Tetrahedron Vol 40, No. 16, pp 2989 to 3051, 1984
Printed in the U.S.A.

0040-4020/84 $5.00 + .00

TETRAHEDRON REPORT NUMBER 169

RECENT ADVANCES IN THE CHEMISTRY OF CONJUGATED ENAMINES

PETER W. HICKMOTT
Department of Pure and Applied Chemistry, University of Natal, King George V Avenue, Durban, Natal, Republic of South Africa

(*Received* 29 *September* 1983)

CONTENTS

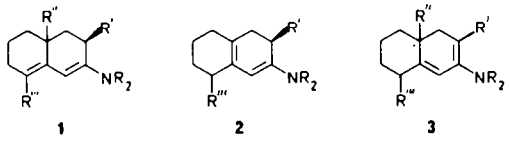
1. INTRODUCTION

In two recent reviews[1,2] we have surveyed the developments in the chemistry of simple enamines which have occurred during the period 1969–80. The purpose of this review is to survey the chemistry of enamine systems which have been further conjugated with additional C=C double bonds (*viz.* dienamines, trienamines, etc.), or with additional electron-donor substituents carrying a lone pair of electrons (*viz.*. enediamines, enetriamines, enetetra-amines, dienediamines, halogeno-enamines, keten aminals, etc.). We have also included brief surveys of metallated tertiary enamines and azadienamines. Enamine systems further conjugated with electron acceptor groups have not been included in this survey since recent reviews have appeared on enaminones,[3] enaminonitriles,[4] enamides,[5] and nitroenamines.[6] The review covers the period 1969–82 but earlier publications have been included where necessary to place the more recent developments in their proper perspective or, as in the case of dienamines, when this earlier work has not been adequately reviewed. As in previous reviews[1,2] we are specifically excluding heterocyclic enamines in which both the nitrogen and C=C bond(s) are in the same ring, such as dihydropyridines, pyrroles, indoles etc., and *exo*-enamine tautomers of oxazolines and imidazolines.

2. CONJUGATION WITH ADDITIONAL CARBON–CARBON DOUBLE BONDS

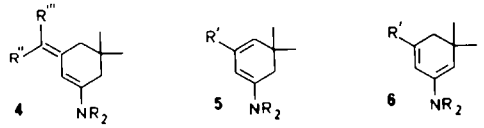
(a) *Dienamines*

(i) *Structure and reactivity*. Dienamines derived from $\delta^{1,8a}$-2-octalones exist as mixtures of mainly the linear exocyclic diene **1** (60–100%; R′ = H; R″,R‴ = H, Me) together with the linear endocyclic diene **2** (15–40%). The presence of a substituent (R′) at C-3 causes the *endo*-isomer 2 to be slightly favoured (53–55%; R′ = Me; R″ = R‴ = H) presumably due to removal of a pseudo 1,3-diaxial Me–H interaction.[7] None of the cross-conjugated isomer **3** was found to be present in any of the



Scheme 1.

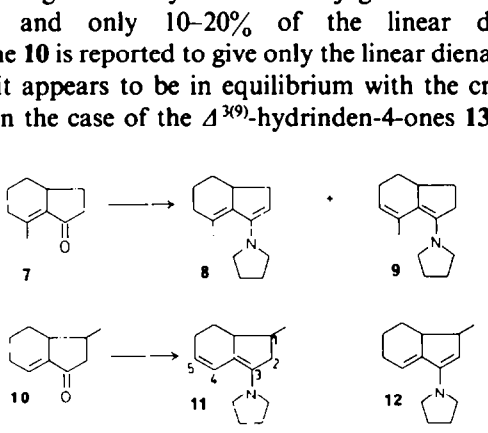
isomers studied, contrary to previous reports.[8,9] Similarly the pyrrolidine dienamine of isophorone exists mainly as the linear *exo*-isomer **4** (65%; R″ = R‴ = H) together with the linear *endo*-isomer



Scheme 2.

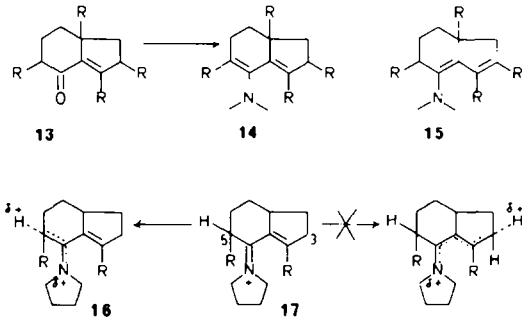
5 (35%; R′ = Me).[7] When R′ = Et, i-Pr, $PhCH_2$, only the linear *exo*-isomer **4** was formed, and when R′ = t-Bu only the linear *endo*-isomer **5** was obtained.[10] For the morpholine and piperidine dienamines the main constituent of the mixtures was the linear *endo*-isomer **5** (R′ = Me), although the amount of *exo*-isomer **4** gradually increased on prolonged standing and in some cases eventually exceeded that of the *endo*-isomer **5**.[11] Only small amounts of the cross-conjugated isomer **6** (4-15%) were produced,[7,11] again contrary to previous reports.[12] Similar results were obtained with the N-methyl and N-phenyl piperazine dienamines of isophorone,[12,13] whereas the corresponding dienamines derived from 3-methylcyclopent-2-enone existed primarily as the linear *exo*-isomer (90%) as would be expected in view of the greater stability of a double bond *exo* to a 5-membered ring.[13] Piperitone (3-methyl-6-isopropylcyclohex-2-enone) has also been shown to give only a mixture of linear *endo* and *exo* pyrrolidine dienamines, no cross-conjugated isomers being observed.[14]

The preference for formation of linear dienamines no longer necessarily appertains when the $\alpha\beta$-unsaturated ketone is fixed in a cisoid arrangement of the double bonds. Thus $\Delta^{4(9)}$-4-methylhydrinden-3-one **7** gives mainly the cross-conjugated dienamine **8** (80–90% depending upon the reaction time) and only 10–20% of the linear dienamine **9**.[15] Although $\Delta^{4(9)}$-1-methylhydrinden-3-one **10** is reported to give only the linear dienamine **11**,[15] presumably due to thermodynamic control, it appears to be in equilibrium with the cross-conjugated isomer **12**. However there is no doubt in the case of the $\Delta^{3(9)}$-hydrinden-4-ones **13** (R = H or Me). Only the



Scheme 3.

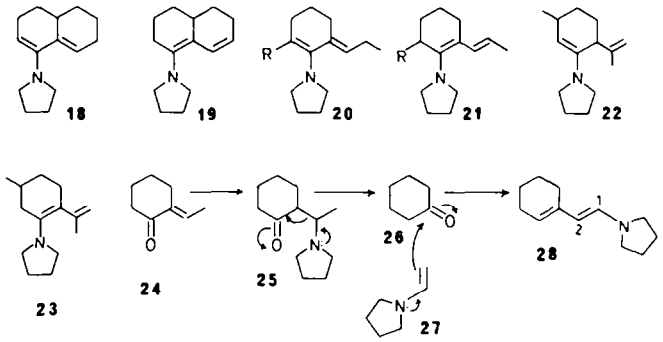
cross-conjugated dienamines **14** were observed; none of the linear dienamines **15** were formed even as transient intermediates.[16]



Scheme 4.

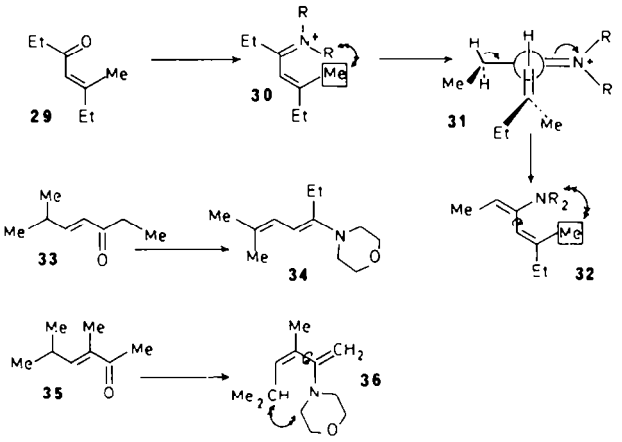
The explanation offered for this change in regioselectivity was that the double bond system in the intermediate iminium ion **17** was non-planar, thus resulting in more effective transmission of the positive charge to C-5, rather than C-3, leading to preferential formation of the cross-conjugated isomer via transition state 16, under presumably kinetically controlled conditions.[16]

Comparable quantities of cross-conjugated and linear dienamines are formed from cisoid $\alpha\beta$-unsaturated ketones in which the steric constraints in the intermediate iminium salts are less demanding, as for example with $\Delta^{8,8a}$-1-octalones and 2-alkylidenecyclohexanones. The former gives **18** and **19** (53% and 47% respectively) and the latter gives **20** and **21** (60% and 40% respectively; R = H or Me).[17] Interestingly pulegone (2-isopropylidene-5-methylcyclohexanone) gives mainly the non-conjugated dienamine **22** (65%) presumably derived from the linear dienamine **23** by a protonation–deprotonation sequence. 2-Ethylidenecyclohexanone also gives the rearranged linear dienamine **28**, presumably via initial conjugate addition of pyrrolidine and subsequent fragmentation (24→25→26 + 27→28).[17]



Scheme 5.

The course of the reaction between acyclic $\alpha\beta$-unsaturated ketones and secondary amines is dependent on the steric interactions present in the intermediate iminium salt (kinetic control) and the resulting dienamine product (thermodynamic control). Thus for example reaction of ketone **29** gives an eniminium salt **30** in which the severe steric interactions shown result in uncoupling of the double bond system to give the non-planar conformation **31** and hence the cross-conjugated dienamine **32** as the main product.[18] Conversely ketone **33** gives a planar eniminium salt, since the boxed Me group (shown in **30** and **32**) has been replaced by H, and leads to the planar linear dienamine **34** as the only product, whereas ketone **35** gives a non-planar enimium salt and non-planar cross-conjugated dienamine **36** as the only product.[18] It appears that planar linear dienamines are more stable than the corresponding isomeric cross-conjugated dienamine, due to increased $p\pi$-interaction,[1] whereas non-planar cross-conjugated dienamines are thermodynamically more stable than the corresponding non-planar linear isomer. However, as with cyclic

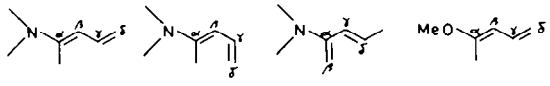


Scheme 6.

dienamines,[11] the equilibrium between the two forms is established much more slowly[18] than the corresponding acid-catalysed equilibration of simple enamines, which occurs in a few minutes at room temperature.[1]

Dienamines differ from simple enamines in that there are three nucleophilic centres in the former (*viz.* the N-atom and the β- and δ-C atoms) compared to two in the latter. However Huckel Molecular Orbital calculations[19] have revealed a distinctly higher electron density at the β-position compared to the δ-position of the dienamine system (Fig. 1). It is not surprising therefore that, although N-alkylation, acylation and protonation undoubtedly occurs, the majority of electrophilic reagents (*viz.* diketene,[20] methyl iodide,[21] *p*-methoxybenzyl bromide,[22] acrylic ester,[23] acryloyl chloride,[24] 1,3-dichlorobut-2-ene,[25] methyl vinyl sulphone[26] and iodoacetic ester[27]) cause substitution at the β-position. The higher electron density favours reaction at this position under conditions of kinetic control. However where initial reaction at the N and the β-C is reversible, or when the transition state is product-like in character, the operation of thermodynamic control results in preferential or complete reaction at the δ-position. For example electrophilic reagents with a formal positive charge such as the Vielsmeier reagent[28] [$HC(Cl)=\dot{N}Me_2$], a proton,[29] arenediazonium salts[19] or, in certain circumstances,[30] electrophilic olefins, give products derived from δ-substitution (*vide infra*). Quite often the regioselectivity is solvent dependent, the same reagent giving different substitution products under different conditions.[19,30,31]

Further consideration of Fig. 1 also reveals that the electron density at C-β of the cross-conjugated form (**C**) (-0.128) is significantly greater than that at the β-position of the linear dienamines **A** and **B** (-0.109 and -0.112 respectively). This is as one would expect since the increased electron density, resulting from nitrogen lone pair interaction with the double bond, is localised at the β-position of **C** but can be transmitted further down the chain in **A** and **B**. However this implies that the cross-conjugated form **C** should be more reactive than the linear isomer **A** and **B**. Support for this contention has been obtained experimentally (*vide infra*). Despite the fact that the cross-conjugated isomer may be the minor component of a dienamine mixture, in some cases

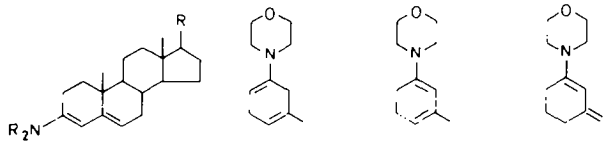


	A	B	C	D
N	+0.105	+0.105	+0.082	—
α	+0.052	+0.054	+0.030	—
β	−0.109	−0.112	−0.128	−0.071
γ	+0.007	+0.045	−0.043	—
δ	−0.055	−0.093	+0.060	−0.053

Fig. 1.

the major product may be that derived from reaction of the cross-conjugated isomer. The calculations also indicate that the reactivity of the C-δ position of the linear s-*cis* dienamine B should be greater than that of the linear s-*trans* dienamine A. However in practice there is often a greater deviation from coplanarity of the double bond system in s-*cis* dienes, compared to s-*trans* dienes, which would tend to nullify these differences (see Section (ii)).

(ii) *Spectroscopic data.* Dienamines give two double bond stretching absorptions in the infrared at *ca.* 1573–1630 and 1613–1675 cm^{-1} [linear exocyclic dienamines: **1**[32] 1594–1610 and 1625–1648 cm^{-1}; **4**[10] 1580–1600 and 1630–1648 cm^{-1}; **11**[15] 1585 and 1625 cm^{-1}; **37**[29] 1602–1613 and 1630–1648 cm^{-1}; **40**[33] 1579 and 1620 cm^{-1}; linear endocyclic dienamines: **5**[10] (R′ = t-Bu) 1573 and

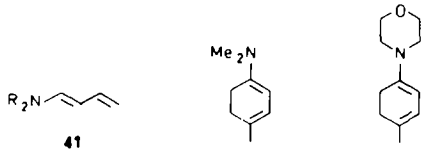


37 38 39 40

Scheme 7.

1635 cm^{-1}; **39**[33] 1585 and 1650 cm^{-1}; linear acyclic dienamines **41**[34] 1601–1625 and 1630–1652 cm^{-1}; **34**[18] 1630 and 1675 cm^{-1}; cross-conjugated dienamines: **8**[15] 1592 and 1645 cm^{-1}; **14**[16] 1598–1608 cm^{-1}; **36**[18] 1630 and 1675 cm^{-1}; non-conjugated dienamines: **38**[33] 1650 and 1698 cm^{-1}].

The increased orbital interaction by the nitrogen lone pair in enamines derived from pyrrolidine, as compared to enamines from other secondary amines,[1] is also reflected in the UV spectra of dienamines. Pyrrolidine dienamines absorb at longer wavelengths, in the range 276–296 nm, whereas morpholine dienamines give absorptions in the range 263–272 nm and piperidine dienamines give intermediate values (268–280 nm). The λ_{max} values also depend on the substitution pattern, the solvent used, and whether the double bond system is acyclic or exocyclic (as in the cases quoted above) or endocyclic (i.e. contained in the same ring). In the latter case absorption occurs at longer wavelength (287–300 nm) as would be expected since *cis*-dienes are known to have lower energy transitions than *trans*-dienes.[35] δ-Protonation to give the conjugate eniminium salt causes a bathochromic shift in the λ_{max} value of morpholine and piperidine dienamines, but has little effect on that of pyrrolidine dienamines. N-Protonation causes marked hypsochromic shifts to *ca.* 239 nm, as would be expected.[29] Some specific examples are as follows: **1**[34] (R_2N = morpholino) 266 nm (ϵ 18000), (R_2N = pyrrolidinyl) 279–283 nm (ϵ 19000–22000); **4**[34]



41 42 43

Scheme 8.

(R_2N = morpholino) 268–271 nm (ϵ 18,000–22,000), (R_2N = pyrrolidinyl) 282–283 nm (ϵ 20,000); **37**[29] (R_2N = morpholino) 263–269 (ϵ 19,600–21,300), (R_2N = piperidino) 264–271 nm (ϵ 20,000–22,000); (R_2N = pyrrolidinyl) 276–284 nm (ϵ 19,000–26,000); **11**[15] 296 nm (ϵ 18,300); **34**[18] 267.5 nm (ϵ 14,500); **41**[34] (R_2N = morpholino) 267–272 nm (ϵ 14,500–22,600), (R_2N = Et_2N) 280 nm (ϵ 23,500), (R_2N = pyrrolidinyl) 280–289 nm (ϵ 14,500–25,000); **42**[33] 300 nm (7500); **43**[33] 294 nm (ϵ 7800). An attempt has been made to extend the use of Woodward's rules, for predicting the λ_{max} value of polyenes, to dienamines. The morpholine and pyrrolidine groups, in conjugation with a diene system, were shown to exert an auxochromic shift on the λ_{max} value of the parent diene of +50 and +63 nm, respectively, whereas the effect of alkyl substituents was found to depend on their position in the carbon chain, varying from −4 to +5 nm.[34] Cross-conjugated dienamines (i.e.

8, **14**) have low extinction coefficients and reported λ_{max} values lie in the range 250–285 nm (ϵ 1700–5500).[15,16] The λ_{max} value for **36** (212 nm) is extremely low, but this is because the diene system is non-planar and the observed UV absorption is that of an enamine rather than a dienamine.[18]

The mass spectra of dienamines shows considerably more complicated fragmentation patterns compared to that of simple enamines. Cleavage α to the double bond (vinylic cleavage) or rearrangement and complex fission processes tend to predominate over the allylic or β-fission processes observed in simple enamines. Fragmentation of cyclic dienamines is dominated by aromatisation of the unsaturated 6-membered ring.[36]

The olefinic ^{1}H chemical shift values (τ) of dienamines derived from cyclic and acyclic ketones (or aldehydes), in $CDCl_3$, or CCl_4, are as follows [M = morpholino, P = pyrrolidinyl, DM = dimethylamino]. For linear dienamines[7,10,13,18,33,34] having an s-trans diene system [R_2N–$C_{-1}H = C_{-2}H$–$C_{-3}H = C_{-4}HR'$] the chemical shifts (τ) of the olefinic protons fall in the range: H_{-1} 3.87–3.94(M), 3.48–3.6(P); H_{-2} 4.77–4.95(M), 4.9–5.15(P); H_{-3} 3.75–4.03(M), 3.4–4.0(P); H_{-4} (R′ = H, two signals) 5.18–5.55 and 5.37–5.75(M), 5.37–5.55 and 5.56–5.74(P). A terminal substituent (R′ = alkyl or ring residue) deshields H_{-4} which then appears in the region 4.62–4.75(M) and *ca.* 4.9(P). If the diene system is non-planar the increased electron density at C-2 arising from the orbital interaction of the nitrogen lone pair (pπ-conjugation) is less effectively transmitted to the terminal position. The C-2 proton (H_{-2}) is therefore shielded and appears to higher field [i.e. 5.14–5.26(M), 5.32–5.53(P)]. Conversely the electron density at C-4 is decreased, relative to a planar dienamine, and H-4 appears to lower field [i.e. *ca.* 4.72(M) and *ca.* 4.8(P)]. Piperidine and diethylamine dienamines usually have chemical shift values intermediate between those of pyrrolidine and morpholine. Some apparent exceptions to the above values have been reported in the literature however. For example the chemical shifts (τ) for the olefinic protons in **11** are reported[15] to be: H-4 5.35, H-5 4.8. This is the reverse of what would be expected. Similarly in **28** the reported[17] values (τ) are: H-1 5.2, H-2 3.8. Presumably these values should be interchanged.

For linear endocyclic dienamines[7,10,33] (fixed in an s-cis diene configuration) [R_2N–$C_{-1}R' = C_{-2}H$–$C_{-3}H = C_{-4}HR'$; where R′,R′ = –$(CH_2)_n$–] the chemical shift values are generally in the range: H_{-2} 5.14–5.32(M), 5.37–5.75(P), 5.05–5.76(DM); H_{-3} 4.11–4.39(M), 3.93–4.37(DM); H_{-4} 4.73–5.15(M), 5.27–5.37(P), 4.67–5.36(DM). Notice here that H_{-2} of the s-cis dienamines is shielded with respect to H_{-2} of an s-trans dienamine and appears 0.37–0.47 ppm (M) or 0.47–0.6 ppm (P) to higher field. This has been attributed[7] to a smaller deviation from coplanarity in acyclic or exocyclic s-trans diene systems. For example, Dreiding models indicate the deviation from coplanarity of the double bonds to be *ca.* 5° in **1** and *ca.* 18° in **2**. The increased electron density resulting from the orbital interaction of the nitrogen lone pair is therefore localised more at C-2 in 2.

For cross-conjugated dienamines[7,13,15–18] [$R''C_{-4}H = C_{-3}H$–$C(NR_2) = C_{-1}HR'$] the reported chemical shifts (τ) of the olefinic protons are in the range: H_{-1} 5.10–6.06(M), 5.19–5.86(P), 5.87–6.17(DM); H_{-3} 4.11–4.53(M), 4.36–4.67(P), 3.77(DM); H_{-4} *ca.* 4.35(M), *ca.* 4.78(P), 4.59–4.98(DM). The higher τ value quoted for H_{-1} of the morpholine and dimethylamine dienamines (M and DM) is simply due to some of these dienamines being unsubstituted at the terminal position (C-1; R′ = H), whereas in all the pyrrolidine dienamines reported H_{-1} is deshielded by an alkyl or ring residue (R′) at C_{-1}.

(iii) *Preparation.* Dienamines are usually prepared from $\alpha\beta$- or $\beta\gamma$-unsaturated aldehydes or ketones and secondary amines under conditions analogous to those used for simple enamines.[1,37] Condensation of secondary amines with $\alpha\beta$-unsaturated ketones in the presence of p-toluene sulphonic acid is slower than that with the corresponding saturated ketones. As observed for simple enamines the rate of reaction depends on the ketone and the amine used. Pyrrolidine, being more reactive than morpholine, requires a shorter reaction time, approximately 24 hr, compared with 1–6 days for morpholine dienamines (Table 1). In some cases satisfactory yields may be obtained when the water formed is removed by azeotropic distillation using a solvent such as benzene or toluene and a Dean and Stark head, but usually better yields result when the condensate is passed for an additional period over a molecular sieve.[24,32] When the preparation is carried out on a small scale, a molecular sieve may be used from the beginning. The pyrrolidine dienamines of certain Δ^4-3-oxosteroids may be prepared by simply mixing the ketone and secondary amine in hot

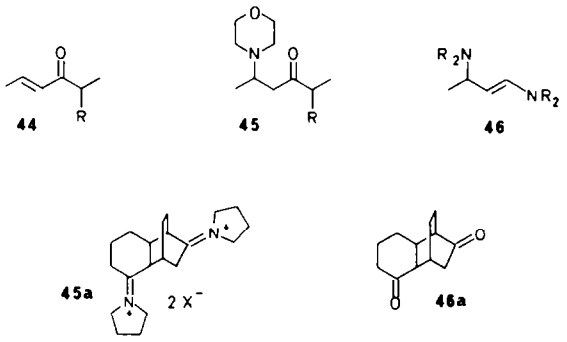
Table 1. Dienamine (1 and 37) preparations. Reaction conditions and yields†

Ketone	Amine	Solvent	Reaction Time (hr) Dean & Stark	Mol. sieve	Total (hr)	Yield (%)
$\Delta^{1,8a}$-2-octalone	M	T	40	16	56	90
	P	B	6	16	22	89
3-Methyl-$\Delta^{1,8a}$-2-octalone	M	T	48	72	120	58
	P	T	18	4	22	78
8-Methyl-$\Delta^{1,8a}$-2-octalone	M	T	72	72	144	89
	P	T	19	6	25	89
4a-Methyl-$\Delta^{1,8a}$-2-octalone	M	T	20	-	20	77
	P	T	-	18	18	80
Cholest-4-en-3-one	M	T	-	24	24	69
	P	M′	immediate reaction			96

†M = morpholine; M′ = methanol; P = pyrrolidine; B = benzene; T = toluene.

methanol.[39] Although dienamines of isophorone are readily prepared,[7] dienamines from cyclohexenone cannot be isolated owing to preferential dimerisation to the tricyclic iminium salt **45a** and hence **46a** on hydrolysis.[38] See also Ref. 2 (Scheme 44) for analogous reactions.

With acyclic $\alpha\beta$-unsaturated ketones, and some cyclic $\alpha\beta$-unsaturated ketones such as 3-methyl-6-isopropylcyclohex-2-enone,[14] the situation is sometimes complicated by conjugate addition of the amine to the carbon–carbon double bond. This is usually a competing reaction which may not lead to dienamine formation. For example attempted condensation of morpholine with hex-4-en-3-one (**44**; R = H) and 2-methylhex-4-en-3-one (**44**; R = Me) gave only the



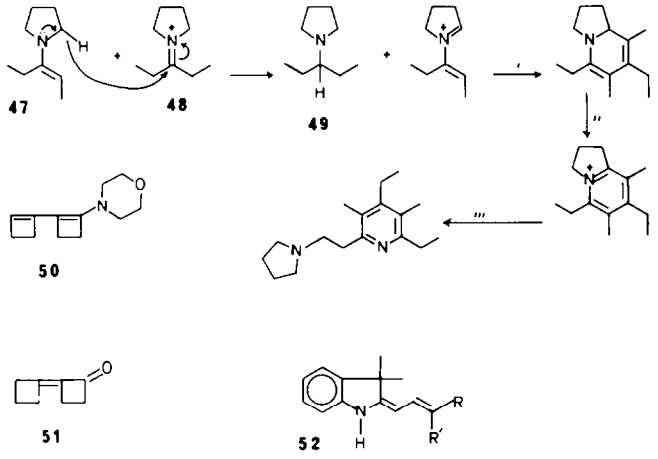
Scheme 9.

β-morpholino ketone (**45**). Further reaction with the CO group to give the dienamine, after elimination of the first morpholine residue, did not occur owing to the increased steric impedient by the bulky substituent.[18] The situation is obviously delicately balanced however, since ketones **33** and **35** gave the corresponding linear and cross-conjugated dienamines (**34** and **36** respectively) (see Scheme 6) as well as conjugate addition to the double bond.

In these cases conjugate addition is presumably impeded by the more bulky isopropyl group. β,β-Disubstitution of the double bond also results in preferential formation of the dienamine (*viz.* **29**→**32**; Scheme 6).[18] In the case of $\alpha\beta$-unsaturated aldehydes conjugate addition of the amine does not prevent dienamine formation owing to the greater reactivity of the CO function. The reaction is then best carried out with two equivalents of amine at low temperatures (−10°) in the presence of anhydrous potassium carbonate. This gives the 1,3-diamino alkene (**46**) which eliminates the β-amine moiety on heating to 100–130° under partial vacuum.[34,49]

Mixtures of linear and cross-conjugated dienamines have also been obtained by dimerisation of monoenamines derived from methyl alkyl ketones,[18,40a] and ketals.[40b] The reaction between acetone diethylketal and morpholine affords, through subsequent autocondensations of the acetone enamine, a complex mixture of enamines from which the cyclic cross-conjugated dienamine 4 - morpholino - 2,6,8,8 - tetramethylbicyclo[4.2.0]octa - 2,4 - diene was isolated.[40c] Aldehyde enamines also dimerise, but with more difficulty at higher temperatures.[50] In contrast, morpholine enamines

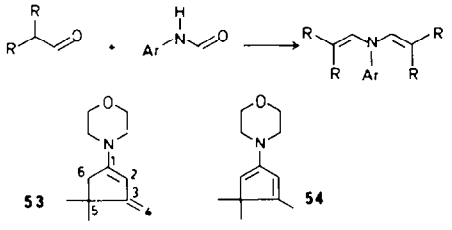
from higher alkyl ketones do not dimerise but undergo disproportion to the reduced enamine and various oxidation products.[41] A complicated series of reactions has been reported for the enamine–iminium salt condensation of the more reactive pyrroldine enamines leading to a variety of fused and polysubstituted heterocyclic systems (Scheme 10).[41] Attempted preparation of



Scheme 10. Reagents: (i) **47**; (ii) **48**; (iii) pyrrolidine.

cyclobutanone enamines is reported to yield dienamine **50** and hence **51** on hydrolysis.[55] Cyclic non-conjugated or conjugated dienamines (*viz.* **38–40**; **42–43**) may be obtained by Birch reduction of the corresponding aromatic amine. The preferred conditions involve the use of lithium and t-pentyl alcohol rather than ethanol, since the latter tends to give a considerably higher proportion of further reduced tetrahydro-derivative (monoenamine).[33,42] Other methods of dienamine synthesis include condensation of amide acetals with alkynyl alcohols. The amine moiety migrates to the triple bond in the intermediate alkynyl amide acetal, and [3,3] sigmatropic rearrangement leads to cross-conjugated dienamines[43] or acetal elimination leads to linear dienamines.[44,45] Cross-conjugated dienamines may also be obtained by base catalysed isomerisation of propargylic amines with potassium t-butoxide in dimethylsulphoxide at ambient temperature.[56] However, isomerisation of 4-methyl-3-morpholino-1-phenylpent-1-yne gave only the allene (4-methyl-3-morpholino-1-phenylpenta-1,2-diene. Condensation of aliphatic aldehydes with Fischer's base (1,3,3-trimethyl-2-methylene indoline) gives dienamines **52**.[46a]

Non-conjugated dienamines such as 1,1,5,5-*tetraphenyl*-3-*azapenta*-1,4-*diene* have been prepared by condensation of formamide with diphenylacetaldehyde. The use of the formanilide gives the corresponding N-arylazapentadiene (Scheme 11).[46b] Isomerization of cumulated enamine systems gives enyne amines.[305]



Scheme 11.

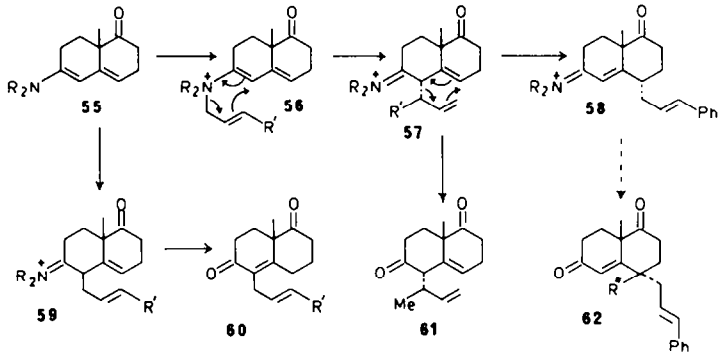
(iv) *Reactions of dienamines.*

(a) *Protonation.* Although the conjugated eniminium salt formed by δ-protonation of a linear dienamine, or β-protonation of a cross-conjugated dienamine, is the facoured product under conditions of thermodynamic control, protonation at other sites also occurs.[29c] For example, reaction of acyclic dienamines with hydrazoic acid gives a mixture of products derived by 1,2- and

1,4- and 3,4 + 1,2- addition of HN_3 to the diene system. In this case C-protonation is followed immediately by addition of the strongly nucleophilic azide anion, so that equilibration of the C-protonated enamines cannot occur.[29c] On the other hand reaction of trichloroacetic acid with the morpholine dienamine of isophorone gave the product of 1,4- addition of a proton and the trichloromethyl anion.[62] The morpholine dienamine of 3,5,5-trimethylcyclopent-2-enone, which exists primarily as the linear *exo*-isomer **53** (90–96%), undergoes deuteriation, in CD_3OD or CD_3COCD_3, at C-2 and C-4 as expected. However, most deuterium was incorporated at C-6, presumably via the small amount of cross-conjugated **54** in equilibrium with **53**.[19b] Although this may not be too surprising in view of the anticipated greater reactivity of the C-6 position in **54** [see Section 2a(i)], it is surprising in view of the much slower rate of interconversion of dienamines compared to enamines.[18] Presumably however the equilibrium is established much more rapidly in deuteriomethanol. In the case of acyclic dienamines it is possible that the conjugated eniminium salt is formed, not by direct C-δ protonation, but from the N-protonated dienamine by a symmetry allowed[1,5] sigmatropic suprafacial hydrogen transfer.[29b]

Although hydrolysis of dienamines is usually accomplished by use of a sodium acetate–aqueous acetic acid buffer,[48] hydrolysis under milder conditions results in a mixture of conjugated and deconjugated unsaturated ketones, the latter being derived of course from the β-protonated eniminium salt.[29,47]

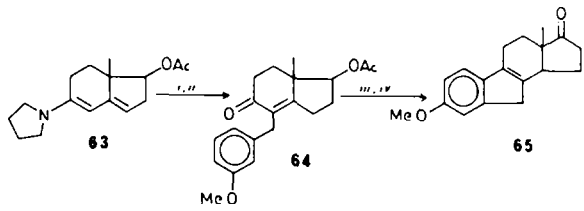
(b) *Alkylation.* Johnson *et al.*, in 1955, reported that alkylation of Δ^4-3-ketosteroid dienamines with methyl iodide in aprotic solvents at low temperatures, gave the "normal" N-alkylated quarternary salt.[29a] However, Julia,[51a] Stork[51b] and Velluz[52] later showed independently that α-C-alkylation of $\alpha\beta$-unsaturated ketones (i.e. β-alkylation of the dienamine) could be effected via the derived dienamine, by reaction with ethyl α-bromoacetate, methyl iodide and 1,3-dichlorobut-2-ene respectively. Stock attributed the preference for β- over δ-alkylation of the dienamine to the lowering of transition state energy by release of the halide counter anion in close proximity to the positively charged iminium ion.[51b] More recently Pandit *et al.* have shown that N-alkylation is favoured by low temperatures but, depending on the nucleophilicity of the counter ion, the N-alkylated product could revert to starting materials at elevated temperatures and thus lead to direct C-alkylation.[53] Intramolecular N→C alkyl transfer was specifically excluded. Reaction of dienamines with allylic halides is intriguing, the course of the reaction depending on both the amine component and the allylic halide. For example, reaction of both crotyl and cinnamyl bromides with the pyrrolidine dienamine **55** gives predominantly or exclusively the product of direct C-alkylation [**55**→(**59**)→**60**]. In the case of the morpholine and piperidine dienamines, crotyl chloride gives predominantly **61**, and its Δ^5-double bond isomer, whereas cinnamyl bromide gives **62** (R″ = H) and **62** (R″ = CH_2CH = CHPh) via double suprafacial [3,3]



Scheme 12.

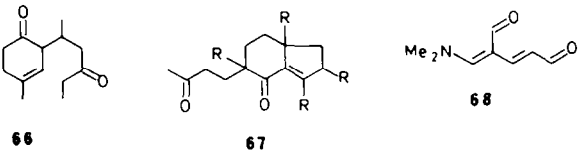
sigmatropic rearrangements [**56**→**57**→**58**→**62** (R″ = H); deprotonation and repition of this process gives **62** (R″ = CH_2CH = CHPh)].[54] Although methylation and benzylation of the pyrrolidine dienamine of 3-methyl-$\Delta^{1,8a}$-2-octalone [a mixture of **1** and **2** (R′ = Me; R″,R‴ = H)] gives only the 1,3-disubstituted octalone in protic and aprotic solvents, the position of attack by acrylonitrile and methyl acrylate is solvent dependent. In protic solvents the 1,3-disubstituted octalone is formed but in aprotic solvents formation of the initially formed zwitterion is reversible (Ref. 1, Section 5B(i))

and the β-cyanoethyl or β-methoxycarbonylethyl residues are introduced either at C-8 or at the bridgehead C-4a position. The evidence is somewhat equivocal at present, but slightly favours the C-4a position. The corresponding reaction with the dienamine from 8-methyl-$\Delta^{1,8a}$-2-octalone gave only the 1,8-disubstituted products in protic and aprotic solvents.[75] Alkylation of dienamine **63** with m-methoxybenzyl bromide gives **64**, which was used as a source of B-norsteroid analogues **65**.[22]



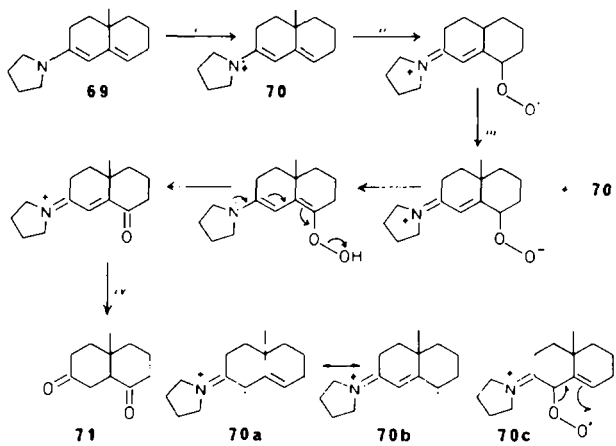
Scheme 13. Reagents: (i) m-methoxybenzyl bromide, DMF, △; (ii) hydrolysis (unspecified); (iii) hydrolysis, oxidation; (iv) H_3PO_4 or P_2O_5.

The corresponding procedure using 2-(*m*-methoxyphenyl)-3-bromopropene yielded 6-methyl-19-norsteroid analogues having a 6-membered B-ring.[57] Similarly endocyclic dienamines such as **42** react at the β-position with 6-methylhept-2-en-3-one to give diketone **66**,[42] and cross-conjugated dienamines such as **14** react with methyl vinyl ketone to give **67**.[58] 1-Dimethylaminobutadiene and its precursor, 1,3-bis(dimethylamino)but-1-ene, are converted by the Vilsmeier reagent [CH(Cl) = N^+Me_2] into 4-dimethylaminomethylenpent-2-ene-1,5-dial **68** by reaction at both the β- and δ-positions of the dienamine.[59] Similarly 3-(N-pyrrolidinyl)-$\Delta^{3,5}$-steroids give the corresponding 4,6-diformyl derivative.[28a] The tropylium ion is also reported to attack the δ-position of steroid dienamines, to give the 6-cycloheptatrienyl derivative.[28b]



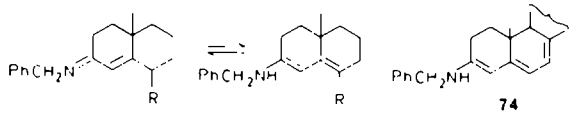
Scheme 14.

(c) *Oxidation.* Although many enamines are stable to molecular oxygen,[1] autoxidation of the pyrrolidine dienamine of 4a-methyl-$\Delta^{1,8a}$-2-octalone occurs on bubbling air through a benzene solution at room temperature and subsequent hydrolysis gives the dione **71** in 20% yield.[60a] The yield was increased to 80–85% in the presence of catalytic amounts of ferric chloride, cupric acetate or cupric chloride (Scheme 15). The reaction proceeds equally well in the dark, thus excluding the intermediacy of photo-generated singlet oxygen (Ref. 1, Section 5D). The preference for attack at



Scheme 15. Reagents: (i) Fe^{3+} or Cu^{2+}; (ii) O_2; (iii) **69**; (iv) hydrolysis.

the terminal δ-position was not discussed but can probably be attributed to the intermediacy of radical cation **70**. Further delocalisation of the radical centre (**70a** ⇔ **70b**) involves no further charge separation and since evidence exists for the reversibility of the coupling of molecular oxygen with dienylic radicals[60b] then δ-attack will be favoured by the thermodynamic stability of the resulting peroxy radical. However it is not clear at present whether **71** is formed by direct attack on the terminal δ-position (**70b**) or initial attack at the β-position (**70a**) followed by rearrangement of the peroxy radical **70c**. This work has been extended to Δ^4-unsaturated-3-keto steroids,[60a] to give the 6-keto derivative, and to Schiff bases of $\alpha\beta$-unsaturated ketones which appear to react in the dienamine form. In the latter case ferric chloride is a better catalyst than cupric chloride (a weak Lewis acid) for Schiff bases containing a smaller proportion of the dienamine form (**73**; R = H) presumably due to enhancement of the prototropic shift (**72**→**73**). In the case of **72** (R = Me),



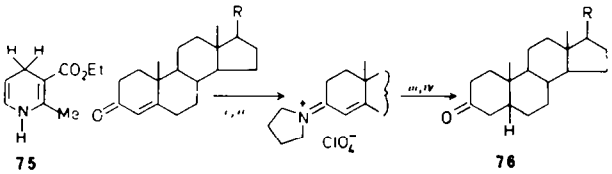
72 **73** **74**

R = H	65%	35%
R = Me	25%	75%

Scheme 16.

where the dienamine form is favoured by the hyperconjugative effect of the C-8 Me group, cupric chloride was equally effective and the product was a 3:1 mixture of the 8β- and 8α-hydroxy derivatives, showing that the oxygenation process is subject to stereoelectronic control. The benzylamine Schiff base of ergosterone, which was shown by NMR to exist entirely in the trienamine form **74**, gave 6-ketoergosterone in 91% yield by uncatalysed oxygenation, presumably due to to the ease of formation of the highly resonance stabilised intermediate radical cation.[60a] More recently photosensitized oxygenation of dienamines has been shown to give the $\alpha\beta$-unsaturated ketone presumably by 1,2-addition of singlet oxygen and cleavage of the C_α–C_β bond,[61] as in the case of simple enamines.[1]

(d) *Reduction.* Reduction of dienamines such as 3-N-pyrrolidinylcholesta-3,5-diene with sodium borohydride and acetic acid in diglyme gave an amine–borane complex which was decomposed by heating with acetic acid to give a 60% yield of 3-N-pyrrolidinylcholest-5-ene.[63a] The reduction was shown not to proceed by hydroboration and did not commence until after the acetic acid was added. These results indicate that protonation at C-4 (C-β of the dienamine) is kinetically favoured over protonation at C-6 (C-δ of the dienamine), as has previously been shown to be the case with dienylic anions,[63b] thus leading to the non-conjugated enimium salt which is attacked rapidly by hydride anion (or diborane) at C-3. Similarly sodium borohydride reduction of the pyrrolidine dienamine of testosterone in methanol gave mainly the 3-β-pyrrolidinyl-$\Delta^{5,6}$-steroid.[64] Treatment of cyclic dienamines with hot formic acid gave the 1,4-dihydro and 1,2,3,4-tetrahydro derivatives, whereas acyclic dienamines gave a mixture of the 1,2- and 1,4-reduction products by initial C-2 and C-4 protonation followed by hydride transfer to C-1 with elimination of carbon dioxide.[65] Preformed eniminium salts have also been reduced with 1,4-dihydropyridine derivatives **75**. The reduction occurred stereospecifically to give the *cis*-ring fused ketones **76** (R = C_8H_{10}, OAc).[66]



75 **76**

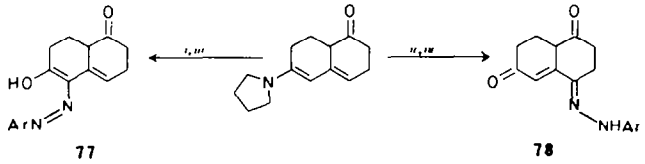
Scheme 17. Reagents: (i) pyrrolidine; (ii) 70% $HClO_4$–HOAc; (iii) **75**, △ 20h in MeCN; (iv) hydrolysis.

Catalytic hydrogenation gives a mixture of partially reduced products (enamine and allylamine) and/or saturated amine depending on the conditions used.[13] Partial reduction of cyclic dienamines

also occurs on treatment with lithium in ammonia, to give mainly the monoenamine. No hydrogenolysis of the amine group occurred, but unsymmetrical dienamines gave mixtures of isomeric enamines rather than the one isomer which had been anticipated.[68]

(e) *Halogenation.* Unlike non-conjugated enamines, little work has been carried out on the halogenation of dienamines, except for the attachment of fluorine to the steroid skeleton. Pyrrolidine dienamines of 3-oxo-Δ^4-steroids are reported to react with perchloryl fluoride ($FClO_3$) and fluoroxytrifluoromethane to give mixtures of the 4,4-difluoro-3-oxo-Δ^5-steroids and 4-fluoro-3-oxo-Δ^4-steroids, in relative amounts which depend upon the conditions.[69]

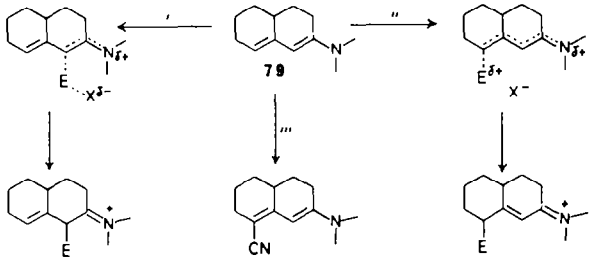
(f) *Miscellaneous reactions.* The coupling of dienamines with arenediazonium salts has shown an interesting regioselectivity which is solvent dependent. In polar solvents such as water or dimethylformamide coupling occurs at the δ-position to give hydrazone **78**, whereas in less polar solvents such as chloroform or methylene chloride coupling also occurred at the β-position to give **77**.[19a]



77 78

Scheme 18. Reagents: (i) ArN_2BF_4, CH_2Cl_2 or $CHCl_3$; (ii) ArN_2Cl or ArN_2BF_4, DMF or H_2O; (iii) hydrolysis.

The explanation offered for this variation in regioselectivity was that in polar solvents the diazonium salt is highly ionised and reaction occurs via a product-like transition state involving the formation of the more stable conjugated eniminium salt **82** (Scheme 19). In non-polar solvents, ionization of the diazonium salt would be incomplete and coupling would proceed at least partially via an S_N2 type mechanism involving simultaneous bond formation and bond cleavage. This would occur preferentially at the centre of highest electron density and, since reaction at the enamine nitrogen is reversible, thus favours reaction at the β-position rather than the δ-position. The

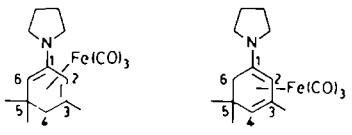


80 81 82

Scheme 19. Reagents: (i) $E^{\delta+}—X^{\delta-}$; (ii) $E^+ X^-$; (iii) ClCN.

electron density is known to be greater at the β-position and, as previously pointed out by Stork,[51b] liberation of the counter ion in close proximity to the developing positive charge would tend to lower the activation energy for formation of **80**. However in a solvent of lower polarity (dioxane) cyanogen chloride is reported[70] to give only δ-substitution (i.e. **79**→**81**)!? Metalcarbonyl complexation of cyclic dienamines has also been investigated. Treatment of the pyrrolidine dienamine of isophorone [i.e. **4** (R″ = R‴ = H) and **5** (R′ = Me); R_2N = pyrrolidinyl] with pentacarbonyliron gave a mixture of the linear and cross-conjugated dienamine tricarbonyliron complexes **83** and **84**.[71] The formation of **83** is interesting since it is derived from the cross-conjugated isomer **6** (R′ = Me, R_2N = pyrroldinyl), which is not present to a detectable extent in the dienamine starting material, there being no apparent interconversion of **83** and **84**. Whereas **84** was unstable and could be isolated only with difficulty, the cross-conjugated complex was considerably more stable. This is also surprising in view of the greater thermodynamic stability of the free linearly conjugated

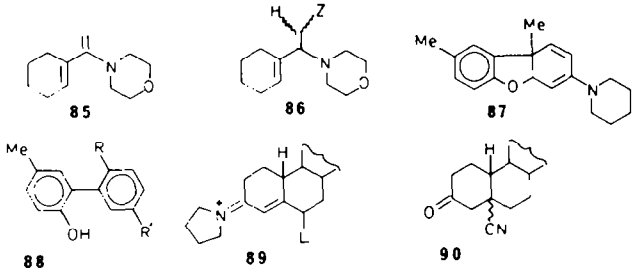
dienamine compared to the free cross-conjugated dienamines.[7,10] From consideration of the spectroscopic properties it was concluded that the greater stability of **83** was due to increased double bond



83 **84**

Scheme 20.

character of the C_1–C_2 bond being in conjugation with the N lone pair (the proton and C-13 signals at C-2 where at higher field in **83** than in **84**) and to greater back donation from the metal to the diene ligand in **83** (the carbonyl stretching frequencies were higher in **83** indicating less back donation to the carbonyl ligands).[71] Cross-conjugated dienamine **85** reacts normally with phenylisocyanate and diethyl azodicarboxylate to give **86** (Z = CONHPh and $N(CO_2Et)NHCO_2Et$), whereas [2 + 2] and [4 + 2] cycloadditions also occur with sulphene and β-nitrostyrene respectively.[72] Thermal rearrangement of the cyclic cross-conjugated dienamine **87** gives biphenyls



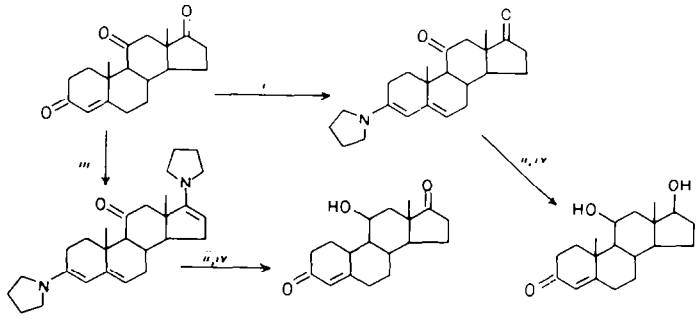
85 **86** **87**

88 **89** **90**

Scheme 21.

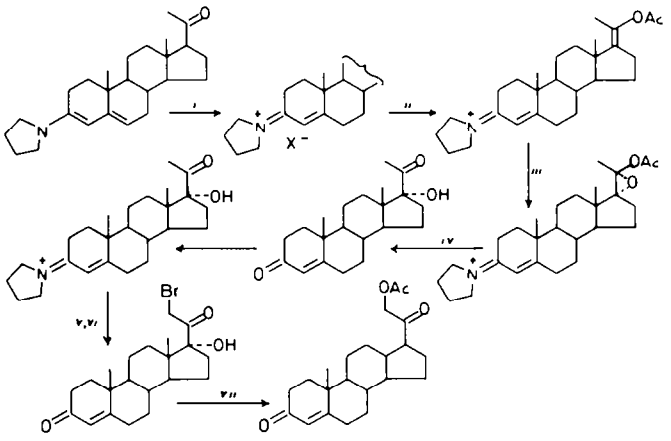
88 (R = piperidino, R′ = Me) and **88** (R = Me, R′ = piperidino) by [1,5] and [1,2] aryl migrations respectively.[73] Conjugate hydrocyanation of dienamines with hydrogen cyanide and an alkylaluminium or diethylaluminium cyanide occurs via **89** (L = H or Et_2Al) to give **90** on hydrolysis.[74]

One application of enamines which we have not previously touched on[1,2] is their use as a protecting group for CO and αβ-unsaturated CO functions (and amines) during both nucleophilic and electrophilic operations on other functional groups. Since many of these applications have been concerned with synthetic elaborations of 3-oxo-Δ^4-steroids it is appropriate to briefly consider them here. The rate of enamine formation is extremely sensitive to steric, electronic and experimental effects.[1] It is therefore often possible, by proper choice of a secondary amine and experimental conditions, to enaminize, and thus protect, one or more CO groups in a polyfunctional molecule while nucleophilic reactions are carried out elsewhere in the molecule. A classical example[39] is illustrated in Scheme 22. Numerous other examples have been reported in the literature.[79]



Scheme 22. Reagents: (i) pyrrolidine (one equiv.); (ii) $LiAlH_4$; (iii) pyrrolidine (excess); (iv) hydrolysis.

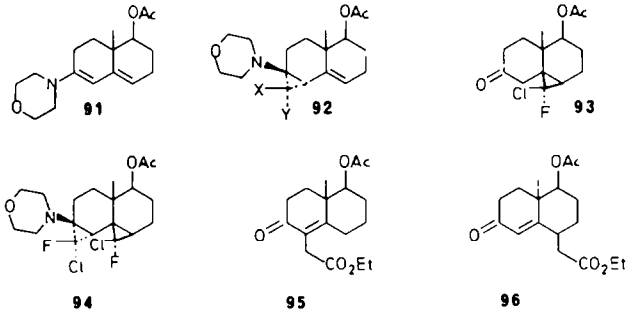
Addition of substituents (methyl, ethyl, ethynyl, etc.) to the 17-position of 3,17-dioxosteroids via reaction of Grignard reagents on the $\Delta^{3,5}$-dienamine is another common application.[76,77] Alternatively, the dienamine may be converted, by protonation, into an eniminium derivative and this enables various electrophilic operations (i.e. oxidation, bromination, etc.) to be carried out elsewhere[78] (Scheme 23).



Scheme 23. Reagents: (i) HX; (ii) Ac_2O, catalytic 70% $HClO_4$; (iii) m-chloro-perbenzoic acid; (iv) aq. ethanolic NaOH; (v) Br_2, hydrogen chloride; (vi) aq. EtOH, $NaHCO_3$; (vii) KOAc, acetone Δ.

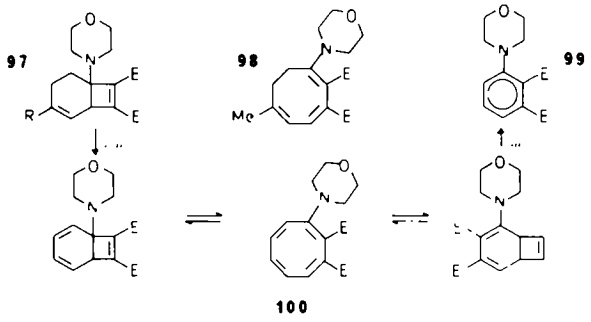
(v) *Carbocyclic synthesis*

(a) 3-*Membered rings*. In addition to ring-expansion products (see Section (v) (d)) a variety of carbenes have been shown to add to the less hindered α-side of the $\alpha\beta$-double bond in the morpholine dienamine **91** to give cycloadducts **92** (X, Y = H, Cl, Br, F, Ph), but in poor to moderate yield. In addition to **92**, chlorofluorocarbene gives cycloadduct **93** derived by addition to the $\beta\gamma$-double bond of **91** from the β-side, and **94** derived by further cycloaddition from the α-side.[80] Ethoxycarbonylcarbene gave only the β- and δ-alkylation products **95** and **96**, presumably derived by ring opening of the corresponding cycloadducts.[80] Only ring expansion products were isolated from pyrrolidine dienamines.[81]



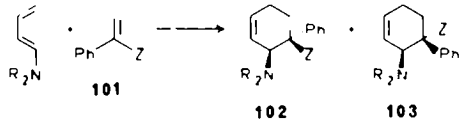
Scheme 24.

(b) 4-*Membered rings*. Reaction of an enamine with an electrophilic acetylene usually proceeds through an initial cyclobutene which may then rearrange, often spontaneously or on heating, to form products whose structures depend on the starting enamine and the reaction conditions.[82] In the case of dienamines the stability of the cycloadduct has been shown to depend on the presence and nature of substituents at C-4.[83] For example cycloadduct **97** (R = Me), derived from **43**, was not isolated owing to the ease of ring expansion to **98**, whereas cycloadduct **97** (R = OMe) was unchanged after heating to 180°. Dehydrogenation of **97** (R = H) led unexpectedly to 3-morpholinophthalate **99** presumably via the cyclo-octatetraene intermediate **100**.



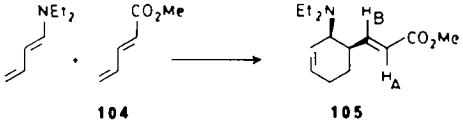
Scheme 25. Reagents: (i) N-bromosuccinimide (R = H); (ii) Li_2CO_3, LiBr, DMF, Δ; (iii) $-CH{\equiv}CH$; E = CO_2Me.

(c) 6-*Membered rings*. Diels–Alder cycloaddition of acrolein,[49,84] ethyl acrylate,[49] acrylonitrile,[49] methyl vinyl ketone,[49] *p*-benzoquinone,[84] 1,4-naphthoquinone,[84] α-chloroacrylonitrile,[86] 2,2,7,7-tetramethyloct-4-ene-3,6-dione[92] and diethoxyphosphinylethene[93] to acyclic dienamines occurs at low temperatures to give the corresponding aminocyclohexenes. These cycloadducts eliminate the amine moiety under acid conditions or high temperatures to give the dihydro benzene derivative.[49,84] In the case of α-chloroacrylonitrile, elimination of hydrogen cyanide and hydrogen chloride results in complete aromatization of the ring.[86] In contrast to the behaviour of 1-acetoxy- and 1-chlorobutadiene, both of which fail to undergo Diels–Alder reactions with ethyl atropate **101** (Z = CO_2Et) and related alkenes (Z = CN, COMe, CO_2Me, CO_2i-Pr), linear acyclic dienamines add smoothly and with complete regioselectivity to these dienophiles. The ratio of the resulting stereoisomeric cyclohexenes **102** and **103** depends on the size of the amine substituent, **102** being the major stereoisomer.[85] Although enamines readily undergo 1,4-cycloaddition to electrophilic



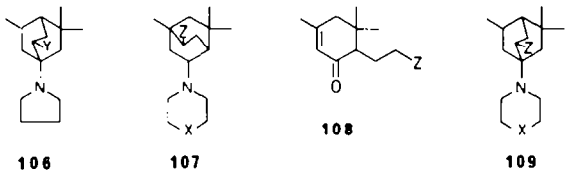
Scheme 26.

dienes,[87,88] in a competitive reaction between a dienamine and trans-2,4-pentadienoate **104** the former became the diene component and the latter the dienophile, leading to **105** [ν_{CO} 1715, $\nu_{C=C}$ 1652, 1640 cm^{-1}; λ_{max} 205 nm (ϵ 16,200); τH_A 4.06q (J 1.5, 16 Hz), τH_B 2.7q (J 9, 16 Hz)].[88]



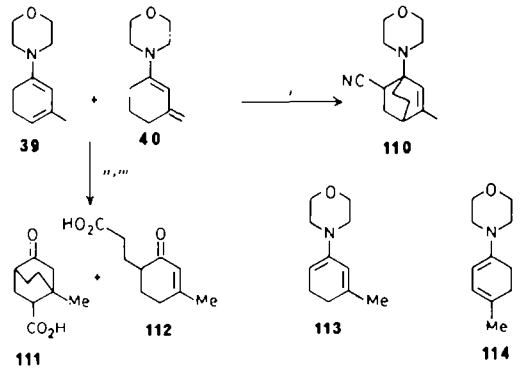
Scheme 27.

Cyclic linear dienamines having an homoannular (s-*cis*) diene system also undergo the Diels–Alder reaction with electrophilic olefins, but the regioselectivity is critically dependent on the conditions. Thus Opitz[89] reports that the pyrrolidine dienamine of isophorone and acrylonitrile gives **106** derived from the linear *endo*-isomer **5** (R_2N = pyrrolidinyl) whereas Nozaki *et al.*[90] report that the corresponding morpholine and piperidine dienamines give cycloadduct **107** and alkylation product **108**, both derived from the cross-conjugated dienamine **6** which is the minor component of the dienamine mixture.[7] Presumably this reflects the greater reactivity of the cross-conjugated dienamine [see Section 2a(i)] and the ready acid-catalysed thermally accelerated dienamine interconversion. The use of high pressures enables the cycloaddition to occur at room temperature and then only cycloadducts **109** were isolated.[87b] Similarly the Birch reduction products **39** and **40** react with acrylonitrile to yield exclusively the cycloadduct **110** derived from *endo*-isomer **39** only.

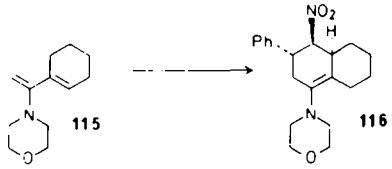


Scheme 28. X = O, CH_2; Y = CN; Z = CN, CO_2Me.

However with the less reactive methyl acrylate the products isolated on hydrolysis were **111** and **112** derived from cross-conjugated dienamine **113** which was not present in detectable amount in the original dienamine mixture.[91] In contrast the linear dienamine **114** adds normally to methyl acrylate presumably due to the stabilising influence of the Me group at C-4. The cross-conjugated

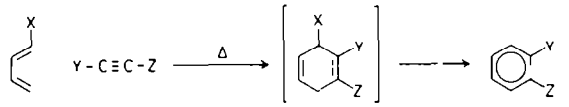


Scheme 29. Reagents: (i) acrylonitrile, 7h 100°; (ii) methyl acrylate, 65h 100°; (iii) KOH.

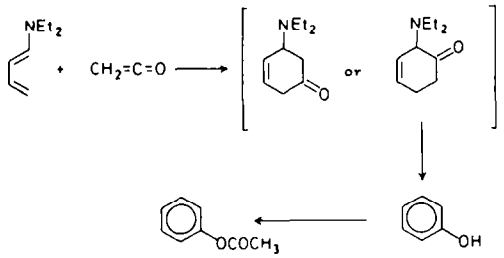


Scheme 30.

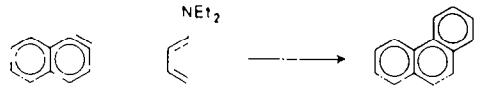
dienamine **115** undergoes a two-step cycloaddition to β-nitrostyrene to give cycloadduct **116**.[94] Acetylene carboxylic esters and ketene have also been employed as the dienophile in the Diels–Alder reactions of acyclic dienamines.[97] In both cases aromatisation occurred, the former giving high yields of aromatic carboxylic esters (Scheme 31) and the latter giving phenylacetate (Scheme 32) in low yield. Aromatic systems have also been obtained by cycloaddition of acyclic dienamines to arynes (Schemes 33).[98]



Scheme 31. X = NEt_2; morpholino, OEt; Y, Z = CO_2Me, CO_2Et, CN.

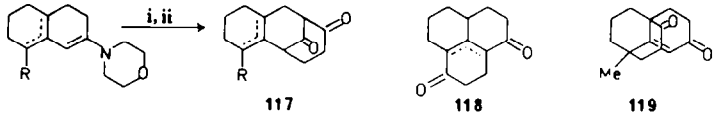


Scheme 32.



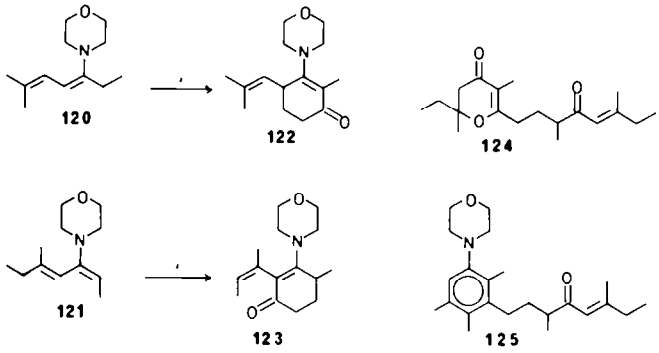
Scheme 33.

Another general method for forming 6-membered rings which we have investigated extensively involves the reaction of enamines with $\alpha\beta$-unsaturated acid chlorides.[2] Application of the reaction to dienamines from $\Delta^{1,8a}$-2-octalones gave mainly the bridged bicyclic dione **117**, on hydrolysis, formed by initial reaction at C-1 and cyclisation at C-3. However small amounts of the 1,8- and 4a,8-bridged products were also isolated (**118** and **119** respectively).[24a] Application of the reaction to dienamines derived from 3-alkyl-5,5-dimethylcyclohex-2-enones similarly gave



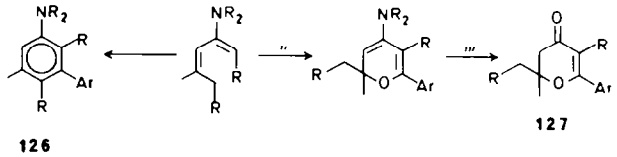
Scheme 34. Reagents: (i) CH_2=CHCOCl, C_6H_6, $\triangle$; (ii) H_2O.

6-alkyl-8,8-dimethylbicyclo[3.3.1]non-6-ene-2,9-diones, but in much lower yield compared to the corresponding reaction with cyclohexanone enamines.[99] Acyclic linear **120** and cross-conjugated dienamines **121** were converted into the cyclohexenones **122** and **123** respectively, in moderate–good yield. Two other products were also isolated in low yield from reaction of **121**, and were identified as the dihydro-γ-pyrone **124** and pentasubstituted benzene **125**.[99] The C=C double bond of the $\alpha\beta$-unsaturated acid chloride is not involved in the cyclisation step leading to these two products (**124** and **125**), but is merely serving to react, as an electrophilic olefin, with a second equivalent of the dienamine to form the 3,6-dimethyl-4-oxo-oct-5-enyl side-chain. This observation



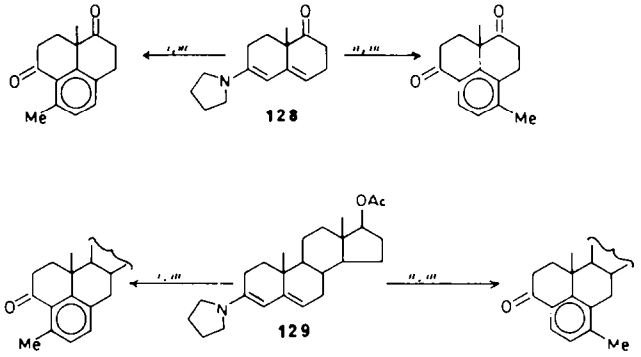
Scheme 35. Reagents: (i) CH_2=CHCOCl, $\triangle$ C_6H_6.

led to the development of the reaction into a general method for the preparation of biphenyls **126** and dihydro-γ-pyrones **127** by reaction of cross-conjugated dienamines with aromatic acid chlorides.[100,101]

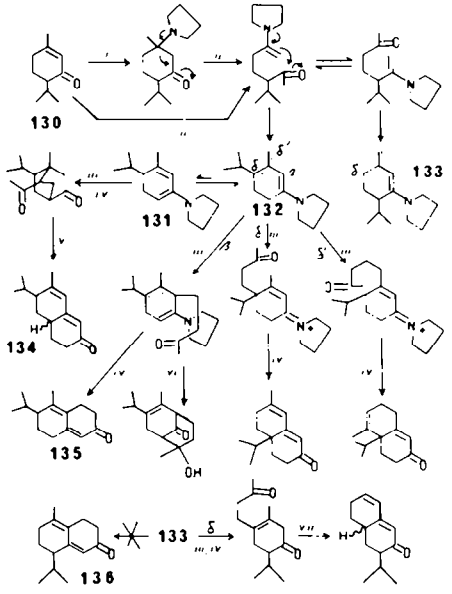


Scheme 36. Reagents: (i) ArCOCl, ether, 24h 20–25° or Et_3N, C_6H_6, $\triangle$ 20h; (ii) ArCOCl*, C_6H_6, $\triangle$ 20h; (iii) water-acetic acid-sodium acetate (2:2:1), 24h 20°; *added under reflux.

Both methyl vinyl ketone and crotonaldehyde have been shown to condense with cyclic dienamines to give fused aromatic ring systems. The reaction is particularly interesting since initial attack occurs at the δ-position of the dienamine, followed by cyclisation onto the β-position (Scheme 37).[102,116] Possibly initial reaction at the more reactive β-position is reversible under the experimental conditions employed (boiling toluene) but it would be interesting to evaluate the effect of the angular Me group in **128** and **129** on the course of the reaction because in other cases β-attack is not reversible. For example annulation of dienamine **42** (Scheme 8) gives **139** (Scheme 39) formed by β-attack by the methyl vinyl ketone on the dienamine.[42] Also Bessiere and Derguini-Boumechal have published a fascinating example of the complications which can beset both the formation and reactions of enamines subjected to steric effects. Condensation of methyl vinyl ketone with the pyrrolidine dienamine derived from (±)-piperitone (**130**) gives, after cyclodehydration, seven different cyclisation products! Furthermore the expected annulation product **136** is not formed!! The explanation for this intriguing result is summarized in Scheme 38 and involves the formation of four isomeric dienamines (**132** and **133**) followed by β, δ and δ' attack and double bond rearrangement and cycloaddition to the cross-conjugated isomer **131**, not present in the dienamine mixture initially formed. However the major products are **134** and **135**.[14] Although dihydropyrans



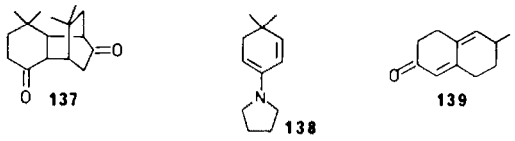
Scheme 37. Reagents: (i) methyl vinyl ketone, △ toluene; (ii) crotonaldehyde, △ toluene; (iii) hydrolysis.



Scheme 38. Reagents: (i) pyrrolidine, ambient temperature 45 days: (ii) pyrrolidine, p-TSA, benzene △ 80h; (iii) methyl vinyl ketone, ambient temperature 96h; (iv) AcOH–AcONa, benzene △ 30 min; (v) 20% KOH–MeOH, △ 6h; (vi) 10% Na_2CO_3, ambient temperature 4h; (vii) p-TSA, benzene △ 5h.

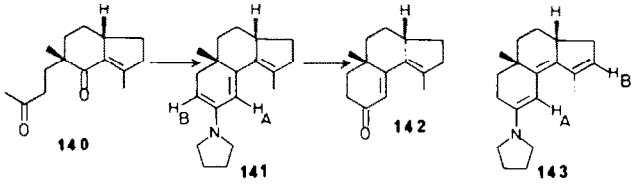
are formed from methyl vinyl ketone and enamines at low temperatures,[103] in refluxing benzene the pyrrolidine enamine of isobutyraldehyde has been shown to yield the tricyclic ketone **137**.[104]

This complex reaction is shown to proceed through the formation and self-condensation of the cross-conjugated dienamine **138**. Alkylation of cross-conjugated dienamines such as **14** (Scheme 4) occurs at C-5[58] to give **140** which was cyclised by treatment with pyrrolidine to give **142** on



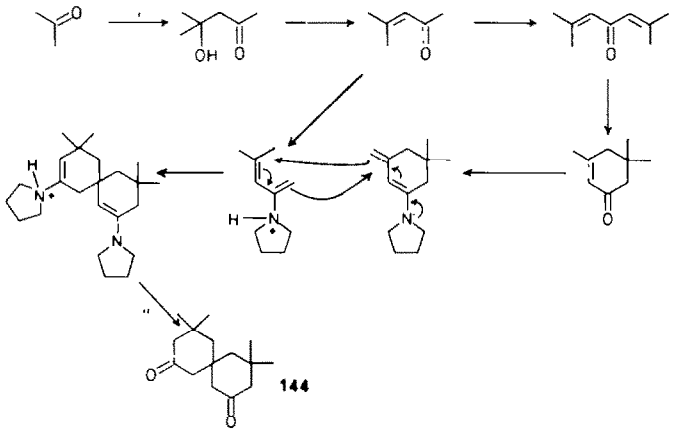
Scheme 39.

hydrolysis.[105] The intermediate trienamine was given the cross-conjugated structure **141** although the chemical shift data would appear to fit the linear structure **143** better [τH_A 5.03s, τH_B 4.57t; see Section 2a(ii)].



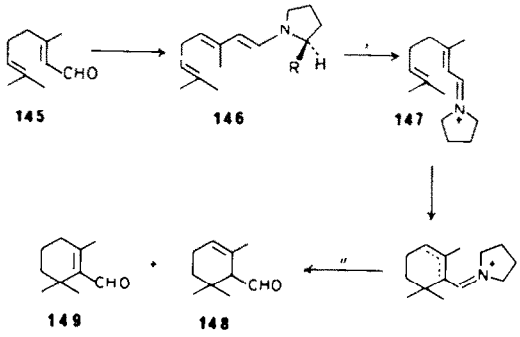
Scheme 40.

A novel synthesis of the spiro diketone **144**, involving acetone as the sole source of carbon has been reported, presumably involving the events depicted in Scheme 41.[106] A biogenetic-type



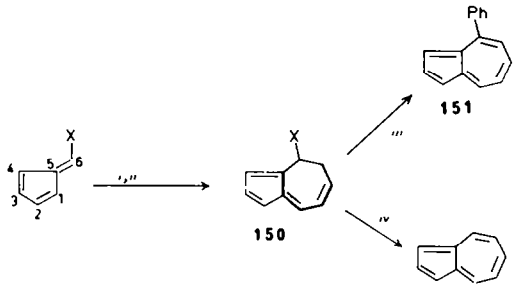
Scheme 41. Reagents: (i) pyrrolidine, alkyl chloride, sodium iodide, acetone, reflux 25h; (ii) aq. HCl.

cyclization of citral **145** to α-cyclocitral **148** involves δ-protonation of the derived pyrrolidine trienamine **146** (R = H) and cyclization of the resulting eniminium salt **147**. Only trace amounts of the conjugated enal **149** were formed.[95] Application of the reaction to optically active dienamines **146** (R = Me, i-Pr, $CON(CH_2)_4$, $CONEt_2$, CO_2Et) gave optically active *S*(+)-α-cyclocitral.[96]



Scheme 42. Reagents: (i) conc. H_2SO_4–H_2O (10:1) 0°, 3h; (ii) aq. NaOH to pH 3–4, △.

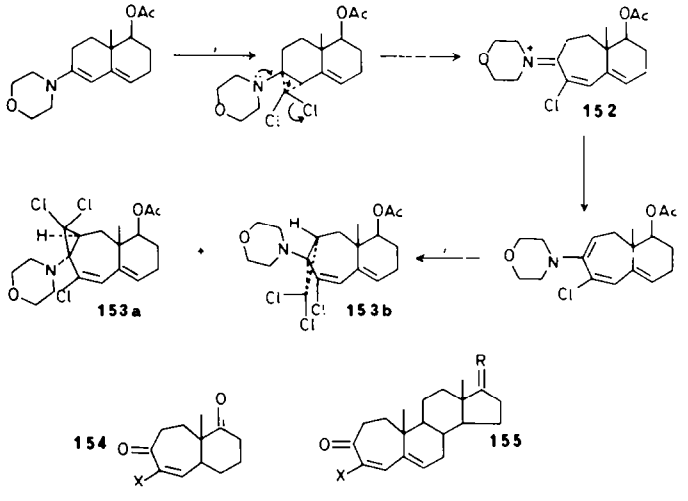
(d) *7-Membered and larger rings.* In agreement with predictions based on frontier orbital arguments,[107] dienamines undergo [6 + 4] cycloaddition to alkyl or aryl fulvenes to give dihydroazulenes **150** which can be subsequently dehydrogenated to azulenes **151** in moderate yield.[108] The dehydrogenation step can be avoided by use of fulvenes containing a good leaving group at C-6.[109]



Scheme 43. Reagents: (i) 1-diethylaminobutadiene, 7 h–1 day in CCl_4, C_6H_6 or $CHCl_3$, 25°; (ii) MeI, chromatography SiO_2; (iii) chloranil, toluene △ 15 min. (X = Ph); (iv) X = OCOMe, p-$OSO_2C_6H_4Me$, p-$OCOC_6H_4NO_2$.

Apparently only powerfully nucleophilic diene systems such as 1-diethylaminobutadiene (ionization potential 6.96 eV; electron affinity ~ −2 eV) have a sufficiently high energy HOMO (compare with the HOMO energies for simple enamines derivable from Table 1 and Fig. 2 in Ref. 1) to be able to interact with the LUMO of fulvene across the 1–6 positions, with the more nucleophilic terminal atom of the diene becoming attached to the C-6 position of fulvene.

Ring expansion of dichlorocarbene cycloadducts of morpholine dienamines, followed by further carbene cycloaddition, is reported to give **153a** and **153b**.[80] The reaction is more general with pyrrolidine dienamines, but owing to the greater stability of the exocyclic double bond (in dieniminium salts analogous to **152**) further cycloaddition does not take place, and thus leads to structures such as **154** (X = Cl, F) and **155** (X = Cl, F; R = β-C_8H_{17}, α-H; β-OAc, α-H) on hydrolysis.[110]



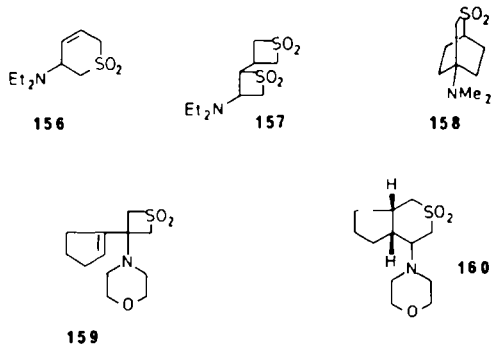
Scheme 44. Reagents: (i): CCl_2.

In contrast to simple enamines (see Section 2E, Ref. 2) very little work seems to have been carried out on the cycloaddition of electrophilic acetylenes to dienamines. An isolated ring expansion to a cyclo-octatriene[83] is referred to in Section (v)(b) of this report (Scheme 25).

(vi) *Heterocyclic synthesis.*

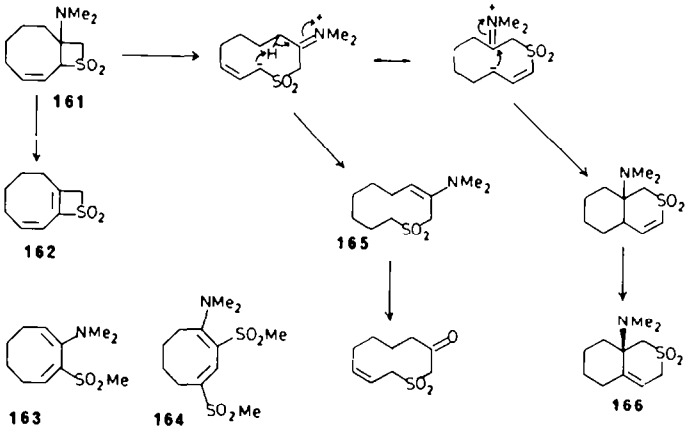
(a) *4-Membered rings.* Sulphenes have been shown to undergo both [2 + 2] and [4 + 2] cycloaddition to dienamines. Thus 1-diethylaminobuta-1,3-diene gives a mixture of **156** and **157**,[111a]

whereas 1-dimethylaminocyclohexa-1,3-diene gives **158**.[111b] Similarly the cross-conjugated dienamine 1-(cyclopenten-1-yl)-1-morpholino-ethene gives a mixture of **159** and **160**.[112]



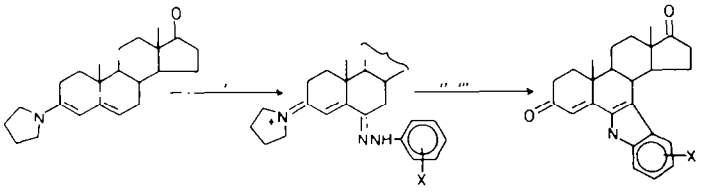
Scheme 45.

The reaction of 1-dimethylaminocyclo-octa-1,3-diene with sulphene is complex. The product distribution has been found to depend upon the temperature, rate of addition of sulphonyl chloride, and the chromatographic purification technique. The [2 + 2] cycloadduct **161** is unstable and could only be isolated in 5% yield on rapid elution of the crude mixture from a Florisil column. Further reaction rapidly occurred to give **162**, **165** and **166**. Also isolated were the mono- and disulphones **163** and **164**.[113] Other methods of forming 4-membered heterocyclic rings, such as 1,2-cycloaddition of isocyanates[114] and N-sulphonylimines,[115] do not seem to have been applied to dienamines.



Scheme 46.

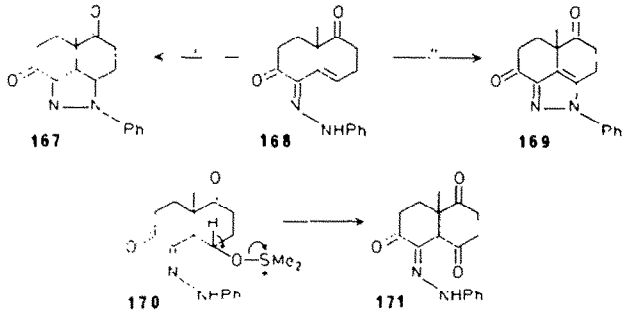
(b) *5-Membered rings.* Indolo-steroids have been obtained by δ-coupling of steroid dienamines with diazonium salts in dimethylformamide as solvent, followed by Fischer-indole cyclisation of the resulting hydrazone (Scheme 47).[116]



Scheme 47. Reagents: (i) $X{\cdot}C_6H_4{\cdot}N_2BF_4$, DMF, -45°; (ii) $POCl_3$, ambient temperature, 64 h; (iii) H_2O.

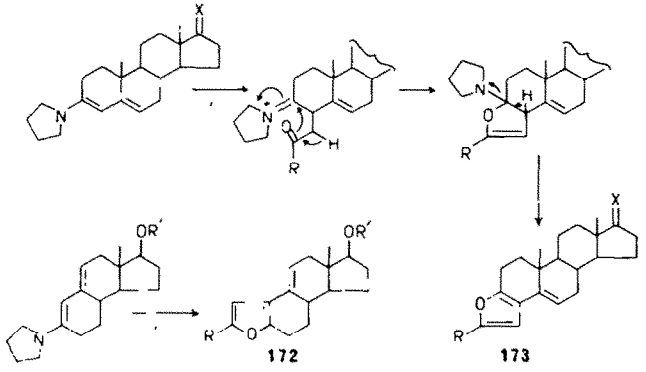
In methylene chloride the β-coupled product **168** was obtained, cyclisation of which gave indazoles **167** and **169**.[19a] However when the phenyl ring contains an electron donor substituent the reaction may be diverted to produce a cinnoline (see next section). The oxidative role of the

dimethylsulphoxide in the formation of **169** was attributed to nucleophilic attack by the solvent on **168** leading to intermediates **170** and **171**, with elimination of dimethyl sulphide, and hence to **169**.



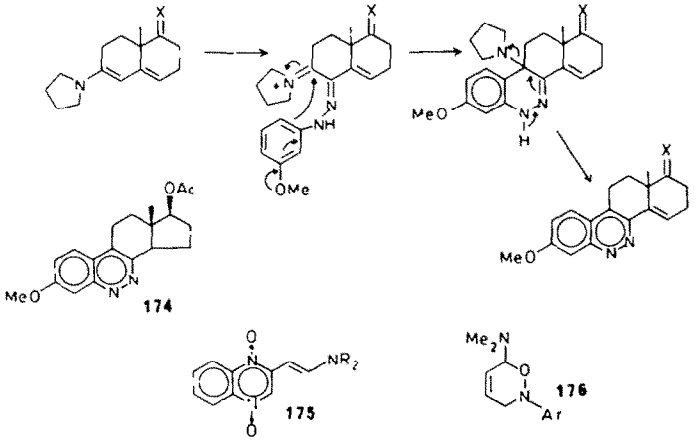
Scheme 48. Reagents: (i) pyruvic acid, aq. acetic acid, △ 0.5 h; (ii) DMSO, polyphosphoric acid, 18 h ambient temperature.

Furano-steroids **173** and 3-oxa-A-norsteroids **172** have been obtained by reaction of α-bromoketones with steroid enamines[116,117] (Scheme 49). Other methods of forming 5-membered rings,[118] such as reaction with isocyanates in the presence of cyclohexylisonitrile or sulphur, or cyclo-addition of 1,3-dipolar reagents, do not seem to have been applied to dienamines.



Scheme 49. Reagents: (i) $RCOCH_2Br$, DMF, 150° 18 h; R′ = H, Ac; X = O; H, OAc; R = C_2H_5, C_6H_5, o-C_6H_4F, p-C_6H_4F, p-C_6H_4Cl, p-C_6H_4Br, o-, m-, p-$C_6H_4CF_3$.

(c) 6-*Membered rings*. Although coupling of aryl diazonium salts at the β-position of dienamines yields indazoles on acid catalysed cyclization (*vide supra*), when the aryl diazonium salt contains an electron donor substituent, such as a *m*-OMe group, the ring becomes sufficiently nucleophilic to cyclise onto the iminium group to give a cinnoline (Scheme 50). In this way 6,7-diaza-steroids (**174**) have been prepared.[19a,119]

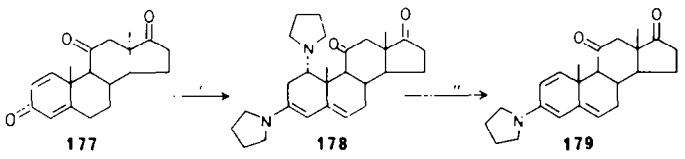


Scheme 50.

Quinoxaline N,N'-dioxides **175** are obtained by reaction of benzofurazan 1-oxide across the γ-position of acyclic dienamines,[126] whereas nitroso compounds undergo 1,4-cycloaddition to give **176**.[121] Cycloaddition of carbon disulphide to linear-and cross-conjugated dienamines gives thiopyran-2-thiones[122] and 5,6-dihydrothiopyran-2-thiones[123] respectively.

(b) *Tri- and poly-enamines*

Condensation of 3-keto-$\Delta^{1,4}$-steroids with pyrrolidine gives the dienamine **178** which undergoes pyrrolysis to the cross-conjugated trienamine **179**. These derivatives have been used as a means of temporary protection of the CO group, but their properties as polydentate nucleophiles do not appear to have been studied.[124]

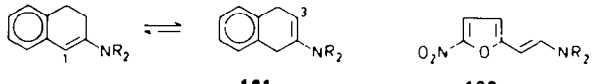


177 **178** **179**

Scheme 51. Reagents: (i) excess pyrolidine, △; (ii) 150°.

Under the conditions employed neither of the less reactive CO functions in **177**, at C-11 and C-17, are converted into enamines. Aryl-substituted enamines, such as those of acetophenone, α-tetralone and indanone have been referred to previously[1,2] and will not be considered further since their properties are similar to those of alkyl-substituted enamines, except that their reactivity is probably somewhat lower owing to steric and electronic factors (i.e. the bulk and electron-attracting action of the aryl group). Interestingly enamines of acetophenone and acyclic secondary amines tend to rearrange to the C-alkylated ketimine during their preparation presumably to alleviate steric interactions with the benzene ring.[125] β-Tetralone enamines exist as a mixture of tautomers (**180** and **181**). Although reaction normally occurs at C-1 with most electrophiles,† in some cases reaction occurs at C-3, even at low temperatures, as for example with β-nitrostyrene.[126]

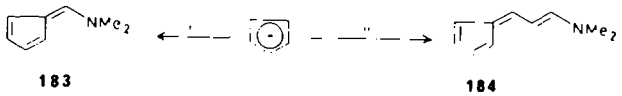
In the case of 3-(1-pyrrolidinyl) thiophenes, it has been shown that their reactivity is of the same order of magnitude as in "normal" enamines, notwithstanding the fact that the reacting C=C double bond constitutes part of a heteroaromatic system. For example reaction with dimethyl acetylene dicarboxylate yields [2 + 2] cycloadducts in apolar solvents, and yields thieno [3,2b] pyrrolizines in polar solvents (see Ref. 2, pp. 3387–3388). Condensation of 5-nitro-2-furylvinyl bromide with secondary amines gives the furylvinylamine **182**,[127] but their behaviour as polydentate



180 **181** **182**

Scheme 52.

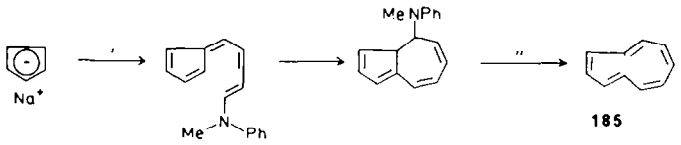
nucleophiles was not investigated. 6-Dimethylaminofulvene **183** and its vinylogues **184** have been prepared by condensation of cyclopentadienylsodium with acid amides or vinylogous amides (Scheme 53). Often these polyenamines will undergo intramolecular cyclisation and β-elimination to give non-benzenoid polycyclic conjugated π-electron systems, such as azulene **185** (Scheme 54).



183 **184**

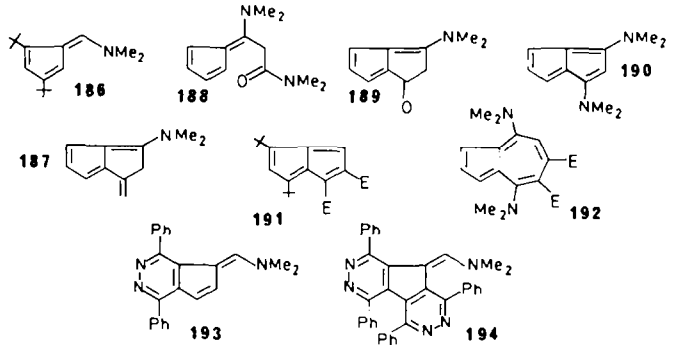
Scheme 53. Reagents: (i) $Me_2NCH{=}O$, Me_2SO_4; (ii) $Me_2NCH{=}CHCH{=}O$.

†Although 1-methyltetralone is readily obtained (98% yield) by methylation with methyl iodide in methanol, only N-methylation occurs in benzene (D. A. H. Taylor, personal communication).



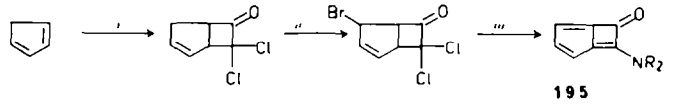
Scheme 54. Reagents: (i) PhNMe(CH=CH)$_2$CH=O; (ii) -NHMePh.

Structures **186–190** have been obtained in similar manner.[128] These compounds give characteristic reactions of polyenamines. For example cycloaddition of dimethyl acetylenedicarboxylate to fulvene **186** gives pentalene **191** (E = CO_2Me),[129] whereas pentalene **190** gives azulene **192** (E = CO_2Me) by ring expansion of the intermediate cyclobutene.[128]



Scheme 55.

Vilsmeier formylation of aminofulvenes has also been effected at the 2, 3 and 4 positions,[130] and 3,6-diphenyl-1,2,4,5-tetrazine undergoes cycloaddition across the 2, 3 and 4 positions, with elimination of nitrogen, to give pyridazines **193** and **194**.[131] 2-Dimethylamino-3,7-dehydrotropones **195** have been synthesized as shown in Scheme 56.[132]



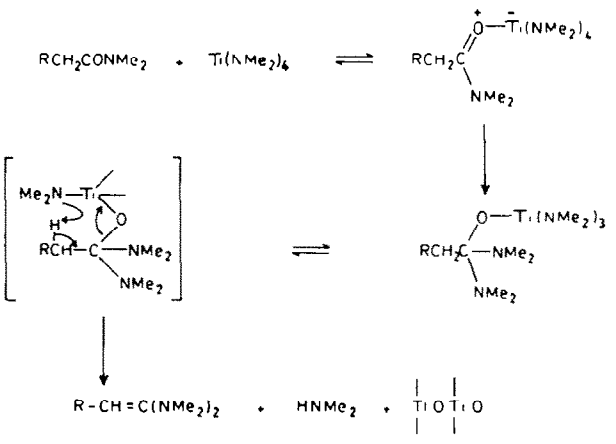
Scheme 56. Reagents: (i) $Cl_2CHCOCl$, Et_3N, 0–5°; (ii) N-bromosuccinimide; (iii) $LiNR_2$, THF, 0°.

3. CONJUGATION OF THE DOUBLE BOND WITH ADDITIONAL ELECTION DONOR GROUPS

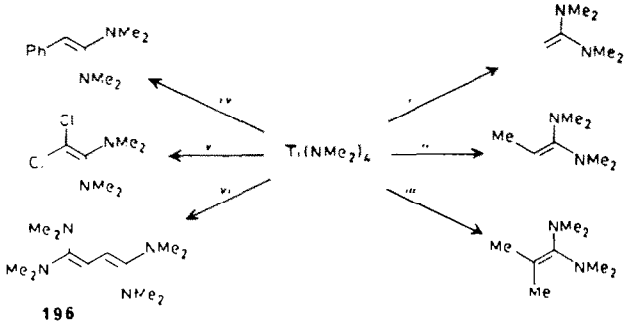
(a) 1,1-*Enediamines*

(i) *Preparation.* In contrast to enamines,[1,2] the chemistry of 1,1-bis-dialkylaminoalkenes (also known as ketene aminals or ketene-N,N-acetals or enediamines) has only been briefly studied. This has been partly due to the limitations of known methods of synthesis in that earlier methods were either multistep, poor to moderate in yield, or not adaptable to use with more volatile amines.[133] However, in 1966 a simple route to 1,1-enediamines was introduced by Weingarten and White,[134] starting from aliphatic amides and titanium tetrakisdialkylamides (Scheme 57). The reaction occurs under mild conditions, other carboxylic acid derivatives can be used (free acid, ester, anhydride), and is generally applicable (Scheme 58).[135]

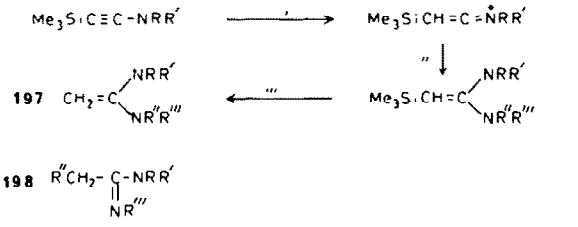
Bis-enediamines such as **196** can also be readily prepared by this means. Other methods available for the synthesis of symmetrical 1,1-enediamines include the reaction of secondary amines with ketene acetal[136] or triethyl orthoacetate,[137] sodium hydride with tetramethylacetamidinium salts,[138] and bis(dimethylamino)-t-butoxymethane (**233**) (see Scheme 79) with aromatic aldehyde azines or aryldiazomethanes (Scheme 81). A route to unsymmetrical 1,1-enediamines **197** involves reaction of silylynamines with secondary amines (Scheme 59) at 150° in the presence of an acid



Scheme 57.



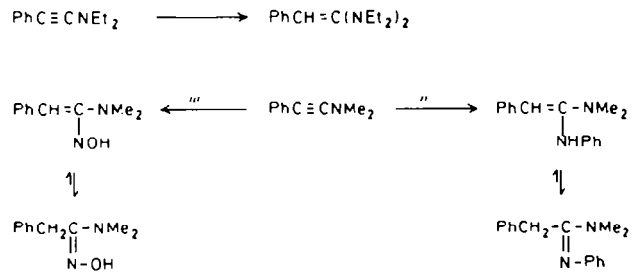
Scheme 58. Reagents: (i) CH_3CONMe_2; (ii) $CH_3CH_2CONMe_2$; (iii) $(CH_3)_2CHCONMe_2$; (iv) $PhCH_2CONMe_2$; (v) $Cl_2CHCONMe_2$; (vi) succinic anhydride.



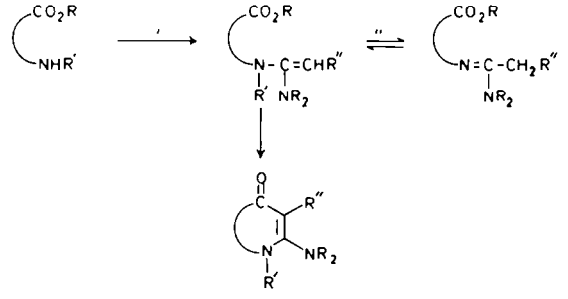
Scheme 59. Reagents: (i) H^+ (ex N-methylaniline hydrobromide) 150°, 1–10 h; (ii) R″R‴NH; (iii) $+H^+$ (ex R″R‴NH), (-Me,SiNR″R‴); R, R′ = Me, Ph; Et, Ph; Et, Et; R″, R‴ = Me, Ph: Et, Ph; Et, Et; n-Pr, Ph; i-Pr, Ph; allyl, Ph; n-Bu, n-Bu: cyclohexyl, Ph.

catalyst.[139] At higher temperatures a 1,3-alkyl shift occurs to give amidine **198** presumably via a radical intermediate. 2-Chloro-1,1-enediamines result from reaction of dichloroacetylene and secondary amines and are rearranged by strong base ($NaNH_2/NH_3$) to ynediamines.[140] The addition of secondary aliphatic, aromatic and heterocyclic amines to 1-dialkylamino pent-3-en-1-ynes gives 1,1-dienediamines [$CH_3CH{=}CHCH{=}C(NR_2)NR'R''$].[141] Addition of amines to simple ynamines has also been reported. Secondary amines give the enediamine[142] and primary amines give the tautomeric amidine[143] (Scheme 60). Addition of primary or secondary aminoesters to ynamines leads to amidines or 1,1-enediamines, respectively, which cyclise on heating to 5- or 6- membered nitrogen containing heterocycles (Scheme 61).[144] Whereas oligomerisation of ynamines **199** by nickel catalysts gives aromatic triamine **200**, in the presence of copper catalysts [Cu(I)] head-to-tail union takes place to give 1,1-ynenediamines 201 (Scheme 62).[145] Treatment of ketenimines **202** with methanesulphonyl azide is reported to give alkylidenediaziridines **203** (Scheme 63).[146]

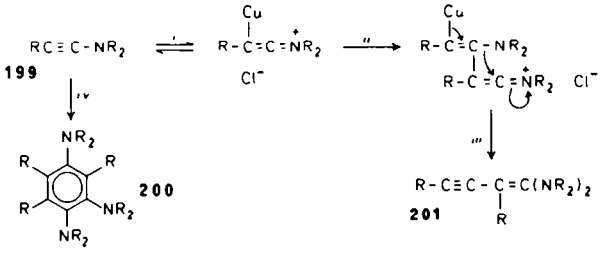
The interconversion of α-chloroenamines and 1,1-enediamines is discussed in Section 3(f).



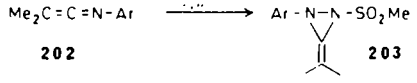
Scheme 60. Reagents: (i) Et_2NH, $\triangle$ 1 h; (ii) $PhNH_2$; (iii) NH_2OH.



Scheme 61. Reagents: (i) $R_2NC{\equiv}CR''$; (ii) $R' = H$.

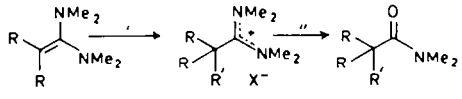


Scheme 62. Reagents: (i) CuCl (0.1 mol/mol **199**), acetonitrile, 16 h, 25°; (ii) **199**; (iii) –CuCl; (iv) $Ni(CO)_2[P(C_6H_5)_3]_2$, acetonitrile, 2 h, 80°.



Scheme 63. Reagents: (i) excess $MeSO_2N_3$, 20°, 1–2 days; (ii) $-N_2$.

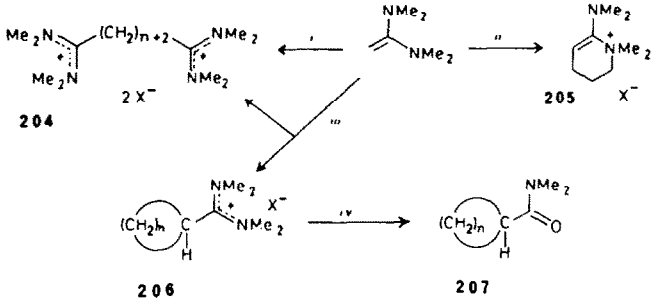
(ii) *Reactions.* Just as alkylation of enamines provides a route to α-substituted aldehydes and ketones,[1,2] so alkylation of enediamines gives substituted carboxylic acid amides (Scheme 64).[147]



Scheme 64. Reagents: (i) R'X, acetonitrile, $\triangle$ 24 h–11 days; (ii) 2N NaOH; R = H, Me; R' = Me, $PhCH_2$, $CH_2{=}CHCH_2$, n-C_4H_9.

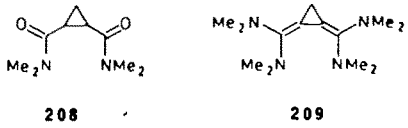
1,1-Enediamines are therefore analogous to ynamines, hydrolysis of which yields the same amides.[148] C-Alkylation is favoured by formation of the charge stabilizing amidinium cation. Alkylation of 1,1-enediamines with alkyl dihalides yields a variety of products. Methylene iodide gives the glutaramidinium salt **204** (n = 1), 1,3-diiodopropane gives the tetrahydropyridinium salt

205, whereas 1,2-dibromoethane, 1,4-diiodobutane and 1,5-diiodopentane give mainly cycloalkylamidinium salts **206**. The latter can be hydrolysed to cycloalkane carboxylic acid amides **207** (n = 2, 4, 5) (Scheme 65).[149] In contrast the reaction of 1,1,4,4-tetrakis (dimethylamino)



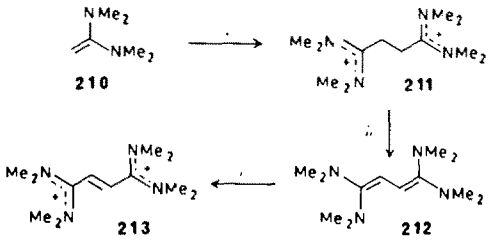
Scheme 65. Reagents: (i) ICH_2I- (ii) $I(CH_2)_3I$; (iii) $Br(CH_2)_2Br$ (n = 2) or $I(CH_2)_4I$ (n = 4) or $I(CH_2)_5I$ (n = 5); (iv) 2N NaOH.

butadiene **196** with methylene iodide resulted in intramolecular displacement of iodide anion to give the cyclopropane bis-amidinium salt which was converted into the cyclopropane dicarboxamide **208** or the cyclopropane bis-enediamine **209**.



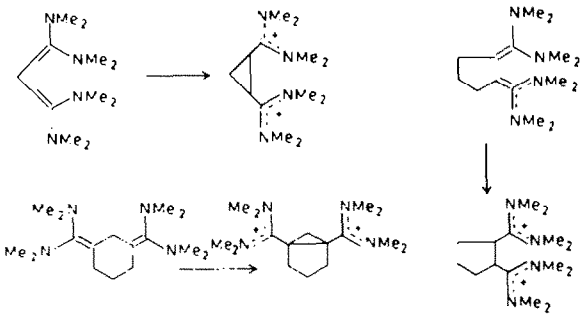
Scheme 66.

Phosgenation[170d] of β,β-bisdimethylaminostyrene and treatment with methanol gives methyl $\beta\beta$-bisdimethylamino-α-phenylacrylate. Chemical or electrochemical oxidation of 1,1-enediamines results in oxidative coupling (**210**→**213**) presumably via a radical cation intermediate.[150] Inter-



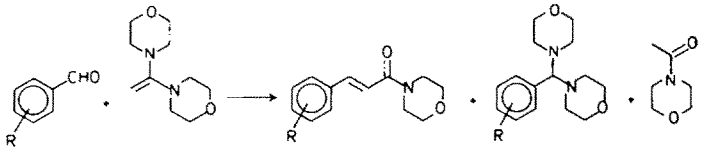
Scheme 67. Reagents: (i) oxidation ($AgNO_3$ or CBr_4 or electrochemical); (ii) **210** ($-2H^+$).

mediate **211** is believed to be formed and converted into **212** by proton abstraction. Further oxidation then gives the bis-amidinium derivative **213**. Application of the reaction to bis-enediamines results in intramolecular oxidative coupling to give cyclic or bicyclic derivatives in some cases (Scheme 68).[150a] Hydration and cyclisation to an indolo-oxazolidine also occurs.[150b]



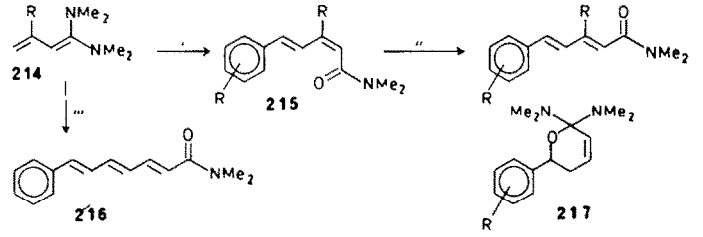
Scheme 68.

During a welcome sojourn in the enamine field, Barton *et al.* have shown that heating 1,1-dimorpholinoethene with aromatic aldehydes in benzene gives the *trans*-cinnamoyl morpholide directly. The amidinium intermediate is hydrolysed by the water liberated in the initial condensation, thus liberating morpholine which condenses with more aldehyde yielding the aminal and more water which hydrolyses unreacted 1,1-dimorpholinoethene to acetyl morpholide (Scheme 69).[151] Furthermore, the strongly nucleophilic properties of 1,1-enediamines were shown to be



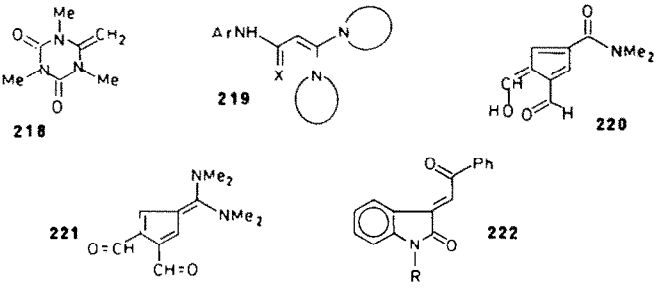
Scheme 69.

transmitted to the terminal carbon of 1,1-dienediamine **214** (R = H, Me) in that condensation with aromatic aldehydes was shown to give a dienamide. The product initially formed was shown to have a *cis*, *trans* double bond system as in **215** ($J_{H\text{-}2} = 11$ Hz). Preferential formation of the thermodynamically less stable *cis*, *trans*-product **215** implies kinetic control during the reaction and it was shown, by ^{18}O-isotope enrichment, that a cyclic intermediate such as **217** was formed which collapses with retention of the *cis*-double bond and intramolecular transfer of oxygen (Scheme 70).[151] Cinnamaldehyde gave a mixture of isomers from which only the all-*trans* product **216** was



Scheme 70. Reagents: (i) $RC_6H_4CH{=}O$; (ii) glacial acetic acid, I_2, Δ; (iii) cinnamaldehyde.

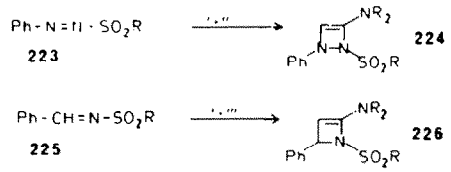
isolated. Similar condensations occur between the cyclic enediamine **218** and aliphatic and aromatic aldehydes.[152] Alkylation and acylation by isocyanates to give unsaturated amides such as **219** (X = O or S), has also been briefly reported.[152] 6,6-Bis(dimethylamino) fulvene also undergoes bis-formylation at the terminal positions of the diene system to give **220** and **221** on hydrolysis.[153] The reaction of 1,1-enediamines with electrophilic olefins such as **222** has been discussed in terms of frontier orbital interations.[154a] A novel synthesis of a cumulated triene system



Scheme 71.

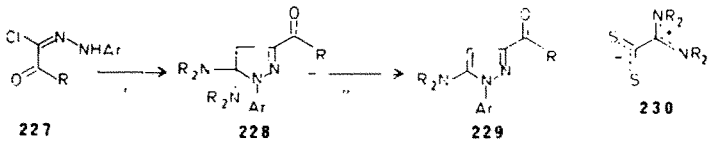
$[(Me_2N)_2C{:}C{:}C{:}C(CO_2Me)_2]$ has been effected by condensation of 1,1-bis-dimethylaminoethene with $Cl_2C{:}C(CO_2Me)_2$.[154b] Organometallic enediamines of type $(Me_2N)_2C{:}CH(MCln)$ (Me = Si, Ge, Sn, P) are obtained by reaction of 1,1-bis-dimethylaminoethene with the corresponding Group IV or V halide.[154c] Pyrano[2,3-b]pyrans have been prepared by condensation of

1-dimethylaminomethyl-2-naphthol or 5-dimethylaminomethyl-6-hydroxyquinoline with 1,1-bis-dimethylaminoethene.[154d] Heterocyclic systems can also be prepared from azosulphones **223** and N-sulphonyl imines **225** which react with 1,1-enediamines by cycloaddition thus affording the hitherto unknown 1,2-dihydro-1,2-diazetes **224** and 1,2-dihydroazetes **226**, respectively.[115]



Scheme 72. Reagents: (i) $CH_2=C(NR_2)_2$; C_6H_6; (ii) 20°, 2 days; (iii) 80°, 2 h.

1,3-Dipolar cycloaddition of nitrile imines, generated from **227**, with 1,1-enediamines gives 4,5-dihydropyrazoles **228**, in almost quantitative yield, ready deamination then leading to pyrazoles **229**.[155] In contrast to the action of sulphur on enamines, which yields thioamides, the reaction of 1,1-enediamines with sulphur under similar conditions leads to high-melting solids having structure **230**.[156] 2-Nitro-1,1-enediamines are reported to be only weakly enaminic in character,[157a] but

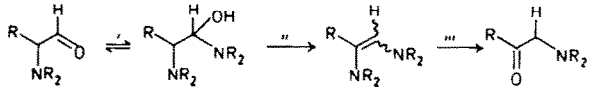


Scheme 73. Reagents: (i) $CH_2=C(NR_2)_2$, Et_3N, ambient temperature; (ii) △, $CHCl_3$ or EtOH/HCl.

nevertheless have been used as a source of both 5- and 6-membered heterocycles by reaction with nitrile oxides,[157b] isothiocyanates,[157b,c] diazonium salts,[157d] and electrophilic olefins.[157e]

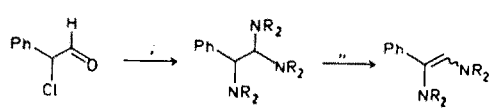
(b) 1,2-*Enediamines*

(i) *Preparation.* 1,2-Enediamines are of course enamines of α-aminoaldehydes.[158a] However, because of the instability of the latter, in particular their tendency to isomerize into the corresponding α-aminoketone, a reaction which involves the intermediacy of enediamines (Scheme 74)[158b] other routes have often been used to prepare them. For example Smolinsky *et al.* treated



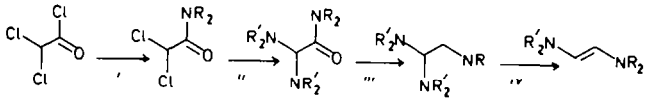
Scheme 74. Reagents: (i) R_2NH, ambient temperature; (ii) $-H_2O$; (iii) $+H_2O$.

1,2-dibromo-1-phenylethane with sodium azide in dimethylformamide and obtained 1-azido-2-bromo-1-phenylethane which in the presence of base gave α-azidostyrene. Thermolysis of this in the vapour phase afforded 3-phenyl-2H-azirine which on treatment with hot N-methylaniline gave 1-phenyl-1,2-bis(methylphenylamino)ethene.[159] A less involved route was used by Wolf *et al.* to give 1,2-bis(diethylamino)hex-1-ene from 1-bromohex-1-yne and diethylamine at room temperature.[160] However, the first method for the preparation of 1,2-enediamines, reported in 1959,[161] involved the condensation of secondary amines with α-halogenoaldehydes, and this method has been further developed by Kirrmann and Duhamel *et al.* (Scheme 75).[158a,162,163] The

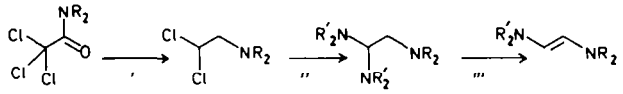


Scheme 75. Reagents: (i) Excess R_2NH; (ii) △.

method yields triamines **231** (α-aminoaminals) which on heating decompose into the enediamine. Triamines can also be produced by amination of α,α-dichloroacetyl chloride (or the methyl ester) followed by lithium aluminium hydride reduction (Scheme 76)[164,165] and by a related method introduced by Halleux and Viehe (Scheme 77).[166]

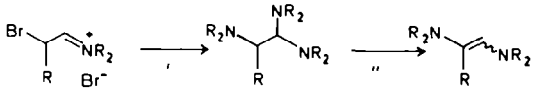


Scheme 76. Reagents: (i) R_2NH, cold; (ii) R'_2NH, △; (iii) $LiAlH_4$; (iv) △.



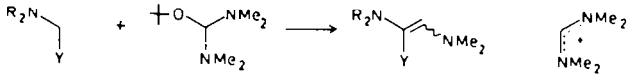
Scheme 77. Reagents: (i) $LiAlH_4$; (ii) $LiNR'_2$; (iii) △, 100°.

All three methods can be used to prepare unsymmetrical 1,2-enediamines (i.e. $R'_2NCH=CHNR_2$). Triamines can also be produced by amination of α-bromoiminium salts obtained by bromination of enamines (Scheme 78).[167]



Scheme 78. Reagents: (i) R_2NH; (ii) △.

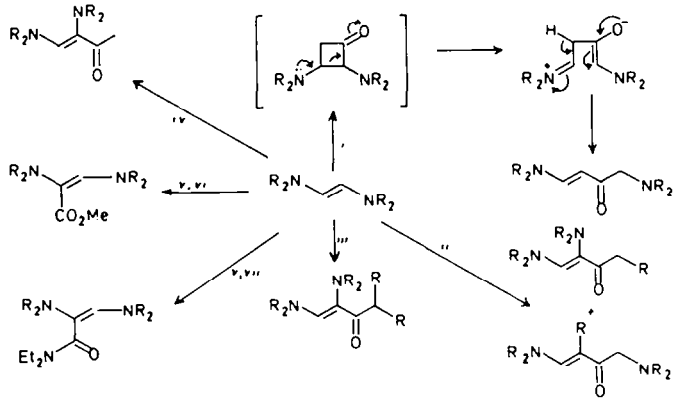
Despite their instability α-aminoaldehydes, and α-aminoketones, have also been converted to 1,2-enediamines by treatment with an excess of secondary amine either alone or in the presence of a molecular sieve or titanium tetrachloride, or by treatment with tripiperidinoarsine.[168] CH-Active dimethylaminomethylene compounds **232** react with the aminal tert-butyl ester **233** to give 1,2-enediamines **234** containing an electron withdrawing substituent (Y = COAr, CO_2Et, CN).[169a] the reaction presumably involves nucleophilic attack by the anion of **232** on the



232 **233** **234** **235**

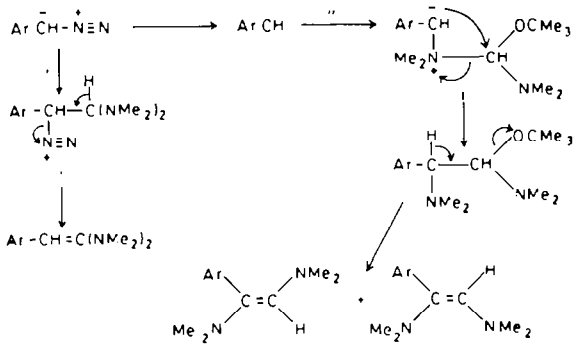
Scheme 79.

tetramethylformamidinium cation **235** derived from **233**. Acylated 1,2-enediamines (**234**; Y = RCO or ArCO) have also been prepared by amination of α-bromo-β,β-dimethoxyketones,[170a] and by acylation of 1,2-enediamines.[170b,c,d] Where cycloaddition of ketenes is involved skeletal rearrangement to β-enaminones occurs (Scheme 80).



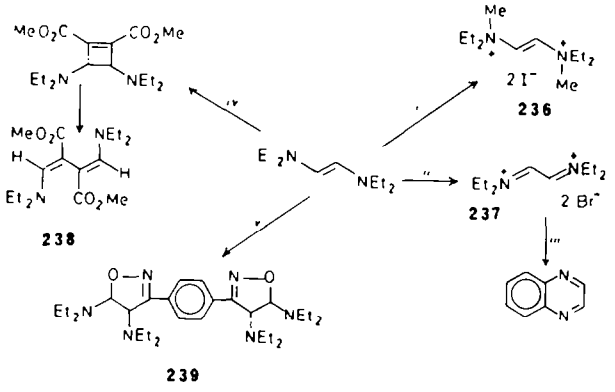
Scheme 80. Reagents: (i) $CH_2=C=O$ or CH_3COCl, Et_3N; (ii) RCH_2COCl, Et_3N; (iii) $R_2CHCOCl$, Et_3N; (iv) CH_3COCl (no Et_3N); (v) $COCl_2$, Et_3N; (vi) MeOH; (vii) Et_2NH.

Aryldiazomethanes also react with the aminal ester **233** to give a mixture of 1,1-enediamines and 1,2-enediamines.[169b] A possible mechanism is summarised in Scheme 81.



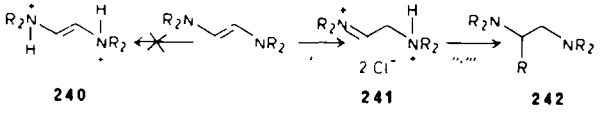
Scheme 81. Reagents: (i) **235**; (ii) **233**.

(ii) *Reactions*. The lower nucleophilic reactivity of the C atoms in 1,2-enediamines compared to that of 1,1-enediamines is reflected in their spectroscopic and chemical properties. Thus the chemical shift of the olefinic proton in 1,1-dimorpholinoethene is $\tau 6.7$[151] whereas that for 1,2-dimorpholinoethene and 1,2-dimorpholinobut-1-ene is $\tau 4.5$[164] and $\tau 5.34$[168] respectively, and reflects the higher electron density at the β-carbon of 1,1-enediamines. Reactions which occur with both 1,1- and 1,2-enediamines usually require a higher temperature for the latter[156] and a greater tendency for N-alkylation is to be anticipated. Thus Halleux and Viehe[166] have shown that reaction of 1,2-bis-(diethylamino)ethene with methyl iodide gives the bis-N-alkylated enediamine **236** and oxidation to the bis-iminium salt **237** occurs with bromine. The latter gives quinoxaline on treatment with o-phenylenediamine. Cycloaddition occurs with dimethyl acetylenedicarboxylate and terephthalonitrile oxide to give **238** and **239** respectively (Scheme 82).[166] Protonation of



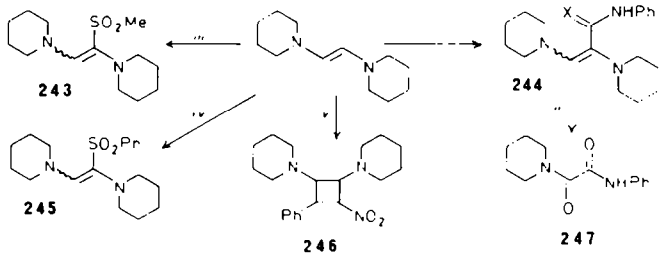
Scheme 82. Reagents: (i) MeI; (ii) Br_2; (iii) o-phenylene diamine; (iv) $MeO_2CC{\equiv}CCO_2Me$; (v) p-O←N≡CC_6H_4C≡N→O.

1,2-enediamines could give the enediammonium salt **240** or the ammonium–iminium salt **241**. Chemical evidence favours the iminium structure **241** in that reaction with Grignard reagents gives the saturated diamines **242** in high yield.[171] Reaction of 1,2-enediamines with aryl isocyanates and thioisocyanates gives the anilide **244** (X = O) and thioanilide **244** (X = S), respectively; ozonolysis



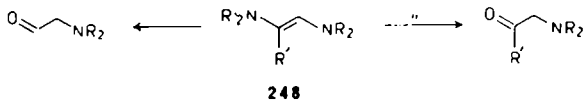
Scheme 83. Reagents: (i) HCl gas, anhyd. Et_2O, ambient temperature; (ii) RMgX; (iii) aq. NH_4Cl.

of the former gives the diamide **247**.[171] Similarly sulphene and benzenesulphonyl chloride gave the enediamine sulphones **243** and **245**, whereas β-nitrostyrene gave the cycloadduct **246** (Scheme 84).[171]



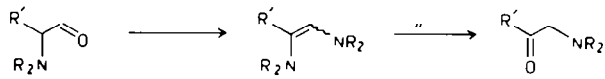
Scheme 84. Reagents: (i) PhN=C=O or PhN=C=S; (ii) O_3; (iii) $MeSO_2Cl$, Et_3N; (iv) $PhSO_2Cl$, Et_3N; (v) $PhCH{=}CHNO_2$.

Vilsmeier formylation gives the formyl enediamine on hydrolysis,[172] utilised in the synthesis of cyanine dyes, 4-aminopyrazoles, and 5-aminopyrimidinethiones.[172b] 1,2-Dipiperidino and 1,2-dimorpholinoethene are also oxidised to the diiminium salts (see **237**) which are converted into diaminoenenitriles **234** (Y = CN) by sodium cyanide and to tetramines $[(R_2N)_2CHCH(NR_2')_2]$ by secondary amines.[165] Although greater than 90% pure as isolated, unsymmetrical enediamines ($R_2NCH{:}CHNR_2'$) undergo partial and spontaneous transamination[165,166] into a mixture of $R_2NCH{:}CHNR_2$ and $R_2'NCH{:}CHNR_2'$, and *vice-versa*.[165b] Hydrolysis of 1,2-diaminoethenes **248** (R′ = H) gives the α-aminoaldelyde.[164] However in the case of higher homologues **248** (R′ = Alkyl or aryl) the hydrolysis is highly regioselective and almost invariably gives the α-aminoketone rather



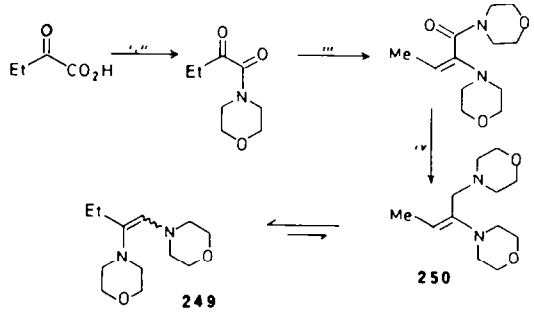
Scheme 85. Reagents: (i) hydrolysis (R′ = H); (ii) hydrolysis (R′ = alkyl or aryl).

than the α-aminoaldehyde.[162,163,168] In fact this gives a method for the transposition of α-aminoaldehydes into α-aminoketones (Scheme 86). The only apparent exception is when R′ is a bulky group, such as mesityl, when the regioselectivity is reversed and the aldehyde $[2,4,6\text{-}C_6H_2(Me)_3CH(NR_2)CHO]$ is formed exclusively.[173a]



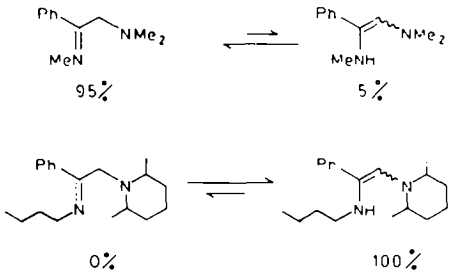
Scheme 86. Reagents: (i) R_2NH; (ii) aq. HCl.

However, in some cases double bond migration can occur to give a mixture of 1,2-enediamines and 2,3-enediamines. Thus preparation of **250** (Scheme 87) gave an equilibrium mixture of **249** (66%) and **250** (33%).[173b] When one of the amine moieties is a secondary rather than a tertiary



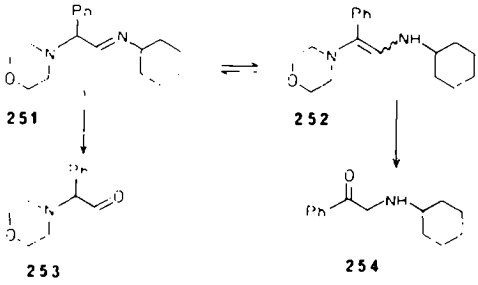
Scheme 87. Reagents: (i) PPh_3, CCl_4; (ii) morpholine; (iii) $TiCl_4$, morpholine; (iv) $LiAlH_4$.

amine, then a tautomeric equilibrium exists between the enediamine and the corresponding α-aminoaldimine or ketimine, which is temperature and solvent dependent, and is sensitive to steric effects (Scheme 88).[174] In other cases the equilibrium can be demonstrated by spectroscopic and chemical techniques.



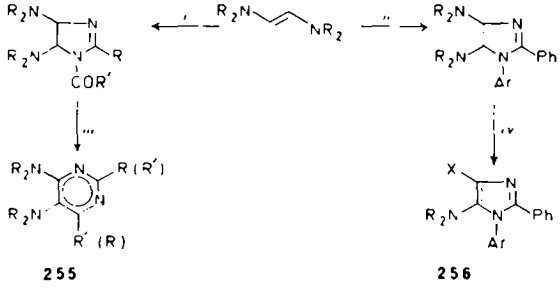
Scheme 88.

Thus hydrolysis of **251** at −5° gives only the α-aminoaldehyde **253** whereas in boiling 20% hydrochloric acid 36% of the α-aminoketone **254** is also produced, rising to 60% if imine **251** is preheated to 150° and then hydrolysed at −5°. As isolated imine **251** shows infra red absorption at 1670 cm^{-1} (C = N) but on heating to 150° new absorptions at 1640 and 3300 cm^{-1} appear, attributed to the $\nu_{C=C}$ and ν_{NH} vibrations of **252**.[174a]



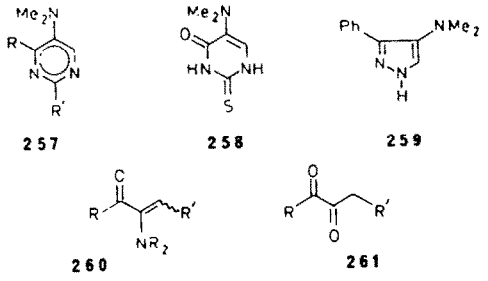
Scheme 89.

1-Acyl and 1-aryl-4,5-diamino-4,5-dihydrimidazoles have been prepared by cycloaddition of N-chloro-N′-acyl- and N-chloro-N′-arylamidines to enediamines (Scheme 90).[175,176] The former undergo thermolysis to pyrimidines **255**[177] and the latter can be oxidised (X = R_2N) or deaminated (X = H) to imidazoles **256**.[176] 1-Benzoyl, 1-cyano- and 1-ethoxycarbonyl-1,2-bis(dimethylamino)-



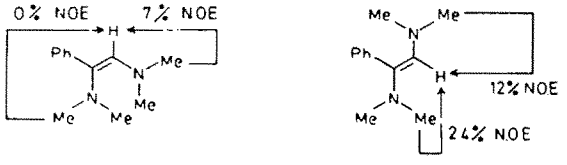
Scheme 90. Reagents: (i) R′CONHC(R)=NCl, C_5H_5N, $CHCl_3$, room temperature; (ii) ArNHC(Ph)=NCl, C_5H_5N, $CHCl_3$; (iii) △, xylene; (iv) $Et_3N^+HCl^-$, 110–125° or chloranil, 80–100°.

ethenes **234** (R = Me; Y = PhCO, CN, CO_2Et respectively) undergo cyclisation with amidines, guanidine or thiourea to give pyrimidines **257** and **258**, and with hydrazine to give pyrazole **259**.[169] α-Enaminones **260** are obtained by the action of Grignard reagents (R′MgX) on 1-acyl-1,2-enediamines **234** (Y = RCO or ArCO) hydrolysis of which gives α-diketones **261**.[170a]



Scheme 91.

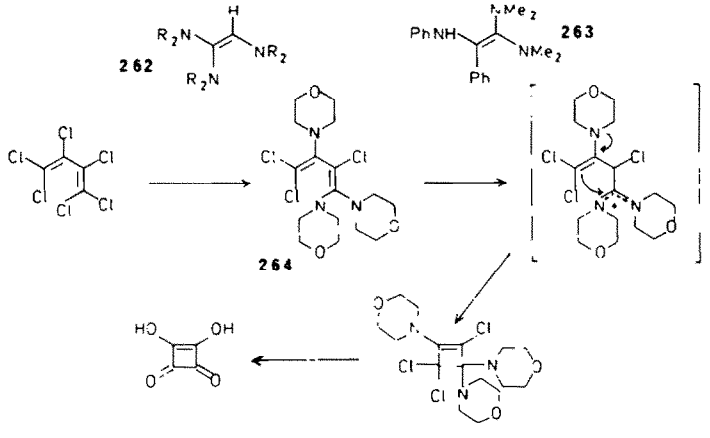
Although enediamines having a disubstituted double bond exist in the *trans*-configuration,[166] trisubstituted double bond isomers can have the *Z* or *E* configuration. The actual configuration can be readily determined by the greater nuclear Overhauser enhancement of the olefinic signal of the latter on irradiation of the amine alkyl substituents (Scheme 92).[178]



Scheme 92.

(c) *Enetriamines*

(i) *Preparation.* The reaction between glyoxal and secondary amines,[179a] or between the bis-iminium salt **237** (Scheme 82) and secondary amines,[165] gives 1,1,2,2-tetra-aminoethanes, which on distillation under reduced pressure yield the corresponding 1,1,2-triaminoethene **262** in high yield. Condensation of aminal ester **233** with benzylideneaniline at 160–170° gives enetriamine **263**, but the reaction does not appear to be applicable to Schiff's bases in general.[179b]



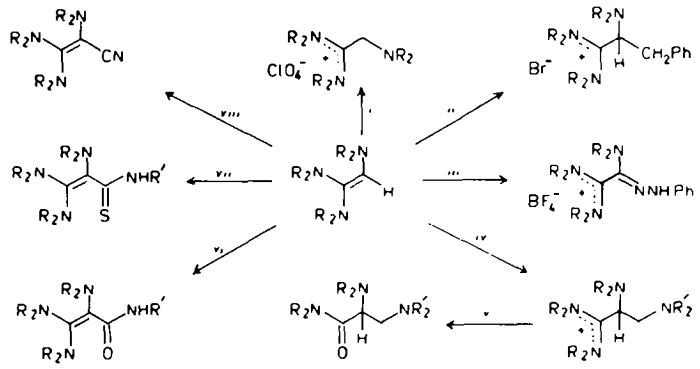
Scheme 93.

1,1,3-Dienetriamines **264** may be prepared by condensation of secondary amines with hexachlorobutadiene. Cyclisation and hydrolysis then leads to squaric acid (Scheme 93).[179b]

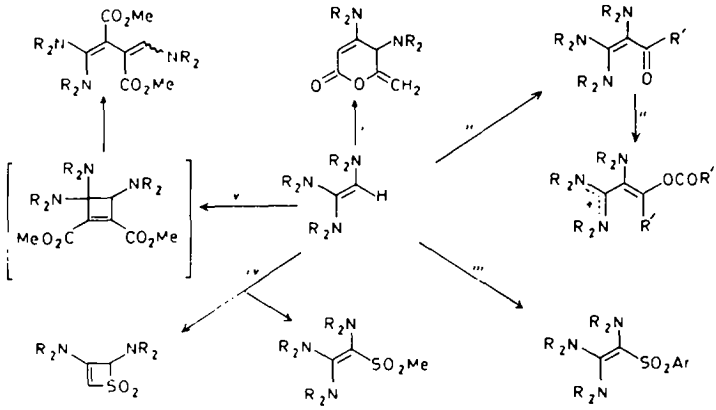
(ii) *Reactions.* The reactions of 1,1,2-enetriamines have been investigated by Böhme and Höver and are summarised in Schemes 94 and 95.[180]

(d) *Di- and tri-enediamines*

(i) *Preparation.* 1,1-Dienediamine **265** has been prepared by nucleophilic attack by lithium dimethylamide on the corresponding α-chlorodienamine (see Section 3(f), Scheme 122).[222] Acyclic 1,4-dienediamines of type **266** are in effect bis-enamines of succindialdehyde. However, there

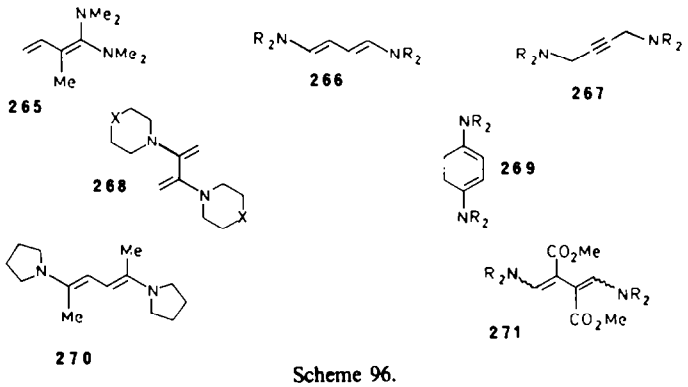


Scheme 94. Reagents: (i) $HClO_4$; (ii) $PhCH_2Br$; (iii) $PhN{=}NBF_4$; (iv) $R_2\overset{+}{N}{=}CH_2Cl^-$; (v) H_2O; (vi) $R'N{=}C{=}O$; (vii) $R'N{=}C{=}S$; (viii) $ClC{\equiv}N$.



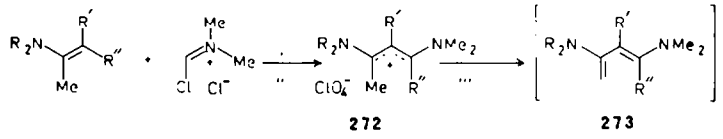
Scheme 95. Reagents: (i) $CH_2{=}C{=}O$; (ii) $R'COCl$, Et_3N; (iii) $ArSO_2Cl$, Et_3N; (iv) $CH_2{=}SO_2$; (v) $MeO_2CC{\equiv}CCO_2Me$.

appear to be no literature reports using this dialdelyde as starting material. The first synthesis by other means appears to be that of McKeever and Nemec,[181] who passed 1,4-bis(dimethylamino)but-2-yne over chromium oxide-containing catalysts at 300–450°, and thus obtained 1,4-bis(dimethylamino)buta-1,3-diene **266** (R = Me). Later Fegley, Bortnick and McKeever showed that the rearrangement could be effected at lower temperatures using a dispersion of sodium in xylene–hexane medium.[182] The initial product isolated was assigned the *cis-trans* diene configuration and this rearranged to *trans-trans*-1,4-bis(dimethylamino)buta-1,3-diene on standing at room temperature (2 months) or more rapidly in the presence of trace amounts of water or acid (24 hr at room temperature or 3 hr at 67–70°).[182] The rearrangement of **267** to **266** could be effected for a variety of amine substituents ($R_2N = Me_2N$, Et_2N, n-Bu_2N, morpholino, piperidino, pyrrolidinyl) using metallic Na or Li in yields of 80–90%. The use of Alfin catalyst, metallic K, and sodamide resulted in reduced yields (55%, 9% and 12%, respectively), and sodium acetylide and metallic Ca were ineffective.[182] 2,3-Dienediamines of type **268** were prepared[183a] from butane-2,3-dione by the titanium tetrachloride method of White and Weingarten.[183b] Cyclic 1,4-dienediamines **269** (R_2N = morpholino, piperidino and pyrrolidinyl) may be prepared from cyclohexa-1,4-dione by heating with a slight excess of the amine in benzene, with azeotropic removal of water.[184,185] However, the reaction failed with cycloheptane-1,4-dione and cyclooctane-1,4-dione.[186] The acyclic dienamine **270** has been prepared from hexane-2,5-dione and pyrrolidine in boiling benzene, in the absence of acid catalyst, but the corresponding reaction with piperidine, diethylamine and di-n-butylamine failed.[186] Dienediamines containing carboalkoxy groups at the 2,3-positions can readily be obtained by cycloaddition of alkyl acetylene dicarboxylates (Section 3b(ii); Scheme 82) and thermolysis of the resulting cyclobutene adduct, as for example **271** (R_2N = piperidino, morpholino).[186] 1,6-Trienediamines have also been prepared by base catalysed rearrangement of non-conjugated diynes. However in this case cyclisation also occurs. For example



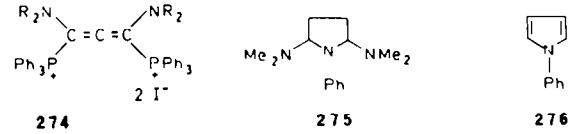
Scheme 96.

1,9-bis(disubstitutedamino)non-2,7-diynes rearrange to 1,2-bis(β-disubstitutedaminovinyl)cyclopentenes on treatment with butyl lithium. The mechanism involves cyclisation of an initially formed allenic carbanion followed by a 1,5-sigmatropic hydrogen shift from the one side chain to the other.[187] Although not isolated 1,3-dienediamines **273** are formed by deprotonation of 1-alkylvinamidinium salts **272** (Scheme 97) (see Section 3d(ii) for their reactions).[188] A



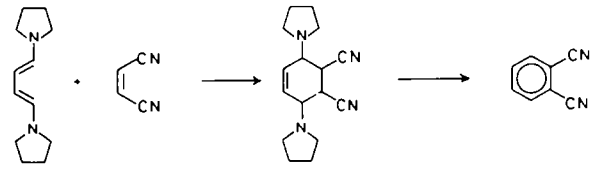
Scheme 97. Reagents: (i) CH_2Cl_2, 0°; (ii) $NaClO_4$, H_2O; (iii) NaH, THF, 25°; R′ = CO_2R, H; R″ = H, Ph.

1,3-allenediamine **274** containing phosphonium substituents has been reported, and its geometry and electronic structure discussed.[189]



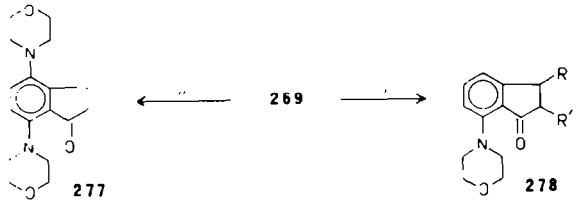
Scheme 98.

(ii) *Reactions.* Treatment of 1,4-bis(dimethylamino)buta-1,3-diene with primary amines, in the presence of acid catalysts, results in cyclisation to a substituted pyrrolidine **275**. When heated dimethylamine is eliminated to give the N-substituted pyrrole **276**, by an overall intramolecular transamination process.[190] Intermolecular transamination occurs on use of secondary amines.[191] As expected 1,1-dienediamines (Scheme 123) and 1,4-dienediamines (Scheme 99) readily undergo the Diels–Alder reaction with electron deficient dienophiles such as fumaronitrile, acrylonitrile and ethyl acrylate. In the case of the 1,4-dienediamines aromatisation of the cycloadducts, by loss of secondary amine, readily occurs on heating (Scheme 99). However methacrylonitrile, styrene and vinyl acetate failed to react, and maleic anhydride and butyl vinyl ether gave only polymeric products.[192]



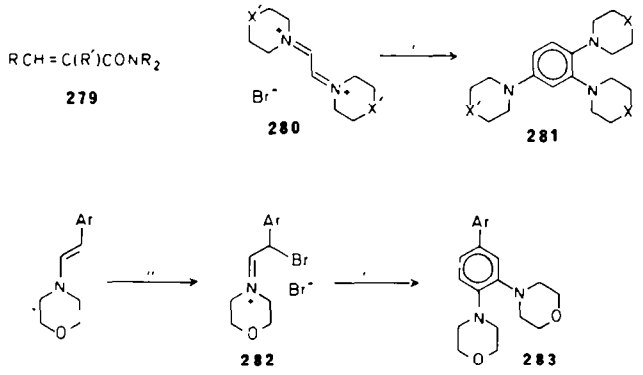
Scheme 99.

The reaction of $\alpha\beta$-unsaturated acid chlorides with cyclic dienediamine **269** (R_2N = morpholino) was shown to give the 7-morpholinoindan-1-one **278** (R = R′ = H; R′ = H, R = Me, Ph; R = H, R′ = Me) or 4,7-dimorpholinoindan-1-one **277**.[193] Yields were low owing to competing aromatisation of **269** and to formation of the $\alpha\beta$-unsaturated acid morpholide **279** (R_2N = morpholino). When the same reaction was applied to the acyclic dienediamines **266** and **271** only unchanged starting material and the unsaturated carboxamides **279** were isolated.[186]



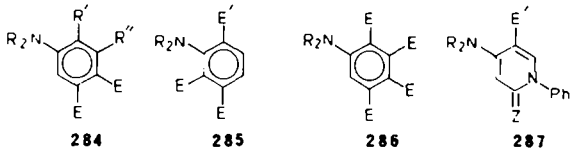
Scheme 100. Reagents: (i) RCH=C(R′)COCl, benzene, △; (ii) ClCH=CHCOCl, benzene, △.

1,2,4-Triaminobenzenes **281** and 3,4-diaminobiphenyls **283** have been formed by reaction of 2,3-dienediamines **268** with 1,2-ethanediiminium dibromides **280** and α-bromoiminium bromides **282**, respectively.[183a,194]



Scheme 101. Reagents: (i) **268**, Et_3N, CH_2Cl_2, $-15°$ to $-50°$; (ii) Br_2, THF, $-5°$.

Evidence for the formation of the unstable 2,3-dienediamines **273** rests on their reaction with dimethyl acetylene dicarboxylate. [4 + 2] Cycloaddition occurred to give **284** as the main product, but **285** and **286** were also isolated. The former (**285**) is presumably formed by [2 + 2] cycloaddition at the less substituted terminal double bond, followed by ring opening of the cyclobutene intermediate and electrocyclic ring closure of the resulting triene. The latter (**286**) is derived by reaction of the initial dipolar intermediate with a second equivalent of acetylenic ester. When heterocumulenes such as phenylisocyanate or isothiocyanate were used as trapping agents for **273**, the α-pyridine and α-thiopyridone **287** (Z = O or S) respectively, were isolated.[188]

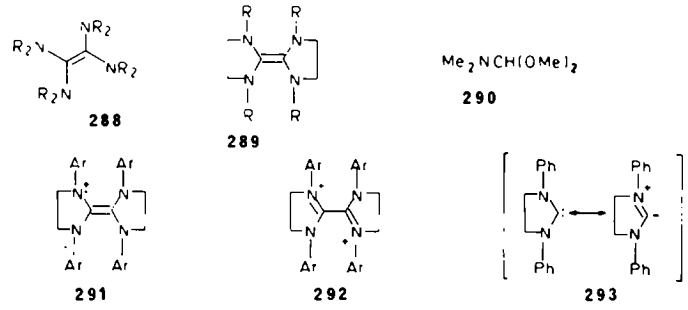


Scheme 102. E = CO_2Me; E′ = CO_2Et.

(e) *Enetetramines*[195]

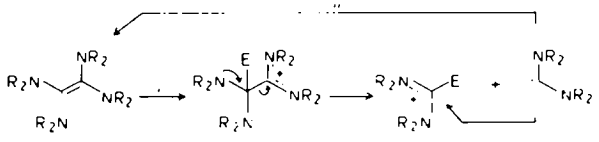
(i) *Preparation.* Tetrakis(dimethylamino)ethylene **288** (R = Me) was first prepared by Pruett *et al.*[196] from dimethylamine and chlorotrifluoroethylene, presumably by alternate amine addition and HX elimination. Tetraaminoethylenes in which the geminal amine substituents are part of the same

ring [i.e. $\Delta^{2,2'}$-bis(imidazolidines) **289**] are derived by condensation of N,N′-diarylethylenediamines with chloral or alkyl orthoformates.[197] A general method for the preparation of tetrakis(dialkylamino)ethylenes **288** (R_2 = dialkyl or cycloalkyl) and N,N′-dialkyl-$\Delta^{2,2'}$-bis(imidazolidines) **289** (R = alkyl) involves condensation of the required aliphatic secondary amine with 1,1-dimethoxytrimethylamine **290**.[198]



Scheme 103.

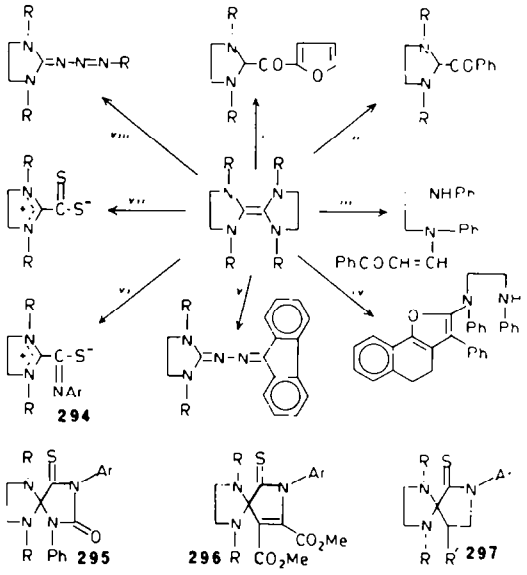
(ii) *Reactions*. Tetraaminoethylenes are extremely reactive and powerful electron donors. Exposure of **289** (R = Aryl) to air and other oxidising agents produces a violet colour due to the radical cation **291**, further oxidation of which gives 1,3-diphenylimidazolid-2-one (air) or the dication **292** (I_2 or Hg^+).[199] In addition the aliphatic tetraaminoethylenes **288** and **289** (R = alkyl) exhibit chemiluminescence† on exposure to air in the presence of protic solvents, emitting visible light in the 500 nm region.[198,200] The high sensitivity of tetraaminoethylenes to oxygen and their ability to chemiluminesce in the presence of oxygen can be used for the removal of traces of oxygen, for the detection of traces of oxygen, for the quantitative determination of oxygen, and for the production of light.[195] Highly coloured charge transfer complexes are also formed with organic π-electron acceptors such as tetracyanoethylene, trinitrobenzene, *m*-dinitrobenzene, nitrobenzene, chloranil, etc. which are sufficiently stable to be used as pigments for coloured inks or for the production of duplicating sheets, the one sheet being treated with the tetraaminoethylene donor and the other sheet with a π-acceptor.[201] However most reactions of tetraaminoethylenes lead to products derived from only half of the molecule and this led Wanzlick *et al.*, who pioneered most of the early work in this area, to postulate an equilibrium between the tetraaminoethylene **289** and the nucleophilic carbene species **293**.[197,202] However, this hypothesis was convincingly ruled out by the absence of any unsymmetrical tetraaminoethylenes in cross-over experiments involving two different but symmetrical bis-imidazolidines being heated to high temperatures under conditions at least as drastic as any of the reported reactions of tetraaminoethylenes.[203] A mechanism proposed[203] for all reactions (except air oxidation) involving C–C bond fission is therefore as shown in Scheme 104. However some uncertainty exists as to whether a free diaminocarbene [$:C(NR_2)_2$] is formed as such or is merely transferred from one reacting species to another.



Scheme 104. Reagents: (i) E^+; (ii) dimerization.

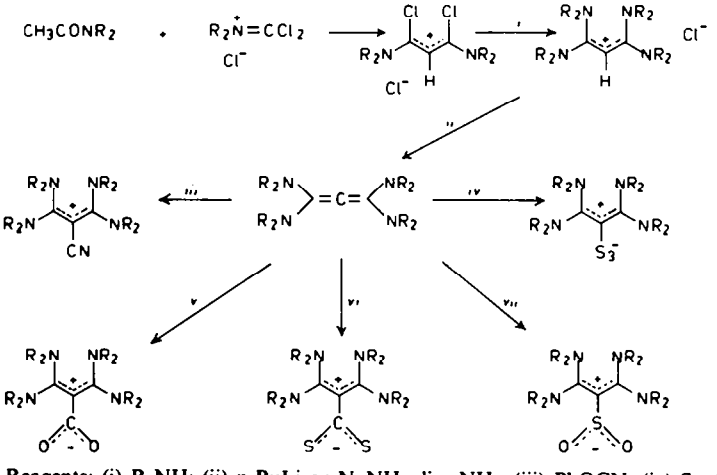
Some of the reactions of tetraaminoethylenes falling into this category are summarised in Scheme 105.[202b,204] The 1,3 dipolar system **294** undergoes further reaction with dipolarophiles such as phenyl isocyanate and dimethyl acetylenedicarboxylate to give **295** and **296**, and methyl vinyl ketone, methyl acrylate and acrylonitrile give **297** (R′ = COMe, CO_2Me, CN, respectively).[205]

†Tetraaryl-$\Delta^{2,2'}$-bis(imidazolidines) (**289**, R = Ar) also exhibit chemiluminescence in the presence of a fluorescer such as dibromoanthracene [F. Roeterdink, J. W. Scheeren and W. H. Laarhoven, *Tetrahedron Letters* 2307 (1983)].



Scheme 105. Reagents: (i) furfural, 135°; (ii) benzaldehyde, 130°; (iii) acetophenone, 110°; (iv) 2-benzylidene-1-tetralone, xylene, 135°; (v) 9-diazofluorene, xylene, 135°; (vi) phenyl isothiocyanate, THF; (vii) CS_2; (viii) p-toluenesulphonyl or p-nitrophenyl or diphenylphosphonyl azides, C_6H_6, 0°.

Tetrakis(dimethylamino)-1,3-dienes, tetrakis(dimethylamino)-1,4-dienes and tetrakis(dimethylamino)-1,6-dienes have been referred to in Section 3(a) (Schemes 58, 66, 67 and 68). Tetrakis(dialkylamino) allenes have also been reported. Reaction of an N,N-disubstituted acetamide with N-dichloromethylene-N,N-dialkylammonium chloride gives the corresponding 1,3-diamino-1,3-dichloroallyl cation. Treatment of the latter with secondary amines yields 1,1,3,3-tetrakis(dialkylamino)allyl cations which can be deprotonated with n-butyllithium or sodium amide in anhydrous liquid ammonia to give the allenetetramine (Scheme 106).[205] These compounds are comparable in reactivity to ynamines and ethylenetetramines. They can be distilled and stored in the absence of air, but react spontaneously with air. They are hydrolysed to the β,β-diaminoacrylamide and react readily with phenylcyanate, sulphur, carbon dioxide, carbon disulphide and sulphur dioxide as summarised in Scheme 106.[205]



Scheme 106. Reagents: (i) R_2NH; (ii) n-BuLi or $NaNH_2$, liq. NH_3; (iii) PhOCN; (iv) S_8, CH_2Cl_2/Et_2O; (v) CO_2; (vi) CS_2; (vii) SO_2.

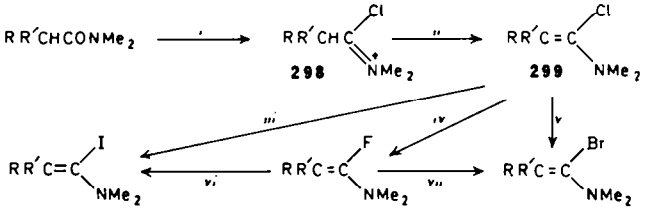
(f) α-*Haloenamines*†

α-Haloenamines and keteniminium salts have been the subject of a detailed and comprehensive review by Ghosez and Marchand-Brynaert, covering literature up to early 1975.[206] Nevertheless,

†β-Haloenamines have been referred to in Refs. 1 and 2 (Sections 5(F) and 2(A) respectively).

in view of their synthetic importance a brief survey of the salient features of α-haloenamine chemistry is included in this review together with further developments which have occurred since 1975. The use of α- and β-haloenamines for the synthesis of metallo tertiary enamines (as opposed to metallo derivatives of secondary enamines[2]) will be referred to in a later section.

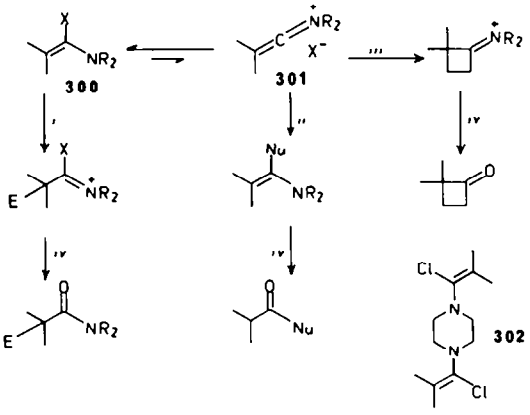
(i) *Preparation.* Several methods exist for the preparation of α-haloenamines, but none of them is entirely general and the method chosen usually depends on the substitution pattern required. α-Haloenamines **299** having a tetra-substituted double bond are the most stable and most accessible, and can usually be prepared by HCl elimination from amide chlorides **298**, which are readily prepared from tertiary amides (Scheme 107).[207] This method is also applicable to di- **299** (R = R′ = H) and tri-substituted α-haloenamines **299** (R = alkyl or aryl, R′ = H) but regeneration of the enamine system may result in further acylation, for example by phosgene[207b] or amide



Scheme 107. Reagents: (i) PCl_5 or $POCl_3$ or $COCl_2$ or pyrocatechol phosphortrichloride; (ii) Et_3N or NaOMe or △; (iii) KI; (iv) KF; (v) excess CH_2Br_2, △ 24 h; (vi) LiI; (vii) LiBr.

chloride, or further elimination to give an ynamine. However these complications can be avoided by optimisation of the experimental conditions, as for example by using phosgene in the presence of collidine followed by reaction with one equivalent of sodium methoxide.[207b] Interconversion of α-haloenamines is readily effected by treatment with the appropriate potassium or lithium halide (Scheme 107).[208,220] The conversion of 1,1-enediamines into tetra-substituted α-chloroenamines (i.e. **299**, R = R′ = Me) has been effected by reaction with phosphorus trichloride or dichlorophenylphosphine,[209] and the reverse process [Scheme 111, Reaction (iii)] also appears to work well in a number of cases.[206,210]

(ii) *Structure and reactivity.* α-Haloenamines differ from other enamines in that the halide anion is a good leaving group and an equilibrium is set up with the ionised keteniminium salt **301** (Scheme 108). Consequently they will react with electrophiles at their β-carbon like an enamine, but at their

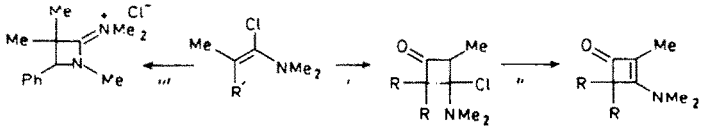


Scheme 108. Reagents: (i) E^+; (ii) Nu^-; (iii) $Ch_2{=}CH_2$; (iv) H_2O.

α-carbon with nucleophiles. Furthermore, in their heterocumulene form **301**, they also undergo extremely facile [2 + 2] cycloaddition† with unactivated olefins[211] including ethylene,[212] (Scheme 108), acetylene,[214] and conjugated dienes (Scheme 113). In the latter case the product depends on

†Recent work indicates this to be a stepwise process involving initial attack at the iminium group [H. Saimoto, C. Houge, A.-M. Hesbain-Frisque, A. Mockel and L. Ghosez, *Tetrahedron Letters* 2251 (1983)].

whether the diene can adopt a transoid conformation or is fixed in a cisoid-configuration. With transoid dienes the keteniminium ion **301** undergoes a [2 + 2] cycloaddition, like a ketene, to give a cyclobutane derivative. With fixed cisoid dienes such as cyclopentadiene and cyclohexadiene, the keteniminium ion behaves like an activated allene and [4 + 2] cycloaddition occurs across the C=N bond.[211,213] As Ghosez and Marchand-Bryaert have pointed out,[206] the difference in behaviour between a ketene and the keteniminium ion **301** can be attributed to the lack of a "push" component in the latter. In ketenes the electron density at the terminal carbon atom is increased owing to conjugative interaction with the oxygen lone pair, whereas the keteniminium ion the terminal carbon is electron deficient owing to electron withdrawal by the positively charged iminium group. In addition to this mode of reaction, cycloadditions also occur with the enamine form **300**. For example ketenes give a chlorocyclobutanone which readily eliminates HCl to give a cyclobutenone (Scheme 109).[206] Unlike "normal" enamines,[1,2] α-chloroenamines also cyclise onto the imine group of Schiff bases to give azetidine salts (and β-lactams on hydrolysis), owing to the displacement of chloride anion (Scheme 109).[217]



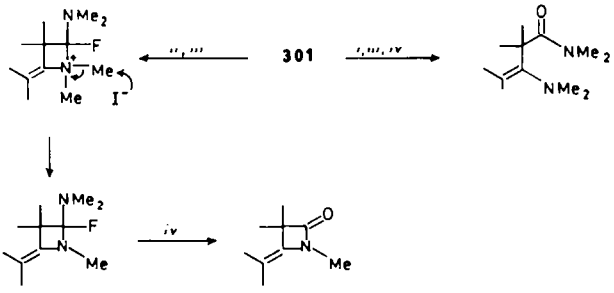
Scheme 109. Reagents: (i) $R_2C{=}C{=}O$ (R = Me, Ph; R′ = H); (ii) Et_3N or NaOH; (iii) PhCH=NMe, CH_2Cl_2, 20° (R′ = Me).

Spectroscopic and X-ray evidence indicate that the covalent structure **300** is the more stable and predominates at equilibrium. For example the IR spectra of α-haloenamines shows no absorption due to cumulenes around 2000 cm^{-1}, but does show the enamine double bond absorption at 1635–1640 cm^{-1}. The direct observation of stable long-lived ketene iminium salts is only made possible by the use of very weakly nucleophilic counterions (i.e. $ZnCl_3^-$, PF_6^- or BF_4^-). These salts are obtained when α-chloroenamines are treated with the appropriate silver salt ($AgPF_6$ or $AgBF_4$) or zinc chloride, or by reaction of an α-fluoroenamine with boron trifluoride. The IR spectra then shows the cumulated double bond absorption at 2020–2030 cm^{-1}.[206] Surprisingly X-ray data on **302** shows that the N lone pair orbital is orthogonal to the π-orbital of the double bond.[206] Normal enamine pπ-conjugation[1] is therefore minimal in the ground state, although clearly this cannot be the case in an enamine-type reaction at the β-carbon[1].

Although there is no quantitative data yet available concerning the reactivity of α-haloenamines, it appears that α-fluoroenamines are more reactive towards electrophiles than are α-chloroenamines which are less reactive than the corresponding enamine. For example attempted acylation of tetramethyl-α-chloroenamine failed,[206] in contrast to the corresponding α-fluoroenamine[208] and "normal" enamine[1]. This can probably be attributed to the inductive electron withdrawal of the halogens being effectively neutralised by the increased mesomeric electron donation of fluorine relative to chlorine. By analogy with normal enamines the reactivity can also be expected to vary with the number and nature of the substituents at C-2, on the amine moiety, and on the solvent.[1] Certainly the thermal stability of trisubstituted α-chloroenamines [$R'CH = C(Cl)NR_2$] depends on the amine moiety. The less basic enamines [R_2N = Ph(Me)N; R′ = Me, Ph] can be distilled and stored, whereas the morpholine enamine dimerizes on standing overnight. The more basic enamines ($R_2N = Me_2N$, pyrrolidinyl) self-condense even more readily and can only be kept for a few hours in solution.[215]

With regard to their reaction with nucleophillic reagents, α-chloroenamines appear to be more reactive than α-fluoroenamines in aprotic solvents as is to be expected from bond energy considerations. Thus, reaction of tetramethyl-α-chloroenamine with sodium methoxide occurs readily at room temperature in ether, conditions under which the corresponding α-fluoroenamine is inert. The rate of nucleophilic displacement of halide anion is increased by Lewis acids and polar solvents. Thus α-chloroenamines react instaneously with silver salts (AgCN and AgN_3) to give the corresponding α-cyanoenamine and azirine respectively (Scheme 111), and tetramethyl-α-fluoroenamine reacts rapidly with lithium methoxide. 1-Chloro-1-dimethylamino-2-phenylprop-1-ene and sodium azide do not react in ether at room temperature, whereas

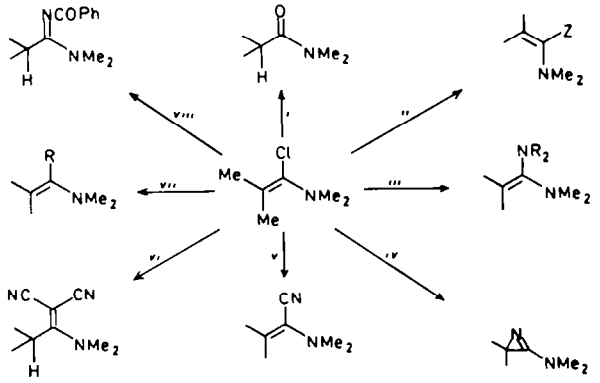
in dimethylformamide the aminoazirine is rapidly formed.[206] The course of the reaction of the keteniminium tautomer **301** can also be affected by the nature of the counter ion (X^-) (Scheme 110).[218] Aminoalkenylation of electron-rich aromatics (furan, pyrrole, anisole, N,N-dimethyl-



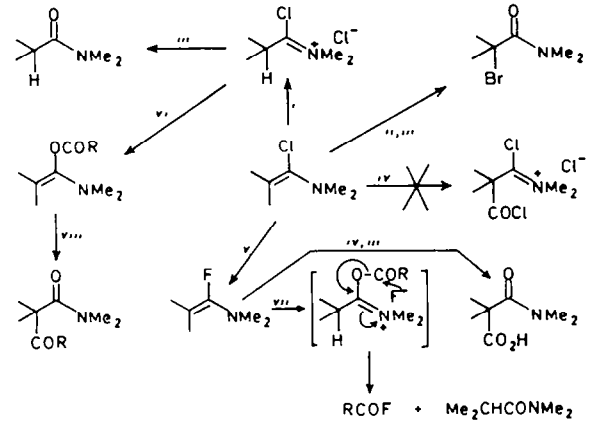
Scheme 110. Reagents: (i) X = BF_4; (ii) X = I; (iii) $(CH_3)_2C{=}C(F){-}N(CH_3)_2$; (iv) H_2O.

aniline) by alkyl-substituted α-chloroenamines readily occurs in the *absence* of Lewis acid catalysts (Scheme 113). The enamine function in the product can subsequently be hydrolysed to the corresponding ketone.[216]

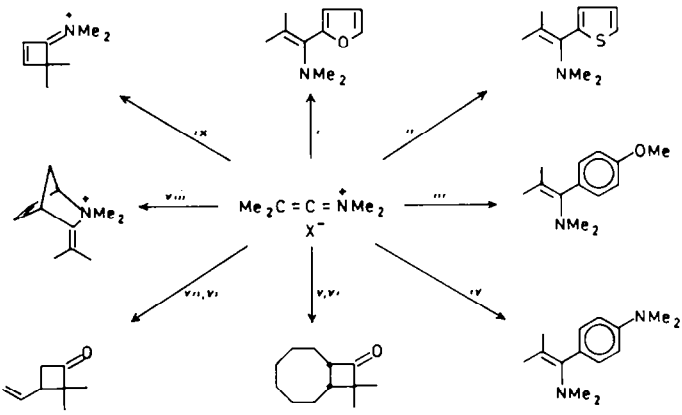
(iii) *Reactions.* It is clear from the preceding discussion that the versatile chemical behaviour and great synthetic potential of α-haloenamines is due to their ability to react at the β-carbon with electrophiles, as an amide enolate anion equivalent [$R_2C{=}C(NR_2){-}O^-$], or at the α-carbon with nucleophiles, as an acyl cation equivalent ($R{-}\overset{+}{C}{=}O$), or at both positions as a heterocumulene ($R_2C{=}C{=}\overset{+}{N}R_2$). Specific examples of all three types of reaction are summarised in Schemes 111, 112 and 113.[206]



Scheme 111. Reagents: (i) aq. NaOH; (ii) RONa (Z = OR) or RSNa (Z = SR); Et_2O or THF, 20°; (iii) R_2NH or $LiNR_2$; (iv) NaN_3, CH_3CN, 20°; (v) KCN, CH_3CN, △ 35 h or Zn $(CN)_2$, $CHCl_3$, △ 4 h or AgCN, CCL_4, −10° 1 h; (vi) $NaCH(CN)_2$, 20°; (vii) RMgBr (R = Me, Ph); (viii) $PhCONH_2$, Et_3N.

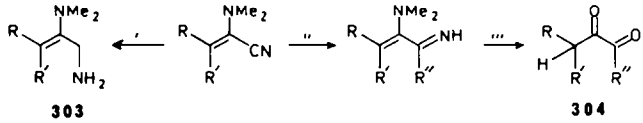


Scheme 112. Reagents: (i) dry HCl; (ii) Br_2, 0°; (iii) H_2O; $COCl_2$, 0°; (iv) $COCl_2$, 0°; (v) KF, △; (vi) RCO_2H, Et_3N, 20°; (vii) RCO_2H, −60° to 20°; (viii) △, 120°.



Scheme 113. Reagents: (i) furan, Et_3N, CH_3CN, Δ (X = Cl); (ii) thiophene, Et_3N, CH_2Cl_2, 40° (X = $ZnCl_3$); (iii) anisole, Et_3N, CH_2Cl_2, 40° (X = $ZnCl_3$); (iv) N,N-dimethylaniline, Et_3N, CH_3CN, Δ 4 h (X = Cl); (v) cyclooctene, CH_2Cl_2, 20° (X = BF_4); (vi) H_2O; (vii) butadiene, CH_2Cl_2, 20° (X = BF_4); (viii) cyclopentadiene, CH_2Cl_2, 20° (X = BF_4); (ix) acetylene, CH_2Cl_2, 20° (X = BF_4).

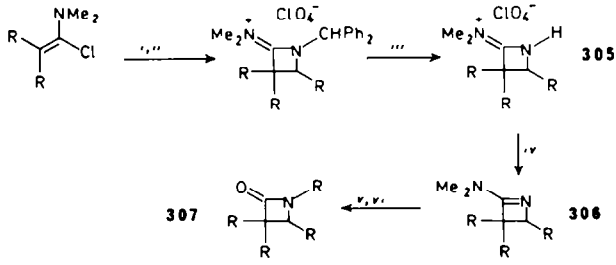
Some of these reactions deserve further comment. For example, the conversion of carboxylic acids into acyl fluorides by treatment with α-fluoroenamines [Scheme 112, Reaction (vii)] can also be applied to α-chloro-, α-bromo and α-iodoenamines to give the corresponding acyl chloride, bromide or iodide.[219] Thermally unstable acyl halides can be obtained in high yields (94–100%) at room temperature or below under essentially neutral conditions. The method has also been used for the stereospecific conversion of phosphorothioic acids [i.e. HS(O)P(OMe)OEt] into phosphoryl halides [i.e. EtO(MeO)P(O)X, where X = F, Cl, Br][220] and alcohols into alkyl halides RX (X = Cl, Br, I).[219] The α-cyanoenamine synthesis [Scheme 111, Reaction (v)] may be used as a means of preparing α-diketones **304** or enediamines **303** from amides (Scheme 114).[221] The synthetic utility



303 **304**

Scheme 114. Reagents: (i) $LiAlH_4$; (ii) R″Li; (iii) 10% aq. H_2SO_4; R, R′ = Me, Et, Ph; R″ = Me, n-C_4H_9, Ph.

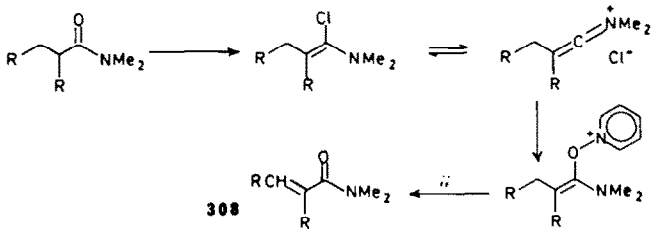
of the Schiff base cycloaddition [Scheme 109, Reaction (iii)] can be increased by using N-benzhydrylimines. Hydrogenolysis of the benzylic C–N bond then gives the N-substituted azetidiniminium salt **305** and the 2-amino-1-azetine **306** on treatment with strong base. These behave as β-aza-enamines and readily undergo alkylation or acylation to yield N-substituted azetidinones **307** (Scheme 115).[222] A method for the asymmetric synthesis of chiral cyclobutanones



Scheme 115. Reagents: (i) RCH=NCHPh$_2$; (ii) $NaClO_4$; (iii) H_2, Pd/C, MeOH; (iv) KOH, MeOH; (v) RX (i.e. MeI, CH_2=$CHCH_2Br$, PhCOCl, CH_2=CHCN; (vi) hydrolysis.

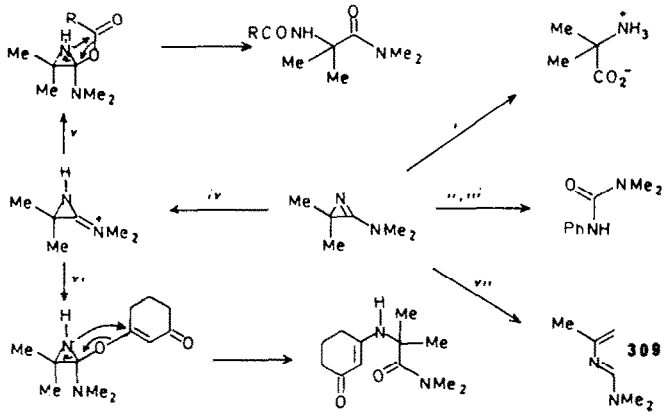
has been reported involving [2 + 2] cycloaddition (Scheme 113) of an alkene to a chiral keteninimium salt derived from a chiral amine [(2*S*)-methoxymethylpyrrolidine].[223] An enantiomeric excess of 55–92% was achieved, depending on the substitution pattern. The method is

of potential value for the enantioselective synthesis of β-lactams by asymmetric [2 + 2] cycloaddition to imines.[223] A method for the αβ-dehydrogenation of carboxamides has been developed and involves addition of pyridine N-oxide to keteniminium salts followed by 1,4-elimination to give **308** (Scheme 116). The method is of potential for the synthesis of dehydro amino acids, after prior conversion to the N-phthaloyl derivative.[224]



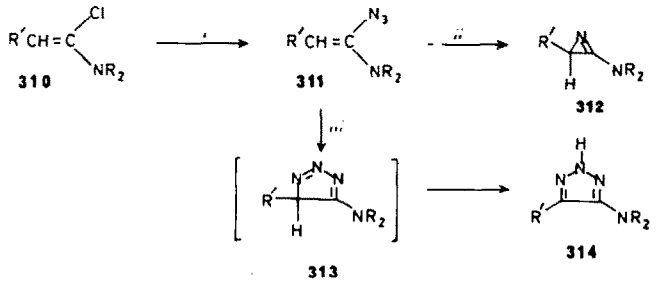
Scheme 116. Reagents: (i) $C_5H_5N{\rightarrow}O$; (ii) Et_3N.

The 2-amino-1-azirine synthesis[225] [Scheme 111, Reaction (iv)] provides access to a variety of structures (Scheme 117).[225,226] The 1-amino-2-azadiene **309** obtained by thermolysis of 2-amino-1-azirines [Scheme 117, Reaction (vii)] undergoes cycloaddition to electrophilic olefins and



Scheme 117. Reagents: (i) H_2O, △; (ii) $PhNH_2$, 170°; (iii) H_3O^+; (iv) HX; (v) $X^- = RCO_2^-$; (vi) X^- = cyclohexane-1,3-dione enolate anion; (vii) 340–400°, 0.1 Torr.

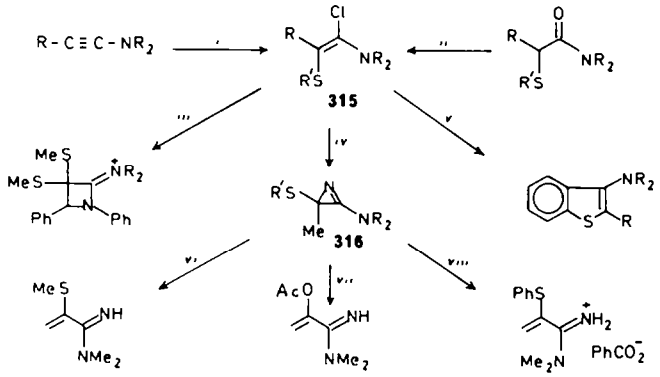
acetylenes followed by loss of dimethylamine to yield dihydropyridines or pyridines. When the sodium azide reaction is applied to trisubstituted α-chloroenamines **310**, then azirines **312** are only obtained with the less reactive enamines [i.e. R_2N = Ph(Me)N]. The more reactive α-chloroenamines give triazoles **314** owing to the cyclisation of the intermediate α-azidoenamine **311** occurring much faster than loss of N_2 (Scheme 118).[215]



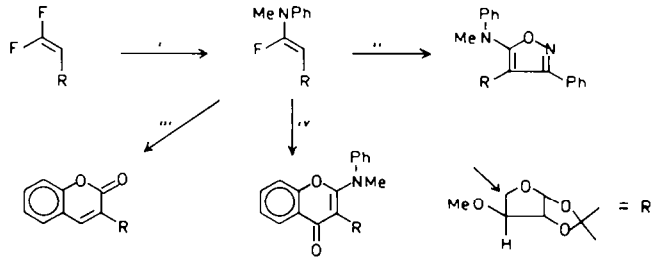
Scheme 118. Reagents: (i) NaN_3, CH_3CN/CCl_4; (ii) R_2N=PhNMe; (iii) R_2N=Me_2N, morpholino, pyrrolidinyl; R′ = Me, t-Bu, Ph.

The 4H-triazole **313** isomerises very rapidly to the aromatic 2H-triazole **314**. 4-H Triazoles have been isolated from the corresponding reaction with tetra-substituted α-chloroenenamines contain-

ing a methoxycarbonyl substituent at the β-position.[207c] Thermolysis gives a mixture of the 2H triazole and the corresponding azirine. 3-Alkyl- or arylthio-2-amino-1-azirines **316** have been obtained by azide addition to the corresponding β-substituted thio-α-chloroenamine **315**. The latter are readily prepared by addition of sulfenylchlorides to ynamines or from the corresponding substituted α-thiocarboxamide and together with **316** provides access to a variety of heterocyclic and acyclic structures (Scheme 119).[228] α-Fluoroenamino sugars have been converted into a variety of heterocyclic systems by the sequence illustrated in Scheme 120.[229]

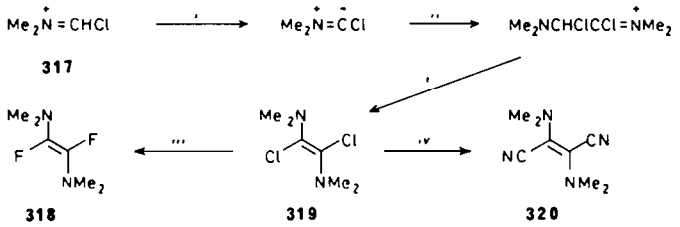


Scheme 119. Reagents: (i) R'SCl; (ii) $HCl/COCl_2$–DMF; (iii) PhCH=NPh (R = MeS, R' = Me); (iv) NaN_3, acetonitrile or DMF; (v) $ZnCl_2$ (R' = Ph); (vi) R' = Me; (vii) AgOAc, 12 days; (viii) $PhCO_2H$ (R' = Ph).



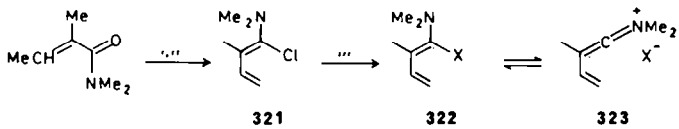
Scheme 120. Reagents: (i) LiN(Me)Ph; (ii) PhC≡N→O; (iii) salicylaldehyde; (iv) methyl salicylate.

1,2-Dichloro-1,2-enediamines **319** (*cis* and *trans*) have been prepared by deprotonation of chloromethyleniminium chlorides **317** and provide access to 1,2-difluoro-enediamines **318** and 1,2-dicyano-enediamines **320** (*cis* and *trans*) (Scheme 121).[230]



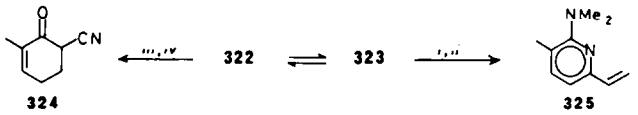
Scheme 121. Reagents: (i) $-H^+$; (ii) +**317**; (iii) F^-; (iv) CN^-.

α-Chorodienamines **321** have been prepared and converted into a variety of 1,1-diheterosubstituted dienes **322** (Scheme 122).[231]



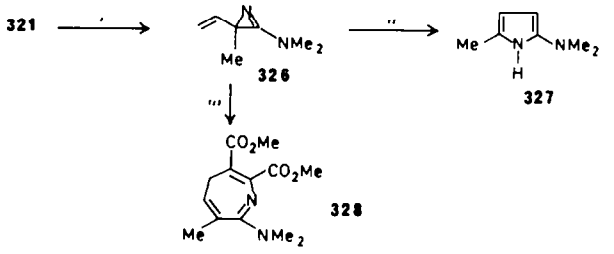
Scheme 122. Reagents: (i) $COCl_2$; (ii) Et_3N; (iii) KF, O–$C_6H_4Cl_2$, △ 29 h (X = F) or KI, C_6H_6, △ 6 h (X = I) or NaOMe, Et_2O, 20° 24 h (X = OMe) or C_6H_5OH, Et_3N, Et_2O, 20° 1 h (X = OPh) or NaSMe, Et_2O, 20° 4 h (X = SMe) or $LiNMe_2$, Et_2O/C_6H_{12}, 25° 1 h (X = NMe_2).

When X is a good leaving group, diene **322** will be in equilibrium with the vinylketeniminium salt **323** and could therefore function as an electron-rich or an electron-poor diene in the Diels–Alder reaction, depending upon the nature of X. For example when X = Cl or I cycloaddition to acrylonitrile occurs across the C≡N group to give pyridine **325**, whereas for X = F or NME_2 cycloaddition occurs across the C = C double bond to give cyclohexene **324**.[231]



Scheme 123. Reagents: (i) CH_2=CHCN, KI catalyst (X = Cl or I); (ii) Et_3N; (iii) CH_2=CHCN, C_6H_6 △ (X = F or NMe_2); (iv) H_3O^+.

Cycloaddition of sodium azide to **321** gives vinylazirine **326** which undergoes thermal rearrangement to pyrrole **327** and ring expansion with dimethyl acetylenedicarboxylate to give azepine **328**.[232]

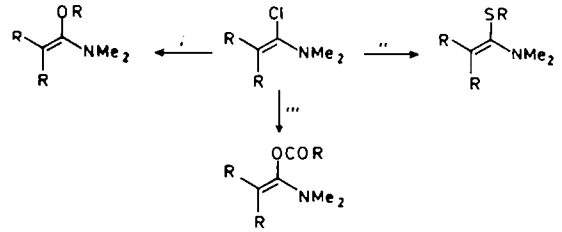


Scheme 124. Reagents: (i) NaN_3; (ii) △; (iii) MeO_2CC≡CCO_2Me.

Secondary α-chloroenamines have also been shown to be intermediates in the conversion of acetanilides into quinoline derivatives by the action of Vilsmeier reagents ($Me_2\overset{+}{N}$=CHCl $OPOCl_2^-$) in phosphoryl chloride: $PhNHCOCH_3 \rightarrow PhN{=}C(Cl)CH_3 \rightleftharpoons PhNHC(Cl){=}CH_2 \rightarrow PhN{=}C(Cl){-}C(CH{=}\overset{+}{N}Me_2){=}CHNMe_2$ → quinoline derivative. Similar α-chloroenamine intermediates are apparently involved in the cyclisation of 2-acetamidothiophens into thienopyridines.

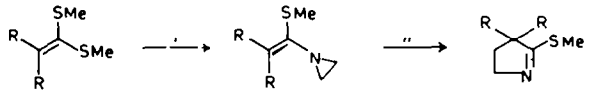
(g) *Ketene*-O,N- *and* S,N-*acetals*

(i) *Preparation.* α-Chloroenamines undergo nucleophilic displacement of chloride anion by alkoxide and thiolate anions to give the corresponding ketene O,N- or S,N-ketal, usually at room temperature; carboxylic acid anions give the α-acyloxyenamine (Scheme 125).[206,203] Similar treat-



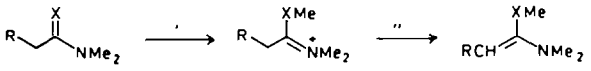
Scheme 125. Reagents: (i) RO^-; (ii) RS^-; (iii) RCO_2Na (80°) or RCO_2Ag (−10°) or RCO_2H (Et_3N).

ment of α-chlorodienamines gives the vinylketene O,N- or S,N-ketal.[222] Acid catalysed addition of alcohol to ynamines gives the O,N-ketal,[143] whereas αβ-unsaturated aldehydes, ketones and esters undergo cycloaddition to give the cyclic O,N-ketal (i.e. α-aminopyran).[234] Secondary amines are reported to add to mercaptoacetylenes to give the S,N-acetal.[235] Ketene dithioacetals are readily converted to the aziridine derivative which undergo iodide catalysed rearrangement to pyrrolines (Scheme 126). Alkylation of amides or thioamides and deprotonation of the resulting adduct



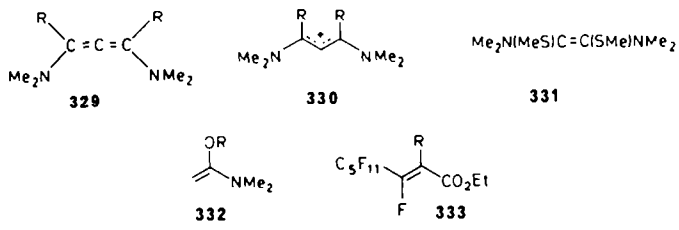
Scheme 126. Reagents: (i) aziridine; (ii) KI, acetone.

provides a general route to ketene O,N- and S,N-acetals (Scheme 127).[236-238] Tertiary carboxamides can also be O-acylated in the presence of silver trifluoromethanesulphonate and the resulting



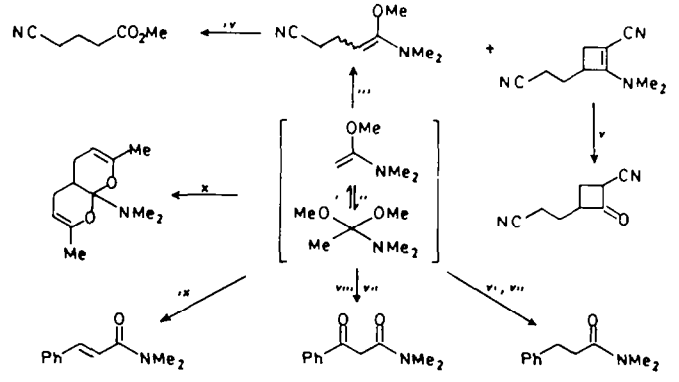
Scheme 127. Reagents: (i) Me_2SO_4 or MeI; (ii) RONa.

acyloxyiminium salt deprotonated to the corresponding 1-acyloxyenamine or dienamine.[239] O-Silyl ketene O,N-ketals are obtained by reaction of lithium N,N-dialkylamide enolates with trialkylchlorosilanes, together with the C-silylated product into which the O-silyl derivatives rearrange on heating.[240] 1,3-Diamino-1,3-dialkoxyallenes (**329**; R = OEt)[241] and their sulphur analogues (**329**; R = SR)[242] have been obtained by deprotonation of the corresponding vinamininium salts **330**. The latter are obtained by alkylation of N,N-dimethyl-β-ethoxy-β-dimethylaminoacrylamide with triethyloxonium tetrafluoroborate or reaction of enamines with an amide chloride. A nucleophilic N,S-carbene has been implicated in the formation of the tetrasubstituted ketene S,N-acetal **331**.[245]



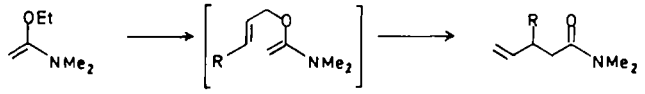
Scheme 128.

(ii) *Reactions.* Although ketene O,N- and S,N-acetals undergo normal enamine type reactions, there is evidence for reduced nucleophilicity due to inductive electron withdrawal by the oxygen or sulphur. For example, whereas enamines undergo C-arylation by perfluoroarenes,[1] reaction of 1-ethoxy-N,N-dimethylvinylamine **332** (R = Et) with hexafluorobenzene at 80° leads only to O- and N-arylation products. C-Arylation does occur with the more reactive pentafluoropyridine, however, to give ethyl 2,3,5,6-tetrafluoro-4-pyridylacetate.[244] Although alkylation of **332** with perfluoroalkyliodides in the presence of UV-irradiation gives $\alpha\beta$-unsaturated esters **333**,[245] with loss of HF, enamines[1] react similarly without the need for UV irradiation. Several authors[246] have shown that 1,1-dimethoxy-1-dimethylaminoethane is in rapid equilibrium with the ketene O,N-acetal **332** (R = Me) and undergoes the same reactions (Scheme 129).[151,246a] Ketene S,N-acetals



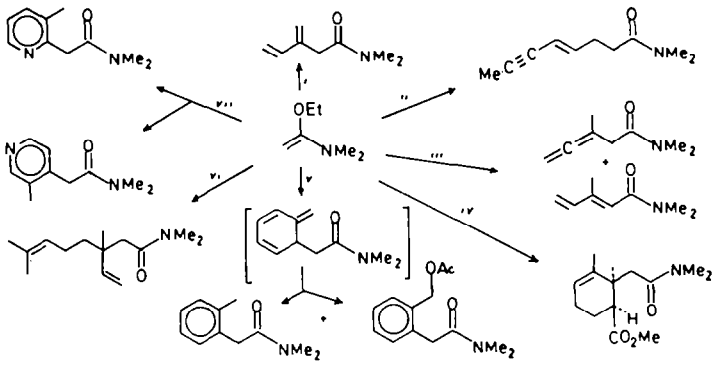
Scheme 129. Reagents: (i) −MeOH; (ii) +MeOH; (iii) CH_2=CHCN; (iv) mild hydrolysis; (v) aq. alc. HCl; (vi) $PhCH_2Cl$; (vii) aq. base; (viii) PhCOCl; (ix) PhCH=O; (x) $MeCOCH{=}CH_2$.

react with electrophiles (R'X) to give the β-substituted ketal [$R'CH{=}C(SMe)NR_2$; R' = PhCO, CO_2Et, CN, $C(CO_2Et){=}C(CN)_2$, $PhNHCO,2,4\text{-}(O_2N)_2C_6H_3$].[236] Diethyl phosphite converts ketene O,N- and S,N-acetals into the enamine phosphonate[247] [(E)-$RCH{=}C(NMe_2)P(O)(OEt)_2$], and reaction with phosphono and phosphothioic acids has been investigated.[257] A useful reaction of ketene O,N-acetals involves transesterification with an allylic alcohol followed by a [3,3] sigmatropic rearrangement to give an α-substituted amide (Scheme 130). Some more examples are



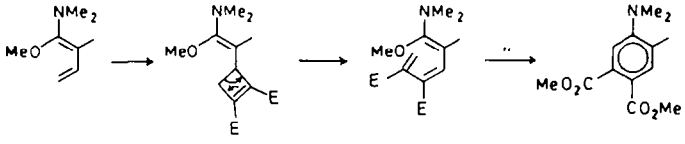
Scheme 130. Reagents: (i) $RCH{=}CHCH_2OH$.

summarised in Scheme 131. Ketene S,N-ketals have been implicated in the α-allylation of thioamides[253] and $\alpha\beta$-unsaturated thioamides.[254] Some aromatic syntheses involving ketene

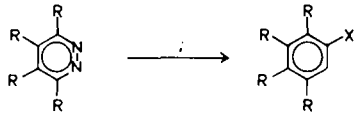


Scheme 131. (i) $CH_2{=}C{=}CHCH_2OH$;[248] (ii) $MeC{\equiv}CCH(OH)CH{=}CH_2$;[249] (iii) $MeC{\equiv}CCH_2OH$;[250] (iv) methyl(±)cis4-hydroxy-2,3-dimethyl-2-cyclohexenecarboxylate;[246b] (v) $PhCH_2OH$;[246b] (vi) $Me_2C{=}CH(CH_2)_2C(Me){=}CHCH_2OH$;[246b,252] (vii) $\beta\text{-}C_5H_4NCH_2OH$.[251]

O,N-acetals have been reported (Schemes 132[222] and 133[255]). The mode of reaction of diphenylcyclopropenone with ketene O,N- and S,N-acetals is analogous to that with enamines (Ref.

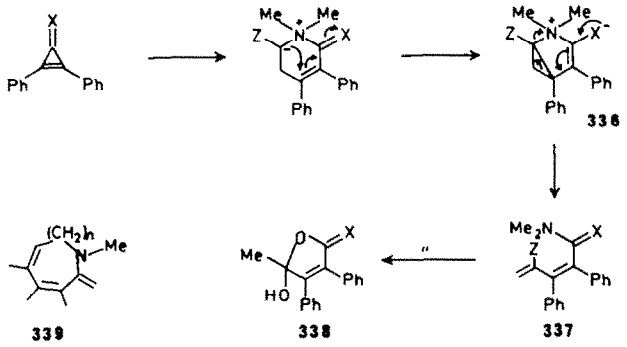


Scheme 132. Reagents: (i) $MeO_2CC{\equiv}CCO_2Me$; (ii) -MeOH; E = CO_2Me.



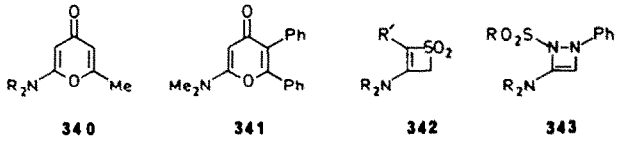
Scheme 133. Reagents: (i) $CH_2{=}C(OMe)NMe_2$; R = H, CO_2Me, Ph; **334**, X = NMe_2 (25–82%); **335**, X = OMe (1.5–19%).

2, pp. 3369–3370), though somewhat less complex. Acyclic ketene acetals give the corresponding amide of 2,3-diphenylpenta-2,4-dienoic acid or thioacid **337** and the $\alpha\beta$-diphenyl-γ-methyl-γ-hydroxy-Δ^{α}-butenolide **338** formed by hydrolysis of **337** and cyclisation. The overall reaction involves C–N insertion and the azonia intermediate **336** can be isolated at room temperature. Cyclic ketene acetals give the ring enlarged lactam **339**.[256] Several syntheses of heterocyclic systems from ketene O,N- and S,N-acetals have been reported. For example diketene[258] and acylketenes[259] cyclocondense with ketene S,N- and O,N-acetals, respectively, to give the



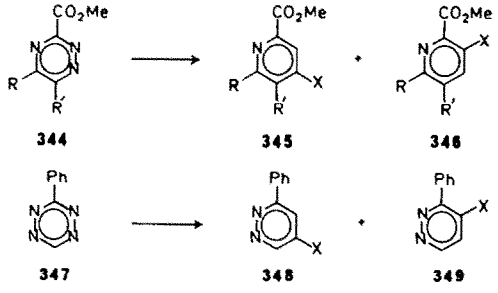
Scheme 134. Reagents: (i) CH_2=C(Z)NMe_2, △; (ii) hydrolysis; X = O, S; Z = NMe_2, OEt, SMe.

γ-pyrones **340** and **341**, with elimination of alcohol or thioalcohol. Sulphenes and azosulphones undergo [2 + 2] cycloaddition to ketene acetals to give **342**[260] and **343**[115] respectively, also after



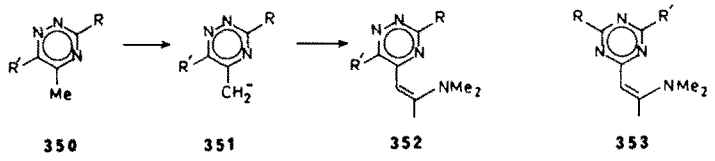
Scheme 135.

elimination of alcohol or thioalcohol. Ketene N,N-, O,N-, O,O- and S,N-acetals react with 1,2,4-triazines **344** by a Diels–Alder reaction with inverse electron demand, to give, after elimination of N_2 and HX (X = OR, SR, NR_2), a mixture of pyridines **345** and **346**.[261] Similarly the tetrazine **347** gives **348** or **349**. The product distribution is critically dependent on the solvent



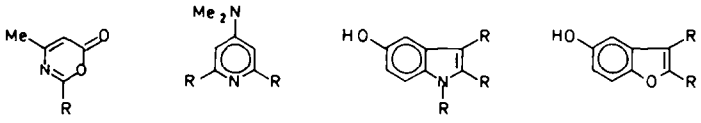
Scheme 136. Reagents: (i) CH_2=C(X)Y; X = O, Et, NMe_2; Y = OEt, SMe, NMe_2; R, R′ = H, Ph, CO_2Me.

employed and the substituents present in both reagents, and when a 5-methyl-1,2,4-triazine is employed the course of the reaction is changed completely to give a triazinylvinylamine **352** (Scheme 137). The mechanism of the reaction apparently involves proton abstraction from **350** by the enamine and nucleophilic attack by the anion **351** produced on the ketene acetal (or derived iminium salt) with elimination of ethanol.[262] 2-Methyl-1,3,5-triazines undergo a similar reaction to give **353**.[263] Nucleophilic attack by the ketene O,N-acetal on a ring carbon occurs when a triazine



Scheme 137. Reagents: (i) CH_2=C(OEt)NMe_2; R, R′ = H, Me, Ph.

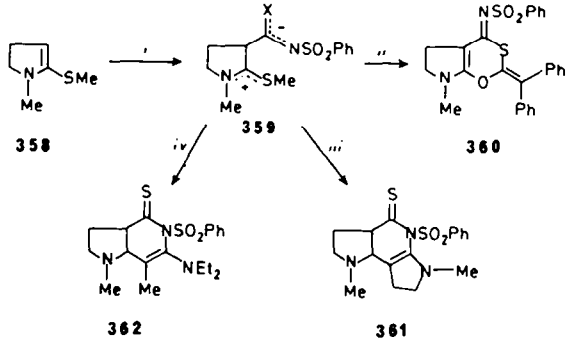
N-oxide is used, to give the corresponding 3-vinyl-1,2,4-triazine N-oxide.[264] Oxazines **354** react with ketene O,N-acetals to give the pyridine **355**,[265] and benzoquinones undergo cycloaddition to ketene N,N- and S,N-acetals to give a mixture of mainly the indole **356** together with the benzofuran **357**.[266] Acyclic and cyclic ketene N,S-ketals react with benzenesulphonylisocyanate and iso-



354 **355** **356** **357**

Scheme 138.

thiocyanate to give adducts of type **359** (X = O or S). The 1,4-dipolar nature of the adduct (X = S) was demonstrated by cycloaddition of diphenylketene to give **360** in high yield, or by further reaction with the ketene N,S-ketal **358** or 1-diethylaminopropyne to give **361** and **362** respectively.[267]



Scheme 139. Reagents: (i) $PhSO_2N{=}C{=}X$, CH_3CN/ether, $-60°$; (ii) $Ph_2C{=}C{=}O$, CH_3CN, 20°; (iii) **358**; (iv) $Et_2NC{\equiv}CMe$; X = O or S.

4. METALLATED ENAMINES[268]

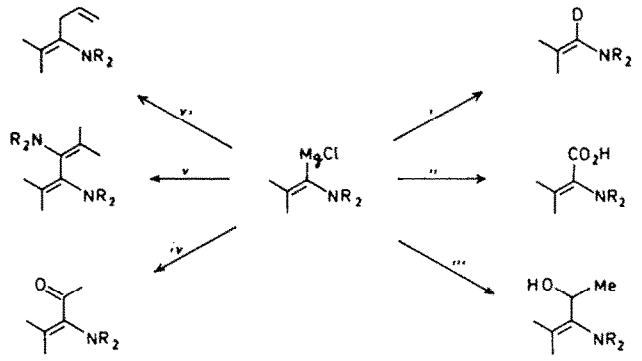
These differ from metalloenamines[2] in that they are metal derivatives of tertiary enamines. Depending upon the substituents present, tertiary enamines may be metallated at the α, β, β' or γ-position and thus acquire the properties of vinyl or allyl anions rather than enamines. However, once the anionic centre thus produced has reacted with an electrophile, further reaction of the enamine system can occur (*vide infra*). Metallated enamines possess a number of advantages over neutral enamines and enolate anions. For example the anions produced are highly reactive and reaction therefore occurs with weakly electrophilic reagents which do not normally react with enamines, such as ketones and nitriles; in other cases yields may be greatly increased. Because of negligible proton exchange between the anion and the neutral product, monosubstitution is easily achieved. The anions usually have a much higher charge density on carbon than do neutral enamines, so N-alkylation is negligible. In addition to normal electrophilic attack at the β-position, metallation of enamines may cause electrophilic attack to be diverted to the α-, β'- or γ-positions in certain circumstances, the metallated enamine thus functioning as an acyl anion, enolate anion or homoenolate anion equivalent, respectively.

Scheme 140.

(i) *α- and γ-Metallation*

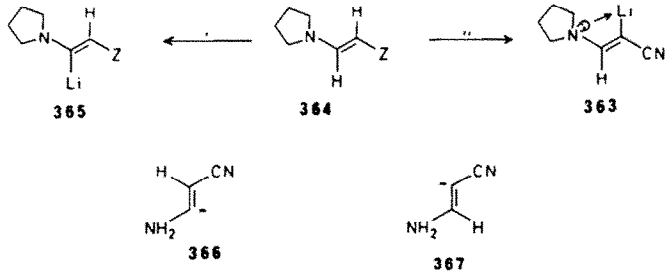
α-Metallated enamines have been obtained by treatment of α-chloroenamines with sodium, lithium or magnesium metal in dry tetrahydrofuran.[269] Since α-chloroenamines are nucleophilic at

C-β, but electrophilic at C-α, replacement of the carbon–halogen bond by a carbon–metal bond confers nucleophilic properties on the C-α position and effectively converts the haloenamine into an acyl anion equivalent. Some examples illustrating the scope of this reaction are summarised in Scheme 141.[206,269]



Scheme 141. Reagents: (i) D_2O; (ii) CO_2; H_3O^+; (iii) $CH_3CH{=}O$; aq. NH_4Cl; (iv) $(CH_3CO)_2O$; aq. NH_4Cl; (v) $Me_2C{=}C(Cl)NR_2$; aq. NH_4Cl; (vi) $CH_2{=}CHCH_2Br$; R_2N = Me_2N or MeNPh.

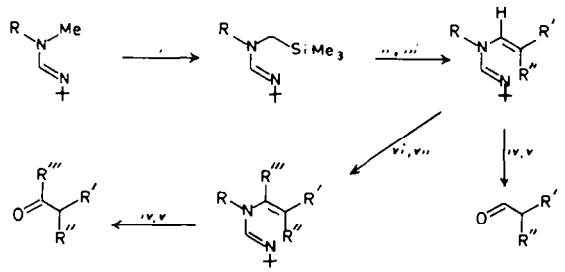
α-Lithiation has also been effected by deprotonation of vinylogous amides, esters, ketones and nitriles of type **364** having an α-hydrogen atom.[274] At temperatures below $-100°$ the enamines were quantitatively converted into **365**. Only in the case of **364d** (Z = CN) was the thermodynamically more stable β-lithio derivative **363** formed, at higher temperatures (*ca.* $-80°$). Although calculations revealed that the *trans*-α-anion **366** was more stable than the *trans*-β-anion **367**, the greater stability of the β-lithio derivative **363** was attributed to increased stabilization by solvation and to the co-ordination of the nitrogen lone pair electrons with the β-lithium in **363** exerting a greater stabilizing effect than complexation of the α-lithium with the nitrile group in **365d**. A similar explanation has been offered for the apparently greater stability of the β-lithio-α-morpholino-*cis*-stilbene compared to the *trans*-stilbene lithio derivative.[275]



Scheme 142. Reagents: (i) t-BuLi or LDA, THF, $-113°$; (ii) LDA, THF, $-76°$; (a) Z = $CONEt_2$; (b) Z = CO_2Et; (c) Z = COPh; (d) Z = CN.

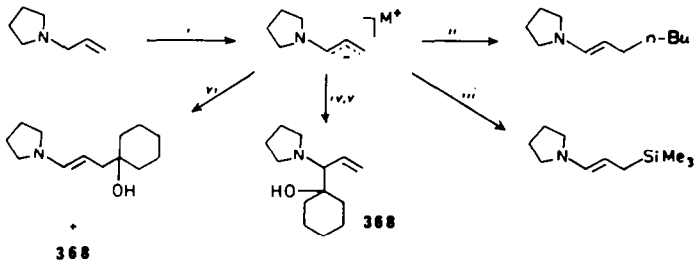
A new technique for homologating aldehydes or ketones to aldehydes by one additional carbon has recently been developed involving the intermediacy of an enamidine, and enables the conversion $R'R''C{=}O \rightarrow R'R''CH{-}CH{=}O$ to be carried out. However if instead of hydrazinolysis of the enamidine to the aldehyde, the enamidine is lithiated, alkylated (at the α-position) and then cleaved, the overall process then becomes one of homologation to a ketone $|R'R''C{=}O \rightarrow R'R''CHC(R''')=O|$ (Scheme 143).[288]

When an enamine containing a hydrogen at the γ-position, or an allylamine containing a hydrogen at the α-position, is metallated a mesomeric anion is formed which can undergo electrophilic attack at the α- or γ-positions. The ratio of α : γ-attack depends on a variety of factors,



Scheme 143. Reagents: (i) s-BuLi, −20°, Me_3SiCl; (ii) n-BuLi; (iii) R′R″C=O; (iv) NH_2NH_2 or Me_2NNH_2–HOAc–EtOH–H_2O; (v) aq. $Cu(OAc)_2$, THF, △; (vi) t-BuLi; (vii) n-BuI or EtCH=O [i.e. R‴ = C_4H_9 or $CH_3CH_2CH(OH)$]; R = Me or n-Bu.

but the nature of the electrophile and the counterion are often important as illustrated in Scheme 144. Ahlbrecht regards the metallated enamine as a contact ion pair with the metal located close

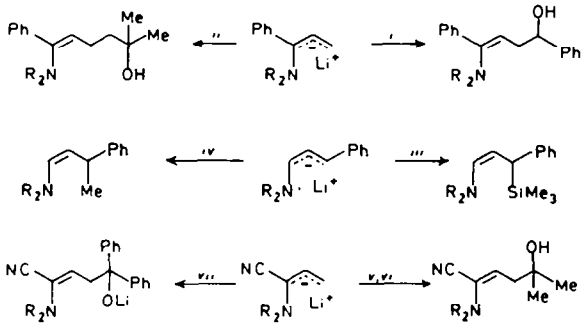


Scheme 144. Reagents: (i) s-BuLi, THF, −78°; (ii) n-BuBr, THF, −78°; (iii) Me_3SiCl, −78°; (iv) $ZnCl_2$; (v) cyclohexanone (α-attack); (vi) cyclohexanone (α- and γ-attack).

to the γ-carbon. The γ-product is then presumed to arise by an S_E2 process and the α-product by an S_E2' process.[268] Similar results were reported for the reactions of **369**, γ-attack occurring preferentially with a variety of electrophiles,[277] whereas **370** showed kinetically favoured α-reactivity.[278]

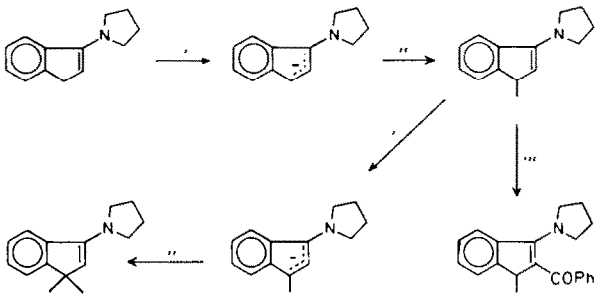
Scheme 145.

Ahlbrecht *et al.* have also examined the lithiation of a number of cyano and phenyl substituted propenamine systems. In every case subsequent reaction with electrophilic reagents occurred exclusively at the γ-position as illustrated in Scheme 146.[282-285]



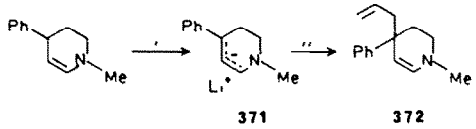
Scheme 146. Reagents: (i) PhCH=O; (ii) 2,2-dimethyloxirane; (iii) Me_3SiCl; (iv) MeI; (v) Me_2C=O; (vi) H_2O; (vii) Ph_2C=O; R_2N=PhNMe.

Similarly, the enamine of indan-1-one can be readily lithiated and alkylated at the γ-position in high yield. Furthermore, the alkylation products can be converted into geminally or vicinally disubstituted compounds by further reaction either as an enamine or as a lithiated enamine, as exemplified in Scheme 147.[281]



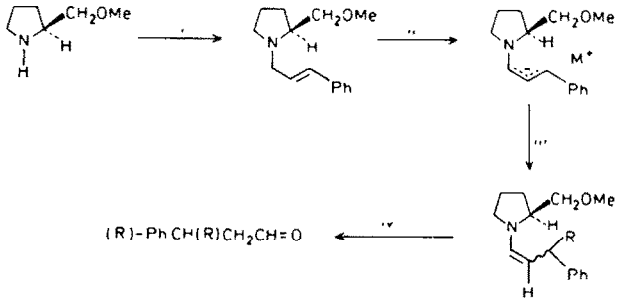
Scheme 147. Reagents: (i) n-BuLi, $-65°$; (ii) MeI; (iii) PhCOCl, Et_3N.

The heterocyclic enamine **371** was also found to react regioselectively at the γ-position to give **372**, which was used as a precursor for the synthesis of morphine-based analgesics.[286] Recently



Scheme 148. Reagents: (i) n-BuLi; (ii) CH_2=$CHCH_2Br$.

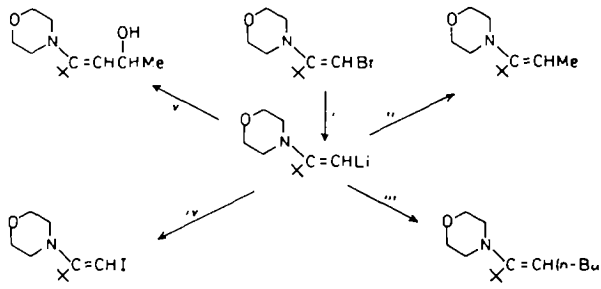
metallated chiral enamines derived from (*S*)-2-methoxymethylpyrrolidine have been utilised as chiral homoenolate anion equivalents and allow, after γ-alkylation and acid hydrolysis, asymmetric carbon–carbon bond formation to β-substituted aldehydes in entantiomeric excesses up to 67% (Scheme 149).[287]



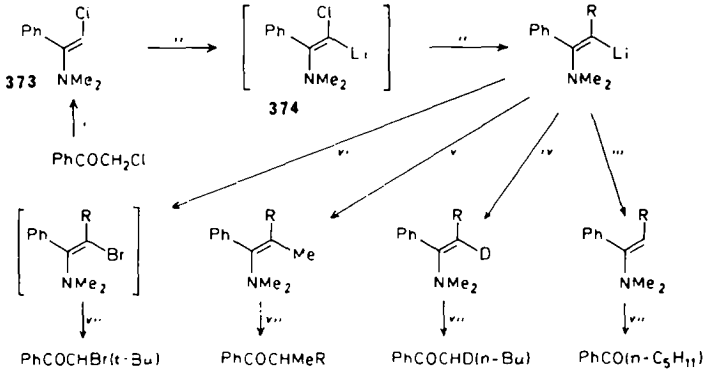
Scheme 149. Reagents: (i) PhCH=$CHCH_2Br$, NaH, THF; (ii) t-BuLi or t-BuLi/t-BuOK, pet. ether, 0°; (iii) RX, $-78°$ to $-100°$; (iv) 4N HCl, ether; R = Me, Et, i-C_3H_7, n-C_4H_9, CH_2=$CHCH_2Br$.

(ii) *β-Metallation*

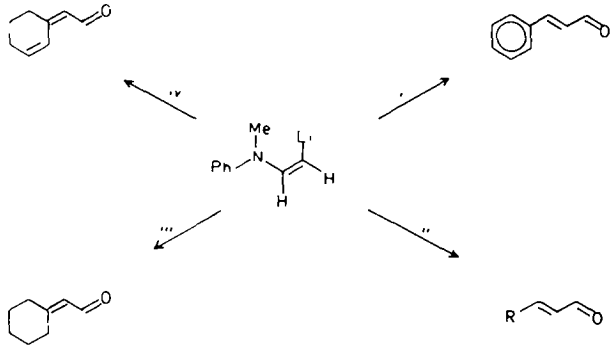
β-Lithiated enamines are prepared in quantitative yield by halogen–metal exchange reaction of an organolithium compound (n-BuLi, t-BuLi) with a β-bromoenamine.[270,275] The β-lithioenamines thus obtained are highly nucleophilic and react vigorously with a variety of electrophiles to give β-substituted enamines (Scheme 150).[270] The reaction of the β-chloroenamine **373** and two equivalents of alkyllithium has been shown to yield highly hindered enamines and ketones (Scheme 151). The reaction is presumed to proceed via the β-lithio-β-chloroenamine **374**.[271] β-Lithioenamines have also been obtained from ynamines and used as an acetaldehyde enolate equivalent to condense with a variety of aldehydes and ketones to give the corresponding $\alpha\beta$-unsaturated aldehyde (Scheme 152) after acid catalysed dehydration of the intermediate aldol.[272]



Scheme 150. Reagents: (i) n-BuLi, THF, −70°, N_2; (ii) MeI; (iii) n-BuI; (iv) I_2; (v)MeCH=O.

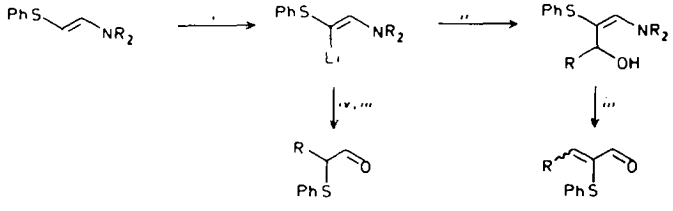


Scheme 151. Reagents: (i) $As(NMe_2)_3$; (ii) RLi, THF, −70°; (iii) H_2O; (iv) D_2O; (v) MeI, THF, −70°; (vi) Br_2; (vii) 10% aq. HCl, 40°; R = n-Bu or t-Bu.

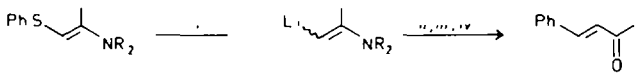


Scheme 152. Reagents: (i) PhCH=O; (ii) $C_6H_{13}CH$=O (R = C_6H_{13}); (iii) cyclohexanone; (iv) cyclohex-2-enone.

β-Lithioenamines have also been prepared by lithiation and reductive lithiation of β-phenylthioenamines.[273] In the former case lithiation is effected with t-butyllithium in tetrahydrofuran–hexamethylphosphoramide (9:1) at −60°, and subsequent reaction with electrophiles produces exclusively products having the same E configuration as the starting enamine. Hydrolysis then gives the corresponding substituted α-(phenylthio) aldehyde or α-(phenylthio)-αβ-unsaturated aldehyde (Scheme 153).[273] Reductive lithiation can be effected with lithium naphthalenide or lithium in liquid ammonia (Scheme 154).



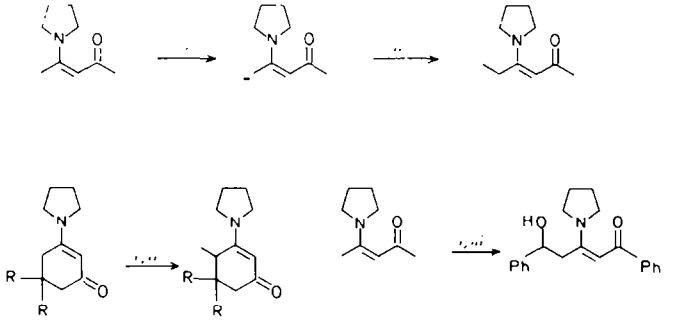
Scheme 153. Reagents: (i) t-BuLi; (ii) RCH=O; (iii) H_3O^+; (iv) RI.



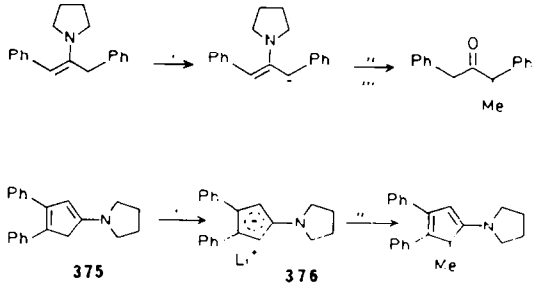
Scheme 154. Reagents: (i) $Li^+C_{10}H_8^-$ or Li–NH_3; (ii) PhCH=O; (iii) H_3O^+; (iv) Δ.

(iii) *β′-Lithiation*

The acidity of the β′- (or γ-) allylic protons of an enamine can be increased by adjacent anion-stabilising groups such as carbonyl, cyano, phenyl and cyclopentadienide systems. Thus monoenamines derived from 1,3-dicarbonyl compounds were one of the first enamine systems to be deprotonated and shown to react with electrophiles at the β′-position (Scheme 155).[279] Surprisingly, in view of the fact that the anionic centre is conjugated with the enamine double bond, no tendency for electrophilic attack at the enamine β-carbon was reported except for the pyrrolidine enamine of indan-2-one. In this case sequential anionic dialkylation led to a mixture of 1,1- and 1,3-dimethylindan-2-ones on hydrolysis, indicating a lack of regiospecificity in the second lithiation–alkylation step.[281] Some examples of phenyl and cyclopentadienide anion stabilisation are shown in Scheme 156. Interestingly the dienamine **375** gave only N-methylation with methyl iodide, whereas the lithiated dienamine **376** gave the C-alkylated product in good yield.[280,281]



Scheme 155. Reagents: (i) BuLi; (ii) MeI; (iii) PhCh=O; R = H, Me.



Scheme 156. Reagents: (i) n-BuLi; (ii) MeI; (iii) H_2O.

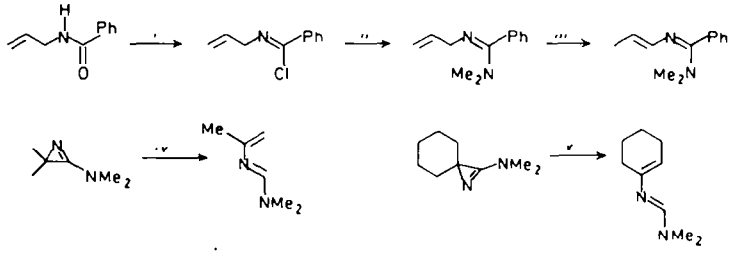
5. AZADIENAMINES[304]

Although 2-azabutadiene **377** could be regarded as an enamine system, the reactivity would be expected to be low owing to the reduced p-character of the nitrogen lone pair orbital. Furthermore in order for pπ-conjugation to be effective the imine double bond would have to be orthogonal to the carbon–carbon double bond with consequent loss in resonance stabilisation. It is therefore

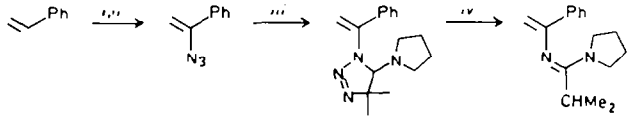
Scheme 157.

not surprising that 2-azabutadienes have been reported to undergo protonation and alkylation exclusively at the nitrogen to give the N-vinyliminium salts; the isomeric 2-aza-allenium salts, which are less stable according to *ab initio* calculations, were not formed.[289] 1-Azabutadiene **378** is of course an $\alpha\beta$-unsaturated imine, not an enamine, and a rather unreactive one[290] too unless converted into the N-acyl derivative.[291] However, introduction of dialkylamino groups into both systems would be expected to increase the reactivity of 2-azadienes to electrophilic reagents and possibly reverse the polarisation of the π-electron system of 1-azadienes and render them reactive to electrophilic attack. In view of the considerable potential of these systems for heterocyclic synthesis the recent developments which have occurred in this area will therefore be briefly discussed.

(i) *Preparation.* 1-Dimethylamino-1-azabutadienes are of course N,N-dimethylhydrazones of $\alpha\beta$-unsaturated aldehydes and hence readily available.[301] 1-Dialkylamino-2-azabutadienes are readily obtained by amination of imine chlorides[292] or thermolysis of 2-dialkylamino-1-azirines[293] (Scheme 158) or thermolysis of 5-dialkylamino-1-vinyl-4,5-dihydro-1H-1,2,3-triazoles[294] which are also readily obtainable by 1,3-dipolar cycloaddition of vinyl azides to enamines[295] (Scheme 159).

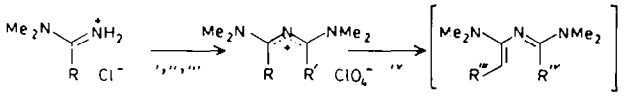


Scheme 158. Reagents: (i) PCl_5; (ii) Me_2NH; (iii) t-BuOK, DMSO; (iv) 340°, 0.1 Torr; (v) 400°, 0.1 Torr.



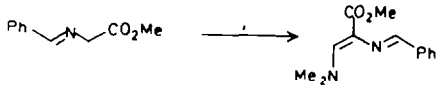
Scheme 159. Reagents: (i) IN_3; (ii) t-BuOK; (iii) 1-pyrrolidinylisobutene; (iv) 80° ($-N_2$).

1,3-Bis(dimethylamino)-2-azabutadienes or 1,1,3-tris(dimethylamino)-2-azabutadiene have been formed, but not isolated, by deprotonation of 1-alkyl-2-azavinamidinium salts.[296] The latter are prepared from amidines or guanidines and carboxamide/dimethyl sulphate adducts (Scheme 160).



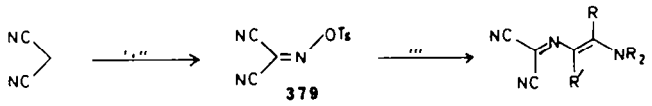
Scheme 160. Reagents: (i) MeONa; (ii) $R'C(OMe)=\overset{+}{N}Me_2MeSO_4^-$; (iii) $NaClO_4$; (iv) NaH, THF, HMPA, 25°; R = Me, $PhCH_2$, Ph, Me_2N; R′ = H, Me; R‴ = H, Ph; Rᴵᵛ = H, Ph, Me_2N..

4-Dimethylamino-2-azabutadienes can be obtained by heating azomethines with dimethylformamide diethylacetal (Scheme 161),[297] and by the action of enamines on tosylated iso-



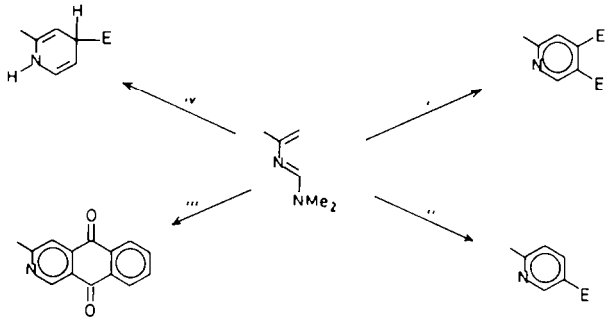
Scheme 161. Reagents: (i) $Me_2NCH(OEt)_2$.

nitrosomalonic acid derivatives **379** (Scheme 162).[298,299] The use of a 1,1-enediamine **380** (R = NR_2) gives the corresponding 4,4-bis(dialkylamino)-2-azabutadiene, whereas reaction of dienamines with **379** gives the corresponding 6-amino-2-azahexatriene.[300]

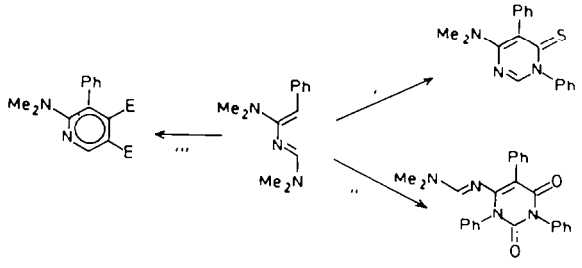


Scheme 162. Reagents: (i) NO_2^-, HOAc; (ii) TsCl, pyridine; (iii) $R_2N(R)C{=}CHR'$ (**380**).

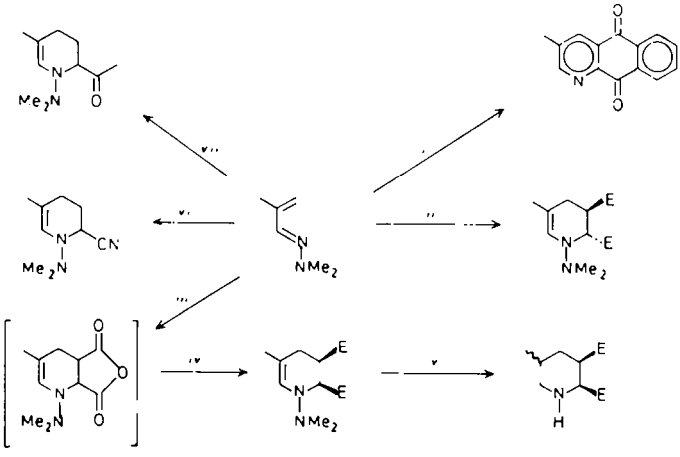
(ii) *Reactions.* Most of the work carried out in this area has been concerned with the cycloaddition of electrophilic olefins and heterocumulenes to azadienamines, to give 6-membered heterocyclic products. Some examples illustrating the scope of these syntheses are summarised in Schemes 163–165.



Scheme 163. Reagents: (i) $MeO_2CC{\equiv}CCO_2Me$, −20°; (ii) $HC{\equiv}CCO_2Me$, −20°; (iii) 1,4-naphthoquinone, 0°; (iv) cis-$MeO_2CCH{=}CHCO_2Me$, −20°;[293] E = CO_2Me.

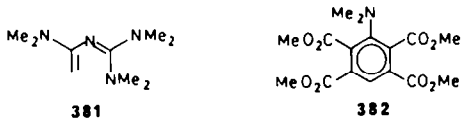


Scheme 164. Reagents: (i) $PhN{=}C{=}S$; (ii) $PhN{=}C{=}O$; (iii) $MeO_2CC{\equiv}CCO_2Me$, −70°; E = CO_2Me.[296]



Scheme 165. Reagents: (i) 1,4-Naphthoquinone; (ii) $MeO_2CCH{=}CHCO_2Me$; (iii) maleic anhydride; (iv) MeOH; CH_2N_2; (v) Zn–HOAc; (vi) $CH_2{=}CHCN$; (vii) $CH_2{=}CHCOMe$; E = CO_2Me.

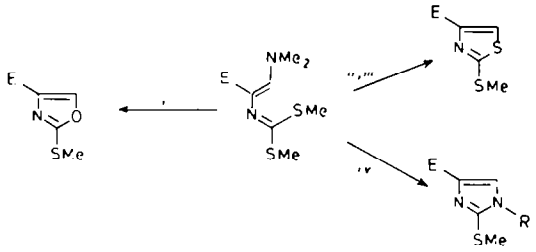
Sometimes the reactions do not go as expected, as in the cycloaddition of dimethyl acetylenedicarboxylate to 2-azadienetriamine **381** which gives the aminobenzenetetracarboxylate **382**. This involves sequential [2 + 2] and [4 + 2] cycloaddition of the acetylene, with ring opening of the intermediate cyclobutene.[296]



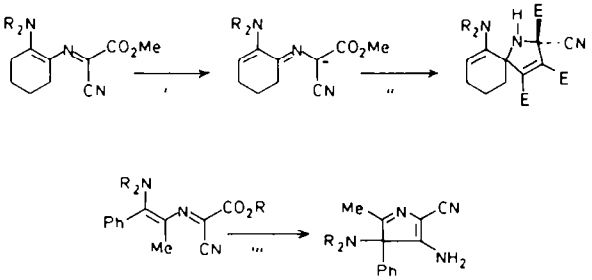
381 **382**

Scheme 166.

Other reactions leading to five-membered rings are illustrated in Schemes 167–168.



Scheme 167. Reagents: (i) dil. HCl, THF, △; (ii) HCl gas, 20°; (iii) H_2S, THF, △; (iv) $RNH_3^+ Cl^-$, dioxane/DMF, △; E = CO_2Me.



Scheme 168. Reagents: (i) MeOH; (ii) $MeO_2CC{\equiv}CCO_2Me$; (iii) KCN, MeOH, 25°; E = CO_2Me.[299]

REFERENCES

[1]P. W. Hickmott, *Tetrahedron* **38**, 2050 (1982).
[2]P. W. Hickmott, *Ibid.* **38**, 3363 (1982).
[3]J. V. Greenhill, *Chem. Soc. Rev.* 277 (1977).
[4]E. C. Taylor and A. McKillop, *Adv. Org. Chem.* **7**, 1 (1970).
[5]G. R. Lenz, *Synthesis* 489 (1978).
[6]S. Rajappa, *Tetrahedron* **37**, 1453 (1981).
[7]N. F. Firrell and P. W. Hickmott, *J. Chem. Soc.* (B) 293 (1969).
[8]H. O. House, B. M. Trost, R. W. Magin, R. G. Carlson, R. W. Franck and G. H. Rasmusson, *J. Org. Chem.* **30**, 2513 (1965).
[9]A. G. Cook (Ed.), *Enamines: Synthesis, Structure and Reactions*. Marcel Dekker, New York (1969).
[10]N. F. Firrell and P. W. Hickmott, *J. Chem. Soc.* (C) 716 (1970).
[11]H. Mazarguil and A. Lattes, *Bull. Soc. Chim. Fr.* 1874 (1972).
[12]H. Nozaki, T. Yamaguti, S. Ueda and K. Kondo, *Tetrahedron* **24**, 1445 (1968).
[13]H. Mazarguil and A. Lattes, *Bull. Soc. Chim. Fr.* 112 (1971).
[14]Y. Bessiere and F. Derguini-Boumechal, *J. Chem. Res.* (S) 204 (1977).
[15]G. Dana, F. Weisbuch and C. Yamagami, *Bull. Soc. Chim. Fr.* 1109 (1973).
[16]F. Weisbuch, C. Yamagami and G. Dana, *J. Org. Chem.* **37**, 4334 (1972).
[17]C. Yamagami, F. Weisbuch and G. Dana, *Tetrahedron* **27**, 2967 (1971).
[18]P. W. Hickmott, B. J. Hopkins and C. T. Yoxall, *J. Chem. Soc.* (B), 205 (1971).
[19a]M. J. M. Pollmann, H. R. Reus, U. K. Pandit and H. O. Huisman, *Rec. Trav. Chim.* **89**, 929 (1970); [b]H. Mazarguil and A. Lattes, *Bull. Soc. Chim. Fr.* 1880 (1972).
[20]B. B. Millward, *J. Chem. Soc.* 26 (1960).
[21]G. Stork and G. Birnbaum, *Tetrahedron Letters* 313 (1961).
[22]U. K. Pandit, K. de Jonge, K. Erhart and H. O. Huisman, *Ibid.* 1207 (1969).

[23]A. A. Brizzolara, Ph.D. Thesis, Columbia University, 1960.
[24]N. F. Firrell and P. W. Hickmott, *J. Chem. Soc.* (C), 2320 (1968).
[25]L. Velluz, G. Nominé, R. Bucourt, A. Pierdet and P. Dufay, *Tetrahedron Letters* 127 (1961).
[26]D. Bertin and J. Perronnet, *Bull. Soc. Chim. Fr.* 1422 (1968).
[27]E. R. Waard, Dissertation, University of Amsterdam, 1967.
[28a]R. Sciaky, U. Pallini and A. Consonni, *Gazz. Chim. Ital.* **96**, 1284 (1966); [b]T. Nozoe, *Pure Appl. Chem.* **28**, 239 (1971).
[29a]J. L. Johnson, M. E. Herr, J. C. Babcock, A. E. Fonken, J. E. Stafford and F. W. Heyl, *J. Am. Chem.* **78**, 430 (1956); [b]G. Opitz and W. Merz, *Annalen* **652**, 139 (1962); (c) *Idem, Ibid.* **652**, 158 (1962).
[30]C. T. Yoxall, Ph.D. Dissertation, University of Salford, 1971.
[31]U. K. Pandit, M. J. M. Pollmann and H. O. Huisman, *Chem. Commun.* 527 (1969).
[32]N. F. Firrell, Ph.D. Dissertation, University of Salford, 1970.
[33]A. J. Birch, E. G. Hutchinson and G. Subba Rao, *J. Chem. Soc.* (C), 637 (1971).
[34]N. F. Firrell, P. W. Hickmott and B. J. Hopkins, *Ibid.* (B) 351 (1971).
[35]J. N. Murrell, *Theory of the Electronic Spectra of Organic Molecules*, pp. 145–155. Wiley, New York (1963).
[36]P. W. Hickmott and C. T. Yoxall, *J. Chem. Soc.* Perkin II, 890 (1972).
[37]F. W. Heyl and M. E. Herr, *J. Am. Chem. Soc.* **75**, 1918 (1953).
[38]N. J. Leonard and W. J. Musliner, *J. Org. Chem.* **31**, 639 (1966).
[39]M. E. Herr and F. W. Heyl, *J. Am. Chem. Soc.* **75**, 5927 (1953).
[40a]P. Madsen and S.-O. Lawesson, *Rec. Trav. Chim.* **85**, 753 (1966); [b]G. Bianchetti, P. D. Croce and D. Pocar, *Tetrahedron Letters* 2039 (1965); [c]G. Bianchetti, P. D. Croce, D. Pocar, R. Stradi and G. G. Gallo, *Gazz. Chim. Ital.* **97**, 564 (1967).
[41]D. A. Evans and P. J. Sidebottom, personal communication.
[42]A. J. Birch, E. G. Hutchinson and G. Subba Rao, *Chem. Commun.* 657 (1970).
[43]K. A. Parker and R. W. Kosley, *Tetrahedron Letters* 3039 (1975).
[44]K. A. Parker, R. W. Kosley, S. L. Buchwald and J. J. Petraitis, *J. Am. Chem. Soc.* **98**, 7104 (1976).
[45]See Ref. 1, Scheme 23.
[46a]C. Hubschwerlen and J.-P. Fleury, *Tetrahedron* **33**, 761 (1977); [b]F. Eiden and B. S. Nagar, *Arch. Pharm.* **299**, 493 (1966).
[47]R. Bucourt and J. Dubé, *Bull. Soc. Chim. Fr.* 479 (1974).
[48]G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz and R. Terrell, *J. Am. Chem. Soc.* **85**, 207 (1963).
[49]S. Hünig and H. Kahanek, *Chem. Ber.* **90**, 238 (1957), and refs. cited.
[50]C. Mannich and E. Kniss, *Chem. Ber.* **74**, 1629 (1941).
[51a]M. Julia, S. Julia and C. Jeanmart, *Acad. Sci., Paris* **251**, 249 (1960); [b]G. Stork and G. Birnbaum, *Tetrahedron Letters* 313 (1961).
[52]L. Velluz, G. Nominé, R. Bucourt, A. Pierdet and P. Dufay, *Ibid.* 127 (1961).
[53]U. K. Pandit, W. A. Z. Voorspuij and P. Houdewind, *Ibid.* 1997 (1972).
[54]P. Houdewind and U. K. Pandit, *Ibid.* 2359 (1974).
[55]F. T. Bond and W. E. Musa, *Chem. Ind.* 1380 (1966); see M. E. Kuehne, *J. Am. Chem. Soc.* **81**, 5400 (1959).
[56]M. L. Farmer, W. E. Billups, R. B. Greenlee and A. N. Kurtz, *J. Org. Chem.* **31**, 2885 (1966).
[57]U. K. Pandit and H. Bieräugel, *Rec. Trav. Chim. Pays-Bas* **95**, 223 (1976); H. Bieräugel and U. K. Pandit, *Ibid.* **98**, 496 (1979).
[58]F. Weisbuch and G. Dana, *Tetrahedron* **30**, 2873 (1974).
[59]Z. Arnold, *Coll. Czech. Chem. Commun.* **25**, 1308 (1960).
[60a]S. K. Malhotra, J. J. Hostynek and A. F. Lundin, *J. Am. Chem. Soc.* **90**, 6565 (1968); V. Van Rheenen, *Chem. Commun.* 314 (1969); [b]P. J. Barker, A. L. J. Beckwith and Y. Fung, *Tetrahedron Letters* 97 (1983), and refs. cited.
[61]A. Murai, C. Sato, H. Sasamori and T. Masamune, *Bull. Chem. Soc. Japan* **49**, 499 (1976).
[62]G. H. Alt and A. J. Speziale, *J. Org. Chem.* **31**, 2073 (1966).
[63a]W. S. Johnson, V. J. Bauer and R. W. Franck, *Tetrahedron Letters* 72 (1961); J. A. Marshall and W. S. Johnson, *J. Org. Chem.* **28**, 421 (1963); [b]A. J. Birch, *J. Chem. Soc.* 1551 (1950).
[64]J. Schmitt, J. J. Panouse, A. Hallot, P. J.Cornu, P. Comoy and H. Plucket, *Bull. Soc. Chim. Fr.* 807 (1963).
[65]G. Opitz and W. Merz, *Liebigs Ann. Chem.* **652**, 163 (1962).
[66]U. K. Pandit, F. R. Mas Cabré, R. A. Gase and M. J. de Nie-Sarink, *J. Chem. Soc.* Chem. Commun. 627 (1974).
[67]H. Mazarguil and A. Lattes, *Bull. Soc. Chim. Fr.* 119 (1971).
[68]A. J. Birch, E. G. Hutchinson and G. Subba Rao, *J. Chem. Soc.* (C) 2409 (1971).
[69]S. Nakanishi, R. L. Morgan and E. V. Jensen, *Chem, Ind.* 1136 (1960); R. Joly and J. Warnant, *Bull. Soc. Chim. Fr.* 569 (1961); D. H. R. Barton, L. S. Godinho, R. H. Hesse and M. M. Pechet, *Chem. Commun.* 804 (1968).
[70]M. E. Kuehne and J. A. Nelson, *J. Org. Chem.* **35**, 161 (1970).
[71]M. G. Ahmed, P. W. Hickmott and M. Cais, *J. Chem. Soc.* Dalton 1557 (1977).
[72]R. A. Ferri, G. Pitacco and E. Valentin, *Tetrahedron* **34**, 2537 (1978).
[73]D. Beck and K. Schenker, *Helv. Chim. Acta* **54**, 734 (1971).
[74]W. Nagata, M. Yoshioka and M. Murakami, *J. Am. Chem. Soc.* **94**, 4654 (1972).
[75]P. W. Hickmott, R. D. Soelistyowati and C. T. Yoxall, unpublished results.
[76]U.S. Patent 3351642 (1967); *Chem. Abstr.* **68**, 114854 (1968).
[77]J. N. Gardner, B. A. Anderson and E. P. Oliveto, *J. Org. chem.* **34**, 107 (1969).
[78]B. Gadsby and M. R. G. Leeming, *Chem. Commun.* 596 (1968).
[79]J. Szmuszkovicz, *Adv. Org. Chem.* **4**, 1 (1963).
[80]S. A. G. De Graaf and U. K. Pandit, *Tetrahedron* **29**, 4263 (1973).
[81]U. H. Pandit and S. A. G. De Graaf, *Chem. Commun.* 381 (1970).
[82]C. F. Huebner, L. Dorfman, M. M. Robinson, E. Donoghue, W. G. Pierson and P. Strachan, *J. Org. Chem.* **28**, 3134 (1963); K. C. Brannock, R. D. Burpitt, V. W. Goodlett and J. G. Thweatt, *Ibid.* **29**, 818 (1964).
[83]A. J. Birch and E. G. Hutchinson, *J. Chem. Soc.* (C), 3671 (1971).
[84]W. Langenbeck, O. Gödde, L. Weschky and R. Schaller, *Ber. Dtsch. Chem. Ges.* **75**, 232 (1942).
[85]G. Satzinger, *Liebigs Ann. Chem.* **728**, 64 (1969).
[86]J. O. Madsen and S. O. Lawesson, *Tetrahedron* **24**, 3369 (1968).
[87a]S. Danishefsky and R. Cunningham, *J. Org. Chem.* **30**, 3676 (1965); [b]W. G. Dauben and A. P. Kozikowsky, *J. Am. Chem. Soc.* **96**, 3664 (1974).

[88]G. A. Berchtold, J. Ciabattoni and A. A. Turvick, *J. Org. Chem.* **30**, 3679 (1965).
[89]G. Opitz and W. Merz, *Liebigs Ann. Chem.* **652**, 163 (1962).
[90]H. Nozaki, T. Yamaguti, S. Veda and K. Kondo, *Tetrahedron* **24**, 1445 (1968).
[91]A. J. Birch and E. G. Hutchinson, *J. Chem. Soc.* Perkin I, 1757 (1973).
[92]I. Saito, A. Nakata and T. Matsuura, *Tetrahedron Letters* 1697 (1981).
[93]S. D. Darling and N. Subramanian, Ibid. 3279 (1975).
[94]G. Pitacco, A. Risaliti, M. L. Trevisan and E. Valentin, *Tetrahedron* **33**, 3145 (1977).
[95]S. Yamada, M. Shibasaki and S. Terashima, *Tetrahedron Letters* 377 (1973).
[96]S. Yamada, M. Shibasaki and S. Terashima, *Ibid.* 381 (1973).
[97]S. Tanimoto, Y. Matsumura, T. Sugimoto and M. Okano, *Ibid.* 2899 (1977).
[98]S. Tanimoto, *Ibid.* 2903 (1977); S. Tanimoto, R. Schäfer, J. Ippen and E. Vogel, *Angew. Chem.* **88**, 643 (1976).
[99]N. F. Firrell, P. W. Hickmott and B. J. Hopkins, *J. Chem. Soc.* (C), 1477 (1970).
[100]P. W. Hickmott, B. J. Hopkins and C. T. Yoxall, *Tetrahedron Letters* 2519 (1970).
[101]P. W. Hickmott and C. T. Yoxall, *J. Chem. Soc.* (C), 1829 (1971).
[102]P. Houdewind, J. C. Lapierre Armande and U. K. Pandit, *Tetrahedron Letters* 591 (1974).
[103]I. Fleming and M. H. Karger, *J. Chem. Soc.* (C), 226 (1967).
[104]J. W. Lewis and P. L. Myers, *Ibid.* (C), 753 (1971).
[105]G. Dana and F. Weisbuch, *Tetrahedron* **30**, 2879 (1974).
[106]M. Miocque, M. Duchon d'Engenieres and O. Lafont, *Tetrahedron Letters* 2133 (1976).
[107]K. N. Houk, J. K. George and R. E. Duke, *Tetrahedron* **30**, 523 (1974).
[108]L. C. Dunn, Y.-M. Chang and K. H. Houk, *J. Am. Chem. Soc.* **98**, 7095 (1976); L. C. Dunn and K. N. Houk, *Tetrahedron Letters* 3411 (1978).
[109]Y. N. Gupta, S. R. Mani and K. N. Houk, *Ibid.* 495 (1982).
[110]S. A. G. De Graaf and U. K. Pandit, *Tetrahedron* **30**, 1115 (1974).
[111a]G. Opitz and F. Schweinsberg, *Angew. Chem.* Internat. Ed. **4**, 786 (1965); [b]H. Mazarguil and L. Lattes, *Bull. Soc. Chem. Fr.* 500 (1974) and refs. therein.
[112]F. Benedetti, G. Pitacco and E. Valentin, *Tetrahedron* **35**, 2293 (1979).
[113]L. A. Paquette and R. W. Begland, *J. Org. Chem.* **34**, 2896 (1969).
[114]M. Perelman and S. A. Mizsak, *J. Am. Chem. Soc.* **84**, 4988 (1962); G. Opitz and J. Koch, *Angew. Chem.* Internat. Ed. **2**, 152 (1963); A. K. Bose and G. Mina, *J. Org. Chem.* **30**, 812 (1965).
[115]F. Effenberger and R. Maier, *Angew. Chem.* Internat. Ed. **5**, 416 (1966).
[116]M. S. Manhas, J. W. Brown, U. K. Pandit and P. Houdewind, *Tetrahedron* **31**, 1325 (1975); M. S. Manhas, J. W. Brown and U. K. Pandit, *Heterocycles* **3**, 117 (1975).
[117]U. K. Pandit, H. R. Reus and K. De Jonge, *Rec. Trav. Chim.* **89**, 956 (1970).
[118]See P. W. Hickmott and H. Suschitzky, *Chem. & Ind.* 1188 (1970), and refs. therein.
[119]U. K. Pandit, M. J. M. Pollmann and H. O. Huisman, *Chem. Commun.* 527 (1969); M. J. M. Pollmann, U. K. Pandit and H. O. Huisman, *Rec. Trav. Chim.* **89**, 941 (1970).
[120]P. Devi, J. S. Sandhu and G. Thyagarajan, *Chem. Commun.* 710 (1979).
[121]G. Kresze and J. Firl, *Tetrahedron Letters* 1163 (1965).
[122]R. Mayer and K. Gewald, *Angew. Chem.* Int. Ed. **6**, 294 (1967); R. Mayer, G. Laban and M. Wirth, *Liebigs Ann. Chem.* **703**, 140 (1967).
[123]J.-P. Sauvé and N. Lozac'h, *Bull. Soc. Chem. Fr.* 2016 (1970).
[124]R. Bucourt and J. Dube, *Bull. Soc. Chem. Fr.* II-33 (1978).
[125]P. Wittig and R. Mayer, *Z. Chem.* **7**, 306 (1967).
[126]G. Pitacco, F. P. Colonna, E. Valentin and A. Risoliti, *J. Chem. Soc.* Perkin I, 1625 (1974).
[127]D. Végh, J. Kováč, M. Dandárová and L. IVančo, *Coll. Czech. Chem. Commun.* **45**, 155 (1980).
[128]K. Hafner, *Pure Appl. Chem.* **28**, 153 (1971) and Refs. therein.
[129]K. Hafner and M. Suda, *Agnew. Chem.* Int. Ed. **15**, 314 (1976).
[130]K. Hafner, K. H. Hafner, C. König, M. Kreuder, G. Ploss, G. Schulz, E. Sturm and K. H. Vöpel, *Agnew. Chem.* **75**, 35 (1963); K. Hafner, K. H. Vöpel, G. Ploss and C. König, *Liebigs Ann. Chem.* **661**, 52 (1963); U. Müller-Westerhoff, *J. Am. Chem. Soc.* **92**, 4849 (1970).
[131]M. Bachmann and H. Neunhoeffer, *Liebigs Ann. Chem.* 675 (1979).
[132]C. E. Dahl, R. W. Gray and A. S. Dreiding, *Helv. Chim. Acta* **57**, 1169 (1974); B. Szechner and A. S. Dreiding, *Ibid.* **59**, 21 (1976).
[133]E. Ott, G. Dittus and H. Weisenberger, *Chem. Ber.* **76**, 84 (1943); H. Böhme and F. Soldan, *Ibid.* **94**, 3109 (1961); H. Bredereck, F. Effenberger and H. P. Beyerlin, *Ibid.* **97**, 3081 (1964).
[134]H. Weingarten and W. A. White, *J. Am. Chem. Soc.* **88**, 850 (1966).
[135]H. Weingarten and W. A. White, *J. Org. Chem.* **31**, 2874 (1966).
[136]S. M. McElvain and B. E. Tate, *J. Am. Chem. Soc.* **67**, 202 (1945).
[137]H. Baganz and L. Domaschke, *Chem. Ber.* **95**, 2095 (1962).
[138]C. Jutz and H. Amschler, *Ibid.* **96**, 2100 (1963).
[139]Y. Sato, M. Kato, T. Aoyama, M. Sugiura and H. Shirai, *J. Org. Chem.* **43**, 2466 (1978).
[140]H. G. Viehe and S. Y. Delavarenne, *Chem. Ber.* **103**, 1216 (1970).
[141]S. E. Tolchinskii, A. V. Dogadina, I. A. Maretina and A. A. Petrov, *J. Org. Chem. USSR* **15**, 1642 (1979).
[142]V. Wolf and F. Kowitz, *Liebigs Ann. Chem.* **638**, 33 (1960).
[143]H. G. Viehe, R. Fuks and M. Reinstein, *Agnew. Chem.* Int. Ed. **3**, 581 (1964).
[144]R. Fuks and H. G. Viehe, *Tetrahedron* **25**, 5721 (1969).
[145]J. Ficini, J. Angelo and S. Falou, *Tetrahedron Letters* 1645 (1977).
[146]G. L'abbé, C.-C. Yu and S. Toppet, *Angew. Chem.* Int. Ed. **16**, 475 (1977).
[147]D. H. Clemens, A. J. Bell and J. L. O'Brien, *J. Org. Chem.* **29**, 2932 (1964); C. F. Hobbs and H. Weingarten, *Ibid.* **33**, 2385 (1968).
[148]J. Ficini, *Tetrahedron* **32**, 1449 (1976).
[149]C. F. Hobbs and H. Weingarten, *J. Org. Chem.* **39**, 918 (1974).
[150a]H. Weingarten and J. S. Wager, *Ibid.* **35**, 1750 (1970); Idem, *Tetrahedron Letters* 3267 (1969); F. Effenberger and O.

Gerlach, *Tetrahedron Letters* 1669 (1970); [b]M. Cariou, R. Carlier and J. Simonet, *J. Chem. Soc. Chem. Commun.* 876 (1983).
[151]D. H. R. Barton, G. Hewitt and P. G. Sammes, *J. Chem. Soc.* (C) 16 (1969).
[152]A. Étienne, G. Lonchambon and P. Giraudeau, *C.R. Acad. Science Paris* **285C**, 321 (1977); D. H. Clemens, J. A. Bell and J. L. O'Brien, *J. Org. Chem.* **29**, 2932 (1964).
[153]K. Hafner and F. Schmidt, *Tetrahedron Letters* 2237 (1971).
[154a]G. Tacconi, M. Leoni, P. Righetti and G. Desimoni, *J. Chem. Soc.* Perkin I, 2687 (1979); [b]R. Gompper and U. Wolf, *Tetrahedron Letters* 4263 (1978); [c]H. Weingarten and J. S. Wager, *Syn. Inorg. Metal.-Org. Chem.* **1**, 123 (1971); [d]M. Von Strandtmann, M. P. Cohen and J. Shavel, *U.S. Pat.* 3,752,830 (1973); *Chem. Abstr.* **79**, 92193x (1973).
[155]D. Pocar, L. M. Rossi and R. Stradi, *Synthesis* 684 (1976).
[156]D. H. Clemens, A. J. Bell and J. L. O'Brien, *Tetrahedron Letters* 3257 (1965).
[157a]S. Rajappa, R. Screenivasan, B. G. Advani, R. H. Summerville and R. Hoffmann, *Indian J. Chem.* **15B**, 297 (1977); [b]S. Rajappa, B. G. Advani and R. Sreenivasan, *Synthesis* **9**, 656 (1974); [c]*Idem.*, *Tetrahedron* **33**, 1057 (1977); [d]H. Schaefer and K. Gewald, *J. Prakt. Chem.* **322**, 87 (1980); [e]*Idem.*, *Z. Chem.* **18**, 335 (1978).
[158a]A. Kirrmann, P. Duhamel and L. Duhamel, *Bull. Soc. Chim. Fr.* 1091 (1968); [b]L. Duhamel and P. Duhamel, *Ibid.* 1999 (1969); L. Duhamel, P. Duhamel and A. Jarry, *Ibid.* 1797 (1970); *Idem.*, *Tetrahedron Letters* 1053 (1970).
[159]G. Smolinsky, *J. Am. Chem. Soc.* **83**, 4483 (1961); G. Smolinsky and B. I. Feuer, *J. Org. Chem.* **31**, 1423 (1966).
[160]V. Wolf and H. Piater, *Liebigs Ann. Chem.* **696**, 90 (1966).
[161]R. C. Doss and H. W. Bost, *U.S.-Pat.* 2881217 (1959) [*Chem. Abstr.* **53**, 19886a (1959)].
[162]A. Kirrmann, L. Duhamel and P. Duhamel, *Bull. Soc. Chim. Fr.* 1732 (1966).
[163]L. Duhamel, P. Duhamel, H. Lamandain and D. Lefèvre, *Ibid.* 4642 (1967).
[164]L. Duhamel, P. Duhamel and G. Plé, *Ibid.* 4423 (1968).
[165a]L. Duhamel, P. Duhamel and G. Plé, *C.R. Acad. Sci. Paris* **271C**, 751 (1970); [b]*Idem.*, *Bull. Soc. Chim. Fr.* 4169 (1971).
[166]A. Halleux and H. G. Viehe, *J. Chem. Soc.* (C), 1726 (1968).
[167]P. Duhamel, L. Duhamel, C. Collett and A. Haider, *C. R. Acad. Sci. Paris* **273C**, 1461 (1971).
[168]P. Duhamel, L. Duhamel, J. L. Klein and A. Jarry, *Bull. Soc. Chim. Fr.* 3883 (1969).
[169a]H. Bredereck, G. Simchen and W. Griebenow, *Chem. Ber.* **107**, 1545 (1974); [b]H. Bredereck, G. Simchen and G. Kapaun, *Ibid.* **104**, 792 (1971).
[170a]P. Duhamel, L. Duhamel and V. Truxillo, *Tetrahedron Letters* 51 (1974); [b]L. Duhamel, P. Duhamel and G. Plé, *Ibid.* **47** (1974); [c]*Idem.*, *Ibid.* 43 (1974); [d]A. Halleux and H. G. Viehe, *J. Chem. Soc.* (C), 881 (1970).
[171]G. Plé, *Bull. Soc. Chim. Fr.* 2213 (1975).
[172a]Z. Arnold, *Coll. Czech. Chem. Commun.* **38**, 1168 (1973); [b]C. Reichardt and K. Schagerer, *Liebigs Ann. Chem.* 530 (1982).
[173a]L. Duhamel and N. Mancelle, *Tetrahedron* **31**, 2691 (1975); [b]P. Duhamel, L. Duhamel and J.-L. Klein, *Bull. Soc. Chim. Fr.* 2517 (1973).
[174a]L. Duhamel, P. Duhamel and J.-C. Legal, *Ibid.* 3239 (1972); [b]L. Duhamel, P. Duhamel and J. Y. Valnot, *C.R. Acad. Sci. Paris* **271C**, 1471 (1970); P. Duhamel, L. Duhamel and J.-C. Legal, *Ibid.* **271C**, 156 (1970); P. Duhamel, L. Duhamel, J.-C. Legal and J.-Y. Valnot, *Bull. Soc. Chim. Fr.* 3222 (1972).
[175]L. Citerio, M. L. Saccarello, R. Stradi and B. Gioia, *J. Chem. Res.* (S), 347 (1979); (M), 4001.
[176]R. Stradi and G. Verga, *Synthesis* 688 (1977).
[177]L. Citerio, M. L. Saccarello and R. Stradi, *J. Chem. Soc.* Perkin I, 722 (1980).
[178]L. Duhamel, P. Duhamel, S. Combrisson and P. Siret, *Tetrahedron Letters* 3603 (1972).
[179a]P. Ferruti, A. Segre and A. Fere, *J. Chem. Soc.* (C), 2721 (1968); [b]Reviewed by A. H. Schmidt and W. Reid, *Synthesis* 869 (1978).
[180]H. Böhme and W. Höver, *Liebigs Ann. Chem.* **748**, 59 (1971).
[181]C. H. McKeever and J. W. Nemec, *U.S. Pat.* 2,617,827 (1952); *Chem. Abstr.* **48**, 1429 (1954).
[182]M. F. Fegley, N. M. Bortnick and C. H. McKeever, *J. Am. Chem. Soc.* **79**, 4140 (1957).
[183a]S. Baroni, R. Rivera and R. Stradi, *Tetrahedron Letters* 889 (1980); [b]W. A. White and H. Weingarten, *J. Org. Chem.* **32**, 213 (1967).
[184]N. J. Leonard and R. R. Sauers, *Ibid.* **21**, 1187 (1956).
[185]W. Reid and W. Köppler, *Liebigs Ann. Chem.* **687**, 183 (1965).
[186]K. N. Woodward, Ph.D. Dissertation, Salford, 1976.
[187]R. Epsztein and B. Herman, *Chem. Commun.* 1250 (1980); R. Epsztein and N. Le Goff, *Tetrahedron Letters* 1965 (1981).
[188]R. Gompper and U. Heinemann, *Angew. Chem.* Int. Ed. **19**, 216 (1980).
[189]R. Weiss, H. Wolf, U. Schubert and T. Clark, *J. Am. Chem. Soc.* **103**, 6142 (1981).
[190]M. F. Fegley, N. M. Bortnick and C. H. McKeever, *Ibid.* **79**, 4144 (1957).
[191]M. F. Fegley, N. M. Bortnick, C. H.. McKeever and F. B. Farnum, *Ibid.* **79**, 4734 (1957).
[192]M. F. Fegley, N. M. Bortnick and C. H. McKeever, *Ibid.* **79**, 4736 (1957).
[193]P. W. Hickmott, B. J. Hopkins, G. Sheppard and D. J. Baraclough, *J. Chem. Soc.* Perkin I, 1639 (1972).
[194]G. Crispi, P. Giacconi, E. Rossi and R. Stradi, *Synthesis* 787 (1982).
[195]Review: N. Wiberg, *Angew. Chem.* Int. Ed. **7**, 766 (1968), and refs. cited.
[196]R. L. Pruett, J. T. Barr, K. E. Rapp, C. T. Bahner, J. D. Gibson and R. H. Lafferty, *J. Am. Chem. Soc.* **72**, 3649 (1950).
[197]H. W. Wanzlick, F. Esser and H. J. Kleiner, *Chem. Ber.* **96**, 1208 (1963), and refs. cited; H. W. Wanzlick, E. Schikora and H. J. Kleiner, *G.P.* 1,163,331 (1964).
[198]H. E. Winberg, J. E. Carnahan, D. D. Coffman and M. Brown, *J. Am. Chem. Soc.* **87**, 2055 (1965).
[199]D. M. Lemal and K. I. Kawano, *Ibid.* **84**, 1761 (1962).
[200]H. E. Winberg, J. R. Downing and D. D. Coffman, *Ibid.* **87**, 2054 (1965); *U.S. Pat.* 3,377,291 (1964); *U.S. Pat.* 3,502,588 (1966); *U.S. Pat.* 3,360,473 (1967).
[201]N. Wiberg and J. W. Buchler, *Agnew. Chem.* **74**, 490 (1962); *Idem.*, *Chem. Ber.* **97**, 618 (1964); *U.S. Pat.* 3,239,518 (1966).
[202a]H. W. Wanzlick, *Angew. Chem.* **72**, 494 (1960); *Ibid.* **73**, 493, 764 (1961); H. Wanzlick and E. Schikora, *Chem. Ber.* **94**, 2389 (1961); H. W. Wanzlick, *Angew. Chem.* Int. Ed. **1**, 75 (1962); [b]H. W. Wanzlick and H. J. Kleiner, *Chem. Ber.* **96**, 3024 (1963).
[203]D. M. Lemal, R. A. Lovald and K. I. Kawano, *J. Am. Chem. Soc.* **86**, 2518 (1964).
[204]H. W. Wanzlick and B. Koenig, *Chem. Ber.* **97**, 3513 (1964); H. E. Winberg and D. D. Coffman, *J. Am. Chem. Soc.* **87**, 2776 (1965).

[205]H. G. Viehe, Z. Janousek, R. Gompper and D. Lach, *Angew. Chem.* Int. Ed. **12**, 566 (1973).
[206]L. Ghosez and J. Marchand-Brynaert, *α-Halo Enamines and Keterinimium Salts*, in H. Böhme and H. G. Viehe (Eds.), *Iminium Salts in Organic Chemistry*, Part I, Vol. 9 in the series *Advances Organic Chemistry* (Edited by E. C. Taylor), p. 421. Wiley, New York (1976).
[207a]J. von Braun and A. Heymans, *Ber. Dtsch. Chem. Ges.* **62**, 409 (1929); H. Eilingsfeld, M. Seefelder and H. Weidirger, *Angew. Chem.* **72**, 836 (1960); H. Gross and J. Gloede, *Chem. Ber.* **96**, 1387 (1963); H. Eilingsfeld, G. Neubauer, M. Seefelder and H. Weidinger, *Ibid.* **97**, 1232 (1964); L. Ghosez, B. Haveaux and H. G. Viehe, *Angew. Chem.* Int. Ed. **8**, 454 (1969); B. Haveaux, A. Dekoker, M. Rens, A. R. Sidani, J. Toye and L. Ghosez, *Organic Synthesis* **59**, 26 (1980); [b]R. Buyle and H. G. Viehe, *Tetrahedron* **24**, 4217 (1968); [c]C. Bernard and L. Ghosez, *Chem. Commun.* 940 (1980).
[208]A. Colens, M. Demuylder, B. Téchy and L. Ghosez, *Nouv. J. Chim.* **1**, 369 (1977).
[209]H. Weingarten, *J. Org. Chem.* **35**, 3970 (1970).
[210]A. J. Speziale and R. C. Freeman, *J. Am. Chem. Soc.* **82**, 909 (1960).
[211]J. Marchand-Brynaert and L. Ghosez, *Ibid.* **94**, 2870 (1972).
[212]A. Sidani, J. Marchand-Brynaert and L. Ghosez, *Angew. Chem.* Int. Ed. **13**, 267 (1974).
[213]J. Marchand-Brynaert and L. Ghosez, *Tetrahedron Letters* 377 (1974).
[214]C. Hoornaert, A. M. Hesbain-Frisque and L. Ghosez, *Angew. Chem.* Int. Ed. **14**, 569 (1975).
[215]M. Henriet, M. Houtekie, B. Techy, R. Touillaux and L. Ghosez, *Tetrahedron Letters* 223 (1980).
[216]J. Marchand-Brynaert and L. Ghosez, *J. Am. Chem. Soc.* **94**, 2869 (1972).
[217]M. De Poortere, J. Marchand-Brynaert and L. Ghosez, *Angew. Chem.* Int. Ed. **13**, 267 (1974).
[218]A. Colens and L. Ghosez, *Nouv. J. Chim.* **1**, 371 (1977).
[219]A. Devos, J. Remion, A-M. Frisque-Hesbain, A. Colens and L. Ghosez, *Chem. Commun.* 1180 (1979).
[220]C. R. Hall and N. E. Williams, *Tetrahedron Letters* 999 (1982).
[221]J. Toye and L. Ghosez, *J. Am. Chem. Soc.* **97**, 2276 (1975).
[222]J. Marchand-Brynaert, M. Moya-Portuguez, D. Lesuisse and L. Ghosez, *Chem. Commun.* 173 (1980).
[223]C. Houge, A-M. Frisque-Hesbain, A. Mockel and L. Ghosez, *J. Am. Chem. Soc.* **104**, 2920 (1982).
[224]R. Da Costa, M. Gillard, J. B. Falmagne and L. Ghosez, *Ibid.* **101**, 4381 (1979).
[225]M. Rens and L. Ghosez, *Tetrahedron Letters* 3765 (1970).
[226]P. Vittorelli, H. Heimgartner, H. Schmid, P. Hoet and L. Ghosez, *Tetrahedron* **30**, 3737 (1974).
[227]A. Demoulin, H. Gorissen, A-M. Hesbain-Frisque and L. Ghosez, *J. Am. Chem. Soc.* **97**, 4409 (1975); F. Sainte, B. Serckx-Poncin, A-M. Hesbain-Frisque and L. Ghosez, *Ibid.* **104**, 1428 (1982).
[228]L. Ghosez, P. Notté, C. Bernard-Henriet and R. Maurin, *Heterocycles* **15**, 1179 (1981).
[229]J. M. J. Tronchet, B. Baehler and A. Bonepant, *Helv. Chim. Acta.* **59**, 941 (1976).
[230]H. Böhme and P. Sutoyo, *Tetrahedron Letters* 1671 (1981).
[231]M. Gillard, C. T'Kint, E. Sonveaux and L. Ghosez, *J. Am. Chem. Soc.* **1101**, 5837 (1979).
[232]L. Ghosez, A. Demoulin, M. Henriet, E. Sonveaux, M. Van Meerssche, G. Germain and J. P. Declercq, *Heterocycles* **7**, 895 (1977).
[233]L. Ghosez, B. Haveaux and H. G. Viehe, *Angew. Chem.* Int. Ed. **8**, 454 (1969).
[234]C. Sevane, J. L. Soto and M. Quinteiro, *Heterocycles* **14**, 337 (1980), and refs. therein.
[235]S. I. Radchenko, *Zh. Org. Khim.* **13**, 504 (1977).
[236]R. Gompper and W. Elser, *Tetrahedron Letters* 1971 (1964).
[237]H. Bredereck, F. Effenberger and H. P. Beyerlin, *Chem. Ber.* **97**, 3081 (1964).
[238]W. Walter and H.-W. Meyer, *Liebigs Ann. Chem.* 19 (1975).
[239]W. E. Bottomley and G. V. Boyd, *J. Chem. Soc.* Chem. Commun. 790 (1980).
[240]R. P. Woodbury and M. W. Rathke, *J. Org. Chem.* **43**, 881 (1978).
[241]H. G. Viehe, Z. Janousek, R. Gompper and D. Lach, *Angew. Chem.* Int. Ed. **12**, 566 (1973).
[242]R. Gompper and C. S. Schneider, *Synthesis* 213 (1979).
[243]T. Nakai and M. Okawara, *Chem. Commun.* 907 (1970).
[244]J.-C. Blazejewski and C. Wakselman, *J. Chem. Soc.* Perkin I, 2845 (1980).
[245]D. Cantacuzene, C. Wakselman and R. Dorme, *Ibid.* Perkin I, 1365 (1977).
[246a]T. Oishi, M. Ochiai, M. Nagai and Y. Ban, *Tetrahedron Letters* 497 (1968); [b]A. E. Wick, D. Felix, K. Steen and A. Eschenmoser, *Helv. Chim. Acta* **47**, 2425 (1964); [c]D. J. Dawson and R. E. Ireland, *Tetrahedron Letters* 1899 (1968).
[247]M. Fukuda, K. Kan, Y. Okamoto and H. Sakurai, *Bull. Chem. Soc. Japan* **48**, 2103 (1975).
[248]P. Cresson and M. Huche, *C.R. Acad. Sci. Paris* **274C**, 2108 (1972): P. Cresson, *Ibid.* **275C**, 383 (1972); M. Huché and P. Cresson, *Bull. Soc. Chim. Fr.* 2040 (1974).
[249]M. Huché, *Tetrahedron Letters* 2607 (1976).
[250]J. Corbier, P. Cresson and P. Jelenc, *C.R. Acad. Sci. Paris* **270**, 1890 (1970).
[251]C. R. Costin, C. J. Morrow and H. Rapoport, *J. Org. Chem.* **41**, 535 (1976).
[252]D. Felix, K. Gschwend-Steen, A. E. Wick and A. Eschenmoser, *Helv. Chim. Acta* **52**, 1030 (1969).
[253]S. Takano, E. Yoshida, M. Hirama and K. Ogasawara, *Chem. Commun.* 776 (1976).
[254]Y. Tamaru, T. Harada and Z. Yoshida, *Tetrahedron Letters* 2167 (1978).
[255]H. Neunhoeffer and G. Werner, *Liebigs Ann. Chem.* 1955 (1973).
[256]M. A. Steinfels, H. W. Krapf, P. Riedl, J. Sauer and A. S. Dreiding, *Helv. Chim. Acta* **55**, 1759 (1972); M. Hirth, H. Krapf, P. Riedl, J. Sauer and E. Oeser, *Chem. Ber.* **109**, 562 (1976); H. Krapf, P. Riedl and J. Sauer, *Ibid.* **109**, 576 (1976).
[257]P. G. Le Gras, R. L. Dyer, P. J. Clifford and C. D. Hall, *J. Chem. Soc.* Perkin 2, 2064 (1973).
[258]R. Gompper and J. Stetter, *Tetrahedron Letters* 233 (1973).
[259]L. Capuano, T. Tammer and R. Zander, *Chem. Ber.* **109**, 3497 (1976).
[260]N. P. Petukhova, N. E. Aristova, A. U. Stepanyants and E. N. Prilezhaeva, *Izv. Akad. Nauk. SSSR, Ser. Khim.* 132 (1976); *Chem. Abstr.* **85**, 20968e (1976).
[261]B. Burg, W. Dittmar, H. Reim, A. Steigel and J. Sauer, *Tetrahedron Letters* 2897 (1975).
[262]H. Neunhoeffer and G. Frey, *Liebigs Ann. Chem.* 1963 (1973); E. Oeser, *Ibid.* 1970 (1973).
[263]H. Neunoeffer and M. Bachmann, *Chem. Ber.* **108**, 3877 (1975).
[264]J. Adler, V. Boehnisch and H. Neunhoeffer, *Ibid.* **111**, 240 (1978).
[265]W. Steglich, E. Buschmann and O. Hollitzer, *Angew. Chem.* **86**, 596 (1974).
[266]V. Aggarwal, A. Kumar, H. Ila and H. Junjappa, *Synthesis* 157 (1981).
[267]R. Gompper and B. Wetzel, *Tetrahedron Letters* 529 (1971).

[268]Review: H. Ahlbrecht, *Chimia* **31**, 391 (1977).
[269]C. Wiaux-Zamar, J.-P. Dejonghe, L. Ghosez, J. F. Normant and J. Villieras, *Angew. Chem.* Int. Ed. **15**, 371 (1976).
[270]L. Duhamel and J.-M. Poirier, *J. Am. Chem. Soc.* **99**, 8356 (1977); Idem, *Bull. Soc. Chim. Fr.* II–297 (1982).
[271]L. Duhamel and J.-M. Poirier, *Ibid.* **79**, 3585 (1979).
[272]J. Ficini, S. Falou, A.-M. Touzin and J. d'Angelo, *Tetrahedron Letters* 3589 (1977).
[273]L. Duhamel, J. Chauvin and A. Messier, *J. Chem. Res.* (S), 48 (1982).
[274]R. R. Schmidt, J. Talbiersky and P. Russegger, *Tetrahedron Letters* 4273 (1979).
[275]S. J. Huang and M. V. Lessard, *J. Org. Chem.* **35**, 1204 (1970).
[276]S. F. Martin and M. T. du Priest, Tetrahedron Letters 3925 (1977).
[277]H. Ahlbrecht and J. Eichler, *Synthesis* 672 (1974).
[278]B. Renger and D. Seebach, *Chem. Ber.* **110**, 2334 (1977).
[279]M. Yoshimoto, N. Ishida and T. Hiraoka, *Tetrahedron Letters* 39 (1973).
[280]H. W. Thompson and B. S. Huegi, *J. Chem. Soc.* Chem. Commun. 636 (1973).
[281]H. W. Thompson and B. S. Huegi, *Ibid.* Perkin I, 1603 (1976).
[282]H. Ahlbrecht and G. Rauchschwalbe, *Synthesis* 417 (1973).
[283]G. Rauchschwalbe and H. Ahlbrecht, *Ibid.* 663 (1974).
[284]H. Ahlbrecht and C. Vonderheid, *Ibid.* 512 (1975).
[285]H. Ahlbrecht and C. S. Sudheendranath, *Ibid.* 717 (1982).
[286]D. A. Evans, C. H. Mitch, R. C. Thomas, D. M. Zimmerman and R. L. Robey, *J. Am. Chem. Soc.* **102**, 5955 (1980).
[287]H. Ahlbrecht, G. Bonnet, D. Enders and G. Zimmermann, *Tetrahedron Letters* 3175 (1980).
[288]A. I. Meyers and G. E. Jagdmann, *J. Am. Chem. Soc.* **104**, 877 (1982).
[289]E.-U. Würthwein, E. Wilhelm and B. Seitz, *Tetrahedron Letters* 581 (1983).
[290]M. E. Jung and J. J. Shapiro, *J. Am. Chem. Soc.* **102**, 7862 (1980).
[291]Y.-S. Cheng, F. W. Fowler and A. T. Lupo, *Ibid.* **103**, 2090 (1981).
[292]S. D. Worley, K. G. Taylor, B. Venugopalan and M. S. Clark, *Tetrahedron* **34**, 833 (1978).
[293]A. Demoulin, H. Gorissen, A.-M. Hesbain-Frisque and L. Ghosez, *J. Am. Chem. Soc.* **97**, 4409 (1975).
[294]Y. Nomura, Y. Takeuchi, S. Tomoda and M. M. Ito, *Bull. Chem. Soc. Japan* **54**, 2779 (1981).
[295]Y. Nomura, Y. Takeuchi, S. Tomoda and M. M. Ito, *Ibid.* **54**, 261 (1981).
[296]R. Gompper and U. Heinemann, *Angew. Chem.* Int. Ed. **19**, 217 (1980).
[297]R. Gompper and U. Heinemann, *Ger. Pat.* 2,919,891 (1979) (*Chem. Abstr.* **94**, 174689n (1981); *Idem.*, *Angew. Chem.* Int. Ed. **20**, 296 (1981).
[298]J. P. Schoeni and J.-P. Fleury, *Tetrahedron* **31**, 671 (1975).
[299]J.-P. Fleury, *Heterocycles* **14**, 1581 (1980).
[300]C. Hubschwerlen and J.-P. Fleury, *Tetrahedron* **33**, 761 (1977).
[301]B. Serckx-Poncin, A.-M. Hesbain-Frisque and L. Ghosez, *Tetrahedron Letters* 3261 (1982).
[302]O. Meth-Cohn, B. Narine and B. Tarnowski, *J. Chem. Soc.* Perkin I, 1520 (1981); O. Meth-Cohn, S. Rhouati, B. Tarnowski and A. Robinson, *Ibid.* 1537 (1981).
[303]O. Meth-Cohn, B. Narine and B. Tarnowski, *Ibid.* Perkin I, 1531 (1981).
[304]D. L. Boger, *Tetrahedron* **39**, 2939 (1983).
[305]P. E. van Rijn, W. Klop, H. D. Verkruijsse, P. von R. Schleyer and L. Brandsma, *J. Chem. Soc. Chem. Commun.* 79 (1983).