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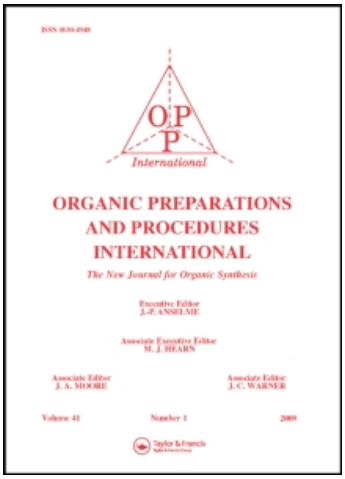

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REACTIVITY OF β-HALOENAMINES. A REVIEW

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REACTIVITY OF β-HALOENAMINES. A REVIEW

Norbert DE KIMPE* and Niceas SCHAMP

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REACTIVITY OF β-HALOENAMINES. A REVIEW

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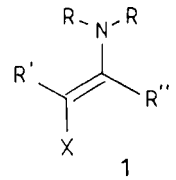
I. INTRODUCTION

Enamines have been widely used in synthetic organic chemistry,[1,2] but functionalized enamines, such as β-haloenamines 1, have not been studied to the same extent because of their relatively limited accessibility. However, in recent years, interest in the chemistry of this class of compounds has been renewed because of the development of novel synthetic routes.[3]



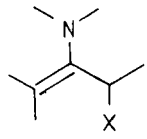
x = halogen

1

The purpose of this review is to focus on the possible uses of β-haloenamines in synthetic and mechanistic organic chemistry. The synthesis of β-haloenamines has been reviewed recently.[3] Because β-haloenamines and α-haloimines[4,5] are both masked α-halocarbonyl compounds, an obvious similarity between the reactivity of the two aforementioned nitrogen derivatives exists. It is therefore useful to compare the reactivity of the title compounds in this review with that of α-haloimines[5] which were

discussed previously in this Journal.

The present survey is divided into several parts, each describing the reactivity of β-haloenamines towards various reagents. Attention will also be paid to the isomeric β-amino-allylic halides 2.



2 X=halogen

The literature has been reviewed up to the first half of 1981. In general, only those β-haloenamines, reflecting a structural similarity with α-halogenated carbonyl compounds, will be treated in this review. For instance α,β-dihaloenamines are not considered in this survey because their chemistry is determined by the α-halogen atom. Finally, although this constitutes a deviation from the general policy followed in this article, functionalized β-haloenamines having α-cyano or α-alkoxycarbonyl substituents (and/or analogs) will also be discussed here.

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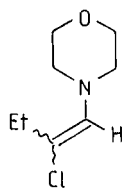
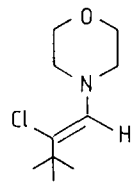
II. REACTIVITY OF β-HALOENAMINES

The stereochemistry about the double bond in β-haloenamines 1 has not always been elucidated but will be added to the schemes when possible. Reference is made to the first comprehensive study of the configuration of β-haloenamines as determined by an NMR study using the proton NOE effect.[6] Some data of E/Z distributions in β-haloenamines are presented here to give an idea of the influence of the various substituents on the equilibrium.


Z/E (85/15)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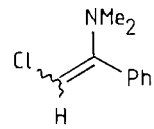
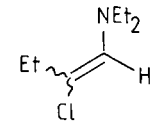
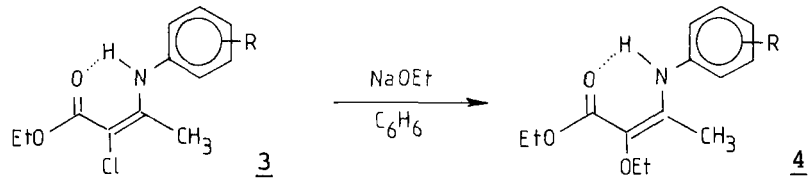

Z/E (10/90)


Z/E (85/15)

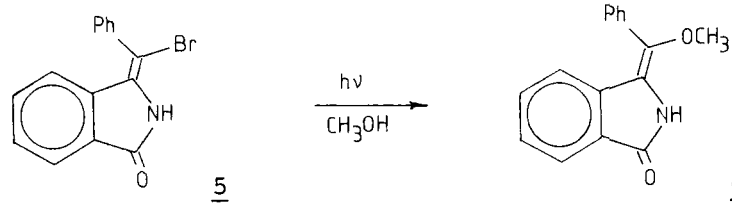
1. Reaction of β-Haloenamines with Oxygen Nucleophiles

Halogen displacements from β-haloenamines by oxygen nucleophiles are rarely reported. In protic solvents such as alcohols, rearrangement *via* an aziridinium halide intermediate takes place with alkoxides and the reaction is initiated by the addition of the oxygen nucleophile at the most electrophilic carbon atom of β-haloenamines, i.e. the carbon atom bearing the amino function (*vide infra*). Only in a non-polar medium, such as benzene, could enaminoester 3 undergo a displacement reaction with sodium alkoxide.[7] One example of a photochemical me-



3 4

thoxylation in the β-position of enamide 5 is known and is limited to secondary derivatives (*vide infra*).[8]



5 6

Finally, less general examples of a displacement reaction with β-alkoxylation were observed with a precursor to β-haloenamines, namely compound 7,[9] and with α-cyano-β,β-dichloroenamines 9.[10,11] With the latter compound, subsequent Michael ad-

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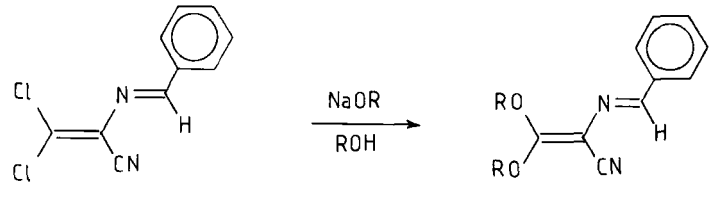
dition to the transient β,β-dialkoxy-α,β-unsaturated nitrile takes place to afford orthoester 10.[10] When the initial adduct, e.g. 12, does not contain a substituent on the nitrogen atom through which delocalization of the N-anion can take place (as in the case of enamides), the α-cyano moiety can be expelled, producing an imidate (13) which does not tautomerize.[12]



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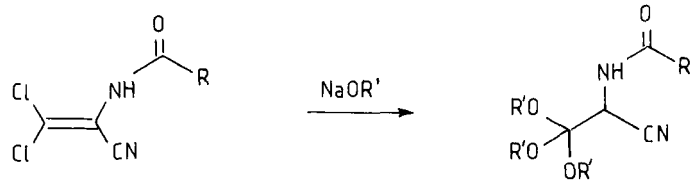
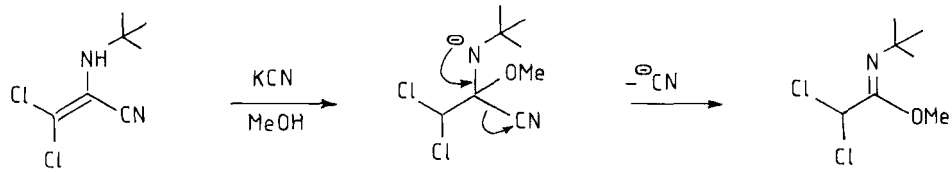


9 R=Me, Ph 10



11 12 13

Beside substitution and exchange reactions, nucleophilic addition to suitable substrates has also been obtained. Functionalized isocyanate 14, which is a precursor to β-haloenamines (e.g. 15), undergoes addition of ethanol at the cumulenic system and at the olefinic double bond.[13] Finally, sodium methoxide has been found only to cause deprotonation of secondary

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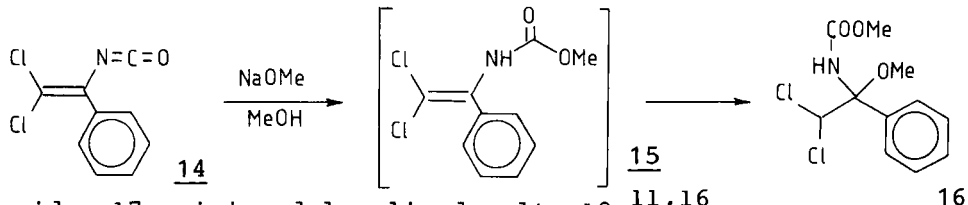
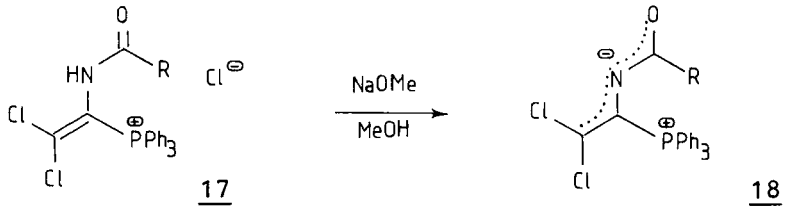


14 15 16

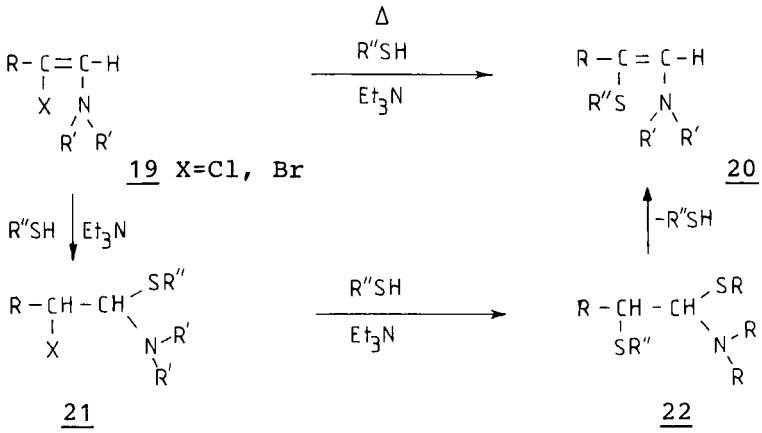
enamides 17, giving delocalized salts 18.[11,16]



17 18

2. Reaction of β-Haloenamines with Sulfur Nucleophiles

β-Haloenamines are readily substituted by aliphatic and aromatic thiols (or thiolates), yielding β-sulfenylated enamines. The mechanism of this reaction was studied to some extent with ordinary β-haloenamines 19 derived from aldehydes.[17] Nucleophilic attack of the thiol (or thiolate if base is added)



at the most electrophilic carbon atom of the β-haloenamine 19 produces adduct 21, which undergoes nucleophilic substitution by the sulfur reagent. The resulting disulfenylated compound (22) subsequently loses the elements of the thiol and furni-

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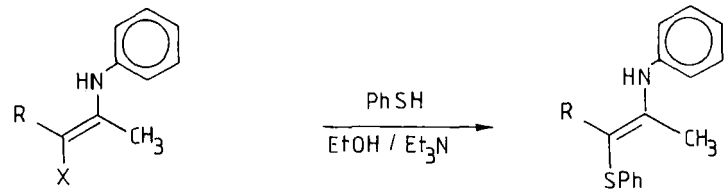
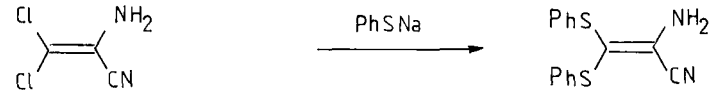
shes β-sulfenylated enamines 20.

When oxygen nucleophiles such as the alkoxides in the corresponding alcohols are used, an analogous addition of the elements of the alcohol takes place at the double bond of β-haloenamines but the remaining halogenated carbon atom undergoes displacement more readily by an intramolecular reaction of the amino moiety than by the alkoxide. This fact explains the occurence of rearrangement in the case of alcohols as compared to the better sulfur nucleophiles (vide infra). Similar displacement reactions have been reported for β-haloenamides,[7,10,11,16,18-21,24] functionalized cyclic[22,23] and acyclic[7,10,25,26] enami-

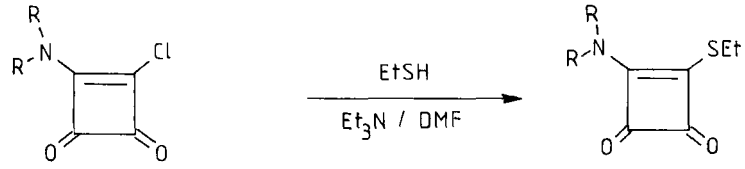


23 X=Cl, Br
R=COOEt, CN

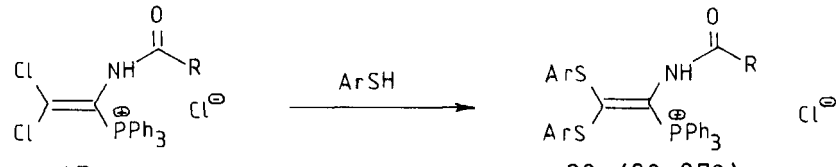
24



25 26



27 28



17 29 (80-87%)

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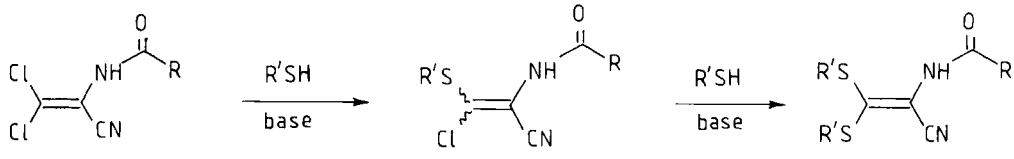
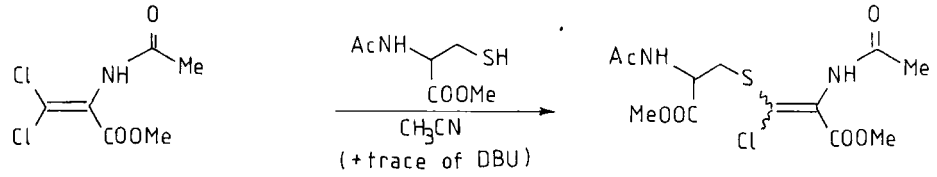
nones, some examples of which are given below. When two halogen atoms are displaceable, the reaction can be controlled to yield the mono- or disulfenylated derivatives, depending upon the amount of thiol used (9 → 30 or 31).[18] The β-sulfenylation

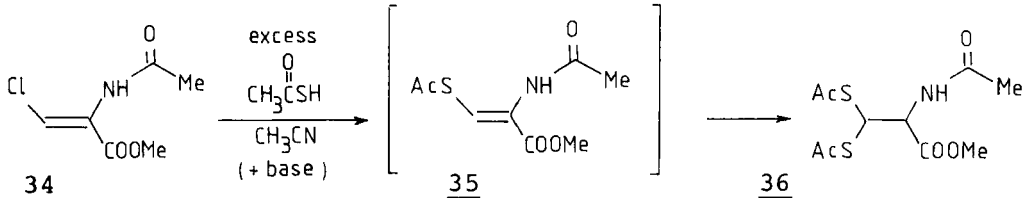


9 30 31

reported in this section is not limited to simple aliphatic or aromatic thiols, but more highly functionalized sulfur reagents, such as N-acetyl-L-cysteine methyl ester or thioacetic acid,can



32 33 (E+Z)



34 35 36

be utilized.[21] However, thioacetic acid also gave a Michael addition to the unsaturated ester 35.[21]

3. Reaction of β-Haloenamines with Nitrogen Nucleophiles

The reaction of β-haloenamines with a variety of nitrogen nucleophiles has been more intensively studied. Attention has mainly been paid to primary and secondary amines, which display a deviating reactivity towards β-haloenamines. Two main types of reaction can be considered, namely formal substitution of

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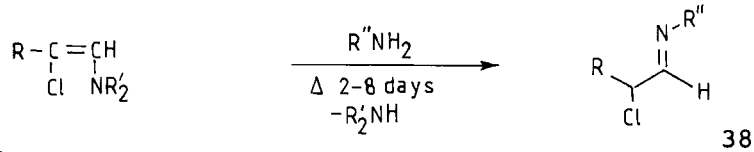
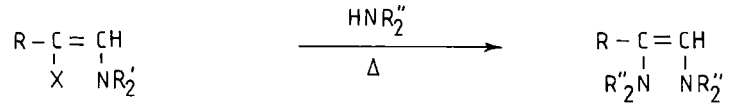
the halide(s) and nucleophilic addition at the electrophilic carbon atom of the β-haloenamine.

Simple β-chloroenamines 37 react extremely slowly with primary aliphatic amines to afford α-chloroaldimines 38 by an exchange reaction involving nucleophilic addition of the primary and elimination of the secondary amine.[17] Secondary amines react analogously but an additional halogen displacement

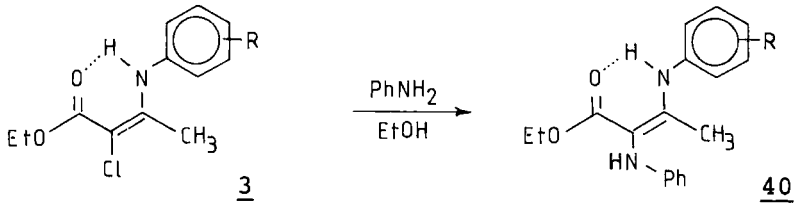


37 38



19 X=Cl, Br 39

takes place to yield enediamines 39.[17] More highly functionalized β-haloenamines, e.g. enaminoesters 3, also yield substituted products 40 with anilines in ethanol.[7,24] Without sol-



3 40

vent at high temperature, the same reaction proceeds further by intramolecular condensation to heterocyclic compounds (vide infra).[24] When β,β-dichloroenamides 41 are condensed with bifunctional reagents, such as ethylenediamine or 2-aminoethanethiol, a double displacement reaction takes place with formation of heterocyclic compounds 43 and 42, respectively.[27] Secondary amines most often furnish substituted products, but

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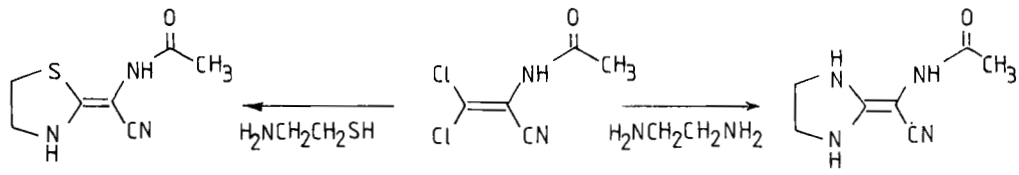
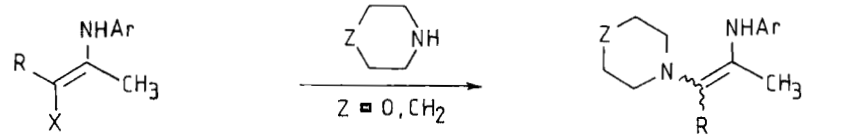
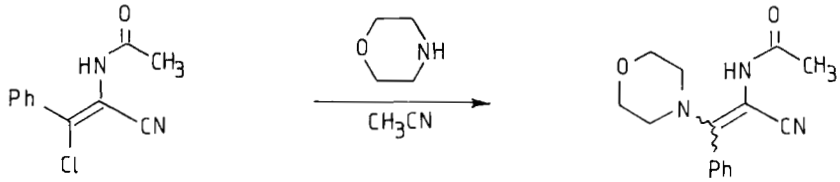


42 41 43

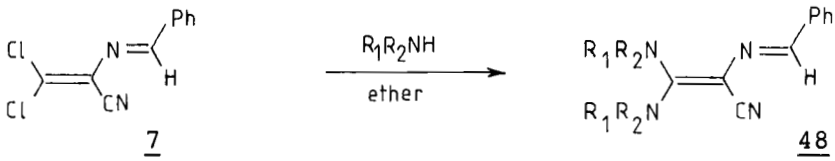
several ring-closures have also been reported (vide infra). This substitution reaction has been applied with enaminoesters 44 (R = COOEt),[7] enaminonitriles 44 (R = CN),[24] enamides 46[27,28] and precursors to β-haloenamines (7).[9]



44 R=COOEt, CN 45 (E+Z)



46 47



7 48

With certain α-cyano-β,β-dichloroenamines, cyanide is expelled after addition of the secondary amine.[11,29,30] In the case of the sulfonamide derivatives 49 and 50, the exchange of the amino function for the nitrile moiety to generate amidines 52 and 53 probably occurs because these compounds are in equilibrium with their imino tautomers, which contain a much more electrophilic carbon atom, thus permitting nucleophilic addition to take place.[11,30]

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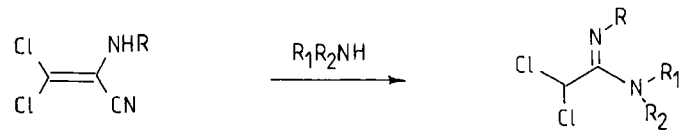
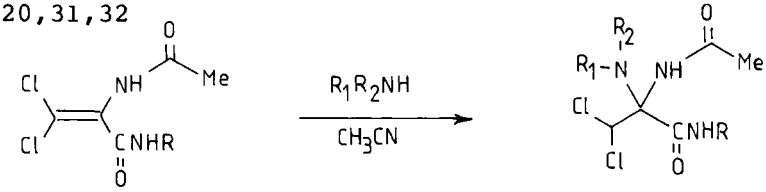


25 R=H
49 R=SO_2Ph
50 R=SO_2NMe_2

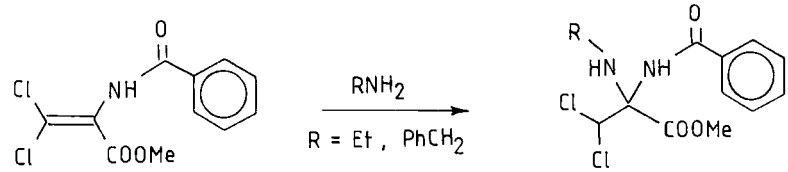
51 R=H
52 R=SO_2Ph
53 R=SO_2NMe_2

When the β-halogenated enamines contain substituents which are not good leaving groups, e.g. amido groups, methoxycarbonyl or carboxyl groups, simple nucleophilic addition of amines takes place.[20,31,32]



54 R=H, Ac

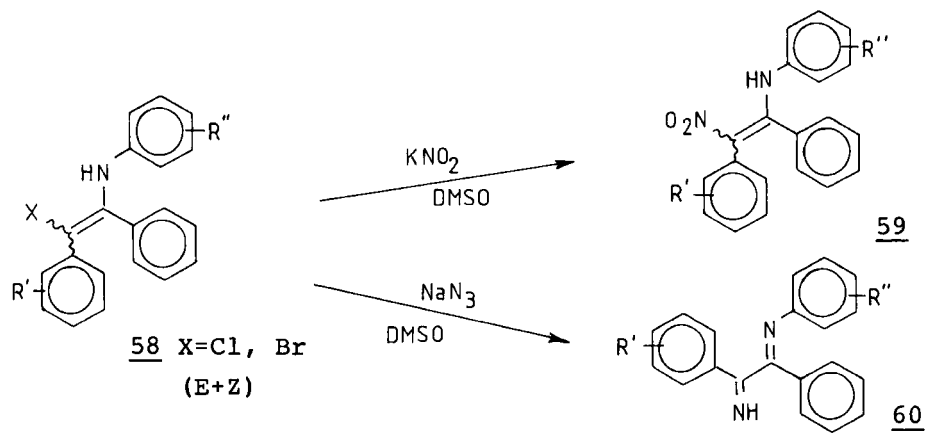
55



56

57

Besides the overwhelming number of reports dealing with condensations of β-haloenamines with amino compounds, only very few other nitrogen nucleophiles have been utilized in these



58 X=Cl, Br
(E+Z)

59

60

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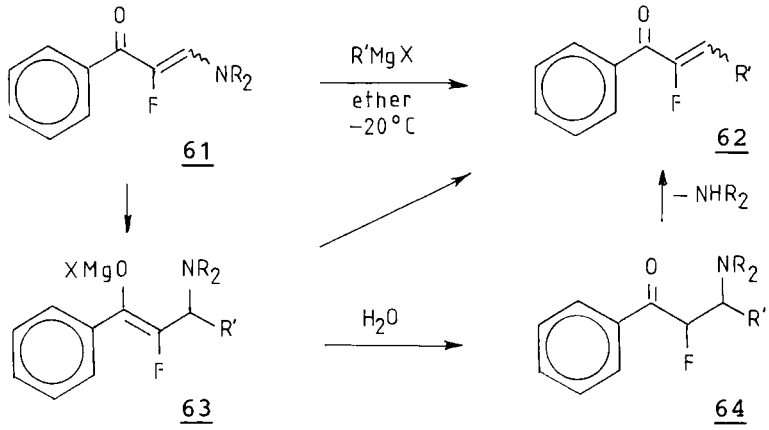
reactions. Potassium nitrite in dimethylsulfoxide converts aromatic β-haloenamines 58 in the (Z)-β-functionalized enamines 59 (no β-nitritoenamine was formed), while with sodium azide in the same solvent α-diimine 60 was obtained.[33] No reaction occurred between these nucleophiles and pyrrolidino β-haloenamines.[33]

4. Reaction of β-Haloenamines with Organometallic Reagents

4.1. Grignard Reagents

Fluorinated enaminones 61 undergo 1,4-addition of organomagnesium halides in ether at -20°C.[34] The reaction proceeds via β-amino-α-fluoroketones 64, which expel the elements of the secondary amine during work-up. The formal replacement of



the dialkylamino group by the alkyl group of the organometallic reagent can be carried out in good yield (76-82%) except for NR_2 = morpholino (33%). Enaminoesters 65 underwent a similar conjugate addition but the ester function was also converted into a ketone moiety (1,2-addition). Yields are only moderate (33-37%) and much of the starting material is recovered.[34]

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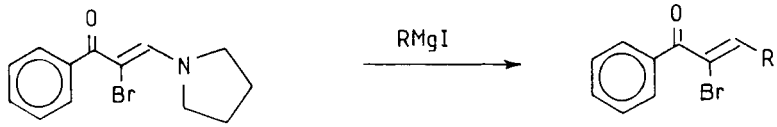
65 66

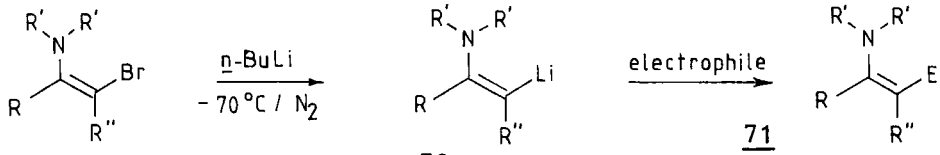
This reaction was recently extended to β-benzoyl-β-bromo-enamines 67, which were converted into α-bromo-α,β-unsaturated ketones 68,[35,36] used as precursors of isoxazoles.



67 68 R=Me, Et, i-Pr, Pr

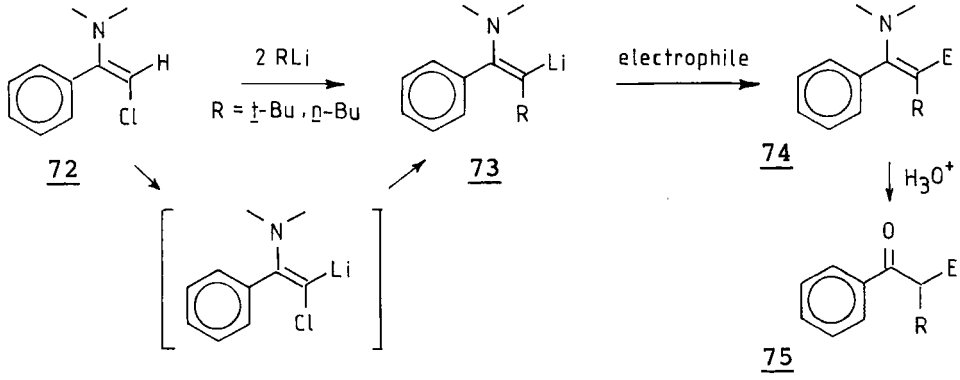
4.2. Organolithium Reagents

β-Bromoenamines 69 are lithiated at the β-position by n-butyllithium in ether or hexane at low temperature. The metallated species may be used for electrophilic substitutions with water, iodine, alkyl iodides and aldehydes (Preparation 1).[37] β-Chloroenamine 72 is first lithiated and subsequently



69 70 71 E=H, I, R, RCHOH

alkylated when two equivalents of organolithium reagent are used.[38] The reaction of β-lithioenamine 73 with electrophiles,



72 73 74 75

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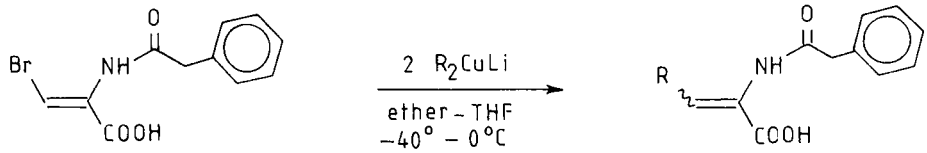
such as water (deuterium oxide), methyl iodide and bromine, furnishes functionalized enamines 74, which are hydrolyzable to ketones 75 (Preparation 2).[38] Because β-chloroenamine 72 originates from acetophenone, the net transformation of this set of reactions consists of the introduction of a nucleophile and an electrophile in the α-position of the starting carbonyl compound. When using alkyl iodides as electrophiles, this pathway allows the nucleophilic and electrophilic alkyl substitution of ketones in the α-position.

4.3. Lithium Dialkylcuprates

The reaction of β-halogenated enamides 76 with dialkylcopper lithium reagents in tetrahydrofuran occurs by replacement of the vinylic halogen and proceeds with complete or predominant retention of configuration about the double bond.[39]



76 (Z)

77 R=Me (100% Z)
R=n-Bu (Z/E = 2/1)

Methylations of (Z)-3-bromo-2-(2-phenylacetamido)acrylic acid 76 occur with complete retention of configuration, but a mixture of isomers is obtained from the n-butylation reaction. In both cases, a minor amount of the reduced product (caused by halogen-metal exchange) is observed. The reaction of dimethylcopper lithium with β-chloroenamide 34 also proceeds with complete retention of configuration, but β-bromo analogue 78 (Z/E = 3/1) showed predominant formation of the Z final product 79 (Preparation 3).[39]

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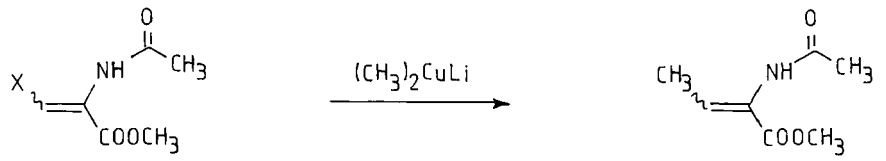
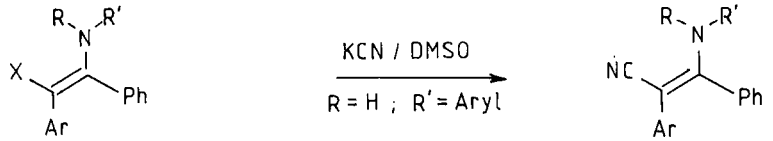


34 X=Cl (100% Z)
78 X=Br (Z/E = 3/1)

79 100% Z for X=Cl
predominantly Z
for X=Br

5. Reaction of β-Haloenamines with Carbon Nucleophiles

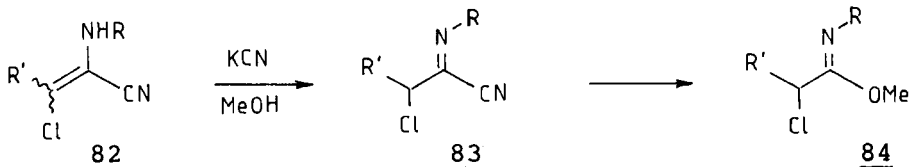
The study of the reactivity of β-haloenamines towards carbon nucleophiles other than organometallic reagents is limited to cyanide anion. Tautomerizable β-haloenamines 80 (R = H, R' = aryl) undergo substitution by potassium cyanide in dimethylsulfoxide, but no reaction is observed with tertiary pyrrolidinoenamines 80 (NRR' = pyrrolidino).[33] This observation



80 R=H; R'=aryl
NRR'=pyrrolidino

81

underscores the importance of the tautomeric ketimine derived from 80 (R = H; R' = aryl), in which the halide is doubly activated by the imino group and the aryl substituent.[33] β-Chlorinated α-cyanoenamines 82 are not substituted by potassium cyanide in methanol under reflux but tautomerize into imidoyl cyanides 83, which are further converted to α-chloroimidates 84.[12,40] The reaction of potassium cyanide with α-bromoimmo-



82 83 84

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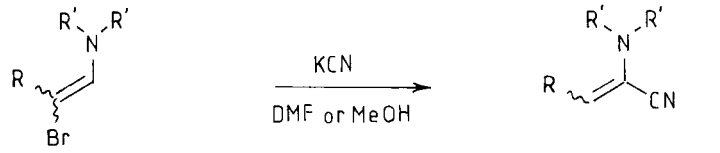
nium bromide, prepared from the addition of bromine to aldehyde enamines, in dimethylformamide, leads most probably to transient β-bromoenamines 85; the latter intermediates are subsequently attacked by cyanide ion to afford β-bromo-α-cyanoamines, the latter being dehydrobrominated to give predominantly (E)-α-cyanoenamines 86.[128] When the β-bromo-α-cyanoamines are isolated and subsequently dehydrobrominated with potassium cyanide in methanol under reflux (30 min), the resulting α-cyanoenamines 86 occur in the (Z)-configuration exclusively.[128]



85 86

6. Dehydrohalogenation of β-Haloenamines

Ynamines can be obtained from β-halogenated enamines, derived from α-halogenated aldehydes, by dehydrohalogenation using strong bases, preferably in an aprotic medium like tetrahydrofuran. In this way, β,β-dichloroenamines 88 are converted into chlorinated ynamines 89, which could not be isolated in pure form.[41] The starting materials 88 are synthesized by dehydrochlorination of β,β,β-trichloroamines 87 with 1.5 equivalents of potassium t-butoxide.[41] With a 4-5 fold excess of potassium t-butoxide in tetrahydrofuran or t-butanol, trichloroamine 87 was converted into the transient chloroynamine 90, which suffered further transformation into β-chloro-β-t-butoxyenamine 91 or α-t-butoxyacetamide 92.[41] β-Functionalized β-bromoenamines 93 undergo a similar dehydrobromination with potassium t-butoxide to yield β-functionalized ynamines 94, carrying electron withdrawing substituents, such as formyl,

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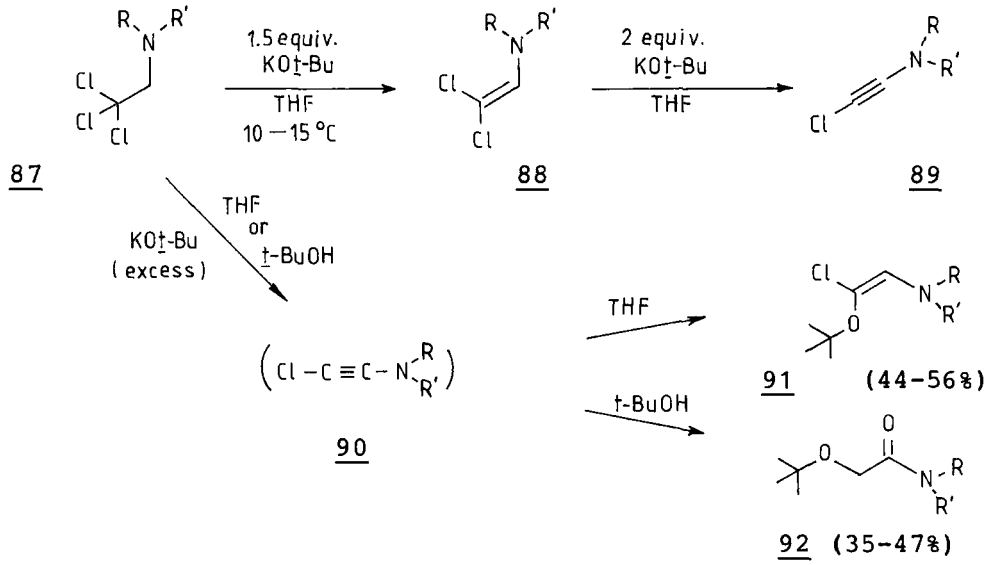
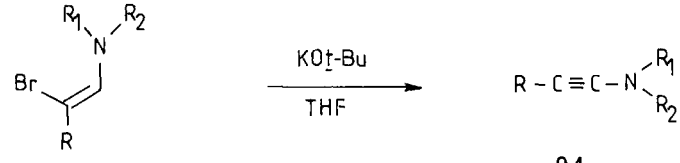
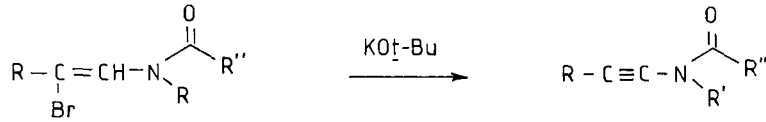


aryl, methoxycarbonyl or nitro, at the β-position (Preparation 4).[42-45,135]



93 R=acyl, NO_2, CHO, COOMe, $CONMe_2$ 94

When this elimination reaction is applied to β-haloenamines, bearing the electron-withdrawing substituent at nitrogen, i.e. β-bromoenamides 95, the synthesis of ynamides 96 could be accomplished.[47]



95 96

Another type of elimination was encountered with some cyclic dibrominated enaminones 97, which aromatized to functionalized phenols 98, but this elimination occurred because the halide was not part of the β-bromoenamino moiety[16] (see also Section

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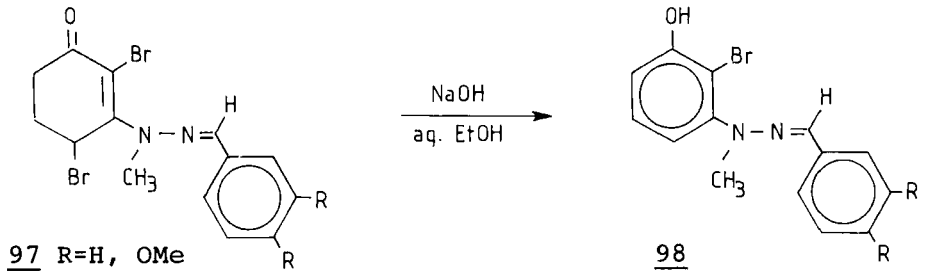
13).[48]

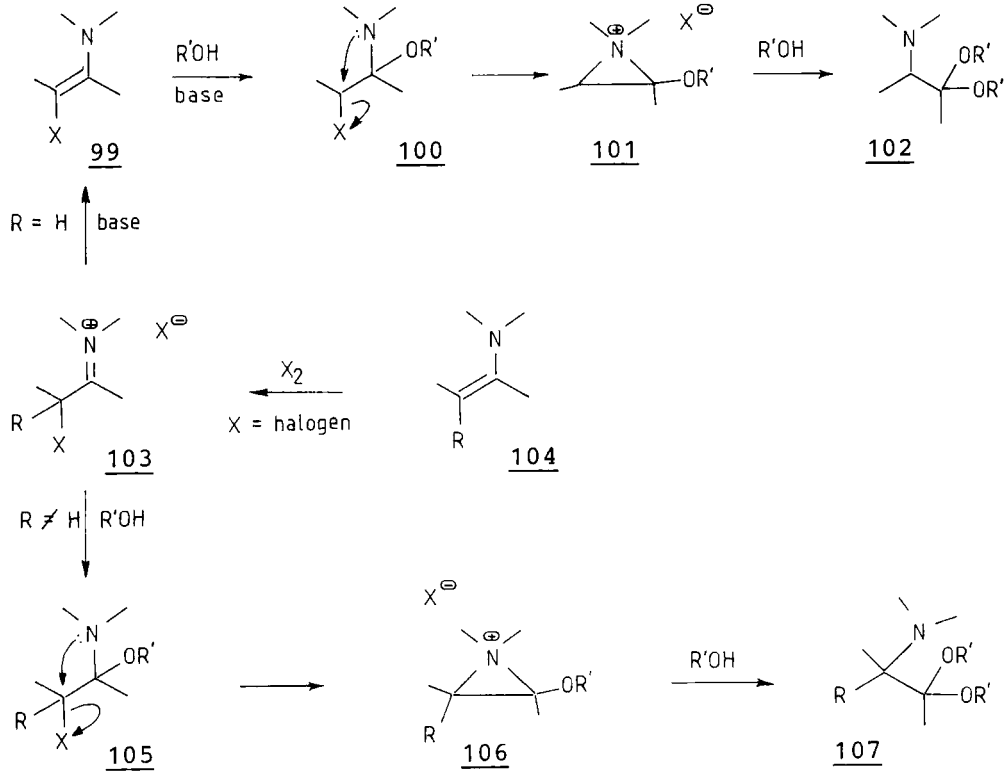


97 R=H, OMe

98

7. Rearrangement of β-Haloenamines via Activated Aziridinium Intermediates

β-Haloenamines 99 are apt to undergo a rearrangement of the amino function to the adjacent (originally halogenated) carbon atom. This rearrangement is most frequently induced by hydroxide or alkoxide and leads to α-aminoketones or α-aminoacetals. It is comparable to a similar rearrangement of α-halo-



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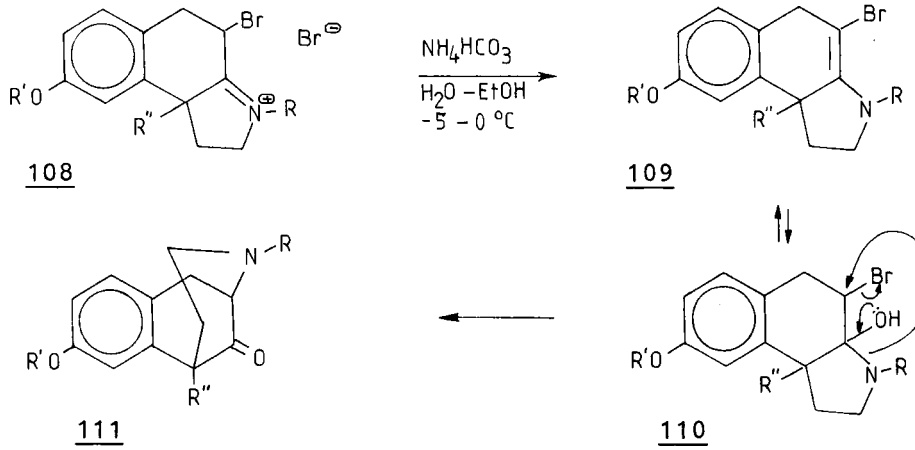
imines[5] and is more directly related to the same reaction of α-haloimmonium halides.[5] β-Haloenamines 99 and α-haloimmonium halides 103 (R = H) with, e.g., alcohols in the presence of a base (tertiary amine or alkoxide) both afford the same α-aminoacetals 102.[17,49] When an α-hydrogen atom is available in α-haloimmonium halides 103 (R = H), the first step consists of α-deprotonation and conversion into the corresponding β-haloenamine 99, which undergoes addition of the alcohol to give 100. The direct addition of alkoxide (or alcohol) to the immonium moiety of 103 (R = H) would also lead to the same adduct 100, but does not occur because of the faster deprotonation. The intermediacy of β-haloenamines in such cases has been demonstrated recently by their isolation (see 109) during the conversion of α-bromoimmonium bromides 108 into 9-oxobenzomorphans 111.[50,51] However, the plausibility of the direct addi-



108 109 110 111

tion of alkoxide or alcohol to the immonium function of α-haloimmonium halides is proven in such cases when α-deprotonation is not possible, namely when a tertiary halide moiety is present in the molecule (103, R ≠ H).[52] The adduct 113 was isola-

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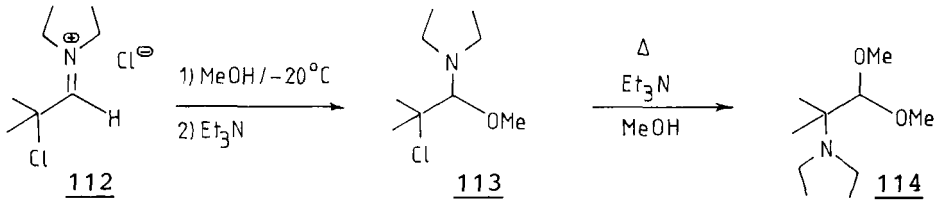
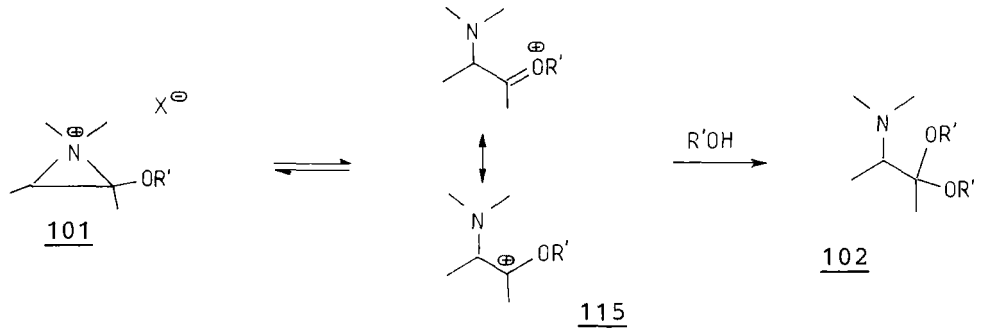
ted under mild conditions and was further transformed in the alcoholic medium into α-aminoacetal 114.[17] A similar reaction was observed with the corresponding α-bromoimmonium bromide and sodium methoxide in methanol.[52] The conversion of adducts 100 into α-aminoacetals 102 entails an intramolecular nucleophilic displacement of the halide by the amino group, generating an



112 113 114

intermediate functionalized aziridinium halide 101 which is cleaved by the alcohol at the activated site. This ring-opening might be viewed as proceeding by attack of the alcohol at the stabilized alkoxycarbenium ion 115, which is in equilibrium with α-alkoxyaziridinium halide 101. As already pointed out



101 115 102

in the synthesis of 9-oxobenzomorphans 111,[50,51] this rearrangement permits ring transformations to take place. Depending upon the substitution pattern in the starting β-haloenamine (or α-haloimmonium halide as its precursor), ring-expansions [50,51,53,54] (e.g. 108 → 111) as well as ring-contractions[55,56] (e.g. 122 → 124 and 126 → 127) have been performed (Preparation 5). It has to be stressed that with certain suitable

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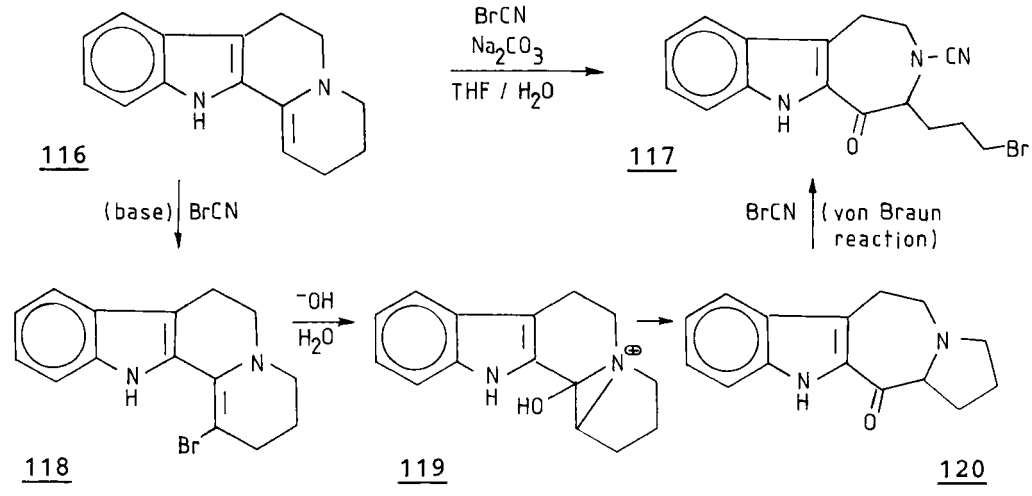
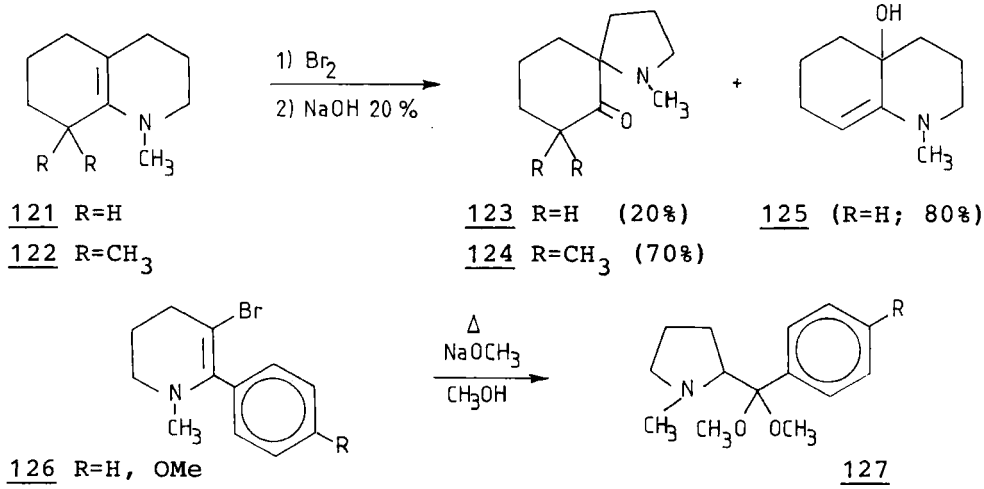
structures a combined ring-contraction and ring-expansion can be obtained. This result was observed during the conversion of 116 into 117 but the tetracyclic derivative suffered the von Braun reaction under influence of cyanogen bromide.[54] A "clean" ring-contraction and expansion was observed during the ethoxide promoted rearrangement of α-bromoimmonium bromide 128 into a pyrroloazepine 129.[57] However, due to the tertiary character of the halide, the reaction did not proceed via a β-bromoenamine.





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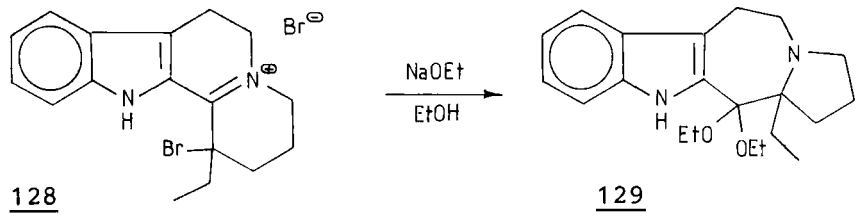
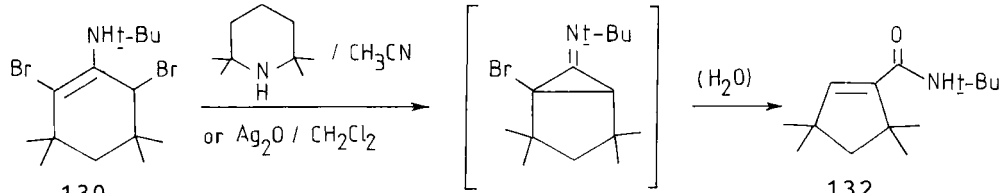


128 129

8. Favorskii-Type Rearrangement

The base-induced Favorskii rearrangement of α-haloketones to afford carboxylic acid derivatives has been extensively studied.[58-60] During the last decade, this rearrangement was also encountered with the corresponding nitrogen analogs, i.e. α-haloimines. Imines do not normally tautomerize to enamines except when conjugation is possible to relieve excessive steric hindrance in the imino form as in the case of dibromoenamine 130, which occurs exclusively in the enamine form. A Favorskii-type rearrangement could be carried out using 2,2,6,6-tetrame-



130 131 (?) 132

thylpiperidine in acetonitrile or silver oxide in dichloromethane[64] (yields of 16% and 25%, respectively). If a Favorskii-type mechanism was operative, the reaction would proceed via an intermediate brominated cyclopropylideneamine 131. Although such nitrogen analogs of cyclopropanones have been isolated or detected in reactions of α-haloimines with bases,[61,64] no indication of the intermediacy of bicyclic compound 131 was adduced.[64] Monobromination of the N-t-butyl imine of 3,3,5,5-te-

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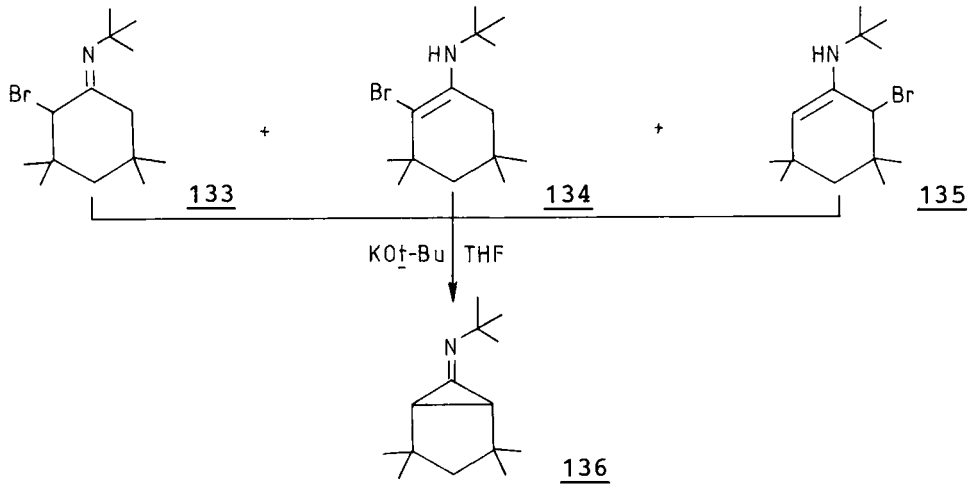
tramethylcyclohexanone with 2,4,4,6-tetrabromocyclohexadienone (TBCH)[5] leads to a mixture of α-bromoketimine 133, β-bromoenamine 134 and its isomeric allylic bromide 135.[67] When this mixture of monobromo compounds was treated with potassium t-butoxide in tetrahydrofuran, the first 2,3-disubstituted cyclopropylideneamine 136 could be isolated in 60% yield.[64] The relationship between α-haloimines, β-haloenamines and β-(alkylamino)allylic halides (and the corresponding deprotonated species) in the mechanistic interpretation of the Favorskii-type rearrangement has been thoroughly discussed in a previous review.[5]



9. Tautomerism of β-Haloenamines

β-Haloenamines containing at least one hydrogen atom connected to nitrogen sometimes occur in tautomeric equilibrium with their isomeric α-haloketimines. This phenomenon is encountered especially in substrates which have an N-acylated or N-aroylated nitrogen atom (enamides)[68] and which in addition, have an electron-withdrawing substituent at the α-position.[11,19,

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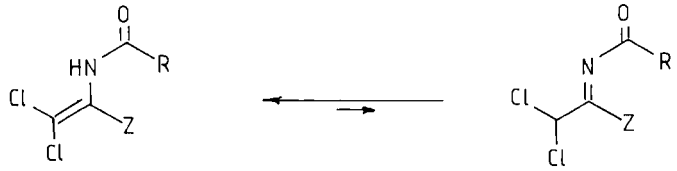
[20,68] In all cases, the equilibrium is predominantly shifted in favor of the β-haloenamino compounds (see also ref. 100).

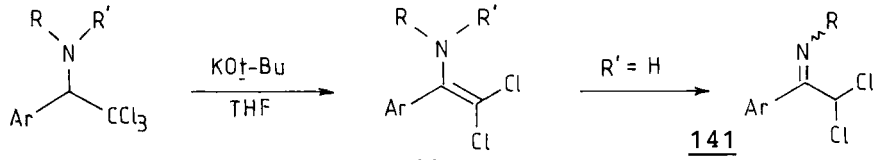


137 R=Ar, alkyl
Z=CN, COOR', $CONH_2$, ...

138

It is clear that, in such cases, the reactive behavior of the α-halogenated imine has to be considered when the reactivity of β-haloenamines is discussed. Hitherto no fundamental studies have been performed in this area and only speculative comments on the importance of either of both compounds in the study of their reactivity may be made.

Without the influence of a substituent which may cause conjugation, the α-haloimino form is the most stable. Phenyl substitution is not sufficient to prevent isomerization to the imine as shown by the base-induced dehydrochlorination of β,β,β-trichloroamines 139, which gave rise to α,α-dichloroketimines 144 via transient β,β-dichloroenamines 140 (R' = H).[41] If additional steric bulk is present at the nitrogen atom, e. g., N-



139 140 141

(R=i-Pr, s-Bu, cycloHex)

t-butyl α,α-dichloroacetophenone imine 142[41] and N-t-butyl α-chloropropiophenone imine 143,[69] these compounds are in equilibrium with the tautomeric enamines. β-Chloro-α-cyanoenamines 82 are easily synthesized from α,α-dichloroaldimines,[40] but they

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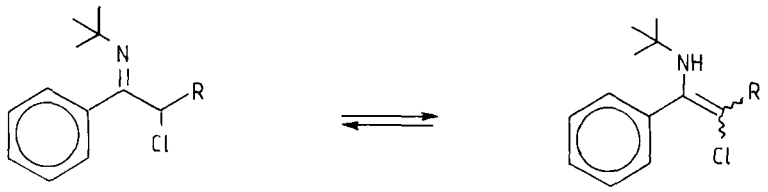
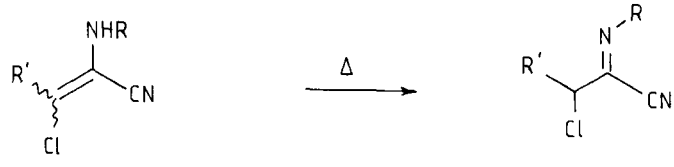


142 R=Cl
143 R=CH_3

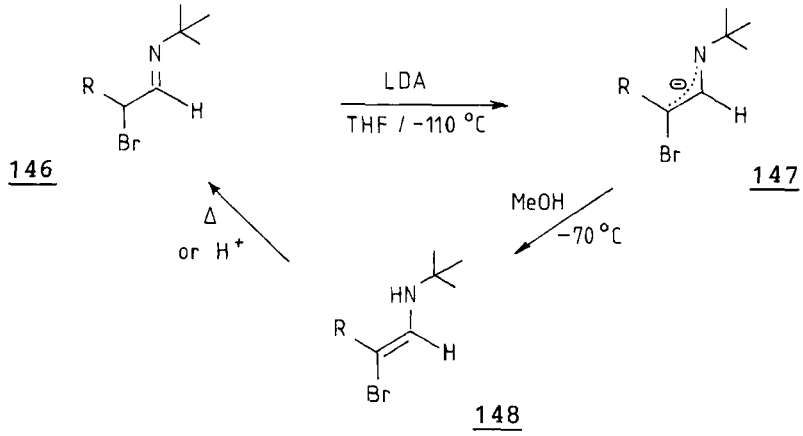
144 R=Cl
145 R=CH_3

rearrange thermally (e. g. gas chromatographic analysis) into α-chloroimidoyl cyanides 83, a phenomenon which was also observed with *non*-halogenated α-cyanoenamines.[70,71]



82 83

Recently, unconjugated secondary β-haloenamines (148) have been successfully generated under mild conditions, i.e. by α-deprotonation of α-bromoaldimines 146 with lithium diisopropylamide (THF; -110°C) and selective reprotonation with methanol at -70°C.[72] β-Bromoenamines 148 are obtained in 79-87% yield but rearrange to the parent α-bromoaldimines 146 by heating or treatment with acid.[72]



146 147 148

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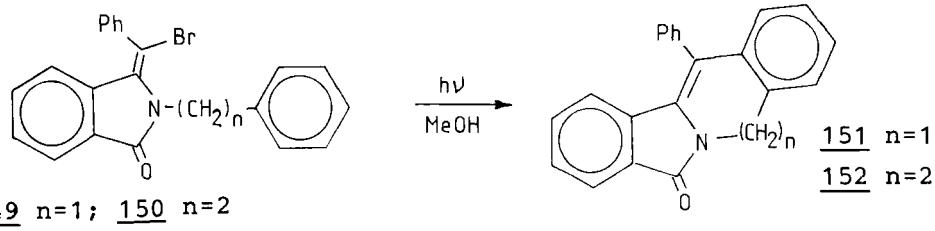
10. Photochemical Reactions of β-Haloenamines

Photochemical ring closures have been performed with β-bromoenamides 149 and 150, which in methanol give rise to 12-phenylisoindolo-[2,1-b]-isoquinolin-7(5H)-one 151 and 7,8-dihydro-13-phenyl-5H-isoindolo[1,2b][3]benzazepin-5-one 152.[8,73]



149 n=1; 150 n=2

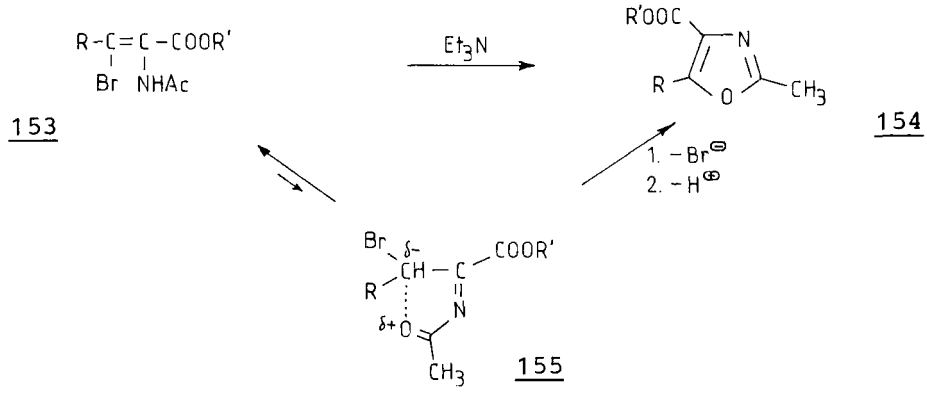
151 n=1
152 n=2

The same transformations were achieved by treatment of 149 and 150 with hydroxide in ethylene glycol, but various side-products were also formed.[8,73] As already mentioned, photolysis in methanol of the N-unsubstituted enamide 5 led to the corresponding β-methoxyenamide 6.[8]

11. Synthesis of Heterocyclic Compounds from β-Haloenamines

11.1. Oxazoles

β-Halogenated N-acyl enamines 153 are readily converted to functionalized oxazoles 154 by intramolecular condensation in the presence of a tertiary amine.[74] This cyclization can be ex-



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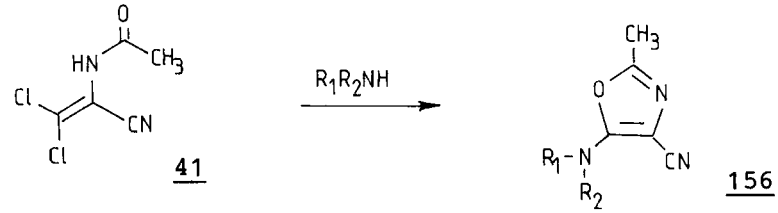
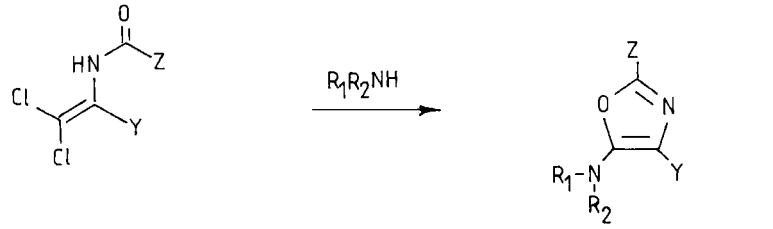
plained by attack of the acetyl oxygen on the brominated α-carbon atom of the tautomeric N-acetyl α-bromoketimine. With secondary amines and β,β-dihalogenated enamides (41), the same reaction takes place but an additional formal substitution of the halide by the amine occurs.[10,11,19,20,27,31] A similar reaction was observed with anilines.[19,20] Comparable oxazole

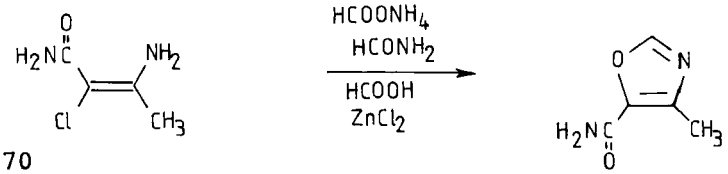


41 156



157	Z=CCl_3; Y=CN	158	Z=CON_1R_2; Y=CN
159	Z=CH_2Cl; Y=CN	160	Z=$CH_2NR_1R_2$; Y=CN
161	Z=CH_2F; Y=CN	162	Z=CH_2F; Y=CN
56	Z=Ph; Y=COOMe	163	Z=Ph; Y=COOMe
164	Z=alkyl; Y=CONHCOR	165	Z=alkyl; Y=CONHCOR
166	Z=Me; Y=$CONH_2$	167	Z=Me; Y=$CONH_2$
168	Z=Me; Y=COOMe	169	Z=Me; Y=COOMe

syntheses using β-haloenamines are the formylation and ring-closure of β-chloroenaminoamide 170 to give 171[75] and the silver ion induced cyclization of β,β-disulfenylated enamides 31, obtained by substitution of β,β-dichloroenamides 9 with thiols in the presence of a base.[18]



170 171

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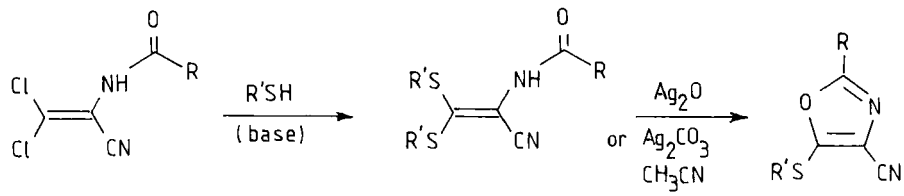
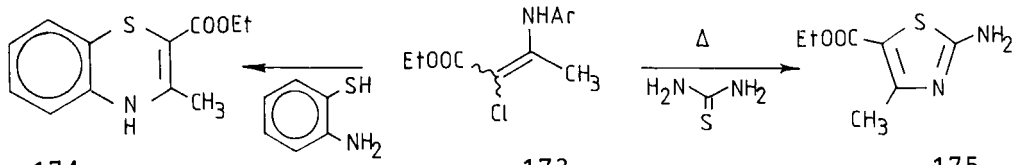


9 31 172

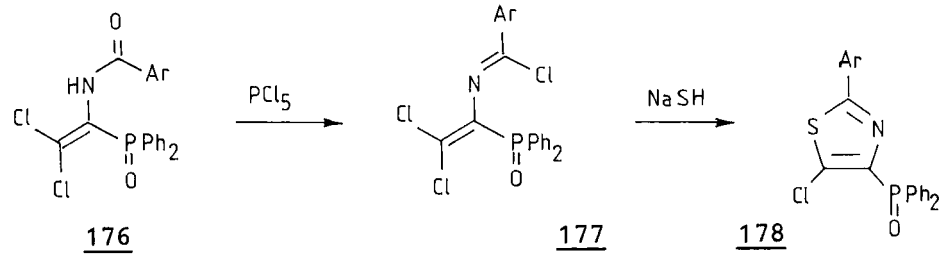
11.2. Thiazoles and other Sulfur Containing Heterocycles

Condensation of β-chloroenaminoesters 173 with thiourea or o-aminothiophenol leads to initial displacement of the chloride by the sulfur nucleophile (*vide supra* : sulfur nucleophiles) after which the remaining amino group of the entering group undergoes an intramolecular Michael addition with subsequent expulsion of the elements of the substituted aniline. These condensations yield 2-aminothiazole derivative 175 and 1,4-benzothiazine derivative 174.[7]



174 173 175

Phosphorylated β-haloenamide 176 is transformed into thiazole 178 by a two-step sequence, namely conversion into imidoyl chloride 177 and treatment with sodium hydrogen sulfide.[76]



176 177 178

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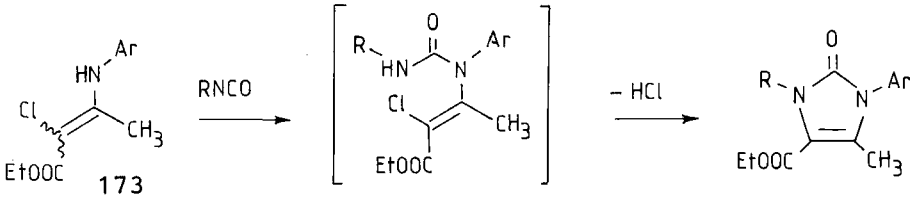
11.3. Imidazolinones and Imidazoles

Imidazolinones 180 are synthesized by the reaction of β-chloroenaminoesters with phenyl isocyanate or cyclohexyl isocyanate via cyclization of the initial adduct 179.[77] The N-cyclohexyl derivative requires additional treatment with base (Et_3N/ether) in order to liberate it from its salt, the form in which it is formed. A similar cyclization which, however, leads to N-monosubstituted imidazolinones 181, is the reaction of aro-

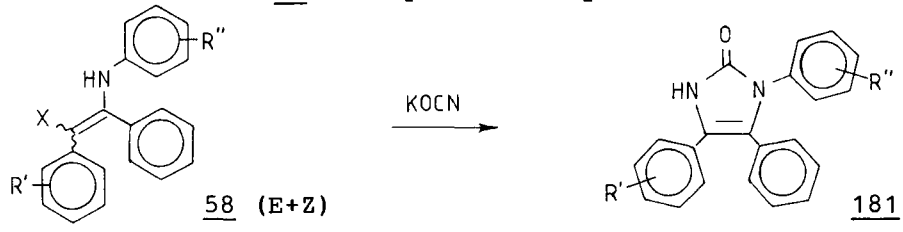


173 R=Ph, cyclohexyl

179

180 Ar=Ph, p-MeC_6H_4, p-ClC_6H_4, p-$MeOC_6H_4$

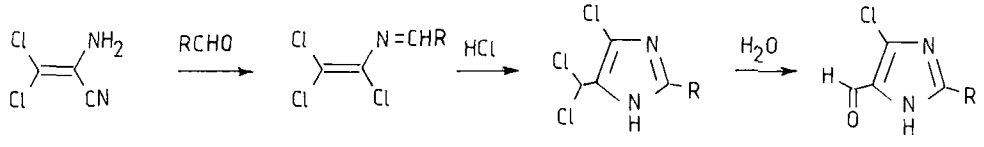
matic β-haloenamines 58 with potassium cyanate.[33] Derivatiza-



58 (E+Z)

181

tion of β,β-dichloroenamine 25 to azadiene 182, followed by treatment with dry hydrogen chloride in ether results in cyclization to imidazole 183, which is hydrolyzed to the formyl-substituted derivative 184.[9]



25 182 183 184

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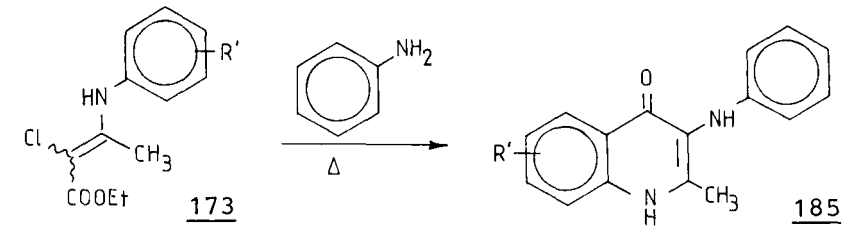
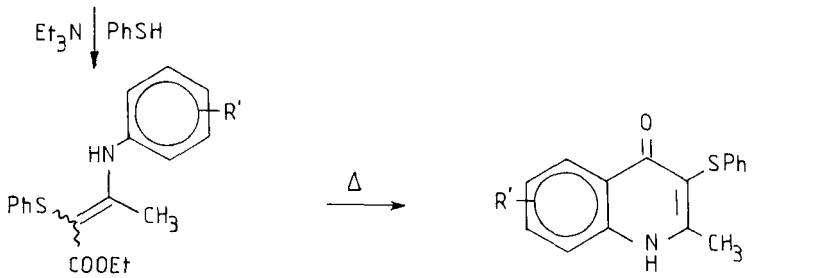
11.4. Various Other Nitrogen Heterocycles

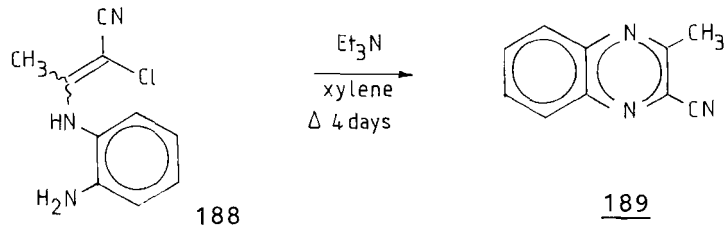
β-Chloroenaminoesters 173 undergo nucleophilic substitutions with anilines in ethanolic solution[7] but in the absence of solvent and an excess of aniline, they produce heterocycles 185.[25] The reaction most probably occurs via the substitution product, which undergoes thermal ring-closure, as evidenced by the substitution of the halide with thiophenol and subsequent thermal cyclization (187).[25] A slow thermal cyclization occurs when β-chloroenaminonitrile 188 is heated in toluene for four days in the presence of triethylamine to afford quinoxaline derivative 189 (Preparation 6).[24] β-Chloroenaminoester 190,



173 185



186 187



188 189

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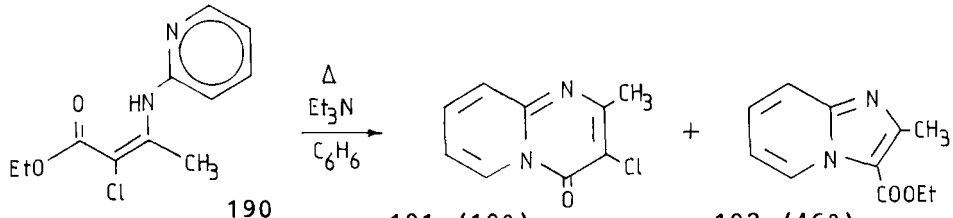
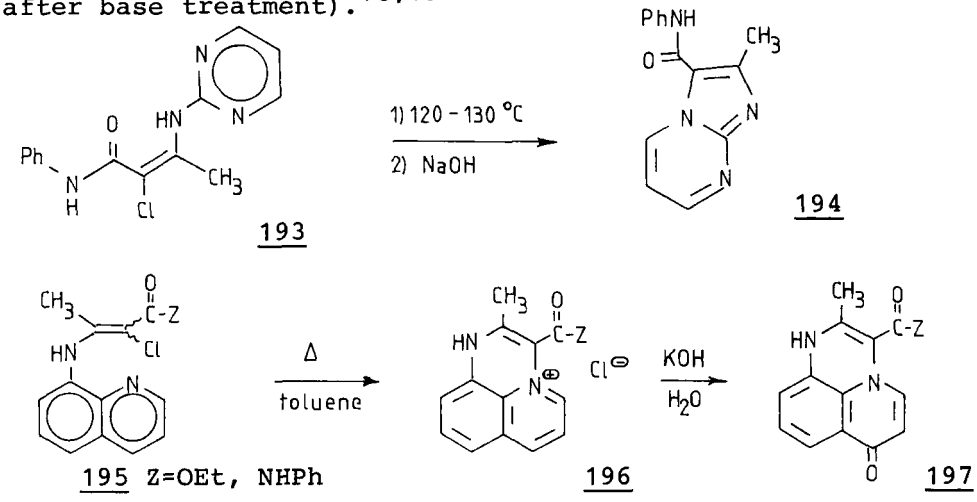
obtained by condensation of ethyl 2-chloro-3-oxobutyrate with 2-aminopyridine in benzene, suffers ring closure to afford two heterocyclic products, namely 3-chloro-2-methyl-4H-pyrido[1,2-a]-pyrimidin-4-one 191 and 3-ethoxycarbonyl-2-methylimidazo[2,1-a]-pyridine 192.[78] More drastic conditions are required to induce



190 191 (10%) 192 (46%)

ring-closure of β-chloroenaminoamide 193 and related compounds 195, which yield 2-methyl-3-phenylcarbamoylimidazo[1,2-a]pyri-midine 194 and pyridoquinoxaline derivative 197, respectively (after base treatment).[78,79]



193 194

195 Z=OEt, NHPh 196 197

Three-membered nitrogen heterocycles are available from α-azido-β-chloroenamine 199 which undergoes ring-closure to afford thermally labile azidoazirine 201 via transient chloroazirine 200.[80]

A special kind of cyclization between the amido moiety of enamides 202 and the α-substituent has been performed with pyri-

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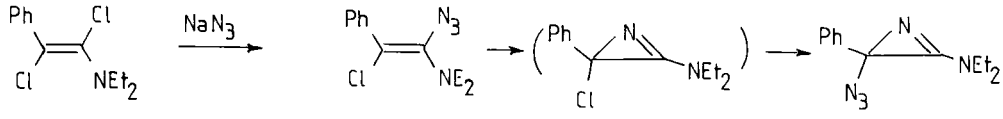
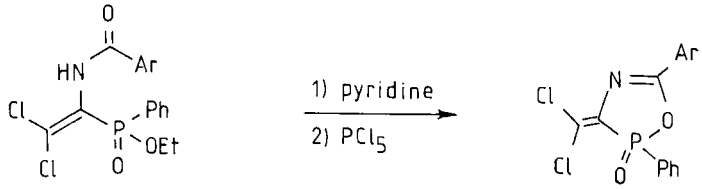


198 199 200 201

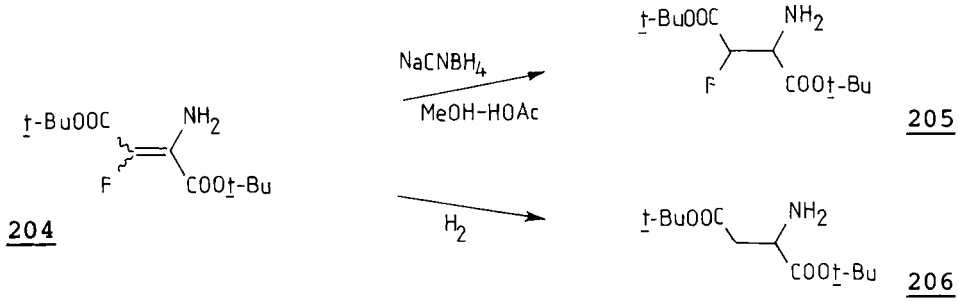
dine and phosphorus pentachloride, yielding phosphorylated heterocycles 203.[81]



202 203

12. Reductions of β-Haloenamines

Not much information is available on reduction of β-haloenamines. The highly functionalized β-fluoroenamine 204, which occurs as a varying mixture of geometrical isomers depending upon the synthetic procedure used, is reduced with sodium cyanoborohydride in methanol/acetic acid to afford di-t-butyl monofluoroaspartate 205, in which the erythro isomer constitutes the major component (Preparation 7).[82]



204 205 206

Catalytic hydrogenation of the same substrate 204 also removed the fluorine atom and leads to di-t-butyl asparate 206.[82] A similar reduction of the halide and the double bond is ob-

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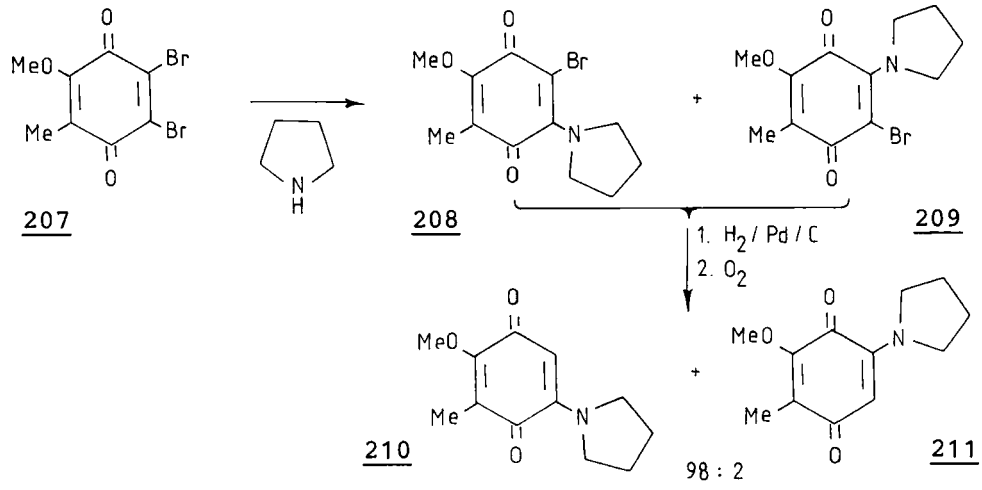
tained with quinoidal isomers 208 and 209, obtained from the addition-elimination reaction of pyrrolidine with quinone 207.[83] The reduction products are further oxidized to afford a 98:2 mixture of quinones 210 and 211 (total yield 97% from 207).



13. Halogenation of β-Haloenamines

β-Haloenamines behave like ordinary enamines where halogenation is concerned. Most of these halogenations have been dealt with in the previous review on the synthesis of β-haloenamines.[3] For the sake of completeness, some general considerations are presented here again.

The electrophilic addition of chlorine or bromine to β-haloenamines produces adducts which can be isolated as such (212)[84] or which are converted into β,β-dihaloimmonium halides (213).[85] When there are β-hydrogen atoms available, base treatment converts them into β,β-dihalogenated enamines (214).[21,93] When the initial adducts are treated with nucleophilic agents, the α-chloroamines are converted into α-substituted amino compounds.[86,87] As an example, β-bromoenamide 215 is brominated with

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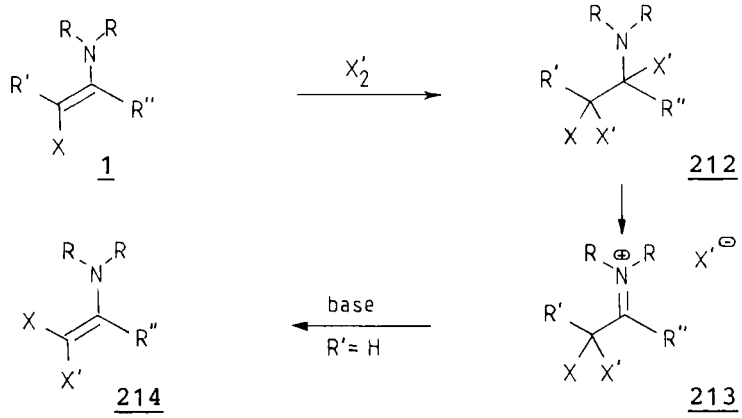
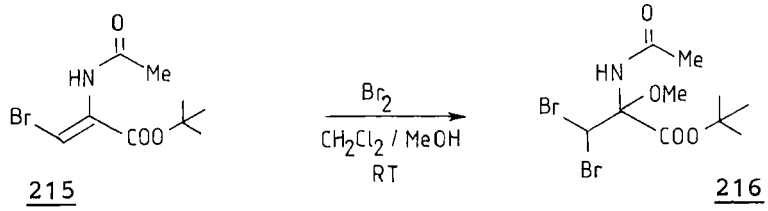


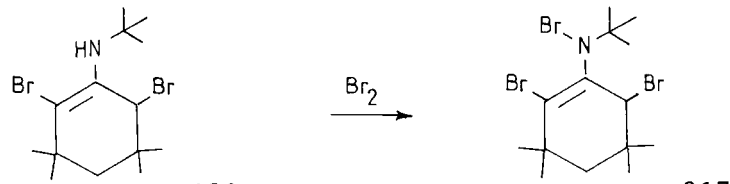
1 212 214 213

bromine in dichloromethane containing methanol, to afford adduct 216.[87] This reaction is a part of a reaction sequence leading to penicillin and cephalosporin antibiotics.[87] A sin-



215 216

gle case of N-bromination with bromine is reported with dibromoenamine 130 which affords tribromo compound 217.[88] A rather



130 217

unusual allylic bromination with bromine is obtained with cyclic enaminone 218.[48] The resulting bromo compound 219 aromatized to 220 by heating with acetic anhydride and p-toluenesulphonic acid. This reaction is used in a sequence leading to the synthesis of maytansine.[48] It is noteworthy to mention here in this context that E.J. Corey's group circumvented the halogenation-dehydrohalogenation (aromatization) step in a re-

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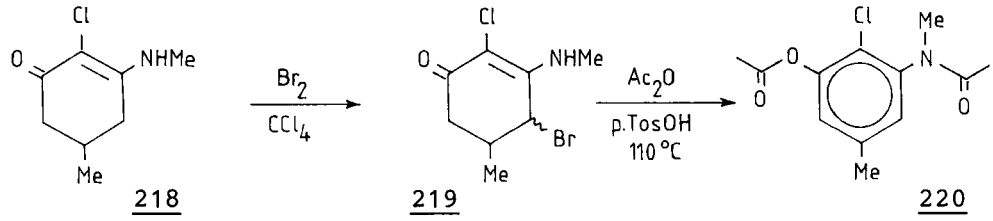
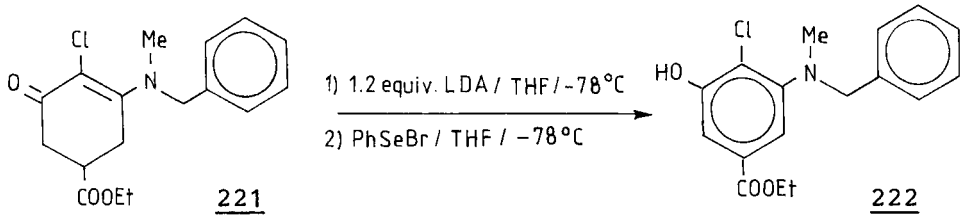


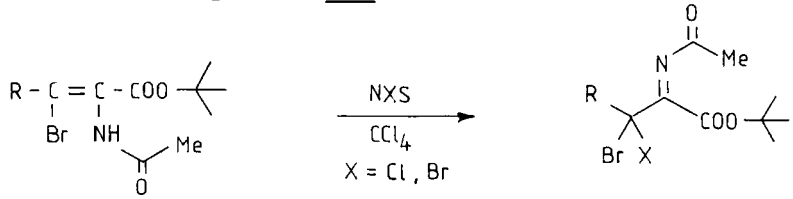
218 219 220

lated approach to maytansine by aromatization of β-chloroenaminone 221 using an intermediate phenylselenylation, allowing this step to take place under very mild conditions.[94]

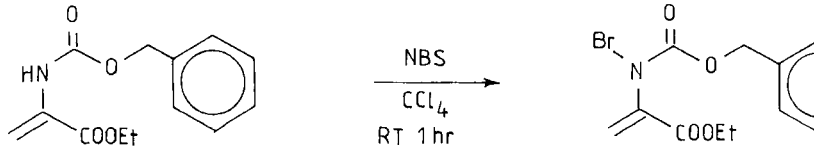


221 222

Halogenations of β-haloenamines with N-halosuccinimides were only reported for tautomerizable substrates such as enamides. The reaction of 223 in apolar medium leads to α,α-dihalogenated imino compounds 224.[74,89] In some cases, N-bromination is observed with N-bromosuccinimide.[90] This allowed substitution of the nitrogen atom with for example azide by a displacement reaction (NaN_3/DMF) but the labile N-azido compounds



223 224



225 226 (100%)

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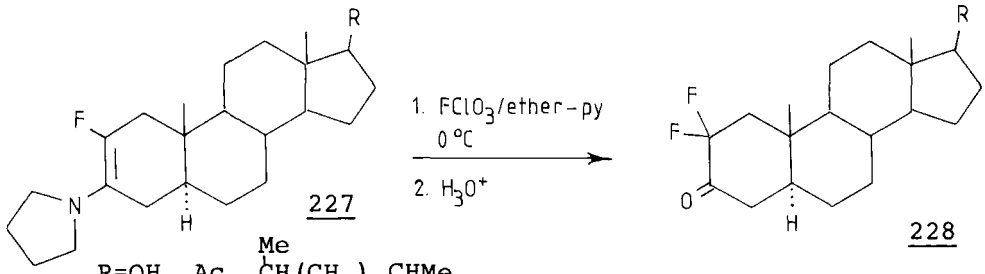
rearrange into the β-azidoenamine compounds.[90]

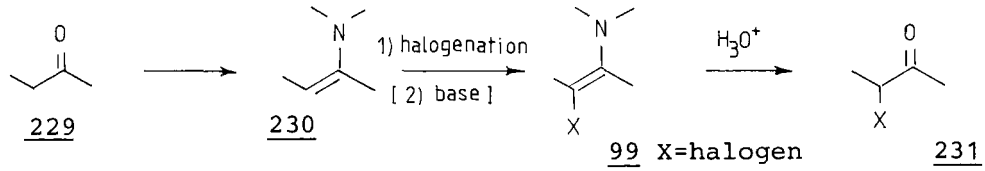
Especially in the steroidal field have fluorinations of β-fluoroenamines been applied with perchloryl fluoride, but the resulting nitrogen derivatives were hydrolyzed in acidic medium to α,α-difluorocarbonyl compounds 228.[91,92]



R=OH, Ac, $\overset{Me}{\overset{|}{C}}H(CH_2)_3CHMe_2$

14. Hydrolysis of β-Haloenamines

A sequence involving masking a carbonyl compound (229) as an enamine (230), followed by halogenation (99) and hydrolysis constitutes a pathway to α-halocarbonyl compounds (231).[93,95,98] This set of reactions deserves special attention if specific halogenations, via enamines, not applicable to carbonyl compounds, are attainable. Up to now, this route has not found widespread application because of the lack of specific halogenations of enamines and because of the fact that the same sequence via halogenations of imino compounds was proven to be more successful.[5]



α-Bromo-α-chloroketones 234 were synthesized by chlorination of enamine 232 to give, after base treatment, β-chloroena-

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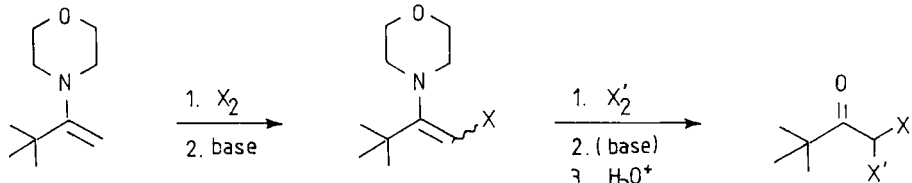
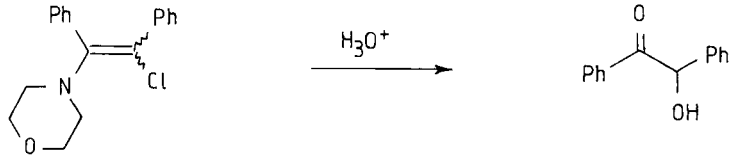
mine 233 which was subsequently brominated and hydrolyzed.[93]



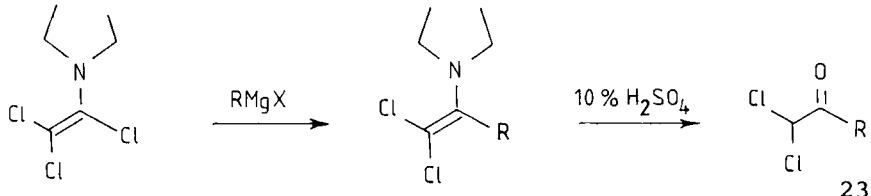
232 233 234 (X, X'=Cl or Br)

Evidence of side-reactions during hydrolysis is limited to a report in which the formation of α-hydroxyketones from β-chloroenamines is mentioned.[95] The production of α-hydroxy ketone 236 from β-chloroenamine 235 is probably caused by the activating influence of the phenyl substituent on the halogenated carbon atom.[95]



235 (E+Z) 236

Another valuable source of α-halogenated carbonyl compounds is the reaction of trichlorovinylamines 237 (easily obtained from trichloroacetyl chloride[96]) with Grignard reagents to give β,β-dichloroenamines 238, which are hydrolyzed into 1,1-dichloro-2-alkanones 239.[97]



237 238 239

R=Me, Et, C_5H_{11}, Ph, i-Pr, vinyl, allyl

15. Derivatives of β-Haloenamines

Various reactions can be performed in which the β-haloena-

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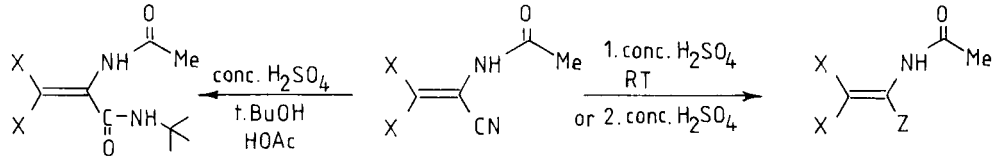
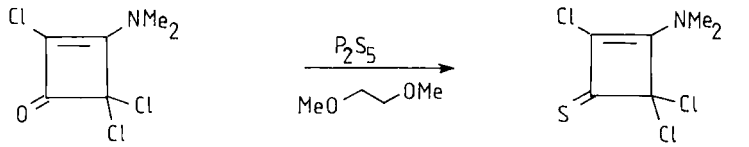
mino moiety remains unaltered, but in which specific transformations of more reactive functional groups take place. In some instances, the intrinsic β-haloenamino character is transformed into a derivative by modification of the nitrogen substituents, e.g. the conversion of β-haloenamines into β-haloenamides.

Functional group transformations of the α-cyano moiety in β,β-dihaloenamides 240 has been accomplished with sulfuric acid under variable conditions.[29] The reaction of cyclic enaminone



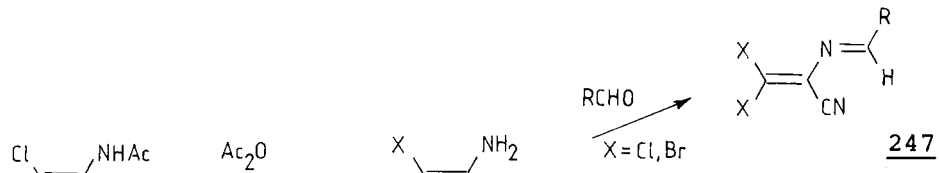
241 240 X = Cl, Br 1) 242 Z=$CONH_2$ 2) 243 Z=COOH

244 with P_2S_5 produces enaminothione 245.[99] N-Unsubstituted β,β-dihaloenamines 246 are easily acetylated with acetic anhy-



244 245

dride or converted into azadienes 247 and 248 by reaction with aldehydes or triethyl orthoformate.[9,10] N-Alkylation is only



41 246 247 248

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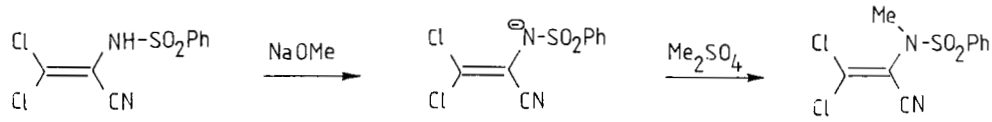
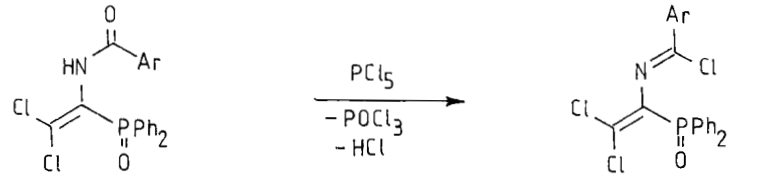
encountered in the methylation with dimethyl sulfate of the sodium salt of enamide 49.[11] More drastic derivatizations are



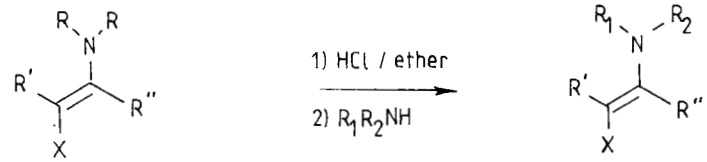
49 249 250

the conversions of enamides 176 into the reactive imidoyl chlorides 251 with phosphorus pentachloride.[76] Another derivatiza-



176 251

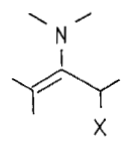
tion is the exchange of the amino moiety in β-chloroenamines by electrophilic addition of hydrogen chloride in ethereal medium to generate α-chloroimmonium chlorides which are subsequently reacted with a secondary amine.[139,140]



1 (X=Cl) 1' (X=Cl)

16. β-Aminoallylic Halides

β-Aminoallylic halides 2 are isomers of β-haloenamines in which the halide is in an allylic position while the amino function is part of an enamine. Attention is paid to this set of



2 X=halogen

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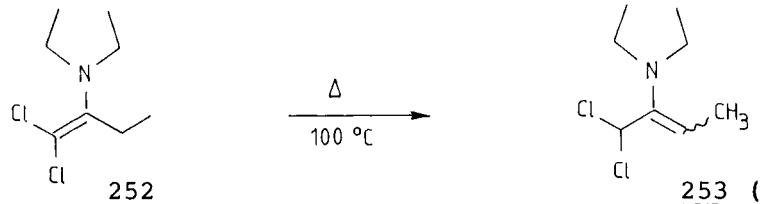
functionalities because of the structural relationship with β-haloenamines and α-haloimines.[5] The discussion of the reactivity of β-haloenamines (and α-haloimines[5]), makes it clear that some results can be understood in terms of the transient β-aminoallylic halides. Essentially no systematic studies have been directed towards this isomerization process. Outside of product analysis in some reactions, the only report which lends support to this hypothesis is the thermal isomerization of β,β-dihaloenamine 252.[97] It should be stressed here that the ma-



252 253 (E+Z)

jority of β-haloenamino compounds prepared hitherto and discussed in the whole review are not capable of displaying this isomerization because of the absence of hydrogens at the appropriate allylic position.

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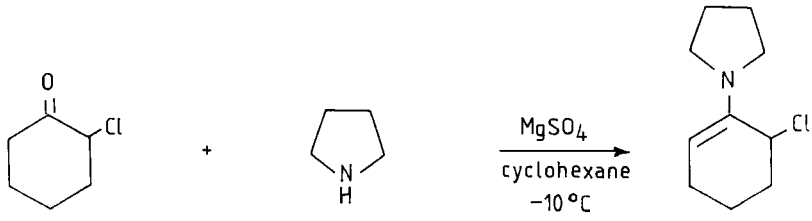
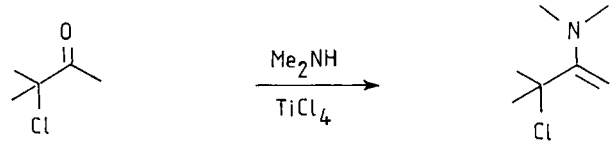
16.1. Synthesis of β-Aminoallylic Halides

Besides the aforementioned thermal isomerization of β-halogenated enamines (e.g. 252),[97] β-aminoallylic halides are synthesized by condensation of α-halogenated carbonyl compounds with secondary amines.[91,101-104] This condensation is best performed in dilute media at low temperature (e.g. 254 → 256) [101,102] or under the influence of titanium(IV) chloride which acts as a Lewis catalyst and effective drying agent by removal of water formed during the reaction as titanium dioxide (e.g. 257 → 258).[102-104]

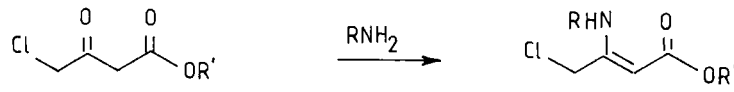


254 255 256



257 258

Condensation of γ-chloro-β-ketoesters 259 with primary amines leads to allylic chlorinated enaminoesters 260 because of the stabilizing effect of conjugation.[107] The resulting products are labile and undergo spontaneous ring-closures (vide infra).[105-107] Care should be taken not to generalize these



259 260

condensation reactions because the overwelming number affords (or may afford) a variety of other results, among others dehydrohalogenation, nucleophilic substitution, elimination-addition reaction, β-haloenamine formation, Favorskii rearrangement, rearrangement via transient α-aminoepoxides, etc...[3]

Allylic halogenation of certain enamines offers an alternative route to β-aminoallylic halides. Allylic bromination has been accomplished with enamines, e.g. 261, and N-bromosuccinimide[108,129] or bromine.[48]

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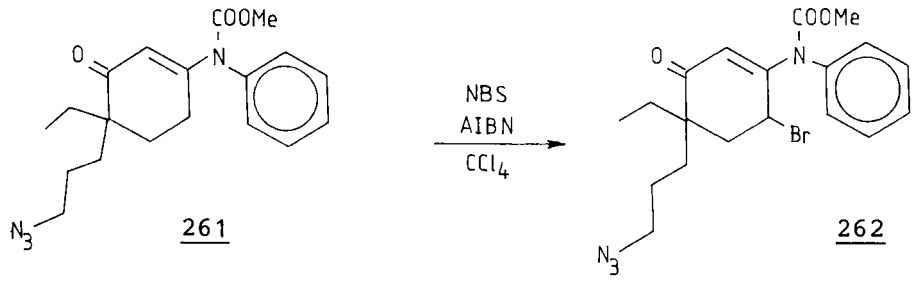
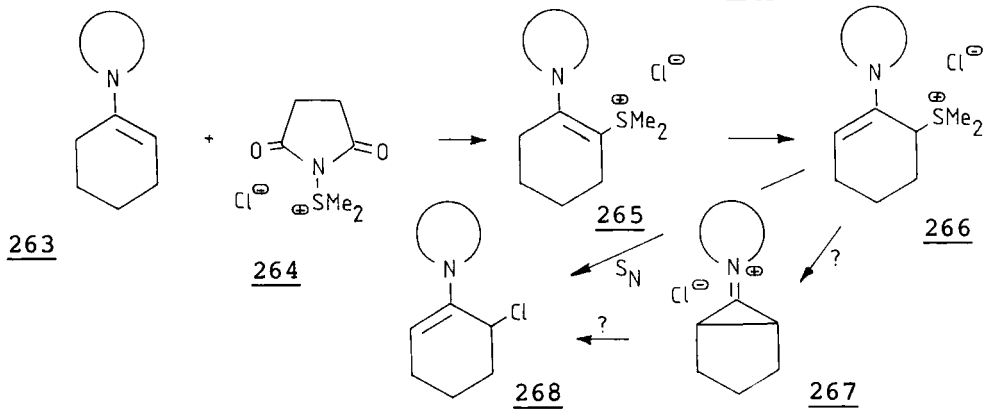


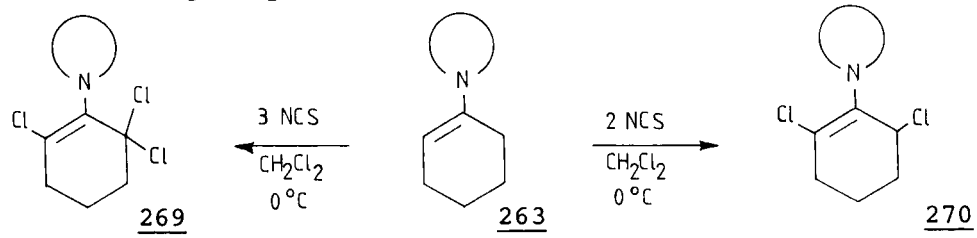
261 262

Chlorination of enamines derived from cycloalkanones and cyclic secondary amines (263) proved to be successful with dimethyl(succinimido)sulfonium chloride 264. The reaction proceeds via enamino derivatives 265 and 266, and finally yields allylic chloride 268 by a substitution reaction or through the intermediacy of cyclopropylideneammonium salt 267.[109,110] Po-



263 264 265 266 268 267

lyhalogenation of 263 with N-chlorosuccinimide leads to substrates having vinylic as well as allylic halogens.[109,110]



269 263 270

Another recent method of allylic chlorination of enamines 271 involves chlorination with phosphorus pentachloride and a sulfoxide 272.[111] The method, which was developed as a deoxy-

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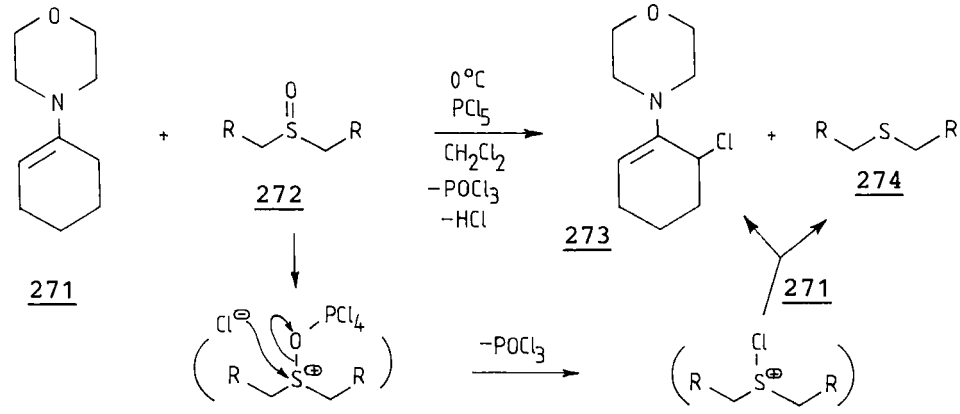
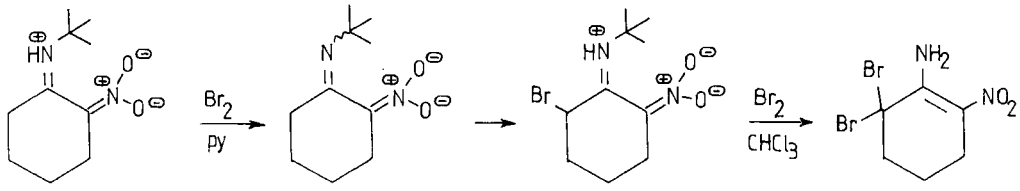
genation reaction of sulfoxides to sulfides, is mechanistically explained in terms of the transient formation of a chlorosulfonium derivative 276 which is responsible for the chlorination of 271.[111]



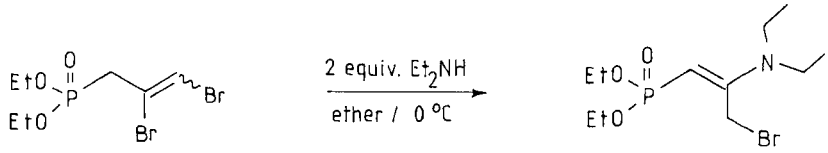
271 272 273 274

Finally, the allylic bromination of 1-nitro-2-t-butylaminocyclohexene 277 with bromine furnished monobromo compound 279 which was further brominated to dibromoenamine 280.[112]



277 278 279 (67%) 280 (53%)

A third approach to β-aminoallyl halides is the condensation of secondary amines with vinylic halides 281; this reaction entails an elimination-addition mechanism engendered by the presence of the phosphorus substituent.[113,114] This reac-



281 282

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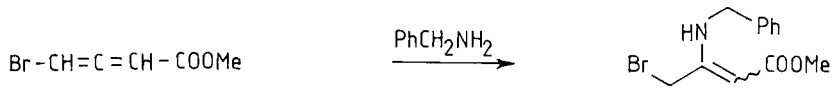
tion parallels the addition of benzylamine to allenic bromide 283.[105] Less general examples related to this third approach

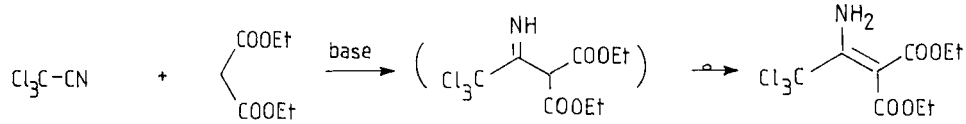


283 284

to β-aminoallyl halides are the reaction of ammonia or methylamine with perchlorocyclopentenone[115] and the conversion of β,γ-fluorinated-α,β-unsaturated esters into β-amino-γ-fluorinated-α,β-unsaturated esters.[116]

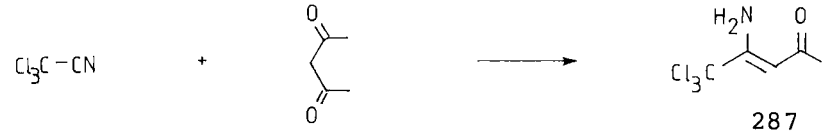
Besides the three approaches mentioned above, β-aminoallyl halides have been prepared by various methods, some of which are presented in the following paragraphs.

Addition of diethyl malonate to trichloroacetonitrile affords imine 285, which tautomerizes to the more stable conjugated enamine 286.[117,145] Acetylacetone also gave a similar



285 286

reaction in methanol, saturated with sodium acetate, but monoacetyl derivative 287 was obtained in 90% yield.[118] Other ac-



287

tive methylene functions as in malonitrile and ethyl cyanoacetate (289) have been condensed with α-fluorinated amines 288 to generate β-aminoallylic halides 290.[119] Cycloaddition of ynamine 291 with halogenated olefins provides an entry into

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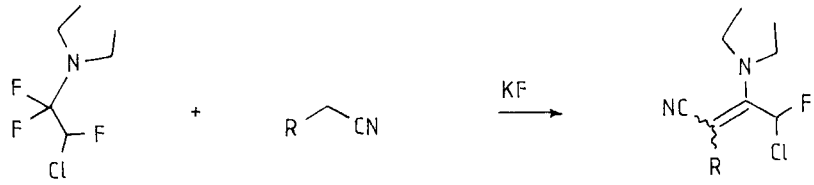
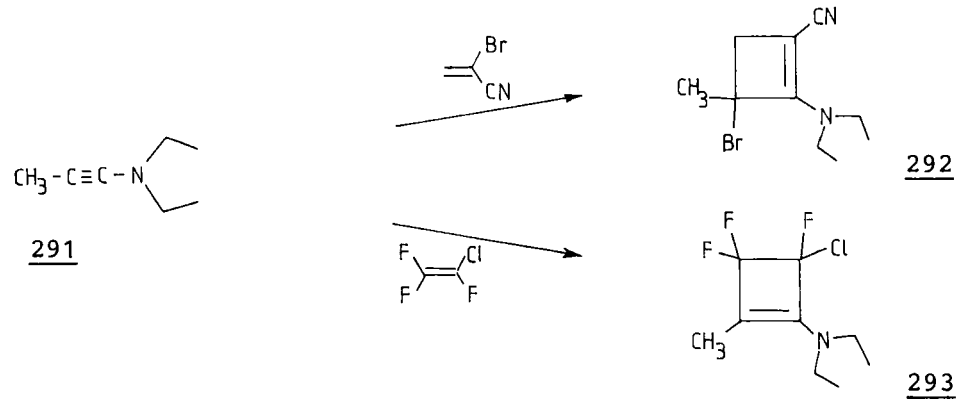


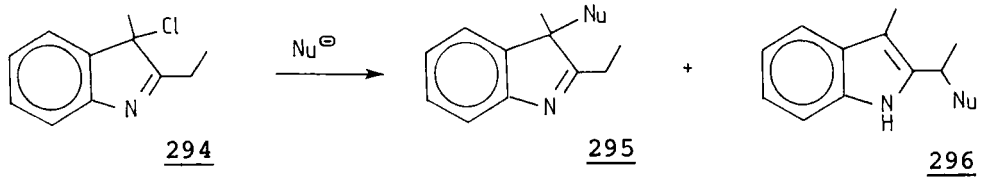
288 289 R=CN, COOEt 290 R=CN, COOEt

four-membered rings, which can undergo allylic rearrangement to the more stable isomer.[120,121] Many reactions of chloroindole-



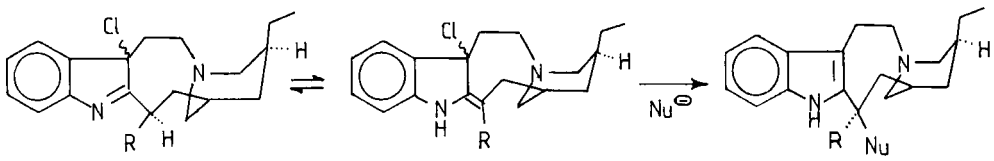
291 292 293

nines and 3-chloroindol derivatives with nucleophiles have been found to result in substitution at the originally unhalogenated site (see 296).[127] This phenomenon has been amply discussed in



294 295 296

one of the previous reviews in this series.[5] In several cases



297 R=H, COOMe 298 299 (Nu=CN or OAc)

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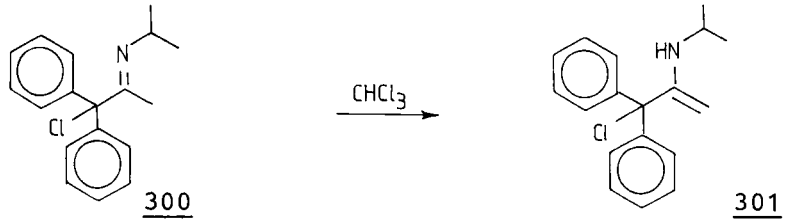
these results have been interpreted in terms of the intermediacy of aminoallylic halides, e. g. 298 (cleavamine series).[5,122-125,127,142-144] An unusual case of tautomerism has been very recently observed for α-chloroketimine 300, a stable compound which crystallizes in octahedral form. When dissolved in chloroform, the imine gradually tautomerizes completely in about 0.5 hr. to the corresponding β-aminoallylic halide 301, which is only stable for a short time and which seems to be the first



300 301

identified secondary enamine with a terminal double bond and a halogen in an allylic position.[128]

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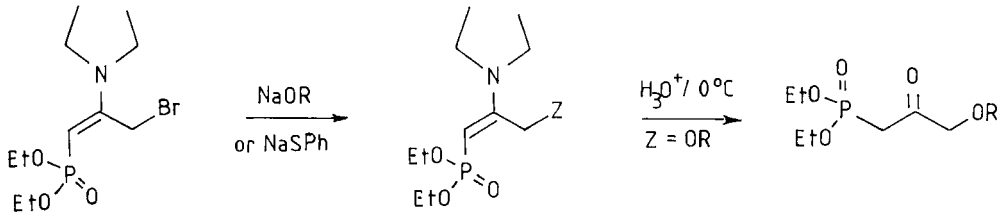
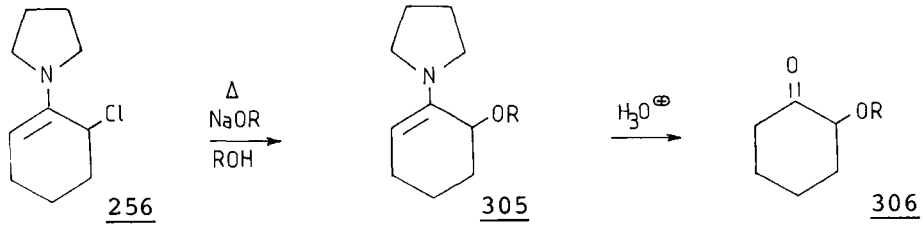
16.2. Reactivity of β-Aminoallylic Halides

Nucleophilic substitution of β-aminoallylic halides is by far the most studied reaction. Alkoxides,[101,113,120] phenolates,[113] thiolates,[113] secondary amines,[103,131] ammonia,[126] iodide,[131] have been utilized in such substitution reactions. These reactions enable the synthesis of α-functionalized carbonyl compounds, e. g. 304 and 306.[101,113]



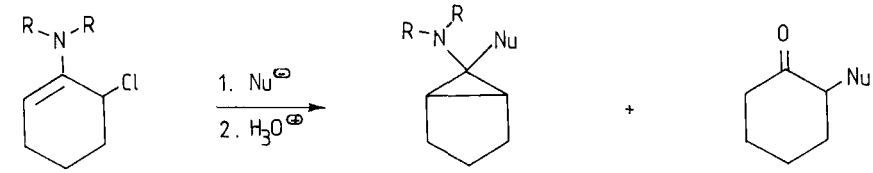
282 302 Z=OR 304

303 Z=SPh

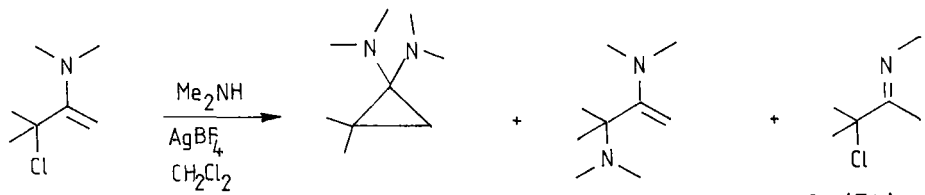


256 305 306

Another important feature of β-aminoallylic halides is their ability to undergo ring-contractions to cyclopropane derivatives in a manner closely related to the Favorskii rearrangement. The reaction is induced by nucleophiles such as hydride, secondary amines and a great variety of organometallic reagents (Li, Mg, Cu) and leads to aminocyclopropane derivatives 308.[101-104] The ring-closure reaction does not take place exclusively, but occurs in competition with nucleophilic substitution (Preparation 8).[102,103] Only with silver tetrafluoroborate and di-



307 308 309



258 310 (20%) 311 (56%) 312 (7%) (ox. product)

methylamine in ether could 3-chloro-2-dimethylamino-3-methyl-1-butene 258 be converted in quantitative yield into aminal 310.[103] The reaction of 307 with organometallics leads to endo 6-alkyl-6-dialkylaminobicyclo[3.1.0]hexanes 308, exclusively, while with lithium aluminum hydride a mixture of isomers (endo/exo) is obtained.[102] The formation of a three-membered ring is explained in terms of a mechanism proceeding via an immonium derivative

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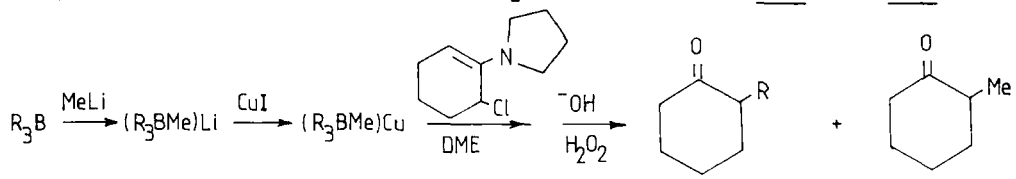
(e. g. 319) or via a concerted mechanism.[102] The preferential formation of the endo isomer might be explained by selective attack of the immonium intermediate at the least hindered side. An attempted formation of cyclopropanes by reaction of β-aminoallylic chloride 256 with copper(I) methyltrialkylborates 315 was unsuccessful and yielded alkylated and methylated substrates, identified as their carbonyl derivatives 316 and 317.[130]



313 314 315 316 317

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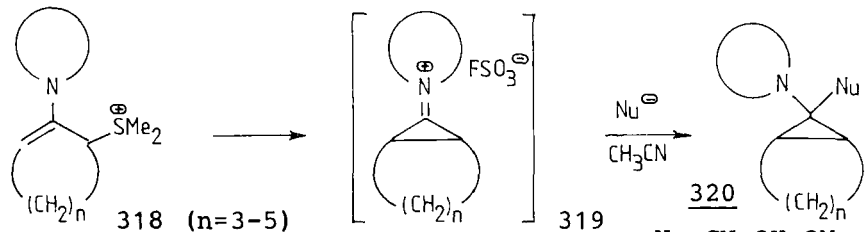
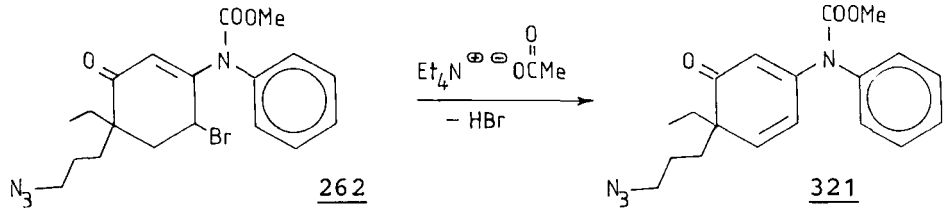
For comparison, the synthesis of bicyclic compounds 320 by analogous nucleophilic interaction on enamine salts 318 is mentioned here.[132-134,136-138,141]



318 (n=3-5) 319 320 Nu=CN, OH, OMe, NR_1R_2

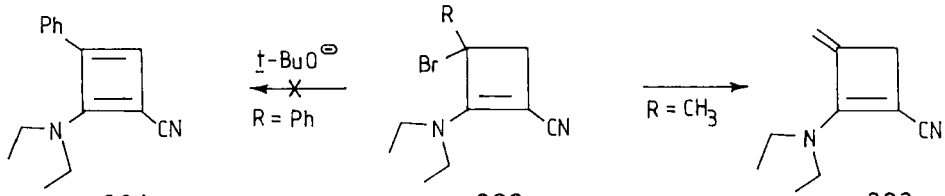
1,2-Dehydrohalogenation appears mainly in cyclic systems (e. g. 262)[48,108,129] and often leads to aromatization.[48,129]



262 321

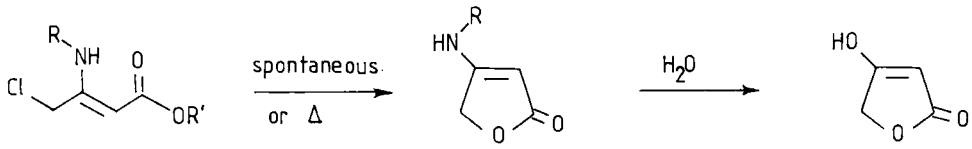
A particular case is four-membered ring 322, which with strong bases, gave dehydrobromination to afford the exocyclic olefin (323), while no cyclobutadiene 324 could be prepared with

phenyl derivative 322 (R = Ph).[120]



324 322 323

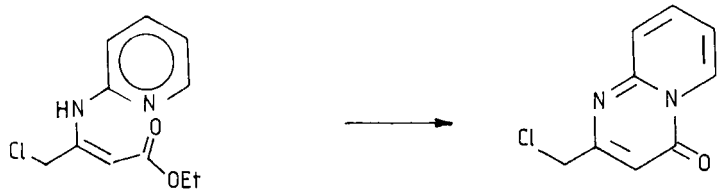
A valuable synthetic reaction is the cyclization of β-aminoallyl halides, containing an ester function in the γ-position.[105,107] These allylic halides 260 cyclize spontaneously or, more rapidly, under the influence of heat to generate unsaturated aminolactones 325, which are precursors to tetronic acid



260 R=Ph, $PhCH_2$
R'=Me, Et

325 326

326.[106] However, when the amino substituent can interact with the ester function as in pyridino derivative 327, the cyclization toward the halide does not take place but furnishes a pyrimidone 328.[107]



327 328

17. Preparations

Preparation 1 : 2,2-Dimethyl-3-morpholino-3-pentene (71, R=t-Bu, R'_2N = morpholino, R" = H, E = CH_3).[37]

n-Butyllithium (4.5 ml of 1.3 M ether or hexane solution)

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was added to 1.24g (0.005 mol) of 4-bromo-2,2-dimethyl-3-morpholino-3-butene 69 (R = t-Bu, NR'R' = morpholino, R" = H) in 10 ml of tetrahydrofuran, at -70°C under nitrogen. After 10 min of stirring at -70°C, a solution of 0.78g (0.0055 mol) of methyl iodide in 1 ml of tetrahydrofuran was added rapidly, while the internal temperature was maintained at about -65 to -70°C. After the addition was completed, the reaction mixture was allowed to warm to room temperature (∿30 min) with stirring. The reaction mixture was then treated with 3 ml of 0.005 M aqueous sodium carbonate. The crude liquid was distilled to yield 0.67 g (75%) of 71 (R = t-Bu, NR'R' = morpholino, R" = H, E = CH_3), bp 62°C/0.75 mmHg.

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Preparation 2 : 1-Phenyl-2,3,3-trimethyl-1-butanone (75, R = t-Bu, E = CH_3).[38]

To a stirred solution of 0.91g (5 mmol) of 2-chloro-1-(dimethylamino)-1-phenylethylene 72[38] in 10 ml of tetrahydrofuran was added dropwise a solution of 12 ml (12 mmol) of t-butyllithium (1M in pentane) at -70°C under N_2. After 3 hrs at this temperature, a solution of 1.42g (10 mmol) of methyl iodide in 2 ml of tetrahydrofuran was added at -70°C, and then the reaction mixture was allowed to warm to room temperature with stirring. The reaction mixture was treated with 5 ml of 10% aqueous hydrogen chloride during 4 hrs at 40°C and subsequently extracted with ether, dried ($MgSO_4$) and distilled to give 0.72g (75%) of 1-phenyl-2,3,3-trimethyl-1-butanone 75 (R = t-Bu; E = CH_3), bp 77°C/0.5 mmHg.

Preparation 3 : (Z) Methyl 2-acetamido-2-butenoate (79)[39]

A solution of 0.30g (1.69 mmol) of methyl 3-chloro-2-acetamidoacrylate 34 in 5.2 ml of tetrahydrofuran was added dropwise over a period of 10 min to 2 equiv. of dimethylcopper lithium, prepared from 0.64g (3.36 mmol) of copper(I)iodide and 4.1 ml (6.72 mmol) of 1.65 M ethereal methyllithium, in 15 ml of tetrahydrofuran at 0°C. The reaction was allowed to proceed for 2 hrs at 0°C and then the reaction was quenched at 0°C with 2 ml of 3N HCl. After warming to room temperature, the reaction mixture was stirred into 125 ml of 3N HCl, which was subsequently saturated with sodium chloride. Extraction (5 x 30 ml) with chloroform, drying ($MgSO_4$ and simultaneous treatment with charcoal) and evaporation afforded a light yellow oil (0.26g; 100%) which consisted of pure (Z)-79.

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Preparation 4 : 4-Dimethylamino-3-butyn-2-one (94, $R_1 = R_2 = CH_3$; $R = CH_3CO$).[42]

A solution of 3.6g (0.09 gram atom) of potassium in 40 ml of dry t-butanol and 100 ml of dry tetrahydrofuran was dropped, with stirring over a period of 40 min., into a solution of 18.8g (0.10 mol) of 3-bromo-4-dimethylamino-3-buten-2-one 93 ($R = CH_3CO$; $R_1 = R_2 = CH_3$) in 50 ml of dry tetrahydrofuran (N_2 atmosphere; 0-5°C). After stirring for 1 hr at 0°C, the precipitated potassium bromide was removed by centrifugation and the reaction mixture was evaporated in vacuo (aspirator) at 10°C, leaving ca. 10g of a brown oil. Distillation at 10^{-4} torr and collection of the product in a cold trap at -70°C afforded 7.5g (75%) of 94 ($R_1 = R_2 = CH_3$; $R = CH_3CO$) as colorless crystals,

which melt at room temperature to a light-yellow oil. This ynone is stable for several months at -70°C but polymerizes at room temperature within 24hrs.

Preparation 5 : 6-Oxo-1,7,7-trimethyl-1-azaspiro[4.5]decane (124).[56]

To a stirred solution of 2.86g (16 mmol) of enamine 122 in 60 ml of dry ether was added at -70°C 2.56g (16 mmol) of bromine in 50 ml of cold (about -60°C) dry ether. After the addition was completed, the suspension of the α-bromoimmonium salt was allowed to warm to room temperature. The yellow reaction mixture was cooled to -20°C and 20 ml of 20% aqueous sodium hydroxide was added dropwise while stirring. The reaction mixture was stirred for 1hr and then stored for 48hrs at -18°C. After warming to room temperature, the mixture was extracted with ether, dried ($MgSO_4$), evaporated (crude yield 70%) and distilled to give 1.81g (58%) of spiro compound 124, bp 79°C/0.65 mmHg.

Preparation 6 : 2-Cyano-3-methylquinoxalin (189).[24]

A solution of 2.08g (0.01 mol) of 2-chloro-3-(2-amino)anilino-2-butenenitrile 188 and 5.0g (0.05 mol) of triethylamine in 200 ml of xylene was heated under reflux for 4 days. After cooling, the precipitated triethylammonium chloride was filtered and the solvent evaporated. The remaining solid was recrystallized from ethanol to afford 0.5g (29%) of yellow 189, mp. 151-152°C.

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Preparation 7 : Erythro-Di-tert-butyl β-Fluoroaspartate (205).[82]

A solution of 12g (46 mmol) of di-tert-butyl 2-amino-3-fluoro-2-butene-1,4-dioate 204 (mixture of E and Z isomers) in a mixture of 120 ml of dry methanol and 30 ml of dry acetic acid (distilled over P_2O_5) was treated with 3.2g (50 mmol) of sodium cyanoborohydride and the mixture was stirred for 16 hrs. The solution was then slowly added to 5% aqueous sodium carbonate and the water layer was extracted with ether. The ether extracts were dried ($MgSO_4$), the solvent evaporated, and the residue was dissolved in petroleum ether. Cooling the solution yielded 5.0g of erythro 205. From the mother liquor an additional 1.6g of erythro 205 and 0.02 g of threo 205 were obtained by column chromatography (silica gel; petroleum ether - ethyl acetate 2:1). Total yield of erythro 205 : 6.69g (55%), mp 53-55°C.

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Preparation 8 : Endo 6-(p-methoxyphenyl)-6-pyrrolidinobicyclo-[3.1.0]hexane (308, NR_2 = pyrrolidino; Nu = p-$MeOC_6H_4$) and 2-(p-methoxyphenyl)cyclohexanone (309, Nu = p-$MeOC_6H_4$).[102]

To a solution of 3g (0.016 mol) of 6-chloro-1-pyrrolidinocyclohexene 307 (NR_2 = pyrrolidino) in 25 ml of dry ether is added dropwise a large excess of p-methoxyphenylmagnesium bromide in ether. The temperature is kept at -10°C for 7hrs after which the reaction mixture is poured onto ice and hydrolyzed overnight with 20% sulfuric acid. Extraction with ether, drying ($MgSO_4$) and evaporation of the solvent gives 2-(p-methoxyphenyl)cyclohexanone 309 (Nu = p-$MeOC_6H_4$) which is purified by

passage through a column of neutral alumina (yield 37%). The aqueous phase is made basic with sodium bicarbonate and extracted with ether. Drying ($MgSO_4$) and evaporation of the solvent affords endo 6-(p-methoxyphenyl)-6-pyrrolidinobicyclo[3.1.0] hexane 308 (NR_2 = pyrrolidino; Nu = p-$MeOC_6H_4$) which is recrystallized from methanol, mp. 84°C (yield 62%).

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