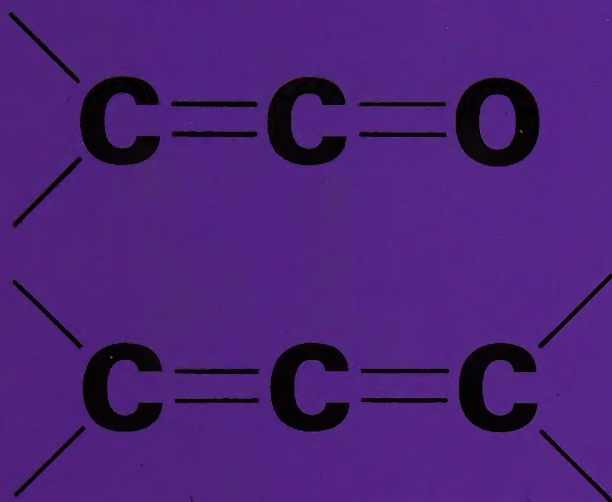
The chemistry of functional groups

Edited by
Saul Patai

The chemistry of ketenes, allenes, and related compounds

Part 2



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The chemistry of

ketenes, allenes and related compounds

Part 2

THE CHEMISTRY OF FUNCTIONAL GROUPS

A series of advanced treatises under the general editorship of Professor Saul Patai

The chemistry of alkenes (2 volumes)
The chemistry of the carbonyl group (2 volumes)
The chemistry of the ether linkage
The chemistry of the amino group
The chemistry of the nitro and nitroso groups (2 parts)
The chemistry of carboxylic acids and esters
The chemistry of the carbon—nitrogen double bond
The chemistry of amides
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Supplement B: The chemistry of acid derivatives (2 parts)
The chemistry of ketenes, allenes and related compounds (2 parts)

The chemistry of
ketenes, allenes and related compounds
Part 2

Edited by

SAUL PATAI

The Hebrew University, Jerusalem

1980

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Foreword

In the first volume of "The Chemistry of Functional Groups", which appeared in 1964 ("The Chemistry of Alkenes"), two chapters dealt with ketenes and cumulenes. In the fifteen years which passed since, the material published on these subjects grew so much that it fully justified the publication of a separate volume. The organization and presentation of this volume is in accordance with the general principles described in the "Preface to the Series", printed on the following pages.

Some of the chapters planned for this volume did not materialize. These were "The Photochemistry of Ketenes and Cumulenes", "Cycloadditions Involving Ketenes and Cumulenes" and "Rearrangements Involving Ketenes". It is hoped to include these chapters in one of the supplementary volumes planned for the Series.

Jerusalem, July 1979 SAUL PATAI

The Chemistry of Functional Groups
Preface to the series

The series 'The Chemistry of Functional Groups' is planned to cover in each volume all aspects of the chemistry of one of the important functional groups in organic chemistry. The emphasis is laid on the functional group treated and on the effects which it exerts on the chemical and physical properties, primarily in the immediate vicinity of the group in question, and secondarily on the behaviour of the whole molecule. For instance, the volume *The Chemistry of the Ether Linkage* deals with reactions in which the C—O—C group is involved, as well as with the effects of the C—O—C group on the reactions of alkyl or aryl groups connected to the ether oxygen. It is the purpose of the volume to give a complete coverage of all properties and reactions of ethers in as far as these depend on the presence of the ether group but the primary subject matter is not the whole molecule, but the C—O—C functional group.

A further restriction in the treatment of the various functional groups in these volumes is that material included in easily and generally available secondary or tertiary sources, such as Chemical Reviews, Quarterly Reviews, Organic Reactions, various 'Advances' and 'Progress' series as well as textbooks (i.e. in books which are usually found in the chemical libraries of universities and research institutes) should not, as a rule, be repeated in detail, unless it is necessary for the balanced treatment of the subject. Therefore each of the authors is asked *not* to give an encyclopaedic coverage of his subject, but to concentrate on the most important recent developments and mainly on material that has not been adequately covered by reviews or other secondary sources by the time of writing of the chapter, and to address himself to a reader who is assumed to be at a fairly advanced post-graduate level.

With these restrictions, it is realized that no plan can be devised for a volume that would give a *complete* coverage of the subject with *no* overlap between chapters, while at the same time preserving the readability of the text. The Editor set himself the goal of attaining *reasonable* coverage with *moderate* overlap, with a minimum of cross-references between the chapters of each volume. In this manner, sufficient freedom is given to each author to produce readable quasi-monographic chapters.

The general plan of each volume includes the following main sections:

(a) An introductory chapter dealing with the general and theoretical aspects of the group.

(b) One or more chapters dealing with the formation of the functional group in question, either from groups present in the molecule, or by introducing the new group directly or indirectly.

(c) Chapters describing the characterization and characteristics of the functional groups, i.e. a chapter dealing with qualitative and quantitative methods of determination including chemical and physical methods, ultraviolet, infrared, nuclear magnetic resonance and mass spectra: a chapter dealing with activating and directive effects exerted by the group and/or a chapter on the basicity, acidity or complex-forming ability of the group (if applicable).

(d) Chapters on the reactions, transformations and rearrangements which the functional group can undergo, either alone or in conjunction with other reagents.

(e) Special topics which do not fit any of the above sections, such as photochemistry, radiation chemistry, biochemical formations and reactions. Depending on the nature of each functional group treated, these special topics may include short monographs on related functional groups on which no separate volume is planned (e.g. a chapter on 'Thioketones' is included in the volume *The Chemistry of the Carbonyl Group*, and a chapter on 'Ketenes' is included in the volume *The Chemistry of Alkenes*). In other cases certain compounds, though containing only the functional group of the title, may have special features so as to be best treated in a separate chapter, as e.g. 'Polyethers' in *The Chemistry of the Ether Linkage*, or 'Tetraaminoethylenes' in *The Chemistry of the Amino Group*.

This plan entails that the breadth, depth and thought-provoking nature of each chapter will differ with the views and inclinations of the author and the presentation will necessarily be somewhat uneven. Moreover, a serious problem is caused by authors who deliver their manuscript late or not at all. In order to overcome this problem at least to some extent, it was decided to publish certain volumes in several parts, without giving consideration to the originally planned logical order of the chapters. If after the appearance of the originally planned parts of a volume it is found that either owing to non-delivery of chapters, or to new developments in the subject, sufficient material has accumulated for publication of a supplementary volume, containing material on related functional groups, this will be done as soon as possible.

The overall plan of the volumes in the series 'The Chemistry of Functional Groups' includes the titles listed below:

The Chemistry of Alkenes (*two volumes*)
The Chemistry of the Carbonyl Group (*two volumes*)
The Chemistry of the Ether Linkage
The Chemistry of the Amino Group
The Chemistry of the Nitro and Nitroso Groups (*two parts*)
The Chemistry of Carboxylic Acids and Esters
The Chemistry of the Carbon–Nitrogen Double Bond
The Chemistry of the Cyano Group
The Chemistry of Amides
The Chemistry of the Hydroxyl Group (*two parts*)
The Chemistry of the Azido Group
The Chemistry of Acyl Halides
The Chemistry of the Carbon–Halogen Bond (*two parts*)
The Chemistry of Quinonoid Compounds (*two parts*)
The Chemistry of the Thiol Group (*two parts*)
The Chemistry of Amidines and Imidates

The Chemistry of the Hydrazo, Azo and Azoxy Groups
The Chemistry of Cyanates and their Thio Derivatives (*two parts*)
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The Chemistry of Diazonium and Diazo Groups (*two parts*)
The Chemistry of the Carbon–Carbon Triple Bond (*two parts*)
The Chemistry of the Carbon–Carbon Triple Bond (*two parts*)
Supplement A: The Chemistry of Double-bonded Functional Groups (*two parts*)
Supplement B: The Chemistry of Acid Derivatives (*two parts*)
The Chemistry of Ketenes, Allenes and Related Compounds (*two parts*)

Titles in press:

Supplement E: The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogs
The Chemistry of the Sulphonium Group

Future volumes planned include:

The Chemistry of Organometallic Compounds
The Chemistry of Sulphur-containing Compounds
Supplement C: The Chemistry of Triple-bonded Functional Groups
Supplement D: The Chemistry of Halides and Pseudo-halides
Supplement F: The Chemistry of Amines, Nitroso and Nitro Groups and their Derivatives

Advice or criticism regarding the plan and execution of this series will be welcomed by the Editor.

The publication of this series would never have started, let alone continued, without the support of many persons. First and foremost among these is Dr Arnold Weissberger, whose reassurance and trust encouraged me to tackle this task, and who continues to help and advise me. The efficient and patient cooperation of several staff-members of the Publisher also rendered me invaluable aid (but unfortunately their code of ethics does not allow me to thank them by name). Many of my friends and colleagues in Israel and overseas helped me in the solution of various major and minor matters, and my thanks are due to all of them, especially to Professor Z. Rappoport. Carrying out such a long-range project would be quite impossible without the non-professional but none the less essential participation and partnership of my wife.

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SAUL PATAI

Contents

CHAPTER **14**

Ketene *O*,*O*-acetals

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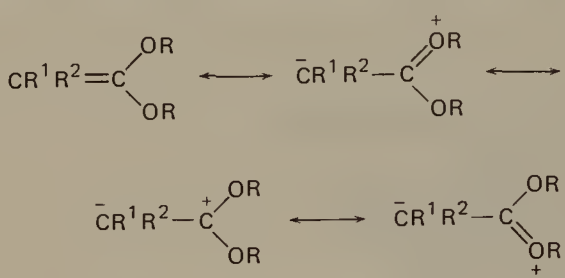
I. INTRODUCTION

Although a small number of ketene acetals had been described earlier, no general, and practical method of obtaining these compounds was devised until the extended investigation undertaken by S. M. McElvain from 1935 onwards. Many of the properties and characteristic reactions of these substances were revealed during the 30 years of this endeavour and since then, ketene acetals have attracted ever-widening attention. The literature on all aspects of the subject has been summarized in detail[1,2] periodically while extensive reference to ketene acetals has been included in recent reviews of Claisen rearrangements[3] and *O*-silylated enolates[4].

The pronounced dipolar character of ketene acetals (1) confers on most members of this series not only great reactivity but extraordinary versatility. Therefore it is not surprising that initial results were sometimes obscured by the formation of complex reaction mixtures, the sensitivity of these reagents to minor changes in structure or experimental conditions and the uncertainty in identifying certain products.



(1)

Much of the early work has not been superseded and so, some fundamental behaviour of ketene acetals is presented very briefly in this chapter. The development of newer types of reagents is emphasized and particular stress is placed on recent or useful solutions to synthetic problems. On the other hand, kinetic studies and the formation of unusual structures are largely neglected. However particular types of derivatives of wide applicability such as tetraalkoxyethylenes, acylketene acetals, vinylketene acetals, etc., are discussed.

II. PREPARATION OF KETENE ACETALS

A. Ketene Dialkyl Acetals

The original preparations published by McElvain and his coworkers are still valid today and references to general, individual and special procedures have been collected[1,2].

One of the first practical methods of obtaining ketene acetals, and one of the most useful, consists in the elimination of hydrogen halide from an α-halo acetal (2) in the presence of strong bases such as potassium *t*-butoxide[1,2] (equation 1). Few modifications, improvements or extensions have been suggested for this process, however, changes of solvent[5] or of base[6,7] have been proposed and a variation allowing the preparation of mixed acetals has also been devised[8-10].

Elimination of vicinal halogen and alkoxyl functions from α-halogenated orthoesters (3), the Boord reaction, using metals such as sodium, magnesium or zinc has been shown to give good results particularly in the case of ketene dimethyl acetal

$$R^1R^2CX{-}CH(OR)_2 \xrightarrow{B^-} R^1R^2C{=}C(OR)_2 \qquad (1)$$

(2)

and is the most suitable procedure for preparing monoalkylketene acetals[1,2] (equation 2).

$$R^1CHX{-}C(OR)_3 \xrightarrow{M} R^1CH{=}C(OR)_2 \qquad (2)$$

(3)

A third method, somewhat limited in scope, is based on the thermal elimination of alcohol from appropriate orthoesters (**4**). This reaction is subject to either acidic or basic catalysis and is often chosen for the preparation of dialkylketene acetals and when substituents capable of extending the conjugation of the system are present[1,2,11] (equation 3).

$$R^1R^2CH{-}C(OR)_3 \longrightarrow R^1R^2C{=}C(OR)_2 \qquad (3)$$

(4)

In a newer approach, some ketene acetals are obtained through substitution of 1,1-dihalo-1-alkenes by alkoxides. The procedure is simple, but remains in general restricted to fluorine-containing compounds[2,12-14] (equation 4), to conjugated substrates[2,15-17] such as β,β-dichloroenones (**5**) (equation 5) and to particular reagents like β-alkoxy- and β-dialkylamino-alkoxides[18,19] (equation 6).

$$FCH{=}CCl_2 \xrightarrow{NaOMe} ClCH{=}C(OMe)_2 \qquad (4)$$

$$R^1COCH{=}CCl_2 \xrightarrow[ROH]{RO^-} R^1COCH_2C(OR)_3 \longrightarrow R^1COCH{=}C(OR)_2 \qquad (5)$$

(5)

$$H_2C{=}CCl_2 + ROCH_2CH_2O^- \longrightarrow H_2C{=}C(OCH_2CH_2OR)_2 \qquad (6)$$

B. Ketene Alkyl Trialkylsilyl Acetals

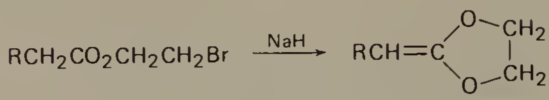
More recently, interest has extended to the trialkylsilyl analogues of ketene acetals. These compounds in general are more readily accessible than the dialkyl derivatives and on occasion show characteristic or unique behaviour. The first identified ketene alkyl trialkylsilyl acetal (**7**) was reported in 1959 as the product of the reaction of triethylsilane with an acrylic ester[20] (**6**) (equation 7). This conversion was later found to be effectively catalysed by tris(triphenylphosphine)-chlororhodium[21].

$$H_2C{=}CHCO_2R + Et_3SiH \longrightarrow CH_3CH{=}C(OR)(OSiEt_3) \qquad (7)$$

(6) (7)

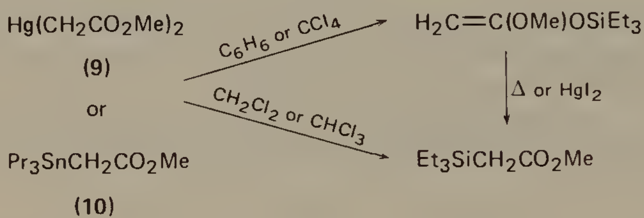
Earlier, Hance and Hauser[22] had obtained sodium enolates of ethyl acetate and ethyl isobutyrate using sodium triphenylmethide and claimed that a subsequent reaction with trimethylchlorosilane yielded only the *C*-silylated product (**8**) (equation 8). In contrast, the intramolecular alkylation of ester enolates to ketene acetal has been reported[23] (equation 9).

$$CH_3CO_2Et \xrightarrow[2.\ Me_3SiCl]{1.\ Ph_3CNa} \underset{(8)}{Me_3SiCH_2CO_2Et} \tag{8}$$



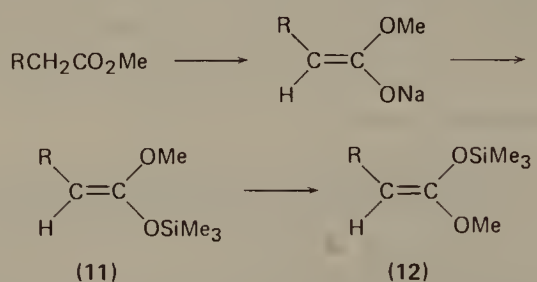
(9)

Reexamination[24] of the reaction of trialkylchlorosilane with enolates produced by sodium bis(trimethylsilyl)amide established that both *C*- and *O*-silylated products are formed, albeit in low yield, and easily distinguished by their spectral properties. Simultaneously it was found that bis(carboxymethyl)mercury[25,26] (**9**) or methyl (trialkylstannyl)acetates[26,27] (**10**) react with triethyliodosilane and, depending on experimental conditions, selectively give either *C*- or *O*-silylated derivatives (equation 10). Moreover the ketene acetal could be converted to the ester by heating or by treatment with mercuric iodide.



(10)

The same group[28] has tentatively assigned configurations to the ketene alkyl trialkylsilyl acetals derived from certain substituted acetic esters. The *E* isomers (**11**) would be the kinetically controlled products which are then spontaneously or catalytically converted to the substances having the *Z* configuration (**12**) (equation 11).



(11)

Ketene alkyl trialkylsilyl acetals are currently prepared, in nearly quantitative yield, from trialkylchlorosilane and the appropriate alkali-metal ester enolate. The latter is obtained with strong bases such as lithium diisopropylamide[29] or *N*-isopropylcyclohexylamide[30,31]. Lithium enolates are preferred for their greater stability[32] while ketene acetals derived from *t*-butyldimethylchlorosilane are easier to isolate[31]. With trimethylchlorosilane, in the absence of HMPA, mixtures are sometimes formed; substitution on the alcohol portion was found to promote *C*-silylation whereas branching in the α-position favours *O*-silylation[31]. The stereochemical outcome of the reaction has also been found to be determined largely by the nature of the solvent used[33].

A convenient route for the preparation of disubstituted ketene alkyl trialkylsilyl acetals has been proposed by Ainsworth and coworkers[29,34]. In this method, a reductive dealkoxycarbonylation of disubstituted malonic esters (**13**) is induced by metallic sodium in the presence of trimethylchlorosilane (equation 12). The mechanism[34] of this reaction and stereochemical assignments[35] have been discussed. An analogous treatment of ethyloxalate gave a mixture of the E and Z isomers of 1,2-diethoxy-1,2-bis(trimethylsiloxy)ethylene[34]. Unsubstituted[24,36] and monosubstituted[35] malonates give the normal products without decarboxylation.

$$R^1R^2C(CO_2Me)_2 + Na \xrightarrow{Me_3SiCl} R^1R^2C{=}C(OMe)OSiMe_3 \qquad (12)$$

(13)

The direct O-silylation of a phenylacetic ester (**14**) by trimethylsilyl trifluoromethanesulphonate[37] (equation 13) as well as the concomitant alkylation and enolization of benzylidenecyanoacetates (**15**) by t-butyltrimethylsilylmercury[38] (equation 14) have recently been carried out. These reactions have been applied in a limited number of cases and are of undetermined scope.

$$ArCH_2CO_2Et \xrightarrow{CF_3SO_3SiMe_3} ArCH{=}C(OEt)OSiMe_3 \qquad (13)$$

(14)

$$ArCH{=}C(CN)CO_2Et \xrightarrow{t\text{-BuHgSiMe}_3} ArCH(t\text{-Bu})C(CN){=}C(OEt)OSiMe_3 \qquad (14)$$

(15)

C. Ketene Bis(trialkylsilyl) Acetals

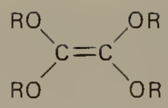
Ketene bis(trialkylsilyl) acetals (**16**) first came to the attention of chemists a decade ago[36,39]. Since then the syntheses[39,40], thermal decomposition[40,41], rearrangement[39] and other properties of these reactive species have been investigated extensively. They seem best prepared by either of two straightforward methods[34,40] involving the silylation of silyl ester enolates or of carboxylic acid dienolates (equation 15). Lower members of the series also give appreciable amounts of the C-silylated product.

$$\left.\begin{matrix} R^1R^2CHCO_2SiMe_3 \\ \text{or} \\ R^1R^2CHCO_2H \end{matrix}\right\} \xrightarrow[2.\ Me_3SiCl]{1.\ (i\text{-Pr})_2NLi} R^1R^2C{=}C(OSiMe_3)_2 \qquad (15)$$

(16)

D. Miscellaneous Ketene Acetals

Tetraalkoxyethylenes (**17**), in view of their high electron density show unusual reactivity and have been studied in detail[42]. They are probably best prepared by the action of sodium hydride on dialkyl p-chlorophenylorthoformate[43] but other methods are also available[2]. The acetal of dimethoxymethyleneketene, tetramethoxyallene (**18**), has been obtained by treatment of 1,1-dibromotetramethoxycyclopropane by butyllithium[44] while the preparation and interesting applications of (2,2-diethoxyvinylidene) triphenylphosphorane (**19**) have been investigated by Bestmann and collaborators[45,46]. Although 1,1-diacyloxyethylenes (**20**) do not seem to have been described, 1-alkoxyvinyl esters (**21**) have been synthesized, usually by the mercuric-ion catalysed addition of carboxylic acids to alkoxyacetylenes[47].



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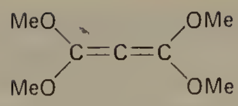

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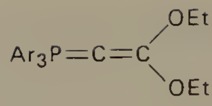

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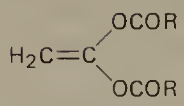

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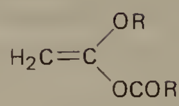


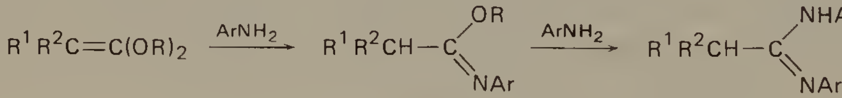
(21)

III. ELECTROPHILIC ADDITIONS

The electron-rich double bond of ketene acetals facililates 1,2-additions of a wide variety of reagents. In some cases the derivatives of orthoacetic acid thus formed are relatively stable but in others, particularly with reactions requiring higher temperatures, the initial products either eliminate alcohol, giving exchange products, or break down to carboxylic esters, their analogues and to dimeric substances. The additions are observed even with very weakly acidic compounds but are severely limited by the presence of electron-attracting groups on the ketene acetal.

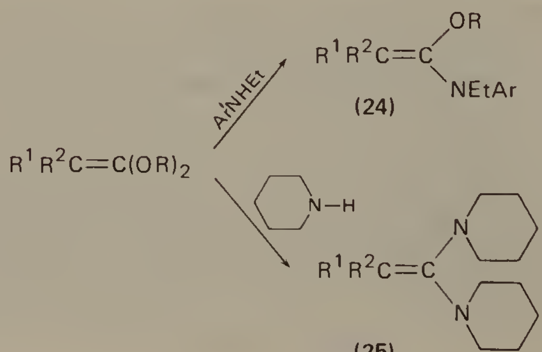
A. Reactions with Compounds Containing Labile Hydrogen

Ammonia and amines react with ketene acetals and give rise to complex addition–elimination sequences[2]. Although these compounds are nucleophilic, the observed reaction rates qualitatively fall in the order of their pK_bs. Primary amines[48–52] yield imino ethers (22) and with excess reagent, amidines (23) (equation 16).



(22) (23) (16)

Secondary amines on the other hand lead to ketene *O,N*-(24) and *N,N*-acetals (25), depending on the nature of the base and on reaction conditions[48,53,54] (equations 17 and 18). Tertiary amines are usually unreactive. Hydrazines[49], hydroxylamines[55], amidines[55] and 2-aminopyridines[52] (in the last case, with chloroketene acetals) give intermediate addition products with eventual ring-closure to heterocyclic derivatives.



(17)

(18)

(25)

The addition of hydroxylated substances and their sulphur analogues to ketene acetals has been extensively studied[1,2]. In many instances acid catalysis has been shown to be operative[56-59]. Thus water, primary and secondary alcohols[2,58,60,61], hydroperoxides[62], mercaptans[61,63], enols[48], phenols[64], oximes[65], and carboxylic[66], sulphonic[67] and hydroxamic[68] acids, etc. readily give derivatives of orthoacids. With the exception of orthoesters (**26**), primary products or intermediates usually react further and give carboxylic esters, dimers or polymers (equations 19–22).

$$R^1R^2C{=}C(OR)_2 \xrightarrow{R^3OH} R^1R^2CH{-}C(OR)_2(OR^3) \quad \textbf{(26)} \qquad (19)$$

$$R^1R^2C{=}C(OR)_2 \xrightarrow{H_2O} R^1R^2CHCO_2R + ROH \qquad (20)$$

$$R^1R^2C{=}C(OR)_2 \xrightarrow{ArOH} R^1R^2CHCO_2R + ArOR \qquad (21)$$

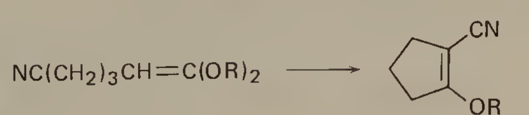
$$R^1R^2C{=}C(OR)_2 \xrightarrow{R^3CO_2H} R^1R^2CHCO_2R + R^3CO_2R \qquad (22)$$

When phenols[66], carboxylic[66] and various phosphorus[69] acids react with unsubstituted ketene acetals dimeric substances are obtained. Hydrogen cyanide and hydrogen halides behave in much the same way, β-alkoxycrotonic esters (**27**) being the principal products isolated from reactions with simple ketene acetals[1,2,70] (equation 23).

$$2\,H_2C{=}C(OR)_2 \xrightarrow{HX} \underset{\textbf{(27)}}{CH_3C(OR){=}CHCO_2R} + ROH + RX \qquad (23)$$

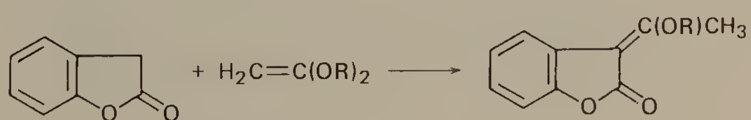
Finally there seem to be few examples of condensations resulting from the addition of ketene acetals to compounds containing active methylene groups[42,48,71-73]. Nevertheless, the reaction shows considerable potential in various synthetic approaches (equations 24–27).

$$H_2C{=}C(OR)_2 + CH_2(CO_2R^1)_2 \longrightarrow CH_3C(OR){=}C(CO_2R^1)_2 \qquad (24)$$



(25)

$$(RO)_2C{=}C(OR)_2 + CH_2(CN)_2 \longrightarrow (RO)_2CHC(OR){=}C(CN)_2 \qquad (26)$$



(27)

B. Halogenation

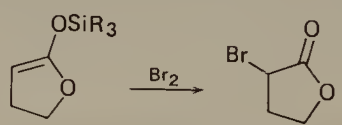
The addition of halogens and other halogenating agents to various ketene acetals has been studied in detail. Under carefully controlled conditions, bromine yields mainly the α-bromo ester[74,75] (28) (equation 28). Similar results are obtained by the use of *N*-halosuccinimides[76]. In the presence of an excess of the ketene acetal, dimeric substances such as **29** become the principal products[70] (equation 29). An analagous reaction starting with tetramethoxyethylene gave a mixture of dimethyl oxalate (**30**) and dimethyl tetramethoxysuccinate[77] (**31**) (equation 30).

$$H_2C{=}C(OR)_2 + Br_2 \longrightarrow \underset{(28)}{CH_2BrCO_2R} + RBr \qquad (28)$$

$$MeCH{=}C(OR)_2 + I_2 \longrightarrow \underset{(29)}{MeCHIC(OR)_2CHMeCO_2R} \qquad (29)$$

$$(MeO)_2C{=}C(OMe)_2 + I_2 \longrightarrow \underset{(30)}{(CO_2Me)_2} + \underset{(31)}{\begin{array}{l} C(OMe)_2CO_2Me \\ | \\ C(OMe)_2CO_2Me \end{array}} \qquad (30)$$

Recently this reaction has been extended to ketene alkyl trialkylsilyl and bis(trialkylsilyl) acetals[78]. The method gives excellent yields and provides convenient access to α-halogenated lactones (**32**), esters (**33**) and acids (**34**) (equations 31 and 32).



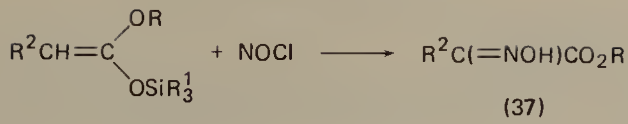
(32) (31)

$$ArCH{=}C(OSiR_3)_2 \xrightarrow{Br_2} \underset{(33)}{ArCHBrCO_2SiR_3} \xrightarrow{H_2O} \underset{(34)}{ArCHBrCO_2H} \qquad (32)$$

Other halogenating reagents such as cyanogen halides[70] and nitrosyl chloride[79] give straightforward 1,2-addition products (**35**) (equation 33) with ketene dialkyl acetals. In the latter case, the nitroso compounds rearrange to the oximes (**36**) (equation 34) while reactions carried out with *O*-silylated substrates yield the corresponding oximino esters[80] (**37**) (equations 35).

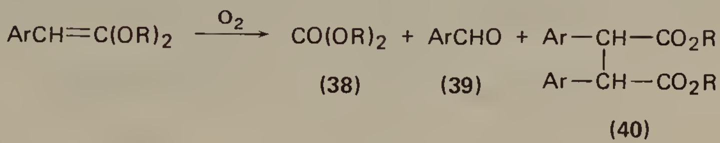
$$R^1CH{=}C(OR)_2 + BrCN \longrightarrow \underset{(35)}{R^1CHBrC(OR)_2CN} \qquad (33)$$

$$H_2C{=}C(OR)_2 + NOCl \longrightarrow \underset{(36)}{HON{=}CH{-}C(OR)_2Cl} \qquad (34)$$

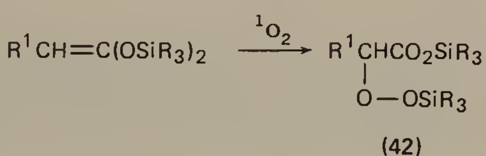
 (35)

C. Oxidation

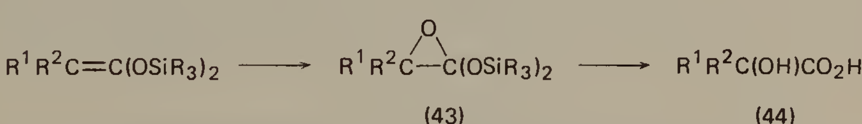
Ketene acetals like other electron-rich substances are particularly prone to attack by various oxidizing agents. Autoxidation of simple substrates generally leads to fragmentation with the formation of carbonates (**38**), the corresponding carbonyl compounds (**39**) and dimers (**40**) or polymers[74] (equation 36). Tetramethoxyethylene reacts somewhat differently giving as principal product methyl trimethoxyacetate[81] (**41**) (equation 37). A rearranged product (**42**) is also observed in quantitative yield when a ketene bis(trialkylsilyl) acetal combines with singlet oxygen[82] (equation 38).

 (36)

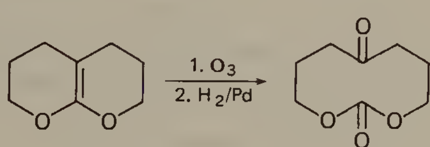
$$(MeO)_2C{=}C(OMe)_2 \xrightarrow[\text{or } O_3]{O_2} \mathbf{38} + \underset{\mathbf{(41)}}{(MeO)_3CCO_2Me} \qquad (37)$$

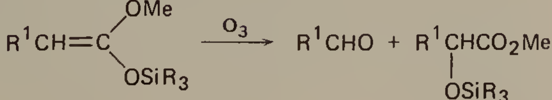
 (38)

The formation of an epoxide has been suggested in one of the pathways taken during the autoxidation of tetramethoxyethylene[81]. A more practical route to epoxides[83] (**43**) and thence to α-hydroxy acids (**44**) has been proposed and applies the use of *m*-chloroperbenzoic acid to ketene bis(trialkylsilyl) acetals (equation 39).

 (39)

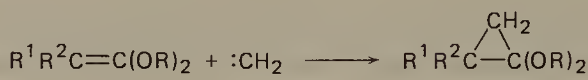
Ozone seems to induce the normal fragmentation process with ketene dialkyl acetals[84] (equation 40). However tetramethoxyethylene[81] and ketene alkyl trialkylsilyl acetals[85] give in part products resulting formally from migration of an alkyl (equation 37) or trialkylsilyl (equation 41) group to oxygen in the α-position.

 (40)

 (41)

D. Reactions with Carbenes

Many types of ketene acetals have been found to react smoothly with various carbenes. Usually the expected cyclopropane (**45**) can be isolated when carbene, dichloro- or phenylchloro-carbenes are used[75,86–88] (equation 42).


(42)

(**45**)

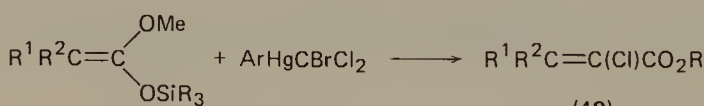
With dibromo-, carbethoxy- and occasionally phenylchloro-carbenes the initial products break down more or less readily to the corresponding acrylic esters[44,75,86] (**46**) (equation 43) or to ketene acetals[75] (**47**) (equation 44). More recently, dichlorocarbene generated from bromodichloromethylphenylmercury has led to the advantageous syntheses of α-chloroacrylic esters[89,90] (**48**) (equation 45).

$$H_2C{=}C(OR)_2 + :CBr_2 \longrightarrow H_2C{=}CBrCO_2R \quad (43)$$

(**46**)

$$H_2C{=}C(OR)_2 + :CHCO_2Et \longrightarrow EtOCOCH_2CH{=}C(OR)_2 \quad (44)$$

(**47**)

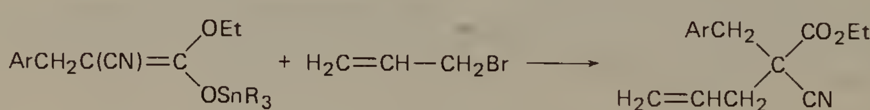

(45)

(**48**)

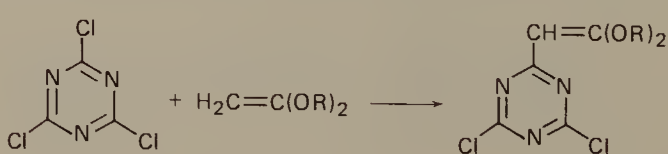
E. Condensations with Reactive Halides

Reactive aliphatic halogen compounds have been known for some time to give definitive products with ketene acetals (equation 46). The reactions occur at high temperatures with allyl[66,76], benzyl[84,91]. benzhydryl[92] and methoxymethyl[93] halides and therefore probably proceed through the intermediate carbonium ions. Yields have been improved on occasion by catalysing the substitution with the weaker Lewis acids[92,94,95] (equations 46 and 47).

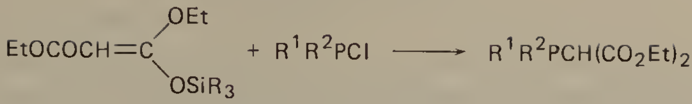
$$R^1R^2C{=}C(OR)_2 + ArCH_2Br \longrightarrow ArCH_2CR^1R^2CO_2R + RBr \quad (46)$$


(47)

Heterocyclic halides such as cyanuric chloride[96] (**49**) or 4,6-dichloro-5-nitro-pyrimidine[97], and organophosphorus halides[98] probably react by an addition–elimination process and, depending on the nature of the substrate, give either substituted ketene acetals or esters (equations 48 and 49).


(48)

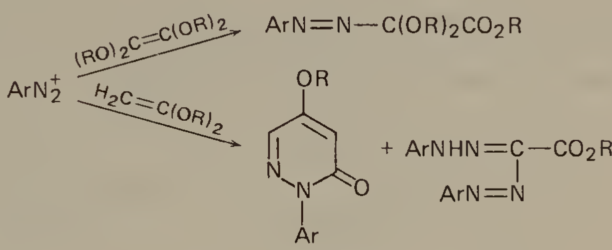
(**49**)



(49)

F. Reactions with Various Cations

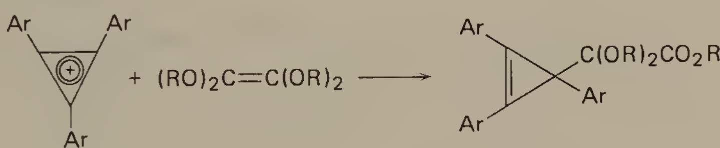
Benzenediazonium salts have been shown to give various types of products with ketene acetals. In the case of tetramethoxyethylene[99], a simple coupling reaction occurs but with dialkyl acetals 1:2- (pyridazones) (**50**) and 2:1-addition products (**51**) are isolated from reactions conducted in the absence of solvent[100] (equation 50).



(50)

(50) (51)

The triphenylcyclopropenylium ion (**52**) reacts analogously with tetramethoxyethylene[99] (equation 51) and mercuric salts with ketene dialkyl acetals provide several types of metalated esters under carefully controlled conditions[101].



(51)

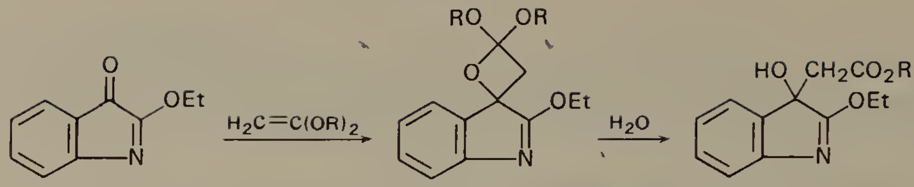
(52)

IV. REACTIONS WITH CARBONYL COMPOUNDS AND THEIR SULPHUR ANALOGUES

A. Additions to Aldehydes and Ketones

At elevated temperatures, formaldehyde is converted to glyoxal in the presence of ketene acetals[102]. However its higher homologues tend to condense with these reagents and give low yields of α,β-unsaturated esters[84,102] (**53**) (equation 52). Cyclic intermediates have been proposed for this reaction but convincing evidence of their existence has only recently been produced[103]. Ketones and aromatic aldehydes in general do not give definite products under these conditions, however exceptions (**54**) to this rule are known[103,104] (equation 53).

$$R^1CHO + H_2C{=}C(OR)_2 \longrightarrow \underset{(53)}{R^1CH{=}CHCO_2R} \qquad (52)$$



(54) (53)

According to a similar procedure[105] β-hydroxy esters (55) can be obtained systematically by the use of ketene alkyl trialkylsilyl acetals. Thus the elimination step can be avoided but only aromatic aldehydes have been found to give the desired products (equation 54). Recently, this process has been reinvestigated using $TiCl_4$ as catalyst[106]. It was found that a variety of aldehydes and ketones react smoothly even with mono- and di-substituted ketene alkyl trialkylsilyl acetals and usually give high yields of the corresponding β-hydroxy esters without dehydration and along with small amounts of the trialkylsilyl esters.

$$\mathrm{ArCHO} + \mathrm{R^2R^3C{=}C}\begin{matrix}\mathrm{OR} \\ \mathrm{OSiR^1_3}\end{matrix} \longrightarrow \underset{(55)}{\mathrm{ArCH(OH){-}CR^2R^3CO_2R}} \qquad (54)$$

An analogous result was obtained by replacing the carbonyl compound by its acetal[106]. In this way, β-alkoxy esters (56) were formed in high yield and at low temperature (equation 55). Even orthoesters are reactive under these conditions and lead to convenient preparations of 3,3-dialkoxy esters (57) (equation 56).

$$\mathrm{R^2R^3C{=}C}\begin{matrix}\mathrm{OR} \\ \mathrm{OSiR^1_3}\end{matrix} + \mathrm{R^5R^6C(OR^4)_2} \xrightarrow{\mathrm{TiCl_4}} \underset{(56)}{\mathrm{R^5R^6\underset{\displaystyle OR^4}{C}{-}CR^2R^3CO_2R}} \qquad (55)$$

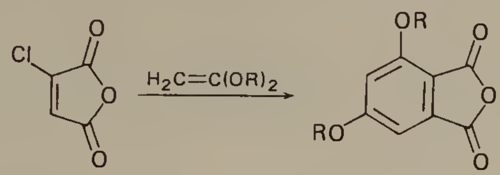
$$\mathrm{ArCH{=}C}\begin{matrix}\mathrm{OR} \\ \mathrm{OSiR^1_3}\end{matrix} + \mathrm{CH(OMe)_3} \longrightarrow \underset{(57)}{\mathrm{CH(OMe)_2{-}\underset{\displaystyle CH_2Ar}{C}HCO_2R}} \qquad (56)$$

Although acyclic α,β-unsaturated ketones generally give cycloaddition products with ketene acetals, the catalysed reaction takes a different course and gives Michael-type condensations. The procedure recommends the use of $TiCl_4$ or $TiCl_4 - Ti(O\text{-}i\text{-}Pr)_4$, for sensitive subtrates, and affords a simple synthesis of δ-keto esters[107] (58). As in the preceding case, the method can also be applied to the corresponding acetals (equation 57).

$$\mathrm{R^2R^3C{=}C}\begin{matrix}\mathrm{OR} \\ \mathrm{OSiR^1_3}\end{matrix} + \mathrm{R^4R^5C{=}CR^6COR^7} \longrightarrow \underset{(58)}{\mathrm{R^7COCHR^6CR^4R^5CR^2R^3CO_2R}} \qquad (57)$$

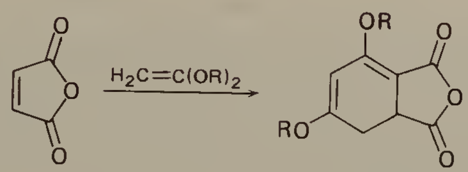
B. Additions to Cyclic Enediones

Reactions between ketene acetals and cyclic enediones usually occur through complex and competing processes, but nevertheless have provided access to a number of useful products or intermediates which are difficult to obtain by other means. With nonenolizable substrates such as maleic anhydrides, two equivalents of the ketene acetal are required and either phthalic anhydrides[108] (**59**) or the dihydro derivatives[109] (**60**) can be obtained (equations 58 and 59).



(59)

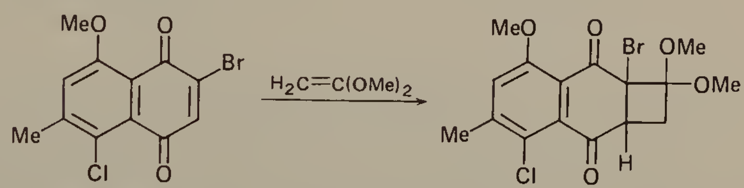
(58)



(60)

(59)

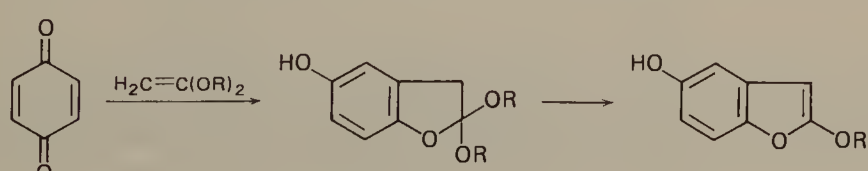
Reactions with quinones are complicated by the fact that at least three distinct pathways have been identified. The nature of the favoured product depends largely on the structure of the substrate and also, to a certain extent, on experimental conditions. The most straightforward process, a simple [2 + 2] cycloaddition, seems to have been observed only once, in the case of a fairly unreactive naphthoquinone[110] (**61**) (equation 60).



(61)

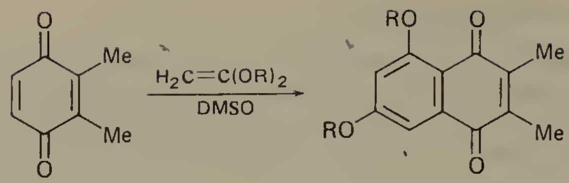
(60)

Dihydrobenzofurans[111] (**62**) and benzofurans[112] (**63**) are the usual products encountered with the use of benzoquinones, and probably arise through the facile enolization and cyclization of intermediate zwitterions (equation 61). The formation of substituted naphthoquinones **64** and **65** can be promoted, however, by conducting the reaction in a dipolar aprotic solvent such as dimethylsulphoxide[111,113,114] (equation 62) or by adding acetic acid to the reaction mixture[115] (equation 63). Earlier, poor yields of naphthoquinones had been obtained by the condensation of ketene acetals with benzoquinone dihalides[116].



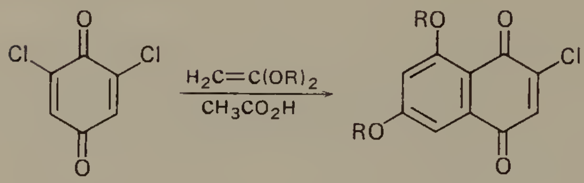
(62) (63)

(61)



(62)

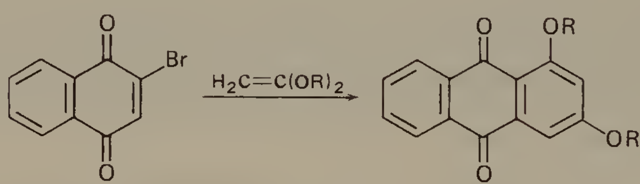
(64)



(63)

(65)

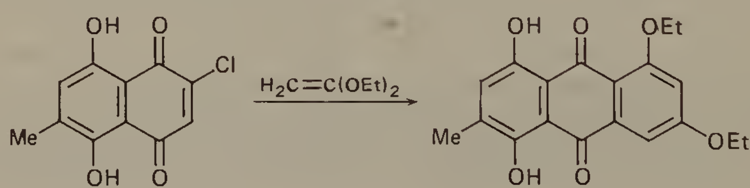
Although 1,4-naphthoquinone with ketene acetals gives only a small amount of the corresponding naphthofuran, the halogenated derivatives (in the 2- and 3-positions) as well as juglones (5-hydroxynaphthoquinones) readily form 1,3-dialkoxy-anthraquinones[112] (**66**) (equation 64). It would seem that the decreased ease of aromatization in this system as well as the stabilization of the keto form through hydrogen bonding favour reaction of the zwitterion with a second molecule of ketene acetal.



(64)

(66)

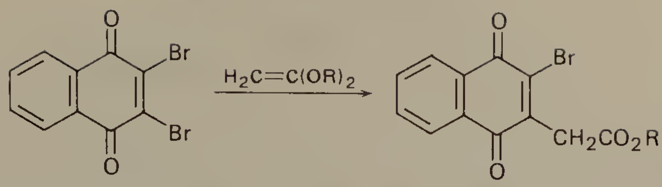
The initial attack was first thought to occur on the halogen-bearing carbon, but subsequent investigation established that the reaction proceeds with complete regiospecificity on the adjacent unsubstituted position[108]. Thus 2-chloro-6-methyl-naphthazarin (**67**) gives only catenarin diethyl ether (**68**) (equation 65) while a derivative of isocatenarin is the sole product formed from the 2,7-isomer. Analogous results were observed using 2- and 3-bromojuglones[108].



(65)

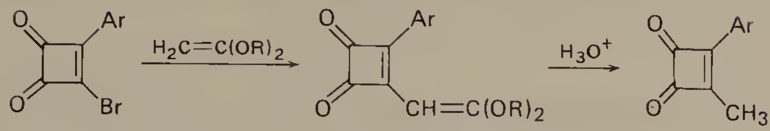
(67) (68)

With completely substituted enediones such as 2,3-dibromonaphthoquinone[112] (**69**) (equation 66) or 3-bromo-4-phenylcyclobutene-1,2-dione[117] (**70**) (equation 67), elimination of halogen halide prevents the usual sequence of transformations and gives the corresponding acetate or substituted ketene acetals.



(69)

(66)



(70)

(67)

C. Reactions with Acid Chlorides, Esters and Lactones

In the absence of tertiary amines, carboxylic acid chlorides react with ketene acetals and sometimes produce good yields of useful synthetic intermediates. Unfortunately the process is complicated by the hydrogen halide given off during the reaction and important amounts of secondary products usually accompany the required substances. (Methods involving bases probably proceed at least in part through the corresponding ketenes and are discussed along with other cycloadditions.)

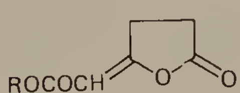
Unrestrained reactions between ketene dialkyl acetals and acid halides yield mainly β-acylacetates (**71**) or the corresponding enol esters[66] (**72**) (equation 68). The alcohols and hydrogen halide given off also react further with the starting material and produce very complex reaction mixtures.

$$H_2C{=}C(OR)_2 + R^1COCl \longrightarrow \underset{(71)}{R^1COCH_2CO_2R} \longrightarrow \underset{(72)}{R^1C(OCOR^1){=}CHCO_2R} + R^1C(OR){=}CHCO_2R + RCl + ROH \qquad (68)$$

At lower temperatures, acylketene acetals (**73**) become the principal products[91,118], a result which is also favoured by the use of a large excess of the ketene acetal[91,119]. Dibasic acid halides[91,120] and chloroformates[121] give analogous reactions while succinoyl chloride behaves abnormally giving γ-(carbalkoxymethylene)butyrolactone[91] (**74**).

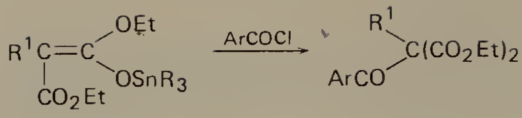
$RCOCH{=}C(OR)_2$

(73)



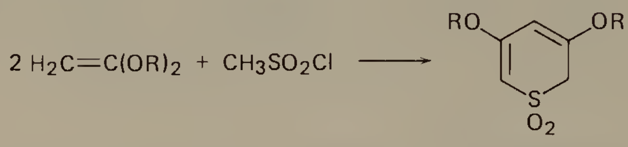
(74)

In contrast, few examples of this type of reaction as applied to mixed acetals seem to have been described. The trialkylstannyl derivatives of malonic ester enolates (**75**) give good yields of aroylmalonates[95] (**76**) (equation 69). Similar results have also been obtained using the trialkylsilyl analogues[36] but extension of this process to simple members of this series gives variable yields of acylacetates[122,123] (**71**).



(75) (76) (69)

Truce and coworkers have undertaken an extensive study of the reaction of ketene acetals with alkanesulphonyl chlorides, mainly in the presence of tertiary amines. However, in the absence of such bases, unusual cyclic 2:1-addition products (77) have been shown to arise[124] (equation 70).

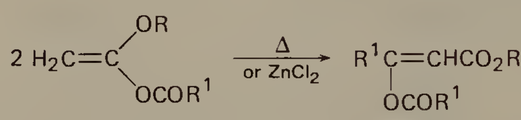


(77) (70)

Among esters, only sulphates and 1-alkoxyvinyl carboxylates seem to give definitive products with ketene acetals. In a unique case, diethyl sulphate reacted with propylketene dimethyl acetal at 145° C and gave a 65% yield of the unexpected 2-methylpentanoate [125] (78) (equation 71). The process is obscure and probably deserves to be better understood. Alkoxyvinyl carboxylates (21) on the other hand, through heating or treatment with zinc chloride[126] are converted by intermolecular acylation to enol derivatives of substituted β-oxobutyrates (79) (equation 72). An analogous intramolecular process is also known[127].

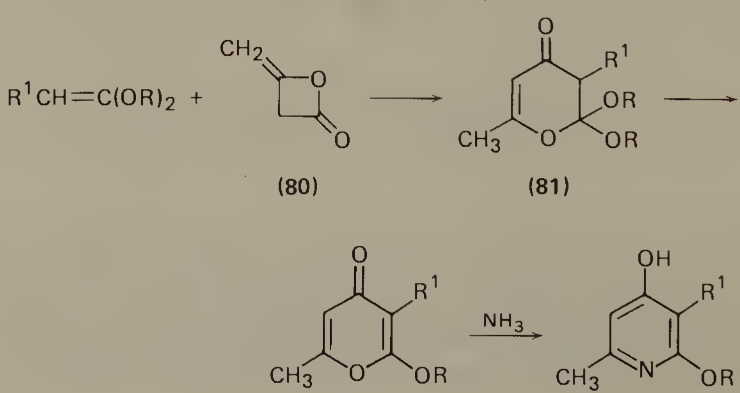
$$PrCH{=}C(OMe)_2 + (EtO)_2SO_2 \longrightarrow PrCHMeCO_2Me \quad (71)$$

(78)



(21) (79) (72)

Finally, as in the preceding case, the behaviour of ketene acetals towards reactive lactones appears to have been little investigated. Diketene (80) has given rise to a number of 2,2-dialkoxy-2,3-dihydro-6-methyl-4-pyrones (81) and to the corresponding 2-alkoxy-4-pyrones[128] (82). The method also provides a convenient route to some pyridine derivatives (83) (equation 73).



(80) (81) (82) (83) (73)

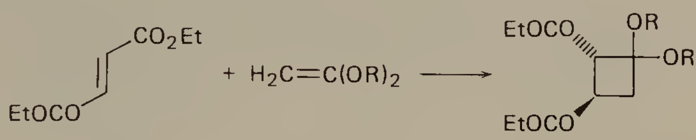
V. CYCLOADDITIONS

A. Thermal [2 + 2] Cycloadditions

Thermal reactions between ketene acetals and isolated double bonds are at least formally [2 + 2] cycloadditions and have been shown to occur with a wide variety of substrates. Considerable controversy has arisen over the mechanisms of these processes, but it now seems likely that most, if not all, involve zwitterion intermediates[129].

1. Additions to Olefins and Acetylenes

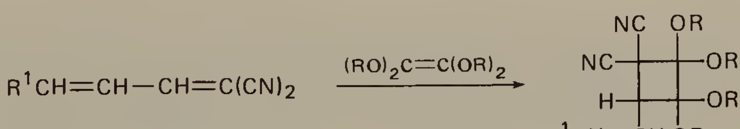
Ketene dialkyl acetals react with alkenes bearing electron-attracting groups and eventually give cyclobutanone acetals. Thus acrylic esters[130,131] fumarates[130] (84), di- and tetra-cyanothylenes[132,133] but not α,β-unsaturated aldehydes and ketones[102], are converted in this way to the cyclic compounds, often with a high degree of stereospecificity (equation 74).



(84)

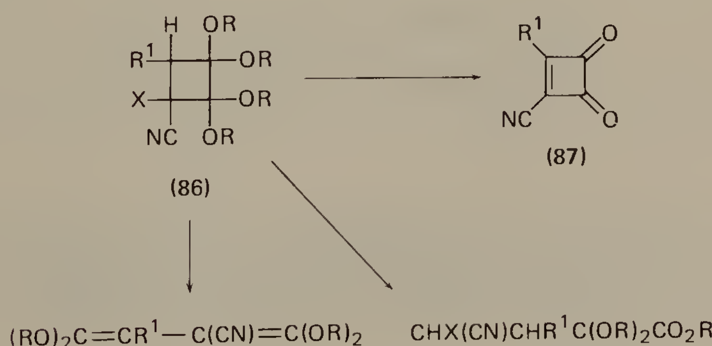
(74)

Electron-rich ketene acetals such as tetramethoxyethylene also give cyclobutanes[132,133] under these circumstances, although the reactions are slow with substrates carrying only one electron-attracting group[133]. Nevertheless [2 + 2] cycloadditions remain the preferred processes even in the case of 1,1-dicyanobutadienes (85) and of related substances[134] (equation 75). Cyclobutanes (86) derived from tetraalkoxyethylenes and substituted acrylonitriles have also been converted to otherwise difficultly accessible compounds such as cyanocyclobutenediones[134,135] (87) cyanotetraalkoxybutadienes[136] (88), and the acetals γ-cyano-α-oxobutanoates[137] (89) (equation 76).



(85)

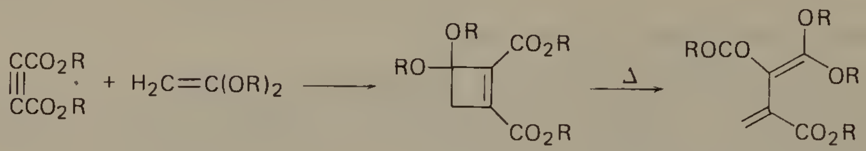
(75)



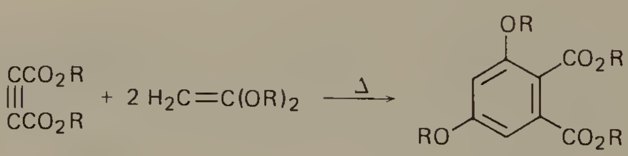
(86) (87) (88) (89)

(76)

Ketene acetals are also known to add to reactive acetylenes in a 1:1 ratio and to form cyclobutene derivatives (90). Usually the latter are not isolated but upon additional heating, undergo electrocyclic ring-opening to the corresponding 1,1-dialkoxybutadiene[115,132,138,139] (91) (equation 77). In the absence of solvent and at higher temperatures, acetylene dicarboxylates react with excess ketene acetal to form substituted phthalic esters[109] (92) (equation 78). Under comparable conditions, the acetylenic monocarboxylic esters and ketones give only 1:1 addition products.



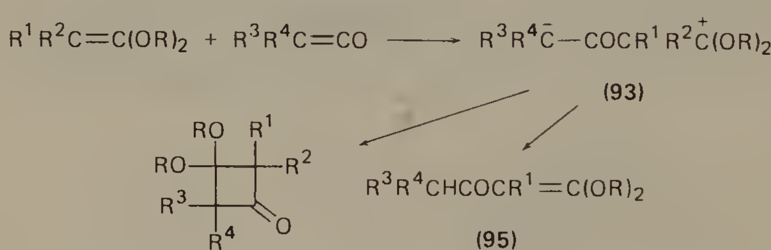
(90) (91) (77)



(92) (78)

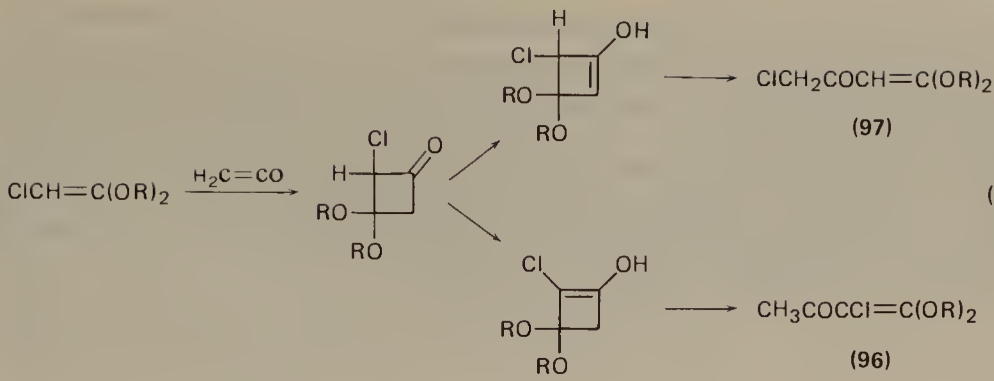
2. *Additions to Ketenes*

Ketenes, either preformed or produced *in situ* from acid chlorides and tertiary amines, react smoothly with ketene acetals and the diversity of products observed seems largely attributable to the nature and extent of substitution on the reactants, but mainly on the acetals. The initial product is probably a zwitterion (93) which then gives either a cyclobutanone (94), particularly with the use of disubstituted ketene acetals or in other cases[118,140–144] (equation 79) by prototropy acylketene acetals (95).



(93) (94) (95) (79)

It has been suggested as well that acylketene acetals arise by the isomerization of initially formed cyclobutanones or oxetanes[132,145,146]. Indeed two products (96 and 97) were isolated after the reaction of ketene with a chloroketene acetal and their formation was ascribed to the electrocyclic ring-opening of intermediate enols[146] (equation 80).



(80)

Ketene alkyl trialkylsilyl acetals in general are thermally unstable. Attempts to purify these substances result in their conversion to ketenes and this procedure sometimes provides an excellent means of preparing some members of the series such as diphenylketene[29]. Most pyrolytic products, however, react with excess starting material and give only the unconjugated silyl enol ether of the β-oxobutyrates **98**[26,29] (equation 81). This reaction has been studied extensively using preprepared ketenes[147].

$$H_2C{=}C(OR)(OSiR^1_3) \longrightarrow H_2C{=}CO \longrightarrow H_2C{=}C(OSiR^1_3)CH_2CO_2R \quad \textbf{(98)} \qquad (81)$$

Ketene bis(trialkylsilyl) acetals give analogous results although less effectively[40]. They also occur as intermediates in a recent method prescribed for the preparation of ketenes[148]. The ketene acetals are formed by thermal decarboxylation of trialkylsilyl *gem*-diesters (**99**) and do not interfere with the end-product (equation 82).

$$\underset{\textbf{(99)}}{R^1R^2C(CO_2SiR_3)_2} \xrightarrow{\Delta} R^1R^2C{=}C(OSiR_3)_2 \longrightarrow R^1R^2C{=}CO \qquad (82)$$

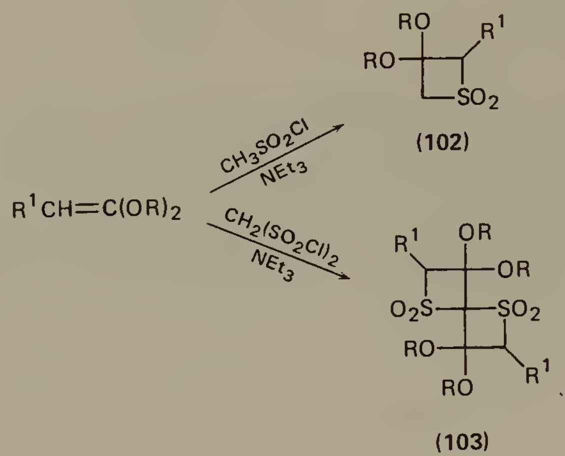
When ketene alkyl trialkylsilyl acetals react with ketenes formed *in situ* from acid chlorides in the presence of tertiary amines, the results are less sharply defined and both isomeric silylated enol esters are obtained[149]. It has been postulated that the α,β-unsaturated compounds **101** derive from the acylammonium salt **100** (equation 83).

$$R^1CH_2COCl \xrightarrow{NEt_3} \underset{\textbf{(100)}}{R^1CH_2CO\overset{+}{N}Et_3\overset{-}{Cl}} \xrightarrow{H_2C{=}C(OEt)(OSiR_3)} \underset{\textbf{(101)}}{R^1CH_2{-}C(OSiR_3){=}CHCO_2Et}$$

$$Et_3\overset{+}{N}H\overset{-}{Cl} + R^1CH{=}CO \xrightarrow{H_2C{=}C(OEt)(OSiR_3)} R^1CH{=}C(OSiR_3){-}CH_2CO_2Et \qquad (83)$$

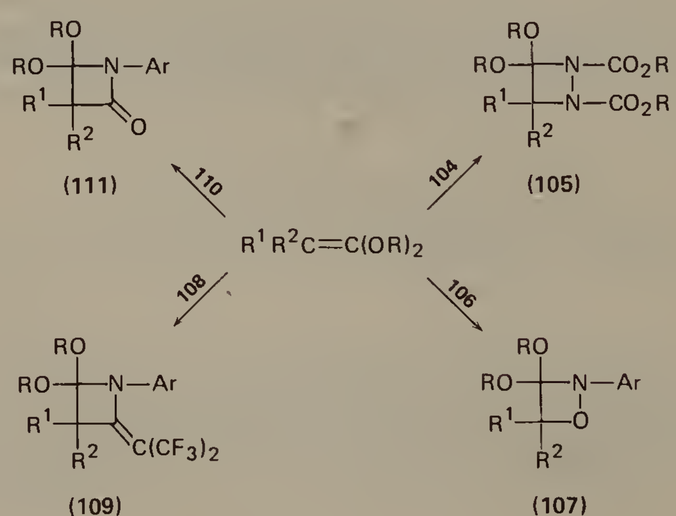
3. Formation of Four-membered Heterocycles

Under the conditions that convert carboxylic acid halides to ketenes, alkanesulphonyl chlorides have also been shown to yield the corresponding sulphenes. The latter react with ketene acetals in much the same way as the previously described ketenes and in the case of simple substrates form the expected thietane dioxides[150] (**102**); even vinylsulphenes give four-membered heterocycles[151] (R^1 = $-CH{=}CH_2$) (equation 84). This process has been studied in detail[150-152] and was later extended to the preparation of spiro compounds[153] (**103**).



(84)

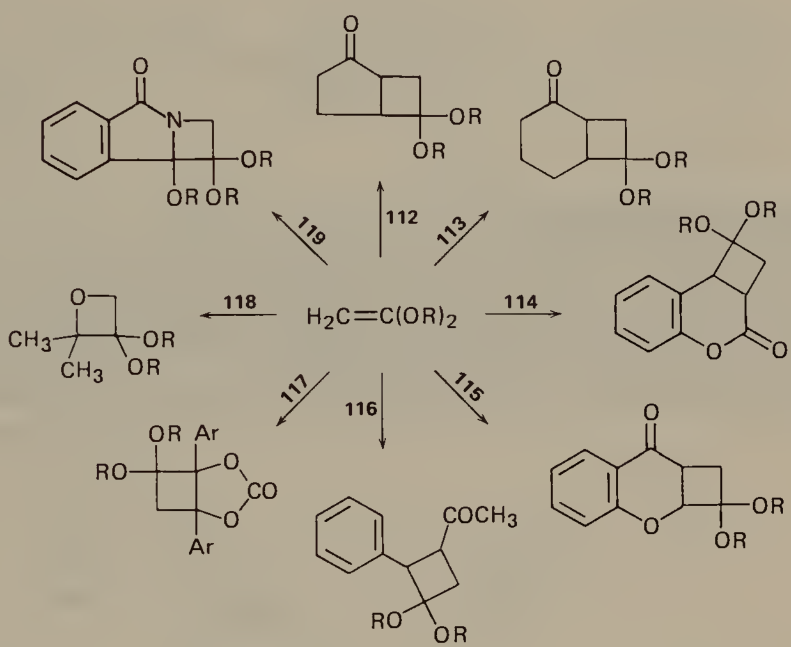
Numerous other thermal cycloadditions to ketene acetals giving four-membered heterocycles have been recorded. The following are but a few examples of such procedures which allow the conversion of dialkyl azodicarboxylates (**104**) to diazetidines[132] (**105**), of nitrosobenzene (**106**) to oxazetidines[132] (**107**), of *N*-phenylbis(trifluoromethyl)ketene imine (**108**) to azetidines[154] (**109**), of phenyl isocyanate (**110**) and phenyl isothiocyanate to azetidones[132,155,156] (**111**) or their sulphur analogues (equation 85). The initial products or intermediates are sometimes unstable and lead to open-chain compounds and six-membered heterocycles.



(85)

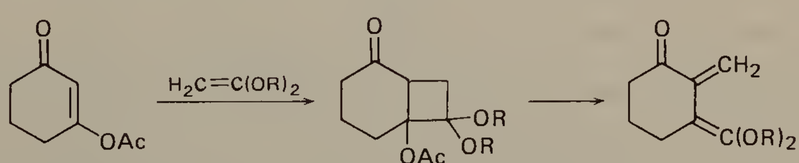
B. Photochemical [2 + 2] Cycloadditions

The Woodward–Hoffmann rules predict a facile [2 + 2] cycloaddition of ketene acetals to double bonds by photochemical means. In practice a large number of such processes have been successfully carried out with a great variety of substrates. These types of reactions have been shown to occur smoothly with cyclopentenones[7,157,158] (112), cyclohexenones[7,159–161] (113), coumarin[162] (114), chromone[163] (115), benzalacetones[161] (116), vinylidene carbonates[164] (117), as well as with compounds containing carbon–oxygen[165] double bonds, such as acetone (118) and carbon–nitrogen[166,167] double bonds, such as 3-alkoxyisoindolone (119). As predicted in theory, the additions proceed with an orientation inverse to that observed in polar reactions (equation 86).

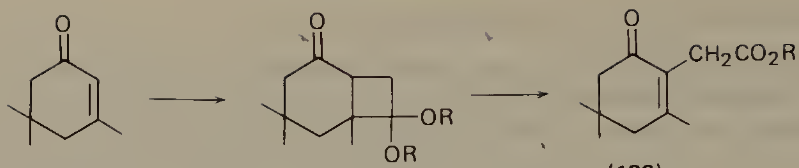


(86)

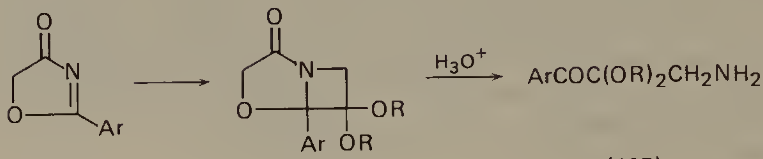
By subsequent transformation of such adducts, unlimited uses can be envisaged and some practical applications have already been proposed. For instance cycloaddition to 1-acetoxycyclohexen-3-one (120) followed by elimination and conrotary opening gives a reactive substituted dialkoxydiene[168] (121) (equation 87). Conjugated enones such as isophorone[161] (122) can be α-carboalkoxymethylated to 123 (equation 88) while the photoannulation products of phenyloxazolinones[167] (124) and alkoxyisoindolones[166] (119) have been hydrolysed to β-aminopropiophenones (125) (equation 89) and to azepine derivatives (126) (equation 90) respectively.



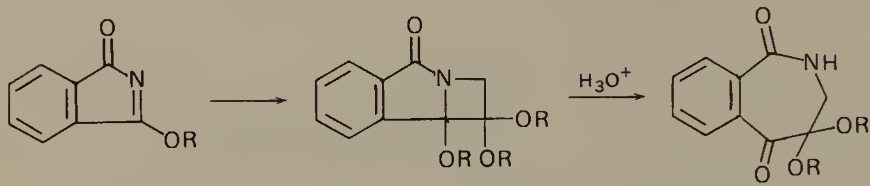
(120) (121) (87)



(122) (123) (88)



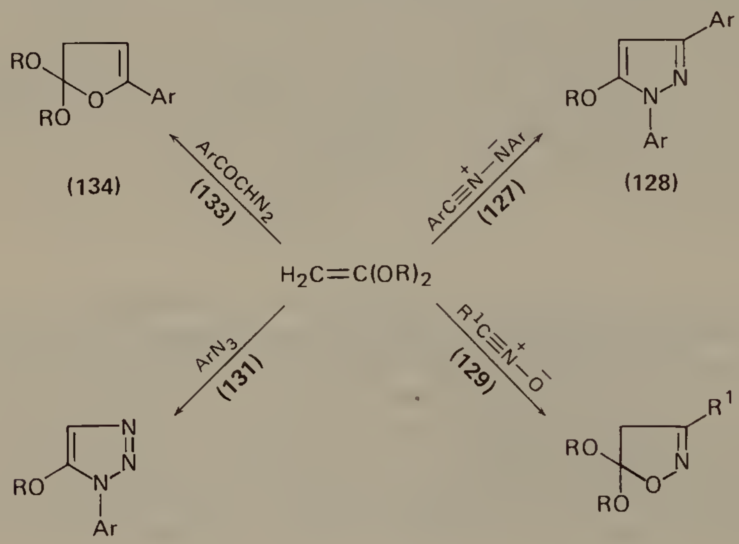
(124) (125) (89)



(119) (126) (90)

C. 1,3-Dipolar Cycloadditions

Most of the usual 1,3-dipolar reagents readily give cycloaddition products with ketene acetals. The expected five-membered heterocycles are obtained; thus nitrilimines (127) are converted to pyrazoles[169] (128), nitriloxides (129) and nitrones to isoxazolines[170] (130) or isoxazolidines[171], azides (131) to triazoles[172] (132) and diazo ketones (133) to dihydro furans[173] (134) (equation 91).



(134) (128) (132) (130) (91)

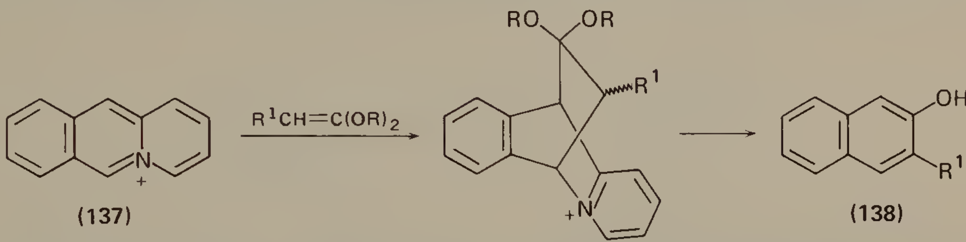
Some annulation products are unstable and either isomerize or break down. Azides in particular seem to form various triazolines[174] initially, but subsequent transformations have been shown to be quite complex. The processes involved have been studied in detail with phenyl azide, sulphonyl azides, acyl azides, azidoformates, etc.[171-176]. Electron-rich ketene acetals such as tetraalkoxyethylenes probably form cycloadducts but these are extremely unstable. Dialkylimidocarbonates (136) are the only products isolated from reactions with sulphonyl azides[177] (135) (equation 92).

$$ArSO_2N_3 + (RO)_2C{=}C(OR)_2 \longrightarrow ArSO_2{-}N{=}C(OR)_2 \quad (92)$$

(135) (136)

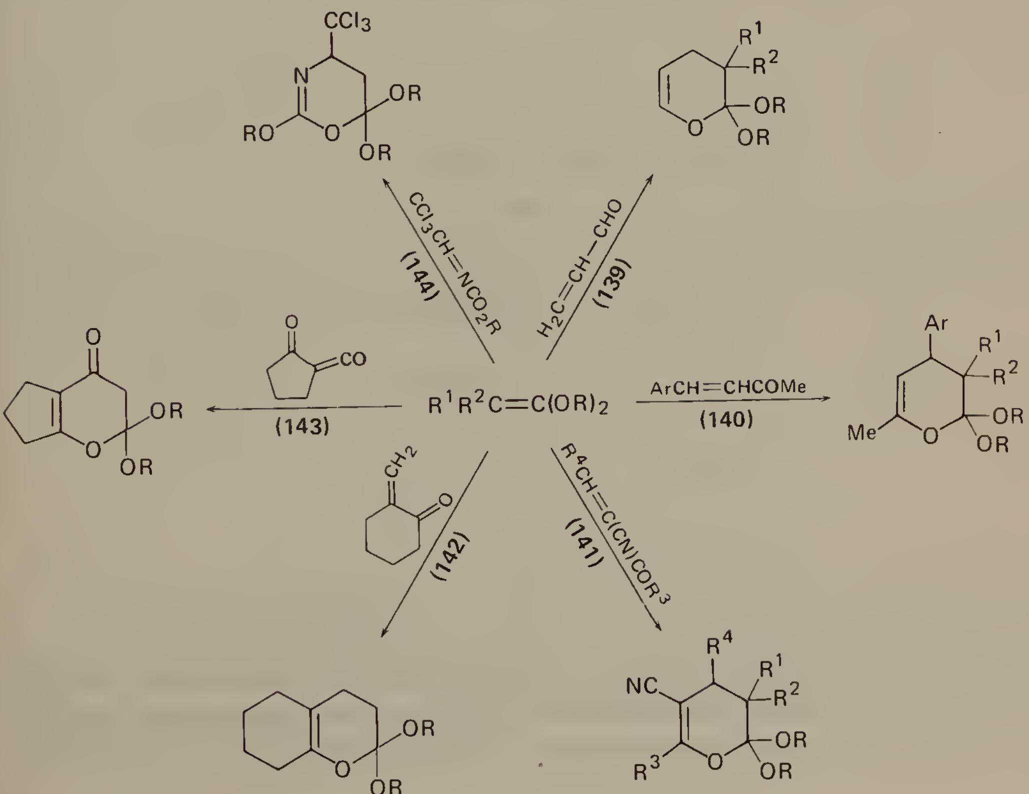
D. Diels–Alder Reactions

[4 + 2] Cycloadditions envisaged with the use of ketene acetals require inverse electron demand in order to be successful. Therefore six-membered carbocyclic products are rarely encountered and seem to have been observed only in reactions with particular substrates such as isoquinolinium salts and 4a-azoniaanthracenes[178,179] (**137**) (equation 93). The adducts can be converted to a number of useful substances, including substituted β-naphthols (**138**) and phenanthrols[180].



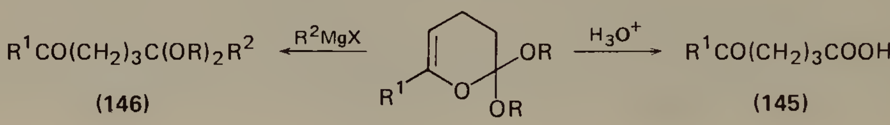
(93)

On the other hand, reactions with α,β-unsaturated aldehydes, ketones, and occasionally esters, are frequently recorded. At first the products were assumed to be cyclobutanone acetals, a view which was later corrected[102], but the process is still sometimes reviewed in the original light[2]. In fact, acrolein[84,102] (**139**), benzylidene acetone[102] (**140**), α-cyano-α,β-unsaturated ketones[181] (**141**), α-methylenecyclohexanones[182] (**142**), α-ketoketenes[183] (**143**), anhydrochloral-urethanes (**144**) and -acetamides[184], etc., all yield the acetals of 3,4-dihydro-α-pyrones (equation 94).

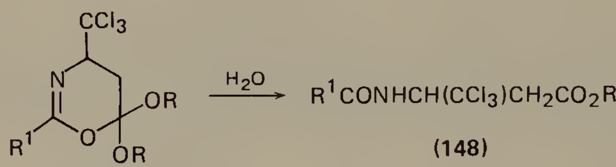


(94)

In most cases the resulting dihydropyrans have served as intermediates for the subsequent synthesis of numerous required products. For example, acid hydrolysis gives the corresponding δ-oxo acids[84] (145) and treatment with Grignard reagents affords the substituted δ-carbonylacetals [185] (146) (equation 95) while the adducts (147) obtained from *N*-(2,2,2-trichloroethylidene)alkoxycarbonyl-amines or -acetamides can be converted to substituted β-amino acid derivatives[184] (148) (equation 96).

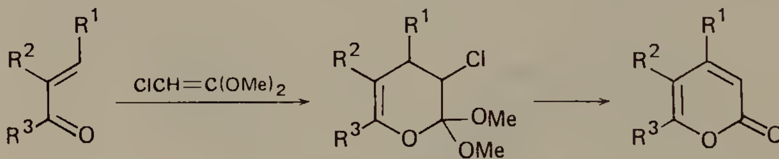


(146) (145) (95)

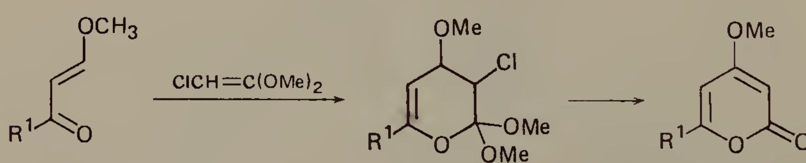


(147) (148) (96)

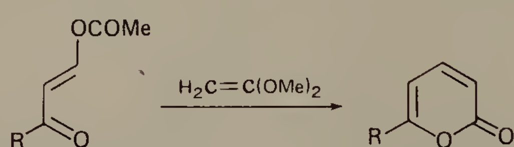
Cycloadditions between chloroketene acetals and enals or enones have also been carried out. Nonstereoselective products (**149** and **151**) were obtained and transformed directly into α-pyrones (**150** and **152**) by the action of strong bases in dipolar aprotic solvents[186,187] (equations 97 and 98). Enones substituted in the β-position by good leaving groups gave α-pyrones (**153**) simply by heating in the presence of ketene dimethyl acetal[186] (equation 99). Somewhat similar syntheses of α-pyrones have been carried out using tetraalkoxyethylenes[181].



(149) (150) (97)

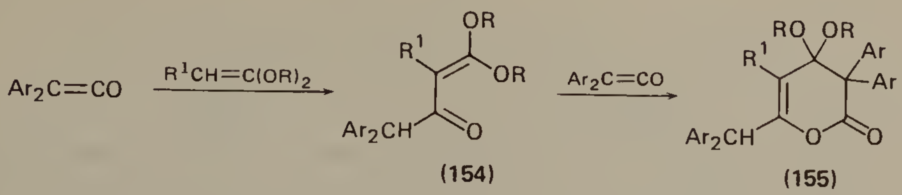


(151) (152) (98)

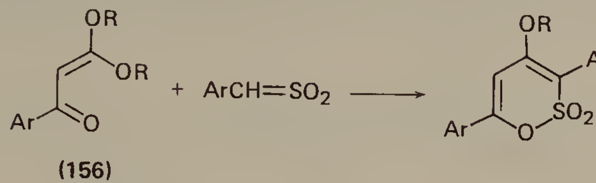


(153) (99)

Acylketene acetals (**154**) have been used only on rare occasions as heterodienes in the Diels–Alder reaction. In one such case, a monosubstituted ketene acetal was shown to react with excess diphenylketene through the acylketene acetal **154** and to yield a pyronone 4-acetal[141] (**155**) (equation 100). An analogous reaction has been described between a benzoylketene acetal (**156**) and a sulphene[151] (equation 101).

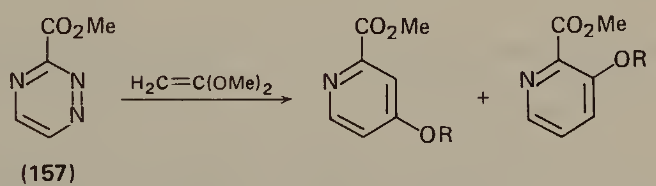


(100)



(101)

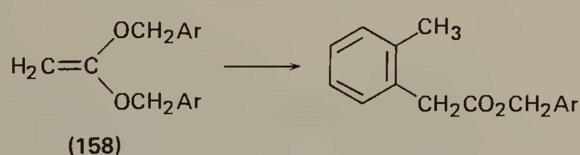
Finally cycloadditions accompanied by retrograde Diels–Alder processes appear to be the rule in certain heterocyclic systems. This has been studied particularly with triazines[188] (**157**) and tetrazines[188]. When the substrates were unsymmetrically substituted, the reaction was shown not to be regiospecific and to give mixtures of products (equation 102).



(102)

VI. CLAISEN REARRANGEMENTS

The thermal isomerization of allyl phenyl ethers, the Claisen rearrangement, has been minutely investigated over the past sixty-five years. A closely related process involving vinyl benzyl ethers was observed in this field when an attempt was made to prepare ketene dibenzyl acetal[64] (**158**) (equation 103).



(103)

Another modification of the original reaction using allyl vinyl ethers, although long known, has been found only recently to be of considerable practical usefulness[4]. In particular allyl alcohols (**159**) can be transesterified with acid catalysis to the corresponding mixed orthoesters (**160**). These readily eliminate a molecule of alcohol giving ketene acetals (**161**), which then isomerize to the γ,δ-unsaturated esters[189,190] (**162**) (equation 104).

$$H_2C{=}CR^1CHR^2OH + CH_3C(OEt)_3 \xrightarrow{H^+} H_2C{=}CR^1CHR^2OC(OEt)_2CH_3 \longrightarrow \quad (104)$$

(159) (160)

$$H_2C{=}CR^1CHR^2OC(OEt){=}CH_2 \longrightarrow CHR^2{=}CR^1CH_2CH_2CO_2Et$$

(161) (162)

Other variations of the basic principle use propargyl alcohols (**163**). In the presence of an acetamide acetal, the latter provide γ-oxo esters (**165**) through the ketene α-aminoallyl ethyl acetal[191] (**164**). When transesterification is carried out with orthoacetates, the intermediate (**166**) leads to a β-allenic ester[192] (**167**) (equation 105).

$$R^3C{\equiv}C{-}CR^1R^2OH \quad (163)$$

$CH_3C(OEt)_2NMe_2$ ↙ ↘ $CH_3C(OEt)_3$

$$R^3CH{=}C(NMe_2){-}CR^1R^2OC(OEt){=}CH_2 \quad (164) \qquad R^3{-}C{\equiv}C{-}CR^1R^2O{-}C(OEt){=}CH_2 \quad (166) \qquad (105)$$

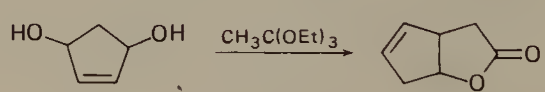
$$\downarrow \qquad\qquad \downarrow$$

$$R^1R^2CHCOCHR^3CH_2CO_2Et \quad (165) \qquad R^1R^2C{=}C{=}CR^3CH_2CO_2Et \quad (167)$$

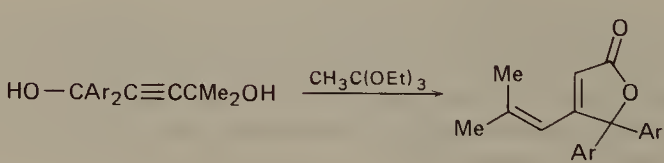
Ingenious structural alterations of the substrates have been proposed and have provided advantageous procedures. Thus β-allenic alcohols (**168**) give nonconjugated dienic esters[193] (**169**) (equation 106); diallylic (**170**) and dipropargylic diols (**172**) can be converted to γ,δ-[194] (**171**) (equation 107) and α,β:γ,δ-unsaturated butyrolactones[195] (**173**) (equation 108) while somewhat analogous results with good stereochemical control are obtained by the use of lactone acetals [196] (**174**) (equation 109).

$$R^4R^5C{=}C{=}CR^3CR^1R^2OH \xrightarrow{CH_3C(OEt)_3} R^1R^2C{=}CR^3{-}C({=}CR^4R^5)CH_2CO_2Et \quad (106)$$

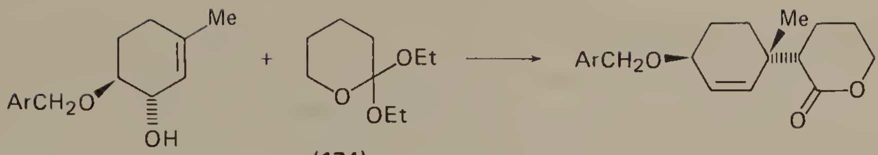
(168) (169)



(170) (171) (107)



(172) (173) (108)



(174) (109)

Finally, allyl esters (**175**) have been converted through the enolate ions to the ketene allyl trialkylsilyl acetals (**176**). The latter rearrange at much lower temperatures than analogous compounds and give directly the γ,δ-unsaturated acids[38,197,198] (177) (equation 110).

$$R^1R^2CHCO_2CH_2CH{=}CHR^3 \longrightarrow R^1R^2C{=}C(OSiR_3){-}OCH_2CH{=}CHR^3 \longrightarrow H_2C{=}CHCHR^3CR^1R^2COOH \qquad (110)$$

(175) (176) (177)

VII. BISKETENE AND VINYLKETENE ACETALS

Recently highly conjugated acetals of bisketene and vinylketene have been the object of considerable attention with respect both to preparative methods and to practical applications. When available these compounds show great potential as synthons, allying as they do the high reactivity of ketene acetals and the versatility of dienes.

Several derivatives of bisketene are known and have been prepared by the ring-opening of cyclobutenes[42,136] for compounds 88 and 179, the silylation of the appropriate di- or tetra-carboxylic esters with bis(trialkylsilyl)mercury in the case of the mixed acetals[199] 180 and 181 or the isomerization of tetraalkoxybutynes for the parent compounds[200] 178. Most of these substances are highly symmetrical and details of their reactivity are awaited.

$(RO)_2C{=}CR^1{-}C(CN){=}(OR)_2$ (88)

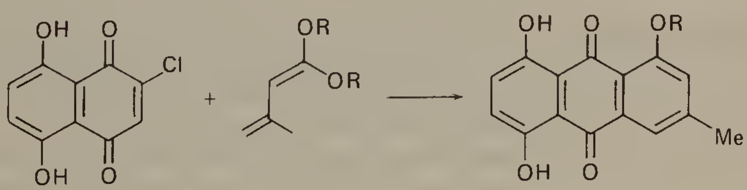
$(RO)_2C{=}CR^1{-}CR^1{=}C(OR)_2$ (178) $R^1 = H$; (179) $R^1 = CO_2R$

$R^1_3SiO(RO)C{=}CR^2{-}CR^2{=}C(OR)OSiR^1_3$

(180) $R^2 = H$

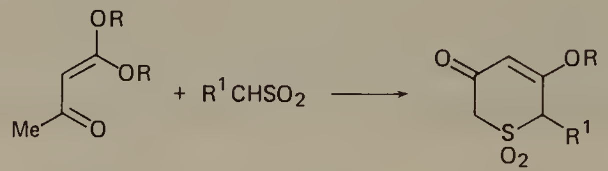
(181) $R^2 = CO_2R$

With the exception of the preparation of isopropenylketene acetals[201], the chemistry of vinylketene derivatives is a recent development in this field[17,108,115,130,139,144,168,202,203]. The practical application of these butadienes was not forthcoming until 1974 when their utilization afforded simple syntheses of naturally occurring quinones such as helminthosporin[108] (182) (equation 111).

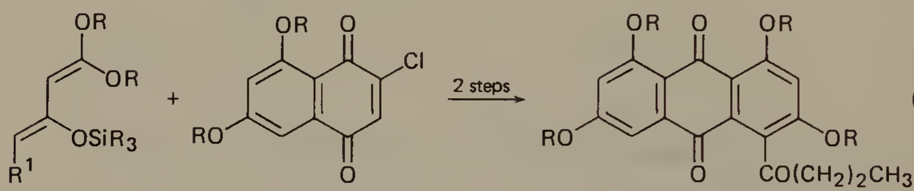


(182) (111)

Acylketene acetals (183) on the other hand, were known in at least one case to give cycloadducts with dienophiles such as sulphenes[152] (equation 112). The process was applicable to quinones but the yields obtained were not very satisfactory[17]. Conversion of the reagents to vinylketene acetals (184) by enolsilylation provided a number of useful new dienes which have allowed effective syntheses of natural products such as rhodocomatulin tetramethyl ether[17] (185) (equation 113) as well as other condensations[115,144,203].

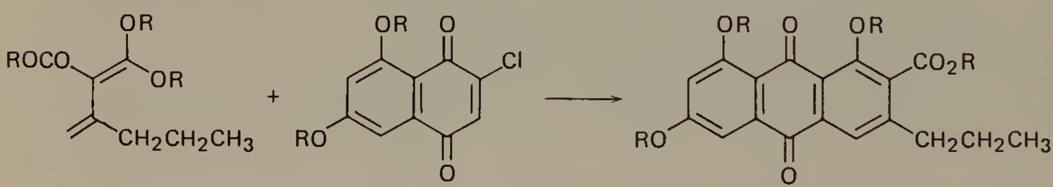


(183) (112)

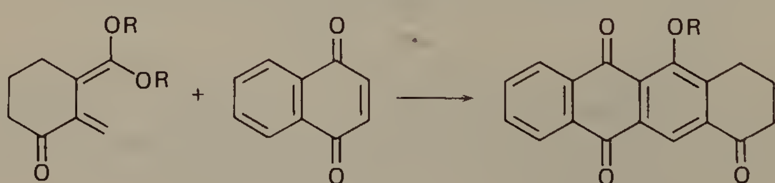


(184) (185) (113)

The formation of vinylketene acetals through electrocyclic ring-opening of intermediate cyclobutenes is a well-documented procedure. Highly substituted dienes produced in this way have shown surprising reactivity and have been used for simple and regiospecific preparations of a number of quinones such as ptilometric acid[115,139,144] (186) (equation 114) and anthracyclinones[168] (187) (equation 115) which can only be obtained with difficulty by other means.



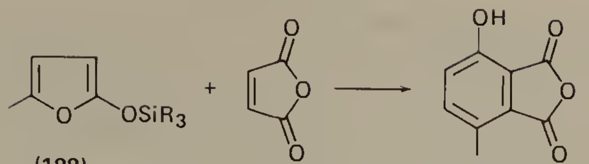
(186) (114)



(187) (115)

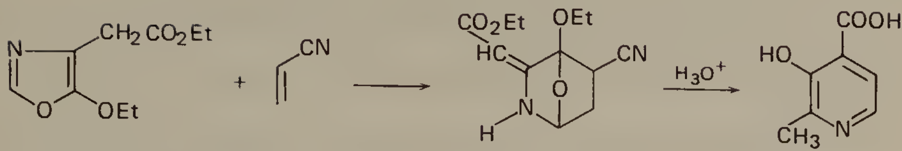
The cyclic analogues of vinylketene acetals, furan[204] (188) and oxazole ethers[205] (189) are known and show many of the characteristics of the open-chain compounds (equations 116 and 117). They are, however, considerably less reactive giving cycloaddition products only with good dienophiles.

Strong bases convert α,β-unsaturated esters to vinylenolates and the latter give Diels–Alder adducts with benzynes[206]. The corresponding trialkylsilyl ethers



(188)

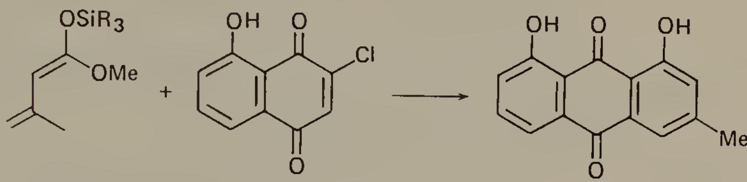
(116)



(189)

(117)

(190) have been mentioned[31] briefly but reactions applying those compounds do not seem to have been used frequently except in Claisen rearrangements[4]. They do however react smoothly with dienophiles and provide yet another direct entry into the group of polycyclic naturally occurring quinones[207] such as chrysophanol **(191)** (equation 118).



(118)

(190) (191)

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CHAPTER 15

Rearrangements involving allenes

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I. INTRODUCTION

A large part of the chemistry of allenes involves rearrangements of one form or another, and the literature is too voluminous to review in detail. An attempt has been made to cover the most important advances, particularly work of the 1970s and late 1960s.

Reactions have been classified according to mechanism, but often the classification is debatable and the decision reflects the author's prejudice. Rearrangements are included in which allenes are believed to participate as intermediates as well as those in which they serve as reactants or are formed as isolable products.

II. PROPARGYLIC AND RETROPROPARGYLIC REARRANGEMENTS

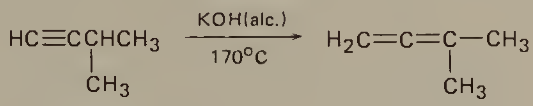
A. Prototropic

1. Hydrocarbons

Favorskii was the first to propose that allenes are intermediates in the base-catalysed isomerization of alkynes (equation 1) and, in support of this hypothesis, he cited the fact that 3-methyl-1,2-butadiene (2), which cannot rearrange to a

$$HC{\equiv}CCH_2R \xrightarrow{\text{base}} [H_2C{=}C{=}CHR] \longrightarrow CH_3C{\equiv}CR \qquad (1)$$

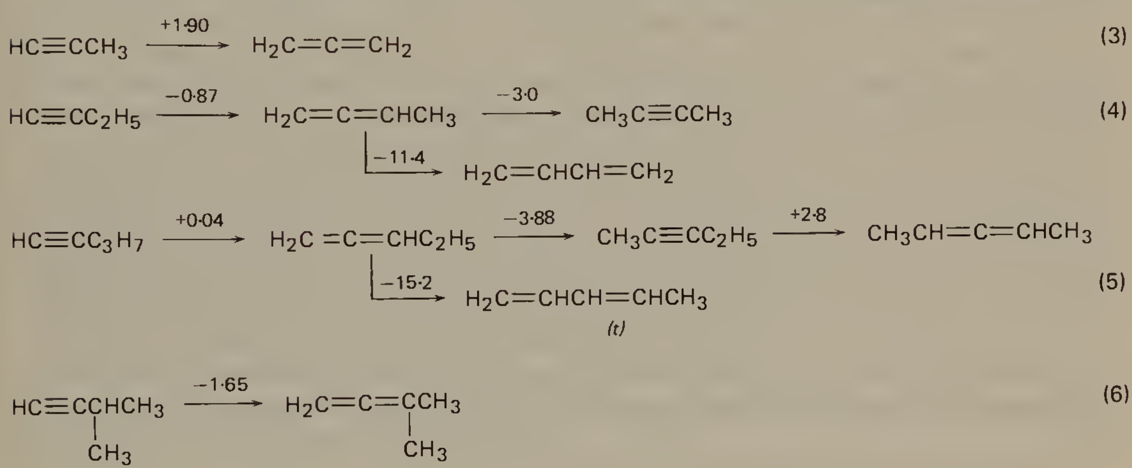
2-alkyne, is obtained from the isomerization of 3-methyl-l-butyne (1), equation (2)[1]. Later workers have substantiated Favorskii's proposal and have added much information about the details of the mechanism of isomerization. Much of the work has been reviewed, and only a brief summary of the results is given here, with particular emphasis on the role of allenes. Additional details are contained in the reviews[2-7]:



(1) (2)

(2)

A knowledge of relative thermodynamic stabilities of alkynes and their diene isomers is helpful toward understanding the results of isomerization studies. The numbers above the arrows in Scheme 1 are the standard free energy changes in kcal/mol at 298 K for the reactions in the direction of the arrow, as calculated from tables of free energies of formation of the compounds[8]. Among the acyclic isomers with formula C_nH_{2n-2}, conjugated dienes are far and away the most stable, as can be seen for 1,3-butadiene and 1,3-pentadiene in Scheme 1. For reactions in which



SCHEME 1.

equilibrium is established among the C_4H_6 isomers at 25° C, for example, 1,3-butadiene will constitute more than 99.9% of the product mixture. As we shall see, however, formation of conjugated dienes is slow, at least for base-catalysed rearrangement of simple alkynes and allenes, and quasi-equilibrium among some or all of the alkynes and allenes can generally be established without formation of detectable amounts of the conjugated isomers. It is these cases that will interest us most.

In general, the order of stabilities for unbranched chains is 2-yne > 2,3-diene > 1,2-diene $\gtrsim$ 1-yne. Increased stability results from alkyl substitution of sp or sp^2 carbons. This may be used to rationalize the differences in relative stabilities of alkynes and allenes in equations (3) and (6). In (3), the unsubstituted allene is significantly less stable than the monoalkyl alkyne, whereas in (6) the disubstituted allene is significantly more stable than the monosubstituted alkyne. Apparently the stabilization is greater for substitution on sp carbon as evidenced by the greater stability of 2-pentyne over 2,3-pentadiene (equation 5).

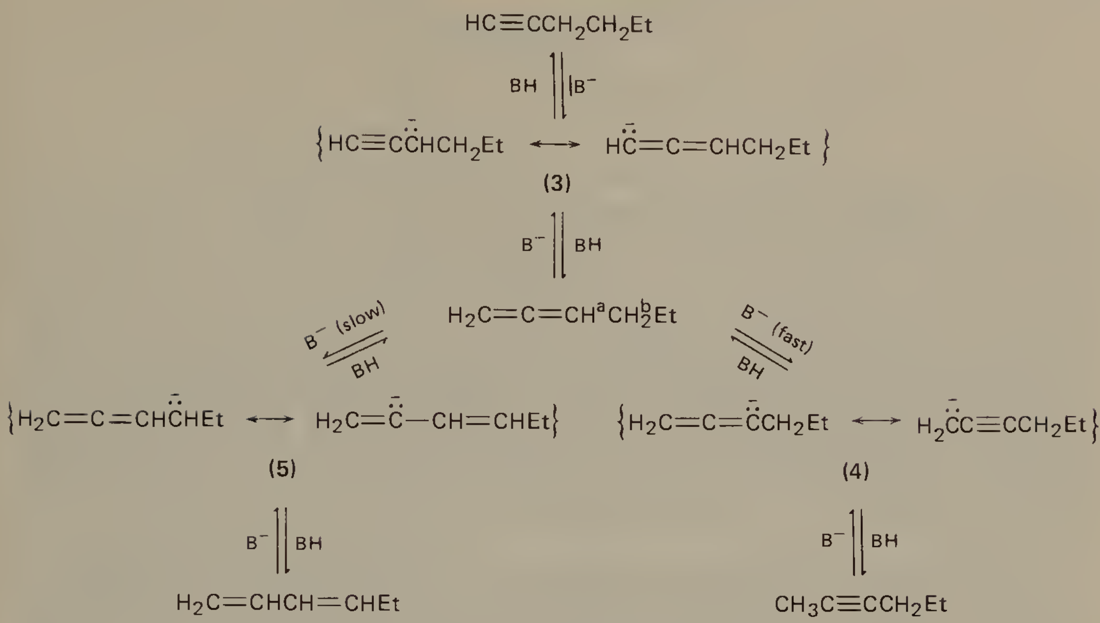
The rate and extent of isomerization of simple 1-alkynes are strongly dependent on the nature of the base, the solvent and the reaction temperature. The bases commonly used in these reactions have been categorized as: (a) ethanolic KOH (125–175° C), (b) alkali-metal alkoxides in alcohols (below 200° C), (c) metal amides in ammonia or an amine at moderate temperatures, and (d) bases in categories (b) and (c), used at higher temperatures[9]. To these should be added a fifth category: (e) bases in dipolar aprotic solvents, e.g. potassium *t*-butoxide in DMSO or HMPT, and $NaNH_2$ or CH_3SOCH_2Na in DMSO. These are arranged roughly in the order of increasing activity, with categories (d) and (e) promoting the most extensive and deep-seated rearrangements.

Product mixtures whose composition is largely kinetically controlled are commonly obtained through the use of less active catalysts, while thermodynamic control may be approached with catalysts (d) and (e), although even here selective isomerizations have been achieved under mild conditions for short periods[6]. For example, it is possible to effect isomerization of 1-butyne to 2-butyne in nearly quantitative yield without detectable 1,3-butadiene formation by means of potassium *t*-butoxide in DMSO at 10° C[10]. As we shall see below, selectivity in these reactions is a consequence of great differences in kinetic acidity of different types of protons in the substrate.

Careful studies of the isomerization of 1-, 2- and 3-hexyne and 1,2- and 2,3-hexadiene by Carr and coworkers[9,11] have provided strong support for the stepwise, acetylene–allene–acetylene mechanism involving carbanionic intermediates first proposed by Jacobs and coworkers[12]. For convenience, these compounds will be referred to as 1-, 2-, 3-, 1,2- and 2,3- respectively. For reactions catalysed by potassium *t*-butoxide in *t*-butyl alcohol at 85° C, the relative rates of isomerization were found to be in the order: 1,2- > 1- ≫ 2,3- ≫ 3- > 2-, i.e. nearly the inverse of the order of stabilities. There is a great difference in reactivity between the first and last member of this sequence. For example, under the conditions stated, 71% isomerization of 1,2- occurs after 15 minutes, whereas only 1% isomerization of 2- occurs after 7 hours and 7.7% after 215 hours[9]. It is the slowness of isomerization of 2-alkynes that caused some earlier workers to conclude incorrectly that migration of the triple bond does not proceed beyond the 2-position.

The rate of isomerization of 1,2- is greater than that of 1- or 2-, and the principal product of isomerization of 1,2- is 2-. Then, in agreement with the stepwise mechanism, which requires that the formation of 2- from 1- occur by the sequence 1- ⇌ 1,2- ⇌ 2-, the isomerization of 1- produces 1,2- faster than 2- initially, but the concentration of 1,2- rises only to a low level and remains nearly constant while the concentration of 2- rises steadily. These steps are summarized in Scheme 2, where the carbanionic intermediates are also included along with the path by which the conjugated 1,3-diene would be expected to arise.

The anion 3, formed by abstraction of a propargylic proton from 1- , can be protonated at the terminal position giving 1,2- . It should be mentioned that the acetylide ion, $C_4H_9C{\equiv}C^{:-}$, formed from 1- by abstraction of the more acidic acetylenic proton, cannot undergo rearrangement. With potassium *t*-butoxide, only a small fraction of 1- will be converted to the acetylide, and the isomerization shown in Scheme 2 is able to occur. With sodium amide in liquid NH_3, however, conversion to the sparingly soluble acetylide salt is essentially complete when equivalent proportions of the base are used, and consequently 1-hexyne fails to

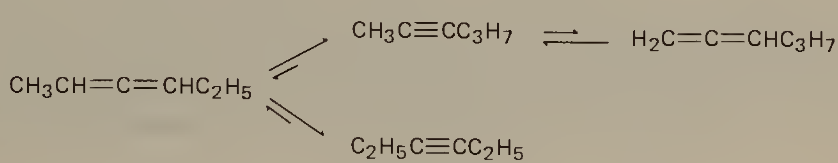


SCHEME 2.

isomerize under these conditions[11]. In this connection it is interesting to note that the isomerization of 1,2- with $NaNH_2-NH_3$ is extremely rapid, giving 2- (98.8%) and 1- (0.72%) after a reaction period of only 12 seconds[11].

Two paths are conceivable for the further rearrangement of 1,2-, depending on whether the allenic proton (H^a) or the allylic proton (H^b) is abstracted. Removal of the latter and subsequent reprotonation of anion **5** leads to 1,3-; the absence of detectable amounts of conjugated dienes signifies that reaction by this path must be very slow. The rapid formation of 2- on the other hand means that the sequence involving abstraction of H^a and reprotonation is fast[9].

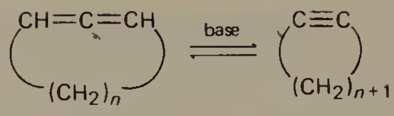
Isomerization of 2,3- with potassium *t*-butoxide in *t*-butyl alcohol yields 2- and 3-, with 2- predominating somewhat; the interconversion of 2- and 3- takes place by way of 2,3- as indicated in Scheme 3[9].



SCHEME 3.

In view of these findings, the results of studies of the isomerization of 1-, 2- and 3-hexyne in the presence of CH_3SOCH_2Na in DMSO are perplexing[13]. The hexyne isomers are interconverted by this catalyst at 25° C giving a quasi-equilibrium mixture containing 82% 2-, 11% 3- and 7% 1-hexyne, but surprisingly allenes are not present. The equilibrium ratio of allenes and acetylenes has been shown to be solvent dependent[14], and it is possible that the equilibrium proportions of 1,2- and 2,3- are much smaller in DMSO than in *t*-butyl alcohol.

The equilibrium ratio of cyclic allene to cyclic acetylene (equation 7) is a

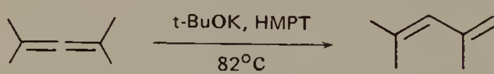


(6) (7) (7)

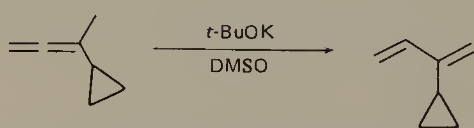
function of ring size[14]. With potassium *t*-butoxide in *t*-butyl alcohol at 79.4° C, the ratio 6:7 is 16.4 for the nine-memebered ring system (n = 6) but it drops to 0.31 for the eleven-membered ring (n = 8). Four carbons are required to be colinear in the acetylene but only three in the allene, and in the nine-membered ring the allene should suffer less angle-strain than the acetylene. The eleven-membered ring is large enough to accommodate the acetylene function without significant strain, and the allene–acetylene ratio corresponds roughly to that of open-chain systems.

Sodium amide in ethylenediamine is a potent catalyst for isomerization of allenes and acetylenes[15,16]. A quasi-equilibrium mixture with the same composition is obtained by starting with any of the hexynes or 1,2- or 2,3-hexadiene. This mixture contains a small amount of 2,3-hexadiene but, surprisingly, no 1,2-hexadiene.

Interconversion of allenes and acetylenes, as well as isomerization of allenes to conjugated and non-conjugated dienes, has been accomplished with potassium *t*-butoxide in aprotic solvents. One of the most intriguing examples is the conversion of 2-butyne by this base in DMSO at 27° C to a mixture containing 49% 1,2-butadiene[17]. Examples of rearrangements to conjugated dienes are given in equations (8)[18] and (9)[19]. Cyclic allenes with 9- to 13-membered rings rearrange to



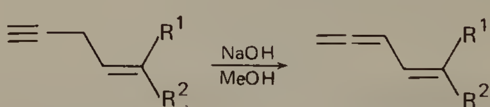
(8)



(9)

give mixtures of conjugated and non-conjugated cyclic dienes whose composition depends on ring size and reaction time[20].

1-Alken-4-ynes and 1,4-alkadiynes undergo acetylene–allene rearrangement under much milder conditions than those required for simple alkynes by virtue of the additional acid-strengthening group. 1-Penten-4-yne (8a) for example, rearranges to 1,2,4-pentatriene (9a) in the presence of methanolic NaOH at room temperature[21–23]. Several interesting features of this rearrangement have emerged.

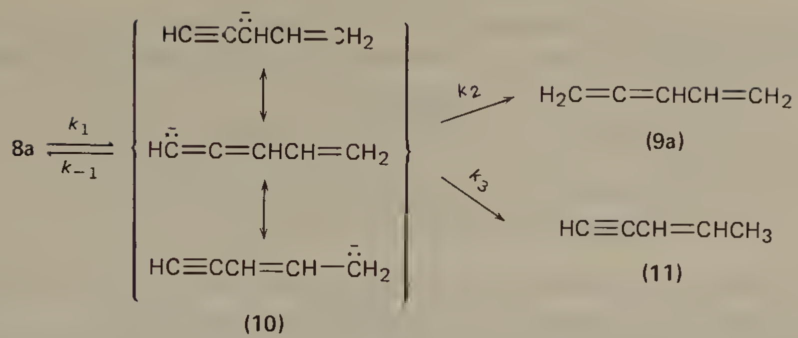


(8) (9)

(a) $R^1 = R^2 = H$ (c) $R^1 = H$, $R^2 = Me$

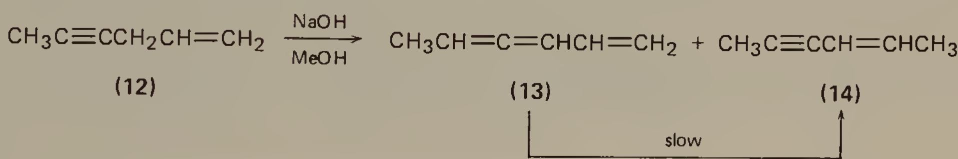
(b) $R^1 = Me$, $R^2 = H$

When the rearrangement of 8a is carried out with NaOD in CH_3OD and interrupted before completion, the recovered enyne does not contain deuterium at position 3.

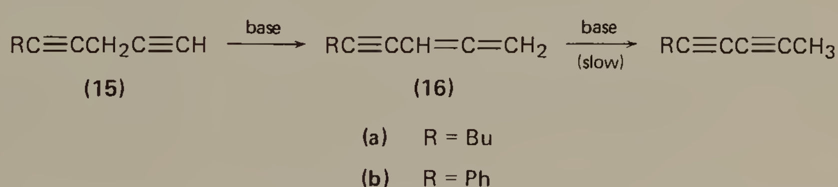


Thus the carbanion **10** is formed in the slow step and undergoes rapid protonation selectively at the terminal acetylenic position, i.e. $k_2 \gg k_{-1}$. In view of the charge delocalization to the terminal olefinic carbon in the carbanion **10**, protonation at this position might be anticipated, but 3-buten-1-yne (**11**) was not formed and thus $k_2 \gg k_3$. Furthermore, stereochemical integrity of the alkene linkage is maintained during the reaction as evidenced by the absence of *cis–trans* isomerization during the rearrangement of **8b** and **8c**[23].

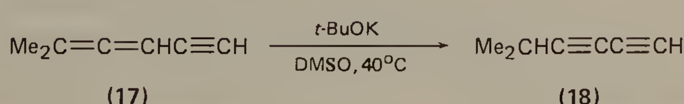
Rearrangement involving migration of the alkene linkage has been observed with 1-hexen-4-yne (**12**) in the presence of methanolic NaOH at 65–112° C[24]. Both **13** and **14** are formed simultaneously from **12**, but **13** also slowly isomerizes to **14**.



The first stage of the rearrangement of 1,4-diynes, which yields 1,2-dien-4-ynes, is significantly faster than the second stage, which furnishes conjugated diynes, and it is usually possible to isolate the dienyne in reasonable yield. Thus, 1,2-nonadien-4-yne (**16a**) can be obtained from the rearrangement of 1,4-nonadiyne (**15a**) with ethanolic NaOH at 25° C[25]. The first stage of the rearrangement of 1-phenyl-1,4-pentadiyne (**15b**) in the presence of sodium ethoxide in ethanol at 26° C is three times faster than the second, making it possible to obtain **16b** by quenching the reaction when the concentration of **16b** reaches a maximum[26].



5-Methyl-3,4-hexadien-1-yne (**17**), in which the allene grouping is stabilized by two methyl substituents, does not rearrange in the presence of aqueous or alcoholic KOH, but does isomerize smoothly to the conjugated diyne **18** in the presence of potassium *t*-butoxide in DMSO[27].



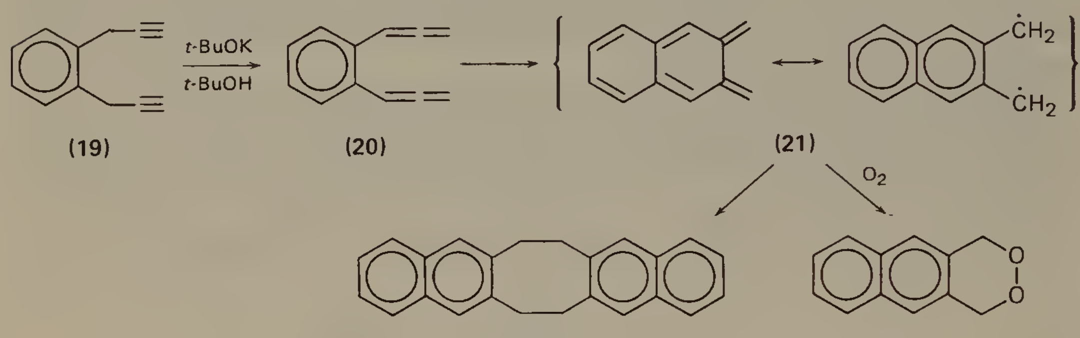
Di- and tri-arylpropynes rearrange to the corresponding allenes under very mild conditions[28-30]. Chromatography over basic alumina causes the rearrangements

$$PhCH_2C{\equiv}CPh \xrightarrow{Al_2O_3(basic)} PhCH{=}C{=}CHPh \tag{10}$$

$$Ph_2CHC{\equiv}CPh \xrightarrow{Al_2O_3(basic)} Ph_2C{=}C{=}CHPh \tag{11}$$

shown in equations (10) and (11). Optically active allenes have been obtained by using alumina which had been pretreated with brucine or quinine.

o-Dipropadienylbenzene (**20**), obtained from *o*-di-2-propynylbenzene (**19**) by base-catalysed rearrangement, is a very reactive hydrocarbon[31]. It dimerizes, apparently by way of the quinodimethane **21**, giving **22** and other more complex dimers, and reacts with oxygen giving the cyclic peroxide **23**.



(19) (20) (21) (22) (23)

The rates of isomerization of $Ph_2CHC{\equiv}CPh$ and $Ph_2CDC{\equiv}CPh$ have been studied in the presence of tetramethylammonium hydroxide in aqueous DMSO[32]. A linear correlation of rate with the acidity function H_- of the medium was found, along with a kinetic isotope effect of approximately 7. It was concluded that hydrogen abstraction is the slow step with an advanced transition state strongly resembling a fully developed carbanion[32].

Up to this point, we have treated acetylene–allene prototropic rearrangements as though they were strictly intermolecular, viz. discrete carbanions are formed and are protonated by an external source such as solvent. This treatment is justified for reactions carried out in proton-rich solvents, but under suitable circumstances the reactions show a high degree of intramolecularity. For example, when the rearrangement of 1,3,3-triphenylpropyne-3d (**24**) is carried out with 1,4-diazabicyclo-[2.2.2]octane in 10% MeOH–DMSO, up to 88% of the deuterium is retained in the product[33]. In this intramolecular process it is proposed that the proton (deuteron)

(24)

is not completely removed, but remains hydrogen bonded to the substrate as the rearrangement progresses – a process which has been called the 'conducted tour' mechanism[33]. When the rearrangement is carried out with potassium methoxide in methanol or potassium *t*-butoxide in *t*-butyl alcohol, the degree of intramolecularity drops to ca 18%.

The rearrangement of 3-phenylpropyne to 1-phenylpropadiene in the presence of CD_3SOCD_2Na in dimethyl sulphoxide-d_6 occurs with less than 10% exchange with solvent[34]. The possibility is considered that the anion in this case is protonated by another molecule of 3-phenylpropyne and not by the solvent.

The acid-catalysed prototropic rearrangement of alkynes and allenes has been realized, e.g. by the use of HBF_4, HPF_6 or H_2SO_4 in sulpholane[35]. Interconversions of 1-, 2- and 3-hexynes and 1,2- and 2,3-hexadienes were studied. Vinyl cation intermediates are involved, as illustrated in equation (12) for the inter-

$$HC{\equiv}CCH_2Pr + H^+ \rightleftharpoons H_2C{=}\overset{+}{C}CH_2Pr \rightleftharpoons H_2C{=}C{=}CHPr + H^+ \rightleftharpoons \text{etc.} \quad (12)$$

conversion of 1-hexyne and 1,2-hexadiene, and the approximate order of reactivities is 1,2-diene > 2,3-diene > 1-yne > 3-yne > 2-yne.

Allenic intermediates have been shown to play important roles in the deep-seated rearrangements of diynes to aromatic hydrocarbons that occur in the presence of strong bases[36-38]. A summary is contained in a recent review[39].

2. *Functionally substituted derivatives*

Base-catalysed isomerization of butynoic and butadienoic acids, as the carboxylate salts, occurs under mild conditions. The order of stabilities is **27** > **26** > **25**, but the conversion of **26** to **27** is relatively slow, making it possible to convert **25** to **26** selectively in high yield[40]. Isomerization of **25** in the presence of K_2CO_3 at 40° C for 3 h, followed by acidification, provides 2,3-butadienoic acid in 92% yield, corresponding to an equilibrium ratio **26**:**25** = 11.5 at 40° C. When the rearrangement is carried out at 90° C, isomerization of **26** to **27** also occurs and 2-butynoic acid can be isolated in 60% yield. Separate determinations established the equilibrium ratio of **27**:**26** to be 2.2 at 90° C.

$$\underset{(25)}{HC{\equiv}CCH_2CO_2^-} \rightleftharpoons \underset{(26)}{H_2C{=}C{=}CHCO_2^-} \rightleftharpoons \underset{(27)}{CH_3C{\equiv}CCO_2^-}$$

Interesting results have been obtained from a study of the rearrangement of pentynoate and pentadienoate isomers[41]. Interconversion of these isomers occurs in the presence of 6.25 M aqueous NaOH, and the equilibrium ratios are 1.28% **28**, 16.5% **29** and 82.2% **30**. It is interesting that the equilibrium ratio of **30** and **28**,

$$\underset{(28)}{CH_3CH_2C{\equiv}CCO_2^-} \rightleftharpoons \underset{(29)}{CH_3CH{=}C{=}CHCO_2^-} \rightleftharpoons \underset{(30)}{CH_3C{\equiv}CCH_2CO_2^-}$$

30:**28** = 64, corresponds fairly closely to the equilibrium ratio found for simple 2-alkynes and 1-alkynes, i.e. 2-yne: 1-yne ≅ 73. It has been suggested on this basis that the carboxylate group and hydrogen have comparable effects on acetylenic equilibria[41]. The greater stability of **30** over **29** can be rationalized in terms of the customary greater stability of dialkyl acetylenes over monosubstituted allenes. In the case of the methyl esters **31** and **32**, the equilibrium ratio is approximately 1,

$$\underset{(31)}{CH_3CH{=}C{=}CHCO_2Me} \rightleftharpoons \underset{(32)}{CH_3C{\equiv}CCH_2CO_2Me}$$

signifying that conjugative interaction of the carbomethoxy groups with the allene linkage is greater than that of the carboxylate group[41].

The conversion of **28** to **29** occurs faster in D_2O than in H_2O, with $k(D_2O)/k(H_2O) = 1.4$; similarly for the conversion of **29** to **30** the ratio is 1.6. These values point to carbanion intermediates in both processes, as summarized in Scheme 4.

$$28 \rightleftharpoons \left[\begin{array}{c} CH_3\bar{\ddot{C}}HC{\equiv}C{-}C\bar{O}_2 \\ \updownarrow \\ CH_3CH{=}C{=}\bar{\ddot{C}}{-}C\bar{O}_2 \end{array} \right] \rightleftharpoons 29 \rightleftharpoons \left[\begin{array}{c} CH_3\bar{\ddot{C}}{=}C{=}CHC\bar{O}_2 \\ \updownarrow \\ \dot{C}H_3C{\equiv}C\bar{\ddot{C}}HC\bar{O}_2 \end{array} \right] \rightleftharpoons 30$$

(33) (34)

SCHEME 4.

From studies carried out in D_2O it was shown that the anion **33** undergoes protonation fastest at position 2 giving **29** preferentially, and carbanion **34** is also protonated preferentially at position 2 giving **30**[41]. Thus in each case, protonation of the carbanion gives the more stable isomer preferentially.

As a result of the activation of the α-protons by the carboxylate group, allenic acids isomerize to the conjugated diene isomers under much milder conditions than are required for simple hydrocarbons. For example, potassium carbonate is sufficiently basic to effect the rearrangement of **35** to the conjugated isomer **36**[42].

$$H_2C{=}C{=}CHCH_2CO_2^- \xrightarrow[60°C]{K_2CO_3} H_2C{=}CHCH{=}CHCO_2^-$$

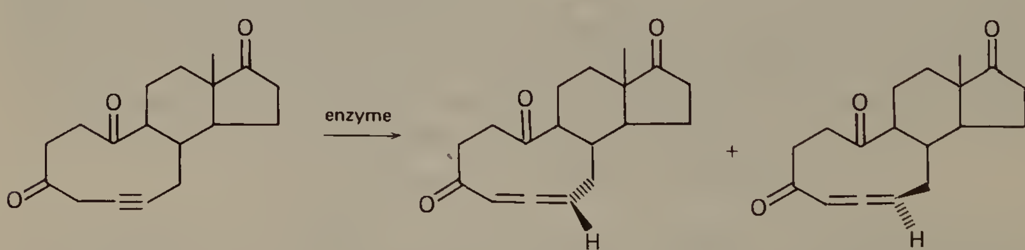
(35) (36)

2,4-Heptadiynoate (**37**) isomerizes to 3,5-heptadiynoate (**38**) at 65° C in the presence of 1N sodium hydroxide, and evidence has been presented which shows that the major path involves the intermediates shown in equation (13)[43].

$$EtC{\equiv}C{-}C{\equiv}CCO_2^- \longrightarrow MeCH{=}C{=}CHC{\equiv}CCO_2^- \longrightarrow MeCH{=}C{=}C{=}C{=}CHCO_2^- \longrightarrow MeC{\equiv}C{-}C{\equiv}CCH_2CO_2^- \quad (13)$$

(37) (38)

β,γ-Acetylenic ketones rearrange under mild conditions, e.g. in the presence of K_2CO_3, and the conjugated allenic ketones are generally stable enough to be isolated. Whether or not the migration proceeds further to the conjugated acetylenic ketone is uncertain[3]. An interesting example is the rearrangement of the secosteroid **39** to a 4:1 mixture of **40** and **41** brought about by the enzyme Δ^5-3-keto steroid isomerase[44].



(39) (40) (41)

Interesting contrasts in behaviour are found in the base-catalysed rearrangement of propargylic ethers and their sulphur and selenium analogues. In equation (14),

$$\underset{(42)}{PhMCH_2C{\equiv}CH} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{(43)}{PhMCH{=}C{=}CH_2} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \underset{(44)}{PhMC{\equiv}CCH_3} \qquad (14)$$

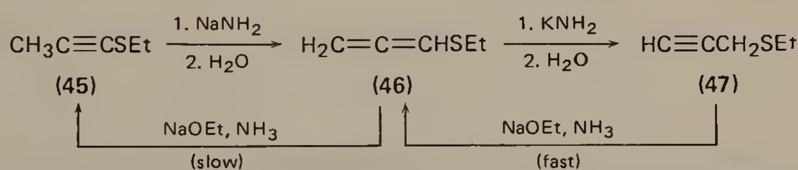
$$M = O, S, Se$$

when M = O, $k_2 = 0$; when M = S, $k_{-1} = k_{-2} = 0$; but when M = Se all four rate constants have finite values[45,46]. Powerful bases are required to effect rearrangement of the ethers, e.g. potassium *t*-butoxide in DMSO or in boiling *t*-butyl alcohol, or sodium amide in liquid NH_3. When phenyl 2-propynyl ether (**42**; M = O) is treated with potassium *t*-butoxide in DMSO at 30–40° C, a mixture containing 68% **43** (M = O) and 32% **42** (M = O) is obtained. None of the 1-propynyl ether, **44** (M = O), is formed[45,47].

Rearrangement of thio ethers occurs much more readily – a manifestation of the well-known ability of sulphur to stabilize α-carbanions. Rearrangement of **42** (M = S) to **44** (M = S) in the presence of dry KOH in THF is complete in 30 minutes. In these rearrangements, k_1 is significantly larger than k_2 and by proper choice of conditions, e.g. by the use of sodium ethoxide in ethanol at 30–40° C, it is possible to isolate the allenyl derivative **43** (M = S)[45,46].

Rearrangement of seleno ethers is somewhat slower than that of their thio analogues. The equilibrium mixture at 25° C contains 1% **42**, 14% **43** and 85% **44** (M = Se)[46].

The anion formed when ethyl 1-propynyl sulphide (**45**) is treated with sodium amide in liquid ammonia protonates fastest at the α-position, making possible the contrathermodynamic conversion of **45** to **46**[48]. By the same token, the anion from **46** protonates fastest at the α-position, and it is possible to convert **46** to **47**. Both processes are reversed by treating the products with sodium ethoxide in liquid ammonia.



The propargyl sulphonium salt **48** rearranges to the allenyl isomer **49** upon treatment with triethylamine in DMSO or simply by dissolving it in methanol without added base[49]. The allenyl sulphone **52** is more stable than either of the acetylenic isomers **50** or **51**, and it is formed in good yield when either **50** or **51** is treated with base under mild conditions[50–52].

$$\underset{(48)}{Me_2\overset{+}{S}CH_2C{\equiv}CH\ Br^-} \longrightarrow \underset{(49)}{Me_2\overset{+}{S}CH{=}C{=}CH_2\ Br^-}$$

$$\underset{(50)}{HC{\equiv}CCH_2SO_2Ph} \rightleftharpoons \underset{(52)}{H_2C{=}C{=}CHSO_2Ph} \rightleftharpoons \underset{(51)}{CH_3C{\equiv}CSO_2Ph}$$

Rearrangement of *N,N*-dimethylpropargylamine (**53**) occurs in the presence of strong base according to equation (15). A kinetic study of the rearrangement catalysed by potassium *t*-pentoxide in DMSO/dioxane at 35° C showed that $k_{-1} \cong 0$ and $k_{-2} = 5.7\,k_2$[53]. The rearrangement is complicated by the concurrent formation of dimers and trimers from **54**. These studies indicate the allenamine **54** to be the

$$\underset{(53)}{HC{\equiv}CCH_2NMe_2} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{(54)}{H_2C{=}C{=}CHNMe_2} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \underset{(55)}{CH_3C{\equiv}CNMe_2} \qquad (15)$$

principal product of isomerization of **53**, but other workers have reported that the ynamine **55** is the principal product and only a small amount of **54** is present when the reaction is carried out in the presence of potassium amide on alumina[54]. With substituted propargyl derivatives such as **56**, however, the allenamine **57** predominates.

$$\underset{(56)}{EtC{\equiv}CCH_2NR_2} \qquad \underset{(57)}{EtCH{=}C{=}CHNR_2}$$

Rearrangement of the *N*-propargylphosphoramide **58** to the allenyl derivative **59** has been observed[55].

$$\underset{(58)}{HC{\equiv}CCH_2N(Me)P(O)(OEt)_2} \xrightarrow[THF]{NaH} \underset{(59)}{H_2C{=}C{=}CHN(Me)P(O)(OEt)_2}$$

With secondary propargylic amines **60**, the rearrangement deviates from the normal course, and the conjugated imines **62** are obtained upon treatment with potassium *t*-butoxide in *t*-butyl alcohol at 100° C[56]. This is a consequence of the enhanced acidity of the proton attached to nitrogen in **61** in comparision with the allenic proton. When the rearrangement is carried out with dipropargylic secondary amines, substituted pyridines are formed, apparently by cyclization of allenic intermediates[56].

$$\underset{(60)}{HC{\equiv}CCH_2NHR} \xrightarrow[t\text{-BuOH}]{t\text{-BuOK}} \underset{(61)}{[H_2C{=}C{=}CHNHR]} \longrightarrow \underset{(62)}{H_2C{=}CH{-}CH{=}NR}$$

Rearrangement of propargyltriphenylphosphonium bromide (**63**) occurs in the presence of potassium *t*-butoxide giving the corresponding allenyl derivative **64**[57].

$$\underset{(63)}{HC{\equiv}CCH_2\overset{+}{P}Ph_3\ Br^-} \xrightarrow[t\text{-BuOH}]{t\text{-BuOK}} \underset{(64)}{H_2C{=}C{=}CH\overset{+}{P}Ph_3\ Br^-}$$

3. *Rearrangements at gas–solid interfaces*

Numerous reports of rearrangements involving allenes in the presence of solid catalysts can be found in the early literature[58]. The reactions were conducted by passing the vapour of an alkyne or allene over the catalyst, usually a silicate mineral such as ‘floridin’. Rearrangements of the types described above for base-catalysed rearrangements were observed, although rearrangement to conjugated dienes was often a more significant reaction.

Ruthenium has been reported to be an active catalyst for isomerization of acetylenes and allenes[59]. For example, allene and propyne are interconverted in the presence of a small amount of ruthenium and 2-butyne is converted to 1,2-butadiene to the extent of 2%. Slow isomerization of 1,2-butadiene to 1,3-butadiene occurs during the hydrogenation of 1,2-butadiene over nickel[60]. Very little deuterium is incorpated in the 1,3-butadiene when D_2 is used instead of H_2, indicating that the rearrangement is largely intramolecular.

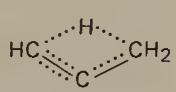
The interconversion of propyne and allene on a zinc oxide surface has been studied[61–63]. Infrared spectroscopy shows that the same adsorbed intermediate is formed from both propyne and allene, and indicates it to be an adsorbed propargyl species, $(H_2C{\cdots}C{\cdots}CH)_{ads}$. Dissociatively adsorbed intermediates are also proposed for the TiO_2-catalysed rearrangement[64].

Certain zeolites, as well as molecular sieves modified by incorporation of various metals, have been found to be active catalysts[65–68].

Treatment of the surface of silica or alumina catalysts with base increases the selectivity for alkyne–allene interconversions[69,70]. Thus, isomerization of 2-butyne to 1,2-butadiene occurs at 400° C in the presence of silica or alumina, but the selectivity is low, and substantial conversion to 1,3-butadiene occurs. With a silica–alumina catalyst containing 15% sodium hydroxide, however, 2-butyne isomerizes to a mixture containing 21% 1,2-butadiene and only 1.5% 1,3-butadiene. The increased selectivity is attributed to the deactivation of acidic sites on the catalyst by the added base[70].

4. *Thermal interconversion of propyne and allene*

The kinetics of the uncatalysed interconversion of propyne and allene, which occurs at very high temperatures, have been studied by shock-tube techniques[71–73]. The reaction is unimolecular, and although widely different values for the activation parameters were obtained by two research groups, the most reasonable values appear to be: $\log k(s^{-1}) = 13.17 - 60{,}400/2.303\,RT$ for the rearrangement of allene to propyne[71,74]. A direct [1,3] sigmatropic hydrogen



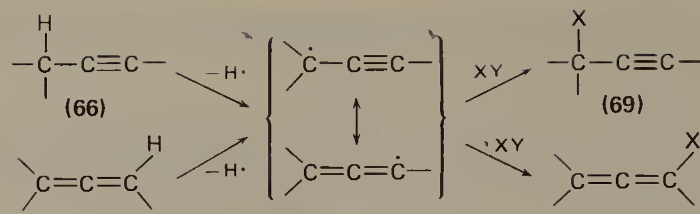
(65)

shift involving the four-centre transition state, **65**, has been proposed[71,73], but the possibility of a two-step rearrangement involving cyclopropene as an intermediate has also been pointed out[74]. Cyclopropene isomerizes at ca 500 K giving mainly propyne, along with a small amount of allene.

Isomerization of propyne and allene has also been effected by means of a pulsed, megawatt, CO_2 infrared laser using SiF_4 as a sensitizer[75,76]. The SiF_4 absorbs the laser radiation (1025 cm^{-1}) and moves to an excited vibrational state. The excess vibrational energy is transferred to the hydrocarbon, effectively producing temperatures in excess of 1000 K while the reaction vessel remains at ambient temperature.

B. Reactions Involving Free Radicals

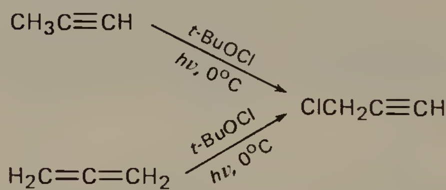
Propargylic radicals (**68**), which can be generated from acetylenic (**66**) or allenic (**67**) precursors by loss of hydrogen or other groups from the position indicated, are theoretically capable of giving propargylic (**69**) or allenic (**70**) products. As we shall see, mixtures of both types of products are obtained in some cases, while in others the propargylic isomer (**69**) is formed exclusively. The proportion of products derived from **68** is dependent on the relative stabilities of the products and on the relative spin density at the two positions[77].



(66) (67) (68) (69) (70)

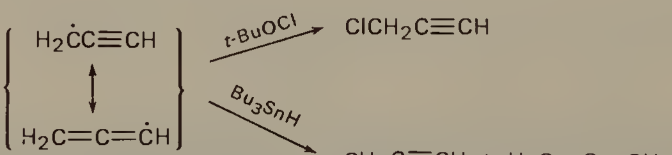
Electron spin resonance studies have shown that identical radicals are formed from isomeric acetylenic and allenic precursors[78].

Only 3-chloropropyne, with no detectable amount of 1-chloropropadiene, is obtained by the light-induced chlorination of either propyne or allene with *t*-butyl hypochlorite (equation 16)[79]. Because the isomeric chlorides are expected to have



(16)

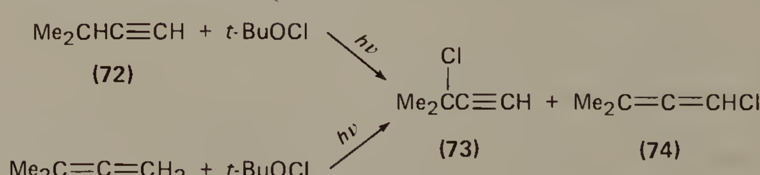
comparable stabilities, the exclusive formation of 3-chloropropyne must be in large part a consequence of the greater spin density at the propargylic position in the intermediate radical **71**. However, the nature of the atom donor that reacts with **71** must also play a role in determining the product distribution, because propyne and allene are produced in the ratio 5.9:1 by the reduction of 3-chloropropyne with tri-*n*-butyltin hydride[77]. In the product-forming step of this reaction, the radical **71** abstracts hydrogen from Bu_3SnH.



(71)

Allenic chlorides are not formed in detectable amounts by the chlorination of 2-butyne[80], 2-pentyne or 2,3-pentadiene[81]. In these cases, spin density distribution and stability factors are complementary and favour the propargylic product.

A small amount (8–9%) of the allenic product, 3-chloro-1,2-butadiene, is obtained by the chlorination of 1-butyne, while the propargylic (73) and allenic (74) products are formed in the ratio 1.7:1 from 3-methyl-1-butyne (72)[82]. These products are formed in the same ratio by the chlorination of 3-methyl-1,2-butadiene (75); in this case, allylic substitution products are also formed[82].



(72) (73) (74) (75)

Interestingly, **72** and **75** are formed in a 1.7:1 ratio by the reduction of **73** with tri-*n*-butyltin hydride[77].

Equilibration of 3-bromopropyne and bromopropadiene can be accomplished by irradiation in the presence of hydrogen bromide (equation 17)[83]. Bromine atoms, formed by photolysis of HBr, serve as the chain carrier. Values of the equilibrium constant, K = [3-Bromopropyne]/[Bromopropadiene], range from 2.69 (135° C) to 2.00 (195° C).

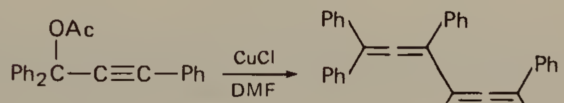
$$\mathrm{Br\cdot + HC{\equiv}CCH_2Br \rightleftharpoons HBr + HC{\equiv}\dot{C}{-}CHBr} \qquad (17a)$$

$$\mathrm{HC{\equiv}\dot{C}{-}CHBr + HBr \rightleftharpoons Br\cdot + H_2C{=}C{=}CHBr} \qquad (17b)$$

The kinetics of the iodine-catalysed isomerization of propyne to allene have been studied in the range 280–330° C[84].

Isomerization to triphenylpropadiene accompanies the autoxidation of 1,3,3-triphenylpropyne (equation 18)[85]. An interesting rearrangement and dimerization occurs when propargylic acetates such as **76** are treated with copper (I) chloride[86]. A free-radical mechanism has been proposed.

$$\mathrm{PhC{\equiv}CCHPh_2 \xrightarrow{O_2} PhC{\equiv}CC(OOH)Ph_2 + PhCH{=}C{=}CPh_2} \qquad (18)$$



(76)

C. Anionotropic

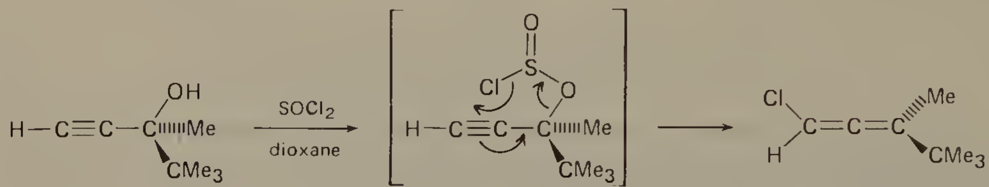
1. *Replacement of OH by halogen*

Extensive rearrangement often occurs during the reaction of secondary and tertiary propargylic alcohols with the reagents commonly used for replacing OH by halogen, i.e. HX, $SOCl_2$, PX_3, PCl_5, etc., giving allenic halides either alone or mixed with the propargylic isomer. Replacement occurs without rearrangement with primary and secondary alcohols by means of triphenyl phosphite dibromide and pyridine[87]. Propargyl alcohol itself reacts with phosphorus tribromide or thionyl chloride without rearrangement[88,89], but with triphenyl phosphite methiodide (equation 19) mixtures are obtained which contain 1-iodopropadiene (**77**) in amounts dependent on the temperature and solvent[90]. It is likely in this case, however, that at least part of the **77** is formed by rearrangement of **78** since it was shown that 3-iodo-1-butyne (**79**) rearranges to **80** at room temperature in the presence of triphenyl phosphite methiodide.

$$\mathrm{HC{\equiv}CCH_2OH \xrightarrow{(PhO)_3\overset{+}{P}Me\ I^-} \underset{(77)}{H_2C{=}C{=}CHI} + \underset{(78)}{HC{\equiv}CCH_2I}} \qquad (19)$$

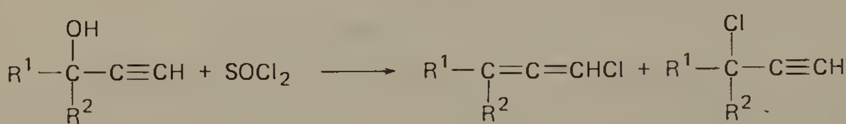
$$\mathrm{\underset{(79)}{CH_3CH(I)C{\equiv}CH} \xrightarrow[DMF,\ 25^{\circ}C]{(PhO)_3\overset{+}{P}Me\ \bar{I}} \underset{(80)}{CH_3CH{=}C{=}CHI}}$$

Allenic chlorides formed by the reaction of propargylic alcohols with thionyl chloride in ether-type solvents have the configuration which corresponds to the introduction of chlorine *syn* to the departing hydroxyl group. Thus, the configuration corresponds to that expected from S_Ni' collapse of the first-formed chlorosulphite ester[91-95]. For example, (*S*)-3,4,4-trimethyl-1-pentyn-3-ol (**81**) gives the allenic chloride **82** having the *S* configuration.



(81) (82)

Simple secondary propargylic alcohols **83** (R^1 = Me, Et, Pr; R^2 = H) with thionyl chloride in ether-type solvents give mixtures containing approximately 60% of the corresponding allenic chloride **84a**; the tertiary alcohol **83** ($R^1 = R^2$ = Me)



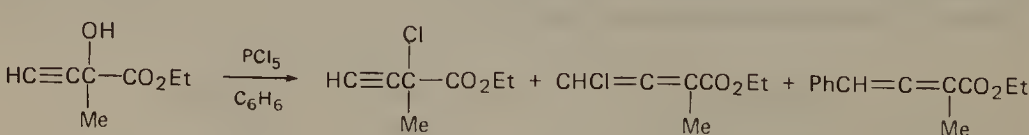
(83) (84a) (84b)

exhibits comparable behaviour, giving 73% **84a** ($R^1 = R^2$ = Me)[89]. The phenyl-substituted alcohol **83** (R^1 = Ph, R^2 = H), however, reacts with $SOCl_2$ in diethyl ether at 0–25° C to give the propargylic chloride **84b** (R^1 = Ph, R^2 = H) exclusively[96]. When optically active alcohol is used, the propargylic chloride is formed with 22% net retention of configuration; the low stereoselectivity is attributed to the stability of the delocalized cation formed by decomposition of the intermediate chlorosulphite ester[96].

The chlorosulphite **85** is unusually stable, and it can be distilled at 110° C (11 torr) without decomposition[97]. Decomposition occurs at 150° C giving the allenic product **86**.

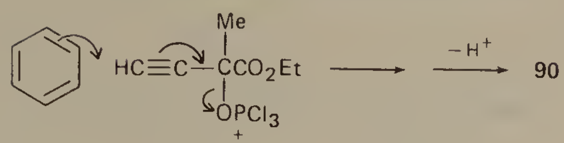
(85) (86)

When benzene is used as solvent for the reaction of hydroxy ester **87** with phosphorus pentachloride, the products include not only the anticipated chlorides **88** and **89**, but also the phenyl-substituted derivative **90**[95]. Formation of **90** can be



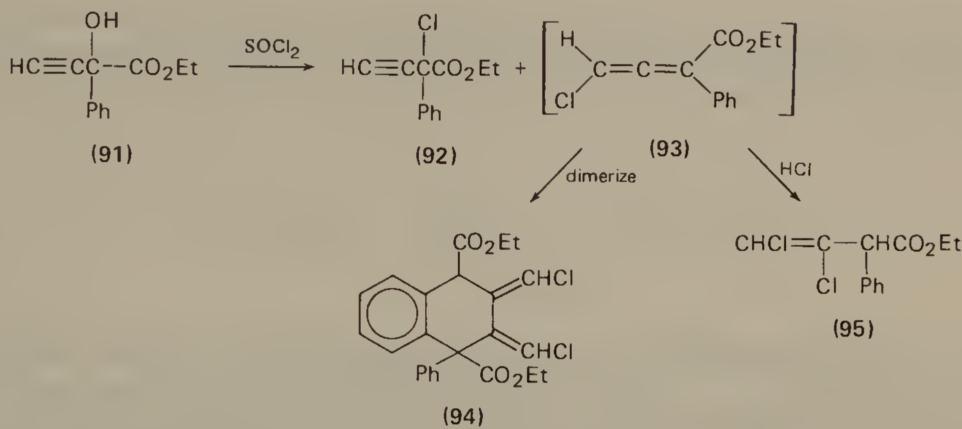
(87) (88) (89) (90)

accounted for in terms of electrophilic attack on benzene as formulated in equation (20).

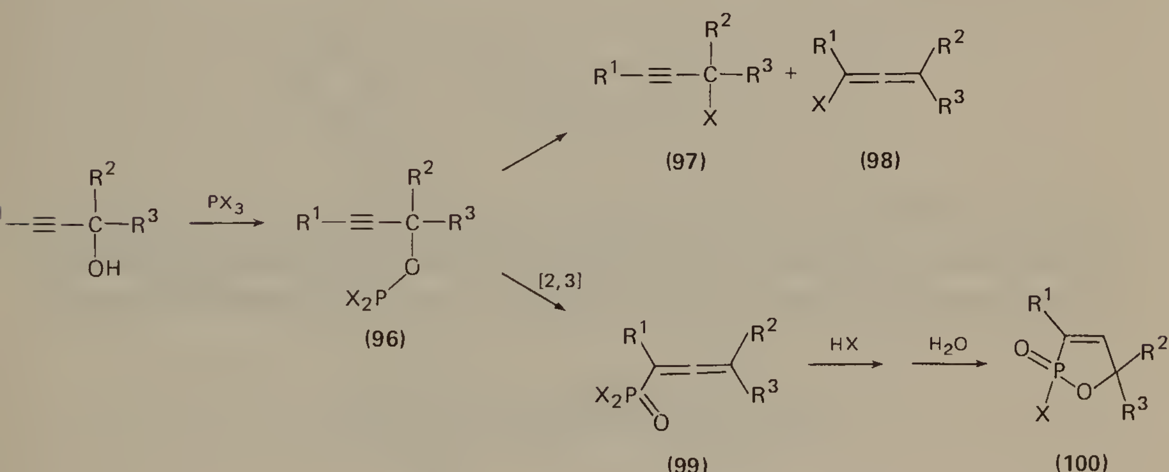


(20)

The allenic chloride **93**, formed by the reaction of **91** with $SOCl_2$, PCl_5 or HCl, is very reactive and either dimerizes or adds HCl as soon as it is formed and the products actually isolated are **92**, **94** and **95**[98,99].



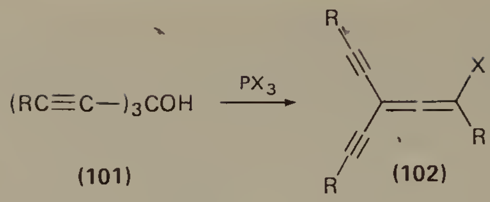
The initial product of reaction of a propargylic alcohol with phosphorus trihalides is a propargylic dihalophosphite **96** (Scheme 5). Cleavage of **96** by HX leads



SCHEME 5.

to the anticipated halides **97** and **98**, but another path is open, i.e. [2, 3] sigmatropic rearrangement giving the allenic phosphonyl dihalide **99**[100-102]. This rearrangement is discussed in Section VIII.B.3. Acid-catalysed cyclization of **99** occurs giving, after aqueous work-up, the oxaphospholene **100**.

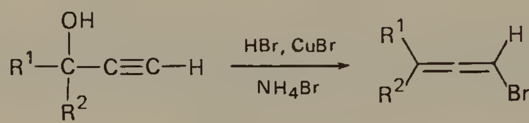
The interesting allenic halide **102** is obtained from the reaction of the trialkynylcarbinol **101** with phosphorus trihalides[103].



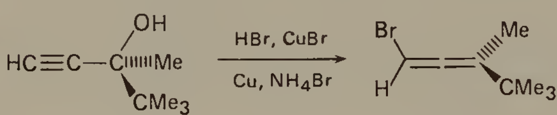
(101) (102)

R = *t*-Bu

Allenic bromides are obtained in good yield by the reaction of secondary or tertiary propargylic alcohols with aqueous HBr in the presence of CuBr and NH_4Br (equation 21)[104]. Tertiary alcohols give pure allenic bromides, but the product

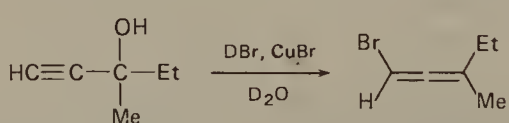
 (21)

from secondary alcohols contains small amounts ($\leqslant 5\%$) of the propargylic bromide. Although the reaction occurs with HBr alone it is slow and incomplete and the presence of CuBr–NH_4Br leads to a dramatic increase in rate. Later studies, cited below, indicate that CuBr is the only essential component of the catalyst. Stereochemical and tracer studies have provided important mechanistic information[105]. The reaction is highly stereospecific with the (*S*) alcohol **103** giving bromo-



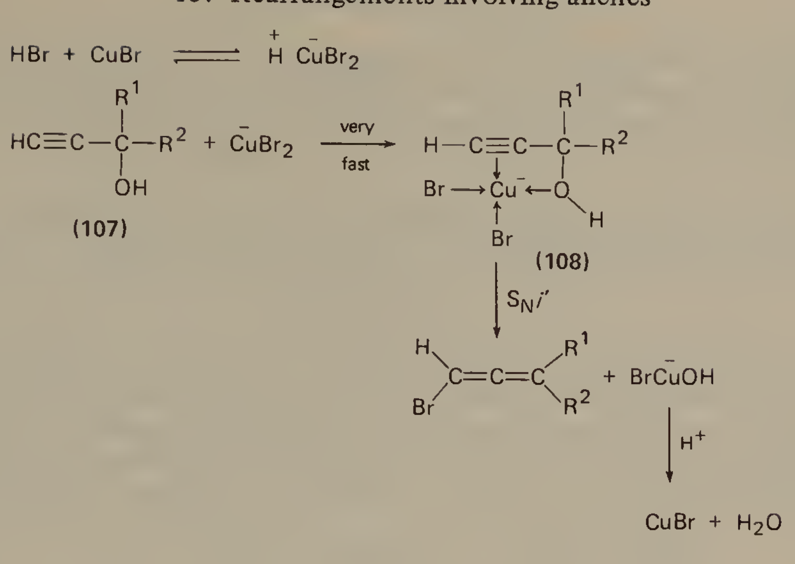
(103) (104)

allene **104** having the retained (*S*) configuration. Deuterium was not incorporated in the product **106**, obtained when the reaction of alcohol **105** was carried out with



(105) (106)

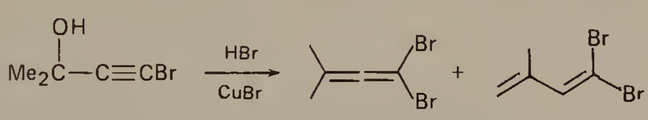
DBr in D_2O, demonstrating that copper acetylide intermediates are not involved. These features are rationalized in terms of a mechanism (Scheme 6) involving rapid formation of a π complex (**108**), followed by a rate-determining, stereospecific S_Ni' process giving the bromoallene[105]. Very rapid π complex formation is evidenced by the immediate disappearance of the acetylenic proton n.m.r. signal when CuBr was added to a solution of the acetylenic alcohol **107** ($R^1 = R^2 =$ Me) and HBr in diglyme. The reaction is first order in alcohol, with an activation energy of 16.8 kcal/mol; the presence of Cu and NH_4Br has no effect on the rate.



SCHEME 6.

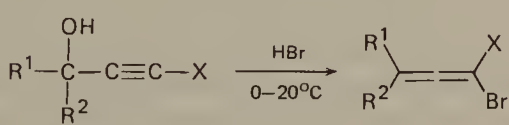
Allenic iodides are obtained, essentially free of propargylic isomers, by a comparable procedure utilizing HI and CuI[106].

An attempt to synthesize the dibromoallene **110** by the reaction of the bromo alcohol **109** with HBr–CuBr gave a mixture consisting largely of the conjugated isomer **111** and only about 10% of the desired product **110**[107]. Furthermore, when the reaction mixture was allowed to stand, **110** quickly isomerized to **111** and it



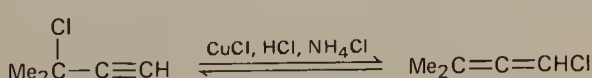
(109) (110) (111)

was not possible to isolate pure **110**. Dihaloallenes can be obtained, however, by treating bromo or chloro alcohols **112** with aqueous HBr alone[106]. The reaction of the chloro alcohol **112** (X = Cl) with thionyl chloride in boiling dioxane furnishes 1,1-dichloroallenes.



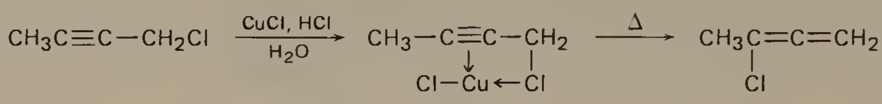
(112) X = Cl, Br

Copper (I) halides, alone or in mixtures with hydrogen halide and ammonium halide, catalyse the interconversion of propargylic and allenic halides as illustrated in equation (22)[108,109]. The reactions can be carried out homogeneously by the

 (22)

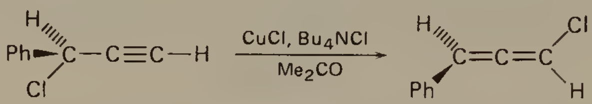
use of CuCl and quaternary ammonium chlorides such as $Bu_4\overset{+}{N}\overset{-}{Cl}$ in aprotic solvents[96]; in these cases the catalyst may be represented as $Bu_4\overset{+}{N}\overset{-}{Cu}Cl_2$.

Intermediate π complexes have been proposed for these reactions[109], and support for the proposal is provided by the fact that a 1 : 1 complex (**114**) which separates when **113** is mixed with aqueous CuCl–HCl, gives 3-chloro-1,2-butadiene (**115**) when it is heated[110]. According to this formulation one would anticipate a



(113) (114) (115)

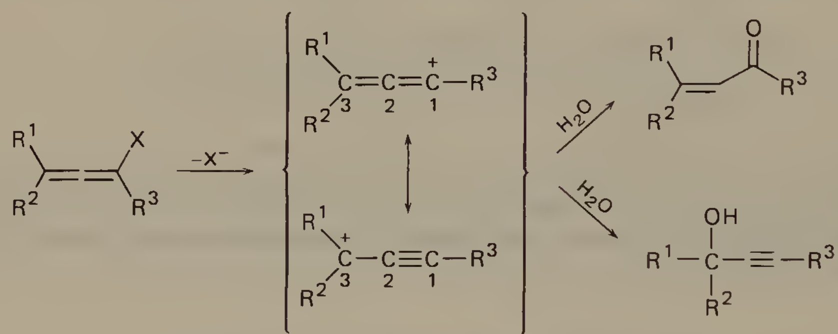
syn relationship between the entering and departing chlorines, but evidence has been presented which indicates that *anti* stereochemistry prevails[96]. Thus, (*R*)-3-chloro-3-phenylpropyne reacts with CuCl and Bu_4NCl in acetone giving the allenic chloride which is believed to have the *R* configuration as shown in equation (23).



(23)

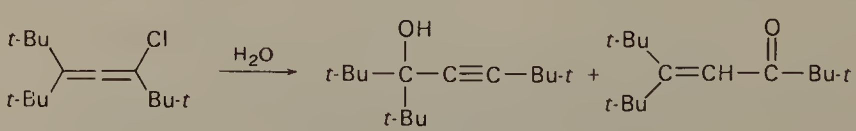
2. *Solvolysis of allenic halides*

The possibility of cationic intermediates **116** in the hydrolysis of allenic halides was first suggested by Jacobs and Fenton to account for the formation of propargylic alcohols[111]. Since that time a wealth of evidence has been amassed, particularly by Schiavelli and coworkers, which supports this hypothesis and provides a detailed insight into many aspects of the reaction[112–116,117a].

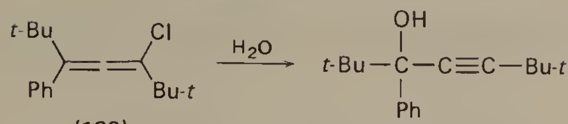


(116)

From consideration of the charge distribution in cation **116** one might anticipate solvent capture at position 1 as well as at position 3, giving α, β-unsaturated ketones in addition to propargylic alcohols. Both types of products have been observed, but the latter always predominate, and only when position 3 is substituted with bulky groups are α, β-unsaturated ketones formed in detectable amounts. For example, hydrolysis of **117** gives **118** and **119** in the ratio 4 : 1, but **120** gives the propargylic alcohol exclusively[114].



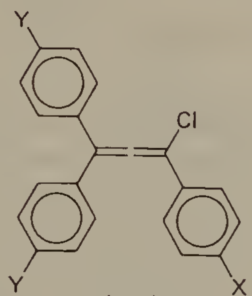
(117) (118) (119)



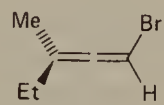
(120)

N.m.r. studies have shown that the charge in cations of type **116** is delocalized extensively, and both positions 1 and 3 bear a significant part of the positive charge[118–121]. *Ab initio* calculations indicate preferential attack of chloride at position 3 in **116** ($R^1 = R^3 = Me$, $R^2 = H$)[122].

Hydrolysis of the trisubstituted allenic chlorides **121** in aqueous acetone follows a first-order rate law accurately, and the value of ρ is found to be $-2{\cdot}0$, which is



(121)



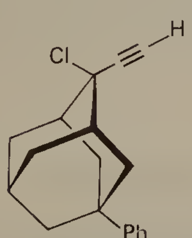
(122)

(a) X = Y = H

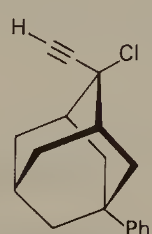
(b) X = OMe, Y = H

consistent with an intermediate carbonium ion **116** with substantial charge delocalization to position 3[112]. The rate of hydrolysis of **121a** increases markedly with increasing solvent polarity, and exhibits common-ion rate depression indicating the presence of dissociated ions[113]. Additional support for a rate-determining ionization mechanism has been provided by studies of leaving-group rate ratios, i.e. (k_{Br}/k_{Cl}), (CH_3/H) rate ratios and α- and β-secondary isotope effects[114–116,123]. The solvolysis of optically active (*R*)-1-bromo-3-methyl-1,2-pentadiene (**122**) has been interpreted in terms of nucleophilic attack on a tight ion pair[117a].

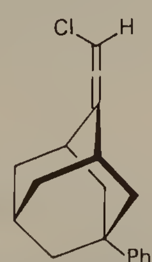
A recent study of the methanolysis of *E*- and *Z*-**123**-Cl has provided results of considerable significance[117b]. Thus, methanolysis of *E*-**123**-Cl provides a mixture containing 15% *E*-**123**-OMe, 45% *Z*-**123**-OMe and 40% *E*-**124**-Cl; no *Z*-**124**-Cl could be detected. Similarly, *Z*-**123**-Cl affords a mixture of 16% *E*-**123**-OMe, 46% *Z*-**123**-OMe and 38% *Z*-**124**-Cl. It is apparent that the solvolytic products are obtained from a common intermediate, whereas the return products are formed completely



(*E*-123-Cl)

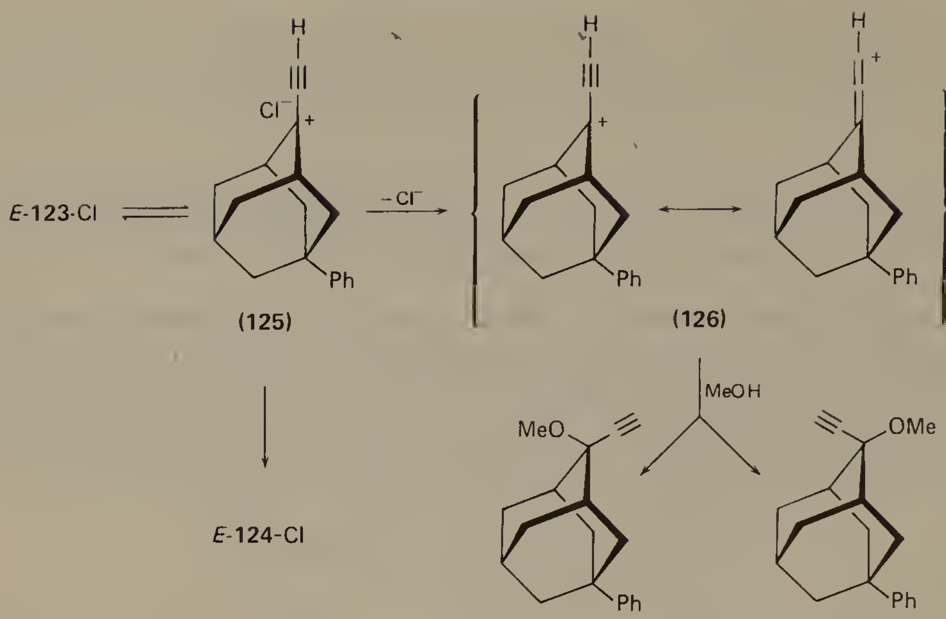


(*Z*-123-Cl)



(*E*-124-Cl)

(*Z*-124-Cl)

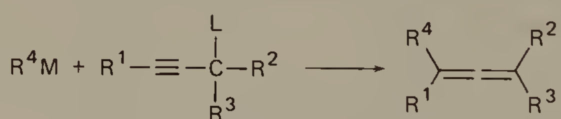


(E-123-OMe) (Z-123-OMe)

stereospecifically, without any detectable crossover. It is proposed that stereospecific return occurs from the ion pair **125**, and that the free carbonium ion, **126**, is the common intermediate[117b]. Interaction of solvent with the phenyl group may be responsible for the high ratio of Z to E products.

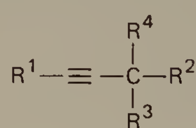
3. *Reaction of organometallics with propargylic derivatives*

The reaction shown in equation (24) summarizes a common type of rearrangement that occurs when organometallic reagents RM react with substrates bearing a



(24)

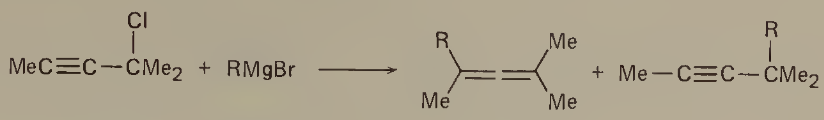
leaving group L at the propargylic position. A wide variety of organometallic reagents have been used, including those derived from magnesium, lithium, copper and boron. Common leaving groups L include halogen, tosylate, alkoxy (including epoxy), acetate and carbamate. The reaction shown in (24) can be viewed as a substitution process with rearrangement and one might also anticipate products from substitution without rearrangement, i.e. **127**. As we shall see, both types of



(127)

products are formed in some reactions, while others show exceptionally high selectivity for allene formation.

Grignard reagents react with propargylic halides to give allenes or mixtures of allenes and acetylenes depending on the structure of the halide and Grignard reagent, the conditions and the presence of trace amounts of transition metal salts[124–126]. It was reported originally that methylmagnesium bromide (129a) and 4-chloro-4-methyl-2-pentyne (128) react to give only the allene (130a)[124], but later



(128) (129) (130) (131)

(a) R = Me

(b) R = Bu

$$HC{\equiv}CCH(Cl)Me + BuMgBr \xrightarrow{FeCl_3} BuCH{=}C{=}CHMe$$

(132)

work has shown that both **130**a and **131**a are formed, with **130**a being favoured by using low concentrations of Grignard reagent and operating at low temperatures[125]. Small amounts of iron (III) chloride catalyse selectively the formation of allenes which, in many cases, are formed in high yield to the exclusion of alkynes[126]. Thus, in the presence of 5 x 10^{-5} M $FeCl_3$, *n*-butylmagnesium bromide (**129b**) reacts with **128** to give **130b** in 87% yield. The same selectivity prevails for reactions involving terminal alkynes, as evidenced by the exclusive formation of **132** from *n*-butylmagnesium bromide and 3-chloro-1-butyne, but interestingly both the allene and acetylene **130**a and **131**a are formed in equal amounts when methylmagnesium bromide reacts with **128** even in the presence of the catalyst. It is proposed that organoiron intermediates are involved[126]. Organolithium reagents generally give higher yields of allenic products than do the corresponding Grignard reagents[125].

The mechanism of reaction of propargylic chlorides with Grignard reagents and organocuprates, and the role of transition metal catalysts have been clarified by recent work[126].

The reaction of methyl Grignard reagents with chlorides such as **133** constitutes a useful synthesis of vinylallenes **134**[127].

$$HC{\equiv}CCH{=}CHCH(R)Cl \xrightarrow{CH_3MgI} CH_3CH{=}C{=}CHCH{=}CHR$$

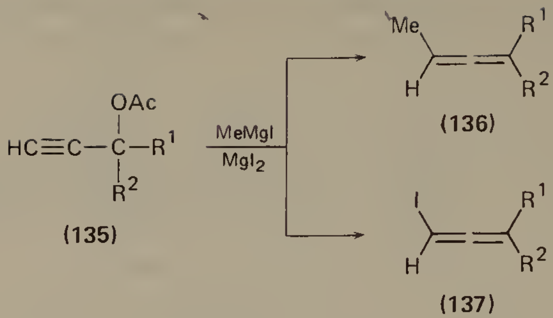
(133) (134)

R = H, alkyl

Allenes, contaminated with only small amounts ($\leqslant$ 10%) of the acetylenic isomers, are obtained by the reaction of Grignard reagents with esters of δ-bromopropargylic alcohols, as shown in equation (25)[128]. Methyl Grignards tend to attack the ester function preferentially, but this can be avoided by using pivalate esters.

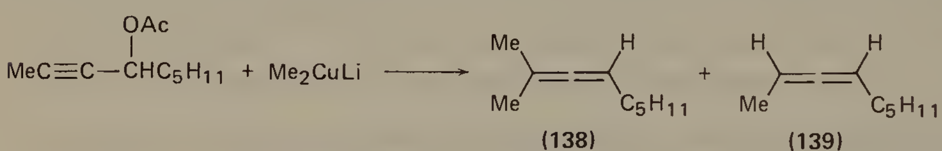
$$CH_3CO_2CH_2C{\equiv}CCH_2Br \xrightarrow{EtMgBr} CH_3CO_2CH_2C(Et){=}C{=}CH_2 \qquad (25)$$

Acetate serves as the leaving group in reactions of propargylic acetates **135** with methylmagnesium iodide and magnesium iodide[129–134]. Methyl- and iodo-substituted allenes, **136** and **137**, are produced, and by proper choice of conditions it is



often possible to make either one the dominant product. The methyl-substituted derivative **136** is favoured when the Grignard reagent is prepared *in situ* by adding methyl iodide to a mixture containing the ester **135**, magnesium, and one equivalent of magnesium iodide. When the ester **135** is mixed with preformed Grignard reagent and four equivalents of magnesium iodide, the iodoallene **137** predominates[132,134]. It has been proposed that the iodoallenes are formed by an ionic mechanism, while the methyl-substituted allenes arise by a free-radical pathway. The predominant formation of allenes by the combination of anions with propargylic cations, however, constitutes a departure from the usual pattern of behaviour.

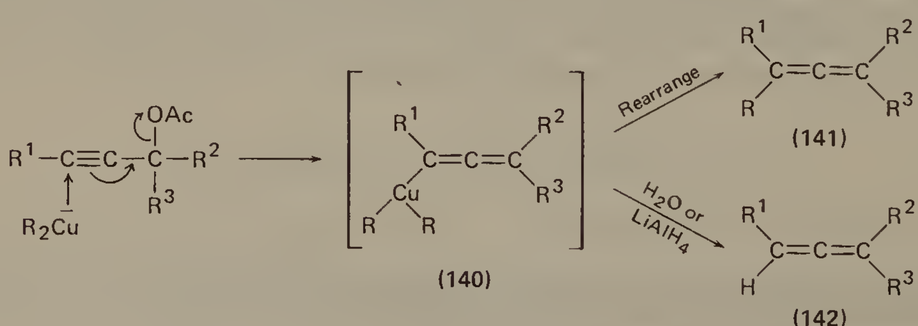
Dialkyl cuprates react with primary, secondary and tertiary propargylic acetates to give allenes, uncontaminated with the acetylenic isomers[135,136,137a,138]. Both alkylated **138** and nonalkylated allenes **139** can be formed, as illustrated in equation (26) and, by proper choice of conditions it is possible to obtain either one



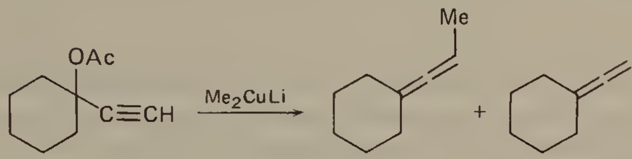
(26)

in high yield. When the reaction is conducted at room temperature, the ratio of alkylated to nonalkylated allene is ca 95 : 5, but when the reaction is carried out at low temperatures (−50 to −75° C) the nonalkylated product **139** is favoured. In a recently reported procedure, yields of nonalkylated product are maximized by mixing the ester and cuprate reagent at −75° C, followed by reaction with lithium aluminium hydride at −75° C; by this procedure, for example, the yields of **138** and **139** are 7.5% and 67.5% respectively[137a].

The coupling of a vinylcuprate reagent with a tertiary propargylic acetate constitutes the key step in a recently reported synthesis of vinylallenes, which, in turn, were converted to 1-hydroxy Vitamin D derivatives[137b].

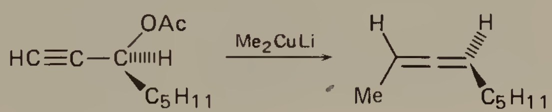


Evidence has been presented which indicates that an intermediate such as **140** is involved. Rearrangement involving migration of R from copper to the sp^2 carbon, which is favoured by higher temperatures and longer reaction periods, provides the alkylated allene **141**. At low temperatures, however, the rearrangement is slowed to such an extent that **140** survives and is converted to **142** during hydrolytic work-up or $LiAlH_4$ treatment[136,137a]. Some of the evidence which supports this mechanism is as follows. By using deuterium-labelled reagents it was established that the hydrogen in the nonalkylated product does not come from the dialkylcuprate reagent. Furthermore, direct distillation of the reaction mixture from **143** and lithium dimethylcuprate, without hydrolytic work-up, gave a product containing 98% **144** and only 2% **145**. Formation of the latter was attributed to traces of



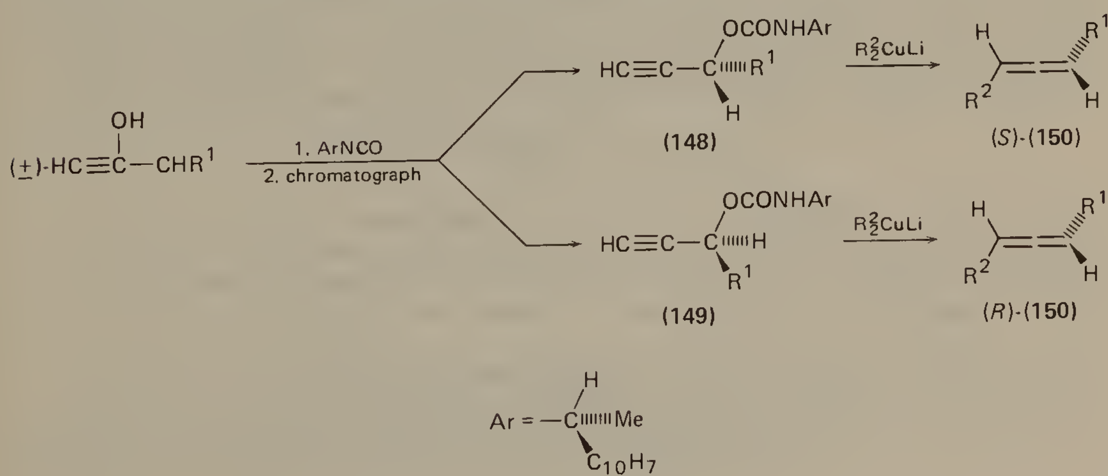
(143) (144) (145)

moisture in the reagents. With esters of secondary propargylic alcohols the alkyl group is introduced *anti* to the C—O bond which is cleaved, as illustrated by the conversion of (*S*)-**146** to (*R*)-**147**[136]. With esters of tertiary alcohols, however, *syn* stereochemistry may be preferred.

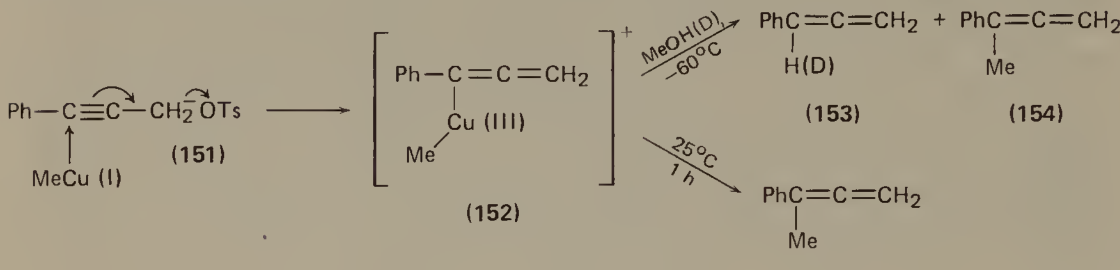


(146) (147)

Through an interesting variation of this reaction it is possible to obtain optically active 1,3-dialkylallenes in high yield with substantial enantiomeric enrichment (60–80%)[139]. The mixture of diastereomeric carbamates **148** and **149** formed by reaction of the racemic alcohol with (*R*)-1-(1-naphthyl)ethyl isocyanate is separated by liquid chromatography. Treatment of the individual carbamates with lithium dialkylcuprate provides the enantiomeric allenes, (*S*)-**150** and (*R*)-**150**. Synthesis of the sex attractant of the male dried bean beetle has been accomplished by utilizing this reaction for introducing a chiral allene grouping[140].



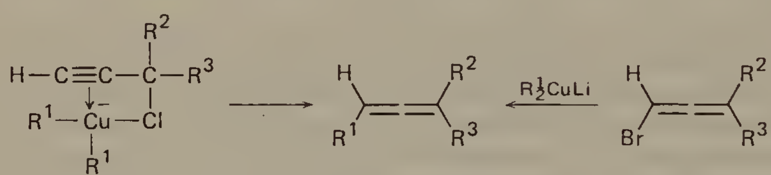
Propargylic tosylates and halides can also serve as substrates in reactions with organocopper reagents[141-143]. An intermediate, comparable to 140 and formulated as the Cu(III) complex **152**, has been postulated to account for the



(151) (152) (153) (154) (154)

behaviour observed in the reaction of **151** with the 'methylcopper' reagent, preformed by mixing equivalent amounts of methylmagnesium bromide and copper (I) bromide[143]. When the reaction is carried out at low temperature and the mixture is hydrolysed by the addition of methanol at $-60°$ C, the nonalkylated allene **153** is the major product; **153**:**154** = 70:30. When CH_3OD is used for the hydrolysis, deuterium appears at position 1 in **153** as shown. If the reaction mixture is allowed to warm to room temperature and stand for one hour, 3-phenyl-1,2-butadiene (**154**) is the product; however, if the period of standing is shortened, 1-phenyl-1,2-propadiene (**153**) begins to appear[144a]. β-Allenic esters are obtained from the reaction of 'copper(I) enolates' with propargylic methanesulphonates, and it has been proposed that copper(III) intermediates are involved[144b].

A different type of intermediate, a π complex (**155**), has been proposed for the reaction of propargylic chlorides with dialkylcuprates[141,142]. The stereochemical outcome for such a process would be expected to be opposite to that described

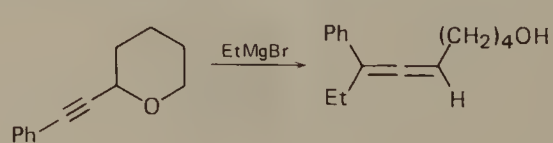


(155) (156)

above for acetate substrates. It is interesting to note that the halogen of 1-haloallenes **156** is replaced without rearrangement by reaction with organocuprates[141,142], but rearrangement does occur during the reaction of 1-methoxyallene with Grignard reagents in the presence of copper(I) halides (equation 27)[145].

$$H_2C{=}C{=}CHOMe \xrightarrow[CuX]{RMgX} RCH_2C\equiv CH \qquad (27)$$

The reaction of propargylic ethers with dialkylcuprates or with Grignard reagents, alone or in the presence of copper(I) salts, gives allenic products as illustrated in equations (28) and (29)[146,147,148a]. Similarly the reaction of alkynyloxiranes with dialkylcuprates, or better with Grignard reagents in the



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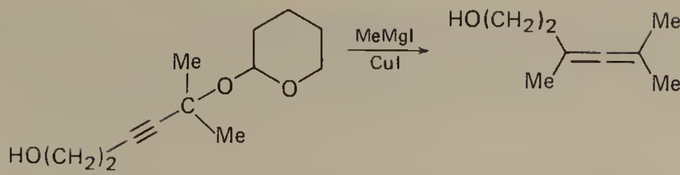
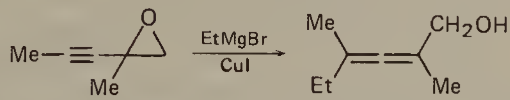


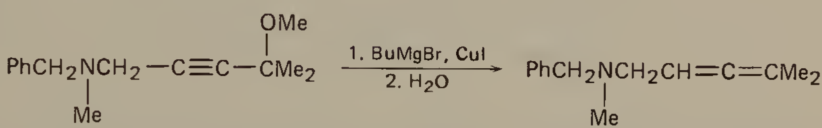
(29)

presence of CuI, serves as a convenient synthesis of allenic alcohols (equation 30)[144,149]. Introduction of hydrogen instead of an alkyl group is also possible,



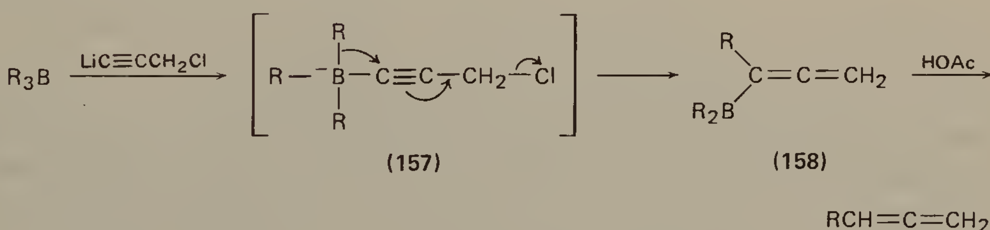
(30)

as illustrated in equation (31)[148b]. The solvent plays an important role in determining the type of product formed.

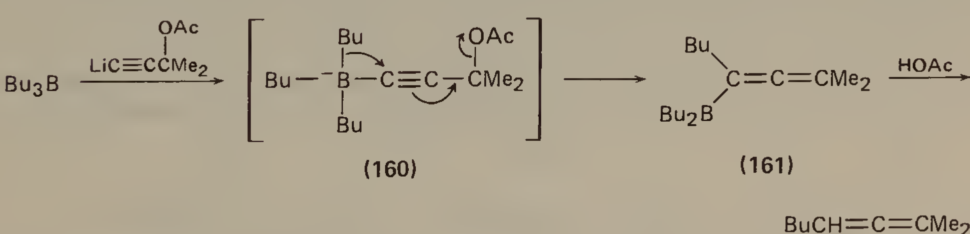


(31)

Borate complexes such as **157** and **160** undergo intramolecular anionotropic rearrangement giving the allenylboranes **158** and **161**[150a,151a]. The alkyl migration from boron to the alkyne carbon occurs predominantly *anti* to the leaving group[151b]. Protonation gives the corresponding allenes **159** and **162**. In the original reports it was proposed that the allenic boranes **158** and **161** are precursors of the allenic hydrocarbons, but more recent work suggests that the allenic boranes isomerize to the more stable propargylic isomers which are protonated, with rearrangement, giving **159** and **162**[150b].

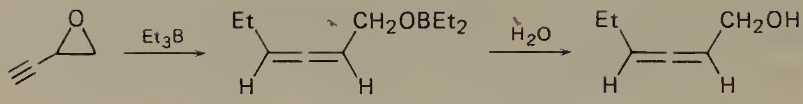


(157) (158) (159)



(160) (161) (162)

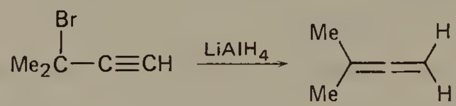
Trialkylboranes react with ethynyloxiranes in the presence of oxygen to give α-allenic alcohols in good yield, as illustrated by the formation of 2,3-hexadien-1-ol (**163**) in 62% yield from triethylborane and ethynyloxirane[152]. The reaction is believed to proceed by a free-radical chain mechanism.

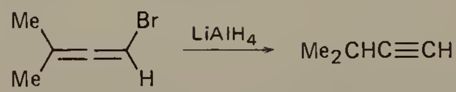


(163)

4. *Reduction of halides, alcohols and ethers*

The rearrangements that have been observed during the reduction of propargylic and allenic halides, as typified by equations (32) and (33), can be considered formally as involving displacement of Br^- by H^- with rearrangement, and in this context can be classed as anionotropic rearrangements[153,154]. Addition reactions giving organoaluminium derivatives, which undergo further reactions, complete with substitution, and often lead to complex product mixtures[154].

 (32)

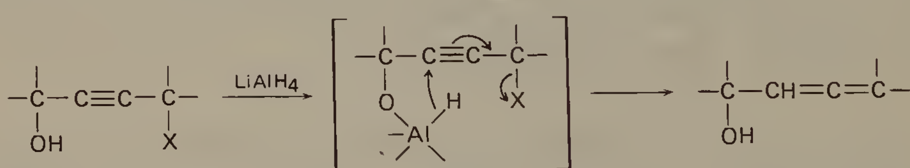
 (33)

Displacement without rearrangement occurs almost entirely with primary propargylic bromides, equation (34), whereas complete rearrangement occurs with 1-bromopropadiene (equation 35) and propyne is formed exclusively[155,156]. Secondary propargylic halides react by both routes to significant extents.

$$HC{\equiv}CCH_2Br \xrightarrow{LiAlH_4} CH_3C{\equiv}CH \qquad (34)$$

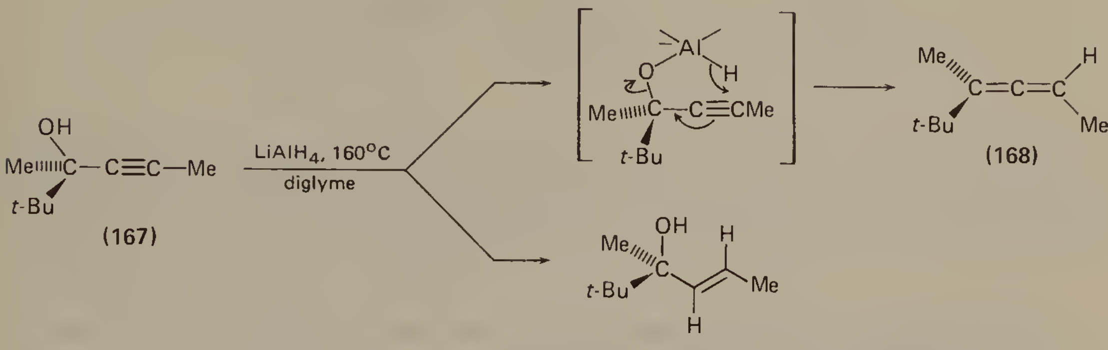
$$H_2C{=}C{=}CHBr \xrightarrow{LiAlH_4} CH_3C{\equiv}CH \qquad (35)$$

Derivatives such as **164** undergo clean-cut rearrangement upon reduction with $LiAlH_4$ giving allenic alcohols **166**, apparently by the S_Ni' mechanism illustrated in **165**, although it is possible that the process is not synchronous and that cyclic organoaluminium intermediates are involved[157,158]. A wide variety of functions can serve as the leaving group X, e.g. halogen, hydroxy (leaving as $^-OAlH_2$), alkoxy (including epoxy), tetrahydropyranyloxy and trialkylammonium[157–161].



(164) (165) (166)

The reaction of propargylic alcohols themselves with $LiAlH_4$ commonly involves reduction of the triple bond to give allylic alcohols, but allene formation is a competing reaction which may predominate under some conditions[158,162]. Allene formation in these cases involves the –OH group, modified as $-O\bar{A}lH_3$, serving first as hydride donor and subsequently as leaving group ($-OAlH_2$). Support for this interpretation was provided by the finding that the configuration of the allene **168** obtained by reduction of (*R*)- 2,2,3-trimethyl-4-hexyn-3-ol (**167**) corresponds to hydride attack at position 5 *syn* to the original OH group[158]. The ratio of allene **168** to allylic alcohol **169** was approximately 2:1.



(167) (168) (169)

While the reduction of **167** fails to occur in boiling ether or THF and requires a temperature of 160° C, the diphenyl derivative **170** is reduced in the lower boiling solvents[162]. The proportion of allene **171** and the ratio of *Z* and *E* isomers of **172** are strongly solvent dependent.

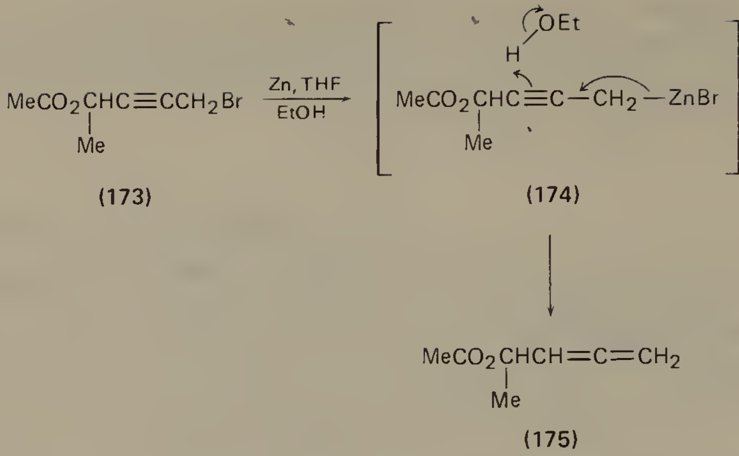
$$\underset{(170)}{Ph_2C(OH)C{\equiv}CMe} \xrightarrow{LiAlH_4} \underset{(171)}{Ph_2C{=}C{=}CHMe} + \underset{(172)}{Ph_2C(OH)CH{=}CHMe}$$

Reduction of propargylic and allenic halides has also been accomplished with a zinc–copper couple in alcoholic solvents. In all likelihood the reaction involves formation of an organozinc intermediate which suffers electrophilic substitution by the protic solvent. Therefore the reaction is not rightfully classified as anionotropic, but because of the close correspondence of the overall reactions, it is considered along with hydride reduction.

Propargylic halides and the isomeric allenic halides give product mixtures of the same composition upon reduction with a Zn–Cu couple[155]. Both 3-bromopropyne and 1-bromopropadiene, for example, give allene and propyne in the ratio 2:1 by reduction with Zn–Cu in EtOH. Under the same conditions, 1,2-hexadiene and 1-hexyne are formed in the ratio 36:1 from both 3-chloro-1-hexyne and 1-chloro-1,2-hexadiene[155]. A single product may be formed from both isomeric halides in some cases, as illustrated in equation (36)[163].

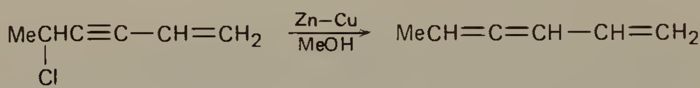
$$Me_2C(Cl)C{\equiv}CH \xrightarrow[EtOH]{Zn-Cu} Me_2C{=}C{=}CH_2 \xleftarrow[EtOH]{Zn-Cu} Me_2C{=}C{=}CHCl \qquad (36)$$

Esters of γ-bromoacetylenic alcohols such as **173** give the ester of the allenic alcohol **175** upon reaction with zinc in THF–EtOH, presumably by way of the organozinc intermediate **174**, which undergoes rearrangement during cleavage with EtOH as shown[164].



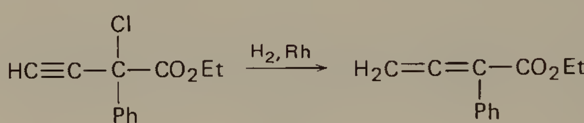
(173) (174) (175)

Alkenylallenes are obtained smoothly by reduction of enynic chlorides with Zn–Cu in methanol at 25–40° C, as illustrated in equation (37)[165].



(37)

Rearrangement has also been found to occur during the catalytic hydrogenolysis of the propargylic halide **176**[166].

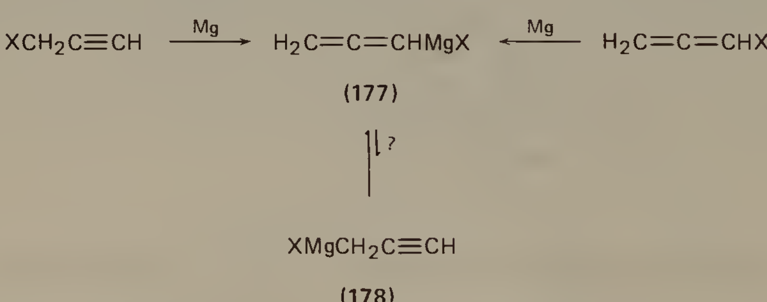


(176)

D. Rearrangements Involving 'Propargylic' Organometallic Reagents

1. Structure of 'propargylic' organometallics

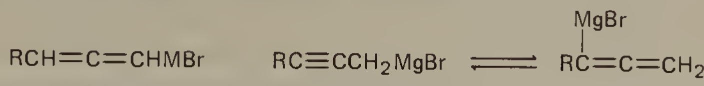
Propargyl and allenyl halides give Grignard reagents in ether or THF which exhibit identical i.r. spectra and which, according to n.m.r. spectroscopy, are best represented as allenylmagnesium halides **177**[167–169]. The possibility of small



(177) (178)

concentrations of the propargyl isomer **178** cannot be ruled out, and evidence has been presented which indicates its existence[170]. Infrared spectroscopy also shows that the corresponding derivatives of aluminium, zinc and cadmium exist entirely in the allenic form[171,172].

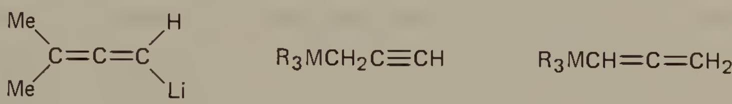
Organometallic reagents derived from 3-bromo-1-alkynes have allenic structures **179**[168,169,173,174], but Grignard reagents formed from 1-bromo-2-alkynes contain the acetylenic (**180a**) as well as the allenic (**180b**) isomers[168,173]. Lithium



(179) (180a) (180b)

M = Mg, Zn, $Al_{2/3}$

derivatives of internal acetylenes, however, are believed to have allenic structures[175]. Dimethylallenyllithium possesses structure **181** and the n.m.r. spectrum fails to reveal any of the acetylenic isomer[176]. The derivatives of tin and lead, **182** and **183**, are capable of independent existence but they can be caused to interconvert under a variety of conditions[177-181].



(181) (182) (183)

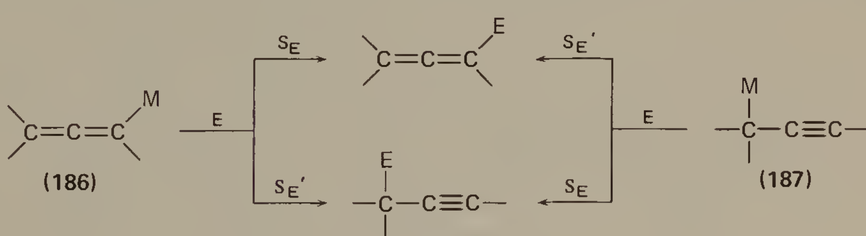
M = Sn, Pb

Besides the propargylic-type rearrangement of organometallics, a slower, prototropic rearrangement may occur. Allenic Grignard reagents such as **184** slowly rearrange to **185**[182], and a similar type of rearrangement has been observed for the lithium derivative **181**[176].

(184) (185)

2. *Electrophilic substitution reactions*

As summarized in Scheme 7, either form of propargylic–allenic organometallic



SCHEME 7.

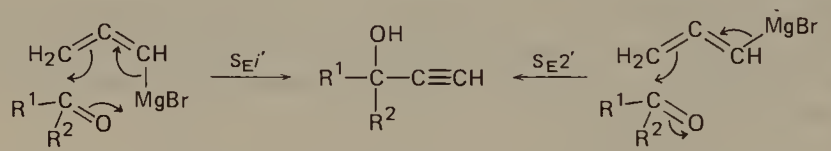
reagents is theoretically capable of undergoing electrophilic substitution either with retention of structure (S_E), or with rearrangement (S_E'). In some cases a single type of product is formed, while in others mixtures of both isomers may be formed, even in cases where the organometallic reagent has been shown by spectroscopic methods to exist entirely in the allenic form within the limits of detection. Some authors have considered the possibility that a small amount of the propargylic form **187**, in rapid equilibrium with the allenic form **186**, is responsible for the formation of mixtures[7]. Others consider this mechanism improbable and propose that mixtures arise as a result of the two modes of attack, S_E' and S_E, on the allenic form **186** of the organometallic[171,183].

Among the factors affecting product composition are: the nature of the metal M, steric and electronic factors in the electrophile, E, and in the substrate, and the solvent.

Recent evidence indicates that some of the reactions of these organometallics may in fact involve electron transfer followed by coupling of the resulting free radicals[176].

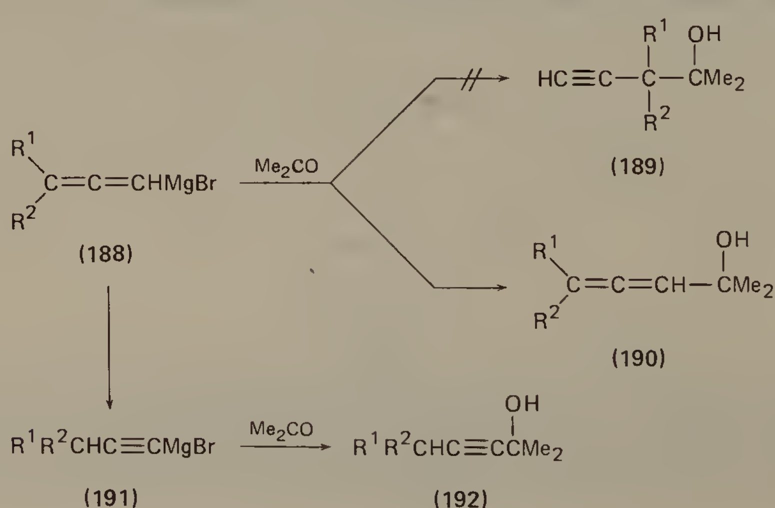
We shall examine briefly the reactions of these reagents with some of the common electrophilic agents with particular emphasis on the factors that influence the isomer ratio in the products. Most of the discussion will be concerned with Grignard and organolithium reagents.

a. With aldehydes and ketones. Allenylmagnesium halides react with aldehydes and unhindered ketones giving acetylenic alcohols containing no more than traces of the allenic isomer (equation 38)[167,172,183]. Mechanisms involving cyclic (S_Ei') or acyclic (S_E2') transition states have been proposed to account for this behaviour[6]. Similar behaviour is found for Grignard reagents derived from 3-bromo-1-alkynes[184].



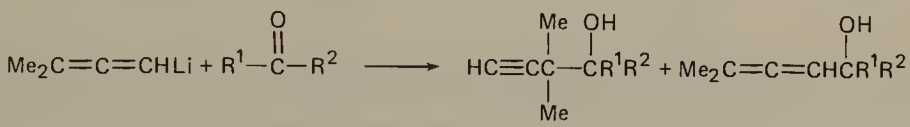
(38)

Increasing amounts of allenic alcohol appear as the steric hindrance around the carbonyl group in the ketone increases, and reach as much as 20% in the case of di-*t*-butyl ketone[183]. Similarly the presence of two substituents at position 3 of the allenic Grignard reagent **188** inhibits electrophilic attack at that position, and β-acetylenic alcohols **189** are not formed[182]. Instead, complex mixtures containing the allenic and propargylic alcohols, **190** and **192**, are obtained from the reaction with acetone, the latter product arising from the isomeric Grignard reagent **191** which is formed by the prototropic rearrangement of **188** mentioned earlier[182].



The extent of rearrangement during the reaction of carbonyl compounds with allenylorganometallics is a function of the metal and increases in the order Cd < Zn < Mg < Al[183]. Allenylaluminium bromide gives β-acetylenic alcohols exclusively even with hindered ketones such as isopropyl *t*-butyl ketone. Allenylzinc bromide gives detectable amounts of nonrearranged alcohol even with simple aliphatic aldehydes, and shows a greater sensitivity to solvent effects than does the Grignard reagent. The presence of HMPT in the solvent causes a significant increase in the proportion of nonrearranged alcohol from the reaction of allenylzinc bromide with ketones, whereas only a minor effect is noted with the Grignard reagent[183].

Unlike the analogous Grignard reagents, 3,3-dialkylallenyllithium reagents do give products that are formed by electrophilic attack of carbonyl compounds at position 3[176,185]. Both acetylenic and allenic products **195** and **196** are formed,



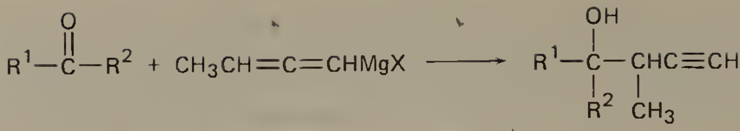
(193) (194) (195) (196)

194		
R¹	R²	195:196
H	H	100:0
Me	H	92:8
Me	Me	19:81
Me	Et	11:89
Me	*t*-Bu	0:100
Ph	H	100:0
Ph	Me	92:8
Ph	Et	80:20
Ph	*i*-Pr	0:100

SCHEME 8

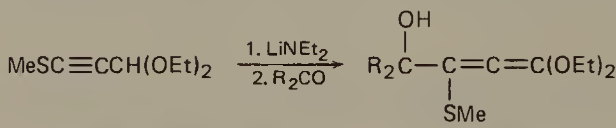
in ratios that depend on the nature of the carbonyl electrophile. From the distribution of products from a variety of carbonyl derivatives, summarized in Scheme 8, it is seen that acetylenic alcohols **195** are the predominant products from aldehydes, while greater amounts of the allenic alcohols **196** are obtained from ketones, with the proportion increasing in the aliphatic series as steric hindrance becomes greater. The formation of greater amounts of acetylenic alcohols from aromatic substrates than from their aliphatic counterparts does not follow the trend expected on the basis of steric considerations, but can be rationalized in terms of hard–soft acid–base theory[176]. Position 3 of **193**, which is classified as being softer than position 1, shows greater reactivity toward softer carbonyl groups, e.g. those conjugated with aromatic rings. Harder electrophiles such as H_2O, CO_2 and Me_3SiCl tend to give allenic products exclusively[176].

Interesting stereochemical results are obtained in the reaction of aldehydes and ketones with 1,2-butadienylmagnesium halides[174,186]. The *threo* isomer of **197** is formed predominantly from aliphatic aldehydes while equal amounts of *threo* and *erythro* isomers arise from aromatic aldehydes and the *erythro* isomer predominates in the product obtained from acetophenone.



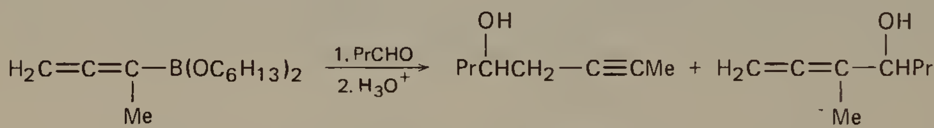
(197)

The lithium derivative of **198** reacts with carbonyl compounds to give allenic products **199** exclusively[187]. Alkylation with alkyl halides follows a similar course.



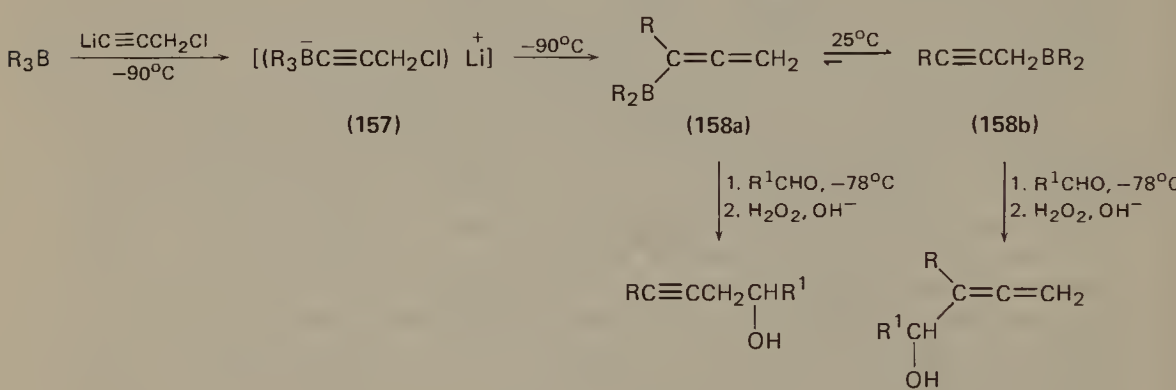
(198) (199)

Extensive rearrangement occurs during the reaction of allenic or propargylic boronates with aldehydes or ketones[188,189]. Thus, alcohols **201** and **202** are obtained in a 93 : 7 ratio by hydrolysis of the borate ester mixture which is formed



(200) (201) (202)

by condensation of **200** with *n*-butyraldehyde. The anionotropic rearrangement of borate complexes **157** to allenic boranes **158a** was described in Section II. C. 3. Recently it was found that treatment of the organoborane with aldehydes, followed by oxidation, gives either homopropargylic (**203**) or α-allenic (**204**) alcohols, depending on the temperature at which the borane is maintained prior to its reaction with the aldehyde[150]. If the aldehyde is added to the organoborane at



(157) (158a) (158b) (203) (204)

-78° C, the homopropargylic alcohol **203** is obtained almost exclusively; however, if the organoborane is first allowed to warm to room temperature, and then the aldehyde is added at -78° C, the allenic alcohol **204** is obtained essentially free of the homopropargylic isomer. It is proposed that the allenic borane **158a**, formed by the spontaneous anionotropic rearrangement of **157**, is stable at -78° C; reaction with the aldehyde occurs with rearrangement and gives, after oxidative work-up, the homopropargylic alcohol **203**. On the other hand, when the allenic borane **158a** is warmed to room temperature it rearranges to the thermodynamically more stable propargylic borane **158b**. The reaction of **158b** with aldehydes also occurs with rearrangement and leads to the allenic alcohol **204**[150b].

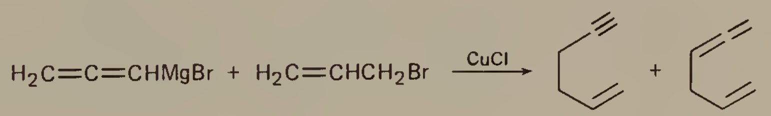
b. With carbon dioxide. Consistent with the classification of carbon dioxide as a harder acid than aldehydes and ketones is the finding that greater proportions of allenic products are formed in the reactions of the former with propargylic Grignard and lithium reagents[176,182,190]. Mixtures in which the allenic acid predominates over the acetylenic isomer are obtained from 1-bromo-2-alkynes as shown in equation (39a)[190]. Allenic acids are formed to the exclusion of the propargylic isomers from the 3,3-dialkylallenic derivatives (equation 39b).

$$RC{\equiv}CCH_2Br \xrightarrow[2.\ CO_2]{1.\ Mg} H_2C{=}C{=}C(R)CO_2H + RC{\equiv}CCH_2CO_2H \qquad (39a)$$

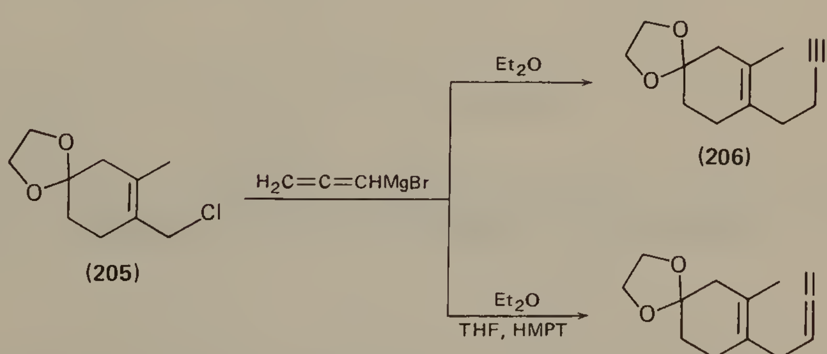
$$R^1R^2C{=}C{=}CHM \xrightarrow{CO_2} R^1R^2C{=}C{=}CHCO_2H \qquad (39b)$$

M = MgBr, Li

c. With alkylating agents. Allenylmagnesium bromide reacts with activated alkyl halides, e.g. allylic halides and α-chloro ethers, to give mixtures of the isomeric coupling products generally. For example, mixtures of 1-hexen-5-yne and 1,2,5-hexatriene are obtained from allyl bromide as shown in equation (40)[167,191]. An interesting effect of solvent on the orientation of coupling is observed in the reaction of allenylmagnesium bromide with the allylic chloride **205**[192]. With ether as solvent, the acetylenic product **206** is obtained along with only a trace of the allene **207**. With mixtures of ether, THF and HMPT, on the other hand, the allenic isomer predominates, **207** and **206** being produced in a 4 : 1 ratio. This type of behaviour can be rationalized in terms of the generalization that HMPT makes anions harder bases.

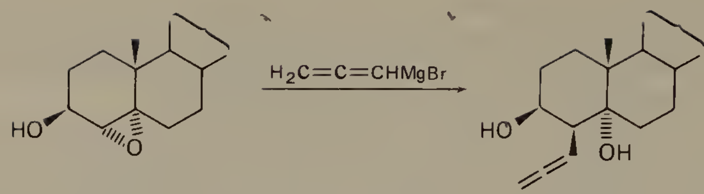


(40)

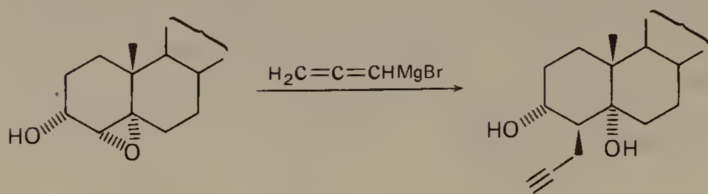


(205) (206) (207)

Another example that illustrates how subtle changes can exert a major influence on product composition in reactions of propargylic Grignards is provided by the reaction with epoxides **208** and **210**[193]. The allenyl derivative **209** is obtained



(208) (209)

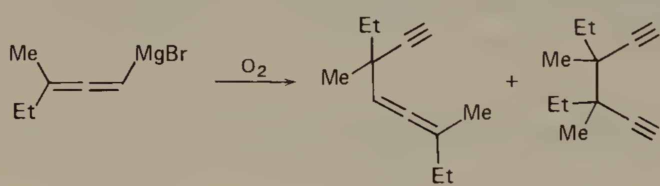


(210) (211)

from the epoxy alcohol **208**, having a β-OH group, whereas the propargyl derivative **211** is obtained from **210** in which the OH group has the α orientation.

An intriguing coupling reaction occurs when oxygen is bubbled into a solution of 3-methyl-1,2-pentadienylmagnesium bromide (**212**). Dienyne **213** and diyne **214** are formed in the ratio 63 : 34, and in virtually quantitative yield[182].

Alkylation of allenyllithium reagents with aliphatic halides yields products consisting of the allenic isomer predominantly or exclusively[185]. 1,2-Undecadiene (**215**) and 1-undecyne (**216**) are formed in the ratio 87 : 13 from allenyllithium and 1-bromooctane, while even greater proportions of allenic products are obtained from mono- and di-substituted allenyllithiums. For example, only the allenic isomer **218** is formed in the reaction of 1-bromooctane with the dimethylallenyl derivative **217**[185].



(212) (213) (214)

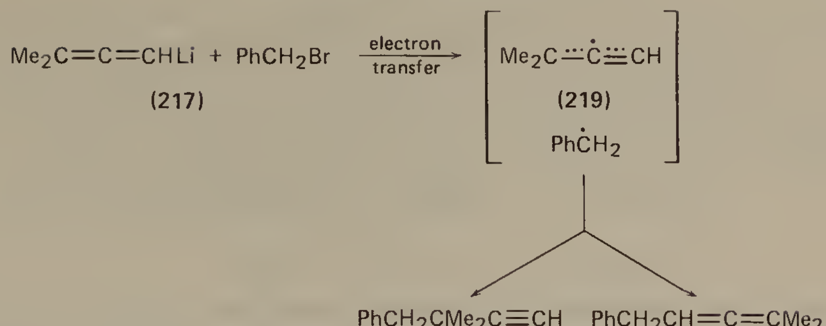
$$H_2C{=}C{=}CHLi + n\text{-}C_8H_{17}Br \longrightarrow H_2C{=}C{=}CHC_8H_{17} + HC{\equiv}CC_9H_{19}$$

(215) (216)

$$Me_2C{=}C{=}CHLi + n\text{-}C_8H_{17}Br \longrightarrow Me_2C{=}C{=}CHC_8H_{17}$$

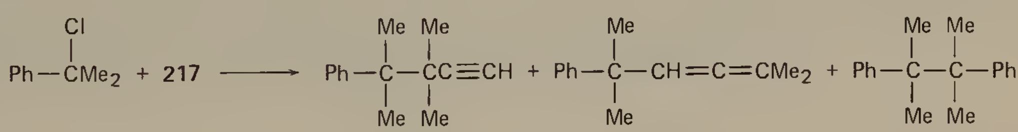
(217) (218)

Reactions of benzyl halides with **217** are more complex, and evidence has been presented for the occurrence of processes involving electron transfer as well as carbenoid intermediates[176]. Benzyl bromide reacts with **217** to give the acetylenic (**220**) and allenic (**221**) coupling products in the ratio 90 : 10. Observation of CIDNP phenomena during the reaction suggests that at least part of the coupling process involves electron transfer followed by radical coupling as indicated. The



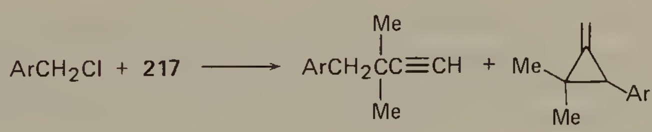
(217) (219) (220) (221)

predominance of **220** is attributed to greater spin density at the propargylic position in the radical **219**. Studies with cumyl chloride provide further support for such a mechanism. It is difficult to imagine the formation of **222** and **223** by nucleophilic processes, but they are readily accounted for by a radical coupling process. Furthermore, the formation of **224**, the product anticipated from the coupling of two cumyl radicals, is convincing evidence for the involvement of free radicals.



(222) (223) (224)

Interestingly, the reaction of **217** with benzyl chloride or *p*-methoxybenzyl chloride affords **225** and **226**, the latter suggesting the existence of carbenoid intermediates[176].

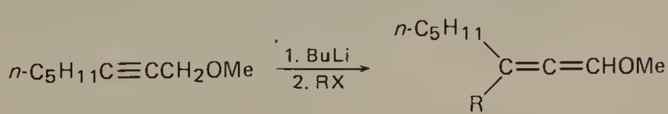


(225) (226)

(a) Ar = Ph

(b) Ar = *p*-$MeOC_6H_4$

Alkylation of lithium derivatives of propargylic ethers and acetals, generally yields allenic products, as illustrated in equations (41)–(44)[187,194–196]. Alkylating agents include alkyl halides, dialkyl sulphates and trimethylsilyl chloride.



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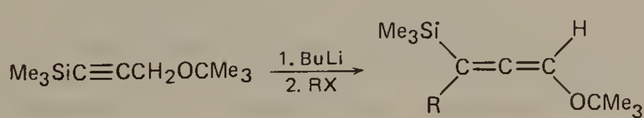


(42)

$$\text{MeSC}{\equiv}\text{CCH}_2\text{OMe} \xrightarrow[\text{2. RX}]{\text{1. }(i\text{-Pr})_2\text{NLi}} \text{(MeS)(R)C}{=}\text{C}{=}\text{CHOMe} \qquad (43)$$

$$\text{MeSC}{\equiv}\text{CCH(OEt)}_2 \xrightarrow[\text{2. RX}]{\text{1. Et}_2\text{NLi}} \text{(MeS)(R)C}{=}\text{C}{=}\text{C(OEt)}_2 \qquad (44)$$

3. *Electrophilic substitution of silicon and tin derivatives*

Rearrangement accompanies electrophilic substitution of propargylic and allenic silanes as summarized in equations (45) and (46)[196–199]. Similarly, iodination of tin derivatives occurs with rearrangement as shown in equations (47) and (48)[200].

$$\text{Me}_3\text{SiCH}_2\text{C}{\equiv}\text{CH} \xrightarrow{\text{ClSO}_3\text{SiMe}_3} \text{H}_2\text{C}{=}\text{C}{=}\text{CHSO}_3\text{SiMe}_3 \qquad (45)$$

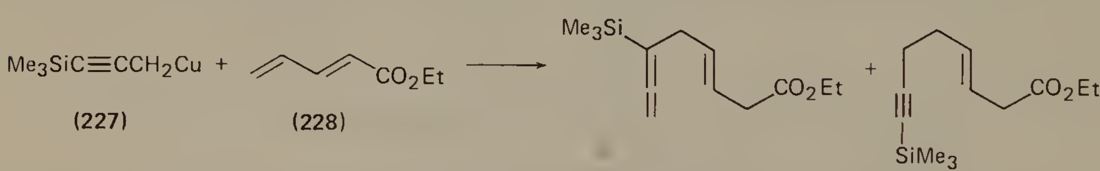
$$\text{Me}_3\text{SiCH}_2\text{C(Me)}{=}\text{C}{=}\text{C(SiMe}_3)_2 \xrightarrow{\text{MeSO}_3\text{H}} \text{Me}_3\text{SiCH}_2\text{CH(Me)C}{\equiv}\text{CSiMe}_3 \qquad (46)$$

$$\text{Ph}_3\text{SnCH(R)C}{\equiv}\text{CH} \xrightarrow{\text{I}_2} \text{RCH}{=}\text{C}{=}\text{CHI} + \text{Ph}_3\text{SnI} \qquad (47)$$

$$\text{Ph}_3\text{SnCH}{=}\text{C}{=}\text{CH}_2 \xrightarrow{\text{I}_2} \text{HC}{\equiv}\text{CCH}_2\text{I} + \text{Ph}_3\text{SnI} \qquad (48)$$

4. *Conjugate addition of copper derivatives*

3-Trimethylsilyl-2-propynylcopper (**227**) adds to unsaturated esters such as **228** to give mixtures of allenic and acetylenic adducts[201]. The isomer ratio in the products is very sensitive to the steric environment around the δ carbon of the ester **228**, but is rather insensitive to substitution at other positions along the chain.

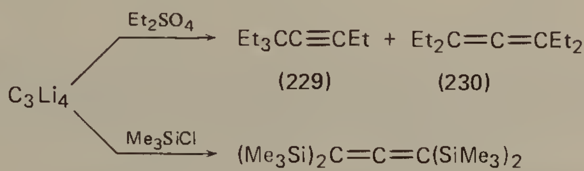


5. *Reactions of polylithium derivatives of alkynes*

The chemistry of polylithium compounds constitutes a fascinating development in organometallic chemistry, but space limitations do not permit more than a cursory treatment here. More extensive coverage can be found in recent articles[175,202,203].

Perlithiopropyne, C_3Li_4, whose properties are illustrative of the family, can be obtained by treatment of propyne with excess butyllithium[175]. Possible structures and orbital interaction patterns have been discussed, and *ab initio* calculations suggest a very curious structure[204]. Reactions with electrophilic reagents provide alkynes and allenes in proportions that depend on the reagent, the solvent, etc.

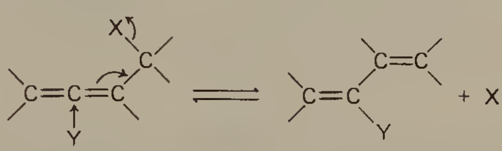
Considerable success has been achieved in rationalizing product compositions in terms of steric factors and hard–soft acid–base theory[175,202]. The proportion of allenic product increases with increasing size and increasing hardness of electrophile. For example, ethylation using diethyl sulphate provides **229** and **230** in a 4 : 1 ratio, whereas trimethylchlorosilane gives the allene **231** exclusively. Both Et_2SO_4 and Me_3SiCl are ordinarily classified as hard acids, but it appears from these results that the former is significantly softer.



(229) (230) (231)

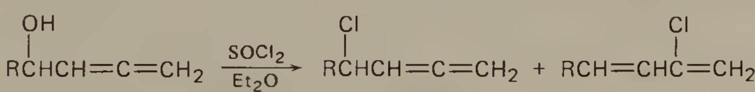
III. ALLENE–DIENE REARRANGEMENTS INVOLVING α-ALLENIC HALIDES, ALCOHOLS, ETC.

Rearrangement of allenic substrates of type **232** to the conjugated diene derivatives **233**, as well as the reverse process, have been observed. Group X may be any of the common leaving groups, and Y is a nucleophile which may be delivered from an external source or as a fragment from the leaving group X.



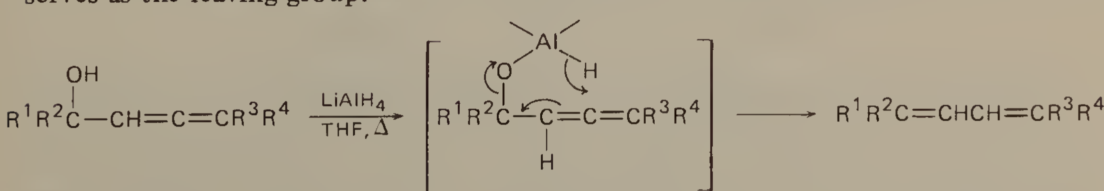
(232) (233)

Secondary α-allenic alcohols **234** react with thionyl chloride to give mixtures containing ca 45% of the unrearranged (**235**) and ca 55% of the rearranged (**236**) chloride[205]. Similarly, mixtures of the two types of halides are obtained when HCl or HBr is used. In the former case, the rearranged product is most likely formed intramolecularly from the chlorosulphite ester, whereas an intermolecular process would be aniticipated in the case of the latter reagents.



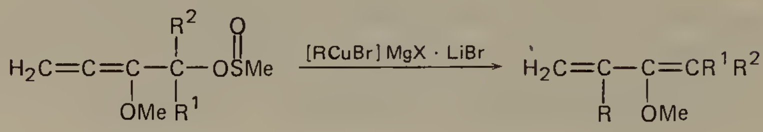
(234) (235) (236)

α-Allenic alcohols **237** are reduced to conjugated dienes **239** by heating them with $LiAlH_4$ in boiling THF[206]. A mechanism has been formulated involving the intermediate **238** in which hydride is transferred intramolecularly and $-OAlH_2$ serves as the leaving group.



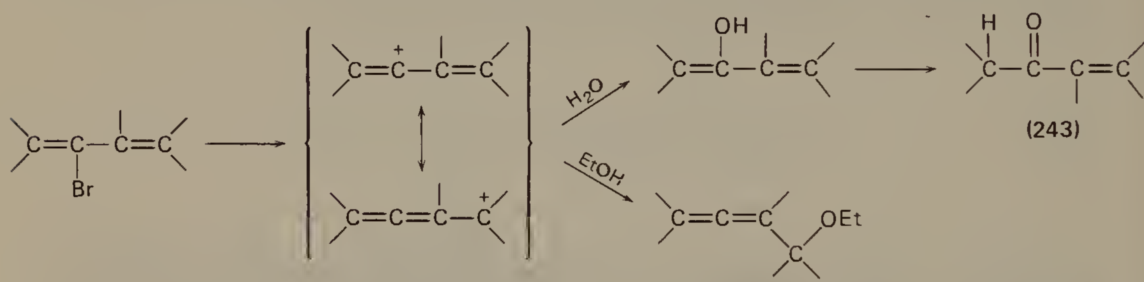
(237) (238) (239)

Methanesulphinate esters of α-allenic alcohols **240** react with organocopper derivatives to give conjugated dienes **241** in good yield[207].



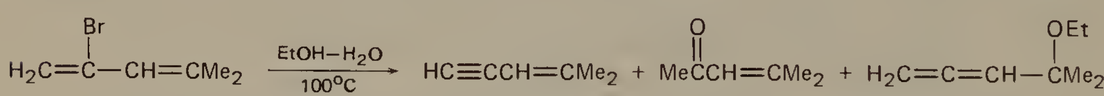
(240) (241)

The reverse of the structural changes that occur in the rearrangements considered above has been observed during the solvolysis of 2-bromo-1,3-dienes[208,209]. The reactions occur when the bromodienes are heated at 100–150° C in aqueous ethanol containing triethylamine which suppresses secondary reactions caused by the HBr liberated. Ethoxyallenes **244** and α,β-unsaturated ketones **243** are formed along with conjugated enynes, formed by elimination. Evidence from kinetic studies, solvent effects and effects of structure on reactivity support a unimolecular mechanism involving a mesomeric vinyl cation **242**[208,209]. Attack by water on the internal cationic centre leads to **243**, by way of the enol, while capture by ethanol at the terminal site provides the ethoxyallene **244**. The reason for the absence of 2-ethoxy-1,3-dienes and allenic alcohols is not clear.

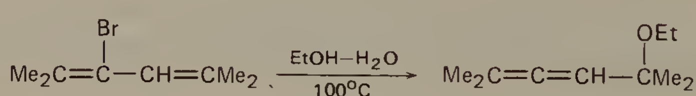


(242) (243) (244)

Ethoxyallenes are the dominant products, typically constituting more than 50% of the product mixture, as illustrated for 2-bromo-4-methyl-1,3-pentadiene (**245**), in which **246**, **247** and **248** are formed in the ratio 29:16:55. Interestingly **250** is the sole product obtained from **249**[208].

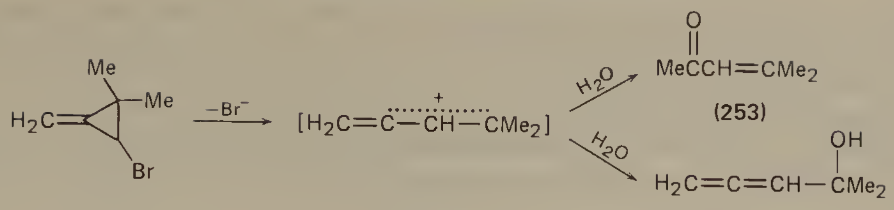


(245) (246) (247) (248)



(249) (250)

The same type of mesomeric cation is generated by solvolysis of 2-methylenecyclopropyl bromides such as **251**[210]. The solvolyses are carried out at 80° C in aqueous dioxane containing suspended $CaCO_3$, and give α,β-unsaturated ketones and α-allenic alcohols. Cation **252**, which arises from **251** through bromide loss and ring-opening, reacts with water at the charged sites to give **253** and **254**. Allenic

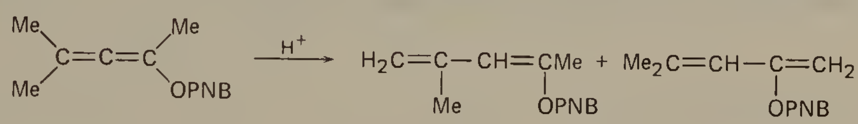


(251) (252) (254) (253)

alcohols predominate in the products: e.g. **254** is obtained in 61% yield. Formation of allenic alcohols in these reactions makes their total absence from the solvolysis products of 2-bromo-1,3-dienes even more interesting.

IV. ACID-CATALYSED REARRANGEMENTS

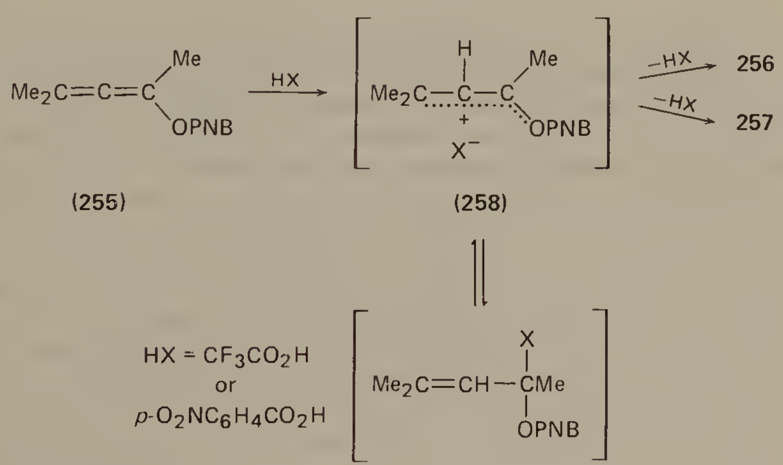
Acid-catalysed rearrangement of allenes to conjugated dienes occurs under relatively mild conditions. Allenic esters such as **255** rearrange to the conjugated derivatives **256** and **257** when they are warmed with *p*-nitrobenzoic acid or trifluoroacetic acid[211]. The reaction is very rapid with the latter catalyst. When the



(255) (256) (257)

PNB = *p*-nitrobenzoyl

rearrangement was carried out in the presence of ^{14}C-labelled *p*-nitrobenzoic acid, the dienol esters **256** and **257** contained labelled *p*-nitrobenzoate corresponding to ca 50% exchange. The findings can be rationalized by the mechanism outlined in scheme 9. Proton addition to the central allenic carbon of **255** giving the resonance-stabilized cation **258** followed by proton loss is one possible path to **256** and **257**, but it cannot be the only one because it fails to account for the incorporation of labelled *p*-nitrobenzoate. These results can be accounted for by postulating the



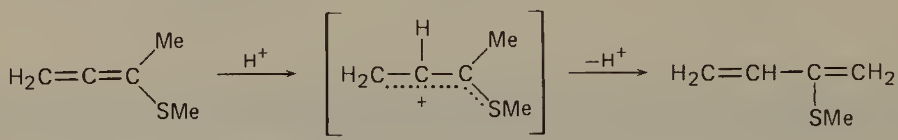
(255) (258) (259)

HX = CF_3CO_2H or p-$O_2NC_6H_4CO_2H$

SCHEME 9.

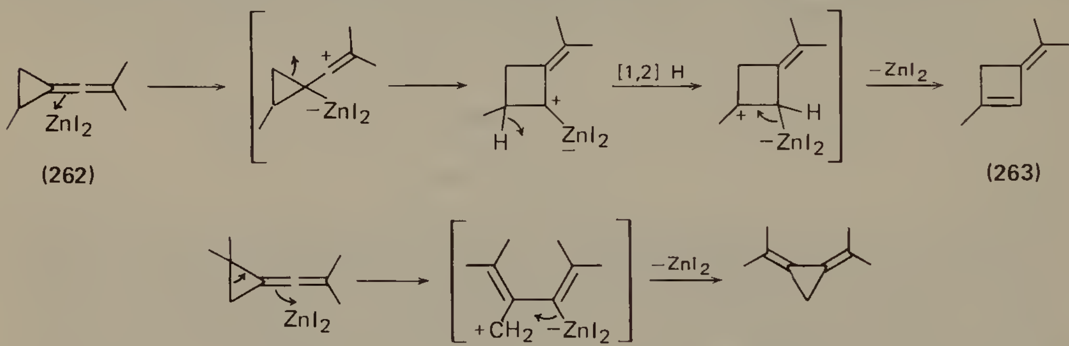
existence of 259, formed by addition of X⁻ to the cation 258. The formation of 256 and 257 from 259 can occur directly by elimination, or by dissociation back to 258 followed by proton loss[211].

Rearrangement of the allenic thio ether 260 to 261 occurs under mild conditions in the presence of a trace of *p*-toluenesulphonic acid or picric acid[212]. Analogous behaviour is exhibited by higher homologues of 260.



(260) (261)

Alkenylidenecyclopropanes undergo interesting rearrangements in the presence of zinc iodide in ether[213]. 3-Isopropylidene-1-methylcyclobutene (263) is formed from 262, while 1,2-diisopropylidenecyclopropane (265) is obtained from 264; both products are formed in virtually quantitative yield. Mechanisms which account for these products are outlined in Scheme 10 where, for simplicity, a single contributing structure is shown for intermediate ions.

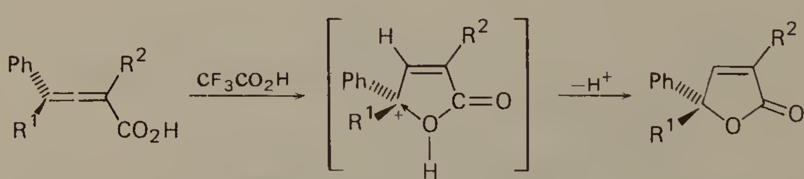


(262) (263)

(264) (265)

SCHEME 10.

Allenes with suitably located electron-donating groups give cyclic products by acid-catalysed rearrangement. 3-Phenylallene carboxylic acids 266, for example, give α,β-unsaturated lactones 268 upon treatment with trifluoracetic acid at room temperature[214]. Optically active acids 266 lead to optically active lactones 268 with the configuration shown, indicating that the cation 267 is formed preferentially by electrophilic attack *anti* to the carboxyl group and that cyclization is rapid[214].

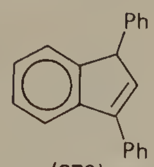


(266) (267) (268)

1,3-Diphenylindene (270), which is one of the products formed by acid treatment of triphenylallene (269), can be accounted for in terms of an intramolecular electrophilic substitution[215].

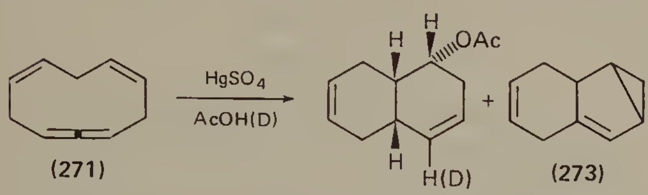
$Ph_2C{=}C{=}CHPh$

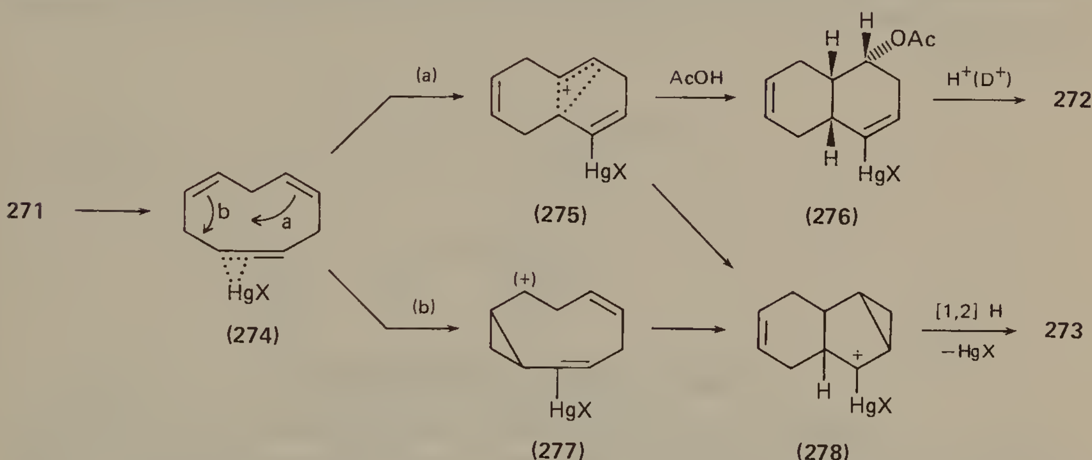
(269)



(270)

Rearrangement involving transannular participation occurs when 1,2,5,8-cyclodecatetraene (271) is treated with mercury(II) sulphate and acetic acid[216,217]. In contrast to most oxymercurations, only rearranged products, 272 and 273, are obtained with this and related cyclic allenes. When the reaction is carried out in acetic acid O-d, deuterium is incorporated in 272 at position 5, but 273 is

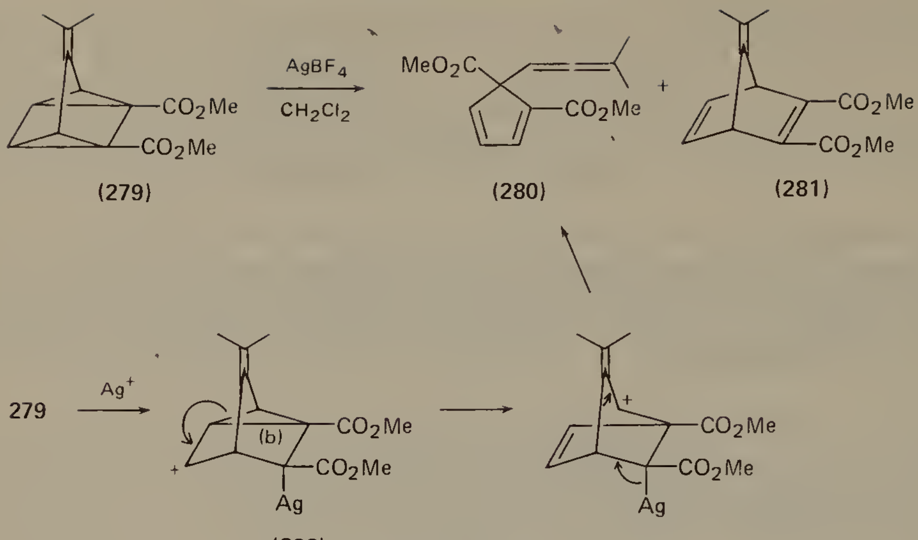




SCHEME 11.

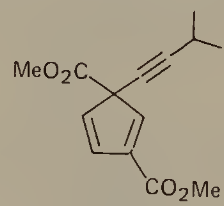
nondeuterated. The results can be rationalized by the mechanisms summarized in Scheme 11. Transannular participation (path a) in the initial complex 274 leads to the bridged ion 275 which may react with solvent to give 276. Demercuration of 276 by addition–elimination accounts for deuterium incorporation at this position. Homoallyl–cyclopropylcarbinyl rearrangement of 275 leads to cation 278, which may be considered to be a metal-complexed carbene. Hydride shift and elimination of HgX complete the sequence to 273. Path (b) involving homoallyl–cyclopropylcarbinyl rearrangement of 274 followed by transannular rearrangement is another possible route to 278[217].

When the tetracyclic diester 279 is stirred for 2 days with $AgBF_4$ in dichloromethane, a 3:1 mixture of 280 and 281 is formed[218]. A possible mechanism for the formation of 280 is shown in Scheme 12; formation of 281 can also be



SCHEME 12.

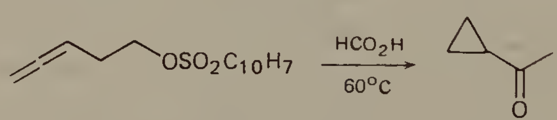
rationalized in terms of intermediate **282** by postulating cleavage of bond (b) of the cyclopropyl ring. The allene derivative **280** undergoes an unusual thermal rearrangement to **283**.



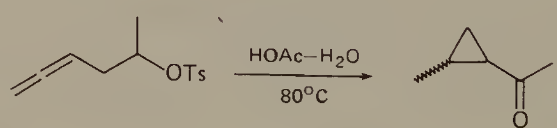
(283)

V. HOMOALLENIC PARTICIPATION

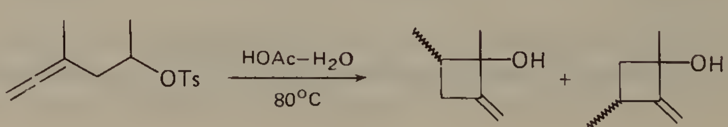
The ability of β-allenic groups to participate effectively in solvolysis reactions in a manner comparable to homoallylic participation has been demonstrated in a variety of studies. In the initial studies suggesting the possibility of participation, cyclopropyl and cyclobutyl derivatives were reported as products of solvolysis of β-allenic substrates, as summarized in equations (49)–(51)[219-221]. Subsequent



(49)



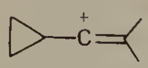
(50)



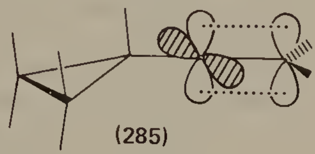
(51)

workers have verified that these products are formed, along with numerous other ones, particularly in the reactions summarized in equations (50) and (51). Non-rearranged products are obtained when potent nucleophiles such as azide ion are present[222].

A great deal of evidence has been accumulated which indicates that cyclopropylvinyl cations (284) are intermediates in these reactions. Some have argued that these cations are the first-formed intermediates, while others postulate methylenebicyclobutonium ions as precursors of the cyclopropylvinyl cations. We shall examine some of the evidence pertinent to the question.

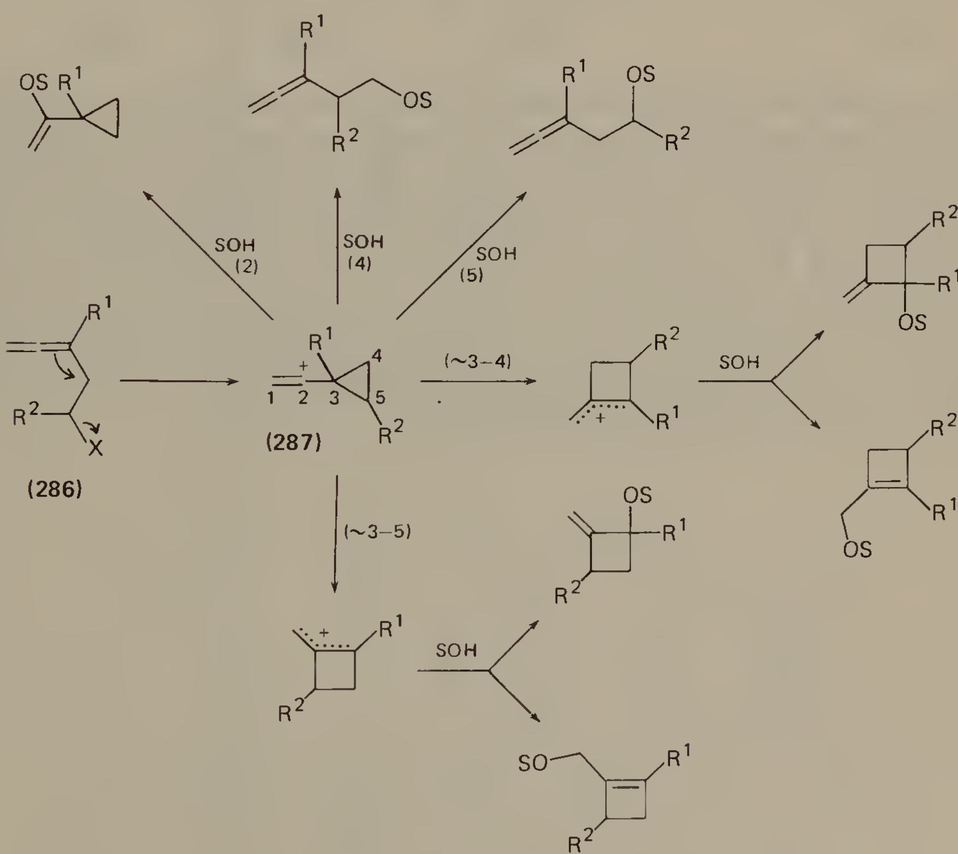


(284)



(285)

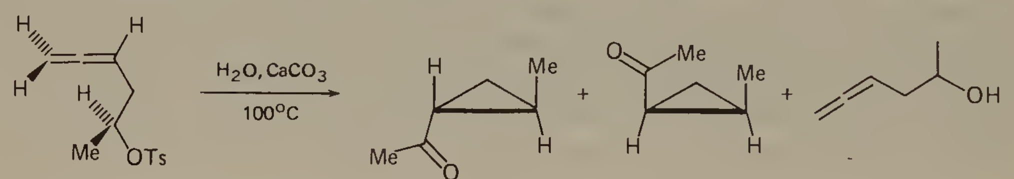
Cyclopropylvinyl cations apparently are most stable in the linear, bisected conformation **285**, presumably because of the charge delocalization made possible by overlap of the vacant orbital (shaded) with the adjacent ring bonds[223]. The basic aspects of the mechanism in which a cation of type **284** is postulated to be the first-formed intermediate are summarized in Scheme 13, where SOH represents



SCHEME 13.

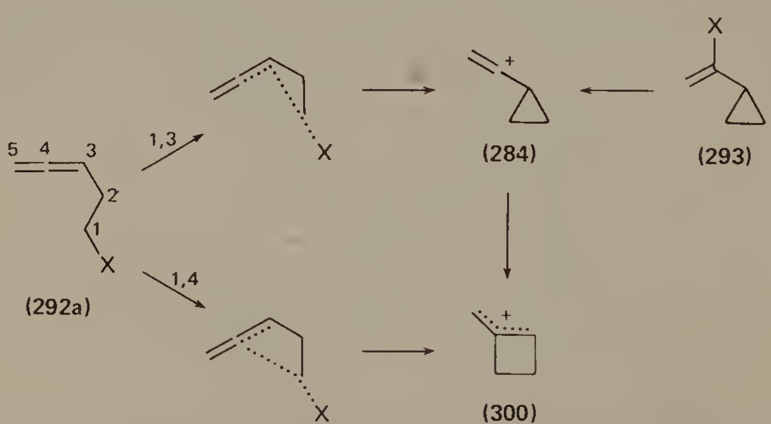
solvent and the numbers in parentheses beside the arrows represent the position of solvent attack on 287, or the bond in 287 which migrates to give a cyclobutyl derivative. No indication of stereochemistry is included, but in products where geometric isomerism is possible, mixtures of *cis–trans* isomers are generally produced. Also, elimination products, such as cyclopropylacetylenes, are not included. It should be noted that the substitution pattern of the allenyl substrate, the nature of the solvent, and the reaction conditions strongly influence the proportions of the various products formed.

Inversion of configuration at the functional carbon was demonstrated by the formation of ketones 289 and 290 upon hydrolysis of (*S*)-1-methyl-3,4-pentadienyl tosylate (288)[224,225]. The ketones were formed without loss of optical purity, thus providing strong evidence for participation by the allenyl group. Interestingly, the allenic alcohol 291 was racemic. Ketones 289 and 290 with the same configuration and optical purity were obtained when 288 was subjected to acetolysis followed by $LiAlH_4$ reduction, but in this case the allenic alcohol 291 showed a slight excess (3.1%) inversion[225].



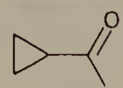
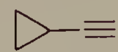
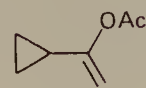
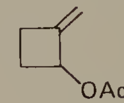
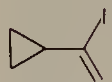
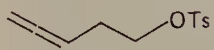
(288) (289) (290) (291)

The products of solvolysis of β-allenic halides have been found to correspond closely to those from the corresponding cyclopropylvinyl halide when the reactions are carried out under similar conditions[226,227]. This can be seen by comparing the distribution of products from the reaction of silver acetate in HOAc with 5-iodo-1,2-pentadiene (292a) and with 1-cyclopropyl-1-iodoethylene (293) (Table 1). With the exception of methyl cyclopropyl ketone (294) and 3,4-pentadienyl acetate (297), the product compositions are seen to be remarkably similar, and the two discrepancies are easily accounted for. The excess acetate 297 from 292a can be attributed to an independent pathway involving displacement by solvent. It was also shown that 293 reacts with AgOAc to give methyl cyclopropyl ketone by an undefined route parallelling the ionization route.



SCHEME 14.

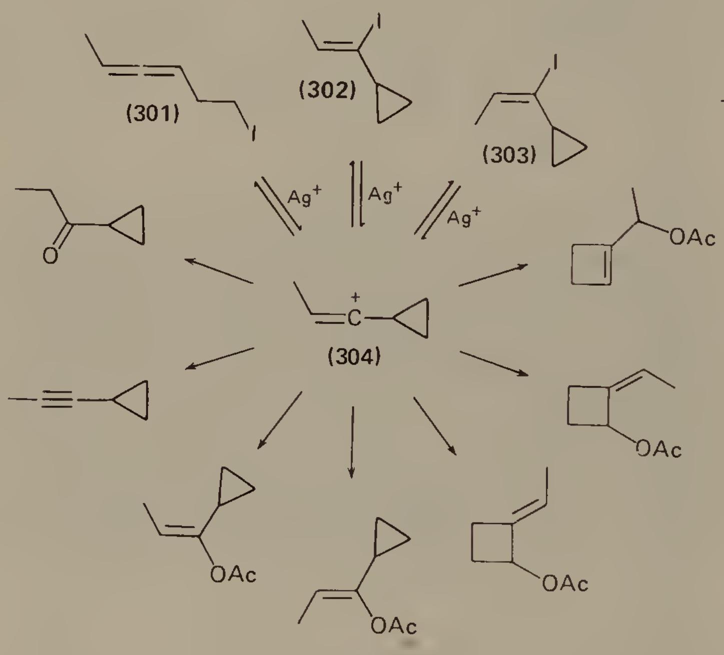
TABLE 1. Acetolysis products from 3,4-pentadienyl substrates (**292**) and 1-cyclopropyl-1-iodoethylene (**293**)

Reactant	Conditions	Products (%)					
							
		(**294**)	(**295**)	(**296**)	(**297**)	(**298**)	(**299**)
 (**292a**)	AgOAc, HOAc, 25° C	4.8	23	61.5	9.4	1.21	0.14
 (**293**)	AgOAc, HOAc, 25° C	12.6	27	58.2	0.97	1.15	0.13
 (**292b**)	HOAc, NaOAc, 100° C	55.9	0.92	0	37.8	4.67	0.38

The possibility must be considered that at least part of the cyclobutyl products **298** and **299** arise from **292a** by a 1,4-cyclization route which gives the cyclobutyl ion **300** directly (Scheme 14). It was shown in separate experiments that the ion **300** gives only cyclobutyl products, and consequently the close correspondence in the amounts of cyclobutyl products **298** and **299** formed from **292a** and **293** is taken to mean that cyclization of **292a** by the 1,4 route is insignificant[226].

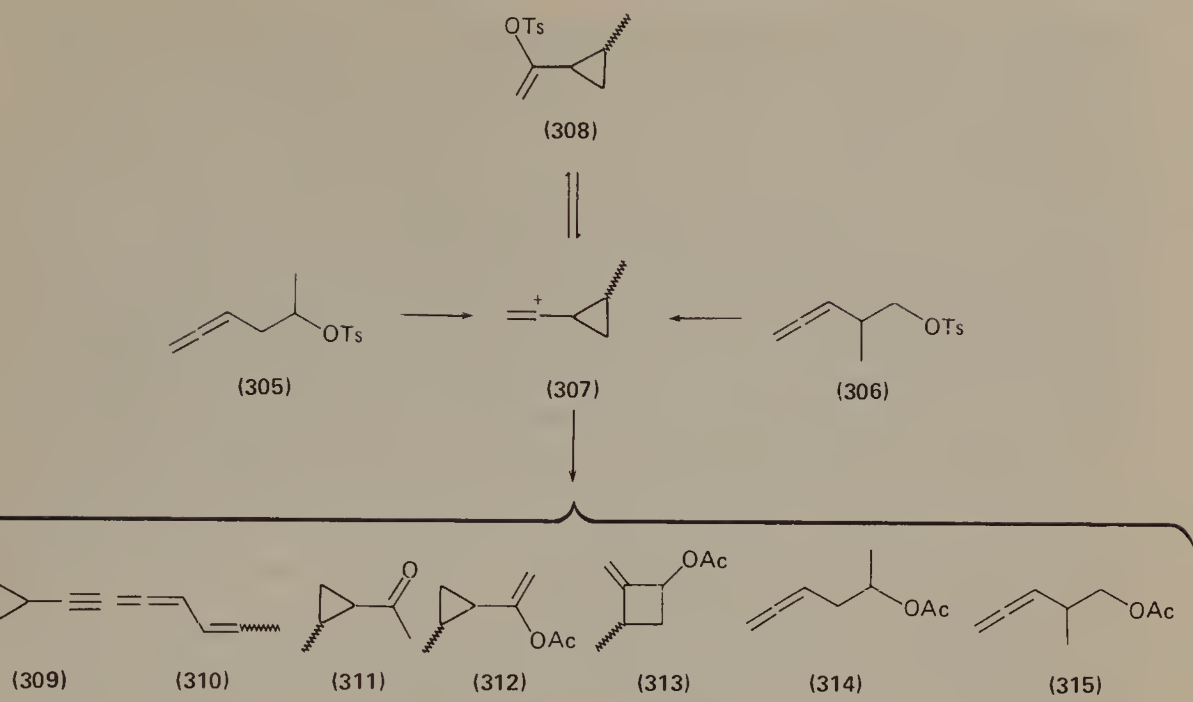
The enol acetate **296** reacts with acetic acid at 100° C to give methyl cyclopropyl ketone (**294**). This accounts for the absence of **296** and the high percentage of **294** from the acetolysis of the tosylate **292b** (Table 1). Furthermore, the acetylene **295** is unstable under the conditions for acetolysis of the tosylate. The solvent-assisted route plays a larger role, and ring-expansion to give cyclobutyl products is also somewhat more significant under these conditions.

The conclusions drawn from these studies are strongly reinforced by studies of the methyl-substituted homologues **301**, **302** and **303**. The distribution of cyclic products obtained (Scheme 15) when these iodides are treated with silver acetate in acetic acid at 25° C is practically identical in all three cases. Again the results can be rationalized in terms of the cation **304** as the first-formed intermediate[227].



SCHEME 15.

Unlike other simple homoallenic substrates, 1- and 2-methyl-3,4-pentadienyl tosylates **305** and **306** show complex kinetic behaviour upon acetolysis (Scheme 16)[228–230]. In the case of **305**, the integrated rate constant decreased rapidly during the reaction whereas with **306** a steady increase occurred. It was suspected that return-rearrangement to the cyclopropyl derivative **308** was responsible for this behaviour, and in fact when the acetolysis of **305** was interrupted before completion the rearranged tosylate **308** was isolated. Furthermore **306** was shown to rearrange to both **305** and **308** during acetolysis[230]. In a separate experiment, tosylate **308** (*cis, trans* mixture) was synthesized and subjected to acetolysis[230]. The spectrum of



SCHEME 16.

products **309–315** was the same from all three substrates, although the proportion of cyclopropyl products, particularly the *trans* ketone **311**, was substantially greater in the case of **308**. Again the products can be accounted for satisfactorily in terms of the intermediate cyclopropylvinyl cation, **307**.

Particularly interesting is the composition of the allenyl acetate fraction. In the case of **305** and **308**, only traces of the primary acetate **315** were formed, while the secondary acetate **314** constituted 55% and 28% respectively of the acetolysis products. Less than 4% **315** was formed from the primary tosylate **306** while the secondary acetate **314** made up 40% of the product, signifying that the solvent displacement route is of minor importance in this case. The preponderance of **314** from these reactions implies that the charge distribution in the cyclopropyl ring of cation **307** is unsymmetrical, with the greater charge residing on the carbon bearing the methyl group. The methyl group in **306** exerts a significant accelerating effect, e.g. the rate of acetolysis at 85° C is approximately 16 times that of the unsubstituted derivative, 3,4-pentadienyl tosylate. This effect is understandable on the basis of the charge delocalization in the ion **307**.

Unlike **305** and **306**, the solvolysis of **308** is strictly first order, and the observed rate constant for its disappearance agrees well with the value calculated to explain the kinetic behaviour of **305** and **306**. Rearrangement to **305** or **306** does not occur during the solvolysis of **308**[230].

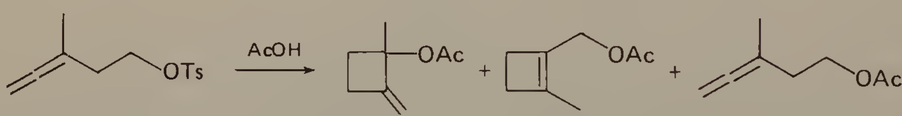
It is postulated that differences in the location of the tosylate counterion of **307**, depending on whether the ion pair is formed from **305**, **306** or **308**, may be responsible for the differences in product distributions, and for the differences in the facility of return vs product formation[230].

The effect of methyl substituents on homoallenic participation has been determined by several groups[225,228,229,231-233]. The rate constant for the neighbouring-group participation component, k_Δ, is given by $(k_t - k_s)$ where k_t is the titrimetric rate constant and k_s is the solvent-assisted component. Jacobs and Macomber used model compounds for estimating the value of k_s[228,229]. The model compounds were tosylates of saturated alcohols having the same skeleton as the homoallenic derivative, and it was assumed that k_s (allene) = k_s (model). It seems likely that k_s for the allenic derivative will be smaller than that of the saturated analogue because of the rate-retarding inductive effect of the allenic group, and the values of k_Δ obtained in this way represent lower limits to the 'true' values.

The rate constant for disappearance of 1-methyl-3,4-pentadienyl tosylate (**305**) upon acetolysis at 85° C is $1.95 \times 10^{-4}\ s^{-1}$ [230], while k_s for the model compound, 1-methylpentyl tosylate, at this temperature is $2.03 \times 10^{-4}\ s^{-1}$ [228]. Apparently this is a case where acceleration by participation just balances the inductive retardation. However, Santelli and Bertrand have estimated that $k_\Delta/k_s = 5.06$ based on the excess of inversion (3%) that occurs in the acetolysis of optically active **305**[225].

A marked acceleration is produced by the methyl group at position 2 in **306**. If the most recent value of the rate constant for disappearance of **306** upon acetolysis at 85° C[230] is used for k_t, one calculates k_Δ to be $9.69 \times 10^{-5}\ s^{-1}$. This value is approximately 36 times greater than the value of k_Δ for the unsubstituted derivative, 3,4-pentadienyl tosylate (**292b**)[228].

Alkyl substituents at position 3 as in **316** increase the rate of solvolysis and also shift the product distribution in favour of cyclobutyl derivatives. The value of k_Δ for acetolysis of **316** is 3.77 times that of the unsubstituted tosylate **292b**, and the products consist of the cyclobutyl derivatives **317** and **318**, and the unrearranged



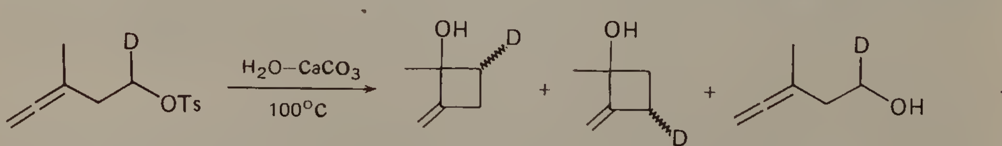
(316) (317) (318) (319)

acetate **319**[228,233]. Stabilization of the cyclobutyl cation **320** by the methyl group is the most likely reason for the increased proportion of cyclobutyl products. It has been pointed out that the initial cation formed by ring-expansion of

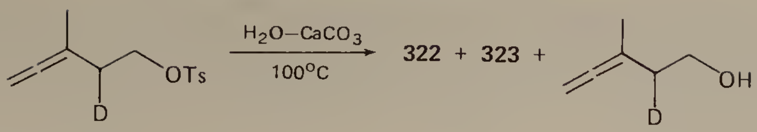
(320)

cyclopropylvinyl cations is a 'buckled' methylenecyclobutyl cation in which very little allylic delocalization is possible because the π system is nearly orthogonal to the newly generated p orbital at position 3[226]. Relaxation to a planar geometry must occur before full allylic stabilization is possible. On this basis the methyl group should play an important role in stabilizing the initial cation **320**.

Hydrolysis of the labelled tosylate **321** gives the cyclobutyl derivatives (75% yield) **322** and **323** in a 40:60 ratio, along with unrearranged alcohol **324**

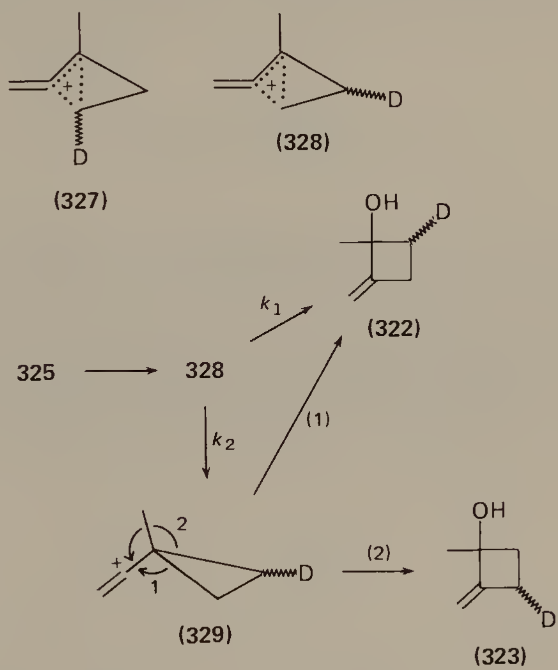


(321) (322) (323) (324)



(325) (326)

(25%), whereas under the same conditions, **325** provides **322** and **323** in the same total yield, but in the ratio 60:40[222]. Alcohol **326** constitutes the remainder of the product in the latter case. The fact that **322** and **323** are not formed in a 50:50 ratio in these reactions is taken as evidence that the cyclopropylvinyl cation **329** cannot be the first-formed intermediate, and the authors propose instead the initial formation of the methylenebicyclobutonium ion **327** from **321** and **328** from **325**[234]. Their analysis of the distribution of products for hydrolysis of **325** is shown in Scheme 17. If isotope effects are ignored, rearrangement of **329** would be



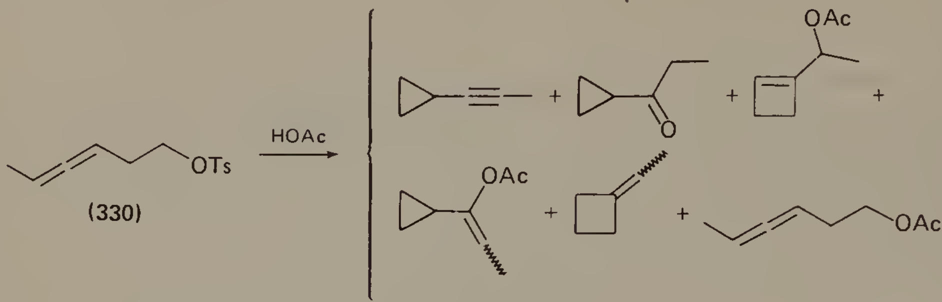
SCHEME 17.

expected to give equal amounts of **322** and **323**. The fact that **322** is formed in greater amount than **323** implies that an alternate pathway exists to **322**, and this is proposed to be solvent capture by **328**. Based on the 60:40 ratio of products, it is calculated that $k_2 = 4\,k_1$.

The formation of unequal amounts of **322** and **323** can be rationalized on the basis of an unsymmetrical location of the tosylate counterion associated with the cyclopropylvinyl cation **329**, without invoking the bicyclobutonium ion **328**[230].

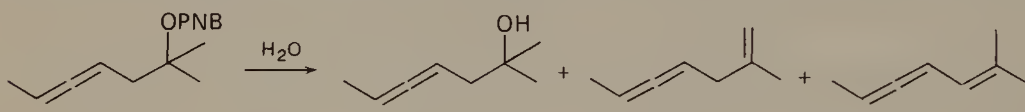
The absence of rearranged allenic alcohols in these reactions is perplexing. Thus, one would anticipate mixtures of **324** and **326** from the hydrolysis of either **321** or **325**.

Significant rate enhancement is produced by alkyl groups at position 5 of the homoallenyl system. Thus the value of k_Δ for acetolysis of 3,4-hexadienyl tosylate (**330**), which gives the complex mixture of products indicated, is 3.20 times that of the parent tosylate[228].



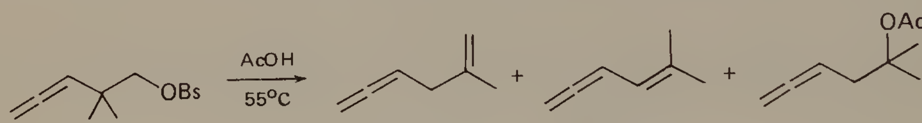
(330)

Only unrearranged alcohols and elimination products were obtained from the hydrolysis of the tertiary derivative **331**[228]. In this case the developing tertiary

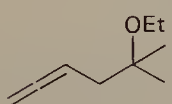


(331)

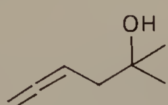
cation is stable enough not to require assistance from the allenyl group. The rate of hydrolysis of **331** was only ca one-third that of analogous saturated tertiary derivatives, presumably reflecting the inductive withdrawal by the allenyl group. Cyclic products were also absent from the solvolysis of 2,2-dimethyl-3,4-pentadienyl brosylate (**332**) under a variety of conditions, but in this case all of the products possessed rearranged skeletons[231]. Thus, the tertiary acetate **335** is the



(332) (333) (334) (335)



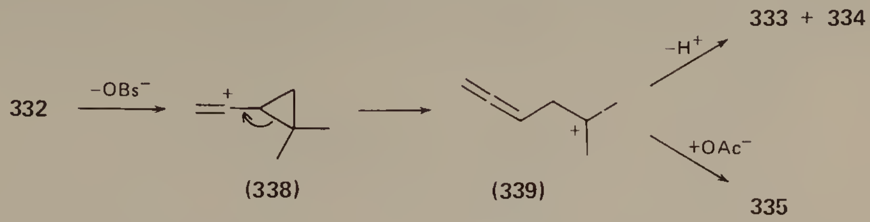
(336)



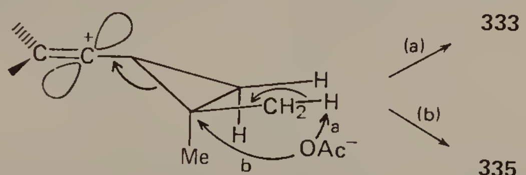
(337)

principal product of acetolysis, accompanied by smaller amounts of the rearranged hydrocarbons **333** and **334**. Similarly, the ether **336** and the alcohol **337** are the major products of ethanolysis and hydrolysis, respectively, the remainder being hydrocarbons **333** and **334**. Careful examination failed to reveal the presence of cyclic products or products with nonrearranged skeletons. Solvent-assisted displacement does not occur with **332** because of steric hindrance, and furthermore its reaction rate in solvents of equivalent ionizing power is unaffected by changes in the nucleophilicity of the medium. The *gem* dimethyl groups greatly increase the rate of the k_Δ process; e.g. **332** is approximately 350 times as reactive as 3,4-pentadienyl β-naphthalenesulphonate toward acetic acid at 60° C[231].

One reasonable mechanism for the solvolysis of **332** involves ring-opening of the initially formed cyclopropylvinyl cation **338** to the stable tertiary cation **339**, which can give trienes **333** and **334** by proton loss or **335** by acetate capture.

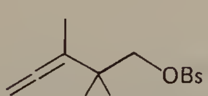


However, the preponderance of nonconjugated trienes over the conjugated isomers in all the cases studied suggests the possibility of product formation directly from the cyclopropylvinyl cation **338** as indicated in Scheme 18[235].

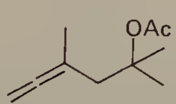


SCHEME 18.

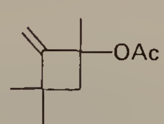
Small amounts of products containing a cyclobutane ring do arise in the solvolysis of 2,2,3-trimethyl-3,4-pentadienyl brosylate (**340**)[232,235]. Acetolysis of **340** at 55° C gave a complex mixture in which the rearranged tertiary acetate **341** predominated (66%), but which also contained the cyclobutyl derivatives **342**, **343** and **344** (2.0, 0.6 and 2.0% respectively) and three acyclic trienes **345**, **346** and **347**



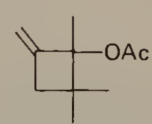
(340)



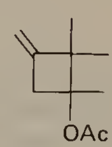
(341)



(342)



(343)



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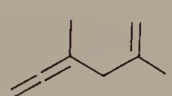

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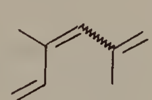
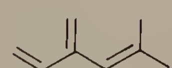
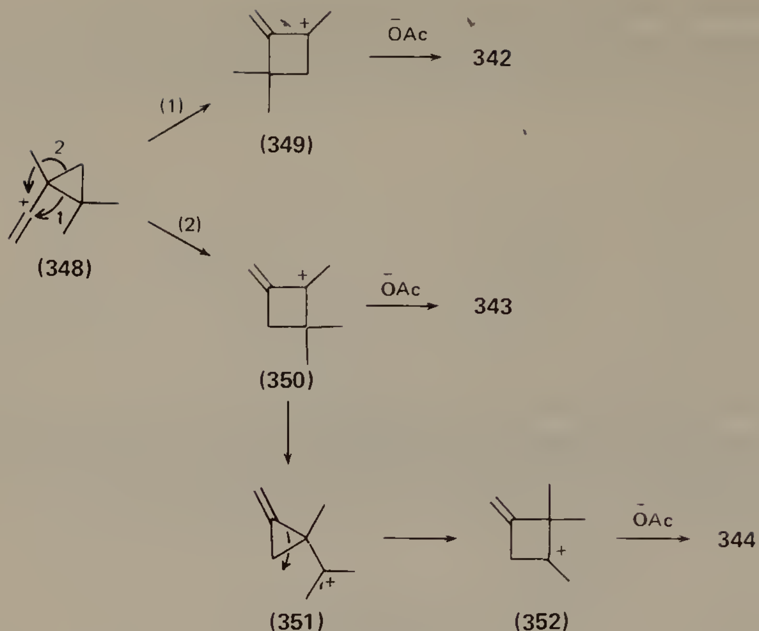


(346)

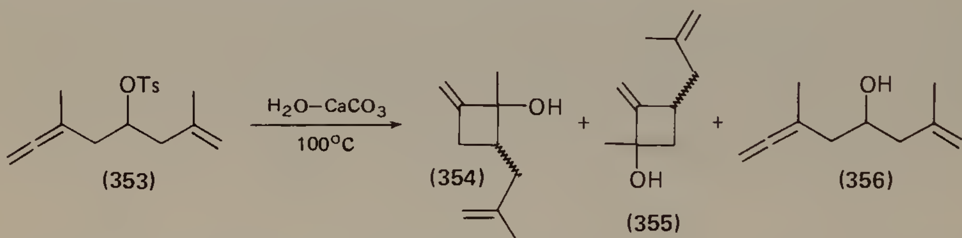


(347)

(16%, 9.0% and 3.7%). The acyclic acetate **341** and triene **345** can be accounted for in terms of the mechanisms discussed for the solvolysis of **332**. Ring-expansion of the cyclopropylvinyl cation **348** to give the two cyclobutyl cations **349** and **350** can account for the formation of **342** and **343**. The formation of **344** requires a more deep-seated rearrangement, and one possibility involves successive ring-contraction to **351** and expansion to **352**[235].



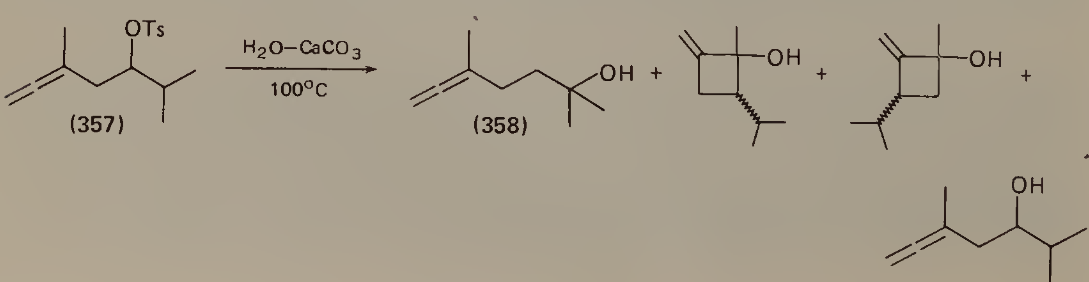
Kinetic studies indicate that homoallenic participation is more effective than the homoallylic counterpart[231], and support for this proposal is provided by the product distribution from substrates in which the two processes can compete. Thus, hydrolysis of **353** gives methylenecyclobutanols **354** and **355** (products of homoallenic participation) and nonrearranged alcohol **356**[236].



Extensive compilations of activation parameters have appeared for reactions involving homoallenic participation[228–233,237].

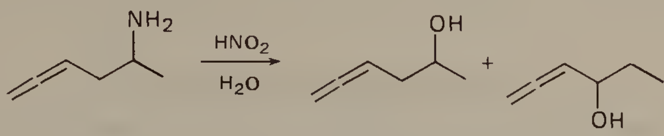
Solvolysis of a variety of cyclic substrates, e.g. 2-allenylcycloalkyl[237,238], 2-vinylidenecyclohexylcarbinyl[239] and 3,4-cyclononadienyl[238] arenesulphonates, in general gives product mixtures comparable to those obtained from acyclic analogues.

Hydride migration competes effectively with homoallenyl participation in the hydrolysis of **357**, as evidenced by the fact that alcohol **358** is the major product[222]. It is proposed that steric congestion around the functional carbon hinders



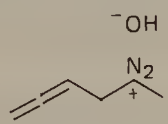
homoallenyl participation, and hydride participation is able to compete because of the stable tertiary cation that is formed.

Homoallenyl participation does not occur in the deamination of 4,5-hexadien-2-amine (**359**), the only products being the nonrearranged alcohol **360** and the alcohol resulting from hydride shift, **361**[240,241]. The absence of participation is attributed to the formation of the highly energetic ion pair **362** in a conformation



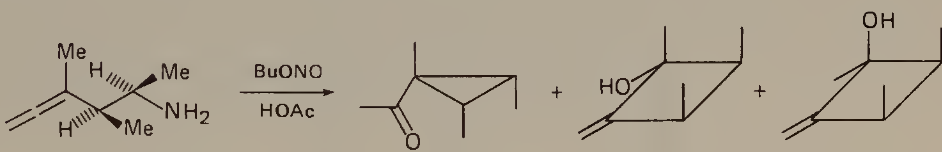
(359) (360) (361)

which is not suitable for homoallenic participation. Collapse to give **360**, or hydride shift to give **361**, takes place before rotation can occur to give a conformation in which interaction with the π bond is possible[234]. However, participation has been



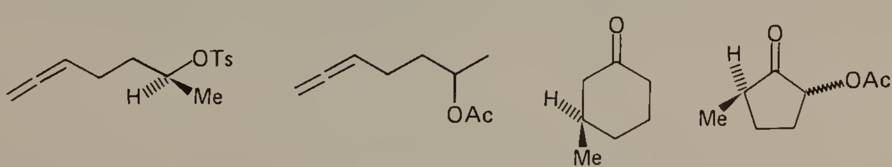
(362)

observed with substituted derivatives of **359**[241,242]. For example, cyclic compounds **364**–**366** constitute the bulk of the product from the *threo* amine, **363**, and each of these is formed with inversion of configuration at the functional carbon[242].



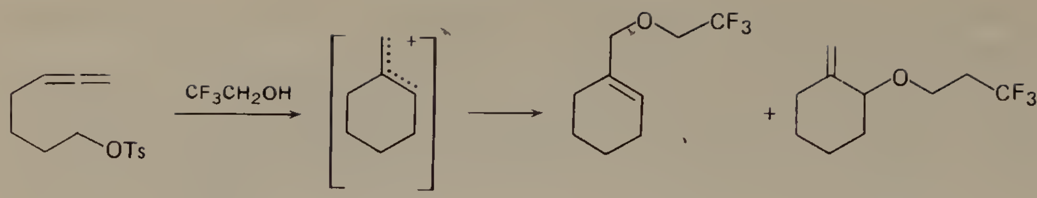
(363) (364) (365) (366)

Finally, participation has been demonstrated to occur in the solvolysis of γ-allenic substrates[243,244]. The products from acetolysis of (*S*)-1-methyl-3,4-hexadienyl tosylate (**367**) are the acetate **368**, with 89% inversion of configuration, and the cyclic derivatives **369** and **370**. The cyclic products are formed with inversion



(367) (368) (369) (370)

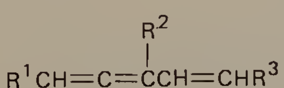
of configuration at the functional carbon, and the reaction proceeds without significant loss of optical purity[244]. Efficient participation has been observed for an allenyl group even more remotely removed from the functional carbon[245]. Trifluorethanolysis of **371** gives **373** and **374**, presumably by way of the 2-methylenecyclohexyl cation **372**.



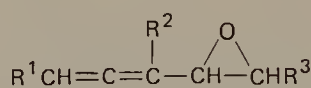
(371) (372) (373) (374)

VI. OXIDATIVE CYCLIZATION

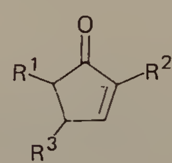
Attack by per acids occurs exclusively on the olefin functions of 1,2,4-pentatriene (375a) giving the allenyloxirane **376a**[246]. The same type of behaviour is observed for trienes bearing an alkyl group on the olefinic function, e.g. **375b** → **376b**, but the behaviour is changed drastically by substituents on the allenyl portion[247,248]. Thus, **375c** and **375d** give cyclopentenones **377c** and **377d** respectively with no detectable amounts of the oxiranes **376c** and **376d**. The selectivity is diminished slightly with **375e**, which furnishes **376e** and **377e** in a 5:95 ratio and it is still smaller when both functions are substituted as in **375f** which yields **376f** and **377f** in a 35:65 ratio.



(375)



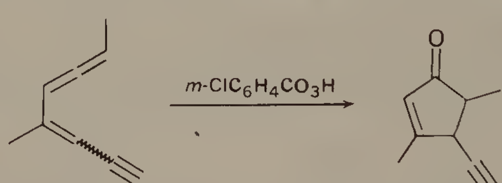
(376)



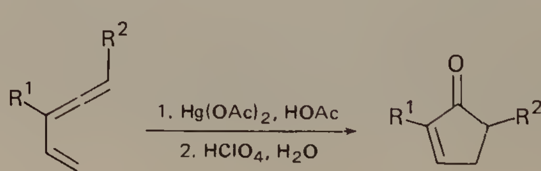
(377)

	R^1	R^2	R^3
(a)	H	H	H
(b)	H	H	Me
(c)	H	Me	H
(d)	H	Pr	H
(e)	Pr	H	H
(f)	H	Me	Me

The reaction has promise for synthetic work, and it has been extended to 1,2,4-trien-6-ynes as illustrated by the conversion of **378** to **379**[249]. A complementary method for converting 1,2,4-trienes to cyclopentenones involves treatment with mercuric acetate followed by dilute perchloric acid (equation 52)[250].

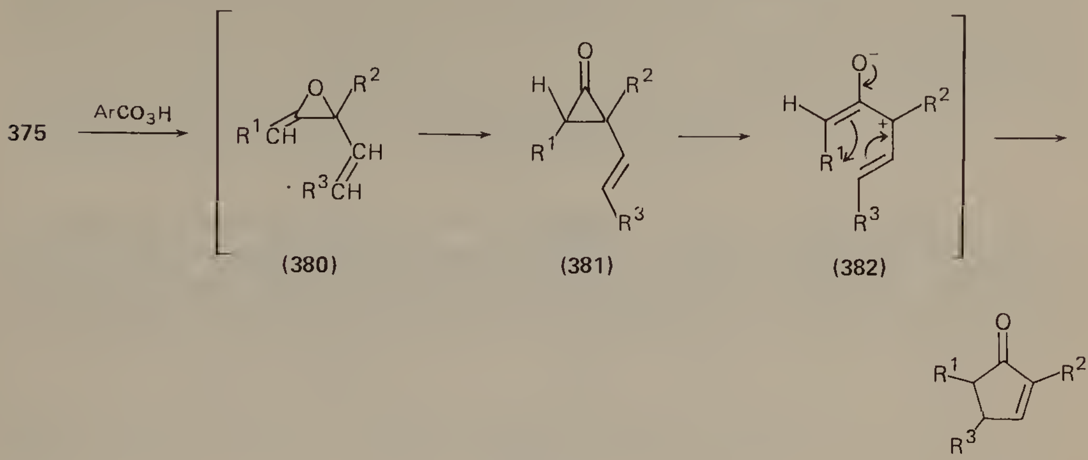


(378) (379)



(52)

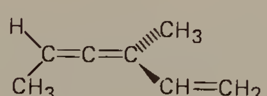
The mechanism originally proposed for the conversion of 1,2,4-trienes to cyclopentenones by peracids consists of the sequence of steps outlined in Scheme 19.



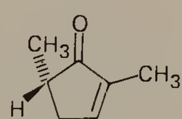
(380) (381) (382) (377)

SCHEME 19.

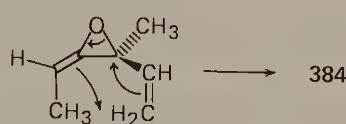
Allene epoxides have been shown to rearrange to cyclopropanones[251,252], thus providing a precedent for the postulated rearrangement of **380** to **381**, and, in cycloaddition reactions, cyclopropanones appear to undergo ring-opening initially to a tautomeric dipolar structure analogous to **382**[253,254]. Recent stereochemical evidence, however, argues strongly against this mechanism and indicates that the epoxide **380** rearranges by a concerted process[255]. Thus, oxidation of (*R*)-3-methyl-1,3,4-hexatriene (**383**) with *m*-chloroperbenzoic acid yields (*S*)-2,5-dimethyl-2-cyclopentenone (**384**), apparently with very little loss of optical purity. These results are accounted for by postulating that peracid attack on **383** occurs preferentially from the less hindered face, giving epoxide **385**, which rearranges to **384** by an allowed ($\pi^2s + \pi^2s + \sigma^2s$) process[255].



(383)

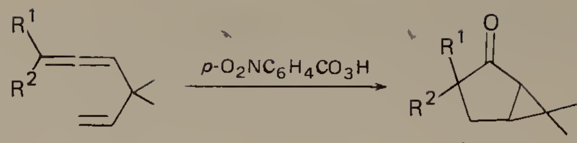


(384)



(385)

1,2,5-Trienes react with peracids analogously to 1,2,4-trienes giving bicyclo [3.1.0] hexan-2-ones as illustrated in equation (53)[256,257]. Dramatic increases in the yield of **387** are noted when the solvent is changed from dichloromethane to methanol; e.g. the percentage of **387a** in the product increases from 50 to 90 while that of **387b** increases from ca 0 to 100. This solvent effect was cited as support for a mechanism involving a dipolar intermediate analogous to **382**, which would be stabilized by solvation by methanol[257]. However, the finding that (–)-**386a** furnishes optically active product, (–)-**387a**, casts doubt on this conclusion, and suggests a concerted process instead[255,257].

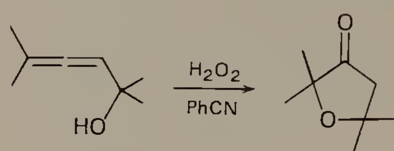


(386) (387) (53)

(a) R^1 = Me, R^2 = Et

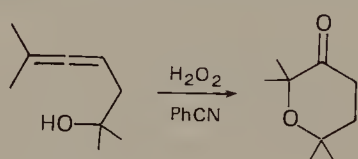
(b) $R^1 = R^2$ = Me

Oxidation of α-allenic alcohols with H_2O_2–PhCN gives 3-oxacyclopentanones, as illustrated in equation (54)[258]. Yields are excellent for tertiary, but fair to poor for secondary and primary alcohols. The behaviour of β-allenic alcohols depends on the substitution pattern. Alcohols that are disubstituted on the terminal allenic



(388) (54)

position, as in **389**, behave in the same fashion as **388** giving 3-oxacyclohexanones (equation 55)[258]. A stepwise mechanism comparable to that in Scheme 19 can be formulated for these reactions, but the finding that optically active products are obtained from active precursors (–)-**390** and (+)-**391** makes more likely a concerted

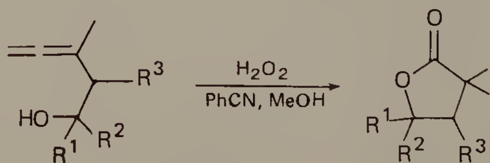


(389) (55)

process involving intramolecular nucleophilic attack on the epoxide by the hydroxyl group[255].

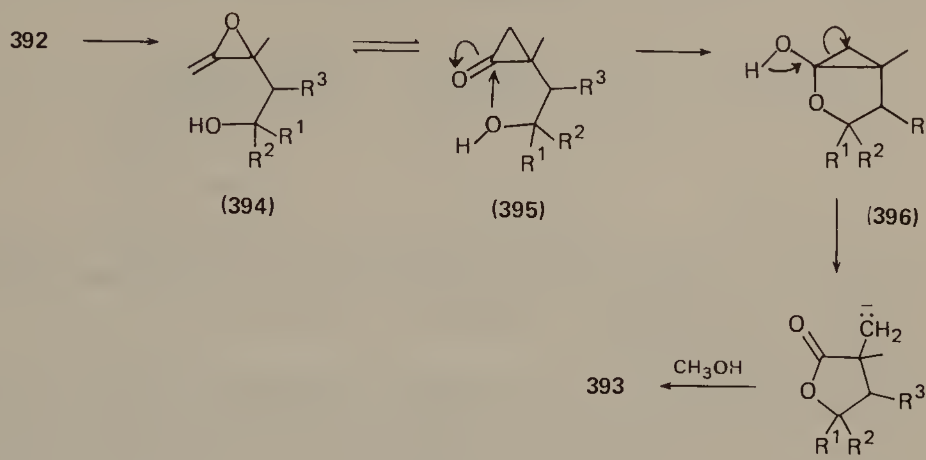
(390) (391)

β-Allenic alcohols substituted at position 3 but unsubstituted on the terminal allenic carbon undergo a more deep-seated rearrangement giving γ-lactones on oxidation with H_2O_2–PhCN[259]. For example, primary, secondary or tertiary alcohols of type **392** lead to γ-lactones **393** in yields of 80% or better. Scheme 20

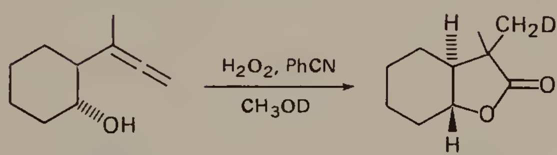


(392) (393)

summarizes a mechanism which has been proposed for the reaction. The cyclopropanone **395**, formed by rearrangement of the epoxide **394**, reacts with the neighbouring hydroxyl group to give the hemiacetal **396**. Ring-opening to give the carbanion **397** and proton abstraction from the solvent then complete the sequence. Evidence cited in support of the mechanism is the fact that deuterium is incorporated in one of the methyl groups in the product **399** obtained when CH_3OD is used as the solvent for the oxidation of **398**[259].



SCHEME 20.



(398) (399)

VII. ROTATION ABOUT THE ALLENE AXIS

1,3-Disubstituted allenes can exist in enantiomeric forms, separated by a barrier which is high enough to prevent their interconversion at ordinary temperatures and thus permits isolation of optically active forms. The height of the barrier, which has been the object of numerous theoretical calculations, has been determined experimentally from a study of the kinetics of racemization of 1,3-dimethyl-(**400a**) and

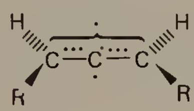
(a) R = Me

(b) R = *t*-Bu

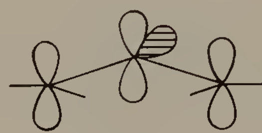
(400)

1,3-di-*t*-butyl-(**400b**) allene at elevated temperatures[260]. The first-order rate constant for isomerization of **400a** (259–309° C) is given by $\log k(\text{s}^{-1}) = 13.61 - 46{,}170/2.303\,RT$, and that for **400b** (293–323°C) by $\log k(\text{s}^{-1}) = 13.39 -$

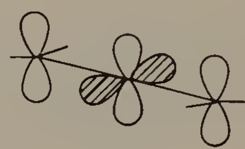
46,910/2.303 RT. The rotational barrier is significantly lower than that observed for simple alkenes (e.g. E_a = 65.0 kcal/mol for CHD=CHD[261] and 62.2 kcal/mol for *trans*-2-butene)[262], largely as a result of allylic resonance stabilization in the transition state (**401**) for isomerization of **400**[260]. By assuming that the methyl groups of **400a** lower the barrier by the same amount as they do in 2-butene, i.e. 65.0 – 62.2 = 2.8 kcal/mol, the rotational barrier in allene itself is estimated to be approximately 49 kcal/mol[263]. This value is in good agreement with those obtained from recent theoretical calculations[263–265].



(401)



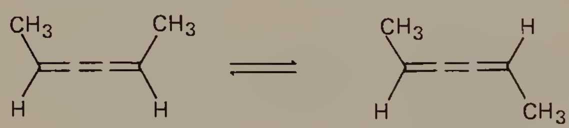
(402)



(403)

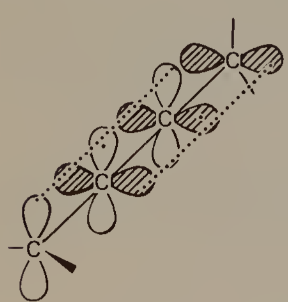
The proposal[260] that the transition state for rotation may have nonlinear geometry as in **402** instead of the commonly assumed linear arrangement **403** has received support from theoretical calculations, which indicate the former to be more stable by ca 6 kcal/mol[263].

A progressive lowering of the barrier occurs as successive cumulated double bonds are added as can be seen in Table 2. Thus (Z)- and (E)-2,3,4-hexatriene (**404**) are interconverted in the temperature range 100–150° C in the gas phase, with rate constant given by $\log k(s^{-1}) = 13.04 - 31{,}800/2.303\,RT$[266], and with an equilibrium constant of unity. The barrier is lower than that for 2,3-butadiene (**400a**)



(Z)-(404) (E)-(404)

by 14.1 kcal/mol. A large part of the lowering is a result of the fact that both of the odd electrons in the diradical transition state **405** have allylic resonance energy, but part is also attributed to increased bonding between the central carbons in the transition state as implied by the contributing structure **406a**.

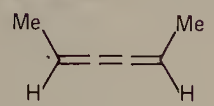
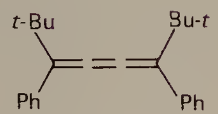
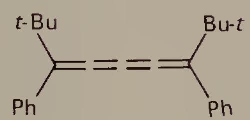
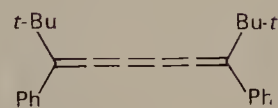


(405)

(406a) (406b)

The geometric isomers, (Z)-**407** and (E)-**407**, are stable at room temperature, but are interconverted on heating. The barrier for rearrangement in solution in the temperature range 75–125°C is somewhat smaller than that found for the gas-phase

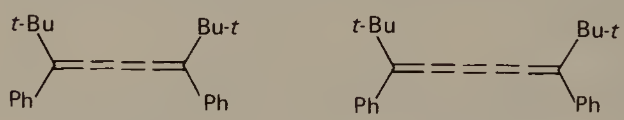
TABLE 2. Rotation barriers for cumulenes

Reactant	Solvent	T(K)	$\Delta H^{\ddagger}$(kcal/mol)	$\Delta S^{\ddagger}$(e.u.)	$\Delta G_T^{\ddagger}$(kcal/mol)	Reference
 (404)	Gas	398	31.0	−1.5	31.6	266
 (407)	PhCl	388	27.0	−7.65	30.0	267
 (408)	Nonane	358	26.1	−4.3	27.7	268
 (409)	$PhNO_2$	298	19	−5.5	20.8	268

(Z)-(407) (E)-(407)

isomerization of the dimethyl analogue **404**, but is relatively insensitive to solvent polarity[267].

The racemic tetraene **408** has been resolved into its enantiomeric forms by chromatography over 'peracetylcellulose' at low temperatures[268]. Racemization occurs when the optically active material is heated at 85° C, and the rotation barrier



(408) (409)

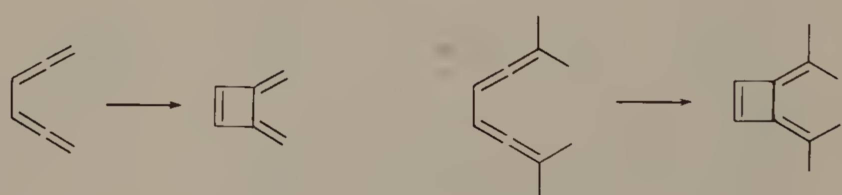
($\Delta H^{\ddagger}$ = 26.1 kcal/mol) is slightly lower than that for **407**. In the case of the pentaene, **409**, the barrier is so low ($\Delta H^{\ddagger}$ = 19 kcal/mol) that rapid interconversion of the Z and E isomers occurs at room temperature[268]. Thus there seems to be no prospect for obtaining optically active heptahexaene or higher cumulenes.

Catalysis of internal rotation in allenic esters by silver salts is described in Section VIII.B.6.

VIII. PERICYCLIC REACTIONS

A. Electrocyclization, Internal Cycloaddition and Related Cyclizations

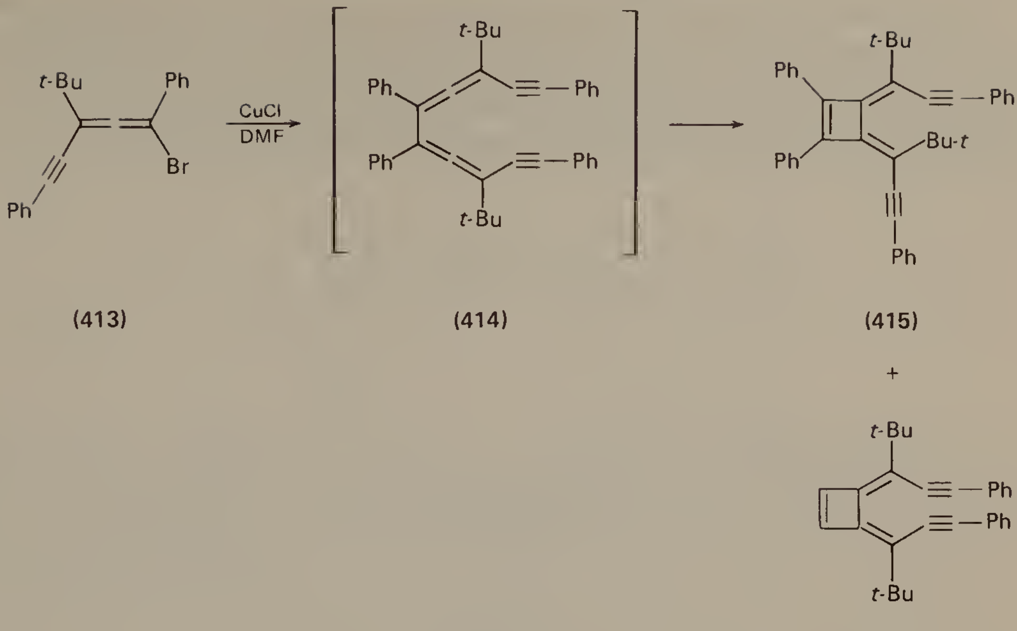
1,2,4,5-Hexatetraene and its derivatives undergo electrocyclization to 3,4-bis-methylenecyclobutenes under mild conditions. The parent member, **410**, cyclizes rapidly at 150° C[269] or at room temperature in the presence of copper(I) chloride[270], and the tetramethyl homologue **411** rearranges to **412** at 250° C[271].



(410) (411) (412)

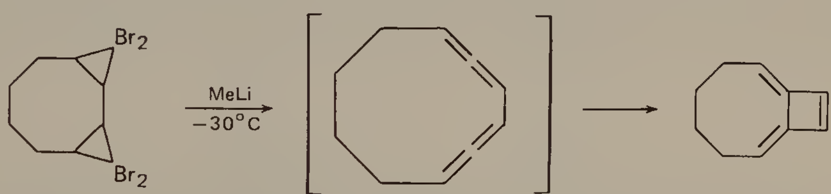
1,2,4,5-Tetraenes are intermediates in the thermal rearrangement of 1,5-diynes to bismethylenecyclobutenes which is discussed in Section VIII.B.4.e.

When bromoallene **413** is treated with CuCl in DMF, a mixture of stereoisomeric bismethylenecyclobutenes **415** and **416** is obtained, apparently by way of the dimer **414**[272].

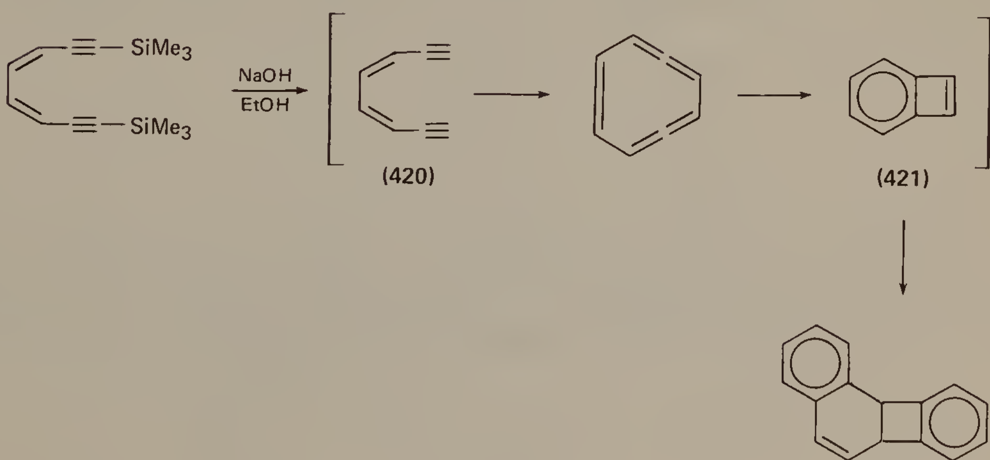


(413) (414) (415) (416)

The tetrabromide **417** reacts with methyllithium at −30° C to give **419** presumably by way of the cyclic bisallene **418**[273]. The rearrangement of *cis*-3,5-octadiene-1,7-diyne (**420**) to benzocyclobutene (**421**), which dimerizes spontaneously to **422** apparently involves two successive electrocyclizations as shown[274].

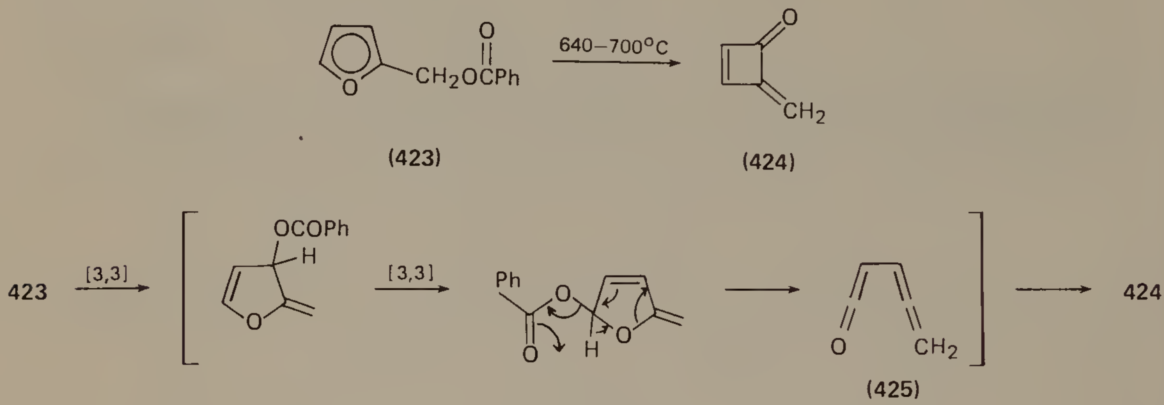


(417) (418) (419)



(420) (421) (422)

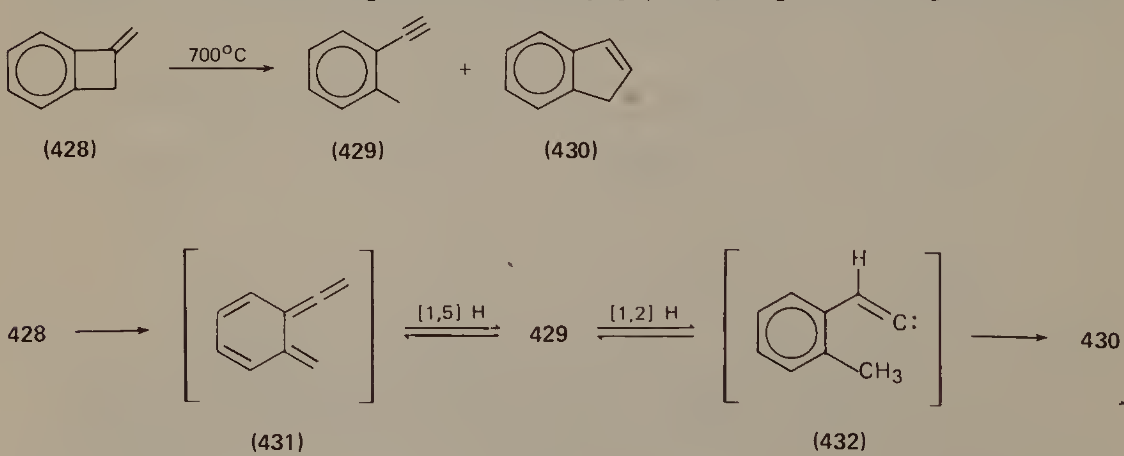
A related electrocyclization of allenylketene (425) has been proposed as the last step in the thermolysis of furfuryl benzoate (423) which gives 2-methylenecyclobutenone (424)[275]. Allenylketene (425) is believed to arise from 423 by two successive [3,3] shifts of the benzoate group, followed by α-elimination of benzoic acid as shown in Scheme 21. Results of studies with deuterium-labelled ester are in agreement with this mechanism[275].



SCHEME 21.

The reversibility of the cyclization of 1,2,4,5-tetraenes to bismethylenecyclobutenes is described in Section VIII.B.4.e. Ring-opening to give the vinylallene 427 occurs when 426 is heated above 175° C[276]. The isomerization is much slower than

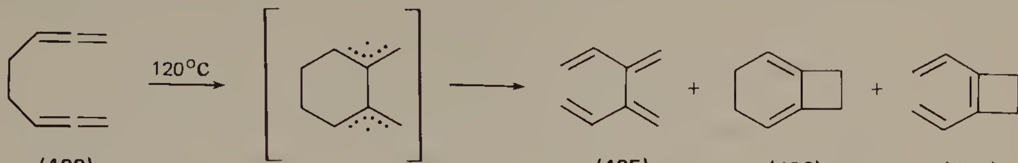
that of simple alkylcyclobutenes, as evidenced by the large activation energy, estimated to be ca 39 kcal/mol. A comparable ring-opening is postulated as the first step in the rearrangement of 428 to *o*-tolylacetylene (429) and indene (430) shown in Scheme 22[277]. Rearrangement of 431 by [1,5] hydrogen shift is postulated as



SCHEME 22.

the route to *o*-tolylacetylene, and rearrangement of the latter to the carbene **432** by [1,2] hydrogen shift, followed by carbene insertion accounts for the indene[277].

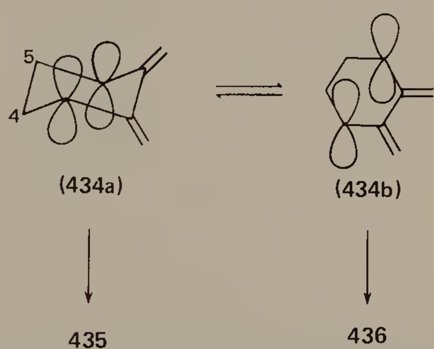
1,2,6,7-Tetraenes undergo rearrangement under mild conditions by processes analogous to the dimerization of acyclic allenes[271,278,279]. Thus, 1,2,6,7-octatetraene (**433**) rearranges to **435**, **436** and **437**, with Arrhenius parameters given by



(433) (434) (435) (436) (437)

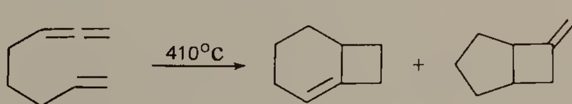
log $k(\mathrm{s}^{-1}) = 9.9 - 24{,}800/2.303\ RT$[278]. In the range 80–150°C the distribution of products is independent of temperature, but does show a marked pressure dependence. For rearrangement in solution, corresponding to infinite pressure, the ratio is 40:60:0, whereas at 1 torr it is 60:25:15 and at pressures below 10^{-2} torr **435** is formed almost exclusively[278]. This behaviour can be rationalized in terms of a vibrationally excited diradical intermediate **434**. At high pressure, rapid collisional deactivation of **434** occurs and the anticipated products **435** and **436** are formed. As the pressure is lowered, **434** transfers increasing amounts of excess energy to its rearrangement products, **435** and **436**, and the fraction of these which is not deactivated by collision can either regenerate **434** or rearrange to **437**. At very low pressures, where the excited molecules have a sufficiently long life-time to equilibrate, the thermodynamic product **435** is obtained almost exclusively. It was shown that **437** rearranges to **435** and **436** at temperatures above 170° C, and at still higher temperatures, e.g. above 250°C, **436** rearranges to **435** irreversibly[278].

It has been proposed that **435** and **436** arise by rearrangement of the diradical in different conformations, **434a** and **434b**[279]. In the chair conformation, **434a**,



(434a) (434b)

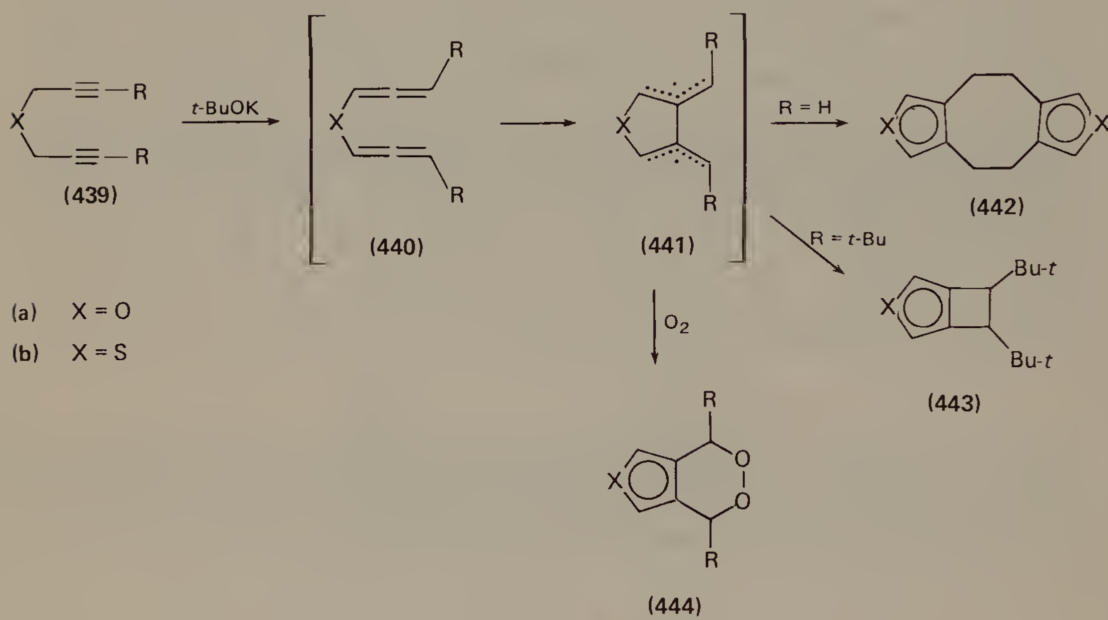
the p orbitals at positions 3 and 6 are properly oriented for rupture of the 4–5 bond giving **435**. In the planar conformation, **434b**, however, the path is open for disrotatory rearrangement to **436**. Evidence in support of this proposal has been obtained from studies of the distribution of the products **435** and **436** when the diradical was generated from a variety of precursors[279].



(438)

Internal cycloaddition involving the allene and alkene functions occurs when **438** is heated[271].

When the bispropargyl ether or sulphide **439** (R = H) is treated with base the cyclic dimer **442** (R = H) is obtained; with the *t*-butyl-substituted derivatives, **439** (R = *t*-Bu), the cyclic isomers **443** are produced[280]. It was proposed that the reactions involve initial prototropic rearrangement to the bisallenyl derivative **440**, which then undergoes intramolecular allene dimerization to give the diradical **441**, or its equivalent. The diradical either cyclizes to give **443** or dimerizes to give **442**[280]. Strong support for this mechanism has been obtained recently[281]. The bisallenyl sulphides, **440b** (R = H) and **440b** (R = *t*-Bu), have been isolated and shown to rearrange thermally to **442b** and **443b** respectively. The unsubstituted sulphide, obtained when **439b** (R = H) was treated with potassium *t*-butoxide at –65° C for one minute, rearranged to **442b** when it was heated to 50° C. When **439b** (R = *t*-Bu) was chromatographed over Al_2O_3 impregnated with KOH, the sulphide **440b** (R = *t*-Bu) was obtained as one of three prototropic rearrangement products; rearrangement to **443b** occurred when this material was allowed to stand at 22° C for 18 hours[281].

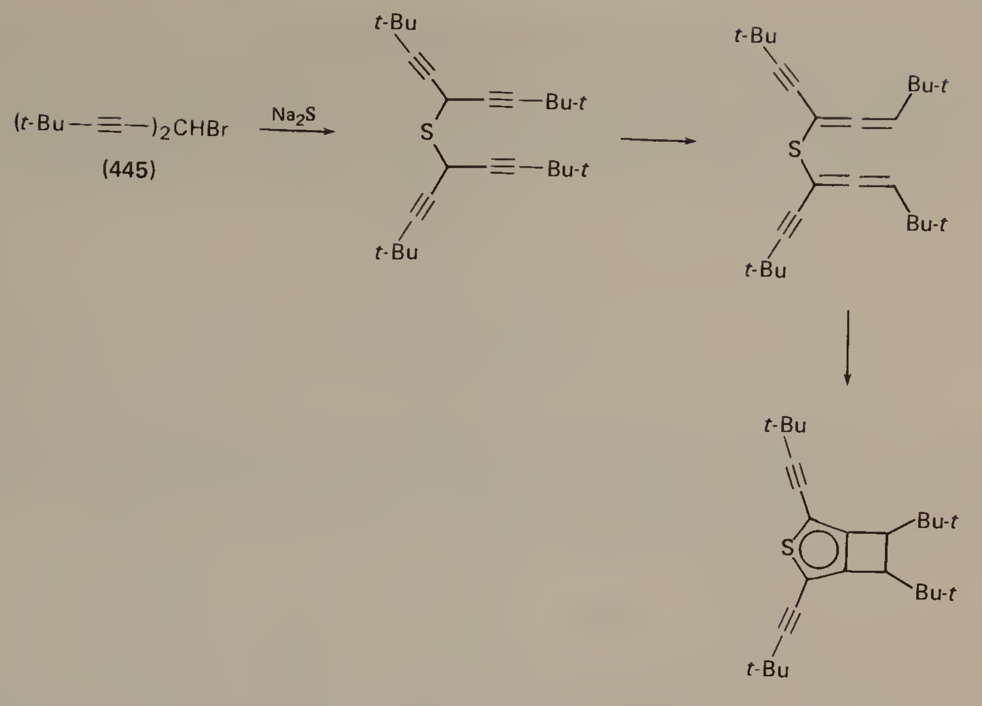


When the rearrangements were carried out in the presence of oxygen the peroxides **444b** (R = H, *t*-Bu) were isolated, thus providing support for the intermediacy of the diradical **441** in these rearrangements[281].

Rearrangement of the amino derivative **439** (X = NMe, R = *t*-Bu) gave results comparable to the ether and sulphide, except that either the dimer **442** (X = NMe, R = *t*-Bu) or cyclic isomer **443** (X = NMe) could be obtained depending on the conditions[280].

The product of reaction of the bromodiyne **445** with sodium sulphide is the thienocyclobutene **446**, and it has been proposed that this product is formed from the initially formed thio ether by the same type of sequence as described above (Scheme 23)[282].

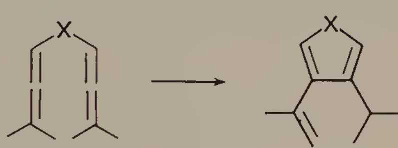
A comparable type of rearrangement occurs with the bis(γ,γ-dimethylallenyl)



(445) (446)

SCHEME 23.

derivatives **447**, except that the cyclization is accompanied by hydrogen migration giving **448**[283-285]. Rearrangement of **447a** occurs when it is heated at 75° C, but



(447) (448)

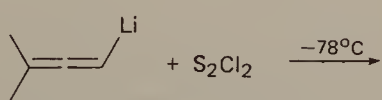
(a) X = SO_2

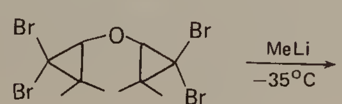
(b) X = S

(c) X = O

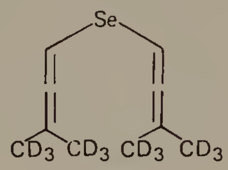
(d) X = Se

447b and **447c** rearrange below room temperature, and attempts to synthesize them have given the cyclic isomers **448b** and **448c** instead, as summarized in equations (56) and (57).

 (56)

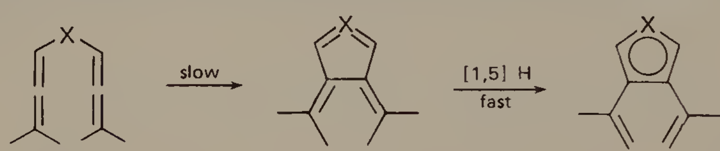
 (57)

The selenide **447d** can be isolated, and a recent study of the kinetics of its rearrangement to the selenophene **448d** at 30° C has provided useful information about the mechanism of the rearrangement[285]. The rate is practically insensitive to the ionizing power of the solvent, ruling out the possibility of ionic intermediates, and only a small isotope effect ($k_H/k_D < 1.1$) is noted for the rearrangement of



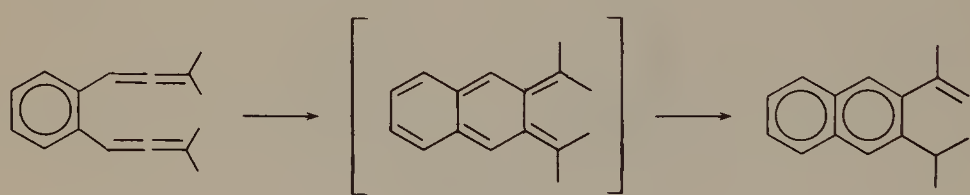
(449)

449, ruling out an ene mechanism. A mechanism is proposed for the sulphur and selenium derivatives which consists of rate-determining cyclization to the quinodimethane-type intermediate **450**, followed by rapid hydrogen transfer.

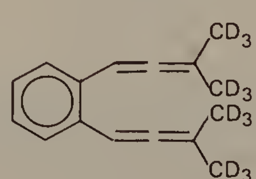


X = S, Se (450)

o-Di(3-methyl-1,2-butadienyl)benzene (**451**) rearranges at 30° C to 2-isopropenyl-3-isopropylnaphthalene (**453**), and a study of the kinetics of rearrangement has shown an absence of solvent effect, and negligible isotope effect for the rearrangement of **454**[285]. Here, also, a two-step mechanism is proposed involving slow formation of the quinodimethane **452** and rapid hydrogen transfer.



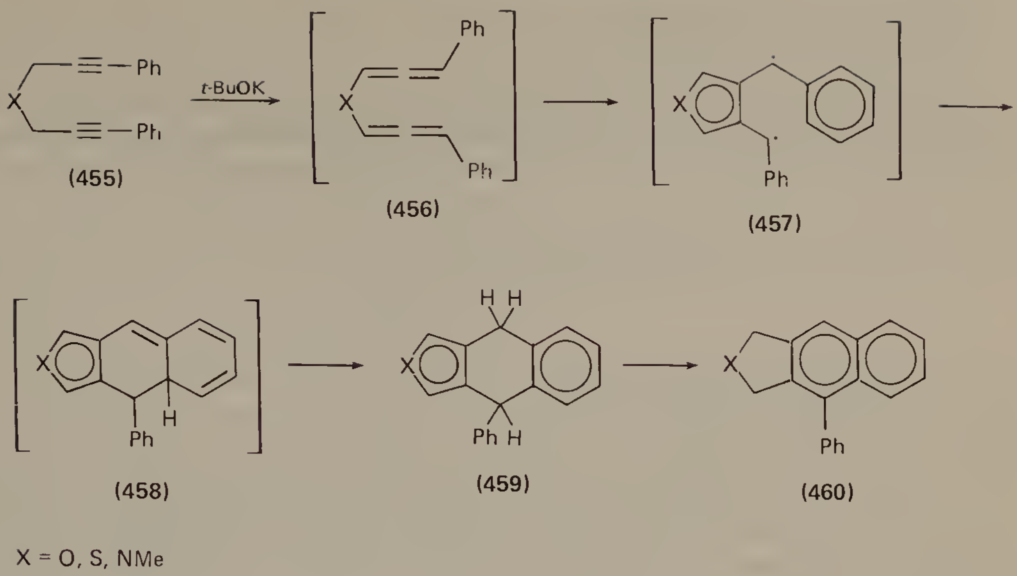
(451) (452) (453)



(454)

A quinodimethane intermediate cannot be formed from the ether **447c**, and the mechanism of rearrangement of this compound remains open.

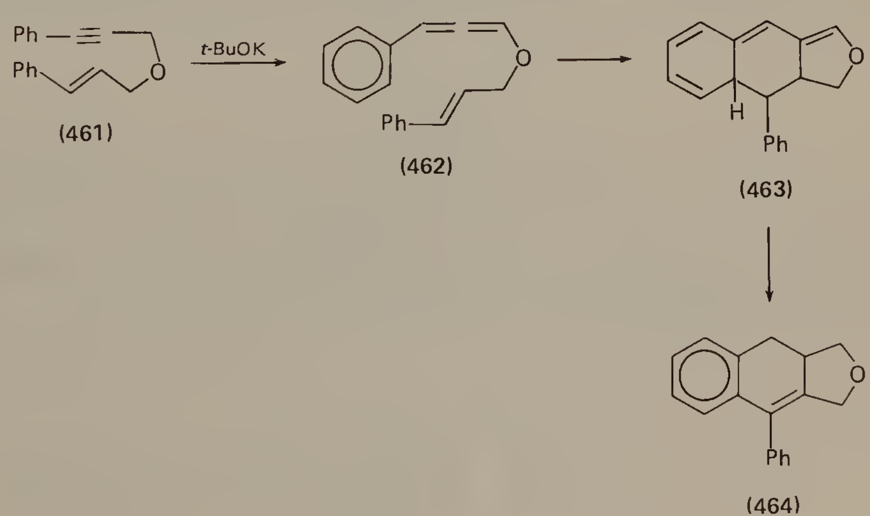
When the phenyl-substituted propargyl derivatives **455** are treated with base, the outcome of the rearrangement is different even though the initial steps are apparently the same as in the rearrangement of **439**[280,286,287]. The primary products obtained by treatment of **455** with potassium *t*-butoxide in THF for short periods



have been shown to be **459**. If the reactions are carried out under more severe conditions or for longer periods of time, further prototropic rearrangement occurs giving the naphthalene derivatives **460**[280].

Prototropic rearrangement to the bisallenyl derivative **456** and cyclization to the diradical **457** are proposed as the initial steps. The presence of the phenyl group in **457** opens another reaction path to the diradical, i.e. aromatic substitution giving **458**, which undergoes prototropic rearrangement to the stable product **459**[280].

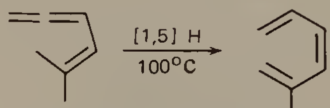
Allyl propargyl ethers such as **461** rearrange in the presence of potassium *t*-butoxide giving **464**[287]. In this case prototropic rearrangement to the monoallenyl ether **462** is the initial step. It has been proposed that the cyclization to **463** occurs in this case by a concerted $[\pi^4 + \pi^2]$ cycloaddition, but it is also possible that the diradical mechanism operates here as well.



B. Sigmatropic Rearrangements

1. [1,5] and [1,7] Hydrogen shifts

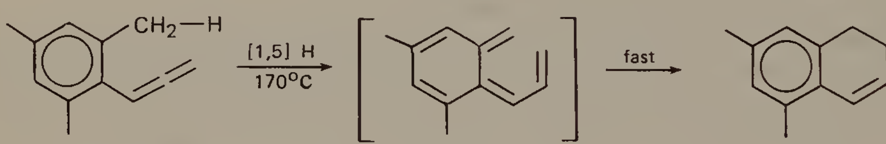
[1,5] Hydrogen shifts occur with unusual ease when the migration terminus is the sp-hybridized carbon of an allenyl system (equation 58), as exemplified by the rearrangement of 5-methyl-1,2,4-hexatriene[288]. This rearrangement, which occurs



(58)

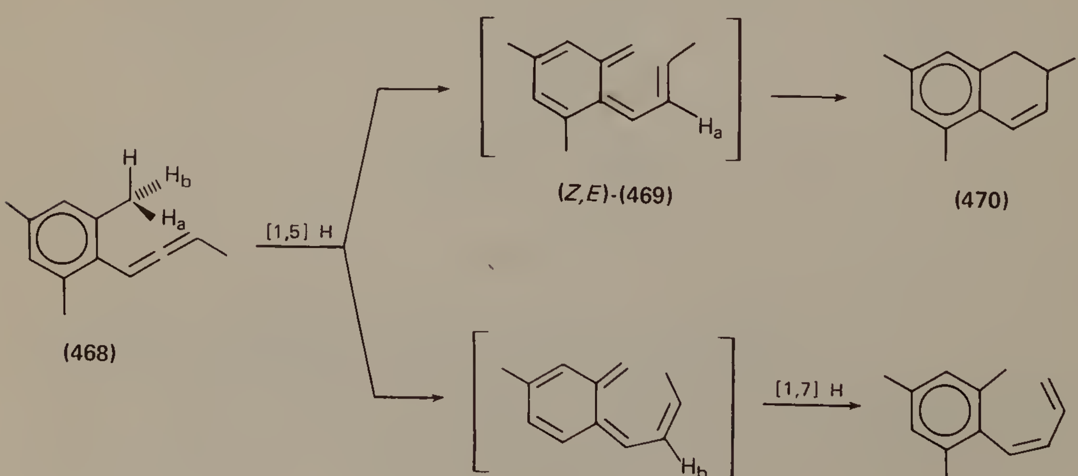
at ca 100° C, has an activation energy of 24.6 kcal/mol, a value much below those found for comparable diene systems; for comparison, a value of 32.8 kcal/mol is found for the rearrangement of 2-methyl-1,3-pentadiene to 4-methyl-1,3-pentadiene. The rearrangement of the allene is exothermic by approximately 12.5 kcal/mol whereas the rearrangement of the conjugated diene is exothermic by only ca 0.5 kcal/mol, and part of the lowering of the energy of activation is undoubtedly a reflection of the greater exothermicity of the former. It is also likely that the smaller steric congestion around the sp-hybridized carbon is responsible for some of the lowering.

When mesitylallene (**465**) is heated at 170°C, the dihydronaphthalene **467** is formed by a sequence involving a rate-determining aromatic sigmatropic [1,5]



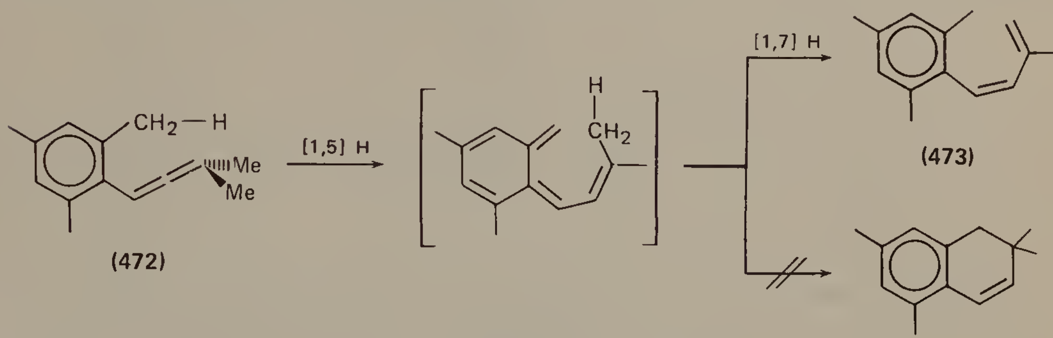
(465) (466) (467)

hydrogen shift giving **466** which undergoes rapid electrocyclization to **467**[289]. The rearrangement follows a first-order rate law, with $\Delta H^{\ddagger}$ = 28.8 kcal/mol and $\Delta S^{\ddagger}$ (170° C) = −140 e.u.[289].

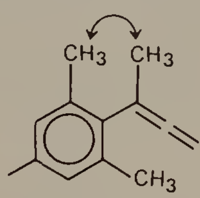


(468) (Z,E)-(469) (470) (Z,Z)-(469) (471)

Besides the anticipated dihydronaphthalene **470**, (*Z*)-1,3-butadienylmesitylene (**471**) is also formed by the thermal rearrangement of **468**. This is a consequence of the formation of two stereoisomeric quinodimethanes, (*Z,E*)-**469** and (*Z,Z*)-**469** in the initial [1,5] rearrangement, the former arising by the transfer of H_a in **468**, and the latter by the transfer of H_b. The only path open for aromatization of (*Z,E*)-**469** is disrotatory cyclization giving **470**, but in the case of (*Z,Z*)-**469**, a competing path – [1,7] antarafacial hydrogen migration – is open, and this is the route followed[290]. It was shown that **470** and **471** are not interconverted under the reaction conditions, and the fact that in the rearrangement of **472** the [1,7] rearrangement product **473** is formed to the exclusion of the cyclization product **474** lends support to the proposed mechanism[290].



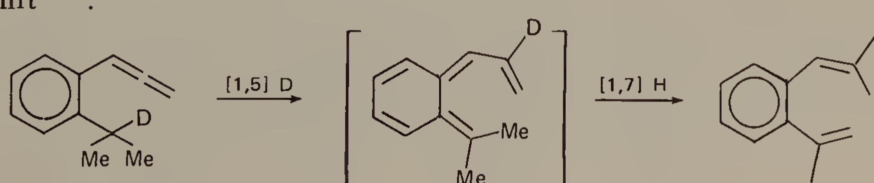
Methyl substituents at the 3-position of the allenyl chain lead to an increase in rate of the [1,5] hydrogen shift. Thus **468** rearranges approximately twice and **472** approximately four times as fast as **465**, presumably as a result of increased stabilization of the intermediate quinodimethanes. Methyl substitution at the 1-position, however, leads to a drastic reduction in reactivity, the rate of rearrangement of **475** being only 0.0053 times that of **465**. The lower reactivity is attributed

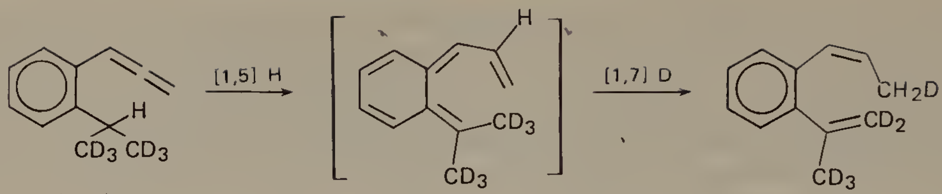


(475)

to steric interactions between the *ortho* methyl and the 1-methyl in the coplanar arrangement required in the transition state[290].

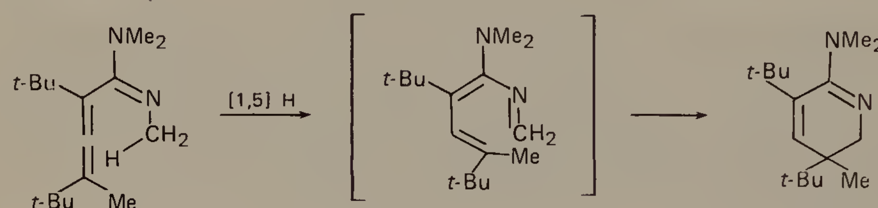
Additional insight into the reaction was obtained from studies of the labelled derivatives **476** and **477**. The location of deuterium in the products is in agreement with the proposed mechanism, and the kinetic isotope effects, $k_H/k_D = 3.45$ for **476** and 1.20 for **477** (both at 170° C), are also in accord with a rate-determining [1,5] shift[290].





(477)

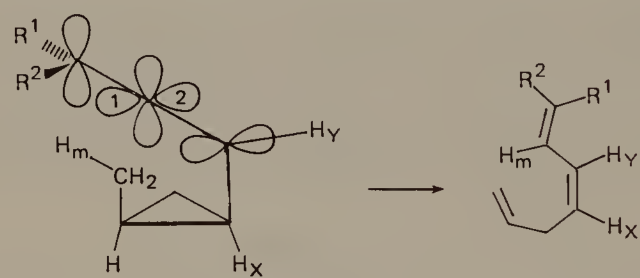
[1,5] Hydrogen migration and subsequent 6-electron electrocyclization have been proposed to account for the rearrangement of the allenamidine **478** to the dihydropyridine **479**[291].



(479)

(478)

The rearrangement of 1-(*cis*-2-methylcyclopropyl)-1,2-butadiene (**480**) to 1,4,6-octatriene (**481**) is stereospecific, with **480a** giving **481a** and **480b** giving **481b**[292]. This is rationalized in terms of the preferred conformation of **480** for the [1,5] homodienyl hydrogen migration as being the one where H_X and H_Y are eclipsed as



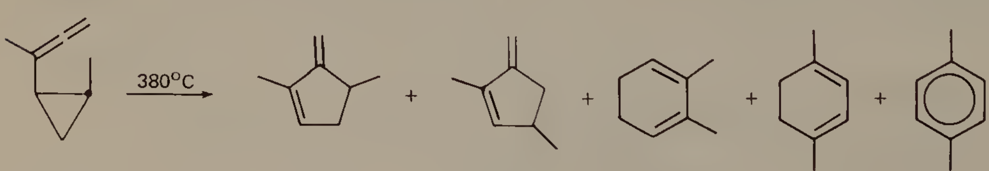
(480) (481)

(a) R^1 = Me, R^2 = H

(b) R^1 = H, R^2 = Me

shown. The migrating hydrogen, H_m, is transferred to the *syn* lobe 1 of the p orbital resulting in *cis* stereochemistry for H_m and R^2 and for H_X and H_Y[292]. As might be anticipated, **480a** rearranges faster than **480b**.

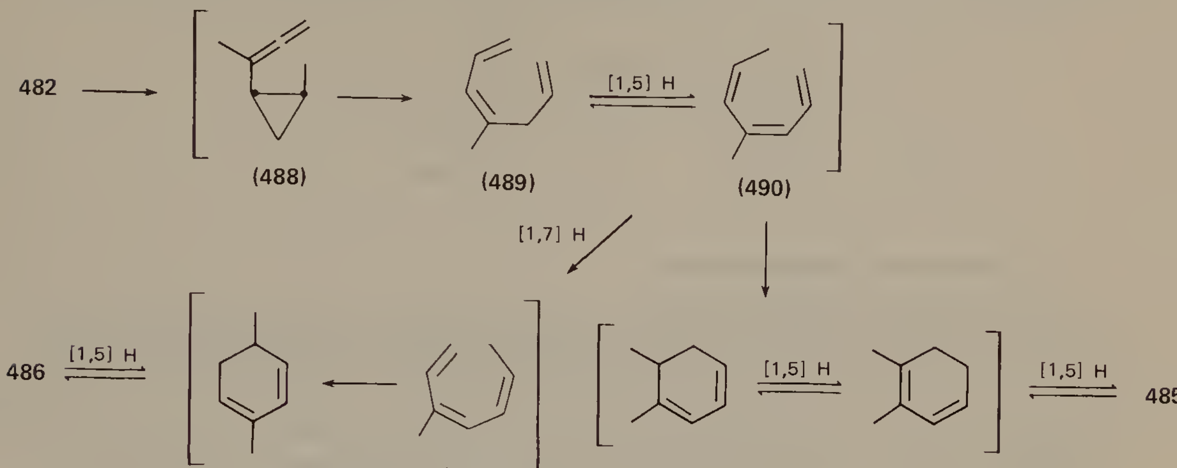
Thermolysis of 3-(*trans*-2-methylcyclopropyl)-1,2-butadiene (**482**) gives the mixture of products shown in equation (59)[293]. The cyclopentenes **483** and **484** are



(59).

(482) (483) (484) (485) (486) (487)

the products anticipated from a vinylcyclopropane-type rearrangement with the major one **483** arising by migration of the more highly substituted group. The formation of **485** and **486** (and the resulting **487**) is particularly interesting, and it is proposed that the initial step in the formation of these products is geometric isomerization to **488** (Scheme 24). Rearrangement of **488** by [1,5] homodienyl

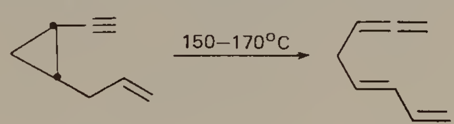


(488) (489) (490) (491)

SCHEME 24.

hydrogen migration would be rapid under the reaction conditions, and the product **489** would be expected to equilibrate rapidly with **490** by [1,5] hydrogen shift. Cyclization of **490** and successive [1,5] hydrogen shifts lead to **485**. To account for **486**, a competing [1,7] rearrangement of **490** is proposed which gives **491**. Cyclization and subsequent [1,5] rearrangement then yield **486**[293].

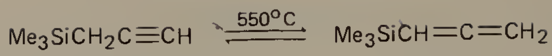
Thermal rearrangement of *cis*-1-allyl-2-ethynylcyclopropane (**492**) occurs under mild conditions and yields *trans*-1,2,5,7-octatetraene (**493**)[294]. From the Arrhenius expression, log $k(\mathrm{s}^{-1}) = 8.2 - 25{,}100/2.303\,RT$, it is seen that the A factor is surprisingly small, corresponding to an entropy of activation (at 170° C) of −24 e.u. It is suggested that [1,5] hydrogen migrations in which an ethynyl carbon is the migration terminus may have an enhanced entropic demand[294].



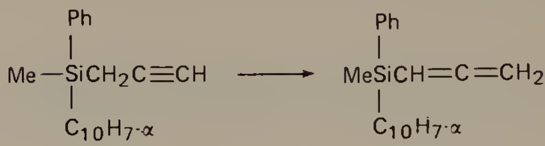
(492) (493)

2. *The silapropynylic rearrangement*

Propargyl- and allenyl-trialkylsilanes are interconverted at elevated temperatures by a process that involves [1,3] sigmatropic shift of the trialkylsilyl group and which is referred to as the 'silapropynylic rearrangement'[295]. The activation energy and entropy for conversion of propargyltrimethylsilane (**494**) to allenyltrimethylsilane (**495**) are 49.9 kcal/mol and −4.0 e.u. (500° C), and the equilibrium mixture at 555° C contains 86.1% **495**. Inversion of configuration at silicon was demonstrated by the formation of (−)-**497** from (+)-**496** with little or no loss of optical purity[295].



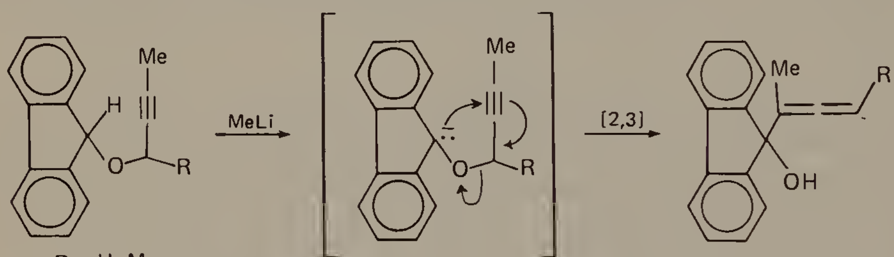
(494) (495)



(496) (497)

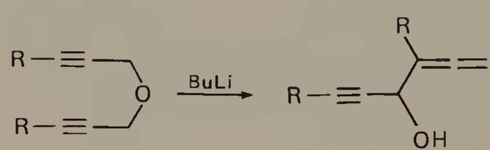
3. [2,3] Sigmatropic rearrangements

Alkyl propargyl ethers in which a stabilized anion can be formed at the α-position of the alkyl group undergo [2,3] rearrangement in the presence of strong bases to give allenylcarbinols as illustrated in equations (60)–(62)[296–298].



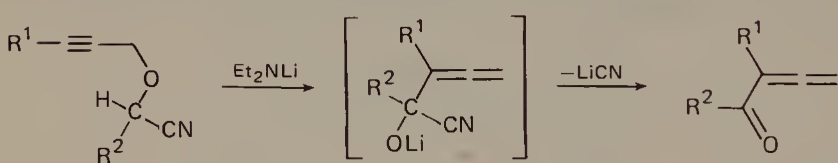
R = H, Me

(60)



R = H, Me, Me_3Si

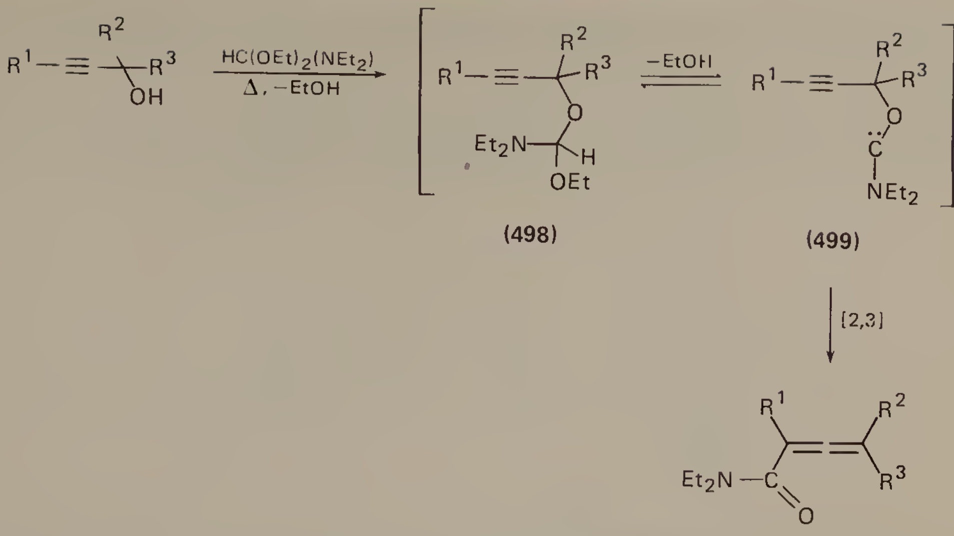
(61)



(62)

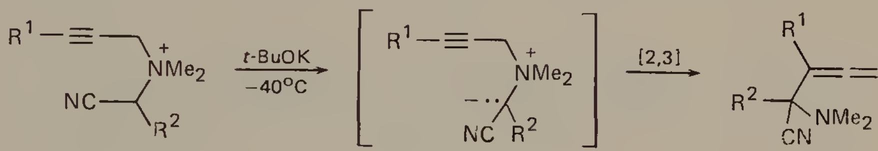
When propargylic alcohols are heated with '*N,N*-diethylformamide diethyl acetal', *N,N*-diethylamides of 2,3-dienoic acids (**500**) are formed in good-to-excellent yields[299]. It is postulated that the initial propargylic derivative **498** loses ethanol by α-elimination in a reversible process giving the stabilized carbene **499** which undergoes [2,3] rearrangement to the final product **500**.

Upon treatment with potassium *t*-butoxide, propargylic ammonium salts **501** rearrange to allenyl derivatives **503** and it is proposed that the reaction involves [2,3] sigmatropic rearrangement of the intermediate ammonium ylide **502**[300]. A comparable rearrangement occurs when the keto derivative **504** is treated with aqueous NaOH, but evidence has been presented which indicates that the rearrangement of the ylide **505** is not necessarily concerted, and may proceed at least in part



(498) (499) (500)

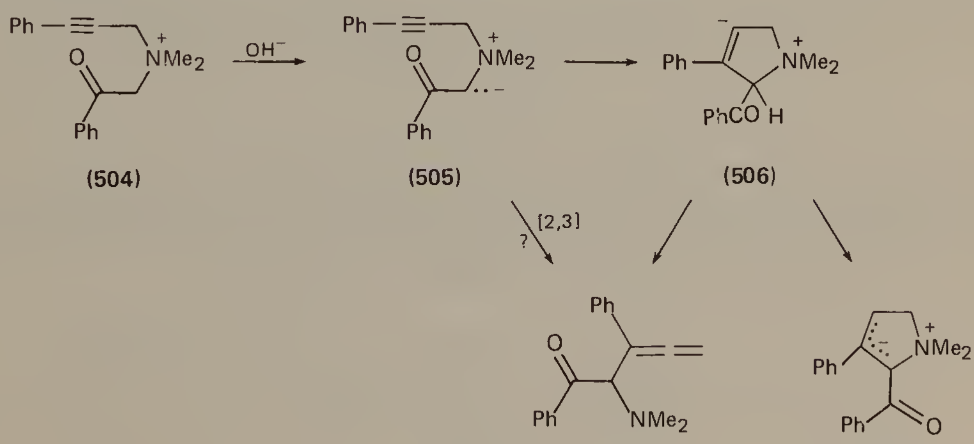
by way of the betaine 506[301,302]. The betaine 506 can undergo *anti* elimination to give 507, the major product, or prototropic rearrangement to the ylide 508,



(501) (502) (503)

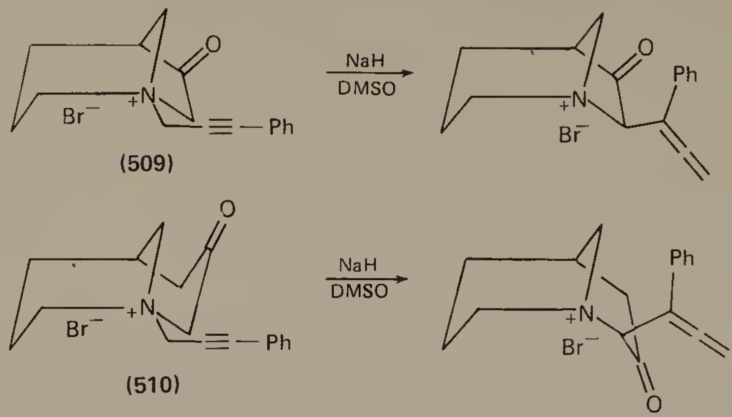
R^1 = Me, Et; R^2 = Me, Et, $PhCH_2$

which is formed in small amounts when the reaction is carried out in water, but is not present when sodium hydride is used in aprotic solvents[302]. Evidence for a nonconcerted rearrangement is provided by the fact that the rearrangement of the bicyclic derivatives 509 and 510 is not retarded significantly[302]. Steric requirements for rearrangement of these derivatives by the concerted mechanism would be severe, leading to retardation. In support of this proposal is the finding that the

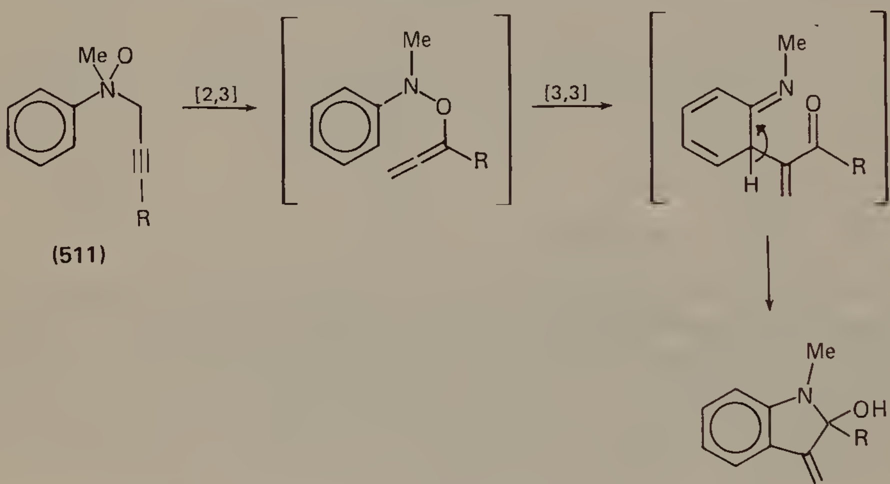


(504) (505) (506) (507) (508)

cinnamyl analogue of 509 fails to rearrange, and the rearrangement of the cinnamyl analogue of 510 is greatly retarded.



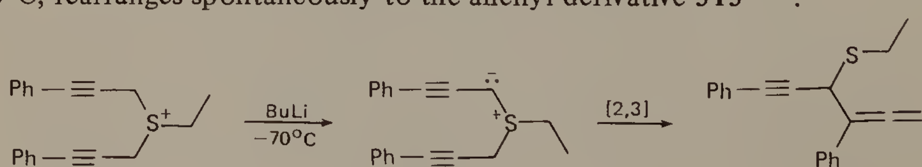
The ease with which the rearrangement of the *N*-oxide 511 to the 3-methyleneindoline 512 occurs is striking[303]. It occurs, for example, when 511 is dissolved in common organic solvents at room temperature, and apparently involves successive [2,3] and [3,3] rearrangements as illustrated in Scheme 25.



(512)

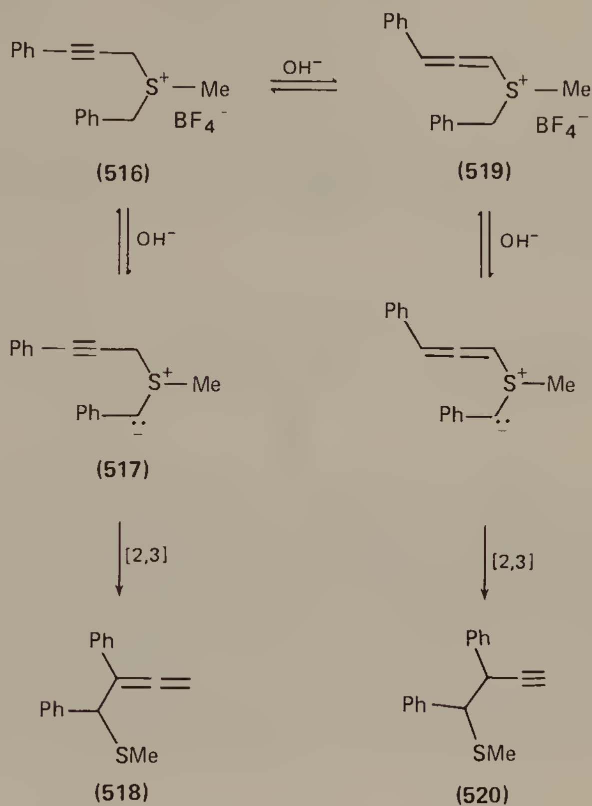
SCHEME 25.

Propargylic and allenic sulphonium ylides, which can be generated in a variety of ways, undergo [2,3] sigmatropic rearrangements under mild conditions. For example, the ylide 514, formed by treating the sulphonium salt 513 with butyllithium at $-70°C$, rearranges spontaneously to the allenyl derivative 515[304].



(513) (514) (515)

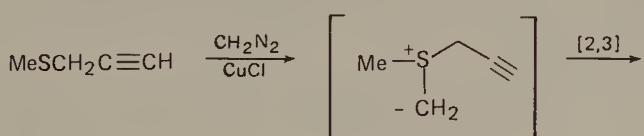
The sulphonium salt **516** rearranges very rapidly at room temperature in the presence of aqueous NaOH or Na_2CO_3 giving a mixture of the allenic and propargylic isomers, **518** and **520**, as shown in Scheme 26[305,306]. Direct formation of the ylide **517** and [2,3] rearrangement leads to **518**, whereas base-catalysed prototropic rearrangement to the allenic sulphonium salt **519**, followed by proton abstraction and [2,3] rearrangement account for the formation of **520**. It



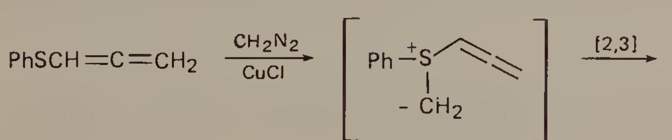
SCHEME 26.

was demonstrated that **518** and **520** are not interconverted under the reaction conditions[306].

Propargylic and allenic sulphonium ylides such as **521** and **522**, formed by the reaction of the corresponding sulphide with diazomethane in the presence of CuCl, rearrange spontaneously as illustrated in equations (63) and (64)[305,307].

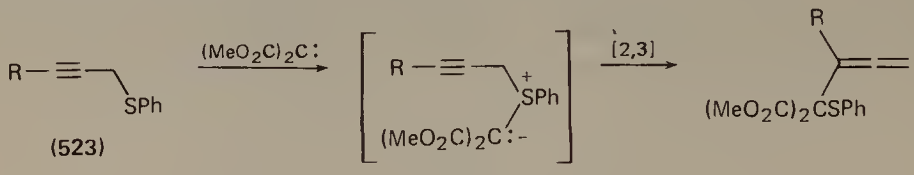


(521) (63)



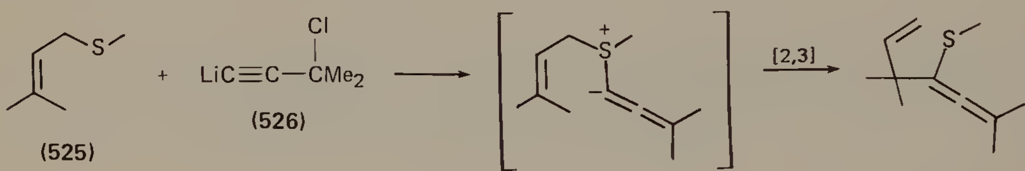
(522) (64)

In a related reaction, the sulphonium ylide **524** is formed by the reaction of dicarbomethoxycarbene with the propargylic sulphide **523**, and it rearranges spontaneously to the allenic derivative as illustrated in equation (65)[308].



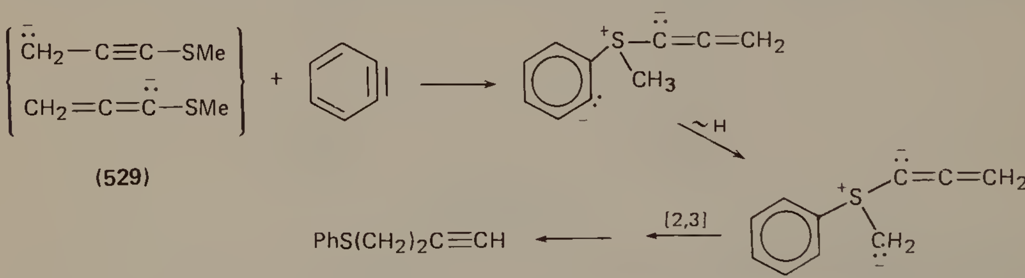
(523) (524) (65)

Treatment of methyl 3-methyl-2-butenyl sulphide (**525**) with **526**, a dimethylvinylidenecarbene ($Me_2C{=}C{=}C:$) precursor, gave a mixture of four products of which the major one was **528**, the product of [2,3] sigmatropic rearrangement of the sulphonium ylide **527**[309].



(525) (526) (527) (528)

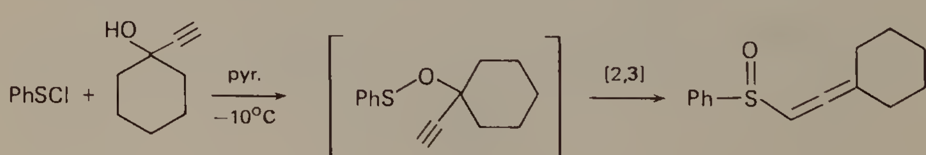
An interesting variant which has been postulated to involve [2,3] sigmatropic rearrangement of a sulphonium ylide consists of the reaction of the thio ether anion **529** with benzyne[310]. Treatment of a mixture of methyl 1-propynyl sulphide and



(529) (530) (531)

bromobenzene with sodium amide produces **529** and benzyne, respectively. Nucleophilic attack by the sulphur atom of **529** on benzyne, followed by proton transfer to the *ortho* anion gives the ylide anion **530**, which after [2,3] rearrangement and protonation yields the thio ether **531**.

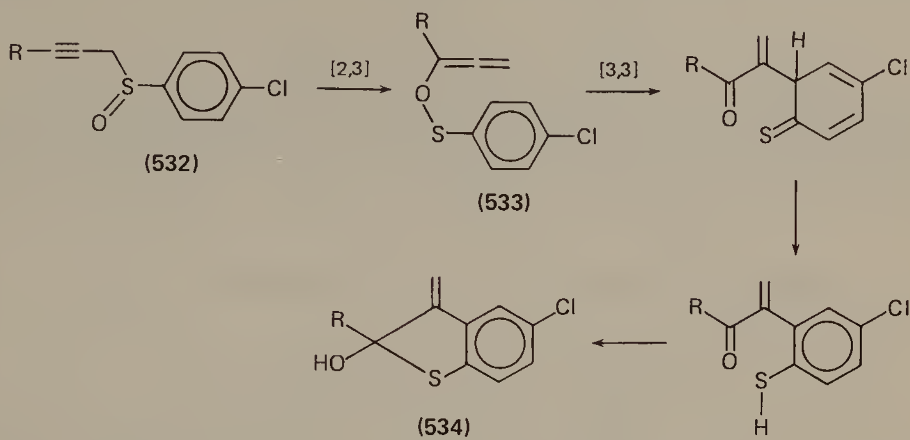
Propargylic sulphenate esters, prepared by the reaction of a propargylic alcohol with a sulphenyl chloride as illustrated in equation (66), undergo [2,3] sigmatropic rearrangement to the allenic sulphoxide[311]. In most cases the rearrangement occurs even at low temperatures and it is not possible to isolate the sulphenate ester, but



(66)

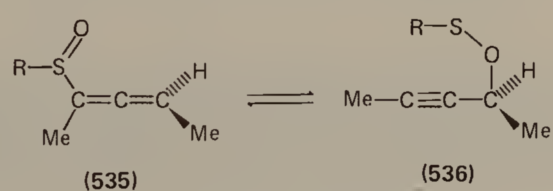
an accumulation of electron-withdrawing substituents on the aromatic ring of propargylic arenesulphenates retards the rearrangement and permits their isolation[311].

The reverse process, the [2,3] rearrangement of the sulphoxide **532** to the sulphenate ester **533** is postulated to be the first step in the rearrangement of **532** to **534** which occurs when **532** is heated in CCl_4 solution[312]. Subsequent [3,3]



rearrangement, tautomerization and hemithioketal formation complete the sequence. This reaction is the basis of a convenient synthesis of condensed thiophenes[313].

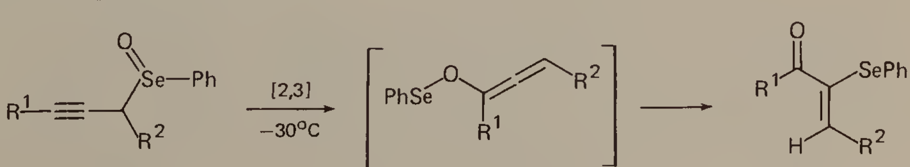
Sulphoxides **535** which possess a chiral sulphur atom and a chiral allenic system undergo mutarotation on standing at room temperature[314]. The p.m.r. spectrum of the product after mutarotation is the same as before, and oxidation yields a sulphone with the same rotation as that from oxidation of the sulphoxide prior to mutarotation. Thus epimerization occurs at sulphur, but not in the allenic system, and it is believed to involve the sulphoxide (**535**)–sulphenate (**536**) equilibration.



R = $PhCH_2$, p-$CH_3C_6H_4$

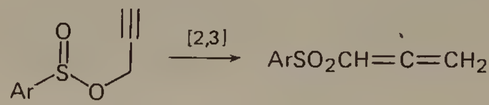
Chirality is transferred stereospecifically between the allenic system in **535** and the asymmetric carbon in **536** and these escape racemization[314].

A dramatic lowering of the activation energy for this type of [2,3] rearrangement occurs when sulphur is replaced by selenium[315]. Thus selenoxides rearrange to α-phenylselenoenones at –30°C, presumably by way of the selenate ester as depicted in equation (67).



(67)

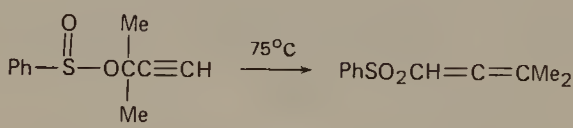
Propargyl arenesulphinates (**537**) rearrange to allenyl arylsulphones (**538**), and the evidence supports the formulation of the reaction as a [2,3] sigmatropic rearrangement[284,316,317]. The reaction goes to completion as a result of the



(537) (538)

increased sulphur–oxygen bond strength in the sulphone group. Inversion of the propargyl chain has been demonstrated by studies with deuterium-labelled and alkyl-substituted chains (equations 68 and 69)[284,317]. The high degree of stereospecificity in the rearrangement of (+)-**540** to (–)-**541**[317], along with the absence

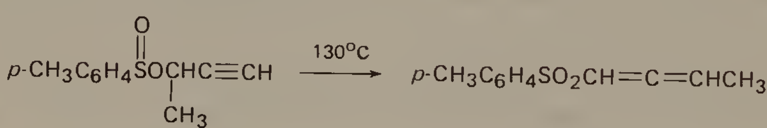
(68)



(69)

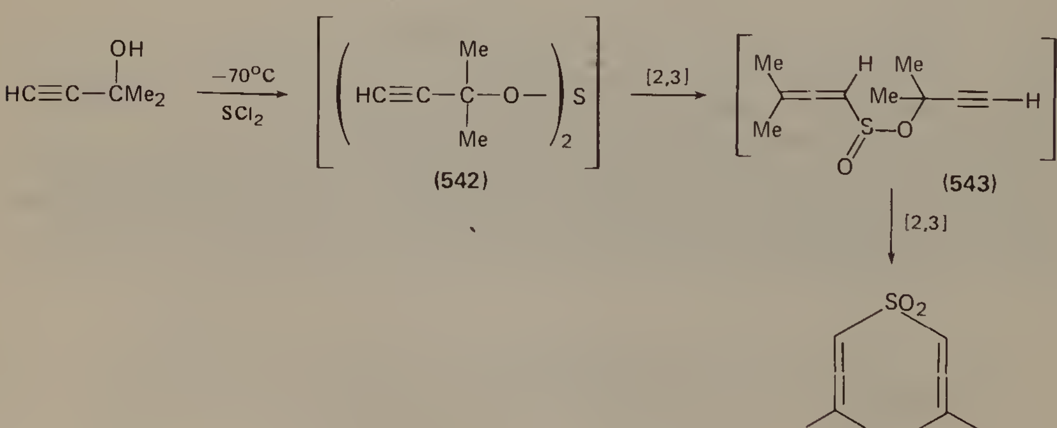
(539)

of significant solvent effects on the rate of rearrangement of **539**, and the negative entropy of activation (–12.8 e.u.) for the rearrangement of this compound lend support to the concerted mechanism[284].



(540) (541)

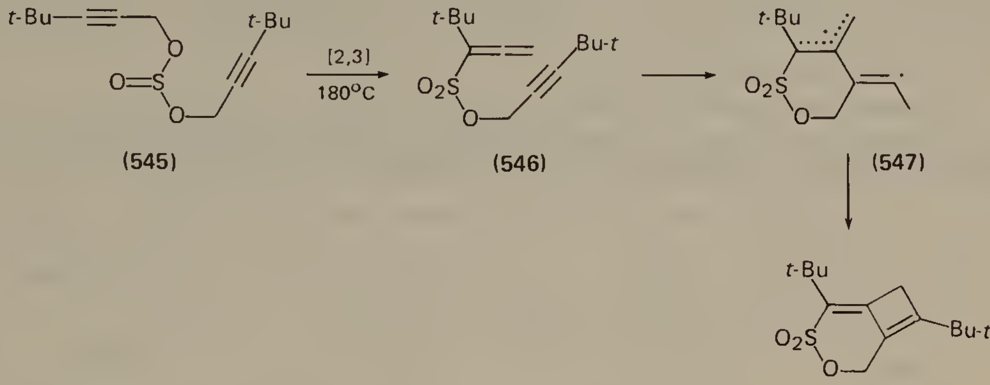
Consecutive [2,3] sigmatropic rearrangements are involved in the conversion of the propargylic sulphoxylates **542** to the diallenic sulphone **544**[318,319]. The first [2,3] rearrangement occurs spontaneously, and **543** is the product obtained from the reaction of the propargylic alcohol with sulphur dichloride at low temperatures.



(544)

When **543** is heated in chloroform solution, the sulphinate–sulphone rearrangement occurs giving **544**[318].

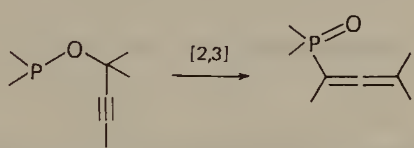
The first step in the rearrangement of the propargylic sulphite **545** to the cyclic sulphonate **548** is believed to be a [2,3] rearrangement to the sulphonate **546** which undergoes intramolecular cycloaddition, presumably via the diradical **547**[320].



(545) (546) (547) (548)

Numerous examples of the [2,3] rearrangement of propargylic esters of phosphorous, phosphonous and phosphinous acids have been reported, and serve to illustrate the wide scope of the reaction. A review appeared in 1969 which contains a thorough discussion of the reaction along with an extensive compilation of properties of reactants and products[321].

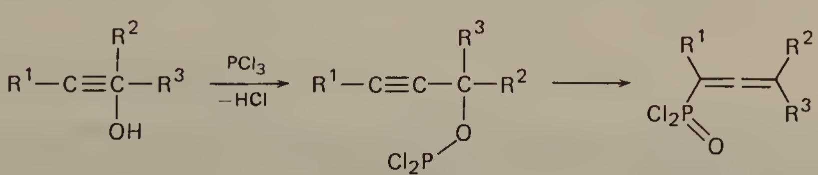
The basic features of the rearrangement are contained in the skeleton equation (70). For the most part, the nature of the two remaining groups on phosphorus is



(70)

immaterial, and the rearrangement has been accomplished with compounds in which carbon, nitrogen, oxygen or halogen atoms were directly attached to phosphorus. Similarly, although substituents on the propargyl group may have a significant effect on the rate, they do not change the nature of the rearrangement. The rearrangement is strongly exothermic largely because of the great strength of the P=O bond in the product[321].

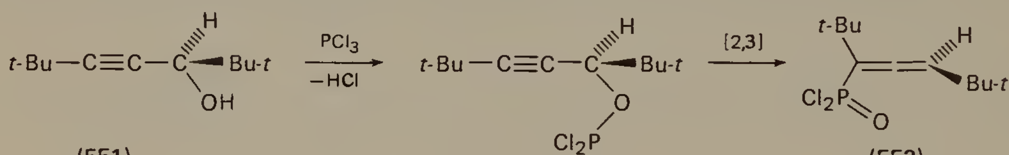
The initial products of reaction of propargylic alcohols with phosphorus trichloride, formed instantaneously, are propargylic dichlorophosphites **549**. The presence of **549** can be shown by n.m.r. spectroscopy, or in cases where the subsequent rearrangement is slow enough, the dichlorophosphite can be isolated[102]. The existence of a propargylic dibromophosphite at low temperatures has



(549) (550)

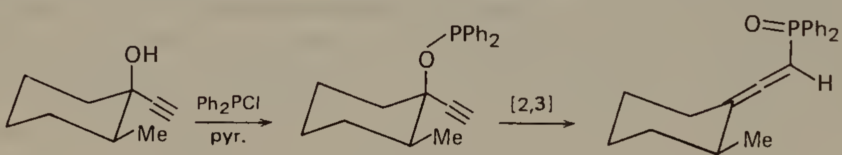
also been demonstrated by n.m.r. spectroscopy[322]. When the hydrogen chloride formed in the first step is removed with a stream of nitrogen, the dichlorophosphites **549** undergo [2,3] rearrangement cleanly to the allenic phosphonyl dichlorides **550**. The rate of rearrangement depends strongly on structure, decreasing in the order tertiary > secondary > primary. For example, the half-life for rearrangement of **549** when $R^1 = H$, $R^2/R^3 = -(CH_2)_4-$ is 20 min at 24° C, but with the unsubstituted derivative, $R^1 = R^2 = R^3 = H$, the half-life is approximately 3 h at 60° C. In the latter case the rearrangement is slow enough to permit isolation of propargyl dichlorophosphite[101].

The optically active allenic phosphonyl dichloride (*R*)-**552** was obtained without loss of optical purity from the reaction of PCl_3 with the (*R*) alcohol **551** thus establishing that the rearrangement is a [2,3] sigmatropic process[101].



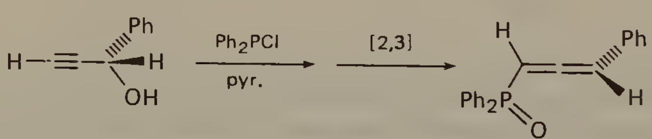
(551) (552)

Allenylphosphine oxides are obtained from the reaction of propargylic alcohols with phosphinyl chlorides in the presence of pyridine, by way of the phosphinite ester, as illustrated in equation (71)[323]. Here, also, the stereospecificity of the



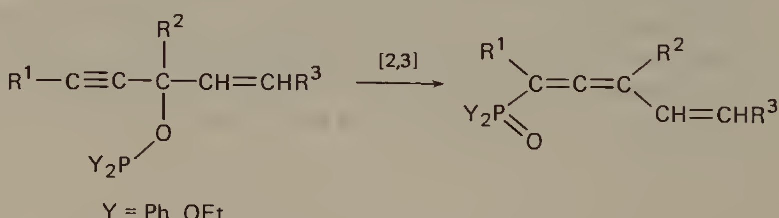
(71)

rearrangement has been demonstrated by the reaction summarized in equation (72)[323].



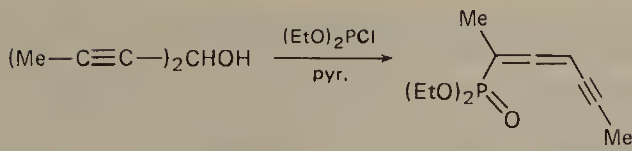
(72)

The rearrangement of propargylic phosphites and phosphinites occurs at much lower temperatures (20–50° C) than those required for their allylic counterparts (100–150° C), and, accordingly, it is found that the rearrangement of esters of enynols involves the triple bond instead of the double bond (equation 73)[324–326].



(73)

When the arrangement is carried out with diynols (equation 74), the anticipated products are obtained[326]. The rearrangement shown in equation (75) has been cited as a possible example of a [2,5] sigmatropic rearrangement[326].



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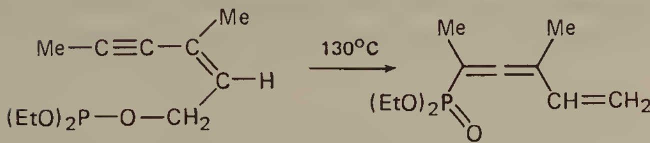
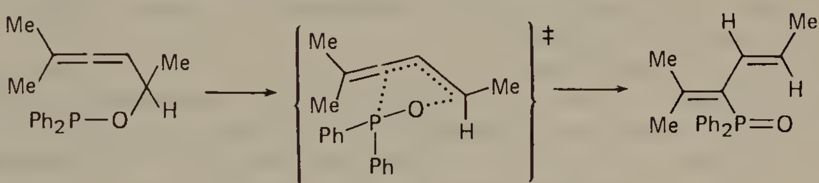


(75)

Tervalent phosphorus esters of allenic alcohols also undergo [2,3] rearrangement, the products being the conjugated diene derivatives (equation 76)[321]. The reaction requires higher temperatures ($\gtrsim 110°$ C) than those for the propargylic analogues

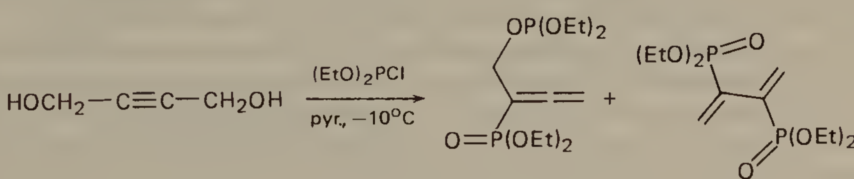
(76)

With esters of secondary alcohols such as **553** the product **555** has *trans* geometry at the disubstituted double bond, and this is ascribed to the preferred geometry of the transition state **554** in which the methyl group occupies an equatorial position, as shown, to minimize 1,3-interactions[326].



(553) (554) (555)

The reaction of 2-butyne-1,4-diol with diethyl chlorophosphite at $-10°$ C gives products of single and double rearrangement, **556** and **557**, in the ratio 10:90. Although **556** can be converted to **557**, a temperature of 140° C is required, and it is suggested that **557** is formed directly by a double [2,3] sigmatropic rearrangement[326].



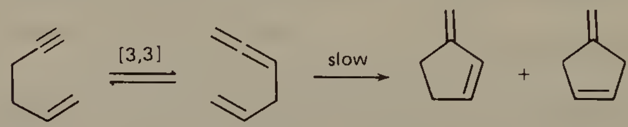
(556) (557)

4. *Cope-type rearrangements*

A review has appeared which covers the Cope and Claisen rearrangements through 1971[327], and the present review will be devoted mainly to work that has appeared since that time.

a. Open-chain 1-en-5-ynes, 1,2,5-trienes and their oxy and amino derivatives. Cope-type rearrangements have been realized with a wide variety of molecules containing allenic groups along with a second, properly located, unsaturated group including olefinic, acetylenic or allenic functions. Allenic derivatives have been formed as products and have also served as reactants for the rearrangements.

The simplest examples include the interconversion of 1-alken-5-ynes and 1,2,5-alkadienes, as illustrated in equation (77) for 1-hexen-5-yne and 1,2,5-



(558) (559) (77)

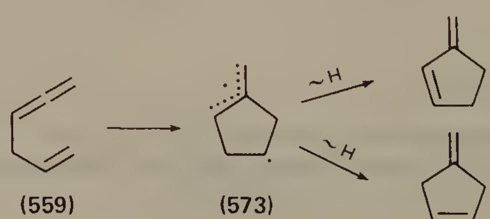
hexatriene[328]. The reversible [3,3] rearrangement is accompanied by a slower, irreversible cyclization of the triene giving 3- and 4-methylenecyclopentene.

Kinetic and thermochemical studies of the rearrangement have been made with **558** and **559**, and with methyl-substituted homologues, and the results are summarized in Table 3[329]. A significant range in reactivity can be seen, with 6-methyl-5-hepten-1-yne (**570**) showing the lowest, and 4,4-dimethyl-1-hexen-5-yne (**564**) showing the highest, reactivity. The *A* factors and energies of activation are typical of those found for Cope rearrangements of simple 1,5-dienes and 1,5-diynes. The compounds with methyl substituents in the propargylic or allylic position exhibit the larger *A* factors, possibly signifying more flexible transition states. Replacement of the terminal acetylenic or olefinic hydrogens by methyl groups causes an increase in the energy of activation.

The substitution pattern has a marked effect on the relative stabilities of the isomers. Qualitatively, at least, the changes can be rationalized in terms of the stabilization that occurs upon substitution of hydrogen by methyl on sp^2- and sp-hybridized carbons, with the effect being somewhat greater for substitution on an sp centre. Thus for the unsubstituted pair, **558** and **559**, the triene **559** is somewhat more stable, but in the case of **560** and **561**, it is the enyne **560** that is more stable. With the **564**–**565** and **566**–**567** pairs, in which the trienes have two methyls on sp^2 carbons and the enynes are unsubstituted, the trienes **565** and **567** are very strongly favoured.

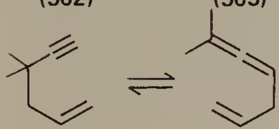
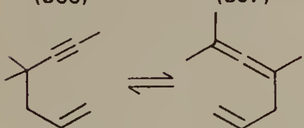
The kinetics of cyclization of the trienes to give mixtures of 3- and 4-methylenecyclopentenes have also been studied, and the results are summarized in Table 4[329]. The *A* factors for these reactions are seen to fall in the same range as those for the [3,3] rearrangements, but the activation energies are substantially larger.

A two-step mechanism has been proposed which involves rate-determining cyclization to a 1,3-diradical **573** followed by 1,2-hydrogen migration in each of the two possible directions giving the isomeric methylenecyclopentenes[328,329]. The first step is endothermic by approximately 18 kcal/mol and thus one would anticipate the transition state leading to **573** to resemble the diradical **573**. For the most part



(559) (573)

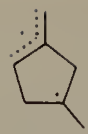
TABLE 3. Rate and equilibrium data for interconversion of 1-alken-5-ynes and 1,2,5-alkatrienes[329]

Reaction	Relative rate at 500 K[a]	Log A (s^{-1})[a]	E_a (kcal/mol)[a]	K_{eq} at 500 K[b]
 (558) (559)	1.00	10.49	32.7	2.73
 (560) (561)	0.16	10.15	33.8	0.22
 (562) (563)	0.23	11.25	35.9	0.88
 (564) (565)	2.82	11.26	33.5	84.0
 (566) (567)	0.65	11.27	35.0	58.8
 (568) (569)	0.44	11.71	36.3	5.83
 (570) (571)	0.04	10.25	35.4	0.14

[a] For the conversion of the enyne to the triene.
[b] Equilibrium constant = [triene]/[enyne].

the effects of methyl substitution can be rationalized in terms of stabilization of the diradical by methyl substituents or destabilization resulting from steric factors, although the two effects are often difficult to disentangle.

The diradical **574** formed from **572** should be more stable than **573**, and a small decrease in activation energy is found for the cyclization of **572**. The large increase in activation energy for the dimethyl derivative **567** can be ascribed to steric congestion at the reaction site. In the dimethyl derivative **565**, on the other hand,



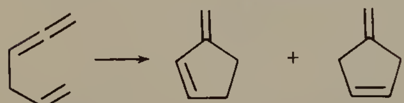
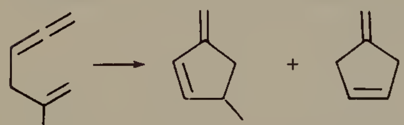
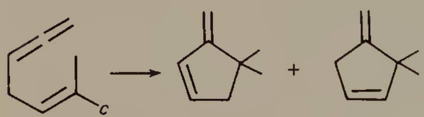
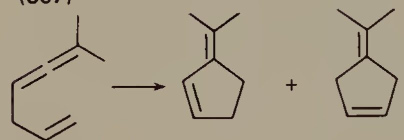
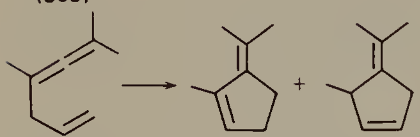
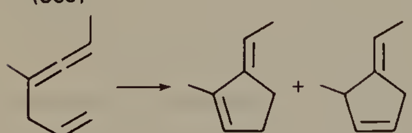
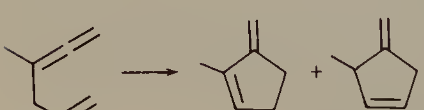
(574)

(575)

(576)

(577)

TABLE 4. Thermal cyclization of 1,2,5-alkatrienes to 3- and 4-methylenecyclopentenes[329]

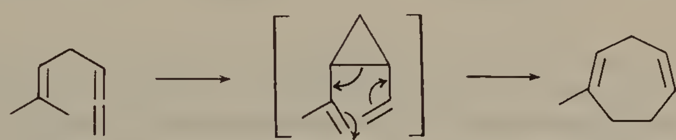
Reaction[a]	Log A(s^{-1})	E_a(kcal/mol)	[3-MCP] : [4-MCP][b]
 (559)	10.85	37.2	1.27
 (572)	10.71	37.0	1.30
 (567)	11.68	41.3	1.76
 (565)	11.05	37.1	1.00
 (569)	11.36	40.3	0.53
 (563)	10.87	36.9	0.98
 (561)	10.60	37.6	1.28

[a]The starting material consisted of the 'equilibrium' mixture of triene and enyne, but all evidence points to the triene as the compound which actually undergoes cyclization.
[b]Ratio of 3-methylenecyclopentene to 4-methylenecyclopentene isomers in the product.
[c]Concurrent cyclization to 1-methyl-1,4-cycloheptadiene occurred.

the methyl groups are removed from the reaction site, and are properly located to provide stabilization of the allylic radical. The barrier for cyclization in this case is ca 4 kcal/mol below that for **567**, and is approximately the same as that for the unsubstituted triene **559**. Failure of the activation energy to drop significantly below that for **559** is attributed to steric interactions between the methyl groups and the '*ortho*' hydrogens in **575**. These steric interactions are strongly magnified in **576** and a large increase in activation energy is found for the cyclization of **569**. Steric interactions are smaller in **577**, the intermediate in the cyclization of **563**, because the *exo* methyl can be oriented away from the offending '*ortho*' methyl as shown.

The second step in the cyclization of **559** is estimated to be exothermic by approximately 50 kcal/mol, suggesting an early transition state and little correlation between product distribution and product stability. This is borne out by the results presented in the last column of Table 4, where it is seen that in most cases the two methylenecyclopentenes are formed in nearly equal amounts, with a slight preference for the conjugated isomer. The notable exception involves the cyclization of **569**, in which the nonconjugated cyclic product predominates. The severe methyl–methyl repulsion in **576** is partially alleviated in the nonconjugated isomer in which the '*ortho*' methyl is no longer coplanar with the ring.

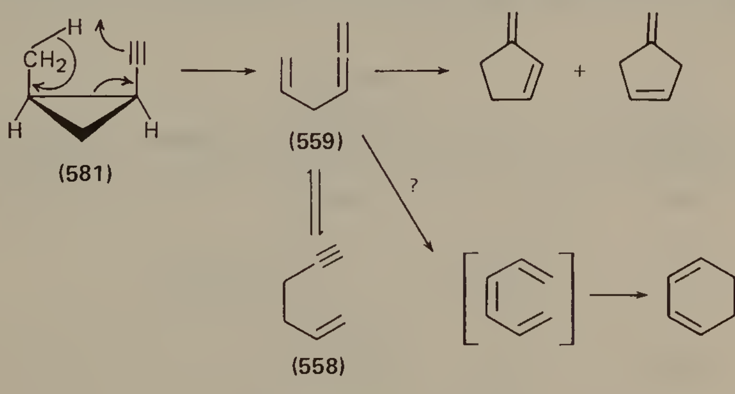
A third cyclic isomer, 1-methyl-1,4-cycloheptadiene (**578**), is formed from **567**, supposedly by the mechanism outlined in equation (78)[329]. 4,4-Dimethyl-1,2,5-hexatriene (**579**), for which the diradical **580** lacks hydrogens that can migrate, fails to undergo cyclization.



(567) (578) (78)

(579) (580)

The products obtained by thermolysis of 1-ethynyl-2-methylcyclopropane (**581**) (Scheme 27) include 1,2,5-hexatriene (**559**), and its rearrangement products des-

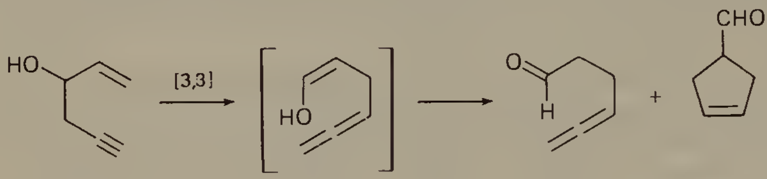


(581) (559) (558)

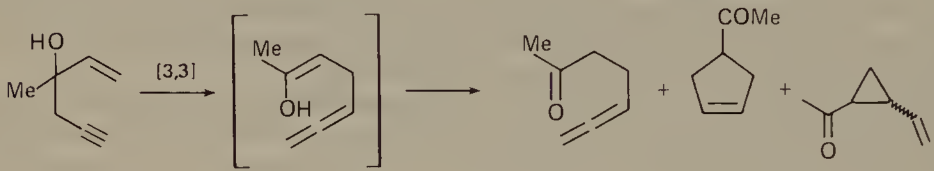
SCHEME 27.

cribed above, as well as 1,3-cyclohexadiene[330]. It was suggested that 1,3,5-hexatriene, formed from **559** by a surface-catalysed [1,3] hydrogen shift, may be the precursor of the cyclohexadiene.

Several studies of the thermal rearrangement of 1-alken-5-yn-3-ols have been reported[331–337]. 4,5-Hexadienal (**584**) and 3-cyclopentenecarboxaldehyde (**585**) are obtained from 1-hexen-5-yn-3-ol (**582**) itself. The analogous products **588** and **589** are obtained from **586**, but in this case methyl 2-vinylcyclopropyl ketone (**590**) is also fomed[332,333,337]. These products can be accounted for in terms of



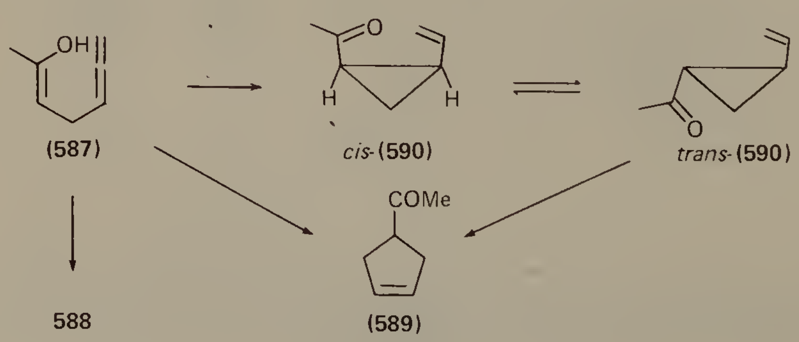
(582) (583) (584) (585)



(586) (587) (588) (589) (590)

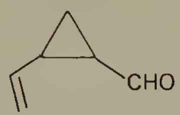
the intermediate enols **583** and **587** which are fomed by [3,3] sigmatropic rearrangement of the starting enynols. For simplicity a single stereoisomer of **583** and **587** is shown, but, undoubtedly, *cis, trans* mixtures are formed[337]. The carbonyl derivatives **584** and **588** arise by simple tautomerization of the respective enols[334].

Studies of the effect of temperature on the distribution of **588**, **589** and **590** from the rearrangement of **586** have shown that **589** arises, at least in part, by rearrangement of **590**. Both the *cis* and *trans* isomers of **590** are present in the product, and are interconverted under the reaction conditions, but the evidence indicates that the *cis* isomer is the initial product formed from **587**. The relationships are summarized in Scheme 28. Formation of *cis*-**590** from **587** by homodienyl [1,5] hydrogen shift requires (*Z*) stereochemistry as shown. The isomerization of *trans*-**590** to **589** is the well-known vinylcyclopropane rearrangement. The possibility remains of direct isomerization of **587** to **589** by the same route that appears to be followed in the isomerization of **583** to **585**[334,337].

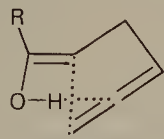


SCHEME 28.

2-Vinylcyclopropanecarboxaldehyde (**591**) is not found among the products of thermal rearrangement of **582**, and, in view of the fact that the temperature required for conversion of **591** to **585** is higher than that required for the rearrangement of **582**[338], another path must be open for the rearrangement of **583**



(591)

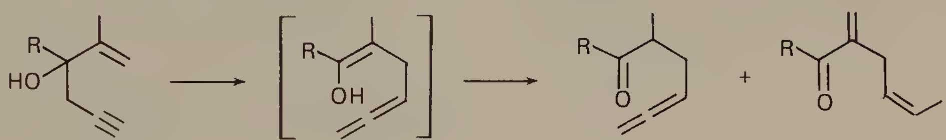


(592) (a) R = H

(b) R = Me

to **585**. A direct process involving the bicyclic transition state **592a** has been proposed[332]. This route may also be open for the rearrangement of **587** to **589**, but steric hindrance introduced by the methyl group in **592b** makes it less favourable in this case[334].

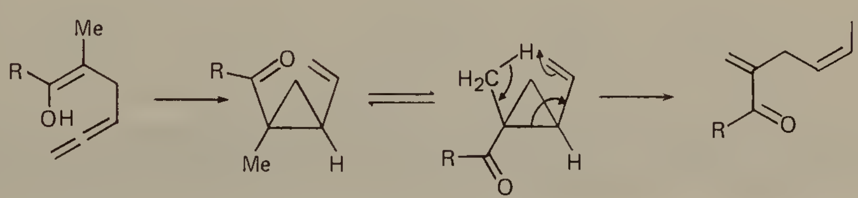
Another reaction path is accessible to 1-en-5-yn-3-ols having a methyl group at position 2[337]. Pyrolysis of **593** gives, in addition to the anticipated product **595**, a



(593) (594) (595) (596)

(a) R = H
(b) R = Me

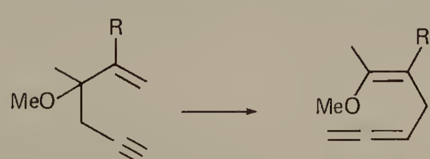
second acyclic carbonyl compound **596**. The formation of this product can be rationalized in terms of a retro-ene reaction of **597** as outlined in Scheme 29. The exclusive formation of the *cis* isomer **596** is understandable, and additional support for the mechanism has been obtained from studies with deuterium-labelled compounds[337]



(594) (597) (596)

SCHEME 29.

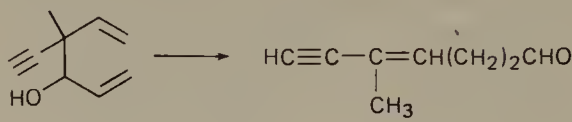
Rearrangement of the methyl ethers **598** stops after the [3,3] shift, and the enol ethers **599** are obtained when the reaction is carried out at 370–450° C[337].



(598) (599)

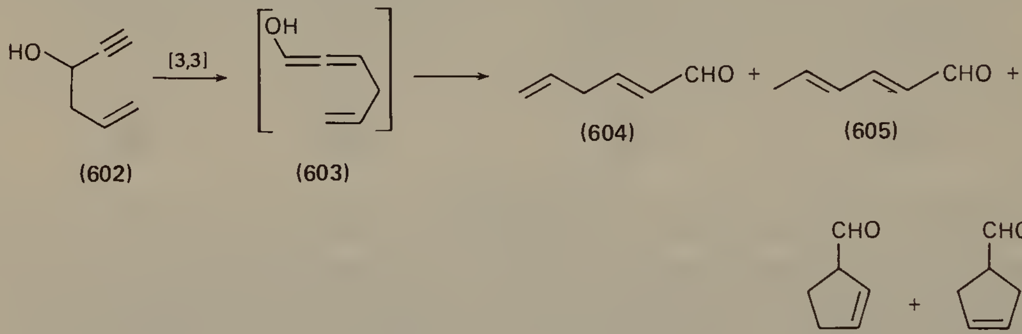
R = H, Me

In the rearrangement of dienynols such as **600**, the reaction involves the diene system to the exclusion of the enyne system and the products are enynals **601**[339,340].



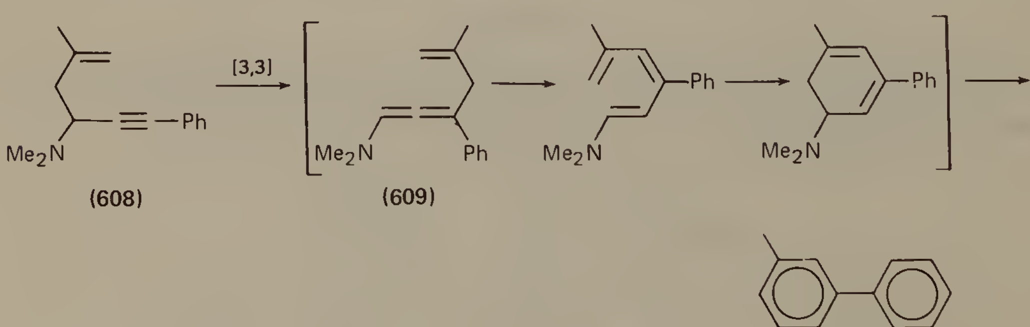
(600) (601)

5-Hexen-1-yn-3-ol (**602**) gives a mixture of four products, **604–607**, upon thermal rearrangement, and again the reaction can be interpreted in terms of an initial [3,3] rearrangement giving the allenol **603**[335]. A mechanism involving a 1,3-diradical, analogous to that involved in the cyclization of simple 1,2,5-alkatrienes, has been proposed to account for **606** and **607**, although the possibility of another route to **607** is considered likely. Kinetic parameters, $E_a = 30 \pm 2$ kcal/mol, $\Delta S^{\ddagger} = -14$ e.u., have been reported for the reaction. Comparative rate studies have shown that the relative rates of [3,3] rearrangement of **602**, **582** and 1,5-hexadien-3-ol at 350° C are 5.4:2.55:1[336].

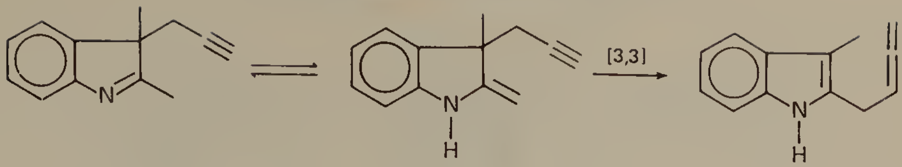


(602) (603) (604) (605) (606) (607)

Amino derivatives of 1,5-enynes, e.g. **608**, rearrange thermally and in this case the initial product **609** undergoes a sequence of changes involving prototropic rearrangement, electrocyclization and elimination of dimethylamine, giving ultimately the biphenyl derivative **610**[341]. The method constitutes a useful synthesis of substituted biphenyls. 3-(2-Propynyl)-2-methyl-3*H*-indoles such as **611** undergo rearrangement consisting of initial imine–enamine tautomerization followed by [3,3] rearrangement of the enyne **612** giving 2-(2,3-butadienyl)-3-methylindole (**613**)[342].

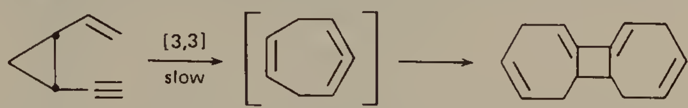


(608) (609) (610)



(611) (612) (613)

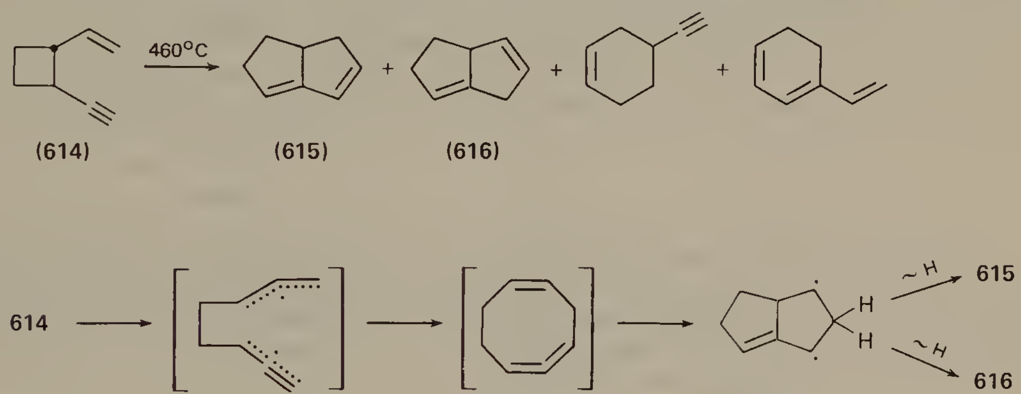
b. 1-Ethynyl-2-vinyl derivatives of small-ring compounds. The rearrangement of *cis*-1-ethynyl-2-vinylcyclopropane occurs under mild conditions (30–48° C) and the 1,2,5-cycloheptatriene that is initially formed dimerizes rapidly (equation 79)[343]. The rate expression, log $k(\mathrm{s}^{-1}) = 9.98 - 19{,}890/2.303RT$, shows a



(79)

small reduction in A factor but a major reduction in activation energy below those found for the acyclic derivatives.

Among the products formed by the pyrolysis of *trans*-1-ethynyl-2-vinylcyclobutane (**614**) shown in Scheme 30, the bicyclic derivatives **615** and **616** are

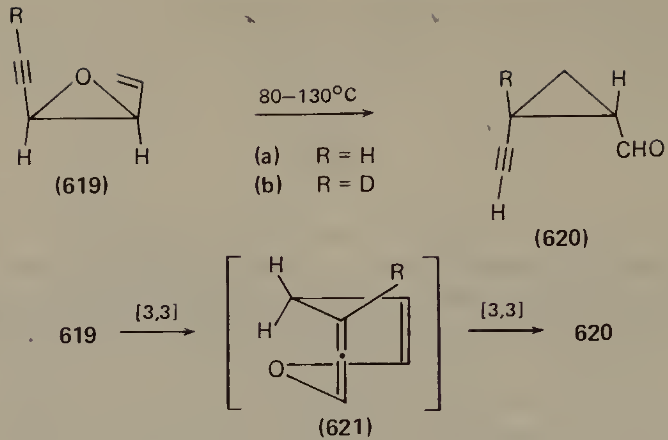


SCHEME 30.

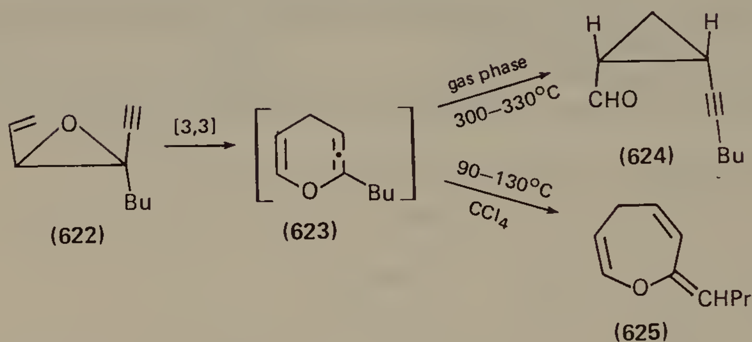
analogous to the methylenecyclopentenes formed from acyclic 1,2,5-trienes[344]. A mechanism has been proposed which involves ring-opening and reclosure to the strained cyclic 1,2,5-triene **617**. The bicyclic products arise by way of diradical **618** in a similar manner to the acyclic analogues.

cis-2-Ethynyl-3-vinyloxirane (**619a**) rearranges under mild conditions either in the gas phase or in solution giving *cis*-2-ethynylcyclopropanecarboxaldehyde (**620a**). Under the same conditions the labelled oxirane (**619b**) yields aldehyde **620b**[345]. The rearrangement obeys first-order kinetics, with $\Delta H^{\ddagger} = 25.1 \pm 1.7$ kcal/mol and $\Delta S^{\ddagger} = -3 \pm 3$ e.u. A mechanism has been proposed (Scheme 31) consisting of two successive [3,3] rearrangements, and involving the highly strained cyclic allene **621**[345].

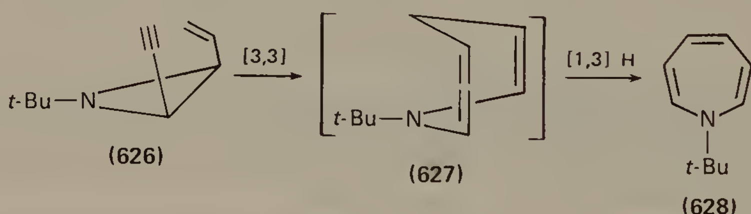
With alkyl-substituted derivatives such as **622**, rearrangement in the gas phase yields the expected cyclopropanecarboxaldehyde **624**, but in solution only minor amounts of **624** were found, the major product being the dihydrooxepin **625**[346]. Evidently **625** is formed from **623** by a bimolecular process because the formation of **625** decreases relative to **624** as the starting concentration of **622** is lowered.



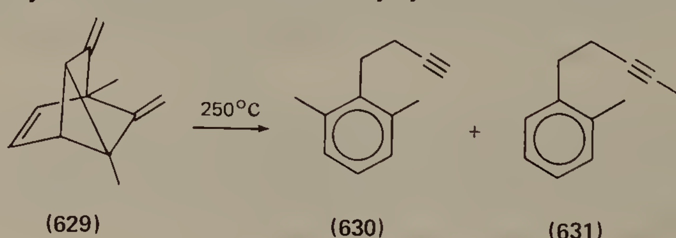
SCHEME 31.

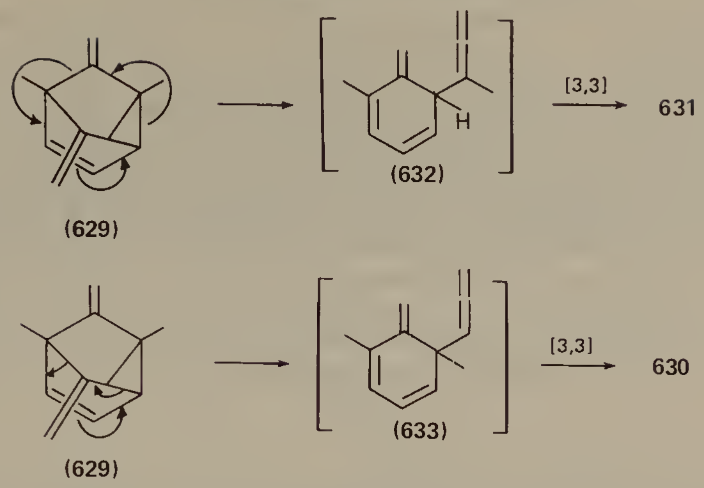


The aziridine **626** rearranges thermally but the product, **628**, is different from that expected by analogy with the oxiranes[345]. Nevertheless, it is likely that the first step involves a [3,3] rearrangement giving **627**, which then undergoes [1,3] hydrogen shift, probably through participation of the basic nitrogen. Pyrolysis of the *trans* isomer of **626** also gives **628**[347].



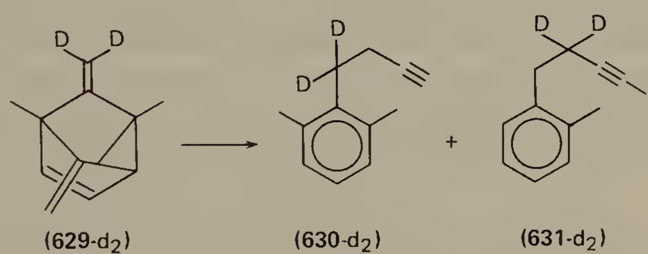
c. Semibenzene–benzene rearrangements involving 1,2,5-trienes. Cope-type rearrangements of intermediate 1,2,5-trienes have been implicated in the rearrangement of the tricyclooctene **629** to the butynylbenzenes **630** and **631**[348]. Several



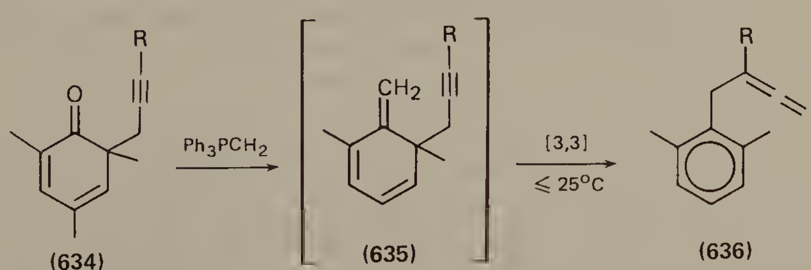


SCHEME 32.

examples of this rearrangement have been studied, and convincing evidence supporting the mechanism outlined in Scheme 32 has been presented[348]. The first step consists of a rate-determining retro-Diels–Alder reaction, which can take either of two paths, as indicated, giving **632** or **633**. The *o*-semibenzenes, **632** and **633**, undergo rapid, irreversible [3,3] sigmatropic rearrangement to **631** and **630** respectively. Rearrangement of the dideutero derivative **629**-d_2 gave **630**-d_2 and **631**-d_2, demonstrating clean inversion of the allenyl group in the second step. The intermediate *o*-allenylsemibenzenes **632** and **633** would not be expected to survive



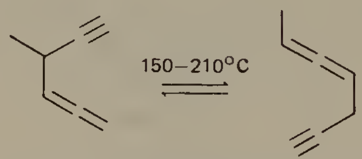
under the reaction conditions, and it is not surprising that they were not detected in the product mixture. Attempts to synthesize the *o*-propargylsemibenzene **635a** from the cyclohexadienone **634** by a Wittig reaction gave instead the rearranged derivative **636a**. Inversion of the propargyl group was demonstrated by the formation of **636b** from **634b**. Thus, the rearrangement of **635** to **636** occurs under



(a) R = H
(b) R = D

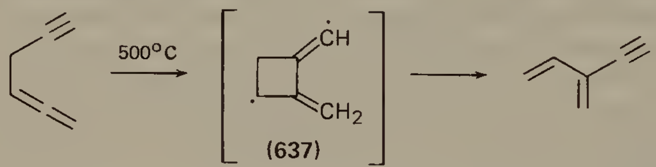
very mild conditions, ⩽25° C, demonstrating the driving force provided by aromatization[348].

d. 1,2-Dien-5-ynes. 1,2-Dien-5-ynes undergo reversible [3,3] rearrangement under mild conditions, as illustrated in equation (80)[349]. From the Arrhenius equation, $\log k(\mathrm{s}^{-1}) = 10.84 - 30{,}800/2.303\,RT$, the A factor is seen to be in the same range as those found for the [3,3] rearrangement of 1-alkene-5-ynes, but the activation energy is significantly smaller. 4,5-Heptadien-1-yne is favoured at equilibrium, the value of the equilibrium constant ranging from 4.3 at 150°C to 3.45 at 210°C.



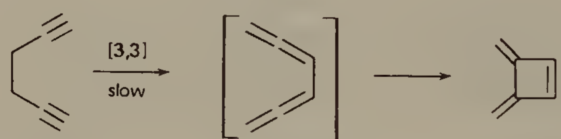
(80)

At higher temperatures a more deep-seated rearrangement occurs[350]. In the range 400–500°C, 1,2-hexadien-5-yne rearranges to 3-methylene-1-penten-4-yne, possibly by way of the diradical **637**.



(637)

e. 1,5-Diynes and their oxy derivatives. 1,5-Hexadiyne rearranges to 3,4-bismethylenecyclobutene in a two-step sequence consisting of rate-determining [3,3]

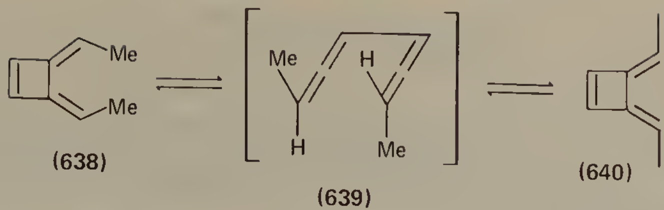


(81)

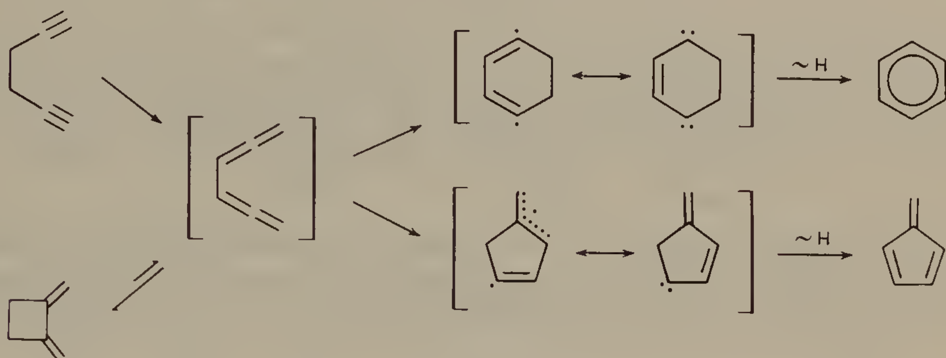
sigmatropic rearrangement to 1,2,4,5-hexatetraene followed by rapid four-electron electrocyclization (equation 81)[351,352]. The cyclization step, described in Section VIII.A, is much faster than the [3,3] shift[269], and the tetraene is not found in the products. Activation parameters, given by: $\log k(\mathrm{s}^{-1}) = 11.41 - 34{,}400/2.303RT$, are consistent with the proposed mechanism[352,353].

The rearrangement has been carried out with a wide variety of substituted 1,5-diynes, and the kinetics of rearrangement of methyl- and dimethyl-substituted derivatives have been determined[39,353]. Studies with stereoisomeric diynes with methyl groups on positions 3 and 4 have shown that the electrocyclization step occurs in a conrotatory manner in agreement with orbital symmetry requirements[352–354].

The reversibility of the cyclization of 1,2,4,5-tetraenes has been demonstrated[353]. Isomerization of (*Z,Z*)-3,4-bisethylidenecyclobutene (**638**) to the (*E,E*) isomer **640** occurs at elevated temperatures, and equilibrium mixtures rich in **640** are obtained. The absence of the (*E,Z*) isomer, which is stable under the reaction conditions, indicates a stereoselective process, and the reaction is formulated in terms of conrotatory opening to the tetraene **639** followed by conrotatory closure in the same sense.



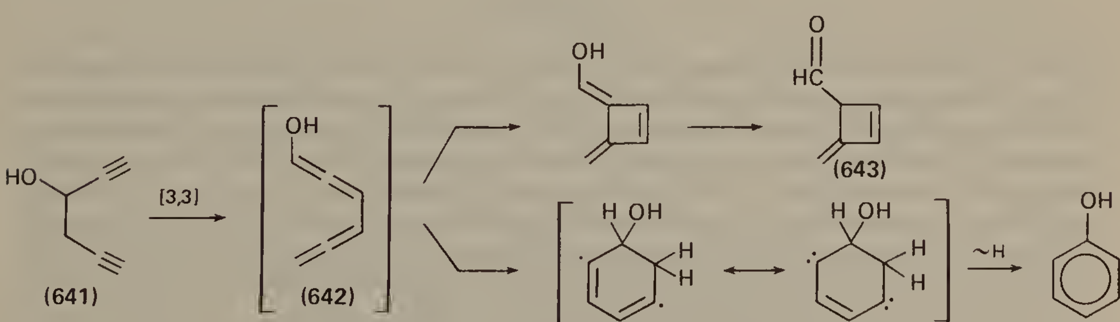
The formation of benzene and fulvene when 1,5-hexadiyne is pyrolysed at temperature above 400° C[355] can be accounted for in terms of reversibility of the cyclization of 1,2,4,5-hexatetraene to bismethylenecyclobutene (Scheme 33)[356,357]. At lower temperatures the cyclization of 1,2,4,5-hexatetraene proceeds by the lower energy path to bismethylenecycyclobutene, but as the



SCHEME 33.

temperature is raised, and reversal of the cyclization becomes significant, the higher energy paths leading to benzene and fulvene by way of the intermediate carbene diradicals become accessible. In fact, flow thermolysis of bismethylenecyclobutene at 620° C gives fulvene and benzene in approximately the same ratio (1:2) as that found on pyrolysis of 1,5-hexadiyne, and studies with deuterium-labelled diyne support the mechanism shown in Scheme 33[356].

Phenol and the aldehyde **643** are the products of rearrangement of 1,5-hexadiyn-3-ol (**641**)[358]. Both of these products can be accounted for in terms of the intermediate allenol **642**, as shown in Scheme 34, the aldehyde arising by 4-electron electrocyclization and subsequent tautomerization, while phenol is formed in a manner analogous to that involved in the formation of benzene from 1,5-hexadiyne as described above.



SCHEME 34.

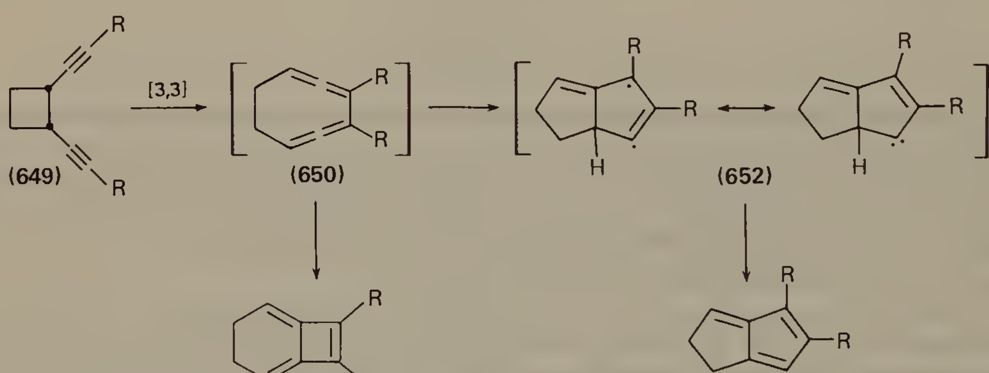
Rearrangement of 1,2-diethylcyclopropane leads to bicyclo-[3.2.0]hepta-1,4,6-triene (**645**) (equation 82), presumably by way of the highly strained cyclic diallene **644**[359-361]. The reactions shows an unusual pressure dependence, with **645** being formed cleanly at atmospheric pressure, but with fulvenallene (**646**), ethynylcyclopentadienes (**647**) 'and heptafulvalene (**648**) appearing when the reaction is carried out at low pressures (⩽1 torr)[359]. This is discussed more fully in Section XI. C.

(82)

(644) (645)

(646) (647) (648)

A rearrangement analogous to the formation of fulvene from 1,5-hexadiyne constitutes the major reaction in the pyrolysis of *cis*-1,2-diethynyl- and *cis*-1,2-di(1-propynyl)-cyclobutane, (**649a**) and (**649b**) (Scheme 35)[362,363]. In the case of the



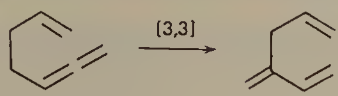
(649) (650) (652) (651) (653)

(a) R = H
(b) R = Me

SCHEME 35.

diethynyl derivative **649a**, formation of the carbene diradical **652a** from the cyclic diallene **650a**, followed by [1,2] hydrogen shift gives 1,2-dihydropentalene (**653a**) in 95% yield. Only a minor amount (2.5%) of the diallene undergoes four-electron, disrotatory cyclization to bicyclo[4.2.0]octa-1,5,7-triene (**651a**). 4,5-Dimethyl-1,2-dihydropentalene (**653b**) is formed in virtually quantitative yield from the rearrangement of **649b**. Large amounts of fragmentation products are obtained by pyrolysis of the *trans* isomers of **649a** and **649b**, but the rearrangement products correspond closely to those obtained from the *cis* isomers[362,363].

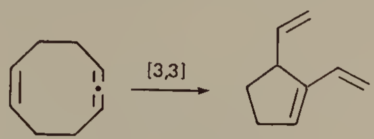
f. 1,2,6-Trienes. The [3,3] rearrangement of 1,2,6-heptatriene to 3-methylene-1,5-hexadiene (equation 83) occurs under mild conditions[271], and the Arrhenius parameters, $\log k(s^{-1}) = 9.97 - 28{,}470/2.303RT$, have been determined[364]. The *A*



(83)

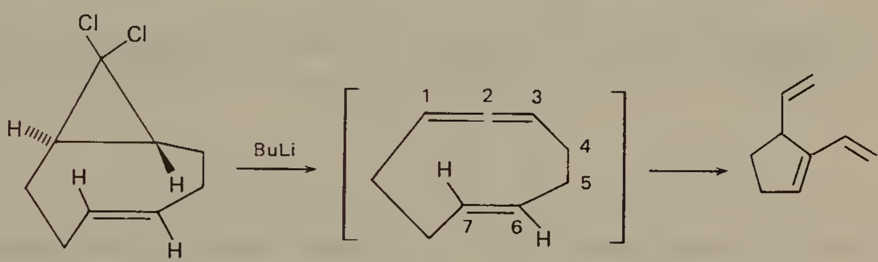
factor corresponds well with values found for [3,3] rearrangement of simple 1,5-dienes, but the activation energy is substantially lower.

cis-1,2,6-Cyclononatriene undergoes an analogous rearrangement at 130–180° C giving 1,5-divinylcyclopentene (equation 84), with activation parameters given by:



(84)

$\log k(s^{-1}) = 12.47 - 31{,}680/2.303RT$[271,365–367]. Absence of free rotation in the ground state is largely responsible for the increase in A factor over that of the acyclic analogue, while the inability to achieve a chair-like geometry in the transition state is responsible for the greater activation energy[367]. *trans*-1,2,6-Cyclononatriene (**655**), on the other hand, rearranges to give the same product at

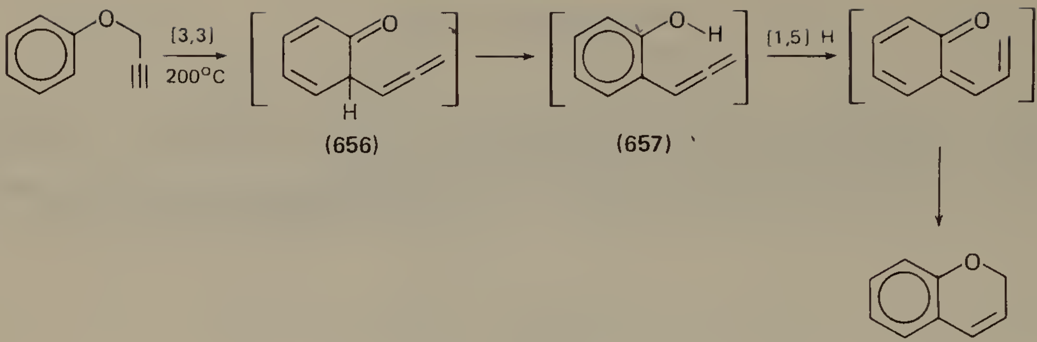


(654) (655)

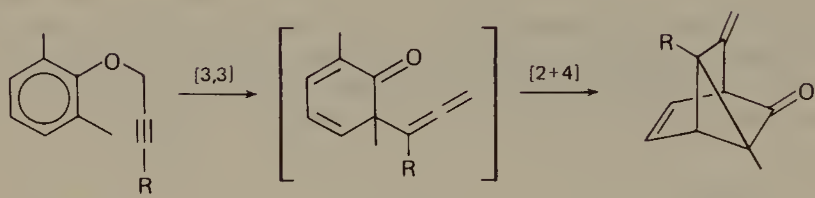
room temperature or below[368]. Thus, when the dichlorocyclopropane **654** was treated with butyllithium at –78° C, and the mixture was allowed to warm to room temperature, only 1,5-divinylcyclopentene and none of the allene **655** was obtained. The great enhancement in rate of cyclization of this isomer is attributed to the ease with which $C_{(2)}$ and $C_{(7)}$ in **655** can approach each other in the proper orientation with relatively little angle strain, and to the ease with which the rupturing 4–5 bond can be oriented parallel to the p orbitals on $C_{(6)}$ and $C_{(7)}$[368].

5. *Claisen-type rearrangements*

a. Aryl propargyl ethers. Aryl propargyl ethers undergo thermal rearrangement readily and although 3-chromenes are generally the products actually isolated instead of allenes, the evidence that allenes are intermediates is convincing[369]. The mechanism of formation of 3-chromene (**658**) from phenyl propargyl ether is summarized in Scheme 36. 6-Allenyl-2,4-cyclohexadienone (**656**), formed in the initial [3,3] rearrangement, undergoes in succession tautomerization, [1,5] hydrogen shift, and finally electrocyclization resulting in **658**. Evidence supporting this sequence includes these findings[369]: *o*-Allenylphenol (**657**) rearranges readily at 80° C giving **658**. The presence of substituents at positions 2 and 6 of the ring, as in **659a**, prevents enolization of the allenylcyclohexadienone **660a**, and an internal Diels–Alder reaction occurs instead yielding the tricyclic ketone **661a**. The location of deuterium in **661b**, obtained by rearrangement of **659b**, shows that reversal of the propargyl chain occurs, as required for a [3,3] rearrangement in the initial step.



SCHEME 36.

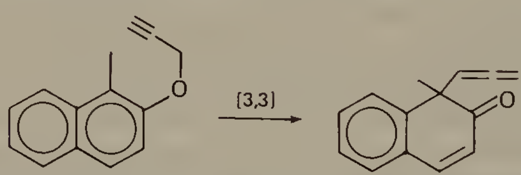


(a) R = H

(b) R = D

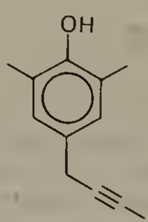
(c) R = Me

The allenyl derivative survives and can be isolated when the rearrangement of propargyl 1-methyl-2-naphthyl ether is carried out at 160–170° C (equation 85)[370].



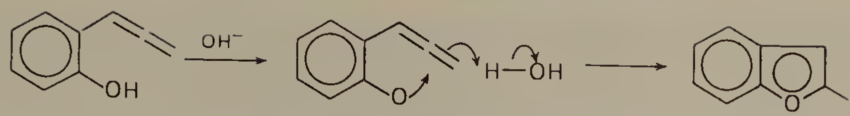
(85)

Unlike their allylic counterparts *o*-allenylcyclohexadienones (**660**) show little tendency to rearrange to the *p*-substituted phenol. With **659**c, however, a small amount of **662** was obtained along with the tricyclic ketone **661**c[369].



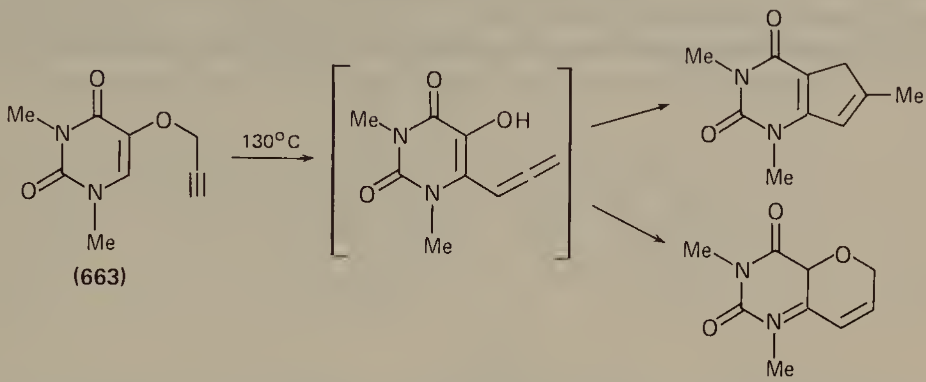
(662)

The effects of substituents on the rate and course of the rearrangement have been reported[371–373]. Benzofurans instead of chromenes may be formed by the rearrangement of *o*-allenylphenols in the presence of base, as illustrated in equation (86)[374]. Accordingly, the thermal rearrangement of aryl propargyl ethers in the presence of certain bases yields benzofurans[375].



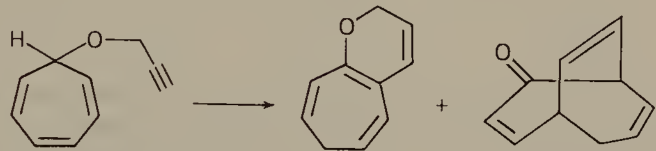
(86)

Both types of products are formed by thermal rearrangement of the pyrimidyl propargyl ether **663**, and the ratio of the products is strongly solvent dependent[376].

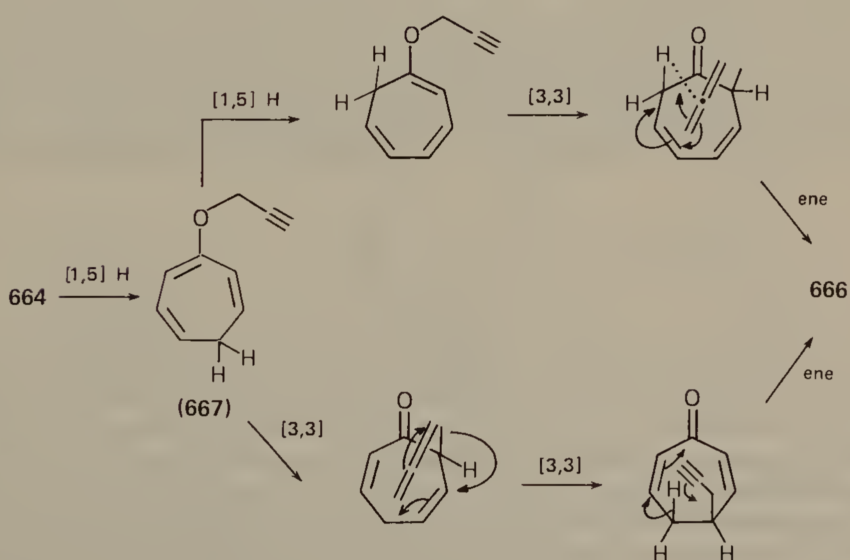


(663)

Two products, **665** and **666**, are formed by thermal rearrangement of the propargyl cycloheptatrienyl ether **664**[377]. Formation of **665** can be understood in



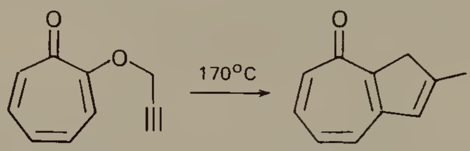
(664) (665) (666)



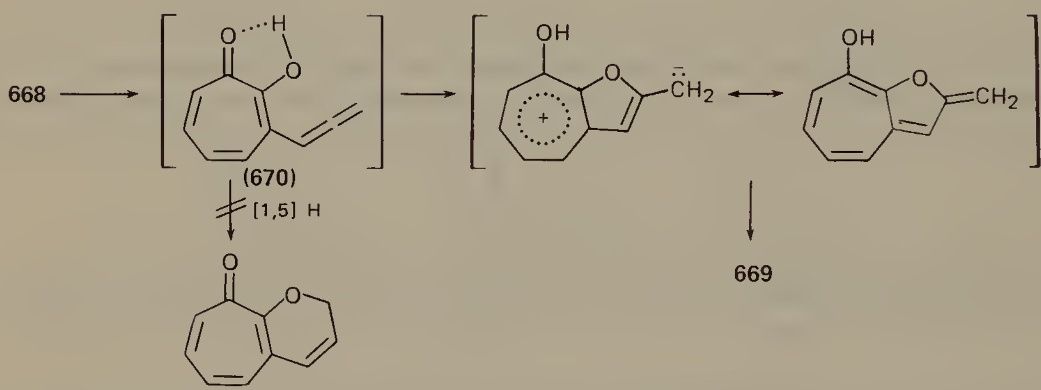
SCHEME 37.

terms of an initial [1,5] hydrogen shift giving **667** followed by the same sequence of steps as involved in the formation 3-chromene from phenyl propargyl ether. The formation of **666** is more involved, and two plausible alternate routes, summarized in Scheme 37, have been proposed. The first step of both paths also involves the formation of **667**, but they diverge from this point on, one involving, in succession, [1,5], [3,3] and ene-rearrangement while the other consists of two [3,3] and an ene-rearrangement. There is little basis for choosing one route over the other, and possibly both are operative[377].

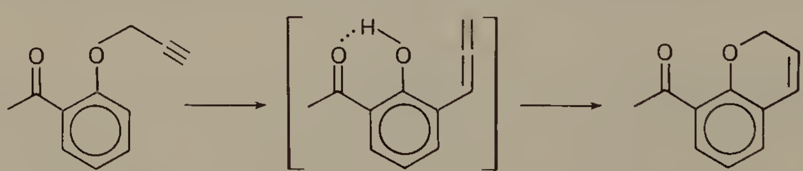
The sole product of thermal rearrangement of propargyl tropolone ether (**668**) is 2-methyl-8*H*-cycloheptal[*b*]furan-8-one (**669**), signifying that cyclization of the



(668) (669)



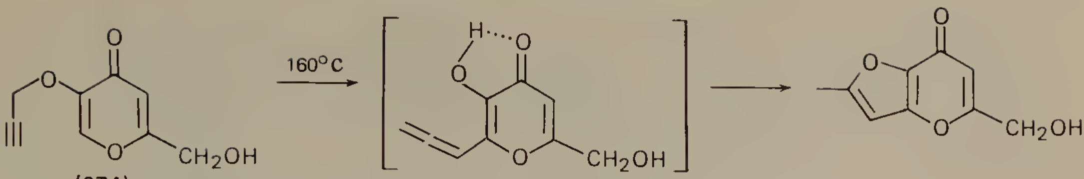
intermediate allenyltropolone **670** involves nucleophilic attack of oxygen on the sp carbon through intramolecular base catalysis. The strong intramolecular hydrogen bridge in **670** may be partially responsible for the failure to rearrange by [1,5] hydrogen migration and cyclization, but it is not the only factor as evidenced by the exclusive formation of 8-acetyl-2*H*-1-benzopyran (**673**) from **671**[377]. Strong intramolecular hydrogen bonding would be anticipated in the intermediate **672**.



(671) (672) (673)

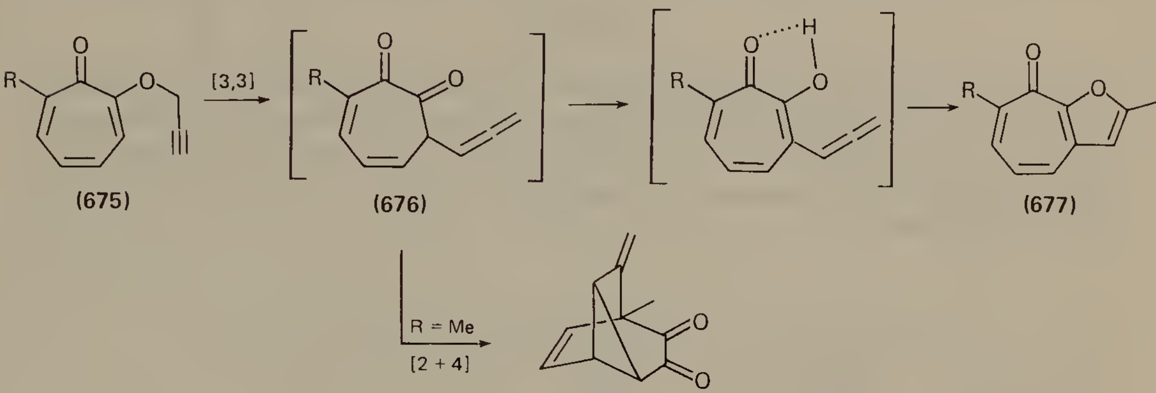
Behaviour analogous to **668** is observed in the rearrangement of the pyranone derivative **674**[378].

The rearrangement of 7-substituted tropolone propargyl ethers **675** affords mainly the cycloheptafuranones **677**, in conformity with the behaviour of the parent **668**[379]. A small amount of the tricyclic diketone **678** was formed from the 7-methyl derivative, signifying that the [2 + 4] path is competitive with the



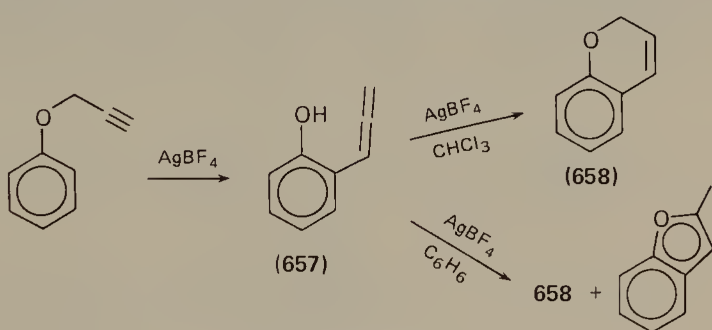
(674)

tautomerization of **676** in this case. The rearrangement of 3-substituted tropolone propargyl ethers can also be understood in terms of allenic intermediates[379].



(675) (676) (677) (678)

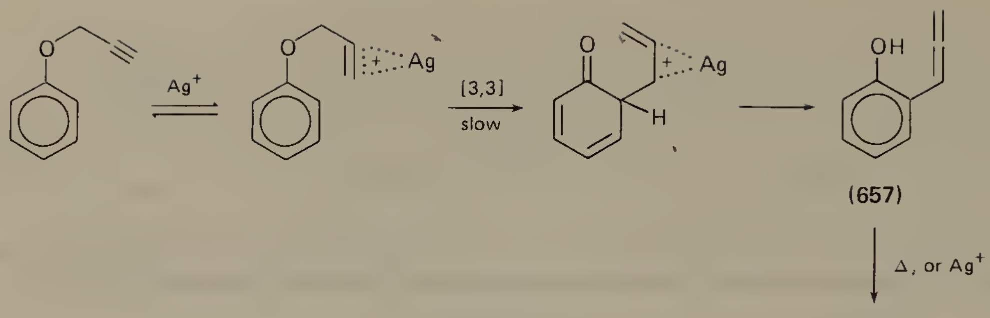
Silver salts exert a dramatic catalytic effect on the rearrangement of aryl propargyl ethers, increasing the rate by factors as large as 10^5 in some cases, and permitting reactions to be carried out at 20–80° C instead of 160–200° C as required for the uncatalysed reactions[370]. Thus, the rearrangement of phenyl propargyl ether to 3-chromene (**658**) occurs at 61° C in the presence of $AgBF_4$ in chloroform; a mixture of **658** and 2-methylbenzofuran is formed when benzene is



(657) (658)

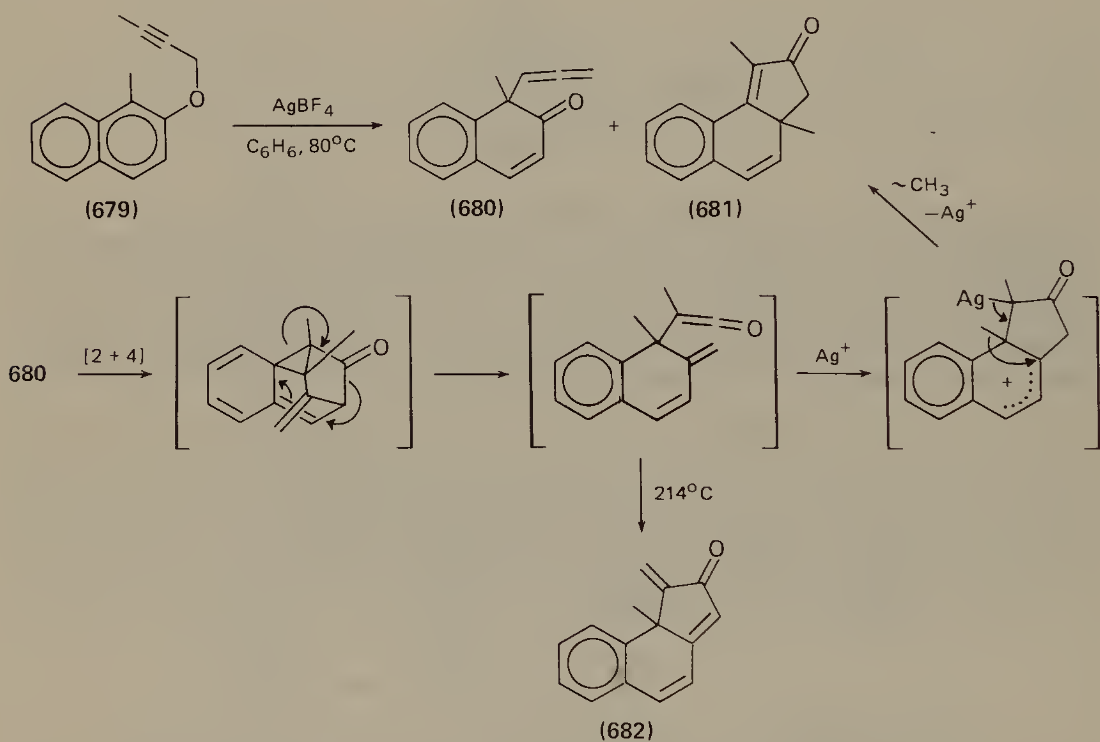
used as solvent. Similarly, treatment of *o*-allenylphenol with $AgBF_4$ in chloroform afforded 3-chromene, while the use of benzene as solvent afforded 3-chromene and 2-methylbenzofuran[370]. A mechanism has been proposed which involves rapid, reversible π complexing of the triple bond, followed by rate-determining silver-ion induced [3,3] sigmatropic rearrangement with subsequent tautomerization and loss of Ag^+ as outlined in Scheme 38. The conversion of *o*-allenylphenol to **658**, which occurs spontaneously at room temperature, is also catalysed by silver ion.

The catalysed rearrangement of propargyl 1-methyl-2-naphthyl ether at 80° C gives the same allenyl ketone as obtained from the thermal reaction at 160–170° C (see equation 85). The analogous 2-butynyl ether **679**, on the other hand, affords a



SCHEME 38.

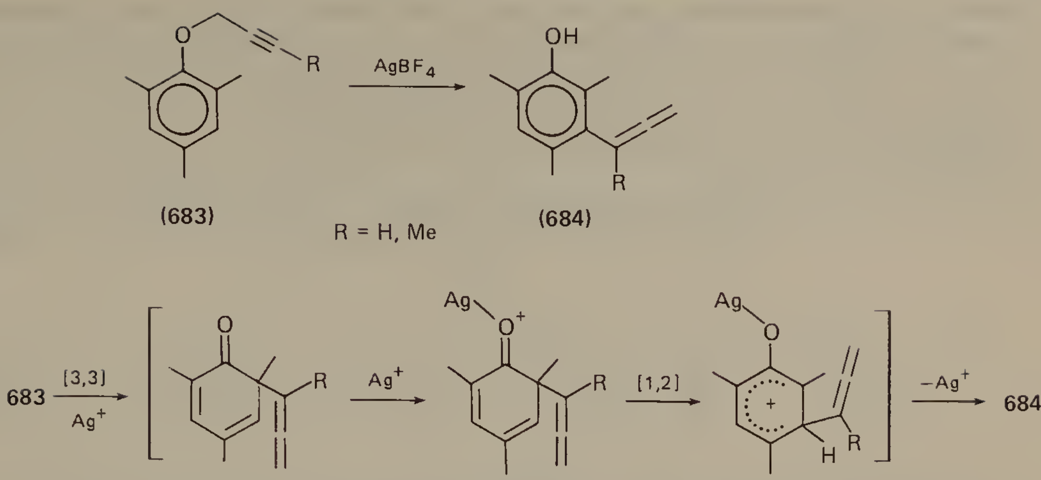
mixture of two ketones **680** and **681**[370]. The tricyclic ketone **681** is formed by rearrangement of **680**, and the mechanism outlined in Scheme 39 has been proposed for the transformation. It is worth noting that the purely thermal rearrangement of **679** at 214°C furnishes the isomeric ketone **682**, apparently by the path shown in Scheme 39.



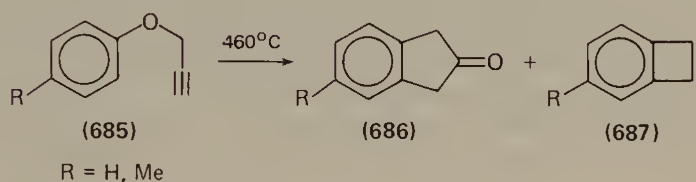
SCHEME 39.

The catalysed rearrangement of mesityl 2-alkynyl ethers **683** yields the *m*-allenic phenols **684**, the reaction occurring with a single inversion of the propargylic group[370]. The initial step (Scheme 40) consists of a [3,3] rearrangement, but in this case the product cannot tautomerize, and undergoes instead a silver-catalysed dienone–phenol rearrangement.

Flash vacuum thermolysis of phenyl propargyl ether at 460° C gives a mixture of 2-indanone and 1,2-dihydrobenzocyclobutene as shown in equation (87), R = H[380]. The *p*-tolyl ether, R = Me, behaves in the same way[381]. The results from these and

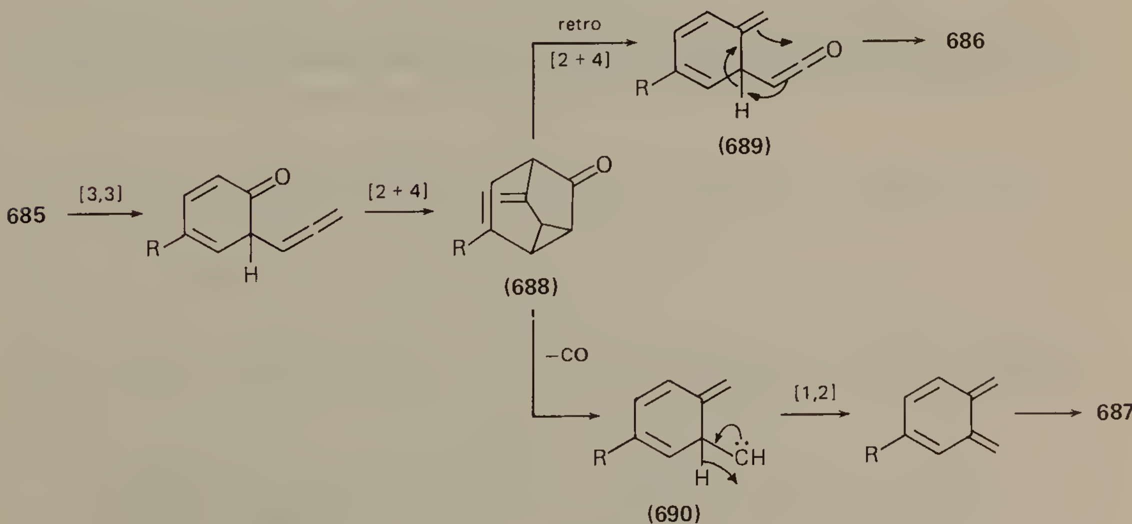


SCHEME 40.



(87)

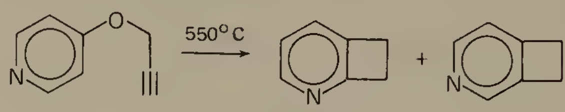
other studies utilizing the *o*- and *m*-tolyl derivatives support a mechanism (Scheme 41) involving initial [3,3] rearrangement followed by intramolecular [2 + 4] cycloaddition giving the tricyclic ketone **688** which serves as a common intermediate for both final products. A retro [2 + 4] process giving the ketene **689** and subsequent cyclization and hydrogen migration affords the indanone **686**. This sequence is reminiscent of that presented earlier for the rearrangement of the naphthyl ether **680** to **682**. The route to **687** consists of decarbonylation of **688** giving the carbene **690** which undergoes [1,2] hydrogen migration and cyclization.



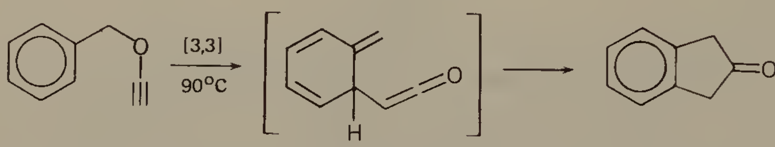
SCHEME 41.

The rearrangement of propargyl 4-pyridyl ether is more deepseated and involves scrambling of the position of the nitrogen atom (equation 88)[382]. [3,3] Rearrangement to the allenyl derivative is believed to be the initial step.

Benzyl ethynyl ether rearranges to 2-indanone under mild conditions, presumably by way of the ketene as shown in equation (89)[383].



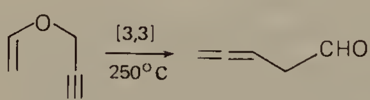
(88)



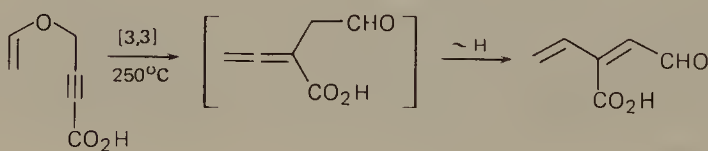
(89)

b. Propargyl vinyl and allenyl vinyl ethers, acetals, etc. Propargyl vinyl ethers undergo Claisen-type rearrangements readily giving β-allenyl carbonyl compounds[327,384]. The rearrangement can be accomplished by heating the previously isolated ether or, more commonly, by heating reaction mixtures in which the ether is formed from suitable precursors and undergoes rearrangement *in situ*.

Vinyl propargyl ether itself rearranges at 250° C in a flow system to give 3,4-pentadienal (equation 90)[385], while the allenic acid that is formed initially in the rearrangement of **691** isomerizes spontaneously to the conjugated diene[386].

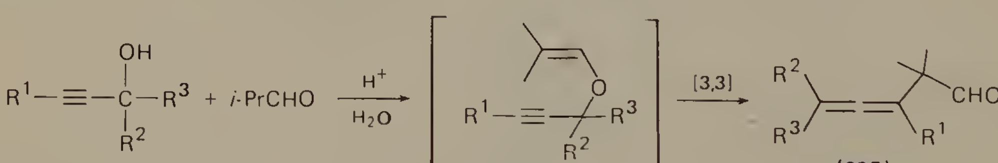


(90)



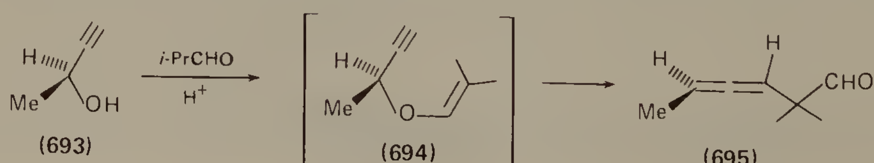
(691)

A variety of β-allenic aldehydes **692** has been prepared by heating propargylic alcohols with isobutyraldehyde in the presence of an acid catalyst[387].



(692)

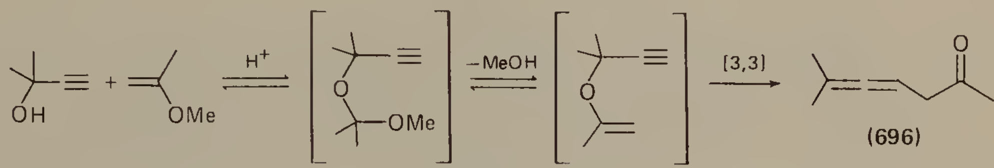
The configuration of optically active allenes can be correlated with that of the propargylic alcohol precursor on the basis of the stereochemistry of the cyclic



(693) (694) (695)

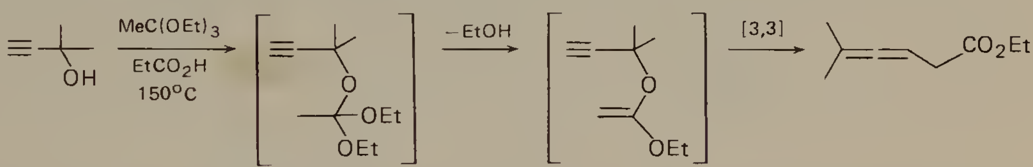
transition state of the [3,3] rearrangement. Thus, rearrangement of the ether **694** derived from (*S*)-(+)-3-butyn-1-ol (**693**) gives (−)-2,2-dimethyl-3,4-hexadienal which can be assigned the (*S*) configuration **695**[388].

Treatment of propargylic alcohols with vinyl ethers in the presence of an acid catalyst provides a convenient route to vinyl propargyl ethers which generally undergo Claisen rearrangement *in situ*[327,389,390]. Thus 6-methyl-4,5-hepta-dien-2-one (**696**) is obtained when 2-methyl-3-butyn-2-ol is heated with excess 2-methoxypropene in the presence of *p*-toluenesulphonic acid[390].



(696)

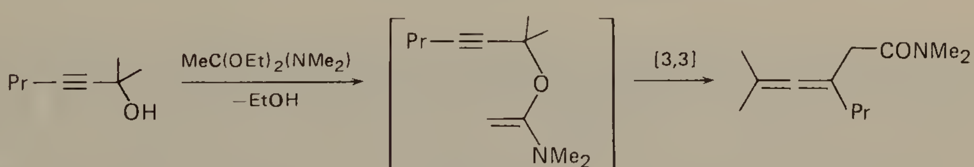
There are several variations of the Claisen rearrangement involving changes in the vinyl portion of the structure which result in the formation of esters, acids or amides as products. In the 'ortho ester Claisen rearrangement' β-allenyl esters are obtained when propargyl alcohols are heated with an ortho ester in the presence of an acid catalyst[391–393]. The reaction sequence involves ester interchange, de-alcoholation, and Claisen rearrangement, as illustrated in Scheme 42. This type of



SCHEME 42.

sequence has found application in the synthesis of insect juvenile hormone analogues[394] and the sex pheromone of the male dried-bean beetle[395].

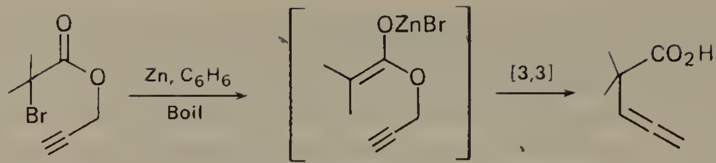
In a variation of the ortho ester reaction, propargyl alcohols are condensed with 'amide acetals'[396,397]. Thus, when *N,N*-dimethylacetamide diethyl acetal is heated with 2-methyl-3-heptyn-2-ol, *N,N*,5-trimethyl-3-propyl-3,4-hexadienamide is formed by a sequence similar to that in the ortho ester Claisen rearrangement (Scheme 43)[396–398]. With alcohols containing a terminal triple bond other products arise from intramolecular transfer of dimethylamine or ethanol to the triple bond.



SCHEME 43.

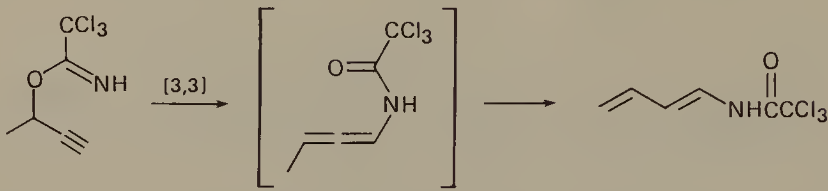
In the 'Reformatsky–Claisen' reaction, the zinc enolate, formed by the reaction of zinc with an α-bromo ester, rearranges spontaneously giving the allenic acid in nearly quantitative yield (equation 91)[399].

Propargylic trichloroacetimidates undergo [3,3] rearrangement, but the allene that is formed initially isomerizes spontaneously to the conjugated diene derivative (equation 92)[400]. Propargylic pseudo ureas rearrange thermally, but here also the



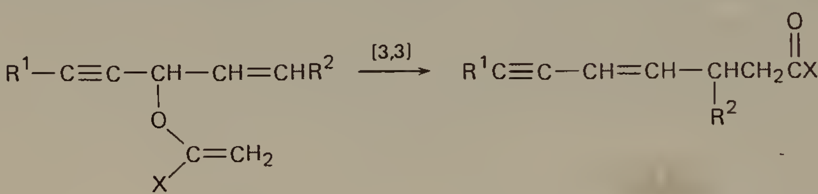
(91)

initially formed allenic derivatives suffer further rearrangement giving, ultimately, 2-pyridones in good yield[401].



(92)

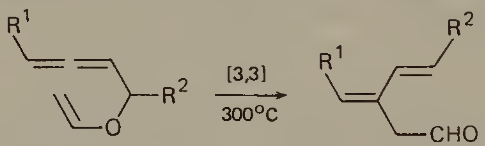
The allylic group, instead of the propargylic group, participates in the rearrangement of ethers of type **697**[88,402–404].



(697)

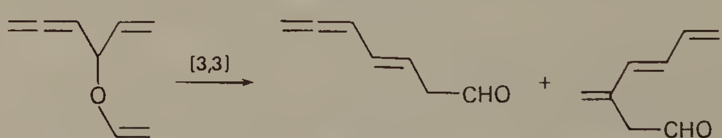
X = H, OEt

Vinyl ethers **698** derived from allenic alcohols undergo [3,3] rearrangement at 300° C giving unsaturated aldehydes in high yield[405]. The very substantial lowering (ca 20%) of the activation energy for Cope rearrangements that is noted when



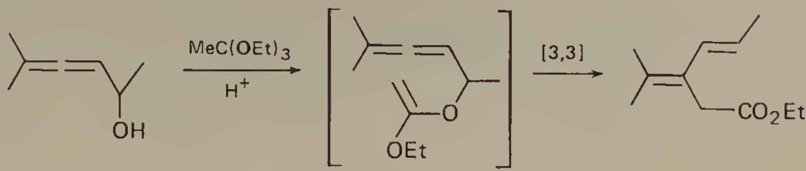
(698)

olefinic groups are replaced by allenic groups is not observed for the Claisen rearrangement. For example, the energy of activation for rearrangement of **698** ($R^1 = H$, $R^2 = i$-Pr) is 28.6 kcal/mol – a value only 2 kcal/mol below that for the unsubstituted ethylenic analogue[88]. Steric interactions involving the isopropyl group may cause some elevation of the barrier, but other studies indicate comparable reactivities of olefinic and allenic groups in Claisen rearrangements; for example, the ratio of **700** to **701** from rearrangement of **699** is 77:23[405].

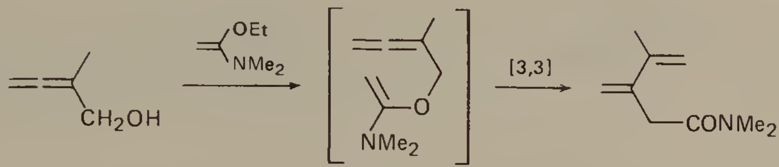


(699) (700) (701)

Typical examples of 'ortho ester' and 'amide acetal' variations of the Claisen rearrangement carried out on allenic substrates are summarized in equations (93) and (94)[406,407].

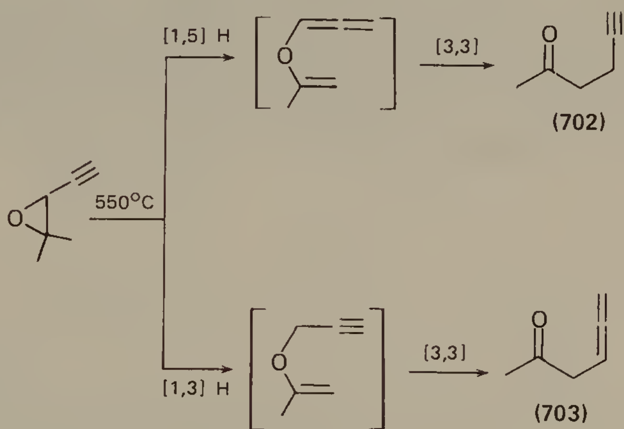


(93)



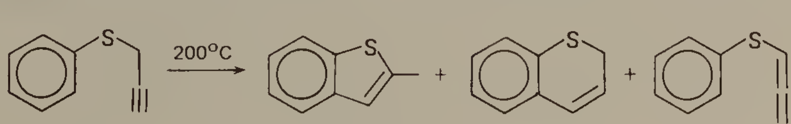
(94)

Mixtures of the acetylenic and allenic ketones **702** and **703** are formed by thermolysis of 3-ethynyl-2,2-dimethyloxirane at 550° C (Scheme 44)[408]. It is believed that these products are formed by Claisen rearrangement of the initially formed allenic and propargylic ethers as shown in Scheme 44.



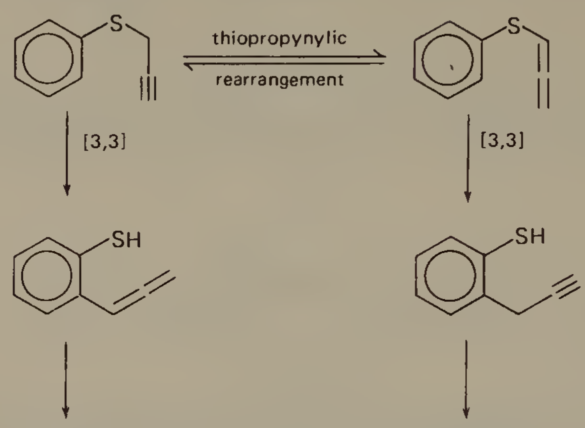
SCHEME 44.

c. Thio-Claisen rearrangements. When phenyl propargyl sulphide is heated at 200° C in quinoline, a mixture containing **705**–**707** is obtained[409]. At short reaction times **706** is not present in the mixture, but does appear at higher temperatures or longer times at the expense of **707** which disappears. Evidence has been presented which shows that **707** is not formed from **704** by prototropic rearrangement; the interconversion of **704** and **707**, referred to as a 'thiopropynylic rearrangement', may involve a direct [1,3] rearrangement analogous to the thial-



(704) (705) (706) (707)

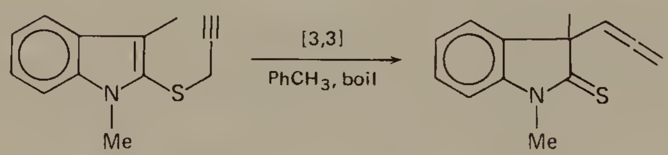
lylic and silapropynylic rearrangements[410]. The mechanisms proposed for the rearrangements are summarized in Scheme 45.



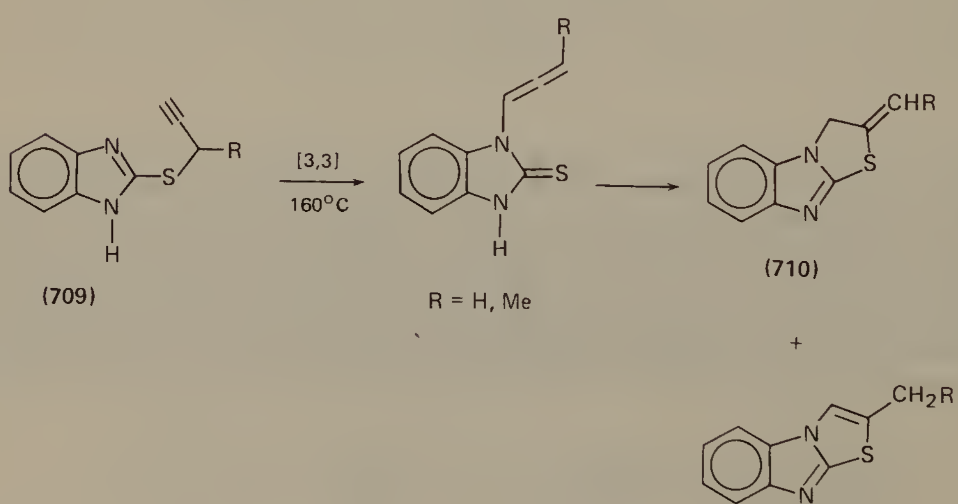
706 705

SCHEME 45.

The rearrangement of 4-quinolyl propargyl sulphide[411] and 2-thienyl propargyl sulphide[412,413] has been studied. In both cases the initial step involves [3,3] rearrangement to the allenyl derivative which undergoes cyclization. The allenic product from rearrangement of the indole derivative, **708**, is stable and can be isolated[414]. In the case of the benzimidazole, **709**, however, cyclization of the intermediate allene occurred giving a mixture of **710** and **711**[415].

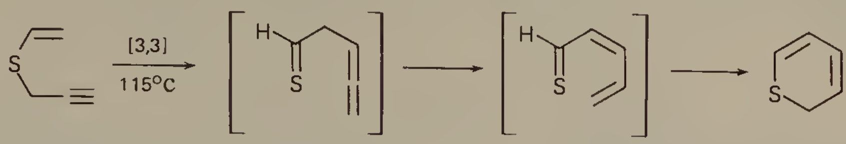


(708)



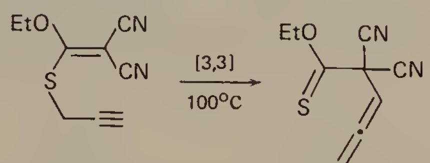
(709) R = H, Me (710) (711)

The thio-Claisen rearrangement has been carried out with acyclic derivatives and the initial allenic products have been isolated in a few instances, but in most cases the products isolated are those formed by further cyclization. Thus, the allenic thio aldehyde formed initially in the rearrangement of propargyl vinyl sulphide (equation 95) isomerizes and cyclizes, and 2*H*-thiopyran is the product isolated[416].



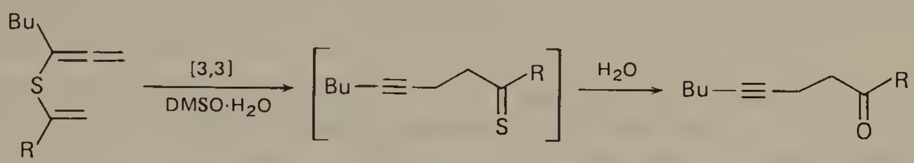
(95)

The allenic thione ester **713**, formed from **712** by rearrangement under mild conditions is stable and can be isolated[417]. Other examples of rearrangements of propargylic sulphides have been reported[417-419].



(712) (713)

Vinyl allenyl sulphides rearrange at 125–135° C giving γ-acetylenic thio aldehydes or ketones (equation 96)[420]. Water, which is present in the reaction

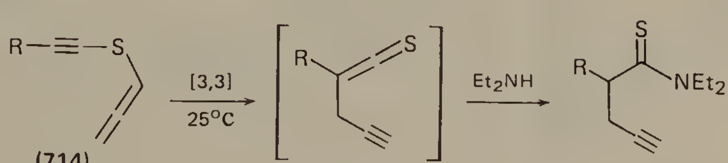


(96)

R = H, Me

medium, serves to hydrolyse thioaldehydes as soon as they are formed and prevents their polymerization.

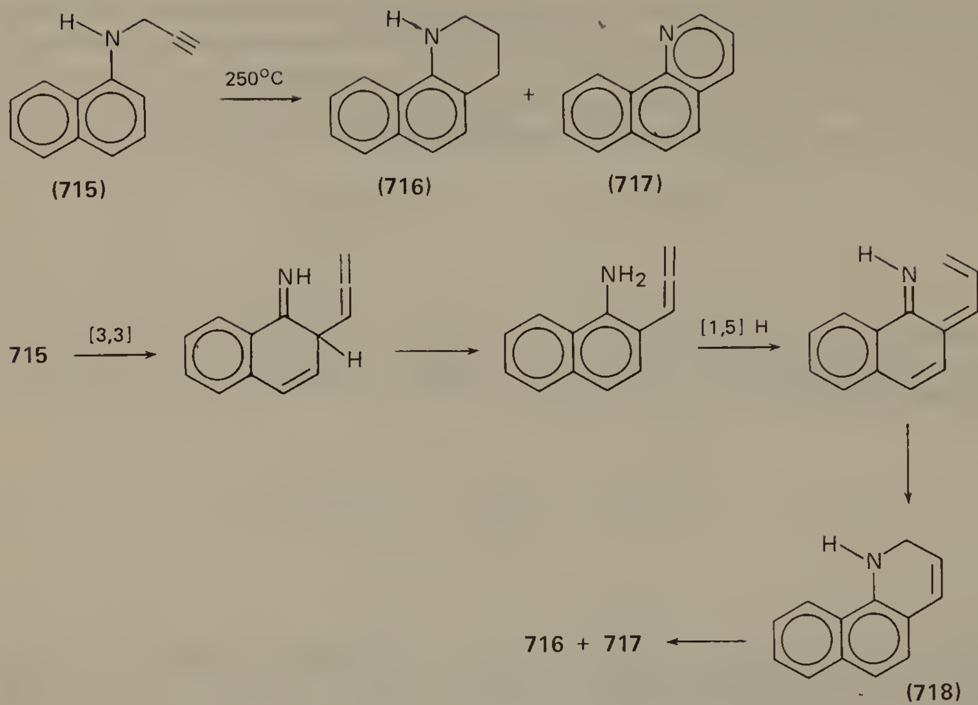
1-Alkynyl allenyl sulphides **714** rearrange at room temperature giving thioketenes, which can be trapped by reaction with amines[421]. Similar behaviour is observed for thioketenes formed initially by the [3,3] rearrangement of 1-alkynyl 2-alkynyl sulphides[422].



(714)

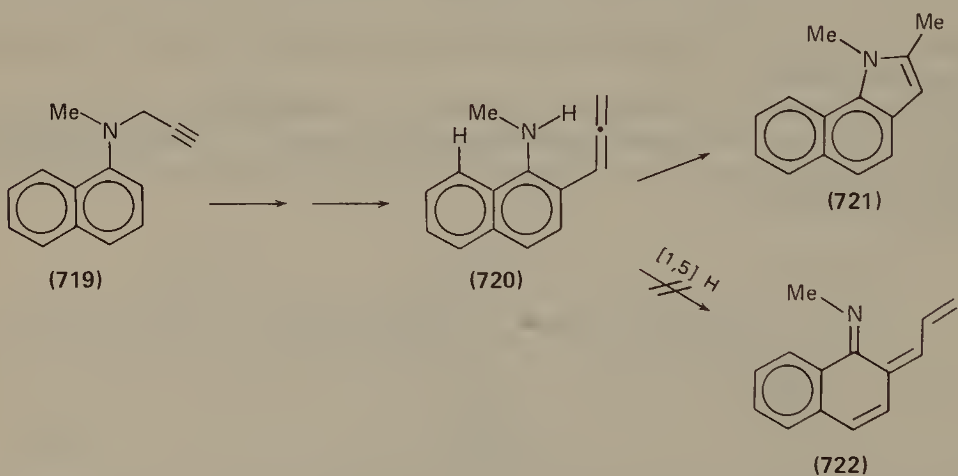
R = Me, Et

d. Amino-Claisen rearrangements. N-Propargylaniline fails to undergo the Claisen rearrangement but *N*-propargyl-1-naphthylamine rearranges at 250° C giving **716** and **717**[423]. Similar behaviour is found for the 2-naphthylamine derivative. The sequence of steps (Scheme 46) is the same as for the *O*-Claisen rearrangement, the difference arising from the fact that **718** is unstable and disproportionates to **716** and **717** under the reaction conditions. Interestingly, the *N*-methyl analogue **719** behaves differently, giving the benzindole **721**. Steric interaction between the

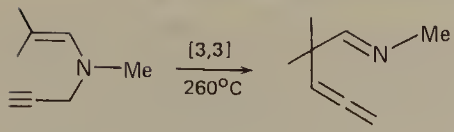


SCHEME 46.

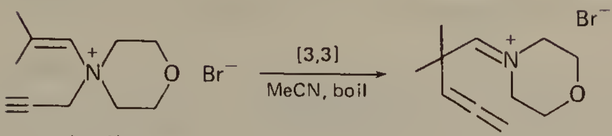
N-methyl group and the perihydrogen in **720** inhibit attainment of the transition state geometry required for [1,5] hydrogen transfer leading to **722**. Instead nucleophilic attack by nitrogen on the sp carbon occurs faster, resulting in the formation of **721**.



Examples of [3,3] rearrangement of acyclic vinyl propargyl amines have been reported, several of which illustrate the facilitation of rearrangement brought about by a positive charge on nitrogen. Thus, rearrangement of the propargyl enamine **723** occurs at 260° C[424], whereas the enammonium salt **724** rearranges in boiling acetonitrile[425]. The rearrangement of allenic allylic ammonium salts has been studied[426].



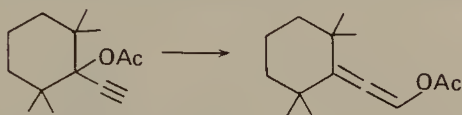
(723)



(724)

6. *Propargyl ester — allenyl ester rearrangements*

Rearrangement of propargylic esters to allenic esters occurs at elevated temperatures, as shown in equation (97)[427]. The parent esters themselves undergo

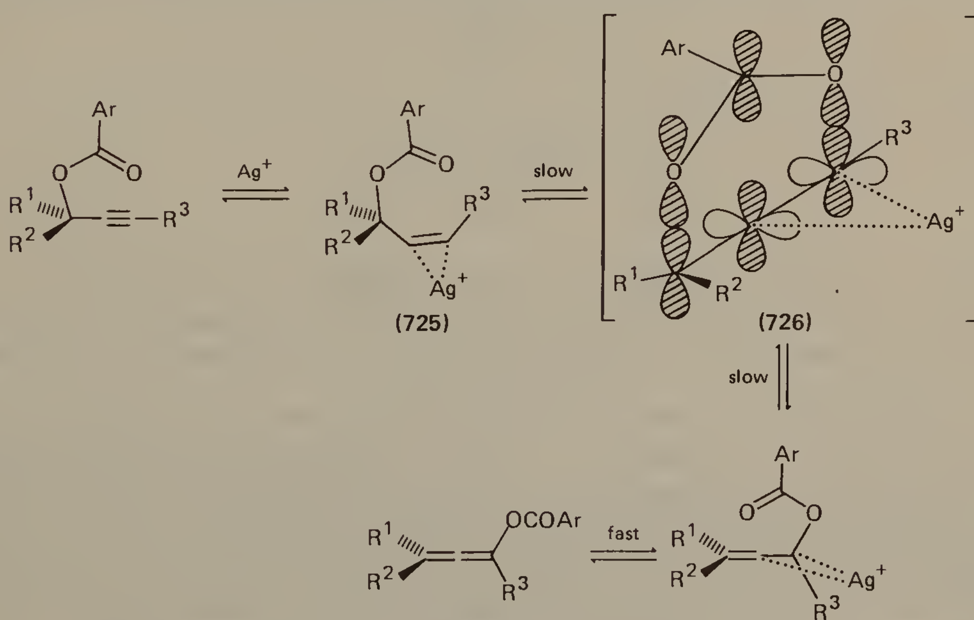


(97)

interconversion in the range 240–276° C (equation 98), but the reaction is accompanied by fragmentation processes[329]. Certain metals and metal salts, notably silver salts, exert a remarkable catalytic effect and permit the interconversion of propargylic and allenic esters under very mild conditions[428–430].

$$H_2C(OAc)\text{—}C\equiv CH \rightleftharpoons H_2C=C=CH(OAc) \qquad (98)$$

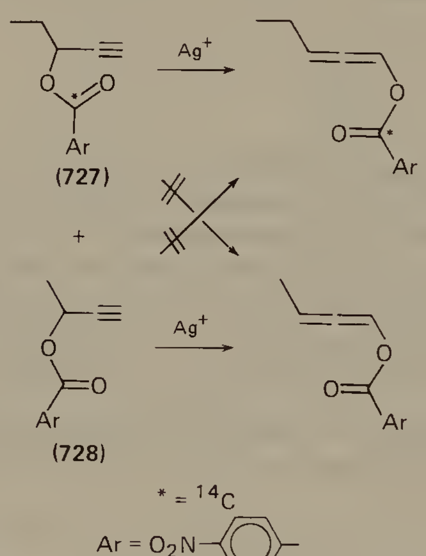
Details of the mechanism of catalysis by silver salts (Scheme 47), have been elucidated in an unusually thorough and exemplary study utilizing isotopic labelling

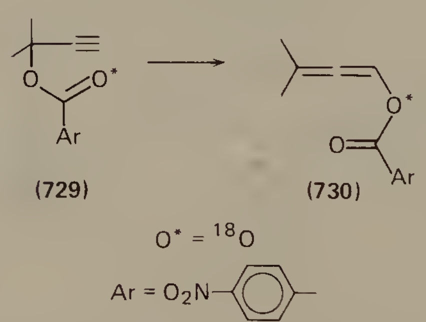


SCHEME 47.

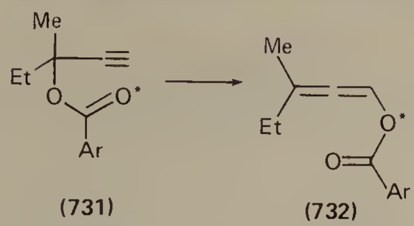
and stereochemical and kinetic techniques[211]. The rate-determining step involves rearrangement of a silver complex **725** which is formed in a rapid pre-equilibrium. As indicated in **726** complexing occurs with the p orbitals that are not involved in the quasicyclic six-electron transition state. The lowering of the energy of activation brought about by silver is attributed to the positive charge, and the rearrangement falls in the category of charge-induced [3,3] sigmatropic rearrangements[211].

The intramolecular nature of the rearrangement was established by the absence of crossover products when the rearrangement was carried out with an equimolar mixture of **727** and **728** in the presence of $AgBF_4$. It was shown in separate experiments that **727** and **728** rearrange at nearly identical rates. Rearrangement of **729**, labelled with ^{18}O in the carbonyl oxygen, gave **730** in which label appeared exclusively in the alkoxyl position. This evidence excludes the possibility of a mechanism involving ion pairs and also confirms the intramolecularity of the rearrangement[211].





Rearrangement of optically active propargyl esters gives inactive allenyl esters, but this is a result of Ag^+-catalysed epimerization of the initial ester, which occurs faster than the rearrangement itself. Thus when the rearrangement of the ^{18}O-labelled optically active ester (+)-**731** was run to 50% completion, the rotation of the recovered **731** was unchanged. The allenyl ester **732**, however, was racemic, even though the ^{18}O was in the alkoxyl portion exclusively. Further evidence for this rapid epimerization was obtained from studies of the interconversion of the

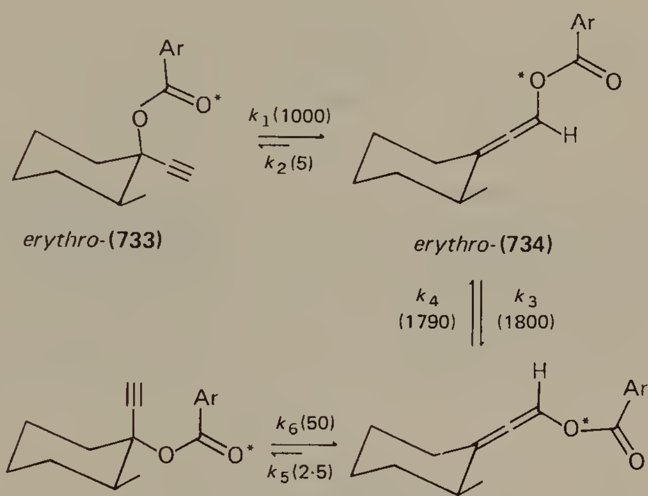


(731) (732)

O* = ^{18}O

Ar = *p*-nitrophenyl

^{18}O-labelled diastereomers **733** and **734** (Scheme 48). Rate constants were determined for a fixed concentration of $AgBF_4$, and relative values are given in parentheses with the appropriate arrow. In view of the great rate with which the allenyl esters, *erythro*-**734** and *threo*-**734**, are interconverted, it is not surprising that the allenyl ester **732** obtained from optically active **731** is racemic[211].



erythro-(733) *erythro*-(734)

threo-(733) *threo*-(734)

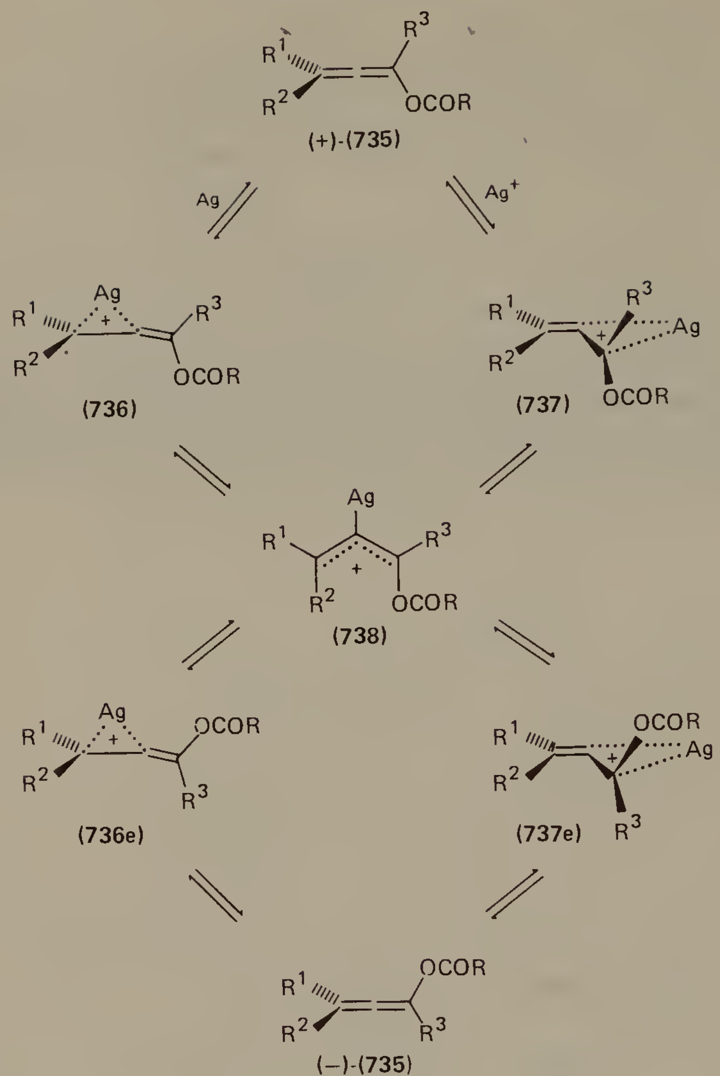
O* = ^{18}O

Ar = *p*-nitrophenyl

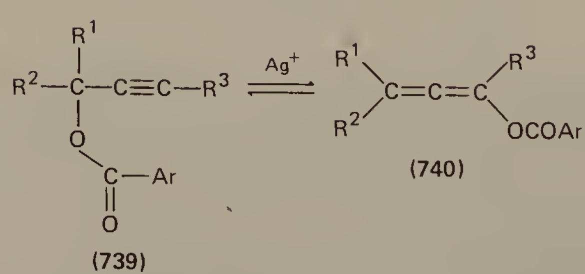
SCHEME 48.

The epimerization of esters by silver ion is probably initiated by π-complex formation, as illustrated in Scheme 49[211]. Two complexes, **736** and **737**, are possible, depending on which π bond is complexed. Rearrangement to the $C_{(2)}$ argentated allylic cation **738**, which is stabilized further by the ester oxygen, results in loss of chirality. Reversion to π-complexes can occur to give either **736** and **737** or their epimers **736**e and **737**e. Loss of Ag^+ from the latter two produces the enatiomer of the original allenic ester.

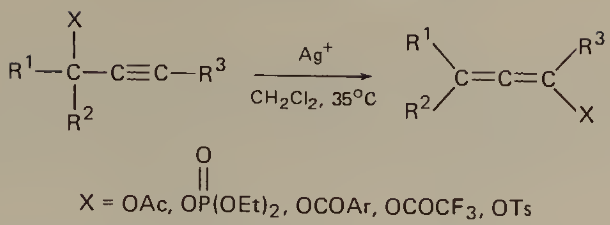
The position of equilibrium between the propargylic and allenic esters depends strongly on the substitution pattern[211]. When R^1 and R^2 are alkyl groups and R^3 is hydrogen, the allenic ester **740** is strongly favoured, but when R^1 is alkyl and both R^2 and R^3 are hydrogen, the allenic ester is only slightly favoured. When all three are alkyl groups, the propargylic ester **739** is slightly favoured.



SCHEME 49.

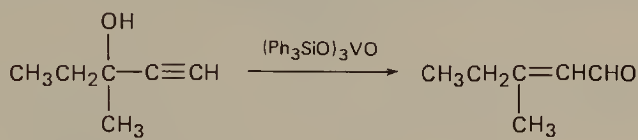


The scope of the catalysed rearrangement has been extended to a wide variety ot esters (equation 99), and a more convenient procedure has been developed in which the reaction is carried out with catalytic amounts (2.5 mol %) of AgOAc or $AgBF_4$ in dichloromethane[429].

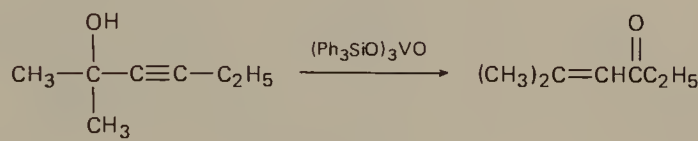


(99)

Tertiary propargylic alcohols undergo rearrangement to α,β-unsaturated aldehydes or ketones in the presence of silylvanadate catalysts, as illustrated in equations (100) and (101)[431]. The key step is believed to be a [3,3] sigmatropic

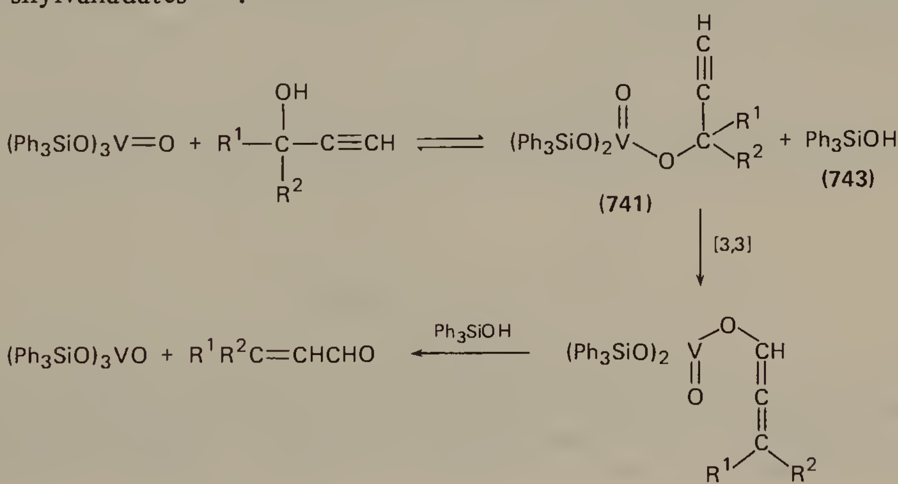


(100)

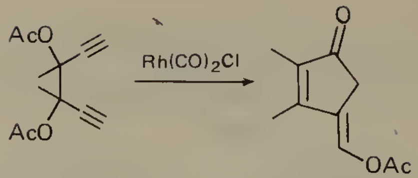


(101)

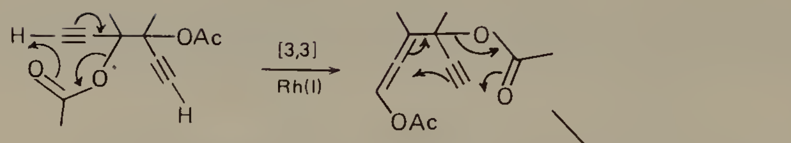
rearrangement of the vanadate ester **741**, which is formed initially by a transesterification reaction. The rearranged ester, **742**, undergoes transesterification with the silanol **743**, which was liberated in the first step, to give the product and regenerate the silylvanadate catalyst[431]. This type of rearrangement constitutes the key step in a recent stereospecific synthesis of Vitamin A[432]. A polymeric silylvanadate catlayst has been developed which has less tendency to undergo hydrolysis than the simple silylvanadates[433].



The rearrangement of 3,4-diacyloxy-1,5-hexadiynes to cyclopentenones in the presence of Rh(I), as illustrated in equation (102), is believed to involve a Rh(I)-catalysed propargylic–allenic ester rearrangement in the first step (see Scheme 50)[434]. Rearrangement of the second propargylic ester in **746** is accompanied by cyclization to **747**, and a retro-ene reaction giving **745** completes the sequence[434].



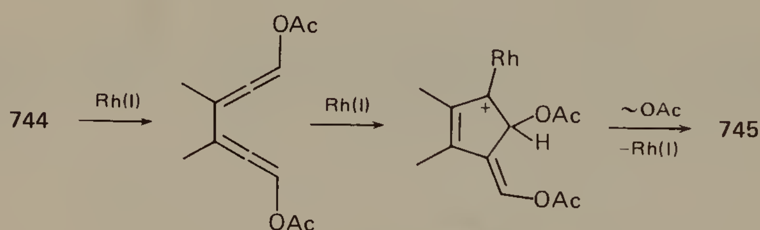
(744) (745) (102)



(744) (746) (747)

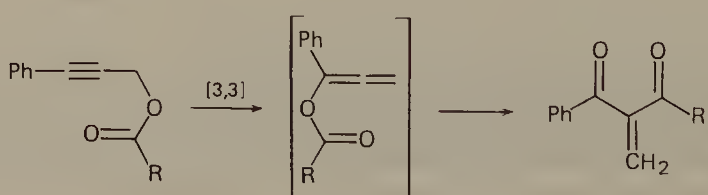
SCHEME 50.

Another possibility involves a double [3,3] rearrangement followed by cyclization to give the rhodium-stabilized carbene **748**. Acetate migration and loss of rhodium complete the sequence. This mechanism is particularly intriguing in view of the well-known stabilization of carbenes by rhodium and other transition metals, and in view of the similarity of this rearrangement to the very high-temperature rearrangement of 1,2,4,5-hexatetraene to fulvene which is believed to involve carbenes (Section VIII.B.4.e).



(748)

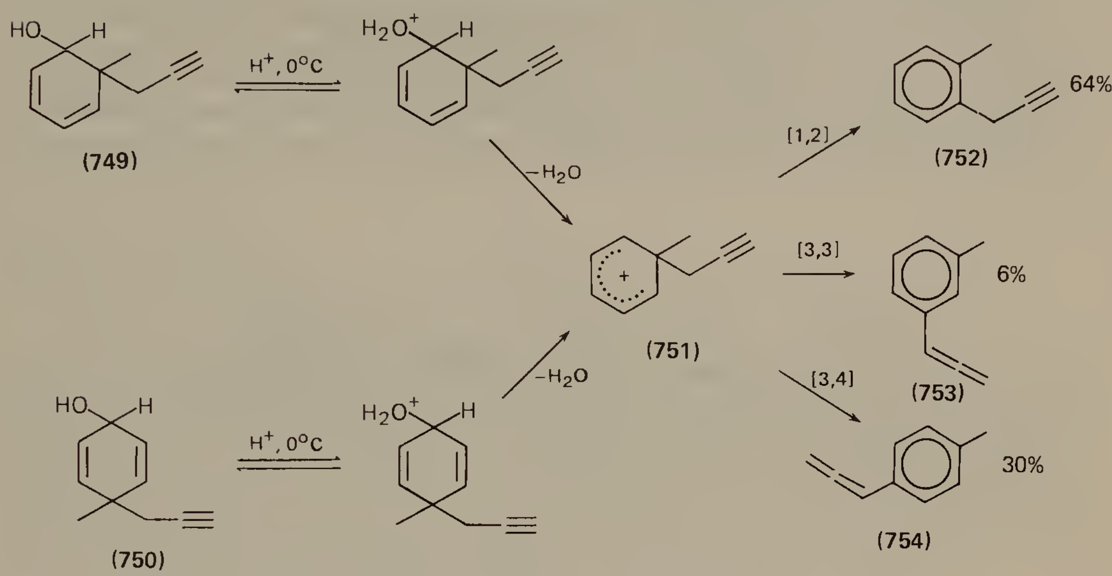
At very high temperatures, propargylic esters rearrange to 2-alkylidene-1,3-diones (equation 103)[435]. A mechanism has been proposed which consists of an initial [3,3] rearrangement to the allenyl ester, followed by a 1,3-acyl shift giving the dione. Vinyl esters are known to undergo 1,3-acyl shifts at 500–600° C[432].



(103)

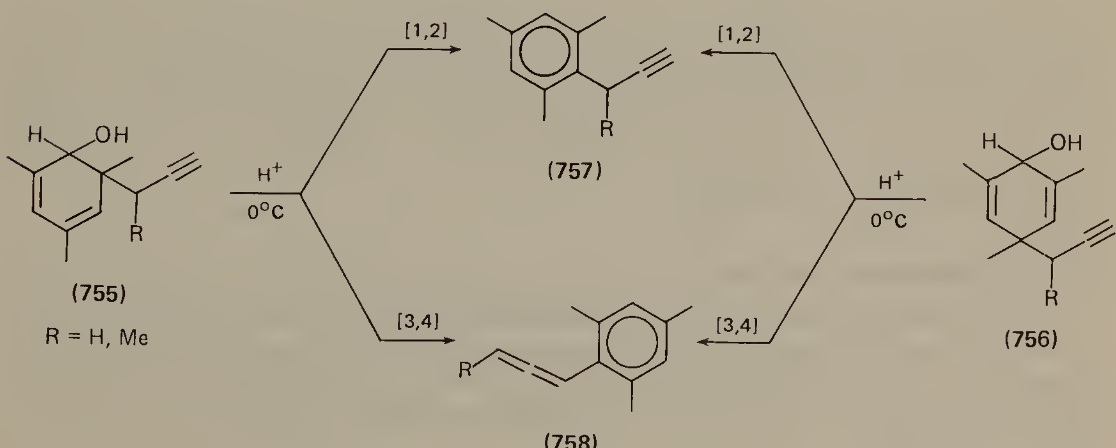
7. *Dienol–benzene and dienone–phenol rearrangements*

Propargylcyclohexadienols undergo three competitive sigmatropic rearrangement processes in the presence of acid, as illustrated in Scheme 51 for 6-methyl-6-propargyl-2,4-cyclohexadienol (**749**) and 4-methyl-4-propargyl-2,5-cyclohexadienol (**750**)[436]. The products, formed in essentially the same proportions from both



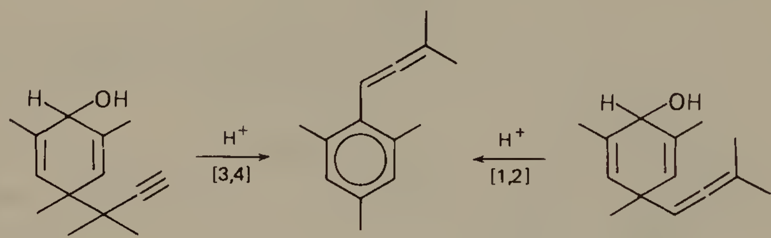
SCHEME 51.

alcohols, arise by rearrangement of the common benzenium ion **751**. The major products, **752** and **754**, are formed by charge-controlled [1,2] and [3,4] sigmatropic rearrangements, respectively, while **753** is the result of a charge-induced [3,3] rearrangement. All three rearrangements are suprafacial in both components. The strong preference for [1,2] and [3,4] processes is attributed to the greater charge delocalization in the transition states for these rearrangements[436]. The ratio of the rate constants, $k_{[3,4]}/k_{[1,2]}$, corrected for the statistical factor, is approximately unity.

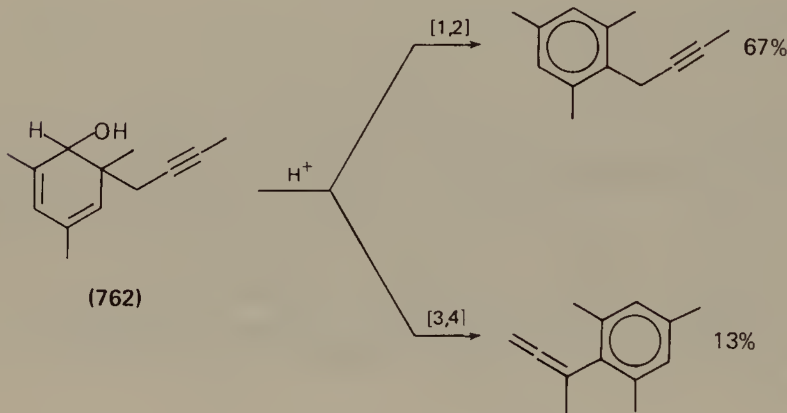


In the rearrangement of the mesitol derivatives, 755 and 756, the products are the propargylmesitylenes 757, formed by [1,2] shift, and allenylmesitylenes 758, formed by [3,4] rearrangement. The possibility that 758 arises by consecutive [3,3] and [1,2] rearrangements cannot be ruled out unequivocally, but it is rendered unlikely by the small yield of the [3,3] rearrangement product 753 which is obtained from 749 or 750[436].

Exclusive [3,4] rearrangement occurs with 759, giving 760, and exclusive [1,2] rearrangement of the allenyl chain occurs with 761, also giving 760. When methyl is substituted at the 3′-position on the propargyl chain as in 762, however, the [3,4] process is inhibited and $k_{[3,4]}/k_{[1,2]} \simeq 0.4$. These effects have been rationalized in terms of steric factors in the transition states for the two types of rearrangement[436].



(759) (760) (761)

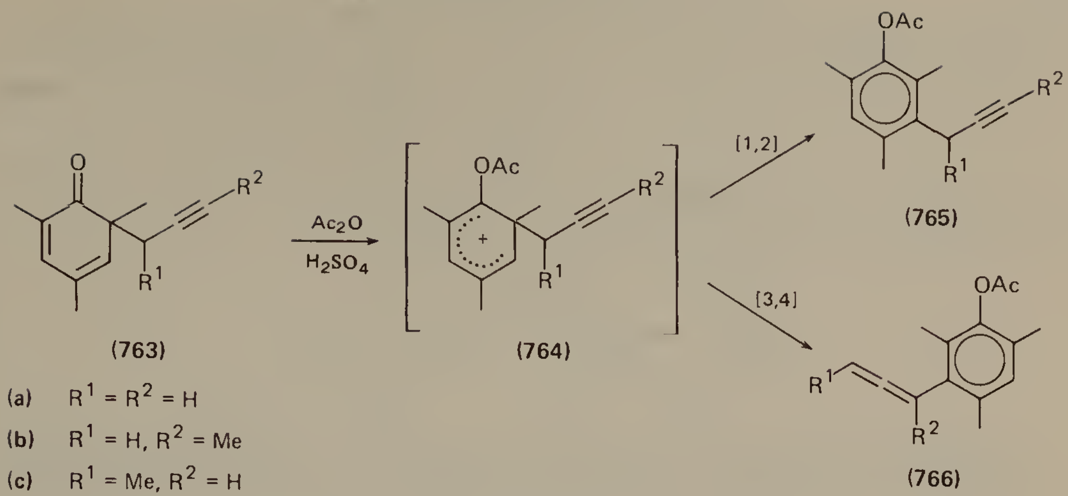


(762)

Analogous rearrangements occur when propargylcyclohexadienones, 763, are treated with acetic anhydride containing a catalytic amount of H_2SO_4[437]. The products, 765 and 766, arise by [1,2] and [3,4] rearrangements of the acetoxybenzenium ion 764. For the most part, the effects of substituents are comparable to those noted for the dienols. The charge-induced [3,3] rearrangement has not been detected for the dienones[437].

8. Ene and retro-ene reactions

The ene and retro-ene reactions, commonly classified as $(\pi^2s + \pi^2s + \sigma^2s)$ processes, are closely related to [1,5] sigmatropic and [1,5] homosigmatropic rearrangements. Reactions have been reported in which allenes are formed as products of ene and retro-ene reactions involving alkynes, and others in which allenes serve as the ene component.



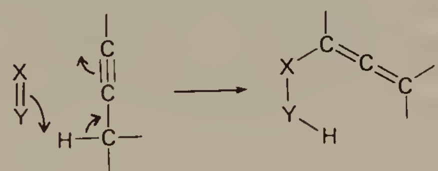
(763) (764) (765) (766)

(a) $R^1 = R^2 = H$

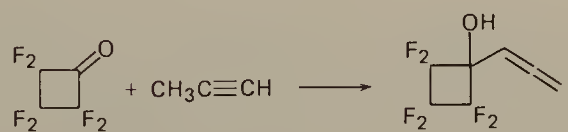
(b) $R^1 = H, R^2 = Me$

(c) $R^1 = Me, R^2 = H$

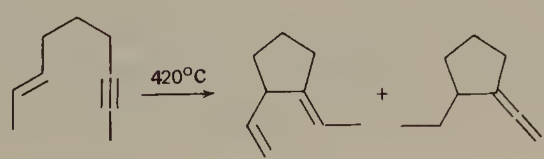
Reactions involving alkynes functioning as the 'ene' component can be represented by the general equation (104) where X=Y represents a π-bonded grouping such as $R_2C{=}O$, RC≡CR, etc. Typical examples include those summarized in equations (105)[438] and (106)[439]. Two competitive intramolecular ene reactions occur in the rearrangement of *trans*-2-nonen-7-yne (**767**), and the products **768** and **769** are obtained in the ratio 8:1. In the formation of the minor product **769**, the alkyne portion of **767** serves as the ene component and the olefin portion as the enophile, while the reverse is true for the formation of the major product.



(104)



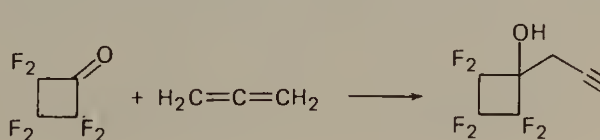
(105)



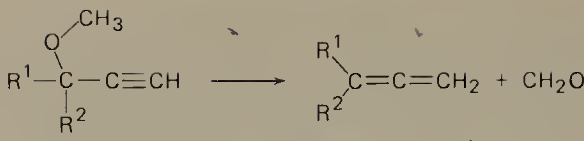
(106)

(767) (768) (769)

Allenes can function as the ene component, as illustrated in equation (107), and can be formed as products of retro-ene reactions, typified by equation (108)[438,440]. Activation energies and entropies for the cleavage of propargyl ethers, illustrated in equation (108), lie in the range 36–42 kcal/mol and –13 to



(107)

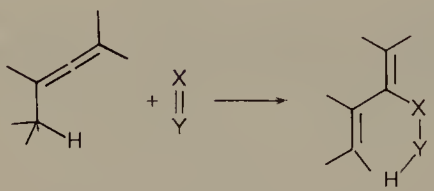


(108)

-6 e.u., respectively. Formation of (*R*)-**771** from (*S*)-**770** established that the rearrangement is concerted[440].

(770) (771)

Alkylallenes show high reactivity as ene components with a variety of enophiles, as summarized in equation (109). The possibility of a nonconcerted, diradical

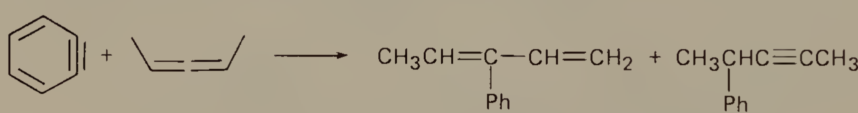


(109)

X=Y = RC≡CR, $R_2C{=}O$, RN=NR

process has been considered to account for the products obtained from the ene reaction of tetramethylallene with hexafluoro-2-butyne[441].

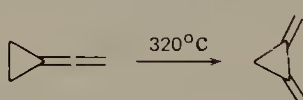
Phenyl-substituted dienes and alkynes are obtained from the reaction of benzyne with alkylallenes, as illustrated in equation (110)[442].



(110)

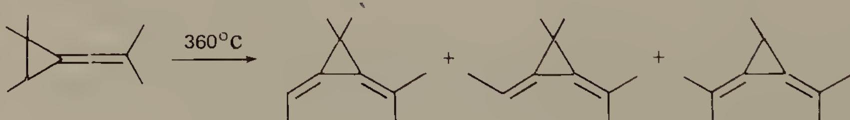
IX. REARRANGEMENT OF ALKENYLIDENECYCLOPROPANES

Alkenylidenecyclopropanes undergo smooth thermal rearrangement giving dimethylenecyclopropanes, as illustrated in equations (111)–(113)[443–446]. The rearrangement of arylalkenylidenecyclopropanes is regioselective giving products in which the aryl groups are on the ring as illustrated in equation (113).



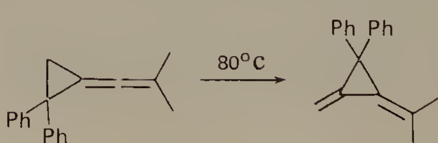
320°C

(111)



360°C

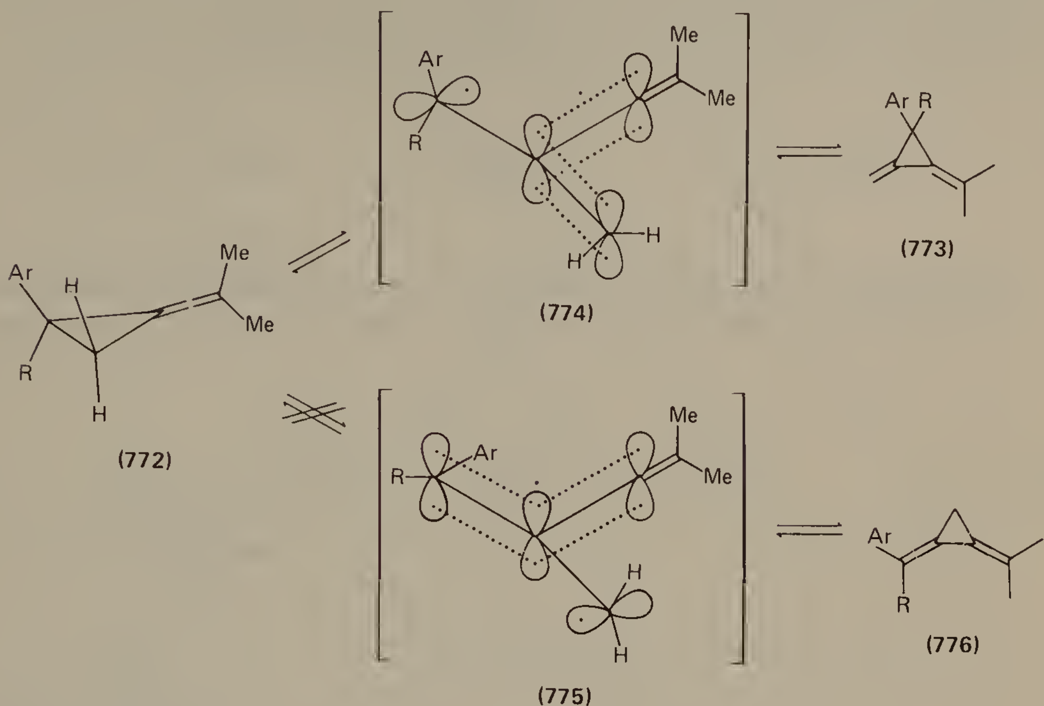
(112)



80°C

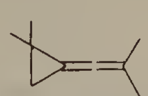
(113)

The bulk of evidence indicates that the rearrangement is a typical methylenecyclopropane-type rearrangement occurring by way of a perpendicular trimethylenemethane diradical, as summarized in Scheme 52 for the rearrangement of **772**



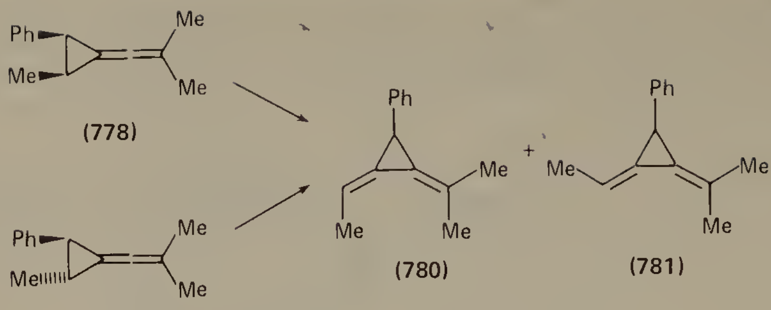
SCHEME 52.

which gives **773**[445,447,448]. Cleavage of the ring-bond opposite the vinylidene group gives diradical **774** which recyclizes giving **773**. The formation of **773** in preference to **776** is attributed to the greater stability of diradical **774** over that of **775**. Thus, **774** is equivalent to a benzyl and an allyl radical, whereas **775** is equivalent to the less stable combination of a primary alkyl and a cinnamyl radical. The importance of the stabilization provided by the benzyl radical portion of diradicals such as **774** is indicated by the fact that the methylated derivative **777** fails to rearrange to a detectable extent at 140° C over a period of 24 days[448].



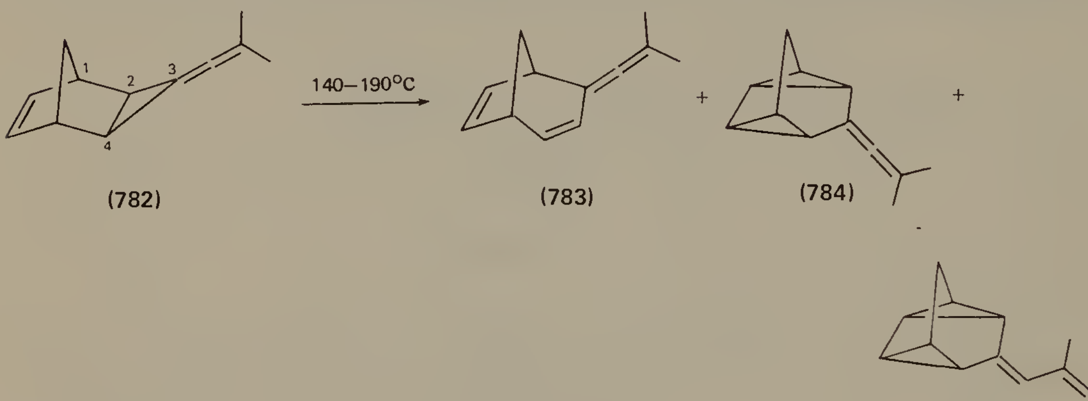
(777)

Rearrangement of **778** and **779** occurs at 90–120° C giving mixtures of **780** and **781**, with **780** being the kinetically preferred product from both precursors[448]. When mixtures of **780** and **781** are heated, slow equilibration occurs with **781** being favoured, e.g. 64% **781** at 117° C. The preferential formation of **780** under kinetic control has been rationalized in terms of steric factors in the ring-opening[448]. Diastereomerization of **778** and **779** occurs during the rearrangement.



(778) (779) (780) (781)

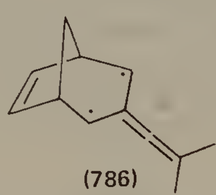
Rearrangement of 782 occurs at 140–190° C by two parallel paths giving 783 and 784; 785 is formed in a subsequent reaction from 784 by a surface-catalysed



(782) (783) (784) (785)

process[449]. The disappearance of 782 is a first-order process with $E_a = 34.8$ kcal/mol and log A (s^{-1}) = 13.6, and the rearrangement is of particular interest because geometrical constraints prevent formation of an orthogonal diradical.

The formation of 784 from 782, a $\sigma^2s + \pi^2s$ process, is symmetry forbidden as a concerted process and is interpreted to occur by cleavage of the 2–4 bond giving the nearly planar diradical 786, followed by rapid addition to the π bond. The free

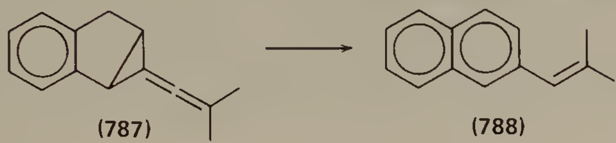


(786)

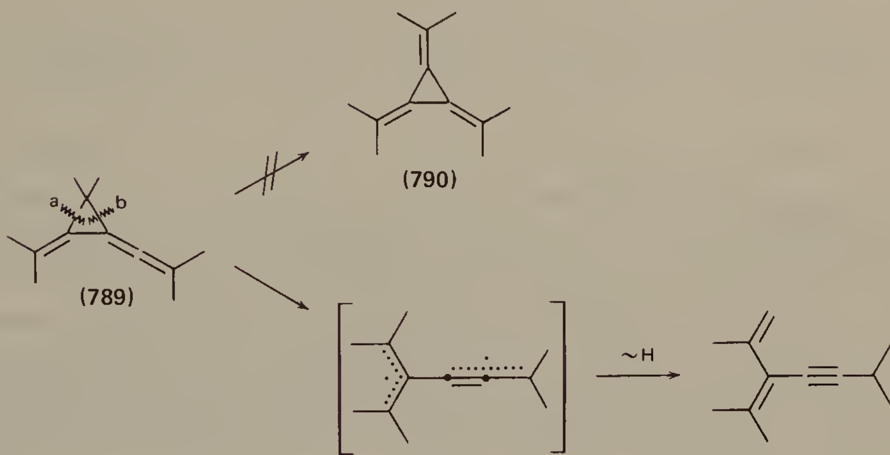
energy of activation for the formation of 786, $\Delta G^{\ddagger}$ (150° C) = 34.3 kcal/mol, is estimated to be only ca 4 kcal/mol less favourable than would be expected for a comparable orthogonal diradical[449]. Possible paths for the formation of 783 have been discussed.

Steric strain inhibits normal dimethylenecyclopropane formation in the rearrangement of 787 and, instead, the naphthalene derivative 788 is formed[450]. A concerted ($\pi^2a + \sigma^2a + \sigma^2s$) mechanism has been proposed involving disrotatory ring-opening, π-bond formation and hydrogen migration to the central allenic carbon.

Instead of the radialene **790**, which would be formed by rupture of bond a and reclosure in the normal manner, the dienyne **792** is formed when **789** is heated at 80° C[451]. Rupture of bond b and rotation of the saturated ring atom giving the doubly delocalized diradical **791**, and subsequent hydrogen migration constitute the path to **792**. Preference for this path is attributed to the greater stability of **791** over that of the singly delocalized diradical that would be formed by cleavage of bond a[451].



(787) (788)



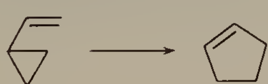
(790)

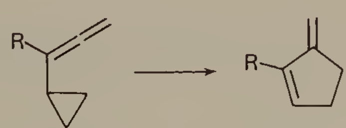
(789)

(791) (792)

X. REARRANGEMENT OF CYCLOPROPYLALLENES

The thermal rearrangement of vinylcyclopropanes to cyclopentenes (equation 114) is a well-known reaction[452], and a limited number of studies of the analogous

 (114)



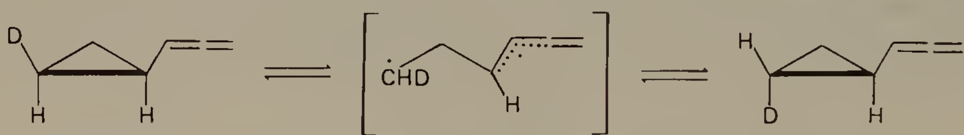
(793) (794)

(a) R = H

(b) R = Me

rearrangement of cyclopropylallenes **793** to methylenecyclopentenes **794** have been reported[453,454]. Quantitative rearrangement of **793a** to **794a** occurs in the range 300–350° C, with first-order rate constant given by $\log k(s^{-1}) = 14.08 - 50{,}200/2.303RT$[453]. The rate of rearrangement is nearly the same as that of vinylcyclopropane itself, for which log $k = 13.61 - 49{,}700/2.303RT$[455], and the enhanced reactivity observed for allenes in Cope rearrangements and [1,5] sigmatropic rearrangements fails to appear here. A diradical mechanism has been proposed, and the interconversion of the deuterated derivatives *cis*-**793**a-d and *trans*-**793**a-d which occurs four to five times faster than the rearrangement of **793**a → **794**a is cited in support of the mechanism. Molecules that are in the transoid conformation shown for *cis*-**793**a-d at the time of ring-opening, cannot rearrange to methylenecyclopentene, but can undergo geometric isomerization[453].

A greatly enhanced rate has been reported for the rearrangement of **793b** to **794b**, with the first-order rate constant given by log $k(s^{-1}) = 12.8 - 41{,}500/2.303RT$[454]. Thus, the activation energy is approximately 8 kcal/mol below those found for vinylcyclopropane and for **793**a. In addition, MINDO/3 calculations give



(*cis*-793a-d) (*trans*-793a-d)

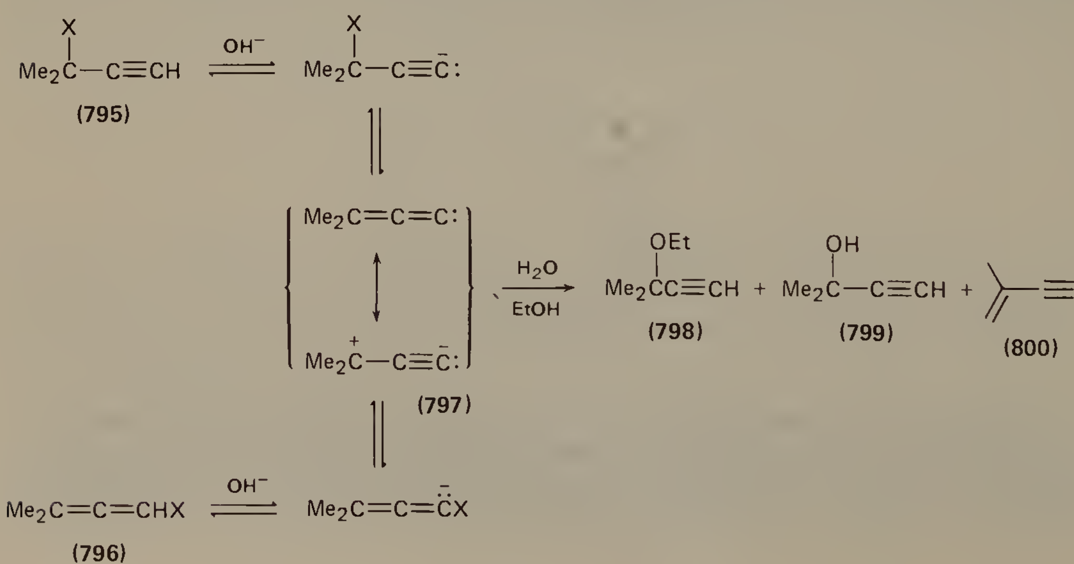
activation energies of 48.4 kcal/mol and 44.6 kcal/mol for the rearrangement of vinylcyclopropane and **793**a respectively, suggesting that the activation energy should be significatly lower for the cyclopropylallene reaction. The lowering is attributed to the greater exothermicity for the **793**a → **794**a process[454].

While the significance of the MINDO/3 calculations has been questioned[456], it is difficult to rationalize the difference in the experimentally determined activation parameters for the rearrangement of **793**a and **793b**. It has been pointed out that the temperature range for the study of **793**a (50° C) was larger than that for **793b** (20° C) and the activation parameters for the former should, therefore, be subject to smaller uncertainties[456].

XI. REARRANGEMENTS INVOLVING CARBENE INTERMEDIATES

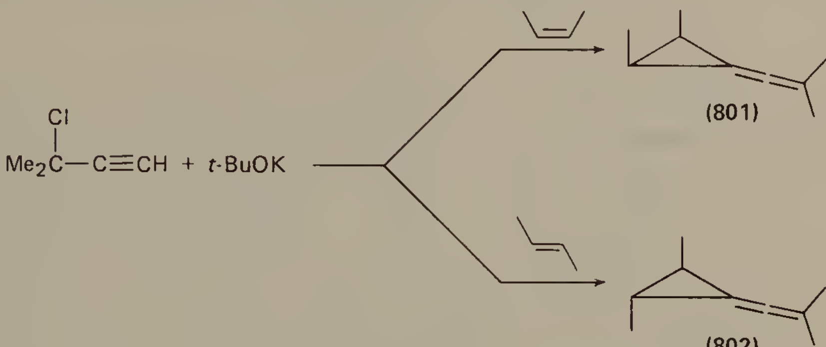
A. Alkenylidenecarbenes

Much evidence has been accumulated in support of Hennion and Maloney's original postulate that vinylidenecarbenes **797** are formed as intermediates in the



alkaline solvolysis of propargylic and allenic halides such as **795** and **796**[457]. The distribution of products **798**, **799** and **800** is the same from both precursors **795** and **796**, with the ether **798** being the principal product formed when the solvent is 80% aqueous ethanol[458,459].

Kinetic studies and studies of secondary isotope effects are in agreement with the proposed mechanism[458–460]. Experiments in which the intermediate carbene is trapped by reaction with olefins also provide convincing support[461–463]. A typical example is the formation of **801** and **802** from the reaction of 3-chloro-3-methyl-1-butyne with potassium *t*-butoxide in the presence of *cis-* and *trans*-2-butene

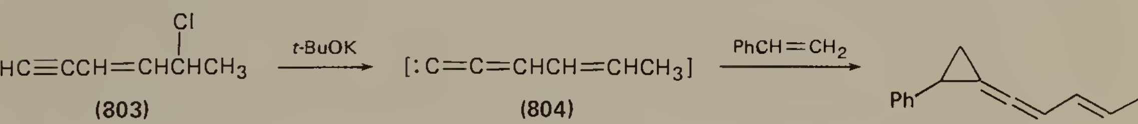


(801)

(802)

respectively[462]. Products arising by insertion of vinylidenecarbenes into C—H and Si—H bonds have also been detected[464].

Recent studies have appeared describing the generation and reactions of vinylidenecarbenes using phase-transfer catalytic techniques[465–467] and crown ethers as catalysts[468]. 1-Bromo-1-alkynes can also serve as precursors of vinylidenecarbenes[469], and the formation of a small amount of **805** when 5-chloro-3-hexen-1-yne (**803**) is treated with potassium *t*-butoxide in the presence of styrene, indicates the intermediacy of the vinylallenic carbene **804**[470].



(803) (804) (805)

B. Cyclopropylidenes

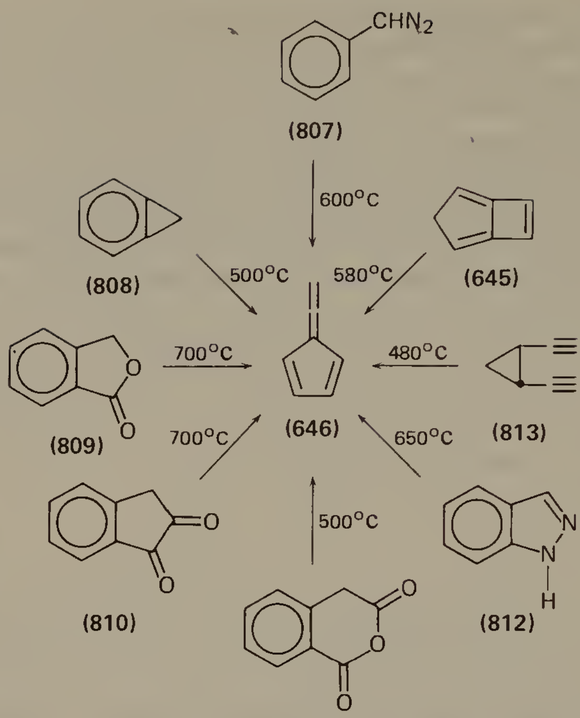
Cyclopropylidenes, **806**, which can be generated from a variety of precursors rearrange spontaneously to allenes. The reaction constitutes the most generally

(806)

applicable synthesis of allenes, and a thorough discussion can be found in the chapter of this volume dealing with synthetic methods.

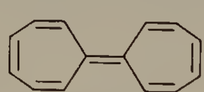
C. Reactions Leading to Fulvenallene

Vinylidenecyclopentadiene (**646**), commonly referred to as fulvenallene, is the product of thermolysis of a host of substrates as can be seen from the typical



SCHEME 53.

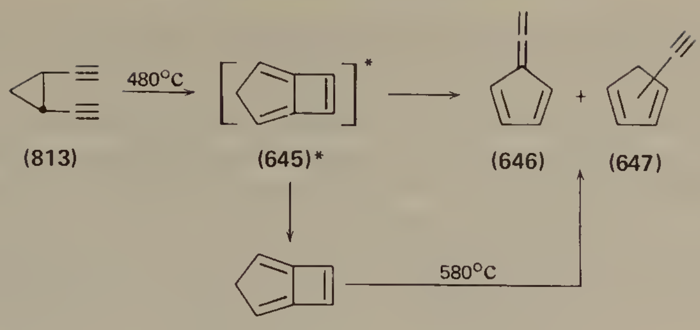
examples that are summarized in Scheme 53[471]. Most often the reactions have been carried out in flow systems at low pressures, commonly by flash vacuum thermolysis techniques[472]. The temperatures cited in Scheme 53 are at or near the lower limit of the range where reaction occurs, and in most cases improved yields of **646** are obtained at higher temperatures[471]. In some cases no reaction occurs, while in others different products are formed at temperatures below this threshold. Thus, below ca 600° C, heptafulvalene (**648**) is the principal thermolysis product of



(648)

phenyldiazomethane (**807**), while **646** predominates at higher temperatures[473]. Ethynylcyclopentadienes (**647**), which accompany fulvenallene in these pyrolyses, are apparently secondary products formed by further isomerization of fulvenallene[471,474].

An interesting pressure dependence has been noted for some of the reactions. For example, *trans*-1,2-diethynylcyclopropane (**813**) rearranges cleanly to **645** at 1 atm and 480° C (flow system) by the mechanism described in Section VIII.B.4.e. At lower pressures ($\lesssim$1 torr), however, fulvenallene (**646**) and ethynylcyclopentadienes (**647**) begin to appear as kinetic products[359,361]. These products, **646** and **647**, are also formed when **645** is pyrolysed, but only at much higher temperatures (580° C, flow system) than are required in the case of **813**. These results suggest that the triene is formed initially in a highly excited vibrational state

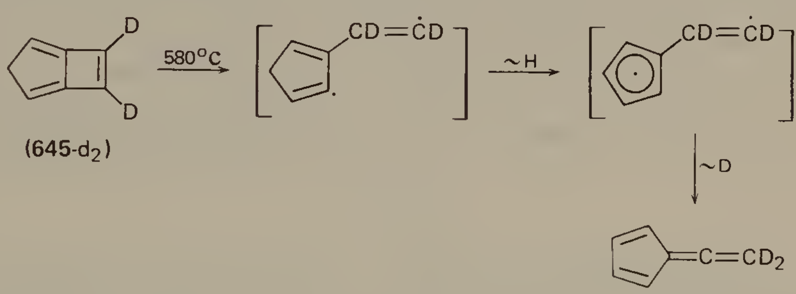


(813) (645)* (646) (647)

(645)

(645)*, and, in fact, it is estimated that the molecule contains ca 80 kcal/mol excess vibrational energy at the moment it is formed. At high pressures this excess energy is quickly dissipated through collision, resulting in **645**, but at low pressures, deactivation is slower and the excited molecules are able to pass over the next barrier to give **646** and **647**[361].

The need for higher temperatures in the rearrangement of **645** can be understood from this standpoint, and information about the mechanism of formation of **646** from **645** has been obtained from deuterium-labelling studies[356]. The labelled triene **645**-d_2 rearranged at 580° C (flow system) giving fulvenallene **646**-d_2 in which most (87%) of the deuterium was in the terminal position. These results are accounted for in terms of initial cleavage of a cyclobutene ring bond and successive hydrogen shifts as illustrated in Scheme 54[356]. Further support for this mechan-



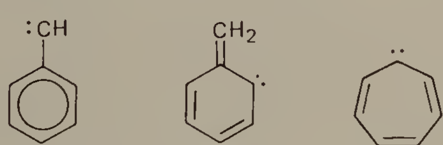
(645-d_2)

(646-d_2)

SCHEME 54.

ism, and consideration of the route that places 13% of the deuterium in the five-membered ring will be presented below.

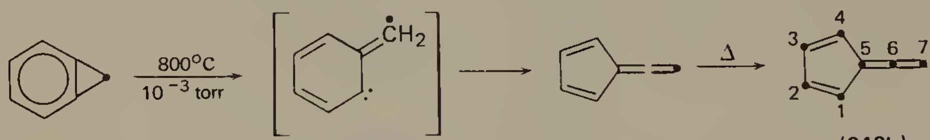
It has been generally agreed that carbenes are involved in the reactions leading from **807**–**812** to **646**, but the mechanism of the ring-contraction and the interconvertibility of possible carbenoid species has been the subject of debate. Phenylcarbene (**814**) is anticipated from the decomposition of **807**, while methylenecyclohexadienylidene (**815**) is anticipated from **808**–**811**, and either or both might be



(814) (815) (816)

anticipated from thermolysis of the indazole 812. In addition, cycloheptatrienylidene (816) has been proposed as an intermediate in the isotopic rearrangement of 814[471,475].

A recent study has helped to answer some of the questions about the rearrangements, and to show that previously suggested mechanisms are untenable[476]. Benzocyclopropene 'labelled' with ^{12}C at position 1, 808a, was heated at 800° C

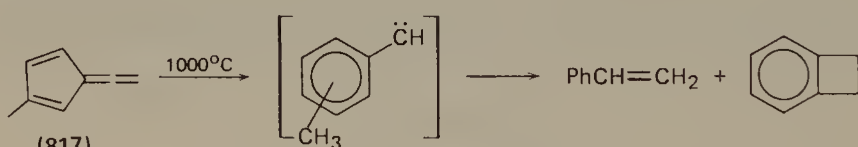


(808a) (815a) (646a) (646b)

• = ^{12}C

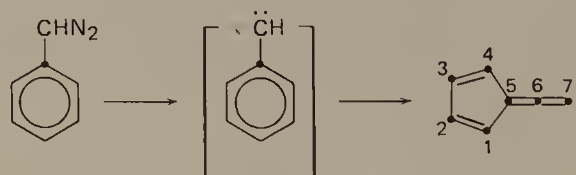
(10^{-3} torr) and the distribution of ^{13}C in the fulvenallene product was determined by n.m.r. spectroscopy. It was found that 14.7% of the ^{13}C appeared at the $C_{(7)}$ position, signifying that approximately 83% of the product was formed by the direct route, **808a** → **815a** → **646a**, and 17% was formed by a route in which carbon scrambling occurred. When a sample of **646a** containing more than 85% ^{12}C in the $C_{(7)}$ position was heated at 1050° C, **646b** was obtained in which ca 100% scrambling had occurred, thus demonstrating that the carbon scrambling noted above occurred with **646a** itself, i.e. **646a** → **646b**.

The mechanism of the scrambling process is not certain, but the fact that phenylcarbene-[7-^{13}C] is known to give isotopically rearranged **646** suggests a possible route to be the thermal interconversion of **646** and **814**. Evidence which supports this postulate is as follows[476]. *o*-, *m*- and *p*-Tolylcarbenes are known to undergo interconversion in the gas phase and all three give styrene and 1,2-dihydrobenzocyclobutene as products[471,477]. The formation of these same products when **817** is heated at 1000° C suggests tolylcarbene as an intermediate in this rearrangement, and supports the proposal that fulvenallene and phenylcarbene can be interconverted[476].



(817)

Evidence pertaining to possible paths for the interconversion was obtained from studies of the rearrangement of phenylcarbene-[1-^{13}C](814a). Pyrolysis of **807a** under the mildest possible conditions for generating fulvenallene (590° C, 5–7 torr, N_2 carrier) gave **646c** with ^{13}C at all positions, but the distribution was not uniform. Position 5 carried approximately three times more of the label than any



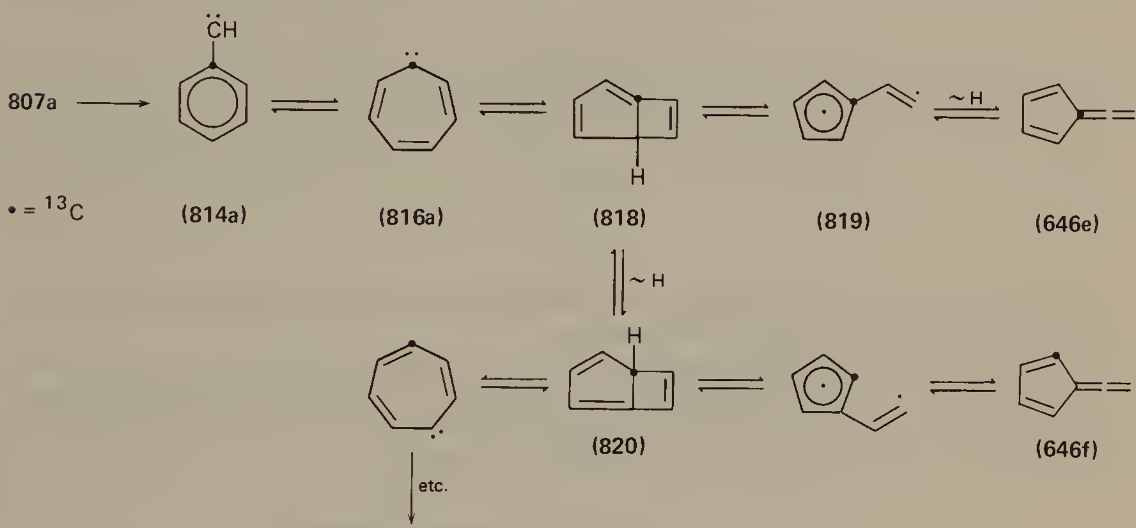
(807a) (814a) (646c)

• = ^{13}C

other carbon, and the extent of labelling decreased in the order: (5) > (1),(4) > (2),(3)>(6)>(7). When the pyrolysis of **807a** was carried out at 700° C (10^{-3} torr), the excess of ^{13}C at position 5 was barely beyond the experimental error, and the n.m.r. spectrum of the product obtained at 1000° C (10^{-3} torr) showed complete randomization.

The excess label at $C_{(5)}$ in the product from the pyrolysis at 590° C rules out mechanisms that involve direct ring-contraction of phenylcarbene as well as those involving pre-equilibrium interconversion of phenylcarbene and benzocyclopropene or methylenecyclohexadienylidene. The mechanism shown in Scheme 54 was suggested as a possible one to account for the findings[476].

Cycloheptatrienylidene (**816a**) labelled at the carbene position, which arises by ring-expansion of phenylcabene-[1-^{13}C](**814a**), undergoes electrocyclization giving the bicyclic triene **818** labelled at the bridgehead position as shown in Scheme 55.

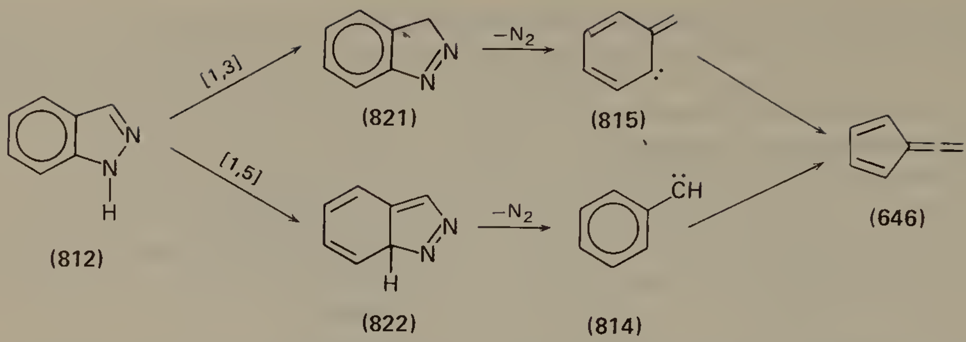


SCHEME 55.

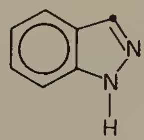
Fulvenallene (**646e**) with the label at position 5 is formed from **818** by way of diradical **819**. Scrambling of the label occurs as a result of isomerization of **818** to **820**. Ring-opening of **820** and rearrangement of the diradical affords **646f** labelled at position 1. The entire process is reversible, as required by the results described for **808a** and **646a**, and it can be seen that complete scrambling will be the result[476]. The finding of excess label at position 5 in the 590° C product, however, requires the ring-opening of **818** giving **819** to be faster than the [1,5] hydrogen migration giving **820**; this order of reactivity is unusual.

The formation of product with deuterium in the five-membered ring from the pyrolysis of **645**-d_2 can be rationalized in terms of this mechanism; furthermore, the formation of small amounts of heptafulvalene (**648**) in the pyrolysis of **645**[361] lends support to this interpretation.

Hydrogen migration must precede loss of nitrogen in the thermolysis of indazole (**812**) and there are two plausible sites for the migration terminus, as in **821** and **822**[475]. Loss of nitrogen from these would be expected to afford cyclohexadienylidene (**815**) and phenylcarbene (**814**), respectively, either of which can rearrange to fulvenallene (**646**). Pyrolysis of indazole-[3-^{13}C] (**812a**) at 650°C gave fulvenallene with ca 30% excess of the label at position 7, the remainder of the label being



distributed uniformly over all positions[475]. These results can be interpreted in the framework of the mechanism given in Scheme 55 if it is assumed that both **814** and



(812a)

• = ^{13}C

815 are involved as intermediates, the excess label at $C_{(7)}$ resulting from direct Wolff rearrangement of **815** to fulvenallene.

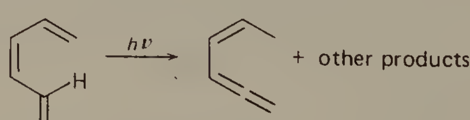
Ring-contractions of the type leading to fulvenallene have also been observed with nitrogen and oxygen analogues of carbenes[471,472]. Recent work has shown, however, that there are some fundamental differences in the mechanisms of ring-contraction of phenylnitrene and phenylcarbene[478].

XII. PHOTOCHEMICAL REARRANGEMENTS

Many of the photochemical rearrangements involving allenes have a counterpart in thermal rearrangements, while others are uniquely photoinitiated. In the paragraphs that follow, some of the more important aspects of these rearrangements are summarized.

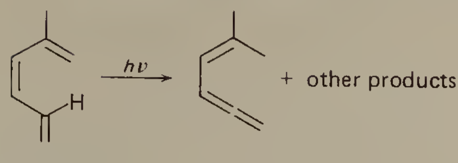
A. Sigmatropic Rearrangements

Allenes have been obtained as products of photoinitiated [1,5] hydrogen migration in a variety of conjugated trienes, as illustrated by the conversion of (*Z*)-1,3,5-hexatriene (**823**) to (*Z*)-1,2,4-hexatriene (**824**)[479]. The low quantum

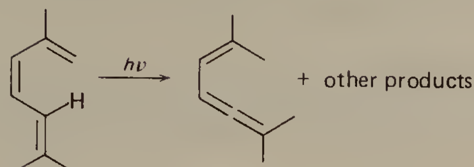


(823) (824)

yield of **824** in this process has been attributed to the low concentration of the *cZt* conformation (**823**) in the ground state[480]. In trienes in which this conformation is more important, e.g. **825** and **826**, higher quantum yields of allenes are obtained[480,481]. These allenes rearrange thermally to the starting trienes at temperatures of 120–150° C.

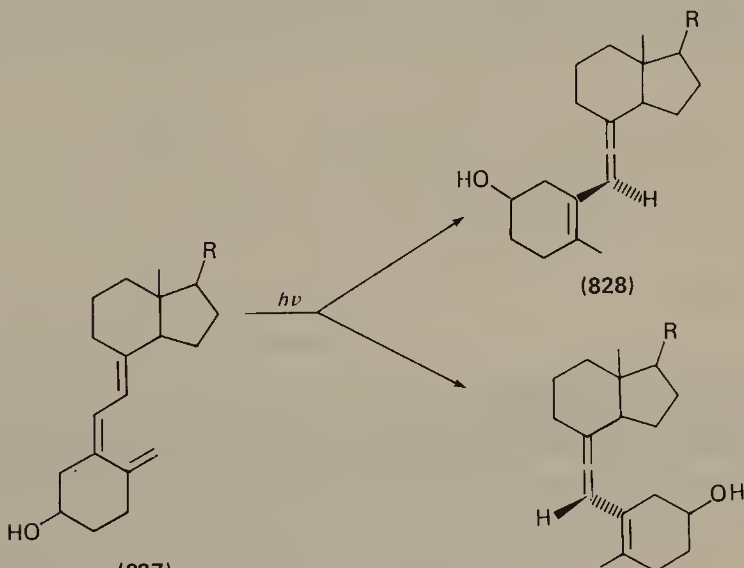


(825)



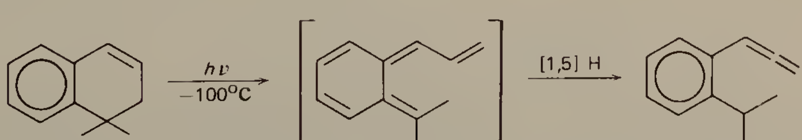
(826)

[1,5] Hydrogen migration occurs when Vitamin D_3 (827) is irradiated and a mixture of the diastereomeric allenes **828** and **829** is obtained, along with other products[482]. In a separate experiment it was shown that **828** and **829** are interconverted photochemically by a process involving internal rotation about the axis of the allene linkage[483].



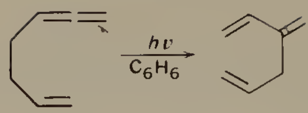
(827) (828) (829)

Allenes are obtained, along with other products, upon irradiation of 1,2-dihydronaphthalenes by a sequence involving cycloreversion and [1,5] hydrogen migration, as summarized in equation (115)[484–486].

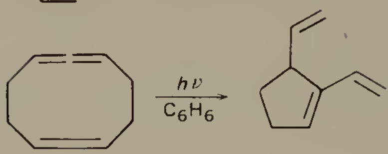


(115)

The conversion of 1,2,6-heptatriene to 3-methylene-1,5-hexadiene (equation 116) and 1,2,6-cyclononatriene to 1,5-divinylcyclopentene (equation 117) by benzene-sensitized irradiation represent photochemical counterparts of the Cope rearrangement[487].

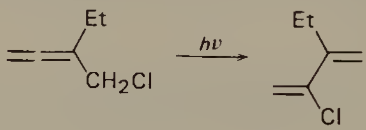


(116)



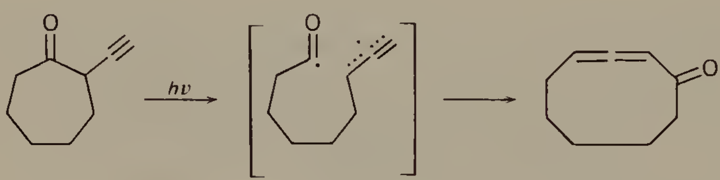
(117)

4-Halo-1,2-dienes undergo photorearrangement to 2-halo-1,3-dienes as illustrated in equation (118)[488,489]. The reaction has been shown to proceed by a free-radical mechanism. The unusual photochemical ring-expansion of 2-ethynylcyclo-



(118)

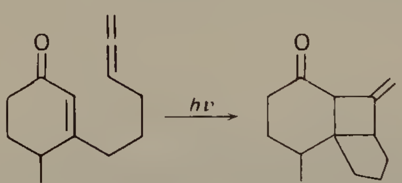
heptanone (**830**) to 2,3-cyclononadienone (**832**) also amounts to a [1,3] rearrangement, and is believed to involve initial type I cleavage followed by cyclization of the diradical **831**[490].



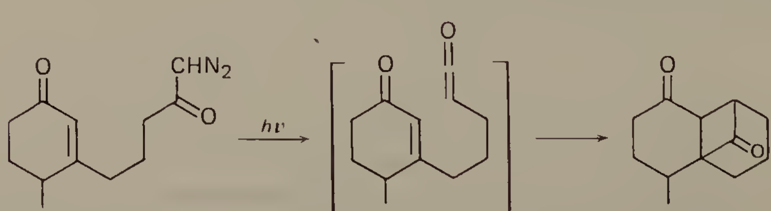
(830) (831) (832)

B. Intramolecular Cycloadditions

Internal head-to-head photocycloaddition of **833** gives the tricyclic ketone **834** in 95% yield, while the corresponding ketene adds with reversed orientation giving



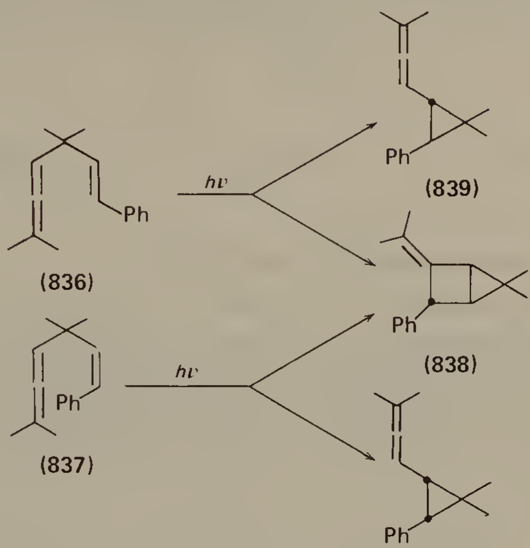
(833) (834)



(835)

835[491]. It has been suggested that differences in ground-state charge distribution may be responsible for the difference in behaviour between the allene and the ketene.

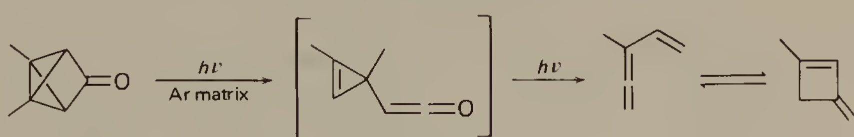
When the stereoisomeric trienes **836** and **837** are irradiated the major product in each case is the bicyclopentane **838**, accompanied by small amounts of the di-π-methane rearrangement products, **839** from **836**, and **840** from **837**[492]. The formation of **838** from both precursors **836** and **837** can be rationalized in terms of a concerted ($\pi^2 s + \pi^2 s$) mechanism, but a diradical mechanism is also possible.



(836) (837) (839) (838) (840)

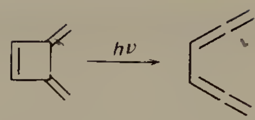
C. Electrocyclization and Cycloreversion

Photochemical interconversion of methylenecyclobutenes and 1,2,4-trienes, or related derivatives, has been observed. For example, when the tricyclic ketone **841** is irradiated in an argon matrix, a photoequilibrium mixture of 4-methyl-1,2,4-pentatriene (**843**) and 1-methyl-3-methylenecyclobutene (**844**) is obtained[493]. Presumably, the initially formed ketene **842** decarbonylates and the resulting carbene isomerizes to the triene **843**. Interestingly, when **841** is irradiated in solution, 1,3-dimethylcyclobutadiene is obtained initially[493].

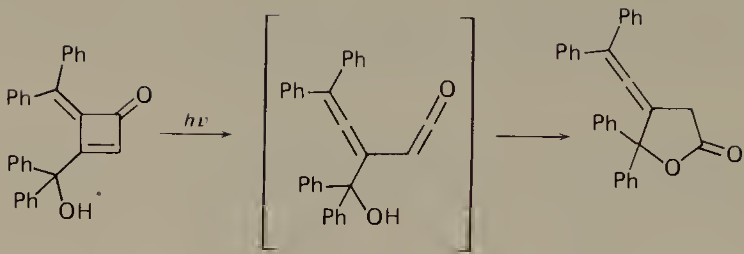


(841) (842) (843) (844)

Cycloreversion of 3,4-bismethylenecyclobutene to 1,2,4,5-hexatetraene has been reported (equation 119)[494]. Photoisomerization of the cyclobutenone **845** furnishes the lactone **847** by way of the intermediate allenylketene **846**[495].



(119)

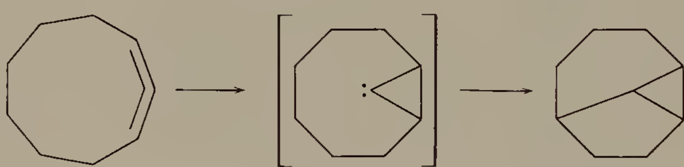


(845) (846) (847)

D. Rearrangements Involving Carbene Intermediates

A host of rearrangements involving allenes can best be accounted for by postulating carbene intermediates, and selected examples of these are considered together here in spite of great differences in the nature of the substrates.

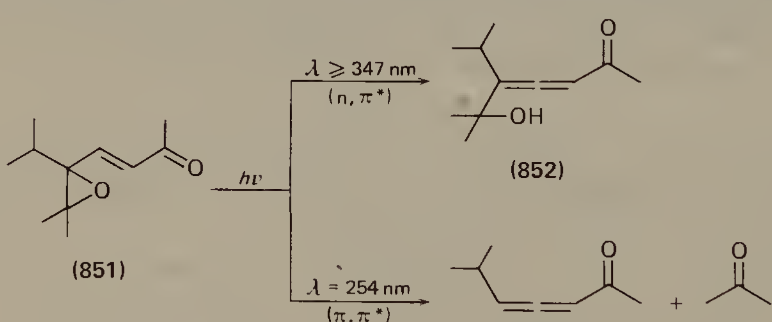
The photochemical conversion of 1,2-cyclononadiene (**848**) to tricyclo-[4.3.0.0^{2,9}]nonane (**850**) apparently involves initial isomerization of the allene to



(848) (849) (850)

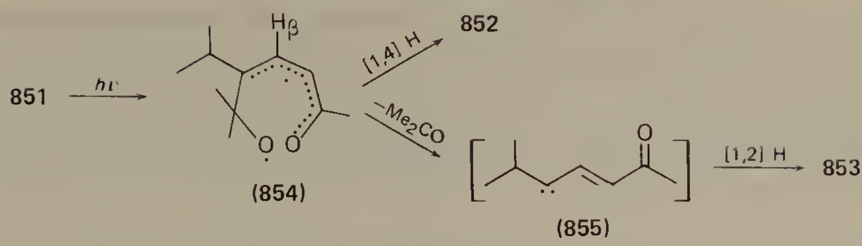
the cyclopropylidene **849** which furnishes **850** by transannular C—H insertion[487,496].

Small amounts of allenes are obtained by irradiation of **851**, the type of product obtained being dependent on the wavelength of the exciting radiation[497]. The ketol **852** is obtained by (n,π*) excitation, whereas the allenyl ketone **853** is

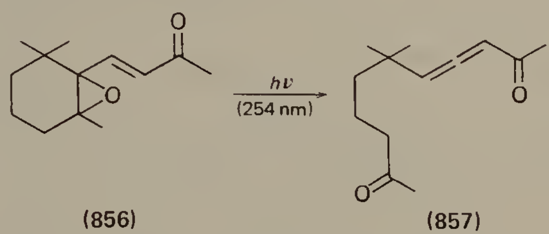


(851) (852) (853)

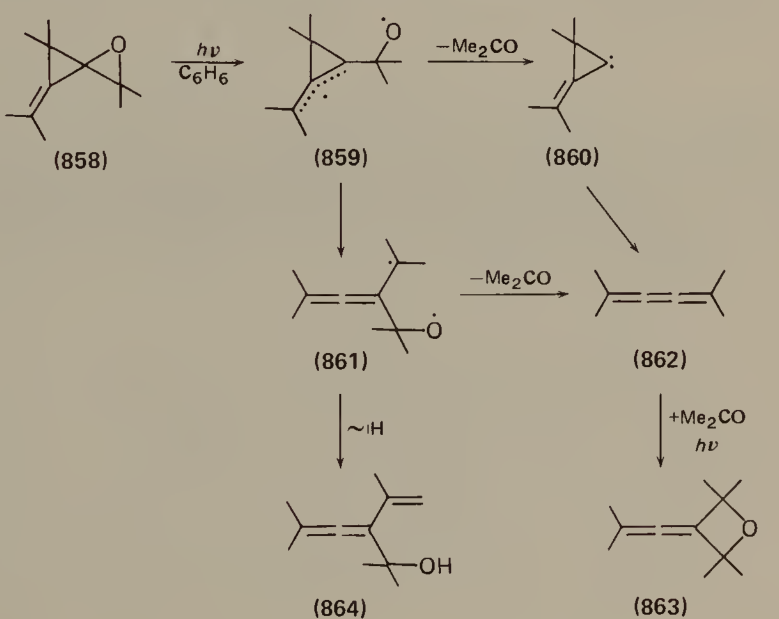
obtained upon (π,π*) excitation. These products can be rationalized in terms of epoxide cleavage giving the diradical **854**. Abstraction of H_β by the oxyradical furnishes **852**, whereas elimination of acetone gives the carbene **855**, and this, by



simple [1,2] hydrogen migration, provides the allene **853**. In a related rearrangement, *trans*-β-ionone epoxide (**856**) furnishes the allenyl ketone **857** in 11% yield[498].

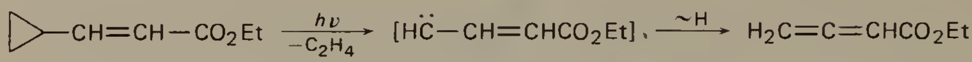


Benzene-sensitized photolysis of the oxaspiropentane **858** yields a mixture of **862**, **863** and **864**, and several steps of the proposed mechanism (Scheme 56) are analogous to those described above for the epoxy ketones[499]. Two routes from the initially formed diradical **859** to stable products are possible. One involves elimination of acetone, giving the cyclopropylidene **860**, which can collapse to the cumulene **862**. The second route consists of ring-opening to the isomeric diradical **861** which can either eliminate acetone giving **862** or undergo [1,5] hydrogen shift giving the alcohol **864**. The remaining product, **863**, arises by photoinitiated addition of acetone to the cumulene **862**[499].



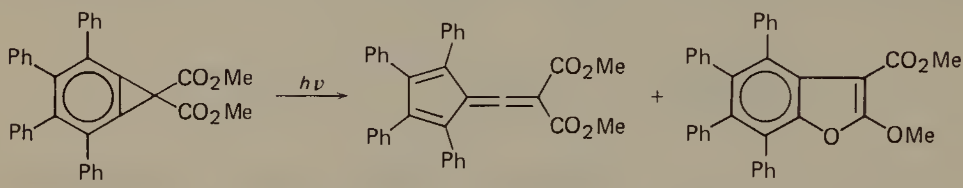
SCHEME 56.

Esters of γ-cyclopropylacrylic acids such as **865** undergo photochemical fragmentation giving, among others, allene derivatives, apparently by way of the intermediate carbene **866**[500].



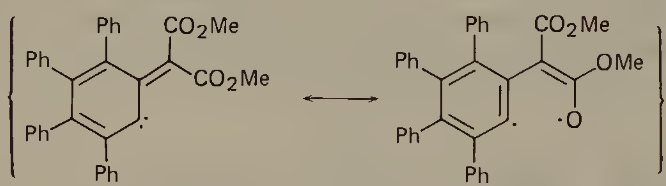
(865) (866)

Irradiation of variously substituted benzocyclopropenes affords mixtures of substituted fulvenallenes and benzofurans as illustrated by the conversion of **867** to **868** (66%) and **869** (9%)[501]. The origin of these products can be understood from



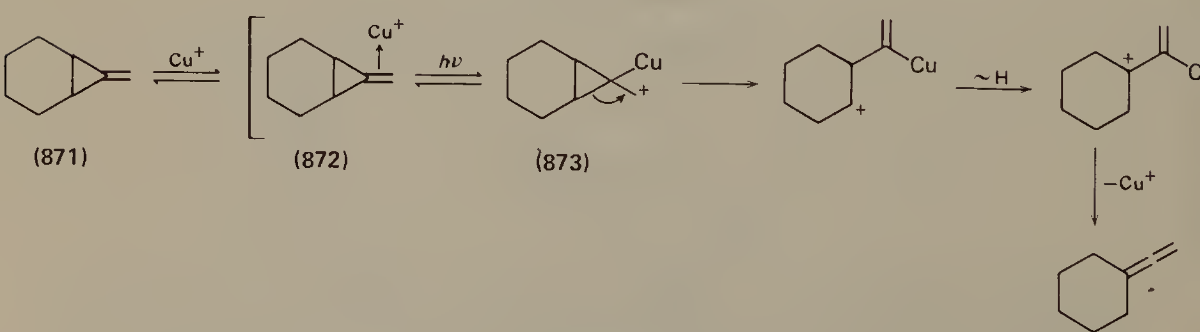
(867) (868) (869)

a consideration of the electron distribution in the diradical carbene **870** which is formed initially by cleavage of the three-membered ring. Ring-contraction by Wolff-type rearrangement gives the fulvenallene **868**, while ring-closure involving the oxygen of one of the carbonyl groups affords the benzofuran **869**. Attempts to



(870)

obtain fulvenallene itself by photolysis of benzocyclopropene gave complex mixtures in which anthracene and phenanthrene were identified. It is believed that fulvenallene was formed initially but reacted rapidly to give other products under the reaction conditions[501].



(871) (872) (873) (874)

SCHEME 57.

E. Metal-catalysed Photorearrangements

One of the products formed by the photorearrangement of 7-methylenenorcarane (**871**) in the presence of Cu(I) salts is vinylidenecyclohexane (**874**)[502]. A possible mechanism, outlined in Scheme 57, consists of photochemical conversion of the initial π complex **872** to the μ′-β-copper(I) carbonium ion **873**. Ring-cleavage, followed by [1,2] hydride shift and loss of Cu(I) complete the route to **874**[502].

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CHAPTER **16**

Ketene thioacetals

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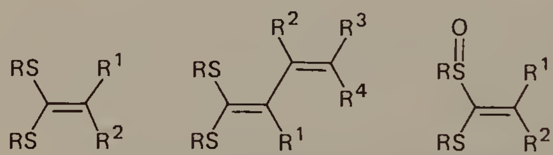
I. INTRODUCTION

In recent years ketene thioacetals have become of interest to organic chemists for theoretical[1–6] and preparative[7] purposes. Although originally synthesized in 1919 by Freund[8], their renaissance can be largely attributed to the new preparative methods developed during the last decade. Today more than ten different routes give access to a variety of ketene thioacetals under diverse reaction conditions. As a consequence it has been possible to develop and exploit the wide spectrum of chemical transformations which ketene thioacetals undergo. These compounds allow the protection and installation of functionalities in molecules so efficently that they have become accepted as useful tools in natural product synthesis.

Ketene thioacetals allow the functionalization of carbon atoms neighbouring a functional group. Classical methods for this purpose are generally limited to the installation of functional groups separated by an *odd* number of carbon atoms [1.(2*n* + 1)]. Molecules with a [1.(2*n*)] relationship (*even*) are made available by using ketene thioacetal chemistry. This 'umpolung' of reactivity has become a slogan, intimately attached to ketene thioacetals[7,9–14].

Today, not only the preparation of ketene thioacetals has become convenient but also the facile demasking of the products of ketene thioacetal chemistry (usually thioacetals), and these processes are adaptable to a variety of reaction conditions[7]. Also, this experience has helped to introduce ketene thioacetals into the repertoire of reactions of synthetically oriented organic chemists.

In the following, I should like to focus on those ketene thioacetals which are of direct synthetic utility. They can generally be described by formulae 1, 2 and 3. In the large majority of examples R, R^1, R^2, R^3 and R^4 stand for alkyl, vinyl, allyl or aryl groups. A few examples contain a triheterosubstituted double bond, but no tetraheterosubstituted case will be considered[15]. These criteria still allow discussion



(1) (2) (3)

of a representative number of ketene thioacetal molecules, demonstrating typical ketene thioacetal chemistry and giving a generally correct picture of this class of molecules to the reader.

II. PREPARATION OF KETENE THIOACETALS

A. General Methods

A wide variety of ketene thioacetals are accessible by the methods outlined in Figure 1. In route (A)[16–23] one forms disulphur-substituted cations, which eliminate a proton to yield ketene thioacetals; X can be any nucleophuge group. Method (B)[24–31] can be considered as a β-elimination process or X extrusion. The possibility (C) has a sulphur-stabilized anion as the intermediate eliminating X[27,32–41] or fragmenting[42] to yield the desired ketene thioacetal. One can also tautomerize α,β-unsaturated thioacetals to form ketene thioacetals (D)[3–5,43–46]. Obviously, olefination of carbonyl compounds with appropriate substituted Wittig or Horner–

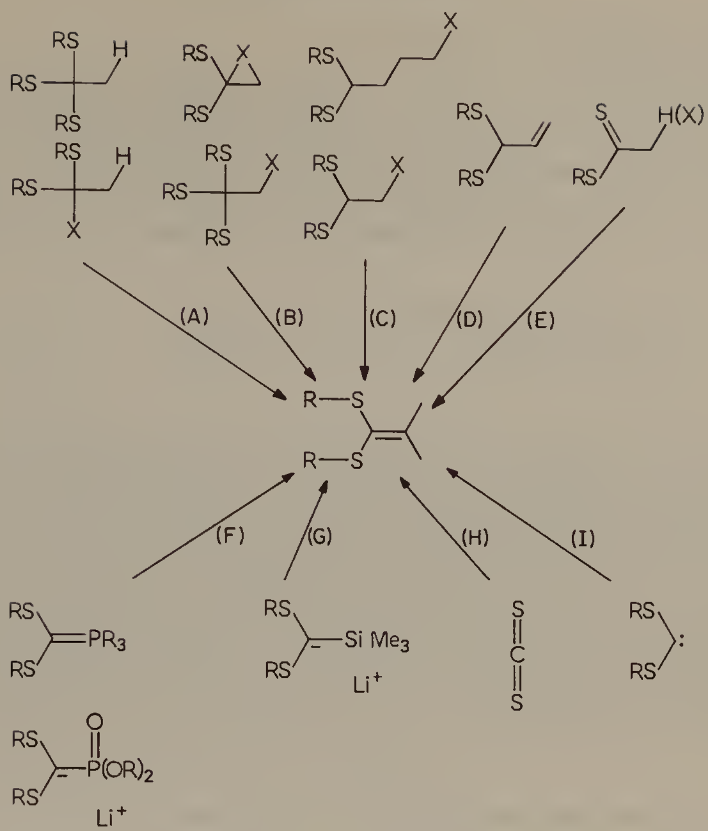


FIGURE 1. Synthetic methods for ketene thioacetals.

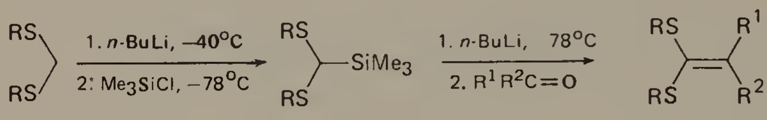
Emmons reagents as formulated in (F)[47–51] will lead to ketene thioacetals. The Peterson olefination[52–55], route (G)[56–60], provides an alternative olefination process with different conditions and feasibility. Closing this list are dithio esters (E)[61–64,66–70], carbon disulphide (H)[8,65,71,76–86,204–206] and the carbene in (I)[35,87–90], which all contain the structural unit to generate ketene thioacetals and are used as starting materials for the synthesis of ketene thioacetals in some special examples.

Having such a choice of methods for the preparation of these molecules, knowledge of the factors limiting these synthetic routes becomes relevant. Compounds for routes (A) or (B) must either be substituted in a way which facilitates the reaction, or drastic conditions must be employed (pH, temperature, . . .). This limits the use of these routes to a small number of compounds. Notice, however, the procedure developed by Corey[21] which uses carboxylic esters as starting material (see Section II.D). Elimination of water in (C) ($X = OH$) requires a benzylic leaving group. Grob fragmentation in (C)[42] is only possible in compounds with a certain three-dimensional orientation of the bonds broken. Method (D) always gives an equilibrium mixture of ketene thioacetal and starting thioacetal. For the Wittig reaction in (F) only aldehydes give reasonable yields. To be useful as synthetic procedures, the pathways (E) and (H) require additional stabilization in either the starting material or the ketene thioacetal product.

Three methods, however, can be considered as convenient, useful and practical for the preparation of ketene thioacetals. The following sections deal in detail with these pathways: (A) Corey, (F) Horner–Emmons and (G) Peterson.

B. By Peterson Olefination

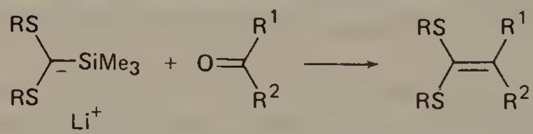
The transformation (G) in Figure 1 was the first "easy" access to ketene thioacetals. Resulting from a reaction between α-silyl carbanions and carbonyl compounds, obseved in 1962 by Gilman and Tomasi[53], developed and extended by Peterson[52,54,55], this observation was used by the groups of Seebach[57], Carey[58] and Lappert[59] to develop a high-yielding, easy procedure for the preparation of ketene thioacetals (equation 1). Metalation of formaldehyde dithioacetal (4) with



(4) (5) (1) (1)

n-butyllithium at –40° C in tetrahydrofuran[72–75] and addition of the so-formed carbanion to trimethylchlorosilane generates **5** in 90% yield[56]. Remetalation of **5** at –78° C, treatment with the carbonyl compound at –78° C and warming up to room temperature affords high yields of the ketene thioacetal **1**[73]. This approach gives access to **1** with a certain variety in R[74,75] and is tolerant of almost all substitution patterns of the carbonyl derivative employed. Table 1 lists the ketene thioacetals prepared in this manner with the corresponding references. Yields in the range of 70–90% can generally be expected. Only highly-hindered ketones give lower yields.

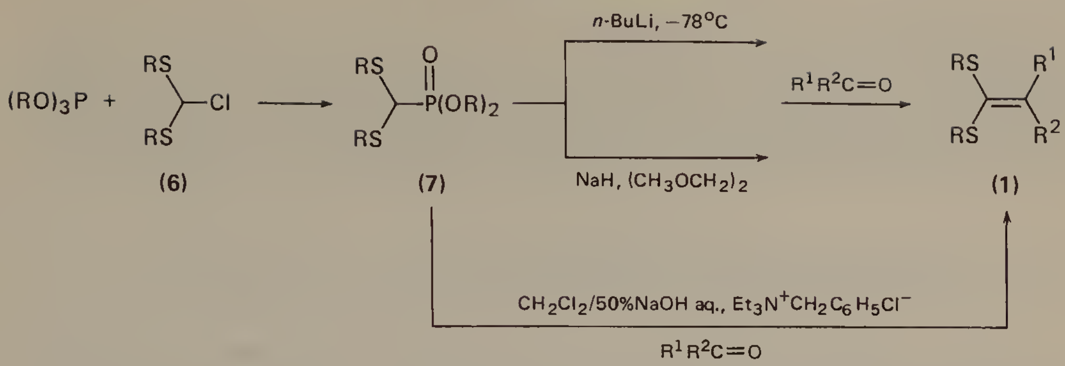
TABLE 1. Ketene thioacetals prepared by Peterson olefination



R	R	R^1	R^2	Yield (%)	Reference
Me	Me	H	Alkyl	80–85	57, 73, 91
Me	Me	H	Aryl	85–90	91
Me	Me	$-(CH_2)_n-$		55–80	91
Me	Me	Ph	Ph	85	57, 73
Ph	Ph	H	CH(Me)Ph	85	57, 73
$-(CH_2)_3-$		H	Alkyl	70–80	57, 59, 73, 92–94
$-(CH_2)_3-$		H	Aryl	70–95	57, 59, 73, 92, 93
$-(CH_2)_3-$		Alkyl	Alkyl	60–85	58, 59, 92–95
$-(CH_2)_3-$		$-(CH_2)_n-$		40–95	57–59, 73, 91–94
$-(CH_2)_3-$		Ph	Ph	75–85	57–59, 73, 92, 93
$-(CH_2)_3-$		H	$RC{=}CR_2$	70–90	57, 73, 92, 93, 59, 58
$-(CH_2)_3-$		Alkyl	$RC{=}CR_2$	60–80	57, 58, 73
$-(CH_2)_3-$		Tropone, adamantone, 2-norbornanone		40–85	58, 96
$-CH_2-S-CH_2-$		Ph	Ph	42	57, 73

C. By Horner–Emmons Olefination

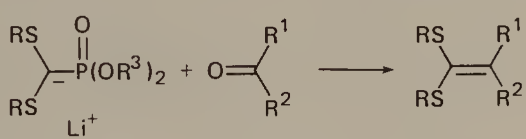
While olefination with phosphor ylids (route (F) in Figure 1) as already mentioned above is of limited applicability[47–50,100], the phosphonate approach[51]



(2)

turns out to be of more general use (equation 2). The synthesis of the starting phosphonate requires halogenated thioacetals (**6**), available in over 90% yield[97–99] by chlorination of the corresponding thioacetal with sulfuryl chloride. At room temperature **6** reacts with $(RO)_3P$ to give the corresponding phosphonate **7**. Metalation of **7** with *n*-butyllithium in tetrahydrofuran at $-78°$ C[98,100,101] or sodium hydride in dimethoxyethane under reflux[51] followed by reaction with aldehydes or ketones gives **1** in excellent yields (Table 2). One report in the literature describes an alternative method, which circumvents the prior generation of the carbanion from **7**. The authors treat **7** with aromatic aldehydes in a two-phase system using triethylbenzylammonium chloride as a phase-transfer catalyst[51] (see Table 2 and equation 2), and obtain the ketene thioacetals **1** in yields comparable to the procedure using *n*-butyllithium.

TABLE 2. Ketene thioacetals, prepared by Horner–Emmons olefination

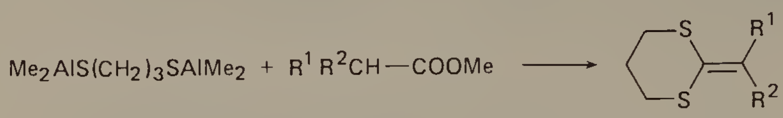


R	R	R^1	R^2	Yield (%)	Reference
Me	Me	H	H	95	51
Me	Me	H	Alkyl	90	51
Me	Me	Alkyl	Alkyl	80	51
Me	Me	H	Aryl	85	51
Me	Me	Aryl	Aryl	80[a]	51
Me	Me	$-(CH_2)_n-$		80–82	51
$-(CH_2)_3-$		H	$HC{=}CR_2$	85	98
$-(CH_2)_3-$		Alkyl	Aryl	70–85	51, 98
$-(CH_2)_3-$		H	Alkyl	85	98
$-(CH_2)_3-$		Aryl	Aryl	70	51
$-(CH_2)_3-$		$-(CH_2)_n-$		95	98
$-CH_2-S-CH_2-$		Aryl	Aryl	66	51
o-C_6H_4		H	Aryl	95	100
o-C_6H_4		H	$HC{=}CR_2$	95	100
o-C_6H_4		$-(CH_2)_n-$		95–98	100
o-C_6H_4		Alkyl	Aryl	90	100
o-C_6H_4		Aryl	Aryl	60–95	101

[a]Phosphonate anion is generated in a two-phase system.

D. From Esters

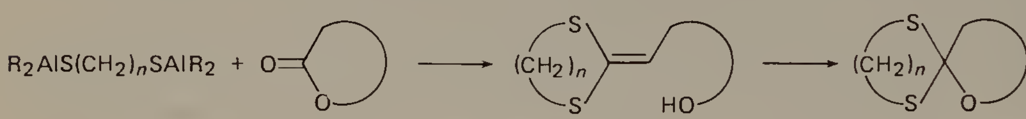
Originally developed as a procedure to protect lactones and esters against nucleophilic attack[20], Corey and coworkers[20,21] have employed the reaction of esters with bis(dimethylaluminium)-1,3-propanedithiolate (**8**) for the synthesis of ketene thioacetals (equation 3). The organoaluminium derivative, prepared prior to



(3)

(8) (9)

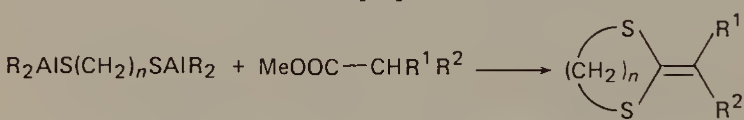
use from trimethylaluminium and 1,3-propanedithiol in toluene/methylene chloride, reacts with methyl esters at room temperature in 48 hours to form ketene thioacetals in good yields (Table 3)[21]. The corresponding reaction with lactones leads to ketene thioacetal derivatives (**10**) possessing a hydroxyl function in the molecule (equation 4). Under acidic conditions these compounds can yield cyclic

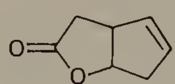
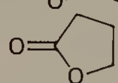
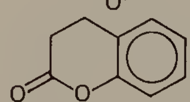
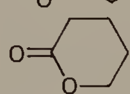


(4)

(10)

TABLE 3. Ketene thioacetals prepared from esters



n	R^1	R^2	Yield (%)	Reference
2			94	20
2			94^a	20
2			81^a	20
2			91^a	20
2	H	n-$C_{16}H_{33}$	93	20
2	H	Ph	98	20
3	H	Ph	86	21
3	H	Alkyl	50–65	21
3	H	Vinyl	60	21
3	$-(CH_2)_n-$		60–85	21
3	H	CH_2SMe	52	21
3	Me	SPh	65	21

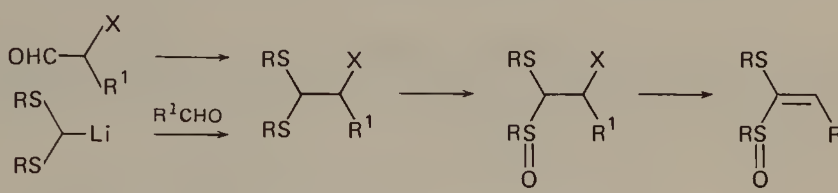
^{a}Isolated after acid treatment to form dithioortho esters (see equation 4).

dithioortho esters[20] (see Section IV.C). This access to ketene thioacetals differs from the two foregoing methods (Section II.B and II.C) in that it retains the carbon skeleton of the carboxyl compound in the ketene derivative **9** or **10**. In both the Peterson olefination and the Horner–Emmons procedure one carbon atom is added to the starting carbonyl compound in forming the ketene thioacetal.

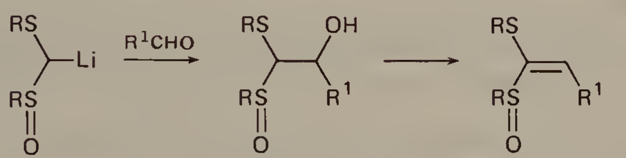
E. Preparation of Ketene Thioacetal Monosulphoxides

The monosulphoxides of ketene thioacetals have been shown to be synthetically especially useful compounds[102–108]. As I will comment on this later, their preparative access only is discussed here.

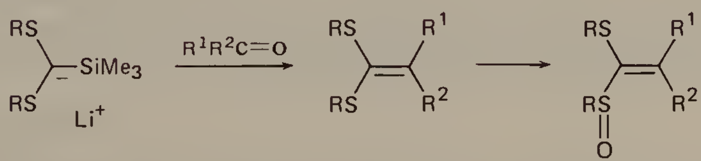
Three principal routes, differing in the sequence of oxidizing the sulphur atom, constructing the carbon skeleton and formation of the bissulphur-substituted double bond, are available for ketene thioacetal monosulphoxides (equations 5, 6 and 7). Aldehydes possessing a potential leaving group in the α-position are



(11) (12) (13) (5)



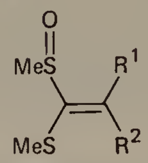
(14) (12, X = OH) (13) (6)



(1) (15) (7)

transformed to the thioacetals **11**, which are oxidized to **12**. Subsequent β-elimination of HX yields **13** (equation 5)[103]. This procedure is exclusively used for the preparation of **13** ($R^1 = H$). Other ketene thioacetal monosulphoxides derived from low molecular weight aldehydes are best prepared by employing the 2-lithium formaldehyde dithioacetal synthon, also mentioned in equation (5)[103]. The intermediate **12** (X = OH) is also accessible by reaction of aldehydes with the organometallic compound **14**. By the elimination of 'water' one generates the desired ketene thioacetal monosulphoxide (**13**) (equation 6)[102]. Oxidation as the last step is developed in another attractive reaction sequence[109]. Equation (7) illustrates the possibility of oxidizing ketene thioacetals, prepared by Peterson olefination, with sodium metaperiodate to form the monosulphoxides. This method seems to have the widest range of choice of R^1 and R^2.

TABLE 4. Preparation of ketene thioacetal monosulphoxides



R^1	R^2	Method	Yield (%)	Reference
H	Ph	Equation (6)	73–99	102
NH_2	·Alkyl/aryl	Equation (6)	72–77	102
H	n-C_5H_{11}	Equation (7)	82	109
$-(CH_2)_5-$		Equation (7)	81	109
H	H	Equation (5)	77	103
H	Me	Equation (5)	50	103

All the preparations mentioned above give access to ketene thioacetal monosulphoxides in reasonable yields (Table 4) and in many cases they allow an easy and convenient entry to these molecules.

III. PHYSICAL PROPERTIES OF KETENE THIOACETALS

A. General Characteristics

Ketene thioacetals generally form colourless liquids or white crystalline solids, which have *no* odour. The frequently experienced mercaptan-like smell is due to impurities in the product[7,56,73].

Liquid ketene thioacetals are purified by short-pathway distillation under high vacuum[73]. Solid compounds generally are recrystallized from hot methanol[73]. Some ketene thioacetals can also be purified by chromatographic means, using benzene/hexane (1:1) as eluant on silica gel[21,56]. The recrystallized compounds can be stored without special precautions while the liquid materials are preferably kept at 0° C to 40° C to avoid slow decomposition[56].

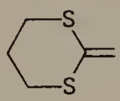
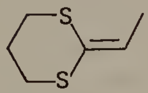
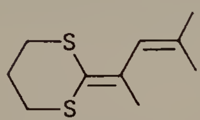
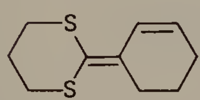
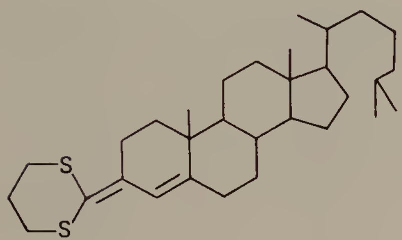
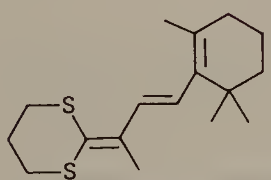
B. U.v. Spectra

Only a few data are available on characteristic absorption bands of ketene thioacetals and moreover, they have been inadequately interpreted[56,73]. Molecules investigated under this aspect do not show absorptions typically different from those observed on thioacetals[32,110–114] (248–252 nm for dithiane). However, in some cases they are overlapped by absorptions of other chromophores, like dienes, trienes, etc. The measured values are given in Table 5.

C. I.r. Spectra

Ketene thioacetals containing the dithiane moiety in the molecule show a sharp, not extensive, but characteristic peak between 900 and 910 cm^{-1}, interpreted as a dithiane skeleton vibration[32]. Open-chain thioacetals as well as the dithiolane compounds lack this peak[32,56]. The bissulphur-substituted double bond is reflected in an absorption at 1550–1630 cm^{-1} depending on the substitution pattern[56,73].

TABLE 5. U.v. absorption of ketene thioacetals

Compound	Solvent	λ_{max}(nm)	ξ	Reference
	MeOH	256	71,000	56, 73
	MeOH	255	5000	56, 73
	MeOH	274	8800	56, 73
	MeOH	296	21,000	56, 73
	EtOH	320		56
	Et_2O	312	22,700	56, 73

D. N.m.r. Spectra

1. ^{1}H-N.m.r.

The ^{1}H-n.m.r. spectra of ketene thioacetals, usually measured in carbontetrachloride or trideuterochloroform with tetramethylsilane as internal standard, show chemical shifts in the range of values given in the literature as typical for protons with comparable electronic environment[115–119]. The CH_2 groups next to the sulphur atoms in 2-alkylidene-1,3-dithianes give multiplets at 2.1–2.3 p.p.m. (δ) for the α-CH_2 and 2.7–3.0 p.p.m. (δ) for the β-CH_2[56,73] with a characteristic structure for all compounds in this series[56]. In ketene bismethylthioacetals the S–CH_3 corresponds to a singlet appearing between 2.0 and 2.2 p.p.m. (δ). The oxidized derivatives, ketene methylsulphinylmethylthioacetals, are obtained as a mixture of isomers, when $R^1 \neq R^2$ in **15**, or $R^1 \neq$ H for **13**[109], yielding more complex ^{1}H-n.m.r. spectra. One expects the CH_3–SO between 2.5 and 3.0 p.p.m. (δ) and the CH_3–S between 2.1 and 2.4 p.p.m. (δ), as singlets. Concerning the proton shifts in R^1 and R^2 the statement made at the onset of this section holds.

2. ^{13}C-N.m.r.

The only ^{13}C data available on ketene thioacetals were measured on 2-alkylidene-1,3-dithiane derivatives[56]. They are summarized in Figure 2. The chemical shifts of carbon atoms $C_{(4)}$, $C_{(6)}$ and $C_{(5)}$ are unaffected by the double bond in the molecule. The data measured for these atoms correspond to those available from dithiane derivatives[120] ($C_{(4),(6)}$: 29.9 p.p.m., $C_{(5)}$: 26.6 p.p.m., TMS as standard in $CDCl_3$). Of interest is the change in the chemical shifts of two sp^2-hybridized carbon atoms in the function of the substituents R^1 and R^2 reflecting the electron distribution in the double bond. Both sp^2 carbon atoms appear between 100 and 150 p.p.m. (TMS as standard) with the disulphur-substituted atom at higher field (110–115 p.p.m.). The dashed line in Figure 2 is calculated from shift increments given in the literature[121–123].

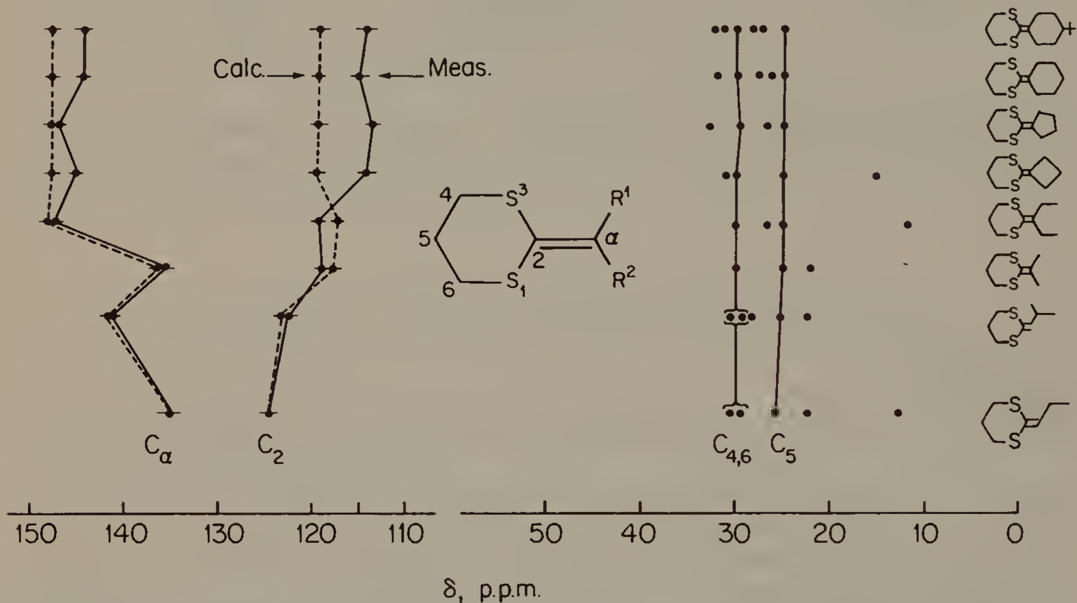


FIGURE 2. ^{13}C-n.m.r. chemical shifts for 2-alkylidene-1,3-dithianes in deuterochloroform, tetramethylsilane as internal standard.

E. Mass Spectra

The mass spectra of ketene thioacetals, extensively studied on 2-alkylidene-1,3-dithianes only[56,124], show several features, which are characteristic of all examples investigated. At 70 eV their parent ion peak is of medium intensity. With high intensity, however, the spectra show $M - 74$ and/or $M - 75$, irrespective of their substitute pattern in R^1 and R^2. This fragmentation has to be interpreted as a loss of C_3H_6S and/or C_6H_7S, typical for the dithiane ring (Figure 3)[125–128].

IV. CHEMICAL PROPERTIES OF KETENE THIOACETALS

A. General

Most chemical transformations achieved on, or with the help of ketene thioacetals are based on the specific properties of the bissulphur-substituted double

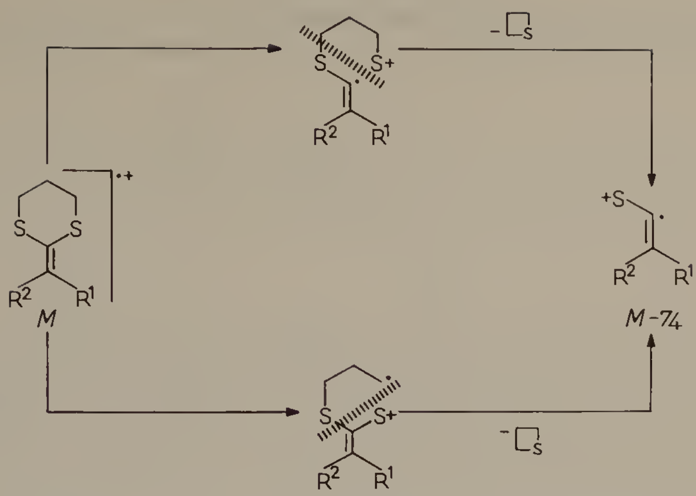
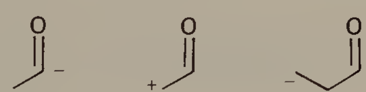


FIGURE 3. Mass spectral fragmentation of 2-alkylidene-1,3-dithianes.

bond[129]. The stabilising effect sulphur exercises on neighbouring positive and negative charges[4,131-142] makes this double bond[1-6,130] reactive towards nucleophiles as well as electrophiles and extremely versatile for organic synthetic purposes. There are almost no limits in the imaginative use of ketene thioacetals as synthons for carbon–carbon bond formation or for positioning of functionality in a molecule. Figure 4 gives only a modest selection of these possibilities. The following sections will consider in more detail the transformation indicated schematically in Figure 4.

B. 'Umpolung' with Ketene Thioacetals

One of the major interests in ketene thioacetal chemistry clearly stems from the potential use of these compounds in masking acyl anions (**16**), enolate cations (**17**), homoenolate anions (**18**) or their vinylogues[7,11-14]. This reactivity pattern, in-



(16) (17) (18)

trinsic to the chemical nature of ketene thioacetals examplifies 'umpolung' activity in carbonyl systems[7,11-14]. A generalized picture of this feature is shown in Figure 5. The chemical behaviour of ketene thioacetals allows their use in the creation of [1.(2*n*)] relationships between functional groups (usually oxygen, sulphur or nitrogen functions), a relative positioning accessible only with difficulty by classical chemical means[7,11-14].

1. *Reaction of ketene thioacetals with nucleophiles*

Ketene thioacetals and their vinylogues are reactive towards nucleophiles generally on carbon atoms $C_{(2)}$, $C_{(4)}$, $C_{(6)}$ etc. . . . (see Figure 5)[7,32,37,109]. We name this pattern schematically N^2, N^4, N^6 etc. . . . reactivity[7,12,109]. Ketene thioacetals add

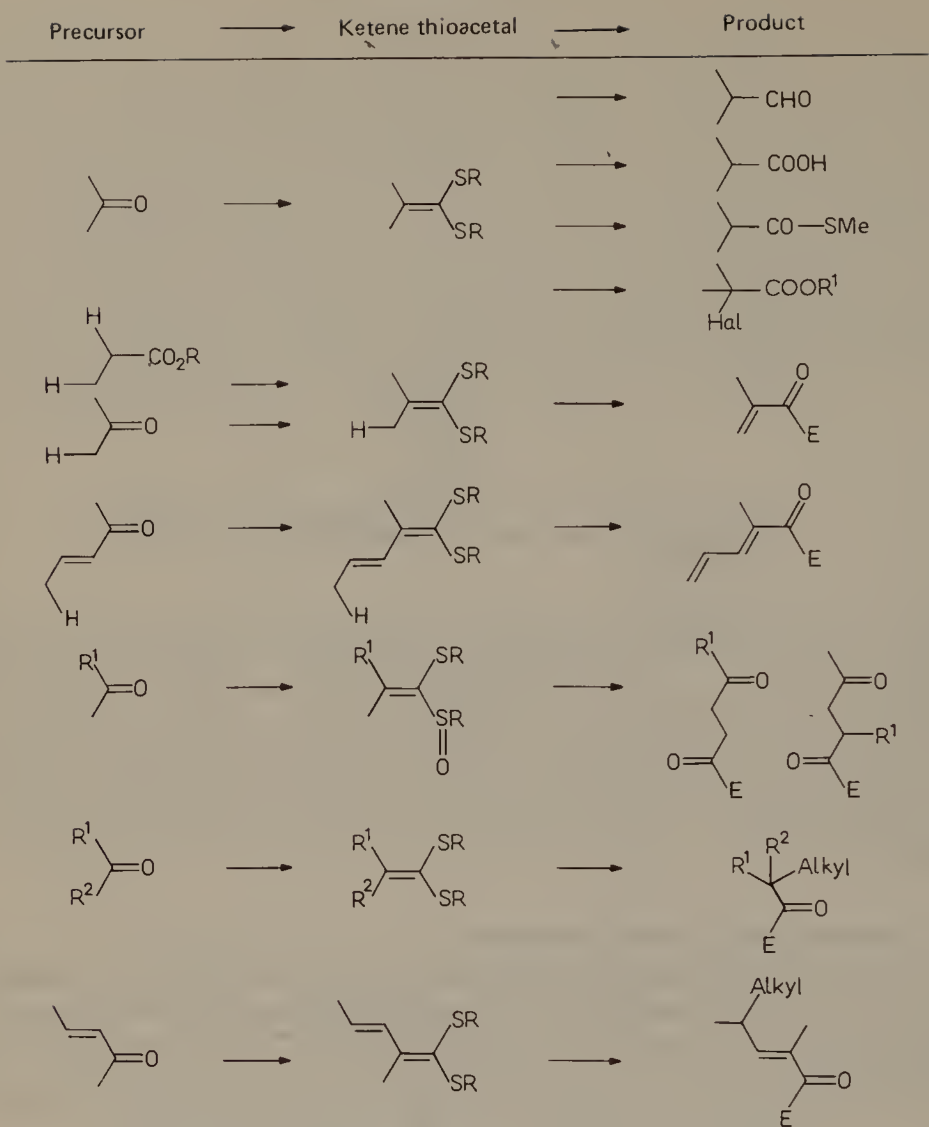


FIGURE 4. Principal synthetic transformations available by ketene thioacetal chemistry.

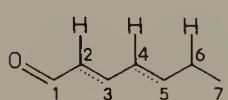
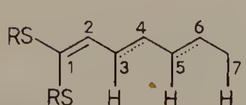
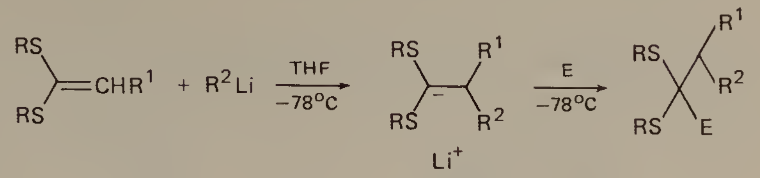
	Proton abstraction at	Electrophilic attack at	Nucleophilic attack at
	C(2),(4),(6),···	C(2),(4),(6),···	C(1),(3),(5),···
	C(3),(5),(7),···	C(1),(3),(5),···	C(2),(4),(6),···

FIGURE 5. 'Umpolung' of carbonyl reactivity with ketene thioacetals.

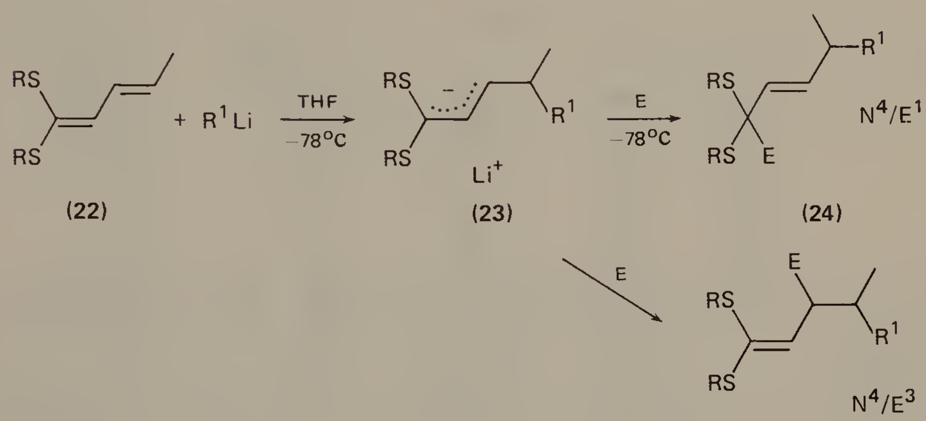
alkyllithium compounds like *n*-butyllithium and *t*-butyllithium at carbon atom $C_{(2)}$ (equation 8)[32,37,109]. The so-generated lithiumorganyl **20** can be trapped by



(8)

(19) (20) (21)

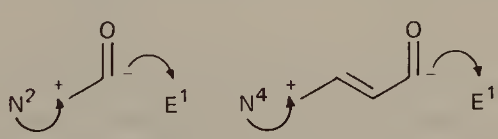
electrophiles (E) to form thioacetals **21**. However, this enolate cation reactivity (**26**) is only found in the absence of allylic hydrogen atoms in **19** (R^1 = H, Ph, *t*-Bu[109]. The overall transformation **19** → **21** consists of attack by a *nucleophile at* $C_{(2)}$, followed by an *electrophile at* $C_{(1)}$ (Figure 5 and structure **26**). This N^2/E^1 reaction[109] can be extended to vinylogous compounds like **22**, allowing N^4/E^1 (equation 9)[109].



(22) (23) (24) (25)

(9)

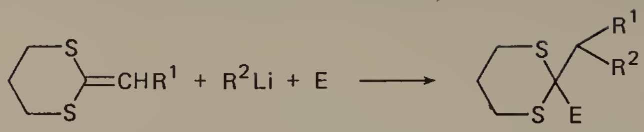
In these reactions alkyllithiums always behave as nucleophiles. Abstraction of pentadienylic or allylic protons has never been observed, with exception of a steroid example given in Table 6. The allyl anion **23** is trapped with electrophiles in general at carbon atom $C_{(1)}$. Exceptions are aromatic aldehydes and ketones which give rise to some N^4/E^3 reaction to form **25**.



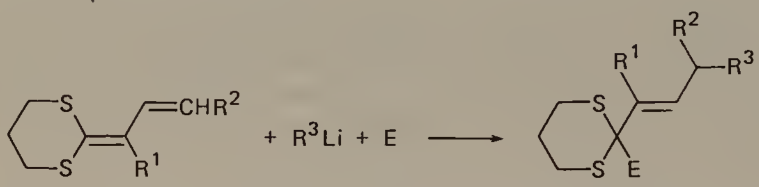
(26) (27)

Limiting the above-mentioned N^2/E^1 (**26**), N^4/E^1 (**27**) and N^4/E^3 transformations, however, is the scarcity of nucleophiles which can be employed; *n*-, *s*- and *t*-butyllithium generally react in high yield (Table 6). Under special circumstances, hydrides can attack ketene thioacetals at carbon atom $C_{(2)}$ (equation 10)[143], which after aqueous work-up lead to a formal reduction of the double bond. 2-Deoxy-4,5-isopropylidene-D-erythro-pent-1-enose diphenyldithioacetal [**28**; R = Ph, $R^1 = HC(O-C(CH_3)_2-O-CH_2]$ reacts with lithium aluminium hydride, whereas the corresponding *O*-methyl ether is unreactive towards this reagent.

TABLE 6. N^2/E^1 and N^4/E^1 reactions on ketene thioacetals

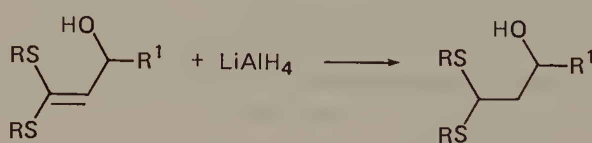


R^1	R^2	E	Yield (%)	Reference
H	*t*-Bu	MeI	90	56, 109
H	*n*-Bu	H_2O	90	56, 109
Ph	*t*-Bu	MeI	98	56, 109



R^1	R^2	R^3	E	Yield (%)	Reference
H	H	*n*-Bu	MeI	89	56, 109
H	H	*t*-Bu	MeI	95	56, 109
H	H	*t*-Bu	H_2O	92	56, 109
H	Me	*n*-Bu	H_2O	80	109
H	Me	*n*-Bu	D_2O	74	109
H	Me	*n*-Bu	MeI	77	109
H	Me	*t*-Bu	MeI	90	109
Me	H	*n*-Bu	MeI	76	56, 109
$-(CH_2)_3-$		*n*-Bu	H_2O	84	109
$-(CH_2)_3-$		*n*-Bu	D_2O	76	109
$-(CH_2)_3-$		*n*-Bu	MeI	82	109
4-cholesten-3-ylidene		*n*-Bu	MeI	0	56, 109, 124[a]

[a]Proton abstraction occurs at carbon atom $C_{(5)}$; see Table 10.



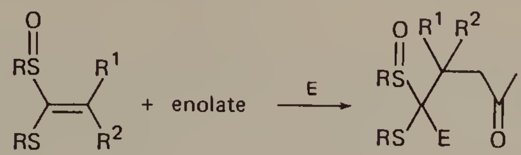
(28) (29) (10)

This, however, already exhausts the list of nucleophiles which can be used. Methyllithium or phenyllithium as well as Grignard reagents fail to undergo this reaction[56], as do other more stabilized organolithium compounds. Organocuprates, known as ideal reagents for Michael additions in α,β-unsaturated carbonyl compounds (N^3 reaction) do not facilitate the N^2 or N^4 reaction on ketene thioacetals **19** either[94].

2. *Reaction of ketene thioacetal monosulphoxides with nucleophiles*

The synthetic applicability of ketene thioacetals was considerably reduced by the factors mentioned above, which limited their use in N^2/E^1 reactions. Since the advent of ketene thioacetal monosulphoxides these problematic criteria have been overcome. Ketene thioacetal monosulphoxides present a convient enolate cation equivalent (26)[102–107], and they can be used under conditions which favour Michael type reactions:

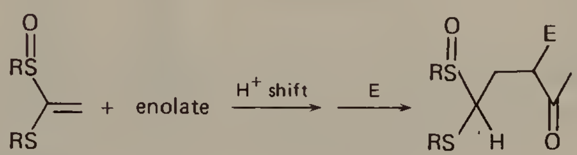
(a) The product anion is thermodynamically more stable than the starting anion and therefore can react directly with electrophiles (E) (equation 11).



(15) (30)

(11)

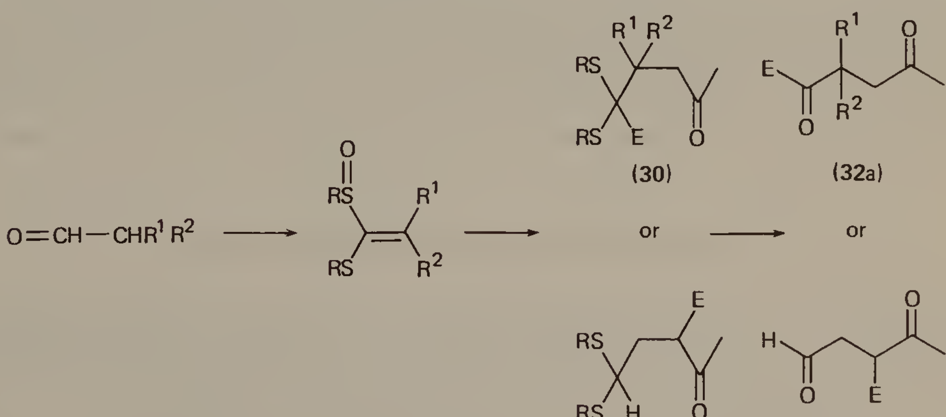
(b) The product anion is thermodynamically less stable than the starting anion, but a proton shift is possible, driving the equilibrium towards the desired product (equation 12).



(15; $R^1 = R^2 = H$) (31)

(12)

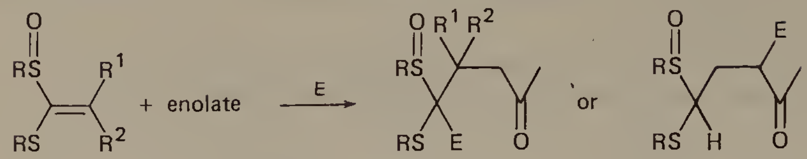
Using these reaction conditions ketene thioacetal monosulphoxides have been coupled with enolate anions from ketones[109], esters[103,104], β-keto esters[103], β-diketones[136], malonates[103,104], α,β-unsaturated esters[103,104] and amides[109] or enamines[103] in a N^2 reaction mode (Table 7). The ease of acidic hydrolysis of the product dithioacetal *S*-oxides 30 and 31 to carbonyl compounds[105,144,145] makes this reaction pattern extremely useful for the preparation of 1,4-dicarbonyl-derivatives 32 (equation 13), a positioning of oxygen functionality frequently



(13)

encountered in natural products. In as much as N^2 reactivity is now accessible by the use of ketene thioacetal monosulphoxides, there is no corresponding example for N^4 reaction with these compounds.

TABLE 7. N^2/E^1 reaction with ketene thioacetal monosulphoxides (R = Me)



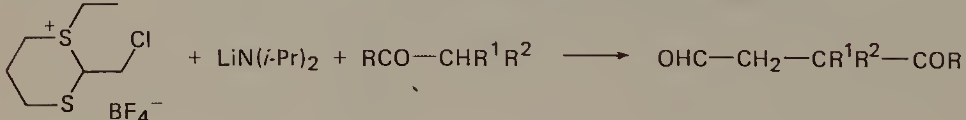
(15) (30) (31)

R^1	R^2	Enolate from	E	Product	Yield (%)	Reference
H	H	Ester	H^+	30	94	103
H	H	α,β-Unsat. ester	H^+	30	88	103
H	H	α-Alkylthio ester	H^+	30	90	103
H	H	β-Diketone	H^+	30	91	103
H	H	β-Keto ester	H^+	30	92	103
H	H	Malonate	H^+	30	98	103
H	H	Ester	CH_3I	30	90	104
H	H	Ester	$H_2C{=}CHCH_2Br$	30	88	104
H	H	Enamine	H^+	30	92	103
Me	H	Ester	H^+	30	90	103
Me	H	Malonate	H^+	30	75	103
H	H	β,γ-Unsat. ester	Alkyl–I Allyl–Br Propargyl–Br	31	74–96	104
H	H	Malonate	Alkyl–I Allyl–Br Propargyl–Br	31	75–98	104
n-C_5H_{11}	H	Ketone	H^+	30	~70	109
n-C_5H_{11}	H	Ester	H^+	30	<20	109
$-(CH_2)_5-$		Amide	H^+	30	35	109
$-(CH_2)_5-$		Ketone	H^+	30	<20	109

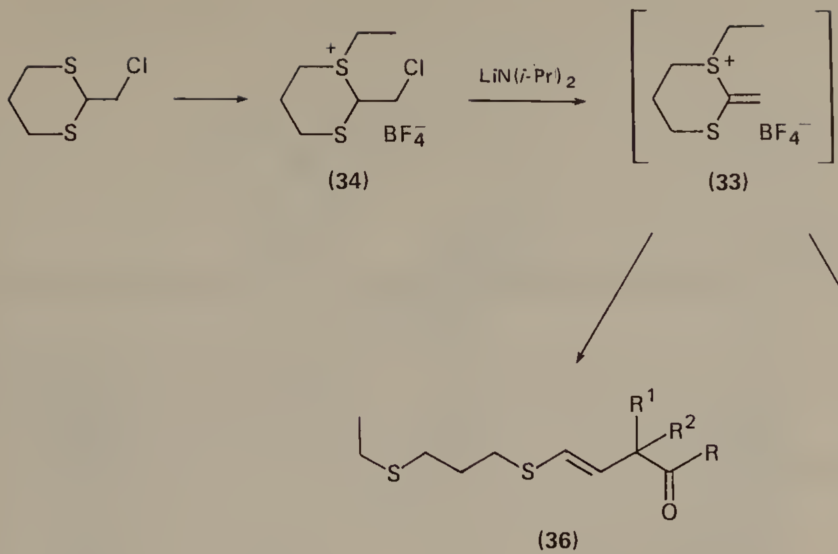
3. *Reaction of ketene thioacetal monosulphonium salts with nucleophiles*

Analogously to the N^2 reaction of ketene thioacetal monosulphoxides discussed above, the corresponding monosulphonium salts 33 undergo the same type of transformation[146]. Under carefully chosen reaction conditions ketene thioacetal monosulphonium salts 33, prepared *in situ* by base treatment of 34[146], react with

TABLE 8. N^2/E^1 reaction with ketene thioacetal monosulphonium salts



R	R^1	R^2	Yield (%)	Reference
OEt	Me	CO_2Et	70	146
OEt	Et	CO_2Et	46	146
OEt	$-CO(CH_2)_4-$		82	146
OMe	Me	COPh	62	146



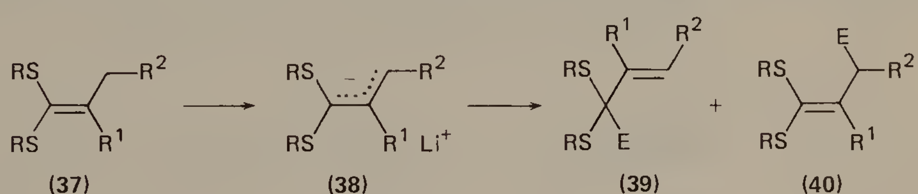
(14)

active methine compounds to give aldehydes **35** containing an oxygen function in the γ-position (1,4-relationship, N^2 reation, equation 14) in moderate yield (Table 8)[146]. The by-products in this reaction are vinyl thio ethers **36**, which under special work-up conditions can become the major product[146].

4. *Metalated ketene thioacetals and their reactivity towards electrophiles*

The foregoing sections indicate that bissulphur-substituted carbon atoms carrying a negative charge, introduced by N^2 additions of carbanions to ketene thioacetals, are quite reactive to electrophiles. Primary and secondary alkyl iodides, primary alkyl bromides, allylic and benzylic bromides and chlorides as well as saturated or unsaturated aldehydes and ketones, always react smoothly, whereas epoxides sometimes need higher reaction temperatures[56].

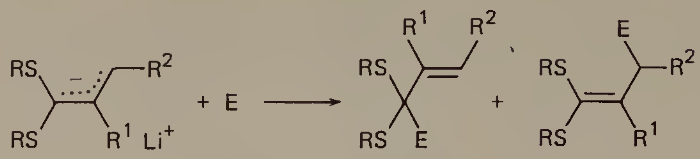
A different route to bissulphur-substituted carbanions in ketene thioacetals involves abstraction of allylic protons (equation 15, **37** → **38**). The large majority of



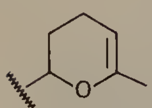
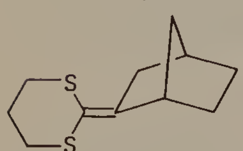
(15)

examples documented in the literature transform **38** to **39** by reaction with electrophiles (E) on carbon atom $C_{(1)}$ (E^1 reaction)[7,12]. Some examples also indicate the possible formation of product **40** (E^3 reaction, Table 9) in reactions with aromatic aldehydes and ketones, when **37** is not further functionalized [7,32,56,124]. This is in agreement with the situation normally found in other vinyl/allyl heterosubstituted systems, namely that proton abstraction is more facile from the α-position to the heteroatom in the allyl compound than from the γ-position in the vinyl derivative[147]. In the latter this effect may be so pronounced, that it kinetically favours formation of a much less stable carbanionoid species, as was found in the metalation of the ketene thioacetal **41** (equation

TABLE 9. Reactions of metalated ketene thioacetals (**38**; R/R = $-(CH_2)_3-$) with electrophiles (E^1 or E^3 reaction)



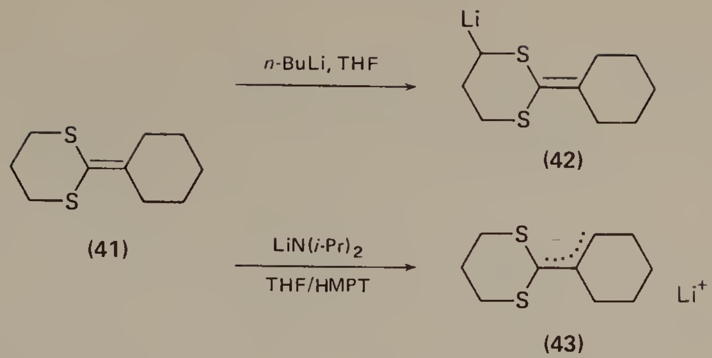
(38) (39) (40)

R^1	R^2	E	Yield (%) 39	40	Reference
H	H	H^+, D^+	75	25	56, 124
H	H	MeI	99	–	56, 124
H	Me, *n*-Pr	MeI	90	–	124, 148
H	Ph	MeI	1:1		4
H	Ph	MeS–SMe	90	–	149
H	CN	Alkyl halide	–	31–75	43, 150
H	SMe	Alkyl–I, benzyl–Br	93–94	–	21
Me	H	Alkyl halide	92	–	124, 148
Et	Me	D^+	87	–	56, 124
Et	Me	Alkyl halide	80–87	–	124, 148
n-Pr	H	H^+	86	–	21
n-Pr	H	Alkyl halide	81–88	–	21
n-Pr	H	MeS–SMe	33	33	21
		MeI, *i*-PrI			56, 124
$-(CH_2)_2-$		MeI, benzyl–Br	80	–	124, 148
$-(CH_2)_3-$		Alkyl halide	75	–	124, 148
$-(CH_2)_4-$		H^+	90	–	21, 124, 148
$-(CH_2)_4-$		Alkyl halide	90	–	21, 124
$-(CH_2)_4-$		Allyl–Br	86	–	21
$-(CH_2)_4-$		Ph_2CO, PhCHO	–	50	56, 124
$-(CH_2)_2-CH(t\text{-Bu})-CH_2-$		MeI	77	–	124, 148
		MeI	81	–	21
		Allyl–Br	61	31	21
3-Cholestanyliden		MeI	75	–	124, 148
$-(CH_2)_2-CH{=}CH-$		H^+	73	–	21
$-(CH_2)_2-CH{=}CH-$		MeI	65	13	21

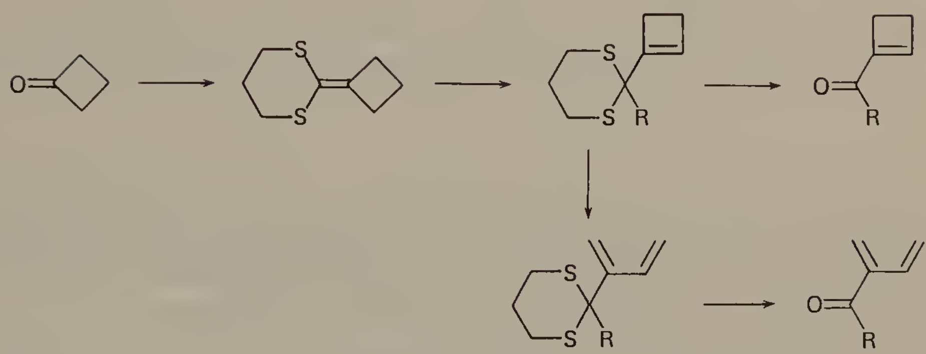
16)[32,56]. Depending on the reaction conditions[56], one can either generate the lithium derivative **42** or the allyl anion **43**.

Table 9 clearly shows the wide applicability of these reactions. Equation (17) illustrates a specific example which indicates further possibilities implicated in this chapter of ketene thioacetal chemistry.

However, not only simple ketene thioacetals, but also the vinylogue compounds



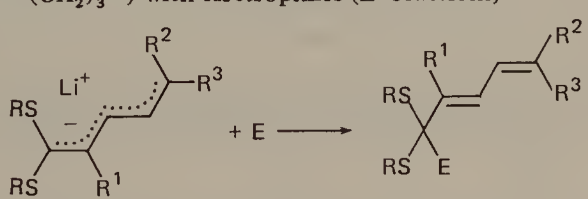
(16)



(17)

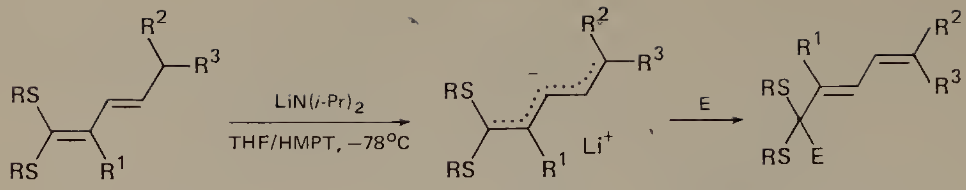
44 can be metalated by using appropriate bases and reaction conditions (proton abstraction occurs on carbon atom $C_{(5)}$, equation 18)[56,124]. For subsequent reaction of the pentadienylic carbanion **45** with electrophiles to yield **46**, the reasoning[147] given in the comment to equation (15) applies by analogy (Table 10). Unpublished experiments indicate that **45** ($R^1 = R^2 = R^3 = H$) can undergo E^3 reaction with benzophenone, since **47** has been isolated from the reaction mixture (equation 19)[56]. The reaction sequence: proton abstraction and subsequent reaction with electrophilic reagents (equation 15 and 18) is, however, limited to

TABLE 10. Reaction of metalated ketene thioacetals (**45**; R/R = $-(CH_2)_3-$) with electrophiles (E^1 reactions)

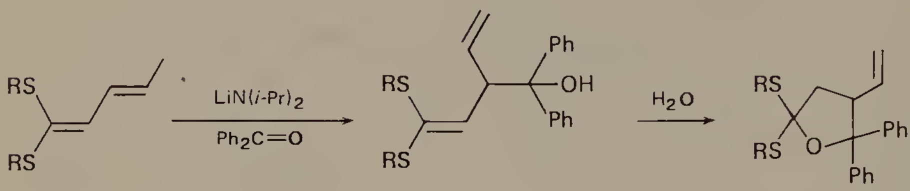


(45) (46)

R^1	R^2	R^3	E	Yield (%)	Reference
H	H	H	MeI	90	124
H	H	H	H^+	90	56
$-(CH_2)_2-$		H	MeI	86	124
$-(CH_2)_2-$		H	H^+	50	56
4-Cholesten-3-yliden			MeI	75	124



(44) (45) (46) (18)



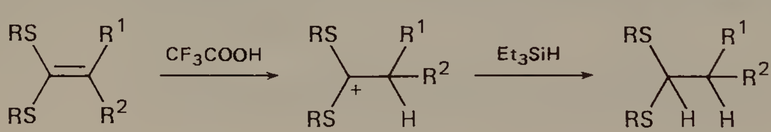
(47) (19)

R/R = —$(CH_2)_3$—

ketene thioacetals and in particular exploited on 2-alkyliden-1,3-dithianes. The ketene thioacetal monosulphoxides (13) and monosulphonium salts (33) successfully employed for N^2/E^1 and N^4/E^1 reactions fail in this transformation, due to the enhanced acidity of the protons next to the oxidized sulphur atom.

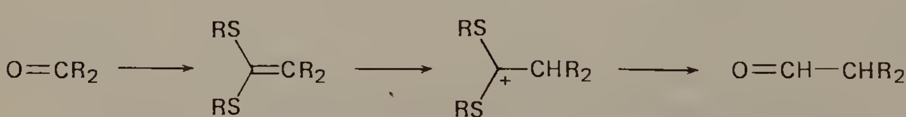
C. Reaction of Ketene Thioacetals with Electrophiles

Sulphur does not only stabilize a negative, but also a positive charge on the neighbouring carbon atom[4,131–142]. Advantage is taken of this in the following transformations. Electrophilic agents can attack the double-bond system in ketene thioacetals at carbon atom $C_{(2)}$, yielding a bissulphur-stabilized cation. Trifluoroacetic acid transfers a proton[151] to the π system of a ketene thioacetal (1) (equation 20), to form cation 48 which is then trapped by adding triethylsilane,



(1) (48) (49) (20)

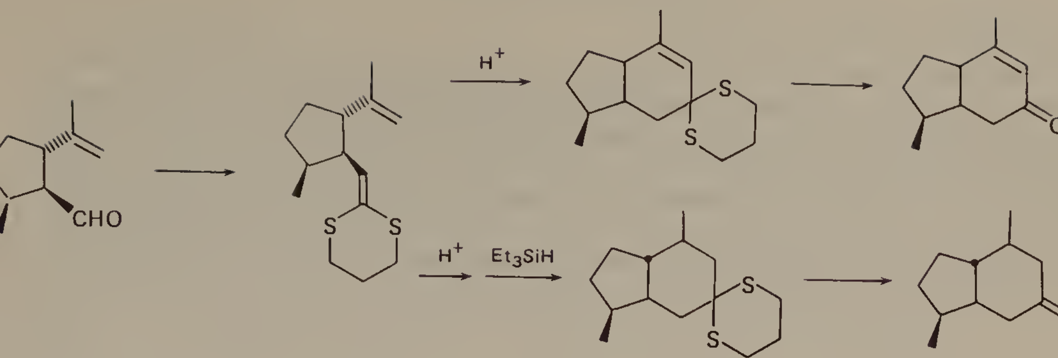
yielding 49[48,58]. This reaction transforms aldehydes or ketones into their next higher homologous aldehyde (equation 21). Cation 48, generated under acidic



(50) (1) (48) (21)

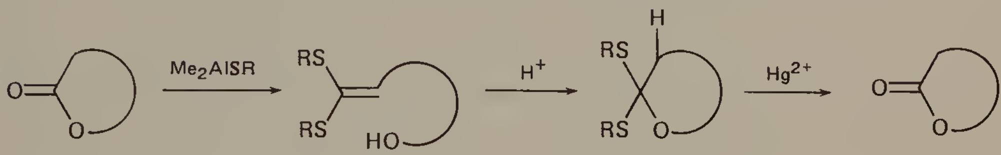
conditions, was also trapped intramolecularly by other nucleophiles, like double bonds. This reaction sequence was utilized in a ring-closing enone or ketone formation (equation 22)[152].

In a similar way intramolecular addition of a hydroxy function to ketene



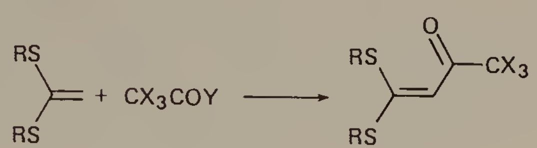
(22)

thioacetals in acidic medium occurs. Corey and coworkers exploited this reaction for protecting lactones and esters against nucleophilic agents (equation 23)[20].



(23)

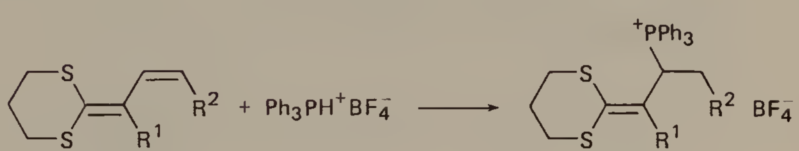
In analogy to protons attacking ketene thioacetals electrophilically, bromonium[48], chloronium[48] and acylium[153] ions are used in the following examples (equations 24 and 25). Trifluoro- and trichloro-acetic acid anhydrides or chlorides



(24)

(51) (52)

X = F, Cl
Y = OOC—CX_3, OOCMe, Cl



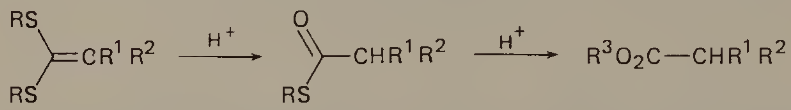
(25)

(53) (54)

(51) add to ketene thioacetals by electrophilic attack at carbon atom $C_{(2)}$; the reaction products are the more complex functionalized ketene thioacetals 52[153]. A recent communication extends this E^2/N^1 reaction pattern of ketene thioacetals with electrophiles to the conjugated unsaturated analogues 53. Reaction with triphenylphosphonium tetrafluoroborate gives compound 54, the addition product of the phosphonium salt to 53 (equation 25)[154]. Mechanistically, electrophilic attack of a proton at carbon atom $C_{(4)}$ precedes the nucleophilic approach of triphenylphosphine to the intermediate allyl cation of the ketene thioacetal 53 (E^4/N^3).

D. Hydrolysis of Ketene Thioacetals

Ketene thioacetals contain a bissulphur-substituted carbon atom at the formal oxidation level of a carboxyl group (see ketene thioacetal formation from esters, Section II). Therefore, hydrolysis unmasks this function to yield carboxylic acid derivatives[20,27,40,79,90,155,156,165–168]. The first isolable compounds in the treatment of ketene thioacetals with acid are thiol carboxy derivatives (54)[27,42,74,157], which on further hydrolysis give the free carboxylic acid derivative (equation 26). In view of the possible formation of 1 from carboxylic acid

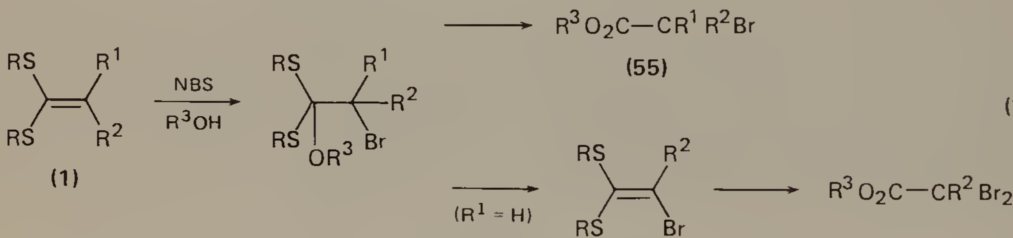


(26)

(1) (54)

derivatives[21] this overall transformation is of interest for the protection of carboxyl groups[20]. The access to 54 from 1 has become of recent importance, due to the synthetic value of thiol carboxyl derivatives in macrolide syntheses[164], their expressed reactivity towards *O*- and *N*-nucleophiles[158–160] and their role in ketone synthesis by reaction with cuprates and Grignard derivatives[161–163]. Table 11 lists examples and yields for 54 (R = Me) the product of trifluoroacetic acid/water treatment of 1 (R = Me; R/R = $-(CH_2)_3-$ are not hydrolysed under these conditions).

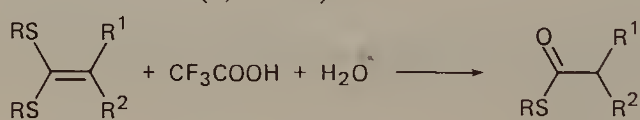
By oxidative solvolysis of ketene thioacetals (1) α-halo (55) or α,α-dihalo (56) esters are accessible (equation 27)[60,169,170]. The mechanism of this reaction seems to imply an intermediate haloketene dithioacetal (57)[48].



(27)

(1) (57) (56)

TABLE 11. *S*-Methyl thiocarboxylates (54; R = Me) from ketene thioacetals (1; R = Me)[169]



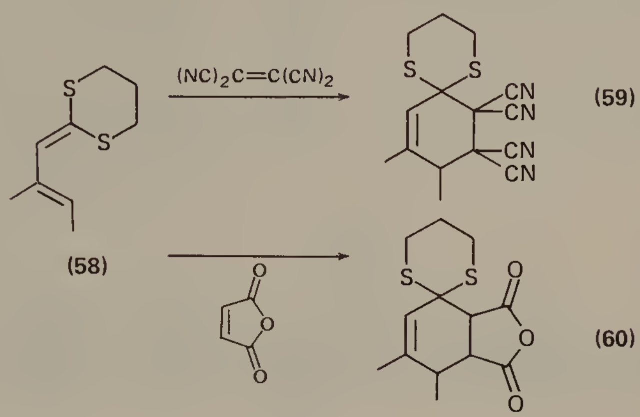
(1) (54)

R¹	R²	Yield (%)
H	Aryl	86–89
H	Alkyl	83–86
$-(CH_2)_5-$		87
$-(CH_2)_4-CHMe-$		63
Me	Aryl	88
Aryl	Aryl	85
3-Cholestanyliden		40

E. Cycloaddition

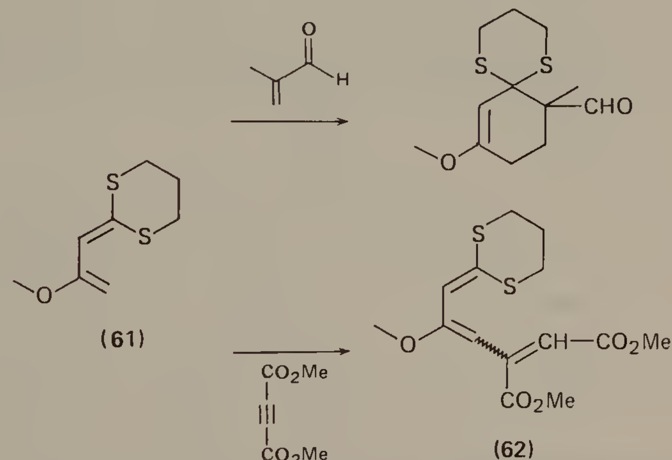
The elevated reactivity of the double-bond system in ketene thioacetals and their α,β-saturated analogues suggests that these compounds could be used as functionalized enes or dienes in cycloaddition reactions. Carey and Court[171] report a study on compound **58** as a potential enophile. This is a synthetic equivalent of the difficultly accessible vinylketene[172–176] which would undergo many undesired side-reactions.

Reaction with tetracyanoethylene and with maleic anhydride yields respectively the Diels–Alder adducts **59** and **60** (equation 28)[171]; **58** does not react with weaker



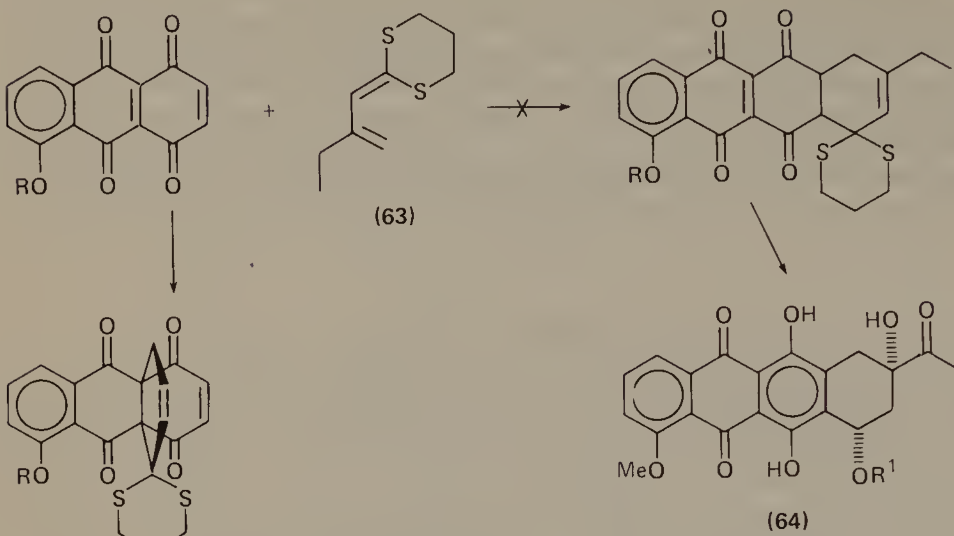
(58) (59) (60) (28)

dienophiles. Danishefsky and coworkers[177] extended this reaction scheme to the more reactive ketene thioacetal compound **61** which undergoes Diels–Alder reactions with methyl vinyl ketone, methacrolein and methyl acrylate in moderate yields. With more reactive agents Michael reactions lead to by-products (e.g. the formation of **62** with dimethyl acetylenedicarboxylate, equation 29)[176].



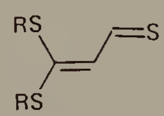
(61) (62) (29)

Although feasible only in a few examples, the transformation mentioned above is of synthetic value, as it generates a fully differentiated highly functionalized molecule with a minimum of reaction steps. Some more data on cycloadditions of conjugate unsaturated ketene thioacetals were obtained by Kelly and coworkers using compound **63** in unsuccessful attempts to synthesize adriamycin (**64**) (equation 30)[178].



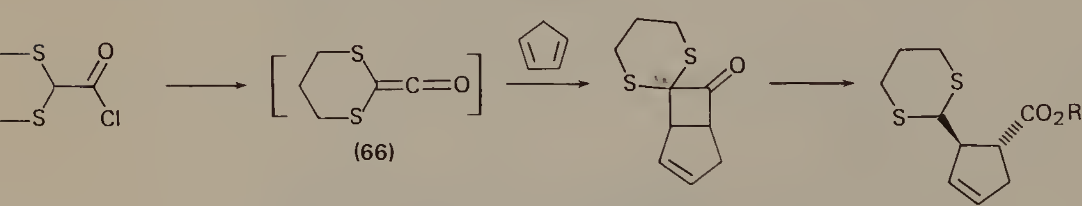
(63) (64) (30)

Examples of cycloaddition reactions with ketene thioacetals of type **65** have been briefly mentioned. Cyclization products are generally complex functionalized heterocyclic compounds[179–181].



(65)

Ketenes with α-carbanion-stabilizing substituents[182–184], like ketene dithioacetals, possess the synthetic possibility of a two-carbon chain addition to an olefinic substrate. From this point of view the reaction of 2-carbonyl-1,3-dithiane (**66**) with cyclopentadiene in a (2 + 2) manner has synthetic value (equation 31)[185]. Ring-opening[186] of the functionalized cyclobutanone yields an interestingly substituted cyclopentene (**67**).



(66) (67) (31)

F. Miscellaneous Transformations with Ketene Thioacetals

The foregoing sections dealt with ketene thioacetal reactivity ascribed to the specific stabilizing effect of sulphur atoms on neighbouring charges. This leads to the general feature that ketene thioacetals are attacked by nucleophiles as well as electrophiles first at carbon atom $C_{(2)}$ (or $C_{(4)}$ in vinylogues) forming a stabilized

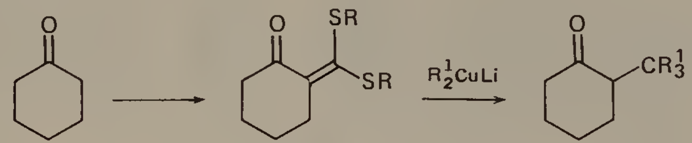
TABLE 12. Reactions of ketene thioacetal 68

(68)

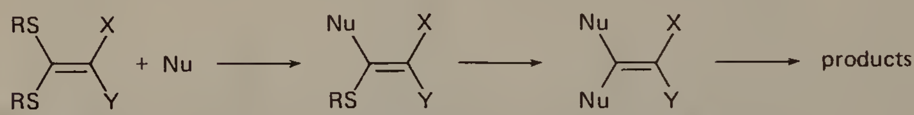
R	R	X	Y	Nucleophile	Product	References
Me, CH_2Ph	Me, CH_2Ph	CN	COR	NH_3, RNH_2	Ketene *N,S*-acetals Ketene *N,N*-acetals Pyrazol derivatives	201, 203
$-(CH_2)_{n=2,3}$		CN	SO_2R	RNH_2, $RNHNH_2$ $RC(=NH)NH_2$	Ketene *N,N*-acetals Pyrazol derivatives	200
Me	Me	COR	SO_2R	P_4S_{10}	*S*-Heterocycles	199
Me	Me	COR	SO_2R	$RNHNH_2$	Pyrazol derivatives	199
Me	Me	COR	H	Guanidine, thiourea, active methylene	Pyrimidine derivatives	191, 192 187–189
Me	Me	S–C(=S)–NR–C(=O)		RNH_2	Ketene *S,N*-acetals Ketene *N,N*-acetals	202
Me	Me	S–C(=S)–NR–C(=O)		Active methylene	Vinyl sulphide derivatives	202
Me	Me	CN, COR	CN, COOR	Aziridine	Pyrroline derivatives	193
Me	Me	H	NO_2	RNH_2	Ketene *N,N*-acetals Ketene *S,N*-acetals	198
Me	Me	CN	CO_2R	$CH_2NO_2^-$	Pyrroline derivatives	197
Me	Me	CN	CN, COOR	Pyridinium *N*-ylides	Pyridinium *N*-allylides Indolizine derivatives	196
Me	Me	COR, COOR	$C_5H_5N^+$	Active methylene	Pyridinium *N*-allylides Indolizine derivatives	195
Me	Me	COR	H	$H_2N\wedge/CH(OR)_2$	Pyrrole derivatives	194

intermediate, and then at carbon atom $C_{(1)}$. There is no doubt that this is the predominating feature in the most useful aspects of ketene thioacetal chemistry.

This section considers reactions not classifiable in the above manner, which normally concern more complex functionalized ketene thioacetals. Quite a few examples have the dithioacetal unit of a ketene thioacetal as a Michael acceptor activator, as well as a potential leaving group. This feature was used by Corey and coworkers[190] to achieve specific multifold β-alkylation in carbonyl compounds (equation 32). In other more complex ketene thioacetal derivatives **68** this feature was exploited in the synthesis of ketene acetals **69** and **70**, also of compounds deriving from further transformations of **70** (equation 33). Table 12 contains a small selection of examples utilizing this reaction sequence with the corresponding literature references.



(32)



(33)

(68) (69) (70)

X, Y = CN, NO_2, O=CR, O_2CR, SO_2R, $C_5H_5^+$, . . .

Nu = nucleophile

V. CONCLUSION

Ketene thioacetals, readily accessible from carbonyl or carboxyl compounds,offer a wide range of transformations, especially useful in organic synthesis. They provide a convenient method for homologation of carbonyl compounds, nucleophilic acylation, and the conversion of ketones and aldehydes to the homologous acid or acid derivative. Furthermore the synthesis of α,β-unsaturated carbonyl derivatives by a reductive transformation or a C–C bond formation between aldehydes, ketones and esters becomes accessible with or without the introduction of nucleophiles and electrophiles. These reactions are especially useful, as they give compounds with a positioning of functional groups, which is only accessible with difficulty when employing classical chemical procedures. In addition to the utility of ketene thioacetals in carbonyl chemistry these compounds were shown to be versatile in the construction of heterocyclic systems. Ketene thioacetals appropriately functionalized are reactive towards nitrogen nucleophiles. These reactions produce useful heterocyclic compounds not otherwise available by such an easy manner.

Further work on ketene thioacetals will certainly be focused on their use as a tool to build molecules, and the selection of transformations with ketene thioacetals given here is meant to inspire the intuition of the reader.

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CHAPTER **17**

Ketene imines

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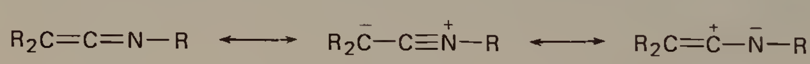
I. INTRODUCTION

Although ketene imines (nitrogen analogues of ketenes) were reported by Staudinger in 1921[1], much of the knowledge of this moiety has been accumulated within the last fifteen years. In this chapter the structure, and some preparations, physical properties and chemical properties of ketene imines are described. The reader is directed to articles by G. R. Krow [*Angew. Chem. (Intern. Ed.) 10,* 435 (1971)] and by N. P. Gambaryan [*Russ. Chem. Rev.,* 45, 630 (1976)] for comprehensive reviews of this function.

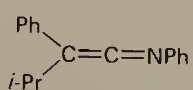
II. STRUCTURE

The formal structure for ketene imines (1) would indicate that the heterocumulene would be linear with two orthogonal double bonds. The observation by Jochims and Anet that the energy barrier to racemization of the *N*-phenyl group in **4** is 9.1 kcal/mol[2] supports this structure. However, resonance-contributing structure 2 may be important also as evidenced by the X-ray work of Daly[3] and of



(1) (2) (3)

Wheatley[4]. Daly found the C = N bond length for 5 to approximate the CN triple-bond length while Wheatley found a similar CN bond length for **6**. The C-N-C



(4)

$(Me_2OS)_2C{=}C{=}NEt$

(5)

$(Me_2OS)_2C{=}C{=}NMe$

(6)

bond angle in 5 was found to be about 145° while the same angle in **6** was 180°. Both the shortened CN bond length and the C-N-C angle of 180° in **6** would be in keeping with a major contribution to the ketene imine structure from 2. One would assume that the strong electron-withdrawing substituents on 5 and **6** are responsible for the enhanced importance of contributor 2 to the structure of these ketene imines.

Contributing structures 1 and 2 can also account for the nucleophilic nature of the nitrogen and of the β-carbon on ketene imines. Contributing structure 3 has been employed to explain the electophilic nature of the ketene imine α-carbon[5];

however, since models of the molecule show clearly that the carbon–carbon π bond is the least sterically shielded and, hence, the more available for attack of the two π bonds and since nucleophilic attack on the α-carbon would lead to a more stable intermediate than attack on the β-carbon, 3 is really not needed in order to explain nucleophilic attack on ketene imines.

III. PREPARATION

The choice of method for preparing 7 from the numerous examples cited in the literature essentially rests with the substituents on 7. If these substituents are all

$$R^1R^2C{=}C{=}NR^3$$

(7)

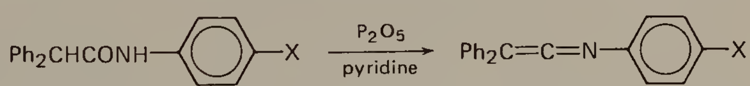
aromatic groups, then the ketene imine will be a solid, thermally stable, easily isolated, and hence, can be prepared by most of the available methods. As the aromatic substituents are replaced by other groups, the ketene imines are more likely to be thermally labile liquids which are more difficult to separate from reagents, and thus, require more specialized conditions for their preparation.

The preparative methods available for ketene imines can be divided into two general classes. The three most commonly employed methods – the linear dehydration of amides, the dehydrochlorination of imino chlorides, and the treatment of amides with triphenylphosphine dibromide in triethyl amine – represent Class A. Class B contains special synthetic techniques designed for the preparation of a particular ketene imine.

A. Class A Methods

1. Linear dehydration of amides

Stevens and Singhal reported in 1964 that anilide derivatives of diphenylacetic acid would undergo dehydration when treated with P_2O_5 in pyridine to produce ketene imines (equation 1)[6]. In their studies they found X could be *o*- or *p*-methyl,



(1)

p-methoxy, *p*-halo, *p*-*n*-butyl and *p*-thiomethyl. The yields obtained ranged from 50% to 87% with the majority of the yields above 70%. The directions call for heating the stirred mixture at reflux for seven hours. The temperature requirement for this reaction makes it unsuitable for the preparation of the thermally labile aliphatic substituted ketene imines. Several modifications have been tried to extend the usefulness of this preparative method to aliphatic systems, but seldom do the yields exceed 20%. However, for aryl-substituted ketene imines, this procedure is a reliable and a good-yield method.

2. Dehydrohalogenation of imino chlorides

Equation (2) illustrates a second general preparative procedure for ketene imines. This procedure, reported by Stevens and French[7], involves the dehydro-

$$R_2CHCONHR \xrightarrow[C_6H_6]{PCl_5} R_2CHC(Cl){=}NR \xrightarrow{Et_3N} R_2C{=}C{=}NR \quad (2)$$

chlorination with triethylamine of an imino chloride produced from the appropriate amide. The method requires maximum temperatures of benzene heated to reflux and of an intermediate distillation to remove phosphorus oxychloride. Thus, the thermal conditions for this preparation are less demanding than those for linear dehydration, and hence, allow for the production of a few more thermally labile ketene imines. The yields for aryl-substituted ketene imines are approximately 70% while that reported for one totally aliphatic substituted moiety (*n*-butylethylketene *N*-*n*-butylimine) is 57%. Therefore, the utilty of this procedure is the elaboration of thermally labile ketene imines in better yields than the dehydration method. However, yields of thermally stable ketene imines prepared by this method are usually lower than those for the dehydration method.

3. *Amides, triphenylphosphine dibromide and triethylamine*

Bestmann and coworkers reported a general procedure for preparing ketene imines in 1968[8]. Their procedure involves treating amides with triphenylphosphine dibromide and triethylamine in a methylene chloride solution. These mild conditions permit the preparation of alkyl- and aryl-substituted ketene imines in yields usually exceeding 80%.

The major disadvantage of this procedure is that often the ketene imine produced and the triphenylphosphine oxide by-product have very similar solubilities and, hence, are hard to separate[9]. Fortunately, an alumina column is usually effective for separating the materials[10].

B. Class B Methods

1. *Condensation of diphenylketene and phosphinimines*

Staudinger and Hauser reported the original preparation of ketene imines. Their procedure involved the condensation of triphenylphosphine alkyl- or aryl-imines with diphenylketene[1]. Although several ketene imines were prepared by this method, no yield data were given. Lee and Singer have modified this method to produce thermally labile ketene imines in good yields[10] (65–85%). The mild conditions utilized by Lee and Singer are illustrated by their ability to prepare chiral ketene imines in which the asymmetric centre is directly attached to the nitrogen.

2. *Alkylation of nitriles*

Several investigators have employed the alkylation of nitriles as a route to ketene imines. Dijkstra and Backer have reported that 8, when treated with diazomethane, yields **6** (equation 3)[11]. This procedure was utilized to prepare *N*-alkyl ketene

$$\underset{(8)}{(Me_2OS)_2CHCN} + CH_2N_2 \longrightarrow \underset{(6)}{(Me_2OS)_2C{=}C{=}NMe} \qquad (3)$$

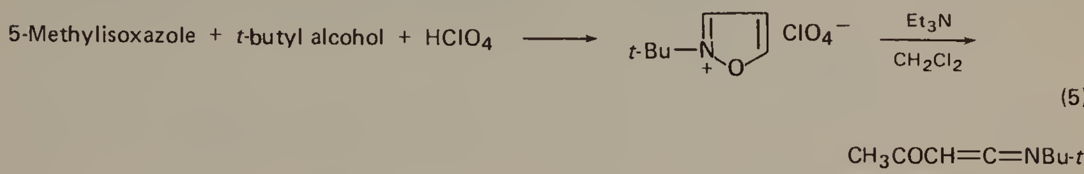
imines for X-ray studies. Newman and coworkers found that nitrile anions produced by treatment of the nitrile with amide ion can be alkylated with alkyl iodides to yield ketene imines[12] and Mueller and coworkers found that metalation of 1,1-dicyano-1-alkenes with trialkyl tin hydride gave nitrogen metal sustituted

$$RR^1C{=}C(CN)_2 + R^2_3SnH \longrightarrow RR^1CH{-}\underset{\displaystyle CN}{\underset{|}{C}}{=}C{=}NSnR^2_3 \qquad (4)$$

ketene imines[13] (equation 4). Other reactions with nitriles have led to *N*-substituted silicon and boron ketene imines[14,15] and ferrocene-substituted ketene imines[16].

3. *Heterocyclic intermediates*

Equations (5)[17], (6)[18], and (7)[19] illustrate the preparation of some unusual ketene imines through the rearrangement of heterocycles.



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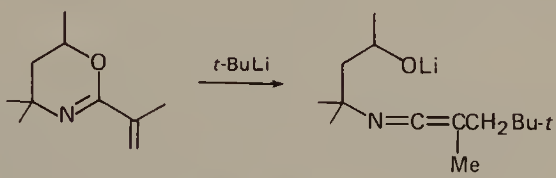

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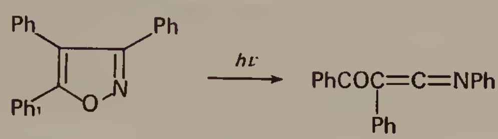


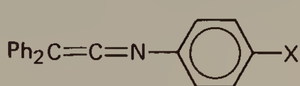
(7)

Several other techniques have been reported for the preparation of ketene imines. The review articles listed in the introduction contain information on these less common syntheses.

IV. SPECTROSCOPY

A. Infrared

Although several workers have commented on both the position and the intensity of the infrared absorption bands of ketene imines, only Stankovsky and Kovac have reported an infrared study of this class of compounds[20]. These investigators studied the spectra of 9 where X was methoxy, methyl, H, chloro,



(9)

bromo and nitro. In general they observed a complex absorption near 2000 cm^{-1} whose wave number was essentially independent of the substituent X. However, both the intensity of the absorption and the half-band widths were substituent-dependent.

A linear relationship between the log of the integrated intensities and both σ_p and σ_p^+ was observed. Thus, a direct relation between the electronic nature of the substituent and the intensity of absorption appears certain. The positive slope of these linear relations would seem to indicate that the $>$C=C=N– function is an electron-releasing group.

B. Nuclear Magnetic Resonance

A ^{13}C-n.m.r. study of ketene imines has been reported[21]. This study was designed to gain at least a qualitative idea of the relative importance of contributing structures 1, 2 and 3 to the actual structure of a ketene imine. The ^{13}C-n.m.r. of a series of ketene imines of structure R^1R^2 C=C=NR^3 were determined in which R^1 and R^2 were all possible combinations of hydrogen, methyl and phenyl and R^3 was phenyl except in one case where $R^1 = R^2$ = Ph and R^3 = Me. The α-carbon of the heterocumulene exhibited absorptions between δ 186.55 and 195.49 while the β-carbon exhibited absorptions between δ 36.94 and 77.79.

The obseved shielding of the sp^2-hybridized β-carbon can be rationalized by assuming a conjugative interaction between the C=C bond and the lone pair of electrons on nitrogen. Such an effect would be illustrated by contributing structure 2. That ketenes exhibit a similar shielding β-carbon while the terminal carbons of allenes absorb nearer to δ 100 (little shielding) is additional support for the importance of contributing structure 2 to ketene imines.

Earlier work by Krow and coworkers[22] with proton-n.m.r. led him to suggest that 2 is not an important contributor to the ketene imine structure. Krow's work is based on the ^{13}C–H coupling constant at the β-carbon in ketene imines and for the similar carbon in allenes. Since both *J* values are approximately the same, electron distributions are considered to be similar indicating little contribution to the structure from 2. Actually, both investigators seem to agree that the lone pair on nitrogen interacts in a conjugative manner with the C=C bond π orbital. However, they disagree as to whether 2 accurately represents this interaction.

The extreme deshielding of the central carbon in ketene imine is not unexpected when the bonding to this carbon is considered.

C. Ultraviolet and Visible

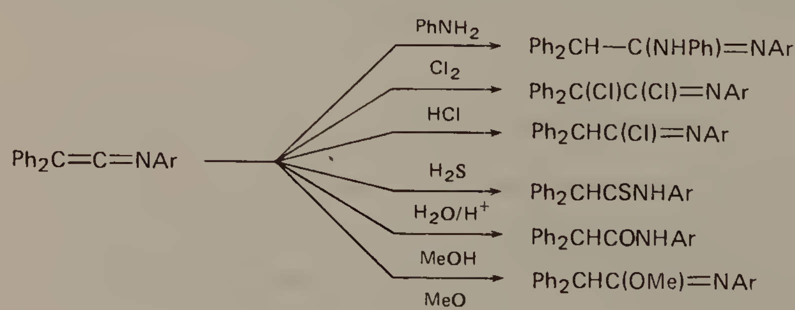
The ultraviolet and visible spectra of ketene imines provide little information beyond the presence of absorptions expected for unsaturated systems.

V. REACTIONS

A. Nucleophilic Additions

1. *General*

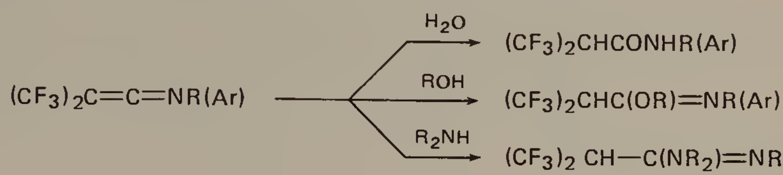
Since triarylketene imines are thermally stable and easily synthesized compared to alkyl-substituted systems, most of the known chemical properties of ketene



SCHEME 1.

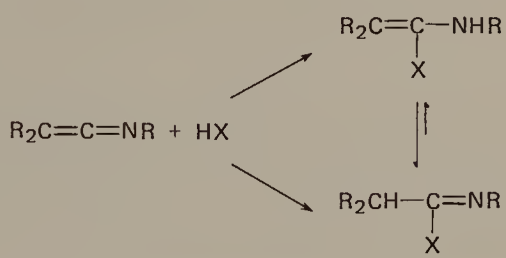
imines come from studies on triarylketene imines. The α-carbon of the moiety is electrophilic and is attacked by numerous nucleophiles to form amide derivatives[23,24] (Scheme 1). Thus, triarylketene imines have been shown to react with amines to form amidines[23], with chlorine or with hydrogen chloride to form imino chlorides, with water in the presence of acid to form amides, and with alcohols in the presence of base to form imidates[24].

The stable bis(trifluoromethyl)ketene imine has been used to examine the chemical properties of alkylketene imines[25]. The addition products of this ketene imine are similar to those of arylketene imines (Scheme 2).



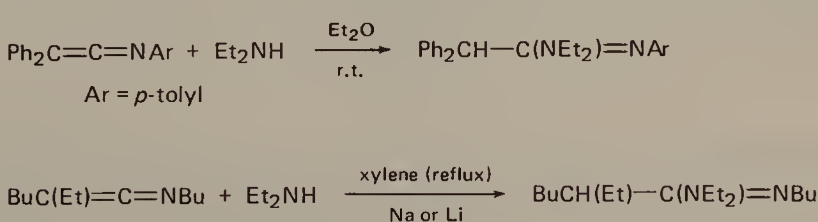
SCHEME 2.

It is not clear in either system (aryl- or alkyl-ketene imines) whether initial nucleophilic addition occurs across the C=C or the C=N bond. If initial addition were across the C=N bond, the adduct formed would immediately isomerize to a more stable product (equation 8)[25].



(8)

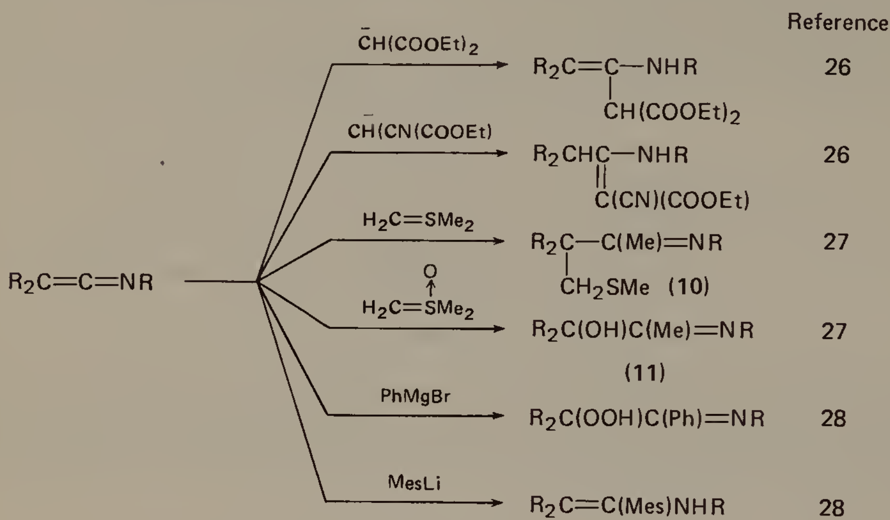
An investigation of the relative reactivities of alkyl- and aryl-substituted ketene imines to nucleophilic addition has been reported[25]. Stevens observed in the reaction of triaryl- and trialkyl-ketene imines with amines to form amidines that triarylketene imines were far more susceptible to nucleophilic attack than trialkylketene imines. For example, diethylamine reacted with diphenylketene *p*-tolylimine in an ethereal solution at room temperature to form *N,N*-diethyl-*N′*-(*p*-tolyl)-diphenylacetamidine in a 93–94% yield whereas, ethyl-*n*-butylketene *N*-butylimine required diethylamine at reflux in xylene using sodium or lithium metal as catalysts for reaction. Apparently, the electron-withdrawing effect of *N*-aromatic-substituted ketene imines increases the likelihood of nucleophilic attack by amines at the α-carbon compared to the *N*-alkyl-substituted ketene imines[25] (Scheme 3).



SCHEME 3.

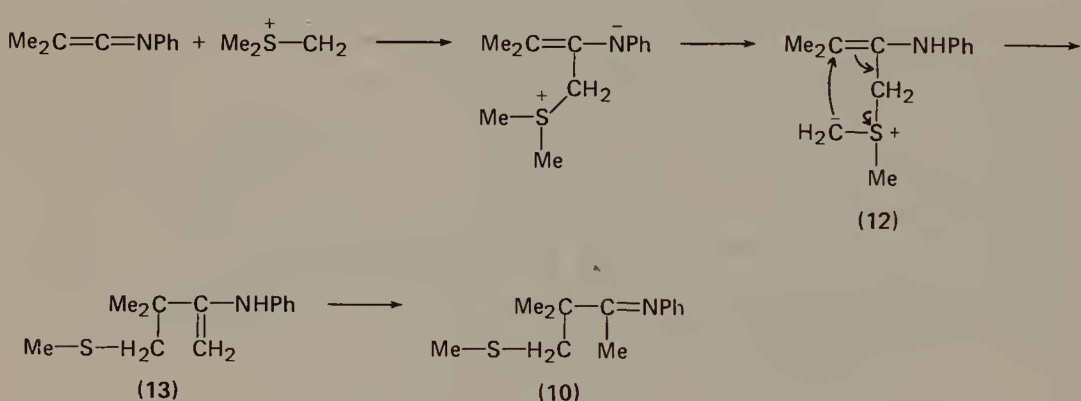
2. *Carbanions*

Nucleophilic attack on an aryl- or alkyl-ketene imine by carbon has been shown to occur at the α-carbon exclusively. This type of nucleophilic addition is not dependent on the nucleophile. Scheme 4 illustrates the synthetic utility of this process.



SCHEME 4.

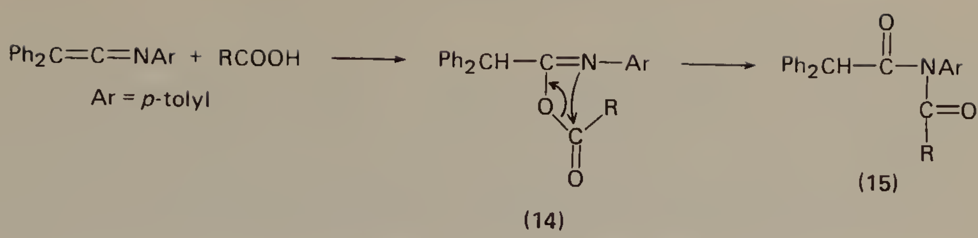
Interestingly, the reaction of dimethylketene *N*-phenylimine with dimethylsulphonium ylide yields **10**, whereas the reaction of dimethylketene *N*-phenylimine with dimethyl oxosulphonium ylide yields **11**. Both products are thought to be formed by 2,3-sigmatropic rearrangements of intermediates formed by nucleophilic attack by the respective ylides on dimethylketene *N*-phenylimine (Scheme 5 illustrates this proposed mechanism for attack by dimethylsulphonium ylide)[27].



SCHEME 5.

3. *Carboxylic acids*

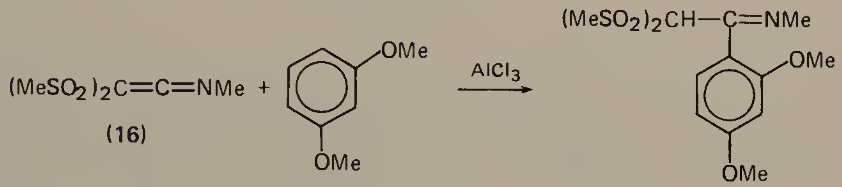
Ketene imines have been shown to react readily with carboxylic acids to form *N*-acyl amides. Evidence was obtained that the reaction of ketene imines with carboxylic acids (equation 9) proceeds via the intermediate **14** which subsequently rearranges through a four-membered transition state to give the imide **15**[29-31].



(9)

4. *Alkylation*

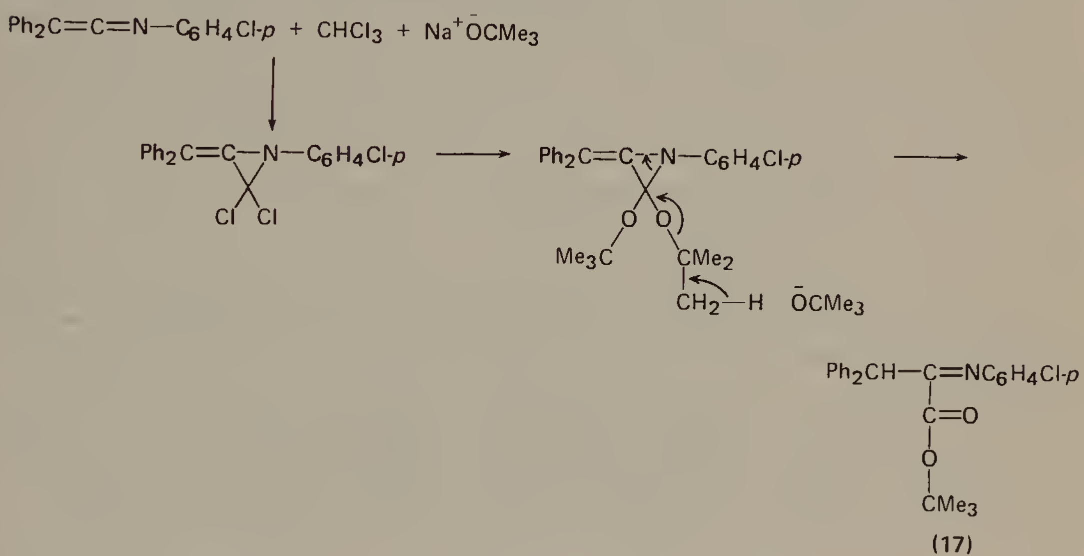
Aromatic rings have been alkylated with ketene imines in Friedel–Crafts-type reactions. For example, ketene imine **16** has been shown to react with resorcinol dimethyl ether in the presence of $AlCl_3$ (equation 10)[5].



(10)

5. *Carbene*

The addition of dichlorocarbene to diphenylketene *N-p*-chlorophenylimine yields **17**. A tentative mechanism for the formation of **17** is given in Scheme 6[32].



SCHEME 6.

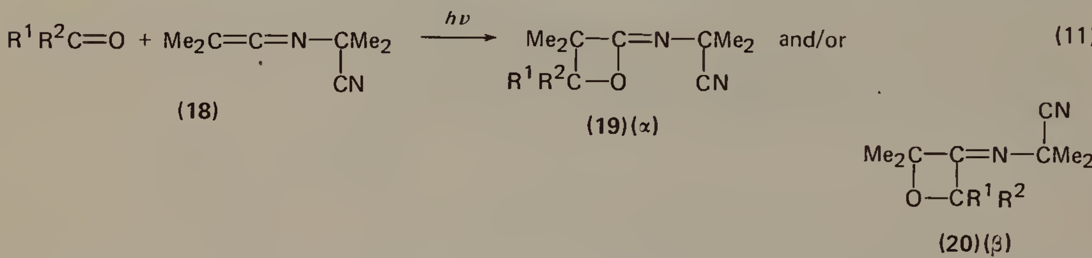
B. Cycloadditions

The most important group of cycloadditions of ketene imines are those which lead to heterocycles. Thus, this discussion will be restricted to examples of this class of reactions and to examples where products are actually isolated. Publications which describe heterocycles from ketene imines as intermediates or which describe the production of cycloalkane derivatives are not included.

1. *Four-membered rings*

Thermal and photochemical cycloadditions of ketene imines with appropriate reagents have led to the preparation of oxetanes, azetidines, thietanes, oxazetidines and diazetidines.

a. Oxetanes. The first isolation of heterocycles from a ketene imine was reported by Singer and Bartlett in 1964[33]. As an extension of the photochemical cycloaddition of aldehydes and ketones with olefins, they investigated the photochemical cycloaddition of carbonyls with **18** (equation 11). The results were most

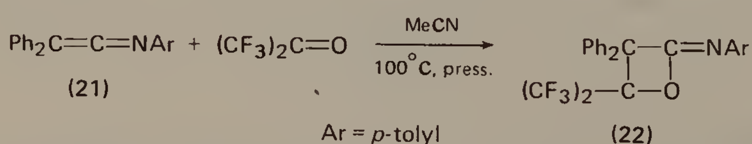

(11)

interesting. While benzaldehyde, *p*-chlorobenzaldehyde and *p*-methoxybenzaldehyde yielded only the β product **20**, acetophenone and benzophenone gave both α and β products **19** and **20**, and flourenone gave only α product **19**. The only mechanistic observation reported by these workers was that reactive carbonyls have a n–π* configuration for their lowest-lying triplet state.

Singer and collaborators have pursued these studies with the goal of explaining the results of Bartlett[34]. Their investigations showed that with benzophenone and ketene imines the reactive state of the ketone is the triplet state; the cycloaddition step itself is within an order of magnitude of diffusion control; energy transfer from triplet to ground-state ketene imine competes with cycloaddition as aryl groups are substituted for alkyl groups on the ketene imine; and for totally aryl-substituted ketene imines energy transfer occurs exclusively (no cycloaddition occurs).

A similar investigation of the photochemical cycloaddition of flourenone with dimethylketene *N*-cyclohexylimine by Singer[34] indicated that the reactive states for the ketone were both the singlet and triplet states. Thus, the replacement of the ketene imine alkyl substituents with aryl substituents does not alter the overall cycloaddition yields of this ketone with ketene imines. Yields for the reaction with several ketene imines bearing totally alkyl through totally aryl substituents ranged from 30 to 78%.

One example of a thermal cycloaddition yielding an oxetane has been reported[35]. Treatment of diphenylketene *N*-*p*-tolylimine **21** with perfluoroacetone in acetonitrile at 100° C with pressure results in the production of the α product **22** in 26% yield (equation 12). No other product from this reaction was described.

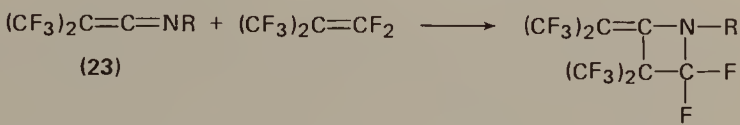

(12)

b. Azetidines. Ketene imines have served as precursors to azetidines through dimerization and through cycloaddition with perfluoro olefins. Two examples of dimerizations of ketene imines leading to azetidines have been reported. In the first publication, Barker and Rosamond reported that thermolysis of diarylketene *N*-alkylimines leads to an unsymmetrical dimer as illustrated in equation (13)[36].

(13)

Ketene imines substituted in any manner other than diaryl *N*-alkyl are reported to either dimerize or trimerize to other adducts or not react at all.

Gambaryan and coworkers reported that ketene imines of structure 23 where R is Ph, Et, Bu or substituted Ph, when treated with perfluoroisobutylene in the presence of nucleophiles, gave azetidines of structure 24 (equation 14)[37]. This

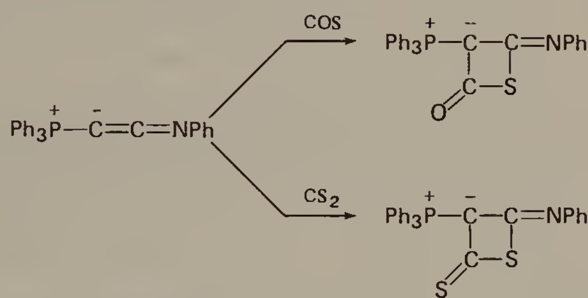


(14)

(24)

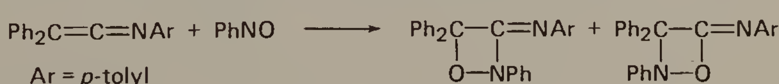
reaction represents one of the few additions known to occur across the carbon–nitrogen double bond of the ketene imine. Along with the thermal cycloaddition product 24, Gambaryan observed a dimer of the same structure as Barker's dimer (see equation 13). This dimer had been reported earlier by Gambaryan as a product of thermolysis of 23[38].

c. Thietanes. Bestmann and Schmid have reported the preparation of two thietanes from a ketene imine[39]. These products are unusual in that the starting ketene imine is an ylide and the heterocycle produced is an ylide (equation 15). Both thietanes were obtained in good yields.



(15)

d. 1, 2-Oxazetidines. Barker and coworkers have shown that the cycloaddition of aryl nitroso derivatives to aryl-substituted ketene imines is an efficient route to 3-imino-1,2-oxazetidines (equation 16)[40]. Only 25 is reported as a product. That is,

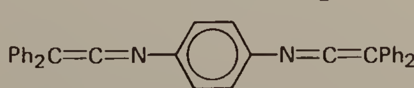


(16)

(25)

both possible modes of addition did not occur with the ketene imines studied while they do occur for nitrosobenzene and ketene[41]. Mechanistic studies led them to conclude that the reaction was occurring through the triplet state of nitrosobenzene and the ground state of ketene imine. The triplet state of nitrosobenzene could be achieved by either photosensitized or thermal conditions[40].

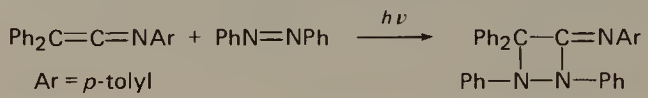
From a synthetic point of view it is interesting to note that bis(ketene imines)



(26)

when treated with nitrosoarenes yield bis(oxazetidines)[40]. The yields reported for the reaction of 26 with several nitrosoarenes ranged from 41 to 84%.

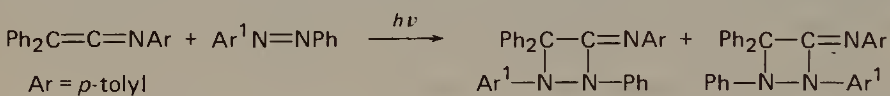
e. 1,2-Diazetidines. Symmetrical substituted azobenzenes condense with diphenylketene *N-p*-tolylimine under photochemical conditions to yield 3-imino-1,3-diazetidines (equation 17)[42]. Barker and Jones have studied this reaction to



(17)

determine the necessity of light[43]. They observed that treatment of ketene imines with *cis* enriched azobenzene without irradiation yielded diazetidines while similar reactions with *trans* azobenzene gave no product. Apparently, irradiation provides the *cis* form of the azobenzene needed for cycloaddition. This postulation was subtantiated by the reaction of diphenylketene *N-p*-tolylimine with dibenzo[*c,f*] diazepine in the dark. This heterocycle has a *cis* locked azo linkage with geometry very similar to *cis*-azobenzene. Cycloaddition with ketene imine occurred with a 68% yield, which would seem to prove that irradiation is necessary in the cycloaddition reaction only to provide the *cis*-azobenzenes.

The cycloaddition of diphenylketene *N-p*-tolylimine with a series of unsymmetrical azobenzenes has been investigated (equation 18)[43]. Solvent studies led



(18)

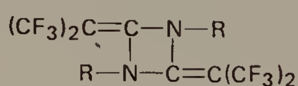
(27) (28)

Ar^1 = *o*-, *m*- and *p*-substituted phenyl

Barker and Jones to propose a concerted reaction mechanism. Of the two possible products from this cycloaddition, 27 was always observed in excess regardless of the electronic nature of the phenyl substituent of the azobenzene. For *o*-methyl, chloro and cyano substituents, only 27 was observed. For *meta* substituents, the ratio of 27 to 28 was approximately 75:25 while for *para* substituents the ratio was about 65:35. These data suggest a steric effect after alignment during the concerted cycloaddition.

The synthetic utility of the azobenzene–ketene imine cycloaddition as a route to 1,2-diazetidines is demonstrated by the production of bis heterocycles from bis(ketene imines)[44]. Again unsymmetrical azobenzenes were found to undergo cycloaddition with the bis(ketene imines) to yield ratios of possible adducts explainable by the mechanism proposed by Barker and Jones.

f. 1,3-Diazetidines. One example of a 1,3-diazetidines from ketene imines have been reported[38]. Gambaryan and coworkers have observed that bis(trifluoromethyl) ketene *N*-arylimines yield symmetrical dimers (29) when treated with 'weak bases'. This reaction is unusual in that the C=N bond of the ketene imine is utilized again.

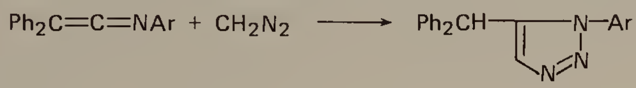


(29)

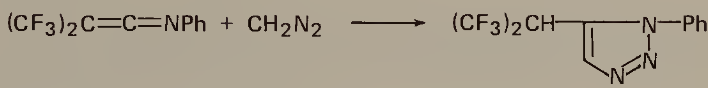
2. *Five-membered rings*

The mechanisms of several of the reactions leading to five-membered heterocycles from ketene imines have not been elucidated. Even though rearrangement or other pathways may be responsible for the generation of these heterocycles, all reported preparations are included in this section .

a. 1,2,3-Triazoles. Barker[45] and Gambaryan[46] each studied the addition of diazomethane to ketene imines and each observed the formation of 1,2,3-triazoles as the major product. Barker's work with aryl-sustituted ketene imines and Gambaryan's work with bis(trifluoromethyl)ketene *N*-phenylimine are illustrated by equations (19) and (20) respectively. Each of these cycloadditions appears to be

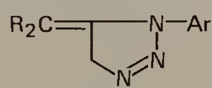


(19)



(20)

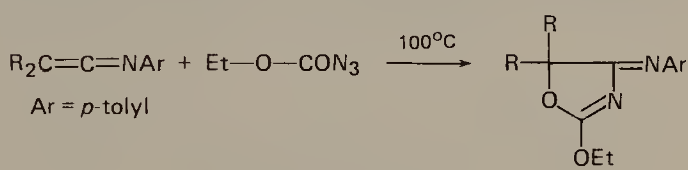
occurring across the C=N bond of the ketene imine to yield an intermediate **30** which then isomerizes to the aromatic triazole. Diazoethane, diazopropane, 1-



(30)

phenyl-diazoethane and diphenyldiazomethane gave no reaction with the aryl-substituted ketene imines.

b. Oxazolines. Kauffman has reported that the reaction of dimethyl- and diethylketene *N*-(*p*-tolyl) imines with ethyl azidoformate gives oxazolines (equation 21)[47]. Since the reaction occurred under thermal but not photolytic conditions, he

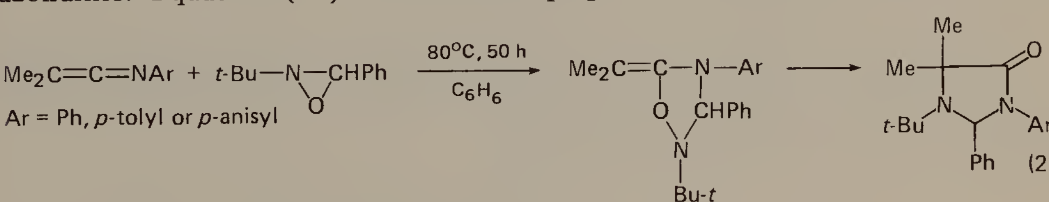


(21)

(31)

suggested that a nitrene intermediate was unlikely. He proposed an acyltriazoline or aziridine intermediate to account for the oxazoline structure 31. As with most ketene imine additions, reaction occurs across the C=C bond not the C=N bond.

c. Oxindoles and 1,3-diazolidines. Ohshiro and coworkers investigated the reactions of ketene imines with oxaziridines, nitrones and sulphur diimide[48]. With oxaziridines and nitrones he found that ketene imines yield oxindoles and 1,3-diazolidines. Equation (22) illustrates the preparation of the 1,3-diazolidines. The



(22)

(33) (32)

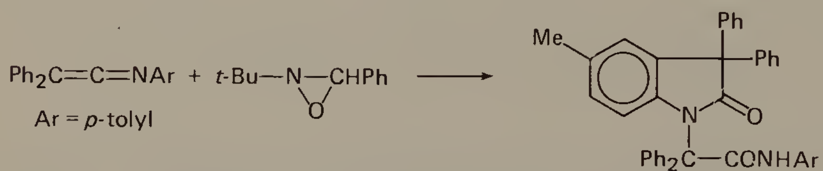
proposed reaction mechanism is a cycloaddition by the oxaziridine across the C=N bond of the ketene imine to give 33 which rearranges to 32. Yields for the systems studied ranged from 40 to 60%. No consistent pattern for ketene imine behaviour versus ketene imine substituent in this reaction was observed. For instance if ketene imines 34 were employed, no reaction occurred and the ketene imines were

$R_2C{=}C{=}N$—cyclohexyl

(34)

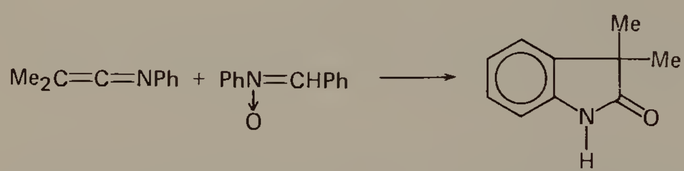
R = Me or Ph

recovered unchanged. If a totally aryl-substituted ketene imine were used, an oxindole was produced, albeit in low yield (equation 23). The formation of an



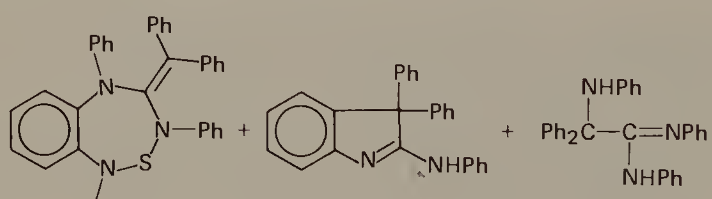
(23)

oxindole in this ketene imine reaction leads one to speculate that an oxygen transfer reaction is responsible for the product. The similarity of this product with that from the oxygen transfer from pyridine *N*-oxides to ketene imines is readily apparent[49]. Furthermore, the related reaction of dimethylketene *N*-phenylimine with *C,N*-diphenylnitrone to yield 3,3-dimethyloxindole (equation 24), as observed by Ohshiro[48], is most certainly occurring through an oxygen transfer to the ketene imine central carbon followed by intramolecular cyclization.



(24)

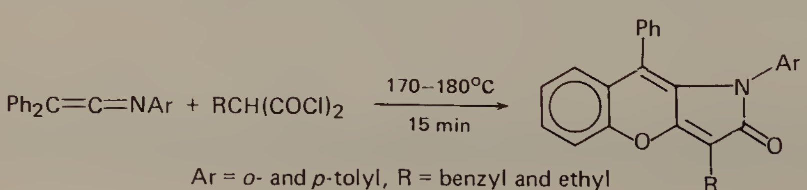
The one reported example of the reaction of a ketene imine with a sulphur diimide would indicate that the reaction is complex[48]. Equation (25) shows the products from this reaction. The thiotriazepine derivative 35 was obtained in an 8% yield, indole 36 in 25% yield and amidine 37 in 4% yield.



(25)

(35) (36) (37)

d. Miscellaneous. Perhaps the most unusual synthesis of five-membered heterocycles from ketene imines is from their reaction with malonyl chlorides[50]. Equations (26) and (27) illustrate these reactions.



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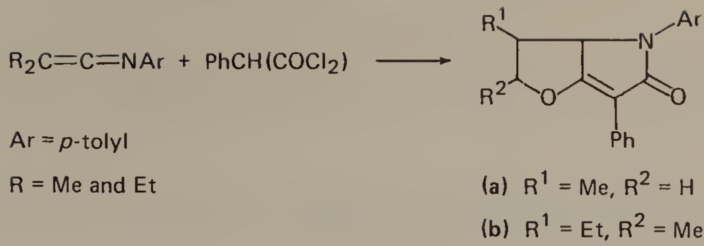
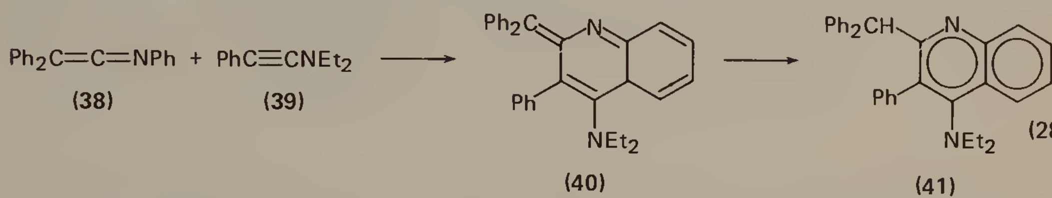


(27)

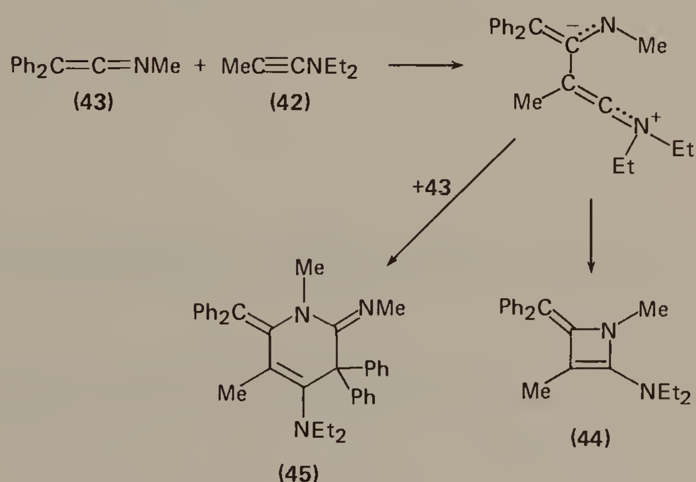
3. *Six-membered rings*

a. Quinolines. Ketene *N*-aryl imines have been shown to react with electron-rich dienophiles such as ethoxyacetylene, ketene acetal, vinyl ethers and amino acetylenes to form quinoline derivatives[46,51]. The reaction between diphenylketene *N*-phenylimine (38) and *N*-diethylaminophenylacetylene (39) demonstrates this type of cycloaddition (equation 28).



(28)

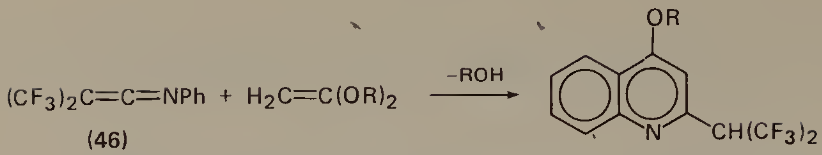
The mechanism proposed for formation of the quinoline derivatives is a cycloaddition involving the initial formation of a stabilized 1,4-dipole which undergoes cyclization to a six-membered ring. Ghosez and Perez[51] have succeeded in demonstrating the presence of this 1,4-dipolar intermediate. In the reaction of *N,N*-diethylaminomethylacetylene (42) and diphenylketene *N*-methylimine (43) the initially formed 1,4-dipolar intermediate either cyclizes to **44** or is trapped by a second molecule of ketene imine to yield **45**. (Scheme 7). A similar reaction has



SCHEME 7.

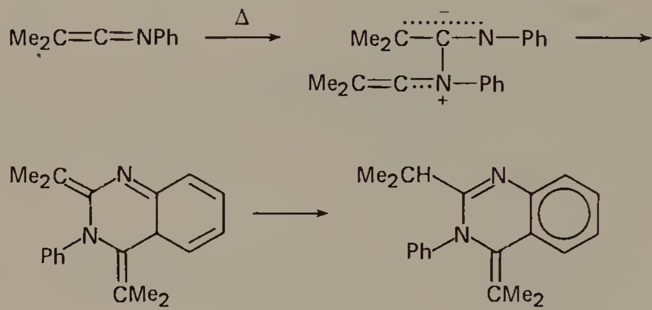
also been shown to occur with bis(trifluoromethyl)ketene *N*-aryl imine (equation 29). The reaction between ketene *N*-aryl imines and electron-rich dienophiles is a valuable route to substituted quinolines.

b. Quinazolines. Barker succeeded in preparing quinazoline derivatives by



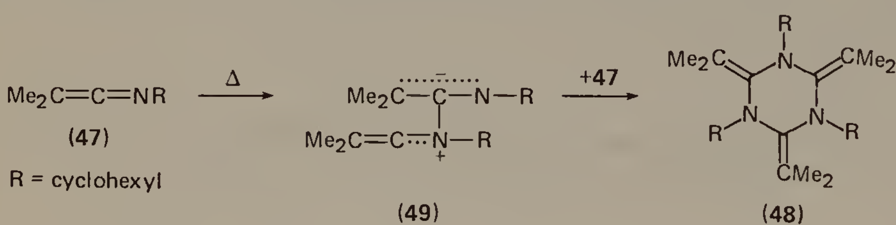
(29)

thermolysis of dialkyl ketene N-aryl imines[52]. This reaction could also occur through inital formation of a weak 1,4-dipole followed by internal cyclization to the substituted quinazoline (Scheme 8).



SCHEME 8.

c. Triazines. Dimethylketene N-cyclohexylimine (**47**) yields the trimer **48** upon thermolysis[53]. As with the quinazoline derivatives, this product can be explained through formation of the 1,4-dipolar intermediate **49** which traps a third molecule of ketene imine **47** to yield the substituted triazine (equation 30).

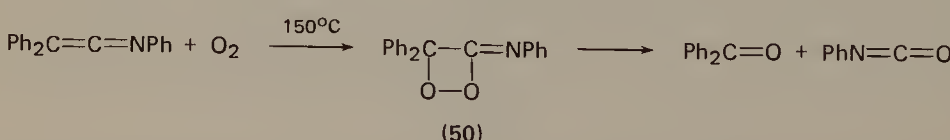


(30)

C. Oxidations

Staudinger and Hauser, in their early report on the preparation and chemistry of ketene imines, observed that oxidation of the moiety occurred when it was treated with air at 150° C[1]. They proposed a dioxetane intermediate **50** to account for the products (equation 31).

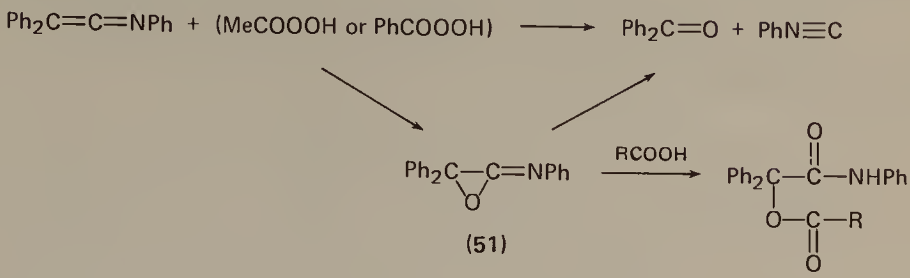
Oxidation of ketene imines with peroxy acids[454], ozone[55], singlet oxygen[56], N-oxides[57] and air under copper (II) chloride catalysis[58] have now been reported.



(31)

1. Peroxy acids

Ketene imines when treated with peroxy acids yield ketones and isonitriles (equation 32). Kagen and Lillien postulated an epoxide intermediate **51** to account for these products and have offered as evidence of 51 the formation of an α-acyloxy amide if excess peroxy acid is employed[54].



(51)

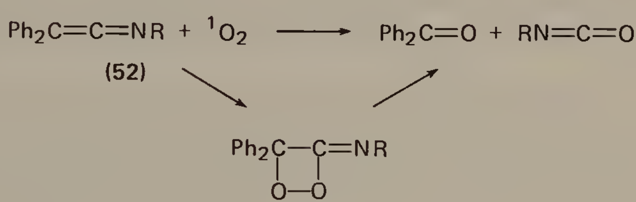
(32)

2. *Ozone*

The only reported oxidation of a ketene imine with ozone is the oxidation of dimethylketene *N*-phenylimine[55]. As with peroxy acid oxidation, ozone oxidation yields a ketone (acetone) and an isonitrile (phenylisonitrile). The investigators involked an α-epoxy imine similar to 51 to rationalize their results.

3. *Singlet oxygen*

Singer, in a brief research abstract, has reported the oxidation of ketene imines with singlet oxygen[56]. He found that 52 (R = α-phenylethyl, phenyl,*t*-butyl and benzyl) when treated with $^1O_2$ gave benzophenone and an isocyanate in high yields (equation 33). The $^1O_2$ could be generated by either photosensitized or thermal conditions. The iminoperoxyoxirane intermediate 53 was proposed to account for the products.

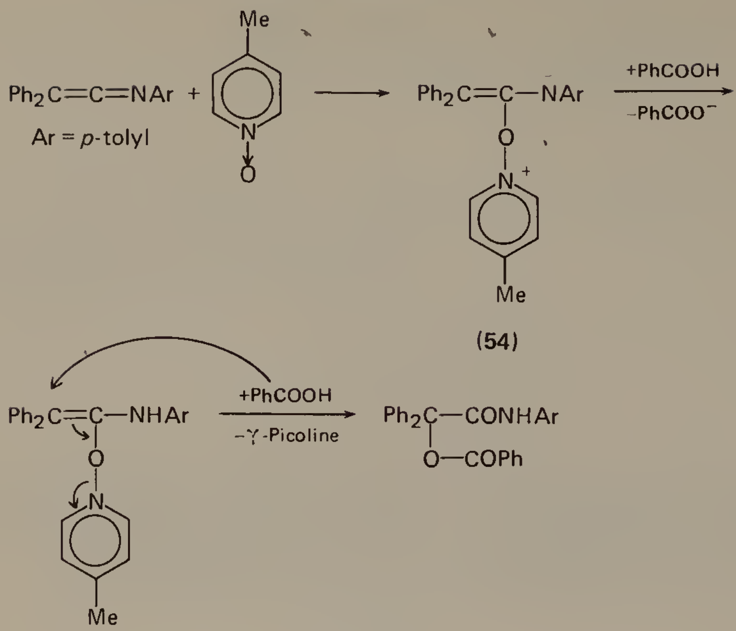


(53)

(33)

4. N-*oxides*

When diphenylketene *N*-*p*-tolylimine is treated with excess γ-picoline *N*-oxide and benzoic acid, an 86% yield of *N*-(*p*-tolyl)-α-benzoxydiphenylacetamide is obtained[57]. This result differs markedly form that when the ketene imine is treated with a carboxylic acid alone. Barker and Sung have suggested a mechanism involving oxygen transfer from the *N*-oxide to the ketene imine to account for the observations (Scheme 9). To test this hypothesis, the same ketene imine was treated with γ-picoline *N*-oxide[57] alone. High temperatures were needed for reaction and the products obtained could not be identified with certainty. However, acid hydrolysis of these products resulted in the formation of *N*-substituted oxindoles. The oxindole formation can be rationalized through intermolecular cyclization of intermediate 54 (Scheme 9). Several pyridine *N*-oxides gave the same result.



SCHEME 9.

5. *Oxygen with copper (II) chloride*

Staudinger's early work on the reaction of ketene imines with oxygen showed that high temperatures were necessary for reaction; however, Barker and Perumal have shown that reaction between oxygen and ketene imine occurs rapidly at room temperature if copper (II) chloride is present[58]. The ketene imines studied were diphenylketene *N-p*-substituted phenylimines and the products of the reaction were benzophenone, aryl isonitrile and aryl isocyanate (equation 34). The yield of

$$Ph_2C{=}C{=}NAr \xrightarrow[Cu(II)Cl_2]{O_2\text{ (air)}} Ph_2C{=}O + ArN{=}C{=}O + ArN{\equiv}C \qquad (34)$$

benzophenone was reasonably constant for the substrates studied but the ratio of isocyanate to isonitrile varied considerably. This ratio favoured isocyanate when a substituent Y in the aryl group was electron-releasing and favoured isonitrile when Y was electron withdrawing. The substituent control of substrate oxidation (different products, not just different isomers) appears to be novel. The authors propose a cation-radical mechanism to account for their observations.

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CHAPTER **18**

Carbodiimides

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I. INTRODUCTION

Carbodiimides have attracted great attention due mainly to their importance in synthetic organic chemistry. The versatility of the carbodiimides can be seen in their various uses as reagents in chemical synthesis; and especially as starting materials in the synthesis of various heterocyclic systems, as condensing agents in peptide and nucleotide synthesis and in combination with dimethyl sulphoxide as a mild oxidation agent.

Carbodiimides were first synthesized, characterized and formulated a little over one hundred years ago[1], but undoubtedly they were obtained as early as 1852[2,3]. Although much of the fundamental work concerning the chemistry of the carbodiimides dates back to the end of the last century and the beginning of this century, the systematic work, as well as the use and application of carbodiimides, is of recent origin.

In 1953 the chemistry of carbodiimides was first reviewed by Khorana[4]. Fourteen years later it was again reviewed, this time by Kurzer and Douraghi-Zadeh[5]. Khorana discussed the use of carbodiimides as condensing agents in phosphorylation reactions in his book on phosphate esters[6]. The use of carbodiimides as condensing agents in peptide synthesis has been reviewed recently in Volume 15 of Houben Weyl's *Methoden der organischen Chemie*[7] as well as in Bodanszky, Klausner and Ondety's book on peptide synthesis[8]. Oxidation by the carbodiimide–dimethyl sulphoxide system is discussed in detail by Moffatt[9].

In this chapter our aim is not to give a comprehensive review dealing with all the physical, chemical and biological properties of the carbodiimide group, but to deal with the most significant aspects of the functional group, followed by illustrative examples.

II. STRUCTURE AND PHYSICAL PROPERTIES

Carbodiimide (1) is isomeric with cyanamide (2). One might look upon carbodi-

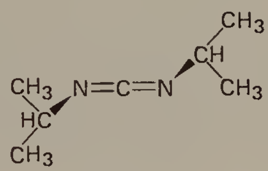
$$\underset{(1)}{HN{=}C{=}NH} \qquad \underset{(2)}{H_2NC{\equiv}N}$$

imide as the symmetrical, and upon the cyanamide as the unsymmetrical anhydride of urea. The free carbodiimide (1) has never been isolated, although the possibility

$$HN{=}C{=}NH \rightleftharpoons H_2N{-}C{\equiv}N \qquad (1)$$

of the existence of carbodiimide and cyanamide as two tautomeric forms (equation 1) has been considered by various workers studying the molecular structure of cyanamide. These studies using i.r. spectra, Raman spectra and dipole moment measurements show that such a tautomerism does not in fact exist and the molecule exhibits only structure 2[5]. These results should not surprise us since if indeed such a tautomerism should exist, the imide form should be favoured only at high temperatures. Carbodiimide was obtained (although it was not isolated) by pyrolysis of cyanamide in a hot nozzle under very low vapour pressure. The carbodiimide produced from the pyrolysis was trapped in solid argon matrix at 20 K and identified from its i.r. spectra[10].

Carbodiimides were expected (mainly from dipole moment measurements) to exhibit the same molecular dissymmetry as the appropriately substituted allenes[11]. This prediction was supported during the last few years by theoretical and experimental studies. INDO–MO calculations for the free carbodiimide molecule, assuming an sp-type bonding for the central carbon atom and an sp^2 hybridization for the two nitrogen atoms, show that the most stable geometry of the molecule is dissymetric with the substituents in perpendicular planes which intersect along the N=C=N axis[12]. Similar results were obtained by calculation for dimethylcarbodiimide[13]. The calculated nitrogen inversion barrier of unsubstituted carbodiimide was found to be 8.0 kcal/mol using the INDO–MO method[12] and 8.4 kcal/mol using the SCF–LCAO method[14]. A MINDO 1-SCF calculation gave an inversion barrier of 9.54 kcal/mol for free carbodiimide and 7.98 kcal/mol for phenylcarbodiimide[15]. The dissymmetry of diisopropylcarbodiimide (3) has been shown by the



(3)

difference in the n.m.r. shifts of the methyl protons of the two isopropyl groups at low temperature – a difference similar in magnitude to the one reported for diastereotopic substituents of allenes. The inversion barrier which was calculated from the above n.m.r. studies was found to be 6.7 kcal/mol[16]. A low molecular symmetry (C_2 point group) and a close analogy with the allene-type structure was found for the dimethylcarbodiimide from i.r. and Raman spectra[17]. X-ray studies on crystals of di-*p*-tolylcarbodiimide showed that the stereochemistry of the molecule is of the allene type with the two C–N=C planes approximately normal to each other with C–N=C angles of 127.2° and 128.4° and with an N=C=N angle of 170.4° [18]. Different is the case with di-*p*-nitrophenylcarbodiimide, a phenomena which was attributed[19] to the interaction of the *p*-nitro group on the aromatic ring and the cumulene chain.

All the above calculations, and some of the experimental data, show that the inversion barrier for the isomerization of the carbodiimides is not higher than 8–9 kcal/mol, a value indicating rapid racemization at room temperature. It is interesting to note that there is just one claim in the literature for the resolution and isolation of an optically active carbodiimide. In 1966 Schlogl reported the resolution of diferrocenylcarbodiimide[20], a report which is now questionable in the light of the low value of the inversion barrier.

Substituted carbodiimides have a characteristic band absorption in the u.v. region below 2000 Å[21]. Dimethylcarbodiimide in the gas phase has an absorption band at 1910 Å and in solution (*n*-heptane) the absorption band appears at 2060–2100 Å. The most important absorption bands in the i.r. region are at around 2300 cm^{-1}

and 1460 cm^{-1} due to the stretching of the N=C=N bands and around 615 cm^{-1} due to the bending of the bands[21]. Again dimethylcarbodiimide has absorption bands at 2365 cm^{-1}, 1418 cm^{-1} and 618 cm^{-1} [17].

III. PREPARATION

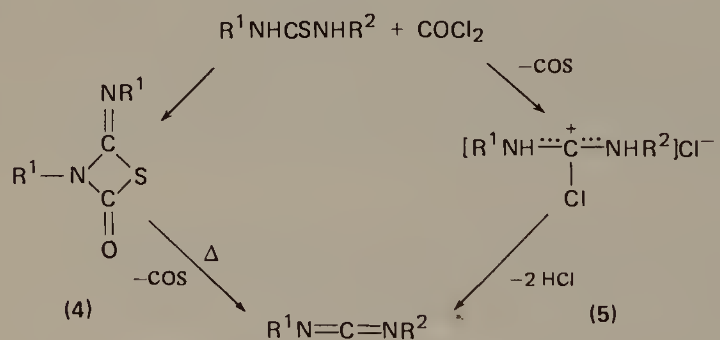
A. From Thioureas

Desulphurization of *N,N'*-disubstituted thioureas to form the corresponding carbodiimides using metal oxides as desulphurization agents is a well-known reaction (equation 2)[5]. The first reported synthesis of carbodiimide is the synthesis of

$$R^1NHCSNHR^2 + MO \longrightarrow R^1N{=}C{=}NR^2 + MS + H_2O \qquad (2)$$

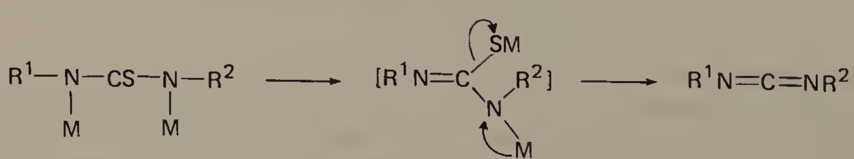
diphenylcarbodiimide from diphenylthiourea using yellow mercuric oxide as a desulphurizing agent[1]. The reaction is carried out in a variety of solvents (e.g. ether, benzene, acetone, toluene, xylene, carbon disulphide) in presence of a suitable dehydrating agent (e.g. $CaCl_2$, $MgSO_4$, Na_2SO_4) which inhibit the addition of the water eliminated during the reaction to the carbodiimide to form the corresponding urea. The most frequently used metal oxide is yellow mercuric oxide, but various other oxides and even salts or complexes of other elements have been used (e.g. PbO, As_2O_3, ZnO, $ZnCl_2$, $PbCl_2$, $[HgI_4]^{2-}$).

Thioureas react with phosgen to yield the corresponding carbodiimides. The reaction proceeds in the case of aliphatic thioureas via the formation of the thiazetidinone 4 which upon heating decomposes to the desired product and carbonyl sulphide. With aromatic substituted thioureas formamidine chloride 5 is formed first, and in turn loses hydrogen chloride upon heating to yield the corresponding carbodiimide (equation 3)[22].



(3)

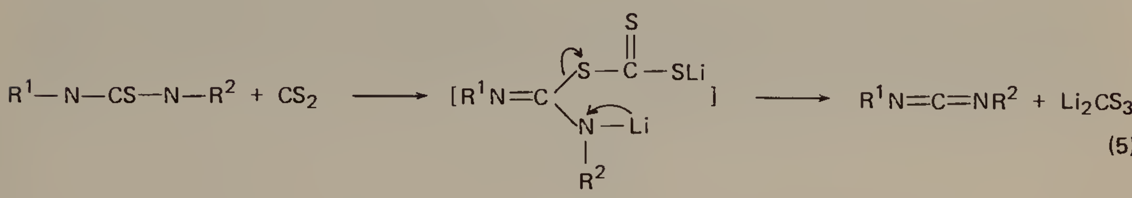
Recently it was observed that *N,N'*-dilithio- or -dibromomagnesio-thioureas could be decomposed at 170° C to give the corresponding carbodiimides in 30–60% yield (equation 4)[23]. These salts are prepared *in situ* from thioureas and



(4)

M = Li, MgBr

either butyllithium or ethylmagnesium bromide. In the case of the lithium derivatives it has been observed that the use of carbon disulphide as a solvent allows a lowering of the reaction temperature to 0° C and increases the yield of the product (up to 90–95%). The carbon disulphide acts not only as a solvent but also reacts with the lithium derivative via an insertion in to the Li–N bond to give compound **6**, which decomposes instantaneously to the corresponding carbodiimide (equation 5).

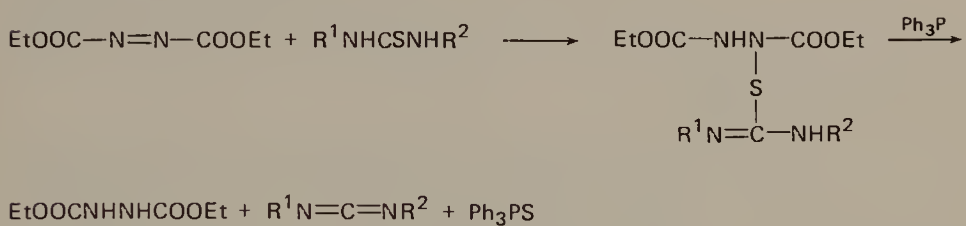


(5)

(6)

Oxidation of thiourea with alkaline hypochlorite is a well-known method for the preparation of carbodiimides[5]. It has been observed that better yields (up to 80–85%) of carbodiimide are obtained using *N*-bromosuccinimide as the oxidizing agent[24].

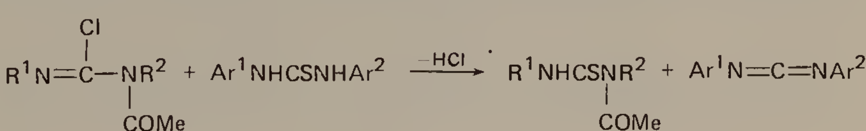
Thiourea reacts with various compounds (e.g. dichlorodicyanobenzoquinone-DDQ[25], 2-chloro-4,6-dimethylpyridine[26], 2,4-dichloropyridine[27], 1-chlorobenzotriazol[28], trichloroisocyanuric acid[28]) to form the corresponding isothiourea. The isothioureas yield upon basic hydrolysis the desired carbodiimide in 70–90% yield. A similar reaction occurs with diethyl azodicarboxylate and triphenylphosphine (equation 6)[29].



(6)

Reaction of compounds containing an S—Cl bond (e.g. $SOCl_2$,SO_2Cl_2,SO_3ClH, SCl_2,S_2Cl_2) with thioureas followed by basic hydrolysis of the reaction product yields the carbodiimide in reasonable yields[30,31].

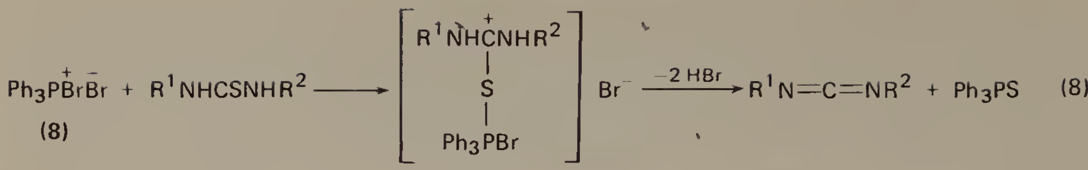
Acyl chloroformamidines (**7**) react with *N,N′*-diarylthioureas in the presence of triethylamine to give the corresponding carbodiimides (equation 7)[32,33].



(7)

(7)

Bromotriphenylphosphonium bromide (triphenylphosphine dibromide, **8**) reacts with thiourea in presence of triethylamine to give the corresponding carbodiimide in 70–75% yield: presumably the reaction proceeds via the intermediate **9** (equation 8)[34]. Instead of using **8** the reaction could be carried out with triphenyl-



(8) (9)

phosphine using carbon tetrachloride or a mixture of carbon tetrachloride–methylene chloride as a solvent. The triphenylphosphine reacts with the carbon tetrachloride to give trichloromethyltriphenylphosphonium chloride (**8a**) which reacts with the thiourea in a similar way to **8**[35].

$$Ph_3\overset{+}{P}{-}CCl_3\overset{-}{Cl}$$

(8a)

B. From Ureas

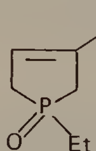
Dehydration of ureas to carbodiimides can take place by using *p*-toluenesulphonyl chloride in pyridine[36], or in methylene chloride in presence of triethylamine[37], the desired products are obtained in 50–80% yield. Dehydration can also be carried out by phosphorus pentoxide[38], in similar yields.

8 and **8a**, which have been shown to react with thioureas to give the corresponding carbodiimides, react with ureas in an identical manner[34,35].

C. From Isocyanates

The thermal decarbonylation of isocyanates to form carbodiimides was observed over 90 years ago[39]. Hofmann was able to isolate diphenylcarbodiimide after prolonged heating of phenyl isocyanate, but it does not appear that he realized the nature of the product he obtained.

Carbodiimides can be obtained from isocynates in high yield and under very mild conditions in presence of suitable catalysts. Among the most active catalysts reported are: 3-methyl-1-ethyl-3-phospholene-1-oxide (**10**)[40], 3-methyl-1-phenyl-3-phospholene-1-oxide (**11**)[41], 1-alkoxy-2-phospholene-1-oxide (**12**)[42], 1-(2-chloroethoxy)-3,4-dimethyl-3-phospholene-1-oxide (**13**)[42], 1,3-dimethyl-2-ethyl-1,3,2-diazaphospholidine-2-oxide (**14**)[43], 1,3-dimethyl-2-ethylhexahydro-1,3,2-diazaphosphorine-2-oxide (**15**)[43]. Other catalysts used are simple phosphine oxides



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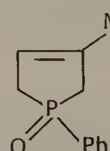

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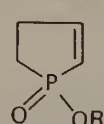

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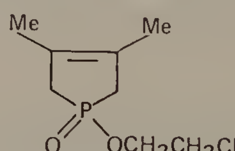

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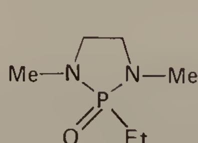

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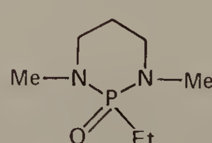
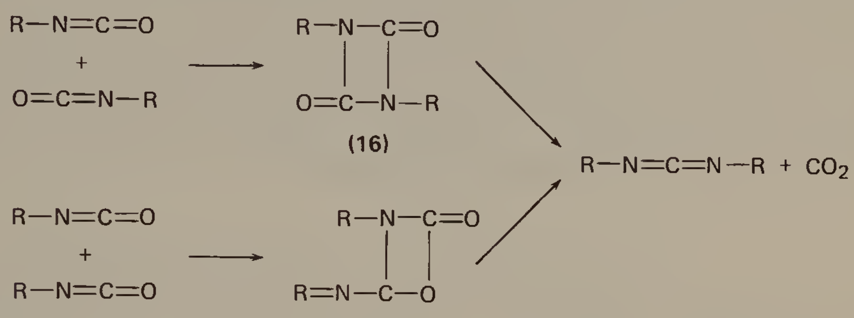


(15)

(e.g. tributyl, triphenyl)[44], certain alkoxides of titanium and zirconium [e.g. $(Me_2CHO)_4Ti$, $(C_8H_{17}O)_4Zr$][45], triarylarsines[46] and various metal carbonyls such as $Fe(CO)_5$, $Fe_2(CO)_4$, $W(CO)_6$, $Mo(CO)_6$[47].

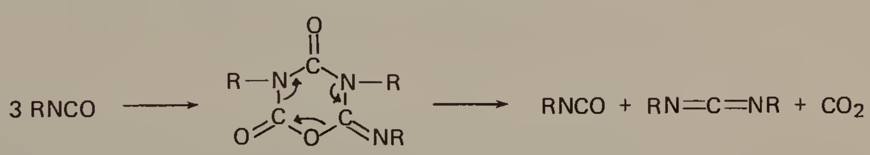
The nature of the isocyanate has a great influence on the ease of carbodiimide formation. In the case of the aromatic isocyanates the presence of an electron-releasing group on the aromatic ring tends to inhibit the reaction while the presence of an electron-withdrawing group tends to increase the reaction rate.

The noncatalysed decomposition of the isocyanate is thought to proceed by initial dimerization[40] or trimerization[48]. In the first case the symmetrical intermediate **16**, or the unsymmetrical **17**, or both, are formed followed by decomposition to the desired product and CO_2 (equation 9)[44]. In the second case the



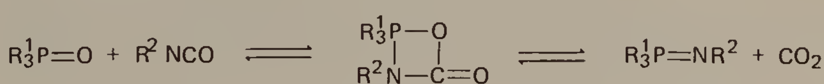
(16) (17) (9)

trimer **18** is formed, which in turn decomposes, probably via a cyclic displacement, to carbodiimide, isocyanate and CO_2 (equation 10).

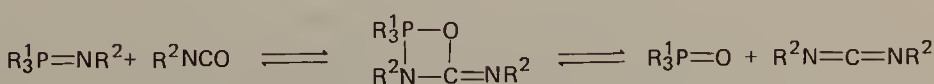


(18) (10)

The various phosphine oxide derivatives which act as catalysts in the decarboxylation reactions act by nucleophilic attack of the polarized oxygen on the C=N bond of the isocyanate to give the cyclic intermediate **19** which decomposes in a rate-determining step to phosphinimide (**20**) and CO_2 (equation 11). The phosphinimide once formed reacts very rapidly with another molecule of isocyanate to form another cyclic intermediate (**21**) which decomposes quickly to the desired carbodiimide and the phosphine oxide (equation 12)[49].



(19) (20) (11)



(21) (12)

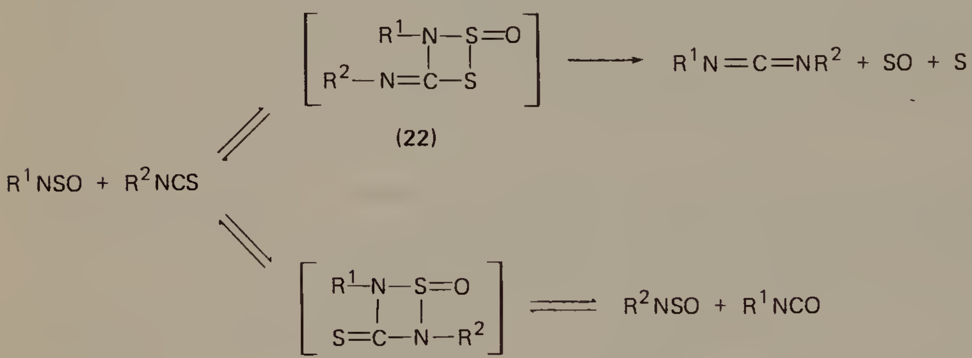
Isocyanate reacts directly with phosphinimide to give the unsymmetrical carbodiimide (equation 13)[50].

$$R^1N{=}PR^2_3 + R^3NCO \longrightarrow R^1N{=}C{=}NR^3 + R^2_3P{=}O \qquad (13)$$

D. From Isothiocyanates

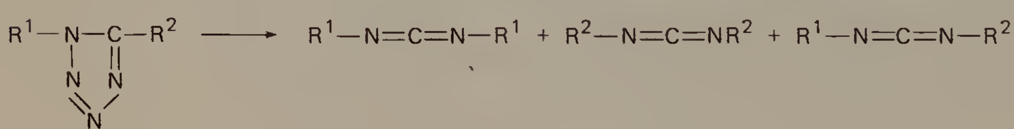
Isothiocyanates react with catalytic amounts of various phosphine oxides to form the corresponding carbodiimides and CS_2 in a similar way to the catalytic decarboxylation of the isocyanates[40]. Like isocyanates, isothiocyanates react also with phosphinimide to give the unsymmetrical carbodiimides.

Isothiocyanate reacts with *N*-sulphinylamine at 180–200° C in an exchange reaction which gives the exchange products in 20–30% yield. Beside the exchange products the unsymmetrical carbodiimide is obtained in about the same yield[51]. The reaction proceeds presumably via the two intermediates **22** and **23**; **22** decomposes to give the desired carbodiimide while **23** decomposes to give the exchange products or the starting materials (equation 14).

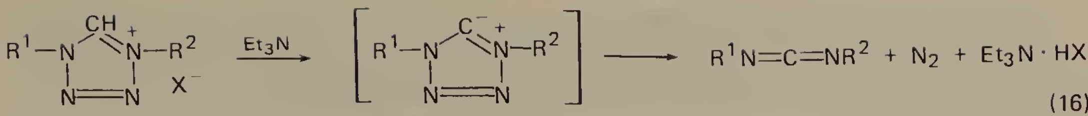

(22) (23) (14)

E. From Tetrazoles

The pyrolysis of 1,5-disubstituted tetrazole derivatives to form carbodiimides is a well-known reaction[5]. Disubstituted tetrazoles with identical substituents yield the symmetric carbodiimide in high yield. In case of nonidentical substituents a mixture of products is obtained – containing the unsymmetrical carbodiimide as well as the corresponding two symmetrical carbodiimides (equation 15). When one of the substituents is phenyl, 2-arylbenzimidazole is formed as a by-product.


(15)

In the case of 1,4-disubstituted, 5-unsubstituted tetrazolium salts (**24**) the corresponding carbodiimide can be obtained just by reacting **24** with one equivalent of base (e.g. triethylamine) (equation 16). Using the above method the carbodiimide can be prepared *in situ* and the product used as it is, since all by-products can be removed easily – nitrogen is bubbled off and the triethylamine hydrochloride



(24) (16)

can be precipitated from the reaction mixture when the reaction is carried out in a nonpolar solvent. Using this method various 'active' or 'sensitive' carbodiimides have been prepared [e.g. *N*-methyl-*N'*-vinylcarbodiimide (**25**), *N*-methyl-*N'*-dimethylaminocarbodiimide (**26**) and *N*-methyl-*N'*-carboethoxymethylcarbodiimide (**27**)].

Me—N=C=N—CH=CH_2

(25)

Me—N=C=N—NEt_2

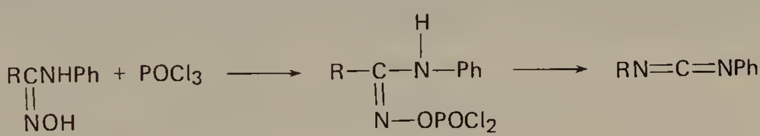
(26)

Me—N=C=N—CH_2COOEt

(27)

F. Miscellaneous

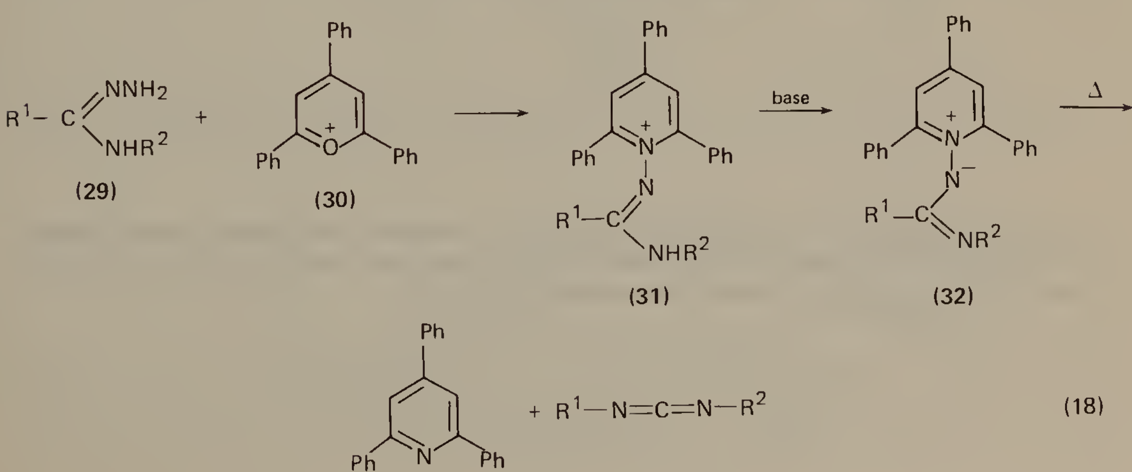
Amidoximes are dehydrated by $POCl_3$ in pyridine to give the corresponding carbodiimides in 50–70% yield (equation 17)[52]. The reaction proceeds via a



(28) (17)

rearrangement of the intermediate **28**. It is interesting to note that the $POCl_3$ can be replaced by phosphorus pentoxide as the dehydrating agent.

Amidrazones (**29**) are converted by triphenylpyrilium salts (**30**) into salts. The salts (**31**) are converted by treatment with mild base into the substituted pyridine *N*-imides (**32**). Pyrolysis of **32** yields the corresponding carbodiimides and triphenylpyridine in a very high overall yield (equation 18)[53].



(29) (30) (31) (32) (18)

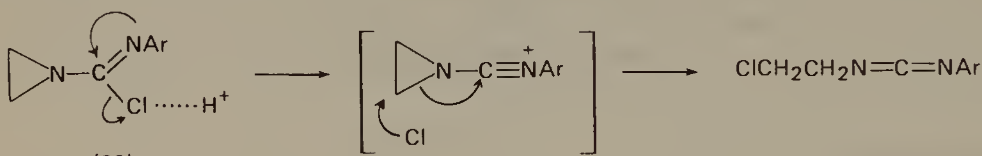
I

N,N'-disubstituted formamidines are converted into the corresponding carbodiimides either by oxidation with *N*-bromosuccinimide (equation 19) or by addition of bromine followed by dehydrobromination by base (equation 20)[54].

$$R^1{-}N{=}CH{-}NHR^2 \xrightarrow{NBS} R^1{-}N{=}C{=}N{-}R^2 \qquad (19)$$

$$R^1{-}N{=}CH{-}NHR^2 + Br_2 \longrightarrow R^1{-}NBrCHBrNHR^2 \xrightarrow{base} R^1{-}N{=}C{=}N{-}R^2 \qquad (20)$$

1-Aryl-1-aziridinecarboximidoyl chloride (33) undergoes rearrangement to form the corresponding carbodiimide in over 85% yield[55]. The rearrangement occurs in the neat state or in solution and is catalysed by strong acids: it probably proceeds via a cationic intermediate formed by acid-assisted heterolysis of the carbon–chlorine bond (equation 21).



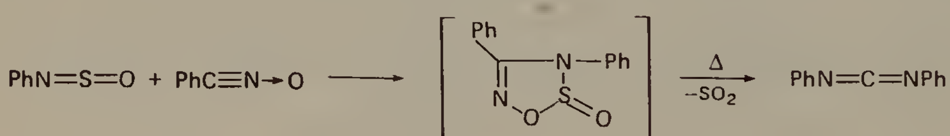
(33) (21)

Isonitriles react with azides in presence of iron carbonyl to yield the unsymmetrical carbodiimides (equation 22)[56]. The reaction proceeds in a similar way to the iron carbonyl catalysed process of the isocynate decarbonylation[47].

$$R^1N_3 + R^2N{\equiv}C \xrightarrow{Fe(CO)_5} R^1N{=}C{=}NR^2 + N_2 \qquad (22)$$

Unsymmetrical carbodiimides are obtained by silver oxide oxidation of the Pd(II) complex of *N'N'*-disubstituted diaminocarbene[57]. The reaction takes place by the addition of silver oxide to a solution of the desired amine and isonitrile in the presence of catalytic amounts of $PdCl_2$.

Diphenylcarbodiimide is obtained in 55% yield by the 1,3-cycloaddition of *N*-sulphinylaniline and benzonitrile oxide (equation 23)[58]. This method is used mainly for the synthesis of unsymmetrical carbodiimides.



(23)

Ditrifluoromethylcarbodiimide is formed by fluoride ion assisted isomerization of perfluoro-2,4-diazapenta-1,4-diene (34)[59]; the reaction proceeds at room temperature in the presence of caesium fluoride (equation 24).

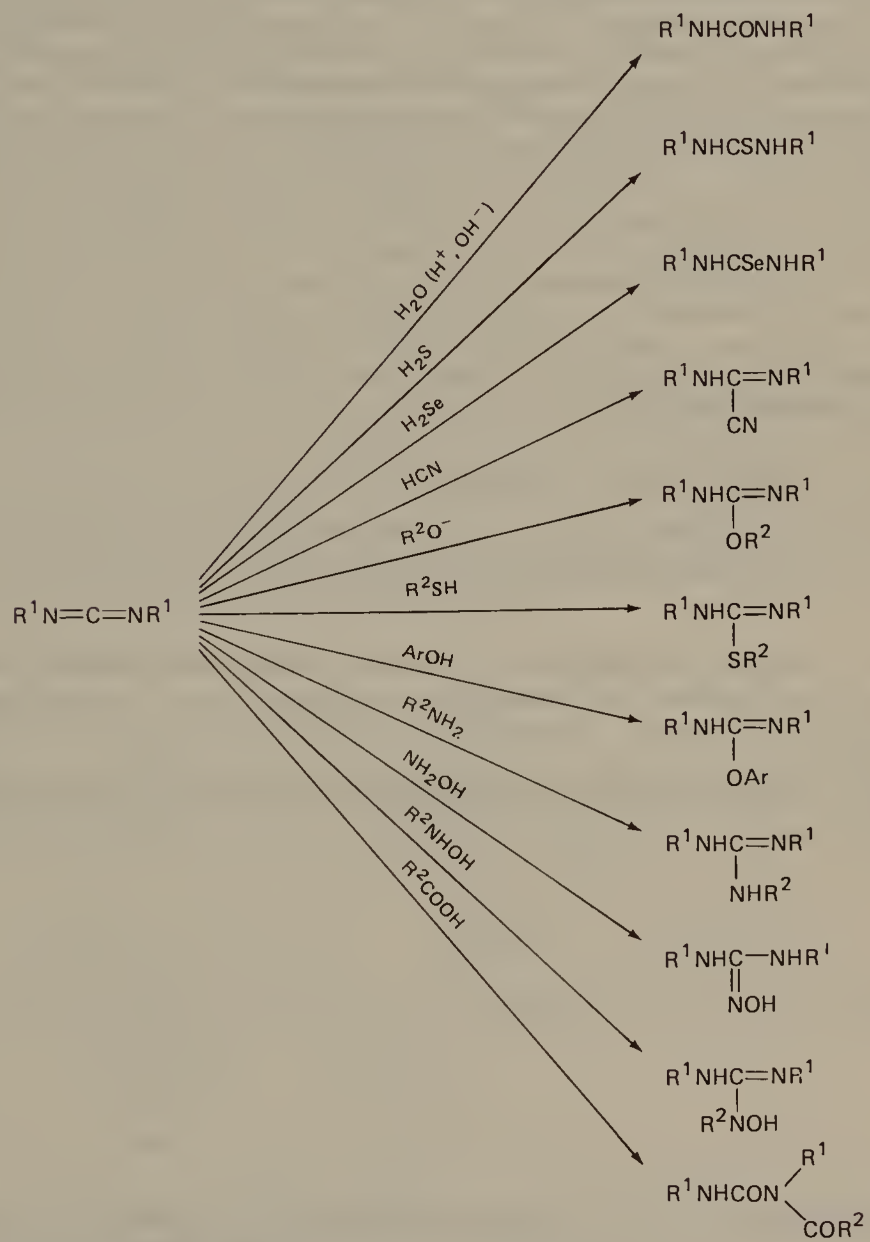
$$F_2C{=}NCF_2N{=}CF_2 \xrightarrow{F^-} F_3C{-}N{=}C{=}N{-}CF_3 \qquad (24)$$

(34)

IV. REACTIONS

A. Additions to the C=N Double Bond

The carbon–nitrogen double bond which is part of the cumulative double-bond system is easily attacked by various nucleophiles and electrophiles (Scheme 1). Water is added to carbodiimides to form the corresponding ureas, and the reaction is catalysed by acids as well as by bases[60]. Hydrogen sulphide[61] or hydrogen selenide[62] form the corresponding thio- or seleno-urea respectively. Hydrogen



SCHEME 1.

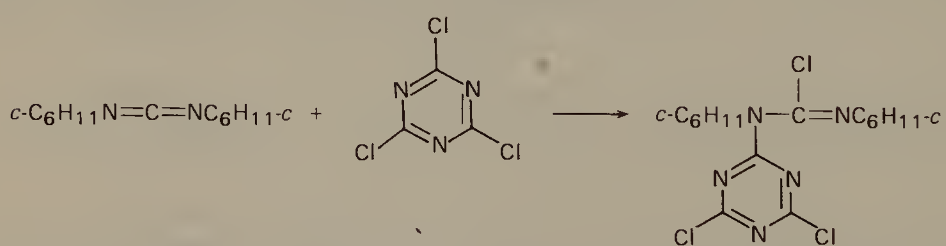
cyanide is added to carbodiimides to yield the corresponding α-cyano-*N,N'*-disubstituted formamidine[63]. While alcohols are usually inert toward carbodiimides, in the presence of a suitable catalyst (e.g. Cu_2Cl_2,$CuCl_2$] they are added to carbodiimide to give the corresponding isoureas[64]. Isoureas are obtained by the reaction of alkoxides with carbodiimides[65,66]. Thioalcohols react very easily with carbodiimides to form the corresponding isothioureas[67]. Weakly acidic phenols react with carbodiimide (either at high temperature or in presence of a suitable catalyst) to yield the corresponding isoureas, while strongly acidic phenols react under very mild conditions to form the corresponding *N*-arylurea[68]. However, this distinction does not hold in all cases and it has been observed that strongly acidic phenols react with cyclohexylcarbodiimide to form the corresponding isourea derivatives (e.g. 2,6-dichloro-4-nitrophenol[69]). Ammonia and amines react with carbodiimides to form the corresponding di- or tri-substituted guanidines respectively[5]. Reactions of hydroxylamine and *N*-substituted hydroxylamines with carbodiimides yield 1-hydroxy- and 2-hydroxy-guanidines respectively[70]. Carboxylic acids add to carbodiimide (using 1:1 mole ratio of reactants) to form *N*-acylurea; the reaction proceeds via the acylisourea as an intermediate[71]. The mechanism of the reaction of carboxylic acids with carbodiimide in various solvents, various ratios of reactants and both in absence and presence of strong and weak bases has been studied[71,72]. In the case of *N*-betaines the product is not the acylurea but the corresponding amide and isocynate, thus trimethylammonium acetate reacts with di-*p*-nitrophenylcarbodiimide to give trimethylammonium *p*-nitroacetanilide and *p*-nitrophenyl isocynate (equation 25)[73].

$$\underset{X^-}{Me_3\overset{+}{N}CH_2COOH} + p\text{-}NO_2C_6H_4N{=}C{=}NC_6H_4NO\text{-}p \longrightarrow \tag{25}$$

$$\underset{X^-}{Me_3\overset{+}{N}CH_2CONHC_6H_4NO_2\text{-}p} + p\text{-}NO_2C_6H_4NCO$$

Various reactions which lead to the formation of heterocyclic systems take place between carbodiimides and bifunctional compounds (e.g. *o*-aminothiophenol, aminoalcohols, hydrazides, hydroxy acids). These reactions will be discussed in Section V.

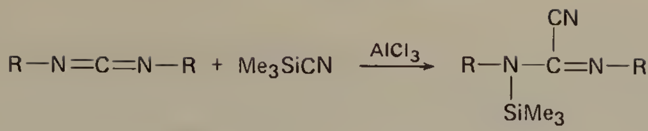
Cyanuric chloride reacts with dicyclohexylcarbodiimide to give **35** (equation 26)[74].



(26)

(35)

Trimethylsilyl cyanide reacts with carbodiimides in presence of catalytic amounts of $AlCl_3$ to give *N*-trimethylsilyl-1-cyanoformamidine (equation 27)[75]. The unsubstituted *N*-trialkylsilyformamidine is obtained by reacting trialkylsilane with carbodiimides (equation 28). These reactions take place at high temperatures



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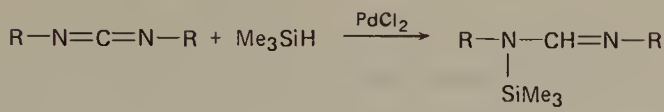
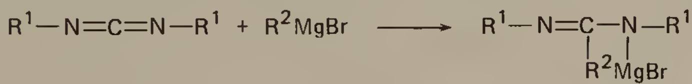


(28)

and in the presence of catalytic amounts of palladium chloride or tris(triphenylphosphine)chlororhodium[76].

Carbodiimides react with various organometallic compounds to give the corresponding formamidine derivatives. Thus reaction of simple organometallic compounds such as butyl- or phenyl-magnesium bromide yields the formamidine **36** (equation 29)[77]. A similar reaction occurs with methylniobium(V) and methyl-



(29)

(36)

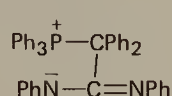
tantalum(V) chlorides which give products of the type $Me_aMCl_b[NR{-}C(Me){=}NR]$ where $a = 0$, $b = 4$; a = 1, b = 3; a = 2, b = 2[78]. These compounds arise from the insertion of the carbodiimide moiety into the metal–carbon bond. A similar type of insertion occurs with titanium(IV) and zirconium(IV) amides[79] where the insertion takes place into the metal–nitrogen bond. In a different manner, phenyl(bromodichloromethyl)mercury (**37**) with diisopropylcarbodiimide gives mainly *N*-isopropyldichloroimine (**38**) with small amounts of isopropylisonitrile and phenylmercury bromide (equation 30)[80].

$$\underset{(37)}{i\text{-PrN=C=NPr-}i + PhHgCCl_2Br} \longrightarrow \underset{(38)}{i\text{-PrN=CCl}_2} + i\text{-PrNC} + PhHgBr \qquad (30)$$

'Active' carbodiimides react with phosphonium ylides: thus diphenylmethyleneetriphenylphosphorane reacts with diphenylcarbodiimide to yield *N*-phenyliminotriphenylphosphorane and triphenylketene imine in good yield (equation 31)[81]. The reaction seems to proceed via a polar addition to the double bond to

$$Ph_3P{=}CPh_2 + PhN{=}C{=}NPh \longrightarrow Ph_3P{=}NPh + Ph_2C{=}C{=}NPh \qquad (31)$$

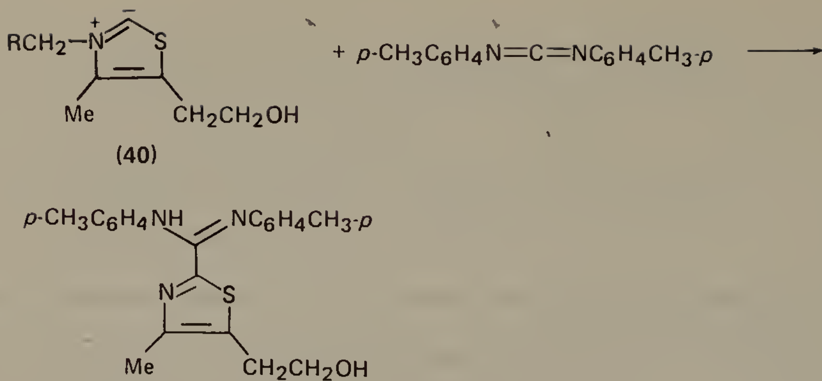
give the intermediate **39** according to a Wittig-type reaction. In a somewhat



(39)

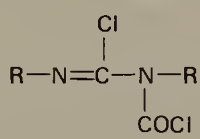
different manner addition of the thiazolium ylide **40** to di-*p*-tolylcarbodiimide gives the salt **41** (equation 32)[82].

Acyl chlorides react with carbodiimides to form the corresponding acylchloroformamidines (**7**)[32]. Phosgen reacts to give the corresponding chlorocarbonyl-



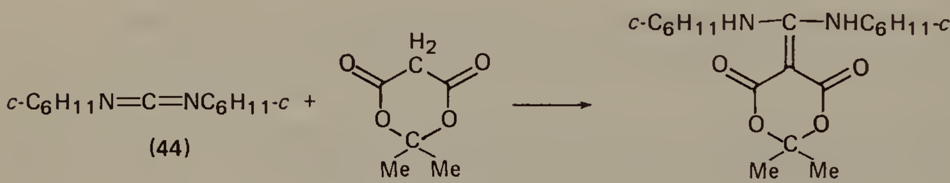
(40) (41) (32)

chloroformamiidines (42)[83] which are unstable products but are important synthetic intermediates.

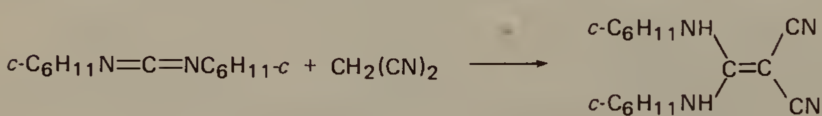


(42)

Strongly acidic C–H adds to the carbodiimide double bond; an example is the case of Meldrum's acid (**43**) which reacts with dicyclohexylcarbodiimide (**44**) in presence of piperidine at room temperature (equation 33)[84]. Malononitrile reacts with **44** in presence of sodium methoxide to form 1,1-dicyclohexylamino-2,2-dicyanoethylene (**45**) (equation 34)[84].



(44) (43) (33)



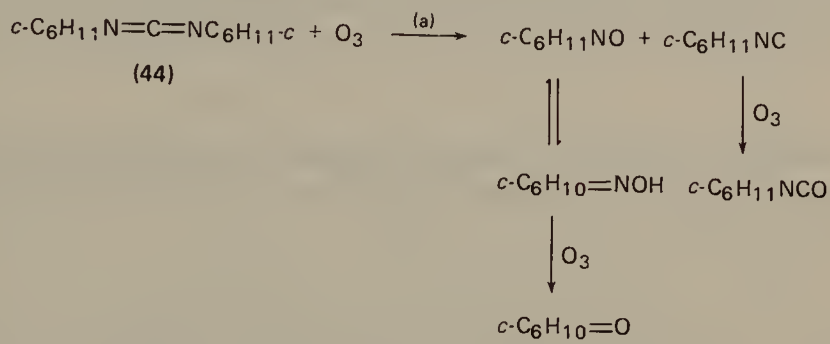
(45) (34)

B. Isomerization

Similarly to the photochemical isomerization of ketene imines to nitriles[85], carbodiimides isomerize into the corresponding cyanamide derivatives[86]. Irradiation of **44** at 2537 Å in degassed dioxane results in conversion of 10% of the carbodiimide to diphenyl cyanamide followed by quantitative recovery of the unreacted carbodiimide.

C. Oxidation

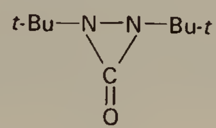
Oxidation of carbodiimides by ozone yields mainly the corresponding substituted ketone, isocyanate and cyanoamidine[87]. Oxidation may occur either at the carbon—nitrogen double bond (path a) or at the carbon—nitrogen single bond (path b). Oxidation at the carbon—nitrogen double bond gives the corresponding isonitrile and nitroso derivatives which upon further oxidation yield the corresponding isocyanate and ketone respectively. Oxidation at the carbon—nitrogen single bonds yields directly the corresponding ketone and cyanamide. Thus oxidation of **44** by ozone gives cyclohexyl ketone, cyclohexyl isocyanate and cyclohexyl cyanamide the latter also yielding finally cyclohexylisocyansite (equations 35 and 36).



(35)

$$c\text{-}C_6H_{11}N{=}C{=}NC_6H_{11}\text{-}c + O_3 \xrightarrow{(b)} c\text{-}C_6H_{10}{=}O + c\text{-}C_6H_{10}NCO \qquad (36)$$

Reactions of carbodiimides with carboxylic acids and hydrogen peroxide usually result in the formation of the corresponding diacyl peroxide[88]. In the case of hindered carbodiimides oxidation of the carbodiimide cumulative double-bond system takes place; thus reaction of di-*t*-butylcarbodiimide and *m*-chloroperbenzoic acid result in the formation of di-*t*-butyldiaziridinone (46) in 20% yield[89].



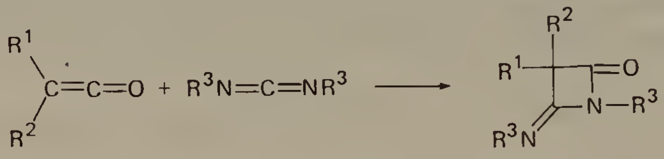
(46)

D. Cycloadditions

The reaction of a substituted carbodiimide with another heterocumulene yields two isomeric [2 + 2] cycloadducts. Linear 1,1-adducts are formed only in cases where the developing charges in the initial bond formation step are sufficiently delocalized, and generally these 1,1-adducts undergo 1,4-cycloaddition to form six membered ring heterocycles. The actual isomer formed in the [2 + 2] cycloaddition is usually identified by ring-opening followed by characterization of the products obtained. Using methyl-*t*-butylcarbodiimide as a marker for the fragmentation reaction (considering that in the reaction of ethyl-*t*-butylcarbodiimide with diphenylketene the addition takes place across the less hindered carbon—nitrogen double bond)[90], it was shown that while aryl isocyanates and arenesulphonyl isocyanates add across their carbon—nitrogen double bond, benzoyl isocyanate adds across its cumulative carbon–oxygen double bond. Reactive isothiocynates add across their carbon–sulphur double bond while *N*-sulphinyl sulphonamides add across their nitrogen–sulphur double bond[91].

1. *Four-membered rings*

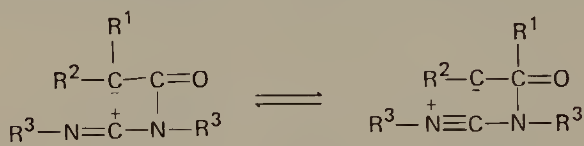
a. Azetidines. Carbodiimides undergo 1,2-cycloaddition reactions with ketenes to form in high yield the corresponding imino-β-lactam (**42**) (equation 37)[92]. The



(37)

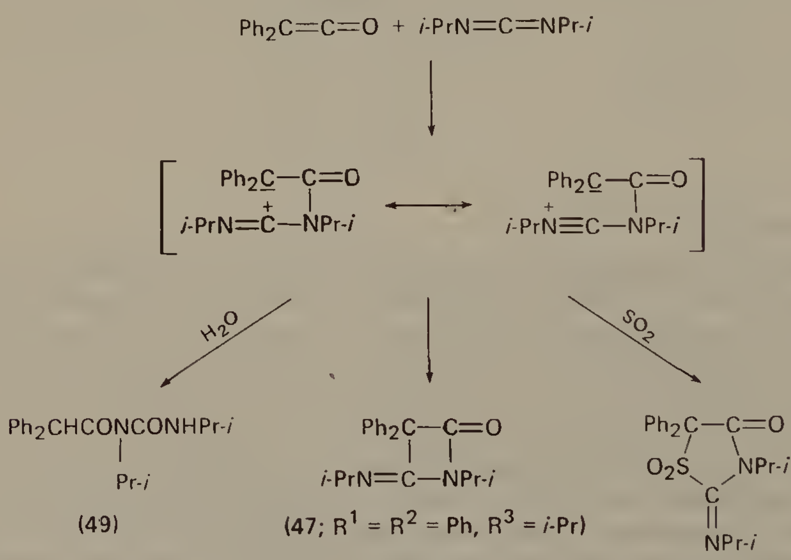
(47)

reaction proceeds in a two-step process via a dipolar intermediate **48**. The two-step process and the presence of the dipolar intermediate was shown in the case of the



(48a) (48b)

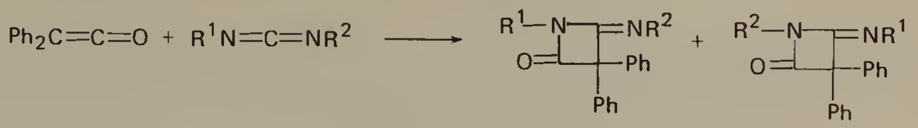
reaction of diphenylketene ($R^1 = R^2 = Ph$) and diisopropylcarbodiimide (R^3 = *i*-Pr). Quenching the reaction mixture with water results in the formation of *N*-diphenylacetyl-*N*,*N*′-diisopropylurea (**49**), diphenylacetic acid and diisopropylurea beside the normal 1,2-adduct (**47**). Another proof for this mechanism is the quantitative formation of 1,1-dioxo-2-(*N*-isopropylimino)-3-isopropyl-5,5-diphenylthiazolidine-4-one (**50**) when the reaction is carried out in liquid SO_2 (Scheme 2)[93].



(49) (47; $R^1 = R^2 = Ph$, R^3 = *i*-Pr) (50)

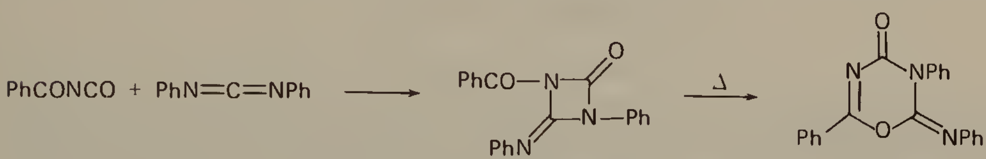
SCHEME 2.

Using an unsymmetrical carbodiimide two isomeric imino-β-lactams are formed (equation 38). The isomer ratio is 95:5 in the case of ethyl-*t*-butylcarbodiimide


(38)

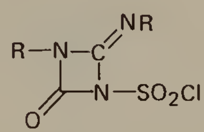
where the addition takes place mainly across the less hindered carbon–nitrogen double bond, but in the case of ethylisopropylcarbodiimide a 50:50 mixture is obtained[90].

b. Diazetidines. Cycloaddition of benzoyl isocyanate and diphenylcarbodiimide gives the diazetidine derivative **51** which is very easily isomerized thermally to the oxadiazine derivative **52** (equation 39)[94]. Another diazetidene derivative is


(39)

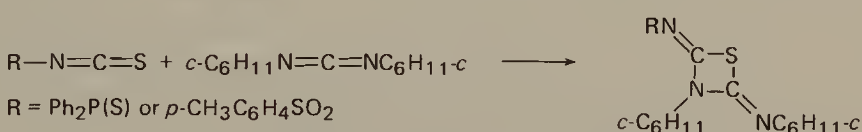
(51) (52)

obtained by cycloaddition of sulphonyl isocyanate to dicyclohexylcarbodiimide in ether or benzene solution (53; R = c-C_6H_{11})[95].



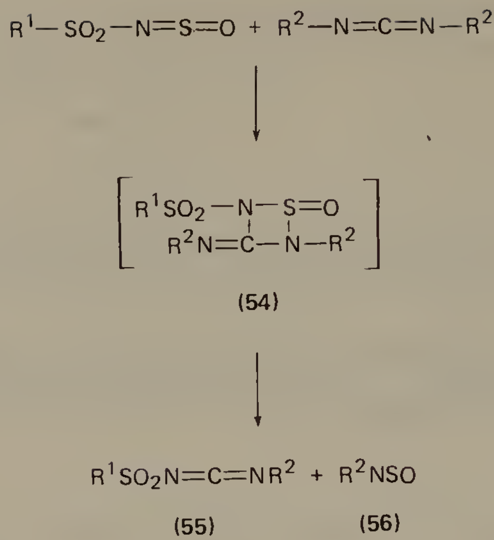
(53)

c. Thiazetidines. Diphenylphosphinothioyl isothiocyanate or *p*-tolysulphonyl isothiocyanate react with dicyclohexylcarbodiimide to yield the corresponding 1,3-thiazetidine derivatives (equation 40)[96]. It has been shown using various substituted phenyl isothiocyanates and dicyclohexylcarbodiimide that the configuration


(40)

of the two exocyclic carbon–nitrogen double bonds is *Z,E*. Formation of this isomer is consistent with a pericyclic process whose stereochemistry is kinetically controlled by steric factors in the transition state[97].

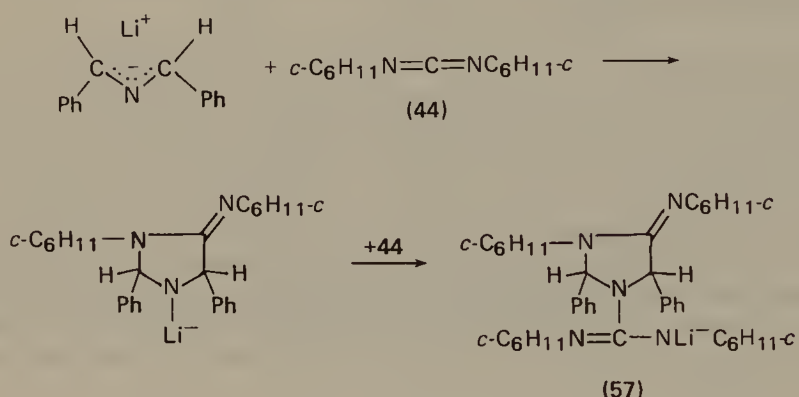
d. Thiadiazetidines. N-Sulphinyl sulphonamides react with carbodiimides to form the corresponding 3-imino-1,2,4-thiadiazetidine-1-oxides (**54**)[98]. The only reaction in which **54** was isolated was the reaction of *N*-sulphinyl p-tolyl sulphonamide and dicyclohexylcarbodiimide (R^1 = p-$CH_3C_6H_4$, R^2 = c-C_6H_{11}). All other cases yield the respective sulphonylcarbodiimides (**55**) and sulphinylamine (**56**), which are obtained from the decomposition of the unstable thiadizetidine derivative (equation 41).



(54) (55) (56) (41)

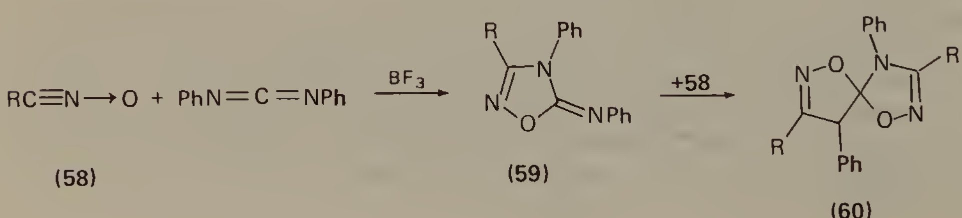
2. *Five-membered rings*

a. Diazolidines. 1,3-Diphenyl-2-azaallyllithium reacts with dicyclohexylcarbodiimide (**44**) to give a 1,1-adduct which can in turn react with another molecule of the carbodiimide to form compound **57** (equation 42)[99].



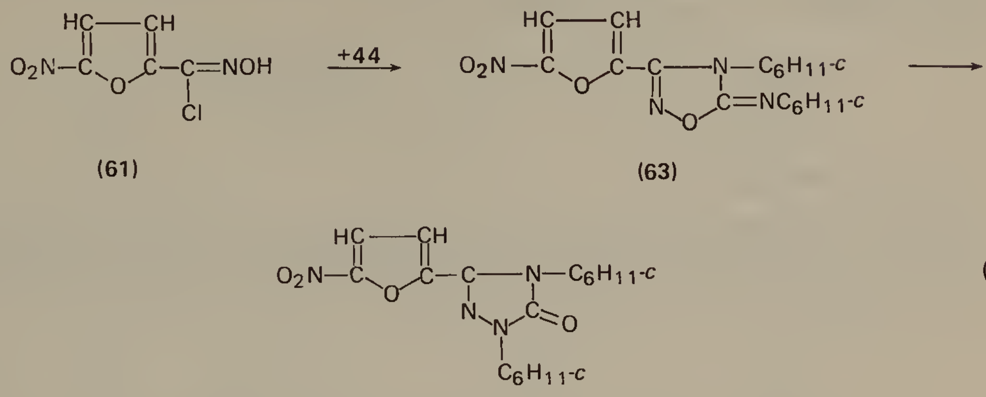
(44) (57) (42)

b. Oxadiazolidines. It has been observed that mesitylnitrile oxide or *p*-nitrophenylnitrile oxide (**58**) react with diphenylcarbodiimide in presence of BF_3 to give the corresponding oxadiazole derivatives (**59**). **59** reacts with another molecule of the nitrile oxide to form the spiro-1,2,4-oxadiazole **60** (equation 43)[100]. A similar reaction occurs between 5-nitrofuran-2-carbohydroxamoyl chloride (**61**) and dicyclohexylcarbodiimide (**44**)[101]. The product of this reaction was found to be



(58) (59) (60) (43)

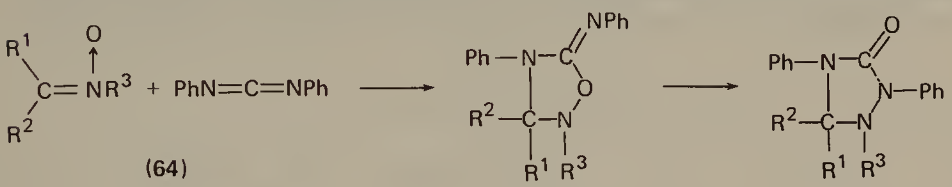
1,4-dicyclohexyl-3-(5-nitro-2-furyl)-4,5-dihydro-5-oxo-1-*H*-triazole **(62)**, a rearrangement product of the oxadiazolidine **63** (equation 44). In the case of the



(61) (63) (62)

(44)

reaction of nitrones **(64)** with diphenylcarbodiimide the corresponding oxadiazolidines **65** or their rearrangement products, the triazolidinones **66**, were obtained (equation 45)[102]. The product obtained depends upon the nitrone used, thus **64a**



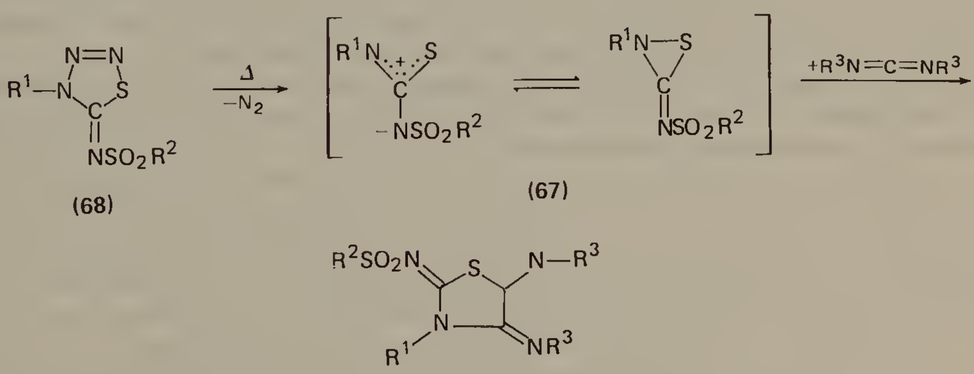
(64) (65) (66) (45)

(a) $R^1 = H$, $R^2 = Ph$, $R^3 = t$-Bu

(b) $R^1 = H$, $R^2 = Ph$, $R^3 = Me$

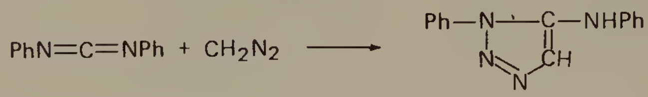
yields the oxadiazolidine **65a** while **65b** yields the rearrangement product, triazolidinone **66b**.

c. *Thiadiazolidines.* Reaction of carbodiimides with *N*-sulphonylimino-thiaziridines **(67)** (generated by thermolysis of 4-alkyl-5-sulphonylimino-1,2,3,4-thiatriazolines, **68**) yields the corresponding thiadiazolidine derivative **69** (equation 46)[103,104].



(68) (67) (69) (46)

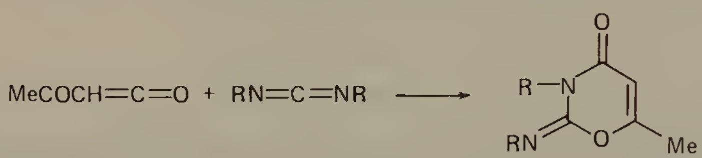
d. Triazoles. Triazoles are obtained by reaction of diazoalkyl compounds with carbodiimides, thus diazomethane react with diphenylcarbodiimide to give 1-phenyl-5-anilino-1,2,3-triazole (equation 47)[105].



(47)

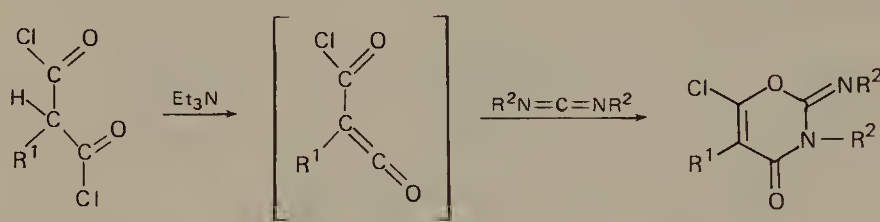
3. Six-membered rings

a. Oxazines. A general method for the preparation of oxazine derivatives is the reaction of suitable ketene derivatives with carbodiimide. Diketene reacts with carbodiimide to give the corresponding oxazine derivatives (equation 48)[106].



(48)

Acylketenes (generated *in situ* either by dehydrochlorination of a monosubstituted malonyl chloride[107] or by thermolysis of 1,3-dioxin-4-ones[108]) yield upon reaction with carbodiimides the corresponding oxazine derivatives (equations 49 and 50).



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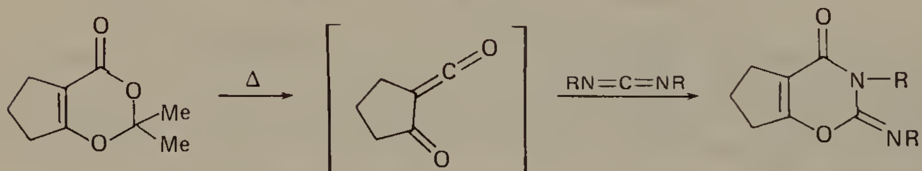
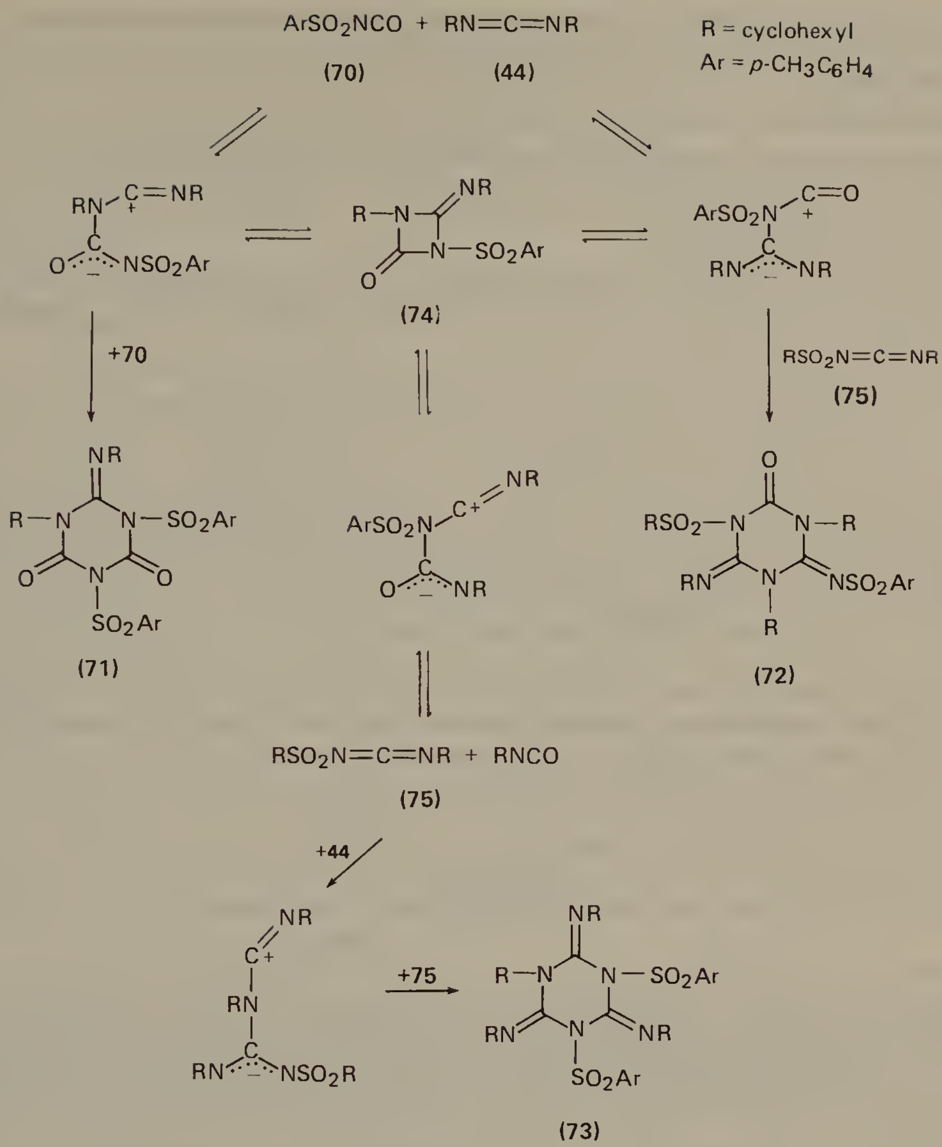


(50)

b. Oxadiazines. As mentioned earlier, oxadiazine derivatives are obtained by the reaction of benzoyl isocyanate and carbodiimide followed by thermal rearrangement of the [2 + 2] cycloaddition product (Section IV. D.1.a)[94].

c. Thiadiazines. The reaction of benzoyl isothiocyanate and carbodiimides proceeds, unlike the reaction of benzoyl isocyanate, via [4 + 2] cycloaddition to yield directly the thiadiazine derivatives[94].

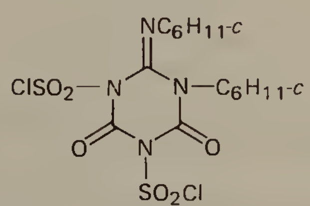
d. Triazines. Arylsulphonyl isocyanates react with dialkylcarbodiimides to yield three triazine derivatives. Thus reaction of *p*-tolysulphonyl isocyanate (70) with dicyclohexylcarbodiimide (44: $R = c\text{-}C_6H_{11}$) will give 1,3-di-*p*-tolysulphonyl-5-cyclohexyl-6-cyclohexylimino-1,3,5-triazine-2,6 dione (71), 1-p-tolylsulphonyl-3,5-dicyclohexyl-2-cyclohexylimino-4-p-tolysulphonylimino-1,3,5-triazine-2-one (72) and 1-cyclohexyl-3,5-di-*p*-tolylsulphonyl-2,4,6-tri(cyclohexylimino)-1,3,5-triazine (73). 71 is formed by the interception of one acyclic polar form of the 1:1 adduct 74 by another molecule of the isocyanate, while interception of a second form of 74 by *p*-tolysulphonylcyclohexylcarbodiimide (75) (which is generated by an



SCHEME 3.

exchange reaction) yields **72**. **73** is formed by interception of the 1,1 acyclic polar adduct of **75** with **44** by another molecule of **75** (Scheme 3)[109].

In the case of chlorosulphonyl isocyanate the picture is much simpler. While addition of the isocyanate to a solution of dicyclohexylcarbodiimide yields the corresponding diazetidinone (see Section IV.D.1.b) the reverse addition gives only one triazine derivative, 1,3-di(chlorosulphonyl)-5-cyclohexyl-6-cyclohexylimino-1,3,5-triazine-2,6-dione (**76**)[95].



(76)

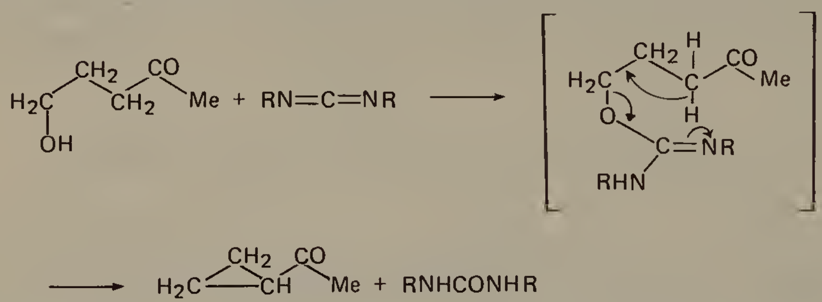
V. APPLICATION OF CARBODIIMIDES IN ORGANIC SYNTHESIS

A. Dehydration

Carbodiimides are best known as dehydrating agents causing either intermolecular or intramolecular dehydration while they are converted into ureas.

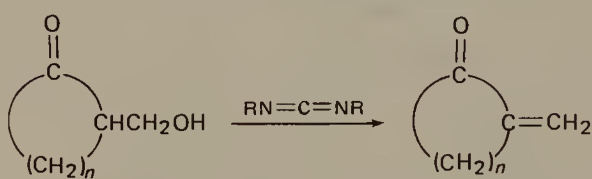
1. *Intermolecular dehydration*

Carbodiimides dehydrate γ-hydroxy ketones to form cyclopropane derivatives. The reaction presumably proceeds via the isourea (equation 51)[110]. γ-hydroxy



(51)

ketones yield under the same conditions the α,β-unsaturated compounds (equation 52)[110]. These dehydration reactions take place at 150° C without a catalyst and proceed in boiling ether solution in the presence of cuprous chloride as a catalyst.

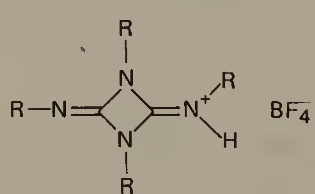


(52)

Hydroxamic acids are dehydrated by carbodiimide to the corresponding isocyanates via a Lossen rearrangement[111]. It has been found that the dehydration reaction and the rearrangement proceeds under unusual conditions in water at pH ~5 using water-soluble carbodiimide (1-benzyl-3-dimethylaminopropylcarbodiimide)[112].

Oximes are converted into the corresponding nitriles by reaction with dicyclohexylcarbodiimide. The reaction proceeds via the isourea which decomposes thermally[113], or decomposes spontaneously in the presence of Cu^{++} as catalyst[114]. It has been shown that aldehydes can be converted to the corresponding nitriles, without isolation of the oximes, in over 90% yield[114].

The 'dimeric' *N,N'*-dicyclohexylcarbodiimidium tetrafluoroborate (77) or the



(77)

R = cyclohexyl

corresponding fluorosulphonate dehydrate alcohols to the corresponding alkene. The reaction takes place in boiling dioxane, toluene or heptane, or also by pyrolysis of the reactants at 100–150°C[115]. Somewhat milder conditions are used for the dehydration of alcohols by *N,N,N'*-trialkylcarbodiimidium tetrafluoroborate[116]. This reagent dehydrates aliphatic glycols to cyclic ethers.

Dicyclohexylcarbodiimide is used also as a cyclization agent by means of intermolecular dehydration. A few examples of this reaction will be given in Section V. C.

2. *Intramolecular dehydration*

Carbodiimides are widely used as condensing agents in peptide and nucleotide syntheses. This subject has been adequately reviewed[5-8] and will not be discussed by us.

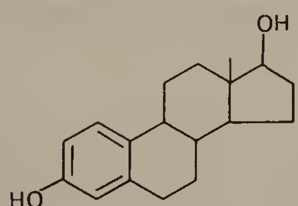
Carboxylic acids are dehydrated by carbodiimides to form the corresponding anhydrides among other products; the nature of the products depends on the reagents present and the reaction conditions[71,72,117]. The dehydration of D_1-acetic acid to $\alpha,\alpha' D_2$-acetic anhydride was reported using dicyclohexylcarbodiimide as a condensing agent[118]. Monothio carboxylic acids are dehydrated by dicyclohexylcarbodiimide to the symmetrical monothio anhydrides (equation 53)[119].

$$2\ RCOSH + c\text{-}C_6H_{11}N{=}C{=}NC_6H_{11}\text{-}c \longrightarrow (RCO)_2S + c\text{-}C_6H_{11}NHCONHC_6H_{11}\text{-}c \qquad (53)$$

Carboxylic acids react with various amines, alcohols, thiols and phenols in the presence of carbodiimide to form the corresponding amide, ester or thio ester and urea[5]. Reaction of carboxylic acids with diazomethane in the presence of dicyclohexylcarbodiimide yields the corresponding diazo ketones in about 50% yield. The method is used when other methods fail, e.g. with benzyloxycarbonylamino acids[120] and 3-cyanopropionic acid[121].

Sulphinic acid derivatives react with alcohols and amines in the presence of dicyclohexylcarbodiimide to give the corresponding sulphinates[122] or sulphinamides[123] respectively and dicyclohexylurea. Sulphuric acid reacts with alcohols, thiols phenols and amines in presence of dicyclohexylcarbodiimide to yield the corresponding sulphate esters (in the case of thiols, thiosulphate esters). These reactions take place in concentrated solutions (2 mol/l), while at lower concentrations (20 mmol/l) the only reaction which takes place is that between sulphuric acid and alcohols[124].

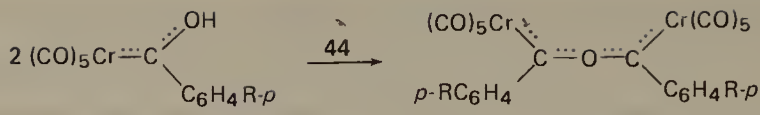
This observation is used for selective sulphatation of e.g. β estradiol (78); using



(78)

lower concentration of reactants results in the formation of the monosulphate ester (sulphatation at the 17-hydroxy group), while working in concentrated solution yields the bissulphate ester.

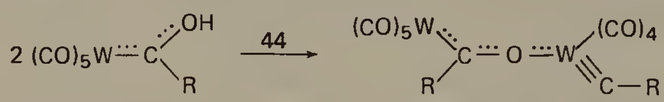
p-Phenyl-substituted (arylhydroxycarbene)pentacarbonylchromium complexes



(54)

(79) (80)

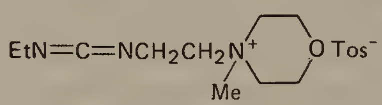
(79) yield by reaction with dicyclohexylcarbodiimide (44) the anhydride complex 80 by intramolecular water elimination (equation 54)[125]. Somewhat different dehydration reactions take place with alkyl- or aryl-hydroxycarbenepenta-carbonyltungsten complexes (81), involving intermolecular water elimination followed by substitution of the *trans*-carbonyl ligand by the alkyl- or aryl-penta-carbonylmetallate to form 82 (equation 55)[126].



(55)

(81) (82)

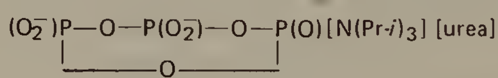
Intramolecular dehydration leading to the crosslinking of proteins is a reaction which takes place in water by water-soluble carbodiimides. This reaction was observed by Sheehan in 1957 when he used 1-ethyl-3(-2-morpholinyl-4-ethyl)carbodiimide metho-*p*-toluenesulphonate (83) for the cross linkage of gelatin[127].



(83)

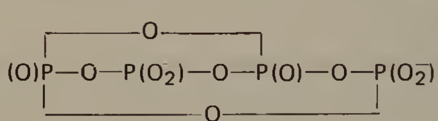
Carbodiimides are used for the attachment of biomonomers and biopolymers to insoluble carriers. Examples are the attachment of uracil to polyvinyl alcohol[128], and the attachment of nucleic acids to cellulose[129]. In both cases the products obtained are used as specific supports for affinity chromatography. Proteins have been coupled to insoluble supports or cell surfaces by carbodiimides[130–132].

Dicyclohexylcarbodiimide is used for the dehydration of various inorganic phosphates to yield oligo- and poly-phosphates. Orthophosphoric acid in presence of a tertiary amine yields mainly the cyclic trimetalphosphate anion with one of the nonbonding oxygen atoms substituted by the urea resulting from hydration of the carbodiimide 84. Dehydration in absence of the amine yields mainly the 1,5-μ-oxo-



(84)

tetrametaphosphate anion (85)[133]. Methylene diphosphoric acid (86) is condensed and dehydrated to the phosphonic analogue of phosphorus pentoxide 87[134]. The



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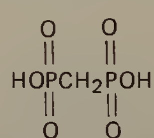

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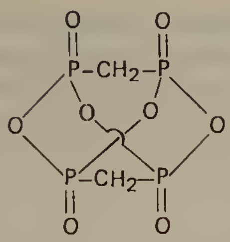
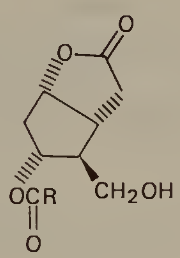


(87)

bridged compound P_4O_{10} was obtained by dehydration of tetramethyl phosphate[135].

B. Oxidation

Dimethylsulphoxide–carbodiimide is a useful combination of two reagents acting as an oxidizing agent in acidic media. A detailed discussion of the use of this combination for the oxidation of alcohols as well as its application in the steroid, carbohydrate and alkaloid systems was given by Moffat[9]. Polymeric carbodiimides[136] have been used for the oxidation of the labile prostaglandin intermediate **88** to the aldehyde **89**. The oxidation in dimethyl sulphoxide formed **89** in over 90% yield[137].



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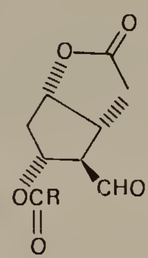
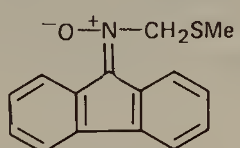


(89)

The combination dicyclohexylcarbodiimide–dimethyl sulphoxide reacts not only with alcohols but also with a variety of other functional groups. Reaction with oximes (3 equivalents of **44**, 0.5 mol equivalents of trifluoracetic acid using a 1 : 1 mixture dimethyl sulphoxide and benzene as solvent) yields a mixture of nitrone and oxime ether (e.g. fluorenone oxime yields 71% of the nitrone **90** and 5% of the isomeric oxime ether **91**[13]. *Syn* and *anti* aldoximes yield the corresponding nitrile



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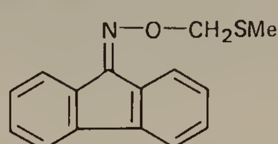
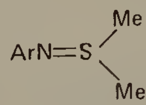


(91)

and nitrone in different proportions. Thus *syn-p*-bromobenzaldoxime gives both *p*-bromobenzonitrile and α-*p*-bromophenyl-*N*-(thiomethoxymethyl)nitrone while the *anti* isomer gives the nitrile in 84% yield with only a small amount of the nitrone[138]. Phenols in presence of both a proton acceptor and a proton donor give a variety of products, all of them derived from the initially formed aryloxysulphonium cation[139,140]. Carboxylic acids yield the corresponding methylthiomethyl ester[141], acylamides form the corresponding *N*-acylsulphilimine[141] and sulphonamides yield the corresponding *S*,*S*-dimethyl-*N*-sulphonylsulphilimine (**92**)[142]. Aromatic amines yield the *N*-aryl-*S*,*S*-dimethylsulphilimines (**93**) which are formed either through a cyclic process or in two steps via proton loss from the corresponding sulphonium salt[143].

$$RSO_2N{=}SMe_2$$

(92)



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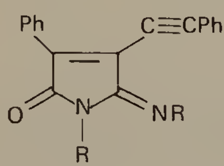
C. Synthesis of Heterocyclic Compounds

A large number of heterocyclic compounds are formed by cycloaddition of carbodiimides (Section IV), or by reaction of carbodiimides with bifunctional compounds. In this section we shall discuss the synthesis of some representative heterocyclic systems by the latter method classified according to the ring size of the product.

1. Five-membered rings

Various pyrroline derivatives (**94**–**96**) are obtained by the reaction of carbodiimides with diphenylbutadiyne (**97**) in presence of iron carbonyl[144].



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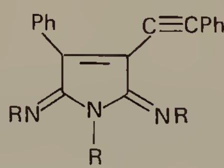

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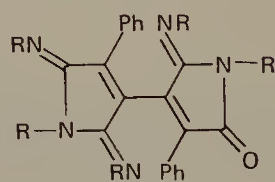
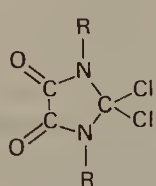


(96)

$$PhC{\equiv}C{-}C{\equiv}CPh$$

(97)

Reaction of oxalyl chloride with carbodiimides yields the corresponding 2,2-dichloroimidazolidinedione (**98**) which could be hydrolysed to the trione or form a large number of imidazolidinedione derivatives via nucleophilic exchange with various hydroxy, thiolo or amino compounds[145]. A similar reaction occurs with disubstituted malonyl chloride derivatives to give the corresponding six-membered ring **99**[145].



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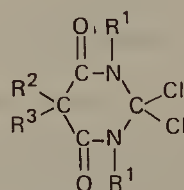
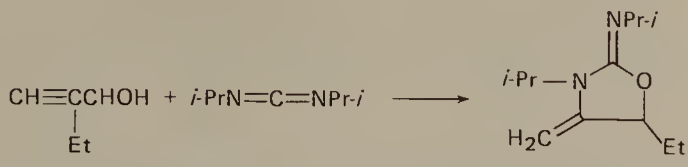


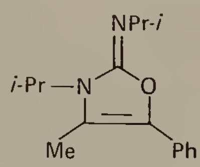
(99)

α-Ethylpropargyl alcohol (**100**) reacts with diisopropylcarbodiimide in the presence of cuprous chloride to give the 2-imino-4-methyleneoxazolidine derivative **101** (equation 56)[146]. α-Phenylpropargyl alcohol gives the 2-imino-4-methyl-



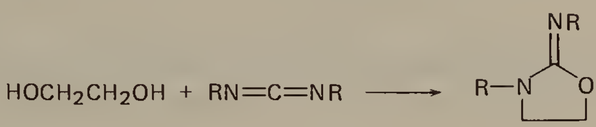
(100) (101) (56)

oxazoline derivative **102**. Iminooxazolidine derivatives are obtained also by the reaction of ethylene glycol and carbodiimides, again in presence of cuprous chloride



(102)

as catalyst (equation 57)[147,148]. It is interesting to note that *trans*-1,2-cyclohexanediol gives upon reaction with dicyclohexylcarbodiimide the desired oxazo-



(57)

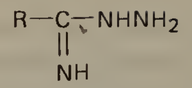
lidine derivative **103** while the *cis* isomer yields the imino ketal **104**[149]. Methylglycolic acid reacts with diisopropylcarbodiimide to yield 2-isopropylimino-3-isopropyloxazolidine-4-one[150].

(103) (104)

Kurzer and his group have shown that various nitrogen compounds (ethoxycarbonylhydrazide (**105**)[151,152], 1,2-diaminophenylguanidine (**106**)[153], thiocarbohydrazide (**107**)[154], amidohydrazines (**108**)[155], carbohydrazides (**109**)[156] and substituted carbohydrazides and thiocarbohydrazides[157]) react with carbodiimides to form various triazole derivatives. The reaction proceeds via the formation of the 1,1-or the 1,2-adduct followed by cyclization to form the five-membered ring.

$NH_2NHCOOEt$

(105)



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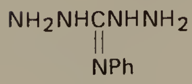

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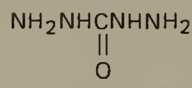

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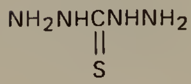
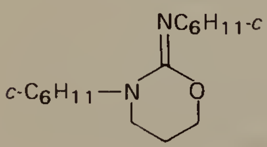


(107)

2. *Six-membered rings*

1,3-Propandiol reacts in a similar way to ethylene glycol with dicyclohexylcarbodiimide to form the corresponding oxazine **110**[148]. Aromatic *o*-hydroxy acids such as salicylic acid and 1-hydroxy-2-naphthoic acid react with 2 moles of dicyclohexylcarbodiimide to form the corresponding benzoxazine **111** or naphthoxazine **112**, respectively, and dicyclohexylurea[158].



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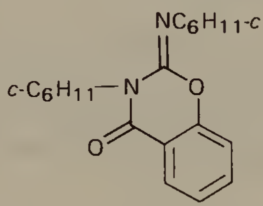

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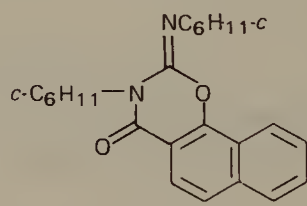
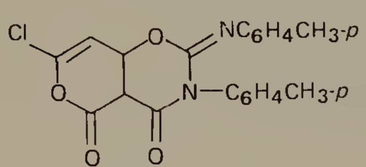


(112)

The pyranoxazine **113** is obtained by the reaction of 6-chloro-4-hydroxy-2-oxo-pyran-3-carboxylic acid chloride (**114**) with one mole of di-*p*-tolylcarbodiimide[159].



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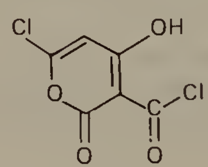
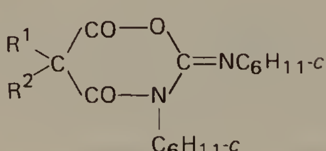


(114)

While dibasic carboxylic acids react with carbodiimides to form the corresponding anhydrides, malonic acid and monosubstituted malonic acid derivatives react with two moles of dicyclohexylcarbodiimide to give the corresponding barbiturates and dicyclohexylurea[160]. Disubstituted malonic acid derivatives yield the corresponding oxazine **115** which can be rearranged to the barbiturate **116**[160].



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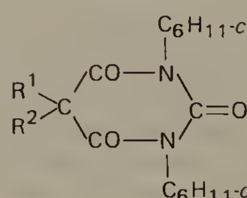
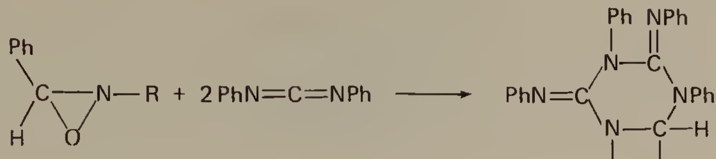


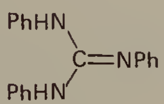
(116)

Triazines are obtained by the reaction of oxaziridines (117) with diphenylcarbodiimide (equation 58)[161]. The only exceptions to this reaction are the *N*-iso-



(117) (58)

propyl- and the *N*-*t*-butyl-aziridines: in the first case the reaction product is triphenylguanidine (**118**) while in the second case the oxazolidine **119** is obtained[161].



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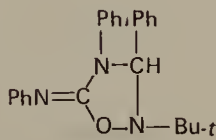
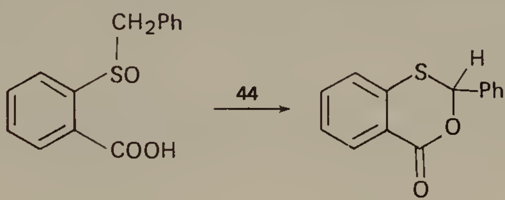


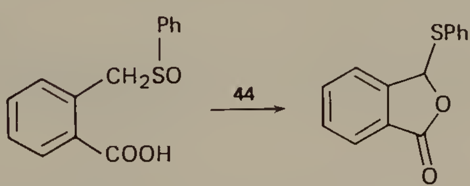
(119)

Dehydration of *o*-benzylsulphinylbenzoic acid (**120**) by carbodiimide gives 2-phenylbenzoxathian-4-one (**121**) via a Pummerer-type rearrangement (equation 59)[162]. The formation of **121** from **120** proceeds in high stereoselectivity: using



(120) (121) (59)

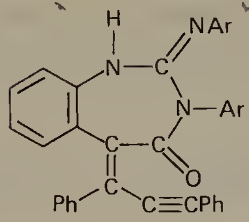
1,2-dichloromethane as a solvent **121** is obtained in 91% yield with 30% stereoselectivity. A similar reaction is observed with the isomeric compound α-phenylsulphinyl-*o*-toluic acid (**122**) which dehydrates to 3-phenylthiophtalide (**123**) (equation 60)[162].



(122) (123) (60)

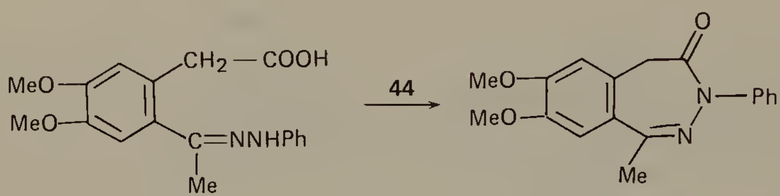
3. *Seven-membered rings*

Aromatic carbodiimides react with phenylbromoacetylene at 90–100° C in presence of iron carbonyl to give the corresponding benzodiazepinone derivatives **124** in 20–40% yield[163]. A route for the synthesis of 1,2-diazepinones is the internal dehydration of *o*-phenylacetic acid phenylhydrazones, thus the ring-closure



(124)

of 2-acetyl-4,5-dimethoxyphenylacetic acid phenylhydrazone (**125**) by dicyclohexylcarbodiimide yields the corresponding benzodiazepin-4-one **126** (equation 61)[164].



(125) (126) (61)

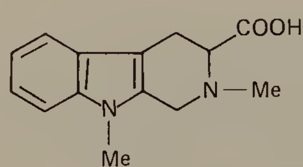
D. Miscellaneous Synthetic Applications

Carbodiimides are used for various synthetic applications beside the ones which have been previously discussed.

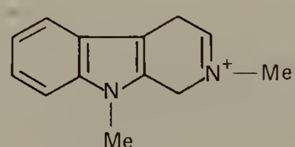
Primary aliphatic amines are converted in 70–95% yield to the corresponding isothiocyanates by reacting them with carbon disulphide and carbodiimide (equation 62)[165].

$$R^1NH_2 + CS_2 + R^2N{=}C{=}NR^2 \longrightarrow R^1NCS + R^2NHCSNHR^2 \quad (62)$$

Carboxylic acids having an adjacent tertiary nitrogen undergo decarboxylation and dehydration by the combined action of dicyclohexylcarbodiimide and *p*-toluenesulphonic acid. Thus the dimethyltetrahydro-β-carboline carboxylic acid (**127**) yields the amine **128**[166].

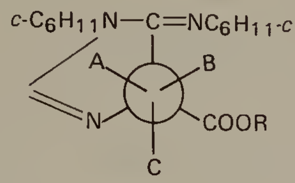


(127)



(128)

An interesting reaction is the stereoselective deamination of phenylalanine and *p*-substituted phenylalanines to the *cis*-cinnamic acids by the decomposition of the corresponding α-diazo-β-phenylpropionic acids in the presence of BF_3 and dicyclohexylcarbodiimide. *cis*-Cinnamic acid is obtained in 80% yield with less than 1% of the *trans* isomer. Similarly *p*-nitrocinnamic acid is obtained without any *trans* isomer while the *p*-methoxy acid is obtained with less than 2% of the *trans* isomer[167]. The mechanism of the reaction is not clear but presumably it proceeds via the formation of the 1,3-cycloaddition product (**129**) of the diazo compound

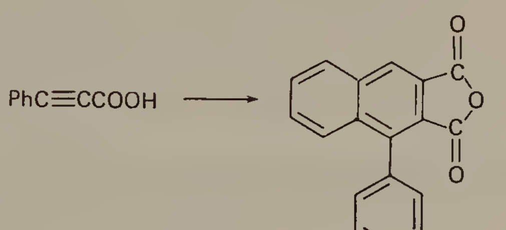


(129)

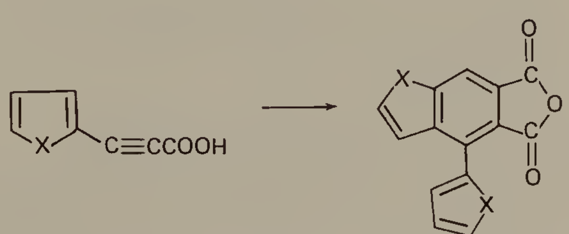
and the carbodiimide. **129** has three possible conformers (a) A = B = H, C = *p*-XC_6H_4; (b) A = C = H, B = *p*-XC_6H_4; (c) B = C = H, A = *p*-XC_6H_4. Among these a must be the most preferred conformer, since it has the least steric repulsion between the aromatic and the cyclohexane rings, and its decomposition should yield the *cis*-cinnamic acid.

Carbodiimides have been used for the modification of the carboxyl groups of proteins, either by esterification (usually with amino acid esters[168]) or by converting them into amines via formation of the hydroxamate followed by a Lossen rearrangement[112]. These reactions proceed under very mild conditions, in water at pH ~ 5.

Substituted phenylnaphthalene-2,3-dicarboxylic acid anhydrides are obtained upon the reaction of substituted phenylpropiolic acids with dicyclohexylcarbodiimide (equation 63). Heterocyclic acetylenic acids form analogous products (equation 64)[169].



(63)



(64)

Thiophenol reacts with dicyclohexylcarbodiimide to form the corresponding isothiourea which in turn will react at elevated temperatures with weakly acidic thiophenols (phenyl, tolyl etc.) to form the corresponding diaryl disulphide (Ar^1SSAr^2). Reaction of the isothiourea with strongly acidic thiopenols (e.g. *p*-nitrophenyl) will result in the formation of the diaryl sulphide (Ar^1SAr^2)[170]. Dialkyl sulphides (R^1SR^2) are obtained by the reaction of thiols with alkylisourea[171]. Aromatic hydrocarbons can be obtained in over 90% yield by the hydrogenation of arylisoureas over Pd/$CaCO_3$ or over Pd/C[172].

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CHAPTER 19

Methyleneketenes

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I. INTRODUCTION

Methyleneketene (propadienone), $H_2C{=}C{=}C{=}O$, is the second member of the series of heterocumulenes, $H_2C{=}(C)_n{=}O$, of which ketene, $H_2C{=}C{=}O$, is the first. The chemistry of methyleneketene and its substituted derivatives is still relatively undeveloped and few generalizations concerning this class of compounds can be made with assurance. However, surprising features have been encountered in the chemistry of these molecules and these may provide new insights into the behaviour of linear heterocumulene systems.

The name methyleneketene has been used to emphasize the close relationship between this compound and ketene. The respective systematic names propadienone and ethenone are less descriptive of this relationship. It should be noted that many of the derivatives of methyleneketene have been indexed under ethenone (ketene) in *Chemical Abstracts*.

The qualitative impressions obtained from valence-bond diagrams and the quantitative information from molecular orbital calculation can provide guidance for the interpretation of the behaviour of methyleneketene. The difference in the magnitude of approximately one Debye unit between the dipole moments[1] of formaldehyde, $\mu = 2.34$ D, and ketene, $\mu = 1.41$ D, can be attributed to resonance contributions from oxonium hybrids, i.e.

$$H_2C{=}O \longleftrightarrow H_2\overset{+}{C}{-}\overset{-}{O}$$

$$H_2C{=}C{=}O \longleftrightarrow H_2C{=}\overset{+}{C}{-}\overset{-}{O} \longleftrightarrow H_2\overset{-}{C}{-}C{\equiv}\overset{+}{O}$$

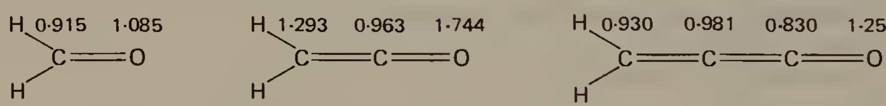
A similar decrease is encountered when the dipole moments of propenal, $\mu = 3.11$ D, and methyleneketene, $\mu = 2.14$ D, are compared and the difference can be attributed to the same cause. (The isomeric propynal has $\mu = 2.39$ D.)

$$H_2C{=}CH{-}CH{=}O \longleftrightarrow H_2C{=}CH{-}\overset{+}{C}H{-}\overset{-}{O} \longleftrightarrow H_2\overset{+}{C}{-}C{=}C{-}\overset{-}{O}$$

$$H_2C{=}C{=}C{=}O \longleftrightarrow H_2C{=}C{=}\overset{+}{C}{-}\overset{-}{O} \longleftrightarrow H_2\overset{+}{C}{-}C{\equiv}C{-}\overset{-}{O} \longleftrightarrow H_2C{=}\overset{-}{C}{-}C{\equiv}\overset{+}{O}$$

From these considerations it appears that methyleneketene may be susceptible to attack by nucleophiles at either the 1- or the 3-position. The compound might be expected therefore to exhibit chemical reactions similar to those of ketenes, but additional reactivity due to the electrophilicity of the 3-position might also be encountered. The polarizability of the extended π-system may further enhance its susceptibility to attack, and there is some evidence from microwave measurements that the heterocumulene system is easily distorted from linearity.

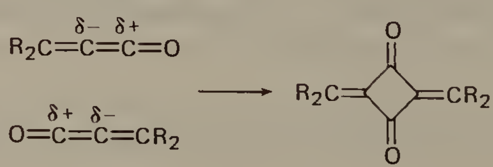
Radom[2] has calculated the π-electron distributions perpendicular to the molecular plane for the various atoms in formaldehyde, ketene and methyleneketene using *ab initio* molecular orbital theory, and these reflect the qualitative interpretation outlined above.



Methyleneketenes are acryloylating agents and reaction with water, methanol or aniline yields respectively acids, methyl esters and anilides of the corresponding acrylic acids. Attack on the methyleneketene may proceed through a carbanion intermediate (equation 1).

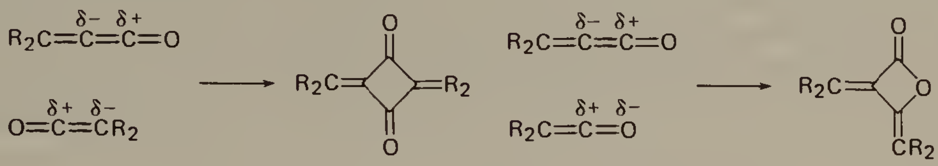
$$R_2C{=}C{=}C{=}O + H_2NPh \longrightarrow R_2C{=}\overset{-}{C}{-}CO\overset{+}{N}H_2Ph \longrightarrow R_2C{=}CH{-}CONHPh \quad (1)$$

The few examples of cycloaddition reactions of methyleneketenes so far observed suggest that their behaviour is analogous to that of ketenes. Aryl-substituted methyleneketenes dimerize in high yields to give bis(arylmethylene)-cyclobutan-1,3-diones (equation 2) while the alkyl-substituted compounds give lower yields of dimers and methyleneketene itself appears to be converted into a polymer rather than into a dimer.

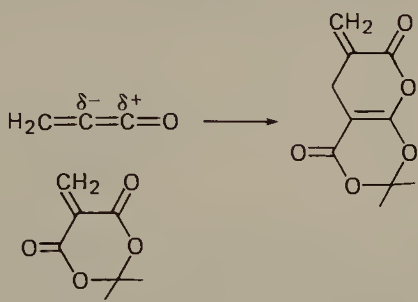


(2)

Interception of this dimerization process and isolation of other cycloaddition products has proved difficult but some examples are known and the classes of compounds that might be expected from simple consideration of charge interactions have been found. Thus, reaction of methyleneketenes with ketenes gives both the diketone and the enol lactone (equation 3). A single example[3] of the parent methyleneketene undergoing a [2 + 4] cycloaddition is known (equation 4).

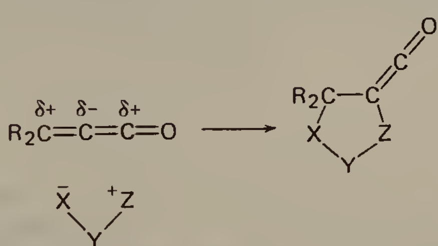


(3)



(4)

Of a number of attempted additions of 1,3-dipolar compounds to methyleneketenes, only one (addition of a cyclic nitrone to dimethylmethyleneketene) has yielded a direct addition product and, surprisingly, this took place on the 2,3- rather than the 1,2-double bond (equation 5). This is the sole evidence found so far that the 3-position of the methyleneketene system has electrophilic reactivity.

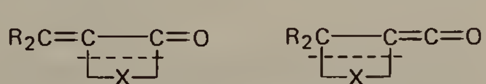


(5)

II. METHODS OF GENERATION

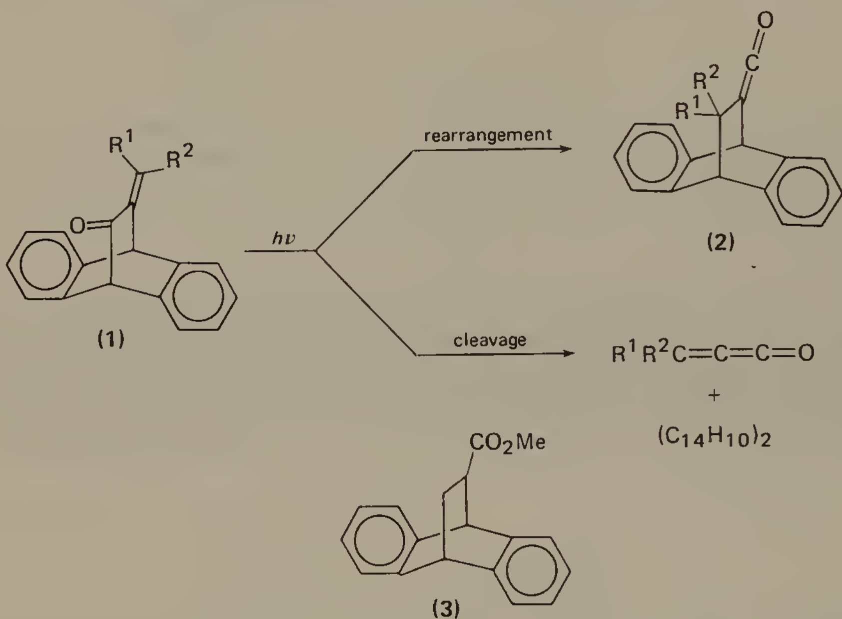
A. By Photochemical Cleavage or Ring-opening

Photochemical approaches to the generation of methyleneketenes have used either the cleavage of an α,β-unsaturated carbonyl compound (Type A) or the fragmentation (or rearrangement) of a suitable ketene (Type B). The groups X, which in the precursors A or B protect either the central or the terminal C=C bond of the desired methyleneketene, have been chosen to produce stable products of fission such as an aromatic hydrocarbon or carbon dioxide.



Type A Type B

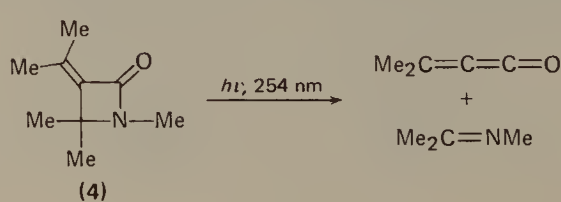
The generation of simple ketenes from derivatives of ethano-bridged naphthalenes or anthracenes requires a high temperature for the thermal fission, but proceeds very efficiently on irradiation[4,5]. On this basis Hart and his colleagues[6] studied the photolysis of a series of α-methylene ketones (1) chosen as Type A precursors of methyleneketenes. Photolysis of the benzylidene derivative 1, $R^1 = H$, $R^2 = Ph$, in methanol gave *E*- and *Z*-cinnamates (1:1) in 37–42% yield together with an equivalent amount of anthracene photodimer. This is consistent with cleavage to form PhCH=C=C=O followed by addition of methanol to the ketene function. A competing process of rearrangement via Norrish Type I cleavage, 180° rotation, and rebonding led to a mixture of stereoisomeric esters (3) (58–63% yield) formed by addition of methanol to the ketene (2). These reactions (equation 6) showed some dependence on wavelength, with rearrangement being favoured at 350 nm (n,π* excitation?) and cleavage becoming more prominent at 300 nm (π,π*?).



(6)

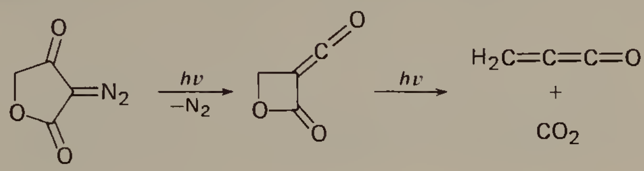
The simple methylene compound 1, $R^1 = R^2 = H$, failed to undergo any significant amount of cleavage to $H_2C=C=C=O$. Thus methyl acrylate could not be detected, only a trace of anthracene dimer was formed, and the major product was the rearranged ester (3; 93.6%). The formation of rearranged esters was shown not to involve cleavage to methyleneketenes and recombination by observing the specific rearrangements of 1-methyl and 4-methyl derivatives of the system 1.

Photolysis of the α,β-unsaturated azetidinone 4 in methanol appears to give dimethylmethyleneketene and an imine[7], (equation 7) although the major product isolated was not the expected α,β-unsaturated ester but the β,γ-isomer $H_2C=CMeCH_2CO_2Me$ which is considered to be a product of secondary photoisomerization. There is no clear evidence in this work for the formation of $H_2C=C=C=O$ from the 3-methylene azetidinone.



(7)

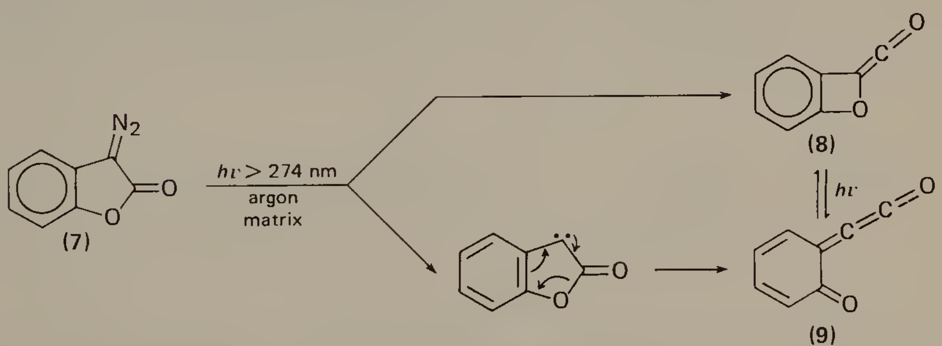
In contrast to the preceding reactions in which the formation of methyleneketene is inferred from the isolation of unsaturated esters, the technique for cleavage of a Type B ketene developed by Chapman and coworkers[8] permits the detection and spectroscopic characterization of the methyleneketene itself. The required ketene is generated by ring-contraction of an α-diazocarbonyl compound; thus photolysis of the diazolactone **5** in argon matrix at 8 K forms the ketene **6** which on further irradiation loses carbon dioxide to form the parent compound $H_2C{=}C{=}C{=}O$, (equation 8) characterized by infrared spectroscopy[9]. This elegant method has the clear advantage over all competing approaches that the other fragments are unlikely to cause serious interference to chemical and spectroscopic study of the product.



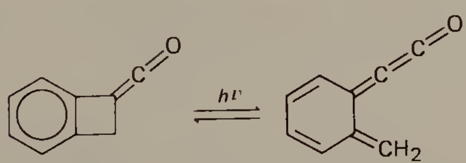
(8)

(5) (6)

Application of the same technique to the photolysis of 3-diazobenzofuranone (7)[8] led to the formation of two primary photoproducts, the colourless ketene **8** and the orange *o*-quinonoid methyleneketene **9** (equation 9). The two products were interconverted in a photochromic system in which irradiation at 254 nm favoured the orange methyleneketene whereas above 350 nm the colourless ketene predominated. Continued irradiation of the system at 254 nm led to decarbonylation of the ketene **8** to benzocyclopropenone and then to benzyne. Irradiation of 2-diazo-1-indanone gave the colourless ketene **10** as the sole primary photoproduct and on further irradiation a photostationary state involving the purple-red methyleneketene **11** was established (equation 10)[8].



(9)

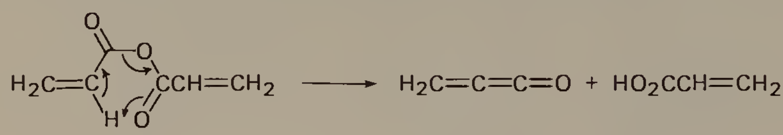


(10)

(10) (11)

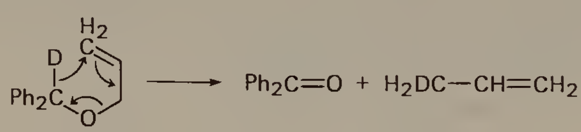
B. By Pyrolysis of Derivatives of Acrylic and Propiolic Acids

The first reference to the possible pyrolytic generation of $H_2C{=}C{=}C{=}O$ appeared in a paper by A. L. Brown and P. D. Ritchie[10] on the pyrolysis of unsaturated and cyclic anhydrides. Acrylic anhydride (12) was pyrolysed at 500° C/760 mm through a packed Pyrex tube with a relatively long residence time (24 sec) to give acetylene, carbon monoxide, acrolein and acrylic acid. Brown and Ritchie proposed that $H_2C{=}C{=}C{=}O$, formed by elimination of acrylic acid, underwent rearrangement to $HC{\equiv}CCH{=}O$ which then lost carbon monoxide to give acetylene. Subsequently the Monash group showed that $H_2C{=}C{=}C{=}O$ is indeed formed on flash vacuum pyrolysis of acrylic anhydride at 510–560° C/0.02 mm (equation 11) and can be detected by infrared and microwave spectrometry[11,12]. No evidence for isomerization of $H_2C{=}C{=}C{=}O$[11] or $PhCH{=}C{=}C{=}O$[13] to the corresponding propiolic aldehydes has been found under flash pyrolytic conditions, and the formation of acetylene by the pyrolysis of acrylic anhydride probably involves direct decarbonylation of methyleneketene (see Section IV.C).

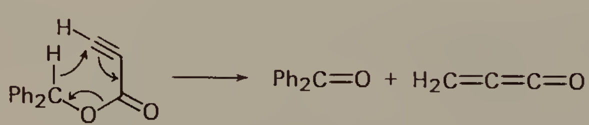


(12) (11)

An alternative approach to methyleneketene involves intramolecular hydrogen transfer in an ester of propiolic acid, a process closely analogous to the pyrolysis of allyl ethers such as **13** investigated by Cookson and Wallis[14] (equation 12). Pyrolysis of diphenylmethyl propiolate (14) at 560° C/0.05 mm gives benzophenone and methyleneketene[11] (equation 13), but the reaction is not a clean source of methyleneketene because other modes of decomposition of the ester also occur.

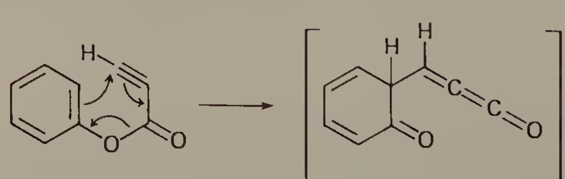


(13) (12)



(14) (13)

A somewhat related process has been proposed[15] as the first step in the pyrolysis of phenyl propiolate (15) at 650° C/10^{-4} mm (equation 14), which leads to 2*H*-cyclohepta[*b*]furan-2-one (see Section IV.D).



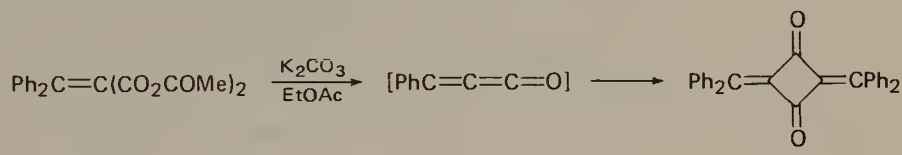
(15) (14)

C. From Methylenemalonic Acid Derivatives

1. *By decomposition of mixed anhydrides*

Pyrolysis of mixed anhydrides of substituted malonic acids is a long-established method for the formation of ketenes. In 1923, Staudinger and Schneider[16] reported unsuccessful attempts to synthesize phenylmethyleneketene and dimethylmethyleneketene by pyrolysis of the mixed anhydrides of diphenylacetic acid and phenylmethylene and dimethylmethylenemalonic acids, $PhCH{=}C(CO_2COCHPh_2)_2$ and $Me_2C{=}C(CO_2COCHPh_2)_2$ respectively. Also, pyrolysis of the supposed cyclic anhydride formed when the silver salt of phenylmethylenemalonic acid was reacted with oxalyl chloride failed to yield the phenylmethyleneketene.

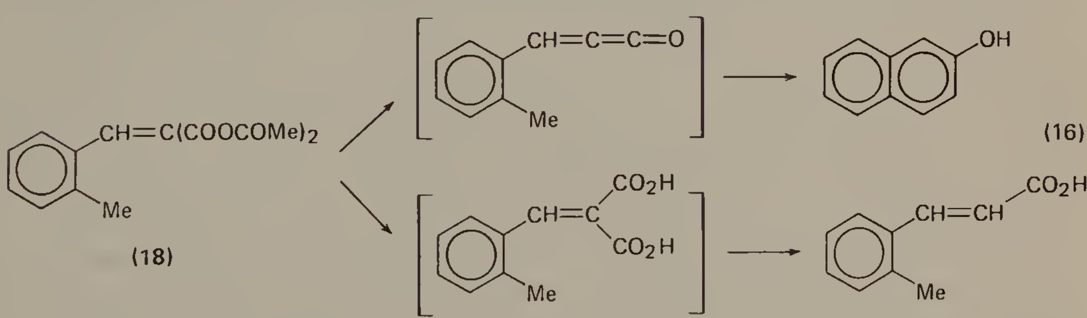
What appears to be the first clear evidence for the formation of diphenylmethyleneketene was obtained by Taylor[17] who prepared the mixed anhydride **16** of diphenylmethylenemalonic acid by reacting it with ketene. The anhydride, on treatment with potassium carbonate in ethyl acetate, yielded 2,4-bis(diphenylmethylene)cyclobutan-1,3-dione (**17**) in 42% yield (equation 15). Diphenylmethyleneketene was postulated as an intermediate in this reaction. The cyclobutanedione **17** has also been obtained in 56% yield by heating a melt of the anhydride **16** at 140° C/0.05mm for 20 minutes[18].



(15)

(16) (17)

It has been found that when (2-methylphenyl)methyleneketene is generated, it undergoes an intramolecular rearrangement with the formation of 2-naphthol in high yield (see Section IV.D). When (2-methylphenyl)methylenemalonic acid was treated with ketene, it was converted into the mixed anhydride **18**. Flash vacuum pyrolysis of this anhydride[18] at 470° C/0.1 mm afforded a mixture of 2-naphthol (26%) and (*E*)-3-(2′-methylphenyl)propenoic acid (**19**) (20%) (equation 16). It



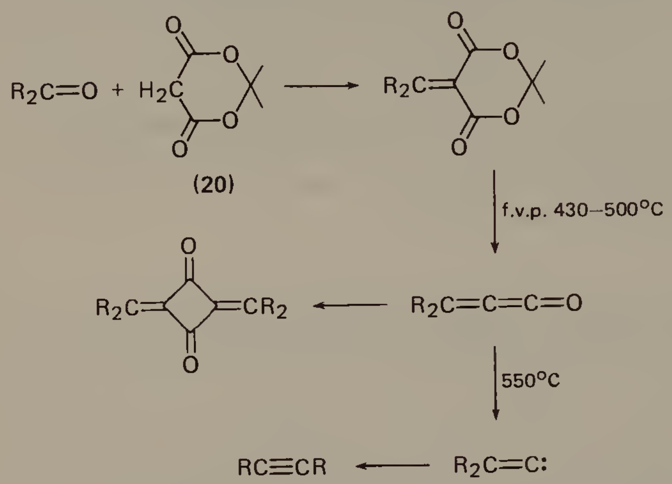
(16)

(18) (19)

appears that a major pathway in these transformations involves the (2-methylphenyl)methyleneketene leading to the formation of 2-naphthol but alternative routes, possibly involving loss of ketene from the anhydride followed by decarboxylation of the malonic acid, lead directly to the cinnamic acid **19**. Flash vacuum pyrolysis of (2-methylphenyl)methylenemalonic acid (470° C/0.05 mm) was shown to yield (*E*)-3-(2′-methylphenyl)propenoic acid (**19**) which was in turn recovered unchanged when pyrolysed under the same conditions.

2. By pyrolysis of 5-methylene-2,2-dimethyl-1,3-dioxan-4,6-diones

Condensation of aldehydes or ketones with 2,2-dimethyl-1,3-dioxan-4,6-dione (Meldrum's acid) (20) followed by flash vacuum pyrolysis (f.v.p.) of the products at 430–500° C provides the simplest and most productive method for obtaining substituted methyleneketenes[19] (equation 17). The product from such a reaction can be collected and retained as the methyleneketene by condensing the pyrolysate directly onto a surface cooled with liquid nitrogen. Warming the product to room temperature generally induces a series of colour changes and a substituted 2,4-dimethylenecyclobutan-1,3-dione is most frequently obtained as the end-product of the reaction. When higher temperatures of pyrolysis (e.g. 550° C) are used, the methyleneketene may be decarbonylated to yield the corresponding acetylene.



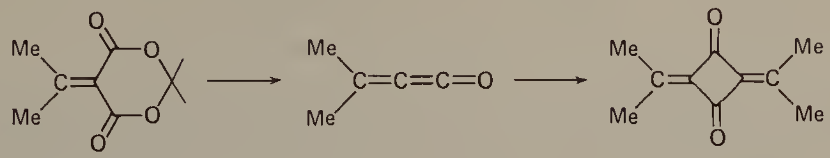
(17)

Benzylidene- and 4′-methyl-, 4′-methoxy-, and 4′-chlorobenzylidene-2,2-dimethyl-1,3-dioxan-4,6-diones on pyrolysis at 430° C gave the 2,4-bis(arylmethylene) cyclobutan-1,3-diones in yield of 54, 27, 10 and 24% respectively. In each case it was possible to demonstrate the presence of the free arylmethyleneketene at the temperature of liquid nitrogen by means of the characteristic infrared absorption at around 2100 cm^{-1}.

4′-Cyanobenzylidene-2,2-dimethyl-1,3-dioxan-4,6-dione when pyrolysed at a relatively low temperature (430° C/0.01mm) decarbonylated to give 4-cyanophenylacetylene rather than the methyleneketene, while at lower temperatures it failed to decompose[19]. Two compounds, namely 2′-methoxybenzylidene- and 2′-phenylbenzylidene-2,2-dimethyl-2,2-dimethyl-1,3-dioxan-4,6-dione, also decarbonylated readily but in these cases the failure to obtain the methyleneketene can be attributed to steric crowding by the *ortho* substituent (see Section IV.C).

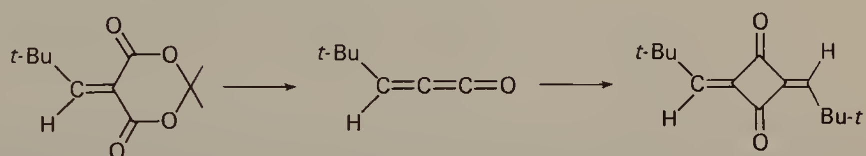
The diphenylmethylene derivative of Meldrum's acid was volatilized only with difficulty at 170° C/0.02 mm but on pyrolysis at 430° C/0.02 mm it gave the brick-red compound 2,4-bis(diphenylmethylene)cyclobutane-1,3-dione in 93% yield[19].

Condensation of acetone or of cycloalkanones with Meldrum's acid proceeds satisfactorily and the products are suitably volatile. 5-(Dimethylmethylene)2,2-dimethyl-1,3-dioxan-4,6-dione (21), on flash vacuum pyrolysis at 430° C/0.03 mm, gave a pyrolysate with an infrared absorption maximum at 2100 cm^{-1} which when warmed to room temperature yielded, after vacuum sublimation, the dimer 2,4-bis(isopropylidene)cyclobutan-1,3-dione in 41% yield (equation 18). 5-Cycloalkylidene-2,2-dimethyl-1,3-dioxan-4,6-diones have not similarly been converted into the analogous derivatives but have been found to decarbonylate readily at temperatures in the range 480–640° C to yield products that are explicable on the basis of the formation of an intermediate methylenecarbene[20] followed by a variety of insertions and rearrangements (see Section IV.C).


(18)

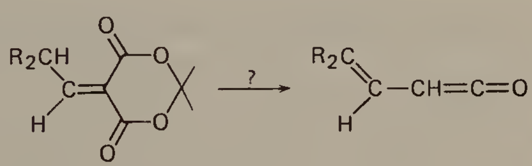
(21)

5-*t*-Butylmethylene-2,2-dimethyl-1,3-dioxan-4,6-dione (22) can be prepared satisfactorily by condensation of 2,2-dimethylpropanal with Meldrum's acid. Pyrolysis of the product at 430° C/0.05 mm gave the corresponding *t*-butylmethyleneketene which had infrared absorption at 2113 cm^{-1}. When warmed to room temperature this pyrolysate gave a complex mixture of products from which trace amounts of the dimer 2,4-bis(*t*-butylmethylene)cyclobutan-1,3-dione could be isolated with difficulty (equation 19). However, the presence of the methyleneketene was confirmed by reacting the pyrolysate with aniline vapour and isolating the anilide of 4,4-dimethylpent-2-enoic acid[19].


(19)

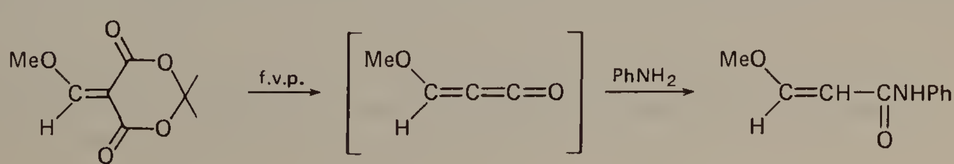
(22)

With both 5-ethylidene- (23, R=H) and 5-isobutylidene-2,2-dimethyl-1,3-dioxan-4,6-dione (23, R=Me) no dimeric products could be isolated on warming the pyrolysate to room temperature, and reaction of the pyrolysate with aniline vapour gave respectively but-3-enanilide and 4-methylpent-3-enanilide[19], suggesting that the intermediate acylating species was the vinylketene (equation 20) rather than the alkylideneketene.


(20)

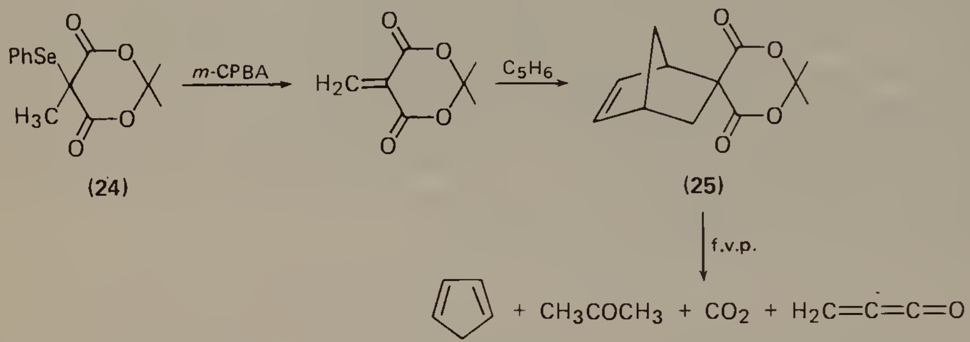
(23)

Condensation of Meldrum's acid with trimethyl orthoformate yields methoxymethylene-2,2-dimethyl-1,3-dioxan-4,6-dione which on flash vacuum pyrolysis and introduction of aniline vapour into the pyrolysate gives 3-methoxyprop-2-enanilide in 18% yield (equation 21). The formation of this product suggests that methoxy-


(21)

methyleneketene is an intermediate[21]. This is the only methyleneketene carrying a heteroatom substituent that has been reported.

Arylmethylene and alkylidene derivatives of Meldrum's acid can be prepared by direct condensation of aldehydes and ketones with Meldrum's acid as described above. The unsubstituted methylene compound is not available by this process and has to be obtained with the double bond protected by a thermally labile group. Preparation of 2,2,5-trimethyl-5-phenylseleno-1,3-dioxan-4,6-dione (**24**) from the anion of methyl Meldrum's acid and phenylselenenyl bromide gave a compound with a potential double bond. Treatment with *m*-chloroperbenzoic acid yielded the powerfully electrophilic methylene derivative which was trapped *in situ* with cyclopentadiene (equation 22). The resultant 5,5-disubstituted Meldrum's acid (**25**) provided a stable precursor for pyrolytic generation of the methylene derivative[3].

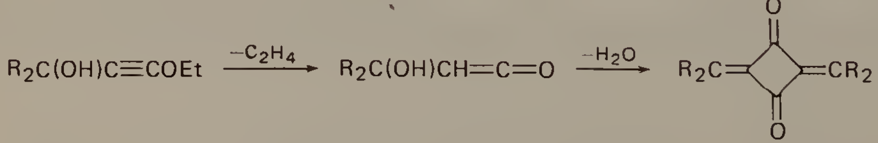


(22)

Flash vacuum pyrolysis of the adduct **25** gave methyleneketene from about 470° C (equation 22). The concentration of methyleneketene in the pyrolysate rose to a maximum at a pyrolysis temperature around 600° C, dropping to about a third of this maximum value at 750° C. The relative abundance of methyleneketene in the (cool) gas stream was measured directly by the signal intensity in the microwave spectrometer. The same technique was used to estimate the stability of the compound when the signal intensity of a microwave transition was monitored with time[18] in a static system; the half-life was found to increase from 8 to 16 sec as the pressure decreased from 0.1 to 0.02 mm

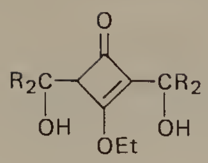
D. Miscellaneous Reactions involving Methyleneketene Intermediates

Rosebeek[22] showed that on heating $Me_2C(OH)C{\equiv}COEt$ in benzene or $Ph_2C(OH)C{\equiv}COEt$ in carbon tetrachloride, ethylene was evolved and 2,4-bis(isopropylidene)cyclobutan-1,3-dione (6% yield) or 2,4-bis(diphenylmethylene)cyclobutan-1,3-dione (59% yield) were obtained (equation 23). The initial reaction was considered to yield the ketene which dimerized and eliminated water to give the cyclobutandione product.



(23)

Two possible intermediates were suggested based on [2 + 2] addition of the ketene intermediates to the initial ethoxyacetylene to yield **26** or dimerization of



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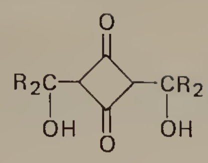
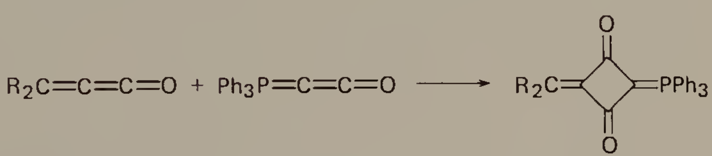


(27)

the ketene to yield **27**. While these suggestions are feasible, the methyleneketenes $Me_2C{=}C{=}C{=}O$ and $Ph_2C{=}C{=}C{=}O$ are known to dimerize to give the products isolated and they cannot be discounted as possible reaction intermediates.

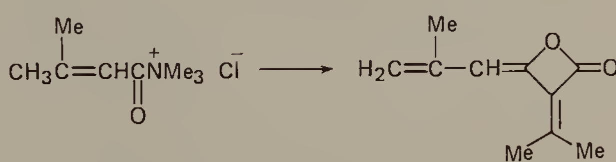
A less ambiguous situation arises in the reaction of triphenylphosphoranylideneketene, $Ph_3P{=}C{=}C{=}O$, with aldehydes and active ketones to yield ylide-substituted cyclobutan-1,3-diones[23]. The reaction was presumed to take place through methyleneketene intermediates formed by addition of the starting ylide to the carbonyl compound followed by loss of triphenylphosphine oxide (equation 24a). A [2 + 2] addition of the starting ylide to the methyleneketene results in the stable products isolated (equation 24b).

$$Ph_3P{=}C{=}C{=}O + R_2CO \longrightarrow R_2C{=}C{=}C{=}O + Ph_3P{=}O \qquad (24a)$$



(24b)

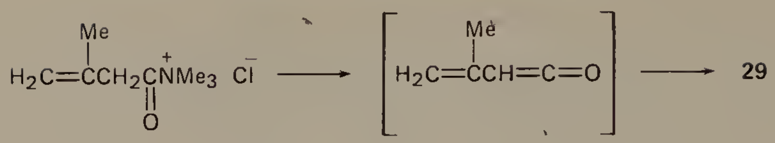
Dehydrohalogenation of acid chlorides with tertiary amines is a well-established method for the synthesis of ketenes but application of this reaction to acryloyl chloride derivatives does not necessarily give rise to methyleneketenes. Payne[24] showed that $Me_2C{=}CHCOCl$ was converted into an acyl quaternary ammonium salt (**28**) when dry trimethylamine gas was bubbled into the acid chloride in hexane. Stirring the product in acetone containing a catalytic amount of sodium iodide yielded the unstable β-lactone (**29**) in 62% yield (equation 25).



(25)

(28) (29)

Two different products from elimination of trimethylammonium chloride from the quaternary salt **28** are possible, namely, dimethylmethyleneketene, $Me_2C{=}C{=}C{=}O$, from 1,2-elimination and isopropenylketene, $H_2C{=}C(Me)CH{=}C{=}O$, from 1,4-elimination. The available evidence points to the latter as the probable intermediate in the dimerization process since reaction of $H_2C{=}C(Me)CH_2COCl$ under the same conditions gave the lactone **29** in 20% yield (equation 26). Also, addition of ethyl vinyl ether to the reaction mixture starting from the quaternary salt **28** gave a mixture of 3-ethoxy-2-isopropenylcyclobutanone (**30**) and 3-ethoxy-2-isopropylidenecyclobutane (**31**), the former isomerizing to the latter at room temperature (equation 27).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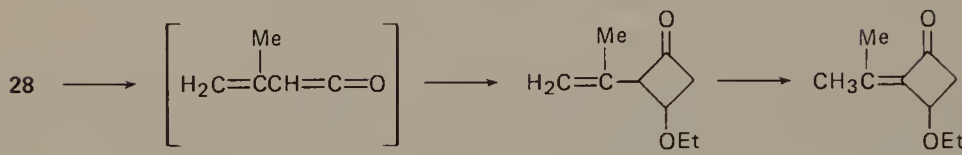
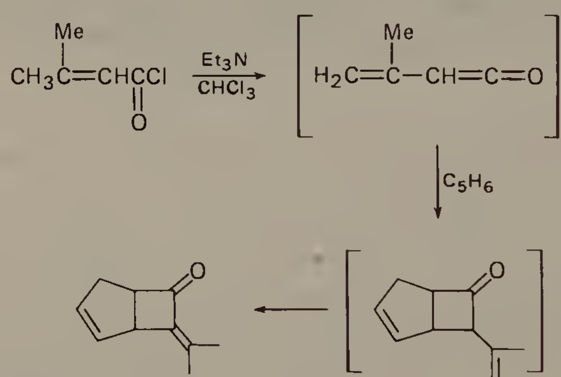

(27)

(30) (31)

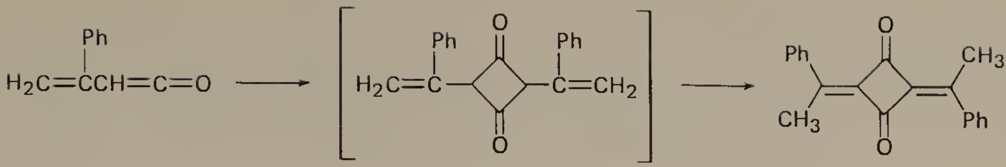
The intermediacy of the ketene $H_2C{=}C(Me)CH{=}C{=}O$ in these reactions appears reasonable since in all cases investigated so far, $Me_2C{=}C{=}C{=}O$ dimerizes to give 2,4-bis(isopropylidene)cyclobutan-1,3-dione. Dimerization of $H_2C{=}C(Me)CH{=}C{=}O$ to the β-lactone **29** requires the shift of a double bond into conjugation with the ester carbonyl, and this process is not without precedent.

This same type of reaction was investigated by Rey and collaborators[25] using triethylamine as the base and chloroform as the solvent. Reaction of $Me_2C{=}CHCOCl$ under these conditions gave the β-lactone **29** as only a minor product (8% yield), the principal ones being 2-pyrones. It was also found that addition of cyclopentadiene to the reaction mixture resulted in the isolation of 7-isopropylidene-bicyclo[3.2.0]hept-2-en-6-one (32) in 30% yield (equation 28). This product is the adduct expected from [2 + 2] addition of cyclopentadiene to $Me_2C{=}C{=}C{=}O$; however, in systems where $H_2C{=}C{=}C{=}O$ or $Me_2C{=}C{=}C{=}O$ have been generated in the gas phase and condensed together with a diene, no such adducts have been found (see Section IV.B)[26]. It is possible therefore that the [2 + 2] addition actually takes place on isopropenylketene and that the isopropenyl double bond moves into conjugation with the carbonyl group after the addition has taken place.


(28)

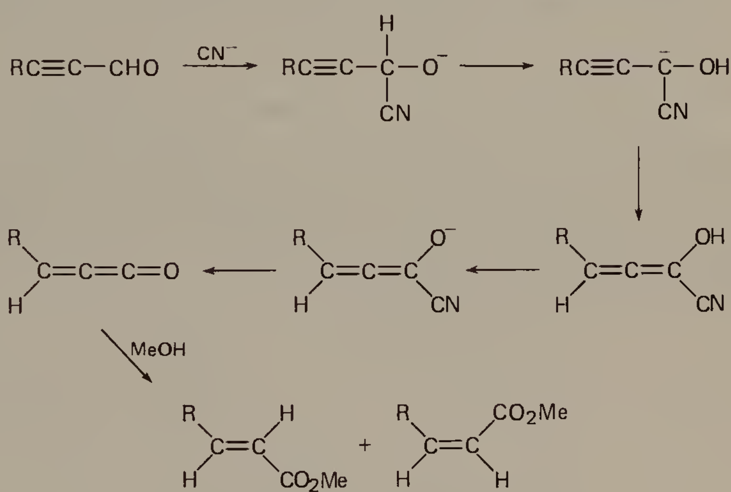
(32)

Under the same conditions $H_2C{=}C(Ph)CH_2COCl$ yielded two pyrones, a resorcinol derivative and only 1% of the cyclobutandione **33**[25]. Methylphenylmethyleneketene, $MePhC{=}C{=}C{=}O$, would be expected to dimerize directly to yield this product, but on the basis of the elimination reaction described above, the initial reaction can as easily yield the ketene $H_2C{=}C(Ph)CH{=}C{=}O$, which on dimerization might yield an intermediate which could isomerize to the conjugated product (equation 29).



(33) (29)

Vishwakarma and Walia[27] showed that reaction of 2-phenylprop-2-ynal with methanol in the presence of potassium cyanide gave a 90% yield of a 1:1 mixture of methyl (*E*)-3-phenylprop-2-enoate and methyl (Z)-3-phenylprop-2-enoate. Similarly, prop-2-ynal yielded methyl prop-2-enoate in 85% yield. The postulated mechanism (equation 30) involves formation of a cyanhydrin, transfer of hydrogen from the 1- to the 3- position and loss of hydrogen cyanide to yield phenylmethyleneketene or methyleneketene respectively in the two cases studied.

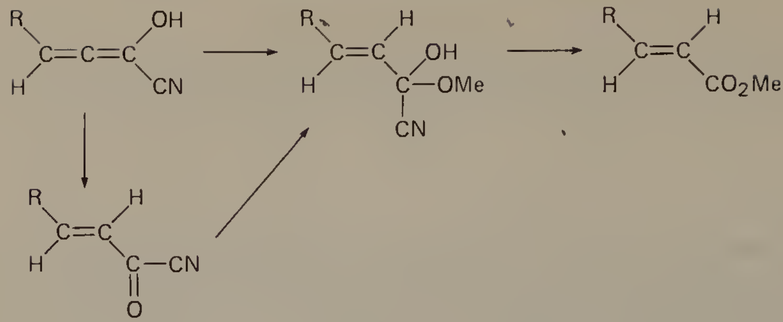


(30)

A more detailed study of the mechanism of the hydrogen transfer was made. 2-Phenylprop-2-ynal was reacted with methanol-d in the presence of potassium cyanide. The resulting methyl esters were separated into the *E* and *Z* isomers by gas chromatography and these were examined by p.m.r. spectroscopy. Each isomer consisted of 90% of the (2,3-d_2) and 10% of the (2-d) species so that no more than 10% of the product resulted from intramolecular transfer of hydrogen from the 1- to the 3-position. Prop-2-ynal in methanol-d and potassium cyanide gave only methyl prop-2-enoate(2,3,3-d_3). The initial exchange of the methyne proton of prop-2-ynal is known to be facile and all subsequent proton transfers were thus shown to be intermolecular.

The above findings are in agreement with the proposed mechanism but, while the mechanism may be plausible for the more stable phenylmethyleneketene, the known properties of methyleneketene would seem to preclude its formation under the reaction conditions described and an alternative mechanism involving addition of methanol to the hydroxyallene or acyl cyanide intermediate should be considered (equation 31).

Earlier, Yanovskaya and coworkers[28] had obtained 2-cyanopropyl, *E*- and *Z*-3-phenylprop-2-enoate from the reaction of phenylprop-2-ynal with acetone cyanhydrin in the presence of triethylamine and this result was interpreted by

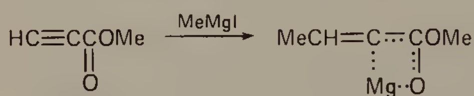


(31)

Vishwakarma and Walia[27,29] as also involving the intermediacy of phenylmethyleneketene.

Based on these mechanistic proposals, Vishwakarma and Walia[30] examined the reaction of the aldehyde PhCH=CBrCHO with methanol in the presence of potassium cyanide. The products isolated were the *E* and *Z* isomers of $PhCH{=}CHCO_2Me$ together with some of the ester $PhCH(OMe)CH_2CO_2Me$. The authors proposed a mechanism involving the elimination of the elements of HBr from the cyanhydrin of the aldehyde leading to the series of intermediates postulated in the previous reactions.

Methylmethyleneketene, MeCH=C=C=O, was proposed by Rhinesmith[31] as an intermediate in the reaction of methylmagnesium iodide with methyl propiolate, but the products obtained from the reaction were later shown by Becker[32] to be explicable on the basis of the addition of the Grignard reagent to the ester to yield a vinylmagnesium compound (equation 32).



(32)

III. GENERAL PROPERTIES

Methyleneketene, $H_2C{=}C{=}C{=}O$, has a lifetime of only a few seconds when kept as a gas under vacuum at room temperature[18], but it can be collected on a sodium chloride plate at the temperature of liquid nitrogen and examined by infrared spectroscopy. The spectrum showed a strong, sharp non-symmetrical absorption band at 2110 cm^{-1} and this absorption persisted for some time[3]. A general impression has been gained that substituted methyleneketenes are more stable than the parent compound. In experiments involving the addition of vaporized nucleophiles to the pyrolysate stream, methyleneketene could only be trapped using the shortest possible path between the region of generation and the point of addition of the reagent[3], while the substituted methyleneketenes underwent the same reactions with less stringent requirements.

Several of the substituted methyleneketenes have been collected at the temperature of liquid nitrogen and examined by infrared absorption spectroscopy[19]. All exhibit strong absorption around 2100 cm^{-1}. The frequencies of infrared absorption of the methyleneketenes $R^1R^2C{=}C{=}C{=}O$ are: $R^1 = R^2 = H$, 2110; $R^1 = H$, $R^2 = Ph$, 2090; $R^1 = H$, $R^2 = 4\text{-}MeC_6H_4$, 2082; $R^1 = H$, $R^2 = 4\text{-}MeOC_6H_4$, 2081; $R^1 = H$, $R^2 = 4\text{-}ClC_6H_4$, 2094; $R^1 = R^2 = Ph$, 2080; $R^1 = H$, $R^2 = t\text{-}Bu$, 2113; $R^1 = R^2 = Me$, 2100 cm^{-1}.

The dipole moment of the unsubstituted $H_2C{=}C{=}C{=}O$ has been determined by microwave spectroscopy[12] to be 2.14D (7.07×10^{-30} Cm). However, the shape of the molecule has not been determined with precision because of phenomena associated with centrifugal distortion. The available data can be interpreted as requiring a low-frequency bending mode of high amplitude in the molecular vibration but this is by no means the only interpretation possible.

IV. REACTIONS

A. Reactions with Nucleophiles

Methyleneketenes tend to behave as typical ketenes in their reactions with nucleophiles, HNuc, such as methanol and aniline, but the α,β-unsaturated primary products may undergo secondary changes under the conditions used for their generation (equation 33). In spite of this, such reactions have been used as evidence for the generation of methyleneketenes even when none of the primary product has been isolated.

$$R_2C{=}C{=}C{=}O + HNuc \longrightarrow R_2C{=}CHCONuc \longrightarrow \text{secondary products} \tag{33}$$

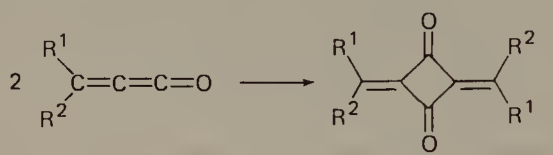
Monosubstituted methyleneketenes generated in solution appear to react with methanol to give approximately equal amounts of the *Z* and *E* isomers of the αβ-unsaturated esters. Thus PhCH=C=C=O generated photochemically from an anthracene adduct[6] or by treatment of PhC≡CCHO with methanolic KCN[27] adds methanol to give both isomers of methyl cinnamate. However, pyrolytic generation of PhCH=C=C=O from the 5-benzylidene derivative of Meldrum's acid and addition of hot methanol vapour to the hot pyrolysate stream gave only the thermodynamically more stable methyl *E*-cinnamate, and *t*-BuCH=C=C=O reacted with aniline under similar conditions to give *E*-*t*-BuCH=CHCONHPh[19]. This stereochemical difference is probably due to secondary *Z*–*E* isomerization in the pyrolytic system.

In some cases alkyl-substituted methyleneketenes react with nucleophiles to give β,γ-unsaturated products, and there may be some uncertainty as to the species in which migration of the double bond has occurred. Generation of $Me_2C{=}C{=}C{=}O$ in methanol by photolysis of an *N*-methyl azetidinone derivative at 254 nm gives $H_2C{=}CMeCH_2CO_2Me$ and a little $H_2C{=}CMeCH_2CONHMe$ rather than the expected α,β-unsaturated derivatives. Mazzocchi and coworkers have proposed[7] that these are formed by secondary photoenolization and deconjugation of the α,β-unsaturated products rather than by isomerization of the methyleneketene to a vinylketene $H_2C{=}CMeCH{=}C{=}O$. In pyrolytic experiments attempted generation of MeCH=C=C=O and $Me_2CHCH{=}C{=}C{=}O$ from Meldrum's acid derivatives failed to give the expected methyleneketene dimers, and mixing of the pyrolysate streams with aniline vapour gave the β,γ-unsaturated anilides $H_2C{=}CHCH_2CONHPh$ and $Me_2C{=}CHCH_2CONHPh$[19]. In these cases thermal or base-catalysed isomerization of the methyleneketene to a vinylketene may have occurred, but the evidence is ambiguous. By contrast $Me_2C{=}C{=}C{=}O$ generated pyrolytically readily formed the orange dimer[19] (see Section IV. B) and reacted with aniline vapour to give $Me_2C{=}CHCONHPh$[33].

B. Dimerization and Cycloaddition Reactions

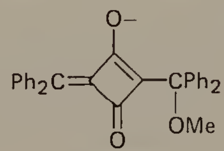
The great ease of dimerization of many substituted methyleneketenes is a striking feature of their chemistry, and the formation of orange or red dimers (34) is a useful indicator of success in the generation of methyleneketenes either in solution or by pyrolysis. Dimerization is inhibited in the monomers deposited at −196° C or lower, so that spectroscopic study of the monomers is possible, but the colour of the dimer appears immediately on warm-up. Dimerization under these conditions is faster than diffusion and reaction with a layer of a reactive nucleophile (methanol or aniline) deposited on top of the methyleneketene layer.

Dimers (**34**; equation 34) have been obtained with the following substitution patterns: $R^1 = R^2 = Ph$[17,19,22]; $R^1 = H$, $R^2 = p\text{-}XC_6H_4$, with X = H, Me, MeO and Cl[19]; $R^1 = Me$, $R^2 = Ph$[25]; $R^1 = R^2 = Me$[19,22]; $R^1 = H$, $R^2 = t\text{-}Bu$[19]. The dimeric benzylidene compound has been found by X-ray crystallography[34] to be the *E*-stereoisomer (**32**), $R^1 = H$, $R^2 = Ph$. No dimers were obtained on attempted pyrolytic generation of $CH_3CH{=}C{=}C{=}O$ or $MeCH_2CH{=}C{=}C{=}O$[19], and isomerization to the corresponding vinylketenes may have occurred in these cases (see Section IV.A).



(34)

(34)

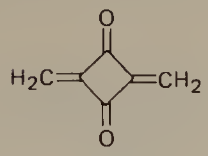


(35)

The properties of the dimers deserve mention. The orange tetramethyl compound (**34**), $R^1 = R^2 = Me$, and the dark-red tetraphenyl compound (**34**) $R^1 = R^2 = Ph$, show infrared carbonyl absorption at rather low frequencies, 1680–1690 cm^{-1} and 1692–1694 cm^{-1} respectively in paraffin mulls or in KBr[17,19,22]. These compounds are thermally rather stable and cannot readily be dissociated to give the monomers on flash vacuum pyrolysis at 400–500° C. The dimers tend to behave as π acids with strong bases; the tetraphenyl compound dissolves in sodium methoxide solution to give the colourless **35**, and the red dimer is regenerated quantitatively on acidification[17].

Pyrolytic generation of $H_2C{=}C{=}C{=}O$ from the cyclopentadiene adduct **25** of the methylene compound **37** at 540° C and collection of the products at −196° C leads after warm-up to a colourless polymeric deposit insoluble in most organic solvents but soluble in aqueous sodium hydroxide[18]. Formation of the cyclobutanedione **36** has not been observed, but this species might itself be expected to polymerize rapidly (cf. the ready polymerization of **37**[3]). Generation of $H_2C{=}C{=}C{=}O$ at a lower temperature, 495° C, at which decomposition of the precursor **37** is not complete in one pass, leads to the [2 + 4] cycloadduct **38**[3] (equation 35). This reaction appears to occur in the gas phase; a deposit containing **38** tended to condense close to the exit of the pyrolysis tube. The structure **38** is based on methanolysis and methylation of the deposit to give $H_2C{=}C(CO_2Me)CH_2CH(CO_2Me)_2$.

There have been no reports of successful [2 + 2] cycloaddition reactions of methyleneketenes with alkenes, whether electron-rich or electron-poor[26], or with 1,3-dienes such as cyclopentadiene[3]. In many cases it appears that such reactions cannot compete with dimerization of the methyleneketene. Cycloadducts between



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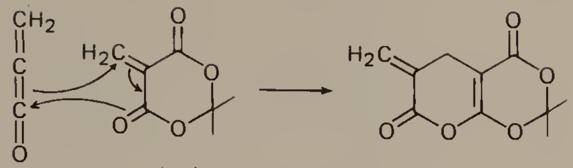
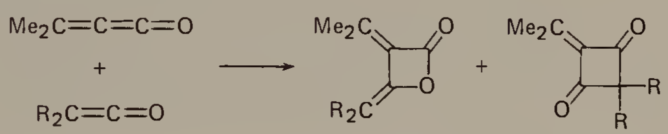


(37) (38)

(35)

dimethylmethyleneketene and simple ketenes have however been obtained by copyrolysis of two derivatives of Meldrum's acid[35]. With ketene itself the products were the β-lactone (**39a**; 27%) and the 1,3-diketone (**40a**; 8%), and dimethylketene behaved similarly in giving the major adduct (**39b**) and the minor adduct (**40b**) in the ratio 2:1 (equation 36). In terms of the discussion of the dimerization of ketenes by Woodward and Hoffmann[36] the methyleneketene in these reactions behaves as the highly electrophilic π^2a component and the simple ketene as the π^2s component. The steric interference which disfavours β-lactone formation in the dimerization of alkylketenes[37] is less serious when one component is a methyleneketene, and so attack on the carbonyl group of the ketene is favoured, just as in the dimerization of ketene itself.



(36)

(39) (40)

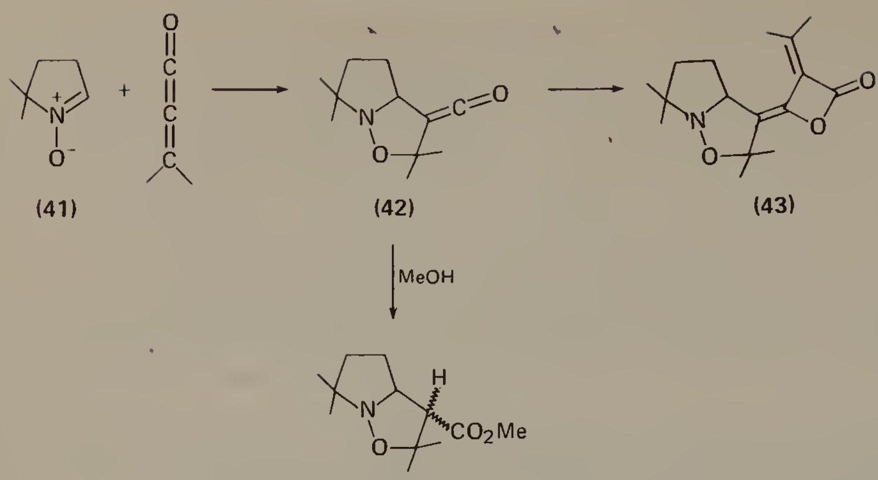
(a) R = H (a) R = H

(b) R = Me (b) R = Me

Cycloaddition of $Me_2C{=}C{=}C{=}O$ to a cyclic nitrone, 5,5-dimethyl pyrroline 1-oxide (**41**), has also been achieved[35] (equation 37). Introduction of the vapour of the nitrone into a stream of pyrolysate containing dimethylmethyleneketene in excess gave a 1,2-adduct, the β-lactone **43**. The first step in this reaction is considered to be addition of the nitrone to the terminal C=C bond of the methyleneketene, leading to the bicyclic ketene **42**, which can react with more methyleneketene to give the β-lactone, in accord with the behavour of simple ketenes. The structure **43** has been confirmed and the stereochemistry established by X-ray crystallography[35]. The bicyclic ketene **42** appears to react rather slowly with further nitrone, and addition of methanol to a pyrolysate containing excess of nitrone gave in low yield the stereoisomeric bicyclic esters **44**.

C. Decarbonylation

Methyleneketenes formed by flash vacuum pyrolysis decarbonylate thermally, usually at temperatures somewhat higher than those employed for their generation, to give methylenecarbenes (ethenylidenes, $R_2C{=}C{:}$)[13]. However, the two temper-



(37)

(41) (42) (43) (44)

ature ranges overlap, and in some cases only products of decarbonylation can be isolated from such experiments. Methylenecarbenes rearrange to alkynes, RC≡CR, and their intermediacy is inferred mainly from the isolation of alkynes. Intermolecular trapping of a methylenecarbene derived from a methyleneketene has not been achieved, although products apparently formed by intramolecular reactions of methylenecarbenes have been isolated[13,20].

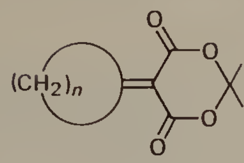
Radom[2] has discussed the thermochemistry of the decarbonylation of propadienone itself using data derived from *ab initio* calculations (STO-3G and 4-31G basis sets) combined with experimental heats of formation for related molecules. He predicts that the activation energy for the overall decarbonylation leading to acetylene and carbon monoxide should be more than 40 kcal mol^{-1}, though this would be somewhat reduced if decarbonylation and rearrangement were concerted, rather than stepwise as shown in equation (38). The overall reaction is predicted to be exothermic by 2–5 kcal mol^{-1}.

$$H_2C{=}C{=}C{=}O \longrightarrow H_2C{=}C{:} + CO \longrightarrow HC{\equiv}CH + CO \quad (38)$$

Optimum temperatures for the pyrolytic generation of $H_2C{=}C{=}C{=}O$ from acrylic anhydride, diphenylmethyl propiolate or the cyclopentadiene adduct of 2,2-dimethyl-5-methylene-1,3-dioxan-4,6-dione (see Section II 0.2) are close to 550° C at 0.02 mm for each of the three precursors as shown by microwave spectrometry; the formation of increasing amounts of acetylene above 520° C can be detected by infrared and mass spectrometry[18].

The decarbonylation of alkyl-substituted methyleneketenes (e.g. the *t*-butyl and dimethyl compounds) formed at 430° C[19] occurs at 600° C to give the corresponding acetylenes, but the pyrolysates have not been fully examined. The pyrolysis of a series of cycloalkylidene derivatives (**45**; $m = 3–7$) of Meldrum's acid has been studied in more detail[20]. In this series the methyleneketenes appear to decarbonylate with great ease, and no dimers have been obtained even on pyrolysis at temperatures as low as 400° C. At 480–640° C the products are mixtures of hydrocarbons formed by processes which include ring-expansion to give cycloalkynes (e.g. **46** → **47**; equation 39) and an insertion–rearrangement process leading to 1,3-cycloalkadienes (**48** → **49**; equation 40) or to bicyclic alkenes.

Aryl derivatives of methyleneketene decarbonylate smoothly in the gas phase at 550-600° C to give arylacetylenes ArC≡CH by rearrangement of the intermediate



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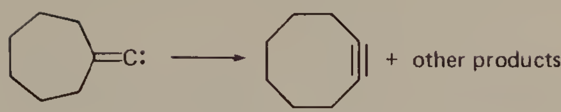
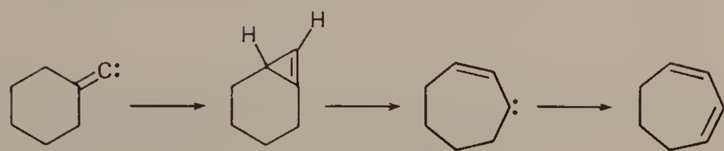
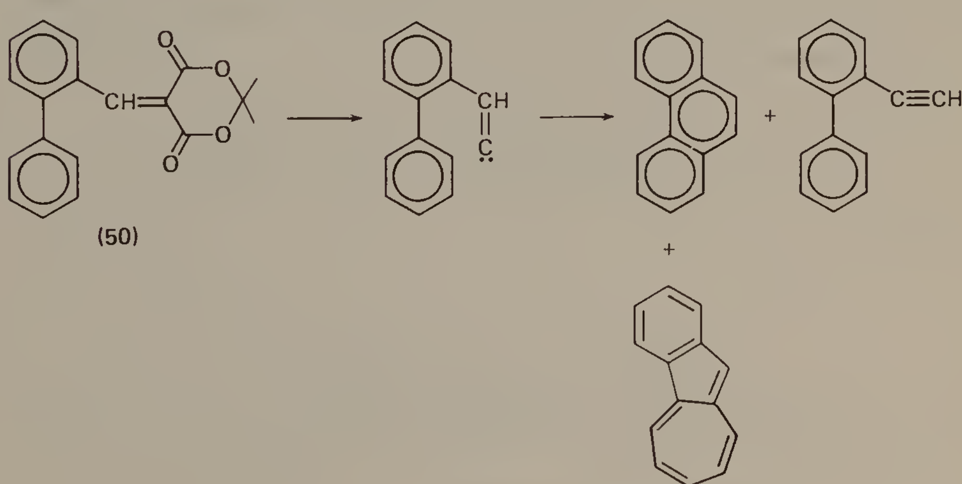


(46) (47) (39)



(48) (49) (40)

methylenecarbenes, and the pyrolysis of 5-arylmethylene derivatives of Meldrum's acid at these temperatures thus providing a convenient method for the preparation of arylacetylenes from aromatic aldehydes[13]. The method has given phenylacetylenes bearing *meta* or *para* substituents (H, Me, MeO, Cl, CN) in 64–98% yield, but cannot be used in the presence of an *o*-CHR_2 substituent (see Section IV.D). Decarbonylation appears to be promoted by other *ortho* substituents, because both *o*-methoxy and *o*-phenyl benzylidene derivatives give the corresponding arylacetylenes even at 420° C. That free carbenes are indeed involved in such decarbonylations is suggested by the behaviour of the *o*-phenylbenzylidene compound **50** which gave, in addition to the arylacetylene, phenanthrene and 1,2-benzazulene (**51**) (equation 41). The formation of the benzazulene is considered to involve carbene addition to an aromatic double bond followed by rearrangement leading to expansion of the phenyl ring.

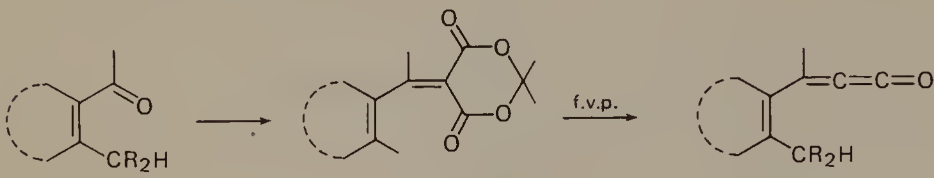


(50) (41)

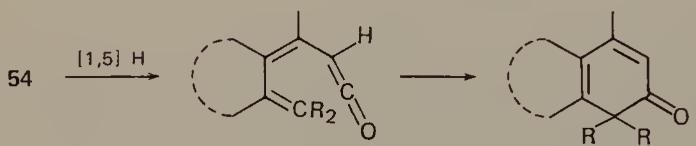
(51)

D. Intramolecular Rearrangements

Methyleneketenes conjugated with a further C=C bond bearing a *cis*-alkyl group in **54** rearrange smoothly in the gas phase at 400–650° C to give intermediate hexatrienones (**55**) which cyclize to cyclohexadienones (**56**) or, where one R group in **56** is also hydrogen, to phenols (equation 43).

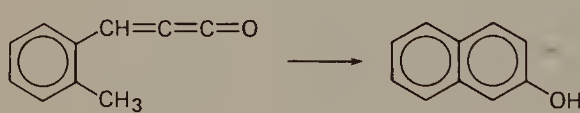


(52) (53) (54) (42)

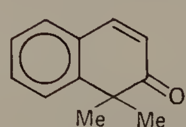


(55) (56) (43)

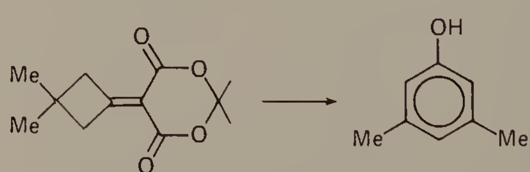
This rearrangement provides a synthetically useful route from a suitably substituted carbonyl compound **52** to a phenol, by condensation with Meldrum's acid and flash vacuum pyrolysis of the condensation product **53**[38] (equation 42). Yields of phenols are frequently better than 90% and the pure products deposit in the exit tube of the pyrolysis apparatus. The further C=C bond usually forms part of an aromatic ring, as in the rearrangement of the *o*-tolylmethyleneketene **57** to 2-naphthol (equation 44) **57** is obtained in almost 100% yield on flash vacuum pyrolysis of the condensation product **53** derived from *o*-tolualdehyde[38]. Application of the same sequence to *o*-isopropylbenzaldehyde gave the (1*H*)-naphthalenone **58**. The aromatic ring is not essential, however; pyrolysis of the condensation product **53** derived from PhMeC=CH–CH=O gives 3-hydroxybiphenyl[38]. The formation of 3,5-dimethylphenol in 84% yield by pyrolysis of the dimethylcyclobutylidene compound **59** (equation 45) is clearly a closely related process[20], but the mechanism of fission of the cyclobutane ring is uncertain.



(57) (44)

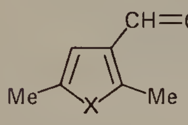


(58)

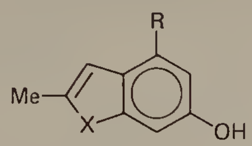


(59) (45)

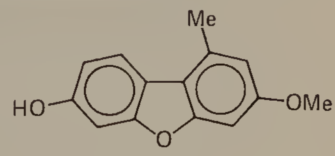
Baxter, Brown and McMullen[39] have applied this synthetic method to the heterocyclic aldehydes **60** (X = O, NH, NMe, or S) and obtained the phenolic benzoheterocycles **61** (R = H). The limit of the method in terms of molecular size is probably indicated by the double annelation of 2,5-dimethylfuran to the dibenzofuran **62** in a seven-step sequence[40]. The yield of the benzofuranol **61** X = O; R = Me) in the first pyrolytic step was 90%, but that in the second pyrolytic step leading to **62** was only 28% because the pyrolytic precursor did not sublime smoothly.



(60)

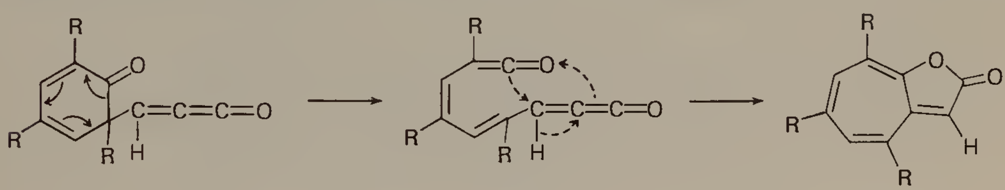


(61)



(62)

Trahanovsky and his colleagues[15] have proposed that the formation of the bicyclic lactones **65** (R = H or Me), by flash vacuum pyrolysis of aryl propiolates at 650° C (see Section II.B), involves the rearrangement of intermediate methyleneketenes **63** and **64**. The formation of the methyleneketene **63** by a [3,3] rearrangement of the propiolate $HC{\equiv}CCO_2Ar$ appears unexceptional, but the mechanism of the subsequent rearrangement of the proposed ring-opened species **64** is less clear. The dashed arrows about structure **64** merely indicate the 'overall bond changes'[15] involved in the formation of the lactone **65** (equation 46).



(63) (64) (65) (46)

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CHAPTER **20**

The preparation of allenes and cumulenes

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I. SCOPE OF THE REVIEW

Since the treatment of the chemistry of allenes and cumulenes appeared in this series in 1963[1] several review articles[2–4] and sections of books[5–8] have summarized the preparative developments in this rapidly expanding field. Furthermore, both The Chemical Society's *Annual Reports* and *Specialist Periodical Reports* (since 1973[9]) regularly contain chapters on the title compounds, so that the need for an additional survey may not be obvious.

However, most of these reviews are organized around specific *reaction* types whereas the following, for the first time, concentrates on various *structural* types. It is the author's opinion that it is not so much the development of new synthetic methods for the preparation of these compounds that has characterized the last decade (the literature covered here extends to the end of 1977, with occasional reference to work published in 1978), but rather the application of more or less established procedures to the deliberate preparation of certain types of allenic or cumulenic structures, e.g. cyclic or highly fluorinated ones.

The review does not include a section on the synthesis of naturally occurring allenes and cumulenes[10,11], although reference to this unusual class of natural products will be made at times.

Diastereomeric and enantiomeric allenes and cumulenes will be treated similarly, since this volume contains a separate chapter on this subject, and a recent review on the preparation of chiral allenes is available[12]. Finally, heterocumulenic systems, although of considerable current preparative interest[13,14], will be excluded altogether.

Each major section opens with a brief summary of the standard methods used in the preparation of allenes and cumulenes. The main emphasis will subsequently be on hydrocarbon systems and their functionalized derivatives. Allenes and cumulenes carrying hetero substituents will be organized according to the appearance of the respective substituent atoms in the Periodic Table.

II. THE PREPARATION OF ALLENES

A. Survey of General Methods

A very useful and comprehensive compilation of methods is available, which is sometimes overlooked in the Western literature, summarizing all allenic compounds which have been prepared up to the end of 1967[15]. The review includes detailed descriptions of experimental methods.

1. Allenes from olefins by elimination reactions

Since allenes are a special class of olefins it is not surprising to find many of the preparative procedures used for the synthesis of alkenes in allene chemistry also. Thus the elimination of halogen atoms with metals, hydrogen halides with bases or water with the aid of acids or catalysts, from suitable olefinic precursors have been applied extensively for the synthesis of allenes. These procedures, which have been reviewed in detail[1,2,5,7,8,15] are valuable for the preparation of simple and stable allenes and halogenoallenes (cf. Section II.D.6) but have been replaced by more selective ones in the case of polyfunctional or polyunsaturated systems. In these latter instances, because of the frequently quite harsh reaction conditions, secondary reactions may take place (isomerization, addition, polymerization) during elimination.

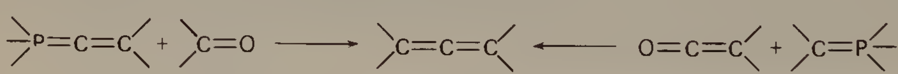
Elimination reactions are nevertheless receiving attention in modern allene chemistry. For example, novel base systems have been developed to induce the process. Thus 2-halogeno-1-*p*-nitrophenylpropenes are transformed in good yields to the corresponding allenes when treated with tetraethylammonium fluoride in acetonitrile or potassium fluoride in various solvents[16]. Another nonconventional base is potassium diphenylmethide in liquid ammonia which has been used to obtain several aryl-substituted allenes[17]. Novel leaving groups include triflate[18] and triphenylsilyl[19]. In earlier work it had already been shown that dihalogeno or halogeno olefins do not necessarily have to be used as substrates in elimination reactions (*inter alia* allenes from 2-chloro-2-alkenylphosphonic acids[20], bromo ethers[21,22]). In an unique and quite general 'double 1,2-elimination' allenes have been obtained by treatment of α,α'-dibrominated ethylene ketals with zinc in hexamethylphosphoric triamide or magnesium in tetrahydrofuran[23,24].

Surprisingly little is known about the detailed mechanisms (stereochemistry, kinetics) of the classical allene-producing elimination reactions. Only in rare cases such as the dehydrobromination of 4-bromo-4-octene under typical E_2 conditions has it been shown that the *cis* isomer prefers elimination to 3,4-octadiene in more than 85% yield (avoiding a *syn* elimination process), whereas the *trans* isomer yields 4-octyne in quantitative yield[25]. Vinyl halide involving S_N1/E_1 processes have only rarely been used for the synthesis of allenes, since the energy needed to produce the vinyl cation in the first step is too great. However, when the precursors carry cation-stabilizing substituents, allene production may occasionally compete favourably with side-reactions. For example, 2-bromo-4-methyl-1,3-pentadiene on solvolysis in 80% aqueous acetone buffered with triethylamine leads to 4-ethoxy-4-methyl-1,2-pentadiene in 55% yield[26].

2. *Allenes by Wittig and related reactions*

Although once thought to be of restricted importance in allene chemistry[27], the Wittig reaction has become increasingly popular in recent years, and is, in fact, the method of choice for the synthesis of various functionalized allenic systems, including the allene carboxylic acids and esters treated in Section II.B.6.

In its simplest form, either vinylidenephosphoranes (1) are reacted with ketones or methylenephosphoranes (2) with ketenes (equation 1)[8,14]. Both procedures,

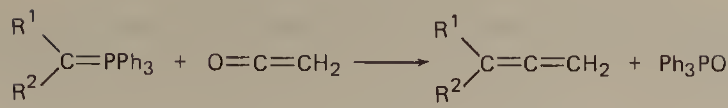


(1) (2) (1)

especially the second alternative, have been applied to the synthesis of aryl-substituted allenes (cf. Section II.B.3). Ketene itself undergoes a Wittig reaction when treated with 'stable' phosphonium ylids yielding the functionalized terminal allenes 3 (equation 2)[28].

Occasionally the ketenes are produced *in situ* as in the reaction of alkylidene-phosphoranes with carbon dioxide[29]. This procedure also allows the preparation of fully alkylated allenes (cf. Section II.C.3).

Possibly a variant of the Wittig reaction is the treatment of ketones of the general structure $R^1R^2CHCOCH_3$ with dibromotriphenylphosphine in the presence of triethylamine. The highest yields of terminal allenes $R^1R^2C{=}C{=}CH_2$ (50–70%) are again realized when one of the substituents is an ester or keto group[30].

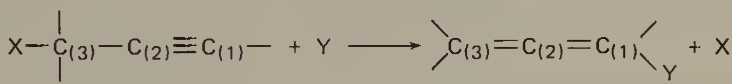


(3) (2)

R¹	R²	Yield 3(%)
H	CN	78
H	COMe	59
H	COOEt	64
Me	COMe	74
Me	COOEt	70
Me	COPh	80

3. *Allenes by propargylic rearrangements*

In a propargylic rearrangement an acetylene of the general formula **4** is reacted with a reagent Y and the allene **5** is produced (equation 3)[2]. Since the acetylenic



(4) (5) (3)

substrates are easily obtainable in most cases, the process is of great preparative value. The range of applicability of the process is broad since propargylic rearrangements are induced by numerous reagents and may take place by a plethora of mechanisms[2,31].

In the case where X = Y = H the isomerization constitutes a *prototropic* reaction, for X = Y = anion the process is said to be *anionotropic*, if X and Y are different groups the isomerization is known as a propargylic *displacement* reaction, and finally when the system **4** is incorporated into certain larger frameworks (see below) *intramolecular* rearrangements of the Cope- and Claisen-type may take place.

The *prototropic* rearrangement of acetylenic hydrocarbons with numerous base systems has been extensively used in the early days of allene chemistry[1,2,5,7,8,15]. Although quite useful for the synthesis of, for example, arylallenes (cf. Section II.B.3), alkyallenes, and especially polyunsaturated ones, are preferably prepared by other methods, since it is in practice difficult to stop the isomerization at the (thermodynamically unfavourable) allene stage[32,33]. The resulting mixture of isomers almost always requires special techniques like gas chromatography for separation, and for this reason the purity of the products isolated by distillation in some of the older literature should be viewed critically. On the other hand the process is very valuable for the synthesis of functionalized allenes, like allenic derivatives of nitrogen (cf. Section II.D.4), oxygen (Section II.D.5) and sulphur (II.D.5), to mention but a few.

Anionotropic rearrangements have been observed preferentially with propargyl halides and esters (acetates, benzoates, tosylates). The acetate or benzoate rearrangement, the so-called Saucy–Marbet reaction[34] is treated in detail in Section II.D.5. These isomerizations do not actually involve an intermolecular attack of an anion on a propargylic substrate as might be expected from equation (3), and in the cases where a detailed mechanistic study has been carried out, not even internal ion pairs could be detected.

In the propargylic *displacement* reaction a propargylic substrate is attacked by a nucleophile (which may be charged or not) and an anionic leaving group is set free (equation 4).

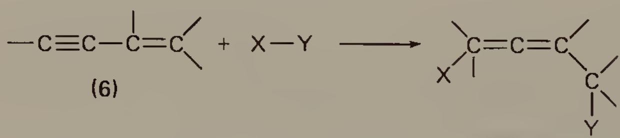

(4)

Again, the actual mechanism for a specific substrate may be entirely different. In the past, propargyl halides and alcohols have been used most often as starting materials for attack by various nucleophiles[2]. In more recent applications acetates and tosylates have been reacted with various organometallic reagents, especially organocopper compounds (cf. Section II.B.1).

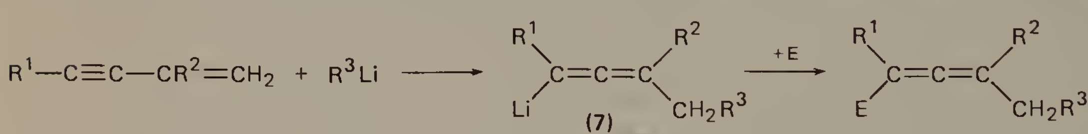
Intramolecular rearrangements involving the change of propargylic to an allenic unit have received increased attention in the last few years. Many diynes, enynes and allenynes undergo Cope-type isomerization reactions as discussed in another chapter in this volume. These rearrangements are however, not restricted to all-carbon systems as shown by the preparatively very useful Claisen isomerization of propargyl vinyl ethers to allenic aldehydes (cf. Section II.B.5.a). Other [3,3] sigmatropic changes have also been reported, e.g. [2,3] rearrangements of acetylenic sulphonium[35] and ammonium yields[36].

4. *Allenes by 1,4-addition reactions to enynes*

The 1,4-addition of a molecule X–Y to a conjugated enyne **6** provides a very useful method for the synthesis of functionalized allenes (equation 5). The reaction has been used successfully in the addition of polar reagents like hydrochloric[37] and hydrobromic acid[38] as well as of halogens[39,40].


(5)

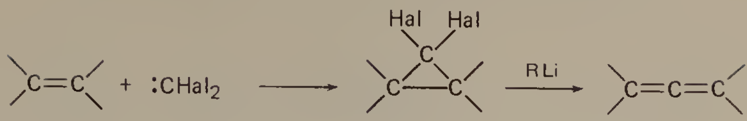
Of particular preparative value is the addition of organolithium compounds to conjugated enynes. This process leads initially to allenyllithium derivatives **7** which may be intercepted by a large number of electrophiles E (equation 6), among them


(6)

water[41,42], carbon dioxide[43], various aldehydes and ketones[44-46], epoxides[45,46] etc. Other additions involve α-chloro ethers[47], amines[48] and lithium dialkylamides[49]. Furthermore, allene-producing radical additions to vinylacetylene have been reported[50,51]. Since the 1,4-addition to conjugated enynes has recently been summarized (with inclusion of literature up to 1975[8]) this brief selection may suffice to illustrate the importance of the method.

5. *Allenes from 1,1-dihalogenocyclopropanes – the Doering–Moore–Skattebøl method (DMS method)*

The addition of dichloro- or dibromo-carbene to double bonds yields 1,1-dihalogenocyclopropanes **8** which, by treatment with a variety of reagents (e.g., lithium alkyls) are converted into allenes (equation 7).


(8) (7)

The reaction was originally discovered by Doering and coworkers[52], and later applied by many authors, notably by Moore[53] and Skattebøl[54] who introduced the use of lithium alkyls. Since each of these names has been attached to the reaction in the chemical literature, it is proposed to name it the Doering–Moore–Skattebøl synthesis (DMS synthesis) of allenes.

Among all approaches the DMS method possesses the greatest general applicability. It has been used for the preparation of a very large number of acyclic, mono-, bi- and poly-cyclic structures, functionalized or not, and has also proven to be useful for synthesizing cumulenes.

The dihalogenocarbenes may be prepared classically[55-57] by adding the haloform to a stirred solution of potassium *t*-butoxide, with the olefin and dry pentane kept below 0° C under phase-transfer conditions with triethylbenzylammonium chloride (TEBA) as catalyst[58] (this procedure is particularly simple when sodium trichloro- or tribromo-acetate is used as carbene precursor[59]) or by thermal decomposition of phenyl(trihalomethyl)mercury[60].

In a direct alkene to allene conversion the isolation of 8 is by-passed altogether by treatment of excess olefin with one equivalent of carbontetrabromide and two equivalents of methyllithium in ether at –65° C[61].

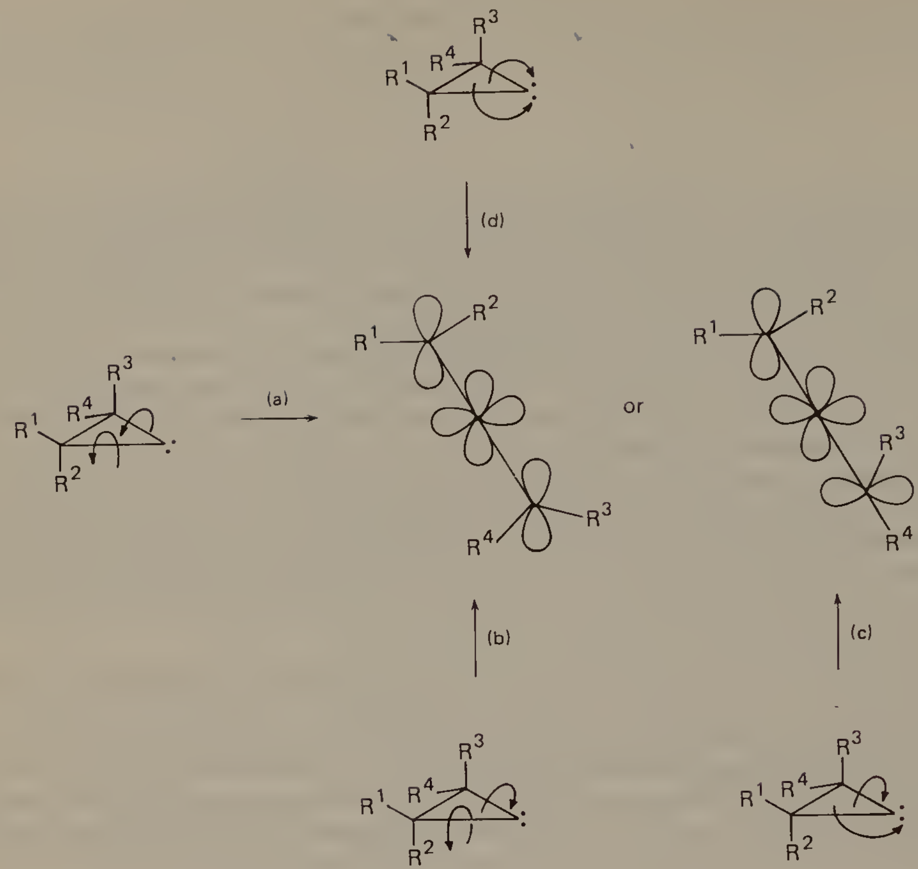
For the dehalogenation of 8 methyllithium in ether at reduced temperatures is most often used nowadays, since *n*-butyllithium may rearrange the allenes produced to their acetylenic isomers[62]. The dibromo derivatives of 8 are frequently preferred over the less reactive dichlorides, although the latter are often prepared in higher yields.

The conversion of 8 into the allene starts by a halogen–metal exchange, the radical character of which has been detected by chemically-induced dynamic nuclear polarization (CIDNP)[63]. Assuming that the subsequent transformation takes place via a free carbene, this species may undergo ring-opening by at least four pathways[64] (equation 8).

A conrotatory opening leads to either an orthogonal or a planar allene (path a), a disrotatory opening gives a planar allene (path b), a 'monorotatory' opening yields an orthogonal (path c), and a 'nonrotatory' opening a planar allene (path d).

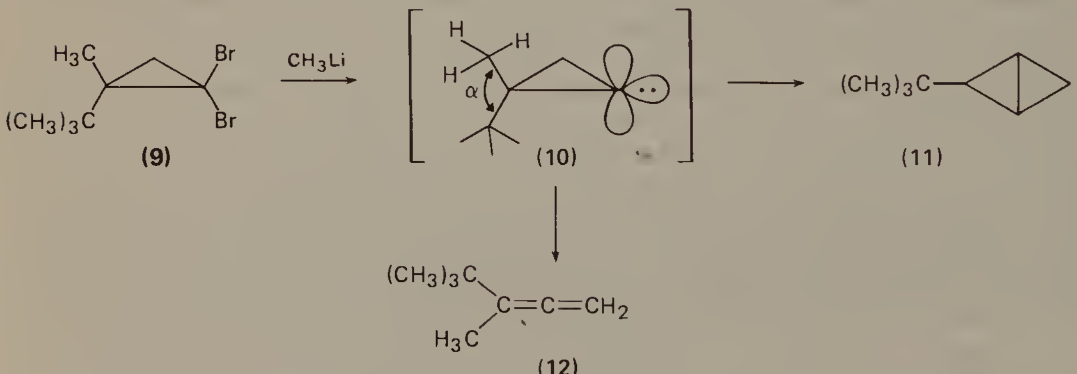
Experimental facts that may be reconciled with either of these modes are available[64]. Potential energy surfaces have been calculated for these four alternatives for both singlet and triplet cyclopropylidene by a Simplex–INDO study[64], and it has been concluded that for the case of singlet cyclopropylidene a 'mixed-mode of opening' is operating, the process beginning with a disrotatory movement, followed by a change of direction of rotation of one of the methylene groups, and ending by a conrotatory movement of the two substituent-carrying carbon atoms.

The DMS procedure occasionally gives rise to side- and unexpected products. For example, when the fully substituted 1,1-dibromo-2,2,3,3-tetramethylcyclopropane is reacted with methyllithium only a trace of the expected tetramethylallene is formed, while 1,2,2-trimethylbicyclobutane is formed in nearly quantitative yield[65,66]. Since other tetrasubstituted derivatives 8 show similar behaviour, but trisubstituted ones yield allenes again, it was once thought that tetrasubstitution is a prerequisite for this unusual behaviour[67]. In fact, reactions in which disubstituted cyclopropanes yield bicyclobutanes[68], and tetrasubstituted ones lead to allenes are known[69,70].



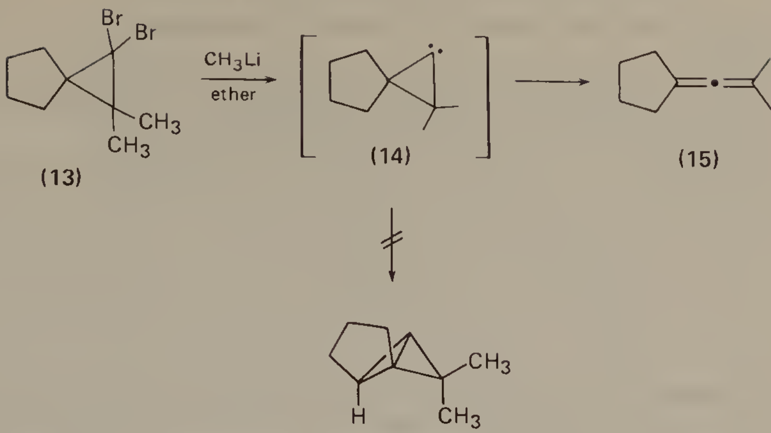
(8)

Thus 1,1-dibromo-2-*t*-butyl-2-methylcyclopropane (**9**) on dehalogenation with methyllithium furnishes a hydrocarbon mixture (70% raw yield) which consists of 1-*t*-butyl-1-methylallene (**12**) and 1-*t*-butylbicyclo[1.1.0]butane (**11**) in the ratio of 3:2 (equation 9)[68].



(9)

The so-called *geminate* dialkyl effect observed in this reaction operates only with sterically demanding substituents; the 1,1-diethyl derivative gives only allenic product. It seems reasonable that the large steric bulk of the *t*-butyl group causes a widening of the angle α in the intermediate **10** by which the carbon–hydrogen



(13) (14) (15) (16) (10)

bond of the methyl group is forced into better orientation for reaction with the empty p orbital of the carbene centre.

When the fully substituted dibromide **13** is treated with methyllithium the exocyclic allene **15** is produced in 60% yield (equation 10)[70]. Insertion of the cyclopropylidene **14** into one of the β-carbon–hydrogen bonds of the five-membered ring is avoided now, evidently because the bicyclobutane **16** which would be generated by such a process is too highly strained.

Another competing reaction frequently occurs when there are functional groups directly attached to the three-membered ring. For example, when 1,1-dibromo-2-methyl-2-isopropenylcyclopropane is reacted with methyllithium only 5% of the expected 3,4-dimethyl-1,2,4-pentatrine is produced whereas 3,4-dimethyl-1,3-cyclopentadiene is produced in 95% yield[71]. This ring-enlargement takes place by a vinylcyclopropylidene–cyclopentadiene rearrangement with subsequent carbon–hydrogen bond insertion as has been confirmed recently by a mechanistic study[72]. The formation of fulvenes during the dehalogenation of various 2,2,2′,2′-tetrabromobicyclopropyl derivatives can presumably be explained by an analogous mechanism (cf. Section II.B.2d)[73].

Intramolecular trapping of the cyclopropylidene by various other functional groups[74], including insertion into the nitrogen–hydrogen bond[75], has also been observed[76,77], as has the formation of 3-methyl-3-phenylpropynes as secondary products in the dehalogenation of 1-phenyl-2,2-dihalogenocyclopropanes with excess methyllithium[78,79].

As already pointed out, the cyclopropylidene–allene conversion is in most cases induced by treatment of 1,1-dibromocyclopropanes with methyl- and sometimes *n*-butyl-lithium. When the latter reagent is complexed with the chiral tertiary amine (–)-sparteine optically active allenic hydrocarbons may be prepared[12,80]. Other organometallic compounds and metals are also known to trigger this ring-opening[81], including several chromium(II) salts[82] and a chromium(III) chloride–lithium aluminium hydride reagent[83].

It should finally be pointed out that other methods exist, different in principle from those mentioned above, for the generation of cyclopropylidenes and hence allenes, among them the addition of atomic carbon to olefins (cf. Section II.A.6) and the decomposition of *N*-nitrosourea or *N*-nitrosocarbamate derivatives of cyclopropane under a variety of conditions[84–93]. The latter process is very important for preparing optically active allenes[90,91], and has provided a deeper understanding of the mechanism of the cyclopropylidene ring-opening process[64,92,93].

6. *Allenes by other reactions involving carbenoid intermediates*

Other reactions proceeding by way of carbene-like intermediates are the addition of carbon atoms to olefins and the dehydrohalogenation of 3-substituted 3-chloro-1-alkynes ($R_2CCl-C\equiv CH$) with strong bases (Hartzler reaction).

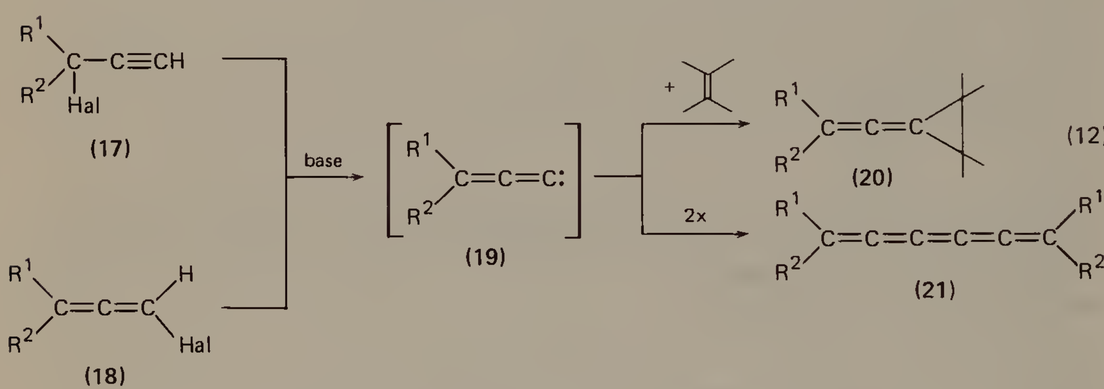
When carbon atoms are trapped by olefins, a cyclopropylidene is formed again, and the allene produced by ring-opening thereof (equation 11)[94-96]. Although the


(11)

process is of considerable theoretical importance, most allenes that have been prepared thereby may be obtained by simpler alternative procedures. On the other hand, 'double trapping' of the higher carbon homologue C_3 with unsaturated reagents has been applied to prepare some unusual allenic structures which are difficult to obtain by more conventional approaches (cf. Section II.C.3).

The primary reactions of free carbon atoms and the related chemistry of C_2, C_3 and C_2O has recently been reviewed[97].

In the Hartzler reaction the propargyl halides **17** or their isomeric allenes **18** are treated with a strong base like potassium *t*-butoxide in aprotic media, and vinylidenecarbenes **19** are generated by dehydrohalogenation (equation 12)[98]:



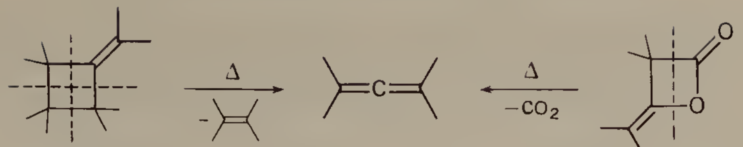
(12)

Since the carbenoid **19** may be trapped by various olefinic substrates to afford vinylidenecyclopropane derivatives **20** or dimerize to hexapentaenes **21** the reaction constitutes a valuable procedure for both the synthesis of allenic and cumulenic molecules (cf. Sections II.C.2a and III.A). Vinylidenecarbenes have been generated from many precursors other than **17** and **18**[98], but these two starting materials are of greatest practical importance because of their ready availability.

7. *Allenes by cycloreversion and fragmentation reactions*

The preparative importance of ring-cleavage reactions is limited, since the starting materials are frequently not easily prepared, and the reaction conditions so harsh as to partially destroy the product allenes by cycloaddition or polymerization reactions. However, these methods are valuable for the synthesis of certain unusually substituted allenes.

In most allene-producing cycloreversions four-membered ring compounds are thermally decomposed. These may be methylenecyclobutanes **22** or methylene

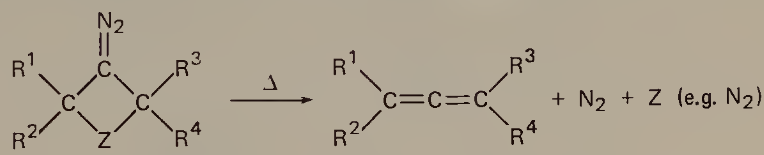


(22) (23) (13)

β-lactones **23** (equation 3). The cleavage of substrates **22** is only rarely as successful as in the pyrolysis of 3-methylene-1,2 bis(methoxycarbonyl)cyclobutane which affords the methyl ester of 2,3-butadienoic acid in 42% yield[99]. In most other cases the two modes of cleavage ('horizontal' or 'vertical') compete and cause the formation of product mixtures[99], not to mention the fact that methylenecyclobutanes are usually prepared from allenes and olefins[100]. In practice the thermal decomposition of the substrates **23** is more important, especially when highly substituted lactones are decomposed allowing the synthesis of otherwise difficult to prepare allenes[101,102]. Some applications of this reaction may be found in Sections II.B.2a, II.C.3, II.D.6a and b.

The Retro-Diels–Alder reaction, which has so far been of no importance for the preparation of allenes, allows the preparation of certain cumulenes that cannot be synthesized by other methods (cf. Section III).

Fragmentation reactions of the type shown in equation (14) are in principle very

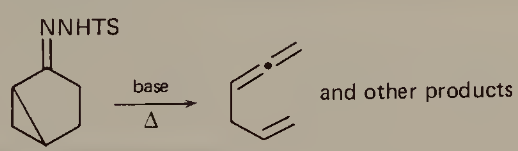


(14)

attractive since the energy required to produce the allene moiety is more than offset by the energy gained by the production of nitrogen or other stable molecules. Although some reactions of this type are known (cf. also Section III) the method does not qualify as general[103,104].

In most other known fragmentations reactions sodium salts of tosylhydrazones are decomposed thermally or photochemically[105,106]. Thus the bicyclic substrate **24** on heating with sodium methoxide in diglyme leads to 1,2,5-hexatriene (**25**), among other hydrocarbons (equation 15)[106].

Other examples may be found in Sections II.C.2c and II.C.2d.



(24) (25) (15)

8. *Allenes from other allenic systems*

Since most types of functionalized allenes are now readily available, preparative procedures that convert these into more complex allenic structures are bound to be of growing importance in this area of organic chemistry.

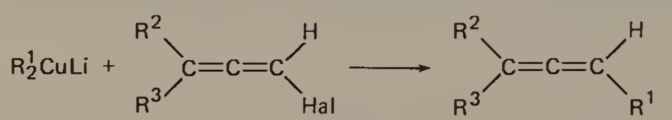
Two examples may serve to illustrate this point. When allene itself is lithiated in tetrahydrofuran at −70° C with *n*-butyllithium and the product allenic lithium reagent trapped with octyl bromide or iodide a mixture of the allene **26** and the alkyne **27** is formed in 86% yield, with the former product dominating strongly (equation 16)[107]. Repetition of the sequence allows the synthesis of allene **28** of

$$H_2C{=}C{=}CH_2 \xrightarrow[2.\ n\text{-}C_8H_{17}Hal]{1.\ n\text{-}BuLi} \underset{(\mathbf{26})\ (87\%)}{n\text{-}C_8H_{17}{-}CH{=}C{=}CH_2} + \underset{(\mathbf{27})\ (13\%)}{n\text{-}C_8H_{17}{-}CH_2{-}C{\equiv}CH} \qquad (16)$$

$$\mathbf{26} \xrightarrow[2.\ CH_3I]{1.\ n\text{-}BuLi} \underset{(\mathbf{28})}{n\text{-}C_8H_{17}CH{=}C{=}CHCH_3}$$

94% purity in 93% yield. In an extension of these reactions various bromoallenes were converted into their lithio derivatives by lithium or *n*-butyllithium treatment and alkylated to trisubstituted allenes[107].

Bromoallenes (cf. Section II.D.6c for preparation) are also used as starting materials in a reaction with lithium dialkylcuprates at low temperatures providing 1,3-di- and 1,1,3-trialkylallenes in good to excellent yield (equation 17)[108,109].



(17)

R^1	R^2	R^3	Yield (%)
Me	Me	Me	74
Me	Me	Et	85
Me	*n*-Pr	H	85
Me	*t*-Bu	Me	87
Et	Me	Me	51
Et	Me	Et	59
n-Bu	*n*-Pr	H	81
and others			

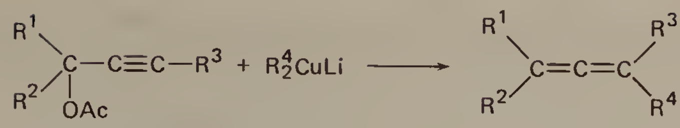
Further highly alkylated allenes are described in Section II.B.1.

B. Acyclic Allenes

1. *Alkyl-substituted allenes*

Many alkyl substituted allenes are listed in the tables of Reference 15. Most of them have been prepared by eliminations or propargylic rearrangements. However, these older methods are occasionally cumbersome and sometimes provide only poor yields. The following selection of recent methods tries to trace some of the more modern developments.

In a considerable number of these syntheses propargyl esters are used as starting materials. Thus the substituted propargyl acetate **29** reacts with lithium dialkylcuprates **30** to afford the alkylallenes **31** in fair to high yields (40–85%) (18)[110,111]. The reaction has been carried out predominantly with cyclic esters **29**, i.e. R^1 and R^2 form a molecular bridge and the products are hence vinylidene-



(29) (30) (31)

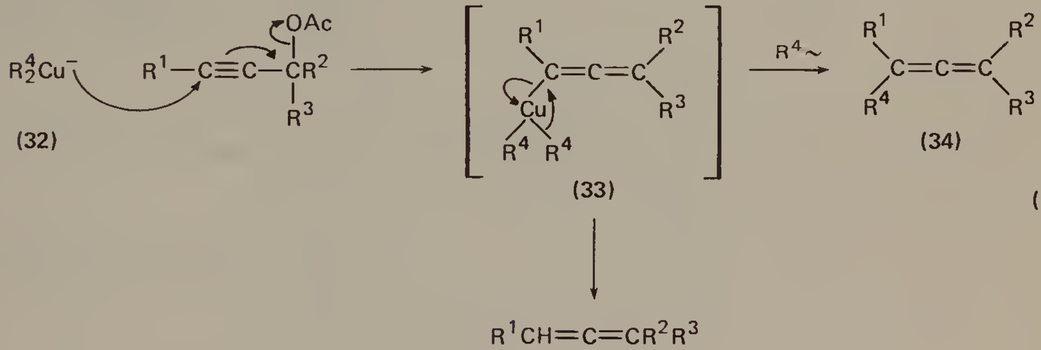
(18)

R^3 = H, Me, *n*-Bu

R^4 = Me, *n*-Bu

cyclopentanes, -hexanes and -heptanes (cf. also Section II.C.2c and d), but some acyclic allenes have also been prepared thereby[112]. Application of the procedure to appropriate derivatives of steroids[112] or prostaglandins[113] leads to the corresponding allenes.

Several mechanisms for this propargylic rearrangement have been considered[110,112,114], the most likely one[112] involving an organometallic intermediate **33**, formed by attack of the dialkylcopper anion **32** on the propargyl acetate (equation 19). Intermediate **33** may subsequently form the allene **34** by



(19)

(35)

alkyl migration from copper to the sp^2-hybridized carbon atom, while its hydrolysis produces the corresponding nonalkylated allene **35**. Since the rate of rearrangement may be slowed down by a decrease in reaction temperature the procedure allows the synthesis of nonalkylated and alkylated allenes, respectively, by suitable control of the conditions[114].

Mechanistically related to this reaction but of greater versatility is the treatment of acetylenic tosylates $R^1C{\equiv}C{-}CHR^2OTs$ (R^1 = H, alkyl, aryl, $H_2C{=}C(CH_3){-}$ or $CH_3C{\equiv}C{-}$; R^2 = H or *t*-Bu) with organocopper(I) compounds formed from Grignard reagents RMgCl or RMgBr (R = alkyl, aryl, 2-thienyl-) and cuprous bromide in tetrahydrofuran, for which the intermediacy of a copper(III) derivative is also likely. Yields of the trisubstituted allenes $RR^1C{=}C{=}CHR^2$ are excellent (80–90%), and the relative amount of contaminating acetylene normally less than 5%[115].

In still other variations 2-propynyl sulphinates $R^1{-}C{\equiv}C{-}C(R^2,R^3){-}OS(O)CH_3$ are converted into allenic hydrocarbons $RR^1C{=}C{=}CR^2R^3$ by treatment with organoheterocuprates (RCuBr)MgX in tetrahydrofuran, again a copper(III) species being most likely formed in the first step of this 1,3-substitution process[116]. Allenes are also formed when propargyl chlorides are treated with lithium dialkyl cuprates[109] and propargyl ethers with Grignard reagents in ether at room temperature in the presence of catalytic amounts of cuprous bromide[117].

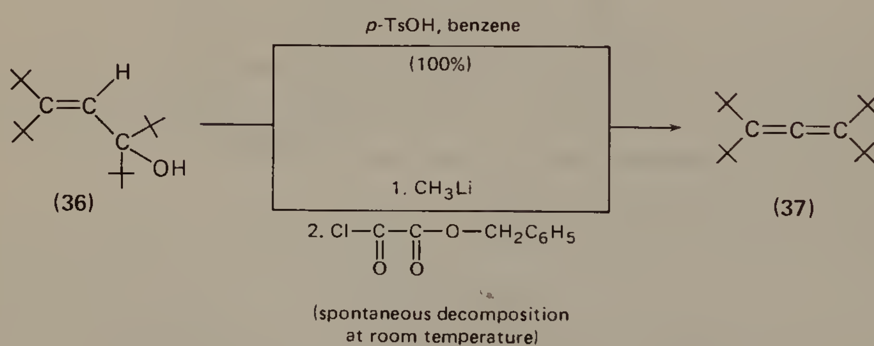
In an improvement of the Zakharova reaction (treatment of propargyl halides $R^1R^2CCl-C\equiv C-R^3$ with Grignard reagents[118]) ferric chloride is used as a catalyst, and this procedure is claimed to possess advantages over the already mentioned reactions using lithium dialkylcuprates as alkylating agents[119]. In a further extension, tetrasubstituted allenes with one substituent being aryl, vinyl, allyl or propargyl have been synthesized (for other procedures leading to these derivatives cf. Sections II.B.3 and II.B.2a and e respectively)[120,121]. Concerning the mechanism of this reaction a S_N2'-type process seems to be favoured[122] over processes involving vinylidenecarbene intermediates[123].

Hydride can also be employed as nucleophile and propargyl halides have been reduced to allenes with lithium aluminium hydride[124,125].

An interesting duality of reaction mechanisms has been observed when the acetates of tertiary propargyl alcohols $R^1R^2C(OAc)C\equiv CH$ are treated with methylmagnesium iodide[126–131]. When performing the reaction with a Grignard reagent prepared *in situ* and in the presence of one molar equivalent of magnesium iodide a methylallene $R^1R^2C=C=CHCH_3$ is formed by a radical pathway. If, on the other hand, the process is carried out with 'normally' prepared Grignard reagent and in the presence of four-fold excess of the iodide a mechanism involving cationic intermediates is preferred, and iodoallenes $R^1R^2C=C=CHI$ are produced. The reaction may also be carried out with other primary and some secondary Grignard reagents[132].

The reaction of lithium chloropropargylides with trialkylboranes which leads to alkylallenes via allenic boranes (cf. Section II.D.2) may be regarded as an intramolecular variant of the 1,3-substitution processes discussed here.

Introduction of the *t*-butyl group has often been of great value in reducing the reactivity of all kinds of hydrocarbons. Various *t*-butylallenes have been synthesized from the mono-*t*-butyl compound[133], various bis-[134–140] and tris-*t*-butyl derivatives[115,137] to tetrakis-*t*-butylallene (**37**) which has been prepared recently from the allyl alcohol **36** by elimination (equation 20)[141].



(20)

Allene **37** is one of the most unique allenes ever prepared: it does *not* react with ozone in methylene chloride at room temperature, *m*-chloroperbenzoic acid in refluxing chloroform, bromine or chlorine in refluxing carbon tetrachloride, potassium–sodium alloy (not even when dibenzo[18]crown-6 is added), and other reagents which attack normal allenes vigorously. One reason for this chemical inertness is of course the steric shielding of the allene part of the molecule by the space-filling substituents. Furthermore, as indicated by model considerations, any attack at the central allene carbon atom would increase the steric hindrance between the bulky substituents, and is hence disfavoured. (This may in fact partly explain why **37** is formed from **36** or its derivatives at all.)

Other allenes substitued with voluminous groups are also known, e.g. mesityl-[142] and various adamantyl-[143,144] allenes.

2. *Allenes carrying unsaturated substituents*

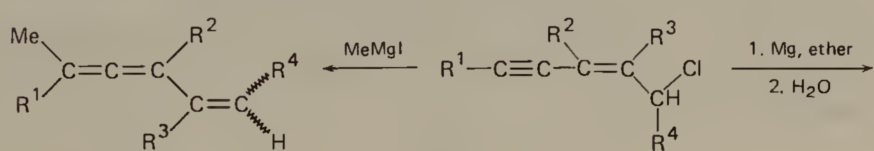
a. Vinylallenes. These constitute a unique class of unsaturated compounds, since 1,2,4-pentatriene is the smallest molecule conceivable that at the same time contains a cumulenic and a conjugated diene system. The vinylallene unit is part of various natural products and recently there has been considerable research activity in this area of allene chemistry. Several general approaches for synthesizing vinylallenes have been developed.

Treatment of various (readily available) 4-alken-1-ynes (**38**) with a solution of 5% sodium hydroxide in methanol under reflux leads to the vinylallenes **39** in good to excellent yield (equation 21)[145]. The mechanism of this isomerization has been investigated by the same authors[146].

$$\underset{(38)}{R^1{-}CH{=}CH{-}CHR^2{-}C{\equiv}CH} \xrightarrow{\text{base}} \underset{(39)}{R^1{-}CH{=}CH{-}CR^2{=}C{=}CH_2} \qquad (21)$$

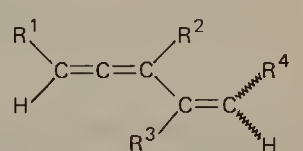
R¹	R²	Yield (%)
H	H	80
Me	H	70
Et	H	70
i-Pr	H	70
H	Me	70
Me	Me	40
H	Pr	40

In the second and third general methods (which also start from easily available materials) α-chloroenynes **40** are either treated with methylmagnesium iodide in ether under reflux for 3–4 hours (formation of **41**) or are converted to their Grignard derivatives, which are subsequently hydrolysed (formation of **42**). Yields are good in both cases (equation 22)[147,148].



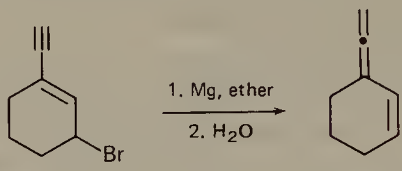
(41) (40) (22)

R¹	R²	R³	R⁴	Yield (%) 41	Yield (%) 42
H	H	H	H	22	31
H	H	H	Me	50	40
H	Me	H	H	52	47
H	Me	Me	H	75	55
Me	H	H	H	28	52
H	Me	Me	Me	78	–



(42)

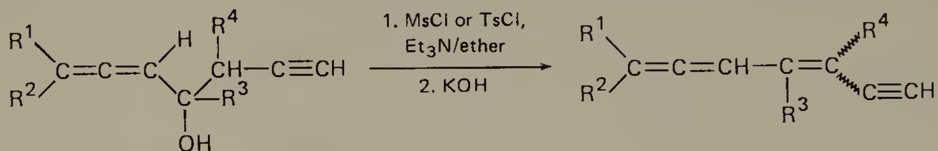
The method is also applicable to various cyclic enynehalogenides. For example from the bromo derivative **43** 3-vinylidenecyclohexene (**44**) can be prepared in 30% yield using the Grignard procedure (equation 23)[148].



(23)

(43) (44)

Higher unsaturated hydrocarbon systems include the chiral 1,3,4,6-heptatetraene (divinylallene)[149], and several 1,2,4-triene-6-ynes (**46**; allenenynes), the latter being prepared in moderate to good yields from the α-allenic alcohols **45** (equation 24)[150].



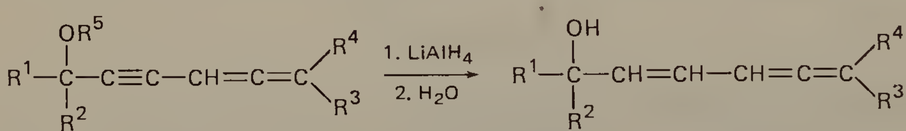
(24)

(45) (46)

R^1	R^2	R^3	R^4	Yield (%)
H	Me	Me	H	35
H	n-C_8H_{17}	Me	H	39
Me	Me	Me	H	70
Me	Me	H	H	65
Me	Me	H	Me	52
Me	Me	Me	Me	35

Mono- and bi-cyclic vinylallenes (with an exocyclic vinylallene system) have been obtained by subjecting 5-halogeno-3-en-1-ynes (general structure **40**) to strong bases (potassium *t*-butoxide or sodium hydroxide under phase-transfer conditions) and intercepting the vinylallene carbenes thus generated with styrene, cyclohexene, tetramethylallene *inter alia* [151] (cf. Section II.C.2a).

Among the functionalized vinylallenes, the α-alcohols **48**, prepared by lithium aluminium hydride reduction of the propargyl allenic alcohols **47** or their acetates are noteworthy (equation 25)[152,153].

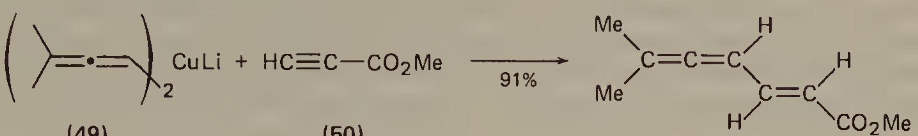


(25)

(47) (48)

R^1	R^2	R^3	R^4	R^5	Yield (%)
Me	Me	Me	Me	MeCO	85
Me	Me	t-Bu	t-Bu	MeCO	83
Me	Me	c-Hex	Mex	H	80
c-Hex	c-Hex	Me	Me	H	60
Me	Me	Me	Ph	H	50
Ph	H	Me	Me	H	60

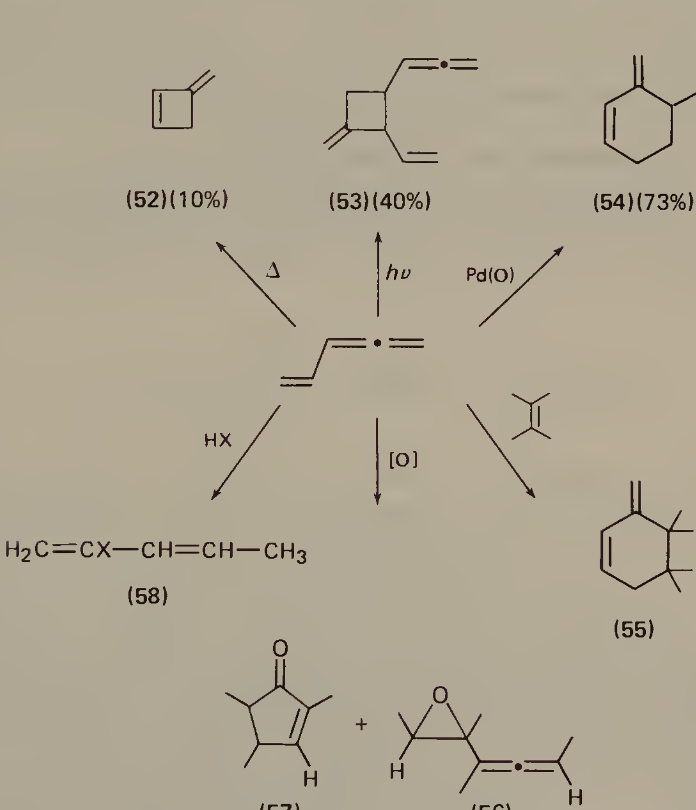
A promising method for introducing substituents into the 1,2,4-pentatriene framework consists in adding cuprates like **49** to unsaturated esters like methyl propiolate (**50**) (equation 26)[154].



(49) (50) (51) (26)

Vinylallenes carrying phosphorus substituents have been prepared by reacting vinylethinylcarbinols with diphenyl- or diethoxychloro-phosphines[155].

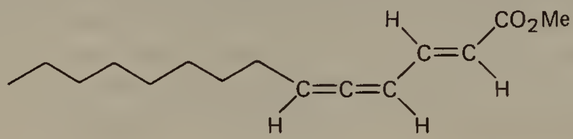
The chemical behaviour of vinylallenes has been studied extensively during the last few years (equation 27). On pyrolysis the parent compound[156] as well as its 4-methyl derivative cyclize to 3-methylenecyclobutenes (**52**)[157]. Sensitized photodimerization yields various products, among them *cis*- and *trans*-3-allenyl-2-vinyl-methylenecyclobutane (**53**)[158]. Catalytic dimerization with a trisisopropyl-



(52)(10%) (53)(40%) (54)(73%) (58) (55) (57) (56) (27)

phosphine-modified Pd(0) catalyst furnishes several dimers, with 3-methylen-4-allenylcyclohexene (**54**) dominanting strongly (73%)[159]. With various double-bond dienophiles vinylallene prefers the [2 + 4] cycloaddition mode, i.e. the Diels–Alder adducts **55** are formed exclusively[160–163]. Epoxidation[164,165] with *p*-nitroperbenzoic acid provides α-allenic oxiranes **56** or cyclopentenones **57** (*see below*), the product ratio being determined by the degree of substitution on the olefin and allene part of the molecule. Cyclopentenones are also formed in fair to good yields (20–60%) during the acetoxymercuration of 1,2,4-pentatrienes[166]. Hydrochloric and hydro bromic acid react readily with vinylallenes providing principally *cis*- and *trans*-2-halogeno-1,3-pentadiene derivatives 58[167]. The Grignard derivatives of these unsaturated hydrocarbons (prepared from 5-halogeno-3-alken-1-ynes, **40**; *see above*) have been reacted with oxiranes[168] and numerous aldehydes and ketones[169–171]. The resulting unsaturated alcohols are useful substrates for syntheses in the pheromone area.

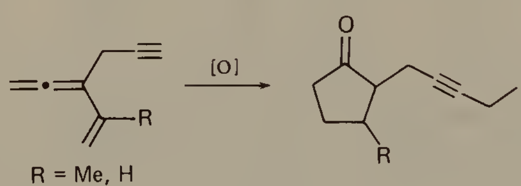
The vinylallenic ester (–)-methyl *n*-tetradeca-*trans*-2,4,5-trienonate (**59**) has been isolated from the male dried bean beetle (*Acanthoscelides obtectus*), and is presumed to be a sex attractant. This is thought to be the first example of an allenic compound occurring in the animal kingdom. Since its isolation and structure elucidation[172] at least five syntheses have appeared in the chemical literature[154,173–176].



(59)

The observation that many natural products of plant origin contain an isobutylamide group conjugated with a *trans* double bond has lead to the synthesis of various 2,4,5-trienamides as potential insecticides[177].

In other natural products work, vinylallenes have been converted by the above epoxidation–cyclization reaction (which presumably occurs via the transposition of an intermediate vinylcyclopropanone) to ketones of the dihydrojasmone type[178] and to dehydrojasmon (**60**, R = Me) and normethyldehydrojasmon (**60**, R = H) (equation 28)[179].



(28)

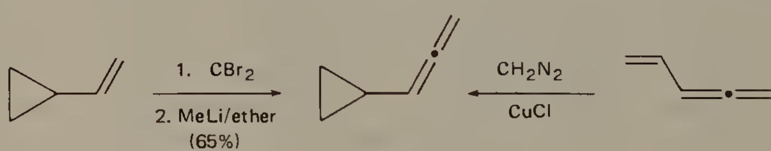
(60)

R = CH_3: 45%

R = H: 70%

It may finally be noted that the 1,2,4-pentatriene system is part of the fungal metabolite mycomycin[180], and that on irradiation of Vitamin D_3 two stereoisomeric vinylallenes (9,10-secocholesta-5(10),6,7-trienes) are produced[181,182].

b. Cyclopropylallenes. The parent molecule cyclopropylallene **61** (1,2-propadienylcyclopropane) is most readily obtained by applying the DMS procedure to vinylcyclopropane[183,184] or by cyclopropanating vinylallene with diazomethane in the presence of catalytic amounts of cuprous chloride (equation 29)[185]. Various

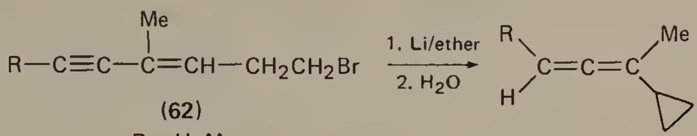


(29)

(61)

alkyl derivatives of **61** are known, e.g. 2,3-butadienylcyclopropane[186], *cis*-(1,2-butadienyl)-2-methylcyclopropane[187], *trans*-(2,3-butadienyl)-2-methylcyclopropane[188] as well as 1,1-dichloro[189,190] and 1,1-dibromo[191] derivatives, all having been prepared by methods analogous to the ones given for the parent molecule.

In a different route to cyclopropylallenes, whose preparative potential has not been explored, the enyne bromides **62** (R = H, Me) were first treated with lithium in ether and the resulting lithium organic compounds then hydrolysed (equation 30)[192].

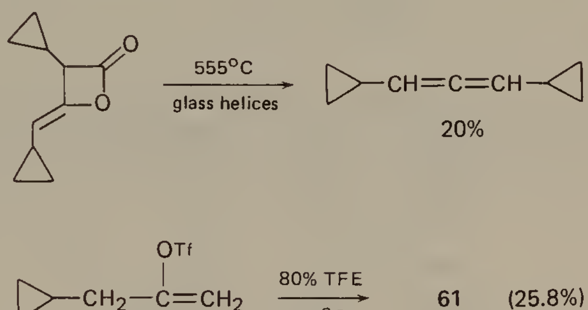


(62)
R = H, Me

R = H: 30%
R = Me: 27%

(30)

Cyclopropylallenes have furthermore been isolated as side-products in the pyrolysis of cyclopropylketene dimer[193] and the solvolysis of various cyclopropylvinyl triflates (equation 31)[194]. For example when the triflate **63** is solvolysed in 80%



(63)

(31)

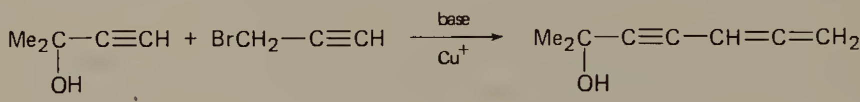
aqueous trifluoroethanol buffered with pyridine for three days at 80° C the parent system **61** is formed in 25.8% yield, the main product (57%) being 3-cyclopropylpropyne[194]. Depending on the type of substituent present, cyclopropylallenes on heating undergo a vinylcyclopropane-type rearrangement[184,188,195,196] or various isomerization reactions involving hydrogen shifts[187,188] (cf. Chapter 15).

c. Ethinylallenes. Interest in this class of allenes stems from the fact that the allenyne unit has been discovered as an important structural feature of various mould metabolities[197]. Of the various methods proposed[198] to prepare this system only the copper-catalysed coupling of appropriate alkynic and allenic substrates seems to possess general applicability. The simplest representative of this group, 1,2-pentadiene-4-yne (ethinylallene) was prepared by the reductive elimination of 3-chloro-1,4-pentadiyne with activated zinc in *n*-butanol (equation 32)[199].

$$HC{\equiv}C{-}CHCl{-}C{\equiv}CH \xrightarrow{Zn} H_2C{=}C{=}CH{-}C{\equiv}CH \qquad (32)$$

Base-catalysed isomerization of diynes, while in principle possible, suffers from the disadvantage that the prototropic process may not or only partially be stopped at the allenyne stage. The resulting mixtures are almost always difficult to separate. The base-induced rearrangement of 1,4-nonadiyne to 1,2-nonedien-4-yne with aqueous sodium hydroxide solution constitutes one of the more successful examples of this method of preparation (yield 44%)[200].

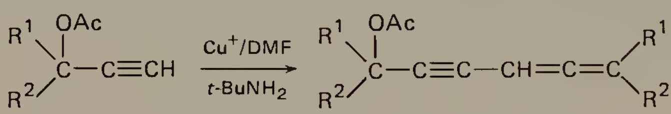
In the majority of cases the coupling reaction has been applied to the preparation of allenynic alcohols. When, for example, 2-methyl-3-butyne-2-ol (**64**) is reacted with propargyl bromide in aqueous ammonia in the presence of a catalytic amount of cuprous chloride the dienynic alcohol **65** is formed in 70% yield (equation 33)[201].


(33)

(64) (65)

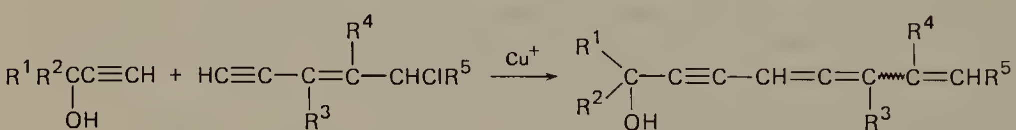
The amount of product formed depends on the kind of base (ammonia being preferred), the substitution of the alcohol, and the leaving group of the propargyl halide; yields are good to excellent.

In a modification and extension of this reaction propargyl acetates were catalytically dimerized (equation 34)[202].


(34)

R^1	R^2	Yield (%)
Me	Me	78
Me	Et	65
$-(CH_2)_5-$		73
Me	*t*-Bu	60
Me	Ph	80

Various types of vinylallenynols **67** were obtained analogously by coupling of propargyl alcohols with functionalized enynes **66** (equation 35)[202].


(35)

(66) (67)

R^1	R^2	R^3	R^4	R^5	Yield (%)
Me	Me	Me	Me	Me	70
Me	Me	$-(CH_2)_4-$		Me	60
Ph	Me	Me	Me	Me	68
c-C_3H_5	Me	Me	$-(CH_2)_4-$		80

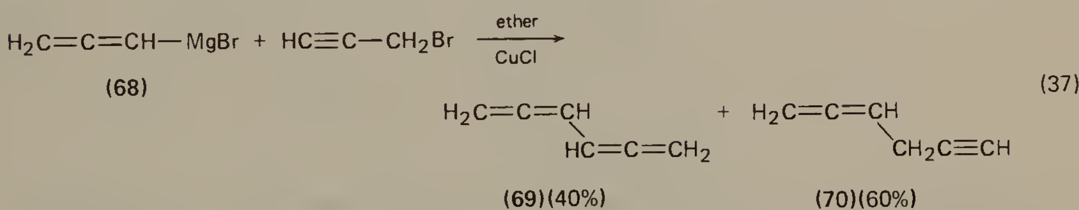
Instead of using propargylic substrates allenic halides may also be reacted with ethynyl compounds in the presence of cuprous ions and a suitable base (equation 36)[198]. 1-Iodo- and 1-bromo-3-monoalkylallenes give best yields and purest products by adding one equivalent of aqueous ethylamine or *t*-butylamine to one

$$RR^1C{=}C{=}CHX + HC{\equiv}C(CH_2)_nR^2 \xrightarrow[\text{base}]{Cu^+} RR^1C{=}C{=}CH{-}C{\equiv}C(CH_2)_nR^2 \quad (36)$$

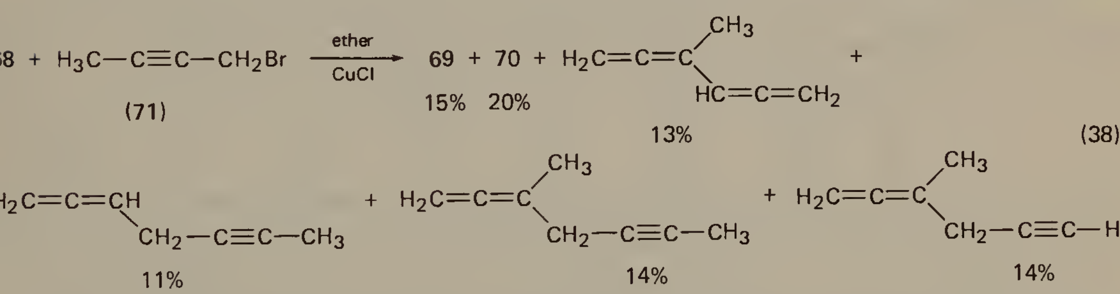
equivalent of cuprous chloride or bromide in *N,N*-dimethylformamide followed by an excess of the terminal acetylene compound and one equivalent of the halogenoallene. Depending on the substituents in the two coupling partners yields are generally between 40 and 70%.

d. Diallenes – (i) Conjugated diallenes. Although there are scattered reports in the older literature[203–205] describing the preparation of molecules that contain two directly joined allene units the systematic investigation of this interesting class of compounds is of recent origin.

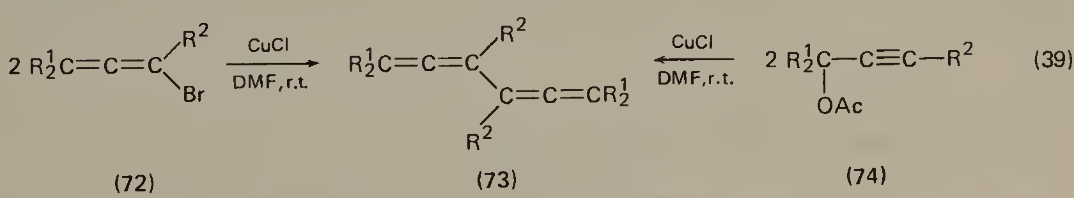
The parent system 1,2,4,5-hexatetraene **69** (biallenyl) is most readily prepared by coupling allenylmagnesium bromide **68** (the Grignard reagent of propargyl bromide) with propargyl bromide in ether in the presence of CuCl (equation 37)[206]. The other main product of the reaction is 1,2-hexadiene-5-yne (**70**), which,



however, does not interfere during most reactions of **69** (*see below*). When the same method is extended to alkyl-substituted propargyl halides complex hydrocarbon mixtures results. For example reaction of **68** with 1-bromo-2-butyne (**71**) leads to at least six products, all formed in similar yields (equation 38)[207]. On the other



hand, diallenes carrying aryl substituents (**73**) may be prepared in good yields (up to 72%) by a formally related coupling reaction in which bromoallenes **72** or prop-2-ynyl acetates **74** are treated with CuCl in DMF at room temperature (equation 39)[208].

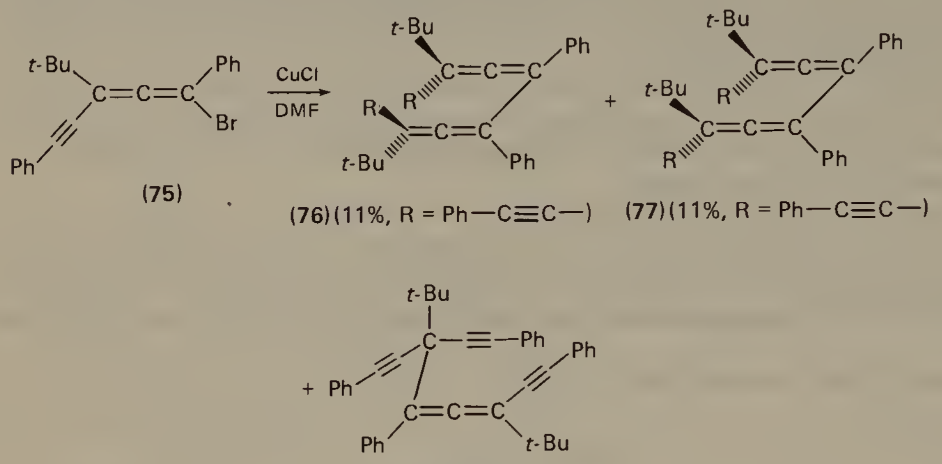


(a) $R^1 = R^2 = Ph$

(b) R^1_2 = biphenyl-2,2′-diyl, $R^2 = Me$

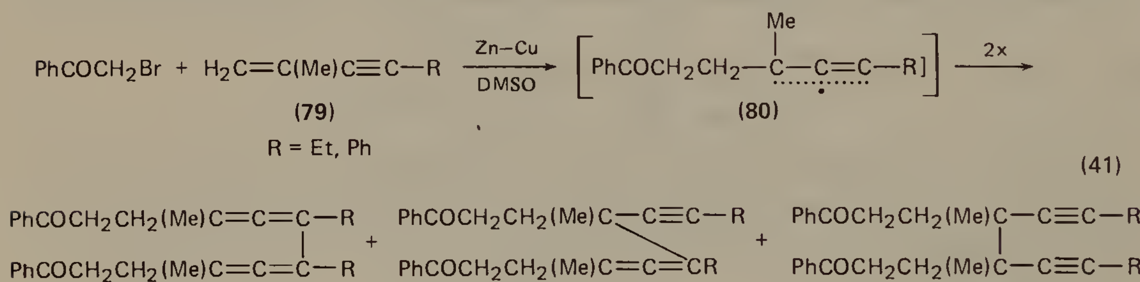
(c) R^1_2 = biphenyl-2,2′-diyl, $R^2 = Ph$

When the ethinylallene **75** is treated with CuCl/DMF according to the same procedure *d,l*- **76** and meso-3,8-di-*t*-butyl-1,5,6,10-tetraphenyldeca-3,4,6,7-tetraene-1,9-diyne (**77**) as well as 3,6-di-*t*-butyl-1,5,8-triphenyl-6-phenylethinyl-octa-3,4-diene-1,7-diyne (**78**) result (equation 40)[209,210].



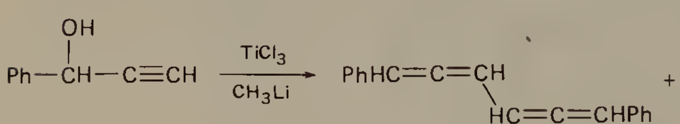
(75) (76)(11%, R = Ph—C≡C—) (77)(11%, R = Ph—C≡C—) (78)(54%) (40)

In another novel coupling reaction, the propargyl radical **80** is produced by the addition of phenacyl bromide to an enyne **79** in the presence of a zinc–copper couple in DMSO (equation 41)[211]. The dimers **81–83** are formed in 78% (R = Et) and 91% (R = Ph) yield, the pure isomers being obtained by column chromatography on silica gel.



(79) R = Et, Ph (80) (41) (81) (B2) (83)

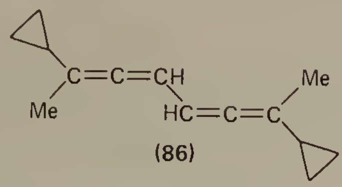
When α-acetylenic alcohols, e.g. 1-phenyl propargyl alcohol (**84**), are subjected to a coupling procedure originally developped by van Tamelen and coworkers[212] diallenes (e.g. 1,6-diphenyl-1,2,4,5-hexatetraene, **85** are formed in small yield (equation 42)[213]. The dicyclopropyl derivative **86** has been analogously synthesized.



(84) (B5)(B%)

PhHC=C=CH—CH(Ph)C≡CH + HC≡C—CH(Ph)CH(Ph)C≡CH (42)

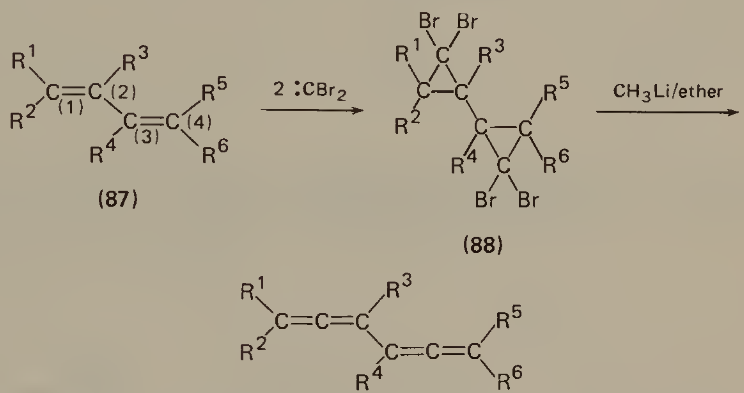
10% B%



(86)

Although convenient in certain cases (*see above*) coupling reactions leading to diallenes suffer from the lack of generality of the method as well as the frequent production of mixtures of isomers.

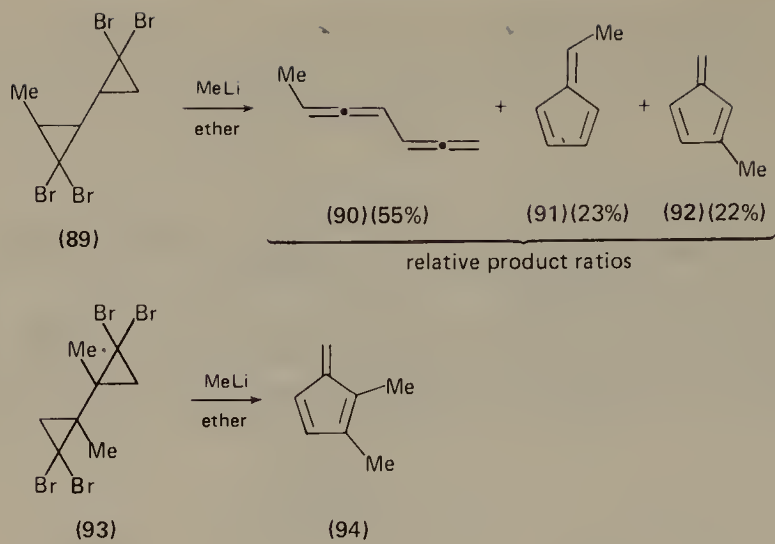
A synthesis which has some general applicability involves the addition of dibromocarbene to a diene (**87**) followed by reaction of the bis adducts **88** with methyllithium, i.e. the DMS allene synthesis (equation 43)[214,215]. As shown in equation (43) both alkyl- and aryl-substituted diallenes may be prepared; the



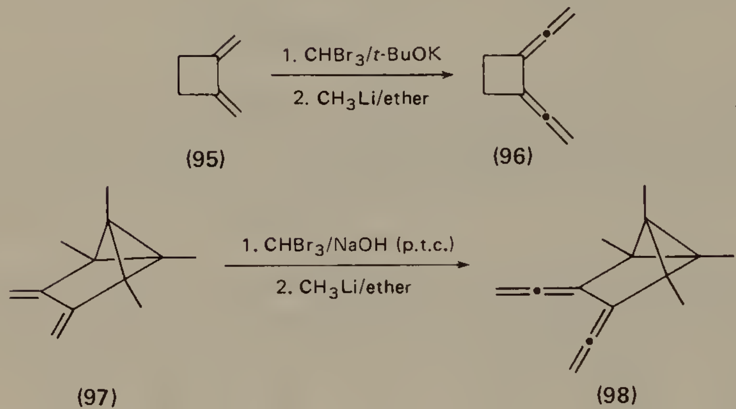
(43)

R^1	R^2	R^3	R^4	R^5	R^6	Yield (%)
Me	Me	H	H	Me	Me	93
Et	Me	H	H	Me	Et	82
Ph	Me	H	H	Me	Ph	90
t-Bu	Me	H	H	Me	*t*-Bu	91

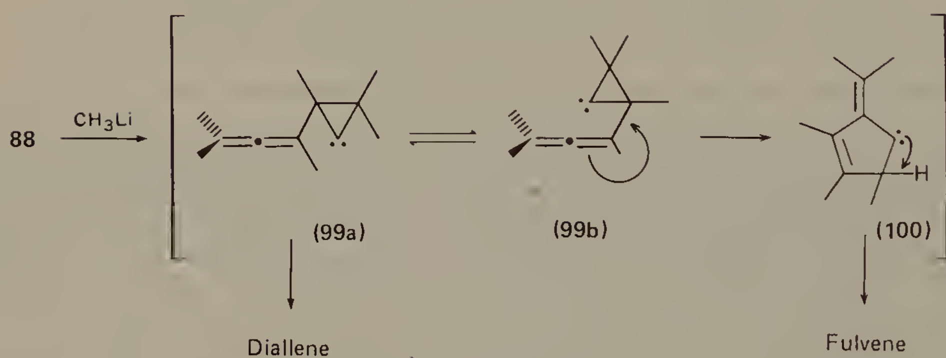
dibromocarbene may be either generated from bromoform with potassium *t*-butoxide or under phase-transfer conditions [bromoform–pentane/50% aqueous sodium hydroxide solution/triethyl-benzylammonium chloride (TEBA)]. With acyclic dienes substituted fully at $C_{(1)}$ and $C_{(4)}$ the yields are excellent. When the number of substituents is reduced or $C_{(2)}$ and $C_{(3)}$ are the substituent-carrying carbon atoms a side-reaction leading to derivatives of fulvene may compete with diallene production and even become the sole observable process. For example when the bisbromocarbene adduct of 1,3-pentadiene (**89**) is dehalogenated with methyllithium in ether the product mixture contains besides the desired 1,2,4,5-heptatetraene (**90**) the two methylfulvenes **91** and **92** (equation 44)[207]. In the case of 1,1′-dimethyl-2,2,2′,2′-tetrabromobicyclopropyl (**93**) 1,2-dimethylfulvene (**94**) is the only volatile product isolated (equation 44)[73]. When $C_{(2)}$ and $C_{(3)}$ of **87** are joined by a short molecular bridge, as in **95**, or by certain polycyclic ring-systems (**97**) diallene formation leading to **96**[216] and **98**[58], respectively, is again favoured (equation 45). It is very likely that these reactions proceed in a stepwise fashion via allenylcyclopropylidene intermediates **93** (equation 46)[215], and it could well be



(44)



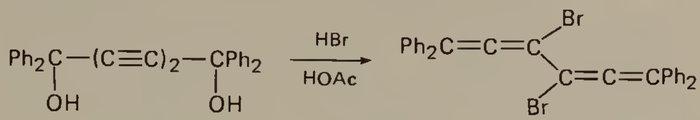
(45)



(46)

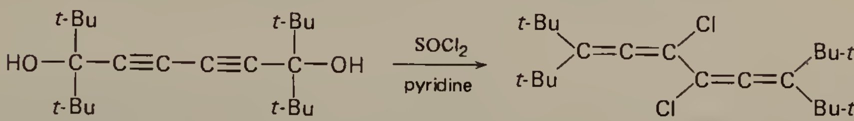
that the diallenes are formed from the transoid conformation **99a** whereas the cisoid intermediate **99b** undergoes what amounts to a vinylcyclopropane rearrangement to the isomerized carbenes **100**. These could then stabilize themselves to fulvenes by an insertion reaction. It is reasonable to assume that the **99a** ⇌ **99b** equilibrium is influenced by steric interference of interal substituents as well as the build-up of strain during the **99b** → **100** interconversion[217].

Diallene syntheses in which the starting material already contains the required number of carbon atoms are also known. For example 1,1,6,6-tetraphenyl-3,4-dibromo-1,2,4,5-hexatetraene (**102**) is prepared in 80% yield by treating the diol **101** in acetic acid with concentrated hydrobromic acid at 0° C for 30 minutes (equation 47)[218]. Similarly, diol **103** is converted into the tetra-*t*-butyldiallene with thionyl chloride in pyridine (0° C, 2h, 34%)[219].



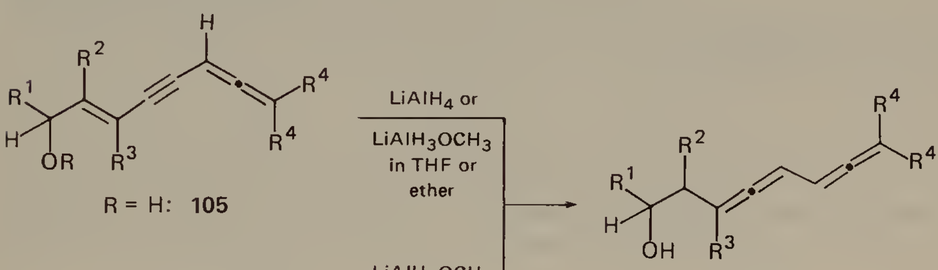
(101) (102)

(47)



(103) (104)

When the highly unsaturated alcohols **105** or acetates **106** are reduced with lithium aluminium hydride reducing agents the functionalized diallenes **107** result in 50 to 75% yield (equation 48)[220,221].



R = H: 105

R = C(=O)—CH3: 106

(107) (48)

(a) $R^1 = R^4 = Me$, $R^2 = R^3 = H$

(b) $R^1 = Me$, $R^2 = R^3 = H$, $R^4—R^4 = —(CH_2)_5—$

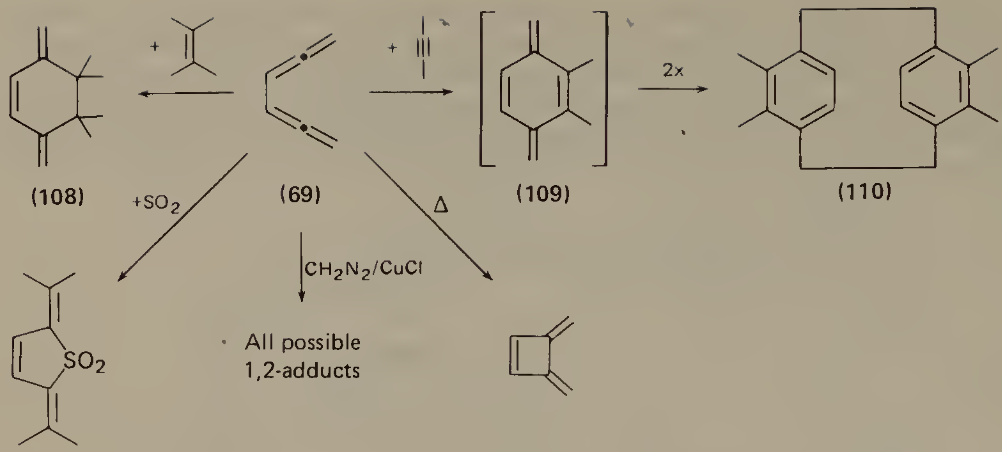
(c) $R^1 = R^2 = H$, $R^3 = R^4 = Me$

(d) $R^1 = R^2 = R^3 = R^4 = Me$

(e) $R^1 = R^2 = R^3 = Me$, $R^4—R^4 = —(CH_2)_5—$

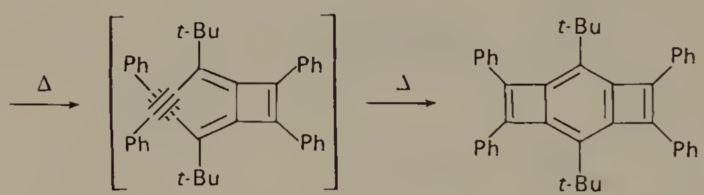
(f) $R^1 = H$, $R^2 = R^3 = R^4 = Me$

Origin for the interest in conjugated diallenes is the unique π-electron system of these compounds: they are at the same time conjugated and cumulenic dienes, and hence one might *a priori* expect to observe both [2 + 2] and [2 + 4] cycloaddition reactions, the typical reactions of allene and 1,3-butadiene (out of which **69** is formally composed). In fact, in most addition reactions, diallenes prefer the Diels–Alder mode. For example, with double-bond dienophiles the Diels–Alder adducts **108** result[73,222], whereas the reaction with various triple-bond dienophiles opens up a particularly simple pathway to derivatives of [2.2] paracyclophane **110** (yield 20–50% depending on dienophile), *p*-xylylenes **109** being the presumed intermediates (equation 49)[223,224]. Reactions with sulphur dioxide at room



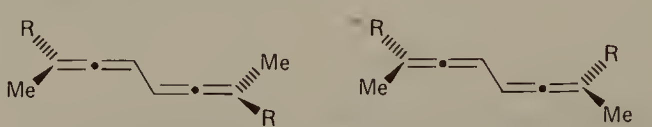
(108) (69) (109) (110) (112) (111) (49)

temperature leads also to 1:1 adducts, that is to say 2,5-bis(alkylidene)-2,5-dihydrothiophene-1,1-dioxides (**112**) in good yields (70–85%)[215]. Treatment of the parent hydrocarbon **69** with diazomethane in pentane in the presence of CuCl affords all possible cyclopropanation products[225]. When diallenes are heated to approximately 100° C they quantitatively cyclize to 3,4-bismethylenecyclobutene (**111**) and its derivatives[206,218]. The same process may also be brought about by CuCl catalysis[214,226]. This type of isomerization was used in the first synthesis of a benzo[1,2:4,5]-dicyclobutene **113**[209]. For that purpose hydrocarbons **76** or **77** were heated in an aromatic solvent (equation 50).



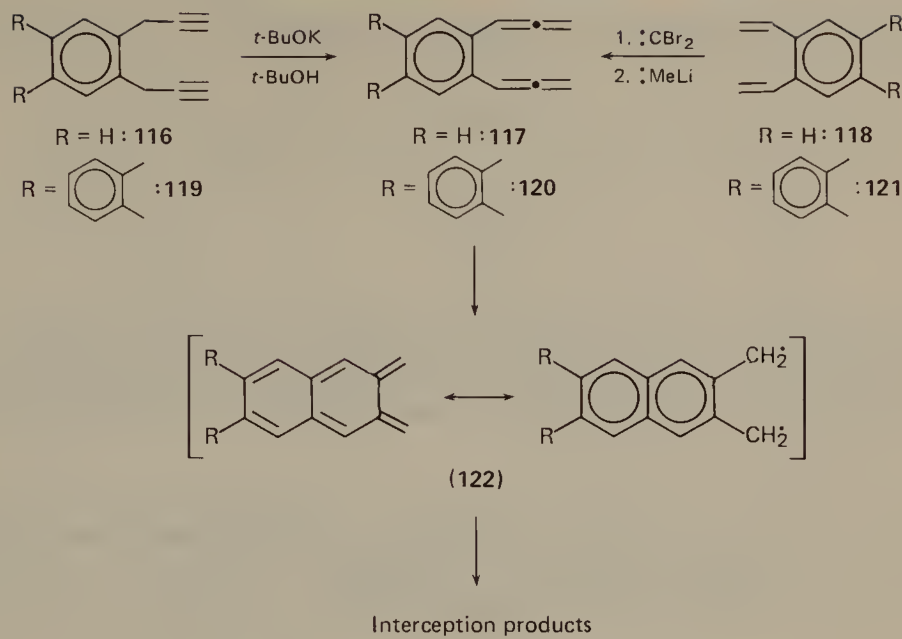
(113) (50)

A final point of interest is the stereochemistry of substituted diallenes: they may occur as either *meso* compounds (**114**) or *d,l* pairs (**115**), and in fact several pure *meso* diallenes are already known[209,215,227,228].



(**114**) (*meso*) (**115**) (*d,l*)

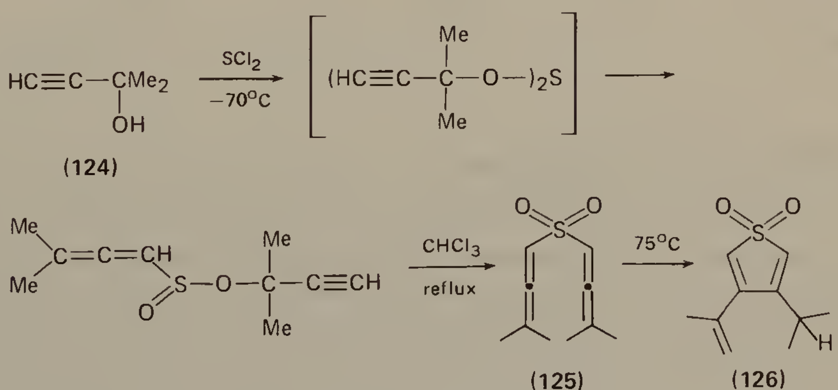
A different type of conjugated diallene, one in which the two allene moieties are separated by an aromatic ring system, has been obtained by either base-catalysed rearrangement of *o*-dipropargyl-benzene **116** and naphthalene **119**, respectively, or by subjecting the corresponding divinyl arenes **118** and **121** to the DMS allene synthesis (equation 51)[229]. On standing, the aromatic diallenes **117** and **120** cyclize to *ortho*-quinodimethanoid systems **122** which may be intercepted by various reagents (oxygen, dimethyl fumarate, dimethyl maleate)[229]. The parent



(51)

system 1,2,4,6,7-octapentaene has been proposed as an intermediate in the base-catalysed isomerization of *cis*-4-octene-1,7-diyne[230].

(ii) Diallenes of the type $H_2C{=}C{=}CH{-}X{-}CH{=}C{=}CH_2$ ($X = CH_2$: **123**). Besides the parent system 1,2,5,6-heptatetraene (**123**) which has been obtained in small yields by base-catalysed rearrangement of 1,6-heptadiyne or from 1,4-pentadiene by the DMS method[231], several diallenes in which X represents various hetero-atoms or functional groups are known. The diallenic sulphone **125** is formed from 2-methyl-3-butyne-2-ol **124** and sulphur dichloride via a double [2,3] sigmatropic rearrangement of the initially formed propargylic sulphoxylates (equation 52)[232,233]. On gentle heating **125** undergoes quantitative cyclization to the

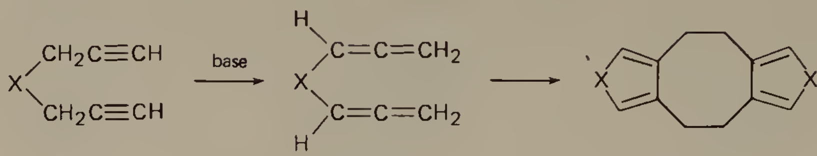


(52)

thiophene-1,1-dioxide **126** providing a novel access to an otherwise difficult to obtain class of compounds.

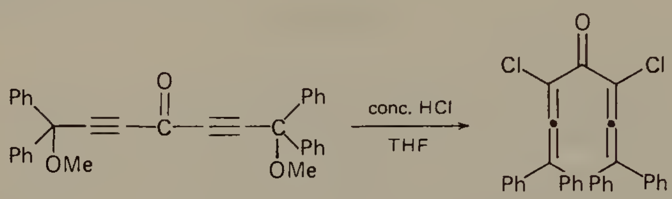
Both the bispropadienyl sulphide **128** (X = S) and ether **128** (X = O) have been synthesized by isomerizing the corresponding dialkynes **127** (X = S,O) with various base systems[234,235]. The allenes are unstable and on standing gradually undergo dimerization to bisthienocyclooctadiene **129** (X = S) and bisfurocyclooctadiene

129 (X = O), presumably via the 3,4-dimethylenethiophene and furane diradicals, respectively (equation 53).



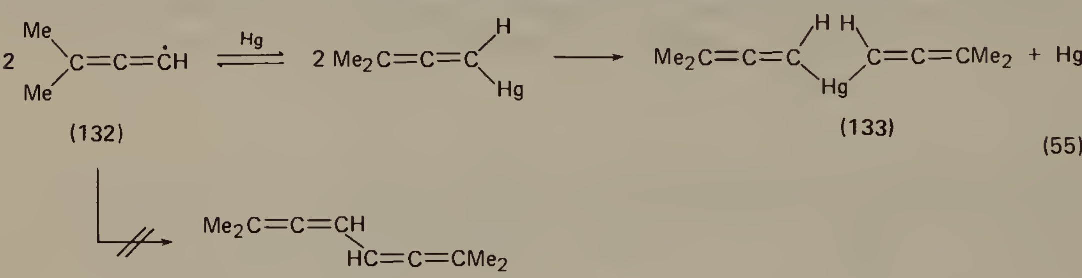
(127) X = S, O (128) X = S, O (129) X = S, O (53)

The only example of an acyclic dialleneketone seems to be 3,5-dichloro-1,1,7,7-tetraphenyl-1,2,5,6-heptatetraene-4-one (**131**) produced in varying amounts (15–30%) by treatment of the diacetylenic ketone **130** with concentrated hydrochloric acid in THF (equation 54)[236].



(130) (131) (54)

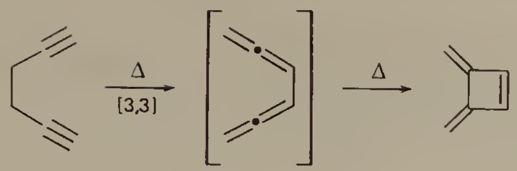
It may finally be noted that the mercury compound **133** is produced during the electrochemical reduction of 3-bromo-3-methyl-1-butyne or its isomer 1-bromo-3-methyl-1,2-butadiene on a mercury electrode in DMF[237]. The organometallic diallene could arise by attack of the allenyl radical **132** on mercury, although it is surprising that the direct coupling product of **132**, the diallene **134**, is not isolated, although it is one of the most stable diallenes known (equation 55).



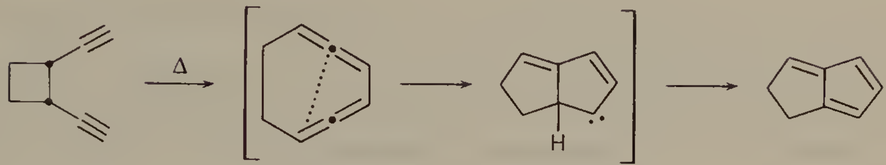
(132) (133) (134) (55)

(iii) Conjugated diallenes as reaction intermediates. Conjugated diallenes have been postulated to occur as intermediates in various reactions, the most thoroughly investigated ones so far being thermal and base-catalysed rearrangements of alkynes.

The parent system 1,2,4,5-hexatetraene (**69**) is presumably formed in the first step of the thermal isomerization of 1,5-hexadiyne (**135**) to 3,4-bismethylenecyclobutene (**111**)[206,238] (equation 56). Similar [3,3] sigmatropic processes have been described for a substantial number of derivatives of **135**, both acyclic and cyclic ones. For example on pyrolysing the 'bridged' 1,5-hexadiyne *cis*-1,2-diethynylcyclobutane (**136**), 1,2-dihydropentalene (**139**) is formed in more than 90% yield. The most likely precursor for this hydrocarbon is the (not isolable) cyclic diallene **137**, which by a 1,5-bridging step can form a vinylcarbene **138** that inserts into the neighboring C—H bond to form **139** (equation 56)[239].

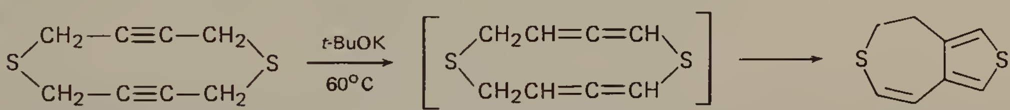


(135) (69) (111)



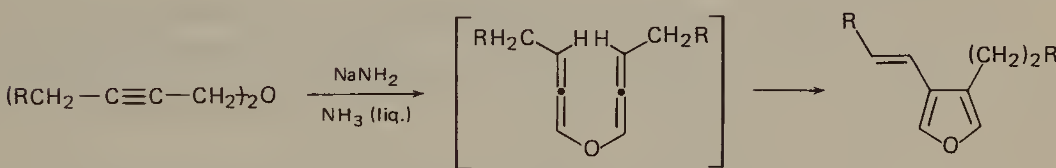
(136) (137) (138) (139) (56)

Base-catalysed rearrangements of appropriate dialkynes to diallene intermediates have also been observed on several occasions. For example 1,6-dithiacyclodeca-3,8-diyne **140** is isomerized by potassium *t*-butoxide in *t*-butanol to **142**, with the diallene **141** as the most reasonable precursor (equation 57)[240]. Similarly, bis-



(140) (141) (142)

(57)

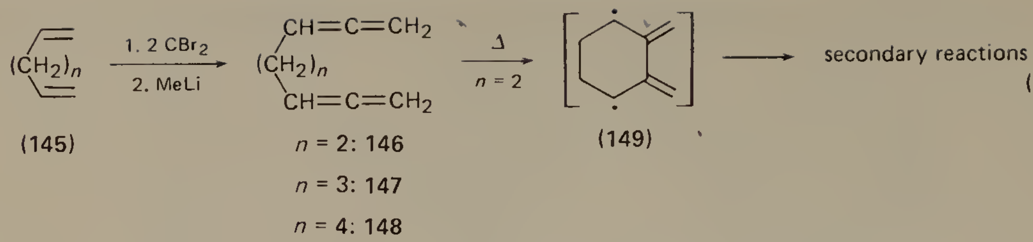


(143) (144)

R = H, Et

2-alkynyl ethers (**143**) rearrange under the influence of alkali amide in liquid ammonia to the vinylfuranes **144**[241]. More recent examples include the isomerization of 4-methyl-4-penten-2-ynyl propynyl ether to 6-methyl-4,5-dihydroisobenzofuran and 5-methyl-1,3-dihydroisobenzofuran[242], the reaction of 1,5-di-*t*-butyl-3-bromo-1,4-pentadiyne with sodium sulphide to thieno[c]cyclobutene derivatives[243], and the base-catalysed isomerization of various bispropargyl sulphides, ethers and amines to a host of new heterocyclic systems[244,245]. Some of the diallenic intermediates postulated in these interconversions have meanwhile been isolated and characterized, e.g. **128** (X = S,O)[234,235].

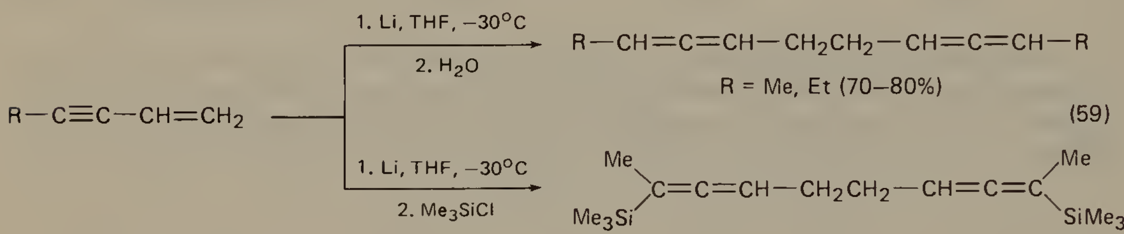
(*iv*) α, ω-*Diallenes*. 1,2,5,6-Heptatetraene (**123**) is the first member of the homologous series $H_2C{=}C{=}CH{-}(CH_2)_n{-}CH{=}C{=}CH_2$ (α, ω-diallenes). The homologues with n = 2,3 and 4 (**146**–**148**) have been prepared by the DMS method from the corresponding α,ω-dienes **145** (equation 58)[74]. The thermal behaviour of **146** has attracted the interest of various groups[246,247] since by an intramolecular allene dimerization the intermediate 2,3-dimethylene-1,4-cyclohexadiyl (**149**) is



(58)

produced which can serve as a model for the diradicaloid species formed in the dimerization of allene itself[100].

A novel and promising method for the preparation of derivatives of **146** consists in the treatment of enynes with lithium followed by demetalation of the first-formed coupling products with water or trimethylsilyl chloride (equation 59)[248]:



(59)

(v) Cyclic diallenes. Besides the not isolated and/or nonisolable cyclic allenes already referred to (e.g. **137**, **141**) several stable cyclic molecules which contain more than one allene or cumulene group are known. They are discussed in Sections II.C.1 and III.C.1.

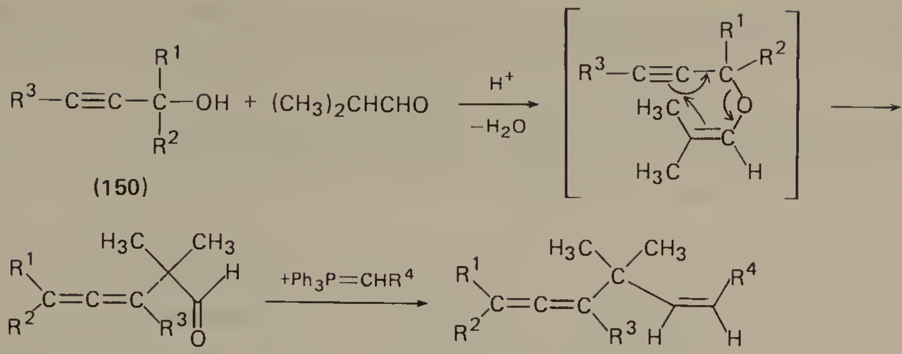
e. Allylallenes. Allylallenes **152** (1,2,5-hexatrienes) have been prepared by various methods (coupling of allenylmagnesium bromide with allyl bromide[249], thermal rearrangement of appropriate enynes[250], solvolysis of homoallenyl brosylates[251], DMS synthesis applied to the 1,4-pentadiene system[74]), but in all these methods isomeric side-products may be formed, and often their general applicability has not been explored.

The most general procedure to date is apparently the reaction of β-allenic aldehydes **151** with Wittig reagents (equation 60)[252]. The starting aldehydes are obtained by a Claisen–Cope rearrangement of the vinyl propargyl ether formed on acid-catalysed condensation of α-acetylenic alcohols (**150**) with isobutyric aldehyde[253] (cf. Section II.B.5 on allenic aldehydes and ketones). The yield of the **151** → **152** conversion is satisfactory (~50%), and simple distillation suffices to purify the allylallenes.

In a more recent report the synthesis of functionalized allylallenes (e.g. **155**) by treatment of various dienoic esters (e.g. **153**) with 1-trialkylsilylpropynyl copper derivatives **154** has been described (equation 61)[254].

Novel hydrocarbons of this general type are 1,2,5,7-octatetraene (**157**), obtained by thermolysis of *cis*-1-allyl-2-ethynylcyclopropane (**156**) (equation 62)[255], and 1,1-diallylallene produced as side-product (15–18%) in the reaction of allylzinc bromide with propargyl bromide in tetrahydrofuran[256].

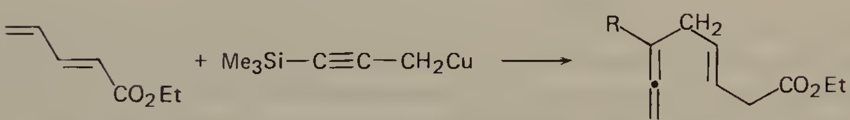
The most frequently studied reaction of allylallenes so far is their oxidation with *p*-nitroperbenzoic acid in methylene chloride which leads to various products, among them derivatives of bicyclo[3.1.0]hexan2-one[257,258]. The photochemical behaviour of 1,1,4,4-tetramethyl-6-phenyl-1,2,5-hexatriene has also been investigated[259,260].



(150)

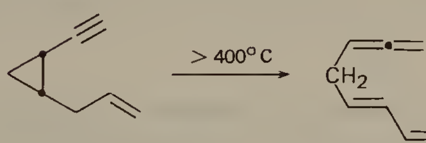
(151) (152) (60)

R¹	R²	R³	R⁴
H	H	H	H
Me	H	H	H
Me	Me	H	H
$-(CH_2)_5-$		H	H
Me	H	Et	H
Me	Et	H	Me
and others			



(153) (154)(3·5 equiv.) (155) (61)

R = Me₃Si—, 64%

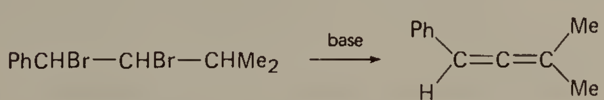


(156) (157)(37%) (62)

3. *Aryl-substituted allenes*

Aryl-substituted allenes have been known since the early days of research about molecules with cumulenic bond systems, and hence much information about them may be found in the older review literature[1,2,5,15]. For their synthesis many of the general procedures presented in Section II.A have been applied.

Thus elimination of two equivalents of hydrobromic acid from 1,2-dibromo-3-methyl-1-phenylbutane (**158**) with various base systems furnishes 1-phenyl-3,3-dimethylallene (**159**), the best yields (65%) being obtained with sodium amide/sodium *t*-butylate in tetrahydrofuran at 60° C (equation 63)[261].



(158) (159) (63)

Likewise, the 2-bromo-1-propenes **160** are readily converted to the corresponding allenes **161** when refluxed with ethanolic potassium hydroxide (equation 64)[262].

$$(p\text{-}R^1C_6H_4)_2CH{-}CBr{=}C(C_6H_4R^2\text{-}p)_2 \xrightarrow[\text{EtOH}]{\text{KOH}} (p\text{-}R^1C_6H_4)_2C{=}C{=}C(C_6H_4R^2\text{-}p)_2 \quad (64)$$

(160) (161)

R^1 = H

R^2 = CH_3, Br, Cl

Almost 100% yield

The Wittig reaction has been applied successfully to the synthesis of arylallenes in several instances. For alkylated systems this methods frequently suffers from the fact that the reaction conditions required to decompose the betain intermediate are so harsh that the allenes produced are destroyed by polymerization and other processes[27]. The more stable arylallenes, however, survive the procedure. For example, when the betaine **162** is heated to 150° C under high-vacuum conditions, 1,1-dimethyl-3,3-diphenylallene (**163**) is formed in 64% yield (equation 65)[263].

$$Ph_3\overset{+}{P}{-}CMe_2{-}C(O^-){=}CPh_2 \xrightarrow{\Delta} Me_2C{=}C{=}CPh_2 \quad (65)$$

(162) (163)

1,1-Dimethyl-3-phenyl-3-mesitylallene is prepared analogously in 50% yield by heating the corresponding phosphonium betaine to 160° C[263].

An interesting extension of this method consists in heating the ylids **164** in the presence of benzalanilins **165** (equation 66)[264].

$$RCH_2\overset{-}{C}H{-}\overset{+}{P}Ph_3 + PhCH{=}NAr \xrightarrow{\Delta} Ph_3P + H_2NAr + RCH{=}C{=}CHPh \quad (66)$$

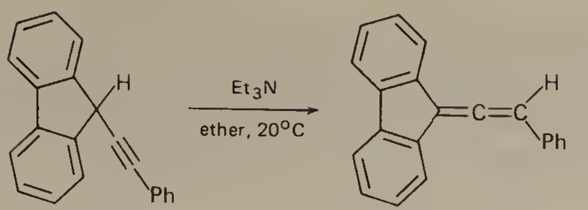
(164) (165)

R	Ar	Yield (%)
H	Ph	43
Me	Ph	45
Et	Ph	47
H	p-$CH_3C_6H_4$	29

Base-catalysed propargylic rearrangements have been used for example for the synthesis of 1-phenyl-3,3-biphenylallene (**167**) from 9-phenylethynylfluorene (**166**)[265], and 1,1,3-triphenylallene (**169**) from 1,3,3-triphenylpropyne (**168**) (equation 67)[266].

Among the more recent methods for synthesizing arylallenes the acid-catalysed dienone–phenol rearrangement ought to be mentioned. Treating the dienone **170** for two hours with a mixture of trifluoroacetic anhydride/boron trifluoride etherate results in the formation of 3-allenylmesitol (**171**) as the sole reaction product (67%) (equation 68)[267,268].

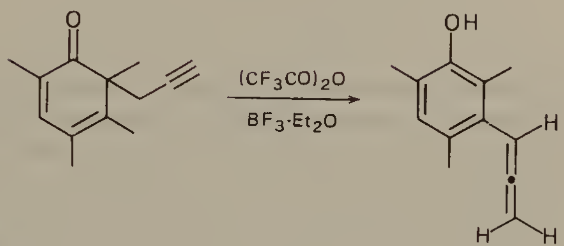
This method has been applied to a wide variety of dienones providing arylallenes with substituents both in the aromatic and allenic parts of the molecule. Other



(166) (167)(58%) (67)

$$HCPh_2C{\equiv}C{-}Ph \xrightarrow[20^{\circ}C]{\text{basic alumina}} Ph_2C{=}C{=}CHPh$$

(168) (169)(84%)

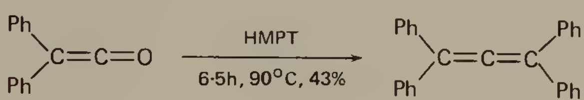


(170) (171) (68)

novel isomerization reactions include the silver tetrafluoroborate-catalysed rearrangement of propargyl phenyl ethers[269], and the photoisomerization of various 1- and 2-alkylated 1,2-dihydronaphthalines[270,271].

The simplest arylallene, phenylallene, is among the products formed in the solvolysis of certain phenylvinyl trifluoromethanesulphonates[272].

One of the oldest arylallenes (and allenes as such) is tetraphenylallene (173)[273]. Of the various methods known for its preparation a recently described one is particularly simple (equation 69)[274].



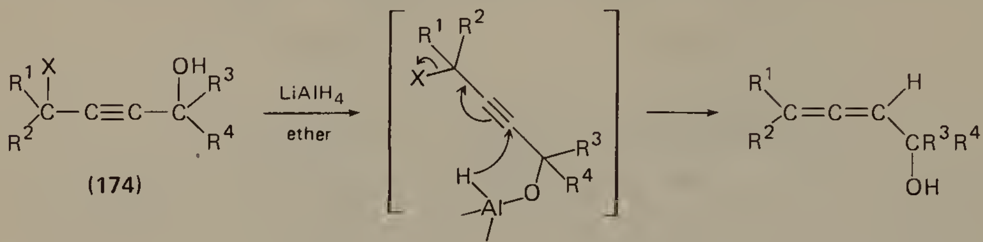
(172) (173) (69)

4. *Allenic alcohols*

a. α-Allenic alcohols. α-Allenic alcohols are of interest as starting materials in other synthetic work [275–278] and as substrates for various mechanistic studies[279–281]. Many natural products and pharmaceutically interesting compounds contain an α-allene alcohol moiety, e.g. grasshopper ketone, fucoxanthin, neoxanthin (cf. Section II.C.2d), various antiinflammatory drugs etc.[282].

A recent review article is devoted solely to the description of synthetic methods[282]. From this collection, only a few will be presented here, all involving a propargylic rearrangement.

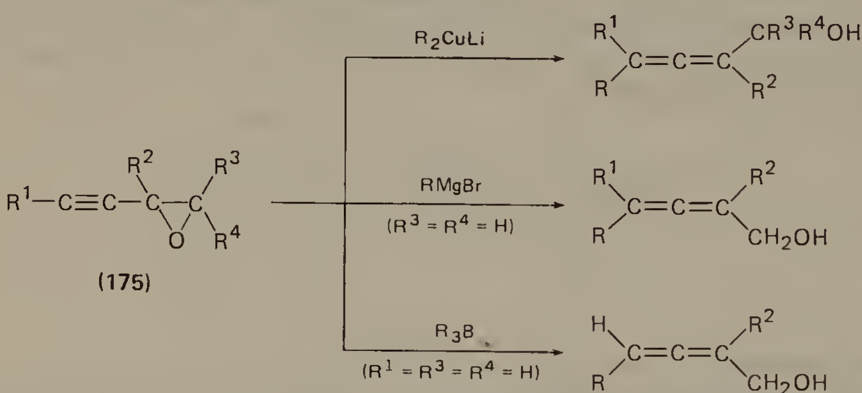
The reaction of acetylenic derivatives of the general structure **174** with lithium aluminium hydride in ether or tetrahydrofuran has proven to be particularly valuable. The starting materials are easily available in most cases, and the yields are often good to excellent. The reaction proceeds via an S_N2'- type mechanism, and since the attacking nucleophile is formally a hydride ion, the allene obtained always carries one hydrogen atom (equation 70). Among the leaving groups X tested are: Cl[283,284], tetrahydro-2-pyranyloxy (X = OXy-THP)[285], tetraalkylammonium[279,286], methoxy[287], *t*-butoxy[287] and others[287].



(70)

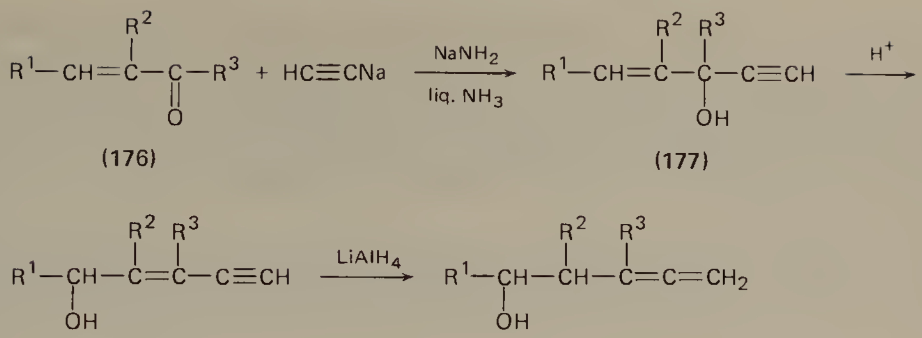
Subjecting the tetrahydro-2-pyranyloxy derivatives **174** (X = OXy-THP) to lithium aluminium hydride in tetrahydrofuran at reflux temperature leads to conjugated diene systems in one step[288,289]. When the ethers **174** (X = OMe, $R^1 = R^2 \neq H$) are treated with *n*-butyllithium, allenic alcohols with a tetrasubstituted allene group result[290]. Optically active α-allenic alcohols are obtained in good yield and with enantiomeric excess of greater than 90%[291] when optically active tetrahydropyranyloxy derivatives are subjected to the above reaction conditions.

Other useful starting materials for α-allenic alcohols are α-acetylenic epoxides **175**, which on treatment with dialkyllithium cuprates[292] (yield 50–70%), Grignard reagents in the presence of cuprous iodide[293] (yield 90%) or trialkyl boranes in the presence of catalytic amounts of oxygen[294] (yield 20–60%) are converted into the desired alcohols (equation 71).



(71)

b. β-Allenic alcohols. Although a considerable number of reactions leading to β-allenic alcohols are known (e.g. lithium aluminium hydride reduction of β-allenic aldehydes and ketones[295], addition of Grignard reagents to allenic aldehydes[296], reduction of hydroxypropargyl halides with zinc–copper couples[297], addition of propadienyllithium derivatives to oxiranes[298]), the number of simple and general procedures is limited. One classical way consists in preparing the non-conjugated enynol **177** from α,β-unsaturated ketones **176** and alkali acetylide, isomerizing **177** with sulphuric acid to its conjugated isomer **178**, and reducing this to the allenol **179** with lithium aluminium hydride in refluxing ether (equation 72)[299,300].



(176) (177) (178) (179)

(72)

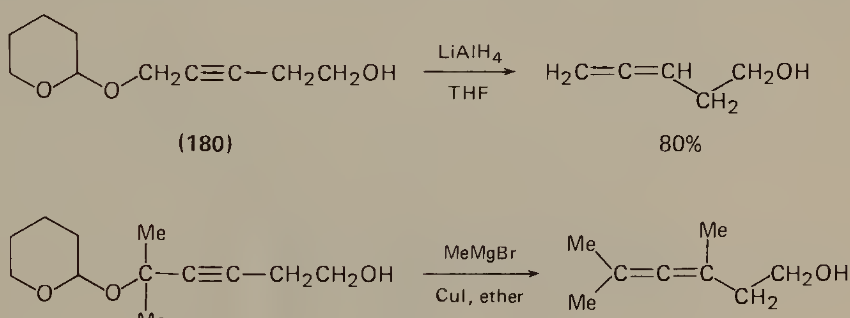
$R^1 = R^3 =$ H, alkyl, cycloalkyl etc.

$R^2 =$ H, alkyl, cycloalkyl, aryl

This reaction sequence has been considerably improved (yields in the vicinity of 70% for each stage) by substituting lithium amide for sodium amide in the first step and by reducing the acetates of the alcohols[178] in the last[301]. Mechanistic investigations have been carried out both for the reduction of the alcohols[302] and their acetates[303].

Another procedure reduces α-allenic aldehydes with lithium aluminium hydride in ether, the starting materials being prepared in good yields by Claisen-type rearrangement of propargyl vinyl ethers[304,253].

In two more recent developments β-allenic alcohols are synthesized in good to excellent yields by treatment of 5-alkoxy-, 5-tetrahydropyranyl-2-oxy- (i.e. **180**) or 5-trialkylammonio-3-pentyn-1-ols with lithium aluminium hydride in tetrahydrofuran at 65° C[305], and by reacting the first two types of compounds (e.g. **181**) with Grignard reagents in the presence of cuprous iodide (equation 73)[306]. Both

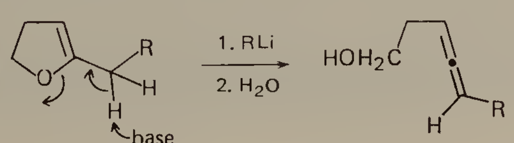


(180) (181)

(73)

processes involve a propargyl rearrangement, and are clearly related to the reactions used to prepare the lower homologues (cf. Section II.B.4a).

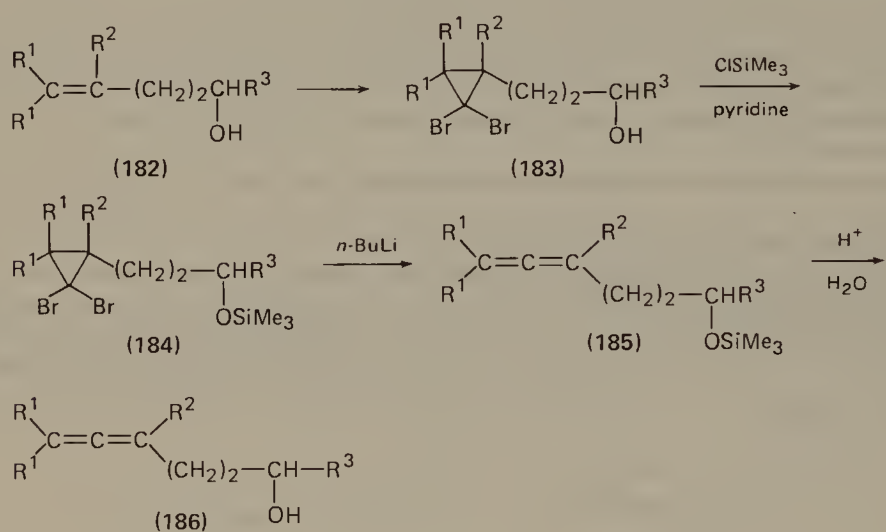
Another novel reaction exploits the ring-opening through β-elimination of 2-alkyl-4,5-dihydrofurans (equation 77)[307].



(74)

The solvolytic behaviour of various derivatives of β-allenic alcohols, especially their tosylates, has received much attention. The homoallenyl participation shown by these compounds is not only mechanistically important but also opens up useful preparative entries to numerous cyclopropane and cyclobutane derivatives[308-312]. Homoallenyl participation is incidentally not restricted to cationic intermediates as is shown by the rearrangement of 3,4-pentadien-1-yl Grignard reagent to its 1-cyclopropyl vinyl isomer[313].

c. γ- and Higher allenic alcohols. In the presently most general sequence to γ-allenic alcohols[314] the carbinol **182** is first converted with bromoform in pentane at −20° C in the presence of potassium *t*-butoxide into the *gem*-dibromocyclopropanol **183**. After protection of the alcohol function the resulting ether **184** is debrominated by treatment with *n*-butyllithium in ether at −40° C. The allenic ethers **185** are finally hydrolysed with dilute ethanolic hydrochloric acid at 45° C, providing the desired carbinols **186** in fair to good yield (equation 75)[314]. The



(75)

R¹	R²	R³	Yield (%)
H	H	H	10
H	H	Me	30
H	Me	Me	60
H	Me	H	50
Me	H	Me	80

procedure has also been applied to the synthesis of a few γ[315]- and ε-allenic alcohols.

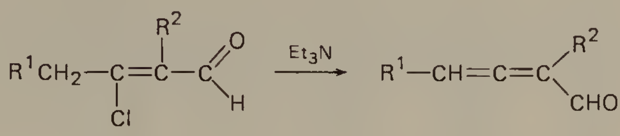
Alternative procedures for the preparation of γ-allenic alcohols involving rearrangement[316] and fragmentation[317] reactions are available, but their scope appears to be rather limited.

Like their lower homologues (cf. Section II.B.4b) secondary γ-allenic tosylates have been subjected to solvolysis experiments which have shown that cyclization to derivatives of 2-methylidenecyclopentanol or cyclohexanone takes place[318,319].

5. *Allenic aldehydes, ketones and their derivatives*

Allenes containing an aldehyde or keto function have frequently been prepared by oxidizing the corresponding alcohols[320,321]. Secondary β-acetylenic alcohols may also be used, undergoing a propargyl rearrangement during the oxidation[322,323]. While 'standard' aldehyde and ketone preparations have also been applied[324], there are procedures that are unique for this class, and some will be presented below.

a. Aldehydes. α-Allenic aldehydes **188** are obtained when α,β-dialkyl-β-chloroacroleins **187** are treated with triethylamine for three hours at 60° C (equation 76)[325].

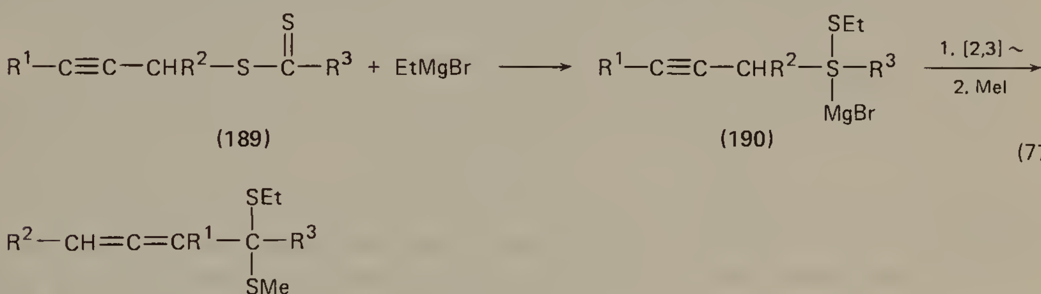


(187) (188) (76)

R^1 = H, Me

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

α-Allenic dithio ketals **191** have been synthesized from *S*-propargylic dithio esters **189** by reaction with ethylmagnesium bromide in tetrahydrofuran at –30° C. The primary product **190** spontaneously undergoes a [2,3] sigmatropic rearrangement to an allenic thiolate which is stabilized by methylation (equation 77)[326].

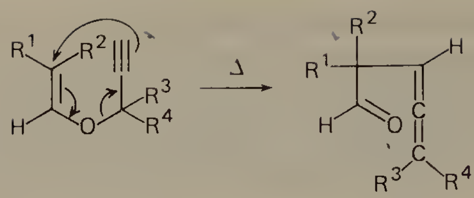


(189) (190) (191) (77)

R^1	R^2	R^3	Yield (%)
H	H	Et	64
Me	H	Et	69
Ph	H	Et	58
Me	H	C_6H_{13}	74
Me	Me	Et	0

When 5,5-dimethyl-*N*-nitrosooxazolidone, a known precursor of dimethylmethylene carbene, is decomposed by various bases in glyme in the presence of ethoxyacetylene, α-allenic acetals are produced in 30–40% yield[327].

The method of choice for the synthesis of *β-allenic aldehydes* **193** is the Claisen–Cope rearrangement of propargyl vinyl ethers **192** (equation 78)[252,253,304,328].



(192) (193)

(78)

R¹	R²	R³	R⁴	Yield (%)
H	H	H	H	20–30
H	H	H	Me	10–20
H	H	Me	Me	10
Me	Me	H	H	70
Me	Me	Me	H	60
Me	Me	Me	Me	76

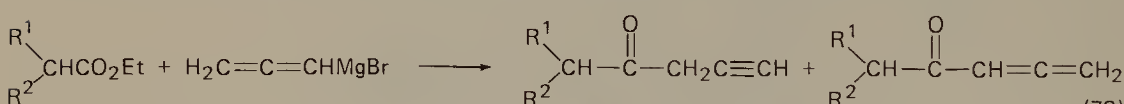
Increased substitution leads to a faster rearrangement at lower temperatures and to higher yields[304]. For the case of $R^1 = R^2 = Me$ this synthesis is particularly simple, since the ethers **192** may be prepared directly by acid-catalysed condensation of various propargyl alcohols with isobutyraldehyde and rearranged *in situ*[252,253]. In most cases the aldehydes **193** are obtained in about 50% yield.

In another [3,3] sigmatropic isomerization vinylpropargylcarbinols are thermally rearranged via γ-allenic enol intermediates to *γ-allenic aldehydes.* With the appropriate substitution γ-allenic ketones may also be prepared, but both reactions suffer from the disadvantage that isomeric compounds are formed as by-products[329].

β-Allenic aldehydes have been used as starting materials for allenic cyanohydrins, amino nitriles and amino acids[330], as well as β-allenic alcohols (cf. Section II.B.4.b).

b. Ketones. A considerable number of methods have been developed for the synthesis of *α-allenic ketones*, and only the more recent ones will be summarized here[331].

When esters are reacted at $-80°$ C with allenylmagnesium bromide in ether a mixture of β-acetylenic and α-allenic ketones is produced (equation 79)[331].



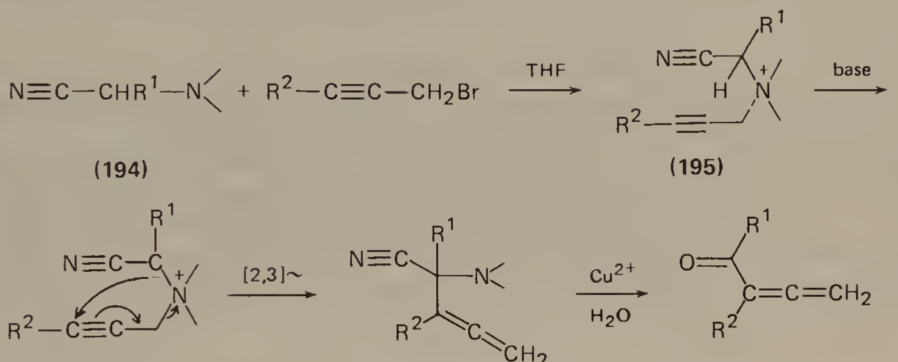
(79)

R¹	R²	Yield of mixture (%)
H	H	20
Me	H	38
Et	H	40
Ph	H	30
Me	Me	25

This mixture isomerizes under the influence of base (potassium carbonate in dimethyl sulphoxide), and its allene ketone content increases. Since by treatment with silver nitrate the acetylenic ketone may be eliminated, the procedure constitutes a useful way to α-allenic ketones. The reaction, whose mechanism has been studied[332], also proceeds with α-halogenated esters, and the substituents of the Grignard reagent have also been varied[333].

Another route to α-allenic ketones involves the acid-catalysed hydrolysis of ethoxyenynes[334]. Since the resulting ketones are known to add water under acidic conditions (to yield β-diketones), the reaction conditions are critical, best yields of allene ketones having been obtained when the hydrolysis is effected with a dilute solution of perchloric or orthophosphoric acid. When ethoxyenynols are subjected to the same conditions allenic ketoalcohols are produced[335,336].

A promising new method for the preparation of α-allenic ketones starts with the easily available nitriles **194** which are alkylated in quatitative yield by propargyl bromides in tetrahydrofuran to the ammonium salts **195**. When these are reacted with potassium *t*-butoxide in tetrahydrofuran at −40° C for 30 minutes the salt **196** is produced which undergoes a [2,3] sigmatropic change to the allenic nitrile **197**. Cupric-ion catalysed hydrolysis of the latter furnishes the ketones **198** in good yields (60% starting from **194**) (equation 80)[337].

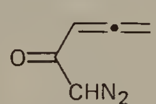


(194) (195) (196) (197) (198) (80)

R^1 = Me, Et, $PhCH_2$

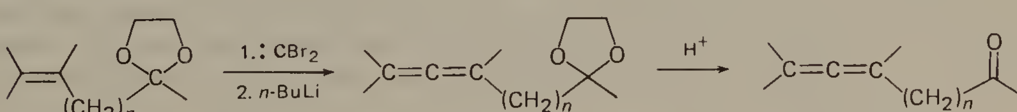
R^2 = Me, Et

An elimination reaction has been used for the synthesis of the unusually substituted allenic ketone **199** (allenyl diazomethyl ketone)[338], and 2,5-diaryl-3-bromofurans have been shown to undergo ring-opening to aryl-substituted α-allenic ketones when treated with *n*-butyllithium[339].



(199)

Concerning β- and γ-*allenic ketones* **202** a general method of preparation consists in applying the DMS method to protected β- and γ-keto olefins **200**, and hydrolysing the thus formed allenic ethylene ketals **201** with acid (equation 81)[340].

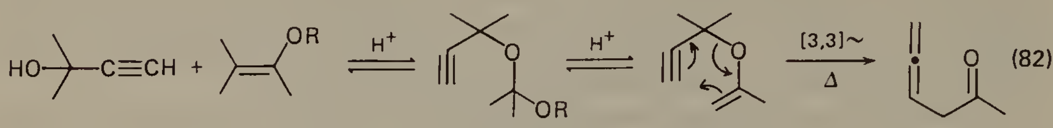


(200) (201) (202) (81)

n = 1: β-ketone

n = 2: γ-ketone

An important and specific method for the synthesis of β-ketoallenes consists in the reaction of tertiary acetylenic alcohols with vinyl ethers in the presence of catalytic amounts of *p*-toluenesulphonic acid or phosphoric acid in hydrocarbon solvents at 60 to 80° C (equation 82)[341]. It is likely that in this process, which has



(203) (204)

been used for example in the synthesis of pseudoionon and some of its mono- and di-methyl derivatives[341], the mixed ketal **203** is initially formed which by a subsequent loss of alcohol is converted to the propargyl isopropenyl ether **204**. This intermediate evidently undergoes a Claisen-type rearrangement to afford the β-allenic ketone.

γ-*Allenic ketones* have also been obtained by a thermal [3,3] sigmatropic isomerization[342], and by condensation of α-allenic bromides with the sodium salt of acetoacetic ester followed by hydrolysis and decarboxylation[343].

Synthetic applications of α-allenic ketones include their reduction with various reagents[344] (cf. Section II.B.4.b), their use as dienophiles in Diels–Alder reactions[345] and their alkylation with lithium dimethyl cuprate[346], which takes place as an 1,2-addition to the activated double bond of the allene system. The latter reaction has been exploited in the synthesis of lavandulol, a monoterpene alcohol[347].

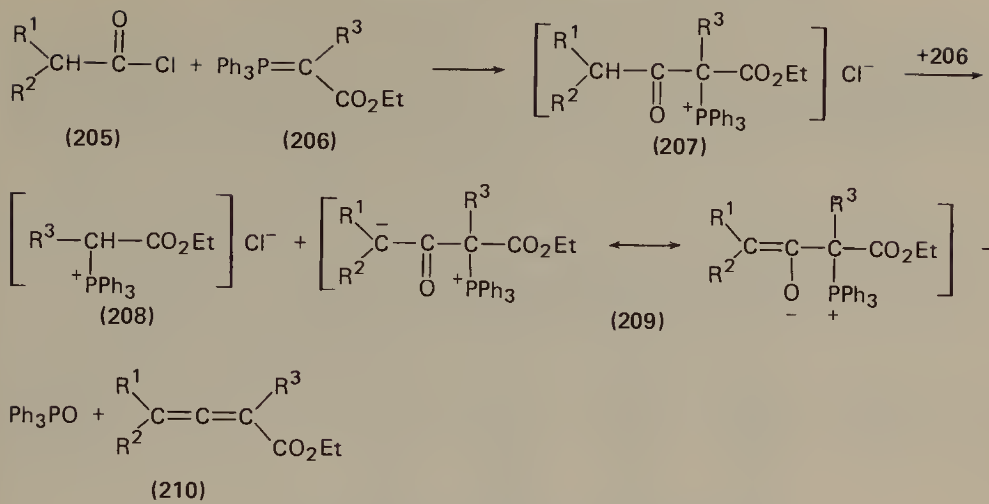
6. Allenic carboxylic acids, esters and amides

The method of choice for the preparation of α-allenic carboxylic acids and their derivatives, especially their esters, is the Wittig reaction.

When acid chlorides **205** are treated with the Wittig reagents **206**, phosphonium salts **207** are formed, which in a subsequent step are dehydrochlorinated by a second molecule of the ylid **206** (which now functions as a base) to yield the phosphonium salts **208** and the betains **209**. Elimination of triphenylphosphine oxide from the latter provides the α-allenic esters **210** in good yields (equation 83)[348,349]. When ylids **206** esterified with optically active alcohols are used, the allenic esters formed show optical activity[350].

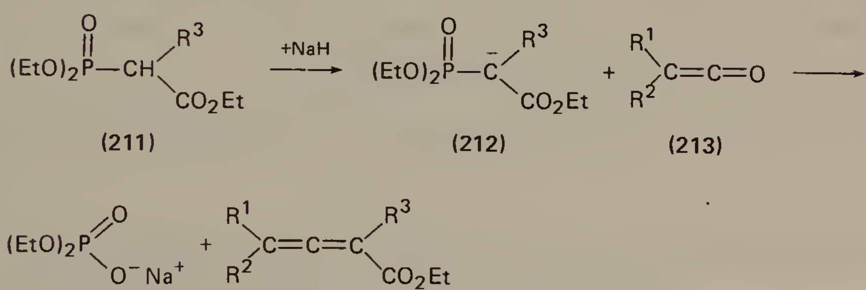
The so-called phosphonate method[351] has also been applied for synthesizing α-allenic esters. In this procedure α-diethylphosphonocarboxylic esters **211** are converted into their salts **212** by base treatment, and the latter reacted with ketenes **213** (equation 84)[352]. Best yields (70–80%) are realized when working in boiling dimethoxyethane as solvent. The free acids are obtained by saponification with a solution of 10% sodium hydroxide in aqueous ethanol[352]. A procedure applicable also for the synthesis of thermally labile α-allenic esters, has recently been developed[353], as has a general procedure for the separation of enantiomers of allene carboxylic acids[353].

α-Alkyl-β-keto esters **214** have been transformed in a single step into allenic esters by initial reaction with hydrazine (giving 5-pyrazolone derivatives **215** in situ) followed by oxidation with thallium (III) nitrate (TTN) in methanol (equation 85)[354].



(83)

R^1	R^2	R^3	Yield (%)
H	H	Me	59
Et	H	Me	55
n-Bu	H	Me	66
n-Pe	H	Me	80
Me	Me	Me	42



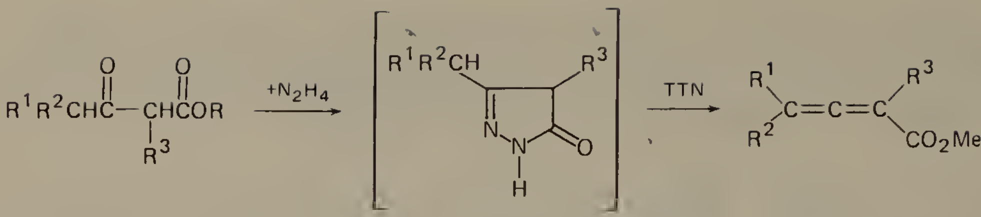
(84)

R^1	R^2	R^3
Me	Et	Ph
Ph	Me	Et
Ph	Et	Me
Ph	Me	Me
Ph	Ph	Ph
	and others	

Propargylic rearrangements have also been exploited for the synthesis of α-allenic esters; thus suitable hydroxy acetylenic esters were treated with thionyl chloride[355] or phosphorous pentabromide[356], or the corresponding acetates were isomerized with mild bases[357] or their chlorides hydrogenated[358].

The reaction of Grignard reagents with carbon dioxide has also been used for the preparation of α-allenic acids[359].

Among the recent applications of these allene derivatives in organic synthesis their use in various addition reactions may be mentioned. 1,3-Diethoxycarbonyl-

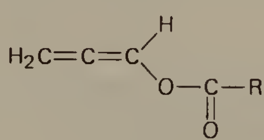


(214) (215) (85)

R¹	R²	R³	Yield (%)
H	H	Me	50
H	H	Et	48
H	H	*i*-Pr	54
H	H	*n*-Pe	70
Et	H	Me	55
Et	H	Et	61

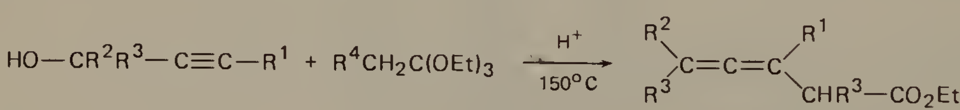
allene is an active dienophile and ethoxycarbonylketene equivalent in the synthesis of antibiotic *C*-nucleosides[360]. The diester allows the preparation of highly substituted 2-pyridones by nucleophilic addition of enamines[361,362]. Addition of diazoalkanes to allenecarboxylic acid esters leads to pyrazolines which are converted to novel spiro systems by attack of a second molecule of the diazo compound[363].

It should be noted that allene esters may also be of the enole ester type **216**. These compounds will be discussed in Section II.D.6.a.



(216)

A general method for the preparation of β-*allenic esters* **217** consists in heating mixtures of 1-hydroxy-2-propynes and orthoesters at 150° C in the presence of catalytic amounts of propanoic acid (equation 86)[364].



(86)

(217)

R¹	R²	R³	R⁴	Yield (%)
H	H	H	H	34
H	Me	H	H	63
H	*n*-Pr	H	H	60
H	Me	Me	H	54
H	Me	Me	Me	59
Me	Me	Me	H	61

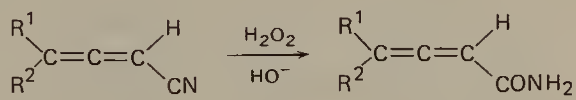
Less general routes to **217** involve the photochemical decomposition of pyrazolenine esters[365], photoisomerization of dienoic acids[366], and application of the Corey aldehyde–ester transformation to certain conjugated enyne aldehydes[367].

β-Allenedithiocarboxylic acid esters have been synthesized from ketene dithioacetals by thermal rearrangement in excellent overall yields[368].

Some *γ-allenecarboxylic acid esters* have been synthesized along more conventional lines, e.g. by reaction of 1-bromo-2,3-butadiene derivaties with acetoacetic ester and subjecting the resulting β-keto esters to ether cleavage[343].

α- and *β-Allenic amides* have been obtained by some special procedures after having been isolated as by- or main-products in base-catalysed rearrangements of their acetylenic isomers[369].

A general method for the preparation of the α-amides **218** consists in treating α-allenic nitriles (cf. Section II.B.7) with alkaline hydrogen peroxide (equation 87)[370].



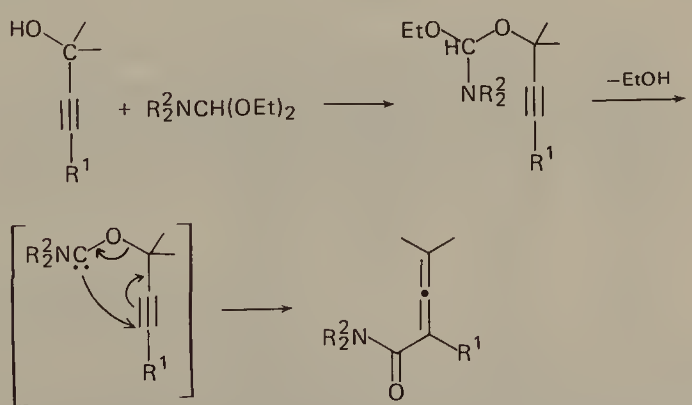
(87)

(218)

R¹	R²	Yield (%)
Me	Me	35
Me	Et	71
Et	Et	57
t-Bu	*t*-Bu	70

Alternatively *N-t*-butylamides are formed in a Ritter reaction when the nitriles are treated with *t*-butanol and concentrated sulphuric acid with yields in the 60% range[370].

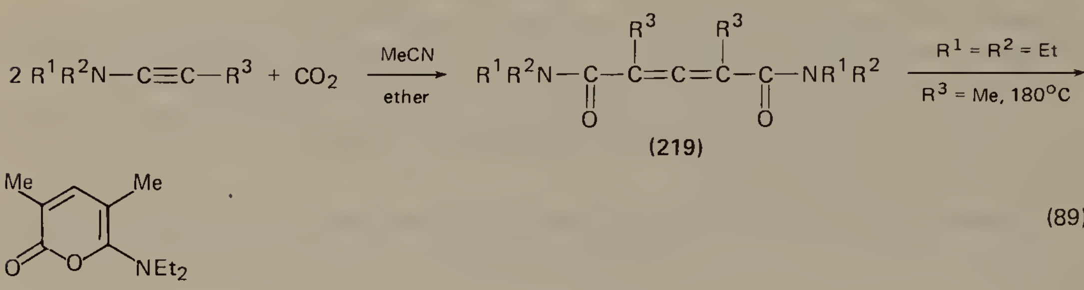
Tertiary allenic amides are produced in high yields by the reaction of propargyl alcohols with diethylformamide acetals in refluxing hydrocarbon solvents, the process occurring via a [2,3] sigmatropic shift (equation 88)[371].



(88)

The reaction of tertiary propargyl alcohols with dimethylacetamide diethylacetal[372,373] or with ynamines[374] leads to *β-allenic amides*. In both cases the operation of a Claisen-type mechanism is likely.

In another application of *N,N*-dialkylynamines these are reacted with carbon dioxide in acetonitrile/ether at room temperature to afford diamides of 1,3-allene-dicarboxylic acid **219** (equation 89)[375]. On heating, the alkyl substituted derivative **219** undergoes an unexpected thermal transformation to the 6-amino-α-pyrone derivative **220**[376].



(219)

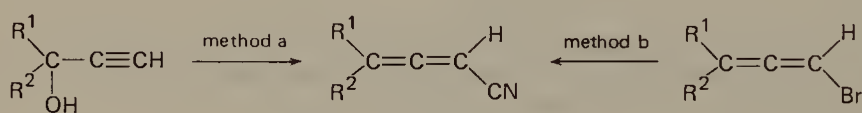
(220) (40%)

(89)

R¹	R²	R³	Yield (%)
Et	Et	Me	95–100
Ph	Me	H	40

7. *Allenic nitriles*

Allenic nitriles (cyanoallenes) **221** may either be prepared by treatment of (preferably tertiary) acetylenic alcohols with 1.5 equivalents of cuprous cyanide, a trace of copper, one equivalent of potassium cyanide and hydrobromic acid (48%, 2.5 equivalents) for three days at room temperature (method a) or by reaction 1-alkyl- or 1,1-dialkyl-3-bromoallenes with cuprous cyanide in *N,N*-dimethylformamide at 35–60° C for two hours (method b) (equation 90)[377,378].

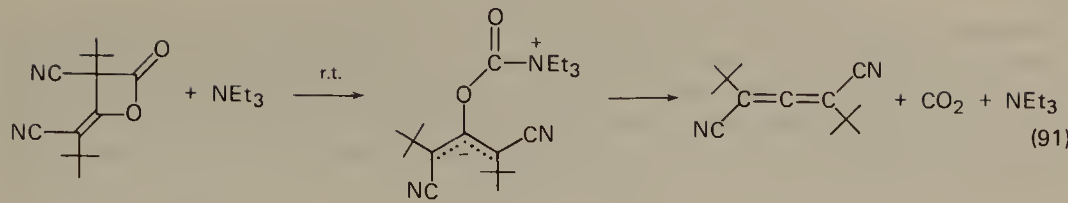


(221)

(90)

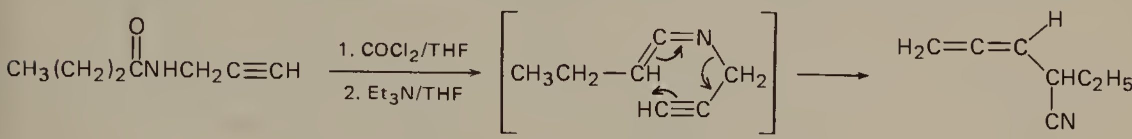
R¹	R²	Yield (%) (method)	
Me	Me	30 (a),	40 (b)
Me	Et	51 (a),	51 (b)
Et	Et	75 (a),	61 (b)
Me	*i*-Bu	40 (a),	50 (b)
Me	*t*-Bu	25 (a),	65 (b)
i-Pr	*i*-Pr		67 (b)
t-Bu	*t*-Bu		90 (b, without solvent)
H	Me		55 (b)
H	*i*-Pr		60 (b)
H	Ph		70 (b)

The dicyanoallene **224** is produced in 68% yield when the β-lactone **222** is treated with triethylamine. This unique decarboxylation presumably occurs via the zwitterionic intermediate **223** (equation 91)[379].



(222) (223) (224)

The *α-cyanoallene* (227) is formed in 28% yield from *N*-(2-propynyl)-butyramide (225). The scope of this process which probably involves a Claisen-type isomerization (intermediate 226) has not been explored (equation 92)[380].

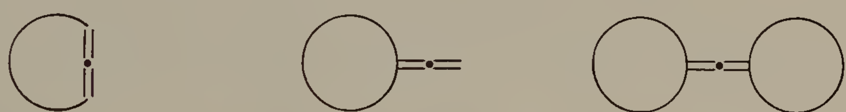


(225) (226) (227) (92)

Cyanoallenes are of interest because of their head-to-tail-dimerization[381,382], and especially as substrates for the preparation of numerous heteroorganic compounds (unconjugated and conjugated enaminic nitriles[383,384], imidazolines and imidazoles[385], oxazolines, thiazolines, oxazoles, thiazoles, and pyrazoles[386,387]). The yields in most of these transformations are good to excellent (70–90%).

C. Cyclic Allenes

Three general categories of cyclic allenes will be discussed in this review: the two monocyclic systems (i) and (ii), which will be referred to as endo- and exo-cyclic allenes, and the bicyclic molecule represented by (iii):



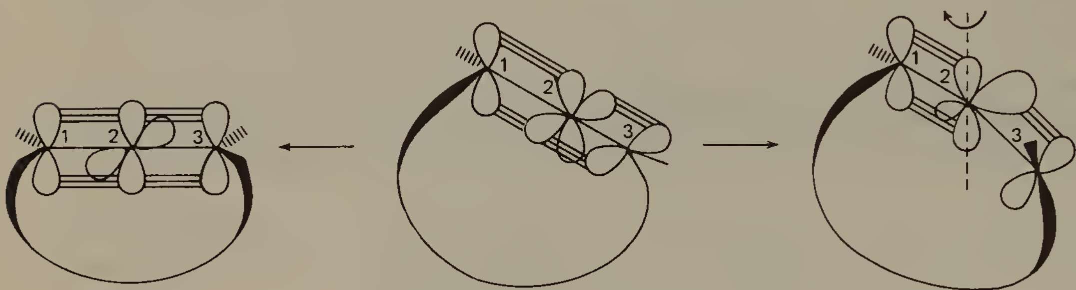
(i) (ii) (iii)

This nomenclature does not take into account the complexity of the ring systems in (i)–(iii). An allene unit incorporated into a polycyclic molecule may therefore be listed under either of these structural types. In other words the 'molecular bridges' in these three general formulae may possess any degree of complexity.

1. *Endocyclic allenes*

It should be noted that medium-sized rings (C_9 to C_{11}) tolerate an allene linkage more readily than the electronically related triple bond[388,389]. Since, however, the isomeric dienes, especially conjugated ones, are thermodynamically considerably more stable than either of the first two combinations of π electrons, isomerization reactions of cycloalkynes normally lead to mixtures of isomeric products.

Ring-strain in cyclic allenes may be reduced by two general modes of deformation[390]. In the first one, exemplified by the process 228 → 229, the normal, orthogonal geometry **228** is modified by a bending of the allene group at $C_{(2)}$ about an axis which is perpendicular to one of the methylene planes. This will introduce s-character into the p orbital at $C_{(2)}$, which is at right angles to the bending axis, and consequently reduce the π-character of the double bond to which this orbital contributes; the perpendicular double bond will remain unchanged (equation 93)[390].



(93)

(230) (228) (229)

In the second deformation, **228**→ **230**, a planar arrangement is produced by a twisting motion of one of the methylene units about the $C_{(1)}C_{(2)}C_{(3)}$ axis. The π system thus generated corresponds to a linear arrangement of p orbitals with one nonbonding p orbital perpendicular to the π system at $C_{(2)}$ (equation 93). A combination of both the bending and the twisting mode seems to be the most effective way for reducing strain in small cycloallens. Detailed INDO–MO calculations on these systems have been performed[390], and it has been concluded that the incorporation of an allenic linkage into a five-membered ring should not be more difficult than into its next higher homologue, and even the intermediate generation of 1,2-cyclobutadiene intermediates should be possible.

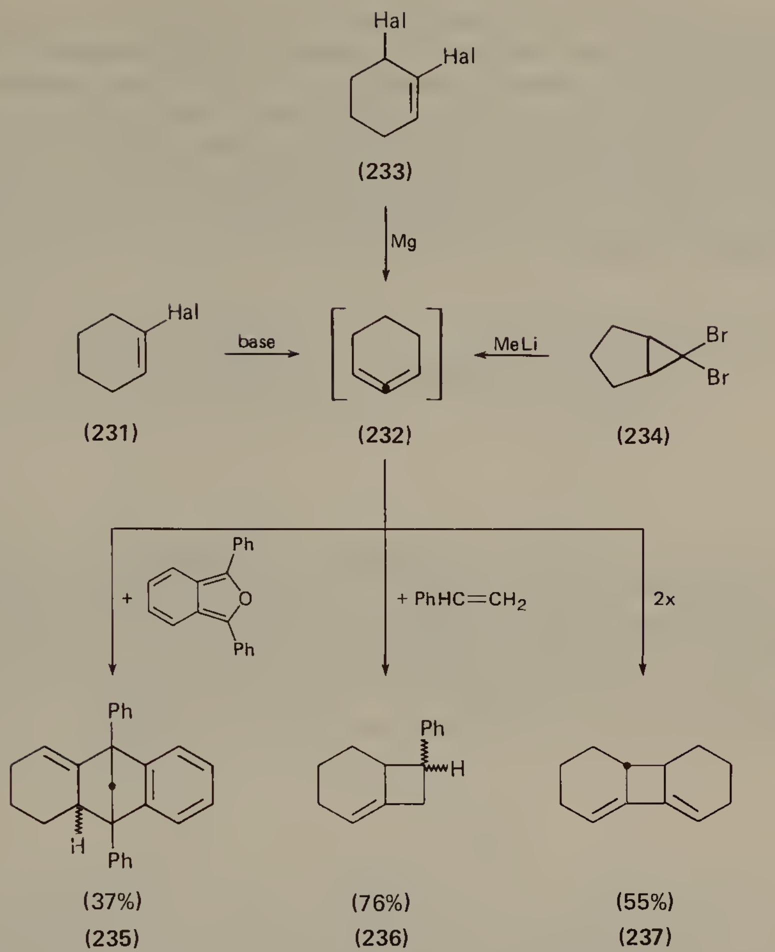
a. Six-membered and smaller rings. The smallest cyclic allene whose existence was proven beyond doubt is 1,2-cyclohexadiene (**232**). All experiments which could have led to 1,2-cyclopentadiene have been proven unsuccessful[391–393].

Hydrocarbon **232** has been generated from various precursors, among them 1-halogenocyclohexene (**231**)[394–396] (by treatment with potassium *t*-butoxide), 2,3-dihalogenocyclohexene (**233**)[397–399] (by treatment with magnesium), and 6,6-dibromo-bicyclo[3.1.0]hexane (**234**) (by treatment with methyllithium)[400] (equation 94).

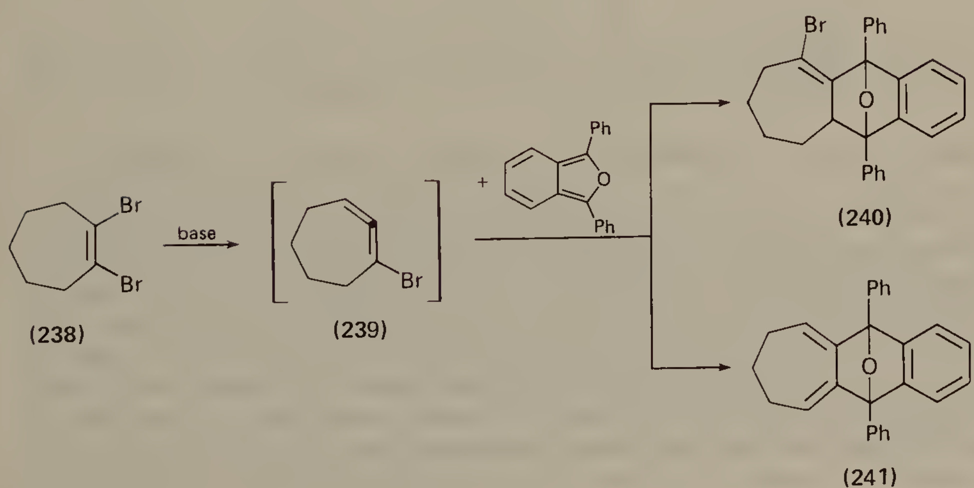
That **232** is indeed produced in these eliminations is shown by various trapping and oligomerization experiments. Thus 1,2-cyclohexadiene may be intercepted with diphenylisobenzofuran to the Diels–Alder adducts **235**[395,401], whereas styrene provides the [2 + 2] adducts **236**[402]. The dimer **237** is formed in good yield when a solution of the dibromide **234** in ether is added to a refluxing ethereal methyllithium solution. Changing reaction conditions cause the formation of tetramers[395,400,403]. The mechanism of the dimerization process has been investigated[404,405], and several other trapping agents – including acyclic and cyclic dienes – provide the adducts expected for the intermediate formation of **232**[398,406,407].

b. Seven-membered rings 1,2-Cycloheptadiene is also too unstable to be isolated in substance. However, the fact that it and its derivatives may be generated is proven by several observations.

When 1,2-dibromocycloheptene (**238**) is treated with potassium *t*-butoxide in the presence of diphenylbenzofuran the two Diels–Alder adducts **240** and **241** are formed in 2.8 and 8.1% yield, respectively (equation 95)[408].

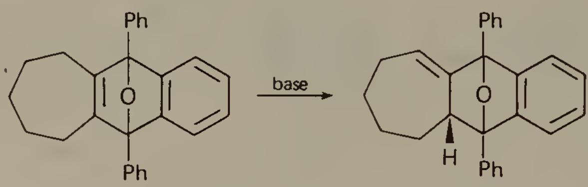

Hal
Hal
(233)
Mg
Hal
base
MeLi
Br
Br
(231)
(232)
(234)
Ph
O
Ph
+
+ PhHC=CH2
2x
Ph
H
Ph
Ph
H
(37%)
(235)
(76%)
(236)
(55%)
(237)

(94)


Br
Br
base
Br
(238)
(239)
+
Ph
O
Ph
Br
Ph
O
Ph
(240)
Ph
O
Ph
(241)

(95)

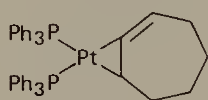
Whereas **240** is the direct addition product of the diene to the intermediate 1-bromo-1,2-cycloheptadiene (**239**), **241** is a secondary adduct formed by attack of the trapping agent at the substituted double bond of **239** and subsequent dehydrobromination. Analogous adducts are produced when 1-bromocycloheptene is reacted with base, indicating the formation of 1,2-cycloheptadiene. However, since the Diels–Alder product **242** of cycloheptyne to diphenylisobenzofuran was shown to rearrange very readily to the cycloallene adduct **243**, these trapping experiments are not unambiguous (equation 96).



(96)

(242) (243)

When the elimination of 1-bromocycloheptene was repeated in the absence of the diene, tricyclic hydrocarbons $C_{14}H_{20}$ are formed – another hint that 1,2-cycloheptadiene has been produced as a reaction intermediate. The same conclusion may be drawn from several other elimination reactions of this general type[409,410]. Particularly revealing is an experiment in the presence of bis(triphenylphosphine)-(ethylene)platinum which leads to the stable metal complex **244**[411].



(244)

Interestingly, 1,2-cycloheptadiene cannot be prepared by the DMS method. Rather, treatment of 7,7-dibromobicyclo[4.1.0]heptane (**245**) with methyllithium yields a variety of products, among them the hydrocarbons **247–249**, formed by intramolecular insertion of the intermediate cyclopropylidene **246** (equation 97)[412].

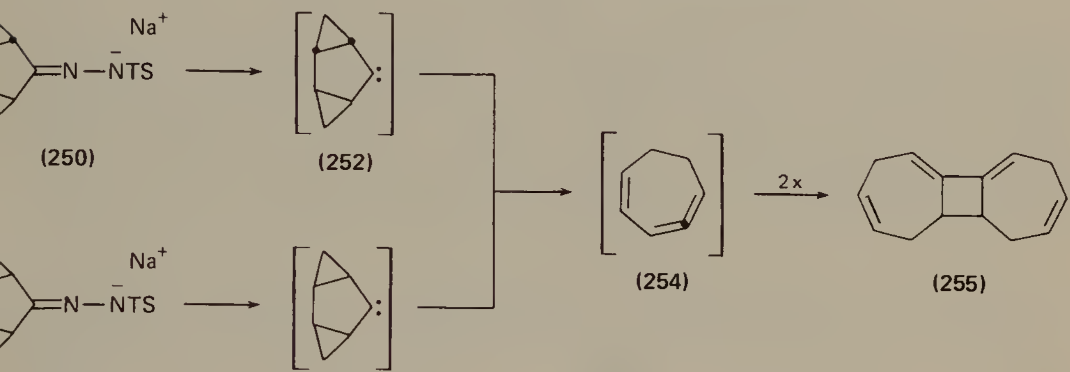
(97)

(245) (246) (247) (248) (249)

From a study with several derivatives of **245** (and hence **246**) it has been concluded that in general a cyclopropylidene incorpated into a bicyclo-[4.1.0]heptane system does not experience ring-opening to an allene prior to carbon–hydrogen insertion. This behaviour is surprising since the next lower (cf. Section II.C.1.a) and higher homologues (cf. Section II.C.1.c) do open to 1,2-cyclohexadiene and 1,2-cyclooctadiene, respectively. To explain this contradiction, it has been assumed that the bicyclo[4.1.0]heptane system lies in a structural region for which opening in the conventional sense to an orthogonal allene is denied because the cycloallene thus produced would be too highly strained; this process is only just barely possible for the next higher homologue. The [3.1.0] system, on the other hand, leads to a (possibly planar) allene, but by a different mechanism. Rather than forming the cyclopropylidene, the α-bromocyclopropyllithium intermediate may rearrange in a manner analogous to the carbonium ion rearrangement found for endo-6-substituted derivatives of bicyclo[3.1.0] hexane, processes which evidently occur because of *relief* of strain[413]. For this mechanism to become operative, the [4.1.0] system may not be strained *enough*.

A growing number of publications have appeared during the last few years in which derivatives of 1,2-cycloheptadiene were postulated as intermediates or even trapped by appropriate reagents.

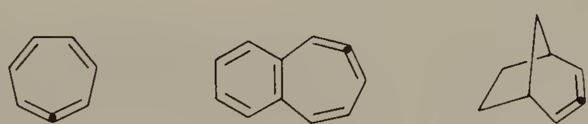
Thus, when *syn*-or *anti*-tricyclo[4.1.0.0^{2,4}]heptan-5-ylidene (**252** and **253**) are produced by pyrolysis of the precursors **250** and **251** the dimer **255** of 1,2,5-cycloheptatriene (**254**) is formed in yields up to 94% (equation 98)[414].



(250) (252) (254) (255) (98)

(251) (253)

The occurrence of the still higher unsaturated tetraene **256** as well as its 4,5-benzo derivative **257** during, *inter alia*, the dehydrochlorination of 2-chloro-1,3,5-heptatriene[415] and 5,6-benzo-1-chloro-1,3,5-cycloheptatriene[416] is made likely by various trapping and dimerization experiments, which all yield the products expected for the structures given.

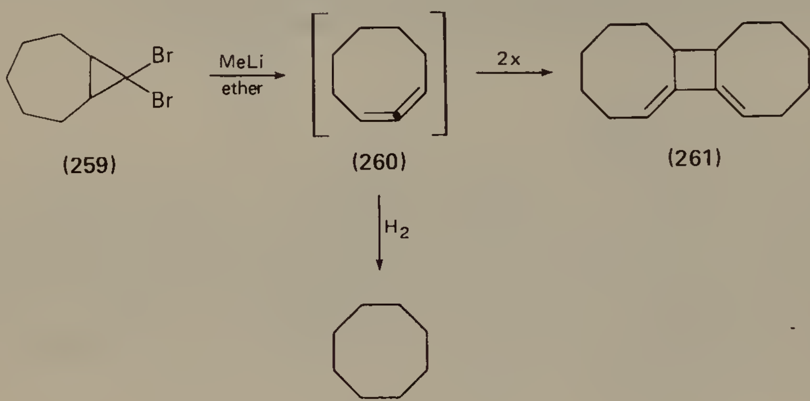


(256) (257) (258)

Bicyclo[3.2.1] octa-2,3-diene (**258**) has been suggested as an intermediate in the dehydrobromination of 3-bromo-bicyclo[3.2.1] oct-2-ene[417] with potassium *t*-butoxide in dimethylsulphoxide. However, other workers have concluded that the enol ethers formed as reaction products were more likely produced by the interception of acetylenic intermediates with *t*-butanol[418,419]. On the other hand, **258** has been generated by treatment of 3,4-dichlorobicyclo[3.2.1] oct-2-ene with magnesium as evidenced by several trapping experiments with *cis*-pentadiene, 2,3-dimethyl-1,3-butadiene, styrene and cyclopentadiene[420].

Oxa and aza derivatives of 1,2-cycloheptadiene have finally been invoked as intermediates in the thermal rearrangements of α-ethylenic, α′-acetylenic oxiranes and aziridines, respectively[421–423].

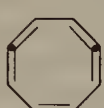
c. Eight-membered rings. When 8,8-dibromobicyclo[5.1.0]octane (**259**) is added to an ethereal solution of methyllithium at 0° C five products are formed, four of which are stable enough to be isolated by gas chromatography. The fifth one, whose maximum yield was 8% immediately after terminating the experiment by quenching with water, is evidently the desired **260** since it shows the characteristic absorption for allenes at 1961 cm^{-1} in the infrared; it could be hydrogenated to cyclooctane (**262**) and trapped with hydrochloric acid/phosphorus pentachloride to 3-chlorocyclooctene (equation 99)[424]. When an aged product mixture was hydrogenated under identical conditions no **262** could be detected. On standing, **260** dimerizes to the tricyclic diene **261** which itself is one of the four stable products referred to.



(259) (260) (261) (262) (99)

Hydrocarbon **260**, which like its lower homologue forms a stable bis(triphenylphosphine)platinum complex[411], is also obtained as an intermediate when 1-bromocyclooctene is reacted with potassium *t*-butoxide in dimethylsulphoxide for four hours at 40° C[425] or the methanesulphonate ester of 3-cyclootynol is reduced with lithium aluminium hydride in ether at 5° C[426]. In both cases the existence of **260** was inferred from dimerization and trapping products, formed for example by cycloaddition of diphenylisobenzofuran[425].

In view of this lack of stability it is not surprising that still higher unsaturated derivatives of 1,2-cyclooctadiene have only been proposed as nonisolable reaction intermediates. These polyolefinic compounds include 1,2,4,5,7-cyclooctapentaene (**263**), a possible intermediate in the converison of *cis, cis*-3,5-octadien-1,7-diyne to the dimer of benzocyclobutadiene[427], 1,2,5-cyclooctatriene (**264**) and 1,2,4,5-cyclooctatetraene (**265**) in the thermal isomerization of *trans*-1-ethynyl-2-vinylcyclobutane[428] and 1,2-diethynylcyclobutane[239], respectively, and the isomeric



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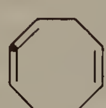

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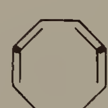

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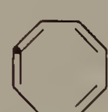

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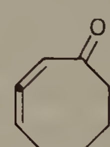


(267)

1,2,4,6-cyclooctatetraene (**266**), which is very likely formed in the photodecomposition of the sodium salt of 2,3-homotropone-*p*-toluenesulphonylhydrazone[429]. **266** yields a typical allene dimer during the photolysis in 70% yield, and may be trapped with diphenylisobenzofuran to a stereoisomeric mixture of 1:1-Diels–Alder adducts when the precursor is decomposed thermally. The same trapping agent has also been used to intercept 2,3-cyclooctadienone (**267**) which is presumably formed when 3-bromo-3-cyclooctenone is treated with base[430].

d. Nine-membered rings. 1,2-Cyclononadiene (**269**) is the first cyclic monoallene that is stable enough to be handled under normal laboratory conditions. The compound may be prepared by either base-catalysed isomerization of cyclononyne (**268**)[388,389] or by the DMS route from cyclooctene (**270**)[431] (equation 100).

(100)

(**268**) (**269**) (**270**)

Since the first reaction is an equilibrium process, the second one is preferred if very pure material is required[431]. The ring-opening of the 9.9-dibromobicyclo-[6.1.0]nonane precursor of **269** can also be effected with chromium (III) chloride–lithium aluminium hydride[83]. Several halogeno olefins have been dehydrohalogenated to **269** by treatment with strong bases[432–435], the product mixtures contain, however, smaller or larger amounts of isomeric hydrocarbons, depending on reaction conditions. Both enantiomers of the chiral hydrocarbon are known[12,436,437].

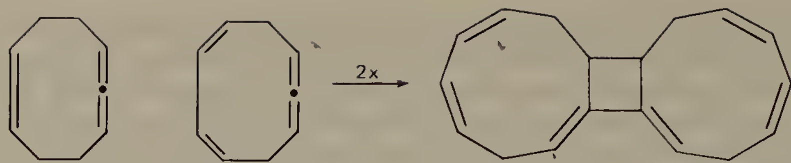
The cyclic allene has been isomerized to 1,3-cyclooctadiene by treatment with potassium *t*-butoxide in dimethylsulphoxide[438], hydroborated with diborane[439] and disiamylborane[440], reacted with hydrogen bromide under various conditions[441,442], and dimerized in both its racemic and optically active form[443]. Under pyrolytic conditions (640° C, 0.3 torr, flow system) it suffers ring-opening to 1-nonen-8-yne and cyclization to *cis*-bicyclo[4.3.0]non-7-ene and *trans*-bicyclo-[4.3.0]non-2-ene, respectively[444].

The photochemical behaviour of **269** is unique since the tricyclo[$3.3.0.0^{2,9}$]-nonane formed on benzene-sensitized irradiation at 2537 Å in the gas phase may be the result of an allene–cyclopropylidene conversion, and as such constitutes one of the very rare examples of the reversion of the decisive step in the DMS synthesis[445].

1,2-Cyclononadiene has furthermore been subjected to oxymercuration[446], treatment with formic acid in the presence of mercuric sulphate[447], peracetic acid in methylene chloride[448] and thallic acetate in glacial acetic acid (oxythallation)[449]. The reduction of this allene with diimide[450] and under Birch conditions[451] has been reported, as has its use in a simple and effective route to *d,l*-isocaryophyllene[452].

A considerable number of derivatives of **269** have been synthesized and their chemical properties investigated. Thus 1-methyl-1,2-cyclononadiene has been obtained from 1-methylcyclooctene using the one-step olefin–allene conversion mentioned in Section II.A.5[453]. Among the higher unsaturated derivatives, 1,2,6-cyclononatriene (**271**) has been most thoroughly studied, especially its thermal behaviour[438,454–461]. The cyclopropanated derivative *cis*-bicyclo[*7.1.0*]-deca-*4,5*-diene of **271** has also been described[459,462].

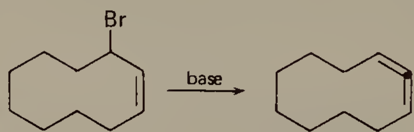
The reactive 1,2,5,7-cyclononatetraene (**272**) dimerizes with a half-life of 10 minutes in deuteriochloroform at 0° C to the tricyclic olefin **273**[463]. Research in progress on the preparation of precursors for the presumably very reactive 1,2,4,6,8-cyclononapentaene has revealed some inconsistencies with the older literature[464].



(271) (272) (273)

The DMS method has also been employed for preparing 5-hydroxy-1,2-cyclononadiene[465] and its 4-hydroxy isomer. The relative configurations of the two diastereisomers of the latter compound have been determined by chemical and physical methods[466,467]. Among cyclic allenones 2,3-cyclononadienone has been obtained both by irradiation of 2-ethinylcycloheptanone[468,469] and from 3-hydroxycyclooctene by the DMS reaction and subsequent oxidation[470], with the second approach also allowing the synthesis of the optically active ketone.

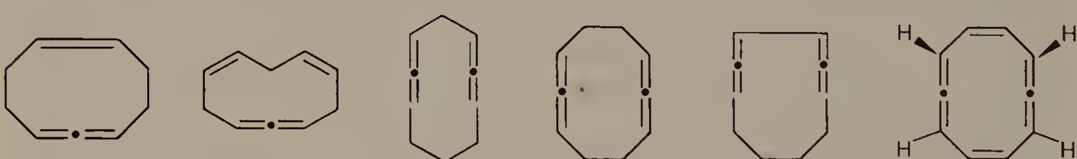
e. Ten-membered rings. 1,2-Cyclodecadiene (**275**) may be prepared by either base-catalysed rearrangement of cyclodecyne[389] or by the DMS method from cyclononene[471]. In a recent synthesis *cis*-3-bromocyclodecene (**274**) is treated with potassium *t*-butoxide in dimethylsulphoxide at room temperature for five minutes (equation 101)[472].



(78%)

(274) (275) (101)

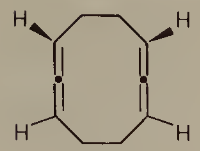
Several derivatives of **275** which contain one or two additional double bonds have been prepared by the DMS procedure from the corresponding cyclic alkenes and dienes, respectively. 1,2,5-cyclodecatriene (**276**) from 1,4-cyclononadiene[473], 1,2,5,8-cyclodecatetraene (**277**) from 1,4,7-cyclononatriene[473,474], 1,2,5,6-cyclodecatetraene (**278**) from the bisdibromocarbene adduct to 1,4-cyclooctadiene[463], and 1,2,6,7-cyclodecatetraene (**279**) analogously from 1,5-cyclooctadiene[54,56]. When this procedure was applied to the synthesis of the conjugated bisallene 1,2,4,5-cyclodecatetraene (**280**) only its valence isomer bicyclo[6.2.0]deca-1,7,9-



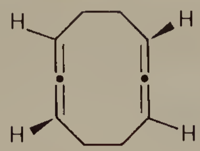
(276) (277) (278) (279) (280) (281)

triene could be isolated[463]. The intermediate formation of meso-1,2,4,6,7,9-cyclodecahexaene (**281**) during the dehalogenation of 3,3,10,10-tetrabromotricyclo[7.1.0.0[4,6]]deca-2,7-diene (a bisdibromocarbeneadduct of cyclooctatetraene) with methyllithium has been postulated[475] and rejected[476].

From the bisallene hydrocarbons, the molecule **279** has so far attracted the greatest attention. Its pyrolytic behaviour has been investigated[477], and several publications have dealt with the stereochemical properties of this molecule, which in principle may exist either as the *meso*(282) or *d,l*(283) isomer[475,476,478].



(282)



(283)

Actually, the literature synthesis[54,56] furnishes the *meso* isomer, as had been concluded earlier from model considerations and chemical evidence[475], and confirmed recently by an X-ray study[478]. The conformational properties of 279 (as well as of the nine-membered ring systems 1,2-cyclononadiene and 1,2,6-cyclononatriene) have been investigated by dynamic n.m.r. spectroscopy and force-field calculations, and it has been concluded that the lowest-energy conformation of this hydrocarbon possesses c_i symmetry[479].

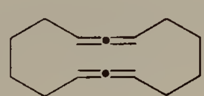
The 4-hydroxy derivative of 1,2-cyclodecadiene has been prepared by reacting 3-hydroxycyclononene with Seyferth's reagent ($PhHgCBr_3$), and subjecting the dibromocyclopropane derivative formed to the influence of *n*-butyllithium[480]. Various 3-oxo-5,10-secosteroids incorporating the 1,2-cyclodecadiene ring have shown to be irreversible inhibitors of Δ^5-3-ketosteroid isomerase[481].

f. Eleven- and higher-membered rings. Endocyclic monoallenes up to 1,2-cyclopentadecadiene have been prepared and their chemical properties studied[440,471,482–485] (*inter alia* hydration to cyclic ketones[482], hydroboration with disiamylborane[440], reduction with sodium in liquid ammonia to *cis* and *trans* cycloalkenes[484], addition of hydrogen bromide[485]).

Most of these allenes have been prepared by the DMS method. When dibromocyclopropane precursors are dehalogenated with chromous (+)-tartrate in 50% aqueous dimethylformamide or by *n*-butyllithium in the presence of (−)-sparteine optically active cycloallenes result[486].

Higher unsaturated derivatives of this group include 1,2,7-cycloundecatriene (284) (obtained from *cis,cis*-1,6-cyclodecadiene by the DMS method[487]), and 1,2,9,10-cyclohexadecatetraene (285)[488], whose tetrakis(trimethylsilyl) derivative 286 has been obtained by metalation of cyclotetradecadiyne with *n*-butyllithium in tetrahydrofuran and quenching of the reaction mixture with trimethylchlorosilane[489].

(284)



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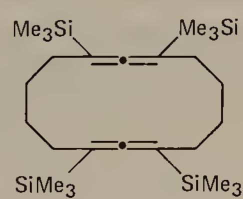
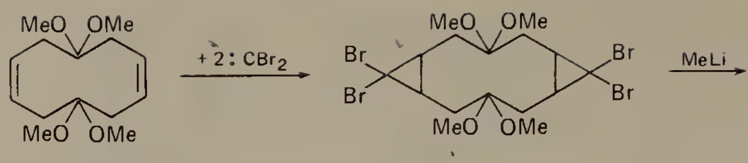


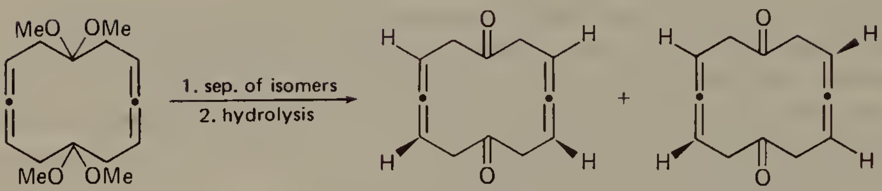
(286)

Monocyclic bisallenes like 285 are of interest in their reactions with metal carbonyls[488], and since they may exist in two diastereomeric forms. The first cycloallene which could be separated into diastereomers was 3,4,9,10-cyclododecatetraene-1,7-dione (290). The tetraacetal 287 was converted to the bisdibromocarbene adduct 288, followed by methyllithium dehalogenation. Separation of isomers was accomplished at this stage by thin-layer chromatography and crystallization, and hydrolysis of the pure *meso*- and *d,l*-allenic acetals 289 afforded the pure *meso*- and *d,l*-diketone 290 respectively (equation 102)[476,490,491].



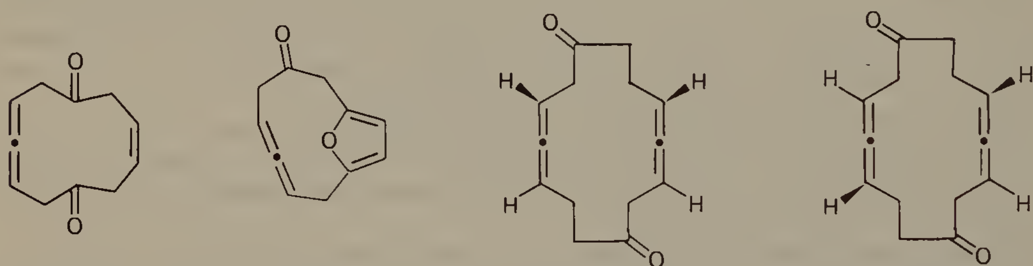
(287) (288)

(102)



(289) (*meso*-290) (*d,l*-290)

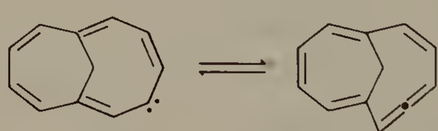
Substrate **287** has also been used to prepare 3,8,9-cycloundecatriene-1,6-dione (**291**), as well as the interesting furanophane **292**[492]. The bisallene **289** has been transformed in several steps into *meso*- and *d,l*-3,4,10,11-cyclotetradecatetraene-1,8-dione (**293**)[491].



(291) (292) (*meso*-293) (*d,l*-293)

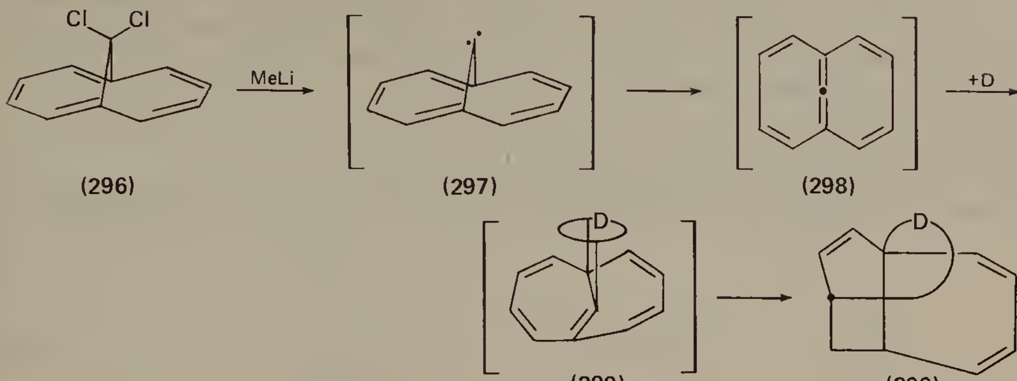
1-Ethoxy-3-methyl-1,2-cyclotridecadiene is generated as a reaction intermediate when the dichlorocarbene adduct of 1-ethoxycyclododecene is reacted with methyllithium[493]. Application of the same sequence to 1-ethoxycyclotetradecene provides a new route to *d,l*-muscone[493].

A carbene–allene conversion has been suggested to account for some anomalies observed in the chemistry of the β-methanoannulenylidene **294**. Some of the



(294) (295)

behaviour of the carbene **294** can be best explained in terms of the allene isomer **295** (e.g. dimerization to polycyclic cyclobutane derivatives)[494,495]. Theoretical calculations indicate that cycloheptatrienylidene may participate in a similar equilibrium (to 1,2,4,6-cycloheptatetraene[495], cf. Section II.C.1.b). In a related experiment, 11,11-dichloro-1,6-methano[10]annulene (**296**) was treated with *n*-butyllithium or methyllithium in the presence of 1,3-diphenylisobenzofuran. The structure of the 1:1 adduct **300** isolated in 65% yield may be rationalized by postulating a conversion of the primary carbene **297** to the bicyclic allene **298**, followed by Diels–Alder addition to **299** and concluding cyclization to **300** (equation 103)[496].

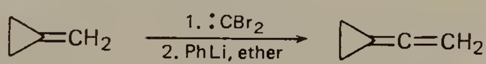


(296) (297) (298) (299) (300) (103)

D = diphenylisobenzofuran moiety

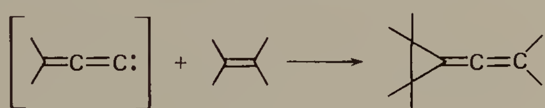
2. *Exocyclic allenes*

a. Vinylidenecyclopropanes. Vinylidenecyclopropane (**301**) has been synthesized by the DMS method (equation 104)[497], or, preferably, by the Hartzler



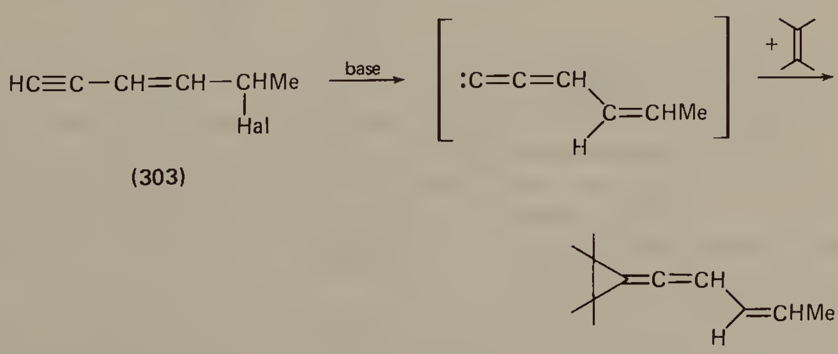
(301) (104)

reaction (cf. Section II.A.6), i.e. the addition of a vinylidenecarbene **304** to an olefin (equation 105)[498–500].



(302) (105)

The intermediates **302** are normally prepared *in situ* by treating tertiary propargyl halides[498–500], chloroallenes[498–500] or bromoallenes[501,502] with strong bases like potassium *t*-butoxide in an aprotic solvent. Whereas the carbene **302** usually carries alkyl substituents, a wide variety of aliphatic and aromatic olefins

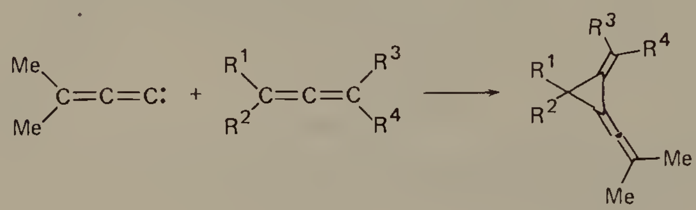


(303) (106) (304)

has been used to trap it, including less conventional cyclic alkenes like norbornadiene[503] and 2,5-dihydrofuran[504,505]. Vinyl derivatives of **302** have recently been generated by treatment of the vinylogous propargyl halides **303** with potassium *t*-butoxide in pentane at $-10°$ C (equation 106)[506]. The interception with aromatic, aliphatic, and functionalized olefins affords the vinylidenecyclopropanes **304** in fair to good yields (up to 45%).

The Hartzler reaction has been reviewed several times, the most recent survey including work that appeared up to 1971[98,507].

When vinylidenecarbenes are added to allenes, methylenevinylidenecayclopropanes **305** result (equation 107)[508]. The fully methylated derivative of **305** has



(107)

(305)

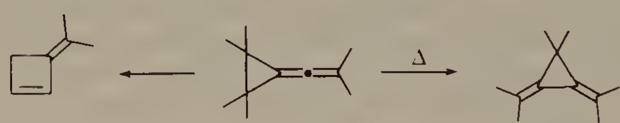
R^1-R^4 = Me

$R^1 = R^2$ = H, $R^3 = R^4$ = Me

also been prepared by adding dimethylmethylenecarbene to tetramethylbutatriene[509].

Novel developments in this area include the generation of vinylidenecarbenes under phase-transfer conditions[510-512], sometimes in the presence of crown ethers[513,514], and the use of 1-bromo-alkynes as precursors of the carbenes [515-517]. A mechanistic study has compared dimethylvinylidene and dimethylmethylidenecarbene with respect to their addition reactions with styrene and insertion reactions into several R–H bonds in aprotic solvents. The results show that the former carbene is much more reactive than the latter in the addition processes[518].

On heating, vinylidedenecyclopropanes (including the parent system **301**) rearrange to 1,2-dimethylenecyclopropanes **306** (equation 108)[497,519-524], or on exposure to zinc iodide in boiling ether to methylenecyclobutenes **307** or **306**, the



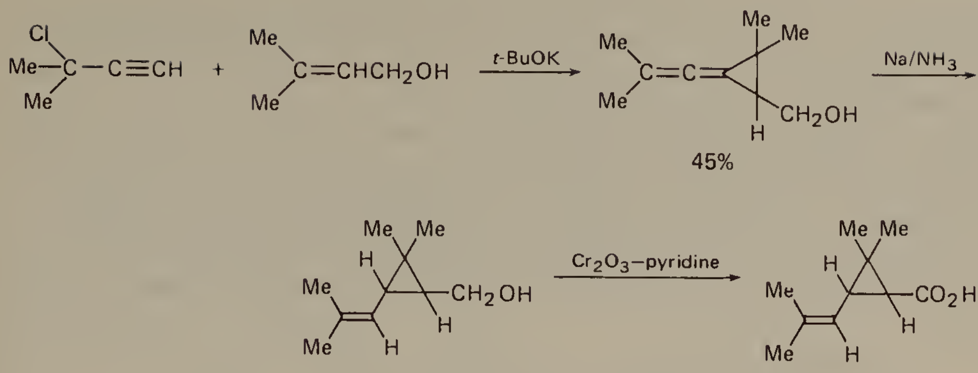
(108)

(307) (306)

direction of isomerization being strongly influenced by the number of substituents present in the starting material[525].

Among additions of alkenylidenecyclopropanes reactions with hydrogen chloride[526], *N*-phenyltriazolindione[527-529], chlorosulphonylisocyanate and tosyl isocyanate[530-532], methylene malodinitriles[533], 1,1-dichloro-2,-difluoroethylene[534], various electrophilic reagents[535] and acetylenic dienophiles[536] have been reported. Most of the allenes used in these mechanistic and preparative studies were prepared by the procedure of Hartzler.

A vinylidene cyclopropane served as the crucial reaction intermediate in a new, stereoselective synthesis of *trans*- chrysanthemic acid (**308**) (equation 109)[537]. From the product mixture formed in the oxidation step, the pure *trans* acid was isolated by gas chromatography and sublimation.



(109)

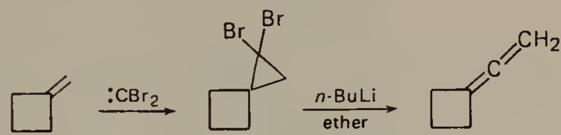
(308)

90% (*cis* and *trans*)

55%, *cis* and *trans*

b. Vinylidenecyclobutanes. Practically all vinylidenecyclobutanes known to date have been prepared by the DMS method.

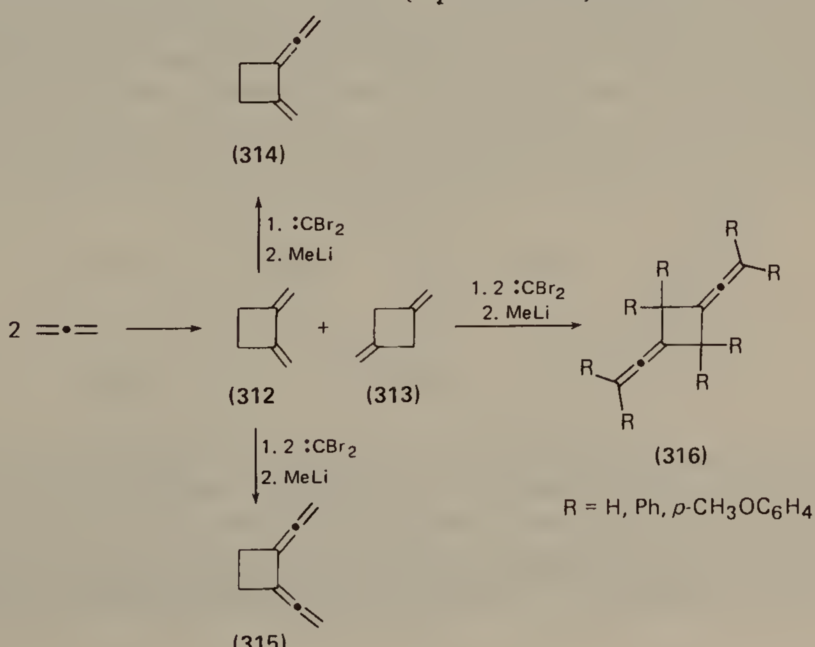
The parent compound vinylidenecyclobutane (**311**) is obtained when methylenecyclobutane (**309**) is first treated with bromoform/potassium-butoxide in pentane (60%), and the resulting 1,1-dibromo-spirohexane (**310**) then dehalogenated (equation 110)[538–542].



(110)

(309) (310) (311)

For the preparation of methylene-2-vinylidene- (**314**), 1,2- (**315**) and 1,3-bis-(vinylidene)cyclobutane (**316**, R = H), allene is thermally dimerized to 1,2- (**312**) and 1,3-bismethylenecyclobutane (**313**). These hydrocarbons are subsequently converted to **314–316** in the normal fashion (equation 111)[543,544].

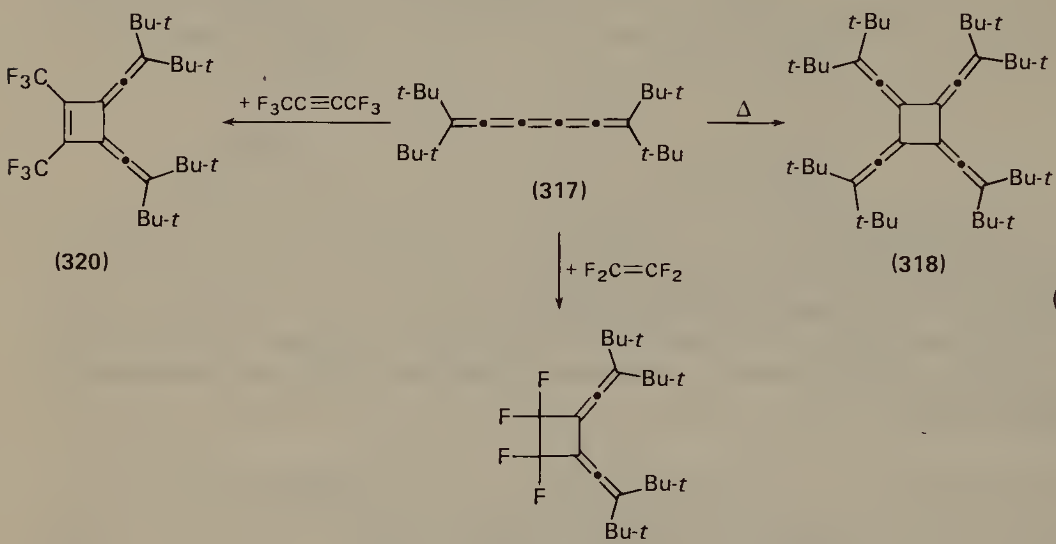


(111)

R = H, Ph, *p*-$CH_3OC_6H_4$

The octaphenyl (**315**) and octa-*p*-anisyl derivatives of **316** have been prepared by photodimerization of the corresponding tetraarylbutatrienes. Originally these dimers were thought of [4]radialene; an X-ray structure analysis has, however, proven this assumption to be erroneous[545].

A cumulene, tetra-*t*-butylhexapentaene **317**, has been used successfully to prepare the tetrakis(vinylidene)cyclobutane **318**, as well as the derivatives **319** and **320** by cycloaddition with perfluoroethylene and perfluoro-2-butyne, respectively (equation 112)[546].

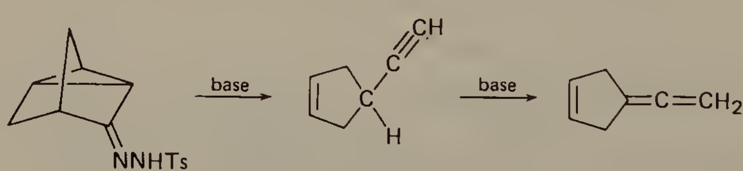


(320) (317) (318) (319) (112)

The synthesis of a tricyclic hydrocarbon incorporating the tetraallene framework of **318** has been reported[547].

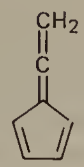
c. Vinylidenecyclopentanes. The parent system[542,548,549] and simple derivatives are obtained most readily from the corresponding *exo*-alkylidenecyclopentanes by the DMS synthesis.

4-Vinylidenecyclopentene (**323**) is isolated in small yield as an isomerization product of **322** in the decomposition (heating with sodium methoxide in diglyme at 160° C) of the *p*-toluenesulphonyl hydrazone of nortricyclanone (**321**) (equation 113)[550,551].



(321) (322) (323) (113)

Formally introducing an additional double bond in **323** produces fulvenallene (**324**). There exist nearly a dozen approaches to this interesting molecule[552], but little is known about its chemistry, although its addition and cycloaddition reactions should prove worth studying. Several phenyl and methoxycarbonyl derivatives of **324** have been reported[553,554], as has its vapour-phase infrared spectrum[555].

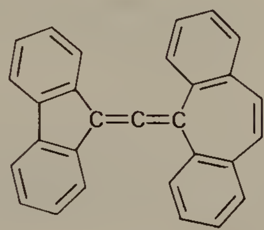


(324)

The incorporation of the fulvenallene system into the more complex frameworks **325** and **326** could in principle impart divalent character to the central carbon atom of the cumulenic linkage (cf. Section II. D.5.a on the discussion of 'push–pull' allenes):

(325)

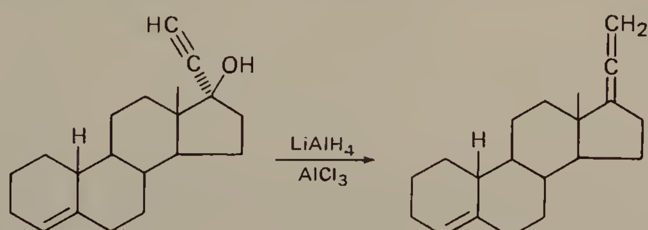
(326)



(327)

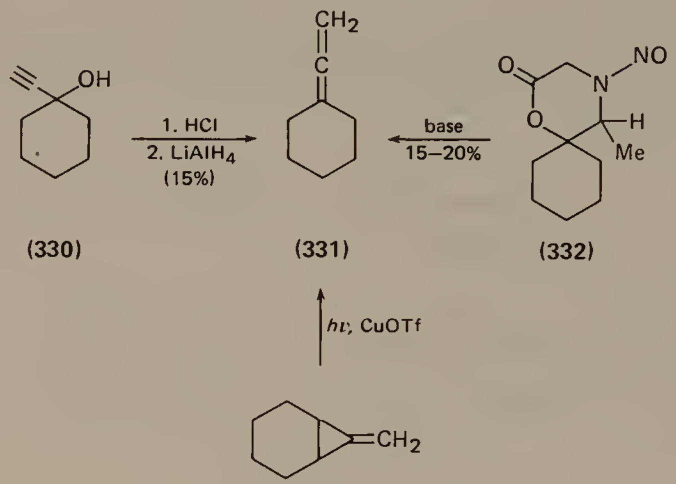
Neither **325** nor **326**, which are obviously closely related to the calicenes, are known. However **327** has been prepared[556] and according to spectroscopic data it does not possess any significant carbene character. This could, however, well be caused by the annelation, and it remains to be seen how lower or non-annelated derivatives of **327** behave.

Vinylidenecyclopentanes have been studied for mechanistic or theoretical reasons, and this structural unit has also been incorporated in a sizeable number of steroids. The allene **329** for example, has been prepared as the major reaction product in 53% yield by reduction of the propargyl alcohol **328** with lithium aluminium hydride/aluminium trichloride (3:1) in tetrahydrofuran (equation 114)[557–559].



(328) (329) (114)

d. Vinylidenecyclohexanes. Various ways of preparing the parent system of this group (**331**) have been proposed, e.g. the treatment of the acetylenic alcohol **330** with hydrochloric acid and subsequent reduction of the presumably formed chloride with lithium aluminium hydride in ether[560], the decomposition of 3-nitroso-4-methyl-5,5-pentamethylene-2-oxazolidone (332) with sodium 2-methoxyethoxide in 2-methoxyethanol[561] and the photoisomerization of 7-methylenenorcarane (333) in ether in the presence of copper trifluoromethanesulphonate (CuOTf)[562] (equation 115).

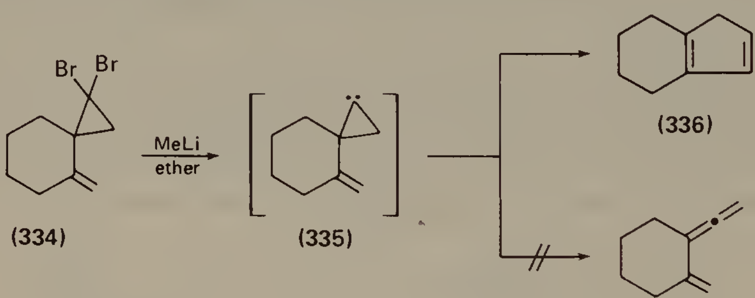


(330) (331) (332) (333)

(115)

The vinylidenecyclohexane skeleton has incorporated into various bi- and polycyclic structures. Thus the bicyclic monoterpenes β-pinene, camphene and sabinene have been converted into the corresponding allenes by the DMS route[563], and vinylideneadamantane, whose chemical behaviour has been investigated thoroughly, has been obtained analogously[564].

The DMS method does not yield the desired methylenvinylidenecyclohexane **337** when the dibromide **334** is treated with methyllithium in ether and **336** is formed as the sole reaction product (equation 116)[543].

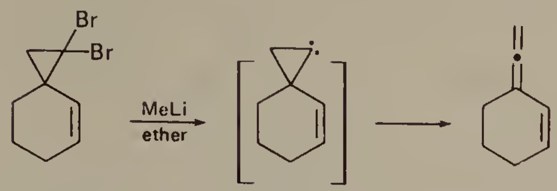


(334) (335) (336) (337)

(116)

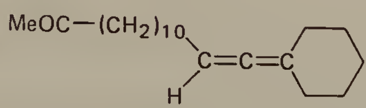
The fixed *s-cis* geometry in the presumed intermediate **335** allowing an energetically favourable vinylcyclopropane-type rearrangement is evidently responsible for the exclusive formation of **336** (cf. Section II.A.5). This is supported by a control experiment in which the *s-trans* system **338** is dehalogenated (equation 117)[543].

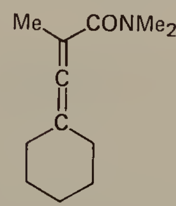
Now an allene (**340**) is formed again, presumably because the fixed *s-trans* geometry of the intermediate **339** negates interaction of the cyclopropylidene with the double bond and subsequent cyclopentadiene production.



(338) (339) (340) (117)

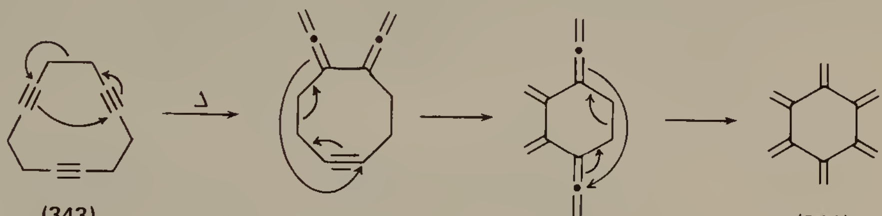
Various functionalized vinylidenecyclohexanes have been reported, e.g. the ether **341**[565] and the amide **342**[566] (cf. Section II.B.6 on the synthesis of allenic .





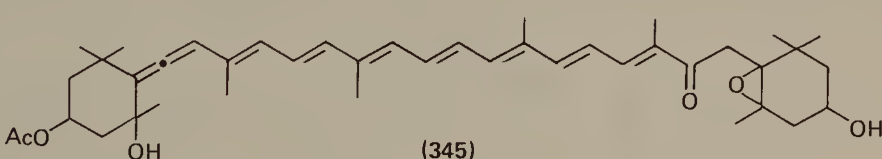
(341) (342)

amides), and reaction intermediates incorporating this allenic ring system have been invoked in several isomerization reactions[567,568], as for example, in the astonishing thermal rearrangement of 1,5,9-cyclododecatriyne (**343**) to [6]radialene (**344**) (equation 118)[569].

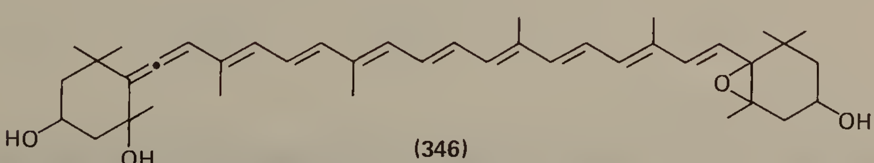


(343) (344) (118)

Numerous natural products incorporate the vinylidenecyclohexane ring system, including fucoxanthin **345** found in brown algae, and the structurally related neoxanthin **346**, which is present in all green leaves[570,571]. The latter pigment may be the precursor of the so-called grasshopper ketone **347**, isolated from an ant-repellent secretion of the large flightless grasshopper *Romolae microptera*[572–576].



(345)



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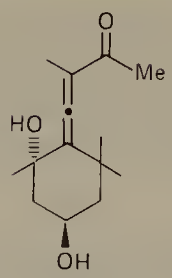
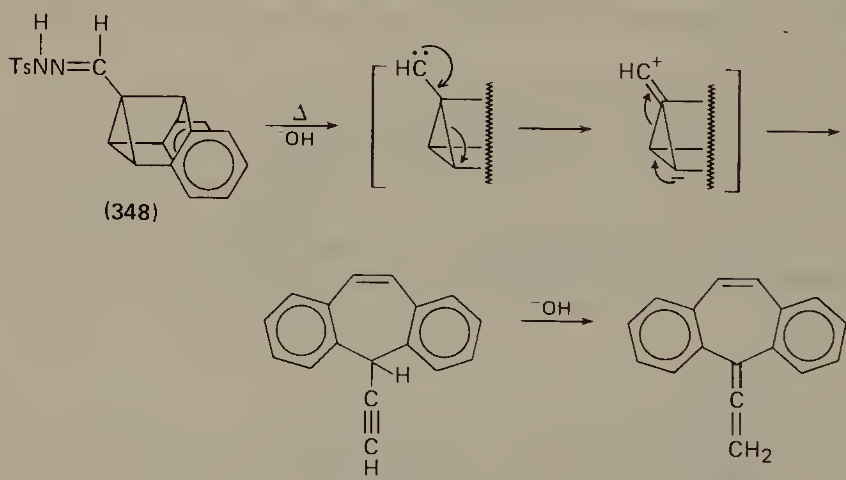


(347)

In another recent development, allenic retinals are used for the preparation of artificial rhodopsin analogues[577].

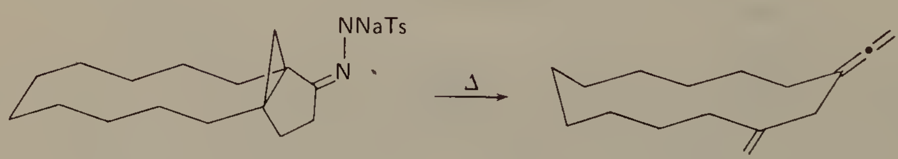
e. Higher vinylidenecycloalkanes. Very few vinylidenecycloalkanes containing a ring larger than six-membered are known, and they have been prepared by base-induced decomposition of various tosylhydrazones.

The dibenzo-annellated 5-vinylidenecycloheptene **350** is formed when dibenzo-semibullvalene 1-carboxaldehyde tosylhydrazone (**348**) is treated with sodium hydroxide (equation 119)[578]. The (not detected) acetylene **349** is the most likely precursor of **350**.



(348) (349) (350) (119)

Decomposition of the sodium salt of the tosylhydrazone **351** under various conditions causes the formation of methylene-3-vinylidenecyclotridecane (**352**) (equation 120)[579].



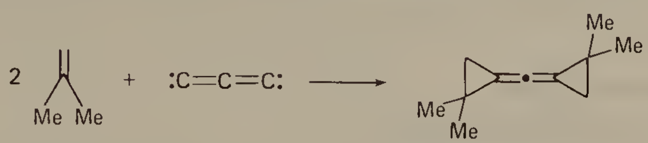
(351) (352) (120)

3. *Bicyclic allenes of type (iii)*

The smallest allene of this type, dicyclo-propylidenemethane (**353**), has been synthesized by the DMS approach[580], or by an elimination[581] (see equation 121).

(353) (121)

Actually the first derivatives of **353** were prepared much earlier in one of the rare preparative applications of the reaction of triatomic carbon, C_3, with olefins. Carbon vapour produced *in vacuo* ($10^{-3}-10^{-5}$ torr) reacts with isobutylene at a liquid nitrogen-cooled surface to produce the tetramethyl derivative **354** in 40% yield (equation 122)[582–584].

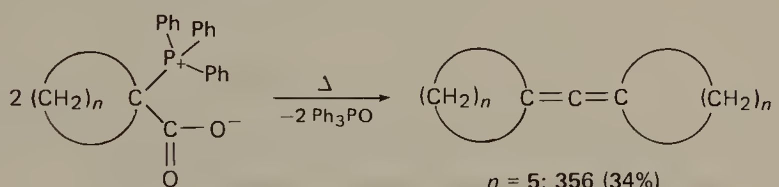


(354) (122)

With propene this reaction provides three isomeric 'bisethanoallenes'[582]. When the same technique is applied to certain imines, diazo derivatives of **354** are formed[585].

Dicyclobutylidenemethane ('1,3-bis(trimethylene)propadiene') has been prepared from the now readily available bicyclobutylidene[586].

While 1,3-bis(tetramethylene)propadiene apparently has not been synthesized, the next two members of the series, **356** and **357**, have been obtained by pyrolysing betains of the type **355** (equation 123)[587]. It is likely that in this dimerization reaction ketenes are produced as intermediates.



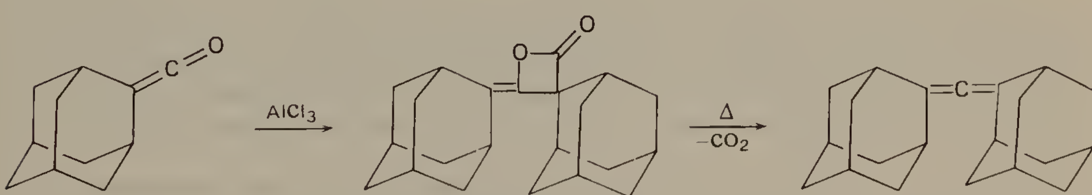
(123)

(355)

n = 5: 356 (34%)

n = 6: 357 (36%)

The ketene **358** has in fact been used as the starting material in the synthesis of bisadamantylidenemethane (**360**) through the β-lactone dimer **359** (50%), which on heating to 260° C decomposes to **360** (95%) and carbon dioxide (equation 124)[588].

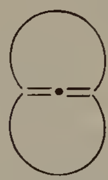


(358) (359) (360)

(124)

An allene of type (iii) containing at the same time a five- and seven-membered ring has been discussed in Section II.C.2.c.

An isomeric structure of iii is conceivable in which the two 'bridges' are not anchored at the same carbon atom but at the end of the allene system, *viz:*



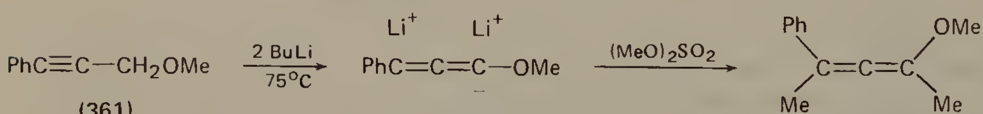
No stable representative of this topologically intriguing molecule seems to be known.

D. Heterosubstituted Allenes

1. *Group Ia and IIa substituted allenes*

Although alkali and alkaline earth derivatives of allenes must be involved in many reactions of allenes and alkynes, not much is known about their structure, and the number of deliberate attempts to prepare these compounds is very limited. For example, the base-catalysed isomerization of acetylenes, which has been studied in great detail[32,589] and used for preparative purposes[1,5], presumably involves allenyl sodium and potassium compounds. These derivatives have, however, never been prepared as such. Allenic salts whose structures have been established by i.r. and n.m.r. spectroscopy are the magnesium, zinc and aluminium derivatives of allene, which are formed when propargyl bromide is reacted with the respective metal[590,591].

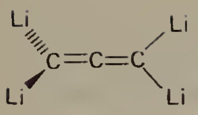
Most publications in this area have been concerned with lithio derivatives. These are for example formed from various allenic ethers $H_3CO{-}CH{=}C{=}C(R)SiMe_3$ [592] and from acetylenic ethers PhC≡C—CHROMe (R = H, Me, Et, *i*-Pr)[593] by treatment with *n*-butyllithium. If one equivalent of **361** is metalated with two equivalents of *n*-butyllithium in ether at –75° C the allenic dianion **362** is generated. Its formation if proven by a host of derivatization reactions, the methylation with dimethyl sulphate to **363** serving as one example (equation 125)[592].



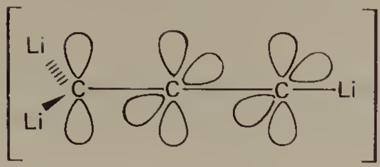
(361) (362) (363) (125)

Unsubstituted allenic hydrocarbons have also been converted into lithioallenes. For example, the reaction of 3,3-dimethylallene (3-methyl-1,2-butadiene) with lithium tetramethyl piperidide or with methyllithium leads to 3,3-dimethylallenyllithium, as evidenced by the n.m.r. spectrum of the derivative generated[594]. The conversion of bromoallenes into allenyllithium reagents has already been referred to[107].

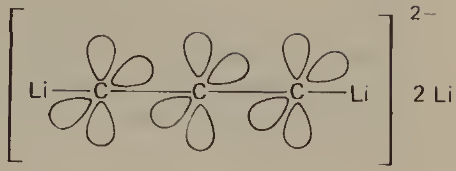
Metalation of various alkynes with alkyllithium agents and subsequent derivatization with, for example, trimethylchlorosilane affords silicon-substituted allenes of great variety and often in good yields[595-597]. This does not, however, necessarily indicate that the intermediate lithio derivatives possess an allenic structure. For example, the 'lithiocarbon' C_3Li_4, which is produced when propyne is polylithiated in hexane, was originally thought[595,598] to have the allenic structure



(364)

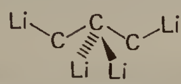


(365)



(366)

364. However, the infrared spectroscopic evidence on which this assignment was based, has been reinterpreted in terms of either a tetralithiopropargylide **365** or a tetralithiosesquiacetylenic structure **366**[596,599], with the second alternative being favoured[600]. *Ab initio* molecular orbital calculations support structure **367** for the



(367)

most stable configuration of C_3Li_4[601]. This structure is very similar to **366**, but according to the authors[601] it is more satisfactory to postulate a multicentre, covalently bonded structure than an ion-pair arrangement, as in **366**. Unfortunately no X-ray structural investigation has been performed on C_3Li_4 as yet.

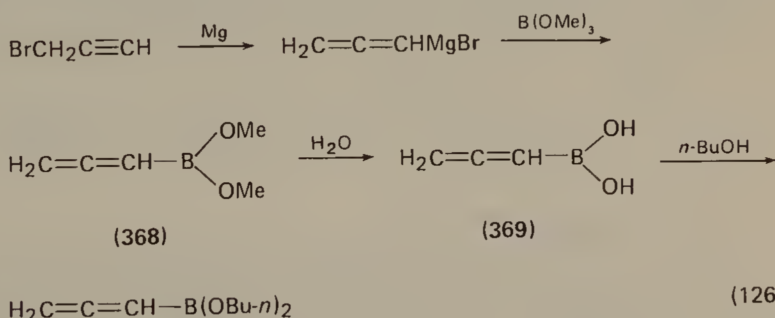
More complicated alkynes like 2,4-hexadiyne also lead to allenic and cumulenic products if submitted to the above metalation–derivatization sequence[597,602], but again, no refined structural data are available and hence the structure assignment is an open question.

Although they are derivatives of a Group IIb element, it should be noted that several allenic mercury compounds, including diallenylmercury[603,604], have been prepared.

2. *Group IIIa substituted allenes*

a. Aluminium. Allenes carrying aluminium substituents have been prepared by the reaction of propargyl halides with aluminium (cf. Section II.D.1), however, no stable derivative has been isolated and characterized. This contrasts with the recent synthesis of a stable aluminium derivative of [3] cumulene (cf. Section III.D.1).

b. Boron. The only stable derivatives in this class are boronates. Thus the bis-*n*-butyl derivative **370** may be obtained by reacting allenylmagnesium bromide with methyl borate via intermediate **368** and the not isolated boronic acid **369**



(368) (369) (370) (126)

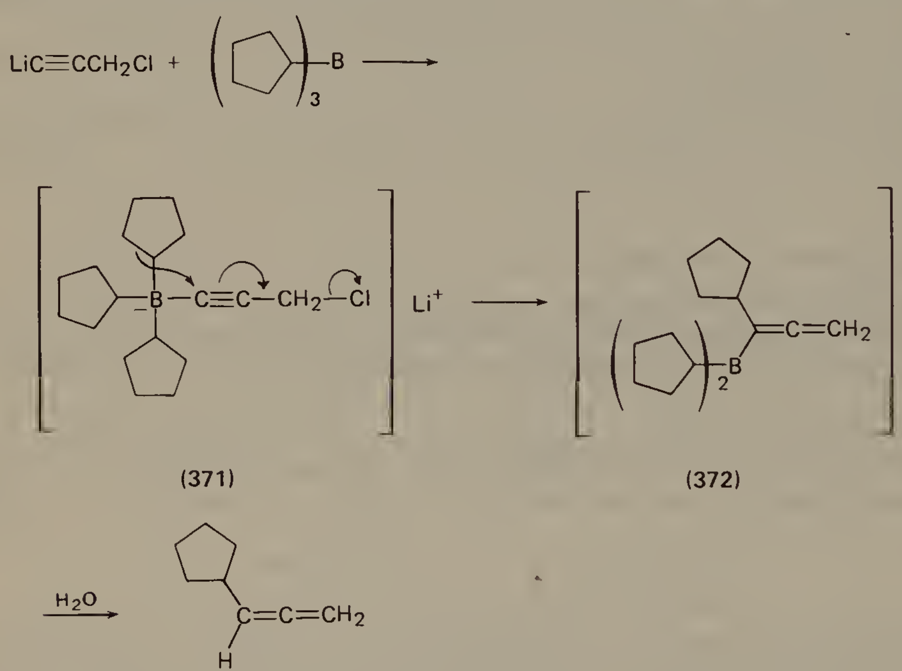
(equation 126)[605]. Several allenyl boronates carrying alkyl substituents at $C_{(1)}$ and $C_{(3)}$ of the allenyl moiety have been prepared by the same method in medium yields (30–60%)[606], and derivatives in which the boron atom is part of a cyclic system are also known[607,608].

It is interesting to note that the allenyl boronates **370** react with aldehydes like allenylmagnesium bromide, providing, after hydrolysis, α-acetylenic alcohols (equation 127)[609].

$$\mathbf{370} + n\text{-PrCHO} \longrightarrow HC{\equiv}C{-}CH_2{-}\underset{\displaystyle n\text{-Pr}}{CH}{-}OB(OBu\text{-}n)_2$$

$$\xrightarrow{3\,H_2O} HC{\equiv}C{-}CH_2\underset{\displaystyle OH}{CH}{-}Pr\text{-}n + B(OH)_3 + 2\,n\text{-BuOH} \qquad (127)$$

Allenic boranes have been suggested as reaction intermediates in a novel allene synthesis[610]. For example when lithium chloropropargylide is treated with tris (cyclopentyl)borane the initially generated ate complex **371** may undergo a spontaneous anionotropic rearrangement in which one cyclopentyl substituent migrates from boron to carbon concomitant with an electron-pair shift and loss of chloride. The boroallene **372** produced is not isolated but hydrolysed to a substituted allene (cf. Section II.B.1) (equation 128)[610].

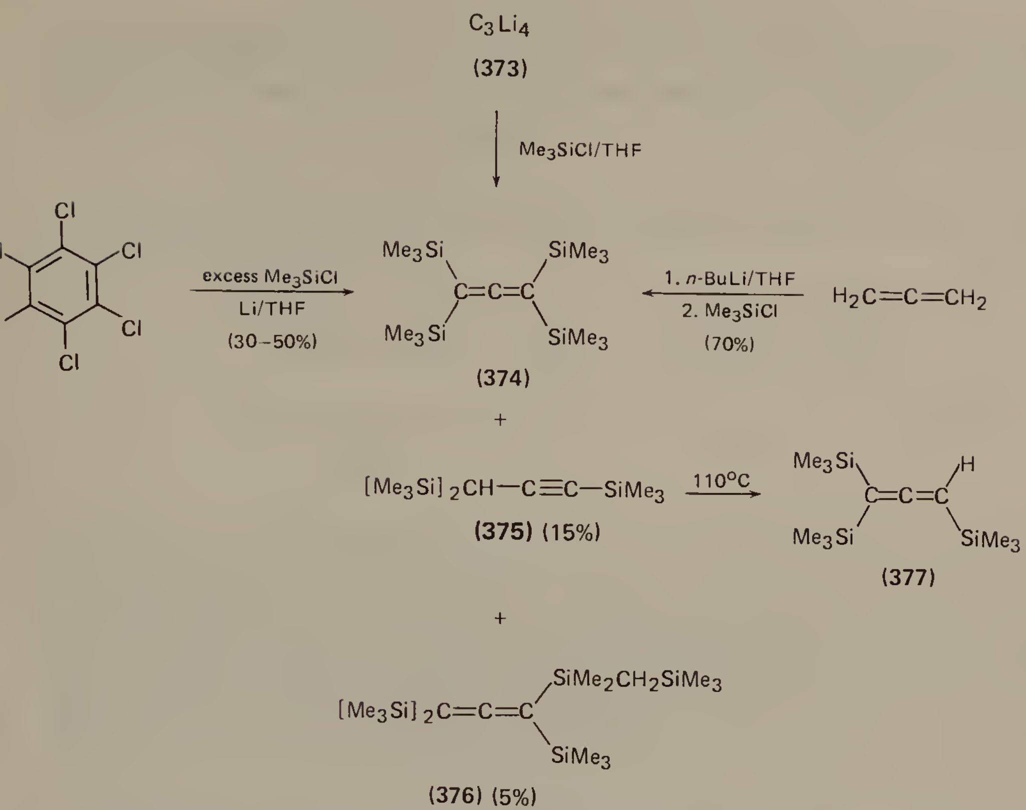


(371) (372)

(128)

3. *Group IVa substituted allenes*

a. Silicon. The number of silicon derivatives of allenes has increased rapidly during the last few years. As shown in equation (129), C_3Li_4 (**373**), obtained by treating propyne in hexane with four equivalents of *n*-butyllithium, may be derivatized with trimethylchlorosilane to tetrakis(trimethylsilyl)allene (**374**), with the tris- (**375**), and penta- (**376**) silicon compounds produced as side-products (equation 129)[598,61].

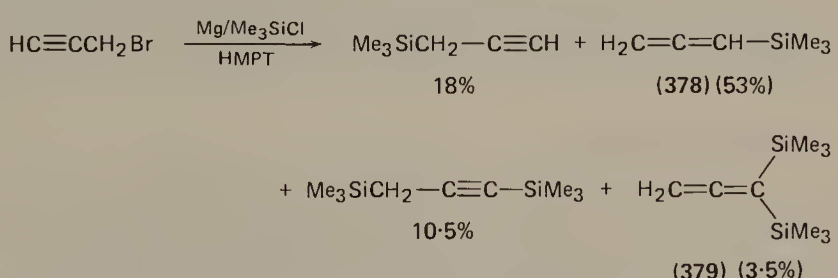


(129)

On heating, compound, **375** is partially isomerized to the trisubstituted allene **377**. Compound **374** has also been prepared, in an unusual reaction, from hexachlorobenzene[612] and other polyhalogenobenzenes[613], as well as by passing gaseous allene into a solution of *n*-butyllithium in hexane/tetrahydrofuran at –50° C and subsequently adding an excess of trimethylchlorosilane[614].

Other alkynes that have been converted into lithiated species and derivatized to silicon-carrying allenes include the isomeric butynes[598,599], 3-methylbutyne[599], 1,3-pentadiyne[615], 2,4-hexadiyne[597,602], 1-phenylpropyne[616] and various enynes[617].

In a more direct, but mechanistically presumably similar, route mono- (**378**) and bis- (**379**) (trimethylsilyl)allene are obtained when propargyl bromide (or allenyl bromide, which leads to the same product mixture) is treated with the system trimethylchlorosilane/magnesium/hexamethylphosphoric amide at 50–60° C (equation 130)[618].



(130)

The preparation of various allenic silicon compounds carrying functional groups [592,619,620] as well as triphenylsilyl-substituted allenes has also been described[621].

b. Germanium, tin and lead. Germanium, tin and lead derivatives of allenes may be prepared by reacting the Grignard reagents of propargyl bromides with halides of the general structure R^1_3MX (**380**), where M stands for the metal atom (equation 131)[622]. In principle, the process can lead to three isomeric structures **381**–**383**;

$$R^1_3MX + BrMgCHR^2{-}C{\equiv}C{-}R^3 \longrightarrow \begin{cases} R^1_3MCHR^2{-}C{\equiv}C{-}R^3 & \textbf{(381)} \\ R^1_3MCR^3{=}C{=}CHR^2 & \textbf{(382)} \\ R^1_3MCR^2{=}C{=}CHR^3 \text{ (not formed)} & \textbf{(383)} \end{cases} \qquad (131)$$

(380)

M = Ge, Sn, Pb

X = Hal.

however, allenes **383** possessing the 'retained' configuration of the propargyl substituents are never formed. The ratio of the two isomers **381** and **382** depends on the nature of the metal atom and the substituents R^1, R^2 and R^3, the highest percentage of allenes being obtained with M = Pb. The strongest substituent effect is exhibited by R^3, and largest allene yields are obtained with R^3 = H. The nature of R^1, whether alkyl or aryl, is comparatively unimportant. The propargyl derivatives **381** of tin (M = Sn) rearrange into their isomers**382** within minutes when heated in electron-donating solvents, thus providing another route to these allene derivatives[622-624].

In a third method[623] triphenyltin bromide is first converted into its lithio derivative**384** which, on addition of propargyl bromide, yields triphenyltinallene **385** (equation 132)[623]. No propargyl isomer is produced in this case.

$$Ph_3SnBr \xrightarrow[THF]{Li} \underset{\textbf{(384)}}{Ph_3SnLi} \xrightarrow[30\%]{+\,HC{\equiv}CCH_2Br} \underset{\textbf{(385)}}{Ph_3SnCH{=}C{=}CH_2} \qquad (132)$$

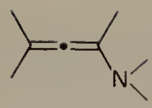
Hydrostannation with trimethyltin hydride of enynes has been reported, but the low yields of the desired 1,4-addition products render this procedure impractical[625]. Derivatization of the polylithio derivative of propyne (cf. Sections II.D.I and II.D.3a) with trimethyltin chloride has been shown to yield tetrakis(trimethylstannyl)allene as the principal product[598]. It seems likely that this technique could be extended to the synthesis of many other Group IVa substituted allenes.

With the exception of a few reactions of allenyltins (electrophilic displacement[626], sulphur dioxide insertion into the carbon–tin bond[627], reaction with iodine[628]), the chemical behaviour of this class of allene derivatives seems to be largely unexplored.

4. *Group Va substituted allenes*

a. Nitrogen. Allenes carrying one or more nitrogen-derived functional groups at one of the allenic carbon atoms (**386**) or in the α- (**387**) or β- (**388**) position have been reported. A systematic investigation of this group is lacking, however.

The derivatives **386** are of preparative interest, since they constitute a special type of enamines. In fact, one of the earliest reports on the synthesis of enamines describes the formation of what is probably *N*-allenylpiperidine[629,630].



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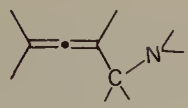

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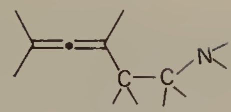


(388)

Allenic amines **390** have been prepared by isomerization of *N,N*-dialkyl-2-alkynylamines, **389** using a dispersion of potassium amide on alumina as a catalyst system (equation 133)[631].

(389) (390) (133)

R^1 = H, Et

$R^2 = R^3$ = alkyl, cycloalkyl

In the case of R^1 = H the product is unstable, giving rise to the formation of olefinic side-products. With R^1 = Et the allenic amine may be distilled, however. Further base treatment converts **390** to *N,N*-dialkyl-1-alkynylamine, i.e. the above isomerization represents a novel procedure for the synthesis of ynamines. An extention of this method has lead to the preparation of derivatives **390** whose nitrogen atom is incorporated into a heterocyclic system[634].

Nearly all of the simple *N,N*-bistrifluoromethylaminoallenes have been obtained by elimination reactions, with only the tetrakis derivative missing. The preparation of 1,3-di(bistrifluoromethylamino)propadiene (**393**) may illustrate the general approach used (equation 134)[633-635].

$$2\,(CF_3)_2NBr + H_2C{=}C{=}CH_2 \xrightarrow{h\nu} \qquad (134)$$

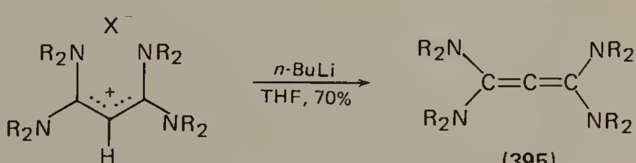
(391)

$$(CF_3)_2N{-}CH_2CBr_2CH_2{-}N(CF_3)_2 \xrightarrow{KOH} (CF_3)_2NCH{=}C{=}CHN(CF_3)_2$$

(392) (93%) (393) (97%)

Irradiation of a 2:1 molar mixture of the *N*-bromoamine **391** and allene in the vapour phase in daylight gives the 2:1 adduct **392** in high yield. When the latter is dehydrobrominated over potassium hydroxide the disubstituted allene[393] is produced nearly quantitatively.

The allentetramines **395** have been prepared by treatment of the 1,1,3,3-tetrakis-(dialkylamino)allyl cations **394** ($X^- = Cl^-$, ClO_4^-) with *n*-butyllithium (equation 135)[636].



(394) (395) (135)

R = Me, Et

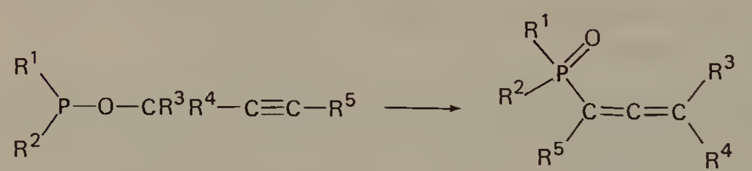
Reactions of **395** with water, phenyl cyanate, sulphur, carbon dioxide, and carbon sulphide have been carried out, and it has been concluded that these allene derivatives are comparable in reactivity to ynamines and ethylenetetramines. Dialkoxydiaminoallenes were prepared by the same method, starting with the corresponding dialkoxydiamino cations[636].

Allenic quaternary ammonium salts are produced in varying amounts when tertiary propargylic chlorides $R^1R^2CCl{-}C{\equiv}CH$ are treated with trialkylamines. Enynes are also formed in this reaction, and the product ratio depends on factors like the size of the substituent R^1 and R^2, basicity and nucleophilicity of the tertiary amine employed[637,638].

Other allenic nitrogen compounds which have been described or postulated in the literature include allenic azides[639], diazoallenes and allenyl diazotates[640], phosphoramides[641] and amides [642] with the nitrogen atom bonded directly to the allene moiety. (For the synthesis of the amides of allene carboxylic acids cf. Section II.B.6.) Allenic amines have been invoked as intermediates in the thermal [3,3] singmatropic isomerization of 4-dimethylamino-1-hexen-5-ynes[643].

α-Allenic amines have been obtained by treatment of *gem*-amino ethers and aldimines with various organometallic reagents derived from propargyl bromide[644-646], and especially by 1,4-addition of amines and lithium dialkylamides to conjugated enynes[8,48,49]. *β-Allenic amines* are formed when 1-azido-2-en-4-ynes are reduced with lithium aluminium hydride[647,648]. They have been deaminated by nitrous acid treatment, and in the large majority of cases do not show homoallenic participation (cf. Section II.B.4b)[649].

b. Phosphorus. A large number of phosphorus-substituted allenes, especially phosphine oxides **397** (R = alkyl or aryl) is known and most of them have been prepared by the propargylic rearrangement of various 2-alkinyl esters **396** of phosphorus, phosphonous and phosphinous acids, respectively. In fact, the acetylenic esters **396** are in most cases not isolated, since they are only stable at room temperature or below (equation 136).



(396) (397) (136)

As indicated in a recent review of this isomerization[650], the substituents in **396** may be varied over a very broad range. The atoms adjacent to phosphorus may be oxygen, nitrogen, sulphur and carbon, and the 2-propynyl moiety may carry all kinds of substituents from hydrogen to saturated and unsaturated[651-653], acyclic and cyclic[654] groups, as well as halogen[655]. Allenic sugar phosphonates have been obtained by this procedure[656]. The reaction proceeds via a five-membered transition state by nucleophilic attack of the terminal acetylenic carbon atom by the phophorus lone-pair electrons. The process is stereospecific, providing optically active allenes from optically active acetylenic alcohols[650,657,658]. The substrates **396** are frequently obtained by reacting diphenylchlorophosphines or dichlorophenylphosphines with propargyl alcohols in the presence of a tertiary base like *N*-methylmorpholine[659], triethylamine[660,661] or pyridine[658].

Allenic phosphonyl halides and their hydrolysis products, allenic phosphonic acids, have been prepared by treatment of propargylalcohols with phosphorus tribromide and trichloride under carefully controlled conditions[662]. Under the influence of Bronsted acids phosphonic acids cyclize to oxaphospholenes[663,664].

Several *allenic phosphines* have been prepared and subjected to a detailed n.m.r. analysis[665-667]. The *allenyl phosphonium salt* **399** is formed when the phosphonium bromide **398** is dehydrobrominated with triethylamine (equation 137)[668].

$$[Ph_3\overset{+}{P}CH_2CBr{=}CPh_2]\,Br^- \xrightarrow{\text{base}} [Ph_2C{=}C{=}CH\overset{+}{P}Ph_3]\,Br^- \qquad (137)$$

(398) (399)

The diphenylphosphine oxide substituent exerts an activating influence on the allene grouping (cf. Section II.D.5.b for a similar effect for certain sulphur-substituted allenes), allowing, among others, the facile addition of lithium dimethylcuprate[669,670].

The stereospecific selective hydrogenation of 1,2-diene phosphonic esters with a 5% palladium on calcium carbonate catalyst as a general route to *cis*-1-alkene phosphonates has been noted[671].

5. *Group VIa substituted allenes*

a. Oxygen. Among the oxygen-substituted allenes most effort has been devoted to the synthesis and applications of allenyl ethers, readily prepared by isomerization of suitable 2-alkynyl ethers with various bases[672-678].

For example, when the propynyl ethers **400** are heated without a solvent in the presence of potassium *t*-butoxide the allenyl ethers **401** are formed in excellent yields (equation 138)[673] and no 1-propynyl ethers $H_3C{-}C{\equiv}C{-}OR$ are produced.

$$HC{\equiv}C{-}CH_2OR \xrightarrow[70^{\circ}C,\ 2-3h]{t\text{-BuOK}} H_2C{=}C{=}CHOR \qquad (138)$$

(400) (401)

R	Yield (%)
Me	82
Et	85
n-Bu	91
n-C_6H_{13}	92
$-CH(Me)OEt$	90

The products **401** are themselves useful starting materials for higher substituted allenyl ethers, since metalation with *n*-butyllithium removes the allenic hydrogen atom next to the oxygen substituent, and the resulting anions react with alkylating and benzylating reagents to afford ethers of the general structure $H_2C{=}C{=}CR^1OR$ in good yield[673]. When propynyl ethers are isomerized with *n*-butyllithium in the presence of TMEDA (tetramethylenediamine) in ether at -78° C the allenic carbanion produced *in situ* can be trapped to polysubstituted allenic ethers with dialkyl sulphates or trimethylchlorosilane in nearly quantitative yield[679].

In more recent investigations, 1,3-dialkoxy-1-alkynes $R^2R^3C(OR^1){-}C{\equiv}C{-}OR$, where R and R^1 are alkyl substituents, and R^2 and R^3 stand for hydrogen or alkyl, have been reacted with organolithium compounds R^4Li to afford mixtures of

1-substituted allenyl ethers $R^2R^3C{=}C{=}CR^4OR$ and 2-alkynyl ethers of the general structure $R^2R^3C(OR^1){-}C{\equiv}C{-}R^4$. The product ratio depends on the nature of R^4Li, the leaving groups OR and OR^1, as well as the solvent[680].

In another novel procedure, Grignard reagents attack propynal diethylacetal **402** at the terminal carbon atom in the presence of cuprous bromide, to provide the allenic ethers **403** in about 80% yield (equation 139)[681].

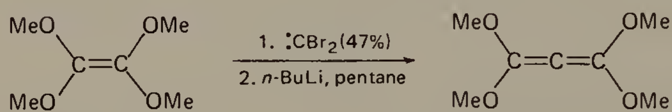
$$\text{RMgX} + \text{HC}{\equiv}\text{C}{-}\text{CH(OEt)}_2 \xrightarrow[-25\text{ to }+30^{\circ}\text{C}]{\text{CuBr}} \text{R}{-}\text{CH}{=}\text{C}{=}\text{CHOEt} \qquad (139)$$

(402) (403)

X = Cl, Br R = *n*-Bu, *t*-Bu, *c*-Pe

Less common methods leading to allenic ethers are the reaction of propargyl and allenyl chloride with sodium alkoxides[682,683], the alkaline cleavage of certain *N*-nitroso-*N*-2-propynyl amides in methanol, and the photolysis of alkynone tosylhydrazones[684].

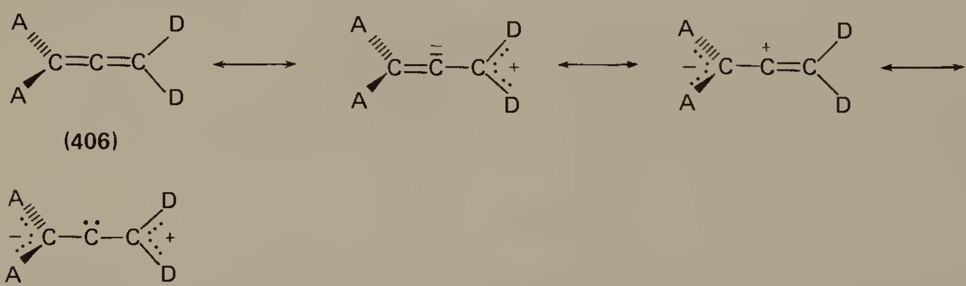
The DMS synthesis has also been used to prepare several alkoxyallenes[685], e.g. in the synthesis of the tetramethoxyallene **405** from the corresponding olefin **404** (equation 140)[686]. Allene **405**, the acetal of carbon suboxide, is another member of



(404) (405) (72%) (140)

electron-rich allenes (cf. Section II.D.5.a and 5.b) whose chemical behaviour towards acids[687], and in various [2 + 2] cycloadditions[688,689] has been studied.

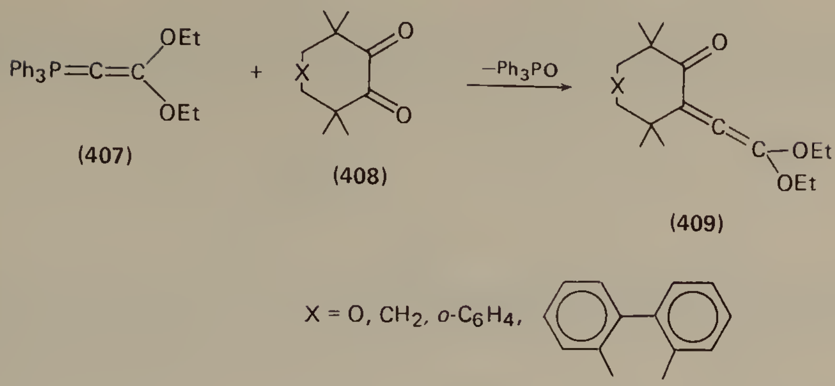
In the so-called *push–pull allenes* **406**, A stands for an electron-accepting and D



for an electron-donating substituent. As indicated by the various resonance structures these substituents can impart either nucleophilic or electrophilic, as well as carbene-like character on the central carbon atom.

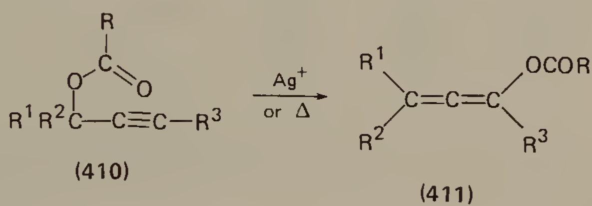
Several push–pull allenes **409** have been synthesized by the Wittig reaction of 2,2-diethoxyvinylidenetriphenylphosphorane (**407**) with nonenolizable 1,2-diketones **408** (equation 141)[690-692].

The reactions of the monocyclic derivatives **409**(X = O, CH_2) with water, ethanol and acid chlorides are best explained by assuming nucleophilic character of the central atom. On the other hand, this position possesses carbenoid properties in the case of the aromatic push–pull allenes, as shown by the reaction of these derivatives with carbon disulphide, sulphur and other carbene traps[693], as well as their dimerization to sterically hindered olefins[694].



(141)

Allenyl enol esters of type **411** may be prepared by thermal or silver-ion catalysed 'Saucy–Marbet rearrangement' of propargyl acetates **410** or substituted *p*-nitrobenzoates (equation 142)[34,695–697]. The yields vary from 40–65% depending upon the degree of substitution and the size of the substituents. Terminal



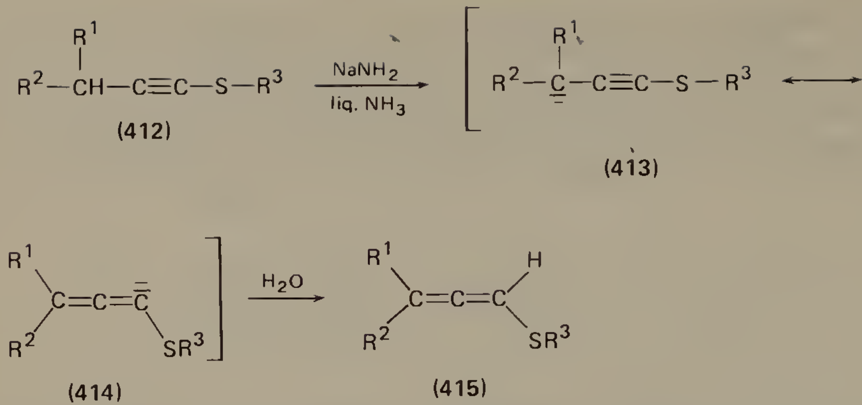
(142)

alkynes give better yields than internal ones, and tertiary esters rearrange normally with higher yields and faster than secondary esters. With aromatic substituents at R^1, R^2 or R^3 mixtures of **410** and **411** result. Solvents used include chlorobenzene, aqueous dioxane and dichloromethane, with various silver salts being used as catalysts. A detailed mechanistic investigation has shown that the reversible **410** ⇌ **411** rearrangement can best be described as a [3s,3s] sigmatropic reaction occurring in a silver(I) π-complex with the carbon–carbon triple bond[698]. Interestingly, the Saucy–Marbet reaction takes a completely different course when the metal salt catalyst is changed to zinc chloride as shown by dehydrolinanyl-acetate which in the presence of this latter catalyst only leads to cyclized products, whereas with silver nitrate the normal, i.e. rearranged acyclic products are formed [699].

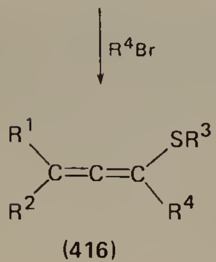
Allenyl ethers can be converted to 2-methoxyvinylacetylenes[700], to furan derivatives[701,702], and hydrolysed to α,β-unsaturated carbonyl compounds[679]. Reaction with Grignard reagents in the presence of copper(I)-halides leads to 1-alkynes[703], and treatment with preformed homo- or hetero-cuprates provides vinyl ethers[704]. The preparation of Wittig reagents (from methoxyallene) carrying a methoxyvinyl substituent has recently been described. After condensation with carbonyl components the enol ether grouping is hydrolysed by acid treatment, affording α,β-unsaturated aldehydes[705].

b. Sulphur. In all cases discussed here the sulphur-derived functional group will be in the position α to the allene unit.

Allenyl sulphides **415** (allenyl thio ethers) are most easily prepared from the readily available[706] alkynyl thio ethers **412** by base-catalysed propargyl rearrangement (equation 143)[707,708].



(143)



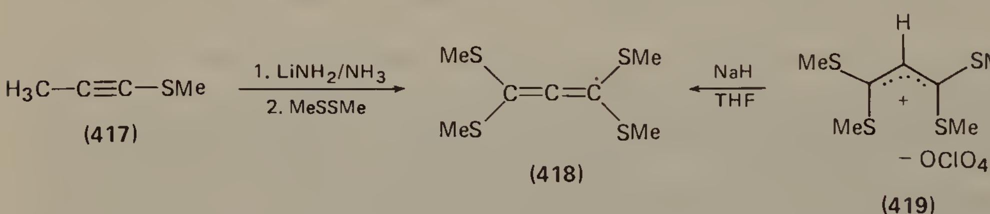
R^1	R^2	R^3	Yield (%)
H	H	Et	70–75
Me	H	Et	
Et	H	Et	
n-Pr	H	Et	

The allenic carbanions **414** formed as intermediates in this process may also be trapped with primary and secondary alkyl bromides, thus opening up a route to the l-alkylated systems **416**.

The isomerization is not restricted to alkyl substituted systems (for example R^1 in **412** may be phenyl[709]), and other bases, like potassium *t*-butoxide in dimethylsulphoxide, have also been applied[710].

1-Alkynylallenyl sulphides are obtained (as secondary products) when alkyne thioacetates are reacted with propargyl bromide in liquid ammonia[711]. A somewhat related approach has been developed to arrive at 1-alkenylallenyl sulphides[712,713].

Various methods are known to prepare 1,1,3-tris- and 1,1,3,3-tetrakis-(alkylthio)allenes. For example, when 1-methyl-thio-propyne (**417**) is added to an excess of lithium amide in liquid ammonia followed by dimethyldisulphide, tetrakis-(methylthio)-allene (**718**) is formed in good yield (equation 144)[714]. The same



(144)

allene, as well as its ethyl, *t*-butyl and phenylderivatives, has also been prepared by deprotonation of the allyl perchlorates **419** with sodium hydride in tetrahydrofuran[715].

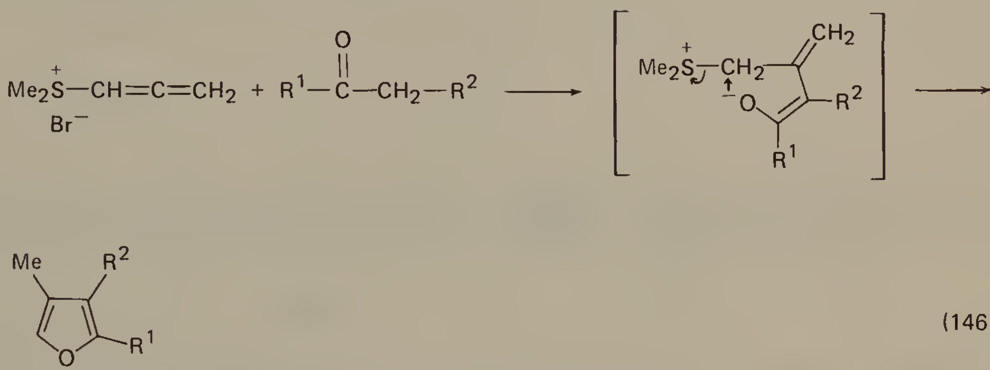
Allenic thio ethers, especially in the form of their carbanions **414**, which react with various electrophiles, have frequently been used in organic synthesis, as indicated by a recent summary[716]. Cycloaddition reactions of tetrakis(ethylthio)-allene with tetracyanoethylene and sulphonyl isocyanate and isothiocyanate occur *via* dipolar intermediates[717].

α-Allenic sulphonium salts **421** are produced from their propargyl isomers **420** (prepared from propargyl bromide and an dialkylsulphide) in neutral or basic solution (equation 145)[718].

$$R^2\overset{+}{S}{-}CH_2C{\equiv}CH \;\; ^{-}Br \longrightarrow R^2\overset{+}{S}{-}CH{=}C{=}CH_2 \;\; Br^{-} \qquad (145)$$

(420) R = Me, Et (421)

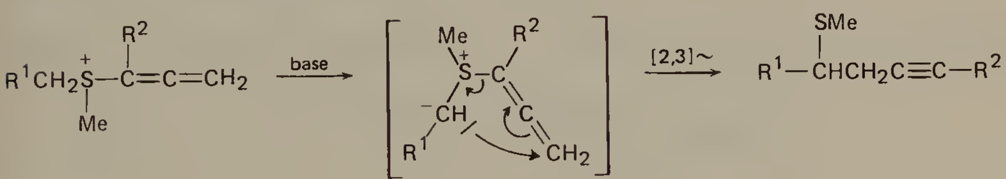
Their reactions with β-keto esters, β-keto sulphones or β-diketones in ethanolic solution in the presence of sodium ethoxide leads to furans **422** in good to excellent yields (equation 146)[719,720].



(146)

(422)(70–90%)

Various unsaturated sulphonium ylids have been prepared *in situ* by treating allenic sulphonium salts with base, and as expected, these species undergo a [2,3] sigmatropic shift (equation 147)[721].



(147)

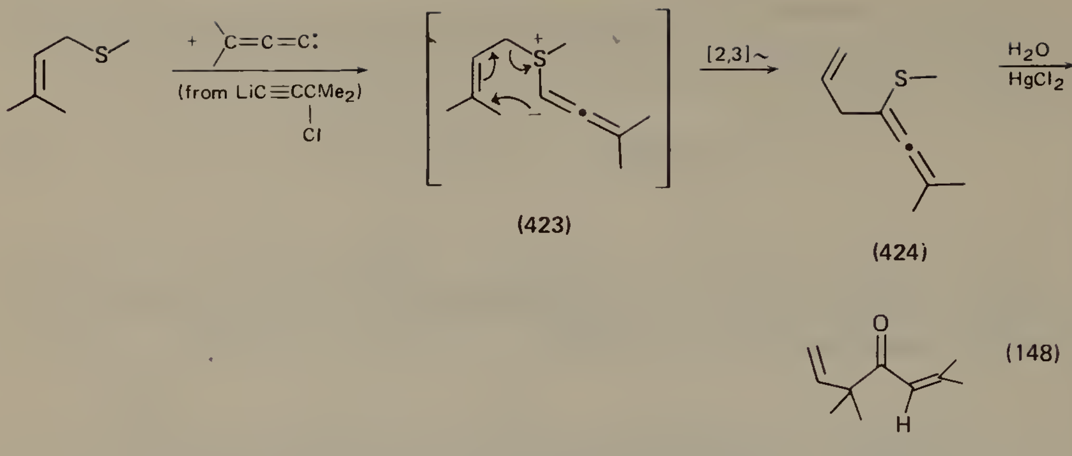
R^1 = H, C≡CH, Ph

R^2 = H, Me

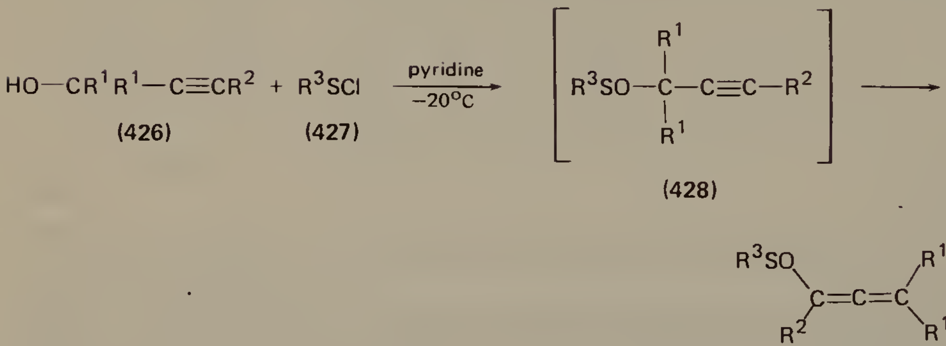
The isomerization of another type of sulphonium ylid (**423**) is exploited in a synthesis of artemisia ketone (**425**) (equation 148)[722].

α-Allenic sulphoxides are generally prepared from propargylic starting materials. Thus treatment of the easily accessible propargyl alcohols **426** with suphenyl chlorides **427** in pyridine leads first to sulphenyl esters **428** as rarely isolable intermediates, which by a subsequent 1,3-intramolecular shift are converted to α-allenic sulphoxides **429** (equation 149)[723–725]. Yields are generally satisfactory and the reaction tolerates a wide variety of substituents (hydrogen, alkyl, cycloalkyl, aryl).

Primary and secondary propargyl halides may serve as starting materials for allenic sulphoxides when they are first transformed into Grignard derivatives, and these are reacted with esters of sulphinic acids, e.g. menthyl toluene-*p*-sulphinate (**430**) (equation 150)[726]. By applying optically active esters **430** active allenic sulphoxides are obtained, which are asymmetric at sulphur and in the allene system.



(423) (424) (425) (148)



(426) (427) (428) (429) (149)

$p\text{-}CH_3C_6H_4SOO\text{—menth} + R^1C{\equiv}C\text{—}CR^2R^3MgBr \longrightarrow RSOR^1C{=}C{=}CR^2R^3$ (150)

(430)

menth = menthan-3-yl

R^1 = H, Et, *n*-Bu

R^2 = H, Me

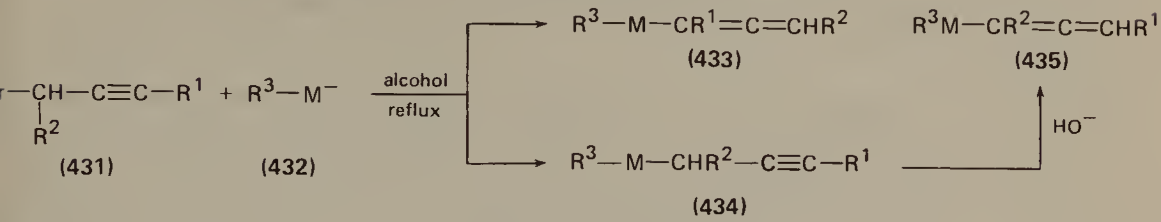
R^3 = H, Me, Et, *n*-Pr

The base-catalysed isomerization of propargyl sulphoxides with triethylamine or on an activated alumina column has also been used for the sunthesis of α-allenic sulphoxides. The reaction conditions seem to be critical, however, since other workers[725] have met with failure applying this obvious method.

α-Allenic sulphones can be prepared by oxidation of the corresponding sulphides and sulphoxides with *m*-chloroperbenzoic acid or sodium metaperiodate[726,727], and by base-catalysed isomerization of propargyl sulphones[728]. In a thermal process, acetylenic sulphinic esters have been transformed to α-allenic sulphones [729]. These allene derivatives undergo addition with various electrophilic reagents, hydrolysis and lithiation[725], as well as cycloaddition[730]. Allylic sulphoxides and sulphones are obtained when the corresponding allenic substrates are treated with symmetrical and nonsymmetrical homocuprates[731,732].

c. Selenium and tellurium Knowledge about allene derivatives of the higher elements of this group is very limited.

Several selenium and tellurium compounds **433** have been prepared by treating propargyl bromides **431** with anions of the general structure **432** (equation 151)[733]. The reaction mixture always contains varying amounts of the propargyl



R^1 = H, Me, Ph

R^2 = H, Me

R^3 = Et, Ph

M = Se, Te

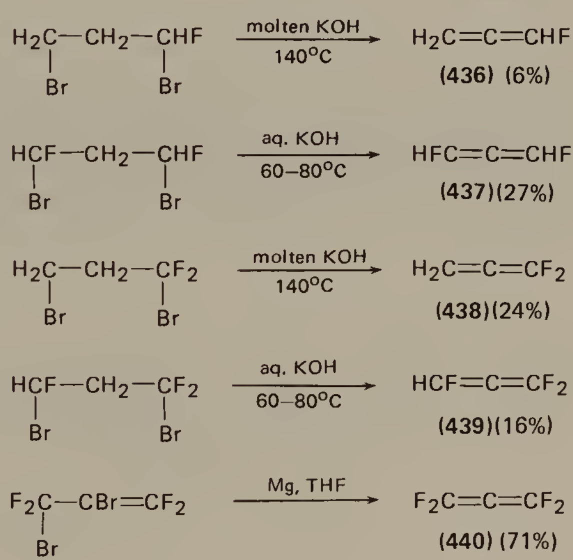
(151)

isomer **434** (which, in fact, may be the sole reaction product). Isomerization with sodium ethoxide in ethanol or potassium hydroxide in tetrahydrofuran converts these derivatives in acceptable yields to the allenic isomers **435**.

6. *Group VIIa substituted allenes*

a. Fluorine. Fluoroallenes proper as well as fluoroallenes carrying perfluoroalkyl groups are predominantly prepared by elimination reactions.

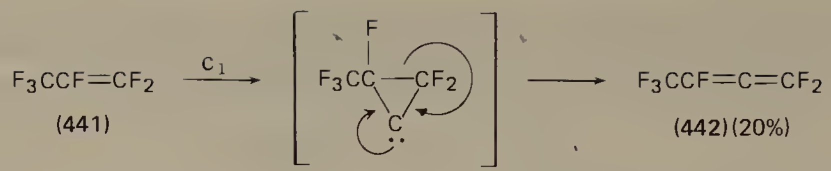
All possible simple fluoroallenes **436–440** have been prepared[734], as shown in equation (152).



(152)

For fluoroallenes **438**[735,736] and **440**[734,737,738] alternative methods of preparation have been developed, but the one given for **440** in equation (152) is apparently the most effective[739].

The simplest perfluoroallene carrying one trifluoromethyl group is perfluoro-1,2-butadiene (**442**). It has been synthesized by reacting carbon vapour with perfluoro-



(441) (442)(20%) (153)

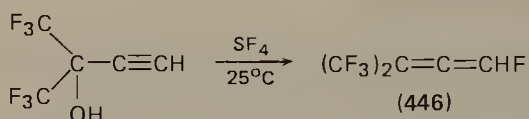
propene (**441**) (equation 153)[740]. The same technique has also been applied to the preparation of trifluorobromoallene[740], although the yield is poorer in this case.

The next higher homologue of **442**, perfluoro-3-methyl-1,2-butadiene (**444**) is obtained in essentially quantitative yield by passing the iodo olefin **443** at 1–2 torr through a silica tube containing freshly precipitated copper powder at 200° C (equation 154)[741]. In an older procedure **444** had been synthesized by dehydrohalogenation of 2*H*,2*H*-hexafluoro-1-iodo-3-trifluoromethylbutane[742].

$$(CF_3)_2C{=}CI{-}CF_3 \xrightarrow[-IF]{\Delta} (CF_3)_2C{=}C{=}CF_2 \qquad (154)$$

(443) (444)

1,1-Bis-(trifluoromethyl)-3-fluoroallene (**446**) has been isolated in 45% yield after treating the propargyl alcohol **445** with sulphur tetrafluoride (equation 155)[743]. This method may also be applied to alcohols **445** in which the fluorine

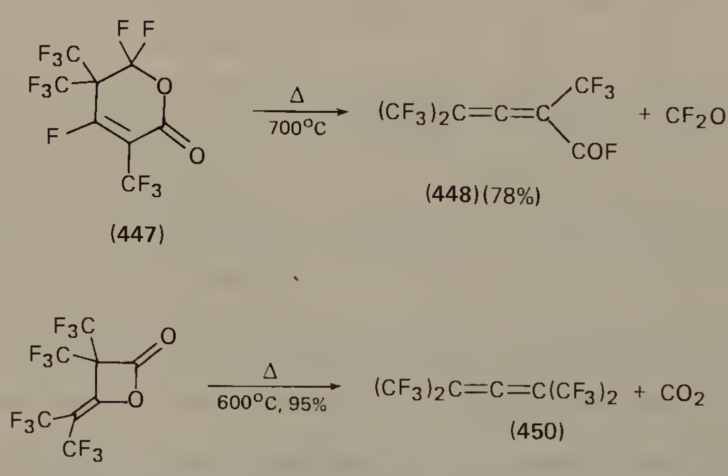


(155)

(445)

atoms have partially been replaced by chlorine and hydrogen, thus providing various chlorofluoroallenes.

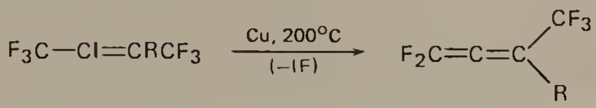
Two polytrifluoromethyl allenes have been prepared by pyrolytic decompositions of lactones. The perfluorolactone **447** leads to the allenic acid fluoride **448** and the β-lactone **449** is cleaved to carbon dioxide and tetrakis(trifluoromethyl)allene (**450**) (equation 156)[744]. Allene **450** has been intensively studied by Russian workers[745,746].



(156)

Perfluoro-1,2-pentadiene has been synthesized by dehydrohalogenation with alkali-metal hydroxides of 2*H*,2*H*-3-chloro-octafluoro-1-iodopentane, 2*H*-3-chloro-octafluoro-1-pentene or 2*H*,2*H*-nonafluoro-1-iodo-pentane[747].

The method developed for the conversion of **443** into **444** has been generalized, and seems to be the most versatile one known presently for synthesizing perfluoro-1,2-dienes (equation 157)[748].



(157)

R	Yield (%)
i-C_{37}	95
n-C_{37}	96
C_{25}	95

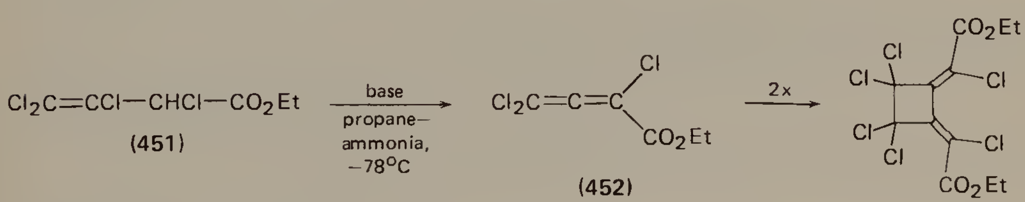
The 4,4,4-trifluoro-1,2-butadienyl unit has also been incorporated into several steroids[749].

Fluoroallenes are of interest as model substances for spectroscopic studies[750] and especially as reaction partners in numerous processes[751–755].

b. Chlorine. Chloroallenes are routinely prepared by elimination reactions and by treating various propargyl alcohols with concentrated hydrochloric acid in the presence of cuprous chloride, or with thionyl chloride and phosphorous trichloride, respectively, in the presence of pyridine, triethylamine or an ether[2,8]. Isomerization and fragmentation reactions leading to chlorine-substituted allenes are also known[15].

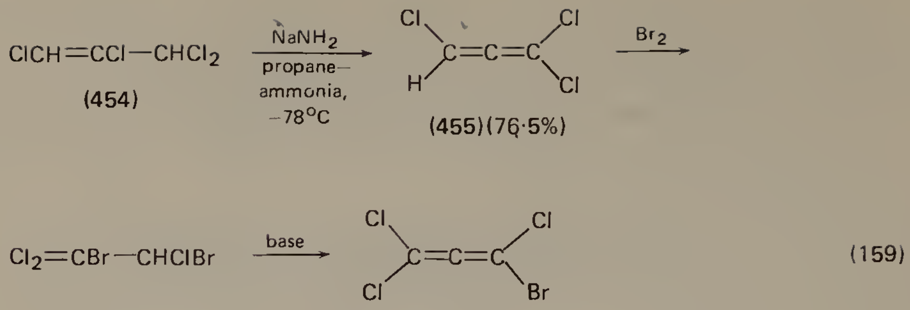
Only representative applications of these methods (whose mechanisms have been discussed extensively in the older review literature[2]), that have appeared in the chemical literature since Taylor's summary (1966) will be discussed here.

2,3,4,4-Tetrachloro-3-butenoic acid ethyl ester (**451**) is dehydrochlorinated by lithium *t*-butoxide at $-75°$ C, using a method previously developed for the synthesis of perchloroallene[756], to the unstable ethyl ester of trichloroallenecarboxylic acid (**452**) (equation 158)[757,758].



(158)

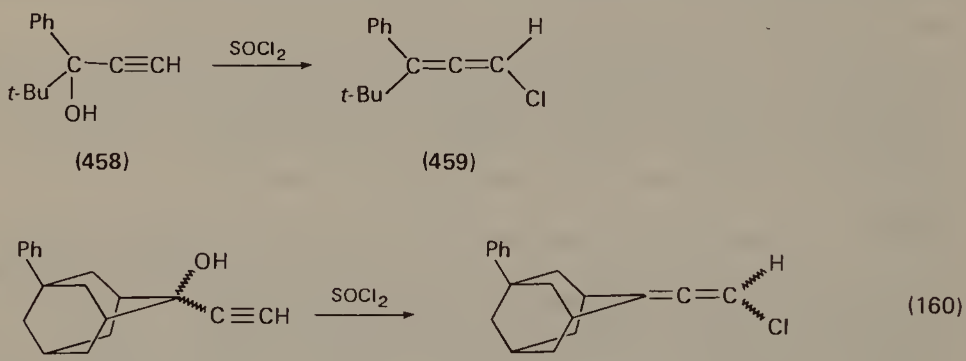
Like many other chloroallenes (see below) **452** dimerizes readily on standing at room temperature, providing the cyclobutane derivative **453** in essentially quantitive yield. The generality of this procedure for the preparation of polyhalogenated allenes is further demonstrated by the synthesis of trichloroallene (**455**) from 1,2,3,3-tetrachloro-1-propene (**454**) (equation 159)[759].



(454) (455)(76·5%) (456)(76%) (457)(80%) (159)

Allene **455**, in turn, is transformed by careful addition of bromine to the dibromide **456** which on treatment with sodium amide in the liquid ammonia/*n*-propane mixture at $-75°$ C[756] furnishes bromotrichloroallene (**457**)[760]. The lithio derivative of **455** has been prepared by reacting **454** with two equivalents of *n*-butyllithium[761].

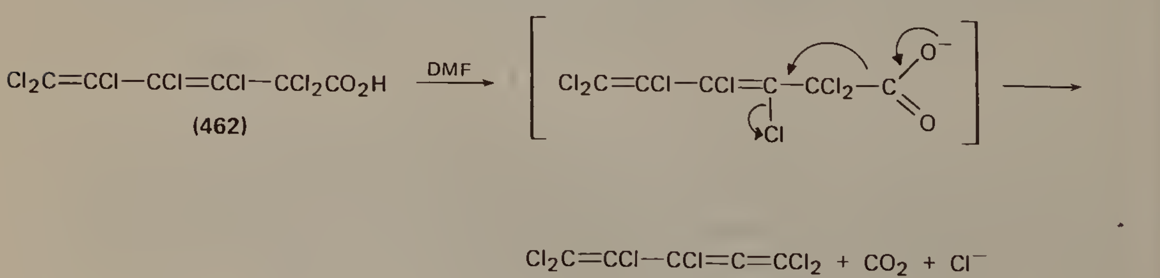
That thionyl chloride reacts also with sterically hindered propargyl alcohols may be inferred from the successful preparation of the *t*-butylallene **459** from the alcohol **458**[762], and the adamantane derivative **461** from **460** (equation 160)[763].



(458) (459) (460) (461) (160)

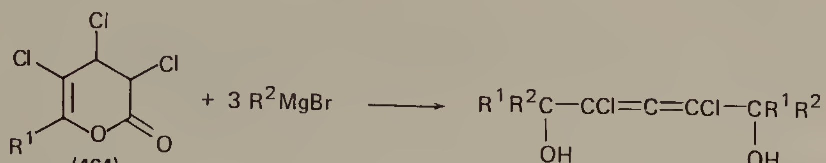
A highly substituted chloroallene has also been prepared from tris(*t*-butylethynyl)-carbinol by phosphorus trichloride treatment[764,765].

Among the recent fragmentation and isomerization processes leading to chloroallenes, the decomposition of the acid **462** to the fully chlorinated vinylallene **463**[766], as well as the surprising ring-opening of perchloro-2-pyrones **464** with Grignard reagents to chloroallendiols **465** ought to be cited (equation 161)[767].

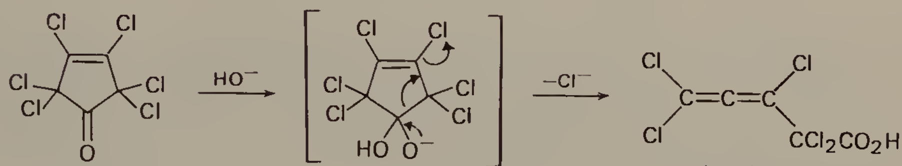


(462) (463)(97%) (161).

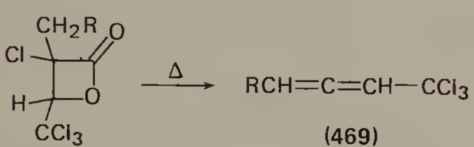
Isomerization and decomposition reactions have also proven successful for the synthesis of *α-chloroallenes*, as shown by the base-catalysed ring-opening of perchlorocyclopent-3-enone (**466**) to 3,4-perchloropentadienoic acid (**467**)[768], and the formation of trichloromethylallenes **469** from the oxetan-2-ones **468** (equation 162)[769].



(464) (465)(30–40%)



(466) (467) (162)



(468) (469)

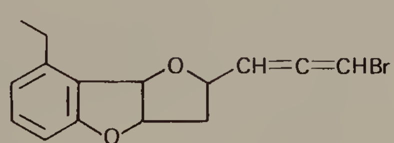
R = H: 66%

R = Me: 50%

R = Et: 40%

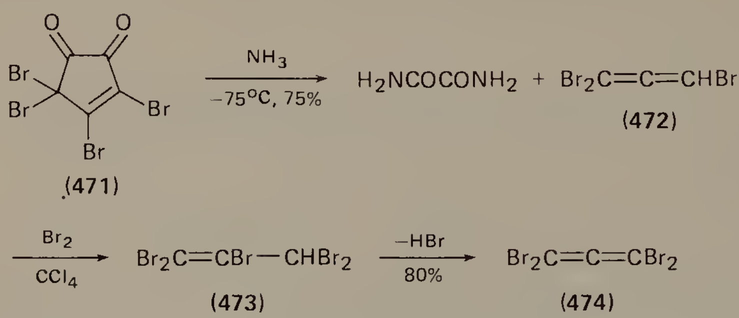
Of all the reactions of chloroallenes, their dimerization to derivatives of 1,2-dimethylenecyclobutane has so far received the largest attention[770–773]. The solvolytic behaviour or di- or tri-aryl-substituted chloroallenes has been extensively studied[774]. The reaction of allenic chlorides with malonic esters has been investigated, and a number of allene derivatives of barbituric and thiobarbituric acid have been synthesized from the allenylalkylmalonic esters produced, with urea and thiourea, respectively[775].

c. Bromine. Knowledge about bromoallenes is quite extensive, and interest in this class of compounds was heightened by the recent isolation of the aromatic bromoallene **470** from a marine mollusk (*Aplysia brasiliena*), which is distasteful to fish and rejected by sharks[776].



(470)

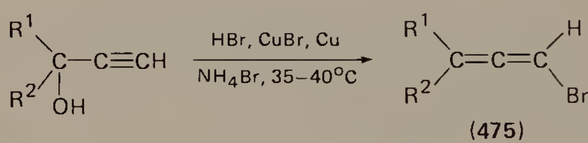
The preparation of 1-bromoallene has been described previously[15], and tribromo- (**472**) and tetrabromo-allene (**474**) have been obtained by a reaction sequence starting with tetrabromocyclopentene-3,4-dione (**471**) (equation 163)[777,778].



(163)

Bromine addition converts **472** into the pentabromide **473**, which may be dehydrobrominated to perbromoallene (**474**). **472** has also been detected as an intermediate in the alkali cleavage of xanthogallol[779].

Allenyl bromides **475** have most often been obtained, besides by elimination reactions, from tertiary and secondary acetylenic alcohols in good to excellent yields (equation 164)[780,781].



(164)

R^1	R^2	Yield (%)
H	Me	37
H	*n*-Pr	67
H	*n*-Pr	43
H	Ph	73
Me	Me	65
Me	Et	79
Me	*t*-Bu	81
t-Bu	*t*-Bu	70
$-(CH_2)_5-$		45

Mechanistic studies support the intermediacy of an acetylene–copper(I) π-complex from which the 1-bromoallene is formed by a stereospecific S_Ni'-process in which the configuration is retained[782]. For the synthesis of various arylallenic bromides the catalyst can be disposed of, and 1,1-dibromoallenes may be obtained by starting with bromoethynyl alcohols[783,784].

Phosphorus tribromide and thionyl bromide may also be used as halogenating reagents[785,786]. Occasionally the acetylenic alcohols initially form the corresponding propargyl bromides, which, however, may be isomerized to the desired bromoallenes by cuprous bromide treatment.

The method for preparing allenes by 1,4-addition reactions to enynes (cf. Section II.A.4) has also been applied to the synthesis of bromoallenes. Thus vinylacetylene is readily converted by bromine addition to 1,4-dibromo-1,2-butadiene, a compound from which other functionalized allenic bromides may be prepared[787,788].

α- and *Higher allenic bromides* are obtained in 40–75% yield from the corresponding alcohols by treating equimolar mixtures of alcohols and pyridine with triphenyl phosphite dibromide at 0° C under strictly anhydrous conditions[789].

α-Bromoallenes have also been obtained by reacting 1,4-dibromo- and 1,4-dichloro-2-butynes with various organomagnesium and organolithium reagents. This propargylic rearrangement depends on the nature of the organometallic reagent as well as the solvent[790,791].

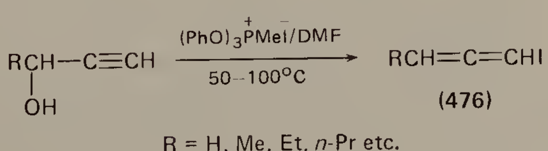
The solvolytic behaviour of bromoallenes has been extensively investigated[792,793], as have various coupling reactions – with dialkyllithio copper reagents to allenic hydrocarbons[109] (cf. Section II.A-8), with terminal acetylenic compounds in the presence of cuprous ions and base to allenynes (cf. Section II.B.2.c[794,795]), with butadiynyl(trialkyl)silane under comparable conditions to allenediynes[795]. Allenic bromides may be converted into Grignard reagents which in turn provide allenic acids with carbon dioxide[796]. The application of allenic bromides as alkylating reagents has also been described[797].

α-Elimination with strong bases in the presence of olefinic trapping agents constitutes a good way of generating vinylidenecyclopropanes, as has been described in Sections II.A.6 and II.C.2.a. Under certain conditions (either with dry cuprous cyanide or with cuprous iodide or bromide in dimethylformamide) 1,4-elimination of suitable 1-bromoallenes competes favourably with 1,1-elimination, giving alkenynes in good yields[798].

Bromoallenes[777,778], like their chloro analogues (cf. Section II.D.6.b) undergo [2 + 2] cycloadditions readily. With suitable dienes they may, however, also take part in [2 + 4] cycloaddition reactions. Thus hexachlorocyclopentadiene and bromoallene react to the Diels–Alder adduct 5-bromomethylene-1,2,3,4,7,7-hexachloro-norborn-2-ene[799]. The α-allenic bromide 1-bromo-2,3-butadiene has been transformed in three steps to the natural product hypoglycin A[800], a compound that exhibits marked hypoglycaemic properties and is of considerable biochemical interest.

d. Iodine. All mono- to tetra-iodoallenes are known[15,801–803], but their chemistry has not been studied as extensively as that of the other halogen derivatives.

One method for preparing iodoallenes[804] consists in the addition of 1-alkyl-prop-2-yn-1-ols to a solution of triphenylphosphite methiodide in dimethylforma-



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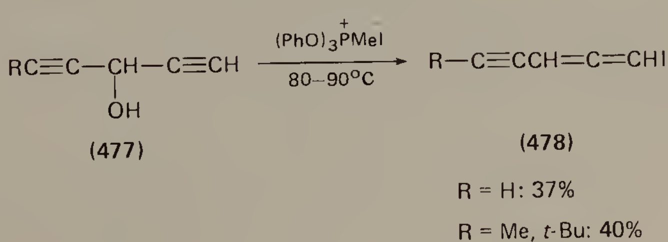


mide. The iodoallene is distilled off and subject to further purification. The reaction, which most likely proceeds by an S_Ni' mechanism affords the iodo derivatives **476** in yields between 50 and 60% (equation 165)[804]. The procedure is applicable to more complex propargyl alcohols as demonstrated by the conversion of the dialkyn-(1)-ylcabinols **477** to the 1-iodo-1,2-pentadien-4-ynes **478** (equation 165)[805].

1,1-Dialkyl-2-yn-1-ols do not react with the above halogenating reagent, presumably owing to steric hindrance to the approach of the oxygen to the phosphorus atom. 3,3-Dialkyl-1-iodoallenes **480** are, however, obtained by reaction of 3-alkyl-3-hydroxy-1-alkynes **479** with aqueous hydriodic acid (45%) in the presence of copper, cuprous iodide and ammonium iodide (equation 166)[806].

$$R^1R^2C(OH)C{\equiv}CH + HI \xrightarrow[NH_4I]{Cu/CuI} R^1R^2C{=}C{=}CHI \quad (166)$$

(479) (480)

R¹	R²	Yield (%)
Me	Me	61
Et	Et	65

A second method involves the reaction of methylmagnesium iodide with acetates of tertiary propargyl alcohols **481** in the presence of an excess of magnesium iodide (equation 167)[131,807,808].

$$R^1R^2C(OAc)C{\equiv}CH \xrightarrow[4\ MgI_2,\ ether,\ 35^\circ C]{MeMgI} R^1R^2C{=}C{=}CHI \quad (167)$$

(481) (482)

R¹	R²	Yield (%)
Me	Me	43
Me	Et	38
Ph	Me	32
c-C_3H_6	Me	27
$-(CH_2)_5-$		20

The substituents may be varied within a broad range as indicated by the examples in equation (167). Mechanistic experiments have shown that the reaction proceeds via a propargyl cation[808]. A variation of this approach, used to synthesize alkylallenes, is described in Section II.B.1.

A promising method not yet fully explored consists in the cleavage of propargyltin compounds **483** with iodine (equation 168)[809].

$$Ph_3Sn{-}CH(R)C{\equiv}CH \xrightarrow{I_2} Ph_3SnI + RCH{=}C{=}CHI \quad (168)$$

(483)

R = H: 80%

R = Me: 70%

III. THE PREPARATION OF CUMULENES

A. Survey of General Methods

Compared to the amount of work directed to the preparation and study of the chemical behaviour of allenes, the investigation of the higher cumulenes is still in its infancy, excepting certain special cases like aryl-substituted butatrienes, which have been studied quite extensively[1]. The generality of the methods leading to the various cumulenes remains, therefore, to be established in the majority of cases.

Most procedures used to prepare the [3] and higher cumulenic systems may also be used, and were, in fact, originally developed in many instances for the synthesis of allenes (cf. Section II.A).

Thus *elimination reactions* of suitable halides like **484** and **486** lead to tetraphenylbutatriene (**485**) and tetraphenylpentatetraene (equation 169)[810,811].

$$Ph_2CH-\underset{\text{Hal}}{C}=\underset{\text{Hal}}{C}-CHPh_2 \xrightarrow[\text{EtOH}]{\text{KOH}} Ph_2C=C=C=CPh_2$$

(484) Hal = Cl, Br — (485) (60%)

$$Ph_2C=CBr-CH_2-CBr=CPh_2 \xrightarrow[\text{DMF}]{\text{KOH}} Ph_2C=C=C=C=CPh_2 \qquad (169)$$

(486) — (487)

Aryl-substituted butatrienes **490** are obtained from the cumulenic *Wittig reagent* **489** (generated from the phosphonium salt **488** by pyridine treatment) with aromatic aldehydes (equation 170)[812].

$$[Ph_3\overset{+}{P}-CH=C=CPh_2]\,\overset{-}{Br} \xrightarrow{\text{pyridine}} [Ph_3P=C=C=CPh_2] \qquad (170)$$

(488) — (489)

$$\xrightarrow[55-70\%]{+\,\text{ArCHO}} Ar-CH=C=C=CPh_2$$

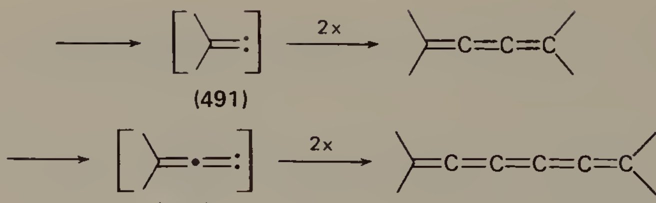
(490)

Propargylic rearrangements have been used most often to synthesize the higher cumulenes. The transformation of various acetylenic and polyacetylenic diols and their derivatives to [3]- [5]- and [7]- cumulenes is of preparative value. This procedure is, however, necessarily restricted to cumulenes with an uneven number of double bonds (even number of carbon atoms). Butatrienes have also been prepared by vinylogous propargyl rearrangements (see below)[813].

Using the *Doering–Moore–Skattebøl* synthesis both acyclic and cyclic cumulenes have been prepared from the corresponding allene precursors. In principle, this is the most general cumulene synthesis, since only one carbon atom may be added to the substrate at a time, and therefore cumulenes with an even or odd number of double bonds may be prepared. In practice, the procedure suffers from the quite drastic reaction conditions, and especially from the great instability of non- or alkyl- substituted cumulenes towards basic reagents.

Syntheses involving other *carbenoid intermediates* have also been described.

Thus both carbenes **491** and **492** provide cumulenic structures (equation 171)[814,815].



(491) (492) (171)

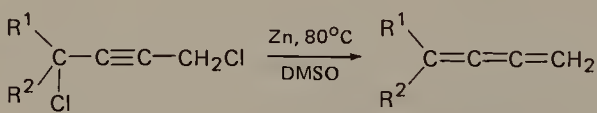
Fragmentation processes like the retro-Diels–Alder reaction have been employed recently to prepare cumulenes, as shown in Section III.B.1.b).

B. Acyclic Cumulenes

1. *Parent systems and alkyl-substituted cumulenes*

a. [3] Cumulenes. Many of the methods reviewed in Section III.A have been applied to synthesize alkyl derivatives of [3] cumulene (1,2,3-butatriene).

Following earlier investigations[816,817] Arens, Brandsma and coworkers have developed a general procedure for the synthesis of aliphatic 1,2,3-trienes **494** by reducing 1,4-dichloro-2-alkynes **493** with zinc dust or sodium iodide in dimethylsulphoxide (equation 172)[818].

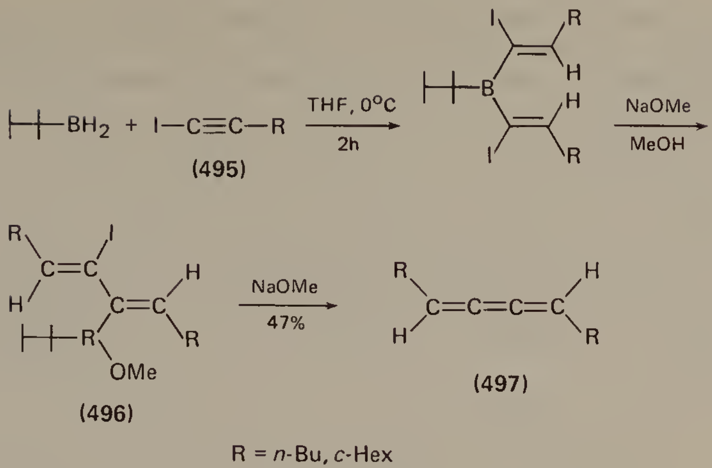


(493) (494) (172)

R^1	R^2	Yield (%)
H	H	80
H	Me	55
H	Et	55
Me	Me	55
Me	Et	55

The decisive improvements over earlier preparations consist in the application of a polar–aprotic solvent as reaction medium and the fast removal of the very unstable cumulenes from the reaction mixture immediately after their formation by applying vacuum. The base-catalysed isomerization of the above trienes[818], the addition of ethanethiol[818] and hydrochloric acid (to 1,2,3-pentatriene[820]) have been studied. The parent system shows the unusual property of thermally dimerizing to 1,5-cyclooctadiyne[819].

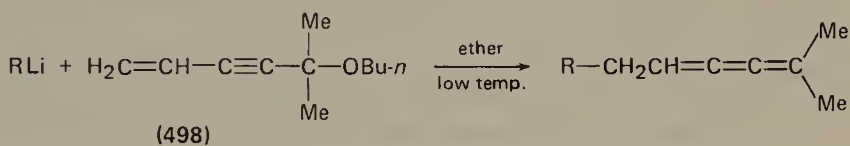
In another elimination reaction, the product formed by reaction of 1-iodo-1-hexyne (**495**, R = *n*-Bu) with 2,3-dimethyl-2-butylborane (thexylborane) is treated with base to provide *trans*-1,4-di-*n*-butyl-1,2,3-butatriene (**497**) (equation 173)[821]. This reaction, which probably proceeds via intermediate **496**, has also been applied to the preparation of *trans*-1,3-dicyclohexyl 1,2,3-butatriene (**497**, R = *c*-Hex); it constitutes the first stereo selective synthesis for derivatives of [3] cumulenes.



(173)

The monocyclohexyl derivative of butatriene is formed in low yield when triphenylpropargylphosphonium bromide is converted by *n*-butyllithium treatment into a Wittig reagent (presumably allenyl triphenyl phosphorane), and the latter condensed with cyclohexylcarboxaldehyde[822].

A vinylogous propargylic rearrangement takes place when the enyne ether **498** is treated with lithiumorganic compounds (equation 174)[823,824]. The aliphatic

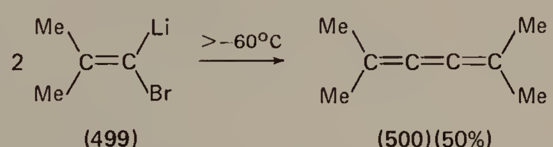


(174)

1,2,3-trienes produced are contaminated with isomeric compounds, however, that are probably formed by a secondary base-cataylsed isomerization.

Most alkyl-substituted [3]cumulenes known to date have been obtained by methods that involve carbenoid intermediates. The DMS procedure has been used to synthesize 4-methyl-1,2,3-pentatriene[825,826], 4-methyl-1,2,3-hexatriene[825], *cis*- and *trans*- 1,3-dimethylbutatriene[827] and tetramethylbutatriene[828], the starting materials in all cases having been prepared by dibromocarbene addition to an allene.

Tetramethylbutatriene (**500**) is also formed when the carbenoid **499** (from 1,1-dibromo-2,2-dimethylethylene and *n*-butyllithium in tetrahydrofuran) is warmed to temperatures above −60° C (equation 175)[829]. Tetrabenzylbutatriene

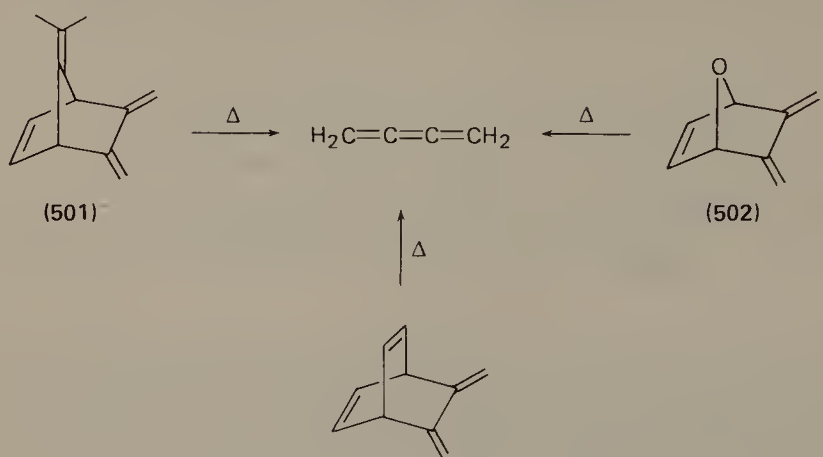


(175)

(1,6-diphenyl-2,5-dibenzyl-2,3,4-hexatriene) has been prepared analogously from 1-chloro-2,2-dibenzylvinyllithium[830,831].

In still another route to hydrocarbon **500** (whose base-catalysed isomerization has been investigated[832]) the disodium salt of tetramethyl-1,3-cyclobutanedione di-*p*-tosylhydrazone has been decomposed thermally[833–835].

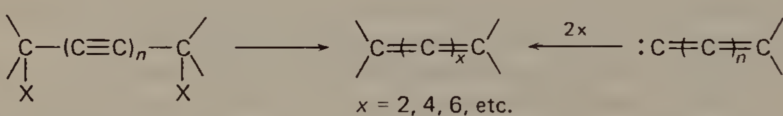
Some retro-Diels–Alder reactions may yield [3]cumulenes. Thus 7-isopropylidene-5,6-dimethylene-7-oxa-bicyclo[2.2.1]hept-2-ene (**501**), 5,6-dimethylene-7-oxa-bicyclo]2.2.1[hept-2-ene (**502**) and 7,8-dimethylenebicyclo[2.2.2]octa-2,5-diene (**503**) all yield butatriene when pyrolysed at temperatures above 500° C (equation 176)[836].



(501) (502) (503) (176)

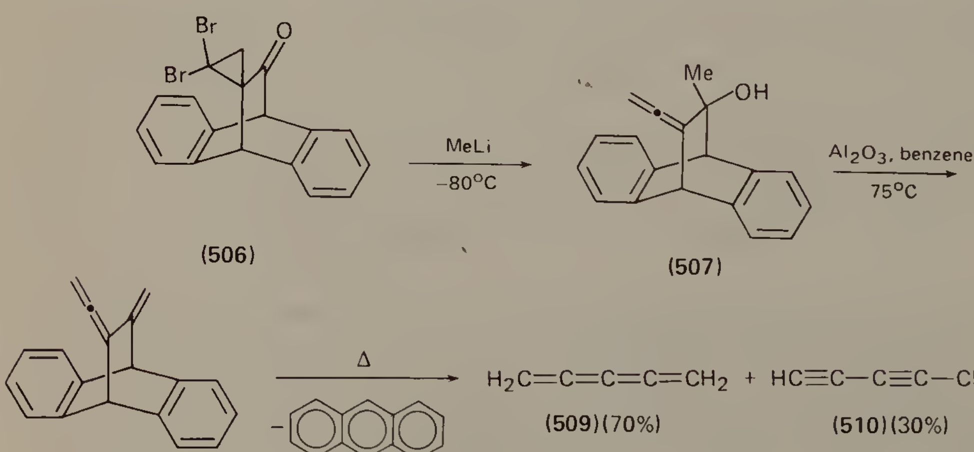
In an interesting catalytic reaction, *t*-butylacetylene is dimerized to *cis*- and *trans*-1,4-di-*t*-butyl-butatriene, with dihydridocarbonyltris(triphenylphosphine)-ruthenium serving as catalyst[837].

b. [4]Cumulenes. Unfortunately both the elimination of functionalized polyacetylenes of the general formula **504** and the dimerization of carbenes of type **505** can only yield molecules with an uneven number of double bonds (equation 177).



(504) (505) (177)

It is hence not surprising that up to 1976 only six pentatetraenes had been reported, the majority carrying stabilizing arylsubstituents (cf. Section II.B.3). In that year the parent hydrocarbon **509** was prepared: the dibromoketone **506**



(506) (507) (508) (509)(70%) (510)(30%) (178)

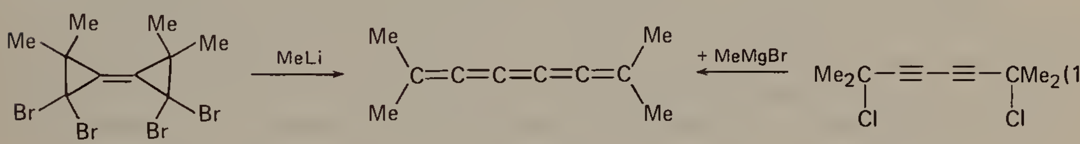
was converted by the DMS approach to the allenic alchol **507**, which on treatment with aluminum oxide oxide under carefully controlled conditions yielded the vinylallene **508**. When the latter is submitted to flash vacuum pyrolysis (700° C, 10^{-3} torr) anthracene is split off, and a mixture of 1,2,3,4-pentatetraene (**509**) and 1,3-pentadiyne (**510**) is produced in 85% yield (equation 178)[838,839]. Hydrocarbon **509** is stable enough to be purified by gas chromatography at 25° C; its spectral properties[839], including the photoelectron spectrum[840], have been reported.

The tetramethyl derivative of **509** is obtained when 2,4-dimethyl-2,3-pentadiene (tetramethylallene) is converted to its bisdibromocarbene adduct, and the spiro compound thus formed is dehalogenated with methyllithium in ether at −78° C. Tetramethyl[4]cumulene was the first aliphatic cumulene with an even number of double bonds[828].

Methyl-1,5,5-tris(trimethylsilyl)-1,2,3,4-pentatetraene is obtained in 23% yield when 2,4-hexadiyne is metalated with an excess of methyllithium in ether, and the reaction quenched with trimethylchlorosilane after 55 minutes[841].

c. [5]- and higher cumulenes. Neither the parent system 1,2,3,4,5-hexapentaene nor any of its simple alkyl derivative have been prepared. Because of the high reactivity to be expected for these compounds (see below), it seems likely that novel synthetic approaches have to be developed for their preparation.

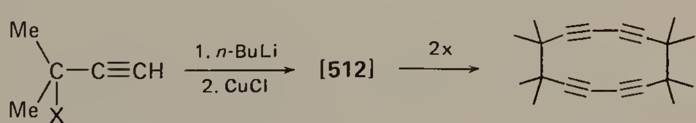
Tetramethyl[5]cumulene (**512** 2,7-dimethyl-2,3,4,5,6-octapenatene) was postulated to be one of the (unstable) reaction products formed by treating the tetrabromide **511** with methyllithium in ether at −78° C (equation 179)[842].



(179)

(**511**) (**512**) (**513**)

More information (infrared spectrum, qualitative electronic spectrum) on the extremely unstable **512** was obtained when 2,7-dichloro-2,7-dimethyl-3,5-octadiyne (**513**) was subjected to the Zakharova reaction with methylmagnesium bromide in ether[843]. In more recent work it has been shown that **512** is formed when the tetrahydropyranyl ether **514** (or the acetate) is deprotonated with *n*-butyllithium in tetrahydrofuran at −78° C, and the anion thus generated decomposed with catalytic amounts of cuprous chloride (equation 180)[844]. In fact, the reaction



(180)

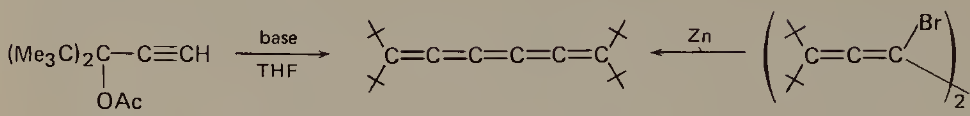
(**514**) (**515**)

X = OThp, OAc

continues to cyclododeca-1,3,7,9-tatrayne **515**. The [5]cumulene hence resembles butatriene which also dimerizes to a strained cyclic acetylene (cf. Section III.B.1.a.).

t-Butyl substituents, known for their stabilizing effect on numerous unstable molecules (cf. Section II.B.1) also reduce the reactivity of [5]cumulenes drastically, so that their physical and chemical properties may be investigated.

Tetrakis(*t*-butyl)hexapentaene (**517**), a solid melting at 188° C, is among the products formed on treatment of the acetate **516** with potassium *t*-butoxide (equation 181)[845,846]. **517** may also be prepared from the dibromide **518** by dehalogenation with zinc[847].



(516) (517) (518) (181)

[5]Cumulenes are presumably formed as reaction intermediates when quaternary salts of diacetylene Mannich bases are reacted with aqueous alkali[848,849].

No [6]cumulenes carrying alkyl substituent have been described in the literature so far.

2. *Cumulenes carrying unsaturated substituents*

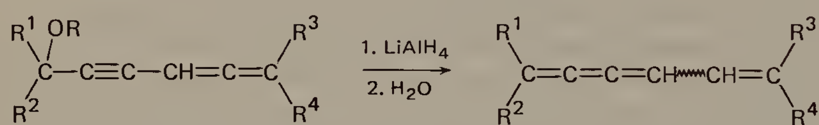
The simplest representative of this class of cumulenes, 1,2,3,5-hexatetraene (**521**), has been prepared in 30% yield by dehalogenating a mixture of the isomeric chlorides **519** and **520** (*cis* and *trans*) with zinc in diethyleneglycol dibutyl ether at 70° C (equation 182)[850].

$$H_2C{=}CH{-}CHCl{-}C{\equiv}CCH_2Cl + ClCH_2CH{=}CHC{\equiv}CCH_2Cl \xrightarrow{Zn} H_2C{=}CH{-}CH{=}C{=}C{=}CH_2 \quad (182)$$

(519) (520) (521)

Like its lower homologue vinylallene (cf. Section II.B.2a), **521** undergoes [2 + 4] cycloaddition reactions with its butadiene part.

Several alkyl- and aryl-substituted derivatives of **521** have been prepared in moderate yields (up to 40%) by reducing the 4,5-dien-2-yn-1-ols **522** or their acetates with lithium aluminium hydride in ether (equation 183)[851,852]. When the

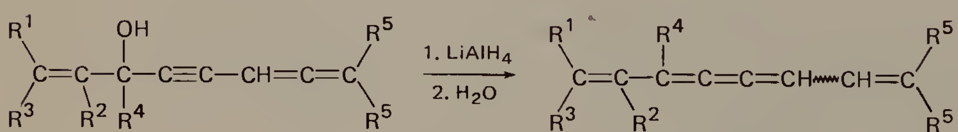


(522)

R = H, MeCO

R^1–R^4 = H, Me, *t*-Bu, Ph

(183)

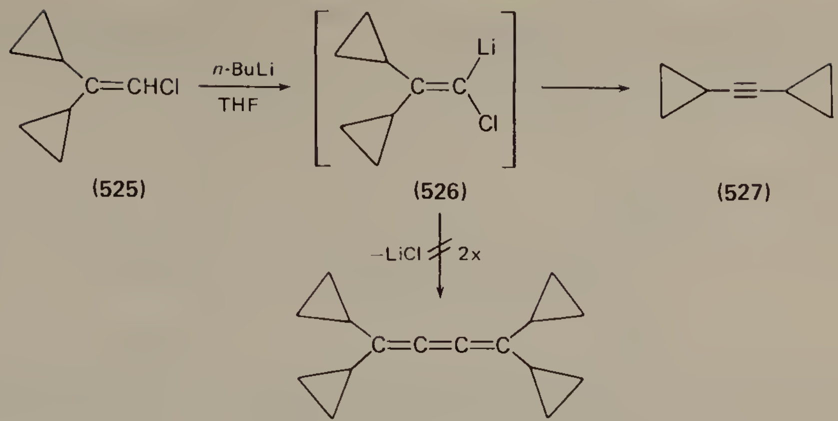


(523) (524)

R^1–R^5 = H, alkyl

same procedure is applied to the carbinols **523**, derivatives of 1,3-divinylbutatriene **524** (which itself is unknown) are produced in 60% yield. The mechanism of both reduction processes has been investigated[851,852].

Apparently no cyclopropyl-substituted cumulenes have been prepared so far. The carbenoid **526**, generated from **525**, on treatment with *n*-butyllithium yields, by the Fritsch–Buttenberg–Wiechell rearrangement, only dicyclopropylacetylene (**527**) and no tetracyclopropylbutatriene (**528**) (equation 184)[853].



(184)

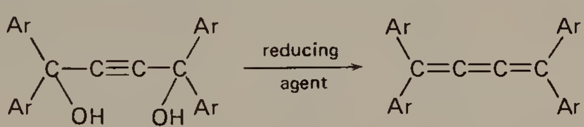
(525) (526) (527)

(528)

3. *Cumulenes carrying aromatic substituents*

Aryl groups stabilize higher cumulenes e.g. tetraphenylbutatriene[854]. In most cases the aryl-substituted representatives were prepared much earlier than the corresponding cumulenes carrying alkyl substituents. The parent compounds are in most cases hardly or not at all known beyond the [4]cumulene stage, whereas arylcumulenes with up to ten consecutive double bonds have been described.

a. [3]Cumulenes. The method of choice for synthesizing aromatic [3]cumulenes **530** consists in reducing tertiary 2-butyn-1,4-diols **529** with stannous chloride in ether in the presence of hydrochloric acid, with potassium iodide in ethanol–sulphuric acid or with phosphorus tribromide in pyridine (equation 185).



(185)

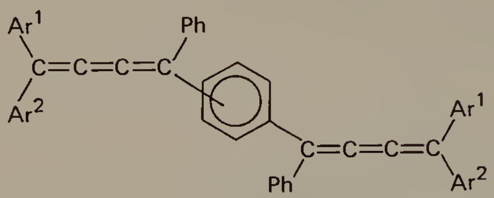
(529) (530)

These preparations and their chemical behaviour has been reviewed several times[1,5,8], hence only some developments of the last decade and some leading references will be mentioned.

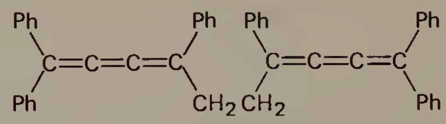
The diols **529** are usually prepared by reacting aromatic ketones with sodium acetylide[1], lithium acetylide–ethylenediamine complex[855] or acetylenedimagnesium bromide[1]. When unsymmetrical ketones are employed unsymmetrical butatrienes will result. Among the recent members of this group of compounds are numerous 1,4-diphenyl-1,4-diarylbutatrienes[856,857] as well as 1,4-diphenyl-1,4-di-(2-pyridyl)- and tetra(2-pyridyl)-butatriene[858].

[3]Cumulenes possessing this type of substitution may exist in either *cis* or *trans* form, and both isomers have been obtained[1,857]. Geometrical isomerism has also been detected for various 'mixed' butatrienes carrying both aryl and alkyl groups. Thus *cis* and *trans*-1,4-di-*t*-butyl-1,4-diphenylbutatriene have been obtained in pure form by column chromatography on aluminium oxide[859,860]. The mixed butatrienes 1,4-dimethyl-1,4-diphenyl [3]cumulene[861], 2,7-dimethyl-3,6-diphenyl-3,4,5-octatriene (1,4-diisopropyl-1,4diphenyl [3]cumulene)[862], 1-methyl-1,4,4-triphenyl [3]cumulene[863] and 1-*t*-butyl-1,4,4-triphenylbutatriene[863,864] have been prepared analogously from the appropriate diols, but attempts to synthesize 1,1-diphenylbutatriene failed[865].

Aryl-substituted bis[3]cumulenes in which the triene linkages are separated by an aromatic ring (general formula **531**) or an ethano group (**532**)[866] have likewise been prepared from acetylenic diols[867].

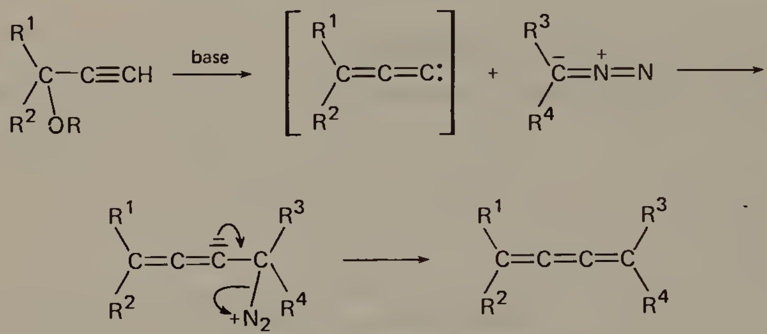


(**531**)

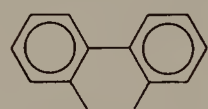
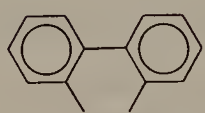
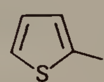


(**532**)

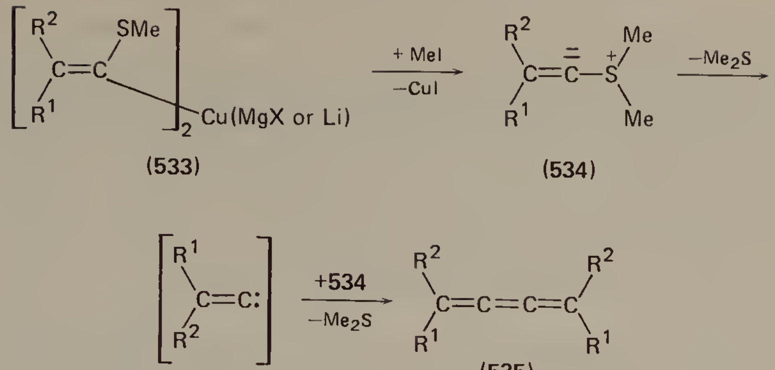
In an interesting extension of the Hartzler reaction (cf. Section II.A.6) vinylidene carbenes are produced from ethynyl carbinols by base treatment in the presence of a diazocompound in an inert solvent (equation 186)[868].



(186)

R¹	R²	R³	R⁴	Yield (%)
Ph	Ph	Ph	Ph	21
Ph	Ph			26
		Ph		7
Me_2CH	Me_2CH			5

That alkylidene carbenes can dimerize to [3]cumulenes has been known for some time[2,869]; in a novel butatriene synthesis these species have been generated in a first step from the easily obtainable copper(I) reagents **533** by alkylation with an excess of methyl iodide in tetrahydrofuran at 0° C via the intermediate sulphur ylide **534**, and then intercepted by a second molecule of **534** . Aryl- and alkylbutatrienes **535** are produced in yields between 20 and 50% (equation 187)[870]. It is interesting to note that the cumulenes formed in this sequence possess the *cis* configuration.



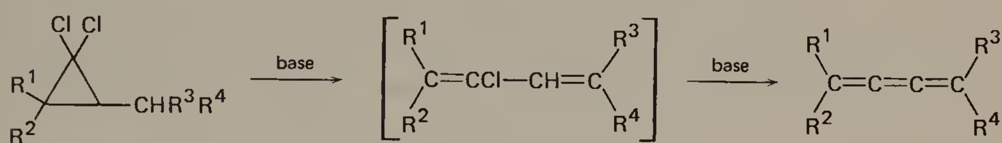
(533) (534) (535) (187)

R^1 = Me, Et, *i*-Pr, Ph, *n*-Pe etc.

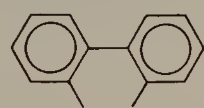
R^2 = H, Ph

Carbenes are presumably also involved when either 1,1,1-trihalogeno-2,2-diarylethanes or 1,1-dibromo-2,2-diphenylethylene are converted into [3]butatrienes in approximately 50% yield by treatment with metallic copper or cuprous chloride in dimethylformamide at 20–45° C[871].

In a new elimination reaction leading to the aromatic [3]cumulenes **538** the *gem*-dichlorocyclopropanes **536** were first prepared by dichlorocarbene addition to the corresponding olefins, and subsequently treated with various alkoxides in alcohol or dimethylsulphoxide (equation 188)[872]. When hot pyridine was used as



(536) (537) (538) (188)

R^1	R^2	R^3	R^4	Yield (%)
Ph	Ph	Ph	Ph	73
				91
MeO	Ph	Ph	Ph	76

base and solvent, the 2-chloro-1,3-butadienes **537** were isolated in good yield, making these compounds likely intermediates in the **536** to **538** conversion.

1,6-addition reactions to divinylacetylenes (1,5-hexadien-3-ynes) also provide [3]cumulenes, the process being a vinylogous pendant of the 1,4-addition reaction to vinylacetylenes, which – as has been discussed in Section II.A.4 – leads to allenes[873].

The chemical behaviour of aromatic [3]cumulenes has been reviewed[1,5]. Novel reactions include complex formation with metal carbonyls[874,875], carbonylation in the presence of dicobalt octacarbonyl[876], and a reinvestigation of the dimerization of tetraphenyl and tetra-*p*-anisyl [3]cumulene[877]. The latter reaction was shown to lead to a derivative of 1,3-bis(vinylidene)cyclobutane, and not to a [4] radiallene as had been assumed previously.

b. [4] Cumulenes. 1,2,3,4-Pentatetraenes carrying aryl groups represent a relatively poorly investigated class of cumulenes. Kuhn, Fischer and Fischer first prepared tetraphenyl- and tetra-*p*-anisyl-[4] cumulene by dehydrobrominating the corresponding tetraaryl-2,4-dibromo-1,4-pentadiene[878,879]. 1,5-Bis(2-isopropylphenyl)-1,5-diphenyl[5] cumulene has recently been prepared by an analogous elimination[880], as have tetrakis(2-methoxyphenyl)- and 1,5-bis(2-benzyloxyphenyl)-1,5-bis(2-methoxy-5-methylphenyl)-pentatetraene from the corresponding dibromopentadienes[881].

Several alkyl–aryl-substituted [4] cumulenes have been prepared from butatrienes by the DMS method, among them 1,5-di-*t*-butyl-1,5-diphenyl-1,2,3,4-pentatetraene[881,882] and 2,2,8,8-tetramethyl-1,3,7,9-tetraphenyl-3,4,5,6-nonatetraene [881,883]. These molecules are of interest in studies concerned with the measurement of rotational barriers around (cumulenic) double bonds[880,884] and for the preparation of optically active cumulenes. In fact, the complete optical resolution of 1,5-di-*t*-butyl-1,5-diphenyl-1,2,3,4-pentatetraenes has been accomplished[885], thus confirming a more than 100 year old prediction by van't Hoff[886] that cumulenes with four consecutive or any even number of double bonds should be chiral.

c. [5] Cumulenes. Two general pathways to hexapentaenes have been known for a long time: the reduction of hexadiynediols[1,887], and the so-called self-condensation of diarylpropynols according to Cadiot which presumably occurs via vinylidenecarbene intermediates[1]. Tetraphenyl[5] cumulene has been prepared by these methods, and also by treating 1,1-diphenyl-3-bromoallene with potassium *t*-butoxide in dimethylsulphoxide / ether (26% yield) or by subjecting 1,1-dibromo-3,3-diphenylallene to butyllithium in ether at room temperature (11% yield)[888].

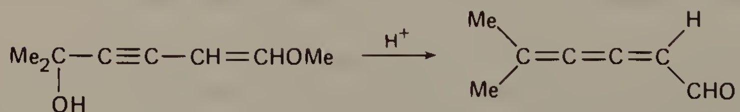
Appropriately substituted diacetylenic diols also serve for the preparation of 'mixed' [5] cumulenes, e.g. 1,6-diphenyl-1,6-di-*t*-butylhexapentaene[884,889,890], 2,2,9,9-tetramethyl-1,3,8,10-tetraphenyl-3,4,5,6,7-decapentaene[884] and 2,7-diphenyl-2,3,4,5,6-octapentaene[891].

d. Higher cumulenes. Several [7]-, [8]-, [9]- and even [10]-cumulenes bearing aromatic substituents have been prepared, but all of them before 1967/68. The reader is therefore referred to the older review literature[1,5].

4. *Functionalized cumulenes*

Functionalized cumulenes, i.e. alcohols, carboxylic acids and esters, nitriles etc. constitute an essentially unexplored area of organic chemistry. General methods of preparation or reactivity patterns are hence unknown.

From the limited information available it seems that conjugated enynols are useful substrates for the synthesis of cumulenic aldehydes and ketones. For example, 5-methyl-5-hydroxy-1-methoxy-1-hexen-3-yne (**539**) under carefully controlled conditions yields 10–15% of 5-methyl-2,3,4-hexatrienal (**540**) (equation 189)[892].

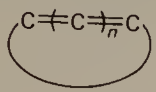


(539) (540) (189)

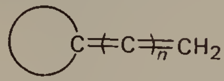
Similarly various phenyl-substituted cumulenic ketones are obtained by treatment of the corresponding enynols with acid[893,894].

C. Cyclic Cumulenes

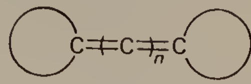
Like their allenic homologues cyclic cumulenes will be grouped into three main categories: endocyclic (i) and exocyclic (ii), and bicyclic cumulenes of type (iii).



(i)



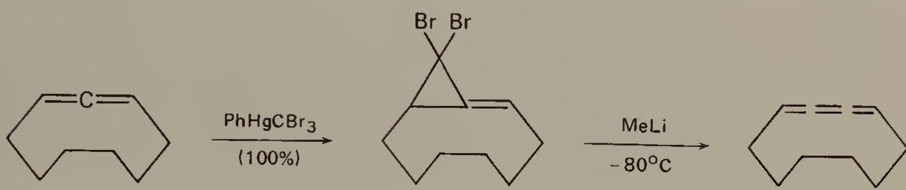
(ii)



(iii)

1. *Endocyclic cumulenes*

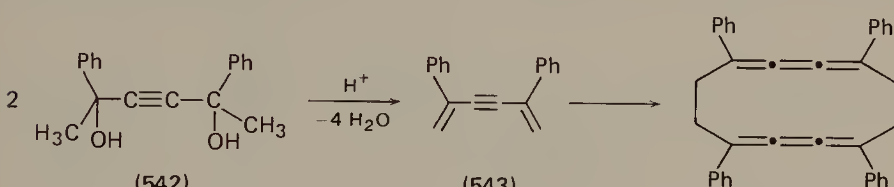
Some simple cyclic cumulenes like 1,2,3-cyclodecatriene (**541**) have been prepared (equation 190)[895], but no systematic investigation has appeared: even the



(541)(>90%) (190)

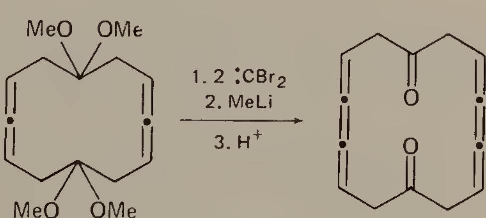
limiting ring size for incorporating a [3]cumulenic unit into a cyclic system is unknown.

1,4,7,10-Tetraphenylcyclododeca-1,2,3,7,8,9-hexaene (**544**) is formed when the diol **542** is dehydrated by acids. The reaction occurs via the divinylacetylene intermediate **543**, which dimerizes under the reaction conditions (equation 191)[896,897]. According to spectroscopic investigations [896] **544** prefers a quasi-boat conformation. Several metal complexes of this unique biscumulene have been prepared[898,899].



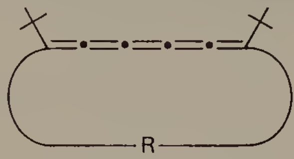
(542) (543) (544) (191)

Another cyclic biscumulene is cyclotetradeca-3,4,5,10,11,12-hexaene-1,8-dione (**546**) which has been synthesized from racemic or *meso*-diallene **545** (cf. Section II.C.1.f) by the DMS method (equation 192)[900,901].



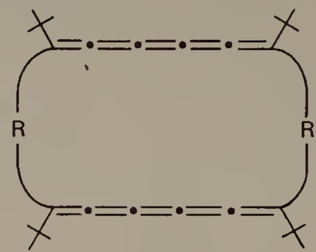
(545) (546) (192)

Several macrocyclic ring systems containing one (**547**) or two (**548**) hexapentaene units have been obtained in multi-step syntheses.[902-904]



(547)

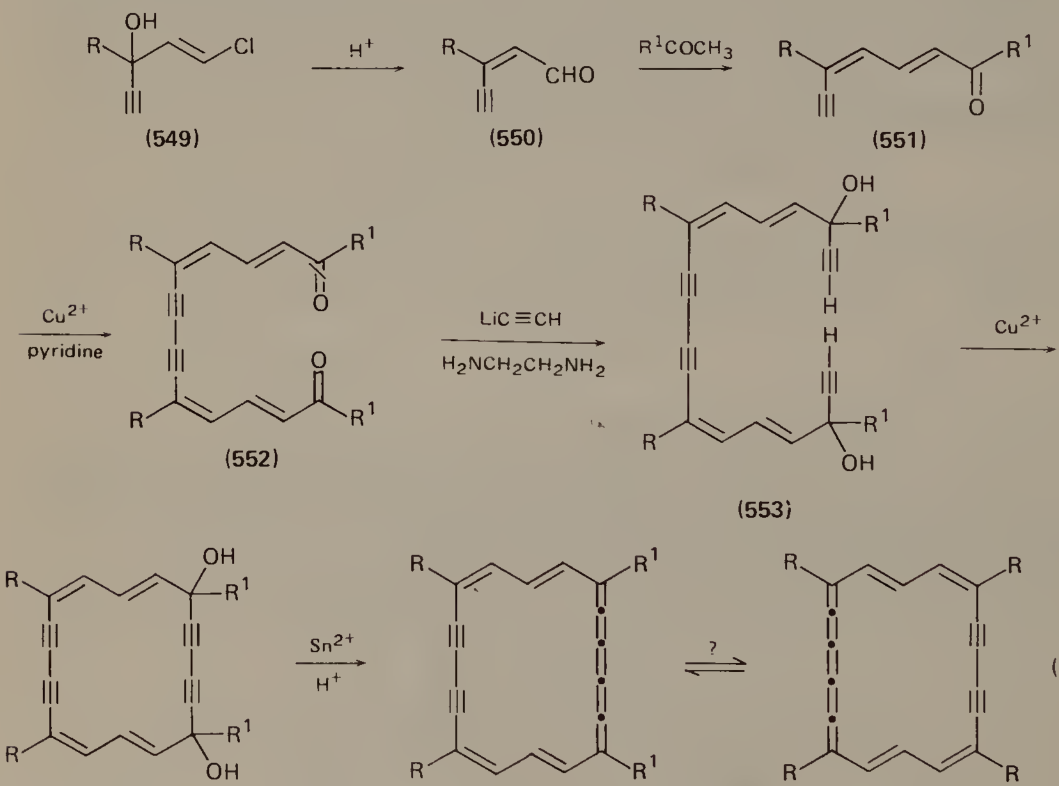
R = $-CMe_2(CH_2)_3C_6H_4(CH_2)_3CMe_2-$,
$-CMe_2(CH_2)_6CMe_2-$



(548)

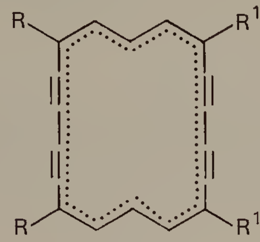
R = $-CMe_2(CH_2)_2C_6H_4(CH_2)_2CMe_2-$

Of great interest for the development of the theory of aromaticity are the so-called 'acetylene–cumulene dehydroannulenes' investigated extensively by Nakagawa and his coworkers[905-908]. For the synthesis of these highly unsaturated mono- or bi-cyclic molecules a combination of oxidative coupling and elimination reactions has proven to be very effective. As illustrated in equation (193) for the tetradehydro[18]annulenes (**555**) the reaction sequence starts with 3-substituted 2-penten-4-ynol (**549**) which is rearranged by an anionotropic isomerization to the aldehyde **550**. Aldol condensation with a methyl ketone affords the diene ketone **551**, which is oxidatively dimerized to the diketone **552**. Bisethynylation yields **553** with terminal acetylene units, and the ring is closed by a second oxidative carbon–carbon coupling. The annulene **555** is finally generated by treatment of **554** with stannous chloride.



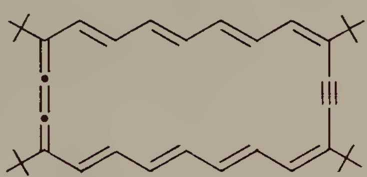
(554) (555) (556) (193)

The problem with **555** and similar ring systems is whether they contain truly acetylenic and cumulenic units or whether the system is delocalized to an aromatic molecule in which these 'halves' of the molecule may no longer be distinguished from each other, as shown in formula **557**.

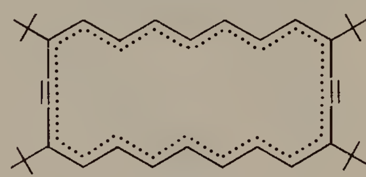


(557)

Chemical as well as spectroscopic evidence (n.m.r. and Raman) prove the tetradehydro[18]annulenes to be aromatic hydrocarbons, with the formal diacetylene and hexapentaene units identical (formula **557**). However, other acetylene–cumulene dehydroannulenes show bond alternation. Thus from an X-ray analysis for 3,11,14,22,-tetra-*t*-butyldidehydro[22]annulene it follows that the alternate bond structure **558** is preferred over the delocalized structure **559**[909].

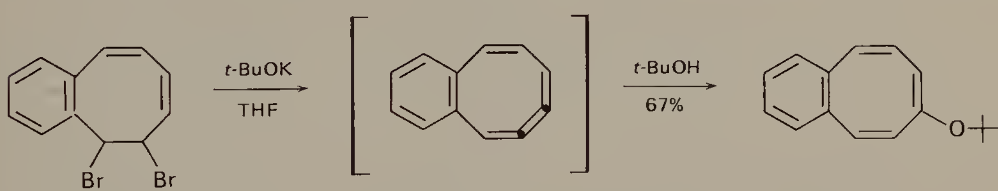


(558)



(559)

Endocyclic cumulenes have also been postulated or proven as reaction intermediates in various processes[910–912], a recent example being the basic elimination of the dibromide **560** which leads mainly to the ether **562** (equation 194)[912].



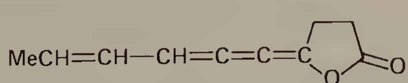
(195)

(560) (561) (562)

According to the authors there is little doubt that the conversion involves the cyclic conjugated eight-membered cumulene **561**.

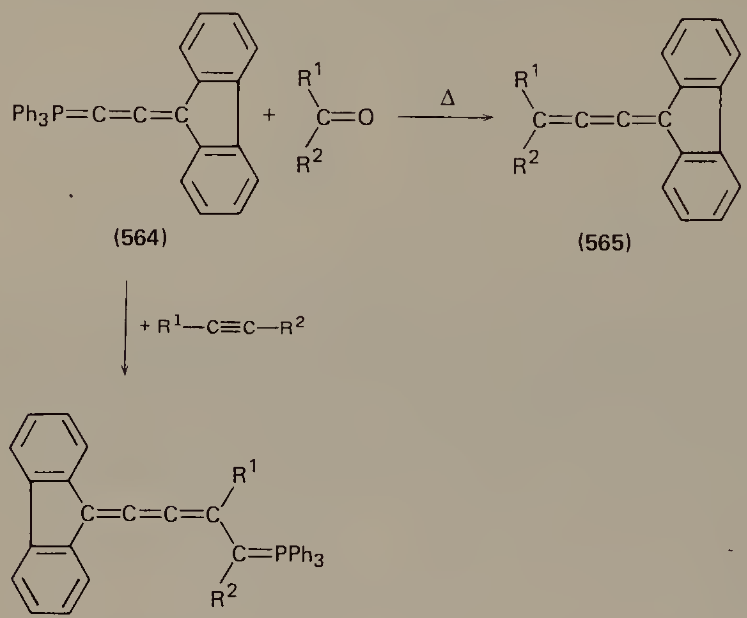
2. *Exocyclic cumulenes*

The first naturally occurring cumulene (**563**) isolated from *Conyza bonariensis* was exocyclic[913].



(563)

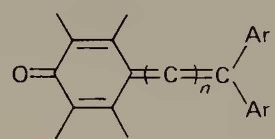
The parent systems of this group have not been investigated, but some derivatives with annelated benzene rings **565** and **566** are known. They have been obtained by reaction of the cumulenic Wittig reagent **564** with carbonyl components or acetylenecarboxylic esters (equation 195)[914].



(564) (565) (566)

(195)

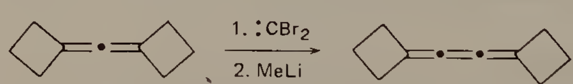
Exocyclic cumulenes of the general structure **567** (n = 1,2,4) have been prepared by the reduction of the corresponding alkynyl diols (see above)[915].



(567)

3. *Bicyclic cumulenes of type (iii)*

The simplest representative of this group described so far is the relatively stable 1,4-bis(trimethylene)butatriene (**569**), which was synthesized from the propadiene **568** (see Section II.C.3) by the DMS method (equation 196)[586].



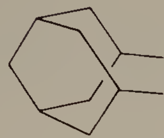
(568) (569)

(196)

Experiments along the same lines gave hints on the formation of the next higher homologue of **569** 1,5-bis(trimethylene)pentatetraene; however, this hydrocarbon could not be obtained in pure form.

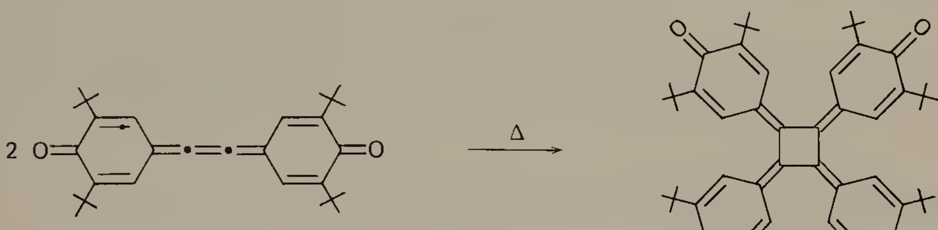
Several 1,n-bis(pentamethylene)cumulenes have been prepared[204,916]. The stabilizing influence of alicyclic ring systems at the end of the cumulenic unit has

AdC=C=C=CAd (570) AdC=C=C=C=CAd (571)

Ad = 

also been experienced with the recently prepared hydrocarbons **570** and **571**[881]. The former molecule was obtained from the corresponding acetylenic diol by the usual route, and served as starting material for **571** using the DMS route. The stabilizing effect of the adamantane skeleton is reflected by the extreme thermal stability of the two molecules: **570** melts at 295° C, and **571** begins to decompose at temperatures above 360° C!

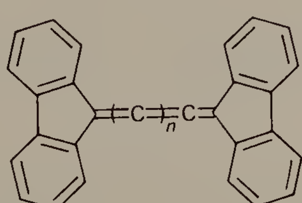
The so-called diquinoethylene **572** has been prepared, and dimerizes in low yield (10–12%) to the [4]radialene derivative **573**, when heated in a refluxing toluene solution for several days (equation 197)[917–920]. Analogous behaviour has been



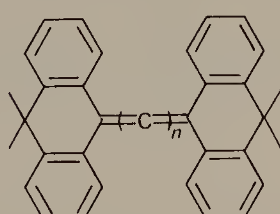
(572) (573) (197)

noted for perchlorobutatriene (cf. Section III.D.3) and tetrakis(*t*-butyl)hexapentaene (cf. Section II.C.2.b).

A very large number of aryl-substituted cumulenes is known in which the aromatic substituents are 'pinned back' by a zero or methano bridge as in **574** and **575**, respectively[1,921–923]. In other words, these are benzoannelated derivatives of 1,4-bis-(tetramethylene)- and -(pentamethylene)-cumulenes. Since this work has partly been reviewed[1] only a few remarks are necessary here. These compounds are as stable as other cumulenes with terminal aryl groups. Because of the molecular bridges, however, the phenyl substituents are in a coplanar arrangement causing extensive delocalization over the whole π system. For their synthesis the standard methods for the preparation of cumulenes with an uneven number of double bonds have been used[1,5] (cf. Section III.B.3). Such cumulenes with electron-donating



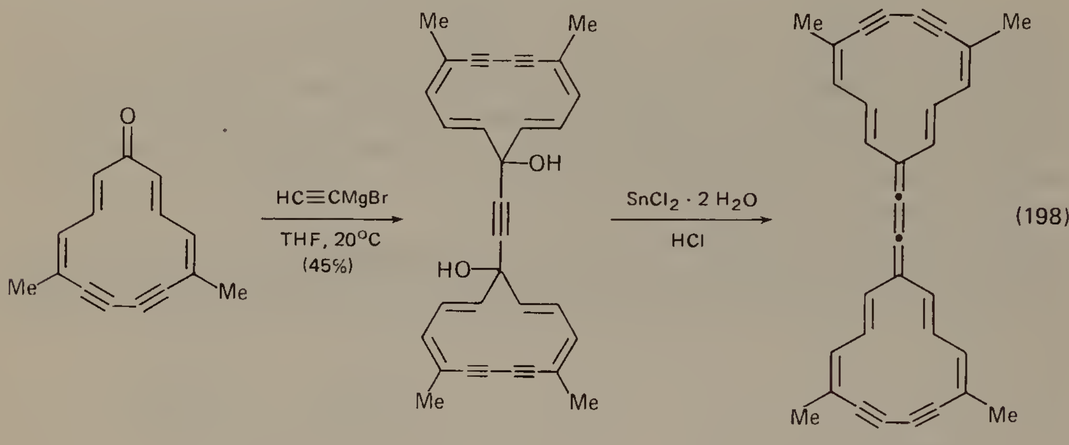
(574)
$n = 2, 4$



(575)
$n = 2, 4, 6$

substituents at one end of the cumulenic system and electron-accepting ones at the other may be prepared. These 'polar cumulenes'[921] are another example of the 'push–pull systems' already mentioned in Sections II.C.2.c and II.D.5.a.

The recently prepared 1,1′-(1,2-ethenediylidene)bis(5,10-dimethylcyclotrideca-2,4,10,12-tetraene-6,8-diyne) (**576**) is the first macrocyclic fulvalene containing a cumulene linkage and ring systems that are nonannelated (equation 198)[924].



(576)(65%)

(198)

D. Heterosubstituted Cumulenes

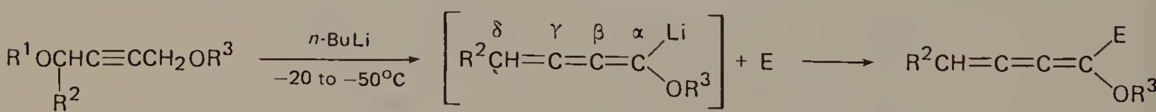
1. *Introduction: miscellaneous systems*

Judging from the number of publications describing heterosubstituted cumulenes, it seems that oxygen, sulphur and the halogens stabilize the sensitive cumulenic grouping most effectively.

Lithiocumulenes may be involved as reactive intermediates in the polylithiation of various diacetylenic hydrocarbons[595,597] and acetylenic diethers of the general type $R^1OCH(R^2C{\equiv}CCH_2OR^1$ [925]. 1,4-Diphenyl-1,4-(diethylaluminium)butatriene, the first organometallic [3] cumulene, has been synthesized recently[926,927].

2. *Group VIa substituted cumulenes*

A general method for the preparation of *[3] cumulenic ethers* **579** involves reacting the acetylenic bisethers **577** with two equivalents of *n*-butyllithium in ether and quenching their metalated derivatives **578** with an electrophile (equation 199)[928]. Yields are good (60–70%), and in none of the examples could products



(577) (578) (579)

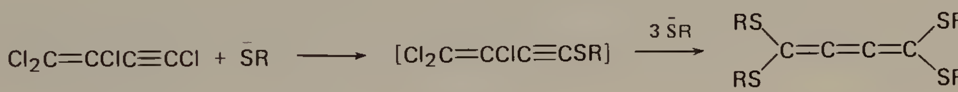
E = H_2O, D_2O, MeI, acetone, etc. (199)

derived from the isomeric enyne form of **578** or from a cumulenic ether lithiated in the δ position be detected. When the trisether $EtOCH_2C{\equiv}CCH(OEt)_2$ is subjected to the same conditions, 1,4-bis(ethoxy)butatriene results.

The chemical behaviour of cumulenic ethers towards bases[928-930], and in metalation, followed by alkylation and hydroxyalkylation reactions[930] has been studied, as has their use in a new synthesis of 3-alken-1-ynes and 1-methoxy-1,3-butadienes[931]. An n.m.r. study of several alkoxybutrienes has revealed that the geminal coupling constant ^2J(H–C–H) is of the same order of magnitude and negative sign (–9.5 Hz) as allenic ^2J. The long-range coupling ^5J(H–C=C=C=C–H)4((*cis* and *trans*)differ only slightly and are positive (+5.5–6.1 Hz), and ^6J(H–C=C=C=C–C–CH) constants are negative again (–0.9 to –1.5 Hz)[932].

Cumulenic thio ethers may be prepared like their oxygen counterparts **579** by treating the bisthio ethers $RSCH_2C{\equiv}CCH_2SR$ with two equivalents of *n*-butyllithium in ether at –50° C, followed by the addition of water[928]. In this case, however, besides the desired derivatives $RS{-}C{=}C{=}C{=}CH_2$ the isomeric enynthio ethers $RSC{\equiv}C{-}CH{=}CH_2$ are also produced. Since it was shown that the isomerization does not take place by prototropy during work-up, it is most likely that both cumulenic and enynic lithium intermediates are generated in the initial metalation. When the acetylenic ditio acetal $MeOCMe_2C{\equiv}CCH(SEt)_2$ was reacted with one equivalent of *n*-butyllithium in ether at –50° C the cumulenic dithio ether $Me_2C{=}C{=}C{=}C(SEt)_2$ could be prepared[928]. Other 1,1-bis(alkylthio) derivatives of [3]cumulenes have also been reported[933].

In an elegant new method, perchlorobutenyne (**580**) has been converted into the tetrakis(alkylthio)butatrienes **582** by treatment with thiolates in dimethylsulphoxide (equation 200)[934,935]. The exchange–isomerization process has been

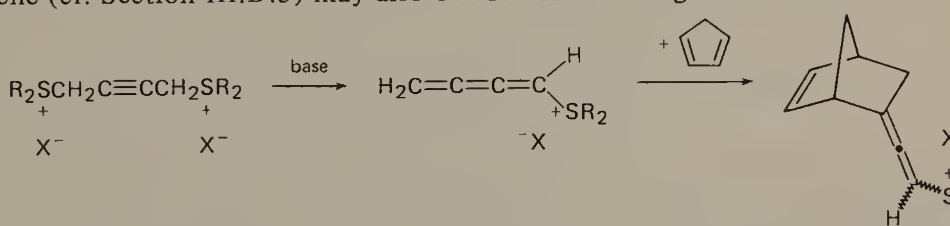


(200)

(580) (581) (582)

R	Yield (%)
t-Bu	62
c-Hex	37
CH_2Ph	36
Ph	50
and others	35–77

shown to begin with the formation of the (isolable) acetylenic thio ether **581**. If these latter derivatives are reacted with a thiolate differing from the one initially employed, mixed butatrienes **582** result. Instead of **580** the isomeric perchlorobutatriene (cf. Section III.D.3) may also be used as a starting material for **582**[934].



(201)

(583) (584) (585)

R = M, X = Cl

R = Et, X = Br

Butatrienylsulphonium salts **584** are obtained when the acetylenic disulphonium salts **583** are treated at –40° C with sodium alkoxides (equation 201)[936,937]. The structures of the (unstable) cumulenes **584** follows from spectroscopic data[936], and from [2 + 4] cycloaddition reactions with cyclopentadiene which yields the (stable) propadienyl sulphonium salts **585** (cf. Section II.D.5.b).

Cumulenic thio ethers are still a rare and poorly investigated class of cumulenes, even though several of these compounds are found in Nature[938–940].

3. Group VIIa substituted cumulenes

Preparative work in this area is likely to be difficult due to the expected high reactivity of halogenocumulenes. Their behaviour in addition reactions should prove to be interesting, and for spectroscopic studies the whole set of halogenated butatrienes would be of importance.

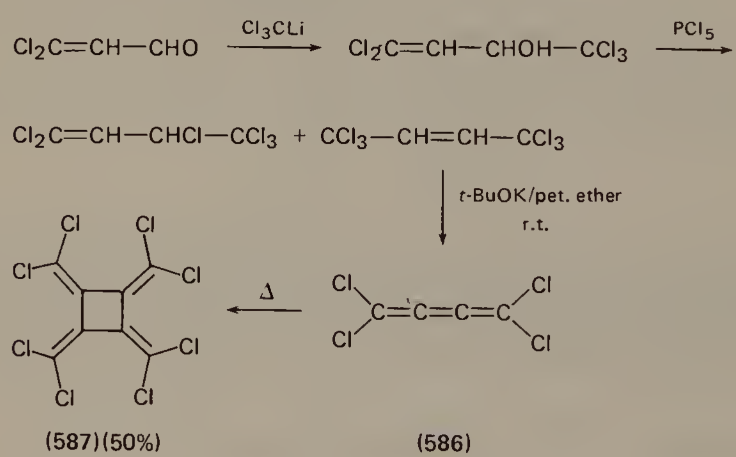
1,1,4,4-Tetrafluorobutatriene has been prepared by the dehydrobromination of 1,4-dibromo-1,1.4,4-tetrafluoro-2-butene with potassium hydroxide. In the liquid state this compound detonates violently at temperatures near 0° C[941].

Tetrakis(trifluoromethy)butatriene has been obtained by flash pyrolysis of 1,2,3,4,5,6-hexakis(trifluoromethyl)tetracyclo[4.4.0.0^{2,4}.0^{3,5}] deca-7,9-diene at 700° C and 10^{-3} torr[942].

The only other trifluoromethylbutatriene known seems to be 1,1-bis(trifluoromethyl-3,3-diphenyl-butatriene[943].

Monochlorobutatriene is one of the dehydrochlorination products of 1,4-dichloro-2-butyne if the reaction is interupted before all the starting material has been consumed. Low reaction temperature seems to favour the butatriene formation[944–946].

The surprisingly stable perchlorobutatriene (**586**) has been synthesized in a three-step sequence starting with β,β-dichloroacrolein (equation 202)[947,948]. On heating to 100° C **586** dimerizes to perchloro [4] radialene (**587**).



(202)

1,1,4-Trichloro-1,2,3-pentatriene has also been prepared by an elimination reaction[949].

Some chlorobutatrienes carrying aryl substituents of varying complexity have been synthesized, and their solvolytic behaviour has been investigated[950–952].

The first cumulene with more than two double bonds, was, in fact, a dibromocumulene, *trans*-diphenyldibromobutatriene, obtained by treating diphenyldiacetylene with one equivalent of bromide[953]. The method has been adopted for the preparation of other diaryldibromocumulenes[950].

Some 'mixed' diarylbromochlorobutatrienes have been isolated after dehydrohalogenation of various chlorobromoolefins[950].

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