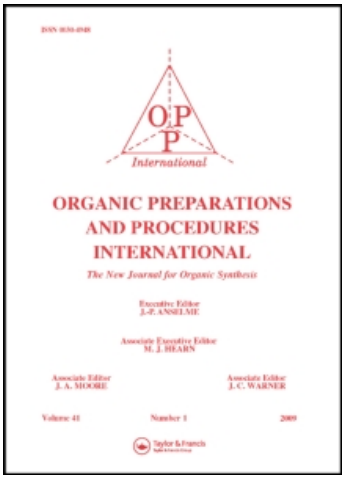

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THE SYNTHESIS OF α-HALOGENATED IMINO COMPOUNDS

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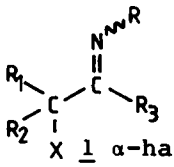
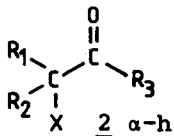
INTRODUCTION

α-Halogenated imino compounds are a class of compounds in which an halogen-bearing sp^3-hybridized carbon atom is directly bonded to the sp^2-hybridized carbon atom of an imino function.



X 1 α-haloimine



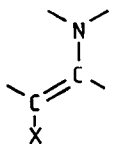
X = halogen

X 2 α-haloketone

Due to the presence of the imino function in the molecule, the title compounds can exist as E or Z isomers, or a mixture of both. When possible, attention will be given to this type of isomerism.[1] In general, α-haloimines 1 having an α-hydrogen (R_2=H) do not tautomerize into the corresponding β-haloenamines, except in some special cases where delocalization may exist (e.g. when CN, COOR, NO_2 substituents[2-4] are present in the molecule).

These compounds 1 are the nitrogen analogues of α-halogenated ketones. The latter class of organic chemicals has been studied extensively in the literature, while only minor attention has been given to the chemistry of α-halogenated imino compounds, due to the fact that no general routes leading to this class of compounds were available. The methods used for the synthesis of α-haloimines 1 and the instability of the derivatives thus obtained, did not allow an exploration of this field of chemistry. Comprehensive investigations in the area of the chemistry of α-halogenated imino compounds is of rather recent origin, although many non-general papers exist on the synthesis of the title compounds.

Because of the importance of α-haloketones in synthetic and mechanistic organic chemistry, efforts have been carried out recently to compare the reactivity of α-halo imino compounds with the reactivity of α-haloketones (or α-halocarbonyl compounds in general). It will be demonstrated in a forthcoming review in this journal that the reactivity of both classes differs considerably and that interesting mechanistic deviations are possible for structurally related compounds 1 and 2. The third part of this series of reviews will deal with the synthesis of β-halogenated enamines 3, which are the tautomers of α-haloimines 1 when one of the α-substituents in 1 is hydrogen.



3 β-haloenamine

Depending on the substitution pattern and the circumstances used, either α-haloimines 1 or β-haloenamines 3 may be obtained. It was, however, advisable to separate the reviews on the synthesis of both classes of structurally related compounds. In the fourth part, focus will be given on the reactivity of β-halogenated enamines.

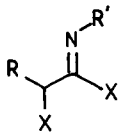
It is the purpose of this series of articles to indicate the usefulness of the synthetic and mechanistic aspects of the reactions of α-haloimines and β-haloenamines.

The literature has been reviewed up to early 1978.

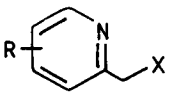
SCOPE OF THE REVIEW

Only those α-halogenated imino compounds, reflecting a structural similarity with α-halogenated carbonyl compounds, will be treated in this review. For instance, no emphasis will

be given on the synthesis of compounds of types 4 and 5. (α-Halogenated imidoyl halides 4 have already been reviewed).[5] On the other hand, to a minor extent, the synthesis of α-haloimidoyl cyanides, α-haloimidates and α-haloamidines will be discussed.



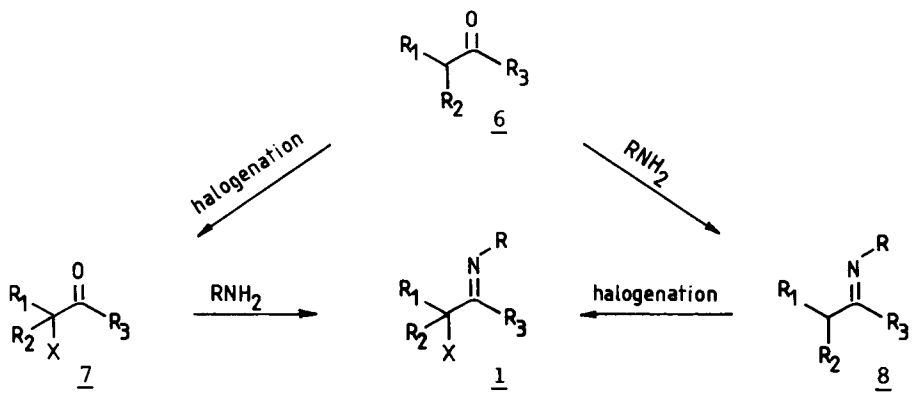
4 (X = halogen)



5 (X = halogen)

SYNTHESIS OF α-HALOGENATED IMINES

Two fundamental approaches to the synthesis of α-haloimines 1 may be considered. The first strategy involves the condensation of an α-halogenated carbonyl compound 7 with a primary amine under suitable conditions, similar to the preparation of imino compounds starting from carbonyl compounds and primary amines. The second involves the halogenation of ini-



tially formed imines 8. Carbonyl compounds 6 are the basic materials for the synthesis of α-halogenated imines, thus the substitution in the carbon skeleton of 1 will be determined by the accessibility of the carbonyl compound used.

At first sight, the pathway involving initial halogenation of carbonyl compounds and subsequent transformation into imino compounds 1 seems to be the most attractive route, since the halogenation of the ketones and aldehydes has received much attention; this has resulted in an overwhelming variety of halogenation procedures.[6,7] However, a major difficulty has been encountered and this may explain why the synthesis and chemistry of α-haloimines have not found wide-spread application. Indeed, the combination of two functional groups, i.e. carbonyl function and halide, opens the possibility for side-reactions to occur, which very often become the major paths. A variety of side-reactions, among others α-substitution, elimination of hydrogen halide, Favorskii rearrangement, rearrangement *via* intermediate epoxides, further reactions of intermediately formed α-haloimines have been encountered in the literature. At the end of this section, emphasis will be given to these side-reactions, which constituted the main obstacles for the development of syntheses of α-haloimines. In some instances, however, under appropriate experimental conditions and with suitable substitution, α-halogenated carbonyl compounds may be condensed with primary amines to afford the corresponding α-halogenated imines (*vide infra*).

The second proposed pathway leading to α-haloimines 1 entails the formation of an appropriate imine 8, by condensation of carbonyl compounds 6 with primary amines followed by halogenation of the imino compound.

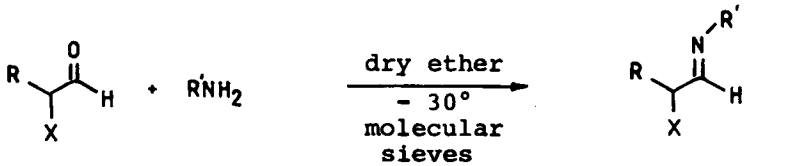
The halogenation step is the limiting factor of this entry into the chemistry of α-haloimines. Halogenation often leads

to immonium-type compounds which are very unstable and give rise to the corresponding α-halogenated carbonyl compounds. It is clear that the halogenation medium will play an important role.

The present review will focus on several entries into α-halogenated imino compounds and will be divided into four parts. The first two parts will cover the two main synthetic pathways already mentioned above. The third part will deal with the halogenation of enamines leading to α-haloimines and the fourth will deal with miscellaneous methods. Finally, an addendum will discuss some aspects of the synthesis of α-halogenated immonium compounds.

I. CONDENSATION OF α-HALOGENATED CARBONYL COMPOUNDS WITH PRIMARY AMINES

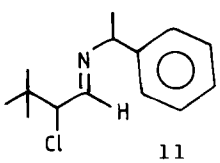
The direct condensation of α-halogenated ketones with aliphatic or aromatic primary amines to afford α-halogenated ketimines has never been described (except for α-fluorinated derivatives; see below). Only α-chloro- and α-bromoaldehydes 9 have been reported to condense with aliphatic primary amines to give the corresponding α-chloro- and α-bromoaldimines 10 in 27-73 % yield.[8] The reaction was carried out at low temperature in very dilute solution in ether and in the presence of molecular sieves (Preparation 1).



9 X = Cl, Br

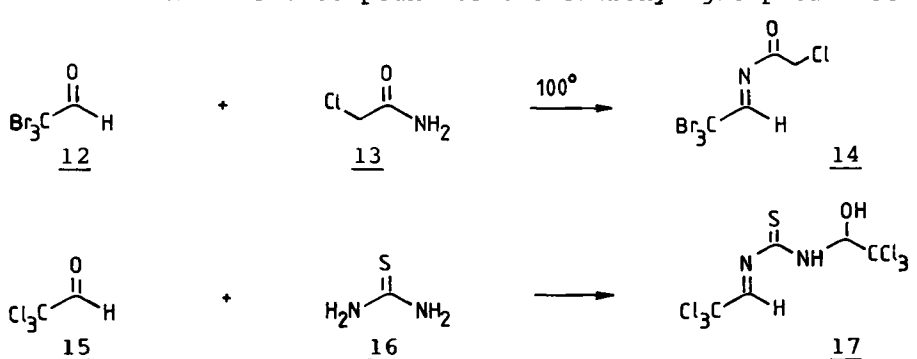
10 X = Cl, Br

Compounds 10 are very labile (the bromo derivatives are less stable than the chloro derivatives). Only the N-t-butyl-α-haloaldimines 10 (R'=t-Bu) seemed to be fairly stable, while N-n-butyl derivatives decomposed spontaneously, even at -30° in an inert atmosphere. Excess primary amines converted α-haloimines 10 into α-alkylaminoaldimines.[8] This report is the most important publication dealing with the direct condensation of an α-chloro or α-bromo carbonyl compound with primary amines. Application of the above mentioned method to the reaction of 2-chloro-3,3-dimethylbutanal with D-(+)-α-methylbenzylamine provided α-chloroaldimine 11, which exists as two diastereoisomers.[9]

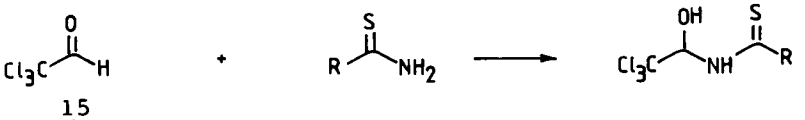


11

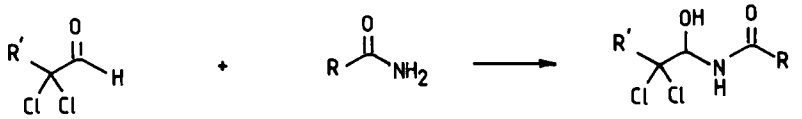
Less general examples of the title reaction were the condensation of bromal 12 or chloral 15 with amide or thioamide type compounds. Bromal was found to react with 2-chloroacetamide 13 at 100° to give tribromoaldimine 14,[10] while a similar reaction of chloral with thiourea 16, resulted in the further addition of the imino compound to the carbonyl group of chloral.[11]



These imino-forming reactions are surprising in view of the known behaviour of chloral 15[12] and α,α-dichloroaldehydes 19[13-15] to condense with amides or thioamides to give the stable adducts 18 and 20. It would thus seem that the aforemen-



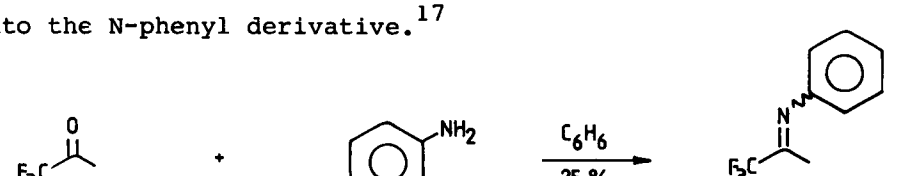
15 18



19 R' = alkyl, CH_2Cl, CCl_3 20

tioned reactions leading to 14 and 17 should be accepted with reservations.

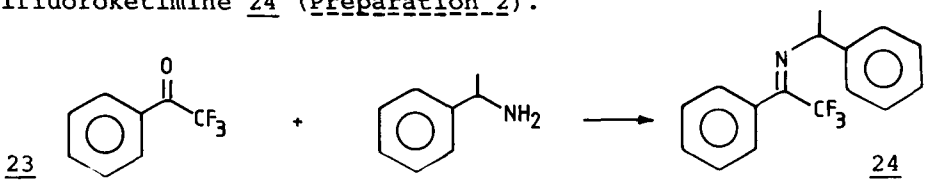
α-Fluorinated ketones, when reacted with primary amines, do not lead to the side-reactions already mentioned above. 1,1,1-Trifluoroacetone 21 with aniline in benzene for two days gave a 25 % yield of N-2-(1,1,1-trifluoropropylidene)aniline 22.[16] The same product 22 was obtained under milder conditions, namely by condensation of 21 with iminophosphorane 23 in ether,[16] while a modified route was used for the conversion of chloral into the N-phenyl derivative.[17]



21 22

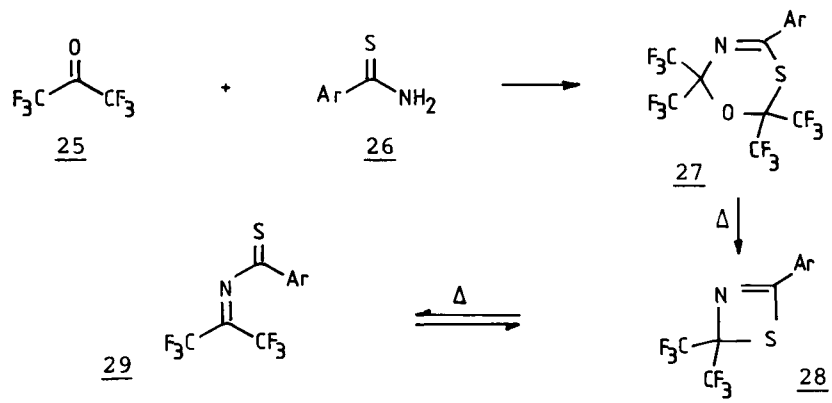
21 23 22

Also aromatic fluoroketones such as 2,2,2-trifluoroacetophenone 23 reacted with α-methylbenzylamine to afford α,α,α-trifluoroketimine 24 (Preparation 2).[18]



23 24

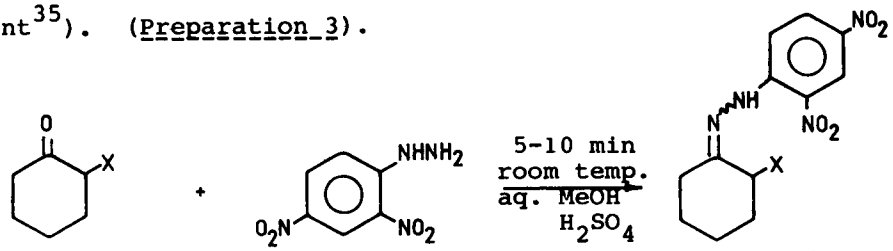
A useful synthon for a variety of heterocyclic compounds is the activated α,α,α,α',α',α'-hexafluoroketimine 29 which was obtained by condensation of hexafluoroacetone 25 with thiobenzamide derivatives 26.[19,20] Initially, 2,2,6,6-tetrakis(trifluoromethyl)-6H-1,3,5-oxathiazines 27 were formed, which were pyrolyzed into four-membered heterocycles 28. The 2H-1,3-thiazetes 28 exist in thermal equilibrium with N-(perfluoroisopropylidene)thiocarboxamides 29.[21]



25 26 27 29 28

The reactive behavior of α-halogenated ketones toward the usual carbonyl reagents showed some interesting features. A variety of α-halohydrazone derivatives,[22-26] semicarbazone-type compounds[13,27-34] and α-halooximes have been obtained by the direct condensation route. α-Halo-2,4-dinitrophenylhydrazones, e.g. 31, were prepared in good yields by means of an aqueous

methanolic solution of 2,4-dinitrophenylhydrazine sulfate containing excess sulfuric acid[22,23] (this is the so-called Brady reagent[35]). (Preparation 3).

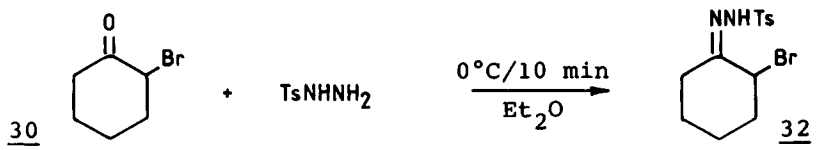


30 X = Cl, Br

31

Another versatile medium consisted of 2,4-dinitrophenylhydrazine in 85 % H_3PO_4/EtOH.[36]

Tosylhydrazine condensed very smoothly with 2-bromocyclohexanone 30 at low temperature in ethereal medium to yield crystalline α-bromotosylhydrazones.[37,38] Recently, α-haloacetone tosylhydrazones were investigated by ^{13}C NMR spectrometry ($CDCl_3$), which showed the predominance of the E-isomer.[39]



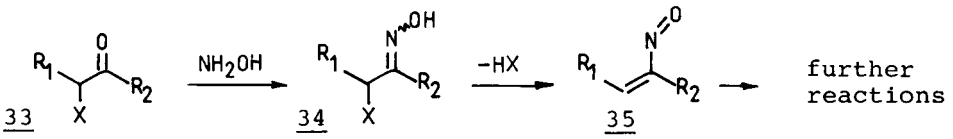
30

32

Other hydrazine derivatives condensed with α-halo ketones to afford intermediate α-halo hydrazones, which further reacted to a variety of products (see examples given below). α-Halosemicarbazones and related compounds were isolated under appropriate reaction conditions.[27-34] These compounds were subject to further transformations into heterocycles when less controlled conditions were used.[27,30,32]

The reaction of hydroxylamine with α-halocarbonyl compounds 33 met with some difficulties because of the possibility of the

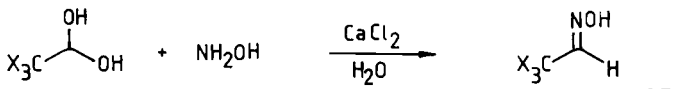
conversion of initially formed α-halooximes 34 into nitroso-olefins 35, especially when the reaction is carried out in alkaline medium.



33 34 35

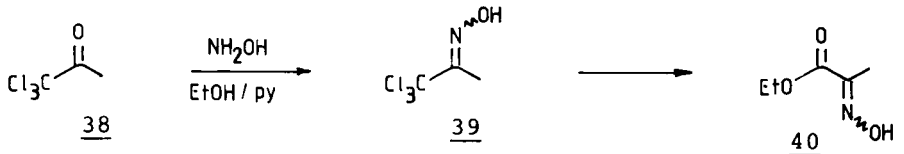
When excess of hydroxylamine was used, 1,2-dioximes were isolated.[40-42] For instance 2-bromoacetophenone was reported to form the dioxime of phenylglyoxal.[41] Accordingly, a slightly acidic medium is recommended and for this purpose, oximations were carried out in the presence of calcium chloride.[43,44]

The oximes of chloral and bromal (37) have been known for a long time,[45] the oxime of the former being used as a pesticide.[46] The starting material in these cases were the stable hydrates 36 (X = Cl, Br).



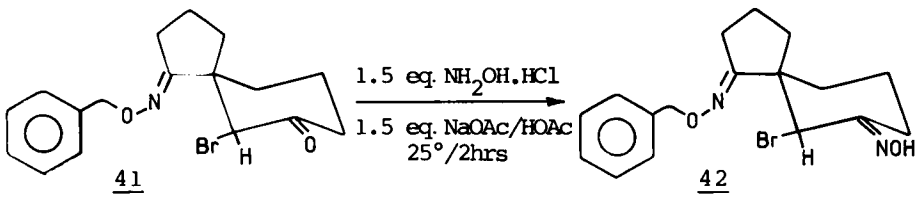
36 37

1,1,1-Trichloroacetone 38 reacted with hydroxylamine in ethanolic solution in the presence of pyridine, according to the classical procedure of oximation.[47] Prolonged heating of oxime 39 in the reaction medium resulted in a further conversion into ethyl 2-oximinopropionate 40. Other types of α-halooximes have been obtained in similar manner.

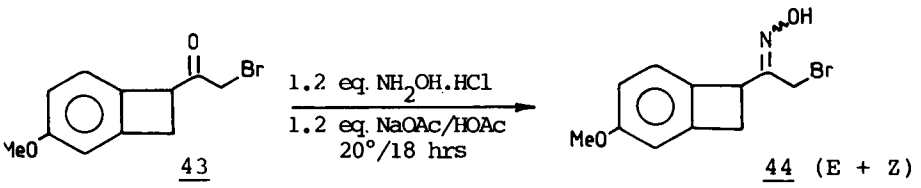


38 39 40

Recently,[48,49] a convenient procedure for the synthesis of α-halooximes involved the use of 1.2-1.5-equivalents hydroxylamine hydrochloride and 1.2-1.5-equivalents sodium acetate in acetic acid at 20-25° (2-18 hr). Accordingly α-bromoketone 41 was quantitatively converted into α-bromooxime 42[48] while a high yield synthesis of α-bromooxime 44[49] was obtained.

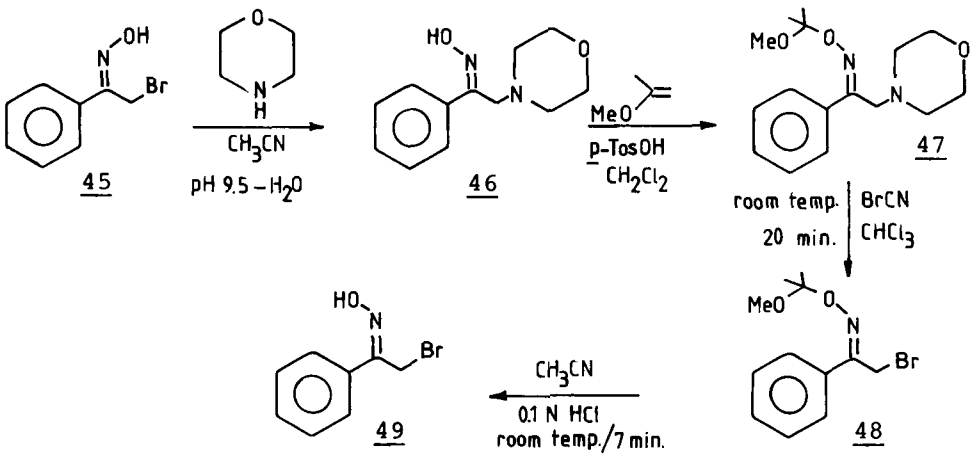


41 42



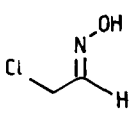
43 44 (E + Z)

Only a few attempts have been made to elucidate the structural isomerism of α-halooximes. Korten and Scholl[50] reported the isolation of two products from the reaction of 2-bromoacetophenone and hydroxylamine hydrochloride in methanol. It was assumed that these compounds were the syn and the anti isomer, but it was later shown that the so-called "anti" isomer was a mixture of syn-α-bromo and syn-α-chloroacetophenone oxime.[51] Some years ago the synthesis and structural elucidation of a thermally labile anti-aralkyl ketoxime was reported.[52] syn-α-Bromoacetophenone oxime 45 was converted into anti-α-morpholinoacetophenone oxime 46 by reaction with morpholine in aqueous acetonitrile at pH 9.5, upon which the oximino-function of 46

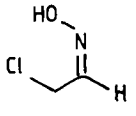


was protected by reaction with 2-methoxypropene in dichloromethane under catalytic influence of p-toluenesulfonic acid. Treatment of the protected oxime 47 with cyanogen bromide in chloroform gave 48 which was hydrolyzed into anti-α-bromoacetophenone oxime 49 (Preparation 4).[52]

No spectral characterization of α-halogenated oximes has been hitherto reported. Recently a comprehensive study in this field was undertaken.[53] For example, chloroacetaldoxime 50 exists in $CDCl_3$ solution as a 2:3 mixture of the Z and E isomers, as revealed by NMR spectroscopy.[53]

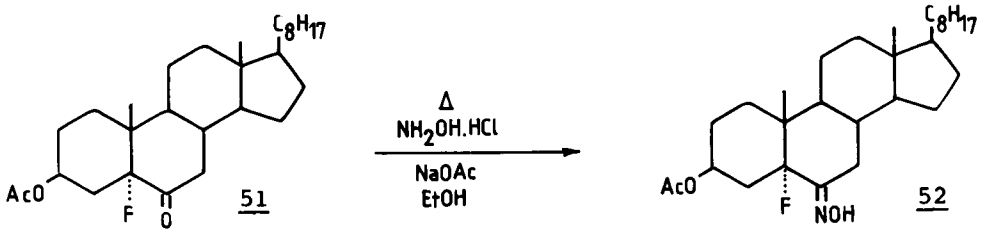


50 (E)

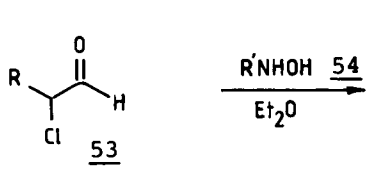


50 (Z)

α-Fluoroketones, such as 51, also formed α-fluorooximes, i.e. 5α-fluoro-6-oximinocholestane-3β-ol acetate 52, on heating with hydroxylamine hydrochloride in ethanol/sodium acetate (Preparation 5).[54]

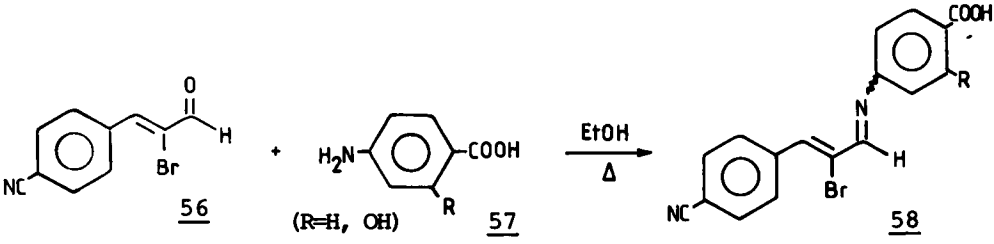


A special type of direct condensation of an α-halo carbonyl compound with an amino compound, leading to an α-haloimino derivative, is the reaction of 2-chloroacetaldehyde or 2-chloropropionaldehyde 53 (R = H, CH_3) with N-alkylhydroxylamines 54 to yield α-chloronitrones 55 (Preparation 6).[55] The cyclohexyl derivatives seemed to be the most stable derivatives, while extension of the carbon skeleton was limited to three carbon atoms.



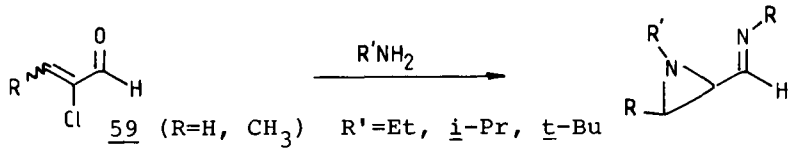
	R	R'
a	H	cycloHex
b	Me	cycloHex
c	H	t-Bu

The section of the direct condensation of α-halo carbonyl derivatives with primary amines will be concluded by an example of the reaction of a primary amine with an α-bromo-α,β-unsaturated aldehyde in ethanol which led to α-bromo-α,β-unsaturated aldimine 58.[56] This reaction of α-haloaldehydes having the



halo atom attached to a sp^2-hybridized α-carbon atom is not general as illustrated by the following example in which aziri-

dinylformaldimines 60 were produced by reaction of primary amines with α-chloro-α,β-unsaturated aldehydes 59.[57] More generally, α-halogenated conjugated enones or α,β-dibromoketones



59 (R=H, CH_3) R'=Et, i-Pr, t-Bu 60

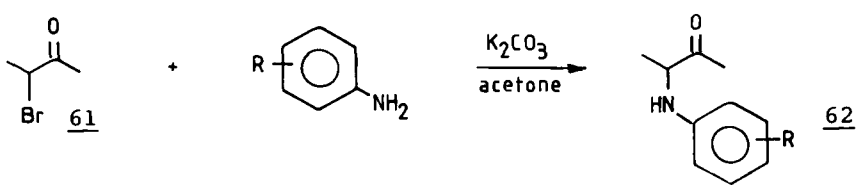
with primary amines give rise to Michael addition and subsequent intramolecular nucleophilic substitution, yielding C-acylaziridines (or their N-alkylimino derivatives).[58-63]

ADDENDUM

Side-Reactions of the Condensation of α-Halo Carbonyl Compounds with Primary Amines

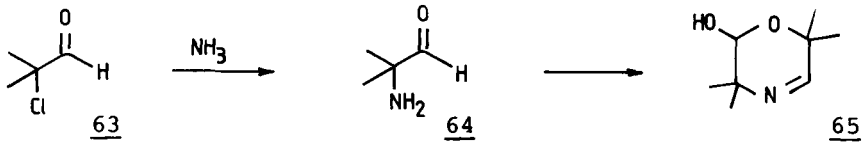
It was stated in the introductory part that a variety of side-reactions have been observed during the condensation of α-halo carbonyl compounds and primary amines. These complications will now be demonstrated by some leading references.

A number of α-substitution reactions of α-halocarbonyl compounds with amino derivatives (primary amines or ammonia) have been observed. 3-Bromo-2-butanone (61) reacted with anilines in ethanol or acetone in the presence of potassium carbonate to form the α-anilinoketone 62, which gave further reaction products.[64,65] Similar observations were reported with ethyl γ-chloroacetoacetate.[66]



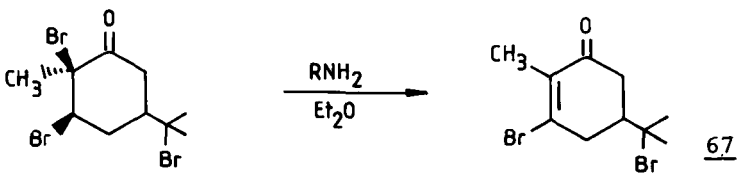
61 62

2-Chloro-2-methylpropanal 63 gave α-substitution with liquid ammonia but the product reacted further to heterocyclic compound 65.[67]



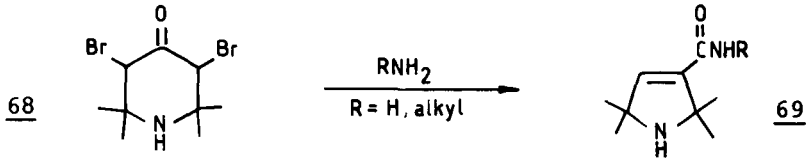
63 64 65

cis-Carvone tribromide 66 afforded the dehydrobromination product 67 when treated with a primary amine in ethereal medium.[68]



66 67

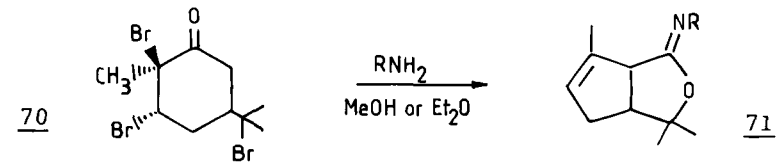
Favorskii rearrangements[69,70] were observed when certain α-brominated ketones were brought into reaction with primary amines or ammonia. Accordingly, 3,5-dibromo-2,2,6,6-tetramethyl-4-piperidone 68 afforded a ring contraction into 2,2,5,5-tetramethyl-3-pyrroline-3-carboxamides 69.[71-73]



68 69

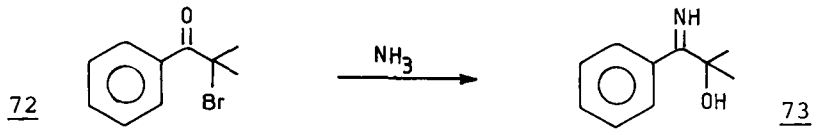
trans-Carvone tribromide 70 underwent a Favorskii rearrangement to afford cyclic imidate 71 when treated with primary amines in methanol or ether.[74] cis-Carvone tribromide 66 yielded cyclic iminoether 71 by reaction with primary amines in methanol.[74]

Another type of frequently occurring side-reactions is the rearrangement of α-halocarbonyl compounds via epoxide interme-



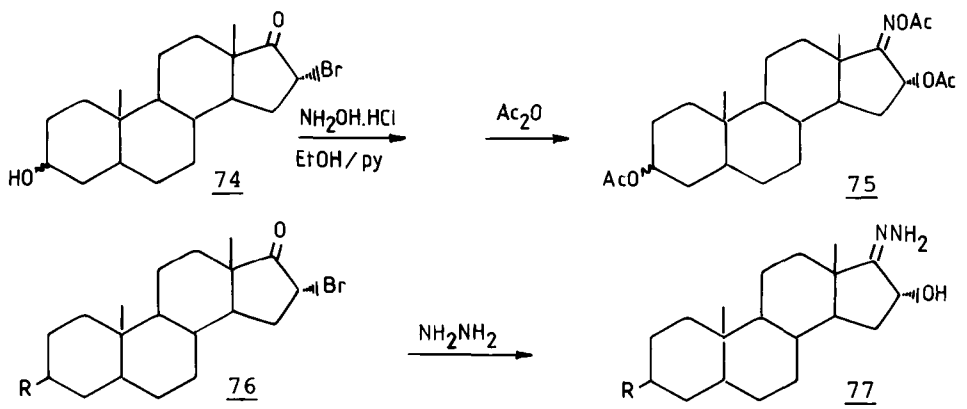
diates.

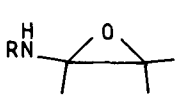
The reaction of 2-bromo-2-methyl-1-phenyl-1-propanone 72 with ammonia gave rise to the rearranged α-hydroxy-imine 73 via a non-isolable aminoepoxide.[75] A related reaction was the con-



version of α-chloroketones ($RCOCH_2Cl$; R = Me, C_6H_5, benzyl) into oxazolines by means of sodium or lithium amide in ammonia.[76]

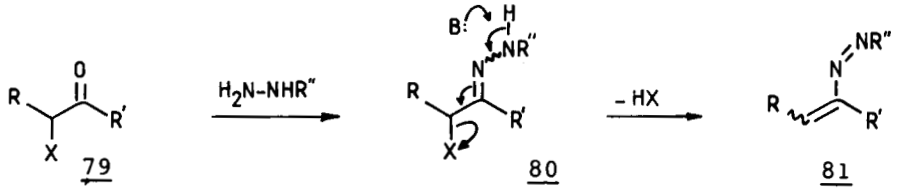
The reaction of steroidal α-bromoketones 74 and 76 with hydroxylamine or hydrazine furnished α-hydroxy oximes (isolated as triacetate)[77] and hydrazones,[78] respectively. The formation of the rearranged products was also interpreted in terms of a rearrangement via an aminoepoxide intermediate.





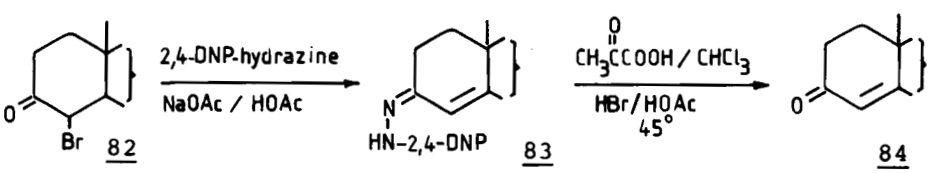
78 R = NH_2, OH, ...

On the other hand the condensation of α-halocarbonyl compounds with hydrazines is known to afford intermediate α-halohydrazones 80 which are easily converted into azoalkenes 81.[7981] Either a basic substance in the medium (hydroxide ion, acetate

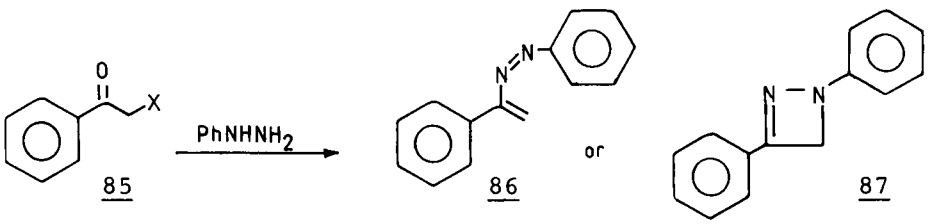


anion, etc...) or excess of the hydrazine used may be responsible for the dehydrohalogenation step.

Only 2,4-dinitrophenylhydrazones of α-halocarbonyl compounds were readily available, when prepared in aqueous methanol in the presence of sulfuric acid.[22,23] When the condensation of α-bromoketones, e.g. 4-bromo-3-ketosteroid 82 was carried out with sodium acetate/acetic acid, elimination of hydrogen bromide from the intermediately formed α-bromo-2,4-dinitrophenylhydrazone resulted.[22,82-84] This reaction was used to introduce a carbon-carbon double bond at C_4-C_5 in 3-ketosteroids.[82-84]

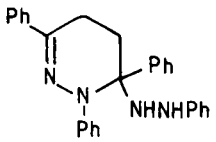


Phenylhydrazine, on the other hand, reacted with phenacyl halides 85 to give products whose structures have only recently been elucidated. The older literature reported that phenacyl halides (X = Cl, Br, I) condensed with phenylhydrazine to yield compounds with molecular formula $(C_7H_6N)_n$. The structure was attributed to azoalkene 86 or the four-membered heterocycle



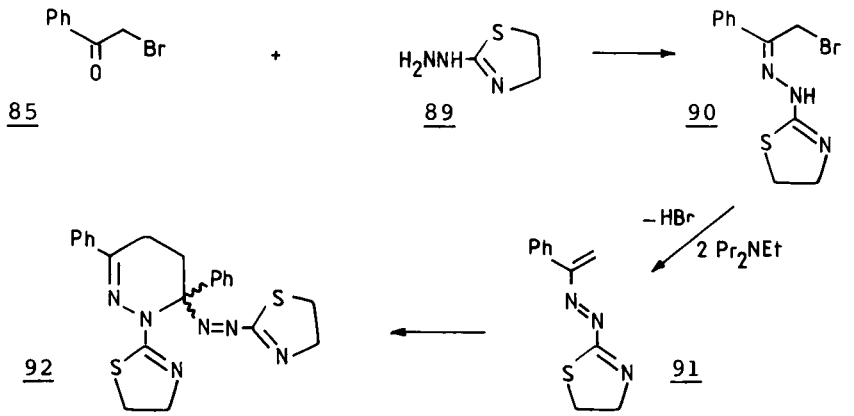
85 86 87

87.[85] Some years later a dimeric structure was proposed,[86] while other reports either accepted azoalkenes 87[87,88] or four-membered heterocycles 87 as possible reaction products until Curtin and Tristam suggested that a tetrahydropyridazine 88 was involved.[89]



88

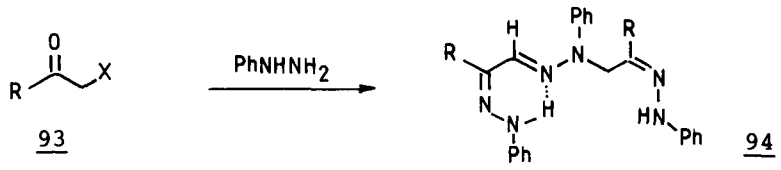
The latter proposal seemed valid since an analogous tetrahydropyridazine 92 was isolated from the reaction of phenacyl bromide and hydrazine derivative 89 (in this case no hydrazine



85 89 90 91 92

moiety was present; instead an azo function was found).[90] However, Schantl provided evidence that phenacyl halides 93 (R = C_6H_5 ; X = Cl, Br) condensed with phenylhydrazine to afford

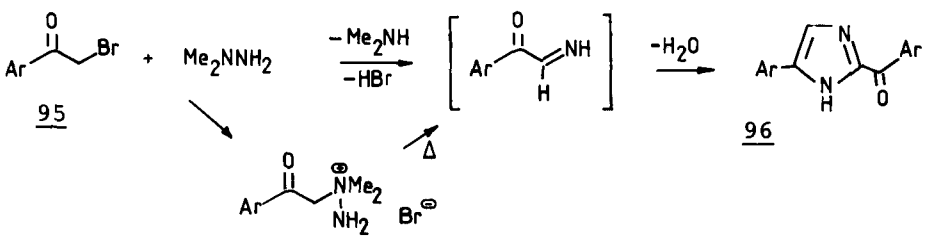
triimino compound 94 (R = C_6H_5).[91] In similar manner, chloro-



93 94

acetone 93 (R = Me ; X = Cl) reacted with phenylhydrazine to yield 94 (R = Me).[92] On the other hand, α-bromoacetophenones 95 condensed with hydrazines in methanol/acetic acid to yield dihydro-1,2,3-triazoles.[93]

N,N-Dimethylhydrazine displayed a different reactivity towards α-bromoacetophenones 95 and gave rise to arylglyoxaldimines, which further condensed to pyrazoles 96.[94]

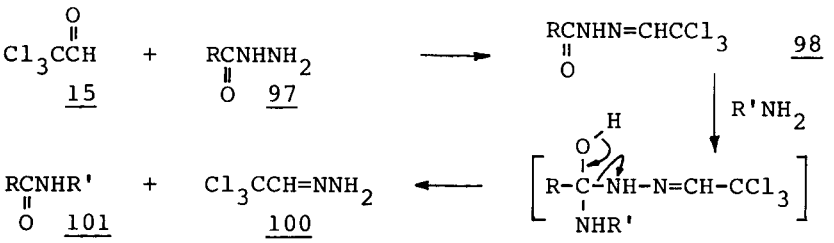


95 96

More recently, α-bromoaldehydes were reported to condense with N,N-dimethylhydrazine to produce α,β-unsaturated hydrazones, which furnished α,β-unsaturated aldehydes on acidic hydrolysis.[95]

Finally, α,α'-dibromoacetophenone azines produced 2,5-diarylpyrazines on reaction with hydrazine in ethanol.[96]

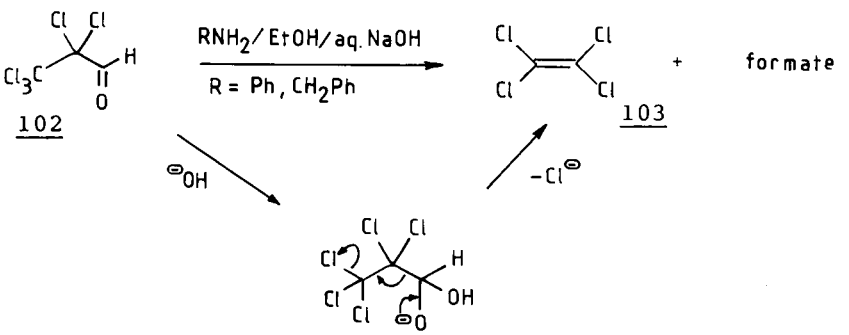
Semicarbazides 97 condensed with chloral 15 to give semicarbazones 98; addition of primary amines (or alcohols) cleaved these semicarbazones into carboxamides 101 (or esters) and chloralhydrazone 100;[97a,b] the latter reactions are known as the Kametani reaction.



Aromatic α-halogenated ketones also gave initial formation of α-haloimino compounds on reaction with semicarbazides, but further reactions led to 3,5,6-trisubstituted 1,2,4-triazines.[98] On the other hand, primary amides condensed with α-bromocarbonyl compounds in dimethylformamide to give rise to oxazoles.[99]

A large number of references dealing with the reaction of α-chlorocyclohexanone with amino compounds were collected by Mousseron et al.[100] This paper gives a good idea of the difficulties that have been encountered with these reagents.

A special type of reaction occurred when an α-halo carbonyl compound was treated with a primary amine in the presence of aqueous sodium hydroxide; 2,2,3,3,3-pentachloropropanal 102 was cleaved into tetrachloroethylene 103 by means of aniline or benzylamine in ethanol.[13] The mechanism was explained by addi-



tion of hydroxide anion at the aldehyde carbonyl and subsequent formation of formate ion and concomitant tetrachloroethylene production (haloform-type reaction).

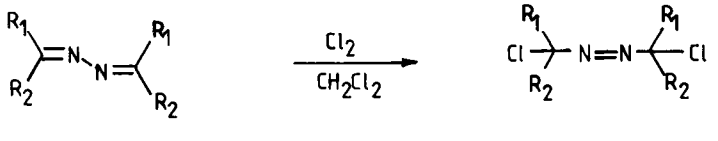
II. HALOGENATION OF IMINO COMPOUNDS

In the following section attention will be paid to the reagents used for the conversion of imino compounds into α-halogenated imino compounds. A great deal of efforts have been spent in order to halogenate by means of molecular halogens (Cl_2, Br_2), but N-halosuccinimide has been shown to be supperior in these halogenation procedures. Other useful reagents were sodium hypochlorite and t-butyl hypochlorite, while phenyltrimethylammonium perbromide was shown to give good results in some cases. Furthermore, reagents of less general use such as 2,4,4,6-tetrabromocyclohexadienone, tosyl chloride and cupric bromide will be treated in some particular cases at the end of this section.

II.1. Halogenation with Cl_2 and Br_2

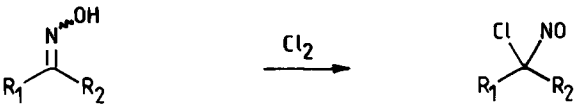
II.1.1. Chlorination

The action of chlorine gas on imines did not receive much attention but parallels the behaviour of bromine. Several reactions did not lead to α-chloroimines. Chlorination of ketazines 105 in dichloromethane at -60° yielded a stereospecific 1,4-addition to α,α'-dichloroazoalkanes 106.[101] Symmetric ketazines 105 produced meso derivatives 106, while unsymmetrical starting materials afforded dl-derivatives 106.[102]



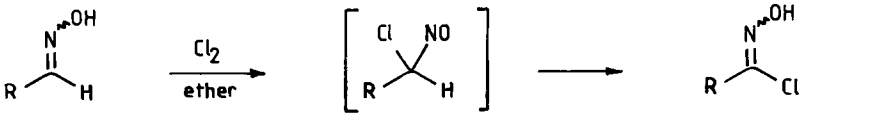
105 106

Chlorination of ketoximes with chlorine gas did not yield α-chlorinated oximes but gave geminal chloronitrosoalkanes 108.[103] Aldoximes, on the other hand, afforded an intermediate



107 108

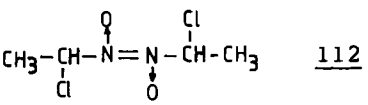
geminal chloronitroso derivative 110, which isomerized into the more stable hydroxamic acid chlorides 111.[104-106] It was shown



109 110 111

R = alkyl, Ph, PhCO, ...

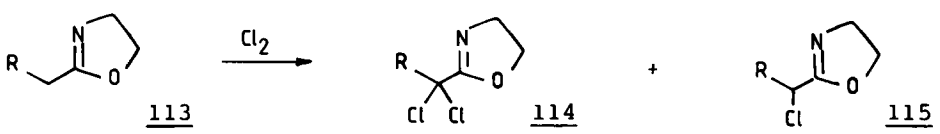
by NMR that the reaction passed through the dimer of the chloro-



112

nitroso compound (see 112).[106]

Treatment of 2-alkyloxazolines 113 with chlorine gave a mixture of the α,α-dichloro- and the α-chloroimino derivatives



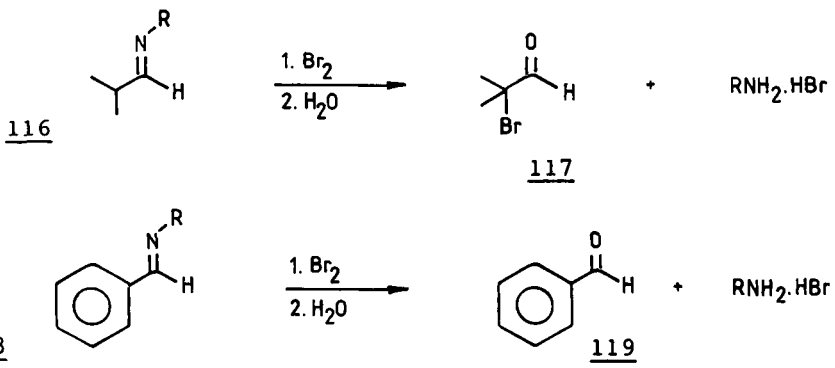
113 114 115

114 and 115.[107]

Finally, chlorination of 3-methyl-2-pyrazolin-5-one was reported to yield 4,4-dichloro-3-methyl-2-pyrazolin-5-one (see also related paper : ref. 108).[109]

II.1.2. Bromination

Early reports on the halogenation of imines described the addition of bromine to the imino function of aldimines. The unstable intermediates were hydrolyzed into α-bromoaldehydes 117 when the imine was derived from aliphatic aldehydes.[110] N-Alkylbenzylideneamines 118 yielded benzaldehyde 119 after reaction with bromine and subsequent hydrolysis.[110] Initially



116 117

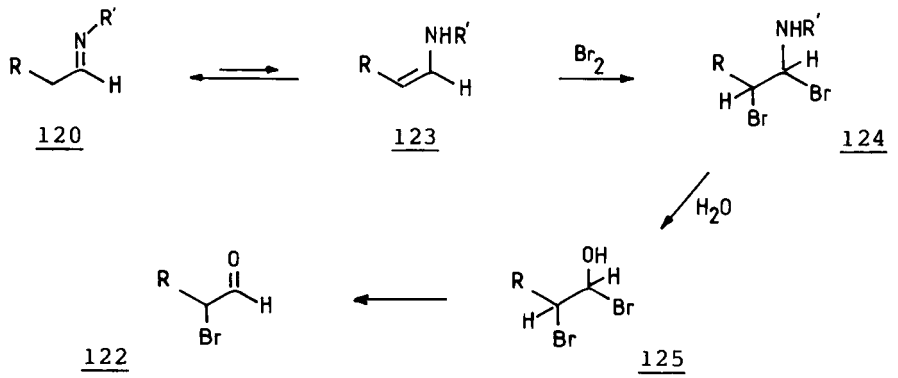
118 119

it was proposed that the bromination took place by addition of Br_2 to the imino function (see 121)[110,111] but it was latter

$$RCH_2CH{=}N{-}R' \quad (120) \quad + \quad Br_2 \longrightarrow RCH_2CHBrNBrR' \quad (121) \xrightarrow{H_2O} RCHBrCHO \quad (122)$$

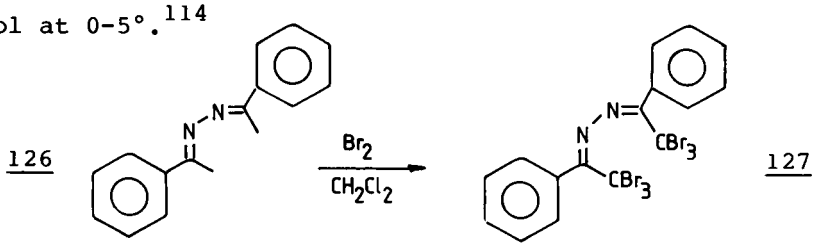
shown that the bromination occurred by Br_2 addition to the enaminic form 123.[112]

In the following paragraphs, some examples of brominations of imino derivatives leading to α-brominated imino compounds

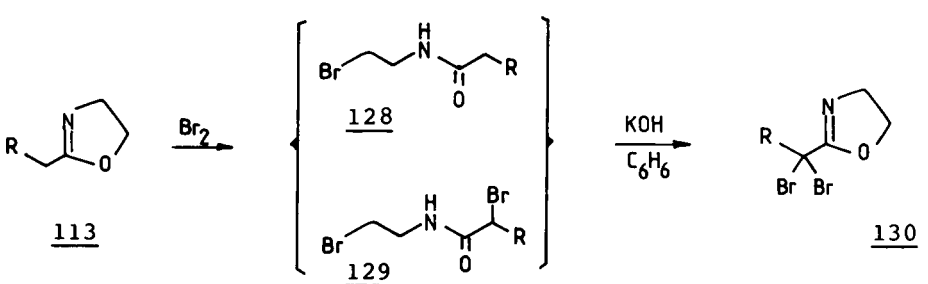


will be given.

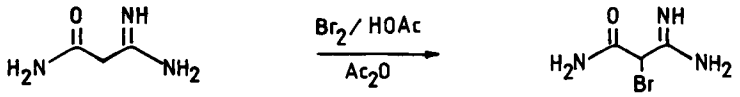
Acetophenone azine 126, when treated with a 6.2 molar excess of bromine in dichloromethane, furnished α,α,α-tribromoacetophenone azine 127 (Preparation 7).[113] The bis-(bromomethyl) derivative was prepared by reaction of 126 with Br_2 in methanol at 0-5°.[114]



2-(1,1-Dibromoalkyl)oxazolines 130 were obtained by bromination of 2-alkyloxazolines 113 with bromine at 0° for two hours, followed by treatment with potassium hydroxide in benzene;[107] the reaction was shown to proceed via the ring opened products 128 and 129.[107]



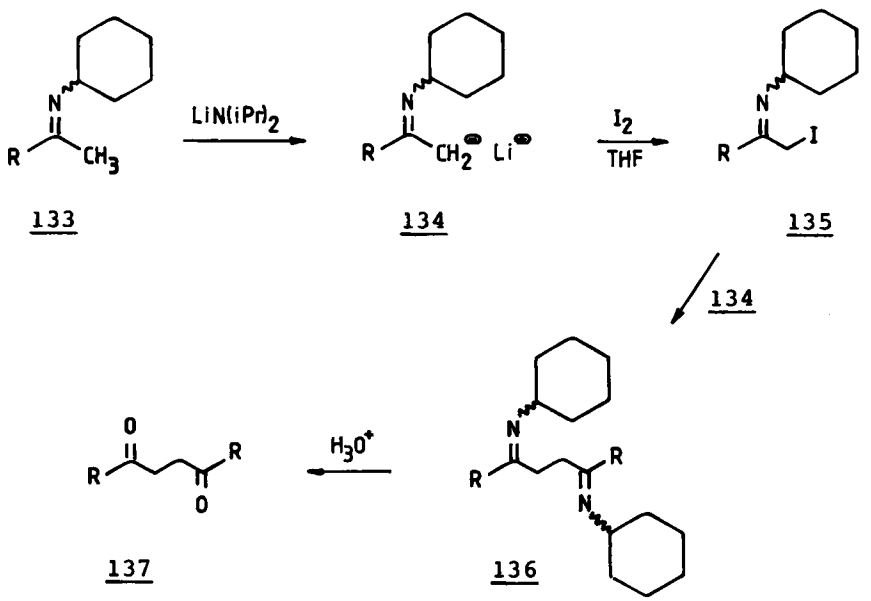
The functionalized amidine 131 has been brominated in acetic acid/acetic anhydride at 8-10° to afford the α-monobromoamidine 132.[115]



131 132

II.1.3. α-Iodoketimines

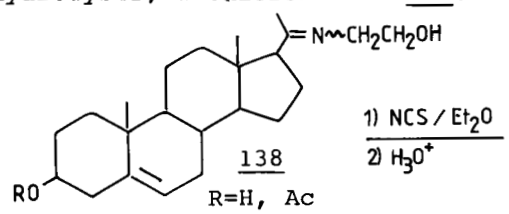
For the sake of completeness the only prepared α-iodoketimine reported hitherto is mentioned in this section. The N-cyclohexyl ketimine anion 134, generated by lithium diisopropylamide treatment of the parent methylketimine 133, reacted with iodine in tetrahydrofuran to yield α-iodomethylketimine 135, which was immediately attacked by anion 134, resulting in 1,4-diimine 136.[116] This method was used as an approach to symmetrical 1,4-diones 137.



II.2. Halogenation with N-Halosuccinimide

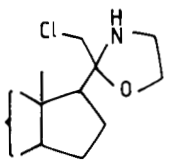
II.2.1. N-Chlorosuccinimide

Chlorination of the steroidal N-(2-hydroxyethyl)imines 138 with N-chlorosuccinimide in ethereal medium gave, after acidic hydrolysis, α-chloroketone 139.[117] On the basis of NMR and IR



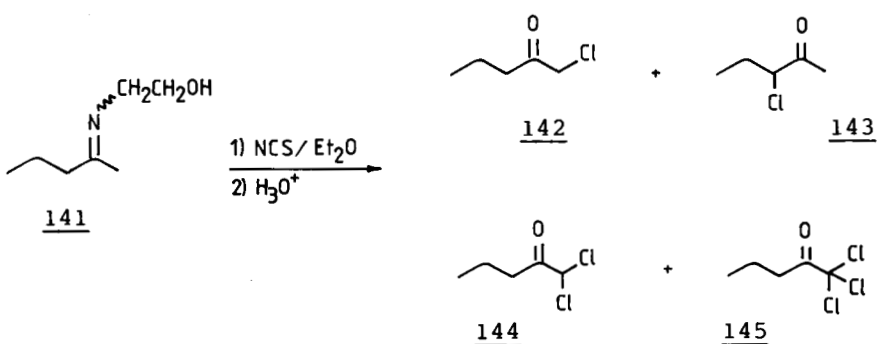
138 139

spectrometry, it was assumed that the intermediate nitrogen compound involved was oxazolidine 140.



140

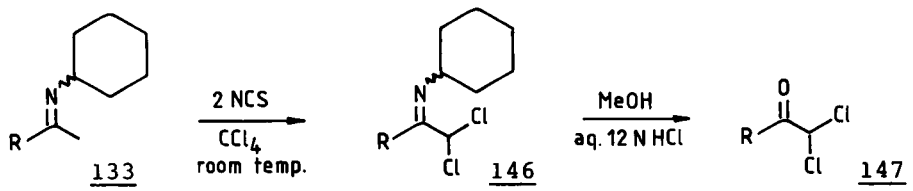
The generality of the reaction was checked by the reaction of N-2-(pentylidene)ethanolamine 141 with NCS/diethyl ether and subsequent acidic hydrolysis. Depending on the amount of NCS



141 142 143 144 145

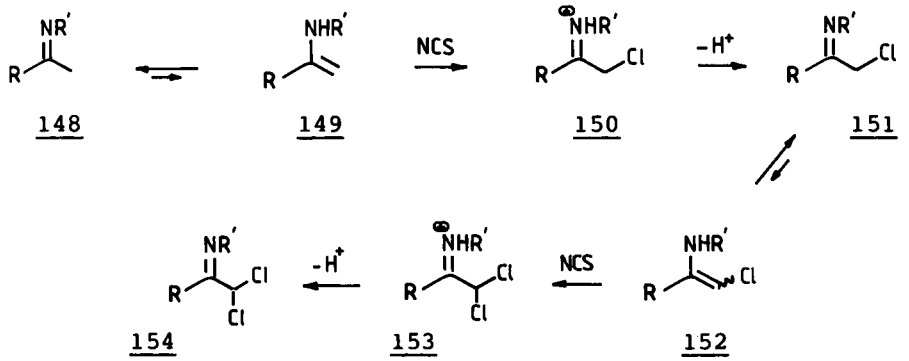
used, various mixtures of α-mono-, α,α-dichloro- and α,α,α-trichloroketones were produced. It was shown that the least substituted side of the imine was chlorinated.[117]

Due to the less convenient N-substituent in 138, side-reactions were possible (e.g. oxazolidine formation and subsequent reactions, etc...). In order to avoid these plausible complications, a study was undertaken to halogenate N-alkyl methylketimines 133 with N-chlorosuccinimide in CCl_4. At room temperature N-cyclohexyl 1,1-dichloromethylketimines 146 were



133 146 147

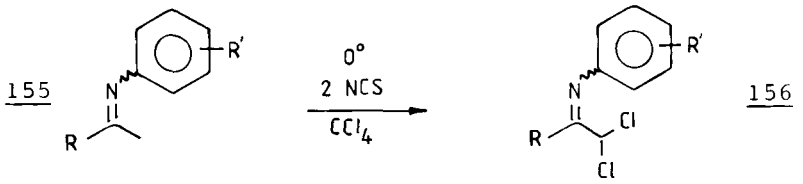
obtained in high yields.[118-120] These compounds have been converted into the corresponding dichloromethylketones 147 by acidic hydrolysis.[118] It was shown that the regioselective chlorination of methylketimines 133 proceeded by a non-radical mechanism via the least hindered enaminic form.



148 149 150 151 152 153 154

Small to negligible amounts of 1,3-dichloromethylketimines and 1,1,1-trichloromethylketimines were formed by this procedure. The formation of these side-products could be practically completely avoided by carrying out the chlorination of methylketimines in CCl_4 at low temperature and by the slow addi-

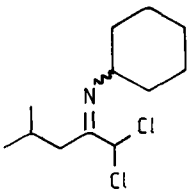
tion of NCS (Preparation 8).[120] This method was also applied for the synthesis of N-aryl α,α-dichloromethylketimines 156.[121,122]

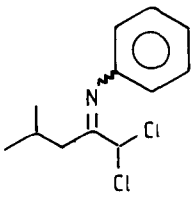


N-Cyclohexyl and N-aryl dichloromethylketimines 146 and 156 were obtained in almost quantitative yield and were found to be thermolabile. They could be stored at low temperature under an inert atmosphere, but it was recommended to use them directly for further reactions. Compounds 146 and 156 existed as a mixture of E and Z isomers in CCl_4 solution, an isomerism which was studied extensively by NMR spectrometry, using the aromatic solvent induced shift method (ASIS).[122] N-Cyclohexyl dichloromethylketimines 146 established predominently the E-isomer, although increased steric crowding of the alkyl group R caused the equilibrium to be shifted to the opposite direction.[120] N-Aryl dichloromethylketimines 156 exist preferentially as the Z-isomer and the equilibrium was completely shifted in this direction when a secondary alkyl group R was present in the molecule.[122]

As an example N-1-(2,2-dichloro-4-methylpentylidene)cyclohexylamine 146 (R = i-Bu) showed a E:Z ratio of 82:18, while the corresponding N-phenyl derivative, i.e. N-1-(2,2-dichloro-4-methylpentylidene)aniline 156 (R = i-Bu) exhibited a E:Z ratio of 45:55.

The chlorination of imines using NCS/CCl_4 is one of the most convenient preparations of α-chloroimines because of the mild reaction conditions (0-25°; neutral medium) and the high



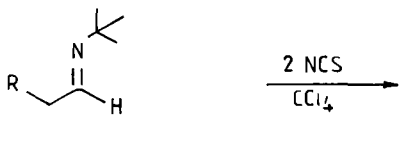


146 (R = i-Bu)
E:Z 82:18

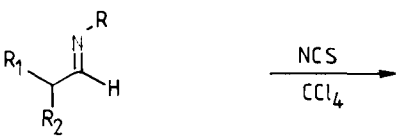
156 (R = i-Bu)
E:Z 45:55

yield.

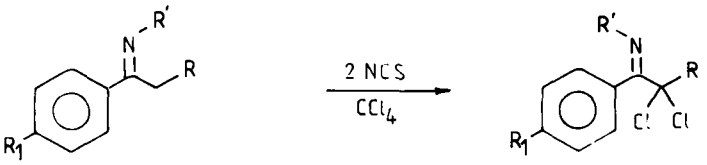
This method was also extended to the synthesis of N-t-butyl α,α-dichloroaldimines 158.[123,124] N-alkyl α-chloroaldimines 160,[125] N-cyclohexyl α,α-dichloroketimines 163[126,127] and N-aryl α,α-dichloroketimines 164 (Preparation 9 and 10).[128]



157 158



159 160



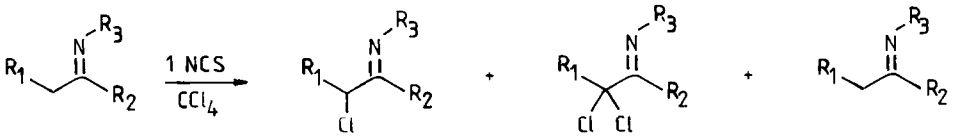
161 R' = cyclohexyl
162 R' = aryl

163 R' = cyclohexyl
164 R' = aryl

In these cases, all available positions α to the imino function were substituted with chlorine atoms. These reactions were performed at room temperature using a 10 % excess of NCS.

Imino compounds 157, 161 and 162 heaving an α-CH_2 function could not be converted exclusively into the α-monochloroimines

when one equivalent of NCS in CCl_4 was used. Instead, a mixture of α-monochloro-, α,α-dichloro- and non-chlorinated imines were obtained. Since α-mono- and α,α-dichloroimines were not separable, this reaction was only of theoretical interest. It



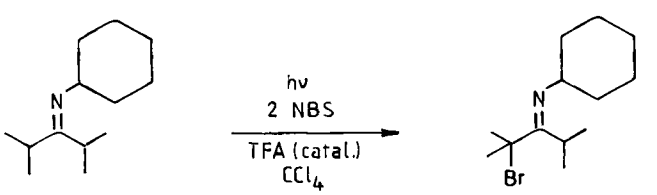
165 (R_2 = H, aryl) 166 167 165

was concluded that the rate of introduction of the first and the second halogen were of the same magnitude.[124,128]

II.2.2. N-Bromosuccinimide

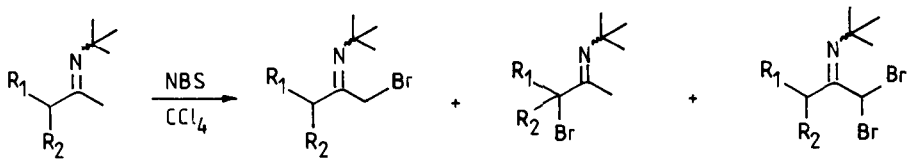
The reaction of imino compounds with NBS yielded α-bromoimines but in many instances catalysis by benzoyl peroxide or an acid was required.

N-3-(2,4-dimethylpentylidene)cyclohexylamine 168 reacted with two equivalents NBS in CCl_4 at 50° under irradiation and in the presence of a catalytic amount of trifluoroacetic acid to afford α-bromoketimine 169 in 34 % yield.[129] The regioselec-



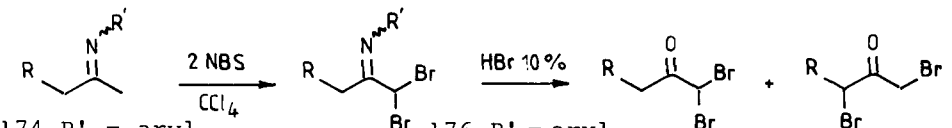
168 169

tivity of this reaction was limited as shown in the case of N-t-butyl methylketimine 170 which, on reaction with NBS in CCl_4 gave a mixture of α-monobromo-(171,172) and α,α-dibromoketimines (173).[129]



170 171 (62-80 %) 172 (11-30 %) 173 (19-20 %)

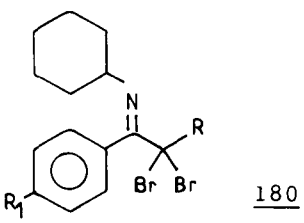
N-Aryl and N-cyclohexyl methylketimines 174 anf 175 gave with two equivalents NBS in CCl_4 at room temperature a α,α-dibromination of high regioselectivity; the high-yield conversion into α,α-dibromomethylketimines 176 and 177 was comparable with the analogous reaction with NCS (see above).[130] Compounds 176 and 177 were thermolabile and unstable; acidic hydrolysis gave a mixture of isomeric dibromoketones 178 and 179, the latter



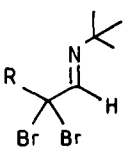
174 R' = aryl
175 R' = cyclohexyl
176 R' = aryl
177 R' = cyclohexyl
178
179

resulting from a 1,3-halogen shift.[130]

By the same bromination procedure, N-1-(2,2-dibromo-1-arylalkylidene)cyclohexylamines 180[126] and N-1-(2,2-dibromo-alkylidene)t-butylamines 181[131] may be obtained in high yield (Preparation 11).

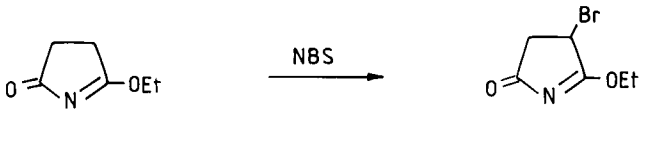


180

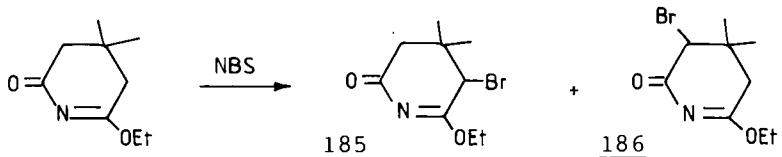


181

Ketimine 138 afforded the bromomethyl derivative by reaction of NBS in diethyl ether.[117] Cyclic imidates 182 and 184 were also brominated in the α-position with NBS.[132] O-Ethyl 4,4-dimethylglutarimide 184, however, gave also an isomeric bromo compound 186.

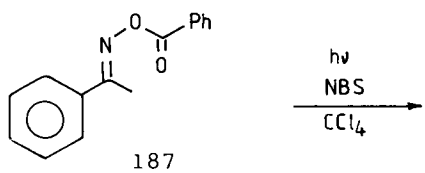


182 183



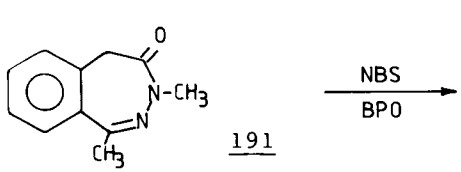
184 185 186

Other imino derivatives such as O-benzoyloxime 187[133], hydrazone type compounds 189[134] and 191[135] and amidines 193[136] required the presence of benzoyl peroxide or an acid catalyst for α-brominations (Preparation 12 and 13).

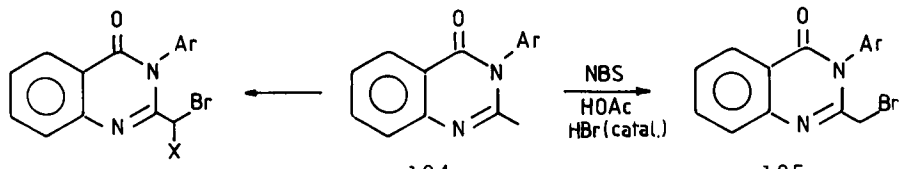


187 188 (84 %)

189 190



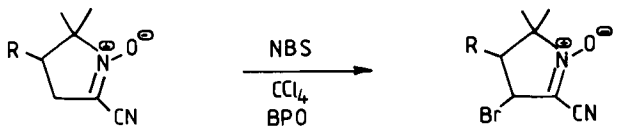
191 192



193 (X = H, Br) 194 195

α-Bromonitrones 199 were obtained in about 70 % yield by bromination of 2-cyano-1-pyrroline 1-oxides 196-198 with NBS (Preparation 14).[137]

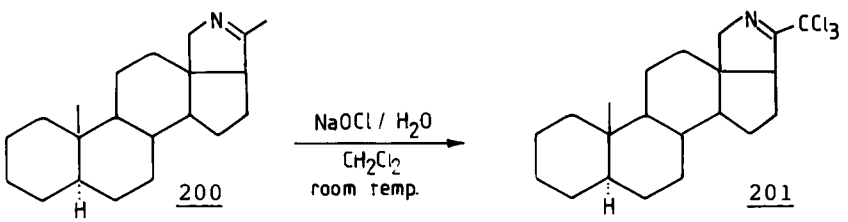
196 R = H
197 R = Me
198 R = Ph



199

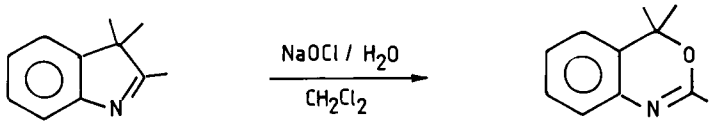
II.3. Halogenation with Sodium Hypochlorite

Steroidal imine 200 was found to undergo a α,α,α-trichlorination with sodium hypochlorite in a two-phase system water-dichloromethane (Preparation 15).[138,139] A different reaction was observed with 2,3,3-trimethylindolenine 202, which gave an



200 201

O-insertion via an intermediate oxaziridine.[140]



202 203

II.4. Halogenation with t-Butyl Hypochlorite

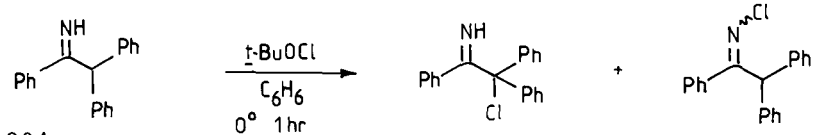
Another method employing a positive chlorine source makes use of t-butyl hypochlorite. Steroidal imine 200, when treated with variable amounts of t-butyl hypochlorite in CCl_4 yielded mixtures of methylchlorinated products.[139]

200 —(1.1 equiv. t-BuOCl, CCl_4)→ 66 % monoCl + 10 % diCl + 3 % triCl + 8 % starting material

200 —(2.0 equiv. t-BuOCl, CCl_4)→ 7 % monoCl + 38 % diCl + 31 % triCl

200 —(3.4 equiv. t-BuOCl, CCl_4)→ 73 % triCl

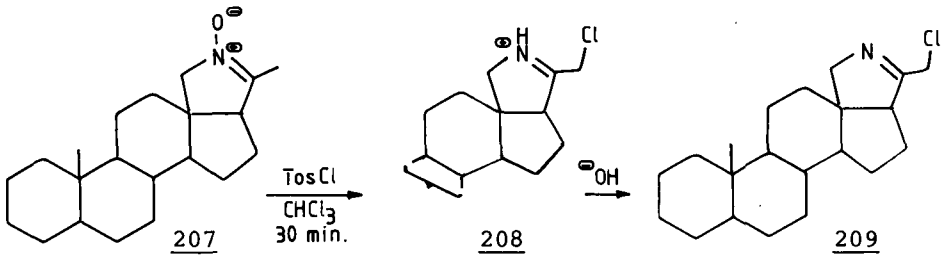
Reaction of N-1-(1,2,2-triphenylethylidene)amine 204 with t-butyl hypochlorite in benzene afforded a mixture of α-chloroimine 205 and N-chloroimine 206.[141]



204 205 206

II.5. Halogenation with Tosyl Chloride

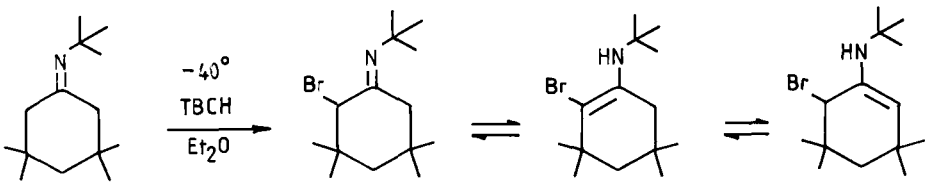
A rather unexpected α-chlorination was observed when the steroidal nitrone 207 was treated with tosyl chloride in chloroform or benzene for thirty minutes and the intermediate salt worked-up with alkali.[142]



207 208 209

II.6. Halogenation with 2,4,4,6-Tetrabromocyclohexadienone (TBCH)

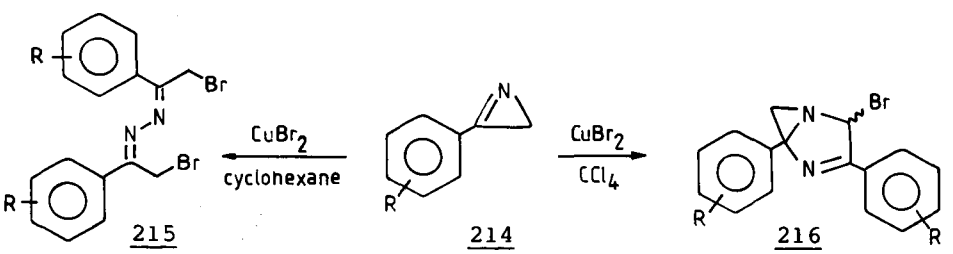
When N-t-butyl ketimine 210 was treated with TBCH in diethyl ether, the resulting product was an inseparable equilibrium mixture of the imino (211) and enamino form (212, 213) of the monobromo compound (total yield 91 %).[129]



210 211 212 213

II.7. Halogenation with Cupric Bromide

A special type of α-bromoimino compounds, e.g. ω-bromoacetophenonazines 215 (R = H), was obtained by reaction of 2-phenylazirine 214 (R = H) with cupric bromide in cyclohexane.[143] In carbon tetrachloride, however, α-bromoimine 216 (R = H) was



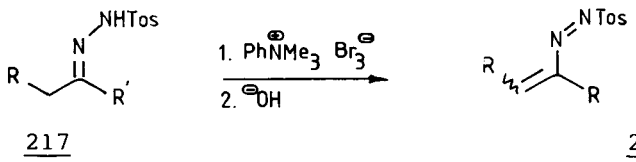
215 214 216

produced. It can be mentioned here that ω-bromoacetophenonazines 215 were also formed in very low yield by reaction of

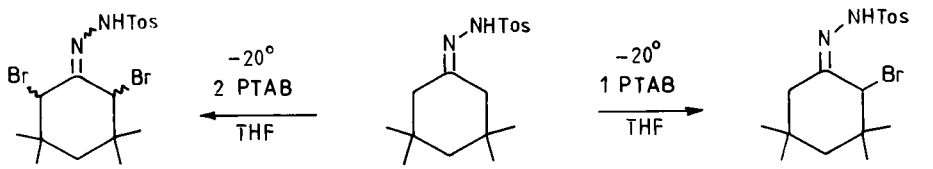
2-arylazirines 214 with NBS in dioxane or CCl_4 at -23°.[144]

II.8. Halogenation with Phenyltrimethylammonium Perbromide (PTAB)

Tosylazoalkenes 218 may be conveniently prepared by reaction of PTAB with tosylhydrazones 217.[145,146] Only in the case of hydrazone 219, intermediate α-bromohydrazone 221 and α,α'-dibromohydrazone 220 were isolated at low temperature as stable compounds (Preparation 16 and 17).[145]



217 218



220 (83 %) 219 221 (55 %)

On the other hand, cyclic hydrazone derivatives, when reacted with PTAB underwent monobromination in moderate yields.[135]

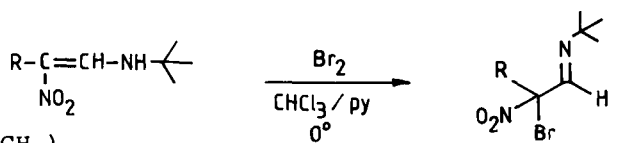
III. HALOGENATION OF ENAMINES

In this section, only these halogenations of enamino compounds will be treated, which lead to α-halogenated imino derivatives. Only secondary enamines, i.e. N,N-disubstituted enamines, lead to the desired reaction products. The halogenations of enamines, leading to β-haloenamines will be subject of a forthcoming review in this journal. A similar classification

of halogenating agents as discussed in the foregoing subdivision will be used.

III.1. Halogenation with Cl_2 and Br_2

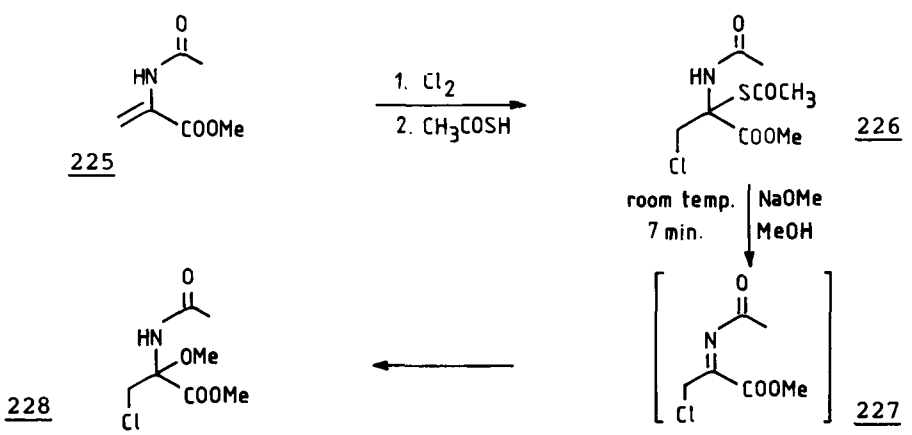
Up to now almost no chlorinations or brominations of enamines using Cl_2 of Br_2 and affording α-haloimines have been reported. 1-Alkylamino-2-nitro-1-alkenes 222 (R = CH_3) reacted with bromine in chloroform in the presence of pyridine to give α-bromo-α-nitroaldimines 224.[147] Higher substituted derivatives, e.g. 223, produced a mixture of α-bromo-α-nitroal-



222 (R = CH_3)
223 (R = Et)

224 (R = CH_3)

dimines and of hydrolyzed materials.[147] In one case, an intermediate α-chloro imino compound 227 was postulated.[148]

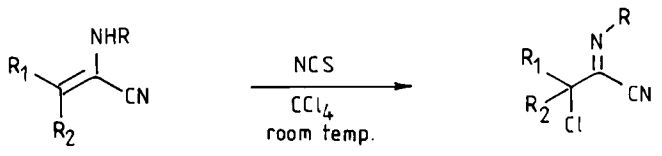


III.2. Halogenation with N-Halosuccinimide

As pointed out above, it has been shown that imino compounds are halogenated in the α-position via their tautomers, i.e. enamines. Accordingly, appropriately substituted enamines react with N-halosuccinimide to form α-haloimines.

III.2.1. Halogenation with N-Chlorosuccinimide

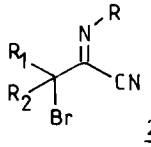
α-Cyanoenamine 229 react very smoothly at room temperature with N-chlorosuccinimide in CCl_4 to afford highly stable α-chloroimidoyl cyanides 230 in nearly quantitative yield.[149]



229 230

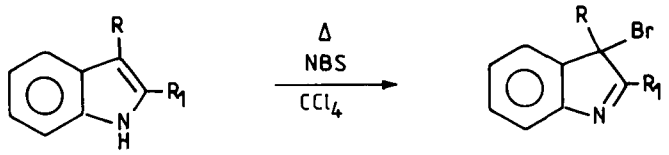
III.2.2. Halogenation with N-Bromosuccinimide

In similar way as described in the above mentioned reaction, α-bromoimidoyl cyanides 231 were synthesized by reaction of α-cyanoenamines 229 with NBS in CCl_4.[149] Compounds 231 were less stable than the chloro derivatives 230 but could be prepared as the sole product from the reaction, thus allowing immediate use in further experiments.



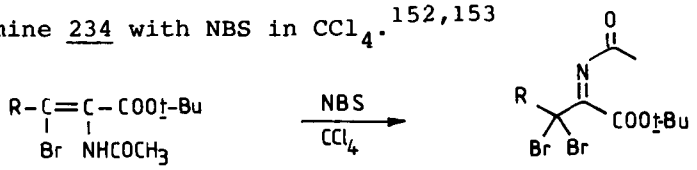
231

Indoles 232 were converted with NBS in boiling CCl_4 into bromoindolenine derivatives 233.[150,151]



232 233

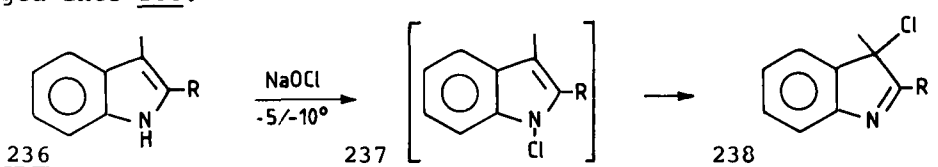
α,α-Dibromoketimines 235 were produced by reaction of β-bromoenamine 234 with NBS in CCl_4.[152,153]



234 235

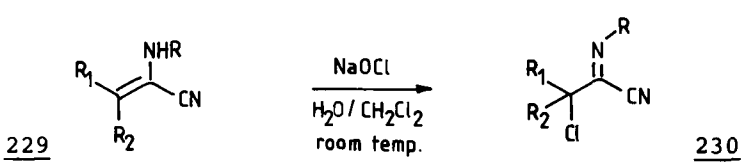
III.3. Halogenation with Sodium Hypochlorite

Chlorination of indoles 236 with aqueous sodium hypochlorite at -5° to -10° gave the unstable 3-chloroindolenine derivatives 238.[154,155] It was later proven that the reaction proceeded via the intermediate N-chloroindole 237, which rearranged into 238.[156]



236 237 238

Analogously α-cyanoenamines 229 afforded the stable α-chloroimidoyl cyanides 230.[149]



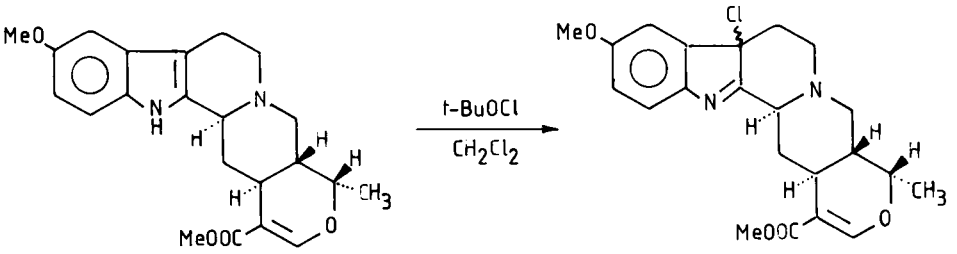
229 230

III.4. Halogenation with t-Butyl Hypochlorite

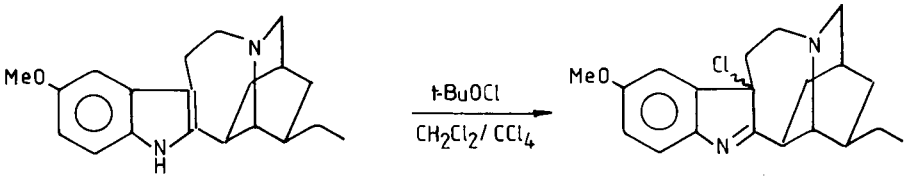
A large variety of alkaloids, having the indole moiety in their molecule, have been converted into the 3-chloroindolenine

derivatives by reaction with t-butyl hypochlorite, e.g. yohimbine,[157,158] ibogaine,[159] cacubine,[160] tetraphylline,[160] etc... (Preparation 18).

Many other indolic substrates such as tetrahydrocarbazole,[161] 1,2,3,4-tetrahydro-β-carbolines[162] and other[163-166] were chlorinated using exactly the same approach.



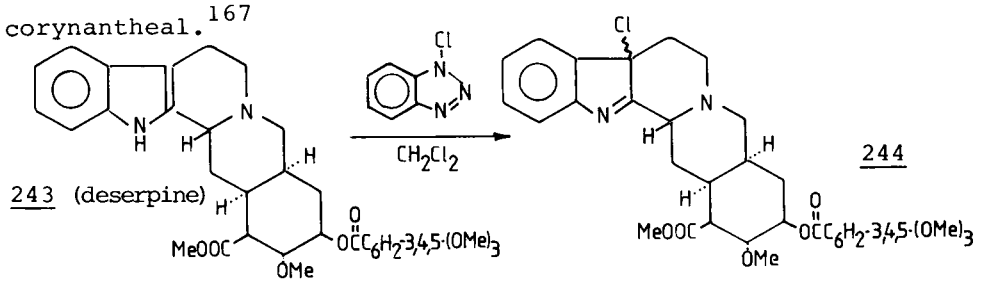
239 (cacubine) 240



241 (Ibogaine) 242

III.5. Halogenation with N-chlorobenzotriazole

1-Chlorobenzotriazole was found to be an highly efficient reagent for conversion of indole alkaloid types into chloroindolenines.[149] Among the compounds successfully chlorinated were deserpine 243, yohimbine, catharanthine and (±)-dihydrocorynantheal.[167]



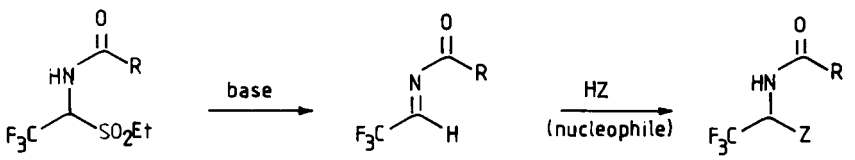
243 (deserpine) 244

Using the same methodology, chlorinated tetrahydrocarbazoleindolenine was obtained from 1,2,3,4-tetrahydrocarbazole by reaction with N-chlorobenzotriazole in benzene in the presence of triethylamine.[161]

IV. MISCELLANEOUS METHODS

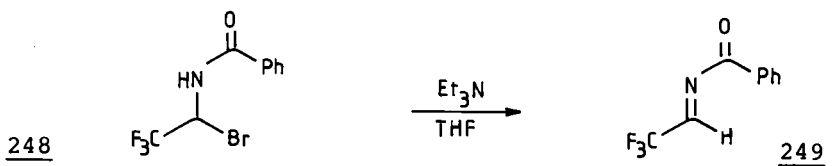
IV.1. N-Activated α-halogenated Imino Compounds

Base-induced sulfinate elimination from 245 produced N-1-(2,2,2-trifluoroethylidene)acetamide 246 as an intermediate which rapidly underwent addition of a nucleophile at the activated double bond.[168] Further attempts to isolate the intermediate reactive imines 246 were successful by using adduct 245



245 (R = Ph, Me, CF_3, OCH_2Ph) 246 247

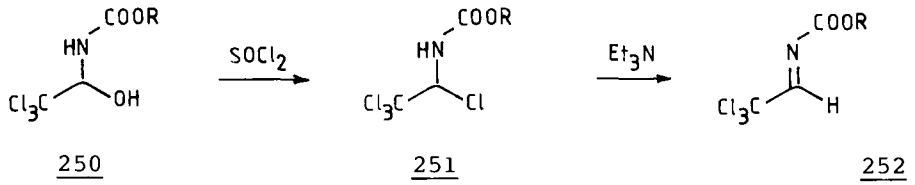
which was converted into the bromide 248 using bromine[169] and subsequently dehydrochlorinated.[170] In similar way the N-benzyloxycarbonyl derivative 246 (R = $COOCH_2Ph$) was obtained while the N-acetyl derivative could not be synthesized due to decomposition.[170]



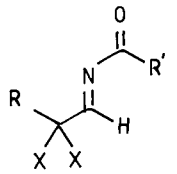
248 249

The first synthesis of "anhydrochloralurethanes" 252 was accomplished by a formal dehydration of adduct 250, produced by addition of carbamates to chloral, via the chloride 251

(Preparation 19).[171]



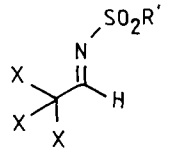
250 251 252



253 R = CH_2Cl ; X = Cl ; R' = Me, Et, n-Pr, Ph

254 R = CH_2Cl ; X = Cl ; R' = OEt

255 R = alkyl ; R' = CH_3, Ph



256 X=Cl ; R' = p-MeC_6H_4

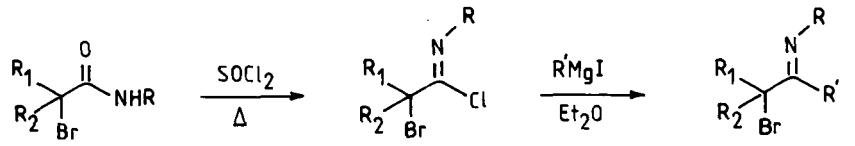
257 X=F ; R' = p-MeC_6H_4

258 X=Cl ; R' = NMe_2

The method was further extended to α,α,β-trichloroimines 253, 254[15] and to the more general N-1-(2,2-dichloroalkylidene)-amides 255[14] starting from α,α-dichloroaldehydes, and to the N-sulphonyl derivatives 256,[172] 257,[173] and 258.[173] Recently, another approach towards chloral derivatives 256 (X = Cl, R' = F, Cl, alkyl, aralkyl, aryl) was developed by means of direct condensation of chloral with sulfonylisocyanates in the presence of a tertiary amine and/or a quaternary ammonium base.[174]

IV.2. Reaction of Imidoyl Chlorides with Grignard Reagents

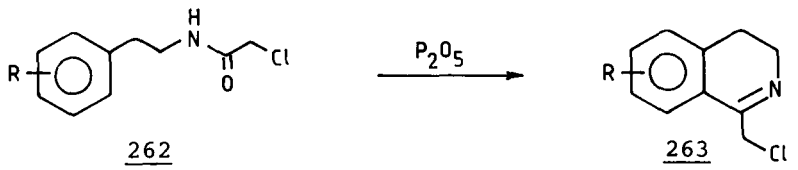
The reaction of α-bromoimidoyl chlorides 260, obtained from α-bromo carboxylic acid amides 259, with methyl- or ethylmagnesium bromide in ether at low temperature yielded α-bromoketimines 261 in 50-90 % yield.[175-177]



259 260 261

IV.3. Bishler-Napieralski Reaction

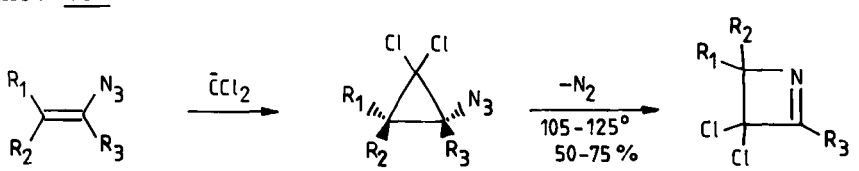
The Bishler-Napieralski reaction of appropriately substituted N-phenetyl α-chloroamides 262 furnished 1-chloromethyl 3,4-dihydroisoquinoline derivatives 263.[178,179]



262 263

IV.4. Rearrangement of 1-Azido-2,2-dichlorocyclopropanes

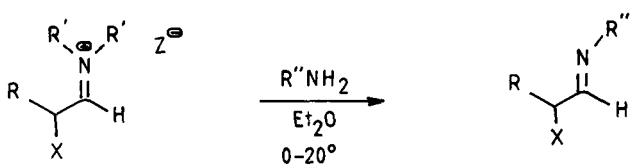
Azidoalkenes 264 underwent dichlorocarbene addition to produce 1-azido-2,2-dichlorocyclopropanes 265 which thermally rearranged under nitrogen expulsion to afford 3,3-dichloroazetidines 266.[180]



264 265 266

IV.5. Reaction of Primary Amines with α-Haloimmonium Halides

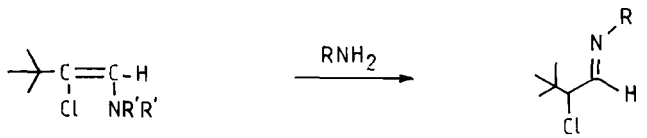
Halogenated immonium halides or perchlorates exchange their amino moiety with primary amines to yield α-haloimines.[181]



267 (Z = ClO_4, Cl) 268

IV.6. Reaction of Primary Amines with β-Chloroenamines

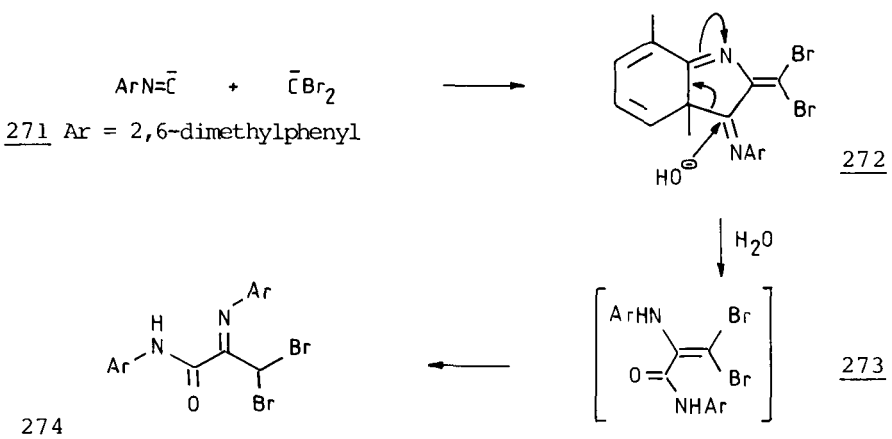
Refluxing β-chloroenamines 269 with excess primary amines during 2-8 days gave a 55-75 % yield of α-chloroaldimines 270.[182]



269 270 (R = t-Bu, cycloHex)

IV.7. Reaction of Isonitriles with Dibromocarbene

From isonitrile 271 and dibromocarbene, 272 was obtained which rearranged upon aqueous work-up to yield α,α-dibromoketimine 274.[183]

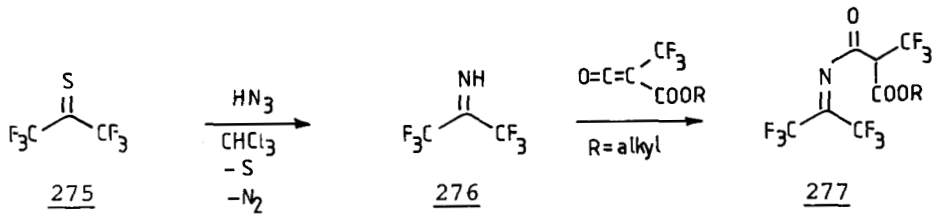


271 Ar = 2,6-dimethylphenyl

272 273 274

IV.8. Perfluoroimines from Perfluorothiones

The conversion of hexafluorothioacetone 275 into perfluoroimine 276 by hydrazoic acid in chloroform has been patented,[184,185] while N-substituted derivatives were obtained by reaction with ketene derivatives.[186]



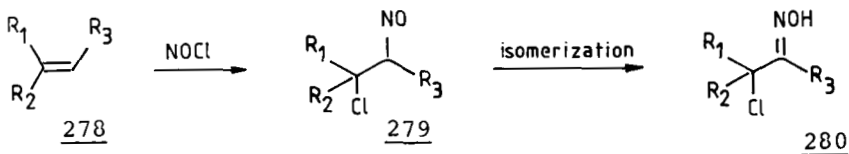
275 276 277

IV.9. α-Halogenated Oximes

Besides the direct condensation of appropriate α-halogenated carbonyl compounds with hydroxylamine (see above), α-halooximes can be obtained by other reactions, viz. 1) addition of nitrosyl halides to alkenes and 2) reduction of nitroalkenes.

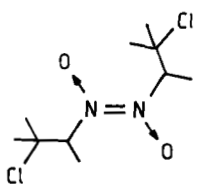
IV.9.1. Addition of Nitrosyl Chloride to Alkenes

Markownikov addition of nitrosyl chloride to alkenes, having at least one ethylenic-hydrogen, yielded β-chloronitroso compounds 279 which isomerized into α-chlorooximes 280.[187-191] In many cases a dimerization is observed (see dimer 281);[192]



278 279 280

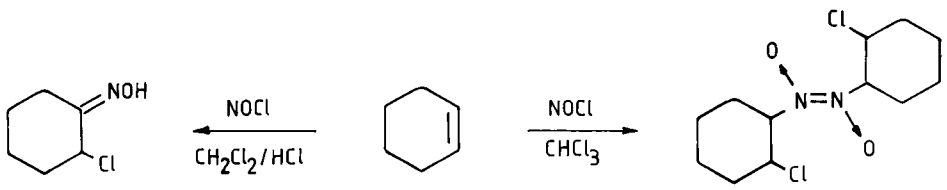
the dimer sometimes thermally dissociates into the monomer which in turn, isomerizes to the α-chlorooxime.[193]



281

The addition of NOCl is acid-catalyzed or can be photo-induced.[194] Ordinary alkenes,[195] endocyclic[194,196] or exocyclic alkenes[195] and more complex alkenes such as caryophyllene[197] are susceptible to the NOCl addition.

The medium of the reaction has been found to be important as cyclohexene 283 was converted into dimer 284 in chloroform[192] while α-chlorooxime 282 was produced in dichloromethane/hydrogen chloride.[198]

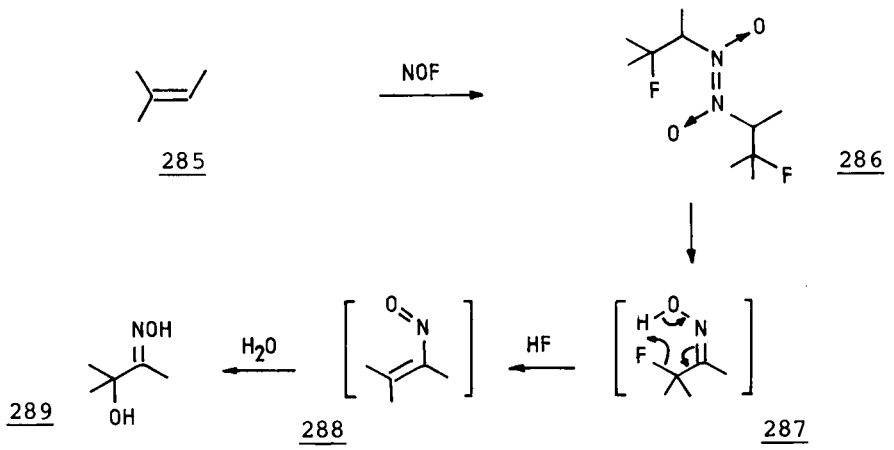


282 283 284

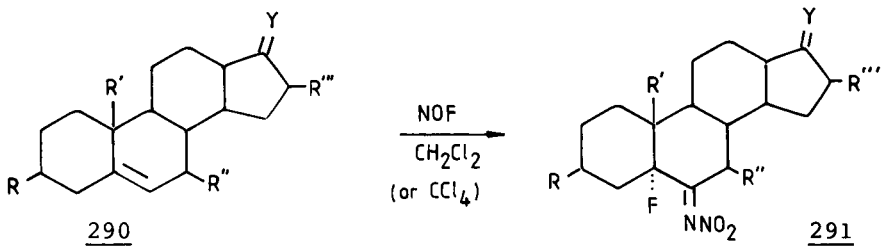
Finally, functionalized olefins, e.g. acrylonitrile, also add nitrosyl chloride[199] while nitrosyl sulfate in the presence of hydrogen chloride also converts alkenes into α-chlorooximes.[200]

IV.9.2. Addition of Nitrosyl Fluoride to Alkenes

Addition of nitrosyl fluoride to a simple olefin, 2-methyl-2-butene 285, in CCl_4 gave as a major product fluoronitroso dimer 286.[54] When fluoronitroso dimer 286 was chromatographed on alumina or refluxed in isopropanol containing water, it isomerized to the α-fluorooxime 287, lost hydrogen fluoride and hydrated to give α-hydroxyoxime 289.[54]

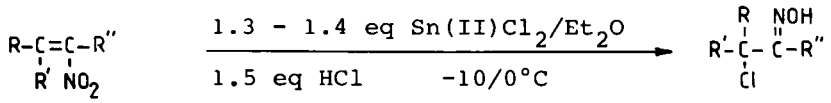


On the other hand, steroid 5-enes 290 underwent reaction with excess NOF at 0° in CH_2Cl_2 or CCl_4 to give crystalline 5α-fluoro-6-nitrimines 291 (yields 23-72 %).[54]



IV.9.3. Reduction of Nitroalkenes.

Reduction of nitroalkenes 292 with stannous chloride in ethereal medium in the presence of hydrogen chloride enabled Dornow and coworkers to synthesize a large variety of α-chloro-oximes 293 (Preparation 20).[201]

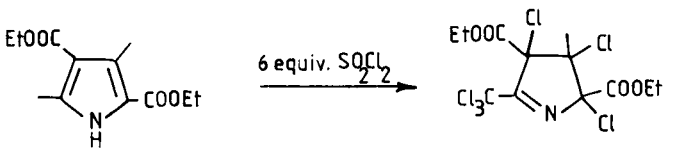


292 293

In some instances, nitroalkenes were prepared *in situ*.[202] The method seemed general as sterically hindered starting materials, e.g. 292 (R = R' = t-Bu) and 292 (R = t-Bu ; R' = Ph), also produced α-chlorooximes.[203,204]

IV.10. Chlorination of Pyrroles

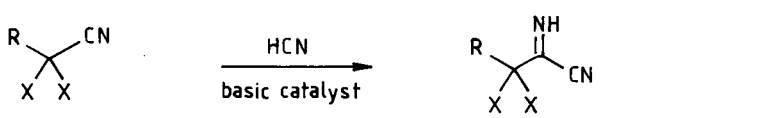
As a non-general reaction, pyrrole derivative 294 reacted with sulfuryl chloride to afford the polychloropyrroline derivative 295.[205]



294 295

IV.11. Addition of Hydrogen Cyanide to α-Halogenated Nitriles

Nummerous reports have been published dealing with the addition of hydrogen cyanide to α-halogenated nitriles to afford N-unsubstituted α-halogenated imidoyl cyanides. The base-catalyzed addition of HCN to α,α-dichlorophenylacetonitrile 296a furnished α,α-dichloroimidoyl cyanide 297a.[2] In the case of dichloroacetonitrile 296c, compound 297c isomerized into the enaminic form.[206]

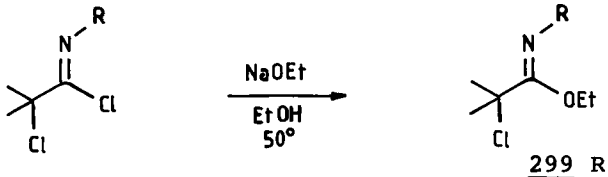


296

297 a : R = Ph ; X = Cl
b : X = R = F
c : R = H ; X = Cl

IV.12. α-Halogenated Iminoether Derivatives

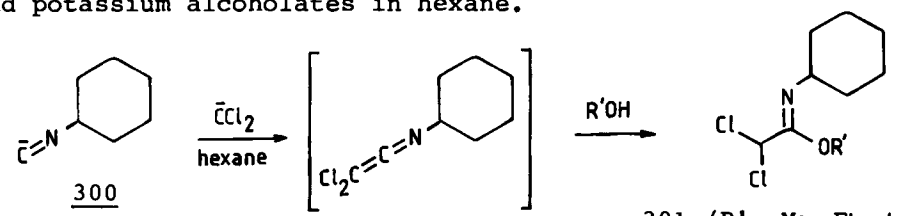
The synthesis of simple α-chloroimidates such as 299 was achieved by the reaction of α-chloroimidoyl chlorides 298 with



298 299 R = Me, Et

sodium ethoxide in ethanol.[207] The corresponding phenyl imidate was prepared from 298 and sodium phenolate in dioxane.[207]

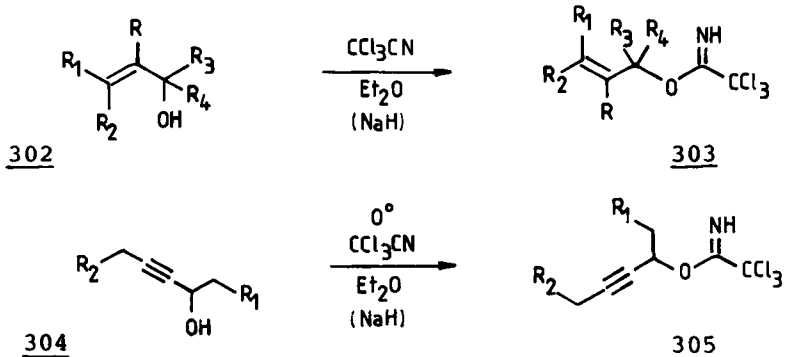
N-Cyclohexyl dichloroacetimidates 301 were synthesized in about 75 % yield by α-addition of cyclohexylisonitrile 300 with dichlorocarbene, generated from chloroform or trichloroacetates and potassium alcoholates in hexane.[208]



300 301 (R' = Me, Et, t-Bu)

Allylic[209,210] and propargylic[211] trichloroacetimidates 303 and 305 were obtained from base catalyzed addition of allylic and propargylic alcohols to trichloroacetonitrile (Preparation 21).

The method had found wide application using various alcohols.[212,213]

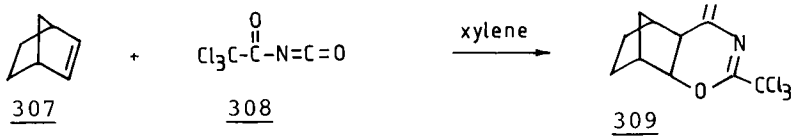


302 303

304 305

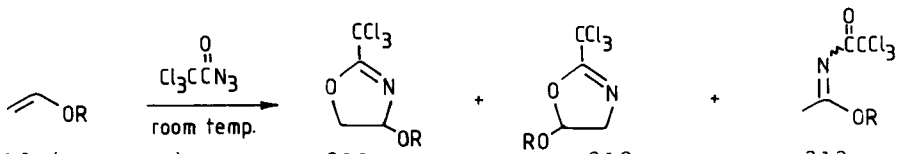
Addition of sulfur trioxide to trichloroacetonitrile gave the cyclic iminoether 306.[214] From norbornene 307, cyclic imidate 309 was formed by [4 + 2] addition of trichloroacetylisocyanate 308 in xylene at low temperature, while at reflux temperature an α,β-unsaturated nitrile was obtained.[215] Another

306



307 308 309

synthesis of cyclic imidates is exemplified by the reaction of simple enolethers 310 with trichloroacetyl azide at room temperature yielding 311, 312 and 313 in a 3:6:1 ratio respectively.[216]

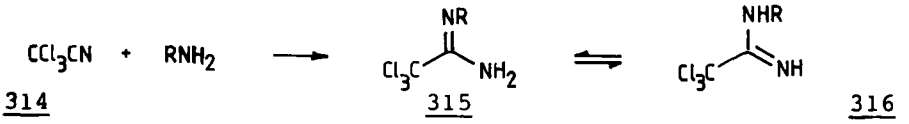


310 (R=Me, Et) 311 312 313

The synthesis of five-membered trifluoromethylimidates, i.e. 2-trifluoromethyl-5-oxo-4,5-dihydrooxazoles, involved the reaction of α,α-disubstituted α-aminoacids with trifluoroacetic anhydride followed by treatment with thionyl chloride.[217]

IV.13. α-Halogenated Amidines

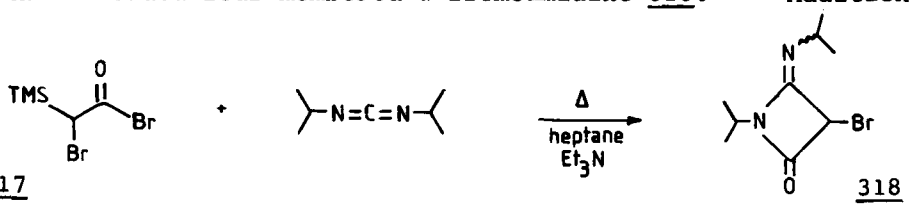
Ammonia and amines gave a direct addition with the activated trichloroacetonitrile 314 to yield amidines,[218,219] which exist as a mixture of tautomers (315⇌316).[220] Similar reac-



314 315 316

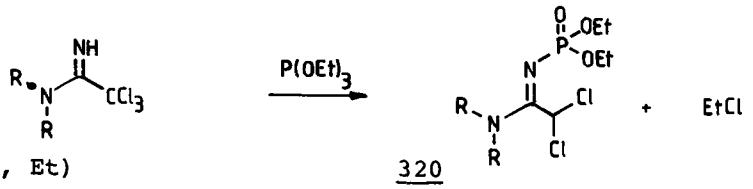
tions were described with dichloroacetonitrile and secondary amines.[221]

Condensation of 2-bromo-2-trimethylsilylacetyl bromide 317 with diisopropylcarbodiimide in the presence of triethylamine afforded four-membered α-bromoamidine 318.[222] Addition



317 318

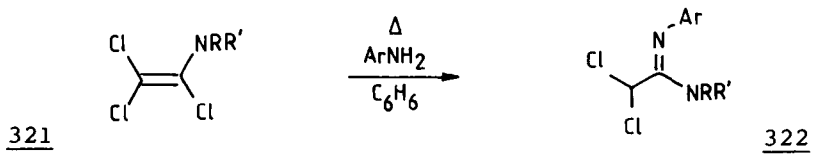
of secondary amines to trichloroacetonitrile led to N,N-dialkyltrichloroacetamidines 319 which reacted with triethylphosphite to yield dichloroamidine derivative 320.[223]



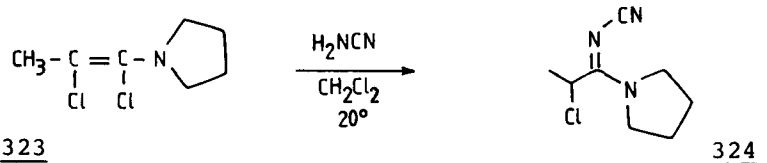
319 (R = Me, Et) 320

In similar way, hydroxylamine added to dichloro- and trichloroacetonitrile.[224]

α-Chlorinated amidines 322[225] and 324[226] were obtained by reaction of β-chlorinated α-chloroenamines 321 and 323 with primary amines. In similar manner, 2-amino-3,3-dichloroacrylonitrile[2] and other β-halogenated α-cyanoenamines [221,227] underwent displacement by secondary amines in ethanol to afford α,α-dichloroamidines.[2]



321 322

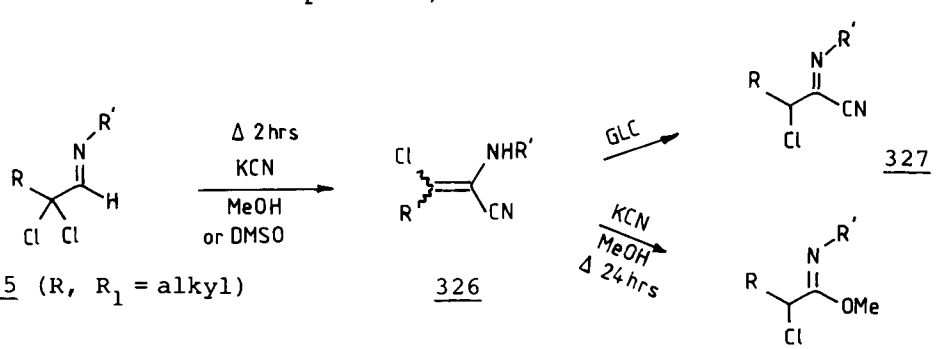


323 324

Another route to α-haloamidines consisted of the reaction of α-haloimidoyl halides with amines,[228] while Friedel-Crafts reactions of dichloro- or trichloroacetonitrile with aromatic compounds afforded the corresponding α-haloamidines after careful work up.[229]

IV.14. α-Halogenated Imidoyl Cyanides

Reaction of N-1-(2,2-dichloroalkylidene)amines 325 with excess of KCN in methanol or DMSO (2 hrs) gave β-chloro-α-cyanoenamines 326 which partially isomerized into the corresponding α-chloroimidoyl cyanides 237 by gas chromatography (preparative isolation was possible).[230] It has to be mentioned here



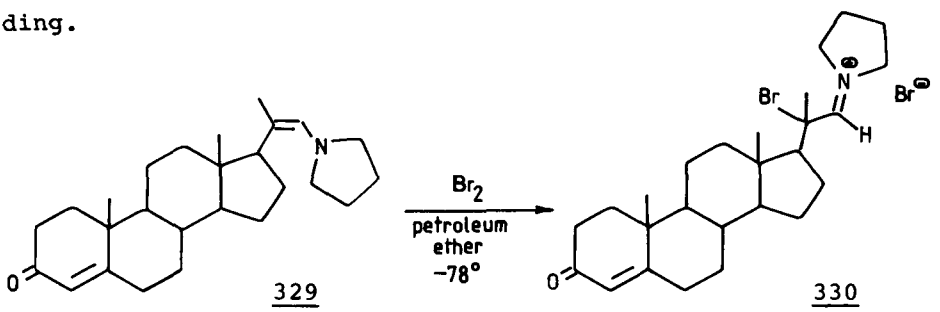
325 (R, R_1 = alkyl) 326 327 328

that prolonged heating of α,α-dichloroaldimines 325 with KCN in MeOH during 24 hrs gave α-chloroimidates 328, except for N-t-butyl derivatives.[230]

Less general types of α-haloimidoyl cyanides were obtained by the addition of hydrogen cyanide to α,α-dichloronitriles or perfluoronitriles, giving rise to N-unsubstituted α,α-dichloroimidoyl cyanides[2,206] or α-iminoperfluoronitriles.

V. ADDENDUM : α-HALOGENATED IMMONIUM HALIDES

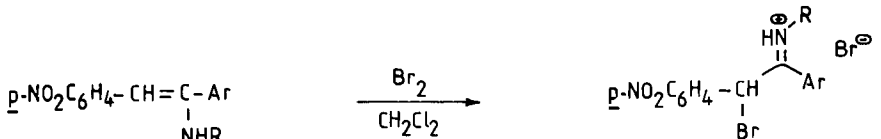
One of the first α-halogenated immonium halides was obtained from the steroid field. Steroidal enamine 329 was converted into α-bromoimmonium bromide 330 on treatment with bromine in petroleum ether/dichloromethane at -78°.[232] Compound 330 was obtained as a granular substance which decomposed on standing.



Other examples of halogenation of tertiary enamines to afford α-haloimmonium halides, have been reported to be useful in achieving syntheses of α-halo carbonyl compounds on simple hydrolysis.[233-235] The reaction may be carried out in dichloromethane,[236,237] ether,[235,238] tetrahydrofuran[239] or pentane.[240]

The description of the first halogenation of tautomerizable (i.e. secondary) enamines is of fairly recent origin. For instance, addition of bromine to enamines 331 in CH_2Cl_2 gave

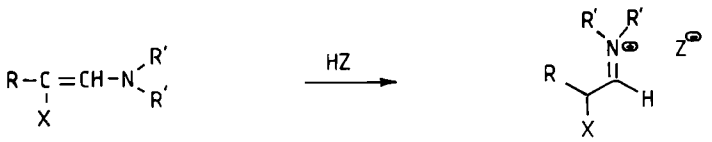
the yellow crystalline α-bromoimmonium bromides 332.[241]



331 a : R = H
b : R = Me

332

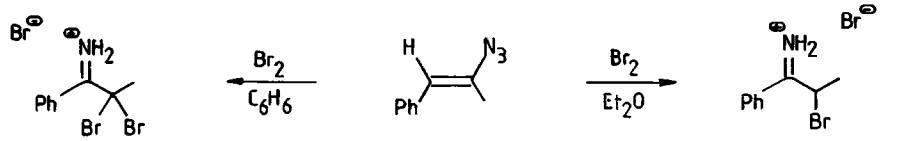
Reaction of a titrated solution of perchloric acid in acetic acid or hydrochloric acid in ether with β-halogenated enamines 333 yielded crystalline α-haloimmonium perchlorates and chlorides 334, the former being more stable than the latter.[181]



333 X = Cl, Br

334 (Z = ClO_4, Cl)

Addition of excess bromine to 1-azido-1-phenyl-1-propene 335 in diethyl ether or benzene furnished α-bromo- and α,α-dibromoimmonium bromides 337 and 336 respectievely.[242] On the



336 335 337

other hand, 1-azido-3,3-dimethyl-1-butene gave an α-bromonitrile alongside with an α,α-dibromoaldehyde as a side-product.

It is worthwile to mention that α-bromoimmonium cyanides have been reported as intermediates when enamines were treated with cyanogen bromide in THF.[243] α-Fluoroimmonium tetrafluoroborates were prepared by condensation of α-fluorinated immonium fluorides (as HBF_4 salt) with electron-rich aromatic compounds.[244] Finally, some intermediate α-iodoimmonium deriva-

tives were obtained by addition of iodine azide[245] or iodine [246,247] to enamines.

VI. PREPARATIONS

Preparation 1 : N-1-(2-Bromobutylidene)t-butylamine (10, R = Et, R' = t-Bu, X = Br).[8]

A solution of 0.1 mol of 2-bromobutanal (9, R = Et, X = Br) in 200 ml dry diethyl ether, cooled at -50°, was treated dropwise with a solution of 0.11 mol t-butylamine in 150 ml dry diethyl ether. The temperature was maintained below -30°. After addition of molecular sieves (4Å), the reaction mixture was kept at -30° overnight, then one day at 5°. Evaporation of the solvent and distillation under nitrogen gave a 62 % yield of N-1-(2-bromobutylidene)t-butylamine 10, bp. 34-35°/0.6 mm.

Preparation 2 : N-1-(1-Phenyl-2,2,2-trifluoroethylidene)-1-phenylethylamine (24).[18]

A mixture of 10.6 mmol of α,α,α-trifluoroacetophenone 23 and 10.7 mmol of 1-phenylethylamine in 30 ml of dry toluene in the presence of ca. 3 % by weight of p-toluenesulfonic acid was refluxed until the theoretical amount of water had collected in a Dean-Stark trap. Distillation gave a 80-91 % yield of trifluoromethylimine 24, bp. 99-101°/0.5 mm.

Preparation 3 : General Procedure for the Preparation of α-Halogenated 2,4-Dinitrophenylhydrazones.[22]

One equivalent of the α-halogenated ketone neat or dissolved in the minimum amount of methanol was treated at room temperature with one equivalent of freshly prepared Brady reagent.[35]

The precipitated hydrazone was filtered within 5-10 minutes, washed well with cold aqueous methanol, dried and recrystallized from a suitable solvent. The yields were above 80 %.

Preparation 4 : anti-α-Bromoacetophenone Oxime (49).[52]

Addition of 0.05 mol syn-α-bromoacetophenone oxime 45[52] in 100 ml acetonitrile to a solution of 0.5 mol of morpholine in 1 liter of water at pH 9.5, followed by $CHCl_3$ extraction and crystallization (chloroform-petroleum ether), gave anti-α-morpholinoacetophenone oxime (46), mp. 121-122°. A mixture of 0.0136 mol of 46, 0.068 mol 2-methoxypropene and 0.0007 mol p-toluenesulfonic acid in 50 ml dichloromethane was refluxed overnight. After extraction with potassium carbonate solution and drying over sodium sulfate, the solvent was evaporated from the reaction mixture and the residue crystallized from petroleum ether to give 0.0103 mol of anti-α-morpholinoacetophenone oxime ether 47, mp. 62.5-64°. Compound 47 (0.007 mol) and cyanogen bromide (0.0078 mol) in 12 ml chloroform were left at room temperature for 20 minutes, after which the darkened reaction mixture was filtered and the solvent removed by evaporation. The resulting oil was chromatographed on silicagel (50 g, benzene) to give 0.0019 mol of a clear colorless oil (48) (the yield varied from 25 to 50 %). This compound (0.0019 mol) was dissolved in 10 ml acetonitrile and added to a mixture of 100 ml of 0.1 N HCl and 40 ml of acetonitrile, which was stirred at room temperature for 7 minutes. Extraction with chloroform, followed by evaporation of the solvent, gave a material which was crystallized twice from chloroform/petroleum ether to give 0.001 mol of anti-α-bromoacetophenone oxime (49), mp.114-115.5°.

Preparation 5 : 5α-Fluoro-6-oximinocholestan-3β-ol Acetate (52).[54]

A solution of 2.0 g of α-fluoroketone 51, 0.43 g of hydroxylamine hydrochloride and 0.43 g of sodium acetate in 80 ml absolute ethanol was refluxed on a steam bath, filtered hot and allowed to stand at room temperature for 6 hrs. Dilution with water afforded a white precipitate which was washed well with water, dried and recrystallized from a mixture of petroleum ether (bp. 30-60°) and hexane to afford 1.22 g of 5α-fluoro-6-oximinocholestan-3β-ol acetate (52), mp. 167-169.5°.

Preparation 6 : α-Chloro-N-cyclohexylpropionaldonitrone (55b).[55]

A solution of 21.1 mmol freshly distilled 2-chloropropanal 53 (R = Me)[248] in 100 ml dry ether was treated with stirring at 0° with 20.0 mmol N-cyclohexylhydroxylamine over a period of 2 hrs. After the first hour, 50 ml ether was added and after the second hour, 50 ml ether and 100 ml CH_2Cl_2 was added. After another hour at 0°, the solution was dried for 15 hrs. over $MgSO_4$ at 0°, filtered and evaporated at 0°. The crude product was dissolved in 10 ml ether, 25 ml pentane were added and the mixture cooled to 0° (2 hrs) to give a 79 % yield of crystals, mp. 73-75° (dec.). It is recommended to store the product in the refrigerator.

Preparation 7 : 2,2,2-Tribromoacetophenone Azine (127).[113]

A solution of 10.0 g (0.042 mol) of acetophenone azine 126 in 50 ml CH_2Cl_2 was treated dropwise over 40 minutes with 41 g (0.26 mol) bromine, while the solution was heated at reflux with magnetic stirring. After another hour at reflux, the sol-

vent was removed by evaporation and the dark red mass remaining triturated with methanol. The unstable yellow crude product was collected on a Buchner funnel, then dissolved at room temperature in CH_2Cl_2 (10 ml per gram of crude product) and recrystallized at -20°, giving 11.9 g (40 %) of light yellow needles of 127, mp. 170° (dec.), which slowly decomposed upon standing in the air.

Preparation 8 : N-2-(1,1-dichloro-4-methylpentylidene)cyclohexylamine (146, R = i-Bu).[120]

A magnetically stirred 10 % solution of freshly prepared N-2-(4-methylpentylidene)cyclohexylamine (133, R = i-Bu) in carbon tetrachloride, protected by a calcium chloride tube, was cooled in an ice-bath and treated portionwise with two equivalents of N-chlorosuccinimide over a period of two hours. The suspension was stirred overnight at room temperature. Succinimide was filtered off and the solvent was evaporated under reduced pressure, until no IR absorption in the 760-800 cm^{-1} region was noted due to CCl_4. Compound 146 (R = i-Bu) was obtained in 98 % yield. It was recommended to store the product in the refrigerator under an inert atmosphere.

Preparation 9 : N-1-(2,2-dichloropentylidene)t-butylamine (158, R = n-Pr).[123]

A mixture of 0.1 mol of pentanal and 0.1 mol of t-butylamine was stirred at room temperature for 5 minutes. After addition of 100 ml carbon tetrachloride and magnesium sulfate, the resulting slurry was stirred for one hour. (Note : when larger mole quantities were used, the water formed was first

removed from the CCl_4 layer using a separatory funnel, after which $MgSO_4$ was added). Filtration gave a clear solution of N-1-(pentylidene)t-butylamine 157, which was stirred and treated portionwise with 0.22 mol of N-chlorosuccinimide at room temperature. After stirring overnight, succinimide was removed by filtration and the filtrate was concentrated under reduced pressure. Distillation in vacuo afforded a 91 % yield of N-1-(2,2-dichloropentylidene)t-butylamine (158, R = n-Pr) as a colorless stable liquid, bp. 78-79°/12 mm.

Preparation 10 : N-1-(2-chloro-2-methylpropylidene)cyclohexylamine (160, $R_1 = R_2 = CH_3$; R = cyclohexyl).[125]

By a similar procedure as described in Experiment 9, N-1-(2-chloro-2-methylpropylidene)cyclohexylamine (160) was prepared, starting from isobutyraldehyde, cyclohexylamine and N-chlorosuccinimide (10 % excess of NCS was used). Compound 160 was obtained by distillation, bp. 90-93°/12 mm. (yield 70 %).

Preparation 11 : N-1-(2,2-dibromo-1-phenylpropylidene)cyclohexylamine (180, $R = CH_3$; $R_1 = H$).-

N-1-(1-phenylpropylidene)cyclohexylamine was brominated with 2.2 equivalents N-bromosuccinimide in CCl_4 at room temperature as described in the Preparations 8, 9 and 10 using N-chlorosuccinimide. Filtration and evaporation afforded compound 180 in quantitative yield. It was recommended to use the α,α-dibromoketimine 180 directly for further purposes.

Preparation 12 : 3-Bromomethyl-4,4-dimethyl-2-pyrazolin-5-one (190) from 1-Acetyl-3,4,4-trimethyl-2-pyrazolin-5-one (189).[134]

A stirred solution of 8.40 g of 1-acetyl-3,4,4-trimethyl-2-pyrazolin-5-one (189) and 9.79 g of N-bromosuccinimide in 200 ml of CCl_4 was irradiated with a 275-W sun lamp (General Electric) for 10.5 hrs. The mixture was cooled, succinimide removed by filtration and the residue, obtained on evaporation of the filtrate by means of a current of air, was recrystallized from benzene-ligroin (bp. 60-70°) to give 4.67 g (53 %) of the pyrazolone 190 as pale yellow needles , mp. 135.5-137°.

Preparation 13 : 3-Bromomethyl-4,4-dimethyl-2-pyrazolin-5-one (190) from Ethyl γ-Bromo-α,α-dimethylacetoacetate.[134]

To a stirred solution of 47.4 g of the β-keto ester[249] and 12.5 g of acetic acid in 180 ml of 60 % aqueous ethanol there was added dropwise over 30 minutes a solution of 10 g of hydrazine hydrate (100 %) in 60 ml of ethanol. The solution was stored in a refrigerator at 5° for 17 days, treated with 175 ml of water and extracted with 800 ml of ether in a liquid-liquid extractor for 3 days. Recrystallization of the residue obtained after evaporation of the ether extracts gave 16.4 g (40 %) of the bromomethylpyrazolone 190, mp. 135-136.5°.

Preparation 14 : 3-Bromo-2-cyano-4,5,5-trimethyl-1-pyrroline 1-oxide (199, R = Me).[250]

2-Cyano-4,5,5-trimethyl-1-pyrroline 1-oxide[251] (197) (3.0 g, 20 mmol) dissolved in 300 ml CCl_4 was added to 7.2 g

(40 mmol) of NBS and a catalytic amount of benzoyl peroxide. The mixture was stirred and heated under reflux for 4 hrs, allowed to cool to room temperature, and the solid residue was removed by filtration and washed with CCl_4 (2x40 ml). The combined organic solutions were concentrated to yield a brown oil which slowly solidified and was recrystallized from ether-light petroleum to afford 3.6 g (79 %) of a mixture of cis- and trans-3-bromo-2-cyano-4,5,5-trimethyl-1-pyrroline 1-oxide (199, R = Me) as colorless flakes, mp. 92-92.5°.

Preparation 15 : 21-Trichloro N-demethyl(5α)20(N)-conenine (201).[138,139]

A solution of 0.5 g (1.65 mmol) of pyrroline 200 in 25 ml dichloromethane was treated with 25 ml of a commercial sodium hypochlorite solution (10 mmol). The phases were vigorously stirred during 5 days. After adding another 10 ml of sodium hypochlorite solution, the mixture was further stirred during 3 days. Usual work up gave 0.63 g of a white crystalline material, which was chromatographed on silicagel plates (1.5 mm thickness). The first fraction gave 0.34 g (50 %) 21-trichloro-N-demethyl(5α)20(N)-conenine 201, mp. 196°.

Preparation 16 : 2-Bromo-3,3,5,5-tetramethylcyclohexanone Tosylhydrazone (221).[145]

3,3,5,5-Tetramethylcyclohexanone tosylhydrazone (219) (3.22 g, 0.01 mol) was dissolved in 100 ml anhydrous tetrahydrofuran and stirred at -20°. PTAB[252,253] (3.79 g, 0.01 mol) was added during a period of 15 min. After another 10 min., the precipitate was collected by filtration and the resulting

solution was evaporated under reduced pressure at a temperature not exceeding 40°. The residue was dissolved in diethyl ether, and methanol was added until precipitation of a white product occurred. The crystals were collected and dried to give 2.2 g (55 %) 221, mp. 122-123° dec.

Preparation 17 : 2,6-Dibromo-3,3,5,5-Tetramethylcyclohexanone Tosylhydrazone (220).[145]

A stirred solution of 3.22 g (0.01 mol) 3,3,5,5-tetramethylcyclohexanone tosylhydrazone (219) in 100 ml anhydrous tetrahydrofuran was treated at room temperature with 7.58 g (0.02 mol) phenyltrimethylammonium perbromide (PTAB)[252,253] during a period of 15 minutes. After another 10 minutes, the precipitate was collected and the solution was evaporated under reduced pressure at a temperature not exceeding 40°. The residue van dissolved in diethyl ether and allowed to stand in a refrigerator until precipitation of a white product occurred. The crystals of 2,6-dibromo-3,3,5,5-tetramethylcyclohexanone tosylhydrazone 220 were collected and dried (4.08 g, 85 %), mp. 112-113° (dec.).

Perparation 18 : Chlorination of Ibogaine with t-Butyl Hypochlorite.[159]

t-Butyl hypochlorite (1.40 g, 13 mmol) in 80 ml CCl_4 was added dropwise over 20 minutes to a stirred solution of ibogaine 241 (3.72 g, 12 mmol) in 160 ml CH_2Cl_2 containing triethylamine (1.21 g, 12 mmol), cooled in an ice-salt mixture. After the addition was completed, stirring was continued for 40 minutes. The reaction mixture was washed with ice water,

dried (sodium sulfate), and evaporated under vacuum to yield the crude chloro derivative as a light brown, viscous oil. A solution of a portion of the material in benzene and hexane was filtered through aluminia (activity III) and crystallized from hexane containing a little benzene to give the pure product 242, mp. 90-92°.

Preparation 19 : Methyl N-1-(2,2,2-trichloroethylidene)carbamate (252, R = CH_3).[171]

Synthesis of Methyl 1,2,2,2-Tetrachloroethylcarbamate (251, R = CH_3)

To a suspension of 222.5 g (1 mol) of methyl 1-hydroxy-2,2,2-trichloroethylcarbamate (250, R = Me) in 1200 ml of CH_2Cl_2, 119 g (1 mol) of thionyl chloride, containing 2.2 g of pyridine, was added. After refluxing for 1 hr a clear solution was obtained and evaporation of the solvent afforded 240 g (99.5 %) of methyl 1,2,2,2-tetrachloroethylcarbamate (251, R = Me), mp. 91-92° after recrystallization from CCl_4.

Synthesis of Methyl N-1-(2,2,2-trichloroethylidene)carbamate (252, R = CH_3)

To a solution of 20.2 g (0.02 mol) of triethylamine in 200 ml of benzene was added dropwise with stirring 48.2 g (0.02 mol) of methyl 1,2,2,2-tetrachloroethylcarbamate (251, R = Me) in 200 ml of benzene over a period of 20 minutes at 25-40°. After cooling and removal of triethylamine hydrochloride by filtration, benzene was evaporated and vacuum distillation of the residue afforded 16.7 g (41 %) methyl N-1-(2,2,2-trichloroethylidene)carbamate (252, R = CH_3), bp. 41-42°/0.1 mm.

Preparation 20 : General Procedure for the Preparation of α-chlorooximes by Reduction of Nitroolefins.[201]

One equivalent of tin(II)chloride dihydrate was dried during several days over P_2O_5 or conc. H_2SO_4 in the dessicator, thereby loosing about 40 % of its water content. This product was dissolved in diethyl ether, containing 1.5 equivalents hydrogen chloride. This solution was added dropwise with stirring and cooling (ice-salt bath) over a period of 2-4 hrs to a solution of 1 equivalent of nitroolefin in diethyl ether, containing 1.5 equivalents hydrogen chloride. After the addition was complete, stirring was continued for another 2 hrs. Water was added and the ether layer washed three times with diluted hydrogen chloride solution, and five times with water. Drying (Na_2SO_4), evaporation and distillation or crystallization in vacuo gave the pure α-chlorooximes 293. As an example, from 50.5 g (0.5 mol) 2-nitro-2-butene (292, R = R" = CH_3 ; R' = H) and 27 g HCl in 250 ml diethyl ether, the reduction was carried out with 157 g (0.7 mol) Sn(II)Cl_2 and 40 g HCl in 750 ml diethyl ether during a reaction time of 4 hrs, to afford 29 g (48 %) 3-chloro-2-oximinobutane (293, R = R" = CH_3 ; R' = H), bp. 79°/11 mm.

Preparation 21 : (E)-3,7-Dimethyl-2,6-octadien-1-yl 2,2,2-Trichloroethanimidate (303) (Geraniol Trichloroacetimidate).[210]

A suspension of NaH [410 mg of a 57 % dispersion in mineral oil (10 mmol), which had been previously washed twice with hexane] and 60 ml of anhydrous ether was treated dropwise with

a solution of 15.4 g (100 mmol) of (E)-3,7-dimethyl-2,6-octadien-1-ol 302 (geraniol) and 15 ml of anhydrous ether. After the evolution of hydrogen ceased (± 5 min), the reaction mixture was cooled to -10° to 0°, and trichloroacetonitrile (10.0 ml, 14.4 g, 100 mmol) was added dropwise to the stirred solution, while the temperature was maintained below 0°. Addition was complete within 15 min, and the solution was allowed to warm at room temperature and was concentrated. Pentane [150 ml, containing 0.4 ml (10 mmol) of methanol] was added, the mixture shaken vigorously, and a small amount of dark, insoluble material was removed by filtration. After washing the residue two times with pentane, the combined filtrate was concentrated to give 27-29 g (90-97 %) of crude 303 (purity ± 95 % by NMR). Rapid distillation through a short Vigreux column gave 24-28 g (80-93 %) of pure 303, bp. 109-111°/0.1 mm.

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