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Isothiocyanates in the Chemistry of Heterocycles†

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I. Introduction

Naturally occurring isothiocyanates are limited in number. These have been found to be present in some species of Cruciferae as progenitors, called glucosinolates, and are released from the injured plant by the enzyme myrosinase. On the other hand, there is a large number of synthetic isothiocyanates which constitute an important class of compounds. The chemistry of these heteroallenes has been delineated in two reviews.[1,2] Construction of heterocycles from enamines and isothiocyanates was previously covered.[3] Also, syntheses and reactions of six-membered heterocyclic isothiocyanates,[4] acyl/thioacyl,[5] and vinyl[6] isothiocyanates were surveyed. Recently, an account of isothiocyanates in heterocyclic synthesis was published.[7] Thus, it is apparent that the chemistry of isothiocyanates has burgeoned over the years, and it continues to be a blossoming field.

The attraction of isothiocyanates as synthons is obviously due to their diverse reactions and also due to their easy availability. It would not be out of place to record that, in comparison to isocyanates, their sulfur analogues, isothiocyanates, are less unpleasant and to some extent less hazardous to work with. In one of our investigations during 1984, we had to abandon the use of isocyanates as cyclocondensing agents because of the reluctance of a research scholar who was in the grip of a fear complex caused by the tragic death and crippling of a large number of Bhopal citizens due to the devastating accident in a chemical plant using methyl isocyanate. Since then we became interested in isothiocyanates. The purpose of this review is to present highlights of the chemistry of these heteroallenes with particular reference to heterocycles. It should be mentioned that the examples already covered in the previous reviews have not been included unless required for the sake of congruity. The literature has been surveyed through January 1990.

II. Syntheses of N-Substituted Isothiocyanates Using Heterocycles

Isothiocyanates can be prepared by various procedures, the choice of which would depend on the target molecule. Heterocyclic isothiocyanates reported so far were obtained by the methods in vogue for the synthesis of alkyl, aryl, and acyl isothiocyanates.[1,2,7] The selection of reagents should be judicious since many of these could bring about the rupture of the ring. It is noteworthy that many heterocyclic reagents were used in the preparation of isothiocyanates. The following account covers syntheses of these heteroallenes by various reactions including those in which heterocyclic chemistry is only a side aspect.

A. Conversion without Ring Cleavage

Synthesis of some heterocyclic isothiocyanates involved the usual nucleophilic substitution with thio-

†Dedicated to the memory of our teacher (late) Dr. S. M. Deshpande.

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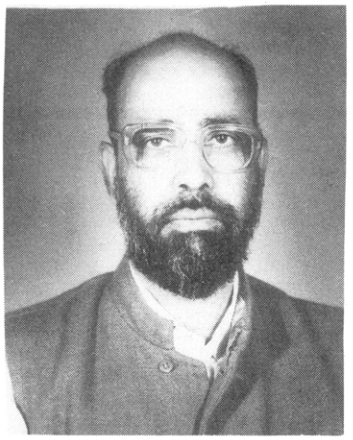
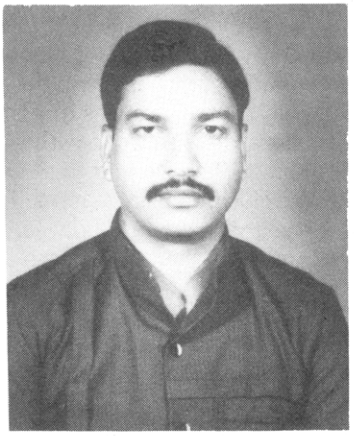


Arya Kumar Mukerjee was born in Chapra, Bihar, India, in 1941. After completing his early education in his home town, he joined Banaras Hindu University where he earned his M.Sc. in organic chemistry. He carried out research under the supervision of the late Dr. S. M. Deshpande and submitted his thesis in 1966. From 1966 to 1970, he worked in the laboratory of Professor N. N. Suvorov of the Mendeleev-Institute, Moscow, USSR, where he earned his Ph.D. degree. On his return to India, he served as a scientist in the C.S.I.R. pool from 1971 to 1973, and subsequently joined B.H.U. as a lecturer in chemistry. At the present he is serving as a Reader. His current research interests are development of new methodologies, synthesis of natural product analogues, and "disciplined organic reactions".



Ram Ashare was born in Jaunpur, Uttar Pradesh, India, in 1958. He received his M.Sc. in 1981 and Ph.D. in 1987 from Banaras Hindu University. Currently he is working as a teacher in the Central Hindu School of Banaras Hindu University. His research interest is in heterocyclic chemistry.

cyanic acid or its salts and manipulation of a primary amino group in the ring.

1. Substitution with Thiocyanic Acid or Its Salts

Reactive organic halides underwent nucleophilic substitution with salts of thiocyanic acid to give thiocyanates or isothiocyanates depending on the nature of the reactants and reaction conditions.[1,2,7] Heteroaryl halides were reported to give organic thiocyanates. 9-Chloroacridines, however, reacted with silver and lead thiocyanates in polar solvents and with potassium thiocyanate in DMF to give isothiocyanates in good yields.[8,9] Alkyl and aralkyl halides generally afforded thiocyanates which rearranged themselves more or less readily to the corresponding isothiocyanates, the isomerization being governed by the nature of the substituent. Also, the reaction conditions played important roles. Recently, ring-substituted benzyl halides were converted into the corresponding benzyl isothiocyanates in 50–66% yields by refluxing with potassium thiocyanate in 1,2-dichlorobenzene in the presence of crown ether 18-crown-6.[10]

Acyl and aroyl halides gave the corresponding isothiocyanates directly on heating with metal thiocyanates. 3-Thienoyl,[11] 2-furanoyl,[12] and nicotinoyl isothiocyanates[12] were obtained in moderate or good yields by the interaction of lead thiocyanate and the respective heteroaroyl chlorides. 2-Oxo-4-imidazoline-1-carbonyl chloride (**1**), however, reacted with ammonium thiocyanate in boiling acetone to give (2-oxoimidazolinyl)carbonyl isothiocyanate (eq 1).[13]

1 **2** (60%) (1)

The condensation of carbonimidoyl dichlorides with potassium thiocyanate or potassium thioacetate in THF afforded the corresponding isothiocyanates (eq 2).[14] In view of the poor yields of the products, this method does not seem to be advantageous.

$$RN{=}CCl_2 \xrightarrow[THF]{KSCN} RN{=}C{=}S\ (20\text{–}30\%) \qquad (2)$$

2. Conversion of Primary Amines with Sulfur Reagents

Primary amines reacted with thiophosgene[1,2,7] to give unstable thiocarbamoyl chlorides which in turn furnished isothiocyanates (eq 3). Yields were moderate or good. This reaction should be carried out under controlled conditions using aprotic solvents like chloroform, toluene etc. Thiophosgene should not be employed for

$$RNH_2 + Cl_2CS \rightarrow RNH{-}CS{-}Cl \rightarrow RN{=}C{=}S \qquad (3)$$

amines with a vicinal reactive group because of cyclocondensation reactions. Also, many heterocyclic compounds would undergo rupture of the ring as a result of interaction with thiophosgene.

This method was modified over the years and diethylthiocarbamoyl chloride,[15] bis(diethylthiocarbamoyl) sulfide or disulfide,[16] di-2-pyridyl thiocarbonate,[17,18] 1,1′-(thiocarbonyldioxy)dibenzotriazole,[19] and 1,1′-thiocarbonyl-2,2′-dipyridone[20] were introduced as the substitute of highly toxic thiophosgene.

3. Use of Dithiocarbamic Acids and Their Salts or Esters

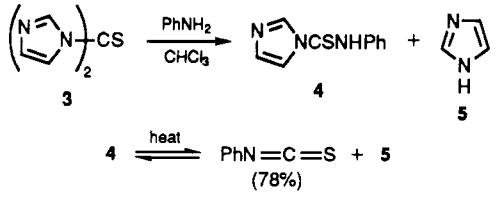
Primary amines with sufficient basicity reacted with carbon disulfide in the presence of alkali, amine, or ammonia, affording dithiocarbamic acid salts which easily underwent reagent-induced conversion into isothiocyanates (eq 4). Desulfurization with metal salts

$$RNH{-}CS{-}\overset{-}{S}\overset{+}{M} \rightarrow RN{=}C{=}S \qquad (4)$$

$$M = Na,\ NH_4,\ Et_3NH$$

was applied in the preparation of ordinary alkyl and aryl isothiocyanates, as previously reviewed.[1,2] Phosgene, methyl or ethyl chloroformate, phosphorus oxychloride, trichloro(*o*-phenylenedioxy)phosphorane, organo silicon compounds, carbodiimides, N,N′-disubstituted propiolamidines, salts of α-halo fatty acids, sodium hypochlorite in alkaline medium, hydrogen peroxide,[1,2] butyllithium and carbon disulfide or sulfur dioxide,[21] cyanogen chloride,[22] 2-chloro-1-methyl-

SCHEME 1



pyridinium salt,[23] cyanamide,[24] and di-2-pyridyl carbonate[25] were also used for desulfurization. Reaction conditions varied considerably depending upon the reagents and substrates employed. Dithiocarbamates derived from heterocyclic amines should be handled carefully and milder desulfurizing agents should be used. Yields by this method were generally very good (60–90%).

Besides primary amines, N-unsubstituted sulfonamides were also converted into the corresponding sulfonyl isothiocyanates (eq 5).[26] A modified version by heating alkyl dithiocarbamates gave sulfonyl isothiocyanates in good yield.[27] A similar approach was

$$RSO_2NH_2 \xrightarrow[2.\ COCl_2]{1.\ CS_2,KOH} RSO_2N{=}C{=}S \quad (60\text{–}88\%) \qquad (5)$$

R = alkyl, aryl, 2-thienyl

used for the preparation of aryl isothiocyanates by heating the corresponding methyl dithiocarbamates in boiling toluene in the presence of sodium hydroxide.[28] This procedure seems to be simple and may have a wider application. Recently, desulfurization of methyl dithiocarbamates with mercury(II) oxide in DMF in the presence of ammonium hydroxide was employed to prepare several aromatic diisothiocyanates[29] in good yields (72–83%).

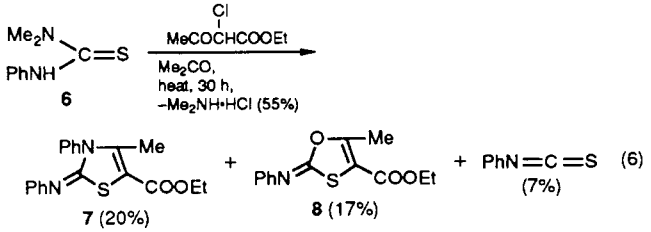
4. Decomposition of Thioureas

N,N′-Disubstituted thioureas underwent decomposition to the corresponding amines and isothiocyanates when heated in the presence of some acids.[1,2] The pyrolysis of acylthioureas in *o*-dichlorobenzene afforded isothiocyanates as the major product.[30]

A convenient method using 1,1′-diimidazolylthiourea in the preparation of isothiocyanates is outlined in Scheme 1.[31] This method was extended to the synthesis of dialkylamino isothiocyanates.[32]

Sterically hindered arylamines were converted into the corresponding isothiocyanates in high yields via their thiourea derivatives prepared by the interaction with phenyl isothiocyanate.[33] In this reaction, phenyl isothiocyanate had been taken in excess which converted the liberated aniline to *N,N′*-diphenylthiourea.

Ethyl α-chloroacetoacetate was used in the conversion of *N,N*-dialkyl-*N′*-arylthioureas to the corresponding 3-aryl-2-(arylimino)-4-thiazolines and 1,3-oxathioles along with a small amount of aryl isothiocyanates (eq 6).[34] This procedure afforded isothiocyanates in poor



yield without any special advantage, thereby ruling out its general applicability.

A better method of conversion of dithioureas to isothiocyanates by using 2,4-dichloro-5-nitropyrimidine was recently reported.[35] Also, treatment of metalated thioureas and ureas with carbon disulfide or 1,3-dithiolane-2-thione afforded isothiocyanates in good yields, as shown in the preparation of phenyl isothiocyanate (eq 7).[36]

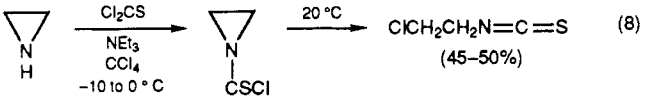
$$PhN^-(Li^+)CSN^-(Li^+)Ph \xrightarrow[\text{heat, 3 h}]{2CS_2,\ THF} 2PhN{=}C{=}S + Li_2CS \quad (72\%) \qquad (7)$$

B. Conversion with Ring Cleavage

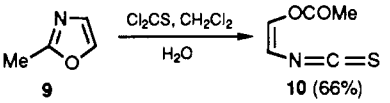
As already mentioned, some reagents brought about rupture of heterocycles leading to the formation of different isothiocyanates.

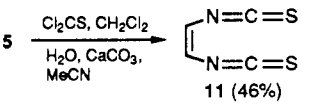
1. Reaction of Heterocycles with Thiophosgene

Generally, nitrogen and oxygen and nitrogen heterocycles underwent facile cleavage with thiophosgene. Thus, the condensation of aziridine with this reagent furnished 2-chloroethyl isothiocyanate in 45–50% yields (eq 8).[37] The adducts of 2-methyloxazole and imidazole

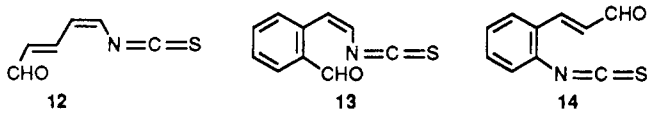


with thiophosgene underwent hydrolytic cleavage to the corresponding isothiocyanates (eq 9)[38,39] and (eq 10).[40] Benzoxazole and benzimidazole afforded similar products.[41]

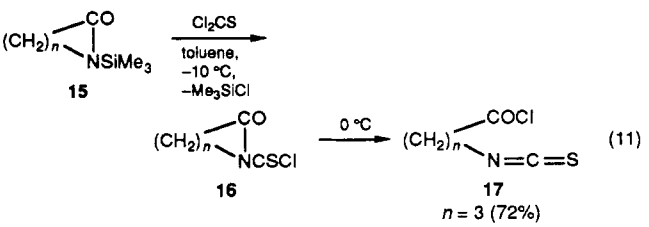




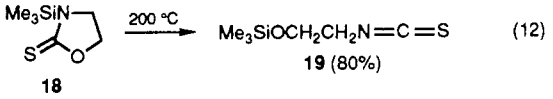
The reaction of pyridine, quinoline, and isoquinoline with thiophosgene led to the formation of isothiocyanates **12**,[42] **13**,[43] and **14**,[43] respectively. Whereas the yields of **12** were only about 8%, those of **13** and **14** were better (46%).



N-Trimethylsilyl lactams **15** (*n* = 3–6) were amenable to manipulation. For example, **15** (*n* = 3) reacted with thiophosgene to give the *N*-chlorothiocarbonyl derivatives **16** which underwent ring opening, affording ω-isothiocyanatocarboxylic acid chlorides **17** in good yields (eq 11).[44] It is noteworthy that on heating *N*-(tri-



methylsilyl)oxazolidine-2-thione (18), [(trimethylsilyl)oxy]ethyl isothiocyanate (19) was obtained in 80% yield (eq 12).[45]

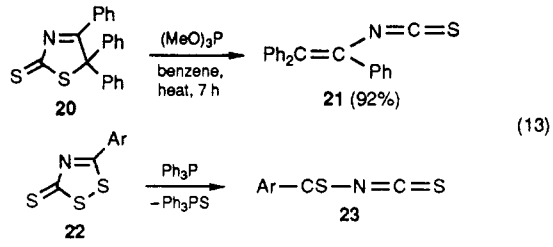


(12)

2. Phosphorus Reagent Aided Conversion of Sulfur Compounds to Isothiocyanates

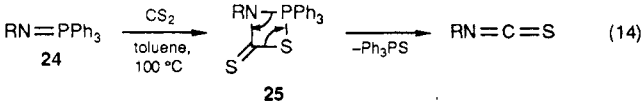
Some phosphorus compounds served as desulfurizing agents and these were used for the conversion of acyclic and heterocyclic sulfur compounds to different isothiocyanates. Recently, the combination of triphenylphosphine and carbon tetrachloride in acetonitrile was used to desulfurize triethylamine salts of different dithiocarbamic acids.[46] Alkyl- and arylamines as well as some amino acid esters were converted into the corresponding isothiocyanates. This method does not seem to have been applied for the conversion of heterocyclic amines.

Photolysis or treatment of 3-thiazolin-2-thione **20** with trimethoxyphosphine furnished isothiocyanate **21** in excellent yield (eq 13).[47] The similar reaction of dithiazolinethione **22** with triphenylphosphine gave thioaroyl isothiocyanates **23**.[48] These conversions ap-



(13)

pear to be useful only in special cases. In comparison, the synthesis of isothiocyanates by the cycloreversion of four-membered rings **25**, obtained by the reaction of (*N*-alkyl- and *N*-arylimino)phosphoranes **24** with carbon disulfide, was more general in nature (eq 14).[49,50] Yields



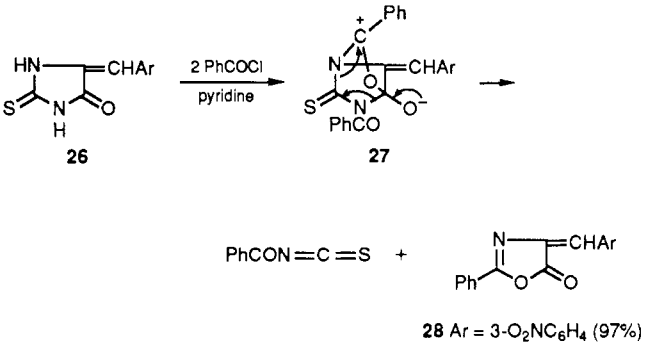
(14)

were reported to be high (75–96%). This reaction was successfully applied to the synthesis of 5-nitro-2-furylvinylene isothiocyanate, potentially useful as an antibacterial agent.[50]

C. Miscellaneous Syntheses of Isothiocyanates

A few esoteric methods were reported to produce isothiocyanates. As already covered in the previous reviews, fragmentation of cycloadducts of some heteroallenes,[1,2] reaction of isocyanates with phosphorus pentasulfide[1,2] or Lawesson's reagent,[51] and conversion of isocyanides[1,2] may be cited as examples. Pyrolysis of some cyclic thioureas and thioamides or their reaction with suitable reagents gave isothiocyanates. For instance, the thiohydantoin derivative **26** with 2–4-fold excess of an aroyl chloride furnished aroyl isothiocyanate and unsaturated azlactone **28** possibly through **27** (Scheme 2).[52] These methods are circuitous and therefore of limited application.

SCHEME 2



III. Syntheses of Heterocycles Using Isothiocyanates

The concept of counterattack reagent, recently proposed,[53] can be extended to isothiocyanates since many of their adducts with compounds carrying an active hydrogen atom undergo cyclization spontaneously or can be manipulated to yield heterocycles. Ring closure of the cyclic intermediate is dependent on the presence of a compatible functionality at an appropriate position within the molecule and on the reaction conditions. It should be noted that the adducts behave as ambident nucleophiles due to the involvement of their nitrogen or the sulfur atom during ring closure. In the case of intermediates from acyl, thioacyl, and imino isothiocyanates, any one of the three hetero atoms of the heteroallene moiety can participate in the heterocyclization step. Isothiocyanates also behave as bielectrophiles in many cyclocondensation reactions. Besides, they undergo cycloaddition with suitable reactants. All these synthetic approaches for the construction of heterocycles are delineated under the following headings. Reactions of different types of isothiocyanates have been covered. As would be expected, the reactivity of N-substituted isothiocyanates would depend on the nature of the substituent, and an electron-withdrawing group such as sulfonyl, acyl etc. would enhance the activity.

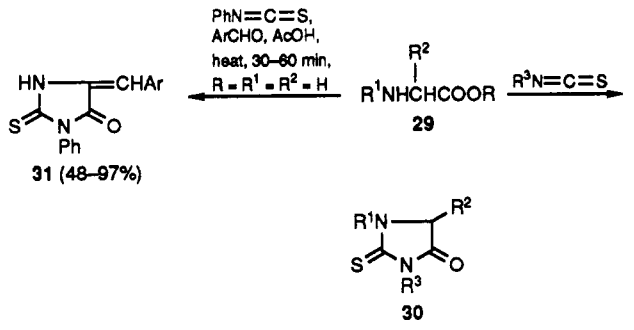
A. Addition–Cyclization Reactions Involving an Amino or Amido Group

The condensation of isothiocyanates with suitable amino/amido binucleophiles or with amino/amido compounds carrying an electrophilic group furnished heterocycles directly. Alternatively, the resultant thioureas were manipulated to yield heterocyclic compounds.[54]

1. Reaction with Amino Acids, Their Derivatives, and Amino Acid Nitriles

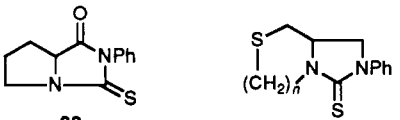
Cyclocondensation of α-amino acids or their esters **29** with isothiocyanates was used as a practical method for the synthesis of 2-thiohydantoins **30** carrying different substituents.[55–61] Yields were generally good (50–85%). The reaction of glycine with phenyl isothiocyanate in the presence of aromatic aldehydes afforded 5-(arylmethylene)-2-thiohydantoins **31**,[62] obviously through the involvement of the saturated compound **30** ($R^1 = R^2 = H$, $R^3 = Ph$) (Scheme 3). The stereochemistry of **31** does not seem to have been studied.

SCHEME 3



a: $R^1 = R^2 = H$, $R^3 = MeCOCH_2CH_2$ (ref 58)
b: $R^1 = NH_2$, $R^2 = H$, R^3 = alkyl, aryl (ref 59)
c: $R^1 = Me_2N$, $R^2 = CH_2COOMe$, R^3 = alkyl, aryl (ref 60)
d: $R^1 = CH_2P(OH)_2O$, $R^2 = H$, $R^3 = H$, alkyl, aryl (ref 61)

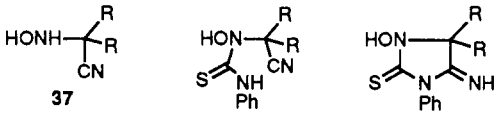
In the widely used Edman's method for the determination of amino acid sequence, the N-terminal amino acid was converted to a thiourea derivative, followed by hydrolysis of the adjacent peptide bond and concomitant cyclization to the corresponding thiohydantoin.[63] The reaction of phenyl isothiocyanate with proline,[64] 1,3-thiazolidine-4-carboxylic acid, and 1,4-tetrahydrothiazine-3-carboxylic acid[65] was employed to prepare the corresponding N-bridged thiohydantoins **32**, **33a**, and **33b**, respectively. Derivatization of 1,4-thiomorpholine-3,5-dicarboxylic acid and its unsaturated analogue with phenyl isothiocyanate enabled their detection by HPLC.[66]



32 **33a:** $n = 1$ **b:** $n = 2$

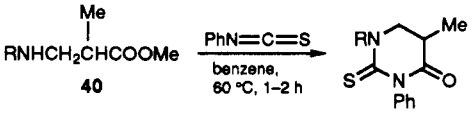
The reaction between isothiocyanates and aminoacetonitriles gave thioureas **34** or imidazolinethiones **35**, depending on the reaction conditions. In polar solvents, a facile cyclization of **34** to **35** was followed by autooxidation to **36** in some cases (Scheme 4).[67]

The condensation of phenyl isothiocyanate with (cyanoalkyl)hydroxylamine **37** furnished **39** via **38**.[68] Obviously, the hydroxyl function being a weaker nucleophile, an attack by the NH group got precedence.



37 **38** **39**

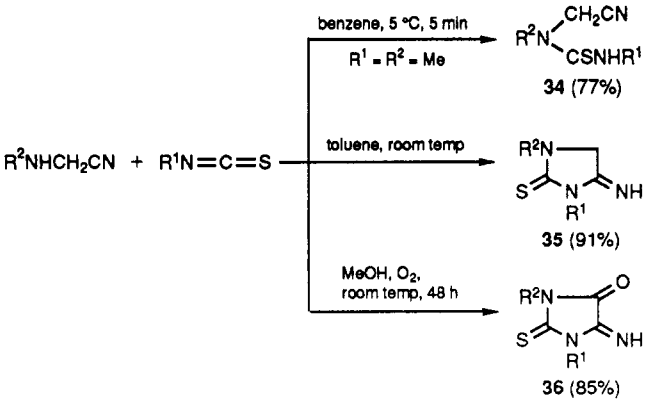
When the amino and carboxylic/nitrile groups were separated by two carbon atoms, the reaction led to the formation of thiopyrimidones.[69–71] Thus, β-amino acid esters **40** with phenyl isothiocyanate afforded **41** (eq 15).[69] A similar reaction of ethyl 3,3-diaminoacrylate



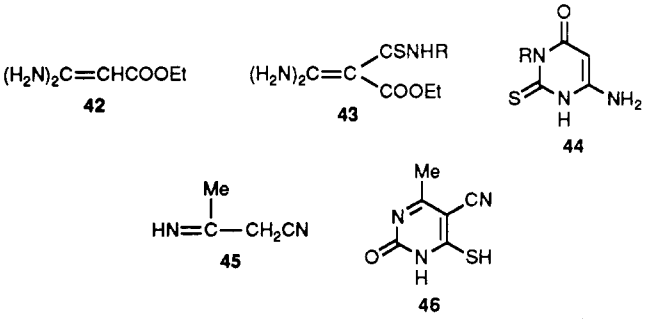
40 **41** (15)

(**42**) with alkyl and aryl isothiocyanates furnished **43** and **44** in low yields.[70] The formation of compound **43** can be rationalized by assuming the involvement of

SCHEME 4

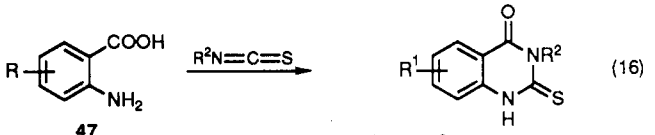


electron-rich β-carbon atom of the enamine **42**. Recently, the pyrimidine derivative **46** was obtained in 90% yield by the interaction of 3-iminobutyronitrile (**45**) and ethoxycarbonyl isothiocyanate.[72]



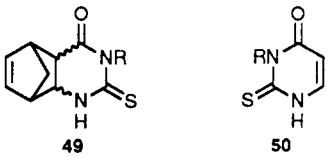
42 **43** **44** **45** **46**

Cyclic compounds carrying amino and vicinal carboxylic groups reacted with isothiocyanates to give the corresponding thioureas which were amenable to yield fused thiopyrimidones. Thus, the condensation of anthranilic acids with isothiocyanates gave 2-thio-4-quinazolones,[1,73,74] as shown in the conversion of **47** into **48** (eq 16).[58]



47 **48:** $R^1 = H$, $R^2 = MeCOCH_2CH_2$ (78%) (16)

Methylene-bridged thioquinazolones **49** were obtained by similar approach and these were converted into new thiouracils **50** via retrodiene decomposition.[75,76] It is noteworthy that the reaction of allyl and aryl isothiocyanates with dimethylsulfoxonium [2-(methylamino)benzoyl]methylide furnished the corresponding thioquinazolones.[77] Also, the condensation of isatoic

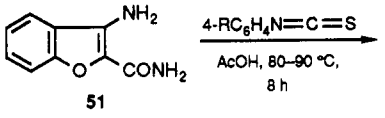


49 **50**

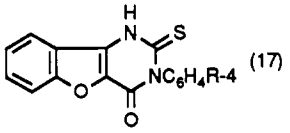
anhydride with aryl isothiocyanates gave 3-aryl-2-thio-4-quinazolones, apparently by cycloaddition of an intermediary iminoketene.[78]

Heterocycles carrying an amino function with a vicinal carbonyl group were exploited for the construction of fused thiopyrimidine rings. Thus, 3-aminobenzofuran-2-carboxamide (**51**) was converted into **52** (eq

17).[79] In this reaction the intermediary thiourea un-



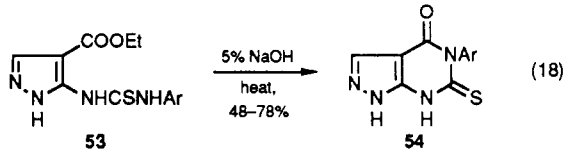
51



(17)

52a: R = Me (42%)
b: R = Cl (55%)
c: R = Br (58%)

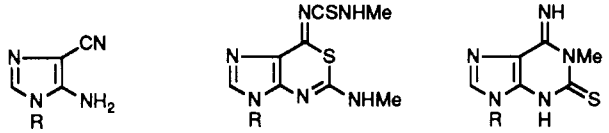
derwent spontaneous cyclization. But in some cases the intermediate was isolated and then subjected to ring closure. For example, several azoles fused with a thiopyrimidone ring were prepared by cyclocondensation of the thiourea derivatives,[80-82] as shown in the preparation of **54** (eq 18).[82]



(18)

53 54

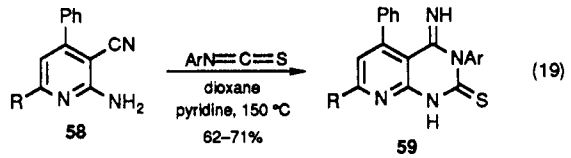
The reaction of an isothiocyanate with 5-aminoimidazole-4-carbonitrile led to the formation of imidazolothiazine or imidazolopyrimidine derivatives, depending on the reaction conditions.[83] Thus, **55** reacted with methyl isothiocyanate in DMF at 50 °C to give the thiazine derivative **56**, whereas the conversion in boiling pyridine afforded **57**.[84] Apparently, the basic medium



55 56 57

R = $CH_2OCH_2CH_2OAc$

facilitated attack by the nitrogen atom of the heteroallene moiety. This was also supported by the aryl isothiocyanate-mediated cyclocondensation of 2-aminonicotinonitriles **58** to pyridopyrimidines **59** in the presence of pyridine (eq 19).[85,86]

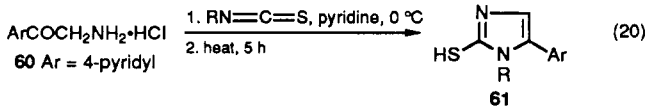


(19)

58 59

2. Reaction with Amino Aldehydes, Amino Ketones, and the Corresponding Oximes

Amino ketone hydrochloride **60** reacted with alkyl and aryl isothiocyanates in the presence of pyridine, affording 2-mercaptoimidazoles **61** in excellent yields (98%) (eq 20).[87] The similar reaction of alkyl and aryl

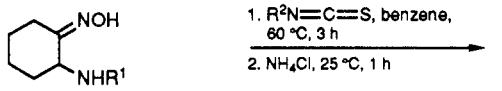


(20)

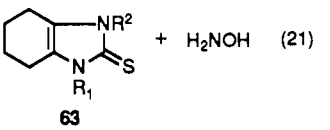
61

isothiocyanates with 2-amino-2-deoxyaldoses,[88] 1-deoxy-1-(methylamino)-D-lyxohexulose,[89] and 2-(alkylamino)-2-deoxy-D-glucose[90,91] gave the corresponding imidazole derivatives.

α-Aminocyclohexanone oximes **62** underwent cyclocondensation with isothiocyanates to give fused thioimidazolone, as a result of extrusion of the hydroxylamine moiety during the cyclization step (eq 21).[92]



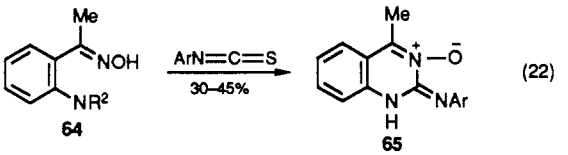
62: R^1 = H, alkyl, aralkyl; R^2 = alkyl, aryl



(21)

63

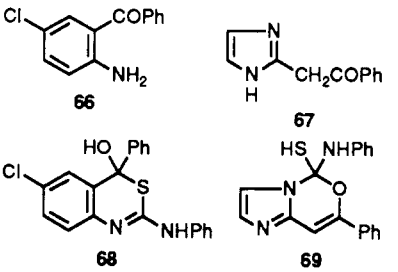
However, the interaction of *o*-aminoacetophenone oxime (**64**) and aryl isothiocyanates produced derivatives of quinazoline 3-oxide **65**, the heteroallene moiety acting as a bielectrophile in this conversion (eq 22).[93] On the



(22)

64 65

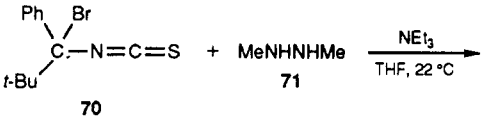
other hand, 2-amino-5-chlorobenzophenone (**66**) and imidazolo ketone **67** reacted with phenyl isothiocyanate to give benzothiazine derivative **68**[94] and N-bridged oxazine compound **69**,[95] respectively, via the thiourea intermediate.



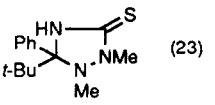
66 67 68 69

3. Reaction with Hydrazines and Hydrazides

The condensation of hydrazines with isothiocyanates led to different products depending on the nature of the reactants. Interaction of the 1,3-bielectrophile **70** and *N,N'*-dimethylhydrazine (**71**) furnished triazolidine derivative **72** (eq 23),[96] whereas benzoyl isothiocyanate



70 71



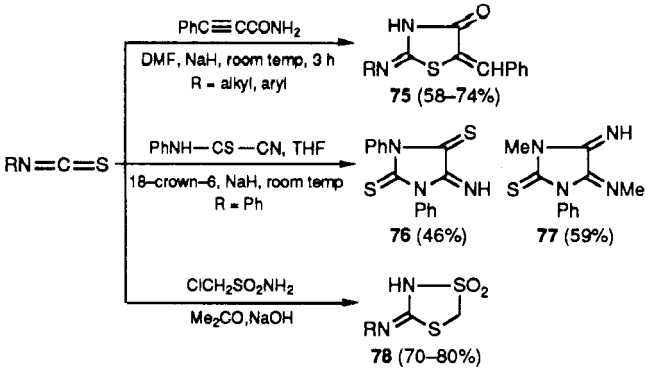
(23)

72 (83%)

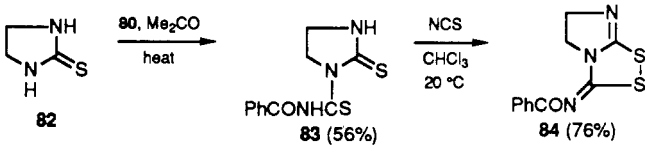
reacted with *N,N'*-diphenylhydrazine to give an intermediate which was cyclized to triazolinethione.[97] It is noteworthy that phenyl and 2-pyridyl isothiocyanates reacted with cyclohexanone phenylhydrazone in dimethylformamide, containing sodium hydroxide, to give the corresponding spirotriazolidinethiones.[98]

Reaction of isothiocyanates with hydrazides furnished thioureas which gave thiadiazoles **73** under acidic conditions, whereas the use of dilute sodium hydroxide

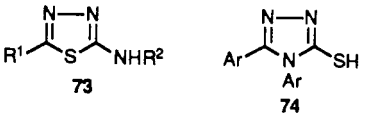
SCHEME 5



SCHEME 6

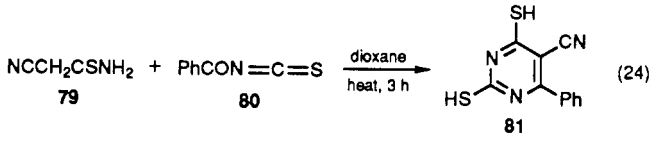


afforded triazoles **74**.[99-104] Triazoles of the type **74** were also obtained by the condensation of amidrazones with aryl isothiocyanate, the amine of the heteroallene moiety being eliminated in this reaction.[105]



4. Cyclocondensation with Amido Group

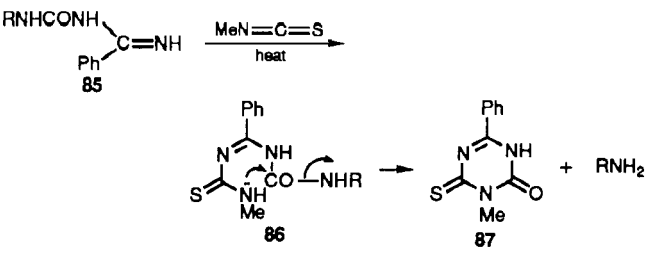
Base-aided reaction of primary and secondary amides, thioamides, and sulfoamides, carrying an electrophilic center within the molecule, formed adducts with isothiocyanates which in turn underwent ring closure to give heterocycles, as shown in the synthesis of derivatives of azolidine **75**,[106,107] **76**,[108-110] and those of dithiazolidine **78**[111] (Scheme 5). By using different substituents in either the cyanothioformamide and/or in the isothiocyanate, the balance between sulfur and nitrogen was displaced.[109,110] Thus, cyanothioformanilide with methyl isothiocyanate gave only the isomeric thiazole derivative **77** as a result of nucleophilic attack by sulfur on the isothiocyanate under a variety of conditions, including sodium hydride, crown ether, and THF.[109] On the other hand, the condensation of cyanothioacetamide (**79**) with benzoyl isothiocyanate (**80**) led to the formation of the pyrimidinedithiol derivative **81** (eq 24).[112]



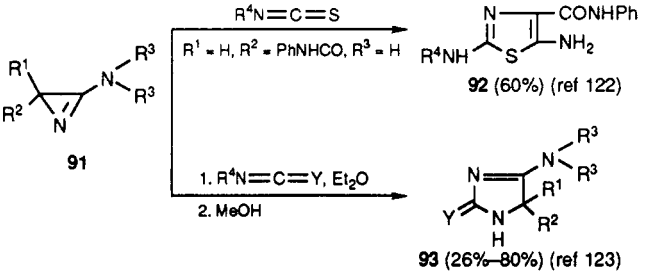
(24)

Imidazolidine-2-thione (**82**) reacted with **80** to give *N*-thiocarbamoyl derivative **83** which was converted to **84** by oxidative cyclization using *N*-chlorosuccinimide (Scheme 6).[113] The formation of **83** could be direct or as a result of S–N transthioacylation, but this aspect does not seem to have been studied. Some reactions initiated by attack on the heteroallene moiety by sulfur nucleophile of cyclic thioureas have been discussed later.

SCHEME 7



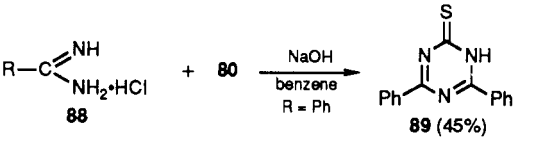
SCHEME 8



R^1 = H, Me, Ph, R^2 = Me,Et, Ph
$CONMe_2$, R^3 = alkyl, R^4 = Me_3Si, Y = O, S

5. Cyclocondensation with 1,3- and 1,4-Aminobinucleophiles

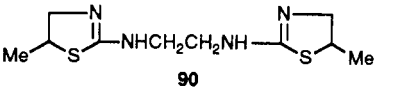
Thermal condensation of the amidine derivative **85** with methyl isothiocyanate afforded thiotriazinone **87** via **86** (Scheme 7).[114] On the other hand, benzoyl isothiocyanate (**80**) reacted with **88** (R = alkyl, aryl, SR, OR, NR_2) to give triazinethiones,[115-117] as shown in the synthesis of **89** (eq 25).[115] The reaction of *S*-benzyl-



(25)

isothiouronium chloride to an aroyl isothiocyanate was found to be influenced by the nature of the base used for the condensation.[118] It should be added that suitable *N*-thiocarbamoylthioureas condensed with alkyl and aryl isothiocyanates affording the corresponding 6-iminotriazinedithiones which were hydrolyzed to 6-oxotrizinedithiones in excellent yields (85–94%).[119]

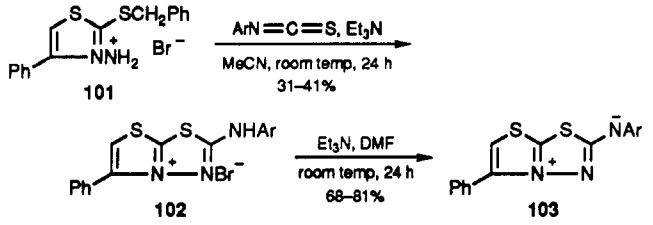
Ethylenediamine with allyl isothiocyanate furnished a linear thiourea which in turn was cyclized to bisthiazoline **90**.[120] A number of α,ω-diamines were con-



verted into bisthiazolines. In some cases, the reaction directly led to the formation of heterocycles. For example, different isothiocyanates, including alkyl 2-isothiocyanatoacetates, reacted with *o*-phenylenediamine to give 2-amino-substituted derivatives of benzimidazoles via the corresponding thioureas.[121] As already mentioned, thioureas are versatile synthons. With proper planning, generation of these intermediates and their conversion into desired heterocycles can be carried out in the same flask.

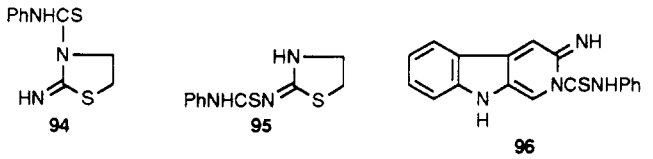
Tautomeric nature of the N–C–N system of nitrogen heterocycles with an α-amino group played important

SCHEME 9

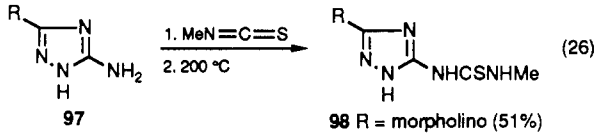


roles in many conversions. In the ring expansion of azirines **91** to five-membered heterocycles, the exocyclic amino group activated the ring nitrogen, thereby enabling it to initiate the reaction which proceeded through a cycloadduct intermediate (Scheme 8).[122,123] Cycloaddition of azirines have been discussed later.

Addition of 2-aminothiazoline and 3-aminopyridoindole to phenyl isothiocyanate produced **94**[124] and **96**,[125,126] respectively. The compound **94** was thermodynamically unstable and on heating changed to **95**.[124]

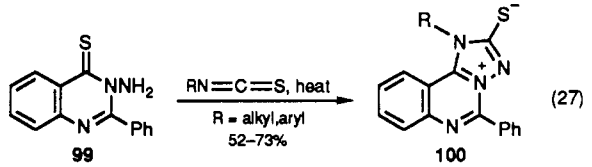


A similar thiocarbamoylation of 5-amino-1,2,4-triazoles **97** with alkyl or aryl isothiocyanate took place regioselectively at the 1-position, but on heating rearranged to 5-thiocarbamoylaminotriazoles, as shown in the preparation of **98** (eq 26).[127]



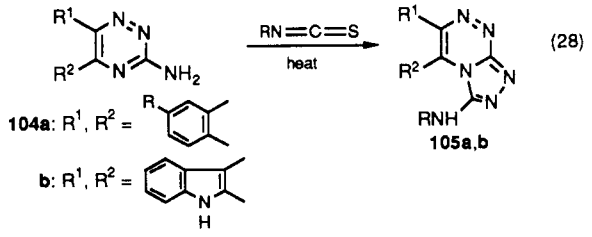
(26)

3-Aminoquinazoline-4-thione **99** did not behave as a 1,4-binucleophile and, with alkyl and aryl isothiocyanates, furnished mesoionic triazoles **100**, as a result of cyclodesulfurization of the resultant intermediate (eq 27).[128] Similarly, 3-amino-2-(benzylthio)-4-phenyl-



(27)

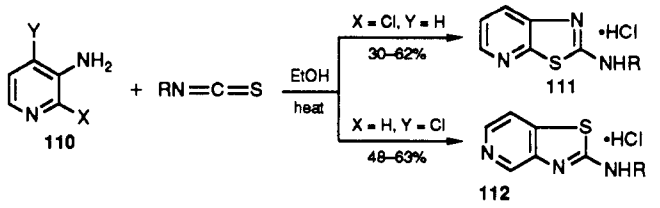
thiazolium bromide (**101**) was converted into mesoionic compounds **103** via **102** (Scheme 9).[129] In contrast, the triazine derivatives **104a** and **104b** reacted with isothiocyanates to give the corresponding thiosemicarbazides which led to the formation of N-bridged compounds **105a**[130] and **105b**,[131] respectively (eq 28). A



(28)

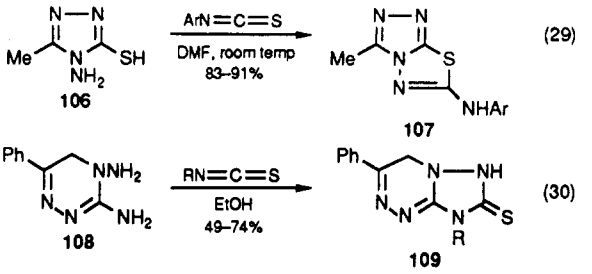
similar cyclocondensation was encountered when 5,6-

SCHEME 10



diphenyl-1,2,4-triazin-3-ylhydrazine was used as a substrate.[132] Also, 1,2,4-triazolo[4,3-*b*][1,2,4]triazoles[133] and 4*H*-1,3,4-thiadiazolo[2,3-*c*][1,2,4]triazin-4-one[134] were obtained by analogus reactions.

1-Aminotriazole-5-thiol **106** served as a 1,4-binucleophile in the reaction with aryl isothiocyanates, affording **107** (eq 29).[135] Triazinediamine **108**, however, reacted with isothiocyanates to give N-bridged compounds, obviously through the involvement of amino–imino tautomerism during cyclization of the intermediary thiosemicarbazide (eq 30).[136]

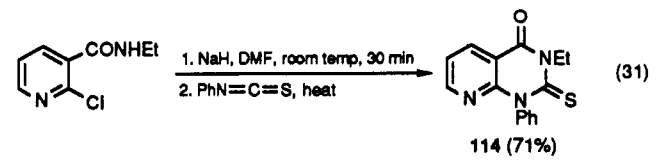


(29)

(30)

6. Cyclocondensation with Amino- and Amidohalopyridines

3-Aminopyridine **110**, having an adjacent chlorine substituent, reacted with alkyl and aryl isothiocyanates to give pyridinothiazole **111** or **112**, depending on the position of the halogen atom (Scheme 10).[137] In both these cases, the sulfur atom of the thiourea intermediate was involved in the cyclization step. A similar reaction of 2-chloro-3-hydrazinopyridine with phenyl isothiocyanate gave 1*H*-pyrido[3,2-*e*][1,3,4]thiadiazine, though with ethoxycarbonyl and with (ethoxycarbonyl)methyl isothiocyanates, only the 1,4-disubstituted thiosemicarbazides were isolated.[138] In contrast, the biologically active pyridopyrimidinethiones, for example **114**, were obtained by the reaction of aryl, aralkyl, and cycloalkyl isothiocyanates with 2-halonicotinamide **113**, as a result of cyclocondensation of the intermediate in which the nitrogen nucleophile of the heteroallene moiety participated (eq 31).[139]

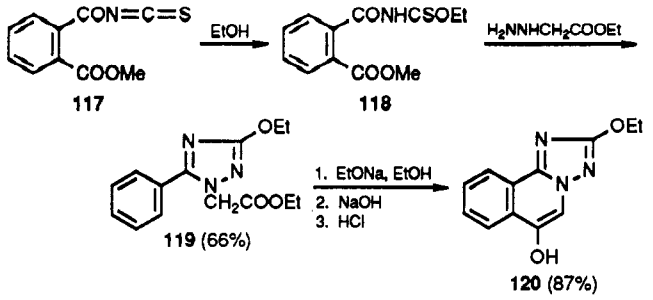


(31)

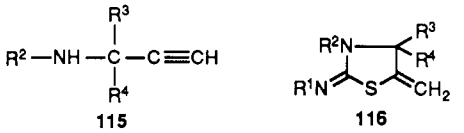
7. Reaction with Aminoalkynes

Unlike the cyclocondensation of aminoacetonitriles[67] and (hydroxylamino)acetonitriles[68] with isothiocyanates, which afforded imidazolidinethiones **35** and **39**, respectively, the addition of alkyl and aryl isothiocyanates

SCHEME 11



to (aminoalkyl)acetylenes **115** led to the formation of 2-imino-5-methylenethiazolidines **116** through the involvement of the sulfur nucleophile. Compounds **116** exhibited hypotensive, antiinflammatory, and analgesic properties.[140]

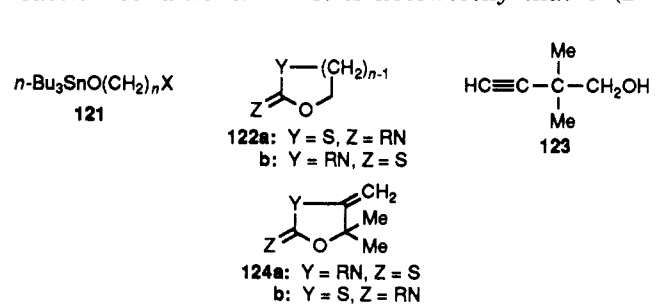


B. Formation of Thiocarbamate or Dithiocarbamate and Its Cyclization

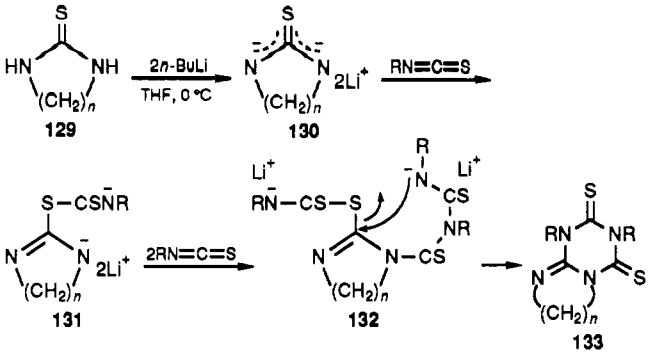
Simple isothiocyanates were found to be stable in neutral water and alcohols. However, the acyl and sulfonyl isothiocyanates, being more reactive, afforded thiocarbamates much more easily.[1] It is noteworthy that N deacylation of acyl isothiocyanates, and hydrolysis of skatylidene and 4-hydroxybenzylidene isothiocyanates were also reported.[1]

2-(Methoxycarbonyl)benzoyl isothiocyanate (**117**) was converted into **118** which on reaction with ethyl hydrazinoacetate gave triazole **119**, the Dieckmann cyclization of which afforded triazoloisoquinoline **120** (Scheme 11).[141]

Metal alkoxides were used for the preparation of thiocarbamates. Thus, tributyltin ω-haloalkoxides **121** (X = Cl, Br, I, n = 2, 3) with isothiocyanates furnished O,S heterocycle **122a** and O,N heterocycle **122b**, the ratio of which depended on the type of substituent and solvent.[142] The reaction obviously involved the corresponding monothiocarbamates as an intermediate. Similarly, acetylenic ethanol **123**[143,144] underwent sodium hydride aided cyclocondensation with alkyl, aryl, and aralkyl isothiocyanates to give 4-methyleneoxazolidine-2-thiones **124a** and 2-amino-4-methyleneoxathiolanes **124b**, depending on the reactants and the reaction conditions.[144] It is noteworthy that O-(2-propenyl) N-acylmonothiocarbamates **125**, prepared by the condensation of acyl isothiocyanates with allylic

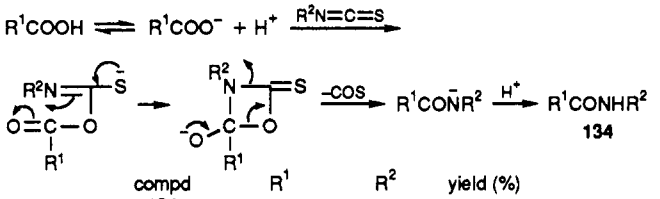


SCHEME 12



a: R = Me, n = 2 (10%); **b**: R = Me, n = 3 (61%); **c**: R = Et, n = 3 (36%); **d**: R = Me, n = 4 (22%); **e**: R = Et, n = 4 (13%)

SCHEME 13



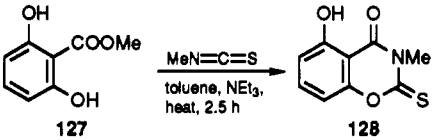
compd 134	R^1	R^2	yield (%)
a	Me	Ph	60
b	n-Pr	Ph	75
c	$PhCH_2$	n-Bu	63
d	4-$O_2NC_6H_4$	n-Bu	60
e	2-HOC_6H_4	Ph	41
f	2-$O_2NC_6H_4$	Ph	35

alcohol, underwent Cope rearrangement to give S-(2-propenyl) N-acylmonothiocarbamates **126** (eq 32).[145]

$$\underset{\mathbf{125}}{\mathrm{RCONHCSOCH_2CH{=}CH_2}} \xrightarrow[50\text{–}98\%]{\text{benzene}} \underset{\mathbf{126}}{\mathrm{RCONHCOSCH_2CH{=}CH_2}} \quad (32)$$

R = aryl, heteroaryl

Aromatic ketoximes reacted with isothiocyanates, whereas phenols of comparable acidity gave no adducts.[146,147] However, triethylamine-aided condensation of **127** with methyl isothiocyanate gave the benzoxazine derivative **128** which exhibited fungicidal property (eq 33).[148] Some spirooxazolidinone thiones were similarly



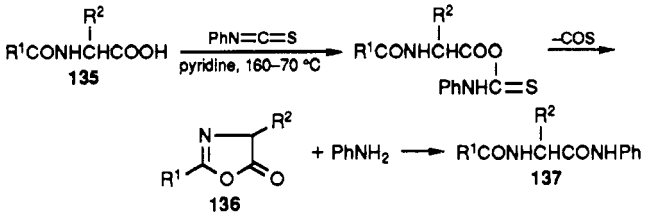
(33)

prepared by the interaction of isothiocyanates and azacycloalkanols carrying the carboxylic and hydroxyl groups at the same carbon atom of the ring, but this reaction occurred only in the presence of sodium hydride.[149]

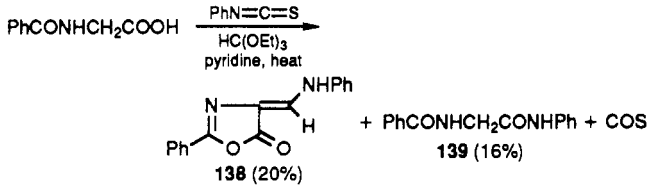
Thiols reacted with isothiocyanates to form dithiocarbamates. Mercaptoacetic and mercaptopropionic acids furnished adducts with isothiocyanates which were manipulated to yield thiazolidine and thiazine derivatives, respectively.[1] The condensation of an isothiocyanate with 2-aminothiophenol was supposed to produce a dithiocarbamate which in turn furnished 2-aminobenzothiazole.[150] But this reaction could also proceed through the thiourea intermediate.

The condensation of isothiocyanates with anions generated from cyclic thioureas **129** was initiated by

SCHEME 14



SCHEME 15



addition of the sulfur nucleophile (Scheme 12).[151]

C. Condensation with Carboxylic Acids

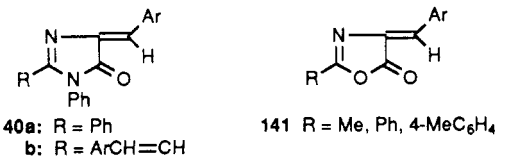
The reaction of isothiocyanates with carboxylic, thiocarboxylic, and N-acylamino acid followed different mechanisms depending on the type of acid used.

1. Reaction with Mono- and Dicarboxylic Acids

The condensation of carboxylic acids with isothiocyanates proceeded through addition–elimination reactions to yield amides (Scheme 13). Pyridine as a catalyst facilitated the reaction, and it was successful even with salicylic acid.[152] In the reaction of phenyl isothiocyanate with dicarboxylic acids, dianilides were obtained.[153] Oxalic and malonic acids gave dianilides in very low yields due to the partial decarboxylation of these acids. Succinic acid produced monoanilides as well as dianilides, whereas phthalic acid gave *N*-phenylphthalimide in moderate yield. The last two dicarboxylic acids underwent partial cyclodehydration, thereby affecting the yields. Glutaric and adipic acids, however, formed the corresponding dianilides in much better yields (60–78%).[153]

2. Reaction with N-Acylamino Acids

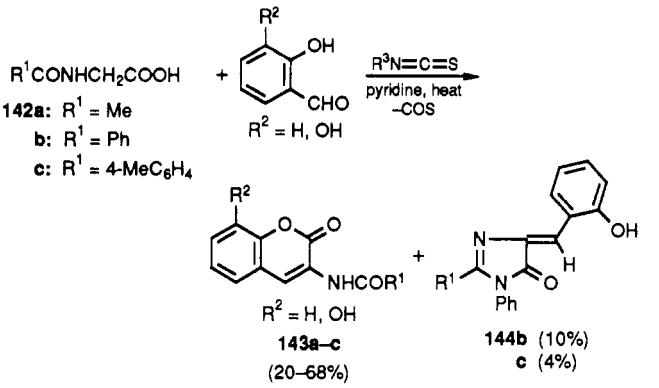
The condensation of α-*N*-acylamino acids with phenyl isothiocyanate afforded the corresponding anilides **137**. This reaction could follow the pathway outlined in Scheme 13. Alternatively, it could proceed via 2-oxazolin-5-one **136** (Scheme 14), which was substantiated by the isolation of 4-(anilinomethylene)-2-phenyl-2-oxazolin-5-one (**138**) in the phenyl isothiocyanate mediated condensation of *N*-benzoylglycine in the presence of triethyl orthoformate (Scheme 15).[154] The similar cyclocondensation reaction of *N*-benzoyl- and *N*-acetylglycines with phenyl isothiocyanate in the presence of aromatic aldehydes furnished 4-(arylmethylene)-1,2-diphenyl- and 4-(arylmethylene)-1-phenyl-2-styryl-2-imidazolin-5-ones **140a**[155] and **140b**,[156] respectively. On cyclocondensation of 2-(benzoylamino)cinnamic acid with phenyl isothiocyanate, **140a** (Ar = Ph) was obtained directly.[157] It should be mentioned that the reaction of isothiocyanates with *N*-acylglycines **142**, in the presence of salicyl aldehydes, led to the formation of 3-(*N*-acylamino)coumarins **143** as the major product along with a small amount of 2-substituted 4-(2-hydroxybenzylidene)-1-phenyl-2-imidazolin-5-ones **144** in a few cases (Scheme 16).[158] The formation of 4-(arylmethylene)-2-imidazolin-5-ones **144** was found to involve the corresponding unsaturated azlactones **141**.[158]



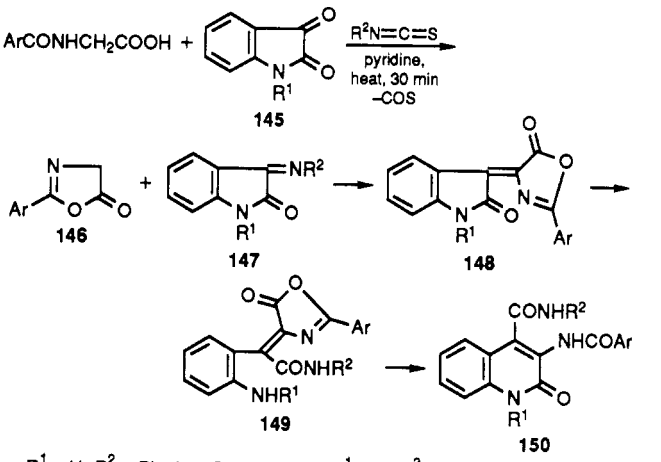
140a: R = Ph
b: R = ArCH=CH

141 R = Me, Ph, 4-MeC$_6$H$_4$

SCHEME 16



SCHEME 17



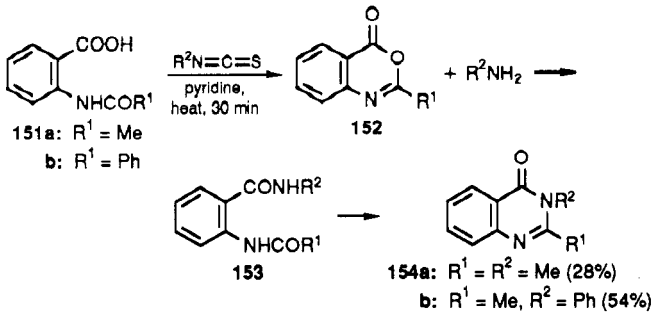
a: R^1 = H, R^2 = Ph, Ar = Ph (37%); **b**: R^1 = H, R^2 = Me, Ar = Ph (29%); **c**: R^1 = Me, R^2 = Ar = Ph (36%); **d**: R^1 = H, R^2 = Ph, Ar = 4-MeC$_6$H$_4$ (49%)

The reaction of *N*-aroylglycines with phenyl and methyl isothiocyanates in the presence of isatin and *N*-methylisatin furnished carbostyryl derivatives **150** (Scheme 17).[159] The mechanism proposed was confirmed by the condensation of authentic isatin imines **147** with **146**. It is noteworthy that compounds **150** would be difficult to prepare by any other route, and the present method offers a facile one-pot synthesis. Isothiocyanate-mediated cyclocondensation of *N*-acylanthranilic acid to 4-quinazolones was reported in the literature. Thus, **151** reacted with methyl or phenyl isothiocyanate to give 2-substituted 3,1-benzoxazin-4-ones **152** and methylamine or aniline which in turn underwent subsequent changes. Whereas **151a** with methyl and phenyl isothiocyanates gave 4-quinazolones **154a** and **154b**, respectively, the reaction of **151b** with methyl and phenyl isothiocyanates gave **152** (R^1 = Ph) and **153** (R^1 = R^2 = Ph), respectively (Scheme 18).[160]

D. Syntheses Involving Carbon Acids and Ylides

The conjugate base of carbon acids, carbanions, added to isothiocyanates affording thioamides, many

SCHEME 18

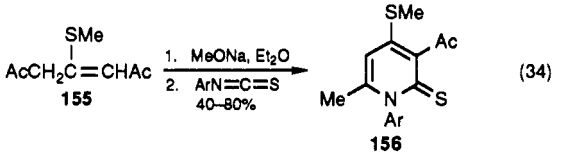


of which were amenable to give heterocycles. These reactions were initiated by the abstraction of proton with a suitable base, the choice of which depended on the acidity of the compound, and the reaction conditions were governed by the sensitivity of the reactants.

1. Reaction with Carbon Bases

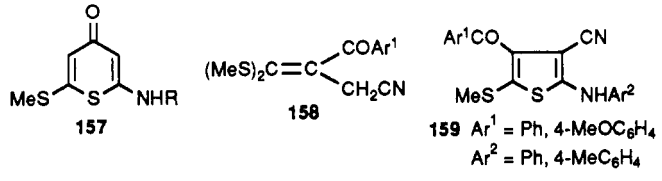
Acyclic[161] as well as cyclic[162,163] ketones, containing at least one α-hydrogen atom, reacted with isothiocyanate to give β-oxo thioamides. In the case of compounds having two activated methyl, methylene, and/or methine groups in the same molecule, the proportion of base should be controlled in order to exercise regioselectivity.

The condensation of aryl isothiocyanates with anion of diketone **155** furnished pyridinethiones **156** (eq 34).[164] Several similar examples were reported.[165-170] Ketene



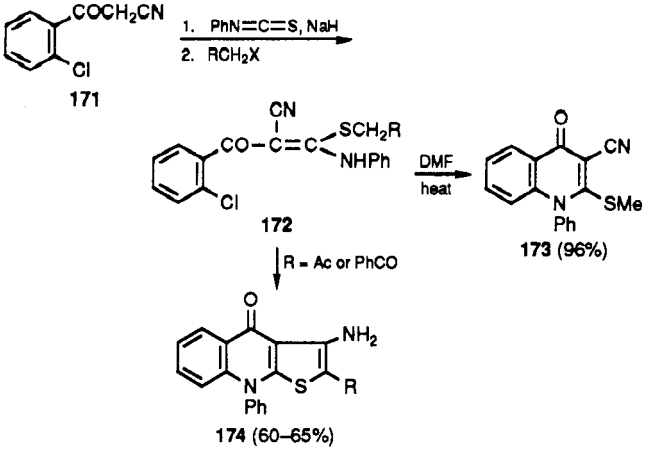
(34)

dithioacetal, derived from acetone, underwent sodium hydride aided condensation with alkyl and aryl isothiocyanates to give thiopyrones **157**.[171] Similarly, anions from the polarized ketene dithioacetals **158** in a step-wise regioselective cyclocondensation with aryl isothiocyanates gave the corresponding 4-aroyl-2-(arylamino)-5-(methylthio)thiophene-3-carbonitriles **159**.[172]

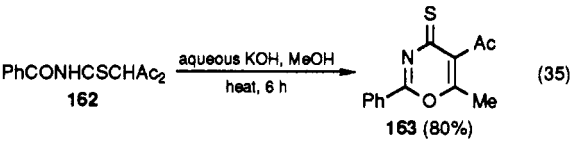


On the other hand, cinnamoyl,[173] furacroylacetonitriles,[173] and unsymmetrical alkenyl arylmethyl ketones[174] were converted into substituted 2-amino-5,6-dihydro-4-thiopyrones via intramolecular Michael addition of the intermediate formed. It is noteworthy that aryl isothiocyanates underwent condensation with acetylenic amides **160** to give an adduct which on base-aided cyclization afforded thiazine derivatives **161**.[175] All these conversions can be rationalized by Baldwin rules.[176]

SCHEME 19

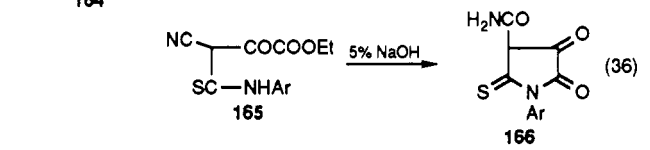


Compound **162**, obtained by the reaction between benzoyl isothiocyanate and acetylacetone, underwent cyclization to oxazinethione **163** in a basic medium (eq 35).[177] Similarly, the condensation of benzoyl iso-



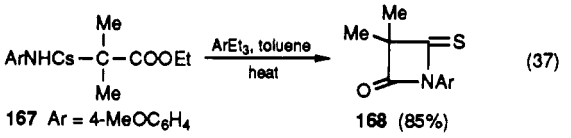
(35)

thiocyanate with ethyl cyanoacetate and malononitrile was exploited in the synthesis of heterocyclic derivatives.[177] Addition of carbanion **164** to aryl isothiocyanates furnished the corresponding thioamides **165** which underwent cyclization to the pyrrolidine derivative **166** in the presence of sodium hydroxide (eq 36).[178]



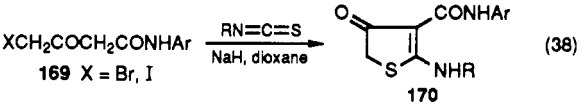
(36)

It should be mentioned that triethyl aluminum was found to bring about a similar cyclocondensation of **167** to thioxoazetidine **168** (eq 37).[179]



(37)

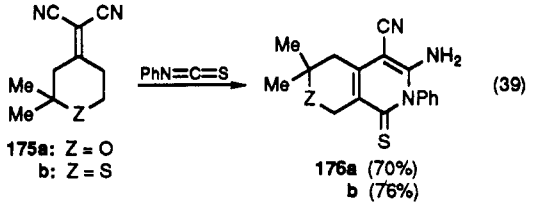
Active methylene compounds **169** reacted with phenyl, benzoyl, and cinnamoyl isothiocyanates, affording thiophene derivatives **170** via cyclodehydrohalogenation of the adduct with the involvement of the sulfur nucleophile (eq 38).[180] On the other hand, the reaction



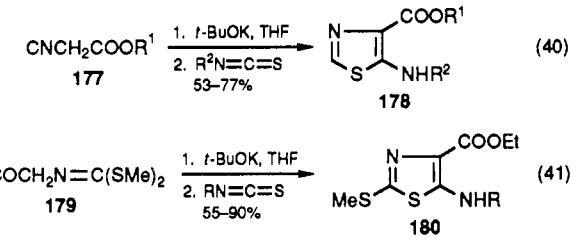
(38)

of 2-(chlorobenzoyl)acetonitrile (**171**) with phenyl isothiocyanate formed an adduct which was converted into quinolones via **172** (Scheme 19).[181] Compound **172** (R = Ac or PhCO) produced **174** by double cyclization. In this reaction, the cyano group was affected only when the substituent R was an acetyl or a benzoyl group. But the condensation of pyran and thiopyran derivatives

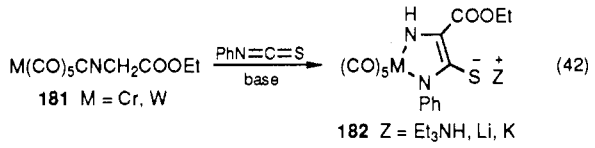
175a and 175b with phenyl isothiocyanate afforded condensed amino pyridines as a result of counterattack by the heteroallene nitrogen on the sterically aligned nitrile group (eq 39).[182]



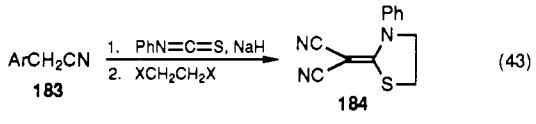
The carbanion of isocyanoacetate 177 added to isothiocyanates leading to the formation of thiazoles 178 (eq 40).[183,184] Recently, the reaction of isothiocyanates with the anion of dimethyl dithiocarbonate *N*-[(ethoxycarbonyl)methyl]imine (179) was used to prepare 5-(arylamino)- or 5-(alkylamino)-4-(ethoxycarbonyl)-2-(methylthio)-1,3-thiazoles 180 (eq 41).[185] These two



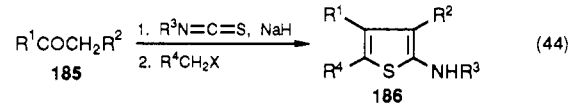
routes seem to be advantageous for the synthesis of different 5-aminothiazoles. It is noteworthy that the metal complexes of isocyano acetate 181 reacted with phenyl isothiocyanate regioselectively, in the presence of a base, to give imidazole derivatives (eq 42),[186] whereas the LDA-mediated cyclization of 2-toluyl isocyanide was used for the synthesis of N-substituted indole-3-thiocarboxamides.[187]



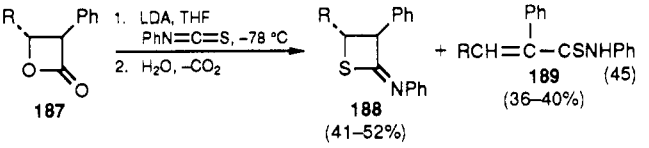
The adduct of isothiocyanates with arylacetonitrile carbanion was found to be useful for the construction of N,S heterocycle, as shown in the conversion of 183 into 184 (eq 43).[188,189] A similar reaction of active



methylenic ketones 185 (R^1 = aryl, heteroaryl, R^2 = CN, NO_2) with phenyl and allyl isothiocyanates furnished intermediates which were converted into 2-aminothiophenes by the base-aided condensation with reactive α-halo ketones or ethers, and α-halo nitromethane (eq 44).[190-192]

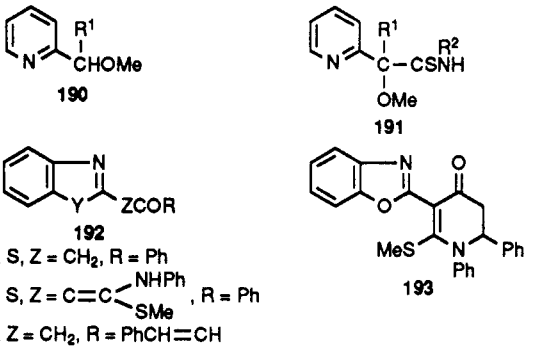


Metalated heterocycles as well as metalated aromatic compounds are important synthons, but their reaction with isothiocyanates does not seem to have been properly exploited. In the case of heterocycles, a carbanion could be generated at the ring or at the side-chain depending upon the type of the ring. For example, the carbanions of 2-oxetanones 187 (R = *i*-Pr, *t*-Bu) added to phenyl isothiocyanate to give iminothietane 188 and an acyclic product 189 in moderate yields (eq 45).[193] It



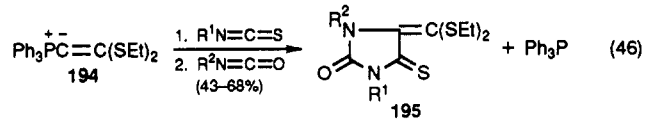
is noteworthy that the reaction of phenyl isothiocyanate with enolates generated from methyl 2-[(trimethylsilyl)oxy]cyclopropanecarboxylates led to the formation of pyrrole derivatives via an anionic 1,3-sigmatropic rearrangement.[194]

2-Pyridylthioacetamides 191, exhibiting gastric acid secretion inhibition activity, were prepared by lithiation of 190 and subsequent condensation with isothiocyanates.[195-197] Similarly, benzazoles 192a and 192c were converted into 192b and 193, respectively.[198]

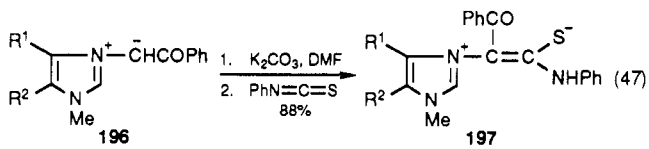


2. Condensation with Ylides

Phosphonate carbanions were successfully added to isothiocyanates.[199] Some of these adducts existed as tautomers and could be converted to *S*-alkyl products.[200] Phosphorus ylide 194 with alkyl and aryl isothiocyanates gave adducts which reacted with isocyanates to afford imidazolidonethiones (eq 46).[201]



Nitrogen ylides, derived from imidazole 196 (R^1 = R^2 = H)[202] and benzimidazole 196 (R^1 = R^2 = C_6H_4),[203] added to isothiocyanates furnishing antiinflammatory compounds 197 (eq 47).



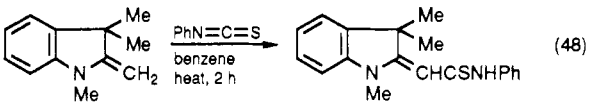
E. Reactions Involving an Activated C=C Bond

Compounds with C=C bond reacted as nucleophiles provided they carried an activating group, such as amino, alkoxy, alkylthio, etc., directly linked to the olefinic carbon atom. Many heterocycles could be considered under this category. It should be emphasized that these could be a part of tautomeric systems, as already described in the reactions of 3,3-diaminoacrylate, 3-iminobutyronitrile, and different stabilized carbanions in

the foregoing sections. The condensation of isothiocyanates with compounds having activated C=C bond is of considerable synthetic utility, as would be evident from the following account.

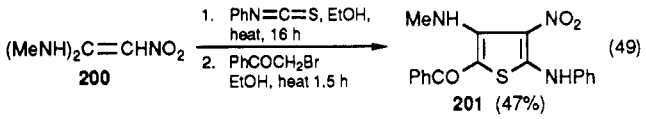
1. Reaction with Enamines

It should be noted that the reaction between enamines and isothiocyanates could proceed through cycloaddition, which has been discussed later. Enamines carrying a β-hydrogen atom reacted with isothiocyanates to give thioamides which on manipulation furnished heterocycles.[1,3] The Fischer base **198** afforded *E*/*Z* isomers of **199** (eq 48).[204]



198 199 (84%) (48)

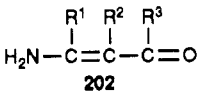
Nitroketene aminal **200** with phenyl isothiocyanate formed an adduct in 28% yield which was converted into thiophene (eq 49). This was the first direct synthesis of a nitroheterocycle from a nitro enamine.[205]



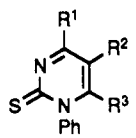
200 201 (47%) (49)

The sodium salt of nitroformaldehyde arylhydrazones formed adducts with aryl isothiocyanates in DMF which gave 6-(arylimino)-1,3-diaryl-5-nitro-1,2,3,6-tetrahydro-1,3,4-triazine-2-thiones, whereas the reaction in acetonitrile furnished 1,3-diaryl-5-oxo-2,3,4,5-tetrahydro-1,3,4-triazole-2-thiones in good yields.[206]

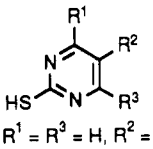
Unlike the foregoing conversions, in which the activated enaminic β-carbon atom was involved, the reaction of 3-aminoacroleins **202** (R^3 = H) with phenyl and benzoyl isothiocyanates was initiated with the nucleophilic attack by the amino group which ultimately led to the formation of pyrimidinethiones **203a** and pyrimidinethiols **204**, respectively.[207,208] A similar condensation of phenyl isothiocyanate with an enamino ketone **202** (R^3 = Me) gave **203** along with the acyclic thioamide **202** (R^2 = PhNHCS, R^3 = Me).[208] 3-Anilinocinnamanilide[209] and aminomaleimide,[210] however, formed acyclic thioamide adducts with isothiocyanates by substituting the enaminic β-hydrogen atom.



202

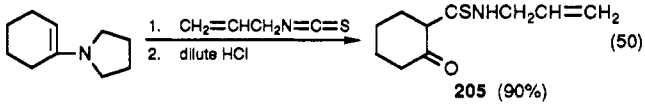


203a: R^1 = R^3 = H, R^2 = alkyl
b: R^1 = R^3 = Me, R^2 = H



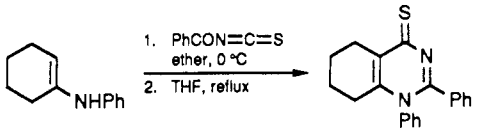
204: R^1 = R^3 = H, R^2 = alkyl

The reaction of α-tetraloneanil with an isothiocyanate proceeded through the enaminic tautomer.[211] Also, cyclopentanone and cyclohexanone were converted into the corresponding α-thioamido ketones via their enamines, as shown in the preparation of **205** (eq 50).[212]



205 (90%) (50)

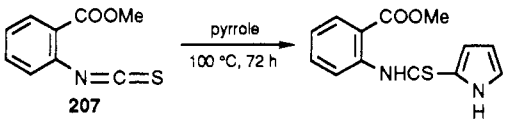
The products of condensation of enamines and ketene-*S*,*N*-acetals with isothiocyanates were amenable to manipulation with suitable hydrazines and amidines to produce aminopyrazoles and aminopyrimidines, respectively.[213,214] It should be noted that an isothiocyanate bielectrophile could react with secondary enamines to give heterocycles, as shown in the synthesis of **206** (eq 51).[215] Several similar conversions have been discussed under cycloaddition reactions.



206 (59%) (51)

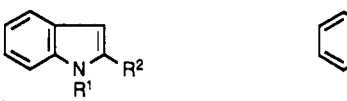
2. Reactions Involving Heterocyclic Rings

Some heterocycles behaved as enamines. The higher electron density at its 2-position enabled pyrrole to react with methyl 2-isothiocyanatobenzoate (**207**) affording **208** which was used for the synthesis of different pyrrole compounds (eq 52).[216] Notwithstanding a

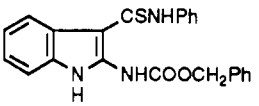


207 208 (61%) (52)

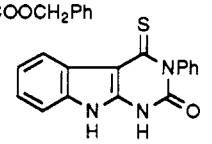
higher electron density at its 3-position, indole underwent substitution at the 1- or 3-position, depending on the reaction conditions. For instance, indolylmagnesium halide or potassium indole (**209a**) reacted with phenyl isothiocyanate to give **209b**,[217] whereas a similar condensation with the indole derivative **209c** produced 3-substituted product **210** which underwent base-aided cyclization to fused indolopyrimidine **211** in 90% yield.[218]



209a: R^1 = MgX or K, R^2 = H
b: R^1 = PhNHCS, R^2 = H
c: R^1 = H, R^2 = NHCOOCH2Ph



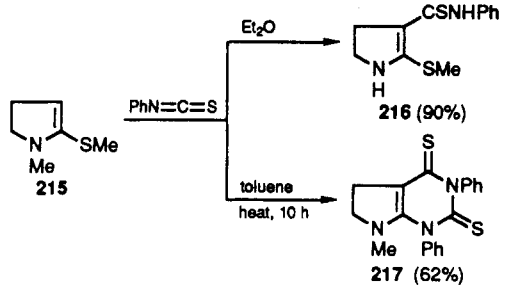
210



211

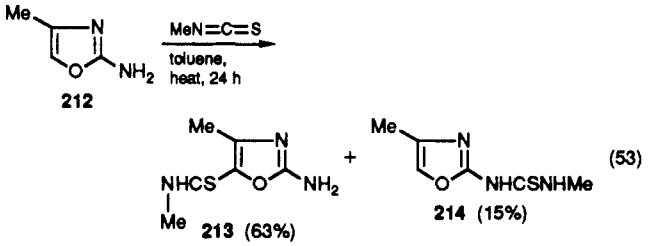
The scanning of literature revealed that only a limited number of heteroaromatic compounds were used as substrates with isothiocyanates as reagents. Thiophenes underwent aluminum chloride aided Friedel–Crafts reaction with alkyl and aryl isothiocyanates in nitromethane. The type of thiocarbamide isomer formed was dependent on the substituent already present in the heterocycle.[219] For example, unsubstituted thiophene furnished 2-substituted product, whereas 2,5-dimethylthiophene gave the corresponding 3-thiocarbamides. Under similar conditions, 2-(ethylthio)-5-methylthiophene was attacked by the reagent at the 3-position, but 2-phenyl-5-methylthiophene afforded a mixture of the 3- and 4-thiocarbamides.[219] It is noteworthy that the Friedel–Crafts reaction of derivatives of benzene and phenol with alkyl and aryl isothiocyanates in nitromethane gave the corresponding

SCHEME 20



thiobenzamides in about 80% yields.[220]

The condensation of methyl isothiocyanate with 2-amino-4-methyloxazole (**212**) afforded thioamide and thiourea as the major and minor products, respectively (eq 53). This conversion was construed as a Diels–Alder reaction,[221] but recently the formation of **213** has been found to be an electrophilic substitution.[222] The type of substituents in the reactants determined the relative amounts of the products.[222]



The semicyclic ketene *S,N*-acetals, for example **215**, reacted with an aryl isothiocyanate to give **216** or **217**, depending on the reaction conditions (Scheme 20).[223,224] Similarly, 6-aminouracils with isothiocyanates furnished 5-substituted thiocarbamoyl derivatives which were manipulated to yield various fused pyrimidines, some of which were found to be biologically active (Scheme 21).[225-227]

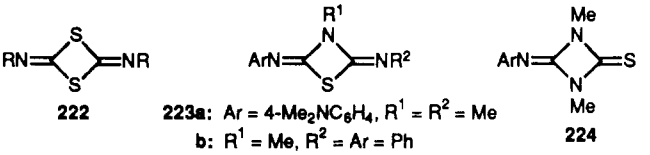
The reaction of isothiocyanates with carbon bases, generated by metalation of heterocycles and other suitable systems, does not seem to have been properly studied and it would be worthwhile to explore further its synthetic utility.

F. Cycloadditions

Different types of cycloaddition reactions of isothiocyanates were reported in the literature.[1,5,228] The course of these conversions was governed by the nature of the substrates as well as by the type of reagent. The addition could take place at the C=S or at the C=N bond of the heteroallene moiety, and it could also lead to polymerization. The reaction of acyl/thioacyl isothiocyanates often led to the formation of 1,4-cycloadducts.[5]

1. [2 + 2] Cycloaddition

Reactive isothiocyanates, such as sulfonyl and alkoxycarbonyl isothiocyanates were found to undergo facile dimerization through the C=S bond, affording dithietanes **219**.[229] On the other hand, the reaction of methyl isothiocyanate with *N*-aryl-*N'*-methylcarbodiimides furnished 48% of a mixture containing 42:58 of thiazetidine **223a** and diazetidine **224**. The similar cycloaddition of phenyl isothiocyanate gave only **223b**.[230] The molecular structures of these compounds were determined by X-ray analysis.[230]

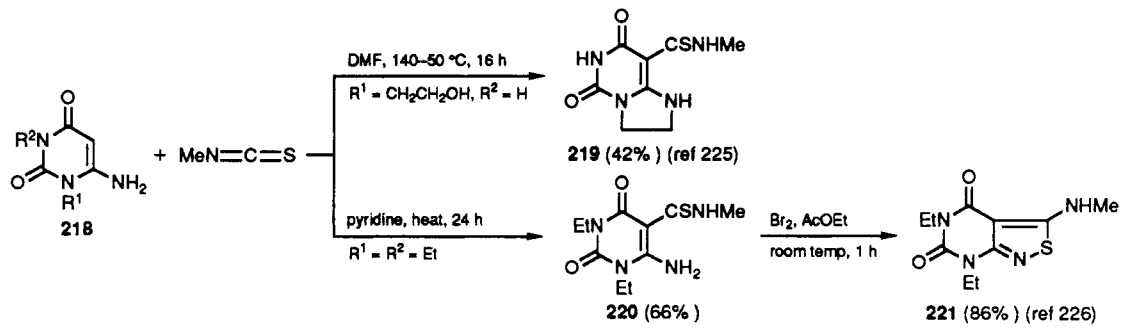


Several authors[229-234] investigated the reaction between isothiocyanates and carbodiimides, and the earlier works were covered in the previous reviews.[1,7,228] Different reactants and various reaction conditions were employed. Since no solvent effect was observed, the cycloaddition was supposed to be a concerted one.[234] However, a step-wise mechanism should not be ruled out altogether and it would be worthwhile to investigate further the electronic as well as steric influences of the substituents of both the reactants. It should be mentioned that isothiocyanates carrying a strong electron-withdrawing group, as in (diphenylphosphino)thionyl-[233] and 4-toluenesulfonyl isothiocyanates,[232] reacted with carbodiimides to give predominantly 1,3-thiazetidine derivatives. Many of these compounds underwent cycloreversion and fragmentation, the monitoring of which were often used for solving the structural problems.

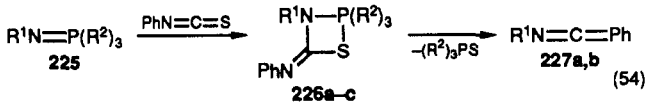
[2 + 2] Cycloaddition of isothiocyanates with isocyanates furnished diazetidines which underwent fragmentation, thereby bringing about an exchange between the reacting heteroallenes. A similar reaction was observed in the interaction of *N*-sulfinylamines and isothiocyanates at 180–200 °C which led to the formation of exchange products in moderate yields (11–35%).[1,234] It should be noted that unsymmetrical carbodiimides were also obtained in this reaction and their formation was rationalized by the assumption of cycloreversion of an intermediary 4-imino-1,2,3-dithiazetidine 2-oxide.[234]

Addition of phenyl isothiocyanate to N-substituted iminophosphorane **225a–c**, followed by cycloreversion of the adducts,[223] gave the corresponding carbodiimides

SCHEME 21

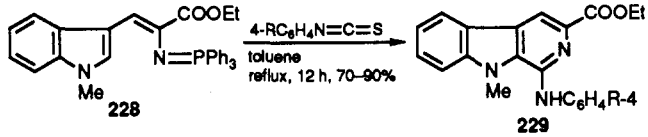


227a,[235] **227b**,[236] and **227c**[237] (eq 54). Recently, **228** was converted into β-carboline **229** by heating with aryl isothiocyanates, apparently via the carbodiimide intermediate (eq 55).[238]



(54)

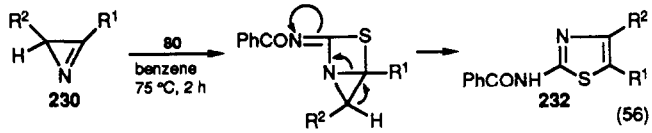
a: R^1 = heteroaryl, R^2 = Ph; **b**: R^1 = Me_3SiCH_2, R^2 = Ph; **c**: R^1 = 1-adamantyl, R^2 = EtO



R = H, Me, MeO, Cl

(55)

Several cycloaddition reactions of isothiocyanates across the C=N bond of imines, amidines, and nitrogen heterocycles were covered in the previous reviews.[1,7] The reaction of 1-azirines **230** with benzoyl isothiocyanate (**80**) was found to be regioselective[239] and the polarity of the solvent played important roles (eq 56). Yields of **232c**, when benzene, ethyl acetate, and nitrobenzene were used as solvents, were found to be 13.4%, 19.3%, and 34.8%, respectively.

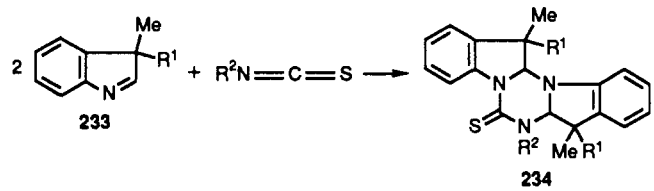


(56)

a: R^1 = R^2 = Ph (67%); **b**: R^1 = Ph, R^2 = Me (65%); **c**: R^1 = Ph; R^2 = H (13%)

As already mentioned, the ring nitrogen of 2-aminoazirines **230** (R^1 = NMe_2 or NH_2) initiated the attack and 2,2-disubstituted 3-(dimethylamino)azirines reacted with isothiocyanates to give zwitterionic products as a result of 1:1[240] and 1:2[241,242] addition, followed by ring expansion.

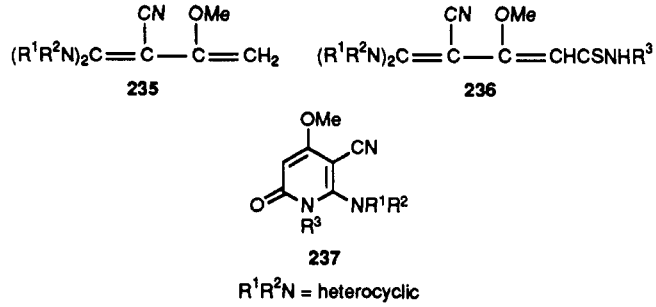
The reaction of isothiocyanates with some imines furnished a six-membered triazine ring,[1,7] as shown in the synthesis of **234** by the interaction of alkyl isothiocyanates and 3*H*-indoles **233** (eq 57).[243] Also, py-



(57)

rolysis of 2-(methylimino)-3-phenyl-1,3-thiazetidine in the presence of isothiocyanates produced triazine derivatives in moderate yields (8–36%).[244] It should be emphasized that imines which could exist as their enaminic tautomers would give different results, as already discussed in a previous section. Compounds, in which such a possibility did not exist, as in 1,2-bis(piperidinyl-1)ethylene,[245] reacted with isothiocyanates to give the corresponding acyclic thioamides. Such reactions were reported to involve [2 + 2] cycloadducts as intermediates.[1,228]

The presence of a methoxy group at the C=C bond of **235** enabled it to form an adduct **236**, possibly via cycloaddition, which underwent thermal cyclization to 5-cyano-6-aminopyridine-2-thiones **237** in good yields.[246]



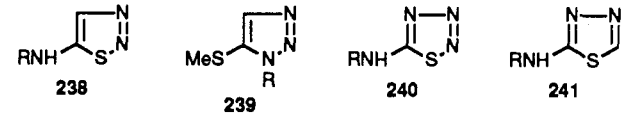
R^1R^2N = heterocyclic

As already indicated, [2 + 2]cycloadducts could lead to exchange reactions. Alternatively, these could be manipulated to yield synthetically useful products. It is noteworthy that ynamines have been found to be versatile synthons,[247] but their reaction with isothiocyanates does not seem to have been explored.

2. [3 + 2] Cycloaddition

Isothiocyanates participated in many 1,3-dipolar cycloaddition reactions leading to a variety of heterocycles. Some substrates, such as nitrones and nitrile imines reacted across the C=N bond, whereas diazo compounds, ketocarbenes, oxiranes, etc. added across the C=S bond.[1,7,228] In some cases, rearrangement or subsequent changes were also encountered, as a result of which the final products were different from the initial adducts.

Diazomethane[248,249] and hydrazoic acid[248] added to isothiocyanates, furnishing thiadiazoles **238** and thiatriazoles **240**, respectively. Compound **238** with diazomethane underwent rearrangement to triazole **239**.[248] A similar cycloaddition was encountered with diazoethane.[250] The process was slow, requiring several days for completion. Lithium (trimethylsilyl)diazomethane, however, added smoothly to alkyl and aryl isothiocyanates affording triazole[251] and thiadiazole derivative **241**.[252] Previously, the reaction of diazo compounds

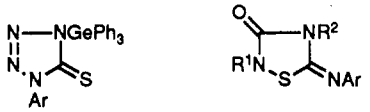


with isothiocyanates was investigated by several workers,[253-257] and it was found to be of general application. Yields and reaction conditions varied from compound to compound, the reactivity of which was influenced by the nature of the substituent. As already mentioned, the presence of an electron-withdrawing group enhanced the electrophilicity of the heteroallene moiety, whereas such a substituent suppressed the reactivity of diazo compounds because of the stabilizing effect. For instance, the interaction of diazomethane and methyl isothiocyanate furnished the product in about 30% yield,[256] whereas the reaction of diazomethane with phenyl isothiocyanate gave 60% of the product.[254] When phenyldiazomethane was used as a substrate with phenyl isothiocyanate as a reagent, the yield was 53%.[255] Poor results were obtained when the esters of diazoacetic acid, ω-diazoacetophenone and similar diazo compounds reacted with less reactive isothiocyanates.[256] Yields improved considerably when a highly reactive isothiocyanate added to a less reactive diazo com-

pound.[256] Some of these results have been summarized in the previous reviews.[1,228] It should be mentioned that ketocarbene and thioketocarbene, generated by thermolysis of tetrachlorobenzene 2-diazo oxide and 1,2,3-benzothiadiazole, reacted with aryl isothiocyanates to give the 1,3-benzoxathiole derivative[258] and 2-(arylimino)-1,3-benzodithiole,[259] respectively.

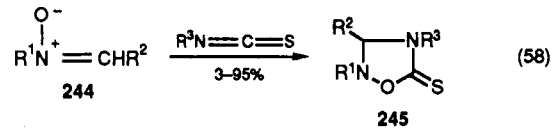
Different 1,3-dipolar compounds and their cycloaddition reactions were developed in the late 1950s and early 1960s[260] and their application to isothiocyanate chemistry has grown over the years.

Various azides were reported to form cycloadducts with different isothiocyanates. Thus, benzyl azide reacted with aryl isothiocyanates at 60 °C to give compounds of tetrazole, thiadiazole, and dithiazole.[261] Germanium-substituted tetrazole **242** was obtained by the interaction of aryl isothiocyanates and triphenylgermanium azide.[262] It is noteworthy that the cycloaddition of azide ion to isothiocyanates was previously used for the preparation of 1-substituted tetrazoline-5-thiones.[1] A three component reaction involving an aryl isothiocyanate, alkyl or aryl isocyanate, and alkyl azides afforded thiadiazoles **243** in good yields.[263]



242 **243**

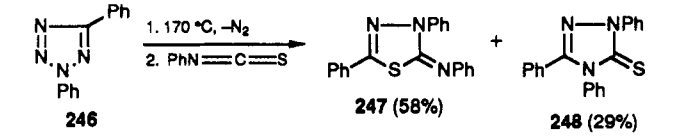
Addition of nitrones to alkyl and aryl isothiocyanates furnished oxadiazolidinethiones **245** in variable yields (eq 58).[264] A similar reaction with cycloheptatrienylideneamine oxide was also reported.[265] It



244 **245** (58)

should be mentioned that cycloaddition of nitrile oxides to isothiocyanates does not seem to have been observed. However, *N*-oxides of some heterocycles were found to react with the heteroallenes. For instance, methyl-substituted 1-pyrroline 1-oxides,[266] isoquinoline 2-oxide,[267] and 1-methylbenzimidazole 3-oxide[268] were reported to undergo 1,3-cycloaddition. Some of the cycloadducts formed were unstable.[267,268]

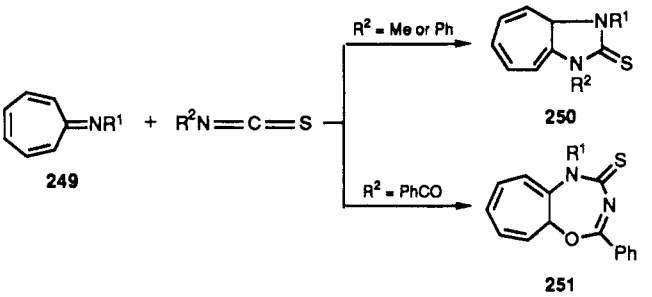
Nitrile imines were found to react with isothiocyanates involving both the C=S and C=N bonds of the heteroallene moiety in a [3 + 2] cycloaddition mechanism.[1] For example, thermolysis of 2,5-diphenyltetrazole (**246**) produced diphenyl nitrile imine which reacted with phenyl isothiocyanate to give **247** and **248** in 58% and 29% yields respectively (eq 59).[269]



246 **247** (58%) **248** (29%) (59)

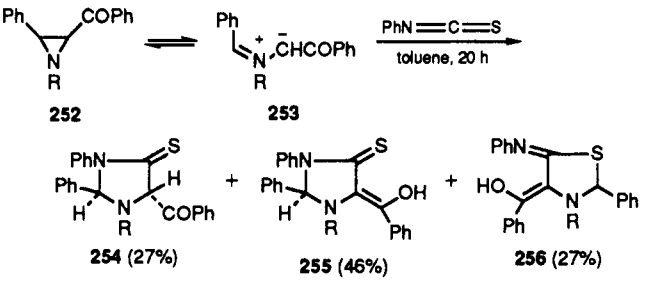
The reaction of methyl or phenyl and benzoyl isothiocyanates with azaheptafulvenes **249** led to the formation of bicyclic imidazoles **250** (R^2 = Me or Ph) and oxadiazepinethione **251**, respectively (Scheme 22),[270] instead of spiroheterocycles. The mechanism involved in these transformations should be considered as [8 + 2] and [8 + 4] cycloadditions.

SCHEME 22



249 **250** **251**

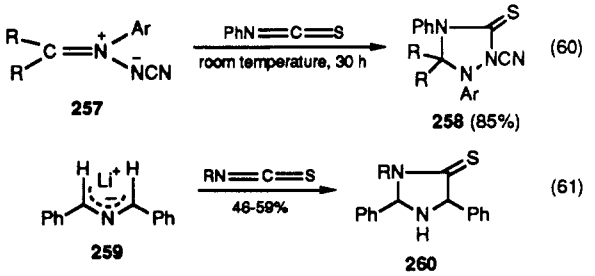
SCHEME 23



252 **253** **254** (27%) **255** (46%) **256** (27%)

As an extension of the earlier work,[1] 1-substituted-2-benzoylaziridine **252** was converted into azomethine ylide and trapped with phenyl isothiocyanate to give imidazolidinethione derivatives **254** and **255**, and iminothiazolidine **256** (Scheme 23). The formation of these products possibly could also be explained by assuming addition of carbanion or by an attack of the ring nitrogen, followed by ring expansion. Yields were dependent on the reaction temperature and also on the period of heating. The shorter duration of heating either in benzene or toluene gave **254** in better yields in comparison to **255** and **256**.[271] It should be mentioned that N-unsubstituted aziridine with phenyl isothiocyanate formed the corresponding thiourea which underwent ring expansion to 2-anilinothiazoline in 91% yields, when heated with hydrochloric acid.[272] The reaction of isothiocyanates with some other three-membered rings has been discussed later.

Azomethine imines with phenyl isothiocyanate afforded triazolidinethiones **258** which were found to undergo cleavage even in cold solution (eq 60).[273] Other products were less vulnerable.[1] Thus, the reaction of isothiocyanates with **259** furnished imidazolidinethiones (**260**) (eq 61) which did not undergo secondary changes.[274] It is noteworthy that pyridinium *N*-imide

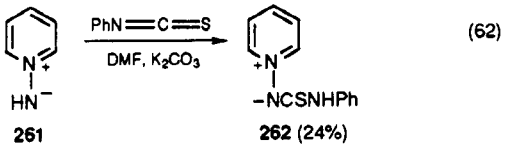


257 **258** (85%) (60)

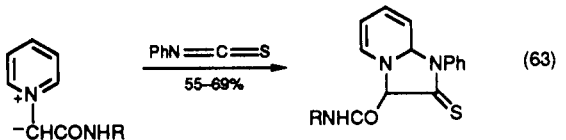
259 **260** (61)

261 formed only a simple adduct **262** (eq 62),[275] whereas the ylide **263** with phenyl isothiocyanate gave imidazopyridines **264** (eq 63).[276]

2-Methyloxirane, aided by complexes of tin halide and Lewis bases, added to benzyl isothiocyanate to give

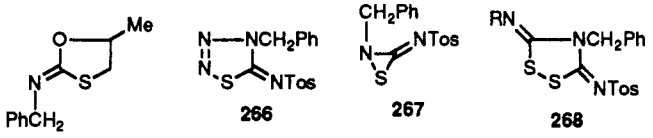


261 262 (24%) (62)



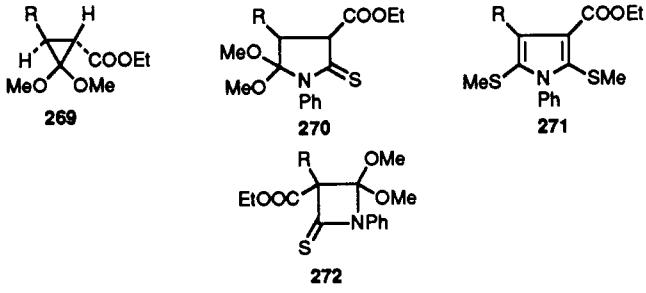
263 264 (63)

2-(*N*-benzylimino)oxathiolane **265**.[277] Also, thiaziridinimine **267**, generated by the thermolysis of 4-benzyl-5-(tosylimino)-1,2,3,4-thiatriazoline (**266**), reacted with isothiocyanates to give dithiazolidine derivatives **268**.[278,279] The intermediacy of **267** was also supported by trapping with other reagents and by kinetic studies.[280]



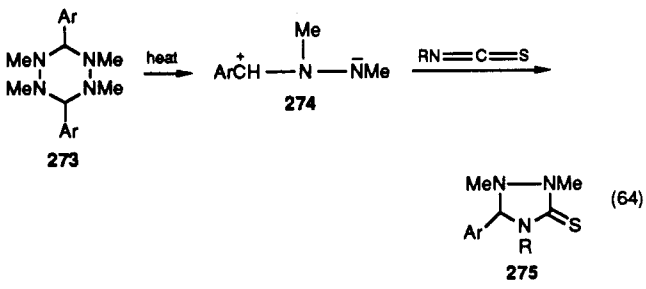
265 266 267 268

The reaction of methyl isothiocyanate with oxirane was found to give 3-methyl-2-oxazolidinone,[281] and the formation of an oxathiolane intermediate was proposed for this conversion.[228] 5-Substituted 2-(*N*-acylimino)-1,3-oxathiolanes were obtained by the interaction of acyl isothiocyanates and 2-substituted oxiranes.[282] Recently, ethyl 2,2-dimethoxycyclopropane-1-carboxylates **269** (R = Me, Et) were found to undergo ring-opening reactions with phenyl isothiocyanate, affording a mixture of pyrrolidinethiones **270**, pyrroles **271**, and azetidinethiones **272**.[283]



269 270 271 272

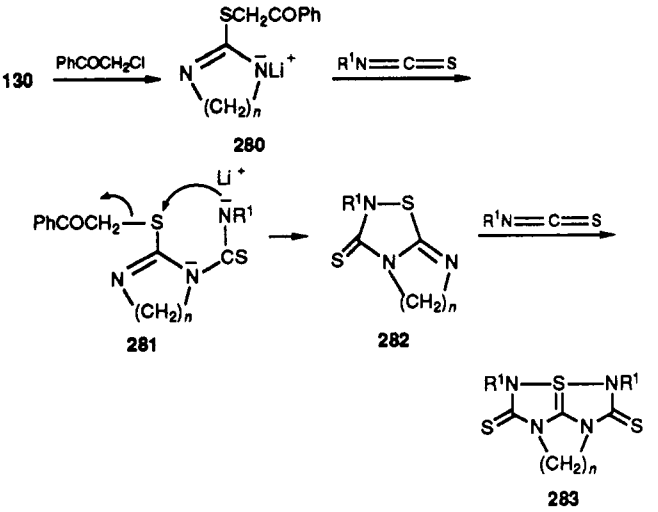
Thermolysis of some six-membered heterocycles was used to generate 1,3-dipole in situ which was trapped with isothiocyanates. For instance, azomethine imines **274**, arising from tetrazines **273**, reacted with isothiocyanates to give 1,2,4-triazolidines **275** (eq 64).[284]



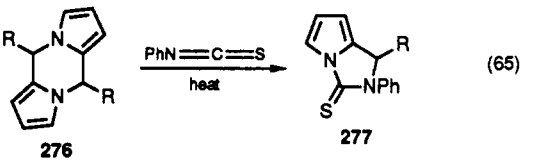
273 274 275 (64)

Yields were very good. A similar 1,3-dipolar intermediate, produced by pyrolitic cycloreversion of **276**, was converted into pyrroloimidazolidinethiones **277** (eq 65).[285]

SCHEME 24

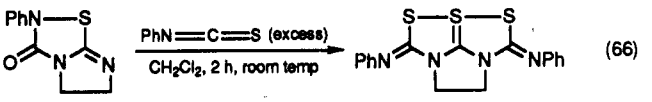


a: R^1 = Me, n = 3 (74%); **b**: R^1 = CH_2=$CHCH_2$, n = 3 (65%); **c**: R^1 = Et; n = 3 (65%); **d**: R^1 = Me; n = 4 (27%); **e**: R^1 = CH_2=$CHCH_2$; n = 4 (9%); **f**: R^1 = Et; n = 4 (14%)



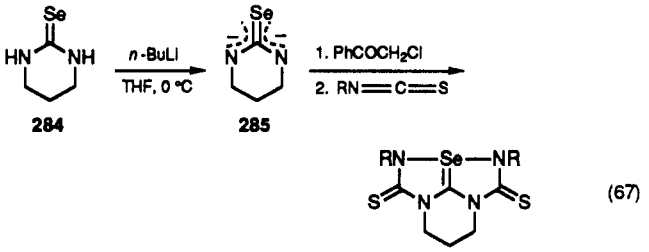
276 277 (65)

Novel heteropentalenes[286,287] were synthesized by the cycloaddition of isothiocyanates to N-bridged iminothiazolidines, as shown in the conversion of **278** into **279** (eq 66).[287] The reaction was also successful with benzoyl and ethoxycarbonyl isothiocyanates.[287] Somewhat



278 279 (66)

variable yields of tetraazapentalenes **283**[286] were obtained when **282**, prepared from the dianion **130**, underwent cycloaddition with different isothiocyanates (Scheme 24).[288] Tetraazapentalene themselves were found to react with ω-haloalkyl isothiocyanates, affording novel fused cyclic systems.[289] Recently, selenatetraazapentalene was synthesized by a similar route (eq 67).[290] It is apparent from the comparative results

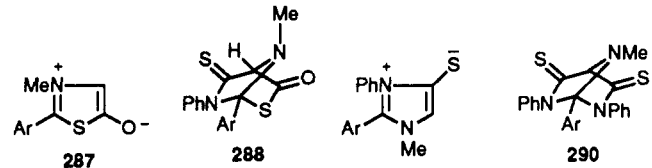


284 285 (67)

286a: R = Me (94%)
b: R = Et (85%)
c: R = CH_2=$CHCH_2$ (60%)

of **283** and **286** that the ring size affected the yields. But it is not clear why yields were somewhat lower when allyl isothiocyanate was used. It would be worthwhile to examine this aspect with reference to the possible N–S transmigration of the allyl group.

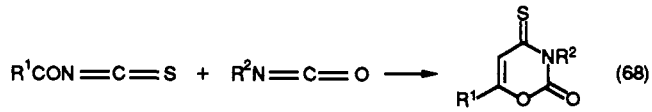
Mesoionic compounds **287** behaved as 1,3-dipoles and reacted with phenyl isothiocyanates in hot benzene to form an intermediate **288** which was converted into anhydro-2-aryl-4-mercapto-1-methyl-3-phenylimidazolium hydroxides **289** by splitting of carbonyl sulfide. It is noteworthy that the reaction without using a solvent also produced **290** as a result of 1,4-cycloaddition of **289** with another molecule of the heteroallene.[291]



287 **288** **289** **290**

3. [4 + 1] and [4 + 2] Cycloaddition

Several [4 + 2] cycloaddition reactions involving isothiocyanates were reported in the literature which have been covered in the previous reviews.[1,5,7,228] Whereas alkyl, aryl, and sulfonyl isothiocyanates participated as dienophiles, acyl, thioacyl, thiocarbamoyl, imidoyl, and alkenyl isothiocyanates behaved as heterodienes in many of their reactions. The interaction of benzoyl isothiocyanate and an isocyanate furnished oxadiazinethione **291** due to the involvement of the acyl group (eq 68).[292] It is noteworthy that benzoyl isothiocyanate (**80**) with benzylidenemethylamine gave an unstable [4 + 2] cycloadduct **292**,[293] but with 4-methoxyphenyl isocyanide it gave a [4 + 1] cycloadduct **293**[294] (Scheme 25).

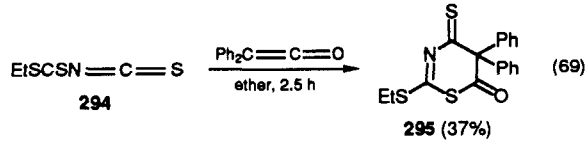


(68)

291

Some carbonyl isothiocyanates entered into 1,4-cycloadditions through the C=C bonds of ketenes, ketenimines, enol ethers, and enamines some of which have been covered under previous sections. Similar reactions of thiocarbonyl isothiocyanates were also encountered. Thiocarbamoyl isothiocyanates added to ketenes and ketenimines to form the dihydro derivatives of 2-amino-6-oxo-4-thioxo-1,3-thiazine and 2-amino-6-imino-1,3-thiazine, respectively.[1]

The reaction of (ethylthio)thiocarbonyl isothiocyanate (**294**) with diphenyl ketene in ether furnished 2-(ethylthio)-5,5-diphenyl-4-thioxo-5,6-dihydro-4*H*-1,3-thiazine (**295**) in 37% yields (eq 69).[295] On the other



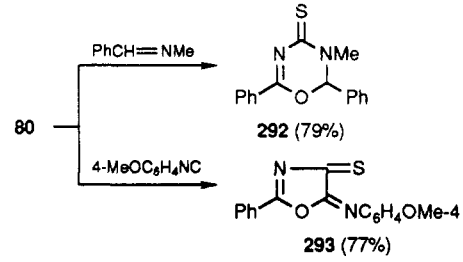
(69)

294 **295** (37%)

hand, imidoyl isothiocyanates reacted with tertiary enamines and ketene diethyl acetal to give the corresponding 1,4-cycloadducts which by elimination of amine or alcohol produced derivatives of 1,4-dihydropyrimidine-4-thiones.[1]

Potentially useful cycloadditions employing *N*-alkenyl isothiocyanates were recently reported. Thus, **296** reacted with tetracyanoethylene and oxovinylidenetriphenylphosphorane to give derivatives of pyridinethione

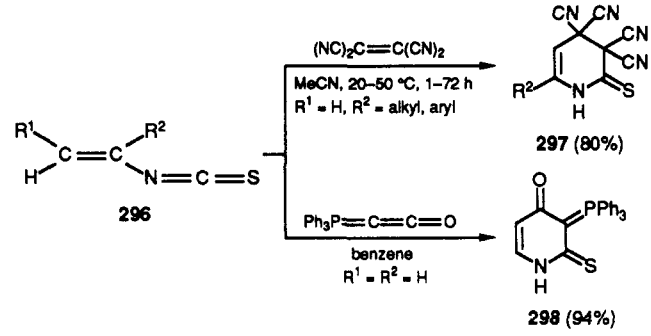
SCHEME 25



292 (79%)

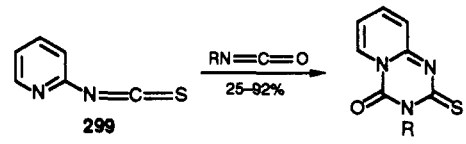
293 (77%)

SCHEME 26



296 **297** (80%) **298** (94%)

297[296] and **291**,[297] respectively (Scheme 26). A similar reaction of 2-pyridyl isothiocyanate (**299**) with an isocyanate furnished N-bridged compound **300** (eq 70).[298]



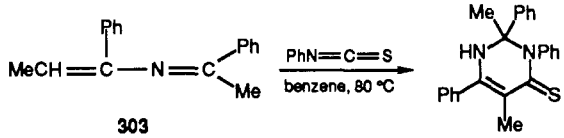
(70)

299 **300**

It should be mentioned that carbamoyl isothiocyanates exhibited dualistic behavior during dimerization and in the reaction with imines.[299]

Aryl isothiocyanates were used as azadienophiles in the synthesis of iminothiazines **301**[300] and N-bridged oxazole **302**[301,302] (Scheme 27). The reaction using 2-(benzylideneimino)-1,3,4-thiadiazole as a diazadiene gave similar results.[303]

Diels–Alder reactions of unactivated 2-aza 1,3-dienes, for example **303**, with dialkyl azodicarboxylates and heteroallenes were also published (eq 71).[304] The reaction was found to be regioselective.[305] 1,4-Dipolar



(71)

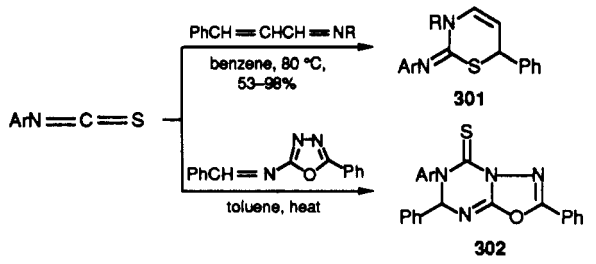
303 **304** (70%)

cycloaddition of a pyrimidinedione internal salt **305** was recently used in the synthesis of **306**.[306] The imino

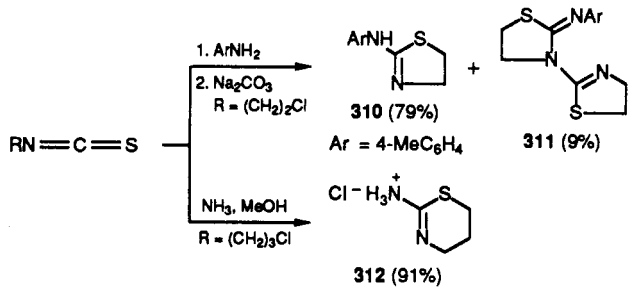
305 **306**

ketene **308**, generated by thermolysis of isatoic anhydride,[300] participated in 1,4-cycloaddition with methyl[307] and aryl[78] isothiocyanates to form derivatives of quinazolones (eq 72). This reaction does not seem to be of any special advantage, and as already described, **309**

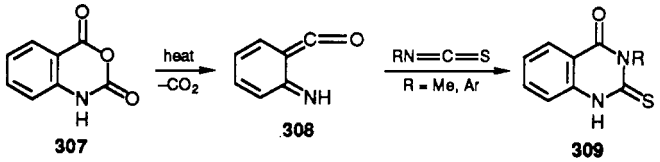
SCHEME 27



SCHEME 28



can be prepared by direct cyclocondensation of anthranilic acid with isothiocyanates.



(72)

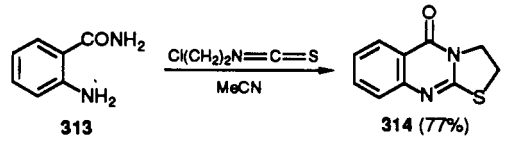
G. Miscellaneous Syntheses

Several isolated reactions of isothiocyanates with different reagents were reported to yield heterocycles.

1. Addition of Nucleophiles to Bielectrophilic Isothiocyanates and Cyclization of the Adducts

Suitable nucleophiles with ω-halo isothiocyanates formed adducts which furnished heterocycles by cyclodehydrohalogenation. For instance, 2-chloroethyl isothiocyanate with 4-toluidine produced 2-aminothiazolines **310** and **311**. Different amines were employed in this reaction and it was found that the ratio of the corresponding thiazolines depended upon the type of the amine used.[307] 2-Aminopyridine failed to react, whereas 3-aminopyridine gave the expected thiazolines.[307] Possibly the lower basicity or the amino–imino tautomerism of 2-aminopyridine was responsible for its failure to undergo the desired conversion. The reaction of ammonia with 3-chloropropyl isothiocyanate gave 2-aminodihydrothiazine salt **312**[308] (Scheme 28). This reaction does not seem to have been used for the construction of 2-aminotetrahydrothiazepine or its higher homologues.

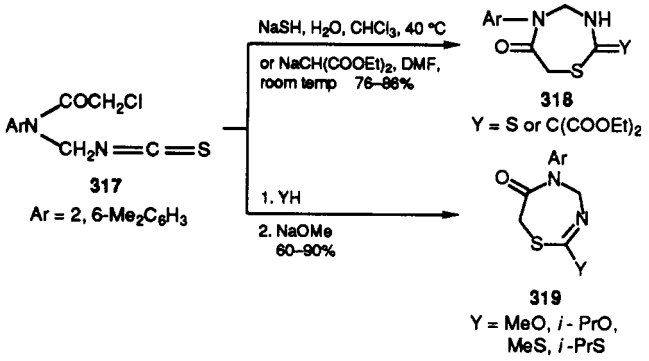
Double cyclization, leading to the formation of N-bridged thiazolidinoquinazolin-4-one **314**, was encountered in the condensation of anthranilamide (**313**) with chloroethyl isothiocyanate (eq 73).[309] On the other



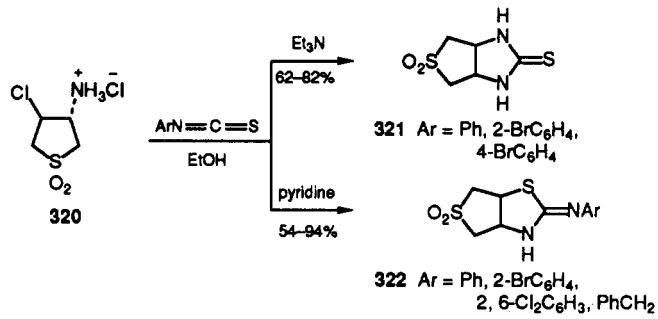
(73)

hand, 2-isothiocyanatobenzyl bromide (**315**) reacted

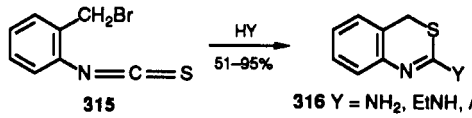
SCHEME 29



SCHEME 30



with amines and phenols to give the corresponding benzothiazine derivatives **316** (eq 74).[310]



(74)

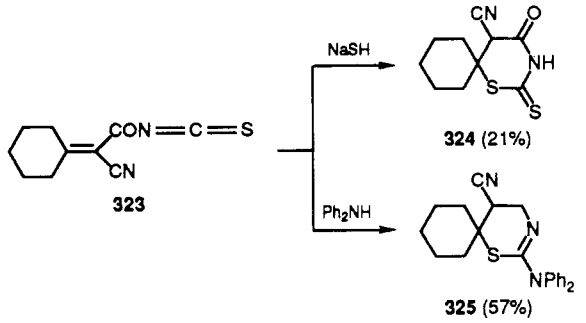
Treatment of [*N*-aryl-*N*-(chloroacetyl)amino]methyl isothiocyanate **317** with diethyl sodiomalonate and sodium monosulfide afforded the corresponding thiadiazepines **318**, whereas simple thiols and alcohols produced acyclic adducts which were converted into **319** with the aid of sodium methoxide (Scheme 29).[311]

Instead of using ω-haloalkyl isothiocyanates, suitable (ω-haloalkyl)amines could be added to alkyl or aryl isothiocyanates for the construction of heterocycles, as shown in the base-aided conversion of chloroaminothiolane dioxide salt **320** into perhydrothienoimidazolethione dioxides **321** and perhydrothienothiazole dioxides **322** (Scheme 30).[312] It is noteworthy that the comparatively stronger base triethylamine favored attack by the nitrogen nucleophile of the heteroallene moiety. The cyclization step in these conversions might not be a simple intramolecular nucleophilic substitution. Instead, it could also proceed by β-elimination, followed by ring closure of the thiourea intermediate.

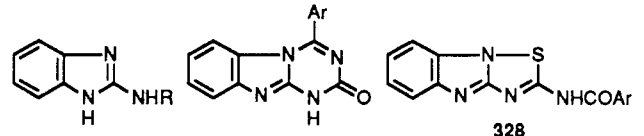
The reaction of sodium monosulfide and diphenylamine with 2-cyclohexylidene-2-cyanoacetyl isothiocyanate (**323**) led to the formation of spiro compounds **324** and **325**, respectively (Scheme 31).[313] These conversions obviously involved nucleophilic addition to heteroallene and subsequent intramolecular Michael reaction.

The condensation of 2-aminobenzimidazole **326a** with aroyl isothiocyanates led to the formation of 2-(aroylamino)benzimidazoles **326b** and *N*-aroyl-*N'*-(benzimidazol-2-yl)thioureas **326c**. Compounds **326c** with phosphorus pentachloride in phosphorus oxychloride and with oxidizing agents gave products which were

SCHEME 31



identified as N-bridged benzimidazolotriazinones **327** and benzimidazolothiadiazolines **328**, respectively.[314]

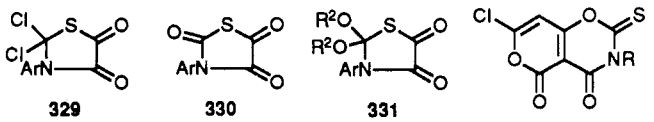


326a: R = H
b: R = ArCO
c: R = ArCONHCS

327 **328**

2. Reaction with Oxalyl Chloride and Malonyl Chloride

Addition of oxalyl chloride to aryl isothiocyanates afforded 2,2-dichlorothiazolidinediones **329** which underwent hydrolysis and alcoholysis to give **330** and **331**, respectively.[315] On the other hand, the interaction of malonyl chloride and an alkyl or aryl isothiocyanate furnished the 7-(chloropyrano)-1,3-oxazine derivative **332** as a result of cyclocondensation reaction.[316] Similar conversions using mono or diacid halides do not seem to have been explored.



329 **330** **331** **332**

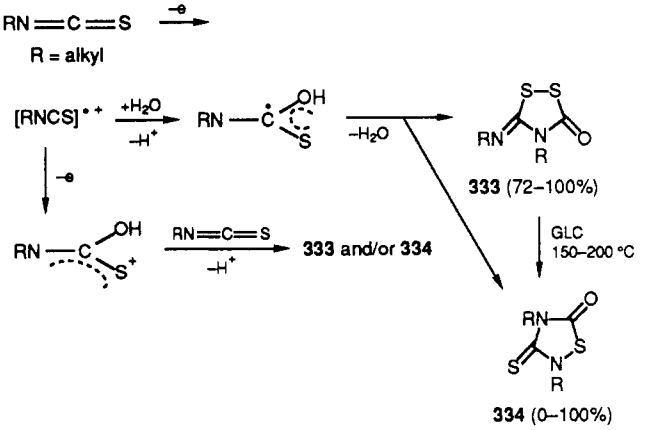
3. Electrooxidative Cyclization

Anodic oxidation of primary and secondary alkyl isothiocyanates in methylene chloride furnished iminodithiazolidinones **333** and thiadiazolidinethiones **334**, their ratio being dependent on the length or bulkiness of the alkyl group in the isothiocyanate molecule.[317] Isomer **333** was favorable when R = Me and Et and exclusive for R = *n*-Pr, *n*-Bu, and cyclohexyl, but during separation by GLC at 150–200 °C, these were completely isomerized to **334**, besides forming the corresponding N,N′-disubstituted carbodiimides (Scheme 32).[317] This anodic oxidation was also carried out in acetonitrile medium and it was observed that primary alkyl isothiocyanates furnished mainly five-membered heterocyclic products while tertiary ones afforded amides due to α-cleavage or isocyanates as a result of substitution of sulfur with oxygen.[318] Recently, cyclization, α-cleavage, and substitution process in the anodic oxidation of alkyl isothiocyanates were reviewed.[319]

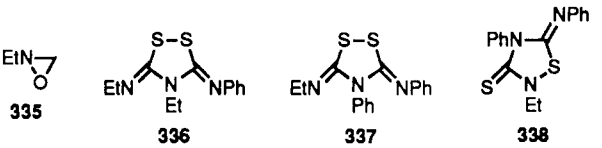
4. Conversion of Preformed Heterocycles to Other Rings

As already mentioned, some heterocycles reacted with isothiocyanates to give other rings. For instance, N-ethyloxaziridine (**335**) with phenyl isothiocyanate afforded three isomeric compounds **336**, **337**, and **338**,

SCHEME 32



respectively, apparently by the involvement of nitrene as an intermediate. These structures were assigned on the basis of reinvestigation and were confirmed by the X-ray diffraction and ^{13}C NMR spectra.[320]



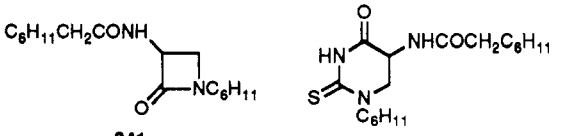
335 **336** **337** **338**

The direct heating of a mixture of *N*-aminophthalimide (**339a**) and an excess of aryl isothiocyanate gave *N*-arylphthalimides **339b**, but on carrying out the same reaction in 2-propanol, the thiourea derivative **339c** was obtained.[321] The formation of **339b** possibly involved decomposition of the thiourea intermediate **339c** into aniline and *N*-phthalimido isothiocyanate, followed by subsequent changes.

339a: R = NH_2
b: R = Ar
c: R = NHCSNHAr

340

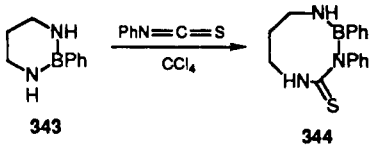
When α-*N*-acylamino acids were heated with ammonium or potassium thiocyanate in acetic anhydride, acylthiohydantoins **340** (R^1 = Me or Ph, R^2 = H) were obtained.[322] The saturated azlactones **136** were found to be the intermediate in this reaction. Unsaturated azlactones failed to undergo the similar conversion.[322] Compounds **136**, being more vulnerable than their unsaturated counterparts **141**, underwent 1,5-bond cleavage with ammonium and potassium thiocyanates to give (*N*-acylamino)acyl isothiocyanate, followed by subsequent cyclization to **340**. In an analogus set of reactions thiocyanic acid was reported to cleave the 1,2-bond of 1-cyclohexyl-3-(cyclohexylacetamido)-2-azetidinone (**341**), leading to the formation of the thiodihydrouracil derivative **342**.[323] The scope of this conversion does not seem to have been properly investigated.



341 **342**

Ring expansion of some heterocycles by insertion with an N-substituted isothiocyanate was reported. For

example, the reaction of diazaborocyclohexane **343** with phenyl isothiocyanate afforded an eight-membered B–N–C heterocycle **344**, besides some isomeric products (eq 75).[324]



343 344 (75)

IV. Concluding Remarks

Isothiocyanates remain very important starting materials for the construction of heterocycles. Notwithstanding the prolific use of addition–cyclization approach for this purpose, its scope continues to be enormous. Carbon bases and organometallic compounds, particularly those hiterto unexplored, can provide adducts suitable for heterocyclic synthesis. Therefore, reactions of isothiocyanates with new substrates should be studied with this perspective in mind. Also, search for novel isothiocyanates and investigation of their photochemistry and cycloaddition reactions would be rewarding. Furthermore, the possibility of desulfurization of isothiocyanate-derived products could be profitably exploited in the preparation of diverse compounds, particularly those having carbonyl in place of thiocarbonyl groups which would obviate the use of harmful isocyanates. In conclusion, it should be added that a judicious application of the knowledge gained over the years in the further exploration of this area would pay dividend.

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