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Carbonylcarbenes in the specific synthesis of natural products

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ABSTRACT. Studies on the specific synthesis of natural products and their analogues, using alkoxycarbonyl- and keto-carbenes as well as their synthetic equivalents, are surveyed. Properties of carbonylcarbenes such as cycloaddition to alkenes and reactions involving intermolecular and (especially) intramolecular insertion in C–H, N–H, and C–X (X = heteroatom) bonds have found wide scale application. These reactions permit the stereoselective and regioselective synthesis of a wide variety of carbon atom and heteroatom molecular skeletons which are difficult to obtain by other procedures.†

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I. Introduction

The varied chemical properties of keto- and alkoxycarbonylcarbenes have been described in a series of reviews and monographs[1–6] and many of their reactions have been recommended as convenient preparative methods for the construction of various structural fragments. This review deals with the way in which these recommendations are used in practice in the specific synthesis of biologically active natural products and their analogues. The author did not attempt to provide an exhaustive bibliography on this question; the studies quoted serve merely as an illustration of the possibility of the synthetic use of carbenes.

† This review was intended for publication in issue No. 7 (1989) of this journal, which was devoted to the chemistry of carbenes.

II. Synthetic equivalents of carbonylcarbenes

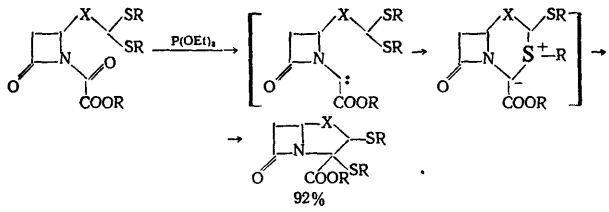
In the selection of a reagent for the creation of a structural element of the target compound, the detailed mechanism of its interaction with the substrate is of secondary importance; the question of the limits of the applicability of the method and the procedures for increasing the regio- and stereo-selectivity of the reagent comes to the fore. For this reason, the differences between free carbenes and carbenes bound in complexes and even between their precursors are unimportant for synthetic chemists provided that these species behave in the same way. All these compounds with the aid of which it is possible to introduce the $R-\overset{|}{\underset{|}{C}}-COOR$ or $R-\overset{|}{\underset{|}{C}}-COR$ synthons into the molecule, are combined in the concept of "synthetic equivalents of carbonylcarbene".

Diazocarbonyl compounds are a traditional source of carbonylcarbenes. Virtually only the catalytic decomposition of the latter is used in specific synthesis, because the carbenes generated by the thermolysis or photolysis of diazo-compounds are too active and their reactions are insufficiently selective. The experiments where it is necessary to carry out the Wolff rearrangement, which is known to occur best under photolytic conditions, are an exception.

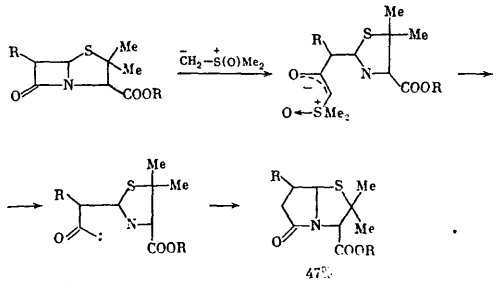
Various compounds are used as catalysts of the decomposition of diazoketones and diazoesters:[7,8] copper, rhodium, ruthenium, platinum, and tungsten complexes. In selecting a particular catalyst, the aim is to reduce the decomposition temperature of the diazo-compound, to alter its regioselectivity, and to increase the stereoselectivity of the reaction.

Bivalent rhodium salts (the acetate, trifluoroacetate, etc.) have been used particularly frequently in the specific synthesis in recent years. Indeed, in the presence of these compounds it is frequently possible (but not always) to carry out the decomposition of diazo-compounds at room or an even lower temperature and the regioselectivity of the reaction proves to be higher than that of the reaction using copper salts. Rhodium acetate is superior to copper compounds as the catalyst of the reactions involving the insertion of the carbene in a C–H bond[9] and its addition to arenes.[10] On the other hand, copper compounds have not lost their importance in the catalysis of reactions involving cycloaddition to alkenes. Copper acetylacetonate [$Cu(acac)_2$] or its hexafluoro-derivative [$Cu(F_6\text{-}acac)_2$] are frequently used for this purpose. The employment of copper complexes with chiral ligands (L*) as catalysts of the decomposition of diazoacetic acid ester enabled a number of investigators[11–15] to achieve a high degree of stereocontrol in the synthesis of chrysanthemic and related acids.

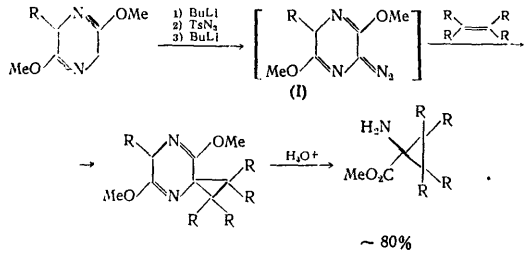
Communications have been recently published about new sources of carbonylcarbenes. Thus, according to Kametani et al.,[16] carbonylcarbene arises when a substituted oxalic acid amidoester is acted upon by triethyl phosphite:



A carbonylcarbene, which underwent the Wolff rearrangement, has been obtained by the reaction of a β-lactam with dimethylsulphoxonium methylide:[17]



A derivative of diazodihydropyrazine (I), which reacts with alkenes with evolution of nitrogen at the instant of its formation, may be called a synthetic equivalent of aminomethoxycarbonylcarbene:



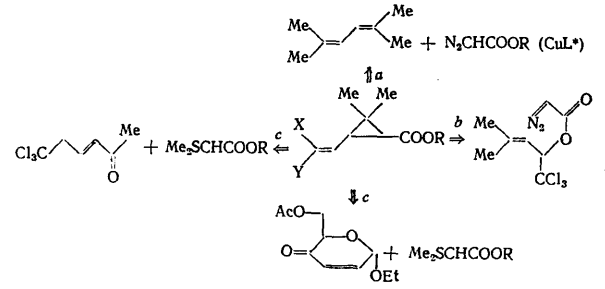
Acid hydrolysis of the spiroadduct led to the formation of aminocyclopropanecarboxylic acid.[18]

The carbene generated in the presence of copper is known[1-6] to possess electrophilic properties. Nevertheless, in certain cases it has been possible to add this species to the "activated" double bond of acrylic esters. This result has been achieved[19] by adding to the reaction mixture copper sulphate and a carbene acceptor—dimethyl sulphide. The addition of the diazoester yielded a sulphonium ylide,[20] which served as a reagent transferring the nucleophilic alkoxycarbonylcarbene.[21] A similar result was obtained in the reaction of "activated" double bonds with dimethylsulphonium methylides, synthesised beforehand by other methods,[22-24] which makes it possible to regard these compounds as the synthetic equivalents of alkoxycarbonylcarbene.

III. The use of the [1 + 2]cycloaddition reaction for the synthesis of the cyclopropane fragment of the molecular skeleton

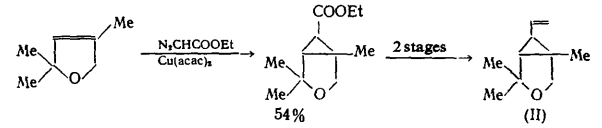
Fairly numerous natural products whose skeleton contains a three-carbon ring are known. The [1 + 2]cycloaddition reactions of carbonylcarbenes are widely used to construct this structural fragment.

The carbene synthesis is most important for the preparation of a wide variety of pyrethroids, which are based on chrysanthemic acid and its derivatives.[25] Various ways of synthesising acids of this group with the aid of equivalents of alkoxycarbonylcarbene are known:

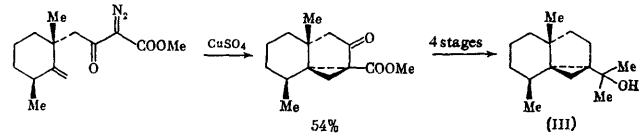


(*a*) Stereoselective[26,27] and asymmetric[11-14] synthesis involving the use of a bulky group in the diazoacetic ester and (or) the application of copper complexes with chiral ligands as catalysts; (*b*) the stereocontrolled intramolecular cycloaddition of the carbene C atom to a weakly nucleophilic double bond;[15,18] (*c*) the use of sulphonium ylides to convert an "activated" double bond into a cyclopropane derivative.[22-24]

The intermolecular conversion of an alkene into a cyclopropane derivative by diazoacetic ester has been used in the unambiguous synthesis of artemiseole (II), a natural monoterpene having a skeleton which conflicts with the isoprene biosynthesis rule:[29]

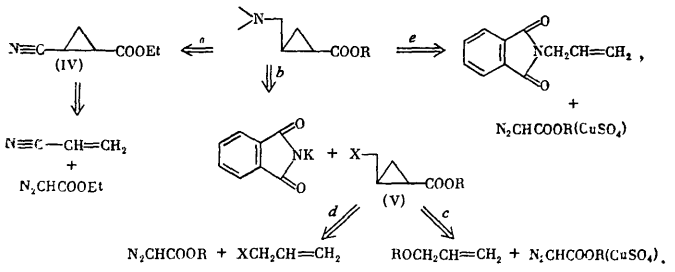


The intramolecular cyclopropane formation reaction has been the key stage in the synthesis of a sesquiterpene antibiotic—cycloeudesmol (III). With the aid of this method, it has been possible to introduce the quaternary C atom common to the three condensed rings and having the necessary configuration:[30]



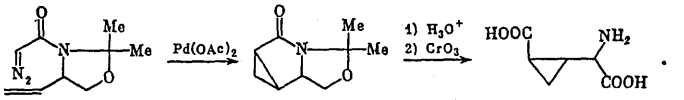
The rigidity of the system in this instance led to the formation of only one stereoisomer of the compound. The intermolecular conversion of the double bond into a cyclopropane derivative with the aid of diazoacetic ester [CuI.P(OMe)$_3$ catalyst, yield 74%] has been used in the synthesis of 23,24-dihydrocalysterol.[31]

Aminoacids of the cyclopropane series occupy an outstanding place among biologically active natural products.[32] Various approaches to the synthesis of the cyclic analogue of γ-aminobutyric acid (GABG) have been demonstrated on the basis of the scheme presented below:



(*a*) The addition of diazoacetic ester to acrylonitrile, the pyrolysis of the resulting pyrazoline, and the hydrogenation of the nitrile (IV);[33] (*b*) the alkylation of potassium phthalimide by the halogenomethylcyclopropanecarboxylic acid ester (V).[34] The ester (V) can be obtained (*c*) by treating allyl acetate[35] or allyl alcohol[36] with diazoacetic ester and subsequent substitution of the hydroxy-group in compound (V) (X = OH) by a halogen.[37] The same ester can be obtained by another procedure (*d*) involving the interaction of diazoacetic ester with allyl chloride in the presence of copper sulphate.[38] The ester of 2-chlorobut-3-enoic acid is then formed as the side product as a result of the rearrangement of the intermediate chloronium ylide.[39] The formation of the ylide and hence of the unsaturated ester can be avoided if the reaction of the diazoester with allyl chloride is performed under the conditions of photosensitised deazotisation, i. e. with participation of triplet ethoxycarbonylcarbene,[40] or if rhodium acetate is used as the catalyst of the decomposition of the diazoester.[41] Finally, the cyclic analogue of GABA can be obtained by converting *N*-allyl-phthalimide into a cyclopropane derivative. By virtue of the influence of the phthalimide group, the nucleophilicity of the nitrogen atom in *N*-allylphthalimide is reduced and the formation of the ylide in the insertion reaction does not therefore take place[42] (pathway *e*).

An analogue of glutamic acid, containing a three-carbon ring, has been obtained[43] by the intramolecular cycloaddition of a diazoamide to the double bond and the subsequent hydrolysis and oxidation of the alcohol group:



IV. The use of the [1 + 2]cycloaddition reaction for the synthesis of active intermediates

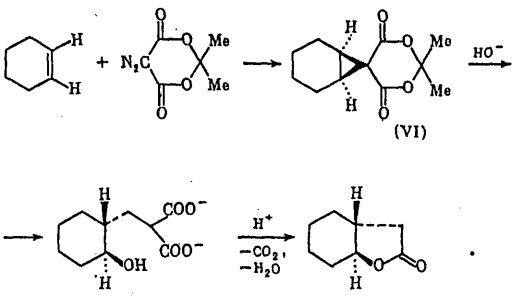
Compounds with a three-carbon ring, obtained as a result of the [1 + 2]cycloaddition of carbonylcarbenes to carbon–carbon double bonds, are frequently convenient synthons for the construction of a wide variety of structural elements. This is associated, on the one hand, with the ease of the formation of carbonyl cyclopropanes by carbene synthesis and, on the other hand, by the large store of energy in these compounds and hence the frequently high tendency towards ring opening, which takes place regio- and stereo-selectively.

A monograph (Ref. 44, Chapter 4) and a review[45] have been devoted to the use of cyclopropanecarboxylic acids, their derivatives, and cyclopropyl ketones in organic synthesis. Here we shall quote only individual examples.

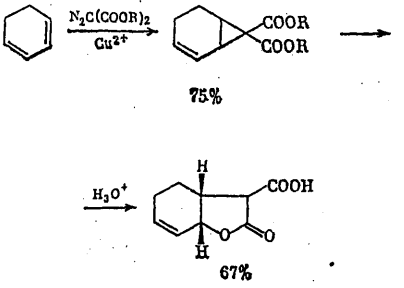
1. The ring opening in cyclopropanes and the problem of the reversal of the polarity of the synthons

The electron density in cyclopropanes containing the electron-accepting carbonyl group is known[46] to be distributed non-uniformly in such a way that the C–C bond of the ring lying opposite the substituent is stronger than the bond adjoining the substituent. The C(1)–C(2) bond is in fact dissociated when carbonylcyclopropanes are acted upon by electrophiles and nucleophiles or, catalytically, by excited hydrogen. The nucleophilic species always add to the second carbon atom of the three-membered ring with inversion of the configuration of the atom; the electrophilic species is found at the first carbon atom. This atom usually undergoes racemisation.[47]

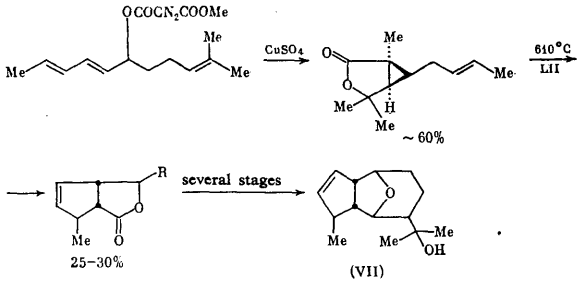
The nucleophilic opening of the ring or the homocoupled addition to carbonylcyclopropanes proceeds under mildest conditions if the compound contains two electron-accepting groups at one carbon atom, the bisecting [staggered] conformation of the two groups being optimal. This is achieved in spiran derivatives of type (VI):[47]



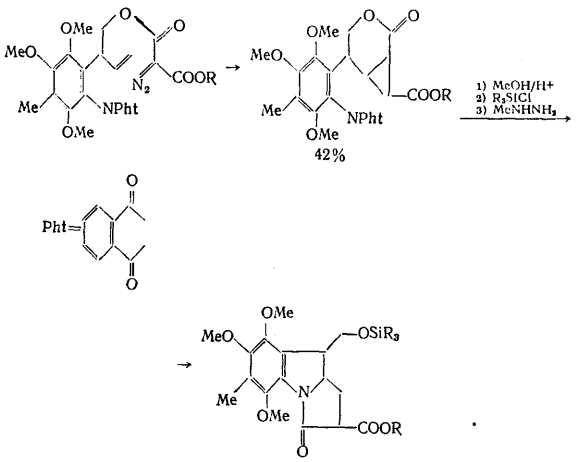
The γ-butyrolactone fragment, condensed with a larger ring, enters into the composition of many natural products.[48] Compounds with both *cis*- and *trans*-fused rings are known. Danishefsky's strategy,[47] consisting in the formation of a spiro-activated cyclopropane and the opening of the three-membered ring of the latter with the aid of a base, makes it possible to obtain *trans*-fused lactones (see above). Conversely, the opening of the ring in cyclopropanecarboxylic acids in an acid medium leads to the formation of *cis*-fused lactones:[49,50]



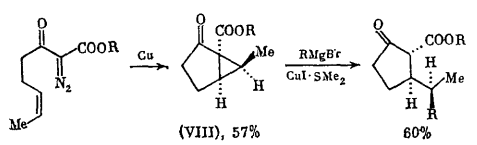
cis-Fused lactones can also be obtained by the intramolecular conversion of the esters of unsaturated alcohols into cyclopropane derivatives. The combination of this method and the vinylcyclopropane–cyclopentene rearrangement (see below) made it possible[51] to devise an approach to the creation of the guaiane system (VII):



If the nucleophilic centre is in the side chain of the cyclopropane carboxylic acid or cyclopropyl ketone, then its homocoupled addition to the activated three-carbon ring proceeds under mild conditions under rigorous stereocontrol and, depending on the character of the nucleophilic centre, leads to the formation of carbocycles or heterocycles.[47] The use of this reaction for the synthesis of a precursor of the alkaloid mitomycin is illustrated below:

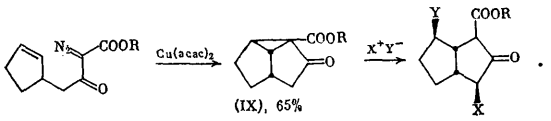


The intramolecular conversion of the double bond into a cyclopropane derivative and subsequent homocoupled addition of alkyl cuprate to the bicyclo[3.1.0]hexan-2-one (VIII) constitutes a convenient method of synthesis of cyclopentanones with control of the stereochemistry of the side chain:[53]



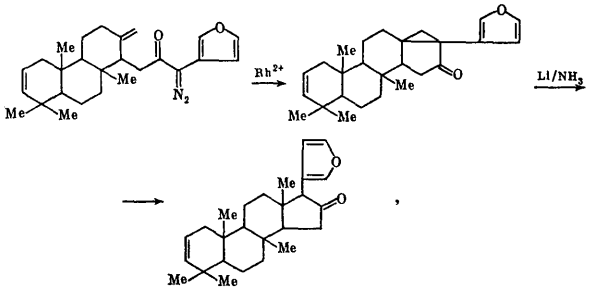
This strategy has found applications in the synthesis of prostaglandins, terpenoids, and other natural products (see, for example, Adams and Belley[54]).

The intramolecular cycloaddition of carbonylcarbene to the double bond of the cyclopentene fragment and subsequent electrophilic or nucleophilic opening of the three-membered ring of the tricyclic compound (IX) afford a condensed system made up of two five-membered rings having a defined stereochemistry:[55]



This reaction is of interest in connection with the synthesis of polyquinanes and iridoid monoterpenes.[56]

Finally the opening of the ring in cyclopropyl ketones, also obtained by the intramolecular cyclopropane formation reaction, with the aid of lithium in liquid ammonia has been used in the synthesis of the cyclic system of limonoids:[57]

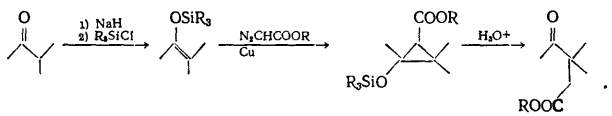


and also in the synthesis of pentalenene.[58]

The acid-catalysed ring opening in cyclopropane derivatives obtained by the carbene synthesis[59–64] is used widely in the synthesis of sesquiterpenes, diterpenes, gibberellins, and steroids. The reaction proceeds especially readily, frequently spontaneously, at room temperature or on slight heating in those cases where there is an electron-donating group at the second carbon atom of the carbonylcyclopropane.

Bifunctional fragments in which the functional groups are separated by an odd number of carbon atoms are known[65] to constitute a definite problem in organic synthesis, because the usual isohypsic reactions lead to the formation of compounds with an odd number of carbon atoms between the functional groups. Carbonylcyclopropanes are synthetic equivalents of the $^{+}C-C-C-C=O$ synthon with inverted polarity at the γ-carbonyl atom. Derivatives of 2-hydroxycyclopropanecarboxylic acids are very useful in synthesis from this point of view.[66]

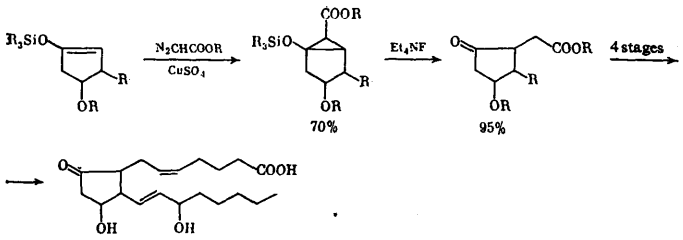
The acid-catalysed ring opening in siloxycyclopropane produces a result equivalent to the α-alkylation of a carbonyl compound:



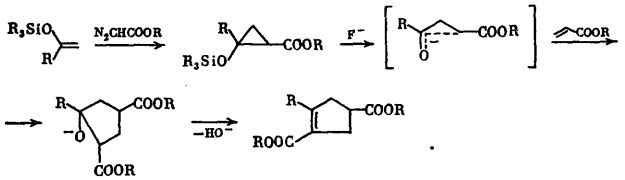
Quaternary centres in the α-position in the ketone can be obtained in this way.

The copper sulphate-catalysed addition of alkoxycarbonylcarbene to the silyl ethers of enols and subsequent ring opening with the aid of the fluoride ion constitutes a new strategy for the synthesis of

1,4-dicarbonyl compounds. In particular, it has been used to synthesise dihydrocompactin,[67] prostaglandins,[68] and related compounds,[69] for example:

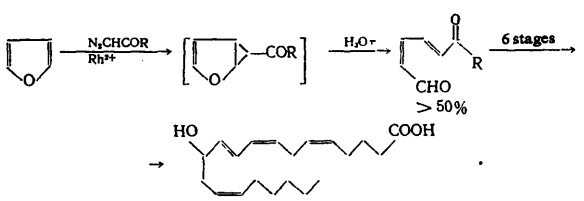


A new strategy for [2 + 3]annelation is based on the interaction of the fluoride ion with siloxycyclopropanecarboxylic acids.[70] The essential feature of this strategy consists in carrying out three consecutive reactions: the conversion of the silyl ether of an enol into a cyclopropane derivative, the opening of the ring in the latter with the aid of the fluoride ion, and the trapping of the carbanion formed in this process by electrophilic alkene.



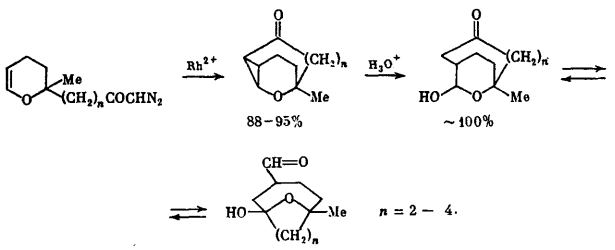
The reaction results in the formation of a cyclopentene derivative.

The reaction of ketocarbenes with furan and its homologues provides a unique possibility for the stereoselective synthesis of (*Z*, *E*)-isomers of dienealdehydes. This method has been used successfully to synthesise isomeric hydroxyeicosanetetraenoic acids:[71-73]



The analogous reaction with sylvan made it possible to obtain (7*E*, 9*Z*)-dodeca-7,9-dien-1-yl acetate[74]—the pheromone of one of the pests on grapevine.

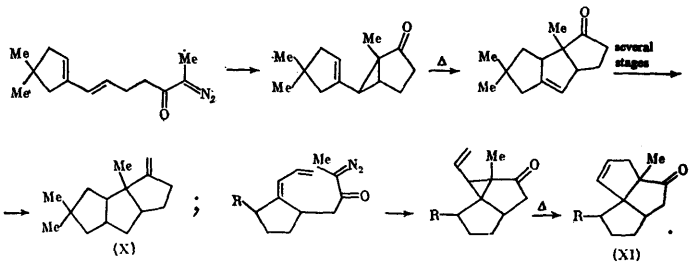
The opening of the ring in 2-alkoxycyclopropyl ketones constitutes a pathway leading to rings of moderate size (7-membered – 10-membered),[75] in particular to widdrol:



The thermal isomerisation of the adducts of ethoxycarbonylcarbene with pyrimidines and isoquinolines led to the synthesis of modified and alkaloids.[76]

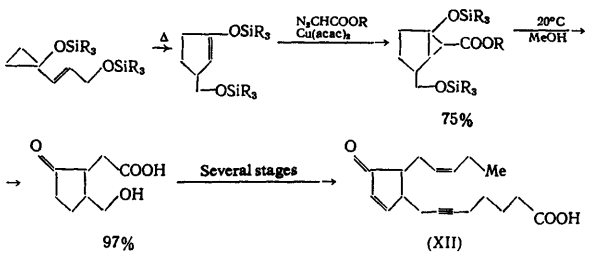
2. The vinylcyclopropane–cyclopentene rearrangement

The conversion of conjugated dienes into cyclopropane derivatives affords vinylcyclopropanes, which are capable of isomerising to cyclopentene on heating.[77] This rearrangement constitutes yet another way of obtaining polycyclic systems. Examples of the synthesis with its aid of the sesquiterpenes hirsutene (X) and isocomene (XI) are presented below:



The two-stage process involving the cycloaddition of the carbene fragment and rearrangement, which can be achieved without isolating the intermediate vinylcyclopropane, is equivalent to [4 + 1]cycloaddition, permitting at the same time the closure of several rings. The vinylcyclopropane–cyclopentene rearrangement ensures an effective stereocontrol of the reaction: *cis*-fused rings are formed. The reaction can be catalysed by lithium iodide.[78]

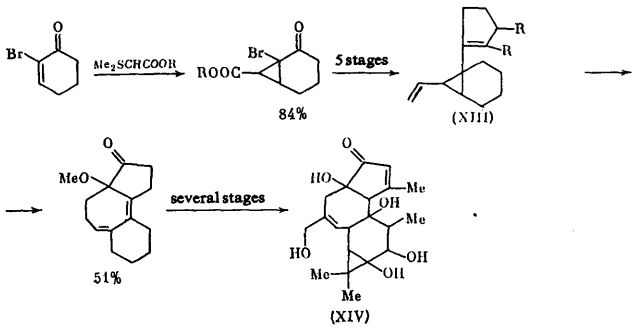
In the synthesis of dicranenone A—an aliphatic acid related to prostaglandins (XII)—the fragment containing the cyclopentane ring and two carbonyl groups in the 1,4-positions and involving the *trans*-dispositions of the ring substituents was constructed using the methodologies described above: the vinylcyclopropane–cyclopentene rearrangement, the formation of the cyclopropane derivative, and the opening of the ring in siloxycyclopropanecarboxylic acid:[69]



3. The Cope rearrangement of divinylcyclopropanes

The Cope rearrangement of *cis*-divinylcyclopropane takes place spontaneously and leads to the formation of cycloheptadiene. The similar reaction of compound (XIII), obtained by the conversion of the corresponding bromovinyl ketone into a cyclopropane derivative by means of dimethylsulphonium methylide, has been used in the

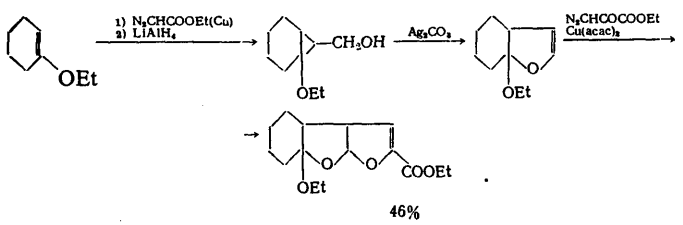
synthesis of tricyclic and tetracyclic diterpenes, in particular phorbol (XIV), which has interesting pharmacological properties:[79]



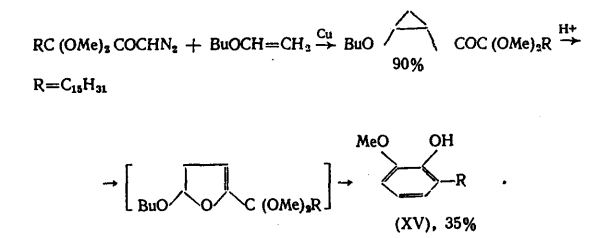
The above rearrangement allows the conversion of bicyclo[4.1.0]-heptadienes into cycloheptatrienes and hence makes it possible to obtain seven-membered rings via the reactions of carbenes with mononuclear aromatic compounds. The carbene method of synthesis of azulenes has been known for a long time. This method has undergone a new development in studies of recent years. It was found that the reaction can be carried out intramolecularly, providing a new and simple method of synthesis of compounds of this class.[80,81] Ring-substituted aryldiazoketones cyclise regio-selectively in the presence of rhodium trifluoroacetate; the bicyclic ketones obtained can be converted into substituted azulenes or into tetralones. McKervey et al.[82] suggest that the method which they describe be used for the synthesis of sesquiterpenes of the perhydroazulene series.

V. The use of other cycloaddition reactions of carbonylcarbenes

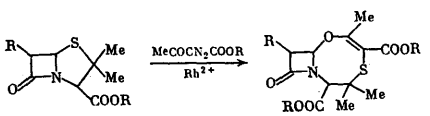
Carbonylcyclopropanes are capable of rearranging to dihydrofuran derivatives. In certain cases, dihydrofurans are formed directly in the reaction of a carbonylcarbene with an alkene.[8,45] This formal [2 + 3]cycloaddition of the 1,3-dipolar form of carbonylcarbene has found an application in organic synthesis. Dihydrofurancarboxylic acid esters, having a structure similar to that of aflatoxin, have been obtained in this way:[83]



A series of natural products containing the furan ring,[84] intermediates in the synthesis of eburnamonine and certain other alkaloids,[85] as well as the monomethyl ether of hydrourushiol (XV), a natural derivative of catechol,[86] have been obtained by the same method:

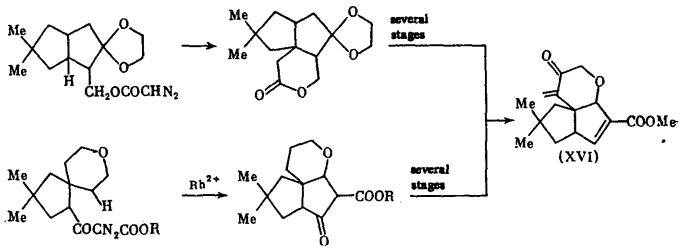


The insertion of the 1,3-dipolar form of a carbonylcarbene in the carbon–sulphur bond of a penicillannic acid, which results in the formation of a new antibiotic of the β-lactam group, has been described:[87]



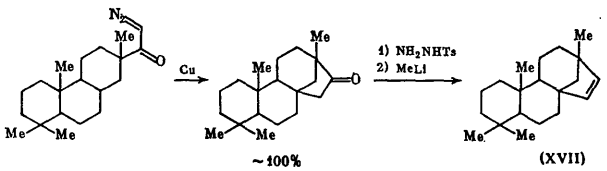
VI. The use of reactions involving the insertion of carbonylcarbenes in a C–H bond

The reactions involving the intramolecular insertion of carbonylcarbenes and their equivalents in C–H bonds have come to be widely used synthetically in recent times. The reaction leads to the formation of cyclopentane derivatives. The rigidity of the transition state in the insertion reaction ensures high regio- and stereo-control. The insertion of the carbene C atom in a tertiary C–H bond has been used[88] in the synthesis of the pentalenolactone (XVI); subsequently, the same compound was obtained[9] by the reaction involving insertion in a secondary C–H bond:

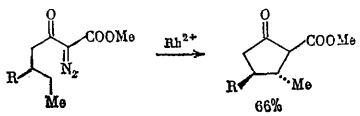


The advantage of this method of synthesis of cyclopentanes is evident: in contrast to other methods of ring closure, which require the presence of two functional groups in the compound, here one is sufficient and it is possible to achieve in one stage an appreciable increase in the complexity of the molecule.

Bridged structures, for example hibaene (XVII), are obtained with the aid of the reaction involving insertion in a C–H bond:[89,90]

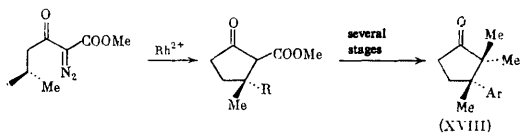


The intramolecular insertion of a carbonylcarbene proceeds with a high degree of regioselectivity via a pathway leading to the formation of five-membered rings.[92,92] The insertion in diastereotopic C—H bonds is characterised in addition by stereoselectivity:[93]



A *trans*-3,4-disubstituted cyclopentanone is formed preferentially.

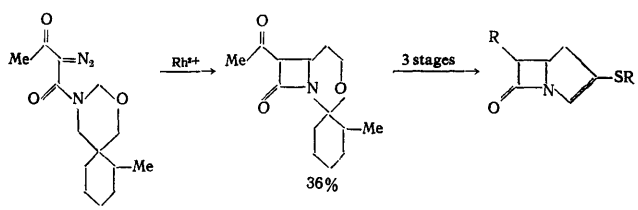
In the deazotisation of a 2-diazo-3-ketoester in the presence of the rhodium catalyst, the insertion in a C—H bond can proceed with retention of configuration, as happened in the synthesis of α-cuparenone (XVIII):[96]



Thus the reaction represents a general strategy for the enantioselective synthesis of carbocycles having a chiral centre.

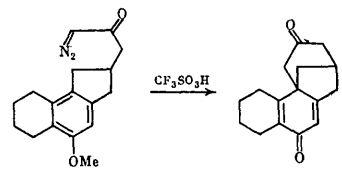
The use of a divalent palladium complex of benzonitrile as the catalyst of the decomposition of a diazoester makes it possible to obtain products of insertion in C—H bonds even when the reacting molecule contains a C=C double bond.[95] The insertion proceeds regioselectively at a decreasing rate in the sequence CH > CH_2 > CH_3. Allyl and benzyl C—H bonds proved to be less reactive than the C—H bonds of saturated compounds. The insertion in aromatic C—H bonds has been achieved successfully.[96,97] In the presence of the rhodium catalyst, the insertion in tertiary C—H bonds predominates over cycloaddition, but secondary and primary C—H bonds are less reactive than the C=C bonds. The replacement of the catalyst by a copper catalyst leads to the predominance of cycloaddition in all cases.[98]

The reaction involving insertion in a C—H bond has not been used solely for the synthesis of carbocycles; heterocycles[99] and intermediates in the synthesis of analogues of thienamycin,[100] penicillin,[101] and cephalosporin[102,103] have been obtained by this method:



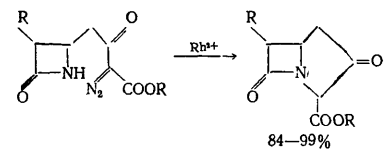
When an attempt was made to carry out the same reaction photolytically,[103] it was found that it is insufficiently selective.

An unusual reaction has been observed for ketocarbenes containing in the δ- or ε-position an aromatic ring with an alkoxy-group in the *para*-position, capable of being converted into a quinone. Treatment of these ketones with a strong acid yielded bridged systems, which were subsequently used in the syntheses of gibberellins and diterpenoids:[104]

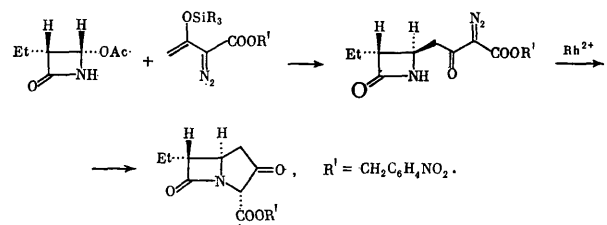


VII. The use of reactions involving insertion of carbonylcarbenes in a N—H bond

The insertion of carbonylcarbenes in N—H bonds is used in the synthesis of β-lactam antibiotics:[105,106]

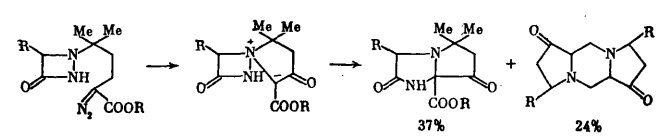


Phosphorus analogues of thienamycin[107] and nuclear analogues of β-lactam antibiotics[108] have been obtained by the same procedure. It is possible to synthesise pure enantiomers of β-lactams and carbapenems by starting with a pure enantiomer of a β-lactam and a diazoester having a bulky alcoholic group:[109]

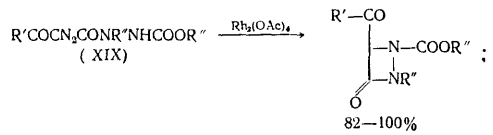


The reaction involving insertion in a N—H bond has been used also in other asymmetric syntheses, in particular for the preparation of a pure alanine enantiomer.[110]

The programme undertaken to synthesise aza-analogues of β-lactam antibiotics by the insertion of a carbene in a N—H bond led to an unexpected result:[111] tricyclic compounds were obtained as a result of the carbene attack not on the lactam but on the amine nitrogen atom in diazetidines and the subsequent rearrangement of the ylide. This afforded a new group of pharmacologically interesting compounds:



At the same time, the decomposition of the diazodihydrazide (XIX) in the presence of the rhodium catalyst was accompanied by the almost quantitative insertion of the carbene in the amide N–H bond:[112]

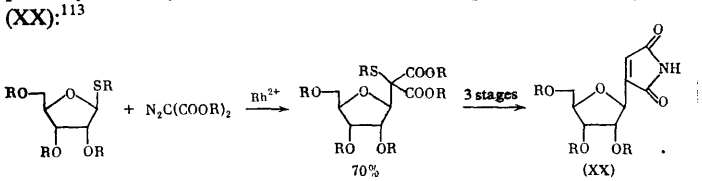


82—100%

R‴ = Bu^t, CH_2Ph; R″ = CH_2Ph, COOEt; R′ = Me, OEt.

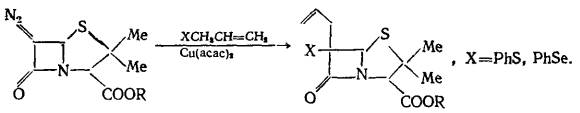
VIII. The use of reactions involving the insertion of carbonylcarbenes in C–X bonds

The interaction of carbenes with compounds containing heteroatoms is known to entail the formation of ylides. Sulphur ylides are formed particularly readily.[21] The rearrangement of the ylides can produce a synthetically interesting result.[39] The insertion in a C–S bond at the anomeric carbon atom in pentoses opens a pathway to the synthesis of the antitumour compound showdomycin (XX):[113]



70% (XX)

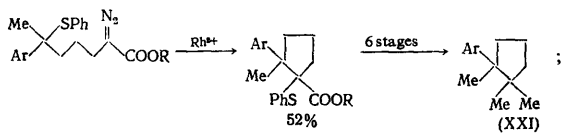
The rearrangement of the ylides formed as a result of the intramolecular attack by a copper carbenoid on the sulphur atom in penicillins constitutes a general method for the formation of a new C–C bond in compounds of this class.[114] The rearrangement of the ylides constitutes the basis of the synthesis of penems and carbopenems from diazopenicillin:[115,116]



33—66%

Another source of a carbonylcarbene for the synthesis of penems and carbopenems with the aid of the reaction involving insertion in a C–S bond was described above.

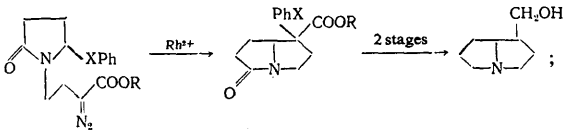
The reaction of diazoacetic ester with benzyl sulphides is used to generate a quaternary centre in the benzyl position in the synthesis of the aromatic sesquiterpene cuparene (XXI):[117,118]



52% (XXI)

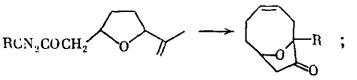
Art = *p*-$C_6H_4CH_3$.

The same procedure has been used in the synthesis of pyrrolizidine alkaloids trachelanthamidine, isoretronecanol, etc.:[119–121]



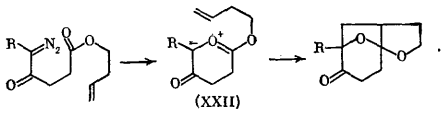
X=S (55%), X=Se (36%).

The formation of oxonium ylides proceeds with greater difficulty than that of the sulphur ylides. Nevertheless, the rearrangement of a tetrahydrofuran ketocarbene, which led to the bicyclic heterocycle oxocane, apparently occurred with their participation:[122]



R = H(81%), R = COOEt (67%).

Oxonium ylides of type (XXII) are intermediates in the recently proposed[123] method of synthesis of complex heterocyclic systems encountered in various groups of natural products:

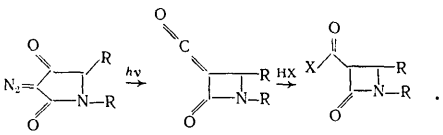


(XXII)

IX. The use of other reactions of carbonylcarbenes

One of the most interesting properties of ketocarbenes—the Wolff rearrangement—has also found an application in the specific synthesis of natural products. This rearrangement is very widely used in the synthesis of homologous acids by the Arndt–Eistert method and in the ring contraction reactions for cycloalkanes and their heterocyclic analogues. A detailed description of this problem is outside the scope of the review and we shall confine ourselves to several examples.

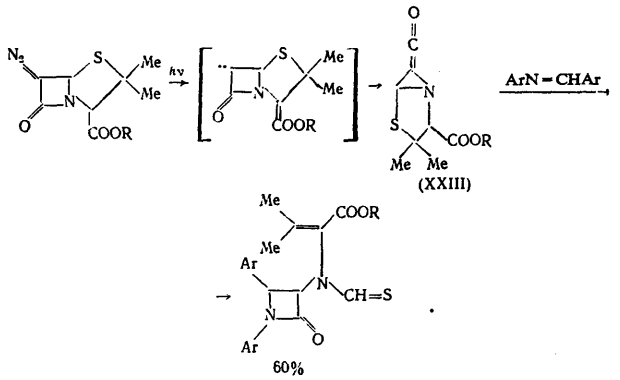
Certain β-lactam antibiotics[124] and their aza-analogues[125] have been synthesised with the aid of the Wolff rearrangement: this method has proved very suitable for the synthesis of a strained β-lactam ring:



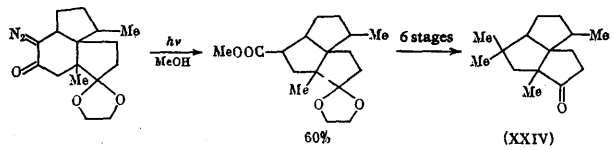
~ 90%

The Wolff rearrangement of a ketocarbene obtained by a non-traditional method[17] has been used, as shown above, for the synthesis of penicillin homologues. The addition of a ketone—the product of the Wolf rearrangement of the amidocarbene (XXIII)—to a Schiff base affords (after the opening of the aziridine ring) new

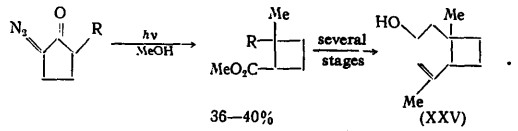
compounds with a β-lactam fragment which are potential antibiotics:[126]



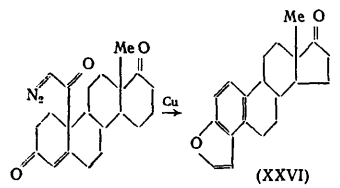
The rearrangement has also been used in the synthesis of 3-oxosilphinine (XXIV):[127]



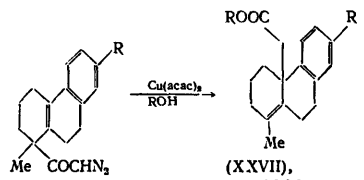
The method of ring contraction with the aid of this rearrangement has proved convenient for the synthesis of precursors of grandisol and fragranol (XXV):[128]



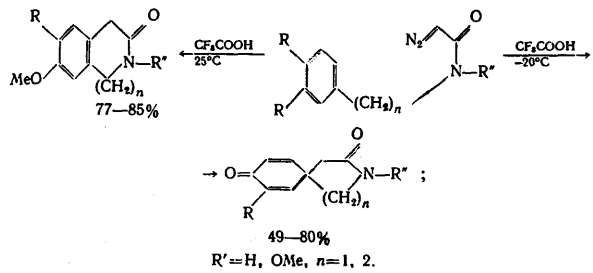
Finally, the vinylogue Wolff rearrangement[129] helped to obtain the modified oestrone (XXVI):



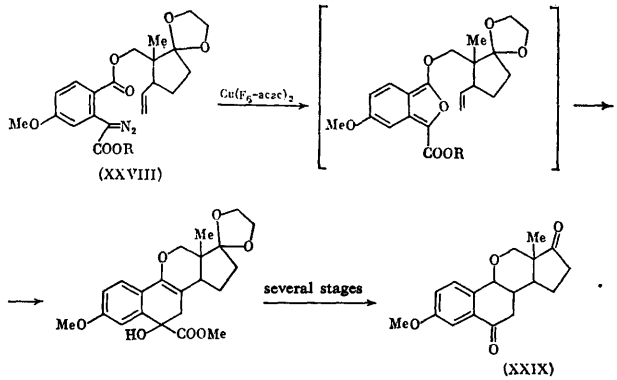
The same reaction can serve as a method of synthesis of angularly substituted polycyclic compounds of type (XXVII):[130]



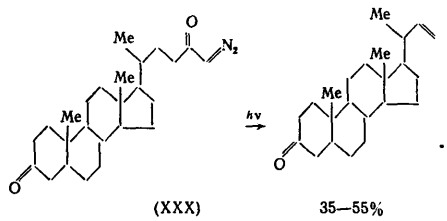
One may note certain other reactions of α-diazocarbonyl compounds, which have been used in the specific synthesis of the structural fragments of natural products and in which either carbonylcarbenes or their synthetic equivalents were involved. Thus the acid-catalysed cyclisation of aromatic diazoacetamides has been used[131] for the synthesis of isoquinolinones and benzazepinones having the structural elements of natural alkaloids:



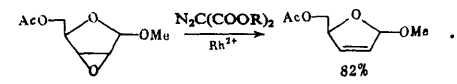
The copper-catalysed decomposition of the diazoester (XXVIII) led[132] to the 6-oxo-11-oxasteroid (XXIX) via the intermediate formation of an isobenzofuran derivative:



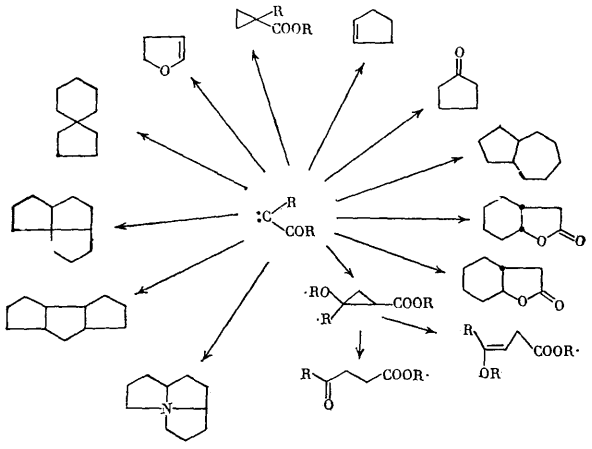
Carbene reactions sometimes play an auxiliary role in the synthesis of natural products. Thus the photolysis of the α-diazoketone (XXX) in the presence of imidazole, leads to the formation of nor-olefins. This method has been used in the degradation of the side chains of bile acids:[133]



Diazomalonic ester has been used to remove the oxiran group protecting a double bond, which has been used in the synthesis of biologically important $\Delta^{2,3}$-nucleosides:[134]



Various structural fragments of natural products, which can be synthesised with the aid of carbonylcarbenes and their synthetic equivalents, are presented in the scheme below:



The wide variety of these structures shows that the chemistry of carbonylcarbenes makes an important contribution to the range of available methods in synthetic organic chemistry.

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