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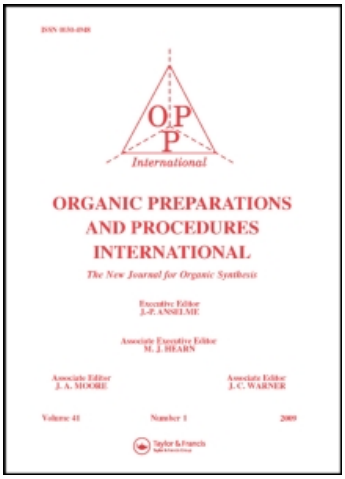

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THE SYNTHESIS OF β-HALOGENATED ENAMINES

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THE SYNTHESIS OF β-HALOGENATED ENAMINES

Norbert DE KIMPE* and Niceas SCHAMP

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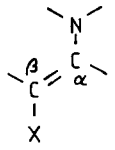
INTRODUCTION

Enamines have received considerable attention in the field of synthetic and mechanistic organic chemistry.[1,2] In principle, the combination of two functional groups such as the enamino function and a halogenated carbon atom offers additional synthetic possibilities. These structural units, when brought together into a β-haloenamino system 1, can be considered as modified α-halocarbonyl systems. Despite these



1 X = halogen

a priori interesting considerations, β-halogenated enamines have not been fully exploited as synthetic tools, mainly because no general routes had been developed to synthesize the title compounds until recently. Although β-haloenamines have been dealt with in many papers, only during the last decade have considerable efforts been devoted to their evaluation as

synthons. This has resulted in the development of approaches for the generation of the title compounds.

β-Haloenamines 2 having one hydrogen atom as a substituent on nitrogen, i.e. secondary β-haloenamines, are not considered here because they exist as α-haloimino derivatives 3, except when stabilizing groups which allow conjugation with the olefinic double bond (e.g. CN, COOR, Ar, etc...) are present either in the α- or the β-position. On the other hand, when the nitrogen atom of 1 bears an electron-withdrawing sub-

2 3

stituent (e.g. acyl, aroyl, sulfonyl, etc...) and a hydrogen atom, the predominating tautomer is the enamino form (vide infra). Only in some special cases does an equilibrium between α-haloimines and β-haloenamines exist; however, in general our main concern will be with tertiary β-haloenamines in which no tautomerism is possible. It is the purpose of this review to indicate the usefulness of β-halogenated enamines 1 as synthons and to correlate their chemistry to that of the α-haloimines.[3,4] The literature has been reviewed up to the end of 1979.

SCOPE OF THE REVIEW

In general, only those β-halogenated enamines, reflecting a structural similarity with α-halogenated carbonyl compounds, will be treated in this review. For instance β-halogenated

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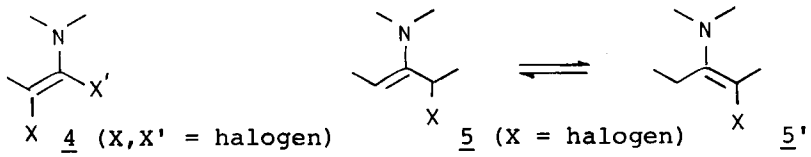
enamines such as 4 (X,X'=halogen) bearing an α-halogen atom, are not considered in this survey because their chemistry is determined by the α-halogen atom and because α-haloenamines have been reviewed recently.[5]



4 (X,X' = halogen) 5 (X = halogen) 5'

The present review will not deal with compounds of type 5 although they are isomeric with β-haloenamines (5') and may indeed be, under certain conditions (presence of base), in equilibrium with their β-haloenaminic isomers 5'; this phenomenon will be discussed in the forthcoming fourth part of this series of reviews in which the chemical behavior of β-haloenamines will be treated. These compounds of type 5 will be discussed only very briefly in the section dealing with the side-products resulting from the condensation of α-haloketones with secondary amines.

Finally, although this constitutes a deviation from the general policy followed in this article, functionalized β-haloenamines having α-alkoxycarbonyl-, α-cyano-, α-amino- or α-alkoxy substituents (and/or analogs) will also be discussed here; the comments regarding other halo derivatives will also apply for these substituents as well.

SYNTHESIS OF β-HALOGENATED ENAMINES

As already pointed out for the synthesis of α-halogenated imino compounds, two fundamental approaches to the synthesis of β-haloenamines must be considered. The first strategy in-

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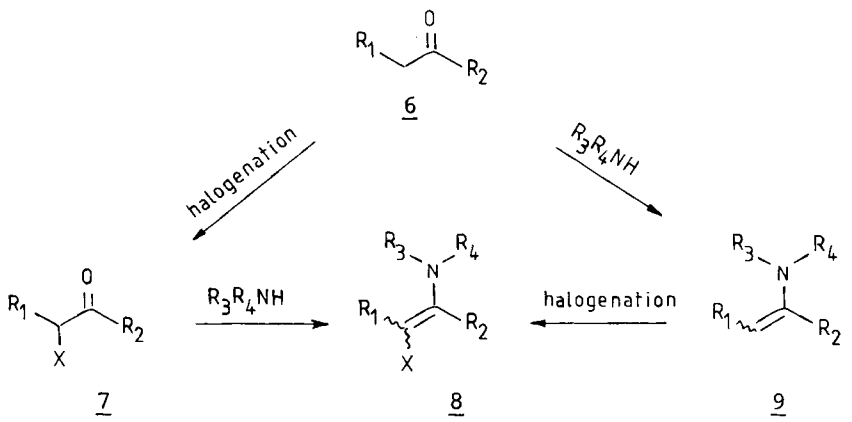
volves the condensation of an α-halogenated carbonyl compound 7 with a secondary amine, under suitable conditions in analogy to the preparation of enamines starting from carbonyl compounds and secondary amines.[1,2] The second route involves the halogenation of initially formed enamines 9 to produce β-haloenamines 8 (with eventual capture of the hydrogen halide produced either simultaneously or by subsequent treatment with base).

Both routes mentioned above contain inherent difficulties in that a variety of side-reactions are encountered. In this



respect, these problems parallel the difficulties encountered during entry into α-haloimino systems.[3] Halogenation of ketones and aldehydes received a great deal of attention in the literature;[6,7] thus an overwhelming variety of halogenation procedures are available. However, the presence of two functional groups in α-halocarbonyl compounds presents the possibility for interaction of the secondary amine with either of these entities, or with both. This major difficulty leads to side-reactions which very often predominate. Such side-reactions, e.g. α-substitution, elimination, elimination-addition,

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Favorskii-rearrangement, further reactions of transient β-haloenamines and many other reaction types, have been encountered during the condensation of α-halocarbonyl compounds and secondary amines (vide infra). However, under appropriate experimental conditions, this reaction can be applied to the synthesis of β-haloenamines (vide infra). The second strategy leading to β-haloenamines entails the halogenation of enamines 9. As with imines, halogenation of enamines often leads to α-halogenated immonium derivatives which are very unstable and which, in most cases, have been further hydrolyzed to the corresponding α-halogenated carbonyl compounds. The medium in which the halogenation takes place is of primary importance and the successful recent advances in this field are due to efforts dedicated to find conditions for isolation of the sensitive β-haloenamines.

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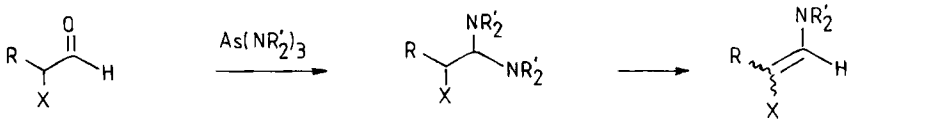
This review will pay detailed attention to the use of both synthetic routes mentioned above, the condensation of α-halocarbonyl compounds with secondary amines and the halogenation of tertiary enamines. The first two parts cover these aforementioned synthetic approaches, while the third part deals with various other entries into β-haloenamines. The fourth part mentions experimental conditions for the preparation of some selected β-halogenated enamines.

I. CONDENSATION OF α-HALOGENATED CARBONYL COMPOUNDS WITH AMINES

In general, the condensation of an α-halogenated carbonyl compound with a secondary amine does not lead to β-halogenated enamino compounds. Various side-reactions have been reported

and a few examples will be given at the end of this chapter.

However, under certain suitable reaction conditions, α-halogenated carbonyl compounds can be transformed into β-haloenamines. The reaction of α-bromo- and α-chloroaldehydes 10 and 11 with tris(N,N-dialkylamino)arsines was originally reported to give β-haloaminals 12, which underwent elimination of the amine (during distillation) to produce β-halogenated enamines 13 and 14.[8]

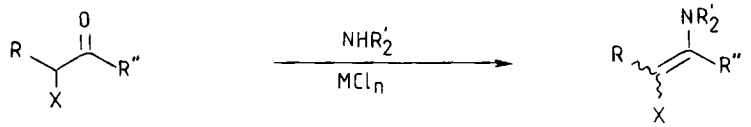


10 X = Br
11 X = Cl

12

13 X = Br
14 X = Cl

The pioneering work in this field by L. and P. Duhamel led to a more general type of reaction in which an α-halogenated carbonyl compound 15 was reacted with secondary amines in the presence of metal chlorides such as $AsCl_3$, $SbCl_3$, $BiCl_3$, $FeCl_3$ and $TiCl_4$ (Preparation 1).[9,10] The latter reagents act as Lewis catalysts and play the role of effective drying agent (formation of metal oxides). The stereochemistry of compounds



15 (MCl_n = $AsCl_3$, $SbCl_3$, $BiCl_3$, $FeCl_3$, $TiCl_4$)

16

16 was not unraveled. The preferred reaction using metal chlorides or its condensation products with secondary amines consisted of the use of $AsCl_3$.[10] The condensation of α-halocarbonyl compounds with tris(N,N-dialkylamino)arsines was performed in ether at -60° or in benzene at ambient temperature

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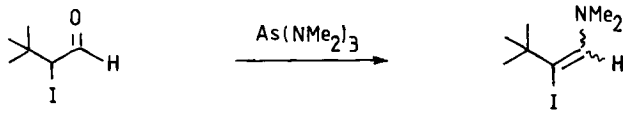
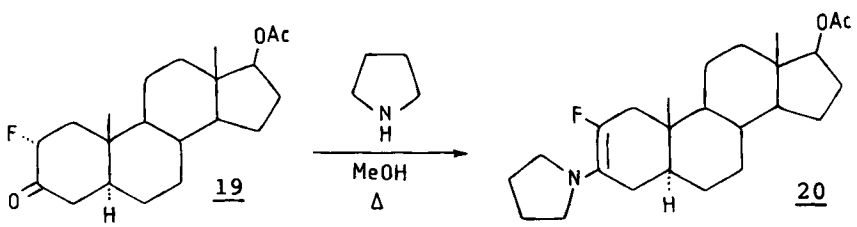
(Preparation 2).[10,11] The generality of this elegant method was demonstrated by the preparation of β-iodoenamine 18 in 27% yield (purity of 90%).[10]



17 18

As expected, α-fluorocarbonyl derivatives also condensed with secondary amines and, in none of the cases reported, were reactions other than enamine formation observed. The reactions of such α-fluoroaldehydes and α-fluoroketones may be classified as ordinary reactions of carbonyl derivatives because of the lack of reactivity of the fluoride. α-Fluoroaldehydes furnished β-fluoroenamines by reaction with secondary amines,[12,13] while the reaction of α-fluoro steroidal ketone 19 with a large excess of pyrrolidine in methanol gave the β-fluoroenamine, i.e. 17β-acetoxy-2-fluoro-5α-androst-2-ene-3-one 3-(N-pyrrolidinyl)-enamine 20 in 83% yield.[14]



The sodium salt of α-activated α-fluoroaldehydes such as α-aroyl- and α-alkoxycarbonyl substituted derivatives 21 and 22, when treated with the hydrochlorides of secondary amines in acetonitile in the presence of p-toluenesulfonic acid, provided β-activated β-fluoroenamines 23 and 24.[15,16]

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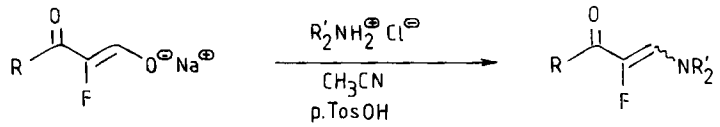
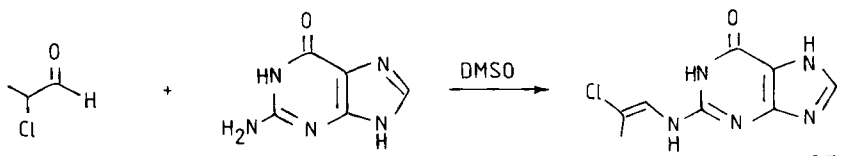


21 R = Ar
22 R = OR"

23 R = Ar
24 R = OR"

A similar reaction was observed with the chloro derivatives, giving rise to β-chloroenamines in 34-48% yield.[16]

In some cases it was possible to obtain β-halogenated enamines by reaction of α-halocarbonyl derivatives with primary amines. For instance, the condensation of 2-chloropropanal 25 with guanine (26), was accomplished.[17] When carried out in dimethyl sulfoxide at 55° overnight, the corresponding β-chloroenamine 27 was isolated.[17] In general, halogenated β-keto-



25 26 27

esters, β-ketoamides, β-ketonitriles or β-ketoketones were found to condense with primary amino compounds, thereby yielding β-haloenamines because of the more favorable conjugation in the molecule as compared to the α-haloimino tautomer. As discussed already in a previous review,[3] only electron-withdrawing substituents such as COOR, CN, NO_2, etc..., cause the α-haloimino form to isomerize to the enamino form.[3] The initial report of such reactions is the condensation of ethyl 2-chloro-3-ketobutanoate 28 with ammonia in ether to produce β-chloroenamine 30,[18] but this experiment could not be duplicated recently.[19] When the reaction was performed with ammonia

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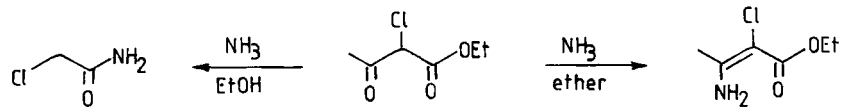
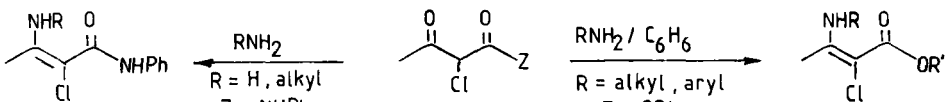


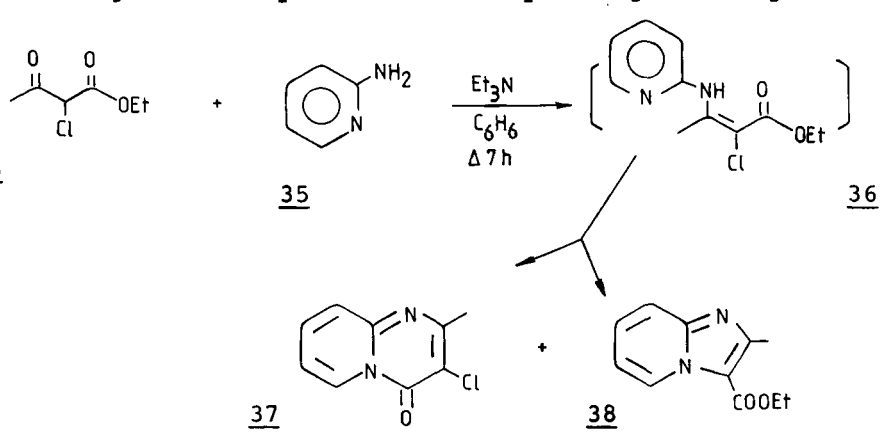
29 28 30

in ethanol, compound 28 underwent fission resulting in 2-chloroacetamide 29.[19] α-Chloro-β-ketoamides, e.g. 31, were reported to condense with aliphatic primary amines or ammonia to yield β-chloroenamino derivatives 32.[20] The same type of reaction was found for α-chloro-β-ketoesters 33 whereby aliphatic as well as aromatic amines were employed.[19] However, more activated anilines, e.g. 2-aminopyridine 35, caused the inter-



32 31 Z = NHPh 33 Z = OR' 34

mediate β-chloroenamine to suffer ringclosure. For example, compound 28, when treated with 2-aminopyridine 35 in benzene in the presence of triethylamine under reflux (Dean-Stark apparatus), yielded 36 as an intermediate, which underwent cyclization to give a 46% yield of 3-ethoxycarbonyl-2-methylimida-



28 35 36 37 38

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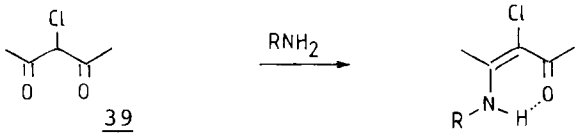
zo[2,1-a]pyridine 38 and 10% 3-chloro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one 37.[21] β-Chloroenamines 40 and 41 were ob-

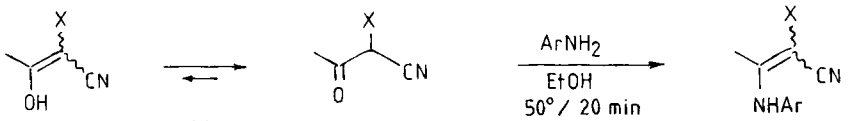


39

40 R = C_6H_5

41 R = cyclohexyl

tained from 3-chloro-2,4-pentanedione 39 and aniline or cyclohexylamine,[19] while similar products were reported from the reaction of 2-halo-3-ketobutyronitrile 42 with aromatic amines in ethanol (Preparation 3).[22]



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43

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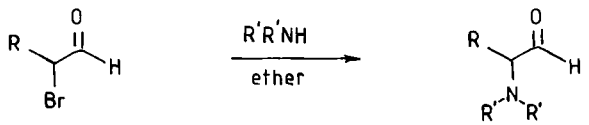
Side-Reactions of the Condensation of α-Halocarbonyl Compounds with Secondary Amines

Numerous examples have been described in the literature dealing with the reactions of α-halogenated carbonyl compounds with secondary amines, whereby no β-halogenated enamines resulted. Some of the most pertinent side-reactions encountered will be discussed here. Additionally, a few literature citations will be reported in which halogenations of enamines are reported which do not lead to β-haloenamine derivatives.

In this review only those α-halogenated carbonyl compounds are mentioned which could produce β-haloenamines, i.e., the α-carbon atom, bearing the halogen atom, must be connected to at

least one hydrogen atom.

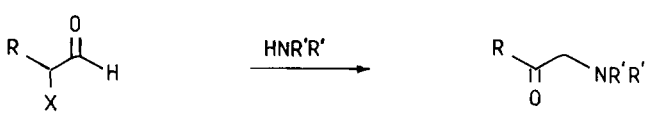
α-Substitutions are frequently encountered during these reactions. The reaction of secondary amines with α-bromoaldehydes 10 was initially reported to give α-aminoaldehydes,[23] but it was later shown that the resulting products were, in fact, the rearranged α-aminoketones.[24] By working at low temperature (4°/16 hr or -16°/several days) in etheral medium it was possible to isolate α-aminoaldehydes 44 in 43-82% yield,[25,26] despite their tendency to rearrange to the isomeric α-aminoketones 45.



10 R = Et, n-Pe

44 (NR'R' = NMe_2, NEt_2, pyrrolidino)

When no precautions were taken (such as rapid work-up in the cold), α-haloaldehydes 10, 11 are transformed into α-aminoketones 45 by reaction with secondary amines.[24] With a ten-fold



10 X = Br
11 X = Cl

45

excess of secondary amine in the cold for a long period of time, α-chloro- and α-bromoaldehydes 10, 11 were converted into enediamines 46, isolated by distillation after isolation of the amine hydrochloride.[29]

On the other hand, 2-bromo-7,7-diphenylcycloheptanone 47 with secondary amines gave the α-substituted product 48.

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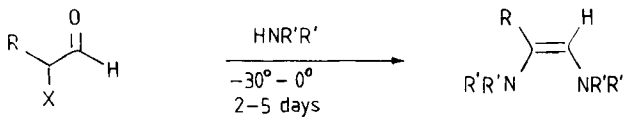
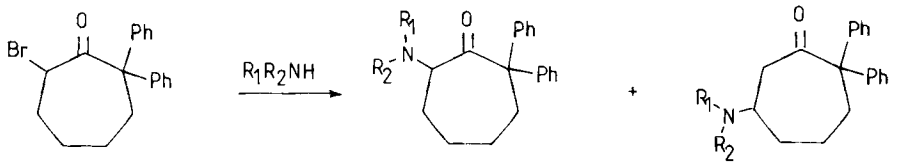


10 X = Br

11 X = Cl

46

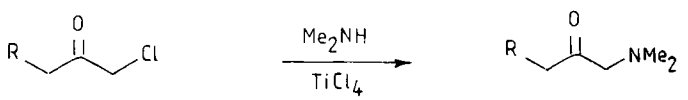
Elimination and subsequent Michael addition also occurred (see 49).[30] α-Chlorocyclohexanone could be substituted in the α-position with diethylamine, piperidine and morpholine;[31]



47 48 49

however, with dimethylamine α-substitution in addition to Favorskii rearrangement (vide infra) was observed.[31]

Effective drying agents such as titanium tetrachloride did not always cause the expected condensation with water removal to occur as illustrated by the reactions of dimethylamine with chloroacetone 50 and 1-chloro-3-phenyl-2-propanone 52 which provided α-substituted products 51 and 53.[32] Ethyl 2-



50 R = H

52 R = Ph

51 R = H

53 R = Ph

chloro-3-oxobutanoate 28 was reported to give low yields of the substituted product when treated with excess secondary amines, e.g. piperidine. The low yield was caused by a side-reaction by which breakdown to amide 55 and ethyl chloroacetate 56 occurred, further leading to ethyl 2-piperidinoacetate

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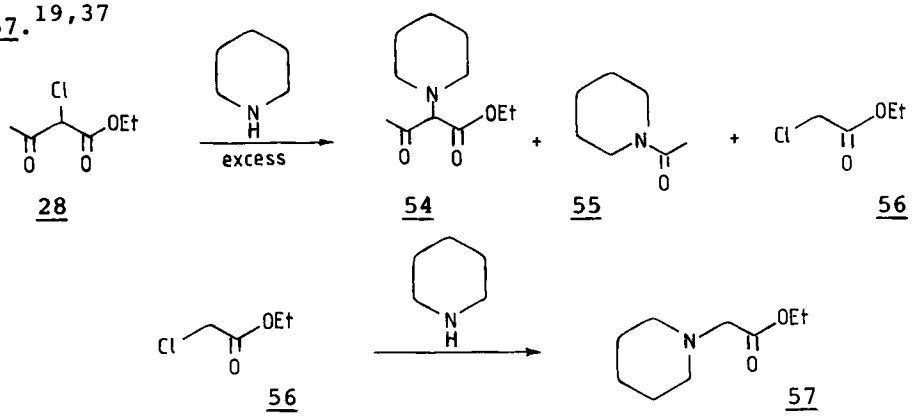
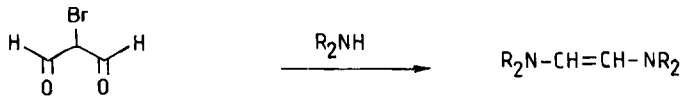
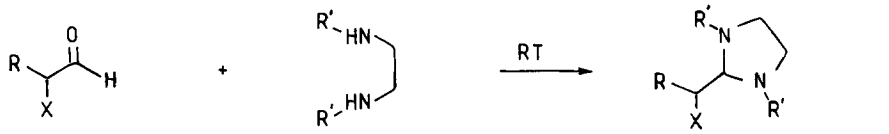
57.[19,37]

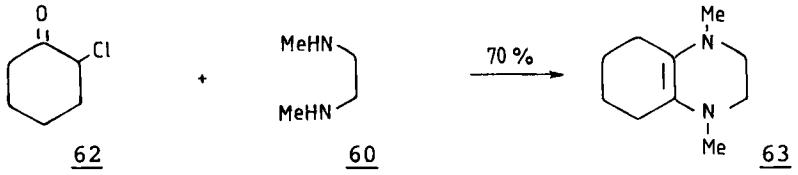


In this respect, the reaction of secondary amines with bromomalonaldehyde 58 can be mentioned because it entailed a substitution/break-down reaction to afford 1,2-diaminoethylene



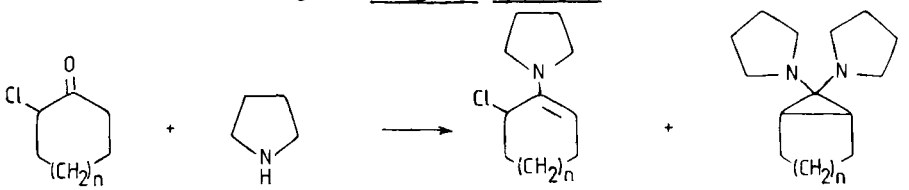
derivatives 59.[34] The reaction of α-haloaldehydes 10,11 with secondary 1,2-diamines 60 led to isolable cyclic aminals 61, which on heating were further transformed into cyclic enedi-





amine derivatives.[35] In contrast with these results, α-chlorocyclohexanone 62 was directly converted into the octahydroquinoxaline derivatives 63.[35]

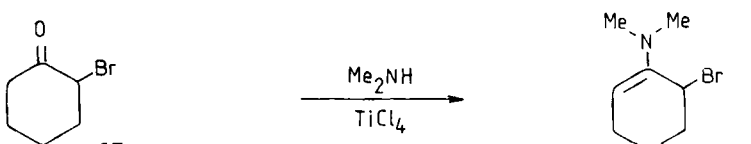
An interesting feature of alicyclic α-haloketones 62,64 is their ability to react at the carbonyl function with secondary amines to give not the β-haloenamine but instead, the isomeric enamine having an allylic halogen. It was originally



62 n = 1
64 n = 2

65 66

found that 2-chlorocycloheptanone 64 reacted with pyrrolidine to yield bicyclic aminal 66 (n = 2),[36] but it was later shown that the aminal resulted from a further reaction of the initially formed enamine 65 with excess pyrrolidine.[37] When the reaction was carried out at -10° in the presence of magnesium sulfate as drying agent, 2-chlorocyclohexanone 62 was converted into enamine 65 (n = 1) in high yield, while only minor amounts of aminal 66 (n = 1) were detected.[38] In similar manner, 2-bromocyclohexanone 67 condensed with dimethylamine in



67 68

the presence of $TiCl_4$ to afford enamine 68.[32,39] In some special cases, the halogenation of enamine derivatives took a different course resulting in N-halogenation. A particular

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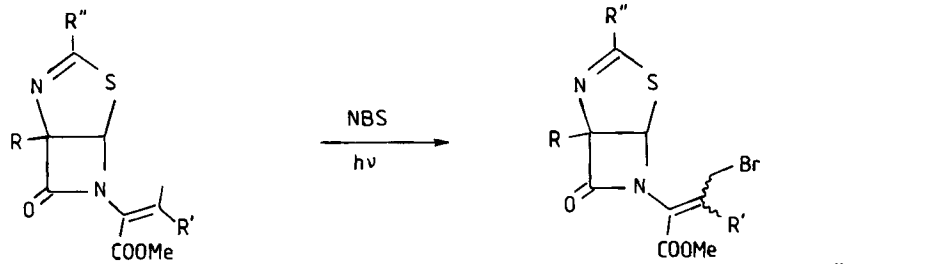
example is the reaction of NBS with ethyl 2-(N-benzyloxycarbonyl)aminoacrylate 69 which afforded quantitative N-bromination.[40]

69 70

It was recently demonstrated in the field of antibiotics and related substrates that enamino derivatives are not necessarely halogenated in the β-position but that allylic halogenations can still be executed.[41] For example, compounds 71 and 72 were photochemically brominated in the allylic positions with NBS to give 73 and 74 (bromination of enamides).[42,43]



71 R = OMe; R' = R" = Me
72 R = H; R' = OMe; R" = CH_2OPh
73 R = OMe; R' = CH_2Br; R" = Me
74 R = H; R' = OMe; R" = CH_2OPh

A classic possibility is the Favorskii-rearrangement of α-halo ketones[44,45] yielding carboxylic amides under the influence of secondary amines. 2-Chloro-6-phenylcyclohexanone 75 rearranged with piperidine in methanol to amide 76.[46] A similar result was observed for the conversion of 1-chloro-3-phenyl-2-propanone 52 to amide 77.[46] It is worth noting that 75 with sodium methoxide in methanol did not give Favorskii-rearrangement, but furnished 2-methoxy-6-phenylcyclohexanone. The superiority of piperidine as compared to methoxide in giving the Favorskii-

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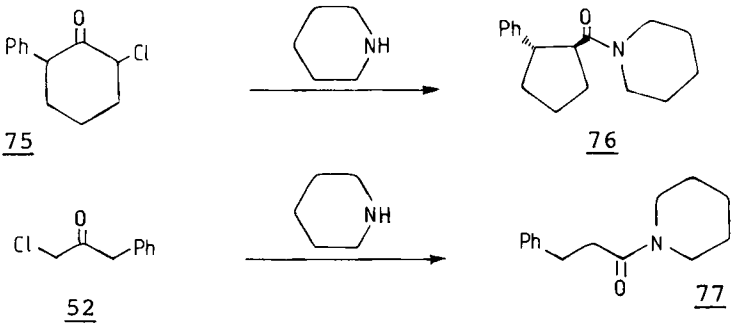
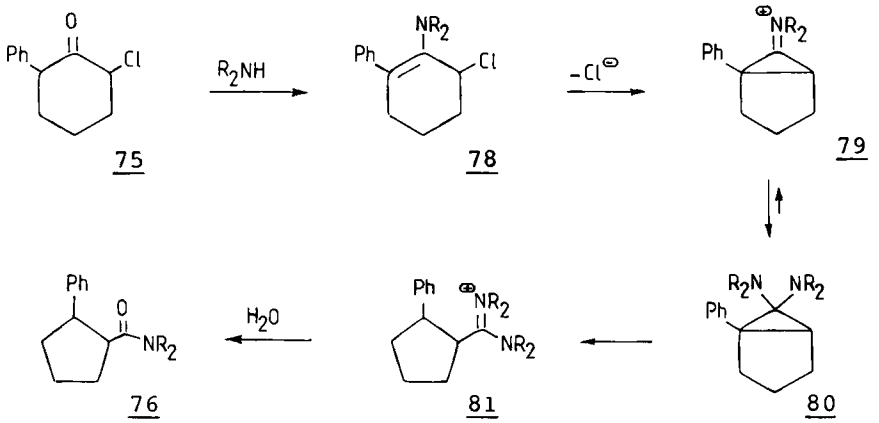
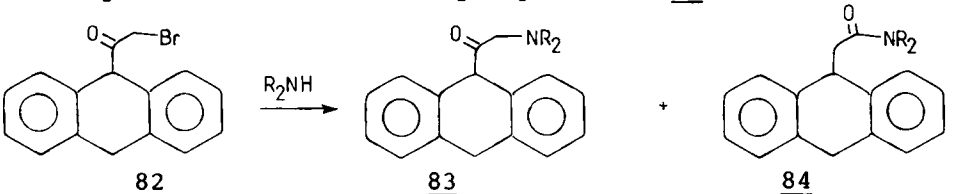


rearrangement in the systems mentioned above is caused by the possibility of forming the rearranged amide via an intermediate, different from the usual cyclopropanone derivatives.[46] Accordingly, it was proposed that an enamine allylic halide 78 was involved, which further rearranged via a cyclopropylideneammonium intermediate 79 into the final amide 76.[46]



In addition to rearrangement with secondary amines, certain α-bromoketones, e.g. 82, also gave α-substitution.[47] α,α'-Dibromocycloalkanones behaved in an unexpected way towards secondary amines. 2,5-Dibromocyclopentanone 85 with excess mor-



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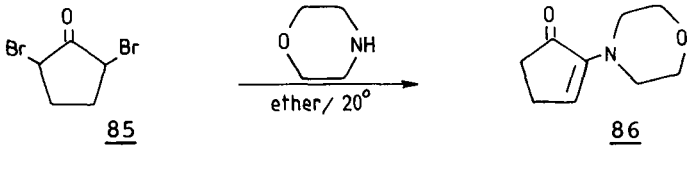
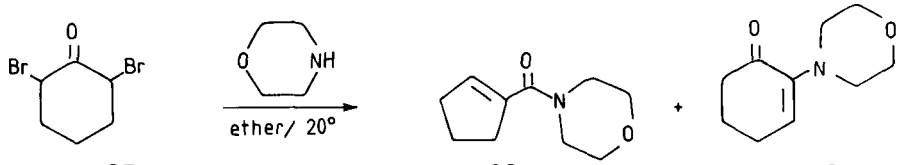
pholine (5 equiv.) in ether at 20° gave 2-morpholino-2-cyclopentenone 86, but 2,6-dibromocyclohexanone 87 under similar reaction conditions afforded in addition the ring-contracted α,β-unsaturated amide 88.[48] Under the same conditions, 2-bromocyclohexanone gave α-substitution as the exclusive reac-



85 86



87 88 89

tion.[48] These results indicated that the Favorskii-rearrangement depends to a large extent on the basicity and nucleophilicity of the basic reagent employed and may be considerably influenced by the steric requirements of the substrate. The solvent in such reactions was of major importance as illustrated by the reaction of 2,6-dibromocyclohexanone 87 with morpholine. In chloroform, a 96:4 ratio of amide 88 over enone 89 was observed while the reverse ratio of 3:97 was found in hexamethylphosphortriamide.[49]

II. HALOGENATION OF ENAMINES

Only those halogenations of enamines leading to β-haloenamines are reported here. Those leading to α-halogenated imino compounds were reported previously.[3] In addition, attention will be focused on some halogenations (in particular with Cl_2 and Br_2) which do not eventually give β-haloenamines but

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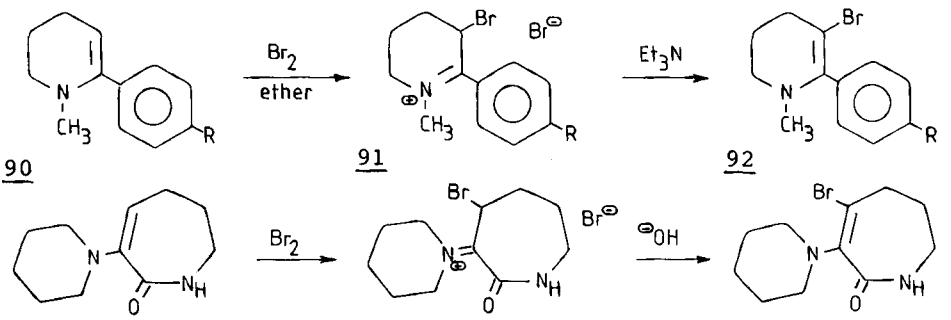
which by aqueous work-up, furnished the corresponding α-halocarbonyl derivatives.

II.1. Halogenation with Cl_2 and Br_2

The halogenations of enamines with chlorine or bromine in a variety of solvents were reported to yield α-halogenated immonium halides, which, upon treatment with base, were converted into β-halogenated enamines.[9,50-52] By far the most experiments have been carried out with bromine because of the inconvenience of using equivalent amounts of chlorine. The method using halogenation and subsequent base treatment seemed generally applicable as functionalized enamines can also be brought into reaction. Hydroxides as well as nitrogen bases can be used in such transformations as illustrated in the following two examples.[51,52]



Care should be taken during base treatment because β-haloenamines are known to rearrange with these reagents.[53] In some instances, base treatment of α-halogenated immonium halides 97 with ammonium bicarbonate in aqueous ethanol afforded the β-haloenamines 98 as unstable intermediates, which rearranged further to 9-oxo-benzomorphans 99.[54,55] Such rearrangements

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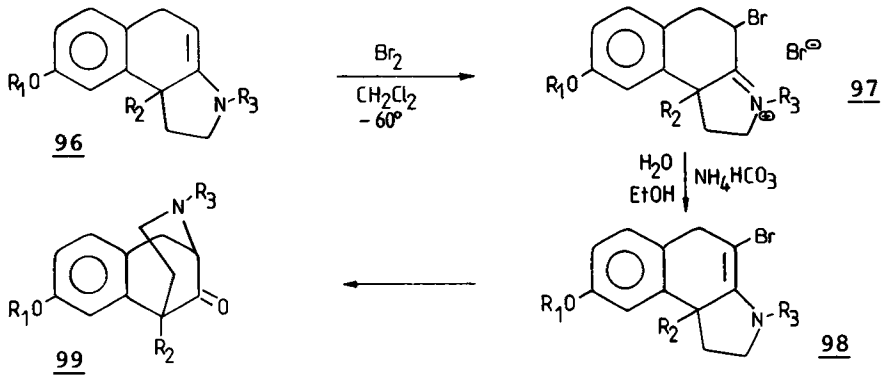
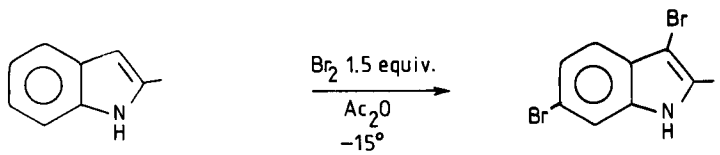
will be discussed in more detail in the forthcoming review on



96 97 98 99

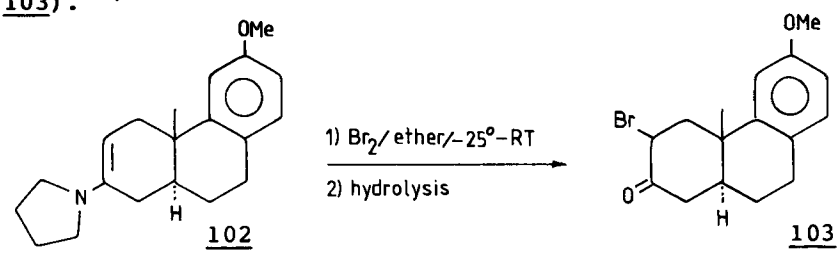
the reactivity of β-halogenated enamines.[56] In one special case in the indole series, bromination led directly to a β-bromoenamine derivative (see 100 → 101).[57]



100 101 (39%)

Most of the efforts which have been conducted in this field entailed the halogenation of enamines with Cl_2 or Br_2 followed by acidic hydrolysis, thereby providing an efficient means of preparing α-halogenated carbonyl compounds.

In a synthetic route to the diterpene resin acids, a selective bromination of a ketone in the presence of a susceptible anisole ring was accomplished by enamine activation (102 → 103).[58,59]



102 103

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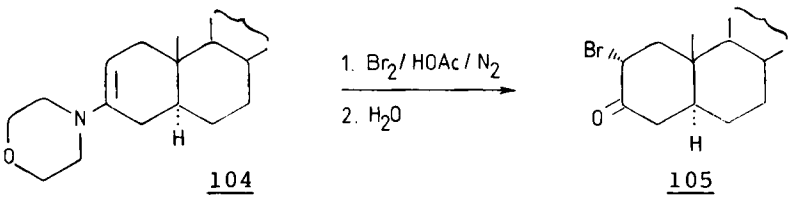
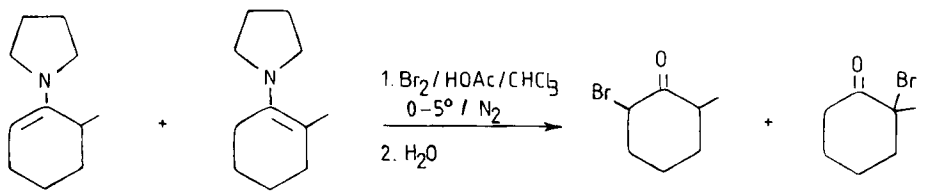
Besides ether,[60,61] dichloromethane[62-64] or chloroform[63] were most commonly used as solvents because simple evaporation allowed the isolation of the initially formed α-halogenated immonium halides, if necessary.[65] Acetic acid was sometimes used as a solvent. The bromination of the morpholine enamine of cholestanone 104 led, after aqueous work-up, to a 96% yield of α-bromoketone 105.[66]



104 105

When the double bond of the enamine is not regiospecifically localized (see 106, 107), bromination in acetic acid-chloroform and subsequent aqueous treatment afforded mixtures of α-brominated ketones 108 and 109 (total yield 80%).[67]



106 9 : 1 107 108 8-9:2-1 109

It is worthwhile mentioning here the iodination of the pyrrolidine enamine of cyclohexanone (110) with iodine in ether at -78° to produce an 80% yield of the α-iodoimmonium iodide 111, which was hydrolyzed to provide a mixture of 2-iodocyclohexanone 112 and cyclohexanone 113.[61]

From the practical point of view, the way in which enamines are halogenated is of major importance. The yield of α-halo immonium halide is influenced by such factors as the sol-

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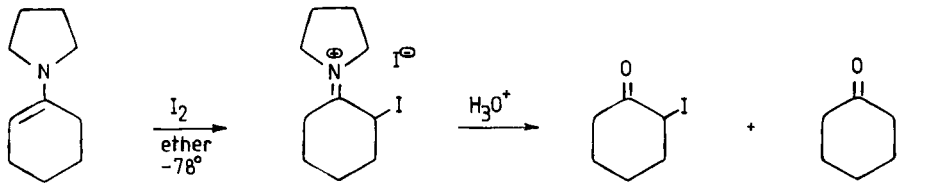
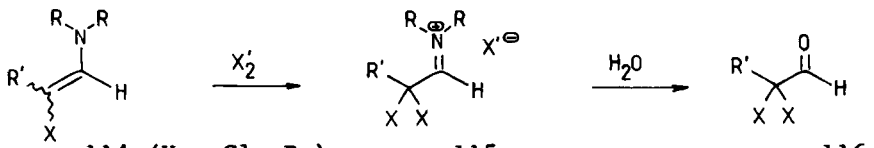


110 111 112 113

vent, the reaction temperature and the mode of mixing of the reagents. Solvents such as ether and dichloromethane are preferred while temperatures between -60 and -78° and short reaction times (5-10 min.) assure good results. The rapid addition of the enamine to a solution of the halogen in dichloromethane or chloroform at -70° gave good results in halogenations of enamines derived from pinacolone,[63] a procedure which has proven useful in more recent and general investigations.[54,55] However, another recent report claimed the reverse addition to be an excellent way to monohalogenate enamines.[61,68]

β-Halogenated enamines themselves suffered halogenation to yield α,α-dihaloimmonium halides 115 (mixed halogenations are possible), which were hydrolyzed into α,α-dihaloaldehydes 116.[9] Enaminones are also suitable substrates for halogenation



114 (X = Cl, Br) 115 116

and special attention has been paid to bromination.[69,70] In general, substrates such as 117 were converted into their brominated derivatives 119 by using bromine in an inert solvent, e.g. dichloromethane, producing salts 118, which were subsequently dehydrobrominated with triethylamine.[69,71] A detailed

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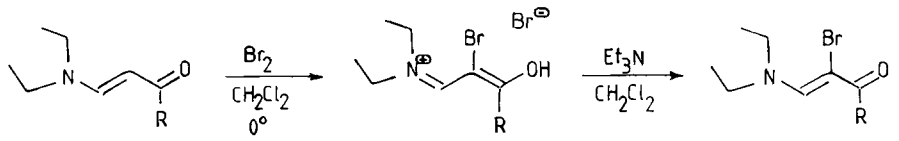
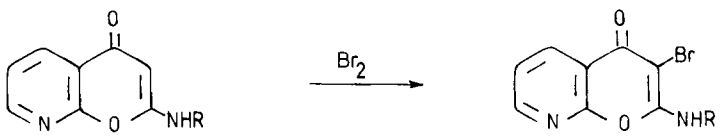
NMR study revealed that in the case of enaminones 117, bromination led to conjugated immonium compounds 118 and not to an α-bromoimmonium compound 120 or a β-bromoenammonium compound 121 (Preparation 4).[70,159]



117 118 119

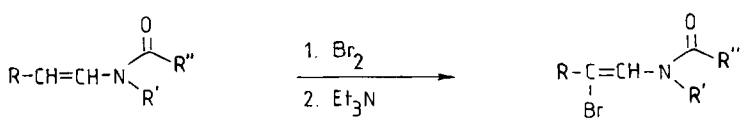
120 121

Another example of such a bromination involved the conversion of 122 into 123 (R = H).[72]



122 123 (R = H, Ac)

On the other hand, enamides 124 were similarly brominated, the initially formed salt being dehydrobrominated with triethylamine.[73]



124 125

Much synthetic work has been devoted to the β-halogenation of enamides substituted in the α-position with electron-withdrawing substituents such as carboxyl derivatives. The halo-

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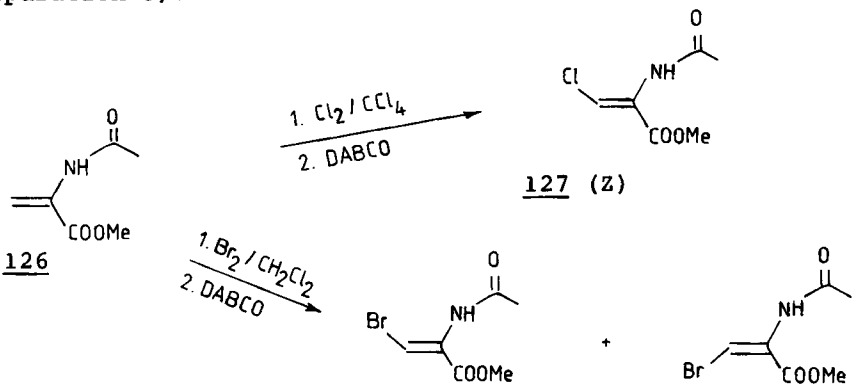
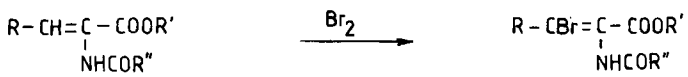
genation also involved treatment with chlorine or bromine in carbon tetrachloride or dichloromethane and subsequent dehydrohalogenation with DABCO, as exemplified for 127 and 128, 129 (Preparation 5).[74]



126 → 127 (Z)

126 → 128 (Z) : 129 (E) 3:1

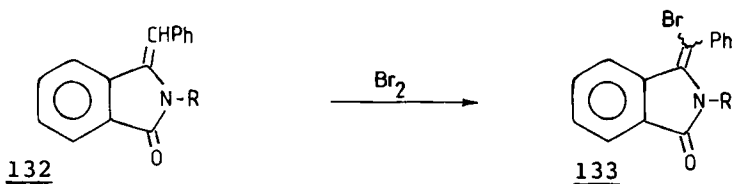
Such a reaction was recently applied to the synthesis of penicillin and cephalosporin antibiotics,[75] while also more general types of α-alkoxycarbonyl- β-bromoenamides 131 were synthesized from the parent compounds and bromine without the use



130 R = Me, Et
R' = t-Bu, Et
R" = Me, OEt, CH_2Br

131

of base.[76] These results correspond to the early results of Gabriel, who discovered about a century ago that bromination of compound 132 led to β-bromoenamide 133.[77] More recent work



132 → 133

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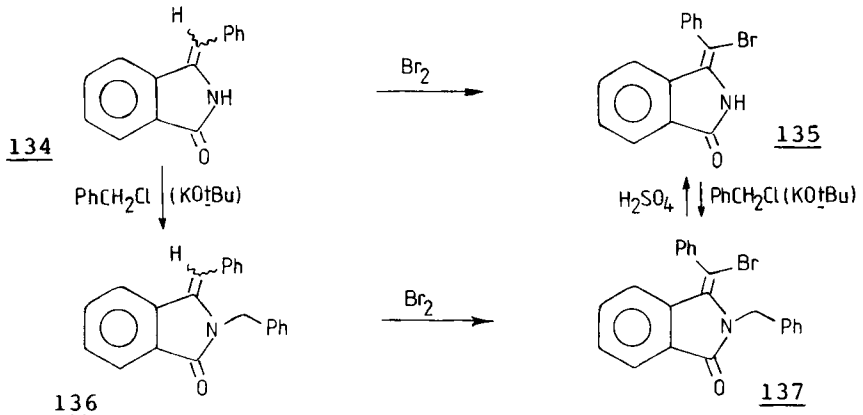
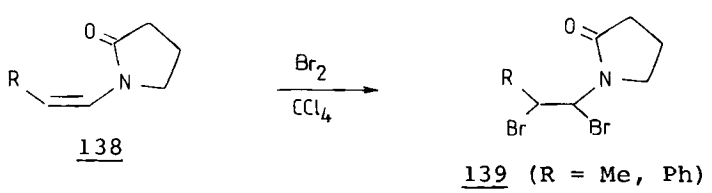
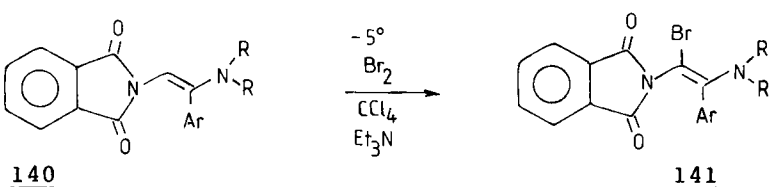
on similar derivatives disclosed analogous results, as shown in the accompanying scheme (Preparation 6).[78-80] In addition, the stereochemistry of some of these compounds was determined.[78]



It must be pointed out that the bromination of enamide 138 with Br_2 in CCl_4 was reported to afford addition product 139,[81] a reaction which was not found with enediamine derivative 140.[82] In the latter reaction, the normal β-bromoenamine resulted after bromination and base treatment in carbon tetrachloride solution.[82]





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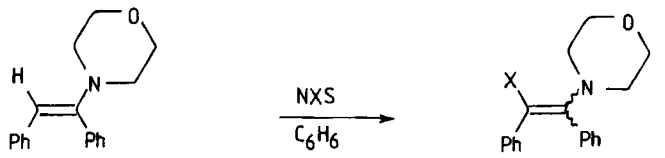
II.2. Halogenation of Enamines with N-Halosuccinimide

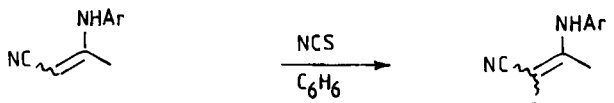
The halogenation of enamines with N-chloro- and N-bromosuccinimide can be carried out in various solvents including aprotic solvents, e.g. dichloromethane, carbon tetrachloride and benzene, or protic solvents such as methanol or acetic acid.

The reaction of NCS or NBS with morpholine enamine 142 in benzene at room temperature under nitrogen was the first report of the isolation of β-haloenamines 143 (X = Cl, Br), obtained in 65 and 79% yield, respectively (in both cases a mixture of E and Z isomers was found).[83] A similar chlorination in benzene using NCS was reported to produce the functionalized



142 (cis) 143 (X = Cl, Br) (cis + trans)

β-chloroenamine 43 (Ar = C_6H_5; p-MeC_6H_4; p-ClC_6H_4; p-OHC_6H_4; o-OHC_6H_4; o-$NH_2C_6H_4$).[22]



144 43

With carbon tetrachloride as solvent, enamine 145, which is in tautomeric equilibrium with ketimine 146, was halogenated in nearly quantitative yield using NCS or NBS.[84]

The chlorination of enaminone 148 with NCS in dichloromethane at room temperature to produce β-chloroenamine 149 was used in

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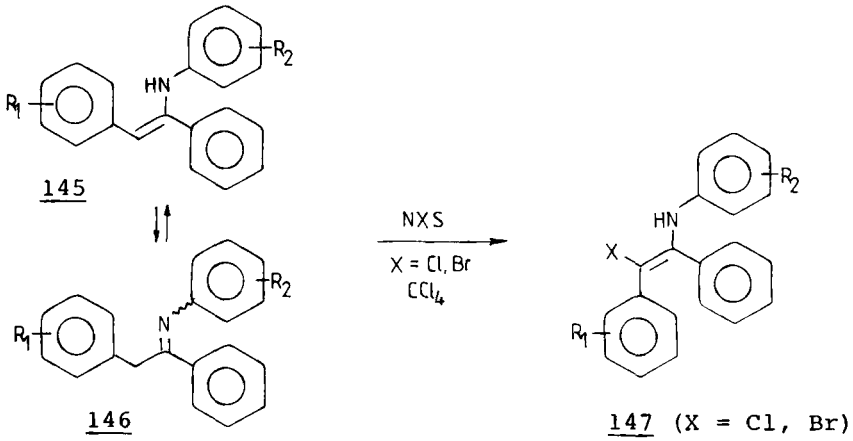
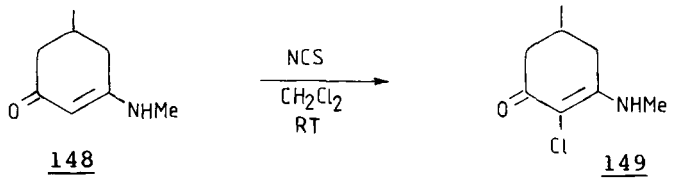
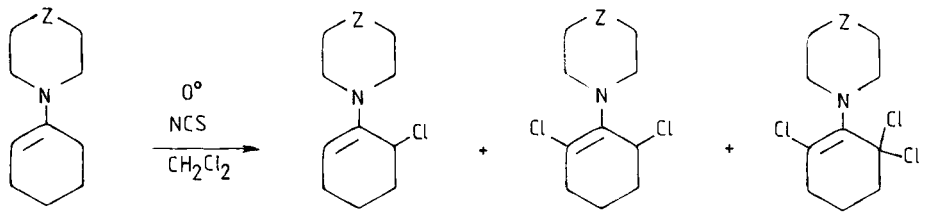


the synthesis of the benzenoid part of the clinically interesting maytansine.[85]



Ordinary enamines such as those derived from cyclohexanone (150) reacted with one equivalent of NCS at 0° in dichloromethane to give a mixture of mono-, di- and trichloroenamines 151, 152 and 153.[86] However, with two equivalents of NCS under the same conditions, high yields of dichloroenamines 154,



150 (Z = O, CH_2,-) 151 152 153

155 could be isolated by distillation (Preparation 7).[86,87] The pyrrolidino enamine afforded 78% of the trichloro derivative (analogous to 153) when treated with three equivalents of

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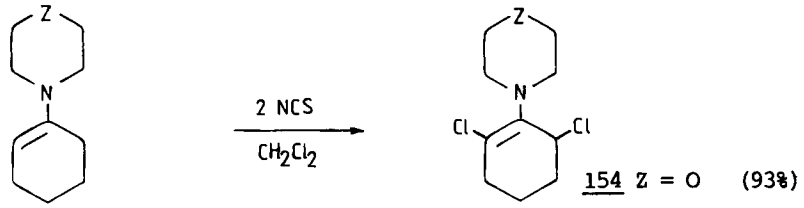
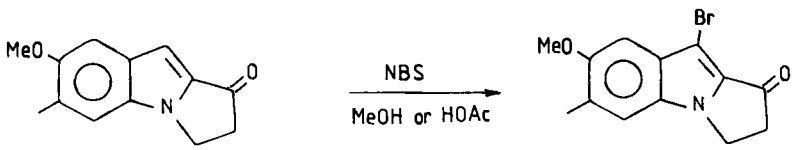


150 (Z = O, CH_2)

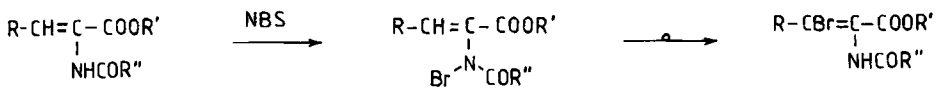
154 Z = O (93%)
155 Z = CH_2 (81%)

NCS in CH_2Cl_2 at 0°.[86,87] Finally some brominations with NBS of certain indole derivatives (156) have been carried out in protic solvents, e.g. methanol or acetic acid, to furnish β-bromoenamino derivatives (157).[88]



156 157

It is worth noting that certain α-alkoxycarbonyl enamides, e.g. 130, were brominated at nitrogen with NBS, after which gradual rearrangement to the β-bromoenamide compound 131 took place.[76] The presence of the N-bromo moiety was verified by reaction of



130 158 131

the brominated species with nucleophiles (cyanide, methoxide) to yield N-substituted enamides.[76]

II.3. Chlorination of Enamines with t-Butyl Hypochlorite

Enaminones and related compounds seemed to be especially susceptible to chlorination with t-butyl hypochlorite. The reaction proceeded very smoothly at -50° in chloroform with

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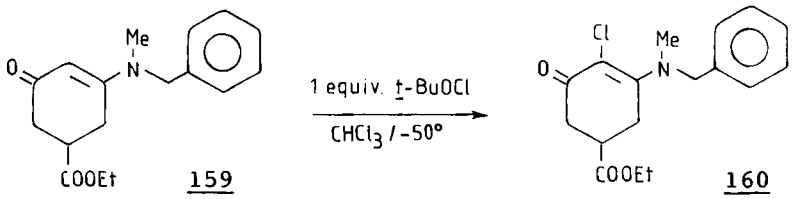
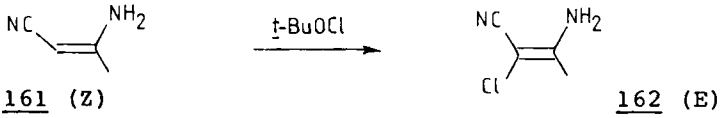
enaminone 159 to give an 80% yield of β-chloroenamine 160.[89] As illustrated for a related chlorination using NCS, this conversion was used in the synthesis of the aromatic part of may-

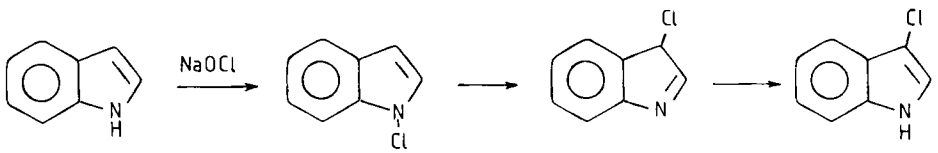


tansine.[89] The Z-isomer of β-cyanoenamine 161 was stereospecifically converted into the E-β-chloroenamine 162 by reaction with t-butyl hypochlorite.[90]



II.4. Chlorination of Enamines with Sodium Hypochlorite

No general reports exist on the use of sodium hypochlorite as a chlorinating agent for enamines which form β-chloroenamines. It can only be mentioned that indole (as an exception to ordinary enamines) reacted with sodium hypochlorite in hexane, carbon tetrachloride or chloroform to afford initially N-chloroindole 164, which rearranged into 3-chloro-3H-indole 165 and further to 3-chloroindole 166.[91] The latter paper claimed direct evidence for the detection of the chloroindolenine 165 for the first time.[91]



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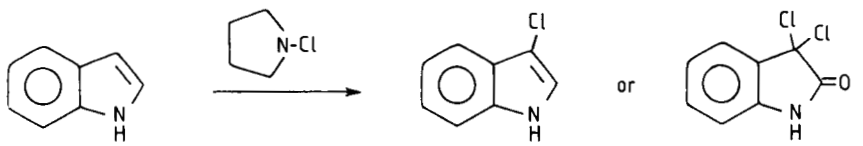
II.5. Chlorination of Enamines with N-Chloroamines and N-Chloroimines

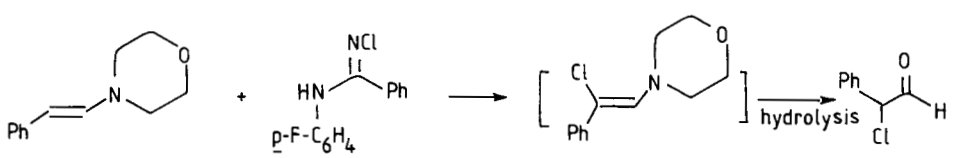
Indole also reacted with N-chloropyrrolidine or N-chloro-N,N-dibutylamine under various conditions with formation of 3-chloroindole 166 or the dichloro derivative 167.[92] The highest yield of 166 (50%) was obtained in acetonitrile at room tempe-



163 166 167

rature in the dark for two days.[92]

Certain N-chloroimines such as 169 can chlorinate enamines having a β-hydrogen atom. The intermediate β-chloroenamine 170 was detected as its hydrolyzed α-chloroaldehyde 171.[93]



168 169 170 171

II.6. Chlorination of Enamines with Hexachloroacetone

Enamines are monochlorinated by hexachloroacetone in tetrahydrofuran at -78° to 0°. The haloenamines formed are not isolated but are hydrolyzed in acidic medium to the corresponding α-chloroketones.[94,95] For instance, the pyrrolidine enamines of 2-methylcyclohexanone (106 and 107), after reaction with hexachloroacetone, subsequent acidic hydrolysis and bicarbonate treatment, afforded 90% of 6-chloro-2-methylcyclohexanone (75% cis-172 and 15% trans-172) and 9% 2-chloro-2-me-

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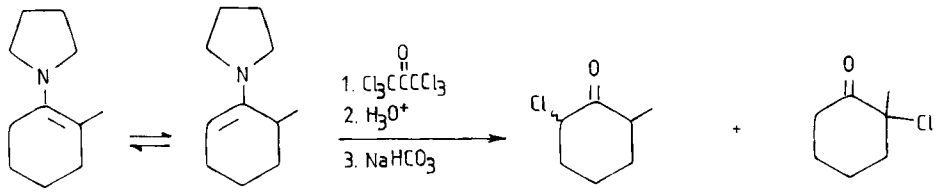
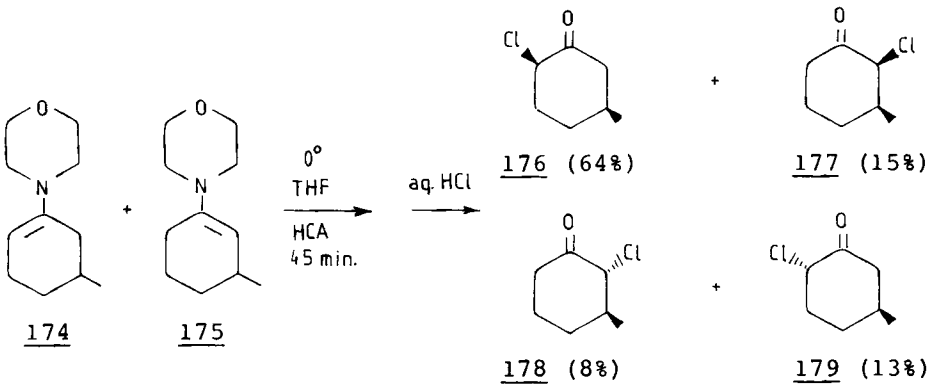


107 106 172 (cis/trans 5/1) 173

thylcyclohexanone (173). Similar treatment of the morpholine enamines of 3-methylcyclohexanone (174,175) produced a mixture of 64% cis-6-chloro-3-methyl-, 15% cis-2-chloro-3-methyl-, 8% trans-2-chloro-3-methyl- and 13% trans-6-chloro-3-methylcyclo-



174 175 176 (64%) 177 (15%) 178 (8%) 179 (13%)

hexanone (GLC values).[95] The reaction exhibits regioselectivity in favoring the formation of the 6-chloro-3-methyl isomer. This regioselectivity was explained as a result of strain between the C-3 methyl group and the C-2 proton, which destabilizes the Δ^1 isomer of the morpholine enamine of 3-methylcyclohexanone. Prolonged standing showed that the kinetic mixture did not correspond to the equilibrium mixture and that the cis-isomer was converted to the thermodynamically more stable trans-isomer via epimerization of the α-chloro carbon by keto-enol tautomerism.[95]

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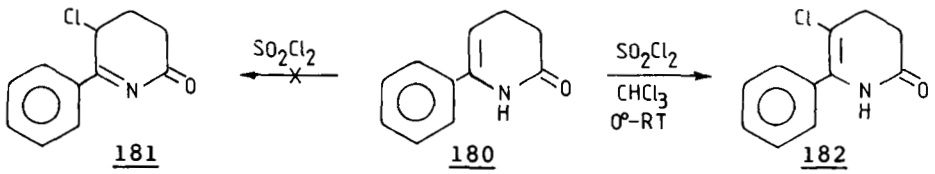
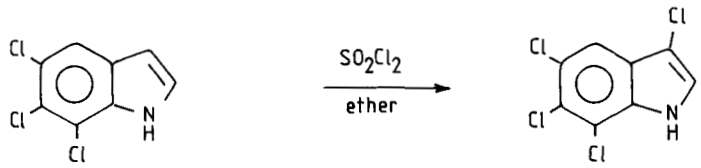
II.7. Chlorination of Enamines with Sulfuryl Chloride

It was originally erroneously claimed that the reaction of 3,4-dihydro-6-phenyl-2(1H)-pyridinone 180 with sulfuryl chloride gave the α-chloroimino compound 181.[96] Instead, as recently shown,[97] a 53% yield of the tautomeric 5-chloro-3,4-dihydro-6-phenyl-2(1H)-pyridinone 182 was obtained from this



181 180 182

reaction (Preparation 8). 5,6,7-Trichloroindole 183 could be converted into 3,5,6,7-tetrachloroindole 184 on trituration with sulfuryl chloride in ethereal medium.[98]



183 184

II.8. Fluorination of Enamines with Perchloryl Fluoride

Although valuable efforts in the field of halogenations of enamines are of fairly recent origin, the initial work was largely performed about two decades ago when extensive fluorinations of enamines were investigated. These experiments were undertaken to introduce fluorine atoms in the position α to a carbonyl function. Thus, enamines were used to mask the carbonyl function and to alter its reactivity in favor of the desired fluorination.[59] Perchloryl fluoride in benzene converted pyrrolidine enamines of 3-cholestanone derivatives 185 into the fluorinated species, which were hydrolyzed in 72-82%

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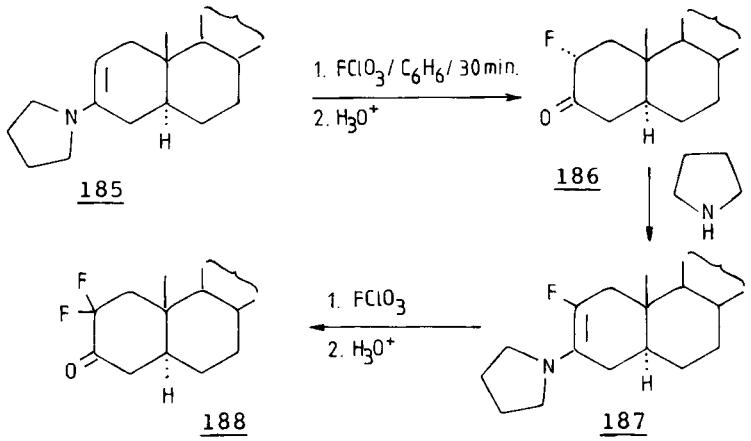
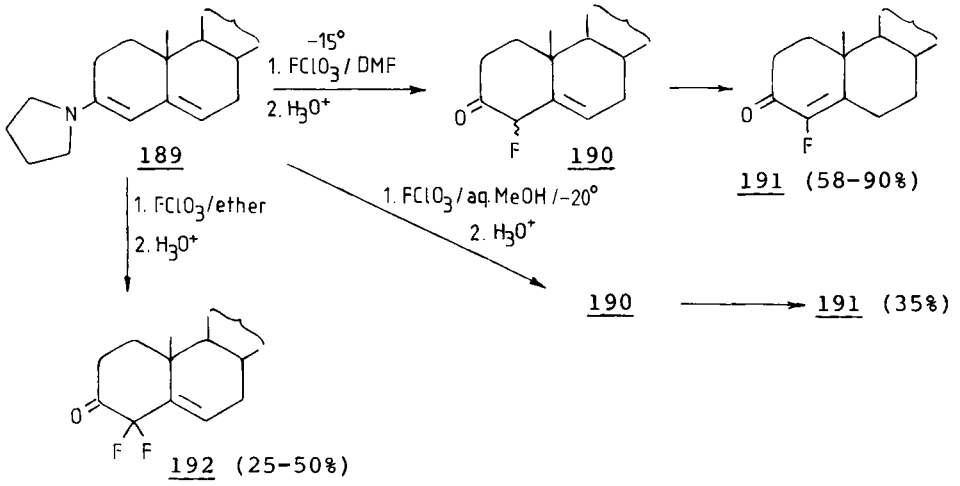


yield to the corresponding α-fluoroketones 186.[99] Condensation of α-fluoroketone 186 with pyrrolidine, subsequent fluorination with perchloryl fluoride and hydrolysis eventually resulted in α,α-difluoroketones 188.[99,100] Besides benzene, dimethylformamide, ether or aqueous methanol were also used as solvents for such fluorinations of enamines as illustrated by the conversion of conjugated enamine 189 into α-fluoroketone 190.[14,101,102] α,α-Difluorination of 189 was accomplished



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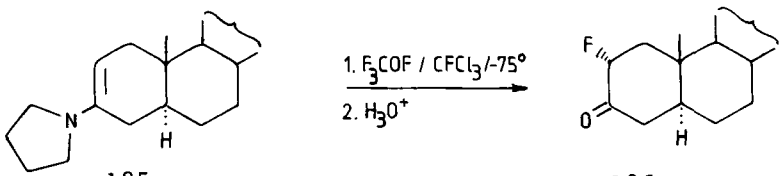
using $FClO_3$ in ether at 0° for 5 minutes,[103] while a 35% yield of 191 was obtained when aqueous methanol at -20° was used.[101]

II.9. Fluorination of Enamines with Trifluoromethyl Hypofluorite

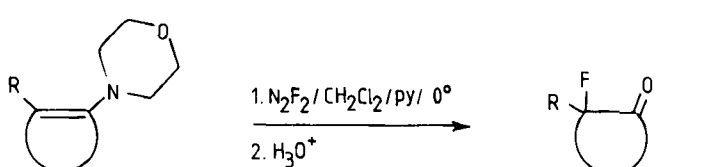
The steroidal enamine 185, when treated with trifluoromethyl hypofluorite in fluorotrichloromethane at -75° gave, after aqueous work-up, a 45% yield of α-fluoroketone 186.[104] As reported for the reactions of perchloryl fluoride, the conjugated enamine 189 was transformed into α-fluoroenone 191 using trifluoromethyl hypofluorite in $CFCl_3$ at -75°.[104]



185 186

II.10. Fluorination of Enamines with Difluorodiazene

Morpholino enamines of cycloalkanones 193 can be converted into the corresponding α-fluoroketones by reaction with gaseous difluorodiazene in dichloromethane at 0° in the presence of pyridine followed by acidic hydrolysis.[105] This reaction should be carried out with safety precautions because an explosion results when N_2F_2 becomes a solid or liquid.



193 194

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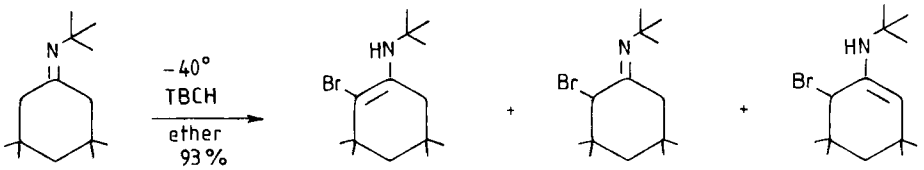
II.11. Bromination of Certain Ketimines with 2,4,4,6-Tetrabromocyclohexadienone (TBCH)

For the sake of completeness, it may be reported here that N-t-butylketimine 195 was brominated with 2,4,4,6-tetrabromocyclohexadienone to afford an inseparable mixture of β-bromoenamine 196, α-bromoimine 197 and enamine 198.[106,107] The equilibrium among the three monobromo compounds is a result of



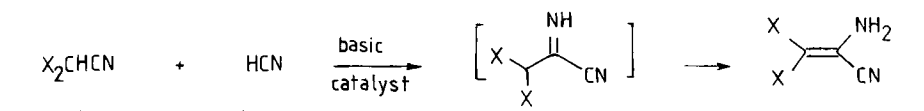
195 196 197 198

the steric congestion in the α-bromoimino form which is released by tautomerism to enamino isomers.

III. MISCELLANEOUS METHODS

III.1. Addition of Hydrogen Cyanide to α-Halogenated Nitriles

Hydrogen cyanide added to dichloroacetonitrile 199 (X = Cl) under basic catalysis, e.g. sodium cyanide, to produce α,α-dichloroimidoyl cyanide 200 (X = Cl), which tautomerized to its more stable α-cyano-β,β-dichloroenamine 201 (X = Cl).[108] This



199 (X = Cl, Br) 200 (X = Cl, Br) 201 (X = Cl, Br)

product was obtained in 96% yield but decomposed on contact with air. It should be stored under nitrogen or in a solvent, e.g. ether. Similarly α-cyano-β,β-dibromoenamine 201 (X = Br) was obtained in 82% yield.[108]

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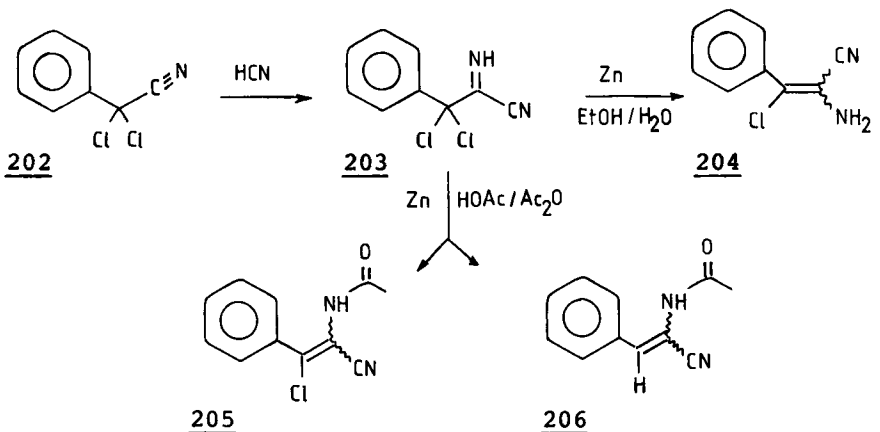
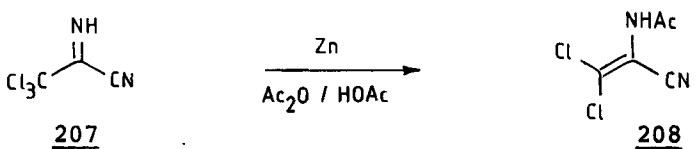
III.2. Reduction of α-Perhalogenated Imidoyl Cyanides

α-Perhalogenated imidoyl cyanides can be reduced to α-halogenated imidoyl cyanides bearing at least one α-hydrogen atom. Such compounds are usually more stable in the enamine form and therefore tautomerize. 2,2-Dichloro-2-phenylethaneimidoyl cyanide 203 was reduced with zinc in aqueous ethanol to form 2-amino-3-chloro-3-phenylacrylonitrile 204, while the reduction in acetic acid in the presence of acetic anhydride afforded the N-acetylated β-chloroenamine 205 and the N-acetylated α-cyanoenamine 206.[109]



Analogously, trichloroacetimidoyl cyanide 207 was converted into 2-N-acetylamino 3,3-dichloroacrylonitrile 208 by reduction with zinc in Ac_2O/HOAc.[108]



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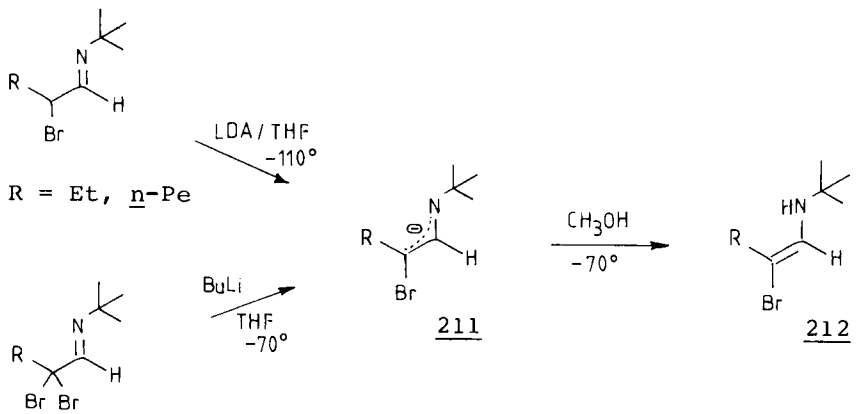
III.3. Selective Protonation of Lithiated α-Bromoaldimines

Lithiated α-bromoaldimines 211 were selectively protonated by methanol at -70° to afford β-bromoaldimines 212 in 79-87% yield.[110] This is the first report of the isolation and characterization of non-conjugated secondary β-haloenamines. Trituration of compounds 212 with acid or simple heating converted them rapidly into the more stable α-bromoaldimines 209.[111]



209 R = Et, n-Pe

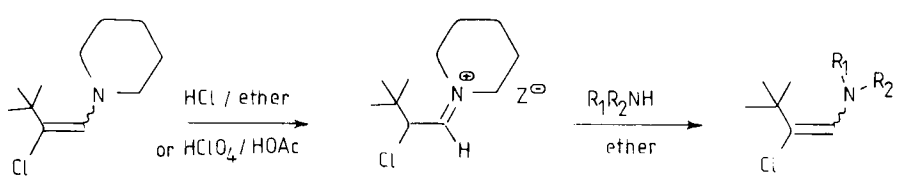
210 R = H, Me, Et, n-Pe

211

212

III.4. Exchange of the Amino Moiety in β-Haloenamines

β-Chloroenamines, e.g. 213, underwent a replacement of the amino moiety via transformation into α-chloroimmonium chlorides 214 and subsequent reaction with a ten-fold excess of a secondary amine in ethereal medium.[10] In this respect, the piperidino group in 214 was exchanged for the morpholino, pyrrolidino or N-methylanilino moiety. Besides immonium chlori-



213

214 (Z = Cl)

215 (Z = ClO_4)

216

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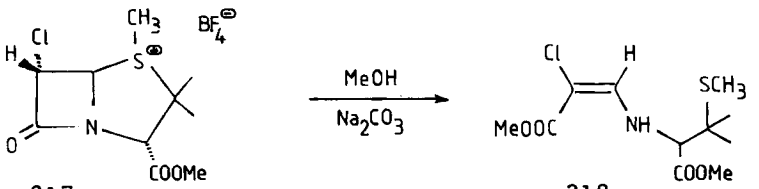
des, immonium perchlorates 215 were also used in such transformations (Preparation 9).[10]

III.5. Cleavage of α-Chloroazetidinone Derivatives

6α-Chloropenicillanate tetrafluoroborate 217 was stereospecifically cleaved by methanol in the presence of sodium carbonate to form the E isomer of β-chloroenamine 218 exclusively in 50% yield.[111] The reaction was proposed to occur

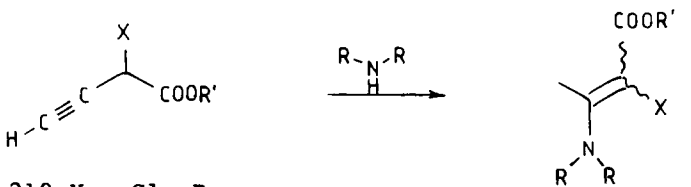


217 218

either via an azetidinyl cation, which was deprotonated and subsequently cleaved or via β-lactam cleavage and stereospecific isomerization to 218.

III.6. Reaction of 2-Halo-3-butynoates with Secondary Amines

The addition of secondary amines to 2-halo-3-butynoates 219 proceeded with double bond migration to the more stable conjugated β-haloenamines 220.[112]



219 X = Cl, Br

220

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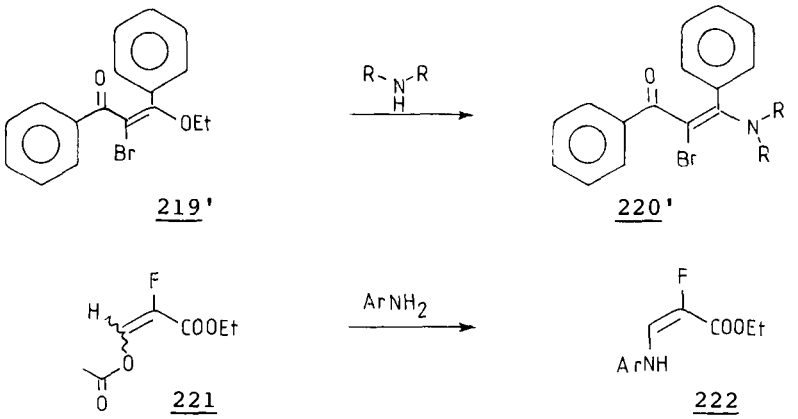
III.7. Reaction of β-Haloenol Ether or β-Haloenol Acetate Derivatives with Amines

Activated β-bromoenol ethers such as the β-benzoyl derivative 219' easily underwent Michael addition and elimination of the alcohol furnishing β-bromoenamines 220'.[113] Similar exchange reactions were observed with the enol acetate of ethyl formylfluoroacetate 221 and aromatic amines.[114]

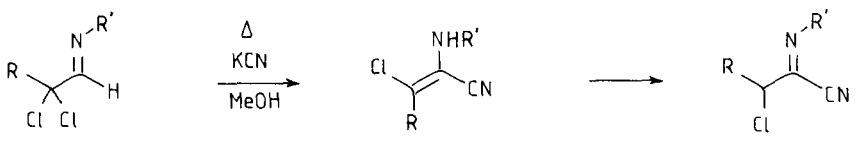


219' 220'

221 222

III.8. Reaction of α,α-Dichloroaldimines with Potassium Cyanide : Synthesis of β-Chloro-α-cyanoenamines

As previously reported, α-chloroaldimines underwent addition-elimination of hydrogen cyanide on reaction with potassium cyanide in various solvents.[4,115,116] This reaction[117] converted α,α-dichloroaldimines 223 to β-chloro-α-cyanoenamines 224.



223 224 225

Only the Z-isomers of 224 were detected when R was a moderately sterically demanding group (R = Me, Et, Pr, C_6H_5), while in the case of R = i-Pr a mixture of E and Z isomers was obtained.

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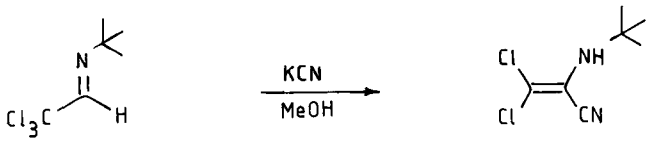
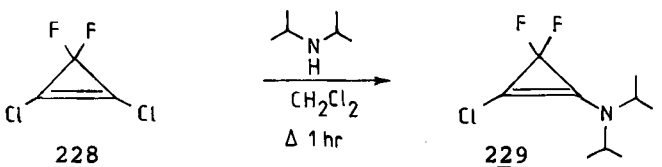
A general characteristic of α-cyanoenamines seemed to be that on heating they partially isomerized into the more stable imidoyl cyanides,[115] a phenomenon which was also found for β-chloroenamines 224. Similarly, N-t-butyl-α,α,α-trichloroacetaldimine (226) underwent addition-elimination with potassium cyanide in methanol to afford α-cyano-β,β-dichloroenamine 227 in low yield.[118]



226 227

III.9. 1-Dialkylamino-2-chlorocyclopropenes

A special type of β-chloroenamine, 2-chloro-3,3-difluoro-1-(N,N-diisopropylamino)cyclopropene (229) was obtained by addition of diisopropylamine to 1,2-dichloro-3,3-difluorocyclopropene 228 in dichloromethane under reflux.[119]



228 229

III.10. Substitution of β-Halogenated α-Haloenamino Derivatives

N-Functionalized β,β-dichloroenamines 234 (Z = CN, SC_6H_5) were prepared from the corresponding α,β,β-trichloroenamine derivatives 233 by reaction with sodium cyanide or sodium thiophenolate in methanol (Preparation 10).[120] The α-chloroenamines 233 were obtained by selective reaction of alcohols, aniline, N-unsubstituted carbamates and O-alkylated hydroxylamines with trichlorovinyl isocyanate 232. This compound was

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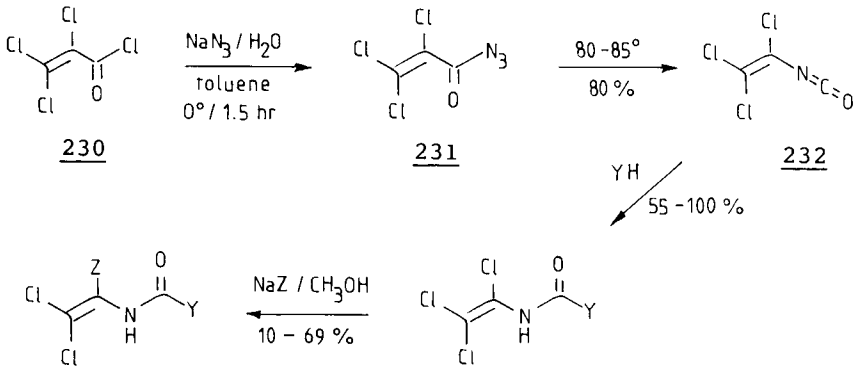
synthesized from trichloroacryloyl chloride (230) and the corresponding azide 231 by thermal rearrangement.[120] It is worth



230 231 232

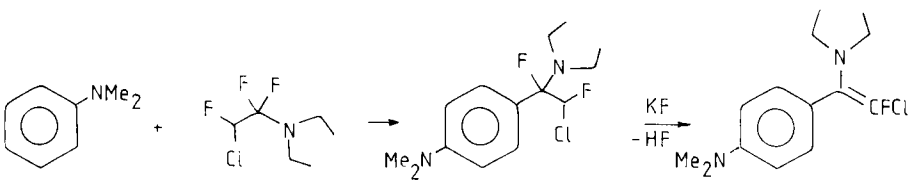
234 Z = CN, SC_6H_5

233 Y = OMe, OEt, OCH_2Ar, OAr, NHC_6H_5, NHCOOEt, NHOMe, N(Me)OMe

noting here that aliphatic amines, e.g. dimethylamine, methylamine and also ammonia, did give products of substitution of the chlorine atom of the α-chloroenamine moiety of compounds 233, but they occur exclusively as imino derivatives, i.e. dichloroacetamidines.[120] Similar reactions but of a more general type are compiled in section III.15.

III.11. Condensation of α,α-Difluoroamine with N,N-Dimethylaniline

α,α-Difluoroamine 236 condensed with N,N-dimethylaniline by electrophilic aromatic substitution to afford intermediate 237, which was dehydrofluorinated by potassium fluoride to



235 236 237 238

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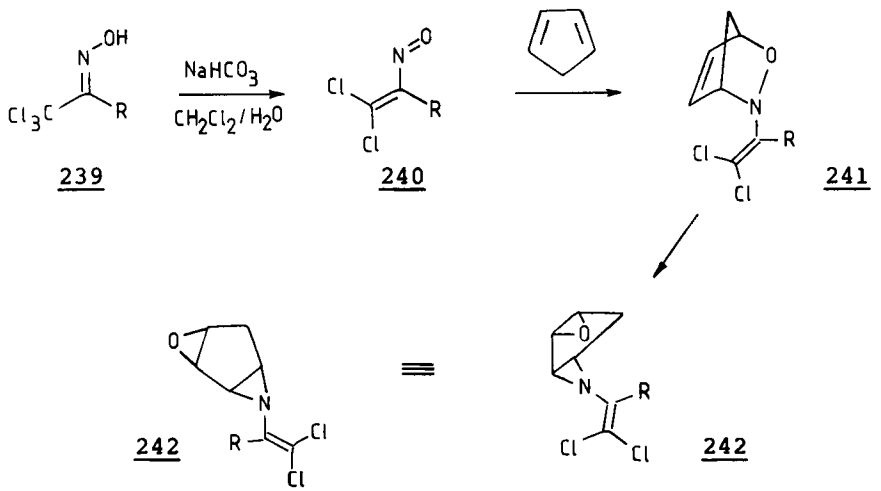
yield β-chloro-β-fluoroamine 238.[121]

III.12. Cycloaddition of Halogenated Nitrosoalkenes with Dienes

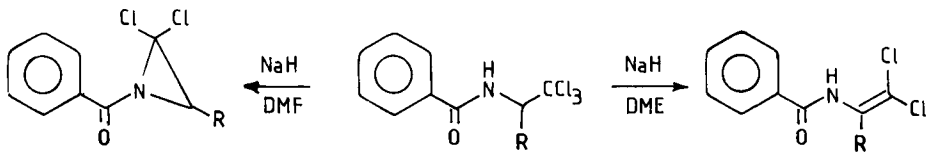
Nitrosoölefins, e.g. 240, easily obtained from the base-induced dehydrohalogenation of α-halogenated oximes,[4] were trapped by cyclopentadiene to furnish adduct 241, which rearranged into 242.[122,123]



239 240 241 242 242

III.13. Dehydrohalogenation of β-Halogenated Amines

Dehydrochlorination of N-benzoyl-β,β,β-trichloroamino compounds 244 in dimethoxyethane was accomplished with sodium hydride, providing β,β-dichloroenamides 245 in 27-83% yield (R = H, CH_3, C_6H_5).[124] When sodium hydride was used in dimethylformamide, an internal nucleophilic substitution occurred



243 244 245 (R = H, CH_3, C_6H_5)

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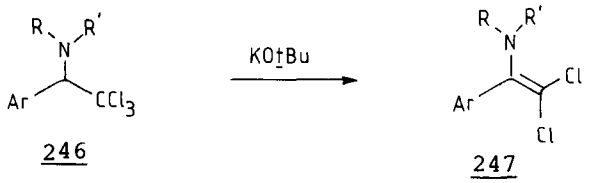
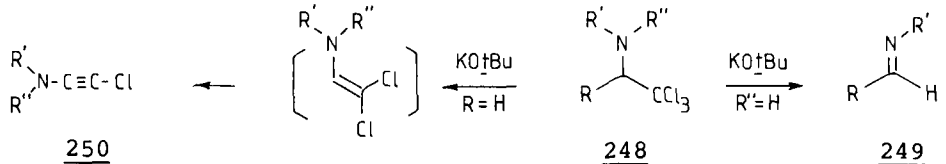
to yield 1-benzoyl-2,2-dichloroaziridines 243 in 45-60% yield.[124] This dehydrochlorination is also applicable to tertiary β,β,β-trichloroamines 246, which gave β,β-dichloroenamines 247 by reaction with potassium t-butoxide.[125,126]



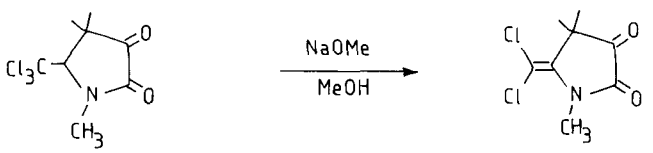
246 247

The corresponding aliphatic derivatives could not be synthesized in this way because it was found that loss of the elements of chloroform occurred (248 → 249).[125]



250 248 249

The simplest members of this series, i.e. 2,2,2-trichloroethylamine derivatives 248 (R = H), were dehydrochlorinated with potassium t-butoxide but the resulting β,β-dichloroenamine reacted further to give the chlorinated ynamine 250. The dehydrochlorination of β-halogenated amino derivatives was also applicable to cyclic amido compounds such as 251 which were converted into 252 by sodium methoxide in methanol.[127]



251 252

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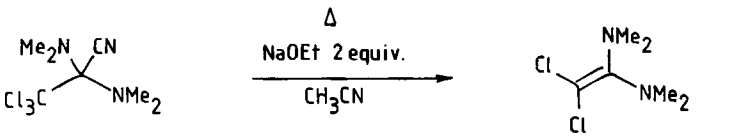
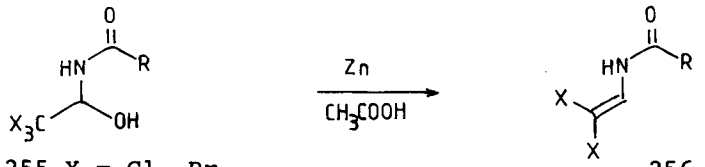
An unusual reaction was found during the reaction of polyfunctional compound 253 with anhydrous sodium ethoxide (2 equiv.) in acetonitrile.[128] A 40% yield of dichlorinated ketene aminal 254 was obtained. Such compounds (254) had been previously obtained from the dehydrochlorination of chloral aminals[164] and from the reaction of formamidinium salts with secondary amines and phenyltrihalomethyl mercury.[165] The latter reaction and the conversion of 253 into 254 are related in that the trichloromethyl anion is probably involved as an intermediate during these reactions.



253 → 254 (40%)

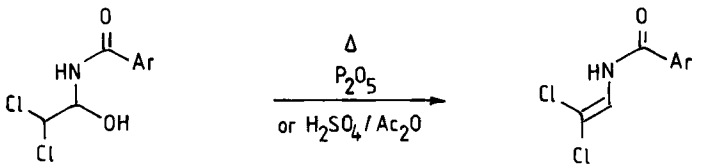
III.14. Dehydration of N-Acylated or N-Aroylated Carbinolamines

The reaction of the electrophilic carbonyl group of α-halogenated aldehydes with N-unsubstituted amides is a well-known reaction.[4] A variety of adducts derived from chloral and bro-



255 X = Cl, Br
R = alkyl, aryl

256



257 → 258

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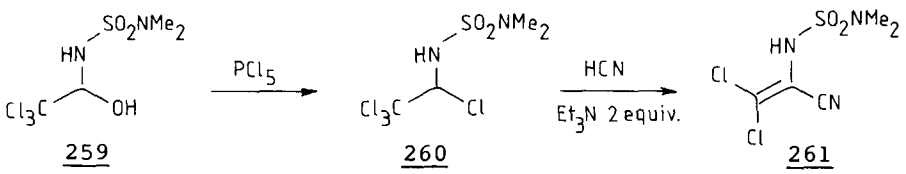
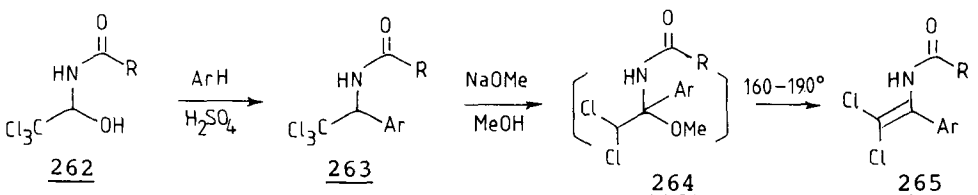
mal are known in the older literature. Such adducts, e.g. 255, have been utilized for the synthesis of β,β-dihaloenamides 256 by reduction and dehydration using zinc in acetic acid.[129-131] When a hydrogen atom is located β to the nitrogen atom, simple dehydration with phosphorus pentoxide or acetic anhydride/H_2SO_4 yielded enamides 258.[130]

The dehydration and reduction can be circumvented by converting the stable carbinolamine into the corresponding chloride with phosphorus pentachloride after which substitution with cyanide and dehydrochlorination with triethylamine affords β,β-dichloro-α-cyanoenamine derivative 261.[132] Recently, stable



259 260 261

carbinolamines 262 were utilized for electrophilic aromatic substitution. The resulting N-acyl- or N-benzoyl-β,β,β-trichloroamino derivatives 263 were dehydrochlorinated with sodium methoxide in methanol but the final product underwent addition of methanol to give 264, which were further converted into N-acyl- or N-benzoyl-1-aryl-2,2-dichlorovinylamines 265.[133]



262 263 264 265

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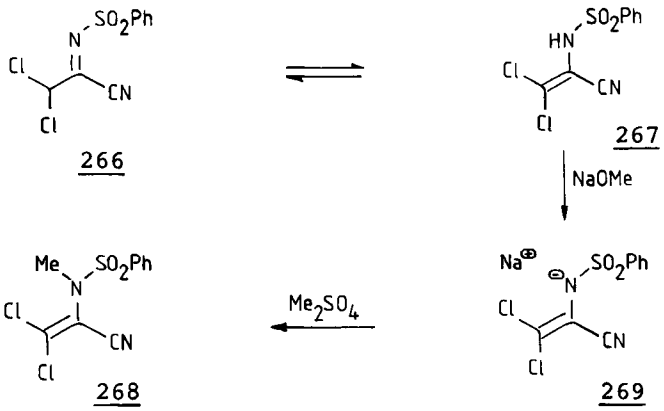
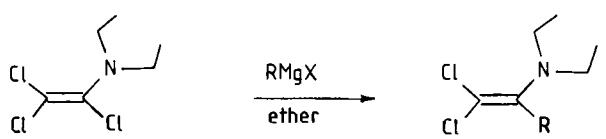
α-Cyanoenamine derivatives such as compound 267 most often occur in tautomeric equilibrium with the imino form (266),[134,135] but treatment with base, e.g. sodium methoxide, converts them into enamine salts (see 269).[136] The tautomeric equilibrium can be blocked by alkylating the salt 269 with dimethyl sulfate.[136]



III.15. Reaction of β-Halogenated α-Haloenamines with Nucleophilic Reagents

α-Halogenated enamines are very reactive compounds, the synthesis and reactivity of which was recently described.[5] Displacement of the α-halo atom occurs readily with a variety of Grignard reagents, thereby yielding the corresponding α-alkylated enamines as exemplified for trichlorovinylamine 270 (Preparation 11).[137] The starting α-chloroenamine was prepared from N,N-diethyl trichloroacetamide and trivalent phosphorus



270

271 R = Me, Et, n-Pe, i-Pr, Ph, vinyl, 1-hexynyl, allyl

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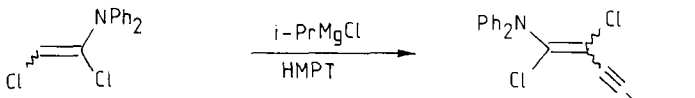
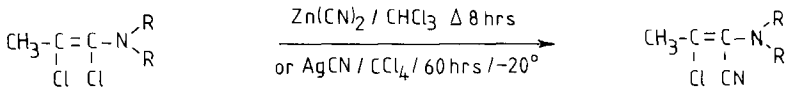
compounds.[139,140] However, the reaction of N,N-diphenyl-α,β-dichlorovinylamine 272 (E/Z mixture) with isopropylmagnesium chloride in hexamethylphosphoramide (HMPT) took a different course in that an unusual product 273 was formed.[138] The latter was rationalized via an obscure mechanism involving an intermediate functionalized methylenecyclopropane.[138]



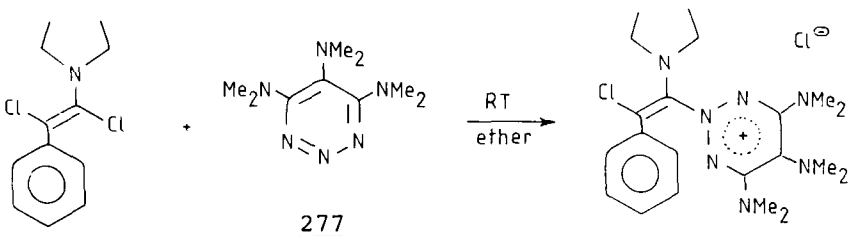
272 (E+Z) 273

Substitution of α,β-dichlorovinylamines 274 (NRR = dimethylamino, pyrrolidino) with zinc cyanide in chloroform or silver cyanide in carbon tetrachloride furnished β-chloro-α-cyanoenamines 275.[141]



274 275

A more recent example showed that α,β-dichloroenamine 276 suffered a similar nucleophilic attack by nitrogen heterocycles, e.g. 1,2,3-triazine derivative 277, producing the red salt 2-(2-chloro-1-diethylamino-2-phenylvinyl)-4,5,6-tris(dimethylamino)-1,2,3-triazinium chloride (278) in 58% yield.[142]



276 277 278

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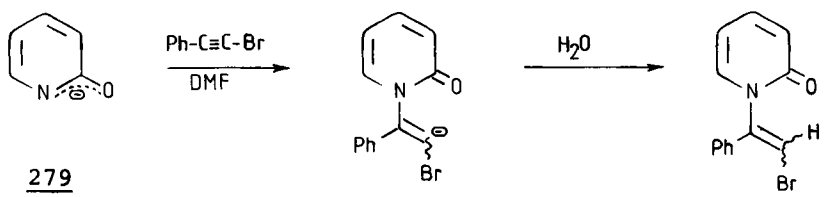
III.16. Vinylation of 2-Pyridone with 1-Bromo-2-phenylacetylene

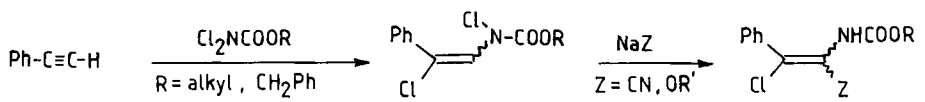
β-Bromoenamines can be synthesized by condensation of an appropriate nitrogen species with a halogenated acetylene derivative as illustrated by the N-vinylation of 2-pyridone (using its sodium salt 279) with 1-bromo-2-phenylacetylene.[143]



279 280

III.17. Addition of N,N-Dichlorocarbamates to Acetylenes and Subsequent Addition-Elimination

When phenylacetylene is condensed with N,N-dichlorocarbamates in the presence of alkoxides or cyanide, the resulting N-chloroenamino intermediate is converted into α-functionalized-β-chloroenamino derivatives 281 by addition-elimination.[163]



281

III.18. β-Haloenimine Type Compounds

In this section attention will be focussed on structures having a 2-azabutadiene moiety (or related derivative) in the molecule. It is clear that these derivatives do not exhibit the general reactive behavior of ordinary β-haloenamines, but are included here for the sake of comparison. These compounds can undergo addition at the carbon-nitrogen double bond usually present in the molecule, to afford functionalized β-haloena-

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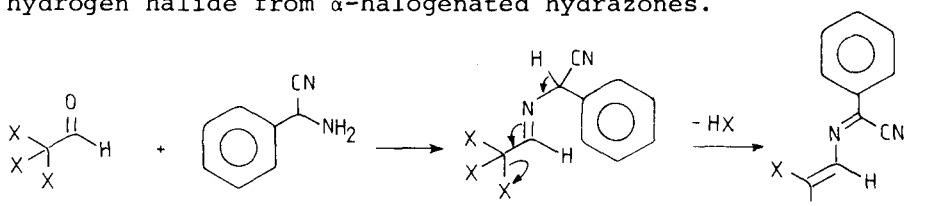
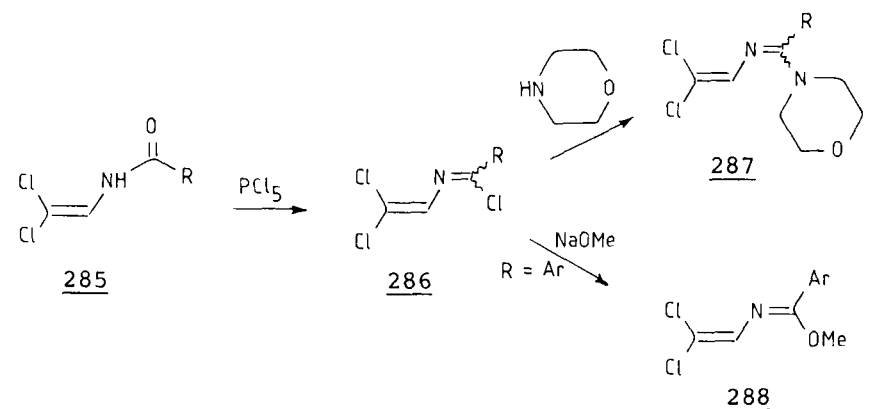
mines. Therefore, the derivatives discussed in this section are regarded as potential β-haloenamines.

The condensation of chloral and bromal 282 (X = Cl, Br) with α-aminobenzyl cyanide yielded imino compound 283 as an intermediate, but elimination of hydrogen halide afforded N-(2,2-dihaloethenyl)-1-imino-1-phenylacetonitrile 284.[144] The dehydrohalogenation of 283 is analogous to the elimination of hydrogen halide from α-halogenated hydrazones.[4]



282 (X = Cl, Br) 283 284

The conversion of β,β-dichloroenamide 285 into 286 was accomplished using phosphorus pentachloride.[145] These imidoyl chlorides 286 were further derivatized into amidines 287 and imidates 288 by reaction with morpholine or sodium methoxide, respectively.[145] Methyl N-(1-phenyl-2,2,2-trichloro)ethylcarbamate 289 reacted with sodium methoxide in methanol to yield



285 286 287 288

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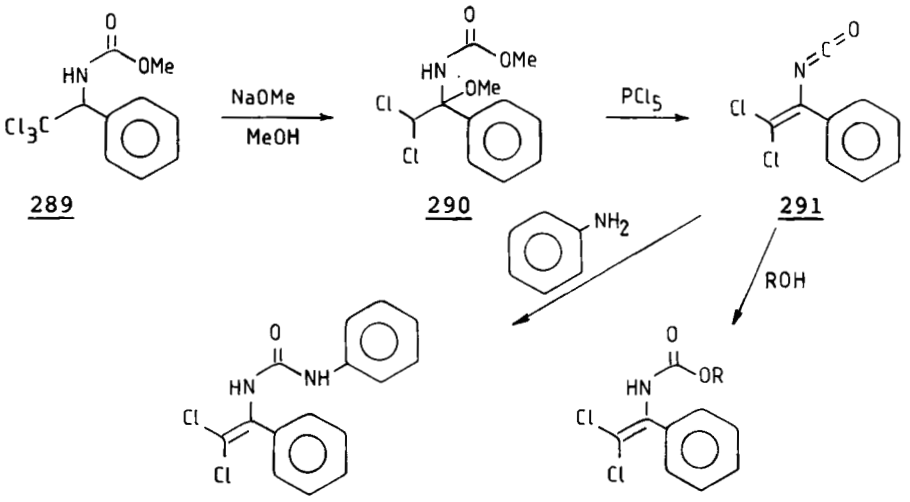
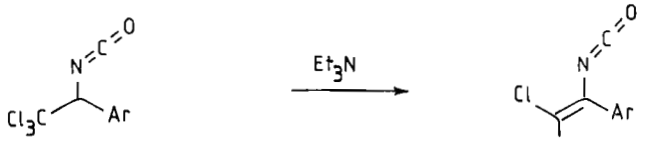
290, which was converted into 2,2-dichloro-1-phenylvinyl isocyanate 291 by reaction with phosphorus pentachloride[146] (see also related work).[147]



289 290 291

292 293 (R = Me, Ph)

Addition of nucleophiles such as alcohols or aniline provided β,β-dichloroenamine derivatives 292 and 293, respectively.[146, 148] An alternative method for the generation of 295 consisted of triethylamine induced dehydrohalogenation of α-trichloromethylbenzyl isocyanate 294.[149]



294 (Ar = C_6H_5, p-ClC_6H_4) 295

Similarly β,β-dichloroenamine derivatives 298 were obtained by functionalization of 296 and subsequent dehydrohalogenation, followed by conversion of the amide function into the imidoyl chloride using PCl_5.[150]

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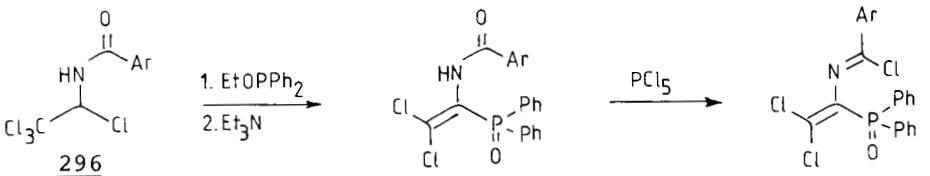
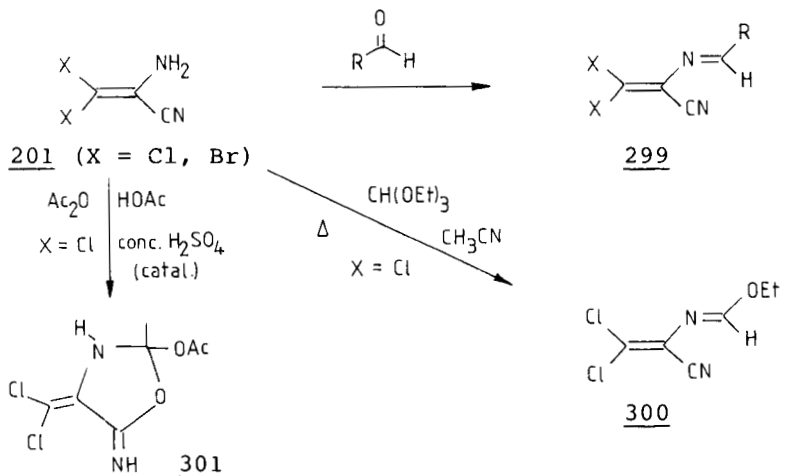


296 297 298

2-Amino-3,3-dihaloacrylonitrile 201 reacted with aldehydes or triethyl orthoformate to afford the 2-azabutadiene derivatives 299 and 300, both being potential β-halogenated enamines.[108,153] The reaction with acetic anhydride in acetic acid in the pre-



sence of catalytic amounts of concentrated sulfuric acid resulted in a heterocyclic β-halogenated enamine 301.[108]

III.19. Reaction of Diketene with Ammonia and Sodium Hypochlorite

A special type of β-chloroenamine (303) was obtained from the reaction of diketene (302) with ammonia in the presence of sodium hypochlorite.[151]

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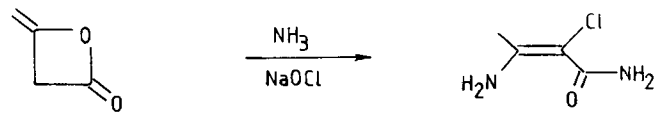
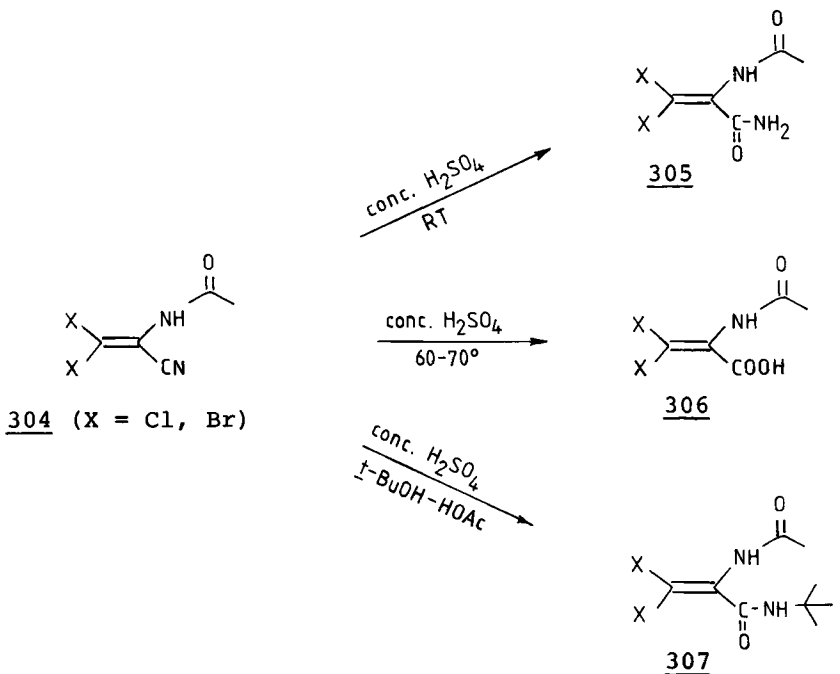


302 303

III.20. Functionalization of β-Haloenamine Type Compounds

The cyano group in α-cyano-β,β-dihaloenamides 304 (X = Cl, Br) could be transformed into a variety of derivatives (305, 306, 307) by employing concentrated sulfuric acid under controlled conditions.[109]



304 (X = Cl, Br) 305 306 307

The acylation of α-amino-β,β-dichloroacrylonitrile 201 with carboxylic anhydrides in the presence of concentrated sulfuric acid yielded the highly functionalized derivatives 308.[154]

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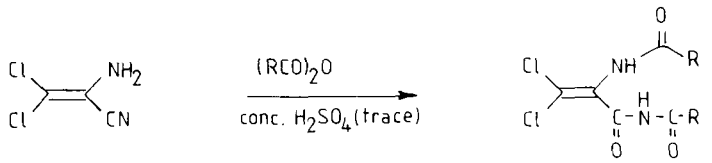


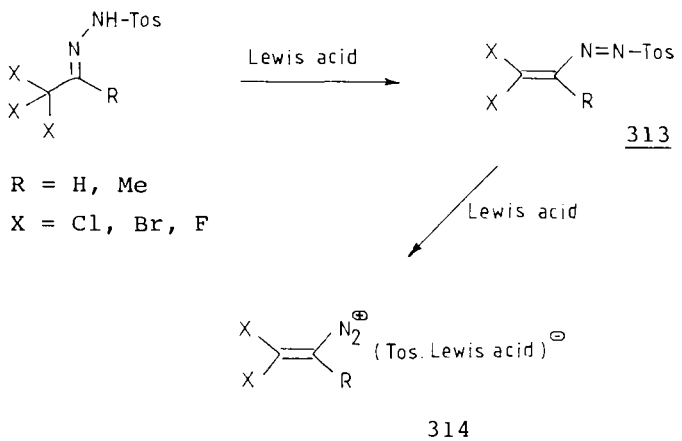
201 308

III.21. Olefin-Diazonium Salts

A very specific example which can be classified in this section is the synthesis of olefin-diazonium salts 311 starting from 2,2-dichlorovinylisocyanate 309 and nitrosyl hexachloroantimonate.[152]

309 310 311

Another approach to such halogenated olefin-diazonium salts (314) was accomplished by the action of Lewis acids (e.g. $SnCl_4$, $AlCl_3$, $SbCl_5$) on α-halogenated tosylhydrazones 312, which involved the intermediacy of tosylazoalkenes 313.[152]



312 R = H, Me
X = Cl, Br, F

313

314

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IV. PREPARATIONS

Preparation 1 : 2-Bromo-1-(N,N-diethylamino)-3,3-dimethyl-1-butene (16, R = t-Bu; R' = Et; R" = H; X = Br)[10]

A solution of 8.95 g (0.05 mol) of 2-bromo-3,3-dimethylbutanal in 100 mL of dry ether was treated with 6.05 g (0.033 mol) of $AsCl_3$, dissolved in 100 mL of dry benzene. The mixture was cooled between 5 and 10° and, under vigorous stirring, a solution of 14.2 g (0.2 mol) of diethylamine in 70 mL of dry ether, was added. After stirring for 30 min., the reaction mixture was left at -30° for 24-36 hrs. Filtration of the precipitate (quantitative formation of diethylamine hydrochloride and As_2O_3) and evaporation afforded a residual oil which was distilled in vacuo to give 7.8 g (67%) of colorless 2-bromo-1-(N,N-diethylamino)-3,3-dimethyl-1-butene, bp. 66°/0.65 mmHg (>95% pure).

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Preparation 2 : 2-Chloro-1-(dimethylamino)-1-phenylethylene (16, R = H; R' = CH_3; R" = C_6H_5; X = Cl)[11]

To a stirred solution of 7.72 g (0.050 mol) of phenacyl chloride in 150 mL of dry ether was added a solution of 6.83 g (0.033 mol) of tris(dimethylamino)arsine[155,156] in 80 mL of dry diethyl ether at 5° under a nitrogen atmosphere. The reaction mixture was stirred at this temperature for 2 hrs. and then stored at -20° overnight. After the solution was warmed to room temperature, the precipitated As_2O_3 was collected by filtration (3.3 g; 100%). After evaporation of the solvent, the residue was distilled to give 7.8 g (86%) of 2-chloro-1-dimethylamino-1-phenylethylene (E/Z : 90/10), bp. 70°/0.7 mmHg.

Preparation 3 : 3-Anilino-2-chlorocrotononitrile (43, X = Cl; Ar = Ph)[22]

A solution of 5.8 g (0.049 mol) of 2-chloro-3-ketobutyronitrile 42[22,157] and 4.7 g (0.05 mol) of aniline in 50 mL of ethanol was kept at 50° for 20 min. Partial evaporation of the solvent afforded 7.4 g (77%) of colorless crystals (43; X = Cl; Ar = Ph) which were recrystallized from ethanol or carbon tetrachloride (mp. 132°).

Preparation 4 : 3-Bromo-4-(N,N-dimethylamino)-3-buten-2-one (119, R = CH_3)[159]

A stirred and cooled (-10°) solution of 11.3 g (0.1 mol) of 4-(N,N-dimethylamino)-3-buten-2-one 117 (R = CH_3)[158] in 50 mL of absolute dichloromethane was treated over a period of 30 min with 17 g (0.105 mol) of bromine untill a persistent yellow color was obtained (N_2-atmosphere). At -10°, 10.1 g (0.1 mol) of triethylamine was added dropwise, 50 mL of diethyl ether was added and stirring was continued for 1 hr at this temperature. After filtration of the precipitated triethylammonium bromide, the filtrate was evaporated in vacuo to afford 18.8 g (98%) of 3-bromo-4-(N,N-dimethylamino)-3-butene-2-one 119 (R = CH_3) of at least 95% purity. Recrystallization of a part of the product from acetic acid at -50° gave an analytical sample, mp. 63-65°.

Preparation 5 : Methyl 3-chloro-2-acetamidoacrylate (127)[74]

Chlorine gas was passed at room temperature into a stirred solution of 28.6 g (0.020 mol) of methyl 2-acetamidoacry-

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late 126[160] in 500 mL of dry carbon tetrachloride (stored over Linde 3Å molecular sieves) until a permanent yellow color developed, after which the yellow solution was stirred for another 10 min. The solvent was removed in vacuo to yield a colorless oil, which was dissolved in 500 mL of dry acetonitrile (stored over Linde 3Å molecular sieves) and 23.2 g (0.027 mol) of 1,4-diazabicyclo[2,2,2]octane was added to the solution. The reaction mixture was stoppered and stirred for 1 hr. at room temperature. The precipitated hydrochloride salt was filtered and the solvent was removed in vacuo to yield a brown precipitate, which was extracted three times with 100 mL of cold ethyl acetate. The combined extracts were filtrered through Celite and the ethyl acetate was removed in vacuo to give a brown oil which solidified upon standing overnight. Recrystallization from ether yielded 14.6 g (41%) of a white solid (127), mp. 96-97°.

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Preparation 6 : E- and Z-3-(α-Bromobenzylidene)-2-phenetylphtalimidine (137)[80]

To a stirred and ice-cold solution of 37.0 g (0.113 mol) of E-3-benzylidene-2-phenetylphtalimidine 136 in 180 mL of chloroform was slowly added 6.5 mL of bromine, dissolved in 20 mL of chloroform. The mixture was then washed with water and 2N sodium carbonate, and evaporated to give an oily residue, which on trituration with methanol partially solidified. The solid (35.5 g; 77%) consisted of a 2:1 mixture of Z- and E-137, respectively. Fractional crystallization from methanol afforded Z- and E-isomers, mp. 135-136° and 116-117°, respectively.

Preparation 7 : 2,6-Dichloro-1-morpholinocyclohexene (154)[86]

An ice-cooled and stirred solution of 2.68 g (0.02 mol) of N-chlorosuccinimide in 60 mL of dichloromethane was treated dropwise with 1.67 g (0.01 mol) of 1-morpholinocyclohexene. The solvent was removed in vacuo at ambient temperature and the residue was extracted three times with 20 mL of pentane. The combined extracts were evaporated and the product was distilled in vacuo (Kugelrohr apparatus) to yield 2.2 g (93%) of 1,3-dichloro-2-morpholino-1-cyclohexene 154, bp. 40-50°/0.05 mmHg.

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Preparation 8 : 5-Chloro-3,4-dihydro-6-phenyl-2(1H)-pyridinone (182)[97]

A solution of 0.7 g (0.0040 mol) of 3,4-dihydro-6-phenyl-2(1H)-pyridinone 180[161,162] in 10 mL of chloroform was cooled in an ice bath and treated dropwise with 0.6 g (0.0044 mol) of sulfuryl chloride in 2.5 mL of chloroform over 15 min. After addition of the chlorinating agent, the reaction mixture was stirred for another 15 min in an ice bath and 30 min. at ambient temperature. After evaporation in vacuo, the residue was dissolved in 20 mL of acetone and triturated dropwise with 40 mL of water upon which 0.45 g (53%) of 5-chloro-3,4-dihydro-6-phenyl-2(1H)-pyridinone (182) precipitated as needles (mp. 175°).

Preparation 9 : 2-Chloro-1-(N-methyl)anilino-3,3-dimethyl-1-butene (216, R_1 = Ph; R_2 = CH_3)[10]

A solution of 2.01 g (0.01 mol) of 2-chloro-3,3-dimethyl-

1-piperidino-1-butene 213 in 100 mL of dry ether was treated with 100 mL of 0.1N dry hydrogen chloride in ether, yielding the α-chloroimmonium salt. The stirred suspension was triturated in the cold with a solution of 10.7 g (0.1 mol) of N-methylaniline in 50 mL of dry ether. Stirring was continued for 30 min. and the piperidine hydrochloride was isolated in quantitative yield by filtration. The filtrate was concentrated in vacuo and distilled to give 2-chloro-1-(N-methyl)anilino-3,3-dimethyl-1-butene (216, R_1 = Ph; R_2 = CH_3) in 60% yield (purity >95%; no bp. reported).

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Preparation 10 : Methyl N-(1-cyano-2,2-dichlorovinyl)carbamate (234, Y = OCH_3; Z = CN)[120]

To a solution of 7.35 g (0.15 mol) of sodium cyanide in 700 mL of methanol was added 30.6 g (0.15 mol) of methyl N-trichlorovinylcarbamate 233 (Y = OCH_3) and the reaction mixture was stirred for 16 hrs. at 20°. After evaporation of the solvent under reduced pressure, product 234 (Y = OCH_3; Z = CN) was purified by chromatography on alumina with benzene-ethyl acetate (4:6) as eluent. (yield 17%; mp. 117°).

Preparation 11 : 2,2-Dichloro-1-(N,N-diethylamino)-1-phenylethylene (271, R = C_6H_5)[137]

A solution of 18.2 g (0.09 mol) of 1,2,2-trichloro-1-(N,N-diethylamino)ethylene (270)[139,140] in an equal volume of dry ether was added dropwise at ambient temperature to a 1.5N solution of phenylmagnesium bromide in ether (obtained from 17.6 g (0.13 mol) of bromobenzene) after which the solution

was refluxed for 2 hrs. The reaction mixture was hydrolyzed at 0° with an aqueous ammonium chloride solution to which some aqueous ammonia was added. The etheral extract were dried and distillation *in vacuo* gave 15 g (70%) of 2,2-dichloro-1-(N,N-diethylamino)-1-phenylethylene (*271*, R = C_6H_5), bp. 82°/0.03 mmHg.

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