethyl-4-*t*-butyl-1,2,4-triazolidine-3,5-dione-1,2-aminimides (**420**) behave towards isothiocyanates as 1,3-dipoles. They undergo addition through the C=N bond of the isothiocyanate group to give 1,1,4-trialkyl-1,2,4-triazolidine-3-one-5-thione-1,2-aminimides (**421**) in good yield[674] (equation 240).



(240)

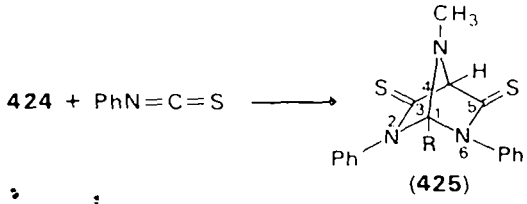
Some mesoionic compounds of the anhydro-2-aryl-5-hydroxy-3-methylthiazolium hydroxide system (**422**) represent 1,3-dipoles which react easily with phenyl isothiocyanate in hot benzene in the way of [3 + 2] cycloaddition[675]. The primary 1 : 1 cycloadduct (**423**) splits off carbonyl sulphide to give anhydro-2-aryl-4-mercapto-1-methyl-3-phenylimidazolium hydroxide (**424**), equation 241).



R = Ph, *o*-ClC6H4, *p*-CH3OC6H4

(241)

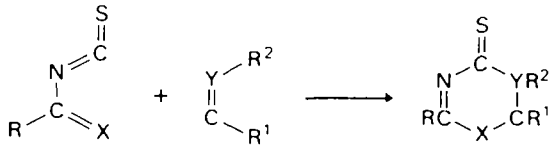
If the reaction is performed in the absence of solvent, it is possible to isolate from the reaction mixture not only product (**424**) but also a cycloadduct containing phenyl isothiocyanate, i.e. the 1-substituted 7-methyl-2,6-diphenyl-2,6,7-triazabicyclo[2.2.1]heptane-3,5-dithione (**425**, equation 242).



(242)

3. [4 + 2] Cycloadditions

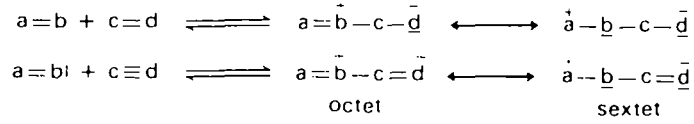
This group comprises mainly the dimerizations and cycloadditions of isothiocyanates of the carbonyl type with electron rich multiple bonds known from the publication of Goerdeler and coworkers[90] (equation 243).



X = O,S,NR
Y = C,N

(243)

These reactions proceed formally in the way of the Diels–Alder reaction with inverse electron demand[609] to produce six-membered heterocycles according to the scheme 4 + 2 → 6. Their mechanism has not been elucidated unambiguously. Owing to a high polarity of multiple bonds of the dienophilic components, a two-step mechanism is not out of the question[677]. It is necessary to distinguish between the Diels–Alder reactions and the 1,4-dipolar cycloadditions which satisfy the scheme 4 + 2 → 6 but involve some unstable substances of 1,4-dipole character arising *in situ* from a nucleophilic ab and an electrophilic cd component in the equilibrium process[631] (equation 244).

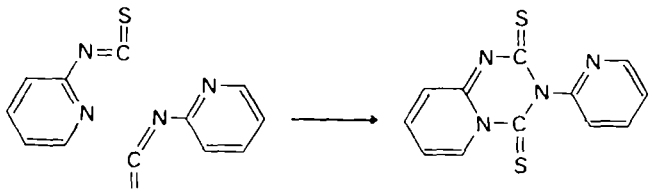


(244)

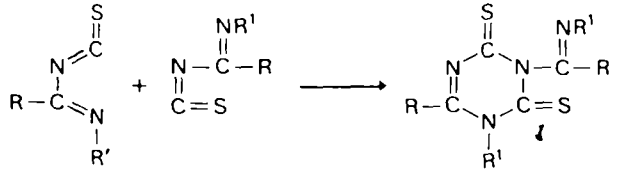
Cycloadditions to such 1,4-dipoles can proceed only in two steps by successive formation of both σ-bonds. The reactions between isothiocyanates and 1,4-dipoles have been given little attention up to now.

a. *Additions of isothiocyanates to C=N bond systems.* The dimerizations of some reactive isothiocyanates in which one molecule functions as a diene component and the other as a dienophile were the subject of the earliest studies. 2-Pyridyl isothiocyanate (**426**)[676] and imidoyl isothiocyanates (**427**)[117,118] dimerize to form derivatives of triazine (**428**, equations 245 and 246).

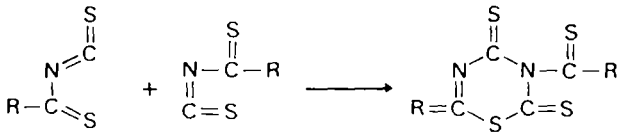
Thiocarbamoyl isothiocyanates (**429**)[105,144] and ethylmercaptothiocarbonyl isothiocyanate (**430**)[90,116] afford dimers of thiadiazine structure (**431**, equation 247).



(426) (428) (245)



(427) (428) (246)

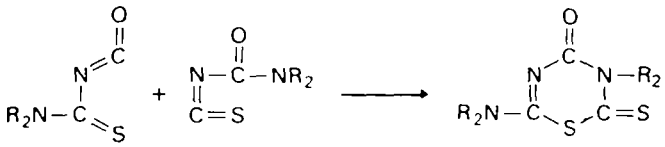


(431) (247)

$R = NR_2'$ (**429**)

$R = SC_2H_5$ (**430**)

Owing to their dual character, carbamoyl isothiocyanates[102,104] dimerize in such a way that the diene component appears in the form of isomeric thiocarbamoyl isocyanate (**432**) while isothiocyanate (**433**) represents the dienophilic component. The resulting products of dimerization are the 2,5-substituted thiadiazine-4-one-6-thiones (**434**, equation 248).

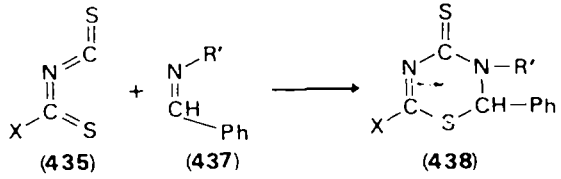


(**432**) (**433**) (**434**) (248)

Alkoxycarbonyl isothiocyanates dimerize to give four-membered heterocycles of the 1,3-dithietane type (**301**).

Considerable attention was given to cycloadditions of carbonyl isothiocyanates to azomethines. Thiocarbamoyl isothiocyanates

(435)[114,678] and (alkylthio)- or (arylthio)-thiocarbonyl isothiocyanates (436)[116] react with benzylidene-alkyl and aryl amines (437) to yield 2-substituted 5,6-dihydro-4*H*-1,3,5-thiadiazine-4-thiones (438, equation 249).

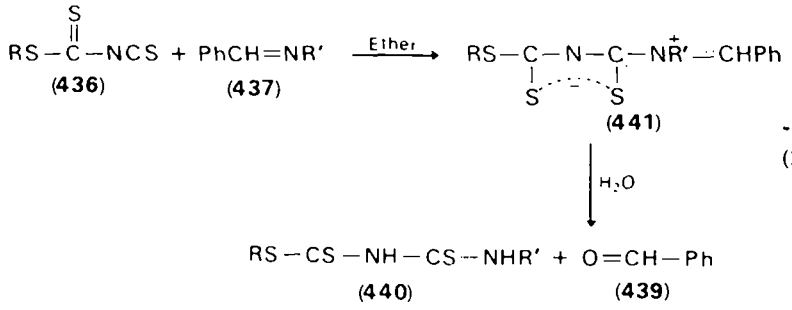


(435) (437) (438) (249)

X = NR_2, (435), SR, SAr, (436)

R' = CH_3, cyclohexyl, Ph, *o,o'*-$(CH_3)_2C_6H_3$

Azomethines containing aliphatic R' are much more reactive than those with an aryl R' group. In dry ether or dichloromethane the cycloaddition terminates at room temperature in the course of few minutes or hours depending on the substituents. In moist ether, isothiocyanates (436) react with azomethines to give benzaldehyde (439) and thiourea (440). As azomethines and cycloadducts (437) do not hydrolyse under the reaction conditions, the authors assume that the reaction proceeds via dipolar intermediate 441 which also seems to be an intermediate for cycloaddition (equation 250).



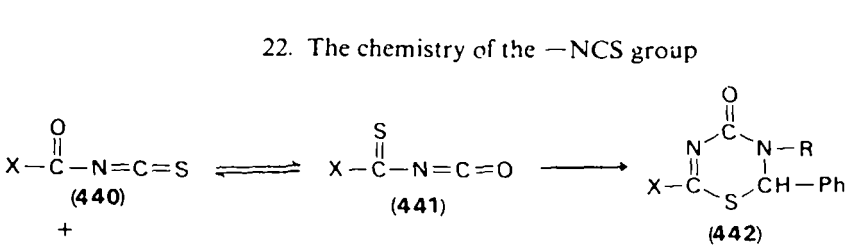
(436) (437) (441) (250)

(440) (439)

Carbamoyl isothiocyanates (440) add azomethines in isomeric thiocarbamoyl isocyanate form (441) to yield the corresponding 5,6-dihydro-4*H*-1,3,5-thiazine-4-ones (442[104], equation 251).

Benzoyl isothiocyanate (443) reacts with benzylidenemethylamine (444) even at room temperature to give a yellow crystalline 1 : 1 adduct to which the structure of 3-methyl-2,6-diphenyl-3,4-dihydro-2*H*-1,3,5-oxadiazine-4-thione (445)[679] has been ascribed (equation 252).

Cycloadduct 445 is thermally unstable and decomposes into the original components even on heating in solution.



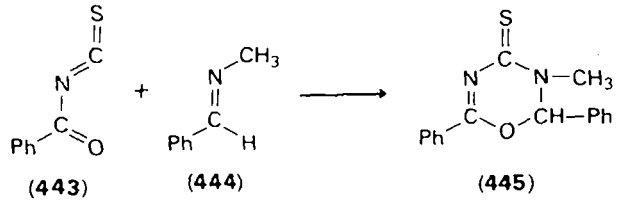
(440) (441) (442) (251)

+

$RN{=}CHPh$

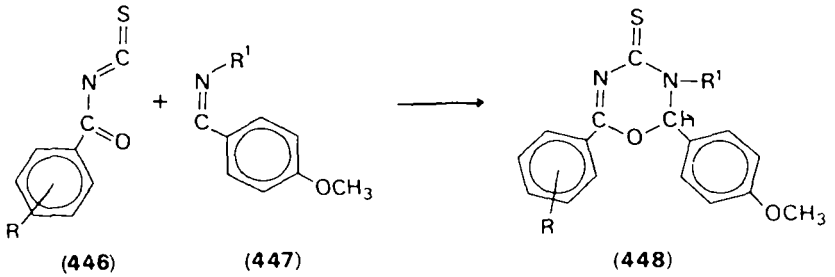
X = $(CH_3)_2N$, $(C_2H_5)N$, $(C_6H_{11})_2N$, piperidino, morpholino, CH_3NPh, C_2H_5NPh, Ph_2N

R = CH_3, C_6H_{11}, $PhCH_2$, Ph, p-CH_3O—C_6H_4, β-$C_{10}H_7$



(443) (444) (445) (252)

Milzner and Seckinger[680] studied cycloadditions of benzoyl isothiocyanates to azomethines. They found that *N*-(*p*-methoxybenzylidene)-amine (**446**) reacted with aroyl isothiocyanate (**447**) in the way of 4 + 2 cycloaddition to give exclusively 1,3,5-oxadiazine derivatives (**448**, equation 253).

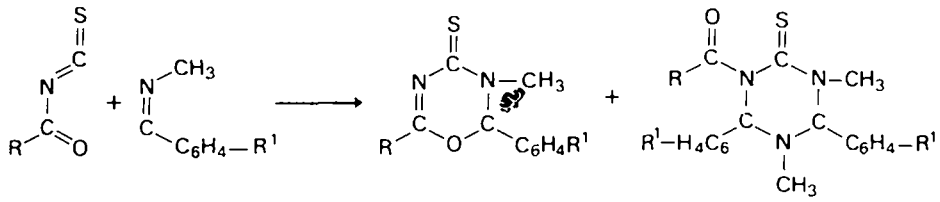


(446) (447) (448) (253)

R = H, 3,4-Cl_2, 4-Cl, 4-CH_3, 4-OCH_3

R^1 = CH_3, C_4H_9-*n*, 3,4-Cl_2–C_6H_3, 4-OCH_3–C_6H_4, 4-ClC_6H_4, 4-$CH_3C_6H_4$

The 4 + 2 cycloaddition (**449**) to azomethines (**450**) with electron-withdrawing substituents gives 1:1 (**448**) and 2:1 (**451**) cycloadducts (equation 254).



(449) (450) (448) (451)

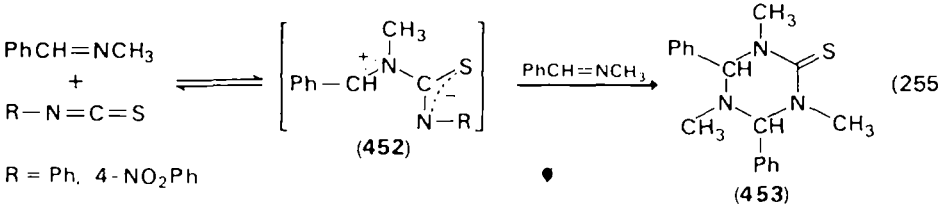
(254)

R = C_6H_4–NO_2-*p*

R^1 = 3,4-Cl_2, 4-Cl, 4-NO_2

The course of cycloaddition depended predominantly on electronic effects of the *C*-aryl substituents in the molecule of azomethine. A substitution in the amine residue of azomethine and the aryl residue of the isothiocyanate does not influence the ratio of products **448** and **451**. The methoxy group in the C residue of azomethine is decisive for the formation of product **448**. The authors consider the two-step mechanism via the 1,4-dipole to be more probable.

Aryl isothiocyanates react with azomethines solely to give 2:1 cycloadducts[679]. The reaction proceeds via the 1,4-dipole **452** while the cumulated system of isothiocyanate represents the electrophilic compounds. Another molecule of azomethine takes part in the subsequent cycloaddition yielding hexahydro-*s*-triazine thione derivatives (**453**, equation 255).

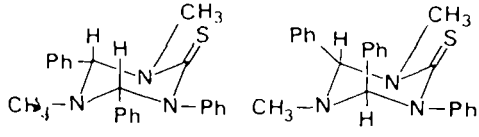


(452) (453)

(255)

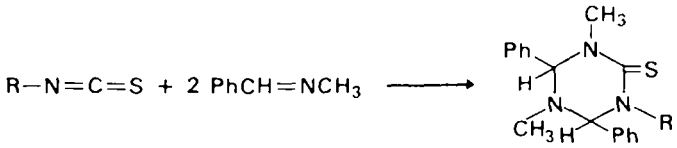
R = Ph, 4-NO_2Ph

In the case of benzoyl isothiocyanate two diastereoisomeric 2:1 adducts **454** and **455** were isolated.



(454) (455)

In a similar way, some carbonyl isothiocyanates react with benzylidene methylamine to give a 2:1 adduct **456**[104] (equation 256).

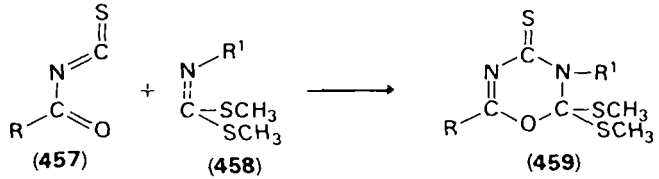


(256)

(456)

R = Ph_2N-CO, C_2H_5O-CO, CH_3S-CO, $PhC=NPh$, $p\text{-}CH_3-C_6H_4-SO_2$

The addition of aroyl isothiocyanates (**457**) to iminothiocyanates (**458**) also belong among the cycloadditions through the C=N double bonds. Irrespective of the molar ratios of reacting components **457** and **458**, 2,2-bis(methylthio)-dihydro-1,3,5-oxadiazine-4-thiones (**459**)[680], arise (equation 257).



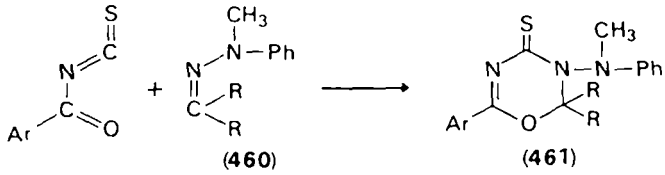
(257)

(457) **(458)** **(459)**

R = $p\text{-}NO_2-C_6H_4$

R^1 = CH_3, $C_3H_7\text{-}i$, $C_4H_9\text{-}n$, $c\text{-}C_6H_{11}$, $CH_2=CHCH_2$, $CH_3OC_3H_6\text{-}n$, $p\text{-}OCH_3-C_6H_4$

Aroyl isothiocyanates react with *N,N*-disubstituted hydrazones (**460**) to give 1,3,5-oxadiazines (**461**) as reaction products[681] (equation 258).



(258)

(460) **(461)**

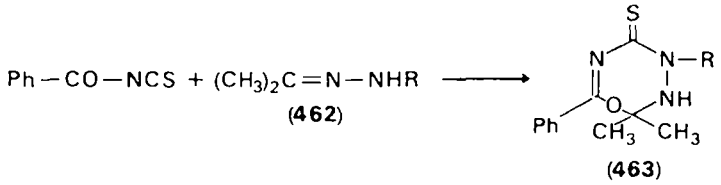
Ar = Ph, $p\text{-}CH_3OC_6H_4$, $p\text{-}NO_2C_6H_4$

R = CH_3, $-(CH_2)_4-$, $-(CH_2)_5-$

An equilibrium is established in solution between the starting components and cycloadducts. The possibility of obtaining oxadiazines

(**461**) in the solid form depends on solubility, rate of crystallization, and irreversible side reactions.

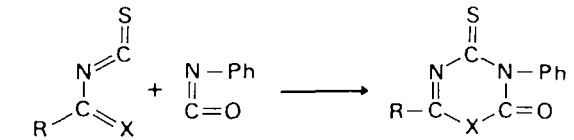
Some monosubstituted acetone hydrazones (**462**) react with benzoyl isothiocyanate to yield oxatriazepine derivatives[682] (**463**, equation 259).



(259)

(**462**) (**463**)

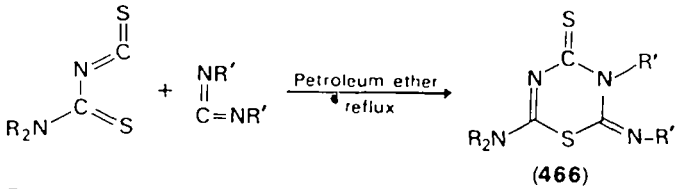
Thiocarbamoyl isothiocyanates[114] and imidoyl isothiocyanates[118] enter into 1,4-cycloadditions with the C=N bond of the isothiocyanato groups to give 2,5-disubstituted 4-thioxo-5,6-dihydro-4*H*-1,3,5-thiadiazine-6-ones (**464**) or 1,2,5-trisubstituted 4-thioxo-1,4,5,6-tetrahydro-*s*-triazine-6-ones (**465**, equation 260).



(260)

X = S (**464**)
X = NR (**465**)

Thiocarbamoyl isothiocyanates add carbodiimides through the C=N bonds to form 5,6-dihydro-1,3,5-thiadiazine-4-thiones[114] (**466**, equation 261).

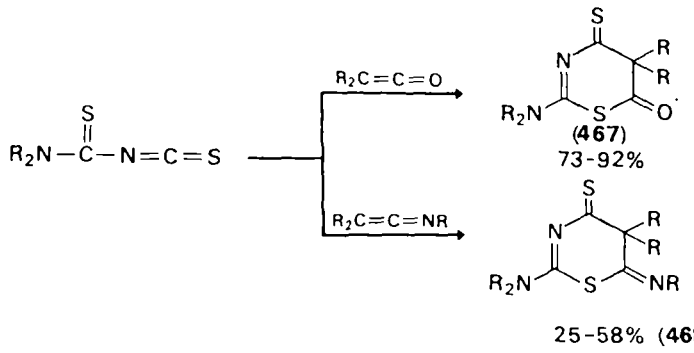


(261)

(**466**)

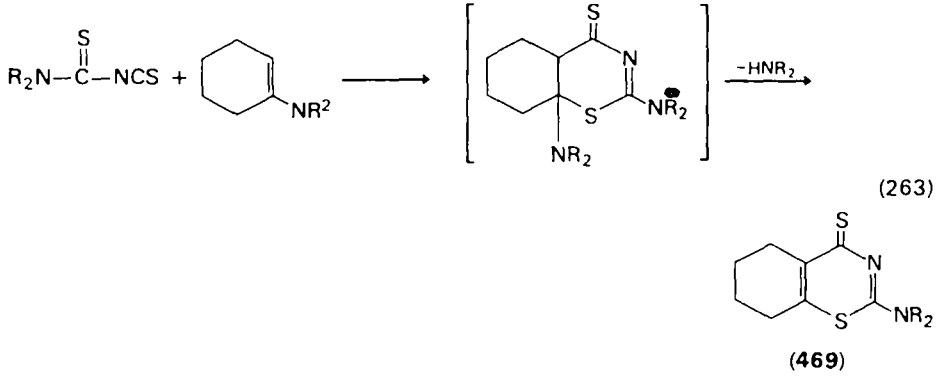
R = *i*-C_3H_7, *c*-C_6H_{11}, $PhCH_2$
R′ = *i*-C_3H_7 *c*-C_6H_{11}

b. *Additions of isothiocyanates to C=C bond systems.* Some carbonyl isothiocyanates enter into 1,4-cycloadditions through the C=C double bonds of heterocumulenes (ketens, ketenimines) or enolethers and enamines. Thiocarbamoyl isothiocyanates[112] give 2-amino-6-oxo-4-thioxo-5,6-dihydro-4*H*-1,3-thiazines with ketens in good yields and 2-amino-6-imino-5,6-dihydro-4*H*-1,3-thiazine-4-thiones (**468**) with ketimines (equation 262).



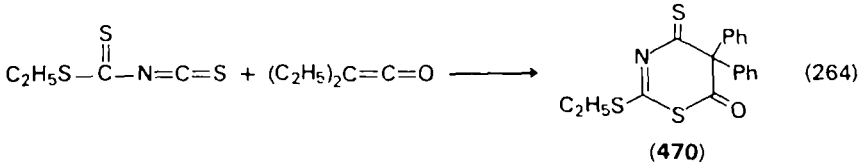
(262)

The reaction between thiocarbamoyl isothiocyanates and tertiary enamines may be regarded as a cycloaddition followed by elimination. The resulting products are 2-amino-tetrahydrobenzothiazine-4-thiones (**469**, equation 263).



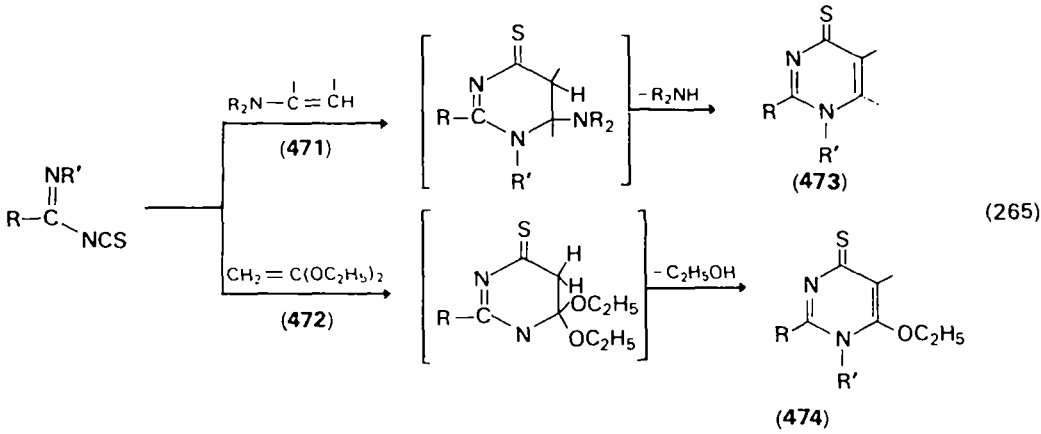
(263)

(Ethylthio)-thiocarbonyl isothiocyanate[116] affords, with diphenylketene, 2-ethylthio-5,5-diphenyl-4-thioxo-5,6-dihydro-4*H*-1,3-thiazine-6-one (**470**, equation 264).



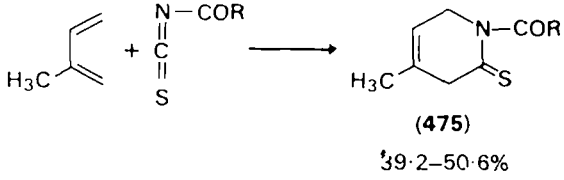
(264)

Imidoyl isothiocyanates react with tertiary enamines (**471**) and ketenediethylacetal (**472**) in the manner of a 1,4-cycloaddition followed by the elimination of a molecule of amine or alcohol to give 1,4-dihydropyrimidine-4-thiones (**473** and **474**, equation 265).



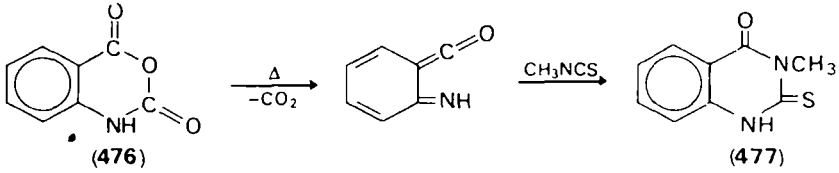
(265)

c. *Isothiocyanates as dienophiles.* In 1966 Arbuzov and Zobova[683] published the diene synthesis of benzoyl and acetyl isothiocyanates with butadiene, isoprene, cyclopentadiene and 2,3-dimethyl-1,3-butadiene. The cycloaddition with the C=N double bond yielded the 1,2,3,6-tetrahydropyridine derivatives (**475**, equation 266).



(266)

The reaction takes place in sealed tubes in an inert atmosphere in the presence of an inhibitor over 6–7 months at 18–20 °C. Similarly, the reaction between isatoic anhydride (**476**) and methyl isothiocyanate gives a tetrahydrochinazoline derivative[684] (**477**, equation 267).

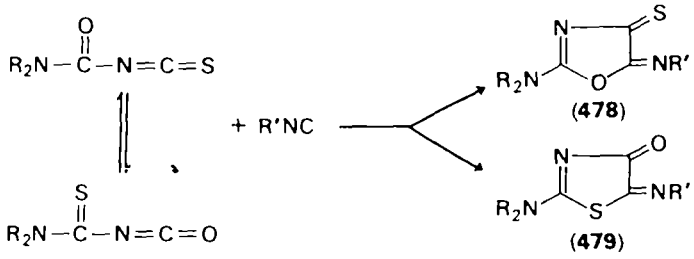


(267)

4. [4+1] Cycloadditions

These reactions comprise the 4 + 1 → 5 cycloadditions of carbonyl isothiocyanates to isonitriles. The reactions between carbamoyl isothiocyanates and isonitriles exhibit the dual character of these cycloadditions[104]. The structure of the main product depends on the

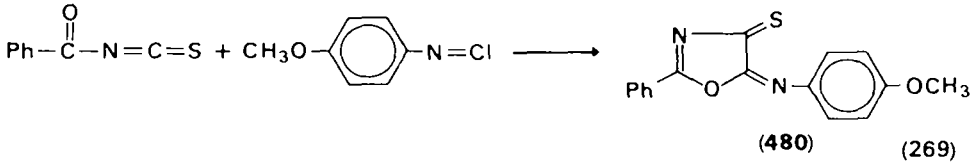
substituents in the molecule of carbamoyl isothiocyanate while oxazoline thiones (**478**) or thiazolinones (**479**) may arise (equation 268). As a rule, an oxazoline derivative (**478**) is formed as the main reaction product.



(268)

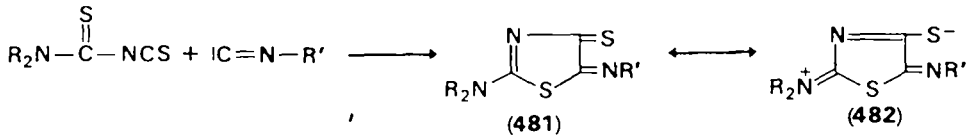
Dicyclohexylcarbamoyl isothiocyanate shows different behaviour. It reacts with isonitriles to give a thiazoline derivative (**479**) which may be due to a greater selectivity caused by steric conditions in the system.

Benzoyl isothiocyanate reacts easily with *p*-methoxyphenyl isonitrile to yield 2-phenyl-5-*p*-methoxyphenylamino-oxazoline-4-thione[104] (**480**, equation 269).



(269)

Analogously, thiocarbamoyl isothiocyanates cyclize with isonitriles to form 2-amino-5-iminothiazoline-4-thiones[114] (**481**, equation 270).



(270)

R = CH_3, C_2H_5, *i*-C_3H_7, *c*-C_6H_{11}

R' = *t*-C_4H_9, *c*-C_6H_{11}, Ar

On the basis of the n.m.r. spectra of derivative **481** the authors have come to the conclusion that the resonance form **482** contributes substantially to the ground state of the molecule.

VII. REACTIVITY OF ISOTHIOCYANATES

The first information obtained from a quantitative study of the reactions of isothiocyanates was achieved by investigating the additions of alkyl and aryl isothiocyanates, in particular, to the OH^- ion[685,687,483], butylamine[686], glycine[688] or other amino acids[537], and 2-mercaptoacetic acid[689,568]. The cited papers published in the years from 1958 to 1965 also give the first experimental proof that all the above-mentioned reactions of isothiocyanates studied are of the type Ad_N. In the following years this study was focused more on the characterization of reactivity of various series mainly comprising new synthetic isothiocyanates with respect to nucleophilic agents, than on a more thorough elucidation of the mechanism of these reactions or a quantitative study of other types of reactions, e.g. some important but more complicated cycloadditions.

The isothiocyanates hitherto investigated, in spite of their variety, represent a certain stereotype characterized by a uniform type of bond between the polyatomic functional NCS groups and the carbon atom of the altered residue. The data concerning the reactivity of acyl or aroyl isothiocyanates used all the time in organic preparative chemistry are very rare and difficult to compare with one another. Up to the present, there have been no quantitative data on the reactivity of other undoubtedly interesting types of isothiocyanates in which the NCS group is bonded to an atom of silicon, nitrogen, sulphur, or phosphorus.

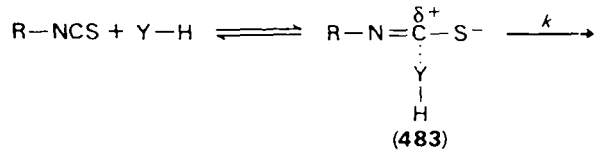
Though the subject matter of this section consists of evaluation of the available kinetic data concerning the reactivity of isothiocyanates, we will also treat briefly other relevant physicochemical data.

A. Nucleophilic Additions

1. Attack by the OH^- ion and amino group

The reactions of isothiocyanates with OH^- ions and amines were for the first time studied quantitatively by Zahradník[685,686]. He investigated a series of 20 alkyl, allyl, and aralkyl isothiocyanates by a polarographic method and confirmed in both cases that the reactions were additions in which the isothiocyanate behaved as an electrophilic component. Both reactions are bimolecular and under the conditions used for the investigation (high $[OH^-]/[ITC]$ or $[RNH_2]/[ITC]$ ratio) they proceeded as first order reactions to give the corresponding *N*-alkyl thiocarbamates or *N*-alkyl thioureas, which were the only expected reaction products. The rate of combination of isothiocyanate with OH^- in a predominantly aqueous medium was found in these experiments to be directly

proportional to the concentration of isothiocyanate and free OH^- ion. It was also found that the reaction with amines was analogous; however, it was proved that this substance took part in the reaction only in the form of a free base, the concentration of which was controlled by the dissociation reaction which precedes the addition. On the basis of these findings, as well as on investigations of the influence of ionic strength, composition of buffer solutions, relationships between the structure of isothiocyanates and their reactivity and other parameters, Zahradník suggested a common formal reaction mechanism for both the additions of isothiocyanates (equation 271). This mechanism is based on the possible intermediate resonance structure $R—N=C^+—S^-$ which was presumed to take part in the formation of complex **483** with both types of nucleophiles. Therefore the rate-determining step is a reaction with the carbon atom bearing an electron sextet in the NCS group.



(483)

(271)

(484) **(485)**

YH = OH^-, RNH_2

For the reaction with the OH^- ion the reaction scheme may be written with more precision by designating the fractional or whole negative charge on the oxygen atom, i.e. on Y in structures **483** and **485** (in this case the structure —CY—S^- is also taken into consideration). For the reactions with amine the presence of a fractional or a whole positive charge on the nitrogen atom of structures **483** and **484** may be taken into account.

A comparison of the second-order rate constants of the reactions of alkyl isothiocyanates (Table 16) shows that the relationships between the structure of isothiocyanates and their reactivity with respect to the OH^- ion and butylamine is similar. The reactivity of isothiocyanates increases with decreasing volume and increasing electrophilicity of the alkyl group. This result is also indicated by the revealed linear dependence of the logarithms of the relative rates of the reaction between alkyl isothiocyanates and the OH^- ions on the Taft σ^* constants. Furthermore, it was revealed that a linear relationship between $\log k_{OH}$ and $\log k_{butylamine}$ exists for a large group of

aliphatic isothiocyanates[686]. Nevertheless, the data in Table 16 demonstrate a rather low reactivity of *t*-butyl isothiocyanate with respect to the OH^- ion.

TABLE 16. Second-order rate constants $k(l\ mol^{-1}\ min^{-1})$ for the reaction of alkyl isothiocyanates with hydroxide ions and butylamine in an aqueous medium[685,686]

Isothiocyanate	k_{OH^-} (25 °C)	$k_{n\text{-}BuNH_2}$ (25 °C)
Methyl	3·76 ± 0·20	3·22 ± 0·15
Ethyl	2·14 ± 0·06	1·54 ± 0·06
i-Propyl	0·91 ± 0·05	0·96 ± 0·05
t-Butyl	0·02 ± 0·002	0·05 ± 0·005
n-Propyl	1·07 ± 0·06	1·30 ± 0·06
i-Butyl	1·05 ± 0·06	1·24 ± 0·06
n-Butyl	1·61 ± 0·08	1·49 ± 0·07
n-Amyl	1·24 ± 0·07	1·15 ± 0·09
Cyclohexyl	0·50 ± 0·02	0·74 ± 0·05
Allyl	3·85 ± 0·20	5·56 ± 0·25
Benzyl	5·95 ± 0·30	5·89 ± 0·25

On the other hand, the values of activation energy found for various alkyl isothiocyanates are within the range 11·8 to 14·8 kcal mol^{-1} (the values found for benzyl and cyclohexyl isothiocyanate) except for the highest value (17·8 ± 1·0) found for *t*-butyl isothiocyanate[685]. A redetermination of the reactivity of some alkyl isothiocyanates (including *t*-butyl isothiocyanate) with respect to the OH^- ion by means of spectrophotometric[688,689,418] and gas–liquid chromatography[690] techniques gave the second-order rate constants which are in agreement with the constants determined polarographically by Zahradnik. But the value for the activation energy ascertained for the reaction between *t*-butyl isothiocyanates and the OH^- ions from the linear relationship given by equation (217) is 14·8 kcal mol^{-1}. This linear relationship was obtained by a computer-fitted least square analysis of the rate data (correlation coefficient $r = -0{\cdot}970$).

$$-\ln k = -7478\left(\frac{1}{T}\right) + 21{\cdot}0 \qquad (272)$$

(T = temperature in kelvin)

Exceptional attention was given to the investigation of the reactivity of the *meta*- and *para*-substituted phenyl isothiocyanates with respect to the OH^- ions and different types of amino compounds, especially glycine. For more

than 45 phenyl isothiocyanates representing mainly new synthetic derivatives, the reaction kinetics with the OH^- ions was studied polarographically[483,499] and for some derivatives spectrophotometry was used as well[688,418], while the reaction between phenyl isothiocyanates and glycine was investigated merely spectrophotometrically[688,537,691].

The reactivity of phenyl isothiocyanates was characterized by the first-order and second-order rate constants, and of some derivatives by the activation parameters also, which made it possible to verify the validity of the isokinetic relationship for the series of derivatives studied as well as to justify the application of the Hammett equation in the discussion of experimental results. The second-order rate constants given in Table 17 enable us to correlate the reactivity at least of phenyl isothiocyanates with the characteristic Hammett substituents.

TABLE 17. Second-order rate constants k (l mol^{-1} min^{-1}) of the reaction of the *meta*- and *para*-substituted phenyl isothiocyanates with glycine and hydroxide ion[483,688,691,499]

Substituent		$k_{glycine}$ (25 °C)	k_{OH^-} (30 °C)
$-NO_2$	*m*	51·5 ± 3·4	–
	p	~ 163	–
—Br	*m*	28·8 ± 2·3	54·7 ± 1·5
	p	21·1 ± 1·3	36·4 ± 1·0
$-COCH_3$	*m*	27·0 ± 0·4	45·7 ± 2·2
	p	42·2 ± 2·4	–
—Cl	*m*	26·2 ± 1·4	63·9 ± 3·6
	p	22·2 ± 2·0	40·4 ± 1·4
—COOH	*m*	13·3 ± 0·4	5·8 ± 0·21
	p	16·8 ± 0·9	14·0 ± 0·7
—I	*m*	31·1 ± 1·1	56·2 ± 1·6
	p	24·8 ± 3·2	37·1 ± 1·1
—OH	*m*	10·1 ± 0·9	23·1 ± 0·8
	p	8·5 ± 1·22	—
$-OCH_3$	*m*	13·3 ± 0·3	24·3 ± 1·6
	p	7·6 ± 0·91	—
$-C_6H_5$	*m*	11·7 ± 1·0	28·1 ± 1·7
	p	13·8 ± 0·3	12·2 ± 2·0
$-CH_3$	*m*	10·8 ± 0·7	9·5 ± 0·90
	p	9·8 ± 1·60	–
$-N(CH_3)_2$	*m*	5·3 ± 0·60	4·0 ± 0·26
	p	5·9 ± 0·61	1·7 ± 0·05
—H		14·6 ± 0·6	7·5 ± 0·2

The data in Table 18 indicate that the reactivity with respect to the OH^- ion as well as glycine in the investigated series of the *meta*- and *para*-substituted isothiocyanates obeys the Hammett equation. The values of correlation coefficients of the corresponding positive ρ constants demonstrate a good correlation in the relationships investigated. The deviations are discussed in more detail in the corresponding references. It is useful to point out those cases which may be explained by the manifestation of a steric effect. For example, lengthening of the carbon chain of the alkoxy group in *meta*-alkoxycarbonylphenyl isothiocyanates leads to a decrease in the reactivity towards glycine[691]:

Substituent:	$COOC_2H_5$	$COOC_5H_{11}$	$COOC_6H_{13}$
k(l mol^{-1} min^{-1}):	18·2	16·4	6·1

The reactivity of different types of amino compounds towards isothiocyanates is mainly determined by the basicity of the amino groups. This fact has been demonstrated by the results of the study of the reactivity of different alkyl amines towards methyl isothiocyanate[686] and amino acids towards aryl isothiocyanates[537]. It follows from the data in Table 19 that the order of reactivity of amino acids towards each of the isothiocyanates investigated is similar but does not correspond completely to the order based on the pK_a values. The reactivity of the isothiocyanates investigated decreases with the assumed decreasing electron-withdrawing effect of R in the order: *p*-acetylphenyl > phenyl > 2-naphthyl > *p*-dimethylaminophenyl.

The investigation of a wider series of reactions of amino acids and some peptides with phenyl isothiocyanates have confirmed the earlier finding that the reactivity of selected amino acids towards phenyl isothiocyanate obeys the Taft equation[693] and decreases with decreasing basicity of the amino group of glycine and peptides in the order Gly > Leu–Gly > Gly–Gly > Gly–Gly–Gly[694,695]. On the other hand, a linear relationship between the logarithms of the second-order rate constants (25 °C) of the reaction of phenyl isothiocyanate with glycine, diglycine, cystine, lysine, or oxidized glutathione and the pK_a values of the α-amino groups, given by equation (273) (correlation coefficient 0·90) was revealed[692].

$$\log k = 0{\cdot}235\, pK_a - 1{\cdot}38 \qquad (273)$$

Since the reactivity of the NCS groups towards nucleophilic agents increases with decreasing density of the π-electrons on the carbon atom a relationship between the reactivities of different types of isothiocyanates with respect to the OH^- ion, glycine, butylamine, and other nucleophilic

TABLE 18. The constants ρ of the Hammett plot for reactions of *meta*- and *para*-substituted phenyl isothiocyanates with hydroxide ions and the amino group of glycine and diglycine in aqueous media, and of butylamine in methanol

Derivatives	Number of substances	Reactant	T(°C)	ρ	r	Method	Reference
m and *p* substituted	13	OH^-	30	1·68 ± 0·17	0·950	A	483
m substituted	12	OH^-	30	1·57 ± 0·12	0·980	A	499
p substituted	6	OH^-	25	1·76 ± 0·18	0·956	B	418
m and *p* substituted	14	Glycine	25	0·84 ± 0·01	0·931	B	688
m substituted	18	Glycine	25	1·03 ± 0·07	0·963	B	691
m and *p* substituted	27	Glycine	25	0·94 ± 0·05	0·955	B	691
p substituted	5	Diglycine	25	0·713 ± 0·06	0·985	B	692
p substituted	5	Butylamine	30	1·13 ± 0·08	0·985	B	505

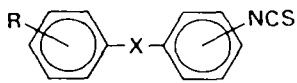
A, polarographic method; B, spectrophotometric method.

TABLE 19. Rate constants, k (l mol^{-1} min^{-1}), the reaction of aryl isothiocyanates with amino acids at 25 °C in 0·1 M-borate buffer of pH 9·8 with 2% dioxane[708]

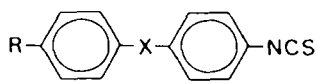
Amino acid	Phenyl	*p*-Acetyl phenyl	*p*-Dimethyl-aminophenyl	2-Naphthyl
Glycine	14·6 ± 0·6	42·2 ± 2·4	5·9 ± 0·6	11·1 ± 1·4
Leucine	9·6 ± 0·4	29·6 ± 0·8	3·7 ± 0·2	7·4 ± 0·6
Valine	9·3 ± 0·3	30·2 ± 0·3	3·5 ± 0·3	7·3 ± 0·6
Phenylalanine	8·8 ± 0·3	31·5 ± 0·9	3·8 ± 0·4	6·3 ± 0·3
Aspartic acid	8·3 ± 0·5	24·2 ± 0·7	2·6 ± 0·3	7·2 ± 0·4
Lysine	8·0 ± 0·4	21·0 ± 0·7	3·5 ± 0·3	5·6 ± 0·4
Alanine	7·8 ± 0·3	22·3 ± 0·9	2·5 ± 0·2	5·9 ± 0·3
Glutamic acid	6·6 ± 0·1	21·3 ± 0·5	2·3 ± 0·2	5·3 ± 0·5
Serine	5·0 ± 0·2	17·3 ± 0·6	1·8 ± 0·1	4·4 ± 0·5
Tryptophan	—	—	8·4 ± 0·4	—

agents is to be expected. In fact a linear relationship between the reactivities with respect to the OH^- ion and glycine was found for the series including phenyl, biphenyl, and naphthyl isothiocyanates (equation 274)[688].

$$\log k_{OH}^{30^\circ} = 1{\cdot}68 \log k_{Gly}^{25^\circ} + 0{\cdot}3 \qquad (274)$$



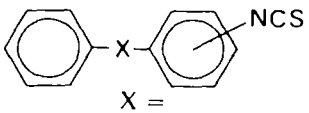
(486)



(487)

Among the substances of type **486** are the isothiocyanato derivatives of biphenyl, diphenylmethane, benzophenone, stilbene, biphenyl ether, azobenzene, diphenyl sulphide, diphenyl, etc. (Table 20). Isothiocyanates of structure **487** were studied in order to determine the influence of low-molecular substituents R on the reactivity of the NCS group and to estimate the transfer of the electronic effects through different conjugated systems. Table 21 shows the obtained linear relationships between the logarithms of the second-order rate constants of the *para*-substituted derivatives of a certain system and the Hammett σ_p constants of the corresponding substituents. It follows from a comparison of the values of ρ for the fundamental series, i.e. benzenoid isothiocyanates, with those for conjugated systems that the transfer of electronic effects in conjugated systems is limited. It may be expressed in terms of the coefficient of electron transfer, π', the value of which is approximately equal to 0·40 for stilbene and to 0·37 for the azobenzene system (calculated from the values of ρ concerning the reactivity with respect to glycine). Other data in Table 21 indicate a still smaller value

TABLE 20. Second-order rate constants (l mol^{-1} min^{-1}) of reaction of conjugated aryl isothiocyanates with glycine and hydroxide ion



		Glycine (25 °C)	OH^- (25 °C)	Reference
C_6H_4	*p*	13·0 ± 0·4	5·35 ± 0·16	688, 696
C_6H_4	*m*	11·7 ± 1·0	—	691
CH_2	*p*	9·4 ± 0·28	4·61 ± 0·14	696
CO	*p*	54·4 ± 1·0	38·6 ± 0·7	697
CO	*m*	10·2 ± 0·5	—	691
CH=CH	*p*	11·3 ± 0·3	6·68 ± 0·20	696
O	*p*	9·8 ± 0·42	6·03 ± 0·34	696, 698
O	*m*	17·2 ± 0·7	—	691
CO—O	*p*	12·1 ± 0·3	—	696
CO—O	*m*	12·6 ± 0·4	—	691
NH	*p*	4·6 ± 0·14	2·17 ± 0·66	696
N=N	*p*	34·3 ± 0·3	25·4 ± 0·5	698
S	*p*	31·1 ± 0·5	12·0 ± 0·1	699
SO_2	*p*	40·7 ± 0·5	66·0 ± 2·0	699
CH_2—S	*p*	15·5 ± 0·3	6·97 ± 0·60	699
CH_2—SO_2	*p*	17·4 ± 0·1	13·5 ± 0·5	699

for the system involving diphenyl ether and the smallest value of π', for the system involving diphenyl sulphide. This sequence ensuing from the evaluation of the kinetic data hitherto published, agrees only partially with the order based on the evaluation of infrared absorption spectra and polarographic half-wave potentials of the isothiocyanates discussed. It was found that in all systems studied the effect of substituents appeared both in the position of the asymmetric NCS vibration absorption bands of the infrared spectrum (2000–2200 cm^{-1}) and in the polarographic half-wave potentials (linear relationship between $\nu_{asym/NCS}$ or $E_{1/2}$ values and the σ_p constants of substituents). Among the values for the coefficients of electron-transfer effect calculated from infrared spectral data (Table 6) the lowest value corresponds to the transfer through carbonyl group. However, it is worth noticing that the calculated value ($\rho = -14{\cdot}8$) has a relatively low value for the correlation coefficient ($r = 0{\cdot}92$)[700]. As is consistent with the result of kinetic measurements, the stilbene and azobenzene systems hold a leading place in the order according to the magnitude of the values of π'. Because of relatively small differences in the slopes, ρ, of the plots expressing the dependence of half-wave potentials on σ_p[500,701], the order of

TABLE 21. Values of the slopes, ρ, of the linear relationships between reactivity (log of the second-order rate constants k_{OH} and k_{Gly}, 25°C) and the σ_p constants for the 4-substituted phenyl isothiocyanates and 4-substituted isothiocyanates of different conjugated systems

System	Glycine (25°C)			OH^- (25°C)			Reference
	ρ	r	n	ρ	r	n	
Benzene	0·94[a]	0·955	27	—	—	—	691
Stilbene	0·38	0·995	8	0·48	0·984	8	698
Azobenzene	0·35	0·972	8	0·39	0·984	8	698
Benzophenone	0·41	0·892	6	0·43	0·941	6	697
Diphenyl ether	0·19	0·866	6	0·35	0·936	6	698
Diphenyl sulphide	0·11	0·816	6	0·25	0·955	6	699

[a] calculated for *m*- and *p*-substituted phenyl isothiocyanates

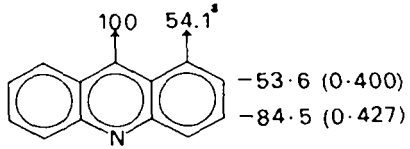
systems fixed according to the values of π' calculated on this base is exceptionally difficult to justify.

Kinetic measurements indicate some important differences in the reactivity of the basic (non-substituted) derivatives of individual systems (Table 20). It has been revealed that a close relationship between the reactivities of these isothiocyanates with respect to the OH^- ions and glycine exists (equation 275)[696]. This finding is of great importance.

$$\log k_{OH}^{25} = 1{\cdot}41 \log k_{Gly}^{25} + 0{\cdot}69 \qquad (275)$$

Aryl isothiocyanates of the polycondensed aromatic hydrocarbon type exceed phenyl isothiocyanate in their reactivity, the only exception being 1-naphthyl isothiocyanate. According to the data in Table 22, for 4-Br-1-naphthyl isothiocyanate the reactivity is 3·7-times higher than it it is for the non-substituted derivative. This increase is, without doubt, due to the $-I$ effect of bromine. A relatively small increase in reactivity of 1-Br-2-naphthyl isocyanate with respect to the OH^- ion on glycine is to be explained by the favourable $-I$ effect as well as the steric hindrance of bromine[483,688]. From the theoretical point of view it is very interesting that a relationship between the reactivity of polynuclear isothiocyanates and the atomic localization energy of the position in parent hydrocarbons where the NCS group is bonded has been revealed[483].

As for heterocyclic isothiocyanates, only the reactivity of the derivatives of acridine (**488**), benzacridines, and 3-pyridyl isothiocyanate[702] has so far been investigated. The values of the second-order rate constants k_{OH} ($l\ mol^{-1}\ min^{-1}$; 30 °C) obtained for the derivatives of acridine with the NCS group in the corresponding positions are written in structure **488** while the data in parentheses stand for the corresponding values of free bonds according to molecular diagram[703].



(488)

The reactivity of 3-isothiocyanato acridine is more than 7-times greater than the reactivity of phenyl isothiocyanate. On the other hand, according to the rate constants k_{Gly} (25 °C) for phenyl isothiocyanate the reactivity is 3·8-times higher than it is for heterocyclic 3-pyridyl isothiocyanate[702].

Aryl alkyl isothiocyanates (Table 23) are less reactive than phenyl isothiocyanate, while conjugated derivatives, for instance β-styryl

TABLE 22. The second order rate constants k (l mol^{-1} min^{-1}) activation energies E_A (kcal/mol) for the reaction of aryl isothiocyanates R—NCS with the OH^- ion[483]

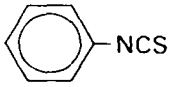
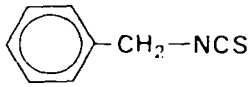
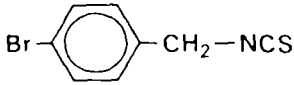
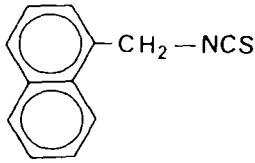
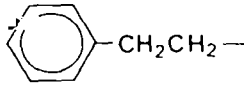
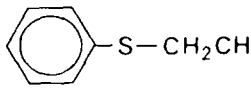
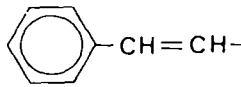
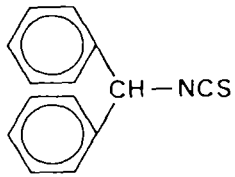
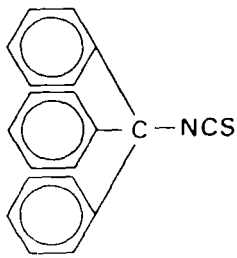
R	k (30 °C)	E_A
Benzene	7·51 ± 0·20	9·5 ± 0·5
Naphthalene-1-	6·13 ± 0·27	12·2 ± 0·3
Naphthalene-2-	11·6 ± 0·6	13·4 ± 0·3
4-Bromonaphthalene-1-	23·0 ± 0·4	—
1-Bromonaphthalene-2-	16·5 ± 2·1	—
Anthracene-2-	15·6 ± 0·2	—
Pyrene-1-	10·5 ± 0·2	—
Chrysene-6-	10·4 ± 0·3	—

isothiocyanate, represent an exception. In agreement with theoretical views, it was ascertained that the substituents (halogens, $—NO_2$, —CN, $—OCH_3$, $—CH_2$ group) in the aromatic residue of benzyl and benzhydryl isothiocyanates had a small influence, especially as regards the reactivity of these derivatives towards glycine. Notwithstanding, the dependence of the vibration frequencies $\nu_{asym(NCS)}$ on the Hammett σ_p constants ($\rho = -21{\cdot}69$, $r = -0{\cdot}94$ for benzyl isothiocyanate and $\rho = -18{\cdot}13$, $r = -0{\cdot}95$ for benzhydryl isothiocyanate) indicates a certain effect of substituents on the character of the NCS group for these derivatives, too[704,705].

It is possible to correlate the second-order constants k_{Gly} with the Taft constants as demonstrated for the series of isothiocyanato derivatives of amino acids[706]. These substances as well as benzyl or benzhydryl isothiocyanates belong among those types of aryl alkyl isothiocyanates which exhibit remarkable biological activity and therefore we shall deal with them again in subsequent sections.

The reactivity of phenyl isothiocyanates with respect to amines has also been investigated in non-aqueous systems. Rao and Venkataraghavan have shown that by the addition of aniline to the *para*-substituted phenyl isothiocyanates the rate data give a linear correlation with the Hammett constants. Similar kinetic studies on the addition of the *para*-substituted anilines to phenyl isothiocyanates show that the reaction rate increases with electron-donating ability of the substituents in aniline as well as with the basicity of aniline[707]. It is worthy of note that this information ensues from the investigation of the reaction in dioxan containing trimethylamine (0·01 M). Akiyama and coworkers[708] measured the rates of the reaction of the *ortho*-, *meta*- and *para*-substituted anilines with phenyl isothiocyanate and *para*-fluorophenyl isothiocyanate in carbon tetrachloride by infrared spectrometry and correlated them with the amino-proton chemical shifts of the substituted anilines in the same solvent. The reactivity of the amino

TABLE 23. The second-order rate constants k ($l\ mol^{-1}\ min^{-1}$) of the reaction of phenyl isothiocyanate and arylalkyl isothiocyanates with glycine

	k (25 °C)	Reference
	14·6 ± 0·6	688
	4·7 ± 0·9	688
	5·8 ± 0·9	688
	5·9 ± 0·4	696
	5·6 ± 0·2	696
	7·0 ± 0·1	699
	41·0 ± 2·3	696
	4·0 ± 0·14	704
	4·2 ± 0·4	696

group of the *m*- and *p*-substituted anilines was found to be linearly dependent upon the electron density on the nitrogen atom of the amino group. For the *o*-substituted anilines a large deviation from the linear correlation was observed. Although this deviation was interpreted in terms of hydrogen bonding of the amino-proton to the *ortho* substituents, the reactivity was mostly governed by steric strain of the amino group in reaction with phenyl isothiocyanate[708].

2. Attack by HS^- and RS^- ions

The first information obtained by quantitative study of the reactions between isothiocyanates and thiols was published by Drobnica and Augustín in 1965[568]. Spectrophotometric investigations of the kinetics of the reactions between 14 aromatic isothiocyanates and thioglycolate in buffered aqueous systems, or in systems consisting of water and organic solvent, demonstrated that isothiocyanates reacted with mercaptoacetic acid through the ionized sulphydryl group. This base-catalysed addition follows an Ad_N2 mechanism and, provided thioglycolate is present in reasonable excess, the reaction advances quantitatively with respect to isothiocyanate, i.e. the side reaction with the OH^- ions is negligible even in strongly alkaline buffer solutions. This inference also follows from the fact that as determined, the second-order rate constants k(l mol^{-1} s^{-1}) of the reaction of aryl isothiocyanates with mercaptoacetic acid were higher by four orders of magnitude on the average than the rate constants of the reaction with OH^- ions or glycine (investigated under identical conditions). The relative rates of reaction of aryl isothiocyanates with mercaptoacetic acid showed a linear dependence when plotted against the relative rates of reaction of aryl isothiocyanates with OH^- ions or glycine.

Finally, determination of the temperature dependence of reaction rates has shown that the isokinetic relationship is fulfilled for the investigated series of aryl isothiocyanates[568].

The spectrophotometric method developed for the investigation of the reaction between isothiocyanates and 2-mercaptoacetic acid was used to advantage for the study of the reactions of isothiocyanates with sodium sulphide, ethanethiol, ethyl mercaptoacetate, 2-mercaptoethanol, 2-mercaptopropionic acid, methyl 2-mercaptopropionate, dithiothreitol, benzenethiol[569], and other thiols[709]. The following conclusions have been drawn from these investigations:

(i) All thiol compounds studied react in dissociated form. This statement is in agreement with the generally accepted idea of extremely different

nucleophilicity of the dissociated and undissociated thiol groups. Some results concerning the reaction of phenyl isothiocyanate with sodium sulphide serve for illustration (Table 24).

TABLE 24. The first- and second-order rate constants, k, for the reaction of phenyl isothiocyanate with sodium sulphide measured at different pH values in buffered reaction mixtures[569]

pH	$k \times 10^3$ [a] (s^{-1})	$c_{HS^-} \times 10^4$ [b] (mol/l)	k ($l\,mol^{-1}\,s^{-1}$)
7·00	5·39	4·08	13·20
7·25	7·34	5·40	13·60
7·50	8·16	6·58	12·40
7·75	9·67	7·52	12·87
8·00	10·81	8·17	13·25
8·25	11·15	8·58	13·00
8·50	11·29	8·80	12·82
9·00	11·80	9·09	13·00
10·00	11·70	9·19	12·85
11·00	11·80	9·20	12·82

[a] 25 °C.

[b] The concentration of HS^- was calculated from the formula $c_{HS^-} = c_0\,[1 + \text{antilog}(pK_a - pH)]$, where c_0 (mol/l) is the analytical concentration of sulphide and K_a is the first dissociation constant of H_2S.

(ii) Under the conditions described in the cited papers isothiocyanates react quantitatively with HS^- and RS^- ions to give dithiocarbamates and the *S*-esters of *N*-substituted dithiocarbamic acids, respectively. Mercaptoacetic acid and its ethyl ester are exceptions because the corresponding 3-substituted rhodanines are the reaction products in this case (addition precedes the cyclization reaction).

(iii) The reactivity of phenyl isothiocyanates with respect to the HS^- and RS^- ions obeys the Hammett equation with positive slopes which vary over a narrow range (Table 25). The differences in the reactivity of phenyl isothiocyanates and benzyl isothiocyanates can be evaluated on the basis of the data given in Table 26.

(iv) The correlation between the values of logarithms of the second-order rate constants k for the reaction of isothiocyanates with the SH^- ion or aliphatic thiols and the values of corresponding dissociation constants shows clearly that the reactivity of thiols increases with their basicity.

TABLE 25. The constants of the Hammett equation $\log k_i/k_0 = \rho\sigma$ for the reactions of the 4-substituted phenyl isothiocyanates with sulphide and different aliphatic thiols at 25 °C[568,569]

R—SH	ρ	r	$\log k_0$ (s^{-1})	n
H^+ (Na^+)	+0·898 ± 0·086	0·979 ± 0·074	1·035	8
HS—CH(OH)—CH(OH)—	+0·969 ± 0·068	0·927 ± 0·086	2·310	6
$H_3COCOCH_2CH_2$—	+0·961 ± 0·107	0·982 ± 0·069	3·223	5
$HOCH_2CH_2$—	+1·170 ± 0·083	0·990 ± 0·064	2·875	6
$HOOCCH_2$—	+0·961 ± 0·094	0·968 ± 0·129	3·359	9
H_3CCH_2—	+0·536 ± 0·072	0·974 + 0·082	2·775	5
$HOOCCH_2CH_2$	+0·767 ± 0·048	0·994 ± 0·039	3·450	5

r = correlation coefficient; n = number of the p-substituted phenyl isothiocyanates.

The experimental study of the reactions of isothiocyanates with 2-mercaptoethylamine, cysteine, cystine, and glutathione or oxidized glutathione, has shown that it is possible to choose the reaction conditions, especially a suitable pH of buffered reaction mixtures, under which only the reaction with the sulphydryl groups occurs[689,692,709]. The possibility of selective occupation of the SH^- groups was also confirmed later for some defined proteins[710]. This suggests an enormous difference in nucleophilicity of the thiol ($—S^-$) and amino ($—NH_2$) groups present in proteins where in comparison with the low-molecular model compounds studied, this difference is still more favoured by the increased difference between the pK_a values of these groups.

The *S*-esters of *N*-monosubstituted dithiocarbamic acids of general formula **489** (equation 276), especially provided R^2 is a low molecular substituent, also represent a vast class of biologically active substances. These substances as well as the thiol proteins modified with isothiocyanates, decompose in alkaline solution to give thiol and isothiocyanate (equation 277) which further reacts with OH^- ions to yield the corresponding monothiocarbamate (equation 278). Recently, Drobnica and Gemeiner[711] showed that a prerequisite of alkaline decomposition was the dissociation of **489** to unstable form **490** (equation 276). On the basis of kinetic and u.v. spectral data they determined the dissociation constants for different types of the mentioned compounds (Table 27).

TABLE 26. Rate constant k of the reactions of the *para*-substituted phenyl isothiocyanates and benzyl isothiocyanates with different aliphatic thiols (25 °C)[568,569]

Thiol	k(l mol^{-1} s^{-1})						
	X—C_6H_4—NCS						$PhCH_2$—NCS
	CH_3O—	CH_3—	H—	Br—	CH_3CO—	O_2N—	
HSCH(OH)CH(OH)SH	89	155	275	220	698	1091	54
$H_3COCOCH_2CH_2SH$	985	1090	1785	2245	5690	—	910
$HOCH_2CH_2SH$	422	485	607	1100	3010	6500	228
$HOOCCH_2SH$	—	—	1900	2495	4500	12050	1900
H_3CCH_2SH	394	515	492	773	1110	—	252
$HOOCCH_2CH_2SH$	1760	1950	2770	4580	6400	—	1250
$H_5C_2OCOCH_2SH$	—	103	128	—	—	—	139

$$R^1NHCSSR^2 \underset{}{\overset{K}{\rightleftharpoons}} R^1N{=}C\begin{matrix}S^- \\ SR^2\end{matrix} + H^+ \qquad (276)$$

(489) (490)

$$\mathbf{490} \underset{k_{-1b}}{\overset{k_{+1b}}{\rightleftharpoons}} R^1{-}NCS + R^2S^- \qquad (277)$$

$$R^1{-}NCS + OH^- \xrightarrow{k_{OH^-}} R^1NHCOS \qquad (278)$$

The determination of the pK_a values and the first-order rate constants of the decomposition of the *S*-esters of dithiocarbamic acids made it possible to discuss in more detail the structure–stability relationship for these compounds, and showed at the same time that the effect of substituents R^1 and R^2 on the pK_a value may be estimated from the pK_a values of the corresponding R^1NH_2 and R^2SH reactants.

The constants characterizing the dissociation–decomposition reaction (equation 276 and 277), i.e. the pK_a values, constants k_{+1b} and k_{-1b}, and other data presented in paper[711], complete the idea of the mechanism of the addition of isothiocyanates to thiols. On the other hand, they may be of good use for the preparation of the compounds of structure **491** starting from *S*-esters of dithiocarbamic acids and different nucleophilic agents R—XH according to equation (279).

TABLE 27. The pK_a constants of the *S*-esters of *N*-monosubstituted dithiocarbamic acids[711]

$R^1NHCSSR^2$		pK_a (25 °C)[a]	
R^1	R^2	A	B
p-BrC_6H_4	C_2H_4OH	8·93 ± 0·04	—
Ph	C_3H_7	9·17 ± 0·03	9·11 ± 0·02
Ph	C_2H_4OH	9·20 ± 0·04	—
p-$BrC_6H_4CH_2$	C_2H_4OH	11·58 ± 0·28	—
$PhCH_2$	C_2H_4OH	11·59 ± 0·04	—
$PhCH_2$	C_3H_7	11·87 ± 0·02	11·88 ± 0·02
$PhCH_2$	CH_2COOH	—	11·99 ± 0·02
Ph	Glutathione	9·17 ± 0·08	—
$PhCH_2$	Glutathione	12·05 ± 0·10	—

[a] Method: A, spectrophotometric; B, kinetic.

$$R^1NHCSSR^2 + R^3XH \longrightarrow R^1NHCSXR^3 + R^2SH \quad (279)$$

(491)

Such exchange reactions are important in connection with some special problems, such as inhibition of thiol enzymes with isothiocyanates and restoring of their activities, use of macromolecular polyisothiocyanates for the preparation of immobilized enzymes and isolation of the low-molecular and polymeric compounds containing thiol groups.

3. Addition of alcohols

Browne and Dyson[554,712] compared the reactivities of various aromatic isothiocyanates with respect to ethanol at its boiling point by isolating and weighing the products after different periods of time. Although they studied this reaction with a great number of substituted phenyl isothiocyanates, no satisfactory correlation of the kinetic data with the electrical properties of substituents was found. Rao and Venkataraghavan[713] found the addition of alcohols to substituted phenyl isothiocyanates to be a second-order reaction. The rate data gave a satisfactory linear correlation with the Hammett's constants of substituents. The second-order reaction rates were determined at 53–55 °C in benzene by using methanol as a reactant and triethylamine as a catalyst. In the opinion of the above-mentioned authors, the mechanism of the catalysis consists of the formation of a complex isothiocyanate–triethylamine (**492**) and its subsequent reaction with alcohol (equation 280).

$$R-C_6H_4N=C=S + NEt_3 \rightleftharpoons R-C_6H_4N=C(^+NEt_3)-S^- \text{ or } R-C_6H_4-N^--C(=S)-{}^+NEt_3$$

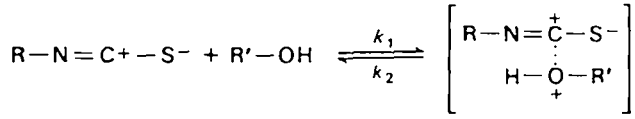
(492)

$$\mathbf{492} + R'-OH \longrightarrow R-C_6H_4NH-C(=S)-O-R' + NEt_3 \quad (280)$$

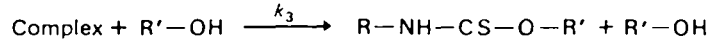
In another study Rao and Venkataraghavan[707] found that the rate of the addition of alcohols to *p*-bromophenyl isothiocyanate decreased in the order $CH_3OH > C_2H_5OH > n\text{-}C_3H_7OH > i\text{-}C_3H_7OH$ in spite of the fact that the basicities of the alcohols changed in the reverse order. Therefore they inferred from this finding that steric factors might operate in the very early stages of the mechanism involving the solvation of isothiocyanate by the molecules of alcohol. The first step in the mechanism may involve the formation of a complex containing the molecules of isothiocyanate and

alcohol while the second step involves the breaking of the solvated molecule of isothiocyanate by another molecule of alcohol.

Iwakura and Okada[714] investigated the kinetics of the reaction of isothiocyanates with a large excess of 1-octanol in *o*-dichlorobenzene at 90–140 °C. However, the second-order rate constants varied with the initial concentration of 1-octanol. Owing to this fact, a reaction mechanism (equation 281) involving the transition state with two molecules of 1-octanol was suggested to be the slow step of the reaction. This reaction mechanism is similar to that of the reaction between organic isocyanates and alcohols[715,716].



(281)

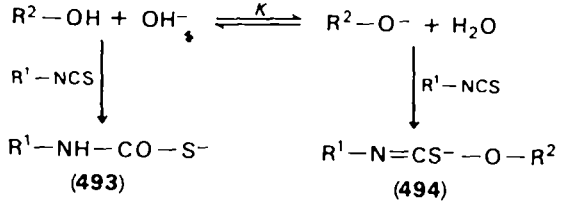


According to Reference 714, the relative rate of reaction of isothiocyanates with 1-octanol decreased at 120 °C in the order benzyl, phenyl, allyl, ethyl, *n*-butyl, *n*-hexyl, isobutyl, and cyclohexyl isothiocyanate. The apparent energies of activation and log *A* were 13·5–16·5 kcal mol^{-1} and 4·65–6·46 (*A* in litre mol^{-1} s^{-1}) respectively. Tributylamine had a slight catalytic effect while dibutyltin dilaurate and ferric acetyl acetonate had a strong catalytic effect in these reactions.

Since they react only very slowly with isothiocyanates, alcohols, especially methanol and ethanol, are commonly used as solvents for the preparation and crystallization of isothiocyanates as well as for the study of the reactions of isothiocyanates with different nucleophiles[685,483,499,720].

Two addition products, i.e. monothiocarbamate **493** and monothiourethane **494**, arise in the reaction of isothiocyanates in aqueous alcohol solutions (equation 282). Two nucleophilic agents compete for isothiocyanate, i.e. the hydroxyl ion and the alkoxide ion, the concentration of which is given by the dissociation equilibrium described by the equilibrium constant *K*. Since the portion of alcohol in the alkoxide form increases proportionally with concentration of OH^- ions, the ratio of the concentration of monothiourethane formed to the concentration of monothiocarbamate formed in the reaction with a given alcohol is independent of the pH value of the reaction mixture. For a constant concentration of alkaline hydroxide in the system, the ratio of the

concentrations of products is a function of the concentration of alcohol in the reaction mixture.



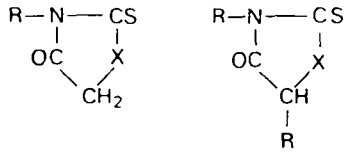
(282)

As the pK_a values of the primary aliphatic alcohols vary from 12·25 (2,2,2-trichloroethanol) to 16·1 (1-butanol) at 25 °C, in alkaline aqueous solutions a considerable part of alcohol is always in the form of alkoxide.

Owing to the near reactivity values of the OH^- and alkoxide ions, it is not possible to perform direct kinetic measurements of the reactivity of the alkoxide ions in alkaline aqueous solutions of alcohols under such conditions that the addition of the OH^- ions could be negligible. It was ascertained by spectrophotometric investigation of the rate of formation of reaction products **493** and **494** that the ratio the reactivities of the methoxide and hydroxyl ions (k_{R-O^-}/k_{OH^-}) was 3·92 for the reaction of phenyl isothiocyanate at 25 °C (analogous value for the ethoxide ion is 5·46)[405].

B. Addition–Cyclization Reactions

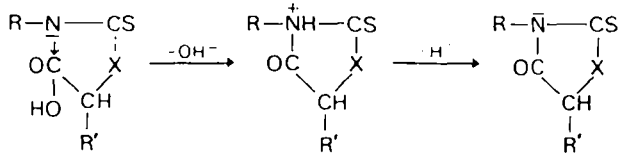
The information obtained from the quantitative study of the addition–cyclization reactions of isothiocyanates has hitherto been limited only to the formation and properties of the 3-substituted and 3,5-disubstituted five-membered heterocyclic compounds of type **495** and **496** containing another heteroatom besides nitrogen.



X = NH (2-thiohydantoins), S (rhodanines), O (2-thiooxazolidine-4-ones)

The reactions of isothiocyanates with glycine and other α-amino acids served for the basic of the methods of preparation of substituted 2-thiohydantoins. In the first step the reaction conditions ensure the reaction

of isothiocyanate with the α-amino group, i.e. the formation of the addition product. The second step, i.e. the cyclization, is achieved by direct acidification of the reaction mixture or by exposing the isolated addition product to the effect of an acid medium[537,717,451]. This reaction may easily be investigated spectrophotometrically. It is relatively slow even at an elevated temperature. For instance, the rate of cyclization of the addition products of the investigated *p*-substituted phenyl isothiocyanates with glycine in 1 M-HCl at 60 °C is characterized by the half-period of cyclization the values of which were in the range 25 to 40 min[537]. By a similar method, i.e. in two steps, it is possible to prepare the corresponding 3-substituted rhodanines[718,441,437] from isothiocyanates and 2-mercaptoacetic acid (equation 283).



X = S, or NH (283)

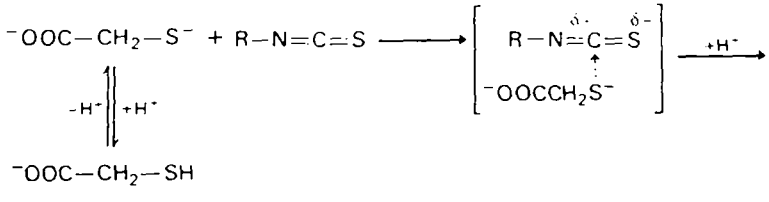
The data in Table 28 show that in case of the *N*-(4-substituted phenyl) thiocarbamoylmercaptoacetic acids, the tendency to cyclization is supported by the electron-donating substituents on the aromatic residue. This is also confirmed by a linear relationship between the logarithms of the rate constants of cyclization k_{obs} (min^{-1}) and the Hammett constants with negative slope $\rho = -0{\cdot}61$ ($r = -0{\cdot}93$)[440].

Further investigation of the reaction between isothiocyanates and mercaptoacetic acid revealed certain remarkable dissimilarities with respect to analogous reactions involving glycine or other α-amino acids. Alkyl and aryl isothiocyanates yield quantitatively 3-substituted rhodanines in the presence of excess mercaptoacetic acid in slightly acid or slightly alkaline buffered systems (pH 7·5)[569,440]. Rhodanines arise even in a more alkaline medium, but the rate of their hydrolysis to the corresponding *N*-substituted thiocarbamoyl mercaptoacetates increases considerably in this case. In the pH region above 10 these addition products are the only probable products of the reaction of isothiocyanates with mercaptoacetic acid. The cyclization of these products to rhodanines is achieved by acidifying the reaction mixture. In slightly acid or alkaline reaction mixtures the addition is immediately succeeded by cyclization (equation 284) owing to which it is very difficult to prove the formation of an intermediary adduct. Furthermore it follows from this fact that owing to nucleophilic attack of $R—S^-$ upon the carbon of the NCS group, the prerequisite of such a cyclization is the

TABLE 28. Rates of cyclization of *N*-substituted thiocarbamoylmercaptoacetic acids in 0·4 M-citrate buffer (pH = 2·91)[440]

Substituent	k(25 °C) (s^{-1})	$t_{1/2}$ (min)
CH_3—CO—Ph—	0·096	430
Br—Ph	0·083	502
CH_3—Ph—	0·239	174
CH_3—O—Ph—	0·276	150
$(CH_3)_2$N—Ph—	0·063	660
Ph—	0·210	198
Ph—CH_2—	0·290	143

formation of adduct **497** in which the protonization of carboxyl anion, and thus the cyclization to the energetically more stable five-membered heterocycle, takes priority over the transfer of proton to the atom of nitrogen[440,437].



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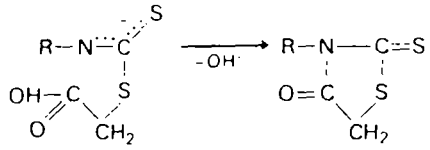


(497)

Similarly, the 3-substituted rhodanines arise in the reaction of isothiocyanates with the methyl ester of mercaptoacetic acid. On the other hand, 2-mercaptopropionic acid adds, under the same conditions, isothiocyanates without subsequent closing of the six-membered ring, i.e. the stabilization of the ionized adduct is founded on the transfer of hydrogen proton to nitrogen[440].

The rate of hydrolysis of the 3-substituted rhodanines as well as of the 3-substituted 2-thiohydantoins is a function of the concentration of OH^- ions. It may be assumed that the OH^- ion attacks the electron-deficient carbon of the carbonyl group in both the mentioned types of five-membered

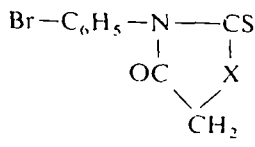
heterocycles as well as in 2-thioxoazolidine-4-ones and other analogous six-membered heterocycles. On the other hand, the rate of hydrolysis may be more or less dependent on the character of the substituents and their position in heterocyclic rings. The data in Table 29 indicate that a similar effect is achieved by changing the substituents on nitrogen in the rhodanine and thiohydantoin ring, i.e. the tendency to decyclization increases with the electron-withdrawing effect of the substituents. This fact is also confirmed by the linear relationship ascertained between the logarithms of the relative rates of decomposition of 3-(*p*-substituted phenyl) rhodanines and the substituent constants σ_p, the slope of this relationship being $\rho = 0{\cdot}585$ ($r = 0{\cdot}973$; $n = 8$)[440]. The value of $\rho = 0{\cdot}873$ ($r = 0{\cdot}94$; $n = 6$)[719] found for the analogous 3-substituted 2-thiohydantoins indicates a still more marked effect by the substituents. It is obvious from the data in Table 29 that the 2-substituted 2-thiohydantoins are more stable in alkaline hydrolysis than the analogous rhodanines. While the hydrolysis of the 3-substituted or 3,5-disubstituted 2-thiohydantoins results in an opening of the ring and in the formation of the corresponding *N*-substituted thiocarbamoyl derivatives (in alkaline buffer solutions up to pH 12), in the case of the 3-substituted rhodanines an opening, or eventually a further decomposition, of the *N*-substituted thiocarbamoylmercaptoacetates sets in and isothiocyanates and 2-mercaptoacetates are formed. These facts may be explained on the basis of the assumption that the dissociation constants of the compounds $R^1NHCSSR^2$ (Table 27) are considerably lower than equivalent constants of the analogous compounds $R^1NHCSSNHR^2$.

It ensues from the above-discussed information, and especially from the data in Table 30, that the stability of the 3-substituted five-membered heterocycles in alkaline hydrolysis increases in the order: rhodanines < 2-thiohydantoins < 2-thioxazolidine-4-ones.

TABLE 29. Second-order rate constants k ($l\ mol^{-1}\ s^{-1}$) of alkaline hydrolysis of 3-substituted 2-thiohydantoins and rhodanines[440,719]

Substituent	k (25 °C) Rhodanines	Thiohydantoins
O_2NPh—	—	783
CH_3COPh—	19·30	621
Ph—	8·21	288
CH_3Ph—	5·96	233
$(CH_3)_2NPh$—	1·75	179
$PhCH_2$—	1·21	175

TABLE 30. Rates of hydrolysis of 5-membered heterocyclic compounds at 25 °C in 0·1 M McIlvain buffer (pH = 8·4)[719]

 X =	$k \times 10^3$ (s^{-1})	$t_{1/2}$ (min)
S	4435	9·4
NH	138	301
O	0·012	3000

C. Supplementary Remarks

In the preceding sections the information obtained from the quantitative study of the reactivity of isothiocyanates with respect to different nucleophilic agents is summarized. This information was mainly obtained by investigating the reactions in aqueous buffered systems. In accordance with theoretical predictions, it was proved that isothiocyanates reacted with OH^-, HS^-, RS^- and RO^- ions and in case of amines their non-protonated form was reactive. By using buffer solutions with an appropriate pH value and sufficient buffer capacity it is possible to achieve the necessary constant concentration of the reactive form of nucleophile $R—X^-$, produced by the dissociation reaction $RXH \rightleftharpoons RX^- + H^+$ which precedes the proper reaction of RX^- with isothiocyanates R'NCS. The condition [RXH] + [RX^-] ≫ [R'NCS] is also fulfilled. Simultaneously, owing to constant concentration of the OH^- ions the reaction of R'NCS with the OH^- ions may, to a lesser or greater extent, be effective depending upon the pH value of the buffered systems. The rate of the R'NCS consumption evidently obeys the following equation under the above conditions (equation 285).

$$v = k_{OH^-}[R'NCS][OH^-] + k_{RX}[R'NCS][RX] \qquad (285)$$

The reactions thus investigated are first order reactions with respect to the isothiocyanate as well as to the OH^- ion or other nucleophile. Hence from the mathematical view point, the processing of experimental data is very much simplified. Of course, the determination of rate constants necessitates the determination of the rate constant of the side reaction, k_{OH^-}, i.e. of the reaction between isothiocyanate and the components of the buffer solution in a separate experiment. The conditions of the reactions of isothiocyanates with different nucleophiles where the side reaction with the OH^- ion is not

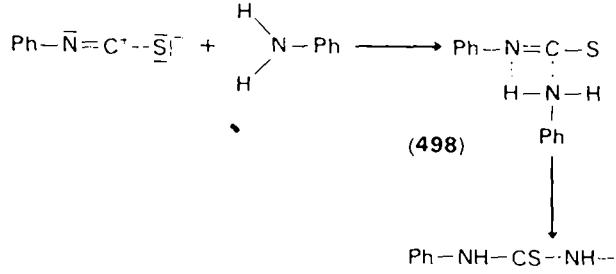
effective are stated and established theoretically in papers[685,688,568,569,418,405]. On the other hand, the results of these studies enable a comparison to be made of the reactivity of different nucleophilic agents with respect to isothiocyanates (see Table 31). In agreement with theoretical knowledge, the reactivity of the investigated nucleophiles with respect to isothiocyanates increases in the order: $OH^- < R—NH_2 < RO^- < HS^- \ll RS^-$. A comparison between the second-order rate constants of the reaction of phenyl isothiocyanate with OH^- and different RS^- ions reveals a 1000-fold and even a 20,000-fold reactivity for RS^- depending on the nature of R. The investigated amino compounds and alcohols ($R—O^-$) are more reactive than the OH^- ions but even in the case of RO^- the differences are less than the order of magnitude.

The kinetics of the reaction of alcohols and amines with isothiocyanates was also investigated in non-aqueous solutions in the presence of different catalysts and at higher temperatures. In spite of the fact that the interpretation of the kinetic constants obtained and their comparison with analogous values found in aqueous systems is an intricate problem, the

TABLE 31. Rate constants of the reactions of phenyl isothiocyanate with different nucleophilic agents and the dissociation constants of these substances[711]

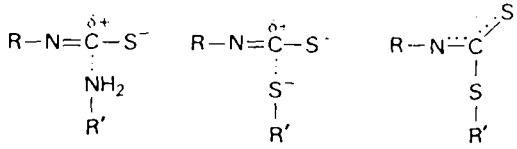
Nucleophile	Reactive form	pK_a (25 °C)	$k_{25\,C}$ (l mol^{-1} s^{-1})	k_1/k_0
Sodium hydroxide	HO^-	13·99	0·119	1·0
Methanol	RO^-	15·09	0·480	4·0
Ethanol		15·93	0·650	5·5
Phenylalanine	RNH_2	9·18	0·146	1·2
Lysine		9·18	0·133	1·1
Serine		9·21	0·083	0·7
Glutamic acid		9·47	0·110	0·9
Valine		9·72	0·155	1·5
Leucine		9·74	0·160	1·3
Glycine		9·78	0·243	2·0
Alanine		9·87	0·129	1·1
Sodium sulphide	HS^-	7·10	13·2	111·0
Ethyl mercaptoacetate	RS^-	7·93	128·0	1182·0
1,4-Dithiothreitol		8·25	275·0	2310·0
2-Mercaptoethanol		9·48	607·0	5100·0
Methyl-3-mercaptopropionate		9·33	2245·0	18,890·0
Mercaptoacetic acid		10·11	1900·0	15,980·0
Ethanethiol		10·35	492·0	4140·0
3-Mercaptopropionic acid		10·40	2770·0	23,250·0
Benzenethiol		7·35	1320·0	11,090·0

results are consistent at least as regards the appreciation of the relationship between the structure and reactivity of isothiocyanates. According to Akiyama and coworkers[708] it may be postulated that the reaction of phenyl isothiocyanate with aniline follows an electron donor–acceptor mechanism (equation 286).



(286)

The product is formed via transition complex **498**. According to the above-mentioned reaction mechanism, not only the electron density on the nitrogen atom of aniline but also the reactivity of the hydrogen atom plays an important role in the reaction with phenyl isothiocyanate. Kristián and coworkers[505] have produced evidence against the assumption of such concerted mechanism. These authors consider a non-concerted mechanism to be more probable, i.e. that the product arises via transition complex **499**.



(499) **(500)** **(501)**

A non-concerted mechanism must be assumed at least for the reactions of isothiocyanates with nucleophiles of the type RX^-, e.g. for the biochemically important reactions of isothiocyanates with thiols where the RS^- anion takes part in the formations of activated complex **500** in aqueous medium.

By investigating the reaction of isothiocyanates with thiols in alkaline buffer solutions containing thiols in excess the formation of an addition product of structure **501** was proved. By acidifying the reaction mixture this product is stabilized by accepting a proton on nitrogen and in this way the common RNHCSSR structure corresponding to the *S*-ester of the monosubstituted dithiocarbamic acids arises. Though the corresponding dissociation constants[711] have been determined for different compounds of this type, direct evidence of the localization of negative charge on dissociated

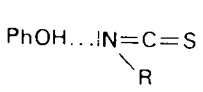
structure **501** is not so far available. As to the compounds hitherto studied the negative charge is assumed to be on the atom of sulphur.

Recently, Akiba and coworkers determined the equilibrium constants for adduct **502** formed from tributylphosphine **503** and phenyl isothiocyanate (equation 287) in some organic solvents. The ^{31}P-n.m.r. chemical shifts of substances **502** and **503** as well as of the *p*-substituted phenyl isothiocyanates were also measured and correlated linearly with the σ_p values of the R groups. On the basis of these observations and the reactivity of **502**, the structure of the adduct in solutions was depicted as a phosphonium betaine **502** with a P—C σ-bond[721].

$$\underset{\textbf{(503)}}{n\text{-}Bu_3P} + Ph{-}N{=}C{=}S \overset{K}{\rightleftharpoons} Ph{-}N{=}\underset{\textbf{(502)}}{\overset{S^-}{\overset{|}{C}}{-}P^+(n\text{-}Bu)_3} \qquad (287)$$

For the reactions of isothiocyanates with alcohols and other types of nucleophilic agents containing a hydrogen atom capable of splitting off easily, it is not possible for the time being to decide whether the primary attack of these substances on the NCS group will be directed to the NC or CS bond. On the basis of a more precise calculation of the electron structure of phenyl isothiocyanate, Zabrodin came to the conclusion that for the reaction with alcohols the primary attack should most likely be directed to the CS bond[509].

Isothiocyanates can act as proton acceptors in H-bonding. The results reported by Stankovski and coworkers, which are based on the investigations of the intermolecular hydrogen bonds of phenols and alkyl isothiocyanates in CCl_4, indicate weaker H-bonding than reported for the systems phenol–alkyl isothiocyanates[722]. The complex of isothiocyanate with phenol is presumed to have structure **504**.



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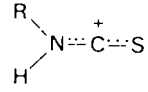


(505)

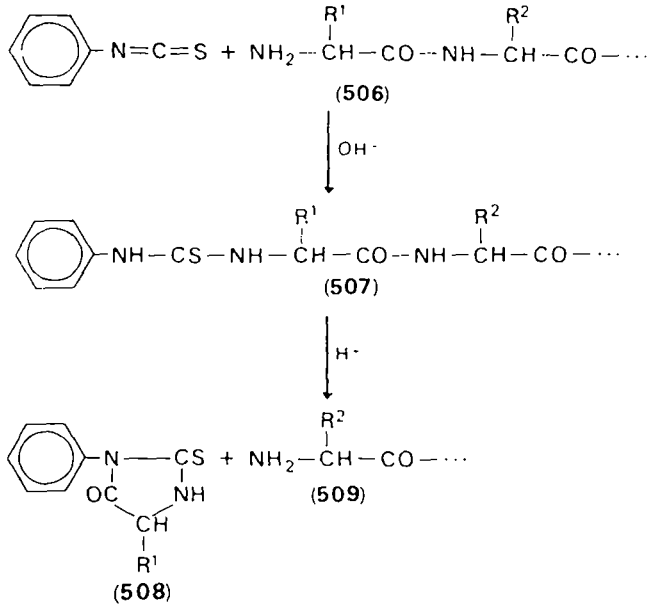
Olah and coworkers[723] proved a possible protonation of alkyl and aryl isothiocyanates in superacid solutions ($FSO_3H{-}SO_2$) giving rise to the corresponding thiocarbamyl cations **505**. This knowledge provided new possibilities for a reasoning concerning different behaviour of isothiocyanates and analogous compounds.

VIII. BIOCHEMICALLY IMPORTANT REACTIONS OF ISOTHIOCYANATES

A. Isothiocyanates as a Tool in the Study of Structure and Functions of Proteins

1. Determination of primary structure of proteins

One of the most useful methods for identifying the NH_2-terminal aminoacid of a polypeptide chain is based on the so-called Edman reaction[725] (equation 288). The free unprotonated α-amino group of peptide **506** reacts with phenyl isothiocyanate (the Edman reagent) to yield the phenylthiocarbamoyl peptide **507**. When this is treated with acid, usually in an organic solvent, the phenyl thiohydantoin (PTH) derivative **508** of the NH_2-terminal amino acid residue and the intact peptide chain minus its original NH_2-terminal residue **509** are the products. The PTH-derivative can be identified chromatographically, most readily by gas–liquid chromatography[726,727].



(288)

Alternatively, the determination of the amino acid composition of the product peptide **509** and comparison with the amino acid composition of the original will reveal the nature of the missing amino acid. The great advantage of the Edman method is that the remaining peptide **509** can be subjected to another cycle of treatment with phenyl isothiocyanate. Thus, careful work

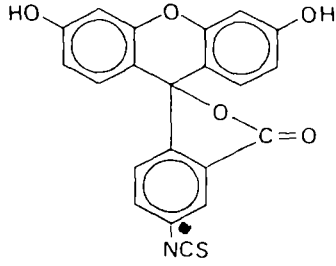
will permit the reaction cycle to be repeated to determine the amino acid sequence of the peptide. In most instances, sequences of not more than 10 amino acids have been identified in this way. Very careful work has permitted identification of 20 amino acids[728-730]. The most impressive example of the manual use of this technique is the complete elucidation of the primary structure of a peptide hormone consisting of a single chain of 32 amino acids[731]. The importance of phenyl isothiocyanate for protein chemistry provoked a series of studies into improving the efficiency with which each cycle of reaction can be repeated[732-735]. Edman has designed automatic equipment–the proton sequenator[735]–by which he has identified the sequence of the 60 residues of whale myoglobin. The development of this technique was followed by the work of many scientists using many techniques. The automated Edman degradation technique can be combined with the mass-spectrometric technique[736], isotope dilution procedure[737] or with other techniques[738]. Results of using different types of isothiocyanates for Edman degradation have been described too[537,739-742].

2. Labelling of proteins

The addition products of reaction by isothiocyanates with amino acids, and also peptides or proteins, are relatively stable in a mildly acidic, neutral or alkaline environment. In a strongly acidic environment the modified *N*-terminal amino acid splits from the peptide, but the product peptide with modified ε-amino groups (of lysine) is not attacked. On the other hand, peptides and proteins modified with isothiocyanates can still hold certain important functional properties. Kaiser and coworkers in 1953 found that modification of the amino groups in the molecule of insulin with phenyl or allyl isothiocyanates did not result in the loss of activity of this peptide hormone[743]. Later, insulin labelled with fluorescein isothiocyanate was successfully used for the study of metabolism and localization in animal tissues[744,745].

Fluorescein isothiocyanate has found an important application in immunology. It enables the visualizing of sites of antibody binding in the antigen–antibody complex and its detection inside the cells[746]. In this procedure, an antibody to a cell constituent is prepared and is then rendered fluorescent by the attachment of fluorescein isothiocyanate. The commercial product is a mixture of the isomers **510** and **511**, which can be separated[747]. Also other isothiocyanates with fluorescent properties are described in the literature[748,749]. Radioactively-labelled isothiocyanates may also be used in cytochemistry (see Section III.B). Thus tritiated 4,4'-diisothiocyanto-2,2'-

dihydrostilbene disulphonate was used for specific labelling of the surface proteins of mammalian cells[750].



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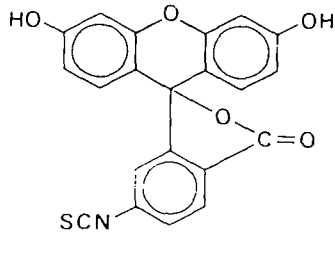


(511)

3. Modification of enzymes

The isothiocyanates are relatively specific and potent inhibitors of enzymes which require thiol groups for their catalytic activity. The basic information about the inhibitory effect of different types of isothiocyanates was received from experiments with glyceraldehyde-3-phosphate dehydrogenase, glutamate dehydrogenase, alcohol dehydrogenase, hexokinase, glutamate-oxalacetate transaminase, glutathione reductase, succinate dehydrogenase and papain[689,751–753,755]. Isothiocyanates do not affect the activity of other types of enzymes such as ribonuclease, cytochromoxidase, plant catalase, lysozyme[689,753], and β-amylase[756] (the modification of amino groups take place).

By selecting appropriate reaction conditions (especially pH) for the reaction of isothiocyanates with SH proteins it is possible to obtain: (i) specific reaction with SH groups; (ii) reaction with SH and NH_2 groups; (iii) the liberation of blocked SH groups; (iv) the splitting away of modified *N*-terminal amino acid by subsequent controlled acid hydrolysis[754]. This suggests an enormous difference in the nucleophilicity of S^- and NH_2 groups in proteins which can be even more favourable owing to the increased difference between the pK_{SH} and pK_{NH_2} values. The results of experiments with yeast alcohol dehydrogenase serve as an example of the specific blocking of SH groups of proteins with isothiocyanates. Using the ^{35}S-labelled 4-bromophenyl isothiocyanate in reaction mixtures at pH $\leq$ 7 it was possible to titrate approximately 36 thiol groups of enzyme. At pH 10, especially after a long time period, the binding of isothiocyanate to another 109 groups of enzyme was obtained[710]. It is known that this enzyme contains 36 of the SH groups and 97–100 NH_2 groups.

Adducts of isothiocyanates with SH groups of proteins exhibit a characteristic absorption of light in the u.v. region (252 and 277 nm). By using the spectrophotometric method the kinetics of the reaction of benzyl isothiocyanate and yeast alcohol dehydrogenase was followed. Complete loss in enzyme activity was obtained by blocking approximately 22 SH groups[710]. For this reaction the second-order rate constant was determined as $k = 0{\cdot}111\ \text{mol}^{-1}\,\text{s}^{-1}$. Comparison with the rate constant for the reaction of benzyl isothiocyanate with cysteine shows the mentioned value to be similar.

Restoring the catalytic activity of thiol enzymes inhibited by isothiocyanates was studied in more detail in the case of rabbit muscle hologlyceraldehyde-3-phosphate dehydrogenase[710]. The mechanism of the liberation of SH group and other basic problems were elucidated in References 711 and 569. For the elucidation of binding and conformation changes at the active site of glyceraldehyde-3-dehydrogenase the fluorescein isothiocyanate was used[757].

The choice of suitable isothiocyanates as specific and reversible inhibitors or 'reporter' groups in the chemical modification of enzymes and as chemical 'yardsticks' for measuring relative dimensions of active sites of SH enzymes, offers new possibilities for the study of structure and function of enzymes. The macromolecular polyisothiocyanates can be used for the preparation of immobilized enzymes (bound by the reaction of NH_2 groups) and for reversible covalent binding of thiol enzymes (covalent chromatography)[710,758].

B. Isothiocyanates as Metabolic Inhibitors

1. Biological activity and mode of action

The biological effectiveness of natural and synthetic isothiocyanates, their mode of action and also the questions of relations between the chemical structure and biological activity, have been systematically investigated at The Institute of Microbiology and Biochemistry of Slovak Polytechnical University in Bratislava. During the last 20 years data were obtained and published on the chemical properties and biological activity for more than 500 predominantly new synthetic isothiocyanates[759].

It appeared suitable to divide the studied isothiocyanates into at least five groups in accordance with their chemical similarities and the similarity of their biological effects[760]. The first group is made up of all natural isothiocyanates which, as a rule, are of the alkyl or aralkyl type, and of their most closely related synthetic analogues (the series alkyl-, benzyl-,

2-phenylethyl-, cynnamoyl-, benzhydryl-ITC and others). Several substances of this group are characterized by a wide spectrum of antimicrobial action, having especially an antibacterial and also antiyeast effect[689,752,760]. Benzyl isothiocyanate which is an effectual component of various medicaments for the treatment of bacterial and yeast-induced diseases of the respiratory and urinary tracts[761,762] is greatly surpassed in its effect by its simple synthetic analogues[763]. Benzhydryl isothiocyanates are specific to Gram-positive bacteria including *Mycobacterium tuberculosis*[763,764]. The second large group is composed of mononuclear aromatic isothiocyanates of which many can be included among the to-date most effective natural and synthetic antifungal agents[765-767]. 4-Bromophenyl isothiocyanate is used in chemotherapy[768]. The third group comprises uncondensed polynuclear aromatic derivatives of the general formula $R-C_6H_4-X-C_6H_4-NCS$ (derivatives of biphenyl, *p*-terphenyl, diphenylmethane, phenylether, diphenylamine, diphenylsulphide, sulphone and of sulphoxide, benzophenone, chalcone, stilbene and azobenzene). Many substances of this group are remarkable because of their specific antimycobacterial activity[466,760,764]. They have a low cytotoxic effect on HeLa cells in tissue cultures and a low toxic effect on macroorganisms[769]. Some substances are effective against pathogenic protozoa *in vitro* and *in vivo*[770]. Also important are their anthelmintic[771] and cancerostatic[772] properties.

Polycondensed aromatic isothiocyanates (derivatives of naphthalene, anthracene, phenanthrene, pyrene, chrysene, fluorene and anthraquinone make up the fourth, and various heterocyclic isothiocyanates the fifth, group. Several isothiocyanates of these groups (also Group Three) are characterized by a cancerostatic[772-775] and antiviral action[776]. Of these, as antibacterial substances only derivatives of acridine and eventually of purine are remarkable[760,777]. The picture of the biological action of isothiocyanates is complemented by information regarding cytotoxic[769,778-780], antiworm[781-783], antithyroidal[784] and other biological effects[785,759].

Generally, for the majority of isothiocyanates having an NCS group as the only reactive centre in the molecule, their antimicrobial and cytotoxic action lies in the exclusion of key processes in the energy and intermediary cell metabolism by the inhibition of those enzymes which require SH groups for their catalytic activity. The reaction of isothiocyanates, especially with the SH groups of proteins, is responsible for the nature and degree of the influence on metabolic and physiological cell functions[759].

This was demonstrated in many important findings about the effects of natural and synthetic isothiocyanates on biochemical processes in various eukaryotic and prokaryotic types of cells, in cell-free systems up to isolated

enzymes, and of other findings which contributed to the elucidation of the mode of action of isothiocyanates at a molecular level[751-753,786-792].

The lethal damage to the cell is the extreme case of isothiocyanate action. The sublethal doses of isothiocyanates regulate the rate of biosynthetic processes and growth of cells by more or less specific primary inhibition of the glycolytic pathway and/or biological oxidation processes.

In the investigated types of eukaryotic microorganisms (yeast, fungi, protozoa) growing on glucose containing simple mineral media, it is possible with addition of antifungal isothiocyanates to stop the glucose metabolism and permanently inhibit the growth[752,753,786]. Following an inquiry into the changes in the level of the intermediates in the glycolytic pathway and in the activity of glycolytic enzymes in fermentating yeast *S. cerevisiae* after a short-term action of *p*-bromobenzyl- and *p*-bromophenyl isothiocyanate, the conclusion was drawn that these substances impair in several ways the process of glucose degradation, primarily by the inactivation of the thiol enzymes hexokinase, glyceraldehyde-3-phosphate dehydrogenase and alcohol dehydrogenase. The second enzyme appeared to be the most sensitive. However, in treated yeast cells the inhibition of glucose-6-phosphate dehydrogenase and some respiratory enzymes was also observed[751,753]. For regulation of growth of oxidative yeast types, e.g. *Candida albicans*, only a few inhibition sites are vital. The crucial sites would seem to be the enzymes of the respiratory chain (inhibition of an early step in the NAD/P/H oxidation) and perhaps some other enzymes[792-794].

With numerous isothiocyanates[759,774,789] and some new types of thiol-combining agents[795], it is possible to depress completely the glycolysis and respiration of Ehrlich carcinoma cells (or HeLa cells) and cause the loss of transplantability. Lower concentrations of these compounds stimulate the aerobic glycolysis and respiration (also endogenous respiration) of these 'model' animal cells, but inhibit the biosynthesis of nucleic acids and proteins — without the loss of transplantability of treated cells. The attack of glycolysis and respiration is multitarget in character. The inhibition of the enzymes glyceraldehyde-3-phosphate dehydrogenase and hexokinase is responsible for the lowering of the rate and full inhibition of glycolysis[759]. The described changes in respiratory activity of treated cells lies in the interference of isothiocyanates with mitochondrial functions. The experiment with ^{35}S-labelled isothiocyanates indicated that their main part is bound to the mitochondria[353]. Higher concentrations of those isothiocyanates studied cause inhibition of respiration by the inhibition of succinate dehydrogenase and the NADH oxidase system[788,799]. Low concentrations probably uncouple the respiration. This selective interference results in a partial limitation of the energy demand of the cells

and is sufficient to cause transient inhibition of biosynthetic processes. These conclusions are supported by recent findings that isothiocyanates represent a new class of uncouplers[796]; this effect can be in connection with modification of mitochondrial thiol groups[797].

The passage of isothiocyanates across the cell membrane is a prerequisite for their antifungal, antialgal and cytotoxic action[798]. By contrast, in bacteria such as *Escherichia coli* the bacteriostatic effect of some isothiocyanates results primarily from the elimination of functions localized in the surface layers of the cell or in their vicinity[353]. For the elucidation of the nature of the antibacterial effect of some isothiocyanates, the findings about the relationship between the inhibition of respiration, the incorporation of radioactive precursors into nucleic acids and proteins, the decrease in the concentration of free thiol groups of proteins and the inactivation of some enzymes in various types of bacteria (*E. coli*, *Bac. subtilis* and *Myco. fortuitum*) are important[466,753,790,791]. Recently the inhibition of polypeptide synthesis in cell-free system from *Escherichia coli*, e.g. inactivation of ribosomes and some elongation factors, was explained by the reaction of SH groups of proteins with isothiocyanates[800].

From reasons mentioned above the isothiocyanates are not only interesting as biologically active compounds and metabolic inhibitors but also as tools for the study of the participation of thiols in complicated biochemical processes such as protein synthesis, oxidative phosphorylation and especially enzyme catalysis.

Finally, we would like to comment on the important differences in chemical reactivity, as well as in the lipophilicity of different isothiocyanates. The data in Table 32 allow a comparison of the reactivity of different thiol combining agents with cysteine. The less reactive isothiocyanates can be compared with well-known alkylating agents and the most reactive isothiocyanates with *N*-ethylmaleimide. On the other hand, in contrast to those isothiocyanates with relatively good solubility in water, it is appropriate to point out the extremely lipophilic compounds, e.g. derivatives of polycondensed aromatic hydrocarbons. Their partition coefficient for the octanol-water system reached values of about one million (Table 33).

C. Structure–Activity Relationships

The first important information on the interrelationships of the chemical structure, physicochemical properties and biological effects and about a possible mathematical formulation of these relations was obtained from a study on the series of *p*-substituted derivatives of phenyl isothiocyanate[801].

TABLE 32. Rate constants for reaction of cysteine with different SH reagents[759,800]

Reagent	k ($l\,mol^{-1}\,s^{-1}$)	Reaction type
1-Iodopropionamide	$1{\cdot}44 \times 10^{-2}$	
1-Iodopropionic acid	$6{\cdot}10 \times 10^{-2}$	
Chloroacetamide	$4{\cdot}29 \times 10^{-1}$	S_N
Iodoacetamide	$9{\cdot}90 \times 10^{-1}$	
Acrylonitrile	1·70	Ad_N
4-Butanoyl-ITC	3·44	
Benzyl-ITC	$2{\cdot}79 \times 10^{1}$	Ad_N
4-Nitrophenyl-ITC	$2{\cdot}54 \times 10^{3}$	
Diphenylsulphon-4-ITC	$>1{\cdot}00 \times 10^{5}$	
N-Ethylmaleimide	$3{\cdot}05 \times 10^{4}$	Ad_N
5,5'-Dithiobis(2-nitrobenzoic acid)	$4{\cdot}10 \times 10^{4}$	Redox
4-Chloromercuribenzoate	$4{\cdot}00 \times 10^{8}$	S_R

The selection of these substances for the above-mentioned purpose was decided by the already existing data indicating significant differences in their antimicrobial effect as well as in their reactivity and solubility. Within this series the correlation of the values log ED_{50} and ID_{100}, characterizing the

TABLE 33. Partition coefficients of isothiocyanates in octanol:water at 25°C[790,759]

Isothiocyanate	log *P*	Isothiocyanate	log *P*
Group I		*Group III*	
4-Butanoyl-	~0·30	Biphenyl-	4·66
Ethyl-	1·47	Diphenylmethane-4-	4·40
Benzyl-	3·16	Diphenyloxide-4-	4·75
1-Phenethyl-	3·46	Diphenylamine-4-	4·94
2-Phenethyl	3·47	Diphenylsulphoxide-4-	4·40
Benzohydryl-	5·09	Benzophenyl-4-	4·88
Phenyl-1-Naphthylmethyl-	6·44	Benzoyloxyphenyl-4-	4·90
Triphenylmethyl-	7·02	Stilbene-4-	5·85
		Azobenzene-4-	5·55
Group II		*Group IV*	
Phenyl-	3·40	1-Naphthyl-	4·34
4-Bromophenyl-	4·03	2-Naphthyl-	4·34
4-Hydroxyphenyl-	2·74	1-Naphthylmethyl-	4·42
4-Carboxyphenyl-	3·52	Anthracene-2-	5·70
4-Methylphenyl-	3·92	Pyrene-1-	>5·70
4-Nitrophenyl-	3·64	Chrysene-6-	>5·70

effect of these substances on the growth and respiration of *Escherichia coli* cells, with the logarithms of second-order rate constants k_{OH}, and the Hammett constants σ was ascertained. On the other hand, for the anti-yeast effect of these very same substances the values of log ED_{50} can be correlated with the logarithms of the molar solubilities S of isothiocyanates in water. Thus their chemical reactivity is the property determining their antibacterial effect and for estimating the significance of changes in substituents the modified Hammett equation was used (equation 289).

$$\log(\tau_i/\tau_r) = \rho\sigma \tag{289}$$

The value τ_i is the biological activity of the ith and τ_r of the reference term of the investigated series of substances. The constant ρ is characteristic for the biological object and σ is the constant of the substituent. The correlation of the anti-yeast effect with the values of the molar solubilities of the derivatives of this series, using the equation (290), proves that it is a physical process that determines the biological effect (Table 34).

$$\log(\tau_i/\tau_r) = \alpha_{II}\beta_{II} \tag{290}$$

$$\log(1/C) = k\beta_{II} + k' \tag{291}$$

Equation (290), the so-called α,β-equation, originally set by Zahradnik[802] and equation (291), as a general form of equation (290), represents the simplest case where biological activity in the whole series of compounds studied is dependent on their lipophilicity. In the equations (289) and (290) instead of β_{II} symbols, molar solubilities in water ($\log S$), partition coefficients in suitable systems ($\log P$) as well as the Hansch constants π of substituents can be used[803,804]. Among these constants there exists a well-known correlation expressed by equations (292) and (293). The symbol C represents the dose of compound needed for standard biological response (ED_{50}; ID_{50}; LD_{50}).

$$\log P = k \log S + k' \tag{292}$$

$$\pi = \log P_X - \log P_H \tag{293}$$

A study of the more extensive series of *m*-substituted phenyl isothiocyanates revealed that their antibacterial effect was directly proportional to their reactivity and indirectly proportional to their solubility. The uniqueness of this series is given by the fact that the arrangement of the derivatives according to the decreasing reactivity is also an arrangement according to their increasing solubility and decreasing antibacterial effect[805]. It was considerably simpler and theoretically easier to explain the determined correlation of antibacterial and antifungal effects

TABLE 34. Correlation of biological activity with the physical constants of the arylisothiocyanates[801]

Biological object	log of the rate constants for the addition of OH^- ions			Hammett constants			log of the molar solubility in water		
	n	*b*	*r*	*n*	*b*	*r*	*n*	*b*	*r*
E. coli growth inhibition	8	−0·98	−0·94	8	−2·29	−0·97	12	—	0·04
E. coli inhibition of respiration	8	−0·63	−0·83	8	−0·99	−0·61	12	—	0·05
C. albicans growth inhibition	9	—	−0·11	9	—	−0·12	13	0·42	0·87
C. albicans growth inhibition	—	—	—	8	—	−0·34	9	0·56	0·89
S. cerevisiae growth inhibition	—	—	—	8	—	−0·26	10	0·61	0·81

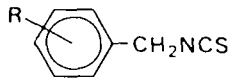
Number of cases (*n*); the tangent of the linear dependences of the biological activity logarithm on the terms characterizing chemical and physical properties of the arylisothiocyanates (*b*) and correlation coefficients (*r*).

TABLE 35. The simple equations describing the structure–antimicrobial activity relationships of isothiocyanates in bacteria, fungi and yeast-like organisms[759,805]

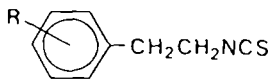
Isothiocyanate	Microorganism	Equation	n	r
Benzyl (*m*- and *p*-substituted)	*Escherichia coli*	$\log(1/ED_{50}) = -0.955 \log S + 1.76$	13	0·978
		$\log(1/ED_{50}) = 0.556\pi + 5.237$	13	0·873
	Candida albicans	$\log(1/ED_{50}) = -0.699 \log S + 3.007$	13	0·956
	Aspergillus niger	$\log(1/ED_{100}) = -1.235 \log S - 0.050$	13	0·915
β-Phenylethyl (*m*- and *p*-substituted)	*Candida albicans*	$\log(1/ED_{50}) = 0.267\pi + 4.896$	6	0·997
	Penicillium cyclopium	$\log(1/ED_{50}) = 0.468\pi 4.325$	6	0·973
Phenyl (*m*-substituted)	*Escherichia coli*	$\log(1/ED_{50}) = -1.12 \log S - 0.30$	11	0·957
	Candida albicans	$\log(1/ED_{50}) = -0.33 \log S + 2.89$	11	0·770

n = number of compounds studied; r = correlation coefficient.

with the solubility of benzyl, β-phenylethyl (see Table 35)[790] and later also other types of isothiocyanates[759] (basic structures **512–521**).



(**512**)



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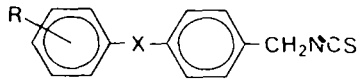

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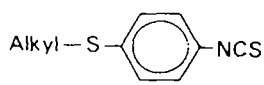

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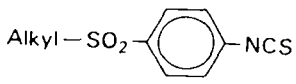

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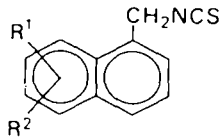

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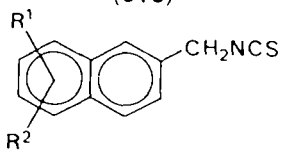

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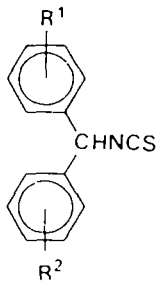

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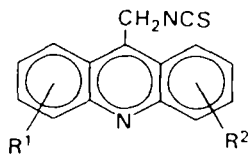

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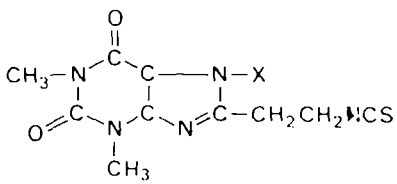

(**521**)

The findings mentioned are in agreement with the facts, that exchange of the substituents in a molecule does not result in noticeable changes in the reactivity of the NCS group. In this connection it is useful to note that none of the isothiocyanates studied in this series did exceed the value of the so-called

optimal lipophilicity P_0. In the opposite case such a function would not be linear but parabolic (equation 294)[803,804].

$$\log(1/C) = -k_1(\log P)^2 + k_2 \log P + k_3 \quad (294)$$

From assessing the antimicrobial activity of all isothiocyanates that have so far been investigated in relation to their lipophilicity (dependence of $\log ED_{50}$ and/or $\log ID_{50}$ on $\log P$) the following values of the logarithms of ideal partition coefficients P_0 in respect to different cell types have been approximated: Gram-negative bacteria *E. coli* 4·1–4·3; Gram-positive bacteria *Bac. subtilis* and *Staph. aureus* 5·3–5·5; *Myco. tuberculosis* 5·5; yeasts *Candida albicans* 4·4; animal cells 4·5. In the mycobacteria and also in animal cells isothiocyanates with pronounced lipophilicity have proved effective; in the remainder of the investigated microorganisms, exceeding the P_0 value has resulted in a pronounced decrease in effectiveness[759]

$$\log(1/C) = -k(\log P)^2 + k' \log P + \rho\sigma + k'' \quad (295)$$

$$\log(1/C) = -1{\cdot}04(\log P)^2 + 8{\cdot}53 \log P + 0{\cdot}776\sigma - 12{\cdot}62 \quad (296)$$

An example of a more complicated relationship, where besides differences in lipophilicities, differences in chemical reactivities take place, is expressed by equation (295). The applicability of this equation for the correlation of antibacterial activity of arylisothiocyanate against *Escherichia coli* was shown by Lien and coworkers and thanks to them the values of the constants (equation 296) have been determined[806].

By studying the relationships between the chemical structure, physicochemical properties and the inhibitory effect of isothiocyanates against enzymes, it is possible to find out also the simple relationships. For *p*-substituted phenyl isothiocyanates it was found that the logarithms of inhibition constants K_i (NAD^+ variable) are the function of the reactivity of PTC's characterized either by Hammett constants σ_p (correlation coefficient $r = 0{\cdot}99$) or logarithms of rate constants[710].

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