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YNAMINE: A VERSATILE TOOL IN ORGANIC SYNTHESIS

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1. INTRODUCTION TO THE REACTIVITY OF YNAMINES

The particular acetylenic amines **2** known as ynamines belong to a family of heterosubstituted acetylenes **1** in which A can be, for example, halogen, oxygen, sulfur, phosphorous, nitrogen. . . .

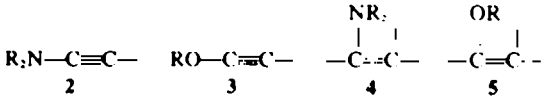
$$A{-}C{\equiv}C{-}R_1 \quad (A = X, OR, SR, PR_2, NR_2 \ldots)$$

1

A. *Comparison of ynamines with heterosubstituted acetylenes and ethylenes*

Whereas many heterosubstituted acetylenes **1** had been known for a long time, especially when A is an alcoxy group (A = OR),[1] the ynamines although expected to be more nucleophilic than their oxygen analogues and therefore even more useful in synthesis, appeared in the literature only fifteen years ago.[2]

The N atom directly bonded to the C≡C triple bond gives to ynamines a more pronounced nucleophilic character than is found in their oxygen analogues. This is similar to the difference between enamines **4** and enolethers **5**:

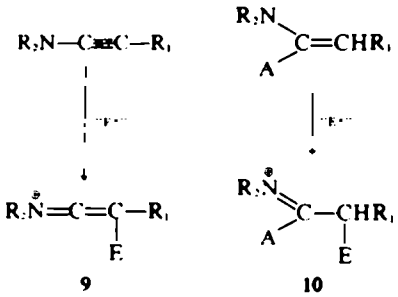


2 **3** **4** **5**

Like enamines **4**[1] in which the N atom is bonded to a C=C double bond, ynamines have a tertiary nitrogen. If the nitrogen is not substituted, e.g. when it is primary as in **6** the ynamine is not isolated, since the equilibrium is completely shifted toward the more stable nitrile **7**.[4]

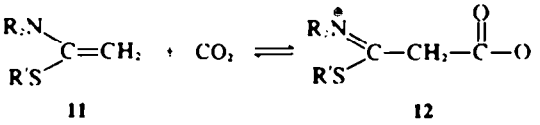
The new function found in ynamines indeed has the oxidation level of acids while enamines have, of course, the oxidation level of ketones or aldehydes. Ynamines are closer to the ketene-acetals **8** the hydrolysis of which yields the same amides.

The main difference in reactivity towards electrophilic reagents between ynamines and ketene-acetals comes, however, from the fact that the intermediate dipolar ion is a very reactive ketene-immonium ion of type **9** in the case of ynamines but a more stable immonium ion of type **10** in the case of ketene-acetals:



9 **10**

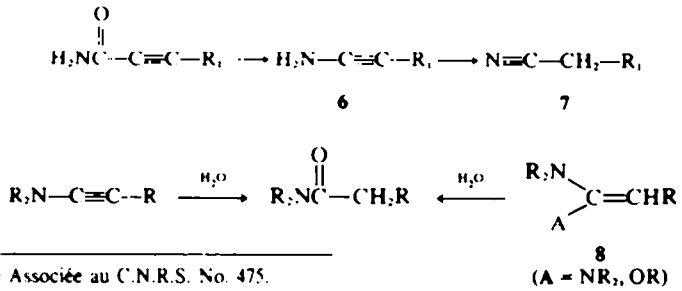
This difference is particularly striking, for example, in the reaction with carbon dioxide. The N,S-ketene-acetal **11** gives at −70° the stable dipolar ion **12** which does not react further and reversibly decomposes to starting materials at higher temperature.[5] By contrast, reaction of the ynamine **13** does not stop at the ketene-immonium ion stage **14**, but reacts further even at −70°:[6]



11 **12**

B. *Effect of substituents on ynamine reactivity*

In general and as one would expect, ynamines have turned out to be particularly reactive substrates toward a large variety of electrophiles although their nucleophilic character is obviously a function of the greater or smaller availability of the unshared pair on the N atom.



6 **7** **8** (A = NR_2, OR)

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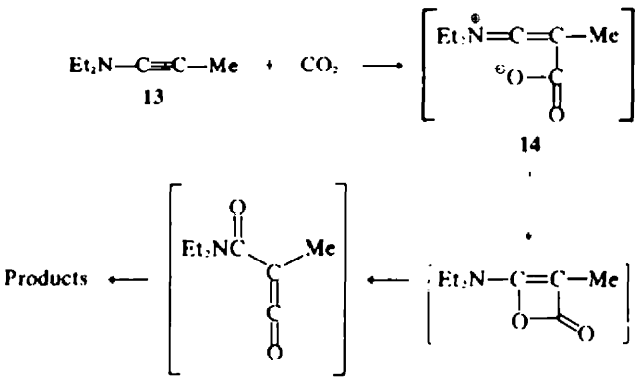
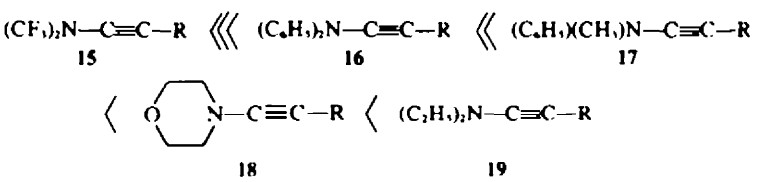


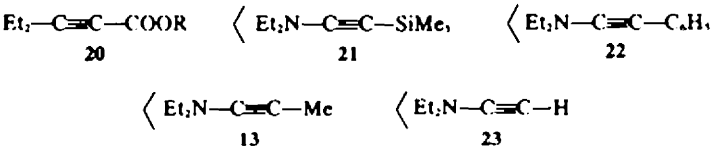
The type of substitution on the nitrogen plays a very large role in determining the reactivity of ynamines: when the nitrogen is substituted by phenyl groups,[7,8] ynamines only react with powerful electrophiles. Even more dramatic, when the nitrogen is substituted by two trifluoromethyl groups,[9] which are very strongly electron withdrawing the N atom loses most of its effect on the triple bond which can now be hydrolyzed, for instance, only in the presence of mercuric ions. At the other extreme, the most reactive ynamines, by far, are those which have alkyl groups such as ethyl or methyl on the nitrogen:[10] the reactivity is in general parallel to the basicity of the corresponding amines.

We can thus arrive at the following qualitative sequence of increasing reactivity of a series of ynamines in which the same alkyl group R is attached to the acetylenic carbon:



The nature of the R group which is carried by the acetylenic carbon also affects the reactivity of ynamines.

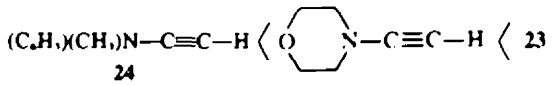
It is possible, as we did above in the case of nitrogen substituents to produce a qualitative sequence of ynamines bearing the same alkyl group on nitrogen in order of increasing reactivity towards electrophilic reagents depending on the substituent carried by the C atom:



The electron delocalization which is possible when the substituent on the triple bond is a carboxylic ester **20**,[11] or a Si atom **21**[12,13] markedly affects the reactivity of the corresponding ynamines.

This effect is, however much less pronounced than that of the substituent on nitrogen, and all of these ynamines have been utilized successfully in synthesis.

The ynamines which bear hydrogen on the acetylene function are the most reactive of this series.[7,14] When the nitrogen is substituted by alkyl groups, their reactivity is such, that it can be difficult in some cases, to utilize them without special precautions to avoid their hydration or their polymerization. N,N-diethylamino acetylene **23** for instance is the most reactive of the unsubstituted ynamines and its polymerization can be faster than the desired reaction. It is preferable, in such a case, to utilize the N-phenyl, N-methylamino-acetylene **24** or even better the N-morpholino-acetylene **25** which, although still very reactive can be handled very easily. We have indeed concluded that N-morpholino-acetylene **25** is the reagent of choice among these ynamines which do not bear a C atom on the triple bond.[14]



The nature of the substituent on nitrogen and on carbon also affects the thermal stability of ynamines.

When the R group carried by the acetylenic carbon of ynamines is another heteroatom such as a nitrogen **26**[14] or a halogen **27**[16] the inductive effect of the substituent decreases the thermal stability of ynamines[10,17] which become difficult to handle especially in the case of halogeno-ynamines **27**.

The substitution of the acetylenic carbon by a silicon atom as in **21** does not decrease the thermal stability of ynamines[12,13] but in the case of an ynamine like **28** in which the acetylenic carbon and the N atom are both substitued by Si atoms the rearrangement takes place at 160°, with formation of the ketene-imine **29**.[18]

$$Me_3Si{-}C{\equiv}CN(SiMe_3)_2 \xrightarrow{160^\circ} (Me_3Si)_2C{=}C{=}NSiMe_3$$

28 29

$$R_2N{-}C{\equiv}C{-}\underset{OH}{CHR'} \xrightarrow{O} \left[R_2\overset{\oplus}{N}{=}C{=}C{=}CHR' \quad OH^{\ominus}\right] \longrightarrow R_2N{-}\underset{O}{C}{-}CH{=}CHR'$$

30 31 32

When the group R bears a carbinol function α to the triple bond, as in the ynamines **30**, these substances, which are ethynylogues of carbinol amines are stable at room temperature but, can neither be distilled nor chromatographed. Under such conditions they are transformed into α,β-ethylenic amides **32**.[19]

By contrast, when the substituents are alkyl groups, ynamines are thermally very stable, more stable in fact than their oxygen analogues: N,N-diethylamino propyne for instance is unchanged at 400°,[10] whereas acetylenic ethers lose ethylene around 110°.[1]

This thermal stability, which makes ynamines very convenient to handle is also accompanied by a high reactivity towards polar substances. This reactivity which makes ynamine particularly useful in synthesis, will be discussed in the following sections.

C. *General outline of ynamine reactivity*

Whatever the ynamine substituents, with the exception of the previously mentioned trifluoromethyl group (section 1B), the activated triple bond can react by addition or by cycloaddition depending on the nature of the electrophilic agent brought into play.

(a) *Addition reactions.* With a polar molecule of the type $B^{+A}\text{-}A^{-A}$, addition of ynamines **2** leads to a ketone-immonium salt **33** which then can be neutralized to give the adduct **34**.

$$R_2N{-}C{\equiv}C{-} \quad + \quad B^{+A}\text{-}A^{-A} \longrightarrow \underset{A^{\ominus}}{R_2\overset{\oplus}{N}{=}C{=}CB{-}} \quad 33$$

$$\rightleftharpoons \quad R_2N{-}\underset{A}{C}{=}CB{-}$$

34

It is possible that attack of the electrophilic reagent on the ynamine may be preceeded by a reversible initial addition to the nitrogen with formation of the salt **35**:

$$2 \quad + \quad B^{+A}\text{-}A^{-A} \rightleftharpoons \underset{B}{R_2\overset{\oplus}{N}{-}C} \; \underset{A^{\ominus}}{{=}C{-}}$$

35

It has been indeed demonstrated that such a reaction takes place when ynamines are protonated in aqueous acid.[20] This is however the only clear example and salts of type **35** have not been described in the chemistry of ynamines. Whatever the mechanism of the reaction may be, the addition to nitrogen, if it occurs, is inconsequential since it is a reversible process as with the related enamines.[1]

The formation of the neutral adduct **34** depends essentially on the strength and size of the base A . If A is a strong and relatively small base such as, for example, EtO ,[21] the dipolar ion **33** leads to the neutral adduct **34**. If however A is a weak base such as Cl [10] or C_6H_5O ,[22] or a strong but bulky base such as that from tertiary alcohols R_3O [22] the ketene-immonium ion is then neutralized not by A but by the initial ynamine **2** itself with the formation of the very stable delocalized cyclobutenyl cation **37**.

$$R_2\overset{\oplus}{N}{=}C{=}CB{-} \quad A^{-} \quad 33 \xrightarrow{2} \underset{A^{\ominus}}{R_2N{-}\overset{|}{C}{=}CB{-}\;\overset{|}{C}{=}C{=}\overset{\oplus}{N}R_2} \quad 36$$

$$\longrightarrow \quad \underset{A^{\ominus}}{R_2\overset{\oplus}{N}} \quad B \quad NR_2 \quad 37$$

This last reaction was utilized in the synthesis of stabilized cyclobutadienes of the type **38**.[23]

$$Et_2N{-}C{\equiv}C{-}R \xrightarrow{C_6H_5OH\ BF_3} \underset{BF_4^{\ominus}}{Et_2\overset{\oplus}{N}} \quad H \quad R \quad R \quad NEt$$

$$\longrightarrow \quad Et_2N \quad R \quad R \quad NEt_2 \quad 38$$

$R = COOEt$[23,24] or $S\text{-}C_6H_5$[25]

The adducts **34** are themselves nucleophilic, they can be isolated (as in eqn a), but can also, depending on the situation proceed by addition of a second mole of the electrophile (as in eqn b) or by rearrangement (as in eqn c).

(a) $R_2N{-}C{\equiv}C{-} + Cl{-}\underset{O}{\overset{||}{C}}{-} \longrightarrow R_2N{-}\underset{Cl}{C}{=}\underset{|}{C}{-}\underset{O}{\overset{||}{C}}{-}$

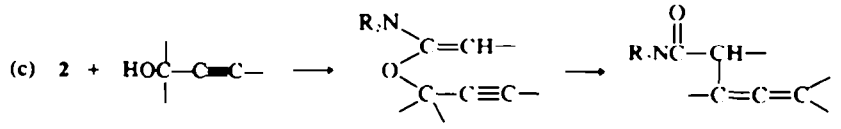
2 39 40

(b) $2 + HOMe \longrightarrow R_2N{-}\underset{MeO}{C}{=}CH{-}$

41

$$\rightleftharpoons \quad R_2N{-}\underset{MeO}{\overset{OMe}{C}}{-}CH_2{-}$$

42

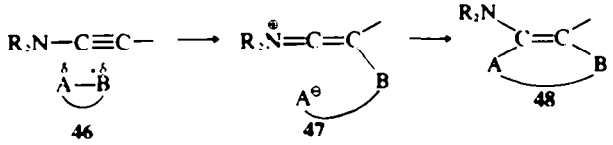


43 44 45

Addition of acid chlorides **39** leads for example, to chloro-enaminoketones **40** (see Section 2C(a)) whereas addition of methanol leads to ketene O,N-acetals **41** which then add a second mole of methanol (**41** ⇌ **42**).

In the case of unsatured alcohols, such as propargylic alcohols **43** for instance, the initial ketene O,N-acetals **44** undergo a Claisen rearrangement with formation of amides **45** (see Section 2D(b)).

(b) *Cycloaddition reactions.* When a suitably constituted polar molecule of type **46** reacts with an ynamine, cyclo adducts **48** are obtained.



46 47 48

Whether this reaction involves a discrete dipolar intermediate such as **47** has not been demonstrated, as such a dipolar ion has never been detected even at low temperature. Nevertheless in most cases the polar character of the reagents is such, that even when a concerted cycloaddition is allowed[24,25] such an intermediate zwitterion seems reasonable.

The cycloadduct **48** like the simple adduct **34** is itself nucleophilic. It can be isolated in most of the cases (as in eqn a) since it is usually less reactive than the ynamine itself, but may also undergo rearrangement (as in eqn b) or react with another mole of the polar reagent (as in eqn c).

The cycloaddition of ynamines with cyclohexenone, for instance, takes place at the C=C double bond, to lead to cycloadduct **49** (Section 3E(b)). These cycloadducts do not undergo rearrangement to cyclo-octatrienones which would not easily tolerate a trans double bond within their medium size ring and their enamine function also does not undergo further addition to the initial cyclohexenone.

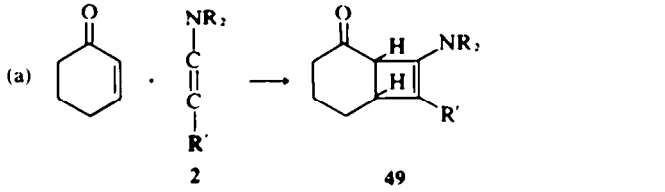
With quinone, cycloaddition does not involve the C=C double bond but, rather, the CO group, thus leading to the adduct **51** via the probable intermediacy of an unstable oxetene of type **50** which then rearranges to the product during the reaction (see Section 3C).

On the other hand, with benzyne, cycloaddition involving the triple bond leads to a benzo-cyclobutadiene **53** which now reacts further with another molecule of benzyne (**52** → **53** → **54**)(see Section 3B).

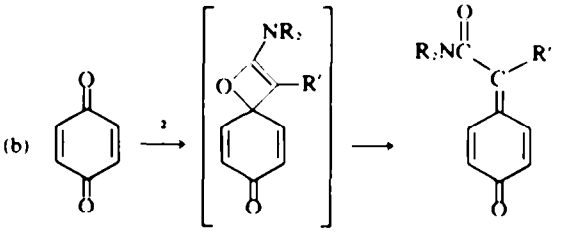
D. *Scope and limitations*

The reactivity, as well as the synthesis of ynamines have been reviewed a few years ago.[10] The aim of this article is not an exhaustive coverage of the chemistry of ynamines, but rather, to show through various examples the unusual capability of ynamines and the new pathways which are made available to synthesis by this versatile tool.

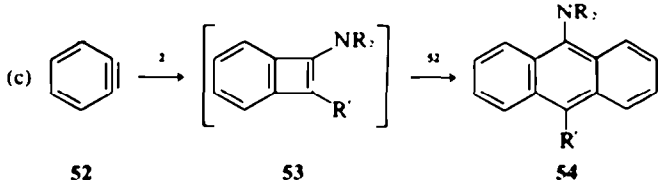
This study which does not deal with the synthesis of



2 49



50 51



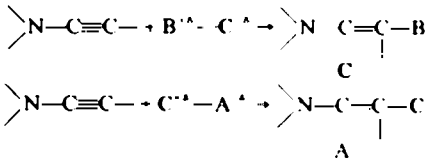
52 53 54

ynamines will cover only addition and cycloaddition reactions which lead to the formation of C–C bonds, putting emphasis on those which have shown themselves most useful with respect to regio and stereoselectivity.

2. ADDITION REACTIONS OF YNAMINES LEADING TO THE FORMATION OF C–C BONDS

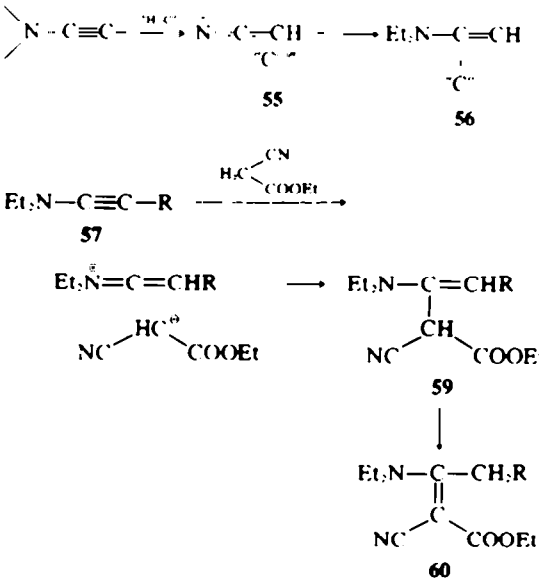
A. *General processes leading to C–C bond by addition reactions*

Formally, the formation of a C–C bond starting with the addition reactions on the triple bond of ynamines, can take place either α or β to the nitrogen depending on the polarity of the carbon which is part of the polar reagent:



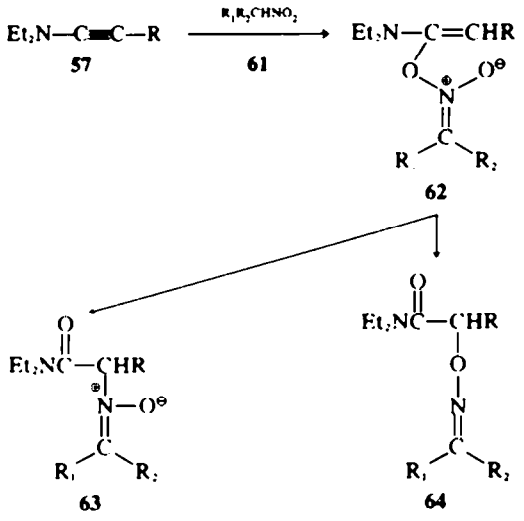
(a) *Protonation of ynamines: amino-vinylation and acylation by ynamines.* The formation of a C–C bond takes place α to nitrogen with polar molecules bearing an acidic C–H bond, the so-called "carbon acids".[27]

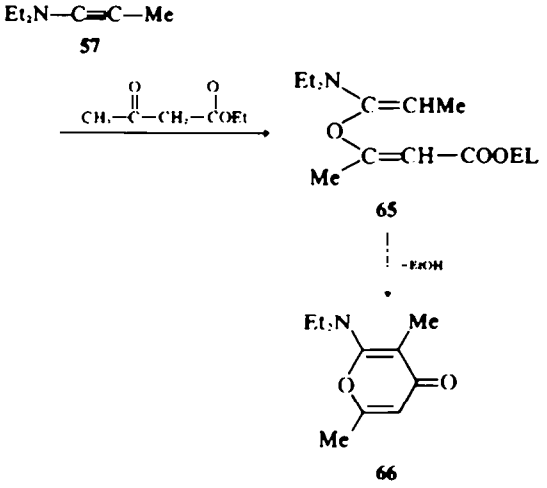
Ynamines are basic enough, in contrast to acetylenic ethers[28] to enolize carbon acids such as, for instance, cyanoacetate **58**.[11c] The reaction leads to a conjugated acid which is, in the special case of ynamines a ketene-immonium ion of type **55**. This very reactive ketene-immonium ion is now neutralized by the carbanion "C⁻" to lead to an enamine of type **56**. The enamines of type **56** rearrange when possible, for instance as with **59**, by transferring a proton, to the more stable conjugated enamines **60**.



The result of this reaction is the aminovinylation, and therefore the acylation of the carbon acids. Some examples described in Section (2B) illustrate this use of ynamines as acylating reagents.

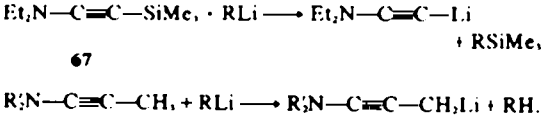
These examples of aminovinylation are the result of region specific alkylation of the enolate ion on carbon rather than on oxygen. In the two following cases which involve very acidic proton donnors such as nitro alkanes and ethyl aceto-acetate, O-alkylation has been observed;

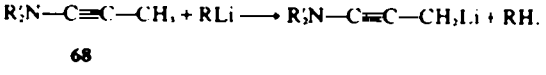




The initial adduct **62** produced by addition of nitroalkanes **61** with ynamines, undergoes a (2-3)-sigmatropic rearrangement which leads to **64** accompanied in some cases by a fragmentation which leads to **63**,[29] whereas the initial adduct of the type **65** obtained from aceto acetic ester undergoes an internal acylation, which gives rise to γ-pyrones **66**,[30] (compare to 2C(b)5).

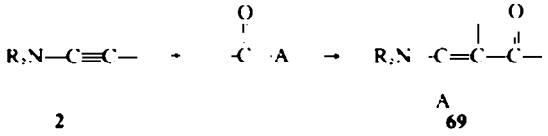
Organometallic compounds such as organolithium reagents, which might have produced a C–C bond α to the nitrogen do not add on the triple bond of ynamines. With ynamines of type **67**[12,31] and **68**,[32] lithium reagents lead instead to metallation reactions:





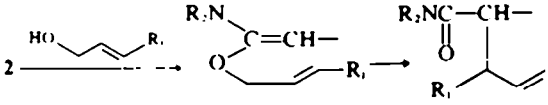
(b) *Acylation and alkylation of ynamines.* The formation of a C–C bond takes place, on the other hand, β to the

nitrogen with polar molecules bearing an electrophilic carbon. Carboxylic acid derivatives, such as acid halides for example, add to the triple bond of ynamines to lead to adducts of type **69**. The result of this reaction is an acylation of the ynamine (see Section C):



2 **69**

Simple alkylation of ynamines cannot be effected by reaction with alkyl halides (see Section 2D). However the use of the Claisen rearrangement of adducts **70** obtained by reaction of ynamines with unsaturated alcohols such as allylic alcohols, is a route to regiospecific alkylation of the parent amides **71** (see Section 2D).



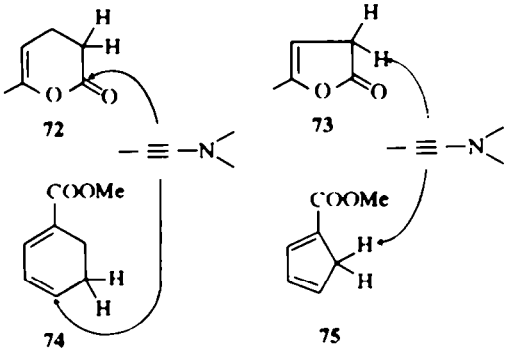
70 **71**

(c) *Competition between cycloaddition reactions and protonation or acylation of ynamines*

(1) *Competition between protonation and cycloaddition.* When the carbon acid, also bears a function which can undergo cycloaddition, it is not easy to predict in all cases which of the two processes (protonation or cycloaddition) will prevail over the other. One involves attack by a proton, while the other requires attack by an electrophilic center.

Some situations lead to clear predictions because they involve either essentially non-acidic substrates, or on the contrary readily enolizable functionalities.

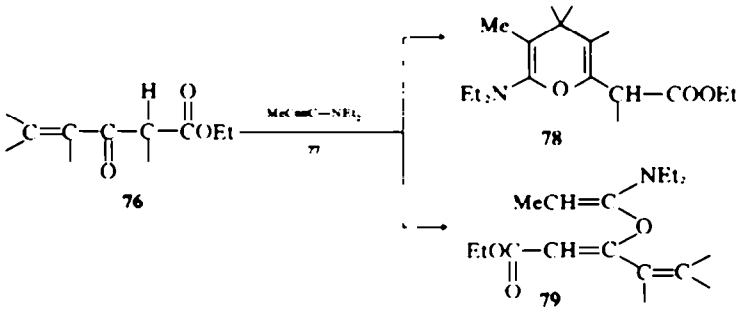
One can expect, for instance, that the reaction with the 6-membered enol lactones **72** or the cyclohexadienic carboxylic ester **74** will involve the electrophilic carbons, rather than the not very acidic hydrogens. By contrast, one could anticipate, that when the same functionalities are part of a 5-membered ring as in **73** or **75**, the reaction will now involve the very acidic hydrogens:



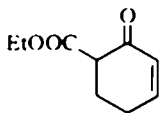
72 **73** **74** **75**

In other cases however, it becomes difficult to predict which of the two processes will prevail over the other. Nevertheless in such cases two factors are crucial in orienting the reaction toward one or the other process: the relative steric hindrance at the two electrophilic centers (proton or carbon) and the polarity of the solvent.

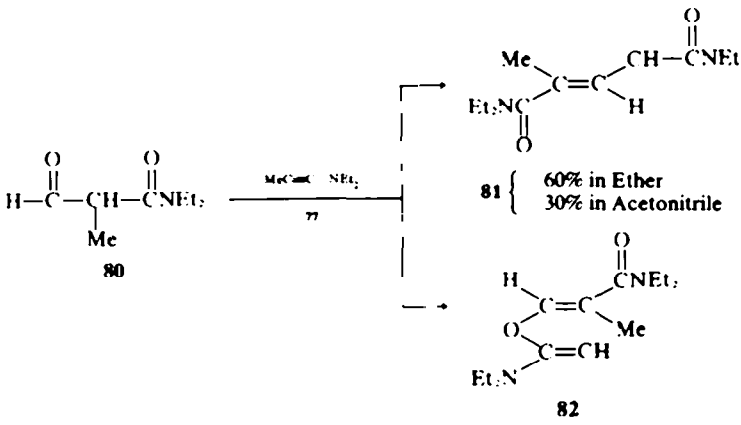
Various examples of steric effect on the competition between protonation and cycloaddition will be found throughout this review. Steric hindrance affects cycloaddition more than it does protonation, as is made clear by the example of the reaction of ynamine **77** with α,β-ethylenic keto-esters **76** in which cycloaddition at the enone moiety, leading to **78**, competes with reaction with the enol of the β-keto-ester leading to **79**:[11]



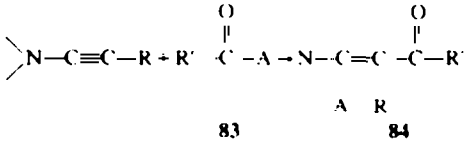
76 **77** **78** **79**

	Cycloaddition **78**	Protonation **79**
$CH_2{=}CH{-}\underset{\underset{O}{\|}}{C}{-}CH{-}COOET$	20%	60%
$CH_2{=}CH{-}\underset{\underset{O}{\|}}{C}{-}\underset{\underset{Me}{\|}}{CH}{-}COOEt$	80%	0%
$CH_2{=}\underset{\underset{Me}{\|}}{C}{-}\underset{\underset{O}{\|}}{C}{-}CH_2{-}COOEt$	0%	80%
$CH_2{=}\underset{\underset{Me}{\|}}{C}{-}\underset{\underset{O}{\|}}{C}{-}\underset{\underset{Me}{\|}}{CH_2}{-}COOEt$	0%	80%
	0%	60%

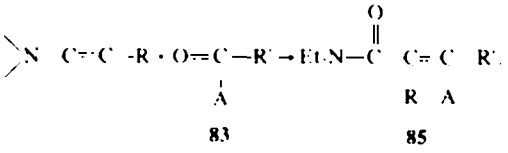
Both processes, protonation and cycloaddition are helped by increasing the polarity of the solvent, but there is greater acceleration of protonation because of the greater charge separation in that case. The amide-aldehyde **80**, for instance, gives both a derivative of glutaconic acid **81** via cycloaddition involving the aldehyde carbonyle, and enamine **82**, via protonation by the acidic hydrogen. In ether **81** is the major product (60%) with ynamine **77**,[6,14] while in acetonitrile it becomes the minor one (30%):



(2) *Competition between acylation and cycloaddition.* Acylation of ynamines results from the addition of carboxylic acid derivatives on the C≡C triple bond which gives rise to enamino-ketones **84**:



This addition reaction can be in competition with the cycloaddition reaction involving the carbonyl which leads to the adducts of the type **85** and which will be described in Section 3C:



The first step of these two processes has to be an attack on the electrophilic carbon giving rise to the intermediate ion **86**.

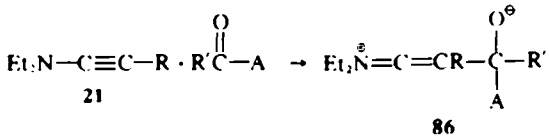
The intermediate **86** can be stabilized by loss of A (**86** → **87**) which then neutralizes the ketene-immonium ion moiety to give the enamino-ketone **84**. This process which results in an addition reaction is observed when A is, for instance, Cl .

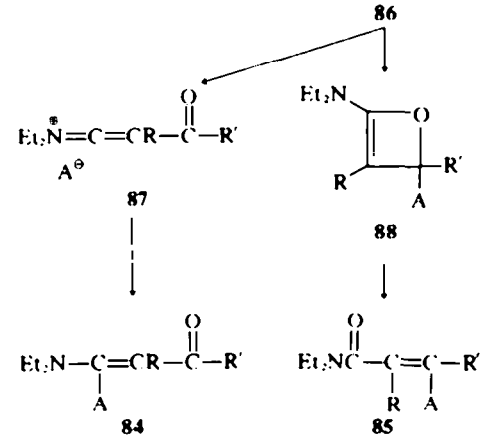
The intermediate **86** can also cyclize to a strained oxetene of type **88** which rearranges to give the α,β-ethylenic amide **85**. This process which results in a cycloaddition reaction is observed when A is for instance EtO .

The direction of the reaction toward one or the other process depends therefore on the nature of the leaving group. A good departing group gives rise to an addition reaction, whereas a poor departing group leads to a cycloaddition reaction. In the cases in which there is competition between the two processes, as for instance with the 6-membered enol lactones (see Section 2C(b)) an increase of the solvent polarity favors the addition process, because of its more pronounced polar character.

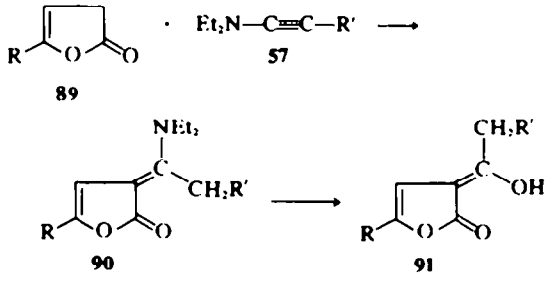
B. *Addition reactions of ynamines with "carbon acids": acylation by ynamines*

(a) *Acylation of 5- membered "carbon acids"*



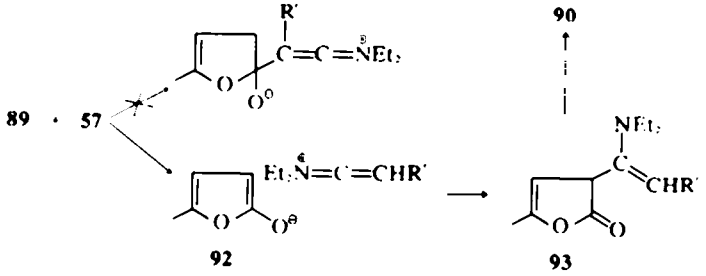


(1) *5-Membered enol-lactones.* The reaction of ynamines **57** with 5-membered enol-lactones **89** leads, with yields of 45–80% to enamino-lactones **90**:[15]



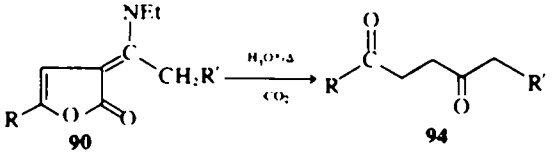
In the case of lactones with particularly acidic hydrogens, reaction of the ynamine does not involve the carbonyl, in contrast to the saturated lactones (3C) or

6-membered enol lactones (2C(b)), but rather, the acidic hydrogens. This reaction leads to an enolate **92**, which is then alkylated on carbon rather than on oxygen, by the ketene-immonium ion. As was already mentioned (2A(a)), the initial enamine **93** is not isolated but is transformed *in situ*, into the more stable adduct **90** in which the double bond is now conjugated with the lactone carbonyl.



92 **93**

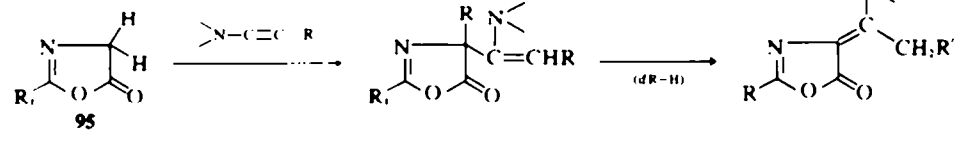
The value of this reaction resides in the fact that the resulting enamine system is a potential carbonyl and that one has, therefore, accomplished the *acylation* of lactones **89**. This acylation is not possible with the usual acylating reagents. Under classical acylation conditions, the strong base which is required to produce the enolate would result in rupture of the lactone ring or polymerization even at low temperature; with other reagents like ketene, for example, the product is the O-acyl derivative of the enol.[16] The importance of this acylation reaction is that enaminolactones **90** are the precursors of 1,4-diketones **94** which they yield by hydrolysis and decarboxylation. The ynamine procedure is therefore a new route to 1,4-diketones **94** in which R comes from the enol lactone and R' from the ynamine:



90 **94**

This method has been illustrated by the synthesis of *cis*-jasmone starting from α-angelicalactone and the appropriate ynamine **91** bearing the *cis*-2-pentenyl side chain.[17]

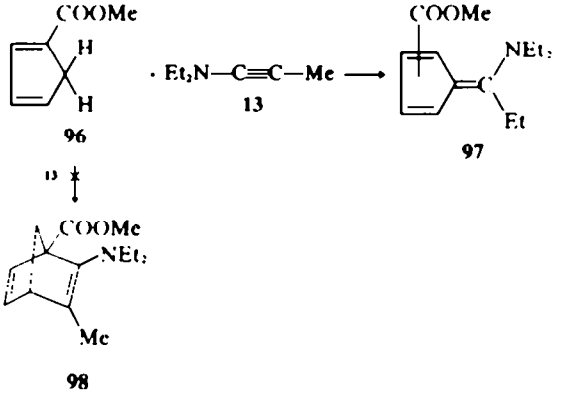
(2) *Oxazolones.* With oxazolones of the type **95** the initial enamine, obtained by reaction with an ynamine is isolated when R is an alkyl group, whereas it rearranges into the more stable conjugated one when R is hydrogen:[18]



95

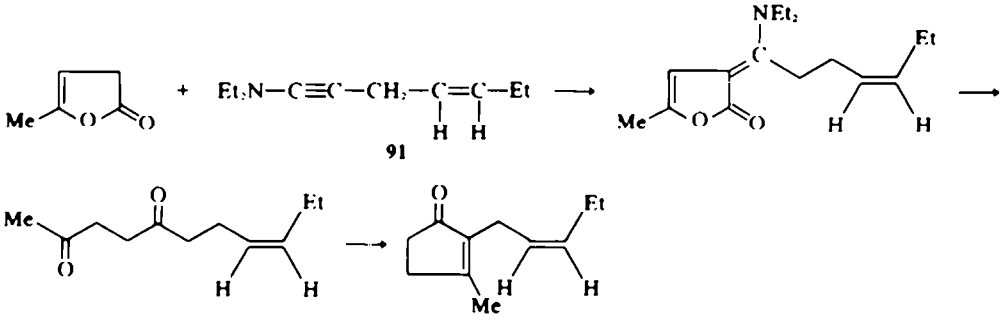
When the oxazolones have no acidic hydrogens (see Section 2C(b)) attack by ynamines, occurs at the carbonyl.

(3) *Cyclopentadiene carboxylic ester.* Ynamines are not protonated by cyclopentadiene itself, since this molecule dimerises faster than it reacts with ynamines. However, the more electrophilic cyclopentadiene carboxylic ester **96** is easily enolized by N,N-diethylaminopropyne **13** and the reaction gives rise to the conugated enamine **97**.[19] One does not observe any cycloaddition of this diene which would have led, as it does with the cyclohexadienic homologue (see Section 3F), to a bicyclo adduct (**98**, in this case).



96 **13** **97** **98**

(b) *Acylation of octalones and decalones.* Another example of acylation by ynamines is that encountered with cyclenones hindered at the β position, such as octalone **99**. One does not obtain, in such a case, a cycloadduct of type **103** as would have been produced by cycloaddition at the C=C double bond of unhindered



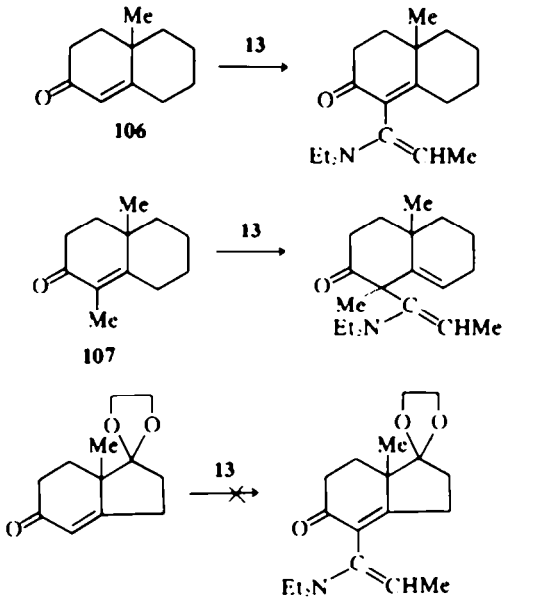
91

enones such as cyclohexenones. The only adduct which is isolated, is enamine **101** as a mixture of two geometric isomeres.[40] This result suggests that the addition of the ynamine is not a concerted process of the type of an "ene synthesis", but a two step one, involving the intermediate **100**. (*A priori*, adduct **101** could also come from the rearrangement of the 4-membered enamine **103** (see Section 3E(b)) but this pathway implies an improbable attack of the ynamine at the very hindered electrophilic center of octalone).

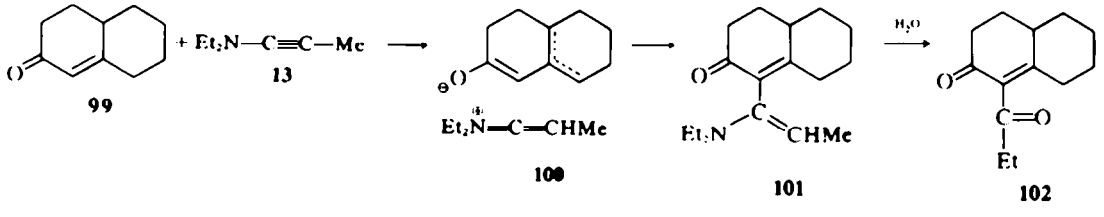
Enamines **101** can be hydrolyzed by water to acyloctalone **102**. They can be selectively transformed to either *cis*-**105** (catalytic hydrogenation) or *trans*-**104** (chemical reduction) acyldecalones.

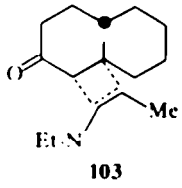
It is known that acylation of cyclenones is difficult to achieve by classical methods utilizing derivatives of carboxylic acids (a case of photochemical acylation of steroidal enones has however been described[41]). Ynamines offer a simple method of regiospecific acylation not only of octalones but also of *cis*- or *trans*-decalones. The possibility of utilizing the resulting acyl group as a directing group in further synthetic operations has been explored starting from **105**.[42]

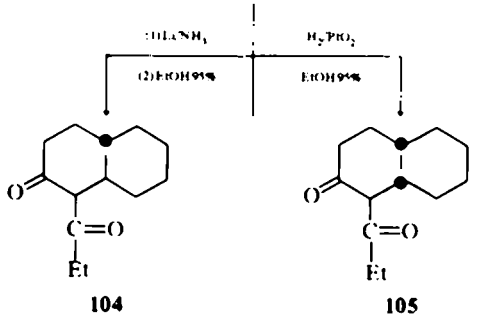
The aminovinylation of the angularly methylated octalones **106**[43] and **107**[41b] also takes place but in lower yield

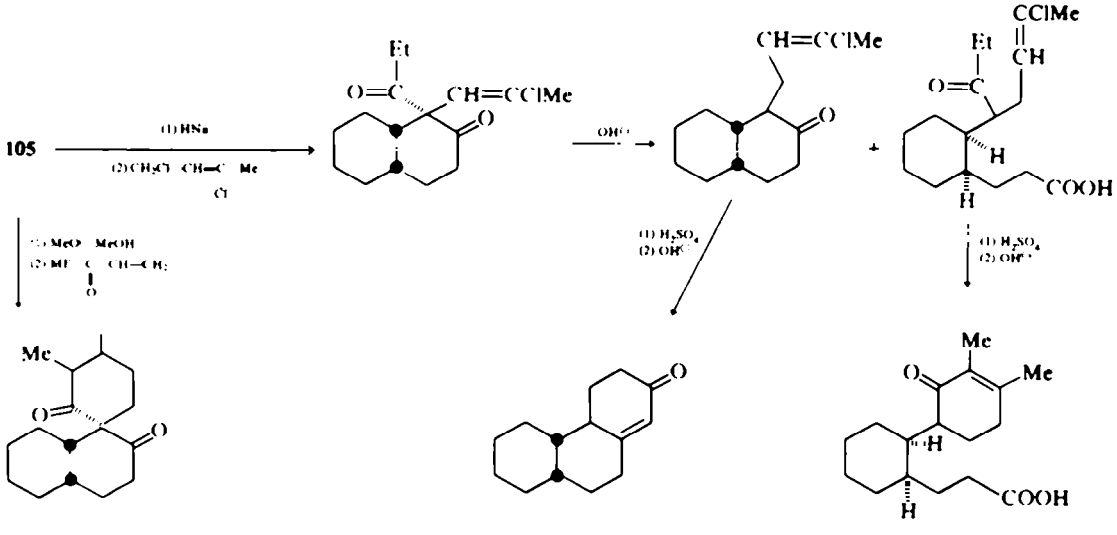


(40%) while it does not take place at all with the hydrindane analogue.[43]



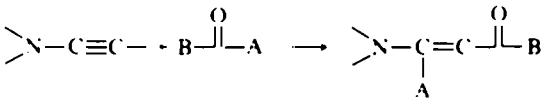






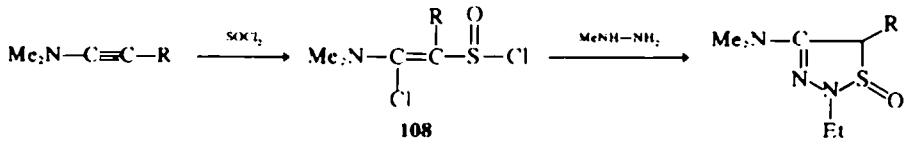
C. *Acylation of ynamines*

(a) *Acylation by acyclic acid derivatives.* Carboxylic acid chlorides, thionyl chloride and derivatives of carbonic acid such as phosgene, add to ynamines to give excellent yields of adducts of type **84**.[10]

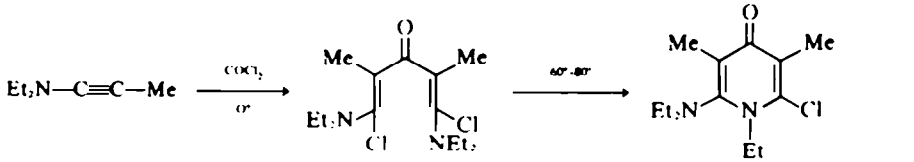


84

A variety of heterocyclic compounds can be synthesized taking advantage of the bifunctionality of adducts of type **84**, as one can see, for instance, in the following examples which involves the adducts obtained by addition of thionyl chloride **108**[44a] or phosgene **109**.[44]

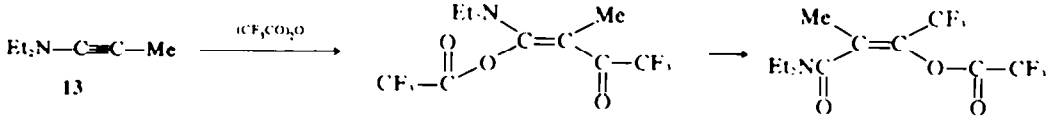


108



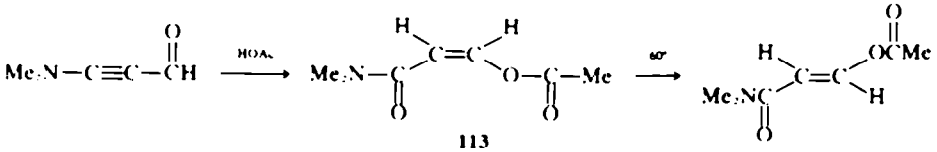
109

Adducts of type **110** which are produced starting with carboxylic anhydrides, from trifluoroacetic anhydride and N,N-diethylaminopropyne, for example, rearrange to give amides of type **111** by stereospecific intramolecular O-acylation:[44]



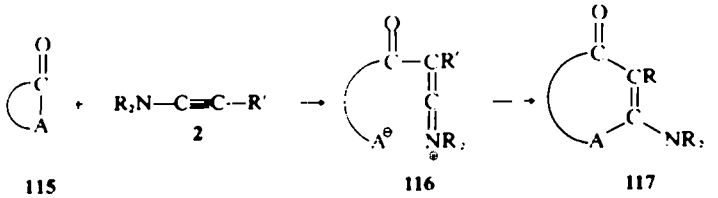
110 **111**

In a related reaction, the addition of acetic acid to ynamino-aldehyde **112** has to produce an initial adduct similar to adduct **110**. The reaction indeed, leads to the amide **113** (cf. **110** → **111**) which rearranges on heating at 60°, to give the thermodynamically more stable *trans*-isomer **114**.[44]

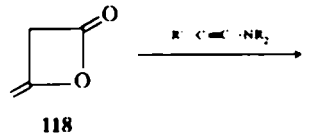


112 **113** **114**

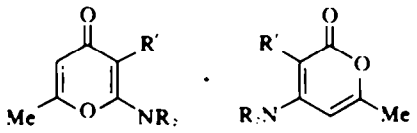
(b) *Acylation by cyclic carboxylic acid derivatives.* If the structure of the acid derivative is of the type **115**, the dipolar ion **116**, resulting from acylation of ynamines can become stabilized by internal neutralization which leads to cycloadducts of type **117**:



115 **116** **117**



118



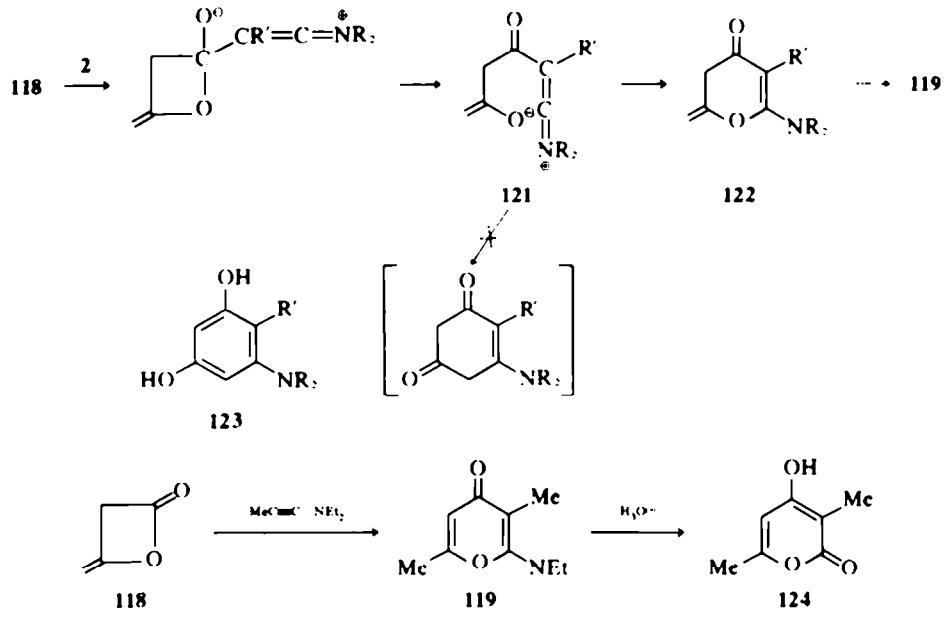
119 **120** (traces)

(1) *Ketene-dimers.* With diketene **118** annulation leads to amino γ-pyrones **119** accompanied by traces of amino-α-pyrones **120**.[46]

The strained ring of diketene is opened following attack on the carbonyl and the resulting dipolar ion **121** becomes neutral exclusively by O-alkylation, with the formation of amino-γ-pyrone **119**, via **122**. One does not find any traces of the amino-diphenol **123** which would have been the result of an *a priori* possible C alkylation. The methylene derivative of type **122** can be isolated when ynamines are acylated by the dimer of dimethylketene.[47]

The previously unknown aminopyrones of type **119** are hydrolized by acid to 4-hydroxy-2-pyrones. The 4-hydroxy-2-pyrone **124**, which is a metabolite of *Penicillium spititatum*, can thus be obtained, in two steps, starting from diketene, in an overall yield of 45%.[46b]

(2) *6-Membered enol lactones: a new annulation sequence.* The reaction of ynamines with the 6-membered lactones **125** give rise to acylcyclohexanedione enamine



131 accompanied or not, depending on the conditions reactions and the nature of the ynamine by unsaturated amides of type **130**.[48] In this case, the reaction is slower than with the strained diketene and requires a stoechiometric amount of Lewis acid ($MgBr_2$).

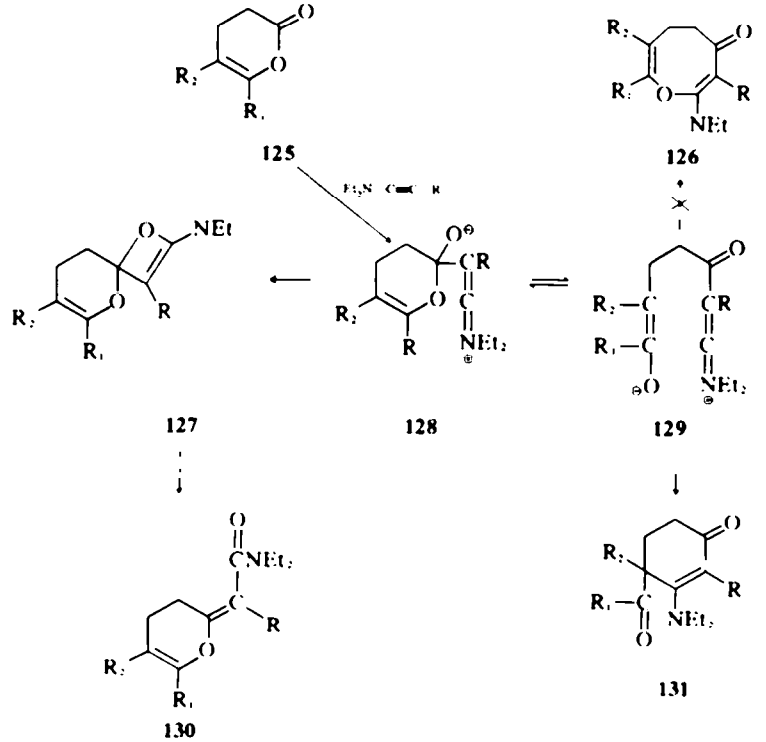
The initial attack of the ynamine at the carbonyl of such lactones, produces a dipolar ion of type **128** which can follow two reaction pathways:

It can be in equilibrium by cleavage of the ring with the dipolar ion **129**, the ketene immonium moiety of which is then trapped by C-alkylation. The C-alkylation gives in this case the 6-membered carbocycle **131** whereas O-alkylation would have led to an unfavorable 8-membered heterocycle of type **126**.

The initial dipolar ion **128** can also undergo further transformation involving an intermediate oxetene **127** with irreversible rearrangement to the amide **130**.

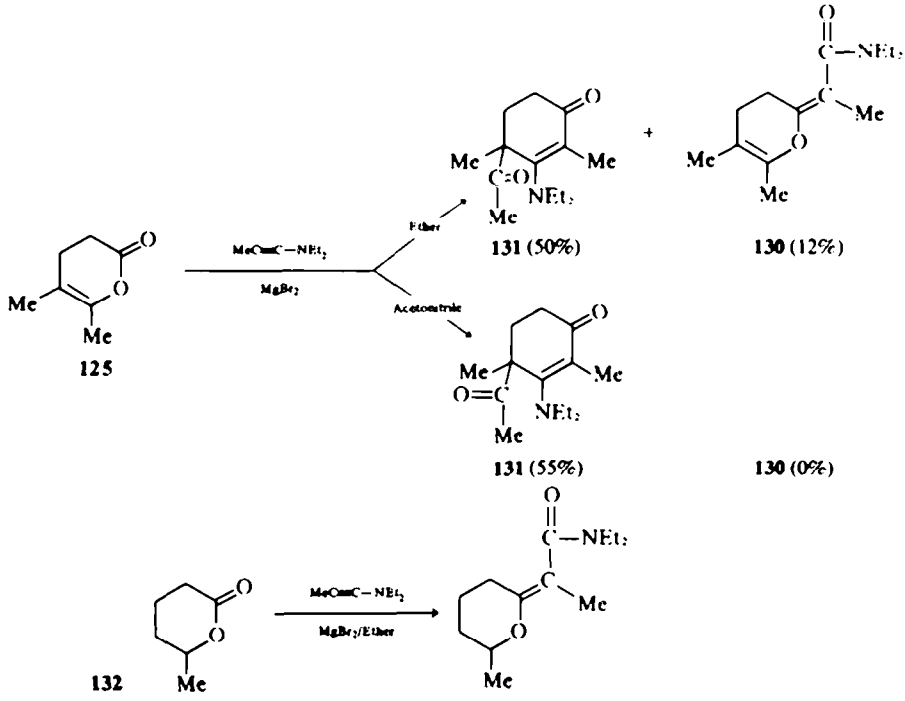
Evolution of the intermediate of the type **128** towards **127** or **129** obviously depends on the rate of the ring opening. This rate is very rapid in the reaction of ynamines with diketene (**118** → **121**) and becomes progressively slower with enol lactones (**128** → **129**) and especially with saturated lactones, as will be discussed later (3C).

Thus, diketene **118** is exclusively acetylated by diethylaminopropyne via ring opening, whereas in contrast saturated lactones such as methyl-valerolactone **132**, for example, undergo exclusively cycloaddition at the carbonyl to give the corresponding α,β-unsaturated amides without any cleavage of the lactone ring. On the other

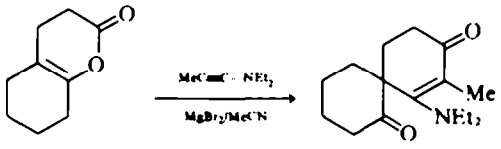


hand there is competition between the two processes with 6-membered enol lactones **125**. As was pointed out previously (Section 2A(c)) the extent of the acylation process via cleavage of the ring is increased by increasing the polarity of the solvent. In the case of 6-membered enol lactones, it is in fact possible to direct the reaction towards the opening of the ring and the annulation process, by using acetonitrile instead of ether, and to obtain selectively **131** for example from **125**:

(3) *Phthalic anhydride and phthalides.* The reaction of one equivalent of ynamine with cyclic anhydrides, such as phthalic anhydride, gives rise to an initial adduct **134**. The 8-membered cycloadduct **134** undergoes internal C-acylation leading to the indanedione **136**, in contrast with the acyclic adduct **110** which undergoes internal O-acylation. With two equivalents of ynamine, the initial cycloadduct **134** leads to the benzoxepinone **135**, by further cycloaddition at the more reactive carbonyl.[49]

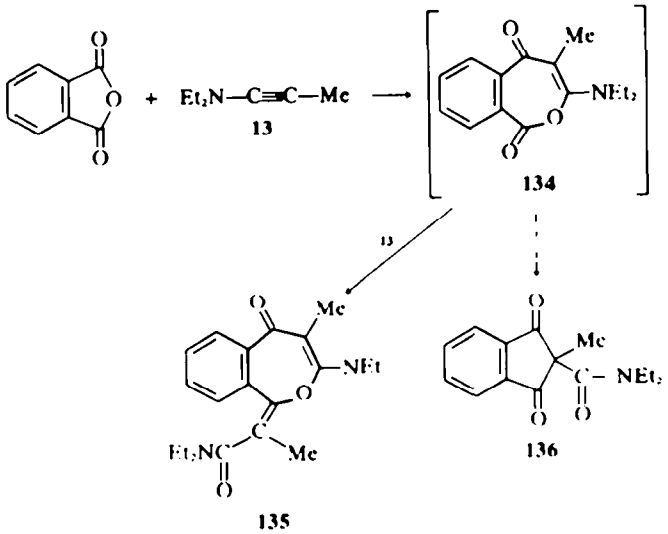


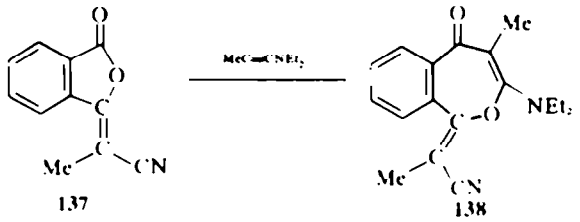
The annulation sequence starting from 6-membered annulated enol lactones opens a new route to the synthesis of spiro systems. The synthesis of spiroketone **133** can be performed for instance, in 50% yields:[48]



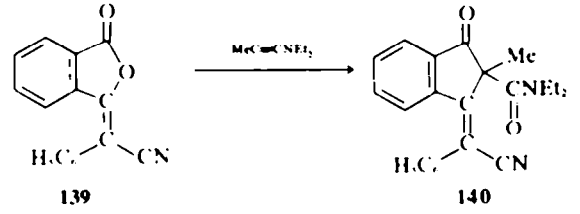
The initial 8-membered adduct of type **138** is isolated from the reaction of N,N-diethylaminopropyne and phthalide **137**, whereas it rearranges into the methylene derivatives **140** when the phthalide is substituted by a phenyl instead of a methyl group as in **139**[47] (cf. **134** → **136**).

(4) *Substituted oxazolones.* The opening of the ring which occurs after the attack at the carbonyl of disubstituted exazolones having no acidic hydrogens is followed, as expected by N- rather than O-alkylation of the intermediate dipolar ion, thus leading to pyrrolones **141**.[50]

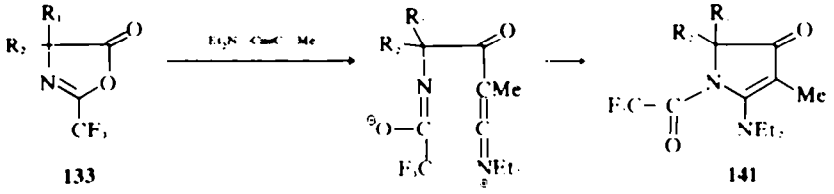




137 138



139 140

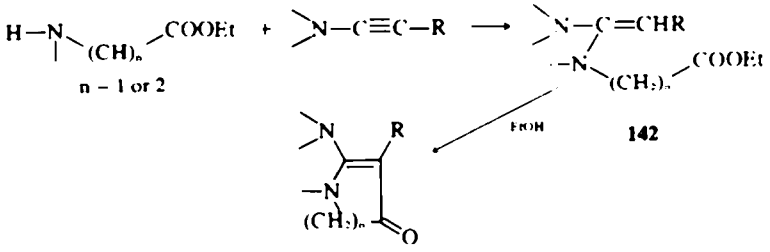


133 141

(5) *Intramolecular acylation of ketene aminal-esters.* To end this section dealing with acylation reactions by ynamines mention may be made of the intramolecular acylation of **142**, which follows the initial addition, of an α- or β-aminocarboxylic ester to an ynamine. The intermediary ketene-amimal **142** which is produced in the first step, undergoes internal acylation with loss of alcohol.[50]

D. *Alkylation of ynamines*

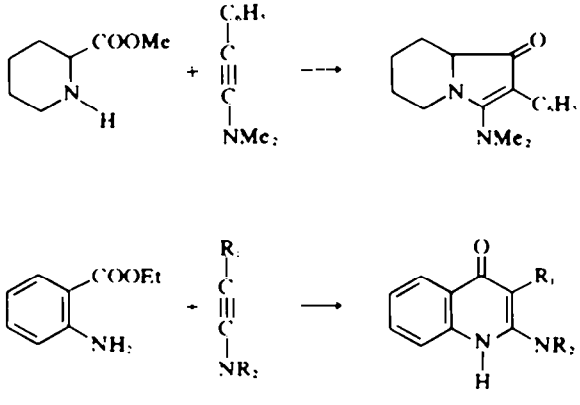
(a) *Alkylation by alkyl halides.* The direct alkylation of ynamines by alkyl halides is complex[10,51] and is not comparable to the alkylation of enamines.[1] This result comes, as was already mentioned (1A), from the difference in stability between the ketene-immonium ion derived from ynamines, and the immonium ion derived from



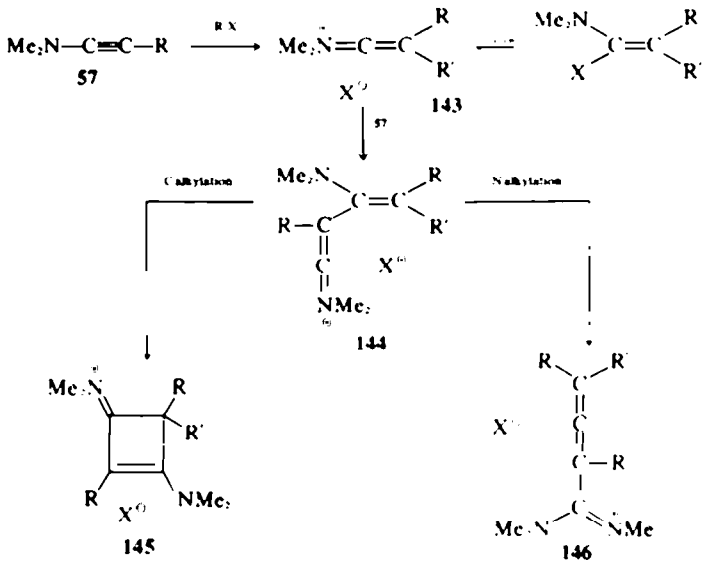
142

This reaction allows the synthesis of a variety of heterocycles:[50]

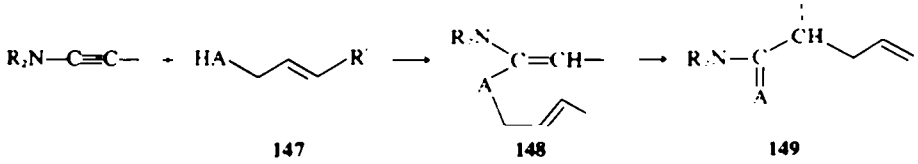
enamines. The ketene-immonium ion **143** cannot indeed be isolated;[52] it adds, *in situ*, to a second mole of ynamine



to lead to another immonium ion **144**, the neutralization of which is achieved by C (**144** → **145**) or by N (**144** → **146**) alkylation:

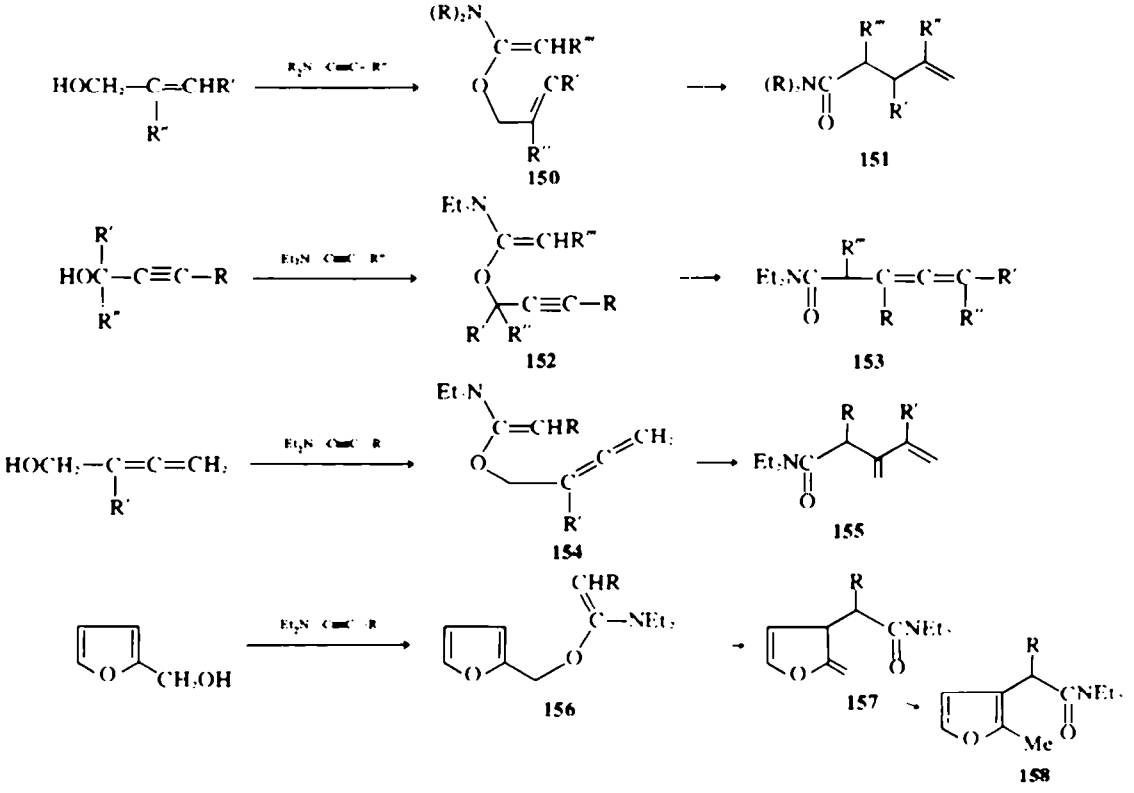


(b) *Alkylation via Claisen rearrangement.* When the initial adduct formed by addition of ynamines with a reagent H-A-R of the type **147**, for example, involves a 6 electrons system such as in **148** it undergoes a (3-3)-sigmatropic rearrangement which gives the parent derivative **149** of the initial ynamine:



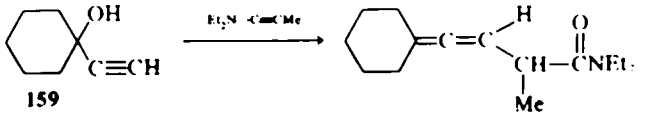
This sequence is therefore an alkylation by an unsaturated chain, in which the double bond is regiospecifically δ to the nitrogen related to the initial ynamine.

A variety of unsaturated alcohols such as allylic,[22,51] propargylic,[54] allenic[55] or furfurylic[56] alcohols react with ynamines to lead, via the sequence shown below to the corresponding γ-unsaturated amides, in good yields.



The initial adducts **150**, **152**, **154** and **156** are not isolated. They smoothly undergo, as soon as they are formed a Claisen rearrangement which leads to stable amides. The effectiveness of the N atom in assisting the Claisen rearrangement, is shown by the ease of the reaction.

Compare to the rearrangement of the corresponding ethers, that of N,O-ketene-acetals **152**, for example, obtained from addition of primary propargylic alcohols, is very easy. The rearrangement occurs at room temperature and is complete at 80° to lead to the allenic amides **153** with 60–80% yields. Even tertiary propargylic alcohols can be used in this reaction. In such a case, however there is partial recovery of the starting alcohols even at higher temperature. The carbinol **159** for instance gives rise, at 115°, to the allenic amide **160** in a 45% yield together with 45% of the recovered alcohol:



159 **160**

The addition of primary allylic alcohol gives an initial adduct **150** which is similar to the intermediate of the previously known reaction between these alcohols and N,N-dimethylacetamide dimethyl acetal.[46] The interest of the ynamine method is that the rearrangement occurs at room temperature instead of at 140°, to lead to γ-unsaturated amides derivatives **151** in 60–80% yields.

The addition of allenic alcohols and furfurylic alcohols to ynamines deserves particular notice, as they give rise to vinylallenic systems **154** the rearrangement of which was not previously described, and to vinylfurfurylic systems **156** the rearrangement of which is particularly laborious with the corresponding vinylethers.[47]

The furfurylic model **156** shows that the allylic double bond, although part of the rather stable furan ring, participate in the rearrangement which smoothly occurs at 80°. The methylene dihydrofuran **157** obtained by this process with 70% yields can be easily transformed by trace of acids into the furan **158**. This method is therefore a useful solution to the problem of introducing a substituent at the 3 position of a furan ring.

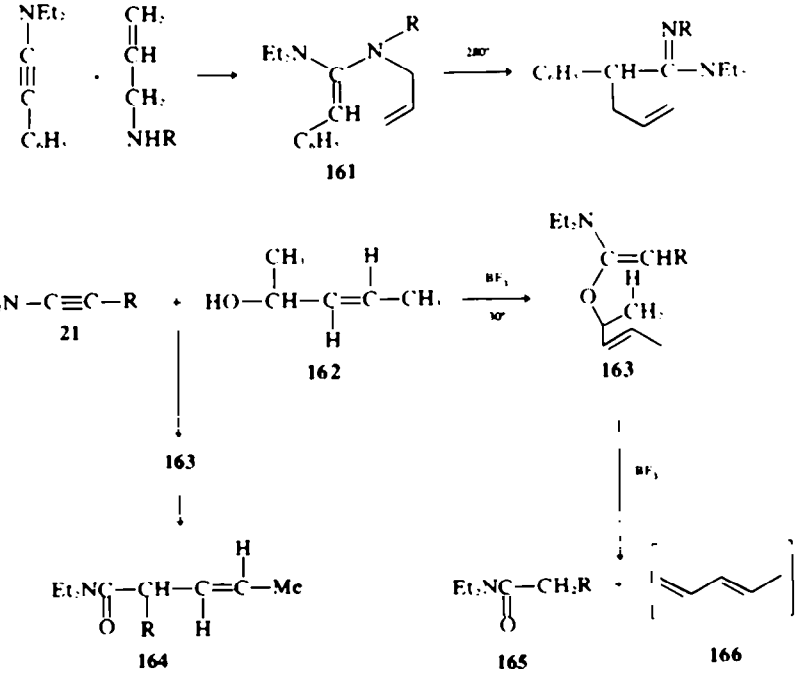
The allenic model **154** emphasizes that the Claisen rearrangement of such a 1-2-6 heptatriene is particularly favored by the relief of strain involved in going from an allene to a conjugated amide.[48] The initial adduct **154**, indeed, rearranges *in situ* to give the dienic amides **155**, the new route opened by this type of rearrangement has been further utilized recently.[49]

In contrast, the addition of allylic amines leads to the N,N-ketene-animals **161** which can be isolated and rearrange only at 280°.[22]

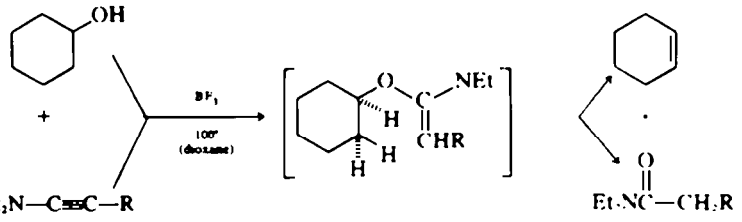
The alkylation of amides by an unsaturated chain through the Claisen rearrangement described above, is however not feasible with tertiary allylic alcohols, as these do not add to the triple bond of ynamines, but lead rather to cyclobutenyl salts of type **37** (see Section 1C(a)).

On the other hand, the Claisen rearrangement can be successfully applied, to secondary allylic alcohols, such as **162** providing that no Lewis acid is used to catalyze the initial addition step: **162** → **163** → **164**. If the O,N-ketene acetal **163** is formed in presence of BF_3, it undergoes an elimination reaction **163** → **165** + **166**, rather than a Claisen rearrangement.[22]

It is possible to take advantage of such an elimination process, for the dehydration of saturated secondary alcohols. Cyclohexanol, for example, is dehydrated at 100° to give cyclohexene in 80% yields.[50]



161 **21** **162** **163** **163** **164** **165** **166**

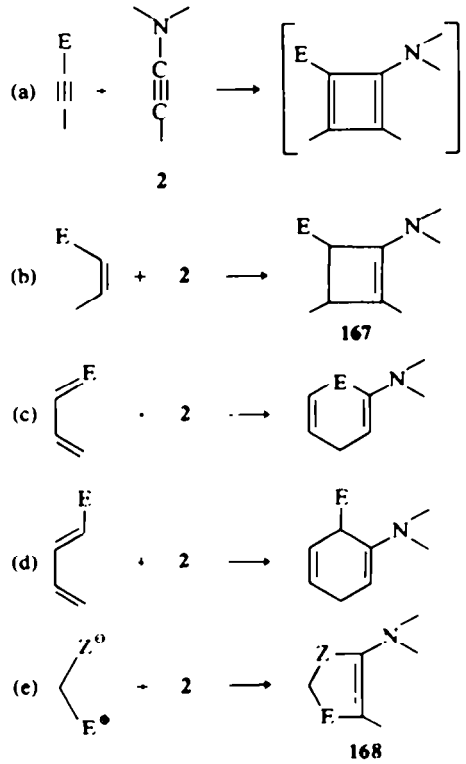


3. CYCLOADDITION REACTIONS OF YNAMINES

A. *General processes leading to carbon-carbon bonds by cycloaddition reaction*

A survey of the results obtained in the field of cycloaddition reactions, evinces particularly well the unusual and versatile capabilities of ynamines. The new function found in ynamines, which is more nucleophilic than that found in other heterosubstituted acetylenes also happened to have a larger range of reactivity toward a variety of electrophilic unsaturated partners.

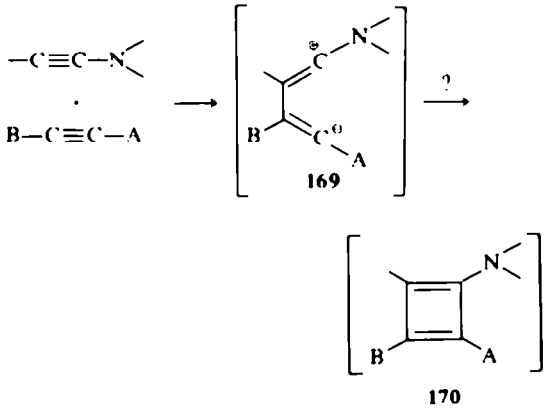
This special propensity towards cycloaddition which will be developed in this section is schematized by the following different types of cycloaddition encountered with electrophilic acetylenes, ethylenes, dienes and 1,3-dipoles:



The cycloadditions of ynamines with 1,3-dipoles (eqn e) which produces 5-membered heterocycles of type **168**[61] will not be discussed here. We will discuss those cycloadditions which lead to the formation of C–C bonds (eqns a, b, c, d), with special emphasis on polar cycloaddition of the 2 + 2-type with electrophilic olefins (eqn b). This process which is observed, in particular with cyclenones (see Section 3E(b)) and α,β-unsaturated nitriles (Section 3E(c)), produces 4-membered enamines of type **167**, which proved to be very useful key intermediates in novel regio and stereoselective synthesis of C–C bonds.

B. *Cycloaddition with carbon-carbon triple bonds*

Some of these cycloadditions were among the first reactions tried, as soon as ynamines became available for they might have led to cyclobutadiene structures of type **170**:



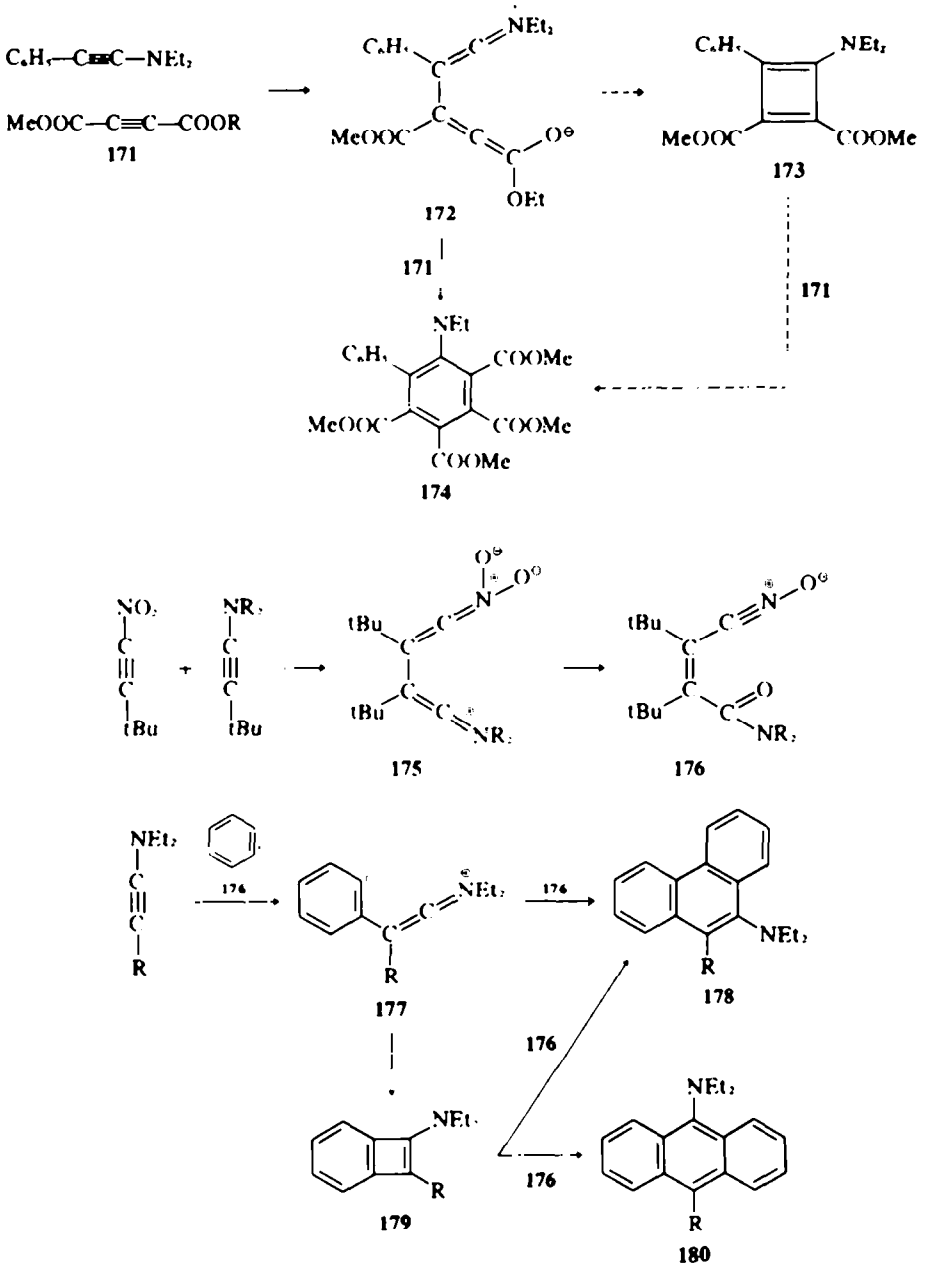
In fact, all the attempts carried out with various electrophilic acetylenes show the great reactivity of ynamines but fail with respect to cyclobutadiene synthesis: in some cases because the dipolar intermediate **169** does not cyclize, in other cases because the cyclobutadiene **170**, although produced, is nucleophilic enough to react, *in situ*, with another mole of the electrophilic acetylene.

It is unlikely for instance that the dipolar ion **172** cyclizes to the cyclobutadiene **173** during the cycloaddition of N,N-diethylaminophenylacetylene with methyl acetylene dicarboxylate.[121] This reaction which requires two equivalents of **171** actually gives rise to the biphenyl derivative **174** as a single regioisomer.

The complete regioselectivity of this reaction suggests that the intermediate ion **172**, rather than the cyclobutadiene **173**, reacts with the second mole of acetylene dicarboxylate. Nevertheless, attempts to trap either the cyclobutadiene (with nickel salts) or the dipolar intermediate (with phenyl acetylene) have been unsuccessful until the present time for acetylene dicarboxylate itself, reacts faster than the additional trapping reagents.[6]

It is also unlikely that the intermediate dipolar ion **175** produced by the reaction of ynamines with nitro-acetylenes proceeds via a cyclobutadiene. In this case, the reaction can be rationalized with the intermediate **175** which does not add a second mole of nitro-acetylene but undergoes a rearrangement to a one to one adduct of the type **176**.[62]

In contrast, a benzocyclobutadiene of type **179** is undoubtedly produced by reaction of ynamines with benzyne for its reaction with another mole of benzyne is necessary to explain the formation of anthracene **180**. The aminophenanthrene **178** which is also isolated can come either from the benzocyclobutadiene **179** (**179** → **178**) or from the dipolar ion **177** (**177** → **178**).[63]

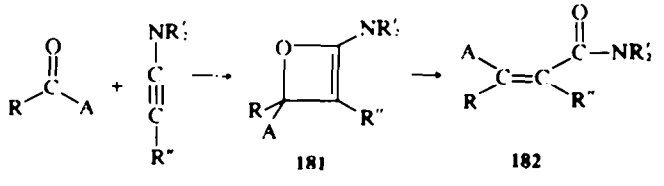


We may recall here that stabilized cyclobutadienes *can* be obtained starting from ynamines, but by another route (see Section 1C(a)).

To end this section dealing with electrophilic triple bonds, it is worth pointing out that the reaction of ynamines with the C≡N triple bond does not take place, even in presence of Lewis acids. This lack of reactivity turns out to be very favourable, for it makes possible to use acetonitrile, for instance, as a polar solvent for ynamine reactions.

C. *Cycloaddition with carbon-oxygen and carbon-nitrogen double bonds*

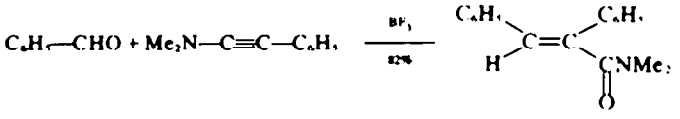
The cycloaddition of ynamines with the carbonyl of aldehydes and ketones[64] is easier than that of acetylenic ethers but is also catalyzed by addition of Lewis acids (BF_3). The cycloaddition of ynamines with the carbonyl of carboxylic esters[64,65] or saturated lactones[64] is slower than that with ketones: the use of a stoechiometric amount of $MgBr_2$, increases the speed and the yield of the cycloaddition in those cases.



A = H, Alkyl, OR

These cycloadditions lead to the corresponding α,β-ethylenic amides **182**, probably via the intermediary oxetenes **181**. The cycloaddition as in the case of acetylenic ethers,[63] is stereospecific with aldehydes[64] and the amide function of the product is *trans* to the R group provided by the aldehyde.

Some examples listed below point out the feasibility of this unsaturated amides synthesis, via the cycloaddition of ynamines with carbonyl functions:



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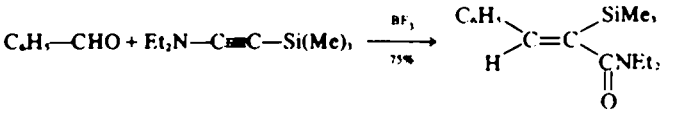

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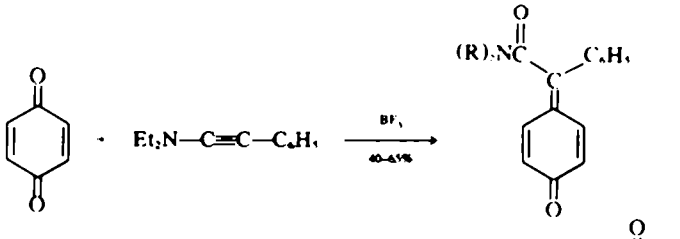

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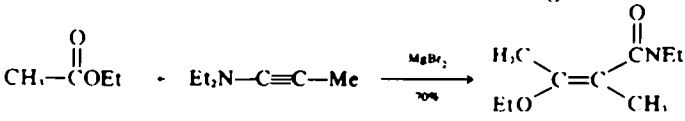

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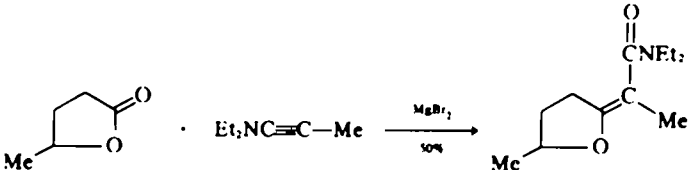


(34)

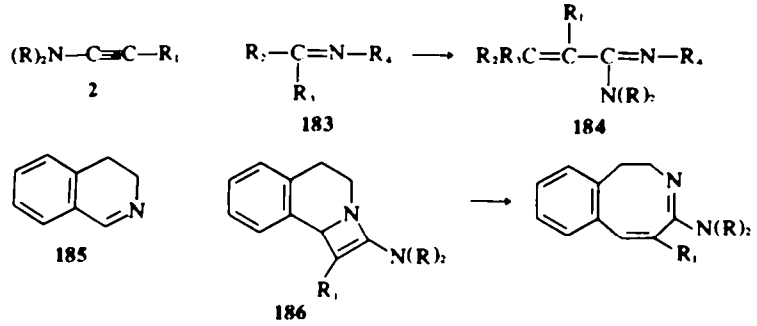
The reaction with immonium perchlorates of type **187** gives rise to conjugated amidinium salts **188** in 60 to 93% yield. When the initial imminium salt is part of ring, as in **189**, there is a ring expansion (**189** → **190**) as with the cyclic imines.[68]

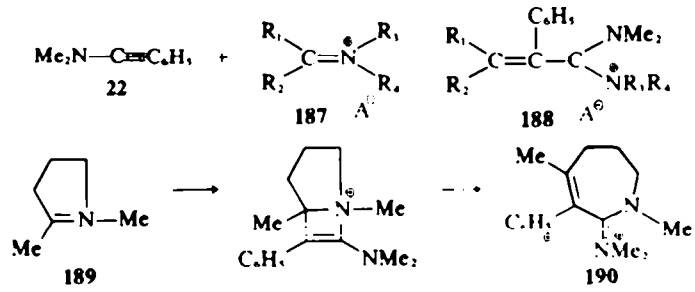
D. *Cycloaddition with hetero-cumulenes*

(a) *Cycloaddition with carbon dioxide.* The litterature records only a very small number of cycloadditions involving carbon dioxide.[69] Ynamines react with great facility with this very simple heterocumulene to give, in quantitative yield, adducts of 2 moles of ynamines and one mole of carbon dioxide.

With N,N-diethylaminopropyne **13** and N-methyl-N-phenylaminoacetylene **24** the cycloaddition leads to

The cycloaddition of ynamines takes place also with the C–N bond of imines and with immonium salts. The imines **183** lead to α,β-ethylenic amidines **184** and when the imine is part of a ring as in **185**, the cleavage of the intermediate **186** leads to expansion of the ring with insertion of 2 C atoms:[67]





amides of allene dicarboxylic acids **191** and **193**, together with very small quantities of aminocyclobutenones **192**.[6] The easy cycloaddition of these ynamines with carbon dioxide represents therefore a particularly attractive route to allene 1,3-dicarboxylic amides.

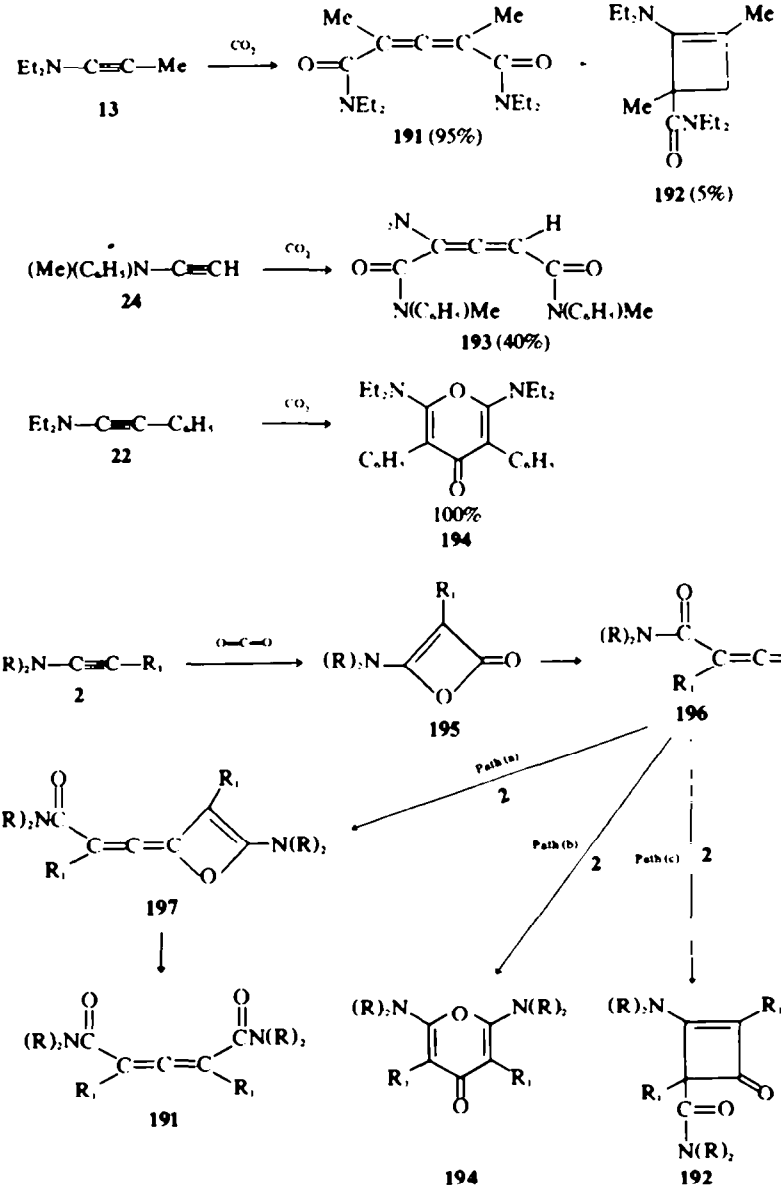
In contrast, the cycloaddition of N,N-diethylaminophenylacetylene **22** with carbon dioxide, leads exclusively to the amino-γ-pyrones **194**.[6a]

One can rationalize these results by assuming that initial cycloaddition of the ynamine and carbon dioxide produces the 4-membered enol-lactone **195** which rearranges to the intermediary ketene **196**. The latter would be expected to react with the initial ynamine, in three different manners (see Section 3D(b)):

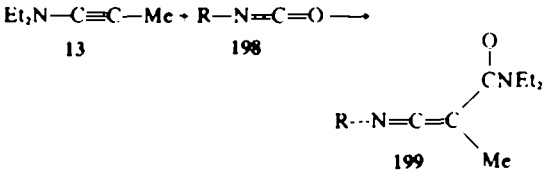
Path (*a*). Cycloaddition at the C=O bond leading to **197** then to allenes **191**.

Path (*b*). (2 + 4)-Cycloaddition at the conjugated amide leading to pyrones **194**.

Path (*c*). Cycloaddition at the C=C bond leading to cyclobutenones **192**.

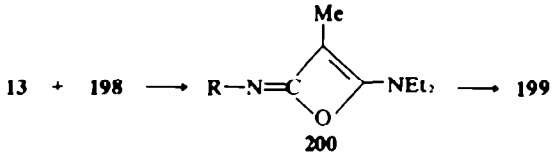


(b) *Cycloaddition with isocyanates and ketenes.* The cycloaddition of N,N-diethylaminopropyne with alkyl isocyanates **198** involves one equivalent of each reagent, and leads to the carbamoyl ketenimines **199** in 40–50% yields:[71,72]



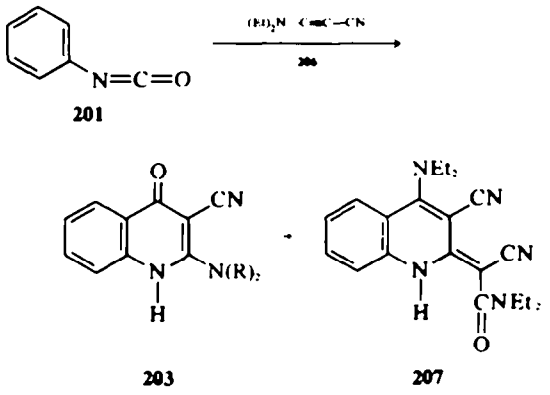
It is likely that the initial attack of ynamines leads to a strained 4-membered intermediate **200**, as in the case of carbon dioxide (Section 3D(a)). This 4-membered system rearranges to give a carbamoyl ketenimine **199** which being less reactive than the carbamoyl ketenes **196** or the N-phenylketenimines,[73] does not add a second mole of ynamine under the conditions of the reaction.

It is worth noting that the formation of the 4-membered intermediate **200**, implies an initial cycloaddition of the ynamine involving the O rather than the N atom of the alkyl isocyanate.



The cycloaddition of ynamines with aryl isocyanates **201** takes place in a different manner and leads to 4-amino-2-quinolones **202**[11c,45,74] together with 2-amino-4-quinolones **203** in less polar solvent (benzene instead of acetonitrile[11c]):

In the special case of the cyano-ynamine **206**, the 2-amino-4-quinolone **203** is formed together with a 4-amino-2-quinolone **207** a 2/1 adduct of ynamine and phenyl isocyanate.[76]

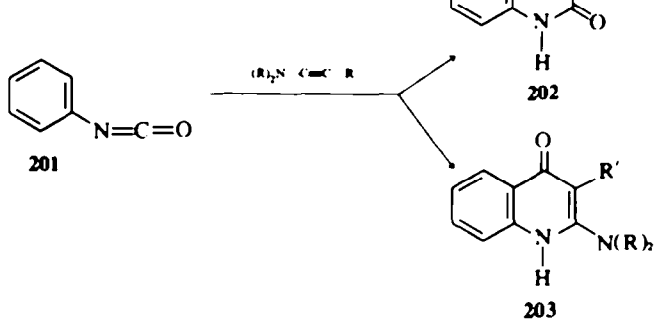


These results can be rationalized by assuming that the different cycloadducts are produced by internal cyclization of an intermediary dipolar ion of type **209**, via three different pathways:

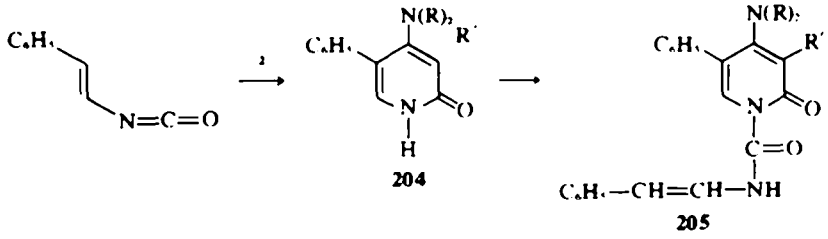
Path (*a*). O-Alkylation of the enolate **209** by the ketene-immonium cation followed by ring opening of the intermediate **208**, thus leading to an intermediary aryl ketimine **211** which adds a second mole of ynamine and cyclizes to give the 4-amino-2-quinolone-methine structure **207**.

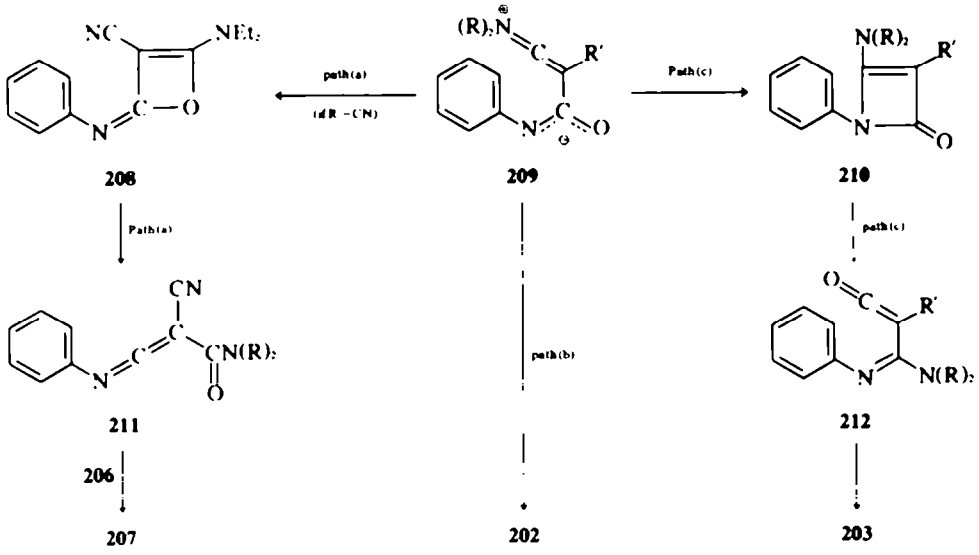
Path (*b*). C-Alkylation, via a 6-center process, of the enolate **209** which gives rise to the 4-amino-2-quinolones **202**.

Path (*c*). N-Alkylation of the enolate **209** followed by the cleavage of the strain lactam **210**, thus leading to an intermediary ketene **212** which cyclizes to lead to 2-amino-4-quinolones **203**.



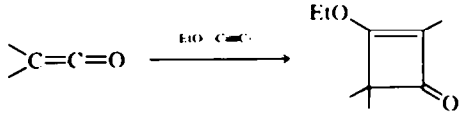
With styryl isocyanates[73] the initial cycloadduct **204** adds a second mole of isocyanates (**204** → **205**):





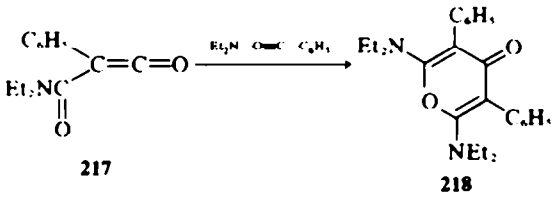
From the results available at the present time, one can observe that the O-alkylation process (path a) which is followed by the reaction of ynamines with *alkyl* isocyanates **198** is an exception with the conjugated *aryl* isocyanates **201**. One can also note that the 6-center cyclisation (path b) which prevails in most cases (it is the exclusive one with the less nucleophilic ethoxyacetylene[1]), is in competition with a direct four center N-alkylation (path c) with decreasing the polarity of the solvent.

The very smooth cycloaddition of ynamines with ketenes can give results as varied as that of isocyanates. Whereas the acetylenic ethers lead to ethoxycyclobutenones **213**[1] (with the exception of diphenylketene[77]), the cycloaddition of ynamines with ketenes gives rise not only to aminocyclobutenone derivatives **215** but also to amides of allenes carboxylic acids **216**, and in one case to the γ-pyrone **218**.



213

N,N-Diethylaminopropyne gives an allene carboxylic acid amide **216** as the major or the exclusive adduct, with various ketenes such as aryl,[11c,78] carbethoxy,[70b] carbamoyl ketenes.[70b] On the other hand, N,N-diethylamino phenyl-acetylene produces mainly the aminocyclobutenones **215** with the same groups of ketenes. Moreover, this last ynamine leads exclusively to γ-pyrone **218** by reaction with the arylcarbamoylketene **217**:[70b]



217 **218**

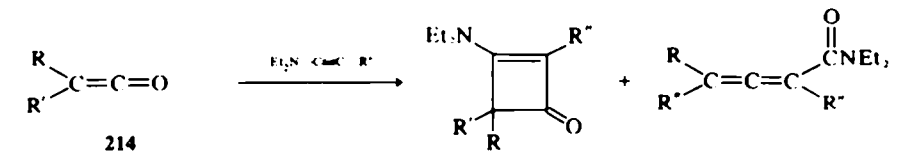
One can assume that the various types of cycloadducts come from the internal cyclisation of an intermediary dipolar ion of the type **220** (compare to dipolar ion **209**) which then follows three different pathways:

Path (*a*). O-Alkylation of the ambident enolate **220**, via a four center process (**220** → **219**), followed by ring opening of the strained oxetene **219**, thus leading to allene carboxylic acid amides **216**.

Path (*b*). O-Alkylation of the enolate **220** via a 6-center process, giving rise to γ-pyrone **218**.

Path (*c*). C-Alkylation of the enolate leading to the aminocyclobutenones **215**.

As was mentioned previously, the formation of the γ-pyrone occurs only in one case (path b). The competition between the two other processes, which are more common, depends mainly on the nature of the ynamines, rather than on that of the ketenes. The more reactive is the substituted ynamine, the more favored is the path (a) leading to allenes. Moreover, the ratio of O-alkylation (path a) vs C-alkylation (path c) decreases when the cycloaddition of a very reactive ynamine, such as N,N-diethylaminopropyne, is carried out in the less polar solvent (hexane instead of in acetonitrile[6]).



214

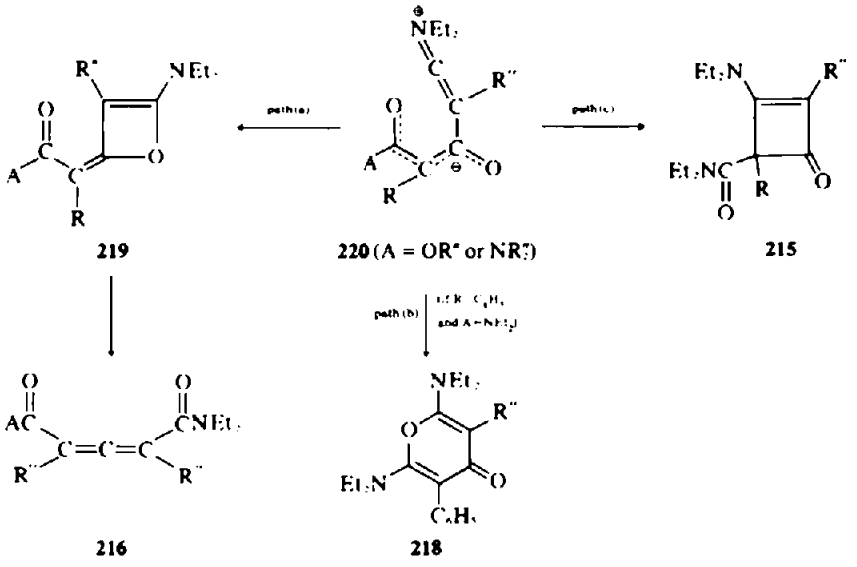
R = C_6H_5, R' = H or C_6H_5
R = Me, R' = COOEt
R = Me, R' = $CONEt_2$

215

R'' = C_6H_5 (Major)

216

R'' = Me (Major)



219 220 (A = OR" or NR'2) 215

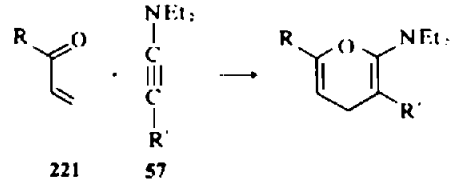
216 218

The variety of results obtained from cycloaddition of ynamines with ketenes as well as with isocyanates, is not simple to rationalize at the present time. It is reasonable to assume, as was done above, that the polarity of the starting reagents favours a two-step process involving the dipolar intermediates **209** and **220** rather than a concerted one. Why the further cyclization of these dipolar intermediates is following one pathway rather than another, is, however not clearly understood. It is possible that the energies of the transition states of these different cyclization processes are close enough to each other so that the effect, even small, of factors such as, polarity, temperature or steric hindrance, is sufficient to guide the reaction towards one or the other route.

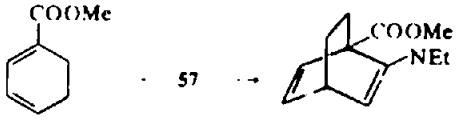
E. *Cycloaddition with electrophilic olefins*

As was already pointed out, the ynamines, in contrast with the less nucleophilic acetylenic ethers, undergo cycloaddition reactions with a large variety of electrophilic olefins. The cycloaddition can follow two different courses depending on the olefinic substrate: a process of the (2 + 4)-type leading to a 6-membered ring, and a process of the (2 + 2)-type leading to a 4-membered ring.

Cycloaddition of the (2 + 4)-type takes place, for instance, with enones **221** which can assume a cisoïd conformation (Section 3E(a)) and with the cyclohexadienic ester **222**, which is fixed in a cisoïd conformation (section 3F).

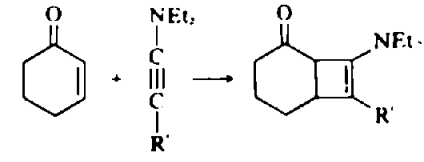


221 57



222

Cycloaddition of the (2 + 2)-type takes place, on the other hand, with, for instance, transoïd cyclenones such as cyclohexenone (Section 3E(b)), and with α,β-ethylenic nitriles (Section 3E(c)).



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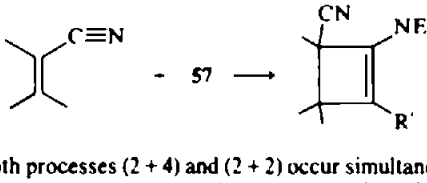
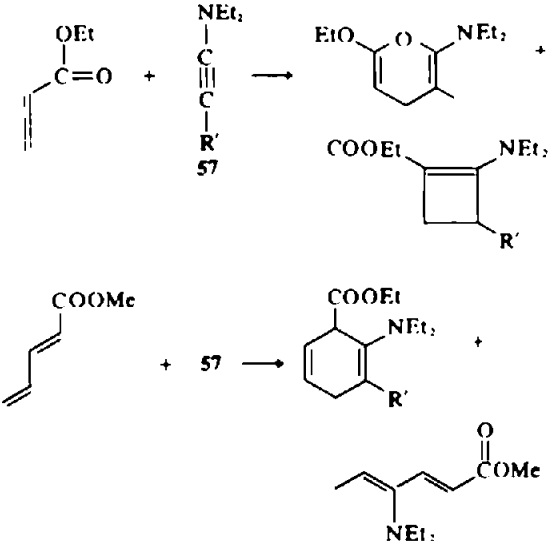


Both processes (2 + 4) and (2 + 2) occur simultaneously, in some cases, such as, for instance, α,β-ethylenic esters (Section 3E(a)) or flexible dienic esters (Section 3F).

Several new synthetic methods were developed using

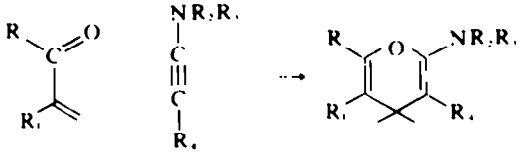


57

the cycloaddition of ynamines with various types of electrophilic olefins. The field of cycloaddition of the (2 + 2)-type with cyclenones and unsaturated nitriles is particularly rich in results and will be discussed separately in the following Sections (b) and (c).

(a) *Cycloaddition with various acyclic electrophilic olefins.*

α,β-ethylenic ketones, aldehydes and esters. The α,β-ethylenic ketones of type **223** which can assume a cisoïd conformation and in which the β-position is not hindered, lead to the previously unknown amino-γ-pyranes **224** in 40–60% yields.[11,14,79,80]



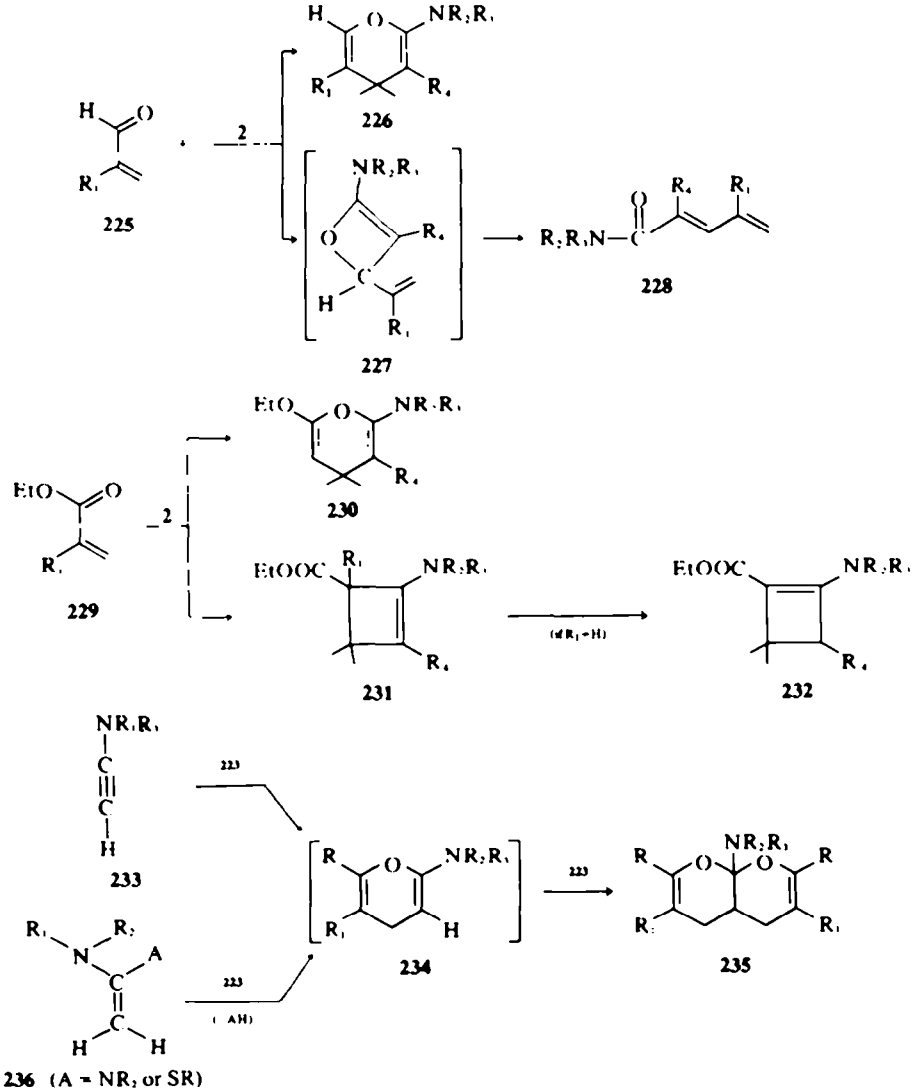
223 **2** **224**

With the α,β-unsaturated aldehyde **225**, however, the γ-pyranes **226** are formed together with the dienic amides **228** which come from cycloaddition at the unhindered carbonyle via the oxetene **227**.[14,79]

With α,β-unsaturated esters **229**,[81] the γ-pyranes **230** are accompanied by the 4-membered enamines **231**. These rearrange to give the more stable enamino-esters **232** when R_1 is an H atom.

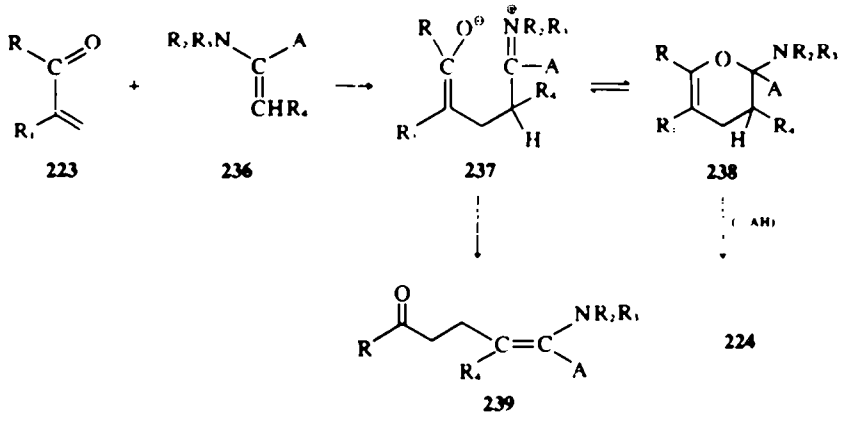
When the ynamines are not substituted on the C atom, such as ynamines **233**, the γ-pyranes **234** are, in this case, as reactive as the starting ynamines and are not isolated. They react, *in situ*, with another enone molecule, to give the pyrano-pyranes **235**[14,82] identical with those obtained from N,S- or N,O-ketene-acetals **236**.[83b,83c]

The success of the synthesis of γ-pyranes **224** from substituted ynamines is therefore the result of the steric hindrance of the resulting γ-pyranes, which reduces the speed of their reaction with the starting enones. It also comes from the acetylenic function found in ynamines compare to the ethylenic function found in ketene-acetals, for the ketene-acetals, even when they are substituted on carbon, as **236** do not lead in all cases to γ-pyranes as do the substituted ynamines. The cycloaddition mechanisms of ynamines and ketene-acetals do not involve the same intermediate, as we pointed out previously (Section 1A): with ketene-acetals **236**, the γ-pyrane **224** has to be formed by elimination of HA from the dihydropyran **238**, which can be in equilibrium with immonium ion **237**. The immonium ion **237** can be neutralized not only by



236 (A = NR_2 or SR)

heterocyclization: 237⇌238, (or carbocyclization) but also by transfering a proton as in the case of enamines, to give the Stork adduct 239:[7]



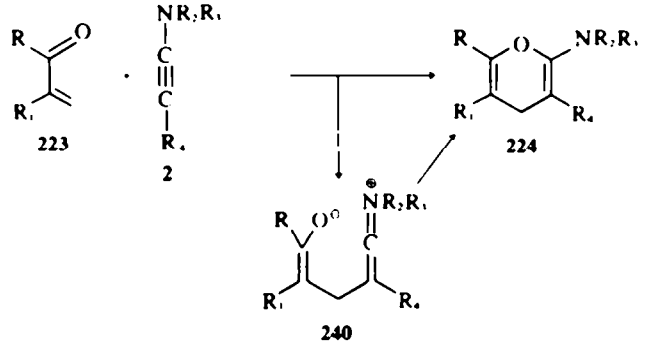
With the ynamines 2 the cycloaddtion leads to pyranes 224 by a process which can be concerted[24-26] or which can involve a ketene-immonium ion such as 240. In either case, such a proton transfer cannot take place, since the related center is fully substituted.

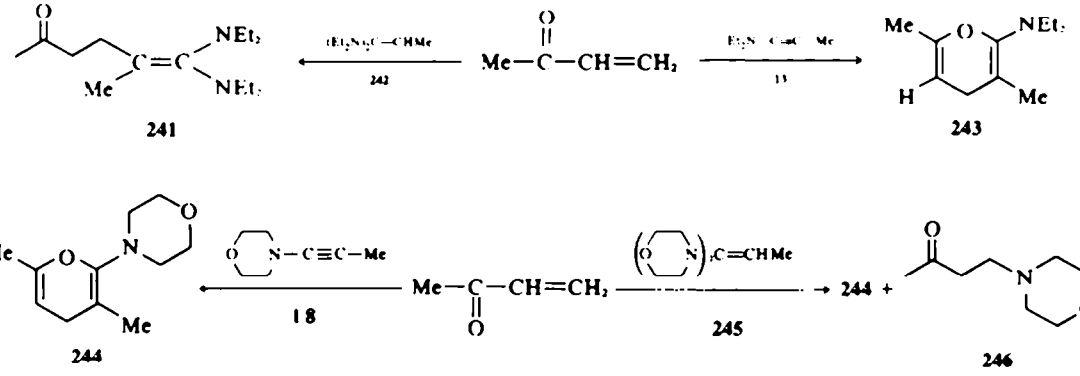
The comparison between the reaction of *bis*-N,N-diethylaminopropene 242 and N,N-diethylaminopropyne 13 with methylvinyl ketone is particularly striking: 242 leads exclusively to 241 by transfer of a proton, whereas 13 leads exclusively to γ-pyrane 243 by cycloaddition reaction.[14,82,84]

The formation of the Stork adduct of type 239 must become less favourable when the amine HA is eliminated more easily, in other words, when the immonium ion 237 is less stable. This happens to be the case for the reaction of methyl-vinyl ketone with N,N-dimorpholinopropene 245. The latter which is less basic than 242, leads to the corresponding γ-pyrane 244, as does the ynamine.[14,18,82,84] However, in contrast with the case of the ynamine, the pyrane is accompanied, in the case of the ketene-aminal by the Mannich base 246 coming from the 1,4-addition of morpholine to the enone.

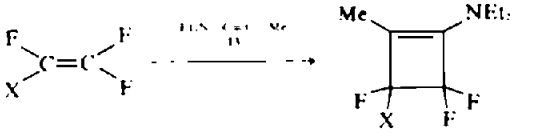
The 1,4-addition of AH which is generally observed in the reaction of ketene-acetals 236 and enones[83b,c] as well as α,β-unsaturated esters[83a,b] or nitriles[83b] results in the loss of half of the conjugated substrate. This side reaction does not take place, of course, with ynamines, which are therefore the reagents of choice, for amino γ-pyrane synthesis. Some of these amino γ-pyranes have recently been shown to have antihypertensive and coronary dilating properties.[80b]

Electrophilic fluoro and nitro olefins. N,N-

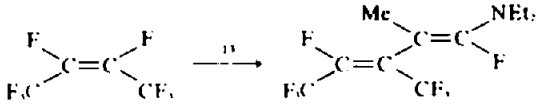




Diethylaminopropyne **13** reacts at room temperature with chloro- or bromo-trifluoroethylenes to give the halogeno 4-membered enamines **247**,[87] whereas the perfluoro-2-butenes, such as the *cis*-isomer, gives rise to the perfluorodienamine **248** (perfluoropropene and dichlorofluoroethylene produce a mixture of the two types of adducts[87]):

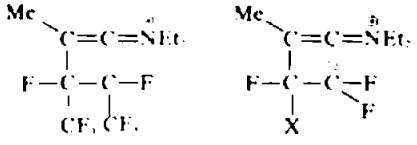


247



248

These results can be rationalized by assuming that the dipolar intermediate of type **250** can be stabilized either by β-elimination of a fluorine ion (**250**-A → **248**), or by internal cyclization (**250**-B → **247**).



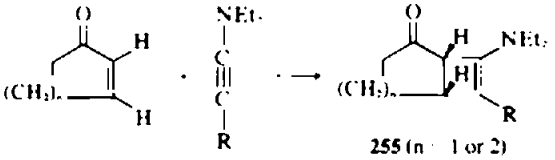
250-A **250-B**

N,N-Diethylaminophenylacetylene reacts also at room temperature with double bonds conjugated with a nitro group even when the double bond is part of a heterocycle such as, for instance, 4-nitro-isothiazole.[88] This cycloaddition which gives rise to **251** is accompanied by a cycloaddition involving the nitro group which leads to a nitrone, probably via the intermediate **252**. In a polar solvent (acetonitrile) this last process is the exclusive one.

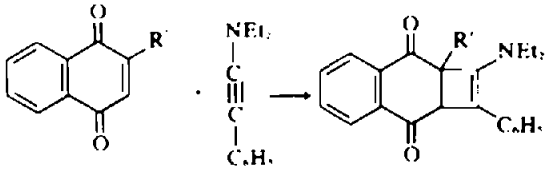
(b) *Cycloaddition with cyclenones.* (1) *The different types of cyclenones.* The reaction of ynamines with 3-, 5- or 6-membered α,β-ethylenic ketones leads to initial bicycloadducts **253**, **255**, **256** which involve a 4-membered enamine with a *cis*-junction.

The very strained (2-1-0) bicyclic enamine **253** is not isolated. It rearranges, *in situ*, to give the amino-ketone **254** hydrolyzed to the corresponding diketone.[87]

In contrast, the bicyclic adducts **255**[88] or **256**[89,90] are thermally stable, for the energy required for the conrotatory opening[24] of the cyclobutene is not available under the conditions of the reaction:

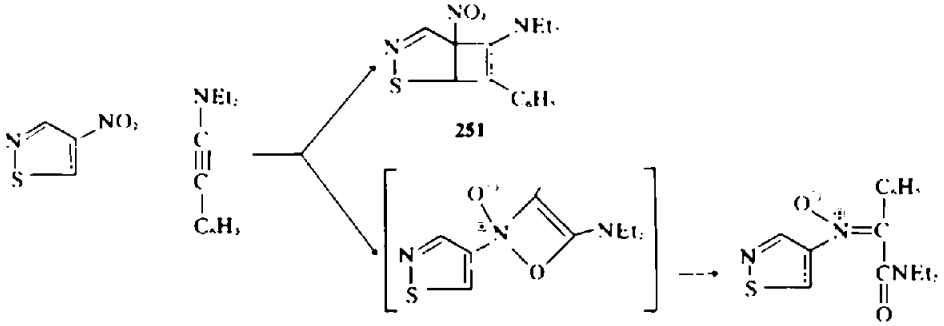


255 (n = 1 or 2)



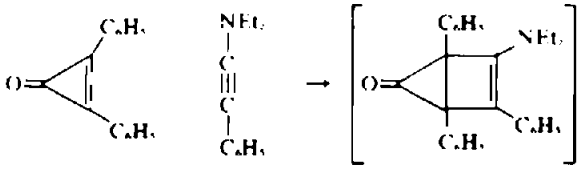
R' = H (89) or OCO$_2$Me (90) **256**

The enamino cyclobutenone **257** which is isolated by reaction of **13** with 1-3 dimethyl cyclobutenone is thermally stable under 170°. However it is opened around this temperature to give an aromatic ring.[91] In contrast



251

252



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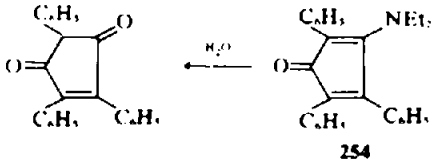
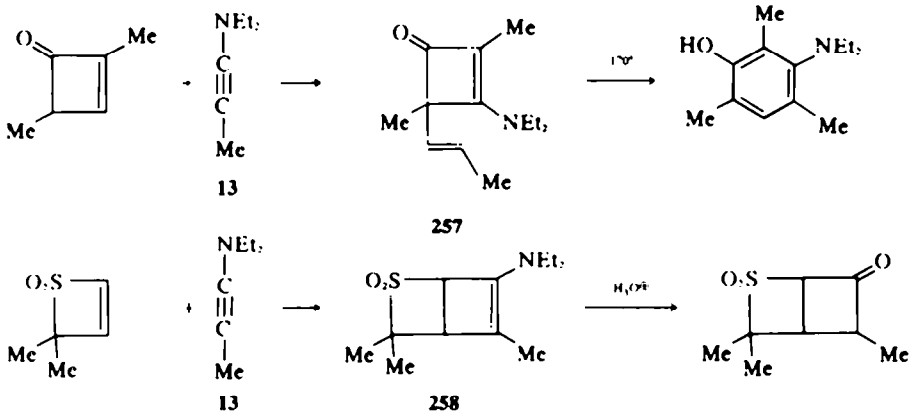


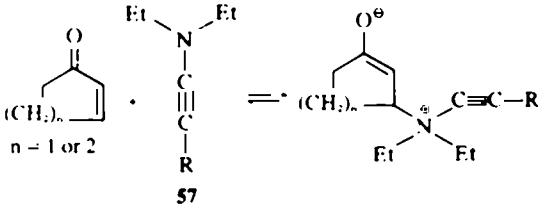
254

the bicyclic system **258** which is obtained from **13** and a four membered unsaturated sulfone can be characterized by hydrolysis of the enamine:[92]



The cycloaddition of ynamines with cyclopentenones and cyclohexenones will now be discussed. This reaction deserves particular attention because of the new possibilities which it opens in regio- and stereo-selective synthesis of C–C bonds.

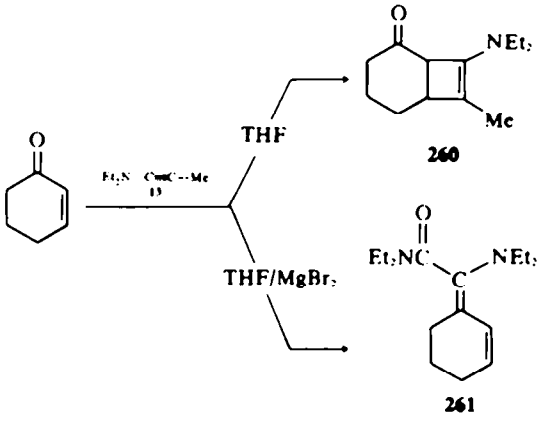
(2) *Regioselectivity of the cycloaddition with cyclopentenones and cyclohexenones.* The formation of cycloadducts **255**, which occurs without any catalyst, shows that, under these conditions, the ynamine reacts at the electrophilic conjugated C atom rather than at the carbonyl.[88] One must notice that if this reaction was preceded by an attack involving the N atom, this reversible process, as it is the case with the enamines[3] would not be observed.



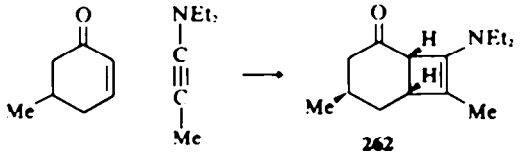
57

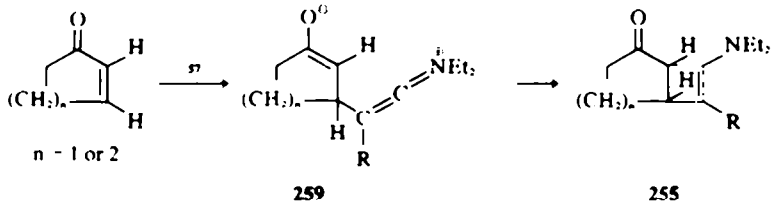
It is reasonable to assume that the synthesis of bicyclic adducts **255** is not a concerted process but involves instead the dipolar ion **259**. This dipolar intermediate does not became neutralized by O-alkylation which would lead to a γ-pyrane with a double bond at the bridgehead. It also cannot transfer a proton as does the immonium ion derived from enamines[3] since the β-carbon of the ketene immonium ion is fully substituted. It therefore undergoes an internal C-alkylation which leads to the 4-membered enamine of the type **255**, part of bicyclic (3-2-0) or (4-2-0) systems, with the more stable *cis*-fusion.

In presence of Lewis acid[91] ($MgBr_2$), in contrast, the ynamines react exclusively at the carbonyl to give conjugated diethylenic amides. The reaction of cyclohexenone with N,N-diethylaminopropyne **13**, For instance, gives the amide **261** in 80% yields in the presence of $MgBr_2$, whereas it leads to a 60% yield of bicyclo adduct **260** without this catalyst:[94]



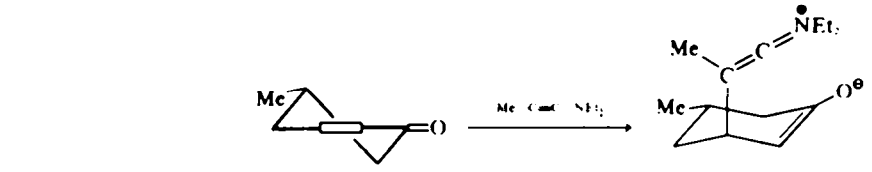
(3) *Stereoselectivity of the cycloaddition with cyclohexenones.* There are not many reactions, in cyclohexenic systems where the presence of an *equatorial* substituent is enough to determine the configuration of a new asymmetric center created 1-3 to the substituent.[94a] The cycloaddition of N,N-diethylaminopropyne with 5-methylcyclohexenone provides a clean example of such a control. The entry of this ynamine is, indeed, selectively *trans* to the Me group and leads to the cycloadduct **262** in which the two angular hydrogens are *cis* to the ring Me:[88c]

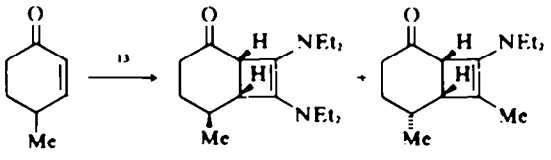




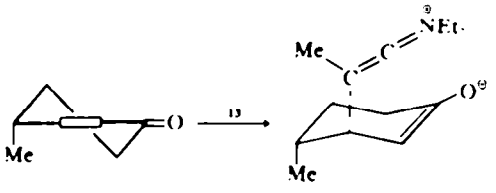
259 **255**

It is likely that this stereoselectivity comes from a better orbital overlap when the bond which is formed in the transition state is axially rather than equatorially oriented. This stereoelectronic control is such, that one does not observe the thermodynamically more stable isomer corresponding to the equatorial entry of the ynamine:

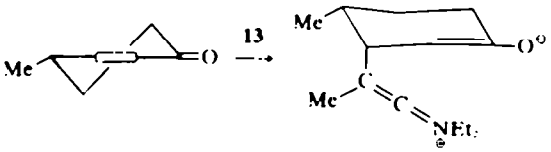




263 (80%) **264** (20%)



Major

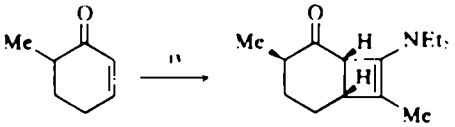


Minor

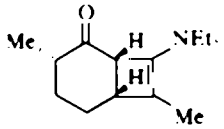
On the other hand, when the cycloaddition of ynamines creates a new asymmetric center 1–2 to the substituent, as the case of 4-methylcyclohexenone, the reaction is only stereoselective. A mixture of two isomers **263** and **264** is produced, in which the *trans* isomer is the major one.[99]

It is likely that in this case, the axial entry of ynamine occurs mainly on the conformer which bears an axial methyl.[99a]

The cycloaddition of ynamines with 6-methylcyclohexenone is also stereoselective, with predominant formation of the *trans* isomer.[88b]

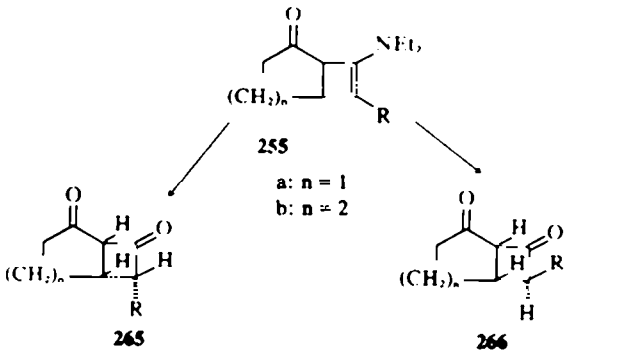


Major



Minor

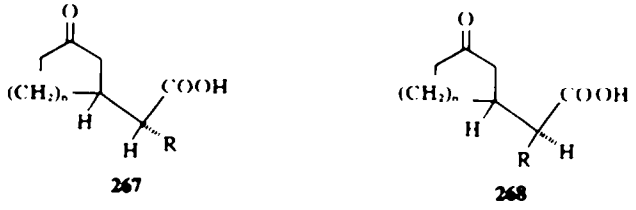
(4) *Stereoselective route to disastereoisomeric five and six membered* 1-5 *keto-acids*, via *controlled hydrolysis of ynamines bicyclic adducts*. The cycloadducts **255** are potential β-diketonic systems since the enamine function can be hydrolyzed into the corresponding four membered cyclobutanones **265** and **266**.



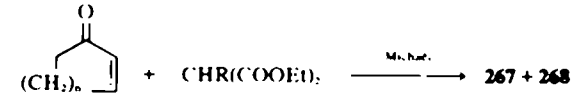
255

a: n = 1
b: n = 2

265 **266**



267 **268**



It would be expected that β-diketones **265a** and **266a** would cleave the more strained ring of the molecule to give the 1,5-keto acids **267** and **268**, which obviously could be obtained via a Michael reaction of alkyl malonates and the corresponding cyclenones.

The main point of the sequence starting from bicyclic enamines **255** is that, in contrast with the Michael reaction which leads necessarily to a mixture of diastereoisomers (**267** + **268**), one can obtain at will, either isomer **267** or **268**.

The ynamine method makes, therefore, possible the formation of a new C–C bond 1-3 to the carbonyl of cyclenones, while establishing, at the same time, the relative configuration of asymmetric centers which are not only part of a ring but also part of a flexible side-chain. We will now discuss the hydrolysis conditions of bicyclic enamines of type **255** which allow the highly stereoselective control of the stereochemical course of the reaction.

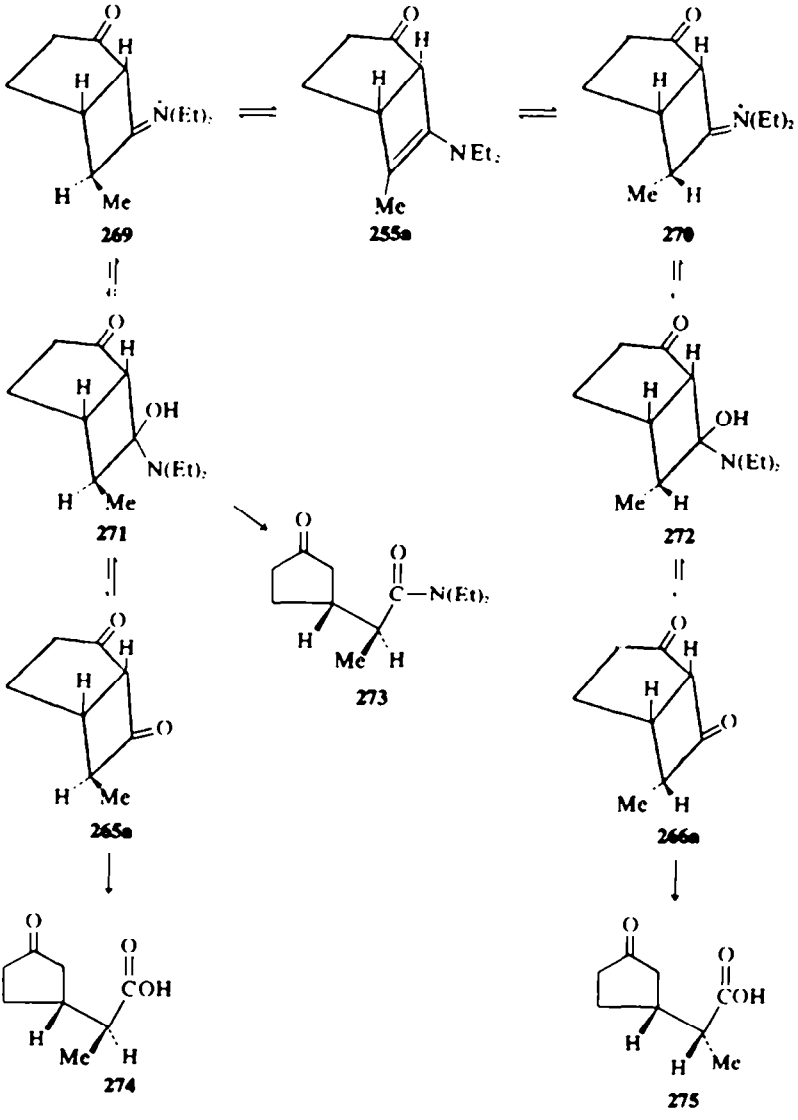
Hydrolysis of (3-2-0) *bicyclic enamines*

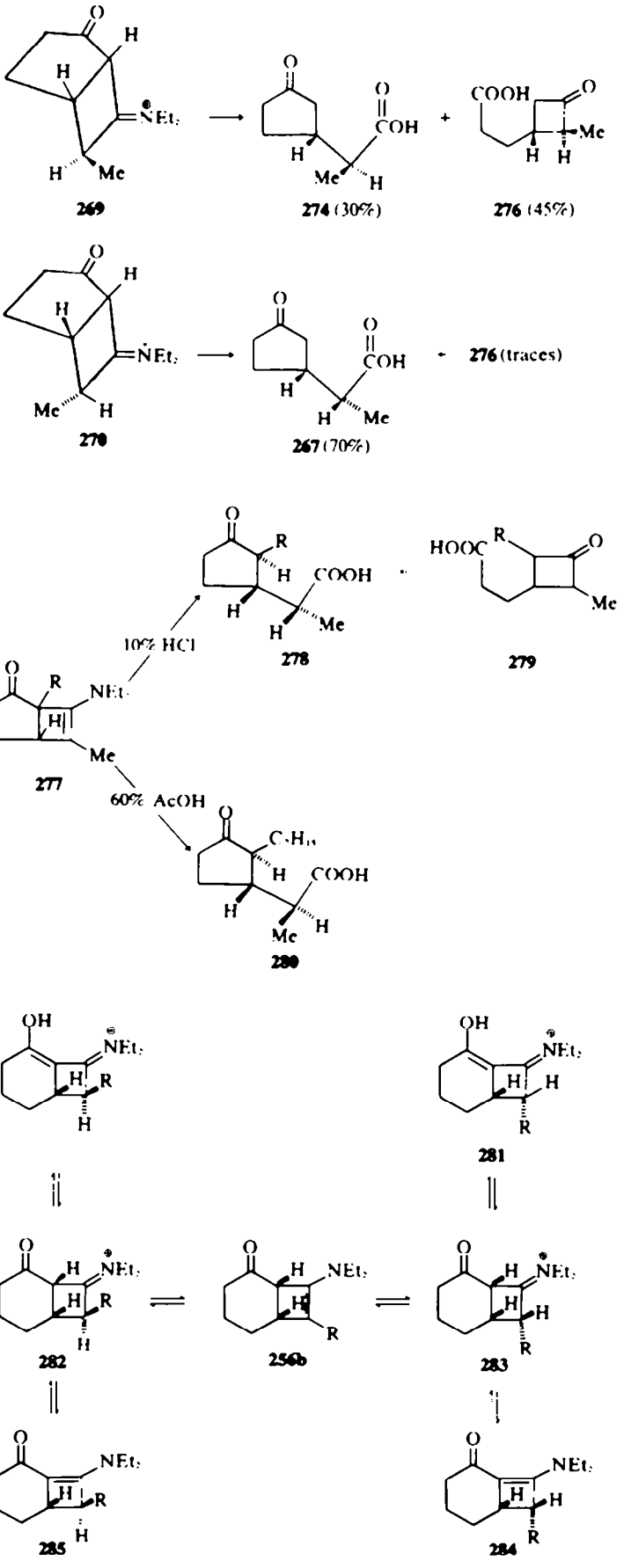
In acidic medium (10% hydrochlorid acid solution) the hydrolysis of **255a** gives the γ-keto acid **275** in 70% yield. In contrast, in neutral of fairly basic medium (catalytic amount of sodium hydroxide), this hydrolysis leads, in 70% yield, to γ-keto amide **273**, the structure of which is diastereoisomeric with **275**.[97,98]

This stereoselectivity can be rationalized by assuming that protonation of the enamine **255a** gives kinetically immonium ion **270** in which the proton is added on the less hindered side of the molecule rather than immonium ion **269**. The immonium ion **270** can be equilibrated to the thermodynamically more stable isomer **269**, via the enamine **255a**. In acidic medium (10% HCl), however, the steps **270** → **272** → **266** → **275** leading to the keto acid **275** are sufficiently faster than the reactions **270** → **255a** → **269** or **266a** → **265a**, that equilibration does not take place. The hypothesis that aqueous acid hydrolysis with HCl is kinetically controlled is supported by the fact that, if immonium ion **270** is allowed to equilibrate, i.e. if the adduct is first treated for 30 min with dry hydrogen chloride in ether, before addition of water or with AcOH[98] 60% (95°), the dione **265a** which can be isolated affords the keto acid **274** free of diastereoisomer **275** in quantitative yield.

Under basic conditions, equilibration of the Me group via **270** → **255a** → **269** or **266a** → **265a** takes place faster than the formation of the cleavage product and **273** is produced via **271**.

It is worth noting that under thermodynamic control in




269
274 (30%)
276 (45%)
270
267 (70%)
276 (traces)
278
279
277
10% HCl
60% AcOH
280
281
282
256b
283
285
284

acidic medium (dry HCl) the keto-acid **274** is produced together with a 45% yield of keto-acid **276** which comes from attack at the CO group of the cyclopentane ring. Under kinetic control (10% HCl solution) this acid **276** is only formed in trace amounts.

It is possible that steric hindrance of the cyclobutane center by the Me substituent on the *exo* side of **269** is responsible for directing the attack on the cyclopentane center. In agreement with this view one observes the same effect when the *exo*-side of the cycloadduct is hindered by an angular alkyl group as it is found in **277**. The angular substituted bicyclic enamine **277** is, indeed, hydrolized by a 10% HCl solution to give with 70% yields a mixture of the two keto acids **278** and **279** in a ratio which depends on the bulk of R. Carried out in presence of a 60% solution of acetic acid this hydrolysis can become highly regio and stereoselective: it leads to keto-acid **280**, if R is an heptyl group. The factors which govern such a control of the hydrolysis by acetic acid are under investigation.[36]

Hydrolysis of (4-2-0) *bicyclic enamines*

The cycloadducts **255b** are thermally stable, but can rearrange via polar processes to give the isomeric enaminoketones **284** and **285** in which the double bond is conjugated with the carbonyl.[35a] The bicyclic (4-2-0) system **255b**, in contrast to the bicyclic (3-2-0) system **255a**, readily allows a double bond to the ring junction.

The rearrangement of the enamine double bond produces asymmetry on the center bearing the R group, and the steric course of this rearrangement can be controlled by the reaction conditions. It is possible to obtain, at will either one or the other of the two stereoisomers which differ from one another by the configuration of the chiral carbon substituted by R.

Carried out in neutral medium, i.e. with water as proton donor, the rearrangement leads stereoselectively to enamino ketones **284** in which the proton is added on the *exo*-side of the initial enamines: (R group, *trans* to the angular hydrogen).

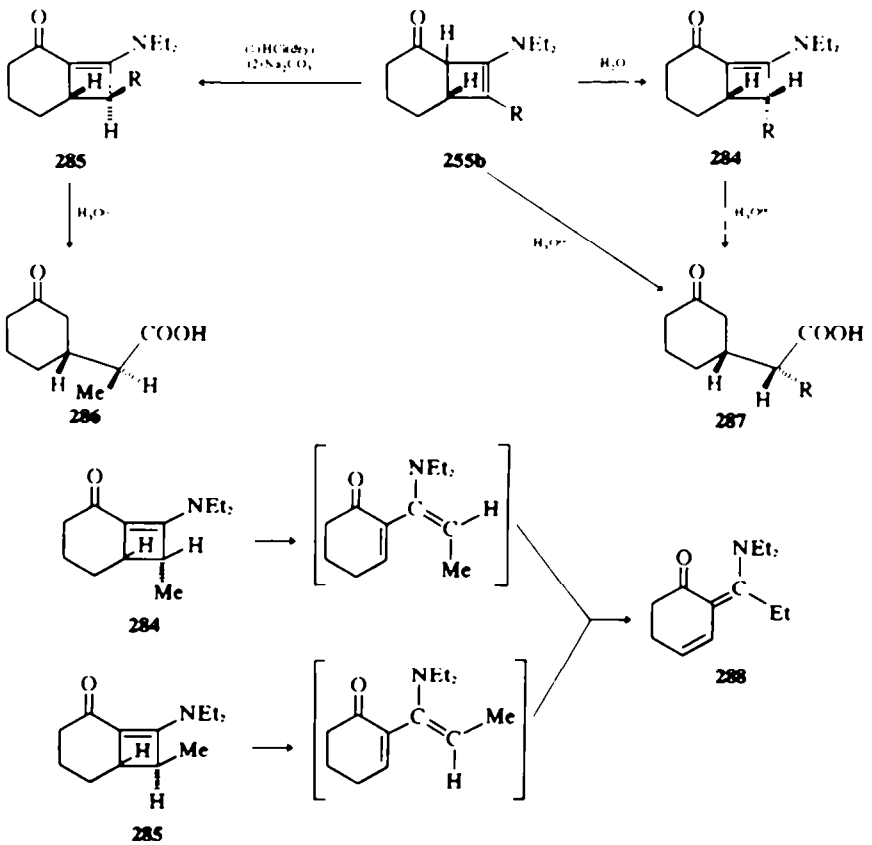
If, in contrast, this rearrangement is carried out in two steps, i.e. by using first dry hydrochloric acid then, sodium bicarbonate, the more stable enamino ketones **285** are produced in which the proton is now bound on the *endo* side (R group *cis* to the angular hydrogen).

The high stereoselectivity of the rearrangement can be rationalized as in the case of (3-2-0) bicyclic enamines, in terms of kinetic vs thermodynamic control.

The kinetically obtained immonium ion **283** can be in equilibrium with **281** or with its thermodynamically more stable isomer **282**, but the equilibrium **283**⇌**282** is not established in presence of water. In aqueous medium, the kinetic immonium ion **283** is indeed neutralized faster than it is equilibrated, to give enamino ketone **284** in which the configuration of the asymmetric center remains unchanged. This enamino ketone can be isolated in this case, for its basicity weaker than the basicity of the initial enamine **255b**, shifts the equilibrium essentially towards **284** which is not hydrolysed in the neutral aqueous medium. In non aqueous medium (dry HCl in ether) the equilibrium **283**⇌**282** is taking place and enamino ketone **285** is produced by neutralization with sodium bicarbonate.

The enamino ketones **284** and **285** can be handled easily but, in contrast with their isomers **255b** they are not, as expected,[24] thermally stable. They rearrange around 110° to give the dienes **288**.[35a]

Upon hydrolysis in *acidic* medium the enamine function of the cycloadducts **255b** or **284** leads to the corres-



ponding diketones which are cleaved, *in situ*, and give rise to γ-keto acids **287** whereas the cycloadducts **285** lead via the same process to diastereoisomeric keto-acids **286**, in 70–80% yield.[99]

The steric course of the hydrolysis of bicyclic (4-2-0) enamines is also selectively controlled when the cyclohexane ring is substituted. For instance, the three asymmetric centers of keto-acids **290** and **289** have been stereoselectively created.[88c] The *cis*-relationship between the Me part of the cyclohexane ring and the hydrogens is established by the cycloaddition of the ynamine, which occurs *trans* to the Me. The relationship between the hydrogen of the cyclohexane ring and the chiral center of the side chain is established by the hydrolysis of the bicyclic enamine **262**.

The stereochemical control of the steric course of the hydrolysis of bicyclic (4-2-0) enamines is fairly general for it occurs not only with cyclohexenone itself and 5-methylcyclohexenone but also with methylcyclohexenones substituted at position 4[96] or 6.[99]

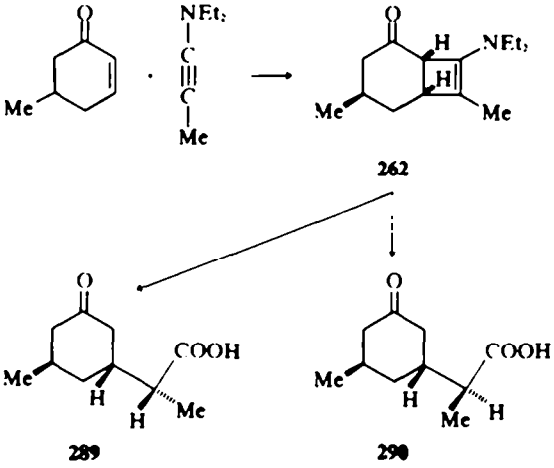
The method of controlling the chiral center of a side chain via the hydrolysis of bicyclic (4-2-0) enamines has been used recently to perform the first stereospecific synthesis of (±) Juvabione **291**.[100] The difficulty of the synthesis of Juvabione comes from the fact that one of the two asymmetric centers is in a free rotating side chain. The application of the ynamine method is especially attractive in this case as it resolves the problem of stereospecific construction of (±) Juvabione from keto-acid **287**, at the very beginning of the synthesis.

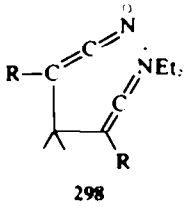
(c) *Cycloaddition with α,β-ethylenic nitriles.* The cycloaddition of ynamines with α,β-ethylenic nitriles **292** and **295** leads to cyclobutene enamines **293** and **297** in 40–80% yields.

The cycloaddition is slower with nitriles **292**[101] than with enones or α,β-ethylenic esters and needs a stoechiometric amount of Lewis acid ($MgBr_2$), except with acrylonitrile itself and with the more electrophilic α-halo α,β-ethylenic nitriles **295**.[102,103]

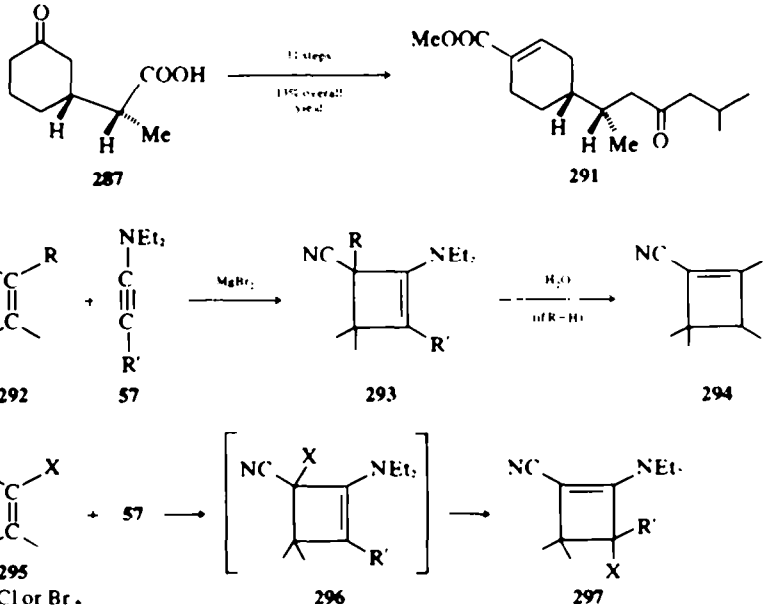
The initial adducts **296** obtained from halonitriles are not isolated: they undergo *in situ*, a 1,3-migration of a halogen which gives the enamino-nitrile **297** in which the enamine double bond is conjugated with the cyano group. In contrast, this rearrangement occurs only in presence of a proton donor **293** → **294** (water, for instance) with the adducts **293**, if R is an H atom.

The cycloaddition is, as expected, of (2 + 2)-type. A cycloaddition of (2 + 4)-type, involving a heterocyclization of the dipolar ion **298**, is energetically unfavorable for it would lead to a ketene-imine function as part of a 6-membered ring.

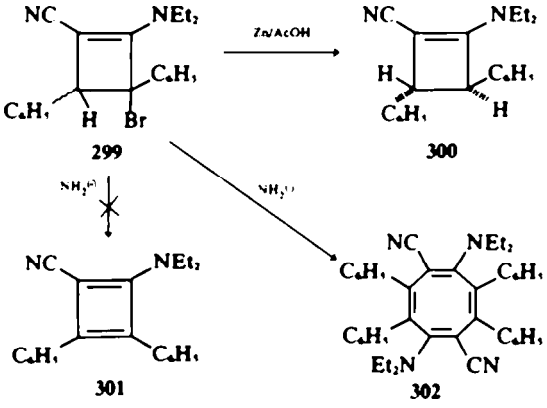




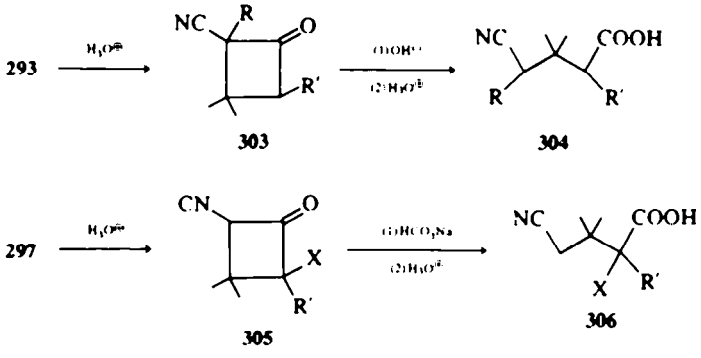
The enamino nitriles of the type **297**, the halogens of which can be smoothly reduced (for instance **299** → **300**) are dehydrohalogenated with difficulty. This process does not lead to cyclobutadienes of the type **301** which were



expected to be stabilized by the push–pull effect of the theoretically favourable amino and cyano groups.[104] The dehydrohalogenation gives instead the cyclooctatetraene **302** in very poor yield.[102]

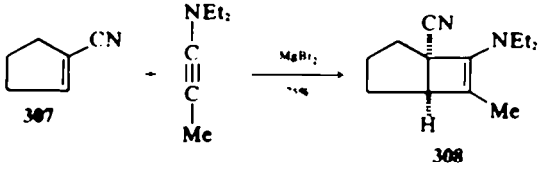


The 4-membered enamines **293** or **297** are hydrolysed in acidic medium in excellent yield (70–90%), and this reaction is a good route to α-cyanocyclobutanones **303** or **305**.

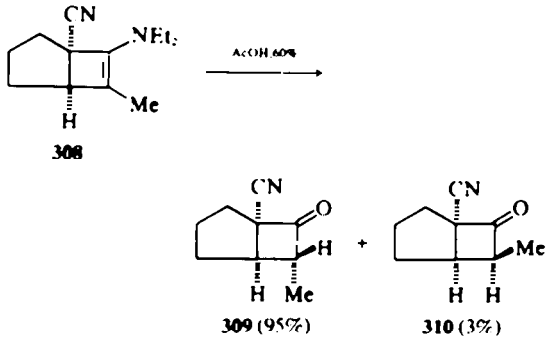


The 4-membered β-ketonitriles systems **303** and **305** behave classically in presence of basic reagents:[101,102] they are cleaved to give the corresponding mono nitrile of glutaric acid **304** and **306** without fragmentation[105] or contraction of the 4-membered ring, whereas this latter process is partially observed with α chlorocyclobutanone.[106]

The use of cycloaddition of ynamines with unsaturated nitriles is particularly attractive when the electrophilic double bond is part of a ring as is the case, for instance, with cyanocyclopentene **307**. The cycloaddition of ynamines with such systems leads, indeed, to bicyclic (3-2-0) cyano-enamines **308** the hydrolysis of which can be highly stereoselective.[96a,107]



For instance, the bicyclic enamine **308** obtained in 75% yield from N,N-diethylaminopropyne and cyanocyclopentene **307**, is hydrolysed by a 60% aqueous acetic acid solution, in 95% yield. This hydrolysis leads to the β-ketonitrile **309** bearing an *exo* Me group, with less than 5% of its isomer **310** bearing an *endo* Me group. The β-ketonitrile **309** is not cleaved upon hydrolysis in acetic acid, in contrast, with the β-diketones derived from hydrolysis of cyclopentenone-ynamine adducts such as **265a** (Section 3E4) but the stereoselectivity of the reaction is similar.

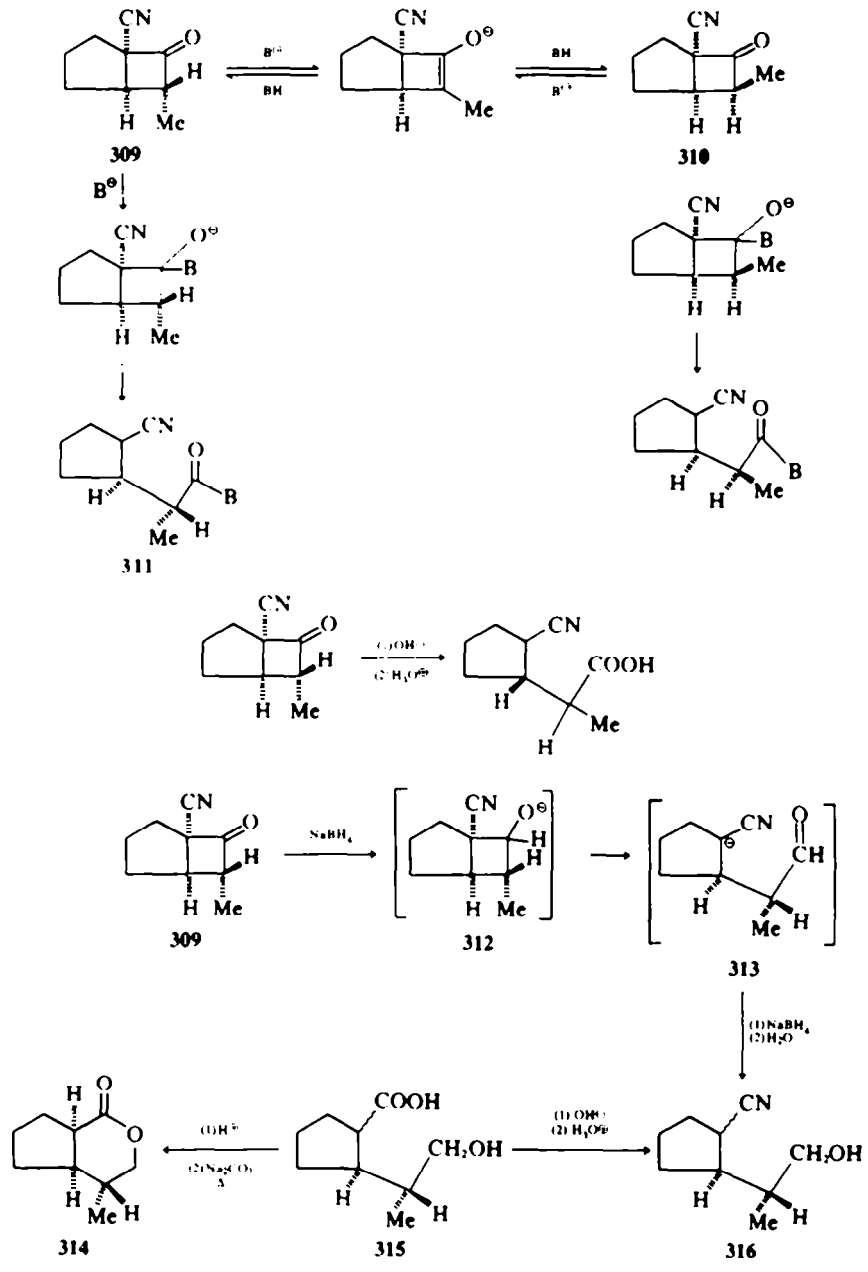


The hydrolysis of bicyclic adduct of the type **308** is therefore a good route, for the stereoselective synthesis of (3-2-0) β-ketonitriles of the type **309**. Moreover, it was shown[107] that the cyclobutane ring, which is part of bicyclic β-ketonitrile of the type **309** can be cleaved stereoselectively. The cleavage of the cyclobutane ring occurs indeed after any nucleophilic attack ($B^{\ominus}$) at the carbonyl center, and can be an efficient route to system such as **311**, in which the asymmetric center part of the flexible side chain has been stereoselectively controlled. The ring cleavage of **309** is a specially favourable process for it releases the strain of the (3-2-0) bicyclic system. However, the carbonyl center is rather hindered and in order to achieve the stereoselective ring opening the attack at the carbonyl has to occur without completing enolization which would epimerize the crucial center (**309**⇌**310**).

These requirements are not fullfilled by strong bases such as sodium hydroxide which gave a mixture of the corresponding cyano-acids.

The solution to the problem is given by the use of non enolizing reagents, such as metallic hydrides. The alkoxide **312** obtained by reaction of sodium borohydride with the ketonitrile **309**, undergoes a fragmentation which releases the strain of the ring, thus leading to the aldehyde **313**, which is immediately reduced to the corresponding primary alcohol **316**. These steps occur without epimerization of the crucial asymmetric center α to the carbonyle, for the lactone **314** of the hydroxy-acid **315** prepared from hydroxy-nitriles **316** is obtained as a single isomer.

The ynamine method thus makes possible the synthesis in a 70% overall yield of the bicyclic lactone **314** in which



the three asymmetric centers are controlled. (The *cis*-junction of **314**, more stable than the *trans*, is achieved during the lactonization and the treatment by K_2CO_3).

The method was used to perform the synthesis of (±) isodihydronepetalactone **319**,[108] a cyclopentanoïd terpene, which occurs in nature as the dextrorotary enantiomer.

The synthesis of Isodihydronepetalactone **319** starts from N,N-diethylamino propyne and 5-methyl-1-cyanocyclopentene **317**. This synthesis clears up two points related to the effect of the additional Me group, on the cyclopentane ring: first, with regard to the control of the stereochemical course in the sequence just described in comparison with cyanocyclo pentene itself, and second, with regard to the stereochemical course of the cycloaddition of the ynamine.

First, it is found that the presence of the Me group on the cyclopentane ring does not affect the control of the steric course either of the hydrolysis of enamine **318** or of the reductive cleavage of the ring. The *cis*-relationship between the two angular hydrogens and the Me part of the lactone ring is indeed clearly established via the sequence: **318** → **320** → **319**.

Second, it is shown that the presence of the Me group on the cyclopentene ring also has no effect on the steric course of the ynamine cycloaddition. The entry of ynamine is not, in fact, stereoselectively *trans* to this Me, for cycloadduct **318** is obtained in 95% yield, as a mixture of the two methyl epimers in a ratio of about one to one.

This result supports the hypothesis of a two step process involving a dipolar intermediate of type **298**, for one would expect that a concerted 4-center addition of ynamines to ethylenic nitriles, would have led in the case of **317**, to some stereoselectivity.

The (±)-isodihydronepetalactone **319** is easily separated from the mixture of isomeric hydroxy-acids by fractional lactonization. The unnatural *cis*-isomer **321** is also obtained pure by fractional lactonization of the corresponding hydroxy-acid. An interesting point is that the un-

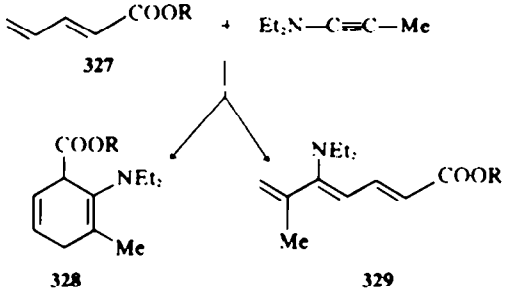
natural *trans*-lactone **323**, which is more difficult to obtain from the corresponding hydroxy-acid **322** is formed together with its *cis*-isomer **321**. These two isomers which were not known previously can be equilibrated to give a 4 to 1 mixture in favor of the *cis*-isomer **321**.

The control of the steric course of the hydrolysis of annulated 4-membered enamines derived from cycloaddition of ynamines with cyclenones and nitriles opens a new route in stereoselective synthesis. It has recently been shown for instance, that this control occurs also with the cycloadduct **325** obtained from cycloaddition of N,N-diethylamino propyne with maleimides **324**. The hydrolysis of this cycloadduct by a 10% aqueous solution of hydrochloric acid leads to the acid **326** as a single isomer.[109]

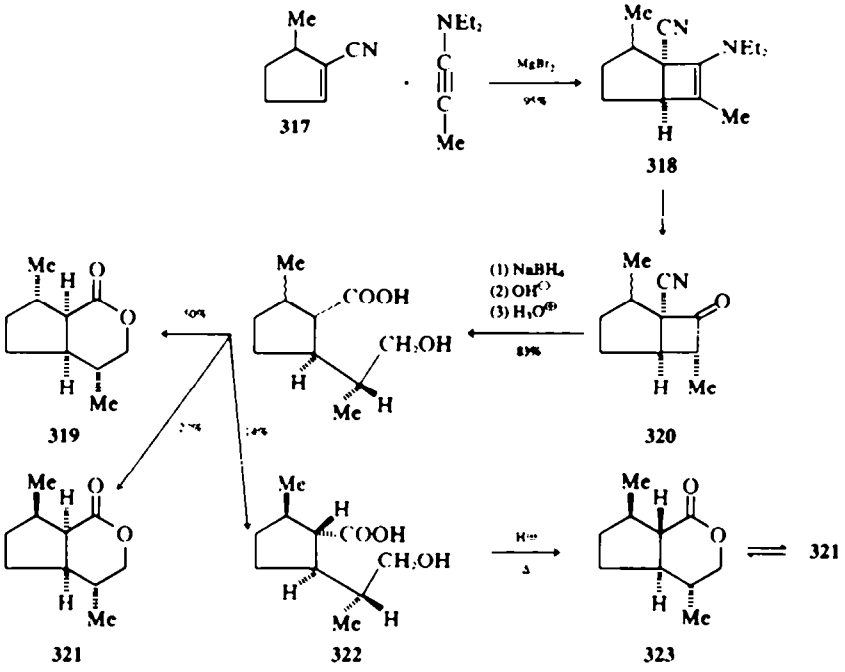
F. *Cycloaddition with electrophilic dienes*

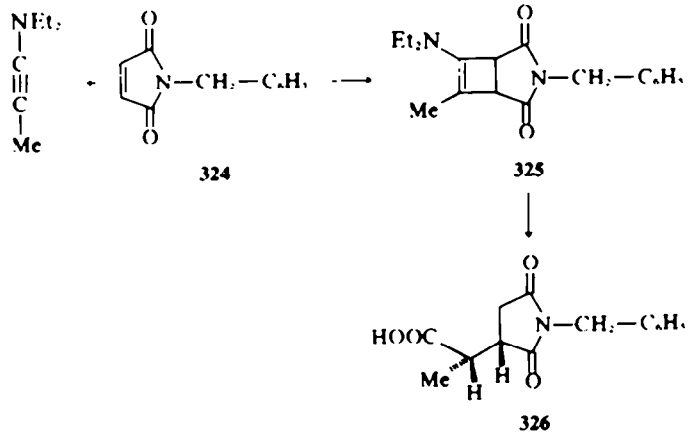
The mode of cycloaddition of ynamines with electrophilic dienes is strongly dependent on the conformation of the diene. A cisoïd conformation would be expected to favour a (2 + 4)-process over a (2 + 2)-process.[25,110]

The cycloaddition of ynamines with flexible dienic carboxylic esters of type **327** leads to cycloadducts **328** and amino-trienic esters **329** in very good yields:[43a,111]

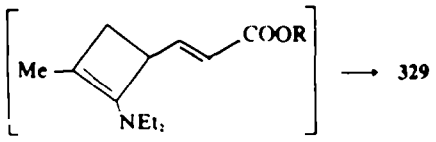


The cyclohexadienic esters **328** come obviously from a cycloaddition of the (2 + 4)-type on the cisoïd conformation of **327** whereas the amino-trienic esters **329** are formed by rearrangement of an intermediary cyclobutene of type **330**, obtained by cycloaddition of the (2 + 2)-type on the



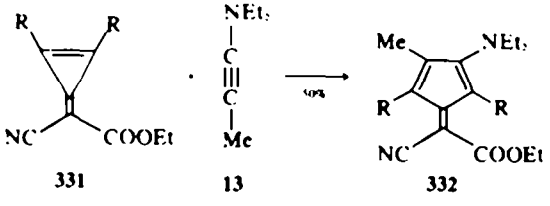


terminal double bond:

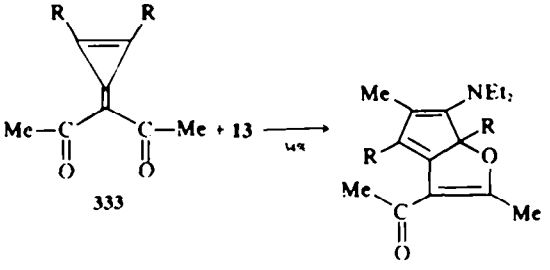


330

When the terminal double bond is part of a cyclopropene ring such as **331** or **333**, the intermediate (2-1-0) bicyclic adduct obtained by (2 + 2)-cycloaddition rearranges to give fulvene derivatives of type **332** which cyclize further in the case of **333** (**333** → **334**):[112]



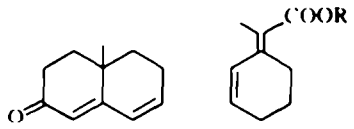
331 13 332



333 334

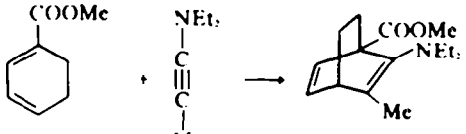
Cycloaddition of the (2 + 2)-type is, in general, the major process with acyclic dienic esters like **327** and ynamines.[43a] It is favoured with respect to the (2 + 4)-process by the presence of a substituent α to the carboxylic ester which probably hinders the cisoïd conformation as is shown in the following examples. These examples show also that there is a greater acceleration of the (2 + 2)-process, the polar character of which is more pronounced than the (2 + 4)-process, when the polarity of the solvent increases:

On the other hand, cycloaddition of ynamines does not occur at all with the fixed transoïd electrophilic dienes **335**[43a,111] and **336**[111]



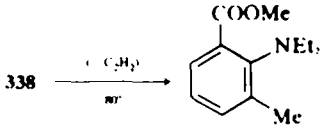
335 336

In contrast, the cyclohexadienic ester **337** which is held in a cisoïd conformation undergoes, as expected, a cycloaddition of the (2 + 4)-type and gives rise to the bicyclic enamine **338** in 50% yield:[43a,111]

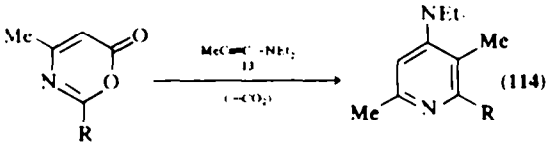


337 13 338

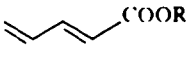
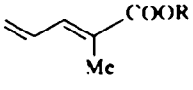
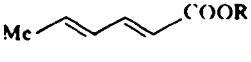
The bicyclic enamine **338**, undergoes an Alder–Rickert reaction with loss of ethylene around 80°, but is stable below this temperature:

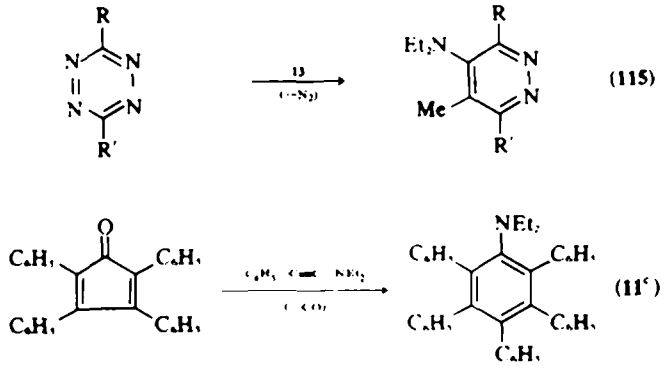


It is worth noting at this point, that some other cycloadditions of the Diels–Alder type, are known in the chemistry of ynamines. In the examples listed below, the initial cycloadduct of the (2 + 4)-type is not isolated as it undergoes *in situ* a retro Diels–Alder reaction:



(114)

	328	329
	20%	80%
	0%	100%
	THF 50% MeCN 20%	50% 80%

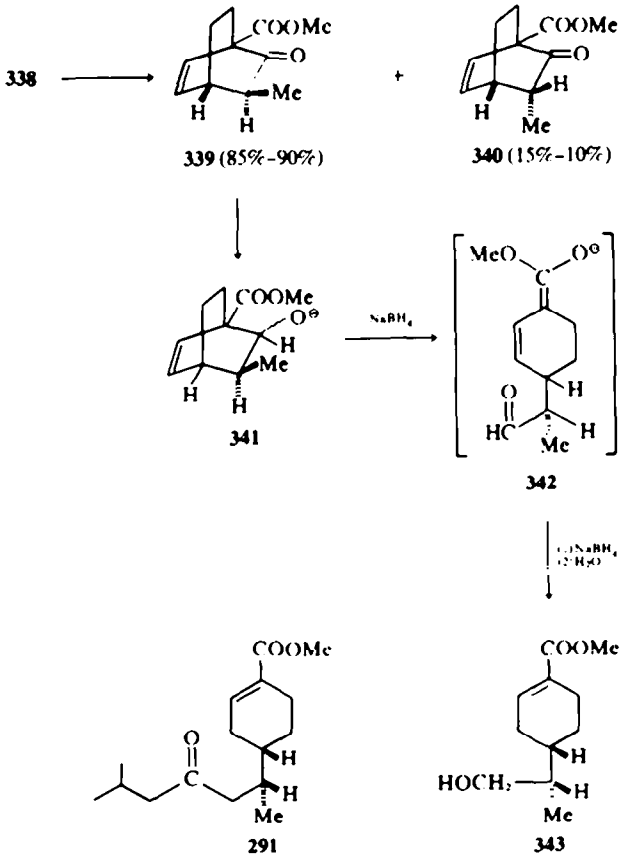


The bicyclic (2-2-2) enamine **338** which is easy to handle below 80°, in contrast to the above examples, is hydrolysed in acidic medium at room temperature to the corresponding bicyclic keto-esters **339** and **340**.

The control of the steric course of the hydrolysis of this bicyclic (2-2-2) enamine **338** is not, as one can expect, as efficient as that of the more regiodifferentiated bicyclo (3-2-0) and (4-2-0) enamines derved from cycloaddition of ynamines with cyclenones and cyanocyclopentene. Nevertheless the selectivity is rather high under kinetic control for the keto-esters **339** and **340**, are obtained in a quantitative yield, in a ratio of about 6/1. This is rather surprising as the only difference between the two directions of approach is hindrance by an athano vs an etheno bridge in the otherwise symmetrical system of **338**.

The method used for cleaving the ring of 4-membered β-ketonitriles **309** or **320** can be applied to the mixture of the 6-membered β-keto-ester **339** (85–90%) and **340** (15–10%). The alkoxides **341** obtained by reaction with sodium borohydride, are cleaved to give the corresponding aldehydes **342** which are reduced, *in situ*, to the primary alcohols **343**. The driving force for the ring opening (**341** → **342**) is in this case, the formation of the stablized conjugated enolate shown in **342**, in addition to strain relief.

The interest of this sequence is that it makes possible the stereoselective synthesis of hydroxy-ester **343**, in three steps and a 45% overall yield starting from the ynamine **13** and cyclohexadienic ester **337**:



This sequence can be used, for instance, in a very rapid and attractive stereoselective synthesis of (±)-Juvabione **291**.[116]

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