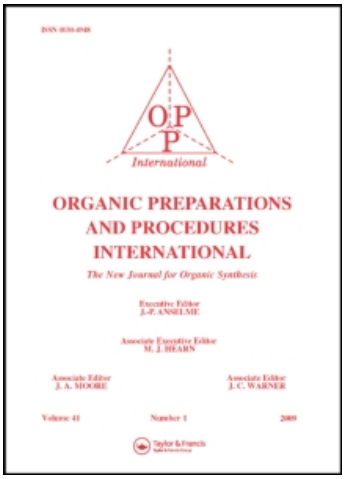

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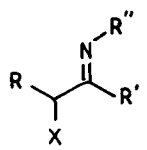
I. INTRODUCTION

The chemistry of α-halogenated imino compounds 1 has been the focus of increasing interest, especially during the last decade, because only recently have efforts been undertaken to develop synthetic pathways leading to these compounds. The studies resulted in some valuable synthetic methods for the preparation of α-haloimines. The synthesis of α-halogenated



X = halogen

1

imino compounds has been reviewed recently in this Journal.[1]

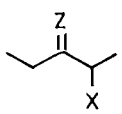
This review is divided into several parts, each describing a fundamental reaction or a set of reactions. Several overlaps occur; for instance special emphasis is given on the formation of heterocyclic compounds, even though it is clear that heterocyclic compounds may result from the subsequent reactions not

discussed in this context. The advantage of this classification system, is that it provides a complete overview of the several synthetic and mechanistic possibilities provided by the chemistry of α-haloimines.

The scope and limitations of the present review which covers the literature up to the end of 1978 will be the same as those discussed previously.[1]

II. GENERALITIES ON THE REACTIVITY OF α-HALOGENATED IMINO COMPOUNDS

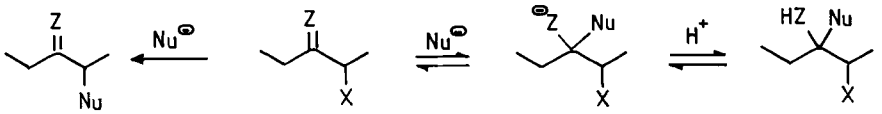
α-Halogenated imines 2 and the corresponding oxygen analogues, i.e. α-halogenated carbonyl compounds 3 are interesting substrates from the mechanistic point of view. Only the latter have been the subject of systematic studies in the literature.



2 Z = N-R
3 Z = O
X = halogen

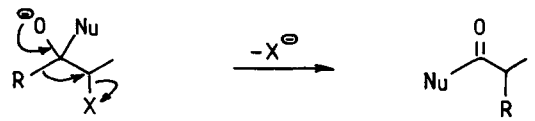
This combination of functional groups possesses great versatility because of the variety of separate and consecutive reactions with selected reagents. From a theoretical standpoint, diverse types of reaction between α-haloimines and nucleophilic reagents (Nu: or $Nu^{\ominus}$), acting as nucleophiles or bases, can be expected. Some of these possibilities are discussed very briefly in the following paragraphs, and comparisons are made with α-halocarbonyl chemistry.[2-5]

1. A nucleophile can either add to the carbon-heteroatom double bond or substitute at the α-carbon atom. The first possibi-



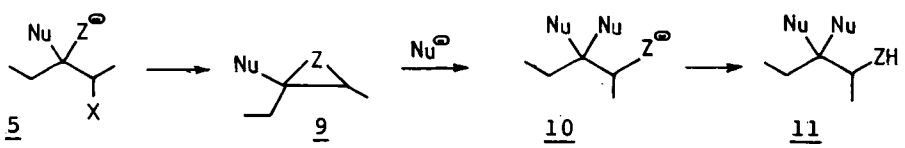
4 2 5 6

lity produces an anion 5, which by proton uptake leads to less stable structures (such as 6); however, polyhalo derivatives yield stabilized products e.g. chloral hydrate. In general, adducts 6 are readily deprotonated, after which the nucleophile is expelled. The semi-benzilic mechanism of the Favorskii-rearrangement of α-haloketones is initiated by the formation of adduct 7 but halide displacement proceeds with migration of a substituent. This route does not occur frequently and is only of importance with substrates having no



7 8

α'-hydrogens or when extreme steric factors inhibit the formation of the normal cyclopropanones.[5-8] Anion 5 can also furnish three-membered rings by intramolecular nucleophilic substitution, but these epoxides 9 (Z = O) or aziridines 9 (Z = N) are usually opened by nucleophilic attack.



5 9 10 11

Nucleophilic substitution on substrates 2 is not the preferred reaction because of the destabilization by two adjacent

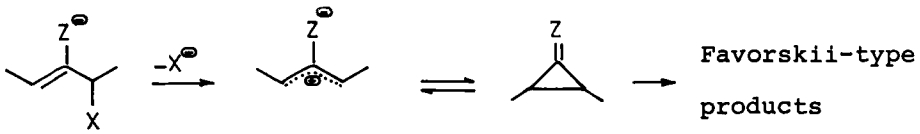
positive centers, namely the positively induced carbon atom of the C=Z bond and the incipient carbonium ion at the α-position.

2. The nucleophilic reagent acts as a base and abstracts an α- or α'-proton. The α-proton is the most acidic one and leads to mesomeric anion 12, but neither this anion nor its protonated form 13, give rise to any further reaction.

2 12 13

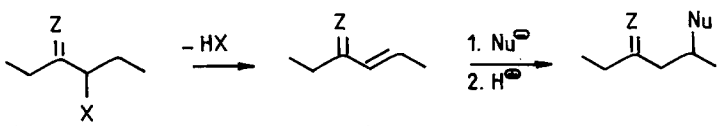
2 14 15

Deprotonation at the α'-position affords a delocalized anion 14, which is protonated to give a β-heterosubstituted allylic halide 15. Either unimolecular or bimolecular halide displacement are possible and lead to solvolysis or substitution products. Instead of protonation, the mesomeric anion 14 can become neutral by halide anion expulsion, generating zwitterion 16 which undergoes disrotatory ring closure to a heteromethylene cyclopropane derivative 17. In the oxygen series (Z = O) this reaction represents a part of the well-known Favorskii-rearrangement.[9-16]



14 16 17

The base can abstract a proton from the β-carbon, resulting in elimination of hydrogen halide. The α,β-unsaturated systems 18 thus formed can also be attained by a unimolecular process. Side-products, especially when excess nucleophilic reagent is present can be formed by Michael addition (e.g. 19).



2 18 19

Many other combinations of these reactions are plausible and can lead to a wide variety of products.

All these reactions are mainly based on the well-known behavior of α-halocarbonyl compounds towards nucleophilic reagents. The reactivity of the corresponding nitrogen-analogues is expected to show similarities. The decreased electronegativity of nitrogen with respect to oxygen lowers the electrophilic character of the carbon atom connected to nitrogen and reduces the acidity of the α-hydrogens. These two fundamental characteristics account for a substantial decrease in reactivity of α-haloimines as compared to α-halocarbonyl compounds. However, this decrease in reactivity allows other reactions to become more important. For in-

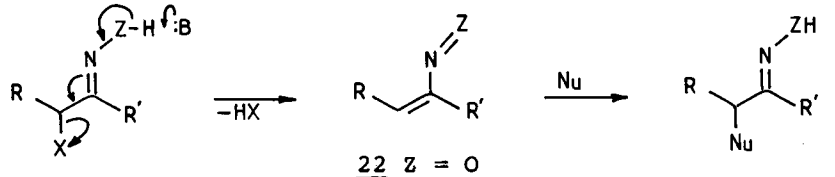
stance, the infrequently encountered elimination reaction of α-halocarbonyl derivatives will be shown to be an important characteristic of α-halogenated imines due to the decreased polarity of the C=N-bond and of the decreased acidity of α-H in the latter class of compounds. Because nitrogen holds an intermediate position between oxygen and carbon, allylic halides 2 (Z = C) can be also treated in this comparison. The reactivity of the so-called "carbon-homologues" of α-haloimines is characterized mainly by various nucleophilic substitutions, e.g. S_N1, S_N2, S_N2', etc...[17] The reactivity of allylhalides is determined mainly by the halocarbon part, while the behavior of α-halogenated carbonyl compounds is primarily controlled by the carbonyl group. As a consequence, the reactivity of α-haloimines 2 (Z = NR) is expected to show features of either of the two classes 2 (Z = O, CR_1R_2) because α-haloimines straddle to the classes.

III. REACTIVITY OF α-HALOGENATED IMINO COMPOUNDS

1. Nucleophilic Substitutions

As discussed in the introduction, nucleophilic substitution at the α-carbon in α-haloimines is not a preferred reaction because of the unfavorable interaction of two adjacent positive centers during the reaction. However, it will be demonstrated that strong nucleophiles easily displace the halogen atom. In addition a variety of oxygen-, nitrogen- and sulphur-nucleophiles gave α-substituted imino compounds. Except for strong nucleophiles, e.g. thiolates, the nucleophilic substitution of α-haloimines occurs in competition with other reactions,

which will be treated as selected mechanistic topics in this review. Among the reactions of α-haloimines leading to α-substituted imines, two types will be discussed in the section describing elimination reactions because the reactions in fact involve an elimination-addition reaction. These reactions which are encountered with α-halooximes 20 or α-halohydrazones 21 upon treatment with nucleophilic reagents, proceed via the intermediacy of nitrosoolefins 22 or azoalkenes 23 respectively, furnishing only formal α-substitution products 24 and 25 (vide infra).

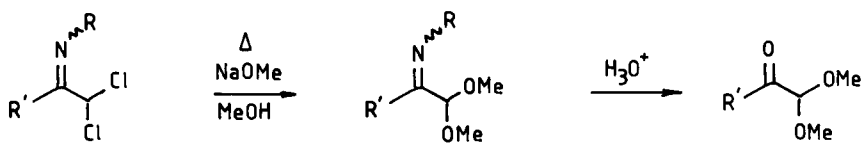


20 Z = O
21 Z = NR"

22 Z = O
23 Z = NR"

24 Z = O
25 Z = NR"

Alkoxides in the corresponding alcohols often produced α-alkoxyimines. N-Cyclohexyl α,α-dichloromethylketimines 26 gave α,α-dimethoxymethylketimines 28 exclusively when treated with excess concentrated sodium methoxide in methanol upon prolonged reflux.[18]



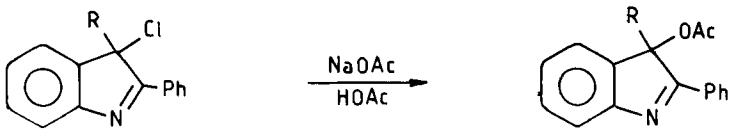
26 R = C_6H_{11}
27 R = aryl

28 R = C_6H_{11}
29 R = aryl

30

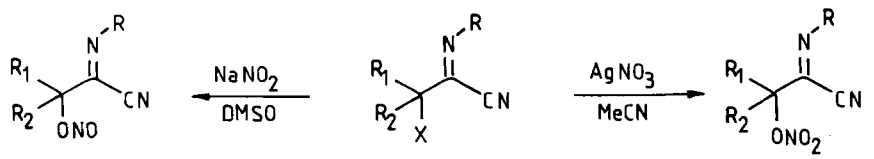
N-Aryl α,α-dichloromethylketimines 27 similarly produced α,α-dimethoxymethylketimines 29, a Favorskii-type rearrangement leading to α,β-unsaturated imidates (vide infra),[19,20] is a competing reaction.

Another example of the occurrence of competitive reactions involved the conversion of N-t-butyl α-chlorobutyraldimine with sodium methoxide in methanol to afford N-t-butyl α-methoxyaldimine (54%) besides N-(2-butenylidene)t-butylamine (10%, elimination product) and the rearranged N-t-butyl-N-(1-dimethoxymethyl)propylamine (30%, rearrangement via aziridine intermediate).[21] With α-chloroindolenines 31,[22] sodium acetate in glacial acetic acid produced α-acetoxy derivatives 32.

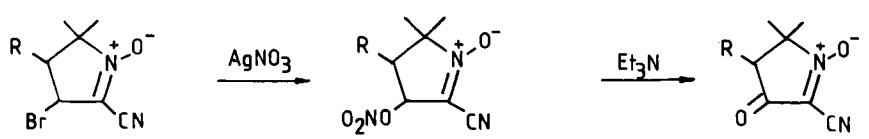


31 32

α-Halogenated imidoyl cyanides 33 reacted with silver nitrate in acetonitrile or with sodium nitrite in dimethyl sulfoxide to form α-nitrato- and α-nitritoimidoyl cyanides 34 and 35 respectively.[23] α-Bromonitrones 36 also provided α-nitrato



34 33 35

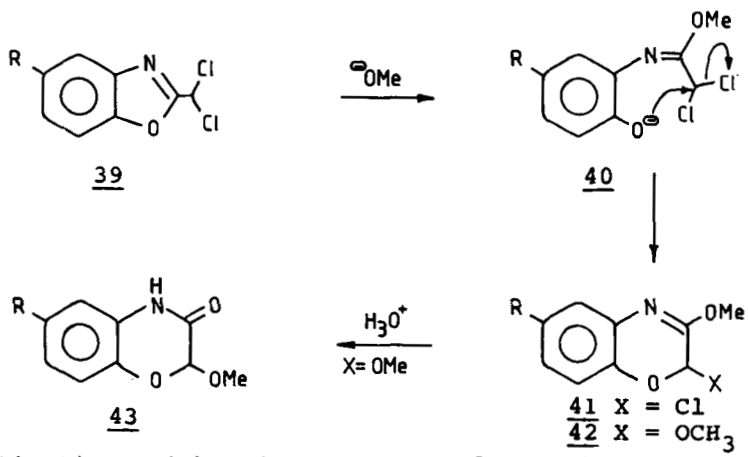


36 37 38

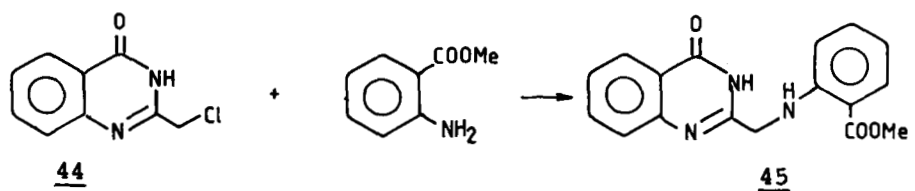
derivatives 37, which underwent base-promoted nitrite expulsion with formation of the α-keto derivatives 38 (Preparation 1).[24]

An interesting reaction was observed with dichloromethylbenzoxazoles 39 and sodium methoxide, yielding initially nu-

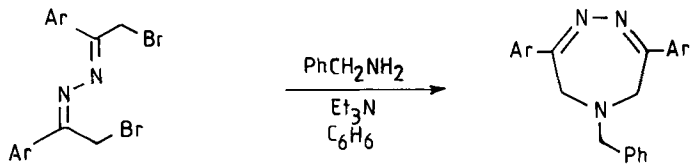
cleophilic addition with ring opening, followed by intramolecular nucleophilic substitution to give 41. This α-chloroether 41 afforded, after solvolysis, 1,4-benzoxazin-3-ones 43 on acidic hydrolysis.[25,26]



α-Substitutions with primary or secondary amines were not frequently observed. Ordinary α-chloro- or α,α-dichloroaldimines do not react with these nitrogen-nucleophiles, but in some selected cases α-amination was observed. α-Chloroamidine 44 afforded an α-substitution product when treated with anilines.[27]

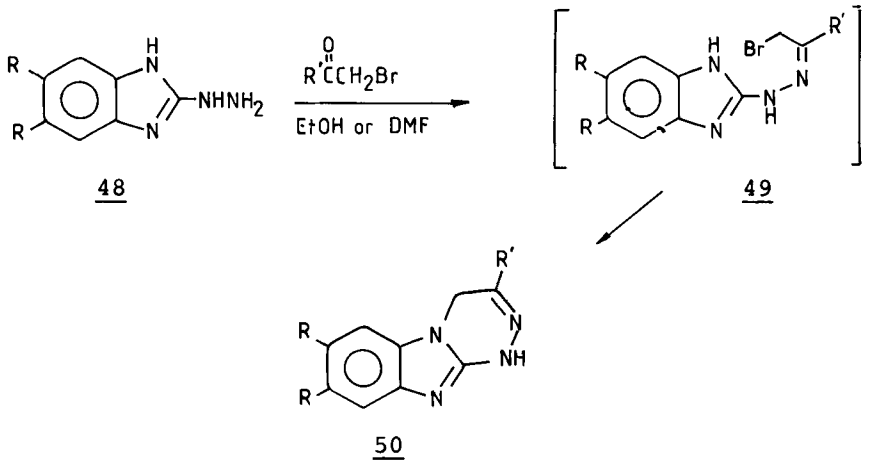


α-Halomethylimines seemed to be the substrates of choice for such reactions. When α,α'-dibromoacetophenone azine 46 (Ar = Ph) was treated with benzylamine in benzene in the presence of triethylamine, 5-benzyl-4,6-dihydro-3,7-diphenyl-5H-1,2,5-triazepine 47 (Ar = Ph) was produced.[28]



46 47

α-Bromomethylketones condensed with heterocyclic hydrazines 48 in ethanol or dimethylformamide to afford intermediate α-bromohydrazones 49, which underwent intramolecular nucleophilic substitution to give heterocycles 50 in 43-51% yield.[29] α,α'-Dibromoacetophenone azines 46 gave also an initial α-substitution with hydrazine, but the product rearranged into 2,5-diarylpyrazines.[30]

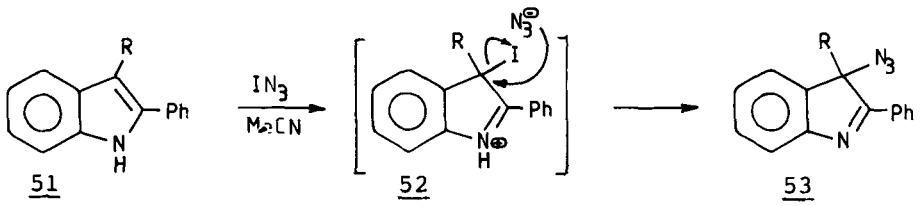


48 49 50

A similar initial α-substitution was observed during the synthesis of 3,5,6-trisubstituted 1,2,4-triazines from α-haloarylketones and hydrazines.[31]

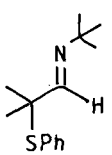
Sodium azide converts α-haloimines into α-azidoimines.[21,22] 3-Chloroindolenines also underwent nucleophilic substitution

with sodium azide in glacial acetic acid,[22] while the parent indoles 51 were converted into α-azidoindolenines 53 by treatment with iodine azide in acetonitrile.[33] The proposed mechanism involved formation of the transient α-iodoimmonium compound 52 which then suffered nucleophilic attack by azide anion.

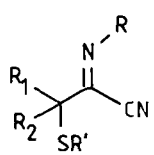


51 52 53

In general, the most convenient α-substitutions of α-haloimines were achieved with powerful nucleophiles such as thiolates. α-Chloroaldimines,[21] α-chloro- and α-bromoimidoyl cyanides[23] were converted into α-alkyl- and α-arylthioimino compounds 54 and 55 by reaction with sodium thiolates in methanol at reflux.

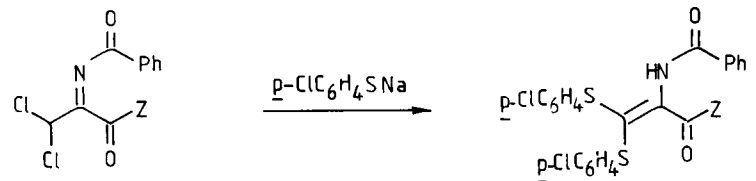


54



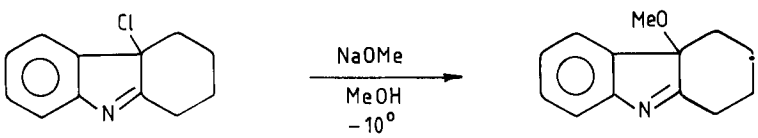
55 (R'=alkyl, phenyl)

1-Chloromethyl-3,4-dihydroisoquinoline reacted with sodium 1-methyl-1H-tetrazole-5-thiolate in ethanol to produce the α-substituted 3,4-dihydroisoquinoline; the imino function was reduced with sodium borohydride to afford the corresponding tetrahydroisoquinolines, which are useful as antispasmodics and vasodilators.[34] Activated α,α-dichloroimines 56, occurring in equilibrium with their enamine form, afforded also α,α-disubstituted products, which however isomerized into the more stable enamines 57.[35]



56 (Z = NH_2, NHMe, OMe) 57

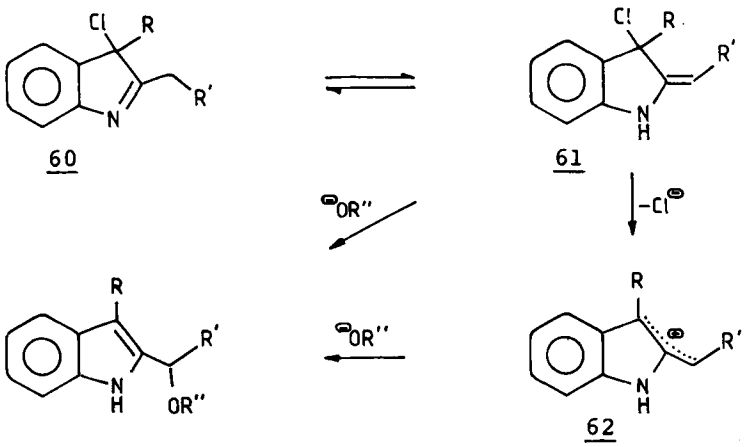
The reactions of 3-chloroindolenines with alkoxides need some additional comment, because of the duality of the final products. When 3-chloroindolenines such as 58 were treated with cold base (e.g. sodium methoxide in methanol or sodium hydroxide in alconol), the products are 3-alkoxyindolenines (59),[36,37] while at elevated temperature[36-40] or with mild acid[41-43] the product is a rearranged spirocompound (see Rearrangement of α-



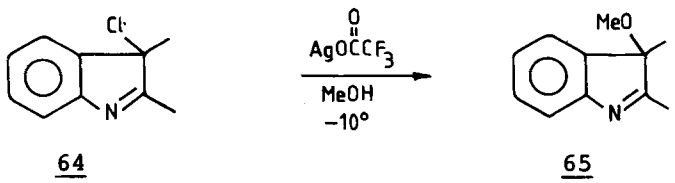
58 59

haloimines), the result of a Wagner-Meerwein type rearrangement (Preparation 2). Certain 3-bromoindolenines with hot sodium methoxide in methanol gave 3-methoxyindolenines to a minor extent.[44]

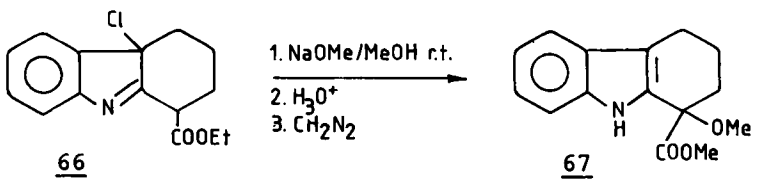
When an α-hydrogen is present, rearrangement of the chloroindolenine 60,[37] either by heat or the action of strong acid,[36,41-43,45] results in the formation of the tautomeric intermediates 61, which can either yield the delocalized carbonium ion 62 readily, or react directly with base to give the α-substituted products observed. As exemplified below, an instantaneous reaction of 3-chloro-2,3-dimethylindolenine 64 with



silver trifluoroacetate in methanol at -10° gave a 94% yield of 3-methoxy-2,3-dimethylindolenine 65.[37]

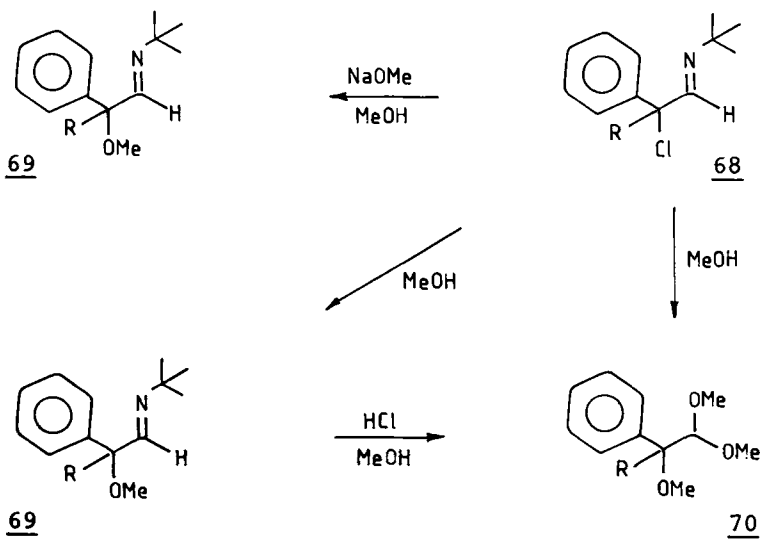


However, when an electron-withdrawing α-alkoxycarbonyl group is present, 1-alkoxy derivatives were obtained directly under cold basic conditions (see 66 → 67).[46] This reaction was ra-



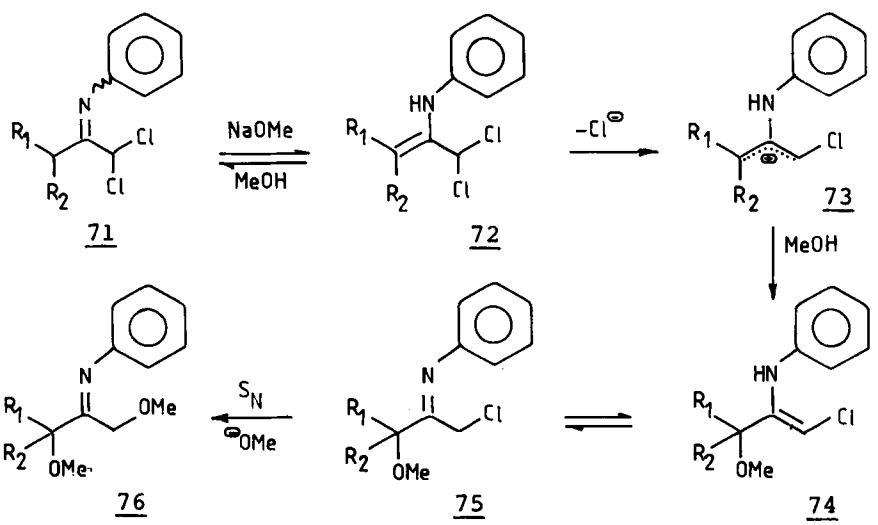
tionalized on the basis that the activating α-substituent promoted a facile tautomerism to a compound related to 61 (see also ref. 47,48). The difference between the formation of an α-alkoxyindolenine and the rearrangement to a spirocompound

(vide infra) was initially ascribed to alternate reaction paths of a rearranging carbonium ion;[36] however it was later proposed to be a result either of a S_N2 type displacement of the halogen by methoxide or of methanol addition to the imino function and subsequent rearrangement.[49] However, it is also plausible to consider the α-methoxylated products to be the result of the solvolysis of the chloroindolenine. The formation of 3-methoxyindolenine 65 from 64 with silver ion in methanol is clearly a solvolysis reaction,[37] while the production of 67 is also compatible with the intermediate delocalized carbonium ion 62. The influence of the α-aryl group in α-arylated α-chloroimines is not to be neglected in these mechanisms as illustrated by the methanolysis of α-chloro-α-phenylaldimines 68 (R = CH_3, Ph).[21] With methoxide in methanol, α-methoxyaldimines 69 were produced exclusively, while β-methoxyacetals 70 were formed in methanol, indicating methanolysis via 69.[21]



69 68 69 70

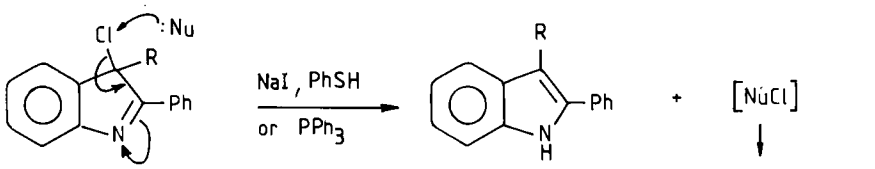
Another example of a solvolysis reaction was the formation of secondary N-phenyl-1,3-dimethoxymethylketimines 76 during the reaction of N-phenyl-1,1-dichloromethylketimines 71 with sodium methoxide in methanol (in addition to Favorskii-type rearrangement and nucleophilic substitution).[20] Primary derivatives 71 (R_2 = H) did not undergo methanolysis[21,22] but secondary derivatives 71 ($R_2 \neq$ H) gave rise to this reaction because of the enhanced stability of the delocalized carbonium ion 73, produced by loss of a chloride anion from the enamine allyl halogenide 72. Tautomerism of 74 to α-chloro-α'-methoxyketimine 75 and subsequent nucleophilic substitution yielded 1,3-dimethoxyketimines 76. The intermediacy of α-chloro-α'-methoxyketimine 75 was supported by spectral evidence as they



71 72 73 74 75 76

were detected in the reaction mixture after a short reaction time.[20] In some cases, the solvolysis of α-haloimines was aided by neighboring α- oxygen or α-nitrogen substituents.[25,26,50] Finally, it must be noted that nucleophiles such as

sodium iodide, phenylthiol and triphenylphosphine converted certain 3-chloroindolenines, e.g. 77, to the parent indoles 51 by direct attack on the chlorine atom.[22]



77 R = Me, Ph 51

Nucleophilic substitutions affording C-C bond formation are included in the next section.

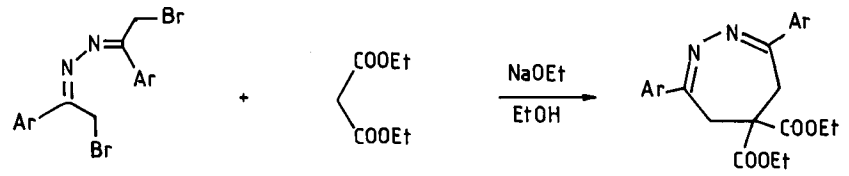
2. Formation of Carbon-Carbon Bonds

Various routes leading to carbon-carbon bonds, including reactions of α-halogenated imino compounds with carbanionic species, Grignard reagents and other organometallic reagents, and with cyanide anion, will be treated in this section.

2.1. Reactions of α-Halogenated Imino Compounds with Carbanions

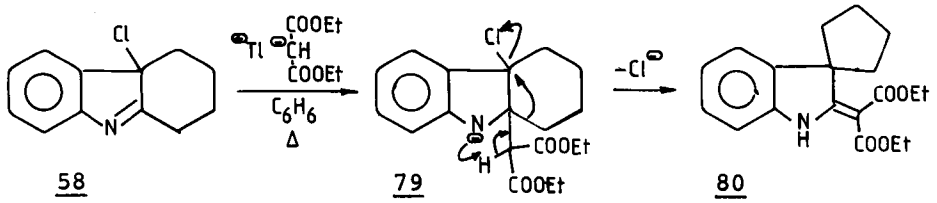
Only a few recent reports have been published concerning the reaction of carbanions, generated from active methylene compounds, with α-haloimines. The condensation of α-bromoacetophenone azines 46 with diethyl malonate in sodium ethoxide in ethanol entailed a nucleophilic halide displacement followed by an intramolecular nucleophilic substitution leading to ring-closed products, i.e. 5,5-bis(ethoxycarbonyl)-5,6-dihydro-3,7-diaryl-4H-1,2-diazepines 78.[51]

The thallium salt of diethyl malonate in benzene reacted with 3-chloroindolenine 58, conveniently obtained from chlorination of tetrahydrocarbazole with t-butylhypochlorite in benzene,



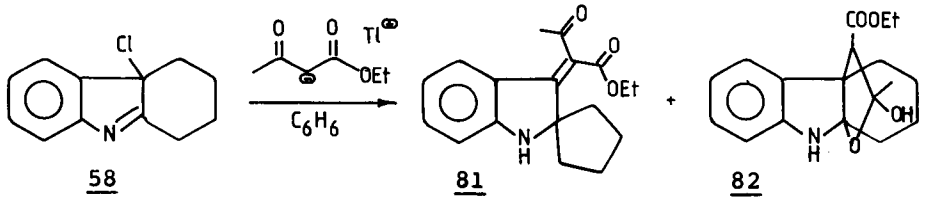
46 78

to afford the nucleophilic addition product, which rearranged into 80 (see also the section discussing rearrangements of α-haloimines) (Preparation 3).[51] On the other hand, the thallium



58 79 80

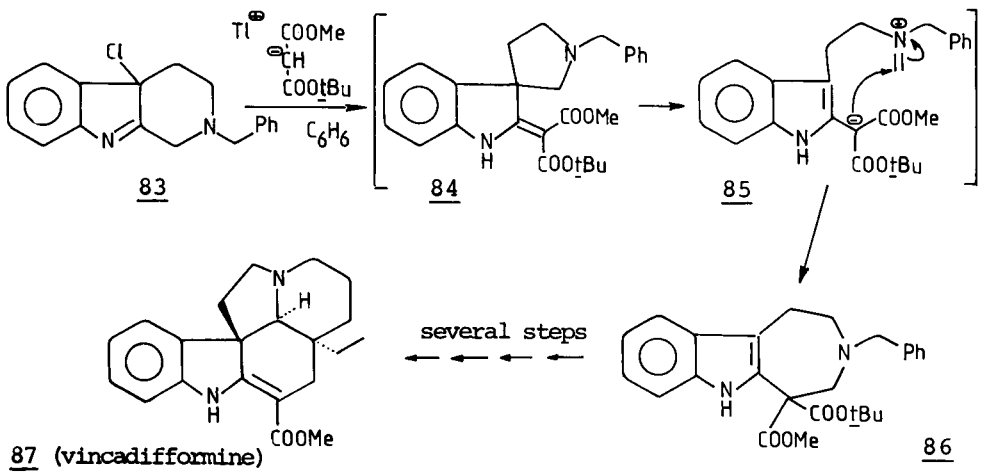
salt of ethyl acetoacetate gave a more complicated reaction with formation of a variety of products, including 81, 82, tetrahydrocarbazole and the α-hydroxyimine, derived from tetrahydrocarbazole.[51] The thallium salts of dimedone, ethyl benzo-



58 81 82

ylacetate, ethyl cyanoacetate, malononitrile, acetylacetone and nitromethane did not give C-alkylation products with 3-chloroindolenine 58, but instead yielded tetrahydrocarbazole and the α-hydroxyimine, corresponding to 58.[51] The addition of malonate anions to 3-chloroindolenines was applied to a synthesis leading to the alkaloid vincadifformine 87.[52] When 2-benzyl-1,2,3,4-tetrahydro-β-carboline 3-chloroindolenine 83 was treated

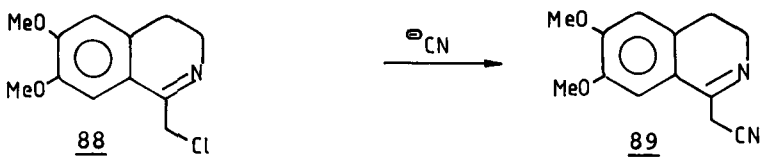
with thallium malonates, indole derivative 86 resulted via the intermediacy of the rearranged spirocompound 84 (vide infra). The alkylidenemalonate again rearranged to the zwitterionic immonium malonate, which cyclized to the indoleazepine 86. The latter transformation provided a conceptual basis for syntheses of secodines and aspidosperma alkaloids. Through this set of rearrangements, the synthesis of vincadifformine 87, passing through a biogenetically postulated secodine, was performed.[52]



Finally, aliphatic α-chloroaldimines were reported to be resistant to any reaction with the carbanions derived from methyl acetoacetate and methyl dichloroacetate.[21]

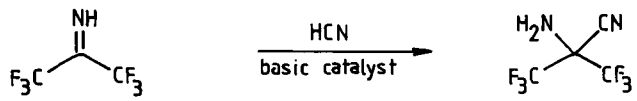
2.2. Reactions of Cyanide Anion with α-Halogenated Imino Compounds

Nucleophilic substitutions and additions have been reported when cyanide was reacted with α-halogenated imines. 1-Chloromethyl-3,4-dihydroisoquinoline 88 underwent nucleophilic displacement when treated with cyanide anion.[53] As will be pointed out in the section describing the elimination reactions, formal substitution products were isolated during the reac-



88 89

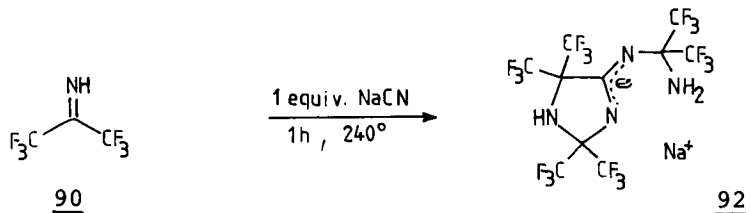
tion of α-chlorooximes with cyanide in dimethyl sulfoxide or ethanol. The reaction mechanism did not proceed by nucleophilic displacement of chloride but involved an elimination-addition mechanism via intermediate nitrosoalkenes (vide infra).[54] Activated imino compounds without displaceable halogens, e.g. hexafluoroacetone imine 90 added hydrogen cyanide at the C=N double bond under the influence of a basic catalyst.[55] When sodium cyanide was used at high temperature, compound 90 pro-



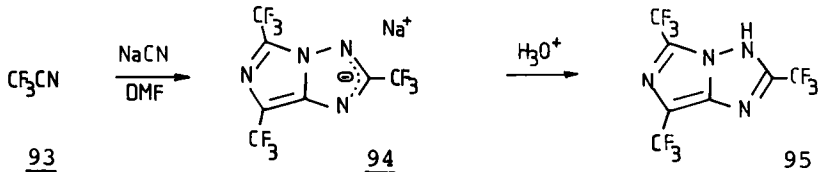
90 91

duced adduct 92,[56] while analogous compounds, e.g. the salt of dihydrotetrazapentalene 94 were isolated when trifluoroacetonitrile 93 was treated with sodium cyanide in dimethylformamide.[57] The water-soluble sodium salt 94 gave the water-insoluble 95, which exists primarily in one tautomeric form.

However, when suitable α-chloroimines were reacted with cyanide in methanol, addition-elimination products were formed. α-Chloroaldimines 96, α,α-dichloroaldimines 98 and α,α,α-trichloroaldimine 99 were converted into α-cyanoenamines 97 and β-chloro-α-cyanoenamines 100, 101 by reaction with potassium cyanide in methanol under reflux (Preparation 4).[58-60] It is

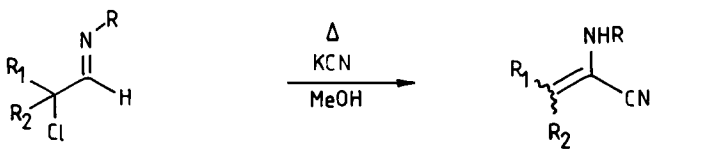


90 92

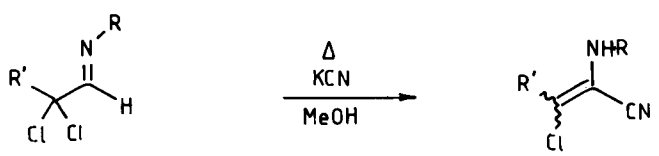


93 94 95

noteworthy that these α-cyanoenamines 97 were shown to be valuable synthons as they were transformed into trialkylketenimines on treatment with methylmagnesium iodide.[61] Moreover α-cyanoenamines 97 constitute an important intermediate in the transformation of aldehydes into amides.[62]



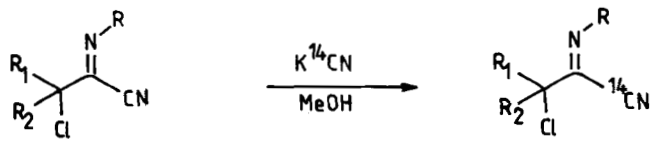
96 97 (E+Z)



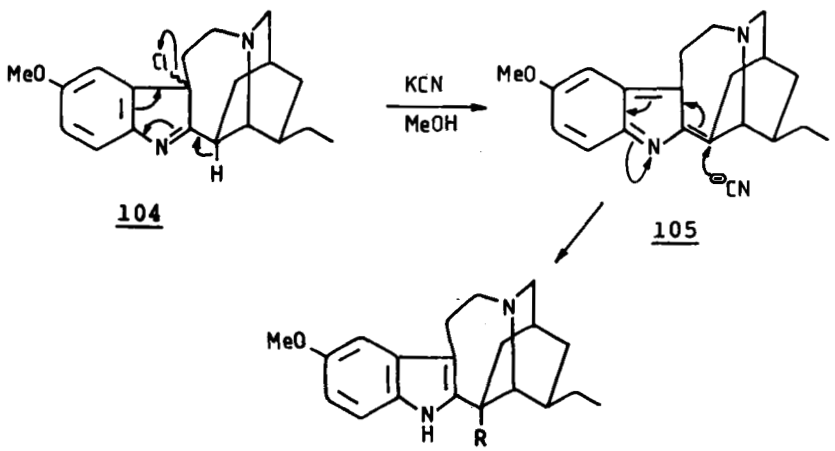
98 R' = alkyl
99 R' = Cl, R = t-Bu

100 R' = alkyl (E+Z)
101 R' = Cl, R = t-Bu

The addition of cyanide to the imino function is the preferred reaction as illustrated further by the reaction with α-halogenated imidoyl cyanides 102; the exclusive reaction was nucleophilic addition at C=N, an exchange which was demonstrated by the incorporation of ^{14}C-labelled cyanide into the molecule.[23]



Exposure of 3-chloroindolenine 104 (derived from ibogaine) to potassium cyanide in aqueous methanol at room temperature furnished 18-cyanoibogaine 106, which was hydrolyzed to the naturally occurring alkaloid voacangine 107.[45]

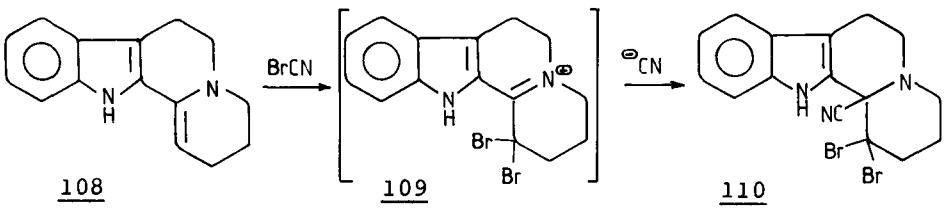


104 105

106 R = CN

107 R = $COOCH_3$ (voacangine)

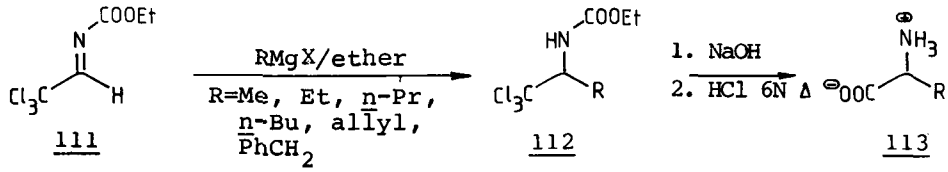
α-Halogenated immonium salts also add cyanide as illustrated by the addition of cyanogen bromide to indole derivative 108. The reaction passed through an α,α-dibromoimmonium salt 109, which reacted with cyanide anion to produce adduct 110.[63]



108 109 110

2.3. Reactions of α-Halogenated Imino Compounds with Organometallic Reagents

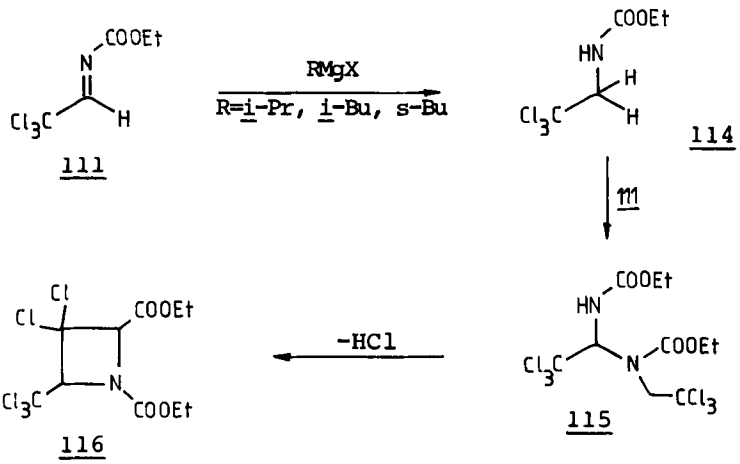
Reactions of organometallic reagents with α-haloimines have not been investigated extensively. Only α-halogenated aldimines provided valuable reactions with Grignard reagents. Anhydrochloralurethans 111 afforded nucleophilic addition with a large variety of organomagnesium halides.[64] The adducts 112 were hydrolyzed to the corresponding α-aminoacids 113 (Preparation 5).[64] With branched organomagnesium halides, reduction of the imino function occurred and the resulting amines added



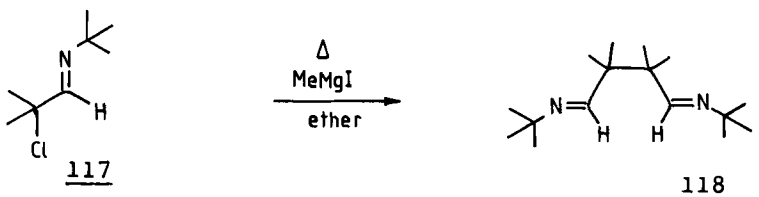
111 112 113

to the starting compounds to yield aminals 115, which furnished azetidine derivatives 116 by cyclization.[64]

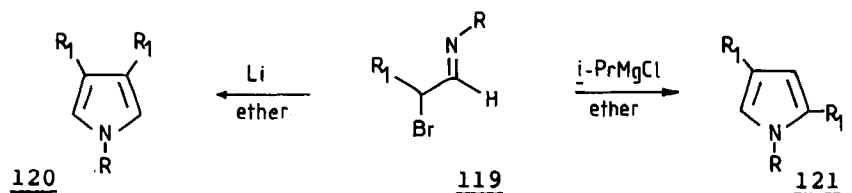
α-Chloroaldimines, e.g. 117, underwent a coupling reaction to 1,4-diimine 118 when treated with methylmagnesium iodide in ether;[21] an α-substitution was also reported with the corresponding N-cyclohexyl α-chloroaldimine.[21] α,α-Dichloroaldimines did not react with methylmagnesium iodide in ether under reflux.[65]



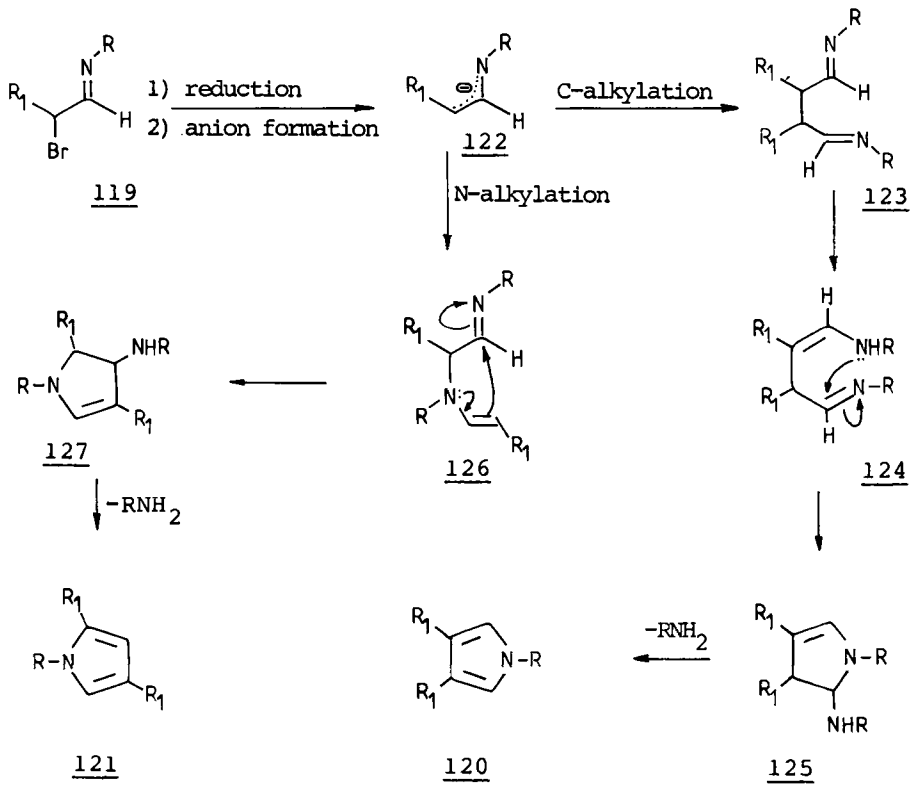
α-Bromoaldimines 119 reacted with two equivalents of isopropylmagnesium chloride in ether at 10° to afford 1,2,4-trisubsti-



tuted pyrroles 121,[66] while the isomeric 1,3,4-trisubstituted pyrroles 120 were obtained by reaction with lithium in ether at -70°C.[66]



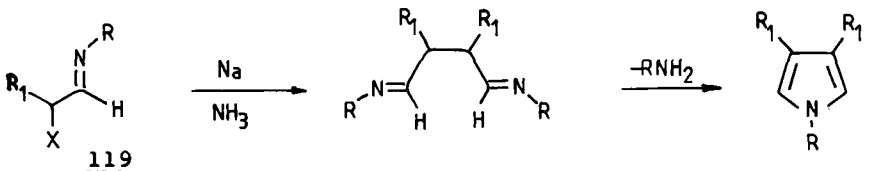
In both cases, the main products were contaminated by the respective isomer (120 and 121). The mechanism was explained by initial reduction and formation of a delocalized carbanion 122, which can either give N- of C-alkylation, the remaining α-bromoaldimine 119 being the electrophilic species.[66]



119 122 123 124 125 126 127 120 121

The 1,4-diimines 123 could be isolated in certain cases and their intermediacy was further supported by the coupling of N-t-butyl-α-bromoisobutyraldimine with lithium yielding 1,4-diimine 118 in 32% yield because the substitution pattern did not permit cyclization to a pyrrole.[67] The influence of several factors on this pyrrole synthesis was investigated and it was found that the yield of 1,3,4-trisubstituted pyrroles increased with increasing electropositivity of the metal (Li > Mg), increasing basicity of the solvent (HMPT > glyme > ether) and increasing electropositivity of the halogen (I > Br).[68] It was demonstrated later that α-bromo- as well as α-chloroaldimines 119 and 128 gave 1,3,4-trisubstituted pyrroles 120 ex-

clusively via diimines 123 by reaction with sodium in liquid ammonia (Preparation 7).[66]

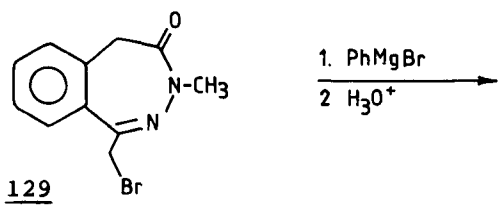


119
128

123

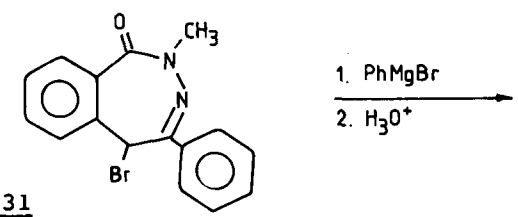
120

α-Halohydrazones such as 1-bromomethyl-3-methyl-3,5-dihydro-(4H)-2,3-benzodiazepine-4-one 129 and 131 were phenylated in the α-position of the imino function with phenylmagnesium bromide in ether.[69,70]



129

130

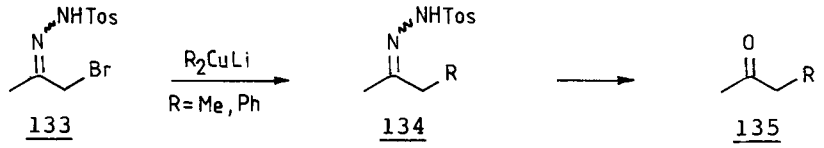


131

132

α-Bromo tosylhydrazones 133 underwent similar α-alkylation with lithium dimethyl- or diphenylcuprate, though an azoalkene intermediate was the reactive species (Preparation 6).[71] The method was also extended to α,α'-alkylation of α,α'-dibromo tosylhydrazones.[71]

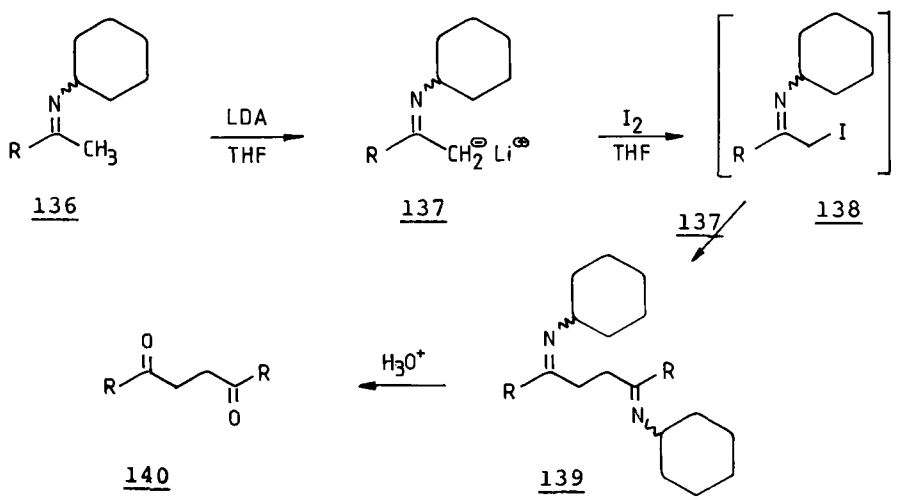
It will be mentioned in a forthcoming section that Grignard reagents[72,73] and lithiated alkynes[74] converted α-halooximes into the α-alkylated oximes by an elimination-addition reaction via nitrosoalkenes.



133 134 135

2.4. Coupling Reactions of α-Halogenated Imino Compounds

Besides the previously mentioned coupling reactions of α-chloroaldimine 117 with methylmagnesium iodide[21] and those of α-haloaldimines 119 with alkali metals or Grignard reagents,[66] selfcondensations of α-halogenated imines do not have ample precedence. Only the in situ generated α-iodoketimine 138 underwent a coupling to yield 1,4-diimino compounds 139, which were converted into 1,4-dicarbonyl compounds 140 on acid hydrolysis.[75]

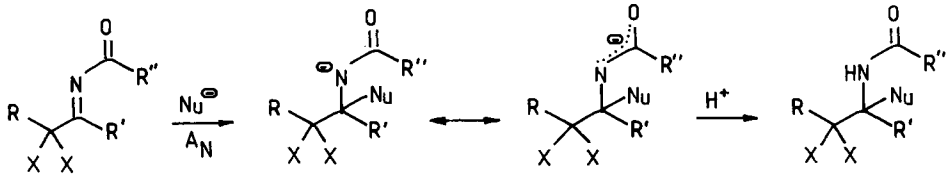


136 137 138 139 140

3. Nucleophilic Additions to N-Activated α-Halogenated Imino Compounds

Nucleophilic additions to the imino function of α-haloimines are of major importance in the total reactivity behavior,

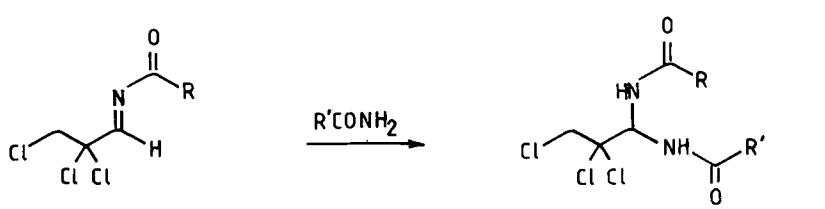
especially when the nitrogen atom can further delocalize its lone pair of electrons (from either the initially formed N-anion or the free pair of electrons) into a N-substituent, e.g. carbonyl or sulfonyl group. This stabilizing effect is generally attained in α-haloimines having an electron-withdrawing substituent and α-perhalogenation. The reaction sequence is generalized by the sequence 141 → 144. N-Activated chloraldimines,[76,77] N-activated trifluoroacetaldimines[78] and N-activated α,α-dichloroaldimines[79-81] were most frequently used in such addition reactions, which proceed smoothly and under very mild conditions (e.g. inert solvent, low temperature) leading



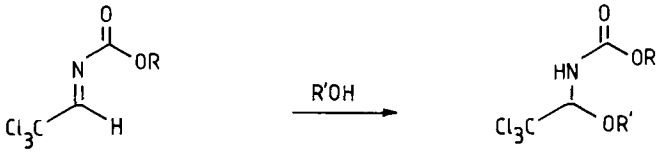
141 142 143 144

$Nu^{\ominus}$ = Nucleophile; X = halogen

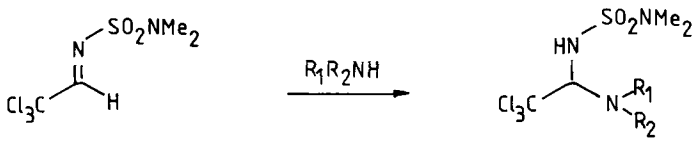
to stable crystalline adducts. A large variety of nucleophilic reagents were condensed with these trihaloacetaldimines, among others alcohols,[76,78,81,82] amines,[76,77,79,80] thiols,[79,80] hydrogen sulfide,[79] water,[76] phenols,[79,80] carboxylic acids,[79,80] N-substituted amides,[79,80] and hydrazines.[80] Some selected examples are presented in the accompanying scheme (Preparations 8 and 9).



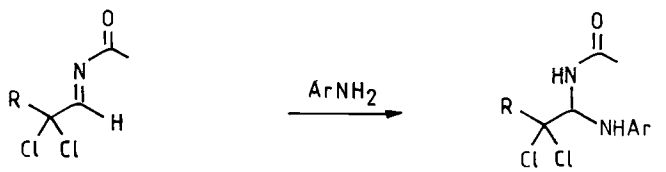
145 146



147 148

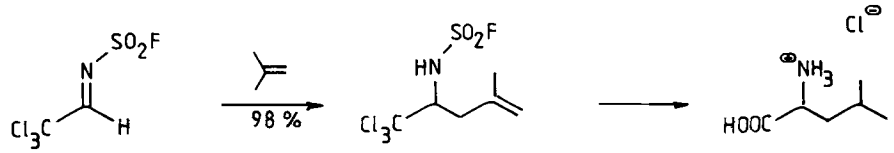


149 150



151 152

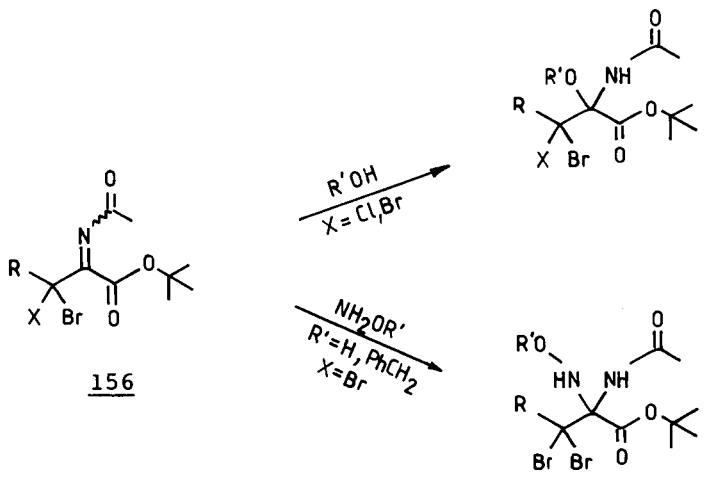
Recently, an unusual reaction was patented, by which N-fluorosulfonyl chloraldimine reacted with isobutene to produce adduct 154, which was used as a precursor for leucine 155.[82]



153 154 155

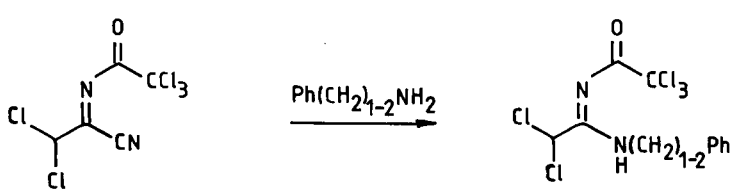
Besides α-halogenated aldimines, α-haloketimines also were found to add nucleophilic reagents at the C=N double bond. In some cases, the α-haloimines occurred as intermediates and were trapped by nucleophiles,[83,84] but in other instances, the stable substrates added the nucleophiles under controlled con-

ditions. N-Acetyl α,α-dibromo- and α-bromo-α-chloroketimines 156 reacted with alcohols and amino compounds to afford the stable adducts 157 and 158.[35,85,86]



156 157 158

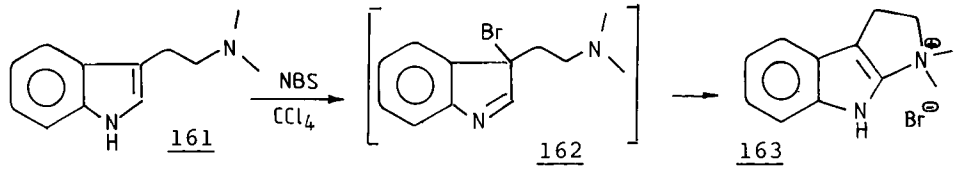
When an α-haloimidoyl cyanide was used as substrate, nucleophilic addition of amines took place with concomitant expulsion of cyanide, thereby yielding the corresponding α-haloamidines.[87]



159 160

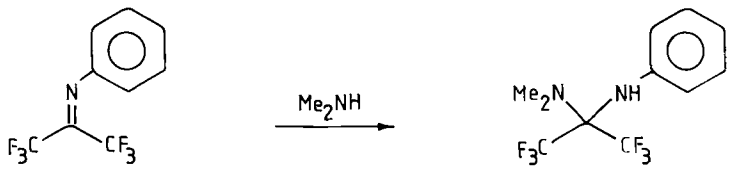
Recently the first intramolecular nucleophilic addition was reported; indole 161 treated with N-bromosuccinimide in carbon tetrachloride afforded intermediate 3-bromoindolenine 162, which underwent cyclization yielding the quaternary salt of pyrrolo[2,3-b]indole 163.[88]

Stable adducts were formed when N-phenyl perfluoroacetone imine 164 was reacted with excess dimethylamine, providing a yield of



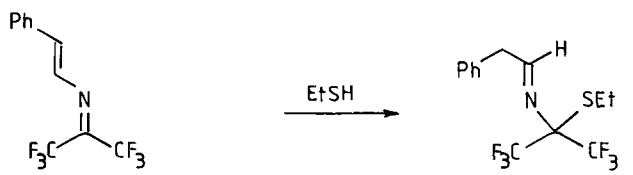
161 162 163

85% of 165.[89] Additions of thiols and amines to perfluoroacetone imines also produced the corresponding adducts.[89]



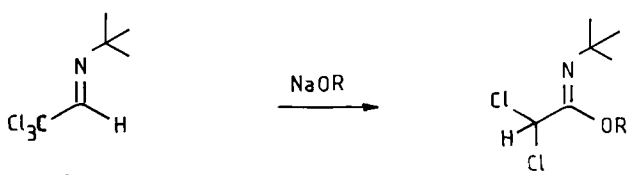
164 165

On the other hand, ethylthiol added to 2-aza-1,3-butadiene system 166 but the final product had isomerized (167).[90]



166 167

Finally, N-t-butyl chloraldimine 99 reacted with sodium alkoxides in alcoholic medium to give mainly α,α-dichloroacetimidates 168, via an addition-elimination reaction.[60]

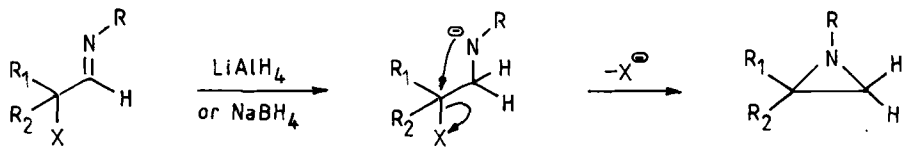


99 168

4. Reaction of α-Halogenated Imino Compounds with Mixed Metal Hydrides

Secondary α-bromo- or α-chloroaldimines 169 and tertiary

α-chloroaldimines 96 reacted with lithium aluminium hydride or sodium borohydride in ethanol to give 1,2- or 1,2,2-substituted aziridines 171 and 172 via a mechanism involving nucleophilic addition of hydride at the carbon-nitrogen double bond followed by intramolecular nucleophilic halide displacement.[66,91] This

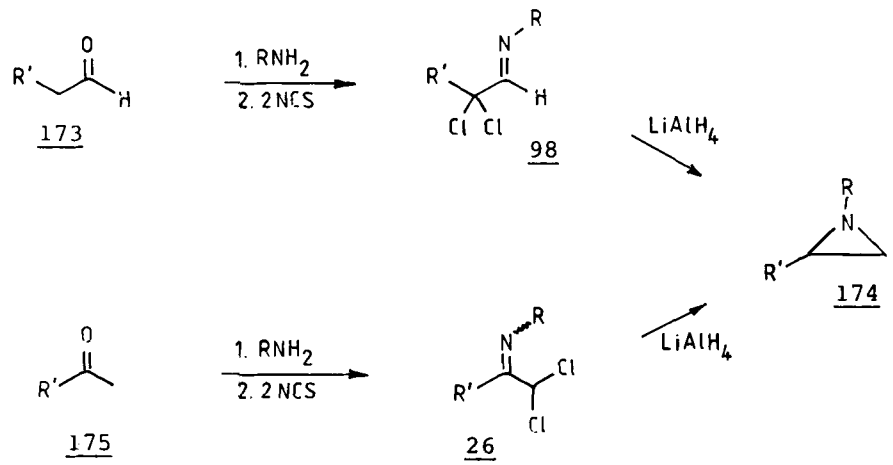


169 R_2 = H; X = Cl, Br
96 R_2 ≠ H; X = Cl

170

171 R_2 = H
172 R_2 ≠ H

method allowed the preparation of spiroaziridines.[91] 1,2,2-Trisubstituted aziridines were found to undergo a thermal rearrangement into the corresponding aldimines by means of either a hydride transfer or an acid-catalyzed isomerization.[91] α,α-Dichlorinated aldimines 98 and ketimines 26 produced 1,2-disubstituted aziridines 174 on treatment with lithium aluminium hydride in diethyl ether at 0°.[92,93] Hence it is possible to synthesize 1,2-disubstituted aziridines 174 starting from either



173

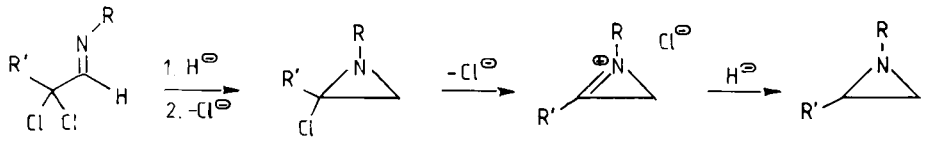
98

174

175

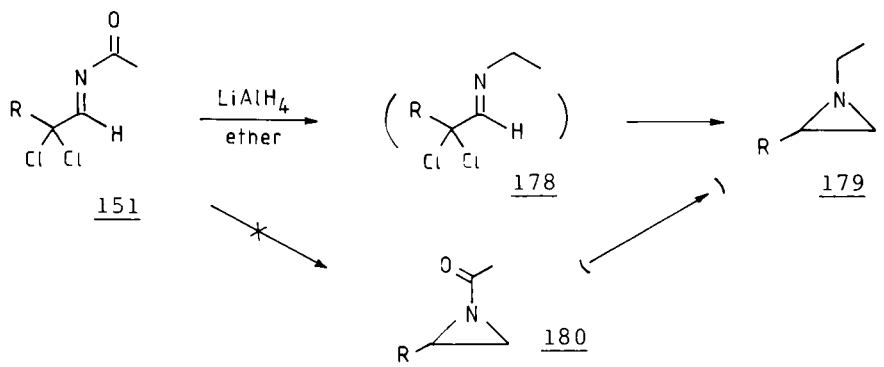
26

aldehydes 173 or methylketones 175 via α,α-dichloroimines (Preparation 10).[92,93] The mechanism for the conversion of α,α-dichloroimines 98 and 26 into 1,2-disubstituted aziridines 174 follows a pathway similar to that outlined above to produce an α-chloroaziridine 176, which ionizes spontaneously to an azirinium chloride 177. This cation adds hydride to yield 174 (the scheme represents the reaction sequence of the transformation of α,α-dichloroaldimines 98 into aziridines 174).[94,95,65]



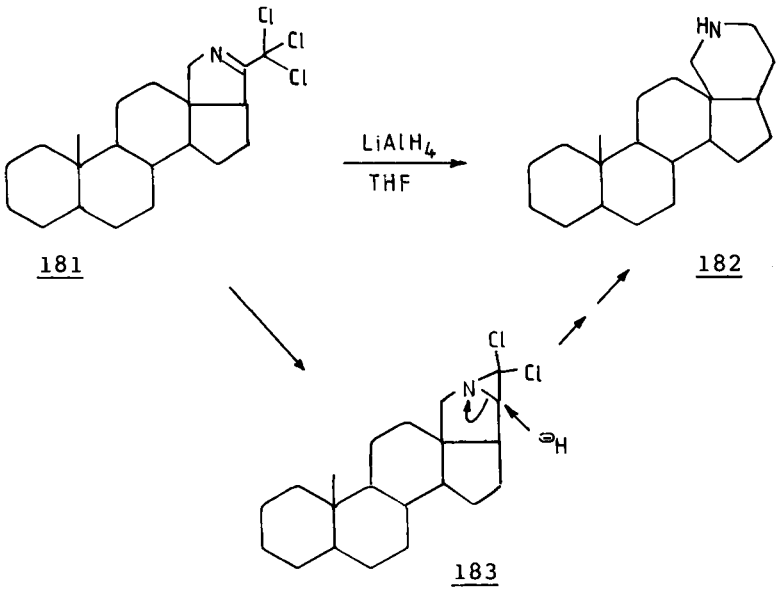
98 176 177 174

N-Activated α,α-dichloroaldimines 151 furnished also 1,2-disubstituted aziridines 179, but the N-acetyl group was reduced to a N-ethyl substituent, prior to transformation as outlined below.[82]

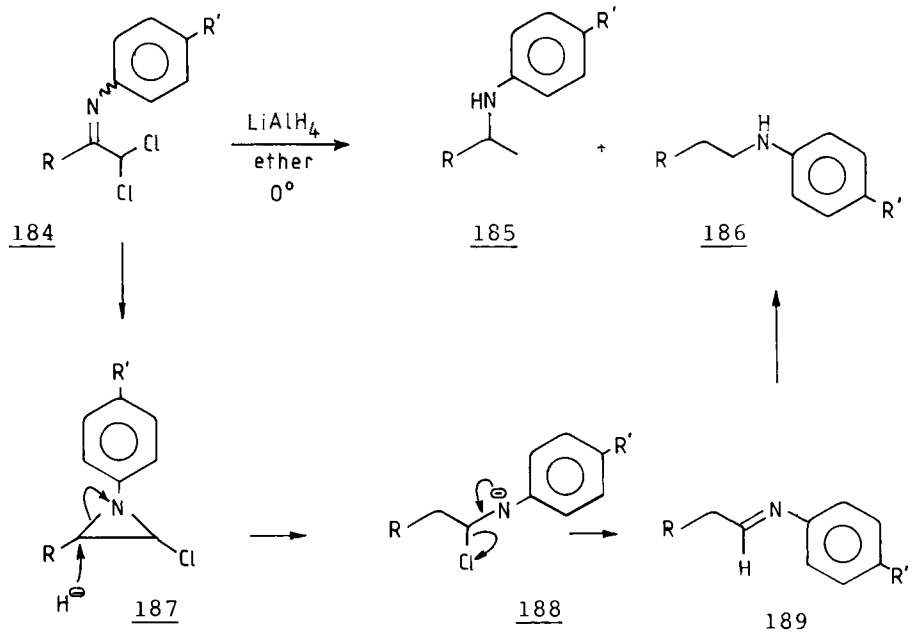


151 178 179 180

The reaction of $LiAlH_4$ in tetrahydrofuran with endocyclic imines and exocyclic halogens provided a useful route to the ring-expanded product 182.[94] Undoubtly the ring opening is caused by the transient occurrence of a highly strained aziridine 183.

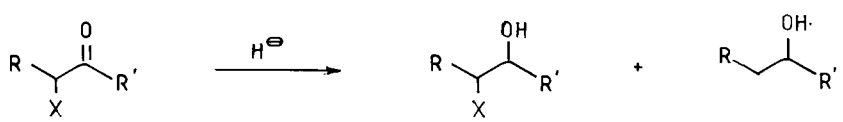


Another ring opening of transient α-chloroaziridines was encountered during the reaction of N-aryl dichloromethylketimines 184 with lithium aluminium hydride in ether at 0°.[95] Two isomeric N-alkyl anilines were isolated, namely aniline 185 and rearranged aniline 186. Aniline 185 is formed by initial reduction of the halogens (S_N2 reactions) and subsequent reduction of the C=N bond. The rearranged aniline 186 is most reasonably explained in terms of α-chloroaziridine 187 formation (vide supra) followed by hydride attack at the carbon atom bearing the alkyl group. The resulting intermediate aldimine 189 is then easily reduced to amine 186. This mechanism is supported by the results for the t-butyl derivative 184 (R = t-Bu; R' = H) in which nucleophilic attack at the t-butyl substituted carbon arom is sterically hindered (see aziridine 187); instead a formal substitution at the halogenated carbon atom in 187 af-



forded 1-phenyl-2-t-butylaziridine in 77% yield.[95] In addition 22% of the fully reduced product 185 (R = t-Bu; R' = H) was isolated.

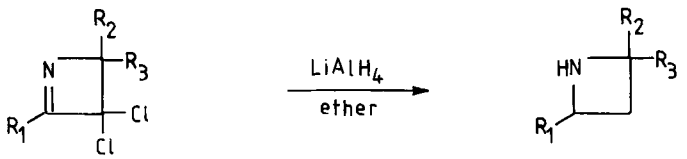
The foregoing results demonstrate that α-halogenated imines are the starting materials of choice for the synthesis of aziridines. This reactivity is in sharp contrast with the reactions of α-halocarbonyl compounds 190 with complex metal hydrides, whereby only reduction and/or substitution of the halogenated carbon atom takes place.



190 X = Cl, Br 191 X = Cl, Br 192

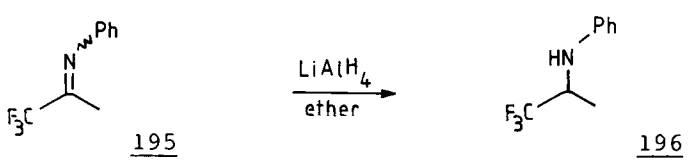
There exist also reports, claiming the formation of compounds, other than aziridines. α,α-Dichloroaldimines 98 reacted with

lithium aluminium hydride to afford aziridines 174, in addition to small amounts of by-products, i.e. β-hydroxyamines and secondary amines.[91,22] Cyclic α,α-dichloroketimine 193 suffered reduction of the imino function as well as of the α-halogens,[96] while the 3-chloroindolenine derived from ibogaine only underwent nucleophilic substitution of the halogenated carbon atom.[4]

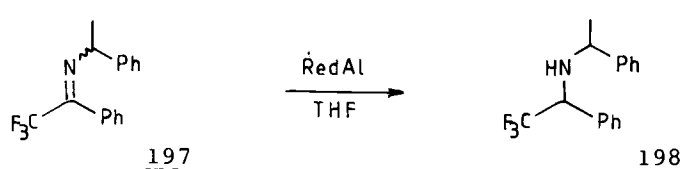


193 194

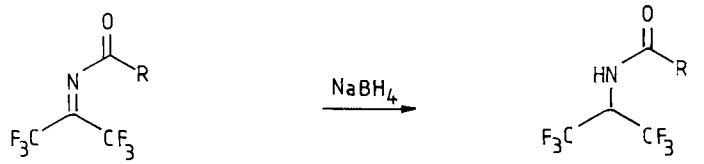
α-Fluorinated imino compounds only added hydride at the carbon-nitrogen double bond to afford β-fluorinated amines. Lithium aluminium hydride in ether, sodium borohydride in ethanol or methanol and sodium bis(2-methoxyethoxy)aluminium hydride (RedAl) in benzene were used for the exclusive reduction of the imino bond in α-fluorinated imino compounds.[89,97,98] N-Phenyl α,α,α-trifluoroacetone imine 195, N-(1-methylbenzyl)-α,α,α-trifluoroacetophenone imine 197 and N-activated hexafluoroacetone imine 199 were converted in high yield into the corresponding β-fluorinated amines.[89,97,98]



195 196

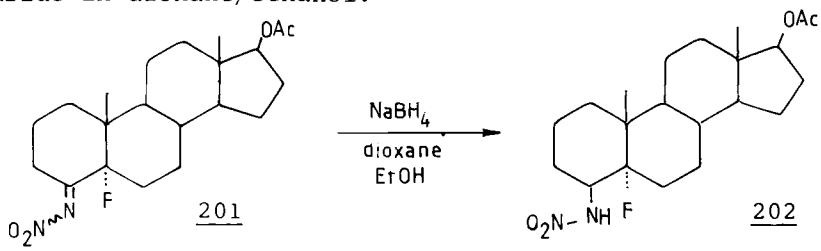


197 198



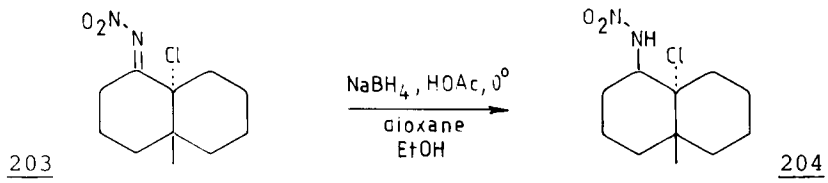
199 (R = alkyl, aryl, O-alkyl) 200

The steroidal 5α-fluoro-4-nitrimine 201 was reduced to the corresponding 5α-fluoro-4β-nitramine 202 by means of sodium borohydride in dioxane/ethanol.[99]



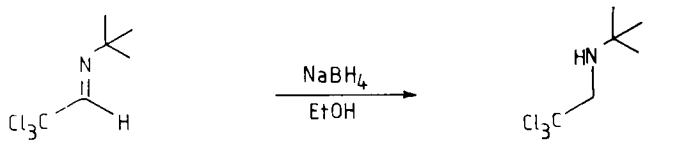
201 202

When the α-halogen was chlorine, the reduction of α-chloronitrimines, e.g. 203, was carried out with sodium borohydride in dioxane/ethanol in the presence of acetic acid, which dramatically increased the yield compared with experiments done in the absence of acetic acid.[100]



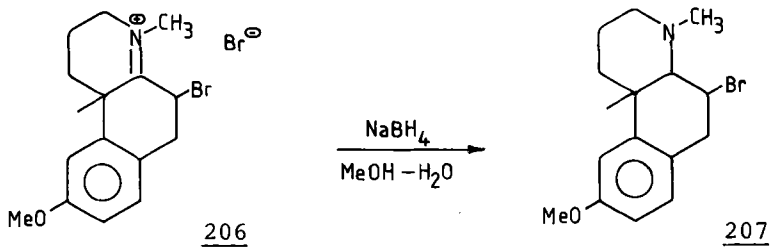
203 204

N-t-Butyl chloraldimine 99 underwent nucleophilic addition only with excess sodium borohydride in ethanol.[60]



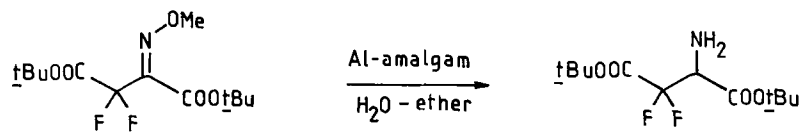
99 205

α-Halogenated immonium salts, e.g. 206, are also susceptible to the above mentioned reductions by nucleophilic addition of hydride to the immonium function.[101]



206 207

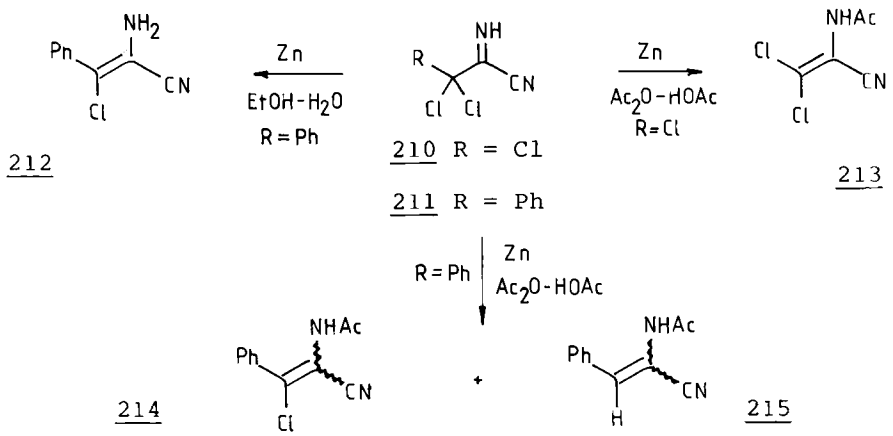
It should be mentioned that imino functions can be reduced by aluminium amalgam even when other reducible functions are present as illustrated by the conversion of α,α-difluorooxime



208 209

ether 208 into the di-t-butyl ester of β,β-difluoroaspartic acid 209 (note : ordinary oximes are converted into the corresponding amines by various reducing agents, e.g. lithium aluminium hydride, etc...).[102]

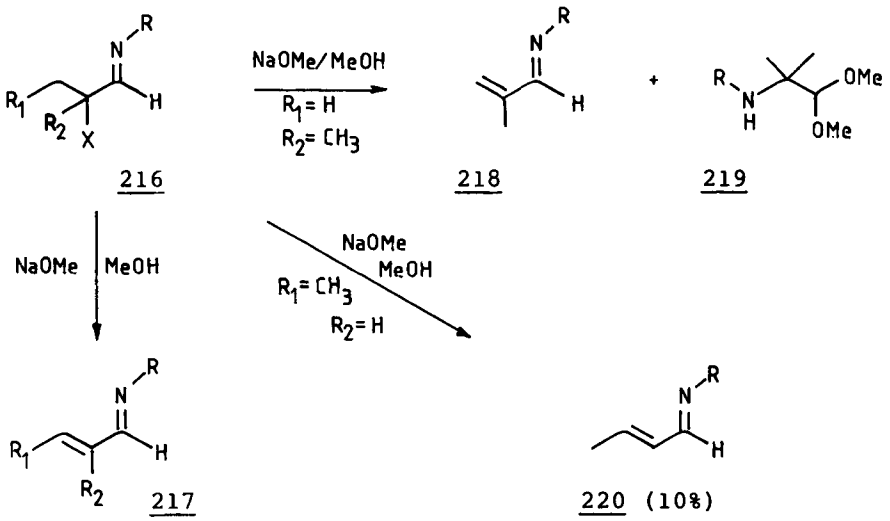
The exclusive reductive dehalogenation of halogens α to an imino group, has been reported in some cases. The reduction of trichloroacetimidoyl cyanide 210 (R = Cl) with zinc in acetic acid/acetic anhydride gave the corresponding N-acetylated dichloro derivative, which tautomerized to its more stable enamino form 213.[103] With α,α-dichloro-α-phenylacetimidoyl cyanide 211 (R = Ph) a mixture of reduced compounds 214 and 215 was obtained when the reaction was performed in the above mentioned medium, while a clean monoreduction was obtained with zinc in aqueous ethanol.[104]



5. Elimination Reactions

5.1. Elimination reactions sensu strictu

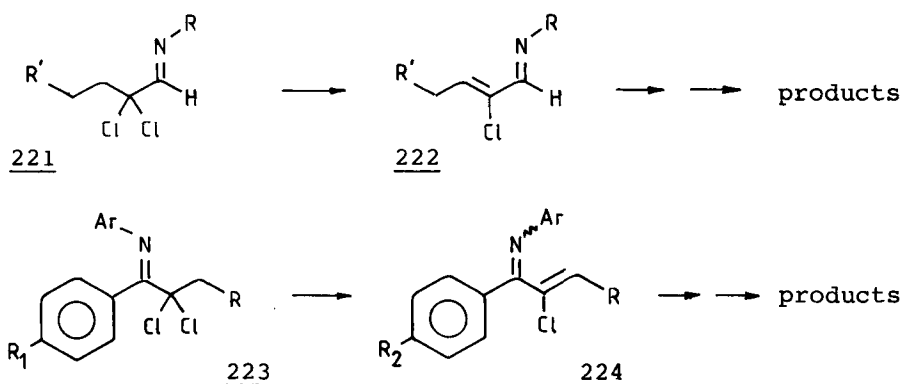
Elimination of hydrogen halide from α-halogenated imino compounds have not been described frequently in the literature. However, it was demonstrated recently that this reaction is in fact one of the basic reactions of simple α-haloimines with basic reagents. The reaction of aliphatic α-chloroaldimines 216 with sodium methoxide in methanol under reflux afforded α,β-unsaturated aldimines 217 (Preparation 11).[21] N-alkyl isobutyraldimines 216 (R_1 = H; R_2 = CH_3) besides elimination, also gave a competitive reaction leading to β-alkylaminoacetals 219.[21] The latter compounds were formed by a rearrangement via an aziridine intermediate (see the section "Rearrangements of α-Halogenated Imino Compounds"). The rearrangement to 219 could be avoided by using an alkoxide of low nucleophilicity, namely potassium tertiary butoxide. Primary α-chloroaldimines, e.g. 216 (R_1 = CH_3; R_2 = H) furnished 220 in only 10% yield, the major products being substitution and rearrangement com-



216 218 219

217 220 (10%)

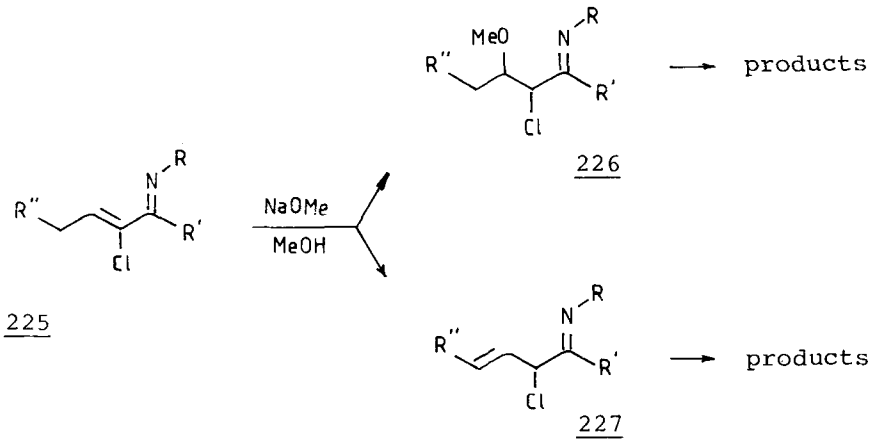
pounds.[21] N-alkyl α,α-dichloroaldimines 221 and N-aryl α,α-dichloroarylalkylketimines 223 exhibited a similar tendency to suffer elimination of hydrogen chloride, but the resulting α-chloro-α,β-unsaturated imino compounds reacted further with sodium methoxide in methanol.[105,106] Migration of the conjugated carbon-carbon double bond or Michael additions created



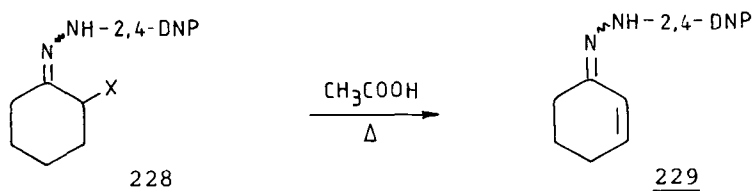
221 222

223 224

new α-haloimino systems, which reacted further to give the final products.[105,106]

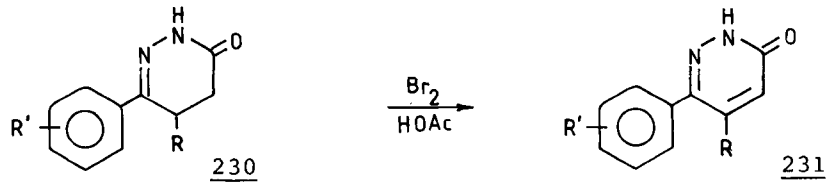


α-Bromohydrazones eliminated hydrogen bromide on heating in acetic acid (Preparation 12).[107,108] This method was used by several research groups to introduce a double bond at C_4-C_5 in 3-ketosteroids by reacting a 4-bromo-3-ketosteroid derivative with 2,4-dinitrophenylhydrazine in acetic acid, after which hydrolysis afforded the α,β-unsaturated carbonyl compounds.[109-111] The latter transformation was also accomplished, albeit in low yields, by boiling the α-bromoketone in pyridine.[112]



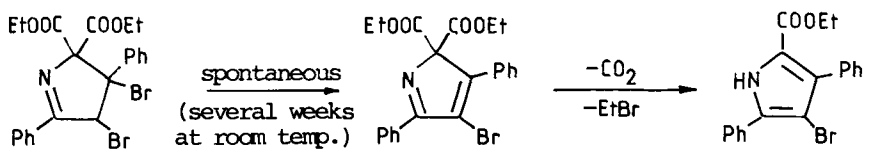
A similar dehydrobromination of an *in situ* formed α-bromohydrazone was found during the bromination of 6-aryl-4,5-dihydro-3(2H)pyridazone 230 with bromine in acetic acid to afford 6-aryl-3(3H)pyridazones 231.[113-115]

Nitrones were shown to undergo dehydrohalogenations also. The conversion of 3-bromo-2-cyano-1-pyrroline 1-oxides 36 (R = H,



230 231

CH_3, Ph) into 2H-pyrrole-1-oxides was performed in 70-90% yield using pyridine N-oxide or triethylamine.[24] α-Chlorooximes were dehydrochlorinated with N,N-dimethylaniline,[116] while in the case of the α-chlorooxime obtained from the nitrosyl chloride addition to caryophyllene (a sesquiterpene), competition between formal α-substitution (via nitrosoolefin; vide infra) and dehydrochlorination was observed.[117] Finally the spontaneous elimination of hydrogen bromide from the α,β-dibromo cyclic imine 232 is in fact a dehydrohalogenation of a β-haloimine, but is added here for comparation purposes.[118]

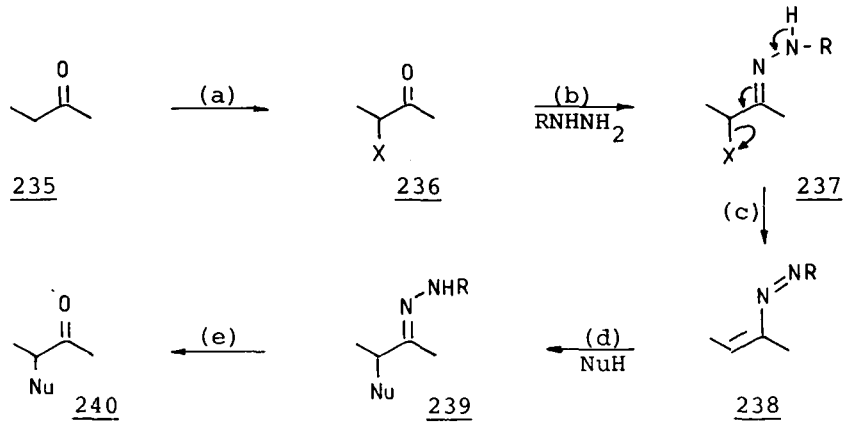


232 233 234

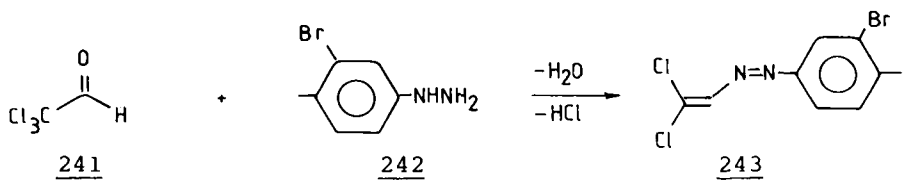
5.2. Elimination of α-Halohydrazone Type Compounds to Azoalkenes and Subsequent Reactions

Recently, considerable attention has been given to the use of α-halohydrazone type compounds 237 in the α-substitution of carbonyl compounds via a reaction sequence involving (a) α-halogenation, (b) α-halohydrazone formation, (c) conversion into azoalkenes, (d) nucleophilic addition to the 1,2-diazabutadiene moiety and (e) hydrolysis. Step (c) is usually

accomplished by an added basic reagent or by excess of the hydrazine used. The suggested mechanism is explained in terms of a base-promoted elimination of hydrogen halide from 237. An earlier path[119] involving spontaneous ionization of the halide in 237, can be rejected on the ground of the previously discussed unfavorable creation of two positive centers in the molecule. In many cases α-halohydrazones 237 and/or azoalkenes



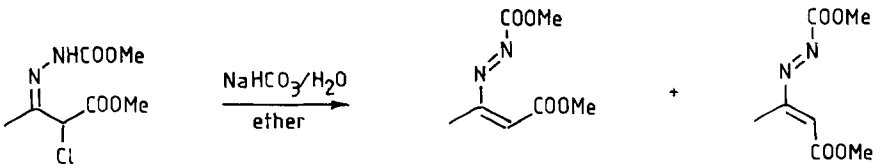
238 were obtained as intermediates in these reactions. The condensation of chloral 241 with 3-bromo-4-methylphenylhydrazine 242 afforded dichlorinated azoalkene 243 via the corresponding hydrazone.[120] The condensation of ethyl 2-chloroaceto-



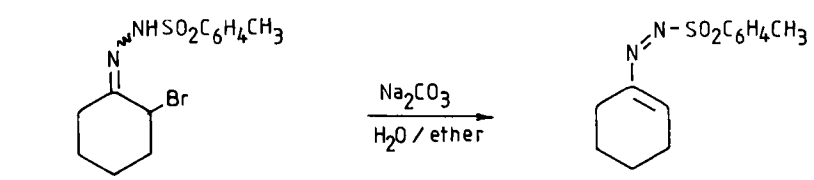
acetate with phenylhydrazine in aqueous ethanol in the presence of sodium acetate gave rise to an azoalkene via the intermediacy of the α-chlorophenylhydrazone.[121]

Recently, such activated azoalkenes have been isolated and characterized by NMR spectrometry.[122] It was shown that the azo-

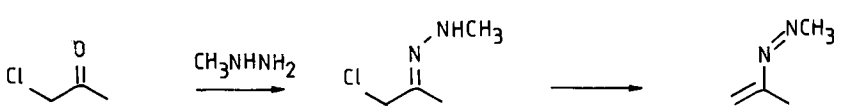
alkene 245 resulting from treatment of α-chlorohydrazone 244 with a two-phase system of aqueous sodium bicarbonate/diethyl ether, existed as a 9:1 ratio of E and Z isomers (245) respectively.[122] As shown by many other examples, the most convenient way of generating an azoalkene moiety consisted of treatment of an α-halohydrazone with sodium carbonate or sodium bicarbonate in a two-phase system (water/ether). By this route, tosylazoalkenes[123-125] and methoxycarbonylazoalkenes,[126] have been obtained. Azoalkenes with terminal carbon-carbon double bond or also available through this procedure, but in this case excess of the hydrazine used was responsible for the elimination of the α-chlorohydrazone formed in situ.[127]



244 Z (10%) 245 E (90%)



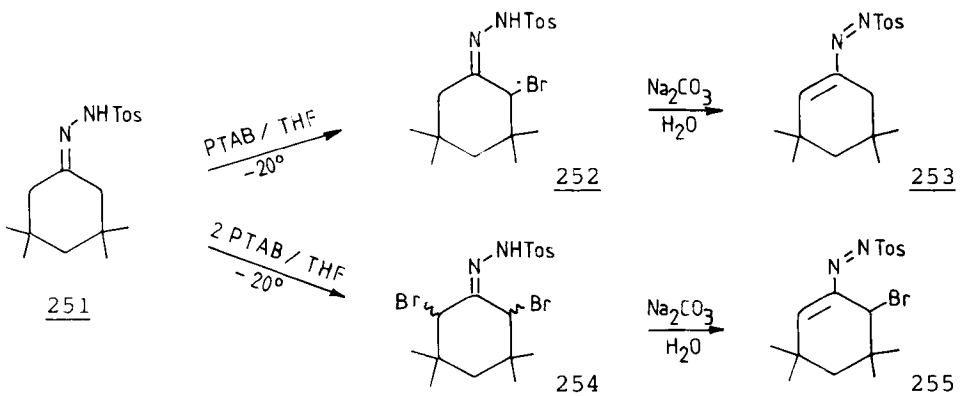
246 247



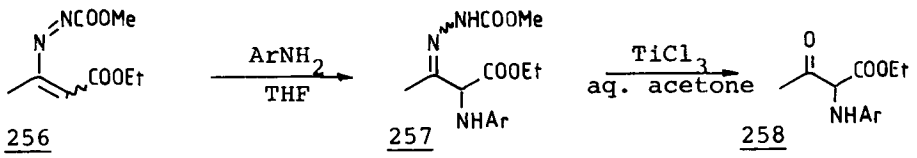
248 249 250

The latter procedure[127,128] could be carried out in various solvents such as dichloromethane, chlorobenzene or even without solvent. Tosylazoalkenes 253, 255 are also available from

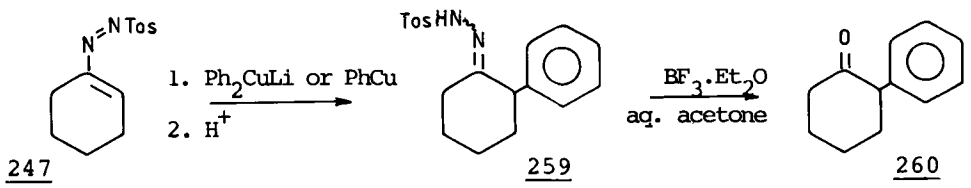
tosylhydrazones 251 by bromination with phenyltrimethylammonium perbromide (PTAB) and subsequent treatment of the intermediate α-bromohydrazones with hydroxide.[129] In the case of 3,3,5,5-tetramethylcyclohexanone tosylhydrazone, the corresponding α-bromo- or α,α'-dibromo-tosylhydrazones 252 and 254 could be isolated at -20°. Subsequent reaction with aqueous sodium carbonate provided the azoalkenes 253 and 255 (Preparation 13).[129]



Azoalkenes are useful intermediates in organic synthesis as they were shown to undergo a variety of transformations, among others additions, cycloadditions and in some cases, nitrogen expulsions. The reaction of α-halohydrazone type compounds with nucleophilic reagents, such as primary and secondary amines, sodium acetate, etc..., probably occurred via addition to intermediate azoalkenes[107,108] as exemplified later by the addition of anilines[126] or organocopper reagents[125] to isolated azoalkenes (Preparation 14). The latter reactions are useful because they lead to the otherwise difficultly accessible α-anilinocarbonyl compounds or α-arylated ketones. A more interesting facet of the chemistry of these azoalkenes is the possibility to give Diels-Alder cycloadditions with dieno-

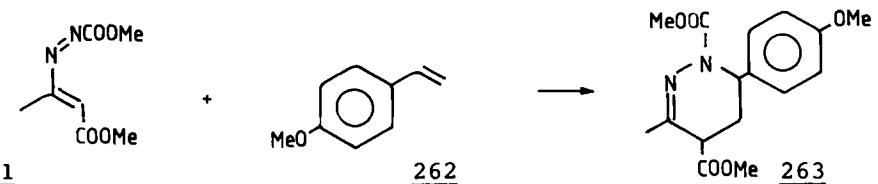


256 257 258



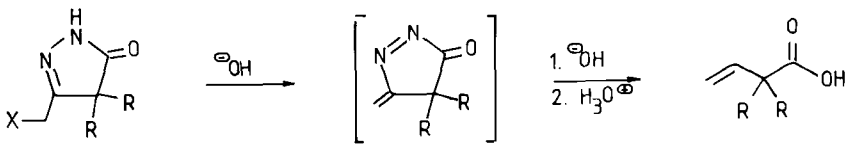
247 259 260

philes. As an example, the electron-poor azoalkene 261 condensed with p-methoxystyrene 262 in ether at room temperature to yield heterocycle 263.[122] A similar type of cyclocondensation was reported for α-bromoacetophenone semicarbazone and 4-(N-pyrrolidino)-3-pentene-2-one.[130]

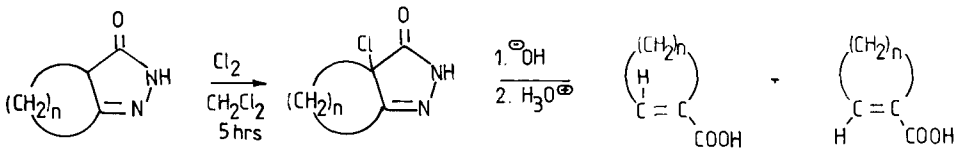


261 262 263

A valuable application of the reactions mentioned in this section is the conversion of cyclic α-halohydrazones 264 with hydroxide to intermediate azoalkenes 265, which were cleaved by hydroxide and transformed into α-vinylcarboxylic acids 266.[131] Similarly 4-halo-3,4-disubstituted-2-pyrazolin-5-ones have been converted into acyclic α,β-unsaturated carboxylic acids;[132-135] this method was recently extended to the synthesis of medium-ring cycloalkene-1-carboxylic acids 269, starting from β-keto-esters (Preparation 15).[136]

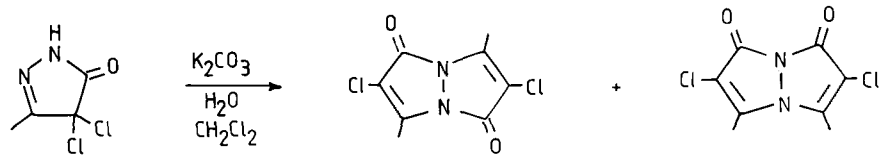


264 265 266



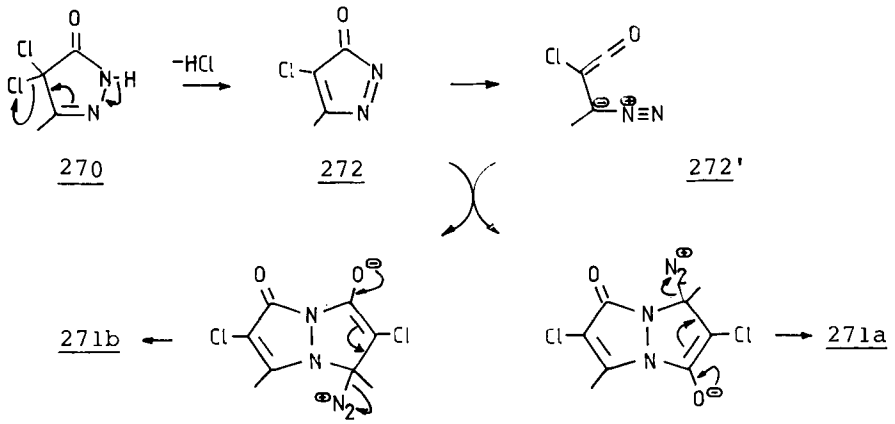
267 268 269 (Z) 269 (E)

More recently, an interesting class of compounds, namely 1,5-diazabicyclo[3.3.0]octadienediones 271a and 271b, became available through treatment of 4,4-dichloro-3-methyl-2-pyrazolin-5-one 270 with potassium carbonate in a two-phase system of water/dichloromethane.[137] The formation of isomeric compounds 271a and 271b was explained by elimination of hydrogen chloride



270 271a 271b

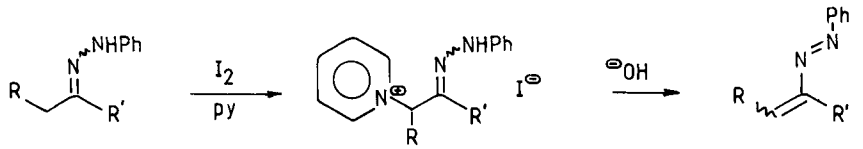
to a cyclic azoalkene 272, which reacts with its isomeric open form 272' to afford two possible bicyclic products. The reaction of phenylhydrazones 273 with iodine in pyridine to afford pyridinium hydroiodides 274 and subsequent 1,4-elimination to azoalkenes 275 also deserves mention.[138-141] The azoalkenes thus obtained were in the E-conformation at N=N and the s-trans conformation in most cases.[138] They were used as hetero-



270 272 272'

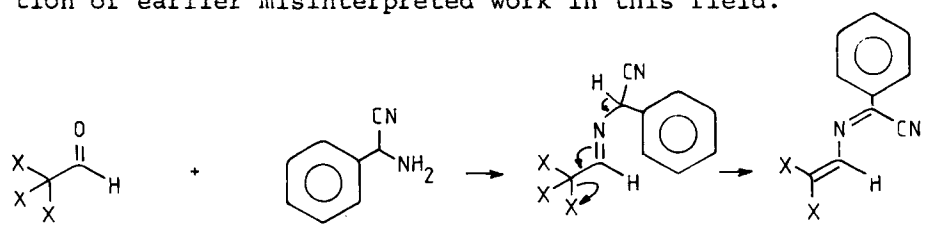
271b 271a

dienes as well as dienophiles in (4+2)cycloadditions.[140] Many other azoalkenes have been utilized in various reactions.[142,143]



273 274 275

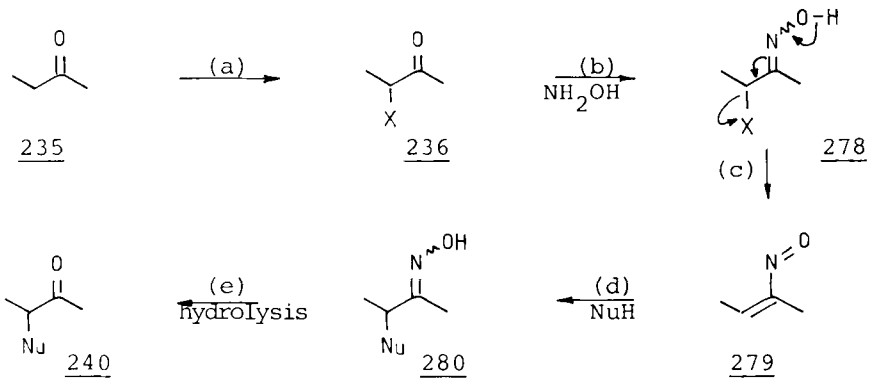
This section will be concluded by examples of a pertinent homologous reaction in α-haloimine chemistry when an acidic α-hydrogen in the nitrogen substituent is present. Condensation of chloral or bromal with 2-amino-2-phenylacetonitrile gave the aldimine 276, which underwent elimination of hydrogen halide, as described above, to afford N-(2,2-dihaloethenyl)-1-imino-1-phenylacetonitrile 277.[144] This reaction is a correction of earlier misinterpreted work in this field.[145]



276 277

5.3. Elimination of α-Halooximes to Nitrosoalkenes and Subsequent Reactions

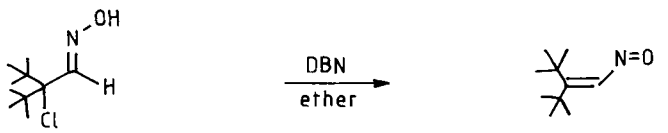
α-Halogenated oximes are known to react with nucleophiles to produce the corresponding α-substituted oximes. These reactions are not the result of nucleophilic substitutions but arise from an elimination-addition mechanism, comparable to that encountered with α-halogenated hydrazones. In the latter case, azoalkenes are intermediates, while with oximes the intermediacy of nitrosoalkenes is presumed. As depicted in the



accompanying scheme, carbonyl compounds are substituted in the α-position via the following sequence : (a) halogenation, (b) oximation, (c) elimination of hydrogen halide to form a nitrosoalkene, (d) addition of the nucleophile and finally (e) hydrolysis.

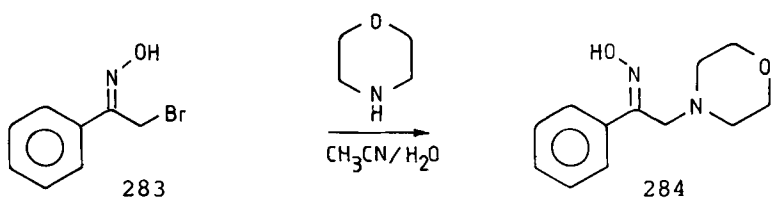
Steps (c) and (d) are usually carried out in one pot by the action of a nucleophilic (and basic) reagent, whereby the intermediate nitrosoalkene 279 is not isolated. The first nitrosoolefin was characterized at low temperature, starting from α-chlorocyclohexanone oxime and calcium hydroxide.[165] The in-

termediacy of nitrosoalkenes in these reactions was further demonstrated by the isolation of a stable derivative 282 from the reaction of α-chloro-α,α-di-t-butylacetaldoxime 281 with diazabicyclo-[4,3,0]-5-nonene in ether;[146,147] the blue crystalline nitrosoalkene was isolated in 84% yield. Similarly, triethyl-



281 282

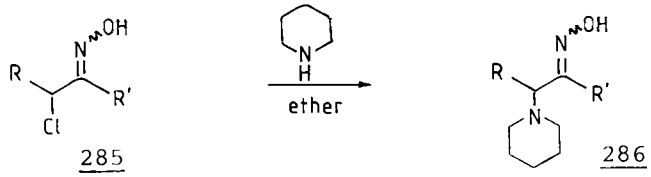
amine in ether was found to produce nitrosoalkenes, trapped by piperidine to afford α-piperidinooximes.[148] In certain instances, attempts to isolate nitrosoolefins were reported to be unsuccesful because of polymerization.[73] A variety of nucleophilic reagents has been added to nitrosoalkenes. The reaction with secondary amines to yield α-dialkylaminooximes has been explored most thoroughly.[72,149-154] The elimination-addition reaction of syn-α-bromoacetophenone oxime 283 with morpholine in aqueous acetonitrile at pH 9.5 gave the product with the opposite configuration, anti-α-morpholinoacetophenone oxime 284.[151]



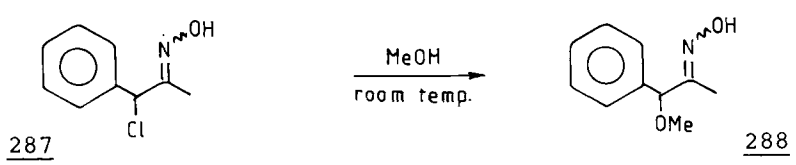
283 284

Non-nucleophilic solvents, such as diethyl ether, are most commonly used and the reagent is simply added to the ether solution. In this way, piperidine, morpholine, pyrrolidine, dime-

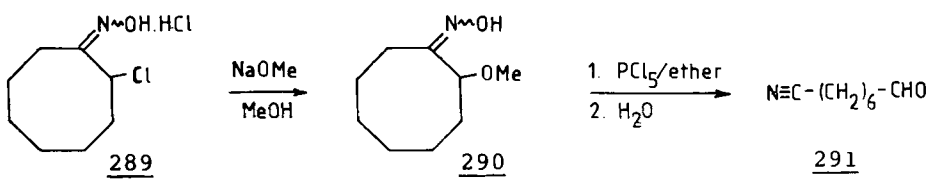
thylamine, N-methylaniline, N-methylbenzylamine, etc... were reported to react with α-halooximes to yield the α-aminooximes.[72,149-154] As an example, 3-chloro-2-butanone oxime 285 (R = R' = CH_3) reacted with piperidine in ether to afford α-piperidinooxime 286 (R = R' = CH_3) in quantitative yield (Preparation 16). Primary amines[72,155] and ammonia[72] also gave the corresponding α-aminooximes with α-halooximes.



When methanol was used as solvent,[149,156] α-methoxyoximes resulted from this reaction, which proceeded at room temperature, as shown for the conversion of α-chlorooxime 287 into α-methoxyoxime 288. The reaction is of course facilitated when tri-

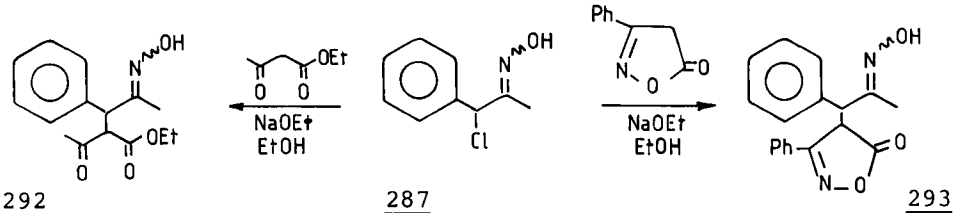


ethylamine[154] or sodium methoxide[116,153,156] in methanol is used, as exemplified for the alicyclic α-chlorooxime 289 (or the hydrochloride).[153,154] The resulting alicyclic α-methoxyoximes were easily cleaved by phosphorus pentachloride to yield ω-cyanoaldehydes 291.[154,157] Similarly, sulfur nucleophiles



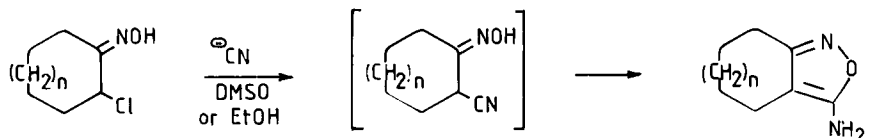
were also found to give a formal α-substitution of α-halooximes.[154]

Carbon-carbon bond formation was demonstrated by the condensation of α-chlorooxime 287 with the anions of ethylacetoacetate and 3-phenyl-2-isoxazolin-5-one to afford the α-substituted oximes 292 and 293 respectively.[73] α-Chlorooxime 289 gave similar α-substituted derivatives with the anions of diethyl malonate and 2,4-pentanedione.[72] Grignard reagents in ether gave the α-alkylated oximes with α-chlorooximes 287 and 294[72,73] while cyanide anion in dimethylsulfoxide or ethanol



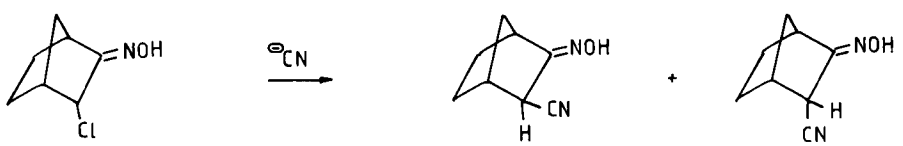
292 287 293

only gave an intermediate α-cyanooxime 295 in the alicyclic series, finally resulting in the ring-closed 5-aminooxazoles 296.[54] Only the bicyclic α-chlorooxime 297 reacted with cya-



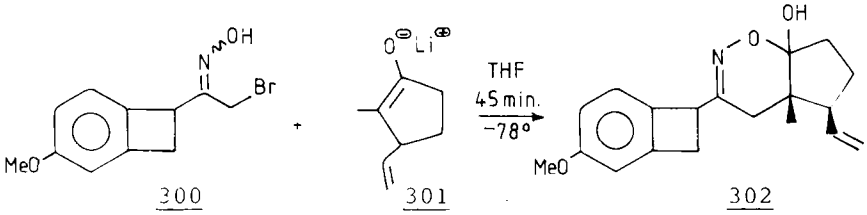
294 295 296

nide anion to produce a mixture of endo and exo α-cyanooximes 298 and 299.[54]



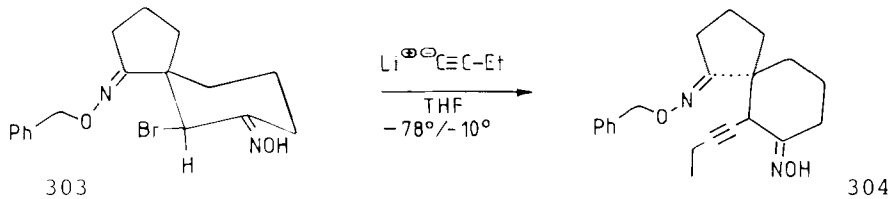
297 298 299

The nucleophile-induced elimination-addition of α-halooximes was used as one of the key steps in a new steroid synthesis. α-Bromooxime 300 and lithium enolate 301 in tetrahydrofuran at low temperature gave a 77% yield of 302 which was further transformed into steroidal compounds.[158] 1-Lithio-1-butyne added



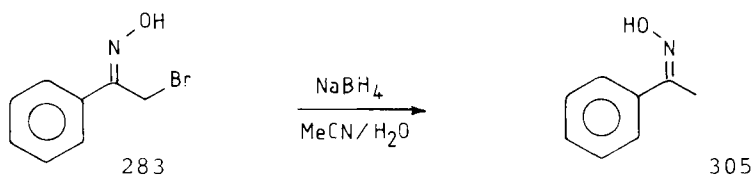
300 301 302

to a transient nitrosoolefin, generated from α-bromooxime 303 to furnish α-(1-butynyl)oxime 304.[74]



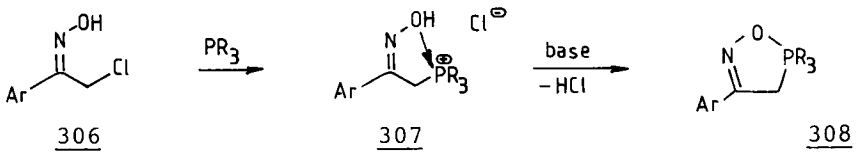
303 304

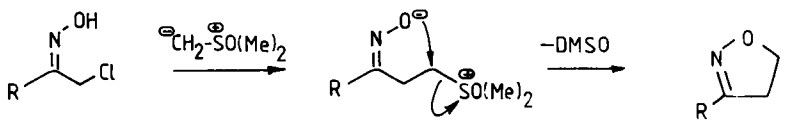
The generality of the elimination-addition reaction of α-halooximes with nucleophilic reagents was demonstrated by their reactions with silver and sodium nitrite, sodium nitrate and sodium azide, to yield α-nitrito-, α-nitrato- and α-azidooximes respectively.[72] Finally, sodium borohydride in aqueous acetonitrile converted syn-α-bromoacetophenone oxime 283 into anti-acetophenone oxime 305 via α-nitrosostyrene.[159]



283 305

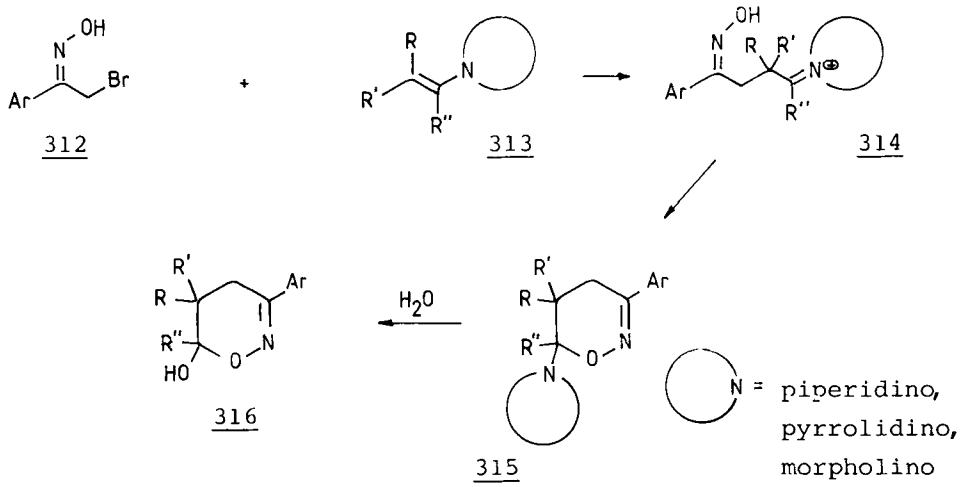
When the group replacing the halogen is sensitive to nucleophilic reagents, intramolecular attack by the oxime oxygen can take place to afford O,N-heterocyclic compounds. Accordingly, α-chloromethylketoximes 306 and 309 react with phosphines or dimethylsulfoxonium methylide to give α-substituted oximes 307 and 310, which undergo ring closure with formation of 308 and 311 respectively (Preparation 17).[160-163]



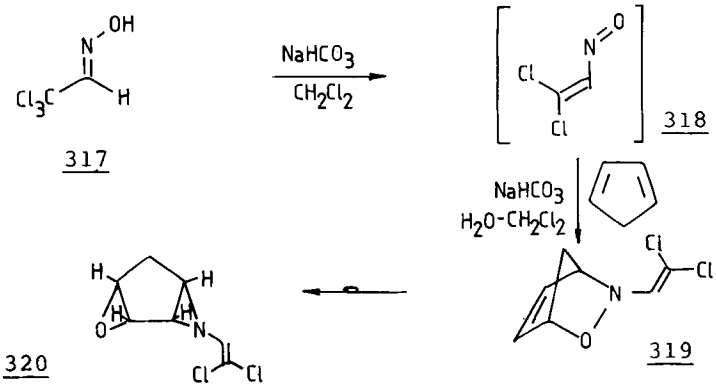


In similar way, alkylation of enamines 313 by substituted α-bromoacetophenone oximes 312 yielded the corresponding immonium salts, which were hydrolyzed into 6-hydroxy-4,5-dihydro-1,2,4H-oxazines 316.[164]

The reactions shown above demonstrate the versatility of the Michael-type additions to intermediate nitrosoolefins, starting from α-halooximes. Moreover, nitrosoalkenes undergo cycloadditions and either the C=C bond or the N=O double bond can act as a dienophile in Diels-Alder reactions. An interesting reaction is the base-promoted conversion of chloraloxime 317 into nitrosoolefin 318, which is trapped in the presence of cyclo-

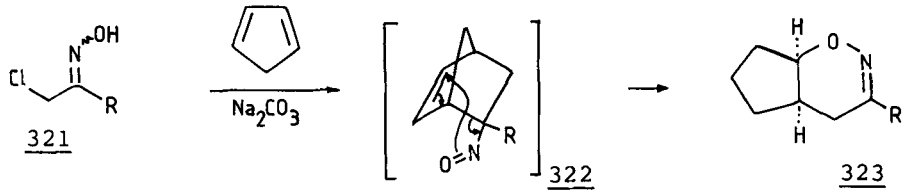


pentadiene to form oxazine derivative 319; the latter compound rearranged spontaneously into tricyclic compound 320.[156,166]

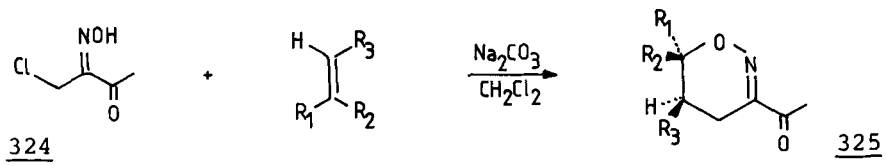


Various analogous examples, e.g. with bromaldoxime and α,α,α-trichloroacetone oxime, were reported recently.[156,166] On the other hand, α-chlorooximes 321 (R = H, CH_3, CH_2Cl, C_6H_5, CN) were transformed into cis-fused oxazine derivatives 323 by reaction with cyclopentadiene in the presence of sodium carbonate.[156]

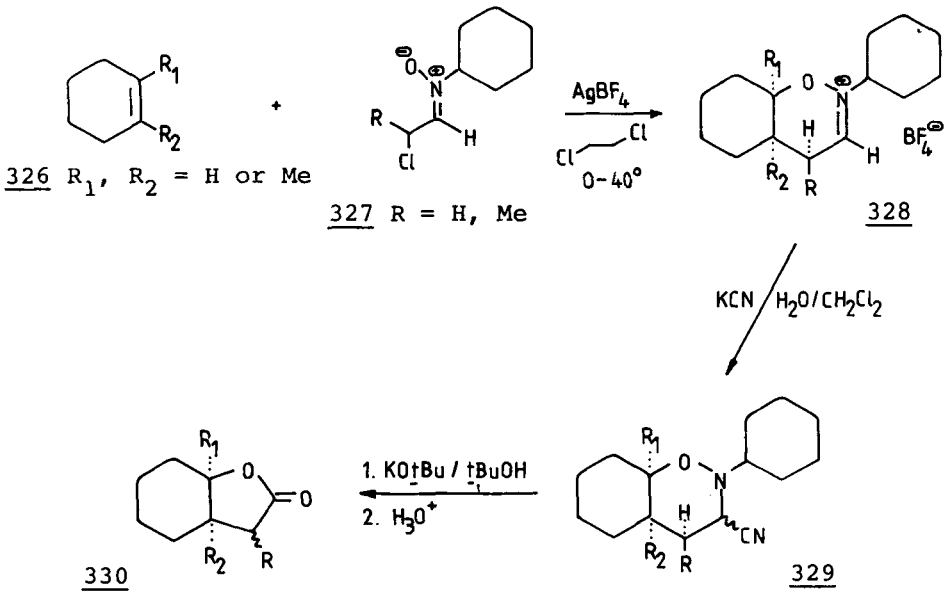
It was further recently demonstrated that nitrosoolefins (from e.g. 324) carrying an electron-withdrawing substituents, easily



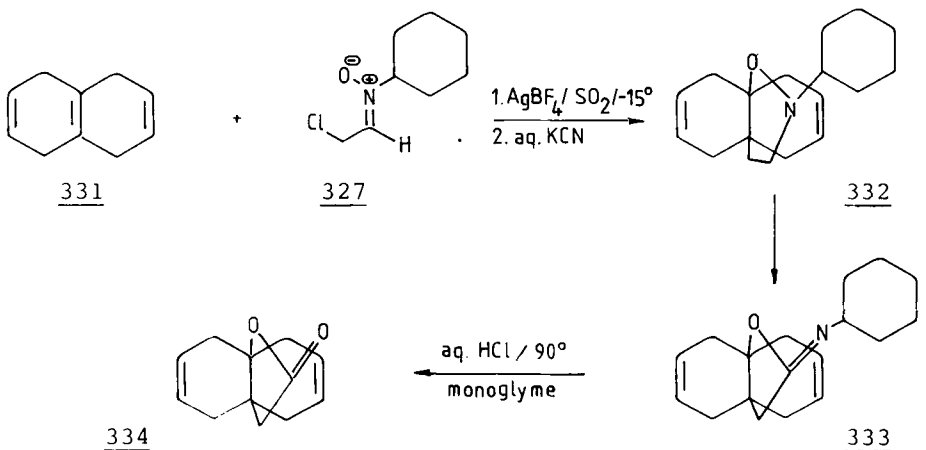
form adducts with olefins, including simple alkenes and electron-rich heterocyclic compounds.[167]



α-Chloronitrones have been shown to give a variety of cycloaddition reactions via transient heterodienes, which are comparable to nitrosoolefins. For instance, N-cyclohexyl α-chloronitrones 327 reacted with cyclohexenes 326 in 1,2-dichloroethane in the presence of silver tetrafluoroborate to yield bicyclic compounds 328.[168] The latter compounds added cyanide

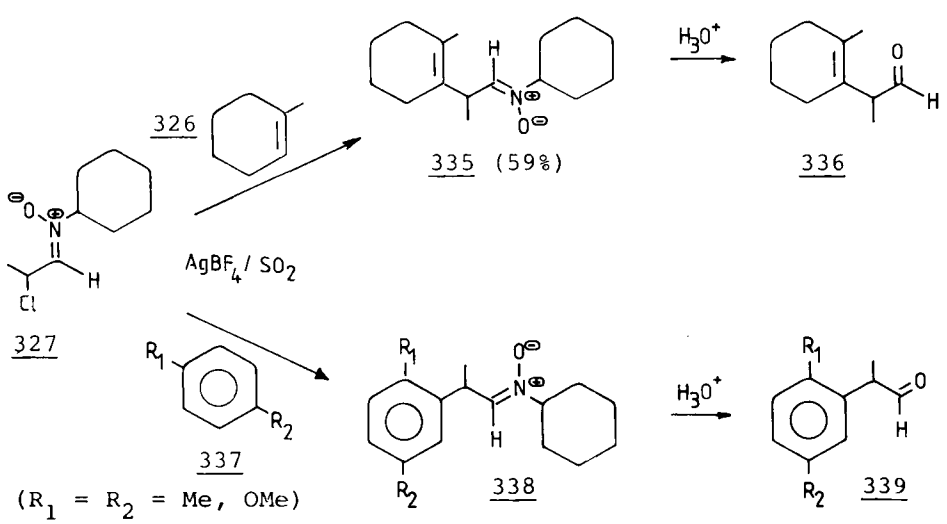


to give 329, which were converted into γ-lactones 330 through a two-step sequence (Preparation 18).[169,170] Other applications of these cyanide adducts involved the synthesis of α-methylene-γ-lactones[170] and their thermal ring-opening reactions to afford α,β-unsaturated carbonyl compounds.[171,172] When the above mentioned reaction sequence was applied to olefin 331, [4,4,3]propellane lactone 334 was produced.[173]



331 327 332 333 334

When the reactions were run in liquid sulfur dioxide in the presence of silver tetrafluoroborate, α-chloronitrone 327 and

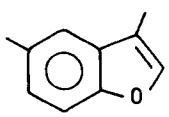


326 327 335 (59%) 336 337 338 339

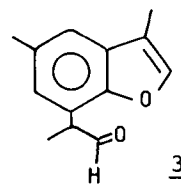
(R_1 = R_2 = Me, OMe)

1-methylcyclohexene 326 or activated arenes 337 furnished substitution products 335 and 338, which were hydrolyzed into the corresponding aldehydes 336 and 339.[174]

On the other hand, when p-cresol was used in these reactions, benzofurans 340 or 341 were formed, when one or 3.5 equivalents of α-chloronitrone 327 was utilized respectively.[174]



340



341

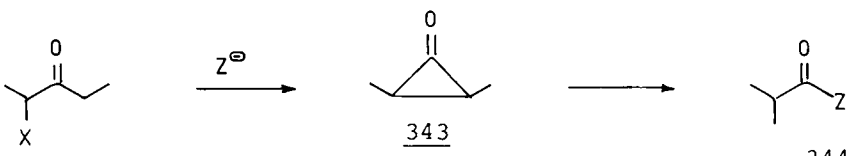
6. Rearrangements of α-Halogenated Imino Compounds

A more interesting facet of the chemistry of α-halogenated imino compounds is their potential to be transformed into a variety of products, having a rearranged carbon-skeleton or which underwent a transposition of the nitrogen atom. About four main types of rearrangements of α-haloimines can be distinguished, namely 1) the Favorskii-type rearrangement, 2) rearrangement via intermediate activated aziridines, 3) rearrangements of 3-chloroindolenine derivatives and 4) a concerted [3,3]sigmatropic rearrangement. Many of these rearrangements have been used in alkaloid and drug synthesis while others have been demonstrated to be versatile tools in certain transformations in organic syntheses.

6.1. The Favorskii-type rearrangement

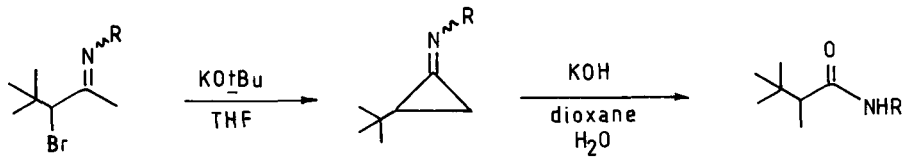
The Favorskii-rearrangement is the base-induced skeletal rearrangement of α-halogenated ketones to afford carboxylic

acid derivatives via intermediate cyclopropanones. This reaction found widespread application in organic synthesis and was of particular value for the synthesis of branched carboxylic acid derivatives and α,β-unsaturated carboxylic acid derivatives.



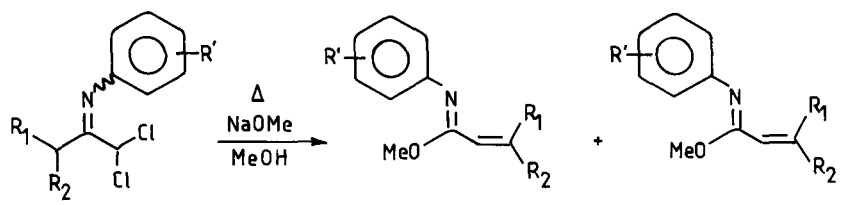
342 ($Z^{\ominus}$ = alkoxide, hydroxide, amine) 343 344

Furthermore, ring contractions in steroidal substrates have been successfully applied. Since its discovery by Favorskii,[175] the reaction has received continuing interest. The Favorskii-rearrangement has been reviewed several times[9-16] already. Because of the related structure to α-haloketones, α-haloketimines can be expected to exhibit similar mechanistic potential under suitable reaction conditions and thus lead to related Favorskii-rearrangements. In the early 1970's, Quast and coworkers performed the first transformation of an α-haloimine into a carboxylic amide via a two-step sequence, which could be accounted for in terms of a Favorskii-type rearrangement.[176,177] Sterically hindered N-alkyl-α-bromoketimines 345 were converted into cyclopropylideneimines 346 (i.e. the imino analogues of cyclopropanones) via 1,3-dehydrobromination with potassium t-butoxide in tetrahydrofuran.[176,177] On treatment of these three-membered ring compounds with potassium hydroxide in aqueous dioxane, ring opening afforded the highly branched carboxylic amides 347.[176,177] So far the only report describing a Favorskii-type rearrangement sensu strictu is the reaction of N-aryl α,α-dichloromethylketimines 71 with sodium methoxide in methanol



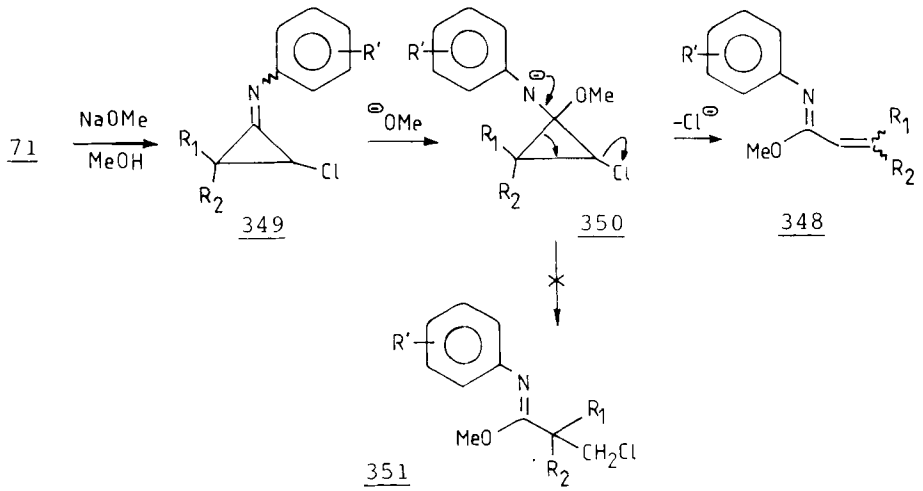
345 346 347

under reflux to yield α,β-unsaturated imidates 348 in addition to α,α-dimethoxyketimines and α,α'-dimethoxyketimines.[19,20,178]



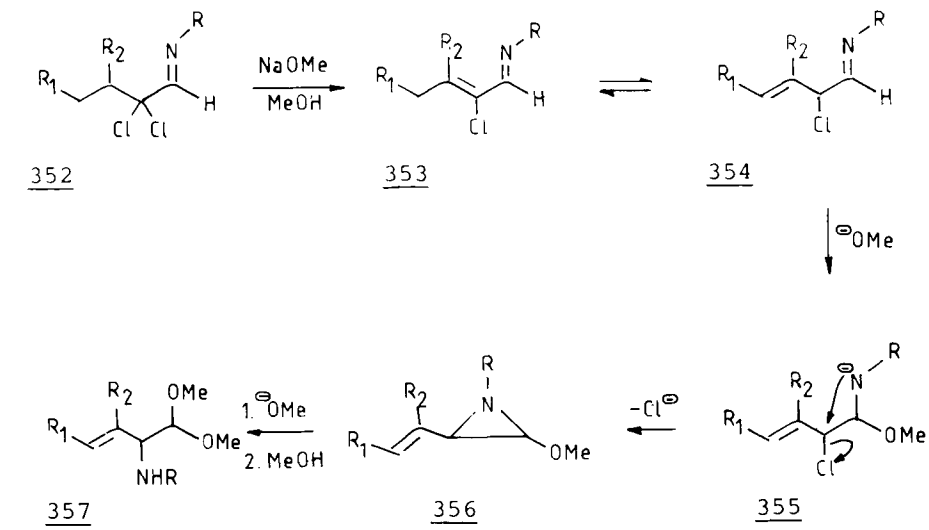
71 348a 348b

Primary dichloromethylketimines 71 (R_2=H) underwent a Favorskii-type rearrangement with exclusive formation of Z-α,β-unsaturated imidates 348a (R_2=H)[19,20] while secondary derivatives 71 ($R_2 \neq H$) gave a mixture of E- and Z-α,β-unsaturated imidates 348a and 348b ($R_2 \neq H$).[20] The mechanism was postulated to occur via an intermediate chlorinated cyclopropylideneaniline 349, which was opened regiospecifically because of the possibility of concomitant expulsion of a chloride anion. Accordingly, no trace of an α-(chloromethyl)imidate 351 was observed. Primary dichloromethylketimines 71 (R_2=H) yielded 348a (R_2=H) exclusively by a Favorskii-like rearrangement with sodium methoxide in a less polar medium such as diisopropyl ether (Preparation 19).[20]

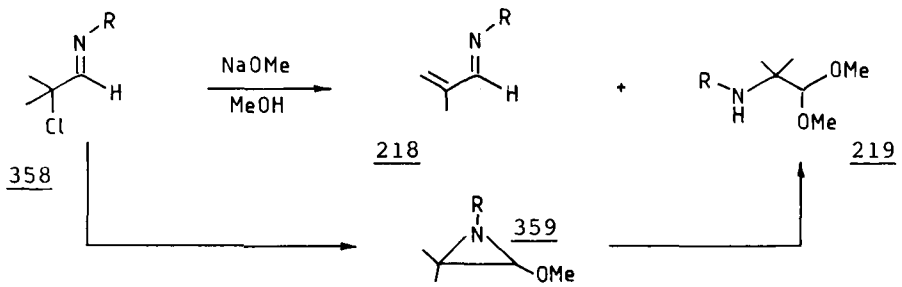


6.2. Rearrangement via Activated Aziridine Intermediates

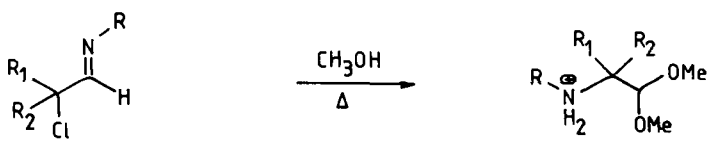
The preferred reaction of α-haloimines when treated with strong basic and nucleophilic reagents is elimination (vide supra). α,α-Dichloroaldimines 352 showed this elimination predominantly when treated with sodium methoxide in methanol, but



the initially formed α,β-unsaturated aldimine 353 isomerized into the β,γ-unsaturated aldimine 354.[105] α-Chloroaldimine 354 underwent nucleophilic addition at the imino function followed by intramolecular nucleophilic substitution to afford an activated α-methoxyaziridine, which reacted with methoxide or the solvent (methanol) to give β-alkylaminoacetals 357.[105] Tertiary α-chloroaldimines and sodium methoxide in methanol only yielded α,β-unsaturated aldimines except for N-alkyl α-chloroisobutyraldimines 358, in which a competition between elimination of hydrogen chloride and rearrangement via a methoxyaziridine 359 was observed.[21]



When no base was added, i.e. when α-chloroaldimines 358 were refluxed with methanol only, the reaction proceeded to complete rearrangement with production of hydrochlorides of β-alkylammoniumacetals 361 (Preparation 20).[21] Secondary α-chloroaldi-



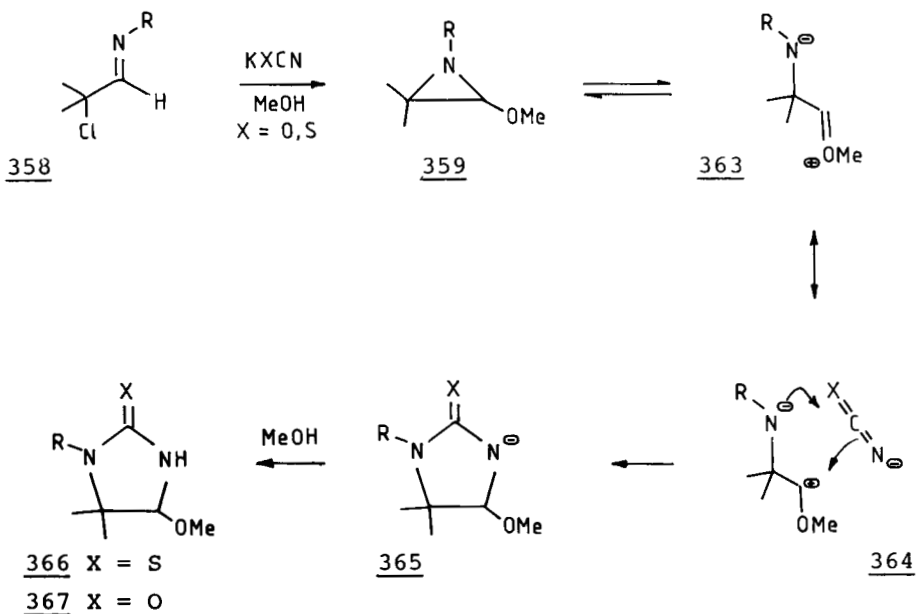
358 $R_1 = R_2 = CH_3$ 361 $R_1 = R_2 = CH_3$

360 R_1 = Et; R_2 = H 362 R_1 = Et; R_2 = H

mines, e.g. N-1-(2-chlorobutylidene)t-butylamine 360, analogously rearranged quantitatively into 362 when refluxed in me-

thanol,[65] but underwent competition between rearrangement, elimination and nucleophilic chloride displacement when refluxed with sodium methoxide in methanol.[21]

The intermediacy of α-methoxyaziridines 359 was established by trapping these intermediates with the ambident thiocyanate and cyanate anions,[179,180] resulting respectively in 2-imidazolidinethiones 366 and 2-imidazolidinones 367 (Preparation 21). The trapping of 359 by thiocyanate or cyanate always occurred in competition with reaction with methanol, whereby β-alkyl-

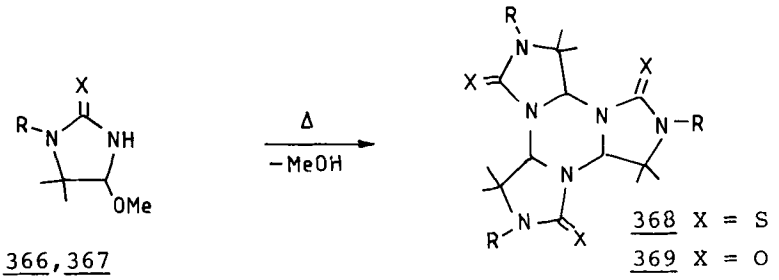


358 359 363

366 X = S
367 X = O

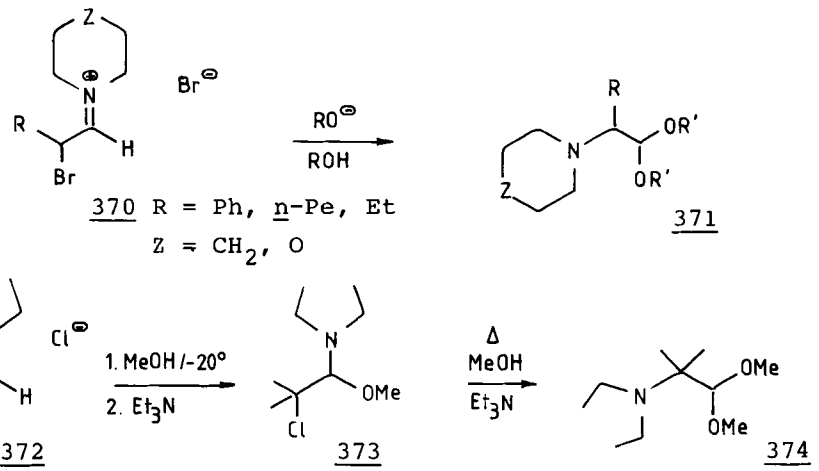
365 364

aminoacetals 219 were formed. 4-Methoxy-2-imidazolidinethiones 366 and 4-methoxy-2-imidazolidinones 367 were furthermore thermally cyclotrimerized into hexahydro[1,3,5]triazines 368 and 369.[181] Analogous rearrangements as described above for α-chlorinated aldimines were encountered with α-bromo- and α-chloroaldimmonium halides 370 and 372, when reacted with alkoxides



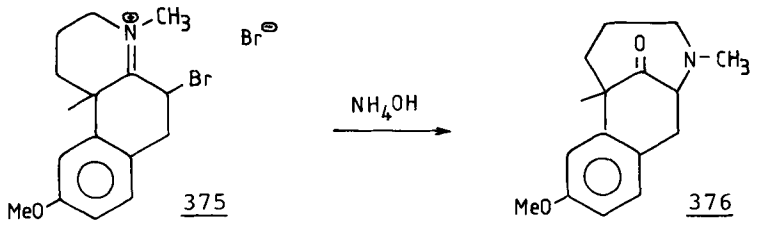
366,367 — 368 X = S; 369 X = O

in alcohol or methanol in the presence of triethylamine.[182-184]



370 R = Ph, n-Pe, Et; Z = CH_2, O — 371 — 372 — 373 — 374

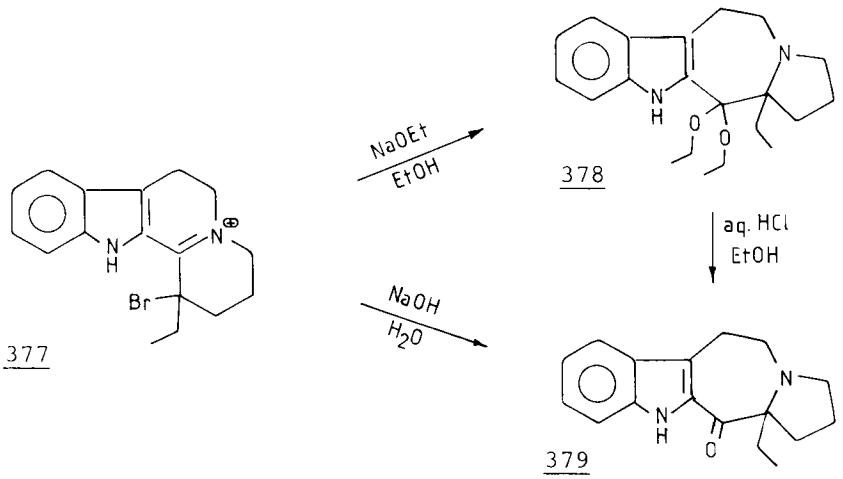
This transformation was applied to the ring enlargement of cyclic α-bromoimmonium bromide 375 with aqueous ammonia to yield heterocyclic compound 376.[101]



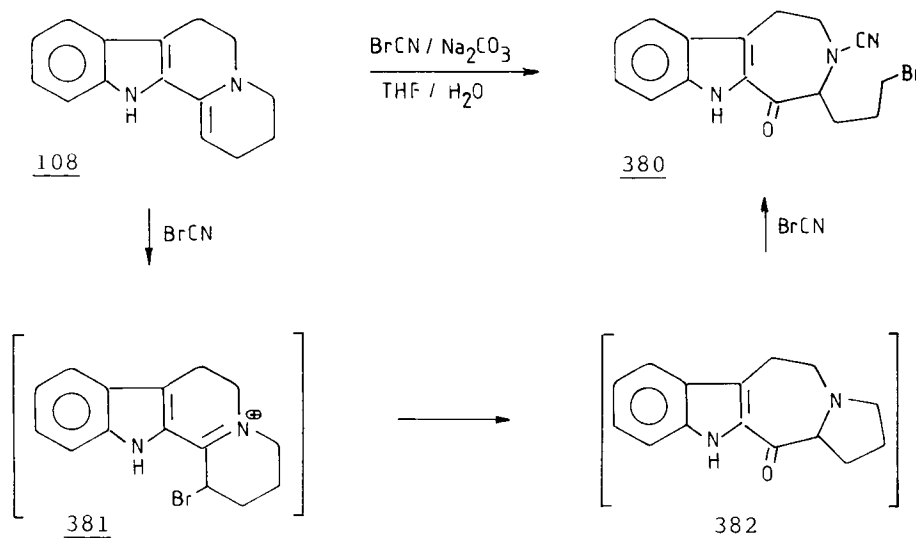
375 — 376

A particular case is the rearrangement of α-bromoimmonium bromide 377 with sodium ethoxide in ethanol whereby, with suitable substitution present in the molecule, ring contraction and

ring expansion occurred at the same time to afford the azepine 378.[185] This rearrangement of 377 was also obtained with aqueous sodium hydroxide.[186] Treatment of 2,3,4,6,7,12-hexahydro-



indolo[2,3-a]-quinolizidine 108 with cyanogen bromide in tetrahydrofuran/water in the presence of sodium carbonate lead to a 47 % yield of 3-cyano-4-(3-bromopropyl)-5-oxo-1,2,3,4,5,6-hexa-



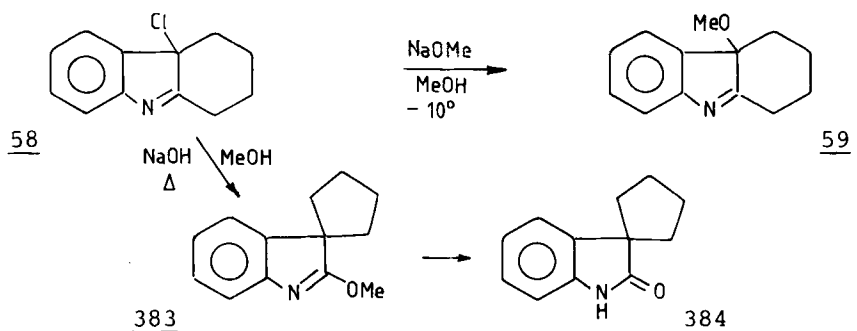
hydroazepino[4,5-b]-indole 380, via a mechanism involving formation of an α-bromoimmonium salt 381, hydroxide induced rearrangement and ring opening by cyanogen bromide.[63] A rearranging α-iodoimmonium salt was postulated recently as an intermediate during transformations of some steroids.[186]

6.3. Rearrangement of 3-Chloroindolenine Derivatives

During the last decade, substantial progress was achieved in the chemistry of 3-chloroindolenine derivatives, which are easily obtained by chlorination of indoles with t-butyl hypochlorite in various aprotic solvents.[2] These compounds showed an unusual rearrangement, which was applied in drug syntheses and total synthesis of alkaloids, and thus deserve more detailed comment in this review.

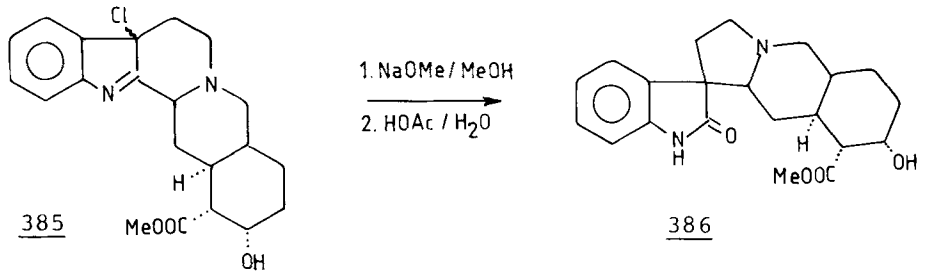
a) Rearrangement in Alkaline Medium

Treatment of 3-chloroindolenines with cold base (alkoxide or hydroxide in alcohol) afforded 3-alkoxyindolenines (this reaction will be discussed more thoroughly in another section), while the reaction with base at elevated temperature yielded rearranged iminoethers or oxindoles.[36,39,40,46] Tetrahydrocarbazole chloroindolenine 58 and sodium hydroxide in methanol

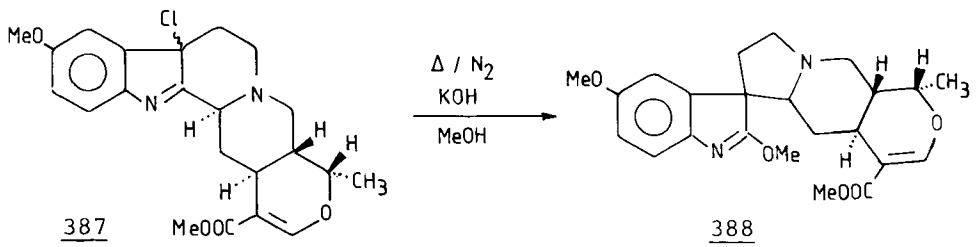


58 59 383 384

under reflux gave spiro compound 383 in 82 % yield (Preparation 22). A similar reaction was observed with the 3-chloroindolenines derived from yohimbine (385),[39-42] cacubine,[187] tetraphilline[187] and related alkaloids.[188]



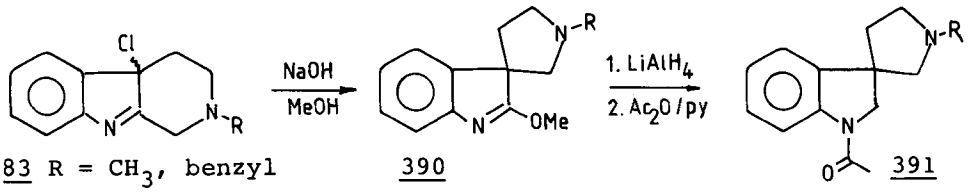
385 386



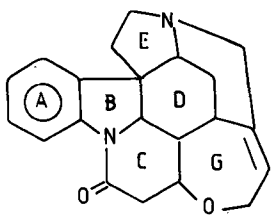
387 388

Recently, 3-chloroindolenines derived from 2-substituted 1,2-3,4-tetrahydro-β-carbolines (83) were rearranged in refluxing sodium hydroxide in methanol to produce exclusively β-spiro-(pyrrolidinoindolenines) 390, which were further converted in two steps into spiro compounds 391.[189] The physiological activity of the latter compounds (they constitute rings A, B, E and a portion of ring C of strychnine 392) was investigated; they were found to have convulsant action.[189]

As already discussed, thallium diethyl malonate and chloroindolenine 58 in refluxing benzene furnished a related rearranged compound 80 in 47% yield.[49] In analogy, a corresponding reaction of 58 with thallium ethoxide in benzene resulted in the formation of an iminoether (ethoxy analogue of 384).

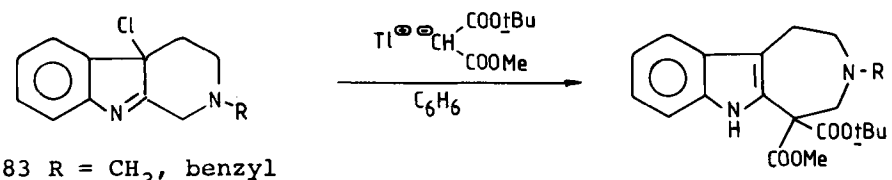


83 R = CH_3, benzyl 390 391



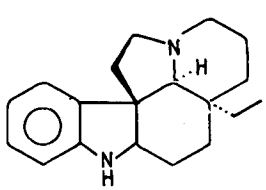
392 (strychnine)

When 2-methyl or 2-benzyl 1,2,3,4-tetrahydro-β-carboline 3-chloroindolenines 83 were treated with thallium dialkyl malonates, indole derivatives 393 resulted via the intermediacy of a rearranged spiro compound 84 (vide supra).[52]



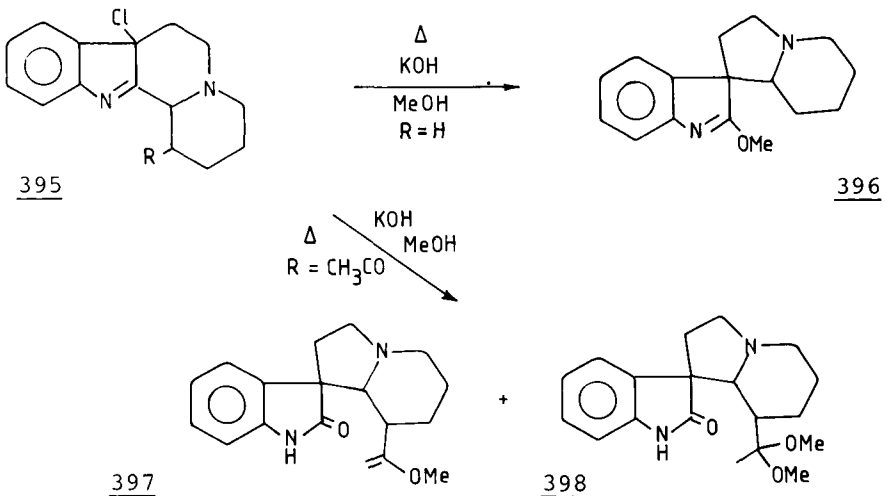
83 R = CH_3, benzyl 393 R = CH_3, benzyl

Another application in the alkaloid field was the synthesis of (±)-aspidospermidine 394 via an alkali promoted 3-chloroindolenine rearrangement.[52]



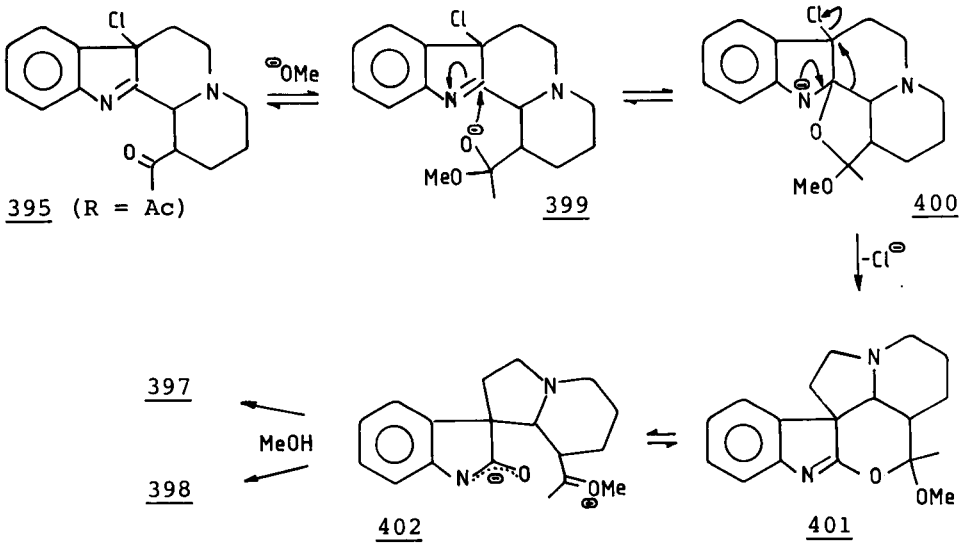
394 (aspidospermidine)

It was also demonstrated that substituents on the alkaloid framework can influence the course of the rearrangement. While the base-catalyzed alcoholysis of the 3-chloroindolenine 395 (R = H) produced the rearranged iminoether 396, an unusual course was observed in the case of the acetyl derivative 395 (R = CH_3CO).[38] The hydroxide-catalyzed methanolysis of 395

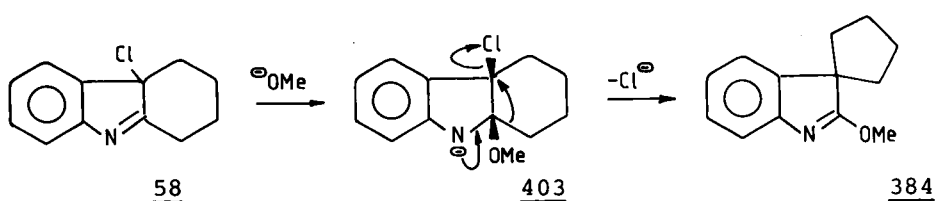


395 396 397 398

(R = CH_3CO) led to two oxindoles, namely enol ether 397 and acetal 398. The three phenomena, first the unprecedented base-catalyzed masking of a keto group in enol ether and acetal, second the formation of oxindoles instead of imino ethers and finally the ease of the reaction sequence, appeared interrelated and were interpreted in terms of an intramolecular nucleophilic attack. Methoxide added first to the acetyl group and the resultant hemiacetal anion 399 attacked the imino function. Subsequent Wagner-Meerwein type rearrangement led to the unstable imino acetal 401, whose zwitterionic form 402 in the presence of methoxide can lead to the enol ether 397 and acetal 398.[38]

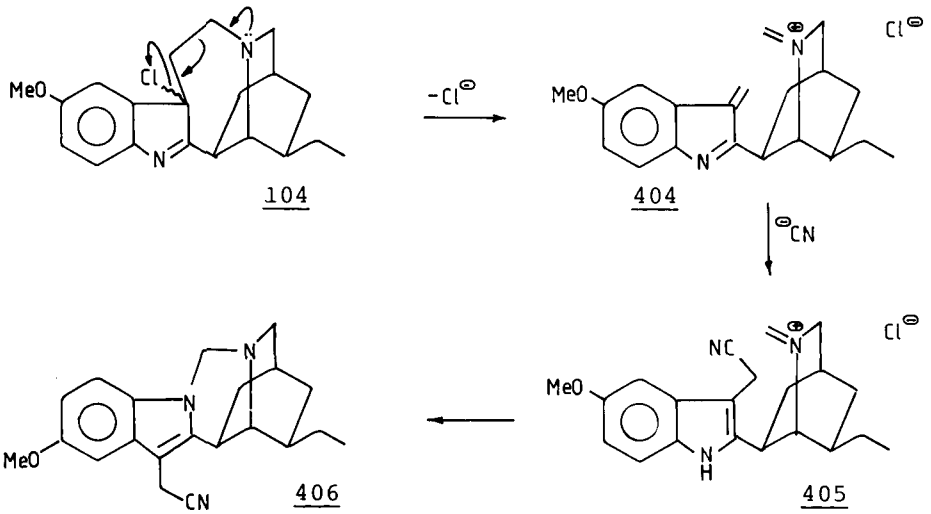


The reaction mechanism of all these base-promoted rearrangements of 3-chloroindolenines was explained by an initial nucleophilic addition of alkoxide to the imino function and subsequent Wagner-Meerwein type rearrangement. It is clear that this transformation can only proceed in the sense indicated when the chlorine atom to be displaced and the migrating carbon-carbon are properly oriented to allow inversion. This de-



mands cis disposition of the chlorine atom and the methoxy group in the intermediate indolenine 403. Finally, it was reported that the 3-chloroindolenine derived from ibogaine (104) also rearranged under alkaline conditions, i.e. potassium cyanide in aqueous methanol. Besides 18-cyanoibogaine (see reactions of α-haloimines with cyanide anion), there was obtained

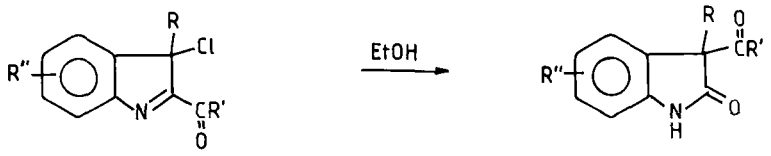
the rearranged nitrile 406. The formation of 406 was rationalized by a mechanism involving neighboring group participation of the amino nitrogen.[45]



The α,β-unsaturated ketimine moiety in 404 underwent a Michael type addition, after which the immonium group in the molecule was attacked by the indole nitrogen.

b) Rearrangement in Acidic and Neutral Media

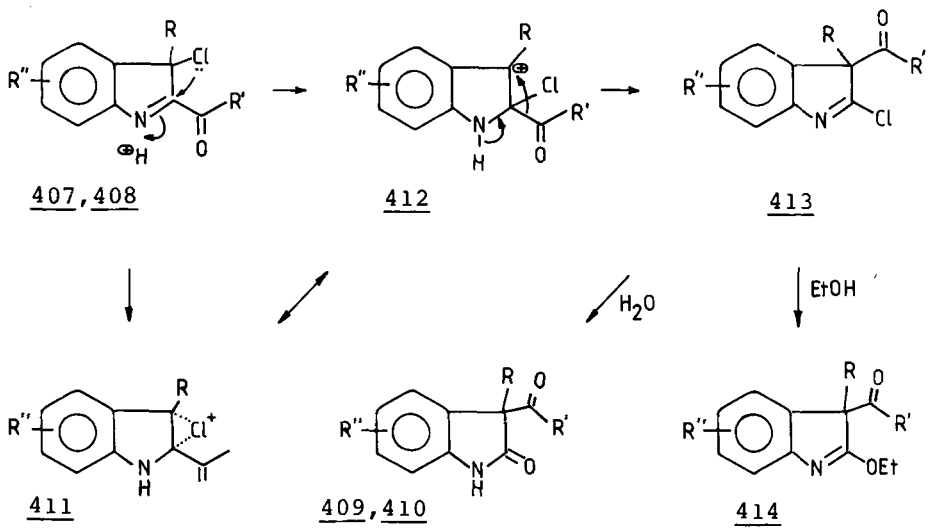
Under neutral conditions, the chloroindolenine of yohimbine and related alkaloids, e.g. 16α-methylyohimbinol, ajmalicine, etc., rearranged into spirooxindoles in aqueous methanol at pH 6.[42] 2-Functionalized-3-chloroindolenines rearranged in protic solvents to oxindoles with migration of the functional group at the 2-position. For instance, compounds 407 and 408 were converted into oxindoles 409 and 410 by refluxing in ethanol.[190] The formation of the oxindoles was explained in terms of carbonium ions 412 via chloronium ion 411. Migration of



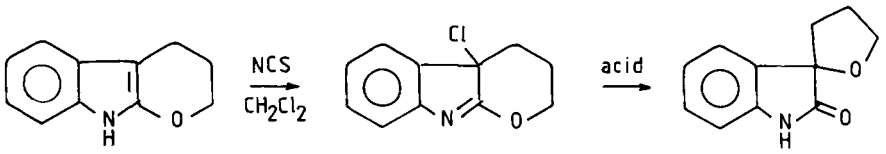
407 R' = OEt
408 R' = NH_2, NHEt, NEt_2, 1-morpholino

409
410

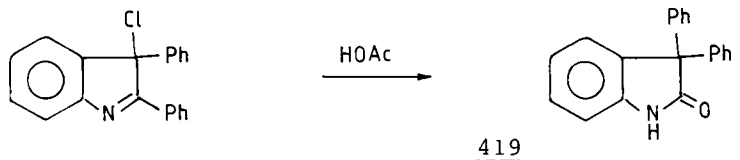
the carbonyl group led to the imidoyl chloride 413 which upon hydrolysis yielded compounds 409 and 410.[190]



Treatment of indole 415 with N-chlorosuccinimide in methylene chloride at -5 to -10° followed by acid gave spirooxindole 417 in 80% yield.[88]

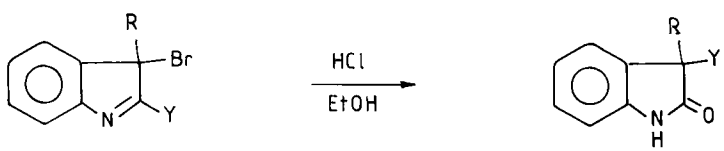


Another example of a rearrangement of a substituent from the 2-position to the 3-position was the slow conversion of 3-chloro-2,3-diphenylindole 418 into oxindole 419 in glacial acetic acid.[22] This rearrangement could be suppressed in the presence of nucleophiles whereby nucleophilic substitution or reversion to the parent indoles occurred.[22]



418 419

Furthermore, 2-ethylthio- and 2-ethylsulfonyl-3-bromoindolenines 420, easily obtained from the parent indoles and N-bromosuccinimide in carbon tetrachloride or dichloromethane,[44] exhibited migration of the sulfur-substituent on treatment with ethanol, containing hydrochloric acid.[44,191,192]

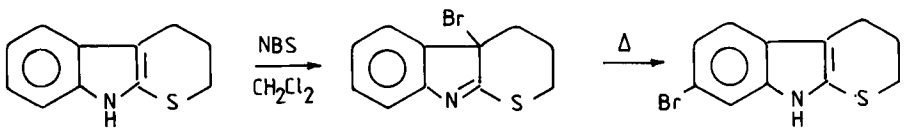


420 Y = SEt, SO_2Et 421

c) Migration of Halogen

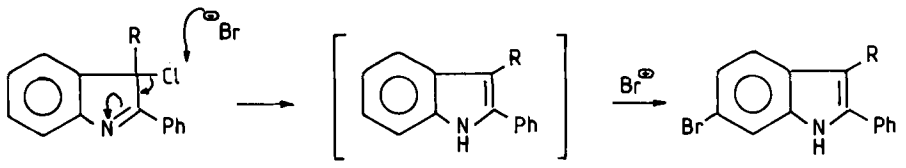
Some 3-bromoindolenines were reported to undergo migration to the aromatic nucleus of the indole moiety, indicating that the bromine atom in these compounds behaves as a brominating agent (Note that the corresponding chloroderivatives did not give this transformation). Reaction of thiopyranoindole 422 with N-bromosuccinimide in dichloromethane at room tempe-

rature afforded the unstable 3-bromoindolenine 423, which was readily converted into the 7-bromo-derivative 424 on heating.[88]



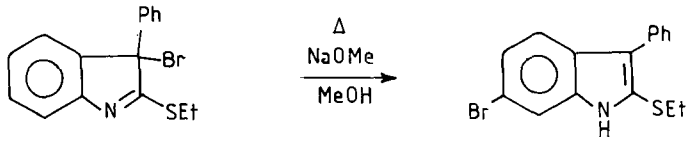
422 423 424

3-Chloroindolenine 77 reacted with sodium bromide to give 6-bromoindole 425, via a mechanism involving initial formation of the parent indole and subsequent electrophilic substitution.[22]



77 R = CH_3, Ph 51 425

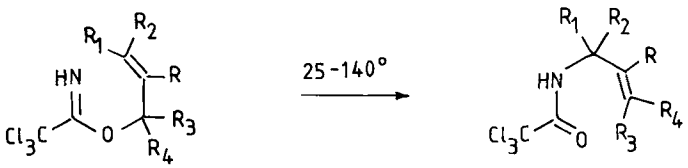
The substituent at the 2-position was reported to influence the position to which the bromine migrated in the aromatic nucleus. The reaction proceeded at reflux in carbon tetrachloride or in acetic acid at room temperature. 2-Ethylthio derivatives gave 6-bromoindoles, 2-bromo derivatives afforded a mixture of 6- and 5-bromoindoles, while 2-ethylsulfonyl derivatives rearranged into 5-bromoindoles.[192] Finally, halogen migration was observed under alkaline conditions. When 3-bromo-2-ethylthio-3-phenylindolenine 426 was heated under reflux with sodium methoxide in methanol, 17% of 6-bromoindole 427, in addition to 19% of 2-ethylthio-3-phenylindole and 23% of 2-ethylthio-3-methoxy-3-phenylindolenine were generated.[44]



426 427

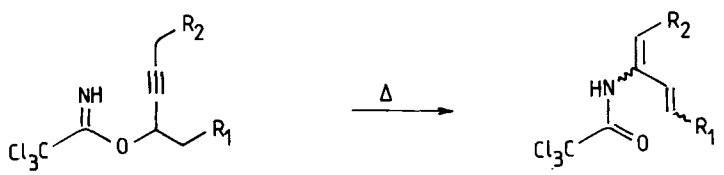
6.4. [3,3]-Sigmatropic Rearrangement

Allyl trichloroacetimidates 428 are known to rearrange thermally by a concerted [3,3]-sigmatropic process to yield N-allyl-trichloroacetamides 429.[193,194] Thermolysis of propargylic trichloroacetimidates 430 provides a convenient one-



428 429

step route to trichloroacetamido-substituted 1,3-dienes 431, which are important substrates for Diels-Alder syntheses.[195] The mechanism was viewed as proceeding via allenic intermediates.[195]



430 431

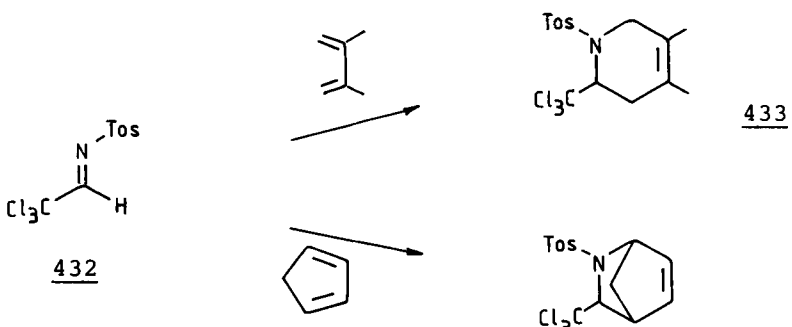
7. Cycloadditions with α-Halogenated Imino Compounds

It has been demonstrated that certain α-halogenated imines are valuable tools for cycloaddition reactions. Especially α-perhalogenated imino compounds served as substrates for the

formation of nitrogen heterocycles. A variety of such reactions has been described including syntheses of three-, four-, five- and six-membered heterocyclic compounds.

(4+2) Cycloadditions

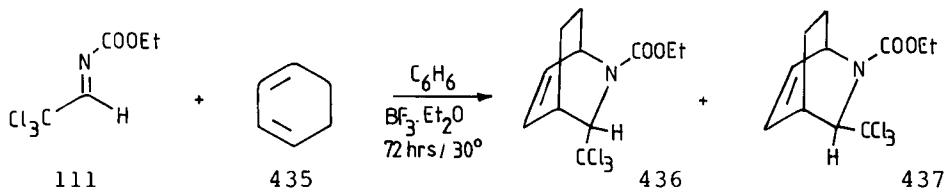
N-Tosyl chloral imine 432 reacted with 2,3-dimethylbutadiene and cyclopentadiene to afford six-membered nitrogen heterocycles 433 and 434.[196,197] A stereochemical study of the for-



432 433 434

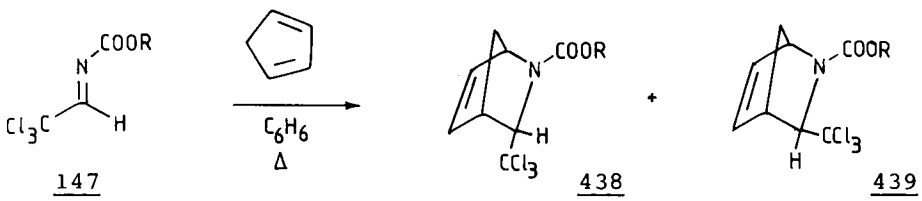
mation of azabicycles via cycloadditions of 1,3-cyclopentadiene or 1,3-cyclohexadiene with N-ethoxycarbonyl and N-p-toluenesulfonyl trichloromethyl imines (111, 432) revealed that exo/endo mixtures were produced.[198] As an example, N-ethoxycarbonyl chloraldimine 111 (R = Et) was reacted in refluxing benzene with 1,3-cyclohexadiene in the presence of boron trifluoride etherate to form 75±5% endo adduct 436, besides the exo adduct 437.[198]

The stereochemical course of the Diels-Alder reaction of anhydrochloralurethane 147 with cyclopentadiene was independently



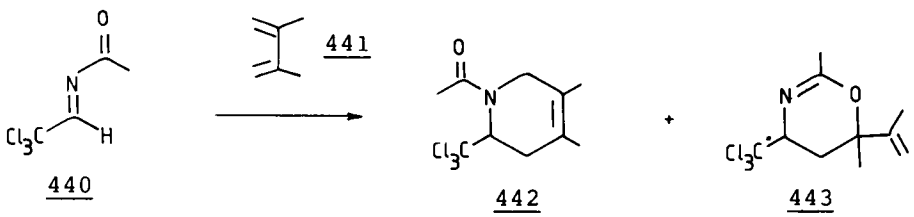
111 435 436 437

investigated by Japanese chemists,[199] who reported a 2:1 exo: endo ratio of the adducts, formed after 3 hrs reflux in benzene (Preparation 23). However, the same reaction was claimed by Krow et al. to give a 1:1 ratio after 48 h at 30° or 3 days at 145° in benzene (sealed tube).[198]



147 438 439

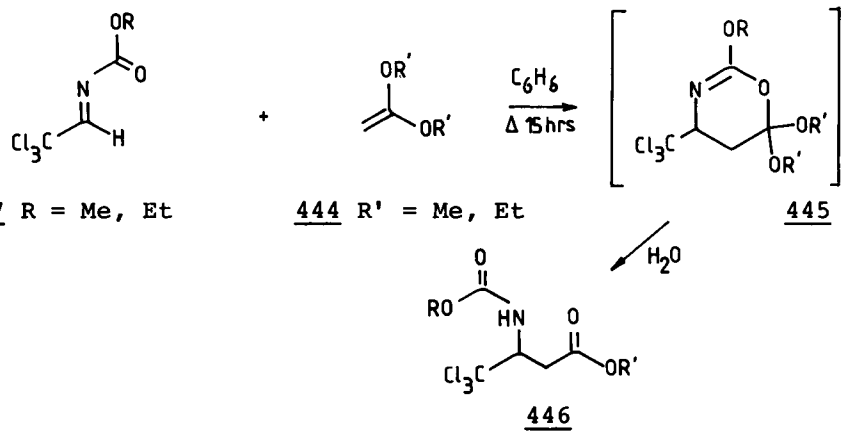
N-Acetyl chloraldimine 440 interestingly reacted in two different ways with 2,3-dimethylbutadiene 441, giving the normal Diels-Alder adduct 442 in addition to the oxazine derivative 443.[200] In the cases of the Diels-Alder cycloadditions, chlo-



440 442 443

raldimines 147,432,440 act as the dienophile, while the oxazine derivative 443 resulted from a reaction in which N-acetylimine 440 behaved as a heterodiene.[200] In contrast, N-alkoxycarbonyl chloraldimines 147 behaved exclusively as heterodienes

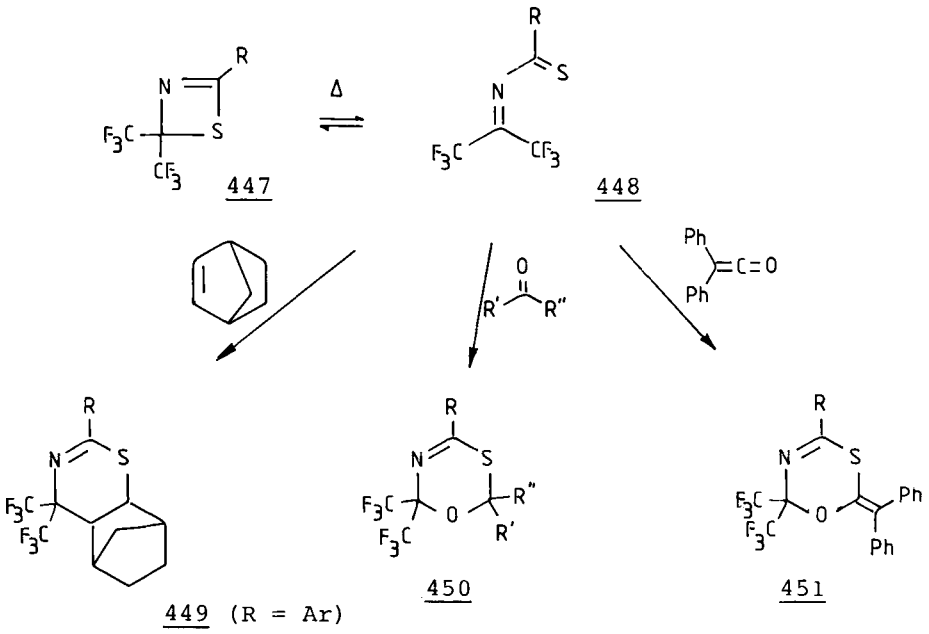
towards electron-rich olefins, e.g. ketene acetals 444.[201] The so-called "anhydrochloralurethanes" 147 yielded an intermediate oxazine derivative 445, the presence of which was confirmed spectroscopically, but which was quantitatively converted into carbamate derivative 446 on ring opening with water (from atmospheric moisture or work-up). A similar reaction was found with the N-acetyl derivative 440.[201]



177 R = Me, Et 444 R' = Me, Et 445

446

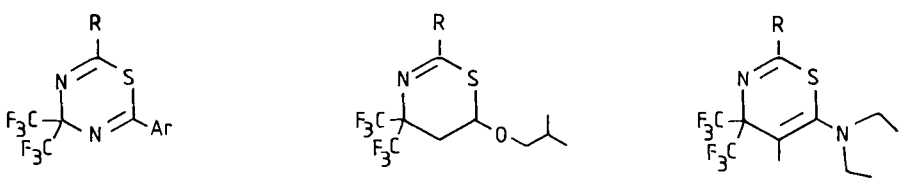
Many more examples of (4+2)cycloadditions in which the α-haloimine serves as a heterodiene have been reported recently for N-activated imines derived from hexafluoroacetone. N-(perfluoroisopropylidene)thiocarboxamides 448, which occurs in thermally mobile equilibrium with 2-H-1,3-thiazete 447, underwent cycloaddition with bicyclo[2,2,1]-2-heptene to give 5,6-dihydro-4H-1,3-thiazines 449.[202] This synthesis seemed generally applicable because α,α'-perfluoroimines 448 were also trapped by aldehydes and ketones and diphenylketene to yield 6,6-bis(trifluoromethyl)-6H-1,3,5-oxathiazines 450 and 451.[203]



447 ⇌ 448

449 (R = Ar)

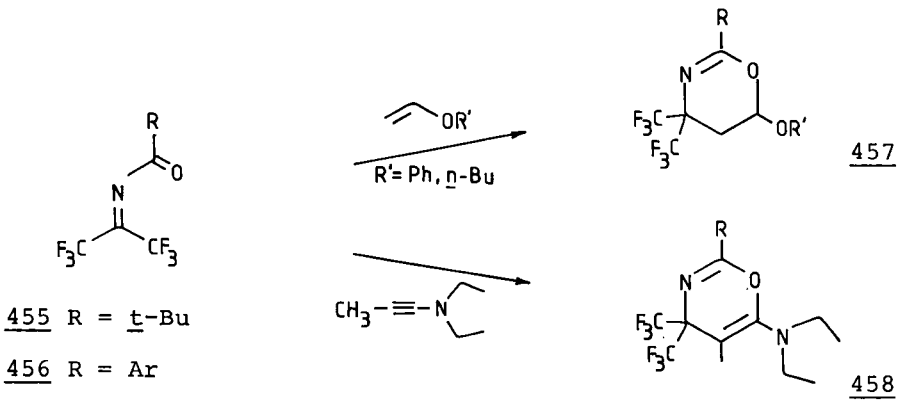
The reaction of the activated imine 448 with reagents such as aromatic nitriles, enol ethers and ynamines furnished the corresponding 4H-1,3,5-thiadiazines 452, 5,6-dihydro-4H-1,3-thiazines 453 and 4H-1,3-thiazines 454, respectively.[204]



452 453 454

N-Pivaloyl and N-aroyl hexafluoroacetone imines 455 and 456 showed similar features and cyclized with enol ethers and ynamines with formation of six-membered heterocycles 457 and 458.[205] (Note that the reaction of ynamines with perfluoroacetone azine was reported to proceed via a (2+2)cycloaddition product.[206])

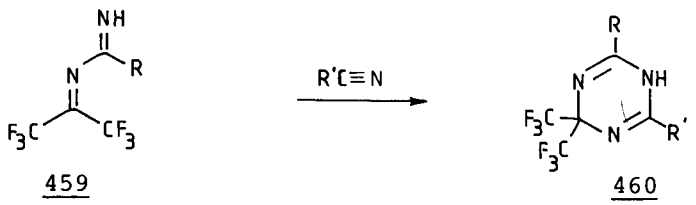
Besides the numerous possibilities of N-acyl or N-thioacyl



455 R = t-Bu

456 R = Ar

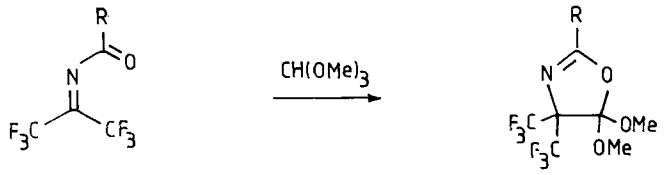
hexafluoroacetone imine, e.g. 448 and 455-456, to serve as substrates for cycloadditions, hexafluoroacetone imines substituted with an imino function, have also been reported recently to cyclize with aromatic nitriles to yield heterocycles 460.[207]



(4+1)Cycloadditions

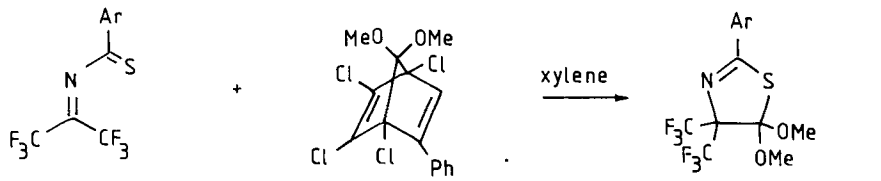
Few data exist on the cycloaddition of α-halogenated imines with carbenes or carbenoids. Recently, it was reported that N-acyl perfluoroimines 461 react with trimethyl orthoformate to afford functionalized 2-oxazolines 462 and it was shown that dimethoxycarbene was generated during the reaction.[209] The corresponding thiones gave a similar (4+1)cycloaddition to 2-thiazolines 465 (R = aryl) by means of the dimethoxycarbene precursor 464.[210]

Another example involved the dimethoxycarbene addition[211] to



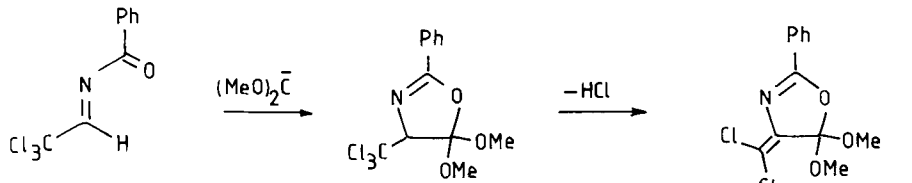
461 R =Me, i-Pr

462



463 464 465

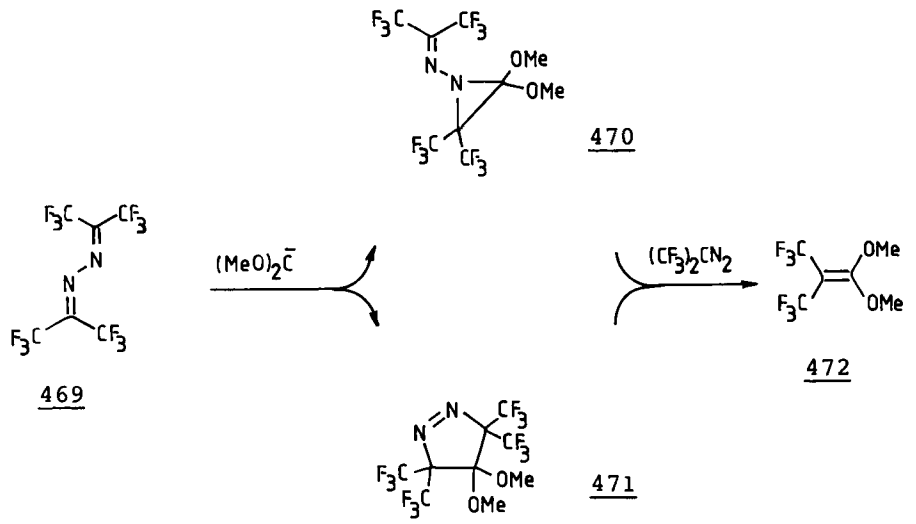
N-benzoyl chloraldimine 466, but the resulting adduct spontaneously dehydrochlorinated to 468.[208]



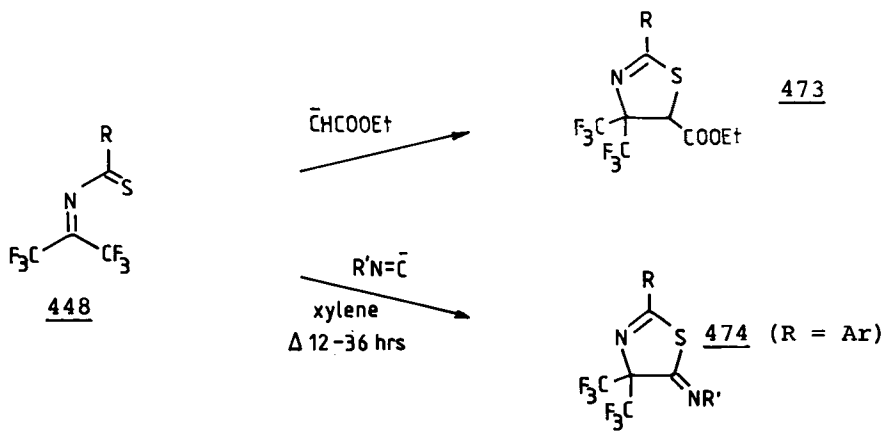
466 467 468

Dimethoxycarbene seemed a suitable reagent for such cycloadditions as it also added to hexafluoroacetone azine 469 to give 471, from which bis-(trifluoromethyl)diazomethane was expelled with formation of ketene acetal 472. Howéver, the mechanism could also proceed via addition of the carbene to an imino function and subsequent loss of the bis-(trifluoromethyl)diazomethane.[208]

Furthermore, ethoxycarbonylcarbene, generated from ethyl diazoacetate, and activated imine 448 cyclized to yield 2-thiazoline 473.[209] Finally, substrate 448 also gave a (4+1)cyclo-

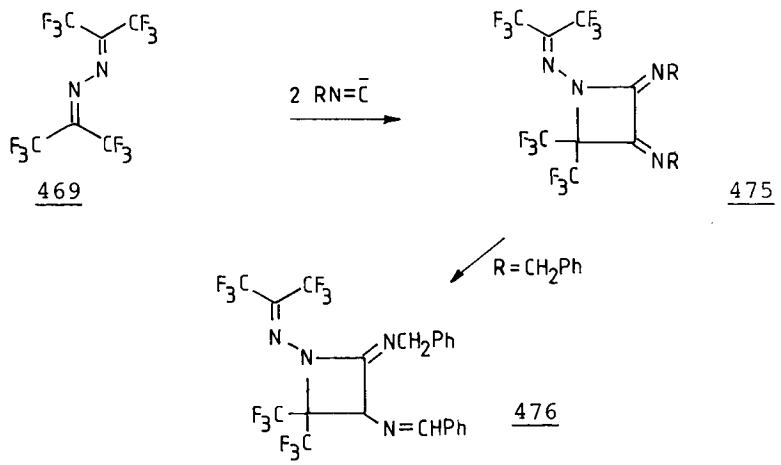


addition with isonitriles in refluxing xylene to form 5-imino-4,4-bis(trifluoromethyl)-2-thiazolines 474.[204]



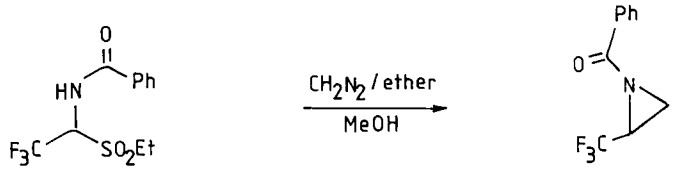
Miscellaneous Cycloadditions

Besides (4+1)cycloadditions (vide supra), isonitriles were found to produce 1:2 adducts with suitable substrates such as hexafluoroacetone azine 469. When R = benzyl, the resulting 2,3-diiminoazetidines 475 tautomerized to 476.[211]



469 475 476

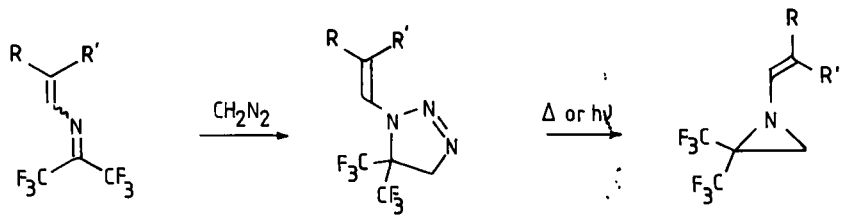
Diazomethane is known to give aziridines by cycloaddition to certain imino functions. Compound 477 reacted with ethereal diazomethane in methanol by sulfinate elimination and subsequent cycloaddition to produce 1-benzoyl-2-trifluoromethylaziridine 478.[78]



477 478

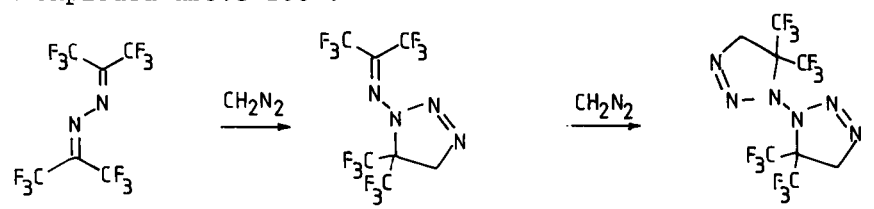
α,α'-Hexafluoroketimine 479 also added diazomethane at the imino bond to yield 1:1 adduct 480, which lost nitrogen thermally or upon irradiation.[212] It should be noted that 2:1 adducts were formed in some cases by reaction of both double bonds in 479.[212]

The structurally related hexafluoroacetone azine 469 showed a similar mechanistic behavior and produced 5,5,5',5'-tetrakis-

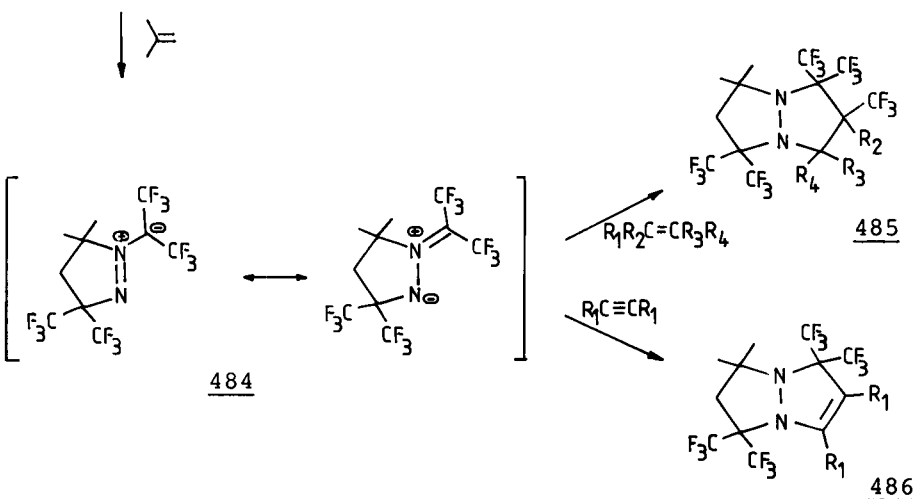


479 480 481

(trifluoromethyl)-4,5,4',5'-tetrahydrobis-(1,2,3-triazole) 483, which exploded above 100°.[213]



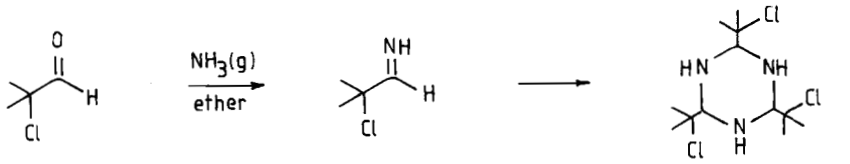
469 482 483



484 485 486

A particularly interesting reaction[214] is the 1:1 addition of hexafluoroacetone azine 469 to isobutylene to afford a 1-pyrazolin-1-ylid 484, which was of practical interest because of its reaction with alkenes and alkynes.[215] Finally, α-chloraldimine 488, obtained from the addition of gaseous ammonia to 2-chloro-2-methylpropanal 487 in ether, was reported to cyclotrimerize

to hexahydro[1,3,5]triazine 489.[216]



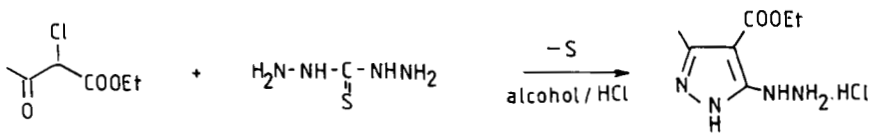
487 488 489

8. Formation of Heterocyclic Compounds

α-Halogenated imino compounds are known to be the starting materials for a variety of heterocyclic compounds. Many reactions can be classified in one of the preceding sections, describing separate mechanistic features of the title compounds. In this section, however, emphasis will be focused on those reactions of α-halogenated imines which cannot be integrated into the foregoing sections and which lead to heterocyclic compounds. A large variety of nitrogen-heterocycles has been reported to result from α-haloimines.

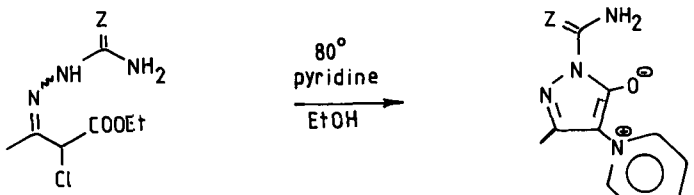
8.1. Pyrazoles

Ethyl 2-chloroacetoacetate 490 condensed with thiocarbohydrazide 491 in alcoholic HCl to produce the functionalized pyrazole 492 via an intermediate α-chloroimino derivative.[217]



490 491 492

The imino derivatives derived from ethyl 2-chloroacetoacetate 490 and semicarbazide, thiosemicarbazide and nitroaminoguanidine (493, 494 en 495 respectively) were converted into the zwitterionic heterocycles 496 by reaction with pyridine in ethanol.[218]

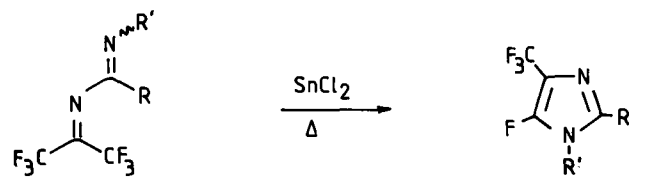


493 Z = O
494 Z = S 495 Z = N-NO_2

496

8.2. Imidazoles

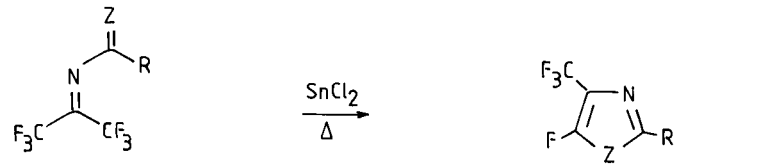
Heating of 4,4-bis(trifluoromethyl)-1,3-diaza-1,3-butadienes 497 in the presence of anhydrous tin(II)chloride gave ring-closure to fluorinated imidazoles 498.[219]



497 498

8.3. Oxazoles and Thiazoles

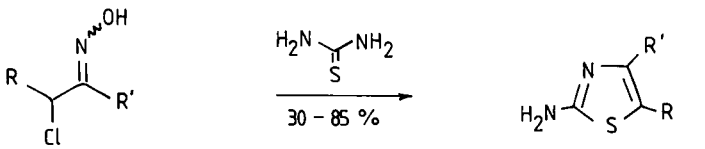
In a manner similar to the preparation of imidazoles 498, oxazoles 500 and thiazoles 501 were synthesized from 4,4-bis-(trifluoromethyl)-3-aza-1-oxa-1,3-butadienes 499 (Z = O) and 4,4-bis(trifluoromethyl)-3-aza-1-thia-1,3-butadienes 448 (Z = S) (the latter ones being in thermal equilibrium at 80° with 2,2-bis(trifluoromethyl)-2H-1,3-thiazetes) by heating with anhy-



499 Z = O 448 Z = S

500 Z = O 501 Z = S

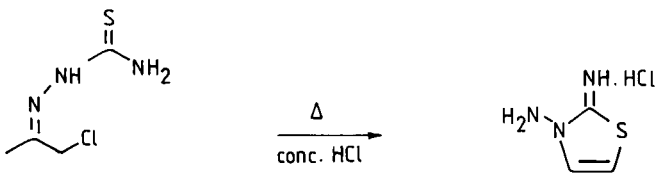
drous tin(II)chloride.[219] Another route to thiazoles consisted of the condensation of α-chlorooximes 285, obtained from nitrosyl chloride addition to alkenes, with thiourea.[220]



285 502

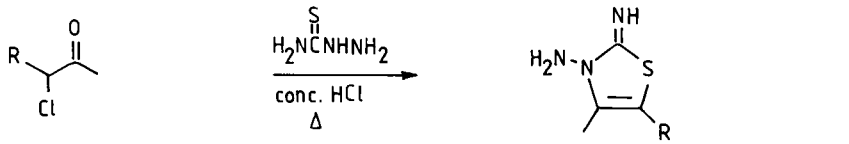
8.4. 2-Iminothiazolines

Heating chloroacetone thiosemicarbazone 503 with concentrated hydrochloric acid afforded a 95% yield of 3-amino-4-methyl-2-imino-4-thiazoline hydrochloride 504,[221] which was er-



503 504

roneously reported to be formed from the reaction of chloroacetone and semicarbazide in ethanolic hydrogen chloride.[222] A similar compound 506 was obtained from 3-chlorobutanone 505 and thiosemicarbazide in concentrated hydrochloric acid.[223] Ethyl 2-chloroacetoacetate 490 also condensed with thiosemicarbazide under similar reaction conditions to yield 2-iminothiazoline 507.[224]



505 R = CH_3

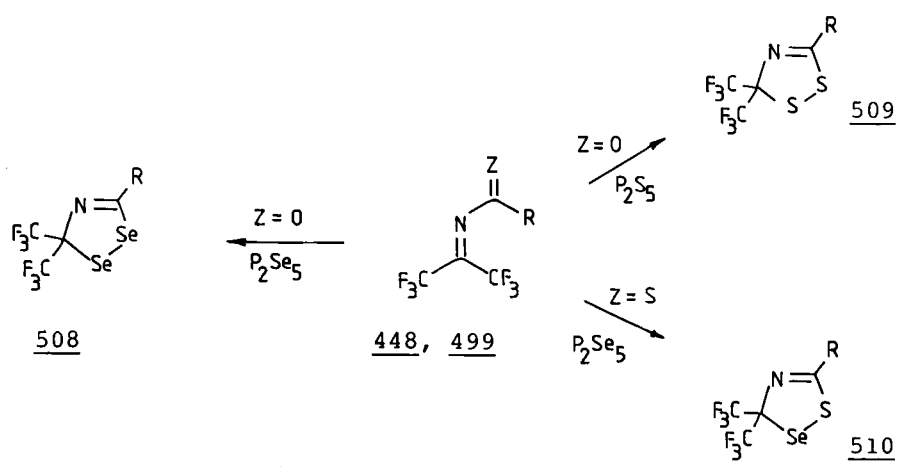
490 R = COOEt

506 R = CH_3 (hydrochloride)

507 R = COOEt

8.5. Dithiazolines, Thiaselenazolines and Diselenazolines

The thermal condensation of α-perfluorinated ketimines 448 and 499 with phosphorous pentasulfide or phosphorous pentaselenide provided high yields of Δ^3-1,2,4-dithiazolines 509, Δ^4-1,2,4-thiaselenazolines 510 or Δ^3-1,2,4-diselenazolines 508.[225-227]

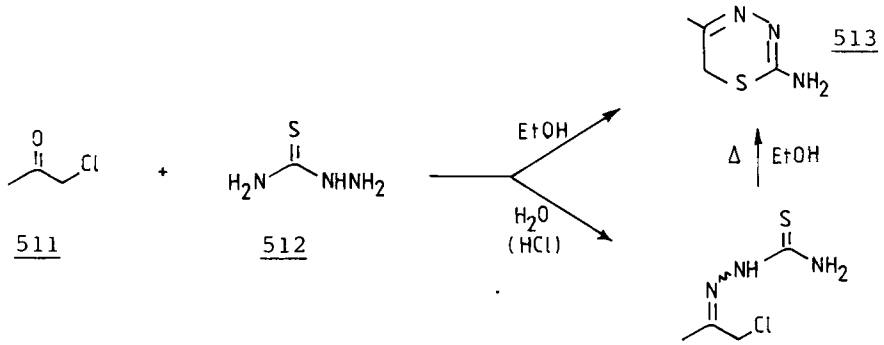


508 448, 499 509 510

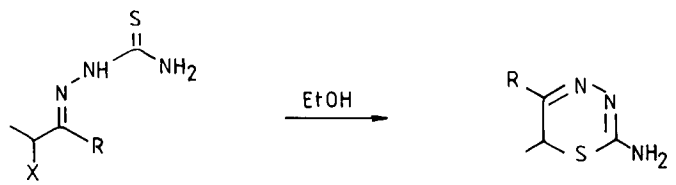
8.6. Thiadiazines

2-Amino-5-methyl-1,3,4-thiadiazine 513 was synthesized from chloroacetone 511 and thiosemicarbazide 512 in ethanol.[222] The α-haloimine 503 was isolated from 511 and 512 in aqueous medium and subsequent heating in ethanol also yielded thiadiazine 513.[221] The latter heterocycle was erroneously reported

to result from chloroacetone and thiosemicarbazide which, under the given reaction conditions, gave rise to 2-iminothiazoline 504.[222]



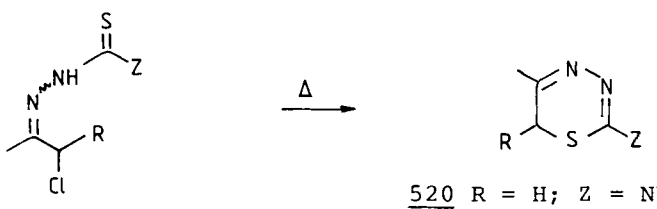
α-Chloro- and α-bromoimines 514 and 515 furnished thiadiazines 516 and 517 by simple heating in ethanol.[223] In similar way,



514 X = Cl; R = CH_3
515 X = Br; R = H

516 R = CH_3
517 R = H

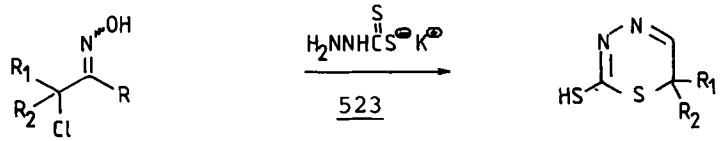
α-chloroimino derivatives 518 and 519 were converted into heterocycles 520 and 521 by heating respectively in ethanol or isopropanol.[224,228]



518 R = H; Z = $NHNH_2$
519 R = COOEt; Z = NH_2

520 R = H; Z = $NHNH_2$
521 R = COOEt; Z = NH_2

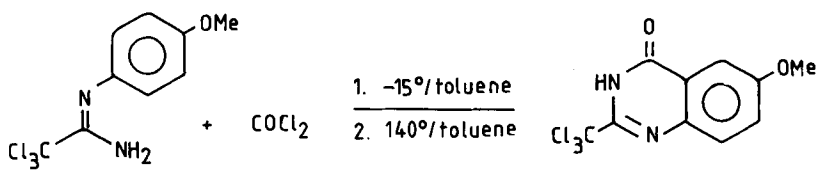
Another route to thiadiazines was recently developed from the reaction of α-chlorooximes 522 with dithiocarbazic acid derivative 523 to afford 2-mercapto-1,3,4-thiadiazines 524 in 60-97% yield.[229]



522 523 524

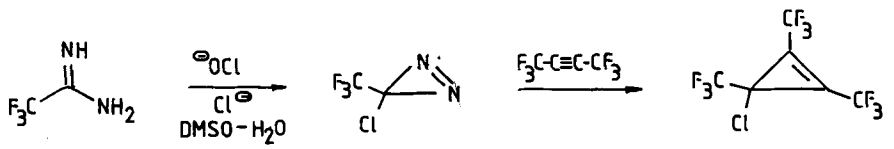
8.7. Miscellaneous Heterocycles

Condensation of α,α,α-trichloroamidine 525 with phosgene in toluene produced 2-trichloromethyl-6-methoxy-4-quinazolone 526 in 90% yield.[230]



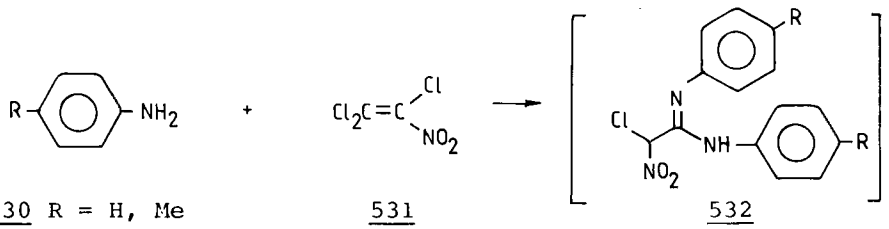
525 526

Trifluoroacetamidine 527 was converted with hypochlorite in aqueous dimethylsulfoxide into diazirine 528, which afforded cyclopropene 529 on reaction with perfluoro-2-butyne.[231]



527 528 529

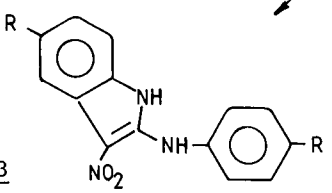
A cyclization of a transient α-chloroimine 532 was observed when anilines 530 were condensed with perchloronitroethylene 531 to yield 2-anilino-3-nitroindoles 533.[232]



530 R = H, Me

531

532

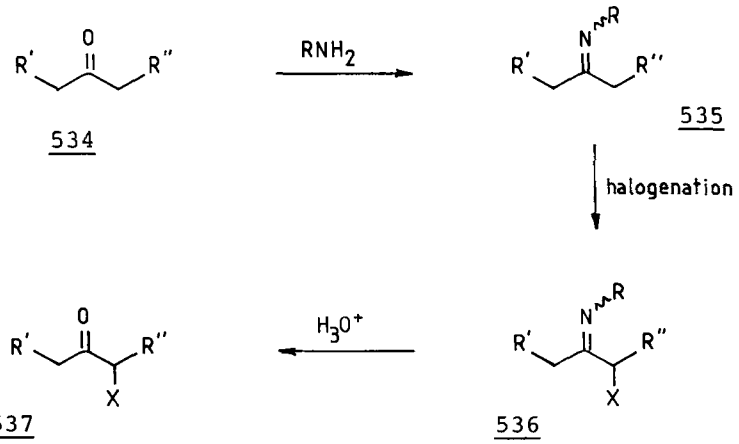


533

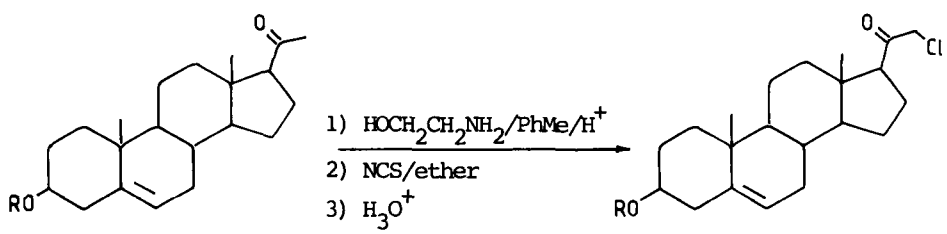
Recently, some other examples of intramolecular cyclizations of α,α-dichloroamidines and α-iodoimmonium salts were reported.[232,234]

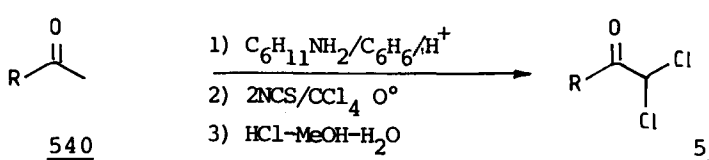
9. Hydrolysis of α-Halogenated Imines

The acidic hydrolysis of α-halogenated imino compounds leads to the corresponding α-halogenated carbonyl compounds and constitutes a valuable synthetic method for obtaining α-halocarbonyl derivatives. Starting from the parent carbonyl compound, conversion into an appropriate imine, halogenation to an α-haloimine and subsequent hydrolysis offers the preferred route to α-halocarbonyl compounds, because in many cases direct halogenation of carbonyl compounds can be problematic.



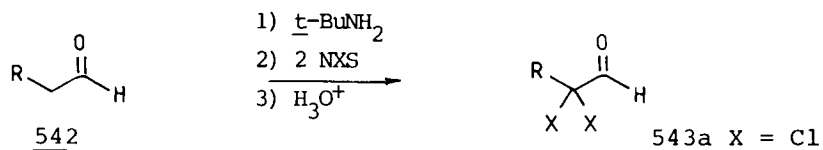
This sequence of reactions was succesfully applied to the synthesis of α-chloro-, α,α-dichloro- and α,α,α-trichloromethylketones.[235-237] This route is especially valuable when a regiospecific halogenation of imines is possible, as illustrated for the chloromethylation of steroidal ketone 538 and the dichloromethylation of methylketones 540.[235,236]



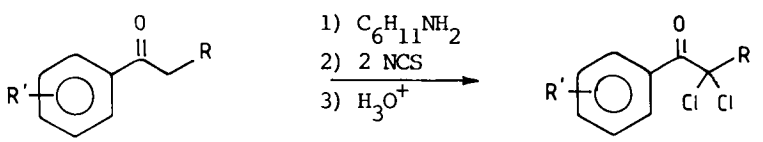


In similar way, α-bromomethylketones were obtained from steroidal ketone 538,[235] but dibromomethylketones, derived from methylketone 540 via imination, bromination with NBS/CCl_4 and hydrolysis, could not be prepared conveniently because of the lability of bromine during the acidic hydrolysis step. The resulting hydrolysate consisted of a mixture of α,α-dibromo- and α,α'-dibromomethylketones.[238]

The halogenation of carbonyl compounds, using a reaction sequence as outlined from 534 to 537 and applied to substrates where no competitive halogenation can take place, has been developed as the most convenient preparation for α,α-dichloroaldehydes 543a,[239] α,α-dibromoaldehydes 543b,[239] and α,α-dichloroalkylarylketones 545 (Preparation 24).[240a] It is to be noted that compounds 543 and 545 are not generally accessible by the



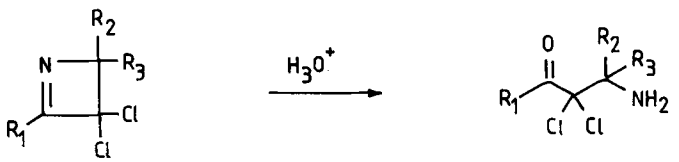
542 543a X = Cl 543b X = Br



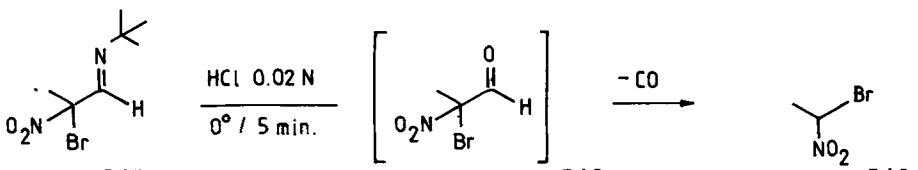
544 545

common halogenation procedures of the parent compounds, except by a new method of chlorination in dimethylformamide.[240b] Many other examples of hydrolyses of α-haloimines have been reported;[241-244] three of these reports deserve special attention. The

four-membered α,α-dichloroimine 193 gave β-amino-α,α-dichloroketone 546 on hydrolysis,[96] while hydrolysis of α-bromo-α-nitroaldimine 547 afforded an intermediate α-bromo-α-nitroaldehyde 548, which decomposed with loss of CO to produce 1-bromo-1-nitroethane.[245]

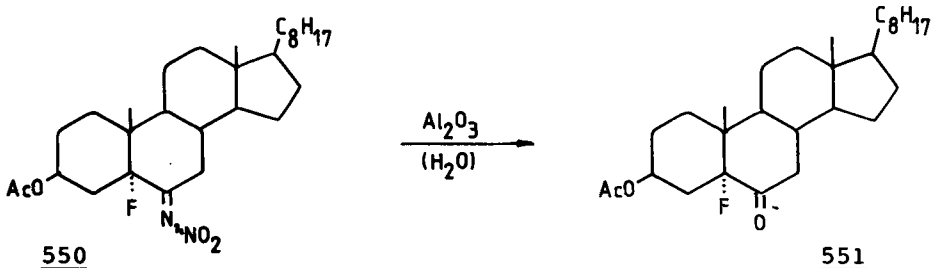


193 546



547 548 549

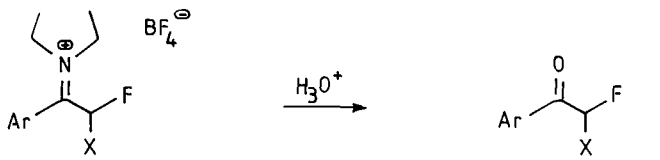
The facile hydrolysis of certain α-haloimines was demonstrated by the percolation of a benzene solution of steroidal 5α-fluoro-6-nitrimine 550 through a neutral alumina column, thereby resulting in a quantitative conversion into 5α-fluoro-3β-hydroxycholestan-6-one acetate 551.[99]



550 551

Finally, α-halogenated immonium salts are known to hydrolyze very rapidly to yield the corresponding α-halocarbonyl derivatives. This hydrolysis step will be discussed in a forth-

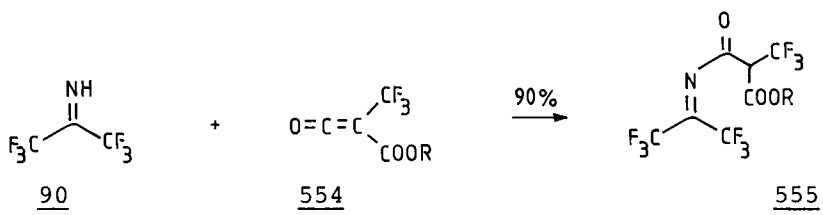
coming review on the chemistry of β-haloenamines because of the initial formation of α-haloimmonium salts on halogenation of enamines. In general, these salts are easily transformed into α-halo carbonyl compounds as exemplified also for α-fluorinated derivatives 552.[246]



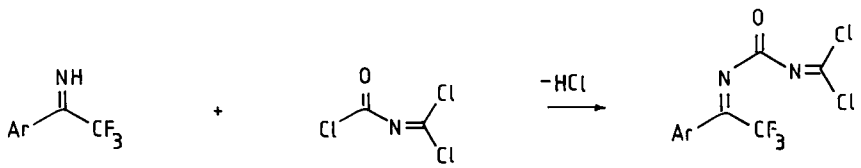
552 X = Cl, F, CF_3 553

10. Functionalization of α-Haloimines

N-unsubstituted α-halogenated imino compounds have not been frequently described in the literature because of their sensitivity to hydrolysis. However, those N-unsubstituted imines stabilized by several halogens in the α-positions can be conveniently handled and transformed into N-substituted derivatives. Acylation of trifluoromethylsubstituted imines 90 and 556 with acyl chlorides or ketenes afforded the N-acyl trifluoromethylderivatives 555 and 558.[247,248] The expulsion of cyanogen chloride from 558 was developed as a synthetic method for α-chloroalkylisocyanates 559.[247] Nitrogen-heteroatom bond formation was also achieved by the reaction of benzenesulfonyl chloride[249] or triethyl phosphite[251] with α-halogenated amidines 560 and 562. The latter reaction occurred with concomitant expulsion of ethyl chloride.[250]

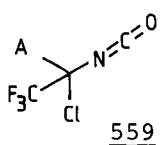


90 554 555



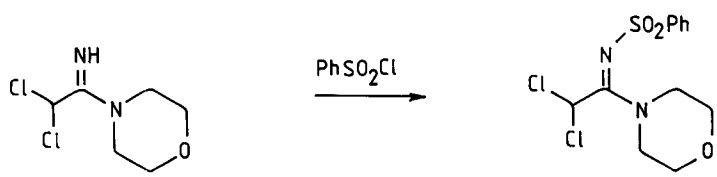
556 557 558

Ar = C_6H_5, 4-ClC_6H_4, 4-$CF_3C_6H_4$

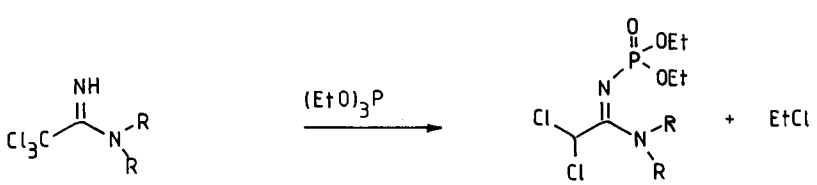


559

It is clear that other α-haloimines, bearing active N-substituents, are susceptible to similar transformations. The

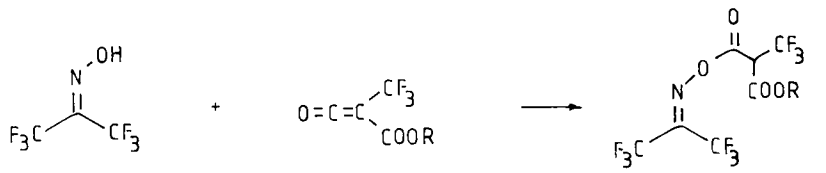


560 561



562 R = Me, Et 563

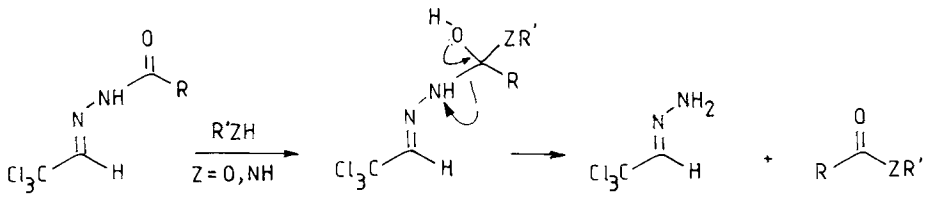
oxime of hexafluoroacetone (564) reacted with the functionalized ketenes 554 to produce O-acylated oximes 565 in 60-97% yield.[248]



564 554 565

(R = Me, Et, n-Pr, n-Bu)

The so-called Kametani reaction also entails a transformation of the N-substituent; chloral semicarbazone 556 undergoes attack of primary amines or alcohols at the carbonyl group, resulting in decomposition of the molecule into chloralhydrazone and a carboxylic acid amide or ester.[251,252]

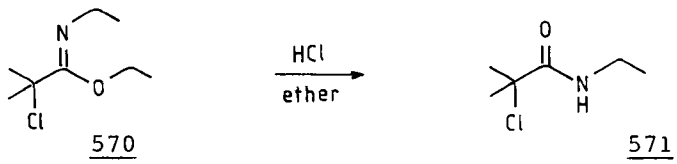


566 567 568 569

11. Miscellaneous Reactions

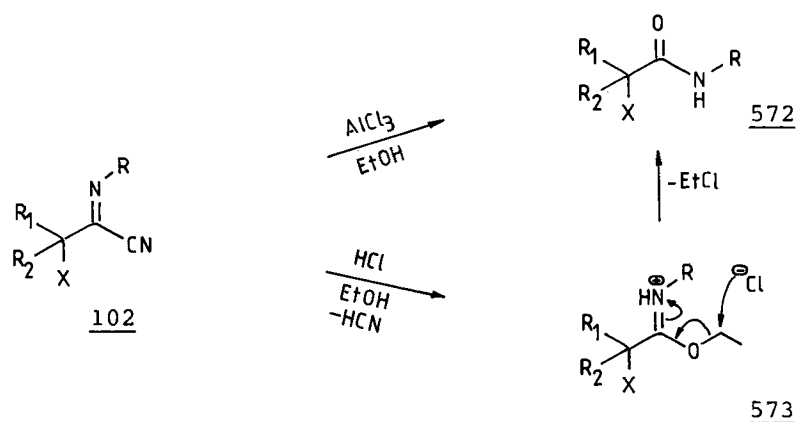
One of the first preparations of α-halogenated imidates was reported by McElvain and Stevens,[253] who claimed that ethyl N-ethyl-2-chloro-2-methylpropionimidate 570 gave 80% yield of N-ethyl-2-chloro-2-methylpropanamide 571 by treatment with dry hydrogen chloride in ether.

This early report shows similarities with the recently published transformation of α-halogenated imidoyl cyanides 102 into

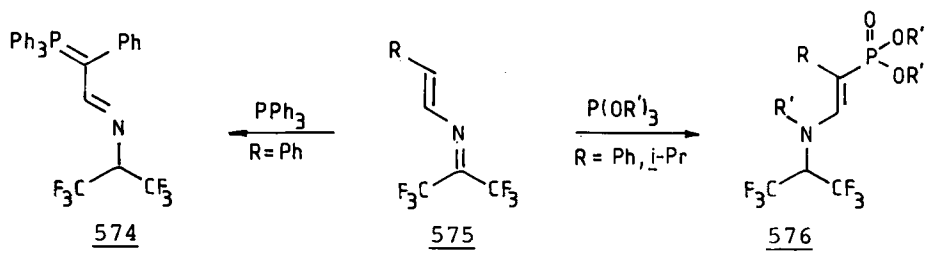


570 571

α-haloamides 572 by treatment with aluminium chloride or hydrogen chloride in alcohol.[254] The mechanism was interpreted in terms of acid-catalyzed addition of alcohol followed by hydrogen cyanide elimination, yielding the protonated imidate 573.[255] Further expulsion of ethyl chloride parallels the transformation of the above mentioned α-chloroimidate 570.[253,254] The application of organophosphorous reagents to reactions with



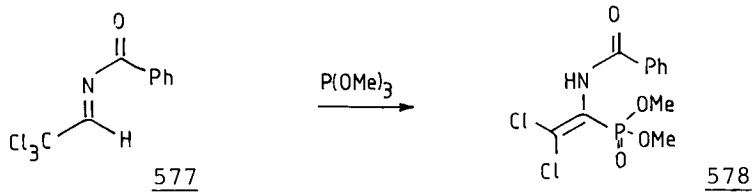
102 572 573



574 575 576

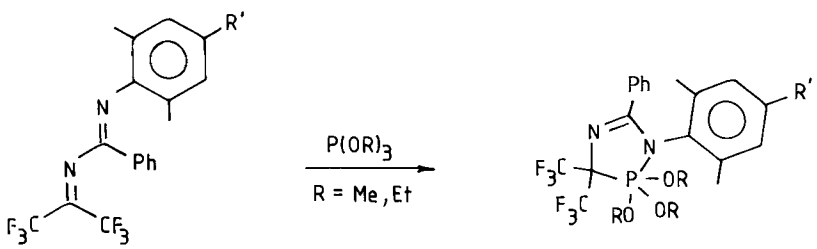
(R' = Me, Et)

α-haloimines has only limited scope. 2-Aza-1,3-butadienes 575 reacted with trialkyl phosphites or triphenylphosphine to yield 576 and 574 respectively.[256] The activated chloraldimine 577 afforded β,β-dichloroenamine 578 by reaction with trimethyl phosphite.[257,258]



577 578

A cyclization was observed during the condensation of 2,4-diaza-1,3-butadiene 579 with trialkyl phosphites, providing a valuable procedure for the synthesis of phosphorus-containing heterocyclic compounds 580.[258]



579 (R' = H, Me) 580

IV. PREPARATIONS

Preparation 1 : 2-Cyano-4,5,5-trimethyl-3-nitrato-1-pyrroline-1-oxide 37 (R = CH_3)[24]

3-Bromo-2-cyano-4,5,5-trimethyl-1-pyrroline-1-oxide 36 (R = CH_3) (300 mg, 1.3 mmol) in 10 ml of acetonitrile was added to a stirred solution of 1.2 g (7.1 mmol) of silver nitrate in 20 ml of acetonitrile at room temperature. Stirring was continued in the dark for 20 min. and the precipitated silver bromide was then filtered and washed with chloroform. The combined filtrate and washings were concentrated to yield a colorless oil. Ethyl acetate (100 ml) was added, the solution filtered to remove any solid material and the ethyl acetate evaporated to afford cis- and trans-2-cyano-4,5,5-trimethyl-3-nitrato-1-pyrroline 1-oxide 37 (R = CH_3) as a colorless oil.

Preparation 2 : 4a-Methoxy-1,2,3,4-tetrahydrocarbazoleindolenine 59[36]

1,2,3,4-Tetrahydrocarbazole (2.0 g) and triethylamine (1.28 ml) in 36 ml of benzene were stirred in an ice bath while t-butyl hypochlorite (1.28 ml) (or an equivalent amount of N-chlorobenzotriazole) was added dropwise. After additional stirring for 30 min, the benzene solution of the tetrahydrocarbazolechloroindolenine 58 was run rapidly into a stirred solution of sodium methoxide (prepared by adding sodium (1 g) to 35 ml of absolute methanol) cooled to -10° in an ice-methanol bath. After 30 min of stirring at -10°, the mixture was evaporated in vacuo, 30 ml of ice water was added, and the solu-

tion was extracted four times with 25 ml portions of chloroform. The extract was dried (Na_2SO_4) and evaporated to afford a viscous oil (2.06 g, 88%). Crystallization from hexane gave large, colorless prisms, mp. 47-51°.

Preparation 3 : Diethyl Spiro(cyclopentane-1,3'-3'H-indole)-2'-(1'H)-ylidenemalonate 80[49]

A solution of 4a-chloro-2,3,4,4a-tetrahydro-1H-carbazole 58 in benzene, obtained from the addition of t-butyl hypochlorite (1.1 ml) to a solution of 1.71 g (10 mmol) tetrahydrocarbazole in 30 ml benzene containing 1.1 ml of triethylamine,[49] was treated with 3.64 g (10 mmol) thallium(I) diethyl malonate. The mixture was refluxed for 18 hrs, then cooled and filtered through florisil. The filtrate was extracted twice with ice cold 2N hydrochloric acid, washed with water and dried over sodium sulfate. Removal of the solvent furnished a dark oil which was cooled to 0°. The crystals were filtered and recrystallized from n-heptane to give 80, mp. 102-103° (1.54 g, 47%).

Preparation 4 : 2-N-t-Butylamino-3-ethyl-2-pentenenitrile 97 ($R_1 = R_2 = Et$; R = t-Bu)[58]

A solution of 10.0 g (0.052 mol) of N-1-(2-chloro-2-ethylbutylidene)t-butylamine 96 ($R_1 = R_2 = Et$; R = t-Bu) in 100 ml of dry methanol was treated with 10.3 g (0.156 mol) of potassium cyanide. The mixture was heated at reflux overnight with vigorous stirring. Slightly more than half of the solvent was evaporated under reduced pressure, after which the reaction mixture was poured into 200 ml of water, extracted with three

portions of ether, dried ($MgSO_4$), filtered and evaporated. The remaining clear liquid was nearly pure 2-N-t-butylamino-3-ethyl-2-pentenenitrile as shown by NMR. Distillation in vacuo furnished 9.0 g (94%) of pure 97 ($R_1 = R_2 = Et$; R = t-Bu), bp. 110-114°/12 mm Hg.

Preparation 5 : General Procedure for the Synthesis of α-Amino-acids from Ethyl N-Trichloroethylidenecarbamate 111[64]

To a stirred suspension of the Grignard reagent, freshly prepared from magnesium (0.01 gram-atom) and alkyl halide (0.01 mol) in dry ether (20 ml), was added dropwise 0.01 mol of ethyl N-trichloroethylidenecarbamate 111 in 10 ml of ether at 0° under nitrogen. The mixture was stirred overnight at room temperature. After hydrolysis with water, the organic layer was separated, dried ($MgSO_4$) and evaporated in vacuo. The yellow liquid was purified by column chromatography on silica gel, and recrystallized from n-hexane to give adducts 112.

To adduct 112 (1.3 mmol) was added 10% sodium hydroxide in ethanol-water (1:2; 20 ml). The suspension was stirred at room temperature for 3 days, the resulting clear solution was acidified with 6N hydrochloric acid and evaporated to dryness under reduced pressure. The residue was dissolved in 20 ml of 2N-hydrochloric acid and refluxed for 24 hrs. Extraction with ether removed the unchanged starting materials and the aqueous solution was evaporated. The dried residue was desalted by the usual method[261] and applied to a Dowex 50 W-X8 column. α-Aminoacids 113 were eluted with aqueous 3% ammonia. The α-amino-

acid fraction was concentrated in vacuo and samples were recrystallized from alcohol. Yields ranged from 15% to 77%.

Preparation 6 : 1,3-Diphenyl-2-butanone Tosylhydrazone[71]

To a solution of 1,3-diphenylpropanone tosylhydrazone (1.00 g; 2.64 mmol) in 40 ml of anhydrous tetrahydrofuran, was added tri-N-methylanilinium perbromide (0.992 g, 2.64 mmol). The mixture was quickly filtered to remove trimethylanilinium bromide and slowly dropped into a stirred solution containing an excess (15.9 mmol) of lithium dimethylcuprate [from copper(I) iodide (15.9 mmol) and 1.62 M methyllithium in diethyl ether] at a temperature not exceeding 0° and under an argon atmosphere. After 10 min the solution was poured into saturated ammonium chloride solution and extracted with ethyl acetate. The extract was dried (Na_2SO_4) and concentrated under reduced pressure. The solid residue (0.91 g) was chromatographed on silica gel (eluent 70:30 cyclohexane - ethyl acetate) to give 0.74 g (64%) of pure 1,3-diphenyl-2-butanone tosylhydrazone, mp. 116-118°.

Preparation 7 : 1,3,4-Trisubstituted Pyrroles 120[66]

A solution of 0.1 mol of α-chloro- or α-bromoaldimines (119 or 128) in the same volume of dry ether was added to 125 ml of anhydrous liquid ammonia. The solution was vigorously stirred and 0.11 gram-atom of sodium was added slowly (small pieces). The reaction mixture was neutralized by adding 5 g of ammonium chloride. Ammonia was evaporated and pentane was added. After filtration, pentane was evaporated in vacuo and

the remaining product was distilled to give 1,3,4-trisubstituted pyrroles 120 in 31-75% yield.

Preparation 8 : Ethyl 1-methoxy-2,2,2-trichloroethylcarbamate 148 (R = Et; R' = CH_3)[76]

N-Ethoxycarbonyl chloraldimine 147 (R = Et) a so-called anhydrochloralurethan, (1.09 g) was added to 5 ml methanol. An immediate exothermic reaction occurred. After the reaction ceased, evaporation of the methanol afforded 1.12 g (90%) of ethyl 1-methoxy-2,2,2-trichloroethylcarbamate 148 (R = Et; R' = CH_3), mp. 59-61°.

Preparation 9 : N-(1-p-anisidino)pentyl-acetamide 152 (R_1 = n-Pr; Ar = p-$CH_3C_6H_4$)[81]

To a 5% solution of N-1-(2,2-dichloroalkylidene)acetamide 151 (R = n-Pr) in dry diethyl ether was added dropwise with stirring a 5% solution of freshly distilled p-anisidine in dry diethyl ether. After stirring overnight at room temperature, evaporation of the ether yielded a 98% yield of crude crystall ne 152 (R = n-Pr; Ar = p-$CH_3OC_6H_4$), which was recrystallized with diethyl ether/hexane, mp. 104°.

Preparation 10 : 1-t-Butyl-1-alkylaziridines 174 (R = t-Bu)[92]

To a suspension of 0.21 mol of lithium aluminium hydride in 50 ml of dry diethyl ether was added slowly at 0° a solution of 0.1 mol of N-t-butyl α,α-dichloroaldimine 98 in an equal volume of ether over a period of 1 hr. The reaction mixture was allowed to warm up to room temperature and stirring was

continued for 12 hrs. Work-up was accomplished by cautious addition of the reaction mixture to a two-phase system of ether and water. The ethereal layer was separated and the water layer extracted twice with ether. The combined extracts were dried ($MgSO_4$), evaporated and distilled in vacuo to afford aziridines 174 in 80-90% yield.

Preparation 11 : α,β-Unsaturated Aldimines 217[21]

A mixture of 0.1 mol N-1-(2-chloroalkylidene)amine 216 and 100 ml of 2N sodium methoxide in methanol (2.0 equivalents) was refluxed overnight with stirring. Methanol was evaporated in vacuo and the residue was poured into water and extracted with diethyl ether. The combined extracts were dried ($MgSO_4$) and evaporated in vacuo leaving an oil, which was distilled at reduced pressure to afford colorless N-1-(2-alkenylidene)amines 217 in 67-98% yield.

Preparation 12 : General Procedure for the Dehydrohalogenation of α-Halohydrazones[107]

A solution of 0.5-1.0 g of α-halohydrazone in a minimum amount of hot glacial acetic acid was kept at its boiling point for 5 min. The solution was cooled until the acetic acid began to crystallize and the crystals of α,β-unsaturated hydrazones which separated were collected.

A related procedure for the synthesis of α,β-unsaturated hydrazones involved the addition of one equivalent of 2,4-dinitrophenylhydrazine to a solution of an α-haloketone in glacial

acetic acid. The solution was kept at its boiling point for five minutes and the products, which separated on cooling, were isolated by filtration.

Preparation 13 : 3,3,5,5-Tetramethyl-1-tosylazocyclohexene 253[129]

A stirred solution of 3.22 g (0.01 mol) of 3,3,5,5-tetramethylcyclohexanone tosylhydrazone 251 in 100 ml of anhydrous tetrahydrofuran at -20° was treated with 3.79 g (0.01 mol) of phenyltrimethylammonium perbromide over a period of 15 min. After an additional 10 min., the precipitate was collected by filtration and the filtrate was evaporated under reduced pressure at a temperature not exceeding 40°. The residue was dissolved in ether and shaken with a saturated aqueous solution of sodium carbonate. After several washings with water, the solution was dried (Na_2SO_4) and evaporated to leave a residue, from which yellow 3,3,5,5-tetramethyl-1-tosylazocyclohexene 253 was precipitated with hexane (2.62 g; 82%), mp. 87° (dec).

Preparation 14 : General Procedure for the α-Phenylation of α-Halotosylhydrazones[125]

Phenyllithium (3.0 mmol) in benzene was added to a suspension of 3.3 mmol of purified cuprous iodide in 5 ml of ether and the mixture was stirred at -5° until a negative Gilman Test[260] resulted (about 5 min.). To this suspension was added 5 ml of tetrahydrofuran and the mixture was cooled to -60°. An appropriate α-halotosylhydrazone (1.0 mmol) in 5 ml of tetrahydrofuran was added via a syringe while the reaction tempera-

ture was kept at -60°. Analysis by tlc on silica gel indicated the reaction to be complete within 5 min. The reaction mixture was quenched by addition of 5 mmol of acetic acid and allowed to warm up to room temperature. The reaction mixture was added to a solution of ammonium chloride in aqueous ammonia and extracted twice with tetrahydrofuran and once with ether. Drying ($MgSO_4$) followed by removal of the solvent and washing the crude solid with hexane (to remove biphenyl from commercial phenyllithium) produced pure tosylhydrazones (259) in 72-94% yield.

Preparation 15 : (E)-Cyclononene-1-carboxylic acid 269 (n = 7)[136]

To a magnetically stirred, ice-cold 2N sodium hydroxide solution (50 ml) cooled in an ice bath at 0-5°, 0.009 mol of 4-chloro-3,4-heptamethylene-2-pyrazolin-5-one 268 (n = 7) was added, resulting in a yellow solution with gas evolution. After gas evolution had subsided (about 3 hrs), stirring was continued for another 2 hrs in the cold at 0-5°; the ice bath was removed and the stirring was continued for an additional 2 hrs. The solution was acidified with 6N HCl to a Congo red end point (pH 3.1). The resulting solid was taken up with two 25 ml portions of ether. The combined ethereal extracts were extracted twice with 25 ml of aqueous sodium bicarbonate, and the bicarbonate extracts were acidified to give a yellow-white solid. The solid was extracted with ether (50 ml), dried ($MgSO_4$), filtered and the ether was removed to afford a 67% yield of (E)-cyclononene-1-carboxylic acid 269 (n = 7), mp. 77-78° (pentane); no Z isomer was observed in this case.

Preparation 16 : 3-Piperidino-2-butanone oxime 286 (R = R' = CH_3)[149]

A solution of 15 ml of piperidine in 100 ml of dry ether was added dropwise with stirring to a solution of 6.0 g (49 mmol) of 3-chloro-2-butanone oxime 285 in 50 ml of dry ether, cooled in an ice bath. After additional stirring of 1 hr., the reaction mixture was treated with water to dissolve the piperidine hydrochloride and the ethereal phase was separated, dried (Na_2SO_4) and evaporated to leave crystalline 3-piperidino-2-butanone oxime 286 (R = R' = CH_3) in quantitative yield, mp. 83°.

Preparation 17 : Oxime of Phenacyltriphenylphosphonium Chloride 307 (R = Ar = Ph)[160]

A mixture of 2.0 g of α-chloroacetophenone oxime[261] and 3.23 g of triphenylphosphine in 70 ml of chloroform was refluxed for 3 hrs. The white precipitate (5.2 g, 100%, mp. 211°) was collected and crystallized from a little ethanol, mp. 215°.

Preparation 18 : Cycloaddition of N-cyclohexyl α-chloropropionaldonitrone 327 (R = CH_3) with cyclohexene[168]

To a solution of 3.56 mmol silver tetrafluoroborate and 1.64 mmol of cyclohexene in 10 ml of 1,2-dichloroethane was added in the dark and under nitrogen a solution of 3.41 mmol N-cyclohexyl α-chloropropionaldonitrone 327[1,168] in 20 ml of 1,2-dichloroethane. The addition was performed at 40° over a period of 1.5 hr., with vigorous stirring. The yellow reaction mixture

was separated from the precipitated silver chloride and shaken for 15 min. at room temperature with a solution of 5 g of potassium cyanide in 10 ml water. Extraction with dichloromethane yielded the crude product, which was chromatographed over 70 g of Alox (Woelm, Activity V, basic) with hexane. Cycloadduct 329 (R_1 = R_2 = H; R = CH_3) was obtained in 85% yield.

Preparation 19 : cis-Methyl N-Phenyl-4-methyl-2-pentenoimidate 348a (R' = R_2 = H; R_1 = i-Pr)[20]

A mixture of 2.44 g (0.01 mol) of freshly prepared N-2-(1,1-dichloro-4-methylpentylidene)aniline 71 (R_2 = R' = H; R_1 = i-Pr) and 5.4 g (0.1 mol) of dry sodium methoxide in 25 ml of dry diisopropyl ether was stirred under reflux for 32 hrs and protected with a calcium chloride tube. After completion of the reaction, the suspension was filtered and washed with dry ether. Removal of the solvent in vacuo left an oil, which was further purified by preparative tlc. (PSC Fertigplatten Merck Kieselgel F 254; 2 mm thickness; isooctane : carbon tetrachloride : toluene 40:30:30 as eluent). Extraction of the band at Rf 0.4-0.5 with dry acetone provided 1.8 g (92%) of pure cis-methyl N-phenyl-4-methyl-2-pentenoimidate 348a (R' = R_2 = H; R_1 = i-Pr).

Preparation 20 : 2-t-Butylamino-2-methylpropionaldehyde Dimethyl Acetal Hydrochloride 361[21]

A solution of 2.0 g (0.0124 mol) of N-1-(2-chloro-2-methylpropylidene)t-butylamine 358 in 50 ml of dry methanol was refluxed during a period of two days (protected with a calcium

chloride tube). Evaporation of the solvent in vacuo afforded a solid residue, which was washed several times with dry ether to leave a white powder (1.9 g, 70%, 361).

Preparation 21 : 1-Cyclohexyl-4-methoxy-5,5-dimethyl-2-imidazolidinethione 366 (R = cyclohexyl)[179]

N-1-(2-chloro-2-methylpropylidene)cyclohexylamine 358 (R = cyclohexyl, 15.0 g, 0.08 mol) was dissolved in 150 ml of dry methanol and treated with 23.3 g (0.24 mol) of potassium thiocyanate. The mixture was refluxed overnight, half evaporated, and poured into 500 ml of vigorously stirred distilled water. The resulting precipitate was collected by filtration and washed with cold methanol/water 25:75. 1-Cyclohexyl-4-methoxy-5,5-dimethyl-2-imidazolidinethione 366 (R = cyclohexyl) was dried in the dessicator to afford 15.1 g (78%), mp. 184°.

Preparation 22 : 2-Methoxyspiro(cyclopentane-1,3'-indolenine) 383[36]

A benzene solution of tetrahydrocarbazolechloroindolenine 58, from 1.25 g of tetrahydrocarbazole as described in Preparation 2 was run rapidly into a stirred refluxing solution of 3 g of sodium hydroxide in 35 ml of methanol, and the mixture was refluxed for 30 min. The solvent was evaporated in vacuo, 30 ml of ice water was added, and the mixture was extracted four times with 25 ml of chloroform. Drying (Na_2SO_4) and evaporation yielded a viscous oil (1.20 g, 82%), which crystallized on standing at -20°. Recrystallization from diethyl ether gave white prisms, mp. 66-68°.

Preparation 23 : 2-Ethoxycarbonyl-3-trichloromethyl-2-azabicyclo[2.2.1]heptene[199]

Refluxing a benzene solution (25 ml) of freshly prepared N-1-(2,2,2-trichloroethylidene)ethoxycarbonylamine 147 (R = Et) (5.0 g) and cyclopentadiene (2.5 g) for 3 hrs gave an oily residue after evaporation. The residue was chromatographed over 80 g of alumina with benzene as eluent. The faster moving zone gave, after removal of the solvent, 3.85 g (59%) of oily 439 (exo trichloromethyl group), bp. 136-138°/4 mm. From the slower moving zone, 2.01 g (30%) of 438 (endo trichloromethyl group) was obtained as colorless crystals, mp. 47.5-48°.

Preparation 24 : 2,2-Dichlorovalerophenone 545 (R = n-Pr; R' = H)[240]

A mixture of 20.0 g (0.123 mol) of valerophenone and 17.0 g (0.172 mol) of cyclohexylamine in 250 ml of toluene was refluxed in the presence of a small amount of p-toluenesulphonic acid. Reflux was continued until the theoretical amount of water separated in a Dean-Stark apparatus (usually 24-28 hrs). N-Cyclohexyl valerophenone imine (29.3 g, 98%) was obtained by distillation, bp. 92-99°/0.03 mm. To a stirred solution of 29.3 g (0.120 mol) of this ketimine in 250 ml of dry carbon tetrachloride was added, over a period of 20 min, 35.7 g (0.268 mol) of N-chlorosuccinimide. The temperature was kept between 20° and 40° with a water bath. After stirring 4 hrs at room temperature, succinimide was filtered, washed with CCl_4 and evaporation of the filtrate left N-1-(2,2-dichloro-1-

phenylpentylidene)cyclohexylamine as a pale yellow oil (quantitative yield). The α,α-dichloroketimine was dissolved in 100 ml of diethyl ether and treated with 30 ml of concentrated aqueous hydrogen chloride and 70 ml of water. After stirring for 3 hrs, the ethereal phase was isolated and, after addition of sodium chloride, the water phase was extracted twice with diethyl ether. The combined extracts were washed with water, dried ($MgSO_4$) and evaporated *in vacuo* to give a clear oil, which was distilled to afford 24.9 g (90%) of 2,2-dichlorovalerophenone **545** (R = n-Pr; R' = H), bp. 73-79°/0.06 mm.

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