Translated from *Uspekhi Khimii*, 53, 1280-1303 (1984) U.D.C. 541.128:572.91:547.381

Nucleophilic Addition of CH Acids to αβ-unsaturated Aldehydes and Ketones

L.A.Yanovskaya, G.V.Kryshtal', and V.V.Kul'ganek

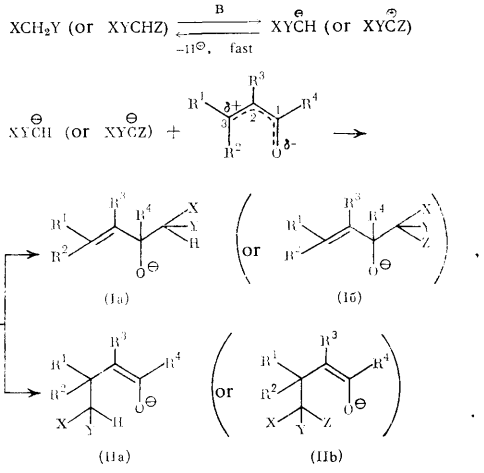
Data on the nucleophilic addition of CH acids of the type XCH_2Y and XYCHZ to αβ-unsaturated aldehydes and ketones are surveyed primarily from the standpoint of the influence of various factors on the mode of reaction (addition to the C=O or C=C bond).
The bibliography includes 116 references.

CONTENTS

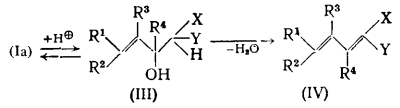
I. Introduction 744
II. The influence of the structure of CH acids on the mode of the reaction 745
III. The influence of the structure of enals and enones on the mode of the reaction 748
IV. Conditions and mode of the reaction 751

I. INTRODUCTION

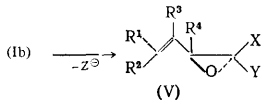
The addition of CH acids of the type XCH_2Y and XYCHZ (X, Y, and Z are atoms or groups stabilising carbanions) to αβ-unsaturated aldehydes (enals) and ketones (enones) in the presence of bases is of great synthetic importance, since it makes it possible to lengthen the carbon chain in a single stage and to introduce various substituents into the molecule. This reaction is also of interest from the theoretical point of view because, as a consequence of the delocalisation of the electron density in the C=C–C=O system, enals and enones behave as ambident electrophiles and the addition of carbanions of the type $\overset{\ominus}{C}HXY$ and $\overset{\ominus}{C}XYZ$ to these compounds can proceed via two pathways: addition to the carbon atom of the carbonyl group C(1) or to the carbon atom involved in the double bond C(3). This results in the formation of oxy-anions of types (Ia) and (Ib) or (IIa) and (IIb):



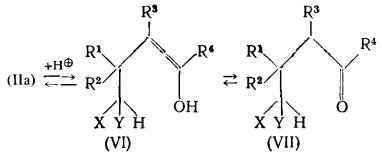
Protonation of the oxy-anions (Ia) leads to the formation of allyl alcohols (III), which are converted into conjugated dienes of type (IV) (products of the Knoevenagel reaction) on elimination of water from the 1,2-position:



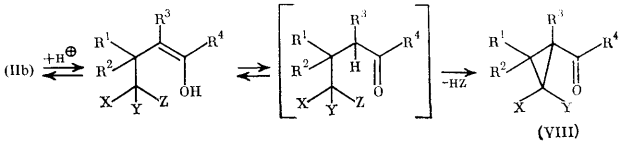
The oxy-anions (Ib) (Z = Hal) are stabilised as a result of the elimination of $Z^{\ominus}$ and cyclisation to the epoxides (V) (the Darzens reaction):



The protonation of the oxy-anion (IIa) leads to the saturated aldehyde or ketone (VII) via the enol (VI) (the Michael reaction):



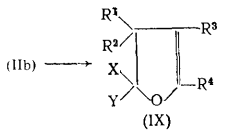
On the other hand, the protonation of the oxy-anion (IIb) and subsequent elimination of HZ from the 1,3-positions yield the cycloproane (VIII):



Thus the stabilisation of oxy-anions of type (I) results in the formation of the products of the 1,2-addition of CH acids to enals or enones (to the C=O group), while stabilisation of oxy-anions of type (II) results in the formation of products of 1,4-addition (to the C=C bond). The nature of the final reaction product depends on the nature of the CH acids, the substrate, the base used to generate the carbanions, and on the reaction conditions. All the reactions described above have been achieved and widely used to synthesise a wide variety of allyl alcohols,[1-3] conjugated dienes,[4,5] epoxides,[6] aldehydes and ketones,[7-11] and cyclopropanes,[12-17] all with functional group substituents.

The possible mechanisms of the stabilisation of the oxy-anions (IIb) examined permit the conclusion that there is yet another type of stabilisation of this oxy-anion, namely its conversion into 2,3-dihydrofuran (IX) via the elimination

of the anion $Z^{\ominus}$ with 1,5-cyclisation [compound (IX) can be formed also from the intermediate enol via the elimination of HZ]:



(IIb) → (IX)

Indeed the first example of such a reaction, involving the formation of 3-formyl-2,3-dihydrofurans by the interaction of bromomalonic ester with arylidenemalonaldehydes, has been observed recently.[18]

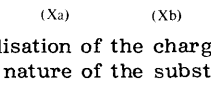
However, it is noteworthy that the addition of CH acids to enals and enones is by no means regioselective in all cases and a mixture of 1,2- and 1,4-addition products is frequently formed in various proportions. In order to ensure the regio-selectivity of the reaction and hence the possibility of the synthesis of the required products (III)–(V) and (VII)–(IX), it is necessary to investigate the influence of various factors and in the first place the structure of the CH acids, the enone, or the enal, the nature of the base used to generate the carbanions, and the conditions (temperature, solvent, and additives) on the mode of reaction and the possible further transformations of the compounds obtained.

In the present review we have considered and attempted to survey the data obtained in the last 10–15 years on the addition of CH acids of the type XCH_2Y and XYCHZ to enals and enones from the standpoint of the influence of the above factors on the mode of addition.

II. THE INFLUENCE OF THE STRUCTURE OF CH ACIDS ON THE MODE OF THE REACTION

The reactivity of CH acids is determined by the ease of deprotonation and the rate of reaction of the carbanions formed. The overall rate of addition of CH acids to enals and enones is limited by the stage involving the formation of oxy-anions. The overall rate increases with the increase in the number of electron-accepting or electronegative groups in the CH acid molecule. For CH acids of the type XCH_2Y, the activating effect of electron-accepting groups increases in the sequence RCO < HCO < ROCO < CN < RSO_3 < RSO_2 < NO_2.[7]

For carbanions generated from XCH_2Y, it is possible to adopt two extreme structures—(Xa) where the charge is localised at the carbon atom and (Xb) where the charge is fully delocalised.[19]



(Xa) (Xb)

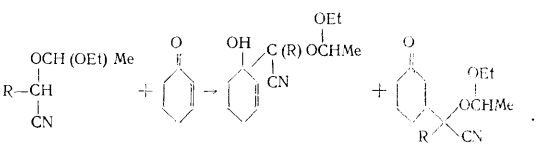
The degree of delocalisation of the charge in the carbanion is determined by the nature of the substituents in the molecule of the initial CH acid and its geometry. Within the framework of the theory of perturbations of molecular orbitals (PMO), an increase of the degree of charge delocalisation leads to an increase of the energy of the highest occupied molecular orbital (HOMO) and to an increase of the stability of the carbanion; the nucleophilicity of the carbanion and the rate of addition to the carbonyl group decrease simultaneously. Other conditions being equal, the addition of CH acids to the C=O group should be favoured by an increase of the localisation of the charge at the nucleophilic centre, by the decrease of the level of the HOMO, and by the increase of the acidity of the CH acid, i.e. the addition to the C=O bond is controlled by the charge. On the other hand, an increase of the degree of delocalisation of the charge at the nucleophilic centre, the raising of the level of the HOMO, and a decrease of the acidity of the CH acid should favour the addition to the C=C bond, i.e. it should take place under orbital control.

By the term "charge control", we understand the electrostatic interaction between the reactants. Its extent can be estimated as the product of the charges on the carbon atoms participating directly in the formation of the new bond. By the term "orbital control", we understand the energy of the interaction between the molecular orbitals of the reactants. This energy has a quantum-mechanical origin, which can be estimated from the equation

$$E_{orb} = \beta^2 C_N^2 C_E^{*2} S_{NE}^2 / (E_E^* - E_N) ,$$

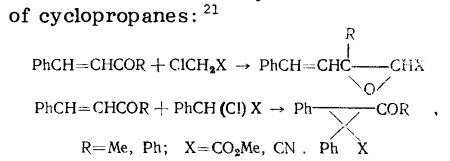
where C_N and C_E are the coefficients of the π orbitals of the carbon atoms which are directly involved in the formation of the new bond, i.e. of the π orbitals of the highest occupied molecular orbital (HOMO) of the nucleophile and the lowest unoccupied molecular orbital (LUMO) of the electrophile respectively, S_{NE} is the overlap integral between these orbitals, E_N and E_E are their energies, and β is a coefficient with the dimensions of energy.

The mode of reaction can be influenced by steric factors. Usually an increase of the bulk of the substituents R in CH acids of the type XYCHR leads to an increase of the contribution of the 1,4-addition. For example, the carbanion generated from 1-cyano-1-(1-ethoxyethoxy)ethane by treatment with lithium diethylamide in tetrahydrofuran (THF) at −78 °C forms predominantly the products of addition to the C=O bond on interaction with cyclohex-2-enone, while the carbanion generated from 1-cyano-1-(1-ethoxyethoxy)hexane gives rise to a mixture of the 1,2- and 1,4-addition products in proportions of 2.7:1.0 under the same conditions:[20]



The role of the charge or orbital control can be traced by studying the reaction of a chalcone and benzylideneacetone with the carbanion generated by treating derivatives of chloroacetic or α-chlorophenylacetic acids with a base [NaH or t-BuONa in hexamethylphosphoramide (HMP), $(Me_3Si)_2NNa$ or $(Me_3Si)_2NLi$ in THF].[21]

Regardless of the method of generation of carbanions, under kinetically controlled conditions at room temperature the reaction involves only the C=O bond in the case of $ClCH_2X$ with formation of epoxides or in the case of PhCH(Cl)X it involves exclusively the C=C bond with formation of cyclopropanes:[21]



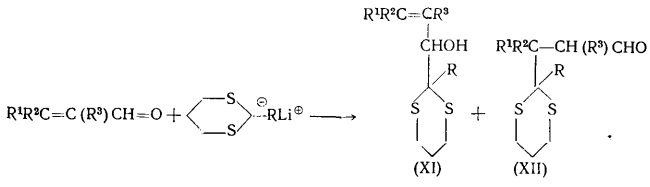
This difference between the modes of reaction is fully explicable when account is taken of the fact that the carbanions generated from $ClCH_2X$ belong to type (Xa), while those generated from PhCH(Cl)X belong to type (Xb); consequently charge control is most probable for the former reaction and orbital control for the latter reaction. In conformity with this, the rate of reaction of the carbanions

$\overset{\ominus}{C}ClCHX$, where X = CO_2Me, or CN, behzaldehyde is higher than that with benzylideneacetone,[22,23] which is associated with the higher formal positive charge on the C(1) atom in the C=O group of benzaldehyde.[24,25] Similarly the carbanions $Ph\overset{\ominus}{C}(Cl)X$, where X = CO_2Me or CN, react with the chalcone faster than with benzylideneacetone, which can be explained by the lower energy of the LUMO in the chalcone (the HOMO levels of the nucleophiles are identical in both reactions).[26,27]

In agreement with the above, the carbanions generated from 2-chloroacetates or 2-chloropropionates react with 4-t-butylcyclohex-2-enone only via the C=O group regardless of the counterion ($Na^{\oplus}$, $Li^{\oplus}$, $K^{\oplus}$, $MgX^{\oplus}$).[28] However, the carbanions generated by treating methyl 2-chloropropionate with bases add to the C=C bond in methyl vinyl ketone, although the yield of the adduct is low (~10%).[28] This can apparently be explained by the specific features of the structure of methyl vinyl ketone [the absence of steric hindrance at the C(3) atom in the vinyl group—see Section III below].

We may note that, when carbanions of the type $Ph\overset{\ominus}{C}(Cl)COOR$ or $Ph\overset{\ominus}{C}(Cl)COCH_3$ are used in the reaction with methyl vinyl ketone, the yields of the corresponding cyclopropanes increase in the former case to 58% and in the latter case to 70–75%,[29,30] which is probably associated with the increase of the orbital control with increase of the degree of delocalisation of the charge in carbanions. This can probably explain the addition of carbanions of the type $Ar\overset{\ominus}{C}(SR)Alk$, $Alk\overset{\ominus}{C}(SeR)CN$, and other anions of the type $R_3\overset{\ominus}{C}$ to cyclohex-2-enone and other enones exclusively at the C=C bond under the conditions of kinetic control at −78 °C.[31,32] Carbanions with a highly delocalised charge, generated from di- or tri-nitromethane and also from dinitroethane by treatment with solid potassium carbonate, pyridine, and other bases in solution in ether, dioxan, or aqueous methanol, add to methyl styryl ketone, phenyl vinyl ketone, methyl vinyl ketone, and acrolein, also giving rise to Michael addition products in yields >90%.[33–36]

Interesting results have been obtained in the study of the reactions of enals with carbanions generated from 2-R-1,3-dithianes by treatment with lithium di-isopropylamide in a THF–HMP mixture. This resulted in a mixture of 1,2- and 1,4-adducts whose ratio depended only on the structure of the enal but not on the nature of the substituents R in the nucleophile:[37]



It follows from the data presented in Table 1 that the carbanions generated from 2-phenyl-1,3-dithiane, where there is a great possibility of charge delocalisation, react preferentially via the C=C bond, while the carbanions generated from 1,3-dithiane, where there is no such possibility, tend to add to the C=O bond. It is noteworthy that the accumulation of the substituents in the 3-position of the enal increases the content of the 1,2-adducts in the mixture (see also Section III); the reaction of 3,3-dimethylacrolein with 1,3-dithane also leads to the formation of only the 1,2-adduct, which can be explained by the steric hindrance in the attack on the 3-position by the carbanion.[37]

Interesting results have been obtained in the study of the reactions of mesityl oxide with the carbanions generated by treating the trimethylsilyl ethers of the cyanohydrins of *p*-substituted benzaldehydes with lithium di-isopropylamide in 1,2-dimethoxyethane (DME). Depending on the nature of the substituent in the *para*-position in the benzaldehyde molecule, a mixture of 1,2- and 1,4-adducts was formed in different proportions and the effect of the substituent was linearly correlated with the Hammett σ_n constants for the addition to both the C=O and C=C bonds:[38]

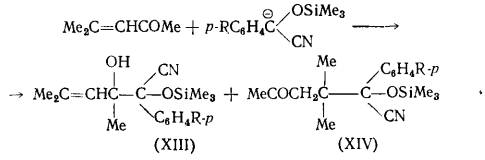


Table 1. The ratio of products (XI) and (XII) formed in the reaction of enals with 2-R-1,3-dithianes.[37]

Enal	R	*W*, %*	Content in mixture, %	
			(XI)	(XII)
MeCH=CHCHO	H	70	55	45
MeCH=CHCHO	Ph	80	5	95
CH_2=C(Me)CHO	H	70	45	55
CH_2=C(Me)CHO	Ph	80	5	95
Me_2C=CHCHO	H	55	100	0
Me_2C=CHCHO	Ph	50	65	35
PhCH=CHCHO	H	75	75	25
PhCH=CHCHO	Ph	85	35	65

*Overall yield of products (XI) and (XII).

Table 2. The influence of the nature of the *para*-substituents in p-$RC_6H_4\overset{\ominus}{C}(OSiMe_3)CN$ on the ratio of products (XIII) and (XIV).[38]

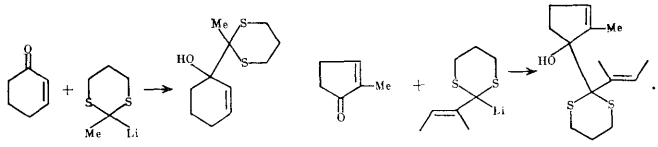
R	*W*, %*	Content in mixture, %		R	*W*, %*	Content in mixture, %	
		(XIII)	(XIV)			(XIII)	(XIV)
Me_2N	96	100	0	Cl	100	62	38
MeO	95	95	5	CF_3	100	28	72
H	92	78	22	CN	95	0	100

*Overall yield of products (XIII) and (XIV).

Table 2 presents data for the influence of the nature of the *para*-substituent in the benzaldehyde ring on the ratio of products (XIII) and (XIV) in the mixture. It is seen that the contribution of the addition to the C=O bond diminishes on passing from clearly electron-donating substituents (Me_2N, MeO) to electronegative or electron-accepting substituents (CF_3, CN). This feature can be fully accounted for by the fact that, owing to the +*M* effect, electron-donating substituents promote a greater localisation of the charge at the nucleophilic centre, while electronegative or electron-accepting substituents actually favour the delocalisation of the charge as a result of the −*I* and correspondingly −*M* effects.

However, one should note that the energy of the HOMO in p-Me_2N-$C_6H_4\overset{\ominus}{C}(OSiMe_3)CN$ is greater than the energy of the HOMO in p-$NCC_6H_4\overset{\ominus}{C}(OSiMe_3)CN$; this should promote orbital control, which is not in fact observed: in the reaction with the trimethylsilyl ether of benzaldehyde cyanohydrin, the product of addition to the C=O bond is formed exclusively. Hence one may conclude that, other conditions being equal, the mode of reaction is influenced to a greater extent by the charge delocalisation than by the height of the energy level of the HOMO (see also Section III). The ratio of compounds (XIII) and (XIV) is determined by the simultaneous influence of the charge and orbital control. The magnitude of the calculated oxidation-reduction potentials of p-$RC_6H_4CH(OSiMe_3)CN$ and enones[38] shows that the mechanism with orbital control is more probable for addition to the C=C bond rather than the mechanism with electron transfer which had been proposed on the basis of a number of data for the addition of lithium dialkyl cuprates to the double bond.[39]

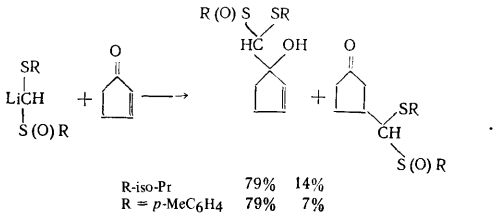
A strong influence of the structure of the nucleophile on the mode of reaction has been observed also for other examples. Thus cyclic thioacetals of the type of 1,3-dithianes, containing alkyl groups in the 2-position (for example, 2-methyl-1,3-dithiane [1]) or alkenyl groups [for example, 2-(but-2-en-2-yl)-1,3-dithiane,[40] add to cyclohex-2-enone in THF at -78 °C only at the C=O bond when the carbanions are generated by treatment with n-BuLi. The reaction with 2-methylcyclopent-2-enone proceeds in the same way:



The carbanions generated under the same conditions from aliphatic thioacetals of the type $R-CH(SR^1)[S(O)R^1]$ react via the C=C bond in enones:[41]

$$R\overset{\ominus}{C}(SR^1)(S(O)R^1) + CH_2{=}CHCOR^2 \rightarrow R^2COCH_2CH_2\underset{\displaystyle S(O)R^1}{\overset{\displaystyle SR^1}{\overset{|}{\underset{|}{C}}}}-R$$

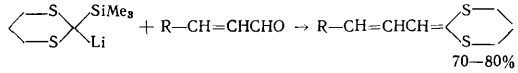
It has been shown for the addition of $CH_2(SR)[S(O)R]$ to cyclic enones using lithium di-isopropylamide in THF at -78 °C to generate the carbanion that the ratio of the 1,2- and 1,4-adducts is also influenced by the nature of the substituent R in the thioacetal component of the CH acid:[41]



R-iso-Pr	79%	14%
R = p-MeC_6H_4	79%	7%

Steric hindrance is apparently manifested in this case.

The carbanions generated from CH acids containing the trimethylsilyl group at the nucleophilic centre, for example, from Me_3SiCH_2X, where X = $P(S)Ph_2$, PPh_2, SPh, or $P(O)(OEt)_2$, or from 2-trimethylsilyl-1,3-dithiane by treatment with n-butyl-lithium always add to the C=O bond in enals and enones:[42]



70—80%

The addition of CH acids to enals via a Michael reaction has been little investigated until recently. The view that nucleophiles add to enals preferentially at the C=O bond is still encountered in the literature.[4,5,8] This view is based on the fact that enals readily undergo the Knoevenagel reaction with CH acids in the presence of pyridine, piperidine, and sodium acetate.[4,5] Furthermore, enals form cyanohydrins on treatment with hydrocyanic acid.[43] The cause of the confusion is that the application of strong bases, such as alkali metal hydroxides, alkoxides, hydrides, or amides, organometallic compounds, ground alkali metals, etc. to the generation of carbanions in the Michael reaction is complicated in the case of enals by the self-condensation and polymerisation of the enals, further reactions of the addition products, the "anomalous" Michael reaction, etc.[44-46] On the other hand, the use of milder bases leads to the Knoevenagel reaction (see above).

Systematic study of the order of the addition of CH acids to enals became possible only after the introduction of the method of phase transfer catalysis into practical organic synthesis.[47-50] In this method the carbanions are generated from CH acids with a 50% solution of NaOH (or other alkalis) in a liquid–liquid system or with solid alkali (NaOH, KOH, K_2CO_3, Na_2CO_3, etc.) in a liquid–solid phase system in the presence of catalysts (onium salts, crown-ethers, etc.). The most successful variant in the reactions with enals proved to involve the application of a liquid–solid phase system [Na_2CO_3–benzene–triethylbenzylammonium chloride (TEBAC)] for the generation of carbanions from malonic, acetoacetic, and cyanoacetic esters.[51-53] Under these conditions, the mode of reaction depends greatly on the nature of the CH acid. Thus the carbanions $\overset{\ominus}{C}H(CO_2Et)X$, where X = CO_2Et or COMe, add exclusively to the C=C bond in enals without substituents in the 3-position (acrolein and methacrolein) and also to 3-monosubstituted enals (for example, crotonaldehyde, cinnamaldehyde, etc.):

$$XCH_2COOEt + R{-}CH{=}CH{-}CH{=}O \rightarrow R{-}\underset{\displaystyle XCHCO_2Et}{\overset{\displaystyle CHCH_2CHO}{\overset{|}{\underset{|}{CH}}}}$$

X=CO_2Et, COMe; 44—75%

Table 3. Certain characteristics of malonic and cyanoacetic acids*.

Carbanion	q_N^{**}, e	c_N	E_N, eV
$[HC(COOH)_2]^{\ominus}$	−0.435	−0.630	−4.424
$[NCCHCOOH]^{\ominus}$	−0.479	−0.660	−3.254

*Calculations performed in accordance with a CNDO/2 programme.[55]

**Here q_N is the π-electronic charge on the carbanionic centre.

The carbanions generated from cyanoacetic ester add to the C=C bond only in enals unsubstituted in the 3-position. 3-Substituted enals react with cyanoacetic ester at the C=O bond, which can be explained if account is taken of the most important characteristics[54] of malonic and cyanoacetic acids and their esters, which determine the charge and orbital control of the nucleophilic addition (Table 3).

In considering the data in Table 3, one should note that, compared with the malonic acid carbanion, the cyanoacetic acid carbanion has a significantly greater coefficient of its HOMO and a higher level of the HOMO, which should favour orbital control. However, the charge on the cyanoacetic carbanion is higher than that on the malonic acid carbanion which is responsible for the predominance of charge control, other conditions being equal. The latter probably obtains also in the reaction of 3-substituted enals with cyanoacetic esters. There is no doubt that steric hindrance due to the substituents in the 3-position in the enals also plays a major role.

It is of interest that the carbanions generated from cyanoacetic ester on treatment with potassium fluoride in acetonitrile in the presence of dibenzo-18-crown-6 ether add only to the C=C double bonds of the chalcone, forming adducts via the Michael reaction in a yield of ~90%.[56] This result is apparently associated with the fact that acetonitrile solvates the $K^{\oplus}$ ion fairly effectively and impairs its complex formation reaction with the CO group, which as a rule alters the regioselectivity of the reaction and leads to preferential attack on the 3-position of the enal.[57]

The reaction between the chalcone and ethyl 2-nitroacetate in a homogeneous medium (in toluene in the presence of 1-dimethylamino-2-hydroxy-1-methyl-2-phenylethane as the catalyst at room temperature) or in a two-phase system [in acetonitrile with KI in the presence of (2-hydroxy-1-methyl-2-phenylethyl)(dimethyl)ethylammonium bromide or (benzyl)(2-hydroxy-1-methyl-2-phenylethyl)dimethylammonium chloride as the catalyst] proceeds analogously:[58]

$$PhCH{=}CHCOPh + XCH_2CO_2Et \rightarrow \underset{\displaystyle XCHCO_2Et}{\overset{\displaystyle PhCHCH_2COPh}{|}} .$$

When X = CN, the yield is 90%, while for X = NO_2 the yield amounts to 10% (in a homogeneous medium) and 40% (in the two-phase system).

The presence of three stabilising substituents at the carbanionic centre frequently causes the reaction to take place only at the C=C bond of the enal or enone. Thus methyl 2,2-di(phenylthio)acetate reacts with acrolein, crotonaldehyde, etc. in DME in the presence of catalytic amounts of Triton B to form only adducts resulting from the reaction involving the C=C bond:[59]

$$R{-}CH{=}CHCHO + (PhS)_2CHCOOMe \rightarrow \underset{\displaystyle (PhS)_2CCOOMe}{\overset{\displaystyle R{-}CHCH_2CHO}{|}} .$$
24—85%

Under the standard conditions of phase transfer catalysis (CH_2Cl_2–50% NaOH solution–TEBAC with addition of NaOH solution to the mixture of components)[16,60,61] or in an alcoholic solution in the presence of sodium alkoxide,[12] enals react with bromomalonic ester to form formylcyclopropanes:

$$R{-}CH{=}CH{-}CHO + BrCH(CO_2Et)_2 \longrightarrow R\!\!<\!\!\begin{matrix}CHO\\ EtO_2C\quad CO_2Et\end{matrix} ;$$

R=H, Me, Ph, $(MeO)_2CH$ (yield 43–48%); R=MeCH=CH, Cl_2C=CH, PhCH=CH (yield 15–29%).

1,1,2,2-Tetra(ethoxycarbonyl)ethane is always formed in the reaction as a side product. Thus in this case the reaction involves the C=C bond. It is noteworthy that, when the alkoxide method is used, the reaction products are formed only in the case of acrolein and crotonaldehyde. The alteration of the order of mixing, i.e. the addition of the reactant mixture to a mixture of the 50% NaOH solution, the solvent, the TEBAC, results in the formation of formylcyclopropane only from acrolein, while the remaining enals polymerise under these conditions.[13] However, enones more resistant to alkalis give rise to acylcyclopropanes in high yields, for example:

$$MeCOCH{=}CH_2 + BrCH(CO_2Et)_2 \rightarrow MeCO\!\!<\!\!\begin{matrix}\\ EtO_2C\quad CO_2Et\end{matrix} .$$

The occurrence of the reaction at the C=C bond in the case of carbanions stabilised by three electron-accepting and electronegative substituents can undoubtedly be accounted for by the increase of the degree of delocalisation of the charge.

In a series of studies devoted to the elucidation of the order of addition of the carbanions generated by treatment of CH acids having between one and three stabilising substituents with lithium di-isopropylamide in THF or DME, the features associated with the influence of the structure of the carbanions on the mode of reaction were elucidated. It was found that highly basic ("hot") nucleophiles of the type of carbanions derived from 2-methyl-1,3-dithianes[62] or 2-(2-ethoxyethoxy)propionitrile[63] and also the salts $H_2\overset{\ominus}{C}COO^{\ominus}.2Li^{\oplus}$[64] and $N\overset{\ominus}{C}CH_2.Li^{\oplus}$[65] add irreversibly to enones even at low temperatures, giving rise to a mixture of products of reactions involving the C=O and C=C bonds. Nucleophiles such as 1,3-dithianyl-2-phenyl-lithium,[66] $NC\overset{\ominus}{C}HPh.Li^{\oplus}$,[65] or $Ph\overset{\ominus}{C}.(CO_2R)X.Li^{\oplus}$ (where R, X = H, SePh; Me, SeMe; Me, OMe; Me, Me)[69] initially add to the C=O bond; however, when the temperature is raised, the 1,2-adducts formed rearrange spontaneously to 1,4-adducts, whose thermodynamic stability is higher. Nucleophiles of the type $N\overset{\ominus}{C}C(CH{=}CHMe)OCHMeOEt,Li^{\oplus}$,[65] $Ph\overset{\ominus}{C}(R)[S(O)R^1].Li^{+}$,[68,69] and $(EtS)_2\overset{\ominus}{C}CO_2Me.Li^{\oplus}$[70] add irreversibly to the C=C bond, but, depending on the structure of the enone, there is also a possibility of the irreversible addition to the C=O bond.

In contrast to the nucleophile $Ph\overset{\ominus}{C}(CN)(OSiMe_3).Li^{\oplus}$,[38] the nucleophile $NC\overset{\ominus}{C}HP(O)(OEt)_2.Li^{\oplus}$[71,72] reacts with enones of the type $R_2C{=}CHCOMe$ at the C=O group. Nucleophiles such as 1,3-dithianyl-2-phenyl-lithium[66] or $Me_2\overset{\ominus}{C}(CO_2Me).Li^{\oplus}$[67] react analogously even in solvents of low polarity at −78 °C.

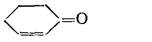
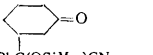
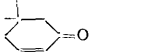
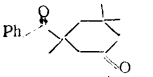
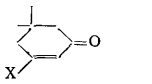
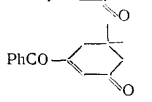
III. THE INFLUENCE OF THE STRUCTURE OF ENALS AND ENONES ON THE MODE OF THE REACTION

The direction of the nucleophilic addition of CH acids of the type XCH_2Y and XCHYZ depends on the structure of the enals. In the case of enones such a dependence is not usually observed. Table 4 presents the results of the reactions of aliphatic and cyclic enones with the carbanions generated from the trimethylsilyl ether of benzaldehyde cyanohydrin by treatment with lithium di-isopropylamide in ether. 1,4-Adducts are formed exclusively under these conditions[73] and hydrolyse smoothly and in high yields to 1,4-diketones on treatment with 2 *N* HCl, Et_3NHF, or $(PhCH_2)Me_3NF$. The method described is convenient for the synthesis of these compounds.

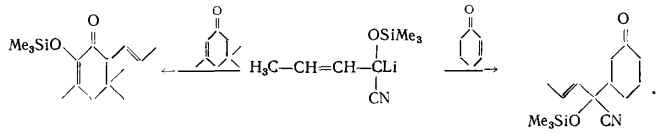
Table 4 shows that all the ketones used in the above study,[73] with the exception of 4-chloropent-3-en-2-one, form adducts in high yields. A decrease of the yield is observed when the cyclic ketones contain a substituent in the 3-position relative to the keto-group and the decrease is in

order of increase of the bulk of the substituent (Cl > EtO > Br). Apparently, the steric hindrance generated in relation to attack by the nucleophile on the 3-position plays the main role in this case. It may be that this also accounts for the absence of reaction in the case of 4-chloropent-3-en-2-one, where, apart from the methyl group, a bulky chlorine atom is present in the 3-position (in addition, account must be taken of the unfavourable influence of the +*M* effect of the chlorine atom).

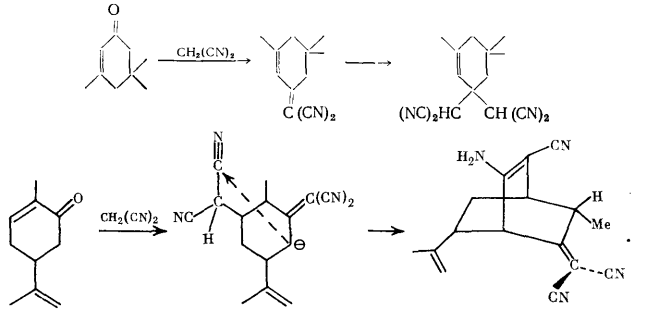
Table 4. Products of the addition of the trimethylsilyl ether of benzaldehyde cyanohydrin to various ketones.[73]

Ketone	Product of addition or subsequent hydrolysis	Yield, %
$Me_2C{=}CHCOMe$	$Me_2C(PhC(OSiMe_3)CN)-CH_2COMe$	84
$PhCH{=}CHCOMe$	$PhCH(PhC(OSiMe_3)CN)-CH_2COMe$	87
		96
$MeCCl{=}CHCOMe$	not formed	0
		45
		40 (X = Cl) 20 (X = EtO) 10 (X = Br)

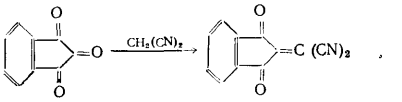
The major role of steric effects is also indicated by the interaction between the carbanion generated from the trimethylsilyl ether of crotonaldehyde cyanohydrin and cyclohex-2-enone or 3,5,5-trimethylcyclohex-2-enone in THF. In the former case the reaction proceeds via the C=C bond (the yield of the adduct is ~72%), while in the latter case the 1,2-adduct is formed in 53% yield:[74]



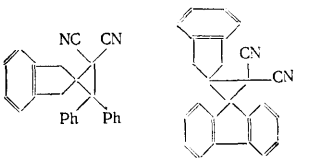
In this connection one should note that the interaction of malonodinitrile with enones in which the C=O group is sterically hindered takes place in DMF in the presence of potassium fluoride via a Michael reaction, while in the absence of steric hindrance the Knoevenagel reaction takes place initially. In a number of instances the formation of an active conjugated system under these conditions promotes the further addition of malonodinitrile to the conjugated system via the Michael reaction and the formation of products of unusual structure, for example:[75–78]



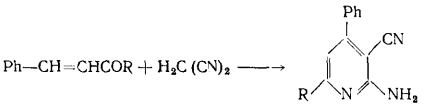
It is of interest that the uncatalysed reaction of malonodinitrile with indan-1,2,3-trione in benzene proceeds via a Knoevenagel reaction with formation of 2-dicyanomethyleneindan-1,3-dione:[79]



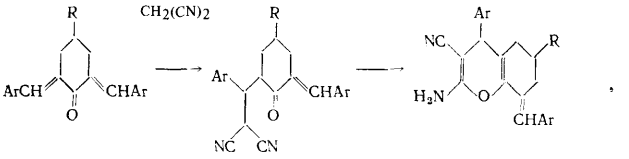
The Michael addition of malonodinitrile to enones makes it possible to introduce two cyano-groups into the molecule and to obtain new interesting compounds by further reactions. Thus 2-dicyanomethyleneindan-1,3-dione reacts with diphenyldiazomethane or 9-diazofluorene[79] to form spirocyclopropanes:



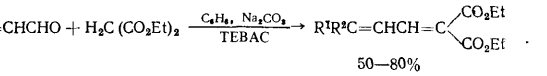
The reaction of equimolar amounts of malonodinitrile with enones in the presence of an excess of ammonium acetate leads to the formation of 4,6-disubstituted 2-amino-3-cyanopyridines in 60–70% yield:[80–81]



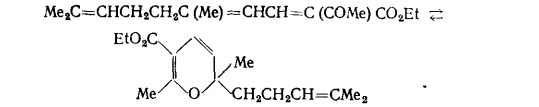
The reaction of chalcones with malonodinitrile results in the formation of 2-amino-4,6-diarylnicotinonitriles, whose hydrolysis leads to substituted nicotinamides.[82] The interaction of diarylidenecyclohexanones with malonodinitrile in the presence of sodium ethoxide or hydroxide can be used to synthesise chromones in 60–90% yield:[82]



A striking example of the influence of the structure of the substrate on the mode of the addition reaction involving enals is the interaction of malonic ester with 3,3-disubstituted enals in which the 3-position is undoubtedly sterically hindered; in this case the reaction is of the Knoevenagel type. Thus the corresponding dienes are formed from 3,3-dimethylacrolein, 3,3-dichloroacrolein, or citral:[51–53]



Citral reacts via a Knoevenagel reaction also with acetoacetic ester to give a mixture of open-chain and cyclic reaction products, which is one of the examples of valence isomerisation:[51–53,83–85]



Very interesting results have been obtained in the reaction between malonic or acetoacetic ester and ω,ω-dichloropolyenals in the C_6H_6–Na_2CO_3–TEBAC system.[53] The simultaneous formation of products of addition to both the C=C and

C=O bonds is observed in this case. Table 5 presents the ratios of the products of the reactions of ω,ω-dichloropolyenals with malonic, acetoacetic, and, for comparison, cyanoacetic esters:

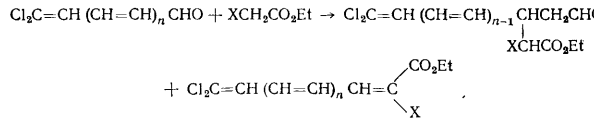


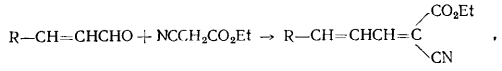
Table 5. The contents (%) of products of the addition of XCH_2CO_2Et (where X = CO_2Et, COMe, or CN) to the C=C and C=O bonds in ω,ω-dichloropolyenals. [53]

CH acid	n=0		n=1		n=2	
	C=C	C=O	C=C	C=O	C=C	C=O
$H_2C(CO_2Et)_2$	0	100	75	25	*	*
$H_2C(COMe)CO_2Et$	0	100	45	55	18	82
$H_2C(CN)CO_2Et$	0	100	0	100	0	100

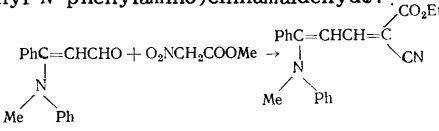
*Does not react.

Evidently, the mode of reaction is determined by the length of the chain of conjugated double bonds. The occurrence of the reaction exclusively at the C=O bond of 3,3-dichloroacrolein (n = 0) can be explained primarily by the steric hindrance in the attack by the carbanion on the 3-position. An increase in chain length naturally leads to the elimination of the steric effect of the terminal substituents and the formation of adducts via the reaction at the C=C bond becomes possible, which is in fact observed in reality in the interaction of 5,5-dichloropenta-2,4-dienal (n = 1) with malonic and acetoacetic esters, the product of the Michael reaction predominating in the former case. 7,7-Dichlorohepta-2,4,6-trienal (n = 2) does not react with malonic ester and the reaction with acetoacetic ester gives rise to a mixture in which the product of the Knoevenagel reaction predominates.

In the same system (C_6H_6–Na_2CO_3–TEBAC), sorbaldehyde, 5-phenylpenta-2,4-dienal, and 7-phenylhepta-2,4,6-trienal do not react with malonic or acetoacetic ester. Enals with markedly electron-donating substituents in the 3-position, for example, 3-dimethylaminoacrolein, also do not react with acetoacetic ester. [86] However, the interaction of enals of the type of 3-dimethylaminoacrolein, [86] 5-phenylpenta-2,4-dienal, and ω,ω-dichloropolyenals [53] with cyanoacetic ester, which most probably takes place under charge control, leads to the formation of the products of the Knoevenagel reaction:

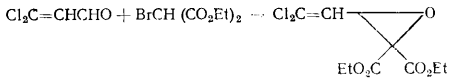


Methyl 2-nitroacetate reacts analogously at the C=O bond of 2-(N-methyl-N-phenylamino)cinnamaldehyde: [87]

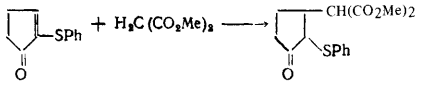


On treatment with nitromethane or cyanoacetic ester in the presence of piperidine, 2-nitro-3-phenylaminoacrolein also gives rise to 1,2-adducts. [88,89]

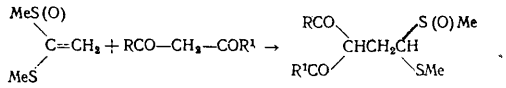
In contrast to acrolein and 3-monosubstituted enals, 3,3-disubstituted enals do not react with bromomalonic ester in the CH_2Cl_2–50% NaOH solution–TEBAC system, while in the DMF–K_2CO_3–TEBAC system the reaction is of the Darzens type. For example, 3,3-dichloroacrolein gives rise to 3-(β,β-dichlorovinyl)-2,2-di(ethoxycarbonyl)epoxyethane under these conditions: [18]



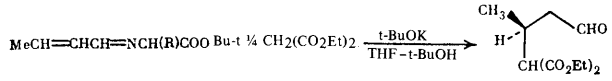
Addition to the C=C bond is apparently favoured by the presence of the thioester residue at the double bond in the α-position relative to the CO group. Thus 2-phenylthiocyclopent-2-enone very readily combines with dimethyl malonate in the presence of sodium methoxide in methanol: [90]



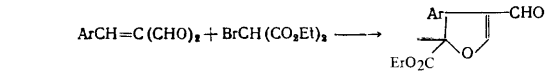
Certain keten derivatives can be introduced into the Michael reaction. Thus the interaction of keten thioacetals with the carbanions generated by treating malonic or acetoacetic ester or acetylacetone with sodium hydride in THF at −78 °C results in the formation of adducts via the reaction at the C=C bond in yields of 91–98%: [91]



In order to synthesise optically active aldehydes, the reaction involving the addition of malonic ester to aldimines, obtained from crotonaldehyde and optically active aminoacids, was employed. [92] The subsequent hydrolysis yielded (*S*)(+)-aldehydes in optical yields from 48 to 54%:



Finally we may mention yet another instance where the structure of the enal has a decisive influence on the structure of the final product. This involves the formation of formyldihydrofurans by the reaction of arylidenemalonaldehydes with bromomalonic ester in the DMF–K_2CO_3–TEBAC system: [18]



The formation of formyldihydrofurans can be explained by the possibility of the stabilisation of the anion of type (IIb) (formed in the reaction) by the elimination of $Br^{\ominus}$ with cyclisation or via the elimination of HBr from the 1,5-position of the enol formed by the protonation of (IIb) (as a consequence of the influence of the CHO group, which increases its stability, this enol can cyclise to dihydrofuran before it isomerises to a saturated aldehyde, which can be converted into a cyclopropane on subsequent elimination of HBr from the 1,3-positions).

Table 6 presents the results of the calculation of the electronic structures of the enals. Evidently, in all the enals investigated, the greatest positive charge is localised at the C(1) atom of the C=O group. Consequently, reactions whose mode is determined by the electrostatic interaction (charge control) should proceed preferentially at this atom. The highest coefficient C_E^* of the LUMO of enals is that of the π electron orbital of the C(3) atom involved in the

C=C bond. The reactions whose mode is determined by orbital control should therefore take place at the C(3) atom.[93]

Table 6. Certain characteristics of enals.[93]

Enal	$e^{\bullet}_{\sigma+\pi}$, e		$c^{\bullet}_{E}$	
	C (1)	C (3)	C (1)	C (3)
H_2C=CHCH=O	0.225	0.003	0.511	−0.576
MeCH=CHCH=O	0.225	0.060	0.461	−0.579
Me_2C=CHCH=O	0.224	0.101	0.423	−0.579
H_2C=C(Me)CH=O	0.217	−0.028	0.503	−0.567
MeCH=C(Me)CH=O	0.217	0.029	0.449	−0.572
ClCH=CHCH=O	0.232	0.124	0.485	−0.523
Cl_2C=CHCH=O	0.234	0.221	0.453	−0.613
Cl_2C=CHCH=CHCH=O	0.160	0.090	0.336	−0.475

*Here $e_{\sigma+\pi}$ are the $\sigma + \pi$ electronic charges on the atoms.

The relative contributions of the Coulombic (charge) and orbital interactions can be estimated by employing the ratio of the terms I_1/I_2, where I_1 characterises the Coulombic interaction and I_2 the orbital interaction. The data obtained for acrolein and its methyl derivatives are presented in Table 7. Evidently, in all cases the introduction of methyl groups hardly alters either ΔE or the index ratio I_1/I_2, so that the mode of reaction cannot be predicted on the basis of the relations obtained, although it does vary as a function of the nature of the reactants, which can be deduced from the experimental data discussed above.[93]

Table 7. Energy data for the reactions of certain enals with the C-anions of malonic and cyanoacetic acids.[93]

Enal	ΔE, eV		$I_1(C(1))/I_2(C(3))$
	⊖CH(COOH)$_2$	⊖CH(CN)COOH	
H_2C=CHCHO	−6.30	−5.43	3.70
MeCH=CHCHO	−6.24	−5.37	3.55
Me_2C=CHCHO	−6.16	−5.29	3.65
H_2C=C(Me)CHO	−6.26	−5.39	3.62
MeCH=C(Me)CHO	−6.13	−5.26	3.52

Notation: $\Delta E = E_N^{HOMO} - E_E^{LUMO}$, $I_1 = q_N q_E$ (π, σ) is the index of Coulombic interaction, and $I_2 = C_N^2 C_E^2/(E_E - E_N)$ is the index of orbital interaction.

The mode of the addition reaction can be significantly influenced by the steric hindrance associated with the different bulks of the H atom and the methyl group (or the chlorine atom), because the addition of carbanions to enals leads to a considerable deformation of the structure of one of the carbon atoms of the enal, which changes from planar to pyramidal as the carbanion approaches. Table 8 presents the "pyramidalisation" energies of the C(1) and C(3) centres for acrolein and its methyl and chloro-derivatives, calculated as differences between the energies of the pyramidal and planar enals. It is evident from these data that in the case of acrolein the conversion of the terminal carbon atom C(3) involved in the C=C bond into a pyramidal form is most favourable. The substitution of one of the hydrogen atoms at C(3) by a methyl group leads to a qualitative alteration of the result. The conversion of the C(1) atom of the carbonyl group into the pyramidal form is energetically more favourable; the substitution of the second hydrogen atom at C(3) by a methyl group increases the difference to 9 kcal mol^{-1}. The substitution of hydrogen atoms by chlorine atoms leads to a qualitatively similar result as the introduction of a methyl group. Thus the substitution of the hydrogen atoms at C(3) by methyl groups or chlorine favours the alteration of the mode of the addition reaction by virtue of steric factors.

Table 8. The relative* energies of the "pyramidalisation" (E) of the C(1) atom for R^1R^2C=CHCH=O (according to the data of Kryshtal' et al.[93]).

R^1	R^2	E, kcal mol^{-1}
H	H	4
H	Me	−3
Me	Me	−9
H	Cl	−1
Cl	Cl	−4

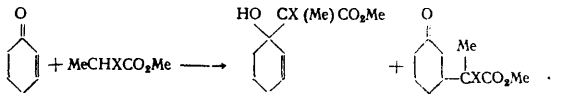
*The energy of the structure with the pyramidalised C(3) atom has been adopted as zero.

IV. CONDITIONS AND MODE OF THE REACTION

Studies in recent years have shown that the mode of addition of CH acids, including those of the XCH_2Y and XCHYZ types, to enals and enones depends very strongly on the reaction conditions—primarily on temperature, the nature of the solvent, and additives.

Temperature

The dependence of the mode of addition of CH acids to enones on temperature has been clearly demonstrated for the addition to cyclohexenones of the carbanions generated from $MeCHXCO_2Me$, where X = OPh, OMe, SPh, SMe, or Me, under the influence of lithium di-isopropylamide.[94] It was established that, under the conditions of kinetic control at −78 °C, the addition is exclusively to the C=O group (except in the case where X = SPh); on raising the temperature, it is possible to alter the mode of addition of the nucleophile (Table 9):



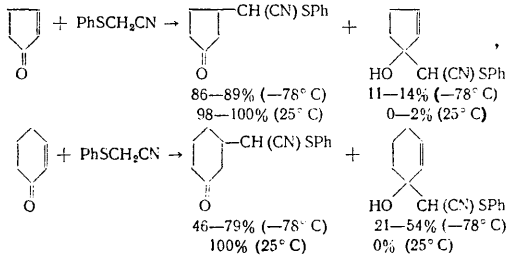
The addition of methyl 2-phenylthiopropionate takes place only in the 1,4-positions both at −78 °C and 25 °C. The introduction pf tje SMe substituent (the $-I$ and $+M$ effects)

probably increases the energy of the HOMO of the nucleophile and leads to a change from charge to orbital control. The absence of this effect when the SPh group is introduced is apparently associated with the fact that this group increases the level of the HOMO to a lesser extent, because the *n* electron pair of the S atom interacts not only with the nucleophilic centre but also with the benzene ring.

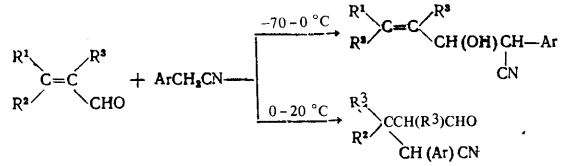
Table 9. The influence of temperature on the mode of addition of methyl 2-X-propionate to cyclohex-2-enone. [94]

X	Yield of 1,2-adduct, %		Yield of 1,4-adduct, %	
	−78° C	+25° C	−78° C	+25° C
OPh	88	—	8	84
OMe	75	5	12	62
SPh	—	—	75	86
SMe	63	—	7	85
Me	88	7	5	83

Analogous results have been obtained in the study of the addition of phenylthioacetonitrile to cyclopent-2-enone and cyclohex-2-enone in THF and in ether using lithium di-isopropylamide to generate the carbanions. [95] The 1,2-adducts are formed in appreciable amounts at −78 °C, while at room temperature the products are exclusively or mainly the 1,4-adducts:



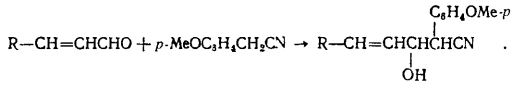
The addition of the carbanions generated from arylacetonitriles by treatment with lithium di-isopropylamide to enals in THF yields at temperatures from −70° to 0 °C the products of the reaction involving the C=O group or at temperatures from 0° to 20 °C the products of the reaction involving the C=C bond: [96]



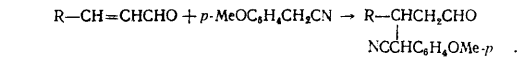
The 1,2-adducts are thus the main reaction products under the conditions of kinetic control, while the 1,4-adducts are the products under the conditions of thermodynamic control. However, the 1,4-adducts can be formed also under the conditions of kinetic control (see below).

Solvents

The very great influence of solvents on the mode of addition of nucleophiles to enones and enals has been frequently noted but has found an explanation only in recent years. [57] The most striking example is the shift of the equilibrium in the reaction of enones towards 1,4-addition in the presence of HMP. [2] Thus the interaction between *p*-methoxyphenylacetonitrile (the carbanion is generated under the influence of n-BuLi at −78 °C) and cyclohex-2-enone or enals of the type R−CH=CHCHO in THF always takes place with the dominant formation of allyl alcohols:

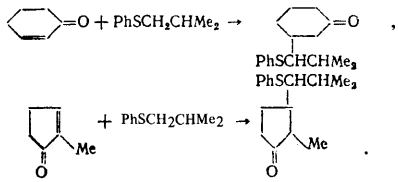


However, when HMP is added to the reaction mixture before the introduction of the enal or enone under the same conditions, the adduct resulting from the reaction involving the C=C bond is formed:

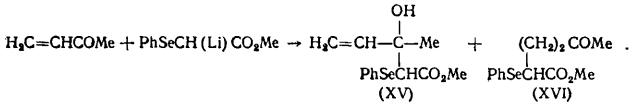


The reaction between cyclohex-2-enone or 5-isopropenyl-2-methylcyclohex-2-enone and the carbanions generated from $Me_2CHCH(SePh)(SPh)$, [2] 2-R-1,3-dithianes, 1,1-di(phenylthio)alkanes, or 1,1-di(methylselenyl)alkanes by treatment with n-BuLi takes place analogously. [97] The 1,4-adducts are formed preferentially under kinetic conditions at −78 °C (the content of the 1,2-adducts does not exceed 1−7%). This is one of the examples illustrating the possibility of the formation of the 1,4-adducts when the reaction takes place under kinetic control. The effect of HMP in this instance consists in the fact that the above solvent solvates vary effectively the lithium ions, which are known [57] to increase the regioselectivity of the process in favour of 1,2-addition under both charge and orbital control as a result of complex formation via the C=O group and the consequent decrease of the energy level of the LUMO of the enone or enal and the increase of the coefficient for the C(2) atom. Solvation interferes with complex formation to a greater extent the greater the solvating capacity of the solvent.

The addition of HMP is widely used for synthetic purposes. For example, the employment of a mixture of THF and HMP at −78 °C in the reactions of the carbanions generated by the action of n-BuLi on isobutyl phenyl sulphide with cyclohex-2-enone and 2-methylcyclopent-2-enone makes it possible to obtain satisfactory yields of the 1,4-adducts: [98]



The addition of HMP has a considerable influence also on the reaction of methyl vinyl ketone with a selenyl-substituted carbanion. [99] Thus, when the reaction is carried out at −78 °C in THF, a mixture containing 81% of compound (XV) and 19% of compound (XVI) is formed; the addition of a small amount of HMP lowers the content of compound (XV) in the mixture to 15% and increases that of compound (XVI) to 85%:



Sometimes, in order to achieve the regioselectivity of the 1,4-addition, it is necessary not only to add HMP but also to increase the reaction temperature. For example,

lithium selenoacetates add to cyclohex-2-enone in THF at −78 °C with formation of a mixture of the 1,2- and 1,4-adducts in proportions of 95 : 5; the addition of HMP alters the ratio to 20 : 80 and only an increase of temperature to −45 °C makes it possible to achieve the ratio 5 : 95.[99]

As a rule, highly polar protic solvents, such as water or alcohols, promote the 1,4-addition. This is also favoured by dipolar aprotic solvents (DMF, DMSO, HMP, etc.) and the change from protic to aprotic dipolar solvents usually increases the rate of reaction, because the basicity of the carbanions in such a medium increases as a consequence of the absence of specific solvation. Incidentally, in certain cases the addition is also facilitated by specific solvation. For example, in solvents such as acetonitrile, carbon tetrachloride, or toluene, the chalcone does not react with nitromethane in the presence of quinine, *N*-methylephedrine, or L(−)-*N*-phenylethylamine as catalysts. However, in methanol the 1,4-adducts are formed in yields of 60–80% under the conditions of weak optical induction (optical yield 1–3%):[100]

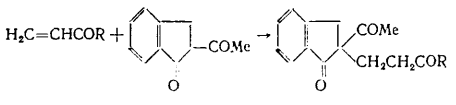
$$PhCH{=}CHCOPh + \overset{\ominus}{C}H_2NO_2 \rightarrow PhCHCH_2COPh \quad (CH_2NO_2)$$

The explanation is that in aprotic solvents chiral amines cannot ensure the generation of a carbanion from nitromethane, while in methanol this process is facilitated owing to the stabilisation of the carbanion formed as a consequence of the formation of hydrogen bonds with the solvent molecule. The use of *N*-benzylquininium fluoride or *N*-dodecylephedrinium fluoride as catalysts in toluene makes it possible to obtain the reaction products in yields of the order of 90% and with an optical yield up to 10–23%, which can most probably be attributed to the involvement of the fluoride anion in the process.[101]

Table 10. The influence of solvents on the mode of addition of 1,3-dithiane to enals.[37]

Enal	Content of adducts, %			
	in THF	in THF + HMP	in THF	in THF + HMP
	Addition to C=C		Addition to C=C	
MeCH=CHCHO	35	95	65	5
PhCH=CHCHO	15	65	85	35
H_2C=C(Me)CHO	35	95	65	5
Me_2C=CHCHO	0	35	100	65

There is no doubt that the structure of the enone and the carbanion plays a major role. Thus methyl vinyl ketone readily reacts with the carbanion generated from 1-nitro-1-*p*-tolylsulphonyloxymethane, 2-acetyl-2,3-dihydro-1-indanone, or 2-acetyl-2-[2-acetyl(or formyl)ethyl]-2,3-dihydro-1-indanone in the presence of quinine to form 1,4-adducts in high yields (87–93%) and with a high optical activity (optical yield up to 56%)[101] both in toluene and in carbon tetrachloride. Acrolein and crotonaldehyde react analogously:



Addition in the 1,4-positions also takes place in reactions with the carbanions generated from methyl 2-methylacetoacetate, ethyl 2-phenylcyanoacetate, and 2-ethoxycarbonylcyclopentanone; however, the carbanion obtained from 2-acetylcyclopentanone does not react with enones and enals under these conditions.[101]

The influence of solvation is strikingly manifested in the reaction between the trimethylsilyl ether of benzaldehyde cyanohydrin and mesityl oxide.[38] A mixture of products of addition to both the C=C and C=O bonds is formed rapidly and irreversibly in THF or DME and also in a mixture of these solvents under the conditions of kinetic control. On the other hand, when the reaction is carried out in ether, also under kinetic control, only the addition to the C=C bond is observed:

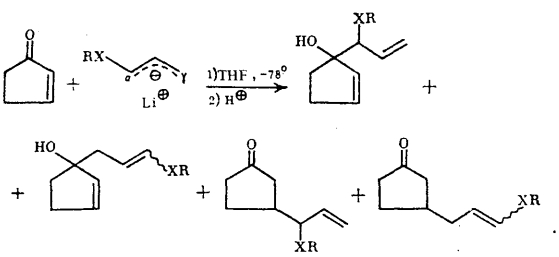
$$Me_2C{=}CHCOMe + Ph\overset{\ominus}{C}(CN)OSiMe_3\ Li^{\oplus} \rightarrow$$
$$\rightarrow Me_2C{=}CH{-}\underset{\displaystyle OH}{\underset{|}{C}}(CN)(OSiMe_3)Ph + Me_2CCH_2COMe \quad (PhC(CN)OSiMe_3)$$

When 1,3-dithiane reacts with enals, a shift towards an increase of the yield of the 1,4-adducts is observed on passing from THF to its mixture with HMP (Table 10).

Thus the above data show that polar solvents frequently promote the addition to the C=C bond.

The influence of solvation of the proportions of the 1,2- and 1,4-adducts has been studied in detail for the following nucleophiles: $(MeCH{=}CH)\overset{\ominus}{C}(CN)OCHMeOEtLi^{\oplus}$, $Ph\overset{\ominus}{C}(SR)S.(O)R^1Li^{\oplus}$, $(EtS)_2\overset{\ominus}{C}CO_2MeLi^{\oplus}$, and $H\overset{\ominus}{C}(CN)P(O)(OEt)_2Li^{\oplus}$. It has been established that, when the counterion is a lithium ion, then in THF or DME at −55 °C the above carbanions exist in the form of solvate-separated ion pairs. On the other hand, in ether, which solvates lithium ions only slightly, the same carbanions exist in the form of close (contact) ion pairs.[102–106] In the first case, the carbanion interacts only weakly with the counterion (lithium), so that a complex is formed between the lithium and the oxygen of the carbonyl group. The complex formation increases the electrophilicity of the carbonyl group by increasing the charge on the C(2) atom and by decreasing the energy level of the π^*(C=O) LUMO, which favours attack by the nucleophile on the C(1) atom.[57] In the second case the nucleophile interacts strongly with the counterion (lithium) and the latter, which interacts only weakly with the oxygen of the carbonyl group, forms an associated species. Ion pair association reduces the nucleophilicity of the carbanion as a result of the decrease of the charge on the nucleophile and the decrease of the energy level of its HOMO, which promotes the attack by nucleophiles on the C(3) atom.[57] The reversal of the direction of reaction when THF (or DME) is replaced by ether in the interaction of mesityl oxide with the carbanion generated from the trimethylsilyl ether of benzaldehyde cyanohydrin by treatment with n-BuLi can be explained by the fact that the solvate-separated ion pairs $Ph\overset{\ominus}{C}(CN)(OSiMe_3)\,||Li^{\oplus}$ are then converted into the close ion pairs $[Ph\overset{\ominus}{C}(CN)(OSiMe_3)][Li^{\oplus}]$,[73,106] which is accompanied by a decrease of the negative charge on the carbanionic centre and is responsible for the preferential attack on the C(3) atom despite some decrease of the energy of the HOMO of the nucleophile.

An interesting example of the change of direction of the reaction as the solvent composition is altered is provided by the reaction of cyclopent-2-enone with the carbanion generated by treating $RXCH_2CH{=}CH_2$ with n-BuLi at −78 °C.[107] In THF the reaction proceeds in accordance with the mechanism



This results in the formation of mainly a mixture of the α- and γ-1,2-adducts. The addition of only one mole of HMP results in a sharp change in regioselectivity and mainly the α-1,4-adduct is obtained (Table 11). We may note that a decrease of the amount of added HMP leads to the appearance of α- and γ-1,2-adducts in the mixture. A complete inversion of the direction of reaction in this instance can probably be accounted for by the fact that the effective solvation of lithium ions increases the energy of the HOMO of the nucleophile and leads to orbital control, which promotes 1,4-addition.[107-110] The change in the regioselectivity of the addition of CH acids to enals and enones by the addition of HMP is nowadays already used fairly widely in organic synthesis, for example, in the synthesis of α,α,β-trisubstituted ketones and natural products (confertin, aromatin, etc.).[111]

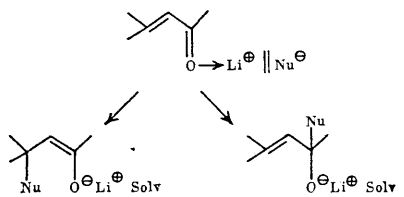
Table 11. The influence of the nature of solvents on the composition of the products of the reaction of cyclopent-2-enone with $RXCH_2CH = CH_2$ (according to the data of Binus and Haynes[107]).

R	X	Solvent	Composition of reaction products, %				Overall yield, %
			α-1,2	γ-1,2	α-1,4	γ-1,4	
Ph	S	THF	60	18(1.0:1.1)	12	8(1.0:4.2)	85
Ph	S	THF + HMP**	0	0	95	5	89
Ph_3C	S	THF	30	70	—	—	30
Ph_3C	S	THF + HMP**	0	0	90	10	30
Me	S	THF	64	36(1.0:0.6)	0	0	87
Me	S	THF + HMP**	0	0	95	5	89
t-Bu	S	THF	42	58(1.00:0.25)	0	0	85
t-Bu	S	THF + HMP**	0	0	95	5	85
Ph	Se	THF	58	20	12	10(1.0:1.9)	79
Ph	Se	THF + HMP**	0	0	95	5	81

*The ratio of the *Z*- and *E*-isomers is given in brackets.
**One mole of HMP was added.

Additives and the Mode of Reaction

It has been established in recent years that the introduction of certain additives into the reaction mixture makes it possible, by the change of solvent, to alter the regioselectivity of the addition of CH acids to enals and enones. Table 12 illustrates, for example, the influence of additives on the ratio of 1,2- and 1,4-adducts in the reaction of mesityl oxide with the trimethylsilyl ether of benzaldehyde cyanohydrin in the presence of n-BuLi.[73] Evidently, the addition of 12- crown-4 ether, which fully displaces the reaction towards 1,2-addition in DME and even in ether leads to the formation of 76% of the products of addition to the C=O bond, evidently exerts the greatest influence. This is undoubtedly associated with the formation of stable complexes between 12-crown-4 ether and lithium ions[112,113] (see the previous Section). The addition of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) and lithium bromide and perchlorate hardly alters the mode of reaction but the introduction of magnesium bromide increases the content of the 1,4-adducts in the mixture. It may be that a complex is formed in this case between the solvated nucleophile ion pair and the enone via the carbonyl group and is capable of ensuring both reaction pathways, involving the 1,2- and 1,4-positions:



The slight tendency towards an increase of the content of the 1,4-adducts (from 22 to 26–28%) following the addition of lithium salts is also probably associated with the analogous complex formation reaction.

Table 12.

Solvent	Additive	Compn. of reaction products, %		Overall yield, %
		via C=O bond	via C=C bond	
DME	—	78	22	98
DME	TMEDA*	80	20	98
DME	12-crown-4 ether*	100	0	88
Ether	12-crown-4 ether*	76	24	90
DME	LiBr**	72	28	91
DME	$LiClO_4$**	74	26	91
THF	$MgBr_2$***	42	58	97

*One mole in relation to the substrate was added.
**Saturated solutions in a 2:1 DME–hexane mixture.
***0.5 of a mole in relation to the substrate was added.

It is noteworthy that the reaction of the t-butylthioallyl anion with cyclopent-2-enone in THF in the presence of three moles of TMEDA leads to an 80% yield of only a mixture of the α-1,2-isomer (41%) and the γ-1,2-isomer (59%), while the addition of copper(I) iodide entails the formation of the 1,4-adduct alone in a 75% yield.[107] The complete shift towards 1,4-addition in the reaction of ethyl propionate with 2-phenylthiocyclopent-2-enone in THF at −78 °C was induced by the addition of a complex of copper iodide with trimethyl phosphite.[111] This resulted in the formation of 2-phenylthio-3-(1-ethoxycarbonylethyl)cyclopentanone in a 64% yield as a mixture of four diastereoisomers in proportions of 18:2:9:71. In the absence of the additive, only the 1,2-adduct was formed, namely 1-hydroxy-1-(1-ethoxycarbonylethyl)-2-phenylthiocyclopent-2-ene.[111]

Finally, mention should be made of the effect of yet another factor on the mode of reaction, namely the pressure. It has been shown that the addition of ethyl- and n-butylmalonic esters to the C=C bond of the chalcone does not take place at atmospheric pressure. However, an increase of the pressure to 10–15 kbar makes it possible to obtain the products of the Michael addition in yields of 70–95%.[114-116]

---oOo---

By virtue of the advances achieved in the study of the nucleophilic addition of CH acids of the type of XCH_2Y and XYCHZ to enones and enals, it has now become possible to achieve the regioselective addition in the 1,2- and 1,4-positions by selecting the appropriate nucleophiles, enones and enals, bases for the generation of the carbanions, solvents, and additives. 1,2-Addition is favoured by selecting nucleophiles with the charge most highly localised on the nucleophilic centre (CH acids with low pK_a), the use of enones and enals with sterically hindered C(3) atoms or with electron-donating substituents in the 3-position, the use of bases whose cations form complexes with the oxygen of the carbonyl group most readily, and the application of solvents promoting the formation of solvate-separated ion pairs comprising the carbanion and the counterion (the base cation) as well as additives forming complexes with the cations.

1,4-Addition is promoted by selecting nucleophiles with the most delocalised charge (CH acids with high pK_a), the employment of enones and enals without substituents giving rise to steric hindrance at the C(3) atom, and the application of bases whose cations are poor complex forming agents in relation to the oxygen atom of the carbonyl group and solvents promoting the formation of close ion pairs between the carbanion and the counterions.

REFERENCES

1. E.J.Corey and D.Crouse, J.Org.Chem., 1968, **33**, 298.
2. L.Wartski, M.ElBouz, J.Seyden-Penne, W.Dumont, and A.Krief, Tetrahedron Letters, 1979, 1543.
3. H.O.House, in "Modern Synthetic Reactions", Benjamin, Inc., New York, 1972, p.647.
4. L.A.Yanovskaya, R.N.Stepanova, and V.F.Kucherov, Izv.Akad.Nauk SSSR, Ser.Khim., 1964, 2093.
5. G.Jones, in "Organic Reactions", Wiley and Sons, New York, 1967, Vol.15, p.204.
6. H.O.House, in "Modern Synthetic Reactions", Benjamin, Inc., New York, 1972, p.660.
7. E.D.Bergmann, R.Pappo, and D.Ginsburg, in "Organic Reactions" (Translated into Russian), Inostr.Lit., Moscow, 1963, Vol.10, p.181.
8. T.H.Eicher, in "Chemistry of Carbonyl Group", Intersci., London, 1966, p.383.
9. S.Toma and Y.Kobayashi, Chem.Listy, 1980, 598.
10. S.Torii, H.Tanaka, and Y.Kobayashi, J.Org. Chem., 1977, **42**, 3473.
11. B.G.Chatterjie and D.P.Sehn, J.Org.Chem., 1977, **42**, 3162.
12. D.T.Warner, J.Org.Chem., 1959, **24**, 1536.
13. J.G.McIntosh and H.Khalil, Canad.J.Chem., 1978, **56**, 2134.
14. C.H.Engel, A.F.de Krassny, A.F.Bélanger, and G.Dionne, Canad.J.Chem., 1973, **51**, 3263.
15. G.Vonquent, M.Cause, and M.Guitard, Bull.Soc. chim.France, 1964, 2462.
16. N.I.Shtemenko, V.F.Kucherov, and L.A.Yanovskaya, Izv.Akad.Nauk SSSR, Ser.Khim., 1979, 1444.
17. L.A.Yanovskaya, V.A.Dombrovskii, and A.Kh.Khusid, "Tsiklopropany s Funktsional'nymi Gruppami" (Cyclopropanes with Functional Groups), Izd.Nauka, Moscow, 1980, p.17.
18. Z.Arnold, V.Kral, G.A.Kryshtal', and L.A.Yanovskaya, Izv.Akad.Nauk SSSR, Ser.Khim., 1983, 2162.
19. M.J.S.Dewar and R.C.Dougherty, "The PMD Theory of Organic Chemistry" (Translated into Russian), Izd.Mir, Moscow, 1977.
20. G.Stork and L.Maldonado, J.Amer.Chem.Soc., 1974, **96**, 5272.
21. G.Kyriakakow, M.C.Roux-Schmitt, and J.Seyden-Penne, Tetrahedron, 1975, **31**, 1883.
22. J.Seyden-Penne, A.Roux, and M.C.Roux, Tetrahedron, 1970, **26**, 2649.
23. M.C.Roux-Schmitt, J.Seyden-Penne, and S.Wolfe, Tetrahedron, 1972, **28**, 4965.
24. J.B.Stothers, "Carbon-13 NMR Spectroscopy", Acad. Press, New York, 1972, p.283.
25. G.Olah, P.W.Westermann, and I.Nishimura, J.Amer. Chem.Soc., 1974, **96**, 3548.
26. J.Bastide, N.El-Chandour, and O.Henri-Rousseau, Tetrahedron Letters, 1972, 4225.
27. J.P.Seguin, P.Beaupere, P.Bauer, and R.Uzan, Bull.Soc.chim.France, 1974, 167.
28. Y.Maroni-Barnaud, M.C.Roux-Schmitt, and J.Seyden-Penne, Tetrahedron Letters, 1974, 3129.
29. M.Mousseron, R.Fraisse, and R.Jacquier, Compt. rend., 1959, **248**, 1465.
30. M.Casse-Loller and R.Fraiss-Jullien, Bull.Soc.chim. France, 1966, 430.
31. A.Brown and A.Yamaichi, Chem.Comm., 1979, 100.
32. D.A.White and M.M.Baizer, Tetrahedron Letters, 1973, 3597.
33. K.Herman and H.Wynberg, J.Org.Chem., 1979, **44**, 2238.
34. T.Yanami, M.Kato, and A.Yoshikoshi, Chem.Comm., 1975, 726.
35. L.A.Kaplan, J.Org.Chem., 1964, **29**, 2256.
36. K.Baum and M.Guest, Synthesis, 1979, 311.
37. E.L.Bauz and L.Wartski, Tetrahedron Letters, 1980, 2897.
38. S.Hünig and G.Wehner, Chem.Ber., 1980, **113**, 324.
39. W.C.Still and A.Mitta, Tetrahedron Letters, 1978, 2659.
40. F.E.Ziegler and J.-M.Fang, J.Org.Chem., 1981, **46**, 825.
41. J.L.Herman, J.E.Richman, and R.H.Schlesinger, Tetrahedron Letters, 1973, 3271.
42. F.A.Carey and A.S.Court, J.Org.Chem., 1972, **37**(12), 1926.
43. W.Nagata and M.Yoshioka, in "Organic Reactions", Wiley and Sons, New York, 1977, Vol.25, p.255.
44. R.K.Mill and N.D.Ledford, J.Amer.Chem.Soc., 1975, **97**, 666.
45. G.E.Risinger and W.G.Haag, J.Org.Chem., 1973, **38**, 3646.
46. L.Baiocehi, H.Giannangeli, and M.Bonamoni, Tetrahedron, 1978, **34**, 955.
47. L.A.Yanovskaya and S.S.Yufit, "Organicheskii Sintez v Dvukhfaznykh Sistemakh" (Organic Synthesis in Two-Phase Systems), Izd.Khimiya, Moscow, 1982.
48. E.V.Dehmlov and S.S.Dehmlov, "Phase Transfer Catalysis", Verlag Chemie, Weinheim, 1980.
49. W.P.Webber and G.W.Gokel, "Phase Transfer Catalysis in Organic Synthesis" (Translated into Russian), Izd.Mir, Moscow, 1980.
50. M.Makosza, in "Modern Synthetic Methods", Schweizerischer Chemiker Verband, Zürich, 1976.
51. G.V.Kryshtal', V.V.Kul'ganek, V.F.Kucherov, and L.A.Yanovskaya, Izv.Akad.Nauk SSSR, Ser.Khim., 1978, 2808.
52. G.V.Kryshtal', V.V.Kulganek, V.F.Kucherov, and L.A.Yanovskaya, Synthesis, 1979, 107

53. G.V.Kryshtal', V.V.Kul'ganek, and L.A.Yanovskaya, "Tezisy Dokladov Vsesoyuznoi Konferentsii 'Khimiya Dikarbonil'nykh Soedinenii'. Riga, 1981" (Abstracts of Reports at the All-Union Conference on 'The Chemistry of Dicarbonyl Compounds', Riga, 1981), p.121.
54. O.A.Reutov, I.P.Beletskaya, and K.P.Butin, "CH-Kisloty" (CH Acids), Izd.Nauka, Moscow, 1980.
55. J.A.Pople and G.A.Segal, J.Chem.Phys., 1966, **44**, 3289.
56. I.Belsky, Chem.Comm., 1977, 237.
57. J.M.Lefour and A.Loupy, Tetrahedron, 1978, **34**, 2597.
58. P.Annunziata, M.Ginguini, and S.Colonna, Chem.Ind.(London), 1980, p.238.
59. G.Massiot, T.Mulambe, and J.Levy, Bull.Soc. chim.France, 1982, 241.
60. N.I.Shtemenko, G.V.Kryshtal', and L.A.Yanovskaya, Izv.Akad.Nauk SSSR, Ser.Khim., 1981, 445.
61. G.V.Kryshtal', V.V.Kulganek, N.I.Shtemenko, and L.A.Yanovskaya, "Tezisy Dokladov Vsesoyuznoi Konferentsii 'Razvitie Organicheskogo Sinteza na Osnove Izucheniya Obshchikh Zakonomernostei i Mekhanizmov Reaktsii Organicheskoi Khimii'. Leningrad, 1980" (Abstracts of Reports at the All-Union Conference on 'The Development of Organic Synthesis on the Basis of the Study of the General Laws and Mechanisms of Reactions in Organic Synthesis', Leningrad, 1980), p.88.
62. D.Seebach, Synthesis, 1969, 17.
63. G.Stork and L.J.Maldonado, J.Amer.Chem.Soc., 1974, **96**, 5274.
64. J.Mulzer, G.Hartz, U.Kühl, and G.Brüntrup, Tetrahedron Letters, 1978, 2949.
65. R.Sauvetre, M.C.Roux-Schmitt, and J.Seyden-Penne, Tetrahedron, 1978, **34**, 2135.
66. P.C.Sostrowski and V.V.Kame, Tetrahedron Letters, 1977, 3549.
67. A.G.Schulz and Y.K.Yee, J.Org.Chem., 1976, **41**, 4044.
68. I.L.Herman and I.E.Richman, Tetrahedron Letters, 1973, 3271.
69. K.Oguta, H.Yamashita, and G.Tsuchinaski, Tetrahedron Letters, 1978, 1303.
70. I.L.Herman, I.E.Richman, and R.H.Schlesinger, Tetrahedron Letters, 1973, 2595.
71. B.Deschamps and J.Seyden-Penne, Tetrahedron, 1977, **33**, 413.
72. B.Deschamps, Tetrahedron, 1978, **34**, 2009.
73. S.Hünig and G.Nehner, Chem.Ber., 1980, **113**, 302, 3783.
74. S.Hünig and M.Öles, Chem.Ber., 1981, **114**, 959.
75. J.W.ApSimon, J.W.Hooper, and B.A.Laishes, Canad.J.Chem., 1970, **48**, 3064.
76. R.M.Moravie, J.Corset, and M.L.Josien, Tetrahedron, 1976, **32**, 693.
77. J.E.Ellis, J.S.Dutcher, and C.H.Heathcock, J.Org. Chem., 1976, **41**, 2670.
78. B.Föhlisch, U.Dukek, I.Graessle, B.Novotny, E.Schupp, G.Schwaiger, and E.Widmann, Annalen, 1973, 1832.
79. A.Schönberg and E.Singer, Chem.Ber., 1970, **103**, 3871.
80. A.Sakurai and H.Midorikawa, Bull.Chem.Soc.Japan, 1968, **41**, 430.
81. H.H.Otto, O.Rinus, and H.Schuelz, Synthesis, 1978, 681.
82. A.L.Fatiadi, Synthesis, 1978, 165.
83. Zh.A.Krasnaya, E.P.Prokof'ev, and V.F.Kucherov, Izv.Akad.Nauk SSSR, Ser.Khim., 1970, 2318.
84. E.P.Prokof'ev, Zh.A.Krasnaya, and K.M.Litvak, Izv.Akad.Nauk SSSR, Ser.Khim., 1979, 766.
85. Zh.A.Krasnaya, E.P.Prokof'ev, and V.F.Kucherov, Izv.Akad.Nauk SSSR, Ser.Khim., 1979, 816.
86. T.S.Stytsenko, Candidate's Thesis in Chemical Sciences, Institute of General Chemistry, USSR Academy of Sciences, Moscow, 1977.
87. Zh.A.Krasnaya, T.S.Stytsenko, E.P.Prokof'ev, I.P.Yakovlev, and V.F.Kucherov, Izv.Akad.Nauk SSSR, Ser.Khim., 1974, 845.
88. S.M.Kvitkov and V.V.Perekalin, Zhur.Obshch. Khim., 1962, **32**, 144.
89. S.M.Kvitkov and V.V.Perekalin, Zhur.Org.Khim., 1973, **9**, 471.
90. H.J.Monteiro, J.Org.Chem., 1977, **42**, 2324.
91. J.L.Herrmann, G.R.Kieczykowski, R.F.Romanet, F.J.Wepplo, and R.H.Schlesinger, Tetrahedron Letters, 1973, 4711.
92. S.Hashimoto, N.Komeshima, S.Yamada, and K.Koga, Tetrahedron Letters, 1977, 2907.
93. G.V.Kryshtal', K.Ya.Burshtein, V.V.Kul'ganek, and L.A.Yanovskaya, Izv.Akad.Nauk SSSR, Ser.Khim. (in the Press).
94. A.G.Schulz and Y.K.Yee, J.Org.Chem., 1976, 41,4044.
95. N.Wang, Sh.Su, and L.Tsai, Tetrahedron Letters, 1979, 1121.
96. M.E.Bouz, M.C.Roux-Schmitt, and L.Wartski, Chem.Comm., 1979, 779.
97. J.Lucchetti, W.Dumont, and A.Krief, Tetrahedron Letters, 1979, 2695.
98. T.M.Dolak and T.A.Bryson, Tetrahedron Letters, 1977, 1961.
99. J.Lucchetti and A.Krief, Tetrahedron Letters, 1978, 2697.
100. S.Colonna, H.Hiemstra, and H.Wynberg, Chem. Comm., 1978, 238.
101. H.Wynberg and R.Helder, Tetrahedron Letters, 1975, 4057.
102. L.M.Jackman and B.C.Lange, Tetrahedron, 1977, **33**, 2737.
103. H.C.Wang, G.Wevin, and M.Szwarc, J.Amer.Chem. Soc., 1977, **99**, 5056.
104. C.Carvajal, K.J.Tölle, J.Smid, and M.Szwarc, J.Amer.Chem.Soc., 1965, **87**, 5548.
105. I.K.Lefour, P.Sarthou, G.Bram, F.Gruibe, A.Loupy, and J.Seyden-Penne, Tetrahedron Letters, 1978, 3831.
106. C.Minot and N.T.Ahn, Tetrahedron Letters, 1975, 3905.
107. M.R.Binus and R.K.Haynes, J.Org.Chem., 1981, **46**, 3790.
108. U.Mayer, V.Gutmann, and W.Gregor, Monatsh. Chem., 1975, **106**, 1235.
109. C.Agami, Bull.Soc.chim.France, 1970, 1619.
110. H.Normant, Angew.Chem., 1967, **79**, 1029.
111. J.M.Fang, J.Org.Chem., 1982, **47**, 3464.
112. G.W.Gokel and H.D.Durst, Synthesis, 1976, 168.
113. C.Riche, C.Pascard-Billy, C.Cambillian, and G.Bram, Chem.Comm., 1977, 183.
114. W.J.le Noble and H.Kelm, Angew.Chem., 1980, **92**, 887.
115. K.Matsumoto, Angew.Chem., 1980, **92**, 1042.
116. J.A.Gladysz, and Y.S.Yu, Chem.Comm., 1978, 599.

Zelinskii Institute of Organic Chemistry,
USSR Academy of Sciences, Moscow