The chemistry of

α-haloketones, α-haloaldehydes and α-haloimines

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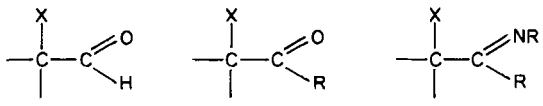

The chemistry of α-haloketones, α-haloaldehydes and α-haloimines

By

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Foreword

'*Updates from the Chemistry of the Functional Groups*' is a new venture which is actually an offshoot of the main trunk, '*The Chemistry of Functional Groups*'.

The aim of the Editors and the Publishers is to present selected chapters on a single topic or on closely related topics from the main series, thus making them available for individual chemists in the form of more modestly sized and priced volumes. However, we believed that the presentation of such chapters should be accompanied by appendices updating the material of the original chapters and in some cases even by the addition of new subjects if these dovetail naturally with the older material. This was the case in the present volume, which contains two original chapters from Supplement D of the main series (published in 1983), each updated by an extensive appendix by the same two authors and also a completely new chapter on α-halogenated aldehydes, which fits naturally in with the other two chapters. Thus a complete picture of the α-halogenated derivatives of the three most important carbon heteroatom doubly bonded functional groups (ketones, aldehydes and imines) is given, covering the preparation, properties, reactivity and synthetic applications of the title compounds.

Other volumes in the '*Updates*' series are already in active preparation and are due to appear shortly. These are a volume on '*Nitrones, nitronates and nitroxides*'; a volume on '*Crown ethers*'; and one on '*Cyclopropyl radicals, cations, anions, cation and anion radicals*'. Other volumes, planned for a slightly later publication date, will be on '*Halogenations*', on '*Synthesis of lactams and lactones*', and on '*Synthetic applications of quinones*'.

We will be very grateful to readers who would call our attention to omissions or mistakes in this and other volumes of the series.

JERUSALEM
June 1988

SAUL PATAI
ZVI RAPPOPORT

Preface

α-Halocarbonyl derivatives are an important class of organic compounds, the chemistry of which occupies a key position in modern organic chemistry. The field dates back to more than 150 years ago, when the chlorination of acetone was described and the first characterized α-haloketone was 1, 1-dichloroacetone, described by Fittig in 1859, while bromoacetone was presumably the first characterized α-bromoketone. Since these early results, many and ramified publications have appeared on the chemistry of α-halocarbonyl compounds and many hundreds of papers are added each year. Especially during the last three decades these compounds have received intensive attention, resulting in new and improved synthetic strategies. The high chemical reactivity of α-haloketones and α-haloaldehydes enables them to undergo a wide variety of reactions, and the literature indeed proves the wide synthetic potential of this class of compounds.

The chemistry of α-haloimines, i.e. the nitrogen analogues of α-halocarbonyl compounds, started to be studied in depth only in the 1970s. α-Haloimines are now increasingly important, especially in view of their ability to act as masked α-halocarbonyl compounds and their wide synthetic potential.

The attempt to publish in one book the most pertinent information on α-haloketones, α-haloaldehydes and α-haloimines is the result of a desire by both authors to present an up-to-date treatise on these heteroallylic halides, to review the most significant advances in this area and to convey knowledge about the availability of the title compounds, their chemical properties and their role in modern organic synthesis. The chapters deal separately with the chemistry of α-haloketones, α-haloaldehydes and α-haloimines, and their reactivity towards selected carbon, nitrogen, oxygen and sulphur nucleophiles. The literature is reviewed up to the first half of 1986.

The monograph is designed for the use of students, researchers and professional workers in industry and at academic institutions where organic synthesis and mechanistic organic chemistry are actively practised.

The structure of the book needs some comment. The publishers and the Editors of the 'Functional Groups' series of books decided to produce some sections of the series as smaller, more accessible monograph volumes. As the first of these selections, the two chapters on α-haloketones and α-haloimines, which appeared in '*Supplement D: The Chemistry of Halides, Pseudohalides and Azides*, pp. 549–601 and 813–931, respectively (1983), have been brought together using the original text published in 1983 and, in addition, extensive up-to-date Appendices to both parts have been added. In order to complete the picture, an entirely new chapter on α-haloaldehydes has been included.

Finally, both authors express their gratitude to Professor Niceas Schamp, Director of the Laboratory of Organic Chemistry, Faculty of Agricultural Sciences, State University of Gent, for his support of our research programme during the last two decades. The

Belgian Nationaal Fonds voor Wetenschapplijk Onderzoek (National Fund for Scientific Research) is thanked for generous support over the same period of time.

Gent, Summer 1987

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The chemistry of α-haloketones, α-haloaldehydes and α-haloimines
Edited by Saul Patai & Zvi Rappoport

CHAPTER 1

Synthesis and reactivity of α-halogenated ketones

I. INTRODUCTION

Although much information on the synthesis and the chemistry of α-halogenated carbonyl compounds is scattered throughout the literature, there appear to be few comprehensive sources of information in this important area, with the exception of a short chapter dealing with the preparation of halogenated ketones in Houben-Weyl's *Methoden der organischen Chemie*[1,2]. In addition, the Favorskii rearrangement of α-haloketones has been reviewed by several authors[3–8], while the reactivity of α-haloketones towards nucleophiles was described by Tchoubar in 1955[9]. The past two decades has seen a considerable expansion in synthetic procedures and mechanistic studies on the reactivity of α-halogenated ketones. It is our hope that putting together a survey of the widely scattered information on the synthesis and reactivity of α-haloketones will focus new attention on the broad potential of these compounds in synthetic and mechanistic organic chemistry.

The presentation of this chapter is divided into two major sections. The first part deals with the synthetic methods for the preparation of α-haloketones. In the second section the reactivity will be considered, with emphasis on preparative applications, although some mechanistic interpretations of the results will be treated in some important cases. The section on reactivity has been subdivided according to the nature of the nucleophile, e.g. oxygen, nitrogen or carbon nucleophiles, and not on the basis of the reaction type, e.g. substitution, elimination.

This chapter has been restricted to halogenated ketones which carry one or more halogen atoms at the α-carbon atom to a carbonyl function, excluding compounds derived from diketones, β-keto esters and quinones. Other α-halogenated carbonyl compounds such as aldehydes, esters and acids will not be treated in this chapter.

II. SYNTHESIS OF α-HALOGENATED KETONES

While a number of reviews have been published during the last decade on the preparation of α-fluoroketones[10–13], practically no general review deals with new syntheses of α-chloro-, α-bromo- and α-iodoketones[14]. The syntheses of α-fluoro-, α-chloro-, α-bromo- and α-iodoketones are treated separately and the procedures are classified according to the starting substrates. Some procedures, using the same class of reagents, are described separately for each class of haloketones.

A. Synthesis of α-Fluoroketones

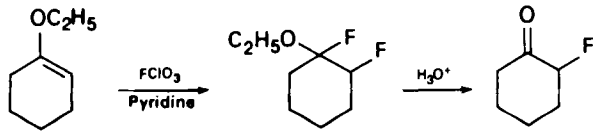
1. α-Fluoroketones from ketones and their derivatives

Conventional methods for the synthesis of α-fluoroketones by direct fluorination of ketones often give rise to side reactions and are therefore of limited use (equation 1).

$$R^1CH_2COCH_2R^2 \xrightarrow{'F'} \underset{\displaystyle F}{\overset{\displaystyle |}{R^1CHCOCH_2R^2}} + \text{polyfluorinated and degradation products} \qquad (1)$$

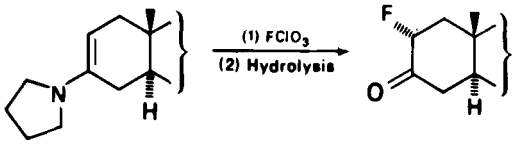
For example, treatment of acetone with fluorine yields a complex mixture of fluoroacetone, hexafluoroacetone and degradation products such as trifluoroacetyl chloride, tetrafluoromethane and carbonyl difluoride[15]. The direct action of perchloryl fluoride on ketones has also met with little success because of degradation reactions.

The reactions of a variety of fluorinating agents on derivatives of ketones appear to be more advantageous. Potential synthetic interest may be found in the reaction of perchloryl fluoride with enol ethers[16], enol esters[17], enamines[18] and lithium enolates[230]. 1-Ethoxycyclohexene (**1**) gives 2-fluorocyclohexanone (**3**) via 1-ethoxy-1,2-difluorocyclohexane (**2**) on treatment with perchloryl fluoride in pyridine at 0°C (equation 2)[16]. The enamines of 3-oxo steroids are transformed into 2α-fluoro-3-oxo steroids on treatment with perchloryl fluoride followed by hydrolysis of the intermediate fluoroenamines.



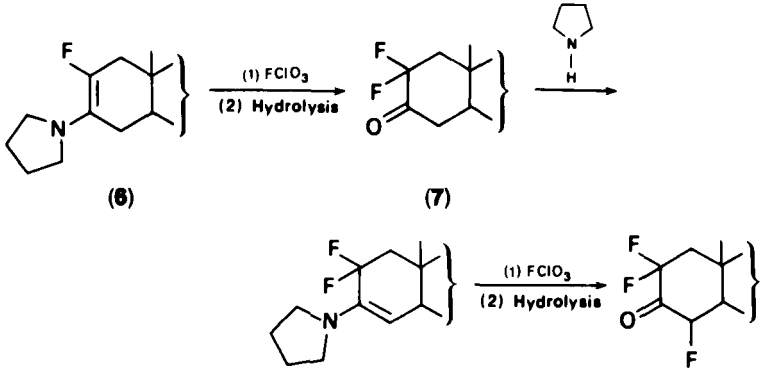
(1) (2) (3) (2)

2α-Fluorocholestan-3-one (**5**) is formed on treatment of 3-(*N*-pyrrolidinyl)-2-cholestene (**4**) with this reagent in benzene in 72% yield (equation 3)[19].



(4) (5) (3)

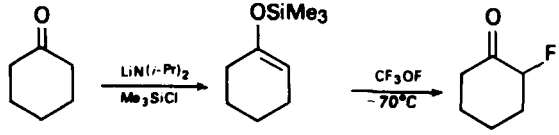
When fluorinated steroidal enamines (**6**) are treated with perchloryl fluoride, 2,2-difluoro compounds (**7**) and 2,2,4-trifluoro compounds (**9**) become accessible (equation 4)[20,21]. A related process for the synthesis of α-fluoroketones employs lithium enolates of ketones and perchloryl fluoride in tetrahydrofuran. In this manner ω-fluoroacetophenone is obtained in 44% yield[22].



(6) (7) (8) (9) (4)

Fluorination of ketones with perchloryl fluoride is also performed via intermediate methoxalyl ketones[23] (i.e. — COCOOMe) and hydroxymethylene ketones[24]. 2α-Fluorohydrocortisone is synthesized from the sodium salt of 20-ethylenedioxy-2-methoxalyl-Δ⁴-pregnentriol-(11β, 17α, 21)-3,20-dione[23] and 2α-fluorotestosterone from the sodium salt of 2-hydroxymethylenetestosterone[24].

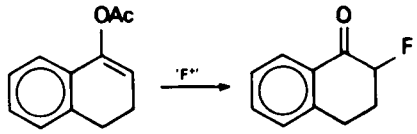
Recently, a new and powerful method for the α-fluorination of carbonyl compounds was developed which utilizes trifluoromethyl hypofluorite with silyl enol ethers, as exemplified by the preparation of 2-fluorocyclohexanone (**3**) in 70% yield (equation 5)[25]. A similar method with enol acetates is used by Rozen, by passing fluorine



(10) (11) (3) (5)

into a suspension of sodium trifluoroacetate in Freon at −75°C. A considerable portion of the oxidizing ability of this solution is due to the presence of pentafluoroethyl hypofluorite (CF_3CF_2OF) and other oxidizing compounds of the

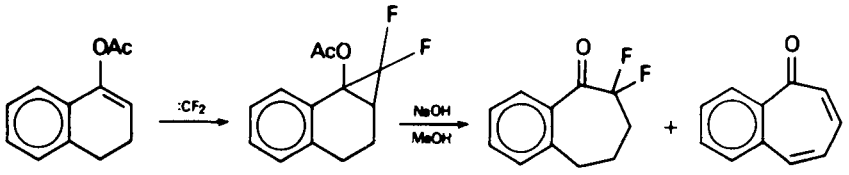
perfluoroxyfluoride type. 2-Fluoro-1-tetralone (**13**) can be obtained by this procedure in 85% yield by starting from the enol acetate of 1-tetralone (**12**) (equation 6)[26].



(6)

(**12**) (**13**)

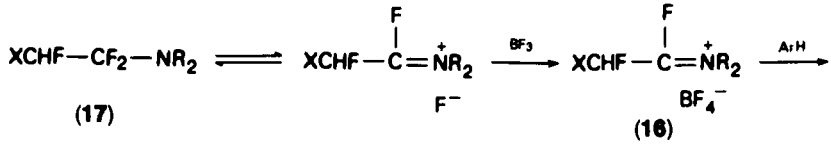
In attempts to react enol acetates with molecular fluorine, no α-fluoroketones could be isolated from the complicated reaction mixtures. Geminal α,α-difluoroketones are formed by decomposition of geminal difluorocyclopropanes (**14**), prepared by difluorocarbene addition to enol acetates. Reaction of these cyclopropanes with sodium hydroxide in methanol provides α,α-difluoroketones (**15**) in addition to other products (equation 7)[27,28]. The corresponding dichloro- and dibromocyclopropanes exhibit completely different pathways, resulting in the formation of halogenated enones.



(7)

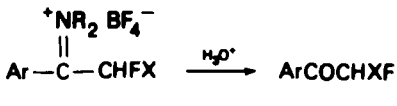
(**12**) (**14**) (**15**) (**16**)

Finally, the action of a Lewis acid on α-fluorinated amines (**17**), easily obtained by addition of secondary amines to fluorinated alkenes, produces fluorinated immonium salts (**18**), which on arylation with electron-rich aromatic compounds and subsequent hydrolysis furnish α-halo-α-fluoroacetophenones (**20**) (equation 8)[29].



(**17**) (**16**)

(8)



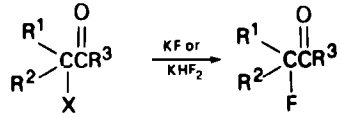
(**19**) (**20**)

X = Cl, Br

2. *α-Fluoroketones from α-haloketones by halogen exchange*

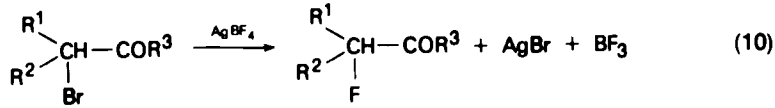
The exchange of a chlorine atom in α-chlorinated ketones by fluorine on treatment with hydrogen fluoride only takes place when there is no possibility of hydrogen

chloride elimination, such as in perchloroketones and chloroacetone. Better results are obtained with potassium fluoride[30,161] and potassium hydrogen fluoride (KHF_2)[31] (equation 9). Excellent results of bromine–fluorine exchange are obtained by the use



(9)

of mercuric fluoride[32,33]. If a chlorine atom is also present in the molecule, it is retained. 1-Aryl-2,2-difluoro- and 1-aryl-2-chloro-2-fluoro-1-alkanones are prepared by this procedure in moderate yields. Another method involves the use of silver tetrafluoroborate in ether. However, this method is not applicable to primary bromoketones or to chloroketones (equation 10). The method does not seem to have a broad scope since several side products, mainly α,β-unsaturated ketones, are formed,



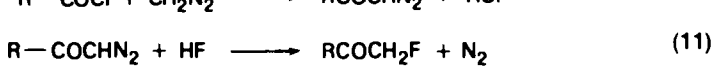
(10)

making isolation on a preparative scale rather laborious. When the reaction is carried out in nucleophilic solvents (methanol, acetic acid), α-methoxy- and α-acetoxyketones are isolated as side products.

Other procedures of bromine–fluorine exchange utilize potassium fluoride in dimethylformamide, glycerine and diethylene glycol[33–35], silver fluoride in acetonitrile–water[36], thallium fluoride[37] and pyridinium poly(hydrogen fluoride) used in conjunction with mercuric oxide[38].

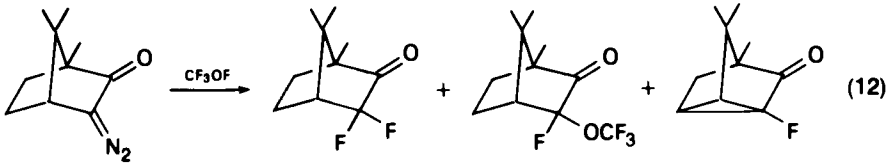
3. *α-Fluoroketones from α-diazoketones*

Fluoromethyl ketones are easily formed when diazomethyl ketones, prepared by condensation of acid chlorides with diazomethane, are treated with hydrogen fluoride[39,40] or pyridinium poly(hydrogen fluoride)[38] (equation 11). α,α-Difluoro-



(11)

ketones (e.g. **22**) are obtained by fluorination of diazoketones such as diazocamphor (**21**) with trifluoromethyl hypofluorite; additionally, minor amounts of α-fluoro-α-trifluoromethoxyketones (e.g. **23**) were isolated[41]. In the case of **21** a rearrangement also occurs, leading to the formation of a fluorotricyclanone (**24**) as another side product (equation 12).



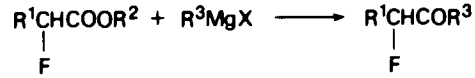
(12)

(**21**) (**22**) (**23**) (**24**)

4. α-Fluoroketones from carboxylic acid derivatives

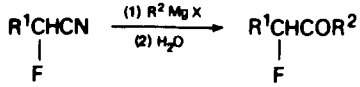
Reaction of fluorinated carboxylic acids and derivatives with organometallic reagents usually gives rise to α-fluoroketones. Treatment of trifluoroacetic acid with phenyllithium in ether at −65°C affords ω,ω,ω-trifluoroacetophenone[42], while the reaction of lithium trifluoroacetate with butyllithium yields 1,1,1-trifluoro-2-hexanone[43].

The condensation of organomagnesium compounds with α-fluorinated esters gives satisfactory yields of α-fluoroketones (equation 13)[44,45]. Condensation of



(13)

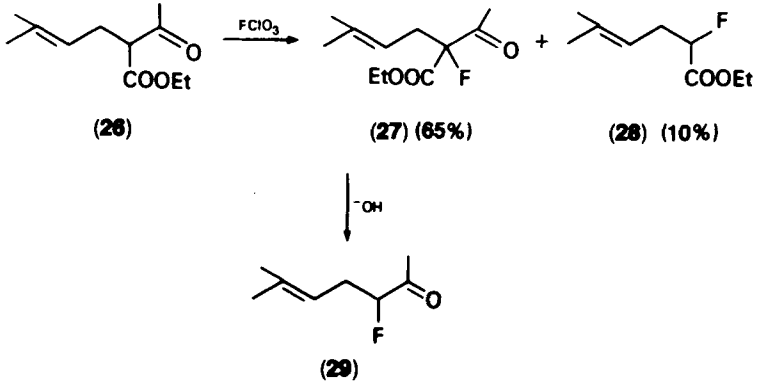
α-fluoronitriles (**25**) with Grignard reagents affords α-fluoroketones in high yields (equation 14)[46,47]. ω-Fluoroacetophenone is produced in good yield by the Friedel–Crafts method, provided that the reaction with fluoroacetyl chloride is carried out rapidly[48].



(14)

(**25**)

An α-fluoroketone (**29**) is formed during the hydroxide-catalysed hydrolysis of an α-fluoro-β-keto ester (**27**), while under the same circumstances the difluoro-β-keto ester (**31**) is transformed into the 1,3-difluoroketone (**32**) (equation 15)[49].



(**26**) (**27**) (65%) (**28**) (10%)

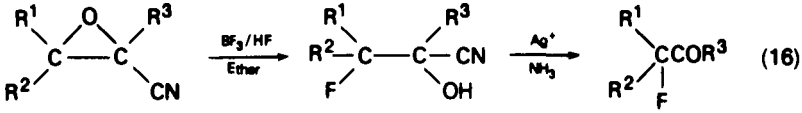
(**29**)

(15)

(**30**) (**31**) (**32**)

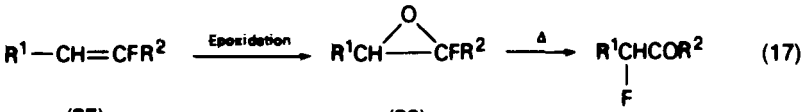
5. α-Fluoroketones from α-functionalized epoxides

A general synthesis of α-fluorocarbonyl compounds is developed from fluorocyanohydrins (**34**), obtained by the simultaneous action of hydrogen fluoride and boron trifluoride on epoxynitriles (**33**). Decomposition (**34**) with silver nitrate in the presence of an equimolecular amount of ammonia gives rise to the formation of α-fluoroketones in moderate yields (equation 16)[50]. Thermal isomerization of



(**33**) (**34**) (16)

α-fluoroepoxides (**36**), prepared by epoxidation of fluorinated olefins (**35**), gives rise to the formation of α-fluoroketones by migration of the fluorine atom (equation 17)[51].



(**35**) (**36**) (17)

6. α-Polyfluoroketones by condensation reactions

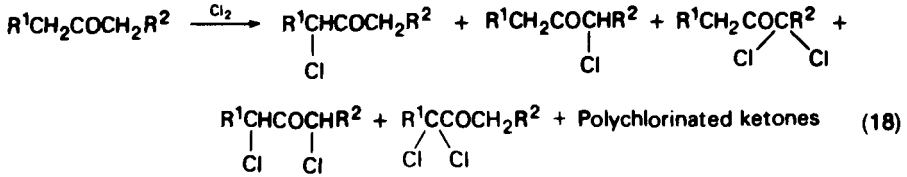
α-Polyfluoroketones are produced by several condensation reactions, e.g. Friedel–Crafts, Hoesch, Claisen, Knoevenagel and aldol condensations. These types of reaction are undoubtedly the most suitable for perfluoroketone synthesis. Much of the literature concerning the various aspects of this topic has been covered elsewhere[2] and will not be repeated here.

B. Synthesis of α-Chloroketones

1. Synthesis of α-chloroketones from ketones and their derivatives

The preparation of α-chloroketones starting from ketones and their derivatives can be achieved by various procedures. The choice of method is dependent upon the nature of the ketone and the degree of chlorination wanted. Therefore no general procedure seems to be available for the synthesis of a given chlorinated ketone. The substitution pattern in the starting ketone determines the method to be employed, as will be demonstrated below.

a. Chlorination with chlorine. In general, reaction of aliphatic ketones with chlorine most commonly affords higher chlorinated products (equation 18).



(18)

During the monochlorination of acetone, minor amounts of dichloroacetone are always isolated. However, good results for the monochlorination of acetone and 3-pentanone are possible when the chlorination is carried out in aqueous solutions of

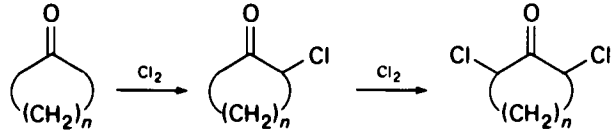
calcium carbonate and calcium chloride; using this procedure 2-butanone furnishes a mixture of 75% 3-chloro-2-butanone and 25% 1-chloro-2-butanone[52].

Further chlorination of monochloroacetone at 100–140°C in the presence of iodine, antimony pentachloride and ferric trichloride gives a mixture of 1,1,1,3-tetrachloroacetone and 1,1,3,3-tetrachloroacetone in a 1:4 ratio[53]. Chlorination of acetone in carbon tetrachloride at 50–70°C gives pentachloroacetone, which is transformed into hexachloroacetone by further chlorination in the presence of antimony trisulphide and iodine[54].

Hexachloroacetone is also formed during chlorination in an acetic acid–sodium acetate medium[55].

In general, α-perchloroketones are produced in very good yields in the presence of light without catalysis[56]. Photochlorination in the gas phase only affords α-substituted ketones[57].

The degree of chlorination in alicyclic ketones is strongly dependent upon the reaction medium. Cycloalkanones are monochlorinated in the α-position in acetic acid[58], water[59,60], methanol[61], or dichloromethane[62], while α,α′-dichloro compounds are produced upon further treatment with chlorine, except for α-tetralone, of course, where 2,2-dichloro-α-tetralone is obtained[62] (equation 19). Tetrachloro- and hexachlorocyclohexanone are formed when the chlorination is carried out in the presence of rhodium(III) chloride and iridium(IV) chloride[63], respectively.



(19)

Chlorine in dimethylformamide seems to be a powerful reagent for the substitution of α-protons in aldehydes and ketones[64,65]. Usually all the α-protons are rapidly replaced at 50–90°C, except in aliphatic ketones, where the last α-proton is substituted only at 120°C, because of the sterically hindered enolization[66]. A clean conversion of cyclopentanone (**37**) into 2,2,5,5-tetrachlorocyclopentanone (**38**) is obtained using this procedure at 20–30°C, when a continuous excess of chlorine is maintained during the course of the reaction.

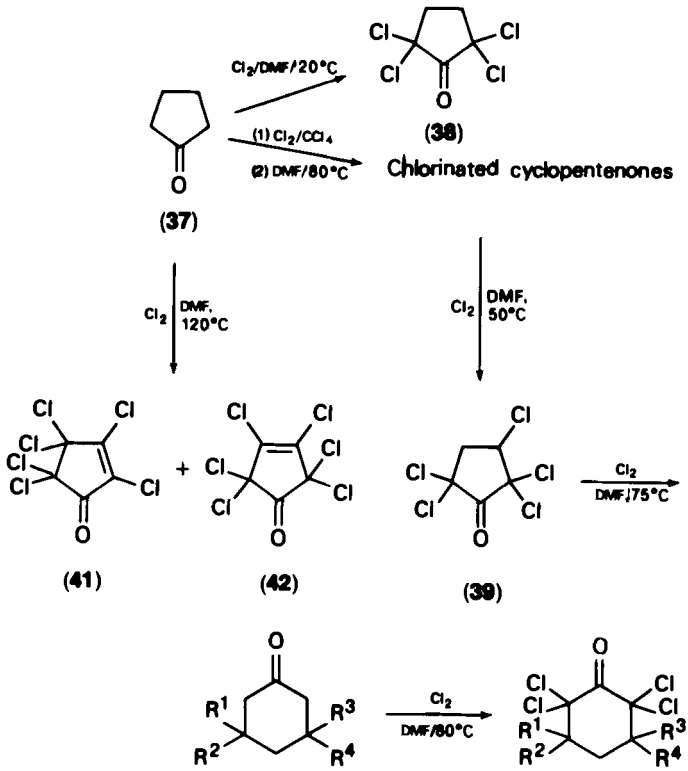
Several intermediate α-chlorinated cyclopentanones are dehydrochlorinated in dimethylformamide (DMF), yielding chlorinated 2-cyclopentenones which are further chlorinated to afford penta- (**39**) and hexachlorocyclopentanone (**40**). Chlorination of cyclopentanone (**37**) in DMF at 120°C gives a mixture of the isomeric perchlorocyclopentenones (**41**) and (**42**) (equation 20)[67].

Chlorination of cyclopentanone with chlorine in dichloromethane and carbon tetrachloride is not a synthetically useful method as rather complex mixtures of mono-, di- and trichloro derivatives are formed[67]. However, 2,2,3-trichlorocyclopentanone can be prepared via chlorination of 2-chloro-2-cyclopentenone; the latter compound is produced upon treatment of 2-cyclopentenone with chlorine in carbon tetrachloride[68].

Direct chlorination of 2-methylcyclohexanone with chlorine yields 2-chloro-2-methylcyclohexanone as the major product, besides *cis*- and *trans*-6-chloro-2-methylcyclohexanone and substantial amounts of the 2,6-dichloro compound[69]. Treatment of cyclohexanones with chlorine in dimethylformamide results in substitution of all the α-hydrogens (equation 21)[66].

Aryl alkyl ketones are mostly monochlorinated in the aliphatic chain using solutions of chlorine in acetic acid, methanol or carbon tetrachloride at low temperatures[70].

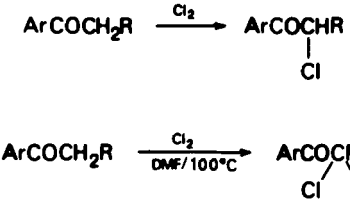
At 60°C ω,ω-dichloroacetophenone is produced[71], which in turn is converted into ω,ω,ω-trichloroacetophenone in the presence of sodium acetate on further treatment



(20)

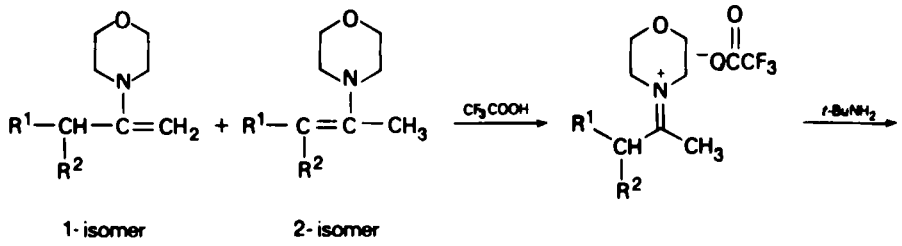
(21)

with chlorine[72]. Surprisingly, the higher homologues, 2,2-dichloro-1-aryl-1-alkanones, could only be prepared by chlorination in dimethylformamide at 100°C[73], with the exception of 2,2-dichloropropiophenone, which is also formed during the chlorination of propiophenone in a solution of sodium acetate in acetic acid[74] (equation 22).



(22)

Chlorination of enamines has been used for the preparation of α-chloroketones. A procedure for the regiospecific synthesis of chloromethyl ketones (**43**) via immonium salts is described by Carlson[75]. By regioselective deprotonation of these salts, mixtures of tautomeric enamines, derived from methyl ketones, are transformed into the less sterically hindered enamines, which upon reaction with chlorine and subsequent hydrolysis yield chloromethyl ketones (**43**) (equation 23). Enamines react with chlorine in ether at −78°C under exclusion of oxygen and moisture to give the isolable α-chloroimmonium halides (**44**), after which acid hydrolysis leads to α-chloroketones (equation 24)[76].



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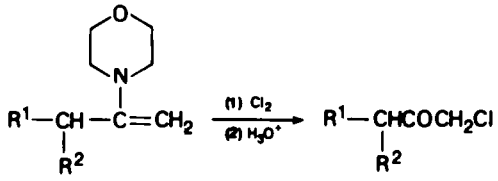
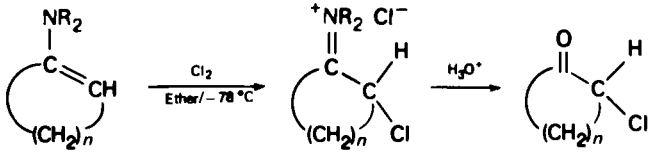


(43)



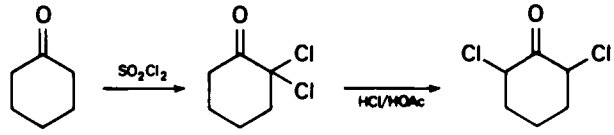
(24)

(44)

b. Chlorination with sulphuryl chloride and selenium oxychloride. As in the case of the chlorination with chlorine, secondary hydrogens are more easily substituted than primary hydrogens and tertiary hydrogens more easily than secondary hydrogens on treatment with sulphuryl chloride. Hydrogens in the α-position next to a carbonyl function react with sulphuryl chloride at room temperature without any catalysts[77]. Chloroacetone[78], 3-chloro-3-methyl-2-butanone[79], 2-chloro-2-methylcyclohexanone[80], 2-chloropropiophenone[33] and 1-benzoyl-1-chlorocyclohexane[81] are prepared in high yields by treatment of the corresponding ketones with sulphuryl chloride (equation 25).

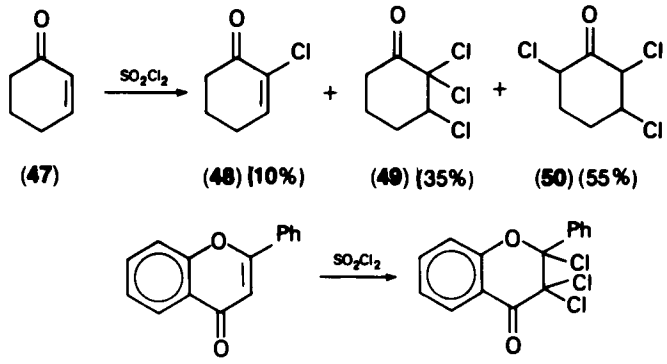
$$R^1CH_2COR^2 \xrightarrow{SO_2Cl_2} R^1\underset{\displaystyle Cl}{\underset{|}{C}}HCOR^2 \qquad (25)$$

Reaction of ketones with two moles of sulphuryl chloride generally leads to mixtures of products. For example, from acetone at 30°C a mixture of 72% 1,1-dichloro-, 6% 1,3-dichloro- and 20% 1,1,3-trichloroacetone is produced, while from 2-butanone a mixture of 42% 3,3-dichloro-, 7% 1,1-dichloro- and 46% 1,3-dichloro-2-butanone is obtained[77]. Chlorination of cyclopentanone with an excess of sulphuryl chloride affords a mixture of 2,2-dichloro- and 2,5-dichlorocyclopentanone, while in the case of cyclohexanone only 2,2-dichlorocyclohexanone (**45**) is isolated when the reaction is carried out in dichloromethane or in acetic acid at 20°C[82]. Heating of α,α-dichlorocycloalkanones in acetic acid–hydrogen chloride results in rearrangement of a chlorine atom with formation of α,α′-dichloro compounds (**46**)[83], but this rearrangement is not applicable to the acyclic series (equation 26).



(45) (46) (26)

Chlorinated cyclohexanones are formed during the chlorination of cyclohexenones. Treatment of 2-cyclohexenone (**47**) with sulphuryl chloride affords a mixture of 2-chloro-2-cyclohexenone (**48**), 2,2,3-trichloro- (**49**) and 2,3,6-trichlorocyclohexanone (**50**)[84], while chlorination of flavone (**51**) gives rise to 2,3,3-trichloroflavone (**52**)[85] (equation 27). Thionyl chloride reacts with 6-methyl- and 7-methoxyflavone to yield 3-chloro derivatives in both cases[85].



(47) (48) (10%) (49) (35%) (50) (55%) (27)

(51) (52)

During the chlorination of methyl ketones with selenium oxychloride, the intermediate dichloroselenium compounds (**53**) are decomposed thermally to furnish α-chloroketones (equation 28)[86].

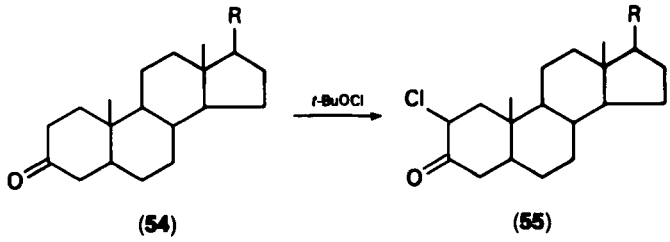
$$RCOCH_3 \xrightarrow{SeOCl_2} (RCOCH_2)_2SeCl_2 \xrightarrow{\Delta} RCOCH_2Cl \qquad (28)$$

(53)

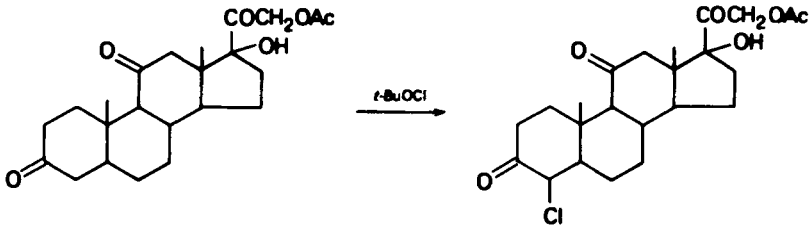
c. Chlorination with hypochlorites. Methyl ketones react with sodium hypochlorite in aqueous alkaline solution to give intermediate trichloromethyl ketones which are further transformed into chloroform and carboxylic acids (i.e. the so-called haloform reaction) (equation 29). Trichloromethyl ketones are isolated when acetophenones are used as substrates[87].

$$RCOCH_3 \xrightarrow{NaOCl} RCOCCl_3 \xrightarrow{H_2O/OH^-} CHCl_3 + RCOOH \qquad (29)$$

Alkyl hypochlorites react easily with ketones; chloroacetone and ω-chloroacetophenone are prepared in good yields using ethyl hypochlorite[88]. *t*-Butyl hypochlorite seems to be an excellent reagent for the chlorination of steroidal ketones[89,90]. By the latter method, 2-chloro-3-cholestanone (**55**) is prepared from 3-cholestanone (**54**), while in pregnantrione derivatives (**56**) chlorination takes place at the 4-position (equation 30).



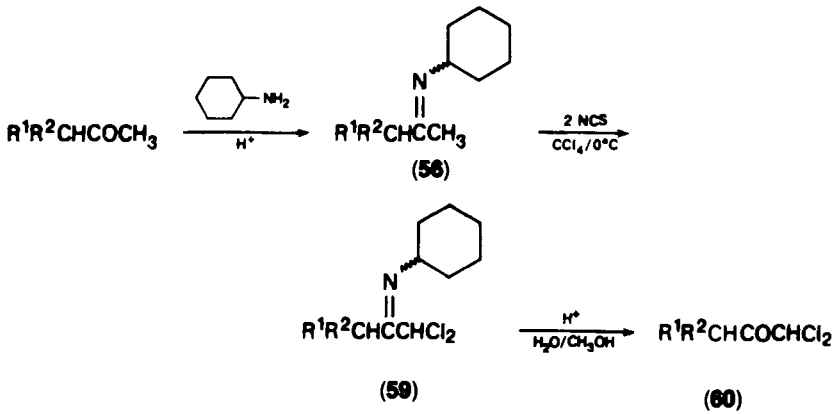
(54) (55) (30)



(56) (57)

d. Chlorination with N-*chlorosuccinimide.* Direct chlorination of ketones with *N*-chlorosuccinimide (NCS) is not a potential method for the synthesis of α-chloroketones because the reaction rate is often too slow and in most cases mixtures of reaction products are formed. Treatment of 2-heptanone with NCS in the presence of benzoyl peroxide gives a mixture of several mono-, di- and trichloro derivatives which are difficult to separate[91].

However, NCS is an excellent chlorinating agent of the corresponding *N*-analogues of ketones and enol ethers, i.e. ketimines and enamines, yielding α-chlorinated ketimines and β-chlorinated enamines. This subject has been reviewed elsewhere[92]. The last-mentioned compounds are potential sources for α-haloketones by a simple hydrolysis procedure. 1,1-Dichloromethyl ketones (**60**) are prepared by chlorination of *N*-cyclohexyl methyl ketimines (**58**) with two equivalents of NCS in carbon tetrachloride at 0°C, followed by hydrolysis in acidic medium[93–95] (equation 31). By

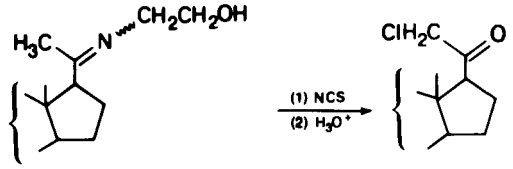


(31)

$ArCOCCl_2R$

(61)

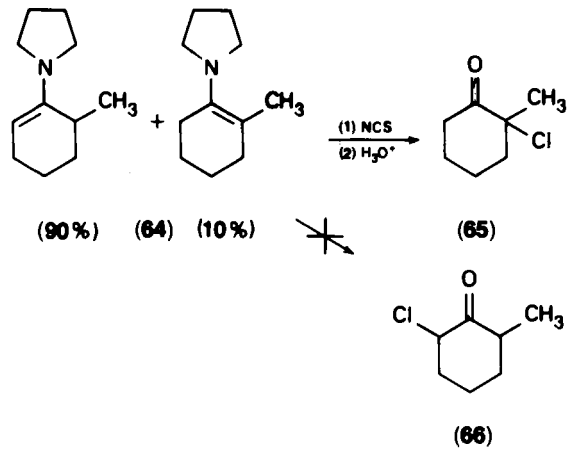
the same procedure 1-Aryl-2,2-dichloro-1-alkanones (**61**) have been successfully synthesized[96]. A similar method has been developed in which steroidal *N*-(β-hydroxyethyl)methylketimines (**62**) are treated with NCS in ether at 25°C, followed by mild acidic hydrolysis leading to the corresponding α-chloromethyl ketones (**63**) (equation 32). However, application of this halogenation method to 2-pentanone yields a mixture 1-chloro-, 3-chloro-, 1,1-dichloro- and 1,1,1-trichloro-2-pentanone[97].



(32)

(62) (63)

Chlorination of the pyrrolidine enamines derived from 2-methylcyclohexanone (**64**) (which exists as a 9:1 mixture of two isomers) with NCS and subsequent hydrolysis gives 2-chloro-2-methylcyclohexanone (**65**), while the isomeric 6-chloro isomer (**66**) is not formed (equation 33)[98].

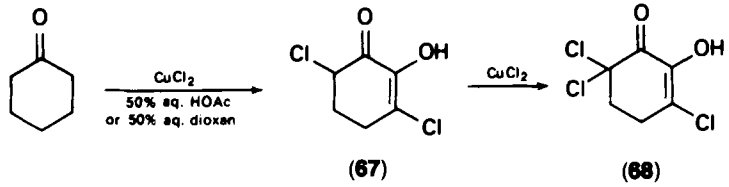


(90%) (64) (10%) (65) (33)

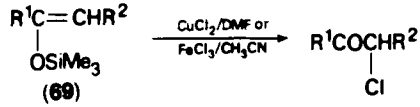
(66)

e. Chlorination with cupric and ferric chlorides. Cupric chloride is known as a chlorination catalyst but it has also been used for the preparation of chloroacetone from acetone[99,100]. Cyclohexanone and its methyl derivatives react with a large excess of cupric chloride in 50% aqueous acetic acid or 50% aqueous dioxan to give dichloro and trichloro derivatives of 1,2-cyclohexanediones (**67**, **68**)[101] (equation 34).

A convenient synthetic method consists of the reaction of silyl enol ethers (**69**) with cupric or ferric chlorides (equation 35)[102]. The mechanism involves a vinyloxy radical, generated from the collapse of the copper(II) or iron(III) enolate which is formed initially. The selection of specific solvents is important; for cupric chloride dimethylformamide must be used, while acetonitrile is the solvent of choice for ferric



(34)

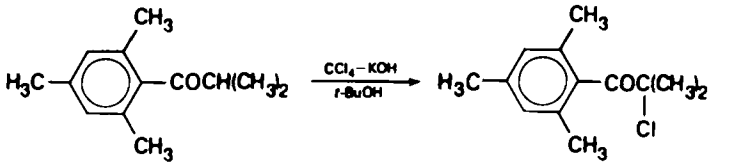


(35)

chloride. This method possesses the interesting feature that α-chlorination of unsymmetrical ketones can be performed regiospecifically and that extra double bonds are left intact. (Note that this does not occur when ferric chloride is used, but only with cupric chloride.)

f. Miscellaneous chlorination agents. Several other reagents or procedures of minor importance have been used for α-chlorination of ketones and their applications are strongly dependent upon the substrate. Treatment of acetophenones and aryl benzyl ketones with phenylchloroiodonium chloride gives rise to α-monochlorination, but reaction of 2-butanone with this reagent affords a mixture of 3-chloro- and 3,3-dichloro-2-butanone[103]. Pyridine hydrochloride perchloride[89] and phosphorus pentachloride[104] have also been used for α-chlorination of ketones.

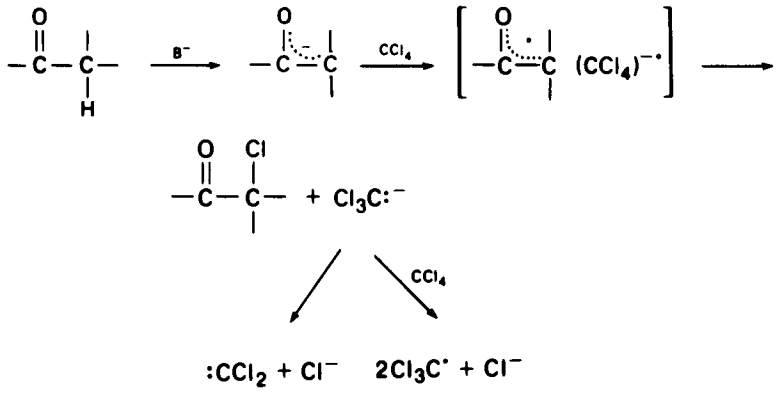
Ketones possessing α-hydrogens are easily chlorinated with a system consisting of carbon tetrachloride, powdered potassium hydroxide and *t*-butanol, but subsequent rapid reactions generally lead to the formation of a variety of products such as Favorskii rearrangement products, α-hydroxy ketones and cleavage products[105,106]. Ketones with only one α-hydrogen, no α′-hydrogens and a sterically blocked carbonyl function such as **70** are especially suitable substrates and are easily converted into α-chloroketones (e.g. **71**), which are resistant to further reaction (equation 36). The



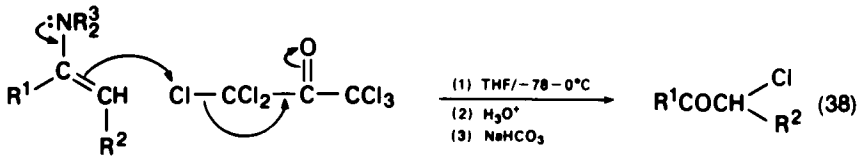
(36)

α-chlorination of ketones with this reagent involves the reaction of enolate anions with carbon tetrachloride in a discrete electron transfer/chlorine atom transfer step proceeding through a radical anion–radical pair (RARP) mechanism. As shown in equation (37), the formation of $Cl_3C:^-$ in the chlorination step leads to the generation of $:CCl_2$ as well as of $\dot{C}Cl_3$.

Hexachloroacetone acts as a source of positive chlorine in its reaction with enamines giving α-chloroketones after acid hydrolysis (equation 38)[107]. This reaction results in regioselective α-chlorination because of the availability of either α- or α′-enamines, thus making routes to 6-chloro-2-alkyl- or 6-chloro-3-alkylcyclohexanones quite feasible. For example, 6-methyl-1-pyrrolidinocyclohexene is transformed into a mixture of *cis*-6-chloro-2-methyl-, *trans*-6-chloro-2-methyl- and 2-chloro-2-methylcyclohexanone in a 93:6:1 ratio. The pyrrolidine enamines of 2-methylcyclohexanone



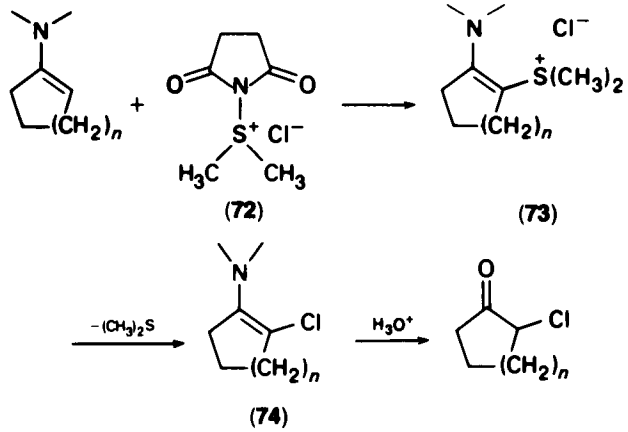
(37)



(38)

react with sulphuryl chloride or NCS to give primarily the 2-chloro-2-methyl isomer.

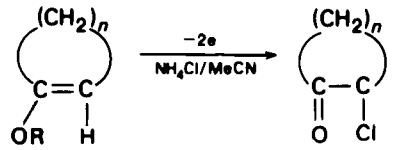
Reaction of enamines with dimethyl(succinimido)sulphonium chloride (**72**) yields 2-amino-1-cycloalkenylsulphonium chlorides (**73**), which decompose into chlorinated enamines (**74**) under expulsion of dimethyl sulphide. Hydrolysis of these chlorinated enamines gives rise to α-chlorocycloalkanones (equation 39)[108].



(39)

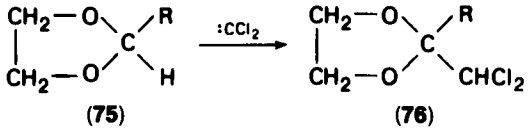
A highly convenient electrolysis procedure for the preparation of α-halogenated ketones from enol acetates, enol ethers and silyl enol ethers has been developed (equation 40)[109]. The method consists of an electrolysis with halide salts in an undivided cell.

Reaction of dichlorocarbene with dioxolane derivatives (**75**) gives rise to dichloromethyl-1,3-dioxolanes (**76**) under phase transfer catalysis. These acetals are



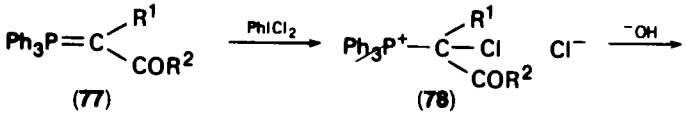
(40)

excellent starting materials for syntheses of α,α-dichloromethyl ketones (equation 41)[110].



(75) (76) (41)

A generally applicable synthesis of unsymmetrical α-chloroketones involves the chlorination of β-oxoalkylidenephosphorane (77) with iodobenzene dichloride followed by alkaline hydrolysis of the intermediate triphenylphosphonium chlorides (78) (equation 42)[111].



(77) (78) (42)

2. *Synthesis of α-chloroketones from alcohols and phenols*

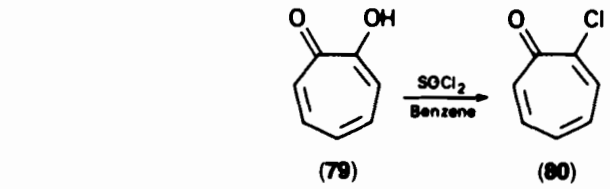
It is obvious that chlorination agents, which are capable of oxidizing alcohols to ketones, will give rise to chlorinated ketones using secondary alcohols as starting materials. The chlorination of isopropanol and 2-octanol, respectively, with chlorine gives 1,1,1,3-tetrachloroacetone and 1,1,1,3,3-pentachloro-2-octanone[112], while 2-chloro- and 2,2,6,6-tetrachlorocyclohexanone could be obtained from cyclohexanol in high yield[113,114]. Sterols are simultaneously oxidized and chlorinated upon treatment with hypochlorites[115].

Other reagents substitute hydroxy functions for chlorine atoms. 2-Hydroxytropolone (79) is transformed into 2-chlorotropolone (80) upon treatment with thionyl chloride in benzene[116] and 3-chloro-3-phenyl-*trans*-2-decalone (82) is formed from the 3-hydroxy derivative (81) by reaction with thionyl chloride in carbon tetrachloride[117] (equation 43). Hydroxyl functions in the side chain of steroids are easily substituted for chlorine by the action of arylsulphonyl chlorides[118].

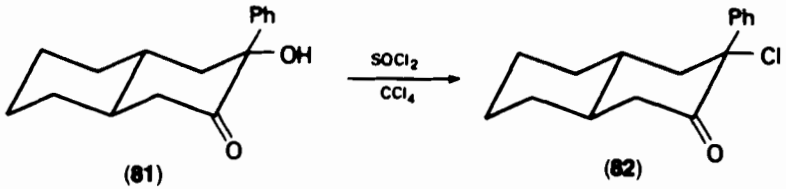
The chlorination of phenols and halophenols with chlorine gives rise to polychlorinated cyclohexanones and cyclohexenones[119–122]. For example 2,4,4,6-tetrachloro-2,5-cyclohexadienone (84) and 2,2,4,5,6,6-hexachloro-3-cyclohexenone (85) are formed on chlorination of 2,4,6-trichlorophenol (83) (equation 44)[123].

1-Aryl-1-chloro-2-propanones (87) are formed from 1-aryl-2,2-dichloro-1-propanols (86) in generally good yields (69–90%) by an acid-catalysed rearrangement involving a 1,2-chlorine shift (equation 45)[124–126].

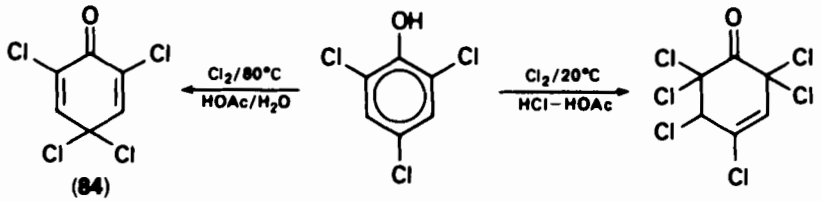
Studies on the acid-catalysed trifluoroacetolysis of 1-(*o*-chlorophenyl)-2,2-dichloro-1-propyl trifluoroacetate (88) indicate that the rearrangement takes place through the intermediacy of a halonium ion (equation 46).



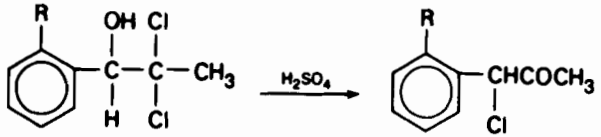
(79) (80)



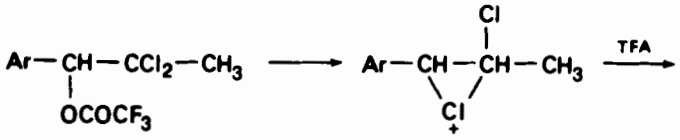
(81) (82) (43)



(84) (83) (85) (44)



(86) (87) (45)

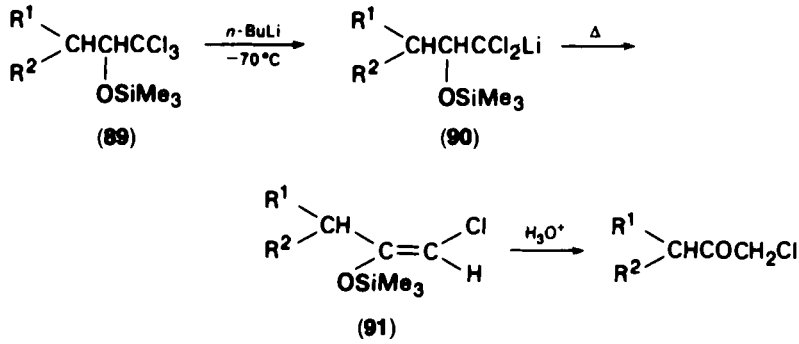


(88)

(46)

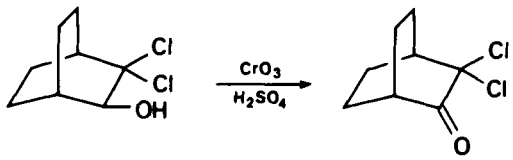
Another procedure for the synthesis of chloromethyl ketones involves the reaction of trichlorosilyl ethers with butyllithium, generating dichlorolithium compounds (**90**), which upon heating furnish chlorinated silyl enol ethers (**91**). Hydrolysis yields α-chloroketones (equation 47)[127].

It is evident that α-chloroketones are easily formed by oxidation of the corresponding β-chloro alcohols. However, β-chlorinated alcohols are not accessible in a general way and are mostly prepared by reduction of α-chloroketones (*vide infra*).



(89) (90) (91) (47)

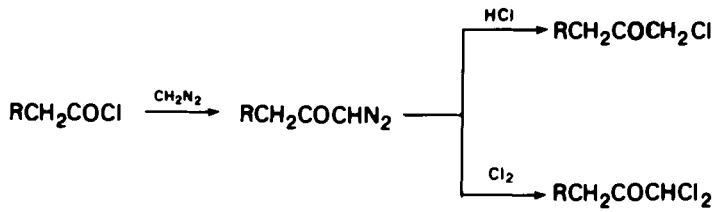
The oxidation is exemplified by the conversion of 3,3-dichlorobicyclo[2.2.2]octan-2-ol (92) into the corresponding ketone (93) on treatment with chromic acid (equation 48)[128].



(92) (93) (48)

3. *Synthesis of α-chloroketones from α-diazoketones*

A general procedure for the preparation of α-chloroketones consists of decomposition of diazoketones in the presence of hydrogen chloride or chlorine yielding chloromethyl[129] and dichloromethyl ketones[130–131], respectively (equation 49). Excellent results are obtained for chloroacetone[132], 1,1,1,3-tetrachloroacetone[133]



(49)

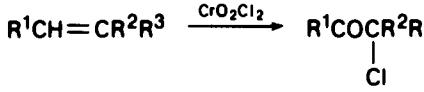
and chloromethyl benzyl ketone[134] on treatment of diazoketones, derived respectively from acetyl chloride, trichloroacetyl chloride and phenylacetyl chloride, with hydrogen chloride. 3,3-Dibromo-1,1-dichloro-2-butanone is synthesized by the reaction of chlorine in ether with the diazoketone derived from 2,2-dibromopropionyl bromide[131].

4. *Synthesis of α-chloroketones from alkenes and alkynes*

Addition of nitrosyl chloride to alkynes affords chlorinated nitroso compounds which upon acid hydrolysis yield monochlorinated ketones in excellent yields (equation 50)[135].

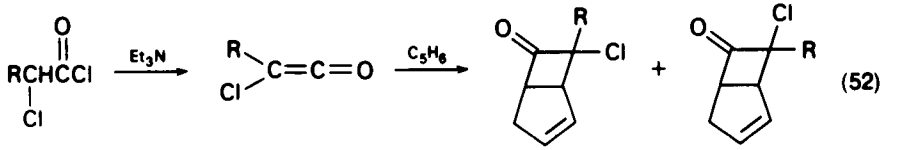
(50)

Oxidation of di- or trisubstituted olefins with chromyl chloride in acetone provides an efficient preparation of α-chloroketones (equation 51). For example, 2-chlorocyclododecanone is prepared by this method from *trans*-cyclododecene in 90% yield[136].



(51)

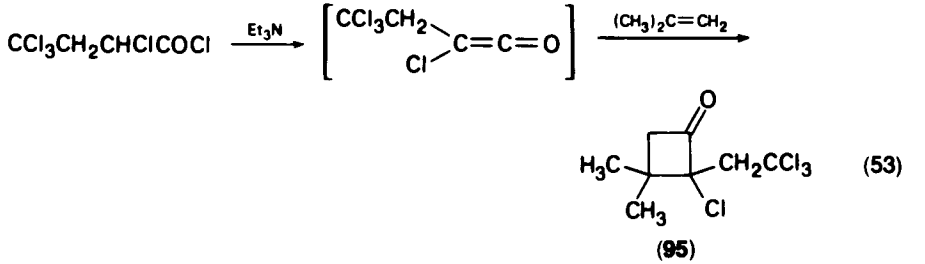
Several mono- and dichlorocyclobutanones have been synthesized by cycloadditions of chloro- or dichloroketenes to olefins. The dehydrohalogenation of 2-haloalkanoyl chlorides with triethylamine generates the chloroketene *in situ*, which in turn adds rapidly to dienes. 7-Chlorobicyclo[3.2.0]hept-2-en-6-ones (**94**) have been prepared in such a way by addition of chloroketenes to cyclopentadiene (equation 52)[137].



exo-alkyl (**94**) *endo*-alkyl

(52)

Chloro(2,2,2-trichloroethyl)ketene gives higher yields of [2 + 2] cycloadducts and a large variety of monochlorocyclobutanones (**95**) can readily be prepared (equation 53)[138].

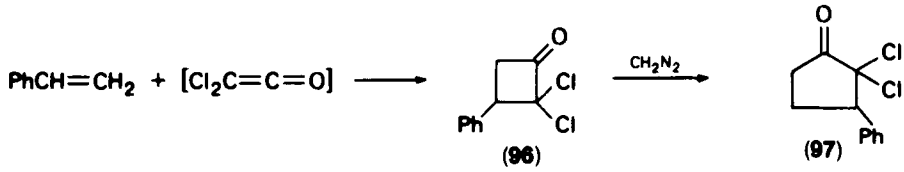


(**95**)

(53)

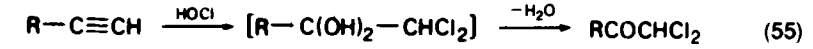
The cycloaddition of dichloroketene, generated *in situ* from trichloroacetyl chloride with triethylamine or with activated zinc in the presence of phosphorus oxychloride, constitutes a useful method for the synthesis of 2,2-dichlorocyclobutanone derivatives[139]. Styrene is converted into 2,2-dichloro-3-phenylcyclobutanone (**96**) in 87% yield (equation 54)[140]. Also silyl enol ethers seem to be suitable substrates for the preparation of functionalized cyclobutanones[141], while the adducts of indene and cyclopentadienes are valuable precursors in the synthesis of tropolones[142].

2,2-Dichlorocyclobutanones easily undergo regioselective one-carbon ring expansion by reaction with diazomethane, yielding 2,2-dichlorocyclopentanones (e.g. **97**). The presence of α-chloro substituents accelerates this reaction. Epoxide formation is not significant, probably because of the strained nature of the four-membered ring[143].



(54)

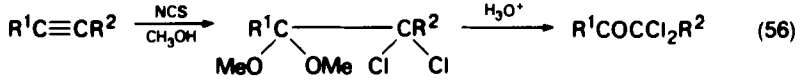
Terminal alkynes can be converted into dichloromethyl ketones by treatment with hypochlorous acid (equation 55)[144–146]. 1,1-Dichloroacetone, 1,1-dichloro-3,3-



(55)

dimethyl-2-butanone and ω,ω-dichloroacetophenone are obtained from propyne, 3,3-dimethyl-1-butyne and phenylacetylene, respectively. Treatment of phenylacetylene with chlorine in methanol gives 1-phenyl-1,1-dimethoxy-2,2-dichloroethane[147].

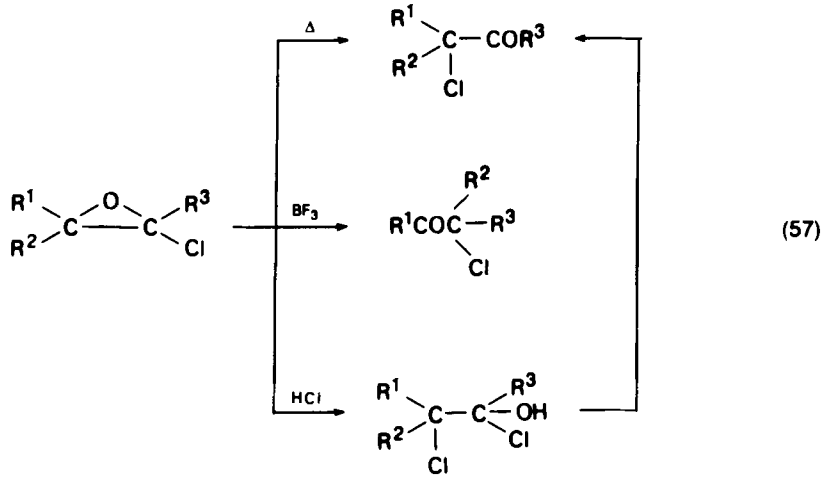
α,α-Dichloroketones are also prepared by reaction of acetylenes with *N*-chlorosuccinimide in methanol, followed by hydrolysis of the resulting dichlorodimethyl acetals (equation 56)[148].



(56)

5. *Synthesis of α-chloroketones from epoxides*

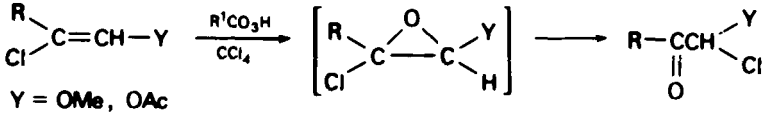
Ring opening of α-chloroepoxides, prepared by treatment of *gem*-dichloroalcohols with bases, gives rise to several halogenated ketones under various conditions (equation 57)[149,150].



(57)

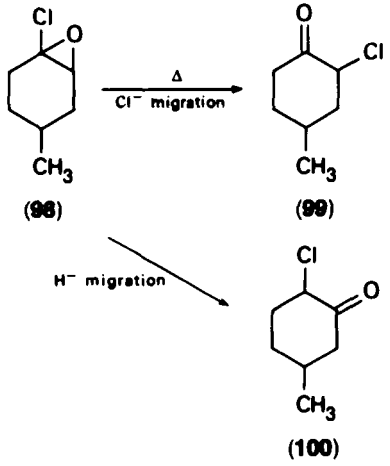
Neat thermal rearrangement of chlorinated epoxides normally gives rise to the formation of α-chloroketones, while on treatment with boron trifluoride a rearrangement takes place with formation of the isomeric chloroketone. Bifunctional

epoxides also afford α-chloroketones on thermal or acid-catalysed isomerization (equation 58)[33,151,209].



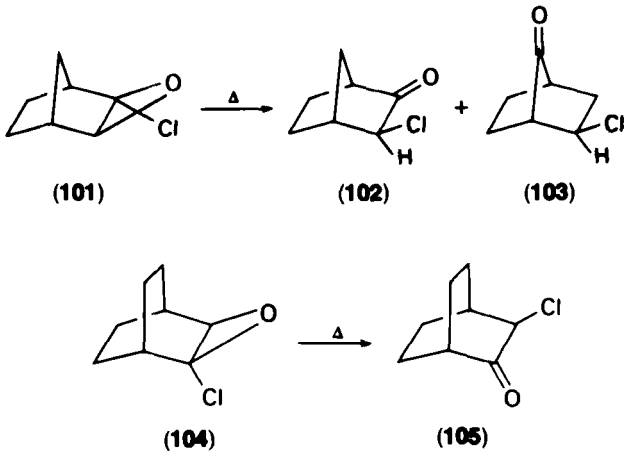
(58)

A stereospecific chlorine migration occurs when a *cis–trans* mixture of 1-chloro-4-methylcyclohexene oxides (**98**) gives exclusively *trans*-2-chloro-4-methylcyclohexanone (**99**) on heating, while a zinc chloride-catalysed rearrangement gives rise to a mixture of the *cis* and the *trans* isomers (equation 59)[152]. If a hydride shift occurred, the other isomer (**100**) would be produced.



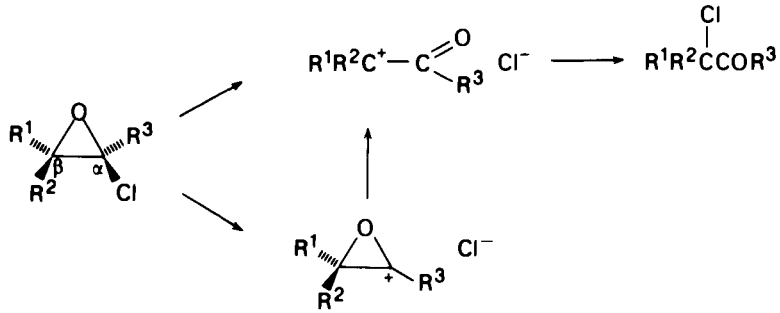
(59)

However, thermal rearrangement of 2-chlorobicyclo[2.2.1]hept-2-ene *exo*-oxide (**101**) gives rise to two major products, *exo*-3-chlorobicyclo[2.2.1]heptan-2-one (**102**, 38%) and *exo*-2-chlorobicyclo[2.2.1]heptan-7-one (**103**, 35%), while 2-chlorobicyclo-[2.2.2]oct-2-ene oxide (**104**) produces 89% 3-chlorobicyclo[2.2.2]octan-2-one (**105**) (equation 60)[153,154].



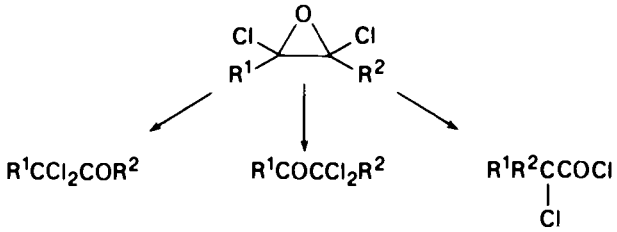
(60)

It has been proved in the case of α-chlorostyrene oxides that such thermal rearrangements occur by disrotatory $C_\beta - O$ bond heterolysis to yield an α-acylcarbenium chloride ion pair (equation 61)[155]. Upon heating 2,3-dichloro-



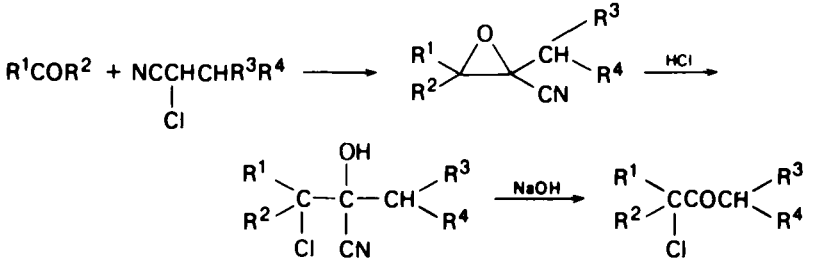
(61)

epoxides rearrange into α,α-dichloroketones, but the reaction course is strongly dependent upon the substitution pattern of the epoxide ring (equation 62)[156].



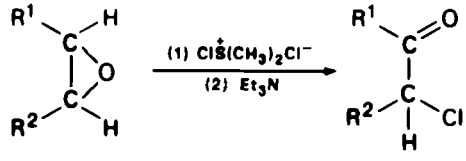
(62)

Ring opening of glycidonitriles (formed by condensation of a ketone with an α-halonitrile) with anhydrous hydrogen chloride leads to chlorinated cyanohydrins, which in turn upon treatment with sodium hydroxide expel hydrogen cyanide, yielding α-chloroketones (equation 63)[157].



(63)

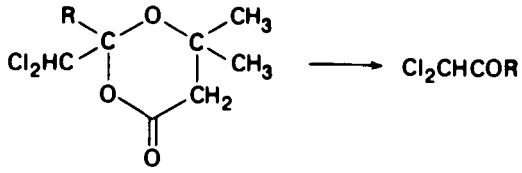
Another excellent conversion of epoxides into α-chloroketones involves the reaction of chlorodimethylsulphonium chloride (generated *in situ* by reacting molecular chlorine with dimethyl sulphide at −20°C) with epoxides in the presence of a tertiary amine (equation 64). For example, 2-chlorocyclohexanone is formed from cyclohexene oxide in 83% yield[158].

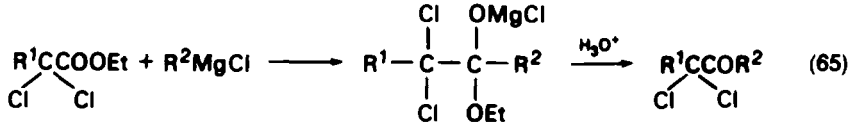


(64)

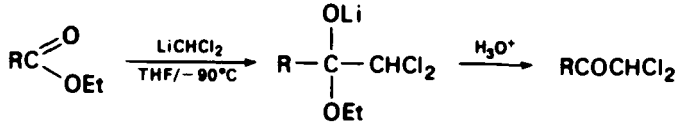
6. *Synthesis of α-chloroketones from carboxylic acids and their derivatives*

Chlorination of diketene gives rise to the unstable γ-chloroacetoacetic acid chloride which decomposes in aqueous medium to yield monochloroacetone[159]. Dichloromethylketones have been synthesised by hydrolysis of lactone derivatives[160], by treatment of α,α-dichloroesters with Grignard reagents[149], and by the action of dichloromethyllithium on esters[162] (equation 65).

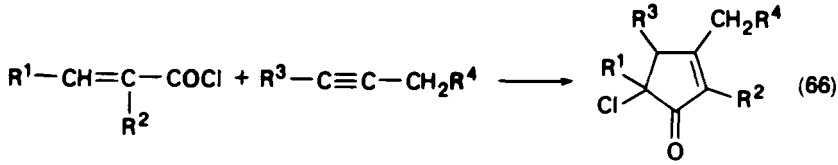




(65)



Acylation of alkynes with α,β-unsaturated acid chlorides provides 5-chloro-2-cyclopentenones (**106**) (equation 66)[163].

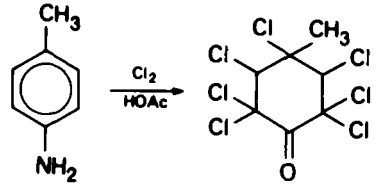


(66)

(**106**)

7. *Synthesis of α-chloroketones from aromatic amines*

Aromatic amines are converted into polychlorinated cyclohexanone compounds upon treatment with chlorine in acetic acid. For example, *p*-toluidine (**107**) gives 2,2,3,4,5,6,6-heptachloro-4-methylcyclohexanone (**108**) (equation 67)[164,165].



(67)

(**107**) (**108**)

C. Synthesis of α-Bromoketones

The synthesis of α-bromoketones can be achieved by methods similar to those mentioned for the preparation of α-chloroketones, in addition to typical procedures and reagents for the introduction of bromine atoms in ketones.

1. *Synthesis of α-bromoketones from ketones and their derivatives*

a. Bromination with bromine. Treatment of ketones with bromine gives rise to substitution of at least one α-hydrogen. However, some side reactions take place during the bromination of ketones which are not encountered during the chlorination[166–169].

The bromination of ketones with bromine is a reversible process and the debrominated ketones are regenerated by reaction of the bromoketones with the liberated hydrogen bromide (equation 67a). In order to shift the equilibrium to the right,

$$RCOCH_3 + Br_2 \rightleftharpoons RCOCH_2Br + HBr \qquad (67a)$$

precautions have to be taken to evaporate the hydrogen bromide or to take it up by an acceptor. In principle all brominated ketones are reducible by hydrogen bromide, but with varying ease depending on their structure. More 'positive' bromine atoms are reduced more rapidly. The tendency to debromination is directly related to the difficulty of introducing more than one bromine atom on a carbon atom in the presence of hydrogen bromide; trapping of the liberated hydrogen bromide is necessary.

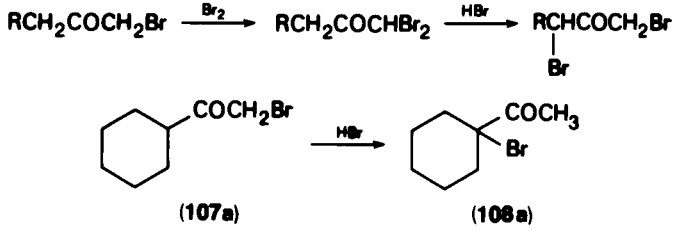
Besides reduction, disproportionation reactions also take place, with the consequence that during the reaction of a ketone with an equimolecular amount of bromine some dibromoketone is always produced (equation 68). The monobromo:dibromo

$$2RCOCH_2Br \rightleftharpoons RCOCH_3 + RCOCHBr_2 \qquad (68)$$

compound ratio is dependent upon the solvent and reaction time. ω,ω,ω-Tribromoacetophenone, with highly 'positive' bromine atoms, is able to brominate acetophenone, yielding phenacyl bromide (equation 69)[4].

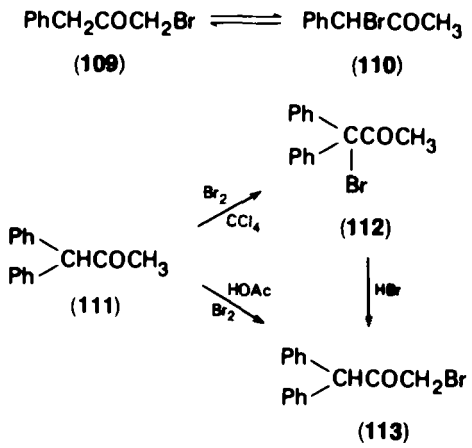
$$PhCOCBr_3 + PhCOCH_3 \longrightarrow PhCOCH_2Br \qquad (69)$$

Another side reaction occurring during the synthesis of bromoketones consists of a rearrangement of a bromine atom under the influence of hydrogen bromide. α,α-Dibromoketones rearrange to 1,3-dibromo compounds, but geminal dibromoketones are formed when the bromination is carried out in the presence of potassium acetate[170]. Bromomethyl cyclohexyl ketone (**107a**) is transformed to 1-acetyl-1-bromocyclohexane (**108a**) (equation 70)[171]. In the case of 1-bromo-3-phenyl-2-propanone



(107a) (108a) (70)

(**109**) an equilibrium is established between both isomers (**109** and **110**)[171]. In addition, the solvent seems to have a great influence on the position of substitution, as exemplified by the bromination of 1,1-diphenyl-2-propanone (**111**) (equation 71)[168].



(71)

Various procedures have been employed for the bromination of aliphatic ketones with bromine. Direct treatment gives very impure products since the liberated hydrogen bromide tends to promote the formation of condensation products and resinous materials next to by-products which are formed during side reactions. These difficulties are minimized by bromination in an inert atmosphere, by the use of acetic acid as solvent or in the presence of calcium carbonate, potassium acetate and potassium chlorate. Bromination of acetone in a mixture of acetic acid and water provides bromoacetone in a 44% yield together with 1,1-dibromo- and 1,3-dibromoacetone[172]. Better results are obtained when the bromination is carried out in an aqueous solution in the presence of potassium chlorate[173]. Further bromination of bromoacetone gives 1,1,3-tribromo- and 1,1,3,3-tetrabromoacetone, while reaction of acetone with an excess of bromine yields pentabromoacetone[174].

Bromination of alkyl methyl ketones always leads to the formation of isomeric compounds. Normally bromo-substitution of methylene groups is faster than of methyl groups, but the rate is nearly identical for methylene and methine moieties (equation 72). For example, acid-catalysed bromination in the presence of potassium chlorate

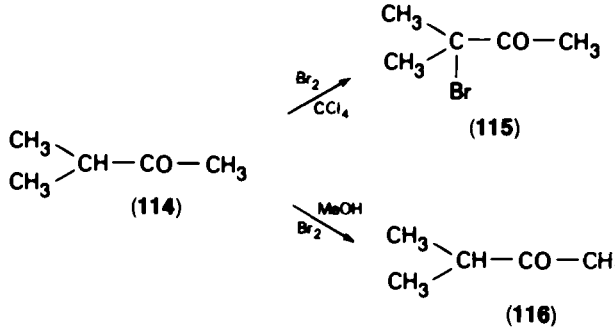
$$CH_3COCH_2R \xrightarrow{Br_2} CH_3COCHBrR + BrCH_2COCH_2R$$

$$CH_3COCHR^1R^2 \xrightarrow{Br_2} CH_3COCR^1R^2 + BrCH_2COCHR^1R^2 \quad (72)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad Br$$

affords mixtures of 73% 3-bromo- and 27% 1-bromo-2-butanone from 2-butanone and 63% 3-bromo- and 37% 1-bromo-2-pentanone from 2-pentanone while 3-methyl-2-butanone gives rise to 76% 3-bromo-3-methyl- and 24% 1-bromo-3-methyl-2-butanone[175–177]. Pinacolone can be converted into the mono- and the dibromo compounds when the bromination is carried out in ether[178], while tribromopinacolone is obtained in a refluxing carbon tetrachloride–water mixture in the presence of mercuric chloride[179].

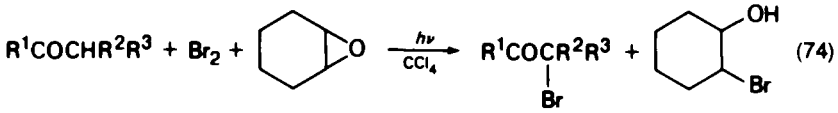
Monobromination of unsymmetrical aliphatic ketones is rarely a regiospecific reaction and seems to be strongly dependent upon the solvent used. While in carbon tetrachloride, ether and acetic acid the substitution mostly occurs at the most substituted α-carbon atom, yielding mixtures of reaction products[180], bromination in

methanol preferentially takes place at the less substituted carbon atom, as illustrated by the bromination of 3-methyl-2-butanone (**114**) (equation 73). The latter procedure constitutes an excellent method for the preparation of bromomethyl ketones, not readily accessible previously by direct bromination[181].



(73)

Bromination of ketones with bromine in carbon tetrachloride during irradiation with a 100 W tungsten lamp in the presence of 1,2-epoxycyclohexane gives monobromoketones in which bromine has entered exclusively the more highly substituted α-position or the benzylic position (equation 74). The extent of substitution α to the



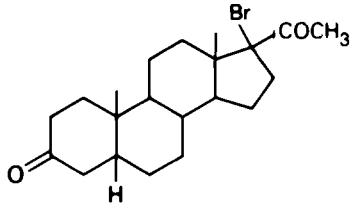
(74)

R^1 = Me, Et

R^2 = alkyl, phenyl

R^3 = H, alkyl

carbonyl group plays a decisive role in the reaction. Ketones with a secondary or a benzylic α-carbon atom are brominated at this position exclusively. With less substituted ketones (2-butanone, acetone) the reaction takes a different course, providing a mixture of 2-bromocyclohexane, 2-bromocyclohexanol and the starting ketone[182]. Under the same reaction conditions a regiospecific introduction of bromine occurred at the C_{17} of 5α- and 5β-pregnane-3,20-dione (**117**). The selectivity of these reactions is due to the epoxide which, by scavenging the hydrogen bromide produced during the reaction, inhibits any ionic acid-catalysed bromination of the ketones.



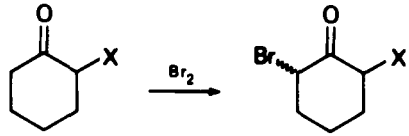
(**117**)

Treatment of aliphatic ketones with two equivalents of bromine in acetic acid or ether results in the formation of stereoisomeric α,α′-dibromoketones and no geminal dibromo compounds are formed (equation 75)[183,184].

$$R^1CH_2COCH_2R^2 \xrightarrow{Br_2} R^1\underset{Br}{CH}COCH\underset{Br}{}R^2 \qquad (75)$$

Monobromocycloalkanones, prepared from cycloalkanones with bromine in an acetic acid–water mixture at 50–70°C, are very air-sensitive and difficult to purify[185–186].

Bromination of 2-chloro-, 2-cyano- or 2-fluorocyclohexanone (**118**) in carbon tetrachloride in the presence of calcium carbonate takes place mainly at the 6-position (equation 76)[187]. Stereoisomeric α,α'-dibromocycloalkanones are formed by bromi-

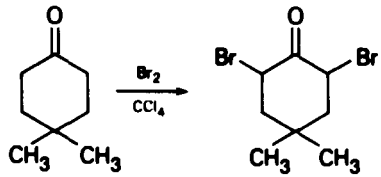


(76)

(**118**) (**119**)

X = Cl, CN, F

nation with two equivalents of bromine in acetic acid or anhydrous ether[183]. Reaction of cyclohexanol with bromine in acetic acid containing 15% hydrogen bromide yields 20% crystalline *cis*-2,6-dibromocyclohexanone and 80% of the *trans* compound, which decomposes upon distillation[188]. Dibromination of 4,4-dimethylcyclohexanone (**120**) in carbon tetrachloride gives *cis*-2,6-dibromo-4,4-dimethylcyclohexanone (**121**) in 66% yield (equation 77). Upon standing in ether, partial *cis–trans* isomerisation is



(77)

(**120**) (**121**)

observed[189]. The *cis* isomers have higher melting points and higher infrared carbonyl stretching frequencies and are more polar as well as less soluble than the *trans* analogues, which are considered to be conformationally more mobile.

Neat bromination of cyclohexanone affords tetrabromocyclohexanone[190], while bromination of cyclohexadecanone with 3.5 mole equivalents of bromine in dichloromethane at 25–30°C gives 2,2,16-tribromocyclohexadecanone in 92% yield[191].

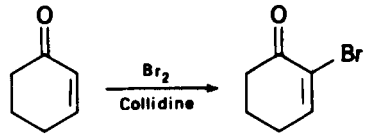
Bromination of aryl alkyl ketones can be carried out selectively and ω-bromo, ω,ω-dibromo- and ω,ω,ω-tribromoacetophenone are synthesised in high yields from acetophenone[192–194]. Monobromo- and dibromopropiophenone are obtained from propiophenone, although for the disubstituted compound to be obtained the bromination must be performed in carbon tetrachloride at reflux temperature under irradiation and in the presence of benzoyl peroxide[33,195]. The bromination of indanone can be carried out selectively. Reaction in ether with one molar equivalent of bromine yields the 2-bromo compound while 2,2-dibromoindanone is obtained upon treatment with two molar equivalents of bromine in chloroform[196]. In general, α,α-dibrominated alkyl aryl ketones are not easily accessible due to exchange processes in the presence of hydrogen bromide[197,198].

During the addition of bromine to α,β-unsaturated ketones which yields α,β-dibromoketones, precautions have to be taken in order to avoid decomposition. The reaction has to be carried out very slowly and at low temperature (0°C) as exemplified by the preparation of 3,4-dibromo-3-methyl-2-butanone[199] and 3,4-dibromo-4-phenyl-2-butanone[200].

Alkoxybromination occurs when α,β-unsaturated ketones are treated with bromine in an alcohol, giving rise to α-bromo-β-alkoxy ketones[1] (equation 78)[201].

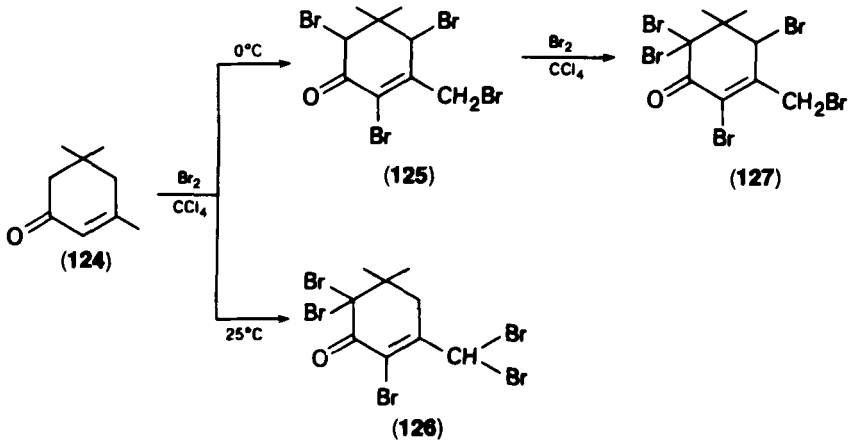
$$R^1CH{=}CHCOR^2 \xrightarrow[R^3OH]{Br_2} R^1CH(OR^3)-CH(Br)COR^2 \qquad (78)$$

2-Bromo-2-cyclohexenone (**123**) is prepared by treatment of 2-cyclohexenone (**122**) with bromine in collidine, the initial adduct being dehydrobrominated (equation 79)[202].



(**122**) (**123**) (79)

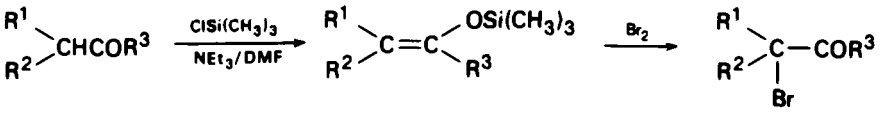
Treatment of isophorone (**124**) with an excess of bromine in carbon tetrachloride gives 2,4,6-tribromo-3-bromomethyl- (**125**) and 2,6,6-tribromo-3-dibromomethyl-5,5-dimethyl-2-cyclohexenone (**126**), respectively at 0 and 25°C. Further treatment of **125** affords the pentabromocyclohexenone (**127**) (equation 80)[202].

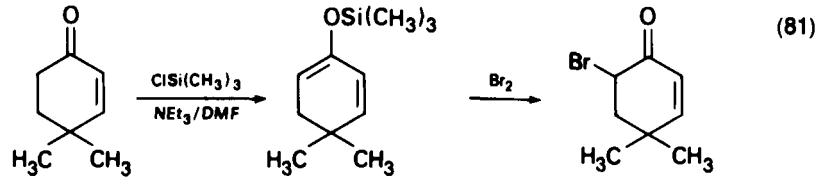


(80)

Just as in the preparation of α-chloroketones, various ketone derivatives serve as substrates for the synthesis of bromoketones. The bromination of trimethylsilyl enol ethers with bromine in carbon tetrachloride at −20°C represents an excellent method for the regiospecific introduction of a bromine atom into aliphatic and cyclic ketones (equation 81)[203].

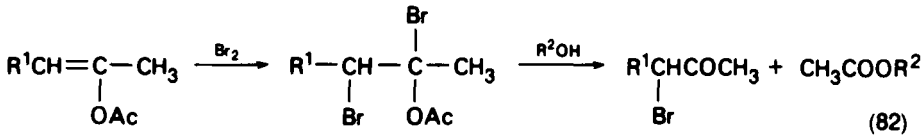
Treatment of enol acetates with bromine gives rise to α-bromoketones: 2-bromo-1-phenyl-1-propanone and 2-bromocycloalkanones are prepared according to this procedure (equation 82)[204].





(81)

(128) (129) (130)



(82)

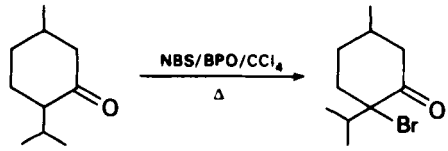
Bromination of enamines constitutes a suitable method for the preparation of bromoketones and the procedures mentioned for the synthesis of α-chloroketones are also applicable here[75,76].

b. Bromination with N-*bromo compounds.* The use of *N*-bromo compounds in the preparation of α-bromocarbonyl compounds, first reported by Schmid and Karrer[205] using *N*-bromosuccinimide (NBS), shows the advantage that neither hydrogen bromide nor free bromine are present during the reaction, with the consequence that side reactions are largely eliminated. Monobromination occurs smoothly and geminal dibromination rarely takes place, so that brominated ketones which are not available by the bromine method can be synthesized. However, the reaction rate is much slower with *N*-bromo compounds and in some cases no bromination occurs at all[206].

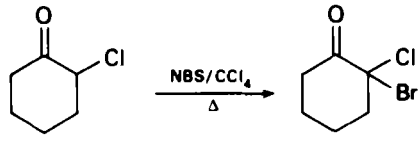
Numerous examples of monobromination of aliphatic and acyclic ketones with *N*-bromosuccinimide are known, mostly in the presence of initiators (benzoyl peroxide (BPO), azo-isobutyronitrile) and/or illumination[207–208]. Geminal dihaloketones (**133**, **135**) are formed when α-chloroketones, such as α-chlorocyclohexanone and α-fluoropropiophenone, are treated with NBS (equation 83)[33,187,209].

Introduction of a bromine atom in α,β-unsaturated ketones takes place at the allylic position and not at the carbon atom next to the carbonyl function[210]. Bromination of isophorone (**124**) with NBS gives rise to 4-bromoisophorone (**136**) (equation 84)[202]. Other *N*-bromo compounds, e.g. *N*-bromophthalimide, *N*-bromoacetamide, *N*-bromotolylsulphonylamide, 3-bromo- and 1,3-dibromo-5,5-dimethylhydantoin have been used less frequently as brominating agents[211]. Besides bromination of ketones with these reagents, derivatives such as enol acetates, enol ethers and enamines have also been treated and excellent yields of bromoketones are obtained, as in the case of the corresponding chloro derivatives[98,212].

However, the bromination of ketimines and subsequent hydrolysis turns out not to be a useful method for the preparation of dibromoketones. Reaction of methylketimines with NBS in CCl_4 gives rise to α,α-dibromoketimines, but hydrolysis of the latter compounds provides a mixture of α,α-dibromo and α,α′-dibromoketones[213]. On the other hand, hydrolysis of *N*-1-(2,2-dibromo-1-phenylalkylidene)cyclohexylamines affords a mixture of mainly 1-aryl-2,2-dibromo-1-alkanones and 1-aryl-1,2-alkanediones[96].

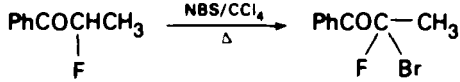


(131) (132)

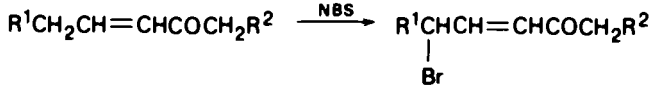


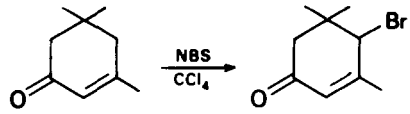
(83)

(118) (133)



(134) (135)

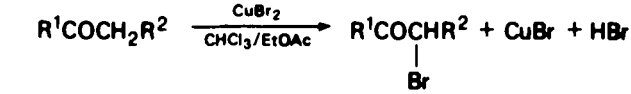




(84)

(124) (136)

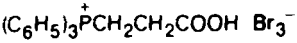
c. Miscellaneous brominating agents. Copper(II) bromide is an excellent reagent for the preparation of α-monobromoketones when the reaction is carried out in refluxing chloroform-ethyl acetate[214,215] (equation 85) (R^1, R^2 = alkyl, phenyl, $-(CH_2)_n-$).



(85)

Selective bromination of C—H α to a carbonyl function can also be achieved by pyridinium hydrobromide perbromide[216], tetrazolium perbromide[217], phenyltrimethylammonium perbromide[218], 2,4-diamino-1,3-thiazole hydroperbromide[219] and 2-carboxyethyltriphenylphosphonium perbromide (**137**)[220].

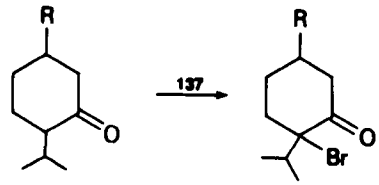
The last-mentioned compound, which is conveniently prepared by heating triphenylphosphine and acrylic acid in 49% hydrobromic acid followed by treatment with bromine in acetic acid, selectively gives monobromination at the α-position of a keto function even in the presence of double bonds. In the case of unsymmetrically substituted ketones, α-bromination occurs predominantly at the most substituted carbon atom due to the preferred enolization in that direction (equation 86).



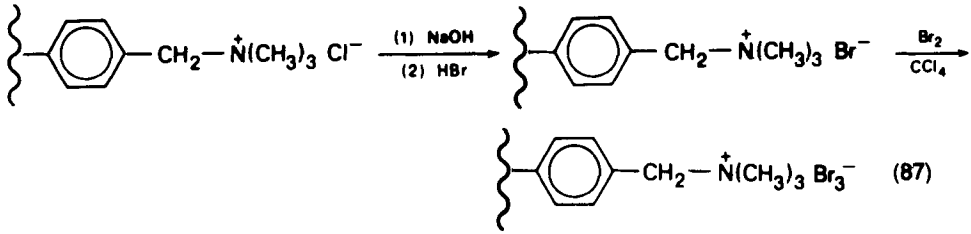
(**137**)

$$ArCH{=}CHCOCH_3 \xrightarrow{137} ArCH{=}CHCOCH_2Br$$

$$ArCH_2CH_2COCH_3 \xrightarrow{137} ArCH_2\underset{\displaystyle Br}{\underset{|}{C}}HCOCH_3 \qquad (86)$$



Recently, an insoluble regenerable brominating polymer has been developed. This polymer is easily and safely prepared from the macroreticular anion exchange resin Amberlyst-A26 Cl^- (Rohm and Haas Co.) (equation 87).

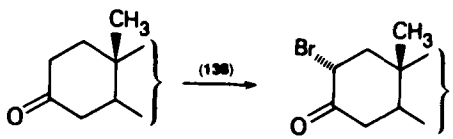


(138)

Amberlyst-A26 bromide form is converted into the perbromide form (**138**) by treating with a carbon tetrachloride solution of bromine. Unsymmetrical ketones are selectively brominated at the more highly substituted position, in the presence of a free radical initiator and methyloxirane as scavenger of the hydrobromic acid. α,β-Unsaturated ketones are completely converted into the corresponding dibromo saturated adducts. In the reaction of steroidal ketones, bromination occurs mainly from the less hindered side of the molecule (equation 88). The advantage of this reagent consists of the ease of operation, the work-up conditions and the capability for regeneration[221-222].

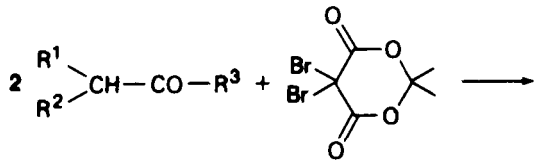
$$R{-}CH_2COCH_3 \xrightarrow[\text{O}\atop\triangle{-}CH_3]{138} R{-}\underset{\displaystyle Br}{\underset{|}{C}}HCOCH_3$$

$$R{-}CH{=}CH{-}COCH_3 \xrightarrow[\text{Hexane/RT}]{138} R{-}\underset{\displaystyle Br}{\underset{|}{C}}H{-}\underset{\displaystyle Br}{\underset{|}{C}}HCOCH_3 \qquad (88)$$

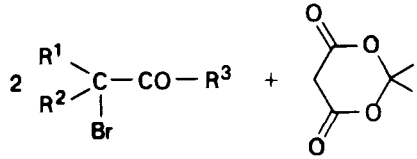


Brominated active methylene functions are also able to act as bromonium ion sources. Monobromo- and dibromomalononitrile are suitable reagents for the bromination of active methylene functions, but they are not active enough to introduce a bromine atom at the α-carbon of monocarbonyl functions[223,224].

An excellent reagent, however, seems to be 5,5-dibromo-2,2-dimethyl-4,6-dioxo-1,3-dioxan (**138a**), which is able to monobrominate saturated aldehydes and ketones and the α′-carbon atom of α,β-unsaturated ketones with high selectivity (equation 89)[225].

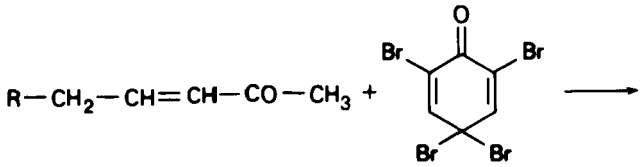


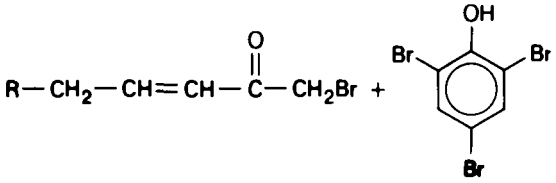
(**138a**)



(89)

In addition, 2-bromo-2-cyano-*N*,*N*-dimethylacetamide is also effective for the synthesis of α-monobromoketones[223], while selective monobromination of α,β-unsaturated ketones has been performed by the action of 2,4,4,6-tetrabromocyclohexa-2,5-dienone without affecting the double bond or any allylic position (equation 90)[226].

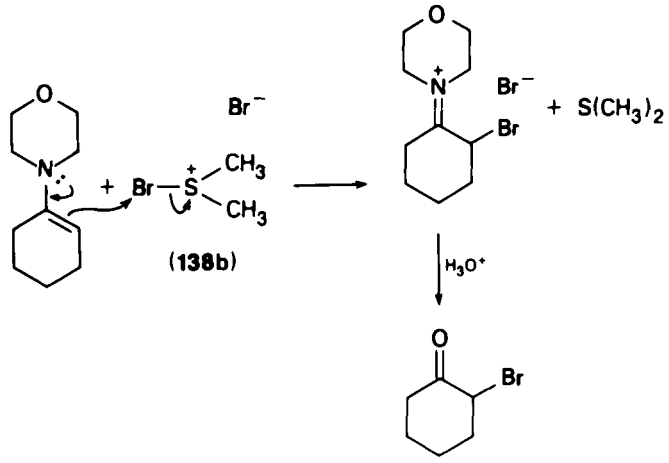




(90)

Dioxan dibromide has been used for bromination in the side chain of electron-rich hydroxy- and methoxy-substituted acetophenones, which often suffer nuclear bromination with other brominating agents[227].

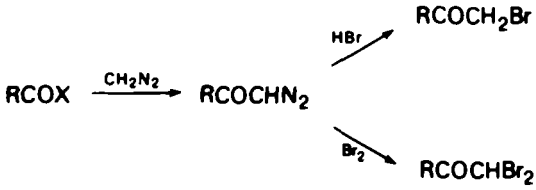
Another procedure involves the attack of bromodimethylsulphonium bromide (**138b**) on enamines followed by hydrolysis of the intermediate brominated immonium salt (equation 91)[158]. Sodium hypobromite is not a suitable reagent for the preparation of bromoketones. Methyl ketones give the haloform reaction; e.g. propiophenone has been oxidized to benzoic and acetic acid[228].



(91)

2. Synthesis of α-bromoketones from α-diazoketones

Monobromo- and dibromoketones are produced by decomposition of diazoketones with hydrogen bromide and bromine, respectively (equation 92)[130,229]. Sometimes minor amounts of the corresponding chloroketones are produced when starting from acid chlorides (X = Cl). Therefore acid bromides are preferentially used for the preparation of the diazoketones[231].

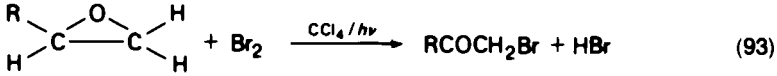


(92)

3. Synthesis of α-bromoketones from epoxides

Most of the procedures mentioned in the section dealing with the synthesis of α-chlorinated ketones using epoxides as substrates are also applicable for the preparation of α-bromoketones. Nevertheless, some specific methods using epoxides are available for the synthesis of the corresponding bromoketones.

Photocatalytic bromination of epoxides in carbon tetrachloride yields ketones directly, exclusively monobrominated at the less substituted α-carbon atom (equation 93)[232].



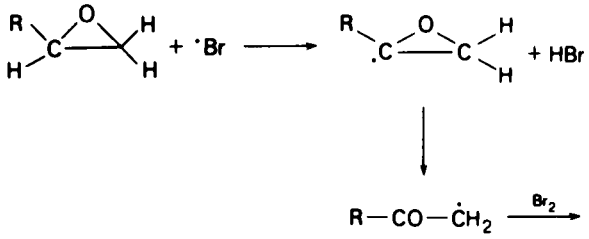
(93)

R = alkyl, phenyl

The majority of epoxides tested react with a stoichiometric amount of bromine to produce only the bromoketones and no bromohydrins, the latter arising from ring cleavage of the epoxide by the generated hydrogen bromide. However, cyclohexene

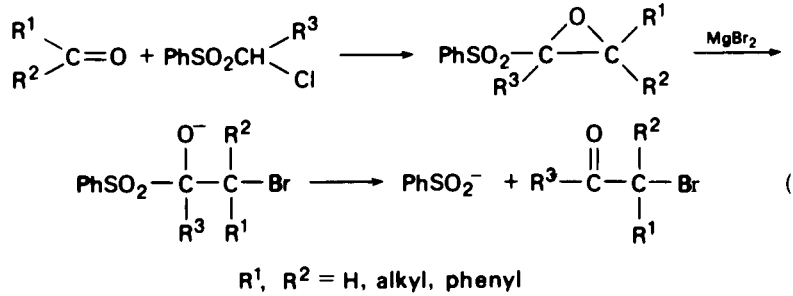
oxide and styrene oxide give, besides the monobromo-, also the dibromoketones and the bromohydrins. The photocatalysis is indispensable and the choice of the solvent is critical. In ether only the two bromohydrins are formed.

The mechanism must involve a free radical hydrogen abstraction process followed by a fast rearrangement to an α-oxoalkyl radical (equation 94).



(94)

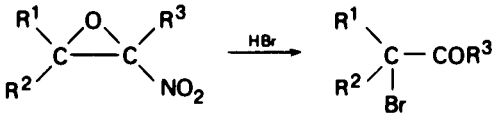
Reaction of epoxysulphonyl compounds, now conveniently available from α-chlorosulphones and aldehydes under phase transfer conditions, with magnesium dibromide in ether at room temperature, affords α-bromo carbonyl compounds (equation 95)[233].



(95)

R^1, R^2 = H, alkyl, phenyl

The epoxysulphone route is more general than the α-chloroepoxide route[149] and can be carried out easily. For example, 1-bromo-1-phenyl-2-propanone can be obtained in a yield greater than 95%. Ring cleavage of nitroepoxides with hydrogen bromide also gives rise to the formation of α-bromoketones (equation 96)[234].



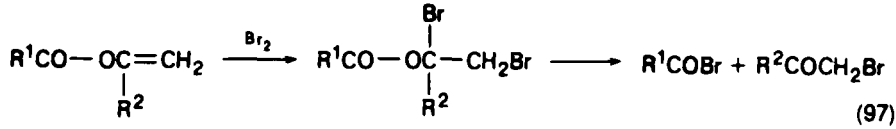
(96)

4. *Synthesis of α-bromoketones from miscellaneous substrates*

Some of the procedures already mentioned in the section concerning the synthesis of α-chloroketones can be utilized for the preparation of bromoketones.

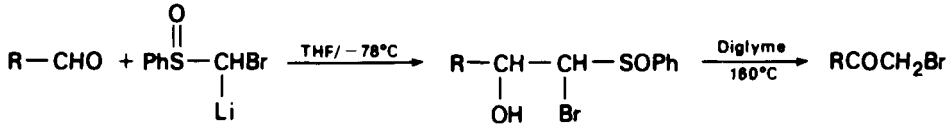
Dibromomethyl ketones are formed by the action of dibromomethyllithium on esters[162]. Jones oxidation and oxidation with pyridinium chlorochromate of brominated cycloalkanols also give excellent results, as in the synthesis of *cis*-2,8-dibromocyclooctanone[235].

Another method uses vinyl esters which are transformed into dibromoesters upon addition of bromine. These esters spontaneously decompose into acyl bromides and



(97)

α-bromoketones (equation 97)[236]. 1-Bromo-2-heptanone is obtained from 2-acetoxy-1-heptene in 75% yield. Pyrolytic elimination of α-bromo-β-hydroxy-sulphoxides, obtained by reaction of aldehydes with lithiobromomethyl phenyl sulphoxide, produces α-bromomethyl ketones in excellent yields (equation 98)[237].



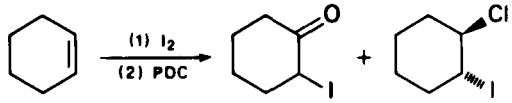
(98)

D. Synthesis of α-Iodoketones

α-Iodoketones are usually prepared by treatment of ketones with iodine in the presence of a strong base[238], by exchange reaction of chloro- or bromoketones with inorganic iodides[212,239,240], by treatment of ketones and their enol acetates with *N*-iodosuccinimide[241], by action of iodine(I) chloride on enol acetates[212] and by decomposition of diazoketones in the presence of iodine[242]. Several of these procedures suffer from disadvantages such as condensation and decomposition reactions and the availability and stability of substrates and reagents.

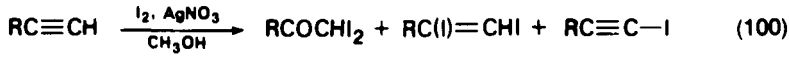
During the last few years successful methods have been developed for the synthesis of α-iodoketones. The reaction of enol acetates with thallium(I) acetate–iodine[243] and the oxidation of alkenes with silver chromate–iodine[244] gives α-iodoketones in moderate yields. However, thallium(I) acetate is highly toxic, and, using the latter method, only 1-iodo-2-alkanones can be prepared from terminal alkenes.

Cyclic α-iodoketones are obtained directly by oxidation of olefin–iodine complexes with pyridinium dichromate (PDC), but the reaction failed with linear olefins (equation 99)[245].



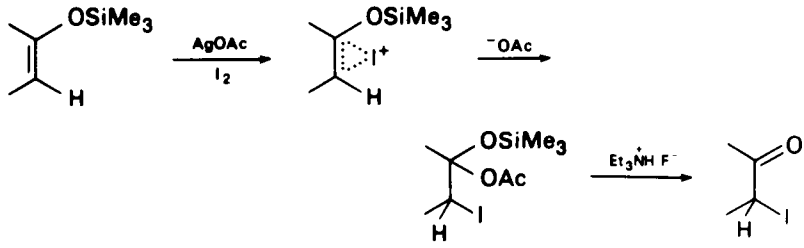
(99)

Terminal alkynes react with iodine in methanol in the presence of silver nitrate to give mainly α,α-diiodoketones together with diiodoalkenes and iodoalkynes (equation 100)[246].



(100)

At present the most general method consists of the sequential treatment of enol silyl ethers with silver acetate–iodine followed by triethylammonium fluoride. High yields of α-iodo carbonyl compounds are reported (equation 101)[247]. The mechanism can be envisioned as occurring with initial formation of an iodonium ion followed by acetate attack.



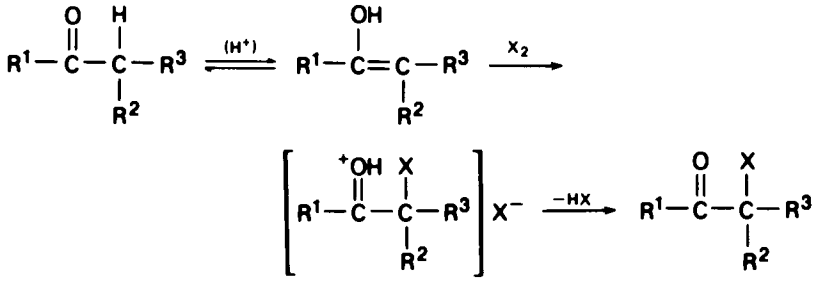
(101)

Iodoketones are relatively unstable and are not widely used in synthesis. Therefore the reactivity of α-iodoketones will not be discussed in the following sections because of their limited applicability.

E. Mechanisms of α-Halogenation of Ketones

As already pointed out during the discussion of the various procedures for the preparation of α-halogenated ketones, the halogenation occurs according to three different types of mechanisms[248,249].

(1) In the presence of acids an electrophilic attack of the halogen on the enol takes place and subsequent loss of a proton from the intermediate oxonium ion leads to the α-haloketone (equation 102). For sufficiently high halogen concentrations, the rate-limiting step is the enolization while the rate of halogenation seems to be independent of the nature and concentration of the halogen.



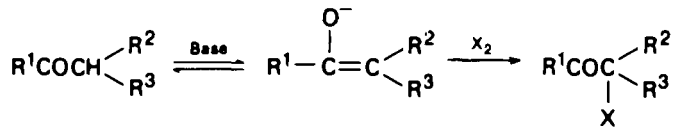
(102)

In the halogenation of unsymmetrical ketones, the substitution position is determined by the relative ease of formation of the isomeric enols. Consequently, the predominant isomer produced on halogenation of a ketone is that in which the halogen enters the more highly substituted α-position, because enol formation is enhanced by the presence of α-alkyl substituents and by other substituents which stabilize the enol.

However, the presence of an α-halo atom results in a decrease of the rate of enol formation and the substitution of each successive halogen atom becomes more difficult.

(2) In base-catalysed halogenations the halogen reacts with the enolate anion rather than with the enol. The rate of enolate formation is retarded by alkyl substituents and enhanced by α-halogen substituents. Therefore, base-catalysed halogenation is not suitable for the preparation of α-monohaloketones (equation 103).

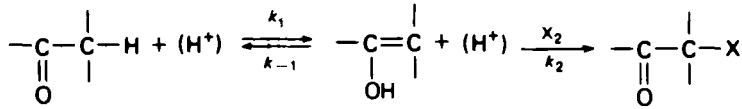
(3) The halogenation can be carried out via halogen radicals, but further introduction of halogens proceeds via an ionic mechanism under the influence of the generated hydrogen halide.



(103)

In the traditional mechanism for halogenation of ketones, which involves halogenation of a reactive enol or enolate, the observed rate of halogenation is independent of the halogen concentration and the nature of the halogen, when the halogen concentration is sufficiently high. Under these conditions the rate of deuteration should also be equal to the rate of halogenation. At sufficiently low halogen concentrations, the reaction between the enol or enolate and the halogen becomes rate determining and the observed rates become dependent on both the nature and the concentration of the halogen species.

At very low halogen concentration and high acidity, Bell demonstrated that the rate of the addition of the halogen to the enol form becomes slower in comparison with the enolization[250]. Nearly the same observations were made when the kinetics of the iodination, bromination and chlorination of acetone, diethyl ketone and diisopropyl ketone were studied at $[X_2] = 10^{-7}$–10^{-5} M (equation 104)[251]. The apparent rate



(104)

$$k_{II} = \frac{k_1}{k_{-1}} k_2 = K_E k_2$$

constants k_{II} for iodination, bromination and chlorination are approximately equal and k_2 is rate controlling only at very low concentrations of halogen (diffusion-controlled kinetics). The order of magnitude of such limiting rate constants of 10^9 M^{-1} s^{-1} leads to new values for K_E in solution, much smaller than those reported earlier[252].

After many years of unchallenged acceptance, the enolization mechanism for halogenation of carbonyl compounds was questioned by two groups. Rappe has postulated no less than five different mechanisms of halogenation for 2-butanone and other related ketones. Of these five reactions two are acid catalysed, two base catalysed and one is a free radical mechanism[253–255]. Rappe has claimed, for example, that base-catalysed bromination of 2-butanone can result in a ratio of monohalides (3-Br/1-Br = 7–7.5) quite different from that predicted on the basis of relative exchange rates (CH_2/CH_3 = 0.6–0.7). In addition there is an apparent 20–30-fold (at pH 5.5–7) and a fivefold difference (at pH 12) in the reaction rates for bromine and iodine. In view of these results a mechanism is postulated which involves a reaction of unenolized ketone with hypohalite anions.

Sytilin also claimed that the initial rate of bromination of acetone is dependent upon the concentration of bromine[256]. However, a few years later several groups proved independently that there is no reliable evidence to suggest that the base-catalysed halogenation of unsymmetrical ketones proceeds by alternative non-enolic halogenation routes other than by a traditional enolization mechanism[257–260].

III. REACTIVITY OF α-HALOGENATED KETONES

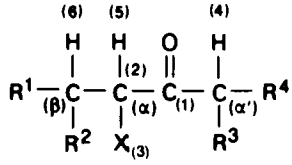
The interest in the reactivity of halogenated carbonyl compounds has grown since the discovery in 1895 of the Favorskii rearrangement, and numerous reports have dealt

with theoretical studies and synthetic applications of α-haloketones. Therefore it is extremely difficult to review all the reactions in which α-haloketones are important intermediates. The main focus will be upon the reactivity with nucleophiles and bases, although other important reactions and transformations will be treated selectively.

A. Reactivity of α-Haloketones towards Nucleophilic Agents and Bases

1. Introduction

On treatment of an α-haloketone with various nucleophiles and/or bases, the attack can take place at six possible electrophilic sites:



The nucleophile is able to attack the carbon of the carbonyl function (position 1), the carbon atom carrying the halogen atom (position 2) and the halogen atom (position 3). In addition, due to the presence of two polar electron-withdrawing groups, namely the carbonyl function and the halogen atom, the hydrogen atoms in the α-, α'- and β-positions also become susceptible to attack by nucleophiles or bases (positions 4, 5, 6).

Theoretically, the following types of reaction can be envisioned during the reaction of an α-haloketone with a nucleophilic reagent. Besides nucleophilic substitution (a), elimination (b) and reduction (c), a nucleophilic addition to the carbonyl (d) can take place, followed by a nucleophilic intramolecular substitution (e) with formation of an epoxide which is able to give further reactions. In addition a Favorskii rearrangement, via an intermediate cyclopropanone, with formation of carboxylic acid derivatives is an alternative route (f) (equation 105).

In most cases it is very difficult to predict which reaction type will occur on treatment of an α-haloketone with a nucleophile. This complexity is mainly due to the following factors:

(1) Several reaction pathways are often occurring simultaneously, resulting in mixtures of reaction products.

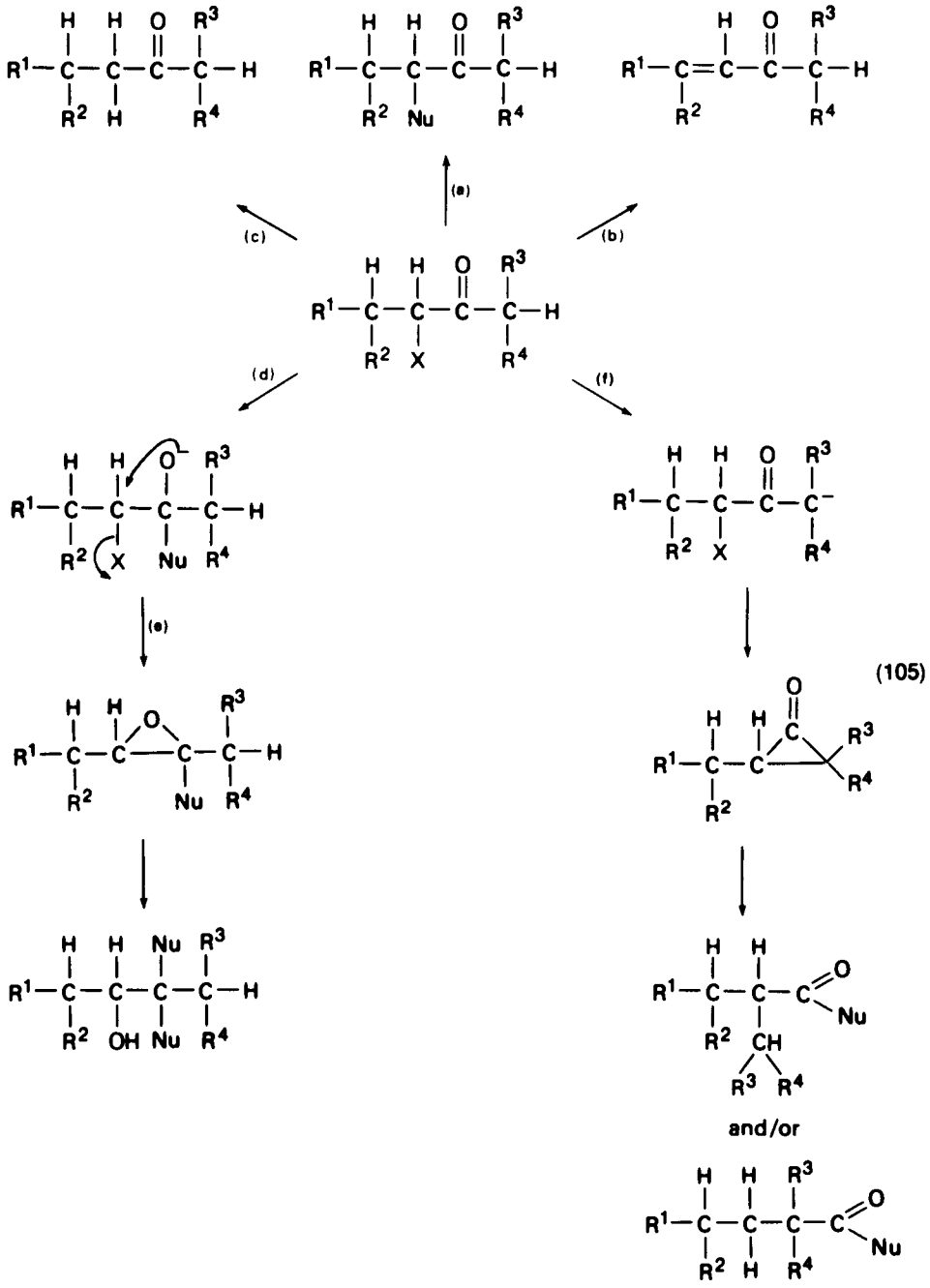
(2) The same reagent gives rise to different reaction products with different ketones.

(3) The same ketone may show completely different reaction pathways with very similar nucleophilic reagents.

(4) The reaction is strongly dependent upon the reaction conditions (solvent, temperature, etc.).

(5) Structurally similar ketones which are substituted with different halogens give different reaction products with the same reagents.

(6) The reaction products can undergo further transformations during the reaction, such as rearrangement, oxidation and dimerization, while the starting α-haloketones can also be transformed into different ketones which then react further, giving rise to unexpected compounds.



(105)

2. *The effect of the carbonyl function on the relative reactivity of α-halocarbonyl compounds with respect to alkyl halides*

The enhanced reactivity of α-halogenated ketones relative to the corresponding alkyl halides in bimolecular nucleophilic substitution is well known[261–265] and is illustrated in Table 1.

TABLE 1. Relative reactivities[a] of α-halo carbonyl compounds, alkyl halides and benzyl halides in nucleophilic substitution

Reaction	n-C_3H_7X	$PhCH_2X$	XCH_2COOEt	CH_3COCH_2X	$PhCOCH_2X$	Ref.
R—Cl + KI/acetone	1	197	1720	35 700	105 000	261
R—Cl + $S_2O_3^-$/water	1	–	220	1400	1600	263
R—Cl + ^-OAc/methanol	1	–	28	198	228	263
R—Br + pyridine/methanol	1	286	56	208	406	261
R—Br + thiourea/methanol	1	300	640	–	10 700	262
R—Cl + $^-N_3$/methanol	1	–	33	210	276	263
R—Cl + ^-OCN/methanol	1	–	75	156	176	263
R—Cl + ^-SCN/methanol	1	–	83	401	770	263

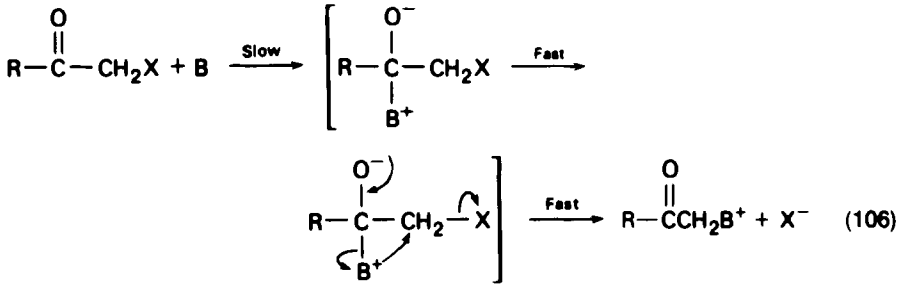
[a]Relative reactivity to C_3H_7.

Ester, cyano and related groups also show this powerful activating effect, but surprisingly the sulphonyl group is deactivating, although the carbonyl and the sulphonyl groups exert the same inductive and resonance effects as expressed by their σ-constants[264].

It is also noteworthy that the activating effect of the carbonyl function is still operative when the group is situated at the β- or γ-carbon atom; $PhCOCH_2CH_2Cl$ and $PhCOCH_2CH_2CH_2Cl$ are respectively 80 and 230 times as reactive as n-butyl chloride[261]. Various mechanisms have been postulated to explain the enhancement of reactivity due to the presence of the carbonyl function. Hughes[266] ascribes the reactivity to the inductive effect of the carbonyl group which enhances the polarity of the carbon–halogen bond by increasing the electron deficiency at the α-carbon atom. The more polar the C—X bond, the faster is the reaction of nucleophiles in bimolecular substitution. Baker[267] has proposed a mechanism in which the first and rate-determining step is the addition of the basic reagent to the carbonyl function, followed by a rapid intramolecular displacement (equation 106).

The isolation of stable epoxides in the reaction of an α-haloketone with sodium methoxide and the evidence that these epoxides are reactive intermediates leading to other products[268] gives rise to another explanation by Pearson and coworkers[262] (equation 107). If any of the steps of the first reaction is slow, then this mechanism is in agreement with the second-order kinetics. A key point is that the reagent B′ is not necessarily the same as B.

The interaction between the carbonyl group and the nucleophile is mainly



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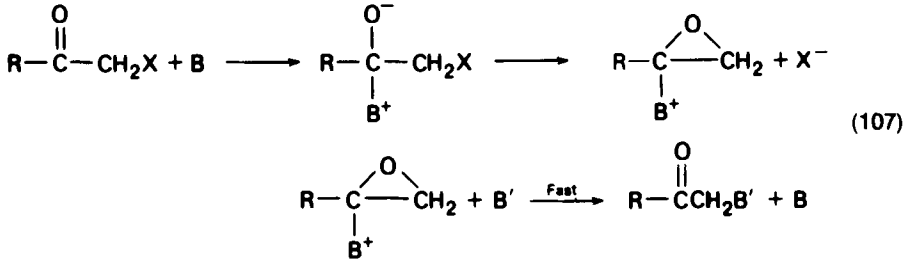
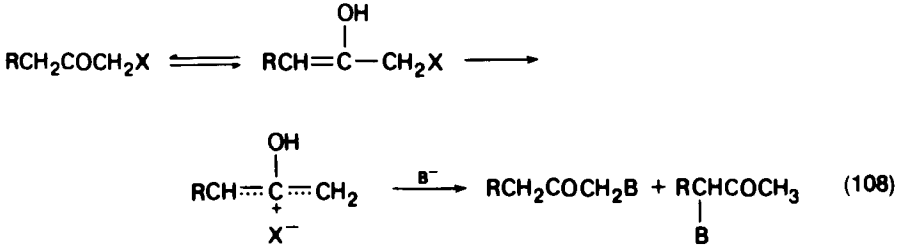


(107)

electrostatic and the high S_N2 reactivity is due to polarization interaction caused by the smaller steric requirement of RCO as compared to RCH_2.

Another interpretation by Dewar[269] and Winstein and coworkers[270] is based upon neighbouring group orbital overlap with the adjacent electron-deficient carbon atom. The transition state for the substitution of α-haloketones is envisaged as including partial bonding of the reagent with the *p*-orbital of the carbonyl carbon.

An alternative explanation is that substitution products are formed via an enolization–solvolysis mechanism as expressed in equation (108)[271].

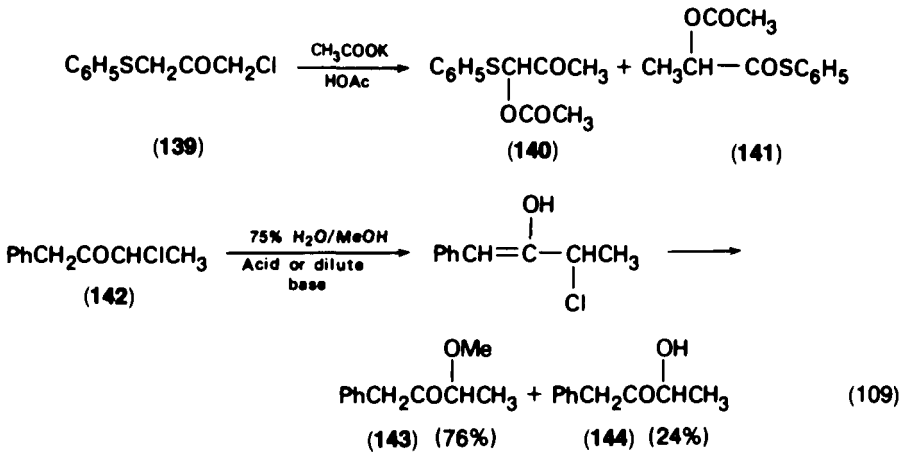


(108)

Many cases have been reported in which this mechanism is operative. An example is the reaction of 1-chloro-3-phenylmercapto-2-propanone (**139**) with acetic acid in the presence of potassium acetate, which yields 1-acetoxy-1-phenylmercapto-2-propanone (**140**) and the thiol ester (**141**) (equation 109)[272].

Another example involving solvolysis of an enol allylic chloride is responsible for the formation of the α-alkoxyketone (**143**) and the α-hydroxyketone (**144**) from the chloroketone (**142**) (equation 109)[273].

A fast rate of substitution could result from fast enolization–solvolysis and comparison with the rates of the corresponding alkyl halides is worthless. Several of



the proposed rationales are in contradiction to experimental data, for example with the substitution of α-haloketones by weakly basic nucleophiles.

The explanation of Hughes[266] fails in these cases where electron-withdrawing α-substituents other than carbonyl should show the same rate enhancement. However, α-halogen, α-alkoxy and α-sulphonyl substituents cause a substantial decrease in the rate of nucleophilic substitution of alkyl halides; α-halosulphones and α-halonitro compounds are quite unreactive. Baker's mechanism[267] does not fit the observation that the rate of substitution of α-haloketones is dependent upon the nature of the halogen. Bromoketones react faster than the corresponding chloro compounds, phenacyl bromide being 120 times as fast as phenacyl chloride with thiourea in methanol. Although a number of epoxides have been isolated or are shown to be important intermediates in reactions of α-haloketones (especially α-halobenzyl ketones react with alkoxides to yield α-hydroxyacetals), cleavage of epoxide intermediates leading to substitution products is dependent on the system and the experimental conditions. Arguments against an epoxide intermediate are presented in the reaction of haloketones with weakly basic nucleophilic reagents and against a rate-determining addition of the reagent to the carbonyl group[262]. Lutz showed that optically active desyl chloride undergoes exchange and racemization at the same rate with radioactive Cl^-, while for an epoxide mechanism an exchange without racemization is predicted[274]. However, Turro and coworkers proved that α-methoxy ketones are formed from α-bromoketones via an epoxide mechanism[275].

Thorpe and Warkentin interpret the bimolecular substitution of α-haloketones with acetate and azide ion, which are remarkably insensitive to steric hindrance, in terms of a normal S_N2 transition state, not involving either special alignment of entering and leaving groups with the π-orbital of the carbonyl function (conjugation) or covalent interaction between nucleophile and carbonyl carbon (bridging) for reaction of conformationally mobile systems. Conformationally fixed systems, on the other hand, may be affected by such factors. *trans*-4-*tert*-Butyl-2-chlorocyclohexanone is 61 times more reactive than the *cis*-isomer in reaction with acetate ion. Activation parameters support the statement that only those α-haloketones which are set up for conjugation and bridging show substitution according to a different pathway from that operating in the corresponding reactions of alkyl halides[276].

TABLE 2. Relative reactivity of phenacyl bromide and methyl iodide in nucleophilic substitution

Nucleophile	$k_2(PhCOCH_2Br)$ / $k_2(MeI)$
Cl^-	110
$(NH_2)_2CS$	63
NCS^-	30.5
$NCSe^-$	26.6
Pyridine	7.07
Ph_3P	4.44
Me_2S	3.22
Ph_3As	2.15
Me_2NPh	0.37
Et_3N	0.14

A recent report of Halvorsen and Songstad concerning comparison of second-order rate constants for reactions of phenacyl bromide and methyl iodide with various nucleophiles in acetonitrile reveals that the rate enhancement due to the carbonyl group is not a general effect but is dependent upon the nucleophile (Table 2).

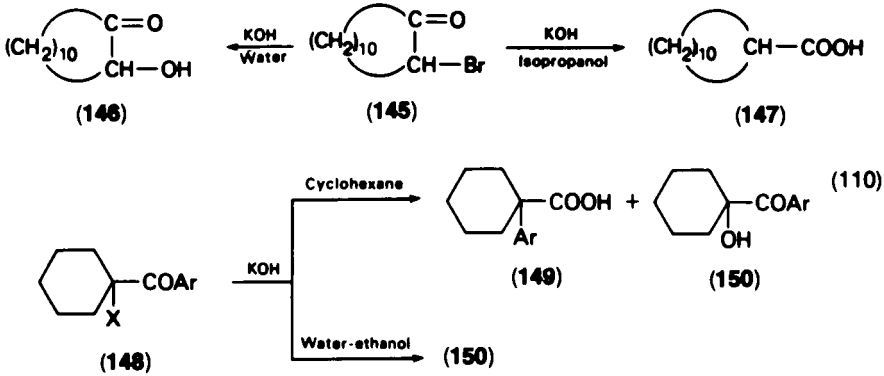
Apparently, reactions with ionic nucleophiles tend to involve a 'tight' transition state (containing a mainly sp^2 hybridized central carbon atom). On the other hand, reactions with uncharged nucleophiles (amines) react via an 'early' transition state (an sp^3 hybridized central carbon atom) where no conjugation with the α-carbonyl group is possible. In the first case, the α-carbonyl function does exert a significant influence upon reaction rates due to its $+E$ effect, while in the latter case a decrease of the reaction rate of phenacyl bromide is observed in comparison with methyl iodide[277]. Considering all these results it is reasonable to postulate that any favourable effect exerted by a carbonyl function on the nucleophilic reactivity stems in part from the absence of rate-retarding steric effects (the enhancement is much lower for propionyl or butyryl functions in comparison with an acetyl function[33]), coupled with a mildly rate-enhancing inductive effect.

3. *Reaction of α-haloketones with oxygen nucleophiles and bases*

a. Reaction with inorganic oxygen nucleophiles. The products of the reaction of α-halogenated ketones with oxygen nucleophiles and bases are strongly dependent upon the substrate, the nature of the nucleophile and the reaction conditions. Besides substitution reactions, eliminations and rearrangements are also occurring, with the result that in many cases the outcome of the reaction cannot be predicted and that several reaction pathways take place simultaneously, resulting in a mixture of products. Several examples are known in which hydrolysis of α-haloketones with hydroxide and carbonate solutions in various solvents (water, alcohols, ether, dioxan, etc.) gives rise to α-hydroxyketones[277–282]. For example, α-hydroxycyclohexanone is formed in 76% yield from 2-chlorocyclohexanone with an aqueous solution of potassium carbonate[283], while ω-hydroxyacetophenone is obtained by boiling ω-chloroacetophenone in water[284].

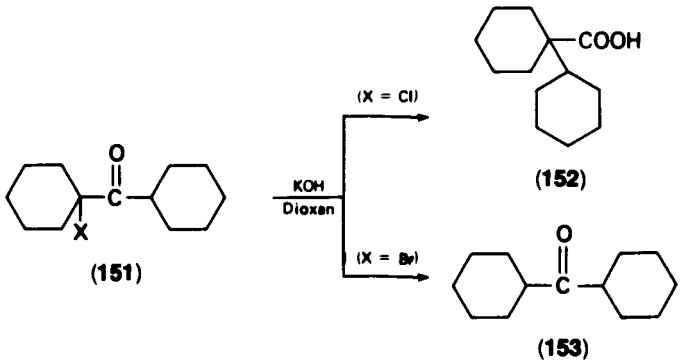
However, during the hydrolysis of α-haloketones, side reactions, and especially Favorskii rearrangements and elimination reactions, are able to occur.

While treatment of 2-bromocyclododecanone (**145**) with aqueous potassium hydroxide gives 78% 2-hydroxycyclododecanone (**146**), the reaction in isopropanol results in the formation of the Favorskii rearrangement product, i.e. cycloundecanecarboxylic acid (**147**)[285]. The same phenomenon is observed during the reaction of halogenated aryl cyclohexyl ketones (**148**) with potassium hydroxide (equation 110)[286,287]. The nature of the halogen also plays an important role in the



(110)

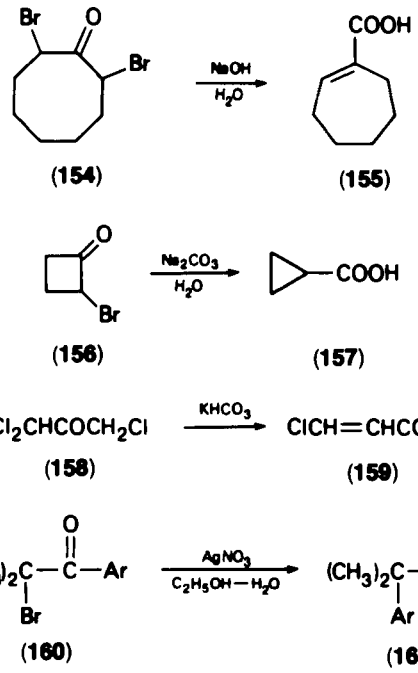
reaction course. Reaction of α-chlorinated dicyclohexyl ketone (**151**) with potassium hydroxide in dioxan gives mainly a carboxylic acid (**152**), while the corresponding bromo compound shows a completely different reaction resulting in a debromination (equation 111)[288]. The initially formed α-hydroxyketones sometimes undergo further



(111)

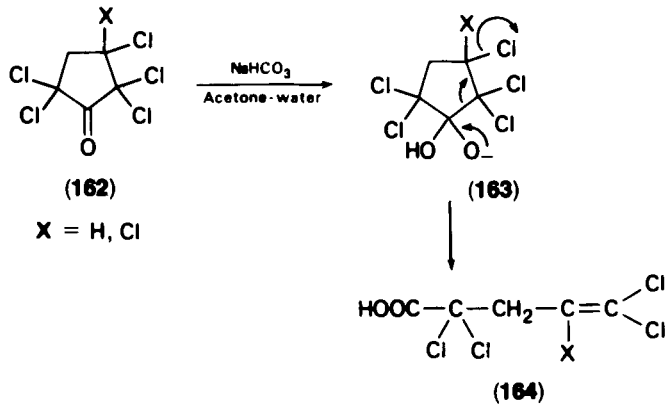
reactions under the basic reaction conditions, such as isomerization[289], oxidation with formation of diketones[290], benzylic rearrangement with formation of α-hydroxycarboxylic acids[291] and dimerization[292].

Numerous examples are known of Favorskii rearrangements of α-halogenated ketones with metal hydroxides[293], carbonates[294], bicarbonates[295] and silver nitrate[296] in water, as depicted below (equation 112). In some cases, such as polyhalogenated cycloalkanones, even treatment with water gives rise to Favorskii products[293].



(112)

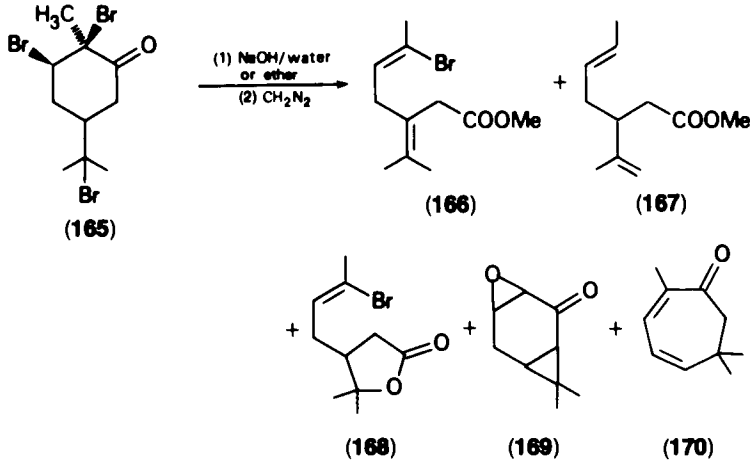
Next to the Favorskii rearrangement, the Grob fragmentation is frequently encountered in reactions of halogenated cycloalkanones such as polychlorocyclopentanones with base[162] (equation 113)[64].



(113)

A similar fragmentation reaction leading to dichlorinated acids takes place during the synthesis of geminal dichloroketones with the system carbon tetrachloride–potassium hydroxide–*t*-butyl alcohol[106]. Also, in the reaction of carvone tribromide (**165**) with sodium hydroxide in water or ether, little or no Favorskii rearrangement occurs; instead the carbonyl group is attacked, leading to compounds

166, **167** and **168** by a Grob fragmentation and to an epoxide (**169**). However, in the reaction of the *trans* isomer (**171**) with sodium hydroxide, the Favorskii rearrangement prevails with formation of unsaturated esters (after treatment with diazomethane) and a lactone (equation 114)[297].



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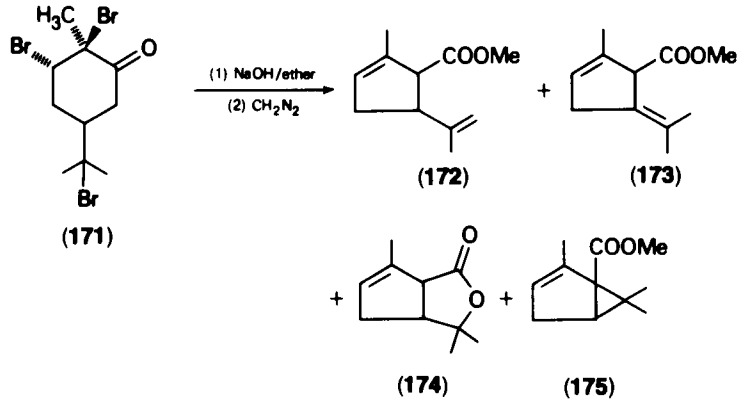
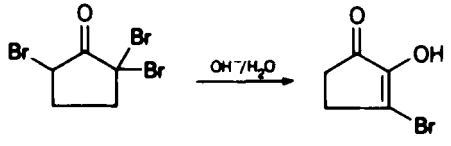


α-Hydroxycycloalkenones (**177**, **179**) are prepared from α-brominated cycloalkanones (**176**, **178**) by hydrolysis with aqueous sodium hydroxide (equation 115)[298,299].

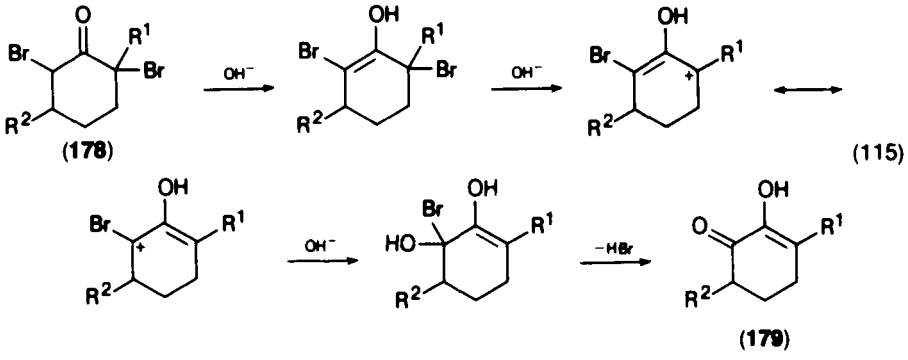
The reaction of 2,2-dihalo-1-arylalkanones (**180**) with hydroxide ion takes a completely different course, yielding α-hydroxycarboxylic acids (**182**) via a benzilic rearrangement of intermediate α-diketones (**181**) (equation 116)[300].

Although a number of dehydrohalogenation reactions by the action of carbonates on α-haloketones have been reported, this reaction has little synthetic value due to rearrangements and aldol condensations already mentioned. In most cases lithium carbonate in dimethylformamide or dimethyl sulphoxide has been used in the elimination reactions.

Cyclohexenones are formed from α-halocyclohexanones. For example, 5-*t*-butyl-2-cyclohexenone (**184**) is produced from the chloro compound (**183**) using

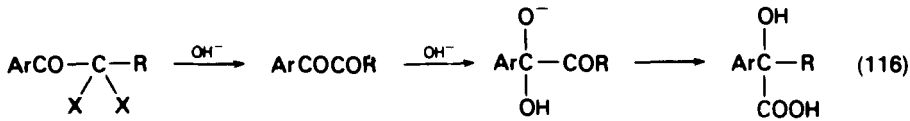


(176) (177)



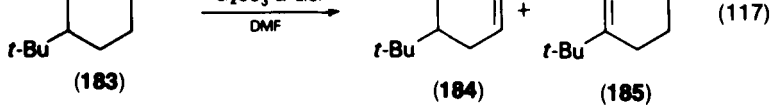
(178) (115)

(179)



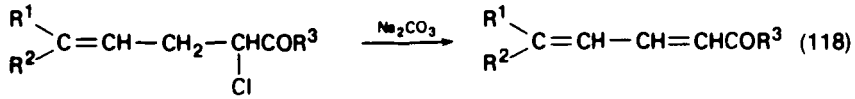
(180) (181) (182) (116)

lithium carbonate in dimethylformamide (DMF), while treatment of (**183**) with lithium chloride results in formation of a mixture of the isomeric cyclohexenones (**184**, **185**) in a ratio 3.5:1 (equation 117)[301]. Similar results are obtained during dehydrochlorination of 9-chloro-1-decalone with lithium chloride[302].



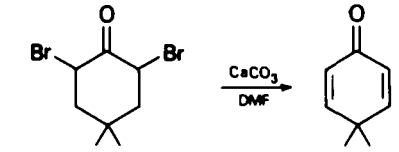
(183) (184) (185) (117)

Dehydrohalogenation readily occurs using alkali carbonates in DMF or dimethyl sulphoxide (DMSO) in reactions with γ,δ-unsaturated α-haloketones, producing dienones (equation 118)[303].



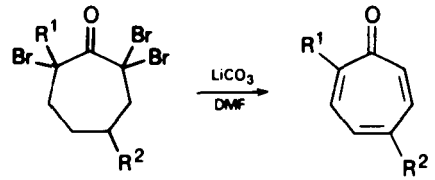
(118)

Dehydrobromination of α,α'-dibromocycloalkanones occurs easily and 4,4-tetramethyl-2,5-cyclohexadienone (**187**) and 2,4,6-cycloheptatrienones (**189**) are formed from 2,6-dibromo-4,4-dimethylcyclohexanone (**186**) and 2,2,7-tribromo-



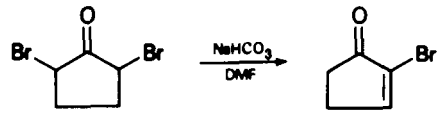
(186) (187)

(119)



(188) (189)

cycloheptanone (**188**), respectively (equation 119)[189,305]. However, the reaction of α,α′-dibromocyclopentanone (**190**) with two equivalents of sodium hydrogen carbonate in DMF affords 2-bromocyclopent-2-enone in high yield (equation 120)[306].



(190) (191)

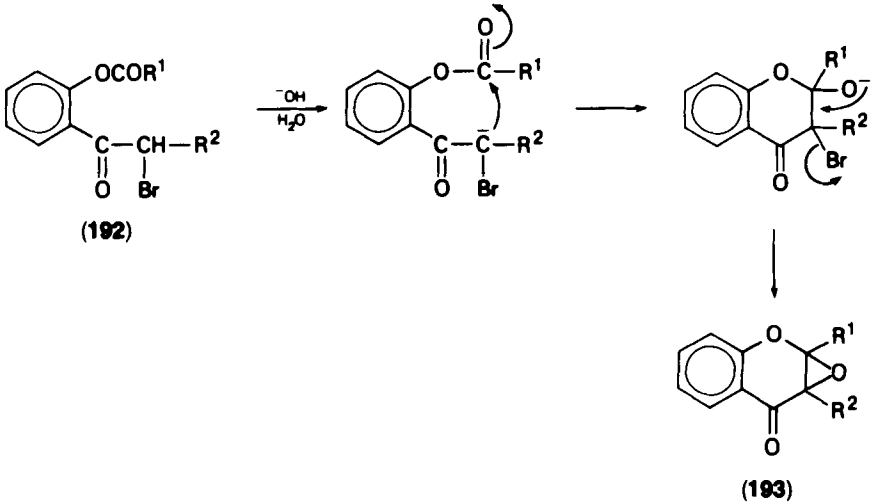
(120)

Hydroxide-catalysed cyclization takes place when α-bromo-*o*-acyloxyaryl alkyl ketones (**192**) and α-bromo-β-methoxydihydrochalcones (**194**) are treated with aqueous sodium hydroxide, yielding respectively 3-substituted chromone epoxides (**193**)[307] and aurones (**195**)[308]. The bromohydrins (**196**) are cyclized to chalcone epoxides (**197**)[309] by reaction with potassium carbonate in aqueous *t*-butanol (equation 121).

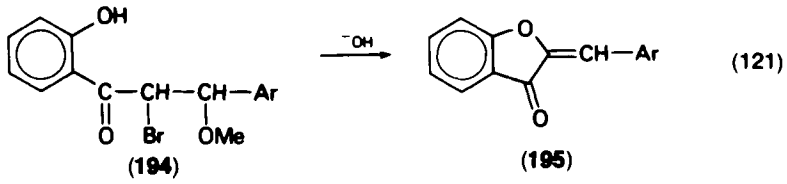
Finally, treatment of bromoketones with sodium hydroxide or potassium carbonate in the presence of peroxides provides olefins as major products via intermediate cyclopropanones (equation 122)[310].

b. Reaction with organic oxygen nucleophiles and bases. There is no doubt that the reaction of α-haloketones with alkoxides is the most profoundly investigated in the field of the reactivity of α-halogenated carbonyl compounds. Nevertheless, prediction of the reaction products of α-haloketones with oxygen nucleophiles turns out to be very puzzling. Nearly all the reaction pathways proposed in the introduction to this section can take place, and the reaction outcome is dependent upon the nature of substrate and reaction conditions.

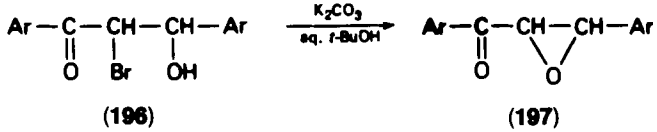
A typical example of the complexity of this type of reaction was given by Turro during study of the isomeric pair of α-bromo-2-butanone and α-bromo-3-methyl-2-butanone with sodium methoxide. The reaction products consist of mixtures of Favorskii esters, α-hydroxy- and α-methoxyketones (**198**, **199**, **199a**) (equation 123)[275]. The ester formation is favoured in ether, while methoxy ketones are the dominant products in methanol. Turro proved that the Favorskii esters are formed via a cyclopropanone intermediate and the hydroxy- and methoxyketones are generated through epoxy ethers, which subsequently decompose directly or upon work-up.



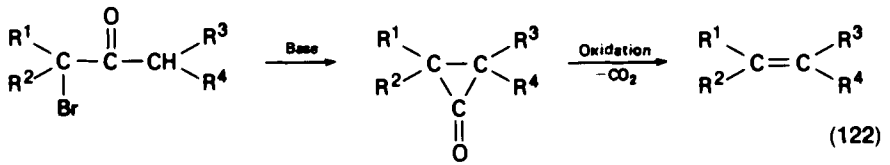
(192) (193)



(194) (195) (121)



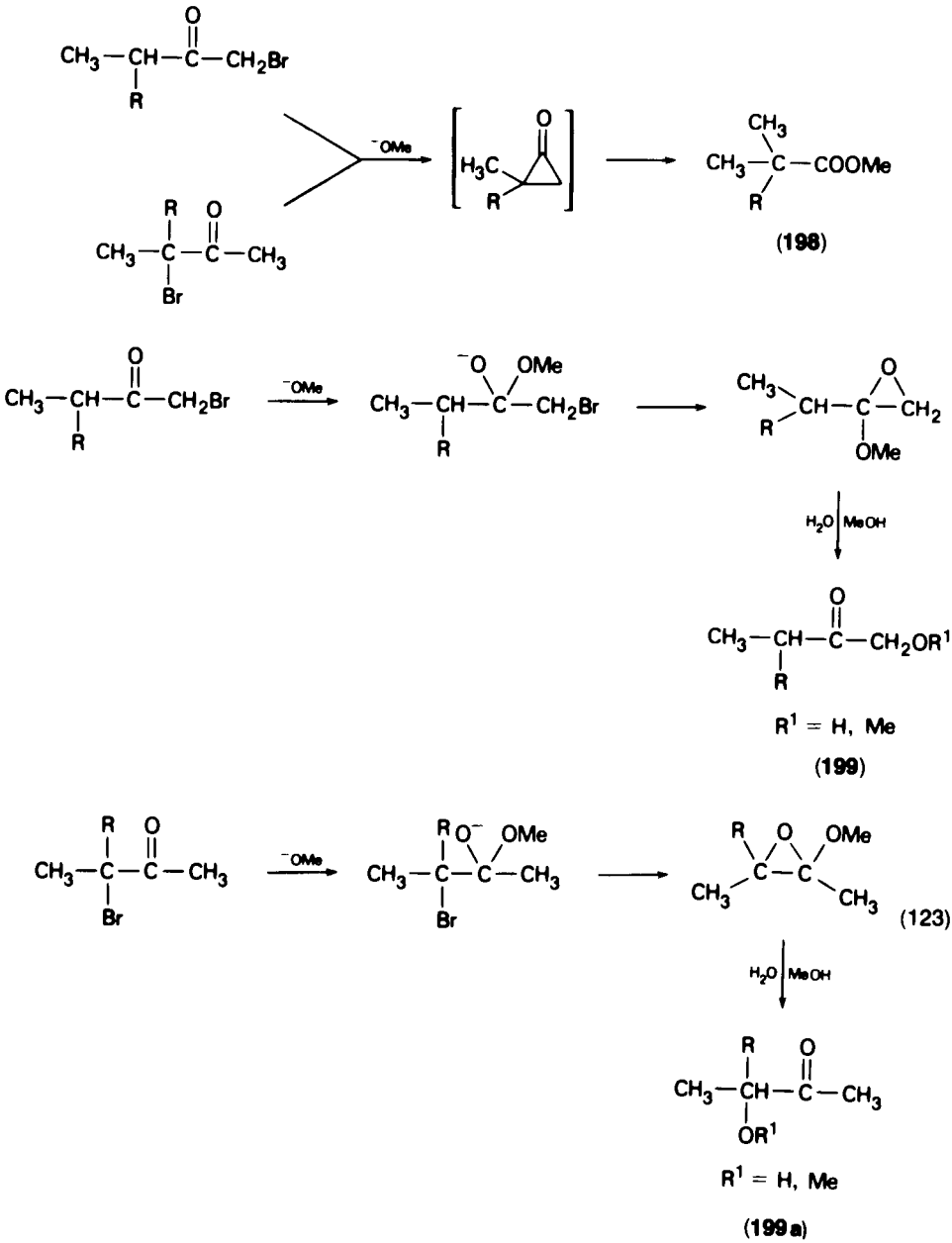
(196) (197)



(122)

Increasing the degree of substitution at the carbon atom to which the halogen is attached usually favours the Favorskii rearrangement by lowering the rate of side reactions, whereas substitution on the α'-atom hinders rearrangement[310]. Replacement of chlorine by bromine favours Favorskii rearrangement most of all[229]. The competition between substitution, epoxide formation and Favorskii rearrangement is illustrated by the following examples, which emphasize the important influence of the structure of the substrate.

Treatment of 3-bromo-3-methyl-2-butanone (**200**) with sodium methoxide gives the ester (**201**)[312,313], while in compounds without α'-hydrogen atoms such as brominated alkyl aryl ketones (**202**), epoxide formation (**203**) predominates (equation 124)[314].

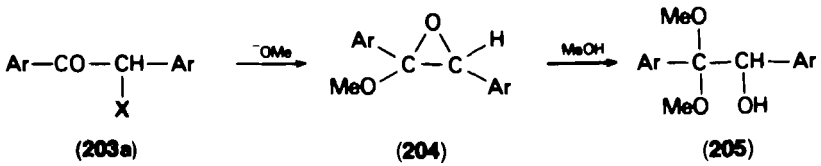


Nucleophilic addition at the carbonyl function followed by intramolecular nucleophilic substitution yielding methoxy epoxides seems to be the most favourable pathway in the reaction of ketones without α′-hydrogen atoms such as in halogenated aryl benzyl ketones (**203a**)[315,316], tetralones (**206**)[317] and steroidal α-bromoketones

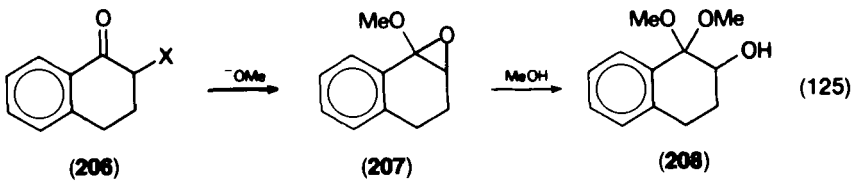
(200) (201)

(202) (203) (124)

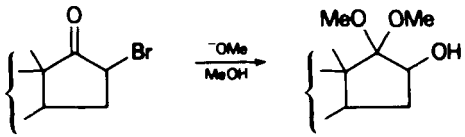
(209)[318]. A number of the epoxides (**204**, **207**) are isolated, although they are readily converted into α-hydroxyacetals (**205**, **208**, **210**) on further treatment with alcohols (equation 125). However, tertiary α-haloketones, e.g. 2-bromo-2-benzyl-1-tetralones



(203a) (204) (205)



(206) (207) (208) (125)



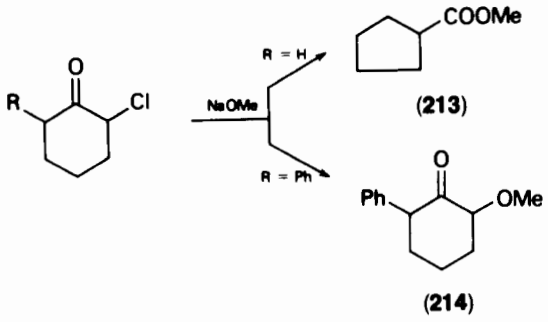
(209) (210)

(**211**), are readily dehydrobrominated with alcoholic sodium methoxide to give excellent yields of α,β-unsaturated ketones (**212**) (equation 126)[319,320].

(211) (212) (126)

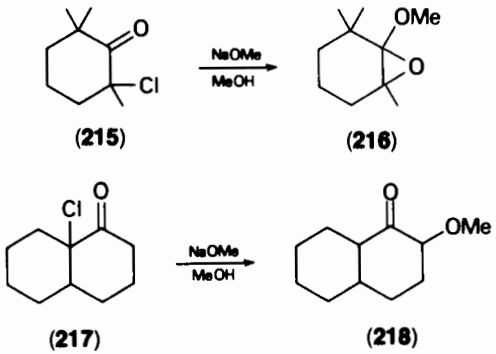
In the field of α-halocycloalkanones the reaction products with alkoxides are also strongly dependent upon the substrate. While 2-chlorocyclohexanone gives rise to the

Favorskii ester (**213**)[321], treatment of 6-phenyl-2-chlorocyclohexanone produces the substitution product (**214**) in different solvents[322] (equation 127). On the other hand,



(127)

2-chloro-2,6,6-trimethylcyclohexanone (**215**) gives a stable epoxy ether (**216**)[323], while 9-chloro-1-decalone (**217**) produces the rearranged substitution product (**218**)[324] (equation 128).

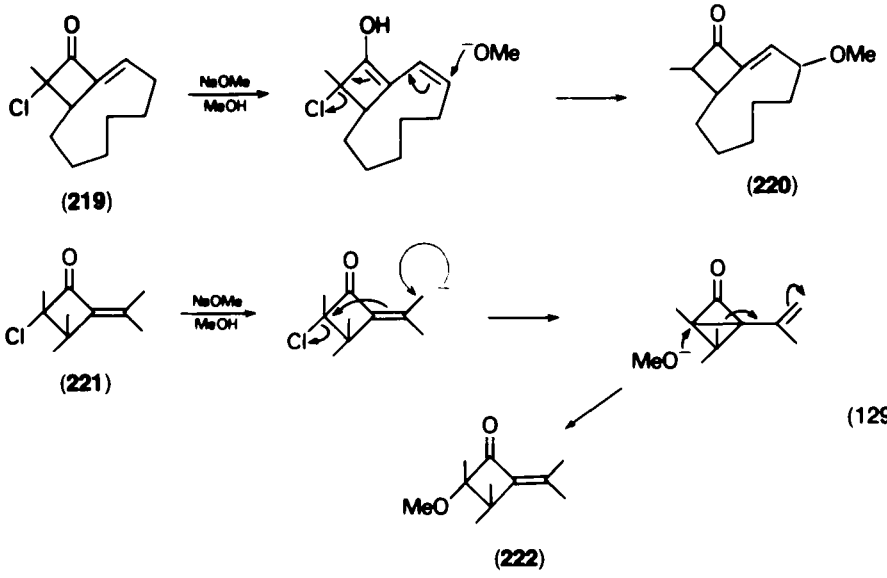


(128)

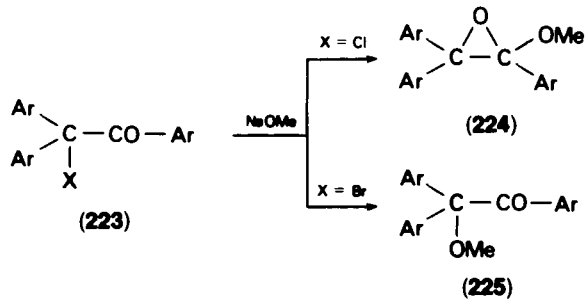
Treatment of 10-chloro-10-methylbicyclo[7.2.0]undec-1-en-11-one (**219**) with sodium methoxide in methanol also results in allylic substitution rather than ring contraction to produce the methoxy ketone (**220**). The substitution apparently occurs through the enol of **219**. Conversely, treatment of 2-chloro-4-isopropylidene-2,3,3-trimethylcyclobutanone (**221**) under identical conditions results in the unrearranged product. It seems unlikely that this substitution product (**222**) is the result of a direct displacement at the tertiary centre. The product probably results from an elimination proceeding through a bicyclobutanone intermediate which adds methoxide to produce **222** (equation 129)[325].

Not only does the nature of the substrate play an important role in the reaction pathway. The halogen atom also influences the reaction, as illustrated in the case of the triaryl ketone (**223**) where the chloro compound gives a methoxy epoxide (**224**) and the bromo compound a methoxyketone (**225**) (equation 130)[316].

Other important factors controlling the reaction course are the reaction conditions and especially the nature of the solvent and the concentration of the nucleophile. In the reaction of α-chlorocyclohexanone or 2-bromo-5-methyl-5-phenylcyclohexanone with sodium methoxide in methanol, the yield of the Favorskii esters has been found to increase markedly at the expense of the α-methoxyepoxide and the α-methoxyketone on increasing the methoxide concentration. The increased yield can be attributed



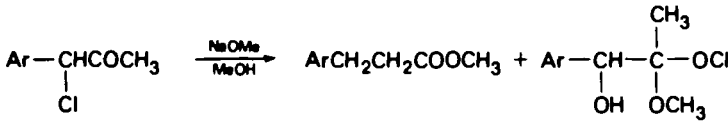
(129)



(130)

partly to a positive salt effect favouring ionization of halide ion from the enolate ion. 2-Chloro- and 2-bromo-4-methyl-4-phenylcyclohexanone are much less subject to this concentration effect due to steric factors: 40% yield of the Favorskii ester is obtained even at low methoxide concentrations[326].

Substituted α-chlorobenzyl methyl ketones (**226**) also give mixtures of Favorskii esters (**227**) and α-hydroxyacetals (**228**) (equation 131)[327]. The yield of the Favorskii ester increases from 9% at 0°C with 0.05 M sodium methoxide to 61% with 2 M sodium methoxide at 63°C. This is believed to be a consequence of a 2–3 kcal mol^{-1}

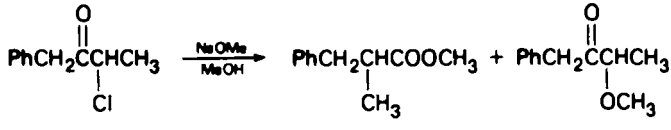


(131)

(**226**) (**227**) (**228**)

Ar = C_6H_5, *p*-$NO_2C_6H_4$, *p*-ClC_6H_4, *p*-$MeOC_6H_4$, *m*-$MeOC_6H_4$, *p*-MeC_6H_4, *m*-MeC_6H_4, *p*-FC_6H_4

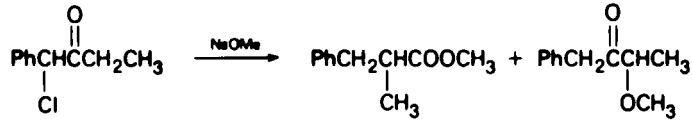
higher activation energy for the Favorskii reaction. The yield of the ester is increased to 68% for Ar = *p*-$MeOC_6H_4$ and is decreased to 0% for Ar = *p*-$NO_2C_6H_4$. Similar effects are observed in the reactions of 3-chloro-1-phenyl-2-butanone (**228a**) and 1-chloro-1-phenyl-2-butanone (**231**) with variable concentrations of methoxide ion yielding mixtures of ester (**229**) and α-methoxyketone (**230**) (equation 132)[328,329].



(**228a**) (**229**) (**230**)

[$^-$OMe], M	229, %	230, %
0.05 (inverse addition)	0	100
0.02	50	50
2	100	0

(132)



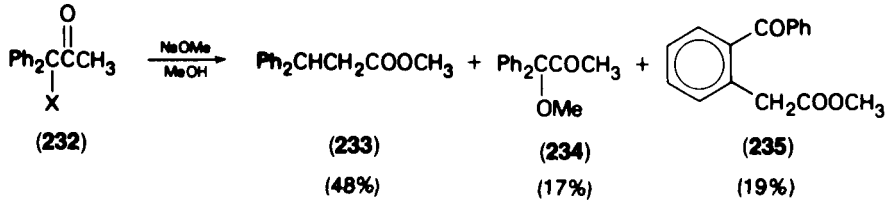
(**231**) (**229**) (**230**)

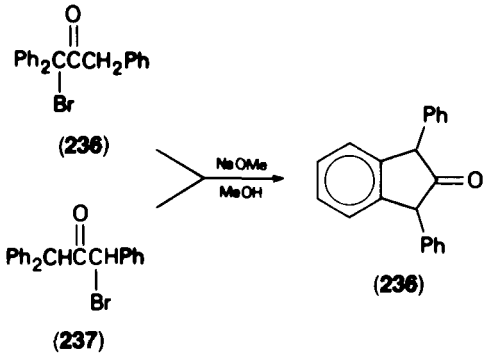
[$^-$OMe], M	229, %	230, %
0.05	70	30

1-Halo-1,1-diphenyl-2-propanones (**232**) react with 0.05 M sodium methoxide to give essentially quantitative yields of Favorskii ester (**233**), while under inverse addition (addition of the nucleophile to the substrate) and low concentration of methoxide ion a mixture of **233**, **234**, and **235** is formed. Reaction of 3-chloro-1,1-diphenyl-2-propanone under the same conditions gives the same product distribution, while α-bromo-1,1,3-triphenyl-2-propanones (**236**, **237**) yield 1,3-diphenyl-2-indanone (**238**) (equation 133)[330].

The mechanisms leading to the various reaction products have been elucidated by Bordwell[273,322,325–330]. The Favorskii rearrangement of α-chloroarylpropanones and α-chloroarylbutanones falls into two classes. The series $ArCHClCOCH_3$ and $ArCH_2COCH_2Cl$ react with methoxide by way of reversible carbanion (enolate ion) formation followed by rate-limiting halide release, while for systems like $ArCH_2COCHXCH_3$, $PhCHXCOCH_2CH_3$ and $PhCH_2COCHXPh$, halide ion release is greatly accelerated and proton removal becomes rate limiting. The alkoxy ketones are formed through solvolysis of intermediate enol allylic chlorides. The various pathways are depicted in equation (134). The same mechanism is observed during the methanolysis of 3-chloro-1,3-diphenyl-2-propanone with lutidine or lutidine–lutidine $\cdot H^+$ buffer, yielding exclusively the α-methoxyketone[328]. No reaction is observed when chloroacetone is treated under similar circumstances[331].

The distribution of the products obtained by reaction of dichlorinated methyl ketones (**239**, **240**) with sodium methoxide in methanol is strongly dependent upon the



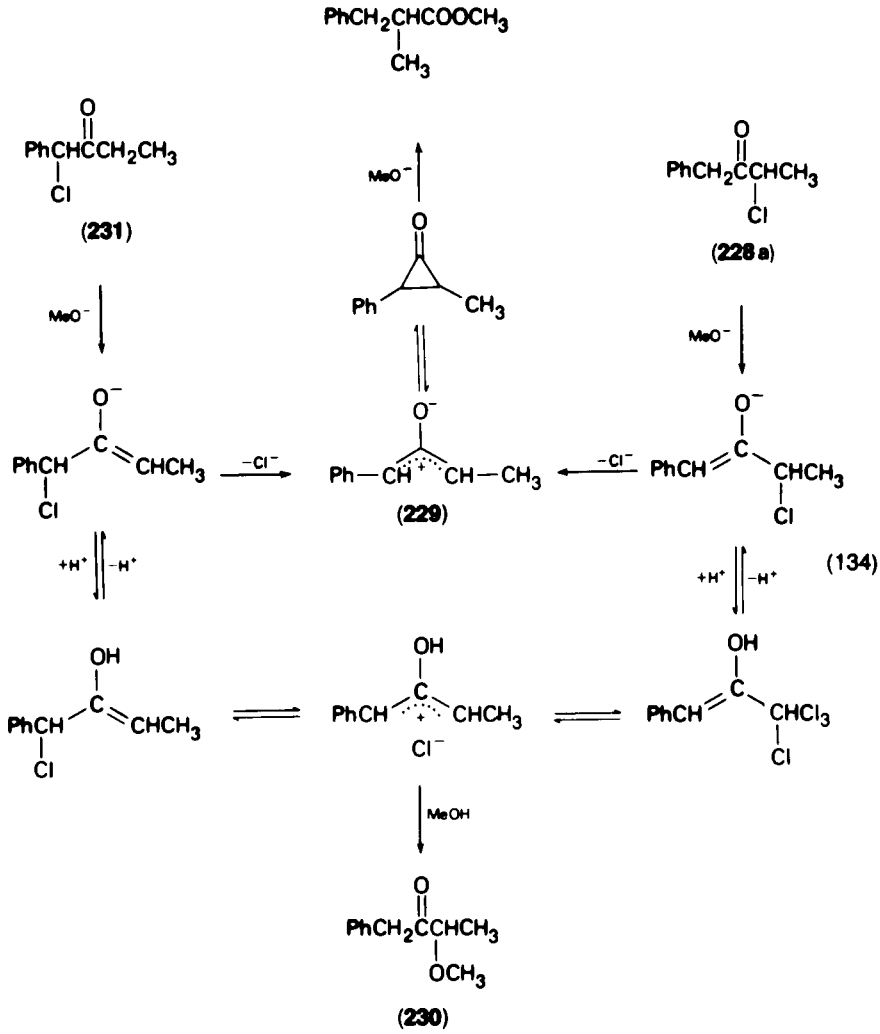


(133)

structure of the ketone. Primary dichloromethyl ketones (R^2 = H) give the normal *cis* acrylic esters (**241**), together with chloromethyl esters (**242**) whose amount increases with the increase in the bulk of the R^1 group, while the secondary dichloromethyl ketones (**240**) afford small amounts of methyl esters (**242**) but variable amounts of methoxyketones (**243**). The stereospecificity is complete for primary ketones and in the secondary derivatives the ratio between the *cis* and *trans* acrylic esters depends on the difference between both alkyl substituents (bulkiness) and on the chlorine substitution (1,1- and 1,3-dichloroketones) (equation 135)[95]. The reaction takes a completely different course when α,α-dihaloalkyl aryl ketones (**244**) react with sodium alkoxides to produce a mixture of isomeric α,α-dialkoxy ketones (**245**, **246**) in variable ratios[33,209]. In the cases where R^1 = H and R^1 = *t*-Bu small amounts of alkyl benzoates (**247**) are detected (equation 136).

2-Chloro-2-fluoro and 2-bromo-2-fluoro compounds give rearrangement to **246** exclusively while α,α-difluoroketones show exclusive reduction of the carbonyl function. It is reasonable that the dichloroketones react by an initial nucleophilic addition and subsequent intramolecular nucleophilic attack with halide displacement, furnishing α-halo-α′-alkoxyepoxide intermediates. The latter compounds rapidly rearrange spontaneously to α-halo-α-alkoxy ketones which further give rise to α,α-dialkoxy ketones by a direct route or via the hemiacetal. Alternatively, the latter product can be deprotonated by the alkoxide, after which intramolecular nucleophilic substitution yields the α,α′-dialkoxyepoxides. The diactivated epoxides are then opened at both sides to produce the final isomeric α,α-dialkoxy ketones **245** and **246** (equation 137). The reaction mechanism was supported by the synthesis of reaction intermediates[33,209]. The intermediacy of α-chloro-α′-methoxyoxiranes seems to be reasonable as compounds of this type have been observed during the reaction of tetrachlorocyclopentanone (**38**) which gives **248** and **249** (equation 138)[64].

In addition, stable α-chloro-α′-methoxy oxiranes (**251**) have been isolated during the reaction of tetrachlorocyclohexanones (**250**) with sodium methoxide in methanol (equation 139)[332].



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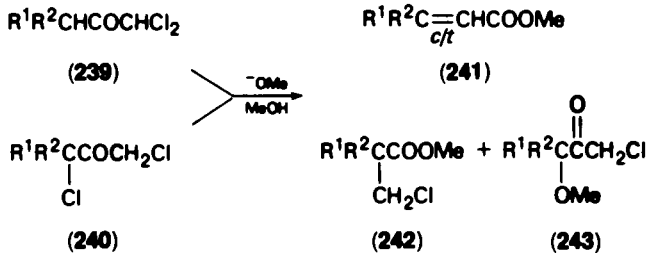
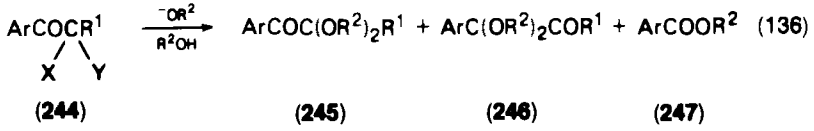


(135)

α,α'-Dibromocycloalkanones react with sodium methoxide via the intermediacy of epoxides to yield α-hydroxy acetals (**253**)[306], although earlier investigations claimed the formation of a Favorskii rearrangement product[333]. The acetals are formed by addition of methanol to the carbonyl group and substitution of one bromine with

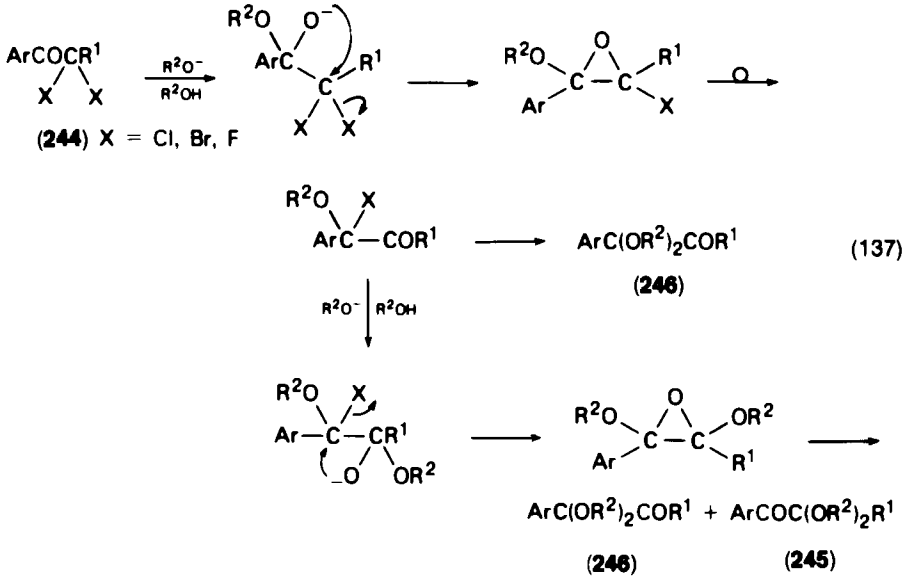


(244) (245) (246) (247)

X, Y = Cl, Br, F

R^1 = H, alkyl

R^2 = Me, Et, *i*-Pr



(244) X = Cl, Br, F

(137)

(246) (245)

methoxide, followed by elimination of hydrogen bromide to produce an epoxide which in turn is cleaved by reaction with methanol. The acetals are transformed into **254** at room temperature (equation 140).

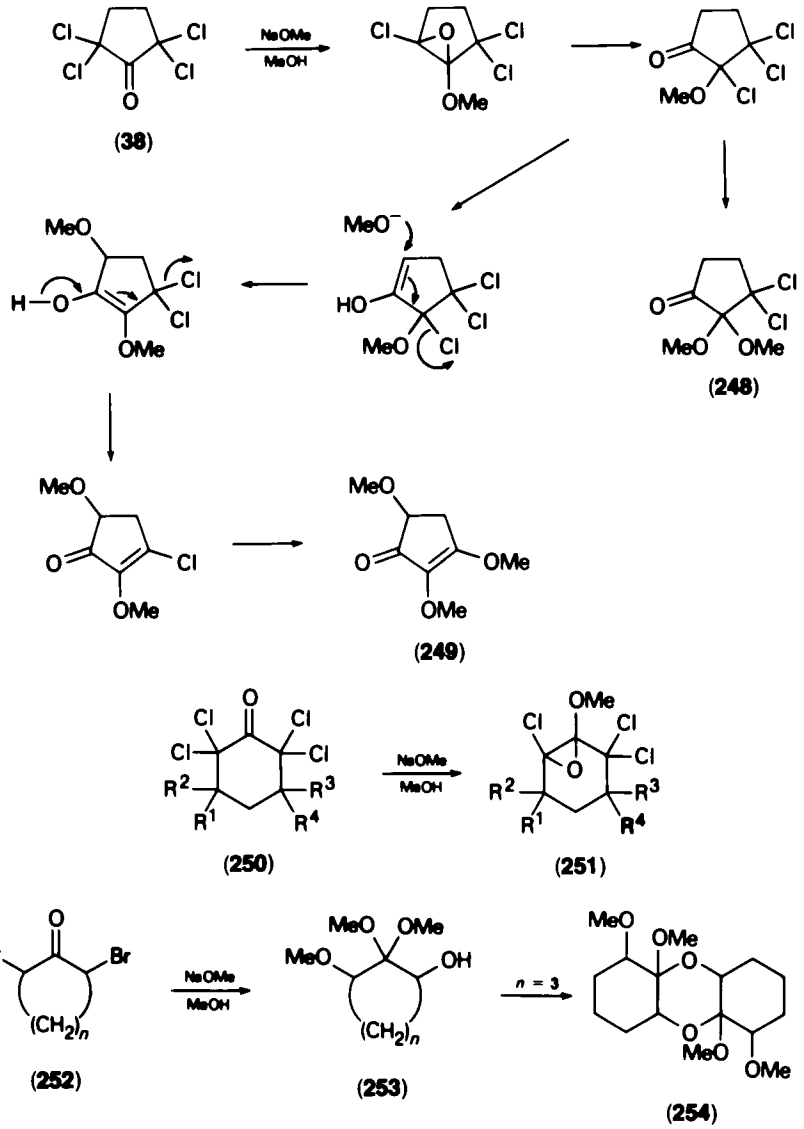
Another pathway observed during the reactions of polyhalogenated cycloalkanones with methoxide ions involves a Grob fragmentation, as illustrated by the reaction of a pentachlorocyclopentanone (**39**) yielding the esters **255**, **256**, or **257** (equation 141)[64] (see also conversion **162** → **164**).

Monofluoroketones show a completely different route in the reaction with sodium alkoxides in ether at −60°C. The exclusive reaction product constitutes of a ketol (**259**) produced by aldol condensation (equation 142)[334].

Finally, reaction of α-bromoketones (**260**, **263**) with methanol in the presence of silver hexafluoroantimonate affords substitution products (**262**) via an α-keto-carbenium ion (**261**) and Favorskii ester (**265**) via an intermediate hemiacetal (**264**) (equation 143)[335].

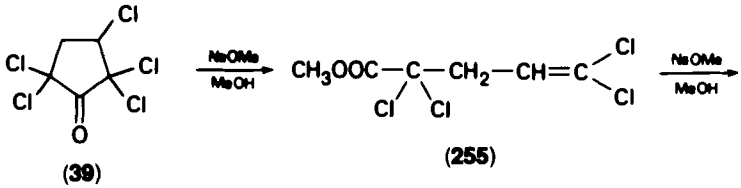
Reaction of the chlorinated bicyclic ketones (**266**, **267**) with potassium *t*-butoxide (strong base, poor nucleophile) in *t*-butanol shows a regioselective elimination–rearrangement via a zwitterionic intermediate leading to a bicyclic enone (**268**) system (equation 144)[336].

Cyclopropanone derivatives are produced when specific α-bromoketones are



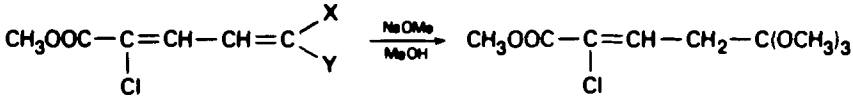
treated with potassium *t*-butoxide in THF. An example is the formation of 2,3-di-*t*-butylcyclopropanone (**271**) from α-bromodineopentyl ketone (**270**). When the reaction is carried out in *t*-butanol, not the *t*-butyl ester, but the corresponding acid (**272**) is formed, presumably from the action of adventitious hydroxide in the *t*-butoxide (equation 145)[337,338]. In addition, reaction of α,α′-dibromodineopentyl ketone (**273**) with potassium *t*-butoxide in THF provides di-*t*-butylcyclopropene (**274**) in 80% yield (equation 146)[339,340].

Addition of a solution of tris(chloroacetonyl)methane (**275**) in THF to a solution of potassium *t*-butoxide in *t*-butanol affords a direct entry to the triasterane structure



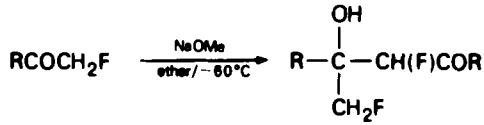
(39) (255)

(141)



X, Y = Cl, OMe

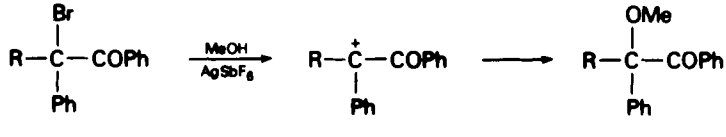
(256) (257)



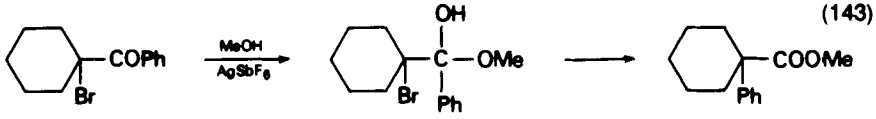
(142)

(258) (259)

R = cyclohexyl, benzyl



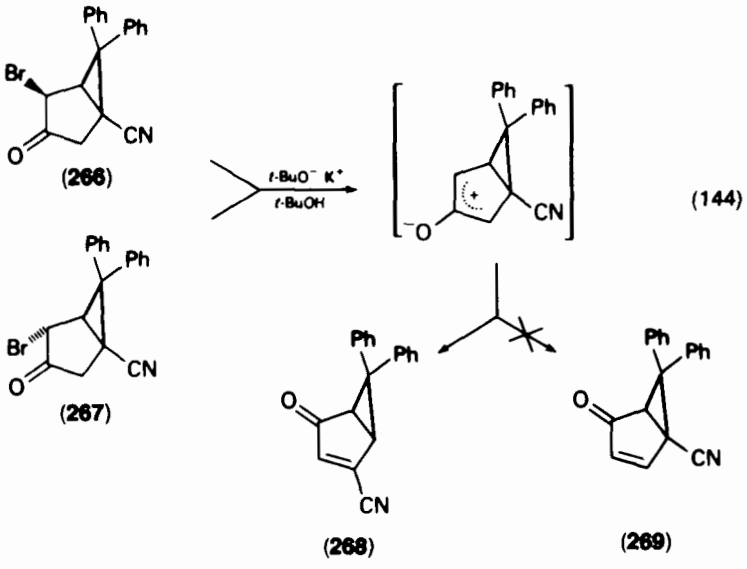
(260) (261) (262)

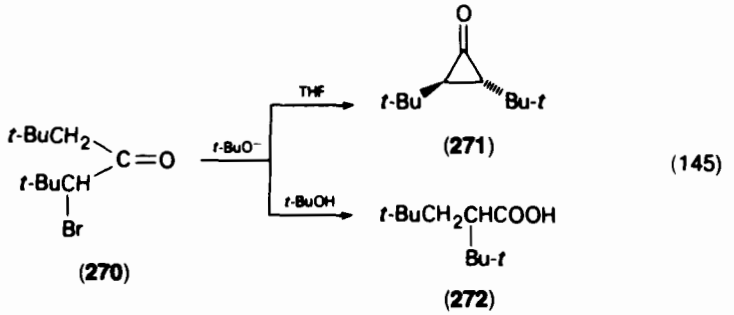


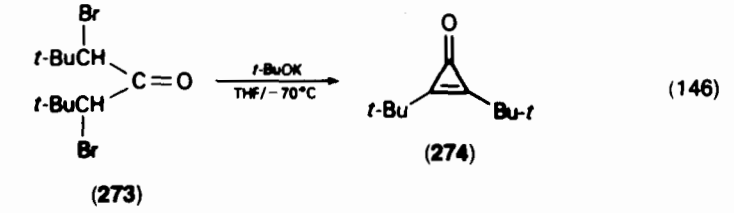
(143)

(263) (264) (265)

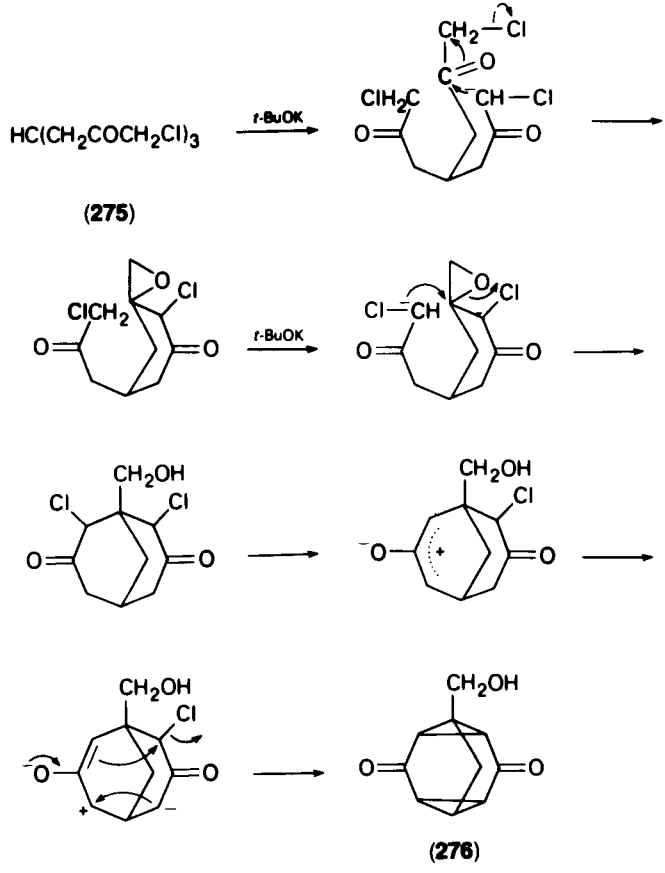
(276) via a series of intramolecular transformations, as outlined in the following scheme (equation 147)[341]. Just as in the case of the reaction of α-haloketones with alkoxides, attack of phenoxide anions gives rise to a variety of products, depending not only on the substrate and the reaction conditions but also on the nature of the phenoxide. While the reaction of 2-chlorocyclohexanone with sodium phenoxide affords the α-phenoxy ketone (277), treatment of the same ketone with sodium (2-isopropyl-5-methyl)phenoxide provides a mixture of the substitution product (277a) and the Favorskii ester (278) (equation 148)[342–344]. Hypothetically, the formation of 2-phenoxycyclohexanone may occur by, first, a S_N2 attack at the α-carbon (path 1), second, a S_N2' attack at $C_{(2)}$ in the enol (path 2), third, an attack at either the α- or α′-carbon of a symmetrical cyclopropanone intermediate (path 3). A decision between the various possibilities is offered by the use of [1,2-^{14}C]-2-chlorocyclohexanone and it is proved that only path 3 is consistent with the results (equation 149)[345].







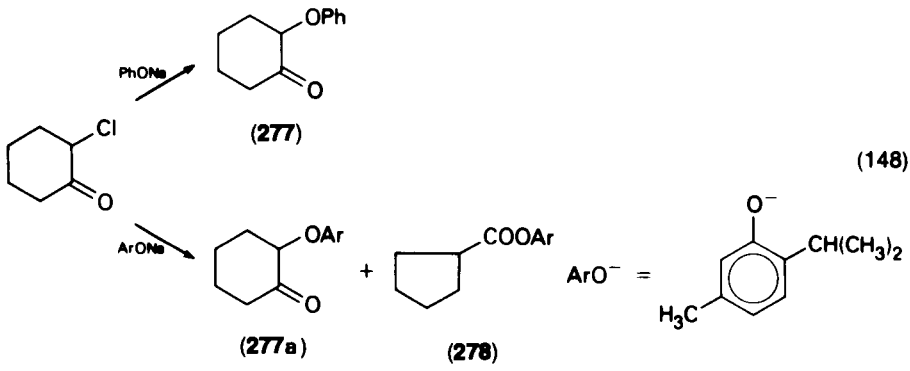
The reaction of 1-chlorocyclohexyl methyl ketone (**279**) with sodium phenoxide in phenol gives a mixture of the substitution and elimination products (**280** and **281**) together with the Favorskii ester (**282**) (equation 150)[346]. On the other hand, α,α′-dibromocycloalkanones (**252**) provide a single reaction product, 2-phenoxy 2-cycloalkenones (**283**) with sodium phenoxide in methanol or DMF (equation 151)[306]. The reaction of chloroacetone with activated phenols in the presence of potassium carbonate and potassium iodide in DMF gives substitution products[347], but 1,3-dichloroacetone reacts with phenols under similar conditions to give mixtures



(275)

(147)

(276)



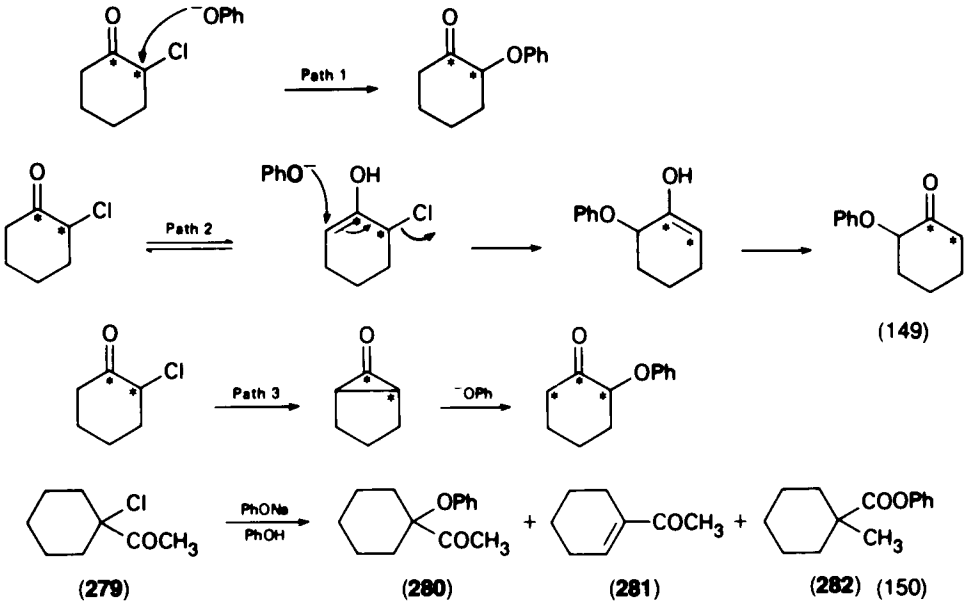
(277)

(277a)

(278)

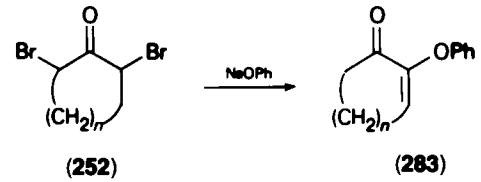
(148)

where 1,1-bis(aryloxy)acetone is the major product, while the more acidic *p*-nitrophenol (which is ionized under the reaction conditions) provides the expected 1,3-disubstituted compound[348]. Reaction of the dibromoketones (**284**) with catechol gives rise to the formation of 1,4-benzodioxan derivatives (**285**) (equation 152)[349].



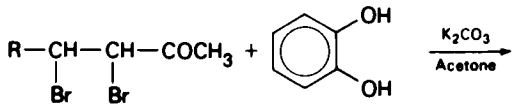
(149)

(279) (280) (281) (282) (150)

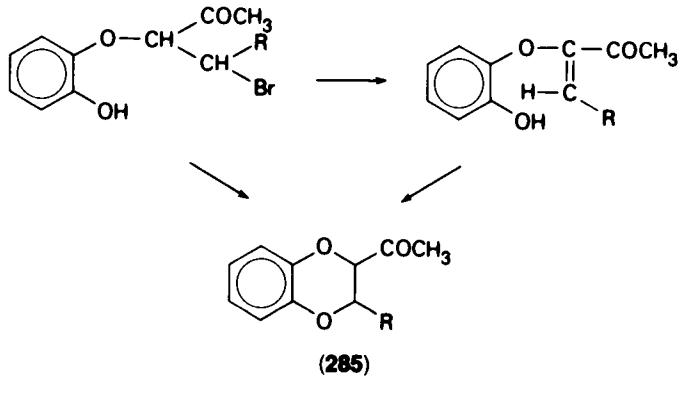


(151)

(252) (283)



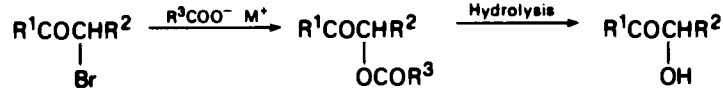
(284)



(152)

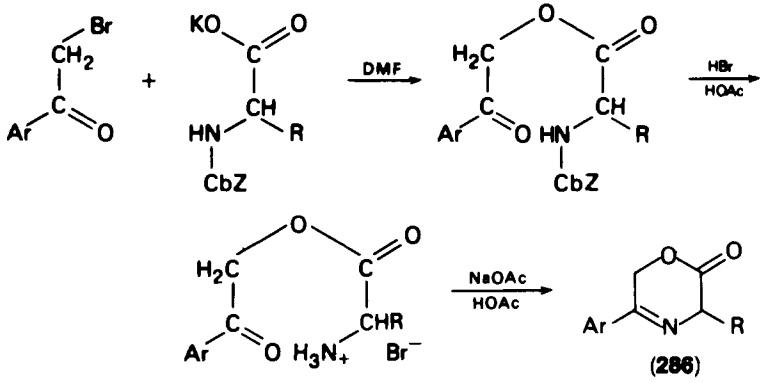
(285)

α-Haloketones readily react with salts of carboxylic acids, especially sodium and potassium formate and acetate, to give substitution products. Hydrolysis of these esters affords α-hydroxyketones. Therefore, this particular reaction sequence constitutes the method of choice for the preparation of α-hydroxyketones because no major side reactions are taking place as in the case of the direct hydrolysis of α-haloketones (equation 153)[350–352]. Another interesting application involves the



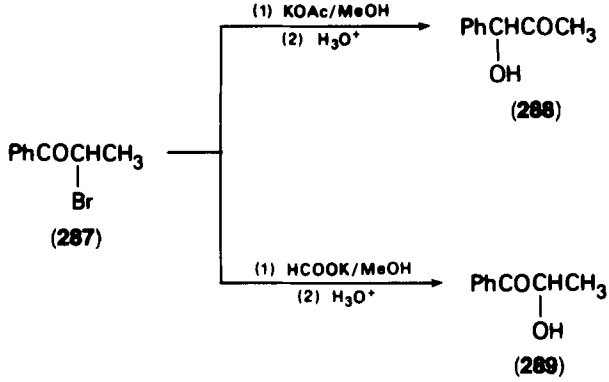
(153)

synthesis of 2,3-dihydro-6*H*-1,4-oxazin-2-ones (**286**) from α-halomethyl aryl ketones and protected amino acids (equation 154)[353].



(154)

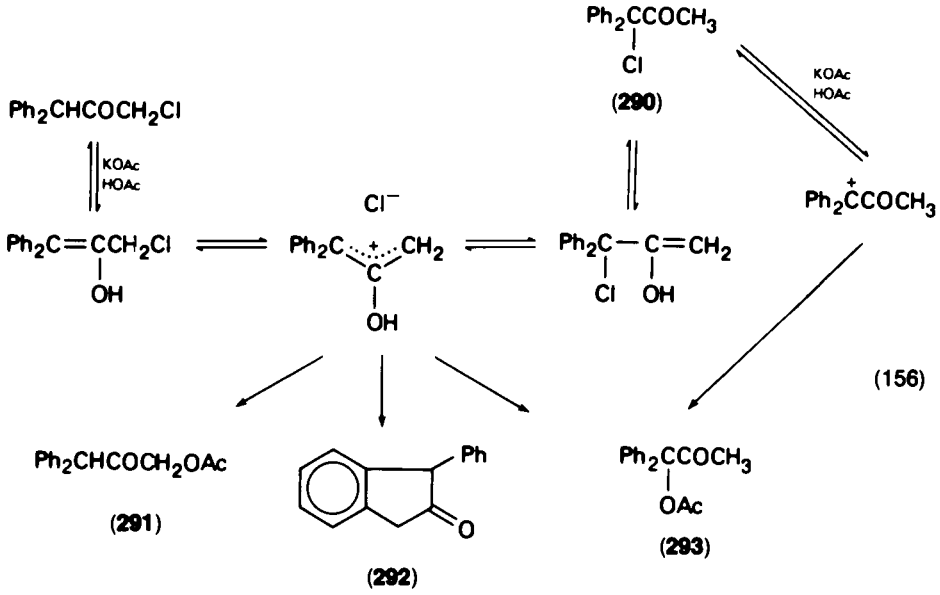
A number of isomerizations are observed during the reaction of α-haloketones with carboxylate anions. Treatment of 2-bromo-1-phenyl-1-propanone (**287**) with acetate ion followed by hydrolysis provides 1-hydroxy-1-phenyl-2-propanone (**288**) while with formate ion the normal product (**289**) is formed (equation 155)[352].



(155)

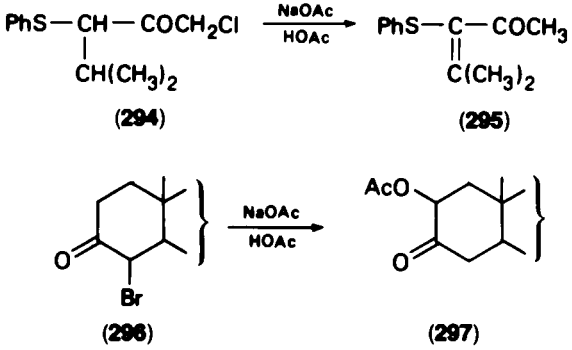
Acetolysis of 1-chloro-3,3-diphenyl-2-propanone in the presence of potassium acetate gives 1-acetoxy-3,3-diphenyl-2-propanone (**291**), 1-acetoxy-1,1-diphenyl-2-propanone (**293**) and 1-phenyl-2-indanone (**292**), while 1-chloro-1,1-diphenyl-

2-propanone (**290**) produces **293** exclusively. The reaction mechanism suggests the intervention of an allylic carbonium ion capable of capturing nucleophilic species at both $C_{(1)}$ and $C_{(3)}$ (equation 156)[354].



(156)

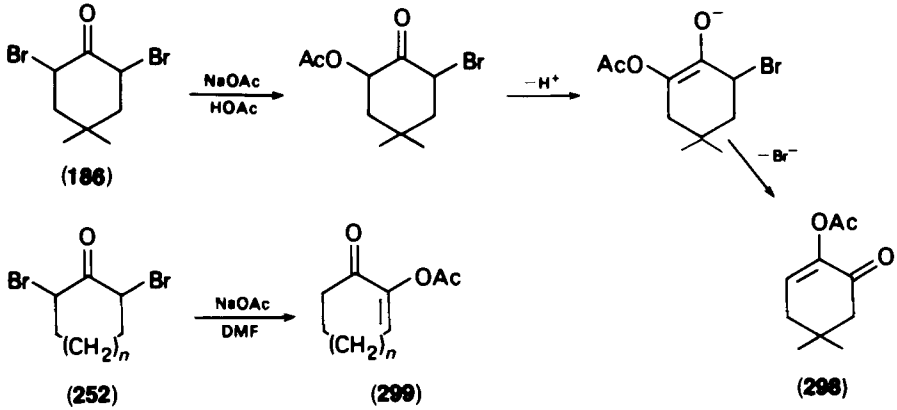
Other examples of cine substitution are illustrated below (equation 157)[355,356]. Rearrangement also occurs when 2,6-dibromo-4,4-dimethylcyclohexanone (**186**)



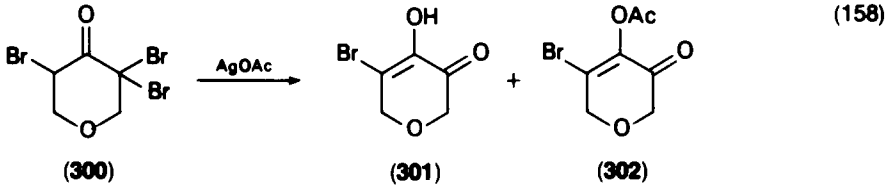
(157)

reacts with sodium acetate in acetic acid yielding **298**. The mechanism involves bromine substitution followed by a 1,3-hydrogen bromide elimination together with an acyl migration[189]. Similar results are obtained in the cases of α,α'-dibromocycloalkanones (**252**) and tribromotetrahydro-4*H*-pyran-4-ones (**300**) with acetate anions[357] (equation 158).

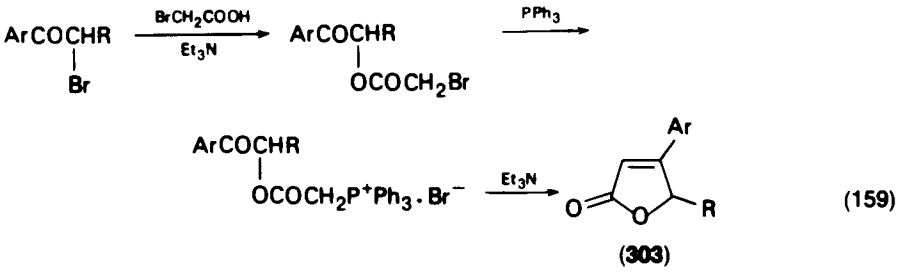
Bromoketones react with bromoacetic acid in the presence of triethylamine to give the substitution products, which, via intermediate phosphonium salts, can be cyclized to α,β-unsaturated lactones (**303**) (equation 159)[358].



(186) (252) (299) (298)



(300) (301) (302) (158)



(303) (159)

The hexafluoroacetone–potassium fluoride complex behaves like a weak oxygen nucleophile and a strong base during its condensation with α-haloketones. Nucleophilic substitution produces α-perfluoroalkoxy ketones (**303a**). Abstraction of a proton leads to the formation of diones (**304**) and cyclic ethers (**305** and **306**) (equation 160)[359].

4. *Reaction of α-haloketones with nitrogen nucleophiles and bases*

a. Reaction of α-haloketones with amines. Amines have been widely used to substitute α-haloketones. Numerous examples are known in which ammonia, primary and secondary amines produce α-aminoketones, while treatment with tertiary amines gives rise to ammonium salts (equation 161)[360]. Geminal diaminoketones are formed when α,α-dichloroketones react with an excess of amines[361].

Aminoketones are rather unstable compounds, and it is therefore advisable to isolate them as salts of strong acids.

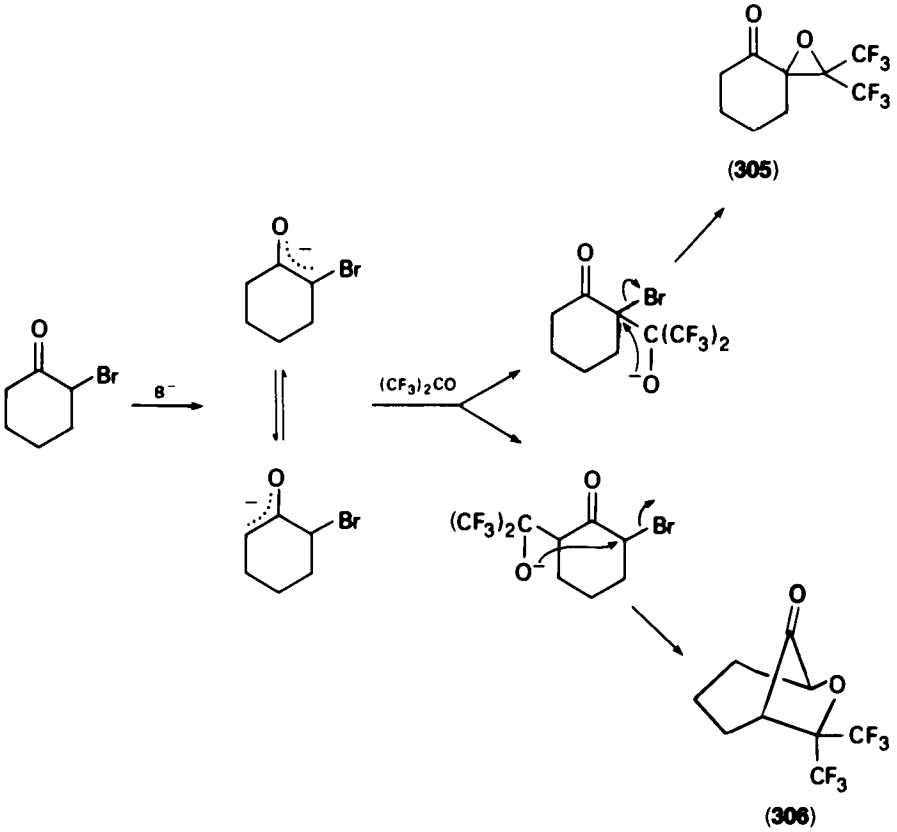
$$PhCOCH_2Br + (CF_3)_2CO/KF \xrightarrow{\Delta} PhCOCH_2OCF(CF_3)_2$$

(303a)

$$PhCOCH_2Br \xrightarrow{B^-} PhCO-\underset{Br}{CH} \xrightarrow{(CF_3)_2CO} PhCOCH(Br)-C(CF_3)_2(O^-) \quad (160)$$

$$\xrightarrow{-Br^-} \left[PhCOC(H)-C(CF_3)_2 \text{ (O)}\right] \xrightarrow{BH} PhCOCOCH(CF_3)_2$$

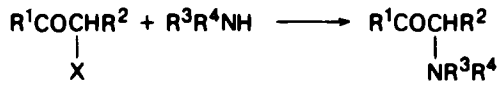
(304)



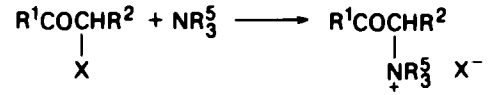
(305)

(306)

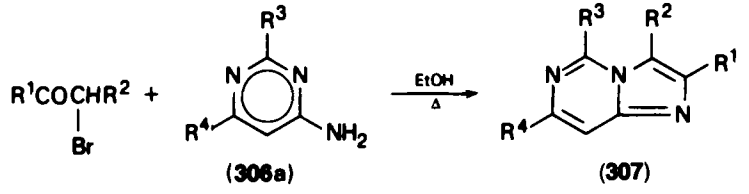
Primary aminoketones are also synthesized by introduction of a protected amino function using the urotropine[362] and the phthalimide method[363] or by hydrolysis of *N*-benzylaminoketones[364]. Substitution reactions of α-haloketones with heterocyclic amines often give rise to cyclized products; e.g. reaction of bromoketones with 4-aminopyrimidines (**306a**) and 3-amino-1,2,4-triazines (**308**) affords



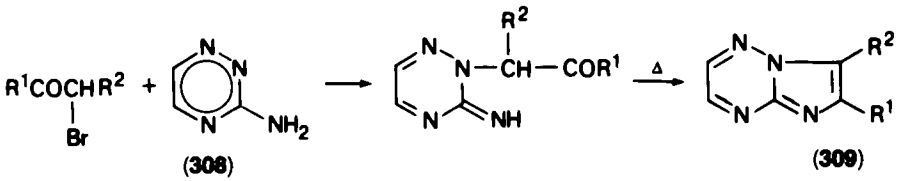
(161)



imidazo[1,2-c]pyrimidines (**307**)[365] and imidazolotriazines (**309**)[366], respectively (equation 162).



(162)



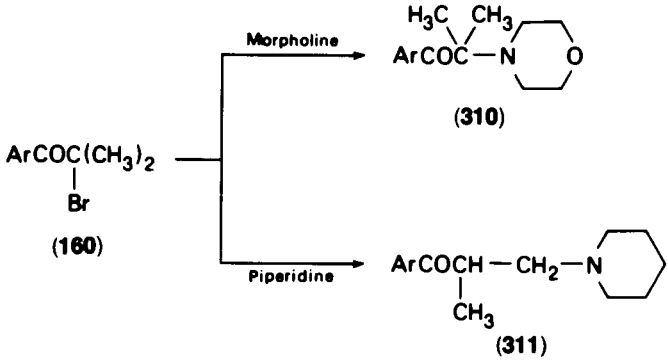
The reaction between α-haloketones and amines is not always a simple substitution reaction. While the reaction of 2-bromo-2-methyl-1-aryl-1-propanones (**160**) with morpholine gives rise to the substitution product (**310**), reaction with the stronger base piperidine affords the elimination–addition product (**311**)[367]. From aniline and 1-bromo-1-phenyl-2-propanone (**312**) and 2-bromo-1-phenyl-1-propanone (**313**) a mixture of the α-aminoketones (**314**, **315**) was obtained (equation 163)[368].

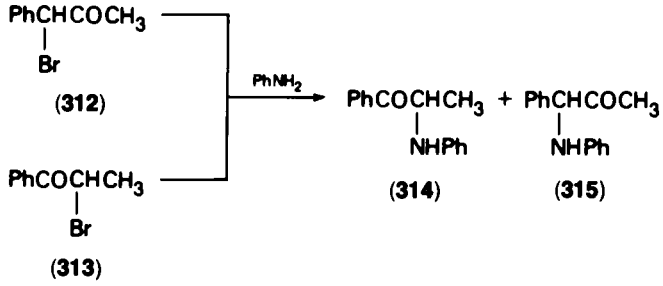
In general, α-halogenated ketones of the primary and secondary type (primary, $ClCH_2CO$; secondary, RCHClCO; tertiary, R^1R^2CClCO) are expected to give substitution, but tertiary ketones are able to give elimination products. High yields of α,β-unsaturated ketones are reported when α-haloketones are treated with pyridine, quinoline, collidine and *N,N*-dimethylaniline, especially with cyclic α-haloketones (equation 164)[369–371].

α,α′-Dibromoketones provide cyclopropenones (**316**) by double 1,3-dehydrobromination on treatment with tertiary amines (equation 165)[372].

The ordinary course of the reaction of α-haloketones with pyridines, resulting in dehydrohalogenation and displacement, is often apparently accompanied by varying amounts of reduction and double bond rearrangement products as illustrated for 2β-bromocholestan-3-one (**317**) (equation 166)[373,374].

Favorskii rearrangement amides are frequently encountered when α-haloketones are treated with ammonia[375], primary amines[376,377] and secondary amines[322] (equation 167). The reaction course is dependent on the kind of base and solvent used. *Cis*-carvone tribromide (**165**) undergoes a Favorskii rearrangement to afford an iminolactone (**320**) when treated with primary amines in methanol but suffers





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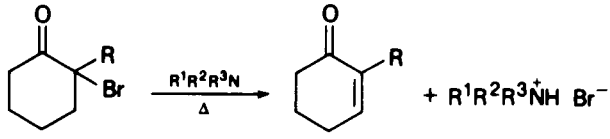

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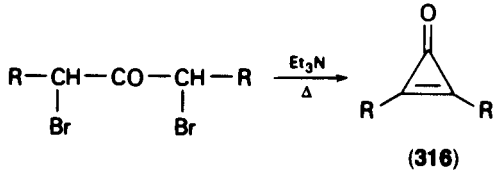

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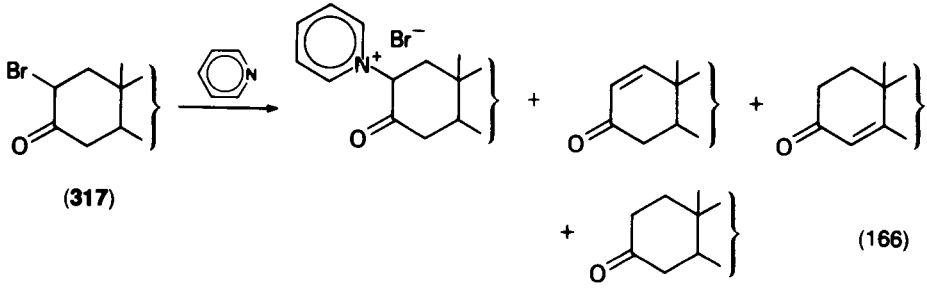

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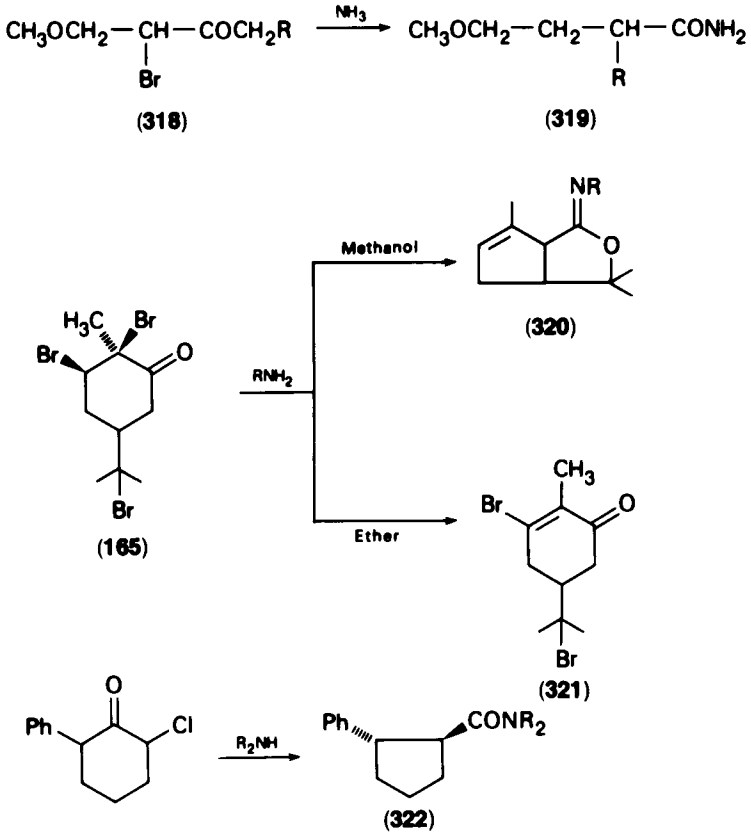


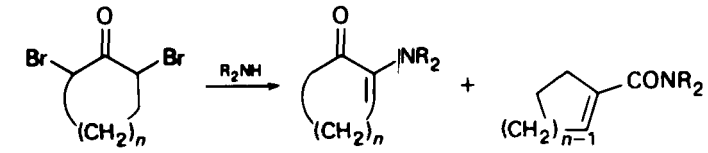
(167)

dehydrobromination when the reaction is conducted in ether[377]. The configuration also plays an important role, as the *trans* isomer yields the lactone **320** in both solvents. Similar solvent effects are reported during the action of amines on α,α'-dibromocycloalkanones, e.g. **252** and **300a**[306,307] (equation 168). In both cases the enamino ketones are the predominant products in polar aprotic solvents such as HMPA, whereas the Favorskii rearrangement products predominate in ether.

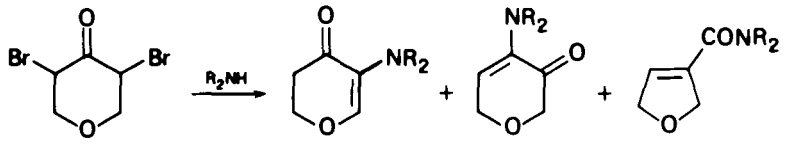
Another type of frequently occurring reaction consists of an addition of the amine to the carbonyl function (e.g. of **202**) followed by an intramolecular substitution yielding an aminooxirane (**329**) which can rearrange into an α-hydroxyketimine (**330**) (equation 169)[378].

Formation of ketimines[405,406] normally does not take place when α-haloketones are treated with primary amines except for α-fluorinated ketones, and especially high yields of trifluoroketimines (**331**) are easily obtained (equation 170)[379,380]. However, we recently developed a general method for the preparation of α-halogenated ketimines (**332**) by condensing α-haloketones with primary amines in ether using titanium tetrachloride as condensing agent (equation 171)[381]. This method is also applicable to dihalo- and trihaloketones[381].

The formation of compounds containing C=N bonds will be discussed in the section dealing with reactions of carbonyl reagents. In general[586], the condensation of α-halogenated ketones with secondary amines does not afford β-halogenated enamines

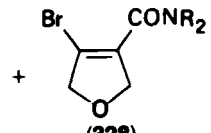


(252) (323) (324)



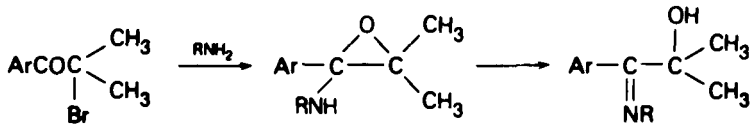
(168)

(300a) (325) (326) (327)



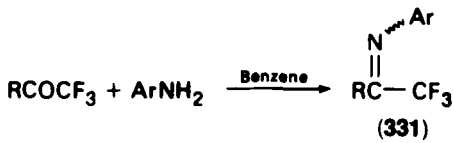
(328)

R_2NH = morpholine, piperidine, pyrrolidine



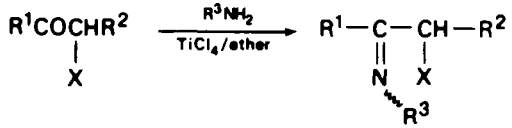
(169)

(202) (329) (330)



(170)

(331)



(171)

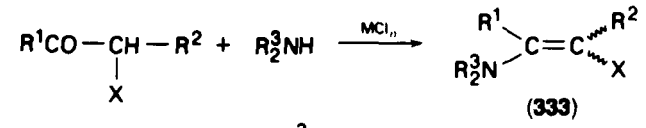
(332)

R^1, R^2 = H, alkyl, aryl

R^3 = alkyl, aryl

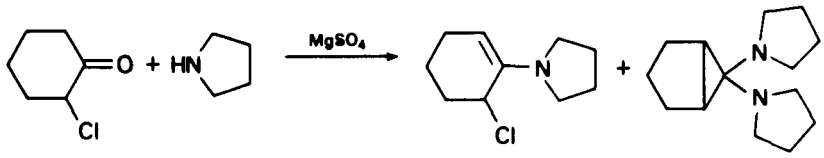
(333) except when the reaction is carried out in the presence of metal chlorides such as $AsCl_3$, $SbCl_3$, $FeCl_3$ and $TiCl_4$[382-383], or by the use of tris(*N*,*N*-dialkylamino)arsines[384] (equation 172).

In addition, reaction of 2-chlorocyclohexanone with pyrrolidine at −100°C in the presence of magnesium sulphate produces an enamine (334) with the chlorine atom in allylic position and minor amounts of a bicyclic compound (335) (equation 173)[385].



(172)

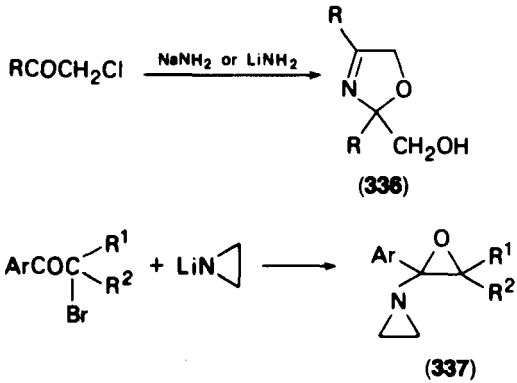
(333)



(173)

(334) (335)

Chloromethyl ketones also react with lithium or sodium amide in liquid ammonia to produce oxazolines (**336**)[386], while stable epoxyamines (**337**) are formed when brominated alkyl aryl ketones are treated with the lithium salt of ethyleneimine[387,388] (equation 174).

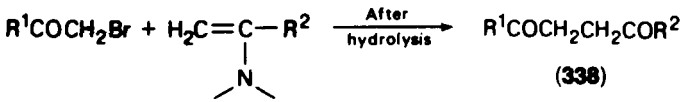


(174)

(336)

(337)

b. Reaction of α-haloketones with enamines. α-Bromoketones react with enamines of methyl ketones to provide immonium salts which upon hydrolysis afford 1,4-dicarbonyl compounds (**338**) (equation 175)[389].



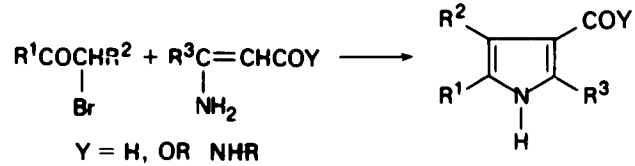
(175)

(338)

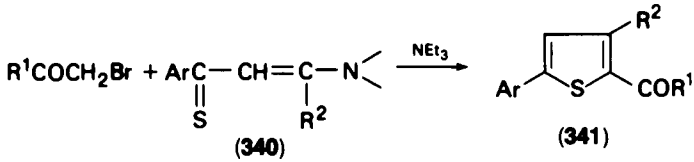
Cycloaddition of β-amino-α,β-unsaturated carboxylic acids and derivatives with α-haloketones gives rise to pyrrole compounds (**339**) (Hantzsch synthesis)[390], while reaction with β-aminovinyl thioketones (**340**) give 2-acylthiophenes (**341**)[391] (equation 176).

c. Reaction of α-haloketones with amides, thioamides and derivatives. Various heterocyclic compounds have been synthesized by the reaction of α-haloketones with amides, thioamides, urea, thiourea, amidines, guanidines and sulphonylamides. Reaction of α-bromoketones with amides produces oxazoles (**342**)[392–393], while reaction with alkynyl thioamides (**343**) gives 1,3-oxathiazoles (**344**)[394] (equation 177).

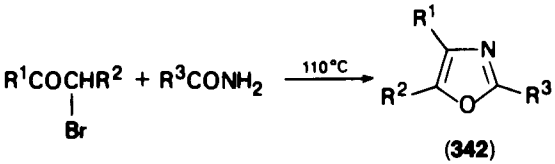
A cyclodehydrohalogenation leading to 2-azetidinones (**346**) is observed when



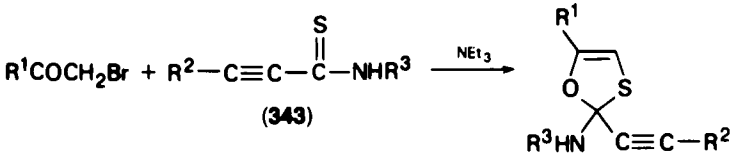
(339) (176)



(340) (341)

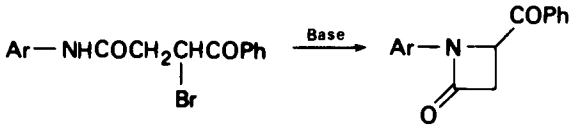


(342) (177)



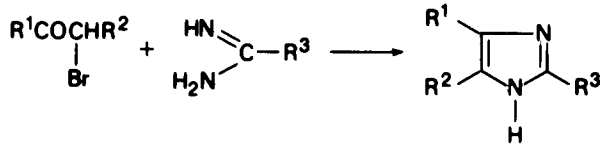
(343) (344)

anilides of α-bromoketones (**345**) are subjected to the action of various bases (equation 178)[395].

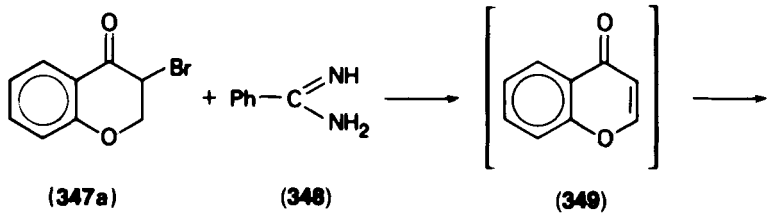


(345) (346) (178)

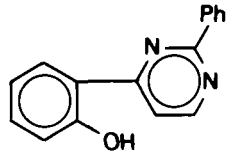
Reaction of α-bromoketones with amidines or formimidates constitutes an excellent method for the synthesis of imidazole derivatives (**347**) (equation 179)[396,375]. However, a pyrimidine ring (**350**) is formed during the reaction of



(347) (179)



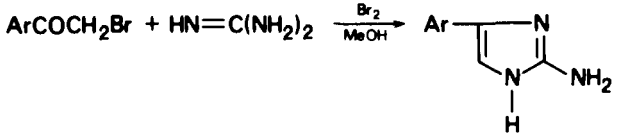
(347a) (348) (349)



(350) (180)

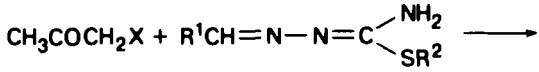
α-bromochromanone (**347a**) with benzamidine (**348**) probably via an intermediate chromone (**349**) (equation 180)[397].

Another synthesis of imidazole compounds (**351**) involves the condensation of phenacyl bromides with guanidine using bromine in methanol as the condensing agent (equation 181)[398]. On the other hand, reaction of an α-haloacetone with

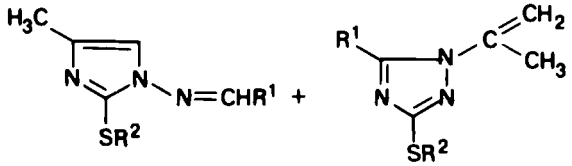


(**351**) (181)

isothiosemicarbazones (**352**) gives rise to a competitive formation of imidazoles (**353**) and triazole compounds (**354**). The ratio is dependent upon the nature of the halogen and the reaction temperature (equation 182)[399].

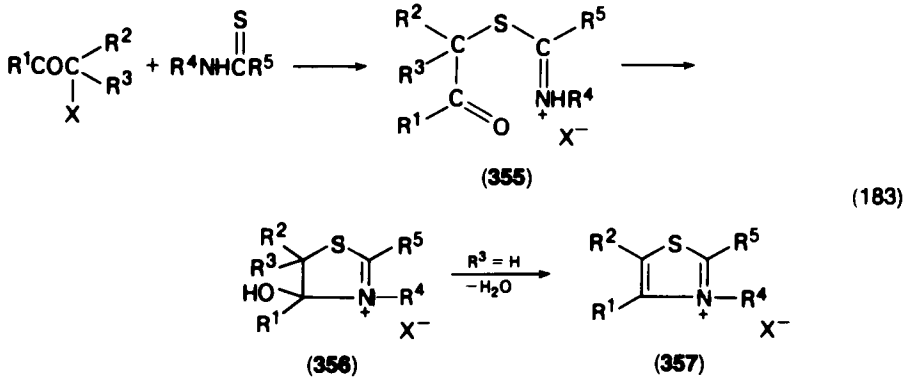


(**352**)



(**353**) (**354**) (182)

The Hantzsch reaction of α-haloketones with thioamides, thiourea and dithiocarbamates affords thiazolium derivatives (**357**). By isolation of intermediate thiazolines it is proved that the first step in this reaction is a direct substitution of the halogen atom and not an addition of the nitrogen atom at the carbonyl function (equation 183)[400–402].

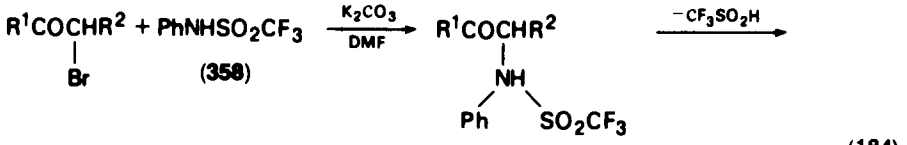


(355)

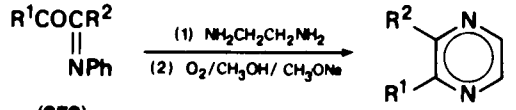
(183)

(356) (357)

Substitution of α-bromoketones with *N*-phenyltrifluoromethanesulphonamides (**358**) under mild conditions gives rise to the formation of α-iminoketones (**359**) which in turn can further be converted into pyrazines (**360**) (equation 184)[403–404].

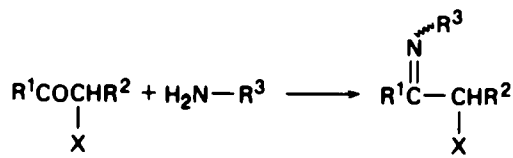


(184)



(359) (360)

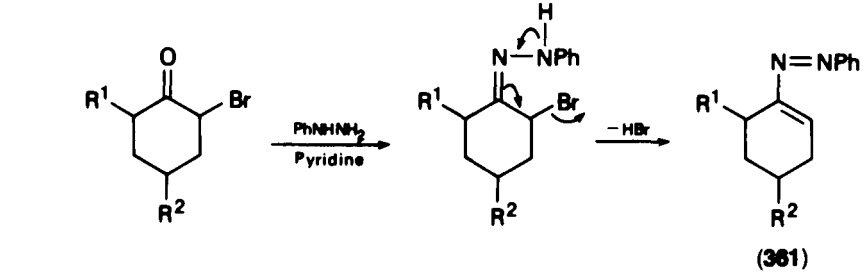
d. Reaction of α-haloketones with carbonyl reagents. The reactivity of α-halocarbonyl compounds towards the usual carbonyl identification reagents has been reviewed by De Kimpe and coworkers in reports dealing with the synthesis and reactivity of α-halogenated imino compounds[405–406]. Therefore, only the most typical reactions will be covered in this section. Except for 2,4-dinitrophenylhydrazones of α-haloketones, which are easily formed when prepared in aqueous methanol in the presence of sulphuric acid[407], α-haloimino compounds are not generally available by the condensation of α-haloketones with carbonyl reagents, due to the reactivity of the imino compounds which lead to further reactions under the normal reaction conditions. Consequently, only a limited number of α-halohydrazones[408], semicarbazones[409] and oximes[410–412] have been obtained by the direct condensation route (equation 185).



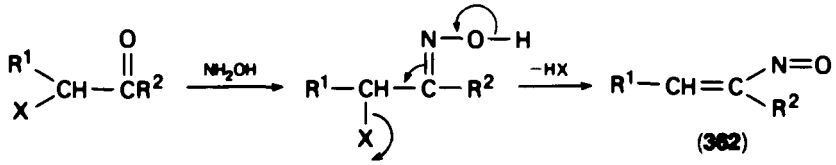
(185)

R^3 = OH, NH_2, NHR, NHCOR, NHCSR, NHAr, NHTos

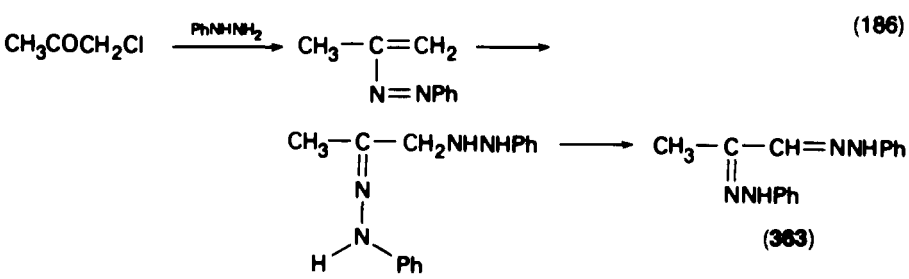
The most frequently encountered side reactions are the formation of azoalkenes (**361**) by 1,4-dehydrohalogenation[413,414], nitrosoolefins (**362**)[410] and the formation of diimino compounds[415], as illustrated in the following examples (equation 186). In



(**361**)

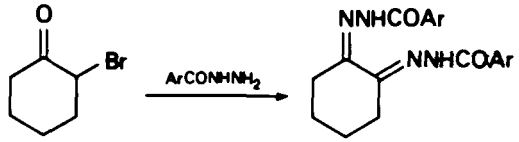


(**362**)



(186)

(**363**)

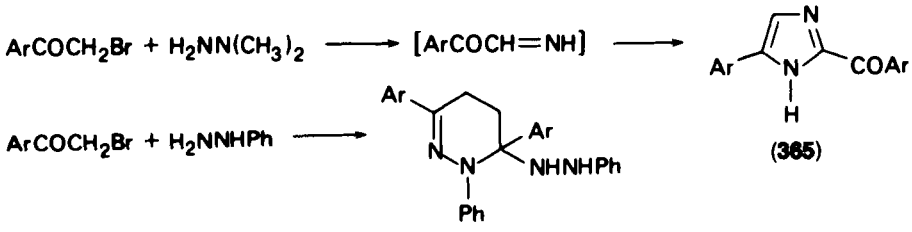


(**364**)

addition, the initially formed α-haloimino compounds are able to undergo ring closure reactions to yield a variety of heterocyclic products. Reaction of phenacyl bromides with *N,N*-dimethylhydrazine and phenylhydrazine gives rise to the formation of pyrazoles (**365**)[416] and tetrahydropyridazines (**366**)[417], respectively. The reaction of dibromoketones with hydroxylamine and hydrazine furnishes isoxazoles (**367**)[418] and pyrazolidinones (**368**)[419] (equation 187).

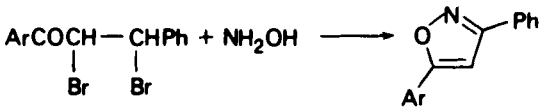
1,2,4-Triazines (**369**)[420,421], 1,3,4-thiadiazines (**370**)[422] and thiazolines (**371**)[423] are formed when α-haloketones are treated respectively with acylhydrazines, thioacylhydrazines and thiosemicarbazide (equation 188).

e. Reaction of α-haloketones with sodium azide. Reaction of α-haloketones with sodium azide produces α-azidoketones, which on pyrolysis afford α-iminoketones via nitrene intermediates (equation 189)[304,424,425]. Action of sodium azide on chalcone dibromides furnishes α-azidochalcones (**372**) and isoxazoles (equation 189a)[418].

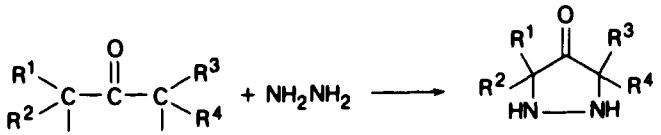


(365)

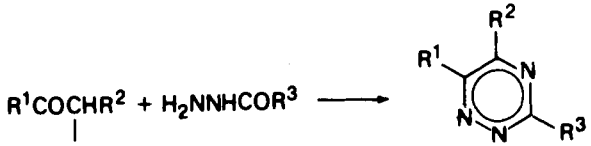
(366)



(367) (187)



(368)



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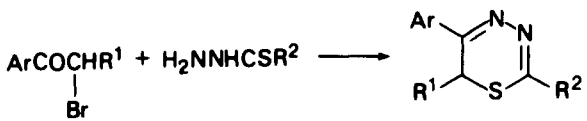
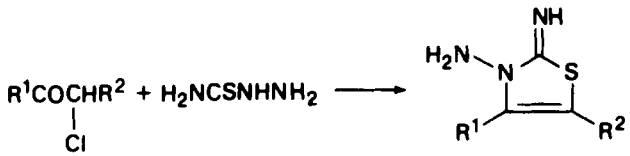
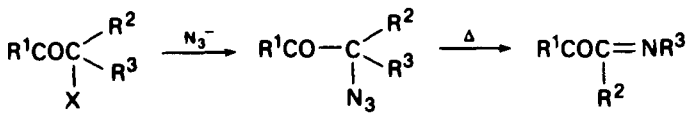


(370) (188)



(371)



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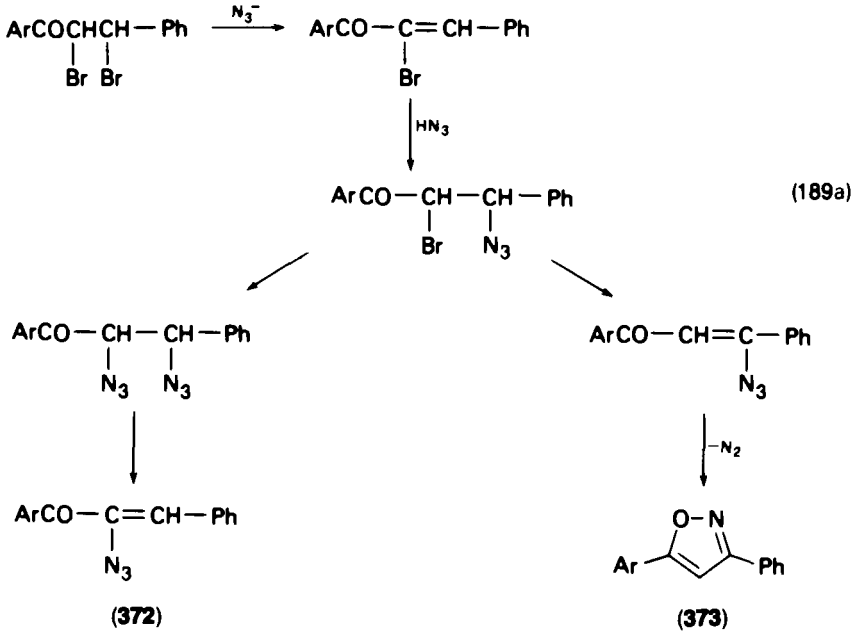
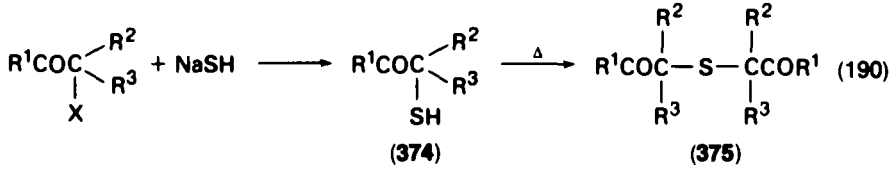


(189a)

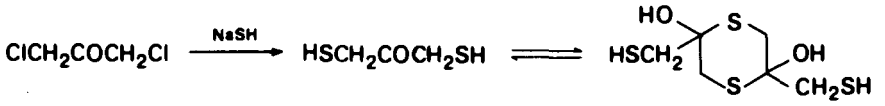
5. Reaction of α-haloketones with sulphur nucleophiles

a. Reaction of α-haloketones with inorganic sulphur compounds. Reaction of α-haloketones with sodium hydrogen sulphide gives rise to α-mercaptoketones (**374**) in 50–80% yield. However, when the reaction temperature is higher than 0°C, sulphides (**375**) can be generated (equation 190)[426,427]. α,α′-Dimercaptoketones (**376**) (isolated



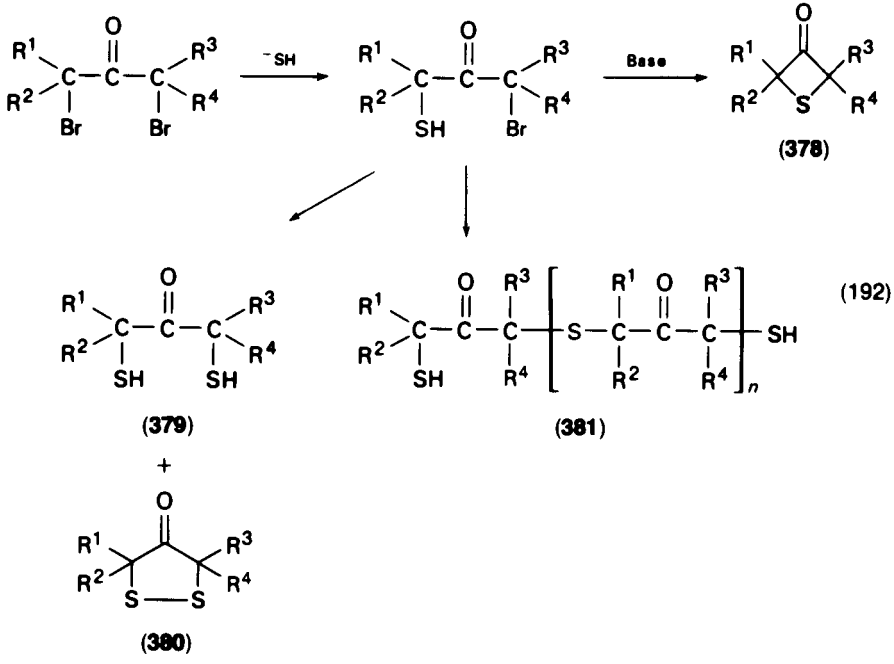
(190)

as the cyclic dimers (**377**)) are also produced on treatment of α,α′-dihaloketones with sodium hydrogen sulphide (equation 191)[428].



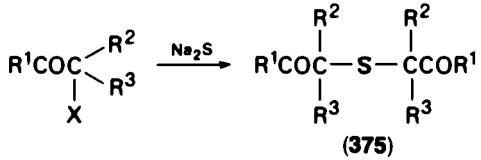
(191)

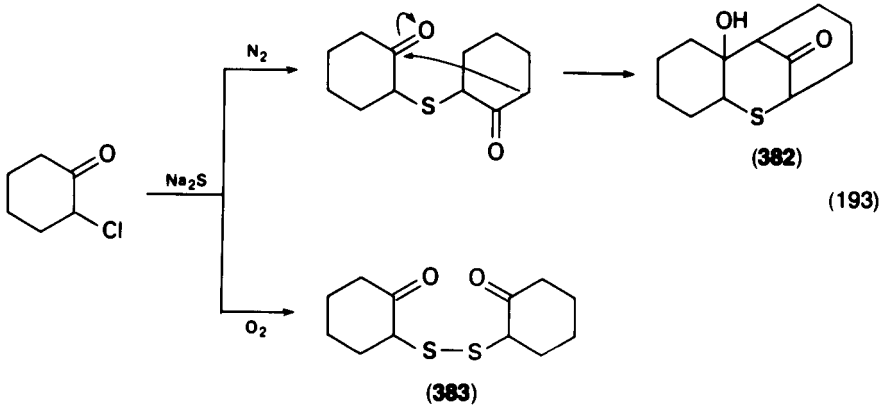
3-Thietanones (**378**) have been synthesized by reaction of α,α′-dibromoketones and sodium hydrogen sulphide, together with minor amounts of dithiols (**379**), 1,2-dithiolan-4-ones (**380**) and polycondensates (**381**) (equation 192)[429]. Mercaptomethyl aryl ketones are also formed when aryl α-halomethyl ketones are treated with hydrogen sulphide in pyridine[430].



(192)

Reaction of α-haloketones with sodium sulphide affords sulphides (**375**)[431]. However, 2-chlorocyclohexanone produces a tricyclic compound (**382**) via aldol-type condensation of the intermediate sulphide in an inert atmosphere, while in the presence of oxygen a disulphide (**383**) is formed[432] (equation 193).





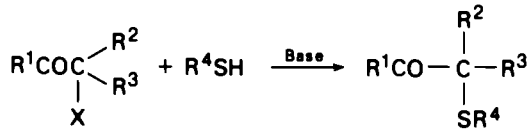
(193)

Finally, β-ketothiocyanates (**384**) are formed by the reaction of α-haloketones with potassium thiocyanate (equation 194)[433].

$$RCOCH_2Br \xrightarrow{KSCN} RCOCH_2SCN \quad (194)$$

(**384**)

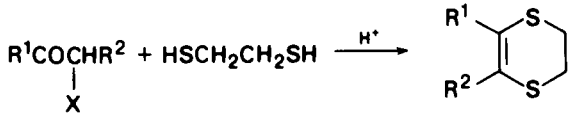
b. Reaction of α-haloketones with organic sulphur nucleophiles. Treatment of α-haloketones with mercaptans in the presence of bases mainly gives α-substitution to afford α-alkylthio and α-arylthio ketones (**385**) (equation 195)[434–436].



(195)

(**385**)

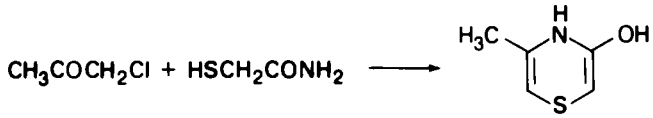
Other reactions involve dehalogenation[437] and transformation of the initially formed mercaptans into the corresponding disulphides[438]. 1,4-Dithienes (**386**) are prepared by cyclocondensation of α-haloketones with 1,2-ethanedithiol in the presence of acids (equation 196)[439,440].



(196)

(**386**)

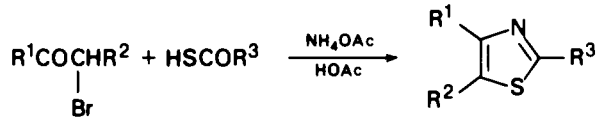
The reaction of chloroacetone with mercaptoacetamide proceeds smoothly to give 3-hydroxy-5-methyl-1,4-thiazine (**387**) (equation 197), while with phenacyl bromide the substitution product is formed[441].



(197)

(**387**)

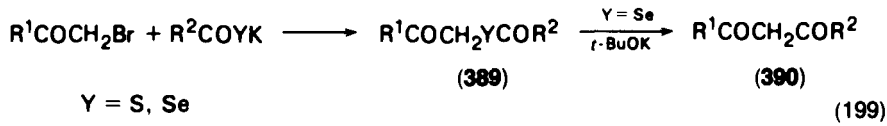
Thioacids and their derivatives react readily with α-haloketones. Treatment with thioacids in the presence of ammonium acetate in refluxing acetic acid gives 1,3-thiazoles (**388**) (equation 198)[442]. Reaction of thioacid salts normally gives rise to



(198)

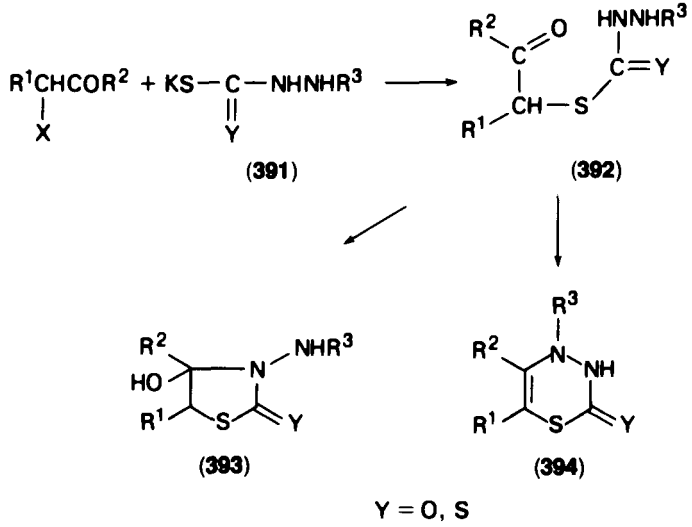
(**388**)

substitution products (**389**)[443]. A useful synthetic application of this reaction is the formation of selenocarboxylates (**389**) on treatment with selenoacids. Selenium elimination from **389** with strong bases yields 1,3-diketones (**390**) (equation 199)[444]. *S*-potassium hydrazino monothio- and dithioformate (**391**) react with α-haloketones to



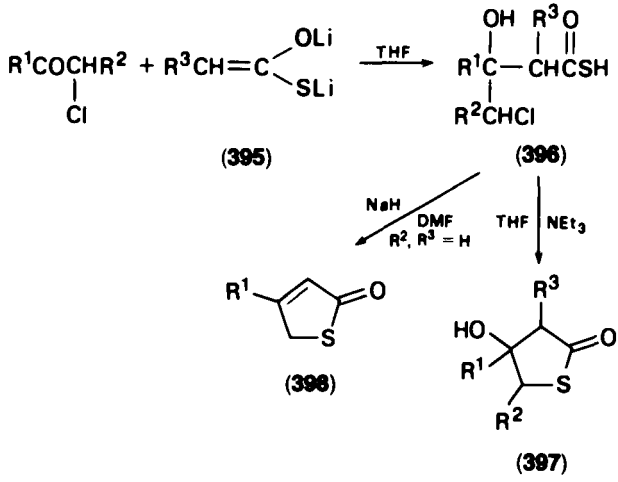
(199)

form acylmethyl (hydrazino)thioformates (**392**) which can be cyclized to 1,3-thiazolin-2-ones (**393**) or 1,3,4-thiadiazin-2-ones (**394**) dependent upon the substitution pattern of the ketone (equation 200)[445]. Dilithium salts of thioacids (**395**) also



(200)

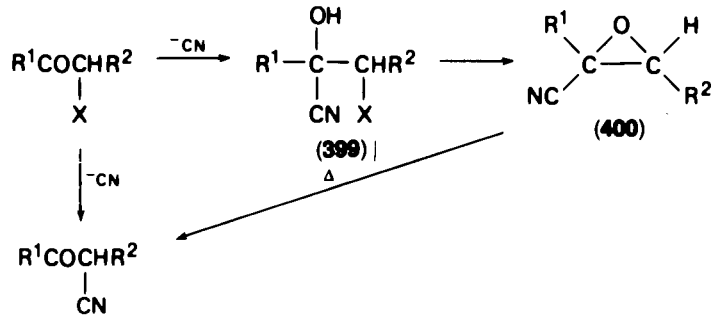
react with α-chloroketones to yield β-hydroxy thioacids (**396**) which are cyclized to thiolactones (**397**) upon action with triethylamine, while unsaturated thiolactones (**398**) are formed with sodium hydride in DMF (equation 201)[446].



(201)

6. *Reaction of α-haloketones with carbon nucleophiles*

a. Reaction of α-haloketones with cyanides. α-Haloketones have been shown to give a variety of reactions when treated with sodium or potassium cyanide[447]. Earlier reports claimed the formation of α-cyanoketones[448]; however, it is proved later that in most cases the reaction products are α-cyanoepoxides (**400**) formed via an addition–substitution mechanism[311,449,450] (equation 202).

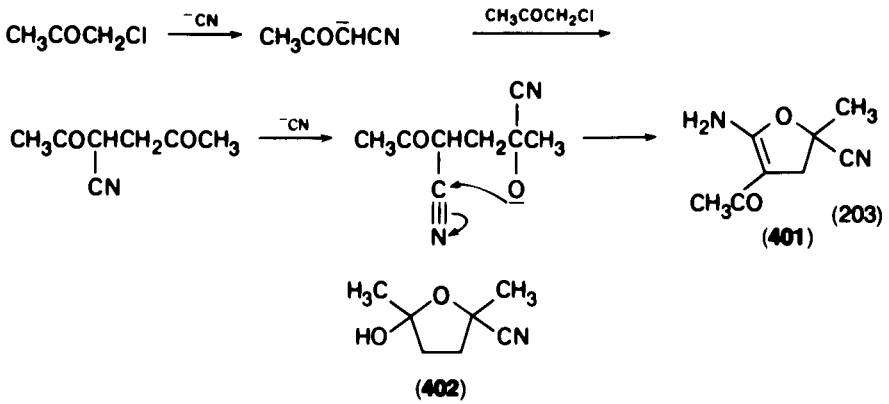


(202)

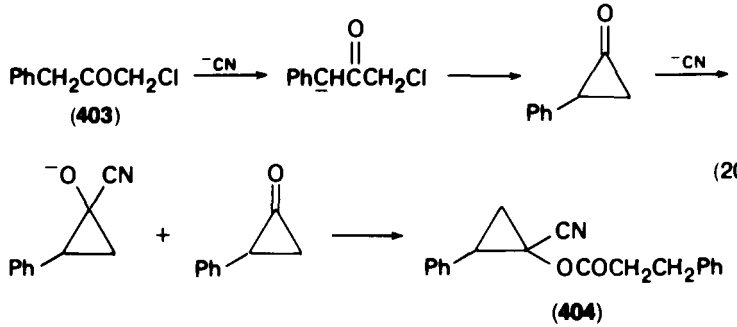
The α-cyanoketones could either be formed via direct substitution or via thermal rearrangement of the cyanoepoxides. Only when R^1 is a *t*-butyl or an aryl substituent are α-cyanoketones produced[451–452]. On the other hand, α-fluoroketones undergo cyanation at the carbonyl function with formation of cyanohydrins (**399**) without substitution of the halogen[453]. Cyanohydrins (**399**) are also produced by condensation with hydrocyanic acid at 0°C in the presence of potassium cyanide as condensing agent[454].

Reaction of α-haloketones with tetraethylammonium cyanide in dichloromethane also gives rise to cyanoepoxides (**400**) which upon heating at 80–135°C in the presence of ammonium cyanide rearrange into α-cyanoketones[455].

Reinvestigation of the reaction of chloroacetone with alkali cyanides in aqueous solution at room temperature shows another route leading to an enaminoketone (**401**)[456] and not to the tetrahydrofuran (**402**) as proposed earlier[457] (equation 203).



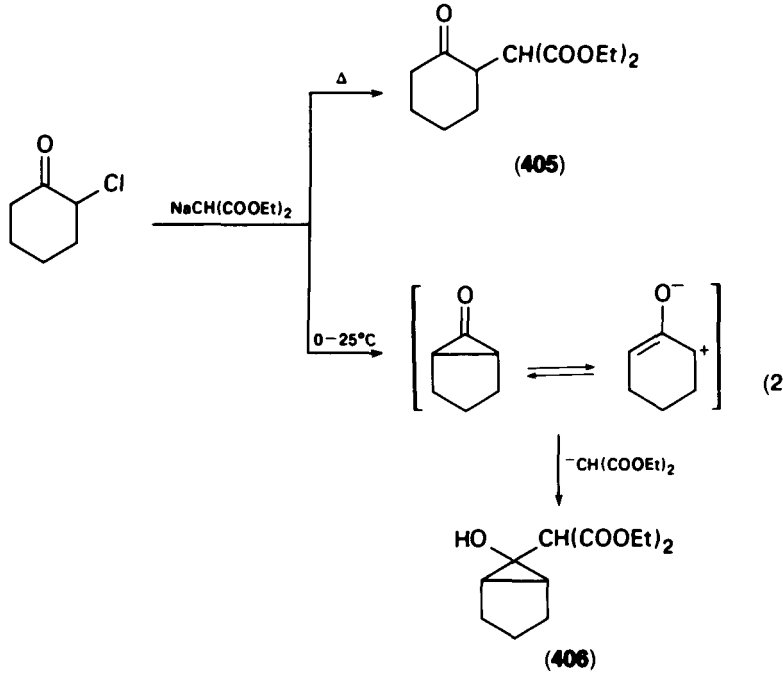
Another reaction involves the formation of a cyclopropane (**404**), induced by a Favorskii-type rearrangement on treatment of 1-chloro-3-phenyl-2-propanone (**403**) with alkali cyanides in the cold (equation 204)[458].



(204)

b. Reaction of α-haloketones with carbanions, ylides and enolates. The reaction of α-haloketones with diethyl sodium malonate and ethyl sodium acetoacetate produces exclusively substitution products via an S_N2 reaction[459–461].

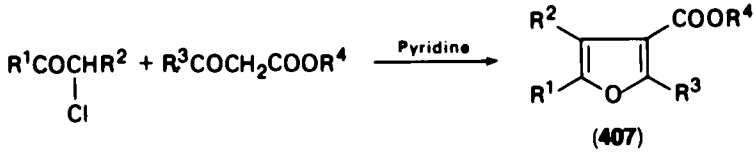
The reaction course, however, is influenced strongly by the temperature. While diethyl (2-oxocyclohexyl)malonate (**405**) is formed during the reaction of 2-chlorocyclohexanone with diethyl sodium malonate in refluxing benzene[460], 6-[bis (ethoxycarbonyl) methyl]bicyclo[3.1.0]hexan-6-ol (**406**) is isolated at 0–25°C via a malonate anion-induced Favorskii-type rearrangement[462] (equation 205).

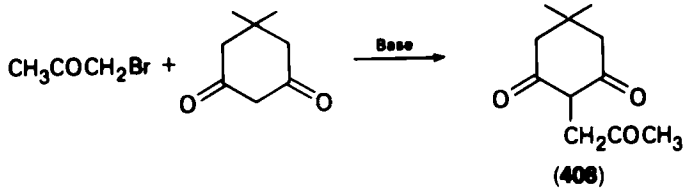


(205)

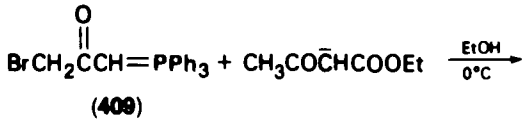
Condensation of α-chloroketones with β-keto esters in pyridine affords furans (**407**)[463] while reaction of α-bromoacetone with dimedone anion furnishes 2-acetonyldimedone (**408**)[464] (equation 206).

Alkylation of ethyl sodium acetoacetate with bromoacetylmethylene triphenylphosphorane (**409**) leads to an intermediate which undergoes an intramolecular Wittig reaction to give the cyclopentenone (**410**) (equation 207)[465].

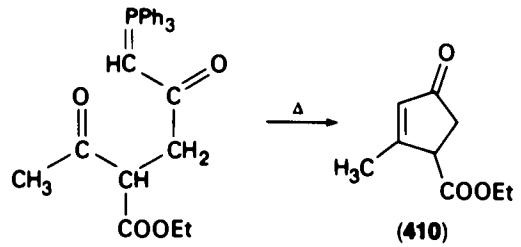




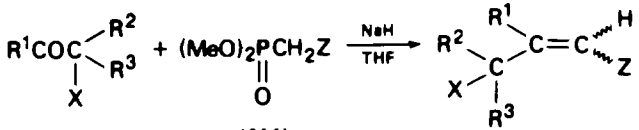
(206)



(207)

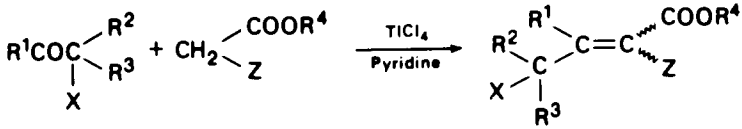


α,β-Unsaturated esters and cyanides (**412**) are formed in high yields by the Emmons–Wadsworth reaction of α-haloketones with the corresponding phosphoranes[466]. Knoevenagel condensation of α-haloketones with active methylene functions gives electrophilic allylic halides (**413**) by the action of titanium tetrachloride–pyridine[467,468] (equation 208).



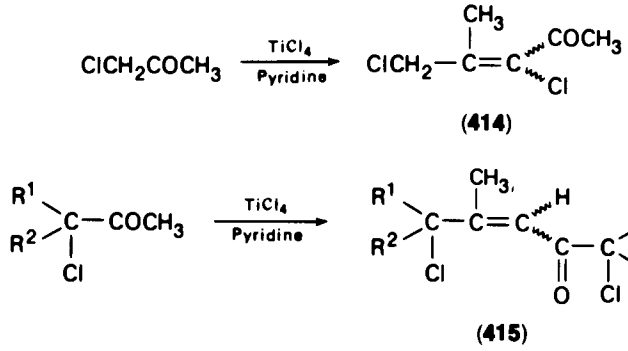
Z = $COOR^4$, CN

(208)



Z = $COCH_3$, $COOR^4$, CN

Another reaction type, namely aldol condensation yielding α,β-enones (e.g. **414**, **415**), is reported when α-chloroketones are treated with pyridine in the presence of titanium tetrachloride (equation 209)[469].

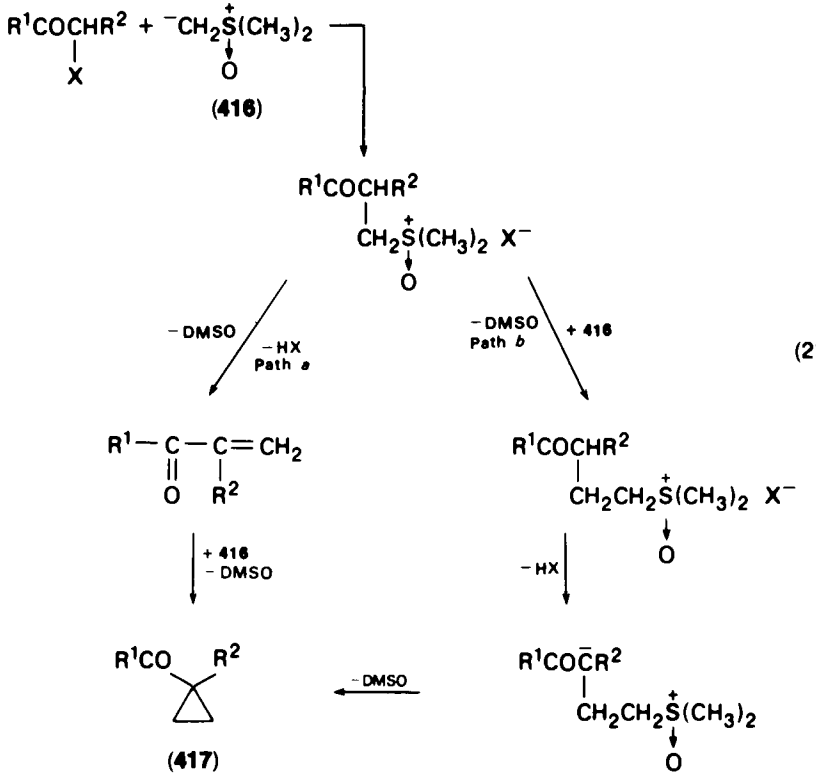


(414)

(209)

(415)

Reaction of α-haloketones with dimethylsulphoxonium methylide (**416**) results in cyclopropanation. First, the halogen is displaced by the methylide to give the intermediate salt. According to path *a* the salt can be converted to an olefin which reacts successively with the methylide (**416**) to give the cyclopropane (**417**). An alternative



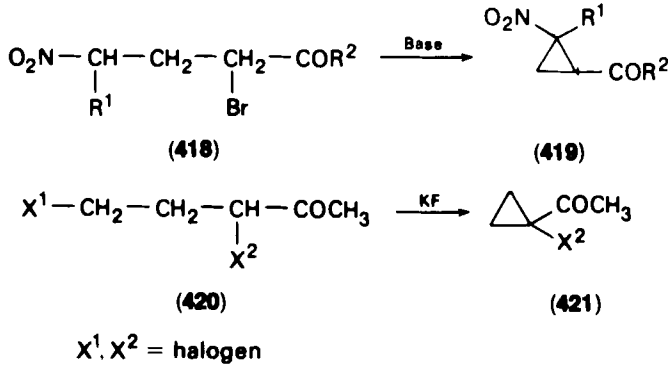
(416)

(417)

(210)

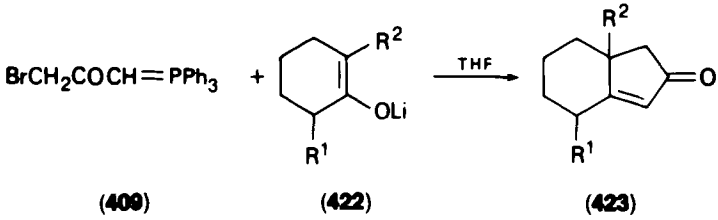
route (path *b*) involves a nucleophilic displacement of the salt to afford an homologous salt which in turn affords a cyclopropane (**417**) by an intramolecular displacement (equation 210)[470,471]

Intramolecular cyclopropanation takes place when α-haloketones, carrying electron-withdrawing groups in the γ-position, are treated with strong bases, providing, for example, nitrocyclopropanes (**419**)[472]. 1-Halocyclopropyl methyl ketones (**421**) may be obtained by simply heating the appropriate 3,5-dihalo-2-pentanones (**420**) with potassium fluoride as base in diethylene glycol[473] (equation 211).



(211)

Lithium enolates (**422**) react smoothly with certain α-halocarbonyl derivatives, e.g. bromoacetylmethylene triphenylphosphorane (**409**), which constitutes a useful annellation reagent, to give cyclopentenones (**423**) (equation 212)[465]

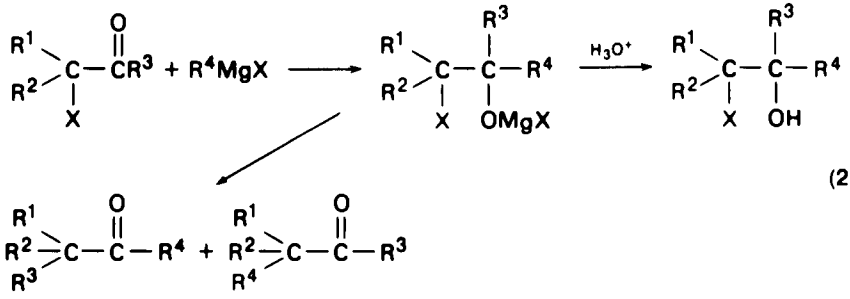


(212)

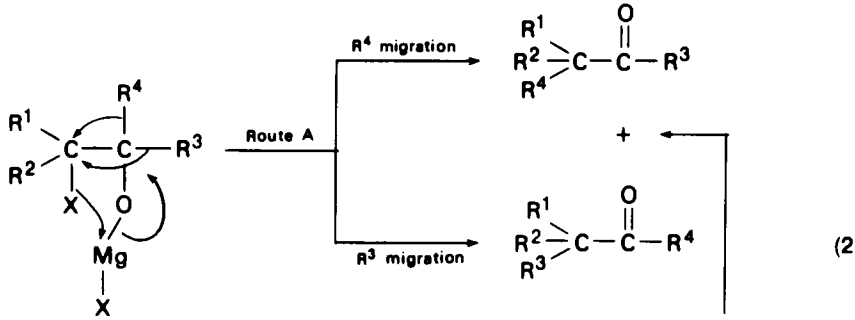
7. *Reaction of α-haloketones with organometallic reagents*

a. Reaction of α-haloketones with Grignard reagents. α-Haloketones react readily with Grignard reagents to afford mainly magnesium salts of halohydrins (which can be hydrolysed to the parent halohydrins) and rearranged ketones in variable proportions (equation 213)[474–478].

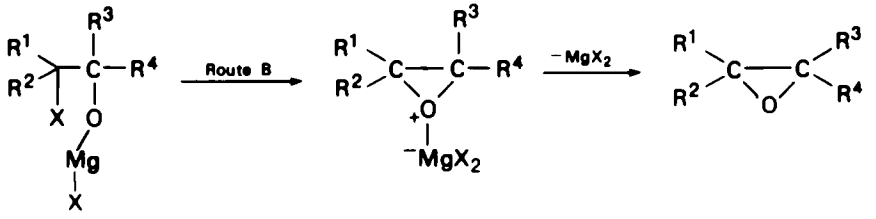
The majority of the rearrangements of halomagnesium derivatives of halohydrins can be accounted for by considering them to be pinacol-like rearrangements induced by an electrophilic attack of the MgX group on the neighbouring halogen atom (route A). A second way consists of an internal nucleophilic substitution (route B) (equation 214). Whether mechanism A or B is followed will be determined by structural factors. Route A should be favoured when the halogen atom is secondary or tertiary, when the migrating group R can participate in the process and contribute to the resonance stabilization of the transition state and when the —X and —OMgX moieties are in a *cis* relationship to one another. When the halogen atom is secondary or tertiary, route A seems always to be followed, but when it is primary the nature of the R^3 and R^4 groups directs the course of the rearrangement, as illustrated below (equation 215)[475].

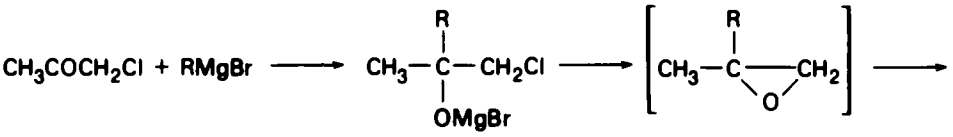


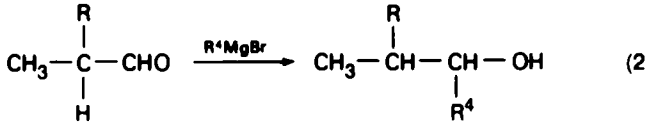
(213)



(214)

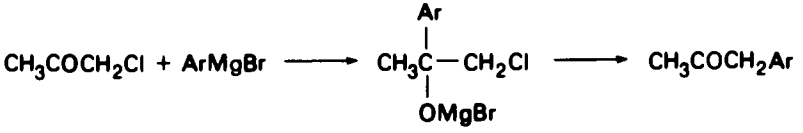






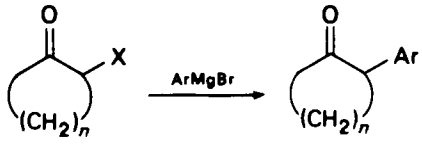
(215)

R^4 = alkyl, benzyl

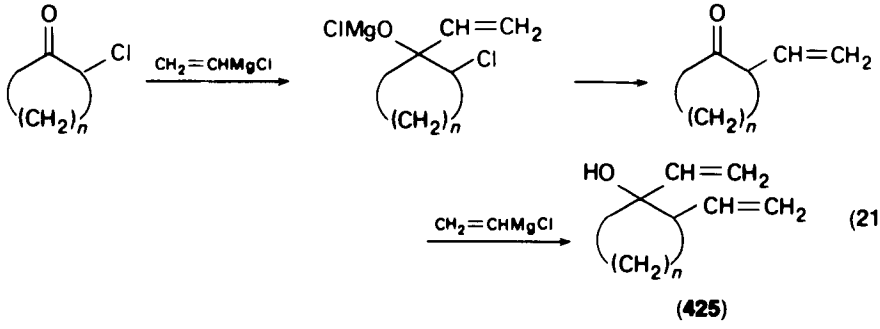


The influence of stereochemical factors is illustrated by the rearrangement, via the halomagnesium derivative, of *cis*-1-methyl-2-chlorocyclohexanol, yielding mostly 2-methylcyclohexanone and a small amount of acetylcyclopentane, while the *trans* isomer exclusively affords acetylcyclopentane[474].

Reaction of cyclic α-chloroketones with arylmagnesium bromide gives rise to α-arylketones (**424**)[479], while with vinylmagnesium chloride 1,2-divinylcycloalkanols (**425**) are formed, except for α-chlorocyclobutanone which furnishes 1-cyclopropyl-4-penten-1-one (**426**) (equation 216)[480].

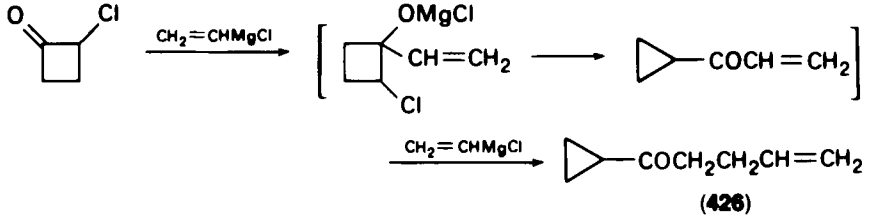


(**424**)



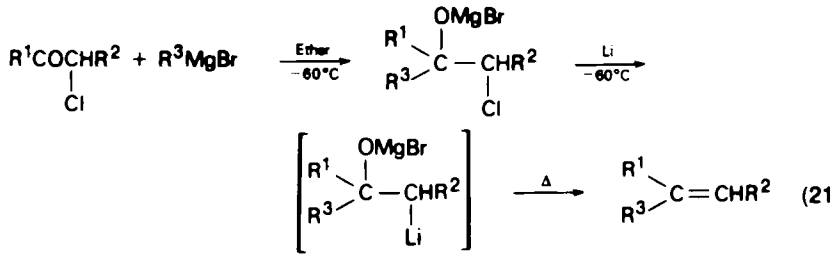
(216)

(**425**)



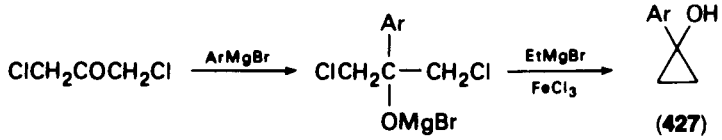
(**426**)

A 'one flask' synthesis of olefins has been described by the reaction of α-chloroketones with Grignard reagents and further treatment with lithium metal at −60°C (equation 217)[481].



(217)

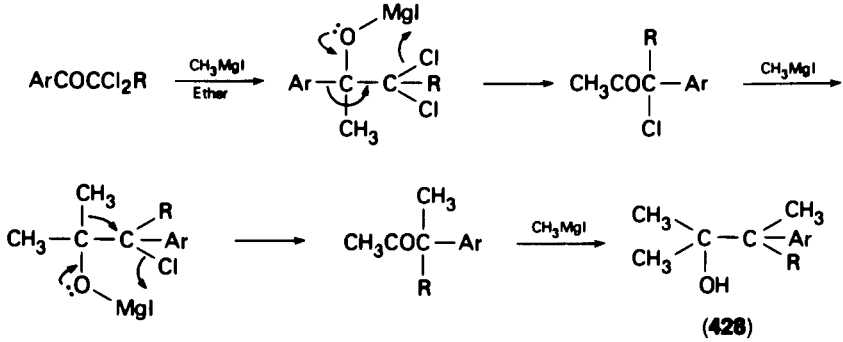
1-Arylcyclopropanols (**427**) are produced when 1,3-dichloro-2-propanone first reacts with arylmagnesium halides and the product is subsequently treated with ethylmagnesium bromide in the presence of ferric chloride (equation 218)[482,483].



(218)

Reaction of phenacyl halides with Grignard reagents gives dibenzyl ketones or deoxybenzoins depending upon the aromatic substitution pattern and the reaction conditions which determine the relative migratory aptitudes of the aryl and phenyl groups[484].

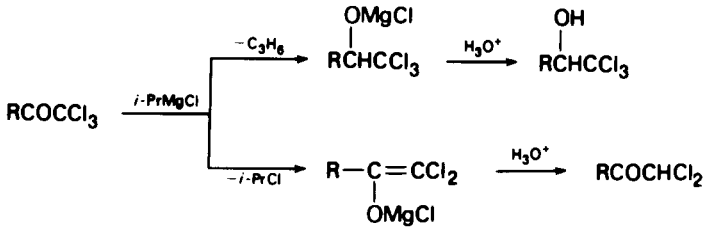
1-Aryl-2,2-dichloro-1-alkanones rearrange with methylmagnesium iodide to highly sterically hindered alcohols (**428**). The mechanism involves two pseudo-pinacol-type rearrangements of the carbonyl adducts (equation 219)[485,486].



(219)

Finally, non-addition reactions of α-haloketones and Grignard reagents (R'MgX) also occur which result in the formation of halomagnesium enolates with elimination of R'H or R'X[487,488].

Reaction of α,α,α-trichloroketones with isopropylmagnesium chloride gives, after hydrolysis, a mixture of alcohols and α,α-dichloroketones, the latter compounds resulting from intermediate magnesium enolates (equation 220)[488]. Magnesium

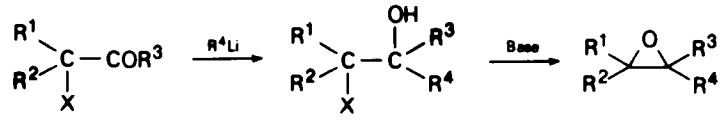


(220)

enolates are stable compounds possessing high nucleophilic reactivity. They can be prepared by reaction of α-haloketones with magnesium (equation 220a)[487].

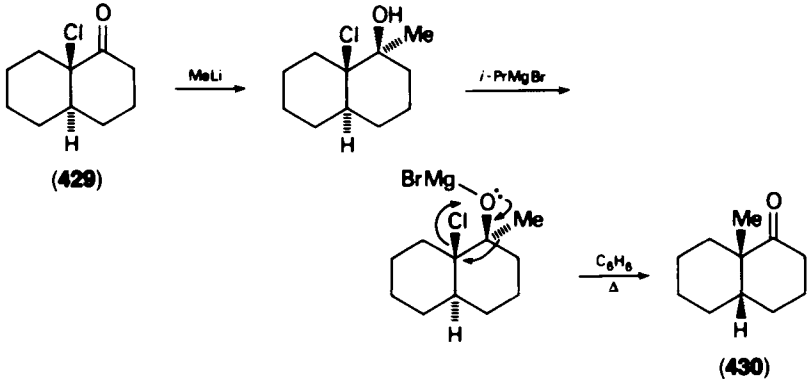
(220a)

b. Reaction of α-haloketones with organolithium compounds. Reaction of α-haloketones with alkyllithium derivatives normally gives rise to halohydrins, which can be converted into epoxides by the action of bases (equation 221)[477].



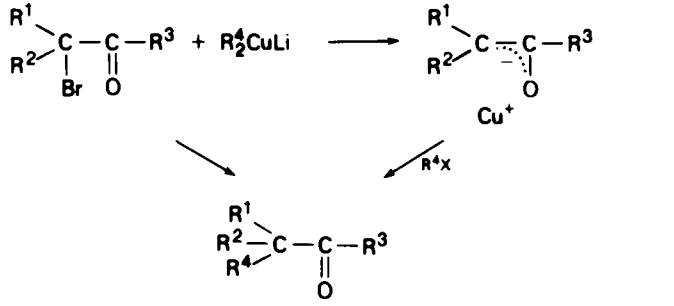
(221)

A very useful synthetic procedure for alkylation of α-chloroketones utilizes halohydrin formation by the action of alkyllithium compounds, followed by addition of Grignard reagents and thermal decomposition of the resulting magnesium salts into the α-alkylated ketones as illustrated below (equation 222)[489]. However, application of the same sequence to 2-chlorocyclohexanone gives rise to a mixture of 32% 2-methylcyclohexanone and 22% 2-acetylcyclopentane[489].



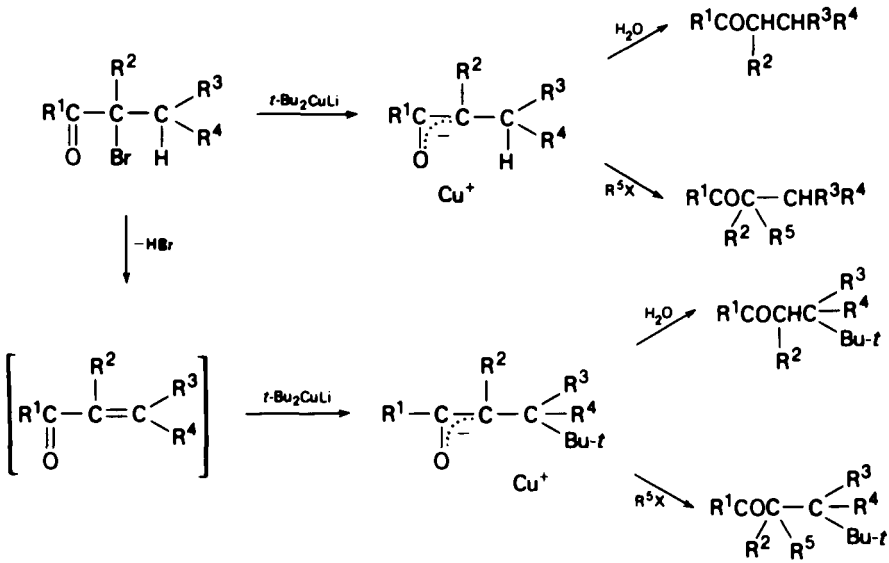
(222)

The reaction of α-chlorocycloalkanones with aryllithium reagents also proceeds to the formation of α-arylketones in high yields[490]. The alkylation of α-bromoketones with alkyllithium cuprates allows the regiospecific introduction of a primary, secondary or tertiary alkyl group on the ketone at the site initially brominated. Two concomitant mechanisms, halogen–metal exchange and nucleophilic substitution occur. While these two mechanisms co-exist in substitution by primary and secondary alkyl groups, only nucleophilic substitution seems possible in the case of tertiary alkyl groups (equation 223)[491,492].



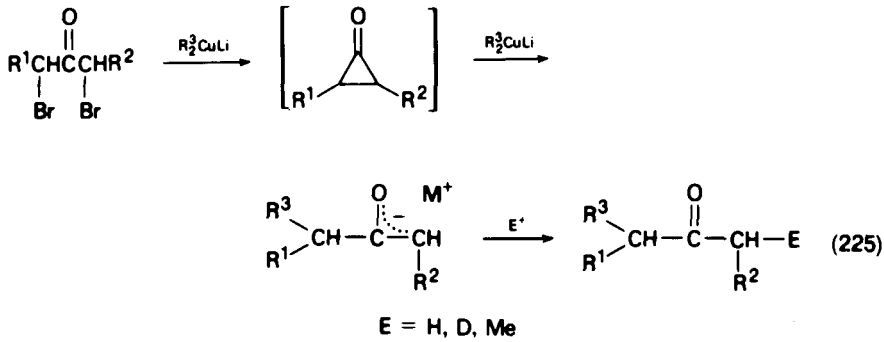
(223)

Complications arise during the action of di-*t*-butyllithium cuprate on α-bromoketones possessing hydrogen atoms at the β-position: products from the halogen–metal exchange are obtained together with alkylation not at the α-position but at the β-position. The latter reaction is explained by a dehydrobromination yielding an α,β-unsaturated ketone, followed by a 1,4-addition (equation 224)[493,494].



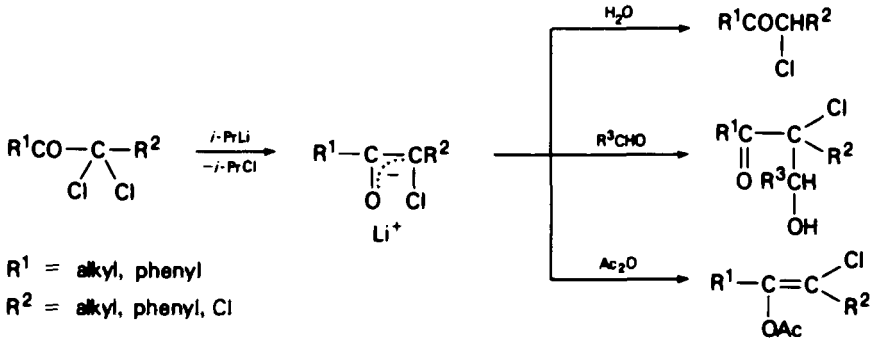
(224)

α,α′-Dibromoketones also react with dialkyllithium cuprates leading initially to enolates in which internal displacement of bromide produces cyclopropanones as in the Favorskii rearrangement. Further reaction with the organocopper reagent affords a new enolate and exposure of the latter to various electrophiles yields α-substituted ketones (equation 225)[495].



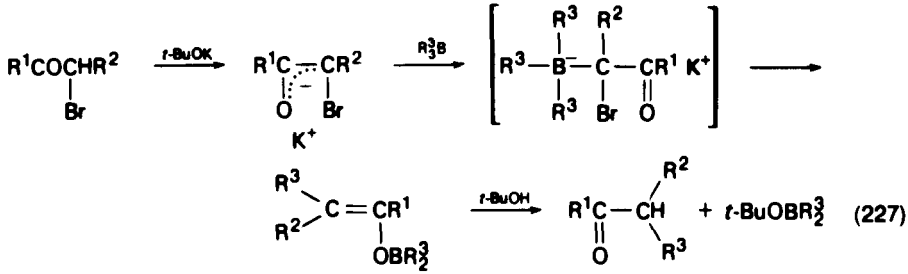
(225)

Enolate formation is reported when α,α-dichloro- or α,α,α-trichloroketones are treated with isopropyllithium. These enolates are stable at −75°C and are hydrolysed to α-chloroketones. Reaction with aldehydes provides *C*-alkylation, while enol acetates are obtained with acetic anhydride (equation 226)[496].



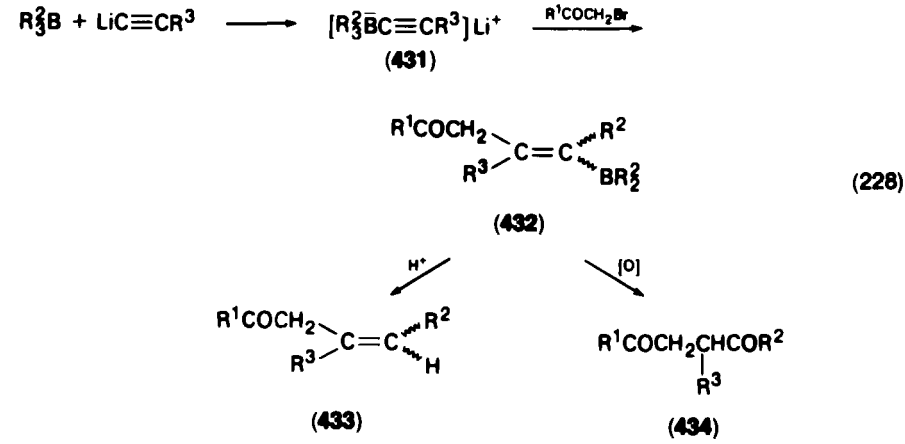
(226)

c. Reaction of α-haloketones with organoboron compounds. α-Bromoketones are alkylated by 9-alkyl-9-borabicyclo[3.3.1]nonanes via their enolates but this reaction is more sensitive to steric hindrance than the analogous reaction using cuprates (equation 227)[497,498].



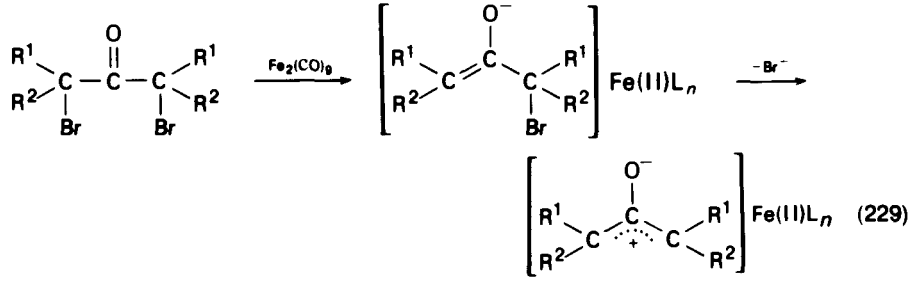
(227)

Reaction of α-bromoketones with alkynyltrialkylborates (**431**) gives intermediate vinylboranes (**432**) which upon hydrolysis or oxidation afford olefins (**433**) and 1,4-diketones (**434**), respectively (equation 228)[499].



(228)

d. Reaction of α-haloketones in the presence of metal complexes. Oxyallyl cations (**435**) are generated when α,α′-dibromoketones are treated with sodium iodide in acetonitrile[500], mercury[500], zinc–copper couple[500,501], iron carbonyl compounds[502], zinc and triethylborate[503] and copper powder with sodium iodide[504]. The formation of these cations, for example with diiron nonacarbonyl, can be envisioned by initial reduction of the dibromide producing an iron enolate (L = Br^-, CO, solvent, etc), which eliminates a bromide ion to form the oxyallyl cations (equation 229)[505].



(229)

(**435**)

Oxyallyl species serve as highly versatile synthons for the construction of carbocyclic frameworks by cycloaddition with alkenes[505], dienes[505], furans[506,507], pyrrols[508] and enamines[509] (equation 230).

Attempted formation of substituted cyclopentanones from oxyallyl species and 2π-systems failed; however, allenic compounds (**443**) and tetrahydrofurans (**445**) are isolated from the reactions of α,α′-dibromoketones with acetylenes (**442**) and 1,1-dimethoxyethylene (**444**), respectively (equation 231)[510].

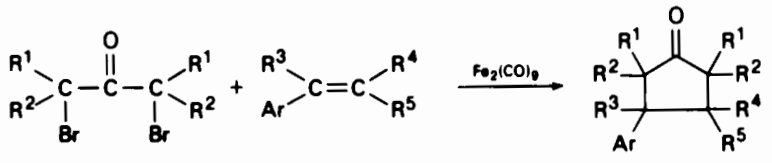
2-(*N*-Alkylimino)cyclobutanones (**446**) are produced on reaction of α,α′-dibromoketones with a copper/isonitrile complex (equation 232)[511].

One of the observed side reactions during the formation of oxyallyl cations is the formation of reduction products. Debromination of α,α′-dibromoketones with a zinc–copper couple in methanol yields the parent ketone and an α-methoxy ketone. The latter is suggested to arise from a selective 2-oxyallyl cation which is produced in an S_N1 reaction[512]. Debromination in DMF gives rise to **447** and reductive coupling products (**448**) (equation 233)[513]. Similar debromination and coupling reactions are obtained with dicobalt octacarbonyl under phase transfer conditions[514]. α-Monohaloketones also give a variety of reactions with various organometallic compounds.

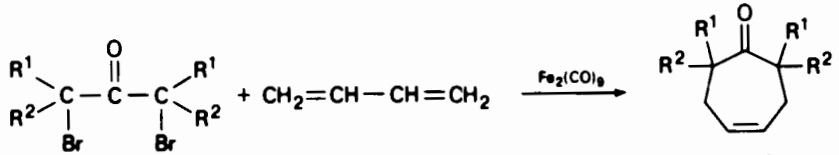
Iron pentacarbonyl reacts with α-haloketones in refluxing 1,2-dimethoxyethane, followed by treatment with water, to give 1,4-diketones (**449**), reduced monoketones (**450**) and β-epoxy ketones (**451**) (equation 234)[515] α-Bromoketones react with zinc in ether to provide organozinc compounds which on further reaction with alkyl chloroformates and aldehydes afford respectively β-keto esters (**452**) and β-hydroxy ketones (**453**) (equation 235)[516,517].

An efficient and regiospecific aldol condensation is reported which consists of a coupled attack on the α-haloketone by dialkylaluminium chloride and zinc generating an aluminium enolate regiospecifically. The enolate is sufficiently reactive to cause a facile addition to carbonyl compounds to give β-hydroxy ketones (**453**) (equation 236)[518].

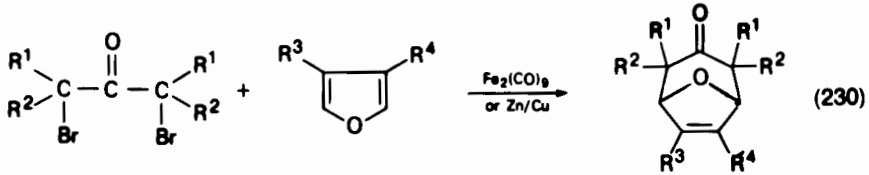
During the debromination of α,α-dibromocamphor (**454**) with diethyl zinc in refluxing benzene, an α-elimination occurs to produce an α-keto carbene (**455**) which leads to the formation of (**456**) (equation 237)[519].



(436)

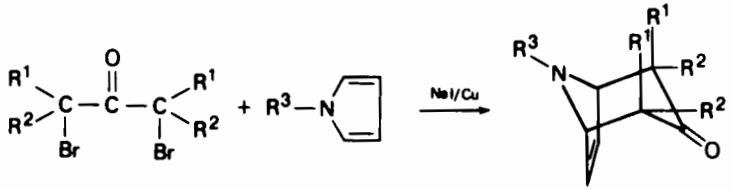


(437)

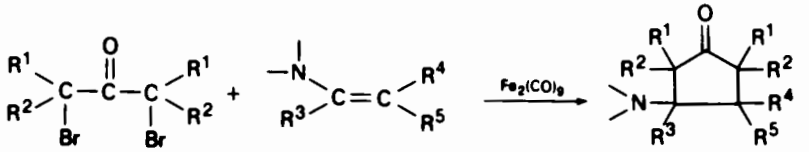


(230)

(438)



(439)



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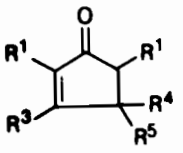

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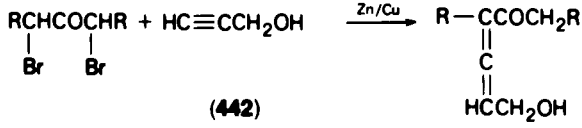
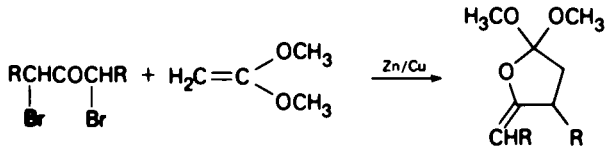
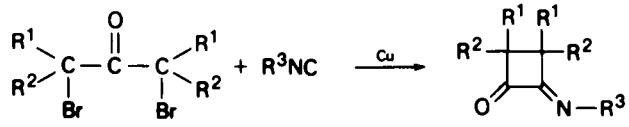


(442) (443)

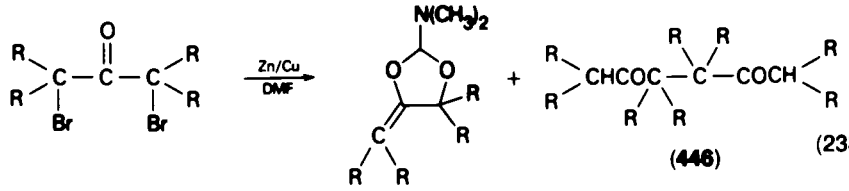
(231)



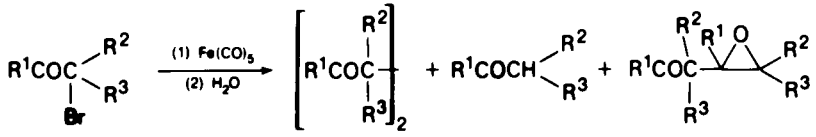
(444) (445)



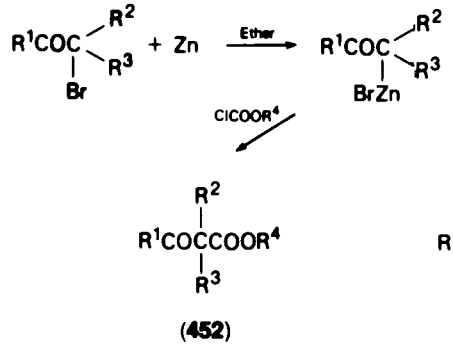
(446) (232)



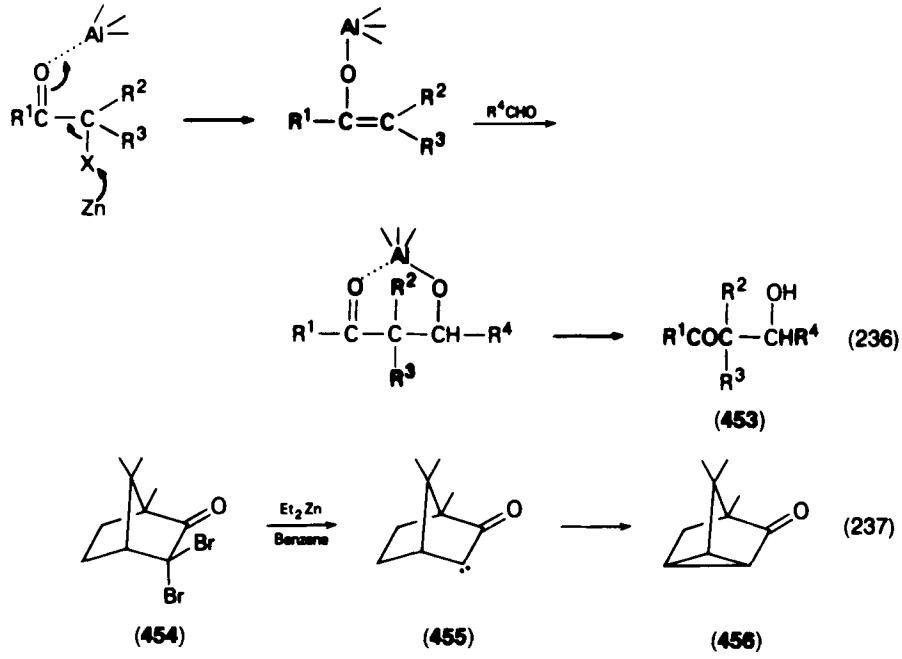
(447) (446) (233)



(449) (450) (451) (234)

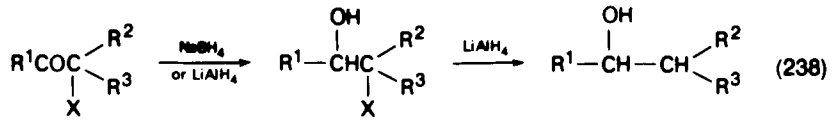


(452) (453) (235)



8. *Reaction of α-haloketones with complex metal hydrides*

Reaction of α-haloketones with sodium borohydride results in reduction of the carbonyl function with formation of halohydrins (equation 238)[520–522]. Reduction with

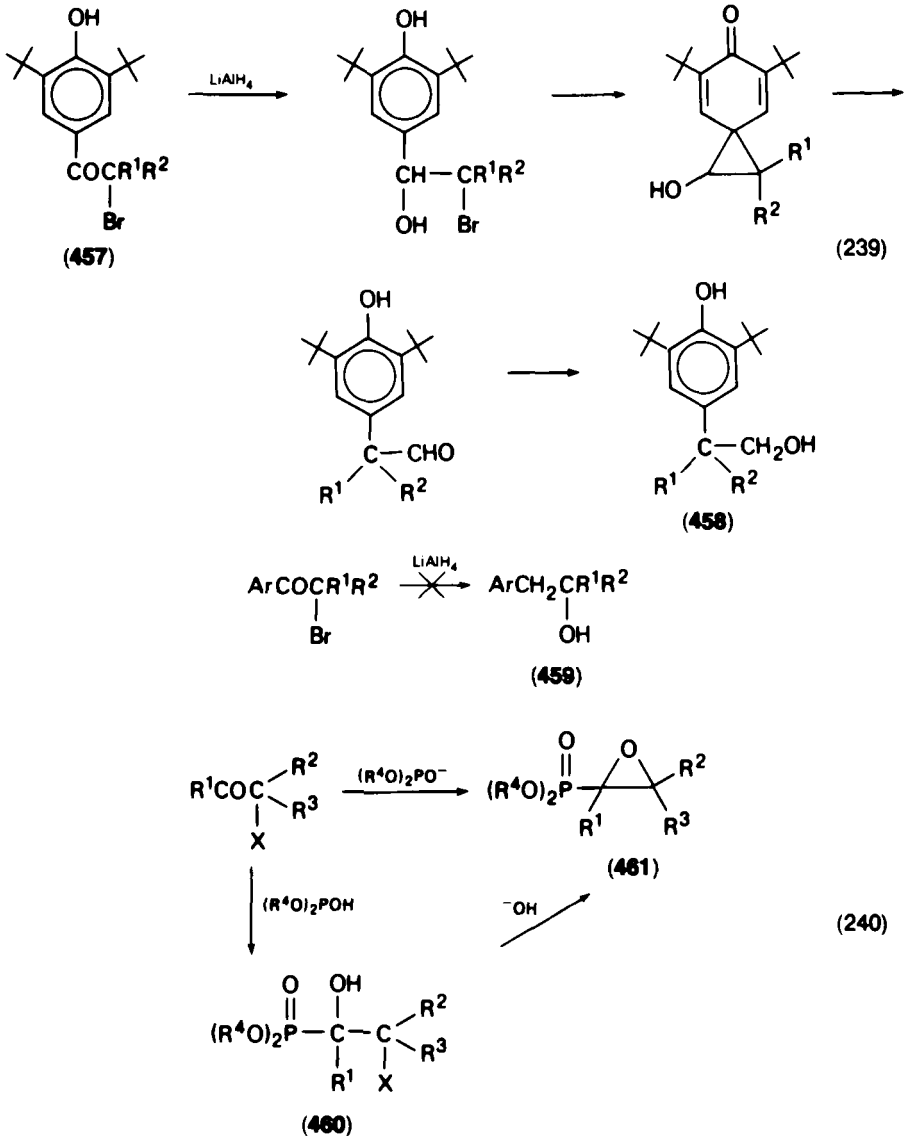


lithium aluminium hydride provides the same halohydrins[523,524], while the reduction of phenacyl halides gives mixtures of 1-aryl-1-ethanols and 1-aryl-2-halo-1-ethanols[525]. However, if the aromatic ring is strongly electron-releasing, e.g. compound **457**, the aromatic ring migrates to give primary alcohols (**458**)[526,527] and not secondary alcohols (**459**) as proposed previously[528] (equation 239).

9. *Reaction of α-haloketones with phosphorus compounds*

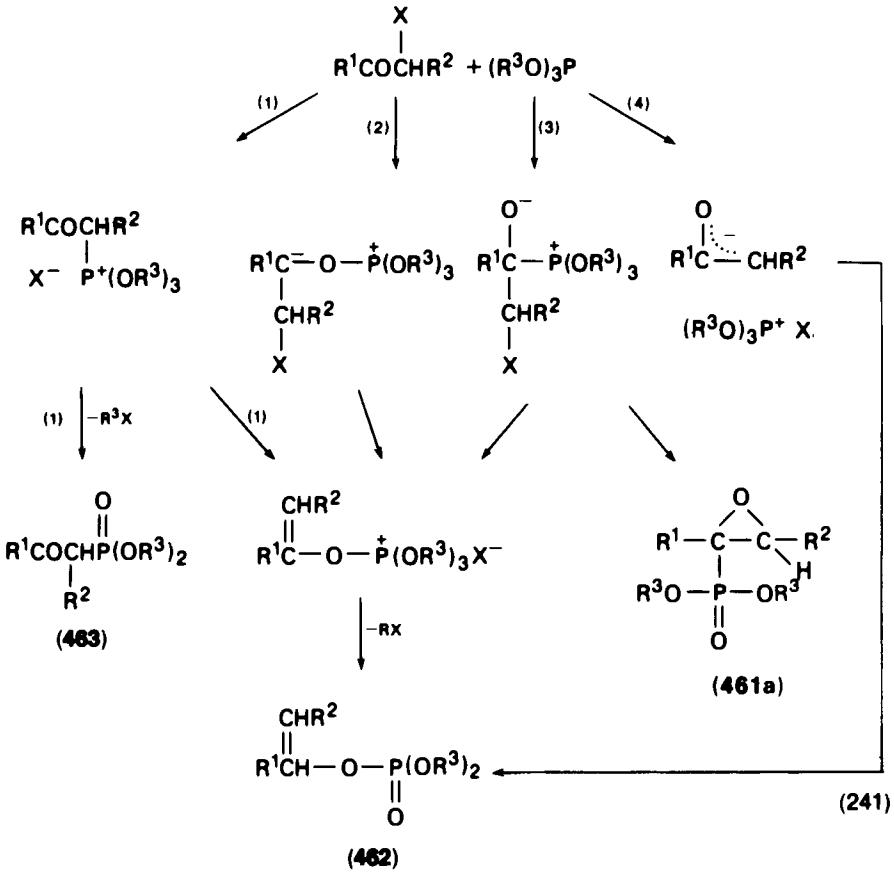
The reactions between α-haloketones and trivalent phosphorous compounds are of rather a complex nature[529]. Dialkyl phosphites normally react at the carbonyl group to give α-hydroxy and/or epoxy phosphonate esters (**460**, **461**) (equation 240)[530].

Trialkyl phosphites react with α-haloketones yielding enol phosphates (**462**) (Perkow reaction) and/or β-ketophosphonates (**463**) (Arbusov reaction)[531–534]. In general the attack of phosphites can take place at four positions (equation 241): (1) attack on the carbon atom carrying the halogen, which gives rise either to an enol phosphate (**462**) or to a β-ketophosphonate (**463**); (2) attack on the carbonyl oxygen; (3) attack on the carbonyl carbon, furnishing an epoxy phosphonate (**461a**) or a vinyl



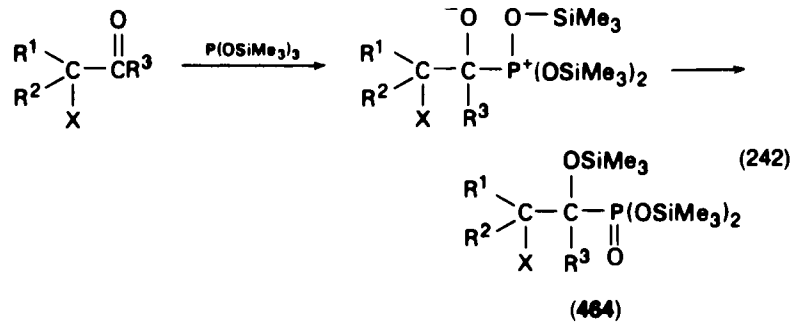
phosphate (**462**); (4) attack on the halogen, leading to the enol phosphate (**462**) via an halophosphonium enolate.

No general agreement has been reached concerning the mechanisms of the Perkow and the Arbusov reactions, and further work is still in progress to substantiate the nature of the intermediates[532,535]. The ratio between the Perkow and Arbusov reaction products is dependent upon the nature of the substrate and the phosphite and the reaction conditions employed. Substitution at the α-carbon atom e.g. by alkyl groups and by strongly electron-withdrawing groups, promotes the Perkow reaction, while a



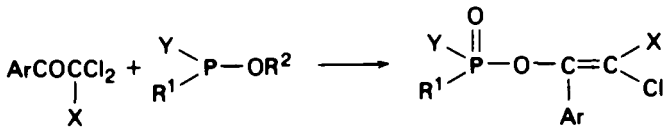
change in the halogen from chlorine to iodine decreases the yield of enol phosphates. An increase in the temperature favours the Arbusov reaction[531,532,536]. The reaction with phosphites in the presence of acids gives exclusively the Arbusov products[537].

In contrast to the results mentioned above, reaction of tris(trimethylsilyl)phosphite with α-haloketones does not give the expected Perkow or Arbusov reaction but produces halogenated phosphonates (**464**) (equation 242)[538].



(242)

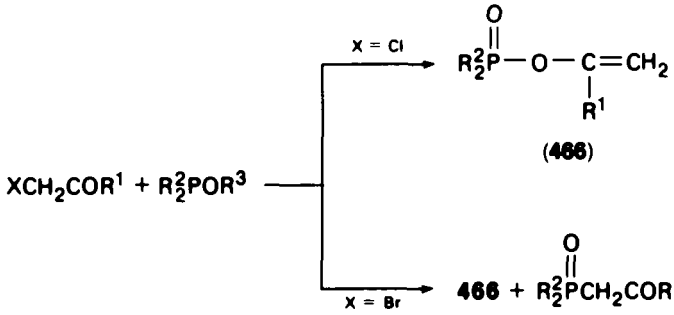
Treatment of chlorinated acetophenones with monoalkyl phosphinites under the standard Perkow reaction conditions gives enol phosphonates (**465**) (equation



(243)

(**465**)

243)[539,540]. On the other hand, reaction of dialkyl phosphinites produces the Perkow (**466**) and/or the Arbusov (**467**) reaction product. With alkyl di-*t*-butylphosphinites only the Arbusov reaction takes place (equation 244)[541,542].

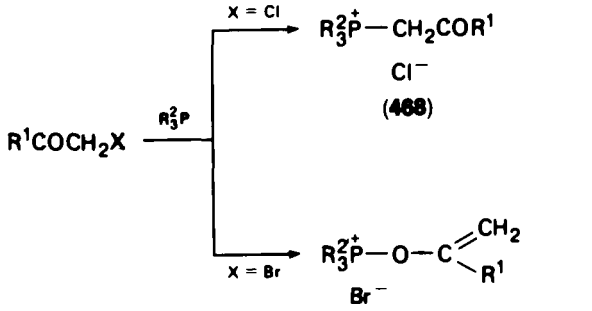


(244)

(**466**)

(**467**)

α-Chloroketones react with tertiary phosphines to give phosphonium salts (**468**), while enol phosphonium salts (**469**) are generated in the case of α-bromoketones (equation 245)[543].



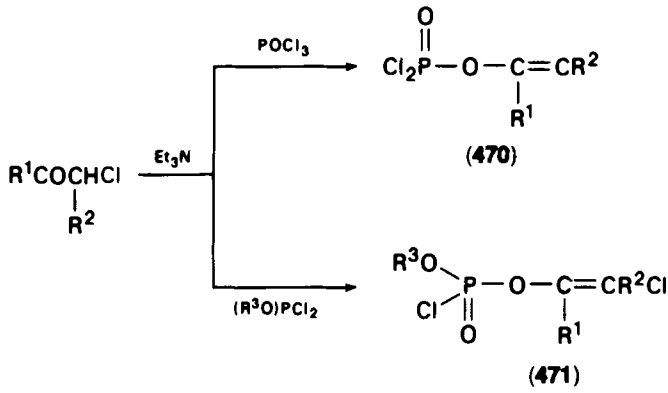
(245)

(**468**)

(**469**)

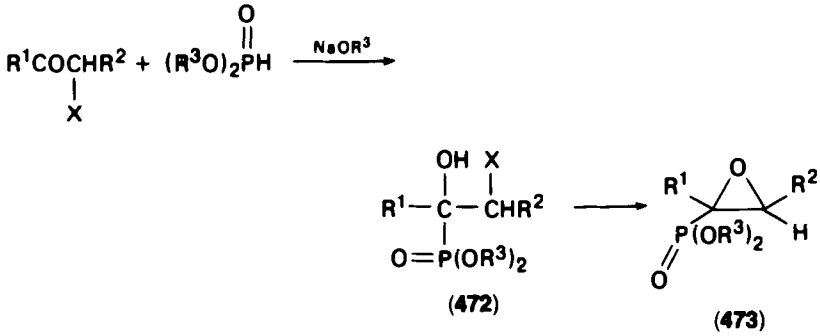
Phosphorous acid vinyl esters (**470**, **471**) are produced on treatment of α-chloroketones with phosphorous oxytrichloride[544] and alkyl dichlorophosphinites[545], respectively, in the presence of triethylamine (equation 246).

Epoxy phosphonates (**473**) have been prepared by the action of sodium alkoxide on a dialkyl phosphonate and an α-haloketone. When the reaction is performed in the



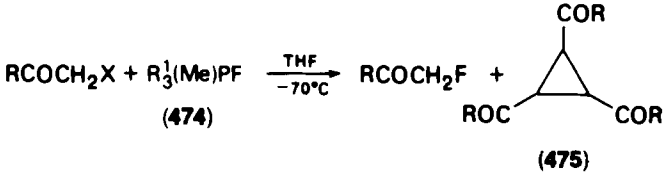
(246)

presence of triethylamine, the intermediate halohydrins (**472**) could be isolated (equation 247)[546,547].



(247)

Monofluorophosphoranes (**474**), especially methyltri(*n*-butyl)fluorophosphorane, are used in exchange reactions to prepare α-fluoroketones. In addition, cyclopropanes (**475**) are produced, due to the high basicity of the reagent which causes the formation of an α-keto carbene by dehydrohalogenation (equation 248)[548].

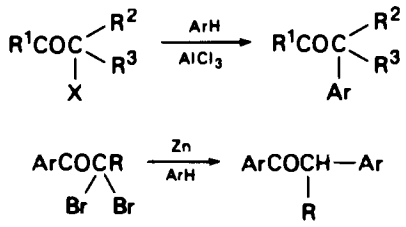


(248)

B. Miscellaneous Reactions of α-Haloketones

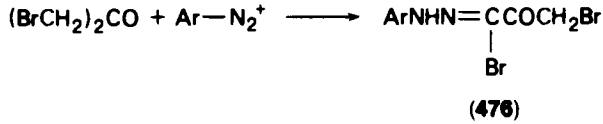
1. *Electrophilic reactions of α-haloketones and their derivatives*

Friedel–Crafts reactions of certain aryl activated α-chloroketones with aromatics in the presence of aluminium chloride gives rise to α-aryl ketones[549,550]. Another method for the synthesis of α-aryl ketones consists of an insertion reaction of an α-keto-carbenoid generated from α,α-dibromoketones in the presence of zinc[551] (equation 249).



(249)

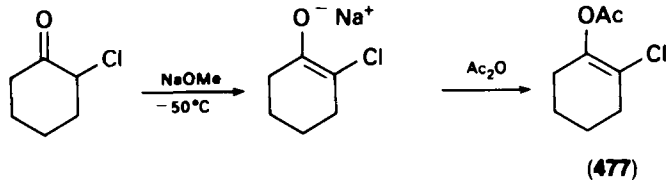
Brominated phenylhydrazones (**476**) are obtained by treatment of α-bromoketones with diazonium salts (equation 250)[552].



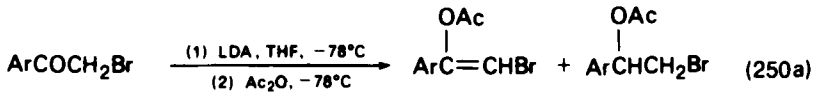
(250)

(**476**)

Finally, α-chloroketones have been converted to the corresponding enol acetates (**477**) by acylation of the intermediate chloroenolates, generated by reaction with a suspension of sodium methoxide in ether at −50°C. This procedure takes advantage of the fact that in unsymmetrical ketones the C—H bond adjacent to both the carbonyl group and the chlorine atom is significantly more acidic (by 2 pK_a units) than the C—H bond adjacent only to a carbonyl group[553]. Certain α-haloketones also undergo rapid reaction with lithium diisopropyl amide (LDA) to produce enol acetates (**478**) in the presence of acetic anhydride in competition with reduction products (**479**) via hydride transfer[554]. Enolate formation also takes place when α-chloroketones are treated with trimethylchlorosilane in the presence of tertiary amines to yield trimethylsilyl enol ethers (**480**)[555] (equation 250a).

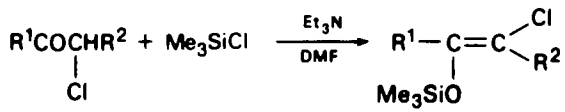


(**477**)



(250a)

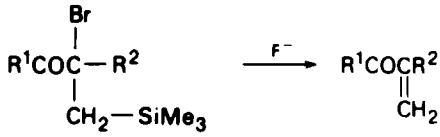
(**478**) (**479**)



(**480**)

2. Reaction of α-haloketones with alkali fluorides

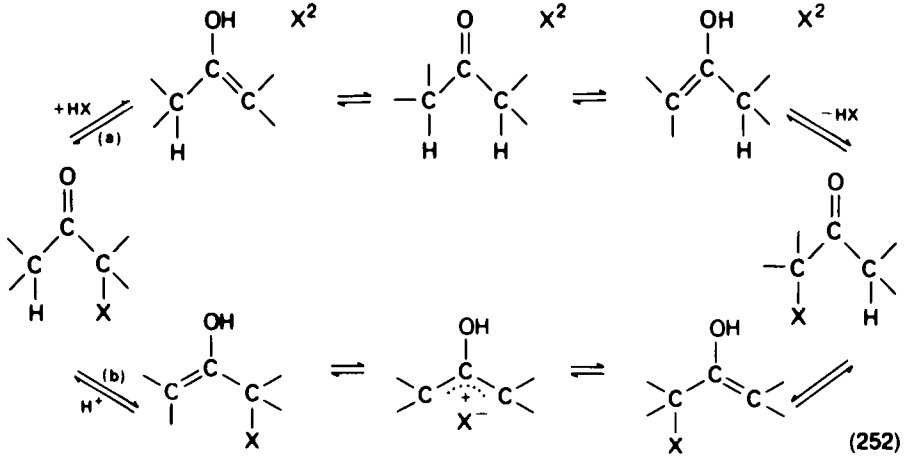
The halogen–fluorine exchange on treatment of α-haloketones with fluoride anion to give α-fluoroketones has already been mentioned (*vide supra*). Another synthetic application involves a desilylbromination and specifically places a double bond between the carbon attached to the carbonyl group and the β-atom to which the silicon atom has originally been bound. Synthetically important α-methylene ketones and lactones have been prepared by using this procedure in which the base- and acid-stable silyl function masks the α,β-unsaturation of enones (equation 251)[556].



(251)

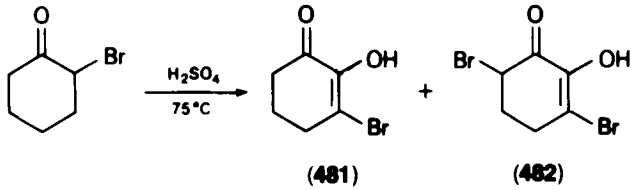
3. Acid-catalysed rearrangement of α-haloketones

Numerous examples of α-haloketone rearrangements into the α'-isomers in the presence of acids are known. They occur via two mechanisms: (a) a cationic halogen path and (b) an anionic halogen path (equation 252)[557].



(252)

Equilibration of *trans*-carvone tribromide (**171**) with hydrogen bromide in acetic acid at 0°C gives a mixture of 45% *trans*- and 55% *cis*-carvone tribromide; this isomerization involves the exclusive exchange of a halo substituent β to the carbonyl group[558]. The reaction of 2-bromocyclohexanone in concentrated sulphuric acid also provides rearranged enols of bromo-1,2-cyclohexanediones (**481**, **482**) (equation 253)[559].

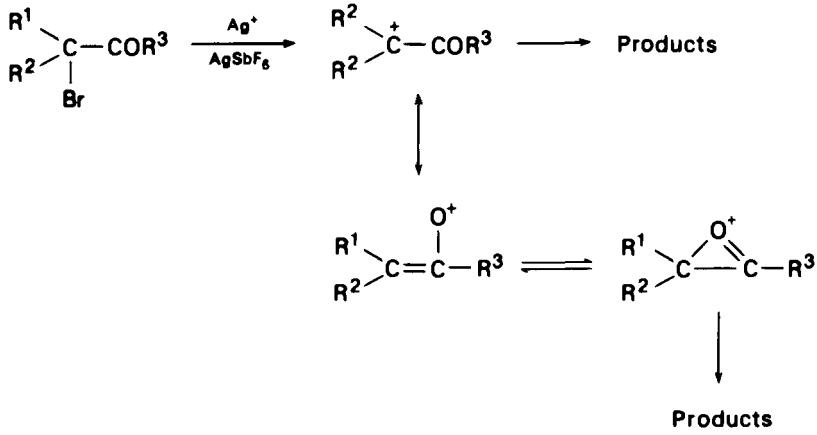


(253)

(481) (482)

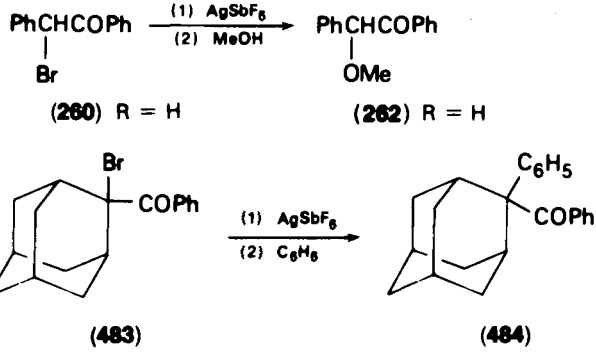
4. Formation of α-acylcarbenium ions from α-haloketones

Silver salts of superacids are able to ionize α-halocarbonyl compounds to α-acylcarbenium ions, and silver hexafluoroantimonate in dichloromethane strikingly promotes this ionization[560,561] (for a recent review dealing with α-acylcarbenium ions, see Ref. 562). In a few cases the reaction leads to the formation of oxonium salts (equation 254).



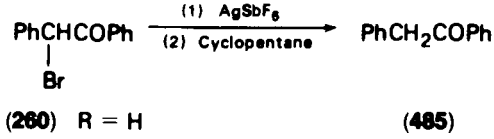
(254)

Acylcarbenium ions are very reactive species which are able to undergo the following reactions: (a) nucleophilic substitution (equation 255)[335,563]



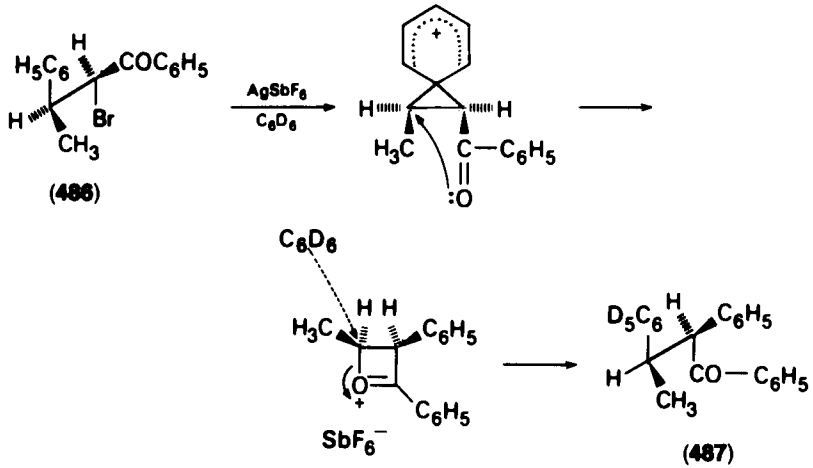
(255)

(b) hydride shift (equation 256)[561]



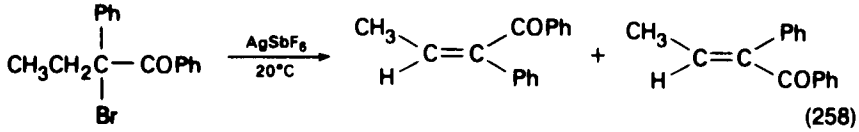
(256)

(c) Wagner–Meerwein-type rearrangement (equation 257)[561].



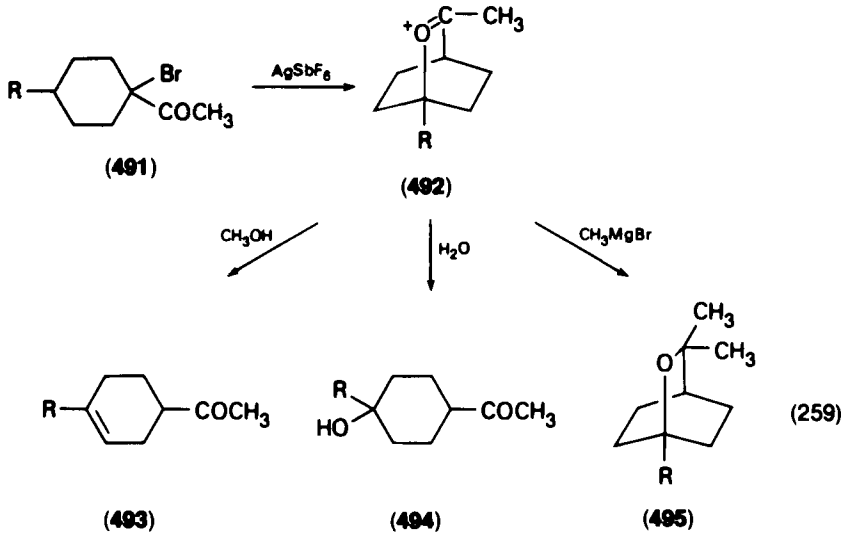
(257)

(d) *E*1-type elimination (equation 258)[561]



(258)

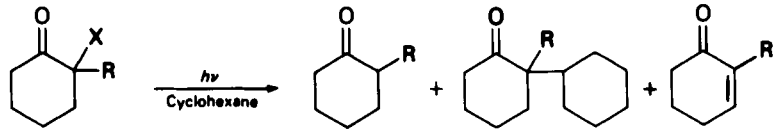
When the structure of the precursor permits, α-acylcarbenium ions are transformed into oxonium salts via hydride shifts. These ambident salts enable further functionalization as illustrated for α-bromocyclohexyl ketones (equation 259)[562].



(259)

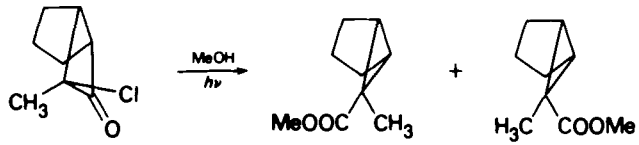
5. *Photochemistry of α-haloketones*

There are a few reports on the study of the photochemistry of α-haloketones involving different types of photoprocesses. α-Halocyclohexanones on irradiation in cyclohexane have been found to give competing radical and ionic photo-behaviour. The principal photoprocess is homolytic β-cleavage of the carbon–halogen bond to afford radical products (**496**, **497**), accompanied by ionic products such as cyclohexenones (**498**) but in much lower proportions (equation 260)[564].

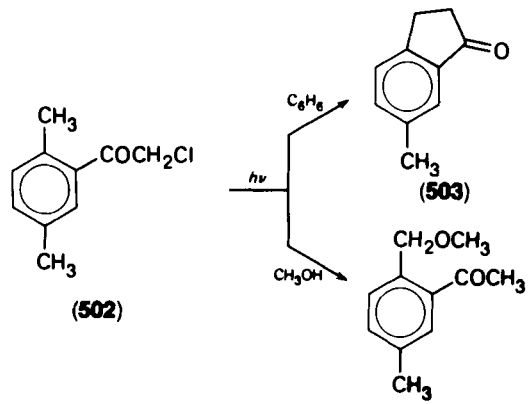


R = H, Me (**496**) (**497**) (**498**) (260)

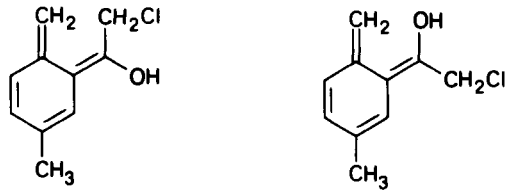
Favorskii-type ring contraction takes place on irradiation of bicyclic α-chloroketones in methanol. A mechanism involving photoionization of chloride, followed by ring contraction to acylium ions which are trapped by solvent, is suggested (equation 261)[565,566].



(**499**) (**500**) (**501**) (261)



(**502**) (**503**) (**504**) (262)



(**505**) (**506**)

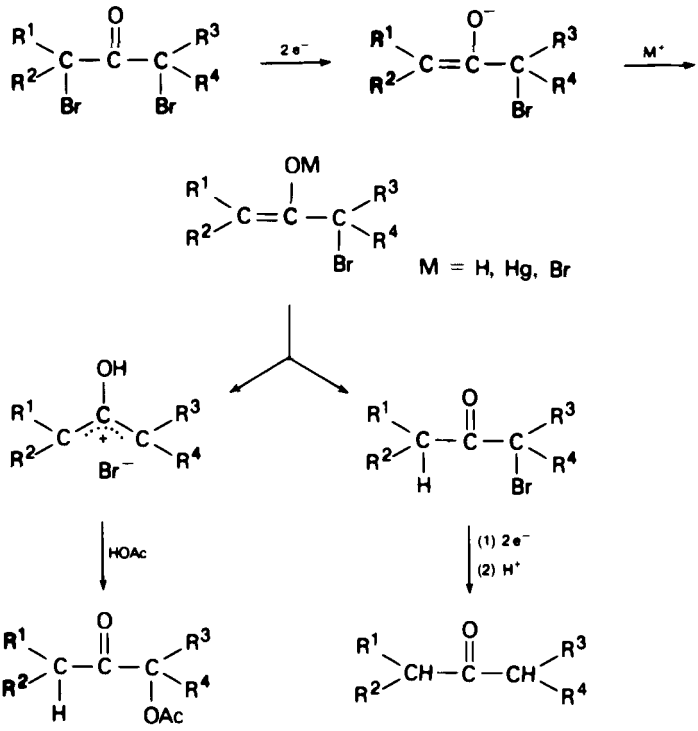
Irradiation of 2,5-dimethyl-α-chloroacetophenone (**502**) in benzene yields 6-methylindan-1-one (**503**) while in methanol the photosolvolysis product (**504**) is obtained. These transformations arise from photoenol intermediates (**505**, **506**) (equation 262)[567].

The behaviour of α-chloro aryl ketones without *ortho* methyl groups is quite different, involving reduction and rearrangement[568]. Irradiation of α,α,α-trichloroacetophenone in methanol affords the alcoholysis products methyl benzoate and methyl benzoylformate along with α,α-dichloroacetophenone. Formation of the benzoate is greatly favoured in the presence of oxygen whereas that of the benzoyl formate is favoured by sensitization (equation 263)[569].

$$ArCOCCl_3 \xrightarrow[CH_3OH]{h\nu} ArCOOCH_3 + ArCOCOOCH_3 + ArCOCHCl_2 \qquad (263)$$

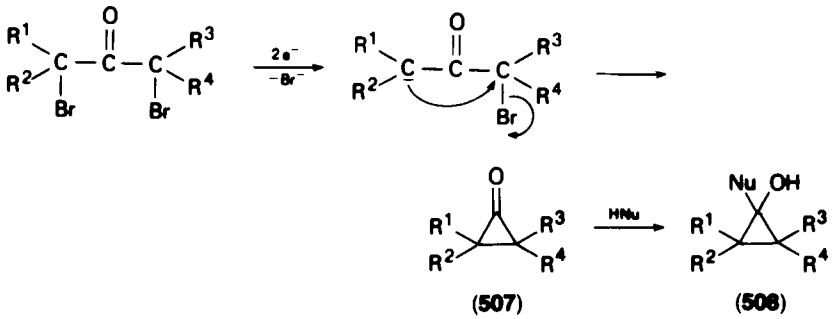
6. *Electrochemistry of α-haloketones*

Electrochemical reduction of α,α′-dibromoketones in acetic acid affords a mixture of the parent ketones and α-acetoxy ketones via an enol allylic bromide intermediate. The same results are obtained when the reduction is carried out by ultrasonically dispersed mercury (equation 264)[570,571].



(264)

Electroreduction of α,α′-dihaloketones to cyclopropanones (**507**) (isolated as the hemiacetals or hemiacylals (**508**)) is accomplished with highly alkylated ketones (equation 265)[572].



(265)

(507) (508)

7. *Dehalogenation of α-haloketones*

Various reagents are able to effect dehalogenation of α-haloketones such as zinc in acetic acid[573], metal carbonyls $Mo(CO)_6$[574], $Fe(CO)_5$[575] and $HFe(CO)_5^-$[576], transition metals in low valency state[577], triphenylphosphine[578], pyridine followed by sodium dithionite[579], tri-*n*-butyltin hydride[580], lithium iodide–boron trifluoride[581], sodium iodide–amine–sulphur dioxide[582], cerium triodide[583], sodium iodide–chlorotrimethylsilane[584] and sodium iodide in aqueous acid–THF[585] (equation 266).

(266)

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The chemistry of α-haloketones, α-haloaldehydes and α-haloimines
Edited by Saul Patai & Zvi Rappoport

APPENDIX TO CHAPTER 1

Synthesis and reactivity of α-halogenated ketones

I. INTRODUCTION

This Appendix on the synthesis and reactivity of α-halogenated ketones covers the literature from early 1980 until the first half of 1986. Whereas in the original chapter the general procedures for the synthesis of α-haloketones and the various reaction pathways were described, the Appendix emphasizes the regioselective introduction of halogens by a variety of methods and the selective transformation of α-haloketones with various reagents.

Identical procedures and transformations which were described during the last 6 years and already treated earlier will not be mentioned unless a major breakthrough or application has been observed.

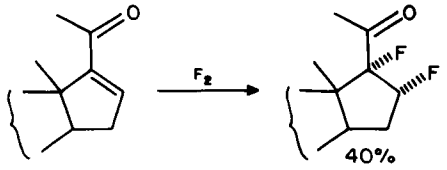
The presentation of this Appendix is identical with that in the original chapter and the reader will find valuable information by referring to each subdivision in the original chapter and Appendix successively. Structures, equations and references are numbered in continuation of those in the original chapter.

II. SYNTHESIS OF α-HALOGENATED KETONES

During the last 5 years, major progress has been achieved in the preparation of α-halogenated ketones. In this section the introduction of halogen atoms in a regiospecific manner with respect to the carbonyl functionality will be emphasized.

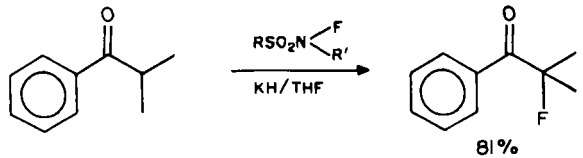
A. Synthesis of α-Fluoroketones

An excellent review by Rozen and Filler[587] describes the synthesis of α-fluorocarbonyl compounds, but most of the references concern procedures published before 1980. We shall mention only references dealing with new methods. Up to several years ago it was commonly stated that fluorination by fluorine is not a useful procedure for the synthesis of α-fluorocarbonyl compounds[588], but it has now been shown that direct fluorination can lead to α-fluoroketones. Addition of elemental fluorine to an enone system in a steroidal ring (**509**) furnished an α,β-difluoroketone (**510**) (equation 267)[589].

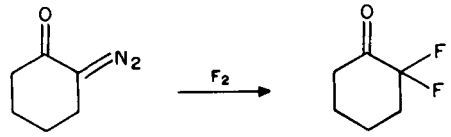


(509) (510) (267)

α-Monofluorination of ketones or enol acetates was carried out by treatment with *N*-fluoro-*N*-alkylsulphonamides in the presence of strong bases (equation 268)[590]. Geminal difluoroketones (**514** and **516**) were formed during the reaction of diazoketones (**513** and **515**) with fluorine, better than with CF_3OF (equation 269)[591].

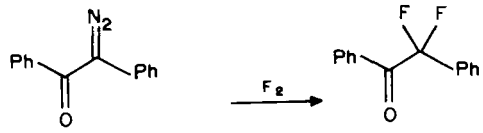


(511) (512) (268)



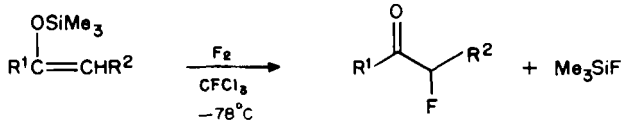
(513) (514)

(269)



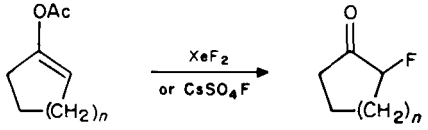
(515) (516)

High yields of α-fluoroketones were obtained when silyl enol ethers reacted with dilute F_2 (5%) in N_2 at − 78 °C in Freon 11. This direct fluorination avoids the use of toxic reagents and by-products (equation 270)[592].



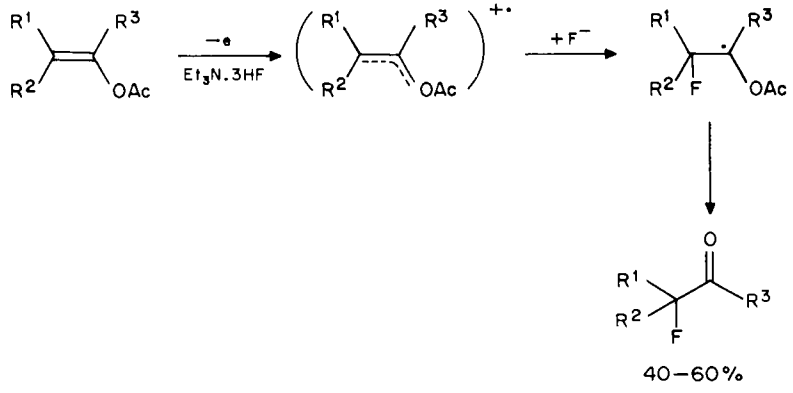
(270)

Enol acetates are transformed into α-fluoroketones by the action of xenon difluoride[593] or caesium fluoroxysulphate (equation 271)[594,595].

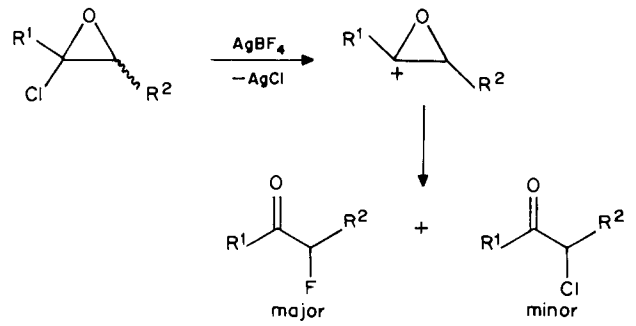


(271)

In the anodic oxidation of enol acetates, $Et_3N.3HF$ served as both the fluorinating agent and the supporting electrolyte (equation 272)[596]. Depending on the structure of the enol acetate, α-acetoxyketones were formed as side products. Halogen exchange reactions of α-haloketones is feasible using potassium fluoride in the presence of a crown ether and tetraalkylammonium fluorides[596,597] or tertiary amine tris(hydrofluorides)[598]. Silver tetrafluoroborate can also be utilized as a fluorinating agent in ring-opening reactions of α-chlorooxiranes[599,600] and α-fluorooxiranes (e.g. **517**) (equations 273 and 274)[601].



(272)



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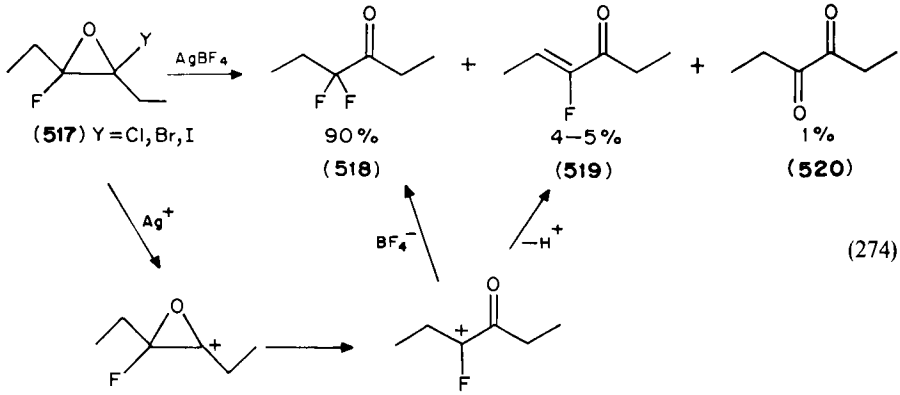
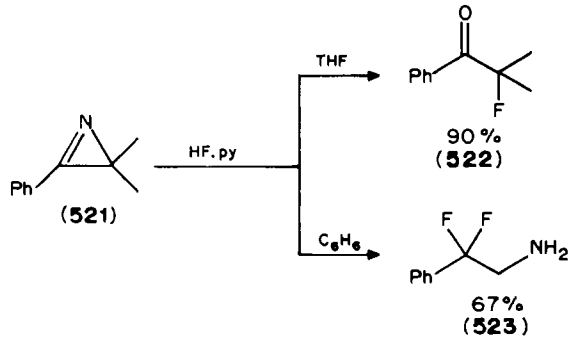
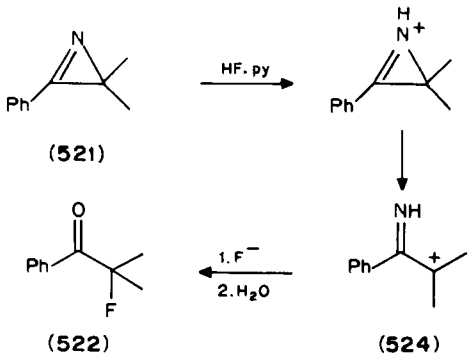


(274)

Ring opening of azirines (**521**) with Olah's reagent (HF–pyridine) resulted in the formation of α-fluoroketones (**522**) in THF, whereas in benzene β,β-difluoroamines (**523**) were produced (equation 275)[602,603]. The reaction involved the formation of α-imidoylcarbenium ions (**524**) followed by reaction with fluoride and hydrolysis (equation 276).

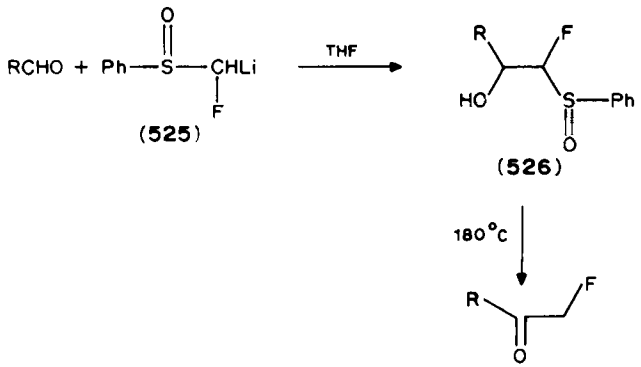


(275)



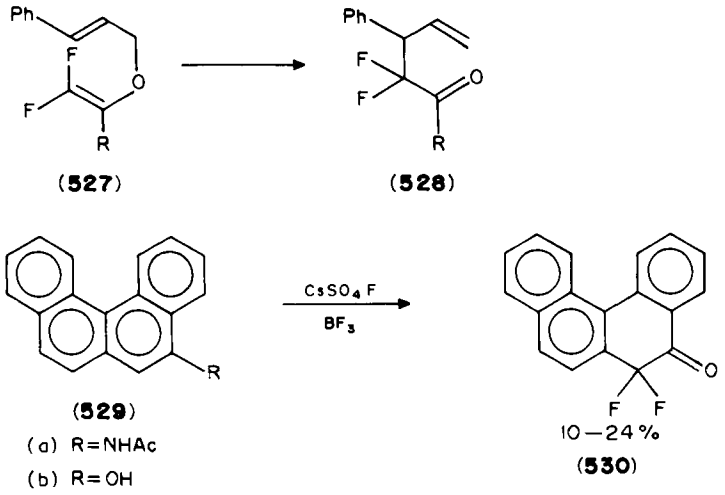
(276)

Fluoromethyl ketones are formed by the condensation of aldehydes with lithiofluoromethyl phenyl sulphoxide (**525**) followed by pyrolysis of the generated β-hydroxy-α-fluoroalkyl phenyl sulphoxides (**526**) (equation 277)[604].



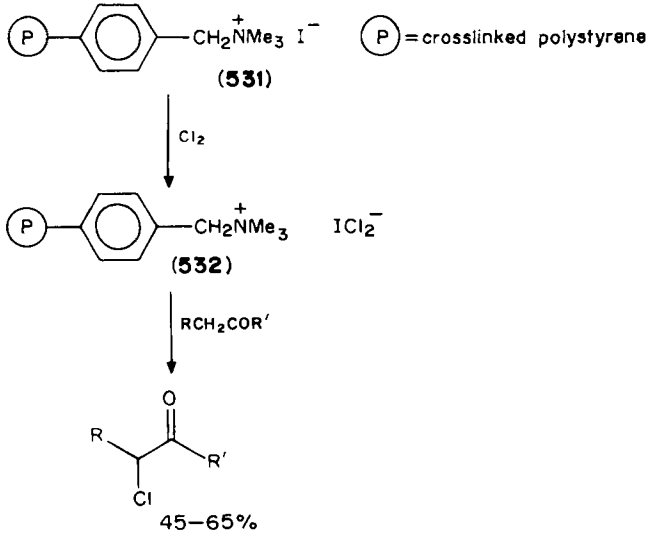
(277)

α,α-Difluoroketones were synthesized via Claisen rearrangement of substrates (**527**) containing fluorine atoms[605] and by fluorination of activated aromatic systems (**529**) with caesium fluoroxysulphate (equation 278)[973].



B. Synthesis of α-Chloroketones

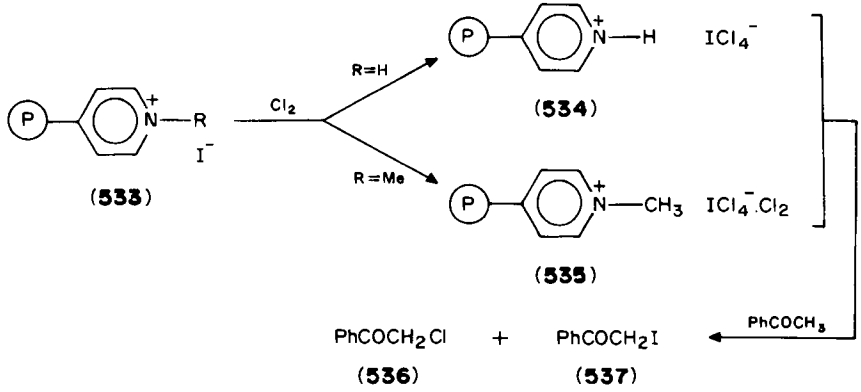
New developments are worth mentioning, especially in the field of the regiospecific chlorination. Chlorination of ketones by means of polymer-supported chlorine has become a routine procedure. The macroreticular anion-exchange resin Amberlyst A-26 (**531**) in the iodide form reacts with chlorine giving **532**, probably carrying ICl_2^- counter ions. This proved to be efficient in the chlorination of carbonyl compounds (equation 279)[606].



(279)

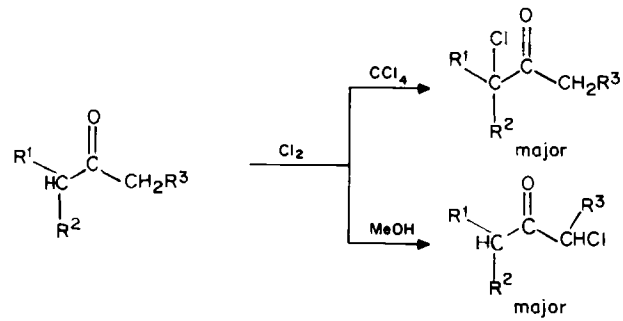
A crosslinked polymer (**533**) of styrene and 4-vinylpyridine was reacted with hydrogen iodide to give a polymer containing pyridinium iodide residues, which on reaction with chlorine gave a polymer containing pyridinium tetrachloroiodate residues (**534**). In a

similar manner using methyl iodide, polymers containing *N*-methylpyridinium tetrachloroiodide residues (**535**) were formed. Both reagents reacted with acetophenone, thus forming 2-chloro- (**536**) and 2-iodo-1-phenylethanone (**537**) in ratios depending on the reagent used and the reaction time (equation 280)[607].



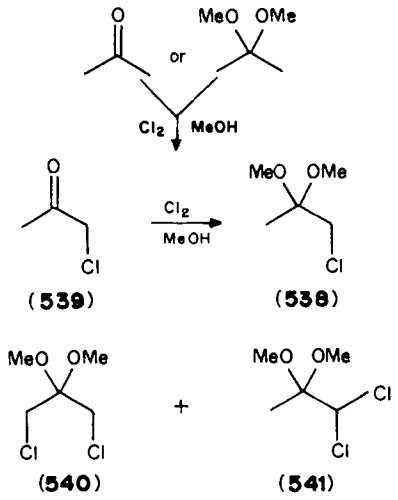
(280)

Regiospecific chlorination of aliphatic ketones in methanol has been examined in detail. The product distributions in methanol differ substantially from those obtained in CCl_4 (equation 281)[608]. In methanol addition of chlorine to the least substituted carbon α to the carbonyl group is favoured. The effect is especially pronounced in an α-carbon bearing two substituents as illustrated in Table 1.



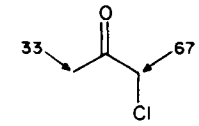
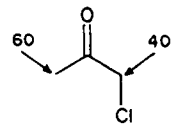
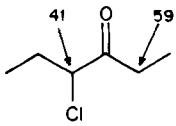
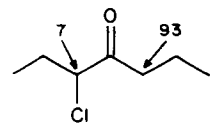
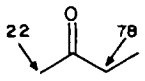
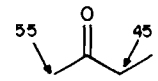
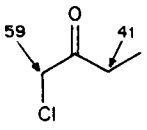
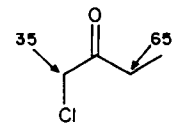
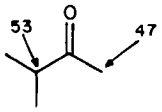
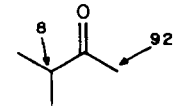
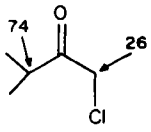
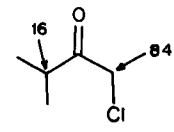
(281)

Chlorination of acetone was also investigated in detail (equation 282). Addition of slightly more than one equivalent of chlorine in methanol gave chloroacetone dimethylacetal (**538**) as the major product. Under anhydrous conditions, acetone chlorination in methanol yielded a 60:40 mixture of 1,3- (**540**) and 1,1-dichloroacetone dimethyl acetals (**541**) together with small amounts of dichloroketones. In acetic acid or carbon tetrachloride a 67:33 mixture of dichloroacetones together with minor amounts of other products was obtained. In ethanol similar results were obtained but chlorination in 2-propanol resulted in oxidation of the solvent. In ethylene glycol the cyclic acetal of chloroacetone was obtained. In water–methanol as solvent 1,1-dichloroacetone was the major product and in 1:1 methanol–DMF a mixture of 1,1-dichloroacetone (55%), 1,1,1-trichloroacetone (5%) and 1,1- (18%) and 1,3-dichloroacetone dimethyl acetal (22%) was

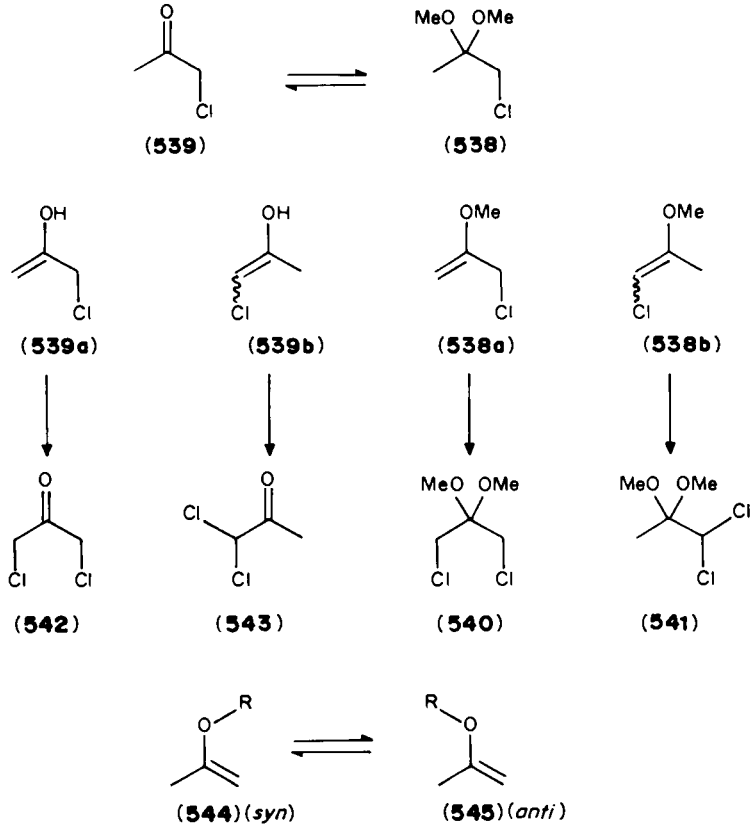


(282)

Table 1. Distribution (%) of the position of chlorine substitution on chlorination of ketones with chlorine

CCl_4 solvent	MeOH solvent
	
	
	
	
	
	

formed. The change in the regiospecificity was a result of a change in the species undergoing chlorination (equation 283). The distribution of products in an apolar solvent depends on the formation of enols (**539a** and **539b**). In methanol the isomer distribution is a function of the amount of enol ethers (**538a** and **538b**) formed. The amount of each enol ether formed will reflect the relative stabilities of the various substrates. It might be expected that the more substituted enol ether would be more stable so that chlorination would proceed on the more substituted carbon, but, this is not the case, and the less substituted α-carbon is favoured in methanol. Stability of the enol ethers appears to be dependent on steric effects. The most stable configuration of enol ethers is assumed to be *syn* (**544**) in which the alkoxy group is coplanar to and eclipsed with the double bond. It is favoured over the *anti* configuration (**545**). The *syn* relationship between the alkyl group on oxygen and the double bond in **544** increases the strain as substitution on the α-carbon increases. During chlorinations in methanol the formation of tetrasubstituted enol ethers is avoided and addition at a carbon having two substituents is not favoured.



(283)

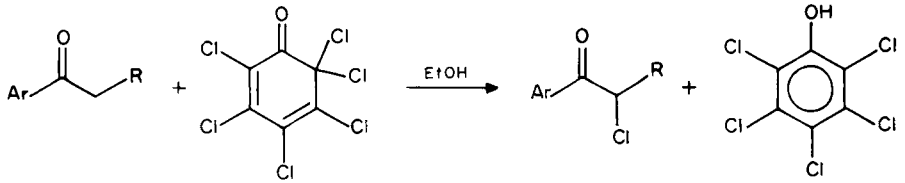
In all chlorinations a small but significant amount of chlorinated products corresponding to the formation of the more sterically hindered enol ethers is also present. Hence, steric considerations are of importance but may not be the only factors determining product distribution. Although chlorination of the enol is a minor competing pathway, it can always take place if the formation of an enol ether is too difficult.

A recent kinetic study of the hydrogen chloride-catalysed chlorination of cyclopen-

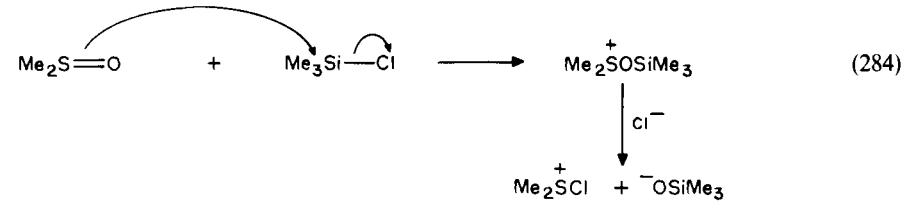
tanone and cyclohexanone turned out to be more complicated than expected. This is mainly due to the fact that the substrate and product themselves also act as basic catalysts and to the self-association of the ketones in carbon tetrachloride[979,980].

Selective α-chlorination of alkyl aryl ketones can be performed using hexachlorocyclohexa-2,4-dienone (**546**), while the use of sulphuryl chloride often resulted in chlorination of activated aromatic rings (equation 284)[609]. The selectivity of this reagent is based on donor–acceptor and hydrogen-bonding interactions between the reagent and substrate. The enolic form of the alkyl aryl ketones is capable of a donor–acceptor interaction with this reagent.

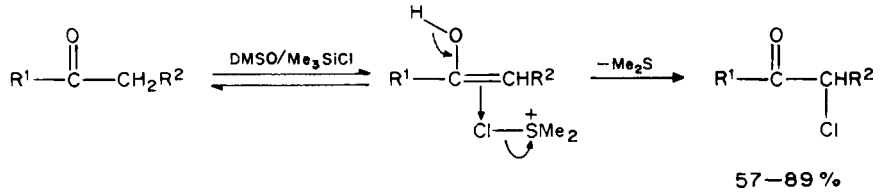
The trimethylchlorosilane–dimethyl sulphoxide system is an efficient reagent for smooth chlorination of aliphatic ketones on the more substituted α-carbon atom. Phenyl alkyl ketones are poorly reactive (equation 284)[981].



(**546**)



(284)

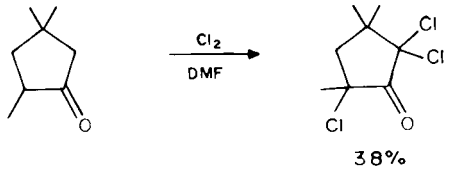


57–89%

Polychlorocycloalkanones can be conveniently synthesized by chlorination with chlorine in DMF. Similarly, cycloalkenones and cyclohexanediols can be chlorinated by this method (equation 285)[610–615].

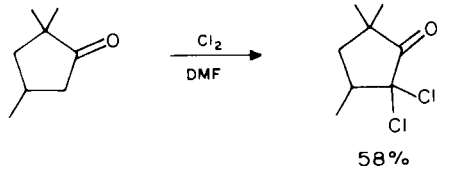
α-Hydroxyketones were chlorinated preferentially at the hydroxy position by application of $(PhO)_3PCl_2$[616].

Inorganic chlorides, e.g. KCl, NaCl, NH_4Cl, $AlCl_3$, $CaCl_2$ and LiCl, were employed as sources of Cl^- ions in the α-chlorination of aryl ketones in the presence of manganese(III) acetate[617,618]. By this procedure 2-arylchroman-4-ones, 1-phenylpropan-1-one, 1,2-diarylethanones and α-tetralone yielded α,α-dichloro derivatives in good yields. 2,2,2-Trichloroacetophenones were obtained from 2,2-dichloroacetophenones, but in the absence of LiCl, 2,2-dichloroacetophenones gave 1,4-diaryl-2,2,3,3-tetrachlorobutane-1,4-diones (**549**). The formation of the dimeric products (**549**, **550**) suggests a radical nature of the oxidation of aryl ketones with $Mn(OAc)_3$/LiCl (equation 286).



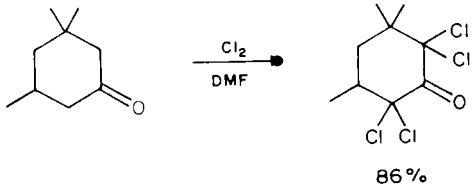
38%

Ref. 610



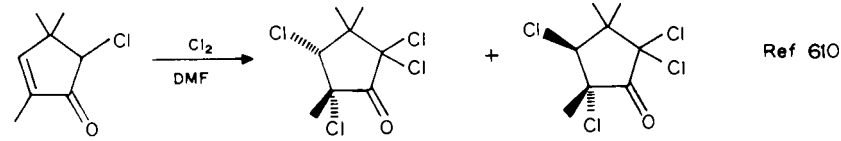
58%

Ref. 610

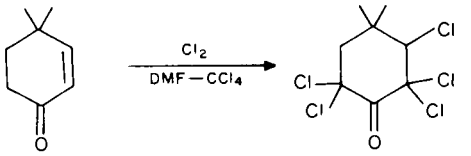


86%

Ref. 610

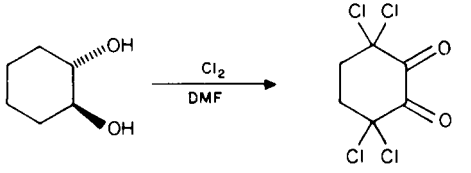


Ref 610



80—90%

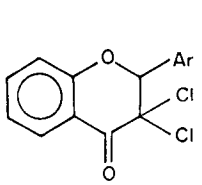
Refs 613,615



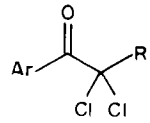
95%

Ref. 614

(285)

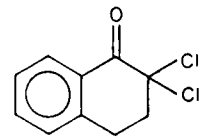


(547)

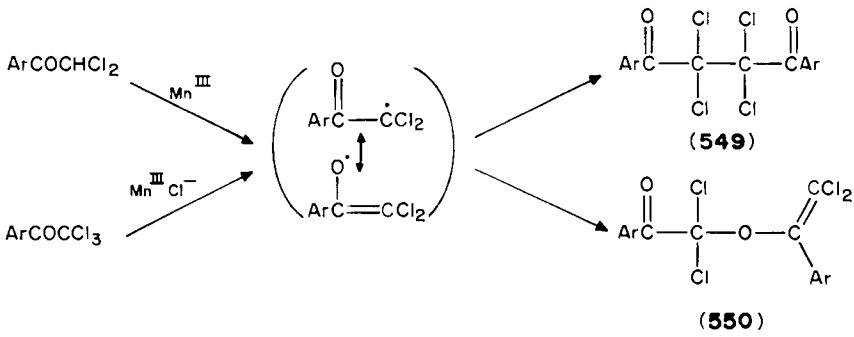


(180)

R = alkyl, aryl, Cl



(548)

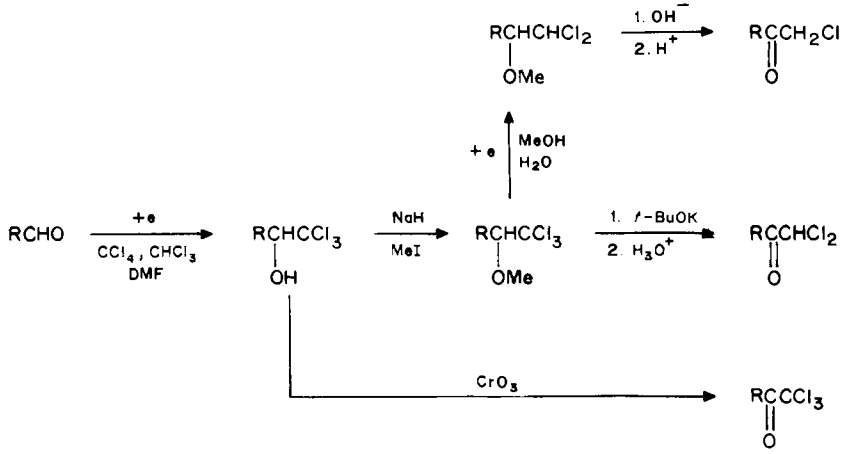


(549)

(550)

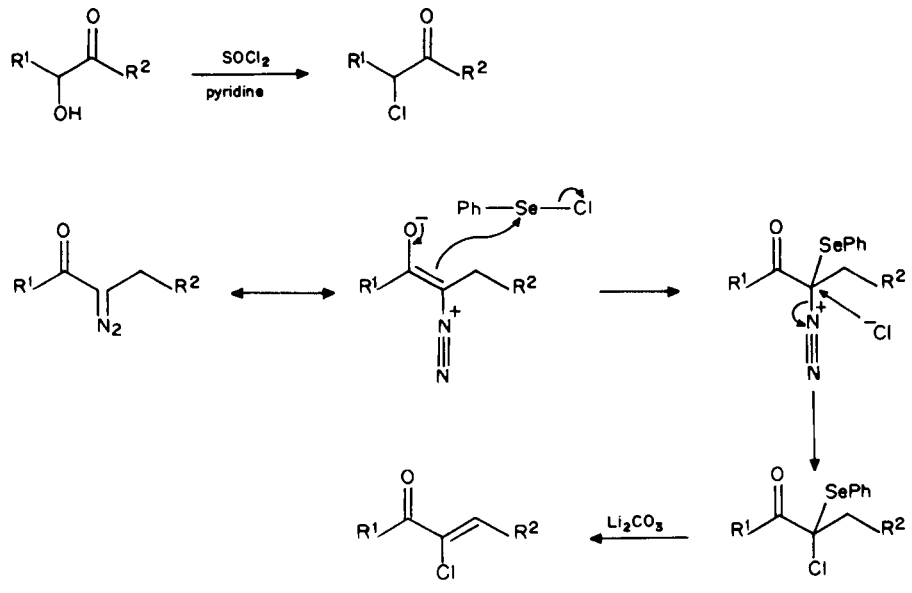
(286)

A variety of α-chloromethyl, α,α-dichloromethyl and α,α,α-trichloromethyl ketones were synthesized starting from aldehydes, utilizing cathodic reduction as the key reaction. The intermediates were trichloromethylcarbinols (equation 287)[619].



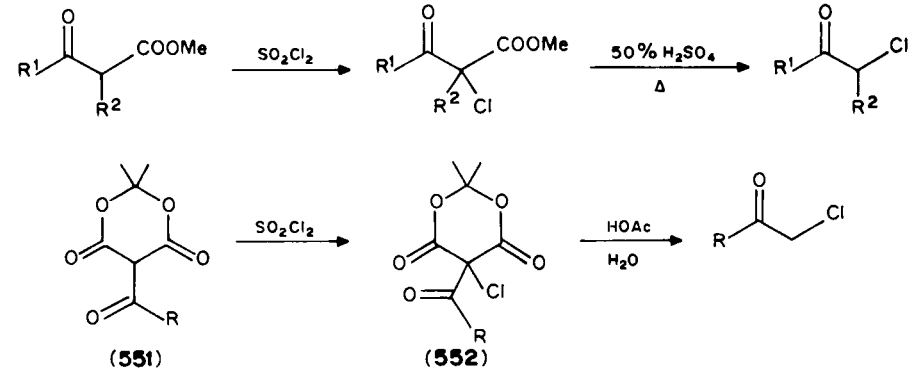
(287)

α-Functionalized ketones such as α-hydroxyketones[620] and α-diazoketones[621,622] were easily converted into α-monochloroketones using thionyl chloride and benzeneselenyl chloride, respectively (equation 288).



(288)

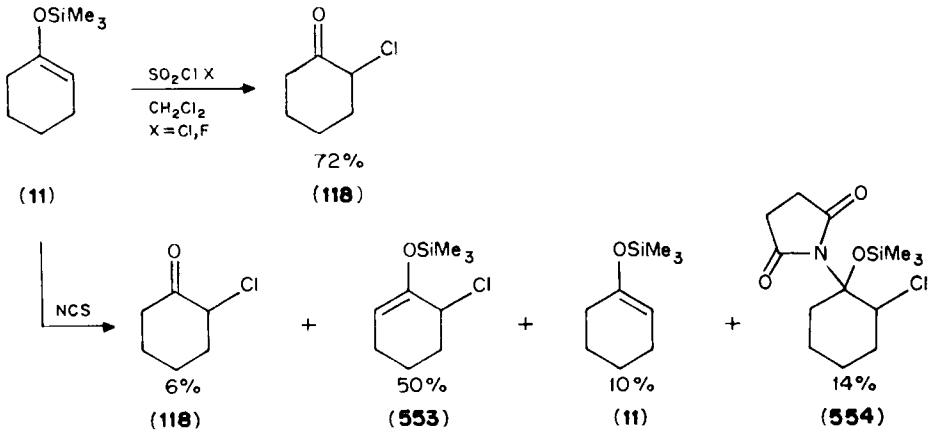
This method represents an easy route to α-chloro-α,β-unsaturated ketones on further treatment with lithium carbonate. A highly efficient regiospecific synthesis of α-chloroketones consisted in the chlorination of β-keto esters with sulphuryl chloride followed by decarboxylation with 50% sulphuric acid[623]. This is a very useful method for the synthesis of α-chloromethyl ketones, which are otherwise difficult to obtain in large quantities[628]. 3-Chloroalkan-2-ones can also be synthesized in this way but not dichloromethyl ketones (equation 289). A similar preparation of 1-chloroalkan-2-ones is based on the chlorination of 2-acyl derivatives of Meldrum's acid (**551**) followed by acid hydrolysis (equation 289)[624].



(289)

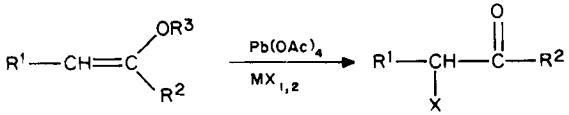
Synthesis of α-chloroketones from enol ethers is an established strategy, and especially the conversion of silyl enol ethers using sulphuryl chloride or sulphuryl chloride fluoride

has attracted much attention[625]. Reaction of silyl enol ethers with *N*-chlorosuccinimide gave disappointing results, however, in contrast with previously reported results (equation 290)[626].



(290)

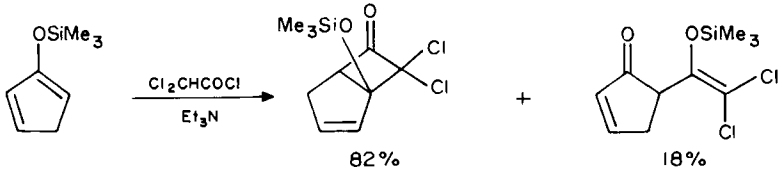
A more recent regiospecific synthesis of α-haloketones is the halogenation of enol ethers or enol esters using a lead(IV) acetate–metal halide reagent. These reagents supplement the use of reagents such as bromine, *N*-halosuccinimides, silver acetate–iodine and thallium(I) acetate–iodine for the conversion of enol ethers to α-haloketones (equation 291)[627].



(291)

R^3 = Me, Et, Ar, Me_3Si
M = Na, K, Ca, Zn
X = Cl, Br, I

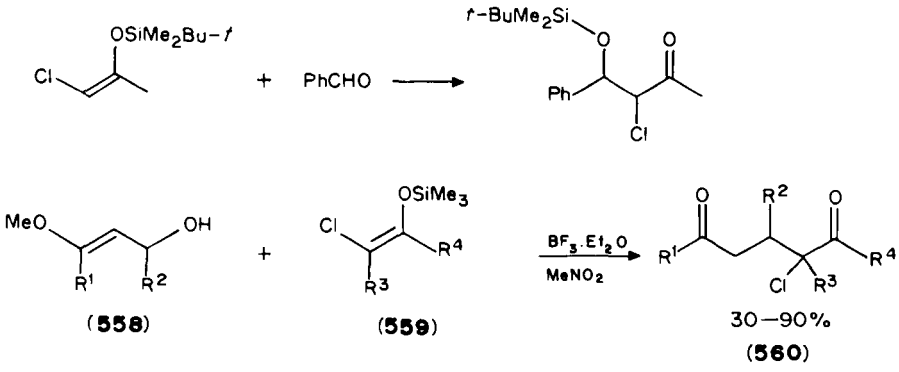
The silyl enol ether **555** is very reactive in ketene cycloadditions and with dichloroketene afforded an α,α-dichlorocyclobutanone (**556**) as the major product (equation 292)[628].



(292)

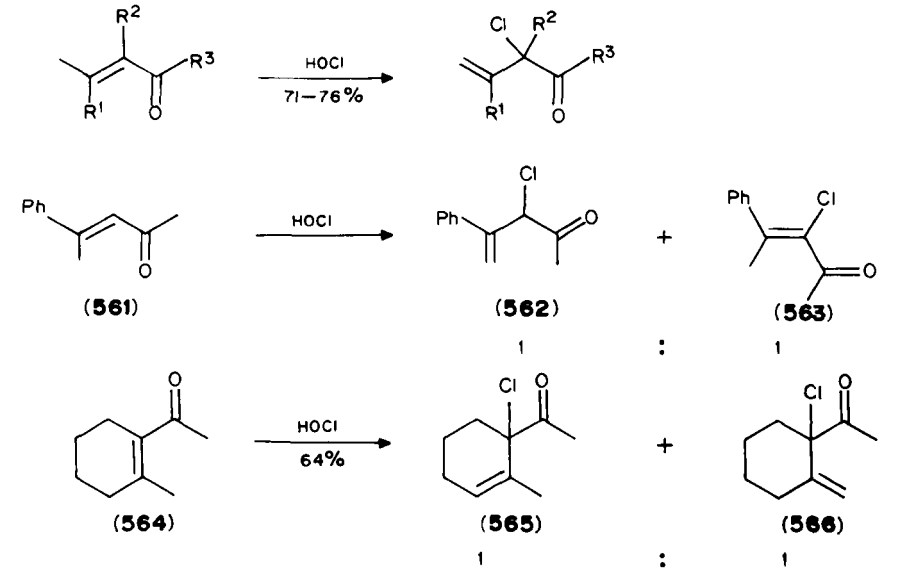
Haloenol silyl esters (**559**) were converted into α-chloroketone derivatives by a

Mukaiyama-type aldol condensation, via condensation of enol ethers in the presence of boron trifluoride etherate (equation 293)[629,630].



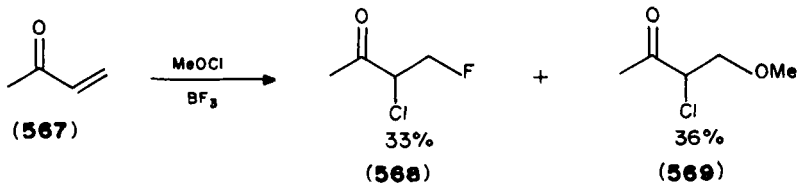
(293)

α-Chloro-β,γ-unsaturated ketones have been prepared from α,β-unsaturated ketones such as mesityl oxide, phorone and pulegone by the action of hypochlorous acid[631]. 4-Phenylpent-3-en-2-one (**561**) yielded a 1:1 mixture of the allylic chloride and the vinyl chloride. The reaction of conjugated ketones, wherein an addition–elimination process can lead to two different allylic chlorides, yielded mixtures of products with varying composition depending on the ring size and ring substituents (equation 294).



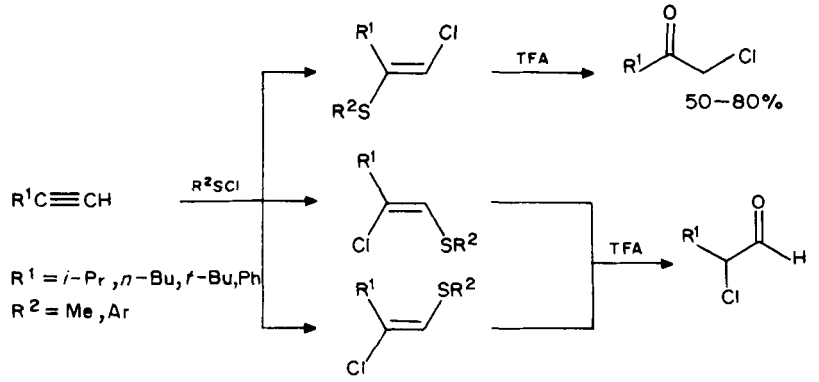
(294)

On the other hand, the reaction of methyl vinyl ketones (**567**) with methyl hypochlorite and boron trifluoride provided a mixture of 4-fluoro- (**568**) and 4-methoxy-3-chloro-2-butanones (**569**) (equation 295)[632].



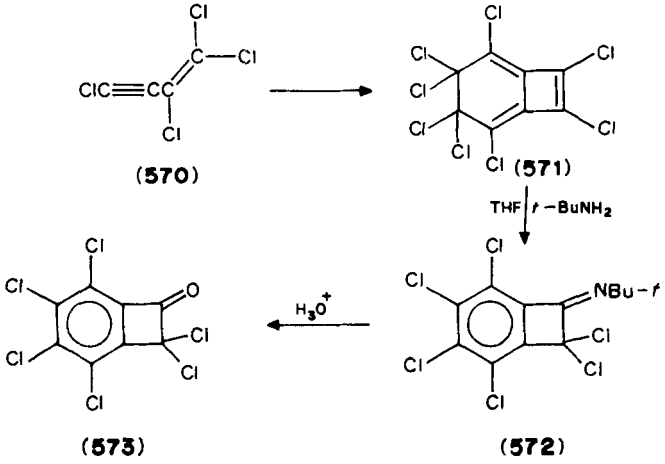
(295)

Hydrolysis of chlorinated enol thioethers, prepared by addition of sulphenyl chlorides to alkynes, gave rise to α-chloroketones. The addition can occur in an anti-Markownikov (AM) or a Markownikov (M) fashion according to the reaction conditions. The hydrolysis of the AM products afforded α-chloroketones whereas the M products were converted into α-chloroaldehydes (equation 296)[633,634].



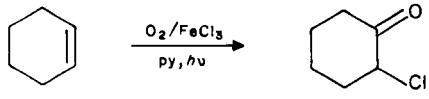
(296)

A specific synthesis of an α,α-dichlorocyclobutanone (**573**) has been performed by hydrolysis of a ketimine (**572**), which was prepared via dimerization of perchlorobutenyne (**570**) to **571** and reaction with *tert*-butylamine (equation 297)[635].



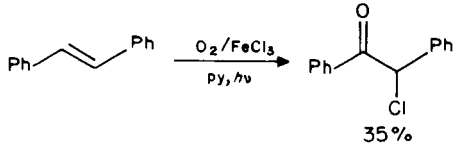
(297)

A variety of methods have been developed for the synthesis of chloroketones from olefins. Photooxidation in pyridine in the presence of iron(III) chloride converted mono- and disubstituted olefins into α-chloroketones, while tri- and tetrasubstituted olefins gave dichloroketones with C—C bond cleavage (equation 298)[636,637].



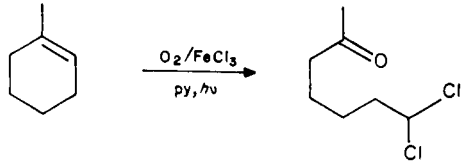
54%

(118)



35%

(574) (298)



30%

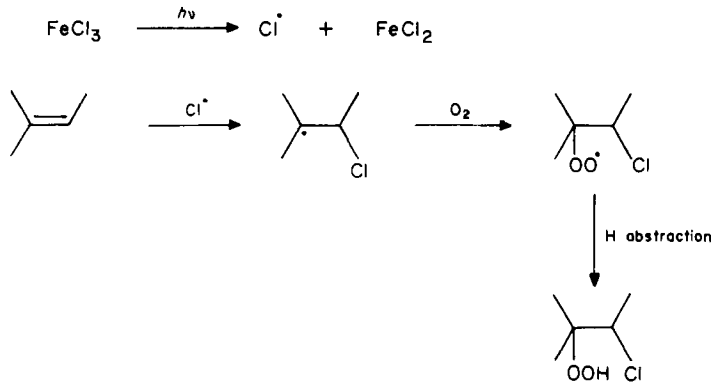
(575)

The mechanism involved the formation of a chlorine atom by the photolysis of $FeCl_3$, its addition to the less substituted carbon atom of the double bond, combination of the radical thus formed with molecular oxygen and hydrogen abstraction from the solvent to produce the β-chlorohydroperoxide. The secondary hydroperoxides from mono- or disubstituted olefins gave α-chloroketones by dehydration (type A), while the tertiary hydroperoxides from tri- and tetrasubstituted olefins gave C—C bond cleavage as the main pathway (type B) (equation 299). Another procedure for converting chlorinated olefins consisted in chlorination with chlorine or calcium hypochlorite in the presence of sodium hydrogen carbonate[638,639] or chlorination in DMF followed by hydrolysis (equation 300)[640].

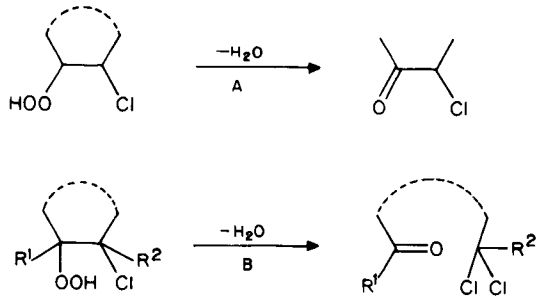
[2 + 2] Cycloaddition of monohalo- and dihaloketenes with alkenes and dienes yielding mono- and dichloro functionalized cyclobutanones (**582**, **583**) with high regioselectivity has been widely used, as illustrated by the equation 301[628,641-645]. The olefin-dichloroketene [2 + 2] cycloaddition can be accelerated by ultrasonic irradiation. Short reaction times (20–60 min), high yields (70–90%) and the use of ordinary zinc instead of activated zinc (Zn–Cu couple) are significant advantages[646].

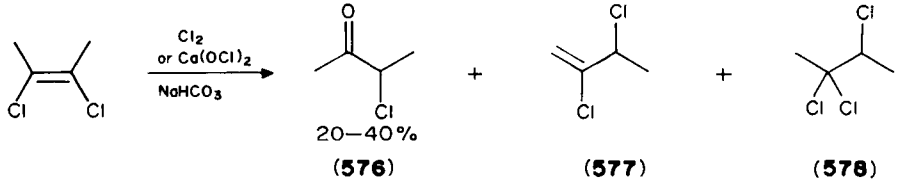
The ring opening or isomerization of 2-chlorooxiranes is an excellent pathway for the regiospecific synthesis of α-chloroketones. Rearrangement of the dichlorooxiranes (**584**) gave the isomeric α,α'-dichloroketones (equation 302)[600].

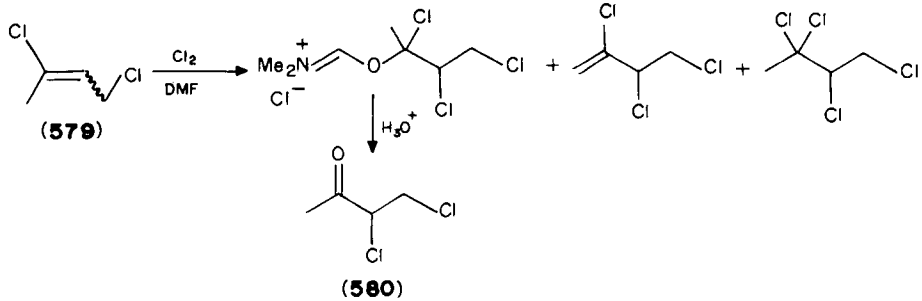
Ring opening of dichlorooxiranes with $AgBF_4$ can give the α-chloroketones via intermediate α-ketocarbenium ions, but the reaction products are strongly dependent on the substitution pattern of the oxirane (equation 303)[599,600,647].


FeCl3
hν
Cl˙ + FeCl2
Cl˙
O2
H abstraction
OOH Cl

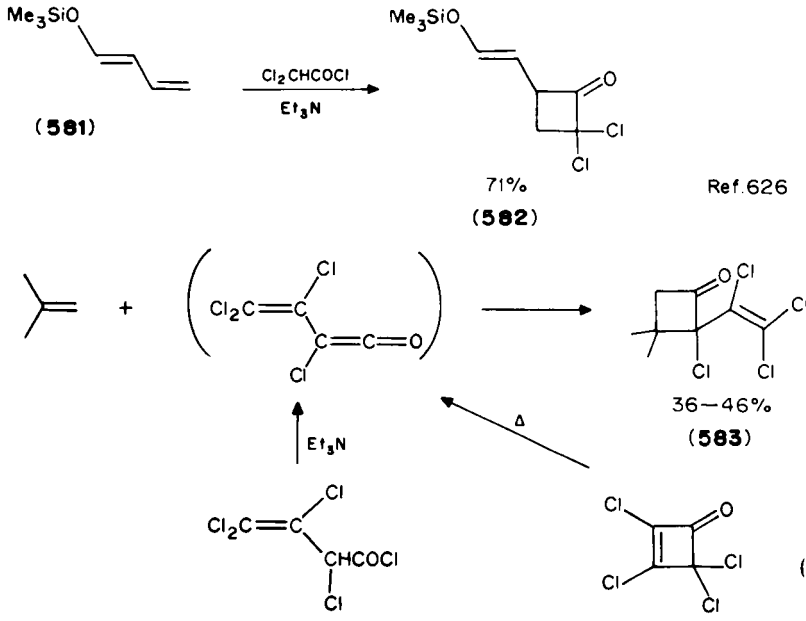
(299)


HOO Cl
−H2O
A
R1 R2
OOH Cl
−H2O
B
Cl Cl

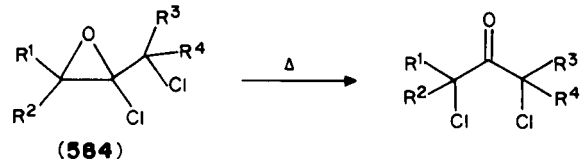

Cl2
or Ca(OCl)2
NaHCO3
20–40%
(576)
(577)
(578)


(579)
Cl2
DMF
Me2N
Cl−
H3O+
(580)

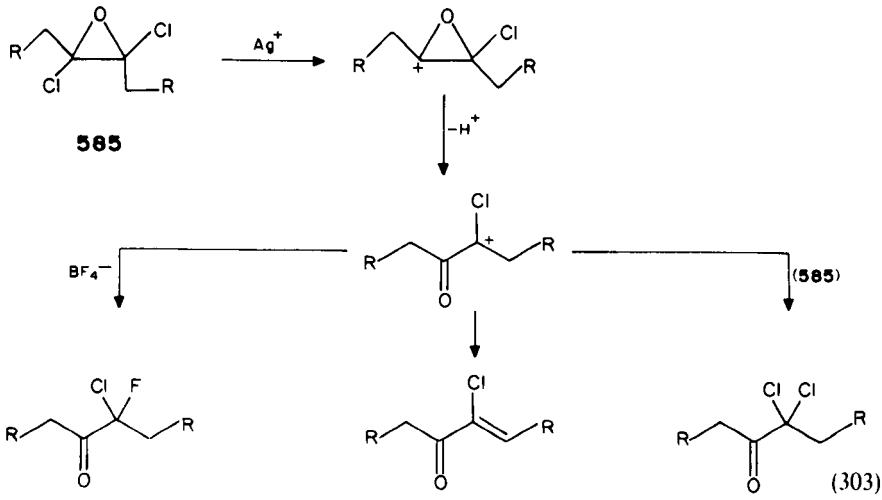
(300)


Me3SiO
Cl2CHCOCl
Et3N
(581)
Me3SiO
O
Cl
Cl
71%
(582)
Ref.626
Cl2C=C
Cl
C=C=O
Cl
O
Cl
Cl
Cl
36–46%
(583)
Et3N
Δ
Cl2C=C
CHCOCl
Cl
Cl
Cl
O
Cl
Cl
Cl

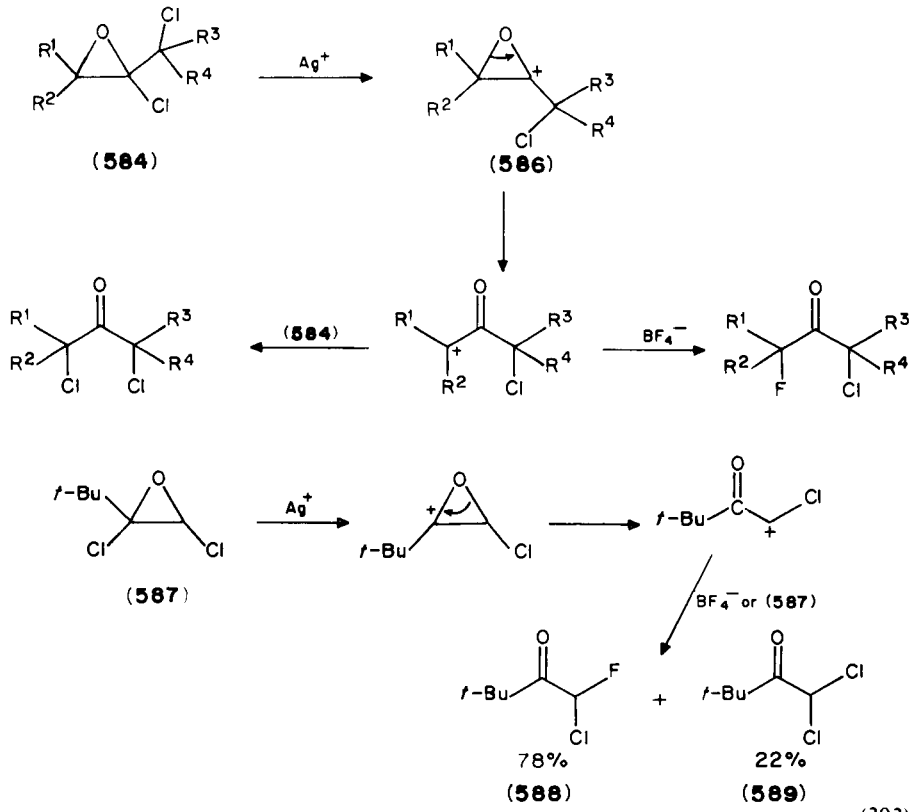
(301)


R1
R2
O
R3
R4
Cl
Cl
(584)
Δ
O
R1
R2
R3
R4
Cl
Cl

(302)

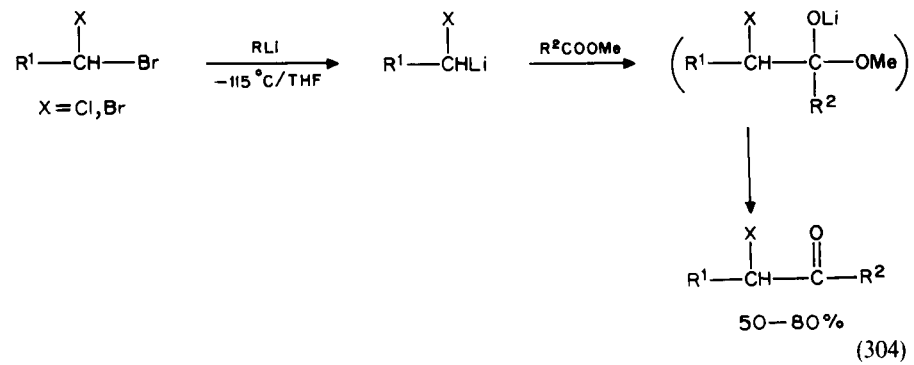

R
O
Cl
Cl
R
585
Ag+
R
O
Cl
+
R
-H+
Cl
R
O
+
BF4−
(585)
Cl F
R
R
O
Cl
R
R
O
Cl Cl
R
R
O

(303)



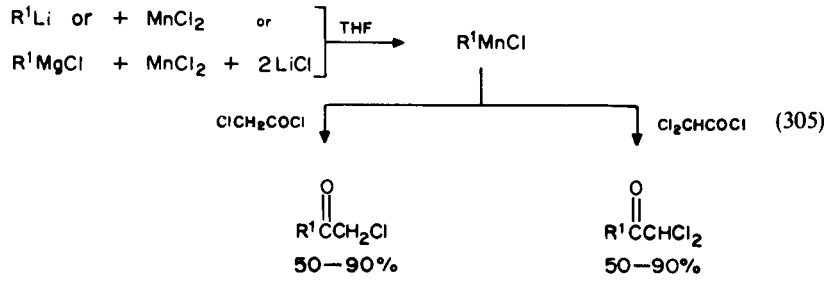
(303)

Regiospecific synthesis of α-haloketones has been performed by the condensation of α-haloalkyllithium reagents with esters followed by hydrolysis of the lithium salts of the halohydrins (equation 304)[648-651].



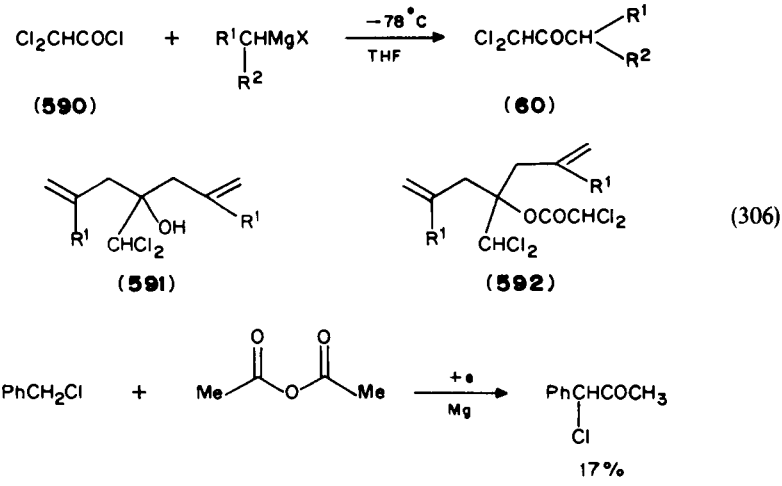
(304)

Acylation of organomanganese(II) chlorides with chloro- or dichloroacetyl chloride gave rise to chloromethyl and dichloromethyl ketones, respectively (equation 305)[652].



(305)

A facile synthesis of dichloromethyl ketones (**60**) is the reaction of dichloroacetyl chloride (**590**) with Grignard reagents (equation 306). With allyl- and methallylmagnesium chlorides the tertiary alcohols **591** and the dichloroacetyl derivatives **592** were obtained[654].



(306)

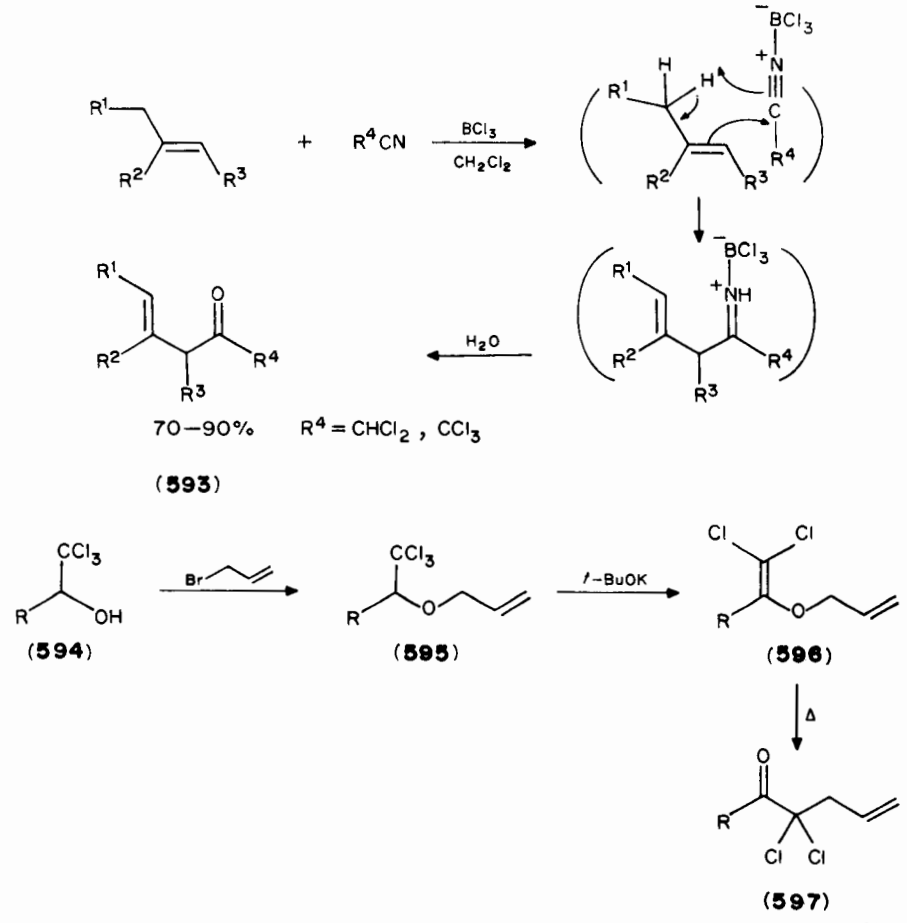
The electroreduction with a magnesium anode of benzyl chlorides in the presence of anhydrides afforded α-chloroketones (equation 306)[974].

Dichloro- and trichloromethyl ketones (**593**) have been prepared by the ene reaction of trisubstituted alkenes with electron-deficient nitriles in the presence of boron trichloride (equation 307)[653].

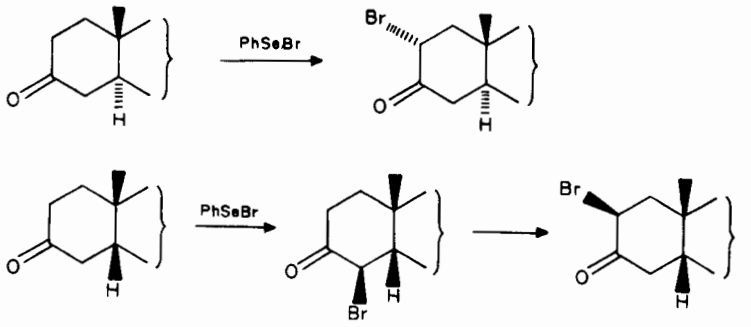
A general route to γ,δ-unsaturated α,α-dichloroketones (**597**) from allyl 2,2,2-trichloroethyl ethers (**595**) via the [3,3]sigmatropic rearrangement of intermediate 2,2-dichlorovinyl ethers (**596**) has been developed. The products can serve as effective synthons possessing three functional groups (equation 307)[655,656].

C. Synthesis of α-Bromoketones

The synthesis of α-bromoketones has been focused on the use of mild brominating agents in order to avoid the disadvantages of bromine and the many side-reactions due to its use. A novel reagent for α-monobromination of 3-keto steroids is benzeneselenenyl bromide. Whereas 3-keto 5α-steroids always gave the 2α-bromo compound, 3-keto-5β-steroids lead to the kinetically controlled 4β-bromo steroid, which isomerized to the thermodynamically stable 2β-bromo-3-keto steroid (equation 308)[975].



(307)

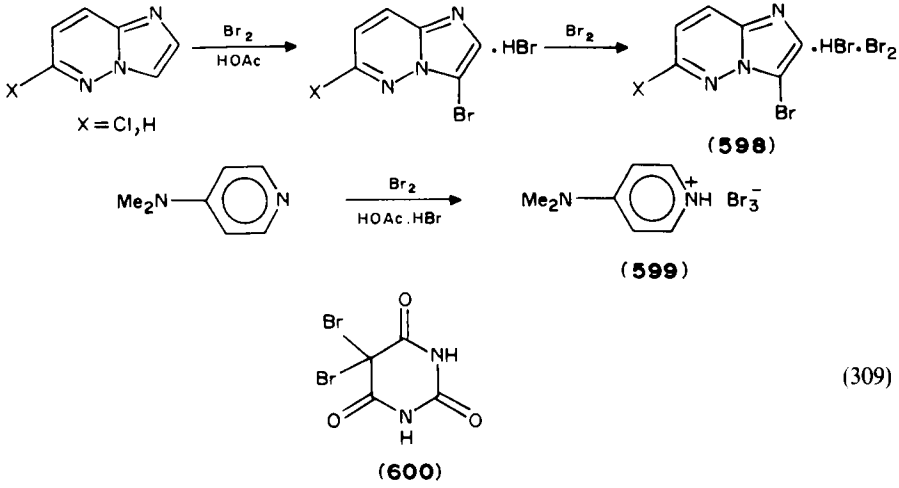


(308)

The use of polymer-supported bromine, such as poly-(4-vinylpyridine–styrene)bromine[657], and of bromine in the presence of crown ethers has been developed[658]

and the use of brominated complexes was stimulated owing to the mild reaction conditions, high yields and easy recovery of the brominating agent.

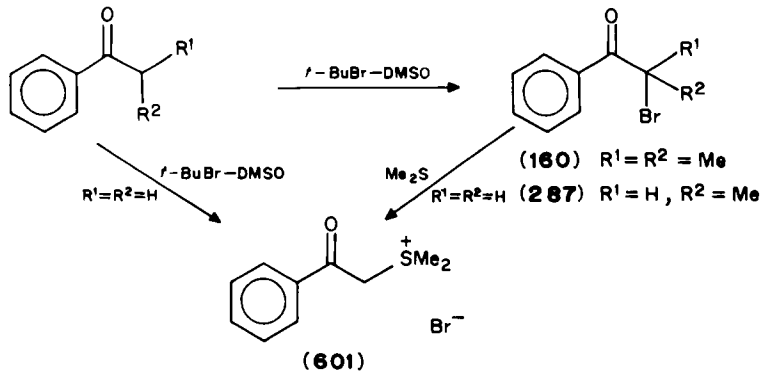
3-Bromoimidazo[1,2-*b*]pyridazine bromine and 3-bromo-6-chloroimidazo[1,2-*b*]pyridazine bromine (**598**, X = Cl) gave monobromoketones when used in equimolecular amounts (equation 309)[659].



(309)

Also 4-(dimethylamino)pyridinium bromide perbromide (**599**) (equation 309) gave nearly quantitative yields in the α-bromination of aromatic ketones[660], and 5,5-dibromobarbituric acid (**600**) was used in neutral medium to monobrominate saturated and unsaturated ketones[661].

tert-Butyl bromide–dimethyl sulphoxide has been used in the preparation of 2-bromo-1-phenylpropanone (**287**) and 2-bromo-1-phenyl-2-methylpropanone (**160**). With acetophenone, however, phenacyldimethylsulphonium bromide (**601**) was obtained directly (equation 310)[662,663].

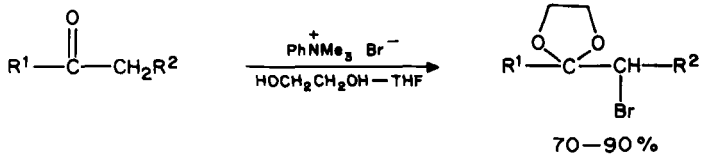


(310)

A similar reagent, trimethylbromosilane–dimethyl sulphoxide, introduced a bromine atom at the more substituted α-position of ketones[982].

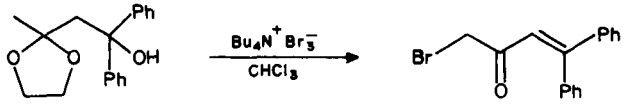
Regiospecific monobromination was also observed on treatment of ketones with hexabromocyclopentadiene. For example, butan-2-one was converted into 3-

bromobutan-2-one in 82% yield[664]. One-pot α-bromoacetalization of carbonyl compounds has been realized by reaction of ketones with 1–2 equivalents of phenyltrimethylammonium tribromide in THF–ethylene glycol (1:1) (equation 311)[665]. The α-bromoacetals are useful precursors to α,β-unsaturated ketones, particularly in cyclic systems where the dehydrobromination is complicated by side-reactions.



(311)

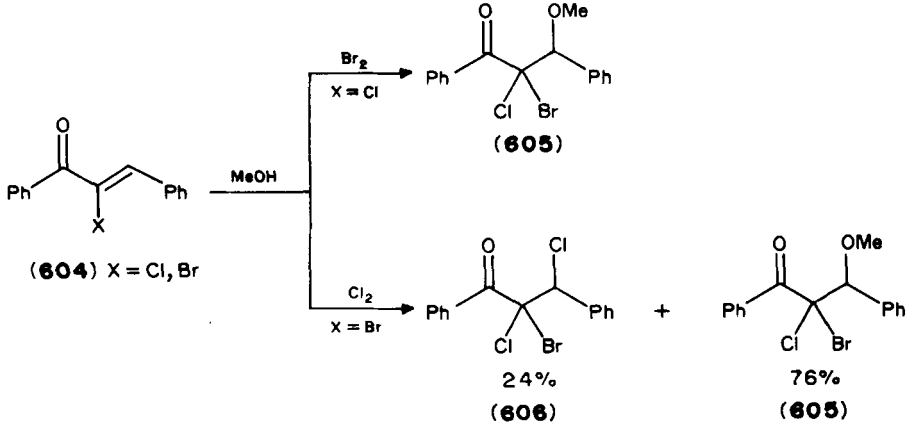
Tetrabutylammonium tribromide has been very useful for the selective α-substitution of acetals[666] and in a convenient one-pot synthesis of 1-bromo-4,4-diphenylbut-3-en-2-one (**603**) from 1,1-diphenyl-3-(ethylenedioxy)butan-1-ol (**602**) (equation 312)[667].



(**602**) (**603**) (312)

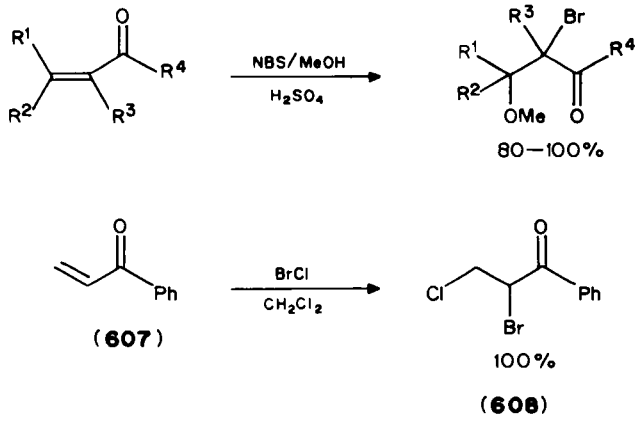
N-Bromosaccharin (NBSac) has been used in benzylic and α-carboxylic bromination[668]. This reagent is sometimes superior to NBS, e.g. in the preparation of α-phenylphenacyl bromide (91% versus 71% yield). However, bromination of several methyl vinyl and methyl aryl ketones gave lower yields than with NBS. The reaction requires visible or ultraviolet irradiation or the presence of a free radical initiator. However, a longer photostimulation could lead to dehydrobromination.

The addition of halogens to α,β-unsaturated ketones has been extensively studied. Bromination in methanol of (*E*)- and (*Z*)-2-chloro-1,3-diphenylpropenone (**604**) led exclusively to the solvent-incorporated adduct 2-bromo-2-chloro-3-methoxy-1,3-diphenylpropan-1-one (**605**). Chlorination of the 2-bromo analogue yielded a mixture of the 2-bromo-2,3-dichloro compound **606** and **605** (equation 313)[669].



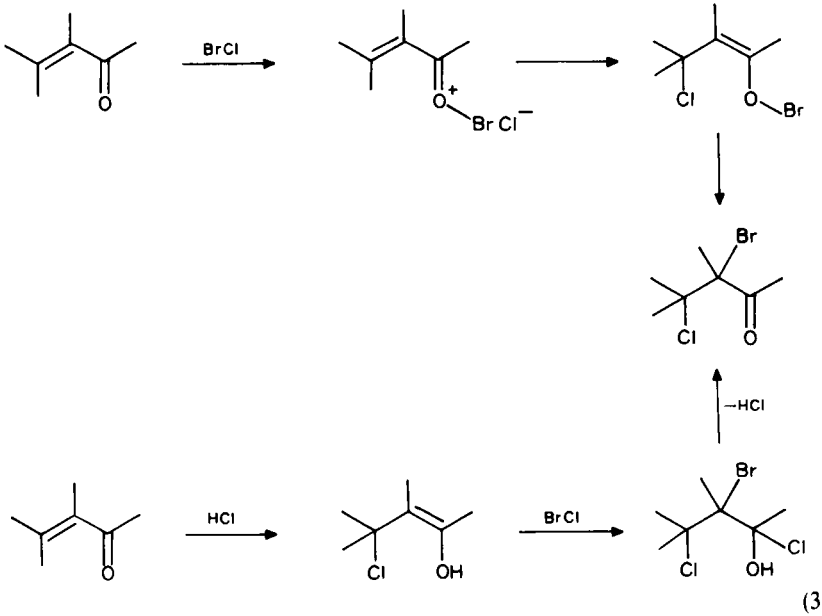
(**604**) X = Cl, Br (**605**) (**606**) (**605**) (313)

The acid-catalysed reaction of NBS in methanol with α,β-unsaturated ketones gave β-methoxy-α-bromoketones[670] whereas the reaction with BrCl furnished β-chloro-α-bromoketones (**608**) (equation 314)[671].



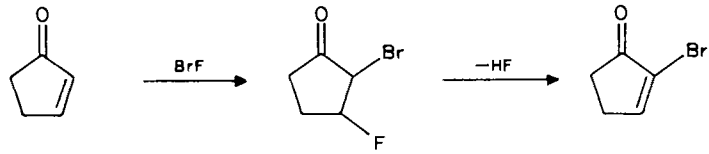
(**607**) (**608**) (314)

As the addition occurred regiospecifically, the mechanism cannot involve electrophilic attack of halogen on the C=C bond, and may involve either an initial attack on the oxygen or an initial addition of a trace of HCl to give a highly reactive enol (equation 315).



(315)

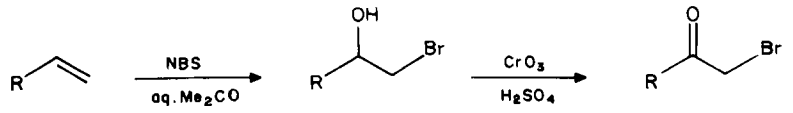
β-Fluoro-α-bromoketones (**610**) were formed when α,β-unsaturated ketones (**609**) were treated with BrF. However, an easy HF elimination can take place, eventually producing α-bromoenones (**611**) (equation 316)[672].



(316)

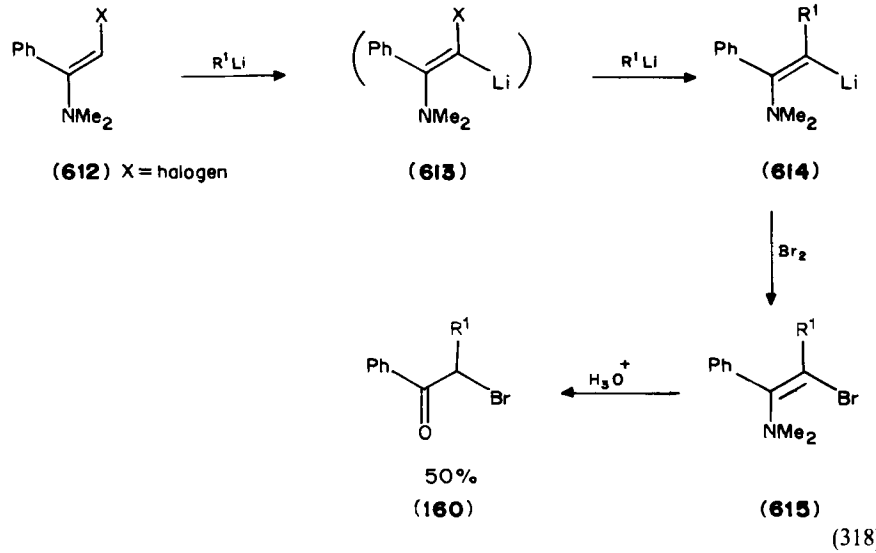
(609) (610) (611)

Other elegant procedures for the production of bromomethyl ketones have been established. The reaction of terminal olefins with NBS in aqueous acetone gave 1-bromoalkan-2-ols, which were subsequently oxidized (equation 317)[673].



(317)

β-Lithioenamines (**613**), prepared by the action of alkyllithium reagents on β-haloenamines (**612**) through deprotonation, were transformed into bromoketones (**160**) via alkylation, bromination and subsequent acidic hydrolysis (equation 318)[674].



(612) X = halogen (613) (614)

(615)

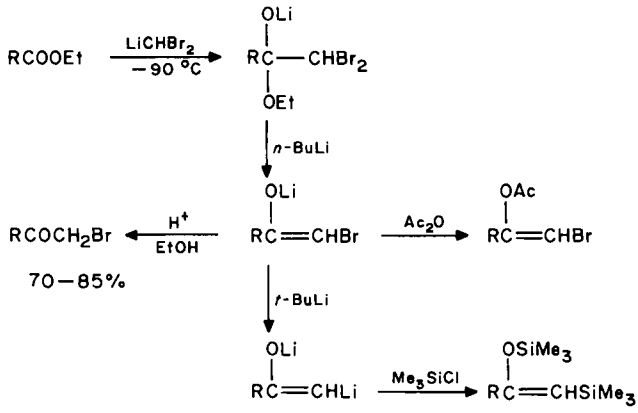
50%

(160)

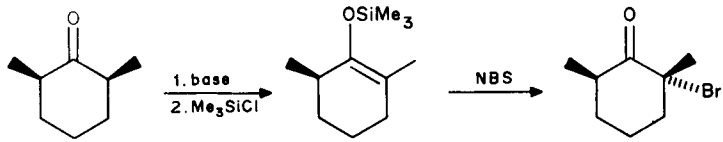
(318)

Bromomethyl ketone enolate anions, generated by the reaction of esters with (dibromomethyl)lithium followed by *n*-butyllithium, could be quenched with acid to afford bromomethyl ketones or with acetic anhydride to afford bromoenol acetates or treated with *tert*-butyllithium to produce α-keto dianions (equation 319)[651].

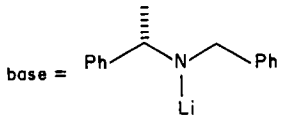
An excellent synthesis of chiral bromoketones has been developed via enantioselective deprotonation of symmetrically substituted ketones under kinetically controlled conditions using a strong hindered chiral base (equation 320)[976].



(319)

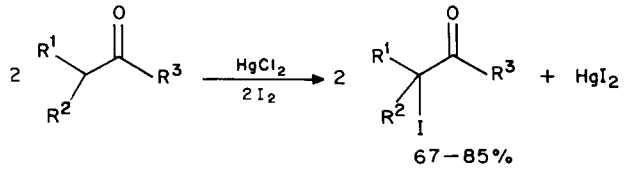


(320)



D. Synthesis of α-Iodoketones

A recent direct regiospecific synthesis of α-iodoketones involves a direct iodination of carbonyl compounds with mercury(II) chloride and iodine (equation 321)[675].

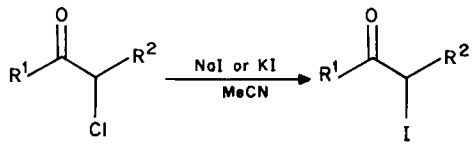


(321)

The reaction takes place under acidic conditions owing to the formation of hydrogen chloride. The iodination agent seems to be first $(HgICl_2)^-I^+$ and in a second step $(HgI_2Cl)^-I^+$ because the reaction is carried out using a 1:2 mercury(II) chloride to iodine molar ratio, the I^+ being the electrophilic agent. Unsymmetrical ketones give only the internal α-iodo derivatives, whereas cyclic ketones give the corresponding α-chloroketones in 100% yield.

The synthesis of cyclic α-iodoacetals was described for the first time in 1984[676].

α-Iodoketones were recently synthesized by treatment of α-chloro- or α-bromo-ketones with sodium iodide in acetonitrile (equation 322)[677].



(322)

E. Optically Active α-Haloketones

So far little information is available concerning the preparations and reactivity of optically active α-haloketones. Owing to the increasing interest in the asymmetric synthesis of natural products and pharmaceuticals, it can be expected that chiral α-haloketones will be valuable bifunctional intermediates in the synthesis of enantiomerically pure compounds.

Optical resolution of racemic α-haloketones is difficult because of their reactivity and the lack of resolving agents for carbonyl compounds. The synthesis of optically active α-haloketones has been carried out by halogenation of optically active ketones obtained by resolution of racemic compounds or from natural sources[989]. Direct asymmetric synthesis of 2-bromocycloalkanones involved bromination of cycloalkanone enamines of L-proline esters followed by hydrolysis (e.e. 15–31%)[990] and bromination of chiral enolates (equation 320). Optically active aryl 1-chloroethyl ketones have been prepared from optically pure (*R*)- and (*S*)-2-chloropropionyl chloride by Friedel–Crafts reaction or by Grignard reaction with the corresponding aromatic derivatives. A slight and variable loss of enantiomeric purity (< 15%) related to the starting acids has been observed[991,992]. Chiral aryl α-bromoalkyl ketones were prepared via bromination with bromine of enantiomerically pure acetals derived from alkyl aryl ketones and the dimethyl esters of (2*R*, 3*R*)- and (2*S*, 3*S*)-tartaric acid followed by hydrolysis, without racemization, by treatment with methanesulphonic acid in methanol[993]. These α-haloketones were easily transformed into optically active 2-arylalkanoic acids, which are highly efficient anti-inflammatory drugs[992,994]. One enantiomer (*S*) showed higher biological and pharmaceutical activity than the other.

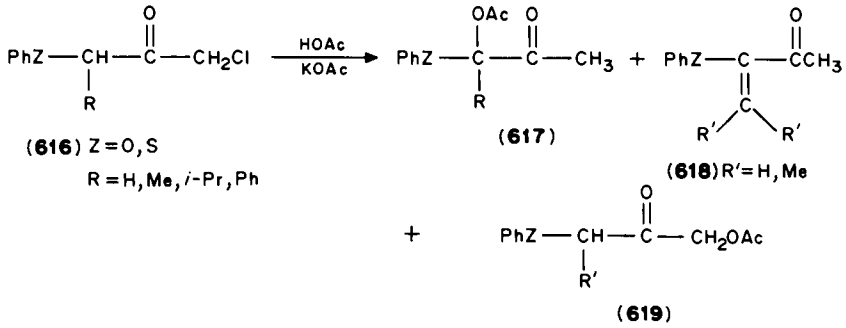
III. REACTIVITY OF α-HALOGENATED KETONES

A. Introduction

Further insight into the mechanisms of nucleophilic substitutions of α-haloketones has been gained in the acetolyses of α-phenoxy and α-thiophenoxy-α-chloro ketones[678] and 1-chloro-3-phenoxy-1-phenylthiopropan-2-ones[679]. The acetolysis of α'-arylthio- and α'-aryloxy-α-chloroketones (**616**) has been shown to proceed through the enolization–solvolysis mechanism, and the products arise from a normal substitution (**619**), cine substitution (**617**) and an elimination (**618**) (equation 323). The ratio of the solvolysis products **617** and **619** to **618** is largely dependent on the absence or presence of acetate ion.

The easier solvolysis of the thioethers can be ascribed to the more efficient participation by sulphur in the ionization of the enol allylic chlorides and the accompanying delocalization of the charge in the cationic species involved in the solvolysis.

The role played by the neighbouring heteroatom was further investigated with the α-chloroketones **620** and **624** (equations 324 and 325).

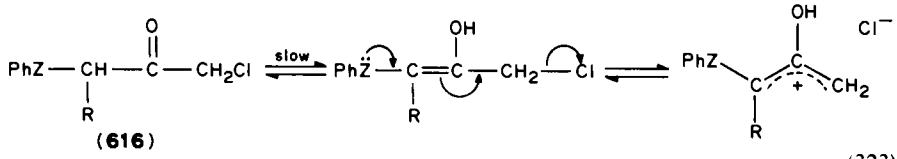


(616) Z = O, S
R = H, Me, *i*-Pr, Ph

(617)

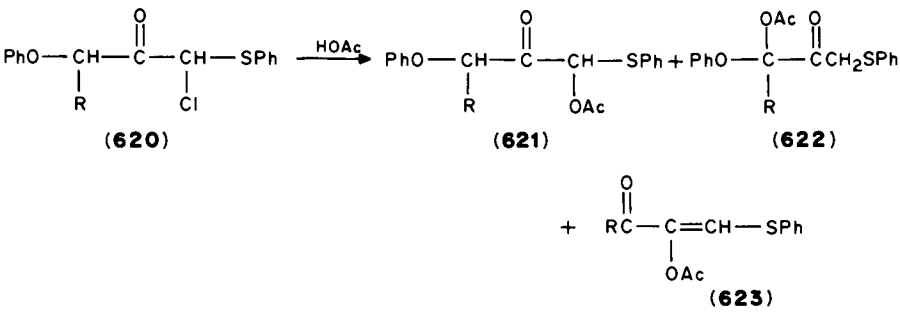
(618) R' = H, Me

(619)



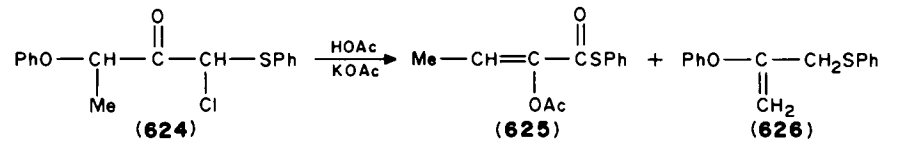
(616)

(323)



(620) (621) (622) (623)

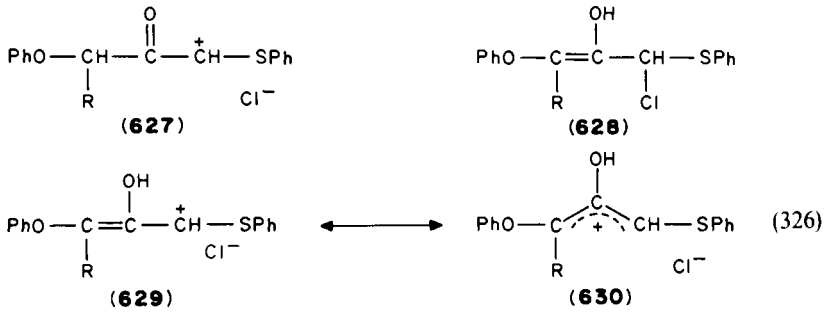
(324)



(624) (625) (626)

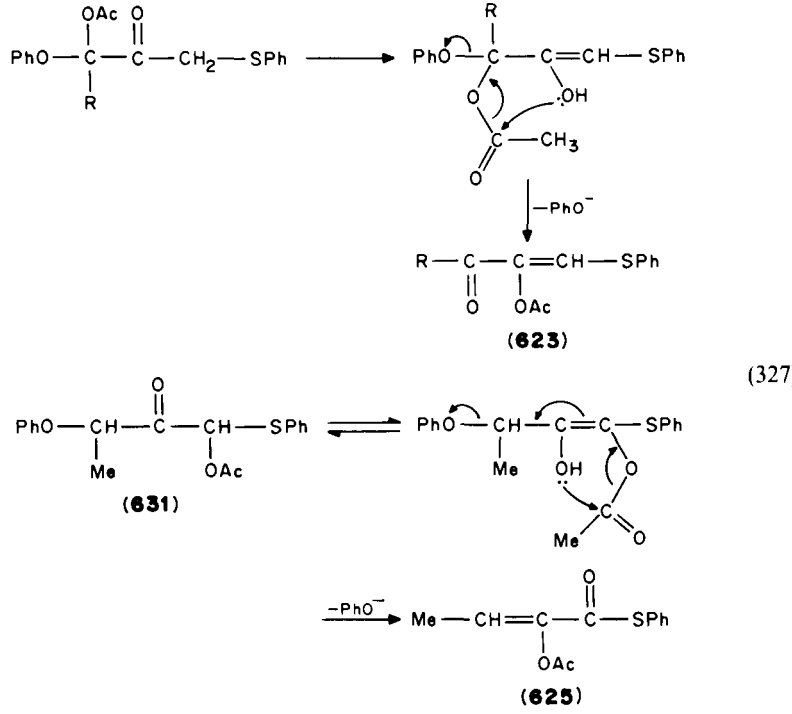
(325)

Different mechanisms are clearly operative in the acetolyses. The α-acetoxyketone (e.g. **621**) is formed by solvolysis via the intimate ion pair (**627**), whereas, preliminary enolization of the substrate to the enol allylic chloride (**628**) is required for the formation of the isomeric α′-acetoxyketone (e.g. **622**) which may originate via an ion pair (**629**, **630**) (equation 326).



(326)

The formation of the unsaturated compounds **623** and **625** can be ascribed to intramolecular *trans*-acylation, ultimately leading to fragmentation of the acetoxyketones (equation 327).



(327)

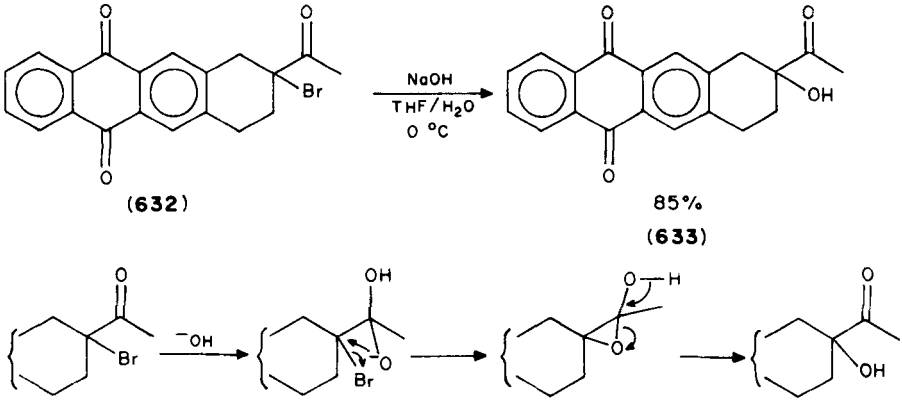
B. Reaction of α-Haloketones with Oxygen Nucleophiles and Bases

Several reagents that serve as nucleophilic sources of oxygen which replace the halogen have been developed.

1. *Reaction with inorganic oxygen nucleophiles*

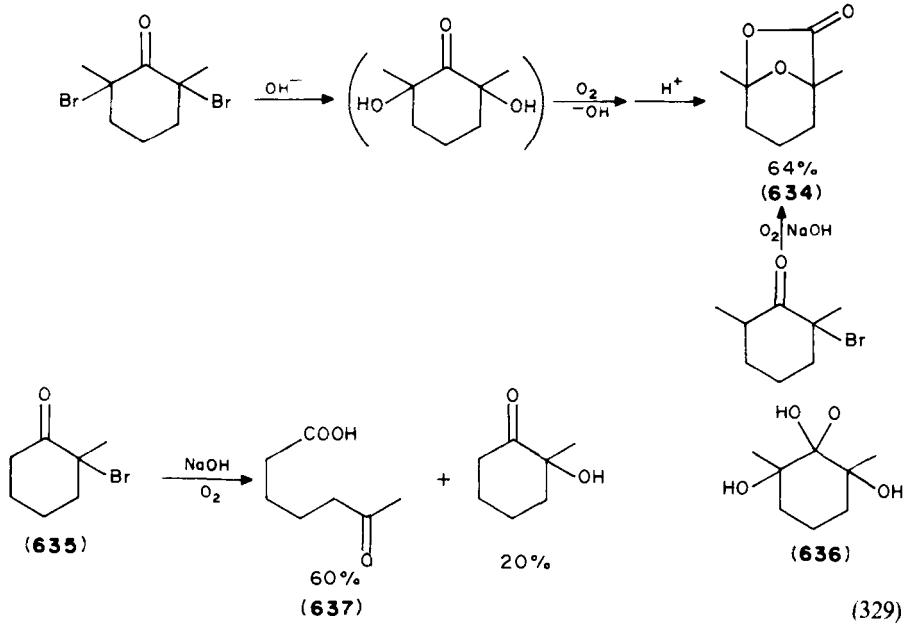
Attempts have been focused on procedures and reagents to provide the desired reaction

pathways exclusively and selectively. During the synthesis of daunomycinone derivatives a clean conversion of the bromoketone **632** to the corresponding hydroxyketone **633** was performed with cold dilute sodium hydroxide, presumably via a carbonyl-participating hydrolysis mechanism (equation 328)[680,681].



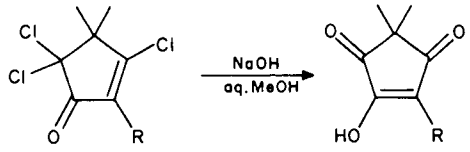
(328)

High yields of α-hydroxyketones were obtained using a combination of water and the polar aprotic solvent *N*-methyl-2-pyrrolidone in the presence of sodium hydrogen carbonate[682]. Base-catalysed oxygenation of α-bromo-α-methylcyclohexanones with sodium hydroxide ($MeOH-H_2O$) and oxygen furnished the tetrahydropyrancarbolactone **634**. The oxygenation proceeds via the hydroxy derivative and the oxy radical **636**, generated from the corresponding oxyanions, is possibly involved in the carbon–carbon bond cleavage. Similar treatment of **635** gave the keto acid **637** (equation 329)[683].



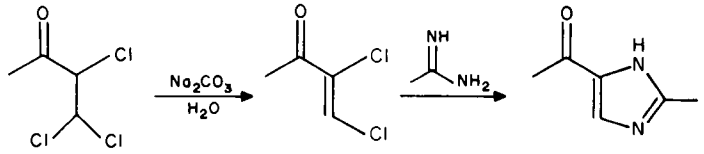
(329)

Polychlorocyclopentenones (**638**) were smoothly hydrolysed to the enol of cyclopentane-1, 2, 4-triones (**639**) by sodium hydroxide in aqueous methanol (equation 330)[612].



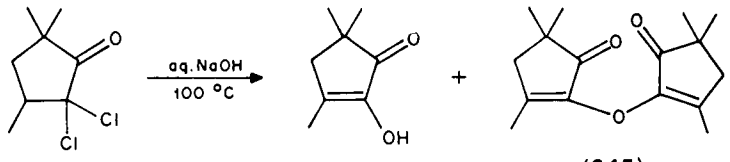
(638) ~90% (639) (330)

Synthesis of α, β-unsaturated ketones from α-haloketones by the action of an alkali can be a very efficient procedure. The trichloroketone **640** gave with sodium carbonate the chlorinated unsaturated ketone **641**, which can be transformed to the imidazoles **642** by condensation with acetamidine (equation 331)[684].

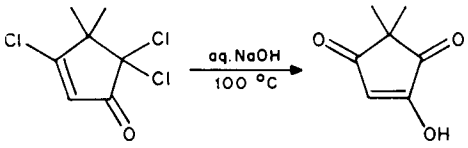


(640) 75% (641) 75% (642) (331)

The cyclopentane-dione **644** and -trione **647** can be prepared from the cyclopentanone **643** and cyclopentenone **646**, respectively, by reaction with aqueous sodium hydroxide (equation 332)[610].



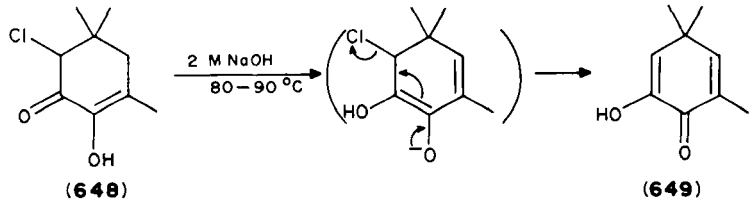
(643) 85% (644) (645)



(646) 90% (647) (332)

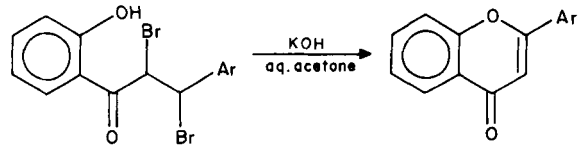
6-Chloro-2-hydroxyisophorone (**648**) can be dehydrochlorinated with NaOH to yield a 2, 5-cyclohexadienone (**649**), useful as a flavoring additive (equation 333)[611].

An excellent synthesis of the flavones **651** involves cyclocondensation and elimination of chalcone dibromides (**650**) under the influence of potassium hydroxide (equation 334)[685,686].



(333)

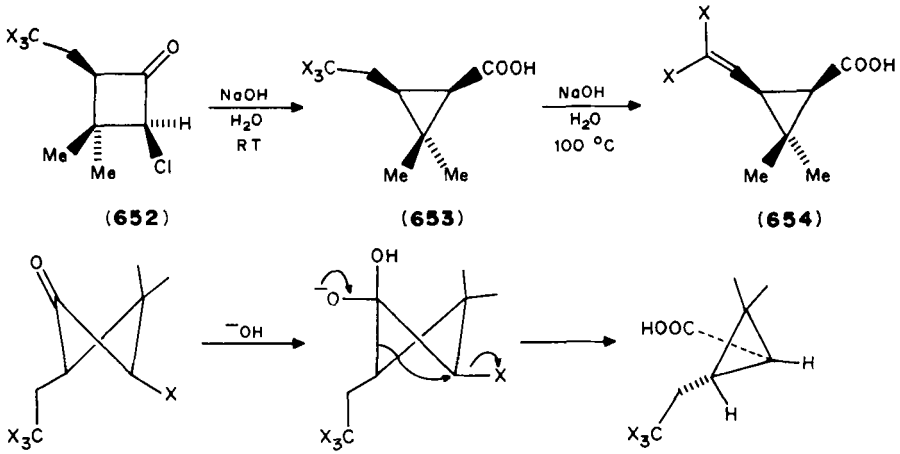
(648) (649)



(334)

(650) (651)

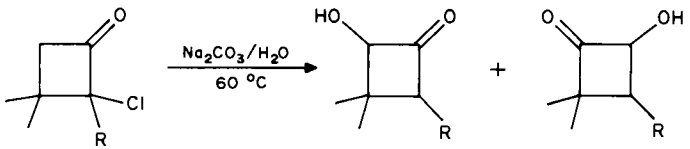
A stereoselective and versatile synthesis of 3-substituted-2,2-dimethylcyclopropanecarboxylic acids (**653** and **654**) can be performed via a Favorskii rearrangement (equation 335). The 2,4-*cis*-isomer of 2-halo-3,3-dimethyl-4-(2,2,2-trihaloethyl)cyclobutane (**652**) can be transformed predominantly to *cis*-cyclopropanecarboxylic acid (**653**) (*cis*:*trans* ratio = 10:1). Further treatment results in *cis*-3-(2,2-dihalovinyl)-2,2-dimethylcyclopropanecarboxylic acids (**654**). Esters of these acids are some of the most potent pyrethroids, known for their excellent insecticidal activity. The base-induced ring contraction of 2-halocyclobutanones proceeds via a semibenzilic acid-type mechanism (equation 335), differing from that in 2-halocyclohexanone, which proceeds via an unstable cyclopropanone intermediate[644,687].



(335)

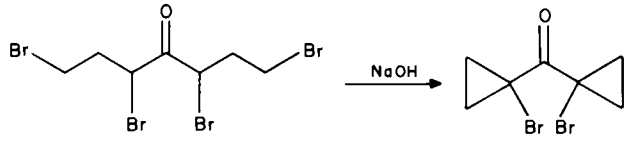
The *cis*:*trans* ratio in the cyclopropanecarboxylic acids depends on the nature of the solvent and the temperature. Higher temperatures gave higher amounts of the *trans*-isomer (*cis*:*trans* ratio = 83:17 at −8 °C and 59:41 at 33 °C). Addition of ethanol and dioxane decreased the *cis*:*trans* ratio (dioxane, 75:25; ethanol, 68:32; toluene, 89:11)[645].

Treatment of the monochlorocyclobutanone **95** with an aqueous solution of sodium carbonate afforded the cine-substitution products **655** and **656** in a 2:1 ratio (equation 336)[688].



(95) R = CH_2CCl_3 (655) (656) (336)

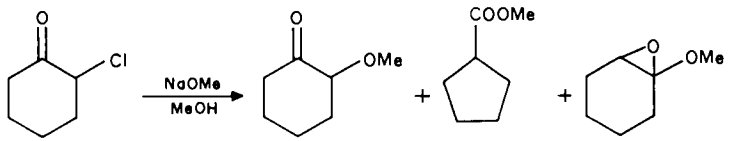
Deprotonation and intramolecular nucleophilic substitution leading to a dibrominated dicyclopropyl ketone was observed when an α, α', γ, γ'-tetrabromoketone (**657**) was treated with sodium hydroxide in diethylene glycol. The ketone **658** could not be obtained by direct bromination of the dicyclopropyl ketone (equation 337)[689].



(657) 24% (658) (337)

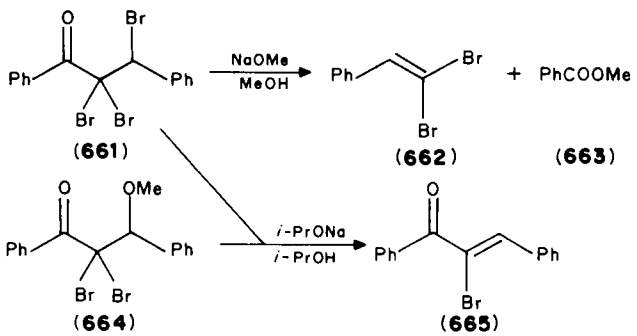
2. Reaction of α-haloketones with organic oxygen nucleophiles and bases

The reaction of α-halogenated ketones with alcohols in the presence of a base can give rise to a variety of products, as exemplified by the reaction of α-chlorocyclohexanone (**118**). On treatment with sodium methoxide in methanol it afforded a mixture of α-methoxycyclohexanone (**659**), methyl cyclopentanecarboxylate (**213**) and 1-methoxy-7-oxabicyclo[4.1.0]heptane (**660**) (Equation 338)[690].

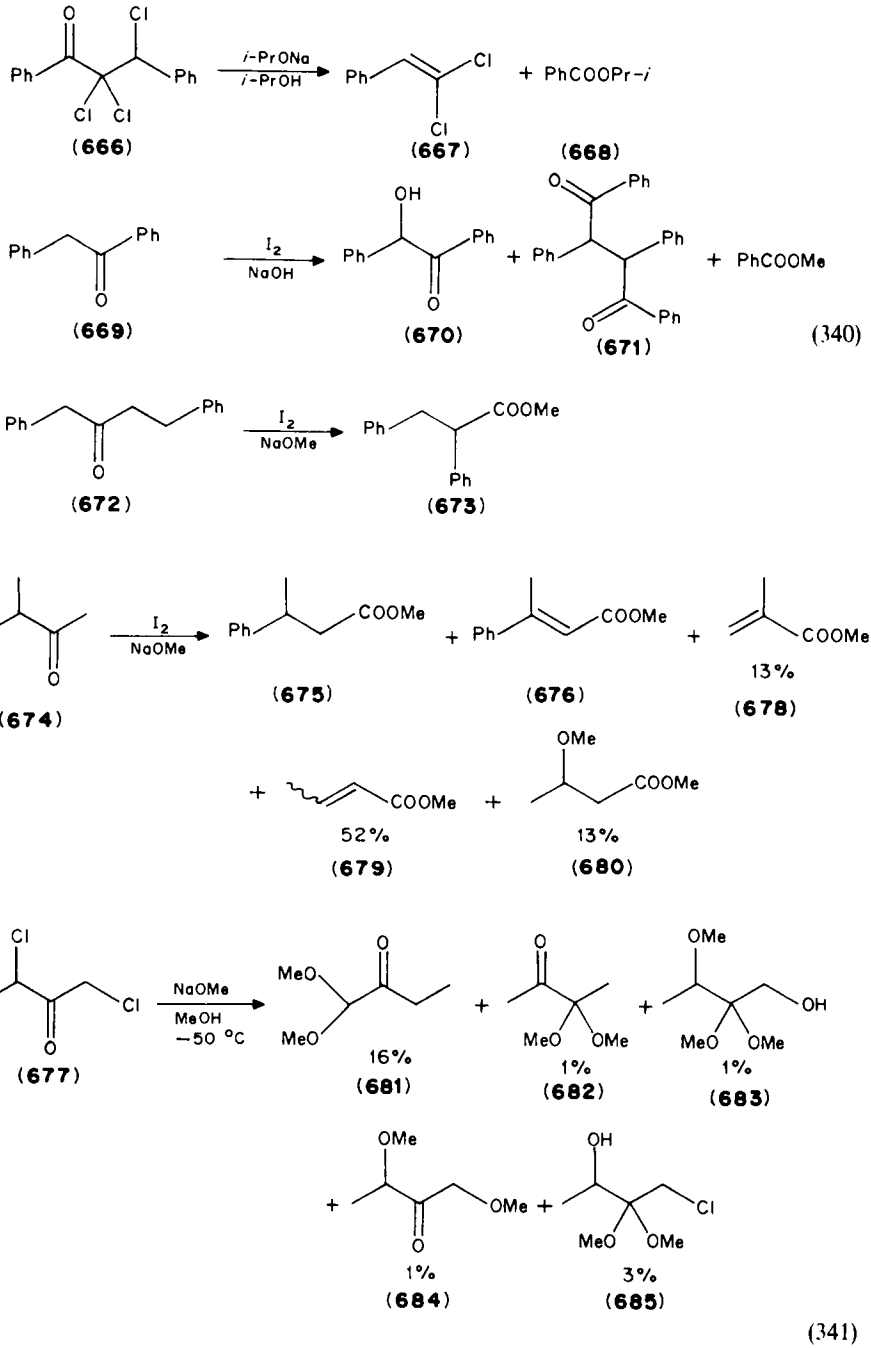


(118) (659) (213) (660) (338)

Other examples involve the reaction of 2,2-dihalo-1,3-diphenylpropan-1-ones (**661**, **664** and **666**) with isopropoxide and methoxide ions[691], the iodine oxidation of arylacetones (**669**, **672** and **674**) in alkaline methanol[692] and the reaction of dichloroketones (**677**) with methoxide ion (equations 339–341)[693].

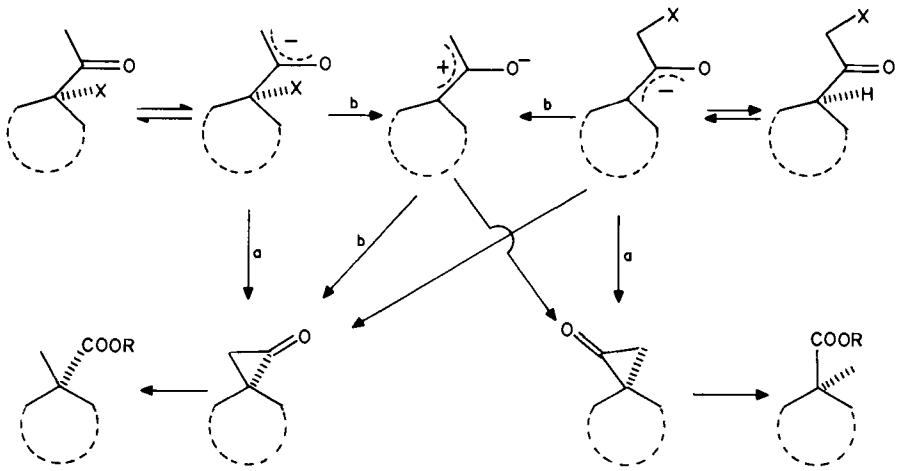


(661) (662) (663)
(664) (665) (339)



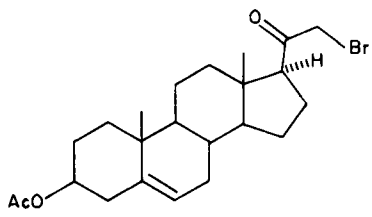
Changes in the conditions and in the nature of the ketone can influence to an appreciable extent the Favorskii rearrangements of α-halogenated acetylcycloalkanes,

especially the stereochemistry and the competing formation of α-hydroxyketones[694,695]. The complex stereochemical results of Favorskii rearrangements of α-haloacetylcycloalkanes, in particular of α-halo-20-keto steroids, in which cyclopropanones are considered to be intermediates, can be explained by the assumption that two mechanistic pathways may be operative, in some cases simultaneously. In one (route a), corresponding to a 'Loftfield-type' mechanism, the initially formed enolate is converted directly, concertedly and stereospecifically into a cyclopropanone, which is then opened to give rearrangement products with a unique stereochemistry at the originally halogenated carbon atom. In the other (route b), which corresponds to a 'Dewar-type' mechanism, the enolate is first transformed into a dipolar intermediate which may lead to two epimeric cyclopropanones, which are opened to give epimeric rearrangement products. A polar and protic medium would favour the formation of a dipolar intermediate whereas a non-protic and mildly polar medium would give a 'concerted ring closure' (equation 342).

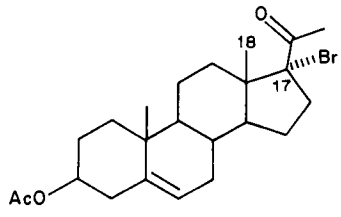


(342)

Engel and coworkers[694,695] have established that the formation of a dipolar intermediate prior to the formation of cyclopropanones can be ruled out. Indeed, an identical dipolar intermediate would have to be formed from both 21-bromopregnenolone (**686**) and 17-bromopregnenolone (**687**), giving rise to the same mixture of rearrangement products.



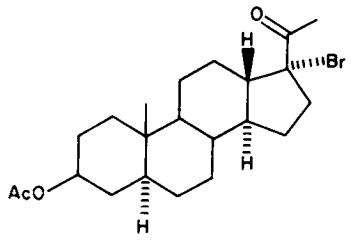
(**686**)



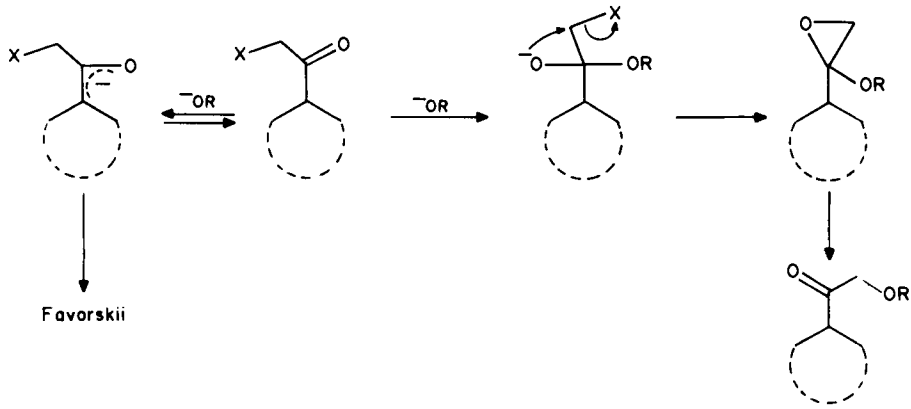
(**687**)

This is true when the reaction is carried out in highly protic and polar medium (hydrogen carbonate–water–methanol), which should favour a dipolar intermediate, but

diametrically opposed stereochemical results were obtained in an aprotic medium (sodium methoxide–dimethoxyethane). The conclusion can be drawn that in an aprotic and mildly polar medium the reaction is concerted, that in a protic and polar medium a delocalized intermediate is involved and that in media of intermediate protonicity and polarity a concerted and non-concerted pathway may be operative simultaneously. The stereoselectivity, however, is strongly influenced by the presence of the 18-methyl function and its absence results in a significant diminution of the stereoselectivity. Also, the substitution was strongly influenced by the reaction medium and steric factors (methyl group in the 18-position). A high proportion of substitution products was observed in dimethoxyethane, whereas in methanol virtually none were formed with **686**. The epoxy ether formation is favoured in aprotic medium (equation 343).



(**688**)



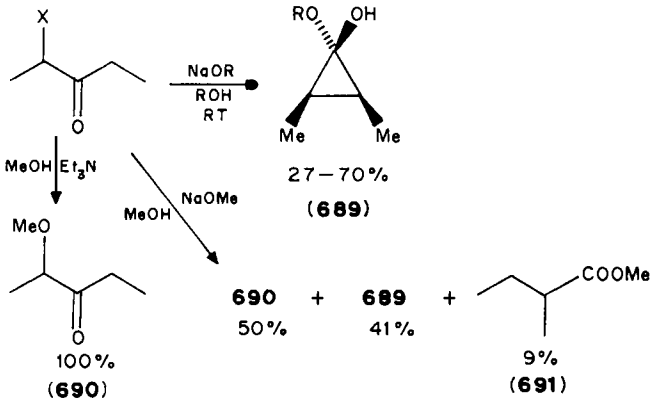
(343)

In the case of the 17-bromo compound the complete absence of substitution products in all media is ascribed to the steric hindrance exerted by the angular methyl group, as proved by the high proportion of substitution product generated from the 18-nor compound in all media.

The occurrence of competing reaction pathways constitutes a serious limitation in the useful conversion of α-haloketones into oxygenated carbonyl compounds and efforts have been exerted to obtain the desired compounds without contamination by side-products.

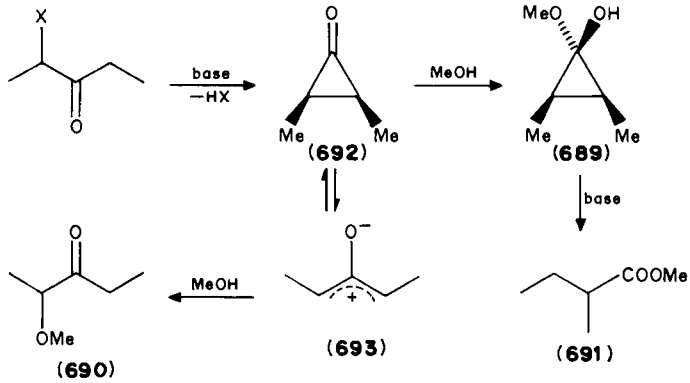
When 2-chloro- and 2-bromopentan-3-one were allowed to react in methanol, ethanol and propan-2-ol and the corresponding sodium alkoxides were added, the hemiacetals of *cis*-2, 3-dimethylcyclopropane (**689**) could be formed in a highly stereoselective manner, when the alkoxides were slowly added to the α-haloketone and an excess of base was

avoided. When the α-haloketone was added to the methoxide solution, the α-methoxyketone **690** and the Favorskii ester **691** were formed. Reaction with methanol in the presence of triethylamine gave the methoxyketone **690** (equation 344)[696].



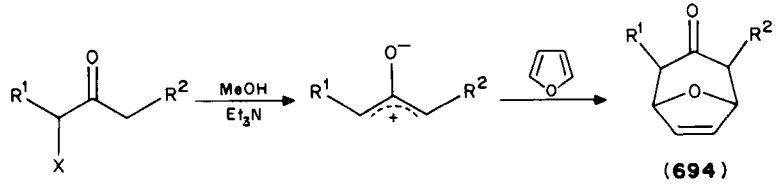
(344)

The formation of the product is explained by the formation of a cyclopropanone (**692**) which is in equilibrium with an oxyallyl species (**693**) with a W-configuration, as illustrated in equation 345.



(345)

The formation of 8-oxabicyclo[3.2.1]oct-6-en-3-ones (**694**) in the reaction of α-haloketones with furans in the presence of methanol and triethylamine is explained by a stereoselective [4 + 3]cycloaddition with the respective oxyallyl species (equation 346)[696–698].

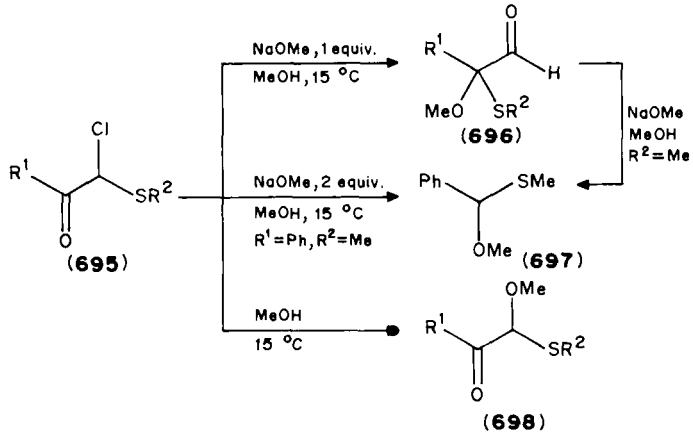


(346)

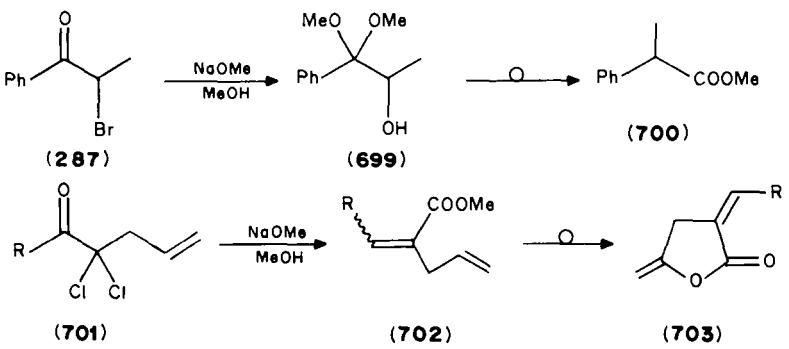
The oxabicyclic compounds were also formed using lithium perchlorate–triethylamine[699,700], trifluoroethanol–triethylamine or sodium 2,2,2-

trifluoroethoxide[701] and silver tetrafluoroborate[702]. 2-(Trimethylsiloxy)allyl cations generated from various 2-(trimethylsiloxy)allyl chlorides with silver perchlorate showed identical reactivity[703].

Other regiospecific reactions include the synthesis of the glyoxal derivatives **696–698** by treatment of the α-chloro-α-(aryl- or alkylthio)ketones **695** with methanol or with sodium methoxide in methanol[704] and the formation of the α-hydroxyacetal **699** from α-bromopropiophenone (**287**), which served as an excellent precursor for α-arylalkanoic esters (**700**) (potent anti-inflammatory and analgesic activities)[705]. The Favorskii rearrangement of the γ,δ-unsaturated α,α-dichloroketones **701** afforded the unsaturated esters **702**, which could be converted into the unsaturated γ-lactones **703** (equation 347)[655,656].

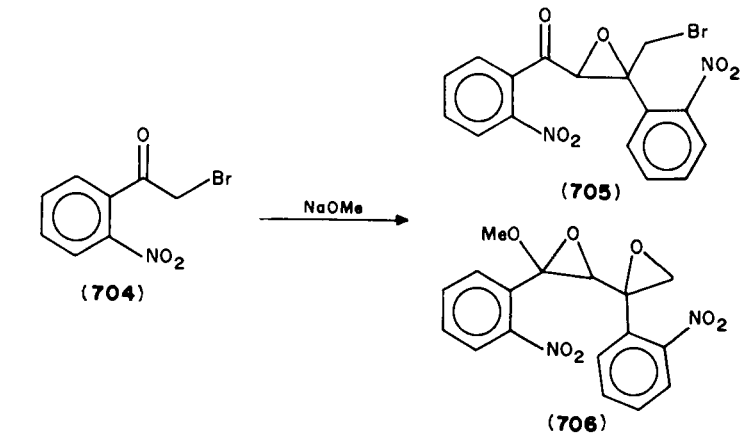


(347)

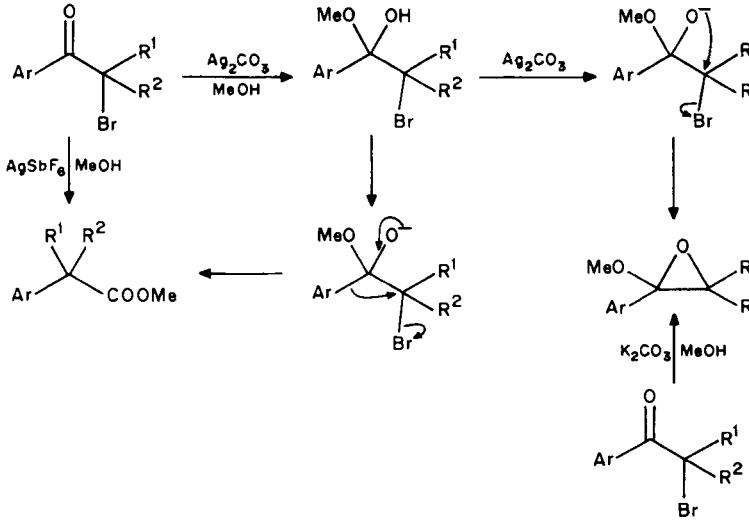


The substitution pattern can also have an important influence on the nature of the products. Whereas *o*-nitrophenacyl bromide (**704**) gave a mixture of the keto epoxide **705** and the *bis*-epoxy compound **706** on treatment with sodium methoxide, the *para* isomer afforded only **706** (equation 348)[706].

Tertiary α-bromoalkyl aryl ketones were converted exclusively into 1-alkoxy-1-aryloxiranes by reaction with excess potassium carbonate in the corresponding dry alcohol. Secondary α-bromoketones afforded α-hydroxyacetals resulting from ring opening. Reaction with silver carbonate in dry methanol yielded competitively 2-alkoxyoxiranes and a semi-benzilic rearrangement product. With silver hexafluoroantimonate in methanol the α-bromoketone afforded the latter product exclusively (equation 349)[707].

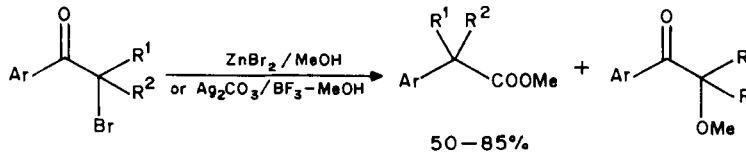


(348)



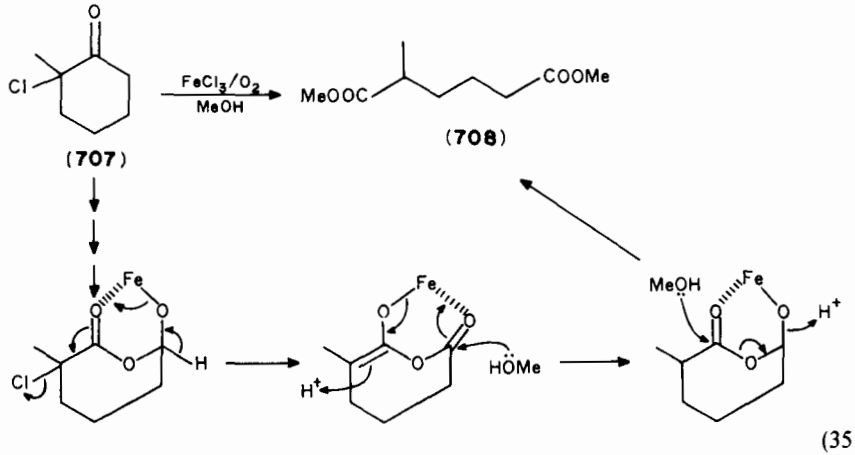
(349)

The Favorskii rearrangement took place via a mechanism by which the methanol adduct undergoes a silver-assisted ionization of the carbon—halogen bond with migration of the phenyl group. Whether or not α-acylcarbenium ions are involved is still a point of discussion. The hemiacetal could also be deprotonated to afford oxiranes. It seems that a less basic silver reagent would give a Favorskii-type rearrangement exclusively whereas a basic non-silver reagent eliminates the rearrangement. Silver or zinc bromide induced methanolysis of α-bromoalkyl aryl ketones, providing α-arylalkanoic esters in moderate to good yields together with α-methoxyketones (equation 350)[708–710].



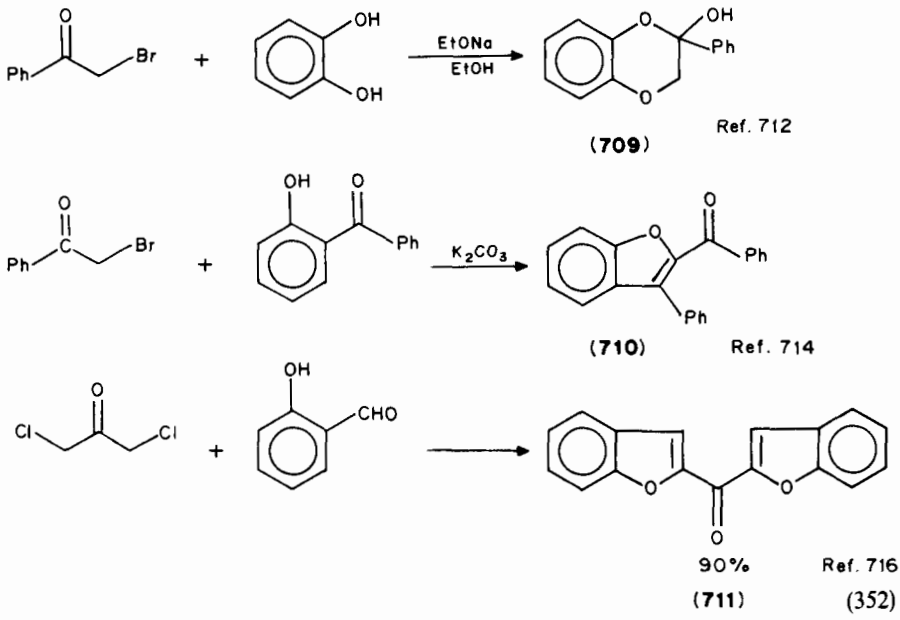
(350)

An iron(III) chloride-catalysed oxygenation of α-halocyclohexanones in methanol yielded adipic acid dimethyl esters (**708**). Without oxygen the reaction afforded the dehydrohalogenation product. A plausible mechanism involves dehydrochlorination of the pseudo-acid intermediate yielding an enolate intermediate, which is successively attacked nucleophilically by methanol (equation 351)[711].



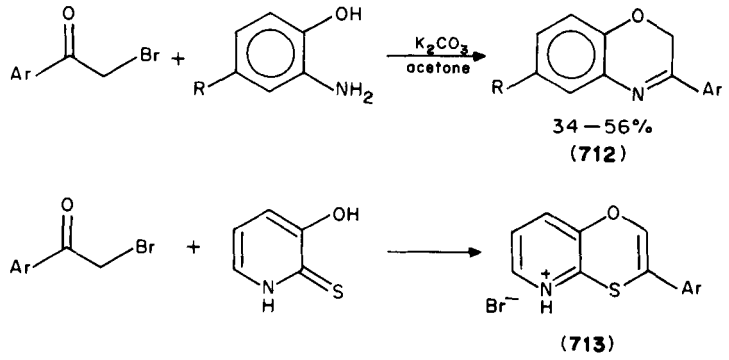
(351)

The reaction of α-haloketones with phenols gave a variety of *O*-heterocyclic compounds. 1,4-Benzodioxane derivatives (**709**) have been formed with catechol and pyrocatechol under basic conditions[712,713], and benzofuran compounds (**710** and **711**) were produced via cyclocondensation with hydroxy-substituted aromatic carbonyl compounds (equation 352)[714–718].



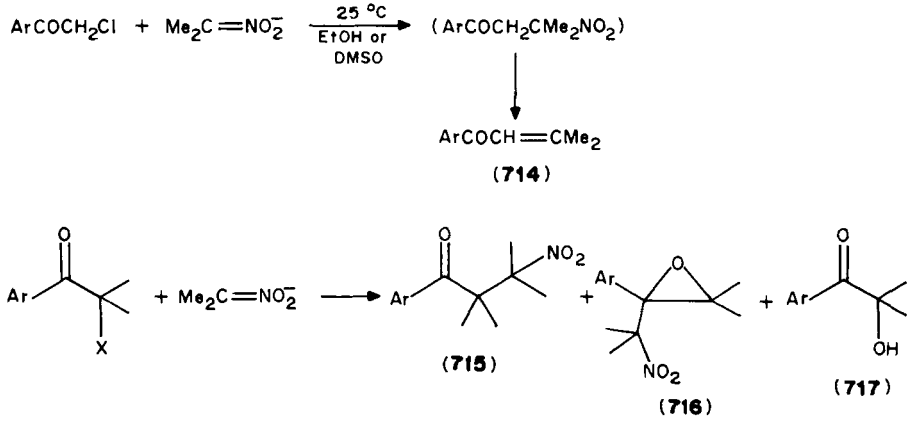
(352)

Similar cyclocondensations with 2-aminophenols and 3-hydroxypyridine-2-thione provided 1,4-benzoxazines (**712**)[719] and 1,4-pyridothioxines (**713**)[720], respectively (equation 353).



(353)

Reaction of phenacyl chlorides and α-haloisobutyrophenones with nitronate anions afforded *C*-alkylation products by a radical chain mechanism ($S_{RN}1$)[721,722]. While the phenacyl chlorides gave the elimination products (**714**), the free-radical substitution of the isobutyrophenones is photostimulated and occurred in competition with ionic reactions, leading to oxiranes (**716**) and hydroxyketones (**717**) (equation 354).

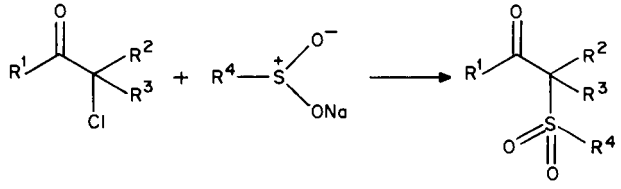


$S_{RN}1$ mechanism:

$$\begin{aligned}
\mathrm{RCOCH_2X} &\xrightarrow{e} \mathrm{RCOCH_2X^{-\bullet}} \\
\mathrm{RCOCH_2X^{-\bullet}} &\longrightarrow \mathrm{RCOCH_2^{\bullet} + X^-} \\
\mathrm{RCOCH_2^{\bullet} + Nu^-} &\longrightarrow \mathrm{RCOCH_2Nu^{-\bullet}} \\
\mathrm{RCOCH_2Nu^{-\bullet} + RCOCH_2X} &\longrightarrow \mathrm{RCOCH_2Nu + RCOCH_2X^{-\bullet}}
\end{aligned} \qquad (354)$$

$$\mathrm{RCOCH_2X + Nu^-} \longrightarrow \mathrm{RCOCH_2Nu + X^-}$$

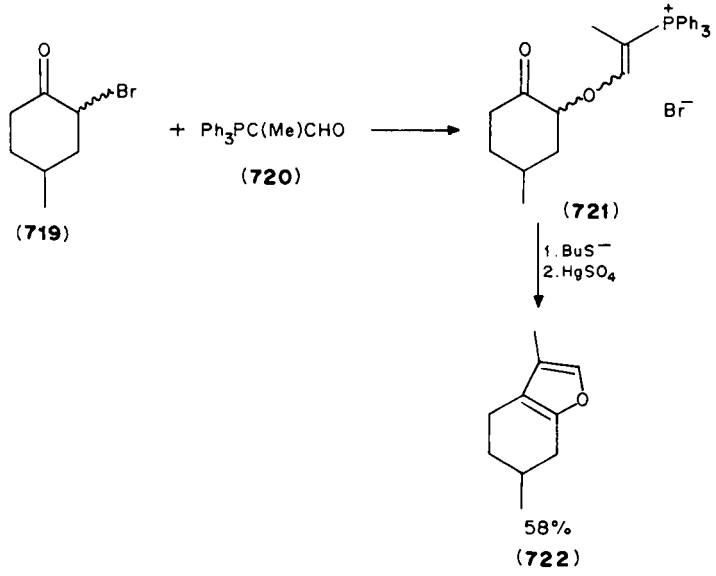
However, reaction of α-haloketones with sulphinate anions mainly gave sulphone substitution products (**718**) (equation 355)[722,723].

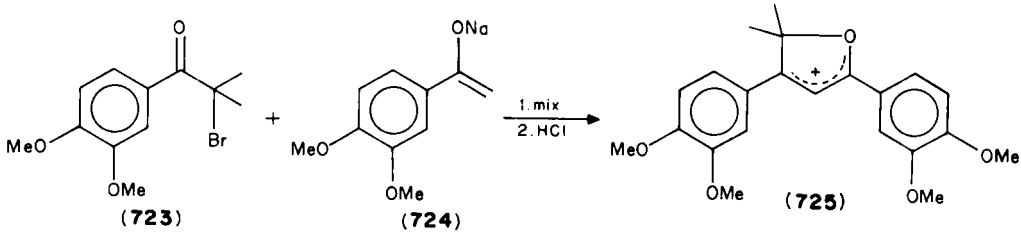


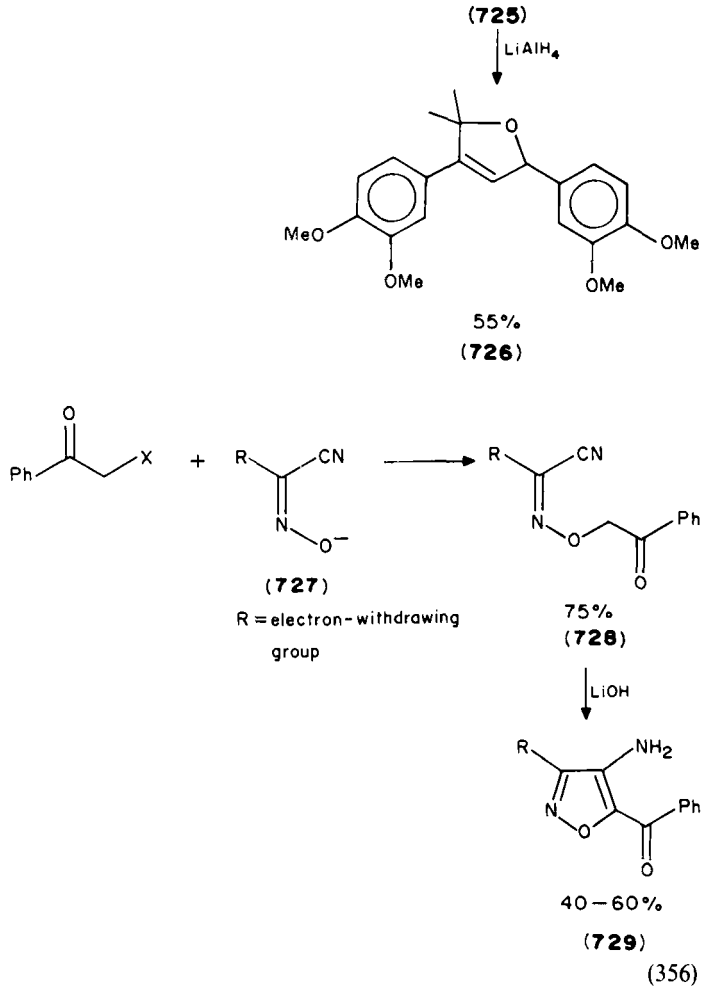
(355)

(**718**)

New syntheses of furan and isoxazole derivatives were found by using alkylation with α-haloketones on oxygen atoms. Reaction of 2-bromocyclohexanone (**719**) with (α-formylethylidene) triphenylphosphorane (**720**) gave the oxophosphorane **721**, which could be converted to isomenthofuran (**722**)[724]. Furylium cations (**725**) were prepared via the condensation of the sodium enolate of 3,4-dimethoxyacetophenone (**724**) with an α-bromoisobutyrophenone (**723**)[725], while the sodium salts of α-oximinonitriles (**727**) were converted into isoxazoles (**729**) via alkylation with phenacyl halides and subsequent ring closure (equation 356)[726].





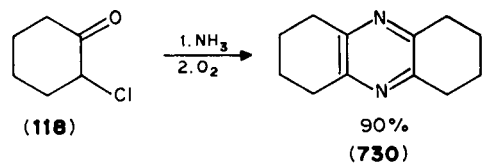


(356)

C. Reaction of α-Haloketones with Nitrogen Nucleophiles and Bases

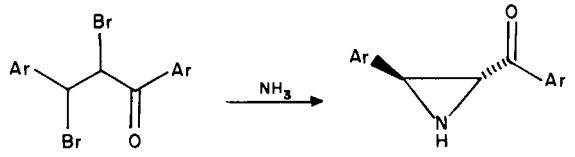
1. Reaction of α-haloketones with amines

In this section, reactions of α-haloketones with amines which do not give rise to α-haloimines and β-haloenamines will be described. The former are treated in another chapter and the latter are not discussed (see leading references 983 and 984). Reactions of α-haloketones with ammonia may give rise to heterocyclic compounds. Reaction of α-chlorocyclohexanone (**118**) afforded octahydrophenazine (**730**)[727], while *trans*-aziridines (**732**) were formed from α,β-dibromoketones (**731**) (equation 357)[728]. Attempted dehydrohalogenation of α-bromo-α'-methylaminoketones using sodium amide in liquid ammonia produced β-lactams (**733**), probably via a quasi-Favorskii pathway. The suggested mechanism is depicted in equation 358[730]. Primary α-aminoketones are obtained by the treatment of α-haloketones with hexamethylenetetramine (equation 359)[729].

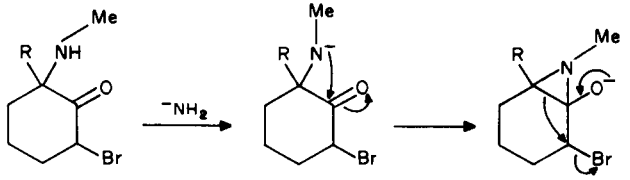


(118) 90% (730)

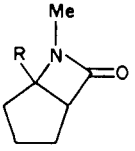
(357)



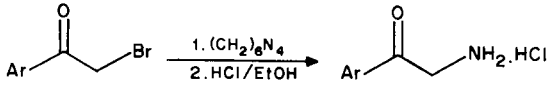
(731) 45–97% (732)



(358)

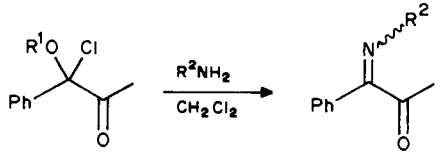


(733)



(359)

α-Haloketones and primary aromatic amines often yield imines or substitution products[731]. A special case is the synthesis of α-iminoketones (735) from α-chloro-α-alkoxy ketones (734) with aliphatic amines (equation 360)[732].

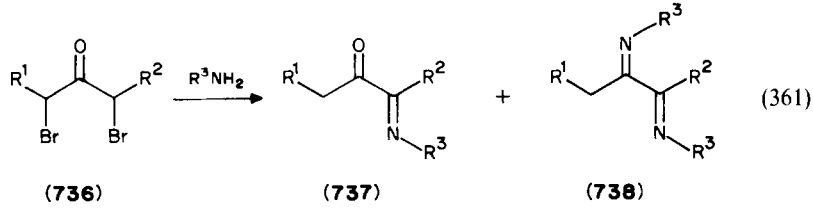


75–80%

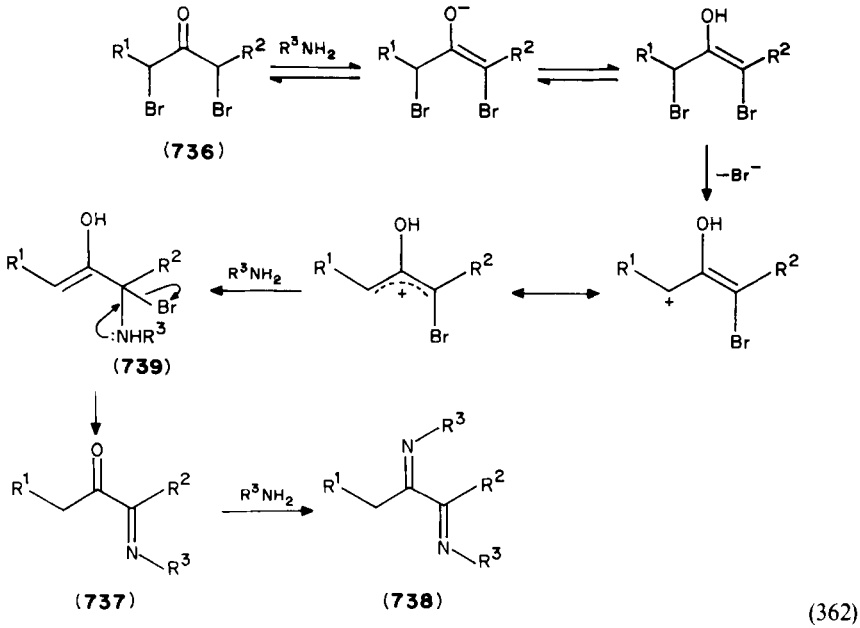
(734) (735) (E+Z)

(360)

α,α'-Dibromoketones (**736**) react with primary amines to provide α-iminoketones (**737**) and α-diimines (**738**) (equation 361)[733] in variable ratios. Isopropylamine afforded **737** as the major product but less sterically hindered primary amines produced increasing amounts of **738**, while sterically hindered ketones gave Favorskii rearrangement products[733]. The formation of **737** and **738** results from a more favourable nucleophilic action of the primary amine compared with the more basic and less nucleophilic secondary amines, which give Favorskii rearrangement. Aminolysis of α-bromoketones (**736**) via delocalized carbenium ions yields intermediates (**739**) which are converted to **737**. Excess of amine causes the transformation of **737** to **738** (equation 362).



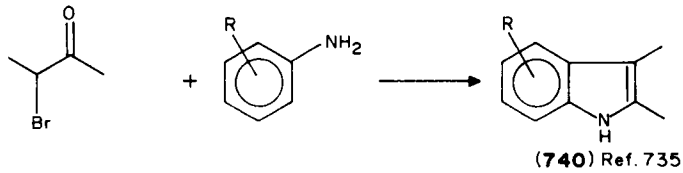
(**736**) (**737**) (**738**) (361)



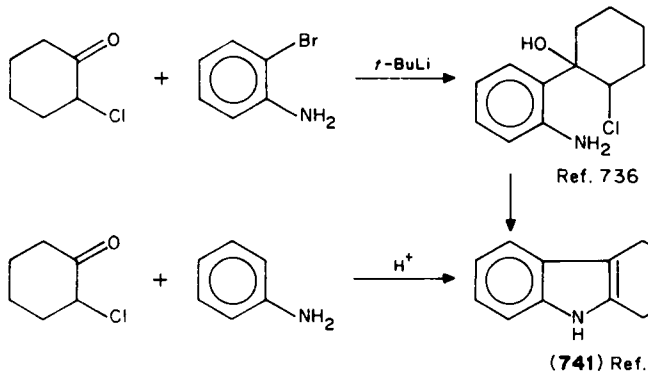
(**736**) (**739**) (**737**) (**738**) (362)

The reaction of primary aromatic amines with α-haloketones is an attractive route to indoles (**740**)[734,735] and carbazole derivatives (**741**) (equation 363)[735–737].

Cyclocondensation of α-haloketones with primary heterocyclic amines afforded condensed imidazole systems (**742**) with a common nitrogen atom (equation 364)[738–744]. The mechanism of the formation of imidazo[1,2-*a*]pyridines (**746**) from α-haloketones and α-aminopyridine has been studied in detail and two relatively long-lived intermediates (**743** and **744**), which are in equilibrium with each other, have been detected (equation 365)[739].



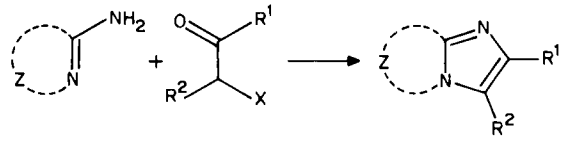
(740) Ref. 735



Ref. 736

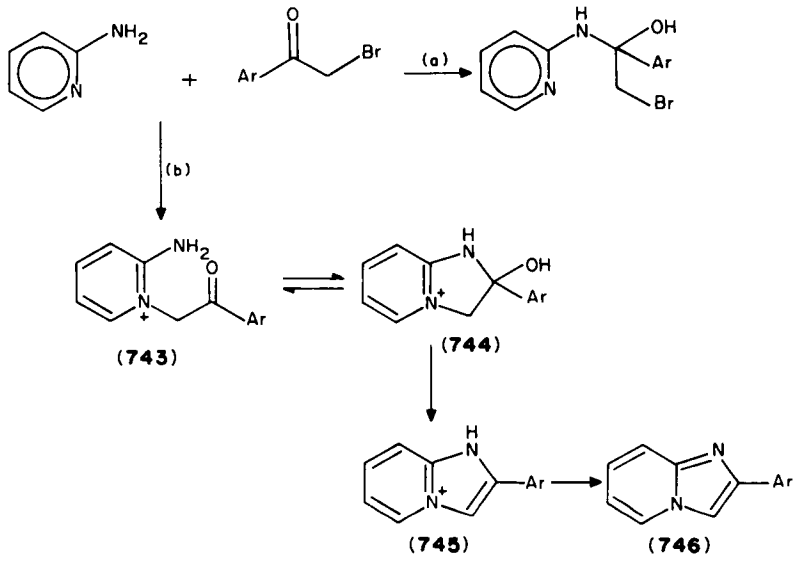
(741) Ref. 737

(363)



(742)

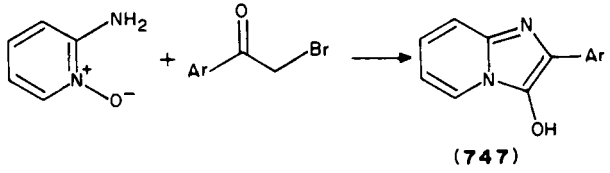
(364)



(743) (744) (745) (746)

(365)

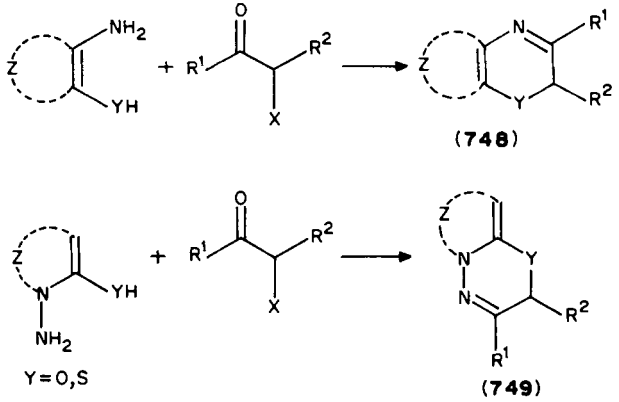
Path (b) seems to be favoured over (a) as the transition state for the displacement of halogen, activated by an adjacent carbonyl group, is of lower energy than that for the addition followed by intramolecular displacement. Also, the reaction of 2-aminopyridine-1-oxide and phenacyl bromides afforded 2-heteroarylimidazo[1,2-*a*]pyridin-3-ols (**747**) (equation 366)[745].



(366)

(747)

Several benzoxazines[746], pyridooxazines and pyridothiazines[747] (**748**) were obtained when 2-aminophenols and 2-aminothiophenols were treated with α-haloketones. A similar cyclocondensation took place with 1-amino-2-pyridones and 1-amino-2-triazolethiones, yielding pyridooxadiazines[748] and triazolothiazines (**749**) respectively (equation 367)[749].



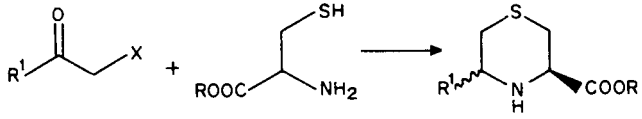
(748)

(367)

Y=O,S

(749)

Stereoisomeric thiazanes (**750**) were prepared by cyclocondensation of aminothiols with α-halomethyl ketones (equation 368)[750].

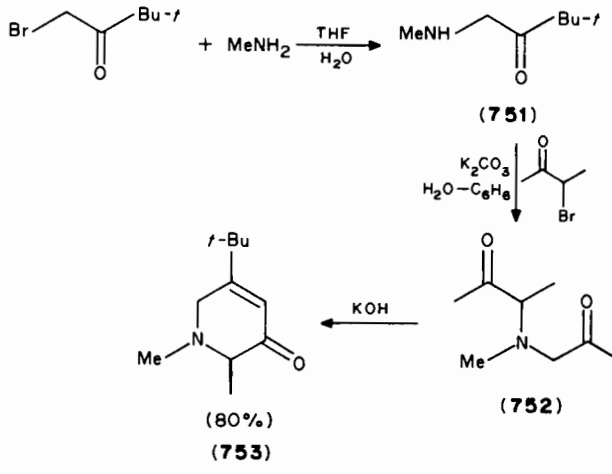


(368)

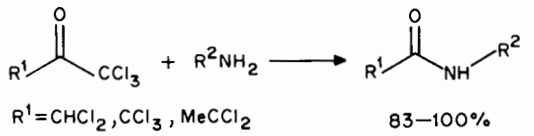
(750)

Dehydrobromination of α-bromocycloalkanones with aniline yielded cyclic α,β-cycloalkenones[751]. α-Haloketones with α-aminoketones (**751**) could also give rise to substitution products (**752**), as exemplified by the synthesis of 3-ketopiperideines (**753**) (equation 369)[752].

Other reaction pathways included the formation of aziridines[714] and of chlorinated amides (equation 370)[753].

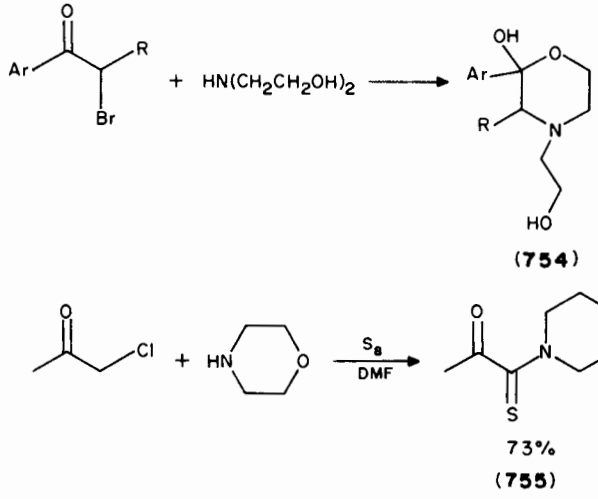


(369)



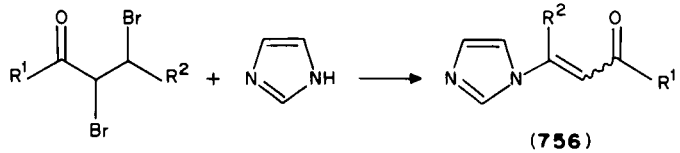
(370)

In general, the reactions of α-haloketones with secondary amines afford α-substitution products[754–757]. Diethanolamine reacted with 2-bromo-1-arylethanones with the formation of 2-hydroxymorpholines (**754**)[758], while aminosulphuration with the formation of thioamides (**755**) was observed when chloroketones reacted with morpholine in the presence of sulphur (equation 371)[759].



(371)

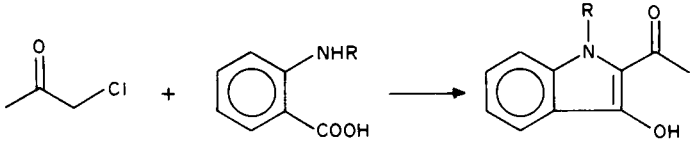
Reactions of α,β-dibromoketones with imidazole give both substitution and dehydrobromination, yielding β-(1-imidazolyl)enones (**756**) (equation 372)[760].



(372)

(756)

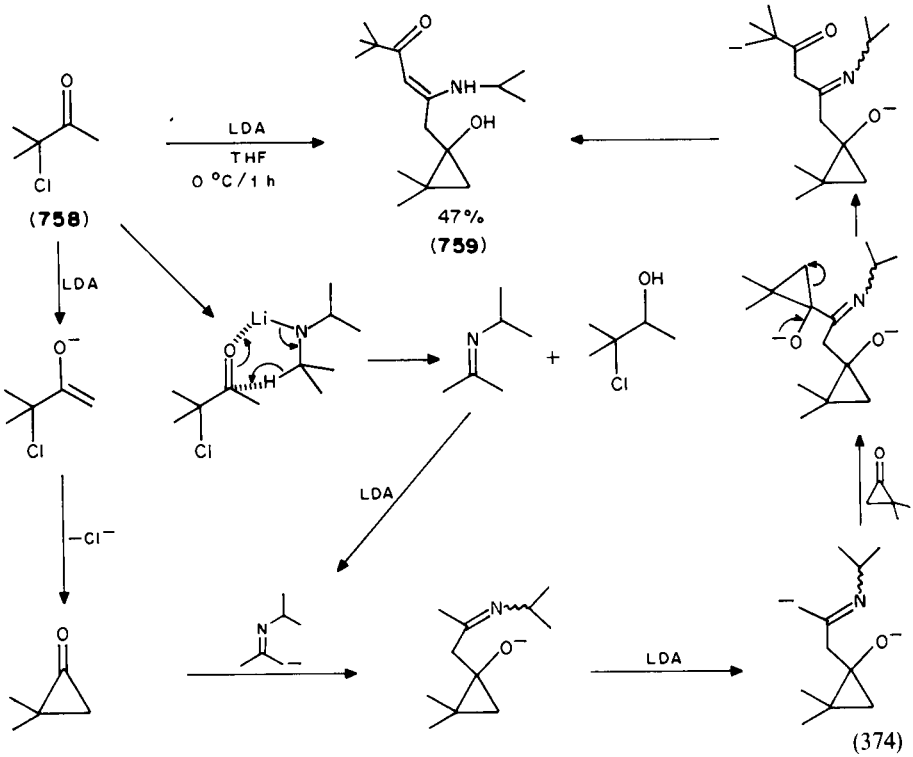
Formation of indoles (**757**) took place when 2-*N*-alkylaminobenzoic acids were treated with chloroacetone (equation 373)[761].



(373)

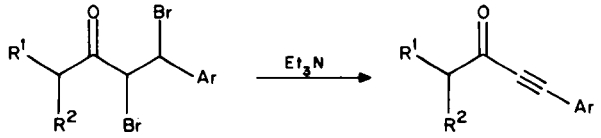
(757)

A highly unusual condensation occurred when 3-chloro-3-methylbutan-2-one (**758**) reacted with lithium diisopropylamide in THF. The product 2,2-dimethyl-5-(*N*-isopropylamino)-6-(2,2-dimethyl-1-hydroxycyclopropyl)hex-4-en-3-one (**759**) apparently resulted from the addition of two molecules of Favorskii-derived cyclopropanone with *N*-(2-propylidene)isopropylamine, i.e. the Meerwein–Ponndorf–Verley oxidation product of LDA (equation 374)[762].



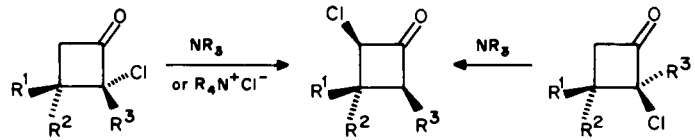
(374)

Aliphatic tertiary amines are often used in dehydrohalogenations, giving rise to α,β-unsaturated ketones[763]. Similarly, α,β-dibromoketones could be converted into acetylenic ketones (**760**) with triethylamine (equation 375)[764].



(760) (375)

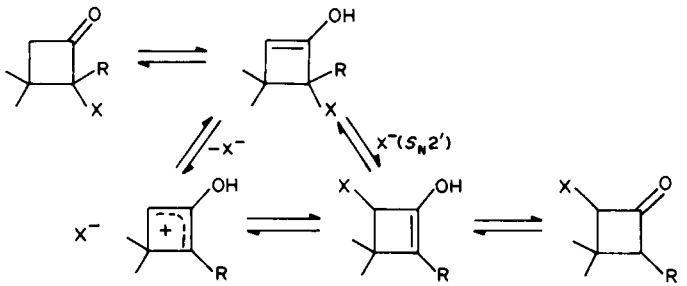
On the other hand, treatment of α-halocyclobutanones with tertiary amines or quaternary ammonium salts gave a stereoselective cine-rearrangement to α'-halocyclobutanones (**761**) (equation 376)[688]. The 2,4-*cis*-disubstituted cyclobutanones **761** are valuable intermediates in a new synthesis of pyrethroids.



(761) (376)

Proposed reaction pathways are shown in equations 377a and b.

a. Via enol



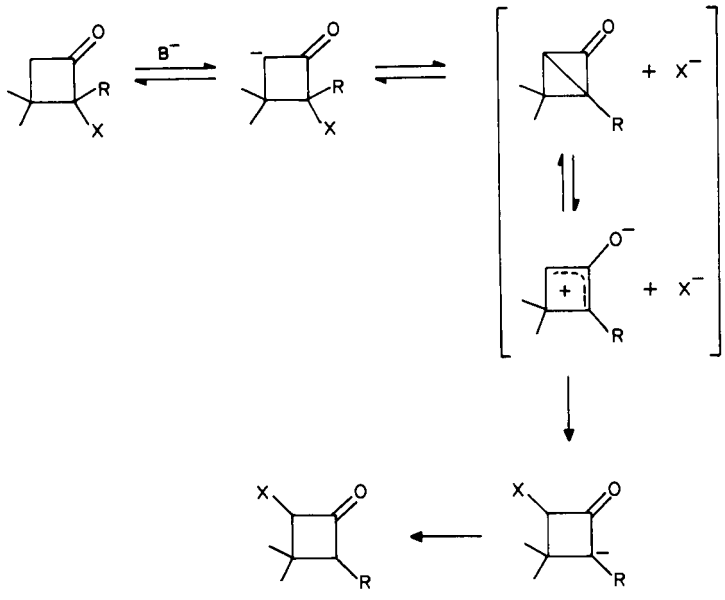
(377a)

b. Via enolate/bicyclobutanones

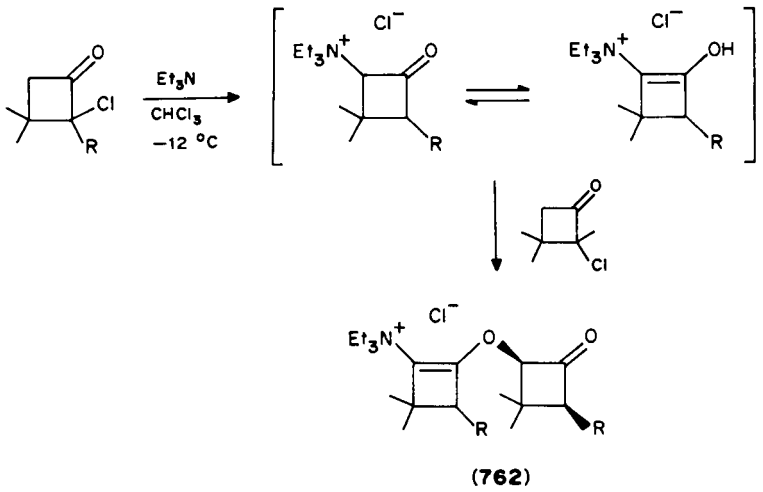
See equation 377b at the top of the next page.

However, triethylamine is capable of giving substitution products with formation of condensed compounds (**762**) (equation 378)[688].

The reaction of α-haloketones with *N*-heterocyclic compounds is completely different and leads to quaternization in most cases[660,765]. This reaction has been used in the Chichibabin quaternization–cyclization for indolizine derivatives (**763**) starting from pyridazines and pyrimidines[765], isoquinolines[766] and pyridines (equation 379)[767]. However, 2-hydroxychalcone dibromide (**764**) gave 8-bromoflavone (**765**) on treatment with pyridine. It is assumed that the first stage involved both debromination and dehydrobromination, followed by bromination, ring closure and dehydrobromination (equation 380)[768].



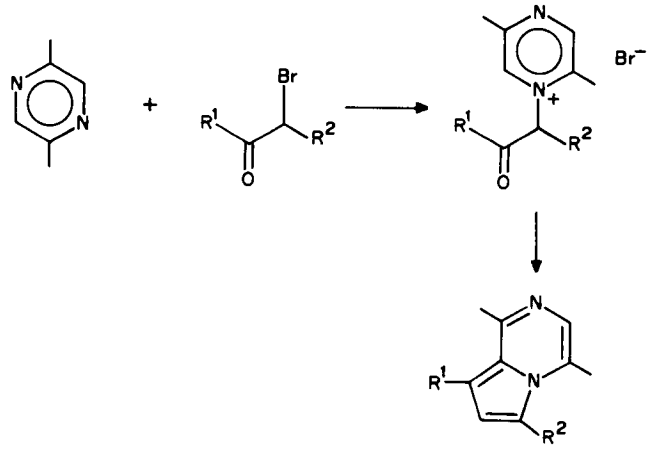
(377b)



(378)

(762)

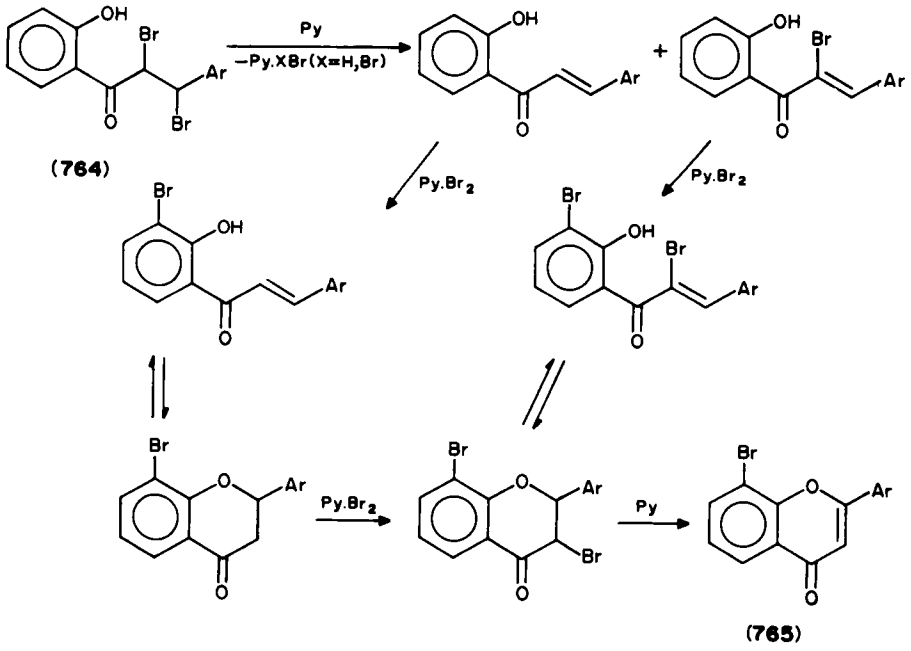
Pyridinium chloride is also able to cause dehydrohalogenation, e.g. 3-aryl-2,2-dichlorocyclobutanones (**766**) yield 3-aryl-2-chlorocyclobutenones (**767**). When the same substrates were heated in a sealed tube the products were but-2-en-4-olides (**768**) (equation 381)[769].



25–65%

(763) Ref. 765

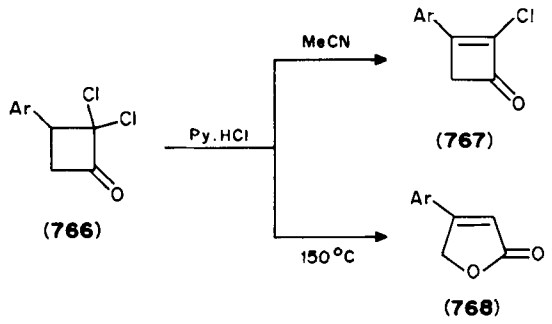
(379)



(764)

(765)

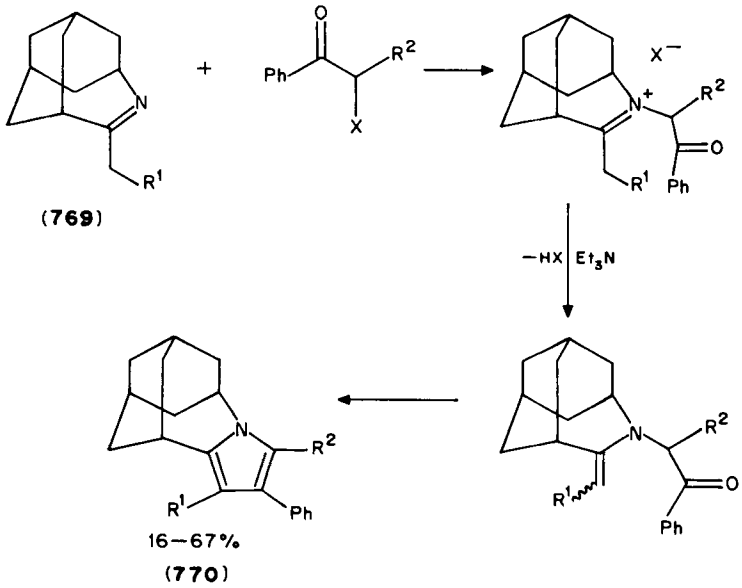
(380)



(381)

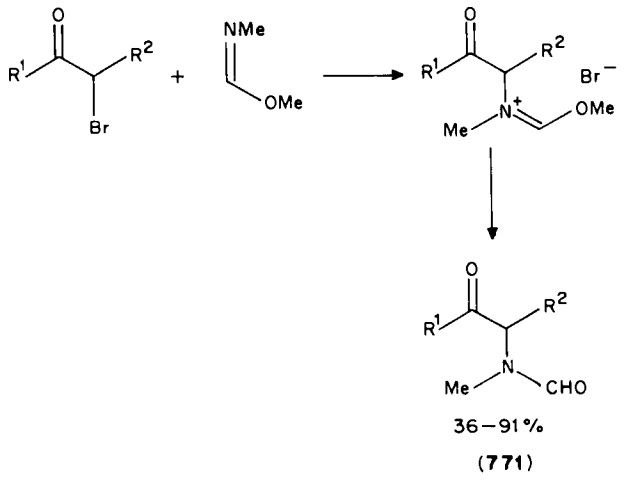
2. Reaction of α-haloketones with imino compounds and enamines

Few reports have dealt with the reactivity of α-haloketones with imines. A novel synthesis of 4-azahomoadamantano[4, 5]pyrroles (**770**) was attained via substitution and enamine cyclization by reaction of the imines **769** with phenacyl bromides (equation 382)[770].

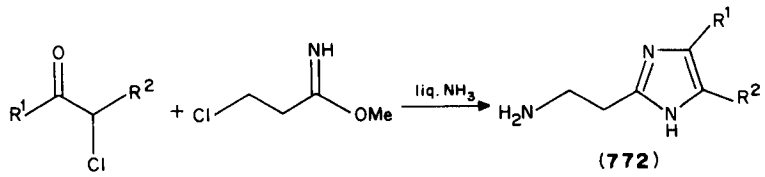


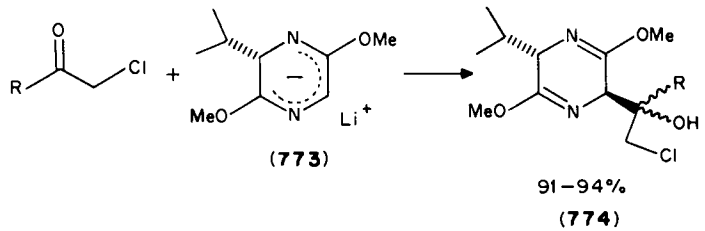
(382)

Imidates are much less basic than the corresponding primary amines from which they are derived but their nucleophilicity is still appreciable and *N*-alkylation occurs relatively readily. Diverse α-bromoketones yielded with excess methyl *N*-methylformimidate the expected *N*-methylformamides (**771**)[771]. On the other hand, substituted isohistamine derivatives (**772**) were formed from imidates with α-chloroketones in liquid ammonia (equation 383)[772]. α-Chloroketones reacted with a lithiated bislactim ether of cyclo (L-Val-Gly) (**773**) in an extremely high diastereofacial way to give virtually only the (3*R*)-addition products (**774**) (equation 384)[773].



(383)





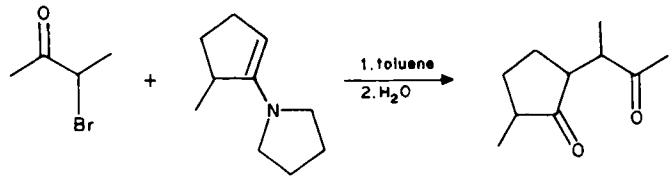
(384)

An excellent synthesis of α-alkylated cyclopentanones (**776**) involves reaction between α-bromoketones and cyclopentanone enamines (**775**)[774]. The Hantzsch pyrrole synthesis using the enamine **777** derived from dimethyl acetonedicarboxylate and ethanolamine was used similarly for the preparation of the pyrrole diesters **778**[775]. The latter were converted into the bicyclic compounds **779** (equation 385).

3. *Reaction of α-haloketones with amides, thioamides and derivatives*

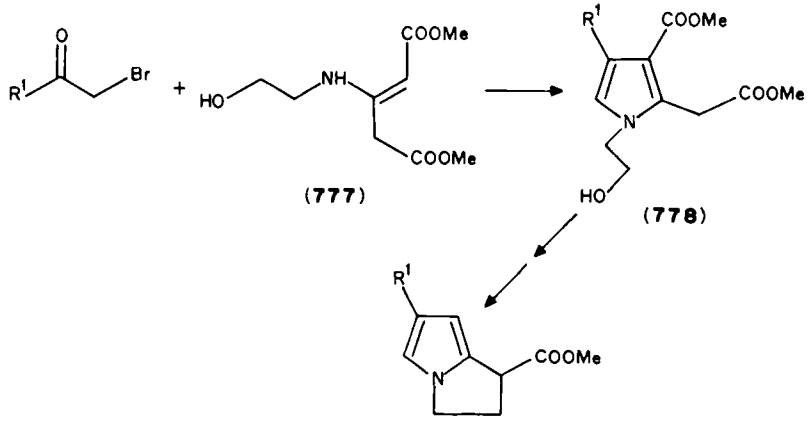
Whereas α-haloketones generally give with amides and urea derivatives oxazole derivatives, α-bromoketones with urea yield mainly imidazoles (**780**) and minor amounts of oxazoles (**781**) (equation 386)[776]. High yields of 2-aminooxazoles could be obtained by reaction of α-hydroxy- or α-bromoketones with cyanamide[777].

Cyclocondensation of α-haloketones with thioamides[778,779], thiourea derivatives[780–785], thioacylamidines[786–789], isothiosemicarbazones[790] and pyrimidine-2-thiones[791] gave a wide variety of thiazole derivatives (**782–786**) (equation 387).



(775) (776)

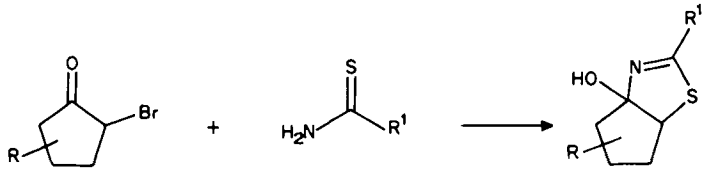
(385)



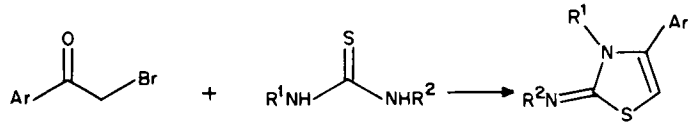
(777) (778) (779)

50% (780) (781)

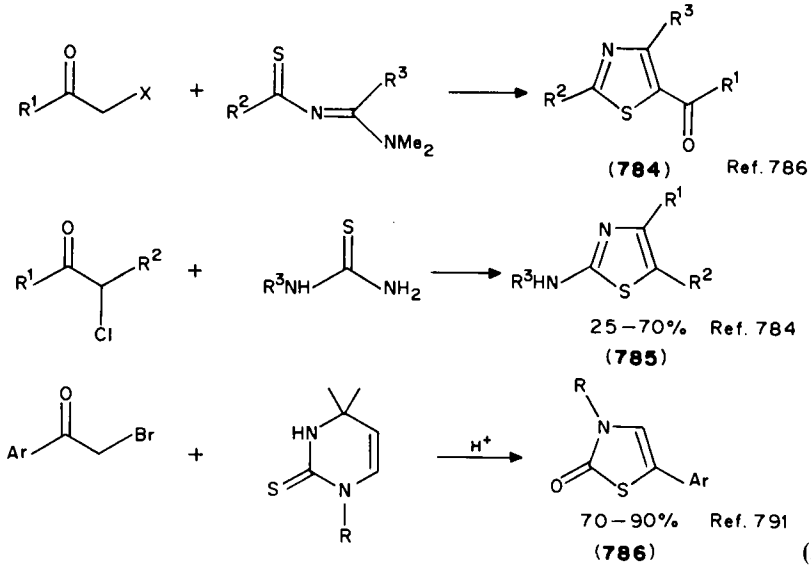
(386)



(782) Ref. 778

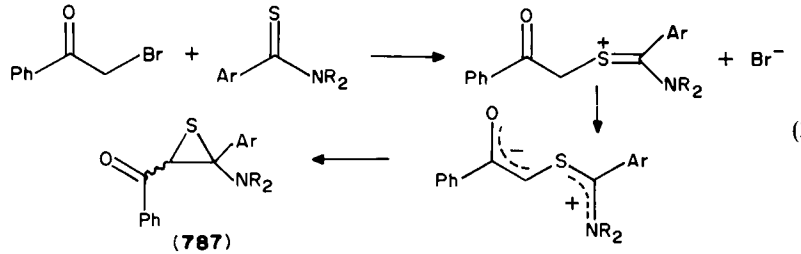


40–85% Ref. 780
(783)



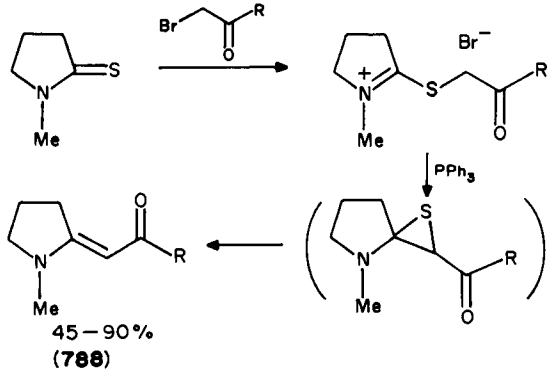
(387)

In a few cases, reaction of phenacyl bromides with substituted thioureas gave minor amounts of 2-imino-1,3-oxathioles together with the expected thiazolines[791]. Also the reaction of α-bromoacetophenone and thiobenzamides did not give the expected thiazoles but instead thiiranes (**787**) were formed via a 4π-electrocyclization (equation 388)[792].



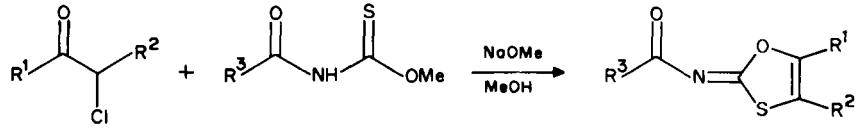
(388)

A similar procedure has been used for the preparation of simple pyrrolidine alkaloids (**788**) (equation 389)[793].



(389)

N-Acyl-1,3-oxathiol-2-imines (**789**) are formed from *O*-alkyl acylcarbamothioates and α-chloroketones in the presence of methanolic sodium methoxide (equation 390)[790].

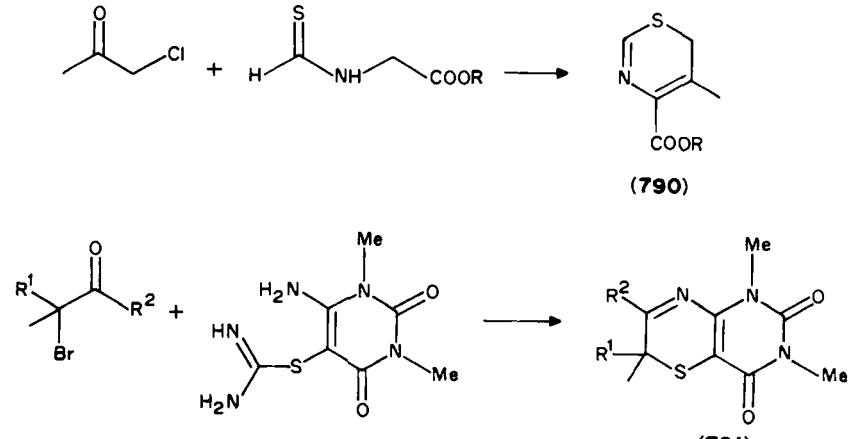


60–85%

(**789**)

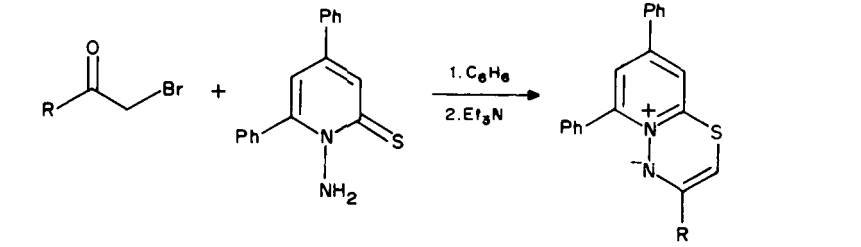
(390)

Efficient syntheses of 1,3-thiazines (**790**)[794], 1,4-thiazines (**791**)[795] and 1,3,4-thiadiazines (**792**)[796,797] are achieved via cyclocondensation of α-haloketones with *N*-substituted thioacyl derivatives (equation 391).



(**790**)

(**791**)



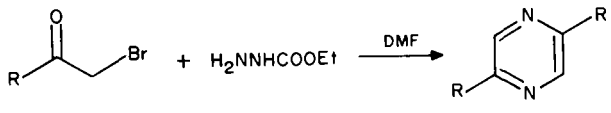
75–95%

(**792**)

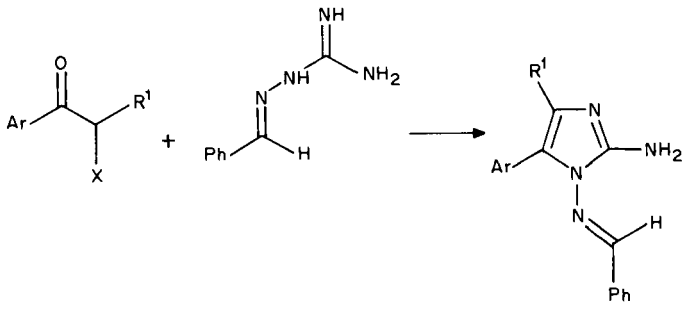
(391)

4. Reaction of α-haloketones with carbonyl reagents

N-Heterocyclic compounds such as pyrazines (**793**)[798], imidazoles (**794**)[799] and pyrazolines (**795**)[800] are prepared from α-haloketones and the appropriate *N*-nucleophiles via cyclocondensation (equation 392).



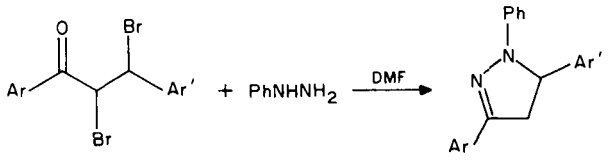
(793)



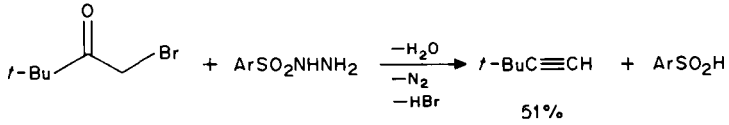
(392)

47–60%

(794)



(795)

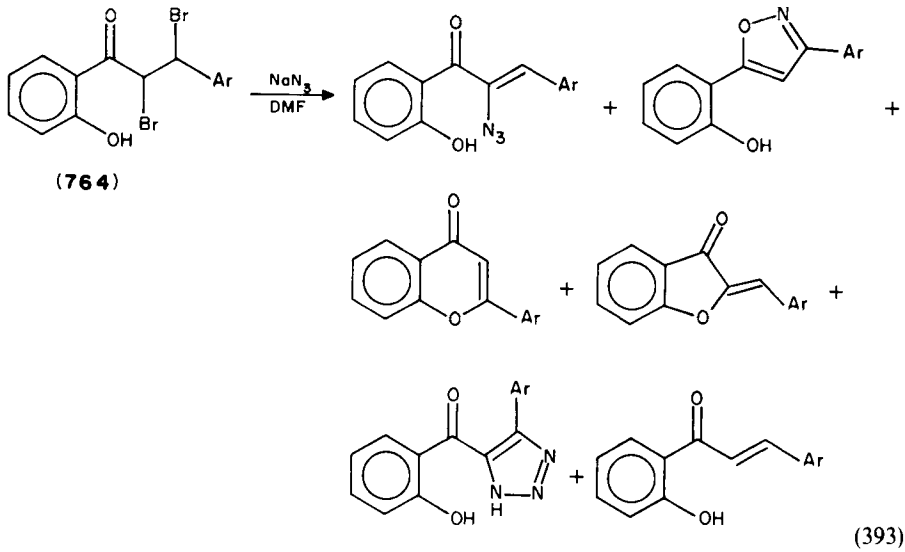


A different reaction yielded 3, 3-dimethylbutyne from 1-bromo-3, 3-dimethylbutan-2-one and arylsulphonylhydrazines (equation 392). The reaction is acid catalysed and mesitylsulphonylhydrazine was the most efficient reagent. The reaction does not proceed via an α-bromomesitylsulphonylhydrazone[801].

An excellent review on the synthesis of azoalkenes from α-haloketones with hydrazine derivatives appeared recently[802].

5. *Reaction of α-haloketones with sodium azide*

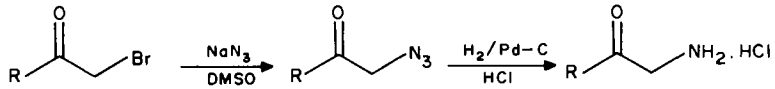
α-Azidoketones, formed via substitution of α-chloroketones with sodium azide, have been used in the total synthesis of peptides. They were hydrogenated and the resulting α-aminoketones could be acylated with *N*-protected amino acid derivatives[803]. In some cases a variety of reaction products were obtained, e.g., when the chalcone dibromides **764** reacted with the azide anion (equation 393)[804].



(764)

(393)

α-Bromomethyl ketones reacted more cleanly with sodium azide in DMSO to yield α-azidomethyl ketones, which were converted into α-aminomethyl ketones by catalytic hydrogenation (equation 394)[977].



(394)

D. Reaction of α-Haloketones with Sulphur and Selenium Nucleophiles

1. Reaction of α-haloketones with inorganic selenium nucleophiles.

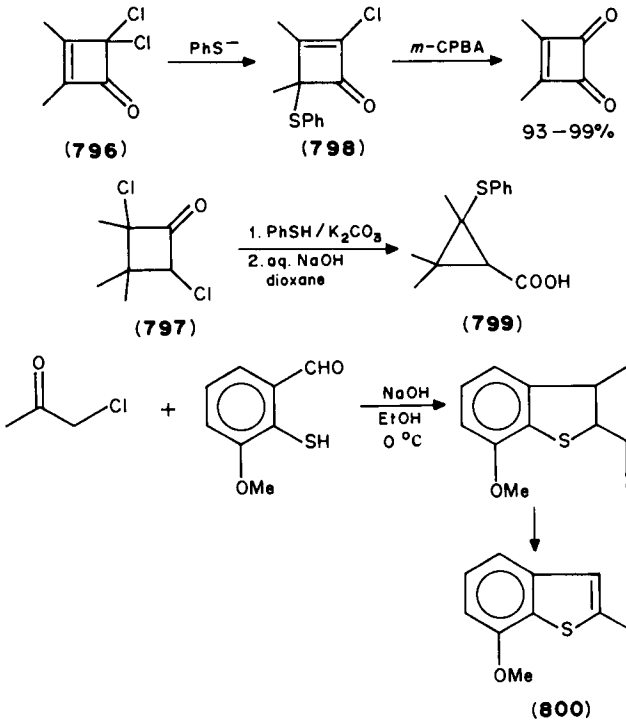
Whereas the reaction of α-chloroketones with sodium hydrogen sulphide gave α-mercaptoketones in excellent yields, treatment of α-haloketones with sodium hydrogen selenide or sodium or magnesium diselenide afforded only the dehalogenated ketones and selenium instead of the α-hydroselenoketones. This is due to the strong reducing power of hydrogen selenide[805].

2. Reaction of α-haloketones with organic sulphur and selenium nucleophiles

The reaction of thiolate anions with α-haloketones in the presence of a base is a simple and efficient method for preparing α-alkyl- and α-arylthioketones[806-808]. This method has been improved using phase-transfer catalysis under neutral conditions and a non-aqueous workup[809]. Thallous phenyl selenide has been used for the preparation of α-phenylselenoketones[810]. On the other hand, substitution and elimination took place when 2-chlorocycloalkanones were treated with thiols yielding 1,2-bis(alkylthio)cycloalk-1-enes[811].

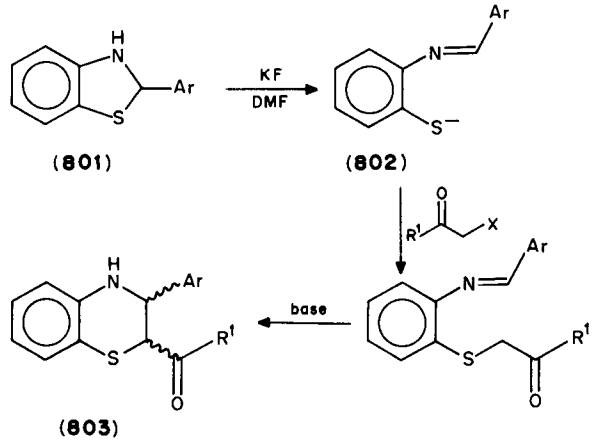
Both S_N2' and Favorskii rearrangements were observed when dichlorocyclobutenones and dichlorocyclobutanones reacted with sulphur nucleophiles. Cyclobutenones (**798**)[812] and cyclopropanes (**799**)[813] were the products when α,α-dichlorocyclobutenone (**796**) and

α,α'-dichlorocyclobutanone (**797**) were treated with thiophenoxide ion or with thiophenol and potassium carbonate, respectively (equation 395).



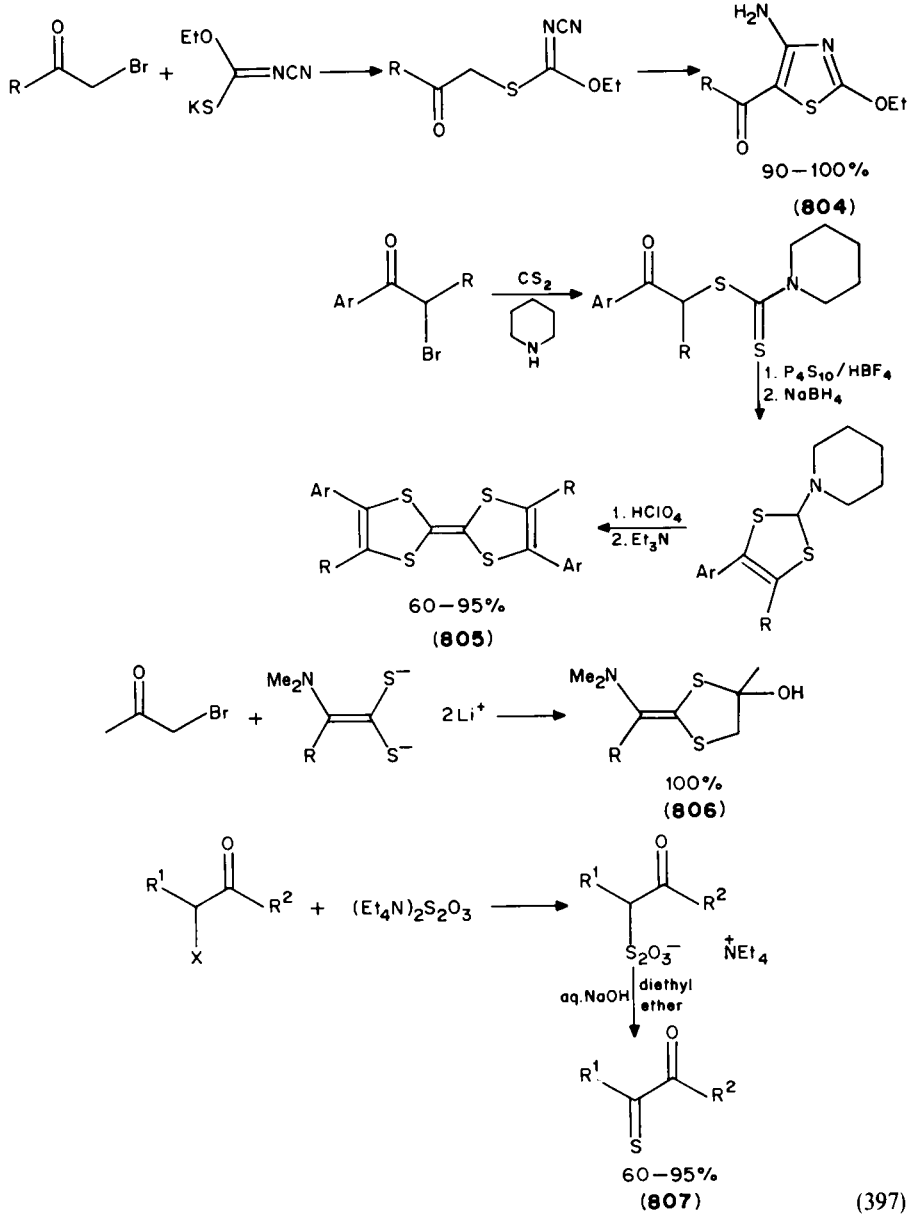
(395)

Base-catalysed condensation of 2-mercapto-3-methoxybenzaldehyde with chloroacetone furnished 2-acetyl-7-methoxybenzothiophene (**800**)[814]. A ring expansion method for the preparation of 2,3-dihydro-1,4-benzothiazines (**803**) from 2-aryl-2,3-dihydrobenzothiazoles (**801**) was developed, involving ring opening to give **802**, substitution with an α-haloketone and ring closure (equation 396)[815].



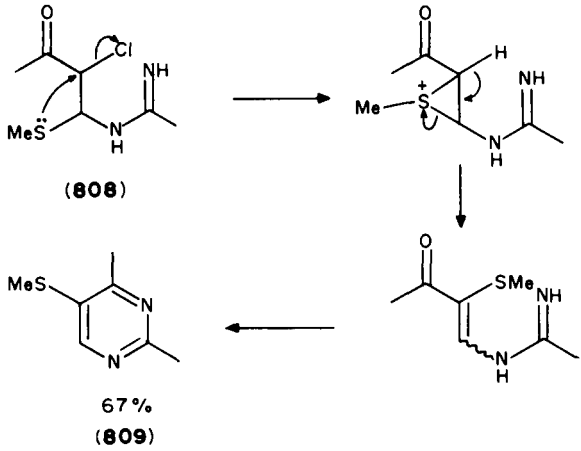
(396)

Reaction of α-haloketones with salts of thiocarbamates[816], dithiocarbamates[817], dithiocarbonates[818], thiocarbonyl cyanamides[819,820], dithiolate dianions[821,822] or tetraethylammonium thiosulphate[620] furnished substitution products. The latter products have been used as intermediates in the synthesis of thiazoles (**804**)[818–820], tetrathiafulvalenes (**805**)[817], 1,3-dithiolanes (**806**)[821] and α-thioxoketones (**807**) (equation 397)[620].



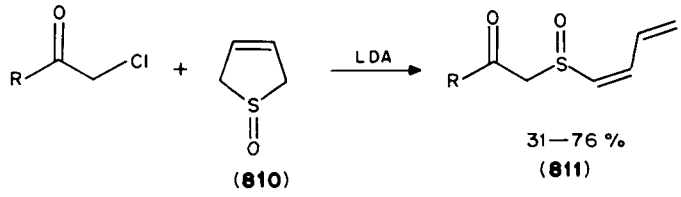
(397)

Similar Se-substitution products were obtained when α-haloketones reacted with Se-nucleophiles such as piperidinium selenocarboxylates[823] and diselenocarbamates[824,825]. Whereas α-haloketones gave with dialkyl or diaryl sulphides and selenides the corresponding salts[826], an intramolecular rearrangement involving replacement of chlorine by a thiomethyl function was observed in **808**, which was transformed into a pyrimidine derivative (**809**) (equation 398)[684].



(398)

Treatment of α-haloketones with the cyclic sulphoxide **810** in the presence of LDA resulted in alkylation with ring opening to **811** (equation 399)[827].



(399)

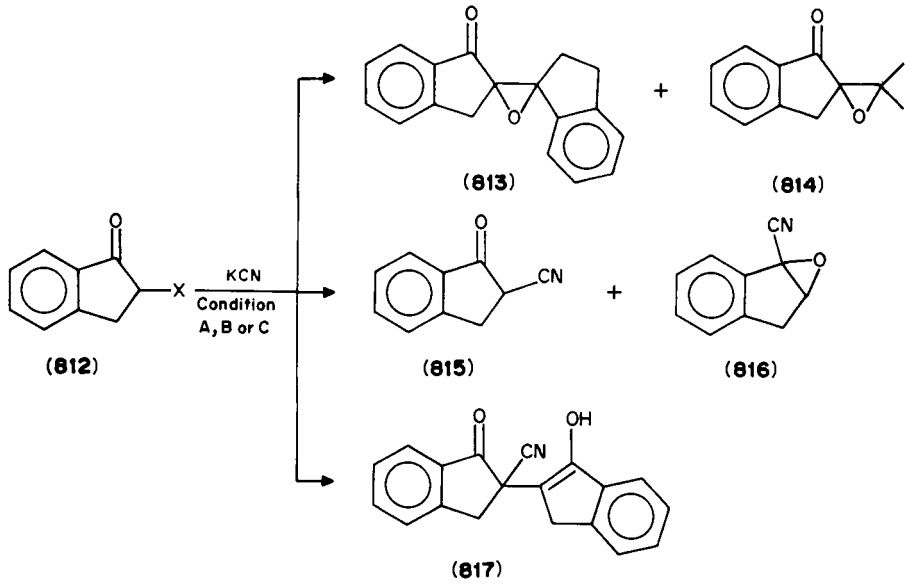
E. Reaction of α-Haloketones with Carbon Nucleophiles

1. *Reaction of α-haloketones with cyanide*

α-Haloketones may undergo two competitive reactions with sodium or potassium cyanide. Nucleophilic addition and intramolecular substitution lead to 2-cyano-oxiranes[828–830] whereas Favorskii rearrangement and nucleophilic addition generate cyanocyclopropanes (**818a**) (equation 400)[830]. The reaction is solvent dependent, with base-induced reactions in methanol or acetone and nucleophilic attack in acetonitrile[831]. With conditions A and B the cyanide anion is acting predominantly as a base, giving rise to Darzens-type reaction products, whereas with condition C cyanide is a nucleophile attacking the carbonyl function and the halogen atom.

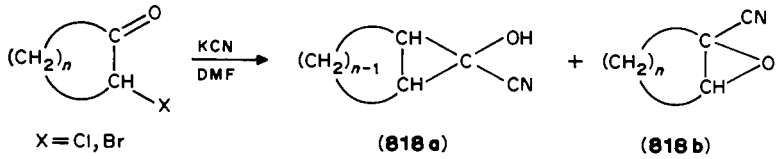
2. *Reaction of α-haloketones with carbanions, ylides and enolates*

The substitution or Favorskii rearrangement products formed from α-haloketones with

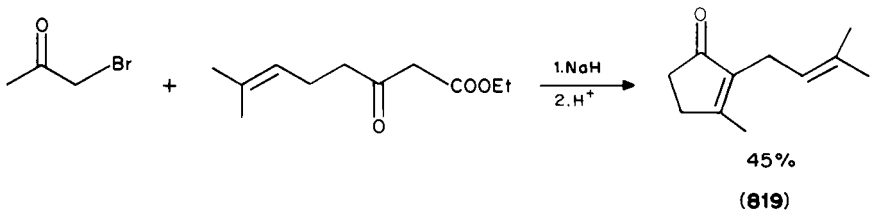


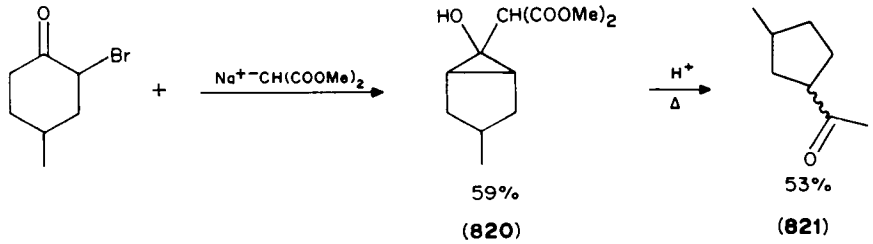
	Yield (%)				
	813	**814**	**815**	**816**	**817**
A. Methanol–H_2O	94				
B. Acetone–H_2O	76	15			
C. Acetonitrile–H_2O			35	5	50

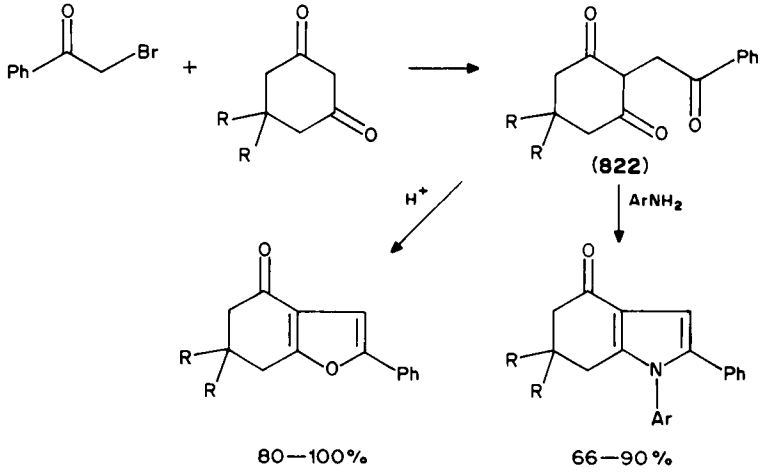
(400)



active methylene functions constituted excellent intermediates for the synthesis of cyclopentenones (**819**)[832], acyl cyclopentanes (**821**)[833], furan (**823**) and indole (**824**) derivatives[834] (equation 401).

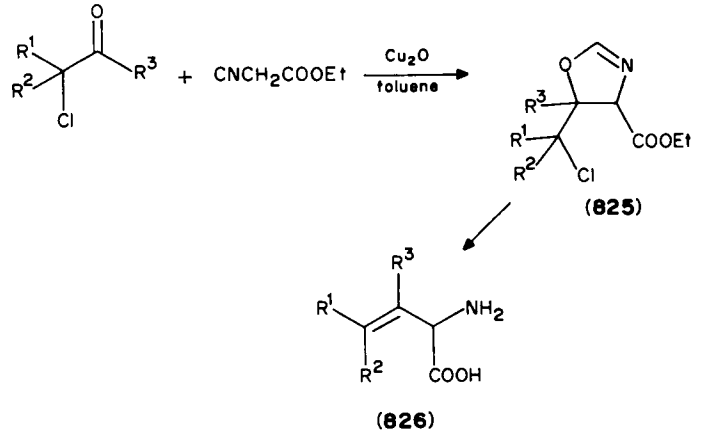






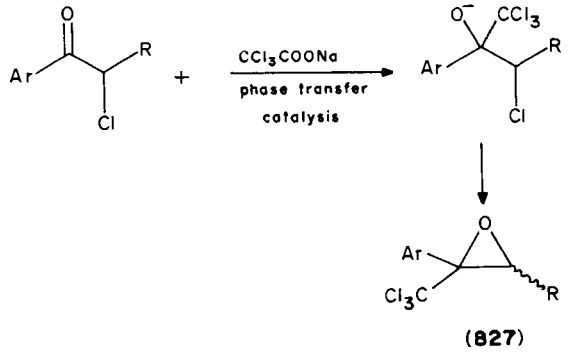
(401)

On the other hand, reaction of α-haloketones with isocyanoacetates gave rise to 2-oxazoline derivatives (**825**)[835], which were easily transformed into β,γ-unsaturated α-aminocarboxylic acids (**826**) (equation 402).



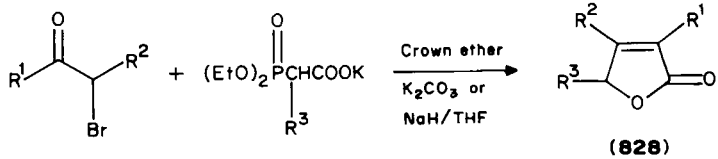
(402)

Treatment of phenacyl chlorides with trichloromethyl carbanion afforded the stable oxiranes **827** via an addition–intramolecular substitution sequence (equation 403)[836].



(827)

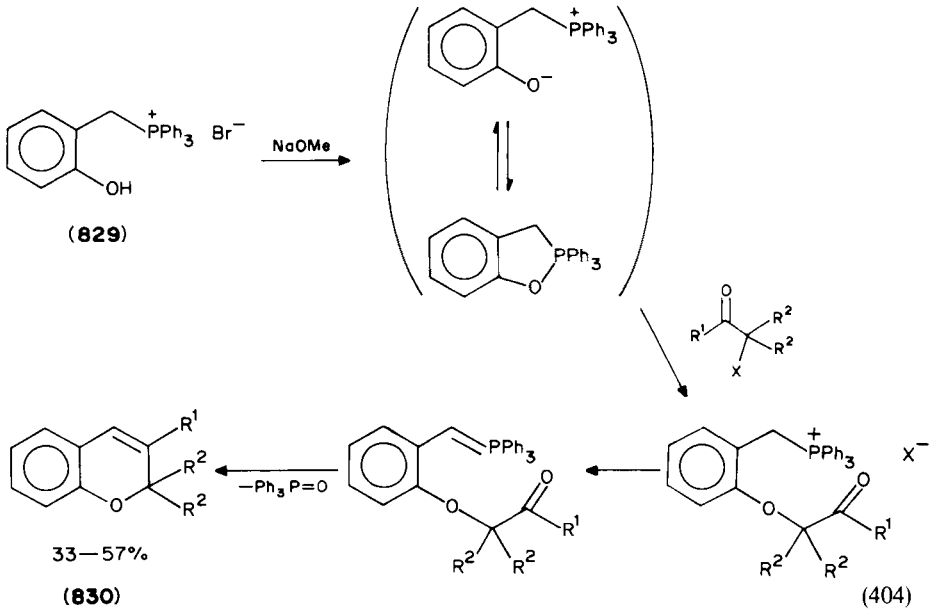
(403)



(828)

Emmons–Horner condensations of α-haloketones with phosphonate anions constituted key steps in the synthesis of chlorinated furanones (**828**)[837,838] (equation 403) and retinal derivatives[839].

α-Haloketones have been alkylated by σ-hydroxybenzyltriphenylphosphonium salts (**829**) in the presence of a base, giving 3-chromenes (**830**) (equation 404)[840].



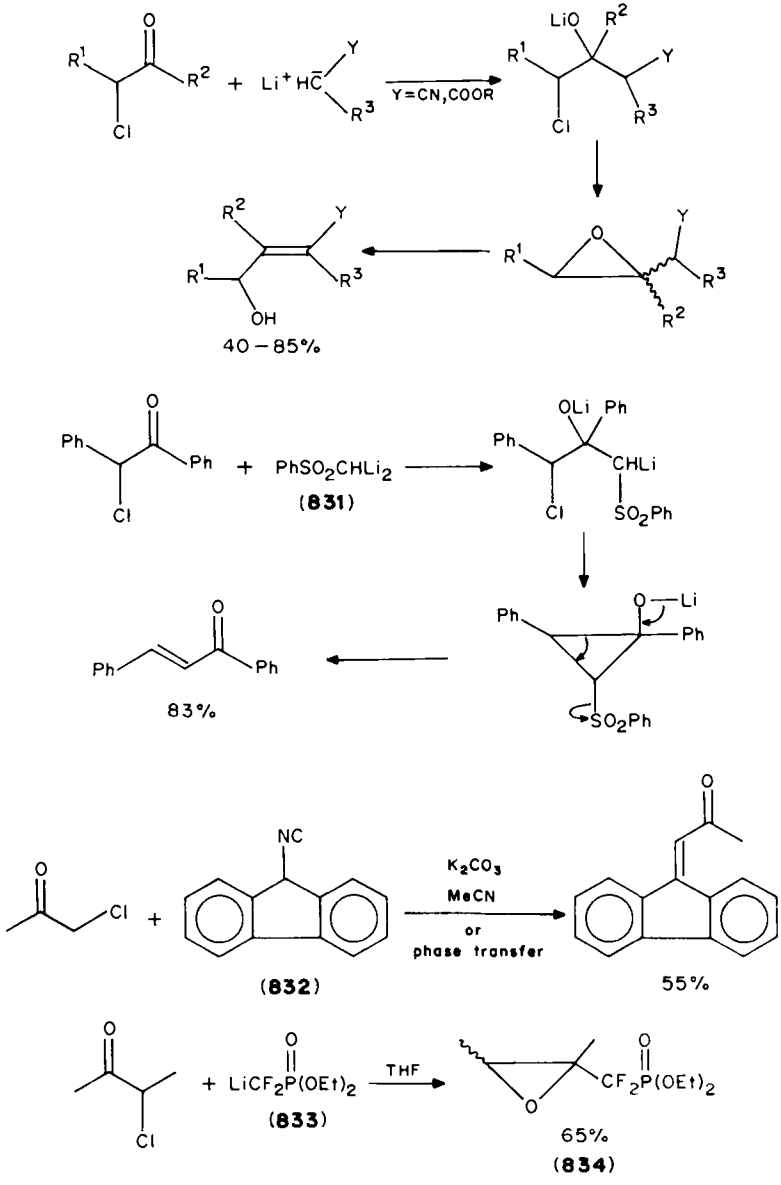
(829)

33—57%

(830)

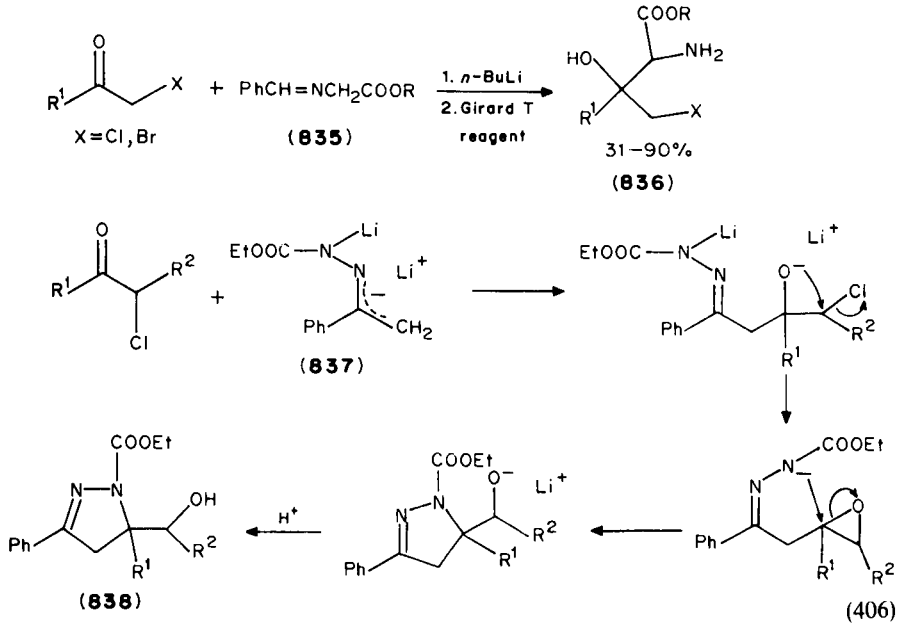
(404)

Carbanions substituted with electron-withdrawing groups act as homologating reagents, forming unsaturated alcohols and ketones. Lithium nitrile or ester carbanions[841], [(phenylsulphonyl)methylene]dilithium (**831**)[842] and the isonitrile **832**[843] have been used in this procedure (equation 405). Reaction of (diethylphosphinyl)difluoromethyllithium (**833**) with α-chloroketones took a different route, leading to difluorinated epoxides (**834**) (equation 405)[844].



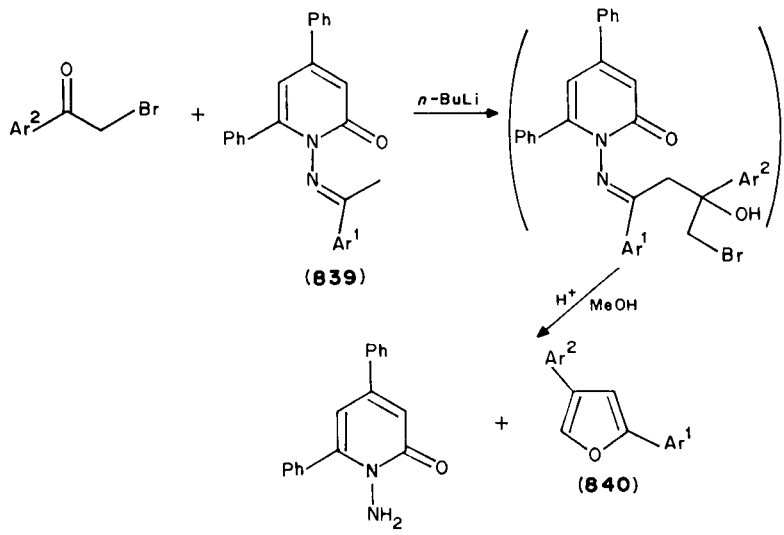
(405)

The lithium salt of the *N*-benzylidene glycinate (**835**) gave rise to products **836**, which can be transformed into α-amino acid derivatives[845], while the 1,4-dianion of acetophenone *N*-ethoxycarbonylhydrazone (**837**) provided pyrazoline derivatives (**838**) (equation 406)[846].



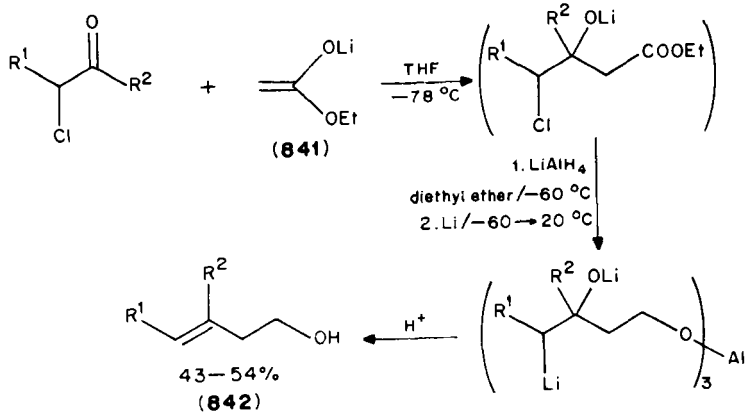
(406)

An efficient regioselective synthesis of 2,4-diarylfurans (**840**) has been developed from metalated ketimines (derived from **839**) and phenacyl bromides and successive treatment with methanolic hydrogen chloride (equation 407)[847].



(407)

The reaction of the lithium enolate of ethyl acetate (**841**) with α-chloroketones followed by reduction and lithiation led to homoallylic alcohols (**842**) in a regioselective manner (equation 408)[848].

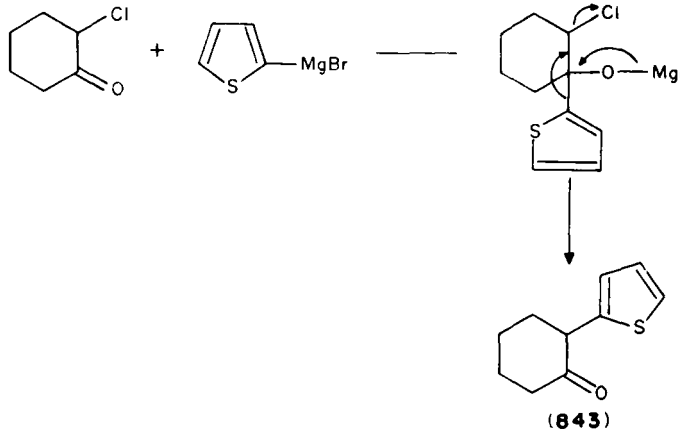


(408)

F. Reaction of α-Haloketones with Organometallic Reagents

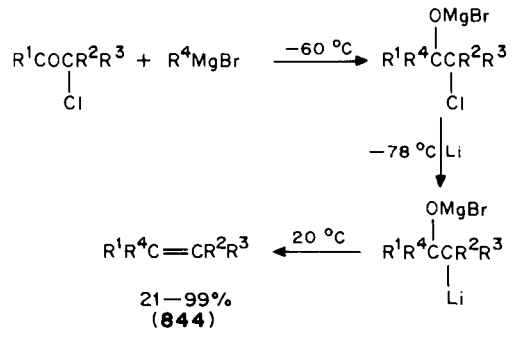
1. Reaction of α-haloketones with Grignard reagents

While in most cases treatment of α-haloketones with aliphatic[849], allylic[850] and acetylenic[851,852] Grignard reagents gave halohydrins, vinylic[853] or thienylmagnesium halides[854] provided 'substitution products' (**843**) (equation 409).

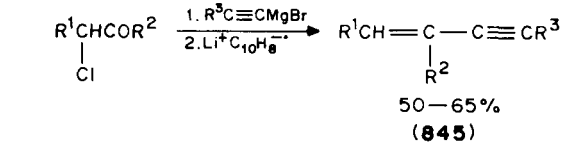


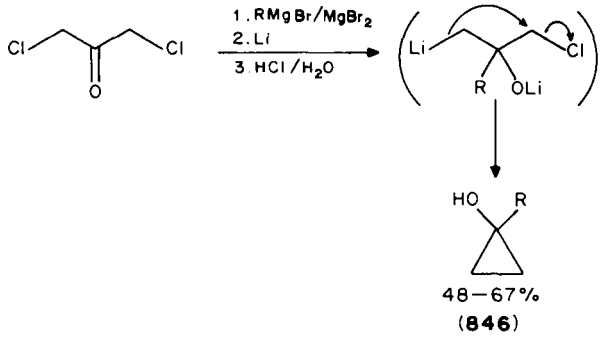
(409)

The Grignard reaction with α-chloroketones has been especially fruitful in the preparation of olefins (**844**)[855–857] and conjugated enynes (**845**)[858] when the originally formed magnesium salts of halohydrins were allowed to react with lithium metal and lithium naphthalenide, respectively (equation 410). 1,3-Dichloroacetone gave the corresponding 1-substituted cyclopropanols (**846**) (equation 411)[859]. A vinyl oxirane (**848**) was formed when the α-bromoketone **847** was treated with vinylmagnesium bromide (equation 411a)[860].

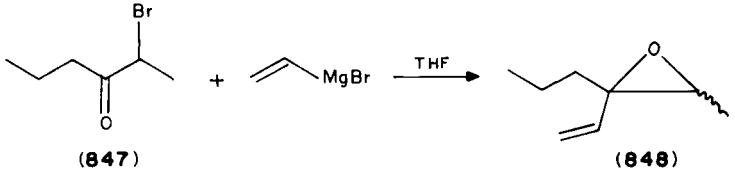


(410)



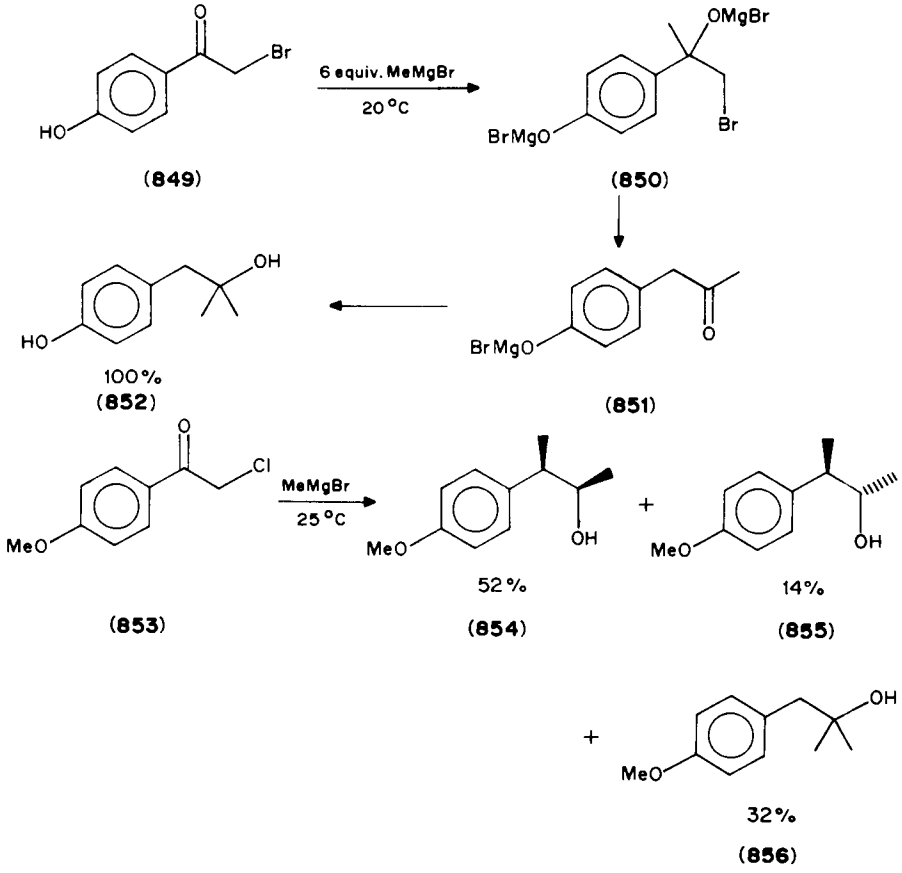


(411)



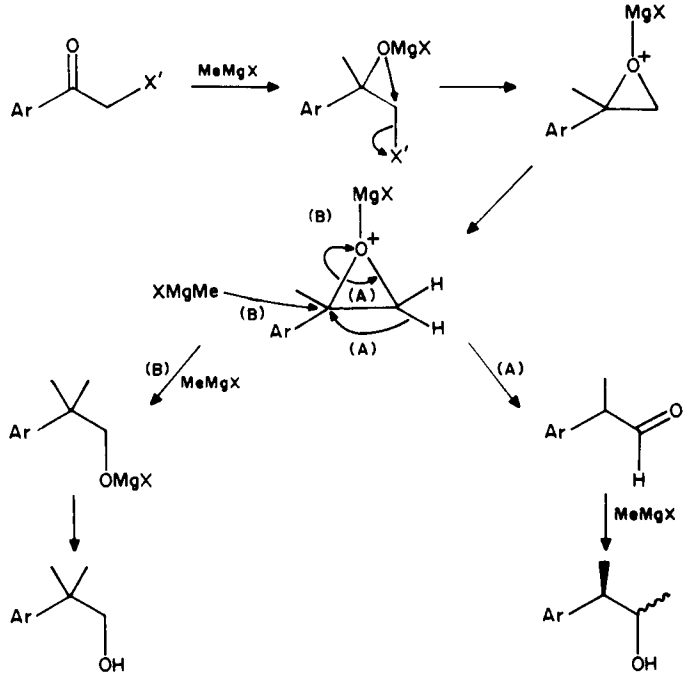
(411a)

The various reaction patterns with Grignard reagents are illustrated by using 4-substituted-α-haloacetophenones[861]. The initial reaction of **849** with an excess of MeMgBr is attack at the carbonyl to form a halohydrin salt (**850**). The various reactions which then follow are substituent-dependent. In the 4-hydroxy case the only product is 1-aryl-2-methylpropan-2-ol (**852**), arising from a [1,2]-aryl shift with simultaneous elimination of magnesium dihalide. When the substituent is 4-methoxy (**853**), epoxide formation and a subsequent [1,2]-hydride migration to the benzylic position become important or attack of the Grignard reagent at the benzylic carbon of the epoxide giving **854**, **855** and **856**. With the 4-bromo compound **857**, the reaction proceeds exclusively via the epoxide **859** and, following a [1,2]-hydride shift, leads to the isomeric butanols **861** and **862** (equation 412).


6 equiv. MeMgBr
20 °C
(849)
(850)
(851)
100%
(852)
MeMgBr
25 °C
(853)
52%
(854)
14%
(855)
32%
(856)
MeMgBr
(857)
(858)
(859)
72%
(862)
26%
(861)
(860)

(412)

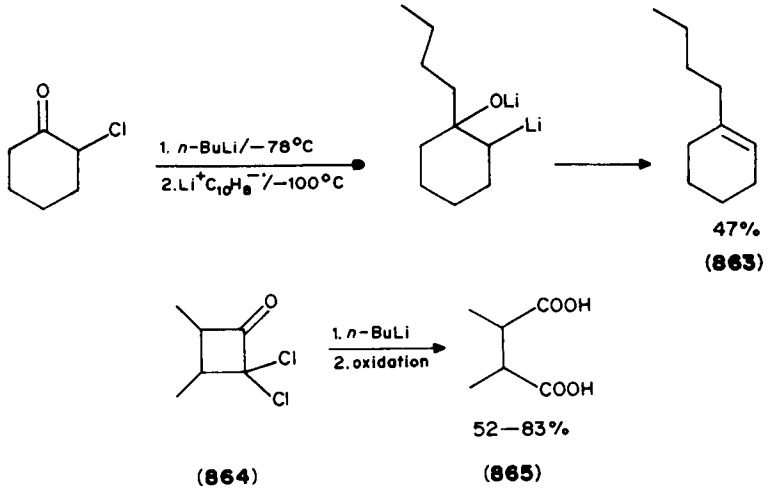
The formation of the reaction products is generalized in equation 413.



(413)

2. Reaction of α-haloketones with organolithium compounds

Whereas alkynyl chlorohydrins constitute the expected reaction products from treatment of α-haloketones with alkynyl lithiums[851,862], reaction of α-chloroketones with *n*-butyllithium and lithium naphthalenide afforded olefins (**863**) (equation 414)[863].

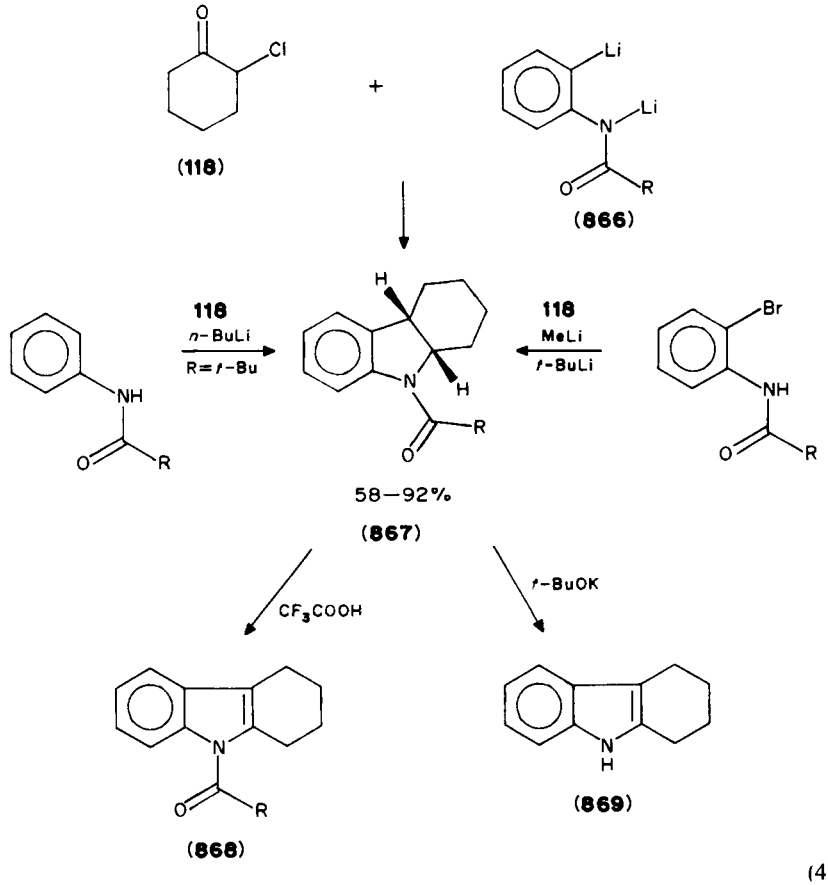


(414)

Treatment of α-chloroketones with trimethylstannylmethyllithium gave rise to allylic alcohols via hydroxyalkylstannanes[864].

Dichlorocyclobutanones (**864**) can be converted into succinic acid derivatives (**865**) using *n*-butyllithium, acetic anhydride and sodium metaperiodate–ruthenium dioxide[865]. The reaction proceeds via oxidation of the corresponding β-chloroenolate (equation 414).

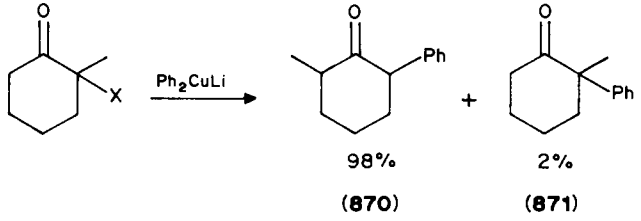
Organodilithium reagents (**866**) with α-chlorocyclohexanone (**118**) yield indole derivatives (**867–869**) (equation 415)[866]. The regiochemistry is determined by the relative nucleophilicities and electrophilicities of the reactants and the regioselectivity realized in their formation. With α-haloketones as bis-electrophiles, the annelation process proceeds with complete regiochemical control in that the carbanionic centre of the dilithium reagent reacts at the carbonyl carbon of the haloketone reactant. Overall regioselectivity is determined, therefore, by the regioselectivity achieved in reactant preparation, which can usually be accomplished by using heteroatom-directed deprotonation or site-specific halogen–lithium exchange.



(415)

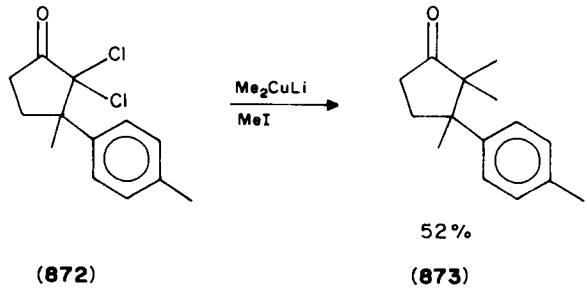
Lithium dimethylcuprate as a nucleophilic reagent for α-haloketones is less selective for alkylation than methyl cyanocuprate, especially in diethyl ether–dimethylformamide. The

inverse addition and addition of ligands, such as dimethyl maleate, also improves the selectivity[867]. Whereas the reaction of acyclic aliphatic ketones with diphenylcopper-lithium gave the normal alkylation products, cyclic α-haloketones afforded the rearranged alkylation product **870** nearly exclusively (equation 416)[868].



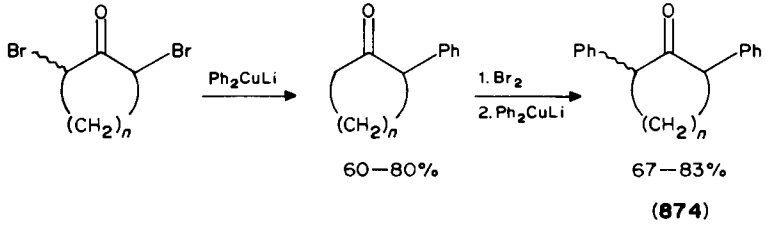
(416)

This alkylation procedure has been applied in the synthesis of α-cuparenone (**873**) using a dichlorocyclopentane derivative (**872**) with dimethylcopperlithium and iodomethane (equation 417)[869].



(417)

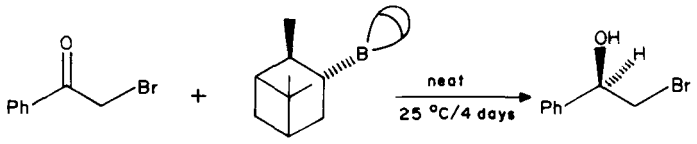
Similarly, α,α'-dibromocycloalkanones can be converted into α,α'-diphenylcycloalkanones (**874**) via the α,α'-dibromo-α-phenylcycloalkanones[870]. The reaction can also be stopped at the α-phenylcycloalkanone stage (equation 418).



(418)

3. *Reaction of α-haloketones with organoboron compounds*

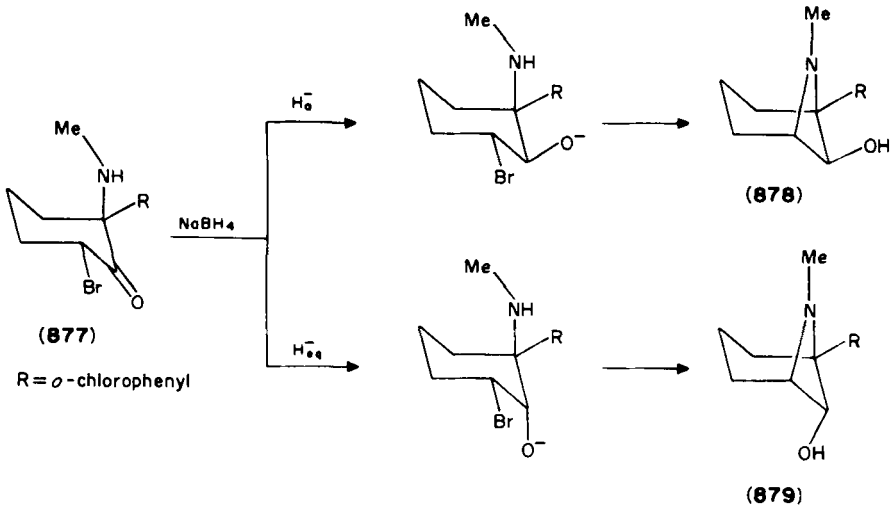
B-3-Pinanyl-9-borabicyclo[3.3.1]nonane (Midland's reagent) (**875**) has recently emerged as an exceptionally valuable reagent for the asymmetric reduction of α-haloketones. Thus α-bromoacetophenone, using 100% excess of reagent (derived from 92% e.e. (+)-α-pinene) produced the bromohydrin **876** in 95% yield and 86% e.e. However, the results proved less satisfactory in other cases (equation 419)[871,872].



(875) [(*R*)-876](86% e.e.) (419)

The bromohydrins may conveniently yield the corresponding chiral epoxides or can be dehalogenated to the parent alcohol with retention of optical activity. Reduction of α-fluoroketones to the corresponding fluorohydrins can be performed using lithium triethylborohydride[873].

A 6-azabicyclo[3.1.1]heptane ring system (**878, 879**) was formed during the sodium borohydride reduction of 2-bromo-6-(*o*-chlorophenyl)-6-(methylamino)cyclohexanone (**877**) via an intramolecular S_N2 reaction (equation 420)[874].

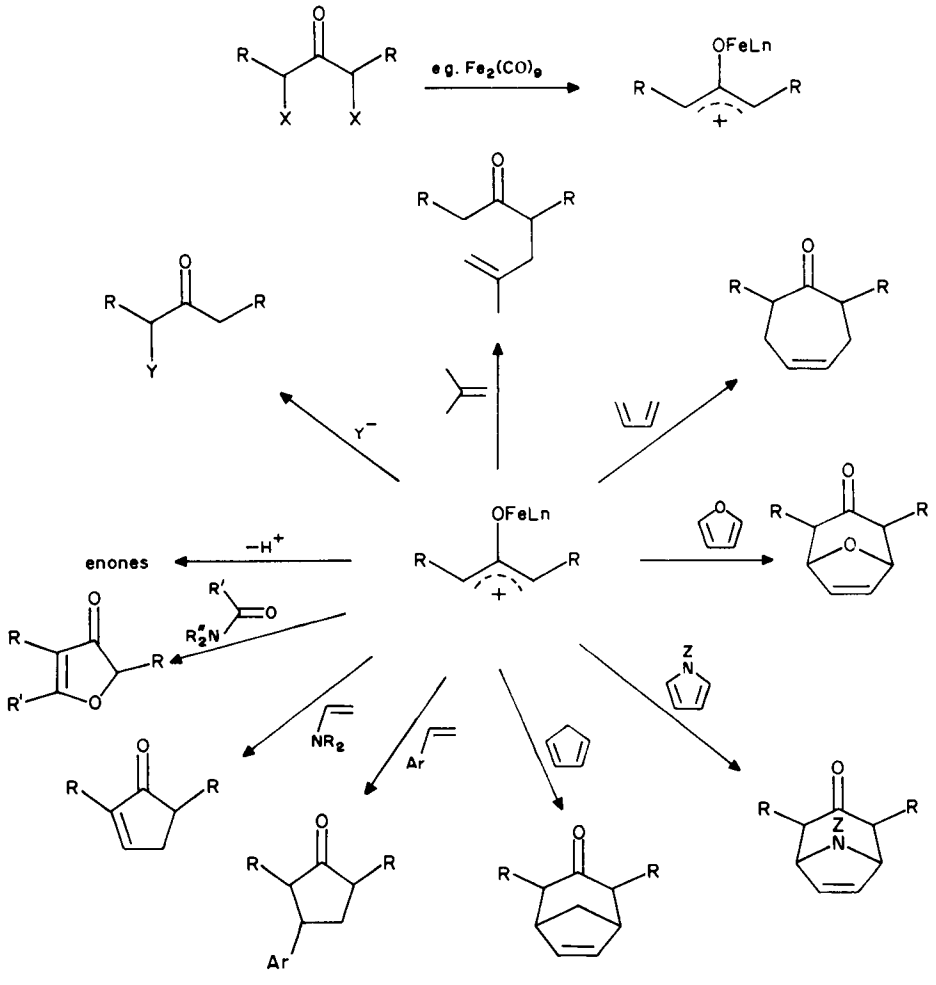


(420)

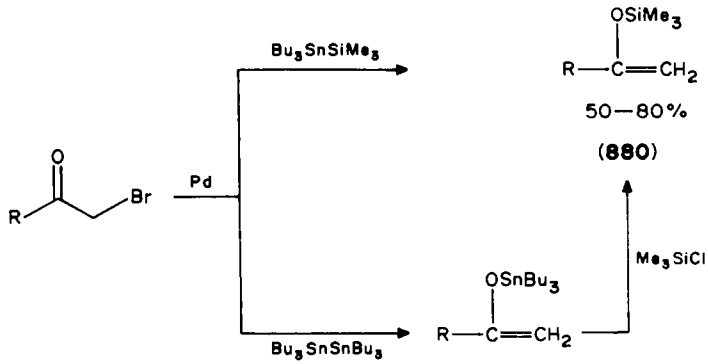
4. Reaction of α-haloketones with metal complexes

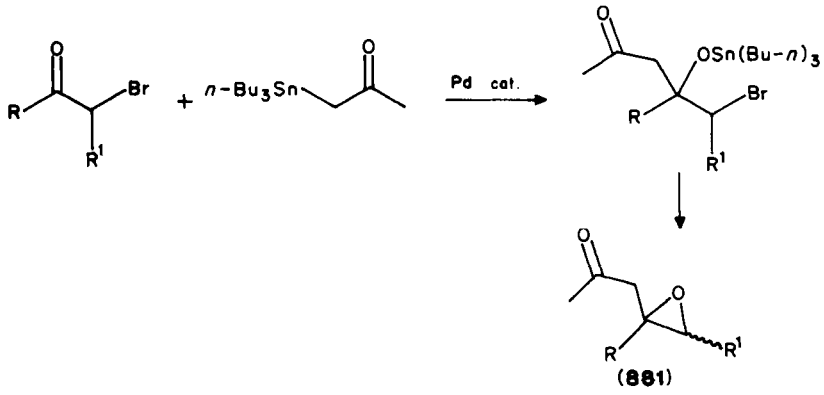
The generation of oxyallyl cations via reaction of α,α'-dihaloketones with a variety of metal complexes, especially $Fe_2(CO)_9$, and subsequent ring closure leading to various carbocycles, has been the subject of excellent reviews[875,876]. The principal widely used reactions are summarized in equation 421[877].

Reaction of α-haloketones with organometallic reagents takes place by a variety of pathways. Whereas the palladium-catalysed reaction of trimethylsilyltributyltin or of hexabutylditin gave rise to enol silyl ethers (**880**)[878,879], oxiranes (**881**) were prepared with acetonyl- and allyl-tin reagents in a palladium-catalysed reaction (equation 422)[880]. If the catalyst does not contain phosphane ligands a 1,4-diketone (**882**) is formed, apparently through an initial oxidative addition at the α-halo position (equation 422)[881]. However, the reaction of tributyltin enolates with α-haloketones afforded substituted furans (**883**), which were not derived from the normal cross-coupling products, i.e. 1,4-diketones, but through addition of the tin enolate (equation 422)[882,883].

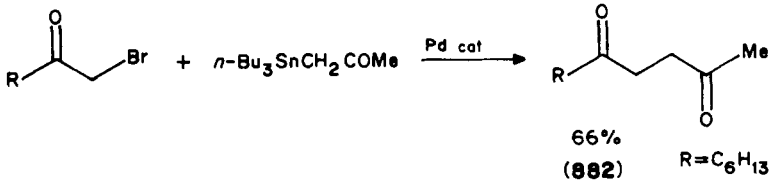

e.g. $Fe_2(CO)_9$
OFeLn
Y^-
$-H^+$
enones
NR_2
Ar
Z
N
Ln=Br^-, CO, solvent

(421)

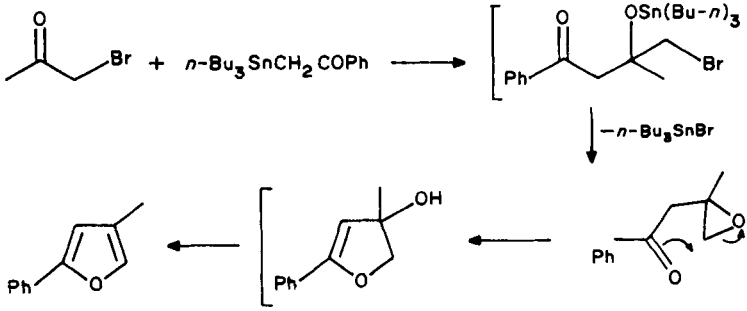

$Bu_3SnSiMe_3$
Pd
Br
OSiMe$_3$
CH_2
50—80%
(880)
Me_3SiCl
OSnBu$_3$
$Bu_3SnSnBu_3$



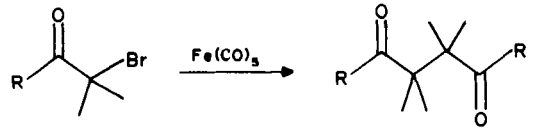
(881)



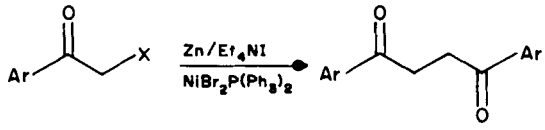
66%
(882)



32%
(883)

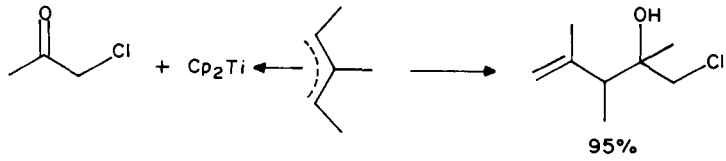


20—28%
(884)



(885)

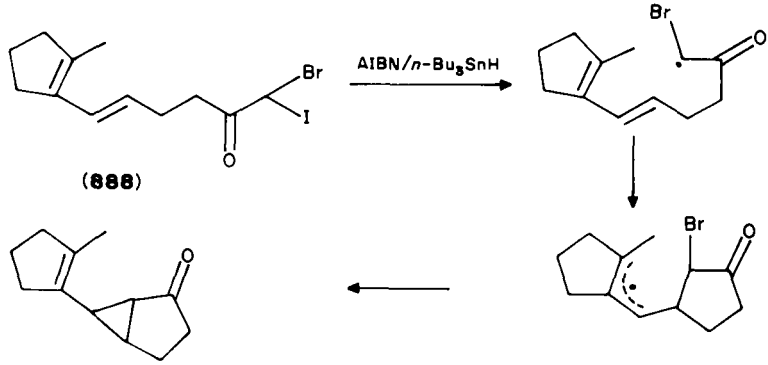
1,4-Diketones (**884**, **885**) were also formed by coupling reactions of α-bromoketones in the presence of iron pentacarbonyl[884] and an active Zn complex (equation 422)[885]. Reaction of π-allyldicyclopentadienyltitanium(III) complexes (**886**) with α-chloroketones gave homoallyl alcohols (**887**) after hydrolysis (equation 423)[886].



(423)

(**886**) (**887**)

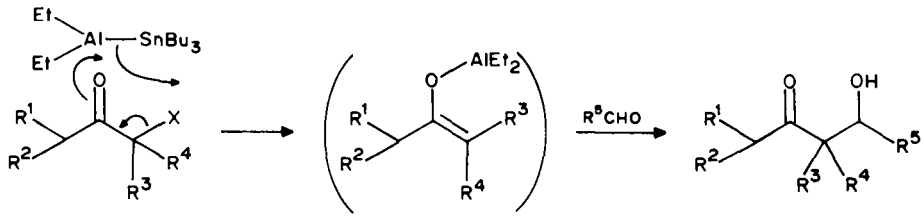
The first example of an intramolecular Simmons–Smith reaction was reported when the mixed α,α-dihaloketone **888** was decomposed in the presence of n-$Bu_3Sn^{\cdot}$, leading to the formation of the cyclopropane **889** (equation 424)[887].



(**888**) (424)

(**889**)

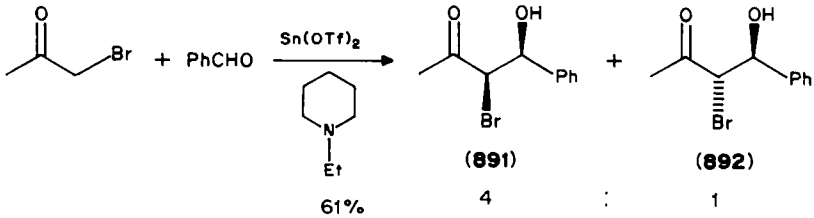
Regiospecific aldol condensations have been demonstrated by the simultaneous addition of α-haloketones and aldehydes or ketones to a mixture of diethylaluminium chloride and zinc[888]. Also, treatment of α-bromoketones with a reagent prepared from n-Bu_3SnLi and Et_2AlCl or from $SnCl_2$ and Et_2AlCl[889] or by means of $Bu_3SnAlEt_2$ or $Bu_3PbAlEt_2$[890] afforded aluminium enolates which reacted with ketones or aldehydes to give β-hydroxycarbonyl compounds (**890**) (equation 425).



(**890**)

(425)

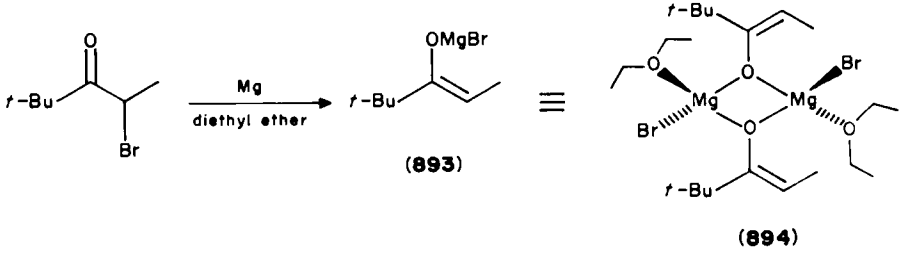
Other cross-aldol condensations of α-haloketones with ketones or aldehydes involved divalent tin enolates formed *in situ* with $Sn(OTf)_2$[891–893] by the oxidative addition of metallic tin[894] or SnF_2[895] (equation 426). Cerium enolates[896,897] gave similar results.



$Sn(OTf)_2$ = tin trifluoromethanesulphonate (426)

High diastereoselectivity was achieved in the directed aldol reaction of lithium enolates of 1-fluoro-3,3-dimethylbutan-2-one with aldehydes, whereas an apparent reversal of diastereoselection was found in Lewis acid-mediated reactions of the corresponding enol silyl ethers[898]. The cross-aldolization of α-bromoketones with aldehydes in the presence of chromium(II) chloride is also an excellent stereospecific reaction[899] but zinc[900,901] and zinc–titanium(IV) chloride[902] react less stereoselectively.

The bromomagnesium enolate of *tert*-butyl ethyl ketone (**893**) crystallized as a dimeric, ether-solvated aggregate in the solid state with *Z* geometry (**894**) (equation 427)[903]. Since the stereochemistry of the aldols can be either thermodynamically or kinetically controlled, it is important to understand the aggregation state of the reactants and the steric requirements of the chelating ligands in order to predict and/or control aldol reaction stereochemistry. Magnesium enolates exist as dimeric aggregates in solution and the magnesium aldol reaction proceeds through dimeric intermediates.

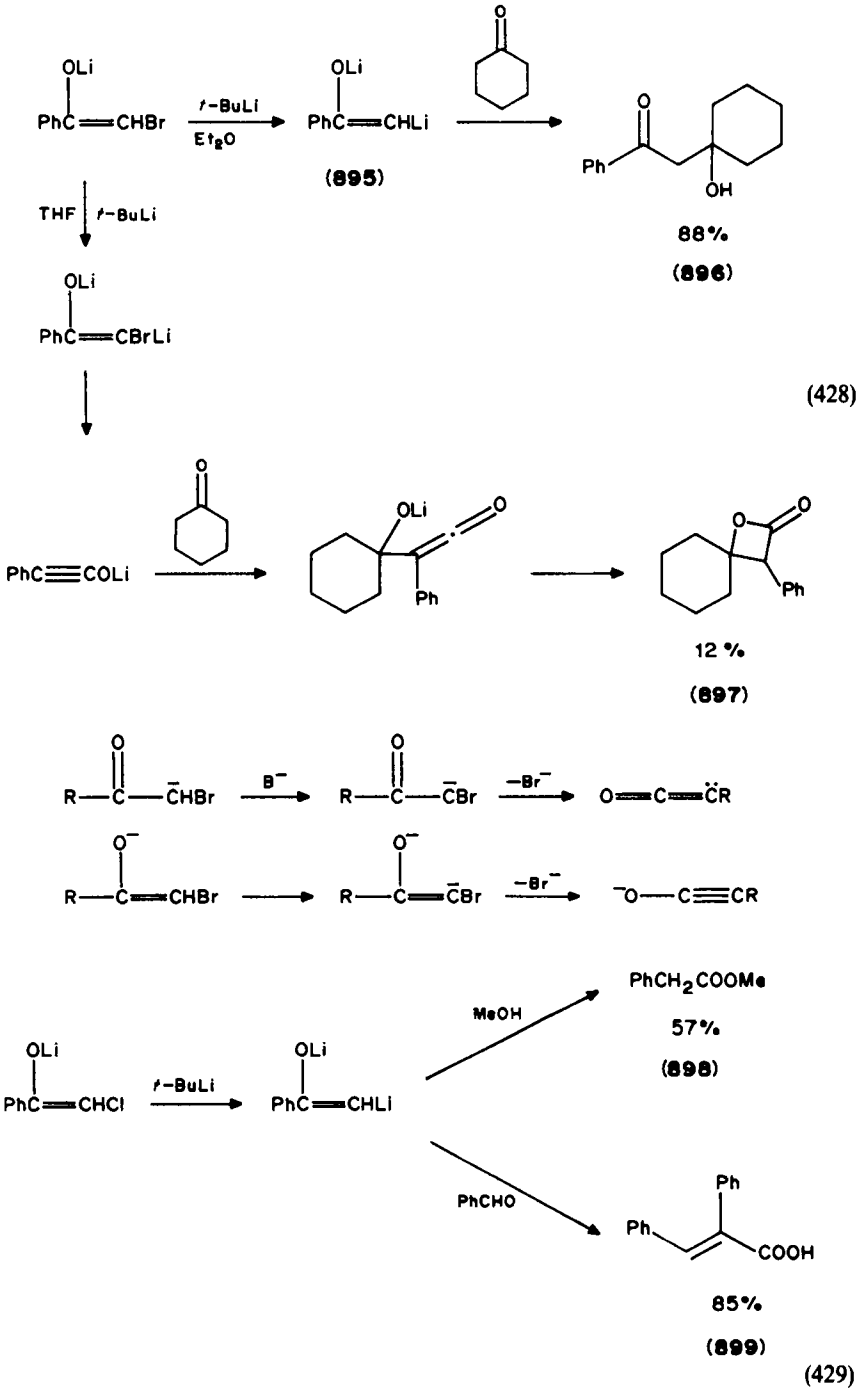


(427)

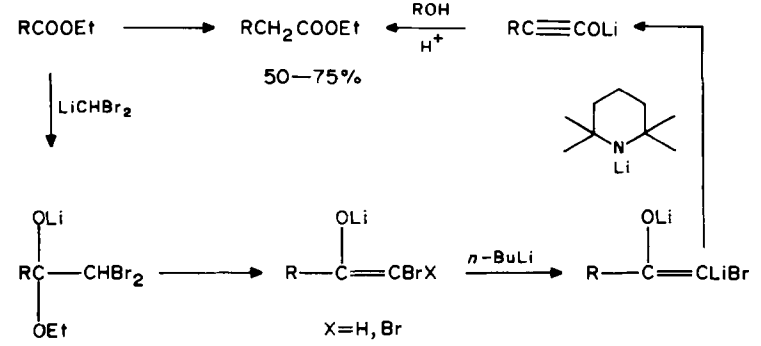
The following reactions cannot be classified as reactions of metal complexes, but they are described here by analogy with the above reactions involving enolates.

α-Keto dianions (**895**) can be trapped by ketones leading to aldol condensation products (**896**), but when the reaction was carried out in THF rather than in diethyl ether a spiro β-lactone (**897**) could be obtained via an alkynolate anion (equation 428)[904]. This reaction represents the carbon analogue of the Hofmann reaction involving deprotonation of an α-bromoketone enolate, followed by rearrangement with loss of bromide to afford a ketene anion (equation 428).

Quenching of the chloroenolate anion of phenacyl chloride with methanol afforded methyl phenylacetate (**898**), whereas the use of benzaldehyde produced α-phenylcinnamic acid (**899**) (equation 429)[904].

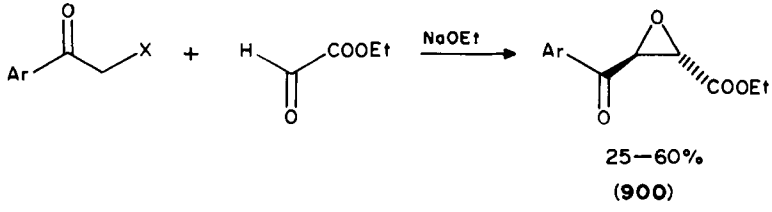

OLi
PhC≡CHBr
t-BuLi
Et2O
OLi
PhC≡CHLi
(895)
O
Ph
OH
88%
(896)
THF
t-BuLi
OLi
PhC≡CBrLi
(428)
O
PhC≡COLi
OLi
O
Ph
O
O
Ph
12 %
(897)
R—C(=O)—CHBr
B⁻
R—C(=O)—CBr
−Br⁻
O=C=CR
R—C(O⁻)=CHBr
R—C(O⁻)=CBr
−Br⁻
⁻O—C≡CR
OLi
PhC≡CHCl
t-BuLi
OLi
PhC≡CHLi
MeOH
PhCH2COOMe
57%
(898)
PhCHO
Ph
Ph
COOH
85%
(899)
(429)

This procedure has been used in ester homologations via the α-bromo-α-keto dianions (equation 430)[905].



(430)

The Darzens condensation of phenacyl halides with aldehydes has been used in the preparation of oxiranes (**900**) (equation 431)[906,907].

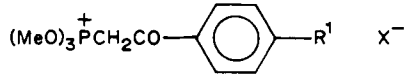


(431)

Tandem Michael ring closures have been developed recently for the efficient formation of cyclopropanes (**902**), via treatment of the ketone enolate with a vinylphosphonium salt (**901**) (equation 432)[908]. A similar Michael addition of α-chloroketones across methyl vinyl ketone gave the cyclopropane derivative **903** (equation 432)[909].

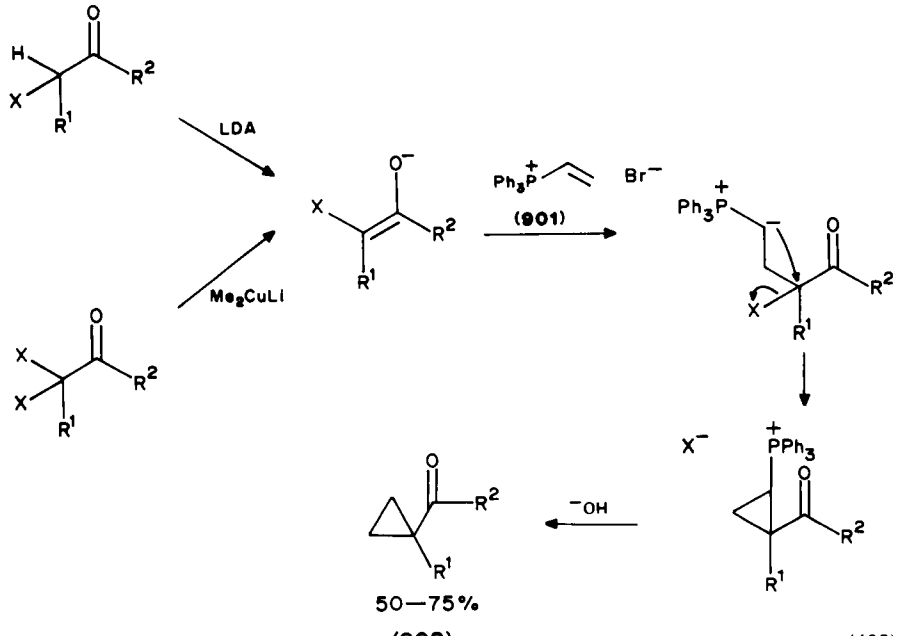
G. Reaction of α-Haloketones with Phosphorus Compounds

Further evidence for a common phosphonium salt intermediate (**904**) in the reaction of trialkyl phosphites with phenacyl chlorides and bromides leading to enol phosphates and phosphonates has been elaborated (equation 434)[910]. If both bromoacetophenone and chloroacetophenone are present, halogen exchange occurs between the phosphonium salt and the haloacetophenone. A new preparation of β-ketophosphonates by reaction of dialkyl chlorophosphate electrophiles with the dilithiated derivative of an α-bromoketone has been described[985]. This umpolung approach is complementary to the classical Arbuzov synthesis, allowing the use of secondary α-haloketones or α-bromoketones where the Arbuzov reaction often fails. It also extends the variety of phosphonates available by allowing, for example, the direct preparation of bis(trifluoroethyl) phosphonates, which are not readily available via the Arbuzov reaction (equation 433).

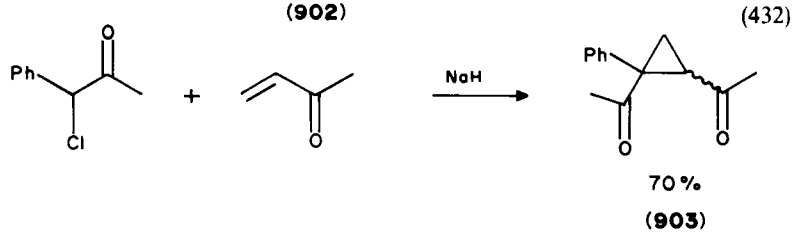


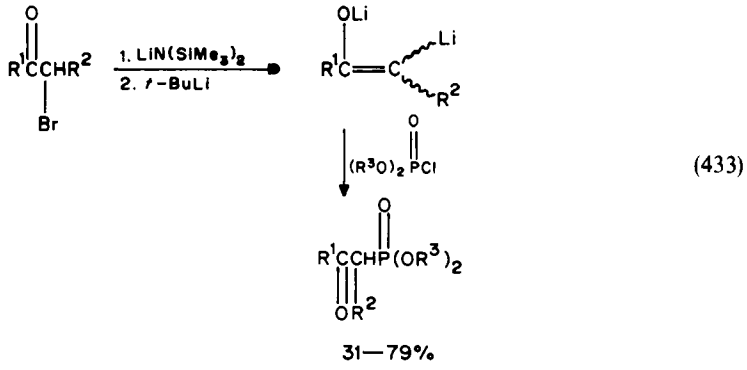
(**904**)

Whereas the reaction of α-chloroketones with dialkyl phosphites gave rise to hydroxyalkylphosphonates without organic solvents, addition of solvent and potassium or caesium fluoride resulted in the formation of epoxides and vinyl phosphates (equation 434)[911-914].

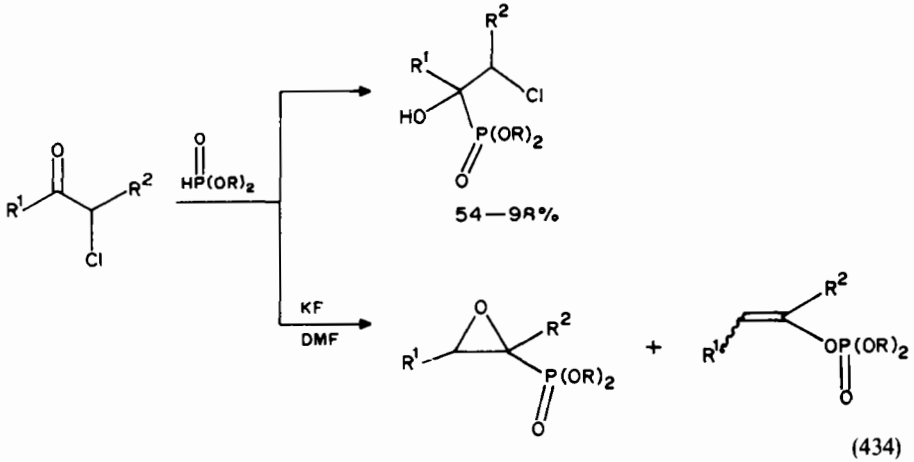


(432)





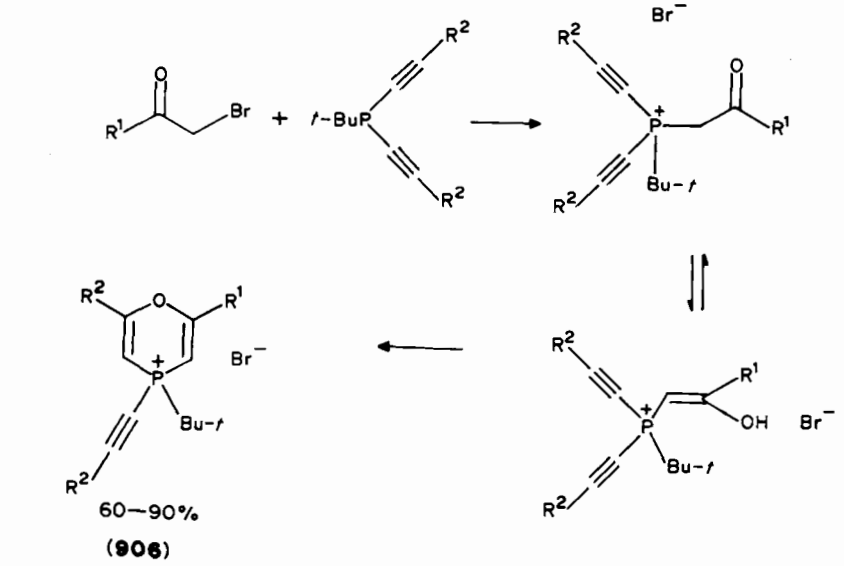
(433)



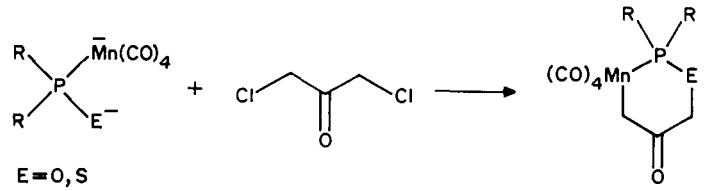
(434)

Using diphenyl phosphites and chlorodifluoromethyl ketones in the presence of triethylamine, 2, 2-difluoro enol diphenyl phosphates were synthesized. On treatment with dibutylcopperlithium, they gave *gem*-difluoroolefins[915]. Diethyltrimethylsilyl phosphite afforded the diethyl enol phosphate and not the 1:1 carbonyl adduct using trimethylsilyl phosphite[916]. Vinyl esters of phosphorus acids have been prepared by treatment of α-chloroketones with dialkylchloro- and monoalkyldichlorophosphonites[917,918].

Phosphonium salts and the derived phosphoranes, obtained by reaction of α-haloketones with tertiary phosphines, have been widely used in the Wittig olefination[919–922]. On the other hand, reaction of α-bromoketones with *tert*-butyldialkynylphosphanes (**905**) gave rise to 1,4-oxaphosphorine salts (**906**) (equation 435)[923,924]. Phosphomanganous cycloalkanes (**907**) could also be prepared by reaction of 1, 3-dichloroacetone with manganophosphorus compounds (equation 435)[925].

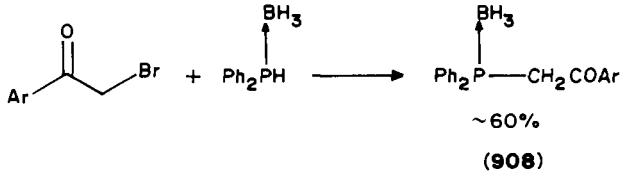


(**906**)



(435)

Phenacyl bromides are able to alkylate phosphine boranes affording tertiary phosphine borane derivatives (**908**) (equation 436)[926].

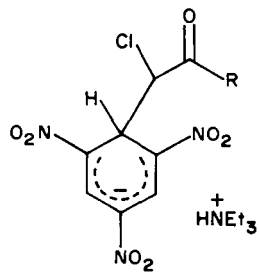


(436)

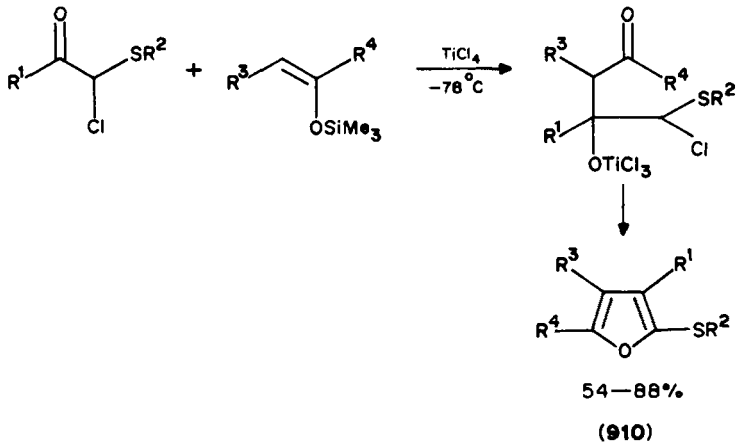
H. Miscellaneous Reactions of α-Haloketones

1. *Electrophilic reactions of α-haloketones and their derivatives*

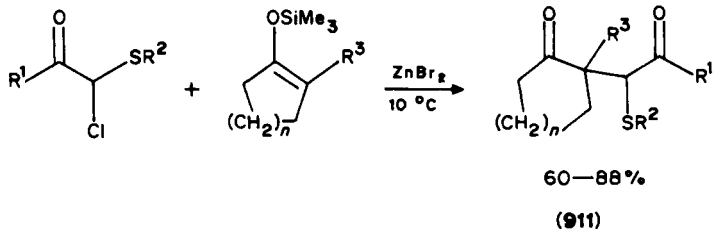
Novel preparative methods for the synthesis of arylacetone derivatives involving Friedel–Crafts reactions of aromatic compounds with α-chloro-α-(methylthio)acetone in the presence of Lewis acids and successive desulphurization with Zn have been reported[927]. The Meisenheimer adduct (**909**) of the 1-chloropropanoyl anion and 1, 3, 5-trinitrobenzene has been isolated by reaction of chloroacetone with triethylamine in DMSO containing trinitrobenzene[928]. This reaction is also applicable for phenacyl chloride.

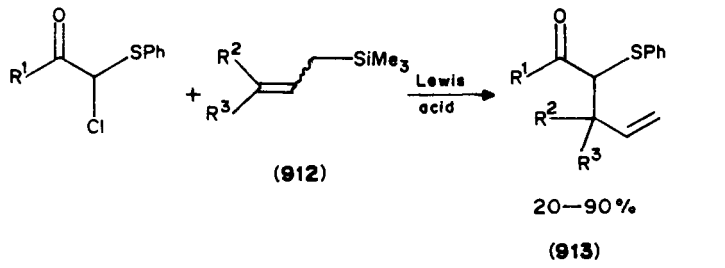


Reaction of silyl enol ethers with α-chloro-α-(alkylthio)ketones in the presence of titanium(IV) chloride[929] afforded furans (**910**) whereas in the presence of zinc bromide[930] the regioselectivity is reversed and γ-diketones (**911**) were generated. However, allylsilanes (**912**) gave exclusively substitution of the chlorine atom with formation of the corresponding α-allyl sulphides (**913**) (equation 437)[931].

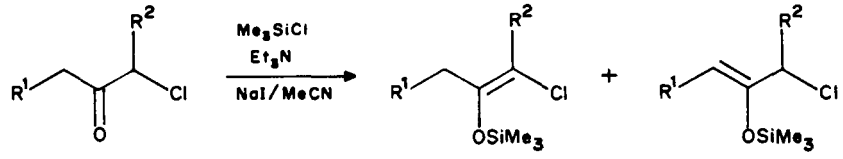


(437)



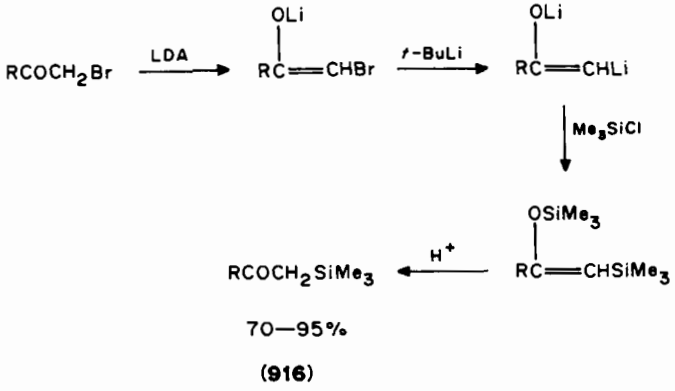


Trialkylsilyl enol ethers of α-haloketones have been prepared by treatment of the latter with trialkylsilyl triflates in the presence of triethylamine at room temperature[932]. The reaction of trimethylsilyl iodide in the presence of triethylamine in acetonitrile with α-chloroketones can give rise to the isomer **915** of chlorotrimethylsilyl enol ethers (**914**) (equation 438)[933,934].

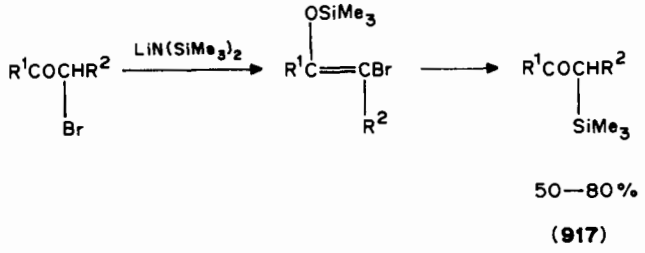


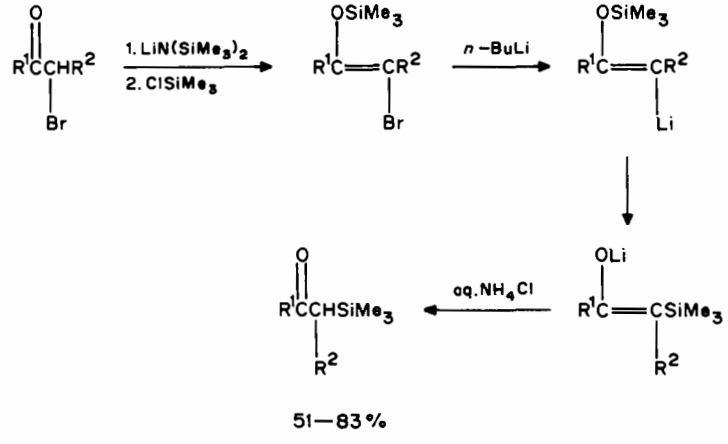
(438)

α-Silyl ketones (**916**, **917**) serve as excellent transfer agents of α-ketocarbanions to an electrophilic centre[935]. Two general methods starting from α-haloketones involve either silylation of α-keto dianions[936] or 1,3-*O*- to *C*-silyl migration in bromotrimethylsilyl enol ethers (equations 439 and 440)[937].



(439)

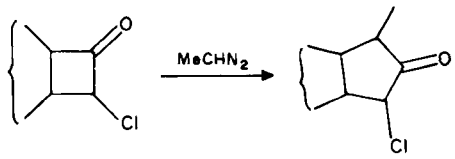




(440)

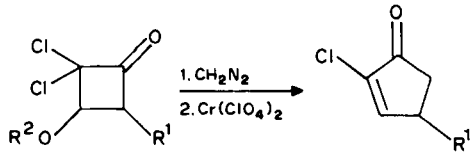
A similar synthesis involved the formation of a vinyllithium species, silyl migration and quenching with aqueous ammonium chloride to give α-trialkylsilyl ketones[938]. Homolog-

ation of α-haloketones has found application in the conversion of α-chlorocyclobutanones into cyclopentanones (**918**) and cyclopentenones (**919**)[939] using diazoalkanes and the transformation **920** → **921** using diazoacetates (equation 441)[940].



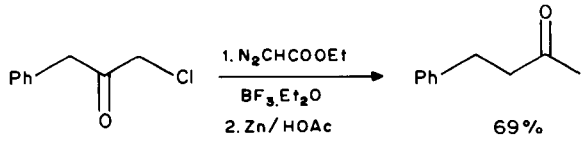
72%

(**918**)



(441)

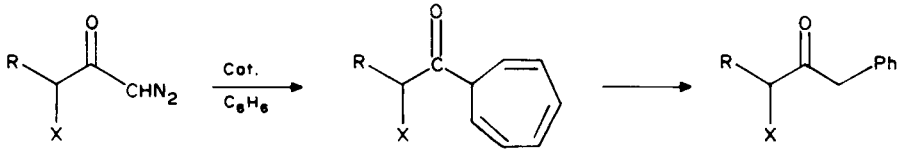
(**919**)



69%

(**920**) (**921**)

The reaction of halogenated α-diazoketones with benzene in the presence of rhodium(III) trifluoroacetate provided benzyl ketones (**923**) via cycloheptatrienyl intermediates (**922**) (equation 442)[941].

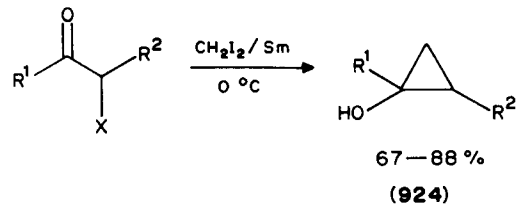


80%

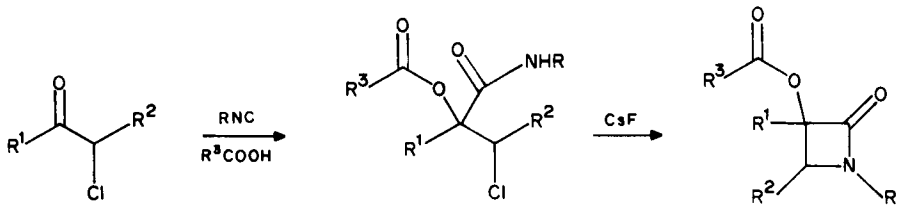
(**922**) (**923**)

(442)

Iodomethylation of α-haloketones utilizing diiodomethane and samarium yielded cyclopropanols[942], and Ullmann coupling in the presence of Cu or Ag afforded unsaturated 1,4-diketones (equation 443)[943]. The Passerini reaction of isocyanides with α-chloroketones in the presence of acids, followed by ring closure, afforded azetidinones (equation 444)[944].

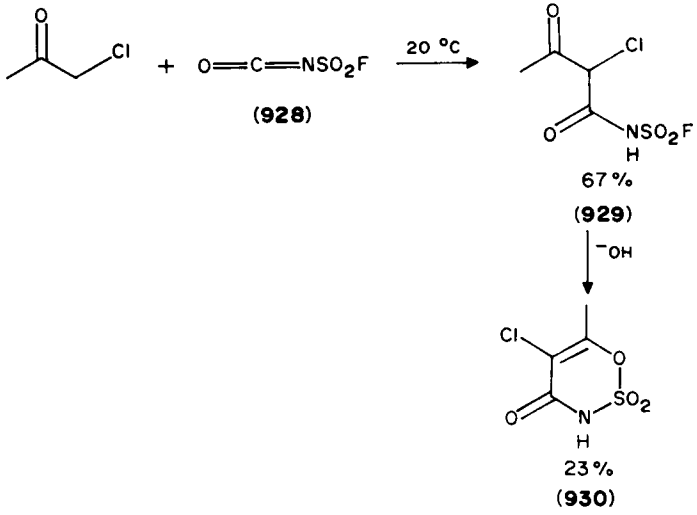


(443)



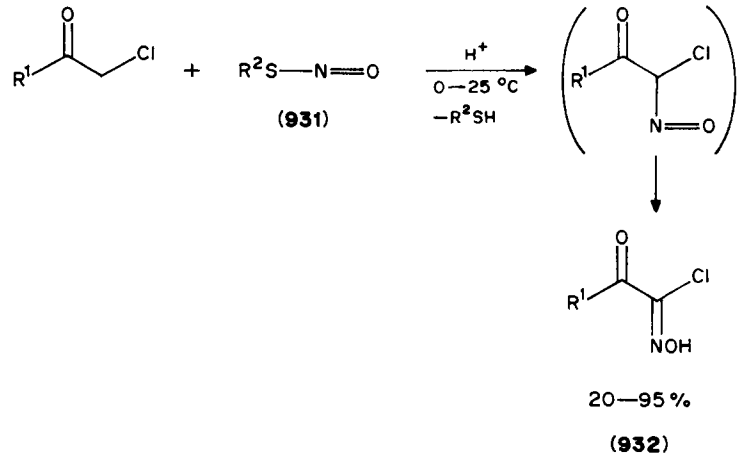
(444)

Acetoacetamides (**929**) were formed when chloroacetone reacted with fluorosulphonyl isocyanate (**928**). The products give oxathiazinones (**930**) on treatment with base (equation 445)[945].



(445)

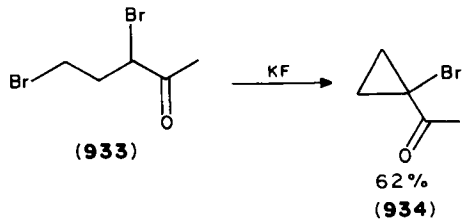
New C—N bonds were formed on treating α-haloketones with alkyl thionitrites (**931**), resulting in the formation of α-oximino-α-haloketones (**932**) (equation 446)[946].



(446)

2. Reaction of α-haloketones with alkali metal fluorides

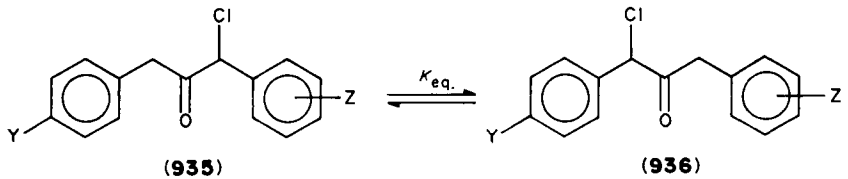
Treatment of 3, 5-dibromopentan-2-one (**933**) with potassium fluoride resulted in ring closure to 1-acetyl-1-bromocyclopropane (**934**) (equation 447)[689].



(447)

3. Acid-catalysed rearrangement of α-haloketones

For the first time a reaction suitable for studying electronic effects on C—Cl bonds in an equilibrium was found (equation 448)[947].



(448)

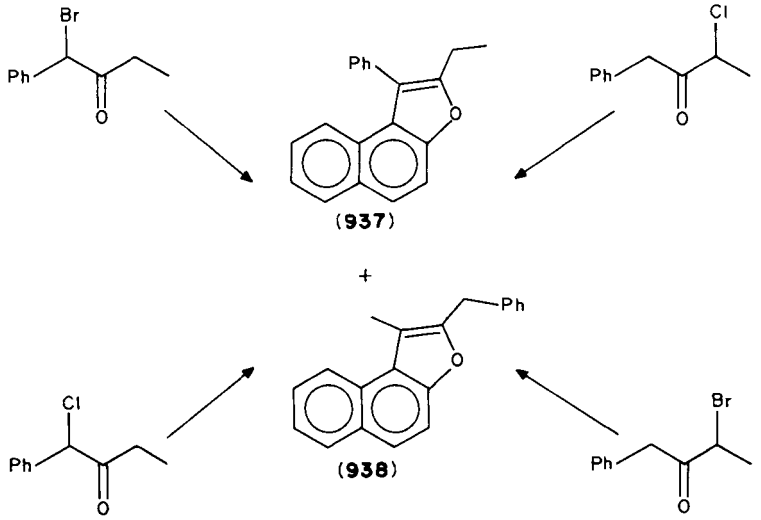
There is a considerable polar effect on the relative stability of the two chloroketones **935** and **936** which is largest for the Y = Me, Z = *p*-NO_2 pair. Since the only difference between the two isomers is the reversed location of a C—Cl and a C—H bond, the substituent

TABLE 2. Equilibrium constants for the process **935**⇌**936** when Y = Me (room temperature)

Z	$K_{eq.}$ (936/935)
H	1.1
p-Cl	1.9
m-CF_3	2.4
p-NO_2	4.9

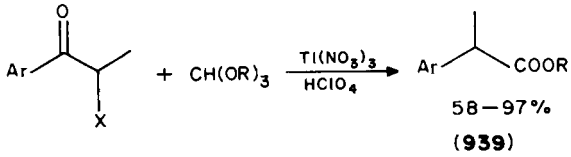
effect must be transmitted (mostly through space) to these two bonds. The $K_{eq.}$ values are given in Table 2[947].

In the course of studying the α,α′-rearrangement a new furan-forming reaction was encountered. α-Haloketones reacted with α-naphthol in the presence of strong acids to give naphtho[2,1-*b*]furans (**937**, **938**) via hydroxyallyl cation intermediates[948]. The reaction is not regiospecific in that more than one furan can result, but the predominant compound was **938**. The same two furans were formed from all four α-chloro and α-bromo isomers whether the acid was HCl, HBr or $HClO_4$ (equation 449).



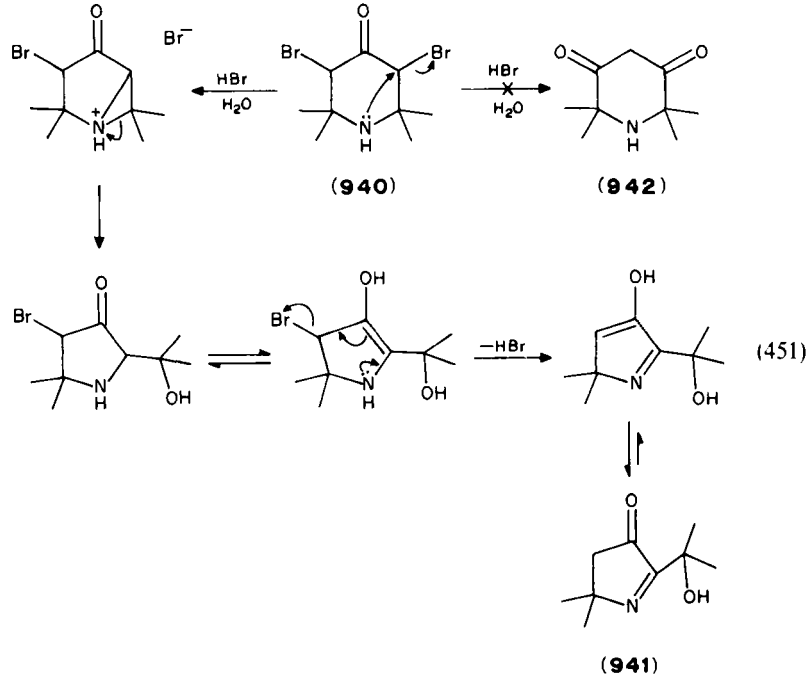
(449)

An efficient synthesis of 2-arylpropanoic esters (**939**) from α-halopropiophenones involving a thallium(III) nitrate-assisted 1,2-migration of the aryl group was found when orthoformates were used as the solvent and as the source of an alkoxy group (equation 450)[949].



(450)

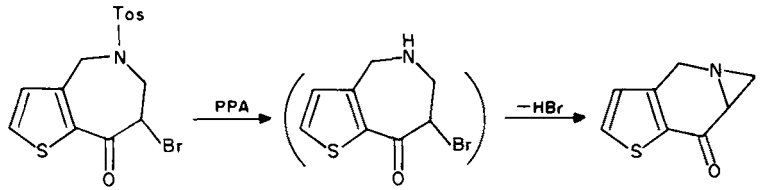
The acid hydrolysis of the 3, 5-dibromopiperidine-4-one **940** did not give the previously reported piperidine-3, 5-dione **942** but instead the reaction product was identified as the pyrroline **941** (equation 451)[950].



(451)

(941)

Attempts to remove the *p*-tolylsulphonyl group from the azepin-8-one **943** with polyphosphoric acid (PPA) gave a novel heterocyclic system, viz. 6, 7-dihydroazirino[1, 2-*a*]thieno[2, 3-*d*]pyridine-8-one (**944**) (equation 452)[951].



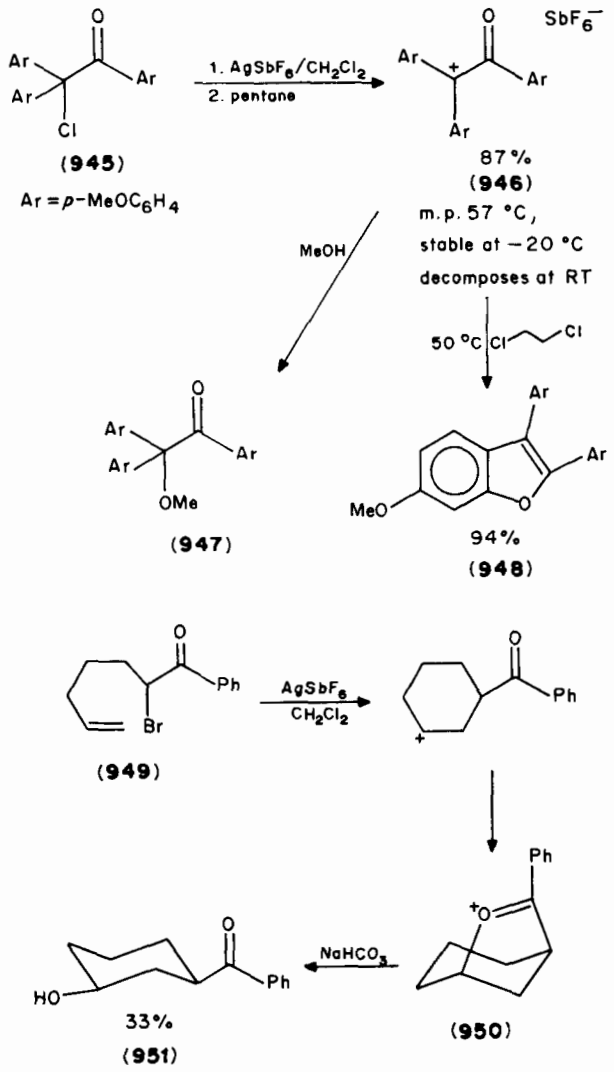
(452)

(943) (944)

4. Formation of α-acylcarbenium ions from α-haloketones

The first isolable α-acylcarbenium ion (**946**) was obtained by treatment of 1, 2, 2-tri(4-methoxyphenyl)-2-chloroethan-1-one (**945**) with $AgSbF_6$ (equation 453)[952,953]. Intramolecular cyclization gave **948**, and capture by methanol gave **947**.

In an intramolecular reaction, action of $AgSbF_6$ on the linear terminally unsaturated α-bromoketone **949** led, via the oxonium salt **950**, to the regio- and stereospecifically substituted cyclohexanol **951** (equation 454)[454].



(453)

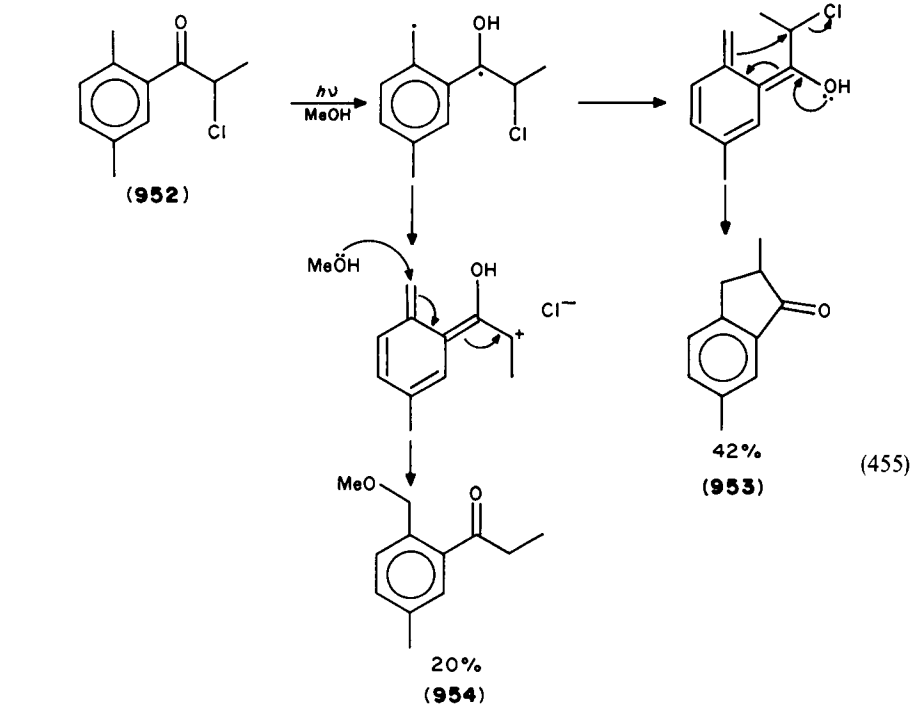
(454)

5. Photochemistry of α-haloketones

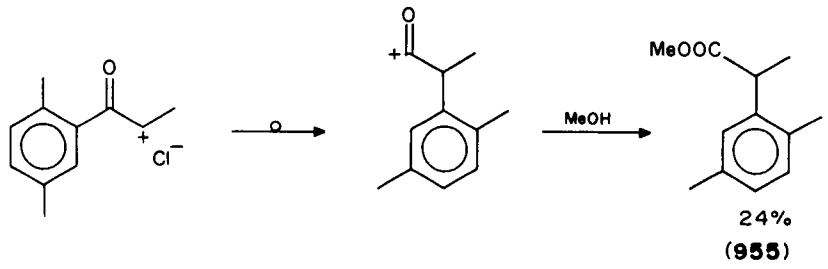
The photoenolization mechanism of phenacyl chlorides in methanol has been elucidated as illustrated by the photolysis of 2, 5-dimethyl-α-chloropropiophenone (**952**) (equation 455)[955].

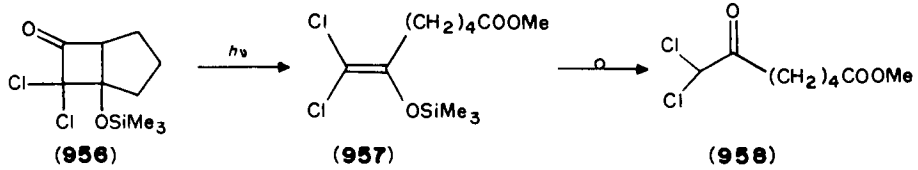
Photoinduced alcoholysis of tribromoacetophenone derivatives gave benzoyl formates (75–85%) together with minor amounts of benzoates and debromination products[956].

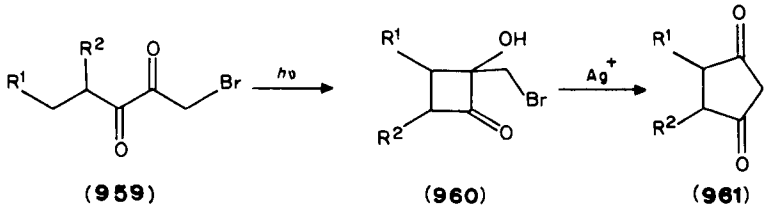
Synthetically useful photochemical transformations of α-haloketones involve the ring cleavage of dichlorocyclobutanones (**956**) with the formation of dichloromethyl ketones (**958**)[957] and the formation of cyclopentane-1, 3-diones (**961**) from brominated diones (**959**) (equation 456)[958].


(952)
hν
MeOH
OH
Cl
MeÖH
Cl⁻
42%
(953)
MeO
20%
(954)

(455)


Cl⁻
MeOH
MeOOC
24%
(955)

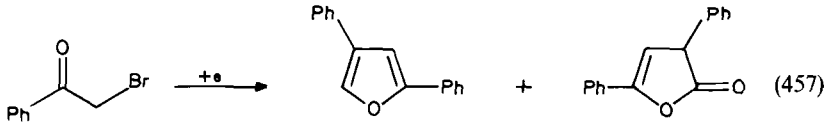

Cl
Cl
OSiMe3
(956)
hν
(CH2)4COOMe
OSiMe3
(957)
(958)


R1
R2
Br
(959)
hν
OH
(960)
Ag+
(961)

(456)

6. Electrochemistry of α-haloketones

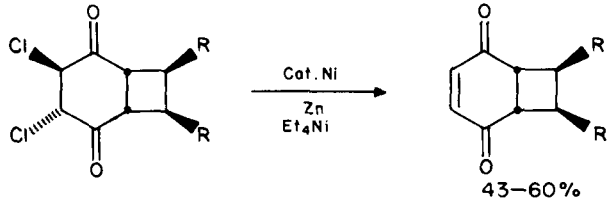
Electrochemical reduction of phenacyl bromide mainly gave rise to 2,4-diphenylfuran (**962**) togehter with minor amounts of 3,5-diphenyl-2(3*H*)-furanone (**963**) (equation 457)[959,960].



(**962**) (**963**) (457)

7. Dehalogenation of α-haloketones

Conversion of α-haloketones into the parent ketones is sometimes used in syntheses and several new reagents have been introduced. Nickel boride[961], lithium and sodium 2-thiophenetellurolates[962,963], zinc and ammonium acetate in THF[964], sodium dithionite[965], samarium diiodide[966], PI_3 or P_2I_4[967], sodium *O,O*-diethylphosphorotelluroate[968], LDA[969,970], iodotrimethylsilane[971], sodium iodide, metal chlorides[972], organotin hydrides[986] and 1,3-dimethyl-2-phenylbenzimidazoline[987] have been shown to reductively dehalogenate α-haloketones. Reductive dechlorination of the bicyclic diketone **964** with an active Ni complex afforded, however, the unsaturated diketone **965** (equation 458)[960].



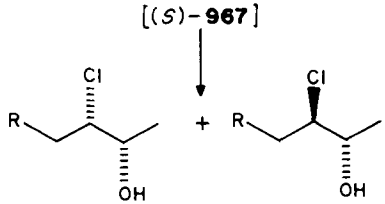
(**964**) (**965**) (458)

8. Enzymatic transformations of α-haloketones

The use of fermenting baker's yeast has been shown to provide a versatile means of chiral reduction in organic synthesis. The asymmetric reduction of (*Z*)-3-chloroalk-3-en-2-ones (**966**) produces initially optically active α-chloroketones (**967**), which are then reduced to optically pure chlorohydrins (**968**, **969**). Interestingly, the reduction of the C=C bond is relatively fast and seems to be independent of the length of the carbon chain, whereas that of the C=O bond is slow and is retarded as the carbon chain length becomes longer (equation 459)[978].

(**966**) 44–84% e.e.

[(*S*)-**967**] (459)



(968)(*syn*) (969)(*anti*)

syn (2*S*,3*S*) : *anti* (2*S*,3*R*) = 2.6—18.3

>98% e.e.

Optically active 2-halo-1-phenylethanols have been prepared by microbial reduction of 2-haloacetophenones with *Candida, Rhodotorula* and *Hansenula* with high optical purity (*ca.* 100%)[988].

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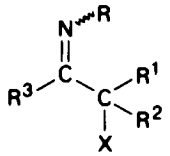
The chemistry of α-haloketones, α-haloaldehydes and α-haloimines
Edited by Saul Patai & Zvi Rappoport

CHAPTER 2

α-Halogenated imines

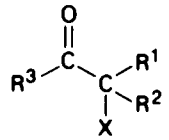
I. INTRODUCTION

α-Halogenated imino compounds (**1**) are the nitrogen homologues of α-halogenated ketones (**2**). While the latter class of compounds has been studied extensively in the literature, α-halo imines have only recently come to be used regularly in organic synthesis despite the fact that they were proven earlier to be valuable synthetic reagents.



(1)

X = halogen



(2)

X = halogen

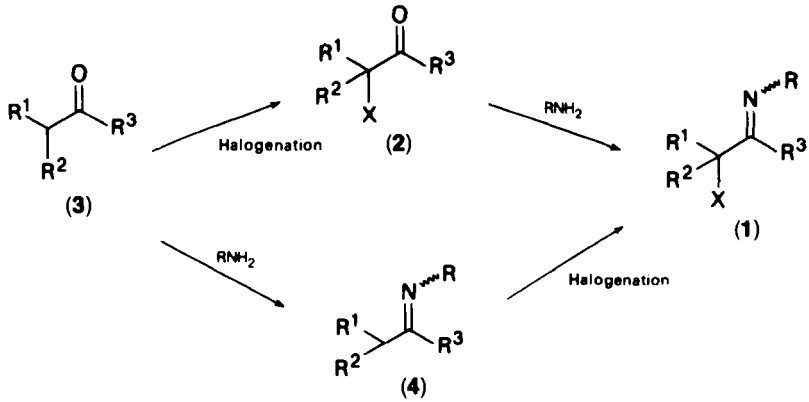
Information regarding the use of α-halogenated imino compounds (1) in organic synthesis remained scattered until very recently when this matter was compiled in a review covering the synthesis[1] and reactivity[2] of these compounds. It is to focus attention on the versatility and potential of these reagents that this information has been brought together. The literature has been reviewed up to early 1980. Only α-halogenated imino compounds having a structural similarity with α-halogenated carbonyl compounds will be treated in this review. However, when necessary, some leading references to the chemistry of α-halo imidates, α-halo amidines and α-halo imidoyl cyanides will be provided. In general, α-halogenated imino compounds (1), having at least one α-hydrogen, do not tautomerize into the corresponding enamines, except when conjugation in the molecule with such substituents as CN, COOR, NO_2, etc. is possible. Such β-halo enamines are not subject to discussion here.

Some novel aspects of the chemistry of α-halo ketones will be discussed in another chapter in this monograph. Throughout the text some comparisons will be made between the reactivities of α-halo carbonyl compounds and α-halo imines.

II. SYNTHESIS OF α-HALOGENATED IMINES

Comprehensive studies in the area of the synthesis of α-halo imines are of rather recent origin. The growing success of the use of these reagents in synthetic organic chemistry is predominantly due to the development of readily available syntheses of the title compounds. Indeed, early investigations in the field of α-halo imines met with difficulties, since no suitable conditions could be found for halogenation of imino compounds. Additionally, several α-halo imines were found to be unstable, especially towards hydrolytic and thermal reaction conditions. Two main strategies for the synthesis of α-halo imines (1) may be considered. The first one is the condensation of an α-halogenated carbonyl compound (2) with a primary amine under suitable reaction conditions, similar to the usual synthesis of imines starting from carbonyl compounds and primary amines[3,4]. The second approach involves the halogenation of imines (4). In both cases, carbonyl compounds (3) are the starting materials for such syntheses. The first method gives rise to the desired α-halo imines (1) only in special cases. Most often, a variety of side reactions is encountered, among others nucleophilic α-substitution[5,6], elimination of hydrogen halide[7], haloform-type reactions[8,36], Favorskii rearrangement[9–12] and rearrangement via intermediate epoxides[13–16,207]. In many cases, intermediately formed α-halo imino compounds were further transformed under the given reaction conditions to various final products[17–35].

The second approach to α-halo imines via halogenation of imines also met with major difficulties, especially in the older literature, because unstable immonium-type compounds resulted from this reaction. The latter were usually transformed into

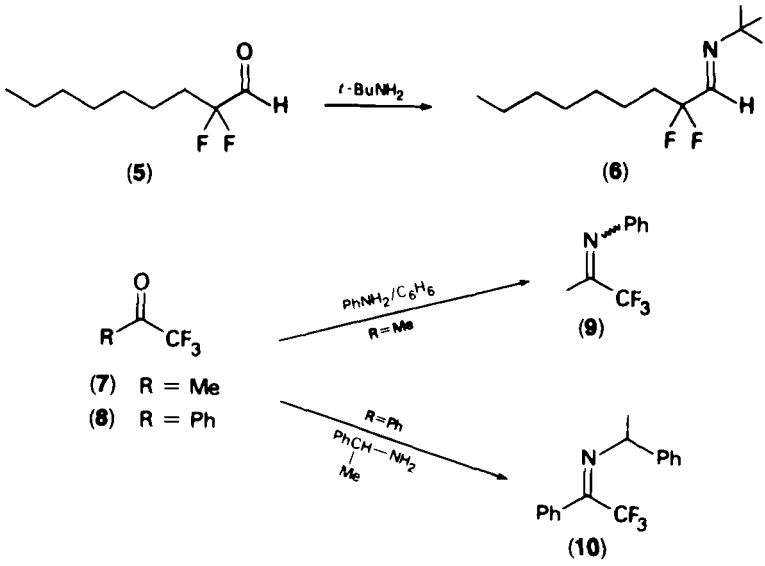


α-halo carbonyl compounds by aqueous work-up. The medium in which the imine is halogenated plays a predominant role, as will be demonstrated in the following sections.

Attention will be given now to the two aforementioned synthetic methods leading to α-halo imines, while the halogenation of enamines giving rise to the title compounds will also be discussed. Additionally, some miscellaneous methods for the synthesis of α-halogenated imines will be treated.

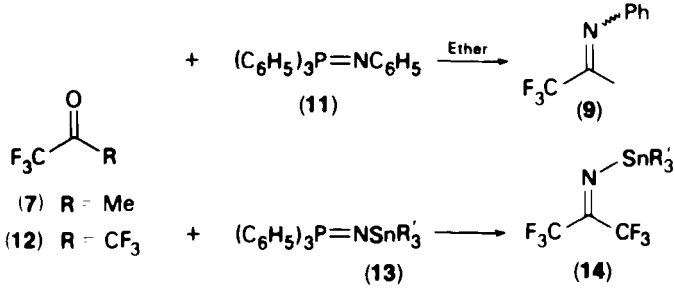
A. Condensation of α-Halogenated Carbonyl Compounds with Primary Amines

The reaction of α-fluoro carbonyl compounds with primary amines usually gives no difficulties in synthesizing the α-fluoro imines. 1,1,1-Trifluoroacetone (**7**) reacted with aniline in benzene for 2 days to give *N*-(1,1,1-trifluoro-2-propylidene)aniline (**9**) in 25% yield[37], while 2,2-difluorononanal (**5**) condensed smoothly with *t*-butylamine at room temperature to give the α,α-difluoro aldimine (**6**)[105]. In similar way, aromatic

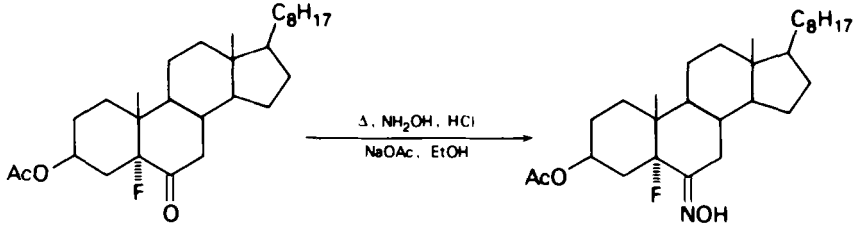


α-fluorinated ketones such as 2,2,2-trifluoroacetophenone (**8**) condensed with α-methylbenzylamine to afford α,α,α-trifluoroketimine (**10**)[38].

Iminophosphoranes can also be used in such iminations of α-fluorinated ketones[105], as exemplified by the synthesis of **9** from **7** by using **11**[37]. When *N*-trialkylstannyltriphenylphosphonimines (**13**) were used as reagents, hexafluoroacetone (**12**) was converted into the *N*-trialkylstannyl-substituted perfluoro ketimine (**14**)[39]. When applied to trimethylsilyltriphenylphosphonimine, the

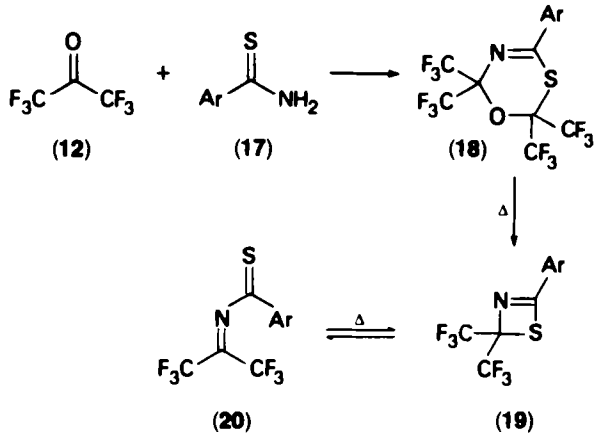


corresponding *N*-trimethylsilylimine could only be isolated in 1% yield[39]. Oximation of α-fluoroketones[441] with hydroxylamine in ethanol in the presence of sodium acetate gives no side reactions, as exemplified by the synthesis of 5α-fluoro-6-oximinocholestane-3β-ol acetate (**16**)[428]. The same is true for the synthesis of α-fluoro hydrazones[412].

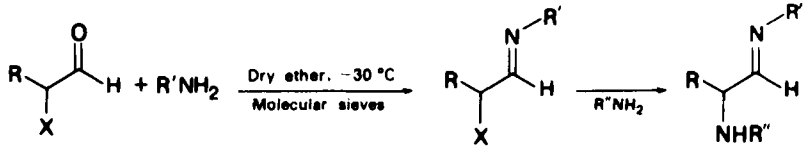


Less reactive amino compounds, e.g. thiobenzamide derivatives (**17**), can also be used for direct condensation with hexafluoroacetone (**12**). Initially, however, 2,2,6,6-tetrakis(trifluoromethyl)-6*H*-1,3,5-oxathiazines (**18**) were formed, which could be pyrolysed into 2*H*-1,3-thiazetes (**19**), existing in thermal equilibrium with *N*-(perfluoroisopropylidene)thiocarboxamides (**20**)[40–42]. It will be demonstrated (*vide infra*) that the activated perfluoroketimines (**20**) show a fascinating reactive behaviour toward a variety of reagents with which they can undergo cycloadditions. Besides the direct imination of α-fluorinated carbonyl compounds, the direct condensation of α-halogenated ketones with aliphatic or aromatic primary amines to give α-halogenated ketimines has never been described*. Only less sterically hindered carbonyl compounds such as α-chloro- and α-bromoaldehydes (**21** and **22**) react in a straightforward manner with aliphatic primary amines in ethereal medium at −30°C in the presence of molecular sieves to afford α-chloro- and α-bromoaldimines (**23**,**24**) in 27–73% yield[43,44]. Compounds **23** and **24** are rather unstable and sensitive to moisture, the *N*-*t*-butyl derivatives being the most stable ones. In the presence of excess primary amine, α-halo imines **23** and **24** are slowly converted into α-alkylamino aldimines (**25**). The latter compounds (**25**) are also obtained in a more rapid reaction from α-halo

*See novel developments in the Appendix.



(12) (17) (18) (20) (19)

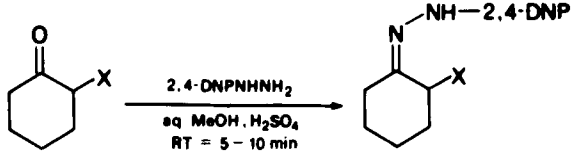


(21) X = Cl (23) X = Cl (25)

(22) X = Br (24) X = Br

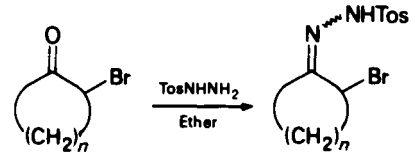
aldehydes and primary amines, indicating that the α-halo aldimines **23** and **24** are not intermediates in these reactions[43]. In more drastic conditions, chloral condensed with primary amines under catalytic influence of zinc chloride and under azeotropic water removal to give trichloroethylideneamines[331-333].

The usual carbonyl identification reagents such as 2,4-dinitrophenylhydrazine, hydroxylamine, semicarbazide, etc., also react with α-halo carbonyl compounds to afford the corresponding α-halo imino derivatives. Care should be taken, however, as regards the reaction conditions employed, since side reactions such as elimination, nitrosoölefin formation, etc., may take place.



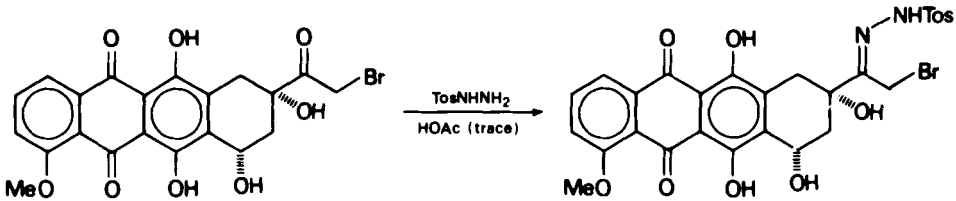
(26) X = Cl, Br (27) X = Cl, Br

The Brady reagent[45], i.e. an aqueous methanolic solution of 2,4-dinitrophenylhydrazine sulphate containing excess sulphuric acid[23,46] could be successfully applied for the synthesis of α-halocyclohexanone 2,4-dinitrophenylhydrazones (**27**). The reaction of α-bromocycloalkanones (**28**; n = 3,5,9) with tosylhydrazine in ether produced crystalline α-bromo tosylhydrazones (**29**; n = 3,5,9)[47,48,50]. In a similar way, α-halogenated aldehydes gave the corresponding α-halogenated dinitrophenylhydrazones[199-202]. This method was also applied for the synthesis of aliphatic α-bromo tosylhydrazones[49,50,212]. The conversion into α-bromo



(28; n = 3, 5, 9) (29; n = 3, 5, 9)

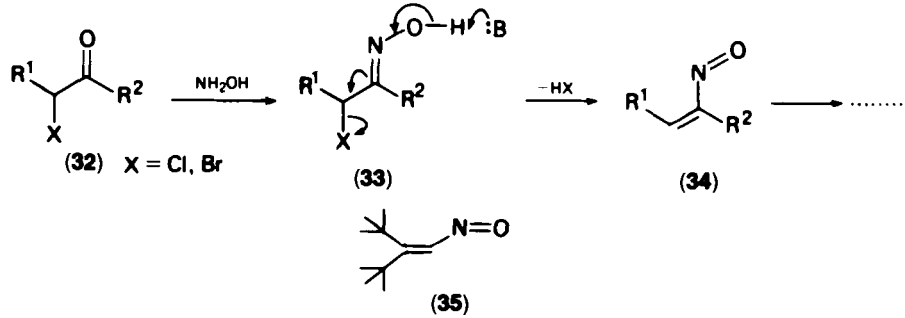
tosylhydrazones seems to be a general reaction, occurring also with complex molecules like 14-bromodaunomycine (**30**)[51].



(30) (31)

In a similar way again, α-halo semicarbazones and related compounds were isolated under appropriate reaction conditions[52–59,109] but these compounds were subject to further transformations[110] into heterocyclic compounds[1].

Oximation of α-halo carbonyl compounds (**32**) requires controlled reaction conditions because of the possibility of side reactions of the initially formed α-halo oxime. Base-induced 1,4-elimination of hydrogen halide from α-halo oximes (**33**) yields nitrosoölefins (**34**) which are apt to undergo a variety of transformations[60–62].



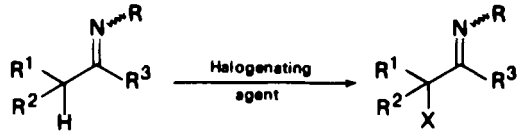
(32) X = Cl, Br (33) (34)

(35)

The intermediacy of these nitrosoölefins (**34**) was demonstrated by their isolation under appropriate reaction conditions (see for example compound **35**[63–65,218]). In order to avoid nitrosoölefin formation, it is recommended that oximations be performed in a slightly acid medium, such as in an aqueous calcium chloride solution[66,67] or with equimolecular amounts of sodium acetate in acetic acid[68,69]. Oximations of α-halo ketones can also be performed under milder conditions (such as NH_2OH/methanol/THF/room temperature, 18 h)[156,157,206,220,266].

B. Halogenation of Imino Compounds

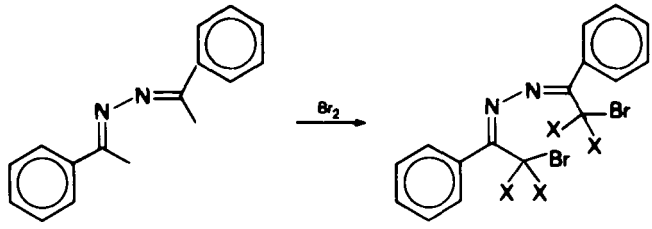
Several halogenating agents have been found to convert imino compounds (**4**) into α-halo imines (**1**). However, most of them were not proven to be of general synthetic



(4) (11)

interest and in many cases the α-halo imine formed could not be isolated, making hydrolysis to the more stable α-halo carbonyl compounds necessary. For example, halogenation with chlorine or bromine met with major difficulties by virtue of the instability of transient α-halogenated immonium halides[70–72].

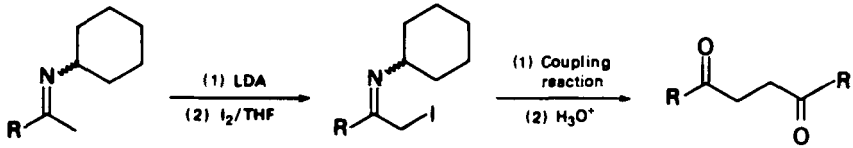
Brominated acetophenone azines (**37**; X = Br) and (**38**; X = H) could be synthesized from the parent azine (**36**) with bromine in dichloromethane[73] or



(**36**) (**37**; X = Br) (**38**; X = H)

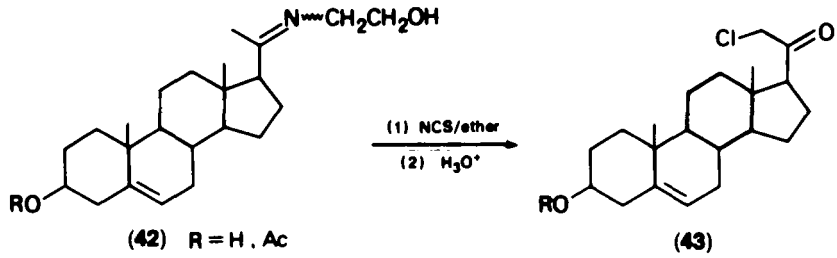
methanol (0–5°C)[74], respectively. 2-Alkyloxazolines were halogenated with chlorine or bromine[75], while 2-pyrazolin-5-ones and 2-isoxazolin-5-ones (and related compounds) were also reported to be chlorinated at the active methylene function at the 4-position[76,77,208,286].

Probably due to their unstable nature, α-iodo ketimines have not been isolated hitherto. Recently, it was reported that a transient α-iodo ketimine (**40**) was used to transform methylketimines (**39**) into symmetric 1,4-diones (**41**) via lithiation (using lithium diisopropylamide = LDA), iodination, coupling of α-iodo ketimine (**40**) with the lithiated ketimine (anion of **39**) and acidic hydrolysis of the 1,4-diimine thus formed[78].

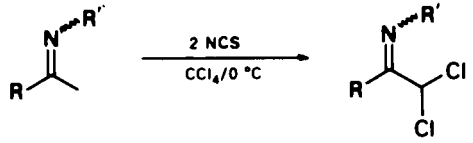


(**39**) (**40**) (**41**)

Among the halogenating agents of imines, *N*-halosuccinimide has been found to be the superior reagent for the synthesis of aliphatic and aromatic α-halogenated imino compounds. Ketimines are chlorinated at the less substituted α-position with *N*-chlorosuccinimide (NCS). The reaction is more regiospecific in carbon tetrachloride[79–83] than in ether[84]. The steroidal *N*-(2-hydroxyethyl)ketimines (**42**) were conveniently monochlorinated in ether, the resulting chloromethylketimine being hydrolysed in acidic medium to the corresponding α-chloroketone (**43**)[84]. *N*-Cyclohexyl and *N*-aryl methylketimines (**44** and **45**) were regiospecifically dichlorinated at the methyl function to produce dichloromethylketimines (**46** and

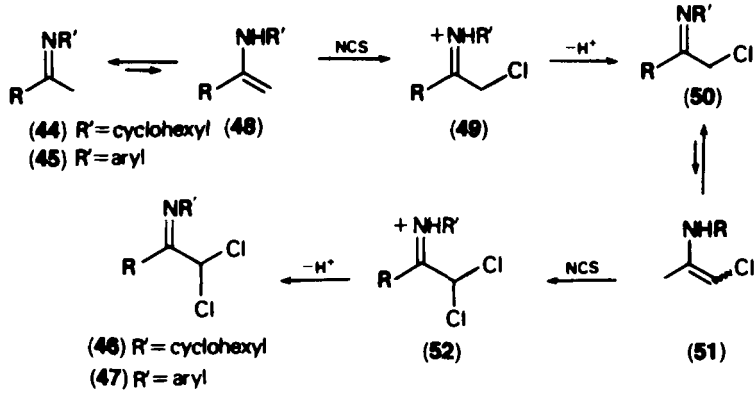


(42) R = H, Ac (43)

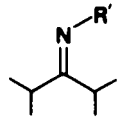


(44) R′ = cyclohexyl (46) R′ = cyclohexyl
(45) R′ = aryl (47) R′ = aryl

47)[79–83], together with negligible amounts of 1,3-dichloromethylketimines and 1,1,1-trichloromethylketimines. The mechanism proceeds via chlorination of the less substituted enamine (48) in a non-radical manner. Steric interactions play an

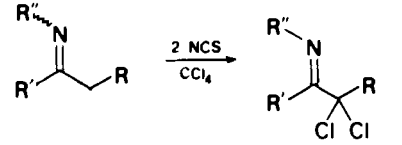


important role in these halogenations and determine the regiospecific dichlorination of methylketimines. Even when the R-group in **44** or **45** is tertiary (R = *t*-Bu), the reaction proceeds to dihalogenation, but *N*-alkyl imines of diisopropyl ketone (**53**) did not suffer chlorination with *N*-chlorosuccinimide in carbon tetrachloride. α,α,α-Trichlorination of acetophenone imines (**45**; R = Ar) proceeds rapidly and quantitatively at reflux with NCS in carbon tetrachloride (5 min), while imines derived from dichloropinacolone (**46**, **47**; R = *t*-Bu) could not be further chlorinated under drastic conditions[91].

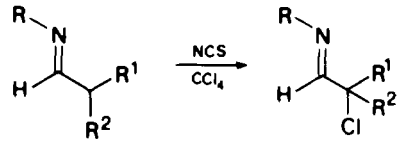


(53)

The reaction of imines with *N*-halosuccinimide requires an initiation period, after which the reaction proceeds smoothly to completion. As expected, and concordant with the proposed reaction mechanism, secondary enamines, i.e. enamines in which stabilizing groups such as a nitrile moiety force tautomerizable substrates to occur exclusively as enamines, react instantaneously with *N*-halosuccinimide (*vide infra*)[115,116]. Imines having no α′-hydrogen atoms, such as **54**, **55** and **58**, are easily chlorinated with NCS in CCl_4[85–90]. Substitution of all available α-hydrogen atoms by chlorine atoms is accomplished without problems. However, methylketimines (**44** and **45**) or imines having an α-CH_2 function, e.g. **54** and **55**, cannot be converted by this method into α-monochloro imines, because the rate of introduction of the first and the second halogen are of the same magnitude. This seems to be a general observation and points to the major limitation of the chlorination procedure of imines with *N*-chlorosuccinimide.

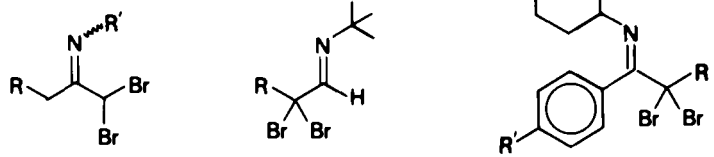


(**54**; R′ = H) (**56**; R′ = H)
(**55**; R′ = Ar) (**57**; R′ = Ar)



(**58**) (**59**)

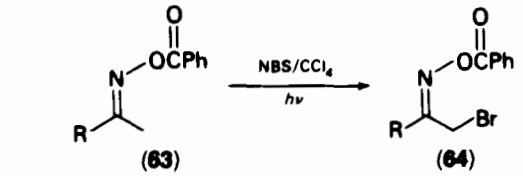
The same comments as given for the α-chlorination of imines using NCS are applicable for *N*-bromosuccinimide (NBS). Bromination of imines **44**, **54** and **55** with NBS in CCl_4 yielded α-bromo imines **60**[91], **61**[92] and **62**[88] in good yield. In many cases



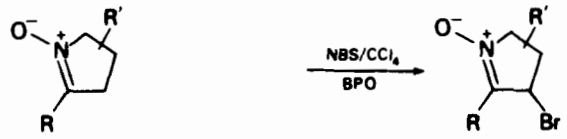
(**60**) (**61**) (**62**)

the use of NBS required the aid of benzoyl peroxide, irradiation or acid catalysis[93], or the combined action of these influences. A variety of classes of imino compounds have been α-brominated with *N*-bromosuccinimide, including oximine benzoates (**63**)[94], nitrones (**65**)[95–97], 2-methoxycarbonyl-1-pyrrolines[98], cyclic imino ethers (imidates) (**67**)[99,100], hydrazone-type compounds (**69**)[101–103], amidines[104] and 1-pyrrolines[448].

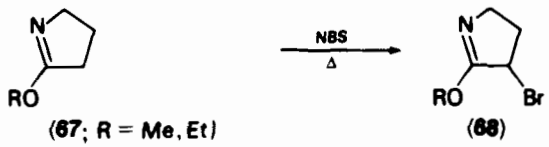
Other sources of positive chlorine, which have been used for α-chlorination of imines, are sodium hypochlorite[106,107] and *t*-butyl hypochlorite[107,108]. These reagents converted steroidal methylketimines (**71**) into mixtures of α-halogenated imines, while



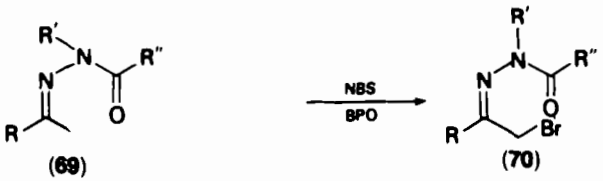
(63) (64)



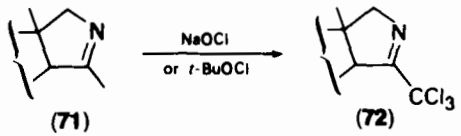
(65; R = CN, Ph, t-Bu) (66)



(67; R = Me, Et) (68)



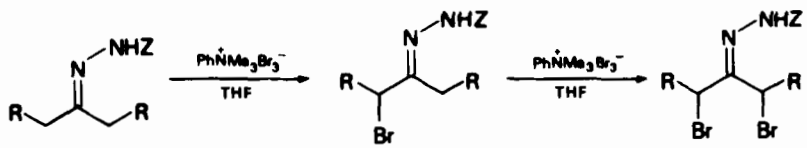
(69) (70)



(71) (72)

only the α,α,α-trichloromethyl derivative (**72**) was obtainable in a synthetically useful manner[107]. Monobromination of ketimines can be performed with 2,4,4,6-tetrabromocyclohexadienone, as exemplified for the *N*-*t*-butyl imine of 3,3,5,5-tetramethylcyclohexanone, but the monobromo compound existed in equilibrium with its enamino form[93].

A superior reagent for the α-bromination of hydrazones (**73**) seemed to be phenyltrimethylammonium perbromide (PTAB) in tetrahydrofuran[102,103,111,112,453]. With two equivalents of the brominating reagent α,α′-dibromination occurred[111,112].

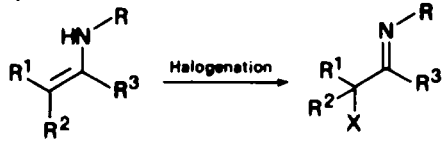


(**73**) Z = 2,4-$(NO_2)_2C_6H_3$ (**74**) (**75**)

Z = Tosyl

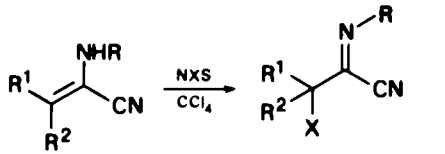
C. Synthesis of α-Halogenated Imino Compounds by Halogenation of Enamines

Only those cases in which secondary enamines (**76**), i.e. enamines having one hydrogen bonded to nitrogen, are converted into α-halo imines will be discussed in this section. Halogenation of other enamines to produce β-halogenated enamines is discussed elsewhere[113].



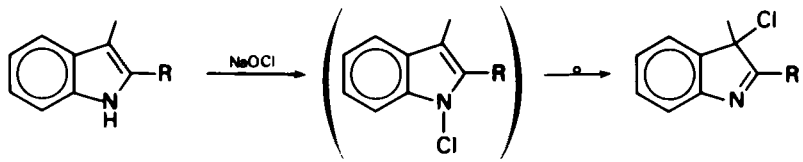
(**76**) (**1**)

Halogenation of enamines with chlorine or bromine to give α-haloimines has not been amply documented[114,119], while the halogenation with *N*-halosuccinimide has been mainly applied to enamines carrying electron-withdrawing groups[115–118]. α-Cyanoenamines (**77**) were halogenated to produce α-halo imidoyl cyanides (**78**; X = Cl, Br)[115,116], while indoles were converted into 3-bromoindolenines by reaction



(**77**) (**78**) X = Cl, Br

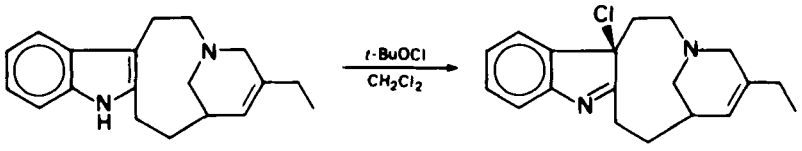
with NBS in carbon tetrachloride[120,121]. Similarly, the conversion of α-cyanoenamines (**77**) into **78** (X = Cl) was accomplished with aqueous sodium hypochlorite[115]. On the other hand, indoles (**79**) were transformed into 3-chloroindolenines (**81**) with sodium hypochlorite[122,123], but it was shown that the reaction proceeded via intermediately formed *N*-chloroindoles (**80**)[124].



(**79**) (**80**) (**81**)

t-Butyl hypochlorite has been proven to be a very efficient reagent for the conversion of indoles into chloroindolenines[119,125–131], and this method found widespread application in the alkaloid field. In the latter field, various indole-type alkaloids have been chlorinated to chloroindolenines such as yohimbine[132,133], ibogaine[134], cleavamine (**82**)[135], 14,15-dehydroquebrachamine[135], voaphylline[135], cacubine[136], tetraphylline[136], hirsutine *N*-oxide[137], pseudoyohimbine *N*-oxide[137], catharanthine[455] and several other examples[138,139,153,215,270,271,373,417,426]. It was recently shown that the chloroindolenines derived from cleavamine, 14,15-dehydroquebrachamine, voaphylline and some related derivatives have their chloro substituent (C-7 position) in a β-orientation, a conclusion which was drawn from detailed investigation of their ^{13}C-NMR spectra[135].

Another source of positive chlorine which was found to be efficient for the



(82) (83)

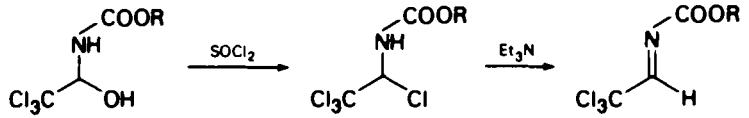
Cleavamine

conversion of indole alkaloids into chloroindolenines was *N*-chlorobenzotriazole[125,140], as reported for deserpine, yohimbine, catharanthine and (±)-dihydrocorynantheal[140].

D. Miscellaneous Methods

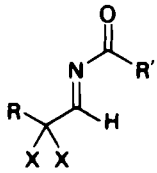
α-Halo imines carrying electron-withdrawing groups, e.g. alkoxycarbonyl, sulphonyl, acyl, aroyl, etc., at the nitrogen atom have a very electrophilic imino carbon, suitable for various reactions, including cycloadditions.

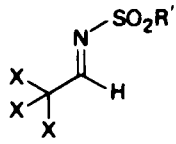
So-called 'anhydrochloralurethanes' (**86**) were synthesized from carbamate adducts of chloral (**84**) via conversion into the chlorides (**85**) and subsequent dehydrochlorination[141]. A similar methodology was applied to the synthesis of other related



(84) (85) (86)

classes of *N*-activated α-halogenated aldimines like α,α,β-trichloroimines (**87** and **88**)[142], *N*-acetyl-α,α,α-trichloroacetaldimines (**90**)[146], α,α-dichloroaldimines (**89**)[143], and *N*-sulphonyl-α,α,α-trihaloacetaldimines (**91**, **92** and **93**)[144,145].



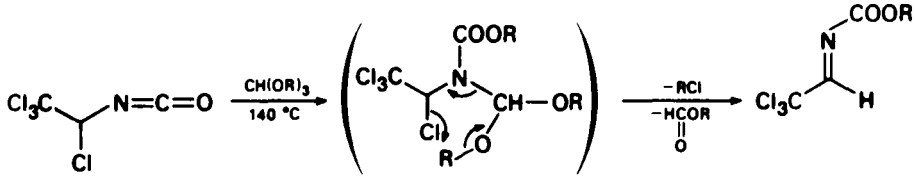


(**87**) R = CH_2Cl; X = Cl, R' = Me, Et, *n*-Pr, Ph
(**88**) R = CH_2Cl; X = Cl; R' = OEt
(**89**) R = alkyl; R' = Me, Ph; X = Cl
(**90**) R = X = Cl; R' = Me

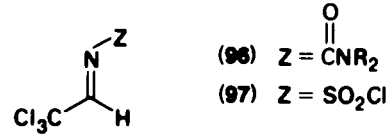
(**91**) X = Cl; R' = *p*-MeC_6H_4
(**92**) X = F; R' = *p*-MeC_6H_4
(**93**) X = Cl; R' = NMe_2

Several other papers have reported the synthesis of *N*-activated α,α,α-trihaloacetaldimines, some of which are shown above[147–152,155].

The reaction of 1,2,2,2-tetrachloroethyl isocyanate (**94**) with alkyl orthoformates, *N*-silylamines or sulphur trioxide led to compounds **86**, **96** and **97**, respectively[147–151]. In many instances, these *N*-activated α-halogenated aldimines were postulated as intermediates[146–154]. For instance, sulphinate elimination from **98** under the influence

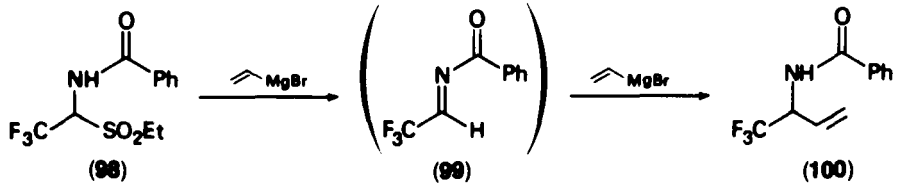


(94) (95) (86)



(96) Z = $CONR_2$
(97) Z = SO_2Cl

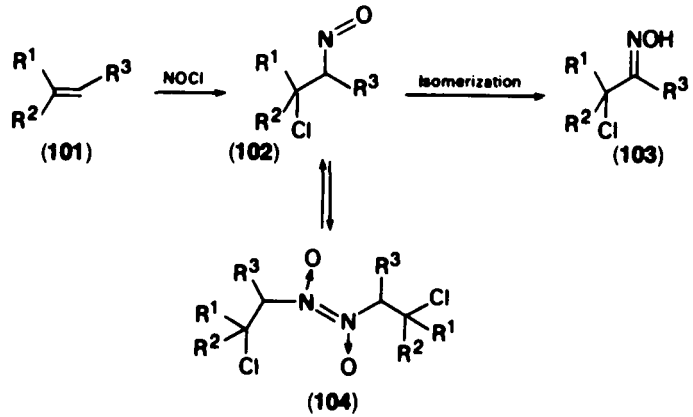
of vinylmagnesium bromide produced the intermediate imine, to which the Grignard reagent added to give adduct **100**[154].



(98) (99) (100)

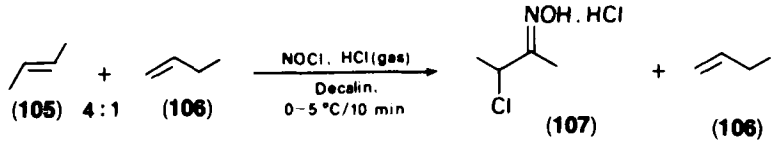
α-Halogenated oximes are available by the direct oximation of α-halo carbonyl compounds (*vide supra*), but can be obtained by two other general routes, namely the addition of nitrosyl halides to alkenes and the reduction of nitroalkenes.

The Markovnikov addition of nitrosyl chloride to olefins (**101**) yields β-chloronitroso compounds (**102**) which isomerize into α-chloro oximes (provided that at least one olefinic hydrogen is present in the starting alkene)[158–162]. Dimerization of the intermediate β-chloronitroso compound (**102**) is frequently observed, but thermal dissociation or acid-catalysed conversion of the dimer (**104**) into the monomer can generate α-chloro oximes (**103**)[163–164,435]. The addition of nitrosyl chloride to olefins is acid catalysed or can be photo-induced[165]. Simple alkenes[166,167,216,217,449], endocyclic[165,168,170,429,435] and exocyclic alkenes[166] or functionalized alkenes (e.g.



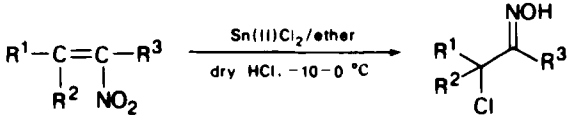
(101) (102) (103) (104)

acrylonitrile)[169,450] react with nitrosyl chloride in a general mode to produce α-halo oximes. Nitrosyl chloride adds preferentially to the more substituted olefin as illustrated by the reaction of NOCl with a 4:1 mixture of 2-butene (**105**) and 1-butene (**106**) in decalin in the presence of dry hydrogen chloride, to afford the hydrochloride of the oxime of 3-chloro-2-butanone (**107**)[167]. 1-Butene (**106**) remained unaffected under these conditions. Nitrosyl sulphate, in the presence of hydrogen chloride, also converts alkenes into α-chloro oximes[171].



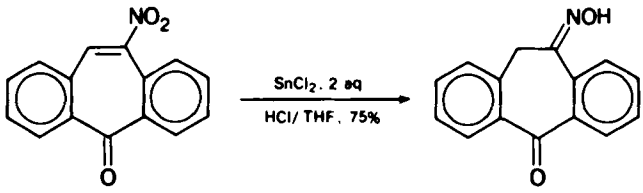
(**105**) 4:1 (**106**) (**107**) (**106**)

Nitrosyl fluoride has been reported to add to alkenes to give unstable α-fluorooximes[418], while steroidal olefins (steroid 5-enes) are known to react with excess NOF at 0°C in dichloromethane or carbon tetrachloride to furnish 5α-fluoro-6-nitrimines (i.e. *N*-nitro-α-fluoro imines)[418]. Another valuable route to α-halo oximes, mainly α-chloro derivatives, entails the reduction of nitroalkenes with stannous chloride in ether in the presence of hydrogen chloride[172,173,221]. Sterically hindered α-chloro oximes are accessible by this method[64,65], but a recent report



(**108**) (**109**)

claimed an unexpected reduction of nitroölefin (**110**) with stannous chloride in tetrahydrofuran, containing hydrogen chloride, to give the non-halogenated oxime (**111**)[174].

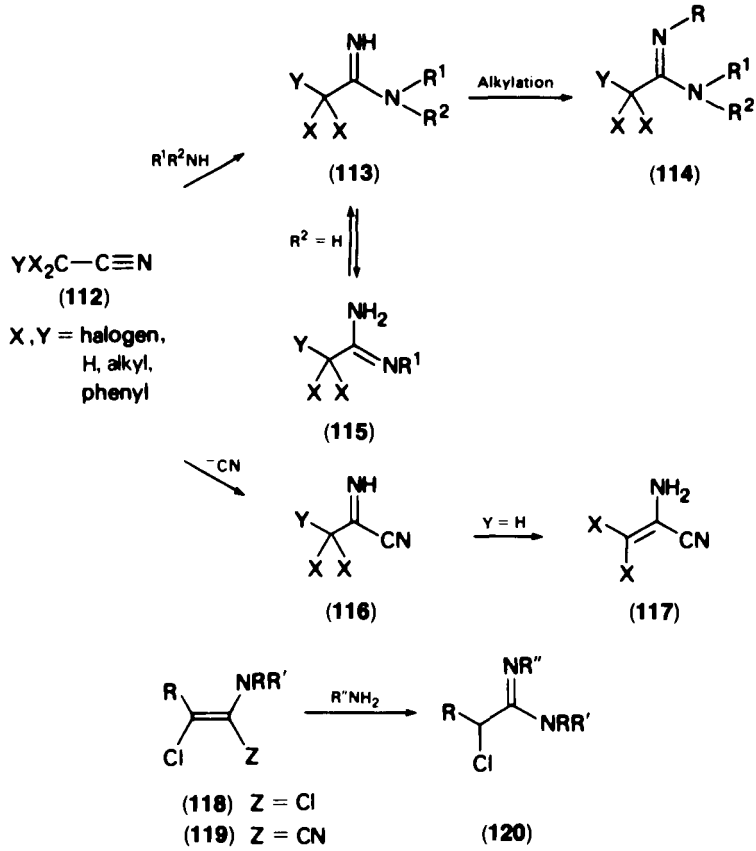


(**110**) (**111**)

An important route to *N*-unsubstituted α-halo imino compounds, e.g. imidoyl cyanides (**116**), amidines (**113**) and imidates (**123**), involves the addition of nucleophilic reagents (amines, cyanide, methoxide) to α-halogenated nitriles. Even sulphur nucleophiles added to the carbon–nitrogen triple bond, as exemplified by the reaction of phosphorus dithioacids with α-chlorinated acetonitriles[436].

All kinds of amines (ammonia, primary and secondary amines) have been shown to add to α-halo nitriles[175–181,190,191,203,204,408]. An equilibrium between isomeric amidines can exist when tautomerism is possible[182]. Alkylations of amidines (**113**) with methyl fluorosulphonate[180] or trimethyloxonium tetrafluoroborate[179] are easily accomplished.

Other approaches to α-haloamidines involved the reaction of β-halogenated α-chloroenamines (**118**)[193,194] or β-halogenated α-cyanoenamines (**119**)[145,177] with primary amines.



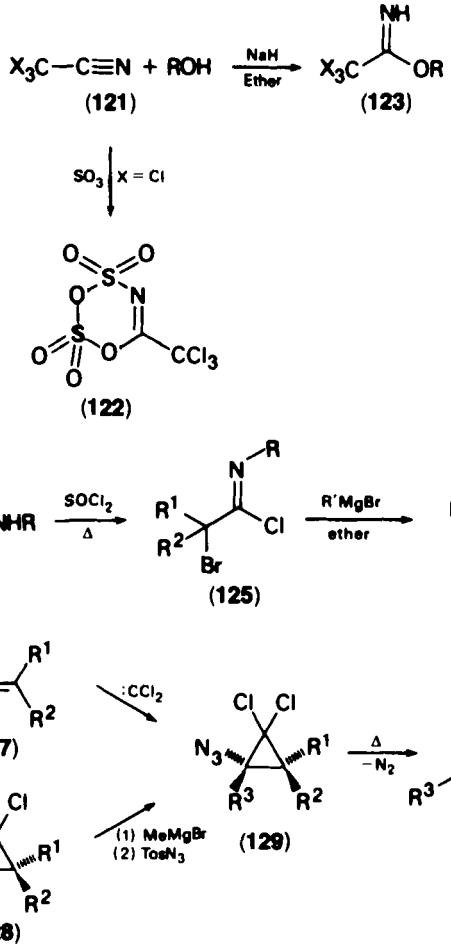
The base-catalysed addition of hydrogen cyanide to α-halo nitriles provides α-halo imidoyl cyanides (**116**)[183,184], which tautomerize to the more stable α-cyanoenamine (**117**) when an hydrogen atom α to the imino function is available[184].

Similarly, base-induced addition of alcohols[183,187,188], including allylic[187,192,425] and propargylic alcohols[189,205,425] to α-halo nitriles (mainly trichloroacetonitrile) to produce α-halogenated imidates (**123**) is a well known reaction. A cyclic functionalized imidate (**122**) was obtained from the reaction of sulphur trioxide with trichloroacetonitrile[192].

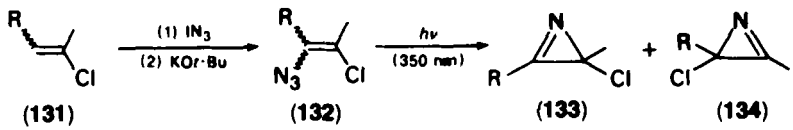
The condensation of α-bromo imidoyl chlorides (**125**), prepared from α-bromo carboxylic amides (**124**), with Grignard reagents in ether at low temperature yielded α-bromo ketimines (**126**) in 50–90% yield[195–198].

Some sophisticated α-halo imines in the small ring series have been synthesized by elegant strategies. Dichlorocarbene addition to azidoalkenes (**127**) gave 1-azido-2,2-dichlorocyclopropanes (**129**), which rearranged thermally under nitrogen expulsion to give 3,3-dichloro-1-azetines (**130**)[209]. The azidocyclopropanes (**129**) were also synthesized from aminocyclopropanes (**128**) via magnesium salt formation and treatment with tosyl azide (Anselme reaction[210])[211], and their pyrolysis furnished the four-membered heterocycles **130**[211].

3-Chloroazirines (**133** and **134**) are available from photolysis of β-chlorovinyl azides (**132**), the latter being obtained by iodine azide addition to vinyl chlorides (**131**) and

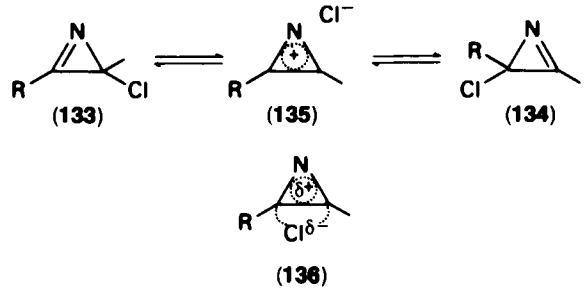


subsequent base treatment[213,214]. Compound **132** (R = Ph) is photolysed to a 5:1 ratio of **133** and **134**, respectively, in carbon tetrachloride while a 3.3:1 ratio was observed in acetonitrile[214]. However, low temperature (−40°C) photolysis of **132** (R = Ph)



produced 3-chloro-3-methyl-2-phenylazirine (**133**, R = Ph) exclusively. The equilibrium mixture of **133** and **134** can be explained by interconversion via the azacyclopropenyl cation (**135**), but it was reasoned that an alternative mechanism involving a polar bridged transition state (**136**) cannot be excluded.

Many other reports dealing with the synthesis of less general types of α-halogenated imino compounds exist in the literature, some of which are reported in a recent review[1].

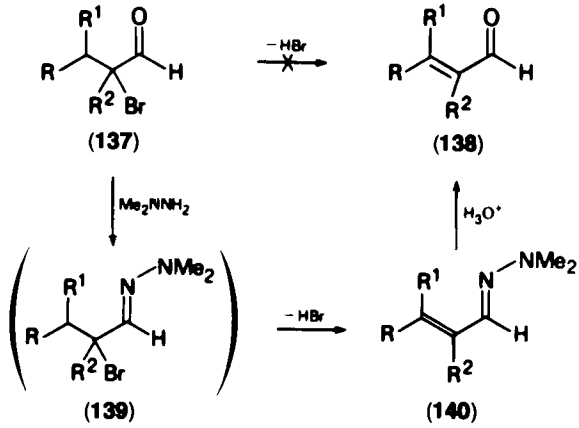


(133) (135) (134)

(136)

III. REACTIVITY OF α-HALOGENATED IMINES

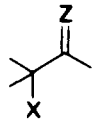
As discussed in the foregoing sections, a great variety of synthetic methods for the synthesis of α-halo imines have become available, especially as a result of efforts in the last decade. Because of these efforts, many useful transformations of α-halo imines have been performed and it will be demonstrated here that their reactivity constitutes, among other things, a broadening of the possibilities for the widely used chemistry of α-halo carbonyl compounds. Indeed, α-halo imines can be regarded as masked α-halo carbonyl compounds and hence very specific transformations of α-halo imines, which cannot be executed with α-halo carbonyl derivatives, may be carried out. Simple hydrolysis of the resulting imines provides the carbonyl compounds. This strategy is outlined in the following scheme by means of an example. Dehydrohalogenation of α-halo aldehydes (**137**) to form α,β-unsaturated aldehydes (**138**) is not applicable in a synthetically useful manner[454], but this transformation is easily accomplished via the corresponding α-bromo *N*,*N*-dimethylhydrazone **139**, which is subsequently dehydrohalogenated in the same reaction; finally, acidic hydrolysis affords the desired unsaturated aldehydes (**138**)[219]. Many other applications will follow in the forthcoming text.



(137) (138)

(139) (140)

α-Halogenated imino compounds and α-halogenated carbonyl compounds are related substances in which the heteroatom determines the difference in reactivity. Also allylic halides can be compared in this context, in that the heteroatom is replaced by carbon. The difference in reactivity between compounds **141**, **142** and **143** is mainly based on the difference in electronegativity between oxygen, nitrogen and carbon.



(141) Z = O
(142) Z = NR
(143) Z = CR^1R^2

X = halogen

Nitrogen holds an intermediate position in this series and it is therefore expected that reactivity of (**142**) will be situated between the reactivity of α-halo carbonyl compounds and allylic halides. Many reactions will demonstrate the intermediate character of α-halo imines (*vide infra*).

The reactivity of α-halo carbonyl compounds has already received considerable attention in the literature and, in an accompanying chapter in this book, some general trends and novel developments in this field will be discussed. Allylic halides (**143**; Z = CR^1R^2) can be considered as the carbon analogues of α-halo imines and α-halo carbonyl derivatives and their chemistry is well known, mainly because of its various nucleophilic substitutions, e.g. S_N1, S_N2, S_N2', etc.[222,223].

When combining an imino function and a halide into an α-halo imino system, one can expect a reactivity which depends on one or other of these functional groups or one can expect a greater versatility of the system by the combined interaction of the halide and the imine. In several aspects, the reactivity of α-halo imines parallels the reactivity of α-halo carbonyl compounds. Reactions such as rearrangements via three-membered heterocycles, elimination, nucleophilic substitution, addition to the carbon–heteroatom bond, Favorskii-type rearrangements, elimination–addition, etc., are frequently encountered. These possibilities have recently been treated in detail[2]. The decreased electronegativity of nitrogen as compared to oxygen lowers the electrophilic character of the imino carbon atom and reduces the acidity of the α-protons. These two fundamental characteristics account for a substantial decrease in reactivity of α-halo imines with respect to α-halo carbonyl compounds. The drop in reactivity permits other reactions to become more important. As already discussed above, the infrequently encountered elimination reaction of α-halo carbonyl derivatives will be shown to be an important characteristic of α-halogenated imines. In the α-halo carbonyl series, this reaction can usually not compete with other reactions such as α-deprotonations and following reactions, substitutions, rearrangements via epoxides, etc.

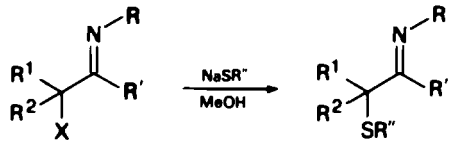
The discussion of the reactivity of α-halo imines will be divided into several sections, each one dealing with different pertinent reaction types.

A. Nucleophilic Substitutions

Many nucleophilic substitutions of α-halo carbonyl compounds have been reported in the literature, but this reaction cannot be regarded as a general feature of these substrates as the substitution pattern in the starting material is determinative in these cases. For example, the well known nucleophilic substitutions of phenacyl halides[224,225] by a variety of nucleophilic reagents, including nitrogen[226], oxygen[227,228], sulphur[229,230] and carbon nucleophiles[231], is not applicable that much to α-substituted and α,α-disubstituted[232,242] phenacyl halides (secondary and tertiary derivatives) as only good nucleophiles (e.g. azide) were found to substitute the latter tertiary α-halo ketones. Other nucleophiles, such as methoxide in methanol, were reported to react with aromatic secondary and tertiary α-halogenated ketones, such as 1-aryl-2-halo-1-alkanones[240,241] and 1-aryl-2,2-dichloro-1-alkanones[233], via an epoxide rearrangement. Several mechanistic propositions concerning the pronounced

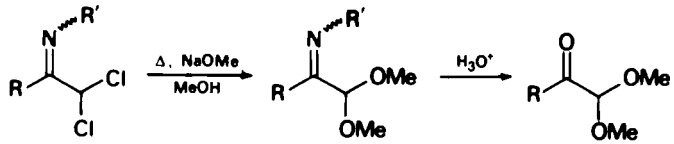
S_N2 reactivity of phenacyl halides have been formulated in the literature [228,234-237]. Introduction of one or two α-alkyl substituents in phenacyl halides drastically reduced the S_N2 reactivity[238]. It seemed that steric factors determine this behaviour, although it was reported that nucleophilic substitutions of α-halo carbonyl compounds are almost unaffected for steric reasons[239]. All these arguments can be considered when overlooking the chemical behaviour of α-halo imines towards nucleophilic substitution. The reduced electronegativity of nitrogen as compared to oxygen is responsible for a less positively induced imino carbon, thus resulting in a decreased repulsive effect of the latter with the adjacent positively induced halocarbon atom. Due to the latter feature, α-halo imines show a reasonable tendency to give α-substitution, despite its decreased general reactivity. Since no mechanistic details for substitutions of α-halo imines are available, distinction between a classical S_N2-type displacement[243], or cases in which considerable positive charge develops in the transition state[247], or displacement on an ion pair intermediate, is, at present, difficult[245].

Strong nucleophiles, e.g. thiolates, gave α-substitution of α-halogenated imines (**144**) to afford **145**[87,116,246,247], but with other nucleophiles competition with other reactions frequently occurred.



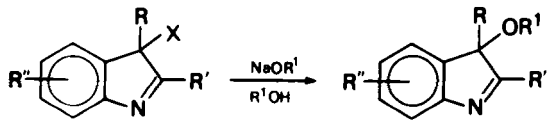
(**144**) X = Cl, Br; R' = H, CN (**145**) R' = H, CN; R" = alkyl, Ph

Alkoxides in the corresponding alcohol often yield α-alkoxy imines. *N*-Cyclohexyl α,α-dichloromethylketimines (**46**) gave α,α-dimethoxymethylketimines (**146**) exclusively when refluxed with concentrated methanolic sodium methoxide solution for a prolonged period[80]. Similarly, *N*-aryl α,α-dimethoxyketimines (**147**) were obtained but a Favorskii-type rearrangement to α,β-unsaturated imidates was a competing reaction (*vide infra*)[82,248].



(**46**) R' = C_6H_{11} (**146**) R' = C_6H_{11} (**148**)
(**47**) R' = aryl (**147**) R' = aryl

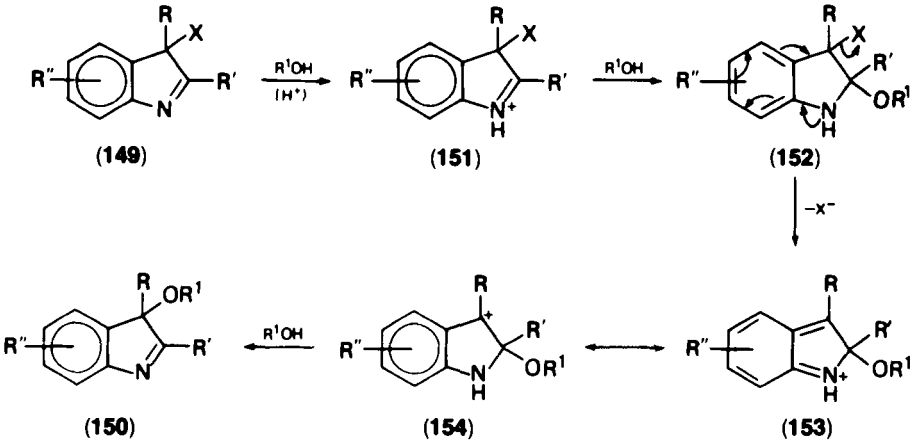
Haloindolenines (**149**) are readily converted into α-alkoxyindolenines (**150**) by treatment with alkoxides, because of the stabilizing effect of the aryl substituent on the halogenated carbon atom; the aryl group participates in the resonance stabilization of



(**149**) X = Cl, Br (**150**)

the developing carbonium ions during nucleophilic substitution. When treated with cold base, the products are alkoxyindolenines (**150**)[119,122,125] while at elevated temperature[121,122,125,132,133,138] or with mild acid[129,249,250] the product is a rearranged spiro compound (see Section III.E).

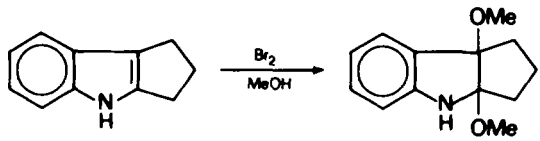
Alcoholysis of the bromo- or chloroindolenines derived from tetrahydrocarbazole or 2,3-dimethylindole produced the alkoxyindolenine **150**[119,251], but the fact that α-bromoindolenines did not react with methanol in the presence of triethylamine strongly suggested that the methanolysis of the haloindolenines is an acid-catalysed process and thus probably proceeded via a transient *N*-protonated bromoindolenine (**151**)[119].



(**149**) (**151**) (**152**)

(**150**) (**154**) (**153**)

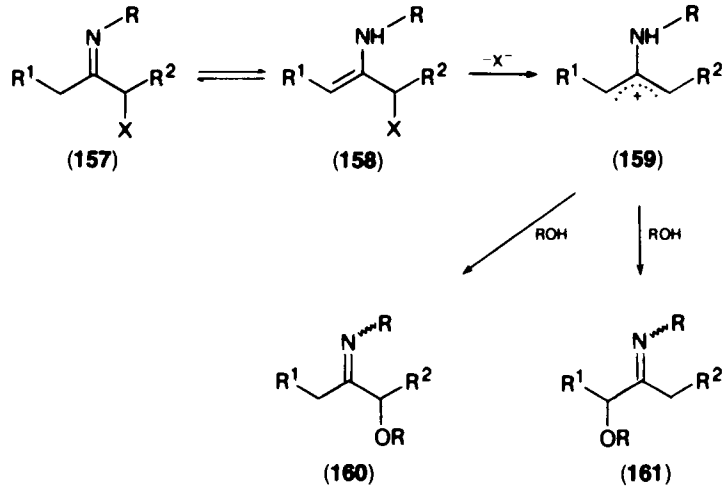
S_N2 displacement of halide ion from the α-bromo immonium derivative (**151**) is unlikely for steric reasons. Additionally, the immonium moiety in the molecule would strongly disfavour development of additional positive charge, as would be required in a transition state for nucleophilic displacement (either S_N1 or S_N2). The enhanced electrophilic character of the imino function after protonation will favour nucleophilic addition to give **152** and subsequent loss of the halide anion affords the resonance-stabilized compound **153**. The latter will be substituted by the alcohol and expelling of the elements of the alcohol from the adduct would generate the alkoxyindolenine (**150**). Support for this mechanism was found in the isolation of dimethoxyindoline **156** from the bromination–methanolysis of 2,3-cyclopentanoindole (**155**)[119].



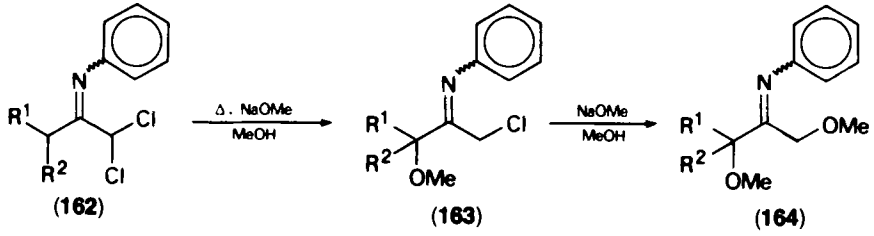
(**155**) (**156**)

Silver trifluoroacetate in methanol gave an instantaneous reaction with 3-chloro-2,3-dimethylindole[122], but it was recently shown that the reaction also proceeded without the aid of silver salts[119].

When an α′-hydrogen is present in α-halo imino systems, tautomerism to allylic halides (**158**) is possible and these substances produce a delocalized carbonium ion (**159**), which is trapped by the solvent. Depending on the stabilizing effect of the substituents in **159**, the solvolysis leads to one or other (or both) of the two α-methoxy

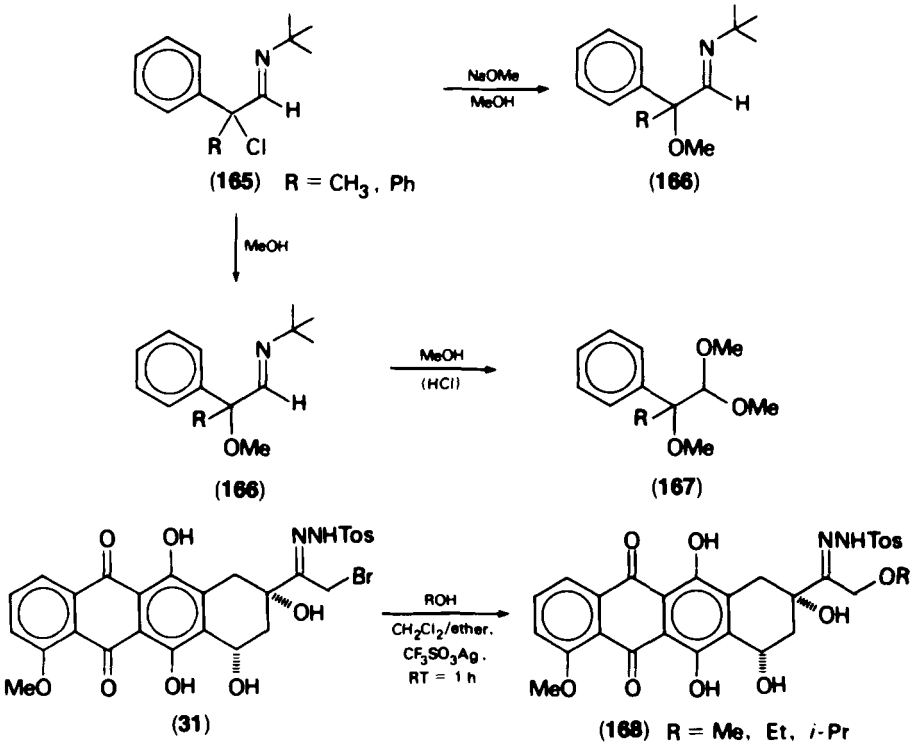


ketimines. Many papers about chloroindolenines have dealt with this topic[122,125,128,130,132,249–252,373]. The conversion of secondary *N*-phenyl-1,1-dichloromethylketimines (**162**) with sodium methoxide in methanol under reflux into *N*-phenyl-1,3-dimethoxymethylketimines (**164**) was explained by a solvolysis mechanism (additionally, nucleophilic substitution and Favorskii-type rearrangement occurred) via an enamine allylic halide[248]. The intermediacy of α-chloro-α′-methoxyketimine (**163**) was substantiated by spectral evidence[248].



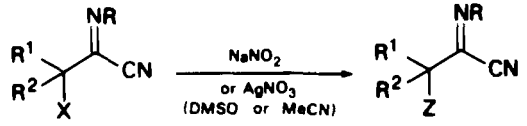
Similarly to the solvolyses in the chloroindolenine series (*vide supra*), the presence of an α-phenyl substituent in α-chloro aldimines (**165**) is of major importance in determining the course of the reaction. With methoxide in methanol, α-chloro aldimines (**165**) afforded α-methoxy aldimines (**166**) exclusively, while α-methoxyacetals (**167**) were produced in methanol, indicating methanolysis via α-methoxy aldimines (**166**)[87]. Silver ion-assisted alcoholysis of the α-bromo tosylhydrazone of 14-bromodaunomycine (**31**) proceeded smoothly at room temperature, giving rise to α-alkoxy tosylhydrazones[51] (**168**; R = Me, Et, *i*-Pr).

Of course, questions arise here concerning the structure and the stability of a carbonium ion at the α-carbon of imines. No mechanistic studies have been directed hitherto towards the identity of α-imidoyl carbonium ions. The terminology 'α-imino carbonium ion' is incorrect as positional labelling in carbonium ions assigns α to the charge-centre carbon atom. Analogously, in the oxygen series, the well-known species α-keto carbonium ions are better referred to a α-acyl carbonium ions[427,428]. As



discussed above, electronic effects reduce markedly the stability of α-imidoyl carbonium ions, but, similar to the case of α-acyl carbonium ions[427], the electronic configuration of an imino group is capable of stabilizing the positive charge on the adjacent carbon by overlapping of the vacant orbital of the carbonium ion with either the occupied lone pair orbital of nitrogen or the π-orbital of the imino function. Accordingly, the intermediacy of an azirinium species, formed by intramolecular nucleophilic halide displacement, seems to be attractive and warrants serious consideration in mechanistic explanations. Quantitative data of α-acyl carbonium ions only very recently became available[427,428], but the corresponding nitrogen analogues have only been postulated as intermediates (*vide supra*).

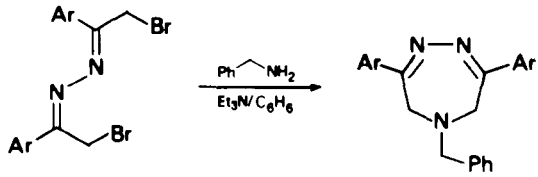
Other examples of nucleophilic substitutions using oxygen nucleophiles entailed sodium acetate in acetic acid[253], intramolecular substitution of α,α-dichloroimidates by aryloxides[254,255], α-substitutions with silver nitrate[95–97,116], sodium nitrite[96,116], hydroxide[98], bicarbonate[96] or phenoxide[98]. The bromination in acetic acid and



(78) X = Cl, Br (169) Z = ONO, ONO_2

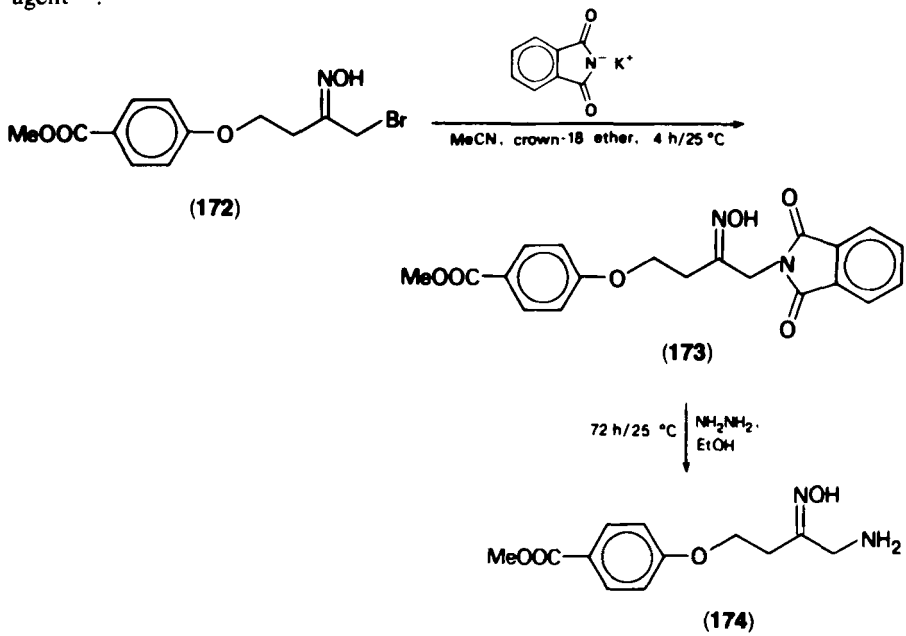
subsequent hydrolysis of tetrahydrocarbazole also provided an example of α-hydroxylation[256].

α-Substitutions with amino compounds are not frequently reported. Ordinary aliphatic α-halo imines show a complete lack of reactivity towards amines. Halomethyl imino compounds seem to be the substrates of choice for α-aminations, as demonstrated by reactions of α-brominated diazines (**170**)[74,258], α-chloro amidines[257] and α-bromo hydrazones[259,260]



(**170**) (**171**)

The introduction of an amino substituent α to an oxime can be accomplished by substituting an α-bromo oxime (**172**) with potassium phthalimide in acetonitrile in the presence of crown-18 ether, after which the α-phthalimido oxime (**173**) is subjected to hydrazinolysis in ethanol, the resulting α-amino oxime (**174**) being used as a key intermediate for the construction of 11-oxahomofolic acid, a potential antitumour agent[156].

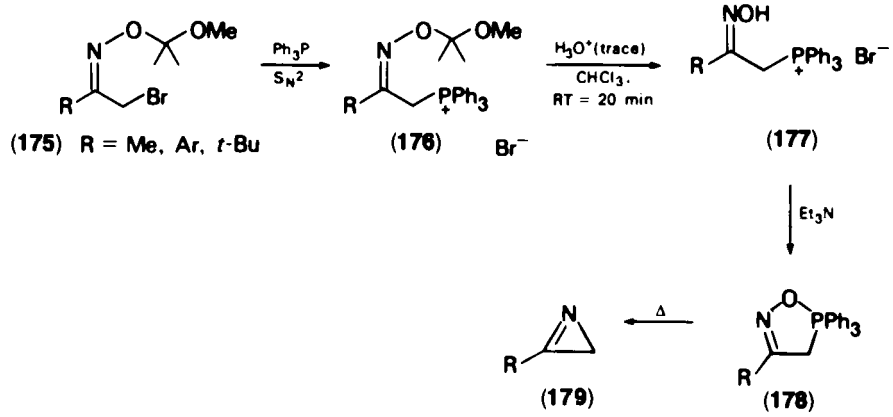


(**172**) (**173**) (**174**)

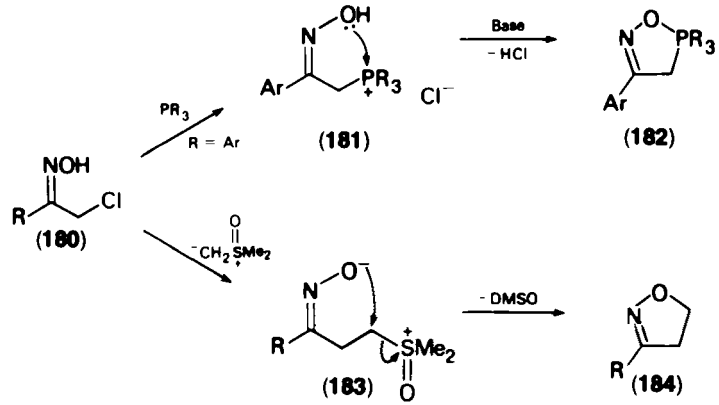
Azide ion, usually in acetone, acetonitrile or acetic acid, converts α-halogenated imino derivatives into unstable α-azido imines[87,253,261]. Phosphorus-containing nucleophiles like trialkyl phosphites do not react with α-chloro aldimines (**59**), but are known to substitute trichloroacetimidates and trichloroacetamidines at the α-position[262] (or at the imino-nitrogen atom[263] in analogy to the Arbuzov or Perkow reaction of α-halo carbonyl compounds[264]).

Triphenylphosphine easily substituted the protected α-bromo oximes (**175**), the α-substituted derivatives (**176**) subsequently yielding oximes (**177**)[157]. The latter

underwent ring closure under basic conditions to give five-membered heterocycles (**178**) which were converted into azirines (**179**) by thermolysis[157]. When the group replacing the halogen is sensitive to nucleophilic reagents, intramolecular nucleophilic

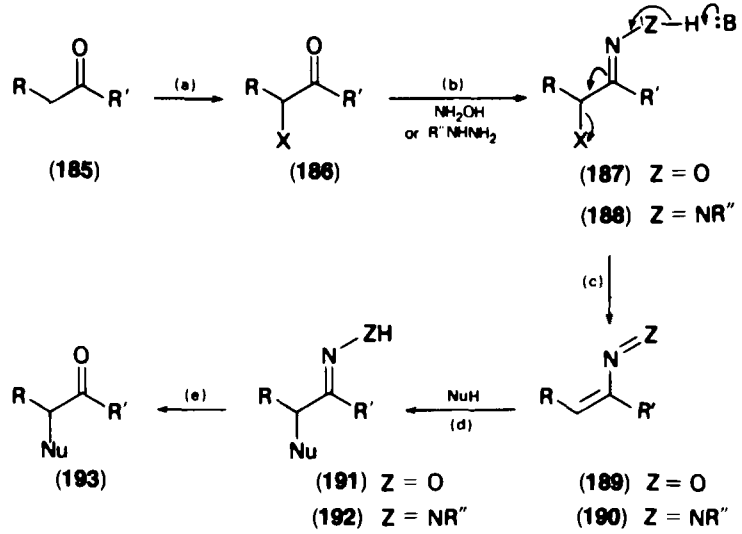


attack by the oxime oxygen can take place to afford *O,N*-heterocyclic compounds. According to this principle, α-chloromethylketoximes (**180**) reacted with phosphines or dimethylsulphoxonium methylide to give α-substituted oximes **181** or **183** and further heterocycles **182** or **184**, respectively[265–268]. It has not been stated whether these reactions involved direct nucleophilic displacement or elimination of hydrogen chloride and subsequent addition of the nucleophile to the nitrosoölefin thus formed (*vide infra*).



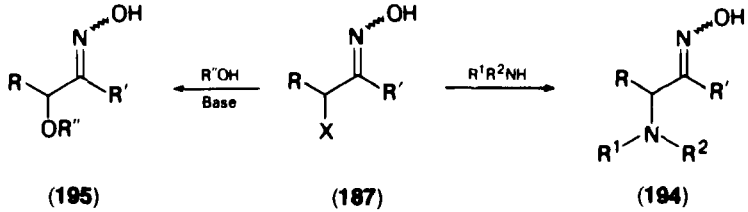
Finally, some displacements by direct attack of the nucleophile (iodide, thiophenolate, triphenylphosphine) at the halogen in chloroindolenines were reported to yield the parent indoles[253]. Nucleophilic substitutions involving carbon nucleophiles are included in the next section.

As pointed out above, α-halogenated oximes (**187**) are known to react with nucleophiles to yield the corresponding α-substituted oximes (**191**), but the reaction involves elimination to a nitrosoölefin (**189**) and Michael-type addition of the nucleophile to the latter intermediate (**189**). A similar type of elimination–addition is known for α-halogenated hydrazones (**188**), which are transformed by nucleophiles



into α-substituted hydrazones (**192**) via the intermediacy of azoalkenes (**190**). As outlined in the accompanying scheme, carbonyl compounds (**185**) are transformed into α-substituted derivatives (**193**) by a sequence involving (a) halogenation, (b) oximation or hydrazone formation, (c) elimination of hydrogen halide to form a nitrosoölefin (**189**) or an azoalkene (**190**), (d) addition of the nucleophile and (e) hydrolysis. Steps (c) and (d) are usually performed in one treatment when the nucleophile displays basic properties.

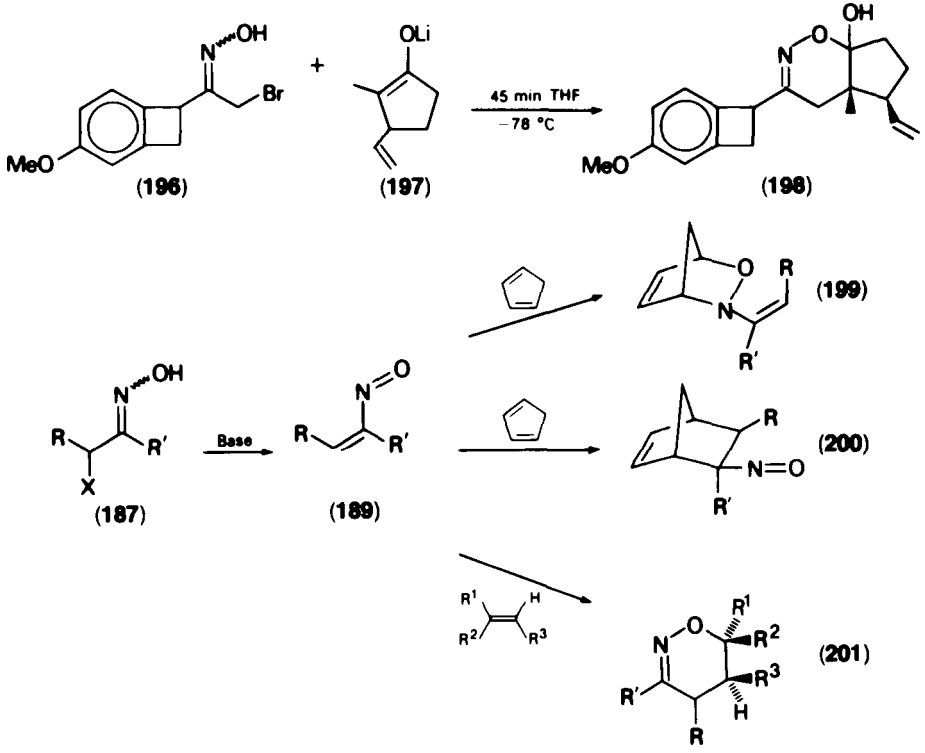
Secondary amines have been widely used to substitute α-halo oximes[94,165,168,172,287–289,409], but also primary amines[287,290,449] and ammonia[287] gave α-amino oximes. α-Alkoxylations, usually α-methoxylations, proceed smoothly for



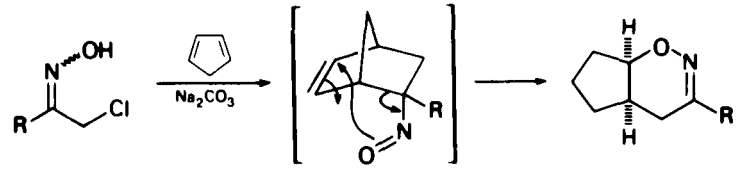
certain substrates with alcohols[172,291,409], but are facilitated when bases, e.g. triethylamine[165] or alkoxides[166,168,291], are used.

Other nucleophilic reagents such as sulphur nucleophiles[165,447], cyanide ion[293], sodium borohydride[297], sodium nitrite[287], sodium nitrate[287] and sodium azide[287] also provided elimination–addition reactions of α-halo oximes to generate α-substituted oximes (**191**). Carbon–carbon bond formation[447] was accomplished using carbanions derived from ethyl acetoacetate[295], 3-phenyl-2-isoxazolin-5-one[295], diethyl malonate[287] and 2,4-pentanedione[287], while Grignard reagents gave the α-alkylated oximes[287,295]. The generality of such reactions was shown by the reaction of α-bromo oxime (**196**) with the lithium enolate **197**, upon which cyclization resulted[69], and by the substitution of an α-bromo cyclohexanone oxime derivative with 1-lithio-1-butyne, which furnished the α-(1-butynyl)oxime[68]. In similar fashion, α-bromo oximes were

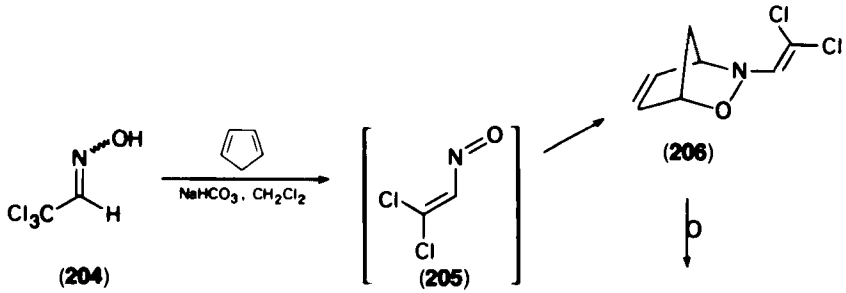
alkylated by enamines[296]. α-Halo oximes (**187**) are in fact useful synthons for the base-induced generation of nitrosoölefins (**189**), which are apt to undergo a variety of cycloadditions. Either the carbon–carbon double bond or the nitroso function can participate as a dienophile in cycloaddition, but examples are also known in which the nitrosoölefin acts as a heterodiene.

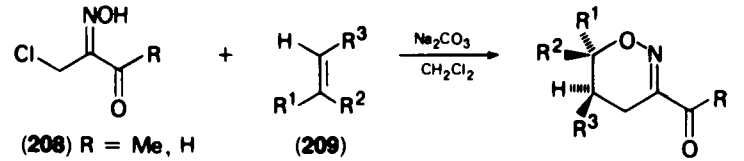


Applications of cycloadditions in which transient nitrosoölefins operate as dienophiles are the reaction of α-chloro oximes (**180**) with cyclopentadiene in the presence of sodium carbonate, the initial adducts (**202**) being transformed spontaneously into *cis*-fused oxazine derivatives (**203**)[292].

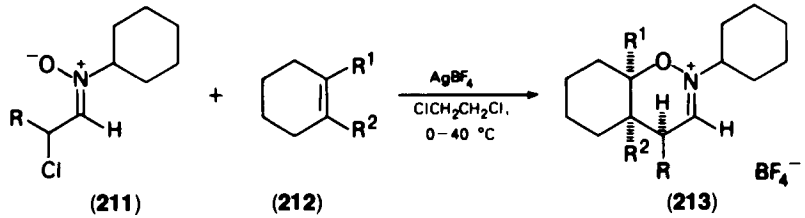


The nitroso function of nitrosoölefin (**205**), generated from chloral oxime (**204**) and sodium bicarbonate, underwent cycloaddition with cyclopentadiene to give oxazine derivative **206**, which rearranged to the tricyclic compound **207**[292,297]. An example in which the intermediate nitrosoalkene acts as a heterodiene in cycloadditions was found recently with α-chloro oximes (**208**), carrying an electron-withdrawing

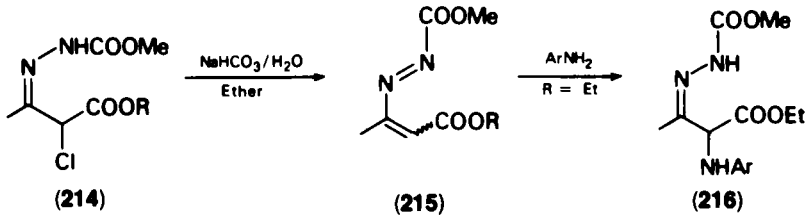




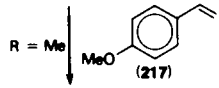
substituent[298,451]. Related reactions are the cyclocondensations of α-chloronitrones[299–305], e.g. **211**, with cycloalkenes (**212**) and alkenes[411] to give bicyclic adducts (**213**). This reaction was recently shown to be applicable also with ketones and α-chloro nitrones to generate 4*H*-1,5,2-dioxazinium salts[456].



According to the general principle of base-promoted elimination–addition of α-halo hydrazones (**188**), a wide variety of α-substituted hydrazones (**192**) are obtainable. Azoalkenes (**190**) have been isolated in many cases[8–10,47,48,111,306,307–309,317–319,334] and their stereochemistry was investigated to some extent[308,317,434]. However, the *in situ* preparation of azoalkenes is most often applied[18,23,46,310]. Addition of nucleophiles, e.g. acetate[23,46], amines[23,46,307], organocopper reagents[49,50,309], Grignard reagents[325–327] or carbanions[112] to azoalkenes (isolated or prepared *in situ*) provided α-substituted hydrazones (**192**) but also cycloaddition products, in which azoalkenes act as diene or dienophile, have been reported (see, for instance, **218**)[308,311,312]. α-Halogenated hydrazone-type compounds (**219**), contained in a ring system, have been used for the synthesis of α-vinylcarboxylic acids (**220**)[101], α,β-unsaturated carboxylic acids[77,313–316]



(214) (215) (216)



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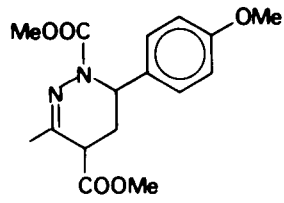
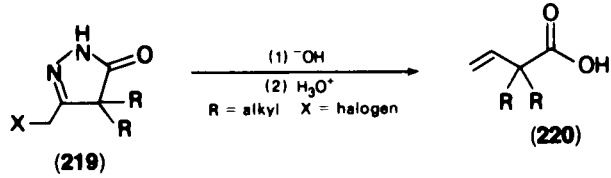


(218)

and 1,5-diazabicyclo[3.3.0]octadienediones (**221** and **222**)[76,286]. Additionally, tosylazoalkenes derived from aldehydes have been used to generate alkylidene carbenes[453].



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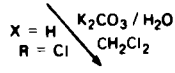
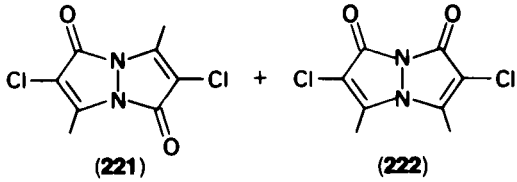




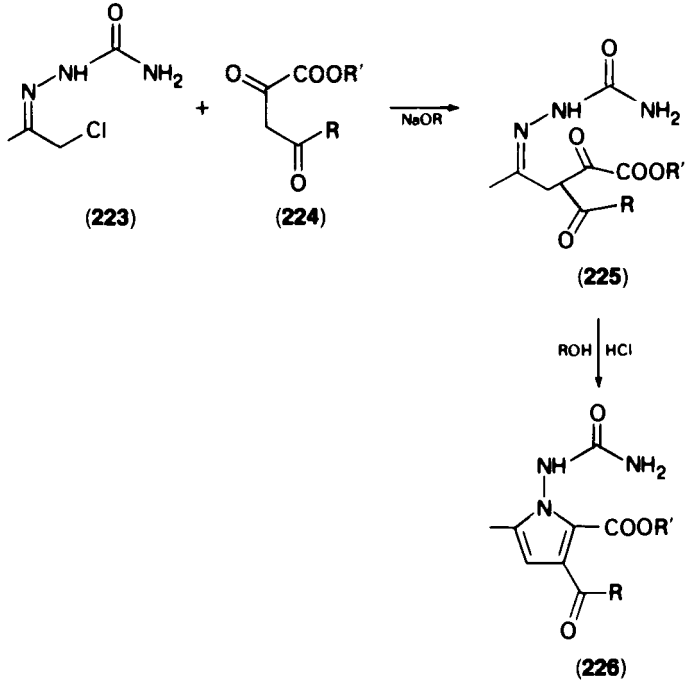
(221) (222)

B. Carbon–Carbon Bond Formation

Because of the importance of carbon–carbon bond formation in synthetic organic chemistry, emphasis to this topic is given in a separate section covering reactions of α-halogenated imino compounds with carbanions, cyanide ion and organometallic reagents.

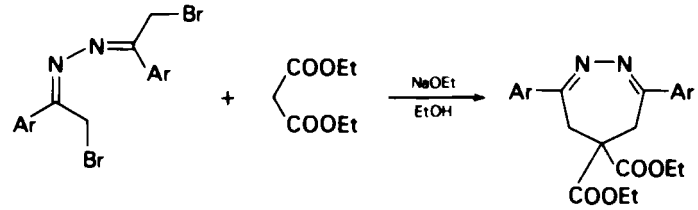
1. Reactions of α-halogenated imino compounds with carbanions

Few reports have been published on the reaction of α-halo imines with carbanions. Tertiary α-chloro aldimines (**59**) are completely resistent to reaction with carbanions derived from active methylene functions[87], but α-halomethyl imino derivatives proved to be more successful in nucleophilic substitutions. Chloroacetone semicarbazone gave α-substitution with the active methylene compound **224** and the resulting product was subjected to ring closure with hydrogen chloride in alcoholic medium to afford functionalized pyrroles (**226**)[109].



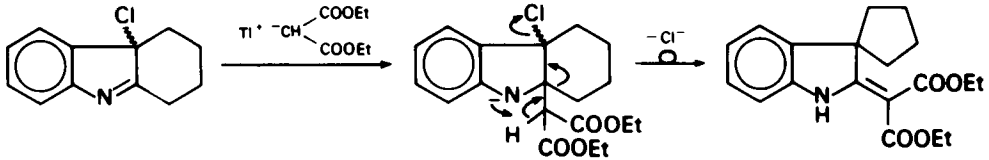
(**223**) (**224**) (**225**) (**226**)

In a similar way, α-bromoacetophenone azine (**170**) gave two fold nucleophilic substitution with diethyl malonate (**227**), to provide 5,5-bis(ethoxycarbonyl)-5,6-dihydro-3,7-diaryl-4*H*-1,2-diazepines (**228**)[269]. The thallium salt



(**170**) (**227**) (**228**)

of diethyl malonate in benzene reacted with the chloroindolenine derived from tetrahydrocarbazole (**229**) to produce the nucleophilic addition product (**230**), which rearranged into compound **231**[271]. Such a rearrangement was applied to a

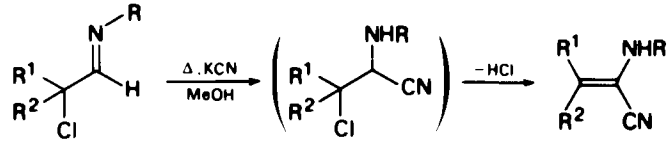


(229) (230) (231)

synthesis leading to the alkaloid vincadifformine[153,271]. The aforementioned base-induced coupling reaction of α-iodomethylketimines (**40**)[78] was similarly observed with 2-bromomethyl-1,3-oxazine derivatives[430].

2. Reactions of α-halogenated imino compounds with cyanide ion

Although nucleophilic displacement of α-halogens by cyanide ion are known[272], the preferred reaction of cyanide is addition to the imino function[273,284], and eventually further reaction of intermediately formed adducts[274,275]. α-Chloro aldimines (**59**), α,α-dichloro aldimines (**232**) and α,α,α-trichloro aldimines (**233**) react with potassium cyanide in methanol to give α-cyanoenamines **235**, **236** and **237**, respectively[276–278]. The last-mentioned compound (**237**), however, is accompanied by several by-products,



(**59**) R^1, R^2 = alkyl (**234**) (**235**) $R^1 = R^2$ = alkyl

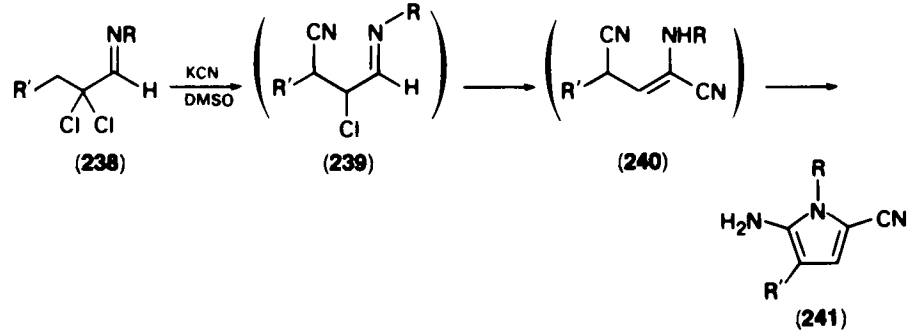
(**232**) R^2 = Cl (**236**) R^2 = Cl

(**233**) $R^1 = R^2$ = Cl; R = *t*-Bu (**237**) $R^1 = R^2$ = Cl; R = *t*-Bu

originating from further reaction of this reactive α-cyanoenamine with methanol[278]. The reaction involves addition of cyanide to the imino function and subsequent dehydrochlorination of the transient adduct (**234**). α-Cyanoenamines (**235**) were found to be valuable synthons as they can be transformed into trialkylketenimines[279] and carboxylic amides[280,457].

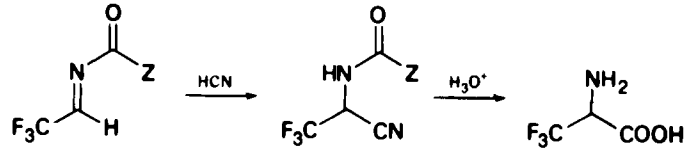
The preferred addition of cyanide to an imine was demonstrated by incorporation of ^{14}C-labelled cyanide into α-chloro imidoyl cyanide (**78**; X = Cl) on reflux with $K^{14}CN$ in methanol[116].

With potassium cyanide in dimethyl sulphoxide, α,α-dichloro aldimines (**238**) gave 2-amino-5-cyanopyrroles (**241**) by a sequence involving elimination of hydrogen



(**238**) (**239**) (**240**) (**241**)

chloride, Michael addition, α-cyanoenamine formation and ring closure[280]. When non-displaceable halogens were incorporated in the starting α-halo imine, e.g. *N*-activated trifluoroacetaldimines (**242**), the adduct **243** was easily isolated and could be hydrolysed into trifluoroalanine (**244**)[285].

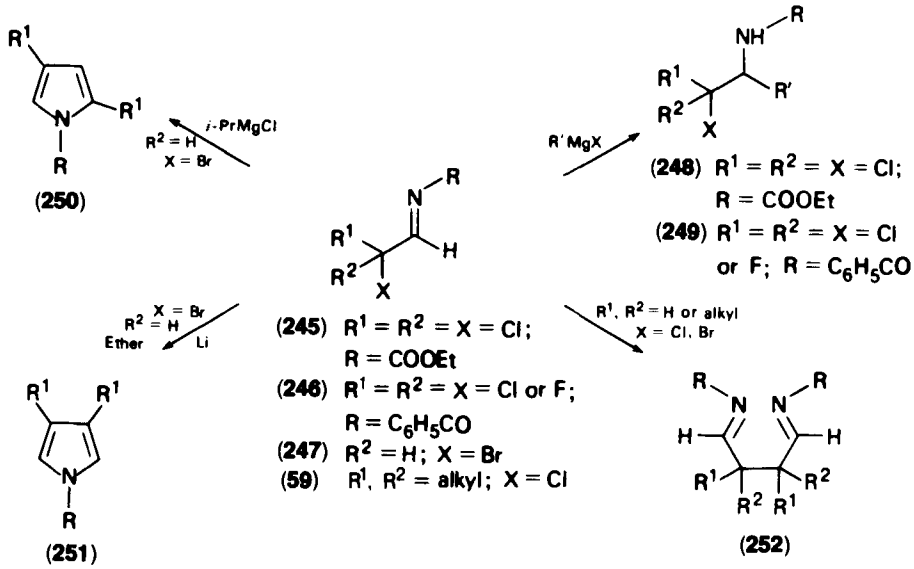


(**242**) Z = C_6H_5CO; Z = $PhCH_2CO$ (**243**) (**244**)

The behaviour of cyanide ion towards α-halo imines parallels the reactivity of this nucleophile towards α-halo carbonyl compounds as the latter are also known to give nucleophilic addition to the carbonyl function, but the adduct is dehydrohalogenated in a different way, namely by intramolecular nucleophilic substitution to produce α-cyano epoxides[231,438-440]. All the above-mentioned examples in the imine series belong to the class of α-halo aldimines and give rise to 1,2-dehydrohalogenation, but aliphatic α-halo ketimines behave like α-halo ketones in that they undergo 1,3-dehydrohalogenation, generating α-cyano aziridines[91].

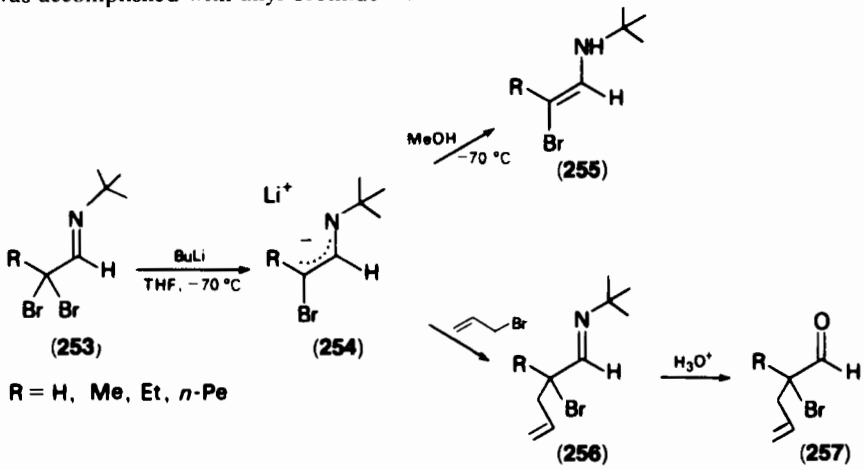
3. *Reaction of α-halogenated imino compounds with organometallic reagents*

Grignard reagents usually add to the carbon–nitrogen double bond of *N*-activated α-halogenated imines (**245** and **246**)[146,154,320]. Aliphatic α-bromo aldimines (**247**) with



isopropylmagnesium chloride produced 1,2,4-trisubstituted pyrroles (**250**), while 1,3,4-trisubstituted pyrroles (**251**) were obtained with lithium in ether[321,323]. On the other hand, coupling reactions to produce 1,4-diimines (**252**) were observed when secondary and tertiary α-haloimines reacted with sodium in liquid ammonia or with

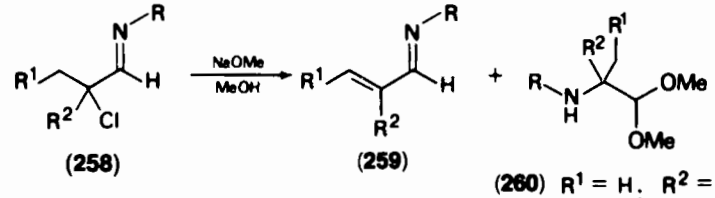
methylmagnesium iodide[87,322]. Metallation of α,α-dibromoaldimines (**253**) with butyllithium in tetrahydrofuran produced lithiated α-bromo aldimines (**254**), which underwent protolysis with methanol at low temperature to give the first non-conjugated secondary β-halo enamines (**255**), while α-alkylation of anions (**254**) was accomplished with allyl bromide[324].



As mentioned above organometallic reagents, e.g. organocopper compounds[49,50,309], alkyllithium compounds[69] and Grignard reagents[102,103,287,295,325–327], substitute halogens α with respect to an oxime or an hydrazone moiety, but the reaction proceeds through intermediacy of nitrosoölefins or azoalkenes.

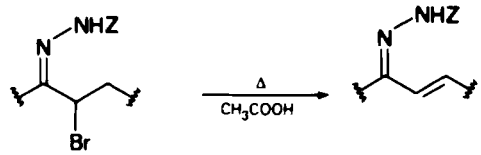
C. Elimination Reactions of α-Halo Imino Compounds

The elimination of hydrogen halide from simple α-halogenated imines is one of their basic reactions, as recently demonstrated. α-Chloro aldimines (**258**) were converted into α,β-unsaturated aldimines (**259**) by reaction with sodium methoxide in methanol, but a competitive rearrangement via an α-methoxyaziridine was noticed for isobutyraldimines (**258**; R^1 = H; R^2 = Me) by which α-aminoacetals (**260**) resulted[87].



Several simple α-halogenated imines were reported to react with alkoxides in the corresponding alcohol to give initial elimination of hydrogen halide[86,90]. α-Bromo hydrazone-type compounds (**261**) suffered elimination of hydrogen bromide[20–23,46,328–330] when heated in acetic acid, and this method was proposed to introduce a double bond at C_4–C_5 in 3-ketosteroids[20–22].

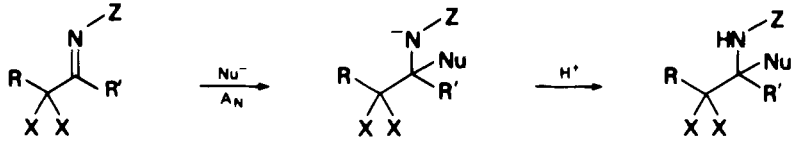
Finally, 3-bromo-2-cyano-1-pyrroline 1-oxides (**65**; R = CN)[95–97] and α-halogenated imidoyl cyanides (**78**)[116] readily underwent base-induced elimination reactions to afford the corresponding α,β-unsaturated imino compounds.



(261) Z = Ar, $CONH_2$ (262)

D. Nucleophilic Additions to *N*-Activated α-Halogenated Imino Compounds

Imino compounds (263), especially aldimines, having an electron-withdrawing *N*-substituent and α-perhalogenation, add nucleophiles at the imino function under very mild conditions[141,143,145,154,335,336,410]. The high electrophilic character of the imino

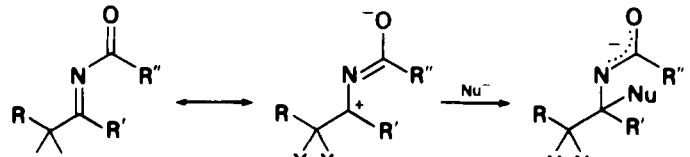


(263) X = halogen
R = halogen or alkyl
R' = usually H
Z = COOR", COR", SO_2R"

(264)

(265)
Nu = OR^1, OAr, NR^1R^2, NHR^1, SR^1, SAr, OH, $OOCR^1$, $NHCOR^1$, $NHNHR^1$

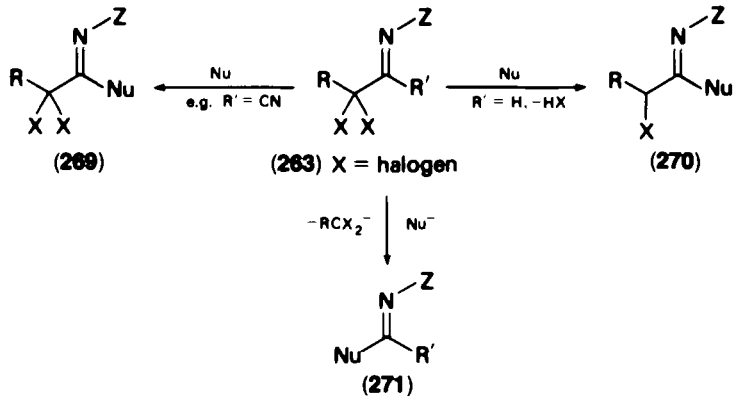
carbon originates from the inductive effect of the α-halogens and the mesomeric effect of the *N*-activating group. The extreme form of the polarization in, for example, *N*-acyl α-halo imines (266) can be expressed as dipolar structure (267), clearly indicating the tendency to give Michael-type additions to such heteroenones. Various



(266) (267) (268)

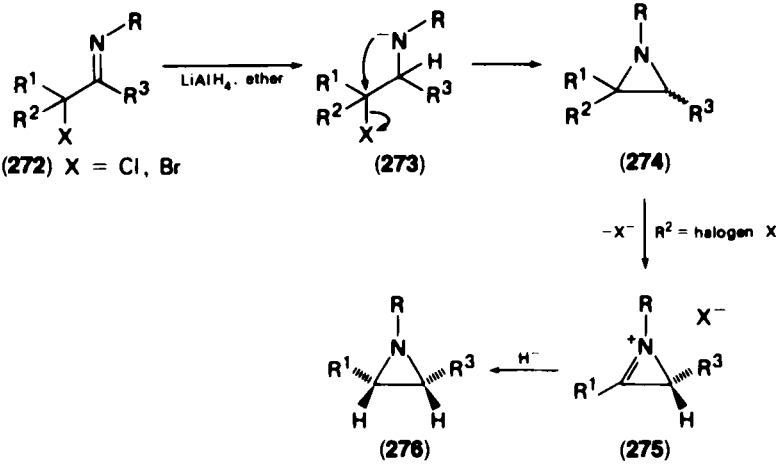
kinds of nucleophiles have been reported to give stable adducts (265; R' = H), among others alcohols[141,143,154,337], amines[141,143,145,335,336], thiols[143,335,336], hydrogen sulphide[335], water[335], phenols[335,336], carboxylic acids[143,335,336], amides[143,335,336] and hydrazines[143,336]. This tendency for nucleophilic addition to the imino function is at maximum for α-halogenated aldimines (266; R' = H) and originated from the decreased steric hindrance as compared to the ketimine case (266; R' ≠ H). An analogous aptitude for nucleophilic addition is well known for α-halogenated aldehydes, which practically always react by such an initial addition reaction[443,444]. Similarly, several examples with α-halo ketimines[37,117,118,247,338-341] or imidate derivatives[452] have been found. However, the nucleophilic addition can be followed by an elimination of hydrogen halide (270)[278,333,343], an expelling of a leaving group (R') connected to the imino carbon (269)[342] or a haloform-type reaction (271)[333].

Of major importance is the reaction of α-halogenated imino compounds with mixed metal hydrides (usually lithium aluminium hydride), which add to the imino function

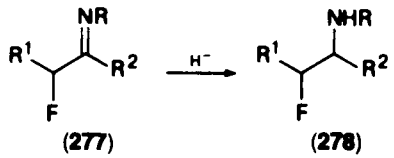


in a very general way. When the halogen is displaceable (X = Cl, Br), the reaction proceeds further by intramolecular nucleophilic attack giving aziridines[85,143,321,344,345,347]. If the reaction is performed with α,α-dihalogenated imines (**272**; R^2 = X = Cl)[85,143,345,346], the intermediate α-haloaziridine (**274**; R^2 = Cl) is transformed into the final aziridines (**276**) by expelling of a halide anion to generate an azirinium halide (**275**), which is stereospecifically attacked from the less hindered side (most remote from substituent R^3) to give *cis*-aziridines[346]. Ring opening, however, of transient α-haloaziridines by hydrides has also been encountered[106,346,348].

These results are in sharp contrast to the reactivity of α-halo carbonyl compounds towards mixed hydrides, from which only β-halohydrins and/or alcohols result.



When α-fluorinated imino compounds (**277**) react with mixed metal hydrides, the exclusive addition reaction leads to β-fluorinated amino compounds (**278**)[37,38,349–351], a



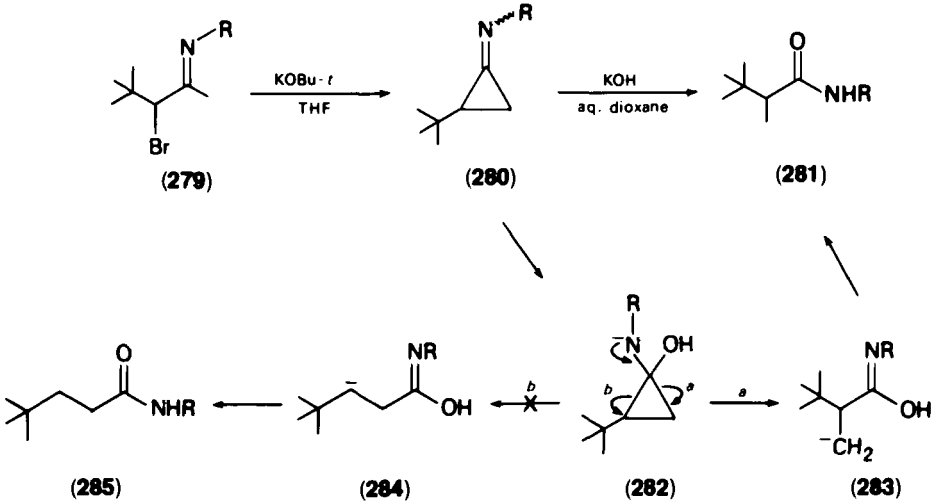
reaction which was also observed with some α-chloro- or α-bromo imino compounds[211,278,351,352].

E. Rearrangement of α-Halogenated Imino Compounds

Three types of more or less frequently encountered rearrangements of α-halo imines will be discussed here, namely the Favorskii-type rearrangement, the rearrangement via activated aziridines and the Wagner–Meerwein-type rearrangement of chloroindolenines. Finally, a single case of the Beckmann rearrangement of an α-bromo oxime will be discussed.

1. *The Favorskii-type rearrangement*

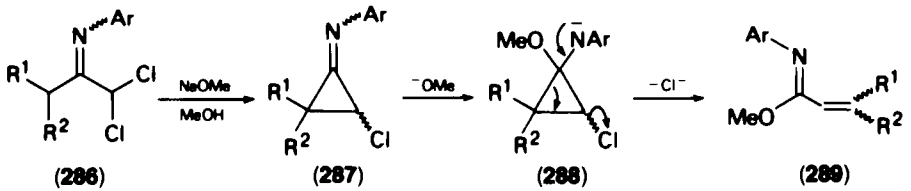
The base-induced skeletal rearrangement of α-halo ketones to afford carboxylic acid derivatives, known as the Favorskii rearrangement[353–360], has also been encountered with α-halo imines. Quast and coworkers performed the first transformation of an α-halo ketimine (**279**) into a carboxylic amide (**281**) via a two-step sequence, which could be accounted for in terms of the Favorskii rearrangement[195,361]. 1,3-Dehydrobromination of α-bromo ketimine (**279**) was obtained with potassium *t*-butoxide to generate cyclopropylidene amines (**280**), which underwent hydroxide-induced opening to give amide (**281**). The opening of the nitrogen analogues of cyclopropanones (**280**) is directed by the stability of the intermediate anion. Accordingly, **280** is opened via path *a*, giving rise to the more branched carboxylic amide (**281**). No trace of the alternative route *b* was observed. Another



(279) (280) (281)

(285) (284) (282) (283)

Favorskii-type rearrangement was observed by reaction of *N*-aryl α,α-dichloromethylketimines (**286**) with sodium methoxide in methanol, affording α,β-unsaturated imidates (**289**) via transient cyclopropylideneamines (**287**)[82,248]. The reaction of primary derivatives (**286**; R^2 = H) was shown to be stereospecific and gave rise to a regiospecific opening of the chlorocyclopropylideneamine (**287**)[82,248]. Secondary derivatives (**286**; $R^2 \neq$ H) also afforded a regiospecific opening of the transient cyclopropylideneamine (**287**) because of the directive aid of the chloride anion expulsion. The latter reaction was not stereospecific in that a mixture of *E*- and

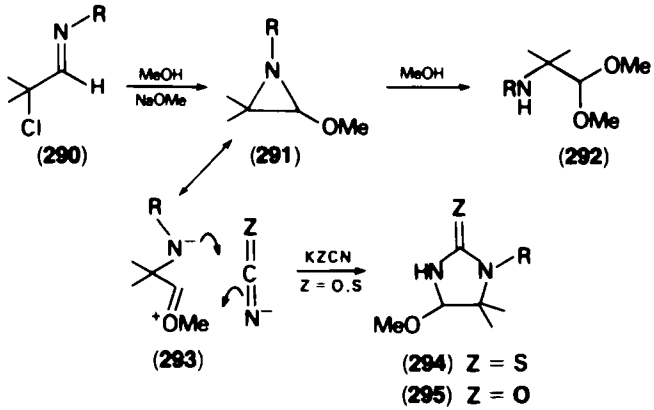


(286) (287) (288) (289)

Z-imidates (**289**) was produced[248]. Side reactions, e.g. nucleophilic substitution and solvolysis of **286** with sodium methoxide in methanol could be avoided by working in ethereal medium[248].

2. *Rearrangement of α-halo imines via activated aziridine intermediates*

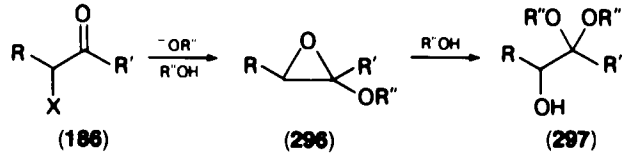
As exemplified for mixed metal hydrides (*vide supra*), the addition of nucleophiles to the imino function of α-halo imines can be followed by intramolecular attack with halide expulsion, by which aziridines result. In the case of nucleophiles other than hydride, but most often with alkoxides (or alcohol), the aziridine thus formed is a very reactive species and undergoes alcoholysis when the reaction is carried out in an alcohol. α-Chloro isobutyraldimines (**290**), when treated with sodium methoxide in methanol, are converted into α-alkylaminoacetals (**292**) and α,β-unsaturated aldimines[87]. The latter competitive elimination reaction was removed by working in methanol only. The intermediacy of α-methoxyaziridines (**291**) was established by trapping these transient species (see dipolarophilic form **293**) with the ambident thiocyanate or cyanate anions[362,363], resulting in 2-imidazolidinethiones (**294**) and 2-imidazolidinones (**295**). Nucleophilic additions of alkoxides across the imino function



(290) (291) (292) (293)

(294) Z = S
(295) Z = O

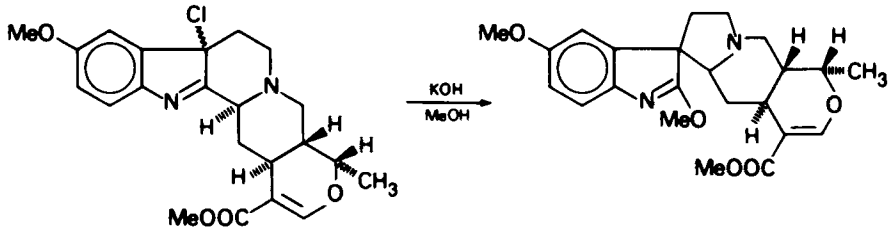
and subsequent intramolecular nucleophilic attack of the nitrogen atom were observed with α,α-dichloroaldimines (**56**)[86], α-monochloroaldimines[87] and α-halo immonium halides[352,364–369]. These transpositions are completely comparable to the alkoxide-induced rearrangements of α-halo carbonyl compounds (**186**) to α-hydroxyacetals (**297**) via intermediate alkoxyepoxides (**296**)[419–424].



(186) (296) (297)

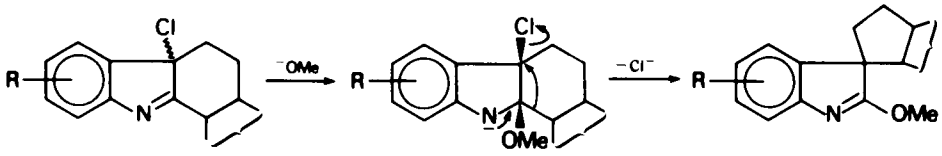
3. Rearrangement of chloroindolenine derivatives

Chloroindolenines, obtained by reaction of indoles with *t*-butyl hypochlorite, yield rearranged iminoethers, e.g. **299** (and/or oxindoles), upon treatment with base (methoxide, hydroxide) at elevated temperature, while α-substitutions were noticed when treated with cold base. This general rearrangement was applied to simple



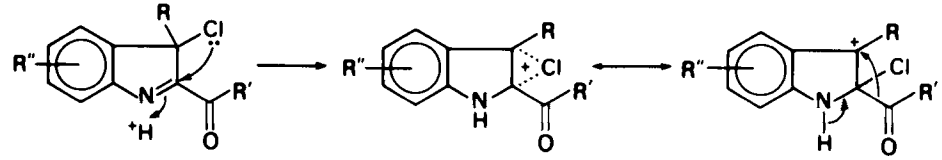
(298) **(299)**

indolenine derivatives, like the chloroindolenine derived from tetrahydrocarbazole, and more complex indole-type alkaloids[125–128,132,133,138,249,250,270,271,370]. From the mechanistic point of view, the rearrangement of chloroindolenines (**300**) was explained by initial nucleophilic addition of methoxide at the C=N double bond, followed by Wagner–Meerwein-type rearrangement to give **302**. This transformation requires *cis* disposition of the chlorine atom and the methoxy group in adduct **301**.

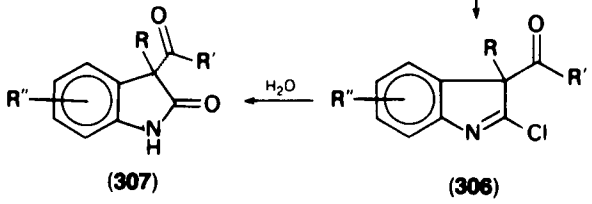


(300) **(301)** **(302)**

Not only under basic conditions but also under neutral conditions were rearrangements of chloroindolenine and related alkaloids observed[250]. 2-Functionalized 3-chloroindolenines (**303**) rearranged in protic solvents into



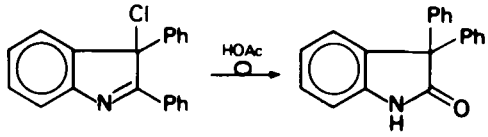
(303) R′ = OEt, NH_2, NEt_2, NHEt **(304)** **(305)**



(307) **(306)**

oxindoles with migration of the functional group from the 2-position to the 3-position[129]. In this case a carbonium ion (**305**), mesomeric with chloronium ion **304**, is involved and migration of the carbonyl group furnishes imidoyl chloride (**306**), which leads to **307** upon hydrolysis.

Many other migrations of substituents from the 2-position to the 3-position, starting from 3-chloroindolenines by treatment in acidic medium, are known[88,121,253,371,372];

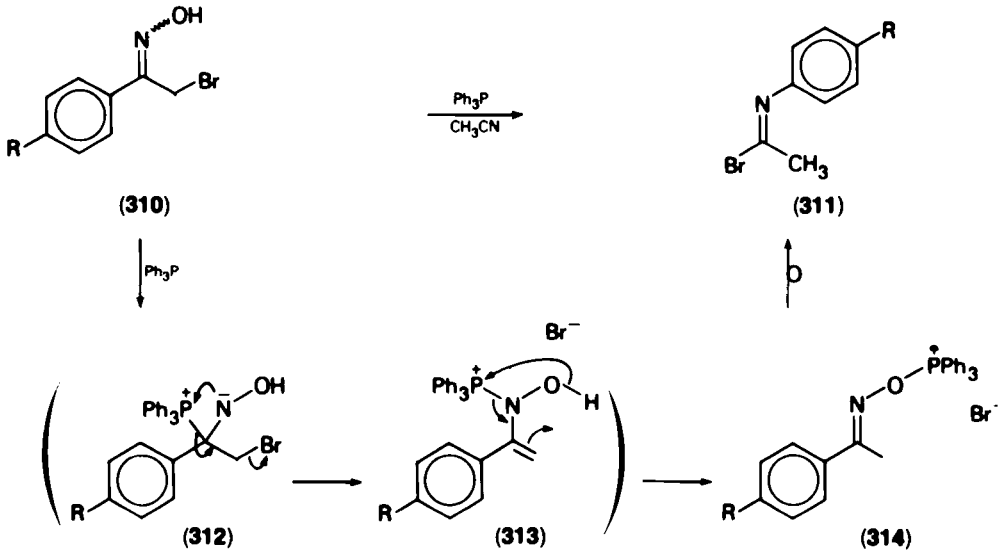


(**308**) (**309**)

one example is given here, namely the spontaneous rearrangement of chloroindolenine (**308**) in acetic acid solution into oxindole (**309**).

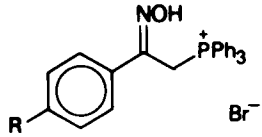
4. Beckmann rearrangement of α-bromo oximes

The reaction of *para*-substituted phenacyl bromide oximes (**310**) with triphenylphosphine in acetonitrile at room temperature produced imidoyl bromides (**311**) and triphenylphosphine oxide[226]. The rearrangement is explained by addition of the phosphine to the imino function after which debrominated oxime derivative (**314**) is formed via a series of tranformations, visualized by the arrows in the accompanying scheme. Compound **314** is then susceptible to the well known Beckmann



(**310**) (**311**) (**312**) (**313**) (**314**)

rearrangement to give **311**. It is important to notice that in the presence of slight amounts of base (e.g. a few drops of an aqueous potassium cyanide solution), the course of the reaction is changed in favour of oximino phosphonium salt (**315**)[266], indicating the importance of the nitrosoölefin route (*vide supra*).

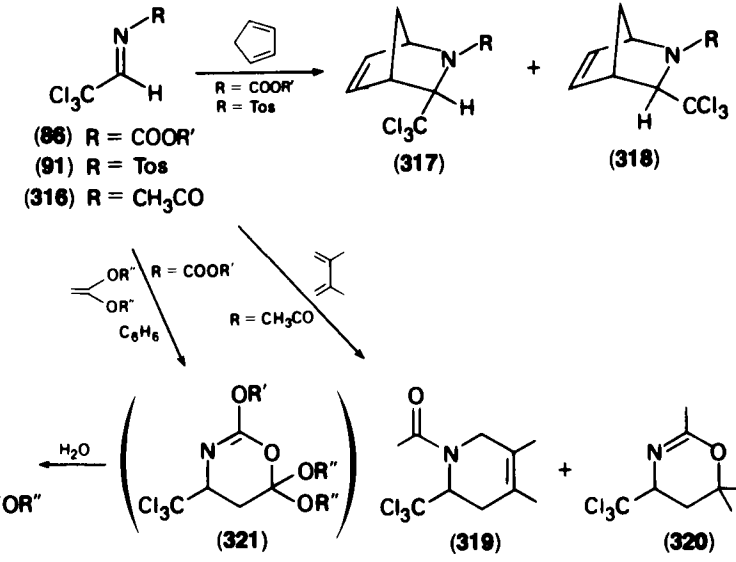


(315)

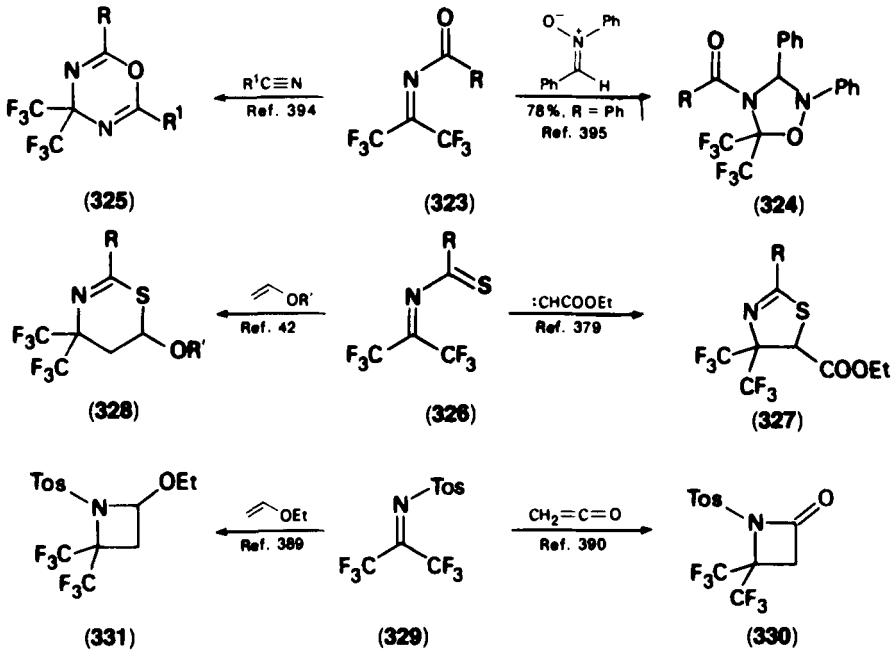
F. Cycloadditions

Numerous cycloadditions have been reported with α-halo imines, practically all of them α-perhalogenated and having an activating *N*-substituent, e.g. alkoxycarbonyl, tosyl, benzoyl, etc. α-Halo imines having a carbonyl substituent directly bonded to nitrogen can act as dienophile or as heterodiene in Diels–Alder reactions. *N*-Alkoxycarbonyl and *N*-tosyl chloralimines (**86** and **91**) gave cycloadducts with dienes, e.g. acyclic and cyclic 1,3-dienes, functionalized 1,3-dienes, etc.[144,396–399,437]. The *N*-acetyl analogue **316** reacted with 2,3-dimethylbutadiene as dienophile to give adduct **319**, but adduct **320** was also isolated, indicating that **316** acted as a heterodiene[399]. On the other hand, *N*-alkoxycarbonyl chloralimines (**86**) behaved exclusively as heterodienes towards electron-rich alkenes, e.g. ketene acetals, resulting in an oxazine derivative (**321**), which was hydrolysed to carbamate derivative **322**[400].

α-Perfluorinated ketimines such as hexafluoroacetone imines especially have been found to give a variety of cycloadditions, but these reactions are not dealt with here in detail because of lack of space.

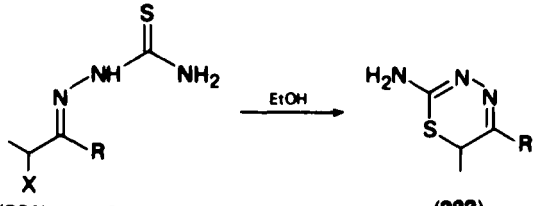


Only some examples of the various possible types of cycloadditions of α-perfluorinated imines are reported in the following scheme, together with some leading references in this area[2,41,42,154,374–395,401,458]. Among the reagents found to give cycloadditions to α-perfluorinated imines are included nitriles, nitrones, enol ethers, carbenes, ketenes, alkenes, ketones, ynamines and isonitriles.



G. Miscellaneous Reactions of α-Halogenated Imino Compounds

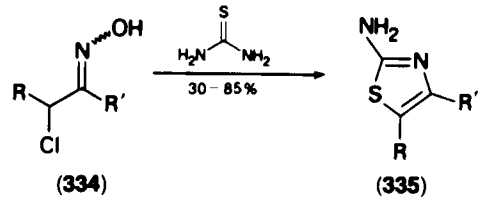
A large number of α-halogenated imino compounds have been used for the synthesis of various heterocyclic compounds. A detailed description has been given in a recent review[2]. This survey will be limited to mentioning some particular examples. α-Halogenated thiosemicarbazones, e.g. **331** and **332**, and related compounds are known to give intramolecular cyclizations to pyrazoles[57,402], 2-iminothiazolines[52,53,55]



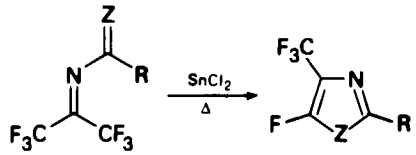
and thiadiazines (**333**)[52–55,403], while α-halo oximes produced thiazoles (**335**) and thiadiazines on reaction with thiourea and dithiocarbazic acid, respectively[216,217].

As pointed out already in the section describing cycloadditions, perfluoroacetone imines (**336**, **323**, **326**) are versatile substrates for syntheses of nitrogen heterocycles as they are known to give rise to imidazoles (**337**)[404], oxazoles (**338**)[404], thiazoles (**339**)[404], dithiazolines, thiaselenazolines and diselenazolines[405–407,459].

This section will be closed by discussing briefly the acidic hydrolysis of α-halo imines as a path in the specific α-halogenation of certain ketones. The acid-catalysed

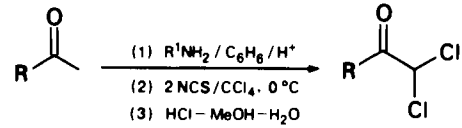


(334) (335)



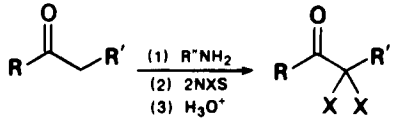
(336) Z = NR′ (337) Z = NR′
(323) Z = O (338) Z = O
(328) Z = S (339) Z = S

hydrolysis of α-halo imines affords α-halo carbonyl compounds. Direct halogenation of carbonyl compounds can be problematic from the viewpoint of regioselectivity, but in some cases the halogenation of carbonyl compounds via imination, subsequent halogenation and hydrolysis offers a complementary method. Via this three-step sequence, the regiospecific mono- and dihalogenation of methyl ketones (**340**) has been accomplished[79,84], but in cases where no competitive α′-halogenation can take place,



(340) (341)

this method has been developed as the synthesis of choice for α,α-dichloroaldehydes (**344**)[92], α,α-dibromoaldehydes (**345**)[92] and α,α-dichloroalkyl aryl ketones (**346**)[88]. However, the direct chlorination of aldehydes (**342**) or alkyl aryl ketones (**343**) with



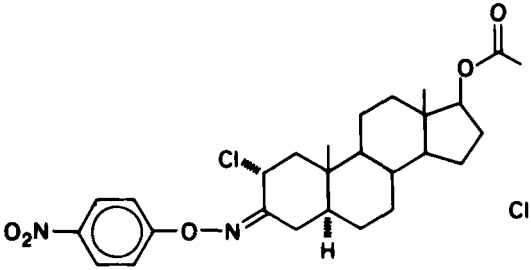
(342) R = H (344) R = H; X = Cl
(343) R = Ar (345) R = H; X = Br
(346) R = Ar; X = Cl

chlorine in dimethylformamide has been shown very recently to be an improved synthetic method for the preparation of α,α-dichlorocarbonyl derivatives **344** and **346**[445,446].

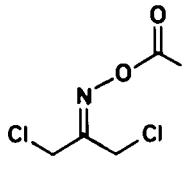
IV. PROPERTIES AND APPLICATIONS OF α-HALOGENATED IMINO COMPOUNDS

Several α-halo imino compounds have been found to have pharmaceutical and phytopharmaceutical properties, while they have also been used for the synthesis of

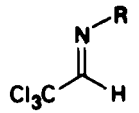
medical products. α-Halo oxime derivatives e.g. 17β-acetoxy-2α-chloro-3-(*p*-nitrophenoxy)imino-5α-androstane (**347**)[220,431] and 1,3-dichloroacetone oxime acetate (**348**)[414], displayed postimplantive antifertility activity and slimicide activity, respectively. The contact acaricide Tranid (**350**) belongs to the important class of oxime carbamates, which were recently successfully applied in various pest controls[432,433]. The fungicidal activity of the 2,4-dinitrophenylhydrazone of chloroacetaldehyde (**351**) is well known, the compound being referred to as 'Fungicide 1763' in pesticide science[442]. Very recently, a great variety of α-halogenated hydrazones (**352**) have been found to display fungicidal activity[460].



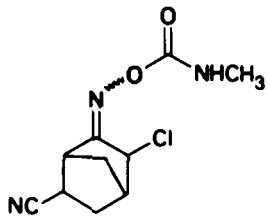
(**347**)



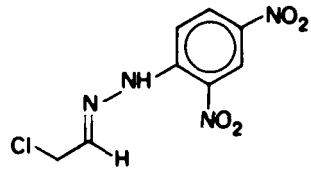
(**348**)



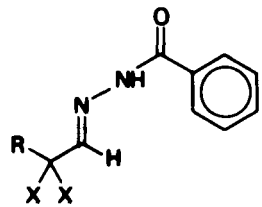
(**349**) R = alkyl
(**204**) R = OH



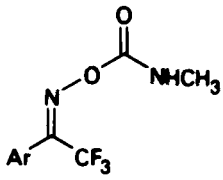
(**350**)



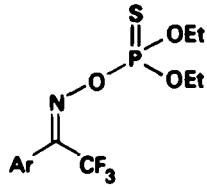
(**351**)



(**352**) R = H, F, Cl, Br, CH_3, $CHClCH_3$
X = Cl, Br



(**353**)



(**354**)

The insecticidal activity of a large number of trifluoroacetophenone oxime carbamates (**353**) and trifluoroacetophenone oxime thiophosphates (**354**) was recently evaluated[441]. Some of these compounds were good aphicides and some were strong cholinesterase inhibitors[441].

Trichloroacetamidines (**113**; X = Y = Cl) showed enzyme inhibitory activity besides bacterial mutagenic and inotropic activity[180,203]. α-Bromoacetimidate acted as cross-linking agent for proteins[415], while choral imines (**349**) were found to be useful as compounding agents for rubber[332]. Imino derivatives of chloral, e.g. **349**, and oxime (**204**), have been proposed as insecticides[331,416]. Besides these industrial uses, α-halo imines have been used for the synthesis of medicinal products, among others antispasmodics[246], vasodilators[246], convulsants[126], glycine antagonists[126], radioprotective agents[204] and products having gastric antisecretory activity[181]. An area of major importance is the transformation of various indole-type alkaloids via their chloroindolenines[132–139,153,215,270–272,417], but also their application as intermediates in the total synthesis of steroids[69] and antitumour agents, e.g. 11-oxahomofolic acid[156] and anthracyclines[51], deserves attention.

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*Note added in proof
A very recent paper described a straightforward general synthesis of α-haloketimines by condensation of α-halocarbonyl compounds with primary amines in the presence of titanium(IV) chloride.[461]

The chemistry of α-haloketones, α-haloaldehydes and α-haloimines
Edited by Saul Patai & Zvi Rappoport

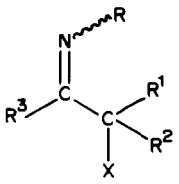
APPENDIX TO CHAPTER 2

α-Halogenated imines

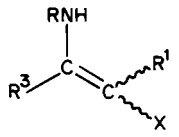
I. INTRODUCTION

This Appendix covers the literature on α-haloimines published from early 1980 up to the first half of 1986. Occasionally, some references earlier than 1980 and not mentioned in the original chapter are given. Nearly the same subdivisions as in the original review have been used, but a section on the generation of α-imidoylcarbenium ions from α-haloimines was added. Only those α-halogenated imino compounds having a structural similarity

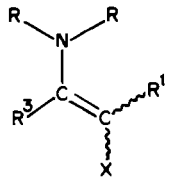
with α-halogenated ketones and α-halogenated aldehydes are covered in this supplementary review. However, some valuable and very often some leading references to α-haloimidates, α-haloamidines and α-haloimidoyl cyanides will also be given. α-Haloimines (**1**) can tautomerize to the corresponding β-haloenamines (**355**) if at least one α-hydrogen with respect to the imino functionality (i.e. R^2) is present. The chemistry of β-haloenamines parallels to some extent the chemistry of α-haloimines because the latter can react by intermediacy of the former (cf. the relationship between ketones and enols). β-Haloenamines having a tautomerizable structure, i.e. a hydrogen substituent on the nitrogen, are not stable entities and usually rearrange to their stable α-haloimino isomers. If the tautomerization of β-haloenamines is structurally blocked by an additional *N*-substituent different from hydrogen, i.e. if enamines (**356**) ($R \neq H$) derived from secondary amines and α-halocarbonyl compounds are involved, then their chemistry is well defined and distinguished from α-haloimine chemistry. The chemistry of β-haloenamines will not be covered here, but their synthesis[113] and reactivity[462] have been reviewed.



(**1**) X=halogen



(**355**) X=halogen

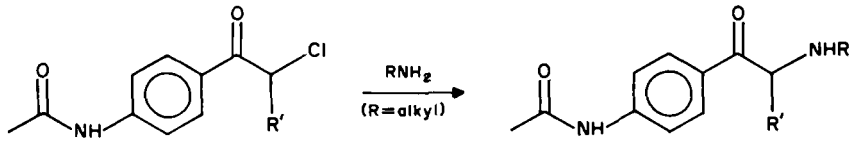


(**356**) X=halogen

II. SYNTHESIS OF α-HALOGENATED IMINES

Two main strategies for the synthesis of α-halogenated imines (**1**) have been applied extensively in the last few years. The first involves the condensation of an α-halocarbonyl compound (**2**) with a primary amine and the second entails the halogenation of imines (**4**) or their corresponding tautomerizable enamines. Historically, the first method met with major difficulties and the α-haloimines (**1**) were only obtained in limited cases. Exceptions are the reactions of α-halocarbonyl compounds with the usual carbonyl identification reagents which provided α-halooximes, α-halohydrazones, α-halosemicarbazones, etc., with reasonable success. However, in other cases the never ending list of side-reactions during the condensation of α-halocarbonyl compounds with primary amines continues to build up. Indeed, the latter condensation in general does not lead to the α-haloimines as could be expected when the reactivity of the heteroallylic halogen is neglected. This reactive halogen, at either the carbonyl or the imine stage, is readily displaced and leads to a great variety of side-reactions, including nucleophilic substitution[463-471], Favorskii rearrangements[472-475], α-iminoketone formation[474,476], haloform-type reactions[477] and dehydrohalogenation[478]. Some representative recent examples of these side-reactions are now discussed. The most common of these is nucleophilic substitution, especially with less sterically hindered substrates. Examples are the transformation of functionalized phenacyl chloride (**357**) and α-chloropropiophenones (**358**) with primary amines to α-(*N*-alkyl)aminoketones (**359**), which display antidepressant and central nervous system (CNS) stimulant activity[464,465]. In contrast, the reaction of 2-carbamoyl-6-bromocyclohexanone (**360**) with ammonia, primary aliphatic amines or 4-chloroaniline yielded the ring-contracted cyclopentane-1,2-dicarboxamides **361** via a Favorskii rearrangement[472]. Aliphatic α,α′-dibromoketones (**362**) reacted with primary amines to afford α-iminoketones (**363**) and/or α-diimines (**364**), depending on the amount of amine used[474], presumably by aminolysis of an intermediate enolic allylic bromide. The α,α,α-

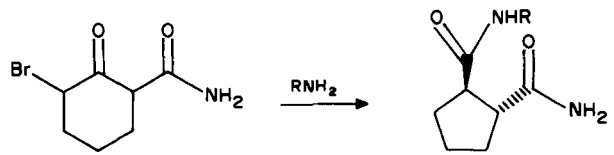
trichloroketone **365** underwent a haloform-type reaction on treatment with aniline or α-aminocarboxylic acids in dimethyl sulphoxide to give **366**[477]. An example of a dehydrohalogenation is the reaction of α-bromocycloalkanones (**367**) with aniline, which yielded enones (**368**)[478]. Frequently, the α-haloimine expected from the condensation of an α-halocarbonyl compound and a primary amine was formed, but it was further transformed into various products, including α-alkoxyoximes[479], α,β-unsaturated oximes[479], isoxazoles[480], indoles[481] and α-chloro-α,β-unsaturated tosylhydrazones[482]. However, many such condensations gave successfully α-halogenated imines, and these syntheses will be treated below.



(357) R'=H

(358) R'=Me

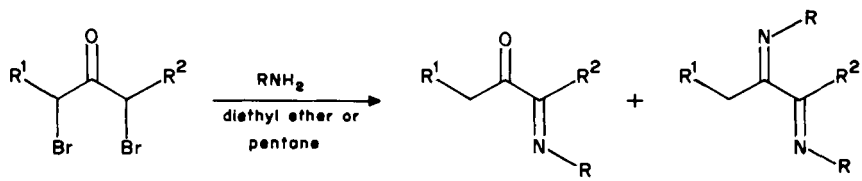
(359) R'=H, Me



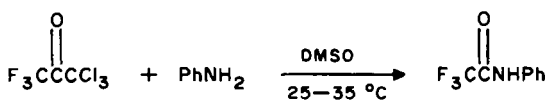
(360)

23—100%

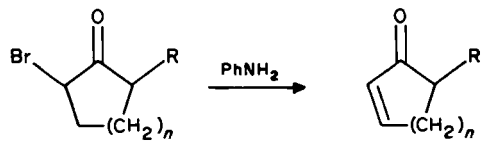
(361)



(362) **(363)** **(364)**



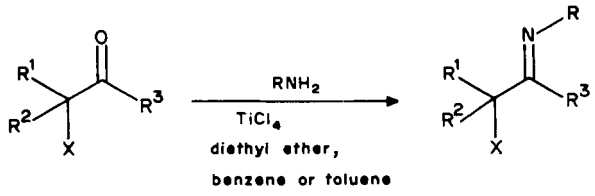
(365) **(366)**



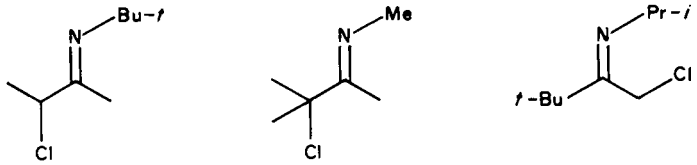
(367) $n=1-4$, R=Me, Et, Pr (368)

A. Condensation of α-Halogenated Carbonyl Compounds with Primary Amines

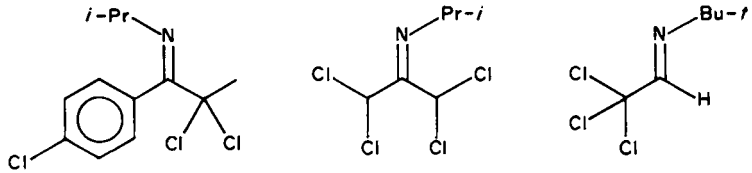
The most successful and general synthesis of α-halogenated imines (1) is the condensation of an α-halogenated ketone (2) or aldehyde (2; $R^3 = H$) with a primary amine in the presence of titanium(IV) chloride[461,483]. The reaction can usually be performed between 0 °C and room temperature, but increasing steric hindrance in either reagent requires a higher temperature. The stoichiometry requires a 6:1 molar ratio of the amine to titanium(IV) chloride, but in practice some excess is used [461]. Titanium(IV) chloride has a dual role: as a Lewis acid activating the carbonyl function and by removing the water formed during the reaction by forming titanium(IV) oxide. The method was originally developed for the synthesis of simple imines[484] and enamines[485,486], and a modification was introduced for the synthesis of β-haloenamines[487,488]. A great variety of α-halogenated imines (1) were synthesized by this method, and the formation of **369–380** examplifies the scope of the method. Primary, secondary and tertiary α-haloimines and α-polyhalogenated imines are accessible.



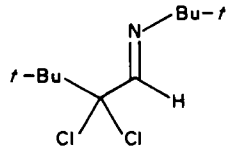
(2) X=Cl, Br, F (1)



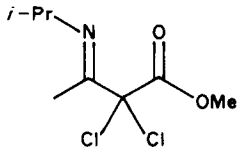
(369) Ref. 461 (370) Ref. 489 (371) Ref. 490



(372) Ref. 461 (373) Ref. 491 (374) Ref. 461



(375) Ref. 461



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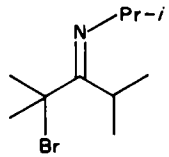

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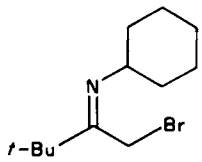

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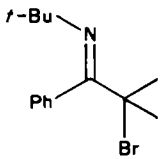

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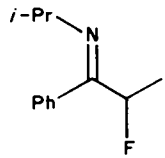
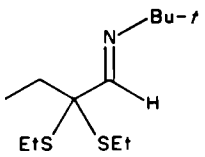


(380) Ref. 461

The method is also applicable to the synthesis of functionalized imines other than α-haloimines, e.g. α, α-di(ethylthio)aldimine (**381**)[497], α-(*N*-alkyl)aminoaldimine (**382**)[494] and β-chloroimines (**383**)[495].



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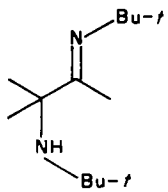
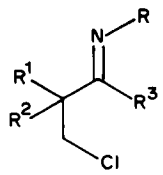
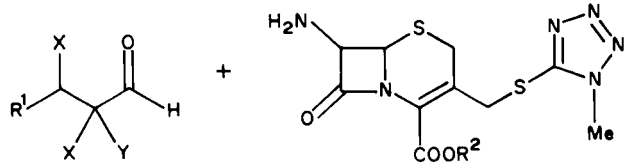


(382)



(383)

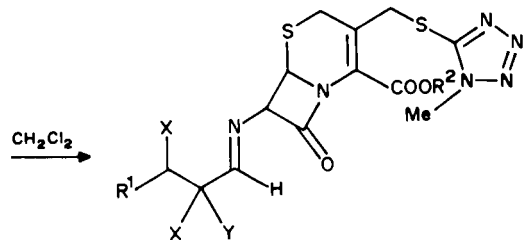
The method is very useful when side-reactions, other than imination, are plausible between the substrate and the primary amine (see above). However, when these are not expected, the usual condensation procedure for imine formation is applicable. Substrates which do not often give these side-reactions are α-halogenated aldehydes and α-fluorinated carbonyl compounds. α, α, β-Trihaloaldehydes (**384**) reacted with 7β-aminocephalosporins (**385**) with azeotropic removal of water to provide the corresponding α, α, β-trihaloaldimines (**386**)[496], while excess of chloral (**387**) was condensed with 7α-amino-3-methyl-1-oxacephem (**388**) to afford the chloral imine **389**[497], and with substituted *o*-aminophenols (**390**) to yield the chloral imines **391**[498]. The chloral imines **394**, useful in peptide synthesis, were prepared by a two-step procedure involving condensation of **387** with α-amino acid ester hydrochlorides in the presence of *N*-methylmorpholine, after which the adduct formed (**393**) was dehydrated with thionyl chloride to **394**[499]. This method was also applicable to the synthesis of *N*-*tert*-butyl- and *N*-benzyl-chloral imines[499]. The reaction of the α, α, γ-trichloroaldehyde **395** with ammonia in glyme probably proceeds via a sequence involving nucleophilic addition and ring closure to generate a 3, 3-dichloro-1-pyrroline derivative (**396**)[500].



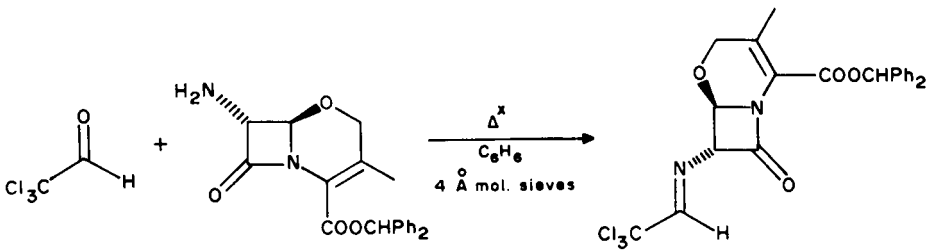
(384) R^1 = Me, Ph

X, Y = halogen

(385) R^2 = *t*-Bu, Ph_2CH

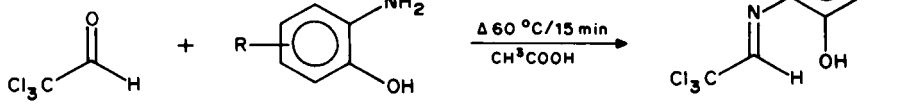


(386)



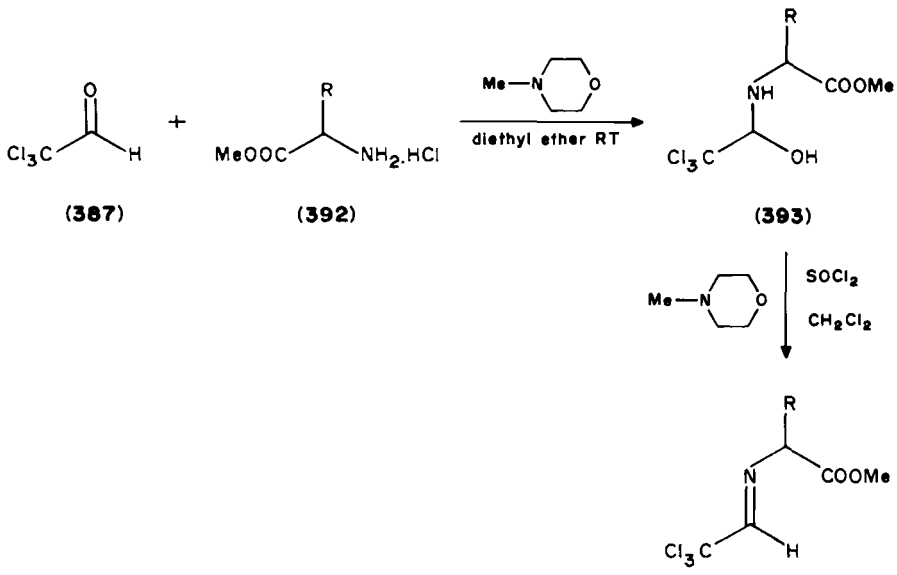
68 %

(387) (388) (389)



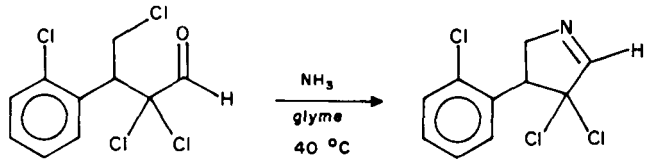
(387) (390) (391)

[a]Throughout, Δ represents boiling under reflux or heating at a given temperature.



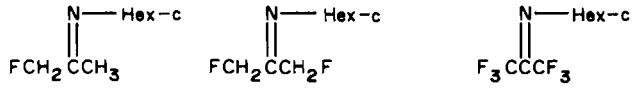
(387) (392) (393)

(394) R=Me, *i*-Bu, CH_2Ph



(395) (396)

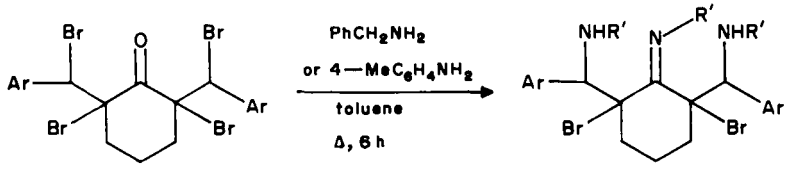
Owing to the strong carbon—fluorine bond, α-fluorinated carbonyl compounds usually give only imination with primary amines, although some exceptions (e.g. haloform-type reactions) are known, as discussed in a review on fluorine-containing imines[501]. α-Fluoroketimines (e.g. **397**)[502,503], α,α′-difluoroketimines (e.g. **398**)[505] and perfluoroacetone imines (e.g. **399**)[504,505] were obtained by reaction of the appropriate α-fluorinated carbonyl compounds with primary amines.



(397) (398) (399)

A doubtful result, in the opinion of the authors, is the reported conversion of the α,α′,β,β′-tetrabromoketone **400** with benzylamine or 4-methylaniline into the α,α′-dibromoketimine (**401**)[506]. The precursor tetrabromide (**400**) would be expected to undergo a double dehydrobromination with loss of bromide from the α- and α′-positions rather than to give imination and concomitant *bis*-substitution. When repeating the

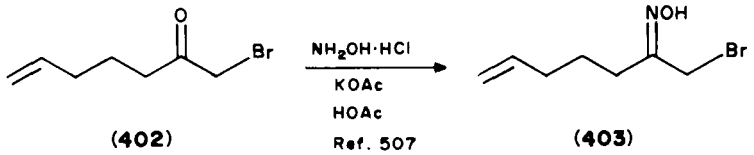
experiment with the diphenyl ketone **400** (Ar=Ph) and benzylamine we could isolate neither the previously reported product (**401**) nor any other well defined product.



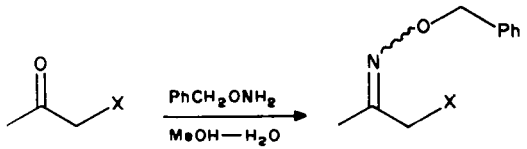
(**400**) Ar=Ph, 4—ClC$_6$H$_4$ (**401**) R'=PhCH$_2$, 4—MeC$_6$H$_4$

The usual carbonyl identification reagents such as hydroxylamine, *O*-substituted hydroxylamines or hydrazines have been frequently condensed with α-halogenated carbonyl compounds because the resulting α-haloimino compounds are valuable synthons for various reactions, including cycloadditions (see below).

α-Halooximes have been synthesized from aliphatic α-haloketones[479], aliphatic α-bromomethyl ketones[507], bromopyruvates[508,509], α-chlorocyclohexanones[510,511], substituted phenacyl halides[512–514], α-chlorocyclobutanones[515], α,α-di- and α,α,α-trihalogenated acetophenones[516,517] and 2,2-dichloro-1,3-diphenylpropane-1,3-dione (but the oxime gave further ring closure to the corresponding 2-isoxazoline)[518]. α-Halogenated oxime ethers have been obtained from α-chloroacetone[519], α-iodoacetone[519], substituted phenacyl halides[513,520], α,α-di- and α,α,α-trichlorinated acetophenones[517,521] and α-chlorocyclohexanones[511]. Representative products are the α-halo oxime derivatives **403**, **406**, **407** and **409**.

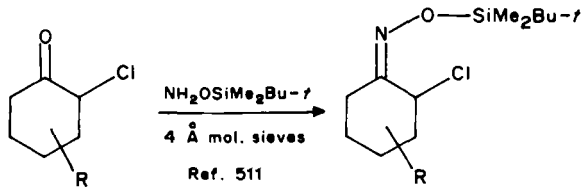


(**402**) (**403**)



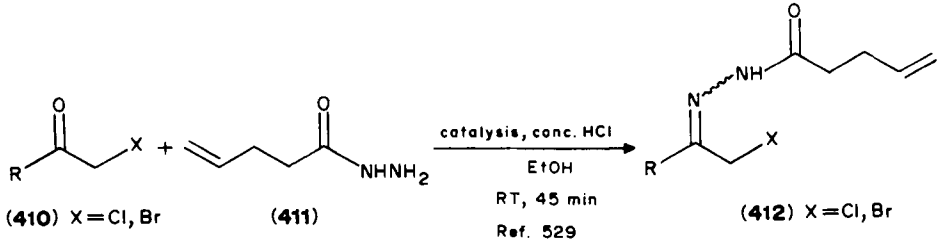
(**404**) X=Cl (**406**) X=Cl

(**405**) X=I (**407**) X=I

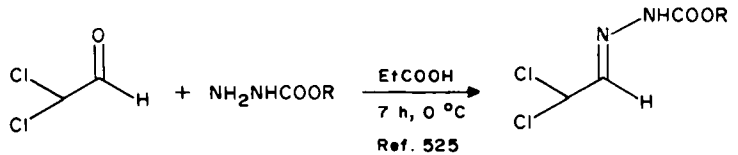


(**408**) (**409**)

Reactions of α-halocarbonyl compounds with hydrazine-type reagents usually form α-halohydrazones, although exceptions are known[522,523]. Such reactions have been conducted with α,α-dichloroaldehydes[524,525], chloral[526], bromal[460], α-halomethyl ketones[527-530], α-chlorocycloalkanones[528], α,α-dichloroketones[482], methyl bromopyruvate[531], alkyl 2-chloro-3-oxobutyrates[532] and α,α,α-trifluoroacetone[533]. The syntheses of α-halohydrazone-type compounds (**412**, **415** and **416**) are representative examples.



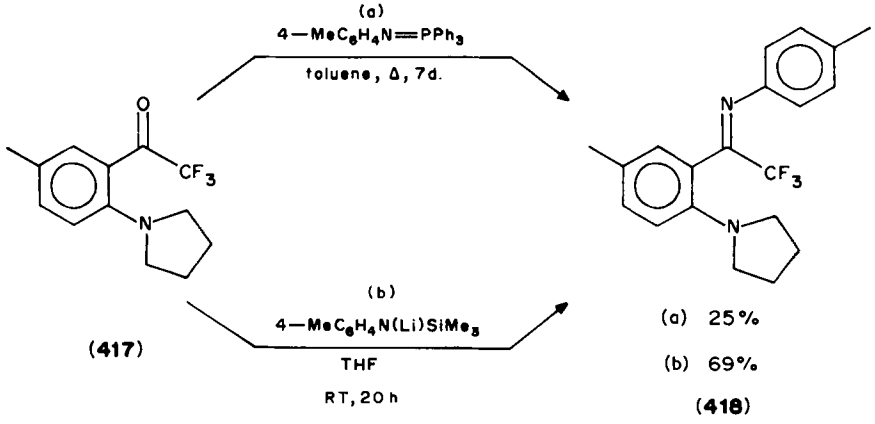
(**410**) X=Cl, Br (**411**) (**412**) X=Cl, Br



(**413**) (**414**) (**415**) R=Me 66%

(**416**) R= *t*-Bu 71%

α-Haloimino compounds have sometimes been prepared from α-haloketones using iminophosphoranes or lithio-*N*-trimethylsilylamides, as exemplified for the synthesis of the trifluoromethylketimine **418**[534]. Other methods, which involve an isolable intermediate adduct, especially in the condensation of α-polyhalogenated ketones with primary amides, make use of dehydrating agents such as thionyl chloride[535] or oleum[536].

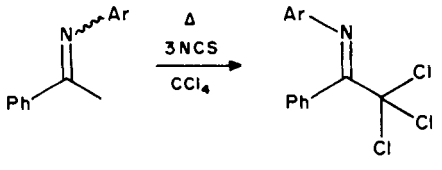


(**417**) (a) 25% (b) 69% (**418**)

B. Halogenation of Imino Compounds

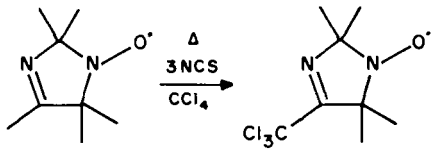
N-Halosuccinimides are good halogenating agents for a great variety of imino compounds. The most recent examples focused on imino compounds with no α'-

hydrogens, which could not give rise to regioisomers. Chlorination of *N*-aryl acetophenone imines (**419**) with *N*-chlorosuccinimide (NCS) in carbon tetrachloride occurred with quantitative yields[537]. The nitroxyl heterocycle **421** was also readily trichlorinated to **422**, but dichlorination was more difficult[538].



~100%

(419) (420)

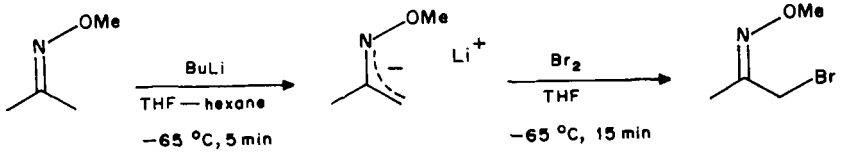


95%

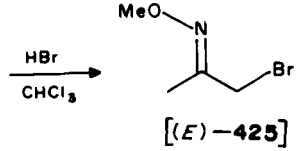
(421) (422)

1-Pyrrolines could be successfully monohalogenated with NCS and NBS in CCl_4 in the presence of catalytic amounts of trifluoroacetic acid[539], but bicyclic 1-pyrrolines could only be brominated to mixtures of α-brominated derivatives[540]. Other brominations with NBS involved nitrones[541] and *N*-methoxy imidates[542].

The older literature did not report many successful halogenations using chlorine or bromine, but some more recent halogenations have led to useful α-halogenated imino compounds. In addition to the classical chlorinations (with Cl_2) and brominations (with Br_2) of 2-pyrazolin-5-ones[543–545] to 4-halo- or 4,4-dihalo-2-pyrazolin-5-ones, the brominations of oxime ethers were executed with or without generation of the α-anion. The monobromination with bromine of *O*-benzylacetophenone oximes proceeded in the dark[546], but it is advantageous to monobrominate *O*-methylacetone oxime (**423**) via the initial generation of the α-anion (**424**)[547]. The (*Z*)-**425** isomer was obtained exclusively but could be isomerized with hydrogen bromide to the more stable (*E*)-**425**. A similar

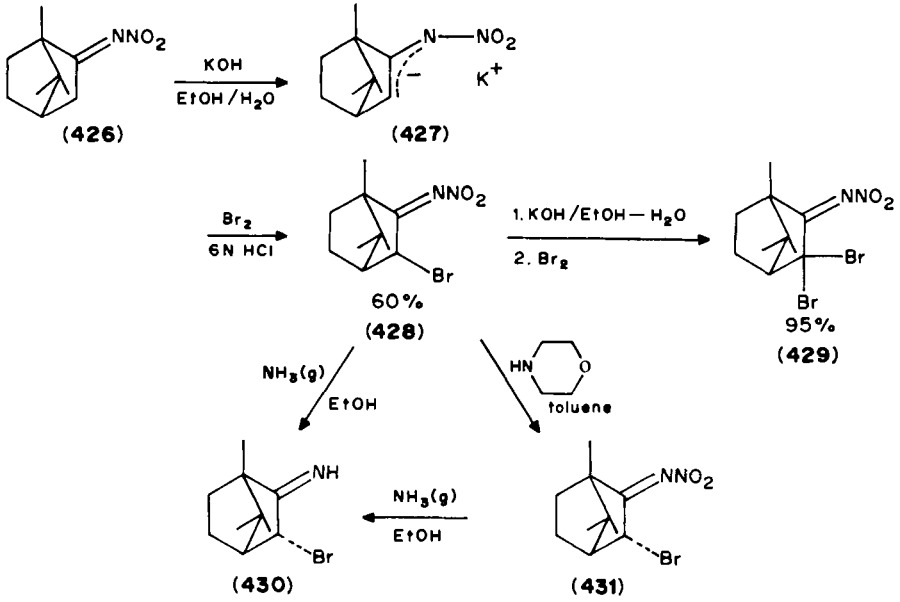


(423) (424) [(*Z*)−425]

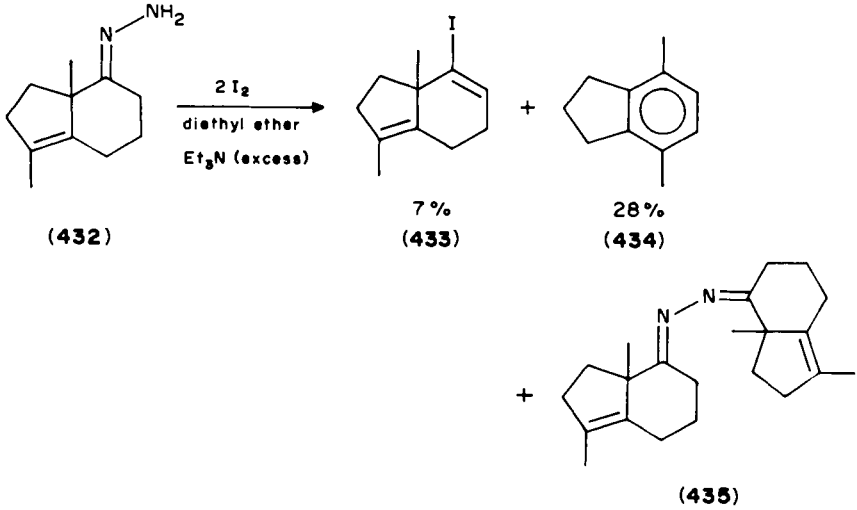


[(*E*)−425]

bromination of the α-anion of camphor nitrimine (**427**) led successfully to the 3-*exo*-bromonitrimine **428**, which could be epimerized into the 3-*endo*-bromonitrimine **431** by morpholine in toluene[548]. Further bromination of the potassium salt of **428** furnished the α,α-dibromoimino compound **429**, while gaseous ammonia in ethanol converted both **428** and **431** into the 3-*endo*-bromoimine **430**[548].

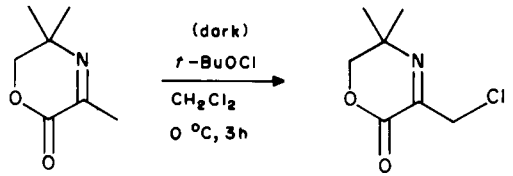


α-Monobromination of the 2,4-dinitrophenylhydrazone of methyl pyruvate occurred smoothly with two equivalents of bromine in dichloromethane[531], but iodination of the bicyclic hydrazone **432** gave a complex mixture in which the vinyl iodide **433**, the indane **434** and the azine **435** were identified[549].



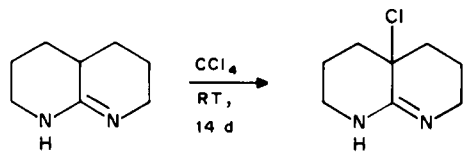
Tosylhydrazones derived from heptanal and isobutyraldehyde were α-monobrominated with phenyltrimethylammonium perbromide (PTAB)[528]. Monohalogenation of 4-unsubstituted-2-pyrazolin-5-ones is difficult owing to dihalogenation, but 4,4-dichlorination or 4,4-dibromination using 1,3-dihalo-5,5-dimethylhydantoin in acetic acid followed by reduction with ascorbic acid–triethylamine offers a new method for the synthesis of 4-monohalo-2-pyrazolin-5-ones[550].

tert-Butyl hypochlorite, a well known chlorinating agent in the indole field (see below), also converts 5,6-dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (**436**) into the unstable chloromethyl derivative (**437**)[551].



(**436**) (**437**)

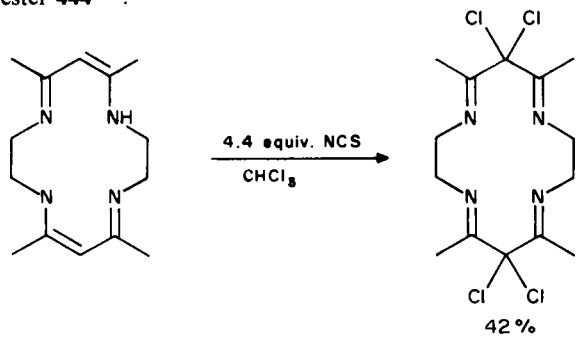
The α-chlorination of bicyclic amidines, e.g. **438**, by carbon tetrachloride (and other tetrahalomethanes) is a very peculiar reaction and deserves to be mentioned[552–554]. A detailed mechanistic study suggested a redox process involving an initial single electron transfer[554].



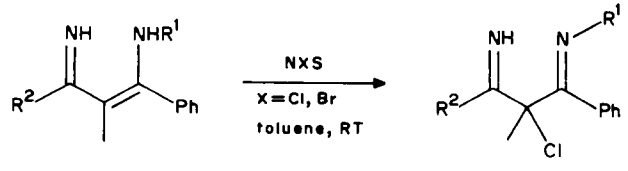
(**438**) (**439**)

C. Synthesis of α-Halogenated Imino Compounds by Halogenation of Enamines

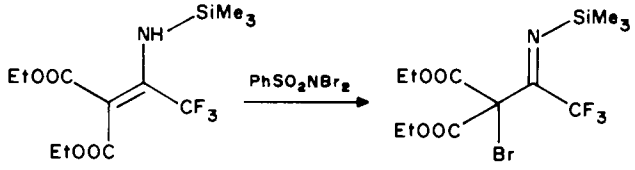
Enamines carrying β-electron-withdrawing groups were easily halogenated with *N*-halosuccinimides[555–557], *tert*-butyl hypochlorite[558], sulphuryl chloride[556], *N*,*N*-dibromobenzenesulphonamide[558], bromine[560] or sodium hypohalites[560], as exemplified for the 1,3-diimines (occurring in the stable enaminimine form) **440**[555] and **442**[556,557] and the enamino diester **444**[558].



(**440**) (**441**)



(442) (443)

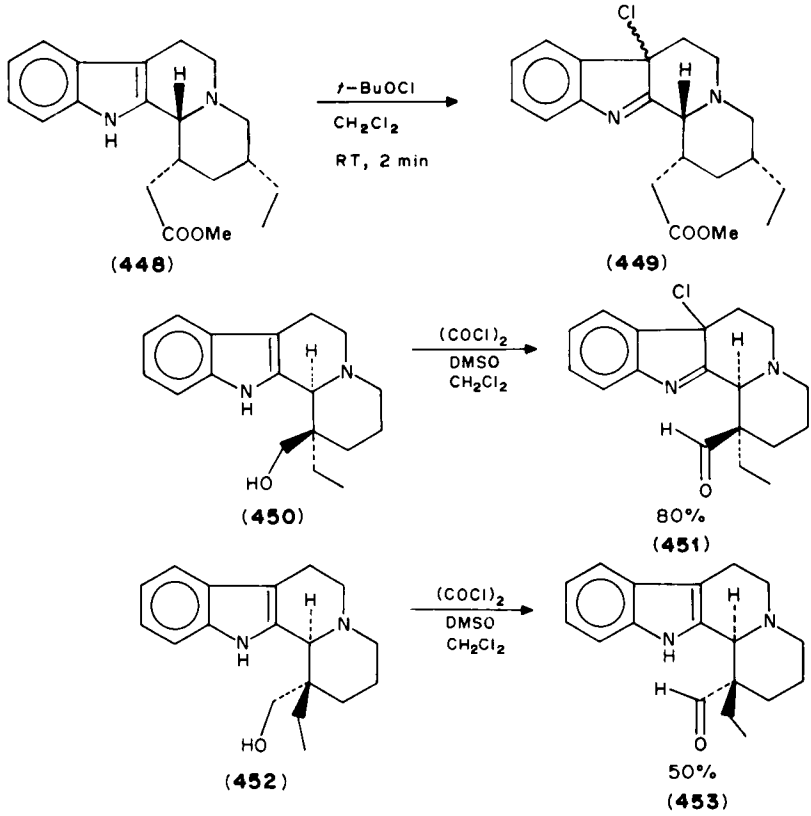


(444) (445)

A related bromination of 1,4-unsubstituted pyrazoles with bromine gives 4,4-dibromo-1,3-diimino compounds[559]. Side-reactions occurred during the bromination with bromine or sodium hypobromite of certain enaminones (cleavage)[560] and during photochemical brominations with NBS in acetic acid of α-alkoxycarbonylenamides (γ-halogenation)[561].

As already pointed out in the original chapter, the halogenation of indoles received considerable attention owing to the potential of halogenated indoline derivatives as precursors in natural product syntheses. Classical reagents for the halogenation of indoles included *tert*-butyl hypochlorite[562–567], NCS[568–570], NBS[569,570,572], *N*-chloroisatin[568], sodium hypochlorite[573], *N*-chlorobenzotriazole[568,574,575], bromine[571] and iodine[576]. Depending on the structure of the indole and the reaction conditions, halogenation takes place at the 3-position (most common), the 2-position (radical halogenation)[569,570] and the α-carbon of a side-chain at the 2-position[571,572]. The halogenation of *N*-unsubstituted indoles is reviewed only because *N*-substituted derivatives[571,572] cannot lead to α-haloimino derivatives, i.e. 3-haloindolenines. An example of the formation of the latter is the conversion of the indole **446** with *tert*-butyl hypochlorite into **447**[563]. Major applications in the alkaloid field include the halogenation of ethyl pseudovincamonate (**448**)[564], isoborrenine[565], 3-oxotabersonine (a pentacyclic 3-substituted indoline derivative with an exocyclic double bond on the indoline ring)[566] and other indole alkaloids[567,575]. An interesting and unexpected result during the attempted Swern oxidation of the hydroxymethyl group of the indole derivative **450**[574] is the introduction of chlorine by oxalyl chloride followed by oxidation by the medium to give the formyl moiety. Under the same conditions the epimeric alcohol **452** yielded the unchlorinated aldehyde **453**[574].

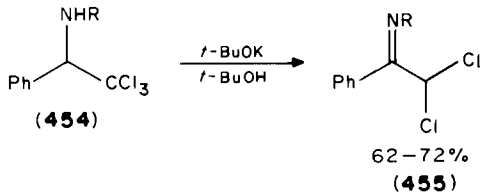
(446) (447)

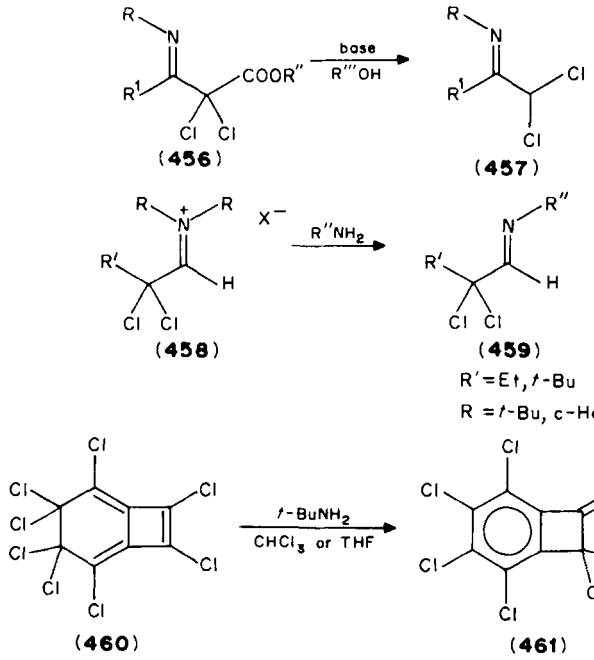


D. Miscellaneous Methods

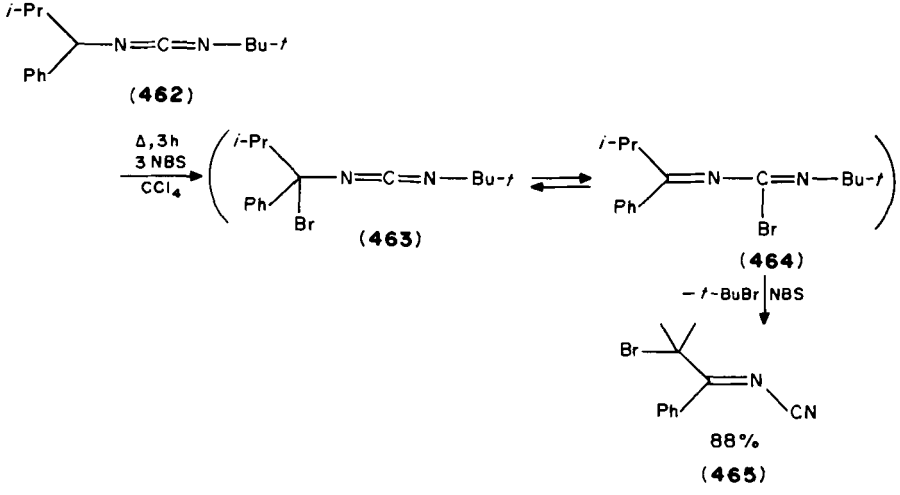
This section contains a wide variety of reactions leading to α-halogenated imino compounds. Owing to the variable nature of these reactions, only a selection of some promising or peculiar syntheses will be discussed in detail and references will be given to others.

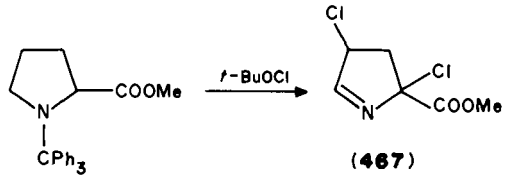
Straightforward routes to α,α-dichloroimines are the dehydrochlorination of *N*-alkyl-β,β,β-trichloroamines (**454**)[577], the nucleophile-induced fragmentation of β-imino-α,α-dichloro esters (**456**)[578] and the reaction of dichlorinated iminium halides (**458**) with primary amines[579]. The latter is an example of a transimination reaction which has also been applied to the synthesis of *N*-phenyl-α-bromoketimines[548] and α-chloro oxime ethers[580]. The perchloro bicyclic compound **460**, obtained from the dimerization of perchlorobutenyne, reacted with *tert*-butylamine to provide the strained α,α-dichloroketimine **461**[581].





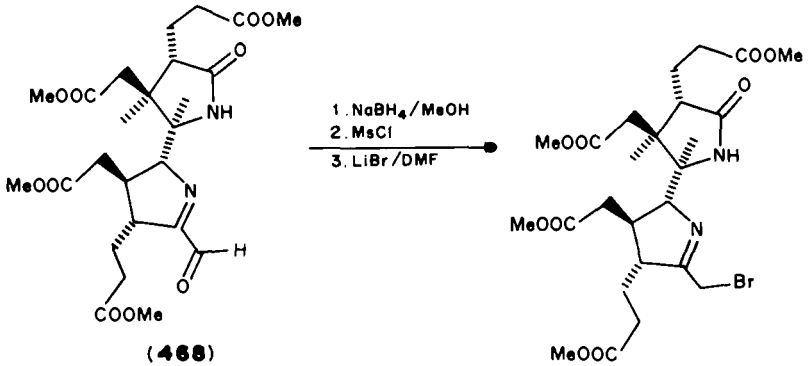
Various halogenations of imino compounds or other nitrogen-containing compounds were reported to afford, often unexpectedly and albeit in low yields, α-halogenated imino compounds. Such substrates include pyrazoles[582], isoxazoles[583], 5-phenacyl-3-phenylisoxazole (*E*)-oxime[584], α,β-unsaturated oximes[585,586], carboxylic amides[587], carbodiimides (**462**)[588] and methyl *N*-trityl prolinate (**466**)[589]. Some reagents, such as acetyl chloride[590] and *p*-toluenesulphonyl chloride[591], have been found to transfer their halogen to compounds such as four-membered nitrones and 2-phenyl-1-pyrroline, respectively.





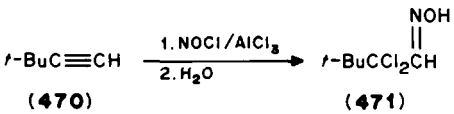
(466) (467)

The conversion of the 2-formyl-1-pyrroline **468** into the 2-bromomethyl-1-pyrroline **469** was a part of the vitamin B_{12} synthesis by Woodward[592]. This transformation, which proceeds by reduction of the formyl group to a hydroxymethyl moiety followed by *O*-mesylation and nucleophilic substitution of the mesylate by lithium bromide in dimethylformamide, may be a more general approach to the generation of halomethylketimines.

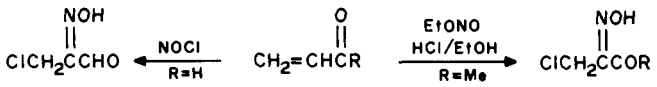


(468) (469)

Various α-halogenated oximes have been obtained by the classical method of addition of nitrosyl chloride to olefins[593–596]. The addition of nitrosyl chloride to the alkyne **470** in the presence of aluminium chloride gave, after hydrolysis, the α,α-dichlorooxime **471**[597]. Other oxygen-functionalized α-halooximes were obtained from nitroolefins[598] and bis(trifluoromethyl)acetic acid[599], but the addition of nitrosyl fluoride to cycloalkenes furnished α-fluoronitrimines[600]. The functionalized α-chlorooximes **472** and **474** were obtained by reaction of the appropriate α,β-unsaturated carbonyl compound (**473**) with nitrosyl chloride or with ethyl nitrite in the presence of gaseous hydrogen chloride, respectively[509].

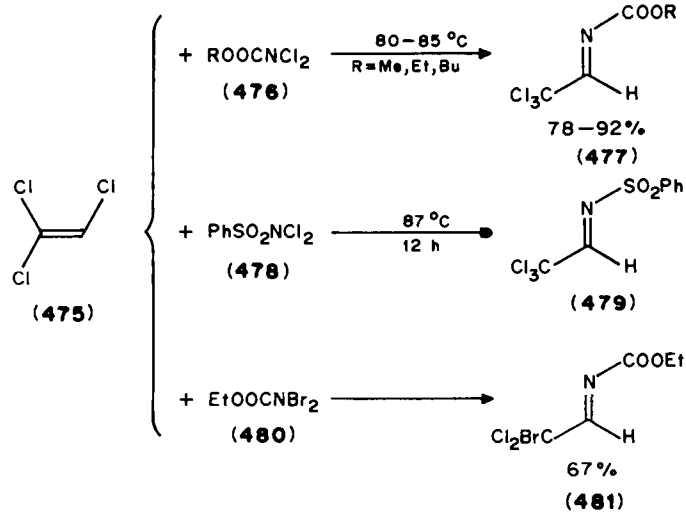


(470) (471)

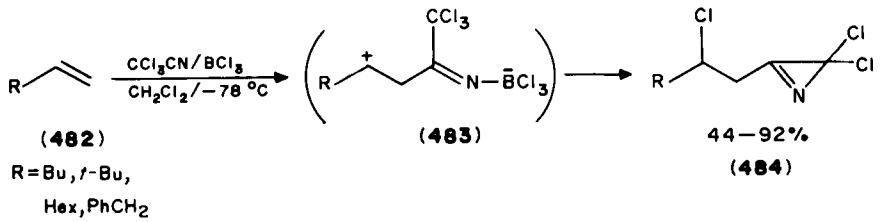


(472) (473) R=H,Me (474)

A fairly general synthesis of α,α,α-trihaloacetaldimines substituted with electron-withdrawing groups involves addition of alkyl *N*,*N*-dichlorourethanes (**476**)[601], *N*,*N*-dichlorobenzenesulphonamide (**478**)[602] or ethyl *N*,*N*-dibromourethane (**480**)[603] to trichloroethene (**475**).

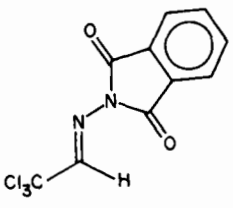


The attempted synthesis of 3,3-dichloro-2-phenylazirine from 1,2-dichloro-1-phenylethene and chlorine azide failed[604], but 3,3-dichloroazirines (**484**) became accessible by boron trichloride-promoted addition of trichloroacetonitrile across monosubstituted ethenes (**482**)[605]. (Di- and tri-substituted ethenes afforded functionalized α,α,α-trichloroketones[605,606]).

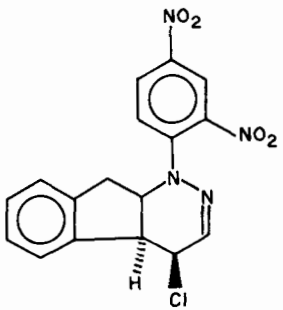


The last paragraph of this section provides an encyclopaedic coverage of various reactions leading to compounds having an α-haloimino functionality. These reactions include the rearrangement of a 2,2,3-trichloroaziridine to a chloral hydrazone derivative (**485**)[526], cycloaddition of a chlorinated azoalkene across indene affording an α-chlorohydrazone (**486**)[607], cycloaddition of a trifluoromethylnitrilimine with styrene[608], the reaction of a five-membered nitrone with α-chloroacrylonitrile affording **487**[609], the condensation of a fluorinated azoalkene with perfluoroisobutene[610], the reaction of perfluoropent-2-ene with ammonia[611], the cyclization of β-arylhydroxylamines with trifluoroacetic anhydride[612], the reaction of perfluorinated nitrosoalkanes with potassium hydrogen sulphite[613] or diphenyldiazomethane[614], the radical reaction of 2,3-dichloropropene with N_2O_4[615], and the reaction of pentachloropentafluorocyclohexanone *N*-chloroimine with hydrogen chloride[616]. Other reactions are the fluoride-induced

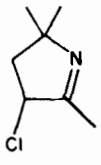
ring opening of a perfluoroaziridinone affording an *N*-acylhexafluoroacetone imine (**488**)[617], the NH insertion of bis(trifluoromethyl)diazomethane into hexafluoroacetone imine[618], the reaction of *O*-nitrosohexafluoroacetone oxime with olefins[619], the fluorination of quinoline with a caesium tetrafluorocobaltate at high temperature to give a perfluoroimine (**489**)[620], the condensation of chloral with *N*-sulphinylperfluorobutanesulphonamide yielding a chloral imine (**490**)[621], the condensation of chlorinated carbodiimides with carboxylic acids[622], the reaction of the phenylhydrazone of trifluoroacetyl bromide with triethylamine[623], the SCl_2-mediated cyclocondensation of ethyl 3-amino-4,4,4-trichlorocrotonate[624] and the reaction of hexafluoroacetone with sodium thiocyanate or potassium cyanate[625]. Many α-haloimino intermediates[626,627] are discussed in the sections dealing with the reactivity of α-haloimines.



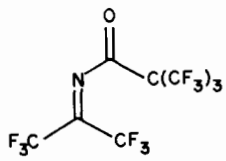
(**485**) Ref. 526



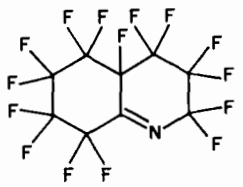
(**486**) Ref. 607



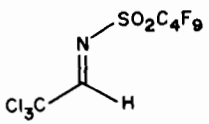
(**487**) Ref. 609



(**488**) Ref. 617



(**489**) Ref. 620



(**490**) Ref. 621

III. REACTIVITY OF α-HALOGENATED IMINES

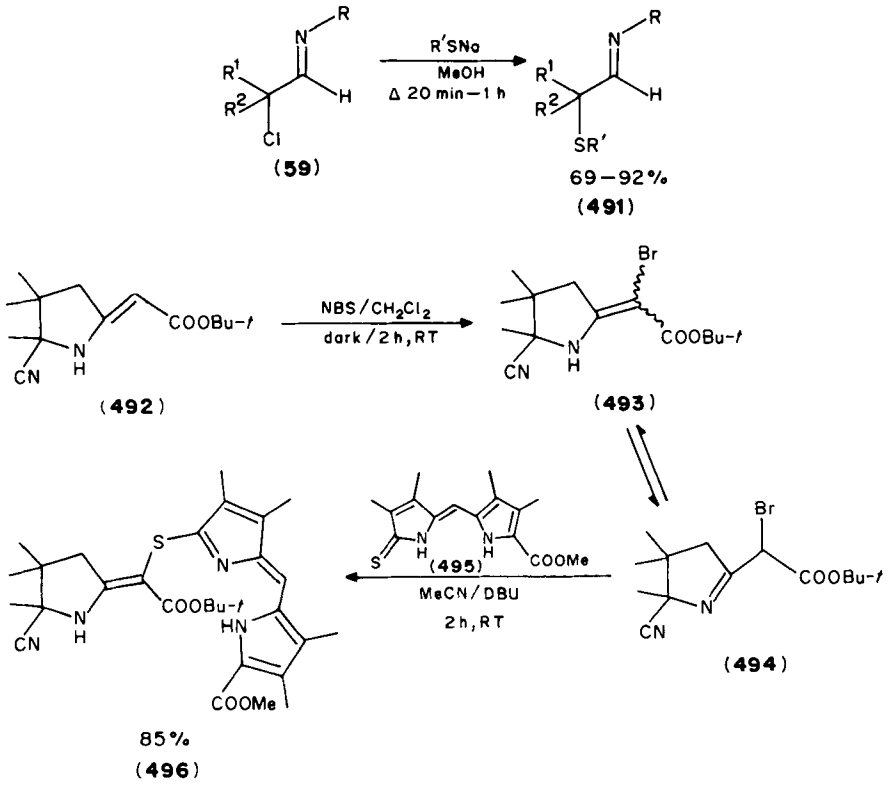
The discussion of the reactivity of α-haloimines will be divided into the same sections as those used in the original chapter. It is necessary to emphasize that the reactivity of α-haloimines can be treated to some extent as the reactivity of masked α-halocarbonyl compounds and the differences between the two classes are useful when the final products still contain the imino functionality. Hydrolysis of the latter into the corresponding carbonyl compounds often leads to functionalized products which are not accessible via reactions of α-halocarbonyl compounds. The fact that α-halocarbonyl compounds can be generally masked into α-haloimines[461] broadens the α-halocarbonyl chemistry via α-haloimines and provides a vehicle for the development of the chemistry of a useful class of bifunctional heteroallyl halides, i.e. α-halogenated imino compounds.

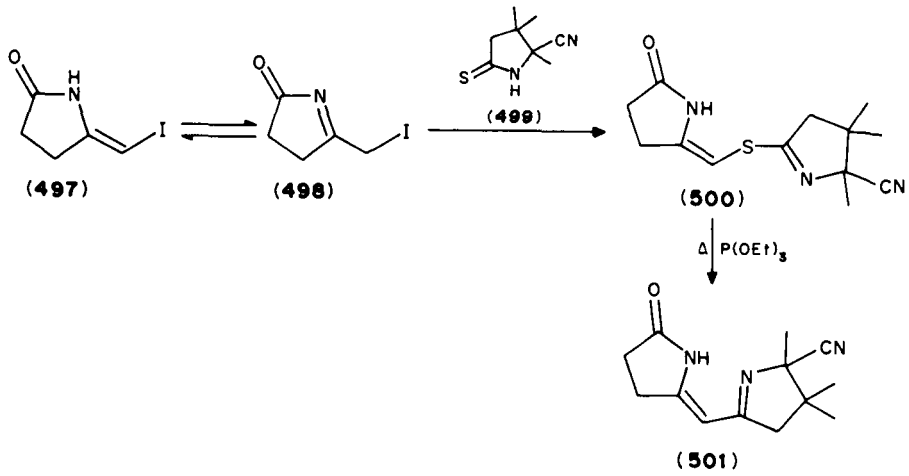
A. Nucleophilic Substitutions

Nucleophilic substitution of α-haloimines affords α-functionalized imines. Many of

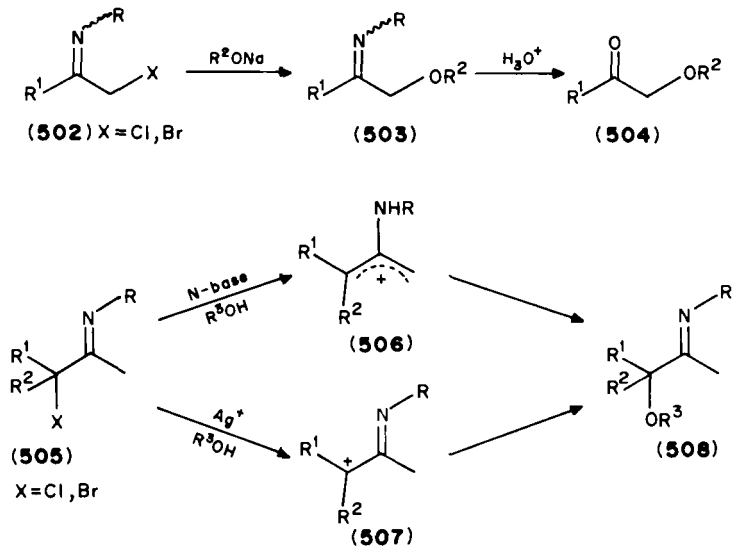
these reactions have been reported in recent years but mechanistic details have not yet been unravelled.

Strongly nucleophilic thiolates easily displace the heteroallylic halide in α-chloroaldimines (**59**) to afford α-sulphenylated aldimines (**491**) in good yields. With higher homologues (R^1 or $R^2 \neq Me$) a small proportion (< 10%) of competitive 1,2-dehydrochlorination was observed[628]. A similar α-sulphenylation was described for 2-substituted 3-halo-1-pyrrolines[539] and for various *N*-alkyl α-halomethylketimines[493]. The most useful application of the substitution with sulphur nucleophiles was found in the synthesis of porphyrins[629], corrinoids[630] and vitamin B_{12}[592]. Five-membered thioamide-type reagents served as good nucleophiles for the displacement of a halogen α to an imino function, even when the halogenated substrate occurred as its more stable β-haloenamine tautomer. As an example, the enamino ester **492** was brominated with NBS to the labile β-bromoenamino ester **493**, which was immediately treated with a thioamide (**495**) in the presence of DBU to afford the substitution product **496**[629]. The latter appears in the enamino form exclusively but its formation was explained by intermediacy of the tautomeric α-bromoimine **494**. The product **496** was further used in the directed synthesis of chlorin systems (porphyrins)[629]. It was found earlier[630] that in substrates without an alkoxycarbonyl group, e.g. **497**, the formal substitution with the thioamides **499** proceeded much better with the iodo than the bromo analogues. The removal of the sulphur atom in **500** with triethyl phosphite provided ready access to the semicorrinoid system **501**[630]. It was suggested that the tautomeric α-iodoimino derivative **498** served as the substrate for the nucleophilic substitution.

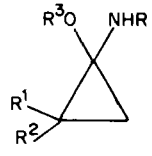




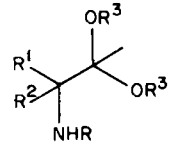
α-Alkoxylation of α-haloimines frequently occurs in alcoholic media. Treatment of α-halomethylketimines (**502**) with alkoxides in alcohols or dimethyl sulphoxide yielded α-alkoxymethylketimines (**503**), which were readily hydrolysed into α-alkoxymethyl ketones (**504**), which were not accessible from reactions of α-halomethyl ketones with alkoxides[493]. Double nucleophilic substitution takes place with α,α-dichloromethylketimines[80,82,248,578]. Very often the α-alkoxylation products are side-products when α-haloimines are treated under Favorskii rearrangement conditions, e.g. alkoxides in diethyl ether or tetrahydrofuran[491,631]. Tertiary α-alkoxyketimines (**508**) are accessible from solvolysis[632] or via metal ion-associated reactions[494,633,634] through the intermediacy of either a pseudo-α-imidoylcarbenium ion (**507**) or delocalized 2-(*N*-alkylamino)allylcarbenium ion (**506**). However, the compounds **508** are usually only minor side-products. For instance, the α-haloketimines **505** reacted with alcohols in the



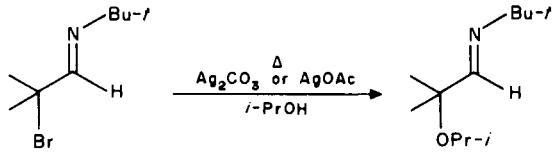
presence of a nitrogen base such as triethylamine, DABCO, DBU or DBN to give mainly the geminally functionalized cyclopropane **509**, presumably via **506**[632]. In addition, some rearrangement via α-alkoxyaziridine intermediates to afford β-(alkylamino)acetals (**510**) was observed (see below)[632]. Metal ion-assisted alcoholysis of tertiary α-haloketimines was found to be a side-reaction when good nucleophiles such as cyanide were present in the medium[494,633,634], but without a competing nucleophile the reaction can be directed exclusively towards α-alkoxylation, as demonstrated by the silver-induced conversion of the α-bromoaldimine **511** into the α-isopropoxyaldimine **512**[494].



(**509**)



(**510**)

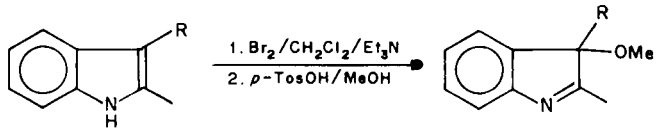


(**511**)

72–86%

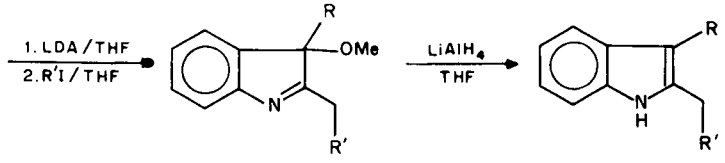
(**512**)

α-Alkoxylations of 3-chloroindolenines to afford 3-alkoxyindolenines can be performed under basic[573,635] or acidic catalysis[636,637]. Such 3-methoxyindolenines (**514**) have been used as intermediates for the $C_{(2)}$ side-chain alkylation of 2-methyl-3-alkylindoles (**513**) to **516**[636].



(**513**) R = alkyl

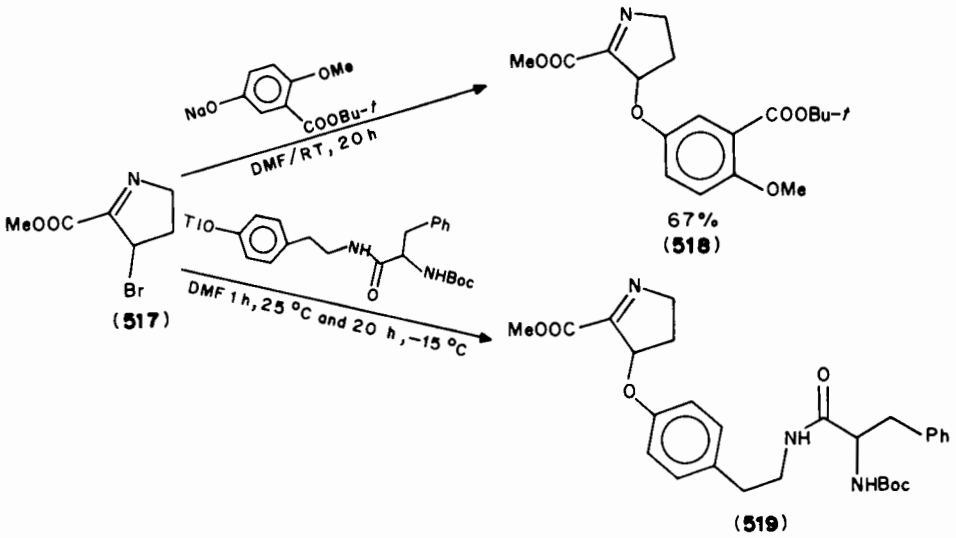
(**514**)



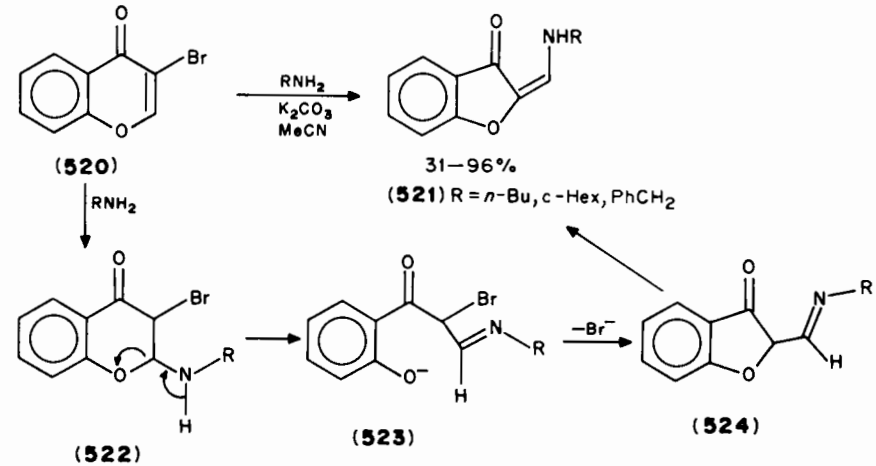
(**515**)

(**516**)

α-Aryloxylations of α-haloimino compounds are known for 3-haloindolenines[573] and especially for 3-bromo-2-methoxycarbonyl-1-pyrroline (**517**)[638–640]. The reactions are mostly conducted in DMF, e.g. for α-acetoxylation of α-chloromethylimines[554], and have been used as a key step in the synthesis of the peptide alkaloid zizyphine A[638] and the cyclopeptide alkaloid dihydromauritine A[639].

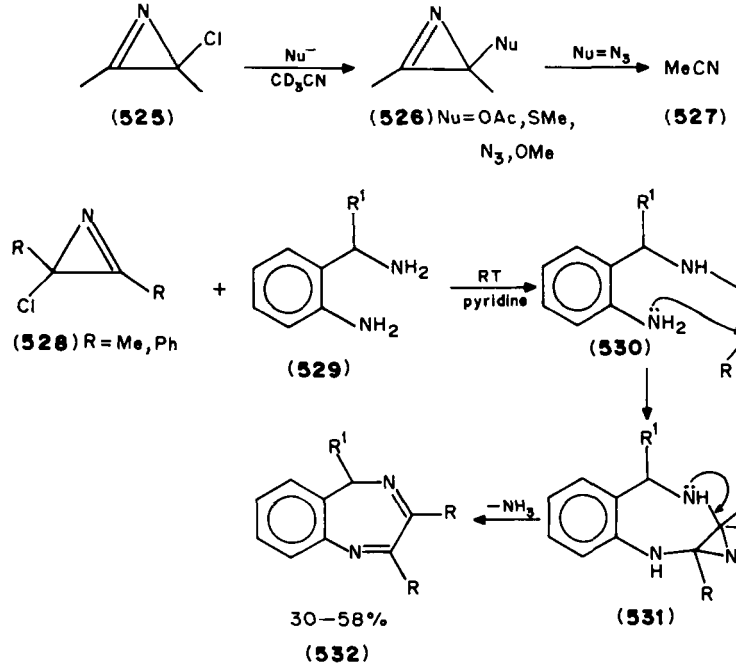


An intramolecular displacement of halogen α both to an imino function and to a carbonyl group by an aryloxy anion was postulated during the ring contraction of **520** into **521** by means of primary amines[641]. After Michael addition of the amine, the intermediate α-bromoaldimine (**523**) formed undergoes an intramolecular nucleophilic substitution.

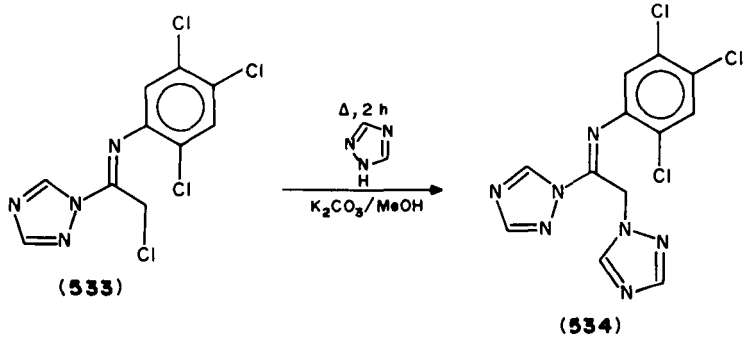


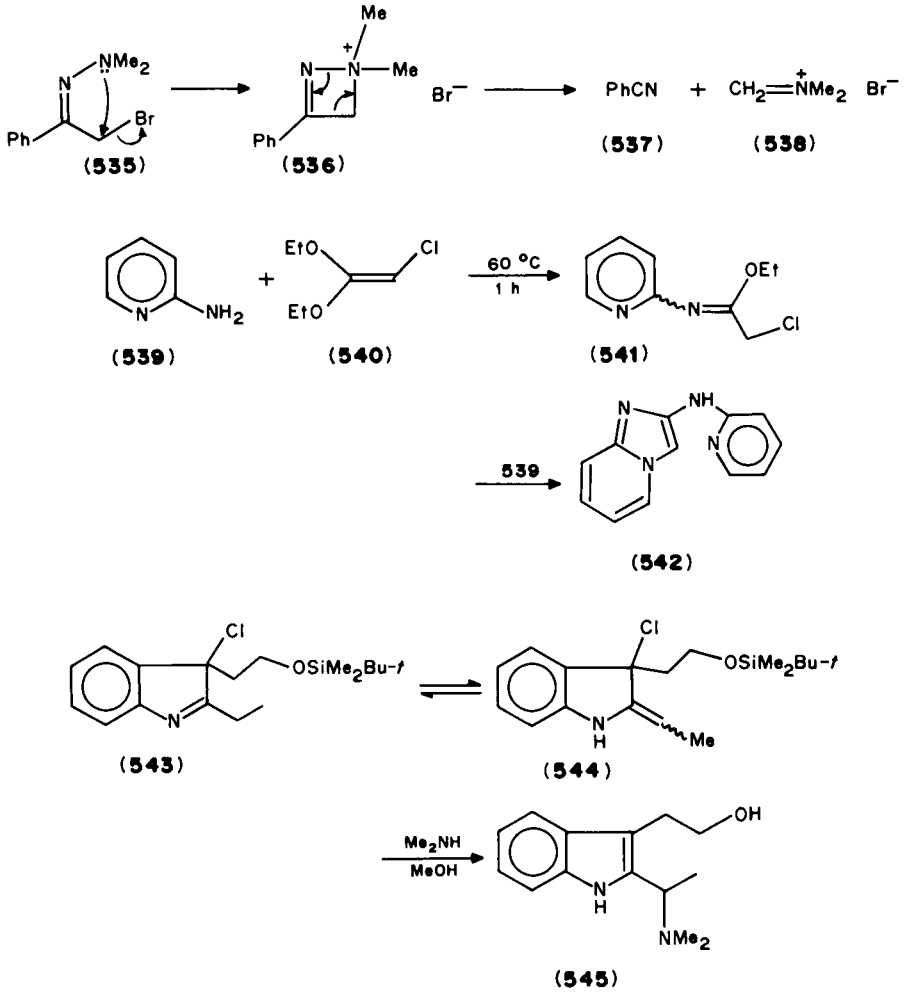
Various nucleophilic displacements have been performed on the 3-chloroazirines **133** and **134**, a peculiar class of α-haloimines. *Ab initio* calculations and experimental observations support the intermediacy of 'azirinyl cations (**135**)–chloride anion' ion pairs. Nucleophilic substitutions with potassium acetate, lithium thiomethylate, lithium azide and methanol were reported for 3-chloro-2, 3-dimethylazirine (**525**)[642]. The sulphenylated derivative (**526**) (Nu = SMe) could be characterized but not isolated and the azido derivative (**526**) (Nu = N_3) decomposed completely into acetonitrile (**527**)[642]. Chloroazirines (**528**) are reactive bifunctional electrophiles, and were used as precursors for the 5*H*-1,4-benzodiazepines **532** by reaction with diamines (**529**)[643]. Benzil also reacted with

these diamines (**529**) to yield the rare benzodiazepine derivatives **532** (R = Ph), thus showing that 3-chloroazirines are equivalents of 1,2-diones[643].



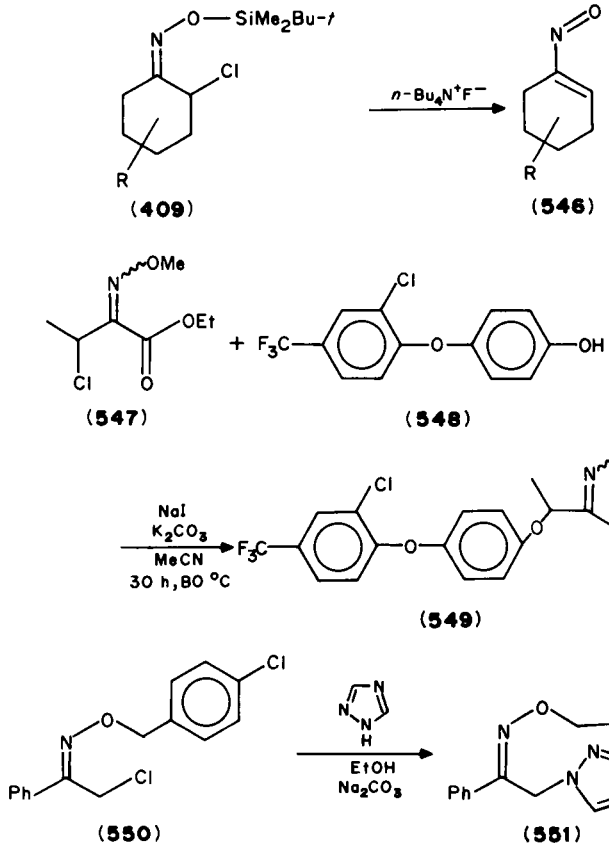
Nitrogen nucleophiles give nearly clean substitution only when the halide is primary, i.e. when α-halomethyl imines are involved. The α-chloromethylketimine **533** underwent substitution with 1,2,4-triazole to provide the ketimine **534**, which showed useful agricultural fungicidal properties[644]. Intramolecular substitutions with nitrogen nucleophiles are exemplified by the decomposition of phenacyl bromide *N*,*N*-dimethylhydrazone (**535**) via a four-membered intermediate (**536**) into benzonitrile (**537**)[645] and the cyclization of *N*-(2-pyridyl)chloroacetimidate (**541**) [from 2-aminopyridine (**539**) and the chloroketene acetal **540**] into **542**[646]. Unexpected reactions were found during the condensation of α,α-dibromoamidines with arylhydrazines, affording the corresponding α-diimino derivatives by nucleophilic substitution[647], and in the S_N2'-type substitution of the 3-chloroindolenine **543** with dimethylamine[562].



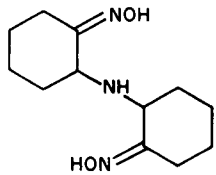


Substitutions with phosphorus nucleophiles are still rare and have concerned α-halogenated five-membered iminoxyl radicals and chloromethyl cyclic imidates, which gave Arbuzov-type products[648,649].

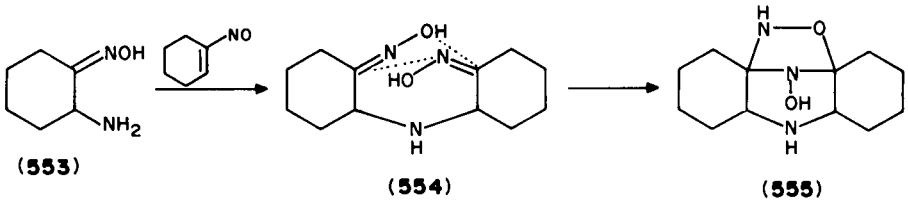
As already discussed in the original chapter, nucleophilic substitution of α-halogenated oximes[511] and α-halogenated hydrazones is well documented and involves a 1,4-dehydrohalogenation followed by addition of the nucleophile across the intermediate nitrosoolefins[650] and azoalkenes. α-Halooxime ethers also give rise to nucleophilic substitution products, while *O*-silylated α-halooximes (**409**) can even afford nitrosoolefins (**546**) by a fluoride ion-induced process[511]. Further examples of nucleophilic substitutions of α-halooximes and related structures such as 2-isoxazolines, nitrones and oxime ethers are reactions with alkoxides[547,597], hydroxide[651], phenolates[542,652] (e.g. the synthesis of the herbicide **549**[652]), acetate[541,653], sulphides[585,586], xanthates[654,823], ammonia[655,656], secondary amines[657,658], tertiary amines[657], pyridine[654] and 1,2,4-triazole[513,520] (e.g. the synthesis of the fungicide **551**[520]).



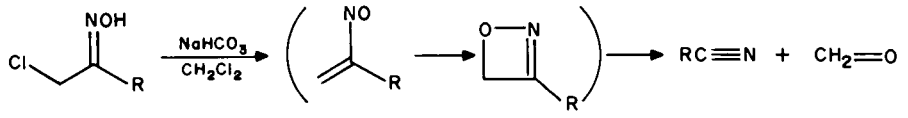
The α-amination of α-chlorocyclohexanone oxime with ammonia was reported to give a major by-product (**552**)[287], but it was shown later[655] that the actual structure was 14-oxa-7,15,16-triazatetracyclo[11.2.1.0^{1,6}.0^{8,13}]hexadecan-16-ol (**555**). Analogously, methylamine yielded the corresponding *N*-methylated tetracyclic compound as major side-product of the α-amination reaction[655]. Other interesting results are 1,4-dehydrochlorination with sodium hydrogencarbonate of the α-chloromethyloximes **180** and the α-chloro-α,α-difluorooxime **560**[597]. The resulting nitrosoolefins (**556** and **561**) underwent intramolecular cyclization into oxazetes (**557** and **562**) which decomposed to the corresponding nitriles (**558** and **537**, respectively). A stable oxazete (**565**) was prepared from the bulky α-bromooxime **563** using DBN as dehydrobrominating agent[659].



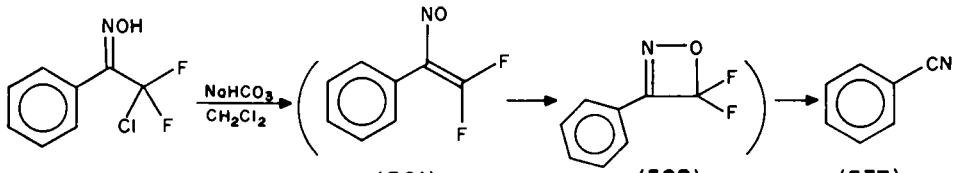
(**552**)



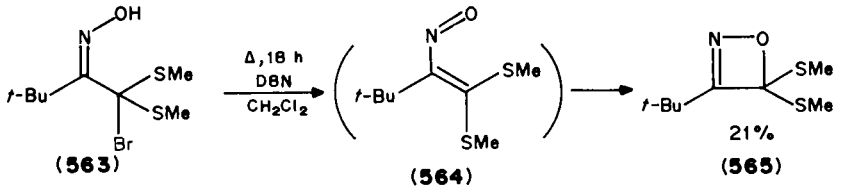
(553) (554) (555)



(180) (556) (557) (558) (559)

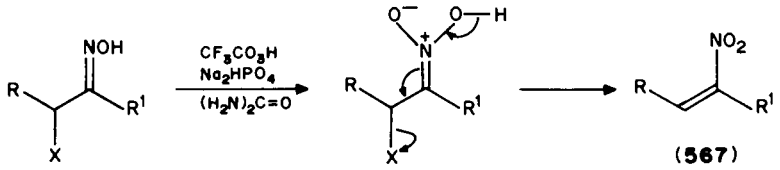


(560) (561) (562) (537)



(563) (564) (565)

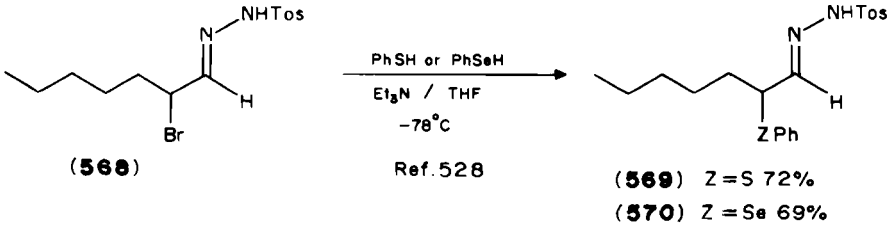
Related to the 1,4-elimination of α-halooximes is the preparation of aliphatic cyclic and acyclic nitroolefins (**567**) from α-halooximes (**187**) by oxidation with trifluoroperacetic acid, disodium hydrogen phosphate and urea[479].



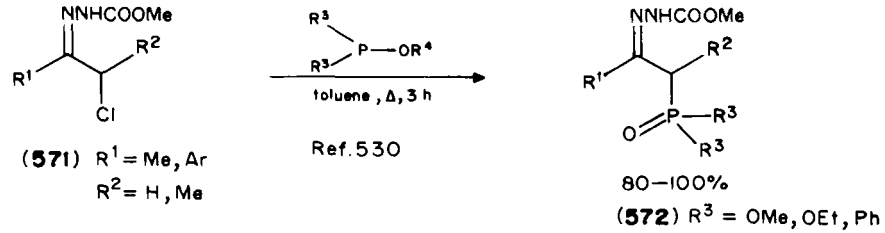
(187) X = Cl, Br (566) (567)

α-Halohydrazone-type compounds underwent nucleophilic substitutions at the α-position by mercaptides[528], selenides[528], azide[543], hydrazides[660], phosphites[530], phos-

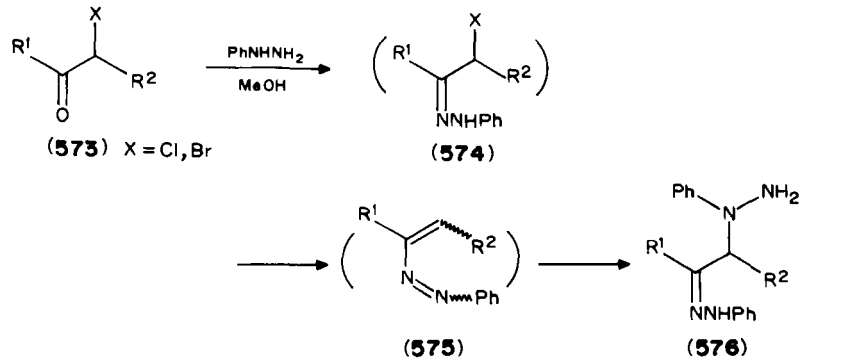
phinites[530], nitroso compounds[661] and hydrazines[469] and some examples are given below. The Arbuzov reaction of **571** into **572** provides ready access to α-phosphorylated carbonyl compounds on hydrolysis of **572** and circumvents in this way the side-reactions, i.e. the Perkow reaction, with α-haloketones by protecting the ketone as a hydrazone moiety[530] (few Perkow reactions with α-haloimines are known[662]). The reaction of the α-haloketones **573** with phenylhydrazine proceeded via the α-halohydrazone **574** and the corresponding azoalkene **575**, but finally gave the substitution product **576**, in which the more substituted nitrogen of the phenylhydrazine is linked to the α-carbon[469].



(**568**) Ref.528 (**569**) Z=S 72% (**570**) Z=Se 69%

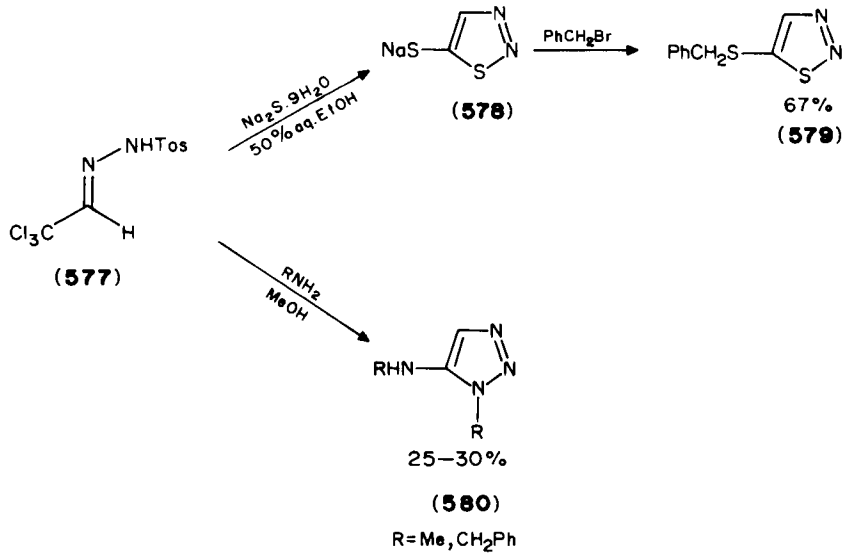


(**571**) R^1 = Me, Ar; R^2 = H, Me — Ref.530 — 80–100% (**572**) R^3 = OMe, OEt, Ph



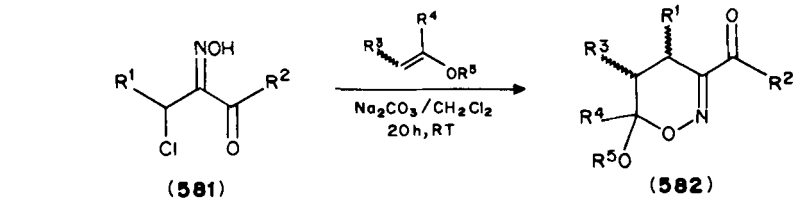
(**573**) X = Cl, Br (**574**) (**575**) (**576**)

In contrast, 2-bromo-2-phenylacetaldehyde and 2-chloro-1,2-diphenylethanone gave the α-hydrazinohydrazones with the terminal less substituted nitrogen atom linked to the α-carbon[469]. The reaction of chloral tosylhydrazone (**577**) with sulphide ion gave, after benzylation, access to 1,2,3-thiadiazole (**579**) while the reaction with primary amines afforded 1,2,3-triazoles (**580**)[482]. These reactions proceeded via 1,4-dehydrochlorination and subsequent nucleophilic addition at the 4-position of the intermediate azoalkene[482].

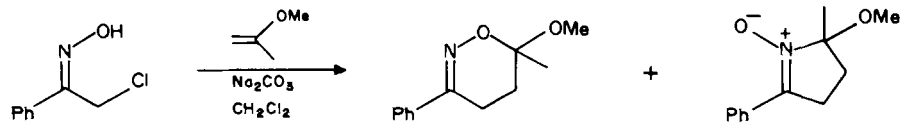


α-Halooximes and α-halohydrazones have been successfully used in recent years for the synthesis of heterocyclic compounds via [4 + 2]cycloadditions of intermediately formed nitrosoolefins and azoalkenes. The pioneering research of Gilchrist and coworkers and the literature on nitrosoolefin cycloadditions have been reviewed[650]. Many useful cycloadditions of nitrosoolefins, generated from base-induced 1,4-dehydrohalogenation of α-halooximes, with dienes or alkenes as a heterodiene, heterodienophile or dienophile[597] were executed. Substrates added include furans[509,597,663], indene[663], cycloalkadienes[514,597,663,666], enamines[663,667], alkenes[509], allylsilanes[824], styrenes[509,514], enolates[507], enol ethers[514,664], 3-methylindole (although indole itself gave nucleophilic substitution)[509] and 1-alkoxycyclohexa-1,3-dienes[666]. Most oximes were α-halomethyl derivatives but higher homologues also reacted in cycloadditions[509,664], as did α,α-dichloro-[665] and α,α,α-trichlorooximes[597]. Pertinent transformations are the conversion of functionalized α-chlorooximes (**581**) with enol ethers into 3-acyl-6-alkoxy-5,6-dihydro-4*H*-1,2-oxazines (**582**)[664] and the formation of the oxazine **584** together with some nitrone **585** from the (*Z*)-α-chlorooxime **583**[514]. Higher yields of cycloadducts were obtained from (*Z*)-α-chlorooximes[514]. Both **583** and the *E*-isomer gave with 2-methoxypropene in the presence of sodium carbonate the same ratio of **584** to **585**, indicating that C=N bond rotation must have occurred before cycloadduct formation[514]. The intramolecular version of these cycloadditions overcomes problems such as the use of a large excess of olefins and in complete regioselectivity[668]. Fluoride-induced cleavage of the *O*-silylated α-chlorooxime **586** to the corresponding α-chlorooxime and then to the nitrosoolefin yielded a suitable substrate in the first example of an intramolecular [4 + 2]cycloaddition, which gave the two epimers of the tricyclic compounds **587** in different ratios. The best results were obtained when the nitrosoolefin was slowly formed with caesium fluoride (20 h)[668].

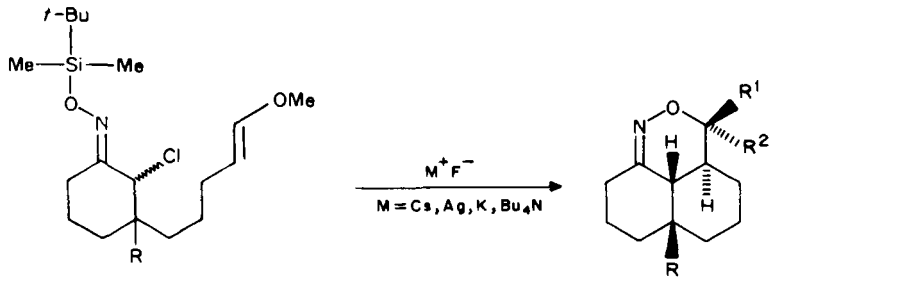
The related α-chloronitrones behaved similarly towards styrenes in a silver-catalysed reaction to yield oxazine derivatives[669], but an exception is the cycloaddition of the α,β-dichloronitrone **588** with bicyclic olefin **589** in the presence of silver tetrafluoroborate, followed by reaction with cyanide, which formed the spiro compound **591** and not the expected oxazine **590**[670]. One carbonyl of **589** apparently underwent cycloaddition yielding **591**.



(581) (582)



(583) 35% (584) 10% (585)

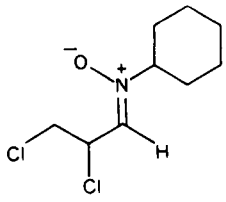


(586) R = H, Me (587) R¹, R² = H, OMe

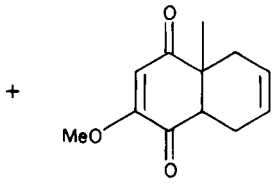
Heteroanalogous cycloadditions to nitrosoolefins are known for azoolefins, accessible from α-halohydrazone-type compounds. The latter reacted with bases, often sodium carbonate or triethylamine, in the presence of cycloalkadienes[663] (see the conversion of **592** into **593**), enamines[671] and enol ethers[672] to form 1,4,5,6-tetrahydropyridazines. Without a dienophile present, α-halohydrazones (**592**; $Z = 2,4$-dinitrophenyl) were transformed into **594**[663].

The α-halohydrazones **412**, carrying remote unsaturation in the *N*-acyl moiety, on treatment with base provided the intermediate azoalkenes **595**, which cycloadded in an intramolecular fashion to afford pyrrolo[1,2-*b*]pyridazine derivatives (**596**)[529].

A number of α-halogenated hydrazones have been converted into various heterocycles by transformation via isolable azoalkenes. *N*-Alkoxycarbonyl and *N*-2,4-dinitrophenyl α,α-dichloroacetaldehyde hydrazones (**597**) were dehydrochlorinated to the chlorinated azoalkenes (**598**), which underwent cycloaddition with electron-rich dienophiles, e.g. indene, ethoxyethene and furan, each providing a novel cyclic α-chloroimino compound (e.g. **599**)[525].



(588)



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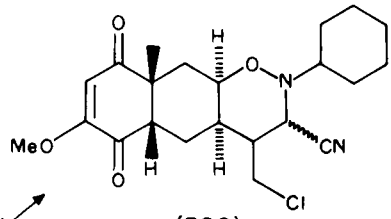
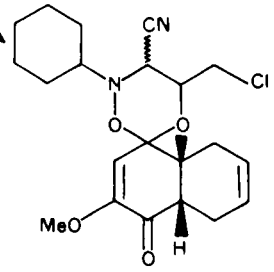
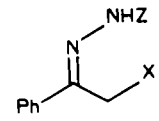


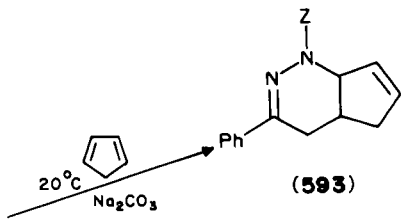
(590)



(591)



(592) X = Cl, Br
Z = 2,4-$(NO_2)_2C_6H_3$, tosyl, COOEt



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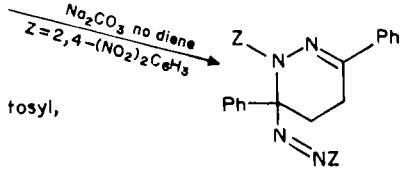

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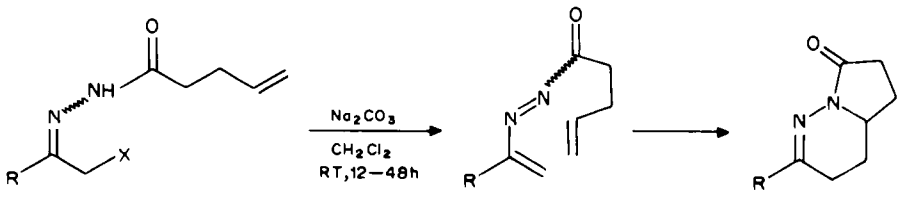
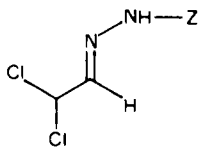


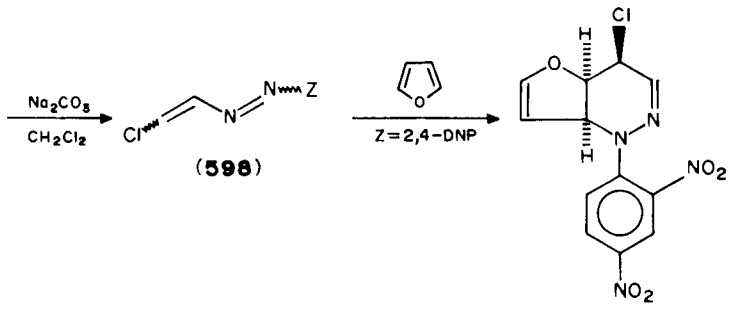
(**412**) X = Cl, Br
R = Me, Ph, COOEt

(**595**)

23—80%
(**596**)



(**597**) Z = COOMe, COOBu-*t*, 2,4—DNP



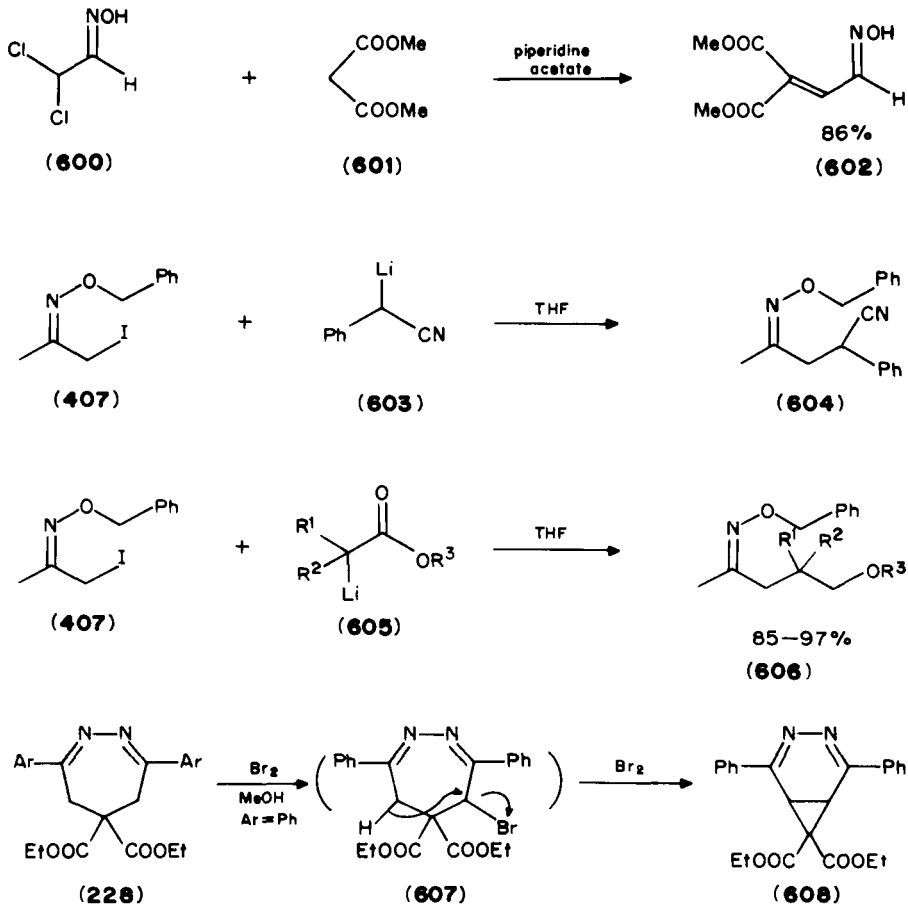
(**598**)

(**599**)

B. Carbon—Carbon Bond Formation

1. Reactions of α-halogenated imino compounds with carbanions

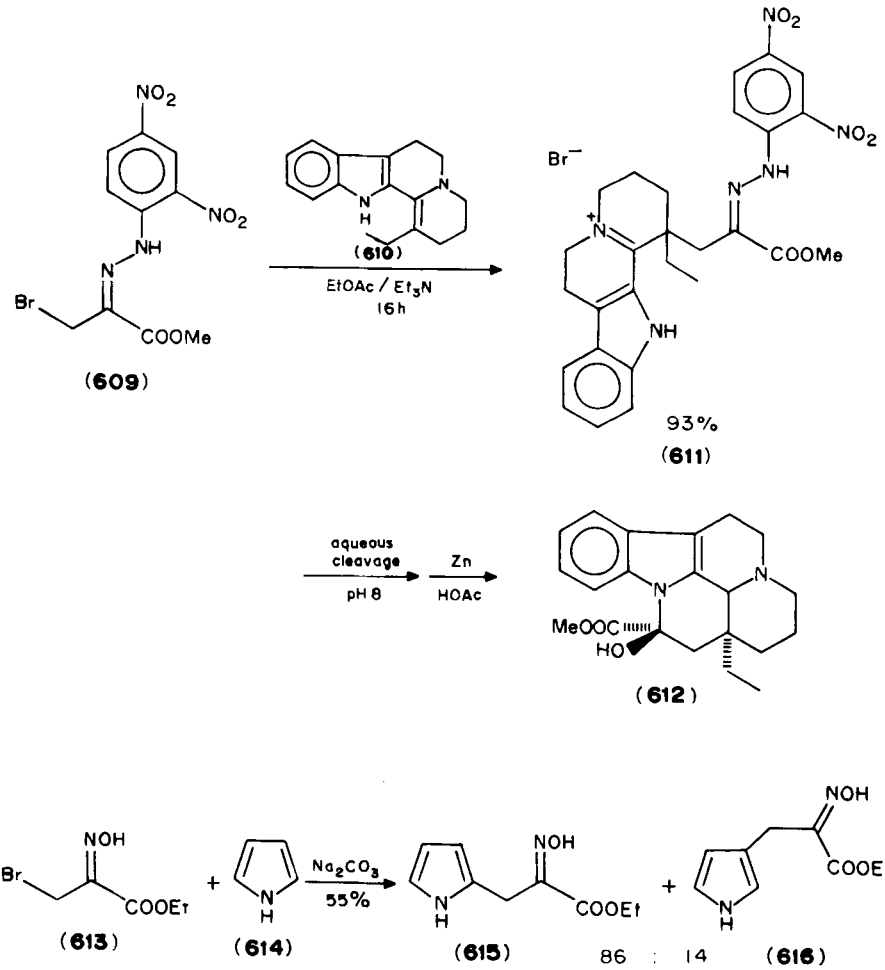
Carbon—carbon bond formation by reaction of α-haloimino compounds with carbanions or equivalent reagents, e.g. enamines or electron-rich aromatics, increased in importance compared with the period before 1980, when only a few reports appeared. The general trend that α-haloimino compounds which are not functionalized on the nitrogen do not react with carbanions continues, but α-halooximes (**600**)[673], α-halooxime ethers (**407**)[519], α-halonitrones[657,674] and α-haloazines (**170**)[269] give formal nucleophilic substitution with carbanions, derived from active methylene functions (such as malonates, cyanoacetates, β-ketoaldehydes, indene, phenylacetonitrile and benzoyldimethylsulphonium ylid[675]) and ester α-anions. The diazepine derivative **228** (Ar = Ph) was brominated with bromine in methanol to give the bromo compound **607** as an intermediate, which underwent intramolecular dehydrobromination to afford 7,7-bis(ethoxycarbonyl)-2,5-diphenyl-3,4-diazanorcaradiene (**608**)[269].



α-Halooximes give [4 + 2]cycloaddition of the intermediate nitrosoolefins with electron-rich alkenes, but cases have been reported in which enamines[531,676] and indoles[508,509,676,677] afforded instead formal nucleophilic substitution and no cyclization (sometimes both reaction types were observed[678] or an additional rearrangement of substituents occurred[826]). The α-bromohydrazone **609** reacted with the enamine **610** to yield the immonium bromide **611**, which was further converted in two steps into vincamine **612**[531].

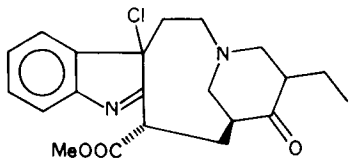
Pyrrole (**614**) and 1,3-dimethoxybenzene were alkylated by the α-bromooxime **613** with low regioselectivity but anisole gave no reaction[509].

Coupling with aromatic substrates at the α'-position was achieved with the 7-chloroindolenine **617**, which reacted with vindoline (**618**) in methanolic hydrogen chloride to afford 55% of the coupled product (**619**) and 11% of the deacetylated coupled compound (**620**)[575]. This reaction is related to the boron trifluoride etherate-catalysed coupling of vindoline and a tautomer of a chloroindolenine structure used in the synthesis of new vinblastine derivatives[679]. On the other hand, an acid-catalysed coupling of the 2-position of 3-bromoindoles with the 3-position of indoles was explained in terms of the intermediacy of α-bromoimmonium derivatives[680].

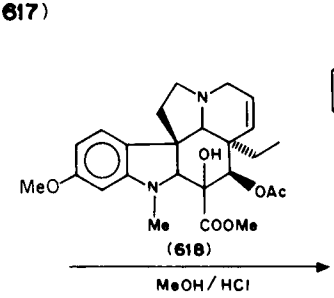


A coupling reaction of aliphatic carbons is that of the α-lithiated oxime ether **424** with iodine giving the (*Z*,*Z*)-1,4-dioxime ether **621**, which isomerized thermally or with acid catalysts into the *E*,*E*-isomer **622**[681]. It is not clear whether the coupling proceeded via an α-iodoimine and subsequent nucleophilic substitution or via intermediate radicals (see Section III.B.3). This coupling reaction could be used for the construction of cyclic derivatives (**623**)[673]. Such carbon—carbon bond formation is also known for α-chloromethyl hydrazones[682] and can be performed similarly in an electrochemical way[683].

An application of α-haloimines as modified α-haloketones opened new entries in the field of α-hetero-substituted carbanions. The latter reagents are rarely prepared from α-halocarbonyl compounds, with the exception of α-halo esters (cf. the Darzens reaction) and α-halocarboxylic acids. α-Haloketones are usually not used for the generation of stabilized α-anions because of their high reactivity. Some haloenolate anions (**624**) have been described[684–688] but most of them lack hydrogens at the α′-position. By masking α-



(617)



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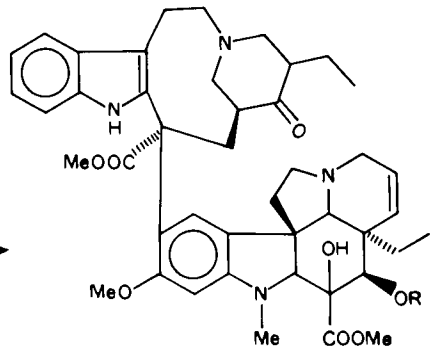
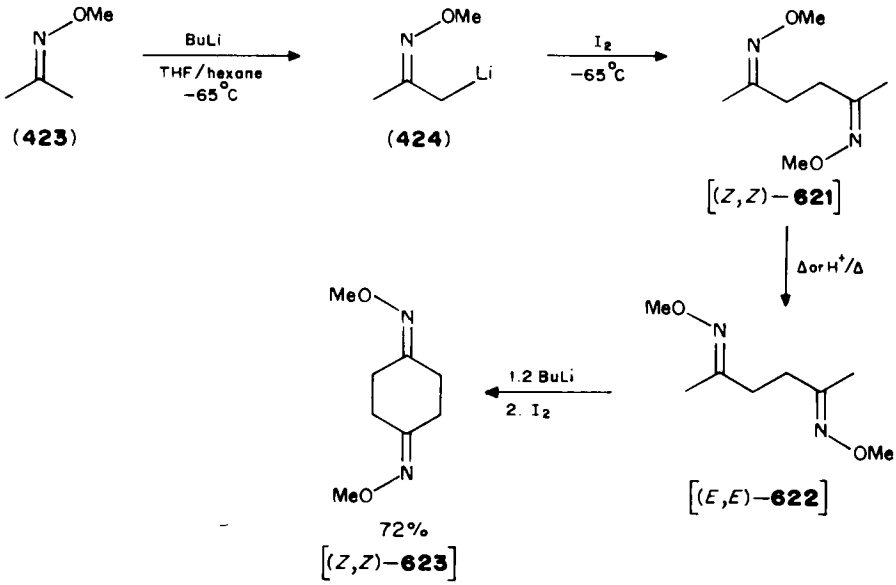
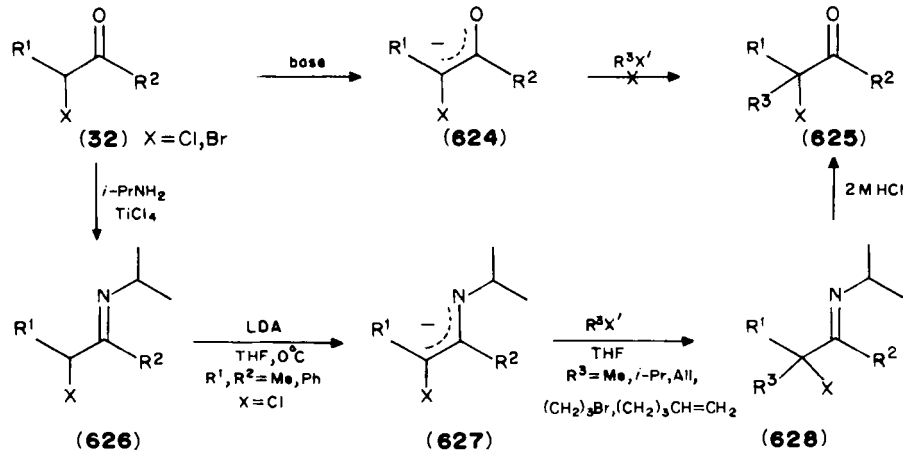


(619) R = Ac 55%
(620) R = H 11%

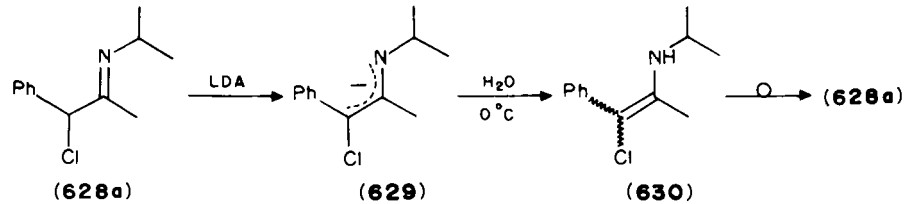


(423) (424) [(Z,Z)-621] [(E,E)-622] [(Z,Z)-623] 72%

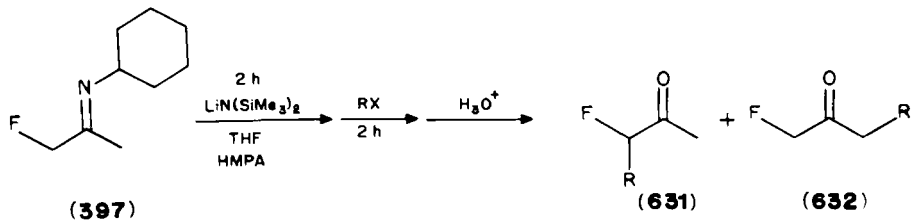
haloketones as α-haloimines having α'-hydrogens it was possible to circumvent these limitations. α-Chloroketimines (**626**) were easily deprotonated with lithium diisopropylamide in THF at 0 °C to give 3-chloro-1-azaallylic anions (**627**), which reacted with (functionalized) alkyl halides to afford *C*-alkylated products (**628**) exclusively[689].



When the phenyl-substituted azaallylic anion **629** was treated cautiously with water at 0 °C, protonation occurred exclusively, on nitrogen, to generate β-chloroenamine **630**, which slowly rearranged to the corresponding α-chloroketimine **628a**[689].



The strategy outlined above allowed the α-alkylation of α-haloketones having α'-hydrogens, since hydrolysis of the α-alkylated α-haloimines **628** provided the α-alkylated α-haloketones **625**[689]. The related alkylation of anions derived from *N*-cyclohexyl-α-fluoroacetone imine (**397**) revealed a temperature-dependent regioselectivity, as shown by the **631**:**632** ratios[690]. The tendency of the metalated ketimine to alkylate on the carbon bearing fluorine at low temperature (− 80 °C) may be rationalized by suggesting that the increased acidity of the protons near the fluorine acts in concert with steric effects of the (*E*)-C=N configuration of the α-fluoroketimine.

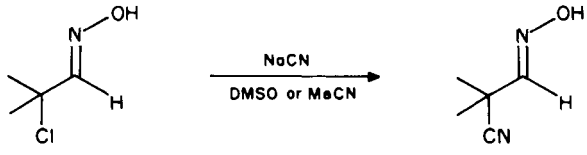


MeI / −80°C	96	:	4
MeI / −30°C	11	:	89
BuI / −80°C	97	:	3
BuI / −30°C	3	:	97

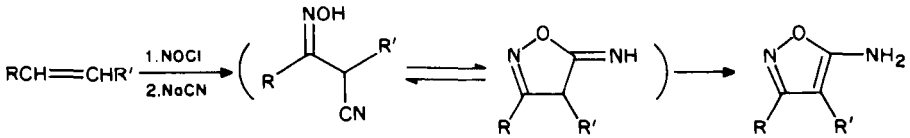
It may be mentioned that α-haloimine α-anions have been implicated already in some reactions[324,548,691–694].

2. Reactions of α-halogenated imino compounds with cyanide ion

Only a few nucleophilic substitutions of halogens α to an imino function are known, largely in α-halomethylimines such as 1-chloromethyl-3,4-dihydroisoquinolines[695]. Surprisingly, the tertiary α-chlorooxime **633** afforded the α-cyanooxime **634**, but a 1,4-dehydrochlorination–addition of cyanide must account for this product[696]. Secondary α-halooximes, generated from nitrosyl chloride addition to alkenes, also reacted in this way, but the substitution products (**636**) ring-closed spontaneously to 5-aminoisoxazoles (**638**)[696].

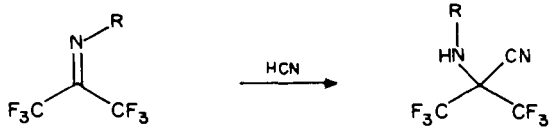


(**633**) (**634**)



(**635**) (**636**) (**637**) (**638**)

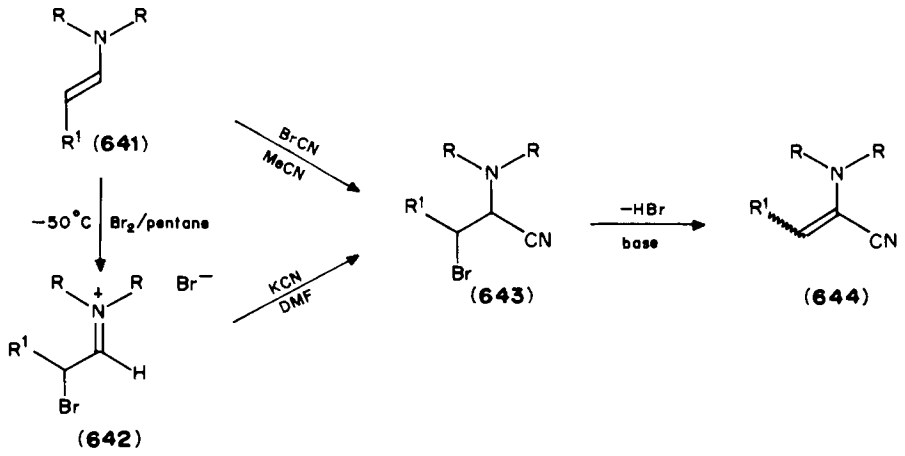
Cyanide has a marked propensity for nucleophilic additions across the imino bond. The adducts are usually not isolated owing to further reactions of the halogen. However, the adduct of cyanide (see **640**) across the perfluoroimine **639** was isolated[501].



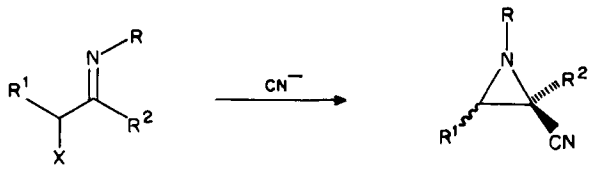
(**639**) (**640**)

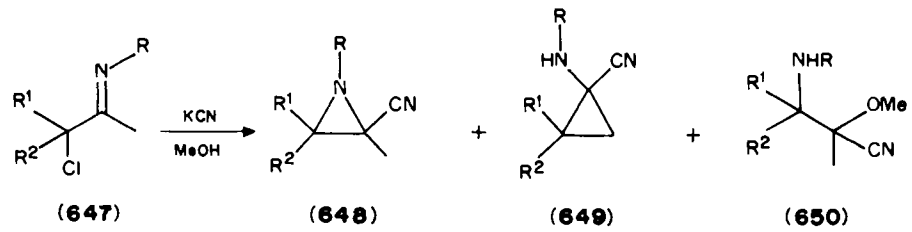
Similarly to the conversion of α-chloroaldimines (**59**) into tautomerizable α-cyanoenamines (**235**)[276], the addition of cyanide across α-bromoimmonium bromides (**642**) generated *in situ* from bromination of enamines (**641**), formed tertiary α-cyanoenamines (**644**) via dehydrobromination of isolable cyanide adducts (**643**)[697]. An alternative and better method for the synthesis of α-cyanoenamines is the addition of cyanogen bromide across enamines (**641**) and subsequent dehydrobromination of the adducts (**643**) with methanolic sodium methoxide[282,697].

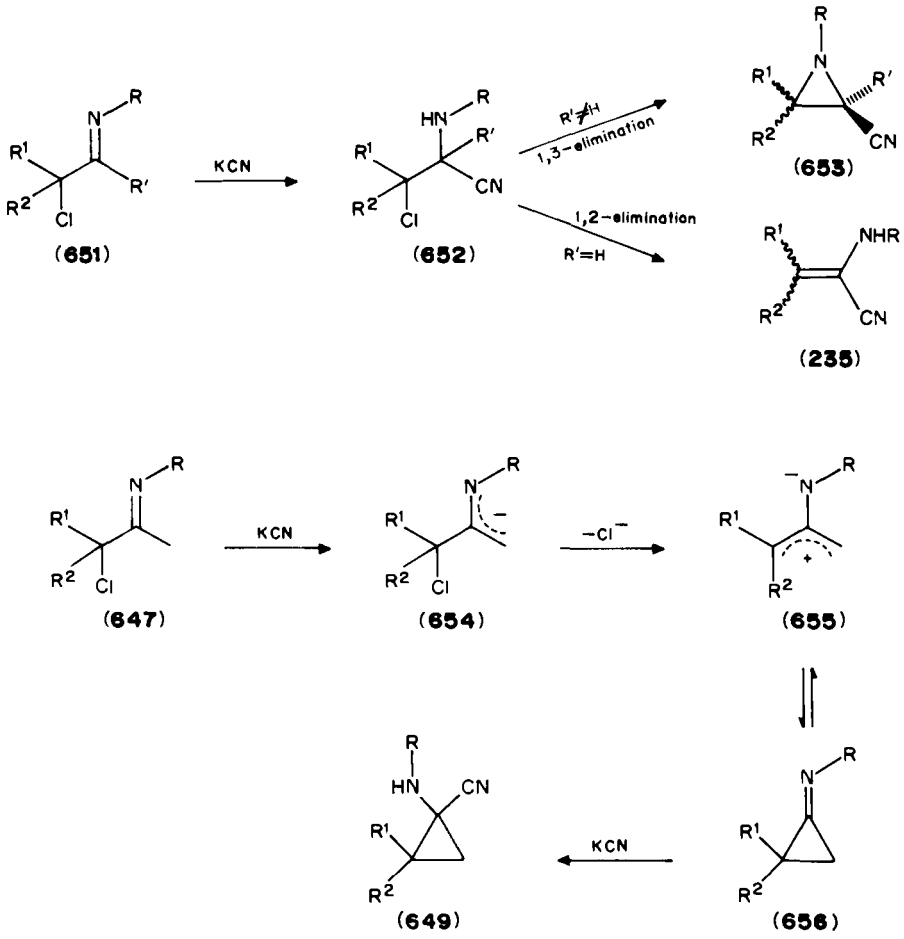
The most general reaction of cyanide with α-haloimines is the nucleophilic addition across the imino bond, which, when applied to a large number of aliphatic α-halogenated ketimines (**645**), led to an excellent synthesis of α-cyanoaziridines (**646**)[633,634,698]. Secondary *N*-alkyl α-chloroketimines gave a mixture of *cis*- and *trans*-α-cyanoaziridines (**646**). The tertiary α-chloroketimines **647** reacted with potassium cyanide in methanol to



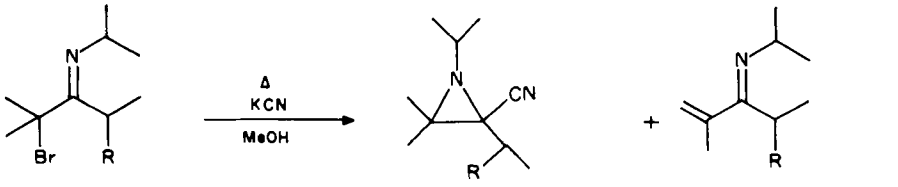
afford mainly the α-cyanoaziridines **648**, together with the 1-(*N*-alkylamino)cyclopropanecarbonitriles **649** and ring-opened products, i.e. the 2-alkoxy-3-(*N*-alkylamino)-nitriles **650**. The formation of the α-cyanoaziridines **646** and **648** was explained by nucleophilic addition of cyanide across the imino function of **651** to yield the adduct **652** (or its anion), which subsequently underwent intramolecular cyclization. The α-cyanoaziridines (**653**) with R′ = H could not be prepared in this way because the cyanide adduct of the α-chloroaldimines **652** (R′ = H) furnished the α-cyanoenamines **235** by 1,2-dehydrochlorination, initiated by deprotonation of the acidic hydrogen α to the nitrile moiety. The cyclopropane derivatives **649** originated from trapping by cyanide of the strained cyclopropylideneamines **656**, formed by formal base-induced 1,3-dehydrochlorination of the α-chloroketimines **647**. Therefore, this reaction can be classified as a variant of the Favorskii rearrangement (see below), which is initiated by α-deprotonation of **647** to generate the delocalized anion **654**, which loses a chloride anion spontaneously. The resulting zwitterion **655** is in equilibrium with the cyclopropylideneamine **656** via a disrotatory ring closure according to the Woodward–Hoffmann rules[633,634,698].





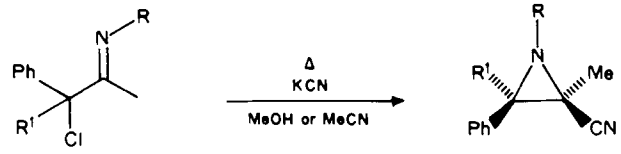


The scope and limitations of the cyanation of α-haloketimines was studied in detail by investigating the nature of the halogen, the carbon skeleton, the nitrogen substituent, the solvent and the source of the cyanide[633,634]. Increasing steric hindrance of the nitrogen substituent favoured slightly the formation of cyclopropane derivatives. Alcohols were the preferential solvents for the formation of the cyclopropanes **649** from **647**. The secondary α-chloroketimines **645** were quantitatively converted into **646** with cyanide in acetonitrile, DMSO and DMF. Sodium, potassium and tetrabutylammonium cyanide gave similar results but zinc, copper(I) and silver cyanide in methanol gave complex reaction mixtures containing α-cyanoaziridines, α-methoxyketones, cyclopropanes and unidentified products. The latter metal cations induced a solvent-assisted ionization of the α-chloroketimine to an intermediate α-imidoylcarbenium ion (**507**), which reacted with the alcoholic medium. On changing the α-halogen from chlorine to bromine, **649** was no longer formed and α-cyanoaziridines were obtained in excellent yields (in addition to small amounts of 1,2-dehydrobromination products as exemplified by the transformation of **657** into **658** and **659**. The α-bromo atom is apparently more readily displaced by intramolecular nucleophilic substitution than by a Favorskii-like process.

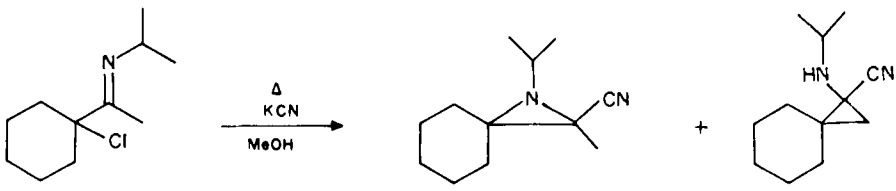


(**657**) (**658**) R = H 100% R = Me 94% (**659**) R = H 0% R = Me 5%

Introduction of one or two methyl groups at the α′-position has a major influence on the cyanation reaction in methanol since α-cyanoaziridines (**648**) are formed exclusively. This observation supported the proposed mechanism for the Favorskii-type rearrangement of **647** to **649** since it is initiated by α′-deprotonation. Hence the factor influencing the production of the cyclopropanes **649** is the acidity of the α′-hydrogens. The α-phenyl-α-chloroketimines **660** with cyanide also did not afford a cyclopropane but yielded the *cis*-α-cyanoaziridines **661** stereospecifically. The highest proportion of cyclopropane was achieved with cyclohexyl derivative **662**, which with potassium cyanide in methanol afforded a 2:3 mixture of the α-cyanoaziridine **663** and the cyclopropanecarbonitrile **664**[634].



(**660**) (**661**)



36% 54%

(**662**) (**663**) (**664**)

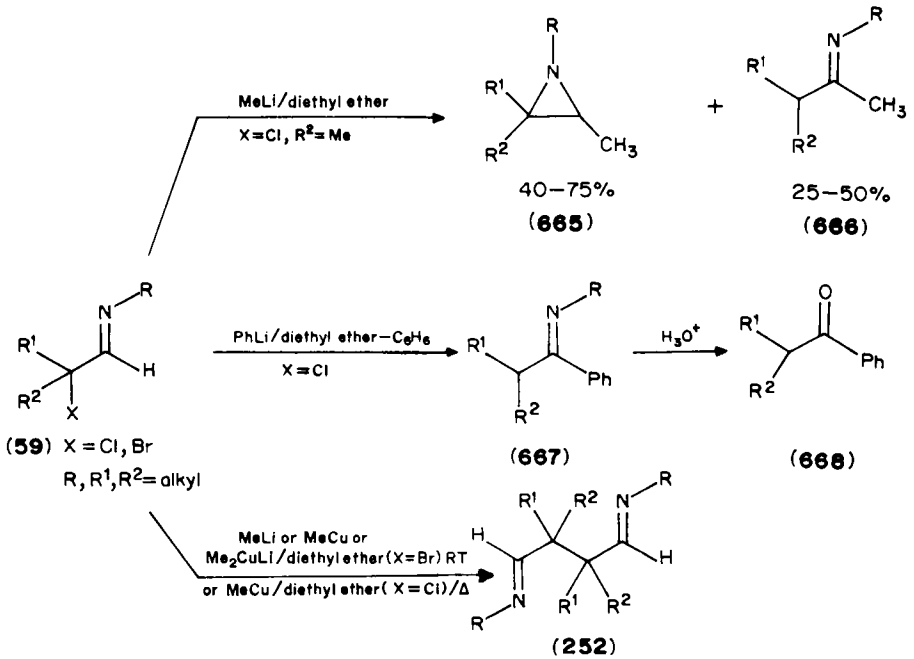
The importance of these reactions is that the α-cyanoaziridines **646** and **648** are precursors of azomethine ylides, which are valuable substrates for 1,3-dipolar cycloadditions, while the 1-(*N*-alkylamino)cyclopropanecarbonitriles **649** are precursors of homologues of 1-aminocyclopropanecarboxylic acid (ACC), the natural precursor for the generation of the phytohormone ethylene.

3. *Reactions of α-halogenated imino compounds with organometallic reagents*

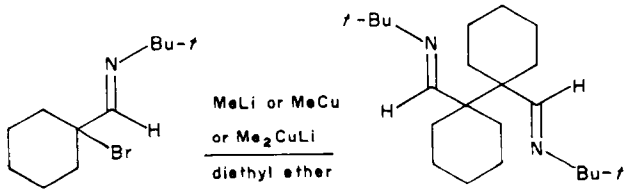
Carbon—carbon bond formation from α-halogenated imines with organometallic reagents has great synthetic potential, but is still an underdeveloped area. This reaction

differs considerably from the reactions of α-halocarbonyl compounds with organometallics.

The reaction of tertiary α-chloroaldimines (**59**), bearing at least one α-methyl substituent (R^2 = Me), with methyllithium (2 molar equivalents) in diethyl ether gave a mixture of aziridines (**665**) and the homologated methylketimines (**666**)[490]. When no α-methyl group was present, e.g. when $R^1 = R^2$ = Et, no aziridine was formed and the homologation was the sole reaction. A similar homologation with phenyllithium afforded phenylketimines (**667**), which were hydrolysed into aromatic ketones (**668**), giving a new acylation of arenes under non-Friedel–Crafts conditions. Since the acylating agents, i.e. α-chloroaldimines (**59**), originate in two steps from aldehydes[87], they are used as modified aldehydes, useful as acylating reagents, for arenes[490].

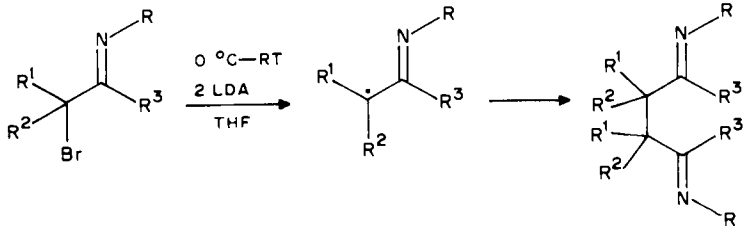


On the other hand, tertiary α-chloroaldimines (**59**) were transformed into 1,4-diimines (**252**) on prolonged reflux with methylcopper in diethyl ether[490]. The same products were obtained under milder conditions (room temperature) with α-bromoaldimines (**59**; X = Br) and methyllithium, methylcopper or lithium dimethylcuprate in diethyl ether[490]. The reaction probably proceeds by dimerization of imidoyl-substituted radicals and not via metal–halogen exchange and subsequent nucleophilic substitution, because the former three organomethyl reagents converted the α-bromoaldimine **669** into the diimine **670** in 90–100% yield. The high steric hindrance in **669** precludes nucleophilic substitution by a tertiary imine α-anion at the tertiary halide centre. A similar coupling of α-bromoimines (**671**) into 1,4-diimines (**673**) was achieved with lithium diisopropylamide (LDA) in THF and was likewise ascribed to a single-electron transfer from the base to the substrate to generate an imidoyl-substituted radical[699]. Again the difference in reactivity between α-bromoimines and α-bromoketones is remarkable because totally different reaction products are obtained, namely 1,4-diimines (**673**)[699] and α-debrominated ketones (**3**)[700,701].



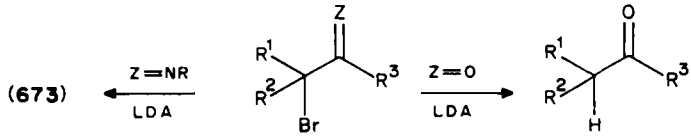
90—100%

(669) (670)



48—89%

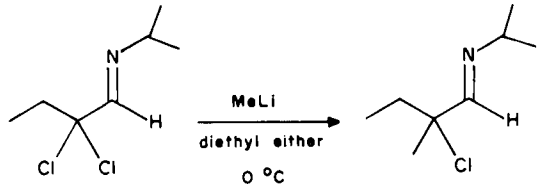
(671) R^3=H, Ph, *i*-Pr (672) (673)



(671) Z=NR (3)

(674) Z=O

α,α-Dichloroaldimines, e.g. **675**, with methyllithium underwent mainly α-methylation to afford α-monochloroaldimines, e.g. **676**[490].

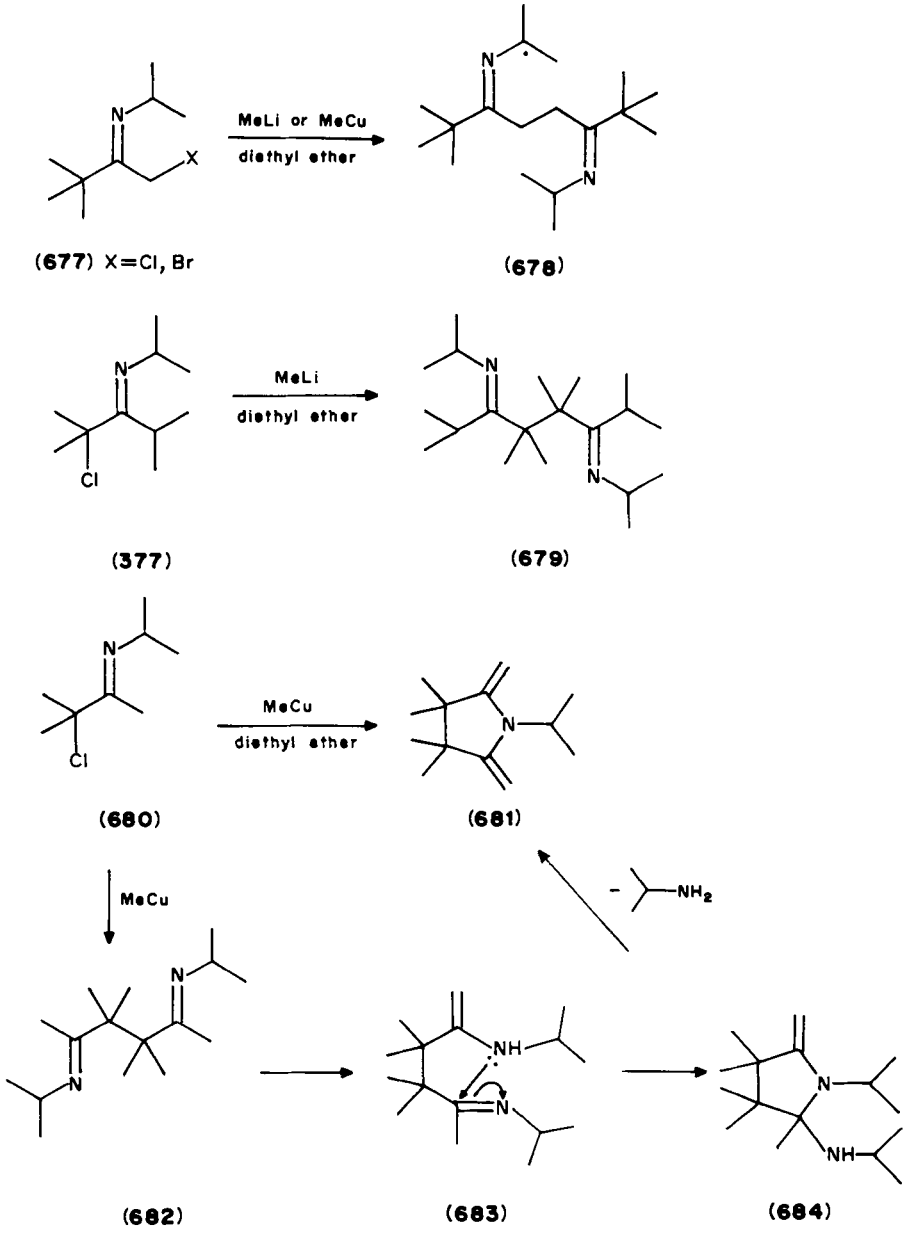


79%

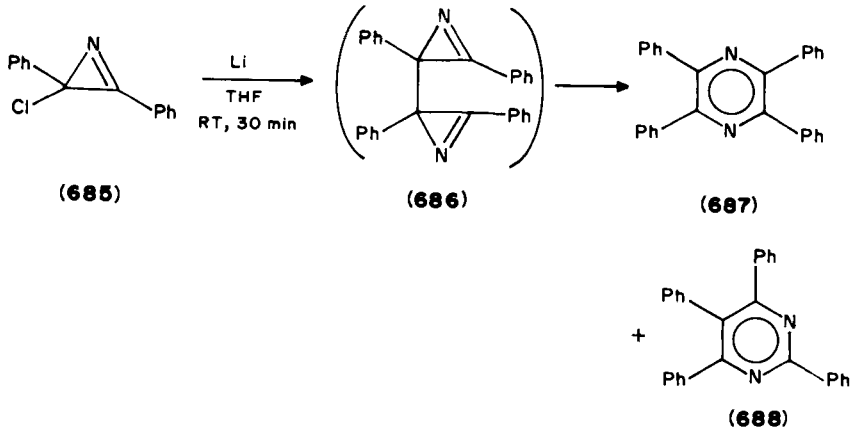
(675) (676)

α-Haloketimines were also subjected to coupling reactions with organometallic reagents. Both primary and tertiary α-haloketimines (**677** and **377**) with methyllithium,

methylcopper or lithium dimethylcuprate could be converted cleanly into 1,4-diimines (**678** and **679**) in high yields (86–100%)[490]. With *N*-(3-chloro-3-methylbut-2-ylidene)isopropylamine (**680**), the 1,4-diimine (**682**), formed by coupling with methylcopper, could not be isolated but underwent intramolecular condensation via **683** and **684** to generate the bismethylenepyrrolidine **681**[490].



A related coupling reaction is the conversion of 3-chloroazirines (**685**) with lithium metal into a transient '1,4-diimine', which rearranged further into a pyrazine (**687**) and a pyrimidine (**688**)[702].



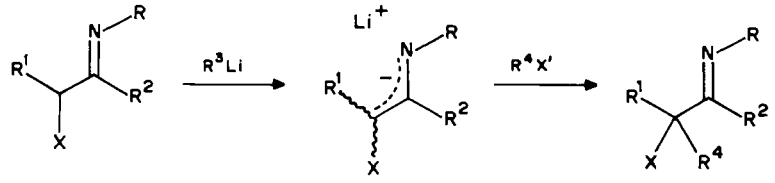
(**685**) (**686**) (**687**)

(**688**)

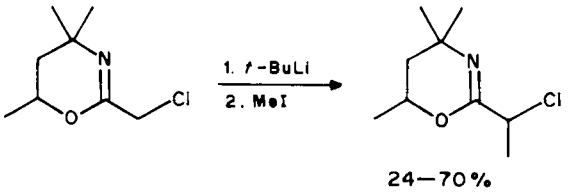
Secondary or primary α-haloimino compounds are usually deprotonated by alkyllithiums at the α-position to give azaallylic carbanions (**689**), which can be readily handled, in contrast to the corresponding oxygen analogues (see above)[689]. Such anions are easily alkylated to **690**, as discussed in Section III.B.1[689,690,693]. However, when *tert*-butyllithium was used to deprotonate the 1,3-oxazine derivative **691**, followed by a reaction with methyl iodide, the desired α-chloro-α-methyl derivative (**692**) was obtained in 24–70% yield, together with products of α-*tert*-butylation (**693**) and coupling–dehydrochlorination (**694**)[693]. The latter two processes were also obtained with substrate **691** and phenylmagnesium bromide[693]. α-*tert*-Butylation of the α-chloroaldimines **59** to **695** occurred with *tert*-butyllithium, but it was accompanied by α-hydroxylation to **696**[494].

Lithium metal converted the bicyclic α-bromoimine **697** within a few seconds at −78 °C into the tricyclic compound **698**, probably via halogen–metal exchange, after which the delocalized 1-azaallylic carbanion displaced the bromide in the neighbouring ring[540]. As expected, the α-bromoimine **699** also afforded **698** on treatment with potassium *tert*-butoxide.

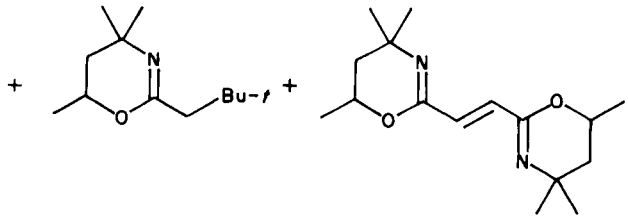
The preponderant reactions of α,α-dichloroimmonium chlorides (**701**) are nucleophilic additions across the immonium moiety. Consequently, methyl- and ethylmagnesium halides afforded alkylation at the 1-position to **702** but hindered reagents such as isopropyl- and *tert*-butylmagnesium halides gave reduction of the immonium bond to **700**[579].



(**645**) X=halo (**689**) (**690**)

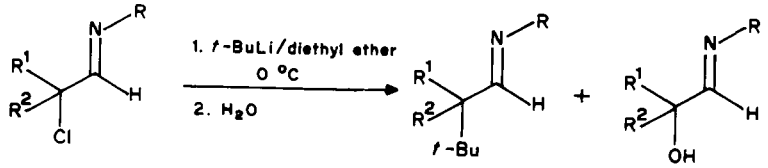


(691) (692)

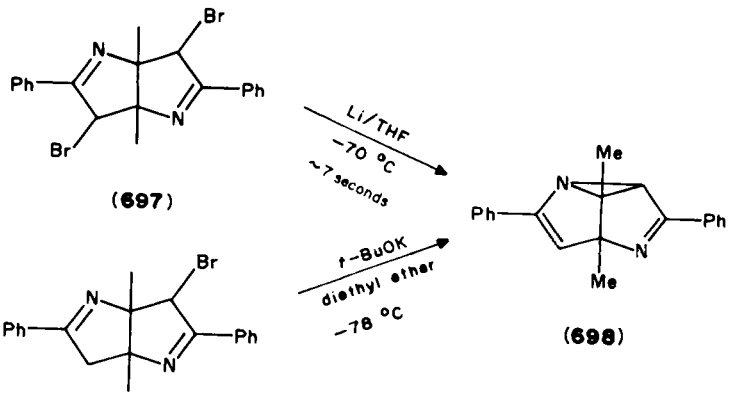


20—38% 3—24%

(693) (694)

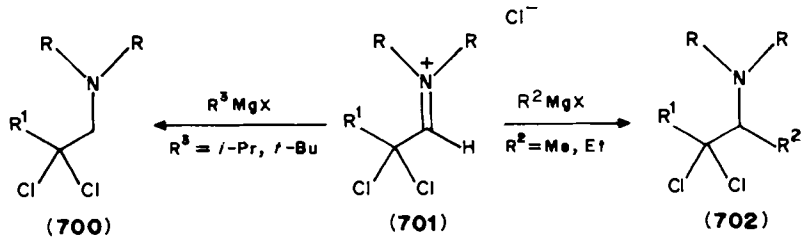


(59) (695) (696)



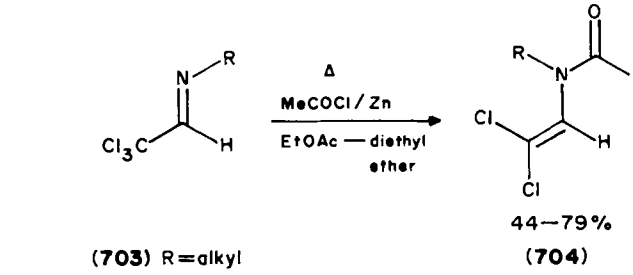
(697) (698)

(699)

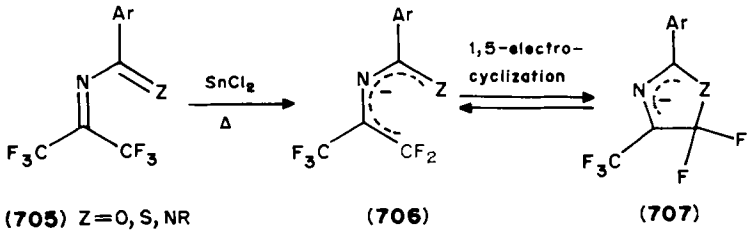


(700) (701) (702)

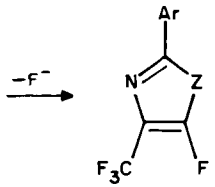
A large number of chloral imines (**703**) give with acetyl chloride in the presence of zinc the *N*-acetyl β,β-dichloroenamines **704**[703]. Reductive fluoride elimination with tin(II) chloride of the heterodienes **705** produced the delocalized anion **706**, which was transformed into oxazoles (**708**; Z = O), thiazoles (**708**; Z = S) or imidazoles (**708**; Z = NR)[704].



(703) R=alkyl (704)



(705) Z=O, S, NR (706) (707)

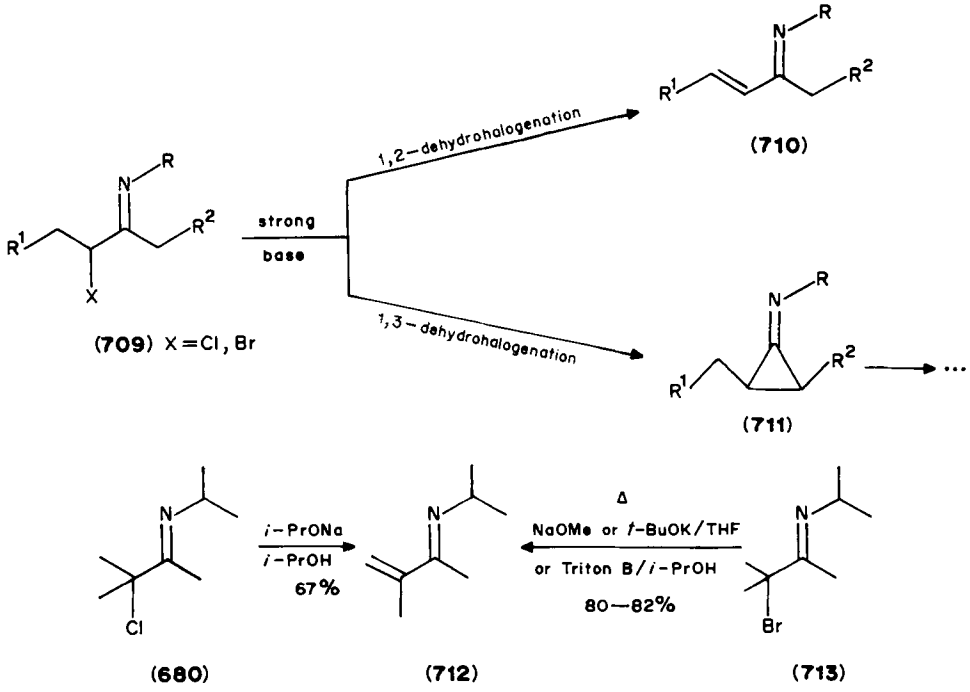


(708)

C. Elimination Reactions of α-Halogenated Imino Compounds

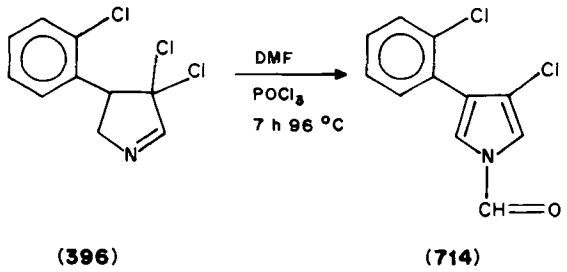
Base-promoted 1,2-dehydrohalogenation of α-haloimines occurs frequently and affords 1-azabutadienes. Treatment of α-haloketimines with strong bases (alkoxides, hydroxides) either gave 1,3-dehydrohalogenation to a cyclopropylideneamine (**711**) if α′-hydrogens are available or 1,2-dehydrohalogenation to **710**. Lower alkoxides such as methoxide or ethoxide often produced other reaction types, thereby affording rearranged α-aminoacetals (see below) and nucleophilic substitution products. More hindered alkoxides

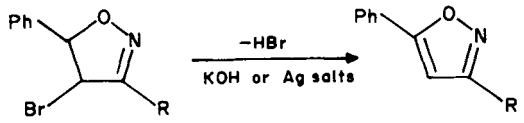
such as sodium isopropoxide rather converted α-chloroketimines, e.g. **680**, into 1-azabutadienes (see **712**) but use of the more powerful potassium *tert*-butoxide resulted predominantly in a Favorskii rearrangement[491]. However, with α-bromoketimines 1,2-dehydrobromination predominated over a Favorskii rearrangement with strong bases, as illustrated by the conversion of the α-bromoketimine **713** to the α,β-unsaturated ketimine **712**[491].



Since the competition between all these reaction types is strongly dependent on the structure of the starting α-haloimine, the halide, the base and the base concentration[491], it is difficult to make generalizations.

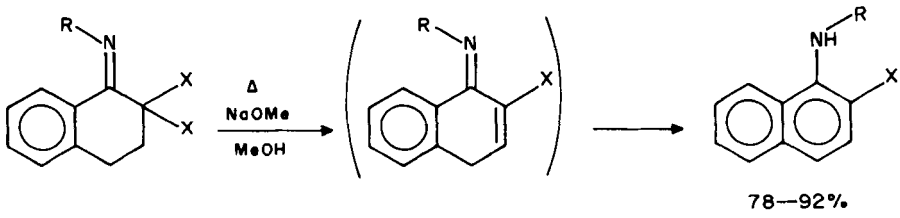
The dehydrohalogenation and formylation at nitrogen of the cyclic α,α-dichloroimine **396** using phosphorus oxychloride in DMF found application in the synthesis of the fungicidal pyrrole **714**[500]. 4-Bromo-5-phenyl-2-isoxazolines (**715**) were easily converted into isoxazoles (**716**), either spontaneously or under the influence of potassium hydroxide[705] or silver salts[706].





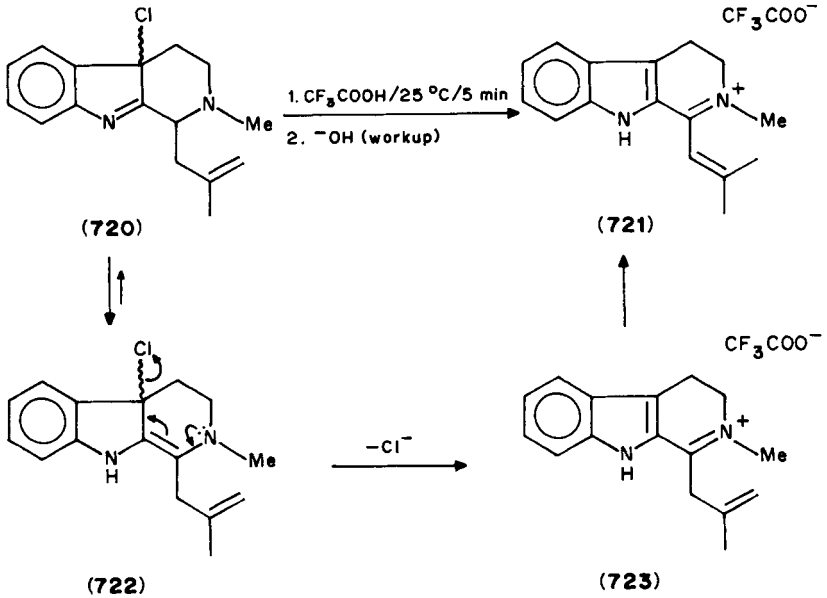
(715) (716)

Dehydrohalogenation of α,α-dihalo 1-tetralone imines (717) with sodium methoxide in methanol proceeded without side-reactions and after aromatization gave 2-halo-1-naphthylamines (719)[493].



(717) X=Cl, Br (718) (719)

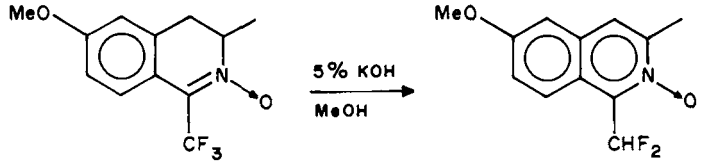
Chloroindolenines such as 720[565] and others[564] did not undergo 1,2-dehydrohalogenation at the original α,β-positions to the imino function but produced unsaturation at the α′,β′-position (cf. 721) when treated with trifluoroacetic acid. This was ascribed to neighbouring group assistance of the nitrogen atom in the adjacent ring.



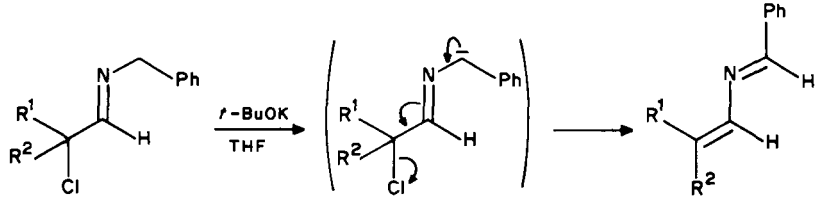
(720) (721) (722) (723)

In addition to 1,2- and 1,3-dehydrohalogenation, α-haloimines carrying hydrogen atoms at C-1 of the *N*-substituent are able to undergo 1,4-dehydrohalogenation. The

fluorinated nitrone **724** was dehydrofluorinated with methanolic potassium hydroxide, and the intermediate fluorinated 2-azabutadiene was isomerized to the aromatic compound **725**[612]. 1,4-Dehydrohalogenation is not limited to endocyclic imino systems, but an activating *N*-substituent is apparently necessary to induce the reaction. The acidity of the hydrogens at C-1 position of the *N*-alkyl substituent play a dominant role in the 1,4-dehydrohalogenation. Increasing their acidity by substitution of $C_{(1)}$ with a phenyl group or a carbonyl moiety results in a base-induced 1,4-dehydrohalogenation. Accordingly, the *N*-benzyl-α-chloroaldimines **726** were dehydrochlorinated with potassium *tert*-butoxide in tetrahydrofuran to the 2-azabutadienes **728** in good yields[493].



(724) (725)

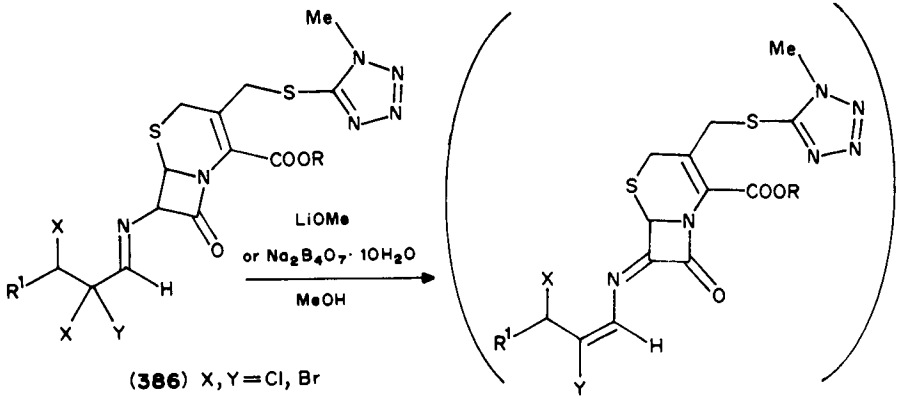


(726) R^1, R^2 = alkyl (727) (728)

This process found an interesting application in the field of cephalosporins. Treatment of the α,α,β-trichloroaldimine **386**, derived from 7β-aminocephalosporins, with lithium methoxide or borax in methanol produced the methoxylated 1-azabutadiene **730** via the intermediacy of the 2-azabutadiene **729**[496]. Hydrolysis of **730** provided the 7β-amino-7α-methoxycephalosporin derivative **731**, which was used as a key intermediate for the synthesis of cephamycin antibiotics[496].

Another application involved the conversion of 7α-amino-3-methyl-1-oxacephem (**388**) into 7β-amino-3-methyl-1-oxacephem (**734**) via the chloral imine **389**[497]. 1,4-Dehydrochlorination of **389** with ethyldiisopropylamine (Hünig base) in dichloromethane at low temperature afforded the dichlorinated 2-azabutadiene **732**, which was reduced from the α-face with high stereoselectivity into the labile β,β-dichloroenamine **733** (we suggest that this compound, which was not characterized, occurs as its more stable α,α-dichloroaldimine form). Hydrolysis of **733** gave **734** in excellent yield. The same conversion was applied to the synthesis of 7β-aminodesacetoxycephalosporanic acid benzhydryl ester[497]. The importance of this four-step procedure for the epimerization of 7α-amino-1-oxacephems is that a useful biological activity of these species is exhibited only when *cis* stereochemistry is present at the 6- and 7-positions.

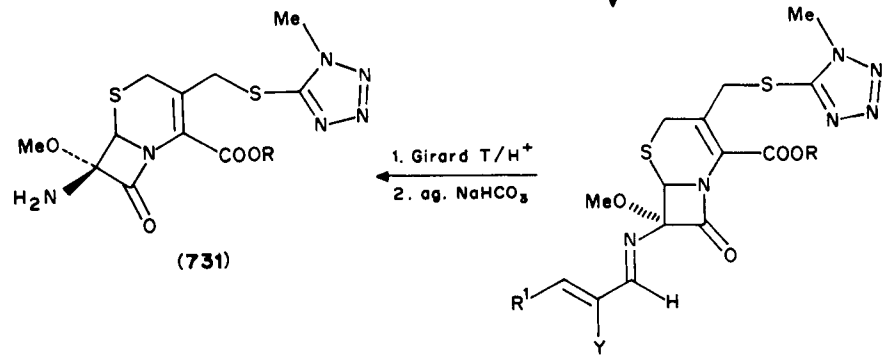
A final example of 1,4-elimination concerns the α-chloroimine **737**, obtained *in situ* by reaction of an α-azido acyl chloride **735** with the ynamine **736**, which afforded the azacyclopentadienone **738**. The latter underwent cycloaddition with the ynamine **736** and was further decarbonylated into functionalized pyridines (**740**)[707,708].

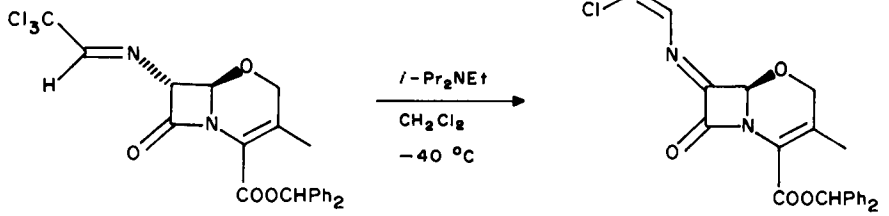


(386) X, Y = Cl, Br

R^1 = Me, Ph

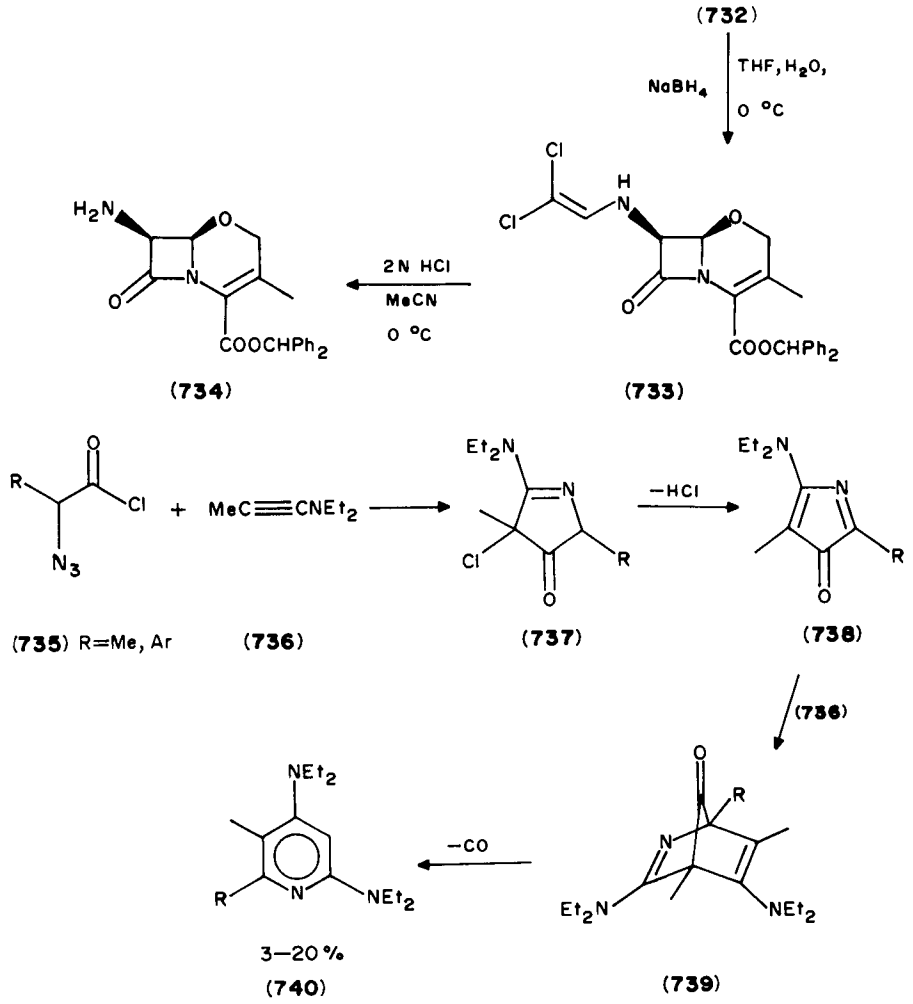
(729)



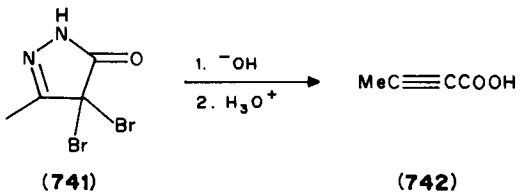


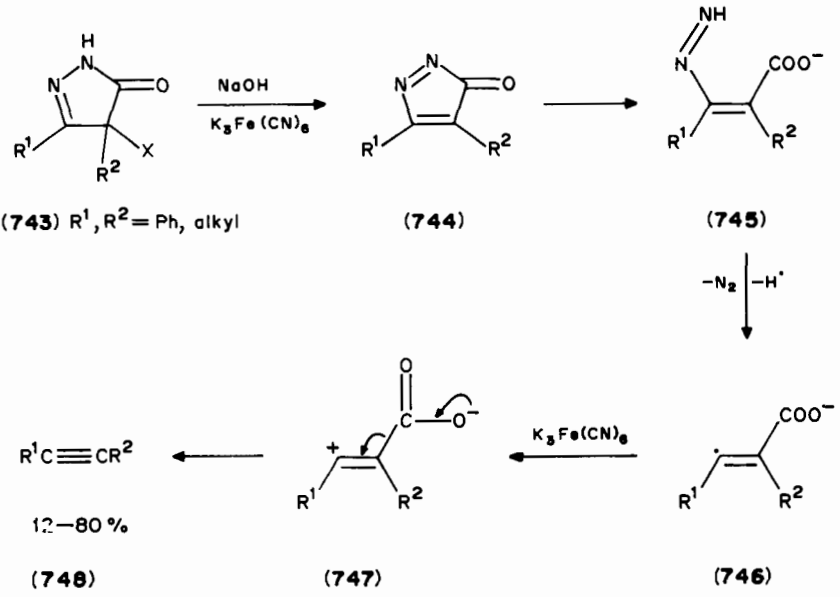
(389)

(732)



The 1,4-dehydrohalogenation of α-haloimines resembles the heteroanalogous 1,4-dehydrohalogenation of α-halooximes into nitrosoolefins[650] and α-halohydrazones into azoolefins (see Section III.A). Salient features of azoalkenes, generated from α-haloimines, include the synthesis of bimanes (see **221** and **222**)[545,709], of tetrolic acid (**742**) from 4,4-dibromo-3-methyl-2-pyrazolin-5-one (**741**)[544] and of alkynes (**748**) from 4-halo-3,4-disubstituted-2-pyrazolin-5-ones (**743**)[710].





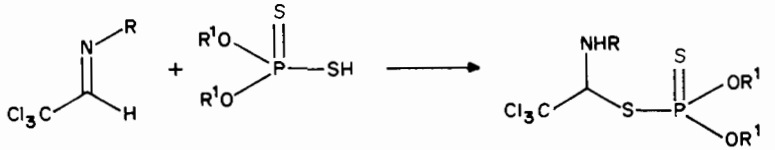
(743) R^1, R^2 = Ph, alkyl (744) (745)

(748) (747) (746)

D. Nucleophilic Additions to α-Halogenated Imino Compounds

α-Haloimines carrying an electron-withdrawing substituent on the nitrogen have a pronounced electrophilic *imino* carbon atom and therefore readily form adducts with a great variety of nucleophiles. In addition to the adducts listed in the original chapter, many more examples have been reported recently. These include mainly reactions of α-perhalogenated imines with nucleophiles such as water[601,603,711], alcohols[712-716], amines[601,712,717], amides[712,718], sulphonamides[718], phosphorus nucleophiles[719,720], amidines[721-723], hydride (generated unexpectedly from triethylamine)[724], 1,3-diones[725], β-keto esters[725], carboxylic acids[602], thiols[602], hydroxylamines[602], indole[726,727], ethyl diazoacetate[728] and alkenes (ene reaction)[621,729]. Some representative reactions are discussed in more detail below.

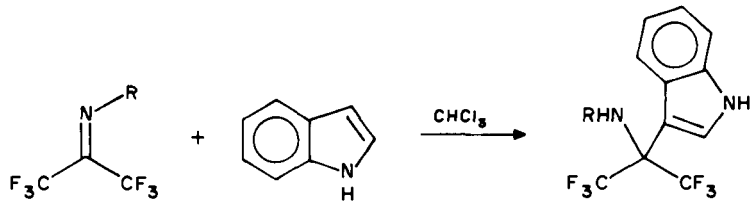
Phosphorus dithioacids (**750**) were added to the *N*-acetylchloral imine **316** and to the *N*-phenyl analogue (**749**) to afford stable adducts (**751**)[719].



(316) R=Ac (750) R^1 = Me, Et, Pr, i-Pr (751)

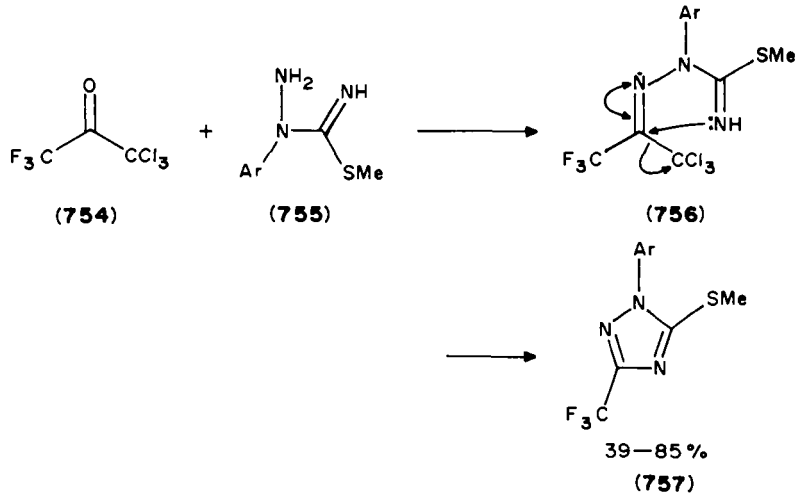
(749) R=Ph

The powerful electrophilic character of α-perhaloimines carrying electron-withdrawing nitrogen substituents was demonstrated by the spontaneous addition of indole across hexafluoroacetone imines (**752**)[726].



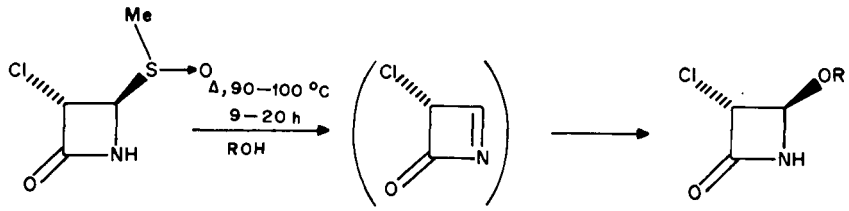
(752) R = $COCF_3$, SO_2Ph (753)

An intramolecular version of the nucleophilic addition across α-haloimines was found during the condensation of 1,1,1-trichloro-3,3,3-trifluoroacetone (**754**) with the hydrazine derivative **755**. The resulting hydrazone (**756**) was not isolable but it underwent an intramolecular nucleophilic addition with expulsion of chloroform affording 1-aryl-3-trifluoromethyl-5-methylthio-1,2,4-triazoles (**757**)[723].



(754) (755) (756) (757)

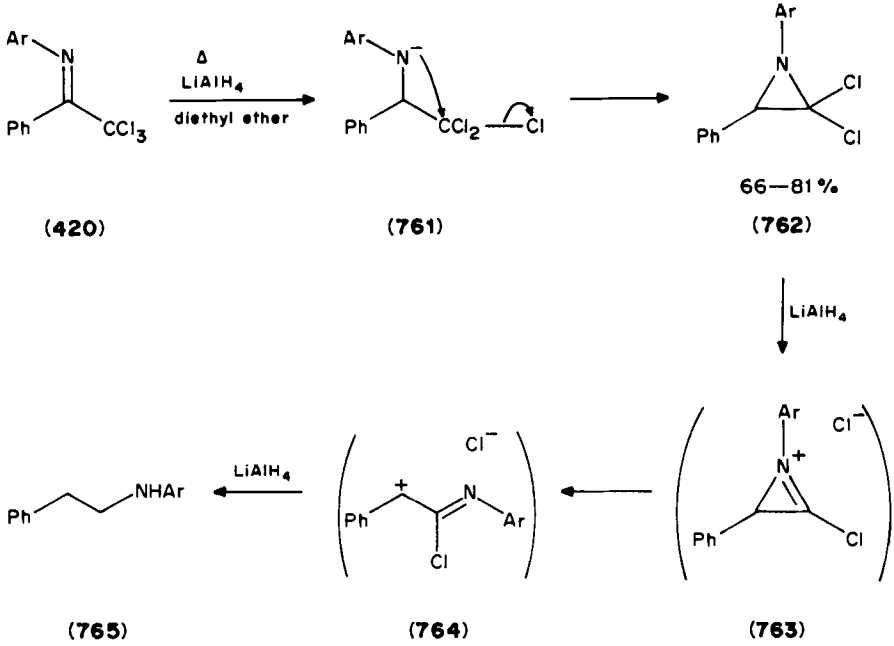
A good example of nucleophilic addition is involved in the synthesis of β-lactamase inhibitors and β-lactam inhibitors. The reaction of (3*S*,4*R*)-3-chloro-4-methylsulphinylazetidin-2-one (**758**) with alcohols produced the alkoxy derivative **760** via the intermediacy of the reactive four-membered α-haloimine **759**[716]. The bulky chloro atom of **759** directed the addition of the alcohol to the less hindered β-side.



(758) (759) (760)

R = Et_2CH, $HC{\equiv}CCMe_2$

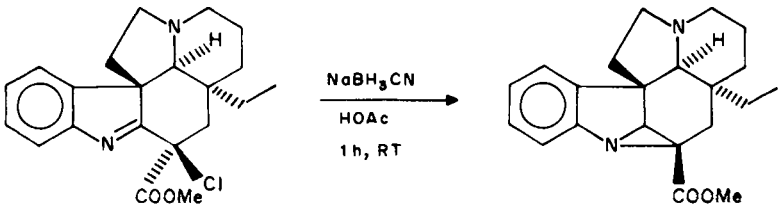
The reaction of α-haloimines with nucleophilic hydrides predominantly afforded nucleophilic addition across the imino function. Sodium borohydride reduced only the carbon—nitrogen double bond of α-fluoroimines[730], cyclic α-haloimines[539] and α-bromoimmonium bromides[731], while only in a few cases was concomitant reduction of the halide observed[731]. The more powerful nucleophilic $LiAlH_4$ usually gives a fast nucleophilic addition across the imino bond but the addition is mostly followed by intramolecular nucleophilic substitution to generate aziridines which are isolable or rearrange further[346]. The earlier synthesis of aziridines[85,143,345,346] from α-haloimines and $LiAlH_4$ was extended to *N*-aryl α,α,α-trichloro ketimines (**420**), which were converted into 2, 2-dichloro-1, 3-diarylaziridines (**762**)[537], which were previously usually prepared by dichlorocarbene addition to benzylidene anilines. When an excess of hydride was avoided and the reaction was run at lower temperature, the initial hydride adduct (protonated **761**) could be isolated. However, if a large excess of $LiAlH_4$ was used, **762** rearranged further into the phenethylanilines **765**[537]. It was not possible to extend the synthesis of **762** to the synthesis of *N*-alkyl-α,α-dichloroaziridines owing to various competitive products[537].



Aziridine formation is not restricted to simple model compounds, as demonstrated by the transformation of 16-chloro-1-dehydrovincadifformine (**766**) with sodium cyanoborohydride in acetic acid into the hexacyclic compound **767**[732]. The same transformation applied to the chloroindolenine derived from Δ^{18}-tabersonine provided an analogous aziridine which was further converted into the tetrahydroquinolone alkaloids scandine and meloscine[733].

On the other hand, α,α,α-trifluoromethyloximes were reduced with lithium aluminium hydride to the corresponding β,β,β-trifluorinated primary amines[734].

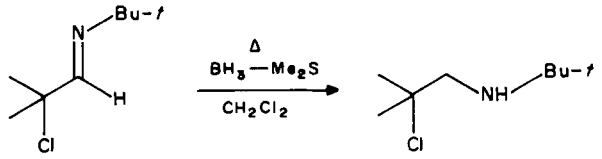
The electrophilic reduction of α-haloimines using the borane–dimethyl sulphide complex in refluxing dichloromethane is an alternative approach to the synthesis of β-halogenated amines. α-Haloaldimines[493] and α-haloketimines[493,735] were reduced with-



70%

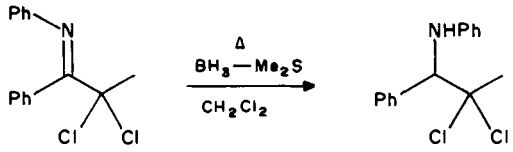
(766) (767)

out interference from side-reactions. The reaction was applicable to α-chloro-, α,α-dichloro- and α,α,α-trichloroimines (e.g. **768**, **770** and **374**), as exemplified by the synthesis of β-chlorinated amines **769**, **771** and **772**.



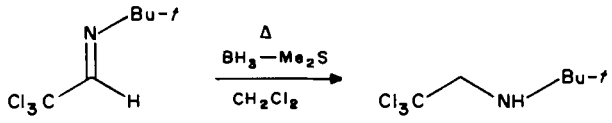
80%

(768) (769)



95%

(770) (771)



89%

(374) (772)

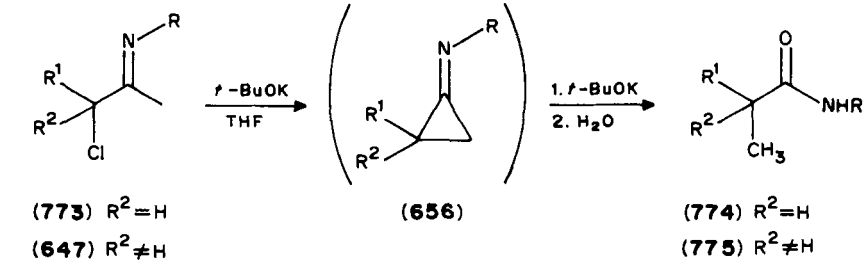
E. Rearrangements of α-Halogenated Imino Compounds

1. *The Favorskii-type rearrangement*

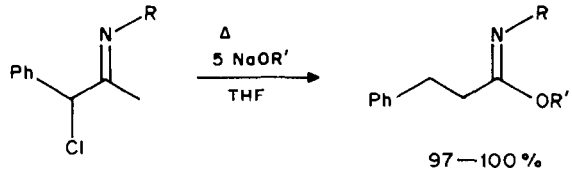
In recent years, the Favorskii rearrangement of α-haloimines has been well documented and a clear view of the scope and limitations of this reaction has been obtained[491,736]. α-Haloketimines are suitable substrates for a base-induced Favorskii rearrangement. They are less reactive than α-haloketones, owing to the lower electronegativity of nitrogen with

respect to oxygen. This certainly influences both possible Favorskii mechanisms in that the cyclopropanone mechanism would be influenced by the reduced acidity of the α-hydrogens while the weaker electrophilic character of the imino function would have an impact on the semibenzilic-type mechanism.

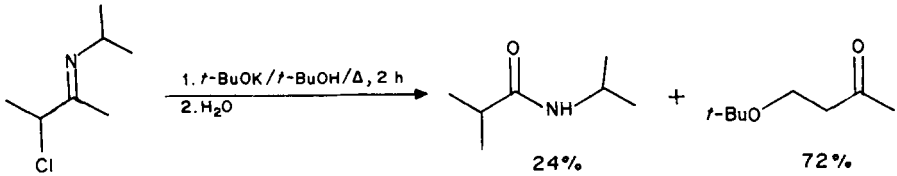
Although *N*-alkyl-α,α-dichloromethylketimines (**46**) undergo substitution with alkoxides in the corresponding alcohols to α,α-dialkoxyketimines[80], the reaction of the aliphatic *N*-alkyl-α-monochloroketimines **773** ($R^2 = H$) and **647** ($R^2 \neq H$) with potassium *tert*-butoxide in THF but not with other base–solvent systems (e.g. sodium methoxide in diethyl ether, diisopropyl ether, THF or DABCO in THF or benzene) afforded the branched carboxylic amides **774** and **775**, respectively[491,631]. *N*-Alkyl-α-chloro-α-phenylketimines (**776**) reacted with a five-fold molar excess of sodium alkoxides in tetrahydrofuran to provide non-branched rearranged carboxylic imidates (**777**) in nearly quantitative yield[491,631]. In a more polar medium, *N*-(3-chlorobut-2-ylidene)isopropylamine (**778**) gave with potassium *tert*-butoxide in *tert*-butanol a 1:3 mixture of the Favorskii amide **779** and 4-*tert*-butoxybutan-2-one (**780**), the latter resulting from an elimination–addition and subsequent hydrolysis. Tertiary α-chloroketimines often showed competitive 1,2-dehydrochlorinations, and this reaction type is the main route for α-bromoketimines[491], except for cyclic and sterically hindered substrates[736]. The cyclic α-bromoketimine **781** and the bulky α-bromoketimines **279** reacted with potassium *tert*-butoxide in THF in a Favorskii manner, but the reaction could be intercepted at the stage of the 1,3-dehydrobromination product, i.e. the cyclopropylideneamines **782** and **280**[736]. The dibromo compound **783**, which did not occur as the imine, could be converted to the Favorskii amide **784** by treatment with 2,2,6,6-tetramethylpiperidine in acetonitrile or with silver oxide in dichloromethane[736].



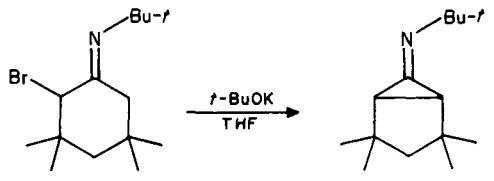
(773) R^2=H
(647) $R^2 \neq H$
(656)
(774) R^2=H
(775) $R^2 \neq H$



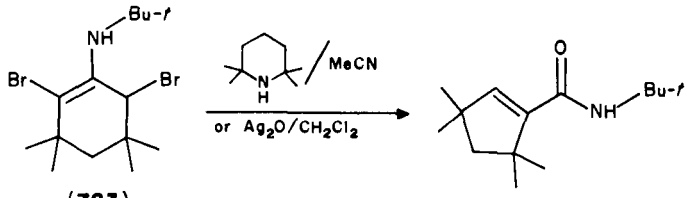
(776) R=*i*-Pr, c-Hex
97—100 %
(777)



(778)
24%
(779)
+
72%
(780)



(781) 60% (782)



(783) 16–25% (784)

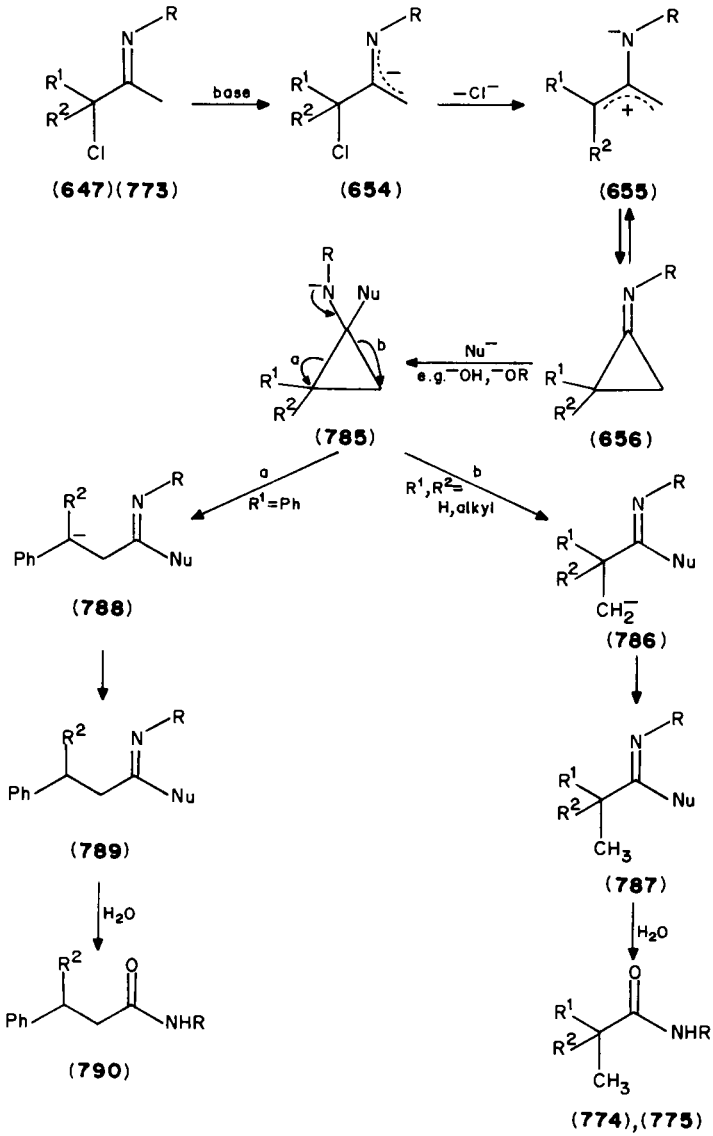
The mechanism of the Favorskii rearrangement of α-haloimines with bases into amides or imidates is explained analogously to the so-called cyclopropanone mechanism for α-haloketones[491]. The base abstracts an α′-proton from the α-chloroketimine to form a delocalized anion (**654**), which by loss of a chloride anion produces a zwitterion (**655**). This species might be viewed as being in equilibrium with the cyclopropylideneamine **656**, which undergoes a rapid addition across the strained imino function. The resulting adduct anion (**785**) opens giving the most stable carbanion. This feature explains the formation of the branched amides **774** and **775** from aliphatic α-haloimines and of linear imidates (**789**; Nu = OMe) or amides (**790**) from α-chloro-α-phenylketimines.

Evidence was presented for the exclusion of the alternative semibenzilic-type mechanism[491]. The reaction of the α-chloromethylketimine **791** with potassium *tert*-butoxide in THF afforded, after aqueous workup, a mixture of a rearranged amide (**792**) and 1-*tert*-butoxypentan-2-one (**793**). The semibenzilic rearrangement of **791** would involve addition of *tert*-butoxide across the imino function (giving **795**), followed by regeneration of an imino moiety and concomitant migration of the propyl group with expulsion of the chloride anion. This process would provide the linear amide **797** (or the imidate **796**), which was not isolated. Instead, the isolation of the branched amide **792** was sufficient to establish the cyclopropylideneamine mechanism via **794** as the operating process.

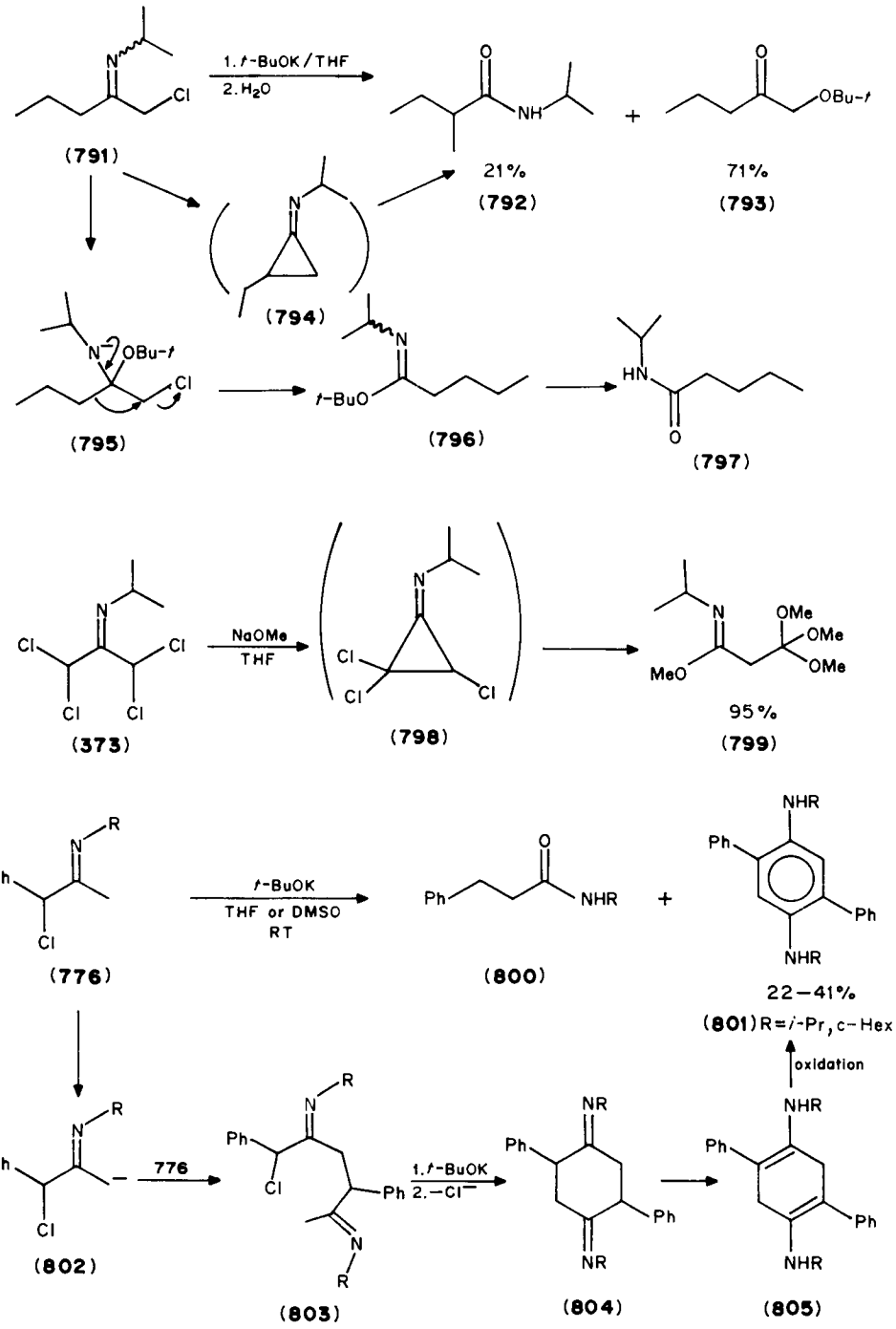
Further support for the proposed mechanism is the reaction of tertiary *N*-alkyl-α-chloroketimines (**647**) with potassium cyanide in methanol, which afforded 1-(alkylamino)cyclopropanecarbonitriles (**649**) together with the major product, α-cyanoaziridines (**648**)[633,634,698]. The formation of these geminally substituted cyclopropanes (**649**) was discussed earlier.

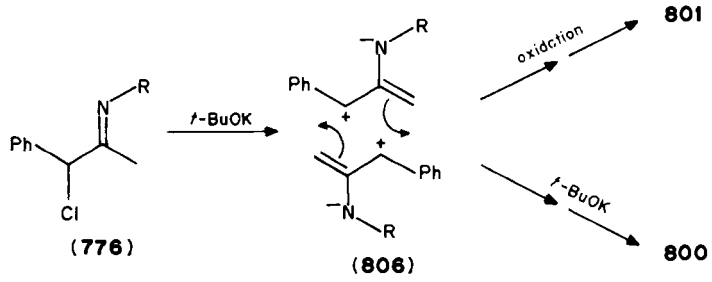
The acidity of the α′-hydrogens in the starting material is a major limiting factor in the Favorskii rearrangement. Lowering this acidity by alkyl substitution reduced the tendency for the rearrangement[491,736].

The Favorskii rearrangement is not limited to mono- and dichloroketimines. The tetrachloroketimine **373** reacted with excess sodium methoxide in THF to afford the ortho ester **799** in 95% yield[491].

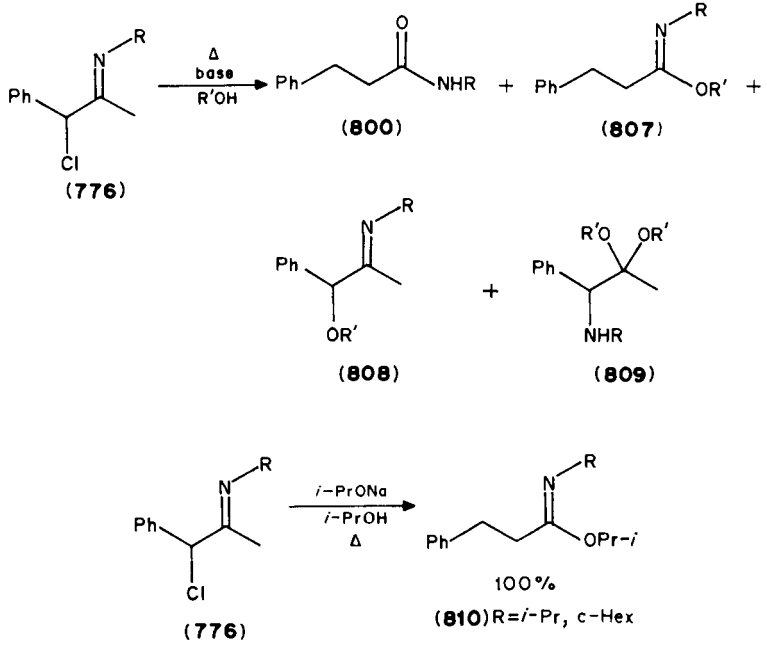


An interesting side-reaction was observed during the reaction of the α-chloro-α-phenylketimines **776** with potassium *tert*-butoxide in THF or DMSO[491]. In addition to the expected Favorskii amide (**800**), *N*,*N*′-dialkyl-2,5-diphenyl-*p*-phenylenediamines (**801**) were also formed. Formation of these condensation products was ascribed to intermolecular nucleophilic substitution of the doubly activated chloride (**776**) by the α′-anion (**802**), followed by an analogous ring closure which furnished the aromatic **801** after an additional air oxidation. An alternative mechanism for the generation of **801** via formation of the zwitterion **806** and subsequent cyclocondensation was also considered[491].

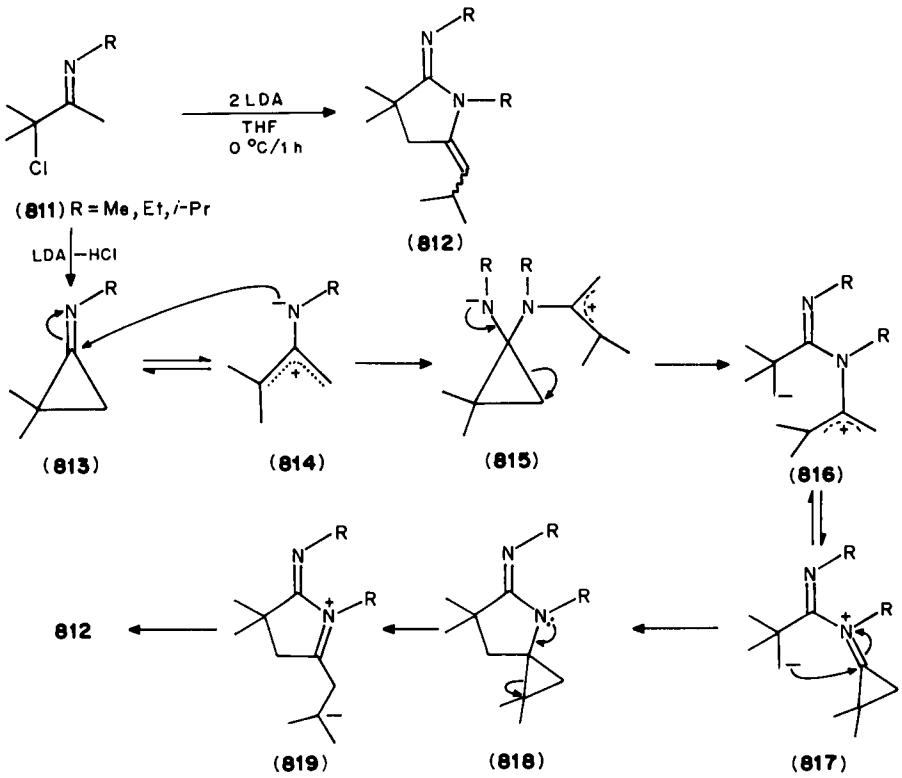

1. t-BuOK / THF
2. H2O
(791)
21%
(792)
71%
(793)
(794)
(795)
(796)
(797)
NaOMe
THF
(373)
(798)
95%
(799)
t-BuOK
THF or DMSO
RT
(776)
(800)
22–41%
(801) R = i-Pr, c-Hex
oxidation
776
1. t-BuOK
2. −Cl⁻
(802)
(803)
(804)
(805)



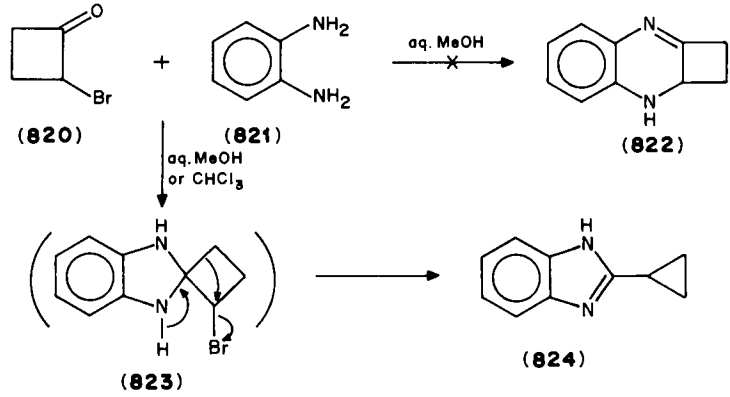
Other types of side-reactions were found when **776** were reacted with bases (sodium methoxide, triethylamine, potassium hydroxide) in alcohols[491]. The Favorskii amide **800** and the imidate **807** were the main products but were always accompanied by the substitution product **808** and the rearranged acetal **809**. The extent of substitution increased on increasing the concentration of sodium methoxide in methanol, whereas the extent of Favorskii rearrangement was independent of the base concentration. Formation of **808** and **809** could be eliminated by using hindered alkoxides, such as sodium isopropoxide in isopropyl alcohol[491].



1,3-Dehydrochlorination of the α-chloroketimines **811** with lithium diisopropylamide in THF led to non-isolable cyclopropylideneamines (**813**), which underwent self-condensation to cyclic amidines (**812**)[737]. It was proposed that the dimerization of **813** passed via an abnormal opening of a functionalized cyclopropane (**818**). 1,3-Dehydrochlorination of chloroindolenines was also considered as a possible explanation for some rearrangements, but was finally rejected[738].

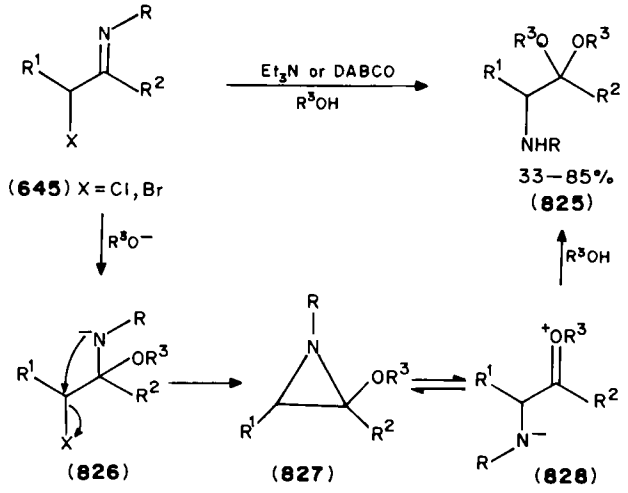


In view of the suggested mechanism of the Favorskii rearrangement, it is worth noting that 2-bromocyclobutanone (**820**) with *o*-phenylenediamine (**821**) gave the ring-contracted compound **824**[739], although it was previously reported that the reaction gave the tricyclic heterocycle **822**[740,741]. The intermediate **823** rearranged in a semibenzilic-type manner to the cyclopropane derivative **824**, and this is probably the first example of a Favorskii-type rearrangement of a transient α-haloimine. In this way, α-haloimino chemistry parallels α-haloketone chemistry because α-halocyclobutanones usually give Favorskii rearrangements via a semibenzilic-type mechanism[354].



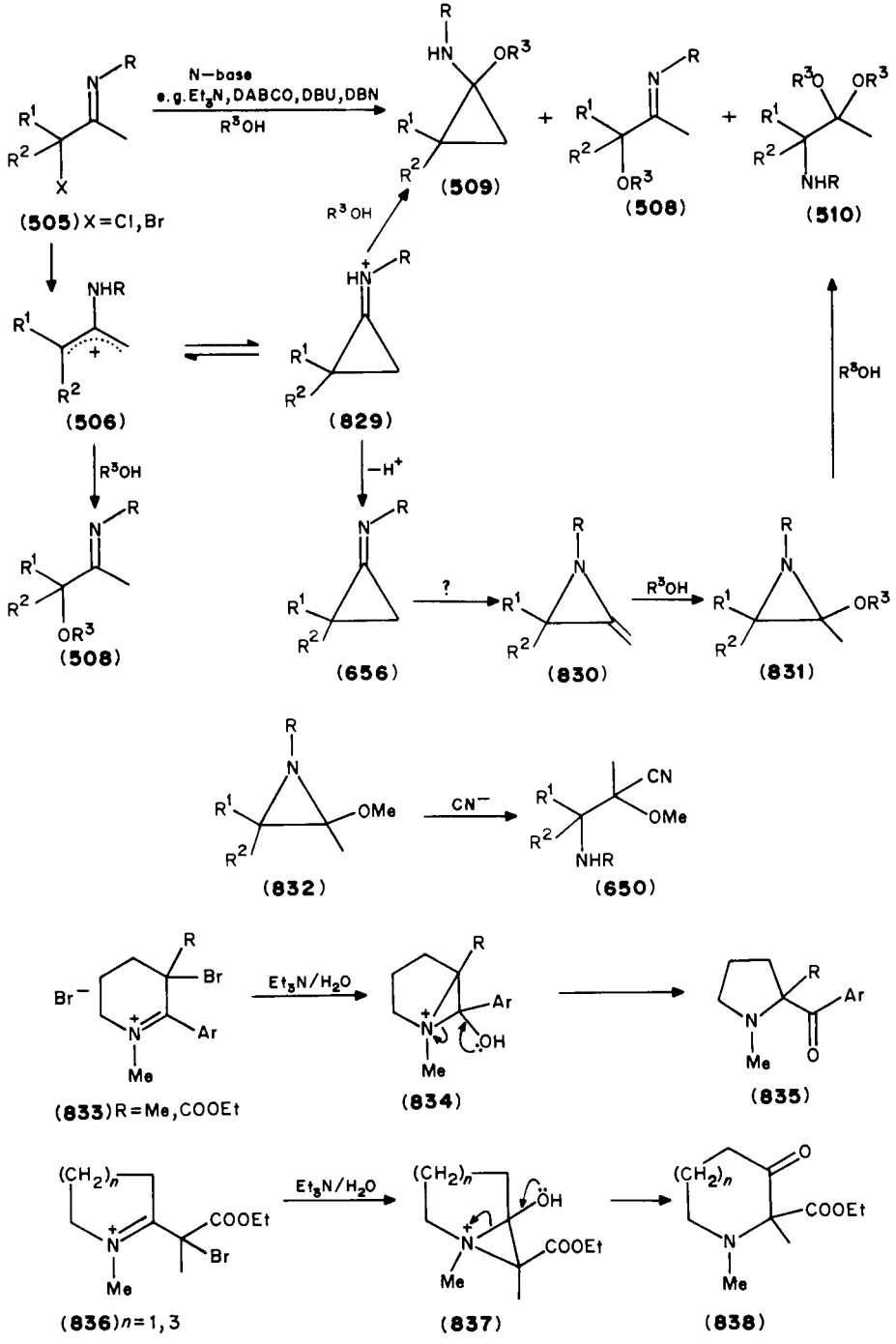
2. Rearrangement of α-halogenated imines via activated aziridine intermediates

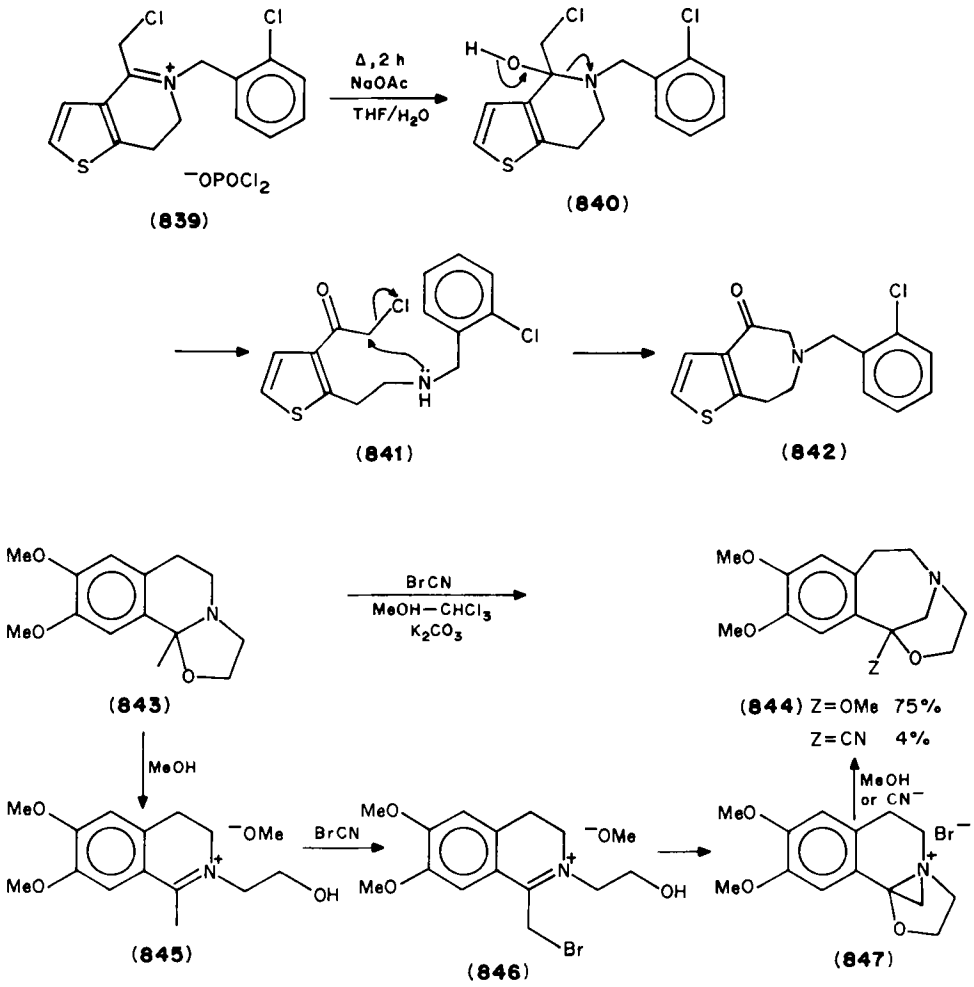
α-Halomethylketimines and alkoxides in alcoholic medium gave mainly nucleophilic substitution[493], but the secondary α-haloketimines **645** readily rearranged into α-(alkylamino)acetals (**825**) via the intermediacy of α-alkoxyaziridines (**827**)[742]. The acetals **825** are valuable synthons in heterocyclic chemistry and are viewed as protected α-aminoketones. In contrast, the tertiary α-chloroketimines **505** give only low yields of α-(alkylamino)acetals since the major reaction with nitrogen bases in alcohols is cyclopropanation and, to a minor extent, alcoholysis[632]. Geminally functionalized cyclopropanes (**509**), obtained in up to 80% yield, and α-alkoxyketimines (**508**) were formed via the intermediacy of 2-alkylaminoallylcarbenium ions (**506**), but possible interconnections with the formation of α-(alkylamino)acetals (**510**) via valence tautomerism of cyclopropylideneamines (**656**) were also considered[632]. When cyanide was present in the methanolic medium, the tertiary α-chloroketimines **647** mainly gave α-cyanoaziridines (**648**) and cyclopropanecarbonitriles (**649**) and minor amounts of β-alkylamino-α-methoxynitriles (**650**)[634]. The latter rearranged compounds indicated that intermediate α-methoxyaziridines (**832**) were more readily trapped by cyanide than by methanol[634].



α-Halogenated immonium halides are reactive substrates and nucleophile-induced reactions most often proceed via initial nucleophilic addition across the iminium bond. Rearrangement of the α-bromoimmonium bromides **833** and **836**, synthesized by bromination of the corresponding enamines, with aqueous triethylamine gave access to the ring-contracted pyrrolidines **835** or the ring-expanded heterocycles **838**, respectively[743,744]. The intermediacy of α-hydroxyaziridines **834** and **837**, which rearranged into **835** and **838**, is a likely possibility. However, an alternative mechanism involving ring opening and subsequent intramolecular nucleophilic substitution was suggested for the conversion of 6,7-dihydrothieno[3,2-*c*]pyridinium derivative **839** into 6-(2-chlorobenzyl)-5,6,7,8-tetrahydrothieno[2,3-*d*]-azepin-4-one (**842**)[745].

A peculiar rearrangement converts the heterocyclic compound **843** with cyanogen bromide in methanol–chloroform into 1-substituted-9,10-dimethoxy-3,4,6,7-tetrahydro-1*H*-1,5-methano-2,5-benzoxazonines (**844**). Suggested intermediates are the α-bromoimmonium derivative **846** and the α-alkoxy-substituted aziridinium derivative **847**, which was ring opened by cyanide or methanol[746].

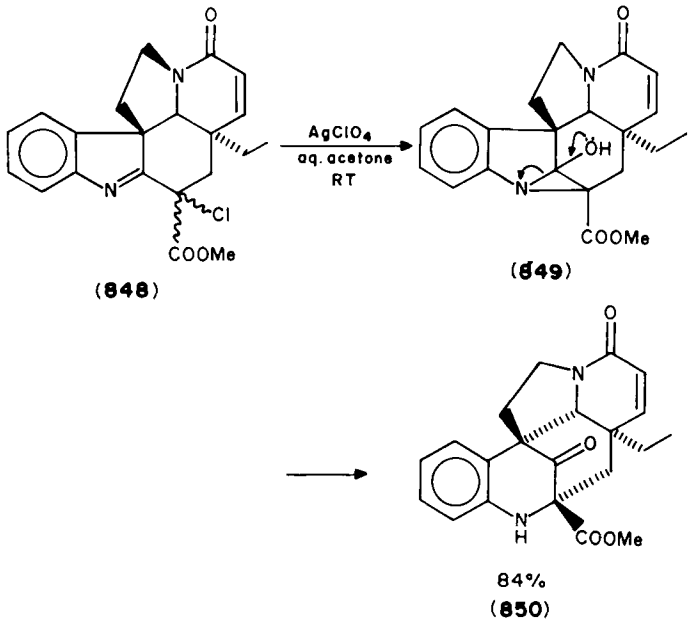

N–base
e.g. Et3N, DABCO, DBU, DBN
R3OH
(505) X = Cl, Br
(506)
(509)
(508)
(510)
(829)
R3OH
–H+
(508)
(656)
?
(830)
R3OH
(831)
(832)
CN–
(650)
Et3N/H2O
(833) R = Me, COOEt
(834)
(835)
Et3N/H2O
(836) n = 1, 3
(837)
(838)



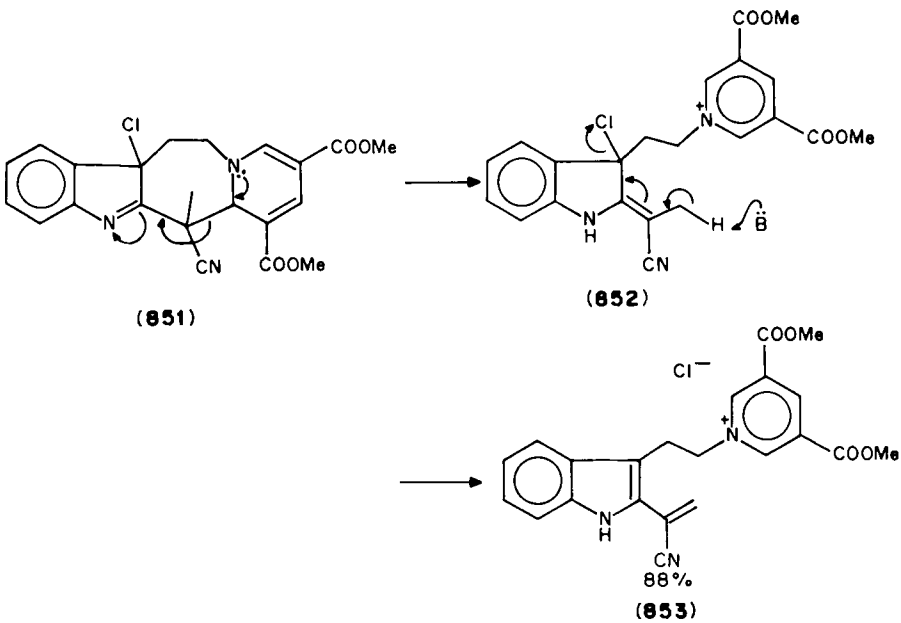
Some rearrangements of α-chloroindolenines to compounds which underwent ring expansion of the indolenine five-membered ring into a 3-piperidone moiety (see **850**) can also be explained via transient α-hydroxyaziridines (e.g. **849**). These rearrangements have been effected on chloroindolenines derived from 3-oxotabersonine (**848**)[566], tabersonine[747], 1-dehydrovincadifformine[748] and 1-dehydrotabersonine[749] by using silver salts, dilute sulphuric acid, aqueous acetic acid or hydroxylic solvents, respectively.

3. *Rearrangement of chloroindolenine derivatives*

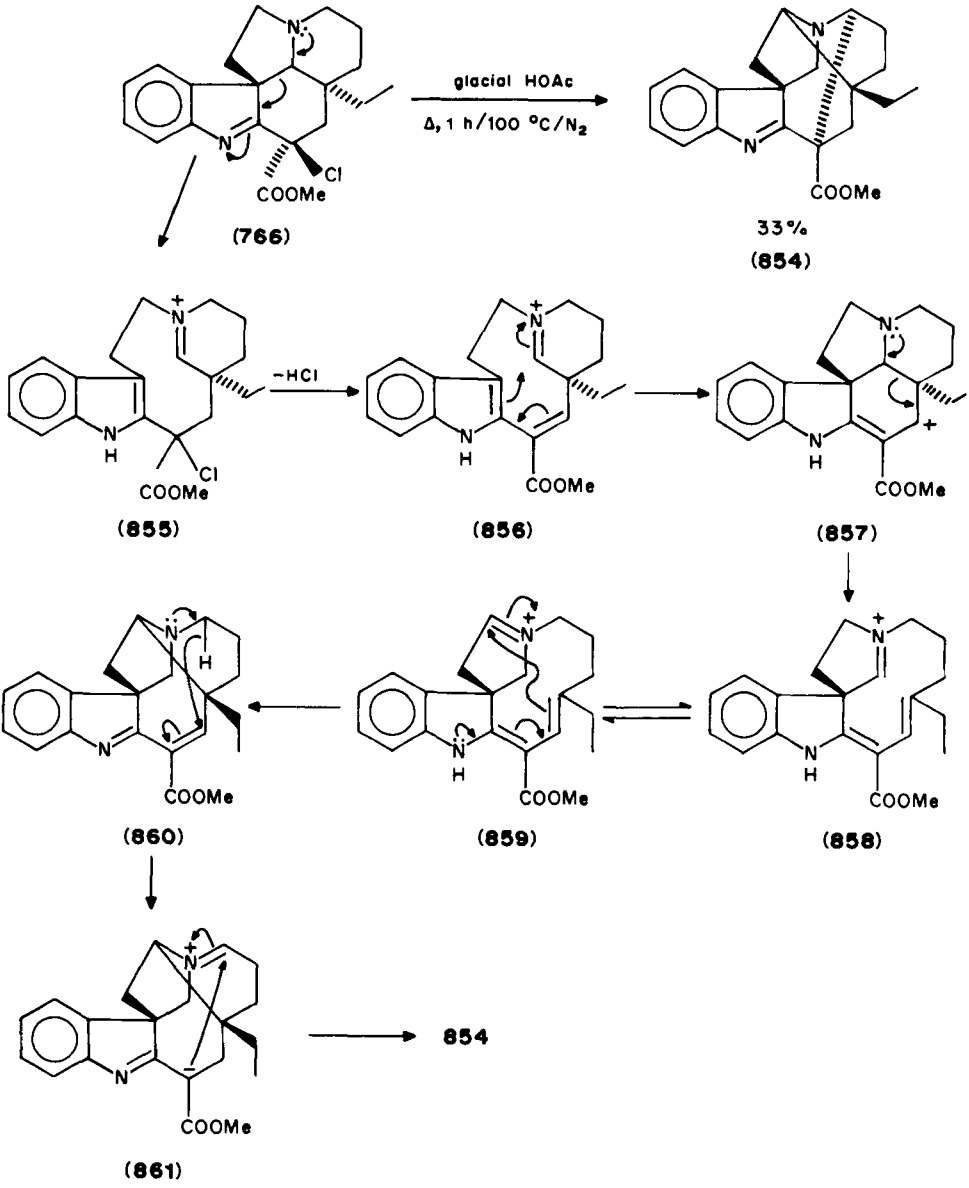
The classical rearrangements of chloroindolenines derived from alkaloids such as deserpine, reserpine and yohimbine with hydroxide or methoxide in methanol were re-examined in detail. It was shown that the rearrangements into spiroimino ethers occurred in a stereospecific manner, i.e. chloroindolenines with an α-chloro atom produced α-spiroimidates whereas substrates with a β-chloro atom gave β-spiroimidates[738].



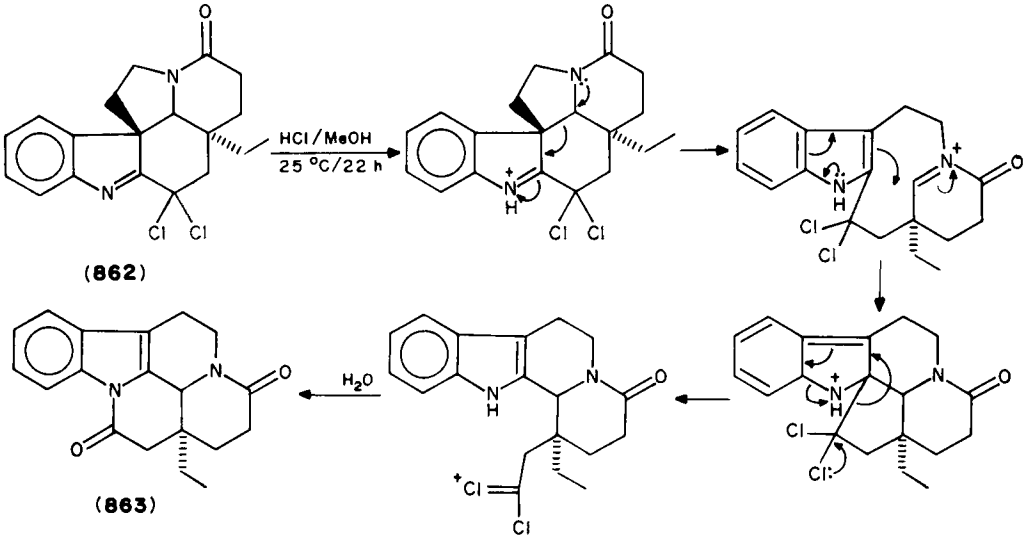
Neighbouring groups play an important role in the occurrence of rearrangements of chloroindolenines. The chloroindolenine **851**, obtained by chlorination of the corresponding indole with *tert*-butyl hypochlorite in dichloromethane, underwent spontaneous rearrangement into the pyridinium salt **853**[562].



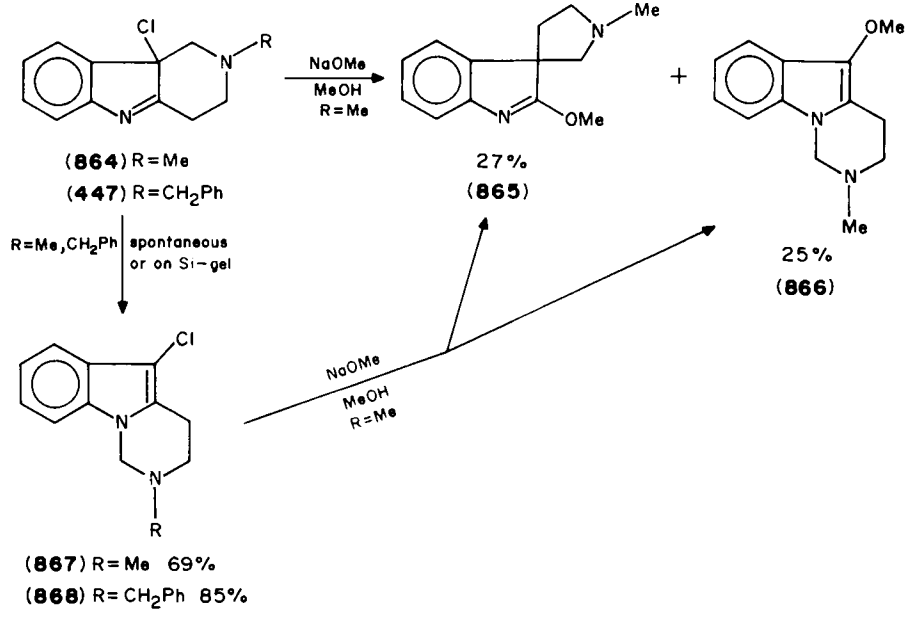
In contrast to the rearrangement of 16-chloro-1-dihydrovincadifformine (**766**) in aqueous acetic acid at room temperature (see Section III.E.2)[748], the rearrangement in glacial acetic acid at 100 °C produced 33% of rearranged compound **854** with a novel skeleton, in addition to 9% of the acetoxy substitution product[750]. The rearrangement was initiated by dehydrochlorination of a ring-opened intermediate (**855**) to **856**. This was followed by an amazing set of ring closures and openings of immonium species which furnished **854**.



The α,α-dichloroimine **862** rearranged with methanolic hydrogen chloride to 19-oxoeburnamonine (**863**) in 95% yield[751]. Again, the neighbouring amide nitrogen initiated the ring opening and afforded **863** after appropriate bond reorganization.

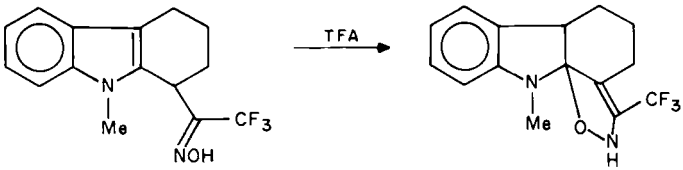


Finally, the rearrangement with sodium methoxide of the chloroindolenine **864** to the spiroimidate **865** was accompanied by the rearranged aminal **866**[127]. The chloroindolenines **864** and **447** rearranged spontaneously or after chromatography on silica gel into the aminals **867** and **868**, from which **865** and **866** were derived[127,563].

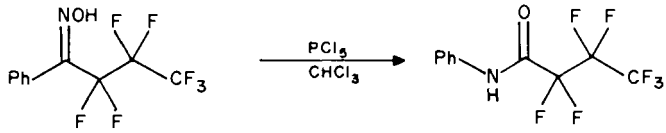


4. Beckman rearrangements of α-halogenated oximes

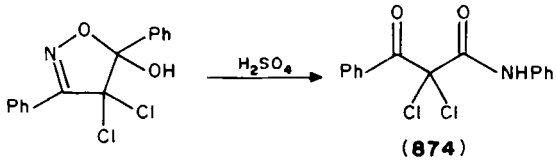
Beckman rearrangements of α-halooximes remain rare. The attempted Beckman rearrangement of the α, α, α-trifluorooxime **869** in trifluoroacetic acid yielded instead the tetracyclic heterocycle **870**[752], but aromatic α-perfluoroketoximes, such as **871**, and some aliphatic analogues rearranged into *N*-substituted α-perfluorocarboxamides (e.g. **872**) by treatment with PCl_5 in chloroform[753]. Further examples were reported for the α, α-dichlorooxime derivatives **873**[754] and **875**[755], which provided the corresponding α, α-dichlorocarboxamides **874** and **876**, respectively.



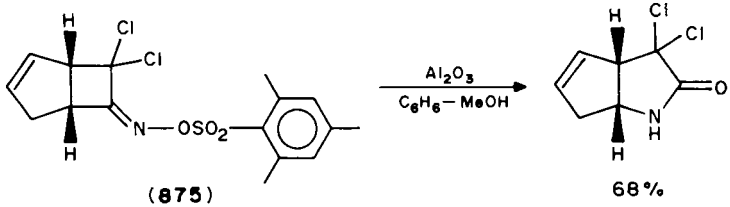
(869) (870)



(871) (872)



(873) (874)

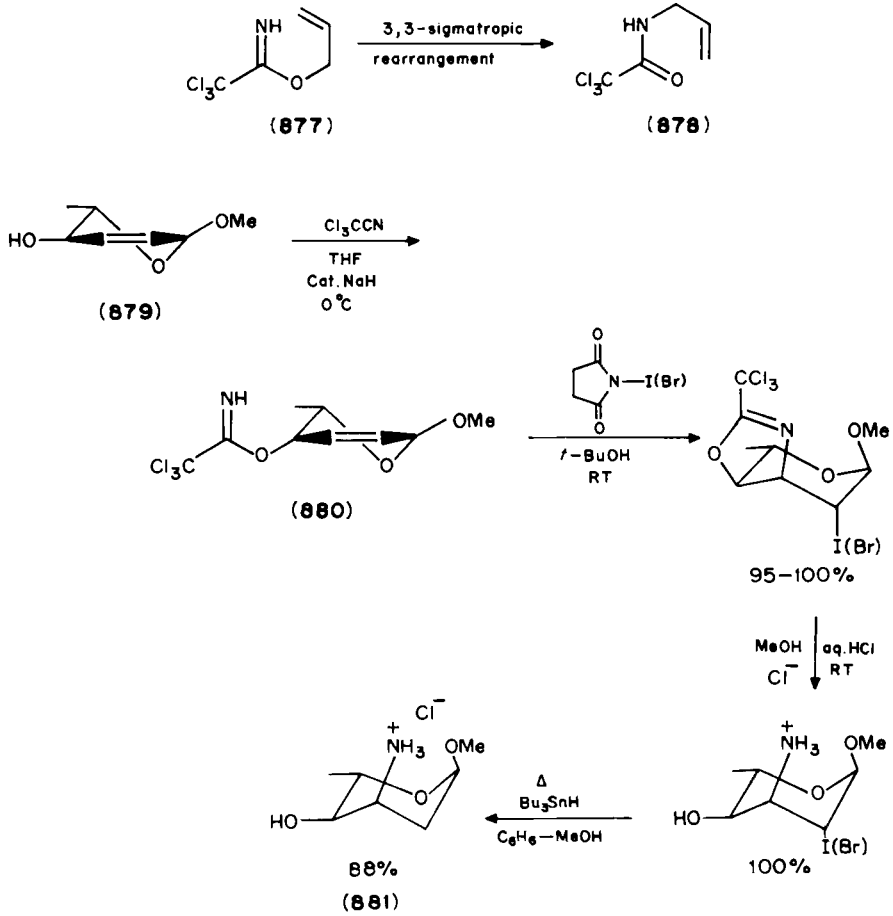


(875) 68% (876)

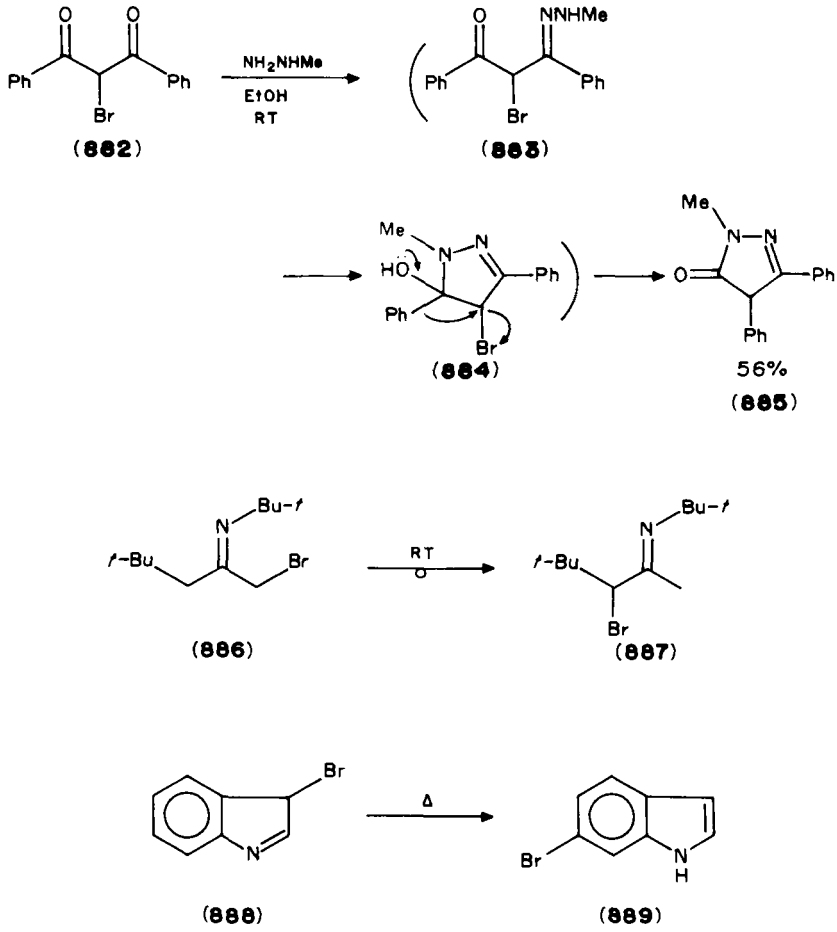
5. Other rearrangements of α-halogenated imines

Although α-haloimidates are not treated in detail in this review, it is useful to mention that allylic trichloroacetimidates (**877**) and propargylic trichloroacetimidates are valuable synthons because of their potential to give allylic amides (**878**) and dienic amides via a 3, 3-sigmatropic rearrangement[425]. Various extensions[756] have emerged since the publication

of a review on this topic[425], and trichloroacetimidates also proved especially useful in glycosyl transfers[757], iodoaminations[758–760,825] and aminations[761], in the phosphorylation of polyprenols[762] and as benzylating reagents[763]. Further, the use of trichloroacetimidates has been fully exploited in the synthesis of methyl α-L-ristosaminide (**881**)[761], *O*-α- and *O*-β-glycosylimidates[764,765], α-aminocarboxylic acids[766], vinylglycine[767], (±)-*erythro*-sphingosine triacetate[760], sphingamine triacetate[825] and amino sugars[768].



In addition to the rearrangements of trichloroacetimidates, some other reactions of α-haloimino compounds involving skeletal rearrangement and rearrangements of the halide can be mentioned. The reaction of 2-bromo-1,3-diphenylpropane-1,3-dione (**882**) with methylhydrazine in ethanol produced 1-methyl-3,4-diphenyl-2-pyrazoline-5-one (**885**) via the α-bromohydrazone **883**, ring closure to **884** and subsequent halohydrin rearrangement[769]. Certain α-haloketones are known to rearrange to the isomeric α′-haloketones. The only example of an analogous reaction of α-haloketimines is the slow rearrangement of the α-bromomethylketimine **886** at room temperature to an equilibrium mixture with the isomeric **887**[736]. Another type of halogen migration is the thermal rearrangement of the labile bromine atom in 3-bromoindolenine (**888**) into 6-bromoindole (**889**)[635].

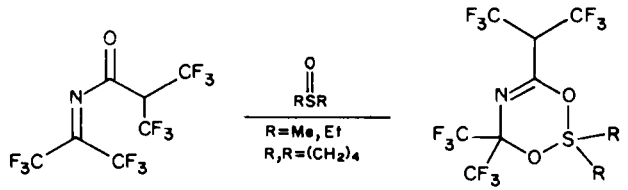


(882) (883) (884) (885) (886) (887) (888) (889)

F. Cycloadditions

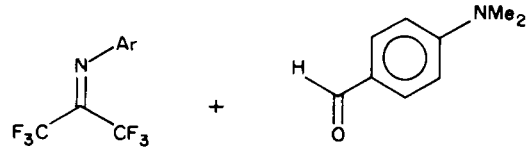
Many examples of cycloadditions of α-haloimino compounds in which they react as dienophile or heterodiene in Diels–Alder-type reactions ([4 + 2]cycloadditions) have been found in recent years. In addition, a rich heterocyclic chemistry has evolved from cycloadditions of α-haloimines in a [2 + 2], [4 + 1], [3 + 2] or [2 + 1] mode. Generally these reactions involve α-polyhaloimines (mainly α-perfluoro derivatives) having an electron-withdrawing activating substituent on the nitrogen atom, such as alkoxycarbonyl, acyl, thioacyl or imidoyl.

The potential of Diels–Alder-type cycloadditions in which the imino bond of α-haloimines acts as a dienophile have been recognized for a long time in heterocyclic synthesis[501,770]. However, most developments in [4 + 2]cycloadditions have been achieved with α-perfluoroimines having a heterodiene structure. Cycloadditions of these *N*-activated α-fluorinated imines included reactions with nitriles[771,772], aromatic aldehydes[771], tetracyanoethene[773], *N*-cyanoamines[774], sulphoxides (e.g. the conversion of the *N*-acylimine **890** into the dioxathiazines **891**[775]) and alkynes[776].

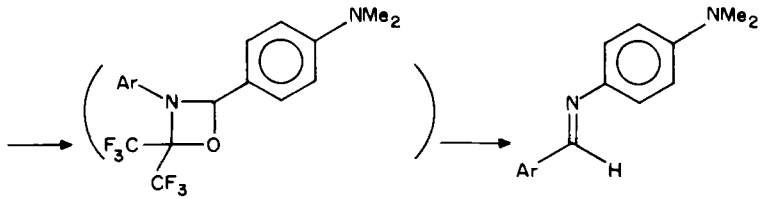


(890) (891)

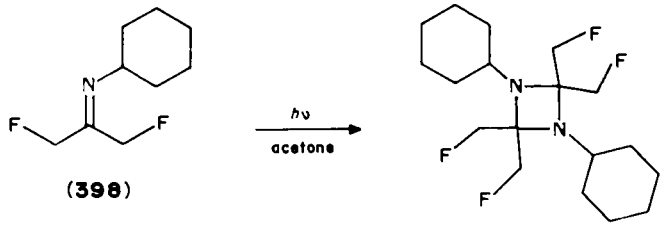
[2 + 2]Cycloadditions remain rare, but this reaction occurred between the *N*-arylhexafluoroacetone imine **892** and 4-(dimethylamino)benzaldehyde (**893**). The resulting 1,3-oxazetidine **894** decomposes into hexafluoroacetone and the aldimine **895**[771]. However, the α,α'-difluoroketimine **398** could be photochemically dimerized into the diazetidine **896**[504].



(892) Ar = 4-$NO_2C_6H_4$ (893)



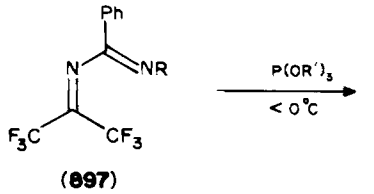
(894) (895)



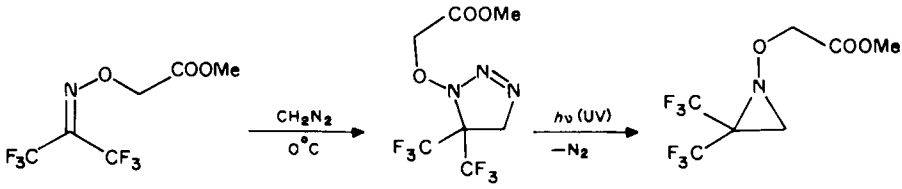
(398) (898)

[3 + 2]Cycloadditions with 1,3-dipolar compounds, e.g. nitrile oxides, have only rarely been reported[501], but the construction of five-membered heterocycles via cyclocondensation of *N*-activated imines (heterodiene structure) with carbenes[771] and phosphites[777,778] [e.g. the synthesis of the new heterocycles 2,2-dihydro-1,4,2-diazaphosphol-4-enes (**898**) from **897**] is an alternative route. Diazomethane has often been reacted with α-perhaloimines to afford five-membered heterocycles, i.e. triazolines[501,614,779,780], which

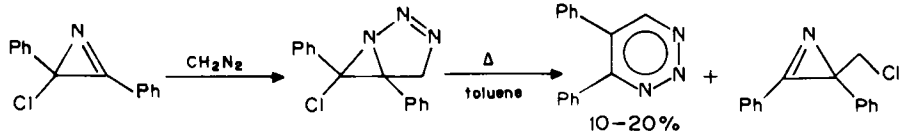
were precursors of aziridines[779,780]. An example is the synthesis of the triazoline **900** from the α-perfluorooxime ether **899** and photochemical expulsion of nitrogen to give the aziridine **901**, which was separated into its two optically active antipodes[780]. The cycloaddition of *N*-tosyl chloral imine with 2,2,2-trifluoroethyldiazomethane also furnished the corresponding pyrazoline[728] but the cycloadduct **902** of diazomethane and the chloroazirine **685** rearranged thermally into the 1,2,3-triazine **903**, the azirine **904** and traces of acetophenone and benzamide[781].



(897) (898)

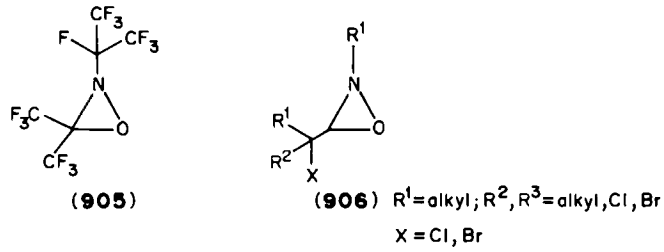


(899) 71% (900) 88% (901)



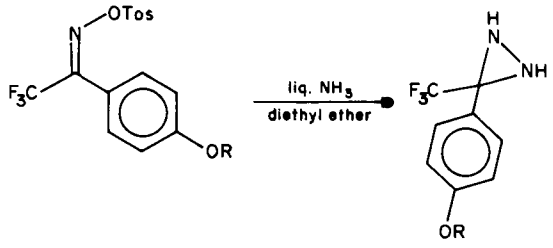
(685) (902) 10–20% (903) (904)

Three-membered oxaziridines (**905**[782] and **906**[493]) are accessible via epoxidation of a perfluoroketimine or α-halogenated aldimines with caesium carbonate–chlorine or *m*-chloroperbenzoic acid, respectively.



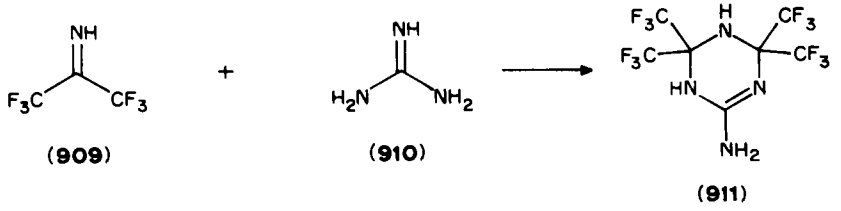
(905) (906) R^1=alkyl; R^2, R^3=alkyl, Cl, Br; X = Cl, Br

Diaziridine formation (cf. **908**) could be accomplished by reaction of *O*-tosyl oximes, e.g. **907**, with functionalized primary amines[599], ammonia[516] and α-amino acid esters[783].



(907) (908)

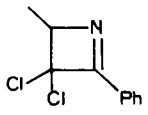
Finally, special types of cyclocondensations involve the reaction of hexafluoroacetone imine (**909**) with guanidine (**910**), affording the heterocycle **911**[784], the reaction of the azetine **912** with diphenylketene (**913**) giving the 1:2 adduct **914**[785], and the reaction of perfluoroacetone azine (**915**) with norbornadiene (**916**) yielding adduct **917**[786].



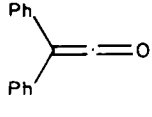
(909)

(910)

(911)



(912)



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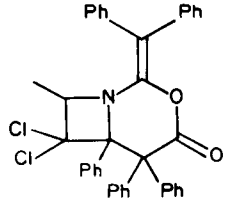

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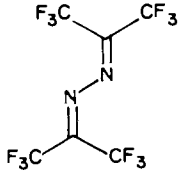

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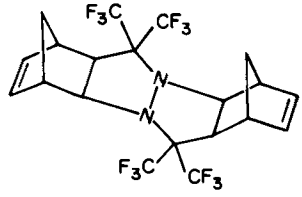


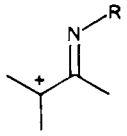
75%

(917)

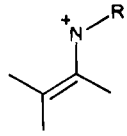
G. Generation of α-Imidoylcarbenium Ions from α-Halogenated Imines

There has been increasing interest in the intermediacy of highly electron-deficient carbenium ions. As a result, it has been recognized that carbenium ions, substituted with electron-withdrawing groups, are not necessarily as unstable as previously thought. A review covers the chemistry of the long neglected α-acylcarbenium ions[427], while

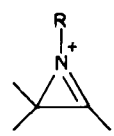
numerous studies have focused on carbenium ions substituted with cyano, alkoxycarbonyl, dialkoxyphosphoryl and other electron-withdrawing groups[787,788]. The nitrogen analogues of α-acylcarbenium ions, i.e. α-imidoylcarbenium ions (**918**), have not been treated extensively in the older literature, but in the 1980s the gap in this area has been filled. The resonance stabilization of the latter species should be considerable, but it is coupled with an important inductive destabilization. Therefore, it seems appropriate to consider the tautomeric vinylnitrenium ions **919** and the bridged azirinium ions **920** also in this context. *Ab initio* calculations revealed that the unsubstituted azirinium ion ($C_2H_4N^+$) is more stable than the corresponding α-formimidoyl carbenium ion[789–791]. The conclusion is that α-imidoylcarbenium ions exist in a bridged structure, and that the energy difference between the planar and the bridged structures is much larger than that for the corresponding α-acylcarbenium ions[791]. Compared with other σ-electron-withdrawing groups, the α-imidoyl substituent does not destabilize the carbenium ion and, therefore, α-imidoylcarbenium ions have to be considered as potentially useful synthetic intermediates.



(**918**)



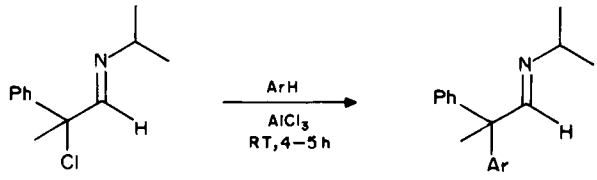
(**919**)



(**920**)

Several reports, especially before the 1980s, have hesitatingly suggested α-imidoylcarbenium ions as reaction intermediates, but most of them concerned ring opening of azirines[792–799]. Another source of α-imidoylcarbenium ions and the bridged azirinium ions are reactions of α-halogenated aziridines[346,537,735,800], which spontaneously ionize and react further with the nucleophiles present in the medium. It was also proposed that α-aryloxyoximes react with alcoholic hydrogen chloride to give α-alkoxy-α-aryloxyketones via the intermediacy of α-imidoylcarbenium ions[801].

α-Haloimines have been shown to be good precursors of α-imidoylcarbenium ions or their isomeric or tautomeric ionic structures. Simple ionization of the carbon—halogen bond assisted by reagents such as silver salts and aluminium(III) chloride provides a route to these species. α-Chloroaldimines, which could create a more stable α-imidoylcarbenium ion, reacted under Friedel–Crafts conditions with aromatic compounds, e.g. benzene, toluene or xylene, to give α-arylaldimines[802]. Aluminium(III) chloride was used as a condensation agent but boron(III) fluoride etherate gave similar results[493,802]. *N*-Isopropyl-α-chloro-α-phenylaldimine (**921**) reacted with aluminium trichloride in benzene or toluene at room temperature to yield α-arylaldimines (**922**)[802]. Aliphatic α-chloroaldimines were less reactive and required higher temperatures to induce arylation, but owing to the side-reaction of 1,2-dehydrochlorination the α-arylation yields never exceeded 50%[802]. The reaction of the α-chloroaldimine **923** with toluene led to 30% α-tolylaldimine, with a *para/ortho* ratio (**924:925**) of 93:7[493]. Only the α-phenylation of **923** showed a side-reaction from which 12% 1-isopropyl-3,3-dimethylindoline (**933**) resulted[802]. The α-arylation, the formation of the 1-azadienes **928** and the side-product **933** were all explained by the intermediacy of α-imidoylcarbenium ions (**927**). Loss of a proton from **927** provides **928**, while trapping of **927** with the aromatic nucleus (shown for benzene in the scheme) afforded **930**, which lost a proton to give the α-arylaldimines **931**. The σ-complex **930** can also be trapped by the weakly nucleophilic imino nitrogen to form **929**, which by a net shift of a double bond and deprotonation generates the indoline **933**. The last step can be visualized as occurring via deprotonation to an azomethine ylide (**932**) and a subsequent hydride shift[493].



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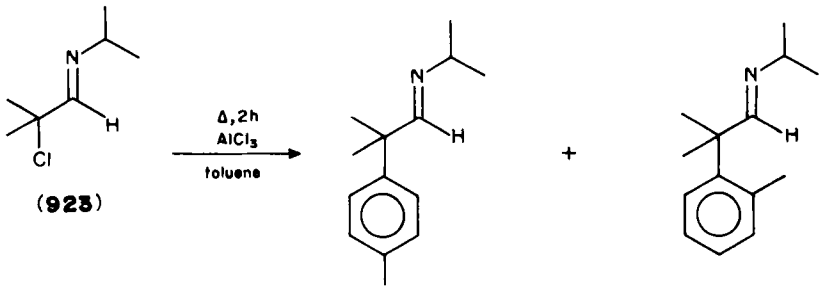

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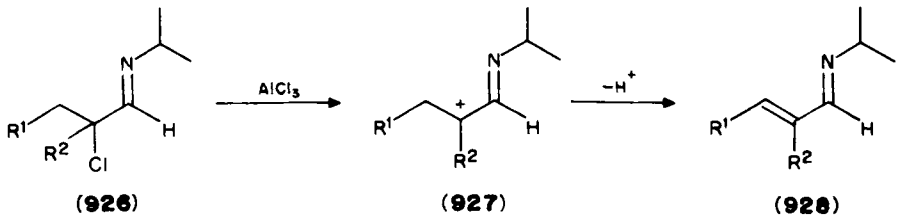
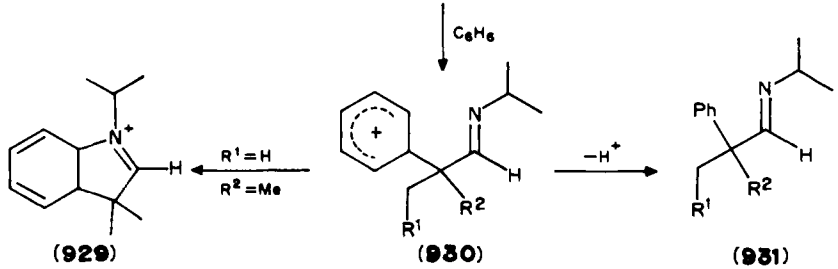
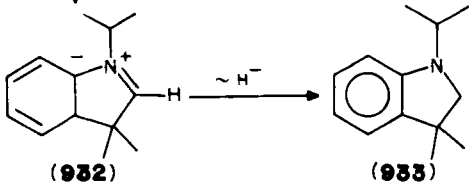


(926) (927) (928)

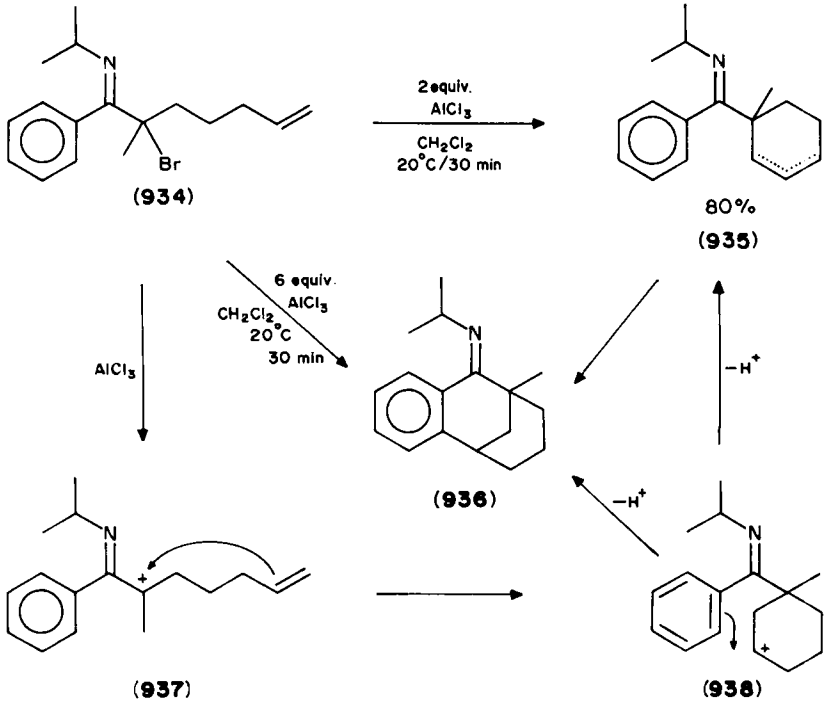


(929) (930) (931)



(932) (933)

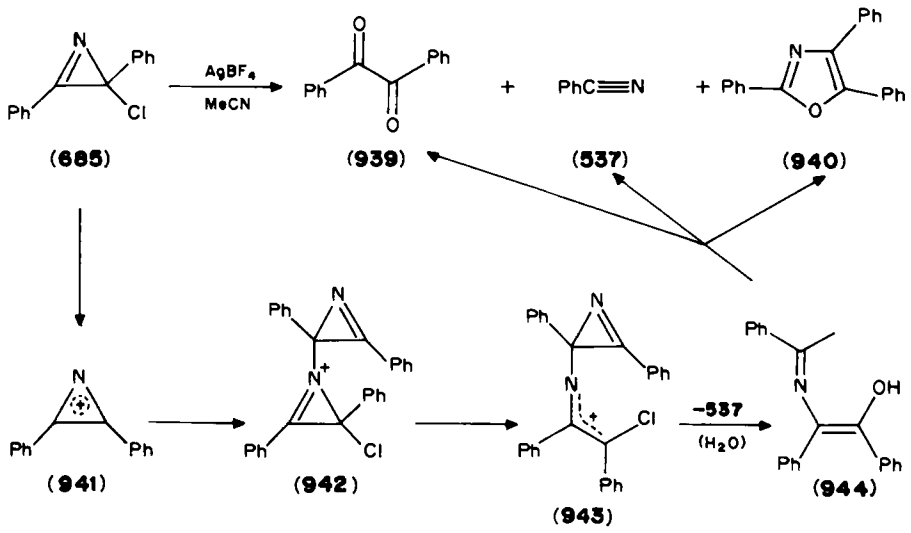
The usefulness of aluminium(III) chloride as an initiator for generating α-imidoylcarbenium ions was demonstrated by the conversion of the α-bromoketimine **934** into **935** or **936**, depending on the amount of Lewis catalyst used[803]. It is reasonable to assume that an intermediate α-imidoylcarbenium ion (**937**) is trapped by the olefin in an intramolecular fashion to give **938**, which loses a proton giving **935** or undergoes another electrophilic aromatic substitution giving **936**.

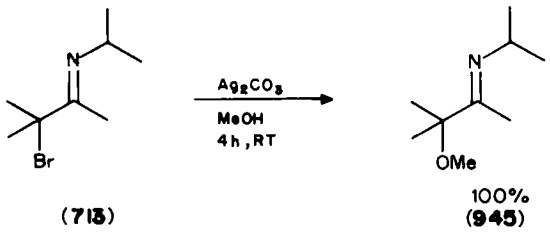


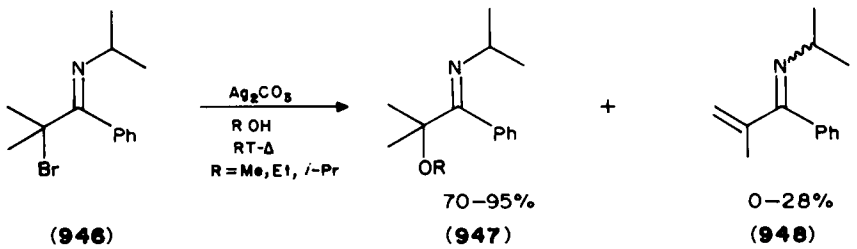
(934) (935) (936) (937) (938)

An alternative route to α-imidoylcarbenium ions consists of a silver salt-assisted ionization of the carbon—halogen bond of α-haloimines. Such ions were postulated to explain the silver-induced conversion of the chloroazirine **685** into the oxazole **940**, together with the dione **939** and benzonitrile[702]. In this particular case the ion **941** is already a bridged entity. Such azirinyl cations were also considered in explaining nucleophilic substitutions of 3-chloroazirines[642].

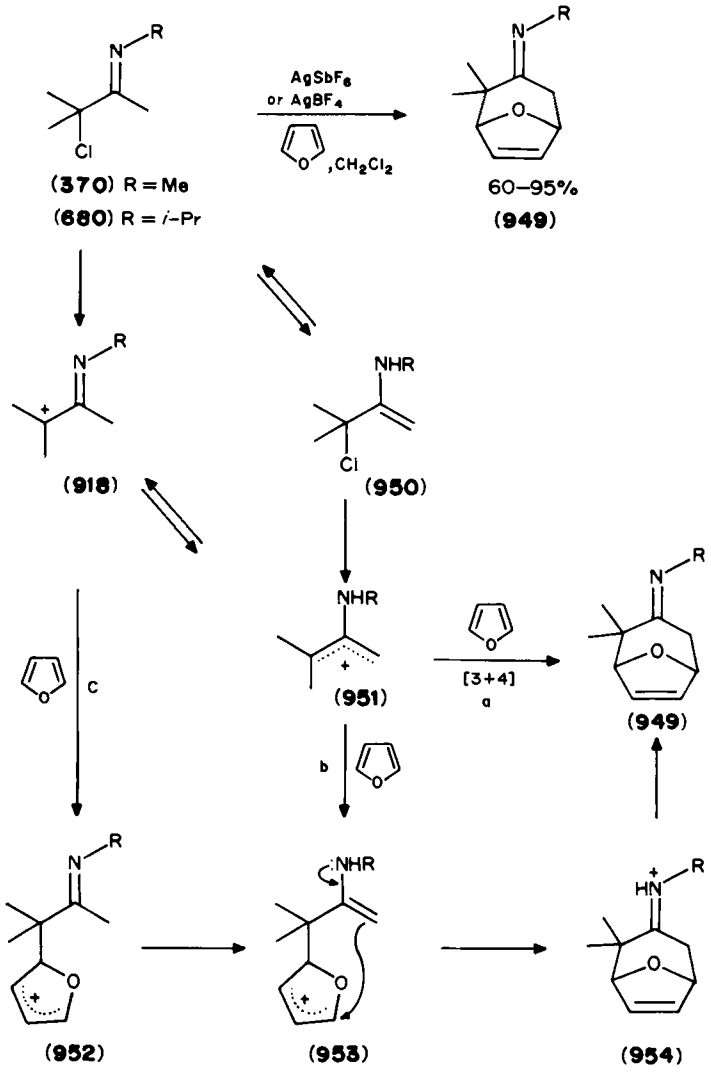
When silver salts were applied with simple α-haloimines in alcoholic solvents, the corresponding α-alkoxyimines were obtained, often accompanied by the 1,2-dehydrohalogenation product[493,494]. This α-alkoxylation of carbonyl compounds via α-haloimines and acidic hydrolysis is a useful method starting with precursors such as the α-bromoaldimine **511** and the aliphatic or aromatic α-bromoketimines **713** or **946**, but generalizations cannot be made as the structure of the starting α-haloimine determines the course of the reaction. For example, the α-bromoaldimine **669** was exclusively dehydrobrominated to the corresponding 1-azabutadiene when treated with silver carbonate in methanol[493]. These α-alkoxylations can be ascribed to alcoholysis of intermediate pseudo-α-imidoylcarbenium ions. This type of reaction was also observed during cyanation of α-haloimines in alcoholic medium in the presence of silver, copper or zinc ions[633,634].







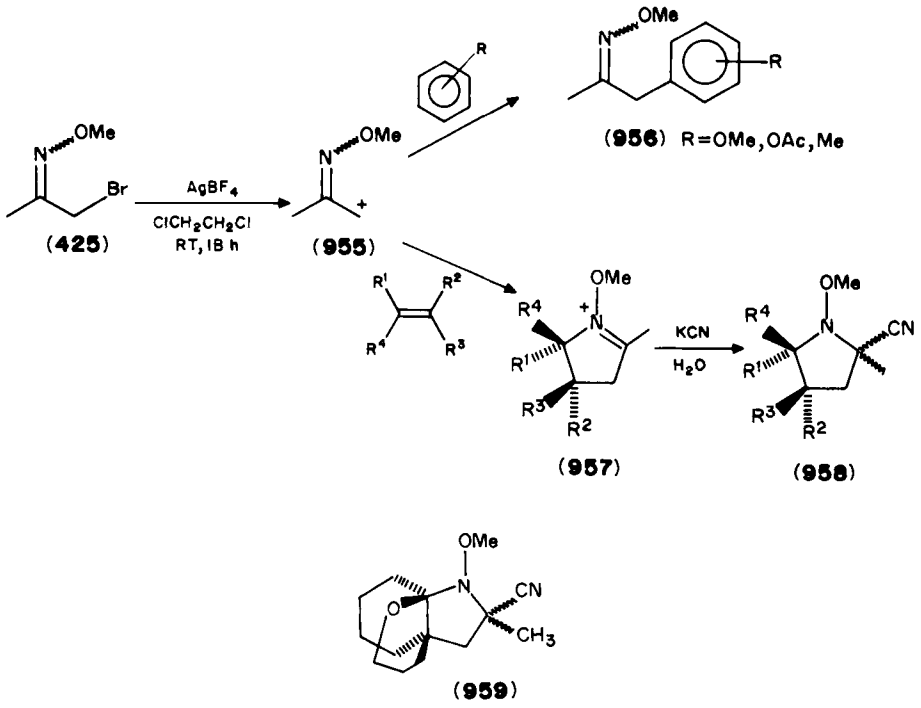
When the tertiary α-chloroketimines **370** and **680** were treated with silver tetrafluoroborate or silver hexafluoroantimonate in dichloromethane in the presence of furan, they afforded bicyclic adducts (**949**)[489]. 2-Aminoallylcarbenium ions (**951**) were postulated as intermediates, which were trapped by furan in a [4 + 2]-type cycloaddition to yield **949**. The cycloaddition could be either concerted (route a) or stepwise (route b), but route c via intermediacy of an α-imidoylcarbenium ion (**918**) should be considered as an alternative for the formation of **949**[489].

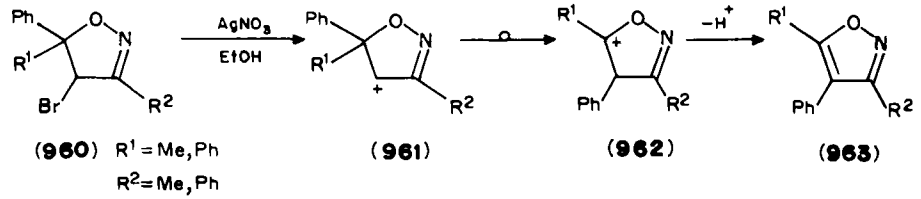


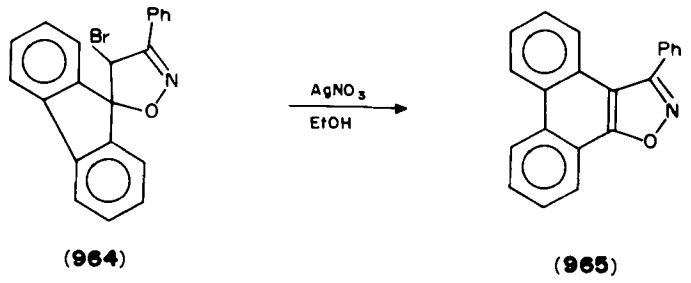
The α-bromooxime ether **425** was shown to be a source of an α-imidoylcarbenium ion. The reaction of **425** with silver tetrafluoroborate in 1,2-dichloroethane generated carbenium ion (**955**), which could be intercepted by electron-rich aromatic compounds[547] or alkenes[804] to afford α-aryloxime ethers (**956**) or cyclic immonium compounds (**957**), the latter being isolated as their cyanide adducts (**958**). The reaction of **955** with alkenes was shown to be both stereoselective and regioselective and allowed the synthesis of the propellane **959**[804].

Other reactions of α-imidoylcarbenium ions, generated from α-haloimino compounds, involve migrations of aromatic and alkyl groups from adjacent positions. The 4-bromo-2-isoxazolines **960** gave with silver nitrate in ethanol the isoxazoles **963**. This was explained by an initial ionization of the carbon—halogen bond to form **961** and subsequent phenyl

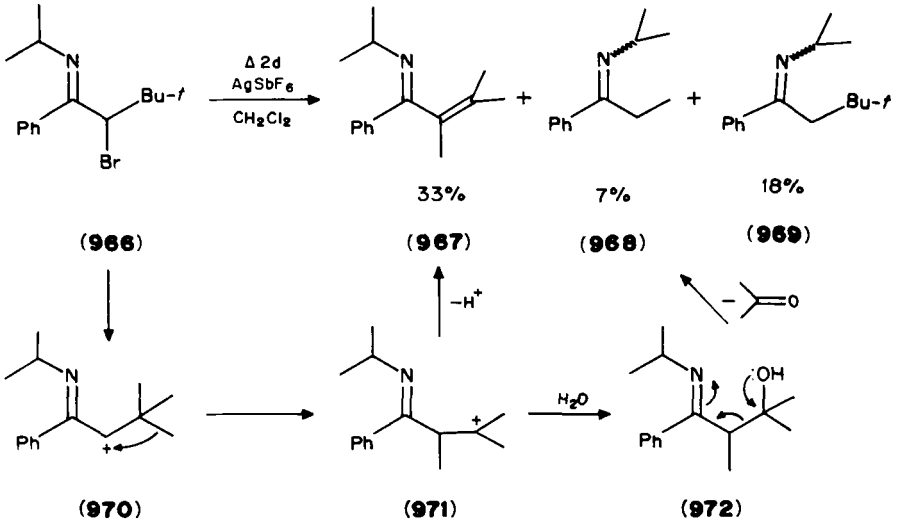
migration (pinacol-type rearrangement) to **962** which lost a proton to give **963**[705,706]. In the same way, the silver-induced rearrangement of 4-bromo-3-phenyl-2-isoxazoline (**964**) into phenanthro[9,10-*d*]-5-phenylisoxazole (**965**) was achieved[706].





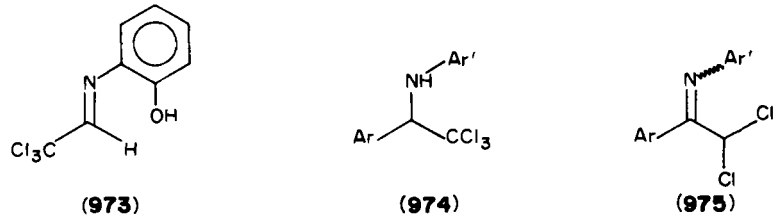


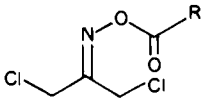
A Wagner–Meerwein type of rearrangement was observed during the reaction of the sterically hindered α-bromoketimine **966** with silver hexafluoroantimonate in dichloromethane. The products were the rearranged ketimine **967**, the fragmented ketimine **968** and the debrominated ketimine **969**[493]. While the unsaturated ketimine **967** can be formed via Wagner–Meerwein migration of a methyl group and loss of a proton, the fragmented ketimine **968** might result from trapping of the carbenium ion **971** by traces of water to give **972** and a subsequent retro-aldol reaction to yield the ketimine **968** and acetone. Similar Wagner–Meerwein rearrangements have been observed for α-acylcarbenium ions[427] and also for a steroidal α-imidoylcarbenium ion, generated from an azirine precursor[793,799].



IV. PROPERTIES AND APPLICATIONS OF α-HALOGENATED IMINO COMPOUNDS

In addition to the properties and applications reported in the original chapter, there are new reports on several properties, mainly in the field of pesticide science. The chloral imine **973** and several other ring-substituted analogues, displayed plant growth-regulating activity[498]. The insecticidal β,β,β-trichloroamines **974**, structurally related to DDT but biodegradable, were shown to degrade and to metabolize via the α,α-dichloroketimines **975**[805,806]. Most of the applications are for α-halooximes and α-halooxime ethers. 1,3-Dichloroacetone *O*-acyl oximes (**976**)[807–812] and 1,3-dichloroacetone oxime carbamates (**977**)[813] showed a variety of pesticidal activities, including slimicide, fungicide, bactericide and herbicide activity, but the parent oxime (**978**) is useful as an antidote against herbicidal use[814].





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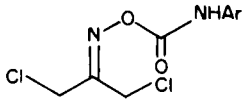

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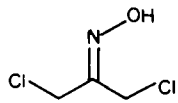
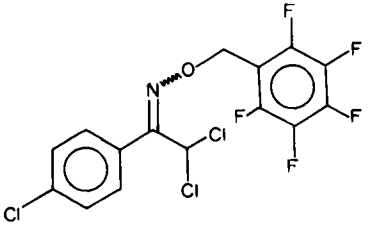


(978)

Other α-halogenated oxime ethers, such as **979**[521], **980**[815], **981**[517,816] and others[817–819], also display insecticidal and acaricidal properties. Of particular interest is the relationship between the activity and the stereochemistry of these oximes, which in general occur as isolable *E*- and *Z*-isomers. It was observed that the *E*-isomer of **979** is a more effective insecticide than **979** with the *Z*-configuration[517,816]. However, the *Z*-isomer of α,α-dichlorooxime ethers with a *m*-phenoxybenzyl substituent on the oxygen showed the greatest activity[517]. Further, the (*E*)-α,α-dichlorooxime ether **982** was 14 times more potent than the standard permethrin by topical testing against *Blatella germanica*[816]. The usual synergists such as piperonyl butoxide and sesamex also activated these α-halogenated oxime ethers[816].



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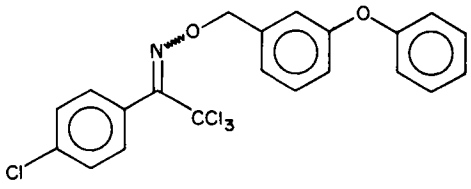

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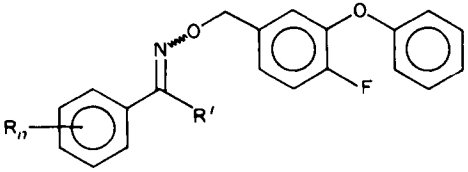
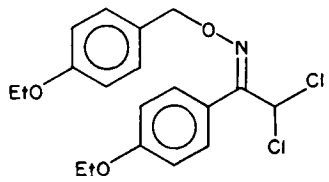
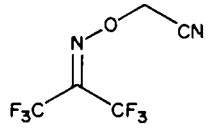


(981) R′ = $CHCl_2$, CCl_3, $CFCl_2$, CF_3
R = halo, EtO, MeO, PrO
n = 1–5



(982)

The recently expanding area of herbicide antidotes was enriched by α-fluorinated oxime ethers, e.g. **983**[820], and the functionalized trichloroacetamidines **984** exhibited bactericidal, fungicidal and herbicidal activity[821].



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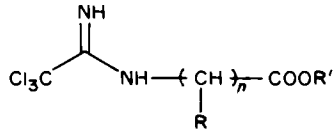

(984) R = H, Ph, CH_2Ph, C_{1-4} alkyl
n = 1,2
R′ = C_{1-4} alkyl

In addition to these intrinsic properties, α-halogenated imino compounds have also been used as key intermediates in the synthesis of dyestuffs[546], pharmaceuticals[546], fungicides[500,644,717], insecticides[822], acaricides[822], herbicides[542,652] and defoliants[542].

It should be emphasized that the developments in recent years in the chemistry of the bifunctional α-haloimines have established the potential of the α-haloimino functionality in synthetic organic chemistry. A wealth of transformations became available, many of which were not possible via the well developed chemistry of α-halocarbonyl compounds or by other synthetic approaches. Consequently, α-haloimines can be utilized as modified α-halocarbonyl compounds and both classes of heteroallylic halides often become complementary. An important feature of α-haloimines is the possibility of variation of the *N*-substituent, leading to (although not yet in a tailor-made manner) important changes in the reactivity. Finally, α-haloimines are very useful synthons for the construction of three-membered rings and, in this respect, their chemistry parallels to some extent that of α-halocarbonyl compounds.

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The chemistry of α-haloketones, α-haloaldehydes and α-haloimines
Edited by Saul Patai & Zvi Rappoport

CHAPTER 3

Synthesis and reactivity of α-halogenated aldehydes

I. INTRODUCTION

Although α-halogenated ketones have been the subject of numerous investigations from the end of the nineteenth century, the study of the chemistry of α-halogenated aldehydes was started only in the mid-1950s when general methods for the preparation of α-monohaloaldehydes became accessible. No comprehensive review of the synthesis and reactivity of α-monohalo- and α,α-dihaloaldehydes has been published, except for limited descriptions of nucleophilic substitution reactions of α-monohaloaldehydes by Müller in 1954[1] and Kirrmann in 1961[2]. However, the chemistry of chloral[3] and monochloroacetaldehyde[4] has been covered in reviews in 1975.

In this chapter, a survey will be given of developments in the chemistry of α-haloaldehydes in synthetic procedures, in mechanistic pathways and in potential applications in organic synthesis. The review is limited to aldehydes which possess one or two halogen atoms in the α-position, thus excluding chloral and bromal. Also, the synthesis and reactivity of mono- and dichloroacetaldehyde will not be treated extensively owing to the exceptional reaction conditions used (often in aqueous solution), unless the reaction is generally applicable to other α-haloaldehydes.

The chapter is divided into two parts. The first deals with synthetic procedures, and is subdivided according to the starting materials. The second part treats the reactivity, and is subdivided according to the nature of the reagents and not according to the observed reaction type. The review covers the literature up to the first half of 1986.

II. SYNTHESIS OF α-HALOGENATED ALDEHYDES

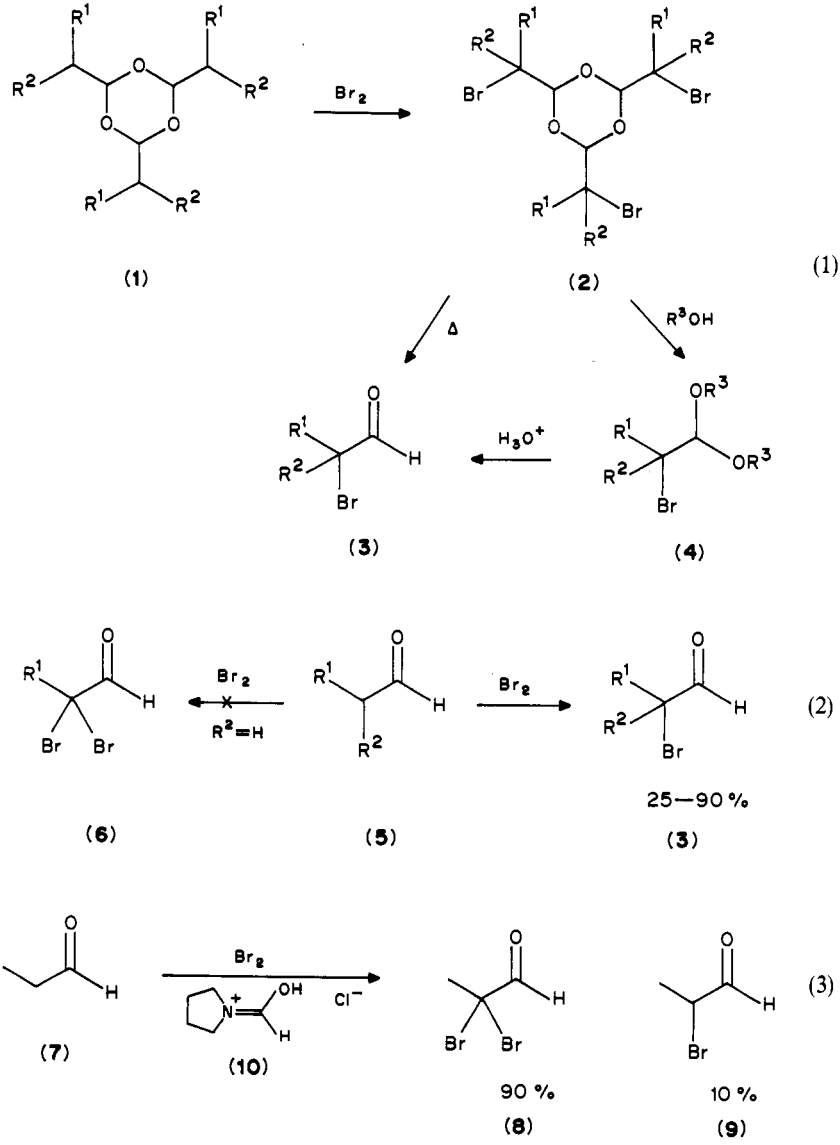
Except for the limited information given in *Houben-Weyl: Methoden der organischen Chemie*[1,5,6] on the synthesis of α-haloaldehydes and their acetals, no comprehensive review has been published hitherto. Whereas in the chapter on α-haloketones the syntheses of chloro-, bromo-, fluoro- and iodoketones were treated separately, this section will describe the general procedures for the preparation of the various α-haloaldehydes according to the nature of the starting materials, because of the limited number of several of the compound types available.

A. Synthesis of α-Haloaldehydes from Aldehydes

Owing to the higher reactivity of the carbonyl function in aldehydes compared with that in ketones, the direct treatment of aldehydes with chlorine or bromine often results in low yields of the corresponding α-haloaldehydes. In addition to the formation of mono- and dihalo compounds, which are difficult to separate, chlorination or bromination gave rise to side-reactions such as the production of the corresponding acyl halides, and the occurrence of aldol condensations, oxidations in alkaline media and the formation of acetals when the reaction was carried out in alcohols[2,5,6]. Therefore, the first preparations of α-bromoaldehydes (**3**) were carried out via bromination of the corresponding paraldehydes (**1**) (i.e. the aldehyde trimers = 1,3,5-trioxanes) followed by pyrolysis[7] or alcoholysis[8] of the bromo derivative **2** (equation 1).

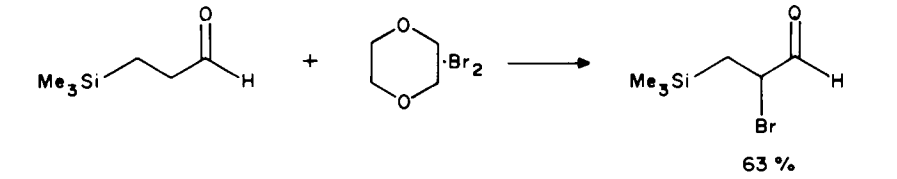
Direct monobromination of aliphatic aldehydes (**5**) could be achieved by using bromine under carefully controlled conditions: low temperature (−10 °C) and dilution with dry dichloromethane[9] or chloroform[10]. The presence of stoichiometric[11,12] or catalytic amounts[13] of dioxane, acetic acid[14] or calcium carbonate[15] increased the yields of the α-monobromoaldehydes (**3**) (equation 2). It should be pointed out that under these conditions only minor amounts of α,α-dibromoaldehydes (**6**) were produced[16]. Nevertheless, 2-bromo-2-chlorobutanal was prepared by bromination of 2-chlorobutanal with bromine[17]. 2,2-Dibromopropanal (**8**), however, could be prepared as the main product by

bromination of propanal (7) in the presence of *N*-formylpyrrolidine hydrochloride (**10**) (equation 3)[18].

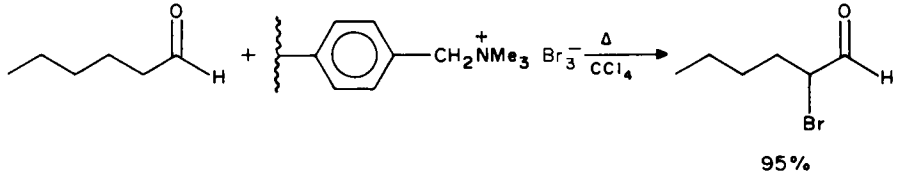


(1) (2) (3)

Other brominating agents which have been successfully used in the monobromination of aldehydes such as **11**, **14** or **17** are the dioxane–bromine adduct **12**[19,20], the ion-exchange resin Amberlyst A-26 in the perbromide form (**15**)[21], polyvinylbenzyltriphenylphosphonium perbromide[22], 5,5-dibromo-2,2-dimethyl-4,6-dioxo-1,3-dioxane (**18**)[23], 5,5-dibromobarbituric acid (**20**)[24], *tert*-butyl bromide–DMSO (**21**)[25] and trimethylbromosilane–DMSO (**22**)[26] (equation 4).

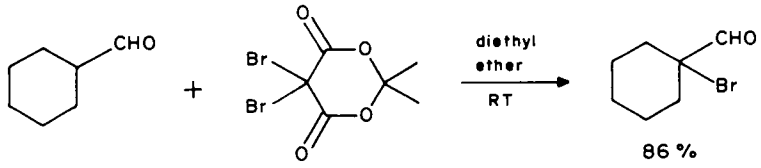


(11) (12) (13) Ref. 20

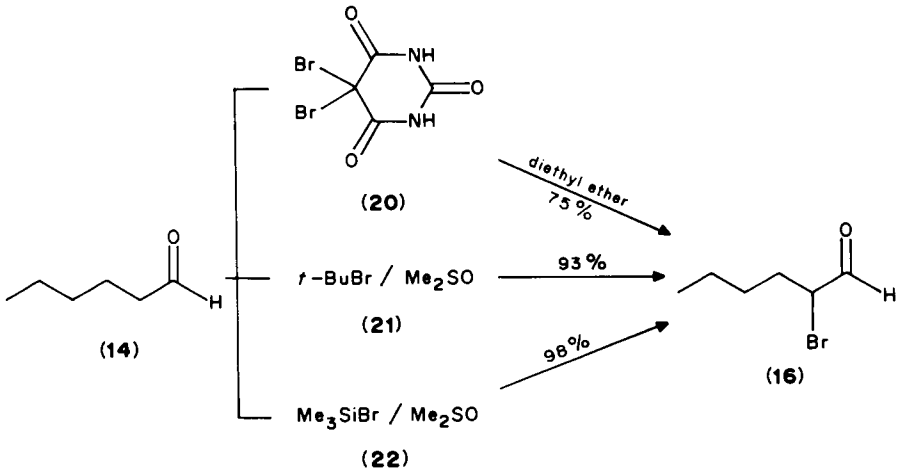


(14) (15) (16) Ref. 21

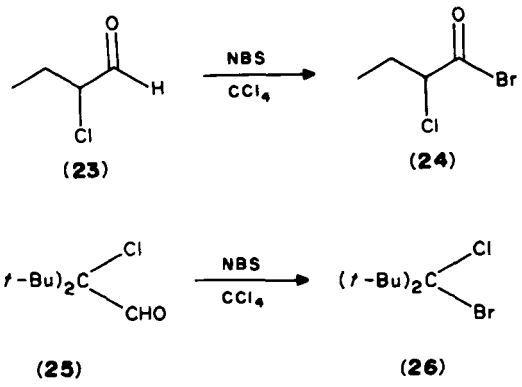
(4)



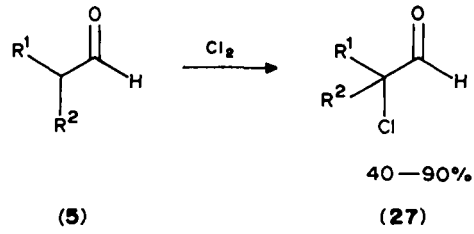
(17) (18) (19)



Reaction of 2-chlorobutanal (**23**) or a bulky α-chloroaldehyde (e.g. **25**) with *N*-bromosuccinimide resulted in the formation of the corresponding acid bromide[17] or of a dihalide[27] (equation 5).



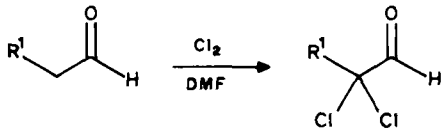
Procedures for the direct chlorination of aldehydes with chlorine to produce α-mono- and α,α-dichloroaldehydes were not generally available until 1980. However, monochlorination and in a few cases dichlorination were successfully performed in aqueous acidic medium. Chlorination of lower aliphatic aldehydes (**5**) without side-reactions takes place in chlorine–water mixtures at low temperature and with high concentrations of hydrochloric acid[28,29] and in 90% sulphuric acid[30]. Only 2-methylpropanal could be α-monochlorinated using chlorine in water[31,32], while the chlorination of propanal in dilute hydrochloric acid could be controlled in such a manner as to produce either 2-chloropropanal or 2,2-dichloropropanal in yields exceeding 85% (equation 6)[33].



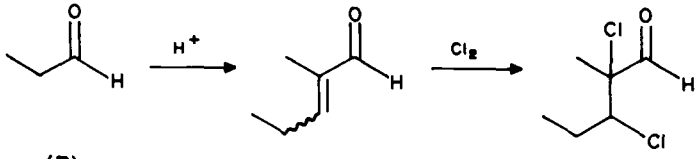
(6)

When α,α-dichloroaldehydes are the target molecules, the main disadvantage of the chlorination with acid catalysts is the relative slowness of the second enolization step, since the basicity of the carbonyl group is decreased considerably by an α-halogen substituent. This procedure therefore frequently yields products contaminated with substantial amounts of α-monochloroaldehydes, rendering the method useless owing to difficulties in the separation of α-mono- and α,α-dihaloaldehydes.

A general synthesis of α,α-dichloroaldehydes (**29**) consisted in direct chlorination of aldehydes (**28**) with chlorine gas in *N*,*N*-dimethylformamide (DMF) solution at 40–90 °C (equation 7)[34,35]. The procedure is based on the special efficiency of DMF–HCl mixtures for catalysis of enolization. In addition to the usual acid catalysis, an efficient base-catalysed enolization of the α-chlorocarbonyl function is observed. Whereas the introduction of the first chlorine substituent into the aldehydes is clearly acid catalysed, the second chlorination is base catalysed or combined acid–base catalysed. The second chlorination step is so rapid that monochloroaldehydes were not detected in samples which underwent incomplete chlorination[34]. A continuous excess of chlorine must be maintained in order to minimize the acid-catalysed aldol condensation, as illustrated in equation 8.

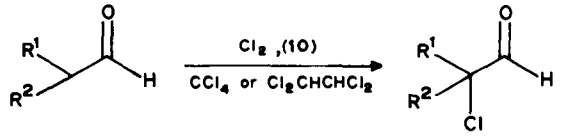


(28) (29) (7)



(7) (8)

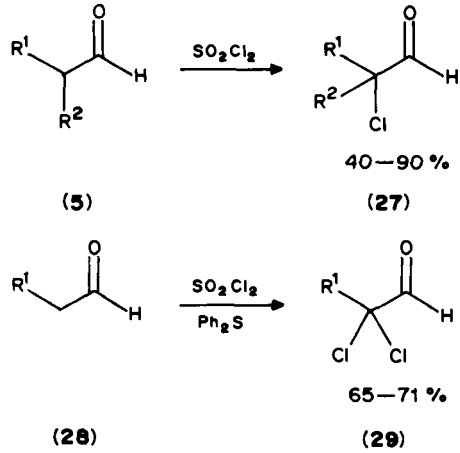
A similar synthesis of α,α-dichloroaldehydes, involving the chlorination of aldehydes using 1,1,2,2-tetrachloroethane or carbon tetrachloride as solvent in the presence of *N*-formylpyrrolidine hydrochloride as catalyst, was developed later (equation 9)[18].



(5) (27,29) (9)

R^2=Cl when R^2=H in 5

High yields of α-monochloroaldehydes were also obtained using sulphuryl chloride[15,35,36,38-40]. On the other hand, addition of diphenyl sulfide resulted in the formation of α,α-dichloroaldehydes (equation 10)[41].

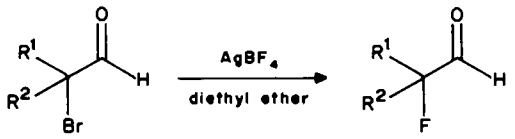


(5) (27) (10)

(28) (29)

Butanal and 2-methylpropanal undergo α-chlorination in almost quantitative yield on refluxing with copper(II) chloride in aqueous isopropanol or acetone[42], and 3-(phenylthio)butanal could be chlorinated with NCS[43]. Chlorination by means of polymer-supported chlorine[44] and trimethylchlorosilane–DMSO[45] can also give rise to high yields of α-monochloroaldehydes.

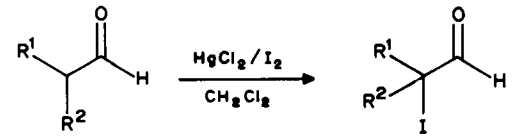
α-Fluoroaldehydes cannot be obtained directly from aldehydes via fluorination. Tertiary α-fluoroaldehydes (**30**) were synthesized by reaction of α-bromoaldehydes (**3**) with silver tetrafluoroborate in diethyl ether (equation 11). When the reaction was carried out in nucleophilic solvents the corresponding substitution products by the solvent were isolated, suggesting that neighbouring group participation by the carbonyl oxygen may account for the products[46].



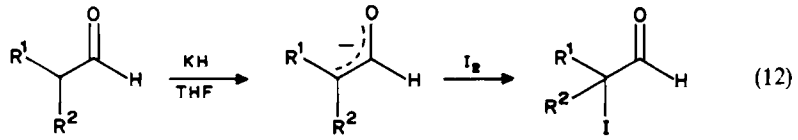
(11)

(**3**) (**30**)

α-Iodoaldehydes (**31**) have been synthesized by treatment of aldehydes with iodine in the presence of mercury(II) chloride[47], direct iodination of aldehyde enolates[48] and by reaction of α-chloro- or α-bromoaldehydes (**32**) with sodium iodide[49] (equation 12).



(**5**) (**31**)



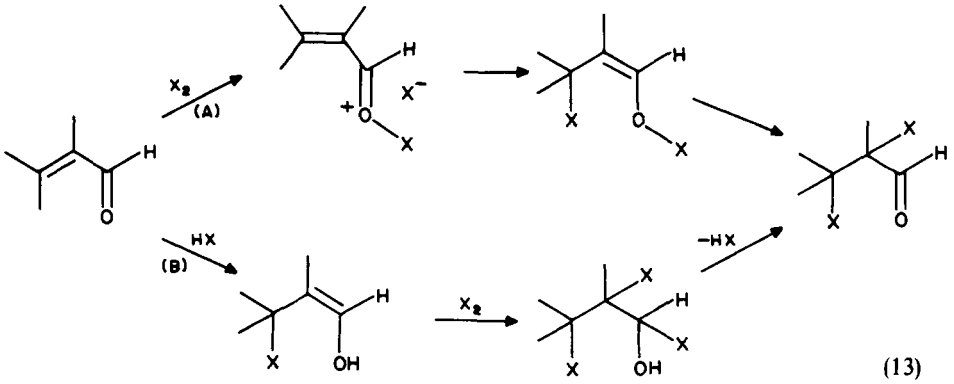
(12)

(**5**) (**31**)

(**32**)
X=Cl, Br

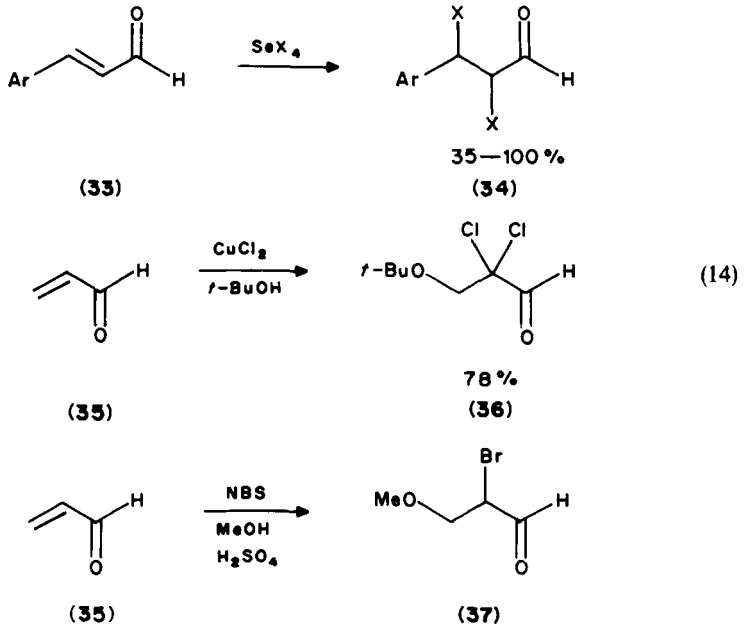
(**31**) R^2=H

Although the transformation of α,β-unsaturated aldehydes into α,β-dihaloaldehydes has been established for a long time[50–52], two mechanisms were proposed to account for the evidence that α,β-unsaturated aldehydes do not react with halogens by the expected attack on the C=C bond. The higher rates of the halogenation of acrolein compared with hept-1-ene and of crotonaldehyde compared with crotonic acid, together with the regiochemistry of the BrCl addition, excluded an electrophilic attack of halogen on the C=C bond. One mechanism (A) involves initial attack of the halogen on the oxygen atom and the other (B) involves initial addition of a trace of HX to give a highly reactive enol (equation 13)[53,54].



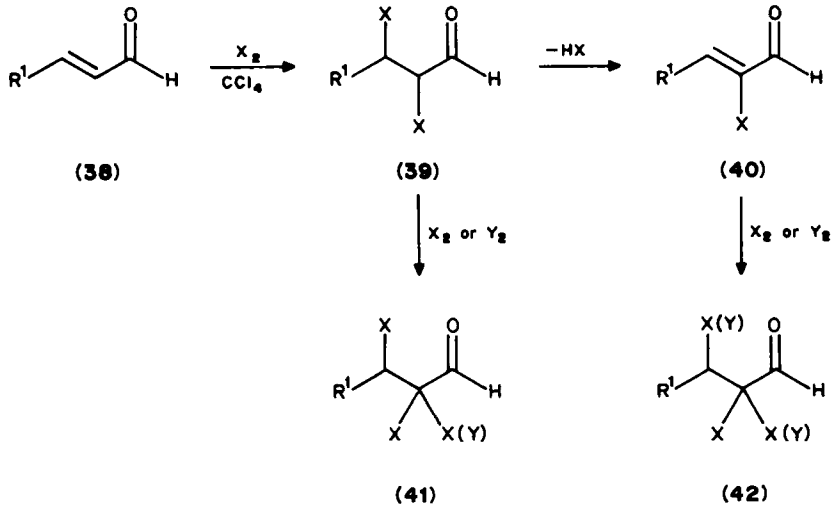
(13)

Other useful transformations of α,β-unsaturated aldehydes into α-haloaldehydes involve reactions with selenium tetrahalides[55] or copper(II) chloride[56] and the acid-catalysed reaction of *N*-bromosuccinimide in methanol[57] (equation 14).



(14)

Polyhalogenated aldehydes (**41**, **42**) have been prepared via halogenation of α,β-unsaturated aldehydes (**38**), followed by halogenation in the presence of water or via a dehydrohalogenation–halogenation sequence (equation 15)[37,57–62]. The chlorination of α,β-unsaturated aldehydes should be conducted in carbon tetrachloride, because otherwise chlorinated acid chlorides are formed as side-products.



(**38**) (**39**) (**40**) (**41**) (**42**)

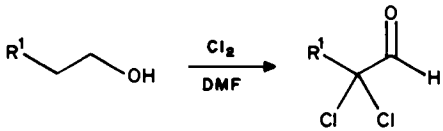
(15)

B. Synthesis of α-Haloaldehydes from Alcohols

The excellent chlorination procedure using Cl_2–DMF is also applicable in converting directly primary alcohols (**43**) into α,α-dichloroaldehydes (**29**), by combining chlorination and oxidation in a one-pot reaction (equation 16)[34]. This procedure involves a very rapid formation of the chlorinated hemiacetal **44**, which in turn is gradually converted into the 2,2-dichloroaldehyde **29** (equation 17).

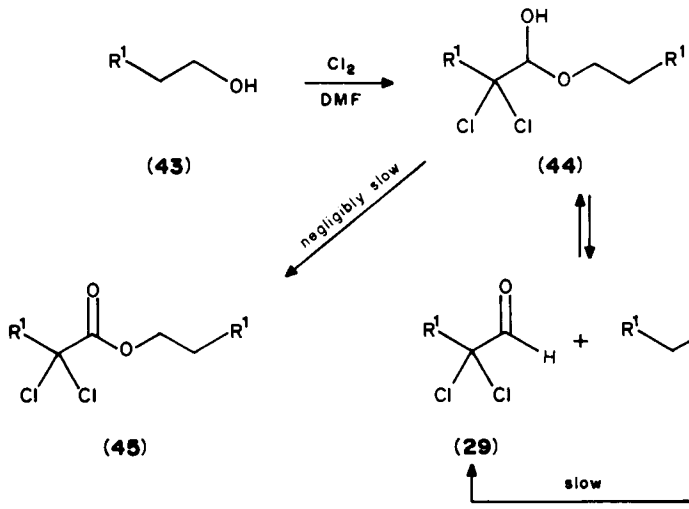
The yields obtained in the chlorination of aromatic substrates were only moderate, owing to competing ring chlorination. From pentane-1,5-diol (**46**) the stable cyclic hemiacetal 3,3-dichloro-2-hydroxytetrahydropyran (**47**) was obtained, and it was partly converted to the trichlorotetrahydropyran **48** (equation 18). However, the chlorination of hexane-1,6-diol produced 2,2,5,5-tetrachlorohexanedial in 63% yield[34].

Other procedures for converting alcohols into α-haloaldehydes involved hydrolysis (via rearrangement) of dichlorohydrins (**50**)[63] and oxidation of β-chloro-α-hydroxyketones (**52**)[64] (equation 19).

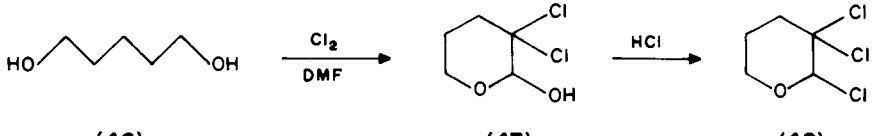


47—78 %

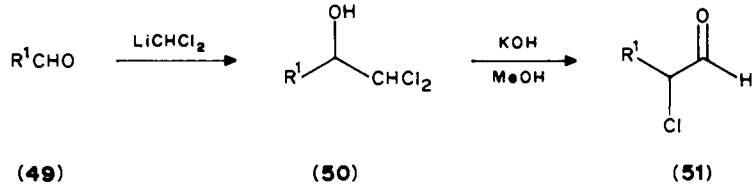
(**43**) (**29**) (16)



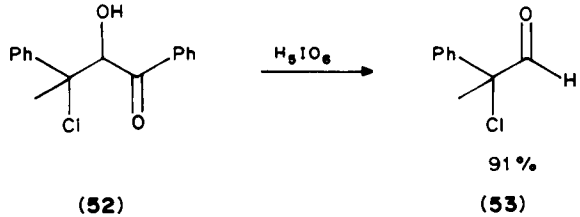
(17)



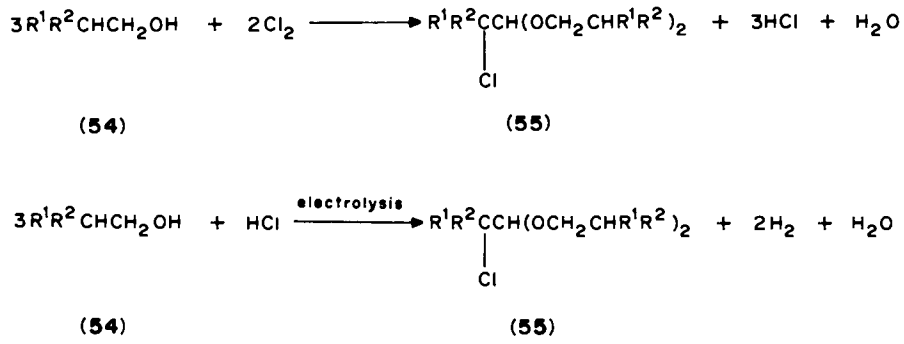
(18)



(19)



Acetals (55) of α-chlorinated aldehydes, which can be easily hydrolysed to the corresponding aldehydes, have been synthesized by chlorination of alcohols with chlorine[65] and by electrolysis of primary alcohols in the presence of anhydrous hydrogen chloride[66] (equation 20).

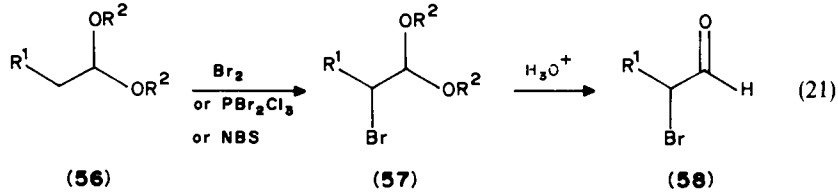


(20)

C. Synthesis of α-Haloaldehydes from Aldehyde Derivatives

It is evident that halogenation of acetals should be a very attractive route for the preparation of α-haloaldehydes via acidic hydrolysis of the halogenated acetals. This indirect method gave high yields except for the lower (C_2–C_4) derivatives.

The bromination of acetals (**56**) was performed using bromine[67], phosphorus dibromide trichloride[68,69] or NBS[70]. In order to capture the liberated hydrogen bromide, the reactions were carried out in the presence of a base, such as calcium carbonate[71,72], sodium ethoxide[73] or pyridine[74]. Except for the formation of 2, 2-dibromoheptanal[69], this procedure gave α-monobromoaldehydes (**58**) after hydrolysis (equation 21).



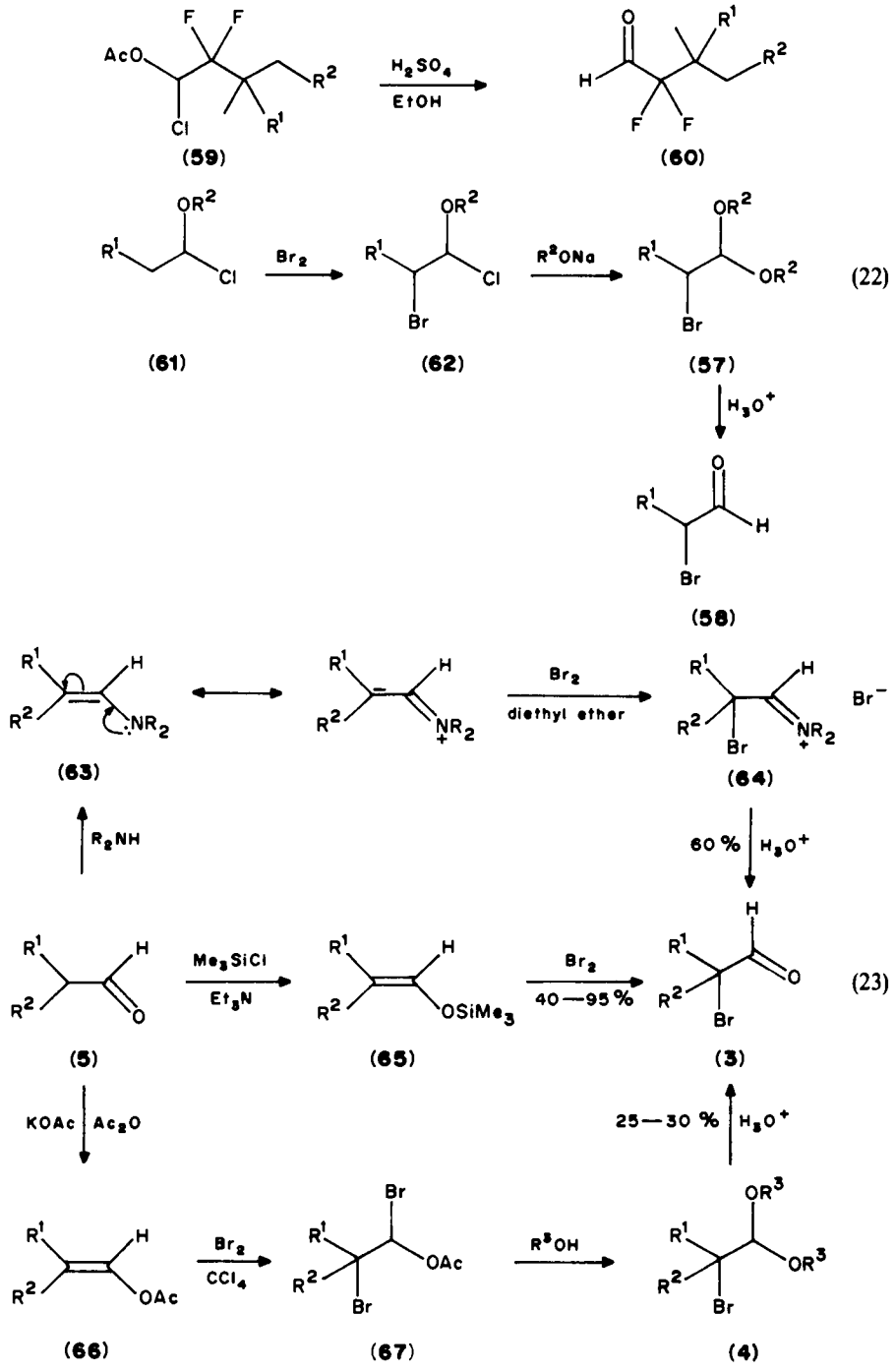
(21)

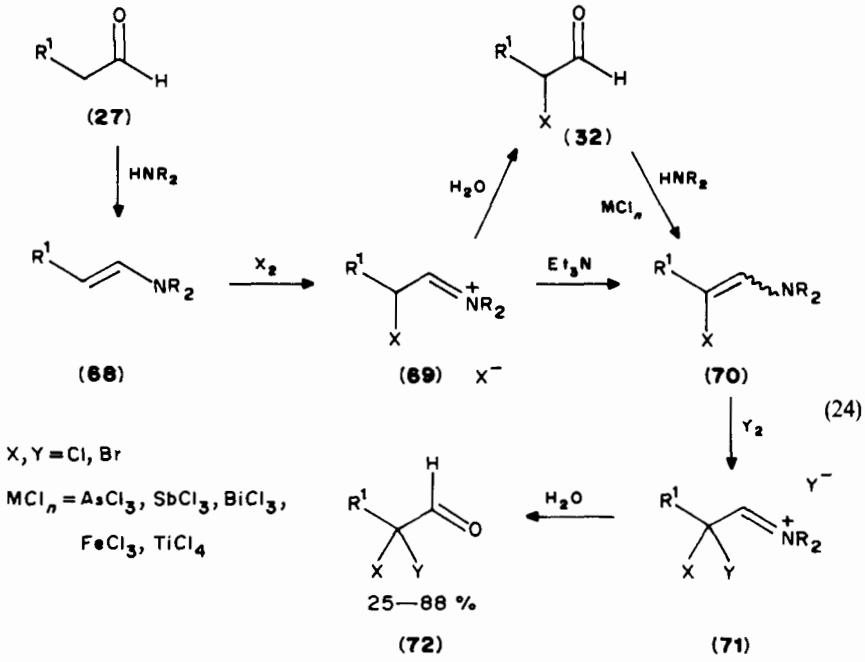
Hydrolysis of fluorinated acetates (**59**) with sulphuric acid gave α, α-difluoroaldehydes (**60**)[75]. The α-chloroethers **61** could be brominated to **62** and transformed into the corresponding brominated acetals **57**[76] (equation 22).

Halogenation of enol derivatives of aldehydes has proved to be very successful in the synthesis of α-halogenated aldehydes. Enol acetates (**66**) can be transformed into α-monobromoaldehydes (**3**) via the corresponding dibromides (**67**) and acetals (**4**)[77,78], while enamines (**63**) on treatment with bromine afforded the intermediate α-bromoimmonium salts (**64**), which can be hydrolysed to the corresponding α-bromoaldehydes (**3**)[79].

In addition, silyl enol ethers (**65**) can be transformed directly into α-chloro- and α-bromoaldehydes on treatment with chlorine or bromine in CCl_4[80], and α-fluoroaldehydes were generated on fluorination with 5% F_2 in N_2 in Freon 11[81] (equation 23).

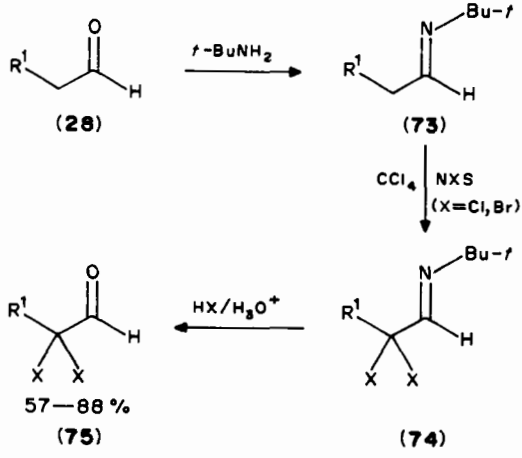
Three general methods for the preparation of α, α-dibromo- and α, α-dichloroaldehydes via halogenation of either enamines or aldimines have been developed. Halogenation of enamines (**68**) followed by treatment with triethylamine afforded β-haloenamines (**70**). The latter can also be obtained via condensation of α-haloaldehydes (**32**) with secondary amines. Treatment of the β-haloenamines **70** with bromine or chlorine gave the α, α-dihalogenated immonium salts **71**, which were easily hydrolysed to the α, α-dihaloaldehydes **72** (equation 24)[82,83].


AcO
F
F
Cl
R1
R2
(59)
H2SO4
EtOH
O
H
F
F
(60)
OR2
R1
Cl
Br2
Br
R2ONa
(61)
(62)
(57)
(22)
H3O+
(58)
NR2
(63)
Br2
diethyl ether
Br−
(64)
R2NH
60 %
Me3SiCl
Et3N
OSiMe3
(65)
40—95 %
(5)
(3)
(23)
KOAc
Ac2O
OAc
(66)
CCl4
(67)
R3OH
25—30 %
OR3
(4)

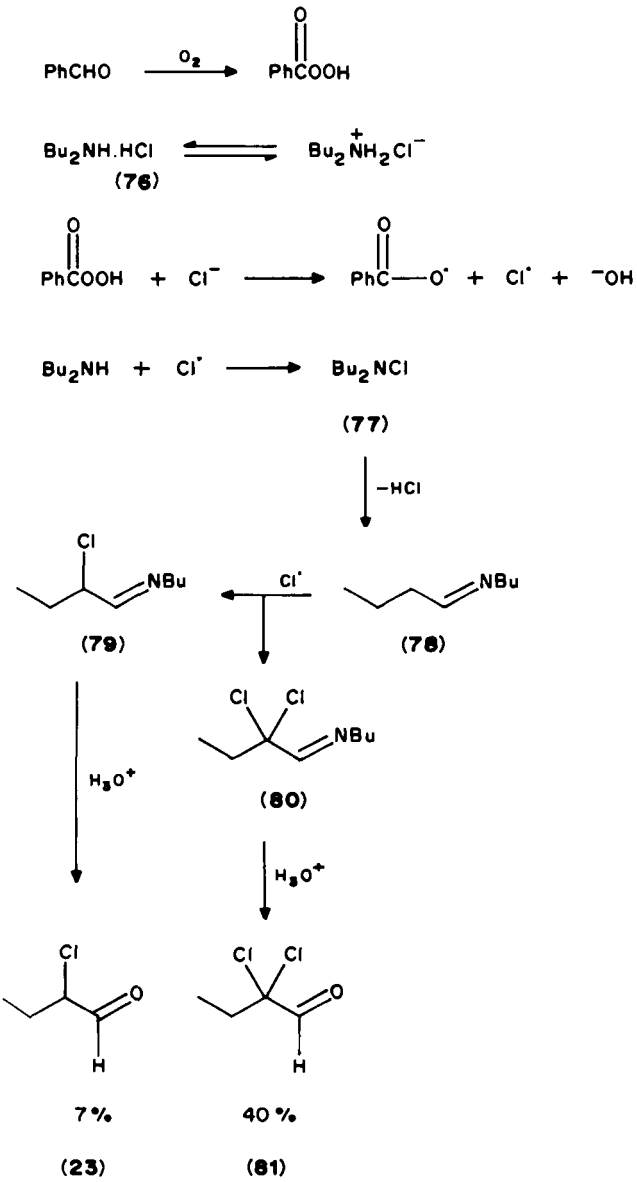


(24)

The second method involved halogenation of aldimines (**73**) with two equivalents of *N*-chloro- or *N*-bromosuccinimide to give **74**. Hydrolysis of **74** with dilute hydrochloric or hydrobromic acid gave α,α-dichloro- and α,α-dibromo-aldehydes (**75**), respectively. The advantage of this procedure is that there is no need to isolate the intermediate imines (**73** and **74**) (equation 25)[84]. In similar manner, 2,2-dichlorobutanal (**81**) was formed, together with minor amounts of α-chlorobutanal (**23**), via hydrolysis of the corresponding aldimines (**79**, **80**). The latter were formed by halogenation during the autooxidation of benzaldehyde in the presence of dibutylammonium chloride, which was successively transformed into *N*-chlorodibutylamine (**77**) and an aldimine (**78**) (equation 26)[85].



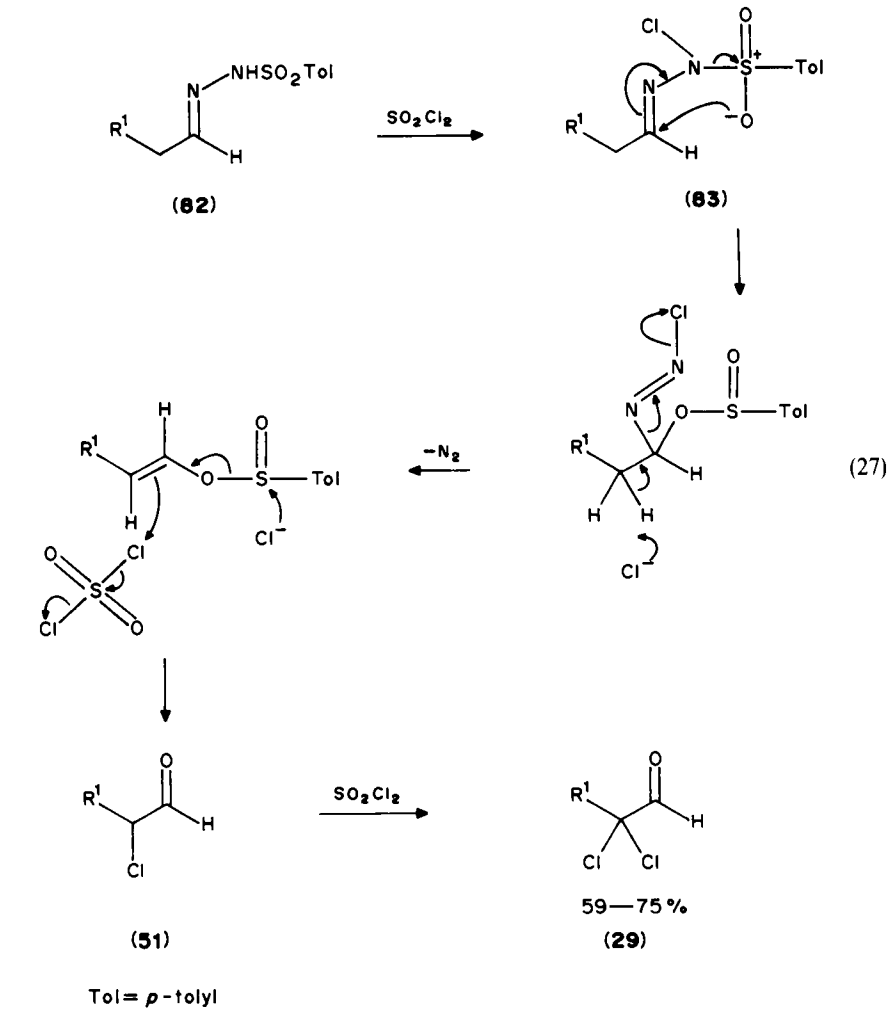
(25)

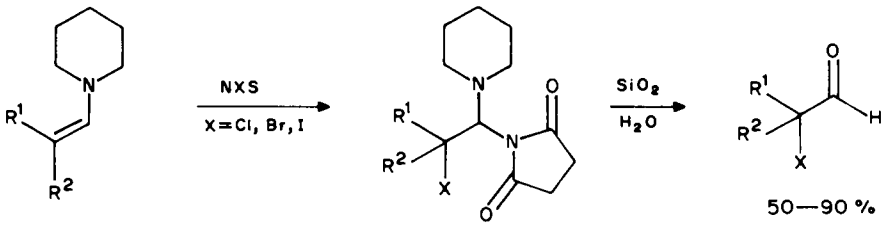


(26)

In the third method, aldehyde *p*-tosylhydrazones (**82**) having two α-hydrogen atoms are transformed into α,α-dichloroaldehydes (**29**). The mechanism suggested involves a sulphinate participated [2, 3]-sigmatropic rearrangement (equation 27)[86].

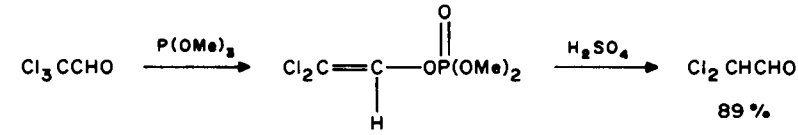
An alternative route in converting *N*-derivatives of aldehydes into α-haloaldehydes consists in the halogenation of enamines (**84**) with *N*-halosuccinimide, which affords the adducts **85**. The latter in turn can be hydrolysed into α-monohaloaldehydes (**86**) by treatment with silica gel (equation 28)[87].


NHSO2Tol
SO2Cl2
(82)
(83)
-N2
(27)
(51)
SO2Cl2
59—75 %
(29)
Tol = p-tolyl


NXS
X=Cl, Br, I
SiO2
H2O
50—90 %
(84)
(85)
(86)

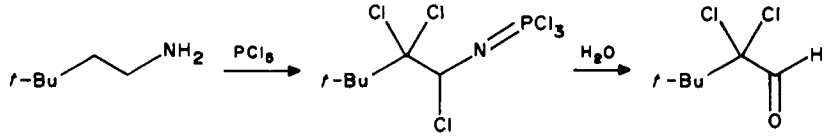
(28)

A very efficient method for the synthesis of dichloroacetaldehyde (**89**) from chloral (**87**) was elaborated via the hydrolysis of the enol phosphate **88**, obtained by the Perkow reaction of chloral with trimethyl phosphite (equation 29)[88].



(**87**) (**88**) (**89**)

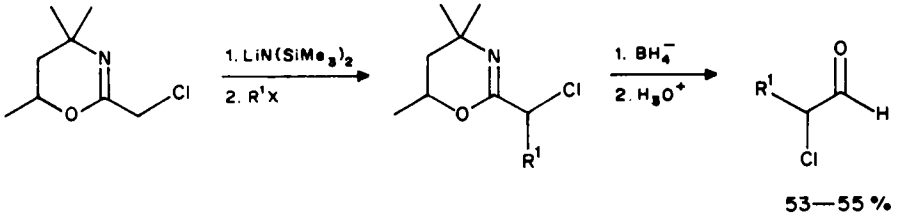
(29)



(**90**) (**91**) (**92**)

The sterically hindered α,α-dichloroaldehyde **92** could also be obtained via hydrolysis of 1,2,2-trichloro-3,3-dimethylbutaniminotrichlorophosphorane (**91**), synthesized by reaction of the amine **90** with phosphorus pentachloride[89].

A particular case of transforming a protected aldehyde function into chlorinated aldehydes (**51**) consisted in alkylation of the 2-(chloromethyl)oxazine **93** followed by reduction with sodium borohydride and hydrolysis (equation 30)[90].



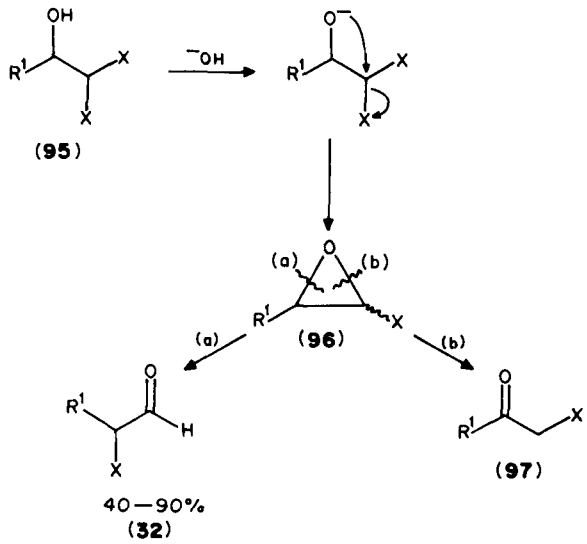
(**93**) (**94**) (**51**)

(30)

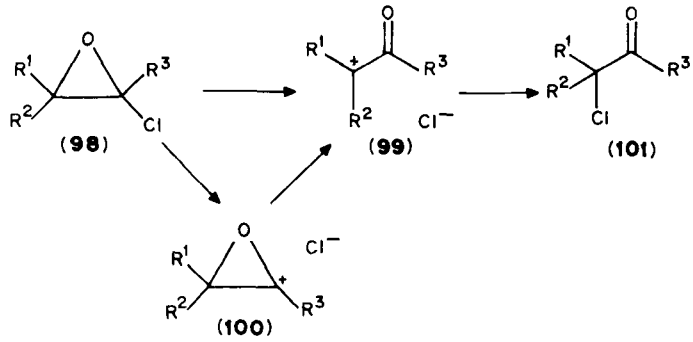
D. Synthesis of α-Haloaldehydes from Halogenated Oxiranes and Ozonides

Thermal rearrangement of halogenated oxiranes (**96**), prepared via base-catalysed ring closure of β,β-dihaloalcohols (**95**), often resulted in the formation of α-haloaldehydes (**32**) (route a), although α-haloketones (**97**) are plausible reaction products via route b (equation 31)[91–97,235].

The inductive effect of the halogen atom caused ring opening via path a (bond b is stronger than bond a) followed by a rearrangement of the halogen anion, while the mesomeric effect resulted in ring opening via b accompanied by a hydride shift. From kinetic studies it was concluded that the thermal rearrangements of halogenated oxiranes (**98**) occurred by disrotatory C_β—O bond heterolysis to yield the corresponding α-ketocarbonium–chloride ion pairs (**99**) (equation 32)[95].



(31)

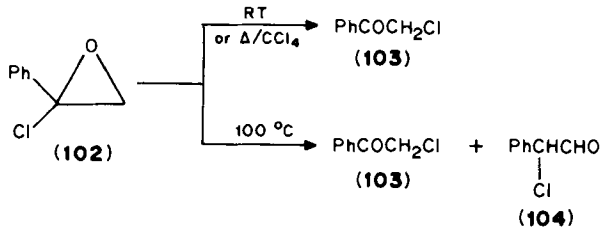


(32)

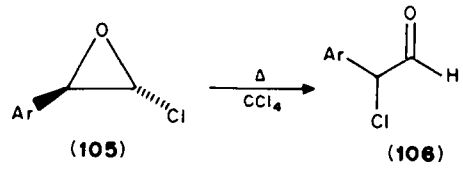
The formation of halogenated aldehydes or ketones is strongly dependent on the reaction conditions. Whereas rearrangement of 2-chloro-2-phenyloxirane (**102**) at room temperature[92] or at reflux in carbon tetrachloride resulted in the formation of phenacyl chloride (**103**), slow heating of the oxirane to 100 °C[92] afforded a mixture of the aldehyde **104** and ketone **103** (equation 33). On the other hand, heating of *trans*-β-chlorostyrene oxides (**105**) gave the α-haloaldehydes (**106**) exclusively (equation 33)[95].

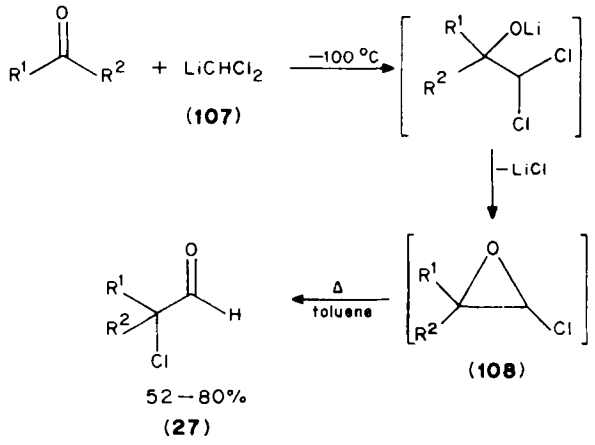
Another entry to the synthesis of α-chloroaldehydes (**27**) via thermal rearrangement of intermediate chlorooxiranes (**108**), which were not isolated, involved the action of dichloromethyllithium (**107**) (prepared *in situ* from dichloromethane and *n*-butyllithium) on ketones (equation 34)[27,98,99].

In addition to thermal rearrangements, catalytic ring opening of halooxiranes, e.g. **102**, **109**, **110** and **116**, under the influence of acids[91,92], magnesium bromide[91,100], boron trifluoride[91], silver tetrafluoroborate[101,141] and bases[102,313] has been performed (equation 35).

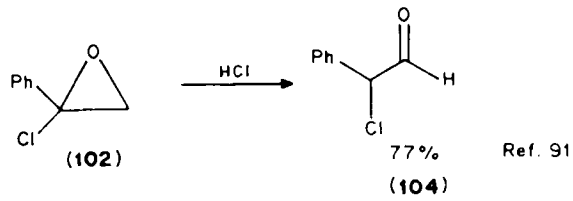

RT
or Δ/CCl4
PhCOCH2Cl
(103)
100 °C
PhCOCH2Cl + PhCHCHO
(103)
Cl
(104)
Ph
Cl
(102)

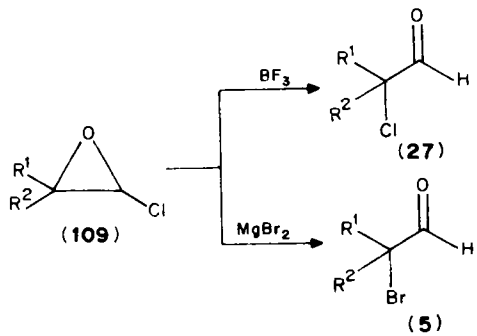
(33)

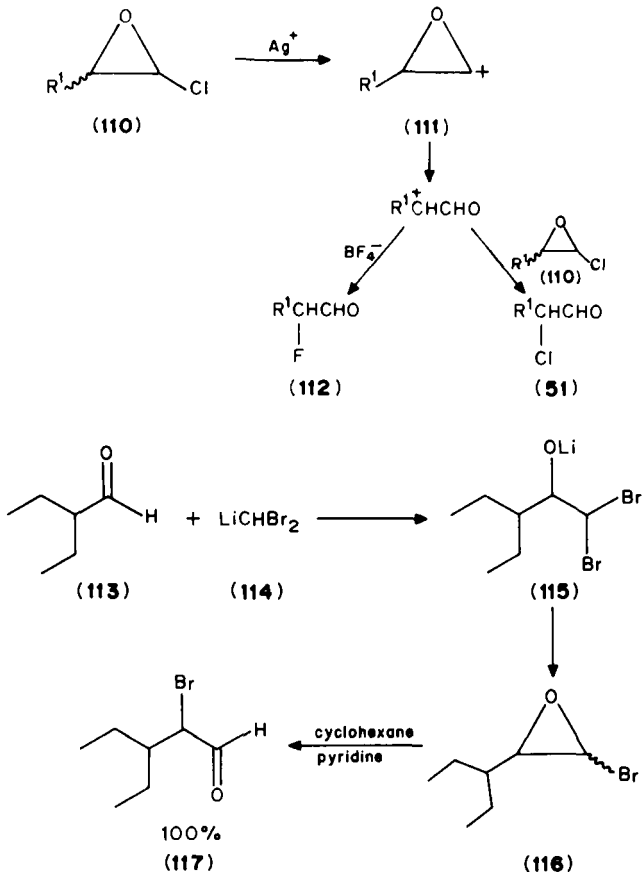

Ar
Cl
(105)
Δ
CCl4
Ar
H
Cl
(106)


R1
R2
+ LiCHCl2
(107)
−100 °C
R1
OLi
R2
Cl
Cl
−LiCl
R1
R2
H
Cl
Δ
toluene
R1
R2
Cl
(108)
52−80%
(27)

(34)

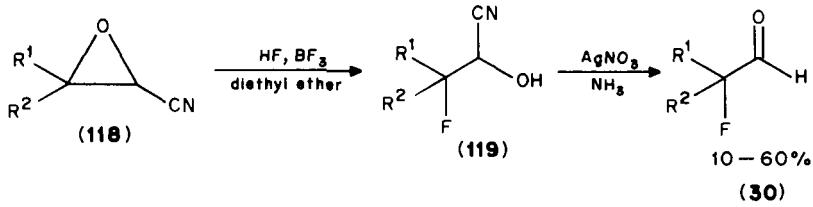

Ph
Cl
(102)
HCl
Ph
H
Cl
77%
(104)
Ref. 91


R1
R2
Cl
(109)
BF3
MgBr2
R1
H
R2
Cl
(27)
R1
H
R2
Br
(5)



(35)

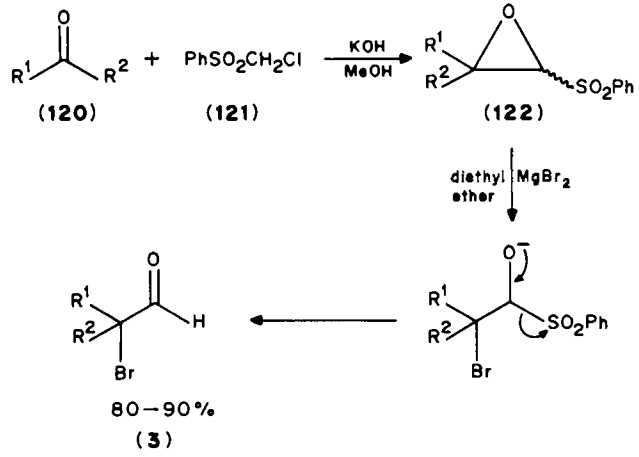
α-Fluoroaldehydes (**30**) have been obtained in a similar way by the simultaneous action of HF and BF_3 on cyanooxiranes (**118**), which afforded fluorocyanohydrins (**119**). These, in turn, are treated with silver nitrate and ammonia (equation 36)[103].



(36)

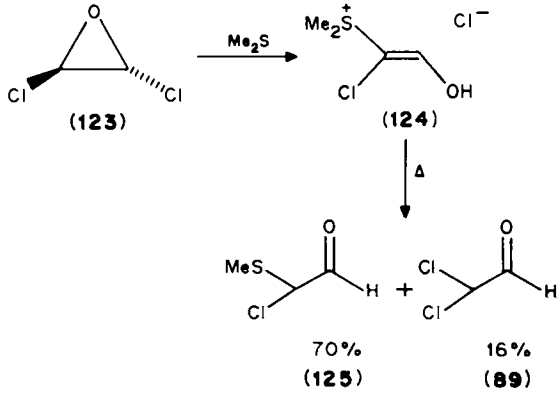
A synthetically more useful procedure involved ring opening of epoxysulphones (**122**) under the influence of magnesium(II) bromide, which led to α-bromoaldehydes (**3**). The required epoxysulphones (**122**) are accessible from a Darzens-type condensation of chloromethyl phenyl sulphone (**121**) and ketones (**120**) (equation 37). The epoxysulphone route has a number of advantages over the α-haloepoxide route. The condensation between α-chlorosulphones and aldehydes or ketones can be carried out conveniently

under phase-transfer conditions, whereas the synthesis of α-haloepoxides requires the generation of dihalomethyllithium at very low temperatures. The epoxysulphones (**122**) are stable, whereas many α-chloroepoxides are not stable enough under the purification conditions (equation 37)[104–106].



(37)

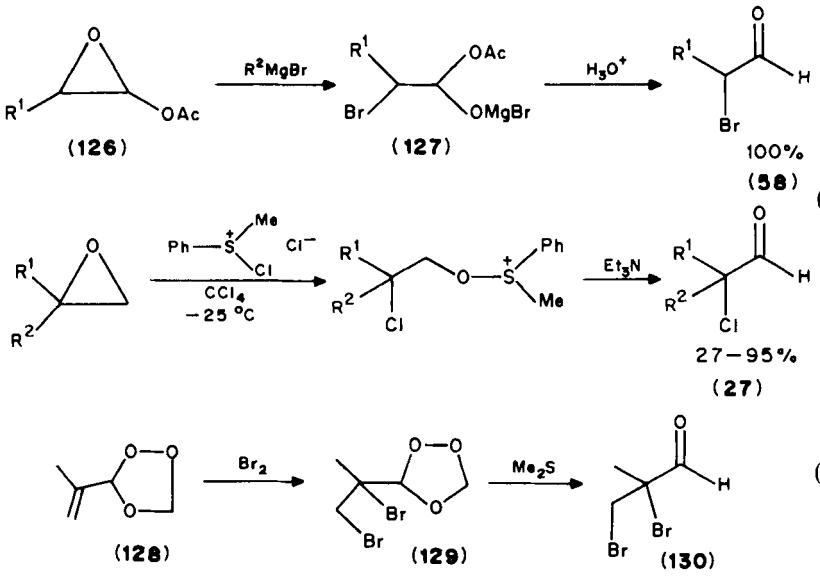
α-Haloaldehydes were also generated when *trans*-2,3-dichlorooxirane (**123**) reacted with dimethyl sulphide, affording dimethyl(1-chloro-2-hydroxyethenyl)sulphonium chloride (**124**). On pyrolysis, **124** provided 2-chloro-2-(methylthio)acetaldehyde (**125**) and dichloroacetaldehyde (**89**) (equation 38)[107].



(38)

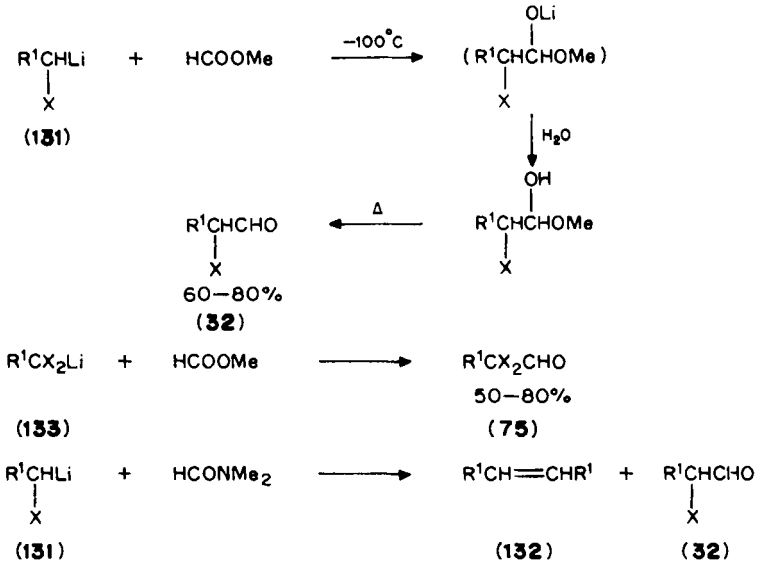
Nearly quantitative yields of α-monohaloaldehydes have been obtained via ring cleavage of epoxyacetates (**126**) with Grignard reagents followed by hydrolysis of **127** in acidic medium (equation 39)[108,109].

Reaction of epoxides with the thioanisole–chlorine complex produced α-chlorosulphoxonium intermediates, which on treatment with triethylamine afforded α-chloroaldehydes[311]. In a similar way, monoozonides (e.g. **128**) are converted into α,β-dibromoaldehydes (e.g. **130**) via bromination and reduction of the stable dibromoozonides (**129**) with dimethyl sulphide (equation 40)[110]. In this respect, a very efficient synthesis of bromoacetaldehyde (56%) has been developed by treatment of the ozonide of 1,4-dibromo-*trans*-but-2-ene with triphenylphosphine at 0 °C[111].

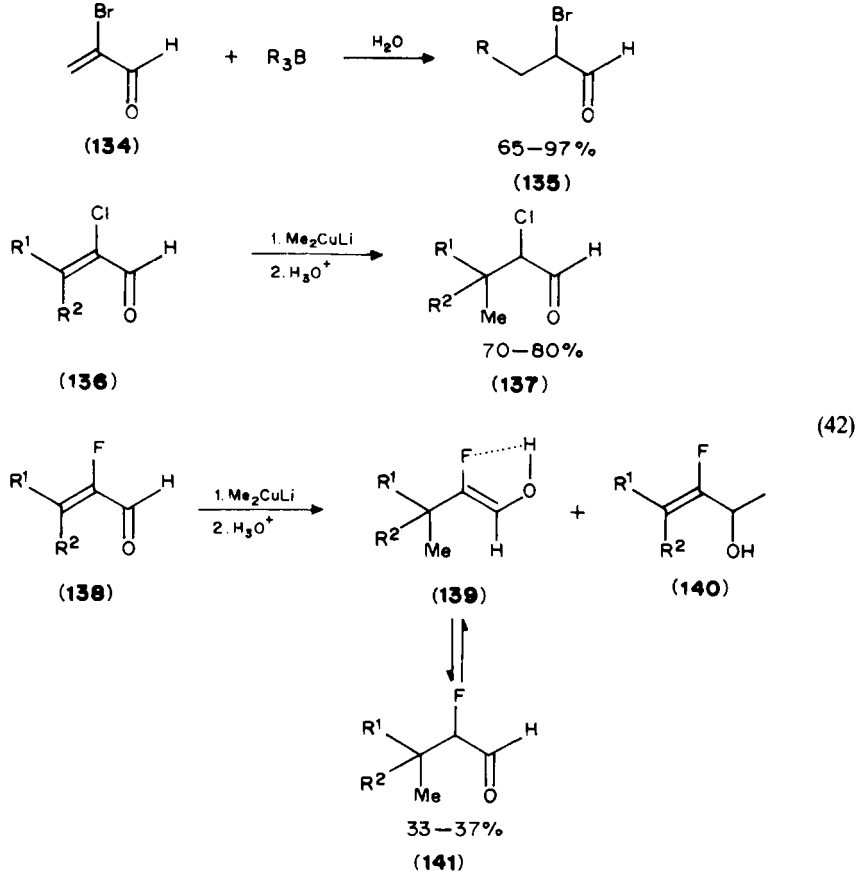


E. Synthesis of α-Haloaldehydes via Homologation of Carbonyl Compounds

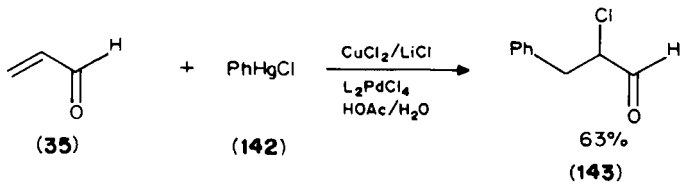
Carbonyl compounds have been converted into α-haloaldehydes via a variety of methods. A related transformation involving ring cleavage of oxiranes has been described in a previous section. Methyl formate gave rise to α-haloaldehydes (**32**) by reaction with 1-haloalkyllithiums (**131**)[112–114] via intermediate hemiacetals. α,α-Dihaloaldehydes (**75**) have been prepared in similar way using 1,1-dihaloalkyllithium carbenoids (**133**)[115]. α-Monohaloaldehydes (**32**) can also be formed in lower yields using *N*,*N*-dimethylformamide as the carbonyl substrate[116] (equation 41).



α-Halo-α,β-unsaturated aldehydes have been the subject of chain elongation with the formation of α-haloaldehydes via the reaction of 2-bromoacrolein (**134**) with organoboranes[117] and via a 1,4-addition of lithium dimethylcuprate to α-chloro- and α-fluoro-α,β-unsaturated aldehydes (**136**, **138**) (equation 42)[118]. Acrolein (**35**) was also converted into 2-chloro-3-phenylpropanal (**143**) via the simultaneous addition of phenylmercury(II) chloride (**142**) and chlorination with copper(II) chloride (equation 43)[119].

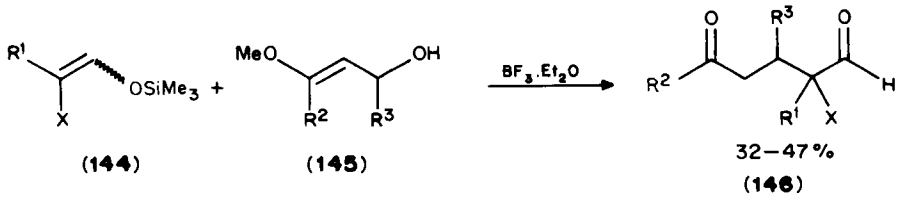


(42)



(43)

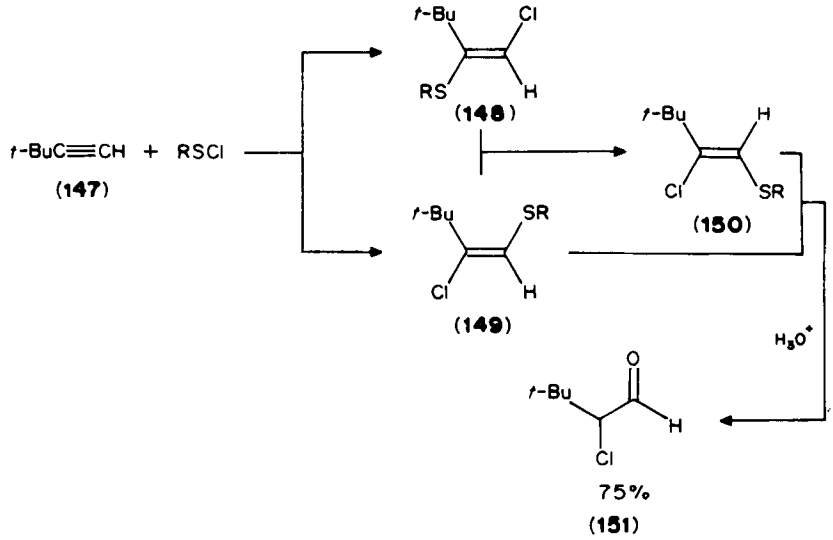
Reaction of hemiacetal vinylogues (**145**) with silyl enol ethers (**144**), derived from α-haloaldehydes in the presence of boron trifluoride etherate, yielded α-halo-δ-ketoaldehydes (**146**) (equation 44)[120].



(44)

F. Synthesis of α-Haloaldehydes from Alkynes

Terminal acetylenic compounds (e.g. **147**), on treatment with an excess of sulphenyl chlorides, furnished the corresponding α-chloroaldehydes (e.g. **151**) via hydrolysis of the mixtures of Markownikov and anti-Markownikov chlorinated enol thioethers (**148–150**) (equation 45)[121,122]. An excess of the sulphenyl chloride is essential because otherwise chloromethyl ketones are produced.



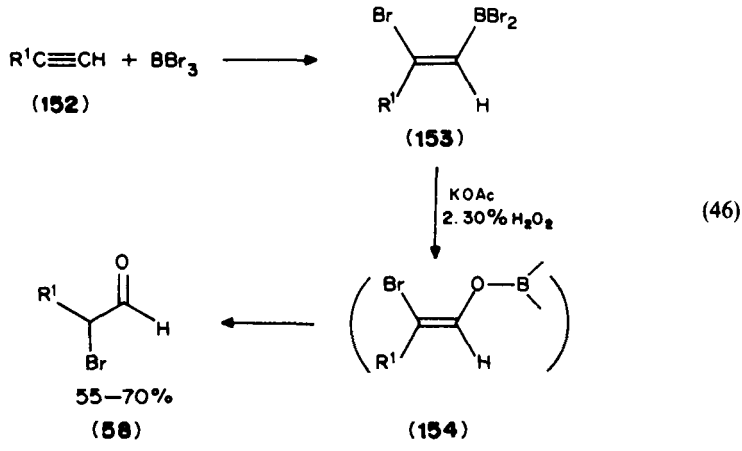
(45)

Haloboration of alkynes (**152**) followed by oxidation of the 2-haloalkenylboranes (**153**) formed served as an excellent procedure for the preparation of α-bromoaldehydes (**58**) (equation 46)[123].

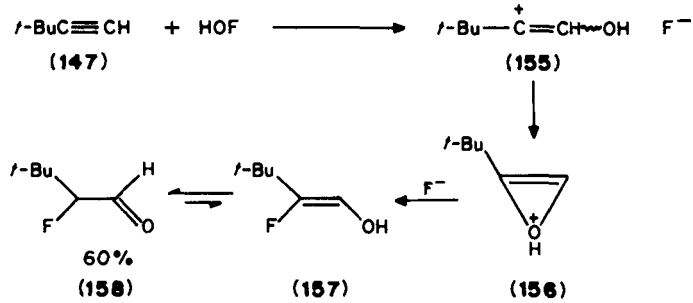
The sterically hindered α-fluoroaldehyde **158** could be synthesized from *tert*-butylacetylene (**147**) by addition of hypofluorous acid. They key intermediate in the reaction mechanism is probably a protonated oxirene (**156**), which reacts with the fluoride anion to generate the final product (equation 47)[124].

G. Miscellaneous Syntheses of α-Haloaldehydes

In this section less synthetically suitable formations of α-haloaldehydes will be discussed, although some reactions may possess potential applications.

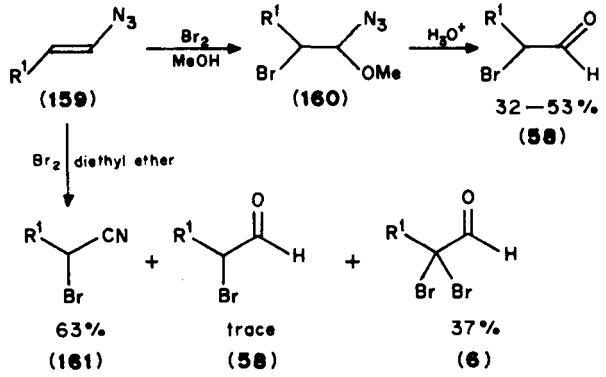


(46)



(47)

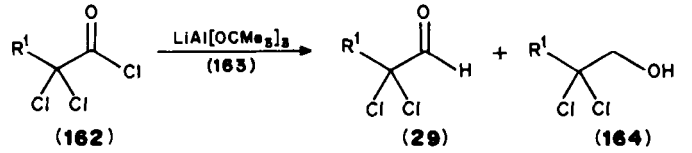
The interaction of vinyl azides (**159**) with bromine in methanol gave rise to α-bromoaldehydes (**58**). When the reaction was conducted in diethyl ether, a mixture of α-bromo-(**58**) and α,α-dibromoaldehydes (**6**) was formed, together with α-bromonitriles (**161**) (equation 48)[125].



(48)

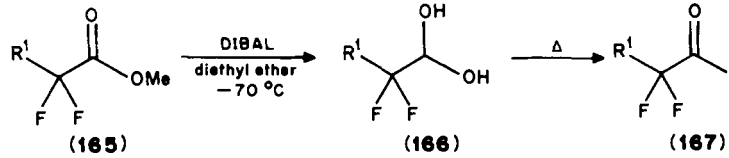
Although the hydride reduction of α,α-dichloroacid chlorides (**162**) can be regarded as a suitable procedure for the synthesis of halogenated aldehydes (**29**), the results are

disappointing, mainly owing to the further reduction of the aldehyde function to **164** (equation 49)[126,127].



(49)

α,α-Difluoroaldehydes (**167**) were synthesized by reduction of α,α-difluorocarboxylate esters (**165**) using diisobutylaluminium hydride (DIBAL). The fluorinated aldehydes were isolated as their hydrates (**166**), which on azeotropic distillation with benzene afforded the free α,α-difluoroaldehydes (**167**) (equation 50)[128]. Finally, Claisen rearrangement of the difluorovinyl ethers **169** provided the functionalized α,α-difluoroaldehyde **170** (equation 51)[129].



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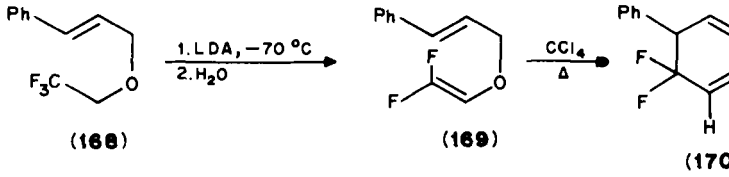
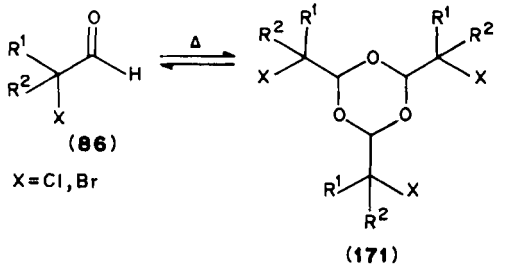


(51)

H. Oligomerization of α-Haloaldehydes

During the preparation of α-monohaloaldehydes (**86**) it was generally observed that trimerization readily occurred with formation of the corresponding 1,3,5-trioxane derivatives (**171**). Traces of acid catalyse the trimerization (equation 52)[36,37]. The reaction is reversible and the α-haloaldehydes can be easily regenerated from the 1,3,5-trioxanes by heating the trimers at 100–150 °C.



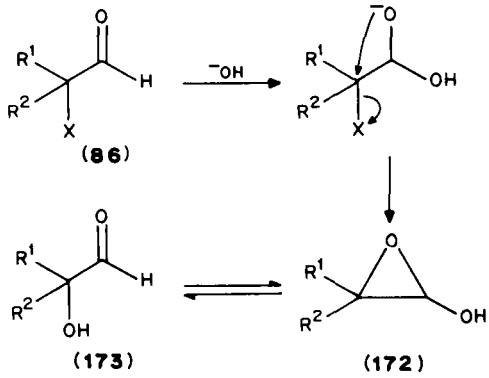
(52)

III. REACTIVITY OF α-HALOGENATED ALDEHYDES

In analogy with the section dealing with the reactivity of α-haloketones, the reactivity of α-haloaldehydes will be discussed according to the nature of the attacking reagent. While transformations of α-haloketones have been widely used in organic synthesis, applications using α-haloaldehydes have found only limited use in synthetic procedures, although the potential value of the α-haloaldehyde as a 'synthon' can be recognized. Therefore, in this section emphasis will be given to valuable preparative aspects hidden in the reactions of α-haloaldehydes with various reagents, without ignoring, however, the mechanistic aspects of the reactions, which can be completely different from those observed in similar reactions of α-haloketones.

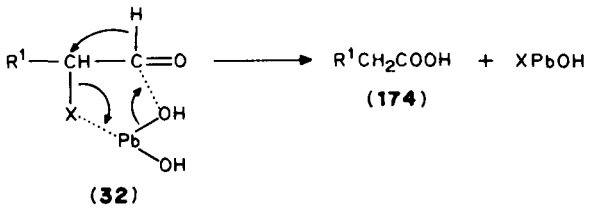
A. Reactivity of α-Haloaldehydes Towards *O*-Nucleophiles

Alkaline hydrolysis of α-monohaloaldehydes with sodium or potassium hydroxide in water or water–dioxane mixtures gave 'substitution' products, i.e. α-hydroxyaldehydes (**173**), in low to moderate yields (< 40%)[130-132]. Kinetic experiments have shown that the formation of **173** was not a result of a direct substitution reaction. Instead, the reaction pathway involved a ring cleavage of an intermediate oxirane (**172**), formed via carbonyl addition and intramolecular nucleophilic substitution (equation 53)[133].

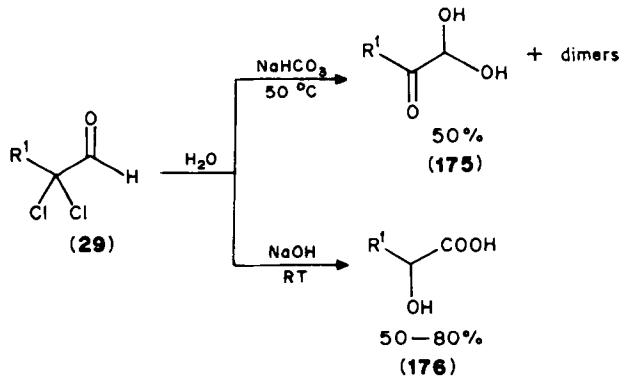


(53)

Using insoluble metal hydroxides such as lead hydroxide, the reaction afforded carboxylic acids (**174**) via an electrophilic attack of the metal atom on the halogen followed by a simultaneous migration of the aldehyde hydrogen and cleavage of the carbon—halogen bond (equation 54)[132,134]. On the other hand, treatment of α,α-dichloroaldehydes (**29**) with sodium hydrogen carbonate or sodium hydroxide in water gave α-ketoaldehydes, isolated as hydrates (**175**), and α-hydroxycarboxylic acids (**176**), respectively. The latter compounds arise from a benzylic acid rearrangement of the intermediate ketoaldehydes (equation 55)[135].

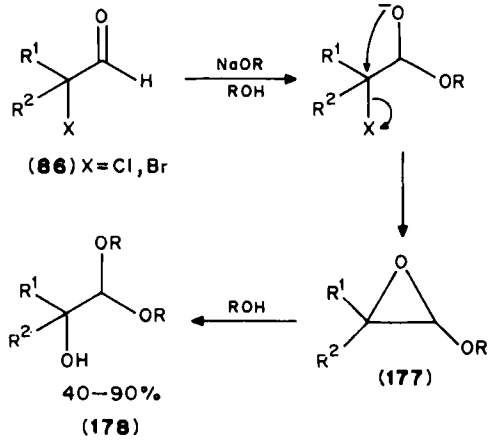


(54)



(55)

In analogy with chloral, α,α-dihaloaldehydes formed stable hydrates[130], whereas with α-monohaloaldehydes the hydrates cannot be isolated but can be detected[136,137]. In an analogous reaction, treatment of α-monohaloaldehydes with sodium alkoxides in the corresponding alcohols gave α-hydroxyacetals (**178**). The reaction involves a nucleophilic addition, followed by intramolecular nucleophilic substitution with formation of an intermediate α-alkoxyoxirane (**177**), which subsequently undergoes solvolytic ring opening (equation 56)[36,37,138–144]. The α-alkoxyoxiranes **177** could be isolated in moderate yields when the reaction was performed with sodium alkoxides in dry diethyl ether[14,15,36,138–140,142]. However, performing the reaction in an inert solvent could yield rearranged esters (**180**), in addition to methoxyoxiranes (**179**) (equation 57)[145].

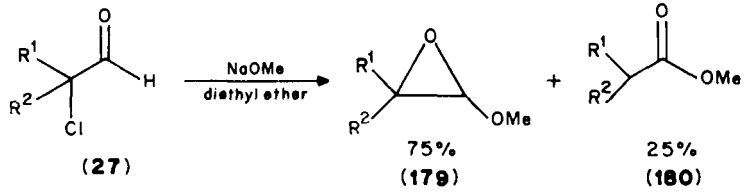


(56)

The epoxide formation is a stereospecific reaction which gives nearly exclusively the *trans* compound (**181**) (equation 57)[146]. α-Methoxyaldehydes (**182**), which are not accessible via a direct substitution route, could be prepared via methoxylation of the anion of α-hydroxyacetals with dimethyl sulphate followed by hydrolysis (equation 58)[120].

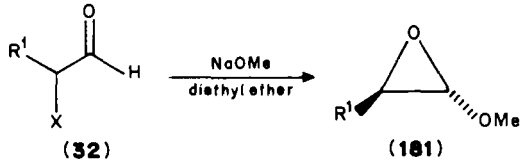
The nature of the metal counter ion of the alkoxide has a dramatic influence on the outcome of the reaction. This effect has been carefully investigated using 2-chloro-2-methylpropanal (**183**) and 2-chlorobutanal (**23**)[147]. Whereas potassium methoxide gave results identical with those obtained with sodium methoxide, although the yields were lower, a completely different route was observed using magnesium alkoxides[148,149].

Treatment of α-chloroaldehydes with the mixed magnesium alkoxides ROMgBr resulted in the formation of α-alkoxyketones (**184**). These were formed via ring opening of the non-isolable α-alkoxyoxiranes **177** with migration of a hydrogen or a methyl group under the influence of the magnesium bromide present in the reaction mixture (equation 59).

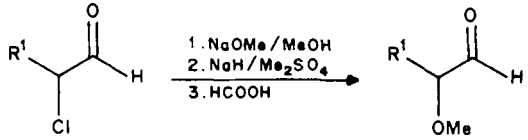


(27) (179) (180)

(57)

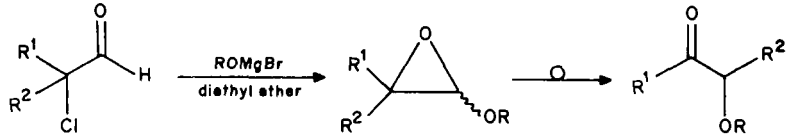


(32) (181)



(51) (182)

(58)

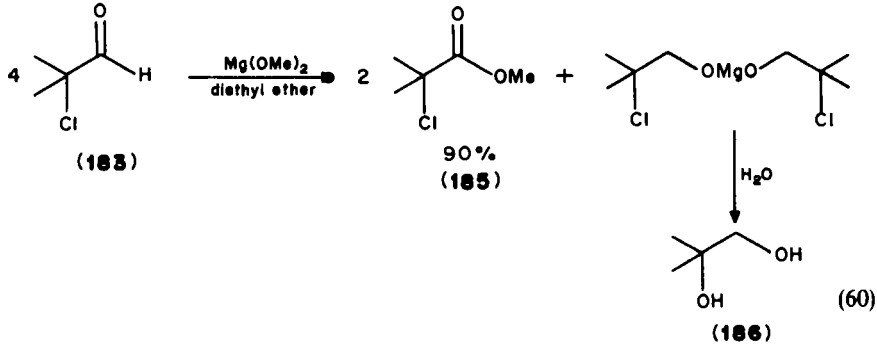


(183) $R^1 = R^2 = Me$
(23) $R^1 = H; R^2 = Et$
(177)
25–70%
(184)

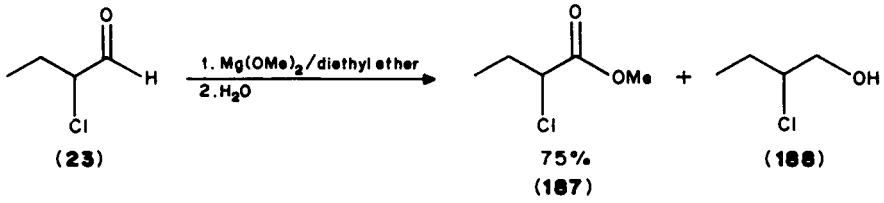
(59)

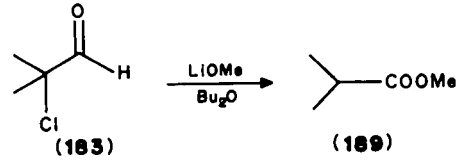
Magnesium dialkoxides gave a Tishchenko dismutation with formation of α-chloro esters (**185**, **187**) together with minor amounts of alcohols (**186**, **188**) (equation 60). On the other hand, treatment of **183** with lithium methoxide gave the Favorskii esters **189** exclusively whereas **23** afforded a mixture of **187** (70%) and **190** (30%) (equation 61). Reaction of both aldehydes with thallium ethoxide gave the Tishchenko ethyl ester analogues of **185** and **187**[147].

The nature of the reaction products formed in the reaction of α, α-dihaloaldehydes with alkoxides in the corresponding alcohol is strongly dependent on the kind of substrate, alkoxide and reaction conditions as illustrated in Table 1. Treatment of the α,α-dichloroaldehydes **29** with 2.5 equivalents of sodium alkoxide at room temperature produced an unseparable mixture of 1,1-dialkoxyalkan-2-ones (**197**) and 2,2-dialkoxy-aldehydes (**198**), except in the case of sodium isopropoxide, which led exclusively to 1,1-diisopropoxyalkan-2-ones (**197**; $R^2 = i$-Pr), albeit in lower yields[150–152].



(60)





(61)

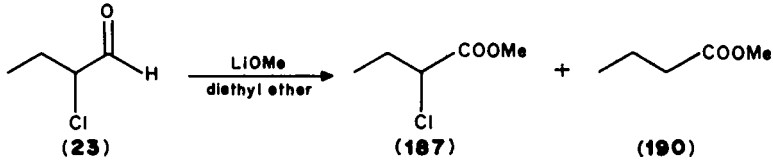
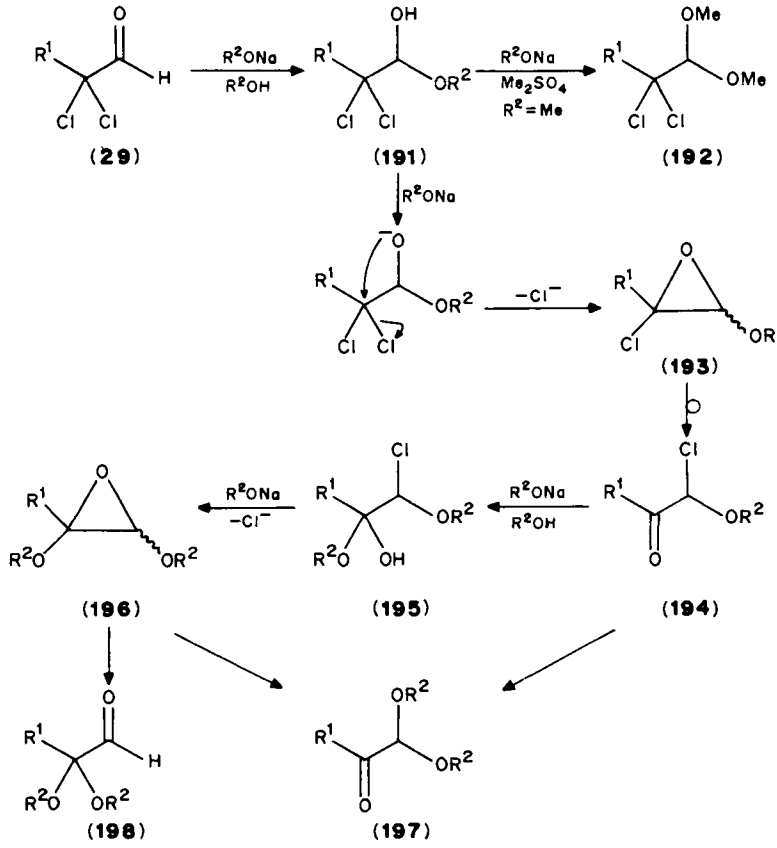


TABLE 1. Reaction of α,α-dihaloaldehydes R^1CCl_2CHO with sodium alkoxides R^2ONa in alcohols[151,152]

R^1	R^2	1,1-Dialkoxy-alkan-2-ones (197)	2,2-Dialkoxy-alkanals (198)
Me	Me	28	72
Et	Me	74	26
n-Pr	Me	65	35
i-Pr	Me	76	24
i-Pr	Et	58	42
i-Pr	*i*-Pr	100	0
t-Bu	Me	65	35
n-Pe[148]	Me	50	50
n-Hex[148]	Me	50	50
Ph	Me	44	56
Ph[148]	Me	33	67

A plausible mechanism consists in hemiacetal (**191**) formation followed by deprotonation. Indeed, the anion can be trapped with dimethyl sulphate giving **192**. Intramolecular nucleophilic substitution affords a very reactive α-alkoxy-α'-chlorooxirane (**193**), which spontaneously rearranges into a 1-alkoxy-1-chloroalkan-2-one (**194**). The latter in turn reacts further via another oxirane intermediate (**196**) or via solvolytic ring opening as reported earlier with 1-aryl-2,2-dichloroalkan-1-ones (equation 62)[153].

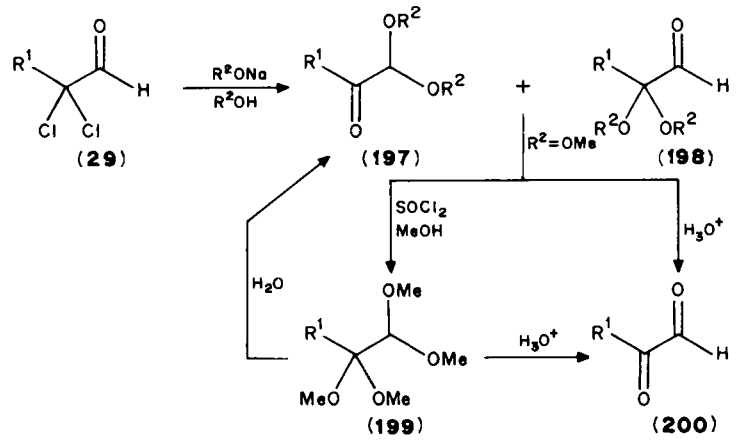


(62)

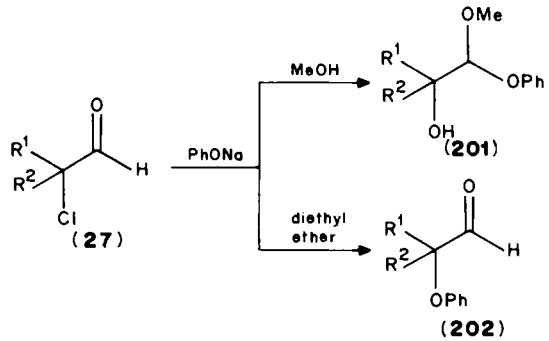
The reaction of α,α-dichloroaldehydes (**29**) with sodium alkoxides has been successfully applied in the synthesis of α-ketoacetals, which are important synthons in organic synthesis[154]. Selective hydrolysis of 2,2-dialkoxyalkanals (**198**) from the mixture of **197** and **198** with 10% phosphoric acid afforded 1,1-dialkoxyalkan-2-ones (**197**). Higher yields of the latter compounds were obtained in a one-pot procedure involving treatment with thionyl chloride of the reaction mixture of the α,α-dichloroaldehydes with alkoxides. The resulting tetraalkoxy compounds (**199**) can be regioselectively hydrolysed. Acidic hydrolysis of the reaction mixture of **197** and **198** provided an elegant and fast method for the preparation of aliphatic α-ketoaldehydes (**200**) (equation 63)[154].

Whereas the reaction of α-monochloroaldehydes with sodium phenoxide in methanol afforded the mixed acetal **201**, treatment with sodium phenoxide in diethyl ether gave the substitution product **202**, presumably via rearrangement of an intermediate α-

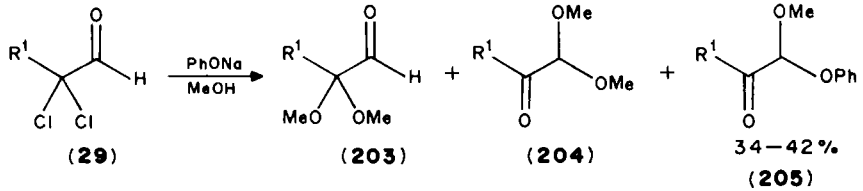
phenoxyoxirane[135]. With α,α-dichloroaldehydes, mixed acetals (**205**) were also isolated together with reaction products (**203, 204**) arising from attack of methoxide (equation 64)[135].



(63)

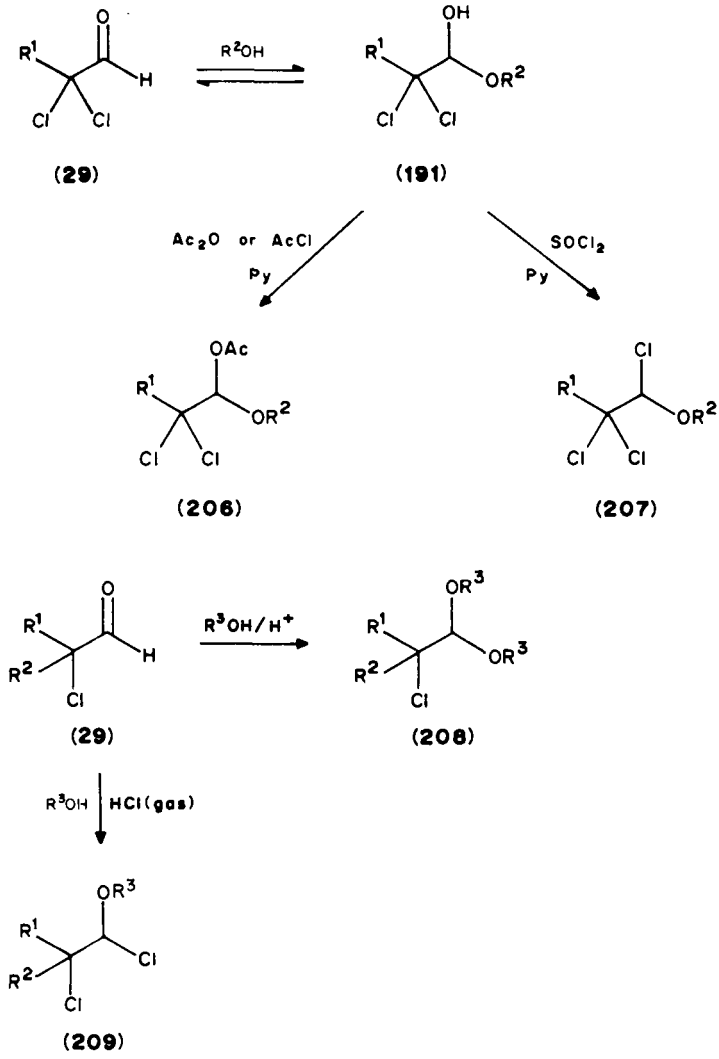


(64)



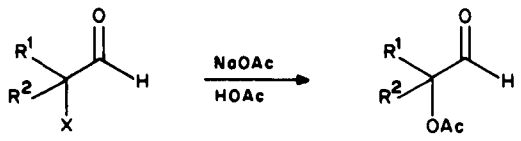
Treatment of α-haloaldehydes and especially α,α-dihaloaldehydes with alcohols gave the hemiacetals (**191**)[150]. The hemiacetals derived from α,α-dichloroaldehydes can be converted into 1-alkoxy-2,2-dihaloacetates (**206**) on treatment with acetic anhydride or acetyl chloride in the presence of pyridine, whereas addition of thionyl chloride furnished 1,2,2-trichloro-1-alkoxyalkanes (**207**) (equation 65)[135]. On the other hand, treatment of

α-haloaldehydes with alcohols in the presence of acids gave acetals (**208**)[155,156] except when using gaseous hydrogen chloride, which caused substitution of an alkoxy by chlorine giving **209** (equation 65)[135].

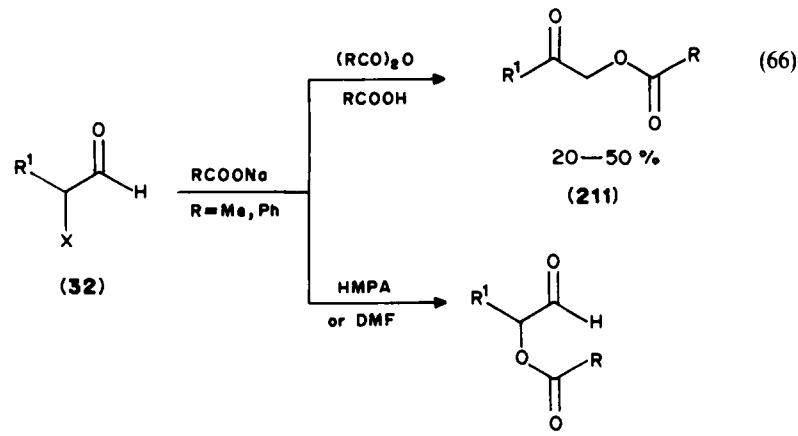


(65)

α-Acyloxyaldehydes are an important class of starting materials for the synthesis of heterocycles such as furans[157] and γ-butyrolactones[158]. Tertiary α-monohaloaldehydes (**86**) were easily transformed into the corresponding α-acetoxyaldehydes (**210**) on reaction with sodium acetate[159,160]. Secondary α-monohaloaldehydes, on the other hand, gave the isomeric α-acyloxyketones (**211**) if the reaction was performed with the sodium carboxylate in the corresponding acid anhydride[161,162] or the α-acyloxyaldehydes (**212**) if the reaction was carried out in polar, aprotic solvents[108,163] (equation 66).



(86) (210)



(66)

(32) (211) (212)

The formation of the acyloxyketones **214** can be envisaged to arise from a rearrangement of an intermediate α-acetoxyoxirane (**213**) (equation 67)[161].

α,β-Unsaturated lactones (**217**) have been prepared via a similar substitution. On reaction with potassium phenylacetate (**215**) in the presence of 18-crown-6, α-bromoaldehydes (**3**) afforded the substitution product **216**, which could be cyclized to a five-membered unsaturated lactone (**217**) on heating (equation 68)[164].

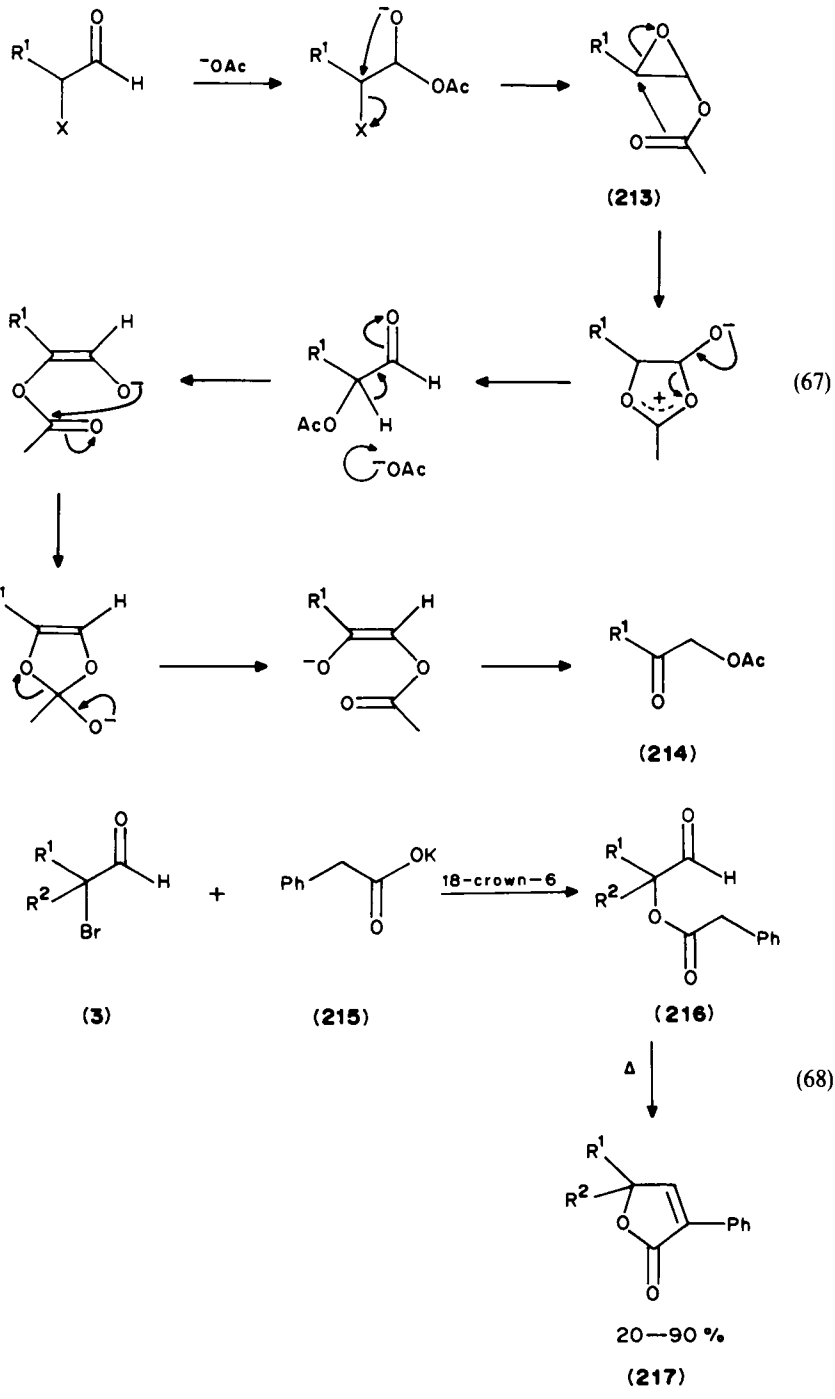
The action of acetate anion on α-haloaldehydes (**218**) can also result in elimination of hydrogen halide, giving the α,β-(**219**) and β,γ-unsaturated aldehydes (**220**) (equation 69)[165].

B. Reactivity of α-Haloaldehydes Towards *N*-Nucleophiles

1. Reaction of α-haloaldehydes with ammonia

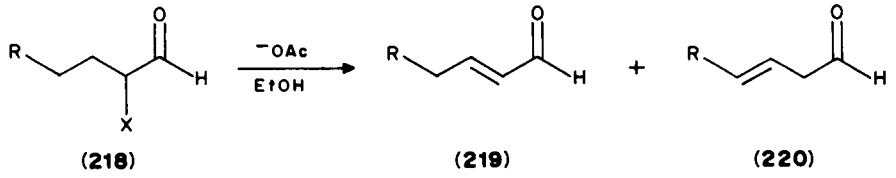
Very few reports have dealt with the reaction of α-halogenated aldehydes with ammonia. On the other hand, the reaction of α-chlorinated aldehyde acetals with ammonia is well documented[1].

Treatment of aryl-substituted butanals (**221**) with ammonia afforded pyrrole derivatives (**222, 223**) (equation 70)[166,167].



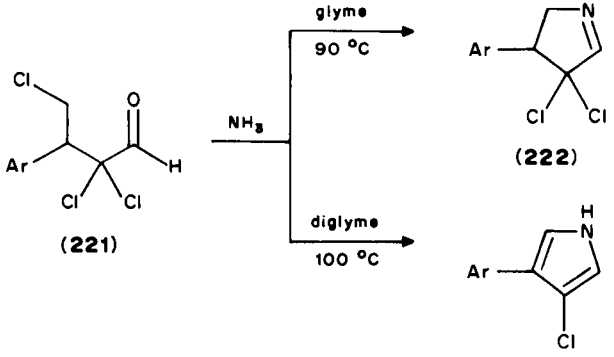
(67)

(68)



(218) (219) (220)

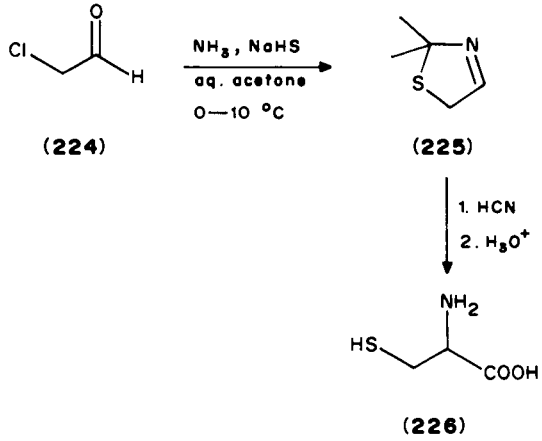
(69)



(221) (222) (223)

(70)

Condensation of chloroacetaldehyde (**224**) with ammonia in the presence of sodium hydrogen sulphide and acetone gave rise to a thiazoline (**225**) which can be converted into racemic cysteine (**226**) by addition of hydrogen cyanide and hydrolysis (equation 71)[168].



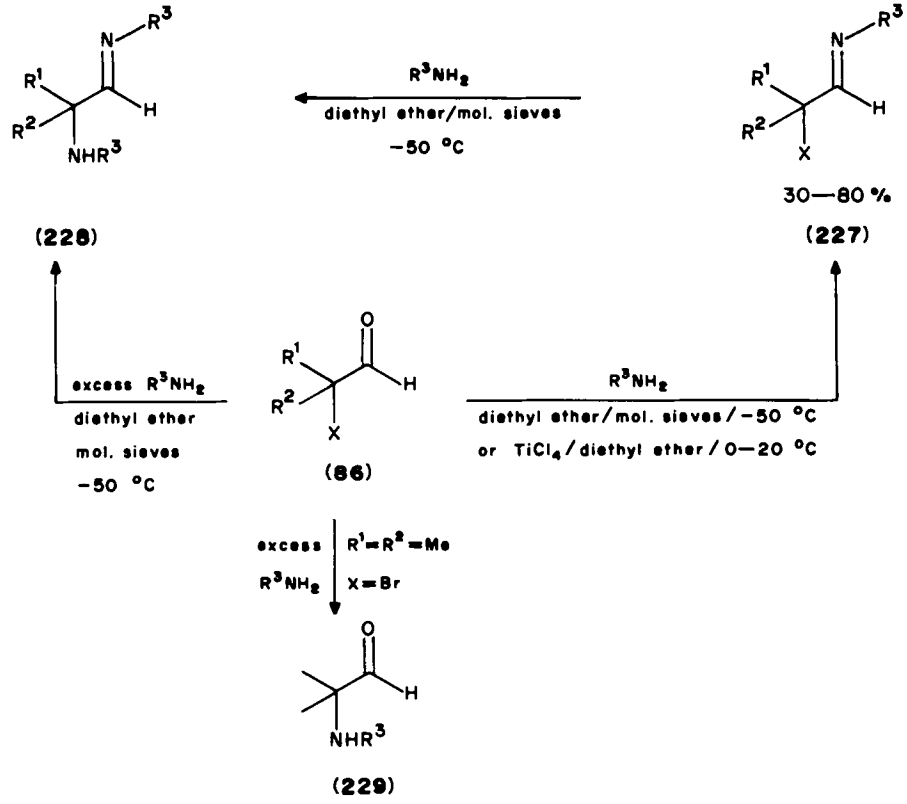
(224) (225) (226)

(71)

2. Reaction of α-haloaldehydes with primary amines

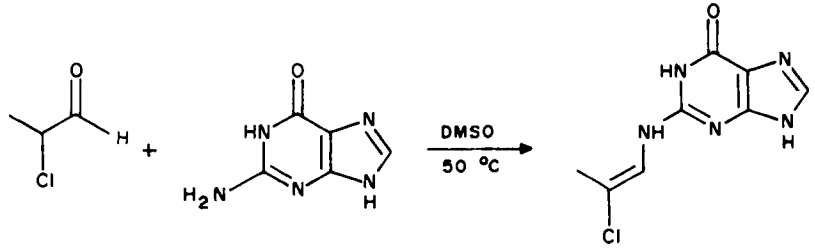
The course of the reaction of α-haloaldehydes with primary amines is strongly dependent on the reaction conditions. Condensation of α-monohaloaldehydes with primary amines in the presence of molecular sieves[169] or titanium tetrachloride[170,171] or

with azeotropic removal of water[172] gave the corresponding α-haloaldimines (**227**). Using an excess of amine, the reaction products were α-aminoaldimines (**228**)[169], except in the case of 2-bromo-2-methylpropanal, which afforded α-aminoaldehydes (**229**)[173] (equation 72).



(72)

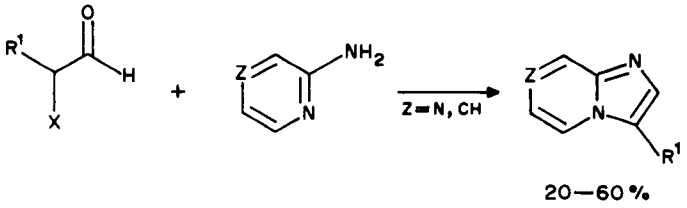
β-Halogenated enamines (**232**) were the reaction products when, for instance, α-chloropropanal (**230**) was treated with guanine (**231**) (equation 73)[174].



(230) (231) (232)

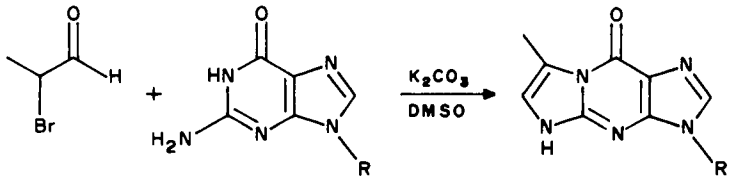
(73)

A series of imidazo[1,2-*a*]-pyridines[175-177] and -pyrazines[178,179] (**234**) were synthesized by condensation and ring closure of α-haloaldehydes with 2-aminopyridines and 2-aminopyrazines (**233**), respectively. The reaction can be viewed as an initial displacement of halide by the amino moiety, followed by cyclization and dehydration (equation 74).



(**32**) (**233**) (**234**)

(74)



(**9**) (**235**) (**236**) Ref. 182

Similar cyclizations (e.g. to **236**) have been observed on treatment of 3-methylguanine[180] and guanosine (**235**)[181,182] with α-monohaloaldehydes (equation 74).

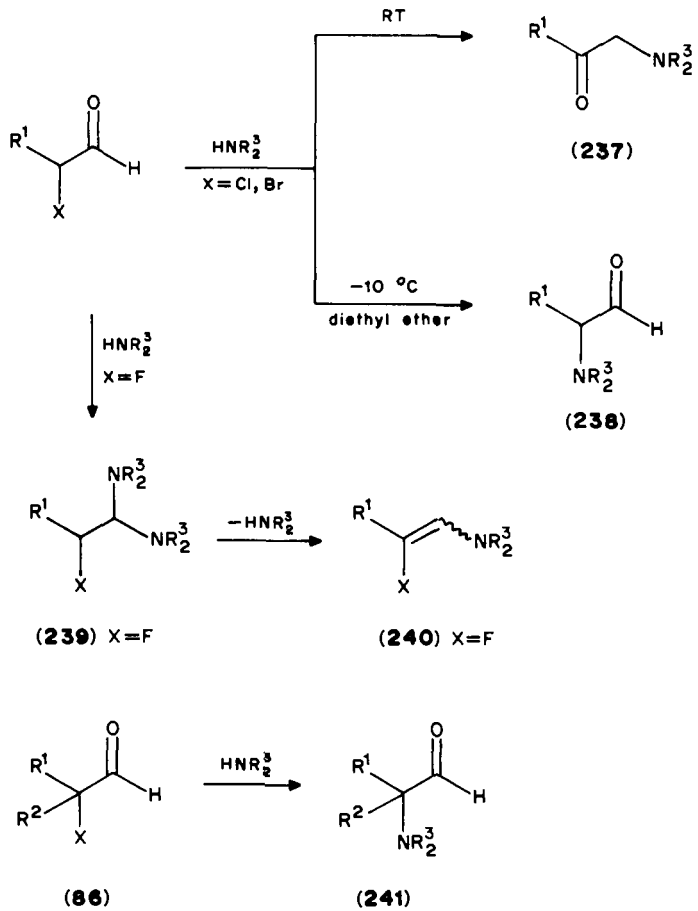
3. *Reaction of α-haloaldehydes with secondary amines*

Reaction of secondary amines with α-haloaldehydes is strongly dependent on the substitution pattern of the aldehyde (secondary or tertiary aldehyde), the nature of the halogen atom and the reaction conditions.

Reaction of secondary α-chloro- and α-bromoaldehydes with secondary amines at room temperature gave rise to α-aminoketones (**237**) via rearrangement of an intermediate α-aminoepoxide[183-185]. If the same reaction was conducted under carefully controlled conditions using α-bromoaldehydes at $-10\,^{\circ}C$ in diethyl ether, α-aminoaldehydes (**238**) were isolated as reaction products[186]. In addition, tertiary α-haloaldehydes always showed the formation of substitution products (**241**)[187]. Reaction of α-fluoroaldehydes with amines involved attack on the carbonyl function with formation of fluorinated enamines (**240**) via intermediate aminals (**239**)[188] (equation 75).

The formation of both the 1-aminoalkan-2-ones (**237**) and α-aminoaldehydes (**238**) can be explained by rearrangement of an intermediate α-aminoepoxide (**242**). On migration of a hydride, **242** afforded ketones whereas migration of the amino function furnished aldehydes (equation 76).

Reaction of secondary α-haloaldehydes with an excess of amines gave 1,1,2-triamines (**243**) which, on heating and hydrolysis, furnished enediamines (**244**) and α-aminoaldehydes (**238**), respectively. The reaction should be conducted under carefully controlled conditions as α-aminoaldehydes easily isomerize to α-aminoketones (**237**) (equation 77)[155,186,189,190].

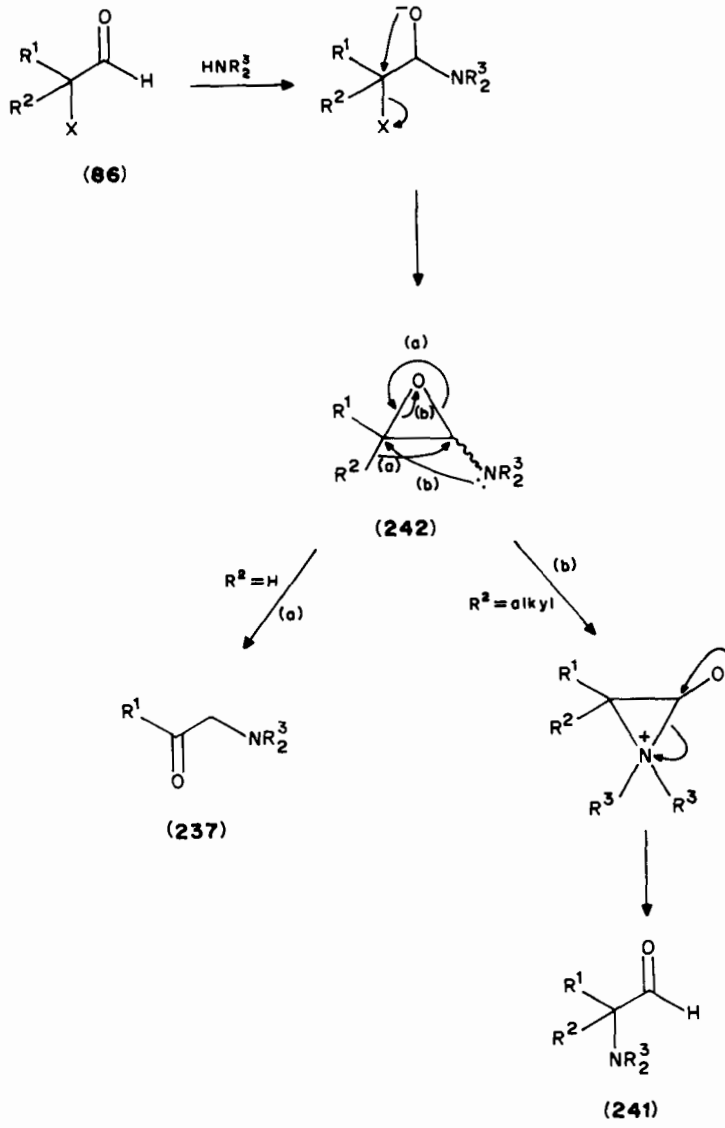


The action of 1,2-bis(alkylamino)ethanes (**245**) on α-haloaldehydes afforded exclusively the corresponding cyclic aminals (**246**). The latter can be converted into pyrazine derivatives (**247**) by treatment with potassium *tert*-butoxide in *tert*-butanol (equation 77)[191].

On treatment of α,β-dibromoaldehydes (**248**) with stoichiometric amounts of secondary amines, the corresponding disubstitution products, i.e. α,β-diaminoaldehydes (**249**), were formed after hydrolysis of the crude reaction mixture. At room temperature the latter are transformed into α-amino-α,β-unsaturated aldehydes (**250**) and/or 1,2-bis(alkylamino)ethenes (**251**). Using an excess of the amine, β,γ-diaminoenamines (**252**) could be obtained (equation 78)[192].

A plausible reaction mechanism involving iminium salts (**253**) is outlined in equation 79.

A general synthesis of β-haloenamines (**240**) involved either the reaction of α-haloaldehydes with tris(*N*,*N*-dialkylamino)arsines[193-196] or their reaction with secondary amines in the presence of metal chlorides ($AsCl_3$, $SbCl_3$, $BiCl_3$, $FeCl_3$ and $TiCl_4$) (equation 80)[82,194]. α-Haloaminals are available from α-haloaldehydes: one α-fluoroaminal was obtained by direct amination[188] and α-chloro and α-bromo compounds by the $AsCl_3$–HNR_2^3 method[193,194,197].



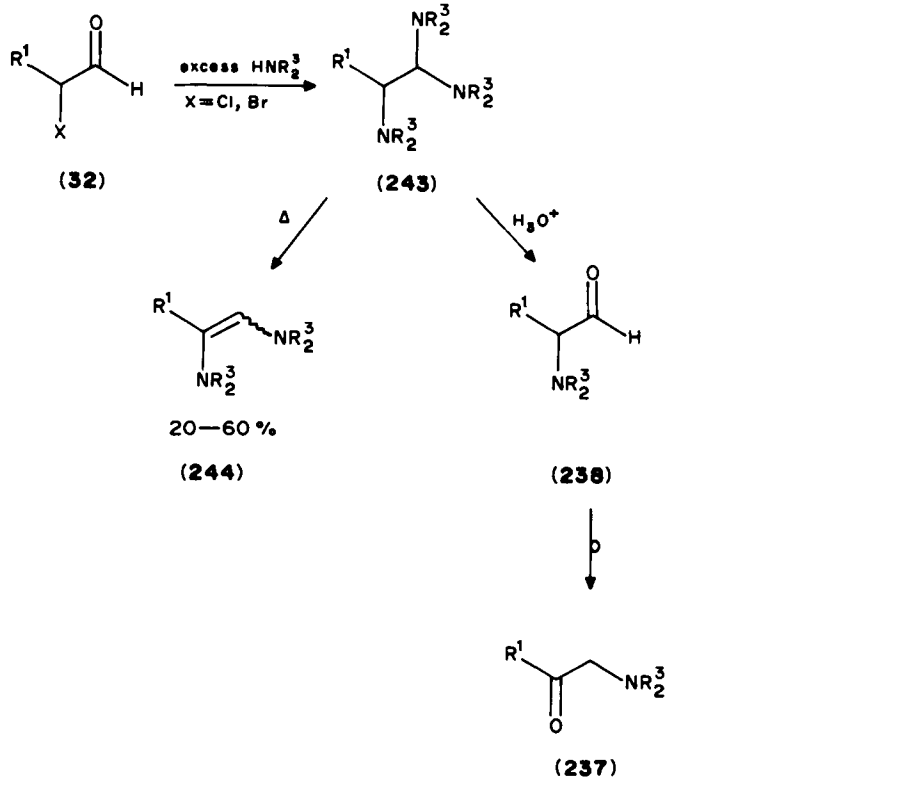
(76)

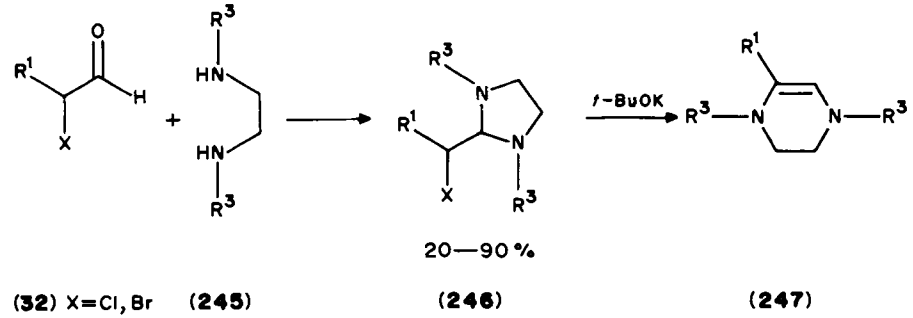
α-Cyanoenamines (**255**) were formed when brominated aldehydes were allowed to react with secondary amines in the presence of sodium cyanide. The intermediate brominated α-aminonitriles (**254**) afforded the enamines (**255**) on reaction with triethylamine (equation 80)[198,199].

4. Reaction of α-haloaldehydes with tertiary amines

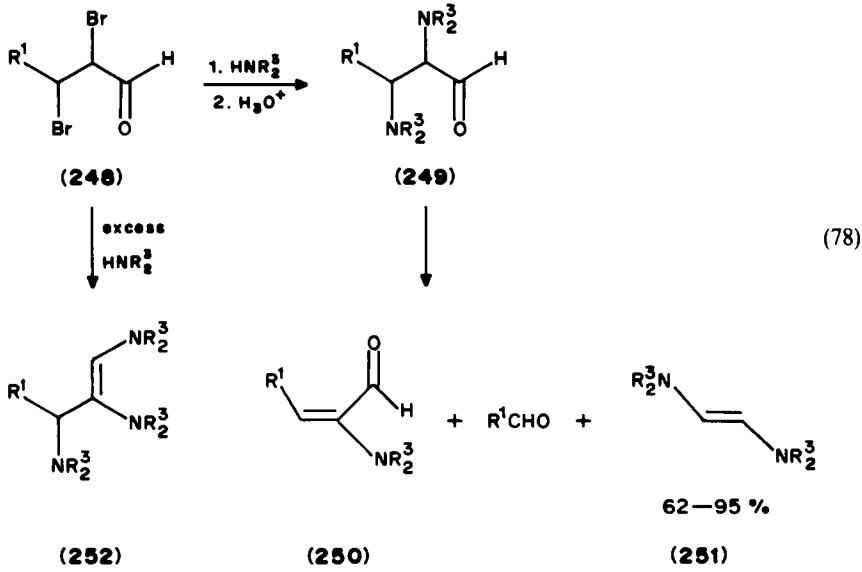
Dehydrohalogenation with tertiary amines such as triethylamine, pyridine or collidine of α-monohalo- and α,α-dihaloaldehydes could be an excellent procedure for the

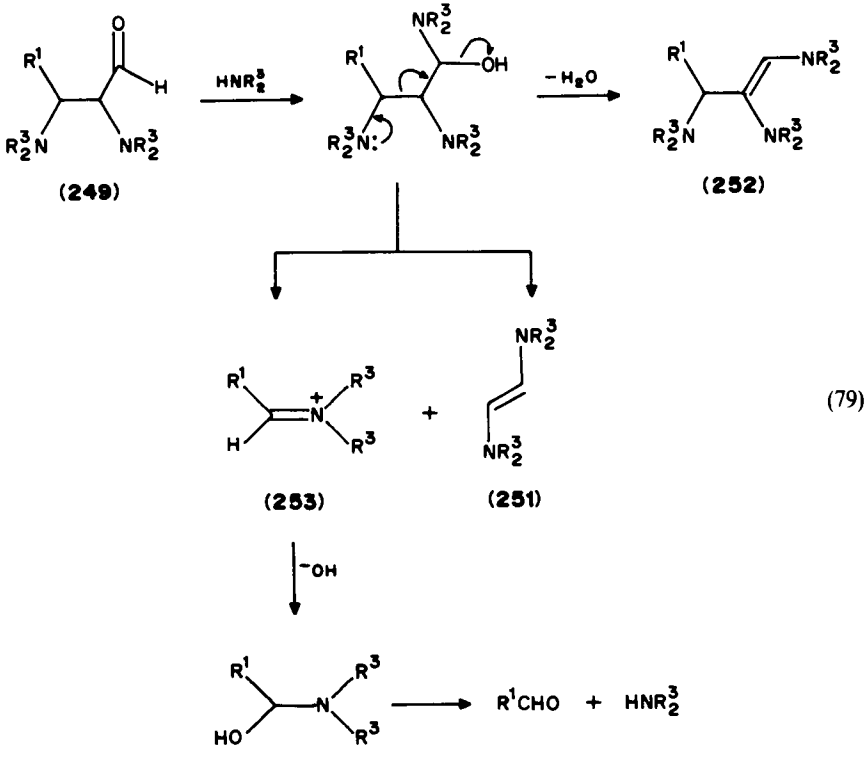
synthesis of α,β-unsaturated and α-halo-α,β-unsaturated aldehydes. Unfortunately, most attempts provided unsatisfactory results and only 1-bromocyclohexane carboxaldehyde (**19**)[200], 2-chloro-3-(phenylthio)aldehydes such as **257**[201,202] and α,β-dibromoaldehydes (**248**)[203] on treatment with diethylaniline and triethylamine, respectively, generated the corresponding α,β-unsaturated aldehydes in acceptable yields (equation 81). In addition, 1,3-dimethyl-2-phenylbenzimidazoline has been found to be an efficient reagent for the mild reductive dehalogenation of α-haloaldehydes[315].

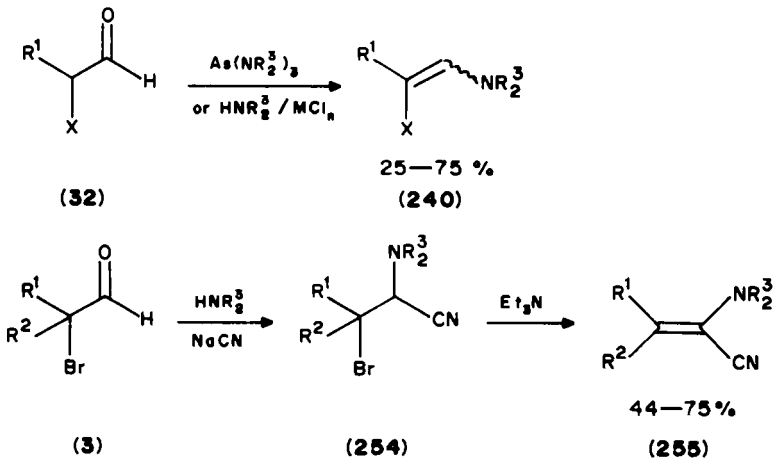




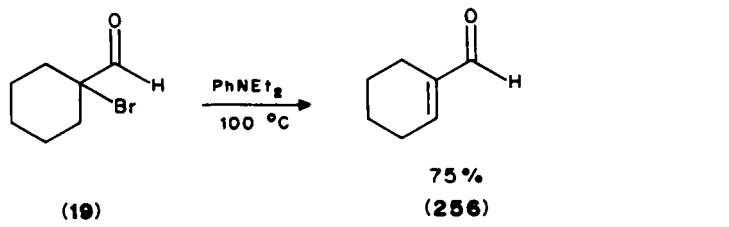
(77)

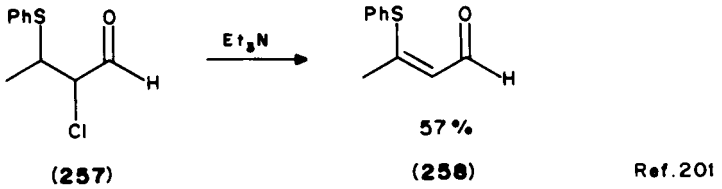

Br
R1
H
Br
O
1. HNR2 3
2. H3O+
NR2 3
R1
H
NR2 3
O
(248)
(249)
excess
HNR2 3
(78)
NR2 3
R1
NR2 3
NR2 3
O
R1
H
NR2 3
+ R1CHO +
R2 3N
NR2 3
62—95 %
(252)
(250)
(251)


O
R1
H
R2 3N
NR2 3
(249)
HNR2 3
NR2 3
R1
OH
R2 3N:
NR2 3
- H2O
R1
NR2 3
R2 3N
NR2 3
(252)
R1
R3
H
N+
R3
(253)
+
NR2 3
NR2 3
(251)
(79)
-OH
R1
R3
HO
N
R3
R1CHO + HNR2 3



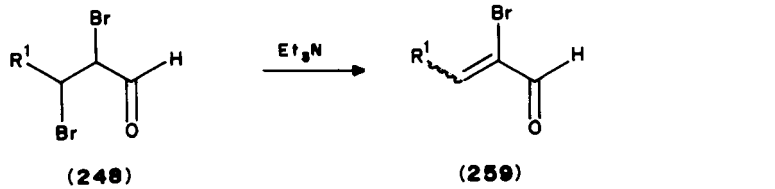
(80)





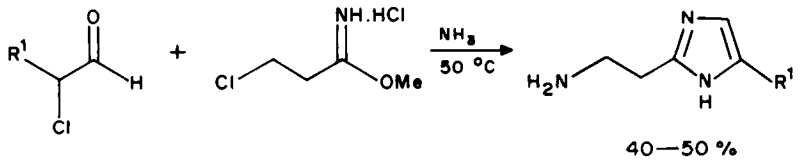
(81)

Ref. 201

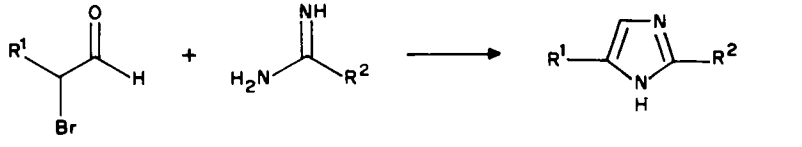


5. Reaction of α-haloaldehydes with imidates, amidines and enamines

Imidazoles (**261**, **263**) have been prepared from α-haloaldehydes via cyclocondensation with imidates (**260**)[204] and amidines (**262**)[205]. Pyrrole dicarboxylate esters (**265**) have been obtained using the enamine (**264**) derived from dimethyl acetonedicarboxylate and ethanolamine[206,207].

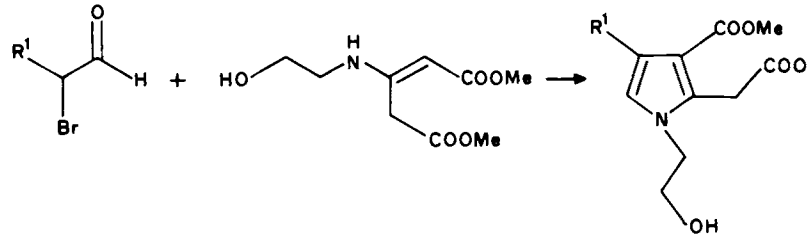


(32) (260) (261)



(82)

(58) (262) (263)



(58) (264) (265)

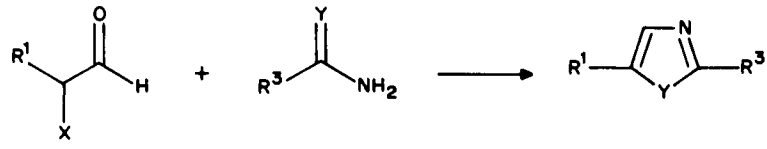
6. Reaction of α-haloaldehydes with amides, thioamides and isocyanates

Cyclocondensation of α-haloaldehydes with amides and thioamides (**266**) provided a general procedure[208,209] for the synthesis of oxazoles (**267**) and thiazoles (**269**) respectively (equation 83). In a similar way, α-haloaldehydes are easily converted into α-amino-oxazoles and -thiazoles (**271**) via condensation with urea[210] and thiourea derivatives (**270**)[211–213], respectively.

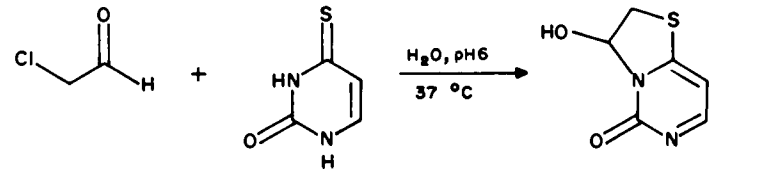
On the other hand, reaction of chloroacetaldehyde (**224**) with the thioformamide **272** provided the thiazine **273** (equation 83)[214], while reaction of **32** with *N*-alkyldithiocarbamic acid salts (**274**) or methyl *N*-alkyldithiocarbamates gave thiazoline-2-thiones (**275**) (via intermediate hydroxythiazolidinethiones) or 2-methylthiothiazolium salts, respectively[215,216]. Finally, cycloaddition of monoisocyanates of P^{III} acids (**276**) afforded the P-containing heterocyclic compounds **277**[217] (equation 83). However, reaction of α,α-dichloroaldehydes with primary amides did not give ring closure but instead the addition products **278** were isolated. These can be dehydrated to the corresponding aldimines (**279**) (equation 84)[218,219].

7. Reaction of α-haloaldehydes with carbonyl reagents

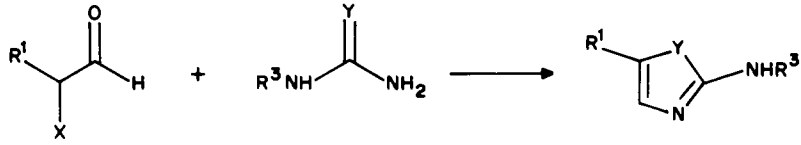
Reaction of 2,4-dinitrophenylhydrazine[220,221] or alkoxycarbonylhydrazines[222] with α-haloaldehydes gave only the corresponding hydrazones under carefully controlled conditions. Otherwise, depending on the temperature, solvent, acidity and



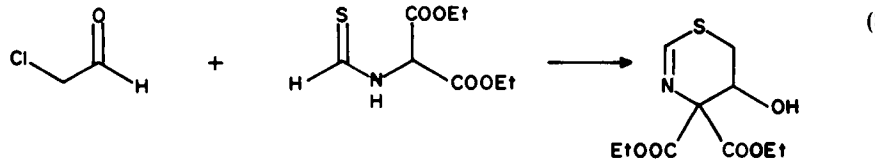
(32) (266) (267) Y=O, S



(224) (268) (269) Ref. 209

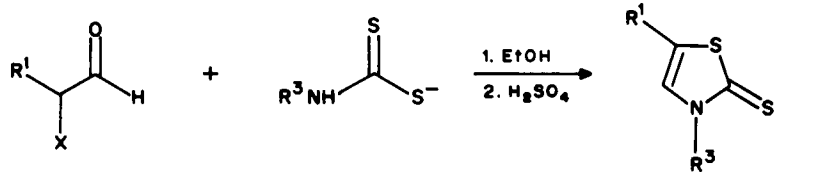


(32) (270) (271) Y=O, S

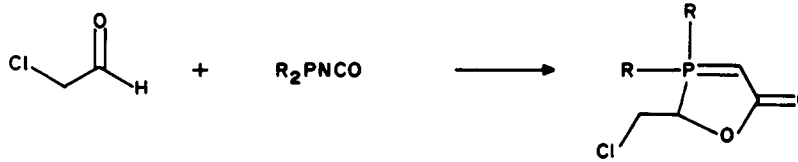


(83)

(224) (272) (273)

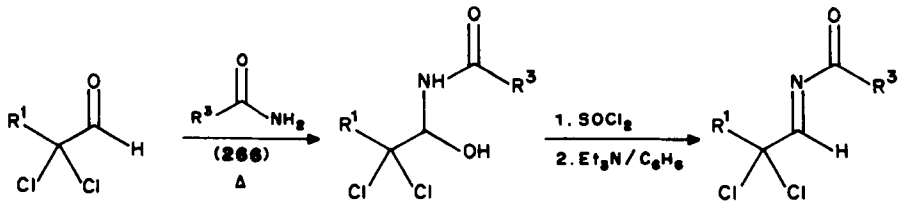


(32) (274) 60—85 % (275)



(224) (276) (277)

aldehyde:reagent ratio the initially formed 2,4-dinitrophenylhydrazones (**280**) can undergo dehydrohalogenation to **281**, substitution of the halogen by the anion derived from the solvent (alkoxide, acetate) to give **282** or osazone (**284**) formation (equation 85)[37,223,224].



(29) (278) (279)

(84)

In an identical procedure, α-bromoaldehydes (**286**) have been converted into α,β-unsaturated aldehydes (**288**) by the action of *N*,*N*-dimethylhydrazine (equation 86)[225].

Other examples and leading references concerning the reactions of α-haloaldehydes with hydrazines, oximes and related reagents have been included in the chapters on α-haloimines.

C. Reactivity of α-Haloaldehydes Towards *S*-Nucleophiles

α-Sulphenylated aldehydes (**289**) are the most commonly encountered reaction products when α-monohaloaldehydes are treated with metal thiolates, $(R^3S)_nM$[202,226–231]. Under appropriate conditions nearly quantitative yields can be obtained (equation 87)[202,231,267].

Secondary α-sulphenylated aldehydes are easily converted into the isomeric ketones (**290**) on standing or on treatment with traces of acids[227]. Performing the reaction in nucleophilic solvents (water, alcohols) can lead to the formation of products arising from attack on the solvent. Therefore, the use of dimethoxyethane or tetrahydrofuran is favourable for the formation of α-sulphenylated aldehydes[231].

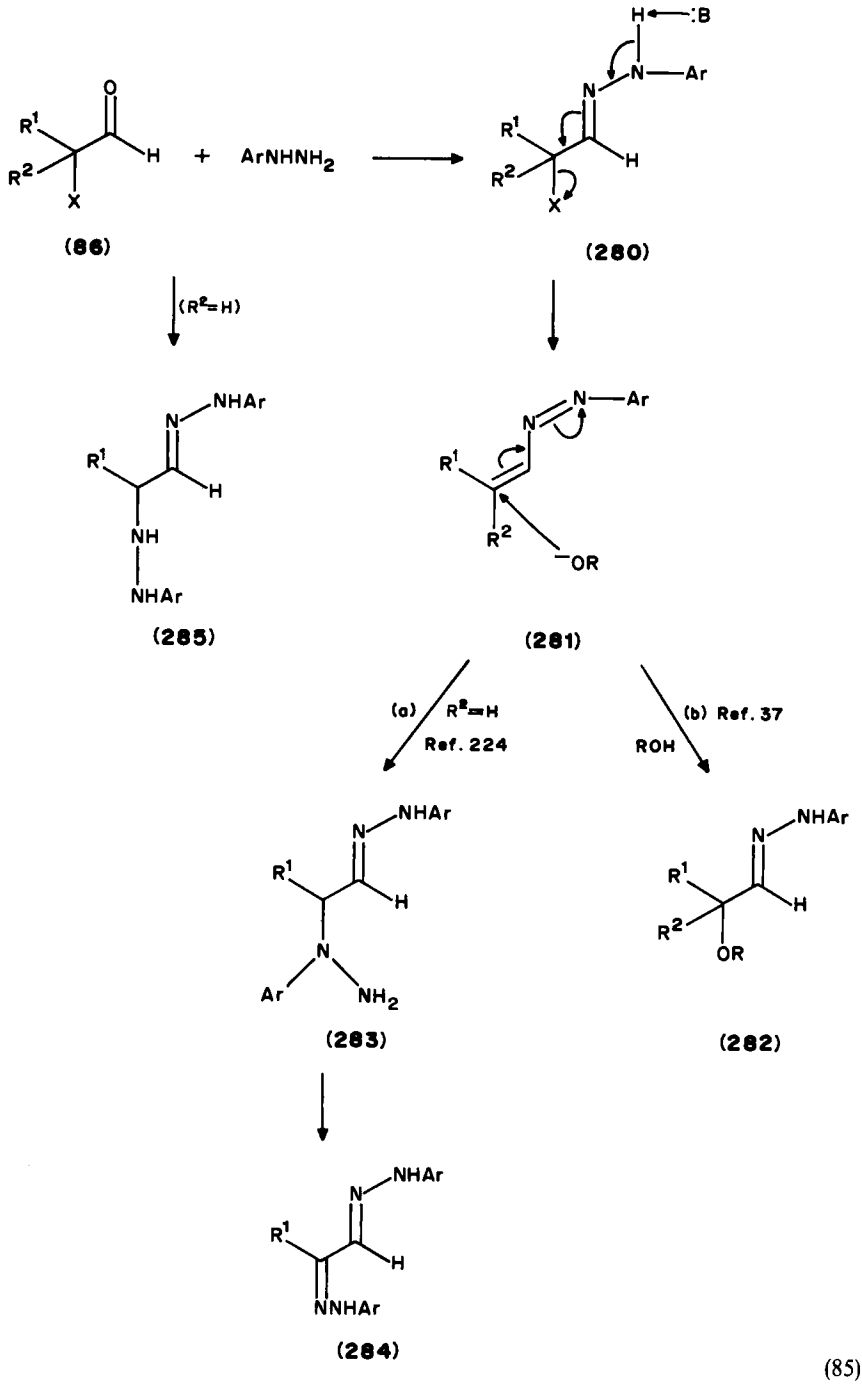
Reactions of α,α-dihaloaldehydes with sodium thiolates have also been investigated under various conditions. Reaction in dimethoxyethane gave rise to mono-α-sulphenylated (**291**) and/or α,α-disulphenylated aldehydes (**292**). When an excess of thiolate was used, the amount of the monosulphenylated product increased significantly. α,α-Disulphenylated aldehydes were isolated as the sole products on performing the reaction in water. On the other hand, performing the reaction in methanol changed the nature of the products dramatically, producing significant amounts of the rearranged ketones **293** (equation 88)[231].

Cyclocondensation of chloroacetaldehyde with sodium hydrogen sulphide gave 2,5-dihydroxy-1,4-dithiane (**294**) (equation 89)[232].

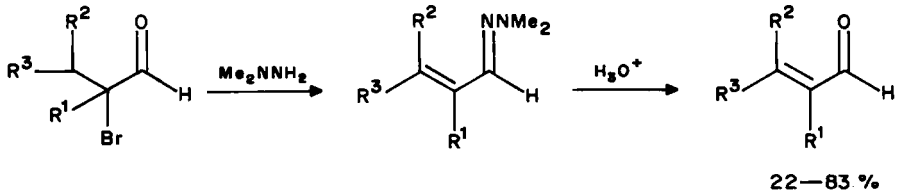
D. Reactivity of α-Haloaldehydes Towards *C*-Nucleophiles

1. Reaction of α-haloaldehydes with cyanide

The reaction of cyanide ion with α-haloaldehydes occurs by a variety of reaction pathways, which are mainly influenced by the substitution pattern of the aldehyde. Two

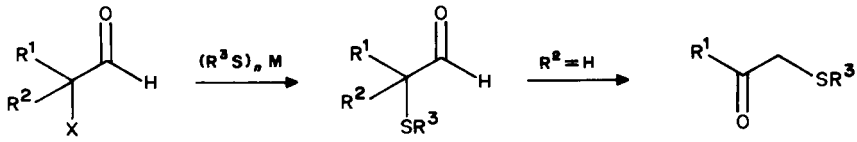


(85)



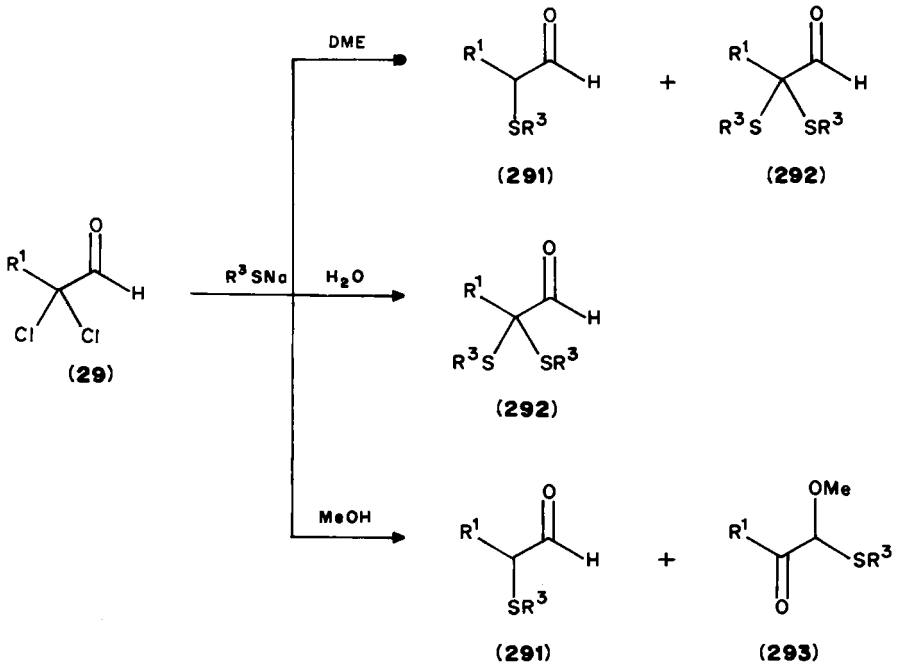
(286) (287) (288)

(86)



(86) (289) (290)

(87)

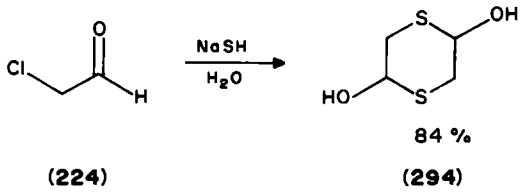


(29) (291) (292) (292) (291) (293)

(88)

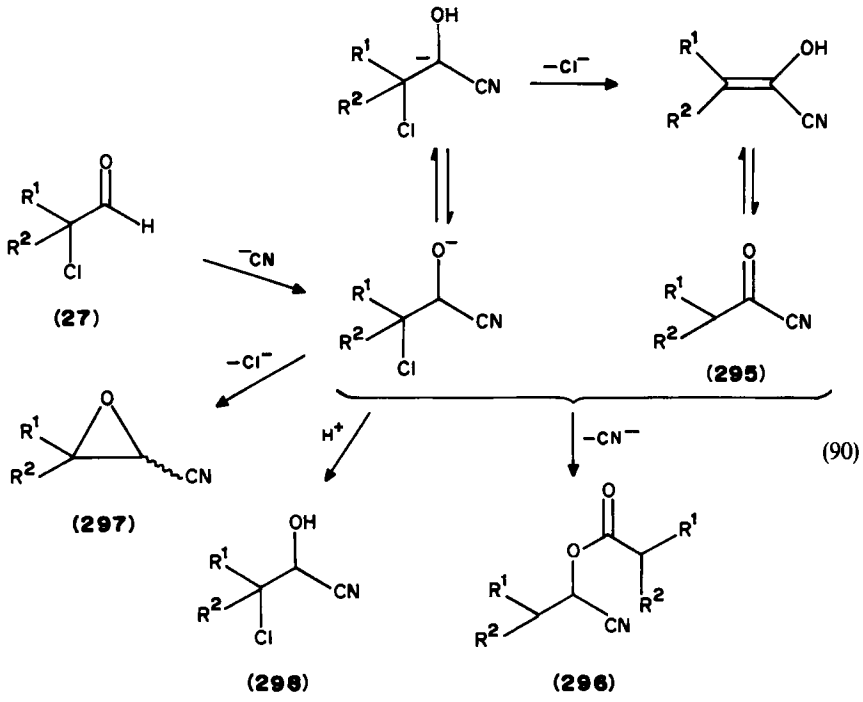
competitive routes give cyanooxiranes (**297**) or esters (**296**). However, when the reaction medium is not basic enough, cyanohydrins (**298**) are isolated. With primary and tertiary aldehydes the sole reaction products were the esters **296** and the cyanooxiranes **297**, respectively, whereas with secondary aldehydes a mixture of both reaction products was

formed when the reaction was carried out in aqueous medium[233,234]. If the reaction was performed in methanol, methyl esters (**180**) were isolated (equation 90)[135].



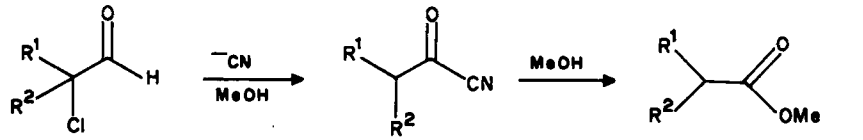
(89)

(224) (294)



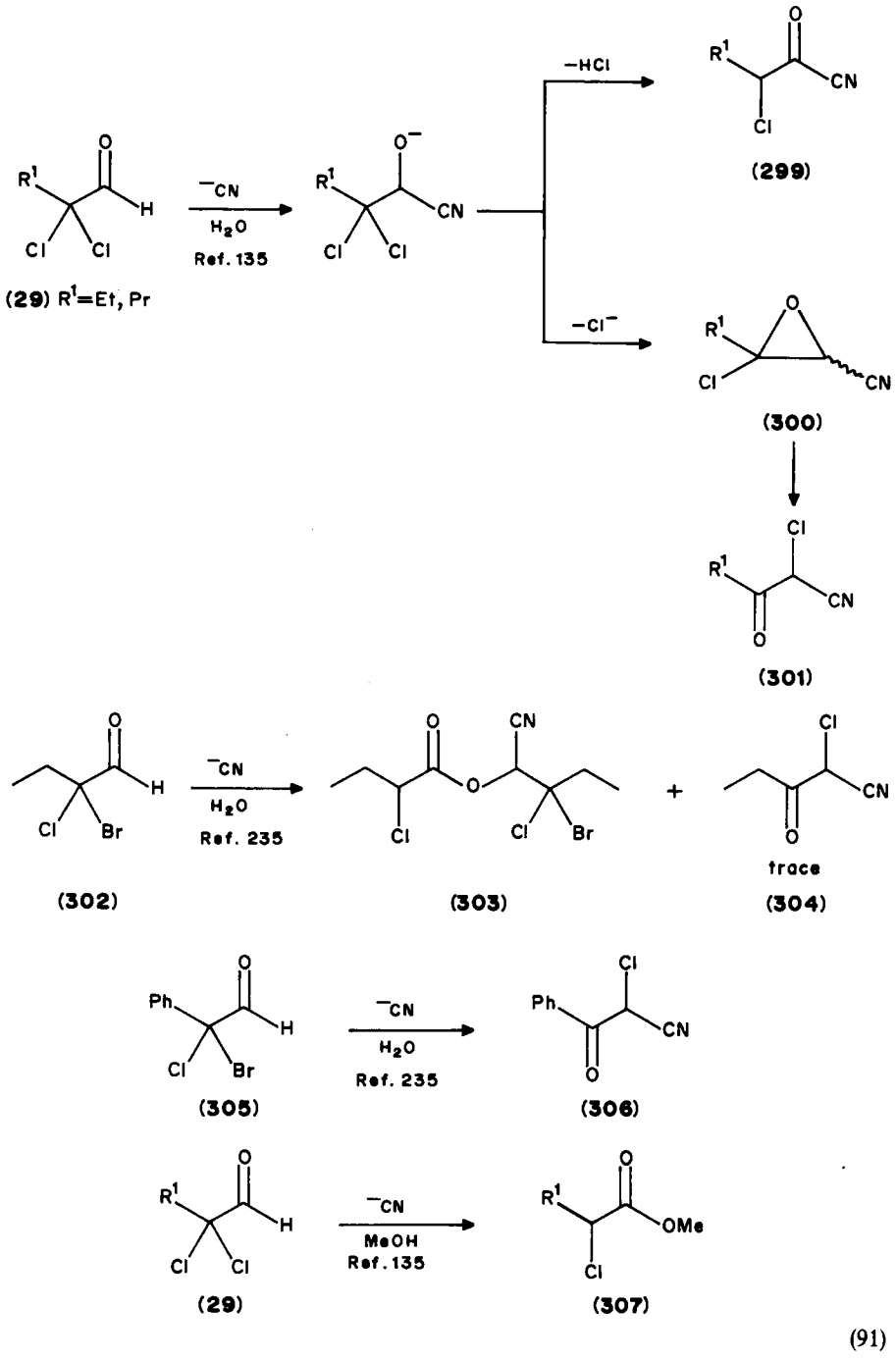
(27) (295) (297) (298) (296)

(90)



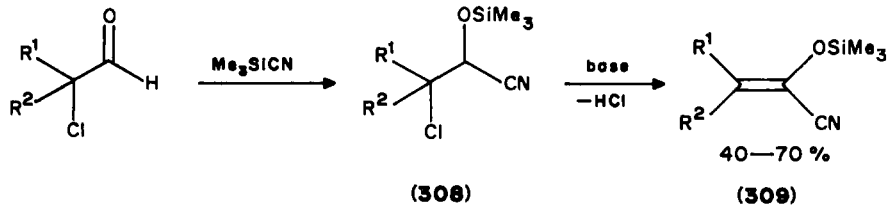
(27) (295) (180)

α,α-Dihaloaldehydes on treatment with cyanide ion react by an identical mechanism and, depending on the nature of the aldehyde and the solvent, α-chloroesters (**307**), α-chloroacyl cyanides (**299**) and α-chloro-α-cyanoketones (**301, 304, 306**) are formed, the latter compounds being generated from intermediate cyanooxiranes (**300**) (equation 91)[17,135].


(29) R¹=Et, Pr
⁻CN
H₂O
Ref. 135
-HCl
-Cl⁻
(299)
(300)
(301)
(302)
Ref. 235
(303)
+
trace
(304)
(305)
(306)
MeOH
Ref. 135
(29)
(307)

(91)

On the other hand, 2-(trimethylsiloxy)-2-alkenenitriles (**309**) can be synthesized via reaction of α-haloaldehydes with trimethylsilyl cyanide and subsequent dehydrohalogenation of the cyanohydrins (**308**) (equation 92)[236].

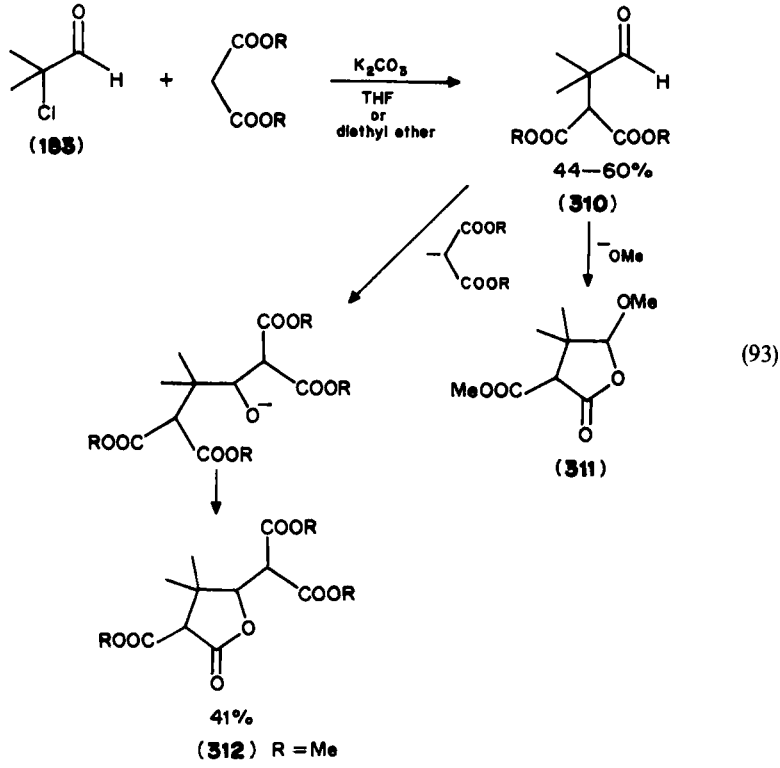


(92)

2. Reaction of α-haloaldehydes with carbanions, enolates and ylides

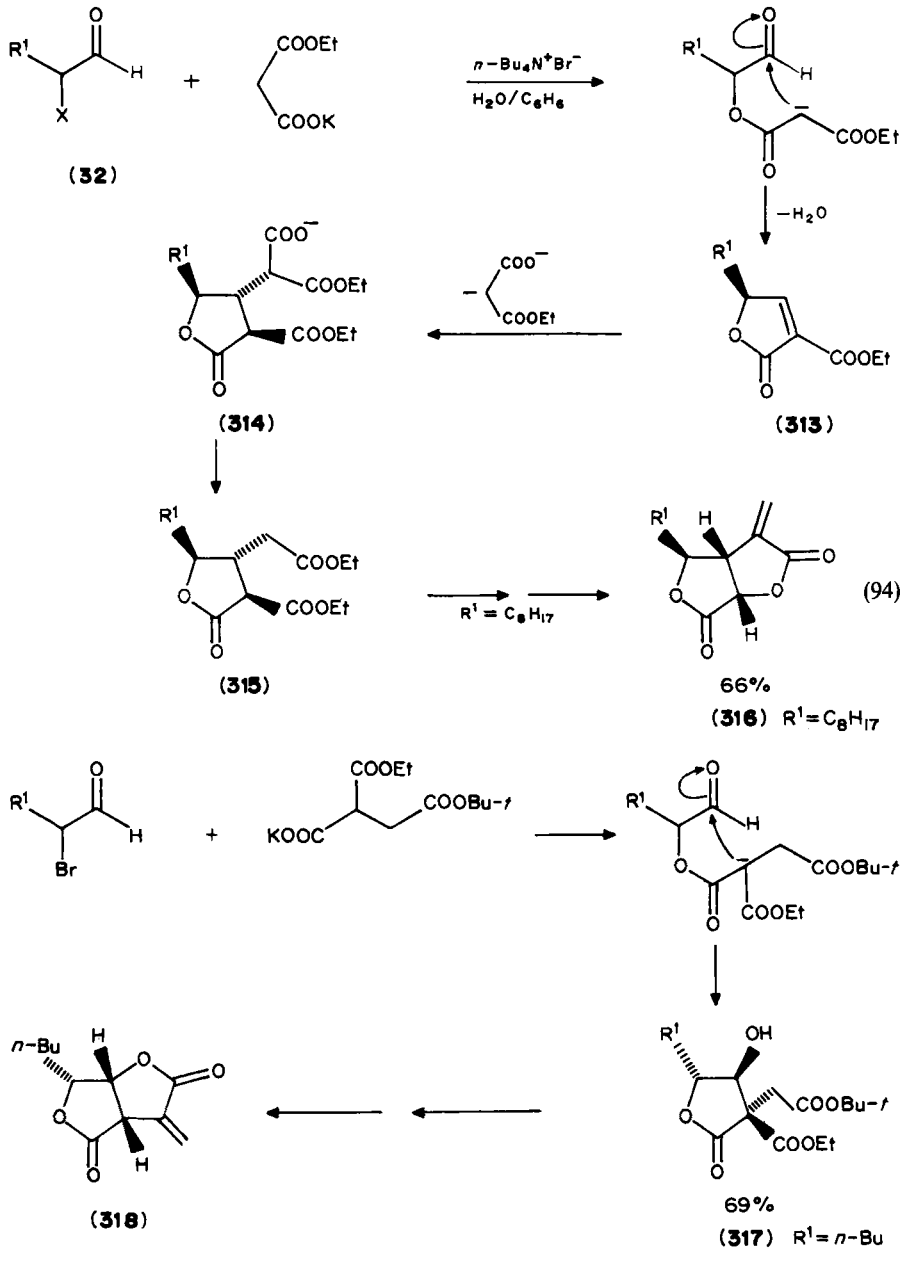
The base-catalysed condensation of α-monohaloaldehydes with active methylene compounds has been investigated in depth by Takeda and coworkers and is of particular interest in the synthesis of natural products.

Reaction of 2-chloro-2-methylpropanal (**183**) with a dialkyl malonate in the presence of potassium carbonate provided the substitution product **310** if one equivalent of malonate was used. The γ-butyrolactone **311** was obtained by reaction of **310** with a base, whereas the γ-butyrolactone **312** was obtained by using an excess of malonate (equation 93)[237]. In



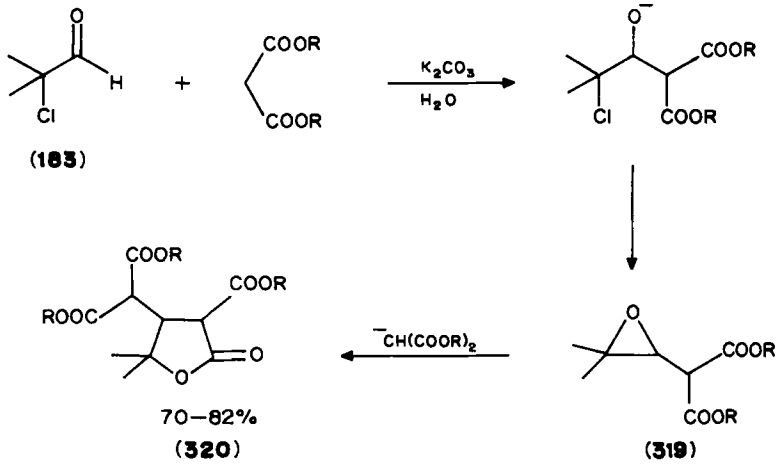
(93)

an analogous manner, treatment of α-haloaldehydes with potassium ethyl malonate gave the butyrolactone **314**, which was transformed into avenaciolide (**316**)[238], while reaction with potassium 1-ethyl 2-*tert*-butyl ethane-1,1,2-tricarboxylate afforded canadensolide (**318**) (equation 94)[239] in a similar way.



(94)

The reaction of 2-chloro-2-methylpropanal (**183**) with malonic esters, conducted in aqueous potassium carbonate, proceeded in a different way, giving the lactone **320** via ring opening of an intermediate oxirane (**319**) (equation 95)[237].



The condensation of α-haloaldehydes with β-keto esters is strongly dependent on the reaction conditions. Using sodium ethoxide in ethanol or diethyl ether or using potassium carbonate in THF, a tautomeric mixture of the substitution product **321** and the dihydrofuran **322** were obtained. This mixture equilibrated to give a **322**:**321** ratio of 40:1.

In contrast to reactions under non-aqueous conditions, the enolate anion attacked the carbonyl group in aqueous medium to give the butyrolactone **324**, which on distillation afforded the butenolide **323**. It is reasonable to consider that **323** is produced first in the reaction and then undergoes Michael addition. In aqueous alkaline solution, α-halo-α-methylpropanal promptly undergoes displacement of halogen to give the α-hydroxy compound. Therefore, it is possible that the hydroxyaldehyde is the substrate undergoing the reaction[240]. The latter reaction sequence has been successfully applied in the preparation of pyrocin (**326**) and related compounds (equation 96)[241].

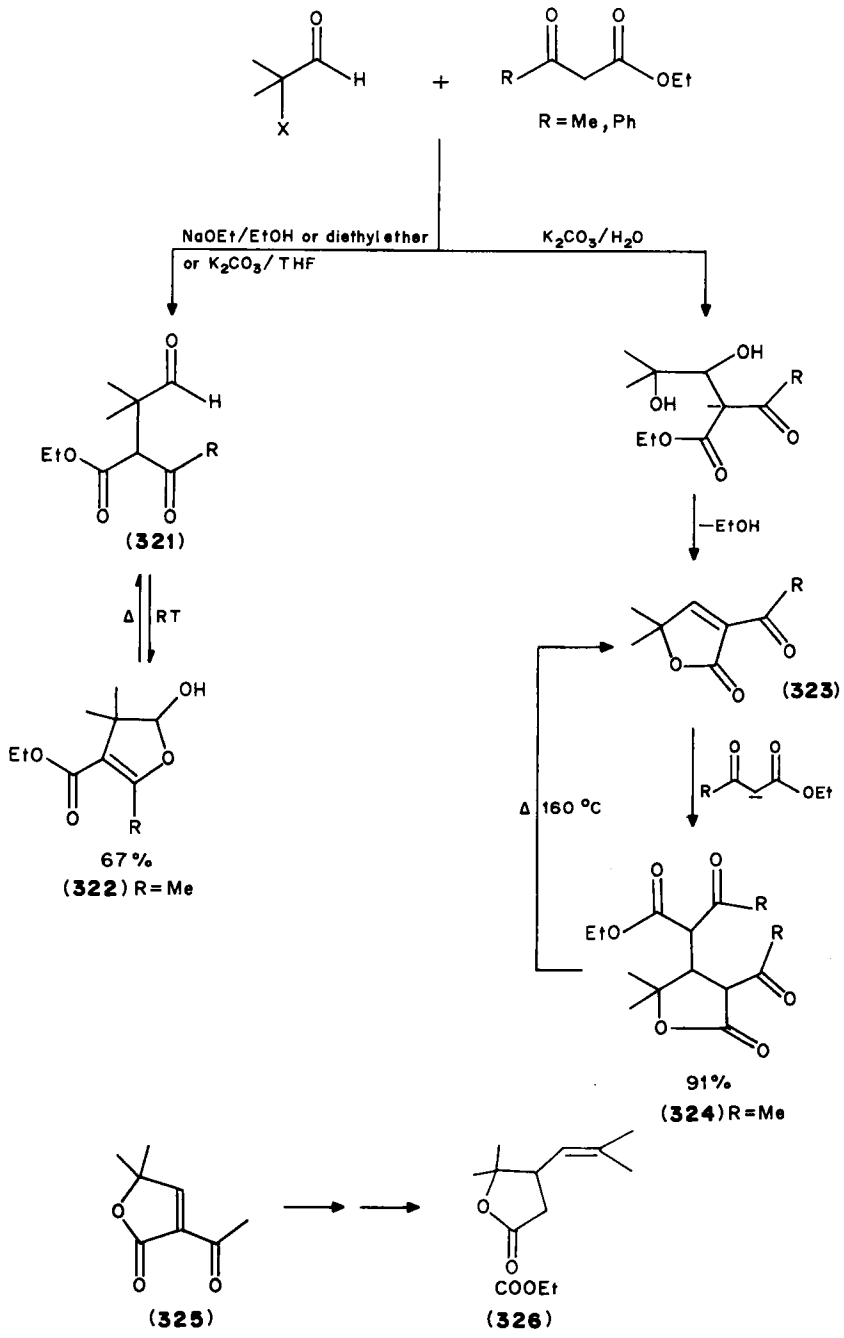
The reaction of α,α-dichloroaldehydes (**29**) with methyl acetoacetate established a similar course and furan derivatives (**329**, **330**) were generated via ring closure of intermediate 1,4-diketones (**328**) (equation 97)[242].

However, under similar reaction conditions, reaction of α,α-dihaloaldehydes with malonate or with cyanoacetate anions only gave the addition products (**331**), which were transformed into the corresponding Knoevenagel compounds (**333**) via successive treatment with thionyl chloride and triethylamine (equation 98)[135].

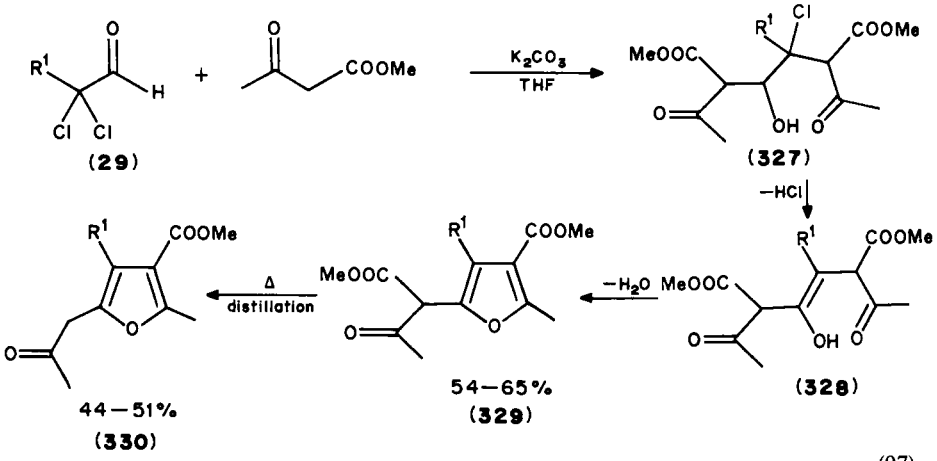
Condensation of α-haloaldehydes with pentane-2,4-dione in the presence of sodium hydride in dimethoxyethane gave the corresponding dihydrofurans (**334**) exclusively. If the reaction was performed with potassium carbonate in dimethoxyethane, the main products consisted of 1,4-diones (**335**), whereas in water α,β-unsaturated ketones (**336**) were isolated (equation 99)[135].

On the other hand, condensation of chloroacetaldehyde with cyclohexane-1,3-diones (**337**) in aqueous base formed tetrahydrobenzofuran derivatives (**338**), which were successively transformed into tetrahydroindoles (**339**) with amines (equation 100)[243,244].

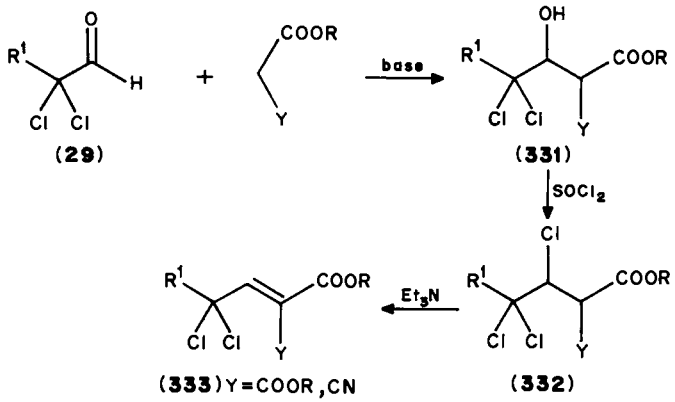
The reaction of α,α-dihaloaldehydes with 1,3-diketones (**340**) in the presence of potassium carbonate in THF took a completely different course and an excellent stereospecific synthesis of (*E*)-α,β-unsaturated ketones (**341** or **342**) was devel-


R = Me, Ph
NaOEt/EtOH or diethyl ether
or K2CO3/THF
K2CO3/H2O
(321)
(322) R = Me
67%
(323)
−EtOH
Δ RT
Δ 160 °C
(324) R = Me
91%
(325)
(326)
COOEt

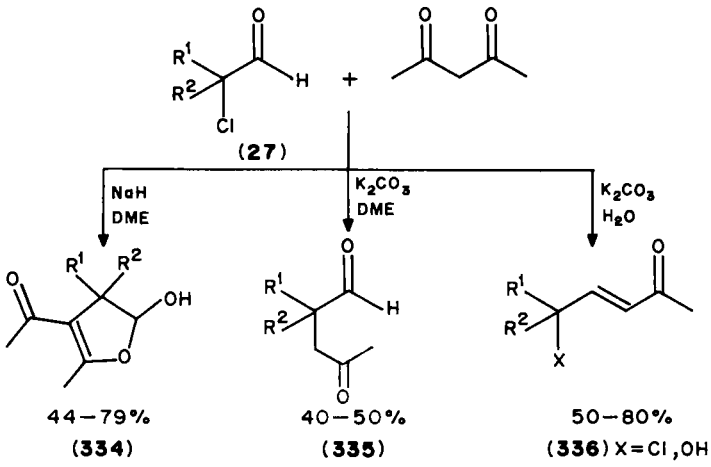
(96)


(29)
K2CO3
THF
(327)
-HCl
(328)
-H2O
54–65%
(329)
Δ
distillation
44–51%
(330)

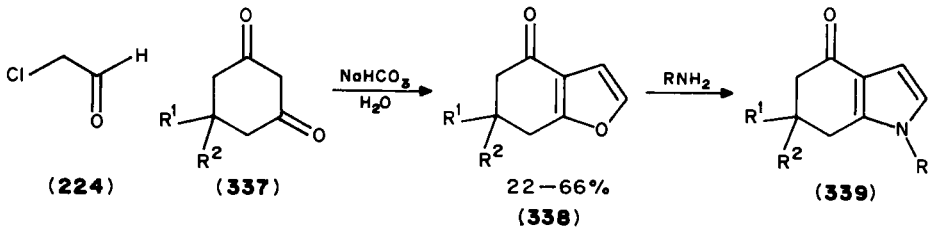
(97)


(29)
base
(331)
SOCl2
(332)
Et3N
(333) Y=COOR,CN

(98)

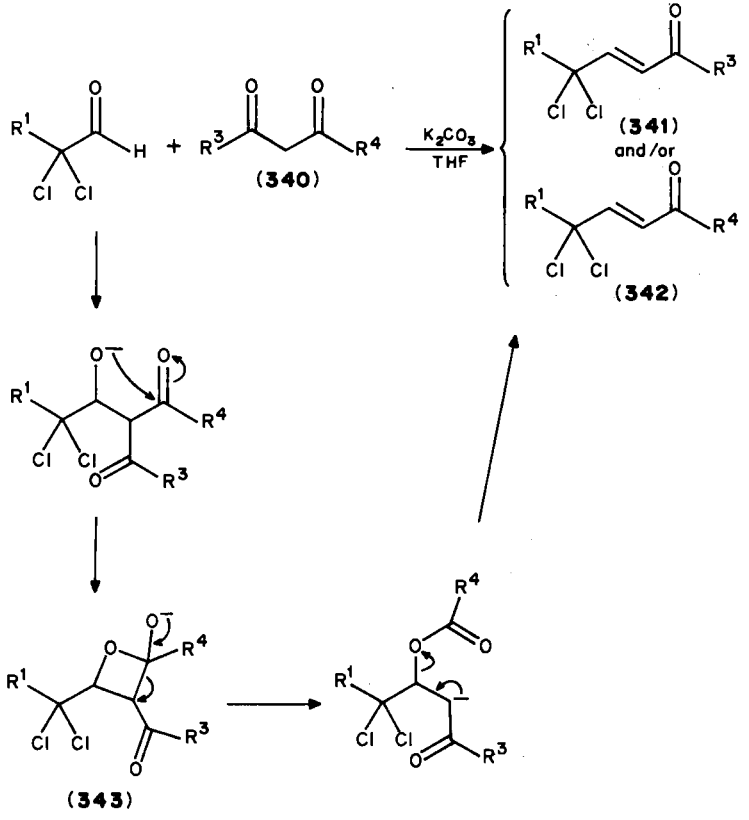

(27)
NaH
DME
K2CO3
DME
K2CO3
H2O
44–79%
(334)
40–50%
(335)
50–80%
(336) X=Cl,OH

(99)

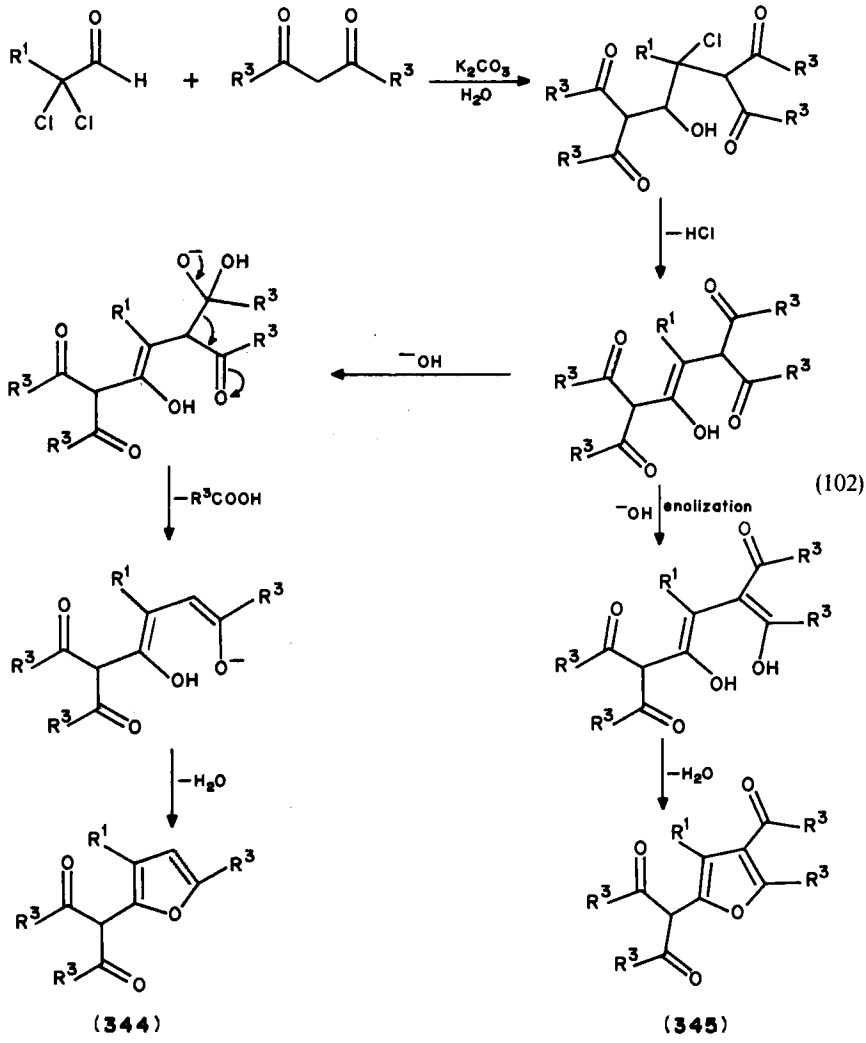


(100)

oped[242,245,246]. The reaction mechanism involved the addition of the enolate across the carbonyl function followed by an intramolecular nucleophilic addition, furnishing an oxetane derivative (**343**). Ring opening and expulsion of a carboxylate anion gave **341** or **342**. It is worth pointing out that in cases of unsymmetrical diketones ($R^3 \neq R^4$) the less sterically hindered carboxylate is expelled. Thus **341** or **342**, with the bulkiest R^3 or R^4 group, is produced. When there is no significant difference in the steric hindrance of R^3 and R^4, mixtures of the two possible α, β-unsaturated ketones were isolated[246] (equation 101). Similar condensations in water led to different compounds, namely a mixture of the furans **344** and **345** (equation 102)[246].

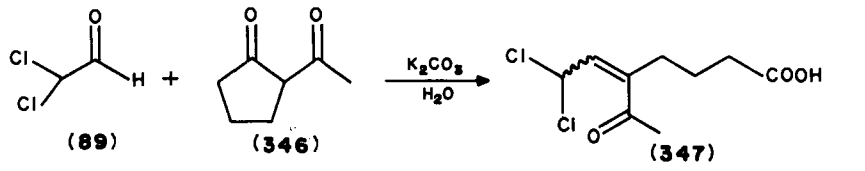


(101)



(102)

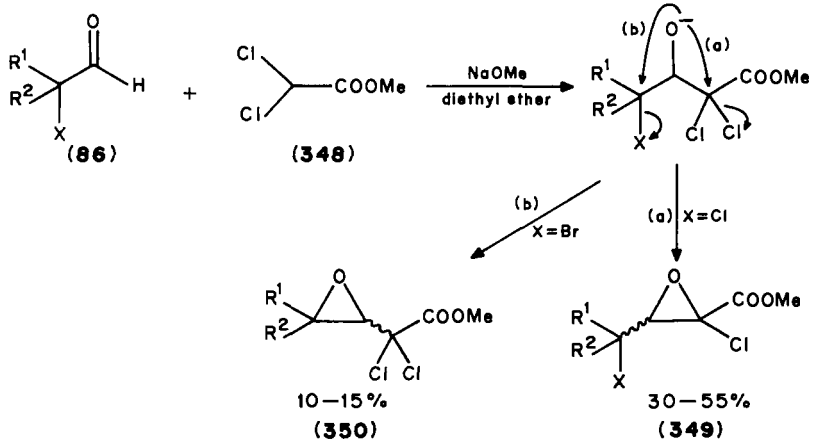
The behaviour of dichloroacetaldehyde (**89**) towards 2-acetylcyclopentanone (**346**) was in a striking contrast to the previous results and 5-acetyl-7,7-dichlorohept-5-enoic acid (**347**) has been isolated via a mechanism which has not been clearly established (equation 103)[247].



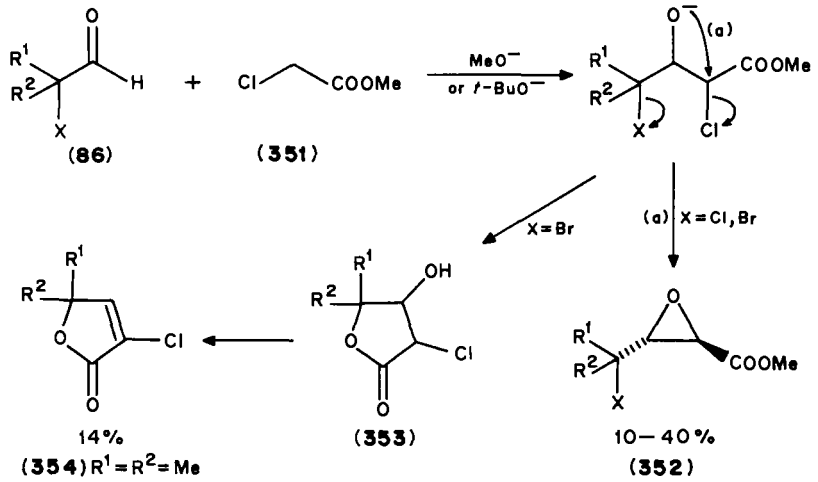
(103)

Darzens-type condensations of α-haloaldehydes with methyl chloroacetate and methyl dichloroacetate in the presence of sodium methoxide turned out to be an elegant entry to the synthesis of epoxyalkanoates. Whereas the reaction of α-chloroaldehydes with methyl dichloroacetate (**348**) usually gave 2,4-dichloro-2,3-epoxyalkanoates (**349**), the corresponding α-bromoaldehydes afforded the isomeric dichloroepoxides (**350**) as a result of the better nucleofugality of the bromine atom attached to the γ-carbon atom of the addition intermediate[248].

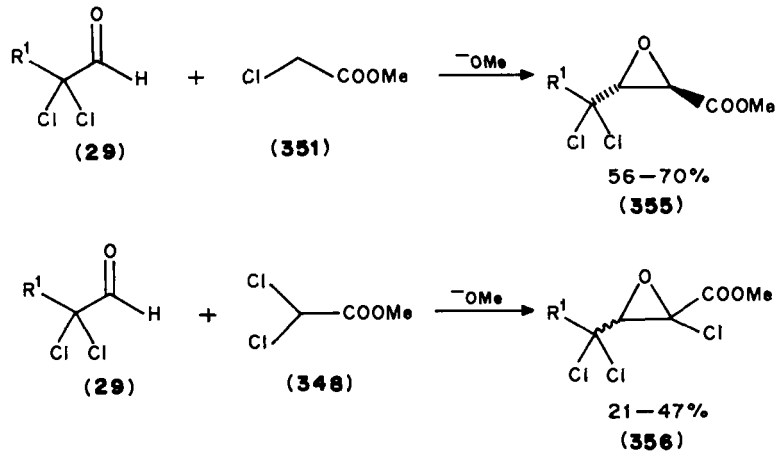
Similar oxiranes (**352**) have been isolated from α-chloro- and α-bromo-aldehydes using methyl chloroacetate (**351**) but, in addition, butenolides (**354**) were isolated as major reaction products starting from α-bromoaldehydes (equation 104)[249].



(104)

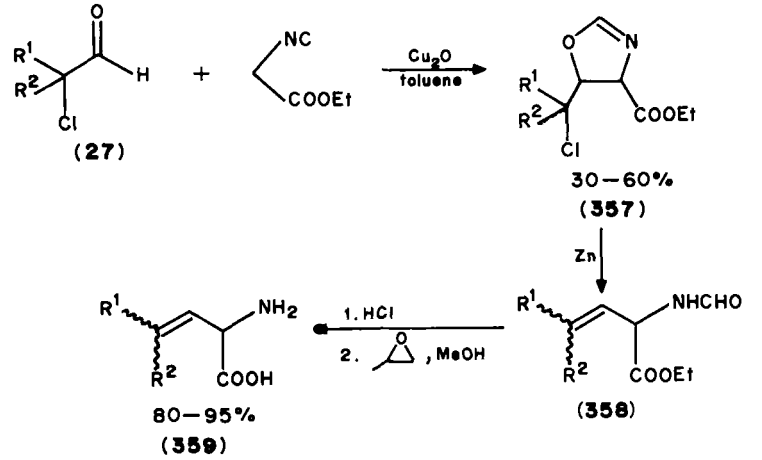


Darzens condensations of α,α-dichloroaldehydes with mono- and dichloroacetates also resulted in a stereospecific formation of oxiranes (**355** and **356**). In all cases the activated chlorine atom in the attacking nucleophile was expelled from the intermediate addition product (equation 105)[135].



(105)

A versatile synthetic pathway for the preparation of β,γ-unsaturated α-amino acids (**359**) was developed making use of Cu^{I}-catalysed addition of ethyl isocyanoacetate to α-chloroaldehydes, affording 2-oxazolines (**357**), which in turn are transformed into **359** (equation 106)[250].



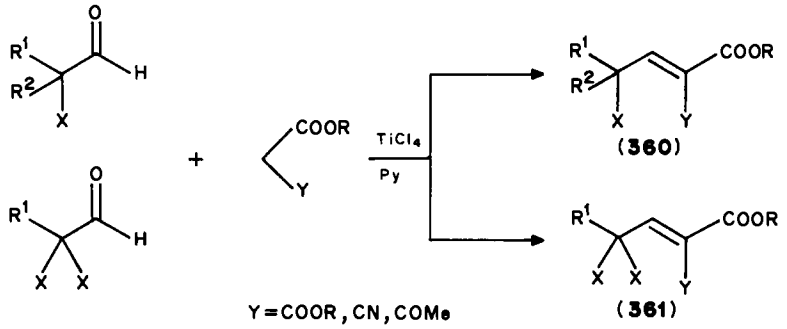
(106)

The classical procedures utilized for Knoevenagel condensations of aldehydes with active methylene functions failed to give the desired products[251]. However, Knoevenagel condensation of α-halo- and α,α-dihaloaldehydes using titanium(IV) chloride–pyridine[252] gave halogenated α,β-unsaturated esters (**360**, **361**). In all cases the reaction occurred stereospecifically with formation of the *E*-isomer, except when Y = Ac, when both stereoisomers were obtained (equation 107)[246].

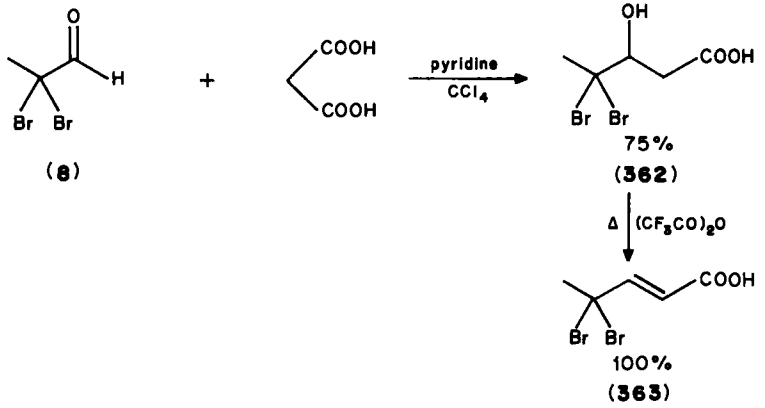
α,α-Dibromopropanal (**8**) could be converted into 4,4-dibromopent-2-enoic acid (**363**) by a Knoevenagel-type condensation using pyridine and trifluoroacetic anhydride (equation 107)[253].

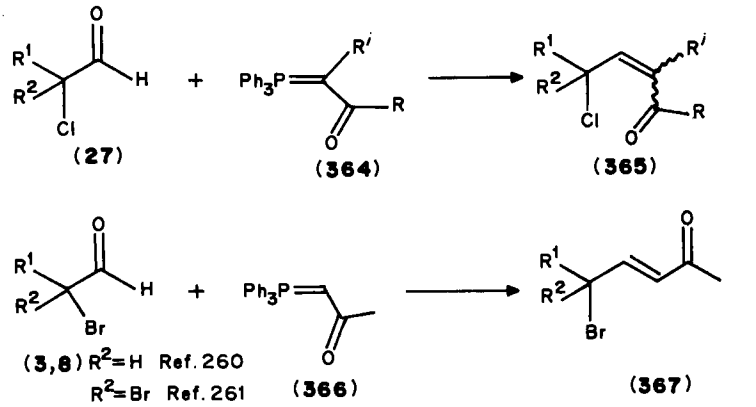
Only a few reactions of α-haloaldehydes with Wittig reagents have been reported. From α-chloroaldehydes a stereoisomeric mixture of (*E*) and (*Z*)-α,β-unsaturated esters

(**365**, R = OR″)[254,255] and ketones (**365**)[254] could be synthesized using the appropriate triphenylphosphoranes (**364**), whereas with α-bromo-[256] and α,α-dibromoaldehydes[253,257] the *E*-isomers (**367**) were exclusively obtained. The *E*:*Z* ratio is usually higher than 1, but can be decreased using protic solvents or via addition of lithium[254] (equation 108).



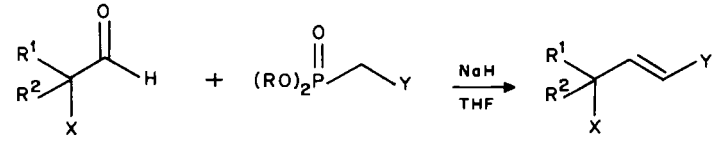
(107)





(108)

The Emmons–Wadsworth–Horner condensation of phosphonates with α-haloaldehydes usually afforded the corresponding α,β-unsaturated esters[246,258] and ketones[259,260] in the *E*-configuration, except for Y = CN, when a stereoisomeric mixture of unsaturated nitriles was formed (equation 109)[246].



X = Cl, Br
R^2 = alkyl, Cl

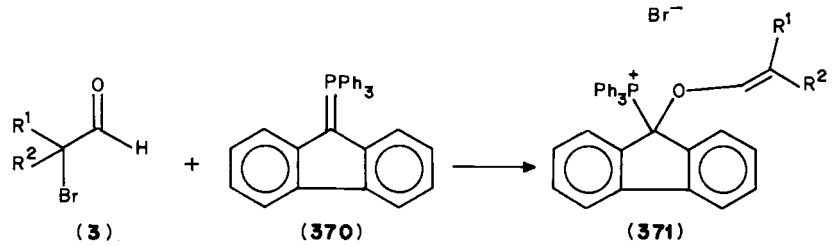
(368)

Y = COOR, COR', CN

70–95%
(369)

(109)

In contrast to the previous results, reaction of fluorenylidene triphenylphosphorane (**370**) with an α-bromoaldehyde (**3**) gave the phosphonium salt **371** instead of the Wittig product (equation 110)[261].



(3) (370) (371)

(110)

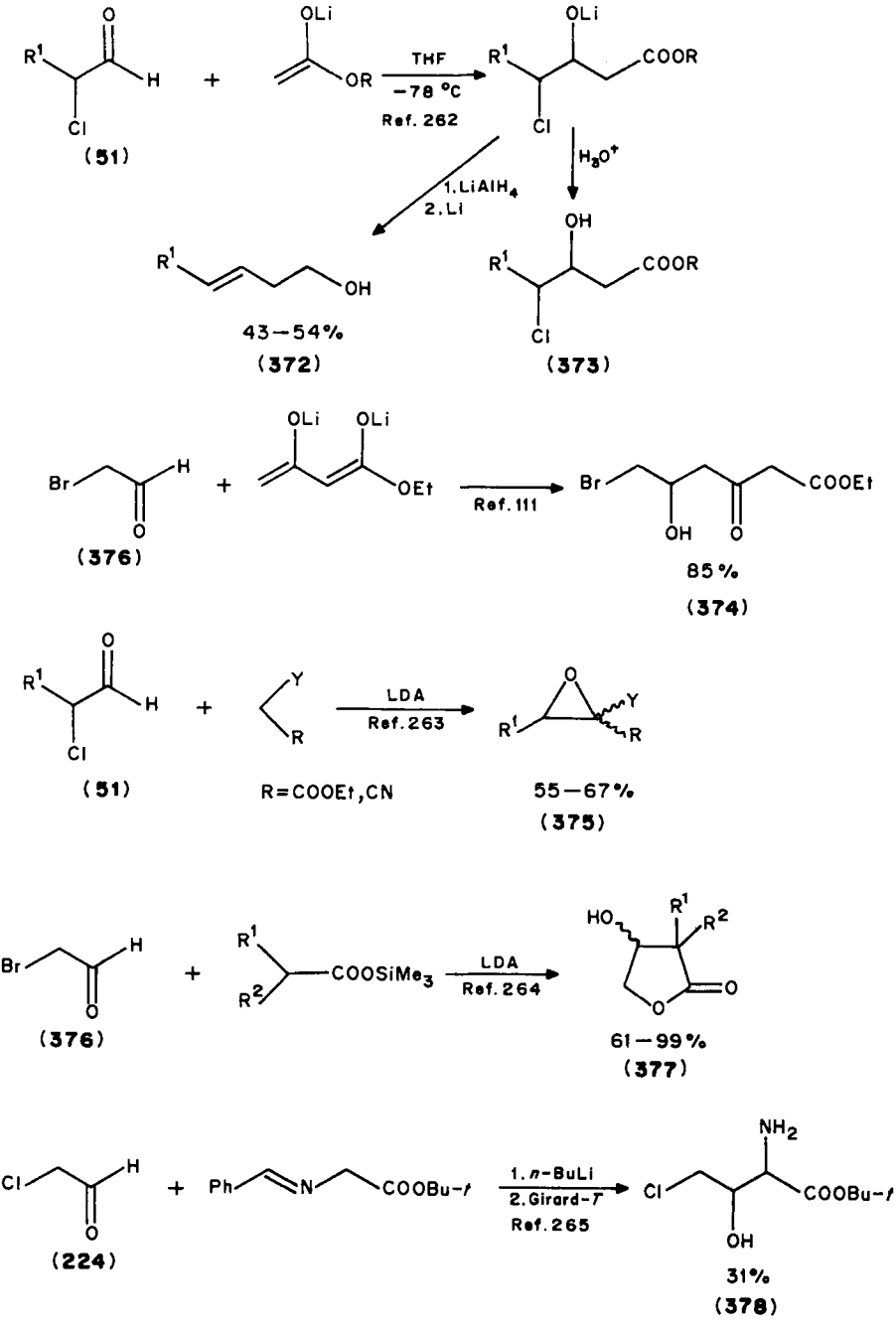
Reaction of α-haloaldehydes with a variety of anions and dianions derived from ketones, esters and cyanides has been used in chain elongation reactions with formation of homoallylic alcohols (**372**), bromohydrins (**374**), oxiranes (**375**), β-hydroxybutyrolactones (**377**) and amino acid derivatives (**378**) (equation 111).

3. *Reaction of α-haloaldehydes with Grignard reagents*

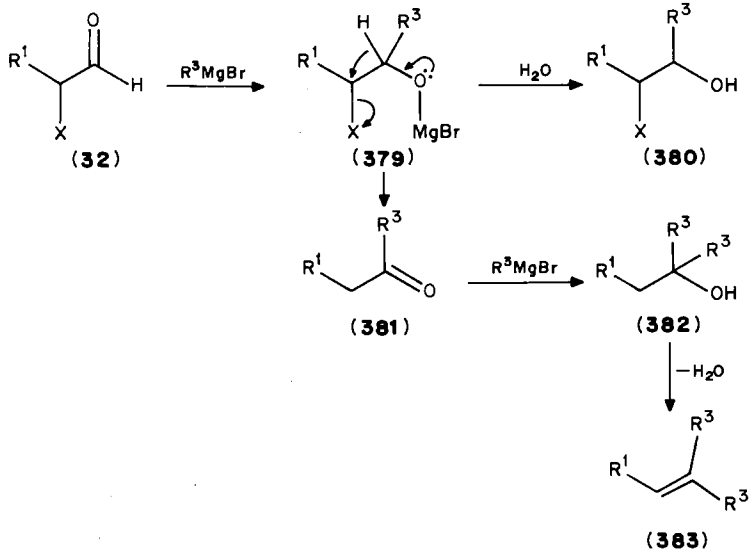
Organomagnesium compounds readily reacted with α-monohaloaldehydes with formation of the normally expected halohydrins (**380**), together with ketones (**381**) and their reaction products with Grignard reagents[29,266,268]. The reaction occurred via addition across the carbonyl resulting in the halohydrin magnesium bromide salt, which is transformed into the ketone **381** via a semi-pinacol type of rearrangement involving hydrogen migration. Further reaction of **381** can give a tertiary alcohol (**382**), which can be successively transformed into an alkene derivative (**383**). A similar reaction giving **384** took place during the reaction of 2,2-dichloropentanal with an excess of methylmagnesium iodide (equation 112)[269].

At low temperature (−70 °C), however, reaction of α,α-dichloroaldehydes with Grignard reagents resulted mainly in reduction with formation of α,α-dichloroalkanols (**385**) together with the expected chlorohydrins (**386**) (equation 113)[135].

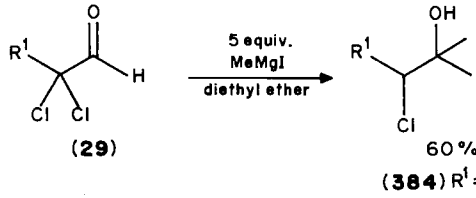
Direct and regioselective transformations of α-chloroaldehydes to alkenes (**389**) have been performed via reaction with Grignard reagents followed by treatment with lithium metal (equation 114)[270–272].

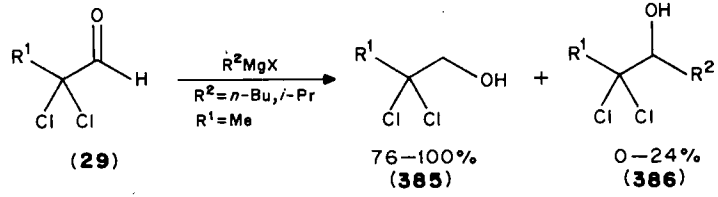

THF
−78 °C
Ref. 262
1. LiAlH4
2. Li
H3O+
43−54%
(372)
(373)
Ref. 111
85%
(374)
LDA
Ref. 263
R=COOEt,CN
55−67%
(375)
LDA
Ref. 264
61−99%
(377)
1. n-BuLi
2. Girard-T
Ref. 265
31%
(378)

(111)

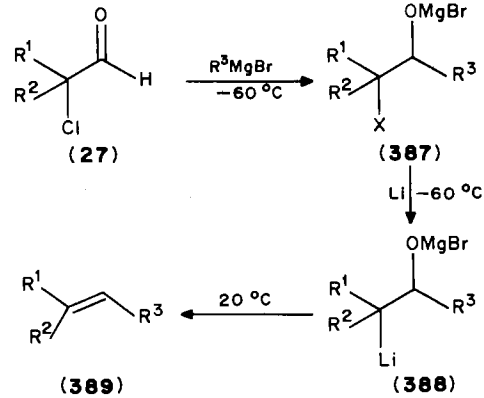

R3MgBr
H2O
(32)
(379)
(380)
(381)
R3MgBr
(382)
−H2O
(383)

(112)


5 equiv.
MeMgI
diethyl ether
(29)
60%
(384) R1 = Pr


R2MgX
R2 = n-Bu, i-Pr
R1 = Me
(29)
76–100%
(385)
0–24%
(386)

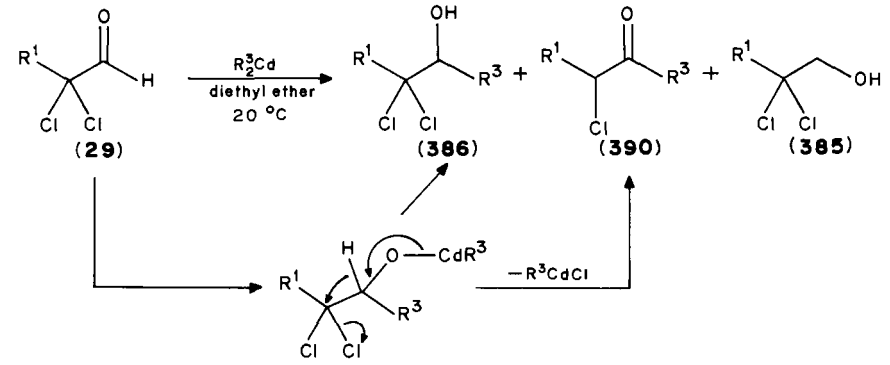
(113)


R3MgBr
−60 °C
(27)
(387)
Li −60 °C
20 °C
(389)
(388)

(114)

4. Reaction of α-haloaldehydes with organocadmium compounds

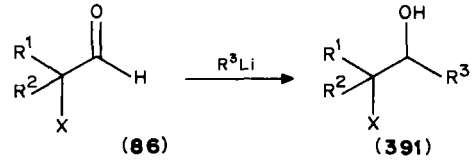
The reaction of organocadmium compounds, prepared via treatment of the corresponding alkylmagnesium halides with cadmium chloride, with α,α-dichloroaldehydes turned out to possess no preparative value, as a mixture of the halohydrins (**386**), α-chloroketones (**390**) and reduction products (**385**) was formed[135]. The ratio of the reaction products is dependent on the reaction time because the halohydrin is gradually transformed into the ketone, whereas the amount of the reduction product rapidly increased with the increase in the steric hindrance of the dialkylcadmium compounds (equation 115)[135].



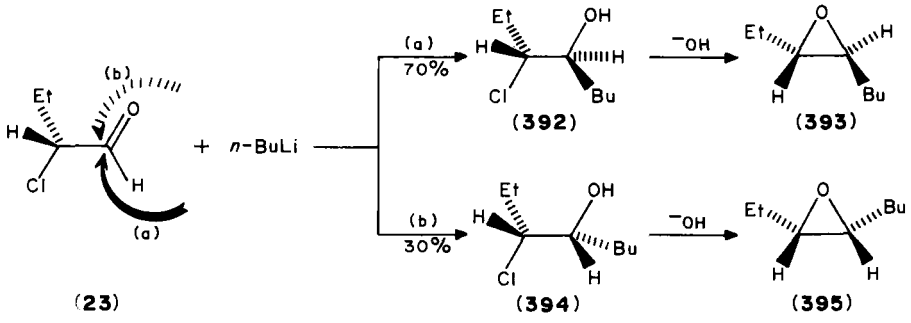
(115)

5. Reaction of α-haloaldehydes with organolithium compounds

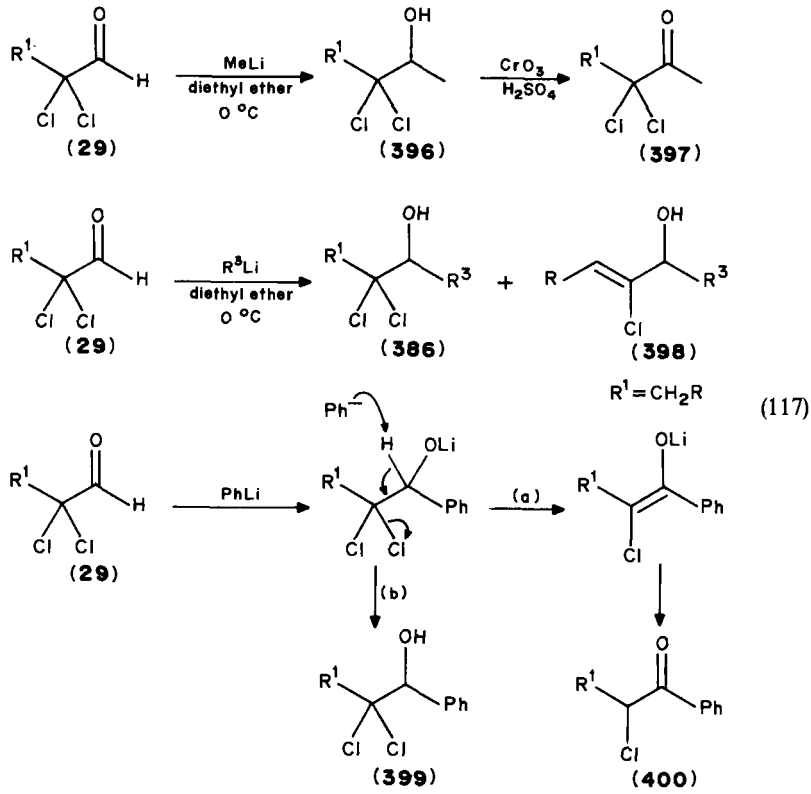
The condensation of α-haloaldehydes with alkyllithium reagents provided an excellent procedure for the preparation of halohydrins (**391**), which in turn were converted into oxiranes under the influence of strong alkali[111,273]. The stereochemistry of the addition of *n*-butyllithium to α-chlorobutanal (**23**) has been investigated and the observed stereoselectivity (cf. **393** and **395**) could be explained by a preferential attack of the reagent at the less sterically hindered site of the aldehyde (equation 116)[273].



(116)



Whereas the reaction of α, α-dichloroaldehydes with methyllithium exclusively afforded the corresponding β, β-dichloroalcohols (**396**), reaction with higher homologues of alkyllithium compounds gave a mixture of the dichlorohydrin (**386**) and the dehydrochlorination product (**398**) (equation 117)[135].



(117)

In addition, using phenyllithium the corresponding dichlorohydrins (**399**) were accompanied by α-chloroketones (**400**), formed via dehydrochlorination under the influence of the phenyl anion. Using an excess of phenyllithium, the chloroketones **400** constituted the major reaction product (equation 117)[135]. A method based on the use of an organodilithium reagent (**402**) was described for the synthesis of indole (**403**) from chloroacetaldehyde (**224**) acting as a biselectrophile (equation 118)[274].

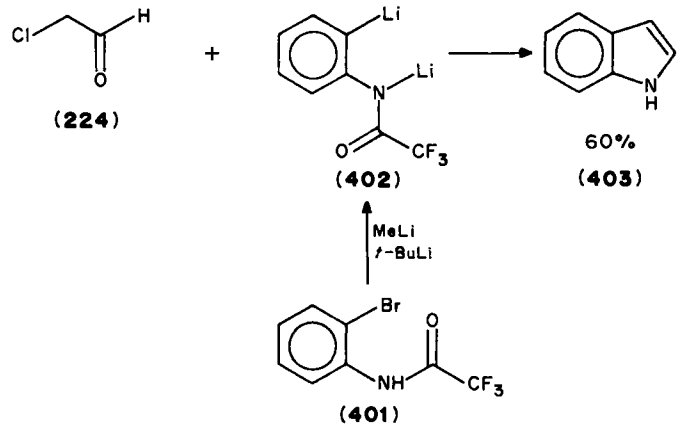
E. Reaction of α-Haloaldehydes with Phosphorus Compounds

In contrast with the halogenated ketones, which on reaction with phosphites gave rise to Arbuzov and/or Perkow reaction products, α-haloaldehydes only exhibited the Perkow reaction with formation of vinyl phosphates (**404**, **405**) (equation 119)[135,275–283].

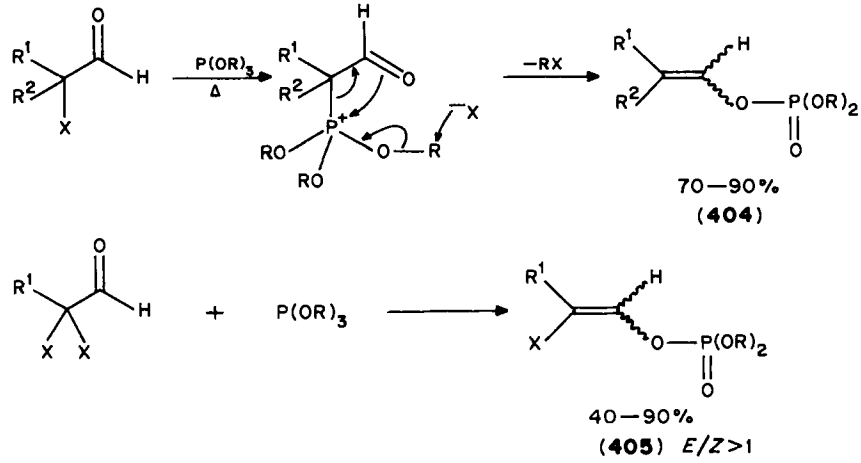
The mechanism involved in the Perkow reaction is similar to that proposed for α-haloketones as described in Chapter 1. The reactivity decreases as the number of halogen atoms on the α-carbon decreases and (*E*)-enol phosphates are formed predominantly. However, the *E*/*Z* ratio is dependent on the nature of the halogen and the phosphite whereas the influence of the solvent and the temperature is negligible[135,281,282].

Chlorinated vinyl phosphates have found many useful applications in the field of insecticides[284].

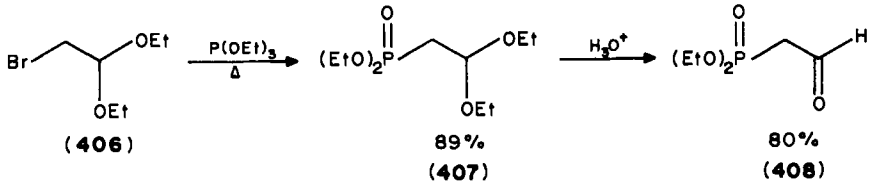
It is remarkable that the brominated acetal **406** reacted with triethyl phosphite to give the phosphonate **407** via an Arbuzov reaction. The latter compounds can give rise to formylphosphonates (**408**) via acidic hydrolysis (equation 120)[285].



(118)

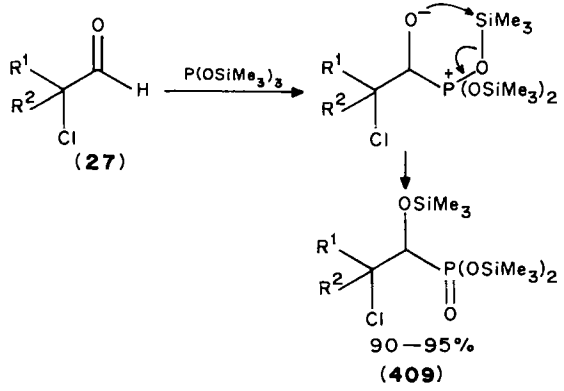


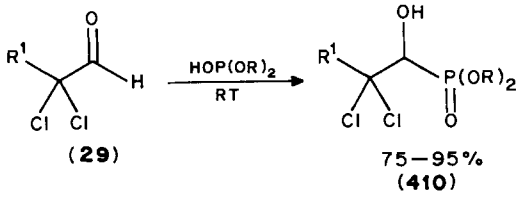
(119)



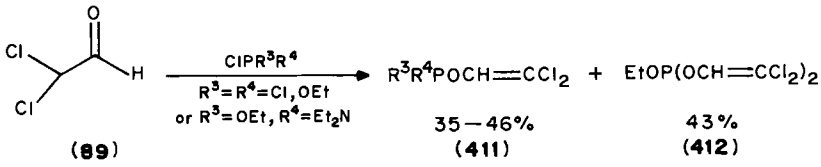
(120)

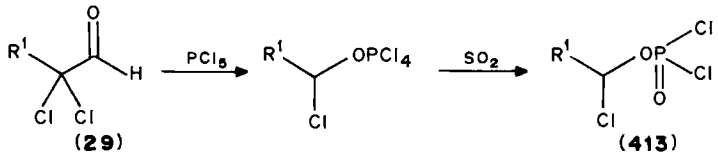
In contrast with the trialkyl phosphites, silyl phosphites reacted with α-haloaldehydes to form phosphonates (**409**)[286,287]. Related phosphonates (**410**) have been prepared from α, α-dichloroaldehydes by treatment with dialkyl phosphites[135], while reaction of mono- and dichlorophosphinites with dichloroacetaldehyde afforded 2,2-dichlorovinyl phosphites (**411**, **412**)[288]. Phosphorodichloridates (**413**) were prepared by reaction with phosphorus pentachloride and subsequent treatment with sulphur dioxide[289], while phosphorylation with phosphoroxy and phosphorthioxy trichloride afforded the dichlorovinyl phosphates (**414**) (equation 121)[288].

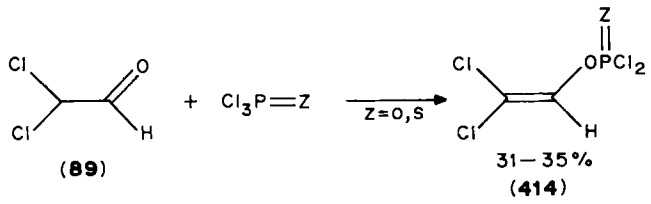




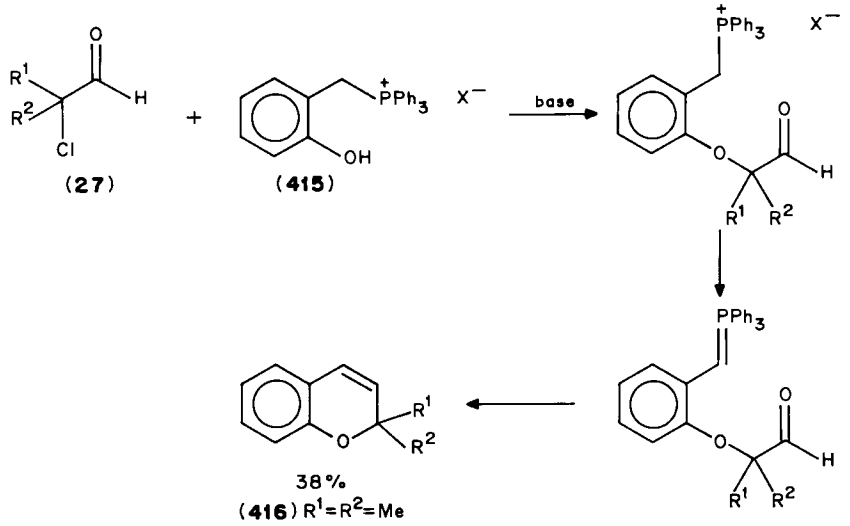
(121)







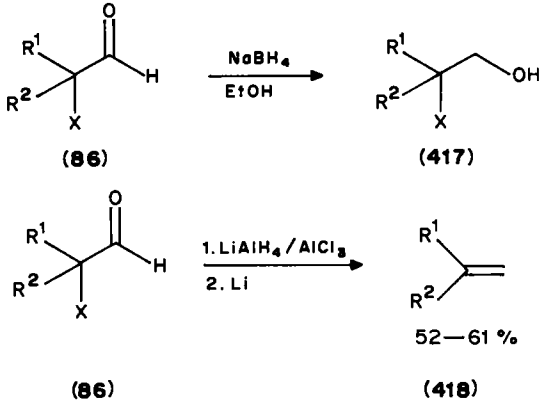
In analogy with α-haloketones, alkylation of *o*-hydroxybenzyl triphenylphosphonium salts (**415**) with α-chloroaldehydes, in the presence of base, gave 2*H*-benzo[*b*]pyrans (**416**) (equation 122)[290].



(122)

F. Reaction of α-Haloaldehydes with Complex Metal Hydrides

Whereas treatment of α-haloaldehydes with sodium borohydride[291] and $LiAlH_4$[314] resulted in the formation of the corresponding β-haloalcohols (**417**), terminal olefins (**418**) have been synthesized via a selective reduction of the carbonyl group using $LiAlH_4/AlCl_3$ followed by treatment with lithium powder (equation 123)[272].



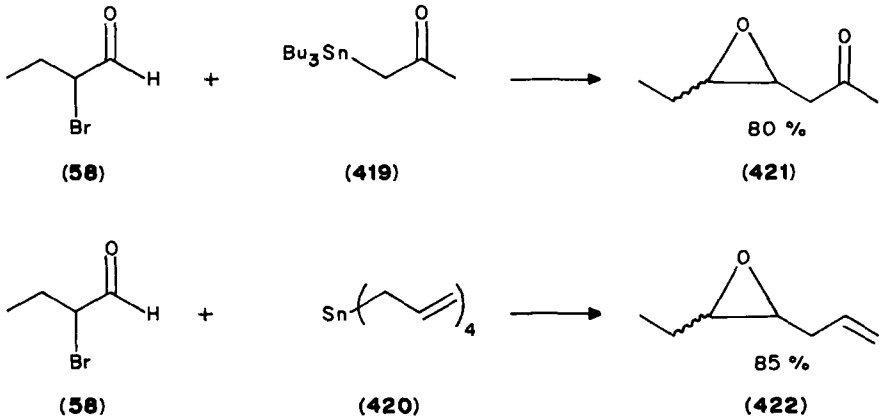
(123)

G. Reaction of α-Haloaldehydes with Organometallic Complexes

In comparison with α-haloketones, little information concerning the reactivity of α-haloaldehydes in the presence of organometallic complexes is available. The palladium-

catalysed reaction of α-bromoaldehydes with acetonyltin (**419**) and allyltin (**420**) reagents gave the corresponding oxiranes (**421**, **422**). However, with α-chloroaldehydes no cyclization occurred[292] (equation 124).

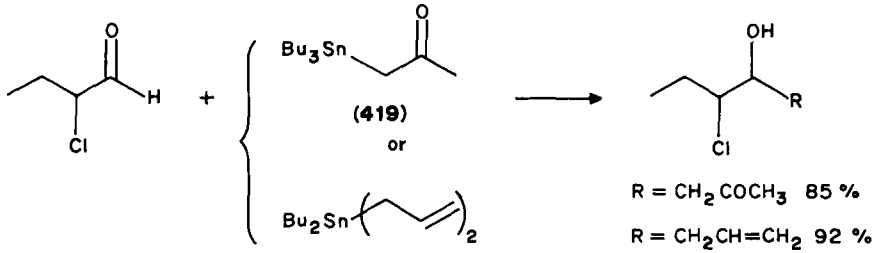
Cross-aldol reaction via tin(II) enolates gave **425** when α-bromoaldehydes were allowed to react with aliphatic and aromatic aldehydes in the presence of tin(II) chloride and potassium[293] (equation 125), whereas the reaction with the manganese complex (**426**) afforded trimethylsilyl enol ethers (**427**)[294]. Other β-trialkylsilyl-β,γ-unsaturated aldehydes (**429**) were formed when α-bromoaldehydes were allowed to react with silylated acetylenes (**428**) and Grignard reagents in the presence of dicyclopentadienyltitanium(III) chloride[295] (equation 126).



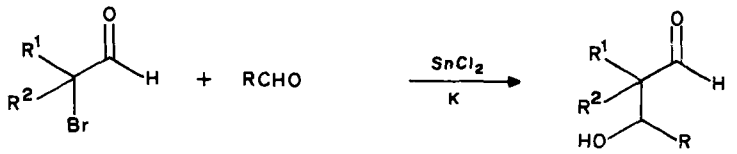
(**58**) (**419**) (**421**)

(**58**) (**420**) (**422**)

(124)

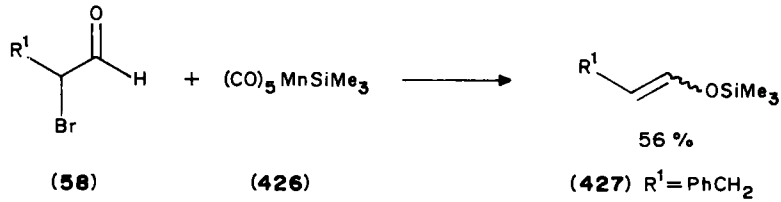


(**23**) (**423**) (**424**)

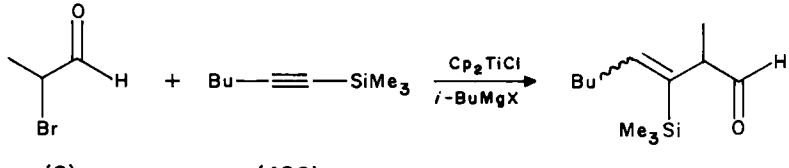


(**3**) (**425**)

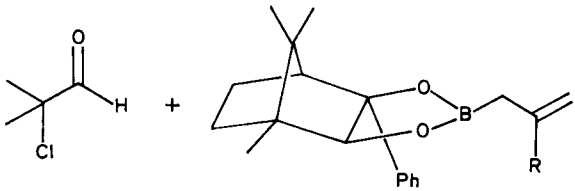
(125)



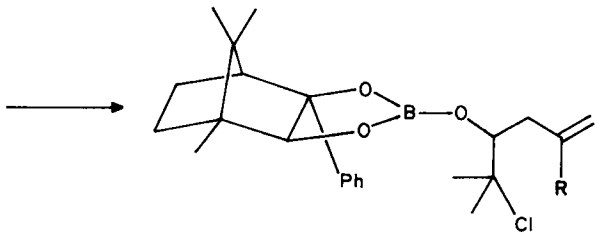
(58) (426) (427) $R^1 = PhCH_2$ (126)



(9) (428) (429)

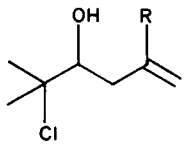


(184) (430)



(431)

$N(CH_2CH_2OH)_3$



83 %

(432)

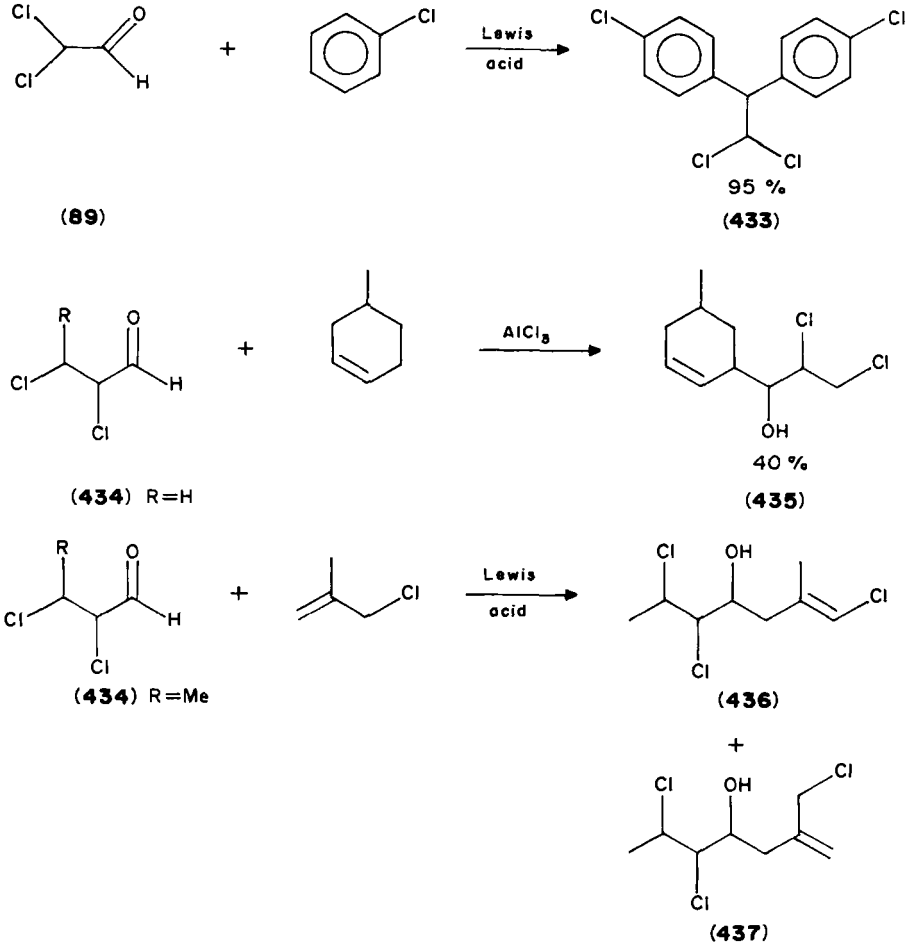
e.e. 70 % (*S*)

(127)

In addition, reaction of allylic boron esters (**430**) with α-chloroaldehydes constitutes an enantioselective synthesis of homoallyl alcohols (**432**) via treatment of the intermediate boron esters (**431**) with triethanolamine[296] (equation 127).

H. Electrophilic Reactions of α-Haloaldehydes

The Friedel–Crafts reaction of α,α-dichloroaldehydes with chlorinated aromatics led to compounds analogous to DDT. For example, 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane (**433**), obtained by condensation of chlorobenzene and dichloroacetaldehyde, is a powerful insecticide with a lower toxicity than DDT[284].

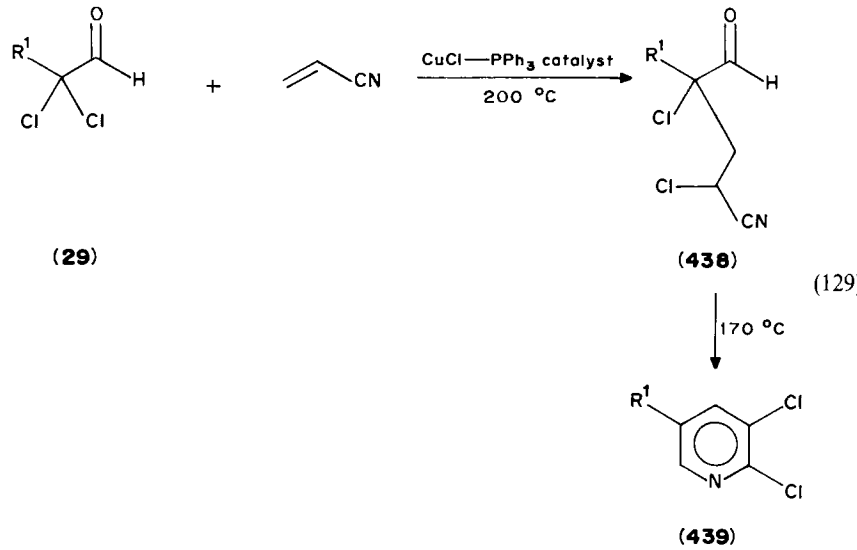


(128)

The Friedel–Crafts reaction of **434** with cyclohexenes[297] and methallyl chloride[298] furnished the carbonyl addition products (**435–437**) (equation 128).

Reaction of α,α-dichloroaldehydes with acrylonitrile in the presence of a copper(I)

chloride catalyst gave the chlorinated nitriles (**438**), which can be transformed to chlorinated pyridine derivatives (**439**) by heating (equation 129)[299,300].



(**29**) (**438**) (129)

(**439**)

Exposure of brominated phenylacetaldehydes to fluorosulphonic acid did not result in aldol condensation or cyclotrimerization, but gave instead a bimolecular reaction with formation of a bicyclic compound (**441**) together with a minor amount of 9-anthrylaldehyde (**442**)[301]. The mechanism of this particular reaction is outlined in equation 130.

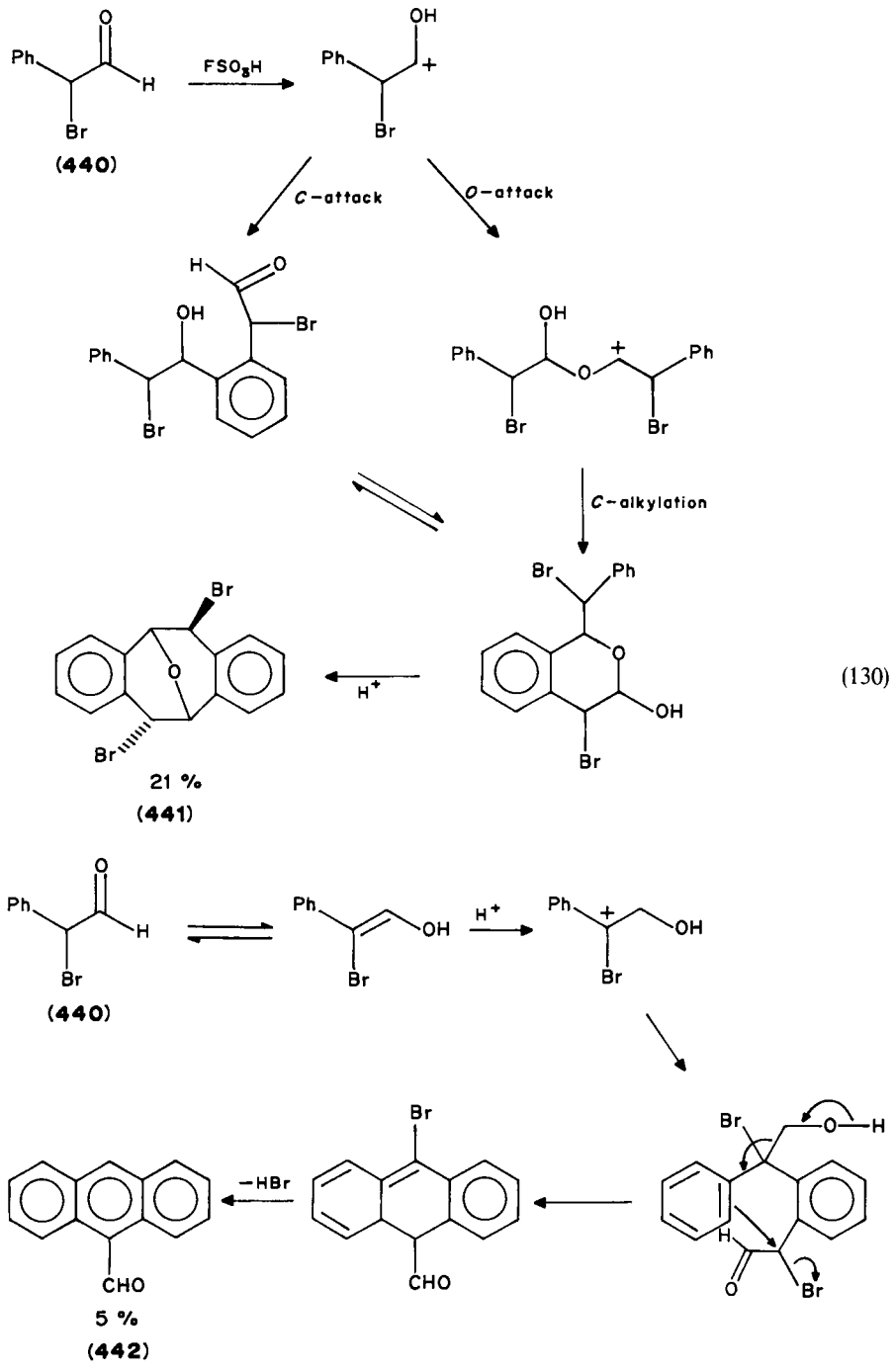
Treatment of α-bromocyclohexanecarboxaldehyde (**19**) with sulphur tetrafluoride in the presence of potassium fluoride afforded a mixture of the fluorinated cycloalkanes (**443**, **444**). Subsequent dehydrohalogenation of **443** with potassium hydroxide gave rise to the difluorocyclohexene (**445**) and difluoromethylidenecyclohexane (**446**) (equation 131)[302].

α,β-Unsaturated aldehydes were obtained in high yields when α-chloroaldehydes were treated with lithium perchlorate and calcium carbonate in hexamethylphosphoric triamide[99]. Enolate formation occurred when α-haloaldehydes were treated with triethylamine in the presence of trimethylchlorosilane to yield the corresponding trimethylsilyl enol ethers **447**[49,303,304] or with potassium hydride in the presence of 1-acetyl-4-(*N*,*N*-dimethylamino)pyridinium chloride to give the enol acetates (**448**) (equation 132)[305].

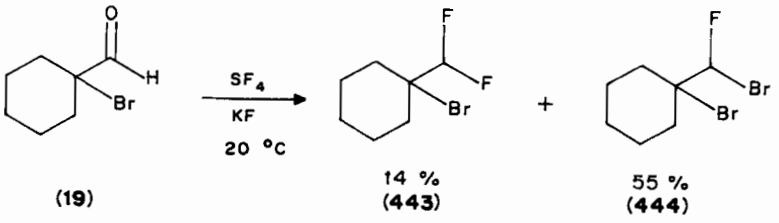
I. Cycloaddition Reactions of α-Haloaldehydes

α-Haloaldehydes have been used in cycloaddition reactions with a variety of dienophiles. Addition of α,α-dibromo- or α-bromoacetaldehyde across 1,1,2-trichloro-4-morpholinobut-1-en-3-yne (**449**) resulted in a stereospecific synthesis of (*Z*)-penta-1,3-dienes (**451**)[306], while Diels–Alder reaction of α-chlorobutanal with 2-azabuta-1,3-dienes such as **452** afforded 1,3-oxazines (**453**) (equation 133)[307].

Using a quinidine-[308,309] or brucine-catalysed[310] cycloaddition reaction of α,α-dichloroaldehydes with ketene, an excellent procedure has been developed for the preparation of chiral 4-substituted 2-oxetanones (**454**). The latter compounds served as excellent precursors for several optically pure (*S*)-methyl 3-hydroxyalkanoates (**456**)[309] (equation 134).


Ph
O
H
Br
(440)
FSO3H
OH
+
C-attack
O-attack
OH
Br
C-alkylation
Br
Ph
O
OH
H+
21 %
(441)
(440)
OH
H+
CHO
5 %
(442)
-HBr
Br
O
H

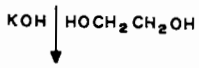
(130)

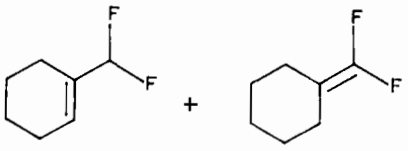


(19)

14 %
(443)

55 %
(444)

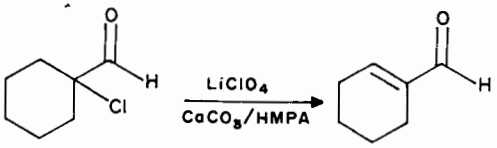




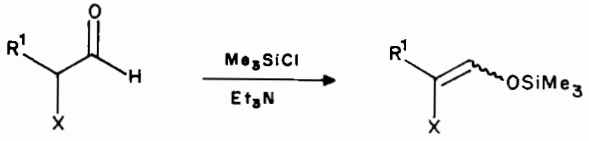
30 %
(445)

49 %
(446)

(131)

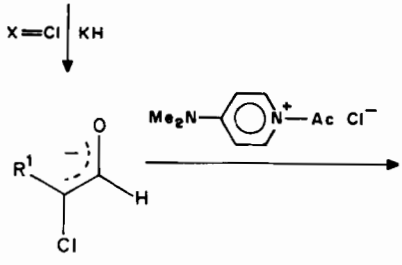


74 %
(256)



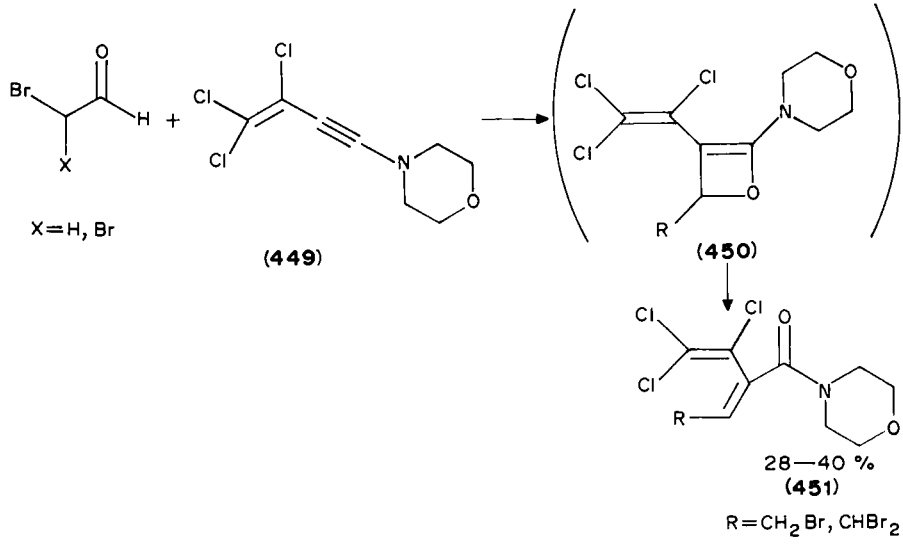
X=Cl, Br, I

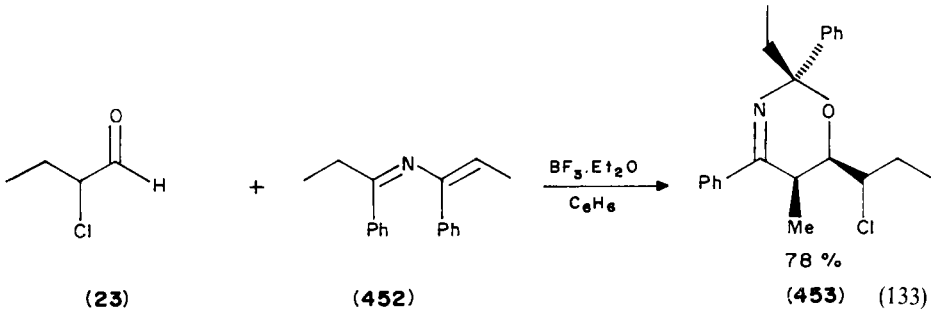
50—70 %
(447)



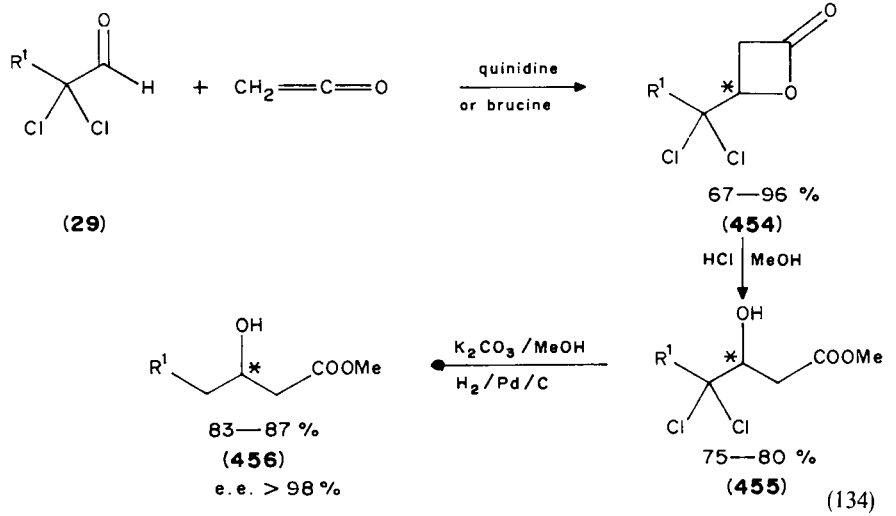
(132)

75 %
(448)


X=H, Br
(449)
(450)
28—40 %
(451)
R=CH2Br, CHBr2


BF3.Et2O
C6H6
78 %
(23)
(452)
(453)

(133)


quinidine
or brucine
67—96 %
(454)
HCl | MeOH
K2CO3 / MeOH
H2 / Pd / C
83—87 %
(456)
e.e. > 98 %
75—80 %
(455)
(29)

(134)

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