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Heterodiene Syntheses with α,β-Unsaturated Carbonyl Compounds

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I. Introduction

The cycloaddition reactions of α,β-unsaturated carbonyl compounds show interesting features both from a synthetic and a theoretical point of view.

This type of 1,4-cycloaddition, because of its similarity to the Diels–Alder reaction, has been covered by several reviews[1-5] not specific to this topic. These reviews considered it only as a part of the more general diene synthesis, the only exception being the article by Colonge and Descotes in Hamer's book[3] which covered the literature up to 1963. However, a decade of organic chemistry is time enough for a revolution, and a sign of this lies in the closing remark of the section concerning the mechanism of dimerization of α,β-unsaturated carbonyl compounds: *"The selectivity of the cycloaddition ... is an experimental fact which remains to be explained satisfactorily."*

The similarity of these 1,4-cycloadditions to the Diels–Alder reaction was emphasized by calling the reagent *"heterodiene"*[1] and the reaction *"Diels–Alder syntheses with heteroatomic compounds"*.[2] We prefer to call them, for the sake of brevity, *heterodiene syntheses* which takes into account both fundamental characteristics.

The extensive development in the field in the sixties, however, showed that slight differences in the reagents or the experimental conditions give completely different adducts. Therefore, for historical reasons, a variety of reaction modes which are alternative to, or in competition with, the original 1,4-cycloaddition can be called *"heterodiene syntheses"*.

II. Scope and Limitations

This review, which covers the literature up to the middle of 1974, deals with the various reaction modes of an α,β-unsaturated carbonyl compound, in which one or more atoms can also be something other than carbon, with a double or a triple bond (Scheme I).

Only thermal cycloadditions will be covered. Photochemical reactions and polar cycloadditions are specifically excluded. The latter, which involve positively charged acyl ions, were covered by a recent excellent review.[6]

With a few exceptions, papers previously reviewed will not be reconsidered.

III. Perturbation Theories of Cycloadditions

Although application of perturbation theory to cycloadditions has been reviewed recently,[7] we wish to recall the fun-

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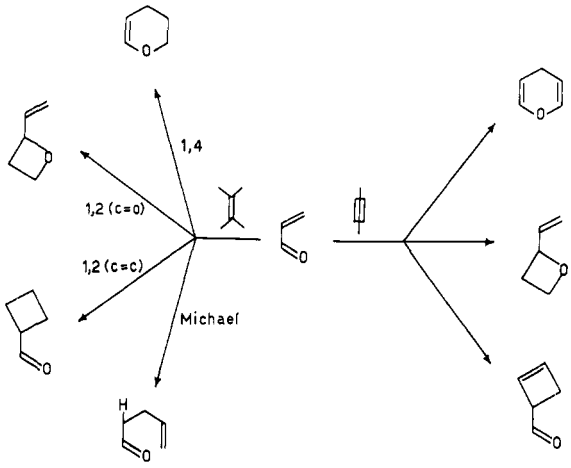


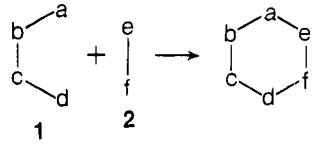
damental theories since this approach allows a better understanding of the previously reported reactions.

Salem has derived a second-order perturbation expression[8,9] which shows the energy gain in the bond formation between centers involved in cycloaddition (eq 1).

$$\Delta E = -\sum_{a,b}(q_a + q_b)\gamma_{ab}S_{ab} - \sum_{a,b}Q_aQ_b\frac{\Omega}{C} + 2\sum_{R}^{occ}\sum_{S}^{unocc} - \sum_{R}^{unocc}\sum_{S}^{occ}\frac{\left(\sum_{RS}c_ac_b\gamma_{ab}\right)^2}{E_R - E_S} \quad (1)$$

The first and the third terms are the closed-shell repulsion term (of relative importance) and the overlap term, respectively, and this sum, usually called $E_{overlap}$, represents the interactions arising from frontier orbitals.[10-12] The second term, the coulombic interaction usually called E_{polar}, includes the polar interactions arising from charge control.[13]

The electrostatic term is sometimes neglected, and the energy gain is considered to be a function of frontier orbitals only. The relative equation for a cycloaddition of the type



1 2

therefore becomes

$$\Delta E = \frac{[(c_{Ho}{}^e c_{Lu}{}^a + c_{Ho}{}^f c_{Lu}{}^d)\gamma]^2}{E_{Ho}{}^{ef} - E_{Lu}{}^{ad}} + \frac{[(c_{Ho}{}^a c_{Lu}{}^e + c_{Ho}{}^d c_{Lu}{}^f)\gamma]^2}{E_{Ho}{}^{ad} - E_{Lu}{}^{ef}} \quad (2)$$

This equation can still predict the regiospecificity of a large number of Diels–Alder reactions[14] and furthermore can distinguish between three types of cycloadditions from the relative positions of the frontier orbitals of the reagents[15-17] (Figure 1).

For case b both terms of eq 2 need to be considered. For case a the dominant interaction occurs between the HOMO (highest occupied molecular orbital) of the diene and the LUMO (lowest unoccupied) of the dienophile, and therefore the first term of eq 2 can be neglected. Case c requires the opposite treatment since the interaction between the LUMO of the diene and the HOMO of the dienophile determine the reactivity.

How do we determine the energies associated with frontier orbitals and therefore determine the type of cycloaddition? The energy of the HOMO's corresponds, in accordance with

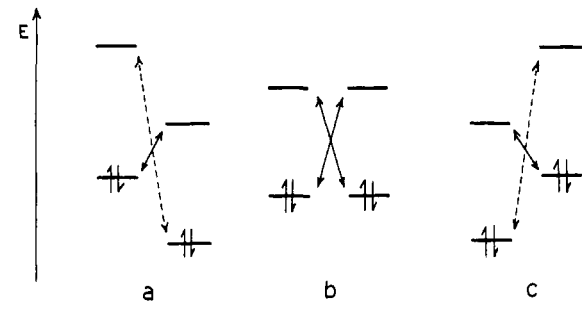


Figure 1. Relative positions of frontier orbitals in *direct* (a), *neutral* (b), and *inverse* (c) Diels–Alder reactions.

Koopmans theorem,[18] to the negative of the ionization potentials (IP) which are usually determined by photoelectron spectroscopy. The LUMO's correspond to the negative of the electron affinity[19] and are usually determined by quantum-mechanical calculations, from polarographic half-wave reduction potentials, and from electronic transitions associated with ionization potentials.[16]

If the frontier orbital energies of acrolein,[20] selected as a model for α,β-unsaturated carbonyl compounds, are compared with the frontier orbital energies of olefins in accordance with Houk's semiquantitative approach[21] (Figure 2), we can easily deduce that the dominant interaction, particularly with nucleophilic olefins (vinyl ethers and enamines), always occurs between the HOMO of the olefin, which acts as a donor, and the LUMO of the α,β-unsaturated carbonyl derivative, which acts as an acceptor. Therefore these cycloadditions can be represented by case c illustrated in Figure 1, and eq 2 can be simplified by neglecting the second term.

Only one case does not fall in the above reported representation: the dimerization reactions.

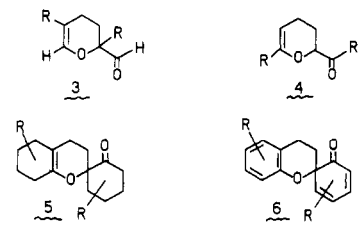
IV. Dimerization of α,β-Unsaturated Carbonyl Derivatives

A. Historical Survey

Since Sherlin[22] first reported the thermal dimerization of acrolein to give a dihydropyran derivative in 1938, several compounds have been found to dimerize[3] if heated with or without solvent, usually under severe conditions.

α,β-Unsaturated aldehydes,[3] e.g., acrolein, α-alkylacroleins, and α-chloroacrolein, gave 2-formyl-3,4-dihydropyran derivatives **3.**

Alkyl and aryl vinyl ketones[3] gave 2-acyl-3,4-dihydropyrans **4,** but α-alkylidene- and arylidenecyclanones gave spirochroman derivatives **5,** and similar behavior was shown by *o*-quinonemethides,[3] leading to **6.**



This work was developed mainly for synthetic purposes. Various mechanisms have been proposed to explain the high regioselectivity of this reaction, which can occur via exo or endo transition states and give **7** or **8** (Scheme II); in fact regioisomer **7** predominates as it is formed in 99% yield in the thermal dimerization of acrolein.

The first proposed mechanism involved diradical intermediates,[23,24] but their existence was strongly contested[25] and a

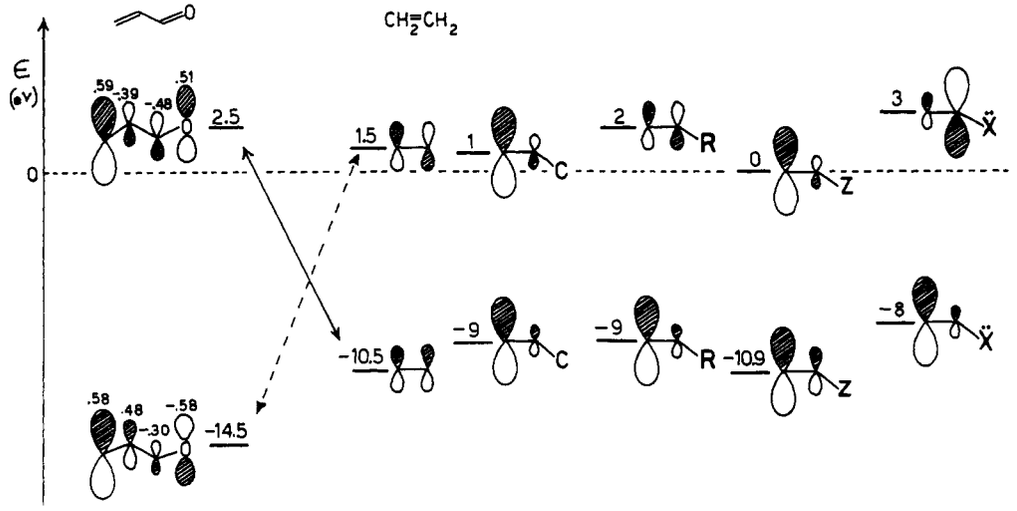


Figure 2. Estimated π frontier orbital energies for acrolein and olefins (R = alkyls; C = conjugated; Z = CO, CN; X = NR_2, OR). Solid arrow indicates the dominant interaction.

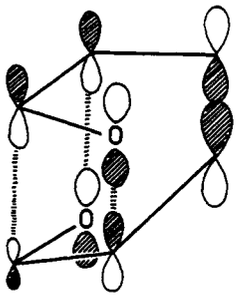


Figure 3. Transition state of the acrolein dimerization.

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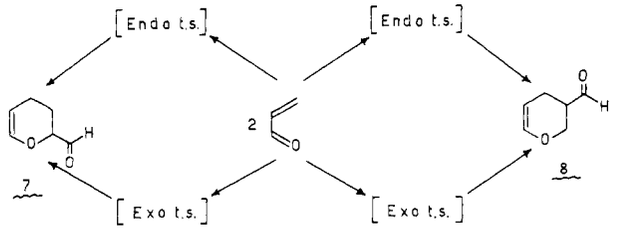


concerted mechanism involving an asymmetrical transition state was proposed by Dewar[26] and Woodward.[27]

B. Theory of Dimerization

Salem's first approach to the acrolein dimerization using perturbation theories employed calculations based on the Hückel MO method.[8] The results were unsatisfactory since both regioisomers are predicted on this basis, but the difficulty seems to be due to the choice of the HMO method. A complete revision using SCF calculations[9] gave the correct prediction if the whole of eq 1 was used. Table I reports the relative importance of polar and overlap energy terms in the exo and endo transition states leading to **7** and **8.**

The above results clearly show the experimental regioselectivity and furthermore support an endo approach of the reagents with the C–C bond closing faster than the C–O bond. Figure 3 represents the preferred transition states with the most favorable secondary orbital interactions.[28,29]

A simple consideration arises: if the whole of eq 1 has to be considered, both terms of eq 2 must be taken into account. This result is trivial if one considers that dimerization reactions are typical (b) cases (Figure 1) where the HOMO's and the LUMO's of the reagents have the same energy value.

TABLE I. Interaction Energies (kcal/mol) for the Dimerization of Acrolein

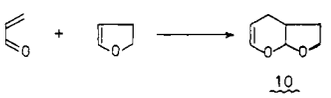
Energy	[7 endo]	[8 endo]	[7 exo]	[8 exo]
$E_{overlap}$	−1.33	+0.19	−0.66	−0.36
E_{polar}	−2.34	−0.58	−1.03	−0.32
E_{total}	−3.67	−0.39	−1.69	−0.68

However, if a Diels–Alder reaction is easier if the energy difference between the frontier orbitals of the two reactants is lower,[30] case b is particularly unfavorable because the presence of a preferred HOMO/LUMO interaction in cases a and c causes a lowering of the energy difference.

This situation must render the dimerization a difficult reaction involving a high energy of activation, and therefore it can only occur if other alternatives are impossible. This conclusion is supported by experimental observations: (a) dimerizations occur under severe conditions;[3] (b) if a mixture of potential dienes is heated, mixed adducts are obtained and dimers are usually absent,[31-33] or are formed in low yield;[34] (c) a methyl group is sufficient to perturb a pure (b) system since the reaction between acrolein and α-methylacrolein gives only **9.**[32]

9

The only exception is the reaction of acrolein and furan under pressure.[35] No mixed adduct is obtained and only the dimer of acrolein is isolated in low yield. This behavior seems unusual if one considers that the IP of furan (8.99 eV)[36] is close to that of methyl vinyl ether (8.93 eV).[37] However, as pointed out by Houk,[38] the stability of both reactants and products must be taken into account and the resonance energy of furan, which would be lost in the reaction, forbids the cycloaddition. If this is absent (e.g., 2,3-dihydrofuran), the cycloaddition occurs easily[39] and **10** is obtained.



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C. Competition between Potential Dienes

An interesting question arises when a diene and a heterodiene are allowed to react. We particularly wish to highlight the reaction between a butadiene derivative and an α,β-un-

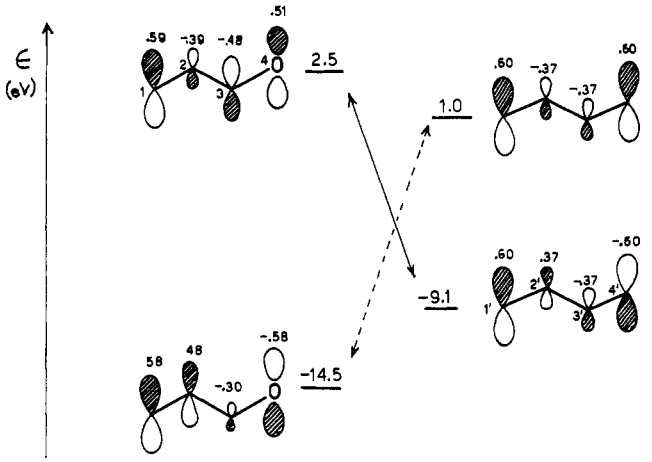
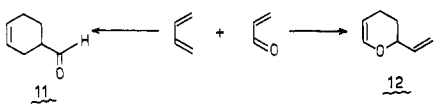


Figure 4. Frontier orbital interactions between acrolein and butadiene. Solid arrow indicates the dominant interaction.

saturated carbonyl compound. Clearly two reaction modes are possible and a cyclohexene **11** or a dihydropyran derivative **12** can be obtained.

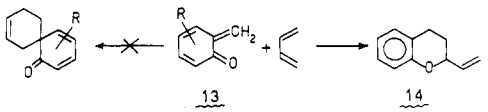


11 **12**

Inspection of the frontier orbital interaction between the model compounds reveals that the dominant interaction occurs between the HOMO of butadiene, which acts as a donor, and the LUMO of acrolein, which behaves as an acceptor (Figure 4).

Application of the "hard and soft" concept allows us to predict that the first bond would link the softest centers,[14,40,41] i.e., atom 1′(4′) with 1. At this stage we can choose between ring closures 4′(1′) → 2 or 4 → 2′(3′). Obviously the greater coefficients favor the first alternative, and therefore the cyclohexene **11** is predicted.

Numerous examples support the above reported prediction: acrolein and butadiene gave 90% of **11** and a maximum 0.5% yield of **12**.[33] Simple derivatives[42-49] or more sophisticated molecules[50-52] gave only cyclohexene derivatives, and this behavior is irrespective of the cisoid conformation of both diene[53] and carbonyl derivative.[54]



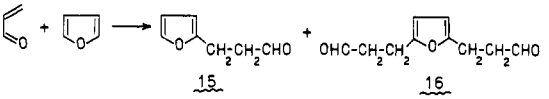
13 **14**

Only one exception is known: when *o*-quinone methides **13** react with butadiene, 2-vinylchromans **14** are the only reaction products.[55,56] However, we must remember to take into account the stability of products.[38] For an aromatic system the simple frontier orbital approach is inadequate since the observed pathway causes a gain in resonance energy which lowers the subjacent occupied levels of the reagent, and these variations cannot be ignored.

D. Alternative Reactions

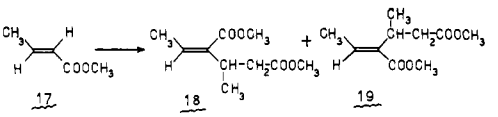
Because of the high energy of activation involved in the dimerization reaction, it is probable that alternative reactions become the main reaction pathway.

In addition to the polymerizations[3,57,58] already mentioned, we recall that open-chain derivatives **15** and **16** are obtained from furan and acrolein[59] if the reaction is performed at room pressure (see ref 35 for the reaction under pressure) and furan aromaticity is retained.



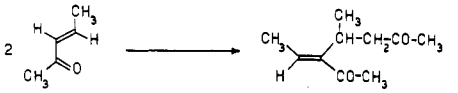
15 **16**

It is not surprising that methyl crotonate (**17**) dimerizes by an alternative route[60] and, in the presence of Cu_2O and cyclohexyl isocyanide, a mixture of 20% (*Z*)- and 80% (*E*)-dimethyl 2-methylpent-3-ene-1,3-dicarboxylate (**18** and **19**) is obtained.



17 **18** **19**

Much more unusual is the analogous behavior of *trans*-pent-3-en-2-one, whose only dimer is (*E*)-4-methyl-5-acetylhept-5-en-2-one (**20**).



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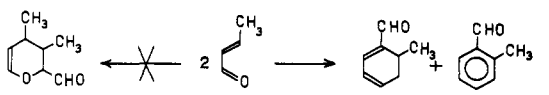
Nevertheless, this behavior is not unexpected since crotonaldehyde is not converted into **21** by heating under pressure but gives instead 6-methylcyclohexadienecarboxaldehyde and *o*-tolualdehyde.[61]



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V. Unsaturated Reagents with No Adjacent Heteroatom

A simple qualitative frontier orbital treatment of the reaction between acrolein and C=C—C and C≡C—C compounds is represented in Figure 5 using typical values of the MO's of these particular classes of compounds.

In general these reactions are expected to be difficult; exceptions perhaps are styrene and alkylethenes with large inductive effects. Nevertheless, with the exception of olefins with electron-attracting groups (ZC=C and ZC=CZ), the reactivity is $HOMO_{olefin}$ controlled.

In general we can predict lower reactivity for acetylenes than for the corresponding alkenes, since lowering of the HOMO can be tested by decreasing the IP by about 0.4–0.9 eV.[62]

A. Olefins

Few examples are known of reactions with this class of reagents, and we do not know if this is due to the above predicted difficulties or not.

Facile reaction occurs only if the α,β-unsaturated carbonyl derivative is an α-quinone methide **13,** generated by the thermal decomposition of a Mannich base (route A) or from the analogous alcohol (route B) (Scheme III). Table II summarizes the adducts with olefins.[55,56]

The reaction between vinylethynyldimethylcarbinol (**22**) and acrolein[63] is much more complicated. Careful analysis of the products reveals that there is competition between 1,4-mixed cycloadducts **23** and **24,** and dimers of both acrolein (**25**) and carbinol (**26**) (Scheme IV).

Cinnamaldehyde is also reported to react with various C=C—C compounds in a 1,4-cycloaddition reaction.[64,65] Second-order rate constants at 170° are reported in Table III.

The reported results are very similar to the predictions.

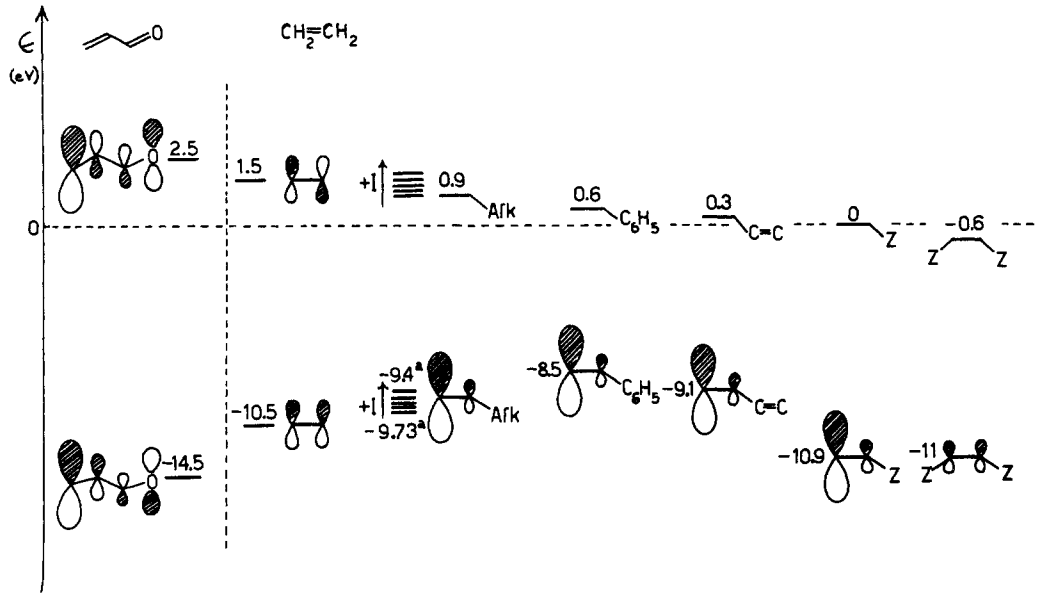


Figure 5. Estimated π frontier orbital energies and coefficients for acrolein and C=C—C compounds. [a] Alkenes IP's: L. S. Levitt, B. T. Levitt, and C. Parkanyi, *Tetrahedron*, 28, 3369 (1972). For other IP's and electron affinities, see ref 62 and hereto reported literature.

TABLE II. Preparation of Adducts from *o*-Quinonemethides and Olefins

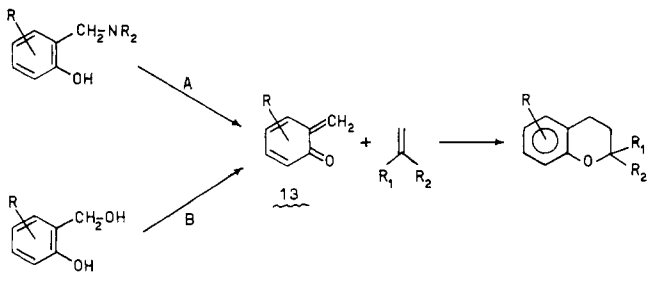
Origin	α-Quinonemethide	Olefin R_1	Olefin R_2	Reaction conditions: Solvent	Reaction conditions: T, °C	Reaction conditions: Time[b]	Yield, %	Mp (bp/mmHg), °C	Ref
A	α-Benzoquinonemethide	$CH=CH_2$	H	Toluene	185	15 h	8–10	(118–120/18)	55
B	α-Benzoquinonemethide	$CH=CH_2$	H	Toluene	170	15 h	30	(118–120/18)	55
A	α-Benzoquinonemethide	CH_3	CH_3	Toluene	200	7 h	5	(125/16)	55
B	α-Benzoquinonemethide	CH_3	CH_3	Toluene	200	7 h	35	(125/16)	55
A	α-Naphthoquinone-β-methide	$CH=CH_2$	H	Toluene	*a*	*a*	10	(145/0.2)	55
A	β-Naphthoquinone-α-methide	$CH=CH_2$	H	Toluene	180	15 h	65	20	56
B	β-Naphthoquinone-α-methide	$CH=CH_2$	H	Toluene	180	*a*	50	20	56
A	β-Naphthoquinone-α-methide	C_6H_5	H		180	2 h	55	86	56
A	β-Naphthoquinone-α-methide	CH_3	CH_3	Toluene	*a*	*a*	45	80	56
A	β-Naphthoquinone-α-methide	C_6H_5	C_6H_5		180	2 h	87	106	56

[a] Not reported in the original paper. [b] h = hours.

TABLE III. Kinetic Data of the Reaction between Cinnamaldehyde and Olefins

Expt	Olefin	$k_2 \times 10^3$, g/(mol sec)	Ref
1	α-Methylstyrene	0.7	64
2	*p*-Methylstyrene	2.6	64
3	Styrene	2.0	64
4	Allyl bromide	1.3 ± 0.2	65
5	1-Dodecene	0.2 ± 0.04	65
6	Isobutyl fumarate	0.8	64
7	Methyl maleate	0	64
8	*n*-Propyl maleate	0	64
9	Isopropyl maleate	2.5 ± 0.2	64, 65
10	*n*-Butyl maleate	1.5	64
11	Isobutyl maleate	0.6	64
12	*sec*-Butyl maleate	3.0	64

SCHEME III



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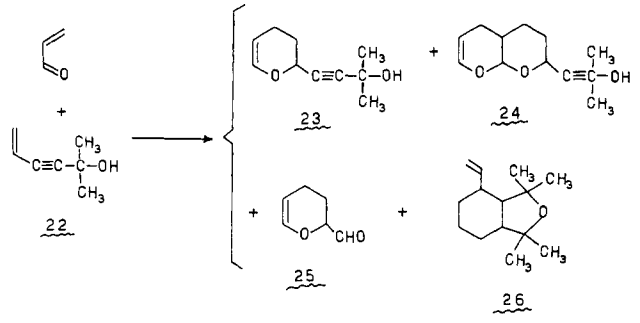


Double bonds with electron-donating groups (expt 1–4) show higher reactivity, whereas simple olefins and esters (expt 5–8) exhibit a low reactivity which, in some cases, is almost zero.

A few other esters (expt 9, 10, 12) have an unexplicably high degree of reactivity. It is hard to believe that styrene, whose IP is about 11 eV,[62] reacts more slowly than some maleates. If one considers that methyl and *n*-propyl homologs show nonappreciable reactivity, a side-reaction which could increase the overall reaction rate cannot be excluded, particularly if one remembers that adducts were not isolated.

Furthermore we must point out that this reaction model assumes only electronic substituent effects, and steric effects may be partly responsible for the low reactivity of some overcrowded molecules such as α-methylstyrene where the in-

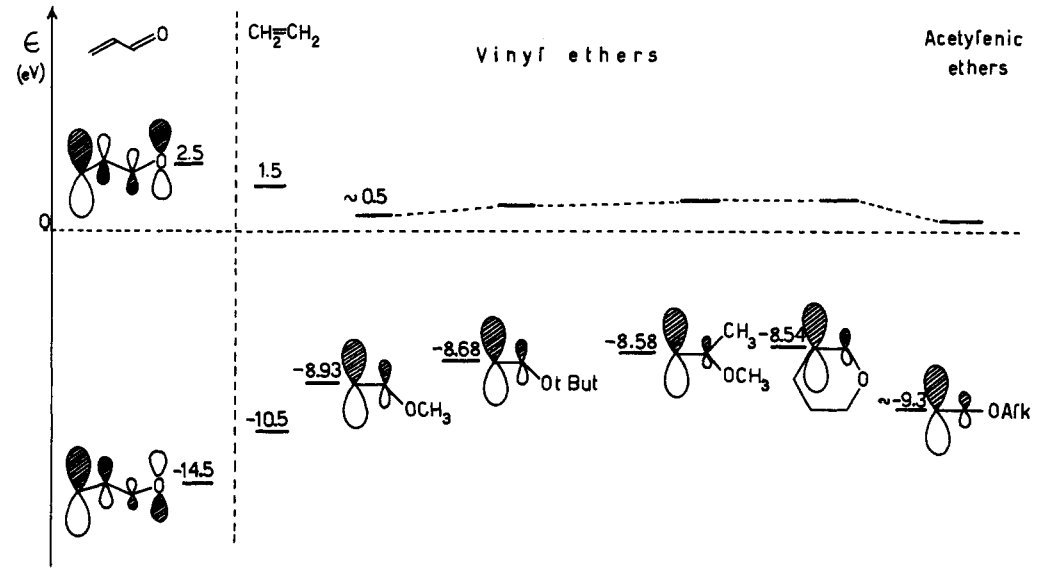
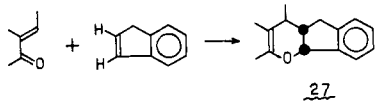


Figure 6. Estimated π frontier orbital energies and coefficients for acrolein and unsaturated ethers.

ductive effect of the methyl group should increase the effect of the phenyl group.

The reactivity of indene should be similar to that of styrene, and it was found to react with acrolein, crotonaldehyde, metacrolein, and α-quinone methide to give **27**.[66]



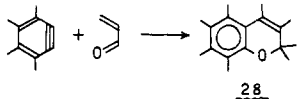
27

The yield varied from 13 to 86%. Obviously, maximum yield and milder conditions were found with quinone methide. Regiospecificity is fully in accordance with a simple frontier approach.

B. Acetylenes

The only examples of reactants of this class are benzyne and its tetrahalo derivatives.

Their reactivity[67-70] is very unusual even though a certain similarity between the adducts could deceive a superficial investigator since flav-3-ene derivatives **28** are the reaction products.



28

However, a careful investigation by Heaney, using ^{14}C labeled cinnamaldehyde,[70] demonstrated that the key step (Scheme V) is a 1,2-cycloaddition leading to the benzoxete derivative **29** which undergoes electrocyclic ring opening to **30** with subsequent valence isomerization to a flav-3-ene derivative **31**. If the reaction is performed at 200° **31** rearranges to the thermodynamically stable 4*H*-flavene derivative **32**.

The mechanism of formation of the benzoxete derivative **29** may involve an intermediate or may be concerted. A $[_{\pi}2_s + _{\pi}2_s]$ concerted mechanism is forbidden but, by utilizing nonbonding electrons from oxygen, this cycloaddition can be regarded as a $[_{\pi}2_s + _{\pi}2_s + _{n}2_s]$ reaction which is allowed. Alternatively the two new orbitals of benzyne could also be involved.

VI. Unsaturated Ethers

Unsaturated ethers are known to be better nucleophiles and have higher IP's than the parent C=C—C compounds because of the C=C—O system. Therefore, the interaction between the HOMO of the olefin and the LUMO of the unsaturated carbonyl compound is dominant, and a rate increasing effect can be predicted for the alkoxy group.

SCHEME V

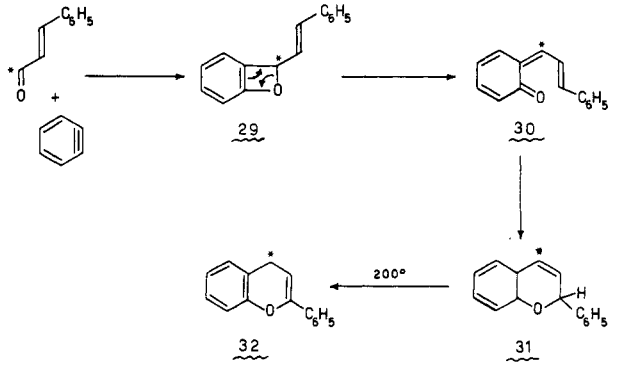


Figure 6 compares the orbital energies of the vinyl ethers, deduced from IP's,[37] with acrolein as a model. A rough estimate of electron affinities is made from substituent effects.

As the alkoxy group increases in size the IP decreases in the series Me > Et > *i*-Bu > *i*-Pr > c-Hex > *t*-Bu;[37] this agrees with the well-known correlation between IP and the inductive effect of substituents. α-Alkyl substitution decreases the IP of the vinyl ether[37] because of its inductive effect.

The behavior of dihydropyran is unusual, but the high value of its IP seems to be due to the forced s-cis conformation between the double bond and alkoxy residue; this has been demonstrated[71] to be the most favorable conformation for overlap between the π orbitals and oxygen lone pairs. Similarly *cis*- and *trans*-propenyl ethers are expected to behave differently since the conformation of the alkoxy group cannot be the same. Qualitatively we have considered the LUMO and the HOMO of alkoxyacetylenes to be lower by about 0.5 eV than the corresponding alkoxyalkene.[62]

A. Vinyl Ethers

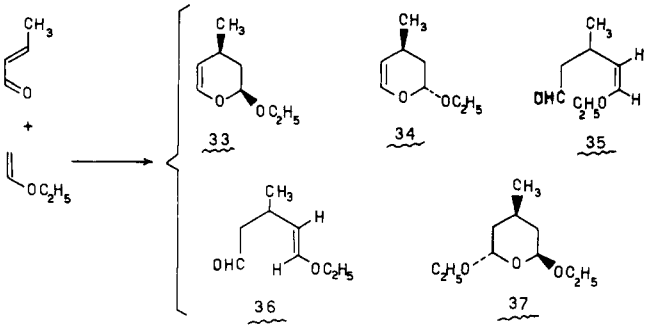
Because of the large amount of material concerning the reaction of α,β-unsaturated carbonyl compounds and vinyl ethers, we have considered separate sections depending on the nature of the carbonyl partner.

1. Acyclic Carbonyls

Several papers[72-86] deal with this topic because the dihydropyrans prepared by this powerful synthetic route (Table IV) are useful intermediates in the preparation of heterocyclic rings or open-chain carbonyl compounds. Unfortunately some papers do not consider the various configurations of the adducts, investigation of which could be a useful tool in order to infer the mechanism.

Some kinetic investigations were made[64,65,72] without taking the stereochemistry into account; these results will be considered later. The conformation of the adducts was inferred in the reaction of crotonaldehyde and ethyl vinyl ether[87] (Scheme VI).

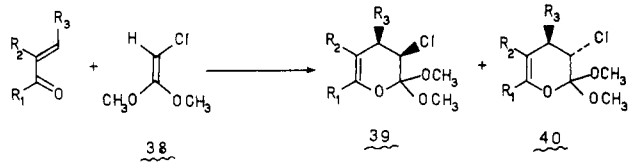
SCHEME VI



The yields are not reported, but **33** should predominate over **34** owing to the more favorable secondary orbital interactions in the transition state (see later). **37** is the product of a side reaction of the adducts, and the severe experimental conditions (3 hr at 225°) make it difficult to determine whether **35** and **36** are the primary adducts. These open-chain unsaturated derivatives, which are common in the enamines field, are rather unusual when dealing with vinyl ethers.

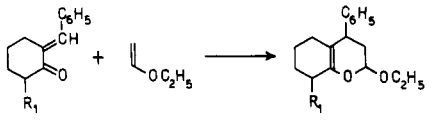
The reaction of chloroketene dimethyl acetal **38** with several unsaturated carbonyl compounds (a good synthetic route to α-pyrones) was investigated,[88] and the results are reported in the Scheme VII. When isolated, isomer **40** predominates.

SCHEME VII



2. Alicyclic Carbonyls

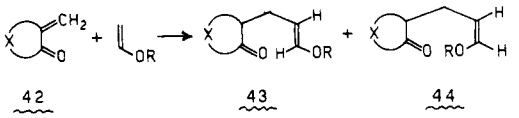
Alicyclic α,β-unsaturated carbonyl compounds react with vinyl ethers to form dihydropyran derivatives.[3,74]



A number of papers[74,88-94] dealing with α-methylene carbonyl derivatives belonging to two classes of compounds, α-methylenecyclanones (**41**) and α-quinone methides (**13**), are relevant.

These compounds can be prepared (A) as a stable compound; (B) from the thermal decomposition of a Mannich base; (C) from the thermal decomposition of Mannich bases obtained "in situ" from alcohols and a secondary amine; (D) from the thermal decomposition of alcohols; (E) from the photochemical cheletropic decomposition of benzofurans; (F) from the photochemical cheletropic decomposition of sultones. The condensed dihydropyran adducts of these 1,4-cycloadditions are reported in Table V.

Mühlstädt and Müller[91] reported that **42** gives, together with dihydropyran derivatives, two open-chain vinyl ethers **43** and **44** which sometimes become the only reaction products.



The formation of these open-chain compounds could have considerable importance from a theoretical point of view (evidence of zwitterionic intermediate which undergoes proton loss and gain!). However, the authors have proven that an equilibrium is reached at 190–195°, dihydropyrans ⇄ **43** ⇄ **44,** and therefore these are not the *primary* addition products. This was further supported by careful inspection of the reaction mixture; open-chain adducts began to appear only after the yield of the dihydropyrans reached 50%.

Similar products **36** and **37,** obtained by Spanish researchers,[87] could have the same origin.

3. Heterocyclic Carbonyls

a. Synthesis of Condensed Dihydropyran Heterocycles

The reaction of vinyl ethers with α,β-unsaturated carbonyl systems belonging to a heterocyclic ring seems to be a powerful and versatile approach to the synthesis of dihydropyran condensed with isoxazole,[95-97] indole,[95,98,99] pyrazole,[96,97,100-103] thiophene,[104] and chromene.[105]

The ease with which these systems undergo 1,4-cycloaddition is related to the aromaticity gained in the adducts. These substrates can be compared, to a certain extent, with the previously discussed quinonemethides.

Tables VI and VII collect the data of β-unsubstituted and β-substituted vinyl ethers, respectively, with yields being in general nearly quantitative.

b. Stereochemistry and Its Implication in Mechanism

First we must point out that reactions with β-unsubstituted vinyl ethers always give a mixture of two diastereoisomers with the cis isomer generally predominating.[101] The only exception is the reaction of 3-benzal-4-thiolen-2-one with ethyl vinyl ether,[104] but the low yield obtained (30%) opens the question whether only one isomer is formed and, if so, which one.

β-Methyl-substituted ethers retain their configuration in the adducts (Scheme VIII), and this suggests a concerted mechanism. This strict rule (which corresponds to the cis principle in Diels–Alder reactions) is violated only when the vinyl ether is dihydropyran. The original cis configuration is lost and some

SCHEME VIII

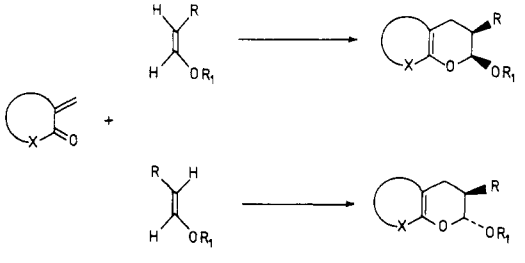


TABLE IV. Adducts from Acyclic α,β-Unsaturated Carbonyl Compounds and Vinyl Ethers

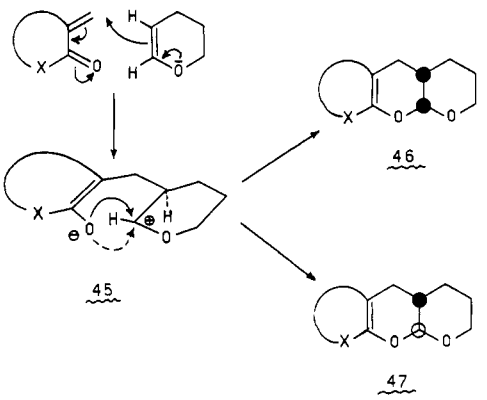
Carbonyl compounds			Vinyl ethers				Reaction conditions		Yield,	Mp	
R_1	R_2	R_3	R_4	R_5	R_6	R	T, °C	Time	%	(bp/mmHg), °C	Ref
H	H	H	H	H	H	CH_3	*a*	*a*	*a*	*a*	83
H	H	H	H	H	H	$CH_2CH(CH_3)_2$	160–180	*b*	88.5	*a*	83
H	H	H	H	H	H	Cyclohexyl	150	6 h	12	(70–92/2.5)	73
H	H	H	H	H	H	2,3-Epoxypropyl	180	3 h	77	73	81
H	H	H	H	H	H	CH_2CH_2O-2,3-epoxypropyl	180	3 h	70	102.5	86
H	H	H	H	H	H	$CH_2CH_2OCH_2CH_2CN$	180	3 h	78	125	86
H	H	H	H	H	H	C_6H_5	150	6 h	99	(62–62.5/19)	73
H	H	H	H	H	H	o-$CH_3C_6H_4$	150	6 h	78	(94–97/3)	73
H	H	H	H	H	H	m-$CH_3C_6H_4$	150	6 h	77	(148–150/11)	73
H	H	H	H	H	H	p-$CH_3C_6H_4$	150	6 h	87	(112–113/4)	73
H	H	H	H	H	H	2,4-Dimethyl-C_6H_3	150	6 h	52	(170/32)	73
H	H	H	H	H	H	2-$CH(CH_3)_2$-5-CH_3-C_6H_3	150	6 h	76	(144.5/6)	73
H	H	H	H	H	H	o-FC_6H_4	190	8 h	92	(136/10)	77
H	H	H	H	H	H	o-ClC_6H_4	190	8 h	85	(138/9)	77
H	H	H	H	H	H	p-ClC_6H_4	190	8 h	71	(112/2)	77
H	H	H	H	H	H	o-BrC_6H_4	190	8 h	74	(155/7)	77
H	H	H	H	H	H	p-BrC_6H_4	190	8 h	71	(160/13)	77
H	H	H	H	H	H	2,4-$(Cl)_2$-C_6H_3	190	8 h	67	(111/0.5)	77
H	H	H	H	H	H	2,4-$(Br)_2$-C_6H_3	190	8 h	14	62	77
H	H	H	H	H	H	CH_2(2-pyridyl)	130	10 h	58	(118/3)	85
H	H	H	H	H	H	CH_2(3-pyridyl)	160	6 h	82	(112/3)	85
H	H	H	H	H	H	CH_2(4-pyridyl)	130	4 h	43	(108–110/6)	85
H	H	H	H	H	OCH_3	CH_3	*a*	*a*	*a*	*a*	80
H	H	H	H	H	OCH_2CH_3	CH_2CH_3	125	14 h	70	(87/25)	82
H	H	H	H	H	$OCH(CH_3)_2$	$CH(CH_3)_2$	130	14 h	37	(77–77.5/11)	82
H	H	H	H	H	CH_2Cl	2,3-Epoxypropyl	180	3 h	30	72–73	81
H	H	H	H	H	$CH_2OCH_2CH{=}CH_2$	2,3-Epoxypropyl	180	3 h	62	104–105	81
H	H	H	H	H	$COOC_2H_5$	CH_2CH_3	180	6 h	49	(107–108/14)	75, 84
H	H	H	H	–$CH_2CH_2CH_2$–		CH_2CH_3	160	18 h	76	(85–87/18)	74
H	H	H	H	–$CH_2CH_2CH_2CH_2$–		CH_2CH_3	160	18 h	62	(98–101/15)	74
H	H	H	H	–$CH_2CH_2CH_2CH_2$–		CH_2CH_3	210	3 h	54.5	(103–104/20)	76
H	H	H	H	–$CH_2CH_2CH_2CH_2CH_2$–		CH_2CH_3	160	18 h	78	(120–122/22)	74
H	H	H	1-Adamantyl	H	H	CH_2CH_3	180	10 h	50	(105–110/0.4)	79
H	H	H	CH_2(1-adamantyl)	H	H	CH_2CH_3	180	9 h	73	(144–147/2)	79
H	CH_3	H	H	–$CH_2CH_2CH_2CH_2$–		CH_2CH_3	210	8.5 h	26	(114–116/22)	76
H	CH_2CH_3	H	H	–$CH_2CH_2CH_2CH_2$–		CH_2CH_3	210	5 h	26.5	(111–113/13)	76
H	H	CH_3	H	H	H	2,3-Epoxypropyl	180	3 h	85	69–70	81
H	H	CH_3	H	H	H	CH_2CH_2O-2,3-epoxypropyl	180	3 h	57	108–109	86
H	H	CH_3	H	H	H	$CH_2CH_2OCH_2CH_2CN$	180	3 h	58	129	86
H	H	CH_3	H	H	H	C_6H_5	180	10 h	75	(128/7)	78
H	H	CH_3	H	H	H	o-$CH_3C_6H_4$	180	10 h	70	(135/7)	78
H	H	CH_3	H	H	H	m-$CH_3C_6H_4$	180	10 h	65	(133/8)	78
H	H	CH_3	H	H	H	p-$CH_3C_6H_4$	180	10 h	72	(143.5/7)	78
H	H	CH_3	H	H	H	2,4-$(Me)_2C_6H_3$	180	10 h	68	(150/10)	78
H	H	CH_3	H	H	H	o-FC_6H_4	180	10 h	87	(136/10)	78

H	CH_3	H	$-CH_2CH_2CH_2CH_2-$	CH_2CH_3	210	10 h	17	(130–132/44)	76
H	C_6H_5	H	H	C_6H_5	180	10 h	63	85–88	78
H	C_6H_5	H	H	*o*-$CH_3C_6H_4$	180	10 h	58	90–92	78
H	C_6H_5	H	H	$CH_2(CH_2)_2CH_3$	150	*c*	*c*	*c*	65
H	C_6H_5	H	H	$CH_2CH(CH_3)_2$	150	*c*	*c*	*c*	65
H	C_6H_5	H	H	$CH_2(CH_2)_4CH_3$	150	*c*	*c*	*c*	65, 72
H	C_6H_5	H	H	$CH_2CH(CH_2CH_3)CH_2CH_2CH_2CH_3$	150	*c*	*c*	*c*	64, 65
H	C_6H_5	H	H	2,3-Epoxypropyl	180	3 h	63	127–128	81
H	C_6H_5	H	H	CH_2CH_2O-2,3-epoxypropyl	180	3 h	61	174–175	86
H	C_6H_5	H	H	$CH_2CH_2OCH_2CH_2CN$	180	3 h	59	190	86
H	C_6H_5	H	H	CH_2CH_3	130	20 h	47	(143/0.5)	65, 82
H	C_6H_5	H	H	$CH_2CH_2CH_2CH_2CH_3$	170	*c*	*c*	*c*	64
H	*m*-$NO_2C_6H_4$	H	H	$CH_2(CH_2)_6CH_3$	150	*c*	*c*	*c*	72
H	*p*-ClC_6H_4	H	H	$CH_2(CH_2)_6CH_3$	150	*c*	*c*	*c*	72
H	*m*-ClC_6H_4	H	H	$CH_2(CH_2)_6CH_3$	150	*c*	*c*	*c*	72
H	*p*-$CH_3C_6H_4$	H	H	$CH_2(CH_2)_6CH_3$	150	*c*	*c*	*c*	72
H	*p*-$OCH_3C_6H_4$	H	H	$CH_2(CH_2)_6CH_3$	150	*c*	*c*	*c*	72
H	CH_2(1-adamantyl)	H	H	CH_2CH_3	180	15 h	75	(133–135/0.2)	79
H	H	H	OCH_2CH_3	CH_2CH_3	120	12 h	35	(76–77/8)	82
H	H	Cl	OCH_3	CH_3	150	72 h	52	(125–130/0.05)	88
H	1-Adamantyl	H	H	CH_2CH_3	180	*a*	0		79
CH_3	H	H	OCH_2CH_3	CH_2CH_3	125	16 h	24	(83–84/17)	82
CH_3	1-Adamantyl	H	$COOC_2H_5$	CH_2CH_3	180	6 h	65	(125–126/30)	75, 84
H	H	H	H	CH_2CH_3	185	6 h	88	(138–140/0.5)	79

[a] Not reported in the original paper. [b] Continuous process. [c] Kinetic data only, reported in the original paper.

[2,3-trans] adducts **47** have been isolated in at least two cases[97] (Scheme IX). This deviation strongly supports a two-step mechanism most likely via the zwitterionic intermediate **45.**

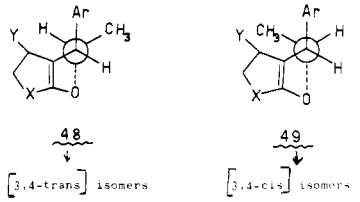
SCHEME IX



Why does only dihydropyran give rise to a zwitterion? Rationalization probably lies in the unusually low IP[37] and in the favorable n/π interactions with high π charge of the β carbon.[71] The former causes a lowering of the HOMO/LUMO separation with large frontier control[10] and enhanced electron transfer. The latter increases the asymmetry of the double bond, and both contribute to the development of nonsynchroneity in the reaction.[38]

The low value of the ratio of the isomer with loss of configuration to the isomer with retention of configuration (Table VII) indicates that the transition state of the concerted mechanism can only in part lose its character to give a discrete intermediate.

The nucleophilic attack is also responsible for the [3,4] configuration of the adducts. When the heterocyclic ring has a methyl or a phenyl group in position 3 (Table VII), [3,4-trans] isomers predominate. This is the result of steric interactions in the transition states **48** and **49.**



49 is strongly disfavored both by "gauche" interactions and the steric CH_3/Y interaction; therefore a [3,4-trans] isomer usually is predominant.[96]

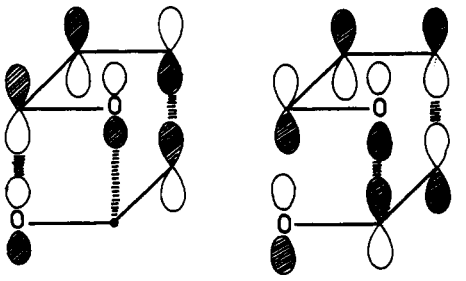
When the CH_3/Y interaction is weak, i.e., when Y is hydrogen as in **50,** cis ether gives mainly [3,4-cis] adducts **51,** whereas [3,4-trans] adducts **52** still predominate from trans ether[102] (Table VII) (Scheme X).

Since steric interactions cannot explain the stereochemical preferences a preferred **endo** t.s. was rationalized in terms of HOMO/LUMO versus LUMO/HOMO interactions. Schematic representation for the reagents is shown in Figure 7.

Obviously **53** (interaction between LUMO of the carbonyl compound and HOMO of the vinyl ether treated in a limit situation as an allyl anion) dominates and the endo transition state is preferred.

An *E* configuration of the reacting species is suggested for pyrazolones independent of their configuration in the ground state.[106] When both *Z* and *E* isomers (**55** and **56**) are available, the latter gives the adducts and the former is recovered unchanged (Scheme XI).[102]

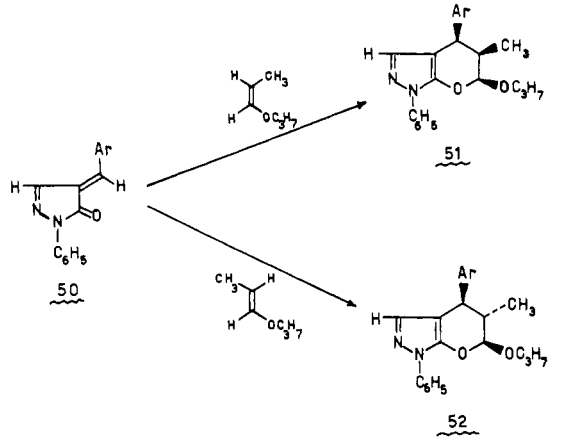
From the reaction of oxindolideneacetophenones **57** and



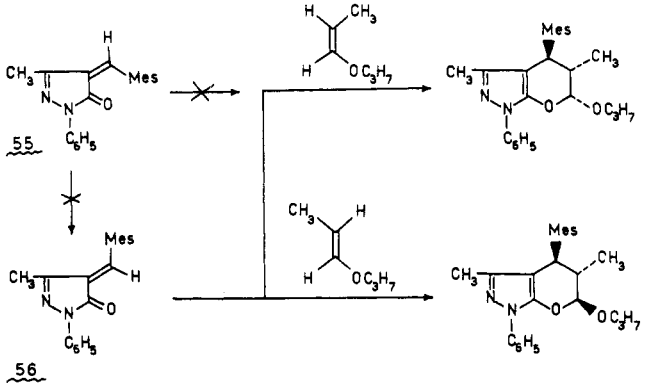
53 54

Figure 7. Schematic representation of HOMO/LUMO (**53**) and LUMO/HOMO (**54**) interactions between α,β-unsaturated carbonyl compounds and vinyl ethers.

SCHEME X

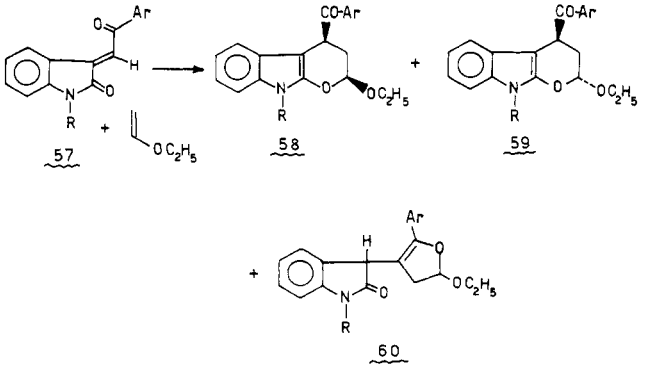


SCHEME XI

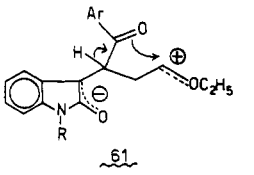


vinyl ether,[99] in addition to the dihydropyran adduct **58** and **59, 60** is formed, and it was demonstrated to be a primary reaction product (Scheme XII).

SCHEME XII



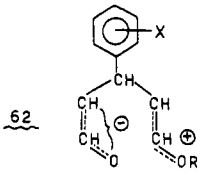
The formation of the dihydrofuran adduct **60** occurs via a two-step mechanism probably involving a dipolar intermediate **61.**



This behavior can be rationalized as for the previously mentioned dihydropyran. The electron-attracting acyl group causes lowering of the HOMO and the LUMO of the unsaturated carbonyl (which results in a diminished separation of the frontier orbitals of the reagents) and increases the distortion of its symmetry. As previously seen, these two effects favor the development of asynchroneity in the cycloaddition.

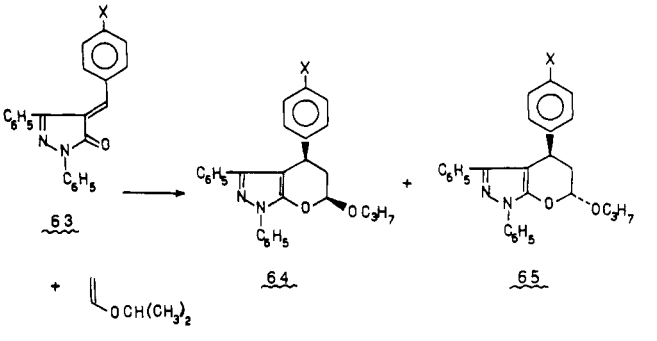
4. Kinetic Data

Kinetic measurements on the reaction already mentioned between aryl-substituted cinnamaldehydes and octyl vinyl ether[72] at 150° followed the Hammett relationship log $k/k_0 = \sigma\rho$, with a ρ value of +0.71. In spite of the small value of the slope, a rather random correlation at higher temperature and the rates of the reaction not being affected by the polarity of solvents,[107] the authors suggest a mechanism involving the dipolar intermediate **62.**



A recent investigation was performed in the heterocyclic field using various 1,3-diphenyl-4-(*p*-substituted)arylidene-5-pyrazolones **63** and isopropyl vinyl ether.[103] From the overall reaction rate both k_{cis} and k_{trans} (second-order rate constants for cis and trans adducts **64** and **65**) have been determined (Scheme XIII).

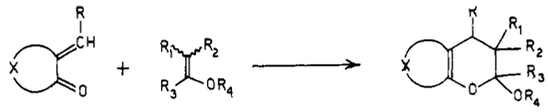
SCHEME XIII



The rate increases from X = $N(CH_3)_2$ to NO_2 by a factor of about 500, and correlation was obtained only with σ^+ constants. The dependence from enhanced substituent constants cannot be explained by a traditional intermediate like **62** but can probably be rationalized if one accepts Sustmann's approximation[17] of eq 2; i.e., coefficients do not vary for a homogeneous series of reagents, and therefore ΔE is a function of the frontier orbitals separation only. For a direct Diels–Alder reaction the first term can be neglected, and for inverse reaction only the first term needs to be considered.[108] Therefore, the logarithm of the rate constants plotted against the

$$\Delta E = A\gamma^2\left[\frac{1}{E_{Ho}^{ef} - E_{Lu}^{ad}} + \frac{1}{E_{Ho}^{ad} - E_{Lu}^{ef}}\right] \quad (3)$$

TABLE V. Adducts from Alicyclic α,β-Unsaturated Carbonyl Compounds and Vinyl Ethers



α,β-Unsaturated cyclanones			Vinyl ether				Reaction condition[f]			Mp	
Origin	–X–	R	R_1	R_2	R_3	R_4	T, °C	Time	Yield, %	(bp/mmHg), °C	Ref
A	$-(CH_2)_3-$	H	H	H	H	CH_2CH_3	*a*	*a*	19	(89–91/14)	91
B	$-(CH_2)_3-$	H	H	H	H	CH_2CH_3	220	1.5 h	19	(115/14)	94
A	$-(CH_2)_3-$	H	H	H	H	$CH_2CH(CH_3)_2$	235	30–60′	17	(43–45/0.25)	90
B[b]	$-(CH_2)_4-$	H	H	H	H	CH_2CH_3	175	7 h	33	(111–113/17)	89
B[b]	$-(CH_2)_4-$	H	H	H	H	CH_2CH_3	265	1.5 h	61	(101–102/10)	94
A	$-(CH_2)_4-$	C_2H_5	Cl[c]	H	OCH_3	CH_3	150	72 h	32	(80–85/0.01)	88
A	$-(CH_2)_4-$	C_6H_5	H	H	H	CH_2CH_3	210	24 h	84	(133–137/0.5)	74
A	$-CH(CH_3)(CH_2)_3-$	C_6H_5	H	H	H	CH_2CH_3	210	24 h	87	(129–130/0.5)	74
A	$-(CH_2)_5-$	H	H	H	H	CH_2CH_3	*a*	*a*	36	(52–55/0.25)	91
B	$-(CH_2)_5-$	H	H	H	H	CH_2CH_3	270	2 h	60	(85/15)	94
A	$-(CH_2)_5-$	H	H	H	H	$CH_2CH(CH_3)_2$	235	30–60′	55	(68–69/0.12)	90
A	$-(CH_2)_5-$	H	H	H	H	$CH_2(CH_2)_2CH_3$	235	30–60′	50	(73–75/0.15)	90
A	$-(CH_2)_5-$	H	H	H	H	C_6H_5	235	30–60′	12	49–50	90
A	$-(CH_2)_6-$	H	H	H	H	$CH_2CH(CH_3)_2$	235	30–60′	63	(72–74/0.12)	90
A	$-(CH_2)_7-$	H	H	H	H	$CH_2CH(CH_3)_2$	*a*	*a*	45	(85–88/0.2)	91
A	$-(CH_2)_8-$	H	H	H	H	$CH_2CH(CH_3)_2$	*a*	*a*	65	(92–93/0.15)	91
A	$-(CH_2)_{10}-$	H	H	H	H	$CH_2CH(CH_3)_2$	235	30–60′	57	Dec	90
A	2-Methylene-1-indanone	H	H	H	H	$CH_2CH(CH_3)_2$	*a*	*a*	30	*a*	91
A	2-Methylene-1-tetralone	H	H	H	H	$CH_2CH(CH_3)_2$	235	30–60′	41	Dec	90
A	2-Methylenenorpinone	H	H	H	H	$CH_2CH(CH_3)_2$	*a*	*a*	41	(95–96/0.4)	91
B	$-(CH)_4-$	H	H	H	H	CH_2CH_3	200	4 h	65	(127–133/27)	74
B[b]	$-(CH)_4-$	H	H	$-(CH_2)_4-$		H	200	2 h	70	98	92
B[d]	$-(CH)_4-$	H	H	$-(CH_2)_4-$		H	200	2 h	37	98	92
C	$-(CH)_4-$	H	H	$-(CH_2)_4-$		H	200	2 h	76	98	92
D	$-(CH)_4-$	H	H	$-(CH_2)_4-$		H	200	2 h	35	98	92
D	$-(CH)_4-$	H	H	$-(CH_2)_4-$		CH_2CH_3[e]	190	10 h	71	(160–162/20)	92
E	$-(CH)_4-$	H	H	H	OCH_3	CH_3	rt		>90	*a*	93
F	$-(CH)_4-$	H	H	H	OCH_3	CH_3	rt		>90	*a*	93

[a] Not reported in the original paper. [b] Dimethylamino derivative. [c] Cis isomer only. [d] Diethylamino derivative. [e] Mixture of cis and trans isomers, but the latter formed from acidic isomerization of the former. [f] rt = room temperature; h = hours; ′ = minutes.

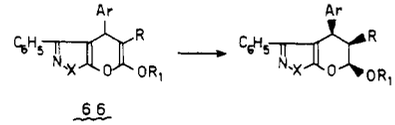
HOMO/LUMO separation decreases in the former and increases in the latter case.

This behavior has already been verified for direct Diels–Alder reactions,[108] and the above reported kinetic results can fit the same model if one considers that E_{Ho} is a constant (same vinyl ether) and E_{Lu} is a function of the substituent on the aryl group only in an homogeneous series of derivatives. If the substituents act on MO energies both with inductive and mesomeric effects, it seems a reasonable approximation to represent the energy variation by σ^+ constants.

Further support was gained from the rate constants of the reactions between 1,3-diphenyl-4-benzal-5-pyrazolone (**64**, X = H) and various alkyl vinyl ethers. A quantitative correlation with their IP's,[37] determined by charge-transfer complexes, was unsatisfactory, but a correlation was obtained with the σ^* constants of the alkyl groups of the vinyl ether. Reinvestigation of IP's by more modern techniques will probably find a correlation with the inductive effect of substituents.

B. Acetylenic Ethers

Few papers report the reaction of α,β-unsaturated carbonyl compounds with acetylenic ethers, and only 1,4-cycloadducts **66** have been isolated[96,100] (Table VIII). The stereospecific reduction of **66** demonstrated the *cis* configuration of some previously described adducts (Tables VI and VII).

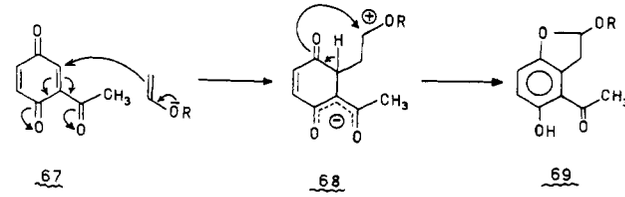


66

C. Alternative Reactions

α,β-Unsaturated carbonyl derivatives which also have a *p*-quinone system **67** show a very different behavior since no 1,4-cycloaddition occurs. Nucleophilic attack of the unsaturated ether[109] (either cyclic or acyclic, ethylenic or acetylenic) occurs in the more electrophilic position, and the zwitterion intermediate **68** is formed, stabilized mainly by resonance. Electrophilic attack on the oxygen atom not involved in the stabilization with a proton loss and gain gives the benzofuran or dihydrobenzofuran derivatives **69**, in accordance with a 1,3-cycloaddition (Scheme XIV).

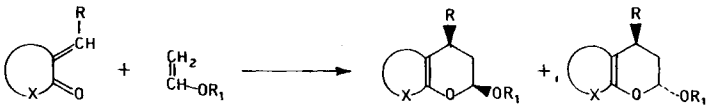
SCHEME XIV



67 68 69

A remarkable analogy with the behavior of oxindolidene acetophenones **57** (section VI.A.3) is evident: a doubly unsaturated O=C—C=C—C=O system occurs in both substrates, and the presence of a dipolar intermediate can be ra-

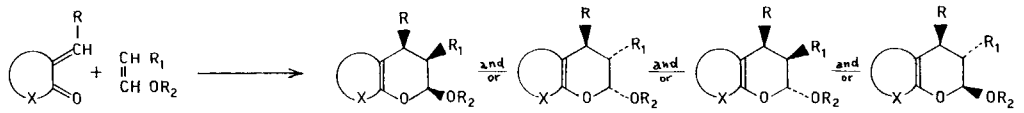
TABLE VI. Adducts from Heterocyclic α,β-Unsaturated Carbonyl Compounds and β-Unsubstituted Vinyl Ethers



Heterocyclic ring	R	R_1	Reaction conditions[l] Solvent	T, °C	Time	Total yield, %	Cis adduct Yield, %	Cis adduct Mp, °C	Trans adduct Yield, %	Trans adduct Mp, °C	Ref
3-Phenyl-5-isoxazolone	C_6H_5	CH_3	*a*	45	10 d	*b*	*b*	176	*b*	143–144	95
3-Phenyl-5-isoxazolone	C_6H_5	CH_2CH_3	*a*	36	4 d	97	*b*	115–116	*b*	82–83	95
3-Phenyl-5-isoxazolone	*o*-$NO_2C_6H_4$	CH_3	*a*	20	5 d	*c*	*b*	156–157	*b*	171–172	95
3-Phenyl-5-isoxazolone	*o*-$NO_2C_6H_4$	CH_2CH_3	*a*	36	4 h	*c*	*b*	151–152	*b*	135–136	95
Oxindole	COC_6H_5	CH_2CH_3	*a*	100	14–17 h	~75[d]	35–60	140–141			99
Oxindole	COC_6H_4-*p*-NO_2	CH_2CH_3	*a*	100	65 h	48	34	153–155	14	182–183	99
Oxindole	COC_6H_4-*p*-OCH_3	CH_2CH_3	*a*	100	47 h	71[e]	50	155–156			99
1-Acetyloxindole	C_6H_5	CH_2CH_3	*a*	140	48 h	89	*b*	114.5–115.5	*b*	134–135	95
1-Acetyloxindole	2-Furyl	CH_2CH_3	*a*	140	7 d	75	*b*	115–116[f]	*b*	112–113.5[f]	98
1-Acetyloxindole	2-Pyridyl	CH_2CH_3	*a*	90	24 h	69	*b*	140–141[f]	*b*	146–147[f]	98
1-Acetyloxindole	4-Pyridyl	CH_2CH_3	*a*	90	24 h	85	57	144–146	43	151–153	98
1-Acetyloxindole	CN	CH_2CH_3	*a*	100	16 h	97	77	158–159	20	139–141	98
1-Acetyloxindole	COC_6H_5	CH_2CH_3	*a*	100	45′	89[g]	76	154–155	8	131–132	99
1-Acetyloxindole	COC_6H_4-*p*-NO_2	CH_2CH_3	*a*	100	3 h	80	67	171–172	13	184–185	99
1-Acetyloxindole	COC_6H_4-*p*-OCH_3	CH_2CH_3	*a*	100	1 h	90[h]	76	123–124	8	175–176	99
1-Methyloxindole	COC_6H_5	CH_2CH_3	*a*	100	22 h	75[i]	50	115–116	9	114–115	99
1-Methyloxindole	COC_6H_4-*p*-NO_2	CH_2CH_3	*a*	100	96 h	29	17	161–162	12	153–154	99
1-Methyloxindole	COC_6H_4-*p*-OCH_3	CH_2CH_3	*a*	100	12 h	70[j]	35	129–131	7	150–152	99
1-Phenyl-5-pyrazolone	C_6H_5	CH_3	*a*	80	50 h	*c*	80	115–116	20	125–126	101
1-Phenyl-5-pyrazolone	C_6H_5	CH_2CH_3	*a*	80	30 h	*c*	73	87–88	27	104–105	101
1-Phenyl-5-pyrazolone	C_6H_5	$CH(CH_3)_2$	*a*	80	60 h	*c*	60	88–89	40	115	101
1-Phenyl-5-pyrazolone	C_6H_5	$C(CH_3)_3$	*a*	80	7 d	*c*	42	119–120	58	122–123	101
1-Phenyl-3-methyl-5-pyrazolone	C_6H_5	CH_3	*a*	80	40 h	*c*	69	103–104	31	110–111	101
1-Phenyl-3-methyl-5-pyrazolone	C_6H_5	CH_2CH_3	*a*	80	46 h	*c*	49	110–111	51	97–98	101
1-Phenyl-3-methyl-5-pyrazolone	C_6H_5	$CH(CH_3)_2$	*a*	80	60 h	*c*	60	81–82	40	82–83	101
1-Phenyl-3-methyl-5-pyrazolone	C_6H_5	$C(CH_3)_3$	*a*	80	7 d	*c*	65	83–84	35	114–115	101
1,3-Diphenyl-5-pyrazolone	C_6H_5	CH_3	*a*	80	40 h	*c*	51.6	161–162	48.4	(230/0.4)[m]	101, 103
1,3-Diphenyl-5-pyrazolone	C_6H_5	CH_2CH_3	*a*	36	24 h	*c*	49.4	163–164	50.6	97–98	100, 101, 103
1,3-Diphenyl-5-pyrazolone	C_6H_5	$CH(CH_3)_2$	*a*	80	48 h	*c*	55.9	141–142	44.1	119–120	101, 103
1,3-Diphenyl-5-pyrazolone	C_6H_5	$C(CH_3)_3$	*a*	80	5 d	*c*	71.4	140–141	29.6	112–113	101–103
1,3-Diphenyl-5-pyrazolone	C_6H_5	$CH_2(CH_2)_2CH_3$	Benzene	70		*c*	52.6	123	47.4	92	103
1,3-Diphenyl-5-pyrazolone	C_6H_5	$CH_2CH(CH_3)_2$	Benzene	70		*c*	47.6	161	52.4	88	103
1,3-Diphenyl-5-pyrazolone	*o*-$NO_2C_6H_4$	CH_2CH_3	*a*	36	40 h	*c*	*b*	154	*b*	119–120	100
1,3-Diphenyl-5-pyrazolone	*p*-$CH_3OC_6H_4$	CH_2CH_3	*a*	36	26 d	*c*	*b*	150–151	*b*	106	100
1,3-Diphenyl-5-pyrazolone	*p*-$NO_2C_6H_4$	$CH(CH_3)_2$	Benzene	70		*c*	64.6	99 dec	35.4	147	103
1,3-Diphenyl-5-pyrazolone	*p*-$COOCH_3C_6H_4$	$CH(CH_3)_2$	Benzene	70		*c*	52.9	158	47.1	152	103
1,3-Diphenyl-5-pyrazolone	*p*-BrC_6H_4	$CH(CH_3)_2$	Benzene	70		*c*	56.6	136	43.4	145	103
1,3-Diphenyl-5-pyrazolone	*p*-ClC_6H_4	$CH(CH_3)_2$	Benzene	70		*c*	56.2	132	43.8	135	103
1,3-Diphenyl-5-pyrazolone	*p*-FC_6H_4	$CH(CH_3)_2$	Benzene	70		*c*	57.5	147	42.5	128	103
1,3-Diphenyl-5-pyrazolone	*p*-$CH_3C_6H_4$	$CH(CH_3)_2$	Benzene	70		*c*	57.9	131	42.1	117	103
1,3-Diphenyl-5-pyrazolone	*p*-$CH_3OC_6H_4$	$CH(CH_3)_2$	Benzene	70		*c*	62.0	128	38.0	92	103
1,3-Diphenyl-5-pyrazolone	*p*-$N(CH_3)_2C_6H_4$	$CH(CH_3)_2$	Benzene	70		*c*	69.9	128	30.1	179–180 dec	103
4-Thiolen-2-one	C_6H_5	CH_2CH_3	*a*	Rt	7 d	39	39	63[f]			104
Chromone[k]	H	CH_2CH_3	*a*	160	4 h	58	58	(114/0.4)[m]			105

[a] Excess vinyl ether as solvent. [b] Not reported in the original paper. [c] Nearly quantitative. [d] Including **60** type adduct (12–18%; mp 159–160°). [e] See footnote *d* (21%; mp 154–155°). [f] Configuration not determined. [g] See footnote *d* (5%; mp 133–134°). [h] See footnote *d* (6%; mp 139–140°). [i] See footnote *d* (16%; oil). [j] See footnote *d* (28%; oil). [k] Obtained by decomposition of the Mannich base. [l] d = days; h = hours; ′ = minutes. [m] Boiling point.

TABLE VII. Adducts from Heterocyclic α,β-Unsaturated Carbonyl Compounds and β-Substituted Vinyl Ethers



Heterocyclic ring	R	Vinyl ether Config	R_1	R_2	Reaction conditions[a] T, °C	Time	Cis (2,3) Cis (3,4) Yield, %	Mp, °C	Cis (2,3) Trans (3,4) Yield, %	Mp, °C	Trans (2,3) Cis (3,4) Yield, %	Mp, °C	Trans (2,3) Trans (3,4) Yield, %	Mp, °C	Ref
3-Phenyl-5-isoxazolone	C_6H_5	Cis	CH_3	$CH_2CH_2CH_3$	80	16 h	5	119–120	95	115–116					96
3-Phenyl-5-isoxazolone	C_6H_5	Trans	CH_3	$CH_2CH_2CH_3$	80	12 h					3	91–92	97	136–137	96
3-Phenyl-5-isoxazolone	o-$NO_2C_6H_4$	Cis	CH_3	$CH_2CH_2CH_3$	80	8 h			100	92–93					96
3-Phenyl-5-isoxazolone	o-$NO_2C_6H_4$	Trans	CH_3	$CH_2CH_2CH_3$	80	8 h					10	138–139	90	124–125	96
3-Phenyl-5-isoxazolone	C_6H_5		$-CH_2CH_2CH_2-$		120	200 h	15	190–191	39	185–186	6	203–204			97
1-Phenyl-5-pyrazolone	C_6H_5	Cis	CH_3	$CH_2CH_2CH_3$	80	60 h	85	104–105	15	94–95					102
1-Phenyl-5-pyrazolone	C_6H_5	Trans	CH_3	$CH_2CH_2CH_3$	80	30 h					16	69–70	84	110–111	102
1-Phenyl-5-pyrazolone	p-$NO_2C_6H_4$	Cis	CH_3	$CH_2CH_2CH_3$	80	30 h	90	102–103	10	158–159					102
1-Phenyl-5-pyrazolone	p-$NO_2C_6H_4$	Trans	CH_3	$CH_2CH_2CH_3$	80	15 h					11	152.5–153.5	89	185–186	102
1-Phenyl-5-pyrazolone	p-$OCH_3C_6H_4$	Cis	CH_3	$CH_2CH_2CH_3$	80	8 d	77	95–96	23	146–147					102
1-Phenyl-5-pyrazolone	p-$OCH_3C_6H_4$	Trans	CH_3	$CH_2CH_2CH_3$	80	5 d					19	109–110	81	143–144	102
1-Phenyl-5-pyrazolone	2,4,6-$(Me)_3C_6H_2$	Cis	CH_3	$CH_2CH_2CH_3$	80	30 d			100	Oil					102
1-Phenyl-5-pyrazolone	2,4,6-$(Me)_3C_6H_2$	Trans	CH_3	$CH_2CH_2CH_3$	80	8 d							100	128–129	102
1-Phenyl-3-methyl-5-pyrazolone	C_6H_5	Cis	CH_3	$CH_2CH_2CH_3$	80	90 h	18	92–93	82	74–75					102
1-Phenyl-3-methyl-5-pyrazolone	C_6H_5	Trans	CH_3	$CH_2CH_2CH_3$	80	48 h					11	186–187	89	163–164	102
1-Phenyl-3-methyl-5-pyrazolone	p-$NO_2C_6H_4$	Cis	CH_3	$CH_2CH_2CH_3$	80	40 h	14	149–150	86	125–126					102
1-Phenyl-3-methyl-5-pyrazolone	p-$NO_2C_6H_4$	Trans	CH_3	$CH_2CH_2CH_3$	80	15 h					12	107–108	88	133–134	102
1-Phenyl-3-methyl-5-pyrazolone	p-$OCH_3C_6H_4$	Cis	CH_3	$CH_2CH_2CH_3$	80	6 d	25	104–105	75	110–111					102
1-Phenyl-3-methyl-5-pyrazolone	p-$OCH_3C_6H_4$	Trans	CH_3	$CH_2CH_2CH_3$	80	5 d					15	104–105	85	124–125	102
1-Phenyl-3-methyl-5-pyrazolone	2,4,6-$(Me)_3C_6H_2$	Cis	CH_3	$CH_2CH_2CH_3$	80	35 d			100	124–125					102
1-Phenyl-3-methyl-5-pyrazolone	2,4,6-$(Me)_3C_6H_2$	Trans	CH_3	$CH_2CH_2CH_3$	80	70 h							100	145–146	102
1,3-Diphenyl-5-pyrazolone	C_6H_5	Cis	CH_3	$CH_2CH_2CH_3$	80	18 h	7	129–130	93	137–138					96, 102
1,3-Diphenyl-5-pyrazolone	C_6H_5	Trans	CH_3	$CH_2CH_2CH_3$	80	12 h							~100	180–181	96, 102
1,3-Diphenyl-5-pyrazolone	o-$NO_2C_6H_4$	Cis	CH_3	$CH_2CH_2CH_3$	80	12 h	<3	134–135	>97	96–97					96
1,3-Diphenyl-5-pyrazolone	o-$NO_2C_6H_4$	Trans	CH_3	$CH_2CH_2CH_3$	80	8 h							~100	152–153	96
1,3-Diphenyl-5-pyrazolone	p-$NO_2C_6H_4$	Cis	CH_3	$CH_2CH_2CH_3$	80	12 h	5	130–131	95	168–169					102
1,3-Diphenyl-5-pyrazolone	p-$NO_2C_6H_4$	Trans	CH_3	$CH_2CH_2CH_3$	80	6 h					<3	241–242	>97	221–222	102
1,3-Diphenyl-5-pyrazolone	p-$OCH_3C_6H_4$	Cis	CH_3	$CH_2CH_2CH_3$	80	48 h	10	97–98	90	140–141					96, 102
1,3-Diphenyl-5-pyrazolone	p-$OCH_3C_6H_4$	Trans	CH_3	$CH_2CH_2CH_3$	80	24 h					3	129–130	97	145–146	96, 102
1,3-Diphenyl-5-pyrazolone	2,4,6-$(Me)_3C_6H_2$	Cis	CH_3	$CH_2CH_2CH_3$	80	40 d			100	145–146					102
1,3-Diphenyl-5-pyrazolone	2,4,6-$(Me)_3C_6H_2$	Trans	CH_3	$CH_2CH_2CH_3$	80	7 d							100	177–178	102
1-Phenyl-5-pyrazolone	C_6H_5		$-CH_2CH_2CH_2-$		120	200 h	52	165–166	32	118–119					97
1-Phenyl-3-methyl-5-pyrazolone	C_6H_5		$-CH_2CH_2CH_2-$		120	200 h	42	211–212	23	128–129	2	194–195			97
1,3-Diphenyl-5-pyrazolone	C_6H_5		$-CH_2CH_2CH_2-$		120	200 h	26	181–182	47	204–205					97
1,3-Diphenyl-5-pyrazolone	p-ClC_6H_4		$-CH_2CH_2CH_2-$		120	200 h	32	245–246	53	203–204					97
1,3-Diphenyl-5-pyrazolone	p-$OCH_3C_6H_4$		$-CH_2CH_2CH_2-$		120	200 h	29	200–201	53	226–227					97

[a] Excess vinyl ether as solvent. h = hours; d = days.

TABLE VIII. Adducts with Acetylenic Ethers

X	Ar	R	R_1	Reaction conditions		Yield, %	Mp, °C	Ref
				T, °C	Time			
NC_6H_5	C_6H_5	H	CH_2CH_3	55	12 h	95	152–152.5	100
NC_6H_5	o-$NO_2C_6H_4$	H	CH_2CH_3	55	48 h	93	161	100
NC_6H_5	p-$OCH_3C_6H_4$	H	CH_2CH_3	55	5 d	83.5	155–156	100
O	C_6H_5	CH_3	$CH_2CH_2CH_3$	70	20 h	*a*	103–104	96
O	o-$NO_2C_6H_4$	CH_3	$CH_2CH_2CH_3$	70	5 h	*a*	139–140	96
NC_6H_5	C_6H_5	CH_3	$CH_2CH_2CH_3$	70	48 h	~100	127–128	96
NC_6H_5	o-$NO_2C_6H_4$	CH_3	$CH_2CH_2CH_3$	70	8 h	*a*	140–141	96
NC_6H_5	p-$OCH_3C_6H_4$	CH_3	$CH_2CH_2CH_3$	70	7 d	*a*	93–94	96

[a] Not reported in the original paper.

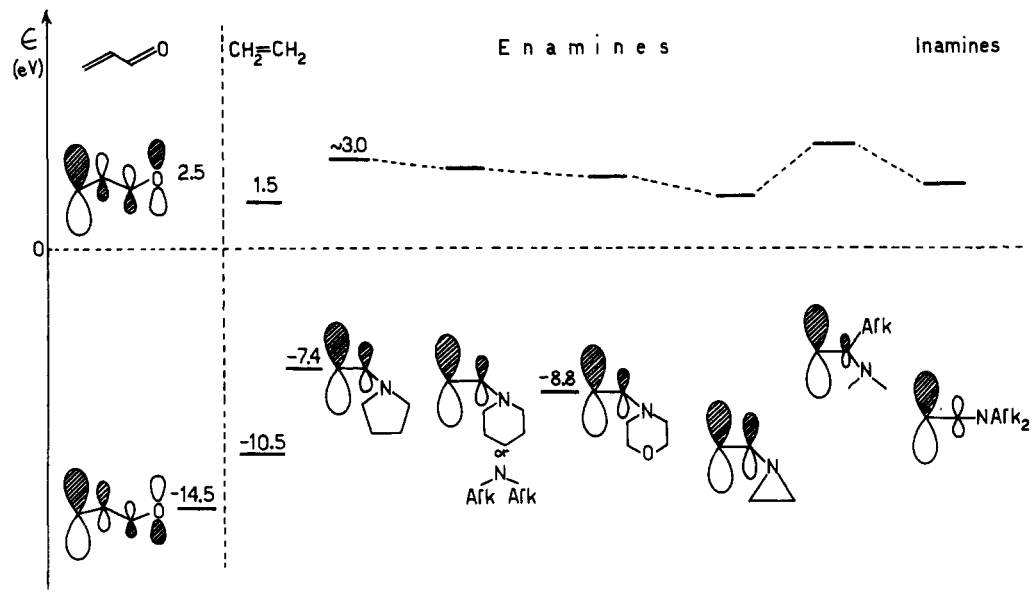


Figure 8. Schematic representation of frontier orbital energies and coefficients for acrolein and unsaturated amines. (For most cases these are estimated from substituent effects.)

tionalized either in terms of charge delocalization or large frontier orbital controlled reactions.

VII. Unsaturated Amines

It is well known that enamines and ynamines are strong nucleophiles, but unfortunately little work has been done on the determination of the MO parameters and levels. Nevertheless, although this does not allow a more rigorous treatment, a qualitative prediction can be made if one considers that enamines have a very low IP.[17,62]

The nucleophilicity, and to a certain extent the IP's, seems to be a function of the nitrogen residue: pyrrolidino[17] > piperidino ≃ dialkylamino > morpholino[17] > aziridino (this order is also supported by NMR chemical shifts of the β protons[110]). The same effect on the nucleophilicity is caused by alkyl residues on the double bond[111] in the order: α-alkyl > unsubstituted ≃ α,β-disubstituted > β-alkyl-substituted.

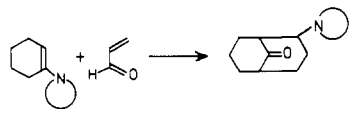
On this basis a rough schematic diagram is proposed in Figure 8 with ynamines at a lower level than enamines.[62]

The asymmetry of the coefficients increases in the same order,[111] and combined with the large frontier control and enhanced charge transfer due to the low HOMO/LUMO separation this provides favorable conditions for the formation of a zwitterion, at least for stronger nucleophilic enamines. Therefore it is not surprising that dipolar intermediates are rather popular in enamine cycloaddition. Furthermore, if a dipolar species is formed in the reaction this can collapse to a 1,4-cycloadduct or can form some different products. This variety of reactions represents the most interesting feature in the field of enamines and ynamines.

A. Enamines

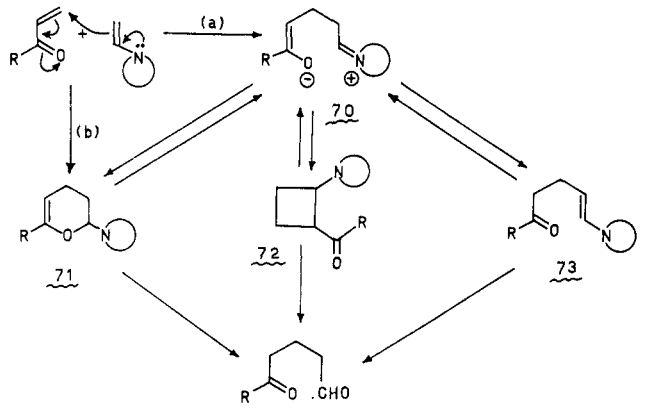
1. Historical Survey

The Robinson annelation reaction,[112] especially in the Stork modification where an enamine acts as the active methylene component,[113,114] has been known for a long time to be the source of various monocyclic and bicyclic adducts which have been claimed to be the primary products formed in the reaction.



In 1963 the fundamental paper by Stork[115] showed that the mechanism consisted of nucleophilic attack of the enamine on the β position of the unsaturated carbonyl derivative. The zwitterionic intermediate **70** could be in equilibrium with the dihydropyran **71**, the cyclobutyl ketone **72**, or the Michael-type adduct **73** (Scheme XV). The choice between the various structures is not well defined since the intermediates usually undergo trans enamination[116–118] or are hydrolyzed to carbonyl compounds.[119] Unfortunately these transformations cannot show the true intermediate. Route b, i.e., a four-center Diels–Alder reaction already proposed by Opitz,[120] is considered as an alternative.

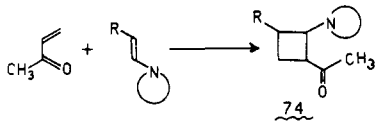
SCHEME XV



The discussion concerning these alternatives filled the literature of the subsequent years and in 1968 the very small carbonyl absorption in the ir of the initial intermediate in the reaction between acrolein and enamines was "noted with surprise".[121] The subject of the forthcoming pages will be a report of this debate.

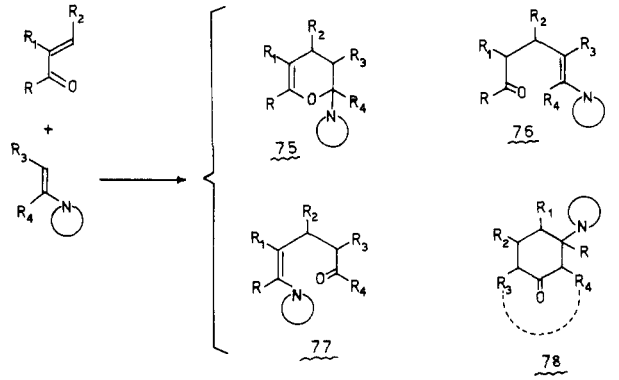
2. Acyclic Carbonyls

The reaction of methyl vinyl ketone with enamines was first analyzed by Fleming and Harley-Mason[122] and these authors proposed a cyclobutane structure for the adduct **74** on the basis of its spectroscopic behavior.



This approach had to be revised when Schut and Liu[123] isolated good yields of dihydropyrans **75** as precursors of the Stork bicyclic adducts. Opitz[124] also showed that dihydropyran adducts were formed when acrolein reacted with enamines. In addition to **75,** variable quantities of enamine-type byproducts **76** and **77** or Stork bicyclic derivatives **78** were sometimes obtained (Scheme XVI).

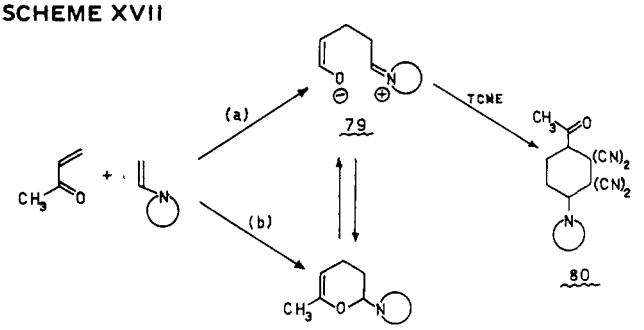
SCHEME XVI



The Michael adducts **76** were isolated from methyl vinyl ketone[124] (32% yield), whereas the rearrangement product **77** was isolated if the enamine was β,β-disubstituted.[124] The Stork bicyclic adducts are sometimes isolated directly,[123] but, since **75** is usually converted into **78** on heating, milder conditions would probably allow the precursor to be isolated every time.

Faithful to his previous reaction model, Opitz described the formation of dihydropyrans as a Diels–Alder reaction.[124] On these bases, Fleming reinvestigated the reaction of methyl vinyl ketone and enamines[125] and showed the presence of a stable dihydropyran. The novelty, however, was the proposed presence of the zwitterion **79** somewhere in the reaction sequence; this was captured with tetracyanoethylene (TCNE) to give **80.** Obviously two possibilities exist (Scheme XVII): the

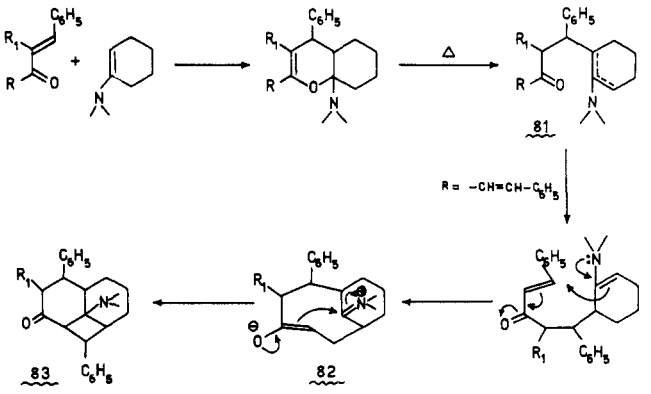
SCHEME XVII



dipolar species is the intermediate of the reaction (route a) or is only in equilibrium with the six-membered ring which therefore remains the primary reaction product (route b). This mechanism was subsequently distorted by the later literature and usually Fleming's paper is quoted when a zwitterion has to be "demonstrated".

The dihydropyrans rearrange to Michael-type adducts under more severe conditions (Scheme XVIII). The first observation by Schut and Liu[123] was further confirmed by Risaliti[126] who noted the rearrangement to **81** in refluxing benzene. When R = $C_6H_5CH{=}CH-$, the Michael-type adducts can undergo an intramolecular nucleophilic attack of the enamine group to the α,β-unsaturated carbonyl system.[127] The intermediate **82** cyclizes to the fused cyclobutane adduct **83,** which seems to be the only four-membered adduct in this section. This dihydropyran → Michael adduct conversion involving a zwitterion was considered as further proof of the polar character of the cycloaddition with enamines.

SCHEME XVIII



Nevertheless, only Risaliti[126] proved the presence of a dipolar intermediate as the reaction of cyclohexanone enamines with both cis and trans α,β-unsaturated ketones **84** and

SCHEME XIX

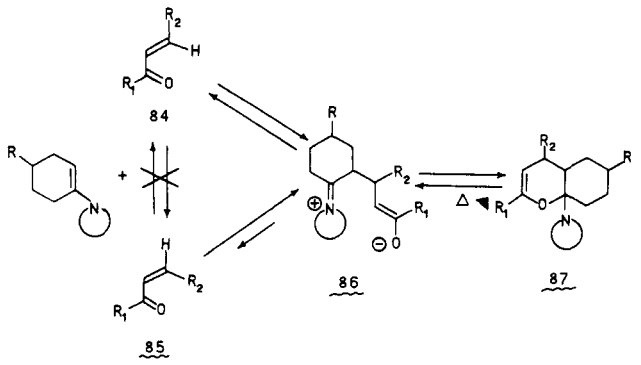
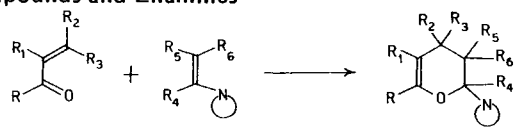


TABLE IX. Adducts from Acyclic α,β-Unsaturated Carbonyl Compounds and Enamines

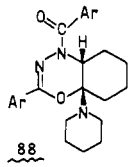


α,β-Unsaturated carbonyl				Enamine				Reaction conditions			Yield,		
R	R_1	R_2	R_3	R_4	R_5	R_6	N ring	Solvent	T, °C	Time	%	Mp (bp/mmHg), °C	Ref
H	H	H	H	H	CH_3	H	Piperidine	Ether	0+rt	1+21 h	86	(104–105/12)	120, 124
H	H	H	H	H	CH_3CH_2	H	Diethylamine	*a*	*a*	*a*	81	(45–46/1)	120, 124
H	H	H	H	H	CH_3CH_2	H	Pyrrolidine	*a*	*a*	*a*	46	(57–58/1)	124
H	H	H	H	H	CH_3CH_2	H	Morpholine	*a*	*a*	*a*	43	(72–75/1)	124
H	H	H	H	H	$CH_3CH_2CH_2$	H	Piperidine	*a*	*a*	*a*	79	(85–86/1)	120, 124
H	H	H	H	H	$CH(CH_3)_2$	H	Piperidine	*a*	*a*	*a*	73	(80–82/1)	120, 124
H	H	H	H	H	*n*-C_5H_{11}	H	Morpholine	*a*	*a*	*a*	77	(110/0.4)	124
H	H	H	H	H	CH_3	CH_3	Pyrrolidine	*a*	*a*	*a*	78	(44/0.05)	124
H	H	H	H	H	CH_3CH_2	CH_3CH_2	Pyrrolidine	*a*	*a*	*a*	66[b]	(80–81/0.05)	124
H	H	H	H	H	*n*-C_4H_9	CH_3CH_2	Pyrrolidine	*a*	*a*	*a*	0[c]		124
H	H	H	H	$-CH_2CH_2CH_2-$		H	4-Phenyl-1-piperazine	*a*	*a*	*a*	0[d]		123
H	H	H	H	$-CH_2CH_2CH_2CH_2-$		H	4-Phenyl-1-piperazine	C_6H_6	5+rt	1.5+5 h	71	117–118	123
H	H	H	H	$-CH_2CH_2CH_2CH_2CH_2-$		H	4-Phenyl-1-piperazine	*a*	*a*	*a*	0[d]		123
H	CH_3	H	H	$-CH_2CH_2CH_2CH_2-$		H	4-Phenyl-1-piperazine	*a*	*a*	*a*	43	126–127	123
H	H	C_6H_5	H	$-CH_2CH_2CH_2CH_2$		H	4-Phenyl-1-piperazine	*a*	*a*	*a*	0[d]		123
CH_3	H	H	H	H	CH_3	H	Piperidine		0+rt	1+12 h	37[e]	(62–64/0.1)	122
CH_3	H	H	H	H	CH_3	H	Piperidine	Ether	0+rt	4+48 h	52[f]	(63/0.03)[f]	124
CH_3	H	H	H	H	CH_3	H	Pyrrolidine	*a*	*a*	*a*	*a*	*a*	125
CH_3	H	H	H	H	CH_3CH_2	H	Piperidine		0+rt	1+12 h	70.5[e]	(70–72/0.1)	122
CH_3	H	H	H	H	CH_3CH_2	H	Pyrrolidine		0	1.5	85	(78–80/0.2)	125
CH_3	H	H	H	H	CH_3	CH_3	Pyrrolidine	Ether	0+rt	5+43 h	46	(57–58/0.03)	124
CH_3	H	H	H	H	CH_3	CH_3	Dimethylamine		rt	12 h	60	(54.5–55/5.5)	125
CH_3	H	H	H	$-CH_2CH_2CH_2CH_2-$		H	Pyrrolidine	Pentane	−50	*a*	*a*	*a*	125
C_6H_5	H	H	H	H	CH_3	CH_3	Dimethylamine		0	48 h	45	(101–102/0.01)	125
C_6H_5	H	H	H	$-CH_2CH_2CH_2CH_2-$		H	4-Phenyl-1-piperazine	*a*	*a*	*a*	75	96–97	123
C_6H_5	H	H	H	$-CH_2CH_2CH_2CH_2-$		H	Morpholine	*a*	*a*	*a*	72	102–103	123
C_6H_5	H	H	H	$-CH_2CH_2CH_2CH_2-$		H	Morpholine	Petrol	10	24 h	75	100–101	126
C_6H_5	H	H	H	$-CH_2CH_2CH(t\text{-Bu})CH_2-$		H	Morpholine	Petrol	rt	24 h	20	98	126
C_6H_5	H	C_6H_5	H	$-CH_2CH_2CH_2CH_2-$		H	4-Phenyl-1-piperazine	*a*	*a*	*a*	44	129–130	123
C_6H_5	H	C_6H_5	H	$-CH_2CH_2CH_2CH_2-$		H	Morpholine	CH_3CN	rt	72 h	60	132	126
C_6H_5	H	C_6H_5	H	$-CH_2CH_2CH_2CH_2-$		H	Piperidine	Ethanol	0	18 h	66	121.5–122.5	127
C_6H_5	H	COC_6H_5	H	$-CH_2CH_2CH_2CH_2-$		H	Morpholine	Ether	rt	12 h	94	90–92	126
C_6H_5	H	H	COC_6H_5	$-CH_2CH_2CH_2CH_2-$		H	Morpholine	Ether	rt	*a*	*a*	90–92	126
C_6H_5	C_6H_5	C_6H_5	H	$-CH_2CH_2CH_2CH_2-$		H	Piperidine	Ethanol	refl	18 h	12	157–158	127
C_6H_5	C_6H_5	C_6H_5	H	$-CH_2CH_2CH_2CH_2-$		H	Pyrrolidine	Ethanol	refl	2 h	47	151–152	127
$C_6H_5CH{=}CH$	H	C_6H_5	H	H	CH_3	H	Piperidine	Ethanol	refl	0.5 h	61	142–143	127
$C_6H_5CH{=}CH$	H	C_6H_5	H	H	CH_3	H	Morpholine	Ethanol	refl	6 h	93	162–165	127
$C_6H_5CH{=}CH$	H	C_6H_5	H	$-CH_2CH_2CH_2CH_2-$		H	Piperidine	Ethanol	0+rt	1+2 h	90	110.5–111.5	127
$C_6H_5CH{=}CH$	H	C_6H_5	H	$-CH_2CH_2CH_2CH_2-$		H	Pyrrolidine	Ethanol	0	Fast	67	110–112.5	127

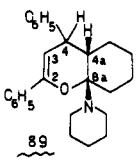
[a] Not reported in the original paper. [b] In addition 19% of **77** type product (rearrangement). [c] Only 40% of **77** type adduct was isolated. [d] Only Stork bicyclic adducts were obtained. [e] Described as cyclobutyl ketone derivative. [f] In admixture with **76** type adduct (Michael).

85 (Scheme XIX) gave the same dihydropyran **87.** If the reaction is performed with excess of **85** the recovered ketone is the thermodynamically more stable **84.** In the opinion of the authors the experimental conditions do not cause equilibration between **84** and **85,** so the result can be regarded as clear evidence for a two-step mechanism with reversible formation of the dipolar intermediate **86.**

A question arises concerning the configuration of the adducts. Because a zwitterionic intermediate was demonstrated the adducts are assumed to be formed under conditions of thermodynamic control. Alternatively a cis[127] or a trans[126] junction was proposed to be the stable one from considerations of the steric interactions in the transition state. This question remains unanswered because the spectroscopic data do not allow a firm assignment. However, a cis ring junction is supported by a recent X-ray determination of the similar structure **88.**[128]



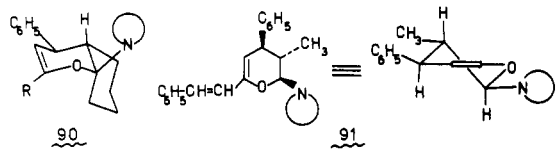
88



89

The stereochemistry of the 4 and 4a chiral centers of **89** has been investigated. A [4,4a-trans] configuration was suggested[126] from the point of view of the more favorable steric interactions, but the proton coupling values (8.5–10 Hz) were proposed[127] as proof of a cis configuration.

In the opinion of the reviewers these *J* values can also be consistent with a trans configuration having an exclusive axial/axial character.[96,100,129-131] Therefore conformation **90** could also be taken into account as well as **91** for adducts



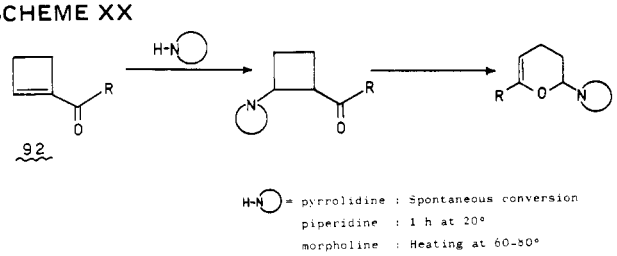
90 **91**

formed from trans aldoenamines and dibenzalacetone.[127] These compounds have *J* values of 10 Hz for both H_5/H_6 and H_4/H_5 couplings. Therefore each dihydropyran seems to retain the configuration of the starting enamine, but of course this is not proof of the concerted mechanism of the cycloaddition since thermodynamic control could lead to this configuration via a dipolar intermediate.

In conclusion, in the aliphatic series, the dihydropyran derivatives (collected in Table IX) are the primary reaction products which can be converted into Michael adducts.

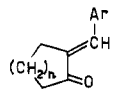
The cyclobutyl ketones have never been isolated in the aliphatic series since their independent synthesis from **92**[132] has shown that they rearrange to the thermodynamically more stable dihydropyrans (Scheme XX).

SCHEME XX



3. *Alicyclic Carbonyls*

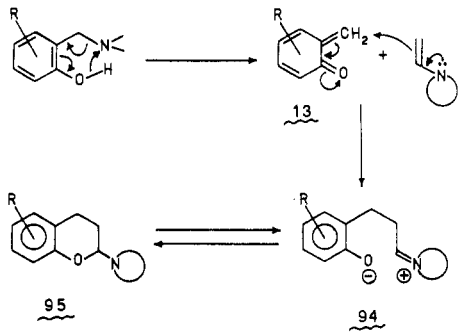
Two series of alicyclic α,β-unsaturated ketones are known to react with enamines: quinone methides **13** and saturated arylidenecyclanones **93.** Quinone methides are formed from



93

phenolic Mannich bases (Scheme XXI) and a likely mechanism for the formation of dihydropyran derivatives is a concerted elimination of the base followed by nucleophilic attack by the enamine.[133-135]

SCHEME XXI

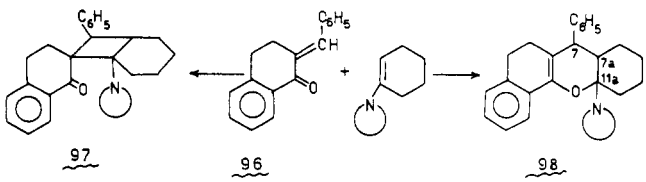


A charged intermediate **94** is suggested from the chemical behavior of the adducts **95.** Epimerization of **94** seems to prevent the formation of diastereoisomers and therefore only one isomer is isolated. Partly reduced heterocyclic systems which contain an endocyclic enamine function undergo an analogous 1,4-cycloaddition[135] and all six-membered ring adducts are collected in Table X.

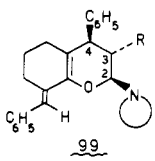
Arylidenecyclanones **93** react with enamines in accordance with 1,4-cycloadditions,[127,136-141] and the dihydropyran derivatives are collected in Table XI.

An alternative 1,2-cycloaddition, leading to cyclobutyl ketone **97,** was reported for the reaction of 2-benzylidenetetral-1-one (**96**) with cyclohexanone-enamines.[142] However, further investigation revealed that the supposed carbonyl stretching at 1650 cm^{-1}, on the basis of which structure **97** was proposed, should be assigned to the dihydropyran double bond of **98**[138,139] (Scheme XXII).

SCHEME XXII



The configuration of the adducts **98** was proposed with a [7a,11a-cis] ring junction,[127,137,141] and this is in accordance with the previously reported structure of **90.** The [7,7a] configuration already suggested as cis[127,137] can alternatively be considered as trans if *J* values are compared with those found by Prasad[140] for **99.**



99

4. *Heterocyclic Carbonyls*

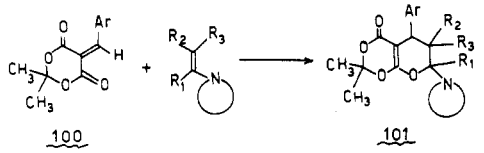
Whereas when 5-arylidene-1,3-dioxane-4,6-diones (**100**)

TABLE X. Adducts from Enamines and *o*-Quinonemethides[a]

Dimethylaminomethyl[b] Mannich bases	Enamine	Yield, %	Mp, °C	Ref
2-DMAM-6-methoxyphenol	1,2,3,4,6,7,8-Heptahydroquinolizine (EHQ)	50	93–95	135
2-DMAM-6-methoxyphenol	1-Methyl-4-(1-pyrrolidinyl)-1,2,3,6-tetrahydropyridine	*c*		135
2-DMAM-4-benzyloxyphenol	1,2,3,4,6,7,8-EHQ	27	66–67	135
2-DMAM-4-phenylphenol	1-Methyl-4-(1-pyrrolidinyl)-1,2,3,6-tetrahydropyridine	*c*		135
2-DMAM-4-styrylphenol	4-Piperidino-2,3,6-trihydrothiopyran	*c*		135
2-DMAM-4-styrylphenol	1,2,3,4,6,7,8-EHQ	29	88–93	135
2-DMAM-3-hydroxypyridine	*N*-Dimethylamino-1-isobutene	*c*		134, 135
2-DMAM-3-hydroxypyridine	1-Pyrrolidinocyclohex-1-ene	*c*		135
2-DMAM-3-hydroxypyridine	1-Benzoyl-4-(1-pyrrolidinyl)-1,2,3,6-tetrahydropyridine	*c*		134, 135
1-DMAM-2-naphthol	1-Morpholino-1-isobutene	*d*	154–156	135
1-DMAM-2-naphthol	1-Pyrrolidinocyclohex-1-ene	52	90–95	135
1-DMAM-2-naphthol	1-Methyl-4-(1-pyrrolidinyl)-1,2,3,6-tetrahydropyridine	*c*		134
1-DMAM-2-naphthol	1-Benzoyl-4-(1-pyrrolidinyl)-1,2,3,6-tetrahydropyridine	*c*		135
1-DMAM-2-naphthol	4-Piperidino-2,3,6-trihydrothiopyran	38	149–153	135
1-DMAM-2-naphthol	1,2,3,4,6,7,8-EHQ	17	209–212	134
1-DMAM-2-naphthol	1-Methylene-2-methyl-1,2,3,4-tetrahydro-β-carboline	38	178–181	135
1-DMAM-6-bromo-2-naphthol	1-Methylene-2-methyl-1,2,3,4-tetrahydroisoquinoline (THIQ)	71	171–174	135
1-DMAMphenyl-2-naphthol	1-Methyl-4-(1-pyrrolidinyl)-1,2,3,6-tetrahydropyridine	55	203–207	135
1-DMAMphenyl-2-naphthol	1-Methylene-2-methyl-1,2,3,4-THIQ	43	172–173	135
1-DMAMphenyl-2-naphthol	1-Methylene-2-methyl-1,2,3,4-tetrahydro-β-carboline	62	197–200	135
2-DMAM-1-naphthol	1-Methyl-4-(1-pyrrolidinyl)-1,2,3,6-tetrahydropyridine	*c*		135
2-DMAM-3-hydroxy-1,4-naphthoquinone	1-Morpholino-1-isobutene	43	153–155	134, 135
2-Methyl-3-carbethoxy-4-DMAM-5-hydroxyindole	1,2,3,4,6,7,8-EHQ	60	166–169	135
2-Methyl-3-carbethoxy-4-DMAM-5-hydroxyindole	1-Methylene-2-methyl-6,7-dimethoxy-1,2,3,4-THIQ	28	176–178	135
5-DMAM-6-hydroxyquinoline	*N*-Dimethylamino-1-isobutene	*d*	201.5–203.5	134
5-DMAM-6-hydroxyquinoline	1-Pyrrolidinocyclohex-1-ene	*c*		135
5-DMAM-6-hydroxyquinoline	4-Piperidino-2,3,6-trihydrothiopyran	*c*		135
5-DMAM-6-hydroxyquinoline	1-Benzoyl-4-(1-pyrrolidinyl)-1,2,3,6-tetrahydropyridine	*c*		135
5-DMAM-6-hydroxyquinoline	1,2,3,4,6,7,8-EHQ	51	178–181	135
5-DMAM-6-hydroxyquinoline	1-Methylene-2-methyl-1,2,3,4-THIQ	63	164–167	135
7-DMAM-8-hydroxyquinoline	*N*-Dimethylamino-1-isobutene	*c*		135
7-DMAM-8-hydroxyquinoline	1-Pyrrolidinocyclohex-1-ene	*c*		135
7-DMAM-8-hydroxyquinoline	4-Piperidino-2,3,6-trihydrothiopyran	*c*		135
3-DMAM-4-hydroxycoumarin	1-Morpholino-1-isobutene	38	142–144	134, 135
3-DMAM-4-hydroxycoumarin	1-Pyrrolidinocyclohex-1-ene	*c*		134
1-DMAM-2-hydroxycarbazole	1-Methyl-4-(1-pyrrolidinyl)-1,2,3,6-tetrahydropyridine	*c*		135
1-DMAM-2-hydroxycarbazole	1-Methylene-2-methyl-6,7-dimethoxy-1,2,3,4-THIQ	12	134–139	135

[a] All reactions performed in refluxing dioxane for 2–8 hr. [b] Dimethylaminomethyl group reported as DMAM. [c] Isolated as the hydrolysis product. [d] Not reported in the original paper.

react with enamines, only condensed dihydropyrans **101** are formed,[143] 3-oxindolidene derivatives give different reaction modes depending on the substituents both in the β position of the enamine and at the oxindole nitrogen atom.



100 101

1-Acetyl-3-benzaloxindole (**102**) gives dihydropyran derivatives **103**[144] whose structure was determined by chemical and spectroscopic methods (Scheme XXIII).

1-Acyl-3-oxindolideneacetophenones or -acetates **104**[145,146] also gave dihydropyran adducts **106** whereas their 1-alkyl derivatives (**104**, R = CH_3 or C_2H_5) gave spirocyclobutaneoxindoles **107** (Scheme XXIV). Both these structures were determined by chemical reactions and ir and NMR spectroscopy.

The cyclic adducts **106** and **107** are thermally unstable since ring opening occurs at room temperature in chloroform and open-chain Michael-type products **108** are obtained.[147]

SCHEME XXIII

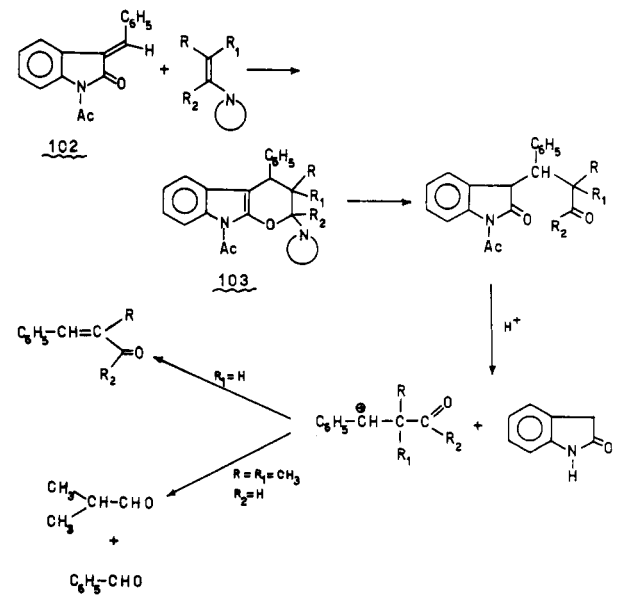
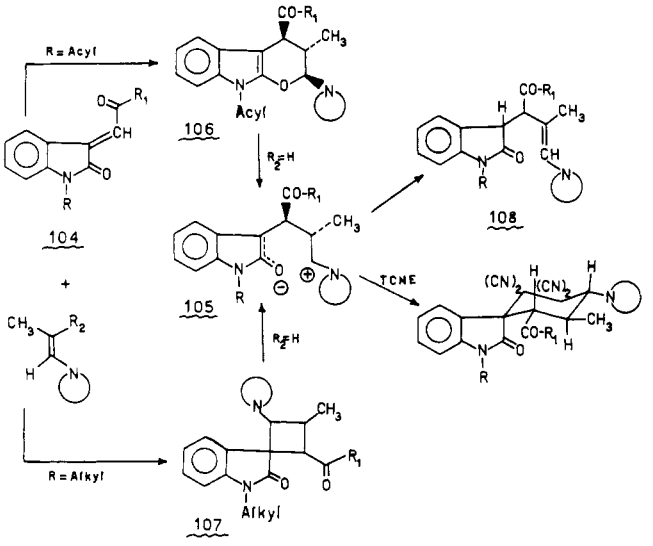


TABLE XI. Adducts from Enamines and Arylidenecyclanones

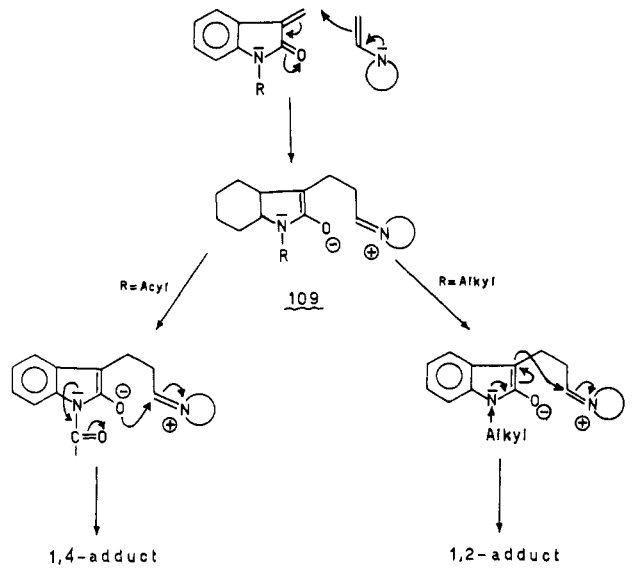
Arylidenecyclanones	Enamines	Reaction conditions			Yield, %	Mp, °C	Ref
		Solvent	T, °C	Time			
2-Benzylidenecyclohexan-1-one	1-Pyrrolidinocyclohex-1-ene	Ethanol	Refl	2 h	96	88–90	137
2,6-Dibenzylidenecyclohexan-1-one	1-Piperidinoprop-1-ene	*a*	*a*	*a*	50	157	140
2,6-Dibenzylidenecyclohexan-1-one	1-Piperidinopent-1-ene	*a*	*a*	*a*	56	144–145	140
2,6-Dibenzylidenecyclohexan-1-one	1-Pyrrolidinocyclohex-1-ene	C_6H_6	Refl	16 h	>75	176–179	136
2,6-Dibenzylidenecyclohexan-1-one	1-Pyrrolidinocyclohex-1-ene	Ethanol	rt	Fast	~100	178–181	137
2,6-Dibenzylidenecyclohexan-1-one	1-Piperidinocyclopent-1-ene	*a*	*a*	*a*	70	140–141	140
2,6-Dibenzylidenecyclohexan-1-one	1-Piperidinocyclohex-1-ene	C_6H_6	Refl	16 h	*a*	179–183	136
2,6-Dibenzylidenecyclohexan-1-one	1-Piperidinocyclohex-1-ene	*a*	*a*	*a*	73	184–185	140
2,6-Dibenzylidenecyclohexan-1-one	1-Morpholinocyclohex-1-ene	C_6H_6	Refl	16 h	*a*	149–152	136
2,6-Dibenzylidenecyclohexan-1-one	1-Morpholinocyclohex-1-ene	Ethanol	Refl	18 h	86	156–159	137
2,6-Dibenzylidenecyclohexan-1-one	1-Morpholinocyclohex-1-ene	*a*	*a*	*a*	70	157–159	140
2,6-Dibenzylidenecyclohexan-1-one	1-(4-Methyl)piperazinocyclohex-1-ene	*a*	*a*	*a*	75	172	140
2-Benzylidenedimedone[b]	1-Piperidinocyclohex-1-ene	C_6H_6	Refl	15 h	70	147–148	127
2-Benzylidenetetral-1-one	1-Pyrrolidinocyclohex-1-ene	C_6H_6	Refl	18 h	>40	126–129[c]	142
2-Benzylidenetetral-1-one	1-Pyrrolidinocyclohex-1-ene	Ethanol	Refl	1 h	89	126–129	127
2-Benzylidenetetral-1-one	1-Pyrrolidinocyclohex-1-ene	C_6H_6	Refl	18 h	40	128–129	139
2-Benzylidenetetral-1-one	1-Piperidinocyclohex-1-ene	C_6H_6	Refl	18 h	*a*	152–154[c]	142
2-Benzylidenetetral-1-one	1-Piperidinocyclohex-1-ene	C_6H_6	Refl	18 h	*a*	153–154	139
2-Benzylidenetetral-1-one	1-Piperidinocyclohex-1-ene	Ethanol	Refl	18 h	58	143–146	127
2-Benzylideneacenaphthen-1-one	1-Pyrrolidinocyclohex-1-ene	*a*	*a*	*a*	*a*	115–116	141
2-Benzylideneacenaphthen-1-one	1-Piperidinocyclohex-1-ene	*a*	*a*	*a*	*a*	*a*	141
2-*p*-Chlorobenzylideneacenaphthen-1-one	1-Pyrrolidinocyclohex-1-ene	*a*	*a*	*a*	*a*	*a*	141

[a] Not reported in the original paper. [b] Prepared in situ from dimedone and benzaldehyde in the presence of piperidine. [c] Erroneously described as cyclobutane derivative.

SCHEME XXIV



SCHEME XXV



This rearrangement occurs via the dipolar intermediate **105** which can be captured in the presence of TCNE. **105** could also be the intermediate to the cyclic adducts.

If **104** has R = H or $CH_2C_6H_5$, some intermediate cases occur and usually β-monosubstituted enamines give 1,2-addition to **107**, whereas β,β-disubstituted enamines give 1,4-addition to **106**. Sometimes the latter spontaneously change into the former.

Coupling constants of dihydropyran ring protons in **106** allow assignment of a [2,3-trans-3,4-trans] configuration identical with that found for **99**.

A mechanism involving the participation of the nitrogen lone pair which causes different ring closures of the intermediate zwitterion **109** (Scheme XXV) could rationalize the alternative 1,4- or 1,2-cycloaddition.

An attempt to prove its presence was made with *cis*-1-aziridino-1-propene[110] hoping to find dihydropyran adducts containing the enamine fragment with the original cis configuration lost. However, no reaction occurred[146] probably because of the low n/π conjugation which reduces the enaminic character of this olefin.

These results are not in accordance with the direction of attack of 1-pyrrolidinocyclopent-1-ene on ethyl 1-benzyloxin-

SCHEME XXVI

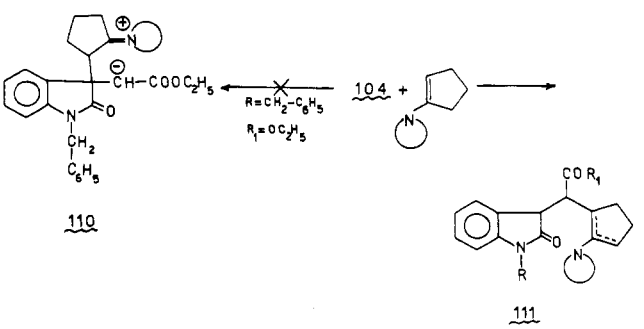
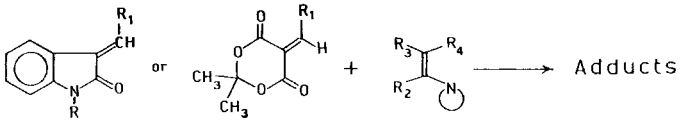


TABLE XII. Adducts from Enamines and Heterocyclic α,β-Unsaturated Carbonyl Compounds

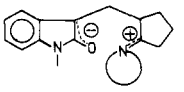


Heterocyclic compound			Enamine				Reaction conditions			1,4-Adduct		1,2-Adduct		Michael adduct		
Ring	R	R_1	R_2	R_3	R_4	–N⌒	Solvent[g]	T, °C	Time	Yield, %	Mp, °C	Yield, %	Mp, °C	Yield, %	Mp, °C	Ref
Oxindole	H	COC_6H_5	H	CH_3	H	Piperidine	C_6H_6	rt	1 h			80	95–97			145
Oxindole	H	COC_6H_5	H	CH_3	CH_3	Pyrrolidine		0	1 d	100	75–77					145
Oxindole	H	$COOCH_3$	H	CH_3	H	Piperidine	PE	rt	*a*			70	110			146
Oxindole	H	$COOCH_3$	H	CH_3	CH_3	Pyrrolidine		rt	*a*	*b*	74–76					146
Oxindole	CH_3	COC_6H_5	H	CH_3	H	Piperidine	PE	0+rt	2 h			80–91	97–98			145
Oxindole	CH_3	COC_6H_5	H	CH_3	CH_3	Pyrrolidine		rt	5–10′			91	92–93			145
Oxindole	CH_3	COC_6H_5	$-CH_2CH_2CH_2-$		H	Pyrrolidine	PE	0	*a*					74	81–83	146
Oxindole	CH_3	$COOCH_3$	H	CH_3	H	Piperidine	PE	rt	*a*			62	158–159			146
Oxindole	CH_3	$COOCH_3$	H	CH_3	CH_3	Pyrrolidine		rt	*a*			81	76			146
Oxindole	CH_3	$COOCH_3$	$-CH_2CH_2CH_2-$		H	Pyrrolidine	PE	0	*a*					58	66–68	146
Oxindole	CH_2CH_3	COC_6H_5	H	CH_3	H	Piperidine	PE	0+rt	2 h			81	105–106			145
Oxindole	CH_2CH_3	COC_6H_5	H	CH_3	CH_3	Pyrrolidine		rt	5–10′			90	113–115			145
Oxindole	$COCH_3$	C_6H_5	H	CH_3	H	Piperidine	C_6H_6	0	5–10′	73.5	99–101					144
Oxindole	$COCH_3$	C_6H_5	H	CH_3	CH_3	Pyrrolidine		0	1 h	76	77–78					144
Oxindole	$COCH_3$	C_6H_5	$-CH_2CH_2CH_2CH_2-$		H	Pyrrolidine	PE	0	45′	95	86–88					144
Oxindole	$COCH_3$	COC_6H_5	H	CH_3	H	Piperidine	PE	0+rt	2 h	99	100–102					145
Oxindole	$COCH_3$	COC_6H_5	H	CH_3	CH_3	Pyrrolidine		rt	5–10′	84–94	74–75					145
Oxindole	$COCH_3$	COC_6H_5	$-CH_2CH_2CH_2-$		H	Pyrrolidine	PE	0	*a*					75	89–91	146
Oxindole	$COCH_3$	$COOCH_3$	H	CH_3	H	Piperidine	PE	rt	*a*	95	95–97					146
Oxindole	$COCH_3$	$COOCH_3$	H	CH_3	CH_3	Pyrrolidine		rt	*a*	95	100–102					146
Oxindole	$COCH_3$	$COOCH_3$	$-CH_2CH_2CH_2-$		H	Pyrrolidine	PE	0	*a*					73	72–73	146
Oxindole	COC_6H_5	COC_6H_5	H	CH_3	H	Piperidine	PE	0+rt	2 h	95	93–95					145
Oxindole	COC_6H_5	COC_6H_5	H	CH_3	CH_3	Pyrrolidine		rt	5–10′	94	90–92					145
Oxindole	COC_6H_5	$COOCH_3$	H	CH_3	H	Piperidine	PE	rt	*a*	84	107–108					146
Oxindole	COC_6H_5	$COOCH_3$	H	CH_3	CH_3	Pyrrolidine		rt	*a*	81	118–120					146
Oxindole	$CH_2C_6H_5$	COC_6H_5	H	CH_3	H	Piperidine	PE	0+rt	2 h			87	111–113			145
Oxindole	$CH_2C_6H_5$	COC_6H_5	H	CH_3	CH_3	Pyrrolidine		0	*c*	100[d]	90–91	100[d]	89–91			145
Oxindole	$CH_2C_6H_5$	COC_6H_5	$-CH_2CH_2CH_2-$		H	Pyrrolidine	PE	0	Fast					87[e]	*e*	146
Oxindole	$CH_2C_6H_5$	$COOCH_3$	H	CH_3	H	Piperidine	PE	rt	*a*			64	88–90			146
Oxindole	$CH_2C_6H_5$	$COOCH_3$	H	CH_3	CH_3	Pyrrolidine		0	*a*			93	120–121			146
Oxindole	$CH_2C_6H_5$	$COOCH_3$	$-CH_2CH_2CH_2-$		H	Pyrrolidine	PE	0	Fast					92[e]	*e*	146
Oxindole	$CH_2C_6H_5$	$COOC_2H_5$	H	CH_3	H	Piperidine	PE	rt	*a*			79	102–104			146
Oxindole	$CH_2C_6H_5$	$COOC_2H_5$	H	CH_3	CH_3	Pyrrolidine		0	*a*	70[d]	75–77	70[d]	75–77			146
Oxindole	$CH_2C_6H_5$	$COOC_2H_5$	$-CH_2CH_2CH_2-$		H	Pyrrolidine	PE	0	Fast					35[e]	*e*	146
Oxindole	$CH_2C_6H_5$	$COOC_2H_5$	$-CH_2CH_2CH_2CH_2-$		H	Pyrrolidine	PE	0	Fast					70[e]	*e*	146
Oxindole	$CH_2C_6H_4$-*p*-OCH_3	COC_6H_5	H	CH_3	H	Piperidine	PE	0+rt	2 h			82	98–101			145
Oxindole	$CH_2C_6H_4$-*p*-OCH_3	COC_6H_5	H	CH_3	CH_3	Pyrrolidine		rt	5–10′			82	98–100			145
Oxindole	$CH_2C_6H_4$-*p*-NO_2	COC_6H_5	H	CH_3	H	Piperidine	C_6H_6	0+rt	2 h			90	112–114			145
1,3-Dioxanedione		C_6H_5	H	CH_3	CH_3	Morpholine	C_6H_6	rt	Fast	80	87–91					143
1,3-Dioxanedione		C_6H_5	$-CH_2CH_2CH_2CH_2-$		H	Morpholine	Ether	*f*	*f*	100	103–106					143
1,3-Dioxanedione		*p*-$NO_2C_6H_4$	H	CH_3	CH_3	Morpholine	C_6H_6	rt	Fast	*f*	*f*					143
1,3-Dioxanedione		*p*-$NO_2C_6H_4$	$-CH_2CH_2CH_2CH_2-$		H	Morpholine	Ether	*f*	*f*	100	121–123					143

[a] Until color of the starting material disappears. [b] Undetermined because of the instability of the adduct. [c] Various times depending upon the ratio of reagents. [d] 1,2- or 1,4-adduct obtained; the latter spontaneously at −18° changes into the former. [e] Detected by spectroscopic methods, isolated as hydrolysis product. [f] Not reported in the original paper. [g] PE = petroleum ether.

dolideneacetate **104** (R = $CH_2C_6H_5$, R′ = OC_2H_5) which, under severe conditions, is reported to give products[148] whose origin is connected with attack in the α-position of the α,β-unsaturated system to give **110** (Scheme XXVI). Reinvestigation of the reaction revealed that attack occurs only in the β position and, under mild conditions (−20°), Michael adducts **111** are obtained.[146]

Rationalization can be proposed in terms of the better stabilization of the positive charge in the zwitterion **112** due to the alkyl residue adjacent to the amine function. In this case the α-proton loss is preferred over ring closure and a Michael adduct is obtained.



112

A further rationalization arises from the lower separation of the frontier orbitals promoted both by the electron-attracting carbonyl group in the β position of the unsaturated C=C—C=O system and by the electron-donating alkyl residues of the enamine. Furthermore, the increased asymmetry of the coefficients, in addition to the large frontier control, strongly favors a zwitterionic pathway.

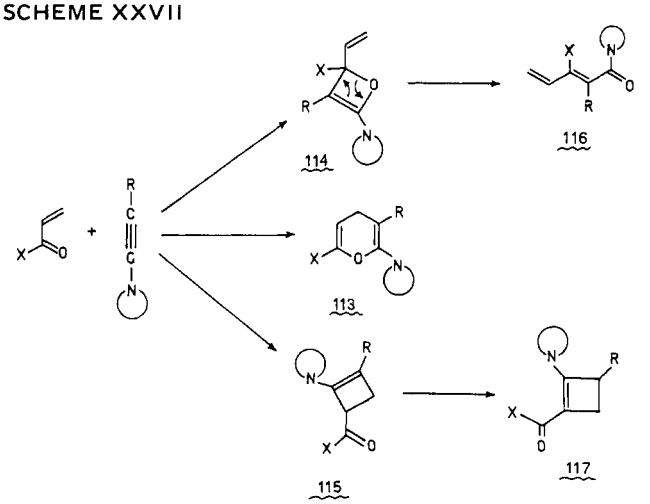
In conclusion, the unusual behavior of enamines in general, and of their reaction with unsaturated heterocyclic carbonyls in particular, must be pointed out. A variety of reactions occurs: 1,4- and 1,2-cycloadditions and Michael reactions (collected in Table XII). A zwitterionic intermediate seems to rationalize this behavior.

Unfortunately these heterodiene syntheses are not general for all heterocycles since 4-benzylidene-5-oxazolones[149,150] undergo ring opening. Enamines do not attack the unsaturated system but attack the carbonyl group whose carbon atom is rendered highly electrophilic by the adjacent oxygen atom of the heterocyclic ring.

B. Ynamines

Ynamines are known to react with a variety of α,β-unsaturated carbonyl compounds and different reactions occur. The most common reaction is a 1,4-cycloaddition[151-153] and amino pyrans **113** are formed (Scheme XXVII). Besides these

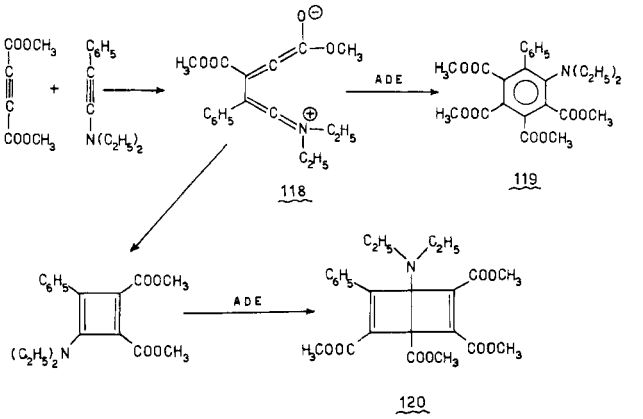
SCHEME XXVII



main products, open-chain amides **116** sometimes occur[151] which originate from 1,2-cycloaddition to the carbonyl group followed by electrocyclic ring opening of the oxete intermediate **114.** If the carbonyl group belongs to an ester, a further alternative occurs[152] with 1,2-cycloaddition to the C=C double bond. These cyclobutane derivatives **115** do not undergo ring opening, but a shift of the double bond occurs giving **117.**

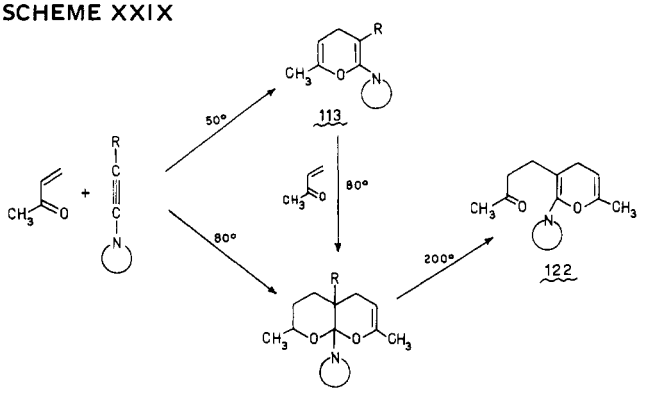
The above reported behavior of unsaturated esters changes for acetylenedicarboxylic esters (ADE).[154] Two moles of ester are involved and hexasubstituted benzene derivatives **119** are obtained (Scheme XXVIII), probably via a dipolar species **118** which undergoes 1,4-dipolar cycloaddition. An alternative ring closure followed by a Diels–Alder reaction with ring opening (disrotatory!) of the bicyclic adduct **120** seems unlikely.

SCHEME XXVIII



The pyran adducts **113** are potential enamines and, under more severe conditions, a second mole of unsaturated carbonyl compound is added.[155] These bis-adducts **121** undergo ring opening on heating and, in accordance with examples described in previous sections, Michael-type products **122** are obtained (Scheme XXIX).

SCHEME XXIX

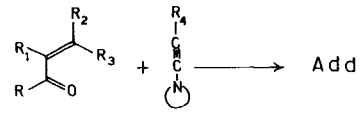


Ynamines also react with acylketenes **123,**[156,157] and adducts from three competitive processes are obtained: (a) 1,2-cycloaddition to the C=O group which gives allene derivatives **127** via **124;** (b) 1,2-cycloaddition to the C=C group giving cyclobutenones **125;** (c) 1,4-cycloaddition giving γ-pyrones **126** (Scheme XXX).

It is very difficult to rationalize the observed selectivity of attack since, e.g., γ-pyrones **126** are isolated only from carbamoyl ketenes (**123;** R = NR_2) if R′ is a phenyl group. Otherwise 1,2-cycloadducts are formed exclusively.[157] Table XIII collects the variety of adducts previously described.

The variety of reaction modes cannot be considered definite evidence of a dipolar intermediate since [2 + 2] cycloadditions with ynamines can also occur in a concerted manner which does not necessarily involve an antarafacial approach. In addition to the 1,4-intermediate (Figure 9, case A), similar alternative 1,2-intermediates (cases B–E) are reported. These 1,2-reactions could in fact be regarded as [2 + 2 + 2] cycloadditions involving 4π electrons from the ynamine[158] (cases B and C) or 2π + 2n electrons from the carbonyl group (case D) or even a second pair of π electrons from the

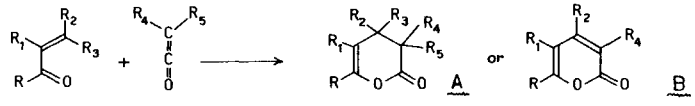
TABLE XIII. Adducts from α,β-Unsaturated Carbonyl Compounds and Ynamines



α,β-Unsaturated carbonyl deriv				Ynamine		Reaction conditions			Total yield, %	1,4-Adduct Yield, %	1,4-Adduct Mp (bp/mmHg), °C	1,2(C=C)-Adduct Yield, %	1,2(C=C)-Adduct Mp (bp/mmHg), °C	1,2(C=O)-Adduct Yield, %	1,2(C=O)-Adduct Mp (bp/mmHg), °C	1,4-Bis-adduct Yield, %	1,4-Bis-adduct Mp (bp/mmHg), °C	Ref
R	R_1	R_2	R_3	R_4	–N◯	Solvent	T, °C	Time										
H	H	H	H	CH_3	Diethylamino	Ether	25	3 h	20	20	(71/13)							151
H	H	H	H	C_6H_5	Diethylamino	THF	80	1.5 h	34	30	(81/0.07)			4	(91/0.05)			151
H	H	C_6H_5	H	CH_3	Diethylamino	Ether	25	15 h	50	10	(84/0.05)			40	(154/0.07)			151
CH_3	H	H	H	H	Diethylamino	Dioxane	20	2 h	60							60	(83–84/0.1)	155
CH_3	H	H	H	H	Morpholino	Dioxane	50	4 h	70							70	72	155
CH_3	H	H	H	H	Methyl-phenyl-amino	Dioxane	70	6 h	45							45	(116/0.07)	155
CH_3	H	H	H	CH_3	Diethylamino	Ether	25	3 h	50	50	(71/7)							151
CH_3	H	H	H	CH_3	Morpholino	*a*	50	*a*	*a*	*a*	(95–100/8)							155
CH_3	H	H	H	CH_3	Morpholino	*a*	80	*a*	*a*	*a*	(95–100/8)					*a*	65	155
CH_3	H	H	H	C_6H_5	Diethylamino	THF	80	6 h	40	40	(85/0.05)							151
OCH_3	H	H	H	CH_3	Diethylamino	THF	–10+rfl	0.5 h	70	50	(37/0.05)	20	(60/0.01)					152
OCH_3	H	CH_3	H	CH_3	Diethylamino	THF	–10+rfl	12 h	35	35	(37/0.01)							152
OCH_3	CH_3	H	H	CH_3	Diethylamino	THF	–10+rfl	12 h	60	60	(36/0.03)							152
C_6H_5	C_6H_5	C_6H_5	H	CH_3	Diethylamino	Ethanol	0+rt	8 h	32	32	111.5–112							153
$CH{=}CHC_6H_5$	H	C_6H_5	H	CH_3	Diethylamino	Ethanol	0+rt	*a*	18[b]									153
$CH_2CH(CH_3)CH_2CH_2$		CH_3	CH_3	CH_3	Diethylamino	Xylene	150	20 h	35	35	(79/0.07)							151
$C(CHC_6H_5)CH_2CH_2CH_2$		C_6H_5	H	CH_3	Diethylamino	Ethanol	0+rt	2.5 h	32	32	80–82							153
OC_2H_5	CH_3	O		CH_3	Diethylamino	Hex/C_6H_6	rt	1 h	65			3	75	62	(85/0.05)			157
OC_2H_5	CH_3	O		C_6H_5	Diethylamino	Hex/C_6H_6	rt	1 h	70			14	83	56	*a*			157
OC_2H_5	C_6H_5	O		CH_3	Diethylamino	Hex/C_6H_6	rt	1 h	65			32.5	(140/0.01)	32.5	(140/0.02)			157
OC_2H_5	C_6H_5	O		C_6H_5	Diethylamino	Hex/C_6H_6	rt	1 h	65			65	85					157
$N(CH_3)_2$	C_6H_5	O[c]		C_6H_5	Diethylamino	CH_3CN	rt[d]	24 h	81	81	220							156
$N(C_2H_5)_2$	CH_3	O		CH_3	Diethylamino	Hex/C_6H_6	rt	1 h	70			3	(120/0.005)	67	Dec			157
$N(C_2H_5)_2$	CH_3	O		C_6H_5	Diethylamino	Hex/C_6H_6	rt	1 h	70			21	*a*	49	Dec			157
$N(C_2H_5)_2$	C_6H_5	O		CH_3	Diethylamino	Hex/C_6H_6	rt	1 h	70	70	(140/0.005)							157
$N(C_2H_5)_2$	C_6H_5	O[c]		C_6H_5	Diethylamino	CH_3CN	rt[d]	24 h	96	96	146							156
$N(C_2H_5)_2$	C_6H_5	O		C_6H_5	Diethylamino	Hex/C_6H_6	rt	1 h	50	50	146							157

[a] Not reported in the original paper. [b] Isolated as hydrolysis product. [c] Prepared in situ from ynamine and carbon dioxide. [d] Under pressure.

TABLE XIV. Adducts with Ketenes



α,β-Unsaturated carbonyl derivative				Ketene		Reaction conditions			Adduct A Yield, %	Adduct A Mp (bp/mmHg), °C	Adduct B Yield, %	Adduct B Mp (bp/mmHg), °C	Ref
R	R_1	R_2	R_3	R_4	R_5	Solvent	T, °C	Time					
CH_3	H	Pyrrolidino	Pyrrolidino[a]	H	H	Ether	0	*b*			58	177–178	187
CH_3	H	Piperidino	Piperidino[a]	H	H	Ether	0	*b*			54	130–131	187
CH_3	H	Morpholino	Morpholino[a]	H	H	Ether	0	*b*			52–68	178–178.5	187

CH_3	CH_3	Piperidino	Piperidino[a]	H	H	Ether	0	*b*			55	125–126	187
CH_3	CH_3	Morpholino	Morpholino[a]	H	H	Ether	0	*b*			51	94–95	187
CH_3	C_2H_5	Piperidino	Piperidino[a]	H	H	Ether	0	*b*			51	156–157	187
CH_3	C_2H_5	Morpholino	Morpholino[a]	H	H	Ether	0″	*b*			53	85–86	187
CH_3	$-CH_2(CH_2)_2CH_2-$		Pyrrolidino	H	H	Ether	*b*	2 h			50	82–83	188
CH_3	$-CH_2(CH_2)_2CH_2-$		Piperidino	H	H	Ether	*b*	2 h			7	*b*	188
CH_3	$-CH_2(CH_2)_2CH_2-$		Morpholino	H	H	Ether	*b*	2 h			0		188
$(CH_3)_2CH$	H	$N(CH_3)_2$	H	CH_3	CH_3	Benzene	20–30	2 h	86	(79/1)			189
$(CH_3)_2CH$	H	$N(CH_3)_2$	H	n-C_4H_9	C_2H_5	Toluene	refl	8 h	52	(110–113/1.5)			175
C_6H_5	H	C_6H_5	H	C_6H_5[c]	C_6H_5		130–140	4 h	22[d]	189–190			178
C_6H_5	H	p-$CH_3OC_6H_4$	H	C_6H_5[c]	C_6H_5		130–140	4 h	42[d]	179–180			178
C_6H_5	H	p-$(CH_3)_2NC_6H_4$	H	C_6H_5[c]	C_6H_5		130–140	4 h	34[d]	199–200			178
$(C_6H_5)_2CH$	CH_3	OC_2H_5	OC_2H_5	C_6H_5	C_6H_5		120	10 h	15	174–175			183
$(C_6H_5)_2CH$	C_6H_5	OCH_3	OCH_3	C_6H_5	C_6H_5	*b*	*b*	*b*	*b*,[e]	*b*,[e]			183
$-(CH_2)_3-$		$N[CH(CH_3)_2]_2$	H	Cl	Cl	Benzene	rt	15′	54	98–99			186
$-(CH_2)_3-$		$N(CH_3)C_6H_5$	H	Cl	Cl	Benzene	rt	15′	48	105–106			186
$-(CH_2)_3-$		$N(C_6H_5)_2$	H	Cl	Cl	Benzene	rt	15′	42	169–170			186
$-(CH_2)_4-$		$N(CH_3)_2$	H	C_6H_5	C_6H_5	Benzene	rt	30′	49	107–108			185
$-(CH_2)_4-$		$N(C_2H_5)_2$	H	C_6H_5	C_6H_5	Benzene	rt	30′	40	109–110			185
$-(CH_2)_4-$		$N[CH(CH_3)_2]_2$	H	Cl	Cl	Benzene	rt	15′	61	116–117			186
$-(CH_2)_4-$		$N[CH(CH_3)_2]_2$	H	C_6H_5	C_6H_5	Benzene	rt	30′	68	97–98			185
$-(CH_2)_4-$		Piperidino	H	C_6H_5	C_6H_5	Benzene	rt	30′	39	124–125			185
$-(CH_2)_4-$		Morpholino	H	C_6H_5	C_6H_5	Benzene	rt	30′	53	141–141.5			185
$-(CH_2)_4-$		$N(CH_3)C_6H_5$	H	Cl	Cl	Benzene	rt	15′	51	122–123			186
$-(CH_2)_4-$		$N(CH_3)C_6H_5$	H	C_6H_5	C_6H_5	Benzene	rt	30′	58	155–156			185
$-(CH_2)_4-$		$N(C_6H_5)_2$	H	Cl	Cl	Benzene	rt	15′	56	183–184			186
$-(CH_2)_4-$		$N(C_6H_5)_2$	H	C_6H_5	C_6H_5	Benzene	rt	30′	36	157.5–158.5			185
$-(CH_2)_5-$		$N(CH_3)_2$	H	Cl	Cl	Benzene	rt	15′	59	90–91			186
$-(CH_2)_5-$		$N(CH_3)_2$	H	C_6H_5	C_6H_5	Benzene	rt	30′	59	92–93			185
$-(CH_2)_5-$		$N(C_2H_5)_2$	H	C_6H_5	C_6H_5	Benzene	rt	30′	15	77–78			185
$-(CH_2)_5-$		$N[CH(CH_3)_2]_2$	H	Cl	Cl	Benzene	rt	15′	50	81–82			186
$-(CH_2)_5-$		$N[CH(CH_3)_2]_2$	H	C_6H_5	C_6H_5	Benzene	rt	30′	20	89–90			185
$-(CH_2)_5-$		Piperidino	H	C_6H_5	C_6H_5	Benzene	rt	30′	43	107–108			185
$-(CH_2)_5-$		Morpholino	H	C_6H_5	C_6H_5	Benzene	rt	30′	49	125–126			185
$-(CH_2)_5-$		$N(CH_3)C_6H_5$	H	Cl	Cl	Benzene	rt	15′	73	93–94			186
$-(CH_2)_5-$		$N(CH_3)C_6H_5$	H	C_6H_5	C_6H_5	Benzene	rt	30′	64	136–137			185
$-(CH_2)_5-$		$N(C_6H_5)_2$	H	Cl	Cl	Benzene	rt	15′	83	169–170			186
$-(CH_2)_5-$		$N(C_6H_5)_2$	H	C_6H_5	C_6H_5	Benzene	rt	30′	49	158–159			185
$-(CH_2)_6-$		$N(CH_3)_2$	H	Cl	Cl	Benzene	rt	15′	46	79–80			186
$-(CH_2)_6-$		$N(CH_3)_2$	H	C_6H_5	C_6H_5	Benzene	rt	30′	29	114–115			185
$-(CH_2)_6-$		$N(C_2H_5)_2$	H	C_6H_5	C_6H_5	Benzene	rt	30′	59	105–107			185
$-(CH_2)_6-$		$N[CH(CH_3)_2]_2$	H	Cl	Cl	Benzene	rt	15′	43	98–99			186
$-(CH_2)_6-$		$N[CH(CH_3)_2]_2$	H	C_6H_5	C_6H_5	Benzene	rt	30′	55	93–95			185
$-(CH_2)_6-$		Piperidino	H	C_6H_5	C_6H_5	Benzene	rt	30′	68	131–132			185
$-(CH_2)_6-$		Morpholino	H	C_6H_5	C_6H_5	Benzene	rt	30′	63	151–152			185
$-(CH_2)_6-$		$N(CH_3)C_6H_5$	H	Cl	Cl	Benzene	rt	15′	54	119–120			186
$-(CH_2)_6-$		$N(CH_3)C_6H_5$	H	C_6H_5	C_6H_5	Benzene	rt	30′	86	153–154			185
$-(CH_2)_6-$		$N(C_6H_5)_2$	H	Cl	Cl	Benzene	rt	15′	36	208–209			186
$-(CH_2)_6-$		$N(C_6H_5)_2$	H	C_6H_5	C_6H_5	Benzene	rt	30′	50	161–162			185

[a] Prepared in situ from ketene and aminals. [b] Not reported in the original paper. [c] As quinoline complex. [d] Variable amounts of butadiene derivatives isolated (see text). [e] Erroneously described as a cyclobutanone derivative: R. Scarpati and D. Sica, *Rend. Accad. Sci. Fis. Mat. Naples*, [IV] 27, 70 (1961).

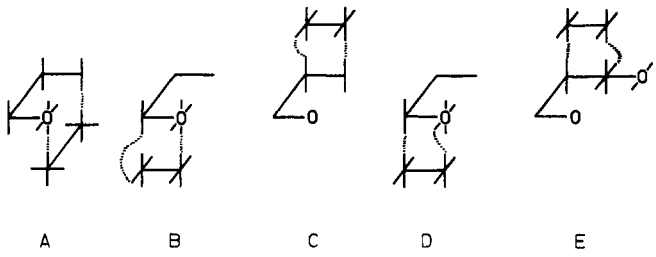
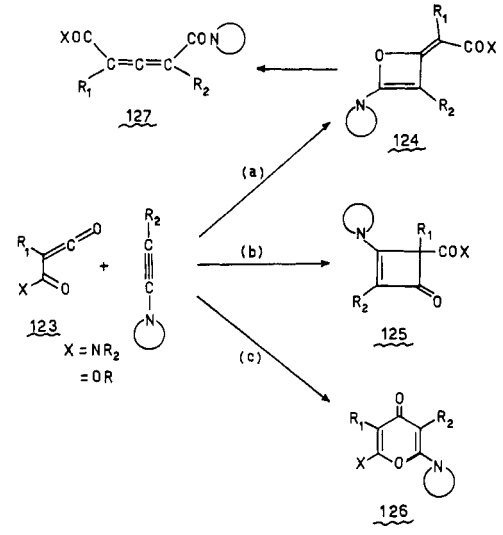


Figure 9. Possible allowed cycloadditions of α,β-unsaturated carbonyl compounds with ynamines (schematic representation).

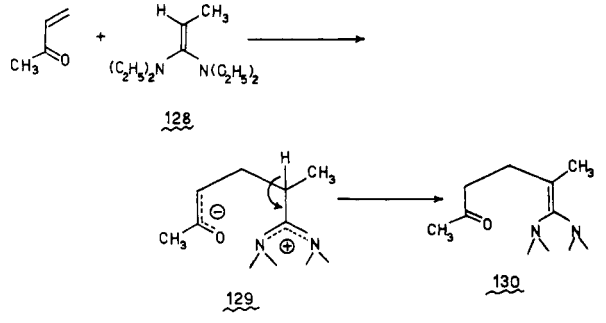
SCHEME XXX



cumulated double bond (case E) in accordance with the concerted process proposed by Huisgen[159] for cycloadditions with ketenes.

On the contrary, a dipolar intermediate has to be proposed for the reaction involving ketene aminals **128** which are sometimes used as alternatives to ynamines. An open-chain Michael adduct **130** is isolated[155] (Scheme XXXI) and the presence of the zwitterion **129** can be rationalized both in terms of increased frontier control, since the energy of HOMO in aminals should be higher than in enamines and therefore much higher than in ynamines, and in terms of better stabilization of the intermediate.

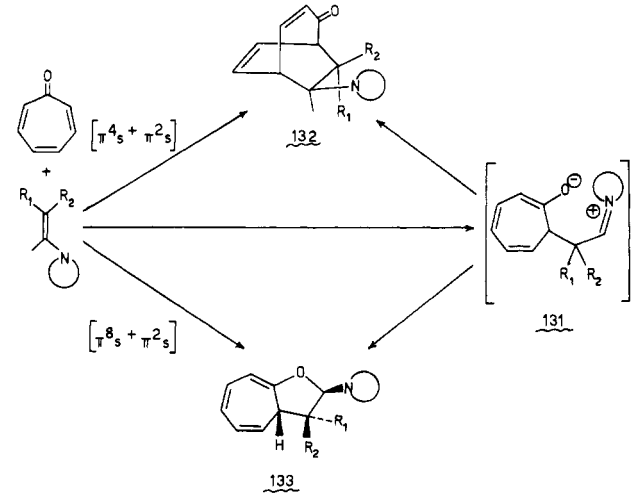
SCHEME XXXI



C. Alternative Reactions

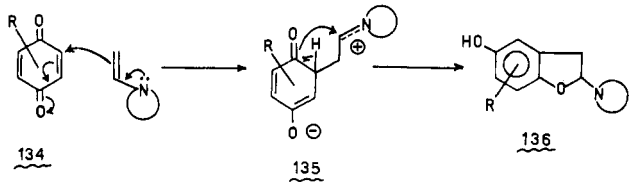
Several α,β-unsaturated carbonyl derivatives are known to react with unsaturated amines in different ways from the schemes reported in the previous sections. If the carbonyl system has a rigid transoid conformation, no 1,4-cycloaddition is possible. In this case a variety of reactions occurs; e.g., cyclopropenones give ring opening,[160-162] whereas esters of quadratic acid give substitution.[163] Tropone undergoes either a Diels–Alder-type reaction with the C=C—C=C fragment to give **132** or 1,8-cycloaddition to give **133**.[164] A dipolar intermediate **131** was early proposed,[164a] but allowed $[\pi 4_s + \pi 2_s]$ and $[\pi 8_s + \pi 2_s]$ routes respectively for **132** and **133** can be proposed in the light of recent work on the same substrate[165,166] to explain the great stereoselectivity (Scheme XXXII).

SCHEME XXXII



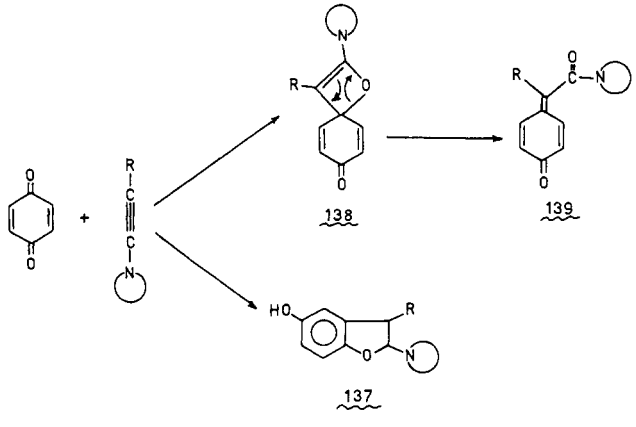
p-Quinone derivatives **134** give benzofurans **136** via the dipolar intermediate **135**[167-173] (Scheme XXXIII).

SCHEME XXXIII



Ynamines give stable condensed cyclobutenes with both cyclopentenone and cyclohexenone derivatives.[174-176] Besides a 1,3-cycloadduct **137**, quinones give a 1,2-cycloaddition to the C=O bond[177] with electrocyclic ring opening of the spiro-oxete intermediate **138** leading to **139** (Scheme XXXIV).

SCHEME XXXIV



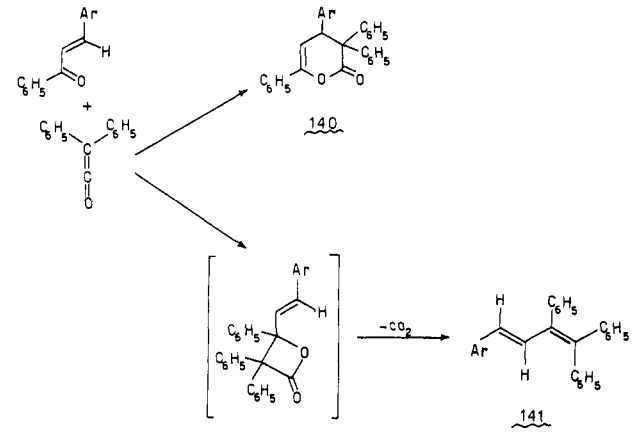
VIII. Reaction of C=C—C=O System with Cumulated Double Bonds

In general the reaction of α,β-unsaturated carbonyl derivatives with ketenes occurs as a formal [4 + 2] cycloaddition involving the cumulated C=C bond.

The first example was given by Staudinger[178] who found δ-lactones **140** as the main reaction products, as well as

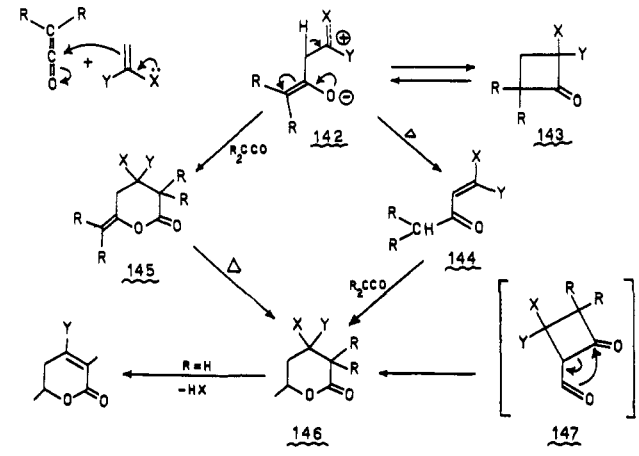
some butadiene derivatives **141** whose origin could involve a [2 + 2] cycloaddition to the carbonyl group followed by elimination of CO_2 (Scheme XXXV). The synthetic usefulness of the reaction was pointed out.[179]

SCHEME XXXV



The most investigated reaction was the cycloaddition between ketenes and stongly nucleophilic olefins such as enamines, ketene aminals and acetals. The reaction involves more than 1 mol of ketene[180] and a heterodiene cycloaddition was suggested as an intermediate stage.[181] Further investigation, however, revealed that the first step (Scheme XXXVI) is nu-

SCHEME XXXVI



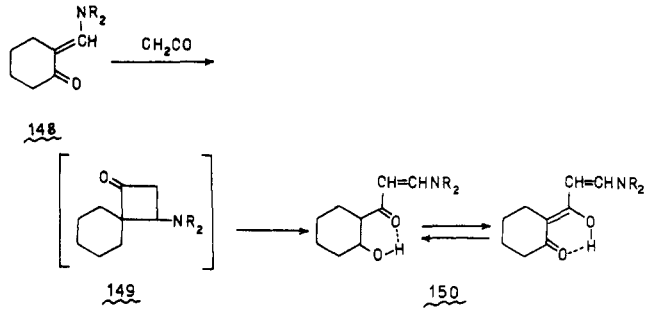
cleophilic attack of the olefin on the ketene carbonyl group, and it was suggested that either the cyclobutane **143**[181,182] or the dipolar intermediate **142**[183] occurs. The dipolar intermediate **142** can undergo either a thermal rearrangement to the α,β-unsaturated ketone **144** or can react with a second mole of ketene to give the unstable pyrone **145**[183,184] in accordance with a 1,4-dipolar cycloaddition.

144 can act as a heterodiene since it reacts with a further mole of ketene to give the thermally stable pyrones **146**.[185-187] These are also formed from **145** and can lose HX depending upon the substituents.[187,188]

Two competitive cycloaddition modes from **144** to **146** are possible: Opitz[188] suggested a "diene synthesis" leading directly to the six-membered ring; Martin et al.[189] proposed the cyclobutanone intermediate **147** which subsequently rearranges to **146**.

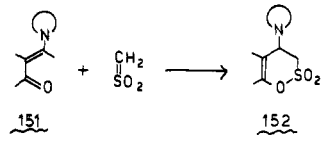
This second pathway, which can be regarded as an allowed [2 + 2 + 2] cycloaddition if the 4π electrons of ketene are involved, seems to be supported by the behavior of cyclic enamino ketones **148** which react with ketene[190] to give **150** via the spirocyclobutanone **149** (Scheme XXXVII). Table XIV collects the six-membered adducts previously described.

SCHEME XXXVII



IX. Reaction of the C=C—C=O System with Double Bonds Containing Heteroatoms

Enamino ketones **151** react easily with sulfene (prepared in situ from mesyl chloride and triethylamine) in accordance with a 1,4-cycloaddition if they can adopt a cisoid conformation.[191] β-Amino δ-sultones **152** are obtained in good yields.



A wide range of substrates were tested, mainly for synthetic purposes: open-chain,[188,191,192] cyclic,[190,193,194] and heterocyclic[195,196] enamino ketones (Table XV). A kinetic investigation of the influence of the substituents in enamino ketones which could determine the mechanism was never performed.

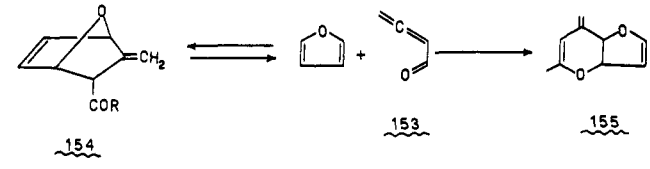
Whereas a concerted [4 + 2] mechanism can be proposed, the low-lying LUMO of sulfene[197] and the resonance of the nitrogen lone pair with α,β-unsaturated carbonyl system, which enhances the carbonyl HOMO, can make the interaction $HOMO_{carbonyl}/LUMO_{sulfene}$ sufficiently great to reverse the usual donor and acceptor characters of the reagents.

X. α,β-Unsaturated Carbonyls Containing Cumulated Double Bonds

The 1,4-cycloaddition reaction of acylketenes, acting as dienes, on substrates like aldehydes, ketones, nitriles, isocyanates, azomethines, carbodiimides, and acylketenes (leading to dimeric products) was reviewed by Ulrich,[198] and some reactions with ynamines[156,157] have already been reported in section VII.B.

α-Allenic ketones **153** react with furan[199] and both reagents can be regarded as potential dienes (Scheme XXXVIII). Kinetically controlled adducts **154** are formed when

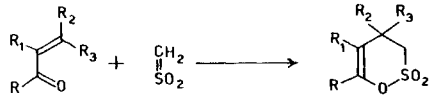
SCHEME XXXVIII



furan acts as the diene, but they slowly undergo a retro-Diels-Alder reaction and thermodynamically more stable pyran-furans **155** are formed via a heterodiene cycloaddition.

The reaction involving α-oxoketenes is far more important. Some new preparations of the starting O=C—C=C=O system **156** (which has to be generated in situ) have been achieved (Scheme XXXIX) (A) from salicylic acid;[200] (B) from diazocyclohexane-1,3-dione;[201] (C) from adipyl chloride deriv-

TABLE XV. Adducts with Sulfene

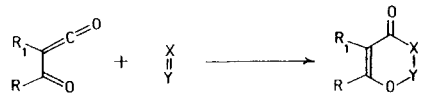


α,β-Unsaturated carbonyl				Reaction conditions			Adduct		
R	R_1	R_2	R_3	Solvent	T, °C	Time	Yield, %	Mp (bp/mmHg), °C	Ref
CH_3	H	CH_3	Dimethylamino	Ether/C_6H_6	0	16 h	6	91–92	191
CH_3	H	CH_3	Pyrrolidino	Ether/C_6H_6	0	21 h	0		191
CH_3	H	Dimethylamino	CH_3	Ether	rt	*a*	7	91–92	192
CH_3	CH_3	Piperidino	H	Ether	0	18.5 h	80	108–109	191
CH_3	CH_3	Piperidino	H	Ether	rt	*a*	80	108–109	192
CH_3	$-CH_2(CH_2)_2CH_2-$		Pyrrolidino	Ether	0	17 h	32–38	80–82	188, 192
CH_3	$-CH_2(CH_2)_2CH_2-$		Piperidino	Ether	0	*a*	9	108–109	188, 192
CH_3	$-CH_2(CH_2)_2CH_2-$		Morpholino	Ether	0	*a*	5	153–155	188, 192
$CH(CH_3)_2$	H	Pyrrolidino	H	Ether	0	20 h	75	94–95	191
$CH(CH_3)_2$	H	Pyrrolidino	H	Ether	rt	*a*	75	94–95	192
$-CH_2(CH_2)_2CH_2-$		Diethylamino	H	Ether	0+rt	1 h	79	76–77	190
$-CH_2(CH_2)_2CH_2-$		Pyrrolidino	H	Ether	0+rt	1 h	80	105–106	190
$-CH_2(CH_2)_2CH_2-$		Piperidino	H	Ether	0+rt	1 h	80	87–88	190
$-CH_2(CH_2)_2CH_2-$		Morpholino	H	Ether/dioxane	0+rt	1 h	91	149–150	190
$-CH_2(CH_2)_2CH_2-$		1-(4-Methylpiperazino)	H	Ether	0+rt	1 h	73	158–159	190
$-CH_2(CH_2)_3CH_2-$		Dimethylamino	H	Ether	0+rt	1 h	79	69–70	193
$-CH_2(CH_2)_3CH_2-$		Diethylamino	H	Ether	0+rt	1 h	71	60–61	193
$-CH_2(CH_2)_3CH_2-$		Di-*n*-propylamino	H	Ether	0+rt	1 h	89	53.5–54.5	193
$-CH_2(CH_2)_3CH_2-$		Pyrrolidino	H	Ether	0+rt	1 h	84	85–86	193
$-CH_2(CH_2)_3CH_2-$		Piperidino	H	Ether	0+rt	1 h	69	114–115	193
$-CH_2(CH_2)_3CH_2-$		1-(4-Methylpiperazino)	H	Dioxane	0+rt	1 h	66	129–130	193
$-CH_2(CH_2)_3CH_2-$		Morpholino	H	Ether	0+rt	1 h	85	103–104	193
$-CH_2(CH_2)_3CH_2-$		1-(4-Methylpiperazino)	H	Ether	0+rt	1 h	82	100–101	193
$-CH_2(CH_2)_3CH_2-$		1-(4-Phenylpiperazino)	H	Ether	0+rt	1 h	77	146.5–147.5	193
$-CH_2(CH_2)_3CH_2-$		1-Hexahydroazepino	H	Ether	0+rt	1 h	65	75–76	193
$-CH_2(CH_2)_3CH_2-$		1-Octahydroazocino	H	Ether	0+rt	1 h	73	88–89	193
$-CH_2(CH_2)_3CH_2-$		1,2,3,4-Tetrahydroquinolino	H	Ether	0+rt	1 h	77	140–141	193
$-CH_2(CH_2)_3CH_2-$		$N(CH_3)(CH_2)_2N(C_2H_5)_2$	H	Ether	0+rt	1 h	*a*	(140/0.05)	193
$-CH_2(CH_2)_3CH_2-$		$N(C_2H_5)(CH_2)_2N(C_2H_5)_2$	H	Ether	0+rt	1 h	*a*	(140/0.05)	193
$-CH_2(CH_2)_4CH_2-$		Dimethylamino	H	Ether	0+rt	1 h	74	86–87	193
$-CH_2(CH_2)_4CH_2-$		Diethylamino	H	Ether	0+rt	1 h	64	64–65	193
$-CH_2(CH_2)_4CH_2-$		Di-*n*-propylamino	H	Ether	0+rt	1 h	65	(150–155/0.1)	193
$-CH_2(CH_2)_4CH_2-$		Pyrrolidino	H	Ether	0+rt	1 h	82	92–93	193
$-CH_2(CH_2)_4CH_2-$		Piperidino	H	Ether	0+rt	1 h	65	126–127	193
$-CH_2(CH_2)_4CH_2-$		1-(4-Phenylpiperidino)	H	Ether	0+rt	1 h	49	181–182	193
$-CH_2(CH_2)_4CH_2-$		Morpholino	H	Ether	0+rt	1 h	85	127–128	193
$-CH_2(CH_2)_4CH_2-$		1-(4-Methylpiperazino)	H	Ether	0+rt	1 h	59	97–98	193
$-CH_2(CH_2)_4CH_2-$		1-(4-Phenylpiperazino)	H	Ether	0+rt	1 h	53	147–148	193
$-CH_2(CH_2)_4CH_2-$		1-Hexahydroazepino	H	Ether	0+rt	1 h	62	84.5–85.5	193
$-CH_2(CH_2)_4CH_2-$		1-Octahydroazocino	H	Ether	0+rt	1 h	50	76–77	193
$-CH_2(CH_2)_4CH_2-$		1,2,3,4-Tetrahydroquinolino	H	Ether	0+rt	1 h	51	147–148	193
$-CH_2(CH_2)_4CH_2-$		$N(CH_3)(CH_2)_2N(C_2H_5)_2$	H	Ether	0+rt	1 h	49	(185–190/0.5)	193
$-CH_2(CH_2)_4CH_2-$		$N(C_2H_5)(CH_2)_2N(C_2H_5)_2$	H	Ether	0+rt	1 h	64	(190–195/0.5)	193
4,5-(*cis*-Carane)		Piperidino	H	Ether	0+rt	1 h	74	(165–168/0.3)	194

$-CH_2CH_2N(CH_2C_6H_5)CH_2-$	Dimethylamino	H	Ether	0+rt	1 h	10	90–92	195
$-CH_2CH_2N(CH_2C_6H_5)CH_2-$	Diethylamino	H	Ether	0+rt	1 h	60	94–95	195
4,3-(2,3-Dihydrochromane)	Pyrrolidino	H	Dioxane	0+rt	4 h	30	124–125	196
4,3-(2,3-Dihydrochromane)	Piperidino	H	Ether/dioxane	0+rt	4 h	30	148–149	196
4,3-(2,3-Dihydrochromane)	Morpholino	H	Ether/THF	0+rt	4 h	45	171–172	196
4,3-(2,3-Dihydro-6-methylchromane)	Pyrrolidino	H	Ether	0+rt	4 h	26	129–130	196
4,3-(2,3-Dihydro-6-methylchromane)	Piperidino	H	Ether	0+rt	4 h	70	145–146	196
4,3-(2,3-Dihydro-6-methylchromane)	Morpholino	H	Ether	0+rt	4 h	33	157	196

[a] Not reported in the original paper.

TABLE XVI. Adducts from α-Oxoketenes



α-Oxoketenes			X=Y		Reaction conditions					
Origin	R	R_1	X	Y	Solvent	T, °C	Time	Yield, %	Mp, °C	Ref
D	C_6H_5	COC_6H_5	C_6H_5N	CO	Benzene	80	1 h	43	242	204
D	C_6H_5	COC_6H_5	p-$CH_3C_6H_4N$	CO	Benzene	80	6 h	45	243	204
D	C_6H_5	COC_6H_5	C_6H_5N	CHC_6H_5	Xylene	Refl	2 h	27	168–169	205
D	C_6H_5	COC_6H_5	p-$CH_3C_6H_4N$	CHC_6H_5	Xylene	Refl	2 h	76[a]	*a*	205
D	C_6H_5	COC_6H_5	p-$NO_2C_6H_4N$	CHC_6H_5	Xylene	Refl	2 h	58[a]	*a*	205
B	$-CH_2CH_2CH_2-$		O	$CHCCl_3$	Xylene	130–140	40′	66	129.5–131	201
C	$-CH_2CH_2CH_2-$		O	$CHCCl_3$	Ether	35	40′	56	134–136	202
C	$-CH_2CH_2CH_2-$		O	$CHCBr_3$	Ether	35	40′	21	153–155	202
C	$-CH_2CH_2CH_2-$		O	CHC_2H_5	Ether	35	40′	88.5	*b*	202
C	$-CH_2CH_2CH_2-$		O	CHC_6H_5	Ether	35	40′	71	97	202
B	$-CH_2CH_2CH_2-$		O	CH-*o*-ClC_6H_4	Xylene	130–140	40′	61	105	201
C	$-CH_2CH_2CH_2-$		O	CH-*o*-ClC_6H_4	Ether	35	40′	40	110–111	202
B	$-CH_2CH_2CH_2-$		O	CH-*p*-ClC_6H_4	Xylene	130–140	40′	54	103	201
C	$-CH_2CH_2CH_2-$		O	CH-*p*-ClC_6H_4	Ether	35	40′	65	104–105	202
C	$-CH_2CH_2CH_2-$		O	CH-*o*-$CH_3C_6H_4$	Ether	35	40′	61.5	102–103	202
C	$-CH_2CH_2CH_2-$		O	CH-*p*-$CH_3C_6H_4$	Ether	35	40′	59	87–88	202
C	$-CH_2CH_2CH_2-$		O	CH-*p*-$CH_3OC_6H_4$	Ether	35	40′	71.5	92–93	202
B	$-CH_2CH_2CH_2-$		O	CH-*p*-$NO_2C_6H_4$	Xylene	130–140	40′	74	129.5	201
C	$-CH_2CH_2CH_2-$		O	CH-*p*-$NO_2C_6H_4$	Ether	35	40′	33	129–130	202
C	$-CH_2CH_2CH_2-$		O	$CHCH{=}CHC_6H_5$	Ether	35	40′	53.5	116–118	202
C	$-CH_2CH_2CH_2-$		O	CH(2-furyl)	Ether	35	40′	54	105–107	202
C	$-CH_2CH_2CH_2-$		O	CH(4-pyridyl)	Ether	35	40′	45	106–107	202
C	$-CH_2CH_2CH_2-$		O	$C(CH_3)_2$	Ether	*c*	*c*	71.5	*c*	203
C	$-CH_2CH_2CH_2-$		O	$C(CH_3)_2$	Ether	35	40′	71.5	38	202
B	$-CH_2CH_2CH_2-$		O	$C(CH_2)_5$	Cyclohexane	120	1 h	72.5	42	201
C	$-CH_2CH_2CH_2-$		O	$C(CH_2)_5$	Ether	35	40′	71	40–41	202
C	$-CH_2CH_2CH_2-$		O	$C(CH_3)C_2H_5$	Ether	35	40′	51.5	*b*	202
C	$-CH_2CH_2CH_2-$		O	$C(CH_3)C_6H_5$	Ether	35	40′	9	93–95	202
B	$-CH_2CH_2CH_2-$		N	CC_6H_5	C_6H_5CN	145	1 h	56–66	193	201
C	$-CH_2CH_2CH_2-$		CH_3N	$C(SCH_3)_2$	Ether	rt	80′	43	69–70	202
C	$-CH_2CH_2CH_2-$		n-C_3H_7N	$CHCCl_3$	Ether	rt	80′	20	104–106	202
C	$-CH_2CH_2CH_2-$		n-C_4H_9N	$CHCCl_3$	Ether	rt	80′	16	63–64	202
B	$-CH_2CH_2CH_2-$		C_6H_5N	CHC_6H_5	Xylene	140+rt	1.5+8 h	25[d]	101–104	201

TABLE XVI (Continued)

α-Oxoketenes			X=Y		Reaction conditions					
Origin	R	R_1	X	Y	Solvent	T, °C	Time	Yield, %	Mp, °C	Ref
C	$-CH_2CH_2CH_2-$		$(C_6H_5)_2C$	CO	Ether	35	1 h	21	179–180	202
C	$-C(CH_3)_2CH_2CH_2-$		O	CHC_6H_5	Ether	35	40′	56	85–86	202
C	$-C(CH_3)_2CH_2CH_2-$		O	$C(CH_3)_2$	Ether	35	40′	85.5	64–65	202
C	$-C(CH_3)_2CH_2CH(CH_3)-$		O	CHC_6H_5	Ether	35	40′	60	72–73	202
C	$-C(CH_3)_2CH_2CH(CH_3)-$		O	$C(CH_3)_2$	Ether	35	40′	85	*b*	202
E	$-C(CH_3)_2CH_2CH(CH_3)-$		3-Cl-4-$CF_3C_6H_3N$	CO[e]	*c*	140	*c*	82.5	*c*	207
f	(5α)-Cholestane		O	$C(CH_3)_2$	THF + Me_2CO	rt	16 h	6.5[g]	177–179	208
f	(5α)-Cholestane		$C_6H_{11}N$	$C{=}NC_6H_{11}$	Benzene	Several	Long	76	*h*	208
f	4-Cholestene		O	$C(CH_3)_2$	THF + Me_2CO	rt	16 h	1.4	155–157	208
f	4-Cholestene		$C_6H_{11}N$	$C{=}NC_6H_{11}$	Benzene	rt+refl	16+1 h	46[a]		208

[a] Isolated as hydrolysis product. [b] Liquid which decomposes upon distillation. [c] Not reported in the abstract. [d] 17% yield of 158 (mp 245°) also obtained. [e] Several other derivatives in the original paper are not reported in the abstract. [f] From α-keto acid with DCC. [g] Plus 32% of adduct with DCC. [h] Amorphous resin.

TABLE XVII. Adducts from *o*-Quinones

o-Quinone	X=Y	Reaction conditions			Yield, %	Mp (bp/mmHg), °C	Ref
		Solvent	T, °C	Time			
o-Benzoquinone	2,3,4,5-Tetraphenylcyclopentadienone	$CHCl_3$	−20+rt	6+24 h	3[a]	230–234	213
o-Benzoquinone	Furan	CH_2Cl_2	−25+rt	6h+2d	1	61	215
o-Benzoquinone	2-Methylfuran	CH_2Cl_2	−25+rt	6+36 h	25	(130–135/5–7)	215
o-Benzoquinone	2,5-Diphenylfuran	*b*	*b*	*b*	*b*	117	212
o-Benzoquinone	Benzofuran	$CHCl_3$	−25+rt	24 h	0		215
Tetrachloro-*o*-benzoquinone	*trans*-Stilbene	*b*	128	*b*	*b*	*b*	211
Tetrachloro-*o*-benzoquinone	*cis*-Stilbene	*b*	128	*b*	*b*	177	211
Tetrachloro-*o*-benzoquinone	$CH_2{=}CHCH{=}CHC_6H_5$	Ether	−40–20	30′	80	148–149	219
Tetrachloro-*o*-benzoquinone	$CH_2{=}CHCH{=}CH$-*p*-$NO_2C_6H_4$	Ether	−40–20	30′	84	230–231	219
Tetrachloro-*o*-benzoquinone	9,10-Anthraquinonedimethide[c]	Benzene	Refl	2 d	18	240 dec	210
Tetrachloro-*o*-benzoquinone	9,10-Anthraquinonedimethide[d]	Benzene	Refl	12 h	16	240 dec	210
Tetrachloro-*o*-benzoquinone	7,12-Benzanthraquinonedimethide	Benzene	Refl	3 d	19	247 dec	210
Tetrachloro-*o*-benzoquinone	2,5-Dimethyl-3,4-diphenylcyclopentadienone	*b*	*b*	*b*	*b*	193–195	212
Tetrachloro-*o*-benzoquinone	2,3,4,5-Tetraphenylcyclopentadienone	Benzene	rt	6 h	86	218–220	213
Tetrachloro-*o*-benzoquinone	Phenylcyclone	*b*	rt	*b*	*b*	280–282	212
Tetrachloro-*o*-benzoquinone	*cis*-1,2-Dimethoxyethylene	*b*	20	*b*	*b*	164	214
Tetrachloro-*o*-benzoquinone	1-Piperidinoisobutene	*e*	*f*	*g*	39	123	216
Tetrachloro-*o*-benzoquinone	1-Morpholinocyclohex-1-ene	*e*	*f*	*g*	26	152–153	216
Tetrachloro-*o*-benzoquinone	Furan	Benzene	Refl	12 h	62	178–180	215
Tetrachloro-*o*-benzoquinone	2-Methylfuran	Benzene	rt	24 h	76	153–154	215
Tetrachloro-*o*-benzoquinone	2,5-Diphenylfuran	Benzene	rt	24 h	78	154–155	215
Tetrachloro-*o*-benzoquinone	Benzofuran	Benzene	Refl	48 h	28	161–162	215
Tetrachloro-*o*-benzoquinone	$CH_3(CH_2)_{17}CH{=}C{=}O$	Toluene	Refl	2 h	77	82–83	218
Tetrachloro-*o*-benzoquinone	*m*-$CH_3C_6H_4CH{=}C{=}O$	Toluene	Refl	2 h	62	133–134	218
Tetrachloro-*o*-benzoquinone	*p*-$CH_3OC_6H_4CH{=}C{=}O$	Toluene	Refl	2 h	64	159–160	218
Tetrachloro-*o*-benzoquinone	β-Naphthyl—$CH{=}C{=}O$	Toluene	Refl	2 h	59	194–195	218
Tetrachloro-*o*-benzoquinone	$(C_6H_5)_2C{=}C{=}NC_6H_5$	Ether	rt	h	78	158–160	217
Tetrachloro-*o*-benzoquinone	$(C_6H_5)_2C{=}C{=}N$-*o*-$CH_3C_6H_4$	Ether	rt	h	65	217–219	217

Tetrachloro-*o*-benzoquinone	$(C_6H_5)_2C{=}C{=}N\text{-}p\text{-}CH_3C_6H_4$	Ether	rt	h	89	170–172	217
Tetrachloro-*o*-benzoquinone	$(C_6H_5)_2C{=}C{=}N\text{-}p\text{-}CH_3OC_6H_4$	Ether	rt	h	74	168–170	217
Tetrachloro-*o*-benzoquinone	$O{=}C{=}CH(CH_2)_4CH{=}C{=}O$	Toluene	Refl	2 h	78[i]	220–222	218
Tetrachloro-*o*-benzoquinone	$O{=}C{=}CH(CH_2)_6CH{=}C{=}O$	Toluene	Refl	2 h	32[i]	180–182	218
Tetrabromo-*o*-benzoquinone	1-Piperidinoisobutene	*e*	*f*	*g*	37	140	216
Tetrabromo-*o*-benzoquinone	1-Morpholinocyclohex-1-ene	*e*	*f*	*g*	35	149–150	216
Tetrabromo-*o*-benzoquinone	$CH_3(CH_2)_{17}CH{=}C{=}O$	Toluene	Refl	2 h	50	86–88	218
Tetrabromo-*o*-benzoquinone	$C_6H_5{-}CH{=}C{=}O$	Toluene	Refl	2 h	58	204–205	218
Tetrabromo-*o*-benzoquinone	$m\text{-}CH_3C_6H_4CH{=}C{=}O$	Toluene	Refl	2 h	45	165–167	218
Tetrabromo-*o*-benzoquinone	$p\text{-}CH_3OC_6H_4CH{=}C{=}O$	Toluene	Refl	2 h	73	192–194	218
Tetrabromo-*o*-benzoquinone	β-Naphthyl—$CH{=}C{=}O$	Toluene	Refl	2 h	38	204–206	218
Tetrabromo-*o*-benzoquinone	$(C_6H_5)_2C{=}C{=}NC_6H_5$	Ether	rt	*h*	69	229–231	217
Tetrabromo-*o*-benzoquinone	$(C_6H_5)_2C{=}C{=}N\text{-}o\text{-}CH_3C_6H_4$	Ether	rt	*h*	71	253–255	217
Tetrabromo-*o*-benzoquinone	$(C_6H_5)_2C{=}C{=}N\text{-}p\text{-}CH_3C_6H_4$	Ether	rt	*h*	96	204–206	217
Tetrabromo-*o*-benzoquinone	$(C_6H_5)_2C{=}C{=}N\text{-}p\text{-}CH_3OC_6H_4$	Ether	rt	*h*	97	190–192	217
Tetrabromo-*o*-benzoquinone	$O{=}C{=}CH(CH_2)_4CH{=}C{=}O$	Toluene	Refl	2 h	71[i]	260–262	218
Tetrabromo-*o*-benzoquinone	$O{=}C{=}CH(CH_2)_6CH{=}C{=}O$	Toluene	Refl	2 h	15[i]	198–200	218
Phenanthrenequinone	1-Piperidinoisobutene	*e*	*f*	*g*	25	119–120	216
Phenanthrenequinone	1-Morpholinocyclopent-1-ene	*e*	*f*	*g*	35	137.5	216
Phenanthrenequinone	1-Morpholinocyclohex-1-ene	*e*	*f*	*g*	27	166	216
Chrysoquinone	1-Piperidinoisobutene	*e*	*f*	*g*	31	129–130	216
Chrysoquinone	1-Morpholinocyclohex-1-ene	*e*	*f*	*g*	60	175–176	216

[a] Plus **174** type adduct (4% yield, mp 148–150°). [b] Not reported in the original paper. [c] From 9,10-dimethylanthracene. [d] From *cis*-9,10-dimethyl-9,10-dihydroanthracene. [e] Benzene, chloroform or toluene. [f] −10° and +90°. [g] Spontaneously or long heating. [h] The reaction is accomplished when the violet color of the starting product turns to rose. [i] Bis adducts (ratio quinone/X═Y 2:1).

SCHEME XXXIX

atives;[202,203] (D) from furan-4,5-dione derivatives;[204–206] (E) from 1,3-dioxin-4-ones.[207]

α-Oxoketenes **156** are useful intermediates because their reaction with double and triple bonds seems to be a promising synthetic approach to condensed heterocyclic derivative. They react easily with carbodiimides,[200,204] carbonyl compounds,[201–203] nitriles[201,206] isocyanates,[203,204,207] and ketenes[202] to form six-membered ring adducts (Scheme XL). With Schiff bases, 1,4-cycloadducts **157**[202,205] are formed, sometimes together with 1,2-cycloadducts **158.**[201]

SCHEME XL

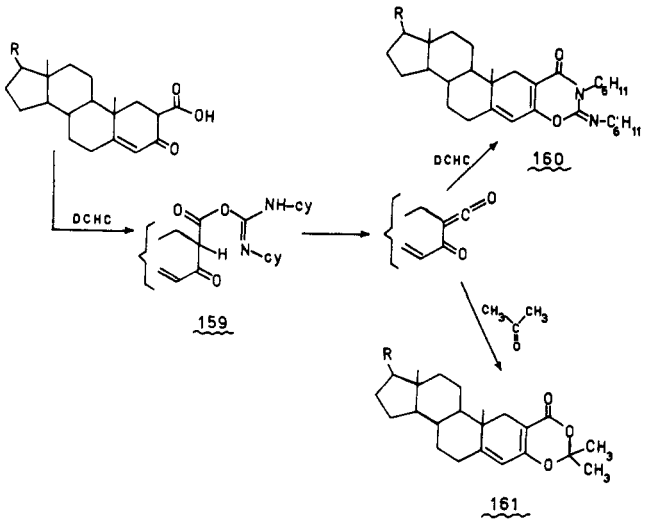
A similar cycloaddition was also performed in the steroid field[208] (Scheme XLI), and dicyclohexylcarbodiimide (DCHC) can act both as a generator of α-oxoketene, via **159,** and as a partner in the heterodiene reaction to give **160.** If the reaction is performed in the presence of acetone, 1,3-dioxin steroids **161** are obtained. Table XVI collects the previously reported adducts.

XI. α,β-Unsaturated Carbonyls Containing Heteroatoms

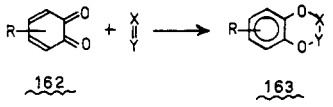
A. Oxygen Derivatives (*o*-Quinones)

The thermal cycloaddition of *o*-quinones **162** to double and triple bonds together with analogous photochemical reactions

SCHEME XLI

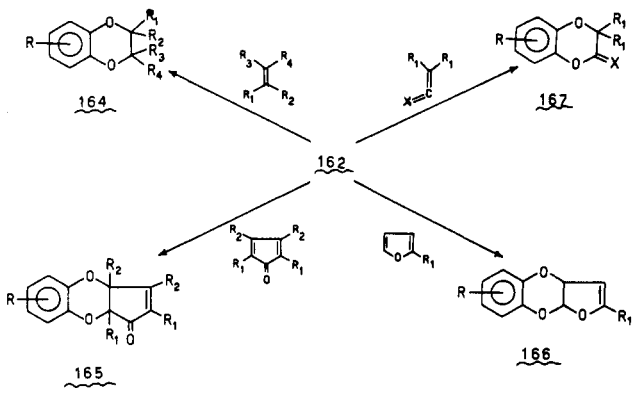


has been reviewed by Pfundt and Schenck in Harmer's book,[209] and several examples of the formation of 1,4-dioxin derivatives **163** have been reported.



Some new examples have been reported in recent years and C=C double bonds belonging to hydrocarbons,[210,211] ketones,[212,213] vinyl ethers,[214] heterocyclic rings,[212,215] enamines,[216] N-substituted diphenylketenimines,[217] and ketenes[218] are reported to give **164–167** (Scheme XLII). The adducts are collected in Table XVII.

SCHEME XLII

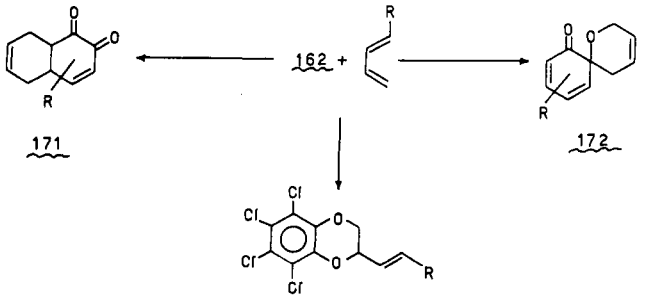


The cycloaddition is sensitive to steric interactions, as the less substituted double bonds reacts to give **166.** Clearly the driving force of this reaction is the aromaticity gain, and therefore the overall situation resembles that of *o*-quinone methides (**13**), previously discussed in section V.A.

Different behavior was shown by isobenzofuran (**168**)[215] which gives ring opening to **170** (Scheme XLIII). **169** is not formed since **170** allows both benzene rings to be aromatic.

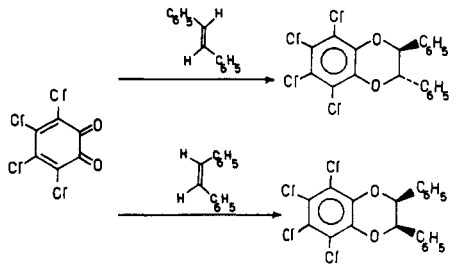
When *o*-benzoquinone is tetrahalo-substituted the cycloaddition becomes easier, yields are sharply increased, and the quinone system also behaves as a heterodiene with butadiene derivatives;[219] otherwise it acts as a dienophile and both C=C[220-222] and C=O bonds[219,221] can react to give **171** and **172,** respectively (Scheme XLIV). The configuration of

SCHEME XLIV



the double bond is strictly retained in the adduct as shown by Bryce-Smith[211] for *cis*- and *trans*-stilbene (Scheme XLV).

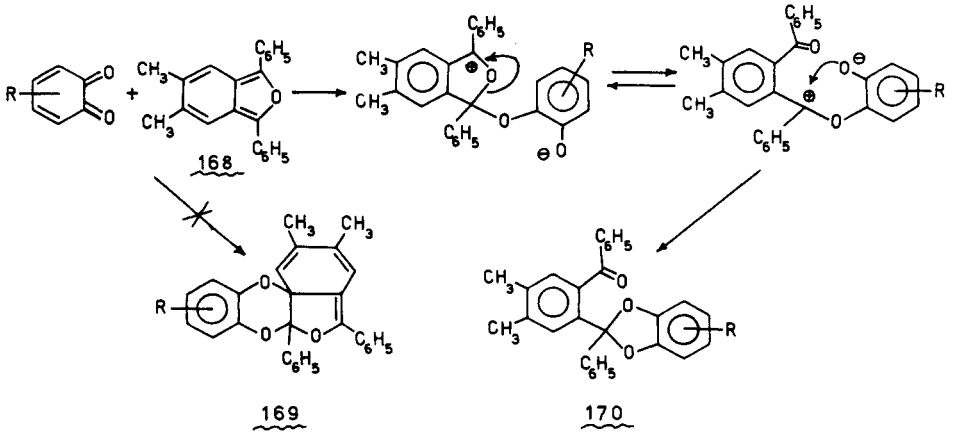
SCHEME XLV



This behavior strongly indicates the existence of an allowed pathway to the concerted thermal cycloaddition in contrast to the previously proposed[214] two-step mechanism with a zwitterionic intermediate.

Herndon and Giles[223] definitively supported the former mechanism. HOMO and LUMO levels of *o*-benzoquinone and stilbene have been calculated and their values (in terms of γ^2/β units, where γ is the perturbation exchange integral and β is the Hückel exchange integral) are reported in Figure 10.

SCHEME XLIII



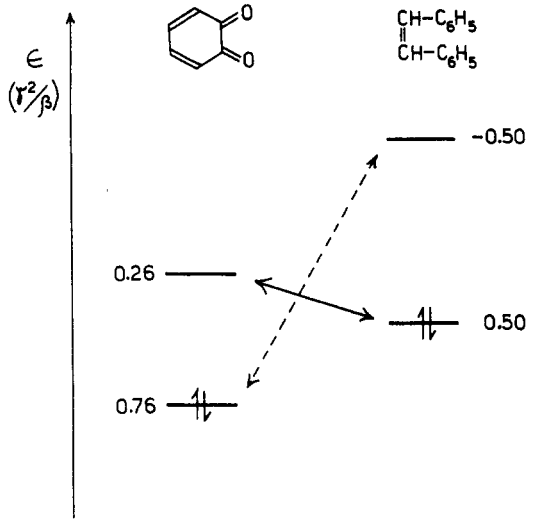


Figure 10. Frontier orbital energies of *o*-benzoquinone and stilbene. Solid arrow indicates the dominant interaction.

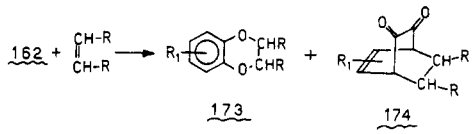
The largest interaction for the thermal cycloaddition occurs between the HOMO of stilbene and the LUMO of *o*-benzoquinone. Even if the proximity of the levels ensures a large frontier control, the symmetry of the reagents forbids the nonsynchroneity of the cycloaddition.

The pathways to 1,4-dioxin derivatives **173** can be compared with those giving rise to bicyclooctadiene derivative **174** taking into account the secondary interactions. The results for some model reactions are reported in Table XVIII. **173** is favored in every case but particularly with tetrahaloquinones; in fact, **174** was only found to be formed in low yield when the quinone is unsubstituted.[213] However, the values found do not explain the behavior of halogen substituents in making the reaction easier.

TABLE XVIII. Energies for Thermal 1,4-Cycloadditions of *o*-Quinones and Olefins

Reagents	173	174
o-Benzoquinone + stilbene	2.62[a]	1.59
Tetrachloro-*o*-benzoquinone + stilbene	2.47	0.69
o-Benzoquinone + but-2-ene	4.60	2.13
Tetrachloro-*o*-benzoquinone + but-2-ene	4.23	0.62

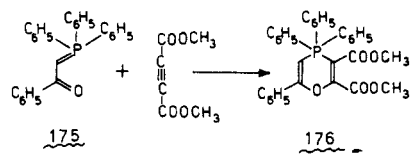
[a] All values in γ^2/β units.



A better rationalization of the experimental observation that reactions which do not occur with *o*-benzoquinone occur easily with its tetrachloro analog,[215] would be that electron-withdrawing halogens lower both the HOMO and the LUMO of quinones, causing a lower frontier orbital separation.

B. Phosphorus Derivatives

The reaction of the 1-oxa-4-phosphabutadiene system **175** with acetylenedicarboxylate to give the 4-phosphapyran derivative **176** has been described,[224] but so far no other phosphorus derivative seems to have been obtained by this route.

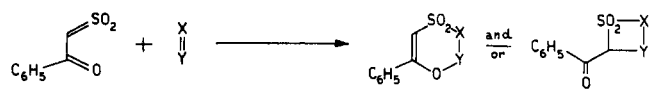


C. Sulfur Derivatives

Few examples are known where acylsulfenes act as α,β-unsaturated carbonyl compounds since, like all sulfenes, they prefer to act as dienophiles.[225] However, benzoylsulfene **177**, prepared in situ from $C_6H_5COCH_2SO_2Cl$ in the presence of triethylamine, can dimerize to **178** in accordance with a 1,4-cycloaddition.[226] The same behavior occurs with vinyl ethers[227] and ketenimines,[228] but enamines undergo a 1,2-cycloaddition[227] (Scheme XLVI).

Both 1,2- and 1,4-cycloadducts **179** and **180** have been obtained with azomethines,[229] and it is difficult to rationalize a behavior which largely depends upon substituents, conditions, and time of reaction; nevertheless, **180** seems to be the kine-

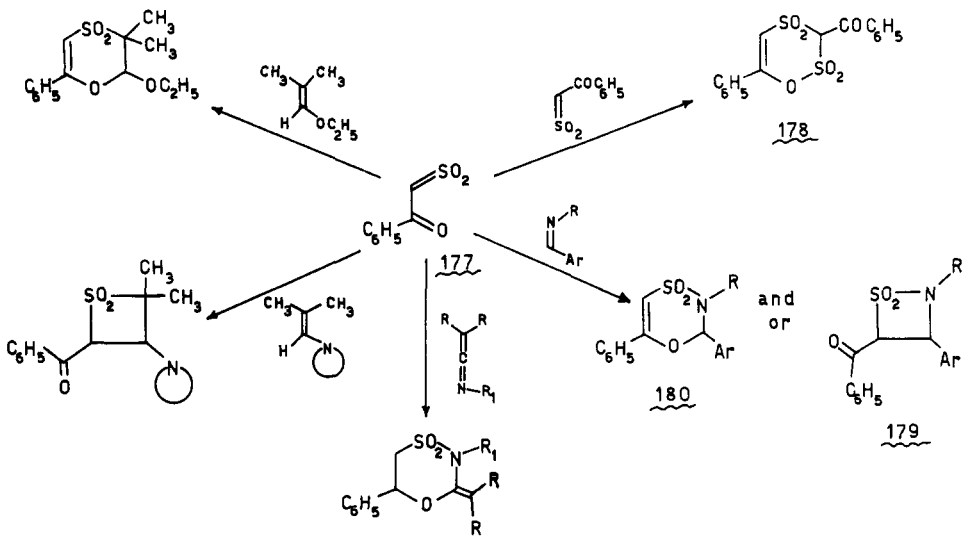
TABLE XIX. Adducts from Benzoylsulfene[a]



Heterodienophile X=Y		Reaction conditions			Total yield, %	1,4-Adduct Yield %	1,4-Adduct Mp, °C	1,2-Adduct Yield, %	1,2-Adduct Mp, °C	Ref
X	Y	Solvent	T, °C	Time						
$(CH_3)_2C$	$CHOC_2H_5$	*b*	*b*	*b*	42	42	*b*			227
$(CH_3)_2C$	CH(1-pyrrolidino)	*b*	*b*	*b*	40			40	*b*	227
C_6H_5COCH	SO_2	$CHCl_3$	0 + refl	10′	45	45	146–147			226
n-C_3H_7N	CHC_6H_5	Dioxane	rt	3 h	82	82	123 dec	*c*		229
n-C_3H_7N	CHC_6H_5	Dioxane	rt	15 h	57	57	123 dec			229
n-C_4H_9N	$C{=}C(C_6H_5)_2$	*b*	*b*	*b*	48	48	137			228
C_6H_5N	CHC_6H_5	Dioxane	rt	1 h	38	38	*d*			229
C_6H_5N	CHC_6H_5	Dioxane	rt	12 h	34	14	*d*	20	164–165	229
C_6H_5N	CHC_6H_5	Dioxane	rt	24 h	30			30	164–165	229
C_6H_5N	CHC_6H_5	Dioxane	rt	25 h	22			22	164–165	229
C_6H_5N	CHC_6H_4-*p*-NO_2	Dioxane	rt	15 h	0					229
p-$CH_3C_6H_4N$	CHC_6H_5	Dioxane	rt	100 h	24			24	163	229
p-$CH_3C_6H_4N$	$C{=}C(CH_3)_2$	Dioxane	rt	2 h	74	74	165			228
p-$CH_3OC_6H_4N$	CHC_6H_5	Dioxane	rt	50 h	10			10	138	229
$C_6H_5CH_2N$	CHC_6H_5	Dioxane	rt	100 h	37	32	158 dec	5	143	229
c-$C_6H_{11}N$	CHC_6H_5	Dioxane	rt	15 h	27	27	153 dec			229

[a] Generated in situ from $C_6H_5COCH_2SO_2Cl$ in the presence of 1 mol of Et_3N. [b] Not reported in the original paper. [c] Isolated only in the absence of NEt_3, with 2 mol of azomethines (13% yield, mp 148°). [d] Unstable and therefore not insolated.

SCHEME XLVI



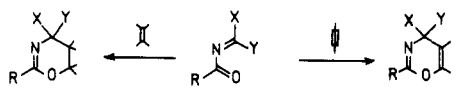
tically controlled adduct and **179** the thermodynamically more stable one. The adducts are reported in Table XIX.

D. Nitrogen Derivatives

This class of reagents is well studied, and examples of heterodiene reactions with one or two nitrogen atoms are known.

1. Compounds with One Nitrogen Atom

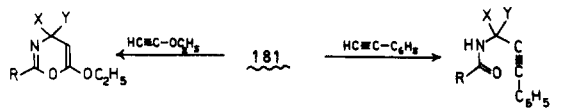
Some 1,4-cycloadditions of *N*-acylimines **181** with olefins and acetylenes have been recently reviewed[230,231] because 1,3-oxazine derivatives are useful synthetic intermediates.



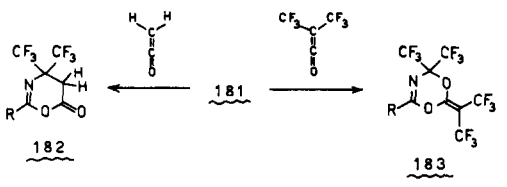
181

Since X and (or) Y are strongly electron-withdrawing groups to counterbalance the polarization of electrons in **181** and render the molecule stable, *N*-acylimines behave as electrophiles and can be in general considered as the acceptor partner in a cycloaddition. **181** reacts with vinyl ethers,[232-234] olefins,[232,233] enamines,[235] and sulfene,[235] and, in accordance with a 1,4-cycloaddition, several heterocyclic rings are formed (Scheme XLVII).

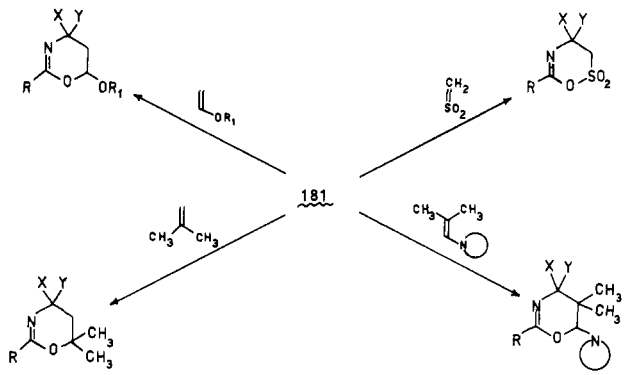
Acetylenes can give either a 1,4-cycloadduct[235] (ethoxyacetylene) or a Michael-type adduct (phenylacetylene).[233]



The reaction of *N*-acylimines with ketenes is far more interesting since a 1,4-cycloaddition always occurs. The reaction sometimes involves the C=C and sometimes the C=O double bond of ketene depending on the substituents.



SCHEME XLVII



182 is formed when the ketene is unsubstituted,[232,233,236] but **183** is produced with bis(trifluoromethyl)ketene.[235] An attempt to explain the low reactivity to give **183** was accomplished in terms of steric factors.[235] In the opinion of the reviewers an alternative rationalization of both the low reactivity and the site of attack could be given in terms of frontier orbitals.

Sustmann[237] pointed out that the better stabilization in the reaction between ketene and olefins involves frontier orbitals of the olefin and the C=C frontier orbitals of ketene. Strong electron-withdrawing substituents on the methylene group make the ketene C=C double bond similar to a C=O group giving rise to competition.

This occurs not only in [2 + 2] cycloaddition, but also in [6 + 4].

The recent CNDO/2 calculation of frontier MO's and coefficients of ketene, performed by Houk,[197] suggests that the stronger interaction occurs between the ketene HOMO and the heterodiene LUMO (Figure 11). The larger coefficient at the methylene carbon atom of the ketene will make this the site of electrophilic attack, to give **182.**

Trifluoromethyl substituents lower both the HOMO and LUMO of the ketene, and therefore the dominant interaction occurs between the heterodiene HOMO and the ketene LUMO. If the latter has the oxygen coefficient competitive with the *C* coefficient owing to the electron-withdrawing substituents, **183** could also be formed by nucleophilic attack of the oxygen atom.

2. Compounds with Two Nitrogen Atoms

Systems with two nitrogen atoms are azodicarbonyl com-

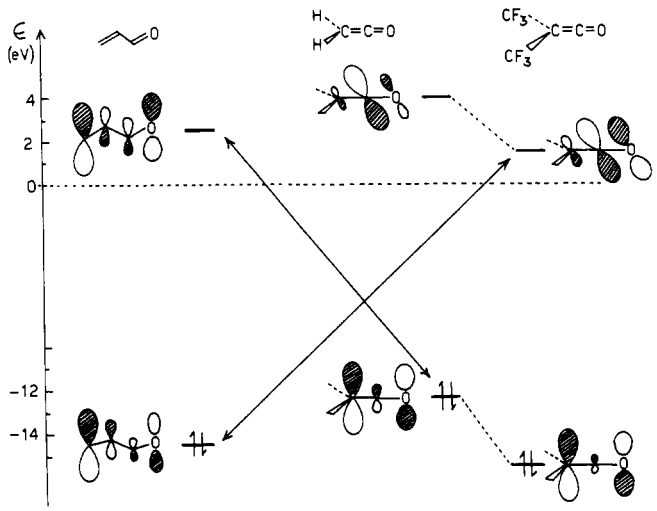
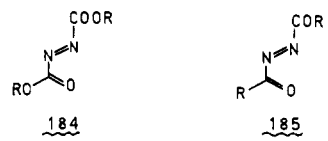


Figure 11. Frontier molecular orbital energies and coefficients of acrolein, ketene, and bis(trifluoromethyl)ketene (parameters of this are estimated from substituent effects). Solid arrows indicate the dominant interaction, that is, $HOMO_{ketene}/LUMO_{acrolein}$ and $HOMO_{acrolein}/LUMO_{ketene}$, respectively, if ketene is unsubstituted or bis(trifluoromethyl)-substituted.

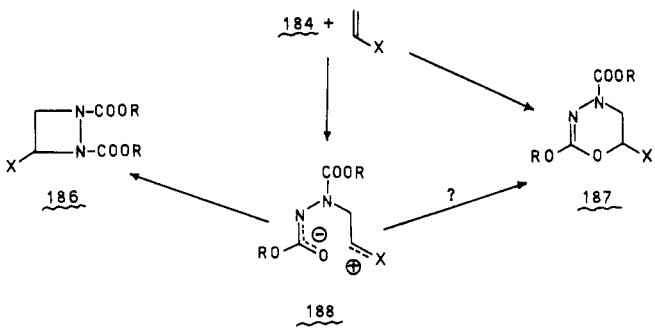
pounds with both ester **184** and keto groups **185.** Their behavior in cycloadditions is an intriguing one since several reaction modes have been discovered; unfortunately the wrong structure was often assigned and it had to be revised.



184 185

Azo esters **184** undergo both 1,2- and 1,4-cycloaddition leading to **186** and **187,** respectively (Scheme XLVIII). The former, giving **186,** predominates with tetramethoxyethane,[238] alkyl vinyl ethers,[239,240] and enamines;[239] the latter, giving **187,** is preferred for *cis*- and *trans*-1,2-dimethoxyethenes,[240] hydrocarbons,[241,242] and pseudo-nucleophilic olefins (vinyl acetate and 1-vinyl-2-pyrrolone).[243]

SCHEME XLVIII



186 187 188

A characteristic borderline case is the reaction with aryl vinyl ethers.[243,244] Both 1,2- and 1,4-cycloadditions occur, and the latter is preferred if an electron-attracting group decreases the nucleophilicity of the vinyl ether. The former is preferred by electron-releasing substituents (Table XX).

The presence of a zwitterionic intermediate (**188**) seems to be supported by large solvent effect: increased polarity stabilizes **188** and the 1,2-cycloadduct predominates.[243]

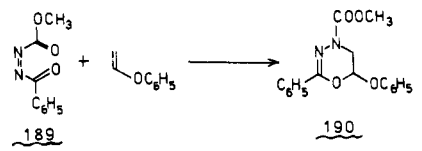
Azo ketones **185** strongly prefer 1,4-cycloaddition[244] which is the only reaction mode with styrene, vinyl ethers, vinyl thioethers, and enamines.[245] With these latter compounds, an early structural assignment[246] had to be revised[128] when an X-ray determination gave the correct structure of a cis-fused 1,4-adduct for **88.** Only 1,3-cycloaddition was obtained with ketenes.[247]

TABLE XX. Azo Dicarboxylate and Aryl Vinyl Ethers: Adduct Distribution[a]

Aryl group	Solvent	186, %	187, %
p-$CH_3OC_6H_4$		87 ± 3	13 ± 3
p-$CH_3C_6H_4$		84	16
C_6H_5	Acetonitrile	80 ± 3	20 ± 3
C_6H_5		77[b]–65	23[b]–35
C_6H_5	Benzene	33	67
p-ClC_6H_4		67	33
p-$NO_2C_6H_4$		5	95

[a] Reference 243. [b] Reference 244.

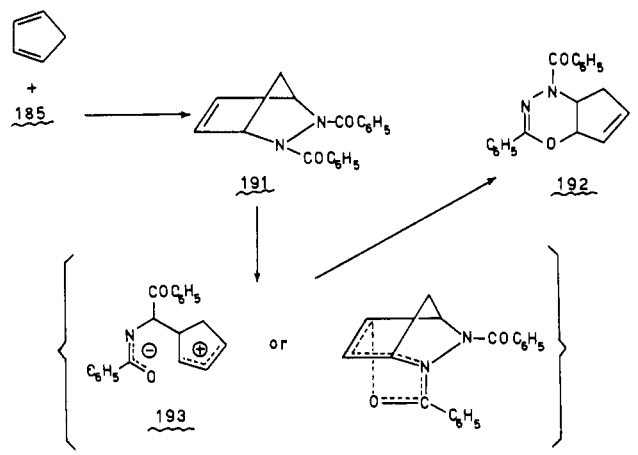
The different behavior of **184** and **185** was neatly demonstrated by the reaction of the asymmetrically substituted azo compound **189** with phenyl vinyl ether[245] in which only **190** was obtained.



189 190

Finally the reaction of **185** with cyclopentadiene was extensively discussed as **191** or (and) **192** is formed depending on the conditions (Scheme XLIX).[248]

SCHEME XLIX



185 191 192 193

191 was found to be the primary adduct (therefore **185** behaved as a dienophile), but it rearranged to **192.** This rearrangement was described as a [3,3]sigmatropic shift,[249] instead of a two-step mechanism involving **193,**[248] since both the energy and entropy of activation and the small solvent effect support a concerted mechanism.

All adducts involving nitrogen atoms in the heterodiene are described in Table XXI.

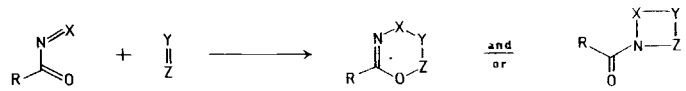
E. Derivatives with Cumulated Bonds

Acyl isocyanates **194** react with several substrates; with phenylacetylene,[250] azomethines,[251,252] and ketenes,[253] a 1,4-cycloaddition was obtained (Scheme L).

Vinyl ethers and vinyl thioethers gave open-chain adducts **195,**[254] probably via a 1,4-cycloadduct since in one case this latter was isolated.

Enamines gave **196** or **197**[255] depending mainly on the nature of the substituents; any attempt at rationalization is prevented by the small number of examples.

TABLE XXI. Adducts with Nitrogen-Containing Heterodienes

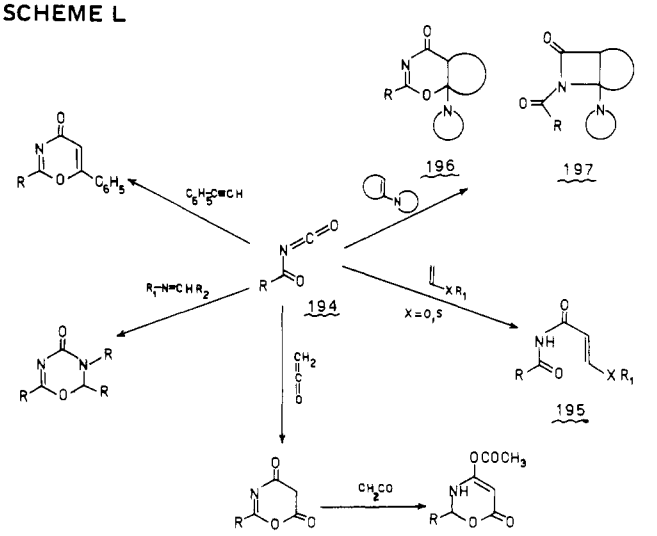


Heterodiene		Y = Z		Reaction conditions			1,4-Adduct		1,2-Adduct		
R	X	Y	Z	Solvent	T, °C	Time	Yield, %	Mp (bp/mmHg), °C	Yield, %	Mp (bp/mmHg), °C	Ref
CH_3	CH—CCl_3	H_2C	$CHOC_2H_5$	H_2O	0+rt	12 h	92	(88–89/0.15)			234
CH_3	$C(CF_3)_2$	H_2C	CO	Ether	rt	1–2 h	80	(61–62/10)			233, 236
C_2H_5	CH—CCl_3	H_2C	$CHOC_2H_5$	H_2O	0+rt	12 h	85	(91–92/0.15)			234
n-C_3H_7	CH—CCl_3	H_2C	$CHOC_2H_5$	H_2O	0+rt	12 h	89	(96–98/0.15)			234
C_6H_5	CH—CCl_3	H_2C	$CHOC_2H_5$	H_2O	0+rt	12 h	94	(153–158/0.08)			234
C_6H_5	$C(CF_3)_2$	H_2C	CO	Ether	rt	1–2 h	91	75–77			233, 236
C_6H_5	$C(CF_3)_2$	H_2C	SO_2	C_6H_6	rt	12 h	63	85–86			235
C_6H_5	$C(CF_3)_2$	H_2C	$C(CH_3)_2$		100	5 h	60	62–63			233
C_6H_5	$C(CF_3)_2$	H_2C	$CHOC_2H_5$		0	*a*	81	(105–107/0.1)			233
C_6H_5	$C(CF_3)_2$	H_2C	CH—O-n-C_4H_9		*a*	*a*	56	(110–111/0.1)			233
C_6H_5	$C(CF_3)_2$	$(CH_3)_2C$	CH(1-morpholino)		100	1.5 h	91	111–112			235
C_6H_5	$C(CF_3)_2$	HC≡	$\equiv CC_6H_5$		20	30 d	*b*				233
C_6H_5	$C(CF_3)_2$	HC≡	$\equiv COC_2H_5$		rt	*a*	80	97–98			235
C_6H_5	$C(CF_3)_2$	O	$C{=}C(CF_3)_2$		100	20 h	53	46–47			235
C_6H_5	$C(CF_3)(CF_2NO_2)$	H_2C	CO	Ether	rt	1–2 h	92	74–75			233
C_6H_5	$C(CF_3)(CF_2NO_2)$	H_2C	$C(CH_3)_2$		100	5 h	55	(92/0.1)			233
C_6H_5	$C(CF_3)(CF_2NO_2)$	HC≡	$\equiv CC_6H_5$		20	3 d	*c*				233
C_2H_5O	$C(CF_3)_2$	H_2C	CO	Ether	rt	1–2 h	94	(50–51/2)			233, 236
C_6H_5	$NCOC_6H_5$	H_2C	CHC_6H_5	C_6H_6	rt	*a*	67	134			245
C_6H_5	$NCOC_6H_5$	H_2C	$CHOC_6H_5$	C_6H_6	rt	*a*	64	112			245
C_6H_5	$NCOC_6H_5$	H_2C	$CHOC_6H_5$	*a*	rt	*a*	>63	112	<3	*a*	244, 245
C_6H_5	$NCOC_6H_5$	H_2C	$CHSC_2H_5$	C_6H_6	rt	*a*	78	114			245
C_6H_5	$NCOC_6H_5$	$(CH_3)_2C$	CH(1-morpholino)	C_6H_6	rt	*a*	81	159			245
C_6H_5	$NCOC_6H_5$	Norbornene		*a*	*a*	*a*	*a*	*a*			241
C_6H_5	$NCOC_6H_5$	1-Pyrrolidinocyclohex-1-ene			rt	*a*	100[d]	100			246
C_6H_5	$NCOC_6H_5$	1-Piperidinocyclohex-1-ene			rt	*a*	100[d]	156			246
C_6H_5	$NCOC_6H_5$	1-Morpholinocyclohex-1-ene			rt	*a*	100[d]	154			246
C_6H_5	$NCOOCH_3$	H_2C	$CHOC_6H_5$	*a*	*a*	*a*	66	105			245
C_7H_7	$NCOOC_7H_7$	1-Morpholinocyclohex-1-ene			rt	*a*	100[d]	149–151			246
CH_3O	$NCOOCH_3$	H_2C	$CHOCH_3$	C_6H_6	rt	4 d			29	(40–50/10^{-5})	240
CH_3O	$NCOOCH_3$	H_2C	$CHOC_2H_5$	YZ exc	rt	2 d			79	(40–54/10^{-5})	240
CH_3O	$NCOOCH_3$	H_2C	$CHOC_2H_5$		rt	*a*			86	(125–130/0.1)	239
CH_3O	$NCOOCH_3$	H_2C	$CHOCH_2CH(CH_3)_2$		rt	*a*			82	38	239
CH_3O	$NCOOCH_3$	H_2C	$CHO(CH_2)_{17}CH_3$	Ether	rt	*a*			78	90	239
CH_3O	$NCOOCH_3$	H_2C	$CHOC_6H_5$	*a*	rt	*a*	17 ± 2	104	56 ± 2	Oil	243, 244
CH_3O	$NCOOCH_3$	H_2C	CH—OC_6H_4-p-NO_2		rt	*a*	38	123	2	*a*	243
CH_3O	$NCOOCH_3$	H_2C	$CHOC_6H_4$-p-Cl		rt	*a*	18	*a*	38	*a*	243
CH_3O	$NCOOCH_3$	H_2C	$CHOC_6H_4$-p-CH_3		rt	*a*	14	*a*	71	*a*	243
CH_3O	$NCOOCH_3$	H_2C	$CHOC_6H_4$-p-OCH_3		rt	*a*	11 ± 2	*a*	71 ± 2	79	243
CH_3O	$NCOOCH_3$	H_2C	$CHOCOCH_3$		rt	*a*	62[d]	87			239, 243
CH_3O	$NCOOCH_3$	H_2C	$CHSC_2H_5$		rt	*a*	80	*a*			239
CH_3O	$NCOOCH_3$	H_2C	CH(1-pyrrolidyl-2-one)	Ether	rt	*a*	87[d]	137			239, 243

CH_3O	$NCOOCH_3$	H_2C	CH(1-carbazolyl)	Ether	rt	*a*		84	135	239
CH_3O	$NCOOCH_3$	CH_3OHC	$CHOCH_3$ (cis)	C_6D_6	rt	12 h	80	20	*a*	240
CH_3O	$NCOOCH_3$	CH_3OHC	$CHOCH_3$ (trans)	C_6D_6	20	12 h	100	128–130		240
CH_3O	$NCOOCH_3$	$(CH_3O)_2C$	$C(OCH_3)_2$	*a*	40–80	*a*		97	(150/0.01)	238
C_2H_5O	$NCOOC_2H_5$	Norbornene		*a*	*a*	*a*				241
C_2H_5O	$NCOOC_2H_5$	Norbornadiene		*a*	*a*	*a*	40[e]	(128–131/0.4)		241
C_2H_5O	$NCOOC_2H_5$	Indene		C_6H_6	Refl	6 h	*a*	103–105		242
C_2H_5O	$NCOOC_2H_5$	H_2C	$CHOC_2H_5$	YZ exc	rt	18 h		100	(108/3 × 10^{-5})	240
C_2H_5O	$NCOOC_2H_5$	H_2C	$CHOC_6H_5$		rt	*a*	29	101	55	54	243, 244
C_2H_5O	$NCOOC_2H_5$	H_2C	$CHOC_6H_5$	CH_3CN	rt	*a*	20 ± 3[f]	101	80 ± 3	54	243
C_2H_5O	$NCOOC_2H_5$	H_2C	$CHOC_6H_5$	Ether	rt	*a*	67[f]	101	33	54	243
C_2H_5O	$NCOOC_2H_5$	H_2C	$CHOC_6H_5$	C_6H_6	rt	*a*	67[f]	101	33	54	243
C_2H_5O	$NCOOC_2H_5$	H_2C	$CHOC_6H_5$	YZ exc	Refl	65 h	25	60–62			240
C_2H_5O	$NCOOC_2H_5$	H_2C	$CHOCOCH_3$		40–80	*a*			100	111	238
C_2H_5O	$NCOOC_2H_5$	$(CH_3O)_2C$	$C(OCH_3)_2$	*a*	*a*	*a*	*a*	*a*			241
C_6H_5O	$NCOOC_2H_5$	Norbornene		*a*	rt	*a*	4	*a*	81	73	244
Cl_3CCH_2O	$NCOOCH_2CCl_3$	H_2C	$CHOC_6H_5$								

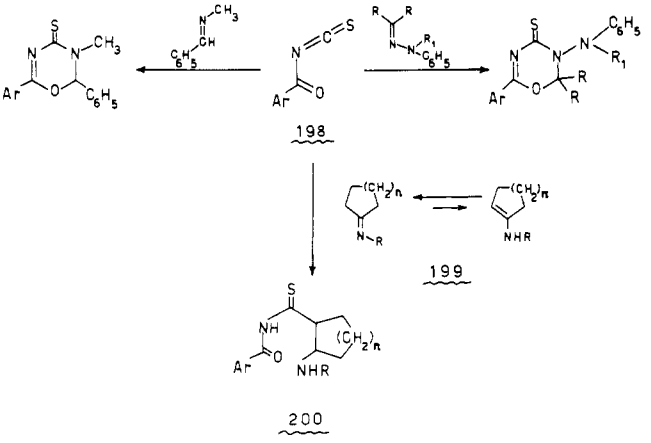
[a] Not reported in the original paper. [b] Michael-type adduct (see text) obtained (92% yield, mp 105–106°). [c] Michael-type adduct (see text) obtained (88% yield, mp 114–116°). [d] Erroneously described as 1,2-adduct. [e] Other products formed, not related with this topic. [f] Ratio of isomers, total yield not reported.

SCHEME L

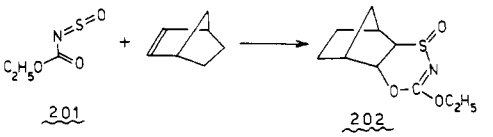


Acyl isothiocyanates **198** gave 1,4-cycloadditions with azomethines[256] and hydrazones;[257] with cyclic azomethines **199**, which behave as enamines, Michael-type adducts **200** were obtained[257] (Scheme LI).

SCHEME LI



Finally *N*-sulfinylurethane **201** reacts with norbornene,[258] and a 1,4-cycloaddition has been suggested to occur to give **202.** Table XXII collects all the adducts.



XII. Natural Products via Heterodiene Syntheses

The Stork modification of the Robinson annelation[113] has been used for a long time for the synthesis of certain alkaloids. These syntheses are particularly expeditious when the nitrogen atom of the enamine intermediate used to introduce the new ring can become the nitrogen of the alkaloid. (±)-Mesembrine (**203**)[259] and (±)-15,16-dimethoxyerythrinan-3-one (**204**)[260] have recently been obtained by this route.

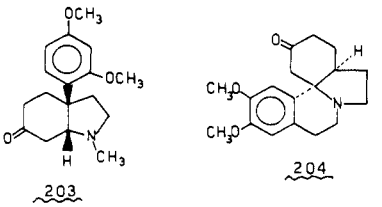
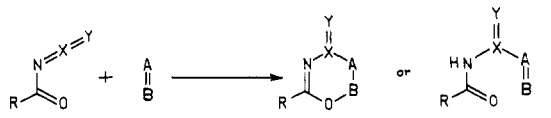


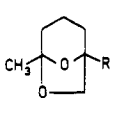
TABLE XXII. Adducts from Cumulated Heterodienes



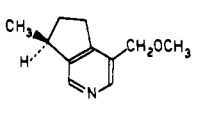
Heterodiene		A=B		Reaction conditions			1,4-Adduct		Michael adduct		
R	X=Y	A	B	Solvent	T, °C	Time	Yield, %	Mp, °C	Yield, %	Mp, °C	Ref
Cl_3C	C=O	H_2C	CHO-*n*-C_4H_9	Ether	10–15	20 h			44	75–76	254
Cl_3C	C=O	H_2C	$CHSC_2H_5$	CS_2	−20+5	30′	76	50–51			254
Cl_3C	C=O	CH_3HC	$CHSC_2H_5$	CCl_4	65–75	2 d			36	68–69	254
Cl_3C	C=O	C_2H_5HC	$CHOC_2H_5$		−40+rt	2 h+10 d			22	98–99	254
Cl_3C	C=O	1-Cyclopentene-1-piperidine		*a*	10–15	*b*			80	49–51	255
Cl_3C	C=O	1-Cyclohexene-1-piperidine		*a*	10–15	*b*			77.5	78–80	255
Cl_3C	C=O	1-Cyclopentene-1-morpholine		*a*	10–15	*b*	76	68–70			255
Cl_3C	C=O	1-Cyclohexene-1-morpholine		*a*	10–15	*b*			83	104–106	255
Cl_3C	C=O	HC≡	$\equiv CC_6H_5$	*b*	90–95	4 h	65	*b*			250
Cl_3C	C=O	HC≡	$\equiv CC_6H_4$-*p*-CH_3	*b*	55	5 h	70	*b*			250
Cl_3C	C=O	HC≡	$\equiv CC_6H_4$-*p*-OCH_3	*b*	35	3 h	61	*b*			250
Cl_3C	C=O	HC≡	$\equiv CC_6H_4$-*p*-Br	*b*	50	5 h	37	*b*			250
Cl_3C	C=O	HC≡	$\equiv CC_6H_4$-*p*-Cl	*b*	18–20	12 h	20	*b*			250
Cl_3C	C=O	HC≡	$\equiv CC_6H_4$-*p*-F	*b*	18–20	2 h	31	*b*			250
C_6H_5	C=O	H_2C	CHO-*n*-C_4H_9		80–130	30′+20′			14	99	254
C_6H_5	C=O	C_2H_5HC	$CHOC_2H_5$		60–0	3 h+20 h			58.5	110–111	254
C_6H_5	C=O	1-Cyclopentene-1-piperidine		*a*	10–15	*b*	70	85–87			255
C_6H_5	C=O	1-Cyclohexene-1-piperidine		*a*	10–15	*b*	66	109–110			255
C_6H_5	C=O	1-Cyclopentene-1-morpholine		*a*	10–15	*b*	78	103–106			255
C_6H_5	C=O	1-Cyclohexene-1-morpholine		*a*	10–15	*b*	64	108–110			255
C_6H_5	C=O	C_2H_5N	CHC_6H_5	Ether	0	*b*	89	109–110			251
C_6H_5	C=O	$C_6H_{11}N$=CHCH=NC_6H_{11}		C_6H_6	rt	*b*	*c*	*b*			252
p-$CH_3C_6H_4$	C=O	C_2H_5N	CHC_6H_5	Ether	0	*b*	78	109–110			251
p-ClC_6H_4	C=O	C_2H_5N	CHC_6H_5	Ether	0	*b*	80	101–102			251
C_6H_5	C=S	CH_3N	CHC_6H_5	C_6H_6	rt	4 h	79	85–86			256
C_6H_5	C=S	$(CH_2)_4C$=NCH(CH_3)C_6H_5 [d]		AcOEt	0	Fast			52	155 dec	257
C_6H_5	C=S	$(CH_2)_5C$=NCH(CH_3)C_6H_5 [d]		AcOEt	0	Fast			10	196 dec	257
C_6H_5	C=S	$C_6H_5(CH_3)NN$	$C(CH_3)_2$	*b*	0	Fast	51	60 dec			257
C_6H_5	C=S	$C_6H_5(CH_3)NN$	$C(CH_2)_4$	*b*	0	Fast	71	67 dec			257
C_6H_5	C=S	$C_6H_5(CH_3)NN$	$C(CH_2)_5$	*b*	0	Fast	88	101 dec			257
C_6H_5	C=S	$C_6H_5(CH_3)NN$	$C(CH_2)_6$	*b*	0	Fast	46	77 dec			257
C_6H_5	C=S	$(C_6H_5)_2NN$	$C(CH_2)_5$	*b*	0	Fast	75	77 dec			257
p-$CH_3OC_6H_4$	C=S	$C_6H_5(CH_3)NN$	$C(CH_2)_4$	*b*	0	Fast	55	67 dec			257
p-$CH_3OC_6H_4$	C=S	$C_6H_5(CH_3)NN$	$C(CH_2)_5$	*b*	0	Fast	86	90 dec			257
p-$NO_2C_6H_4$	C=S	$C_6H_5(CH_3)NN$	$C(CH_2)_5$	*b*	0	Fast	67	61 dec			257
p-$NO_2C_6H_4$	C=S	$(C_6H_5)_2NN$	$C(CH_2)_5$	*b*	0	Fast	45	85 dec			257
C_2H_5O	S=O	Norbornene		Ether	rt	1 h	80	79–81			258

[a] Heptane or cyclohexane. [b] Not reported in the original paper. [c] Bis-adduct (ratio heterodiene/A=B 2:1). [d] Behaving as enamine (see text).

An intermediate dihydropyran, obtained by a heterodiene synthesis, has been used in the preparation of frontalin (**205**, R = CH_3),[34] brevicomin (**205**, R = C_2H_5),[34] valerianine (**206**),[261] and adaline (**207**).[262]



205



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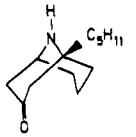

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The above reported examples would not justify an entire section devoted to natural products, but a brilliant synthesis has been developed recently[263] to obtain carpanone, a lignan from the bark of the carpano tree. The extreme efficiency of the phenolic coupling of 2-(*trans*-1-propenyl)-4,5-methylenedioxyphenol (**208**) with $PdCl_2$ is notable, and the dimer **209** has the correct stereochemistry to give rise to an internal heterodiene reaction giving carpanone (**210**) in 46% yield (Scheme LII).

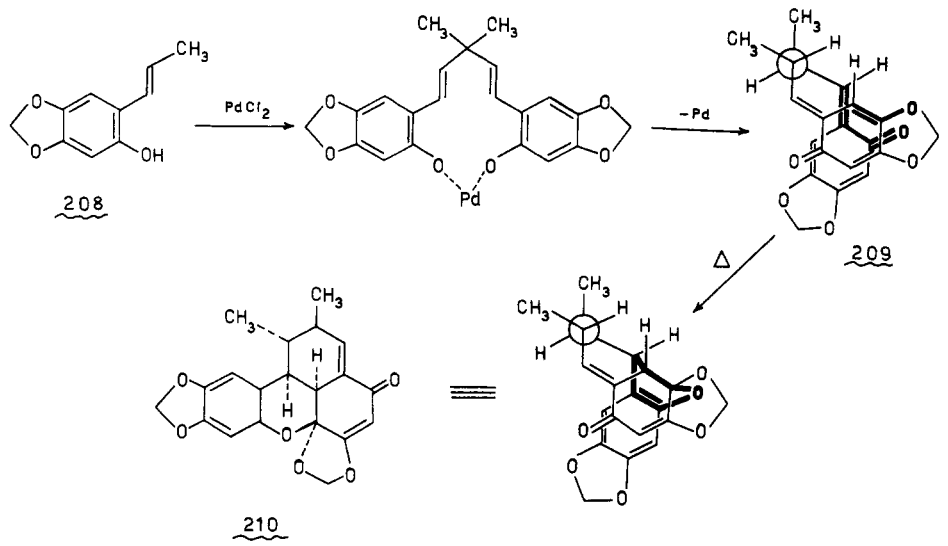
Using the dimerization of 1-oxo-1,2,3,4-tetrahydroanthraquinones **211** as the model, in accordance with a $[\pi 4_s + \pi 2_s]$ cycloaddition with exo approach of the monomers to give **212**[264] (Scheme LIII), a heterodiene reaction can be suggested as an alternative to phenolic coupling in the biosynthetic pathway to (−)-Flavoskyrin (**213**), a yellow coloring matter of *Penicillum islandicum*.

The previously reported sequences are excellent examples of the powerful tool of heterodiene synthesis and the great possibilities for future development. In the opinion of the reviewers, many other examples of its application in the synthesis of natural products will be reported in the near future since very few synthetic methods offer comparable efficiency with such powerful control of the stereochemistry of the products. Furthermore, dihydropyran rings are common in this field.

XIII. Acid-Catalyzed Reactions

The acid-catalyzed Diels–Alder reactions are well studied both from preparative and theoretical aspects.[265] Nothing similar is known for the effect of acids on the reaction between α,β-unsaturated carbonyl compounds and dienophiles even though two recent patents[266,267] have shown that the

SCHEME LII



SCHEME LIII

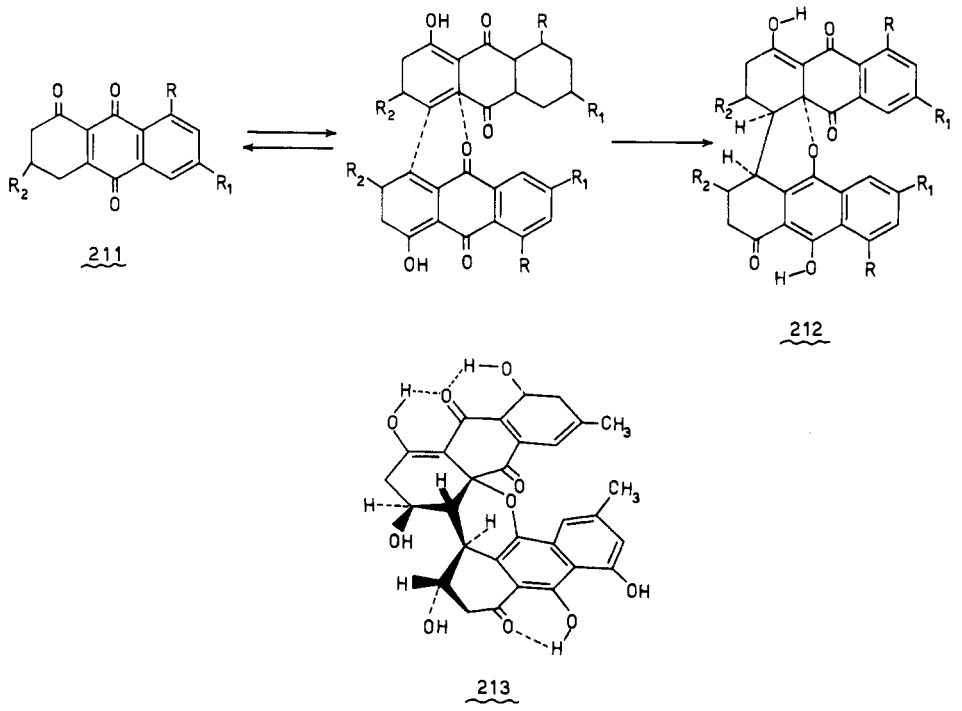


TABLE XXIII. Kinetic Data of Acid-Catalyzed Heterodiene Reactions

Expt	Olefins	$k_2 \times 10^3$, g/(mol sec), at 170°		
		Without acid	Acid 0.006–0.014 mol/kg	Acid 0.055–0.065 mol/kg
1	Ketene di-*n*-butyl acetal	8.4 ± 0.3	4.6 ± 0.2	1.8 ± 0.1
2	2-Ethylhexyl vinyl ether	6.3 ± 0.2	3.9 ± 0.3	1.7 ± 0.1
3	Diisopropyl maleate	2.5 ± 0.2	0.6 ± 0.1	0
4	Allyl bromide	1.3 ± 0.2	1.5 ± 0.2	2.9 ± 0.2
5	1-Dodecene	0.2 ± 0.04	0.3 ± 0.04	0.6 ± 0.1

reaction of unsaturated aldehydes with vinyl ethers occurs under milder conditions and with higher yields in the presence of Lewis acids.

Only one paper[65] reports the effects of the addition of acid on the 1,4-cycloaddition between cinnamaldehyde and various olefins. Table XXIII reports the effect of two different concentrations of acid compared with the rate constants of the uncatalyzed reaction. It was found that the action of acid appears to have a negative effect on the rate of reaction if the olefins contain proton-attracting groups (expt 1–3), whereas the presence of acid enhances the rate of the reactions with expt 4 and 5. The authors suggest that these processes are initiated by proton transfer from the acid to the cinnamaldehyde or to the olefins. An explanation of this can be given in terms of frontier orbitals, using the acrolein and the protonated acrolein MO's[20] as a model (Figure 12).

If the IP of the olefin is higher than that of the n orbital of the unsaturated carbonyl compound (for acrolein 9.9 eV[268]),

TABLE XXIV. Thermodynamic Data of Retro-Heterodiene Reactions

Dihydropyran		Products		Log A, sec^{-1}	ΔH^*, kcal/mol	ΔG^*, kcal/mol	Ref
R	R_1	Carbonyl compound	Olefin				
H	H	Acrolein	Ethylene	14.63	52.5	48.2	269
CH_3	H	Methyl vinyl ketone	Ethylene	14.45	51.2	47.5	270
H	OCH_3	Acrolein	Methyl vinyl ether	14.42	48.5	44.9	271

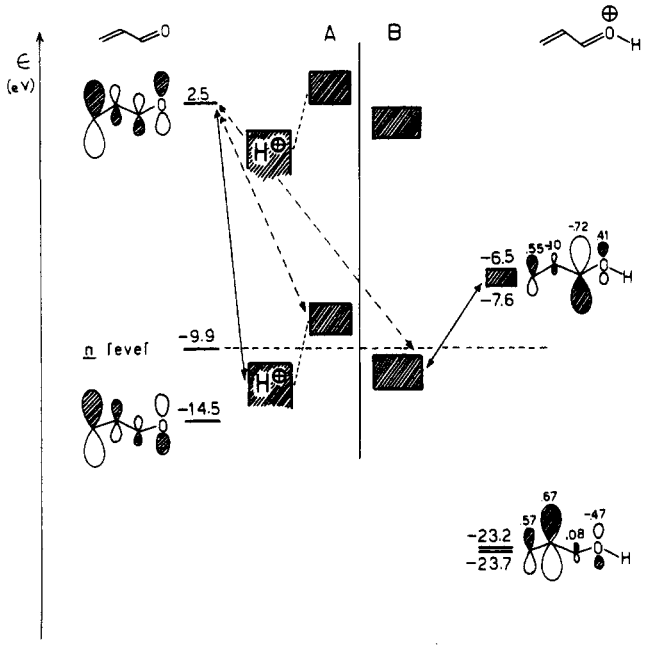


Figure 12. Frontier orbital energies in acid-catalyzed heterodiene reactions: (A) acrolein and protonated olefins; (B) olefins and protonated acrolein. Broken arrows indicate the dominant interaction in the uncatalyzed reaction, whereas solid arrows indicate the dominant interaction in the presence of acid. Diagram is schematic.

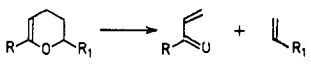
protonation occurs on the olefin. Its HOMO and LUMO decrease, the frontier orbital separation increases, and this causes a lowering of the rate constants (expt 1 and 2).

If the HOMO of the olefin is lower than the nonbonding orbital of the unsaturated carbonyl compound, protonation occurs on this and two new levels are involved. The dramatic lowering of the frontier orbital levels rationalizes the increased rate (expt 4 and 5).

XIV. Retro-Heterodiene Reactions

Few papers have been devoted to the study of the retro-heterodiene reaction but the mechanism seems to have been determined.

The thermal decomposition of 3,4-dihydro-2*H*-pyrans (**214**)[269-271] has been shown to be a first-order homogeneous process which yields equal amounts of α,β-unsaturated carbonyl derivatives and olefins as the only products. The available thermodynamic data are collected in Table XXIV.



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The lowering of both activation energy and free energy from unsubstituted and 6-methyl-substituted to 2-methoxydihydropyran can be explained, at first approximation, using the principle of microscopic reversibility, from the frontier orbital energies of products (Figure 13). The lower energy separation between frontier orbitals if ethylene has a methoxy substituent ensures a lowering of ΔG^* and ΔH^* in the retro-

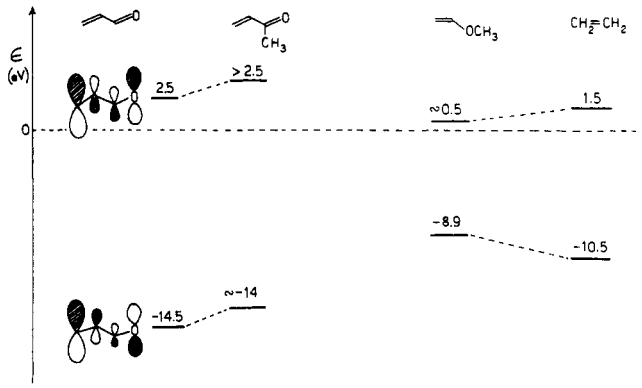
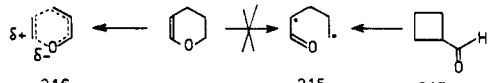


Figure 13. Frontier orbital energies of products formed from retro-heterodiene reaction of 3,4-dihydro-2*H*-pyrans (**214**).

cycloaddition. However, methyl substitution on the carbonyl of the α,β-unsaturated system will slightly raise both the HOMO[272] and the LUMO, the former more than the latter. Therefore, the small decrease in ΔG^* and ΔH^* cannot be explained by the previous method.

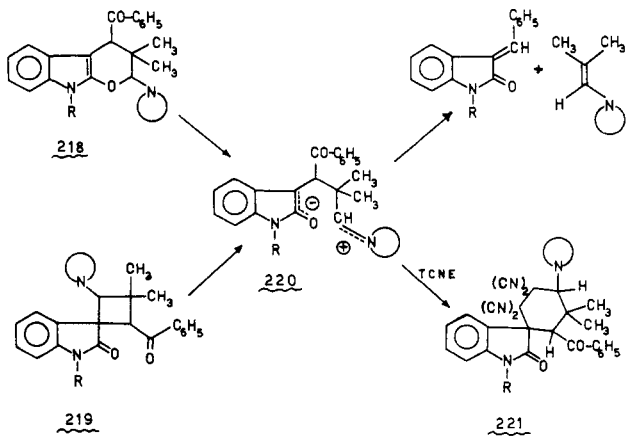
The similarity of the *A* factors strongly supports an essentially similar transition state for all three reactions. Thermodynamic considerations[271] suggest that the C–O rupture leads to that of the C–C bond, and therefore the transition state can have either diradical (**215**) or polar character (**216**). The former can be rejected since the rate of decomposition of cyclobutanecarboxaldehydes (**217**), whose reaction products are the same as dihydropyrans and whose process cannot be concerted, differ greatly from previous results.



216 215 217

A slightly polar character can therefore be suggested for the transition state, and this character increases with the presence of suitable substituents. The polar character of the transition state could become great enough to give a true zwitterionic intermediate. This was shown in the retro-cycloaddition of the adducts **218** and **219** from 3-oxindolidenea-

SCHEME LIV



cetophenones and β-dimethyl-substituted enamines[147] (Scheme LIV). At room temperature, in chloroform, they reverted to the starting materials. However, if the reaction is performed in the presence of tetracyanoethylene (TCNE), the dipolar intermediate **220** is captured and spirocyclohexane oxindoles **221** are obtained.

XV. Addendum

After submission of the manuscript to the Editor, additional papers (as usually happens dealing with reviews) have appeared. In this Addendum the authors briefly list some recent contributions, since these update the review through the early 1975. The order used in the contents will be followed.

A reexamination of the origin of regioselectivity in the dimerization of acrolein was carried out using the frontier orbital approach.[273] The result was that the dimerization of acrolein is under overlap control and there is no evidence that the polar interaction has a relevant role in determining the regioselectivity which is in contrast with Salem's results.[9] Furthermore both INDO and CNDO methods predict the HOMO of acrolein as a π MO, and the energy of the oxygen nonbonding orbital is placed between those of the two occupied π orbitals. This n–π inversion was earlier found by calculations[274] but seems in contrast with the interpretations of the electronic absorption spectrum of acrolein.[275-278] From uv data a clear representation of the electronic configuration of acrolein was given by Birge and Leermakers[279] with the n level higher than the π ones. The uv transitions do not take into account both coulomb and exchange integrals;[280] nevertheless, these results parallel those of photoelectron spectroscopy, which indicate the first ionization related to electron loss from the nonbonding orbital.[281,282] This is still a point to be decided upon and the calculations may perhaps overestimate the π energy levels. If it is not the case, the interpretation of the acid effect on the acid-catalyzed heterodiene reactions can simply be modified, assuming the protonation of the π level of acrolein might be a gap between two mechanisms.

The reaction between 1-(OH or OR)-butadienes and acrolein was confirmed to be an asymmetric concerted reaction[283] under frontier control.[284] Further examples of the cycloaddition between *o*-quinone methide (from saligenol) and substituted olefins were reported[285] to give discrete yields of flavans with complete retention of the configuration of the dienophile.

The previously reported Cu_2O–isocyanide catalyzed dimerization of methyl crotonate[60] was reexamined using aluminum alkyl–tertiary amine and the coordination number of the complex seemed to control the dimerization mechanism.[286]

The formation of a zwitterion intermediate was suggested in the reaction of enones with allylidene–triphenylphosphorane[287] followed by proton transfer to generate an ylide which then undergoes an intramolecular Wittig reaction to give cyclohexadienes.

Depending on substituents of the unsaturated carbonyl compound, benzyne does not give only 1,2-cycloaddition to C=C and C=O bonds but also some 1,4-cycloadducts and some open-chain derivatives from ene reaction.[288] An intermediate biradical was excluded in favor of the reactivity of the initial carbonyl as the determining factor.

Still very popular is the reaction of open-chain α,β-unsaturated carbonyl compounds with vinyl ethers, and several papers[289-297] are concerned with this synthetic approach to dihydropyrans.

A dipolar intermediate was proposed both with 1,1-dialkoxyethylenes[298] (and the low IP[299] of these nucleophilic olefins support the suggestion) and for the reaction of acetylenedicarboxylate with 2-methoxy-6-methyl-3,4-dihydro-2*H*-pyran[300] which is apt to give a proton transfer or a ring closure to [2 + 2] cycloadduct. In the latter case, the crucial effect of the 6-methyl group can be explained in terms of increased HOMO and distorted symmetry.

The low IP of enamines was further tested.[301] The formation of cyclobutane adducts via zwitterion was described from the disubstituted electron-poor α,β-unsaturated carbonyl compounds,[302] which seems to be a true example of 1,2-cycloaddition in section VII.A.2.

An important paper of Risaliti et al.[303] stated by X-ray analysis the cis-fused configuration of the naphthopyran adduct from phenyl vinyl ketone and decalin enamines. This is in full accordance with what was proposed in section VII.A.2 of this review. The anti–trans or syn–trans relationship of the further chiral centers is determined mainly by steric reasons.

Arylideneisoxazolones and -pyrazolones were found to react with enamines,[304] and intramolecular-stabilized Michael adducts were obtained through a reaction pathway which probably does not differ much from that of oxindolideneacetophenones.[146]

The suggestion that the behavior of aminals could be due in part to the high energy of the HOMO was confirmed by the low value of their IP's.[299]

Further examples of [2 + 2][305] and [4 + 2][306] cycloadditions of ynamimes were described, the latter adducts having been used as antihypertensive and coronary-dilating agents.

Enamino ketones react with dichloroketene,[307] thus further supporting their behavior as "donors".

Good examples of cycloadditions of α,β-carbonyls were described on C=Si (1,4),[308] C=P (1,4 and/or 1,2),[309] and C=O (1,4)[310] dienophiles.

Cyclic acyl ketenes react with C=N double bond of isocyanates,[311] whereas the reaction of 1,1-diethoxy-α-cyclopentanon allene and diphenyl ketene[312] give first a largely stabilized 1,4-zwitterion on account of the favorable electronic effect of the substituents. It further reacts with a second mole of diphenyl ketene.

The reaction of *o*-benzoquinones with various olefins was reported to give benzodioxin derivatives[313-315] together with some dimeric adducts.[315] If two C=C bonds are present, the electron-rich one is preferred[314] even if it belongs to an heteroaromatic ring. No dioxin derivatives, but only Diels–Alder adducts, were obtained from fulvene.[316]

Cyclic α-ketosulfenes can dimerize or react with Schiff bases to give [4 + 2] or [2 + 2] cycloadducts,[317] and some interesting considerations can be given on the configuration of the latter adducts.

N-Acetylchloralimine was reported to react with 2,3-dimethylbutadiene;[318] rather surprisingly the heterodiene cycloaddition predominates the Diels–Alder reaction.

The cycloaddition reactions of acyl isocyanates were reviewed[319] and some interesting 1,4-cycloadditions described.[320,321] Several reaction pathways were found for aroyl isothiocyanates: iminodithiocarbonate and *N*-arylideneamines gave a [4 + 2] cycloaddition,[322] azomethynes[322] gave first a dipolar intermediate followed by ring closure or 1,4-dipolar cycloaddition with a second mole of azomethyne, and finally 1-azirines[321] were reported to give a [2 + 2] cycloaddition on the C=S bond followed by hydrogen shift.

The synthesis of natural products gave no recent spectacular result; nevertheless, heterodiene reactions were found useful for a synthetic approach to iridoids,[323] (±)-thalphenine,[324] and bevicomins.[325]

Lewis acids were found useful catalysts for the preparation of 2-substituted-3,4-dihydro-2*H*-pyrans,[326,327] but in this field much more interesting seems the acidic decomposition of saligenol in the presence of olefins, which sharply increases the yields of the resulting chromans.[328] If an intermediate is formed (*o*-hydroxybenzyl cation ↔ protonated *o*-benzoquin-

onemethide), its LUMO is lower than that of the nonprotonated species and this rationalizes milder conditions and better yields.

Finally the retroheterodiene reaction of 2,3-dihydro-*p*-dioxin giving quantitatively ethylene and glyoxal was kinetically studied.[329] Both log A/sec^{-1} and ΔH^* (14.55 and 52.9 kcal/mol, respectively) were found to be very similar to the same parameters of the thermal decomposition of 3,4-dihydro-2*H*-pyran[269] (Table XXIV).

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XVI. References

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