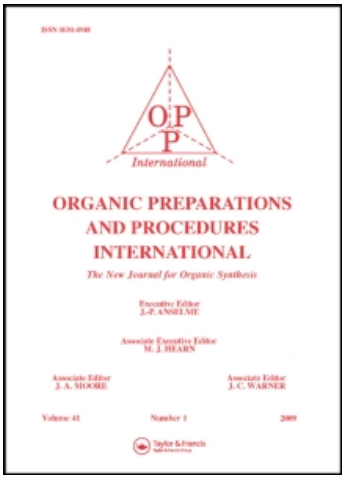

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THE USE OF ISOCYANIDES IN HETEROCYCLIC SYNTHESIS. A REVIEW

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INTRODUCTION

Isocyanides regarded for years as unnatural compounds, with unpleasant odor and very few chemical and pharmaceutical applications[1] are now well described chemical compounds,[2] synthetic tools,[3-5] and an emergent class of natural occurring compounds[6-8] with intriguing structures and surprising properties. Although isocyanides are interesting *per se*, the main current thrust to their study lies in applications in heterocyclic chemistry. Synthesis of heterocyclic compounds from isocyanides was of minor importance until 1959, when the discovery of the Ugi four-component condensation disclosed new horizons in this field. About 10 years later, Schöllkopf and his group began to study the reactivity of the α-anions of isocyanides and the community of organic chemists began to understand the potentiality of these compounds in organic synthesis. At the present time, this class of compounds can be regarded as one of the most powerful tools for the synthesis of heterocyclic compounds. Isocyanides are involved in many cycloadditions and cyclizations of general importance. Extension of each type of heterocyclic synthesis depends upon previous addition reactions to isocyanide, the number of components or reactants, the presence of lateral groups of isocyanide moiety and the presence or absence of metals as catalysts. We now report a brief summary of each type of useful heterocyclic synthesis based on isocyanides and a more extensive account of recent advances in each one.

The syntheses of heterocyclic compounds from isocyanides belong to the following main classes:

1. Syntheses in which the cyclization step follows an electrophilic attack on the isocyano group.
2. Syntheses based upon cycloadditions, insertion of the isocyano group in multiple bonds and ring enlargement.
3. Syntheses in which the cyclization step consists in a nucleophilic attack on the isocyano group.
4. Syntheses with isocyanide complexes
5. Syntheses with α-metalated isocyanides.

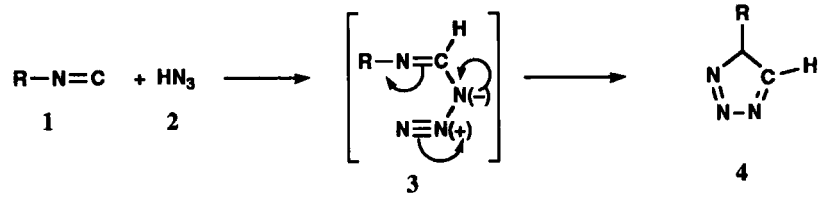
I. SYNTHESES INVOLVING ELECTROPHILIC ADDITION TO THE ISOCYANO GROUP FOLLOWED BY CYCLIZATION

Many reagents give α-adducts with isocyanides. These can cyclize spontaneously or upon

treatment with an additional reagent.

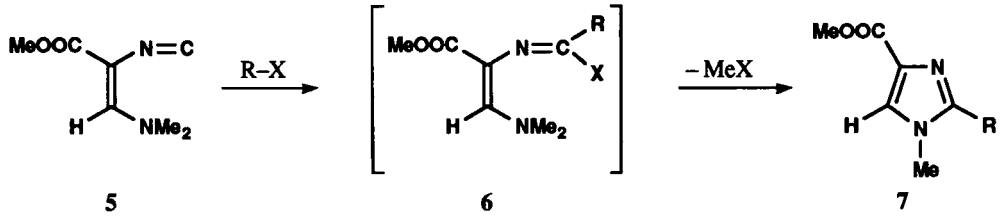
1. Syntheses Based on Simple α-Additions

The well-known tetrazole synthesis of Olivieri-Mandalà and Alagna[9-10] belongs to this group, and represents the first example of heterocyclic synthesis starting from isocyanides. This synthesis can be regarded as an α-addition of hydrazoic acid **2** and the isocyanide **1** followed by a spontaneous 1,5-dipolar cyclization of the adduct **4** *(Scheme* 1).



Scheme 1

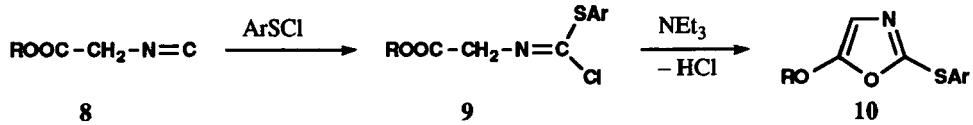
The reaction of reactive halides with methyl dimethylaminomethylene isocyanoacetate **5** affords[11] methyl 2-substituted 1-methylimidazole-4-carboxylates **7** *(Scheme* 2).



Scheme 2

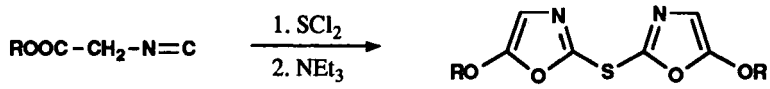
This synthesis is especially noteworthy since alkyl imidazole 4-carboxylates are not readily available because of the small number of unequivocal syntheses.

The reaction between arenesulfenyl chlorides and alkyl isocyanoacetates **8** gives *N*-alkoxycarbonylmethyl-*S*-arylisothiocarbamoyl chlorides **9** which, upon treatment with triethylamine,[12] cyclize to 5-alkoxy-2-arylthiooxazoles **10**. This synthesis provides oxazoles in very high yields by an experimentally simple one-pot procedure *(Scheme* 3).



Scheme 3

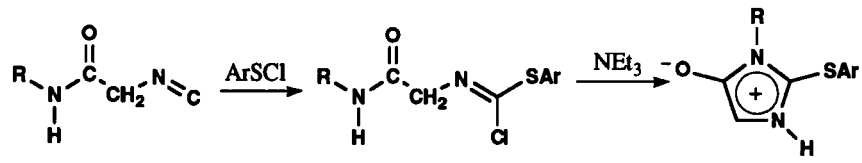
When dichlorosulfane is employed in place of the arenesulfenyl chloride, 5,5'-dialkoxy-2,2'-dioxazolyl sulfides **11** are obtained[13] (molar ratio isocyanide:SCl_2:NEt_3 = 2:1:2) in high yields *(Scheme* 4).



8 11

Scheme 4

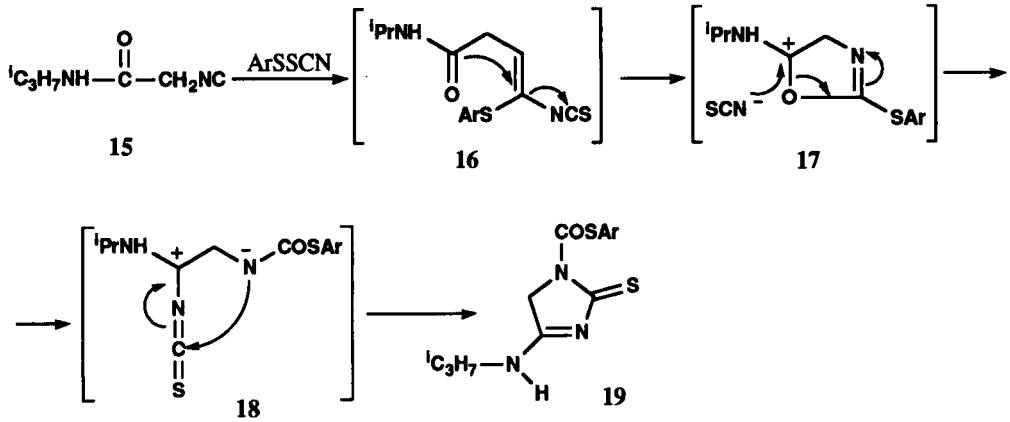
The reaction between *N*-substituted isocyanoacetamides **12** and arenesulfenyl chlorides affords unstable α-adducts **13** which, upon treatment with NEt_3, give[14] mesoionic 3-alkyl-2-arylthio-1,3-diazolium-4-olates **14** *(Scheme* 5).



12 13 14

Scheme 5

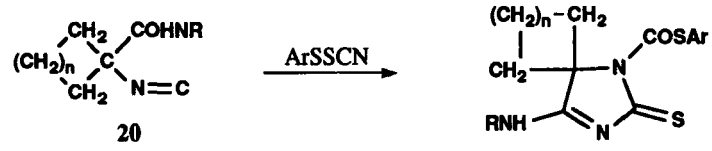
When the reaction is performed by employing arenesulfenyl thiocyanates (prepared *in situ* by reacting arenesulfenyl chlorides with ammonium thiocyanate in benzene) in place of the arenesulfenyl chlorides, a different ring-closure reaction takes place[15] leading to 1-arylthiocarbonyl-4-isopropylamino-2,5-dihydro-1*H*-imidazole-2-thiones **19** *(Scheme* 6).



15 16 17 18 19

Scheme 6

The reaction between *N*-substituted 1-isocyano-1-cyclohexanecarboxamides **20** and arylsulfenyl thiocyanates affords *N*-substituted 4-amino-1-arylthiocarbonyl-1,3-diazaspiro[4.5]dec-3-en-2-thiones **21** in good yields.[16] Similarly 4-benzylamino-1-(2-nitrophenyl)thiocarbonyl-1,3-diazaspiro[4.4]non-3-en-2-thione and 4-phenylamino-1-(2-nitrophenyl)thiocarbonyl-1,3-diazaspiro[4.6]-undec-3-en-2-thione are obtained *(Scheme* 7).



20 21

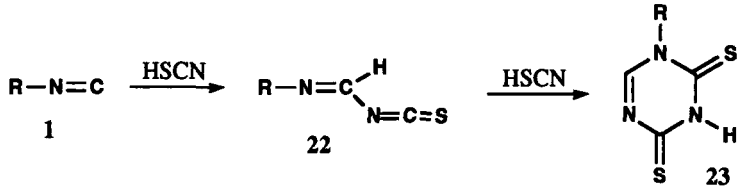
n = 2, 3, 4; R = Aryl, Benzyl, Cycloalkyl

Scheme 7

2. Syntheses Based on More Complicated α-Additions

In some cases the α-addition step is followed by other addition or substitution reactions and more complicated cyclization products are obtained.

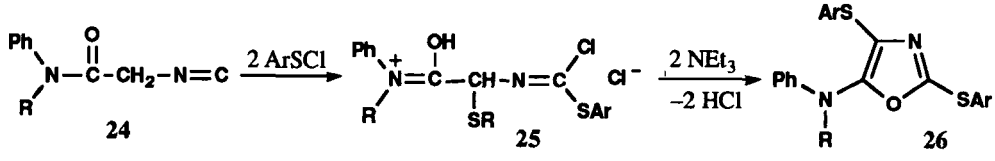
The reaction between isocyanides **1** and thiocyanic acid leads to the formation of an α-adduct that reacts with another molecule of thiocyanic acid to give[17a-b,18] 1-alkyl(or aryl)-2,4-dithioxo-1,2,3,4-tetrahydro[1,3,5]triazines **23** *(Scheme* 8).



1 22 23

Scheme 8

In the reaction between *N*-alkyl isocyanoacetanilides **24** and arenesulfenyl chlorides, in addition to the α-addition, a substitution on the methylene group takes place. Upon treatment of these intermediates with NEt_3 a ring-closure to 2,4-diarylthio-5-(*N*-phenyl-*N*-alkyl)aminooxazoles **26** takes place[19] *(Scheme* 9).

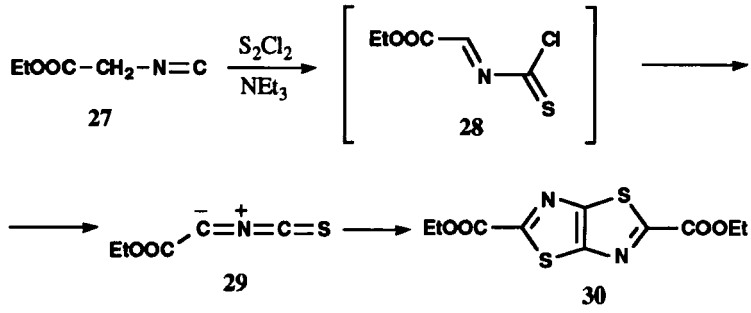


24 25 26

Scheme 9

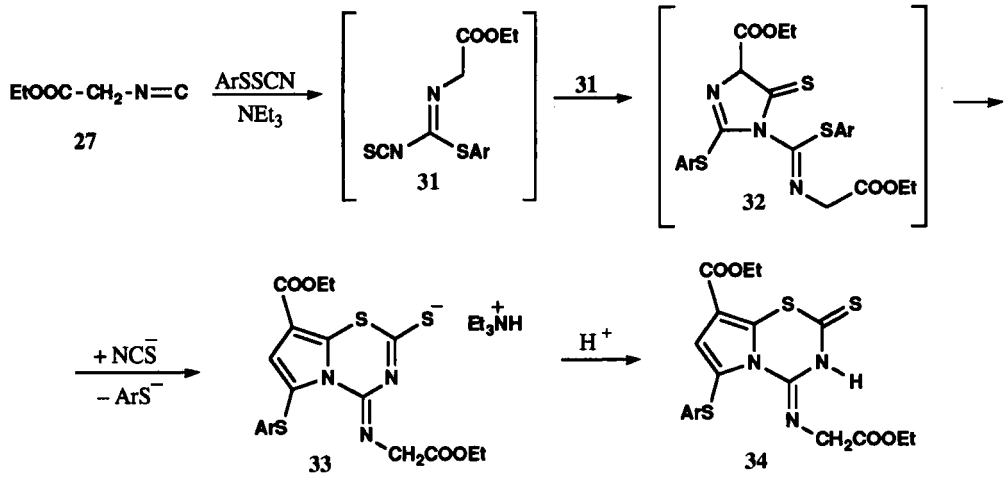
The replacement of a methylene hydrogen with a -*S*Ar group can be explained on the basis of the high degree of enolization of *N*-substituted isocyanoacetanilides.[20]

Upon treatment of ethyl isocyanoacetate **27** with dichlorodisulfane in the presence of triethylamine, an unusual ring-closure reaction that affords diethyl thiazolo[5,4-d]thiazole-2,5-dicarboxylate **30** occurs.[21] This reaction provides facile access to the above ring system *(Scheme* 10). In fact, the only known alternative synthesis of thiazolo[5,4-d]thiazoles consists in a tedious multi-step procedure.[22]



Scheme 10

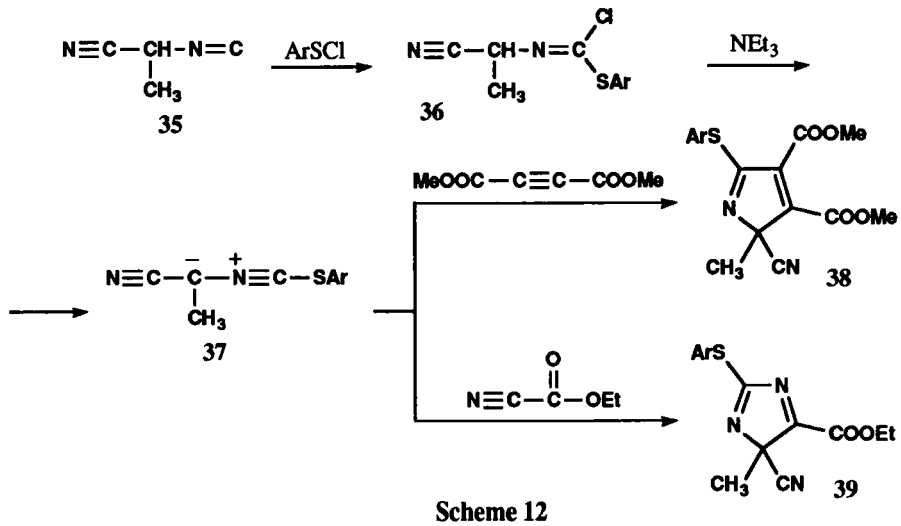
When ethyl isocyanoacetate **27** is reacted with arenesulfenyl thiocyanate in the presence of triethylamine, an unexpected ring-closure to imidazo[5,1-b][1,3,5]thiadiazine derivatives **33**, **34** is observed[23] *(Scheme* 11).



Scheme 11

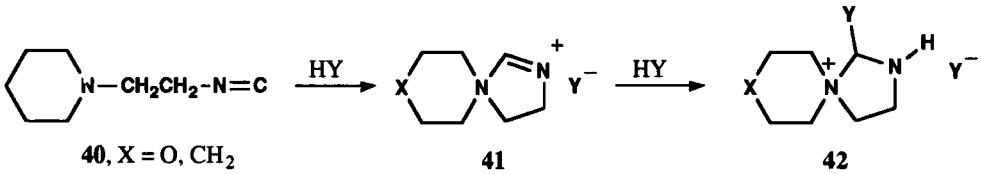
The reaction between arenesulfenyl chlorides and 2-isocyanopropionitrile **35** affords *N*-(1-cyanoethyl)-*S*-arylisothiocarbamoyl chlorides **36**. These adducts cannot cyclize with bases, but are useful starting materials for the synthesis of heterocyclic compounds. In fact, upon treatment with NEt_3, they give nitrile ylides **37** that react with dimethyl acetylenedicarboxylate and ethyl cyanoformate to give 2*H*-pyrroles **38** and 4*H*-imidazoles **39**, respectively[24a] *(Scheme* 12).

If *N*-(4-nitrobenzyl)-*S*-arylisothiocarbamoyl chlorides are employed as the precursors of the nitrile ylides, 1*H*-pyrroles and 1*H*-imidazoles are obtained.[24b] Similarly nitrile ylides, generated from *N*-(tosylmethyl)- and *N*-(dietoxyphosphorylmethyl)imino chlorosulfides, undergo 1,3-dipolar cycloadditions to produce pyrroles and pyrrolines.[25]



Scheme 12

2-Piperidine or 2-morpholine-1-isocyanoethane **40** with hydrochloric or *p*-toluenesulfonic acids afford spiroimidazolidinium salts **41** which react with an excess of acid to give the adducts **42** shown below[26] *(Scheme* 13).

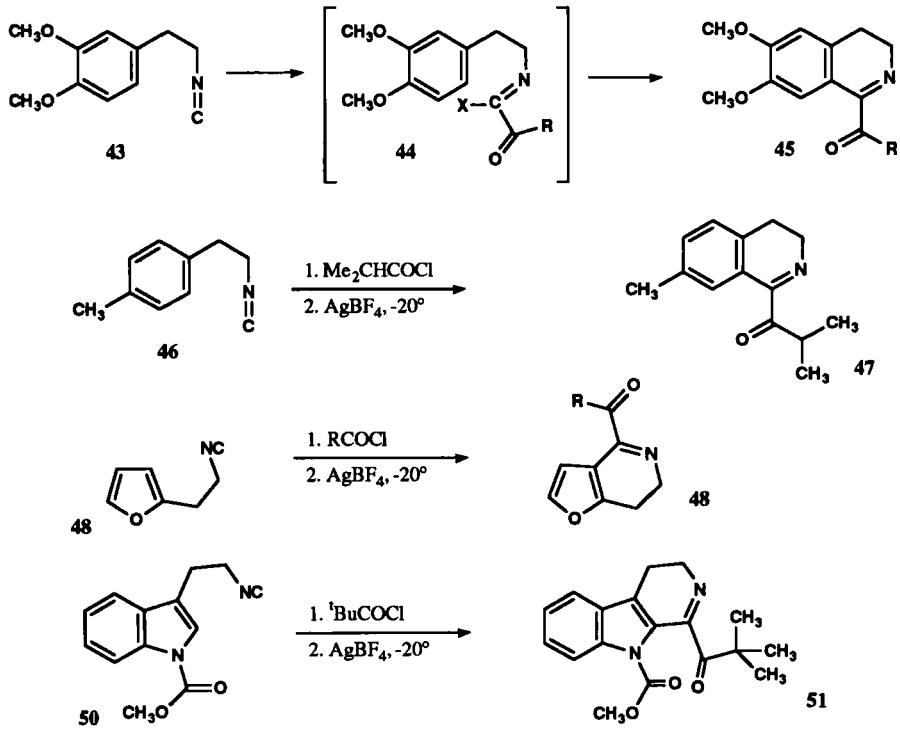


Scheme 13

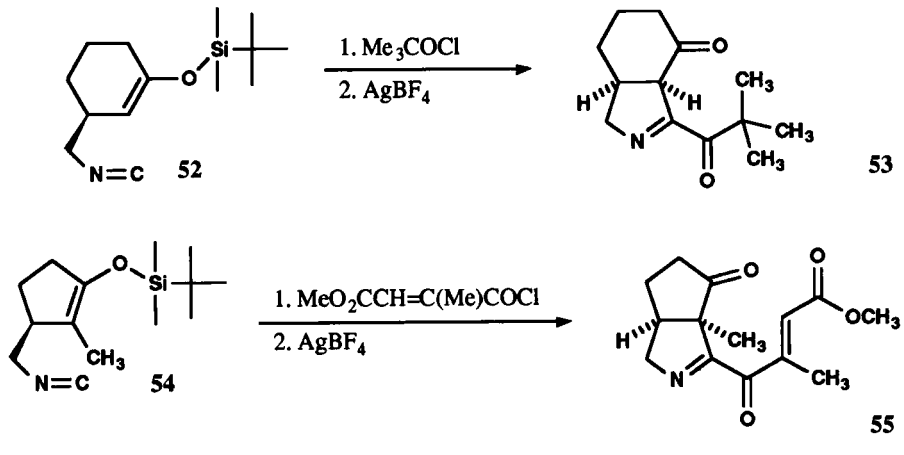
Isocyanides have found an interesting application in the heteroannulation of aromatic and heterocyclic compounds.[27] The reaction of isocyanides **43**, **46**, **48**, **50** with acyl halides affords α-ketoimidoyl halides **44** which are cyclized to heterocycles **45**, **47**, **49**, **51** with a variety of Lewis acids such as silver fluoroborate, silver triflate, or triflic acid *(Scheme* 14).

This cyclization pathway has found application in the synthesis of the erythrinane skeleton.[27] Acylnitrilium ion cyclizations[28a-c] have been used for the preparation of 2-acylpyrrolines **53**, **55** *via* the intramolecular acylation of silyloxyalkenes with α-ketoimidoyl chlorides, obtained by acylation of appropriate isocyanides **52**, **54** *(Scheme* 15).

The same kind of cyclization can be conducted in the presence of an arene moiety instead of the silyloxyalkene group. In this case, cyclization can be controlled by remote substituent effects, affording either spirocyclic or fused ring systems.[28b] On the other hand, these 2-acylpyrrolines are of interest as precursors for the synthesis of some *Orchidaceae* alkaloids. Thus the silver ion mediated cyclocondensation of a related isonitrile with an unsaturated acyl chloride is the key step of an unusually efficient, stereocontrolled, total synthesis (eight linear steps, 6.2% cumulative yield) of the *Orchidaceae* alkaloid (±)-dendrobine.[28c]



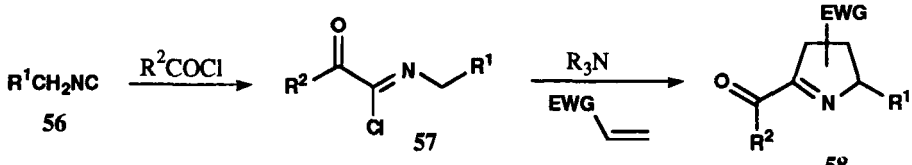
Scheme 14



Scheme 15

An efficient synthesis of Δ^1-pyrrolines and related heterocycles has been developed by using the base induced cyclocondensation of α-ketoimidoyl chlorides with electron deficient alkenes. The treatment of α-ketoimidoyl chlorides **57**, obtained from isocyanides **56**, with amine bases in the pres-

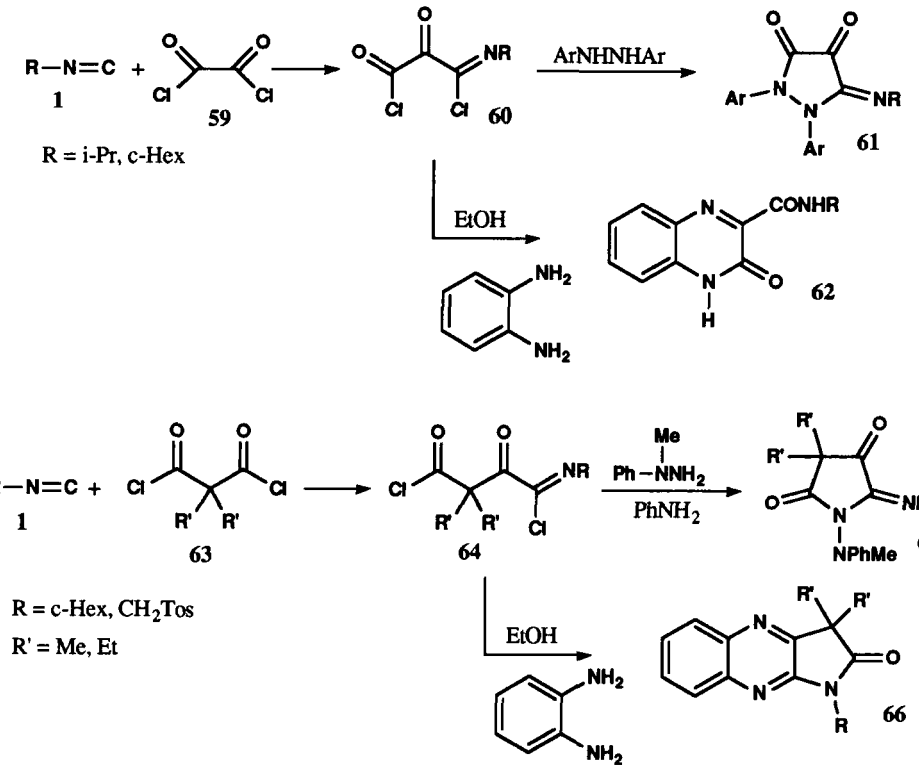
ence of a variety of dipolarophiles provides the corresponding Δ^1-pyrroline derivatives **58** in good to moderate yields, presumably involving acylnitrile ylides as reactive intermediates[29] *(Scheme* 16).



R^1 = H, Ph, *p*-$SO_2C_6H_4CH_3$; R^2 = alkyl

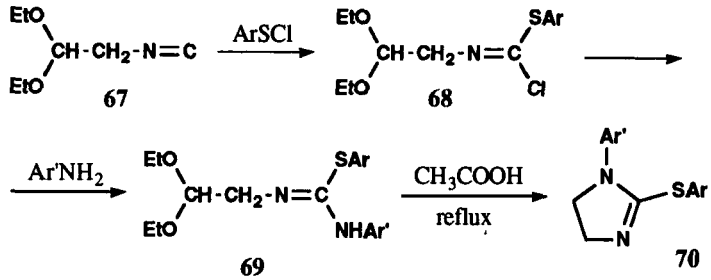
Scheme 16

α-Ketodicarboxylic acid chloride imide chlorides **60, 64** have been used in a different way in the synthesis of heterocycles.[30] These compounds are prepared by addition of dicarboxylic acid dichlorides **59, 63** of varying lengths to isocyanides. They are characterized by the high reactivity of the terminal carbons and readily undergo cyclization reactions with hydrazines, amines or water, affording imino derivatives of pyrazole **61**, pyridazine **62, 66**, pyrrole **65**, and isoquinoline, naphthyridine or pyridopyrazine, respectively.



Scheme 17

The reaction between 2,2-diethoxy-1-isocyanoethane and arenesulfenyl chlorides affords the corresponding isothiocarbamoyl chlorides **68** that, upon treatment with amines give the corresponding *S*-arylisothioureas **69**. These compounds when refluxed in acetic acid cyclize[31] to 1-aryl-2-arylthio-1*H*-imidazoles **70** *(Scheme* 18).

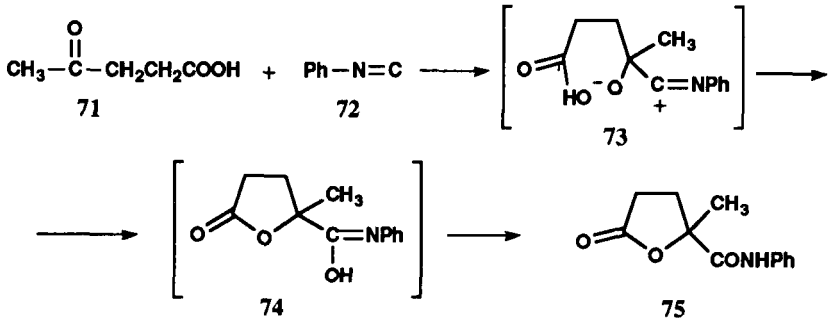


Scheme 18

This synthetic route allows 1-aryl-2-arylthio-1*H*-imidazoles in which the aromatic moiety linked to the sulfur does not contain electron-withdrawing groups to be obtained. These compounds, in fact, can not be prepared by arylating 1,3-dihydro-1-aryl-2*H*-imidazole-2-thiones.

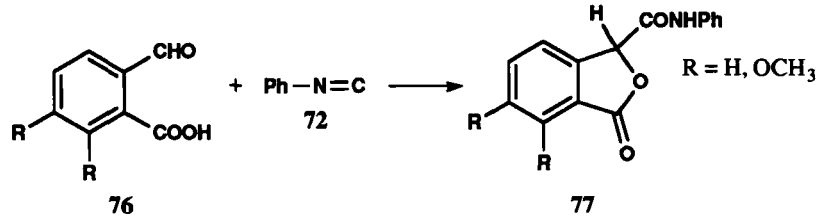
3. Syntheses Based on the Passerini Reaction

The reaction between isocyanides, carboxylic acids, and carbonyl compounds (Passerini Reaction) is an elegant and viable route to *N*-substituted α-acyloxycarboxamides.[32a-i,33] If the carbonyl group and the carboxylic one belong to the same molecule, heterocyclic compounds are obtained. The reaction between phenylisocyanide **72** and levulinic acid **71** affords[32d] *N*-phenyl-2-methyl-5-oxo-2,3,4,5-tetrahydrofuran-2-carboxamide **75** *(Scheme* 19).



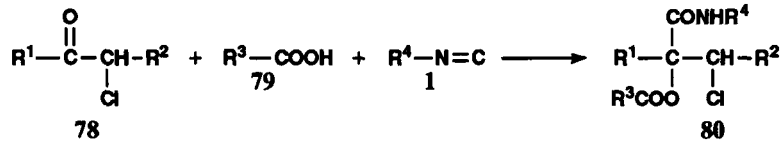
Scheme 19

If 2-formylbenzoic acids **76** are employed in place of levulinic acid, the benzo-fused derivatives **77** of the above functionalized lactone are obtained[33] *(Scheme* 20).



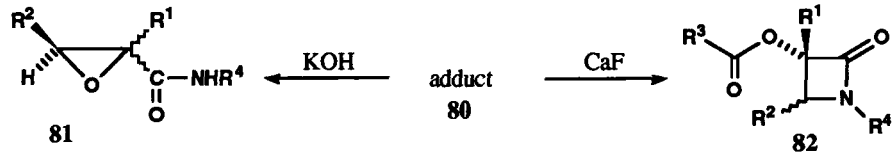
Scheme 20

The reaction between α-chloroketones **78**, carboxylic acids **79**, and isocyanides **1**, affords[34] the corresponding *N*-substituted 2-acyloxy-3-chlorocarboxamides **80** *(Scheme* 21).



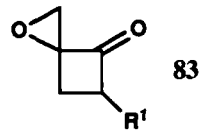
Scheme 21

These compounds are converted in high yields to oxiranes **81** (with powdered KOH in THF) and to azetidones **82** (with CsF in THF)[34] *(Scheme* 22).



Scheme 22

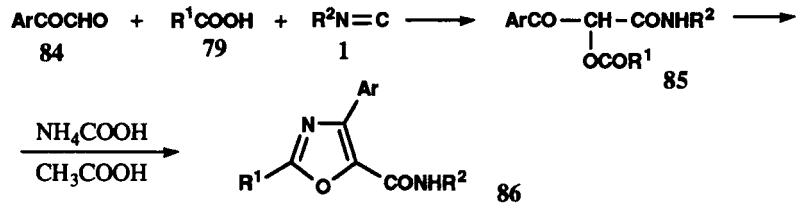
If 1,3-dichloroacetone is utilized as the starting carbonyl compound, 1-oxa-4-oxo-5-azaspiro[2.3]hexanes **83** are obtained in high yields by a two-step procedure[35] *(Scheme* 23).



83

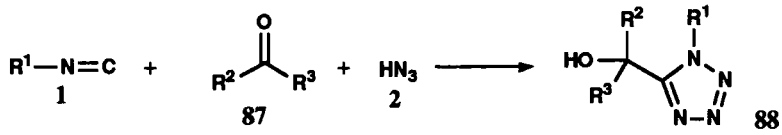
Scheme 23

The reaction between arylglyoxals **84**, isocyanides **1**, and carboxylic acids **79** affords *N*-substituted-2-acyloxy-3-oxoarylpropionamides **85** which are useful starting materials for the synthesis of oxazoles **86**, according to the Davidson procedure.[36-38] A wide variety of *N*,2,4-trisubstituted oxazole-5-carboxamides **86** are obtainable, depending upon the choice of the arylglyoxal, the isocyanide, and the carboxylic acid[39-41] *(Scheme* 24).



Scheme 24

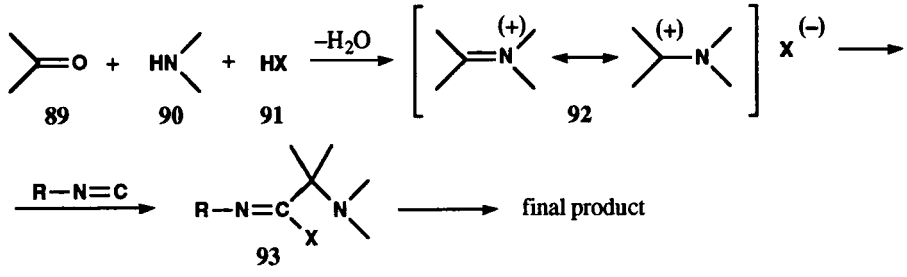
If hydrazoic acid **2** is employed in place of the carboxylic acid, 1,5-disubstituted tetrazoles **88** are obtained[42] *(Scheme* 25).



Scheme 25

4. Syntheses Based on the Ugi Four Component Condensation (*4CC*)

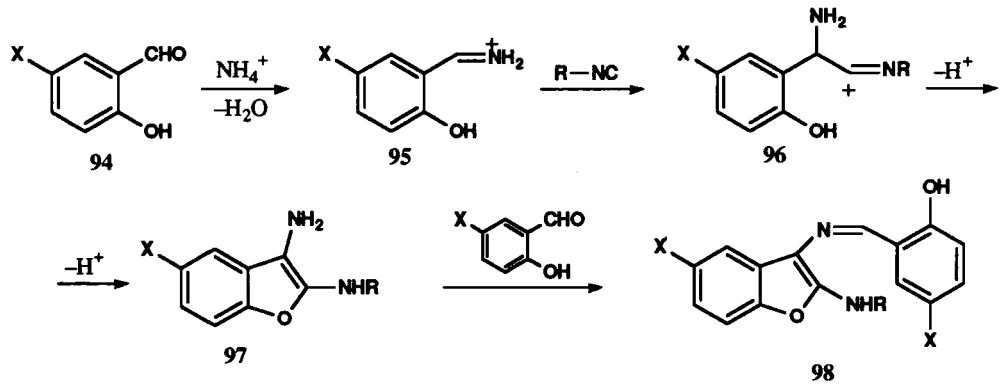
Immonium ions **92**, generated from carbonyl compounds **89** and salts of amines **90**, give α-additions on the carbenoid carbon of isocyanides. The primary adducts **93** undergo rearrangements to afford stable final products[1,2,43-46] *(Scheme* 26).



Scheme 26

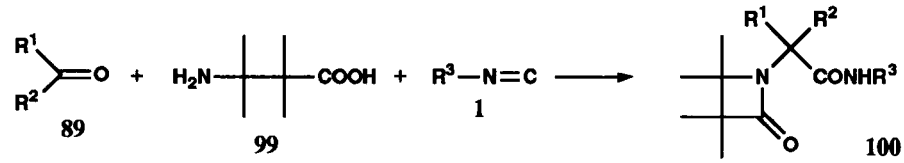
Sometimes the final product is a heterocycle. The reaction between carbonyl compounds, isocyanides and cyanates or thiocyanates of primary amines affords hydantoin imides[47] and thiohydantoin imides.[48] By employing hydrazoic acid as the acid component, tetrazole derivatives are obtained.[49] Tetrazoles are also obtained from dienamines, isocyanides, and hydrazoic acid.[50]

An anomalous behavior is observed when *o*-hydroxybenzaldehydes **94** are reacted with ammonium carboxylates and isocyanides under the Ugi *4CC* conditions. In this case, the intermediate imidoyl compound **96** undergoes nucleophilic attack of the oxygen of the phenoxy group to give benzofuran derivatives **98**.[51]



Scheme 27

The reaction between carbonyl compounds **89**, isocyanides **1**, and β-aminoacids **99** leads to the formation of β-lactams **100**, an extremely important class of compounds, due to their presence in natural and synthetic antibiotics[5] *(Scheme* 28).



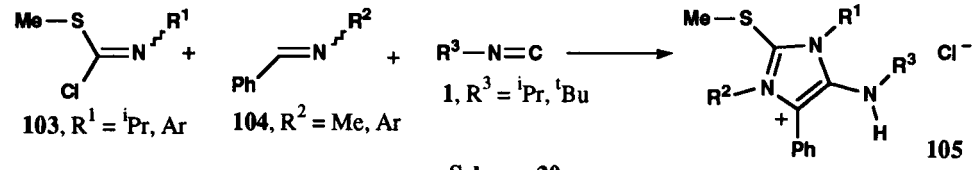
Scheme 28

The Ugi four-component condensation has found very interesting applications in the synthesis of antibiotics and naturally occurring compounds.[52,53] The Ugi reaction has been reviewed[54] in reference to the synthesis of β-lactams and peptides. As an example of the last, the general applicability of a four-component condensation for the formation of *N*-acyl-β-aryloxyprolines[55] has been demonstrated in several model studies directed toward the total synthesis of 14-membered cyclopeptide alkaloids.

Other heterocycles can be obtained through multicomponent condensation involving isocyanides. Cyclocondensation of ketones $RCOR^1$, isocyanides R^2NC, and $MeNH_2$•HCl-KSCN or NH_4SCN affords imidazolium salts **101** which on treatment with base affords the imidazolimines **102** shown below.[56] Crystal structures of the imidazolium salt **101** R,R^1 = $(CH_2)_5$, R^2 = $PhCH_2$, R^3 = Me and the imidazoline **102** R,R^1 = $(CH_2)_5$, R^2 = 4-MeC_6H_4, R^3 = Me have been determined *(Scheme* 29).

Scheme 29

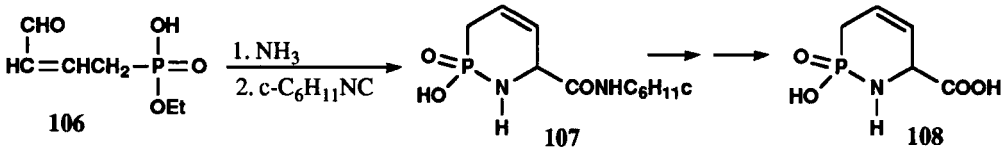
Stirring a mixture of alkyl or aryl chlorothioimidates, alkyl- or arylimines and isopropyl- or *tert*-butylisocyanide results in the formation[57] of imidazolium salts **105** *(Scheme* 30). When ketimines instead of aldimines were used, the corresponding 2-thioxodiazolidines are obtained.[57]



103, R^1 = ^{i}Pr, Ar **104**, R^2 = Me, Ar **1**, R^3 = ^{i}Pr, ^{t}Bu **105**

Scheme 30

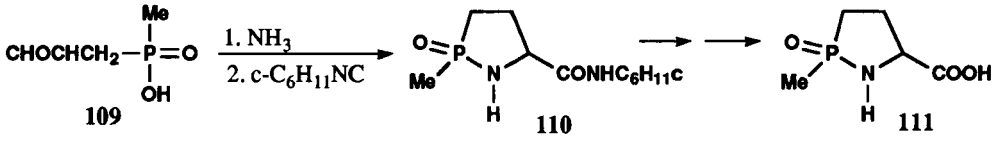
The cyclic analog **108** of the unusual natural amino acid 3,4-didehydro-5-phosphono-D-norvaline, has been synthesized by a three-component condensation of a phosphonoaldehyde **106**, ammonium, and isocyanocyclohexane[58a] *(Scheme* 31).



106 **107** **108**

Scheme 31

In the same way, the cyclic analog of *DL*-phosphonotricine has been synthesized using an Ugi-analogous three-component condensation[58b] *(Scheme* 32).



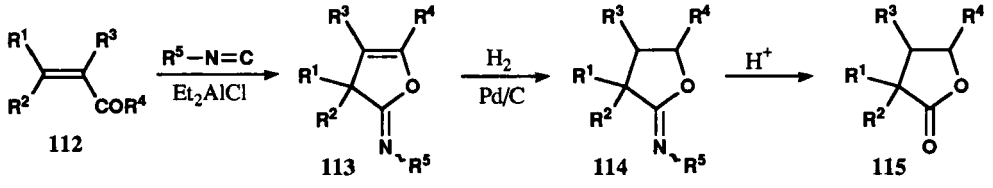
109 **110** **111**

Scheme 32

II. CYCLOADDITIONS AND CYCLIZATIONS WITH ISOCYANIDES

1. [1+4] Cycloadditions

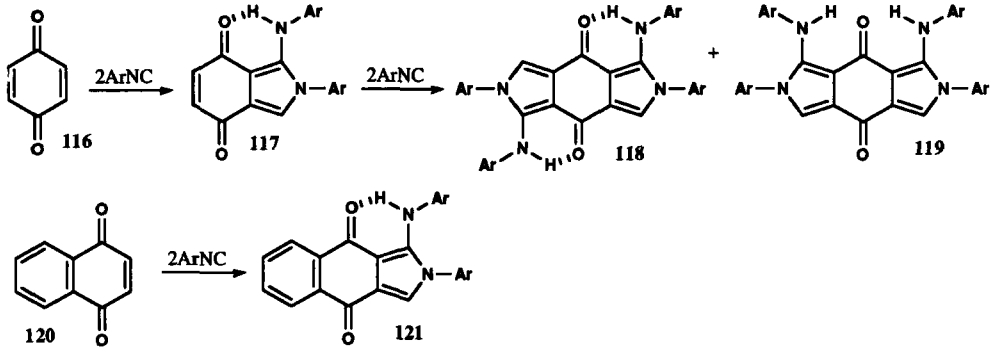
Isocyanides give [1+4] cycloaddition with α,β-unsaturated carbonyl compounds **112** in the presence of diethylaluminum chloride to afford unsaturated iminolactones **113**, which are stereoselectively converted to γ-butyrolactones **115** by hydrogenation followed by acid hydrolysis[59] *(Scheme* 33).



112 **113** **114** **115**

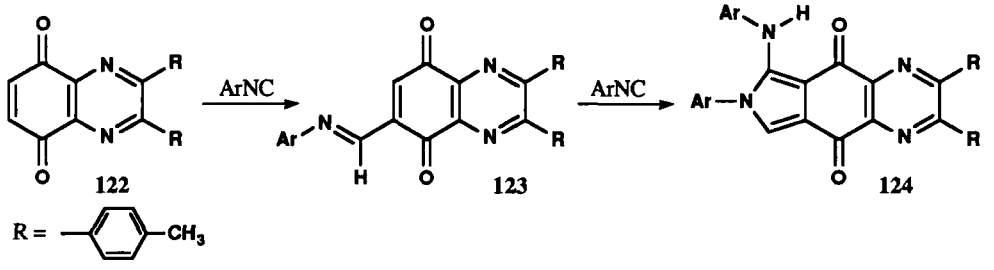
Scheme 33

The reaction between isocyanides ArNC (Ar = Ph, 4-$CH_3C_6H_4$, 4-ClC_6H_4, 4-$NO_2C_6H_4$) and 1,4-benzoquinone **116** in boiling toluene or xylene leads to the formation of the dark-blue 1:2 adducts 4,7-isoindolediones **117** and to the 1:4 adducts 1,5- and 1,7-bis(arylamino)benzodipyrrolediones **118** and **119** respectively. The reaction of 1,4-naphthoquinone **170** with 4-tolylisocyanide and 4-nitrophenylisocyanide leads to the formation[60] of 1:2 adducts **121** *(Scheme* 34).



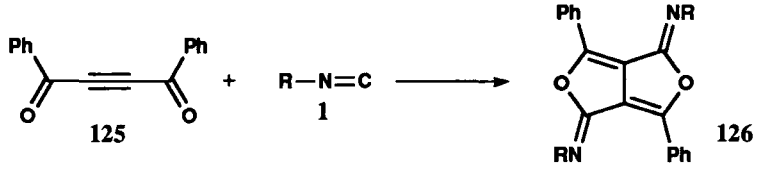
Scheme 34

The reaction of quinoxaline quinone **122** with tolylisocyanide gives pyrrolo[3,4-*g*]quinoxaline quinone **124** in low yields[61] *(Scheme* 35).



Scheme 35

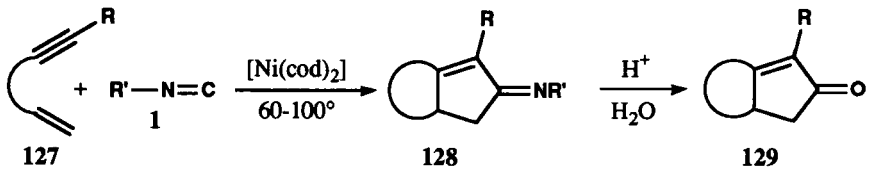
Isocyanides react with conjugated triple bonds *via* [1+4] cycloaddition. The cycloaddition of isocyanides with 1,4-diphenylbutyne-1,4-dione **125** yields[62] 1*H*,4*H*-furo[3,4-*c*]furans **126** *(Scheme* 36).



Scheme 36

The reaction between isocyanides and dimethyl acetylendicarboxylate leads to a variety of products including pyrroles, furans, and annulated pyridines.[63]

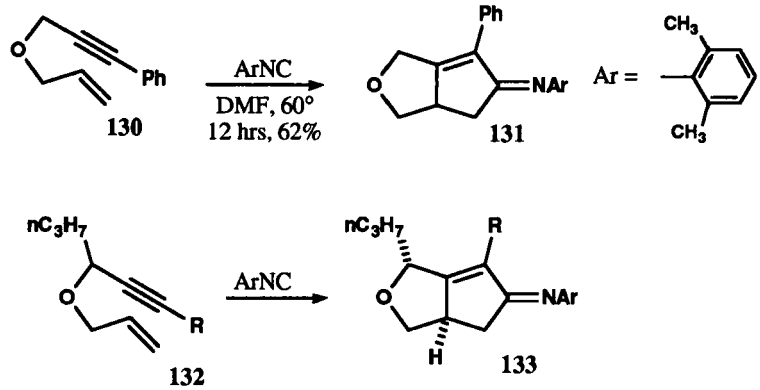
Tamao, Kobayashi, and Ito[64] have reported the first example of Ni(0)-promoted cyclization of enynes with isocyanides. The reaction affords 1-imino-2-cyclopentenes **128**, which can be hydrolyzed to the corresponding cyclopentenones **129** *(Scheme* 37).



127 **128** **129**

Scheme 37

If the chain contains oxygen, annulated tetrahydrofurans **131**, **133** are obtained[64] *(Scheme* 38).

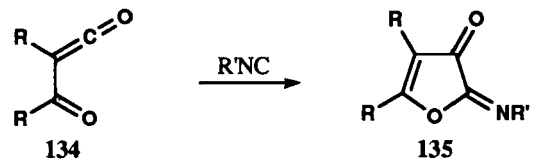


130 **131** **132** **133**

Scheme 38

The conditions for the last reaction are: R = Ph, DMF, 60°, 10 hrs, 92% yield, and R = *n*-C_5H_9, DMF, 60°, 12 hrs, 47% yield.

Other groups can undergo [1+4] cycloadditions with isocyanides. The reaction of α-acylketenes **134** with isocyanides affords 2-imino-3-furanones **135** *(Scheme* 39).

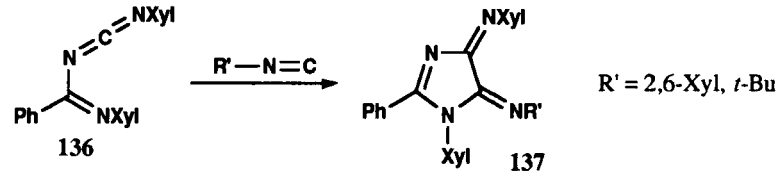


134 **135**

Scheme 39

These compounds are very reactive and undergo a variety of rearrangements to nitrogen-containing heterocycles.[65] If the addition is carried out with α-acyl- and α-sulfonylketene imines, furan, indole, and indene derivatives are obtained, depending upon the nature of the ketene imine and the isocyanide.[66] By employing imidoylketene imines as the starting material, 2,3-diiminopyrroles are

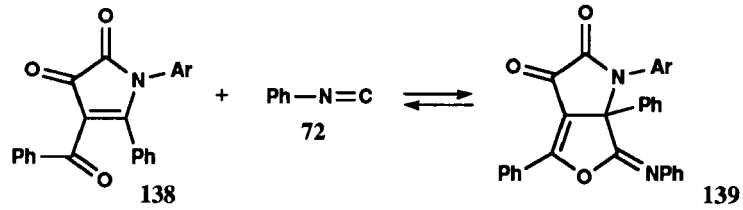
obtained. If the imidoyl carbodiimide **136** is reacted with isocyanides, 4,5-diiminoimidazoles **137** are obtained.[67] This kind of cyclization, that is shown forwards, is the first example of a synthesis of the imidazole ring by formation of 1,5- and 4,5-bonds *(Scheme* 40).



Scheme 40

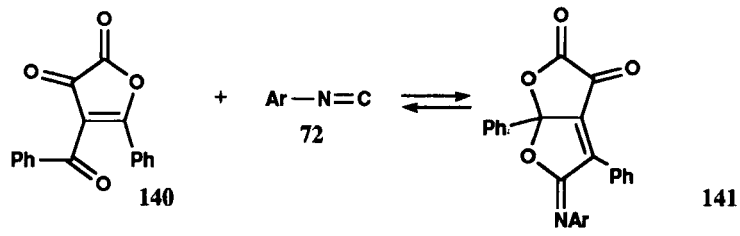
If *bis*(1,2-diphenylvinyl)carbodiimide is reacted with isocyanides a cyclodehydrogenation leading to 1*H*-pyrrolo[2,3-*b*]pyrazines takes place.[67]

Aryl isocyanides give a reversible [1+4] cycloaddition with pyrrole-2,3-diones **138** to afford[68] furo[3,4-*b*]pyrrolediones **139**, that undergo the furane ring-opening with nucleophiles to give pyrrole-diones *(Scheme* 41).



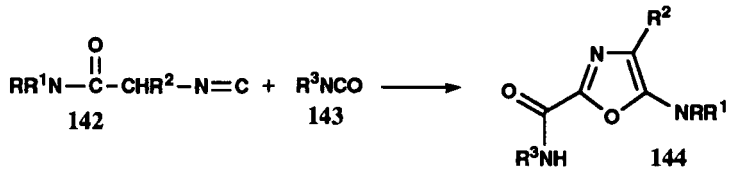
Scheme 41

If benzoylfuranedione **140** is employed as the starting material, furo[2,3-*b*]furane-2,3-diones **141** are obtained.[69] A variety of ring-opening reactions with nucleophiles is described[69] *(Scheme* 42).



Scheme 42

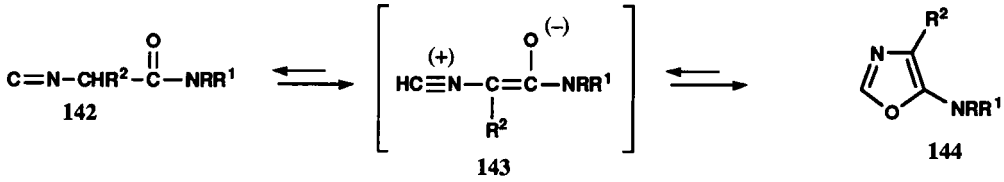
Chupp and Leschinsky found that *N,N*-disubstituted 2-isocyanocarboxamides **142** react with reactive aryl and sulfonyl isocyanates **143** to afford 5-amino-2-oxazole carboxamides **144**. A mechanism, which involves the formation of a nitrile ylide intermediate, has been proposed[70] *(Scheme* 43).



Scheme 43

If the reaction is performed with acyl isocyanoacetates a variety of products, such as iminooxazoline diones, 5-amino-2-oxazolecarboxamides, and pyrazinones, are obtained.

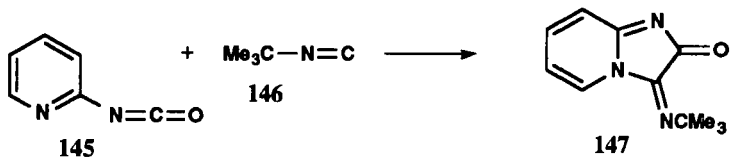
It is interesting that *N,N*-disubstituted 2-isocyanocarboxamides **142** are easily cyclized to oxazoles **144** upon heating.[20] These cyclizations are an interesting example of ring-chain tautomerism through a nitrilium intermediate *(Scheme* 44).



Scheme 44

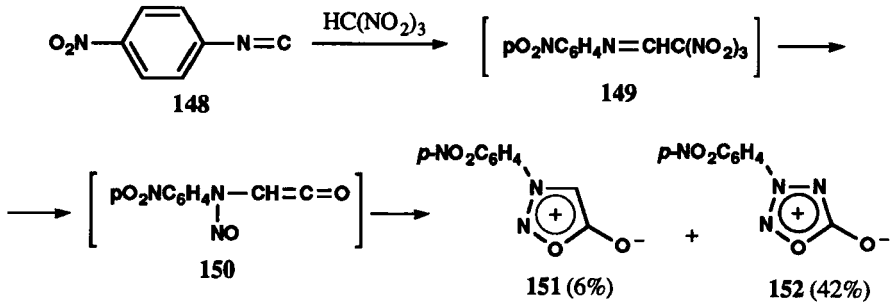
The facile cyclization of *N,N*-disubstituted 2-isocyanocarboxamides must be related to the high degree of enolization of these compounds. In fact, the less enolizable ethyl isocyanoacetate cyclizes to 5-ethoxyoxazole in only 5% yield.[71]

The cycloaddition of 2-isocyanatopyridine **145** with *tert*-butyl isocyanide **146** leads to the formation[72] of the imidazopyridinone **147** shown below *(Scheme* 45).



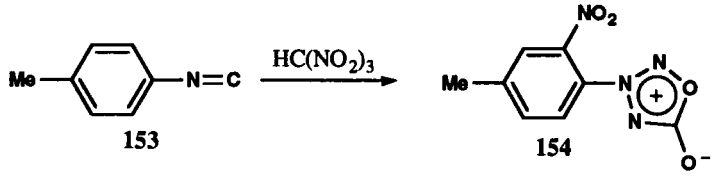
Scheme 45

The reaction between nitroform and 4-nitrophenylisocyanide **148** affords[73] a mixture of 3-(4-nitrophenyl)-1,2,3-oxadiazolium-5-olate **151**(6%) and 3-(4-nitrophenyl)-1,2,3,4-oxatriazolium-5-olate **152**(42%). Only a plausible mechanism for the formation of compound **151** is given *(Scheme* 46).



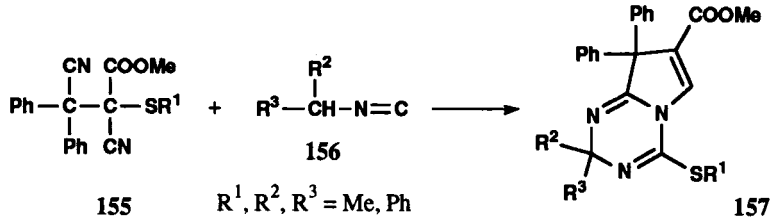
Scheme 46

By employing *p*-tolylisocyanides only the mesoionic 3-(2-nitro-4-methylphenyl)-1,2,3,4-oxatriazolium-5-olate **154** is obtained[73] *(Scheme* 47).



Scheme 47

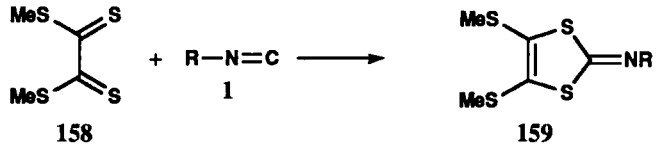
The reaction between sulfides **155** and isocyanides **156** leads to the formation[74] of pyrrolodihydro[1,3,5]triazines **157** *(Scheme* 48).



Scheme 48

The formation of pyrrolodihydro[1,3,5]triazines takes place *via* intermediate diazatrienes that can be trapped with isocyanides to give imidazolines.[74]

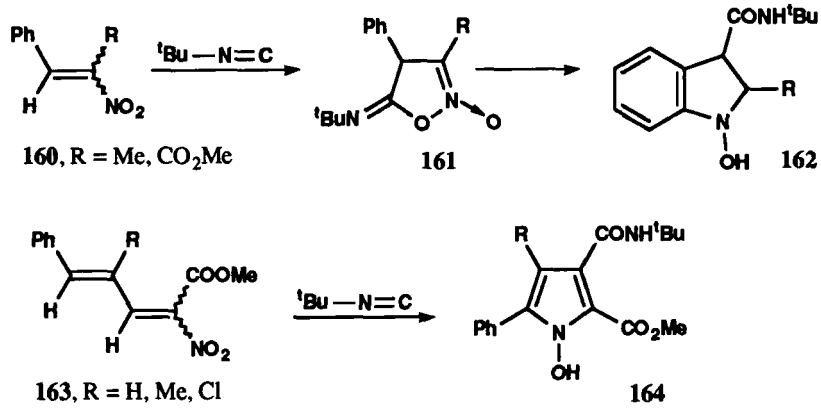
Dimethyl tetrathiooxalate **158** gives [4+1] cycloaddition with isocyanides **1** to form[75a-b] 2-imino-1,3-dithioles **159** *(Scheme* 49).



Scheme 49

When isocyanides are reacted with methyl dithiooxalate, complex mixtures of products are obtained. The predominant products are 1,3-thiazetidines but also azetidine thiones and 3,3'-biazetidine-2,2'-dithiones are obtained.[75b]

The cycloaddition reaction of isocyanides with nitroalkenes give unstable isoxazoline *N*-oxides. When the hydrogen atom in the 3-position of isoxazoline is replaced by an alkyl or ester group, the evolution of isoxazoline *N*-oxide affords the formation of compounds with a 1-hydroxypyrrole ring.[76] Thus, the reaction of 2-methyl(or methoxycarbonyl)-1-aryl-2-nitro-1-alkenes **160** with *tert*-butylisocyanide gives the corresponding *N*-(*tert*-butyl)-1-hydroxy-2-methyl(or methoxycarbonyl)-3-indolecarboxamides **162**, and the reaction of methyl 5-phenyl-2-nitro-2,4-pentadienoates **163** affords[76] 3-[(*tert*-butylamino)carbonyl]-1-hydroxy-5-phenylpyrrole-2-carboxylates **164** *(Scheme* 50).

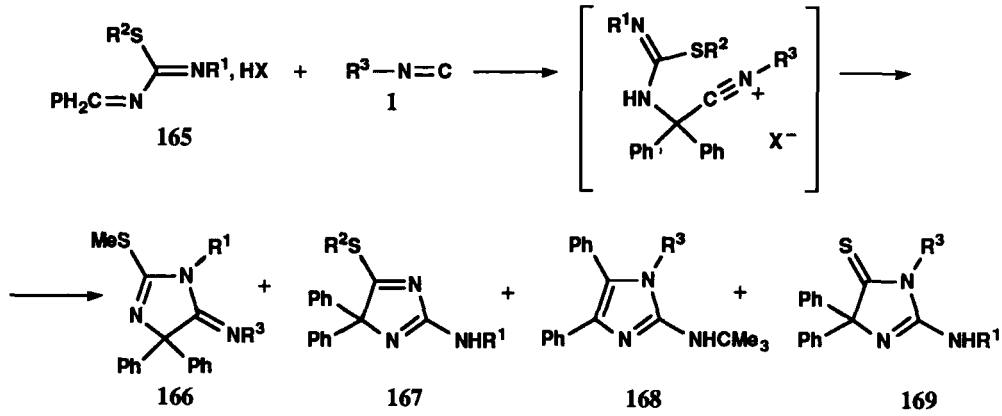


Scheme 50

When the aryl group is 2-pyridinyl, thienyl or furyl, fused 1-hydroxypyrroles are obtained.

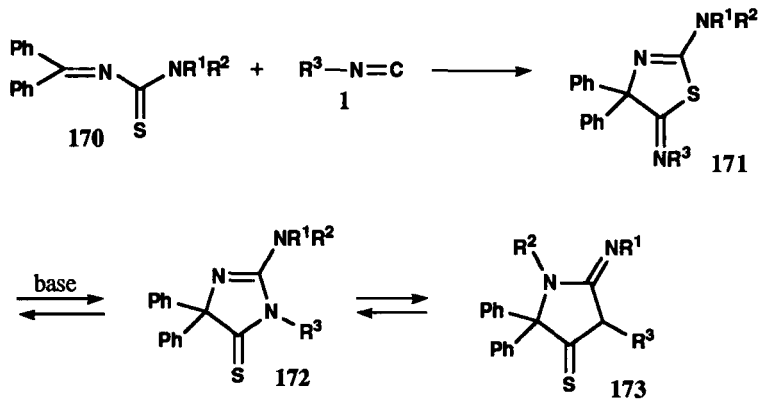
Heterosubstituted butadienes react with isocyanides in a [1+4] cycloaddition fashion, affording five-membered heterocycles.[77a,b]

Protonated 1,3-diaza-4,4-diphenyl-2-(methylthio)butadienes **165** react with isocyanides **1** much faster than with non-protonated ones. The 5-iminoimidazolines **166** (R^2 = CMe_3, $CHMe_2$, 2,6-$Me_2C_6H_3$, H) which are expected [1+4] cycloaddition products, are generally obtained. However, rearranged imidazoles **167** (R^2 = Me, R^1 = $CHMe_2$, CMe_3; R^2 = 4-MeC_6H_4, R^1 = CMe_3) and **168** (R^3 = $CHMe_2$, 2,6-$Me_2C_6H_3$) and 5-thioxoimidazolines **169** (R^1 = Me, $CHMe_2$, CMe_3, R^3 = $CHMe_2$, 2,6-$Me_2C_6H_4$) are predominantly formed in some cases. A mechanism is suggested to explain this rearrangement.[77a]



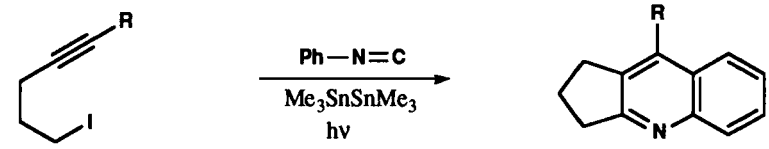
Scheme 51

Cycloaddition reaction of isocyanides **1** with 2-amino-3-aza-1-thiabutadienes **170** gives the 2-amino-5-imino-4,5-dihidrothiazoles **171** (R^1 = Me, Et, Ph, CMe_3, 4-$O_2NC_6H_4$, Bz, R^2 = H, Me, 2-$O_2NC_6H_4$, R^3 = alkyl, substituted phenyl).[77b] The rearrangement of **171** (R^2 = H), was induced by 1,5-diazabicyclo[4.3.0]non-5-ene and leads to 4*H*-imidazoline-5-thiones **172** or 4-thioxo-1,3-diazolidines **173** depending upon the substituent R^1 *(Scheme* 52).



Scheme 52

Sunlamp irradiation of 1-substituted 5-iodo-1-pentynes **174**, 5 equivalents of phenyl isocyanide, and 1.5 equivalents of hexamethylditin in *tert*-butylbenzene (0.01-0.025 M) at 150° produces 9-substituted 2,3-dihydro-1*H*-cyclopenta[*b*]quinolines **175** in 36-70% yields.[78] A mechanistic proposal for this first example of a 4+1 radical annulation includes the following: *(1)* radical addition to an isocyanide, *(2)* cyclization of the resulting imidoyl radical to the alkyne, *(3)* addition of the so-formed vinyl radical to the aromatic ring, and *(4)* rearomatization *(Scheme* 53).



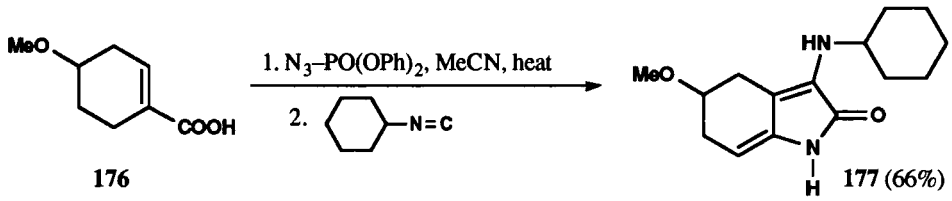
174, R = CH_3, CH_2Ph, Ph

175

Scheme 53

When substituted (*p*-F, *p*-OMe, *m*-F)phenyl isocyanides are employed, the major unrearranged products are accompanied by 7-30% of rearranged products. A mechanism for the rearrangement is given.[78]

Vinyl isocyanates, obtained from α,β-unsaturated acids **176**, undergo [1+4] cycloaddition with cyclohexyl isocyanide to yield[79] substituted pyrrolinones **177** *(Scheme* 54).



176

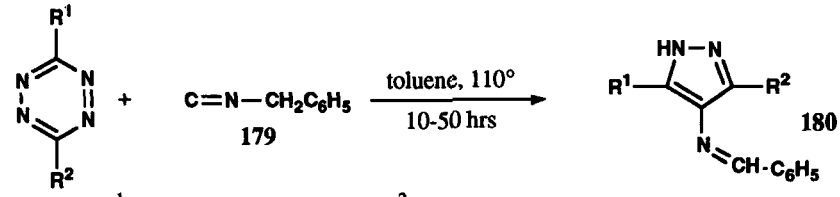
177 (66%)

Scheme 54

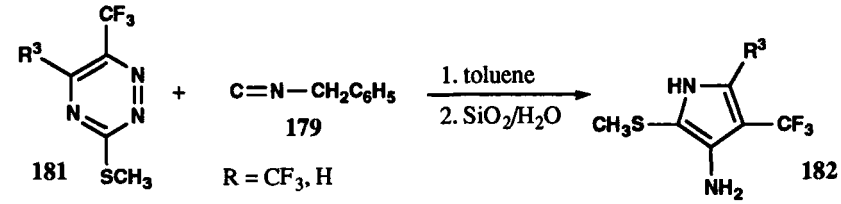
This novel approach can be applied to alkaloid syntheses of substances which include the hydroindole unit, such as the *Amaryllidaceae* alkaloids. The reaction has been used for the formal total synthesis of the *Erythrina* alkaloid, erysotrine, *via N*-alkylation at the enamide nitrogen of the [1+4] cycloadduct shown above, followed by smooth acid-mediated cyclization which affords a compound with a fully intact *Erythrina* carbon skeleton.

Other types of dienes or related compounds can react with isocyanides. Various donor substituted 1,2,4,5-tetrazines **178** and 1,2,4-triazines **181** react with benzyl isocyanide **179** in a sequence of [1+4] cycloaddition and [4+2] cycloreversion steps to yield unstable intermediates which afford stable pyrazole azomethines **180** after [1,5-*H*] shift, and stable aminopyrroles **182** after [1,5-*H*] shift and SiO_2/H_2O hydrolysis of the corresponding intermediate[80a] *(Scheme* 55).

On the other hand, vinylaminodialkylboranes react with isocyanides to give [1+4] cycloadducts, which undergo thermal anionotropic rearrangements producing 2-amino-1,2-azaboroline derivatives.[80b]



178 $R^1 = N(CH_3)_2, SCH_3, C_6H_5$; $R^2 = SO_2CH_3, SCH_3, OCH_3, H$



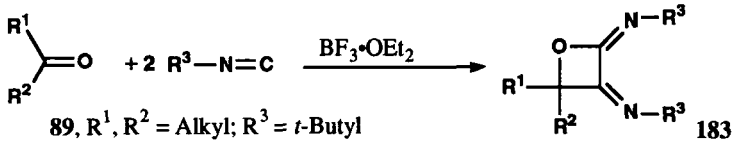
Scheme 55

2. Other Cycloadditions, Insertions, and Ring Expansions Involving Isocyanides

Isocyanides give a wide variety of cycloadditions and insertions with multiple bonds, 1,3-dipoles, and 3-membered rings that afford four-membered heterocycles which, in many cases, are not easily available with alternative syntheses. An excellent review concerning the formation of four-membered rings is available.[81] The same type of reactions sometimes gives five-membered heterocycles. Formation of three-membered heterocycles is also known.

The [1+1+2] cycloadditions of two isocyanide molecules to double or triple-bonded functionalities give four-membered cyclic compounds. Sometimes, a reverse ratio of reactants is observed, thus by [2+2+1] cycloaddition, to yield a five-membered ring. Four- or five-membered heterocycles can be obtained when the double or triple-bonded compounds bear a heteroatom. Some examples are given below.

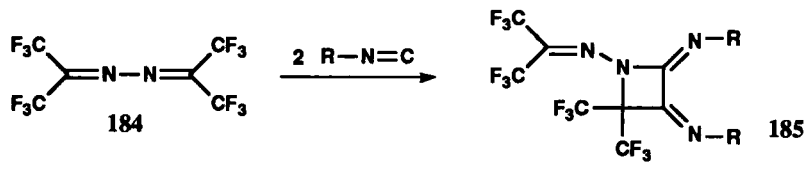
Aliphatic and aromatic aldehydes and aliphatic ketones **89** react with alkyl isocyanides **1** in a [1+1+2] manner to produce[82] 2,3-*bis*[alkylimino]oxetanes **183** *(Scheme* 56).



89, R^1, R^2 = Alkyl; R^3 = *t*-Butyl

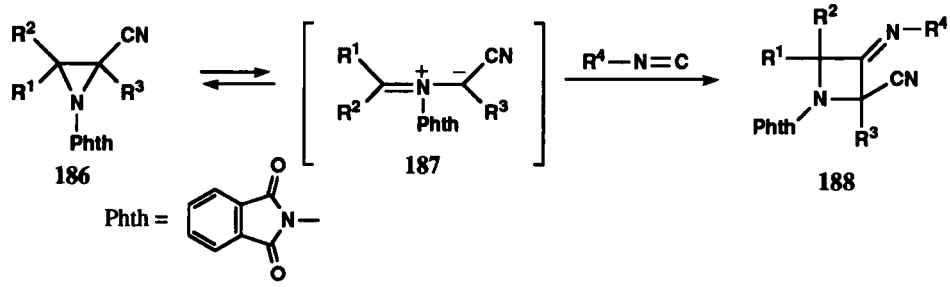
Scheme 56

Azomethines undergo cycloaddition with two molecules of *tert*-butyl isocyanide to give the 2,3-*bis*[*tert*-butylimino]azetidines. These reactions are acid-catalyzed. Hexafluoroacetone azine **184** produces[83] 1-amino-2,3-diiminoazetidines **185** *(Scheme* 57).



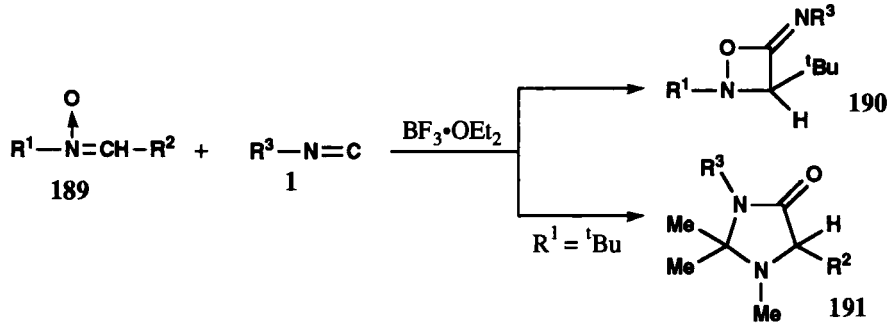
Scheme 57

1,3-Dipoles react with isocyanides giving the [1+3] or [2+3] cycloaddition products. Azomethine ylides **187** cyclize with isocyanides to give[84] the 3-iminoazetidines **188**. The intermediate 1,3-dipoles **187** are generated by thermal ring-opening of aziridines **186** *(Scheme* 58).



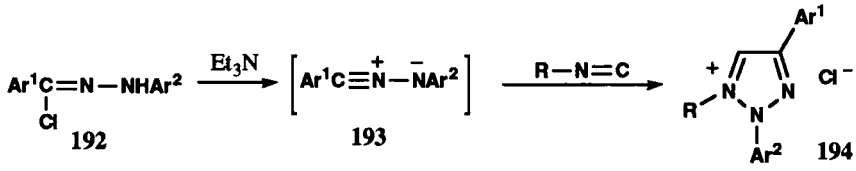
Scheme 58

Nitrones **189** react with alkyl isocyanides **1** in the presence of boron trifluoride etherate, affording 4-imidazolidinones **191**, which are shown to be ring expansion products of the 4-imino-2-oxazetidines **190** initially produced[85] *(Scheme* 59).



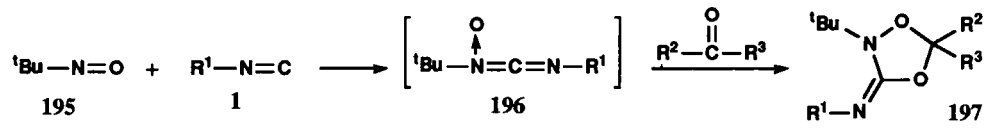
Scheme 59

In a different way, diarylnitrilimines **193**, obtained from *N*-phenylbenzohydrazonoyl chloride **192** and triethylamine, react with alkyl isocyanides to form, through proton transfer, the 1-alkyl-2,4-diaryl-1,2,3-triazolium chlorides **194**, involving a [2+3] cycloaddition *(Scheme* 60).[86]



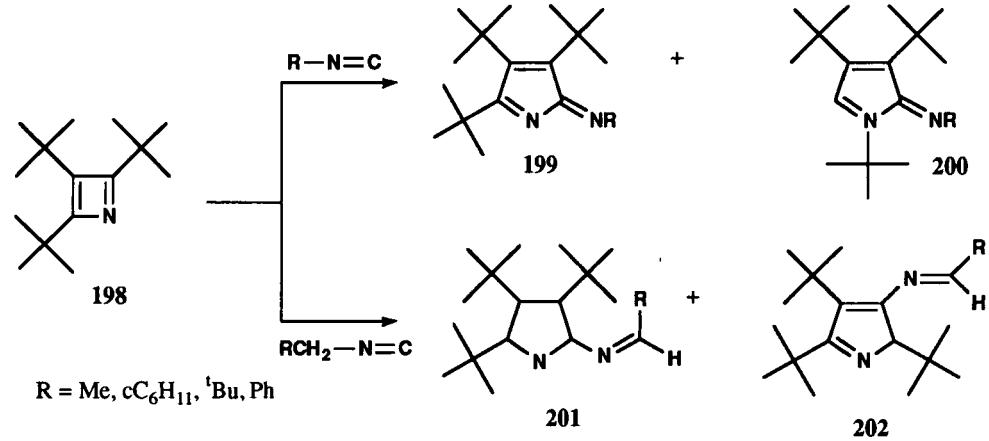
Scheme 60

The [1+2+2] cycloaddition of an alkyl isocyanide **1**, 2-methyl-2-nitrosopropane **195**, and a carbonyl compound, aldehyde or ketone, gives 3-imino-1,4,2-dioxazolidines **197**. The mechanism involves formation of a transient 1,3-dipole **196** trapped by the carbonyl compound[87] *(Scheme* 61).



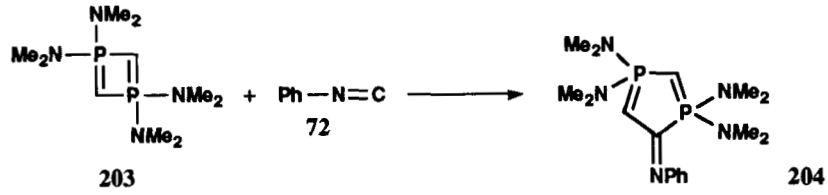
Scheme 61

Kinetically stabilized tri-*tert*-butylazete **198** reacts with isocyanides in a sequence of [4+1] cycloaddition and ring-opening steps to yield[88] 2- and 3-iminosubstituted 2*H*- and 3*H*-pyrrole derivatives **201**, **202**. The α-methylene isocyanides react analogously, but the formation of 2- and 3-iminopyrroles is still followed by a [1,5]-shift which leads[88] to 2- and 3-aminopyrrole derivatives **201**, **202** *(Scheme* 62).



Scheme 62

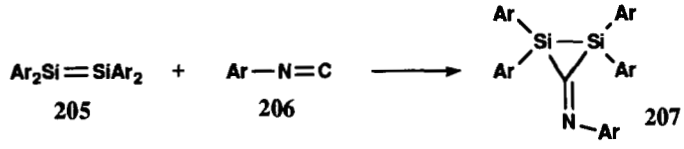
Cycloaddition reaction of diphosphacyclobutadiene **203** with phenyl isocyanide **72** in toluene gives azadiphosphafulvene **204** in a 20% yield[89] *(Scheme* 63).



203 204

Scheme 63

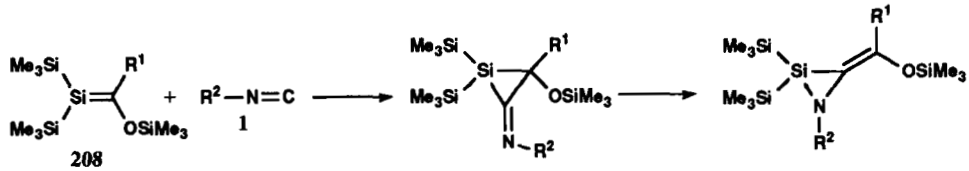
The reaction of disilene **205** with 2,6-dimethylphenyl isocyanide **206** affords the disilacyclopropanamine **207** shown below[90] *(Scheme* 64).



205 206 207

Scheme 64

On the other hand, stable silenes **208** react with isocyanides to yield unstable silacyclopropanimines **209** which rapidly rearrange below room temperature to form the isomeric silaaziridines **210**. These three-membered rings contain both silicon and nitrogen[91] *(Scheme* 65).

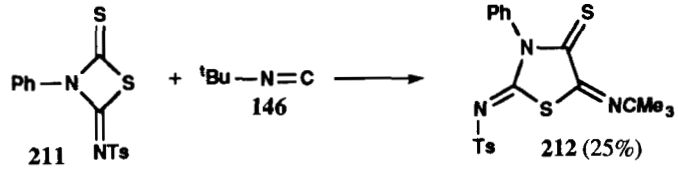


208

R^1 = Adamantyl, ^{t}Bu; R^2 = ^{t}Bu, Isooctyl 209 210

Scheme 65

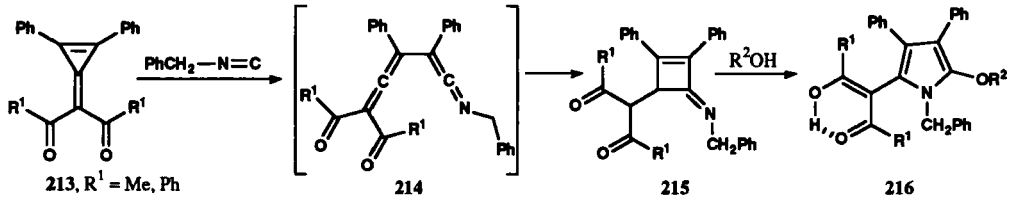
Upon treatment of the thiazete **211** with *tert*-butyl isocyanide **146**, the thiazole derivative **212** is obtained in 25% yield[92] *(Scheme* 66).



211 212 (25%)

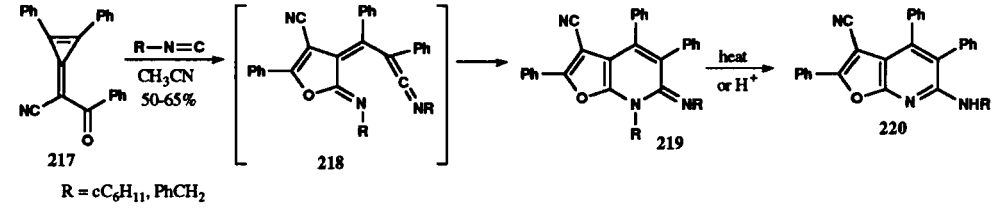
Scheme 66

The reaction of triafulvenes **213** with isocyanides in refluxing acetonitrile leads to the formation of 2-methylenecyclobutene-1-imines **215** in 50-75% yields.[93] Upon treatment of some of these compounds with alcohols or secondary amines, pyrrole derivatives **216** are obtained *(Scheme* 67).



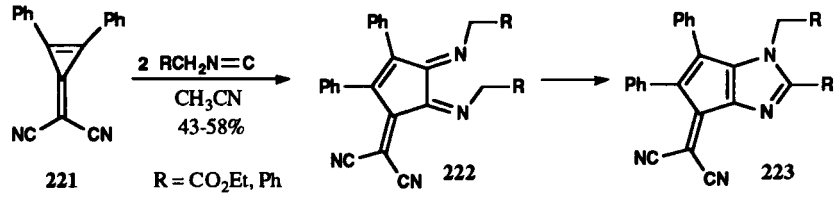
Scheme 67

Ring cleavage of substituted triafulvene **217** with isocyanides affords compounds **219** which are converted into furo[2,3-*b*]pyridines **220** upon heating or treatment with ethanolic hydrochloric acid[93] *(Scheme* 68).



Scheme 68

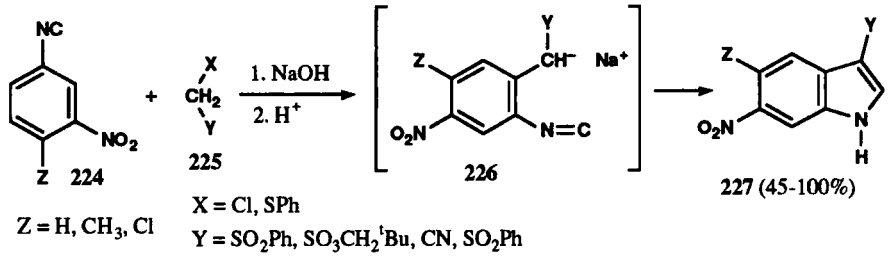
Upon treatment of the dicyano fulvene **221** with benzyl isocyanide or ethyl isocyanoacetate, fused imidazoles **223** are obtained, the reaction mechanism is discussed[93] *(Scheme* 69)



Scheme 69

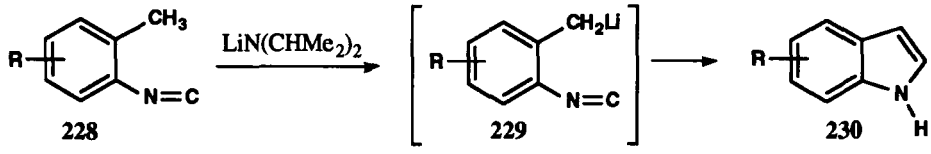
III. CYCLIZATIONS UNDER NUCLEOPHILIC ATTACK ON THE ISOCYANO GROUP

Carbanions bearing leaving groups react with *m*-nitrophenyl isocyanides **224** to form products of nucleophilic substitution of hydrogen which subsequently cyclize[94] to corresponding indoles **227** *(Scheme* 70).



Scheme 70

Treatment of *o*-methylphenyl isocyanides **228** with LDA gives cyclization to the corresponding indoles **230** in 82-100% yield[95] *(Scheme* 71). In addition, LDA-treated isocyanides **228** react with electrophiles, such as alkyl halides and alkylene oxides, to give *o*-alkylphenylisocyanides, which were lithiated and cyclized to afford 3-substituted indoles. 1-Substituted and 2,3-disubstituted indoles are obtained in a similar way.

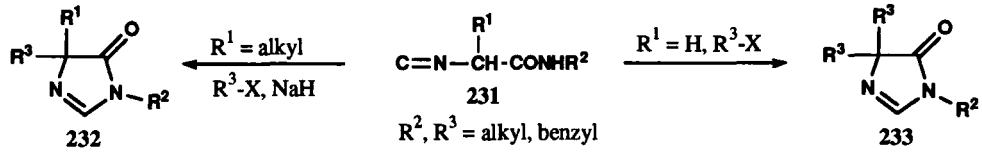


228 **229** **230**

R = H, 4-, 5-, 6-Me, 4-MeO, 4-Cl

Scheme 71

When *N*-monosubstituted isocyanoacetamide **231**, which is prepared by the amidation of methyl isocyanoacetate, is allowed to react with two equivalents of an alkylating agent such as alkyl halide in the presence of sodium hydride in tetrahydrofuran, the 4,4-dialkylated 1-substituted 5-oxo-4,5-dihydroimidazoles **232**, **233** are obtained in good yield[96] *(Scheme* 72).

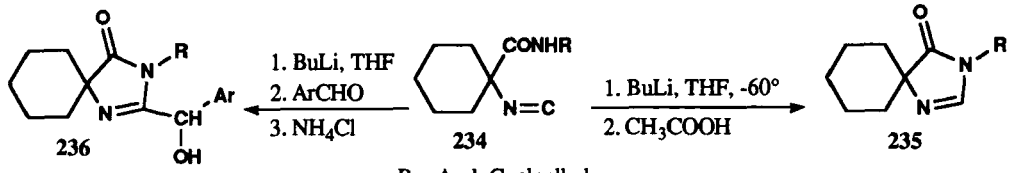


232 **231** **233**

R^2, R^3 = alkyl, benzyl

Scheme 72

The Ugi four-component condensation between cycloalkanones, isocyanides, and ammonium formate affords 1-formylamino-1-cyclohexane carboxamides which are converted into the corresponding isocyanides **234**. By cyclizing the obtained *N*-substituted 1-isocyano-1-cyclohexanecarboxamides **234** with *n*-butyllithium and then with acetic acid, 3-substituted 1,3-diazaspiro[4.5]dec-1-en-4-ones **235** are obtained.[16] The reaction takes place under very mild conditions to give the spiroimidazolones in high yield. If the solution containing the anion is treated first with aldehydes and then with acids, a series of 2-substituted spiroimidazolones **236** is obtained[97] *(Scheme* 73).



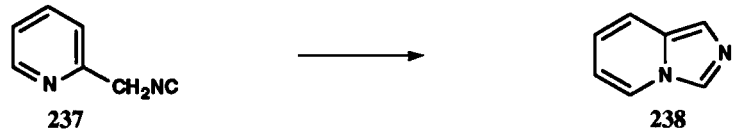
236 **234** **235**

R = Aryl, Cycloalkyl

Scheme 73

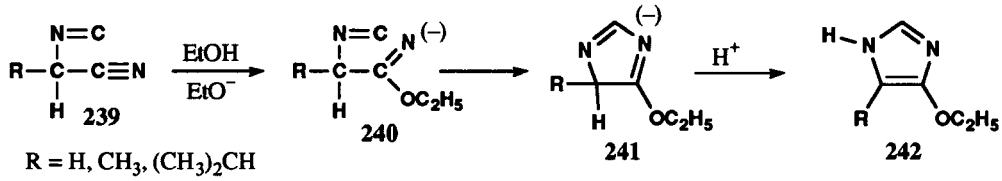
2-Isocyanomethylpyridine **237** shows a great tendency to cyclize to imidazo[1,5-*a*]pyridine **238**. The cyclization takes place upon treatment with bases and even spontaneously during its distilla-

tion[98] (*Scheme* 74).



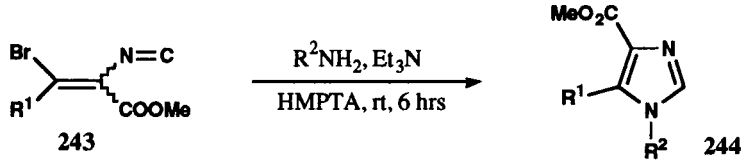
Scheme 74

2-Isocyanonitriles **239** undergo addition of ethanol to the cyano group. The primary adducts **240** cyclize[99] to 4-alkoxyimidazoles **242** (*Scheme* 75).



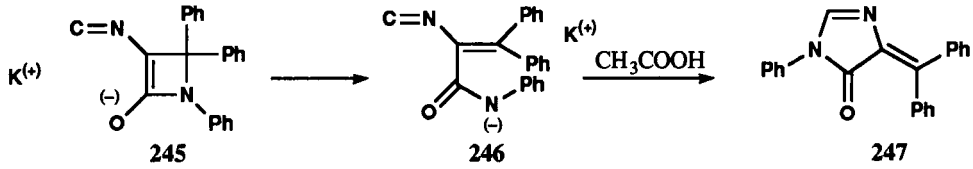
Scheme 75

Recently, an unequivocal synthesis of methyl 1,5-disubstituted imidazole-4-carboxylates **244** has been reported.[100] The above imidazoles are obtained, in 54-90% yields, by reacting primary amines with 3-substituted 3-bromo-2-isocyanoacrylates **243** (*Scheme* 76). This synthesis is noteworthy since only one alternative synthetic method is known.[101]



Scheme 76

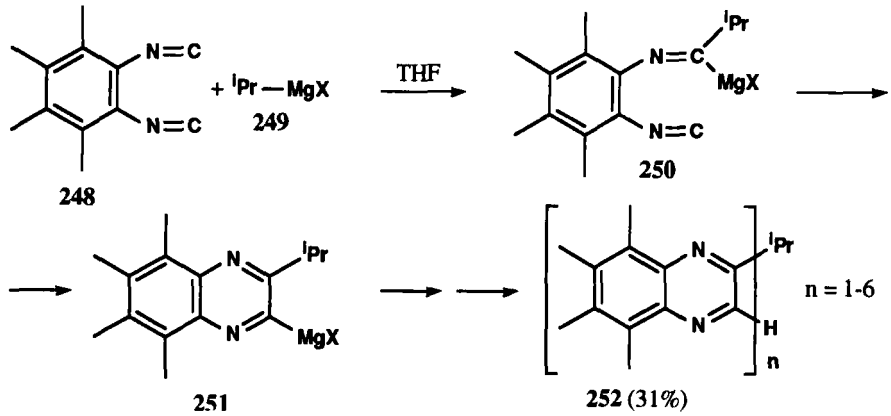
The potassium salt of the isocyanoazetidinone **245** shown below, upon standing and subsequent acidification cyclizes[102] to 4-diphenylmethylene-1-phenyl-2-imidazoline-5-one **247** through an intermediate anion **246** (*Scheme* 77).



Scheme 77

Polymerization reactions of isocyanides to heterocyclic compounds have been reviewed.[2] Recently the oligomerization of 1,2-diisocyanoarenes to quinoxaline oligomers has been reported.[103a,b]

These reactions have been recently reviewed.[104] Thus, the reaction of 1,2-diisocyano-3,4,5,6-tetramethylbenzene **248** and 0.33 equivalent of isopropylmagnesium halide **249** affords[103a] poly(2,3-quinoxaline) compounds **252** with 1 to 6 units of the quinoxaline monomer. Yields are low, and the mechanism is supposed to proceed *via* successive attacks of organomagnesium compound over an isocyanide group followed by cyclization *(Scheme* 78).



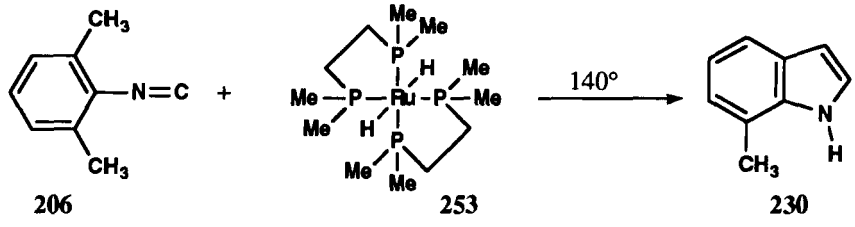
Scheme 78

A closely-related reaction has been conducted on the same diisocyanide and others, by using a palladium complex, $Me(PPhMe_2)_2PdBr$, in the place of organomagnesium compound. In this case, the overall yield of reaction is improved to 87%, which includes 49% trimer.[103b] Although the reaction occurs through nucleophilic attack on the isocyano group, this reaction is an example of a formal synthesis with isocyanide complexes, which are explained below.

IV. HETEROCYCLIC SYNTHESES WITH ISOCYANIDE COMPLEXES

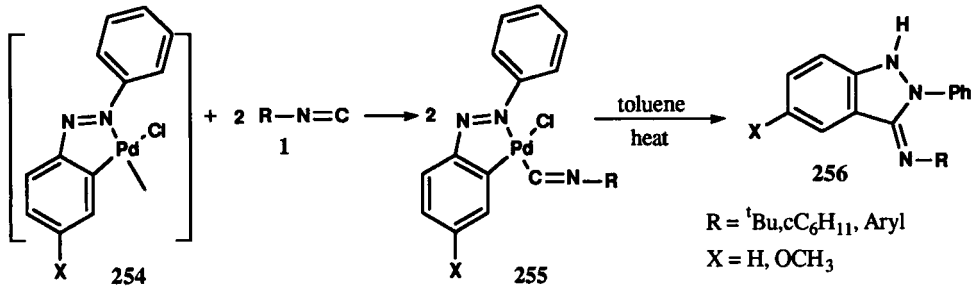
1. Catalytic Activation by Complexes

Catalytic activation of methyl group in 2,6-xylyl isocyanide can be accomplished by the use of a homogeneous organometallic ruthenium complex. Thermolysis of 2,6-xylyl isocyanide **206** in the presence of 1 equivalent of $Ru(DMPE)_2H_2$ (**253**) (140°, 24 hrs) in C_6D_6, in a sealed tube, results[105] in the conversion of the isocyanide into free 7-methylindole **230** *(Scheme* 79).



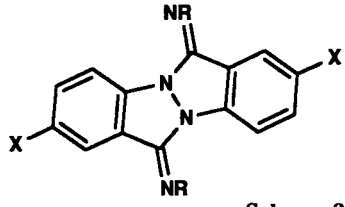
Scheme 79

Palladium and cobalt complexes are suitable catalysts for the preparation of some heterocyclic compounds such as indazoline and indazoles,[106] starting with isocyanides. The azobenzene complexes **254** shown below react with isocyanides to give complexes **255** which, upon heating at 100-130°, afford 3-imino-2-phenylindazolines **256** *(Scheme* 80).



Scheme 80

If azobenzene is reacted with isocyanides in the presence of $Co(CO)_8$, 6*H*,12*H*-indazolo[2,1-*a*]-6,12-diiminoindazoles **257** are obtained as well as indazolines *(Scheme* 81).



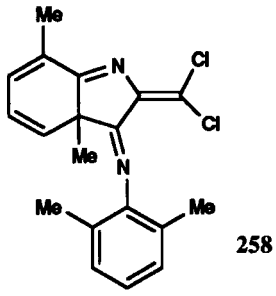
257

X = H, CH_3

R = ^{t}Bu, c-C_6H_{11}, Ar

Scheme 81

When carbon tetrachloride is added to a mixture of dicobalt octakis(2,6-xylyl isocyanide) and 2,6-xylyl isocyanide in benzene, the reaction gives the indolenine derivative **258** shown below.[107] Similar reactions occur to give the corresponding indolenine derivatives when other dicobalt octaisocyanides or carbon tetrabromide are used[107] *(Scheme* 82)



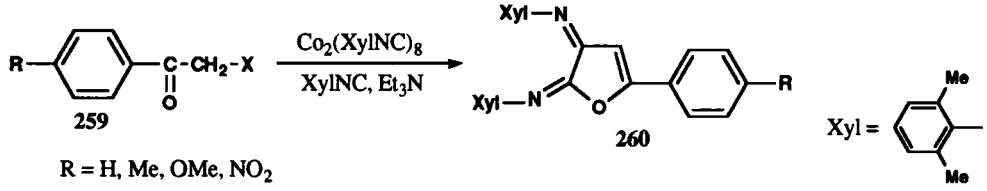
258

Scheme 82

Isocyanide palladium complexes undergo a [3+2] cycloaddition with nitrile imines to give 1,2,4-triazole derivatives.[108a,b] μ-(1,2-Diisocyanobenzene)*bis*(chlorogold) reacts with 1,2-diaminoben-

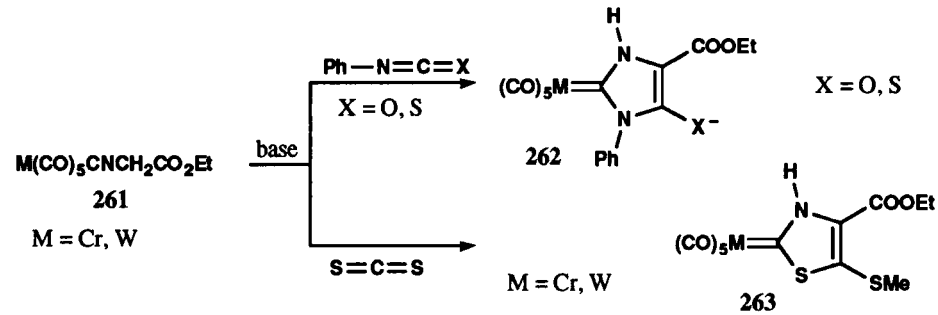
zene (1/1) to give benzimidazolin-2-ylidene(chloro)gold as the only reaction product.[108c]

The reaction of 2-bromoacetophenones **259** with 2,6-xylyl isocyanide in the presence of triethylamine and a cobalt complex such as $Co_2(XylNC)_8$, where Xyl = 2,6-xylyl, $CoBr_2(XylNC)_4$, $(Co[XylNC]_5)(PF_6)$ or Co(*acac*)$_3$, gave[109] 2,3-*bis*-*N*-(2',6'-xylyl)imino-5-phenyl-2,3-dihydrofuran **260**. A plausible mechanism is proposed, suggesting that a cobalt(I) isocyanide complex is the active species in the catalytic system (*Scheme* 83).



Scheme 83

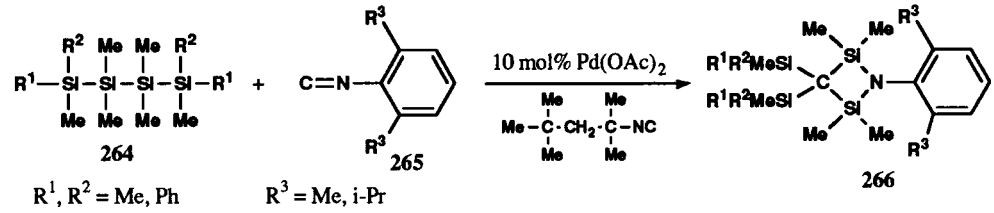
In the presence of bases (NEt_3, *t*-BuOK, *n*-BuLi) the isocyanoacetic ester ligand in pentacarbonyl chromium or tungsten complex **261** reacts with the heteroallenes PhN=C=O and PhN=C=S regio- and site-selectively to give[110a] the 1,3-imidazolin-2-ylidene complexes **262**, and with CS_2 to give[110b] 1,3-thiazolin-2-ylidene complexes **263**, the exo-sulfur function of which is methylated.



Scheme 84

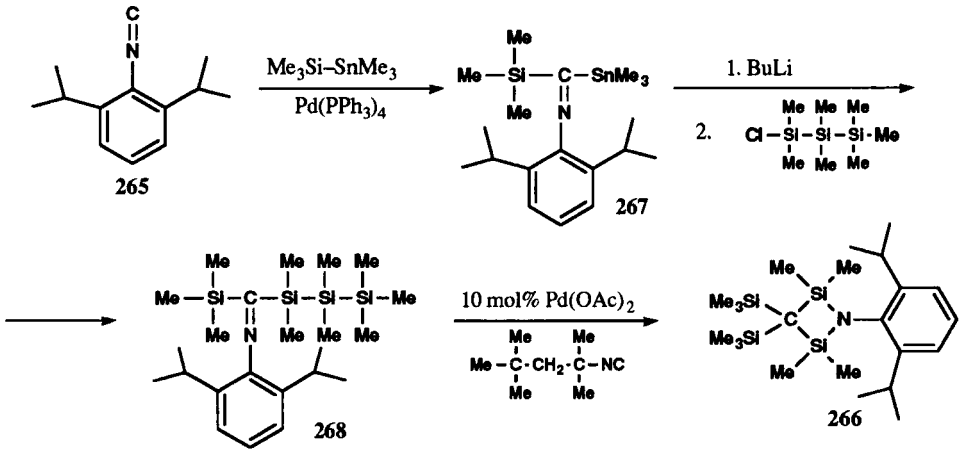
The exocyclic olate and thiolate functions have been alkylated and acylated. The reactions can be considered as formal α-metalated isocyanide [3+2] cycloaddition reactions of the isocyanide ligand moiety of the complex, which are explained below.

Metallation of isocyanides can be achieved by an insertion of isocyanides into metal-metal or metal-carbon linkage of a variety of organometallic compounds giving the corresponding *N*-substituted (α-iminoalkyl)metal compounds. These reactions have been recently reviewed.[104] In addition, isocyanides insert into silicon-tin or silicon-silicon bonds in reactions catalyzed by palladium complexes, giving in some cases heterocyclic compounds. Thus, 2,6-disubstituted isocyanobenzenes react with tetrasilanes **264** in the presence of 10 mol% of $Pd(OAc)_2$ and an isocyanoalkane, affording[111a] disilaazetidine derivatives **266** (*Scheme* 85).



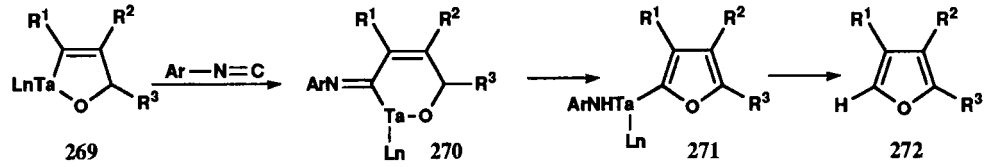
Scheme 85

The reaction has been conducted stepwise. Thus, a 2,6-disubstituted isocyanobenzene **265** reacts with a silastannane compound under palladium complex catalysis. The corresponding insertion compound **267** is then lithiated, reacted with the appropriate chlorosilane derivative, and the obtained product **268** reacted with 10 mol% of palladium diacetate and the second isocyanide, affording a similar disilaazetidine derivative **266** in 43% yield *(Scheme* 86).



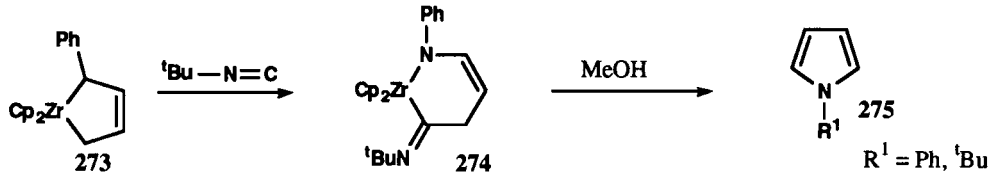
Scheme 86

Insertion of isocyanide into metal-carbon bonds is a typical method for introducing one carbon unit into organometallic compounds. Recently, Takai and co-workers reported a regioselective synthesis of substituted furans **272** by treatment of tantalum-alkyne complexes with aldehydes, followed by addition of an isocyanide. Insertion of the isocyanide into the carbon-tantalum bond, and rearrangement of the intermediate complex **270**, affords[111b] tantalofuran derivatives **271** *(Scheme* 87).



Scheme 87

In the same way, 1-azadiene complexes of zirconocene, best described as 1-zircona-2-azacyclopent-3-enes **273**, insert *tert*-butyl isocyanide into the carbon-zirconium bond, affording a mixture of *N*-substituted pyrroles **275** on work-up with methanol[111c] *(Scheme* 88).



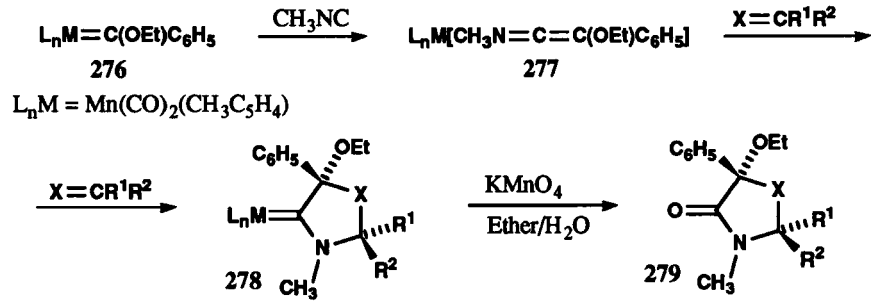
Scheme 88

2. Heterocyclic Syntheses *via* Ketenimine Complexes

A different possibility of cycloadditions or cyclizations using transition metal complexes and isocyanides is given by the formation of ketenimine complexes prior to cyclization with dipolarophiles or another isocyanide molecule. Ketenimine (or 1-alkenylideneamine) complexes are readily available in great variety by reaction of isocyanides with carbene complexes. They have proven to be useful building blocks in new synthetic approaches to carbocyclic and *N*-heterocyclic four-, five-, and six-membered rings. These reactions have been recently reviewed by Aumann.[112] A brief summary and some important and new reactions are shown below. The reactions involve metal-induced bond formation patterns of the ketenimine ligands, which can be influenced across a wide range by varying the metal, the ligands, and the three substituents on the N=C=C unit.

By reacting isocyanides with carbene or carbyne complexes[113a] or by treating isocyanide complexes with carbene sources, such as diazoalkanes,[113b] ketenimine complexes with different substitution patterns can be prepared. The 1,3-dipolar properties of ketenimine complexes made [3+2] cycloaddition reactions possible with aldehydes or isocyanates, affording oxazolidine or imidazolidine complexes, respectively. These conversions can be carried out as three-component reactions without isolation of the intermediate ketenimine complexes. Oxidative decomposition of the obtained complexes with heterocyclic ligands allows free heterocycles to be obtained in good yield.

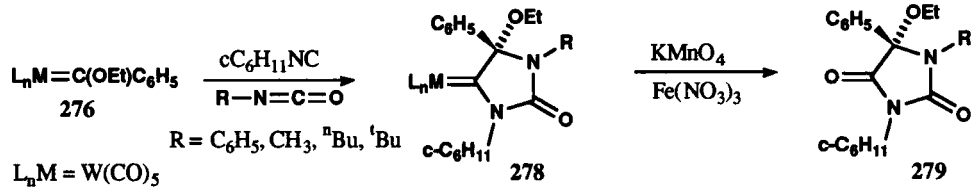
Aminocarbene manganese complexes **278** with heterocyclic ligands (oxazole, thiazole, imidazole) are obtained[114] by three-component reactions of a carbene manganese complex **276** with methyl isocyanide and a variety of unsaturated substrates $R^1R^2C{=}X$ (R^1, R^2 = H, CH_3, C_6H_5, O, S, NC_6H_5), (X = O, S, NCH_3, NC_6H_5). The C=C=N ligand of the formed intermediate ketenimine complex **277** adds to polarized C=X bonds like a 1,3-dipole *(Scheme* 89).



Scheme 89

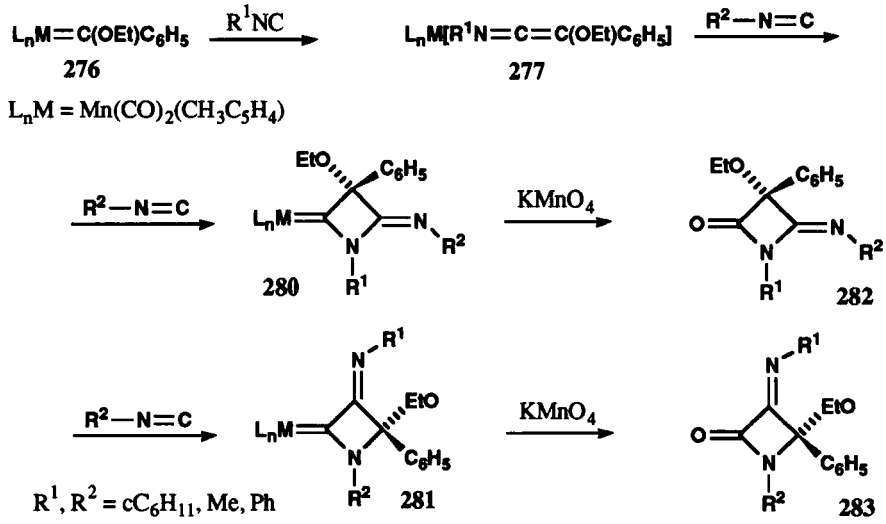
The heterocyclic ligands may be disconnected by oxidation with $KMnO_4$ in water/ether; oxazolidinones, thiazolidinones and imidazolidinones **279** are obtained by this method.

A pentacarbonyl tungsten carbene complex is used instead of manganese complex in reactions with isocyanides and aldehydes.[115] The same system is used with isocyanates. Thus reaction between cyclohexyl isocyanide with $(CO)_5W{=}C(OEt)C_6H_5$ and isocyanates affords imidazolidinylidene complexes **278** by a three-component condensation. On oxidative decomposition with $KMnO_4/Fe(NO_3)_3$ gives the previously inaccessible 5-ethoxyhydantoins **279** in high yields[116] *(Scheme* 90).



Scheme 90

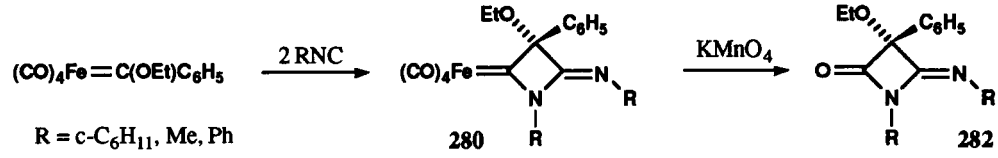
Ketenimine complexes add to isocyanides to yield four- and five-membered *N*-heterocycles. The construction of four-membered *N*-heterocycles from isocyanides and ketenimine complexes is interesting for synthetic purposes. Four-membered *N*-heterocycles can be constructed from isocyanides and ketenimine complexes through [3+1], [2+2], and [1+1+2] cycloadditions. Both [3+1] and [2+2] cycloaddition reactions are competitive, yielding regioisomers under different reaction conditions.[117] The formation of product from [2+2] cycloaddition is favored by higher reaction temperatures. Thus 4-imino and 3-imino-2-azetidinones **282, 283** can be obtained in good yields from isocyanides and manganese carbene complex **276** and subsequent decomposition with $KMnO_4$ in water/ether *(Scheme* 91).



Scheme 91

The reaction between carbene complexes X=C(OEt)Ph [X = $(CO)_5Cr$, $(CO)_5W$], isocyanides, and 1-diethylamino-1-propyne affords azetidinones and 2,3-dihydroazete complexes of the above methods.[118]

A further possibility for the synthesis of azetidines from carbene complexes and isocyanides involves a metal induced [1+1+2] cycloaddition. Tetracarbonyl(α-ethoxybenzylidene)iron reacts with two equivalents of alkyl isocyanides at 20° to give 3-iminoazetidinylidene complexes **280**. From these complexes 4-imino-2-azetidinones **282** are obtained[119] in high yields with $KMnO_4$ in water/benzene (*Scheme* 92).

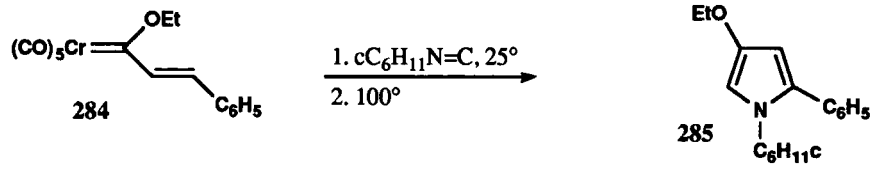


Scheme 92

Arylketenimine complexes of Cr, Mo and others can react with aryl isocyanides through a [4+1] cycloaddition reaction. By means of these reactions, 3-amino-2-aroyl (or acyl)indoles, 2-alkylideneindolenines and pyrazinodiindoles are obtained[120] in addition of azetidines, depending on the substituents at the aryl group of isocyanide. Electron-rich aryl isocyanides favor the formation of indoles, electron-poor aryl isocyanides the formation of azetidines.

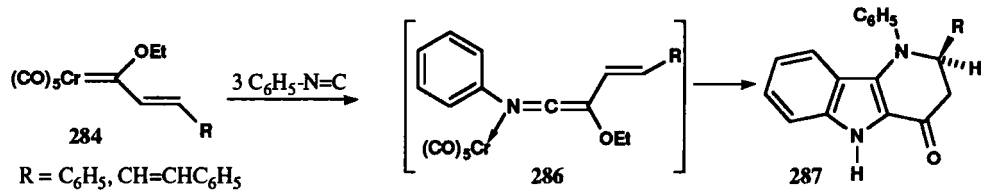
As an extension of the previous methodology, the reaction between alkenylcarbene complexes **284** and alkyl isocyanides affords 1-aza-1,2,4-pentatriene or 1-aza-1,2,4,6-heptatetraene complexes,[121] which are suitable as building blocks for syntheses of pyrroles **285** (*via* an intramolecular cycloaddi-

tion), carbocyclic five- (*via* [4+1] cycloaddition) or six-membered rings (*via* [4+2] cycloaddition) as well as 3-imidazolines (*Scheme* 93).



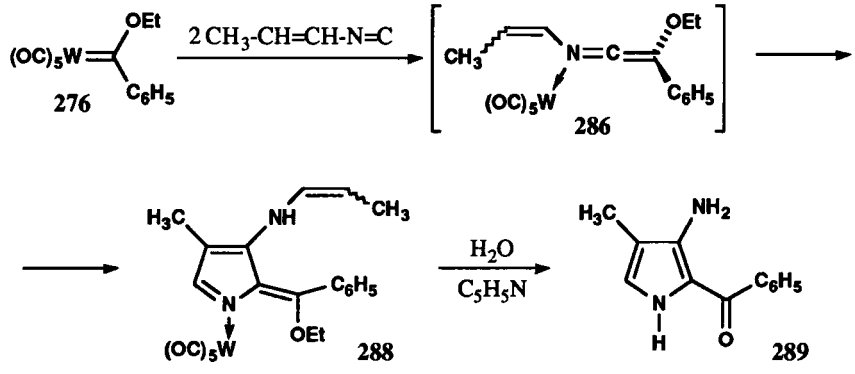
Scheme 93

When alkenyl- or dienylcarbene complexes **284** react with phenyl isocyanide **72** δ-carbolinones **287** are obtained[122] (*Scheme* 94).



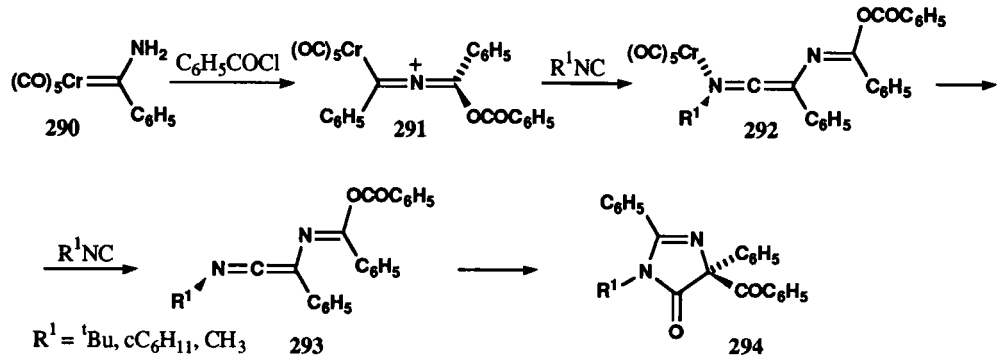
Scheme 94

Pyrroles **289** are also obtained by reaction between alkenyl isocyanides **279** and carbene complexes of tungsten **276**, through an *N*-alkenylketenimine complex **286** as intermediate[123] (*Scheme* 95).



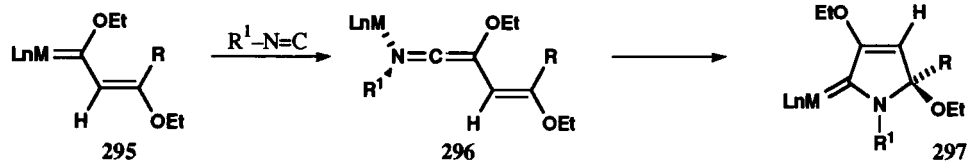
Scheme 95

Coupling of alkyl isocyanides with (alkylideneamino)carbene chromium complexes **290** affords *C*-(alkylideneamino)ketenimines[124] (1,4-diaza-1,2,4-pentatrienes) **293**, that are thermolabile in solution and spontaneously isomerize to give mainly 2-imidazolin-5-ones **294** (*Scheme* 96).



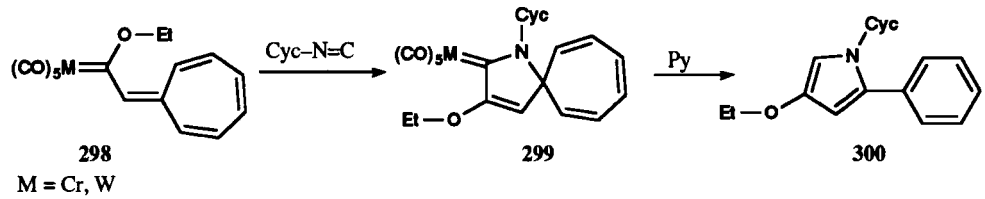
Scheme 96

On the other hand, 2*H*-pyrrole complexes **297** can be obtained by reaction of 1-metalla-1,3-diene systems.[125a,b] A stepwise insertion of alkynes and isocyanides into M=C bonds of carbene chromium or tungsten complexes **295** affords[125a] 1-aza-1,2,4-pentatriene complexes **296**, which are open-chain precursors of the synthesized 2*H*-pyrrole complexes **297** *(Scheme* 97).



Scheme 97

Heptafulvenylcarbene complexes of chromium and tungsten **298** add isocyanides *via* labile ketenimines, which cyclize spontaneously with formation of azaspiro compounds **299**. Pyridine-induced ligand cleavage leads[125b] under ring contraction to the corresponding pyrrole **300** *(Scheme* 98).



Scheme 98

V. HETEROCYCLIC SYNTHESES USING α-METALATED ISOCYANIDES

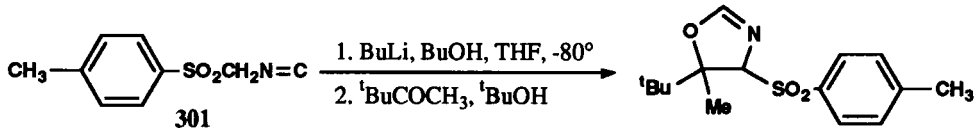
α-Alkali metalated isocyanides, which can be obtained from alkyl isocyanides and bases, were discovered by Schöllkopf and Gerhart[126] in 1968. α-Metalated isocyanides are very valuable organic reagents in heterocyclic synthesis because they possess a nucleophilic center, the metalated carbon atom, which can add to polar multiple bonds, and an electrophilic center, the isocyanide carbon atom, which makes subsequent heterocyclization possible. Being both nucleophilic and electrophilic,

α-metalated isocyanides add not only to polar double bonds, but also to ambivalent 1,3-dipoles, forming heterocycles. Because α-metallation of activated methylene isocyanides is accomplished with the usual bases employed in anion chemistry such as buthyllithium, potassium *tert*-butoxide, sodium methoxide, sodium hydride, DBU or triethylamine, the possible reaction conditions are very varied, allowing optimization in many cases, and considerably expanding the scope of the methodology. The importance of α-metalated isocyanides for organic and heterocyclic synthesis has been shown by two consecutive reviews,[127,3] which describe and systematize procedures for the preparation of 2-oxazolines, 2-imidazolines, 2-thiazolines, oxazoles, thiazoles, triazoles, imidazolinones and 2-imidazolidinones, pyrroles, 5,6-dihydro-1,3-oxazines and -thiazines, and 4,5,6,7-tetrahydro-1,3-oxazepines.

A brief summary of the recent advances in the synthesis of these heterocycles and some other new ones is given in the following section.

1. Reaction of α-Metalated Isocyanides with Aldehydes. Synthesis of Oxazolines

Reaction between α-metalated isocyanides and aldehydes or ketones affords 2-oxazolines. Intermediates are known to be carbonyl adducts which are transformed into 2-oxazolines on addition of a proton donor such as water or an alcohol. Some recent examples of the oxazoline route are given[128a-b] by van Leusen *et al (Scheme* 99).



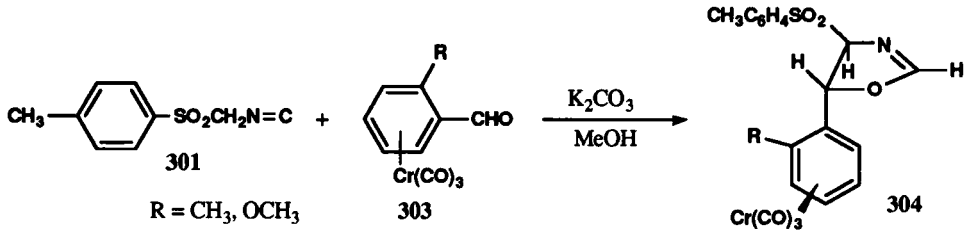
301 302

Scheme 99

Obtained oxazoline **302** is then converted[128a] to isomeric unsaturated isocyanides and 2,3,3-trimethylbutanenitrile. The reaction has been used for the synthesis of progesterone in 93% overall yield in three steps from 17-[(*E*)isocyano(tosyl)methylene]-3-methoxyandrosta-3,5-diene, obtained by the oxazoline procedure.[128b]

When α-metalated isocyanides add to aldehydes or ketones, two new chiral centers are formed. Asymmetric induction plays, in these reactions, a vital role for the stereoselective synthesis of chiral oxazolines. Diastereoselectivity in the synthesis of oxazolines has been reached by the use of three different approaches. The use of a chiral aldehyde is the first. An efficient stereoselective synthesis of 2-amino-2-deoxy-*D*-arabinose and 2-deoxy-*D*-ribose is accomplished by the nucleophilic addition of ethyl isocyanoacetate to 2,3-*O*-isopropylidene-*D*-glyceraldehyde with high *erythro*-selectivity. Subsequent intermolecular cyclization gives a *trans*-oxazoline derivative converted to sugar compounds.[129]

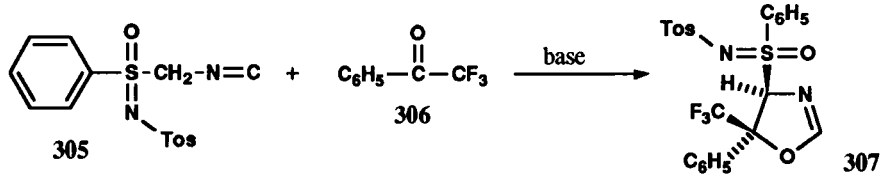
Chirality has been introduced into aromatic aldehydes by the use of chiral arene-chromium-tricarbonyl complexes of *ortho*-substituted benzaldehydes **303**, that are employed in additions to isocyanides. Thus, by reacting equimolecular quantities of tosylmethyl isocyanide (TOSMIC) and the chiral aldehyde complexes with K_2CO_3 in methanol, oxazolines **304** are obtained with more than 98% asymmetric induction[130a,b] *(Scheme* 100)



Scheme 100

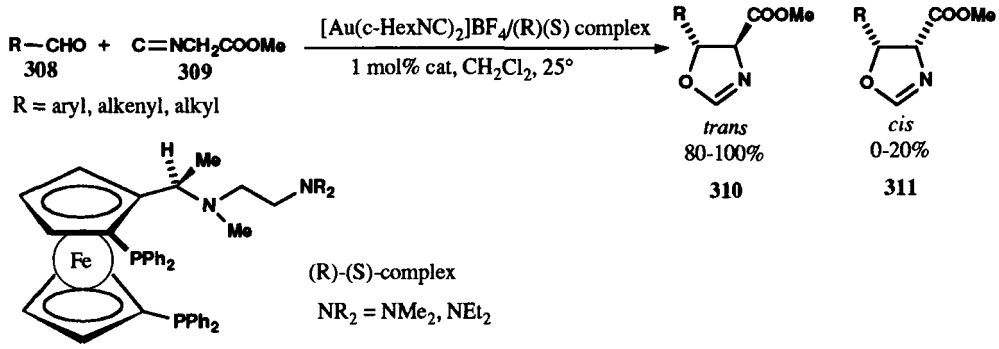
The obtained oxazolines are used as a route to optically pure amino alcohols, after $LiAlH_4$ reduction. The method establishes a convenient access to various optically pure halostachine analogues of (*R*) and (*S*) configuration, starting from an optically pure η^6(*o*-tolualdehyde)-chromium-tricarbonyl complex.[130b]

The second pathway to asymmetric induction is given by the use of chiral analogues of tosylmethyl isocyanide. TOSMIC reacts with ketones to produce racemic 2-oxazolines.[131,132] Chiral analogues of TOSMIC in which the *p*-tolyl group is replaced by a chiral entity or modified in the SO_2 group into a chiral functionality have been synthesized. When these chiral analogs are used in base-mediated cycloadditions to acetophenones, diastereomeric 2-oxazolines **307** are obtained.[133] The highest asymmetric induction (80%) is obtained with *S*-phenyl-*N*-tosylsulfonimidoylmethylisocyanide **305** and α,α,α-trifluoroacetophenone **306**, showing that a chiral center next to the reactive methylene is more efficient than remote chirality *(Scheme* 101).



Scheme 101

The third route to the stereoselective synthesis of oxazolines has been developed by Ito, Sawamura and Hayasi. They have found a different way to obtain optically active 2-oxazolines by the use of a chiral catalyst. As they reported, a chiral ferrocenylphosphine-gold(I) complex catalyzes the asymmetric aldol reaction of methyl isocyanoacetate **309** with various types of aldehydes **308**, producing optically active 5-alkyl-2-oxazoline-4-carboxylates **310**, **311** with high enantio- and diastereoselectivity which are useful synthetic intermediates to optically active β-hydroxy-α-aminoacids and their derivatives[134] *(Scheme* 102).

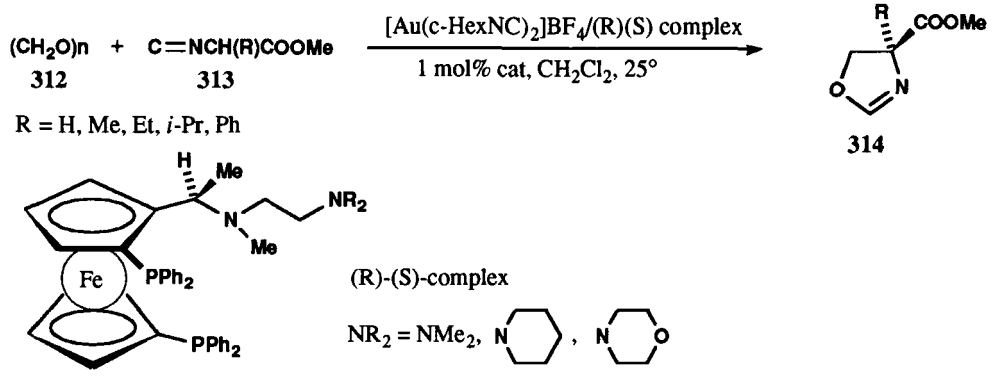


Scheme 102

The highest enantioselectivity (>90%) and trans selectivity (>97%) were observed in the reaction of secondary and tertiary alkyl aldehydes. Overall yields of oxazolines were 83-100%. The gold catalyst was also effective for the reaction of α,β-unsaturated aldehydes to give the corresponding oxazolines of 87% e.e. and 95% e.e. respectively.

Further modification of the ferrocenylphosphine ligands by introducing 2-morpholino or piperidino group at the terminal position of the ferrocene side chain improves both enantio- and diastereoselectivity.[135,136] The ratios of *trans/cis* oxazolines and enantiomeric purities of *trans*-oxazolines obtained in the reaction of methyl isocyanoacetate with gold-(*R*)-(*S*)-catalyst and some aldehydes are as follows: PhCHO: 95/5, 98% e.e., MeCHO, 93/7, 90% e.e., *i*-PrCHO, >99/1, 96% e.e.

In the same way, aldol reaction of methyl α-isocyanocarboxylates CNCH(R)COOMe (**313**), R = H, Me, Et, i-Pr, Ph, with paraformaldehyde **312** in the presence of 1 mol% of the chiral (aminoalkyl)ferrocenylphosphine-gold(I) complex gives optically active 4-alkyl-2-oxazoline-4-carboxylates **314** (up to 83% e.e.) which were readily hydrolyzed to α-alkylserines,[137] α-alkyl-β-phenylserines,[138] and α-alkylthreonines (*Scheme* 103).



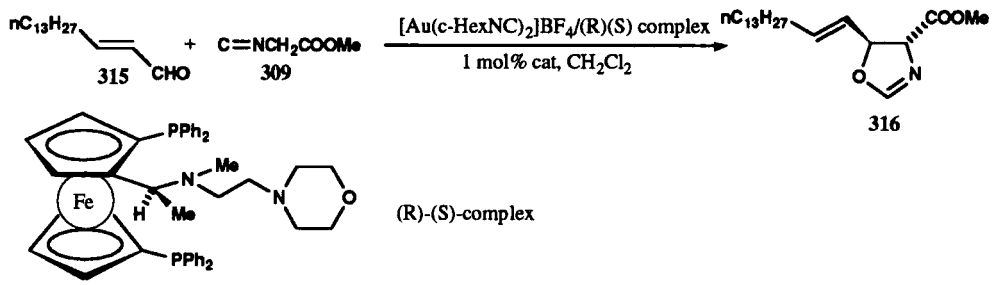
Scheme 103

The same Au(I)/(*R*)-(*S*)-complex (NR_2 = piperidino, morpholino) has been applied successfully to the asymmetric aldol reaction of *N,N*-dialkyl-α-isocyanoacetamides with primary aldehydes,

to obtain *trans*-5-alkyl-2-oxazoline-4-carboxamides of up to 98.6% e.e., which are converted into optically active *threo*-β-hydroxyamino acids.[139]

In the same conditions, α-ketoesters (RCOCOOMe, R = Me, *i*-Bu, Ph) react with methyl isocyanoacetate or *N,N*-dimethyl isocyanoacetamide giving the corresponding oxazolines of up to 90% e.e., which are converted into optically active β-alkyl-β-hydroxyaspartic acid derivatives.[140]

Asymmetric aldol reaction of methyl isocyanoacetate **309** with (*E*)-2-hexadecenal **315** in the presence of 1 mol% of the diastereomeric gold(I) [(*S*)-(*R*)]complex gives optically active *trans*-4-(methoxycarbonyl)-5-((*E*)-1-pentadecenyl)-2-oxazoline **316** (93% e.e.) which was readily converted into *D-threo*- and *erythro*-sphingosines[141] *(Scheme* 104).



Scheme 104

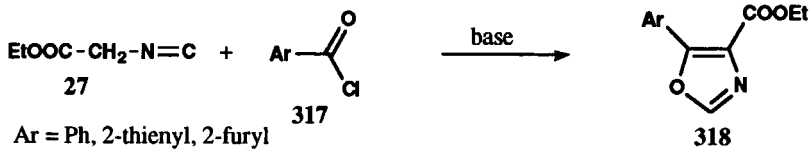
After some other variations in the gold(I)-catalyzed aldol reaction,[142a,b] the same group has recently reported that high stereoselectivity (over 80% e.e.) is also obtained in the silver(I)-catalyzed asymmetric aldol reaction of methyl isocyanoacetate with aldehydes in the presence of a chiral (aminoalkyl)ferrocenylphosphine-silver(I) [(*R*)-(*S*)]complex.[143] In addition, the silver-catalyzed reaction of tosylmethyl isocyanide has been reported by this group.[144] At the moment, nineteen optically active ferrocenylbisphosphine ligands containing various 2-(dialkylamino)ethylamino groups on the ferrocenylmethyl position are prepared and tested in the gold(I) catalyzed asymmetric aldol reaction between aldehydes and methyl isocyanoacetate. Best results are obtained whith the morpholino derivative as the ligand to give optically active *trans*-oxazolines, the stereoselectivities being among the highest observed in asymmetric carbon-carbon bond forming reactions.[145]

A large effort has been made by Togni and Pastor to words ascertaining the nature of the stereoselective step in the gold(I)-catalyzed aldol reaction.[146-151] Enantioselectivity in the gold(I)-catalyzed aldol reaction with chiral ferrocenylamine ligands is strongly dependent upon both the steric and electronic effects of the substrates.[147] In the reaction of pyridine-2-, 3-, and 4-carbaldehydes with ethyl isocyanoacetate, different enantioselectivities are observed in the formation of the *cis*- and *trans*-oxazolines, due to electronic effects. As they demonstrated, the central chirality of the stereogenic carbon atom in the ferrocenyl side chain strongly affects the resultant product stereochemistry. Optimum diastereo- and enantio-selectivity is obtained for the *trans*-oxazoline when the ferrocenylamine ligand has opposite planar and central chirality.[149] Some other studies confirm the mechanistic

pathways of the reaction.[150a] This constitutes the first example in a chiral transition-metal ligand containing both central and planar chirality of internal cooperativity of chirality in the control of product diastereo- and enantioselectivity.[150b] The conclusions about cooperativity of chirality in homogeneous catalysis in the gold(I)-catalyzed aldol reaction heve been recently reviewed.[151] Other chiral ferrocenyl ligands have been synthesized in order to compare the stereoselectivity of the reaction.[152] The lower diastereo- and enantioselectivity obtained using different ligands is consistent with the transition-state model proposed for the stereoselective step of the reaction.

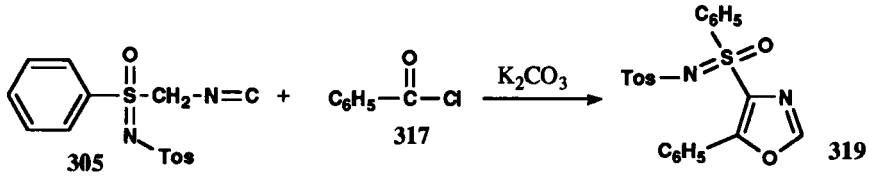
2. Reaction of α-Metalated Isocyanides with Acylating Agents. Synthesis of Oxazoles, Thiazoles and Related Compounds

Oxazoles are formed on treatment of α-metalated isocyanides with acylating agents[153] such as acyl chlorides, esters, *N,N*-dialkylamides, or imidazolides, in the presence of bases. By reaction of ethyl isocyanoacetate **27** and acyl chlorides **317**, oxazoles **318** are obtained, some of them show pharmacological activity as platelet aggregation inhibiting agents[154] *(Scheme* 105).



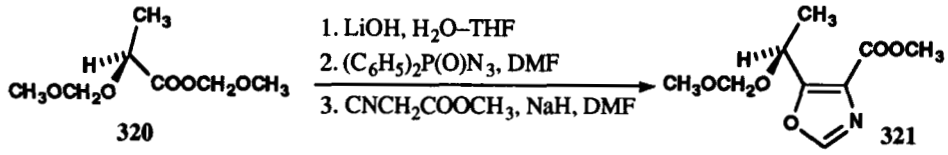
Scheme 105

Cycloaddition of (*p*-toluensulfonyl)methyl isocyanides[131] or (*N*-methyl-*S*-phenylsulfonylimidoyl)methyl isocyanide[155] with benzoyl chloride or acetic anhydride and a base produces substituted oxazoles **319** *(Scheme* 106).



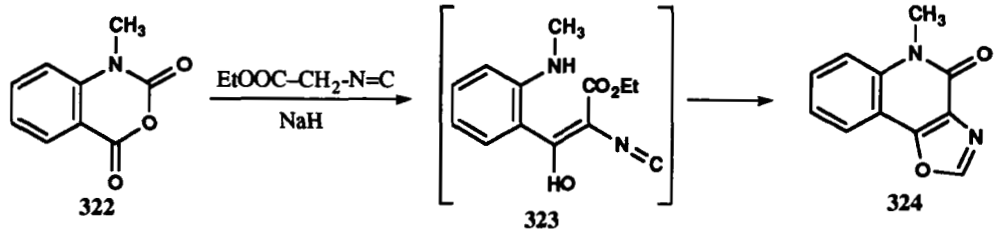
Scheme 106

Sometimes other acylating agents have been used. Diphenyl phosphorazidate can be used efficiently for the direct *C*-acylation of methyl isocyanoacetate with carboxylic acids to give 4-methoxycarbonyl oxazoles. The reaction has been succesfully used for the synthesis of prumicin,[156] a 2,4-diamino sugar antibiotic, *L*-daunosamine,[157a] the carbohydrate component of a group of anticancer anthracycline antibiotics, and a derivative of *L*-vancosamine,[157b] a carbohydrate component of the antibiotics vancomycin and sporaviridin. In a typical reaction sequence, a lactic acid derivative **320** is treated with lithium hydroxide, and the lithium salt is treated with diphenyl phosphorazidate followed by the addition of the sodium salt of methyl isocyanoacetate, giving an oxazole derivative **321**, converted to *L*-daunosamine *(Scheme* 107).



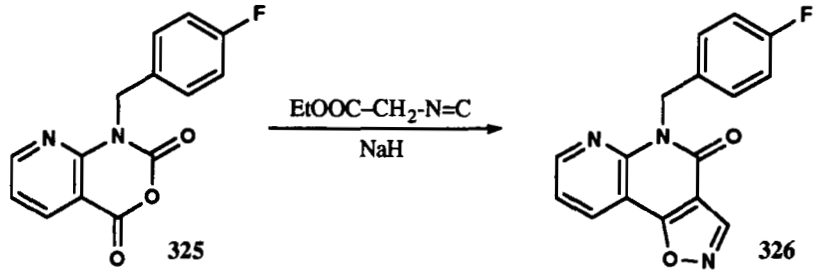
Scheme 107

There are two conflicting reports concerning to the chemistry of 2*H*-3,1-benzoxazine-2,4(1*H*)-dione (isatoic anhydride) and derivatives on their reactions with metalated ethyl isocyanoacetate.[158a,b] When *N*-methylisatoic anhydride **322** is treated with the sodium salt of ethyl isocyanoacetate, the 5-methyloxazolo[4,5-*c*]quinolin-4(5*H*)-one **324** is obtained[158a] *(Scheme* 108).



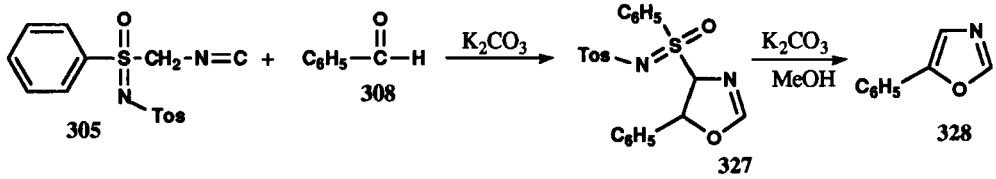
Scheme 108

On the other hand, when *N*-(4-fluorobenzyl)-3-azaisatoic anhydride **325** is treated with metalated ethyl isocyanoacetate, a tricyclic isoxazole **326** is obtained[158b] instead of the corresponding oxazole *(Scheme* 109). The mechanism of isomerization is not given.



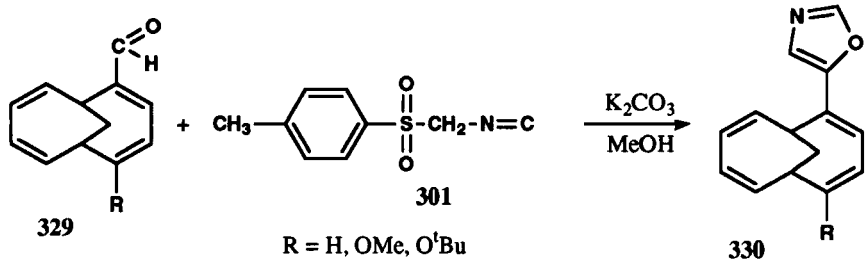
Scheme 109

Oxazoles are sometimes obtained by reaction of aromatic aldehydes and α-metalated isocyanides bearing leaving groups.[131a] Reaction between benzaldehyde **308** and an arylsulfonimidoylmethylisocyanide **305** gives[155] 5-phenyloxazole **328** *via* the unstable 4-sulfonimidoyl-2-oxazoline **327**, by elimination of PhS(O)NKTos *(Scheme* 110).



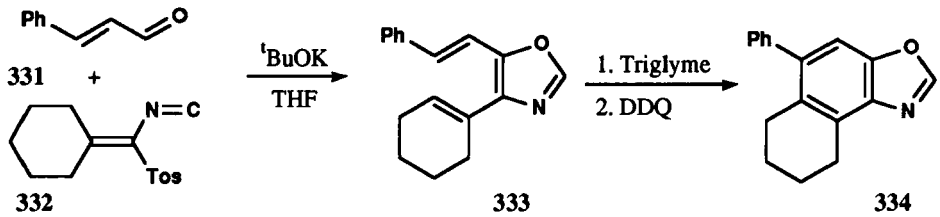
Scheme 110

The reaction between tosylmethyl isocyanide **301** and substituted 1,6-methano[10]annulene-2-carbaldehyde **329** in the presence of potassium carbonate affords[159] the corresponding oxazolylannulenes **330** *(Scheme* 111).



Scheme 111

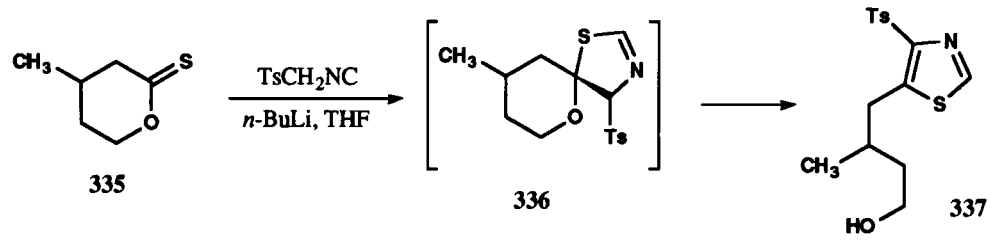
The base-induced cycloaddition of 1-tosylalk-1-enyl isocyanides **332** to α,β-unsaturated aldehydes **331** affords dialkenyloxazoles **333**, which are converted to benzoxazoles **334** *via* thermal electrocyclic ring closure[160] *(Scheme* 112).



Scheme 112

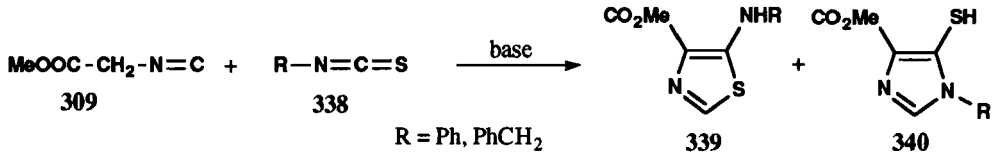
This benzoxazole synthesis involves the construction of a benzene ring on to a preformed azole, which is a reversal of the classical approach.

The reaction of thioacylating agents with α-metalated isocyanides affords thiazoles. Isocyanomethyllithium reacts with carbon disulfide, affording 5-(methylthio)thiazole, by cyclization of $CNCH_2CS_2Li$ followed by methylation with iodomethane.[161] The lithioderivative of TOSMIC reacts with the highly electrophilic C=S bond of a thionolactone **335** to provide a thiazolic alcohol **337** used[162] as starting material for the synthesis of terpenes of the menthane and eremophilane class *(Scheme* 113).



Scheme 113

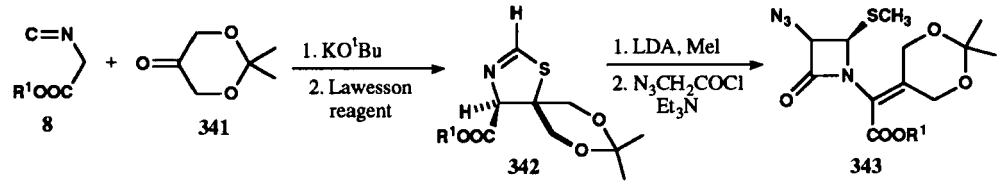
When methyl isocyanoacetate **309** is reacted with phenyl isothiocyanate **338**, a thiazole ester **339** is obtained[163] in good yield as main product, in addition of a minor amount of an imidazole derivative **340**. In a similar reaction of the isocyano ester and benzyl isothiocyanate, the thiazole derivative is obtained as the single product *(Scheme* 114).



Scheme 114

When benzyl isocyanate is used instead of isothiocyanate, the corresponding oxazole is obtained in low yield, showing less synthethic utility.

Beta-lactams can be obtained from α-metalated isocyanides. In a sequence of studies directed toward the total synthesis of 1-oxacephalosporins,[164] racemic *trans*-3-benzoylamino-4-methylthio-2-azetidinones are obtained from 2,2-dimethyl-1,3-dioxan-5-one **341**, alkyl isocyanoacetates **8** and azidoacetyl chloride. The synthesis starts with the addition of α-metalated isocyanide onto the ketone. The addition product is then converted to a thiazoline **342** with Lawesson's reagent. Then the thiazoline is opened to give an intermediate imide which is reacted with azidoacetyl chloride to give azetidinone **343**. The formed 3-acylamino-4-methylthio-2-azetidinones are then converted to 1-oxacephems in several steps *(Scheme* 115).



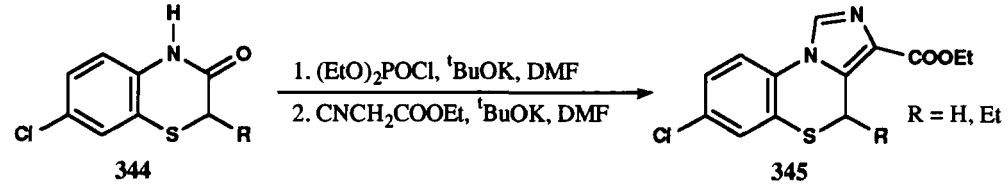
Scheme 115

Analogously, (±)-*trans*-7-benzoylamino-3-carbamoyloxymethyl-1-oxa-3-cephem-3-

carboxylate is constructed from 1,3-dihydroxyacetone, methyl isocyanoacetate, and azidoacetyl chloride in 10 steps.

3. Reaction of α-Metalated Isocyanides with Imines. Synthesis of Imidazoles and Related Compounds

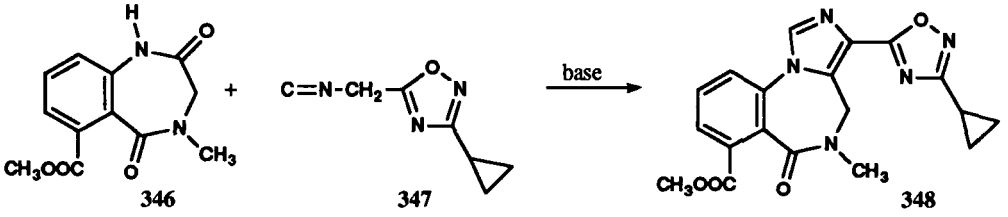
α-Metalated isocyanides can also add to the carbonyl analogous imine group, giving 2-imidazolines[3] and to carbodiimides or nitriles, giving imidazoles.[3] Imidazoles are often obtained from imidazolines by elimination of leaving groups. Because imidazoles possess potential pharmacological activity, their synthesis is of interest. Fused imidazoles are obtained by addition of α-metalated isocyanides to heterocyclic amides or their derivatives. Thus, iminophosphate derivatives of benzothiazines, generated *in situ* from 2*H*-1,4-benzothiazin-3(4*H*)-ones **344**, react with the anion of ethyl isocyanoacetate, to give the 4-*H*-imidazo[5,1-*c*][1,4]benzothiazine derivatives **345** shown below[165] *(Scheme* 116).



344 **345**

Scheme 116

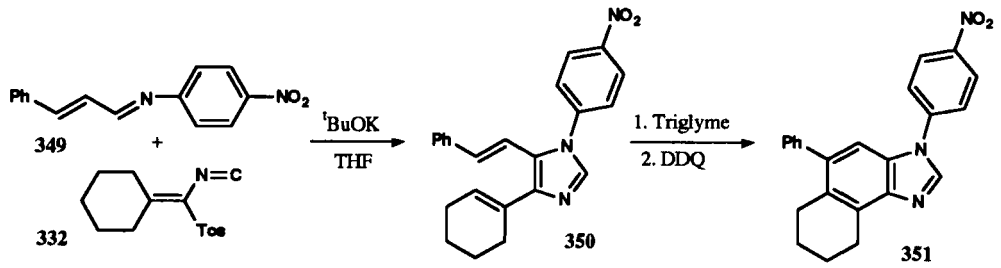
The 5-(isocyanomethyl)-3-cyclopropyloxadiazole **347**, obtained from the corresponding formamide, is cyclocondensed with 3,4-dihydro-6-(methoxycarbonyl)-4-methyl-1*H*-1,4-benzodiazepine-2,5-dione **346** to give the 6*H*-imidazo[1,5-*a*][1,4]benzodiazepin-6-one derivative **348**, which have affinity for brain benzodiazepine receptors[166] *(Scheme* 117).



346 **347** **348**

Scheme 117

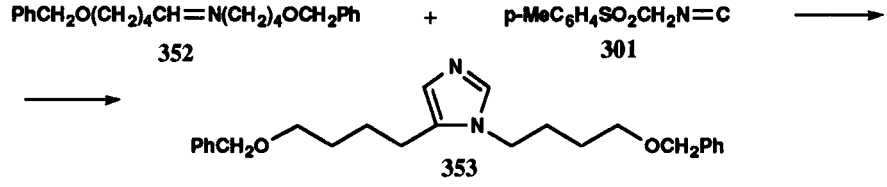
Benzimidazoles are synthesized by a reversed approach, involving the construction of a benzene ring onto a preformed imidazole. Thus the base-induced cycloaddition of 1-tosylalk-1-enyl isocyanides **332** to α,β-unsaturated imines **349** affords dialkenylimidazoles **350**, which are converted to benzimidazoles **351** *via* thermal electrocyclic ring closure[160] *(Scheme* 118).



Scheme 118

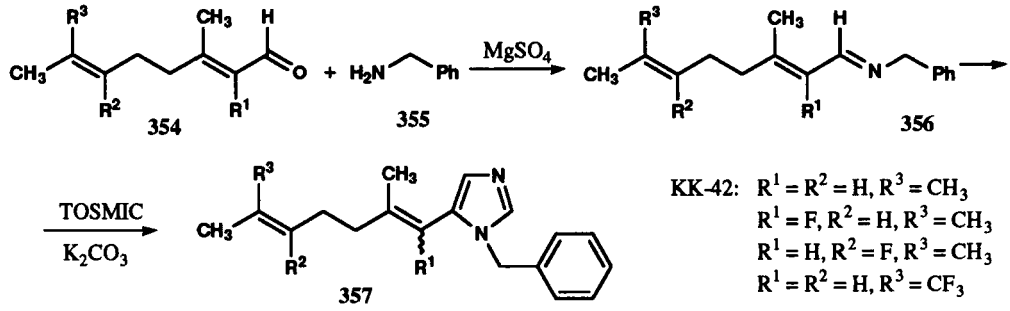
4-Phenyl-, 4-tosyl-, or 4-(ethoxycarbonyl)imidazoles, tested as antibacterial agents, are prepared by electrophilic reaction of *s*-triazine on the isocyanide anions and subsequent intramolecular ring closure.[167]

Imidazoles are obtained in good yields by reaction of tosylmethyl isocyanide and imines, in the presence of bases, *via* the cycloaddition of α-metalated isocyanide onto the imine and succeeding elimination of *p*-toluenesulfinic acid or its salts.[168] The cycloaddition reaction of (*p*-tolylsulfonyl)methyl isocyanide **301** to a substituted imine **352** affords the imidazolic diether **353** that is hydrogenated to yield the diol, converted to a doubly-bridged porphyrin used as a model for Haemoglobin-Myoglobin in studies of oxygen carriers with imidazole ligands. The Fe(II)-complex of this porphyrin binds oxygen reversibly at ambient temperature[169] *(Scheme* 119).



Scheme 119

The imidazole derivative KK-42 (**357**) shown below has been developed[170a,b] by Kuwano *et al.* KK-42 represents the optimized molecule from a series of 1,4- and 1,5-disubstituted imidazoles[170a] tested for insect antijuvenile hormone activity.[170b] The procedure reported by Kuwano *et al* for the synthesis of KK-42 ($R^1 = R^2 = H$, $R^3 = CH_3$) is depicted below. Thus, condensation of geranial **354** with benzylamine **355**, in the presence of magnesium sulfate, afforded a intermediate imine **356**, which was allowed to react with tosylmethyl isocyanide, to give a 2:1 mixture of imidazole KK-42 (**357**) (($R^1 = R^2 = H$, $R^3 = CH_3$) and its corresponding *Z*-isomer. An optimized preparation of KK-42 and the synthesis of monofluoro- ($R^1 = R^2 = F$) and trifluoromethyl ($R^3 = CF_3$) analogs has been reported[171] starting from the corresponding monofluoro- or trifluoroaldehydes and a similar reaction sequence *(Scheme* 120).

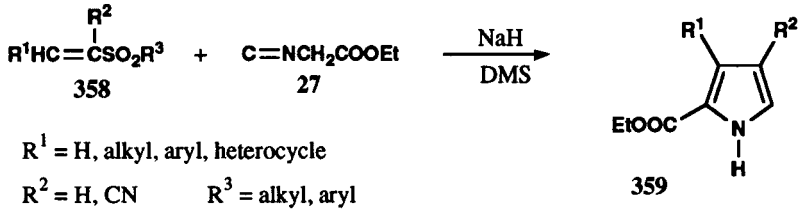


Scheme 120

4. Reaction of α-Metalated Isocyanides with Michael Acceptors. Synthesis of Pyrroles and Related Compounds

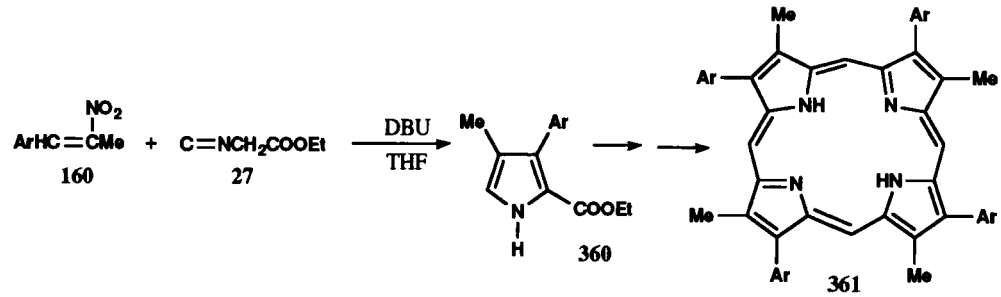
The reaction of α-metalated isocyanides and Michael acceptors, as α,β-unsaturated carbonyl compounds affords pyrrolines,[172] after Michael addition and cyclization. If the resulting pyrroline has a leaving group, its elimination gives rise to pyrrole. The leaving group can arise from the activated olefins or from starting isocyanide. Different substitution patterns on the pyrrole nucleus are obtained in each case.

Cyclocondensation[173a] of vinyl sulfones **358** with ethyl isocyanoacetate **27** and NaH gives rise to ethyl 3-substituted pyrrole-2-carboxylate **359** and reaction of α-cyanostyryl sulfones in the same conditions gives rise to ethyl 3-aryl-4-cyanopyrrole-2-carboxylate[173b] *(Scheme* 121).



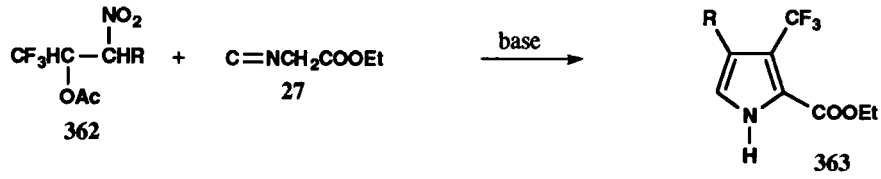
Scheme 121

The nitro group behaves as a leaving group when it is bonded to alkyl or aryl nitroalkenes.[174] Thus, reaction between nitroalkenes and ethyl isocyanoacetate in the presence of 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) affords ethyl 3,4-disubstituted pyrrole-2-carboxylate derivatives.[174-180] The reaction between *gem*-disubstituted nitroalkenes **160** and isocyanides affords pyrroles **360**, which are converted[177] to sterically hindered porphyrins **361** after reduction with $LiAlH_4$, tetramerization with *p*-toluenesulphonic acid and oxidation with chloranil *(Scheme* 122).



Scheme 122

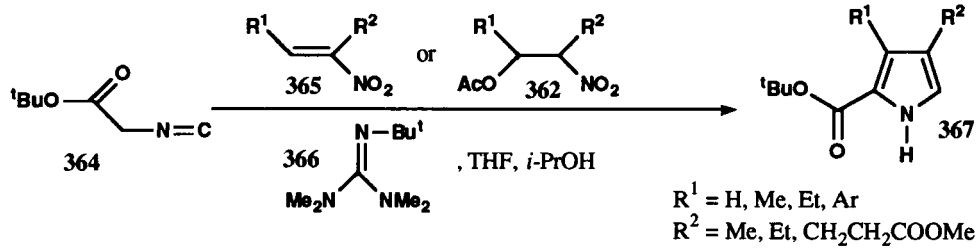
Other examples are, 3,4-dialkylpyrrole-2-carboxylic acid esters having long alkyl chains at the 3-position, prepared[178] by reaction of ethyl isocyanoacetate with nitroalkenes such as $H(CH_2)_nCH=CH(Me)NO_2$, and 4-alkyl-3-trifluoromethylpyrrole-2-carboxylic acid esters **363**, conveniently prepared[179] by reaction of the same isocyanide with 1-(trifluoromethyl)-2-nitroalkyl acetates **362**, both reactions taking place in the presence of a base *(Scheme* 123).



Scheme 123

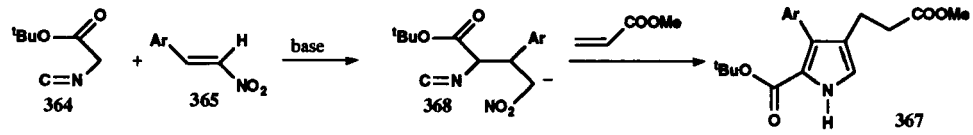
The trifluoromethylated pyrroles **363** are converted to the corresponding porphyrins *via* tetramerization of 2-(hydroxymethyl)pyrroles.

tert-Butyl isocyanoacetate **364** reacts with β-substituted β-nitrostyrenes **365** or α-substituted β-acetoxy nitroalkanes **362** in the presence of pentaalkyl or tetraalkyl guanidine bases **366** affording[180] *tert*-butyl 3,4-disubstituted pyrrole-2-carboxylate derivatives **367** in high yields (70-98%). In the latter case, nitroalkyl acetates act as precursors of the corresponding base-sensitive nitroalkenes. When the isocyanide is reacted with methyl 4-nitrobutanoate and a base, a pyrrole derivative with a propionate side chain (important for the synthesis of naturally occurring porphyrins) is obtained in high yield (97%)(Scheme 124).



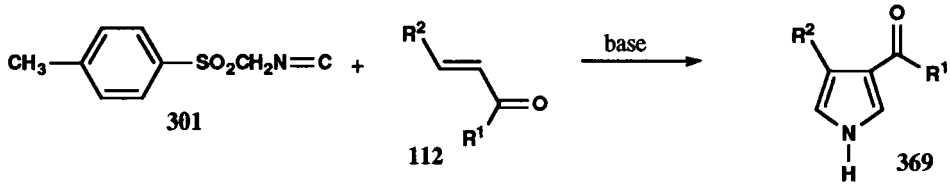
Scheme 124

When the same isocyanide **364** is reacted with β-nitrostyrene **365** in the presence of a base and an excess of methyl acrylate, a pyrrole derivative **367** containing the same propionate side chain is obtained[180] directly in 62% yield *(Scheme* 125).



Scheme 125

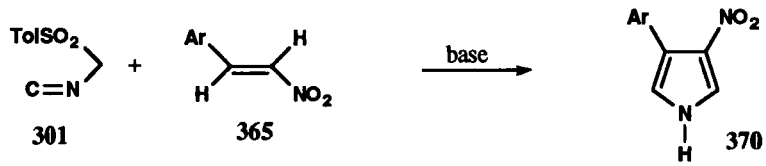
In the formation of pyrroles, aromatization is a consequence of an elimination process and a [1,5]sigmatropic shift of hydrogen. The leaving group can come from the starting isocyanide. The initial examples relative to this method are given by van Leusen *et al*, concerning the reaction of TOSMIC[181] with activated olefins and a base. As an example, the reaction between α-metalated TOSMIC and α,β-unsaturated carbonyl compounds **112** gives[181a] 3-acylpyrroles **369** *(Scheme* 126).



Scheme 126

The sulfone group acts as a leaving group in such condensations. Loss of toluenesulfinate generates the double bond necessary for aromatization. The reaction leads to the formation of different substituted pyrroles than in the case of leaving groups coming from olefin. Perfluoroalkylpyrroles are prepared *via* reaction of $F_3C(CF_2)_nCH{=}CHCOMe$ (n = 1, 2) with TOSMIC in moderate yields. Oxidative cyclization of them allows tetrakis-(perfluoroalkyl)porphyrins[182] to be obtained. The 3-(trifluoromethyl)pyrrole is prepared by cyclocondensation of *tert*-butyl *E*-4,4,4-trifluorobutenoate with TOSMIC followed by cleavage of the ester moiety and decarboxylation.[183]

Addition of β-nitrostyrene **365** to a mixture of TOSMIC **301** and DBU in THF/*i*-PrOH gives[180] the 4-aryl-3-nitropyrrole **370** in moderate yield *(Scheme* 127).

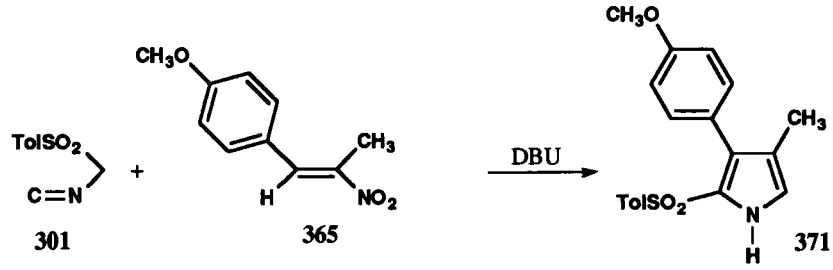


Scheme 127

The yield of 3-nitropyrroles prepared by this method is low for practical use. Ono and co-

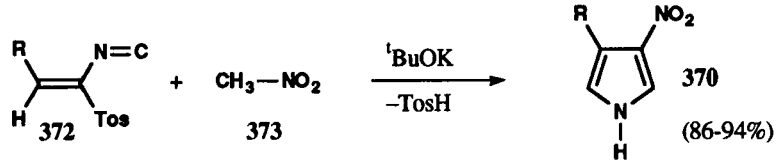
workers reported a modified procedure for the preparation of 3-nitropyrroles, by the use of TOSMIC and NaH in DMSO-ether, in which the yield was greatly improved.[184]

If the starting nitroolefin **365** contains a geminal subtituent, reaction with TOSMIC in the presence of DBU leads to a sulfonyl pyrrole **371**. In this instance, it is the nitro group that acts[180] as the leaving group *(Scheme* 128).



Scheme 128

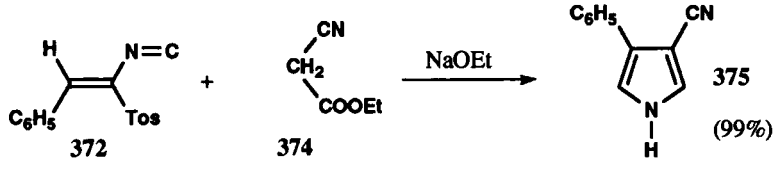
Similar 3-nitropyrroles are synthetically accessible by the opposite method. Thus, 3-nitropyrroles are formed in high yield by reaction of nitromethane **373** with 1-isocyano-1-tosyl-1-alkenes **372** and potassium *tert*-butoxide in 1,2-dimethoxyethane. By this method, 3-nitropyrroles **370**, which are accesible with difficulty by other routes, are obtained[185a] in 86-94% yield *(Scheme* 129).



R = C_6H_5, *p*-ClC_6H_4, *p*-$MeOCH_6H_4$, ^{t}Bu

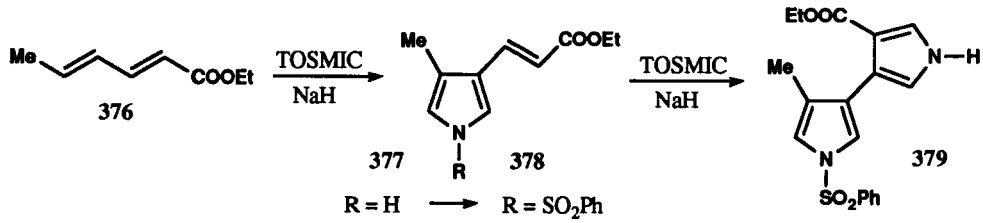
Scheme 129

Reaction of 1-isocyano-1-tosyl-1-alkenes **372** with different Michael donors forms 3,4-disubstituted pyrroles **375** bearing substituents of electron-withdrawing and/or electron-donating nature.[185b] The best yield is obtained by using ethyl cyanoacetate **374**, as is shown below *(Scheme* 130).



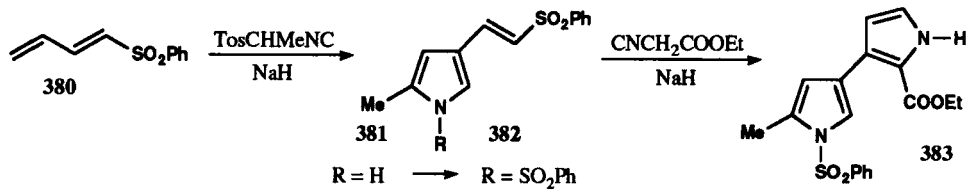
Scheme 130

Treatment of ethyl sorbate **376** with TOSMIC and NaH/DMS-ether gives rise to a 3,4-disubstituted pyrrole **377**, converted to its *N*-(phenylsulfonyl) derivative **378**. Treatment of this derivative with TOSMIC in the same conditions provides[186] 3,3'-bipyrroles **379**, prepared as simple analogues of the antitumor agent CC-1065 *(Scheme* 131).



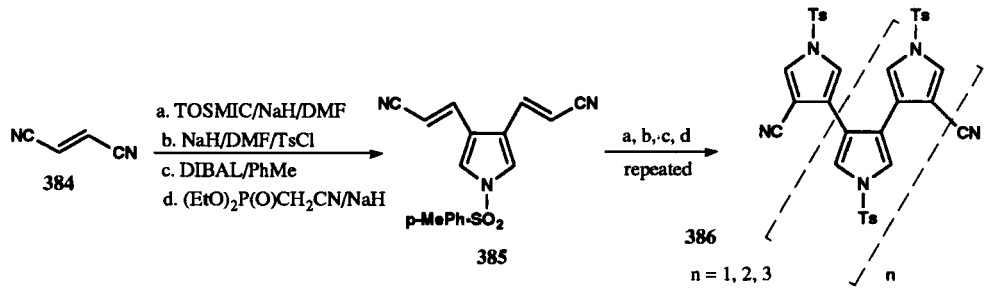
Scheme 131

A similar strategy is applicable to the synthesis of different 3,3'-bipyrroles **383** using 1-phenylsulfonyl-1,3-butadiene **380** and consecutive cycloaddition[187] of TosCHMeNC and ethyl isocyanoacetate *(Scheme* 132).



Scheme 132

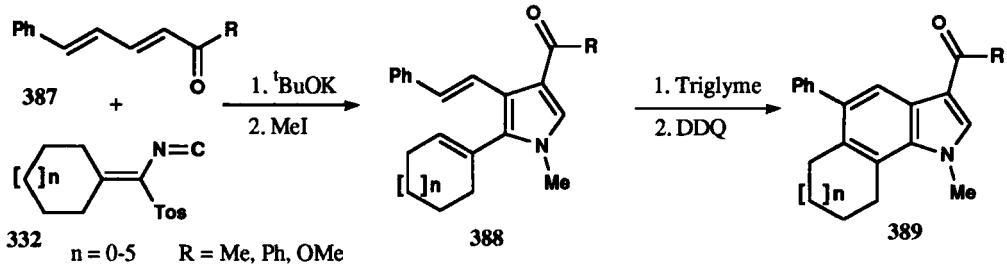
Treatment of fumaronitrile **384** with TOSMIC and NaH in DMF gives 3,4-dicyanopyrrole. *N*-Tosylation and reduction with DIBAL gives pyrrole-3,4-dialdehyde, which is treated consecutively with diethyl(cyanomethyl)phosphonate/NaH and TOSMIC/NaH affording *N*-tosylated tri-β-pyrrole. DIBAL reduction and repetition of the same sequence of transformation, Horner-Wittig reaction, TOSMIC treatment and *N*-tosylation, gives rise to penta-β-pyrrole and hepta-β-pyrrole.[188] The β-oligopyrroles **386**, obtained in good yields by this route, assume a helical secondary structure in the solid state and in solution. These compounds could potentially mimic the topology of the α-helical domains of proteins *(Scheme* 133).



Scheme 133

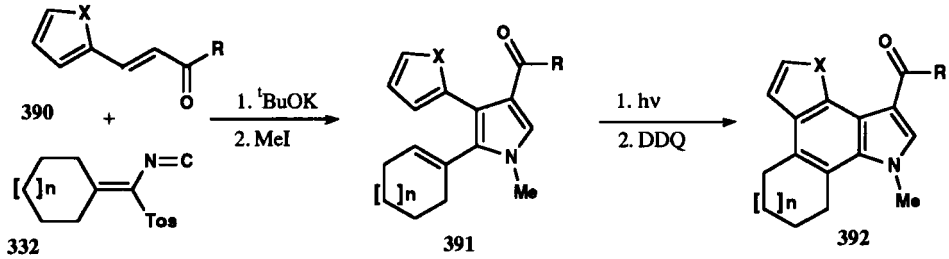
2,3-Dialk-1'-enylpyrroles are formed in one operation by a base-induced regiospecific cycloaddition of 1-tosylalk-1-enyl isocyanides **332** to α,β-γ,δ-unsaturated ketones **387** and esters.[160,189] The obtained pyrroles are converted, without being isolated, to *N*-methyl or *N*-acetyl

derivatives **388**. *N*-Protected pyrroles are transformed into indoles **389** by a thermal or photochemical electrocyclic ring closure, followed by dehydrogenation with DDQ *(Scheme* 134). The same type of reaction produced 5-azaindoles in moderate to high yields by electrocyclization of 2-vinyl-3-iminopyrroles obtained by base-induced cycloaddition of 1-tosylalk-1-enyl isocyanides.[190]



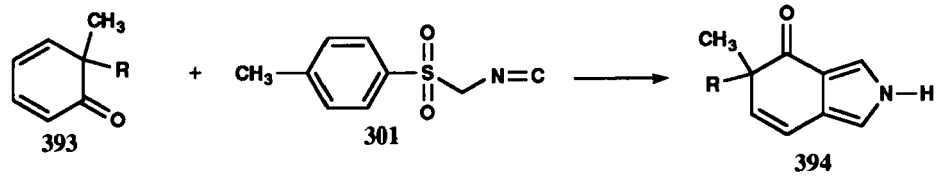
Scheme 134

A similar reaction sequence takes place when aryl or heteroaryl substituted unsaturated ketones **390** are used instead of α,β-γ,δ-unsaturated ketones. In these cases the subsequent electrocyclic ring closure has to be carried out photochemically on the *N*-protected pyrroles **391**, affording[160,189] fused indole derivatives **392** in good yields *(Scheme* 135).



Scheme 135

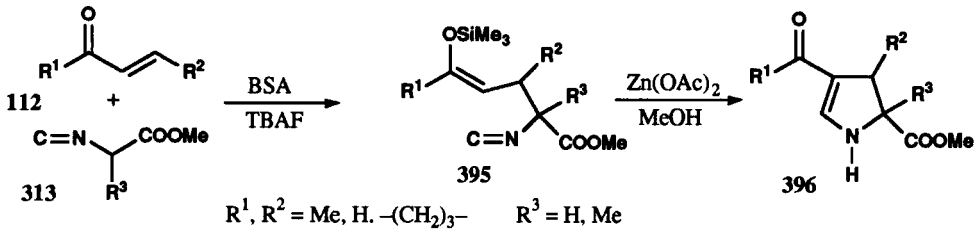
A cycloaddition of TOSMIC is the basis of the synthesis of 4*H*-isoindoles. Tosylmethyl isocyanide **301** attacks to 6,6-disubstituted cyclohexadienones **393** selectively in position 3 to furnish[191] 4*H*-isoindol-4-one derivatives **394**. This is caused by conjugate addition, characteristic of cyclohexadienones, and for sterical reasons *(Scheme* 136).



R = CH_3, C_6H_5, $C_6H_5CH_2$, $HC{\equiv}CCH_2$, $H_3C{-}C{\equiv}C$

Scheme 136

A convenient synthesis of 2-pyrroline-5-carboxylates can be achieved by step-by-step regioselective addition of an α-isocyano carboxylate to the carbon-carbon double bond of an enone. Thus, methyl isocyanoacetate, or its derivatives **313**, undergo fluoride-catalyzed 1,4-addition to α,β-unsaturated ketones **112** in the presence of *N,O*-bis(trimethylsilyl)acetamide to give the 1,4-adducts **395**, as the corresponding silyl enolates, in high yield.[192] Intramolecular cyclization of the γ-isocyano silyl enolates, catalized by zinc(II) acetate in the presence of methanol as proton donor, leads[193] to 2-pyrroline-5-carboxylates **396** in good yield *(Scheme* 137).

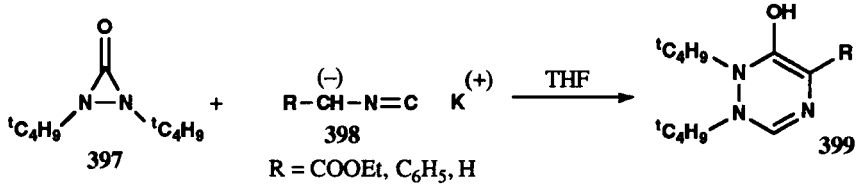


Scheme 137

Some 2-pyrroline-5-carboxylates so obtained were transformed into the corresponding pyrrolidine-2-carboxylic esters *via* hydrogenation of the *N*-protected derivatives. This method for preparing pyrrolidine-2-carboxylic acids was applied in a total synthesis of racemic α-allokainic acid.[193]

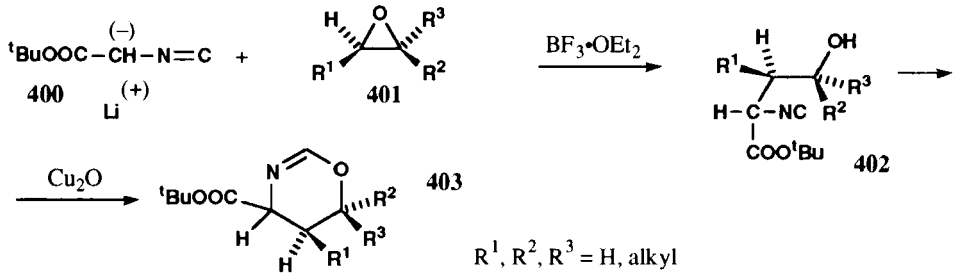
5. Other Cycloadditions of α-Metalated Isocyanides. Synthesis of Six- and Seven-Membered Heterocycles

Three-membered heterocycles are known to undergo ring enlargement on reaction with compounds containing an unsaturated function or with carbanions. Treatment of 1,2-di-*tert*-butyldiaziridinone **397** with metalated ethyl isocyanoacetate **398** at room temperature gives 1,2-di-*tert*-butyl-5-ethoxycarbonyl-6-hydroxy-1,2-dihydro-1,2,4-triazine **399**. Starting from benzyl or methyl isocyanide, the corresponding triazines are also prepared[194] *(Scheme* 138).



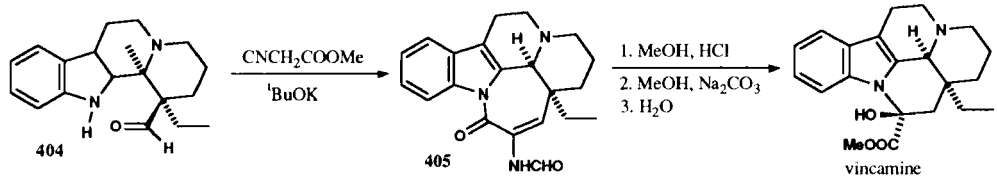
Scheme 138

Lithiated *tert*-butyl isocyanoacetate **400** reacts with epoxides **401** in the presence of boron trifluoride etherate to give *tert*-butyl 4-hydroxy-2-isocyanoalkanoates **402**. By heating the obtained adducts with cooper(I) oxide in toluene, the *tert*-butyl 5,6-dihydro-4*H*-1,3-oxazine-4-carboxylates **403** are obtained,[195] which are of interest as starting materials for the total synthesis of structural variants of the cephalosporins *(Scheme* 139).



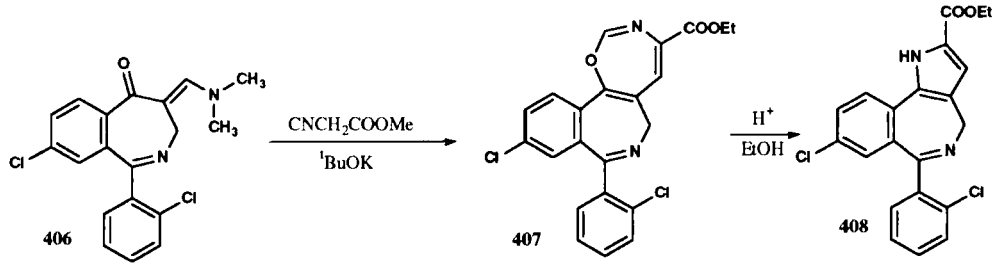
Scheme 139

α-Metalated isocyanides react with various dipolar systems and, after subsequent cyclization, seven-membered heterocycles are sometimes obtained. The reaction of a indoloquinolizidine aldehyde **404**, used in syntheses of the indole alkaloid vincamine, with the potassium salt of methyl isocyanoacetate in THF, affords an intermediate lactam **405** which is directly transformed into vincamine by acidic and basic treatment. The possible mechanism of the formation of the lactam derivative **405** is given[196] *(Scheme* 140).



Scheme 140

2-Benzazepines are carbon isosteres of the extensively investigated 1,4-benzodiazepines. The reaction between a 4-dimethylaminomethylene-3,4-dihydro-2-benzazepin-5-one derivative **406** and the anion of ethyl isocyanoacetate gives a mixture in which the oxazepino[6,7-*d*][2]benzazepine derivative **407** shown below is the main product.[197] This compound is converted to a pyrrolo[3,2-*d*][2]benzazepine derivative **408**, as the main product, by acidic treatment *(Scheme* 141).



Scheme 141

The reaction is interesting because several *d*-fused 2-benzazepines show activity on the central nervous system comparable to that of the well known *a*-fused 1,4-benzodiazepines.

VI. CONCLUSIONS

Isocyanide chemistry occupies an area between organic and inorganic chemistry, and any report on the chemistry of isocyanide compounds should cover some aspects belonging to both chemical specialties. The panorama given here has been limited to the use of isocyanides in synthesis of organic heterocycles, and some inorganic aspects of isocyanide chemistry have not been covered, as for example the four or five-membered metallaheterocycles, obtainable from isocyanide compounds,[198] which are clearly far removed from the purpose of the review. When the border between organic and inorganic heterocycles was uncertain, as for example in the case of boron or silicon-containing heterocycles, the main aspects of their synthesis using isocyanides have been included. The facile synthesis of rare heterocycles from isocyanides is in contrast to other methods. The most striking conclusion of the review is the fact that isocyanides are the starting point of numerous heterocycles used as crucial intermediates for the synthesis of very important natural compounds, as antibiotics, alkaloids, aminoacids, porphyrins or antitumor agent analogues. Another significant conclusion of this review, concerns to the impressive number of reaction pathways to afford heterocycles that an apparently simple functional group such as the isocyano group is able to undergo.

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