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Carbene methods for the introduction of acyl and acylmethyl groups into organic molecules

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ABSTRACT. A systematic account is given of data on the reactions involving the insertion of dihalogeno-, keto-, and alkoxycarbonyl-carbenes in carbon–hydrogen and carbon–heteroatom bonds as well as reactions involving the conversion of alkenes into cyclopropane derivatives followed by ring opening, leading to the introduction of acyl, acylmethyl, and alkoxycarbonylmethyl groups into organic substrates.†

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I. Introduction

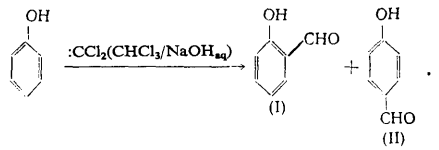
Many important methods for the synthesis of organic compounds with functional group substituents are based on the creation of a carbon–carbon bond as a result of the introduction of acyl or acylmethyl groups into an organic substrate.[1] Together with the traditional methods for the introduction of these fragments into organic molecules by means of reactions with participation of anions, radicals, and cations, methods based on the use for such purposes of carbene reactions have been acquiring recently increasing synthetic importance. The wide availability of dihalogeno-, keto-, and alkoxycarbonyl-carbenes and their specific reactivity in relation to carbon–hydrogen and carbon–heteroatom bonds as well as carbon–carbon multiple bonds constitute a basis for the effective employment of these highly reactive species as agents transferring acyl and acylmethyl groups. In the present review, an attempt is made to give a systematic account of the literature data on this question, individual aspects of which have also been examined in monographs[2,3] and other reviews.[4–12]

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

II. Insertion in carbon–hydrogen and carbon–heteroatom bonds

1. The Reimer–Tiemann reaction

Despite the potentially great possibilities of the method for the introduction of acyl groups into organic substrates by the insertion of heterosubstituted carbenes in carbon–hydrogen or carbon–heteroatom bonds, they remain little investigated at the present time. However, the Reimer–Tiemann reaction is an exception.[13,14] In its classical version, the yield of salicylaldehyde (I) is 20–25% and that of 4-hydroxybenzaldehyde (II) is 8–10%. Quaternary ammonium salts do not exhibit activity as phase-transfer catalysts in this reaction, whilst in the presence of catalytic amounts of tertiary amines the yield of salicylaldehyde increases to 49–65% while that of compound (II) changes only slightly:[15]



In the presence of β-cyclodextrin, dichlorocarbene attacks exclusively the *para*-position.[16] Then an essential condition for the attainment of high process selectivity is the maintenance of a chloroform : cyclodextrin molar ratio less than unity throughout the reaction. The catalytic action of cyclodextrin can be explained by the formation of its ternary complex with chloroform and phenol in which spatial proximity between the *para*-position of the aromatic ring and dichlorocarbene, formed in a cyclodextrin cage as a result of the reaction of chloroform with the hydroxide ion, is ensured.[17]

The selectivity of the Reimer–Tiemann reaction also increases after the addition of poly(ethylene glycol) to the reaction mixture as a result of the formation, according to Neumann and Sasson,[18] of its complex with the phenoxide anion in which the *ortho*-positions in the benzene ring are sterically blocked.

2. Insertion of keto- and alkoxycarbonyl-carbenes in carbon–hydrogen bonds

The introduction of acylmethyl and alkoxycarbonylmethyl groups into organic substrates via the insertion of keto- and alkoxycarbonyl-carbenes, generated from the corresponding diazocarbonyl compounds, in carbon–hydrogen bonds is an important synthetic method, to the development of which numerous studies have been devoted (see the relevant reviews[7,9,19,20]). The highest yields of the products

are then produced when rhodium carboxylates are used as catalysts:[21-24]

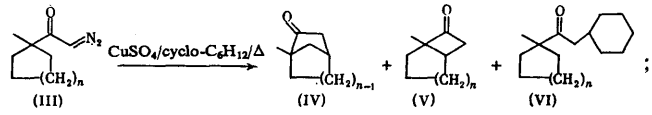
$$R-H+N_2CHCOOC_2H_5 \xrightarrow{Rh(OCOCF_3)_2/22\,^\circ C} \underset{29-92\%}{R-CH_2COOC_2H_5} + N_2,$$

$R = C_5-C_8$ alkyl, cycloalkyl.

The synthetic value of the method is limited owing to the low regioselectivity of the reaction and also the necessity to use a large excess of the alkane to prevent the oligomerisation of the carbene and the poisoning of the catalyst.[22]

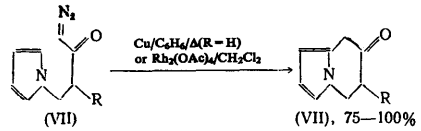
The insertion of keto- and alkoxycarbonyl-carbenes in C–H bonds of alkenes, alkynes, arenes, and heteroarenes usually competes with processes involving cyclo-addition to multiple bonds.[7,9,20,25] Diethyl diazomalonate and α-diazoacetophenone are also capable of affording the products of the insertion of the corresponding carbenes into the allyl C–H bonds of vinyl ethers.[26]

In contrast to intermolecular reactions in which ketocarbenes are inserted in non-activated C–H bonds, intramolecular processes of this kind are frequently characterised by a higher regioselectivity.[25,27-33] Thus the thermal decomposition of diazomethyl ketones (III) in cyclohexane over anhydrous copper sulphate affords mixtures of cyclopentanones (IV), cyclobutanones (V), and the products (VI) of the insertion of the ketocarbene in the solvent:[27]



$n = 3$ (a), 2 (b), 1 (c), 0 (d).

With the exception of the reaction of 1-diazoacetyl-1-methylcyclobutane (IIId), derivatives of cyclopentanone (IV) are the main products [the yields are 50–75% of (IVa), 58% of (IVb), 19% of (IVc), and 1% of (IVd)] for a cyclopentanone : cyclobutaneone = 8–16 : 1 ratio; the products of insertion in the C–H bonds of cyclohexane (VI) are formed in an insignificant amount. The diazoketone (IIId) is converted under these conditions predominantly into compound (VId) (yield 29%). The authors demonstrated the possibility of using this method for the construction of the cyclopentane ring in steroids.[27] On the other hand, the reactions involving the intramolecular insertion of ketocarbenes in non-activated C–H bonds in conformationally less mobile systems proceed with a low regioselectivity and as a rule lead to products in low yields.[27] This method has been used effectively for the synthesis of bicycloanones containing the indole fragment.[34,35,41] Thus the decomposition of 1-diazo-4-(1-pyrrolyl)-2-butanone (VII) in the presence of copper powder leads to a quantitative yield of dihydroindolizinone (VIII):[34]



R = H (a), C_6H_5 (b), 4-$CH_3OC_6H_4$ (c); 4-$NO_2C_6H_4$ (d).

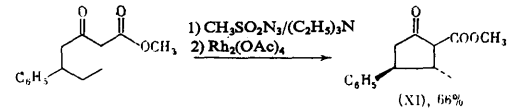
In the case of compounds (VIIb–d), the corresponding indanones are formed in 14–22% yield as a result of the competing insertion of the ketocarbene in the benzene ring.

In view of the important role which β-dicarbonyl compounds play in organic synthesis and the possibility of their ready conversion into α-diazo-derivatives,[35] the results of studies[25,28,30,32,33,36,37] on the intramolecular insertion of α-acetyl-substituted alkoxycarbonylcarbenes in C–H bonds have atttracted attention. In contrast to the corresponding α-diazoketones (see above), in this case the conformationally mobile compounds (IX) exhibit a much more marked tendency towards intramolecular cyclisation with formation of 2-methoxycarbonylcyclopentanones (X):[28]

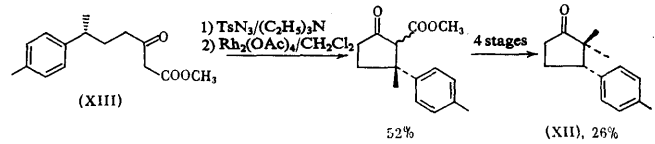


$R^1 = CH_3$, iso-C_3H_7, C_8H_{17}, $CH=CH_2$, $CH_2CH=C(CH_3)_2$;
R^2, $R^3 = H$, CH_3.

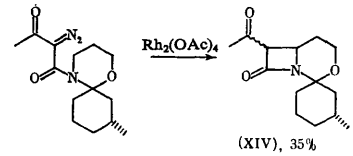
Detailed study of the dependence of the regioselectivity of this reaction on the electronic and steric effects of the substituents[28,29] led to the conclusion that the reactivity decreases in the following sequence in relation to the carbene centre: tertiary > secondary > primary C–H bonds. The allyl and benzyl C–H bonds are less reactive. The reactions are also characterised by a high degree of diastereoselectivity.[30,33] For example, the cyclopentanone derivative (XI) with the *trans*-disposition of the phenyl and methyl substituents is formed on cyclisation of the δ-phenyl-substituted α-diazo-β-ketoester:[30]



An important advantage of this method is also the retention of the absolute configuration of the carbon atom subjected to carbene attack.[7,9,32] The effective synthesis of (+)-α-cuparenone (XII) from the chiral β-ketoester (XIII) serves as a good illustration of this:[32]



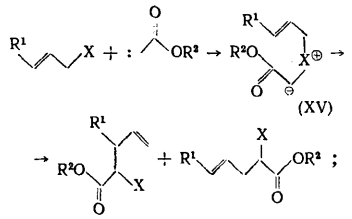
It has been found recently that the cyclisation of α-diazo-β-dicarbonyl compounds containing carbocyclic[36] and heterocyclic substituents[37] can also be used effectively for the synthesis of four-membered rings, which has been demonstrated, in particular, in relation to the synthesis of compound (XIV)—a key intermediate in the synthesis of thienamycin analogues:[37]



3. Insertion of keto- and alkoxycarbonyl-carbenes in carbon–heteroatom bonds

A specific method for the introduction of acyl and acylmethyl groups into organic substrates is also based on reactions involving the insertion of the corresponding carbenes in carbon–heteroatom bonds (see the relevant reviews[7,9,11]). Compounds containing

heterosubstituents in the allyl position relative to the multiple bond exhibit an increased tendency to undergo reactions of this kind. The generally accepted mechanism of these reactions includes the initial attack by the carbene on the heteroatom with formation of the corresponding ylide (XV), which then undergoes a [2,3]- or [1,2]-sigmatropic rearrangement:[7,8,11,38,45]

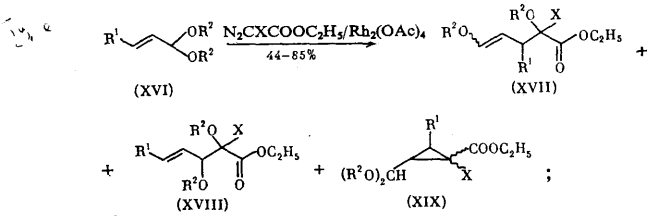


(XV)

X=Cl, Br, I, OR^3, SR^3, NR^3_2.

As in the reactions involving insertion in C–H bonds (see above), the yields of the products of the intermolecular reactions in which carbonyl-containing carbenes are inserted in carbon–heteroatom bonds are as a rule low and the conversion of the substrate into a cyclopropane derivative is frequently a competing process. It was of interest that the ratio of the insertion of cycloaddition products depends to a large extent on the conditions in the generation of the alkoxycarbonylcarbene. The decomposition of diazo-compounds by direct photolysis or under the influence of metallic catalysts leads to the preferential formation of insertion products, while photosensitised decomposition of diazo-compounds, affording a triplet carbene, gives rise to cycloaddition products. The difference in the behaviour of the carbene species is apparently caused by the inability of triplet carbene to form the corresponding ylides (XV).[7,9,11] It has also been established that the use of rhodium(II) acetate or the hexarhodium carbonyl cluster $Rh_6(CO)_{16}$ as catalysts of the decomposition of diazoacetic ester leads to the exclusive formation of the products of the [2,3]sigmatropic rearrangement in reactions with allyl iodides, aryl sulphides, and dialkylallylamines (yield 49–96%). In order to obtain similar products in the reactions with allyl bromides and chlorides, it is preferable to use copper catalysts.[38,39]

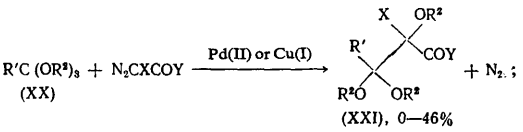
In contrast to alkyl allyl ethers, which afford products of conversion into cyclopropane derivatives in reactions with ethyl diazoacetate and dimethyl diazomalonate, the acetals (XVI) are converted into the corresponding 2,5-dialkoxy-4-alkenoates (XVII); the products of the "direct" insertion in the C–O bond [compounds (XVIII)][40,43] and of conversion into cyclopropane derivatives [compounds (XIX)] are formed only as minor components:



(XVI) (XVII) (XVIII) (XIX)

R^1 = H, C_6H_5; R^2 = CH_3, C_2H_5, $(CH_2)_2$; X = H, $COOC_2H_5$.

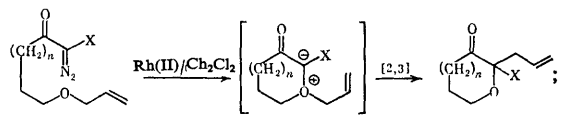
The decomposition of diazocarbonyl compounds in the presence of the orthoesters (XX) and copper (II) triflate or rhodium(II) acetate also leads to the insertion of the corresponding carbenes in the C–O bond, but the yields of the products (XXI) are in most cases low:[46]



(XX) (XXI), 0—46%

R′=H, CH_3, C_2H_5; R^2=CH_3, C_2H_5, X=H, $COOCH_3$; Y=OCH_3, OC_2H_5, C_6H_5.

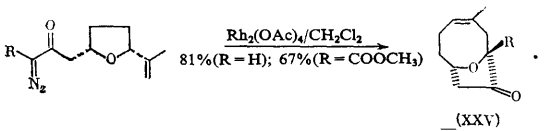
The intramolecular generation of the allyloxonium ylides (XXII) from α-diazocarbonyl compounds (XXIII) and their subsequent [2,3]sigmatropic rearrangement constitute a convenient method of synthesis of five-membered oxygen-containing heterocycles:[44,45]



(XXIII) (XXII) (XXIV)

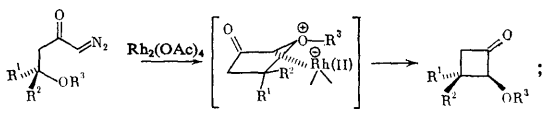
X = H, $COOCH_3$, $COOC_2H_5$; n = 0,1.

The yields of 2-substituted 3-furanones (XXIV, n = 0) are 67–95%, while an increase in the chain length by one carbon atom (n = 1) greatly increases the fraction of the products of insertion in the C–H bond.[44,45] A similar reaction has been used effectively in the synthesis of the bicyclanones (XXV) with an eight-membered oxygen-containing ring:[45]



(XXV)

The insertion of ketocarbenes in C–O bonds has also been used to synthesise the cyclobutanones (XXVI):[44]



(XXVIII) (XXVII), 45–68% (XXVI)

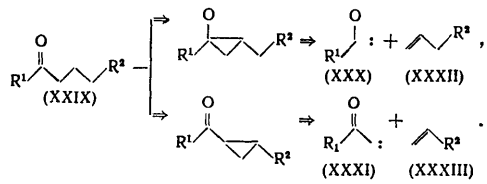
R^1 = H, CH_3; R^2 = CH=CH_2, C_6H_5; R^3 = CH_3; R^2R^3 = $(CH_2)_2$.

It is suggested[44] that the reaction proceeds via the formation of the oxonium ions (XXVII) and their subsequent decomposition with regeneration of the rhodium catalyst. It is remarkable that the cyclisation of the ketone (XXVIII, R^1=R^3=CH_3, R^2=C_6H_5) proceeds under these conditions with retention of the absolute configuration of the quaternary carbon atom.[44]

III. Conversion into cyclopropane derivatives and subsequent ring opening

Apart from the methods for the insertion of carbonyl groups via carbene reactions, examined in the previous Section, the use of the two-stage sequence of reactions involving the cycloaddition of the carbene to the alkene and the opening of the ring in the product formed also frequently proved effective. As in the insertion reactions, methods based on the conversion of alkenes into cyclopropane derivatives by dihalogeno-, keto-, and alkoxycarbonylcarbenes have the greatest synthetic importance. The retrosynthetic analysis of the formation of the carbonyl compounds (XXIX) with

the aid of this reaction leads to the carbenes (XXX) and (XXXI) and the corresponding alkenes (XXXII) and (XXXIII):

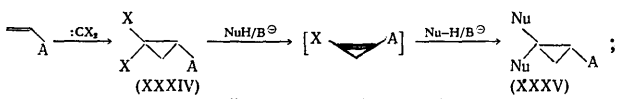


(XXIX) (XXX) (XXXII) (XXXI) (XXXIII)

Evidently, the efficiency of the formation of compound (XXIX) with the aid of the synthetic equivalents of the carbene synthons (XXX) and (XXXI) is determined not only by the efficiency of the cyclopropane formation stage but also by the possibility of the regiospecific ring opening in the cyclopropane intermediate. By virtue of the high internal strain in the three-carbon ring and the pronounced influence of substituents on the strength of its carbon–carbon bonds,[47,50] ring opening in many cyclopropane derivatives with functional group substituents can be achieved under mild conditions with high degrees of conversion and a high regioselectivity. The so called "donor–acceptor cyclopropanes", containing *p*-electron-donating and π-electron-accepting substituents in the vicinal positions, are especially promising in this respect. Their concerted activating effect weakens the C–C ring bond nearest to the two substituents and the bond undergoes ready heterolytic cleavage.[2,4,6,11,12,50]

1. Reactions of dihalogenocarbenes

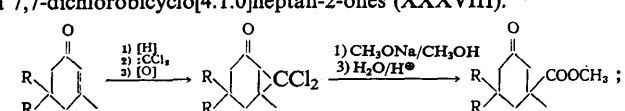
The dihalogenocarbene precursors are at the present time the most convenient synthetic equivalents of the carbene synthons (XXX) for preparative purposes. The cycloaddition of dihalogenocarbenes to alkenes has been investigated in a large number of instances and can be readily achieved experimentally in many cases.[3,51] However, reactions of the type of cyclopropyl–allyl isomerisation with the opening of the C–C ring bond located opposite to the halogen atom are characteristic of the *gem*-dihalogenocyclopropanes formed.[3,12,52] Favourable conditions for the dissociation of one of the nearest C–C ring bonds can be created by substituting the halogen atoms by *p*-electron-donating groups. Such reactions can be achieved fairly easily only between nucleophiles and *gem*-dihalogenocyclopropanes (XXXIV) containing a mobile hydrogen atom in the α-position relative to the π-electron-accepting substituent:[2,3,8,12,53–63]



(XXXIV) (XXXV)

A=CHO, COAlk, COAr, COOAlk, CON(Alk)$_2$, CN, Ar; X=F, Cl, Br; Nu=AlkO, ArO, ArS, Alk$_2$N.

The substitution of halogen atoms in compounds (XXXIV) takes place via the elimination–addition mechanism and leads to the corresponding "donor–acceptor" cyclopropanes (XXXV) or the products of their subsequent reactions with ring opening. Thus 3-substituted 2-cyclohexenones (XXXVI) can be readily converted into the corresponding 3-methoxycarbonylcyclohexanones (XXXVII) via 7,7-dichlorobicyclo[4.1.0]heptan-2-ones (XXXVIII):[56,62]

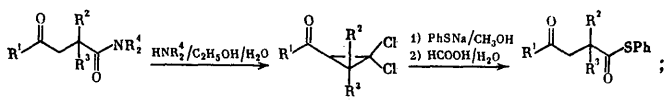


(XXXVI) (XXXVIII) (XXXVII), 70–90%

R=H, CH$_3$.

The electrophilic dichloroacarbene plays in this sequence of reactions the role of a synthetic equivalent of the nucleophilic alkoxycarbonylanion and ensures the formation of compounds (XXXVII), in which the alkoxycarbonyl group is linked to a quaternary carbon atom. Similar reactions have been observed between sodium alkoxides and monocyclic 1-acyl-2,3-dichlorocyclopropanes (XXXIX) and derivatives of 2,2-dichlorocyclopropanecarboxylic acids.[2,3,8,12,53–55,59,61]

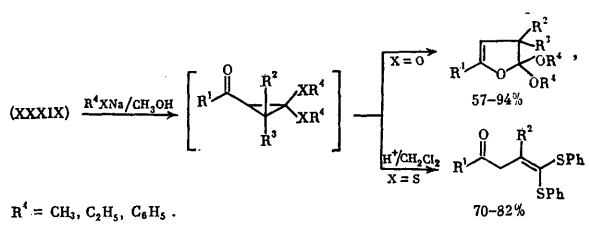
When secondary amines or sodium thiophenoxide are used as nucleophiles in reactions with acylcyclopropanes (XXXIX), it is possible to obtain high yields of the corresponding dialkylcarbamoyl derivatives (XL)[57] and phenylthiocarbonyl derivatives (XLI):[64]



(XL) (XXXIX), 60–90% (LI)

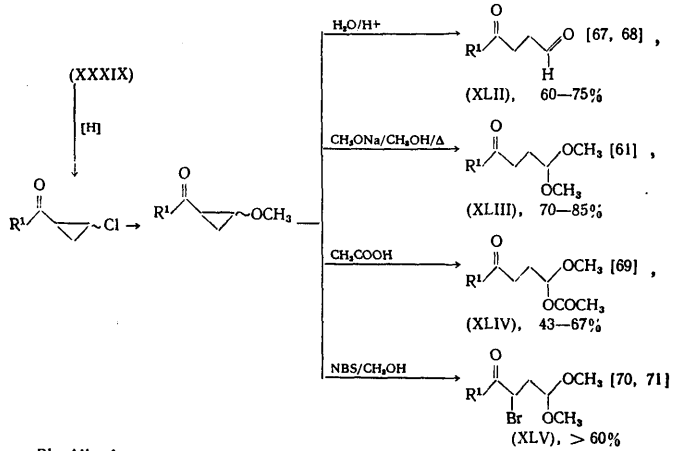
R^1, R^2, R^3 = H, Alk, Ar; R^4 = C$_2$H$_5$; R$_2^4$ = (CH$_2$)$_5$, (CH$_2$)$_2$O.

One of the advantages of this method for the introduction of acyl substituents into organic substrates is the possibility of their generation in a protected form at the stage involving the opening of the cyclopropane ring:[64,65]



R^4 = CH$_3$, C$_2$H$_5$, C$_6$H$_5$. 57–94% 70–82%

This gives rise to the possibility of modifying one of the carbonyl groups of the latent 1,4-dicarbonyl compounds and also of achieving the regiospecific introduction of additional substituents.[64,66] The latent ester group can also be modified at the stage involving the dihalogenocyclopropane intermediate, because the corresponding monohalogenocyclopropanes exhibit similar properties in relation to nucleophiles:[61,68–71]‡



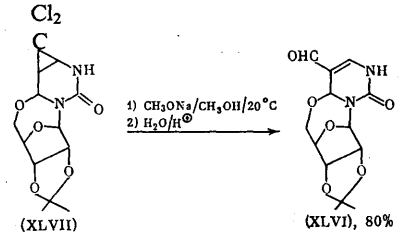
(XXXIX) (XLII), 60–75% (XLIII), 70–85% (XLIV), 43–67% (XLV), > 60%

R^1=Alk, Ar.

‡ In the formulae below and henceforth, the numerals in square brackets denote references (Ed. of Translation).

Thus the addition to a double bond of the formyl group, in the free or protected form, with formation of compounds (XLII) and (XLIII)–(XLV) respectively can be achieved with the aid of dichlorocarbene.

An interesting example of the introduction of the formyl group via the formation of *gem*-dichlorocyclopropane is also provided by the formation of the aldehyde (XLVI) on treatment of the cyclopropa[4,5]pyrimidine system (XLVII) with sodium methoxide:[72]

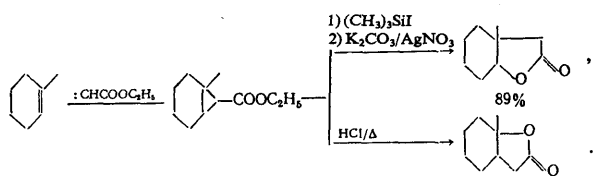


(XLVII) (XLVI), 80%

The key stages in this reaction are probably the elimination of a proton from the nitrogen atom of the pyrimidine ring under the influence of the base, the opening of the cyclopropane ring induced by the anion formed under these conditions, and the subsequent nucleophilic substitution of the chlorine atoms.[72]

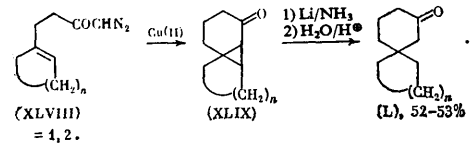
2. Reactions of keto- and alkoxycarbonyl-carbenes

The main difficulties in the introduction of functional groups into alkenes not containing *p*-electron-donating substituents at the double bond via conversion into cyclopropane derivatives by means of keto- and alkoxycarbonyl-carbenes are associated with the carrying out of the stage involving the opening of the cyclopropane ring. Although the opening of the ring in cyclopropanes having two π-electron-accepting substituents usually proceeds comparatively readily (see the relevant reviews[2,5,6]), the analogous reactions of the corresponding monosubstituted compounds require much more severe conditions and the use of acid reagents or catalysts.[2,6] It has recently been possible to overcome these difficulties in many respects by using trialkylhalogenosilanes as the electrophiles.[73,76] When the latter are allowed to react with acylcyclopropanes having different structures, the ring is as a rule opened under mild conditions and with a high regioselectivity. Examples of the successful use of these reagents are provided by the general methods for the conversion of alkenes into γ-butyrolactones[75] and α-methylene-γ-butyrolactones.[73] The formation of the lactone can then exhibit the opposite regiospecificity compared with the proton-catalysed reactions:[75]



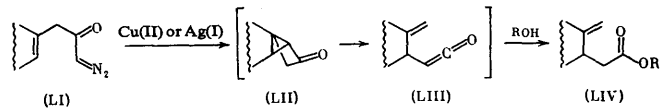
Pyridine hydrochloride[77] and acylmethanesulphonates[78,79] are also effective reagents for the opening of the ring in acylcyclopropanes.

The reactions involving the reductive cleavage of the ring in cyclopropyl ketones are likewise of considerable preparative value.[80] For example, the intramolecular conversion of monocyclic unsaturated diazoketones (XLVIII) into cyclopropane derivatives and the subsequent regioselective reduction of the tricyclic ketones (XLIX) with lithium in liquid ammonia constitutes a general method of synthesis of spiran bicyclic systems (L), which has been used successfully in the synthesis of certain natural sesquiterpenes:[80]



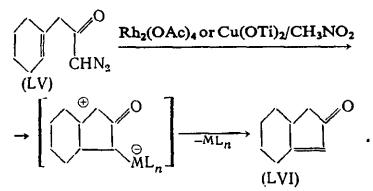
(XLVIII) (XLIX) (L), 52–53%
= 1, 2.

Acyclic and monocyclic βγ-unsaturated α′-diazoketones (LI) undergo the vinylogue Wolff rearrangement in the presence of copper(II) or silver(I) in alcohols, affording satisfactory yields of the esters of the corresponding γδ-unsaturated acids.[82,83] Evidence has been obtained showing that the skeletal rearrangement involves the initial conversion of the double bond into a cyclopropane derivative with formation of substituted bicyclo[2.1.0]pentan-2-ones (LII). The subsequent cleavage of the three-carbon ring leads to the substituted ketens (LIII) and, after the addition of an alcohol, to the final products (LIV):[83]



(LI) (LII) (LIII) (LIV)

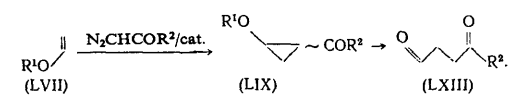
On the other hand, in the absence of protic solvents, the decomposition of the diazoketone (LV) by copper(II) and rhodium(II) leads to the corresponding bicyclic ketone (LVI), which the authors believe to proceed via the stage involving the intramolecular addition of the electrophilic metallocarbene complex to the double bond:[46]



(LVI)

$Cu(OTf)_2$ = copper(II) trifluoromethanesulphonate.

The introduction of functional group substituents into the enol ethers (LVII) by diazocarbonyl compounds, leading to 1,4-dicarbonyl compounds (LVIII) and their derivatives (important intermediates in the synthesis of five-membered carbocycles and heterocycles), is of great preparative value:

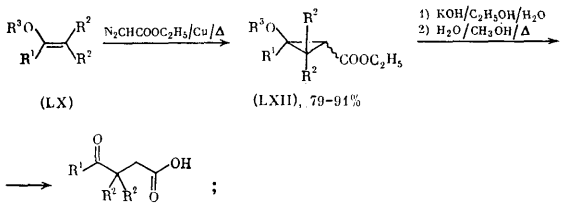


(LVII) (LIX) (LXIII)

The key stage of the process is the formation of the corresponding hydroxycyclopropane intermediates (LIX), usually achieved by the copper-catalysed decomposition of diazo-compounds in the presence of an excess of the enol ether (see the relevant reviews[4,7,9,10]). The use of copper catalysts sometimes induces the formation of considerable amounts of products of rearrangements or of insertion i- C–H bonds. The employment of rhodium catalysts h- advantages as regards the selectivity of the process for a nearly equimolar reactant r characteristics of each reactant also have the course of the reaction. Among diazoc esters of diazoacetic,[7,9–11] diazopyruvic,[85] a

diazoacetoacetic acids[86–88] as well as diazoketones[4,89–93] and derivatives of diazodiacetyl[95,96] have been investigated in reactions with alkyl vinyl ethers. Under these conditions, the corresponding acylcyclopropanes are formed as a rule in satisfactory yields when diazocarbonyl reagents containing only one π-electron-accepting group conjugated with the diazo-group are used. Otherwise the formation of derivatives of the dihydrofuran series, formally corresponding to the 1,3-dipolar cycloaddition of the ketocarbene to the double bond of the enol ether, is normally observed.[9,85,86] The reactions of the dialkyl acetals of ketens with diazoketones leads to similar compounds,[92] while the reactions with ethyl diazoacetate make it possible to obtain, together with products of rearrangements, also cyclopropane adducts.[92,94–96] The latter are likewise formed readily in the reactions of alkyl diazoacetates with silyl ethers of enols.[9,97–104]

Depending on the nature of the substituent at the ether oxygen atom in compounds (LIX), reactions involving the cleavage of the C(1)–C(2) bond in three-membered ring take place under the conditions of acid or base catalysis. Thus the conversion of the double bond into a cyclopropane derivative by ethyl diazoacetate, the hydrolysis of the resulting stereoisomeric esters of 2-alkoxycyclopropanecarboxylic acids (LXII), and the hydrolytic cleavage of the three-membered ring in the latter by brief refluxing in aqueous methanol constitutes a convenient method for the conversion of the enol ethers (LX) into 4-ketocarboxylic acids (LXI):[100]

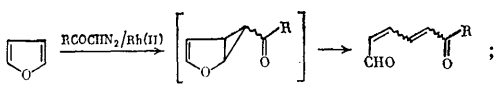


(LX) (LXII), 79–91%

(LXI), 84–95%

R^1 = C_6H_5, 3,4-$(CH_3O)_2C_6H_4$, $(CH_3)_2CH$, $(CH_3)_3C$; R^2 = H, CH_3; R^3 = CH_3, C_2H_5.

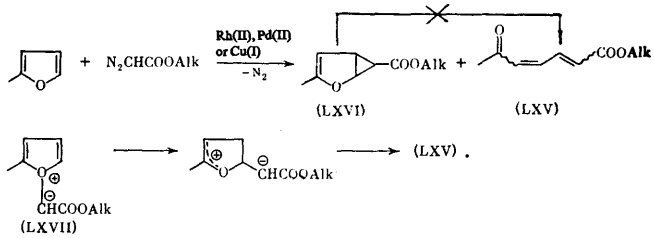
The acid-catalysed solvolysis of 2-alkoxycyclopropanecarboxylic acid esters and 2-alkoxycyclopropyl ketones, leading to the formation of the corresponding 1,4-dicarbonyl compounds or their derivatives, also takes place under mild conditions.[61,67–70, 93–97] On the other hand, the adducts (LXIII) of ketocarbenes with furan, which are bicyclic analogues of 2-alkoxycyclopropyl ketones, are spontaneously converted into *cis,trans*-6-oxoalka-2,4-dienals (LXIV) with a high stereoselectivity:[105]



(LXIII), 50–72% (LXIV)

R = CH_2—C≡C—$(CH_2)_3COOCH_3$, CH_2—C≡C—CH_2—C≡C—C_5H_{11}.

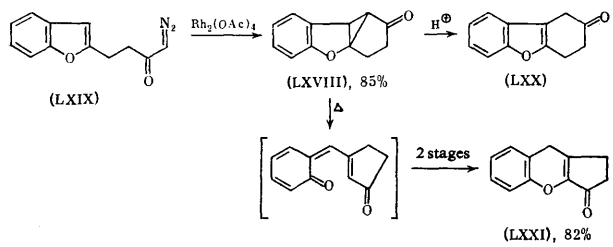
In this case, the process proceeds via the dissociation of the C(1)–C(3) bond in the 2-alkoxycyclopropyl ketone fragment of compound (LXIII), which may be induced by factors similar to those which are responsible for the preferential attack by the electrophile on the α-carbon atom of the furan ring. The reaction is probably general,[20,106] but it has been found that, in the interaction of alkoxycarbonylcarbenes with sylvan, the stereoisomeric esters of 6-oxoheptadionoic acids (LXV) are not formed from the cyclopropane precursors (LXVI) but are probably generated by the rearrangement of the ylides (LXVII):[106]



(LXVI) (LXV)

(LXVII)

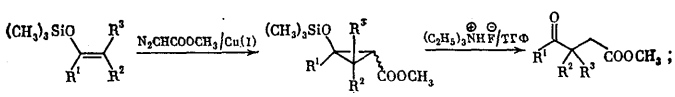
The ring opening reactions in the products of the intramolecular conversion of furyl-substituted ketocarbenes into cyclopropane derivatives proceed similarly and lead to the corresponding cycloalkenones.[107] On the other hand, in the reaction with the benzofuran derivative (LXVIII), obtained by the intramolecular cyclisation of the diazoketone (LXIX), the regiospecificity of the ring opening changes rapidly as a function of the conditions selected. Treatment of the ketone (LXVIII) with trace amounts of protic acids leads to high yield of the benzofuran (LXX), while heating of the ketone (LXVIII) at 180 °C affords the benzopyran (LXXI):[107]



(LXIX) (LXVIII), 85% (LXX)

(LXXI), 82%

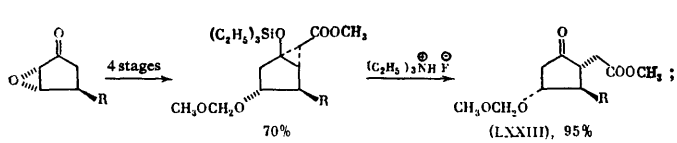
The opening of the three-membered ring in 2-trimethylsiloxycyclopropanecarboxylic acid esters (LXXII) takes place both in the presence of strong acids[102,108] and under virtually neutral conditions on treatment with triethylammonium fluoride:[98,101,109]



(LXII), 55–97% 67–93%

R^1, R^2, R^3 = H, alkyl, alkenyl, $OSi(CH_3)_3$.

Trialkylsilyl ethers of enols can be usually obtained under much milder conditions and with a higher regioselectivity than the corresponding alkyl ethers, which made it possible, in particular, to use successfully suitable cyclopropane intermediates in the key stage of a new synthesis of the familiar prostaglandin precursor (LXXIII):[101]

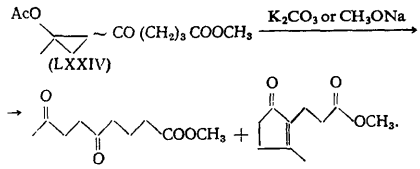


70% (LXXIII), 95%

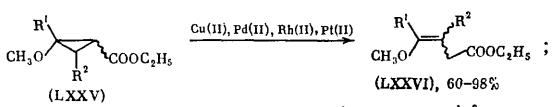
R = $OSi(CH_3)_2C(CH_3)_3$.

When functional groups are substituted into enol acetates by diazocarbonyl compounds, the opening of the three-membered ring

in the cyclopropane intermediates (LXXIV) takes place readily in an alkaline medium:[90]



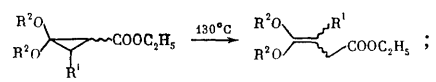
2-Alkoxycyclopropanecarboxylic acid esters (LXXV) are capable of isomerising to the corresponding vinyl esters (LXXVI) in the presence of catalytic amounts of transition metal salts:[110–112]



(LXXV) (LXXVI), 60–98%

$R^1 = CH_3$, $CH_2{=}CH$, C_6H_5, $CH_2{=}C(OCH_3)$; $R^2 = H$, C_6H_5; $R^1R^2 = (CH_2)_4$.

Ethyl 2,2-dialkoxycyclopropanecarboxylates (LXXVII) rearrange to keten dialkyl acetals (LXXVIII) in the absence of catalysts[92] at 130 °C:

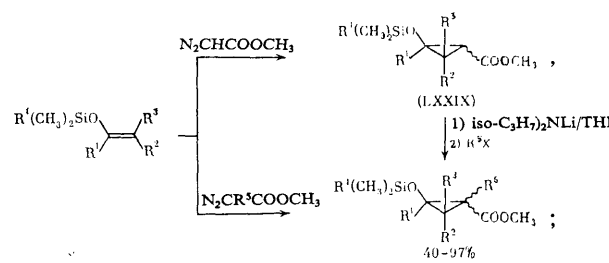


(LXXVII) (LXXVIII), ~100%

$R^1 = H$, CH_3; $R^2 = CH_3$, C_2H_5.

The similar isomerisation of 2-trimethylsiloxycyclopropanecarboxylic acid esters in the presence of iodotrimethylsilane or nonafluorotrimethylsilylbutanesulphonate has also been reported.[113]

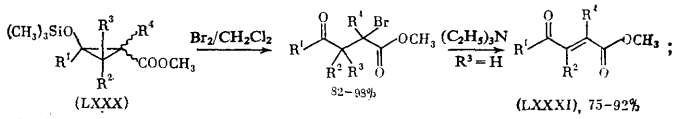
An important advantage of the methods for the introduction of functional groups into alkenes via the intermediate formation of activated cyclopropanes is the possibility of modifying the cyclopropane intermediate by carrying out reactions with retention of the three-membered ring and also the possibility of using ring opening reactions for the introduction of additional functional groups into the molecule or the formation of new carbon–carbon bonds. Since diazocarbonyl compounds containing substituents in the geminal position relative to the diazo-group are as a rule much less readily available than the corresponding unsubstituted reagents, a more convenient pathway to the target molecule may proceed via the intermediate stage involving the alkylation of alkoxycarbonylcyclopropanes (LXXIX):[109,114,115]



(LXXIX) 40–97%

R^1, R^2, R^3, R^4, R^5 = H, alkyl, alkenyl, aryl; X = Br, I, OSO_3CH_3.

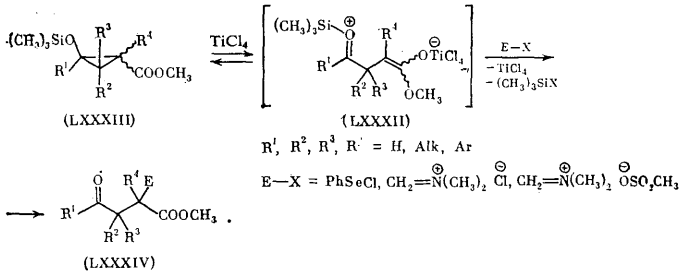
The oxidative cleavage of the three-membered ring in the donor–acceptor cyclopropanes (LXXX) by successive bromination–dehydrobromination reactions proceeds under mild conditions and constitutes a convenient method of synthesis of 4-oxo-2-alkenoates (LXXXI):[116]



(LXXX) 82–98% (LXXXI), 75–92%

R^1, R^2, R^3, R^4 = H, D, CH_3, $C(CH_3)_3$, SCH_3.

The enolate (LXXXII), formed as an intermediate from substituted 2-trimethylsiloxycyclopropanecarboxylates (LXXXIII) in the presence of Lewis acids, reacts readily with electrophiles, affording the corresponding esters of 2-substituted 4-oxoalkanoic acids (LXXXIV):[117–120]



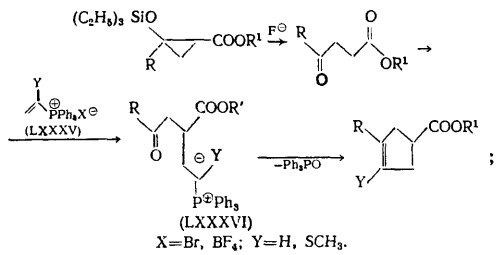
(LXXXIII) (LXXXII)

R^1, R^2, R^3, R^4 = H, Alk, Ar

E—X = PhSeCl, $CH_2{=}\overset{\oplus}{N}(CH_3)_2\ \overset{\ominus}{Cl}$, $CH_2{=}\overset{\oplus}{N}(CH_3)_2\ \overset{\ominus}{OSO_2CH_3}$

(LXXXIV)

The use of triphenyl(vinyl)phosphonium salts (LXXXV) as the electrophiles in a similar reaction leads to the intermediate phosphonium ylides (LXXXVI), which subsequently undergo the Wittig reaction:[121]



(LXXXV) (LXXXVI)

X=Br, BF_4; Y=H, SCH_3.

The entire sequence of reactions constitutes a new type of [3 + 2]annelation, which has been used effectively in the synthesis of tricyclo[6.3.0.$0^{2,6}$]undecanes with functional group substituents.[121]

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It follows from the data presented in this review that the introduction of acyl and acylmethyl fragments into organic substrates by means of carbene reactions makes it possible in many instances to achieve unique reactions ensuring the formation of new carbon–carbon bonds under mild conditions with a high regioselectivity and stereoselectivity. The carbene species then frequently behave as reagents with "inverted" polarity of the reaction centre, and the significant dependence of the chemical properties of the carbene intermediates on their spin state and on the presence of a complex forming agent imparts additional flexibility to the synthetic methods. The possibility of achieving alternative pathways leading to the opening of the ring in cyclopropane intermediates and their great synthetic possibilities also give rise to excellent prospects for the introduction of functional groups into alkenes by means of carbene reactions.

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