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ENAMINES: RECENT ADVANCES IN SYNTHETIC, SPECTROSCOPIC, MECHANISTIC, AND STEREOCHEMICAL ASPECTS—I

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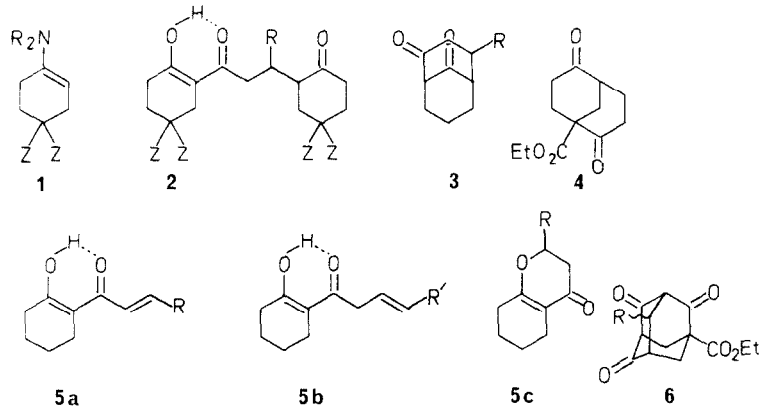
1. INTRODUCTION

There can be few papers that have created as much activity as the reports by Stork *et al.* on the synthetic applications of enamines.[1] Although enamine reactivity has been known since 1883 when first Collie[2] and later Benary[3] and then Robinson,[4] described the C-alkylation or acylation of aminocrotonic esters, there can be no doubt that the generality and wide ranging applicability of the reaction of enamines with electrophiles was not realised until the pioneering work of Stork in 1954. The C-alkylation and acylation of a carbonyl compound *via* an enamine intermediate has consequently become known as the Stork reaction.[5] However this is too narrow a definition. In the definitive paper[6] on this subject Stork referred to factors affecting the structure and reactivity of enamines, the spectroscopic properties, preparation, alkylation with alkyl halides and electrophilic olefins, acylation, synthesis of carbocyclic

compounds, and the synthesis, alkylation and hydrolysis of dienamines. In other publications the tosylation of enamines,[7] the synthesis of bridged bicyclic compounds and ring enlargement,[8] heterocyclic synthesis,[9,10] natural product synthesis,[11] and formation and reaction of metallo-enamines[12] were described. This covers most of the sections into which this report is divided.

Much further work on enamine chemistry has been carried out by other chemists, too numerous to mention individually, since Stork's early reports, and many different types of product have been isolated. However the majority of this work is conceptually no different to that exemplified by Stork, and is really an extension to the scope of the reaction. Unlike say the Wittig reaction, with its predictable reaction pathway,[5] the product of the Stork reaction is critically dependent on the experimental conditions. The same electrophilic reagent may give completely different types of product if relatively trivial changes are made in the solvent, temperature, amine moiety in the enamine, presence or absence of additional base, molar proportion of reagents, order of adding reagents, substituents present in the enamine, etc. This of course adds to the fascination of working in this field. As an example consider the action of α,β-unsaturated acid chlorides (RCH=CHCOCl) on enamines **1** (Z=H or CO_2Et), one of several aspects of the Stork reaction which we have studied over a period of almost twenty years! Depending upon the substituents (R, Z, R_2N) and the experimental conditions, the main products obtained may be the bis-compound **2**[13,14] the bicyclic diones **3**[13,15] or **4**,[14] the C-acylated ketone **5a** together with its double bond tautomer **5b** and its cyclised derivative **5c**,[15,16] or the adamantanetrione **6**.[17]



Scheme 1.

We would therefore extend the definition of the Stork reaction so as to include the conversion of an aldehyde or ketone into a C-alkylated, acylated, carbocyclic or heterocyclic derivative by reaction of an electrophile with an enamine intermediate.

The explosive development of the Stork reaction which took place in the '60s has continued virtually unabated in the 1970s. The difference is that the Stork reaction is now no longer the sole property of a few specialists working in this field, but has taken its proper place as a valuable addition to the arsenal of synthetic methods now available to the organic chemist whatever the field he may be working in.

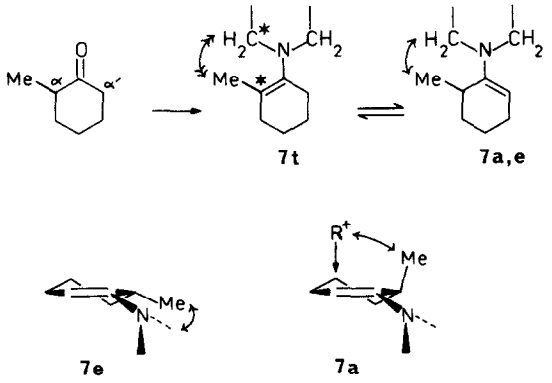
This review covers the period from 1969 to 1980. Publications prior to this have been included where necessary to put the recent developments in proper perspective. Heterocyclic enamines,[18] in which both the nitrogen and the C=C bond are in the same ring, such as tetrahydropyridines, Δ^1-pyrrolines, indoles etc., and their exo-enamine tautomers, are outside the scope of this review. In addition since recent reviews have appeared on enaminones[19] (N–C=C–C=O), cyano-enamines,[20] enamides[21] (R. CON–C=C), and iminium salts[22] ($\rangle C{=}\overset{+}{N}R_2$), these topics have also been omitted. Reviews or books published before 1969 include ones dealing with the general chemistry of enamines,[23] preparation of aldehyde enamines,[24] reactions with carbon disulphide and sulphur,[25] and allylic strain.[26] Reviews of enamine chemistry published since 1969 have dealt with general aspects,[27] synthesis of natural products,[28] acylation,[29a] and formylation of activated methylene or methyl groups with formamide acetals to give conjugated enamine intermediates (i.e. Ar.CH=CHNR$_2$, Het. CH=CHNR$_2$, etc.).[29b] In view of the volume of work still to be covered this review has been divided into two parts.

Some aspects of the Stork reaction have still not received a completely satisfactory explanation. Nevertheless we have attempted to present an underlying theme of mechanistic continuity. This has in

some cases led to a mechanistic interpretation different to that propounded in the original literature. Hopefully any controversy which ensues as a result of this will serve to catalyse the additional work necessary to elucidate the point at issue.

2. STRUCTURE AND REACTIVITY

Mixtures of structurally isomeric enamines are usually obtained from unsymmetrical ketones, such as 2-alkylcyclanones and branched chain acyclic ketones. Johnson *et al.* have shown that these isomers undergo rapid acid catalysed equilibration, but no thermal or base catalysed equilibration was observed after one week in pyrrolidine at 80°.[30]



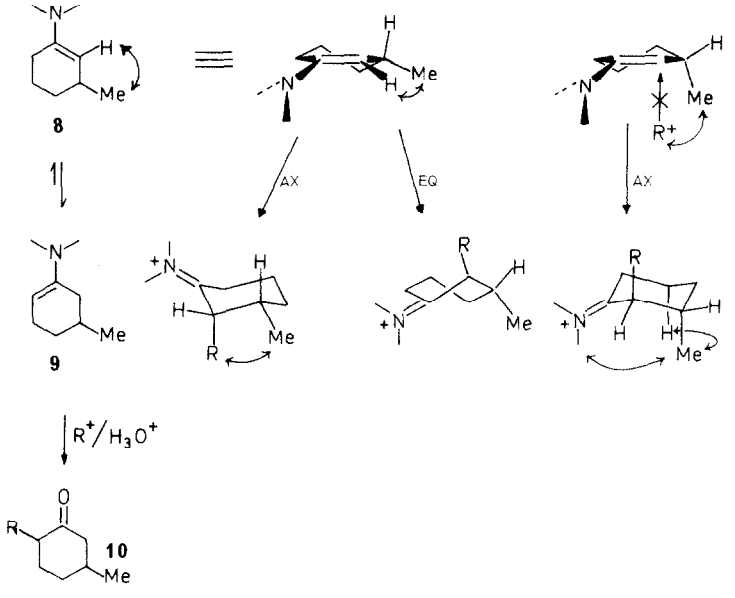
Scheme 2. a = (quasi)axial; e = (quasi)equatorial; t = tetrasubstituted.

The isomer distribution varies with the amine used. The pyrrolidine enamines of 2-methylcyclohexanones exist as <10% in the more substituted form (**7t**) whereas in the case of morpholine, isomer **7t** may form 30–65% of the enamine mixture.[30] Optically active (+)-methylpiperidine gave only the more substituted enamine **7t**. Similar differences exist between pyrrolidine and morpholine enamines of 2-alkoxycyclohexanones and 3-alkoxy-trans-decal-2-ones.[31] These differences can be attributed to different conjugating ability and steric requirements of the amine moiety which must be greater than that of a phenyl group since enamines of 1-phenylindan-2-one[32] and propiophenone[33] exist with the phenyl group twisted out of the plane of the double bond, the latter in the E-configuration. This is confirmed by the equilibrium trans-$C_6H_5CH{=}CHCH_2NMe_2 \rightleftharpoons$ trans-$C_6H_5CH_2CH{=}CHNMe_2$ which is 90% in favour of the enamine. This study also showed that dimethylamino is a better double-bond-stabilizing substituent than acetyl or n-butylsulphonyl.

The isomer containing the tetrasubstituted double bond (**7t**) would be destabilised by severe steric interactions ($A^{1,3}$ strain)[26] between the methyl and amine α-methylene groups if these were coplanar. In the ground state these steric interactions can be reduced by rotation about the N–C(sp^2) bond. However this will reduce the nitrogen lone pair interaction with the double bond, so a balance between these two conflicting requirements must clearly exist in order to minimise the energy of **7t**. The less substituted double bond isomer exists in two conformations in which the methyl substituent is quasi-equatorial (**7e**) or quasi-axial (**7a**). The former is destabilised by less severe allylic interactions ($A^{1,2}$ strain)[26] so the most stable isomer is **7a**, other factors being equal. This has several important consequences. First, α,α-dialkylation of ketones *via* their enamines is rarely observed (for exceptions see later) since, for maximum orbital interaction between the nitrogen lone pair and the π-electrons of the double bond, the starred groups (see **7t**) must become coplanar.[6] A product-like transition state would then be destabilised by the increasing $A^{1,3}$-interactions. Further alkylation, or acylation, therefore takes place at the less substituted α'-position (of the ketone) but at a reduced rate owing to developing 1,3-diaxial interactions (as shown in **7a**), or the developing steric interactions associated with a twist or boat conformation if reaction occurs from the other side of the double bond (i.e. equatorial approach). We consider axial attack on **7e** to be a higher energy process (than axial attack on **7a**) owing to developing $A^{1,3}$-interactions (see Section 5B); the evidence available indicates that equatorial attack is also less favoured.[35]

A further consequence of allylic strain is that when an equatorial 2-substituent cannot be converted into the axial conformer by ring-flipping, as with *cis*-4-t-butyl-2-methylcyclohexanone, then epimerisation to the *trans*-isomer occurs. This gives a method for the conversion of a more stable *cis*-diequatorial

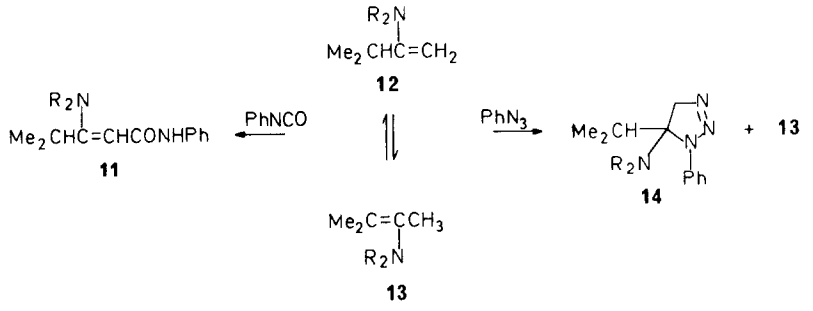
2,4-disubstituted cyclohexanone to the less stable *trans*-isomer,[30] but not for 2,6-disubstituted cyclohexanones since protonation of the resulting enamine is non-stereoselective (see Section 5A(ii) for exceptions) and a *cis–trans* mixture of ketones is obtained on hydrolysis. Allylic strain is also the reason why enamines of 3-methylcyclohexanones exist mainly as isomer **9**.[36] Other 3-substituted cyclohexanone enamines do not always follow this trend however. For example the morpholine, piperidine, and pyrrolidine enamines of 3-phenylcyclohexanone exist 100% as the Δ^1-isomer **307b** (Scheme 80; Table 6). Alkylation,[37] acylation,[38] and halogenation[39] of the enamine mixture (**8**, **9**) has been shown to give the 2-substituted-5-methylcyclohexanone as the major product. However this regioselectivity cannot be attributed to the isomer distribution of the enamines *per se*, as sometimes stated in the literature. Provided that the activation energy of the reaction is greater than the barrier to isomer interconversion it follows, from the Curtin-Hammett principle,[40] that the product distribution must reflect transition state energies rather than ground-state isomer populations. Indeed 2,5-disubstituted cyclohexanones have been obtained in yields much higher than the percentages of the Δ^6 isomer present in the parent enamines,[37] thus demonstrating the rapid equilibrium between the enamine isomers. At least in the case of product-like transition states, formation of 2-substituted-3-methylcyclohexanones will be inhibited by developing steric interactions shown in Scheme 3 [see also Section 5B(i) (e)].



Scheme 3. AX = axial attack of electrophile R^+; EQ = equatorial attack.

Similar considerations appertain to acyclic enamines. An important investigation by Pocar *et al.* has demonstrated unequivocably that (i) the less substituted enamine is the more reactive isomer and (ii) interconversion of enamine isomers may, or may not, occur during a reaction, depending upon the reagent and experimental conditions used. For example the dimethylamine enamine of methyl isopropyl ketone exists as a 50:50 mixture of **12** and **13**. However reaction with phenylisocyanate gives only 3-dimethylamino-4-methyl-2-pentenoic acid anilide (**11**) in 100% yield.[41] Under the reaction conditions the more substituted isomer (**13**), which is deactivated by $A^{1,3}$ strain, rearranges into the more reactive less substituted form (**12**). Conversely if the equilibrium mixture **12–13** is treated with 4-nitrophenylazide at room temperature in an amount equivalent to the less substituted isomer, only triazoline **14** is obtained, and the other unreacted isomer **13** can be isolated by rapid distillation.[42] Pure isomers **12a** and **12b** are obtained directly by the $TiCl_4$ method of preparation (Section 4). Similar results were obtained with the morpholine enamine, which exists as a 30:70% mixture of **12b** and **13b**, respectively. With phenyl azide the less substituted enamine reacts completely in 30 min whereas the remaining more substituted enamine takes 4 days to react (but in the less substituted form).

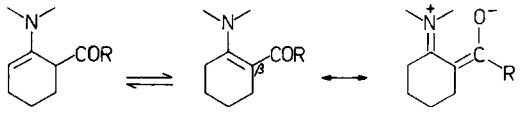
Surprisingly, however, bromination results in both enamine isomers reacting (Section 5F) and would seem indicative of a reactant-like transition state. Cyclopropyl methyl ketone enamines exist only as the less substituted form[43] whereas cyclohexyl methyl ketone enamines exist as a 27:75 mixture of more



Scheme 4. (a) R_2N = dimethylamino; (b) R_2N = morpholino.

and less substituted forms, respectively.[44] However only the less substituted form reacted with diethyl azodicarboxylate, phenylisocyanate, mesyl chloride and β-nitrostyrene.[45]

Acylated enamines also exist as an equilibrium mixture of more (**16**) and less (**15**) substituted forms, and the isomeric distribution again varies with the amine used. However in this case it is the pyrrolidine



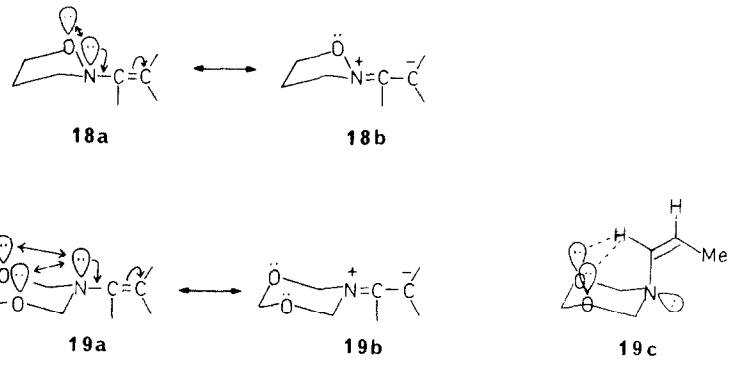
Scheme 5. R = COMe, CO_2Me, CO_2Et, COPh, CONHPh.

enamine which appears to exist mainly in the more substituted or conjugated form (**16**) whereas morpholine and piperidine enamines usually have the less substituted or non-conjugated form (**15**).[46,47] The other important difference is that the more substituted acyl enamine (**16**) may now undergo further reaction but at the oxygen rather than the β-carbon (as **17**).[48,49] See Ref. [19] for further reactions of the N–C=C–C=O system.

The reactivity of an enamine depends on the amine moiety and on the degree of substitution at the α- and β-positions. Alkyl substituents at C-α increase the electron density[50] and reactivity at C-β, by hyperconjugative and inductive effects, provided that steric interactions do not impair the lone pair interaction. Conversely, the steric and electronic effects of β-substituents decrease the reactivity at C-β. The order of reactivity is therefore normally $R_2NC(R)=CH_2 > R_2NC(R)=CHR > R_2NCH=CHR > R_2NCH=CR_2$. Thus cyclic and acyclic ketone enamines are more readily C-alkylated than aldehyde enamines which, unless precautions are taken, tend to react preferentially at nitrogen, and the enamine of acetone was, until recently, considered to be too reactive to be isolated (see Section 4).

In the case of enamines from cyclic ketones spectroscopic evidence suggests that reactivity may vary with ring size of the ketone in the order $5 > 12 > 8 > 6 > 7$.[51]

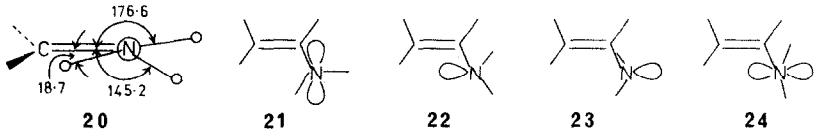
The increased orbital interaction by the nitrogen lone pair in enamines derived from pyrrolidine, as compared to enamines from other secondary amines, is well known from their increased chemical reactivity[6,52,53] and their reduced stereoselectivity of reaction (Section 5A(ii)), as well as from spectroscopic (Section 3) and, more recently, X-ray crystallographic evidence (*vide infra*). The second most reactive type of enamine seems to be that derived from hexamethylenimine.[53,76] In an attempt to increase this reactivity still further we have investigated the effect of incorporating additional heteroatoms into the amine moiety of enamines. The idea was that the lone pair-lone pair electron repulsion illustrated in partial structures **18a** and **19a** could be alleviated by greater involvement of the nitrogen lone pair with the π-electrons of the double bond as in **18b** and **19b**. However the spectroscopic and reactivity data indicated reduced $p\pi$-conjugation. This was attributed principally to inductive electron withdrawal by the oxygen atoms and, in the case of **19**, to the molecule adopting a conformation in which the double bond was axially orientated and orthogonal to the nitrogen lone pair (**19c**). This



Scheme 6.

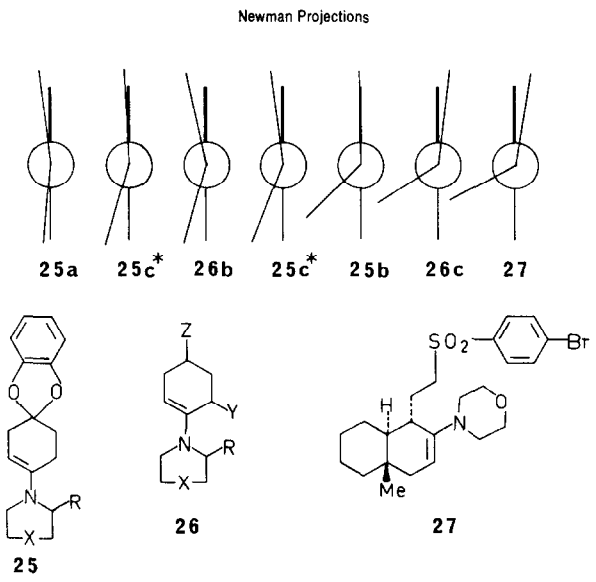
enamine was so unreactive that it could not be isomerised into the trans double bond isomer without fission of the heterocyclic ring.[54]

A recent calculation of the theoretical molecular structure of vinylamine shows some interesting features.[55] The preferred equilibrium configuration is the non-planar pyramidal structure **20** which is 2.4 kcal/mol more stable than the planar sp^2 hybridized structure **21**. This supports previous semi-empirical calculations[56,57] and a microwave spectroscopic analysis.[58] This represents an upper limit to the barrier to pyramidal inversion (experimental values of 1.0–1.3 have been reported[59,60]) which is therefore a considerably lower energy process than rotation about the C–N bond since structures 22–24 are calculated to be 7.1, 7.9 and 14.9 kcal/mol, respectively, more energetic than **20**. Energy barriers for rotation about N–C(sp^2) and C=C bonds of conjugated enamines have been determined to be in the range 10–20 kcal/mol.[61,62]

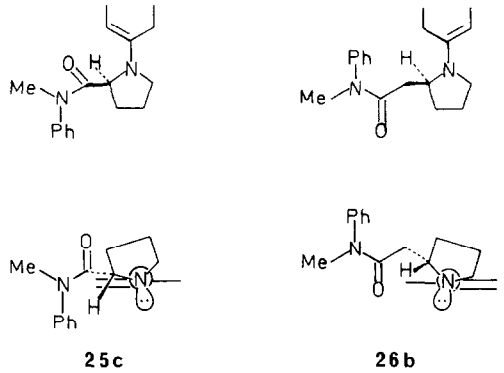


Scheme 7.

These theoretical implications have recently been substantiated by several X-ray crystallographic analyses of enamines.[63–65] This has shown that the amine moiety in the crystalline enamines 25–27 varies from virtually tetrahedral (**27**) (sp^3 hybridized N) to virtually planar (**26a**) (sp^2 hybridized N). The pyramidality is most pronounced in morpholine and piperidine enamines, and least so in pyrrolidine enamines, a fact long assumed by enamine chemists from reactivity and spectroscopic considerations (Section 3). The Newman projections are shown looking down the N–C(sp^2) bond (the heavy line represents the C=C). These show that one of the C–N bonds of the amine moiety is virtually eclipsed with the C=C [maximum C–N–C=C torsion angle = 11° (in 26b)]. With decreasing pyramidality the N–C(sp^2) bond distance decreases from 1.42 to 1.38 Å, indicative of increased double bond character and $p\pi$-conjugation. There are intriguing differences in the steric relationships between the enamine double bond and the amide substituents in the proline derivatives **25c** and **26b** (Scheme 9). In the former the amide substituent is syn to the double bond and the carbonyl group directed into the pyrrolidine ring whereas in **26b** the amide substituent is anti to the enamine double bond and the carbonyl group is directed away from the pyrrolidine ring.[63] The preference for one of the N–C(sp^3) bonds of the amine moiety to be syn-periplanar to the enamine C=C bond is analogous to the situation apertaining to vinyl ethers, olefines, and carbonyl compounds. It would be interesting to know the relationship between the amine moiety and the double bond in a tetra-substituted enamine such as 28. Dunitz *et al.* (Ref. 63, p. 3123) appear to assume the same syn-periplanarity of N–C and C=C bonds. However this is very unlikely to be the case. The severe $A^{1,3}$-interactions engendered between the methyl and α-methylene groups in **28b** must cause rotation about the N–C(sp^2) bond. The fact that the tetra-substituted enamine of 2-methyl-cyclohexanone is formed as the main constituent of the isomeric enamine mixture from amines such as piperidine (48%), diethylamine (75%), and N-methylaniline (100%), indicates that $A^{1,3}$-strain is not operating in the ground state of these enamines. In other words, in view of the reduced $p\pi$-



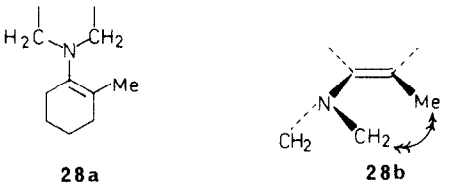
Scheme 8. **25**(a) R = H, X = –; (b) R = H, X = CH_2; (c) R = $CH_2CON(Me)Ph$, X = –. **26**(a) Z = OCOPh, R = Y = H, X = –; (b) R = CON(Me)Ph, Z = Y = H, X = –; (c) R = Z = H, Y = SO_2CH_2CN, X = 0. The asterisk indicated two forms of 25c differing mainly in the degree of pyramidality of the enamine nitrogen.

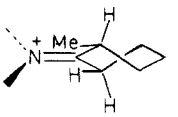


Scheme 9.

conjugation in these enamines compared to pyrrolidine enamines, there is less to be lost energetically by twisting about the N–C(sp^2) bond, out of the syn-periplanar conformation. The greatly reduced reactivity of these tetra-substituted enamines, including the corresponding pyrrolidine isomer, indicates that $A^{1,3}$-strain is in fact only present to its full extent in the transition state. Furthermore, as we discuss in more detail in Section 5, reaction only occurs at the tetra-substituted enamine position under special circumstances, because of the developing $A^{1,3}$-strain. For example when the transition state is reactant-like, as in protonation and possibly halogenation, or when alternative low energy pathways do not lead to product formation (see Section 5). The ready equilibration of enamines, which involves protonation or deprotonation at the more substituted position, can occur through a boat or twist conformation of the iminium salt.[66] The dihedral angle between the methyl and methylene substituents in the intermediate iminium salt (i.e. **29**) is thereby increased and the $A^{1,3}$-strain would be reduced accordingly.[67]

From the MO point of view, conjugative interaction in an enamine precludes orbital assignments which can be classified as the nitrogen lone pair (p) or π-bond (π). When two orbitals of different energy interact, the lower energy one becomes stabilised by "mixing into itself the higher energy one in a bonding way, while the higher energy orbital mixes into itself the lower one in an antibonding way" and thus becomes destabilised.[68] The highest occupied molecular orbital (HOMO) can be represented as





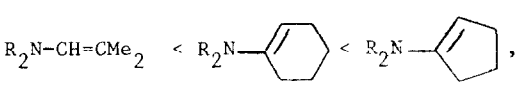
29

Scheme 10.

(p-π) and the second highest occupied MO as (p + π). Nevertheless it is usual to refer to the higher energy orbital as the lone pair or amine-like orbital, and the lower one as the π or alkene-like orbital, for reasons to be discussed. Throughout this review we refer to these interactions simply as pπ-conjugation (or pπ-interaction) and an energy level diagram illustrating this point is shown in Fig. 1.

The energies of these filled orbitals are assumed to correspond to the negative of the ionization potential. This quantity has been determined for a series of enamines[69–72] by photoelectron spectroscopy. Typical values, together with those of reference compounds, are shown in Table 1. Each of the enamines has a broad low energy ionization (IP_1) at 7.1–8.4 eV, and a second sharper band (IP_2) at 8.9–10.1 eV. The broadness of the former indicates that it has largely lone-pair character, as in an amine where the broadness has been ascribed to the large difference in geometries between ground-state amines (pyramidal) and their radical cations (planar). These results therefore indicate that the amine portion of the enamines is pyramidal. The second band, from its vibrational spacing, is considered to be essentially alkene-like in nature.[71b]

The decrease in IP_1 in going from a secondary to tertiary amine has been ascribed to inductive destabilization of the lone pair, and stabilization of the positive charge in the radical cation, owing to the inductive and hyperconjugative electron release of an alkyl group relative to a hydrogen atom.[72] If inductive electron donation destabilizes the lone pair orbital, then the inductive withdrawing effect of an sp^2 hybridized carbon should stabilize the lone pair orbital in an enamine. This appears to be substantiated by the increased IP_1 value for dehydroquinuclidine **30** relative to quinuclidine **31** (ΔIP_1 = +0.42). In the other enamines the IP_1 value is reduced relative to the parent tertiary amine and this is indicative of the conjugative interaction between the nitrogen lone pair and a lower energy alkene π orbital. Such an intereaction is not possible in dehydroquinuclidine since the p- and π-orbitals are orthogonal. The net lone pair destabilization (ΔIP_1) can be taken as a measure of the pπ-interaction and appears to increase in the order:



and morpholine, piperidine, dimethylamine enamines < pyrrolidine enamines. This is in agreement with previous conclusions derived from spectroscopic (Section 3) and reactivity data,[75,76] as long as the

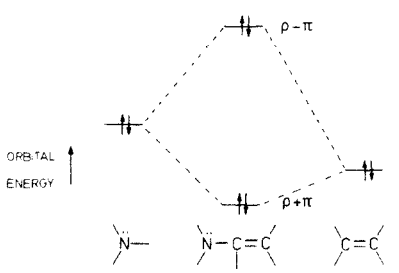
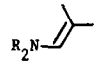
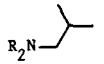
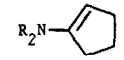
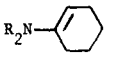
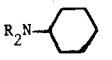
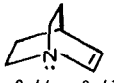
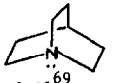
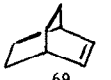


Fig. 1. pπ-Conjugation in an enamine.

Table 1. Vertical ionization potentials (IP/eV) of enamines and related compounds*

R_2N						R_2NH
Dimethylamino	-	-	7.46, 9.76[69] (−0.88) [0.55]	7.56, 9.70[69] (−0.53) [0.56]	8.09[69]	8.64[73+]
Pyrrolidino	7.79, 8.97[70] 7.66, 9.53[72] (−0.45) [−0.18]	8.17[72]	7.10, 9.66[71] [0.45]	7.14, 9.58[71] 7.10, 9.51[70] (−0.84) [0.41]	7.96[72]	8.82[72]
Piperidino	7.95, 9.25[70] 7.93, 9.30[72] (−0.22) [−0.15]	8.16[72]	7.4, 9.55[71] [0.34]	7.50, 9.31[71] 7.42, 9.31[70] 7.44, 9.36[72] (−0.48) [0.18]	7.93[72]	8.66[72]
Morpholino	8.20, 9.41, 9.69[70] 8.20, 9.41, 9.67[72] (−0.26) [−0.02]	8.46[72]	7.60[71]	7.67, 9.40, 9.88[71] 7.66, 9.42, 9.91[70] 7.65, 9.41 9.89[72] (−0.52) [0.27]	8.18, 9.50[72]	8.91, 9.77[72]
N-Methylanilino	7.11, 8.89, 9.03, 9.92[70]	-	-	-	-	7.65[74]
	 9.43[73+]		 9.21[73+]	 9.14[73+]	 8.34[69]	
	30  8.44, 9.41[69] (+0.42) [0.40]		**31**  8.02[69]	 9.01[69]		

* *Values* in ( ) = IP_1 (enamine) − IP_1 (tertiary amine) = ΔIP_1. Values in [ ] = IP_2 (enamine) − IP_1 (alkene) = ΔIP_2

\+ Where adiabatic values have been determined, 0.2 and 0.4 has been added on to the reported values for alkenes and amines, respectively, in order to allow for band widths.

enamines are strictly comparable (i.e. same amine or same alkene moiety). The low IP_1 value for N-methylaniline (7.65 eV) and its isobutyraldehyde enamine (7.11 eV) is undoubtedly due to strong $p\pi$-interaction with the aromatic ring rather than the enamine double bond, although this enamine does surprisingly undergo $CuCl_2$-catalyzed oxygenation faster than other isobutyraldehyde enamines[70] (see also Section 5D).

From the frontier orbital point of view it has been established that the transition state of a reaction is stabilized principally by interaction between the HOMO of one reactant and the LUMO of the other which are closest together in energy.[77] Typical frontier orbital energies and the relative magnitudes of the coefficients for some olefins are shown in Fig. 2.[78] This shows that conjugating substituents (C) compress the HOMO–LUMO frontier orbital separation, electron withdrawing substituents (Z) lower both frontier orbitals, and electron donating substituents (X) raise both frontier orbitals. The HOMO energies of enamines (−7.1 to −8.2 eV; Table 1) are higher than the average values for nucleophilic alkenes given in Fig. 2, and comparison of the HOMO energy (i.e. $-IP_1$) obtainable from Table 1 shows why pyrrolidine enamines are more reactive than morpholine or piperidine enamines to electrophilic olefins. Despite the HOMO of an enamine having largely the lone pair character of a pyramidal amine, there appears to be at least a qualitative relationship between ionization potential (IP_1) and the rate of cycloaddition of phenyl azides[79] and other "frontier-controlled" reactions.[80]

A remaining question about which nothing is apparently known as yet is whether, other factors being equal, electrophilic attack at the β-carbon occurs preferentially syn or anti to the nitrogen lone pair; or whether the orientation of the lone pair can have any effect on the stereochemical outcome of reaction at the β-position. The problem here, of course, is that the possibility of N-inversion, rotation about the N–C(sp^2) bond, or partial rehybridization (orbital bias[81]) makes it difficult, if not impossible, to relate ground state situations with the stereochemical result of a reaction.

3. SPECTROSCOPIC DATA

Enamines give medium to strong absorption in the infrared at *ca.* 1610–1675 cm^{-1}. This absorption is shifted to higher wave number on protonation due to formation of the iminium salt (1640–1690 cm^{-1}).[82]

In the case of 2-methylcyclohexanone enamines, the less substituted double bond isomers absorb at lower wave number (1635–1640 cm^{-1}) than the more substituted isomer (1668–1675 cm^{-1}).[30] In the ultraviolet both free enamines and iminium salts give absorptions at *ca.* 220–235 nm (ϵ 4000–10,000).[82] N-Protonation causes a hypsochromic shift in the λ_{max} value (i.e. 198 nm). Mass spectra of enamines show M-1, M and M + 1 ions, but the base peak is usually that due to formation of an eniminium ion[83] ($\overset{+}{R_2N}$–CH=CH–CH_2–R → $R_2\overset{+}{N}$=CH–CH=CH_2 + R·).

The β-olefinic ^1H chemical shifts (τ) of a number of cyclic and acyclic ketone enamines in CCl_4 ($CDCl_3$) [neat liquid] at 60 MHz are listed in Table 2.[76,84] The enamines are described by amine ring size (i.e. 5 = pyrrolidine, 6 = piperidine)/ketone ring size; additionally *m* = morpholine, DM = Me_2N, DE=Et_2N and MA=Ph(Me)N. As can be seen, the chemical shifts in carbon tetrachloride are similar to those of the neat liquid and to high field of the values in deuteriochloroform. In so far as the β-vinyl proton is shielded by increasing electron density on the β-carbon, these values can be taken as a

Table 2. Olefinic ^1H NMR chemical shifts (τ) of cyclic ketone enamines

5/5	6.09(5.98)	–		5/6	5.87(5.72)	[5.84]	5/7	5.64	–	–	5/8	5.92	–	–
6/5	5.75(5.63)	–		6/6	5.47(5.34)	–	6/7	5.25	–	–	6/8	5.52	–	–
m/5	5.65(5.57)	–		m/6	5.44(5.36)	[5.45]	7/6	5.75(5.65)	–		6/12	5.7	–	–
DM/6	–	–	[5.63]	DE/6	–	–	[5.57]	MA/6	–	–	[4.73]			

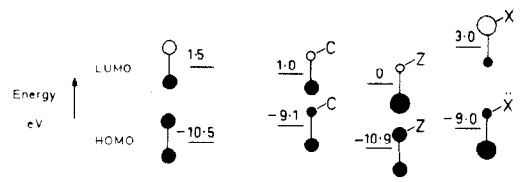
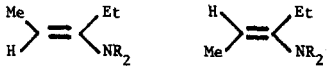


Fig. 2. Frontier orbital energies and relative atomic orbital magnitudes of alkenes (C = CH_2=CH, Ph, etc; Z = CN, CO_2Et, etc; X = R, OR, NR_2 etc).

measure of the amount of charge delocalization due to pπ-conjugation. A correlation of enamine reactivity and chemical shift can therefore be expected if steric factors are identical, or at least similar, and spatial direct shielding effects are negligible or identical. In practice therefore, a correlation between reactivity and β-proton chemical shift only apertains in a series of enamines of similar structure and only then when the chemical shift differences are appreciable. The thermodynamically controlled isomer distribution of a number of enamines derived from 2-methylcyclohexanone, and the olefinic ^{1}H chemical shift of the less substituted double bond isomers, are as follows {amine moiety (% less substituted form) [τ value for neat liquid]}: pyrrolidine (90) [5.82], dimethylamine (60) [5.55], morpholine (52) [5.4], piperidine (46) [5.38], diethylamine (25) [5.45], 2,5-dimethylpyrrolidine (10) [5.47], N-methylaniline (0) [4.68?]. As pointed out by Gurowitz and Joseph,[85] the proportion of the less substituted isomer increases with increasing pπ-conjugation between the amine moiety and the enamine double bond. The configuration of acyclic ketone enamines has been determined and the factors affecting their stability, reactivity, and spectroscopic properties discussed.[86] The results (Table 3) are interesting. Not only are the olefinic proton signals of the E-isomers always to higher field than those of the corresponding Z-isomers but, except for No. 11, there is no observable allylic coupling between H and Et in the E-isomers [$^{1,5}J_H$ = OHz for E-isomers (1–10), 0.5 Hz for (11); $^{1,5}J_H$ = 1.2–1.5 Hz for Z-isomers (1–11)]. This is attributed to reduced pπ-conjugation in the Z-isomers owing to steric interference ($A^{1,3}$-strain) between the Me and amine groups. The olefinic character of the double bond is therefore higher in the Z-isomers. For the same reasons the E-isomers are thermodynamically more stable than the Z-isomers except for No. 10 where the N lone pair conjugation is with the aromatic π-electron system. When this is prevented by an ortho methyl group (No. 11) the E-isomer is again favoured owing to the pπ-conjugation with the enamine double bond. The decreasing contribution of the E-isomers to the mixture as one descends the series from (No. 1→4 and 6→7) reflects the increased steric interactions with the Et group ($A^{1,2}$-strain). The consequent reduced pπ-conjugation is reflected in the shift of the olefinic proton signal to low field (τ 5.87→4.76).

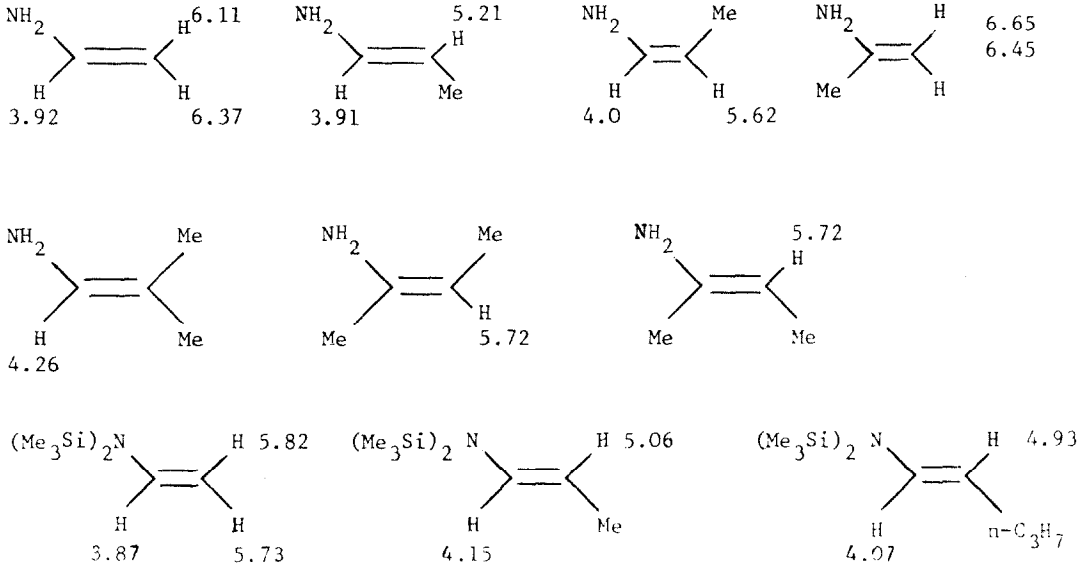
Table 3. % Composition and olefinic ^{1}H chemical shifts (τ) of acyclic ketone enamines.



	32E		32Z		
No.	%	τ_H	%	τ_H	NR_2
1	97	5.87	3	5.46	Me_2N
2	86	5.75	14	5.00	Et_2N
3	80	5.65	20	5.10	n-Pr_2N
4	55	4.76	45	4.66	i-Pr_2N
5	88	5.66	12	5.28	Morpholino
6	90	5.65	10	5.30	Piperidino
7	65	5.63	35	5.00	2-Methylpiperidino
8	98	6.08	2	5.76	Pyrrolidino
9	83	5.81	17	5.19	C_6H_{11}(Me)N
10	20	5.55	80	5.16	Ph(Me)N
11	83	4.91	17	4.80	O-MeC_6H_4(Me)N

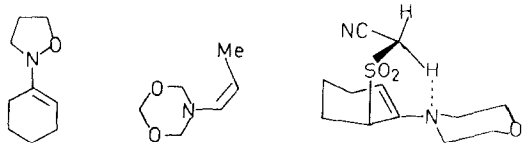
The E or Z configuration of a number of unsymmetrical β,β-disubstituted aldehyde enamines has been determined by chemical shift differences[88] and the nuclear Overhauser effect, the Z-isomers undergoing a 28% signal intensity enhancement.[87] The olefinic ^{1}H chemical shifts of some acetone enamines,[89] and primary enamines,[90] at one time both considered to be too reactive to be isolable, are listed below, together with those for bis(trimethylsilyl) enamines, which can be considered as masked primary enamines.[91]

$R_2NC(Me) = CH_2$ τ(C_6D_6; 100 MHz)
Dimethylamine 6.3, 6.16; Diethylamine 6.34, 6.25; Pyrrolidine 6.56, 6.37;
Piperidine 6.17, 6.13; N-Methylaniline 5.81, 5.77.



The olefinic signal of 1-N-aziridinylcycloalkenes appears at low field (τ 5.0) reflecting the minimal interaction of the electron pair on the aziridinyl nitrogen with the olefinic π-electrons.[92] Similarly the isoxazolidine and 1,3-dioxa-5-azacyclohexane enamines **33** and **34** give olefinic signals at τ 4.7–4.9 owing to inductive electron withdrawal by the oxygen atoms and reduced pπ-conjugation.[54]

The olefinic signal of enamine 35 (Scheme 11) occurs at even lower field (τ 4.5), owing to H-bonding between the acidic SO_2CH_2CN protons and the N lone pair, thus reducing the pπ-conjugation (H—N 2.47 Å).[65,93]



33 **34** **35**

Scheme 11.

The C-13 NMR spectra of cyclic and acyclic enamines have been determined[89–91,94–96] and compared with those of the corresponding saturated amines.[97] The C-1 olefinic carbon gives a signal in the range 124–156 ppm (downfield from TMS) and the C-2 carbon in the range 79–131 ppm. Substituents deshield the olefinic carbon to which they are attached (α-effect) but the magnitude of the shift varies greatly. This has been attributed[94] to an alteration in the electronic contribution of the amine moiety ($\Delta\delta$C) (corrected for variation in α- and β-effects of alkyl substituents with increasing substitution) to the chemical shift of the olefinic carbons by the steric and electronic effects of introducing an alkyl substituent [$\Delta\delta C = \delta$(enamine)–δ(alkene)]. The amine contribution to the chemical shift of C-1 (i.e. $\Delta\delta$C-1) is relatively constant, as one would expect if the α-effect of the amine moiety is determined mainly by its electronegativity. The surprising feature is that the magnitude of the shift (*ca.* 26 ppm for morpholine and 23 ppm for pyrrolidine) is similar to the deshielding effect of an isopropyl group on the chemical shift of an attached olefinic carbon (i.e. 23 ppm), despite the greater electronegativity of the amine moiety, and is some 10–20 ppm less than the corresponding deshielding effect of an amine moiety on the α-carbon of a saturated amine.[97] The reason for this difference has not been satisfactorily explained. The amine contribution to the chemical shift of C-2 in the enamine ($\Delta\delta$C-2) is very variable, causing high field shifts of *ca.* 5–43 ppm relative to the chemical shift of the β-carbon of the corresponding olefin in which the amine moiety has been replaced by H. It appears that substituents reduce the mesomeric electron donation of the amine moiety to the β-carbon of the enamine.[94] The effect is much greater for substituents cis to the amine moiety (steric and electronic effect) rather than trans or geminal, and thus provides a means of distinguishing between E- and Z-isomers. The ^{13}C chemical shift of the iminium groups ($C\overset{+}{=}N$) appears in the region 188–195 ppm.[98]

The ^{15}N chemical shifts of simple cyclic ketone enamines (natural isotope abundance) occur in the range 298–320 ppm (upfield from $D^{15}NO_3$), compared to 308–325 ppm for the corresponding tertiary amines produced on hydrogenation. Although the enamine nitrogen is always less shielded than the nitrogen of the corresponding tertiary amine,[99,100] it appears that relatively small decreases in electron density at a particular nitrogen do not necessarily result in a downfield shift owing to dominating second-order paramagnetic effects associated with the $n \rightarrow \pi^*$ transition. However, introduction of substituents at C-2 and C-6 of cyclohexanone enamines do produce upfield shifts in the ^{15}N resonance which have been attributed to steric inhibition of $p\pi$-conjugation.[99] In secondary enamines a linear dependence between the ^1J (15N–H) coupling constant and the percentage s-character of the nitrogen orbital has been established.[101]

4. PREPARATION[102]

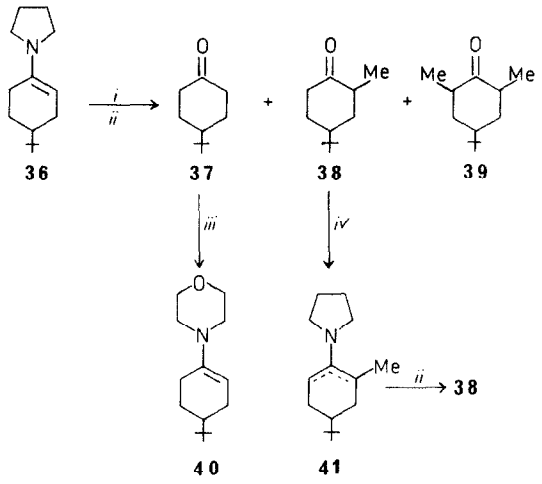
A. *Reaction of carbonyl compounds with amines*

(i) *Ketones.* Enamines of ketones are usually prepared by azeotropic procedures[6,103] which involve refluxing the carbonyl compound and amine in a suitable solvent such as benzene, toluene or xylene in the presence of an acid catalyst. The water eliminated may be removed from the condensate by means of a Dean and Stark head or a molecular sieve. Alternatively a chemically inert drying agent (i.e. potassium carbonate, magnesium sulphate or molecular sieve) may be suspended in the reaction mixture. This enables the preparation to be carried out at lower temperature and forces the equilibrium to higher conversion of enamine. Reported[104] catalytic activity of molecular sieves (5A), when used in this way, has been shown to be due to the binding agent rather than the molecular sieve *per se.*[105] Similar reports[106] that 3A molecular sieves are better than 4A molecular sieves again probably reflect a greater proportion of acidic sites in the binding agent used in the molecular sieve. In fact in a comparative study the best percentage conversions of cyclic ketones to enamines were obtained with a 5A molecular sieve in cyclohexane employing a commercial silica–alumina cracking catalyst as catalyst at room temperature.[105] Conditions for optimal synthesis of morpholine enamines of acyclic ketones have also been studied using molecular sieves (5A) and titanium tetrachloride as water scavengers.[107] Application of the titanium tetrachloride route[108] to the preparation of enamines of alkyl methyl ketones has been shown to occur under kinetic control. Thus methyl isopropyl ketone was converted into the less substituted isomer **12** (Scheme 4). On heating an acid catalysed conversion to a mixture of **12** and **13** rapidly occurred. As mentioned previously (Section 2) isomer **13** can then be isolated by selective reaction of **12** with an aryl azide.[42] Similar separations have been effected by Rappe *et al.* who have employed regioselective protonation–deprotonation techniques to separate isomers **12** and **13** [see Section 5A(i)]. Enamines have also been obtained by acid catalysed condensation of silylamines (i.e. Me_2NSiMe_3) with ketones at room temperature.[109].

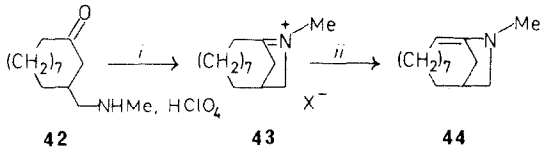
Increased substitution alpha to the carbonyl group of a ketone greatly reduces the rate of enamine formation. This may be utilised[110] to advantage in the separation of the mixtures of ketones which are often formed on alkylation of enamines with alkyl halides [Section 5B(ii)]. For example methylation of **36** gave a three component mixture of **37–39** on hydrolysis, which could not be separated by distillation. However, a clean separation was achieved by making use of their different rates of enamine formation, the reaction being followed by glc. The mixture was treated with gradually increasing amounts of *morpholine* in boiling benzene under a Dean and Stark head until the glc peak due to **37** had disappeared owing to selective conversion to enamine **40**. Unchanged **38** and **39** were then distilled off and the mixture treated with increasing amounts of *pyrrolidine* until the glc peak due to the mono-alkylated ketone 38 had disappeared. The di-alkylated ketone **39** was then distilled off and the residual enamine 41 hydrolysed to give pure 4-t-butyl-2-methylcyclohexanone **38**.[110]

A bridgehead bicyclic enamine **44** has been isolated by intramolecular self-condensation of amino-ketone **42** and deprotonation of the resulting bridgehead iminium salt **43**. However a bridgehead double bond can be accommodated in such a large ring system without difficulty and the chemical shift of the olefinic proton (τ 6.05) is indicative of normal $p\pi$-conjugation. The bicyclic iminium salt was also isolated from the corresponding cyclooctanone but attempted deprotonation to the bridgehead enamine failed.[111]

(ii) *Aldehydes.* The first general method developed for the preparation of enamines involved the reaction of an aldehyde with a secondary amine (2 equivalents) in the cold in the presence of anhydrous potassium carbonate.[112] This gives a 1,1-diamine (aminal) which affords the enamine on destructive distillation. The azeotropic procedure has also been employed using one equivalent of amine with[103] and



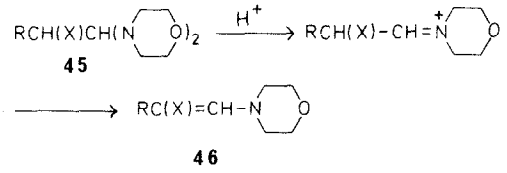
Scheme 12. Reagents: (i) MeI, C_6H_6, EtOH, Δ; (ii) H_3O^+, Δ; (iii) morpholine, C_6H_6, Δ(–H_2O); (iv) pyrrolidine, C_6H_6, Δ(–H_2O).



Scheme 13. Reagents: (i) Δ, i-PrOH; (ii) aq. NaOH, R.T.

without solvent[113] to give the enamine directly. For enamines of straight chain aldehydes or acyclic amines the Mannich–Davidson procedure may be modified by using ether as solvent and one equivalent of amine.[114] This also gives direct access to the enamine which can be alkylated, for example, without purification.[115]

Aminals **45** are thermally stable up to temperatures of about 170° in the presence of base,[116] their decomposition to enamines **46** at lower temperatures being acid catalysed. The effect of kinetic and thermodynamic control on the E/Z configuration of the resulting enamine has been investigated.[117]

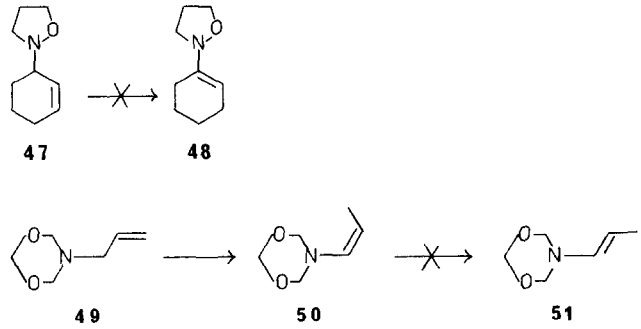


Scheme 14. R = Me, Ph; X = H, Me, morpholino.

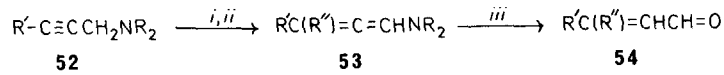
B. *Base catalysed rearrangement*

The base catalysed allylamine to enamine rearrangement corresponds to a gain in stability of *ca.* 5.0 kcal/mol, of which about 2.5 kcal/mol is attributed to pπ-conjugation in the enamine.[120] Despite this, attempted isomerisation of **47** to **48** failed. Normal azeotropic methods of preparation also failed and the titanium tetrachloride route,[108] normally reserved for hindered ketones, had to be employed. However base catalysed isomerisation of **49**, obtained from allylamine and formaldehyde, gave enamine **50**, but more slowly than the corresponding N-allyl derivatives of pyrrolidine and morpholine.[54] Enamine **50**, obtained as the cis-isomer as expected from the work of Sauer and Prahl,[121] defied all efforts to isomerise it to the trans-isomer **51**[54] (see Section 2). The corresponding rearrangement of propargylamines **52** gives allenic enamines **53** which can be hydrolysed to the $\alpha\beta$-unsaturated aldehydes **54**.[122] If instead of protonation of the lithio derivative with methanol, the reaction mixture is worked up with dimethyl sulphate then the methylated derivatives (**53**, **54**; R″ = Me) are obtained.

Interestingly the trideuterio enamine **56** has been shown to catalyse the rearrangement of 1-

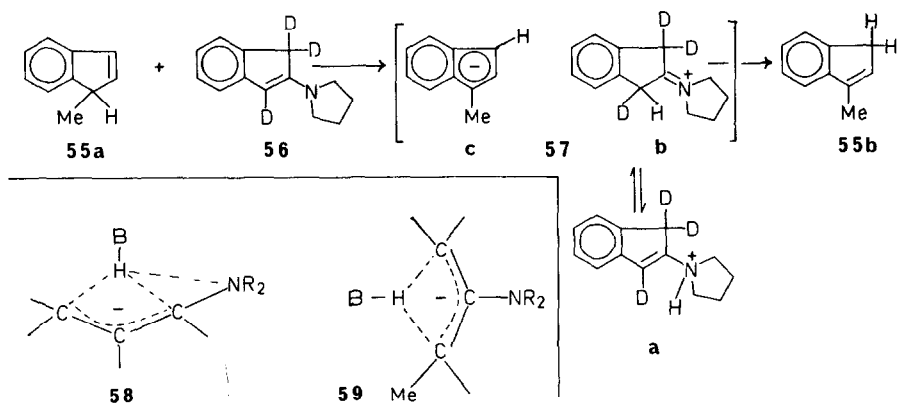


Scheme 15.



Scheme 16. Reagents: (i) BuLi, hexane; (ii) MeOH or MeOD or Me_2SO_4; (iii) CH_3CO_2H, H_2O; R′ = n-Bu, Ph; R″ = H, D, Me; R_2N = piperidino, morpholino.

methylindene **55a** into 3-methylindene **55b**. No incorporation of deuterium into the indene was observed.[123] This and other evidence available[124] indicates that base-catalysed 1,3-proton shifts of this type may occur via cyclic transition states such as **58**[125] for the allylamine→enamine rearrangement, or **59** for a base catalysed less substituted⇌more substituted enamine rearrangement, in which an allylic car-

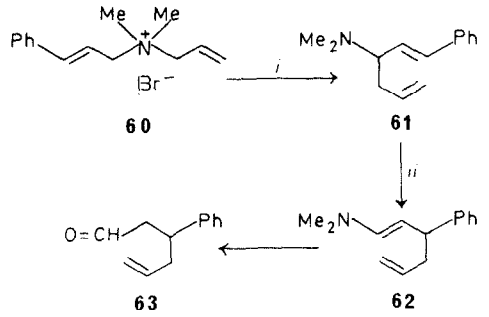


Scheme 17.

banion is formed which is hydrogen bonded at each end to the proton removed by the base. Attractive interaction between the amine lone pair electrons and this proton (in **58**) could also account for the cis-(or Z-) stereochemistry of the enamine produced. However in the rearrangement **55a**⇌**55b**, the proton transferred is likely to be located on the N of the enammonium ion **57a** of the ion pair produced (**57**) rather than the C of the iminium ion **57b**, since N-protonation of an enamine is kinetically favoured (Section 5A), and hence the deuterium would not be activated sufficiently to compete with the proton transfer back to the indene anion **57c**.

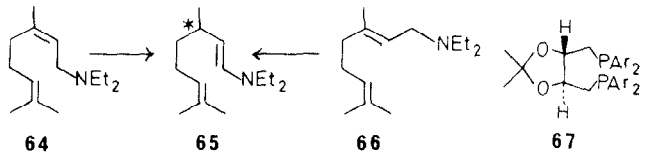
An ingenious series of rearrangements has been reported by Ollis *et al.*[141] in which the diallylammonium bromide **60** is induced to undergo a base catalysed [3,2] sigmatropic rearrangement to **61** followed by a thermal [3,3] sigmatropic rearrangement to **62** and hence the aldehyde **63** on hydrolysis.

Recently an enantioselective transition metal catalysed isomerisation of prochiral allylamines to chiral enamines has been reported,[126] involving a stereospecific hydrogen migration. Isomerisation of N,N-diethylnerylamine **64** and N,N-diethylgeranylamine **66** with $HCo(N_2)(PPh_3)_3$ gave racemic citronellal-trans-enamine **65** (85%), but the use of cobalt catalysts prepared from chiral diphosphine ligands resulted in a



Scheme 18. Reagents: (i) NaH, DMSO, R.T., 8h; (ii) 170°; (iii) H_3O^+.

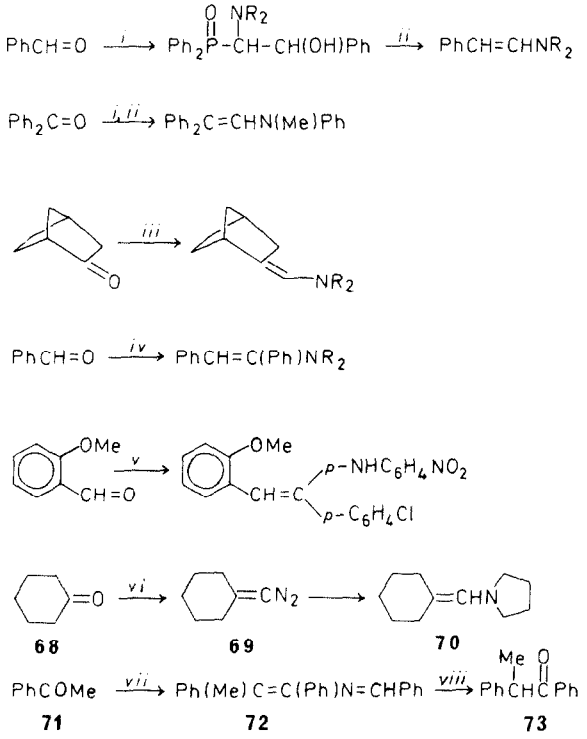
moderate degree of asymmetric induction. For example the catalyst prepared from (+)-diop **67** converted **64** into (3R)-65 in 32% enantiomeric excess, whereas **66** gave (3S)-**65** in 33% enantiomeric excess.[126]



Scheme 19.

C. *Horner-Wittig reaction*

Recently the Horner-Wittig reaction has been applied successfully to the synthesis of both aldehyde and ketone enamines.[127-131] Since the amine moiety is supplied together with its end of the double bond, this is a valuable method for enamine or carbonyl homologation (Scheme 20). An analogous reaction

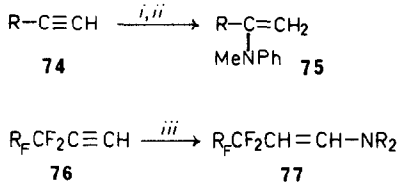


Scheme 20. Reagents: (i) $Ph_2P(O)CH_2NR_2$, BuLi, THF, 0°[128,130]; (ii) KH, THF, R.T., 3h; (iii) $(EtO)_2P(O)CH_2NR_2$, BuLi, THF, −78°[127]; (iv) $(EtO)_2P(O)CH(Ph)NR_2$, NaH, dioxan, 40°;[129] (v) $(PhO)_2P(O)CH(Ar)NHAr$, LDA, THF, −78°[131]; (vi) $(MeO)_2P(O)CHN_2$, KOt-Bu, pyrrolidine;[132] (vii) $(EtO)_2P(O)CH(Ph)N=CHPh$, NaH, THF, Δ;[133] (viii) oxalic acid, aq. EtOH, 2h, R.T.; NR_2 = morpholino; R.T. = room temperature.

involves treatment of a ketone with dimethyl diazomethylphosphonate to give a diazoalkene. When this is produced, or allowed to decompose to the carbene, in the presence of nucleophiles such as secondary amines, an aldehyde enamine is produced[132] (**68**→**69**→**70**). Use of anions from iminoalkanephosphonic esters lead to 2-aza-1,3-dienes which can also be hydrolysed to homologous aldehydes or ketones[133] (**71**→**72**→**73**).

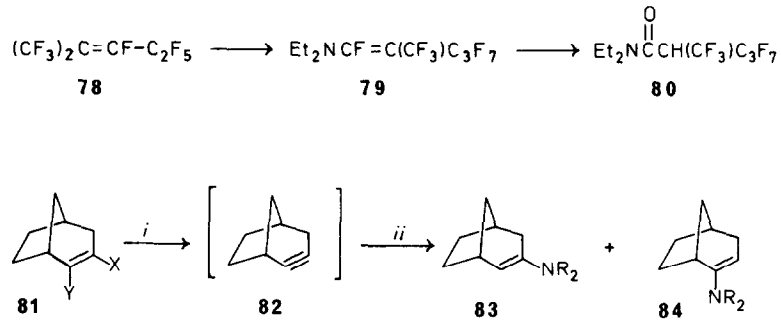
D. *Reactions of alkenes, alkynes and allenes*

The addition of amines to electrophilic alkynes and allenes to give conjugated enamines is well known.[23c,134] However enamines have also been obtained by an aminomercuration–demercuration procedure involving addition of aromatic amines to the inner carbon of unactivated terminal acetylenes[135] (**74**→**75**) (see also Section 4E). Aliphatic amines add to the terminal carbon of perfluoroalkylacetylenes without catalyst[136] (**76**→**77**). The perfluoroalkyl enamines (**77**) thus produced are singularly unreactive to the usual electrophilic reagents (i.e. Br_2, Ph–CH_2Br, PhCOCl), the dominant feature of their chemistry being the lability of the allylic C–F bonds.[136a]



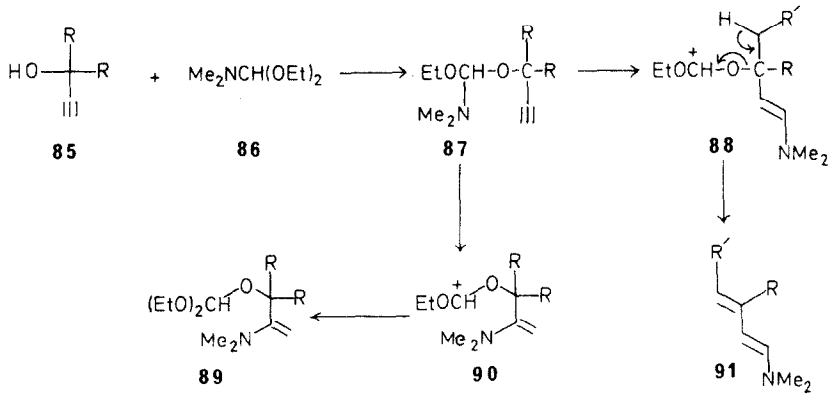
Scheme 21. Reagents: (i) PhNHMe, HgX_2; (ii) $NaBH_4$, NaOH; (iii) R_2NH, solvent (various); R = n-Bu, n-C_6H_{13}, Ph; R_F = n-C_7F_{15}; R_2N = Et_2N, i-Bu_2N, $(PhCH_2)_2N$, piperidino, pyrrolidino, morpholino.

Diethylamine adds to perfluoro-2-methylpent-2-ene (**78**) after rearrangement to the terminal olefin, with expulsion of fluoride to give the enamine **79**, which is hydrolysed by water to the amide **80**.[137] A bicyclic acetylene **82** is postulated as the reactive intermediate in the conversion of 2- or 3-chlorobicyclo[3.2.1]oct-2-enes **81** to enamines **83** and **84** in the presence of strong base[138] (Scheme 22).

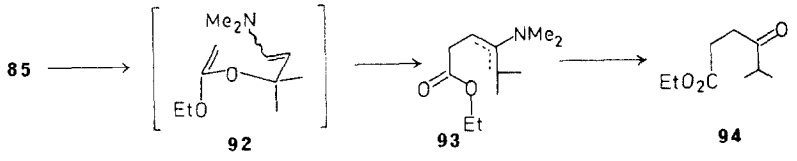


Scheme 22. Reagents: (i) $NaNH_2$, t-BuONa; (ii) R_2NH; X = H, Y = Cl; X = Cl, Y = H.

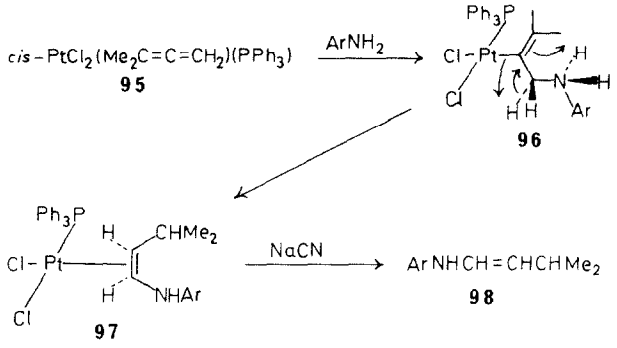
Tertiary ethynyl carbinols **85** are converted by N,N-dimethylformamide acetals **86** to a mixture of dienamines **91** and enamine orthoformates **89** via carbonium ions **88** and **90** (or corresponding carbenes) which subsequently eliminates (**88**→**91**) or adds ethanol (**90**→**89**).[139] When N,N-dimethylacetamide acetal is used the carbonium ion corresponding to **90** is deprotonated to give the enol ether **92** which undergoes a [3,3] sigmatropic rearrangement to **93** and hence **94** on hydrolysis.[140] Aromatic amines add to platinum(II) coordinated allene complex **95** to give β-ammonioalkenyl complexes **96** which rearrange in solution to the enamine complex **97** (structure confirmed by X-ray analysis). Treatment of **97** with sodium cyanide results in displacement of the coordinated organic ligand to give the secondary enamine **98** (stereochemistry not given, but presumably cis) without any evidence of enamine–imine isomerisation.[142]



Scheme 23. R,R = Me, $Me_2C = CH(CH_2)_2$; $(CH_2)_4$; $(CH_2)_5$; Me, $CH_2 = CH$; or 85 = 17α-ethynylestradiol 3-methyl ether.

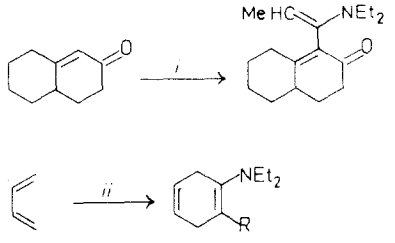


Scheme 24.



Scheme 25.

The addition of ynamines to unsaturated systems provides access to a variety of cyclic and acyclic enamine systems (Scheme 26).[143]

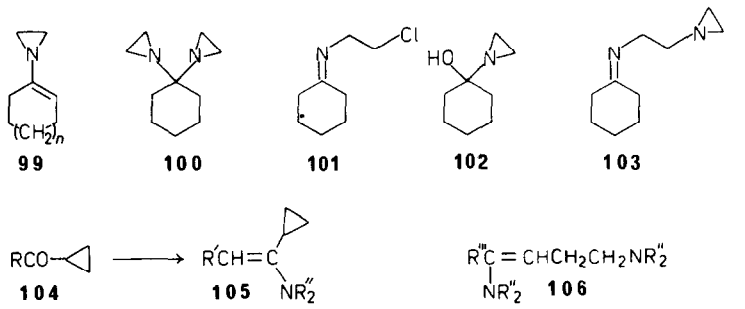


Scheme 26. Reagents: (i) $CH_3C \equiv CNEt_2$, CH_3CN, Δ;[144] (ii) $RC \equiv CNEt_2$, Fe, 25° (R = Me, i-Pr, C_5H_{11}, Ph).[145]

E. *Aziridine and cyclopropane enamines*

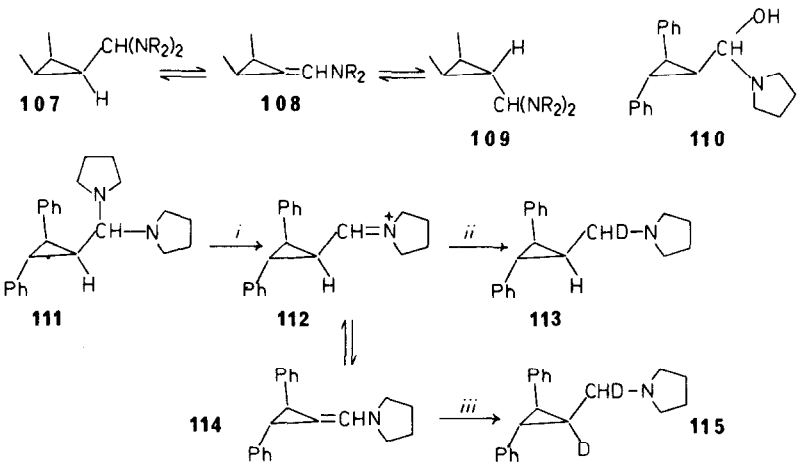
Aziridine enamines **99** of cycoheptanone and cyclooctanone have been prepared, by the titanium tetrachloride method, but cyclohexanone gave compounds **100–103** as the only low molecular weight

products.[146] Cyclopropyl ketones **104** have been converted to enamines **105** with $TiCl_4$, but if R =



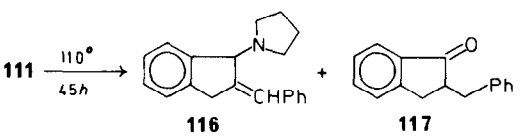
Scheme 27. R = Me, Et, cyclopentyl; R''_2N = Me_2N, Et_2N, pyrrolidino, morpholino; R''' = cyclopropyl, Ph.

cyclopropyl or aryl, ring opening to enamines of type **106** occurs.[147] Cyclopropane enamines of type **108** have not as yet been isolated presumably owing to the increased steric strain which would result from an $sp^3 \rightarrow sp^2$ rehybridisation of a ring carbon.† The ring strain also explains why carbinolamines such as **110** (and **102**) are isolable.[148] However the rearrangement of aminal **107** to **109** at room temperature has been taken as evidence for the transitory existence of **108**.[148] The fact that reduction of aminal **111** with



Scheme 28. Reagents: (i) D^+; (ii) DCO_2^-; (iii)DCO_2D.

perdeuterio formic acid gives a mixture of mono- and di-deuteriated derivatives **113** and **115** is also interpreted as evidence for a fast equilibrium between iminium ion **112** and enamine **114**.[149] These are also regarded as plausible reactive intermediates in the thermal rearrangement of aminal **111** to (E)-N-2-benzylidene-1-indanylpyrrolidine **116** and its hydrolysis product 2-benzyl-1-indanone **117**.[149]

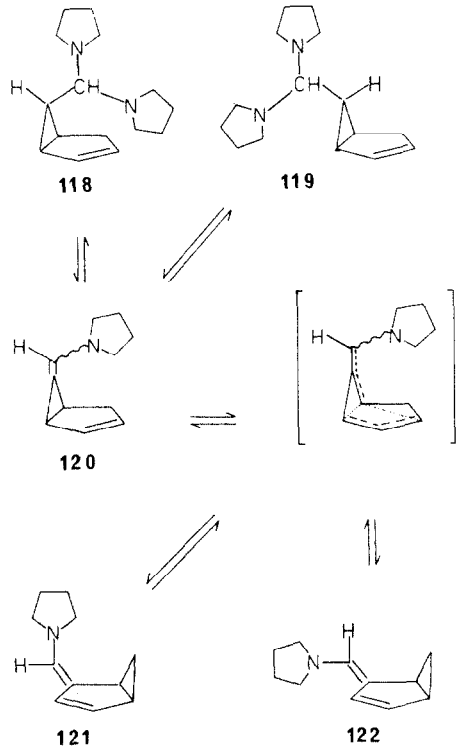


Scheme 29.

Rey and Dreiding[118] have also demonstrated that the endo-bicyclic aminal **118** undergoes a mildly acid catalysed isomerisation to the exo-aminal **119** at 80°, thus providing evidence for the intermediacy

†However N-alkyl-2-methyleneaziridines have been known for a long time (A. T. Bottini and R. E. Olsen, Organic Syntheses, Coll. Vol. V, Wiley, New York, 1973, p. 541 and references therein).

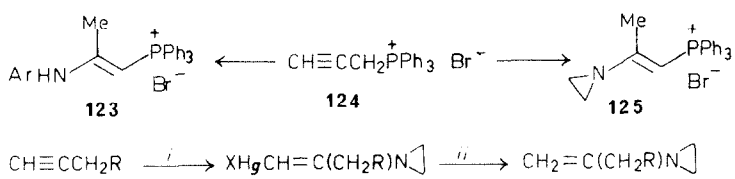
of enamine **120** (not isolated). At higher temperatures (140°) both aminals were smoothly converted into a 1:1 mixture of syn- and anti-4-(pyrrolidinomethylidene)bicyclo[3.1.0]hex-2-ene **121** and **122**. This is in contradiction to earlier reports by Cook *et al.*[119]



Scheme 30.

Addition of amines to prop-2-ynyltriphenylphosphonium bromide **124** gives secondary enamines of type **123** or aziridine enamines **125** which can be cyclised to heterocyclic derivatives.[150–152]

Aziridine enamines have also been prepared by an aminomercuration–demercuration procedure with terminal acetylenes. When applied to the attempted preparation of pyrrolidine enamines only the corresponding saturated amine was obtained [i.e. CH_3CH $(C_4H_8N)CH_2R$] owing to borohydride reduction of the iminium salt. The use of aziridine effectively prevents the formation of an iminium salt because of the strain involved in generating an sp^2 centre in a three-membered ring.[153] A similar result was obtained with N-methylaniline (Section 4D).

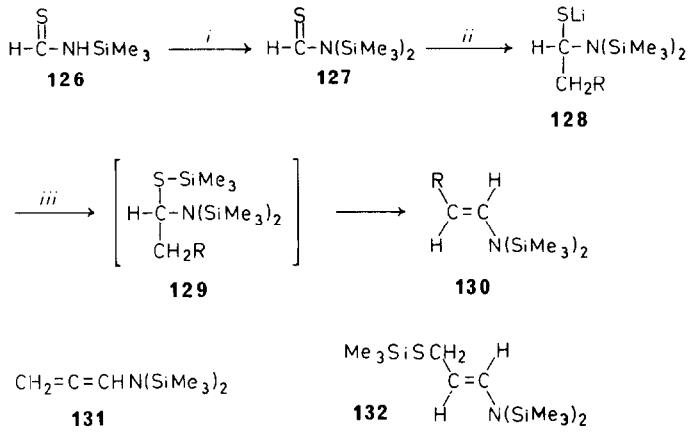


Scheme 31. Reagents: (i) $Hg(OAc)_2$, aziridine; (ii) $NaBH_4$, aq. NaOH.

F. *Silicon and Selenium reagents*

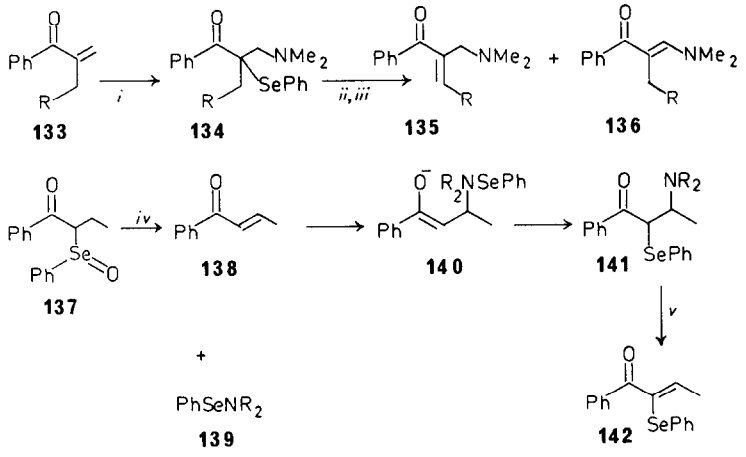
Trimethylsilylamines are useful alternatives to volatile secondary amines for condensation with carbonyl compounds (Section 4A). An interesting recent development[154] is the synthesis of N,N-bis(trimethylsilyl) enamines. These are of potential preparative value as masked N-unsubstituted enamines (i.e. protected primary enamines). The stereoselective synthesis starts from the silylated thioamide **126** which is protected by conversion to the bis-silyl derivative **127** and alkylated on carbon by the required alkyllithium to give the adduct **128**. Treatment with trimethylchlorosilane gives the silylated

derivative **129** which decomposes spontaneously to the E-enamine **130**. Alkylation of **127** with vinyllithium failed to give the allenic enamine **131** but afforded the trimethylsilylthioenamine **132** instead, by allylic rearrangement. N-Mono(trimethylsilyl)enamines have been prepared by trimethylsilylation of metallo-enamines.[155]



Scheme 32. Reagents: (i) BuLi, Me_3SiCl; (ii) RCH_2Li, −45°, (iii) Me_3SiCl.

Addition of benzeneselenenamides to $\alpha\beta$-unsaturated ketones **133** gives α-phenylseleno-β-dialkylamino ketones **134**. However oxidative deselenylation gives mainly the enone **135** rather than the



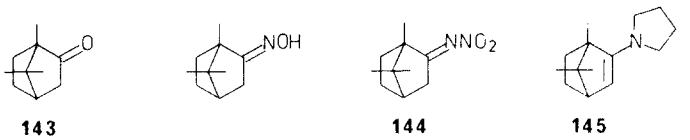
Scheme 33. Reagents: (i) $PhSeNMe_2$; (ii) m-chloroperbenzoic acid, −40°; (iii) 25°; (iv) Et_2NH; (v) SiO_2.

enaminone **136**. Similarly condensation of secondary amine with ketone **137** splits out the selenenamide **139** which undergoes Michael addition to the enone (**138**→**140**→**141**). Attempted chromatographic purification of **141** on silica resulted in elimination of amine to give **142**.[156]

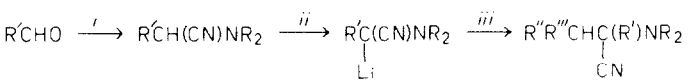
G. *Miscellaneous methods*

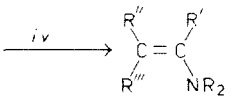
A new but devious route to terpenoid enamines **145** involves conversion of a ketone to a nitrimine **144** followed by condensation with a secondary amine. The method may sometimes work with ketones such as camphor **143** which do not otherwise give enamines.[157]

A versatile synthesis of enamines (and dienamines) has been developed via α-aminonitriles[158] and provides a synthesis of the relatively unstable enamines of acetone **146** (Scheme 35).[159] N,N-Dimethylpropen-2-ylamine **148** has also been prepared from acetone and tris(dimethylamino)arsine[160] and the diethylamine enamine **147** has been obtained from the corresponding reaction of an aminostannane with acetone.[161]

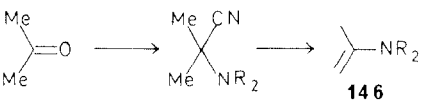


143 144 145





Scheme 34. Reagents: (i) $NaHSO_3$, R_2NH, KCN; (ii) lithium diisopropylamide, THF, −78°; (iii) R″R‴CHX; (iv) KOH or KOt-Bu, C_6H_6, Δ; R′ = Me, Ph; R″ = H, Me, $CH=CH_2$; R‴ = H, Me; R″R‴ = $(CH_2)_4$; R_2N = Me_2N, MePhN, morpholino.



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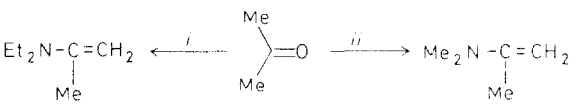
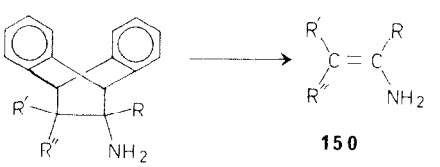


147 148

Scheme 35. Reagents: (i) Bu_3SnNEt; (ii) $(Me_2N)_3As$, 20°, 1 hr; R_2N = Me_2N, Et_2N, pyrrolidino, piperidino, morpholino, MePhN.

Primary enamines have been obtained by flash thermolysis of adducts **149** at 600° *in vacuo*. A retro-Diels–Alder reaction occurs to give vinylamine **150** (R = R′ = R″ = H) and its methyl derivatives. These primary enamines have been identified by their spectroscopic properties (Section 3) at −80°; at higher temperatures than this isomerisation to the imine occurs and self-condensation leads to various nitrogen heterocycles or acyclic azadienes.



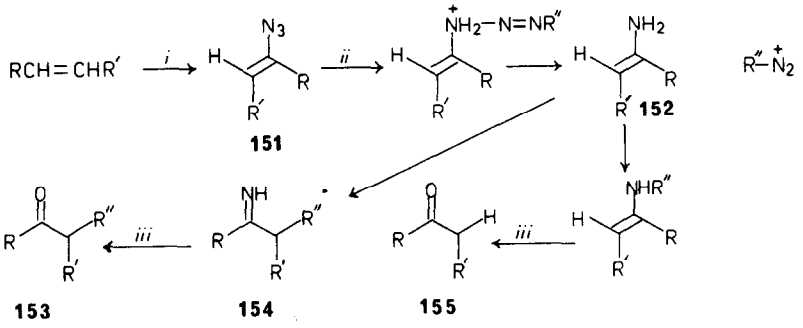
149 150

Scheme 36. R, R′, R″ = H or Me.

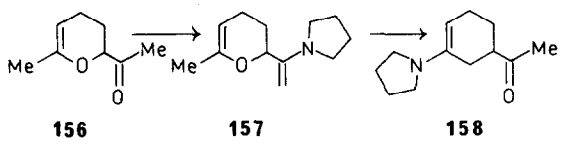
Primary enamines are also postulated as intermediates **152** in the conversion of vinyl azides **151** into ketones or aldehydes (**153**, **155**). The major product **153** is that derived by C-alkylation of the enamine (**152** → **154**).[163]

The apparatus and procedure for the efficient conversion of 2-acetyl-6-methyl-3,4-dihydro[2H]pyran **156** into the cyclohexene **158** via Cope rearrangement of the derived enamine **157** has been described.[164]

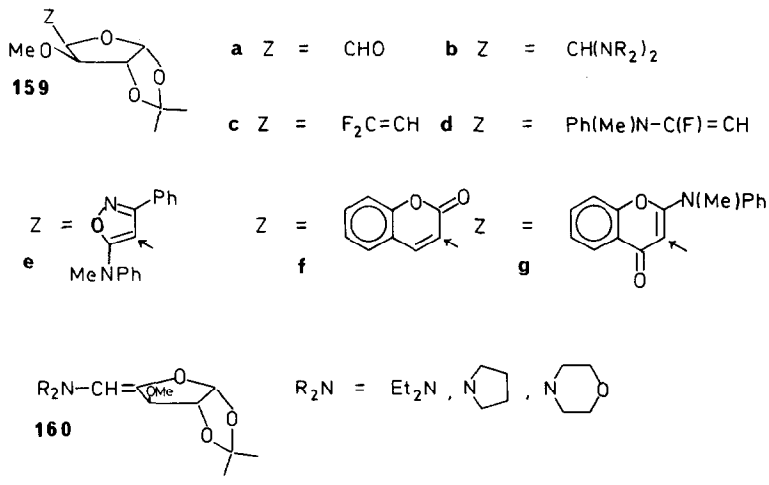
Enamino sugars **160** have been prepared[165] in quantitative yield from the corresponding aldehyde **159a**, via the aminal **159b**. Alternatively treatment of gem-difluorovinyl sugar **159c** with lithium methylphenylamide gave α-fluoroenamine **159d**. This gives access to a variety of C-glycosyl heterocyclic systems (**159e–g**).



Scheme 37. Reagents: (i) IN_3, KOt-Bu; (ii) R″Li; (iii) aq. HCl; R = H, Bu, Ph; R′ = H, Me, t-Bu; R″ = Me, Et, t-Bu.

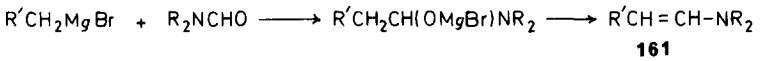


Scheme 38.



Scheme 39.

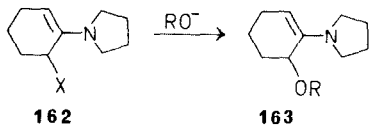
Reaction of Grignard reagents with N,N-dialkylformamides gives addition products which eliminate spontaneously to give aldehyde enamines **161** (30–80%).[166] α-Hydroxyketones (acyloins) condense with



Scheme 40. R′ = Me, n-Pr, n-C_5H_{11}, n-$C_{11}H_{23}$, Ph, CH_2 = CH; R = n-Bu, i-Bu, sec-Bu.

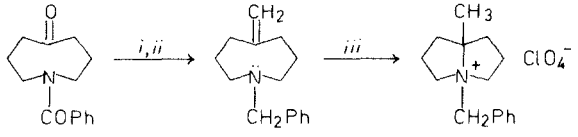
secondary amines to give α-aminoketones not enamines,[167] apparently by direct replacement of the OH-group[168] rather than by condensation with the carbonyl group and tautomeric rearrangement. However alkoxyenamines **163** have been obtained from haloenamines **162**.[169] Nucleophilic displacement of the reactive halogen in enamines derived from α-halogenoaldehydes has also been studied.[170]

Finally a transannular enamine **165** has been reported! Microbial oxygenation of N-benzoyl-heptamethylenimine gave the 5-oxo derivative **164** converted by the Wittig reaction into **165**. This undergoes C-protonation to give the pyrrolizinium salt **166**.[171]



162 163

Scheme 41. X = F, Cl, Br; R = Me, Et, i-Pr, t-Bu, Ph.



164 165 166

Scheme 42. Reagents: (i) $Ph_3P=CH_2$, DMSO; (ii) $LiAlH_4$; (iii) $HClO_4$.

5. REACTIONS OF ENAMINES

Enamines are ambident conjugated systems with high, but variable, nucleophilicity at both the nitrogen and the β-carbon atoms. In attempting to arrive at a detailed understanding of their chemical reactivity one is therefore faced with a number of intriguing problems. Firstly the relative site preference for electrophilic attack depends on the type of electrophile and the experimental conditions used, as mentioned previously (Section 1). Secondly it is necessary, but on the evidence available often not possible, to differentiate between kinetic and thermodynamic control, and between reactant-like and product-like transition states. Thirdly there is the structure of the enamine to be considered. This includes the amine moiety, steric effects, and pyramidality of the nitrogen, all of which affect the degree of $p\pi$-conjugation.

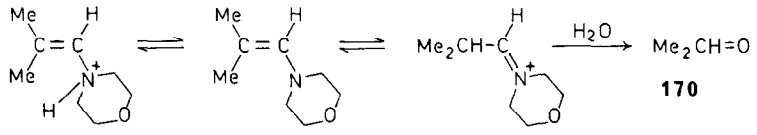
The stereoselectivity, regioselectivity, and the course of apparently similar enamine reactions can therefore vary dramatically, as will become apparent in the discussions which follow.

A. *Protonation and hydrolysis*

Aspects of protonation which have received considerable attention are (i) the regioselectivity (i.e. N- vs C-protonation, and Cβ- vs Cβ'-protonation of a mixture of unsymmetrical ketone enamines) (ii) the stereoselectivity (i.e. axial vs "equatorial" protonation of cyclohexanone enamines) (iii) the mechanism of hydrolysis, and (iv) asymmetric induction.

(i) *Regioselectivity.* There has been considerable disagreement in the literature as to whether enamines are stronger or weaker bases than the corresponding saturated amines. This disagreement has resulted from the fact that enamines are ambident nucleophiles and have two sites for protonation. As regards N-protonation, enamines are weaker bases than the corresponding amine. This can be attributed to the electron-withdrawing effect of the double bond and the electron delocalization of the nitrogen lone pair. Cases where enamines have been reported to be stronger bases than saturated amines are situations in which C-protonation of the enamine is compared with N-protonation of the saturated amine.[172] However even for C-protonation, enamines may be stronger or weaker bases than the parent amine.[173] This depends on the substitution pattern, β-substituents being base weakening and α-substituents base strengthening (only true when the steric interactions engendered, between the α-substituent and the α-methylene or methyl group of the amine moiety, are weak) at least as regards cyclic enamines such as indoles, Δ^2-pyrrolines, and 1,2,3,4-tetrahydropyridines (outside the scope of this report).

Both UV and NMR spectroscopy have been used to demonstrate the rapid formation of the N-protonated enamine (enammonium ion) in acid solution, followed by slow conversion to the thermodynamically more stable C-protonated enamine (iminium ion).[82,174,175] For example a freshly prepared solution of **168** in 6M aqueous perchloric acid showed λ_{max} 196 nm and NMR signals at τ8.08, 8.17 (**167**) and τ8.69 (**169**). After 24 hr UV absorption appeared at 215 nm, no NMR signals at τ8.08 and 8.17, but doublets at τ8.69 (**169**) and 8.88 (**170**). Recent *ab initio* molecular orbital calculations for proton affinities at the C and N sites in vinylamine (NH_2–CH=CH_2) have indicated that C-protonation is thermodynamically favoured by 18.7 kcal/mol over N-protonation.[178] Earlier calculations gave somewhat

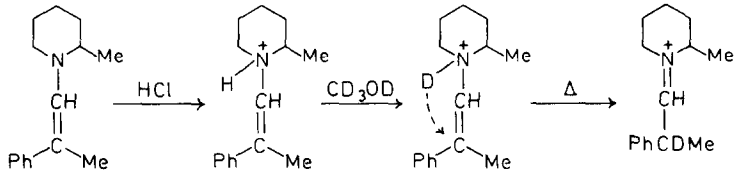


167 168 169 170

Scheme 43.

lower values of 9.7[55] and 16.2[180] kcal/mol. Calculations also indicate that for non-planar pyramidal vinylamine N-protonation is kinetically favoured, but for planar vinylamine C-β protonation is both kinetically and thermodynamically favoured.[55] However the degree of N- vs C-protonation has been shown to depend on the nature of the protonating agent.[176,177] N-Protonation is favoured by hard acids such as anhydrous hydrogen chloride or aqueous perchloric acid, whereas C-protonation occurs with carboxylic acids.

The problem which remains to be answered is whether the N-protonated form is converted directly into the C-protonated form or first into the free enamine which then undergoes direct C-protonation. The former possibility appears to have some literature support. For example the N-protonation→C-protonation conversion occurs even in the solid state, over a period of 7–10 days at ambient temperature.[177] Furthermore protonation of enamine **171** [τ($CDCl_3$) 8.97 (2-Me), 7.9 (=CMe), 4.01 (=CH); $\nu_{C=C}$ 1637 cm^{-1}] gave enammonium salt **172** [τ($CDCl_3$) 8.37 (2-Me), 7.28 (=CMe), 4.1 (=CH); $\nu_{C=C}$ 1658, ν_{NH} 2350–2600 cm^{-1}]. On warming **172** in deuteriomethanol the iminium salt 174 [τ($CDCl_3$) 8.60 (2-Me), 8.31 (CDMe), 1.0 (=CH); $\nu_{C=N}$ 1671 cm^{-1}] was formed. This was assumed to occur by rearrangement of the N-deuteriated salt (172→173→174).[179] There are also misleading statements in the literature[181,209] to the effect that "recent work has shown that protonation (of enamines) takes place rapidly on nitrogen and is



171 172 173 174

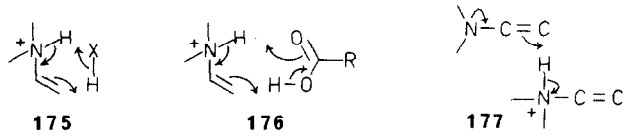
Scheme 44.

followed by a relatively slow transfer of the proton to the carbon". *However to our knowledge there is no evidence to support an intramolecular proton transfer of the type implied here.* It could not be a concerted process since continuous overlap of orbitals cannot be maintained.[182] Molecular orbital calculations also indicate that low-energy pathways for intramolecular N→C proton shift are unlikely.[55] Furthermore in the early work on the hydrolysis of enamines, the mechanism proposed involved a rate-determining proton transfer to the β-carbon of the *free enamine.*[183a] A tautomeric equilibrium ($\rangle C{=}C{-}\overset{+}{N}H\langle \rightleftharpoons \rangle CH{-}C{=}\overset{+}{N}\langle$) was specifically excluded by the kinetic data.[183b] The mechanism proposed was as follows [for further details see Section 5A (iii)]:

$$Me_2C{=}CH{-}\overset{+}{N}HR_2 + H_2O \overset{Fast}{\rightleftharpoons} Me_2C{=}CH{-}NR_2 + H_3O^+ \xrightarrow{Slow} Me_2CH{-}CH{=}\overset{+}{N}R_2 + H_2O \dashrightarrow Me_2CH.CHO.$$

We conclude therefore that the thermodynamically more stable iminium salt must arise either by step-wise reversion of the enammonium ion to the enamine followed by direct C_β-protonation or by concerted *intermolecular* or solvent assisted processes such as those depicted in **175–177**. Mechanisms such as those depicted in **175** and **176** imply that C-protonation would occur from the same side as the nitrogen lone pair electrons.

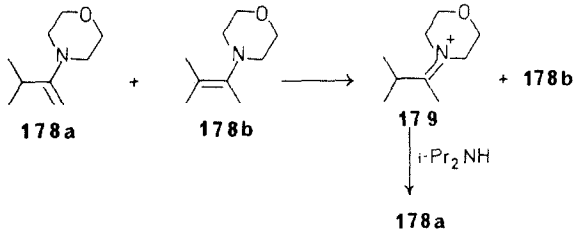
As regards C_β- vs $C_{\beta'}$-protonation, the previously mentioned greater reactivity of the less substituted enamine derived from an unsymmetrical ketone (Section 2), has recently been utilised to achieve a separation of these isomers. For example careful titration of the enamine mixture **178** derived from methyl isopropyl ketone and morpholine, with trifluoroacetic acid in pentane at 0°, gave a precipitate of



175 176 177

Scheme 45. X = HO, RO, RCO_2, RSO_3, HSO_4, Cl, etc.

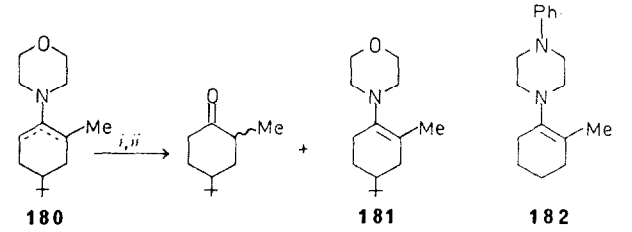
the C-protonated iminium salt **179** derived exclusively from **178a**. This was filtered off leaving the more substituted isomer **178b** in solution. Treatment of the iminium salt with diisopropylamine then regenerated the less substituted isomer **178a** without trace of **178b**. No interconversion of **178a** and **178b**



Scheme 46.

via **179** occurred under these conditions. Selective protonation has also been achieved using an ion exchange resin (Amberlyst 15) but with somewhat lower selectivity and scope of application.[184] The fact that the conversion **179**→**178a** can be effected with a secondary amine indicates that the previously mentioned base strengthening effect of an α-substituent is in fact base weakening here. This can be attributed to increased steric interactions between the isopropyl group and the α-methylene group of the amine ring in going from **178a** ($A^{1,2}$-strain) to **179** ($A^{1,3}$-strain). Further work[98] has shown that the method is applicable to a number of alkyl methyl ketone enamines, but the regioselectivity is lower for n-alkyl methyl ketones as would be expected from consideration of steric and electronic effects (Section 2). Tertiary amines such as triethylamine, N-methylmorpholine, N-ethyldiisopropylamine, are completely non-selective, the greatest regioselectivity of deprotonation being displayed by primary and secondary amines such as t-butylamine, morpholine, and diisopropylamine.

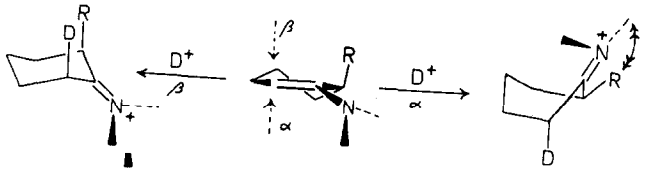
A further example reflecting regioselective protonation during hydrolysis is the isolation[30] of the tetra-substituted enamine **181** from the three component mixture **180**. This enamine (**181**) was shown to



Scheme 47. Reagents: (i) 0.1NHCl, petroleum ether, 5 min ambient temperature; (ii) aqueous layer neutralised with 0.1N NaOH.

be stable indefinitely in the solid state at 5°, and was unchanged after 7 days in benzene solution at ambient temperature, or pyrrolidine at 80°. However a trace of acid led to the equilibrium mixture 180 very rapidly. Similar equilibration studies were carried out with **182**.[185]

(ii) *Stereoselectivity.* Consideration of the factors affecting the product stability leads to the conclusion that electrophilic attack on a 2-substituted cyclohexanone enamine, in which the substituent is in a quasi-axial orientation in order to minimise $A^{1,2}$ strain,[26] should occur from the axial or β-direction rather than from the "equatorial" or α-direction. The latter process would be expected to be less favourable since it leads to a boat (or twist) conformation of the resulting iminium salt, destabilised by $A^{1,3}$ interactions[26] between the substituent and the α-methylene of the amine group of the enamine, in addition to torsional strain in the ring Scheme 48.



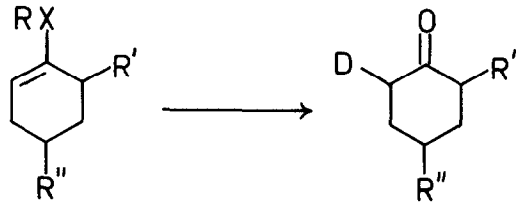
Scheme 48.

The early work on the deuteriolysis of enamines appeared to indicate that deuteriation, and hence protonation, occurred predominantly from the axial direction. Thus Malhotra and Johnson[186,187] reported that deuteriolysis of the pyrrolidine enamine **186** (Table 4) of 2-methylcyclohexanone gave 6-e-deuterio-2-methylcyclohexanone as the major product. If the methyl substituent is assumed to be in the quasi-axial orientation in the enamine, and in an equatorial orientation in the ketone, this indicated that deuteriation had occurred from the β-(axial) side of the enamine. Similarly Schaefer and Weinberg[188] reported that the deuteriolysis of the morpholine enamine **184** of 4-t-butylcyclohexanone gave 2-β-deuterio-4-t-butylcyclohexanone, and House *et al.*[189] also reported that the corresponding enol ether **183** *and* the pyrrolidine enamine **185** gave greater than 90% axial deuterium incorporation.

However we later showed that this mechanistic reasoning and the experimental results were incorrect.[192] The product stability can only be relevant if the transition state for protonation is product-like. If the transition state is reactant-like, as has been reported for the alkylation and protonation of enolate anions[189,190] then high axial stereoselectivity in the protonation and deuteriation of enamines should not be observed. Our results,[192] using the literature methods for deuteriolysis of the enamines, but using $Eu(fod)_3$ to resolve the axial and equatorial α-proton NMR signals[191] (a technique not available to the previous investigators) are summarised in Table 4. The relatively low D_2 contents [except for Expt. (v)] indicate that the deuterolysis is essentially kinetically controlled and that the iminium salts do not undergo appreciable deprotonation–redeuteriation before conversion to the carbinolamines (see later) which then decompose to the ketones.

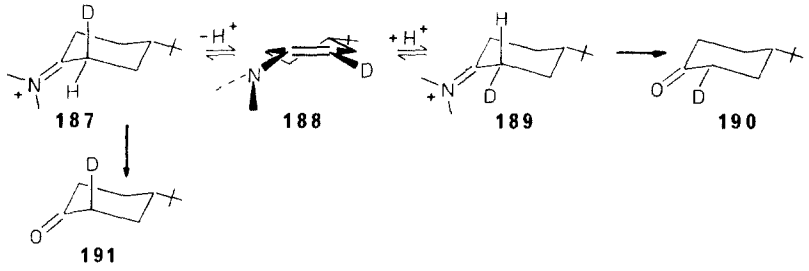
These results confirm that the enol ether undergoes mainly axial deuterium incorporation, although the stereoselectivity is not as great as previously supposed,[189] but deuteriolysis of the enamines shows low stereoselectivity. Very little deuterium incorporation into the ketones occurs under the conditions used, confirming that the products are not being isomerised via the enol form of the ketone. Unfortunately, as a consequence of the different rate profiles for hydrolysis [see Section 5A(iii)] different experimental conditions have to be used for the deuteriation in order to ensure conversion to the ketone. For example deuteriolysis of the morpholine enamine [Expt (ii)] was complete after 20 min at room temperature, whereas for the corresponding pyrrolidine enamine the mixture had to be diluted with water and left 15 hr more [Expt (iii)]. Under these conditions epimerisation could occur via the

Table 4. Deuteriolysis of an enol ether and enamines



Expt	Compound	RX	R'	R''	Conditions	Equat:Axial		Deuterium incorporation D_0	D_1	D_2	D_3
(i)	**183**	EtO	H	Bu^t	DOAc-D_2O;100°;10 min[189]	30	70	11	77	10	2
(ii)	**184**	C_4H_8NO	H	Bu^t	DCl-D_2O;20°;20 min[188]	43	57	6	78	15	1
(iii)	**185**	C_4H_8N	H	Bu^t	(1) DCl-D_2O;20°;20 min[189]	47	53	55	81	12	1.5
					(2) H_2O;20°; 15 hr.						
(iv)	**185**	C_4H_8N	H	Bu^t	(1) DCl-D_2O;20°;20 min	48	52	11	81	5	3
					(2) D_2O-NaOD to pH 6.5						
(v)	**186**	C_4H_8N	Me	H	DOAc-D_2O;20°; 5 min[187]	50	50	22	48	29	1
						(55)	(45)				

regenerated deuteriated enamine **188**. The step (**187** → **188**) is not meant to imply the loss of an equatorial proton *per se*. It is more probable that this occurs by flipping of the conformationally mobile end of the ring into a boat or twist conformation so that the proton can be lost under stereoelectronically favourable circumstances.

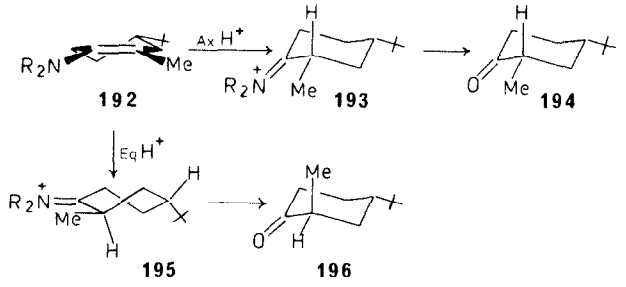


Scheme 49.

However replacement of water by D_2O gave the same equatorial:axial ratio and no increase in the D_2-isomer [Expt. (iv)]. The possibility of incorporating equatorial deuterium by an axial deuteriation–inversion process can therefore be ruled out under these conditions.

We are therefore forced to conclude that deuteriation (and protonation) of an enamine occurs via a reactant-like transition state. Since there is no obvious steric impediment to approach from either side of the double bond, the stereoselectivity is low. It is possible that the slightly higher stereoselectivity (a small but real difference, consistently reproduced in our laboratory) of deuteriation of the morpholine enamine [Expt. (ii)] compared to that of the pyrrolidine enamine [Expt. (iii)] is due to an orbital bias[192] which slightly favours attack from an axial direction even in a reactant-like transition state. In the case of **186** if allowance is made for the high proportion of D_2 relative to D_1 isomers in this product, the results (in parentheses) [Table 4; Expt. (v)] indicate a slight preference for equatorial attack as would be expected if the quasi-axial methyl group is shielding the β-face of the enamine to some extent. Since enol ethers are relatively unreactive their transition states would be expected to be more product-like compared with those for enamines, and hence display greater stereoselectivity of reaction as a consequence of the thermodynamic factors which favour a developing chair over a developing boat or twist transition state. Similarly in the reaction of enamines with less reactive electrophiles, such as alkylating agents, a greater degree of rehybridization[192] of the β-carbon and nitrogen atoms would be required in order to reach the transition state (i.e. a more product-like transition state) and hence a greater degree of stereoselectivity would be expected and has been observed [see Section 5B].

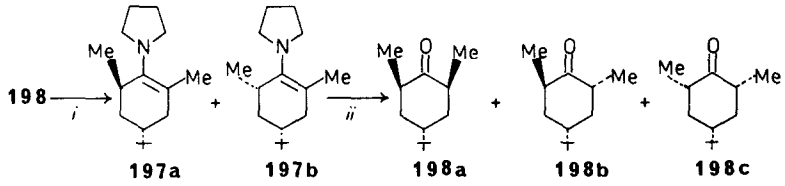
In agreement with the arguments presented above Johnson *et al.*[30] have also shown that protonation of tetra-substituted enamine double bonds is completely non-stereoselective in that hydrolysis of the morpholine and N-methylaniline enamines **192** gave roughly equal amounts of cis and trans ketones **194** and **196**.



Scheme 50. R_2N = morpholino or PhNMe.

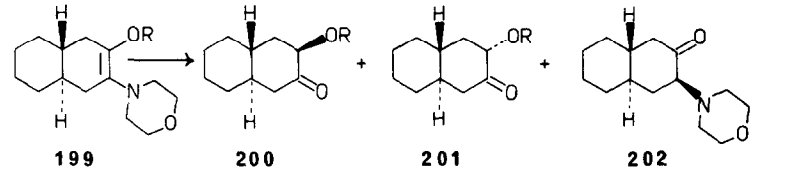
By carrying out the reaction in D_2O/DCl, Johnson *et al.* demonstrated that there was no interconversion of the two iminium salts (**193** and **195**) via the tetra-substituted enamine **192**. Similar results were obtained with the conformationally biased 2,4,6-trisubstituted enamine **197**, shown to exist primarily with

the C-6 group quasi-axial (94% **197a**; 6% **197b**), which was C-protonated equally from both sides of the double bond to give equal amounts (48%) of cis- and trans-ketones (**198a**, **198b**) and only a small amount of **198c** (4%). Again little or no enamine-iminium salt equilibration occurred during hydrolysis since only 4% d_2-species were formed in the presence of D_2O.[30] Similarly the hydrolysis of the alkoxy-enamines **199**



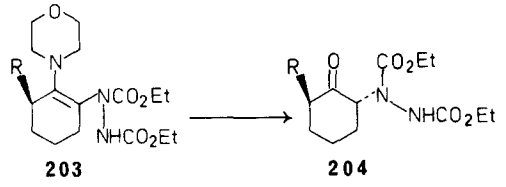
Scheme 51. Reagents: (i) pyrrolidine, $TiCl_4$; (ii) 0.1N HCl, petroleum ether, 28 hr.

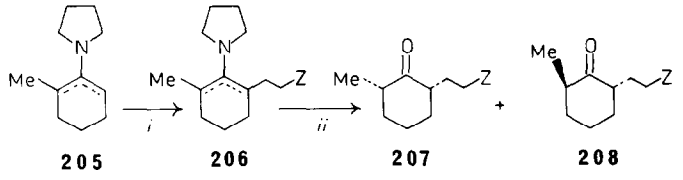
has been shown to occur non-stereoselectively to give equal amounts of **200** and **201**, and a small amount of **202** formed by hydrolysis of the enol ether function.[193]



Scheme 52.

The absence of any significant degree of stereoselectivity in the enamine protonations noted above stands in marked contrast to some reports by Risaliti *et al.*[194] who have shown that kinetically controlled hydrolysis of a series of 2,6-disubstituted enamines **203** [R = Me; $CH(Ph)CH_2NO_2$; $CH(Ph)CH_2COPh$; CH_2CH_2Ph] gives the trans-ketones **204** exclusively.



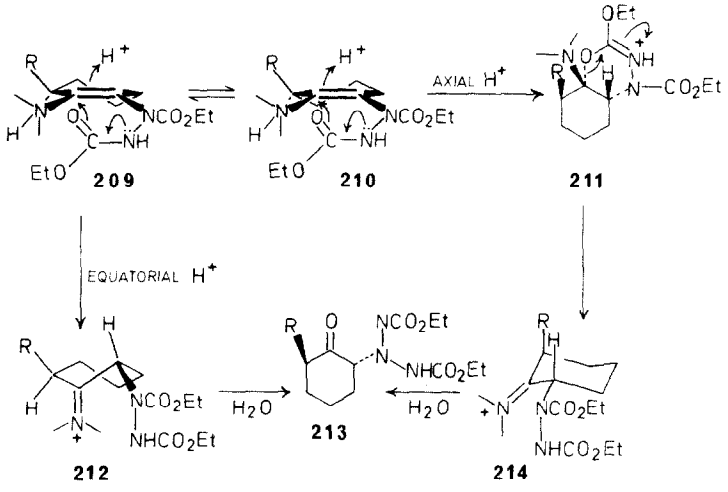


Scheme 53. Reagents: (i) methyl acrylate or acrylonitrile, various solvents; (ii) aq. $NaOH/KH_2PO_4$/HOAc (non-epimerising conditions, pH 6.0–6.5).

We have obtained somewhat analogous results in that alkylation of the pyrrolidine enamine of 2-methylcyclohexanone **205** gives, on hydrolysis, a mixture consisting of largely the thermodynamically less stable trans-ketone **208** (approx. 64%).[195] We have attributed this increased stereoselectivity to an increased product-like nature of the transition state.[195] The more bulky the C-2 substituent is, then the greater will be the steric impediment ($A^{1,3}$ strain) to $p\pi$-conjugation in the ground state of the enamine. This will result in reduced electron density at the C-2 position of the enamine and therefore necessitate increased rehybridization of this position in order for a bonding interaction to take place.[81] The transition

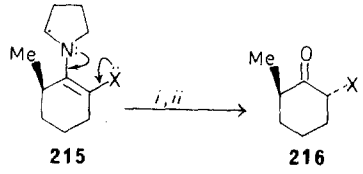
state will therefore be displaced along the reaction co-ordinate and the torsional and allylic interactions which favour axial over equatorial attack will exert increasing dominance over the course of the reaction.

In addition to this, however, a common structural feature in **203** and **206** is the presence of a terminal ester group in the C-2 substituent. It is therefore tempting to suggest that this could be involved in an attractive or bonding interaction with the enamine double bond in the transition state, and thus lower the activation energy for the protonation step. Stéric effects would prevent this interaction from occurring from the same side as the C-6 substituent. The attractive or bonding interaction shown in **209–211** would therefore occur from the opposite side and thus direct protonation from the same side as the C-6 substituent, whether this is quasi-axial (**210**) or quasi-equatorial (**209**) (Scheme 54). Since the hydrazodicarboxylate in **203** will be more nucleophilic than the carboxylic ester in **206**, the interaction could be stronger in the former case and the stereoselectivity of reaction consequently higher. However the steric effects will also be greater in the former case, so the transition state would be expected to be more product-like anyway. Similar reasoning will be applicable to any C-2 substituent carrying a nucleophilic group.



Scheme 54.

However this cannot be the whole story since 2 - chloro - 6 - methyl - 1 - pyrrolidinocyclohexene **215a** has been reported to give almost only trans - 2 - chloro - 6 - methylcyclohexanone **216a** on hydrolysis, indicating stereoselective axial protonation.[196] So perhaps another factor to be considered is the electronic opposition to the $p\pi$-conjugation of the enamine by a C-2 substituent carrying lone pair electrons at the β-position of the enamine (i.e. Ẍ in **215**). This would render the enamine less reactive, and the transition state would again be expected to be more product-like and thus favour axial protonation.

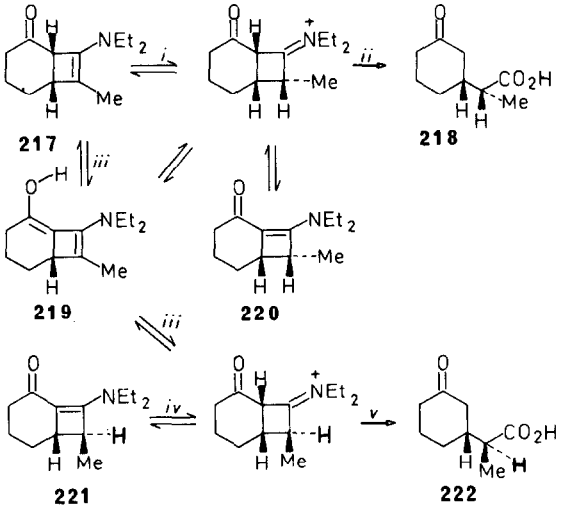


Scheme 55. Reagents: (i) axial H^+; (ii) H_2O; (a) X = Cl; (b) X = $N(CO_2Et)NHCO_2Et$.

In contradistinction, hydrolysis of the disubstituted product derived from 1-pyrrolidinocyclohexene and methyl acrylate is reported[197] to give dimethyl cis-cyclohexanone-2,6-dipropionate! However epimerisation to the more stable isomer is the probable explanation for this anomaly.

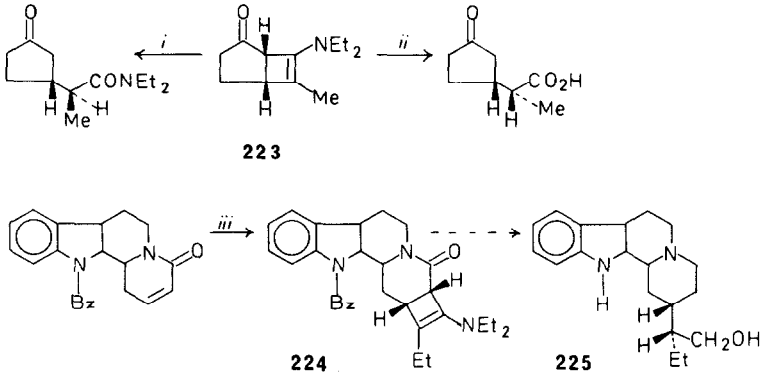
Another impressive demonstration of stereoselective enamine protonation has been provided by

Ficini *et al.*[198] The bicyclic enamine **217** is sterically inaccessible from the endo direction and kinetically controlled protonation in aqueous media occurs from the exo direction to give **220** and, on hydrolysis, the ring opened acid **218**. Under conditions of thermodynamic control, on the other hand, using anhydrous hydrogen chloride, an equilibrium is set up, possibly involving the enol form **219** since enolisation will flatten the molecule and render the enamine double bond more accessible from the endo direction; protonation then leads to the formation of the thermodynamically favoured exo isomer **221** and the diastereoisomeric keto acid **222** on hydrolysis.



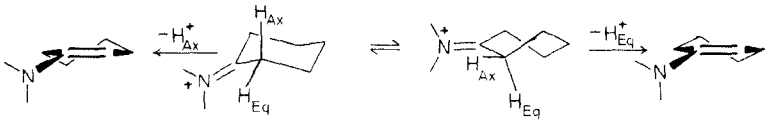
Scheme 56. Reagents: (i) H_2O; (ii) aq. HOAc or 10% aq. HCl; (iii) dry HCl; (iv) aq. Na_2CO_3; (v) aq. HOAc.

Similar stereochemical control occurs in the protonation and hydrolysis of bicyclic enamine **223**,[199] and the same technique has been used in the stereoselective conversion of bicyclic enamine **224** into the indole alkaloid (±)-dihydroantirhine **225**.[200]



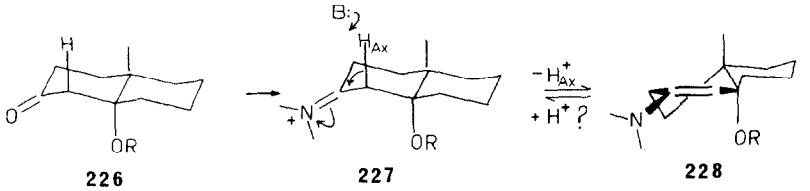
Scheme 57. Reagents: (i) aq. NaOH; (ii) aq. HCl; (iii) $Et_2NC \equiv CEt$.

Finally it is worth noting that, from the principle of microscopic reversibility, if protonation of an enamine is non-stereoselective, then the reverse process, deprotonation of the resulting iminium salt, should also be non-stereoselective. Loss of an equatorial proton can occur under conditions of stereoelectronic control[35] provided, in the case of 6-membered cyclic ketone enamines, the ring can adopt a twist conformation. Reports[201,202] that 9α-hydroxy or acetoxydecal-2-ones **226** and their iminium salts **227** undergo stereoelectronically controlled deprotonation from the β-direction suggests that protonation of **228** would also be stereoselective. However this would not be unexpected even for a reactant-like transition state since protonation from the α(equatorial) direction would be very hindered.



Scheme 58.

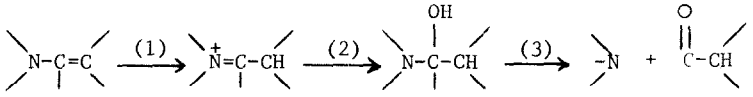
It has been estimated that conversion of a carbonyl compound to an iminium ion increases the rate of proton elimination from the position α to the carbonyl by *ca.* 10^4–10^6, and it seems likely that such nucleophilic catalysis is the basis of some enzymic processes.[203]



226 227 228

Scheme 59.

(iii) *Hydrolysis.* The rate determining step in the hydrolysis of an enamine has been shown to vary with the pH of the solution.[204,205] Furthermore the pH at which a change in the rate determining step occurs depends in turn on the amine moiety and the substituents at the α- and β-positions of the enamine. In general a fast equilibrium is built up between the enamine and the N-protonated enamine. The double bond in the latter is unreactive since the activating effect of the nitrogen lone pair electrons has been removed. This process therefore serves to rapidly decrease the concentration of free enamine available for hydrolysis. The rate determining steps may then be either (1) protonation of the β-carbon to give the iminium salt; (2) hydration of the iminium salt to give a carbinolamine; (3) elimination of the amine moiety from the carbinolamine and formation of the carbonyl group:



The rate profiles for the hydrolysis of the morpholine (I), piperidine (II), and pyrrolidine (III) enamines of isobutyraldehyde are shown in Fig. 3.

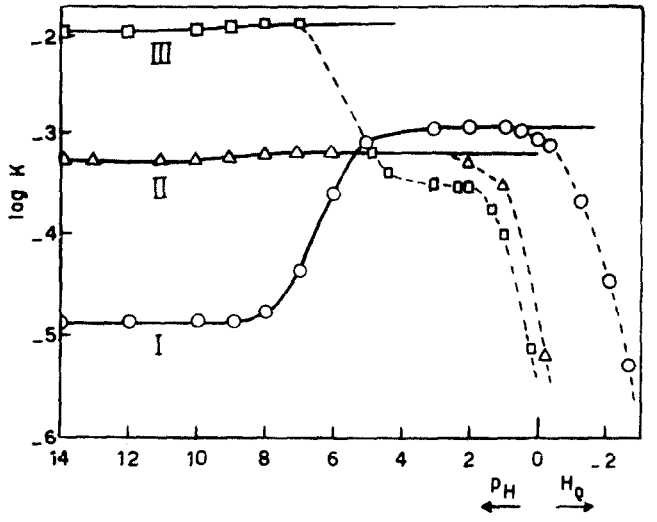
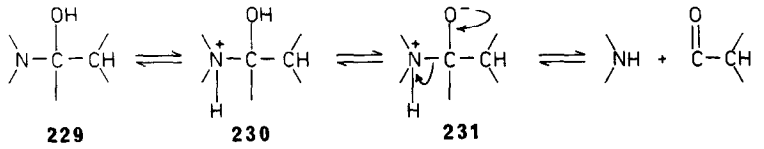


Fig. 3. Rate profiles for the hydrolysis of isobutyraldehyde enamines. Full lines: calculated log K values; observed values: O for the morpholine enamine (I), Δ for the piperidine enamine (II), and □ for the pyrrolidine enamine (III). Reprinted with permission from the Journal of Organic Chemistry, **32**, 1111 (1967). Copyright (1967) American Chemical Society.

The abrupt changes in the rates of hydrolysis which occur as the acidity of the medium is increased may be explained as follows. Under alkaline conditions protonation of the β-carbon is the slow rate determining step, and the order of reactivity is pyrrolidino > piperidino > morpholino. The greater reactivity of the piperidine enamine II as compared with the morpholine analogue I is due to the electron-attracting influence of the oxygen atom of the morpholine ring, which reduces the electron density at the β-carbon atom. The much higher protonation rate of the pyrrolidine enamine relative to the piperidine enamine, for which the basicities are closely similar, was attributed to the tendency of the five membered ring of the amine to form an energetically favourable exocyclic double bond.[213] In the light of recent X-ray analyses[63] and the proposed reactant-like nature of the transition state for protonation,[192] the increased reactivity of the pyrrolidine enamine is better attributed to increased p π-conjugation resulting from the greater sp^2 hybridization and more planar character of the nitrogen atom and the amine moiety respectively.

In weakly acidic media (pH 2–6) the rate of hydrolysis of the pyrrolidine enamine falls since the stabilization of the exocyclic double bond in the iminium ion prevents rapid nucleophilic attack by water. The formation of the carbinolamine then becomes the rate determining step. The rate of hydrolysis of the morpholine enamine I increases since the rate of β-protonation is increased. The iminium ion derived from the morpholine enamine is highly reactive, and it has been estimated[204] that its rate of hydration, and of that of the piperidine enamine, exceeds its rate of formation from the enamine.

In strongly acid solution the rate of hydrolysis of all three enamines fall indicating a further change in the nature of the rate determining step, from hydration of the iminium salt in the case of III and β-protonation in the case of I and II, to elimination of the amine from the carbinolamine. This is suggested to occur in three steps as follows:



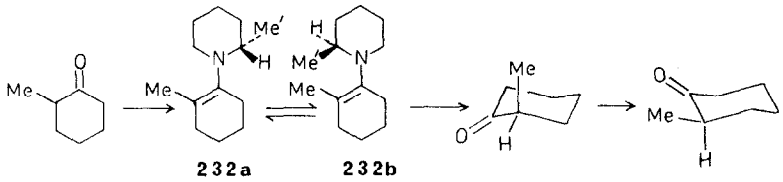
229 230 231

Scheme 60.

In strongly acidic media formation of the zwitterion **231** will be suppressed. Under these conditions the rate of hydrolysis is reversed (i.e. morpholino ≫ piperidino > pyrrolidino) since (1) the concentration of carbinolamines **229** and **230** will be greater for I and II due to the greater ease of hydration relative to that of III and (2) the acidity of the hydroxyl group in the carbinolamines will be increased in I due to the inductive effect of the oxygen atom of the morpholine ring.

Similar conclusions have been reached with regard to the hydrolysis of the morpholine, dimethylamine, piperidine and pyrrolidine enamines of propiophenone.[205] The mechanism of hydrolysis differs to that apertaining to the isobutyraldehyde enamines mainly in that hydration of the iminium ion is rate determining over a wider range of pH for propiophenone enamines. This may be attributed to the conjugative electron release of the phenyl group which accelerates β-protonation and retards iminium ion hydration. Monobasic phosphate and bicarbonate ions were found to exhibit unusually large catalytic effects on the rate of iminium ion formation (and on rate of hydrolysis where this step is rate-determining) but a mechanism involving a concerted cyclic N → β-C proton shift was ruled out.

(iv) *Asymmetric induction.* Asymmetric induction has been observed in the protonation and hydrolysis of chiral enamines derived from optically active (+)-α-pipecoline [i.e. S(+)-2-methylpiperidine]. Racemic 2-methylcyclohexanone surprisingly was converted entirely into the more substituted form of the enamine **232**. Of the two rotational conformations **232a** and **232b** necessary to maintain p π-conjugation between the N lone pair electrons and the double bond, **232b** will clearly shield the enamine double bond from attack from above. We assume Me′ to be largely axial in **232a** in order to minimise $A^{1,2}$-interactions (by analogy with the less substituted form of a 2-methylcyclohexanone enamine); this must certainly be the case in **232b** in order to minimise $A^{1,3}$-interactions with the cyclohexene Me group. Protonation from below therefore leads to an enantiomeric excess (*ca.* 20%) of R(−)-2-methylcyclohexanone, on hydrolysis[206] (kinetic control). An alternative explanation[207] was provided by the authors of this work, based on the stability of the diastereoisomeric iminium salts produced. Certainly the optical yields were shown to vary considerably with changes in the acid used for protonation (achiral or chiral) and the diastereoisomer composition varied with temperature.[207] However

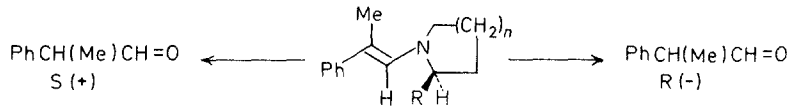


232a 232b

Scheme 61.

as we have already pointed out [Section 5A(ii)], arguments based on product stability are inappropriate for reactant-like transition states. We believe that a thermodynamic argument is only applicable under special circumstances, for example when the iminium salts are deliberately allowed to equilibrate by prolonged standing or heating prior to hydrolysis (see later).

Asymmetric induction was also observed in the protonation and hydrolysis of the corresponding chiral enamines derived from α-phenylpropionaldehyde [e.e. 34% R(−) and, using R(−)-2-methylpyrrolidine, 22% S(+) PhCH(Me)CHO] and 2-ethylhexanal.[208] Interestingly the optical activation was found to change in the opposite chiral sense when the substituent on the chiral amine was changed from methyl to ester, amide, or amine substituents.[209]

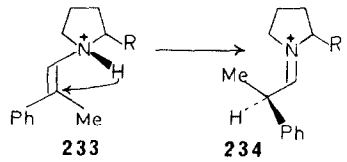


	$[\alpha]_D^{23}$
R = Me, n = 1	+ 51.6
R = Me, n = 2	+ 80.8
R = CO_2Et, n = 1	+ 0.34

	$[\alpha]_D^{23}$
R = $CONH_2$	− 3.1
R = COR'	− 18.6
R = CH_2R'	− 12.9
R = COR''	− 2.3
R = CH_2R''	− 9.7

Scheme 62. R' = pyrrolidino; R'' = piperidino.

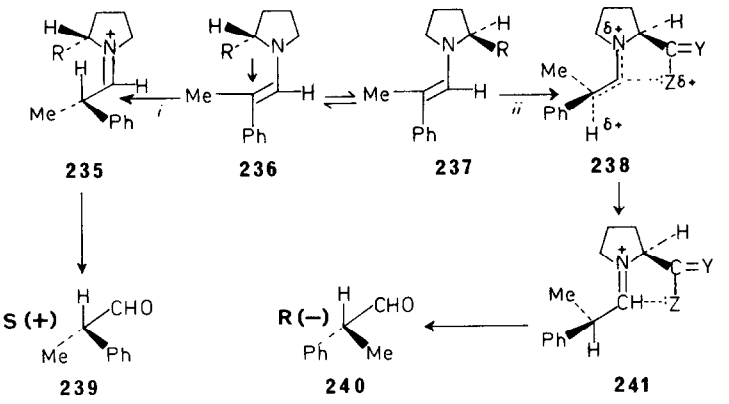
To explain these surprising results the authors postulated the operation of two different mechanisms. Formation of the S(+) α-phenylpropionaldehyde was attributed to the greater thermodynamic stability of the corresponding iminium salt and formation of the R(−) α-phenylpropionaldehyde was attributed to direct transfer of a proton from the N-protonated enamine to the β-carbon of the enamine[209] (i.e. **233** → **234**).



233 234

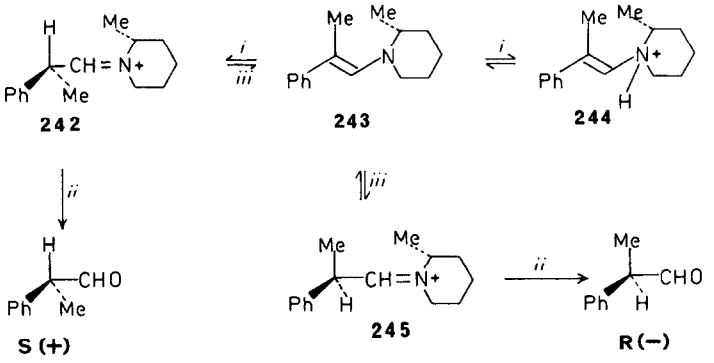
Scheme 63.

An alternative explanation which we suggest for these interesting results is as depicted in Scheme 64. When R = Me, since conformation **237** can be protonated from either side of the double bond, the asymmetric induction must arise from conformation **236** which can be protonated, via a reactant-like transition state, more easily from above the double bond (↓). This leads to iminium salt **235** and hence the S(+) aldehyde **239** on hydrolysis. When R = ester, amide, or amine, conformation **236** can still lead to the S(+) aldehyde **239**, but now conformation **237** must contribute to the asymmetric induction, but in the opposite chiral sense. We suggest this is due to the Z lone pair electrons undergoing an attractive interaction with the α-carbon of the developing iminium ion. The resulting closer proximity of the substituent to the α-carbon could hinder protonation from above the double bond and thus favour formation of iminium salt **241** and hence the R(−) aldehyde **240**.



Scheme 64. (i) R = Me; (ii) R = ester, amide or amine; Y = O, H_2; Z = OEt, NH_2, pyrrolidino.

Furthermore Yoshikawa *et al.* have shown that the chirality of the α-phenylpropionaldehyde changes from predominantly S(+) to predominantly R(−) if the protonated enamine is heated to 50–60° before hydrolysis.[210] Clearly this is an example of thermodynamic control. The surprising feature of these results, however, is that the protonated enamine formed (and isolated) at low temperature is the N-protonated enammonium ion **244**.[179a] This is presumably stabilised by conjugation with the benzene ring. The Japanese workers then conclude that the chirality of the iminium salt formed from the enammonium salt at low temperature is governed by the stereochemistry of the N-protonation step. It is suggested that upon hydrolysis of the enammonium salt, water is added from the opposite side to the enammonium proton. However we again suggest that the stereoselectivity can be rationalised more plausibly as we have already explained, by reversion to the enamine (**244**→**243**) and preferential protonation from the less hindered side to give iminium salt **242**. On heating this rearranges to the presumably more stable iminium salt **245** and hence gives R(−) α-phenylpropionaldehyde (predominantly) on hydrolysis.

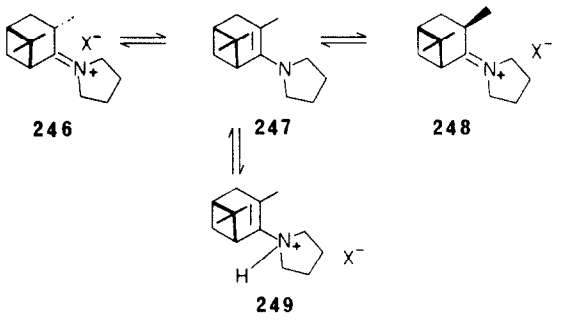


Scheme 65. Reagents: (i) dry HCl, 0°; (ii) H_2O; (iii) 50–60°.

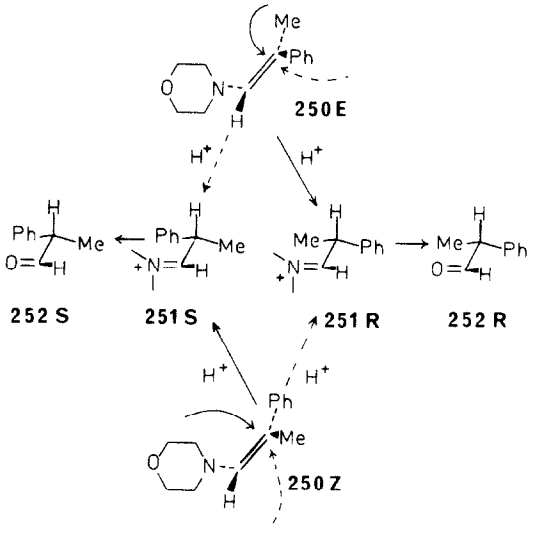
An analogous example of kinetic and thermodynamic control has been reported by Barthélémy and Bessière.[211] At pH 5 (AcOH–AcONa) enamine **247** protonates from the least hindered side to give the cis iminium ion **248** which isomerizes to the thermodynamically more stable trans iminium ion **246**. Under more strongly acidic conditions (aq. HCl or $HClO_4$) the enammonium salt **249** is formed, which isomerizes to cis **248**, stable under these conditions.

Recently it has also been shown that protonation of achiral enamines may be to some extent enantioselective when a chiral protonating agent is used, provided that the rate of hydrolysis is rapid compared with the interconversion of the iminium salts (**251S** and **251R**).[212a]

Interestingly the enantiomeric excess obtained was greatest for the more hindered Z isomer (10–15%). Very little optical enrichment occurred with the E isomer (e.e. 2–4%)[212a] This was increased to 25% however by increasing the spatial requirements of the proton carrier, by esterifying the tartaric acid



Scheme 66.



Scheme 67. $[\alpha]_D^{24} - 24°$ **252R** $\xleftarrow{ii}$ **250Z** $\xrightarrow{i}$ **252S** $[\alpha]_D^{24} + 25°$; $[\alpha]_D^{24} + 4.8$ **252S** $\xleftarrow{ii}$ **250E** $\xrightarrow{i}$ **252R** $[\alpha]_D^{24} - 4.6°$. Reagents: (i) L(+) tartaric acid; (ii) D(−) tartaric acid.

hydroxyl groups.[212b] Optical activation of 2-methylcyclohexanone (e.e. 6.4%S) and 2-chlorohexanal (e.e. 32.4%S) has also been achieved by hydrolysis of the corresponding morpholine enamines in the presence of L(+)-dibenzoyltartartic acid.[213] In the former case the optical yield was increased to 13.2% by separation and hydrolysis of the more substituted form of the enamine (i.e. 1-N-morpholino-2-methylcyclohexene).

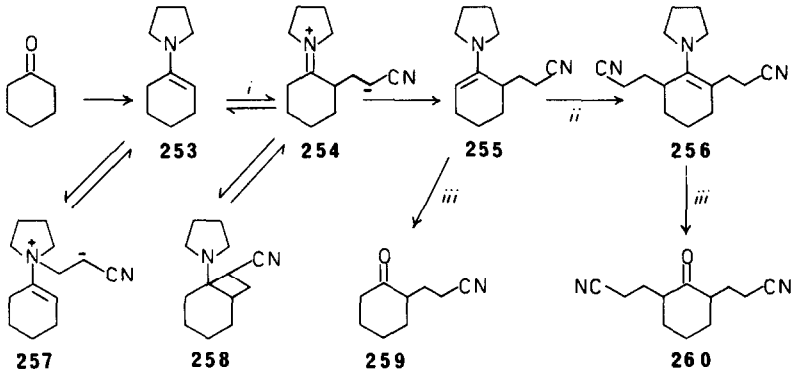
Scheme 68. (e.e. 2.5%) **252R** $\xleftarrow{ii}$ **250Z** $\xrightarrow{i}$ **252R** (e.e. 25%); (e.e. 25%) **252S** $\xleftarrow{ii}$ **250E** $\xrightarrow{i}$ **252S** (e.e. 6%). Reagents: (i) L(+) HO_2C $CH(OCOCH_2t\text{-}Bu)$ $CH(OCOCH_2t\text{-}Bu)$ CO_2H; (ii) L(+) $HO_2CCH(OCOC_6H_4CH_3)$ $CH(OCOC_6H_4CH_3)$ CO_2H.

Japanese workers have also carried out optical activation of α-substituted aldehydes and ketones in an independent series of investigations using similar techniques. Carbonyl compounds which have been to some extent deracemized by enantioselective protonation of the achiral enamines include α-phenylpropionaldehyde, 2-ethylhexanal, 2-methylcyclohexanone.[214] Matsushita *et al.* have provided evidence that at low temperatures the asymmetric transformation is explicable in terms of kinetic control, as implied by Duhamel,[212a] but at higher temperatures this is due to the difference in free energy between

the mutually interconvertible diastereoisomeric iminium salts (chiral iminium cation and chiral acid anion) (i.e. thermodynamic control).[215]

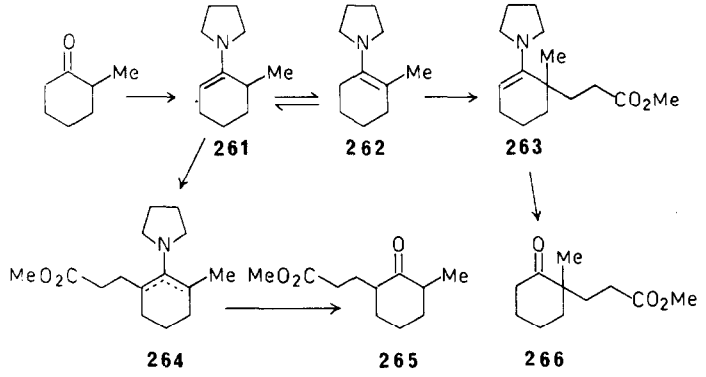
B. *Alkylation*

(i) *With electrophilic olefins.* As pointed out by Stork *et al.* in their definitive 1963 paper,[6] this reaction is especially successful since reaction at nitrogen of the enamine (**253**→**257**) is reversible whereas reaction at carbon is rendered irreversible by proton transfer (**253**→**254**→**255**). Exceptions, in which C-alkylation is also reversible even after proton transfer, have been reported.[216a,248] Ketone and aldehyde enamines can therefore be alkylated in high yields by this method. A zwitterionic intermediate (**254**) is produced which at low temperatures can collapse reversibly to the cyclobutane adduct **258**.[222]



Scheme 69. Reagents: (i) acrylonitrile in benzene or dioxane, Δ, 12 hr; (ii) acrylonitrile in absolute ethanol, Δ 4 hr; (iii) H_2O, Δ 1 hr.

Depending on the experimental conditions used the reaction can be controlled so as to produce the mono (**255**, **259**) or dialkylated (**256**, **260**) products and, in the latter case, the overall reaction is that of α,α'-disubstitution (2,6-disubstitution in the case of 6 membered rings) of the original ketone. Normally the reaction of morpholine enamines in aprotic solvents stops at the monosubstitution stage. An exception to this is the conversion of 1-morpholinocyclohexene to 2,6-bis(β-nitroethyl)cyclohexanone with nitropropene in benzene at 10°.[216b] This was rationalised in terms of steric interactions in the monosubstituted enamine, and in the transition state of the reaction, which favour reaction at the least substituted β-position of an isomeric mixture of enamines (see Section 2). However House and Schellenbaum[217] then reported that prolonged reaction (66h) of the pyrrolidine enamine of 2-methylcyclohexanone with methyl acrylate in dioxan under reflux gave a 1:1 mixture of 2,2- and 2,6-disubstituted cyclohexanones (**265** and **266**).

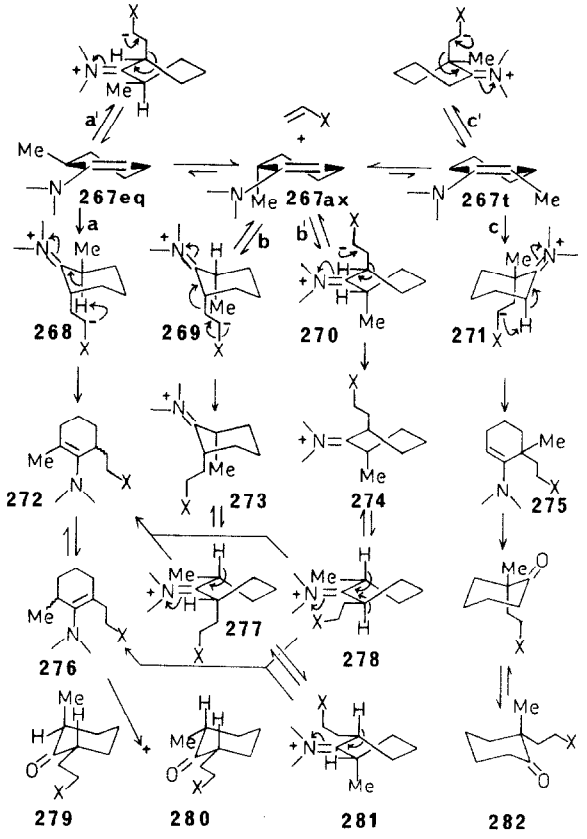


Scheme 70.

The conclusion reached was that the preference for attack at the least substituted position (i.e. **261** not **262**) was not as great as had previously been supposed. The theoretical foundations of enamine

chemistry, which had hitherto seemed firmly based, were apparently undermined by this observation. It therefore came as a great relief, at least to the reviewer, when Malhotra and Johnson[187] suggested in 1965 that the formation of the 2,2-disubstituted product **266** occurred in the hydrolysis step, by pyrrolidine-catalysed Michael reaction of methyl acrylate with 2-methylcyclohexanone. However since no experimental verification was provided we were still doubtful about this explanation since the conditions were very mild for an enolate-anion mechanism.

In view of the theoretical implications of House's observation we therefore repeated this reaction and showed unequivocally[67] that the 2,2-disubstituted product **266** was derived by alkylation of the more substituted form of the enamine **262**. The disubstituted enamine **263** was detected in the crude reaction product [τ 8.83 (s, Me), 5.25 (t, CH=)] prior to hydrolysis. Since **265** and **266** are formed in equal amounts it would appear as if reaction at the more substituted β-positions of enamines **262** can in some cases occur with equal ease as reaction at the less substituted β-position of enamine **261**. *However this is not true.* Enamine **261** always has lower energy pathways open to it than has enamine **262**, but in some cases these low energy pathways are reversible and may not lead to products. Higher energy routes then determine the course of the reaction and then reactions of enamine **262** can contribute to the product distribution. The experimental basis[218] for this statement is summarised in Table 5 and the low and high energy pathways summarised in Scheme 71.



Scheme 71.

The explanation which we suggested and which is applicable to most electrophilic olefin reactions (the only exception which we are aware of concerns the strange reactivity of dibenzoyldi-imide (Section 5G)) with 2-substituted cyclohexanone enamines is as follows.

(a) *Energetics and reversibility of competing reaction pathways.* The low energy pathways referred to above involve axial (path b) or equatorial (path b') attack by the electrophile on the enamine conformer having the methyl substituent quasi-axially orientated (i.e. **267** ax). The energetics of these two paths can be expected to be similar since the main steric interactions are 1,3-diaxial methylene–methyl (~3.6 kcal/mol[219]) in **269** and nonbonded twist interactions (~2.7 kcal/mol[220]) in **270**. However both paths are reversible in aprotic solvents of low dielectric constant and do not lead to products under conditions of high dilution (Table 5; No. 1). Although reversion to starting enamine could be prevented

Table 5. Effect of reaction conditions on the ratio of 2,2- to 2,6-disubstitution[a]

No.	Electrophilic olefin	Solvent	Reaction time (h) (under reflux)	Yield (%)	Disubstituted cyclohexanone (% composition)		
					trans-2,6 (279)	cis-2,6 (280)	2,2- (282)
1	Methyl acrylate	Dioxan	66[b]	10	28	20	52
2	Methyl acrylate	Dioxan	66	65	45	20	35
3	Methyl acrylate	Dioxan	66[c]	70	46	36	18
4	Methyl acrylate	Acetonitrile	66	65	65	30	5
5	Methyl acrylate	Methanol	3	70	70	30	0
6	Methyl acrylate	Methanol	66	50	56	44	0
7	Methyl acrylate	Benzene	66[d]	60	55	25	20
8	Methyl acrylate	Mesitylene	66[e]	65	43	24	33
9	Methyl acrylate	Mesitylene	66[f]	40	30	20	50
10	Acrylonitrile	Dioxan	66	70	32	20	48
11	Acrylonitrile	Methanol	66	70	69	31	0
12	Methyl acrylate	None	66 d	80	52	33	15

[a]Enamine concentration 2.3 mol l^{-1} unless stated otherwise. [b]Enamine concentration 0.11 mol l^{-1}. [c]Enamine concentration 36.5 mol l^{-1}. [d]Temp. 80°C. [e]Temp. 100°C. [f]Temp. 160°C, under pressure.

by protonation of the anionic centre, under conditions of high dilution and short lifetimes for the zwitterionic intermediates produced (**269** and **270**), this would have to involve intramolecular transfer of an equatorially orientated hydrogen. This would be expected to be a high energy process owing to the unfavourable stereoelectronic factors[221] involving a four-membered transition state and negligible overlap of the C–H orbital with the p orbital of the iminium group. Charge neutralisation by collapse to the cyclobutane introduces strain into the system and has been shown to be reversible even at room temperature.[222] Similar considerations apply to paths a′ and c′ except that these will be higher energy processes since there are additional $A^{1,3}$-interactions in the iminium salts formed. This leaves paths a and c, involving axial attack on **267** eq and **267**t. Both iminium salts formed (**268** and **271**) are destabilised by $A^{1,3}$-strain between the methyl and α-methylene groups of the amine ring (~7.6 kcal/mol for a methyl–methyl interaction[26]). These are therefore also high energy processes but can be rendered irreversible by stereoelectronically controlled intramolecular proton transfer via a six-membered cyclic transition state (**268** → **272** and **271** → **275**). Since the destabilising steric interactions are the same then the activation energies should be similar for both routes, thus leading to roughly equal amounts of 2,2- and 2,6-disubstituted products as is observed under conditions of high dilution in which intermolecular processes are reduced to a minimum (Table 5; No. 1.). The probability of interaction between the starting reagents is of course also reduced under these conditions, with consequent reduction in yield.

Although the energy differences between the alternative routes summarised in Scheme 71 are small it is worth bearing in mind that it requires somewhat less than 3 kcal free energy to change a 9:1 product ratio into a 1:9 ratio.

(b) *Effect of concentration and solvent.* As the concentration of enamine is increased so the possibility of intermolecular proton exchange is increased. Once the anionic centres of **269** and **270** have been protonated, stable iminium salts **273** and **274** are produced which can undergo stereoelectronically controlled deprotonation to enamines **272** and **276** via conformations **277**, **278** and **281**. The amount of 2,6-disubstitution increases (48 → 65 → 82%) as the enamine concentration is increased (0.11 → 2.3 → 36.5 mol l^{-1}) (Table 5; Nos. 1–3), rising to a maximum of 85% in the absence of solvent (Table 5; No. 12). The fact that 2,2-disubstitution still occurs at high enamine concentration can be attributed to the short lifetime of the zwitterionic intermediates **269** and **270** in media of low dielectric constant. This will cause a reduction in the rate of product formation via routes b and b′ so that routes a and c are still able to compete. Conversely in polar solvents of high dielectric constant (acetonitrile) the lifetimes of **269** and **270** are presumably increased sufficiently to enable intervention by intermolecular protonation processes at lower dilution, thus increasing product formation via paths b and b′ (Table 5; No. 4). In protic solvents the formation of **269** and **270** will be rendered virtually irreversible by the combined effects of the increased dielectric constant and solvating power of the solvent together with the fact that the anionic centre can now be protonated directly by the solvent. Under these conditions only 2,6-disubstitution occurs, via the low energy paths b and/or b′ (Table 5; Nos. 5, 6 and 11).

(c) *Evidence for the intermediacy and reversible formation of zwitterionic intermediates.* When the reaction between the enamine mixture (267 eq, ax, t) and methyl acrylate was carried out in monodeuteriomethanol the ^1H NMR spectrum of the 2,6-disubstituted cyclohexanones obtained on hydrolysis (**279** and **280**) showed the axial and equatorial methyl signals as doublets, indicating that no deuterium incorporation into the enamine had occurred. Mass spectroscopy indicated however that *ca.* 70%

deuteriation of the α-position of the methoxycarbonylethyl side-chain had occurred, thus demonstrating the intermediacy of the zwitterionic intermediates **269** and **270**. Risaliti *et al.* have demonstrated that the formation of such intermediates is reversible, by showing that the isomerisation of maleate to fumarate esters is catalysed by enamines but not by tertiary amines.[223] Fleming and Harley-Mason showed that the cyclobutanes formed by cycloaddition of electrophilic olefins to enamines reverted to starting materials on heating or even in some cases at ambient temperature.[222] We have also used the reversibility of zwitterion formation to develop conditions for changing the regioselectivity of reaction of certain dienamines. Thus although methylation of the pyrrolidine dienamine of 3-methyl-$\Delta^{1,8a}$-2-octalone gives only the 1,3-disubstituted octalone in protic and aprotic solvents, the position of attack by acrylonitrile and methyl acrylate is solvent-dependent.[224]

(d) *Other factors affecting the lifetime of zwitterionic intermediates.* In addition to the effect of the dielectric constant and solvating or protonating ability of the solvent, the lifetime of the initially formed zwitterionic intermediate will also be affected by the temperature, the stabilisation of the anionic centre, and the ease of charge neutralisation by cyclisation. The change in the ratio of 2,6- to 2,2-disubstitution in going from dioxan (2:1) to benzene (4:1) is undoubtedly largely a temperature effect (Table 5; Nos. 2 and 7). At the lower temperature (benzene) both the lifetime of the zwitterionic intermediates **269** and **270** will be increased and therefore the probability of intermolecular protonation of the anionic centre. Product formation via the low energy routes b and b′ consequently becomes more feasible, thus leading to increased amounts of 2,6-disubstitution. This is confirmed by the fact that, at the same concentration in mesitylene the ratio (2,6- to 2,2-) changes from *ca.* 2:1 at 100° to 1:1 at 160° (Table 5; Nos. 8 and 9). This can be attributed to the lifetime of the zwitterionic intermediates **269** and **270** being still further reduced at this higher temperature. Further confirmation is provided by the fact that at ambient temperature in the absence of solvent, only the 2,6-disubstituted product is obtained, albeit in low yield.[222] This must be due to the now longer lifetime of the zwitterionic intermediates **269** and **270**, in equilibrium with their cyclobutane adducts, and to the inability of the molecules to surmount the higher energy barriers leading to the zwitterionic intermediates **268** and **271** at these low temperatures.

In addition to the effect of temperature, the lifetime of the zwitterionic intermediates produced by reaction with an enamine can be expected to be increased by factors which increase the stability of the anionic centre such as increased electronegativity of the atom bearing the negative charge (O > N > C) and by substituent groups, the stabilising effect of which appears to increase in the order[225] NO_2 > C=O > SO_2 > CO_2H > CO_2R > CN > $CONH_2$.

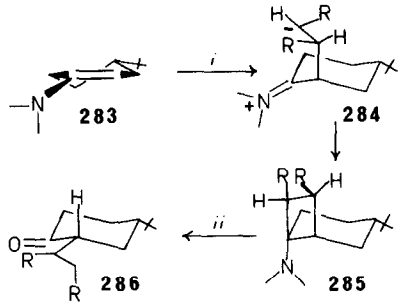
This is supported by the observation that acrylonitrile gives a greater amount of 2,2-disubstituted ketone than does methyl acrylate at the same medium enamine concentration (2.3 mol l^{-1}) (Table 5; Nos. 2 and 10). This can be attributed to reduced stabilisation of the anionic centre by a cyano relative to an alkoxycarbonyl substituent, with consequent reduced lifetime of the corresponding zwitterionic intermediates. This factor is also reflected in the reactions of 2-substituted cyclohexanone enamines with isocyanates,[226,227] acid chlorides,[228] diethyl azodicarboxylate[226,229–234,236] and nitro-olefins;[235] in every case only the product of 2,6-disubstitution has been isolated, thus demonstrating the increased stability of the initially formed zwitterionic intermediates derived by path b or b′.

Furthermore Pitacco *et al.*[236] have recently demonstrated that the formation of the corresponding 2,6-disubstituted cyclohexanone from diethyl azodicarboxylate does not occur by axial attack on the equatorially orientated enamine (i.e. **267** eq), thus providing evidence for our conclusion that path a is a higher energy route than paths b or b′. When a zwitterionic intermediate is not produced, as in the reaction with acryloyl chloride, the problem of 2,2-disubstitution does not arise.[13,66]

(e) *Stereoselectivity.* The stereoselectivity summarised in Table 5 (i.e. the preference for formation of trans-ketone **279** over the thermodynamically more stable cis-ketone **280**) has been discussed in Section 5A (ii).

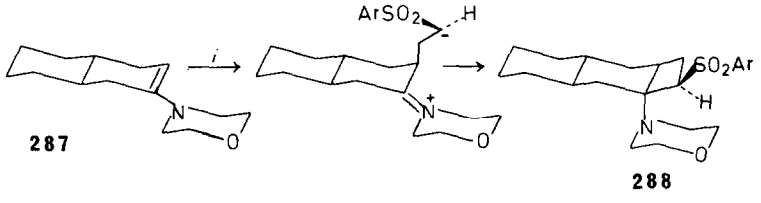
If in Scheme 71 the 2-methyl substituent is replaced by a hydrogen atom, then clearly path b (axial attack) is of lower energy than path b′ (equatorial attack). Unfortunately reaction with an electrophilic olefin produces a new enamine, or a mixture of isomeric enamines, so the stereochemistry of the ketone obtained by hydrolysis may depend on the stereochemistry of protonation. This is certainly the case when the product is a 2,6-disubstituted cyclohexanone. Alternatively the ketone may isomerise during the hydrolysis. It is therefore not always possible to determine the stereochemistry of the initial alkylation process. Exceptions to this generalisation are when a cyclic product is formed. For example in the reaction[237] of 1-morpholino-4-t-butylcyclohexene with diethyl maleate or diethyl fumarate the product obtained on hydrolysis was the cis-ketone **286**. However X-ray analysis of the intermediate cyclobutane

285 produced at ambient temperature showed that the initial alkylation step occurred by axial attack on the enamine **283** to give the zwitterion **284**:



Scheme 72. Reagents: (i) diethyl maleate (or fumarate); (ii), H_2O–EtOH–HOAc, Δ 2 hr; R = CO_2Et.

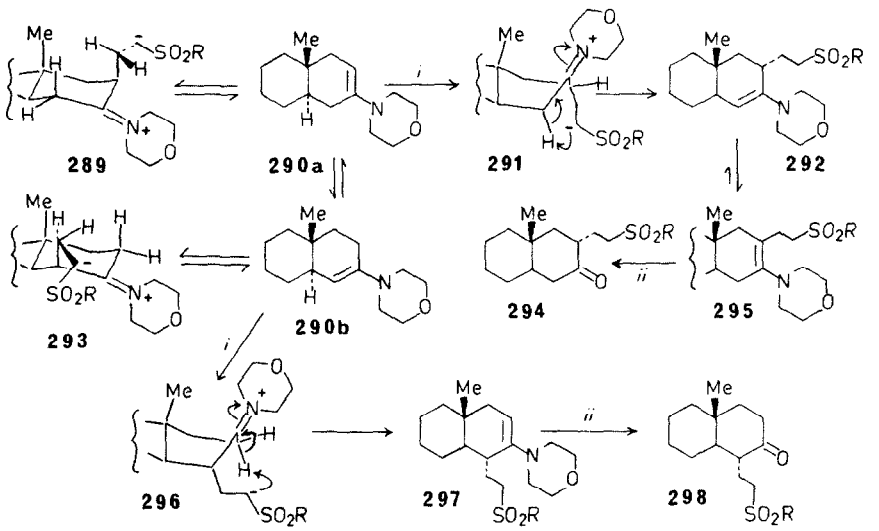
Similarly the reaction of the trans-2-decalone enamine **287** and aryl vinyl sulphones gave the cis-fused cyclobutane adduct **288** again derived by axial alkylation of the enamine.[238]



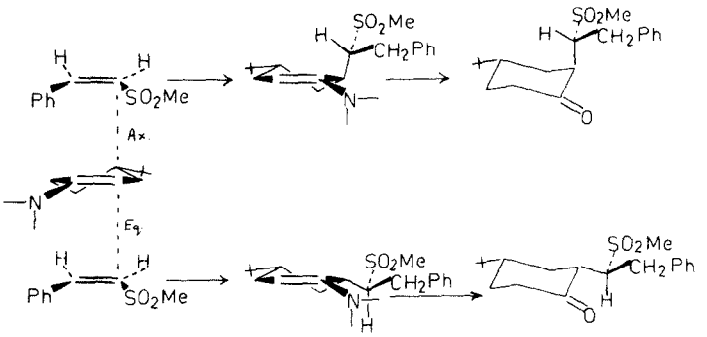
Scheme 73. Reagents: (i) $CH_2 = CHSO_2Ar$, C_6H_6, 5°; Ar = C_6H_5, p-BrC_6H_4.

The corresponding enamine from 4a-methyl-trans-2-decalone **290** failed to react under the above low temperature conditions. On prolonged heating at 100° equatorial attack occurred at C-1 and presumably at C-3 to give the two Δ^2-isomers **295** and **297**.[239] Clearly the stereoselectivity can be attributed to steric hindrance to axial attack by the axial 4a-methyl group. It should be emphasized that the steric effect of an axial substituent at C-4a of a Δ^1- or Δ^2-octalin in hindering axial approach to the double bond is much greater than the effect of a quasi-axial substituent at C-3 or C-1 respectively. Similarly in cyclohexanone enamines, an axial substituent at C-4 exerts a greater steric impediment to axial attack at C-2 than does a quasi-axial substituent at C-6. Even if axial attack on **290b** occurred at C-1, to give zwitterion **293**, the 4a-methyl group would certainly prevent intramolecular abstraction of the C-3 axial proton by the anionic centre produced. This would therefore be reversible, whereas equatorial attack can be rendered irreversible by abstraction of the C-3 proton in the boat conformation produced **296**. Similar considerations apply to attack at C-3. Axial attack (**290a** → **289**) would be both sterically hindered and reversible. The only difference is that the Δ^1-isomer **292**, produced by proton abstraction by the anionic centre in **291** must rearrange to the more stable Δ^2-isomer **295** under the prolonged reaction conditions. The alternative, that the Δ^2-isomer **295** is formed directly from zwitterion **291** is less probable since it would involve abstraction of an equatorial proton in which the C–H orbital is virtually orthogonal to the p-orbital of the iminium group and must therefore be a higher energy process. Hydrolysis of the two Δ^2-isomers gave the thermodynamically stable ketones **294** and **298**. The hydrolysis conditions are presumably non-epimerising so again it would appear that stereoselective protonation is occurring from the most hindered β-side. Possible reasons for this have been discussed in Section 5A (ii).

Although equatorial attack by electrophilic olefins normally occurs only when axial attack is inhibited for steric reasons, Risaliti *et al.* have observed both axial and equatorial attack by 1-nitropropene[240] and methyl β-styryl sulphones.[241,242] In the latter case the regioselectivity of reaction of the electrophilic olefin varies surprisingly with the stereochemistry of the double bond; the Z-isomer reacts almost exclusively at the carbon α to SO_2 whereas the E-isomer reacts with similar lack of stereoselectivity, but at the β-carbon in the usual way.

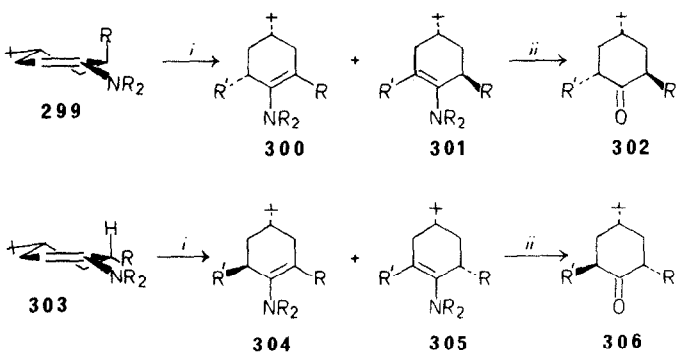


Scheme 74. Reagents: (i) p-CH_2 = $CHSO_2C_6H_4Br$, 100°, 72hr, (ii) aq. HOAc, 25° 96 hr.



Scheme 75.

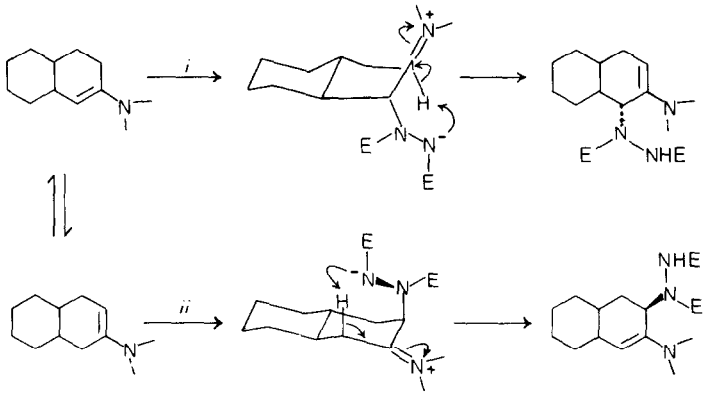
The reaction of diethyl azodicarboxylate (DAD) with cyclohexanone enamines can occur from an axial or equatorial direction depending upon the steric effects in the transition state, which is assumed to be product-like.[243] For example reaction of DAD with **299** under kinetically controlled conditions gives **300**, by equatorial attack, and **301** (in a 1:9 ratio), whereas the epimer **303** gives **304**, by axial attack, and **305** (in a 3:7 ratio).



Scheme 76. Reagents: (i) DAD, 5°; (ii) H^+, H_2O, R.T.; R = $CH(CH_3)CH_2NO_2$; R′ = $N(CO_2Et)NHCO_2Et$; R_2N = morpholino.

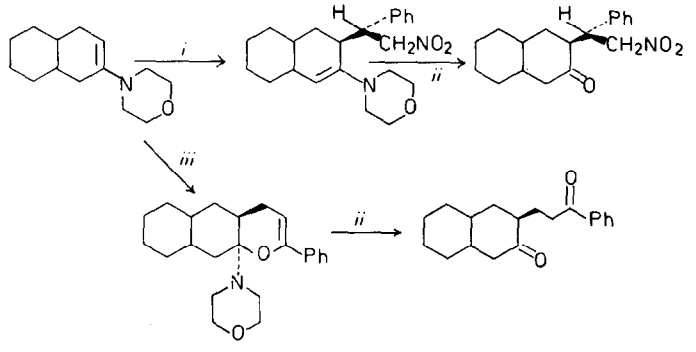
Interestingly enamine **301** undergoes stereospecific axial protonation and hydrolysis to **302**, whereas **305** undergoes stereospecific equatorial protonation to **306** [see Section 5A (ii)]. The regioisomers **300** and **304** do not undergo hydrolysis under these conditions since protonation apparently occurs on nitrogen rather than on carbon.

The morpholine enamine of trans-2-decalone exists as a mixture of Δ^1- and Δ^2-isomers (21 and 79% respectively). Both isomers react with the highly electrophilic dialkyl azodicarboxylates, though by different stereochemical routes[244] (Scheme 77).



Scheme 77. Reagents: (i) diethyl azodicarboxylate (EAD), equatorial attack; (ii) EAD, axial attack; E = CO_2Et.

The less electrophilic β-nitrostyrene and phenylvinyl ketone react only with the Δ^2-isomer at C-3 however, by axial attack.[245]

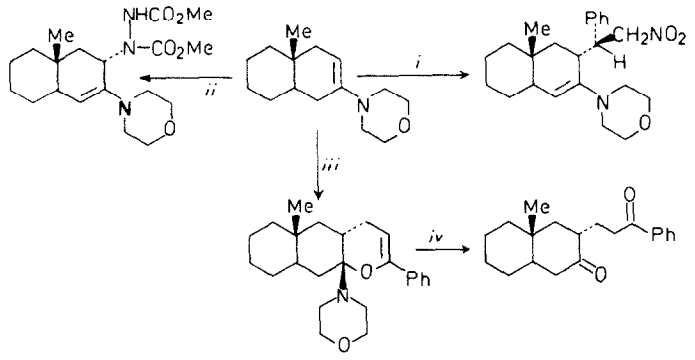


Scheme 78. Reagents: (i) PhCH = $CHNO_2$, ether, 5°, 72 hr; (ii) H_3O^+, 25°; (iii) CH_2 = CHCOPh, petroleum, 5°, 60 hr.

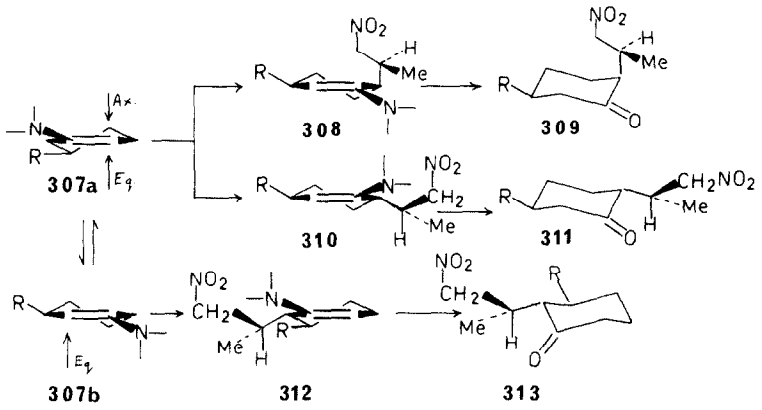
When axial attack was impeded by the presence of an axial methyl group at C-4a, reaction with these electrophilic olefins again occurred with high stereo and regioselectivity but from the equatorial direction at C-3[245] (Scheme 79).

Both axial and equatorial attack have been observed in the reaction of 1-nitropropene with the morpholine enamines of 3-phenyl, 3-t-butyl, and 4-t-butylcyclohexanone enamines.[246] Interestingly, in the case of the 3-substituted enamines **307** the Δ^1-isomer **307b** reacts only from the equatorial direction, presumably due to developing gauche butane interactions from the axial direction (see Scheme 3; Section 2). The ratio of 2,3-disubstitution to 2,5-disubstitution (i.e. **313**:**309** + **311**) was 20:80 (R=Ph) and 10:90 (R=t-Bu) reflecting the increased steric impediment to reaction. The Δ^6-isomer **307a** underwent axial:equatorial attack in the ratio 67:33.

The threo configurations are assigned to **309**, **311** and **313** on the logical assumption that the methyl group assumes an exo position with regard to the cyclohexene ring in the zwitterionic intermediates leading to **308**, **310** and **312**.



Scheme 79. Reagents: (i) $PhCH = CHNO_2$; (ii) $MeO_2CN = NCO_2Me$; (iii) $CH_2 = CHCOPh$; (iv) H_3O^+.



Scheme 80.

The Δ^1- and Δ^6-isomers of 3-substituted cyclohexanone enamines have been shown to be in rapid equilibrium, even at low temperatures.[37a,247] In fact, in reactions with β-nitrostyrene the amounts of 2,5-disubstituted ketones (derived from the Δ^6-isomer **307a**) obtained on hydrolysis were greatly in excess of the percentage of Δ^6-isomers present in the parent enamines[37b] (Table 6).

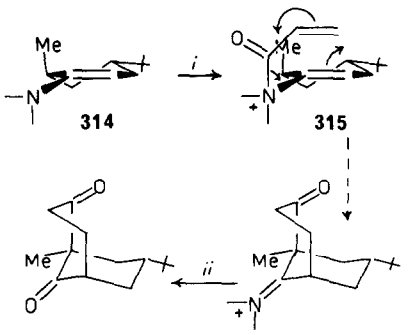
In contrast to 1-nitropropene, β-nitrostyrene only underwent axial attack on the Δ^6-enamines **307a** (R=Me, Ph, t-Bu), although the Δ^1-enamines **307b** underwent equatorial attack as before.

In the reaction of acryloyl chloride with enamines the first carbon–carbon bond formed involves an intramolecular alkylation[13,15] by an electrophilic olefin (i.e. the N-acylated enamine **315**). Application of the reaction to the morpholine enamine of 2-methyl-4-t-butylcyclohexanone **314** showed that at least 80% of the product was formed by axial attack on the enamine despite the developing 1,3-diaxial interactions with the quasi-axial methyl substituent.[35]

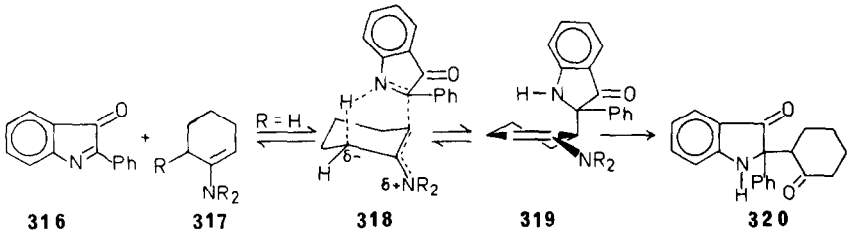
(f) *Miscellaneous.* An interesting reaction is that of enamines with 2-phenyl-3H-indole-3-one **316** which could react as a heteroelectrophilic olefin at nitrogen. However reaction occurs at the imine carbon to give adduct **319** and hence **320** on hydrolysis.[248] This reaction is unusual in that the adduct **319** is formed reversibly since it reacts with nucleophiles and electrophiles as if it were in equilibrium with starting materials **316** and **317**, although there is no spectroscopic evidence for this. Formation and retrogression of **319** is therefore proposed to be a synchronous process as indicated in **318**.

Table 6. 2,3- vs 2,5-Disubstitution in 3-substituted cyclohexanone enamines

R	% 307a[256]	% 307b[256]	% 2,5-Disubstitution	% 2,3-Disubstitution
Me	55	45	80	20
Ph	0	100	80	20
t-Bu	45	55	85	15

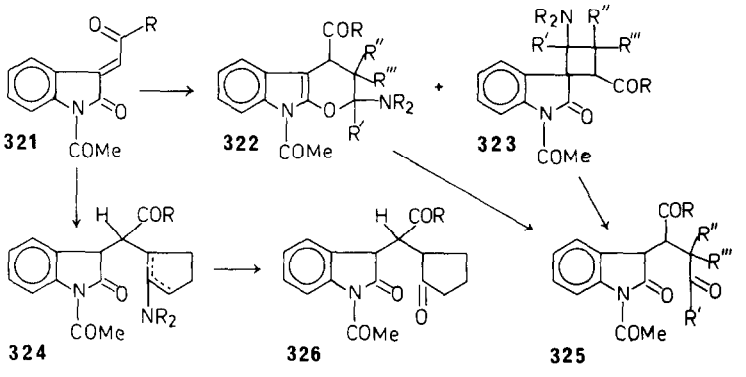


Scheme 81. Reagents (i) $CH_2=CHCOCl$, C_6H_6, Δ; (ii) cold H_2O, 3 hr.



Scheme 82. R = H, Me; R_2N = pyrrolidino, morpholino, piperidino.

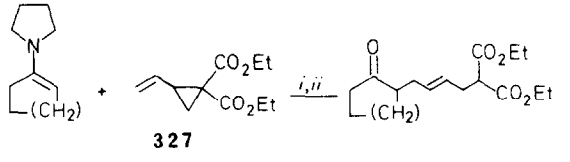
The oxindole **321**, which has two electrophilic olefin positions, reacts with complete regioselectivity at only the one position.[249] With ketone enamines the Michael addition compound **324** is formed whereas with aldehyde enamines the intermediate zwitterion collapses to the pyran **322** or cylobutane adduct **323**.



Scheme 83.

All the adducts gave the open-chain aldehydes or ketones **325** and **326** on hydrolytic cleavage. The zwitterionic intermediate has also been trapped by cycloaddition of tetracyanoethylene to give a spirocyclohexane oxindole.[250]

Enamines also attack the *terminal* position of the electrophilic vinylcyclopropane **327**, in contrast to other nucleophiles, and thus provides a method for introducing a six carbon fragment α to a carbonyl group.[251]



Scheme 84. Reagents: (i) p-cymene, Δ; (ii) H_3O^+.

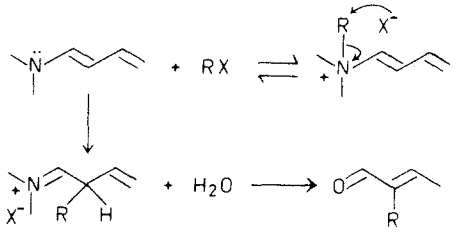
(ii) *With alkyl halides.* In general alkylation of ketone enamines with simple unactivated alkyl halides is unsatisfactory since complex mixtures of unalkylated, monoalkylated, dialkylated, and N-alkylated products are formed. Unalkylated iminium salt may be formed by proton exchange between starting enamine and C-alkylated iminium salt. Methylation has been reported to be especially bad in this respect, the reaction of methyl iodide with the pyrrolidine enamine of cyclohexanone giving 30% recovered starting ketone, 44% 2-methylcyclohexanone, and considerable 2,6-dimethylcyclohexanone.[6] Owing to the closeness of their boiling points it is often difficult to separate the components of a mixture such as this. Separation may be achieved by selective conversion to the corresponding enamine however [see Section 4A (i)].

The problem of N- vs C-alkylation has been investigated by Elkik,[252] and by Kuehne and Garbacik,[76] but it was not found possible to establish any general predictive rules. For example although the pyrrolidine enamine of cyclohexanone showed a greater ratio of C to N alkylation with methyl iodide at room temperature, than did the morpholine enamine, this situation was reversed for the reaction with benzyl bromide. However in the majority of cases there was an increase in the C to N alkylation ratio on heating the reaction mixtures obtained at room temperature to 100° for 18 hr, due to N to C alkyl transfer. The facility of N alkylated enamines to act as carbon alkylating agents was found to vary with the structure of the amine and ketone used to form the enamine, and with the alkylating agent. On this basis morpholine enamines were particularly poor (i.e. showed the least increase in C to N ratio on heating) whereas hexamethylene imine enamines were best. As regards alkylating agents the more reactive, such as benzyl bromide, showed the greatest increase in C to N alkylation ratio on heating.

This of course merely substantiates the early work of Stork *et al.*[6] who showed that good yields of C-alkylated ketones were obtained with strongly electrophilic halides such as allyl halides, benzyl halides, propargyl halides, α-halo ethers, α-haloketones, α-haloesters, and α-halonitriles, the enhanced reactivity of which would facilitate reversal of N-alkylation.

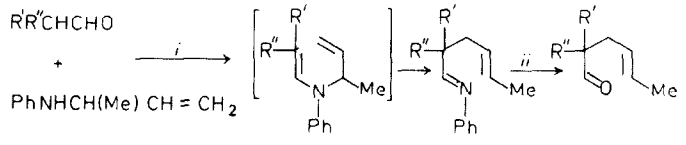
Even here yields can be considerably improved by optimisation of the experimental conditions, as for example in the use of acetonitrile as solvent in the benzylation of indanone or tetralone enamines, and the simple expedient of washing the crude product mixture with acetone prior to hydrolysis avoids the need for chromatographic purification.[253]

As regards the mechanism of N to C alkyl transfer, Pandit *et al.*[254] have concluded that direct intramolecular N→C alkyl transfer does not take place and have interpreted the data available from the alkylation of dienamines in favour of a dissociation to alkyl halide and subsequent C-alkylation (Scheme 85) rather than an intermolecular alkyl transfer from an ene-ammonium salt to the enamine.



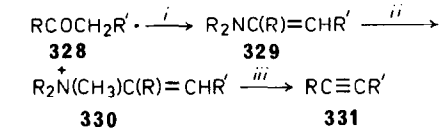
Scheme 85.

In the case of alkylation with allyl or propargyl halides, intramolecular N→C rearrangement may occur of course, via a [3,3] sigmatropic reaarangement.[255,262] Such aza-Claisen rearrangements are catalysed by Lewis acids such as $TiCl_4$. This makes it possible to prepare and rearrange N-allylamines of aldehydes in a single step.[257] The stereochemistry of the aza-Claisen rearrangement was not altered by the titanium(IV) chloride catalysis.



Scheme 86. Reagents: (i) $TiCl_4$; (ii) H_3O^+; R',R'' = Me, Ph; H, Me; H, Et; H, n-Bu; $CH_2CH=CH(CH_2)_2$; $(CH_2)_3CMe_2$.

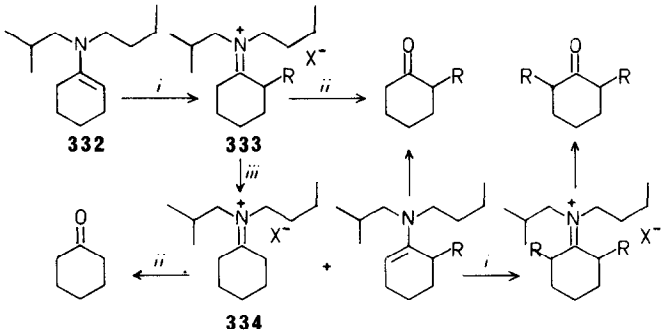
N-Alkylation of enamines has been put to synthetic use by Hendrickson and Sufrin,[258] who showed that some quaternised enamines underwent the Hofmann elimination and thus provide a route from acyclic ketones to acetylenes. However the method only worked well with the pyrrolidine enamine of



Scheme 87. Reagents: (i) (a) pyrrolidine or (b) 3,3,4,4-tetramethylpyrrolidine or (c) 3,3-dimethylazetidine; (ii) methyl fluorosulphonate; (iii) 40% aq. KOH, Δ 2 hr.

deoxybenzoin **328a** (R=R'=Ph) which methylated almost exclusively on N (>95%), the quarternised enamine being converted to diphenylacetylene **331** in 86% yield. Enamines **329b** and **329c** were prepared to avoid the possibility of Hofmann elimination in the amine moiety; however acetylenes were not obtained from their quarternary salts presumably due to incorrect geometry (i.e. trans-stilbene in **330a** but cis-stilbene for the more bulky tetramethylpyrrolidine enamine **330b**). Enamines from acetophenone and diethyl acetonedicarboxylate (**328**; R=CH_2CO_2Et, R'=CO_2Et) were mainly or exclusively C-alkylated, and dibenzyl ketone (**328**; R=CH_2Ph, R'=Ph) gave diphenylallene (25%).

Recently a significant improvement in the alkylation of ketones has been reported by Curphey *et al.* which involves the use of enamines derived from sterically hindered amines.[259] For example reaction of the n-butylisobutylamine enamine of cyclohexanone, with methyl iodide in boiling acetonitrile gave 56% 2-methylcyclohexanone (14% cyclohexanone and 14% 2,6-dimethylcyclohexanone). By employing trimethyloxonium tetrafluoroborate as the alkylating agent in the same solvent at room temperature, these figures were further improved of 74% 2-methylcyclohexanone (9% cyclohexanone and 1–3% 2,6-dimethylcyclohexanone). The possibility that the unchanged cyclohexanone arose from incomplete reaction was ruled out; instead it appears to be formed by hydrolysis of the iminium salt **334** which in turn is most probably formed by proton exchange between alkylated iminium salt **333** and unchanged enamine **332**. Interestingly, not only does the use of hindered amines prevent N-alkylation, it also inhibits hydroxylation of the iminium salt **333**, which can withstand boiling aqueous acid virtually unchanged and has to be hydrolysed to the ketone using sodium acetate–acetic acid buffer, a method normally reserved for the hydrolysis of enamines further conjugated with an unsaturated group.[6]

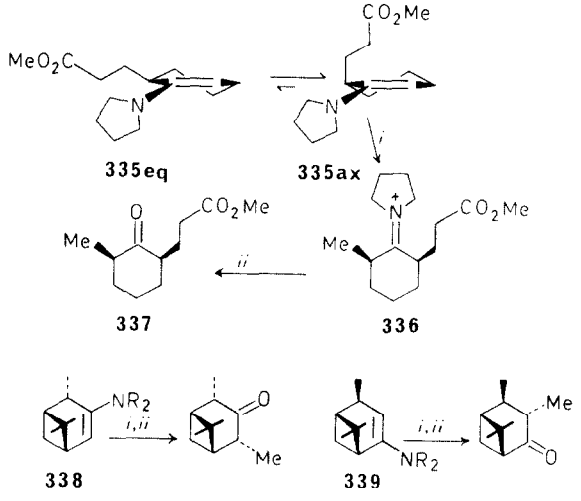


Scheme 88. Reagents: (i) RBr, RI in boiling C_6H_6 or CH_3CN (R = Me, Et, n-Bu, $CH_2=CHCH_2$, CH_2CO_2Et) or R_3OBF_4 in CH_2Cl_2 or CH_3NO_2 at room temperature (R = Me, Et); (ii) sodium acetate, acetic acid, water, 100°; (iii) enamine **332**.

In the case of aldehyde enamines only allyl and benzyl halides give good yields of C-alkylated aldehydes unless hindered enamines are used.[260] Otherwise N-alkylation or aldol condensation are often the only reactions observed.[261,262] The optimum conditions for C-alkylation appear to involve reaction of the n-butylisobutylamine enamine with an alkyl iodide (or possibly equimolar amounts of alkyl bromide and sodium iodide) in refluxing acetonitrile. The method failed with the acetaldehyde enamine, probably due to the marked instability of the enamine. Hindered aldehyde enamines have also been made and

alkylated *in situ*.[115] The method has also been used to achieve direct C-alkylation of isobutyraldehyde with propargylic halides,[263] thus circumventing the formation of allenic products, which arise from the more usual unhindered enamines by initial N-alkylation followed by N→C sigmatropic rearrangement.[264]

Although methoxycarbonylethylation of the pyrrolidine enamine of 2-methylcyclohexanone in aprotic solvents gives 2,2- and 2,6-disubstitution [Section 5B(i)], the methylation of the pyrrolidine enamine **335** of methyl 3-(2-oxocyclonexyl)propionate with methyl iodide gives only the 2,6-disubstituted product in protic and aprotic solvents.[218] Furthermore this product was obtained almost entirely as the cis-isomer **337**. In this case a zwitterionic intermediate is not formed, so the initial C-alkylation step is virtually irreversible, in contradistinction to alkylation with electrophilic olefins. The high stereoselectivity which we have found for the methyl iodide reaction can be attributed to the fact that in this case it is not an enamine which is being hydrolysed but an iminium salt **336** (Scheme 89). The fact that predominantly the cis-isomer is obtained indicates high preference for axial attack on the axially orientated enamine conformer **335** ax, as one would expect for a reaction involving what must be a product-like transition state. The alternative possibility, that the cis-isomer is formed by equatorial attack on the equatorially orientated enamine conformer **335** eq, is less likely. This follows from our previously mentioned observation that, in the reaction between acryloyl chloride and the morpholine enamine of 2-methyl-4-t-butylcyclohexanone, initial carbon–carbon bond formation occurs predominantly from the axial side of the enamine double bond.



Scheme 89. Reagents: (i) MeI, (ii) H_2O.

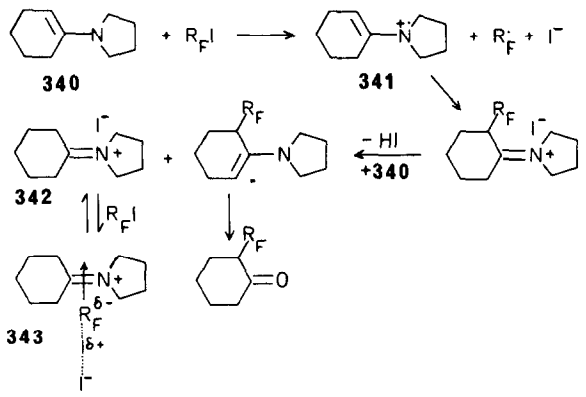
Alkylation of pinocamphone and verbanone enamines (**338** and **339**) with methyl iodide and allyl bromide also occurs stereoselectively,[265] as is to be expected.

Perfluoroalkyl iodides (R_FI) have been shown to react with enamines via a free radical mechanism;[266] in some cases an initiator or UV irradiation may not be necessary. Formation of a radical cation **341** is suggested as the initiation step and an intermediate charge transfer complex **343**, formed by interaction between an iminium iodide **342** and the perfluoroalkyl iodide, has been detected.[267] The solid complex **343** [λ_{max} 290 nm (see λ_{max} *ca.* 220 nm for enamines and iminium salts)] decomposed on heating in vacuum to R_FI (70%) and iminium iodide **342**, and could be hydrolysed to cyclohexanone and R_FI.

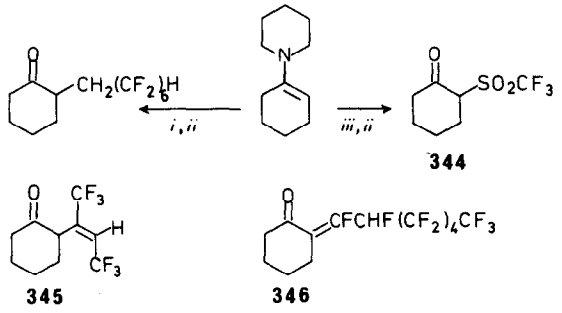
Although alkyl trifluoromethanesulphonates can be used for the alkylation of enamines, the trifluoromethyl sulphonate gives the trifluoromethanesulphonyl derivative **344**.[268] Enamines add to perfluoroalkynes and can be alkylated by perfluoroalkenes to give ketones such as **345** and **346** respectively, on hydrolysis.[269]

The alkylation of enamines by α-halocarbonyl compounds is known to proceed smoothly to give 1,4-dicarbonyl compounds.[115,270,271] However, in the case of benzyl α-bromoacetate, reaction occurred preferentially α to the phenyl group rather than the carbonyl function Scheme 92.[272]

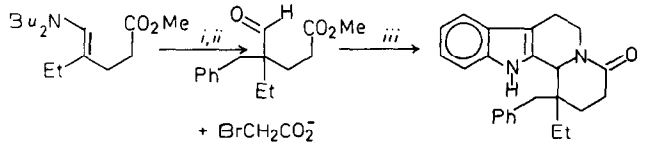
Formation of 1,4-dicarbonyl compounds in which one of the carbonyl groups is an aldehyde residue can readily be achieved by reaction of enamines (or enolates) with ketene thioacetal monoxides **347**.[273]



Scheme 90. $R_F = CF_3, C_2F_5, C_6F_{13}$.

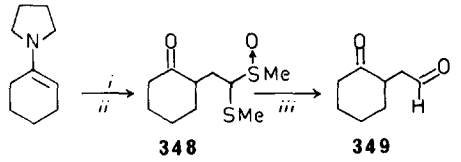


Scheme 91. Reagents: (i) $CF_3SO_2OCH_2(CF_2)_6H$; (ii) H_3O^+; (iii) $CF_3SO_2CF_3$.



Scheme 92. Reagents: (i) $BrCH_2CO_2CH_2Ph$ (or $PhCH_2Cl$), CH_3CN, Δ 5 days; (ii) HOAc, H_2O, Δ 1 hr; (iii) tryptamine, HOAc, Δ 72 hr.

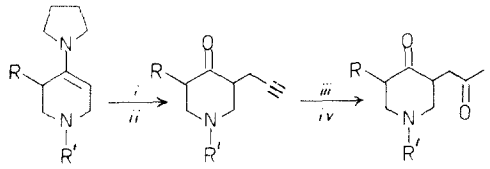
These act as two-carbon Michael receptors to give 348 which can readily be hydrolysed to the terminal carbonyl compound **349**.



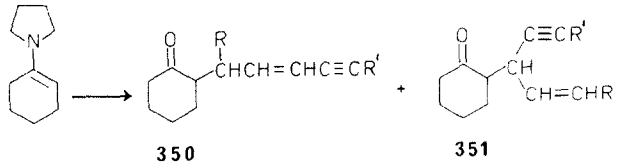
Scheme 93. Reagents: (i) $CH_2 = C(SMe)S(O)Me$ (**347**), CH_3CN, Δ; (ii) H_2O, Δ; (iii) $HClO_4$, aq. CH_3CN.

1,4-Dicarbonyl compounds may also be prepared by propenylation[274] of enamines followed by ozonolysis or propynylation followed by hydration.[275]

Propenylation of enamines has also been effected with allyl phenoxides or acetates in the presence of palladium complexes.[276] Alkylation with 5-halogenoalk-3-en-1-ynes gives a mixture of isomeric ketones **350** and **351**.[277] Primary halides lead essentially to **350** and secondary halides to **351**.



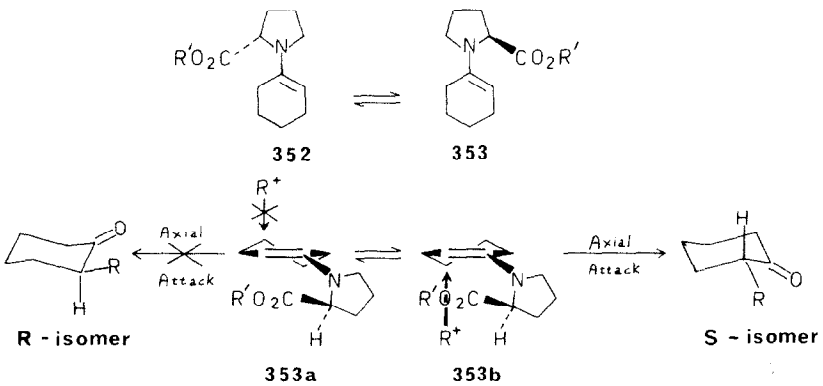
Scheme 94. Reagents: (i) $CH \equiv CCH_2Br$, CH_3CN, Δ 1 hr (or C_6H_6, 20°, 40 hr); (ii) H_2O, Δ; (iii) BF_3OEt_2, HgO, H^+, MeOH, 20°, 3 hr; (iv) 10% aq. H_2SO_4, 50°; R = H, Me; R' = Me, CH_2Ph.



350 351

Scheme 95.

(iii) *Asymmetric induction.* Asymmetric induction has been observed in the alkylation of chiral enamines with both electrophilic olefins and alkyl halides. This was first observed by Yamada *et al.*[278] in the alkylation of chiral enamines derived from various proline esters. Optical yields were found to be increased by the use of bulky ester groups and low temperatures, as would be expected, and to vary with the solvent used. Although the best optical yields obtained were in the range 50–60%, more typical values fell in the range 10–30%. The optically active 2-substituted cyclohexanones obtained were all shown to have the S-configuration. As pointed out by Whitesell and Felman,[281] of the two enamine rotamers which maintain pπ-conjugation (**352** and **353**) the ester group would be expected to exert a significant steric interaction with an approaching electrophile only in **353**. Consideration of the two half-chair conformations of **353** shows that a product-like transition state resulting from axial attack on **353a** would be destabilised, by the above mentioned steric interactions, relative to the transition state resulting from axial attack on **353b**. The predominance of the S-2-substituted cyclohexanones must therefore result from the kinetically controlled enantioselective alkylation of **353b**. An alternative explanation was given by the authors[278,279] who concluded, from consideration of the ground state conformations of the enamine, that the observed enantioselectivity resulted from preferential axial attack on rotamer **352**. Of course both the half-chair conformations of **352** can undergo axial alkylation, thus leading to a mixture of R- and S-2-substituted cyclohexanones.

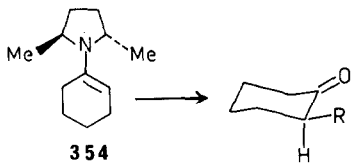


352 353

R - isomer 353a 353b S - isomer

Scheme 96. R = CH_2CH_2CN, $CH_2CH_2CO_2Me$, $CH_2CH=CH_2$, CH_2CO_2Me; R' = Me, Et, t-Bu.

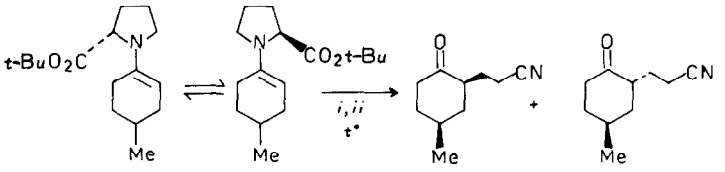
Whitesell and Felman therefore concluded that an amine with a C_2 axis of symmetry was required in order to ensure that the same side of the cyclohexene ring was shielded from attack whatever conformation of the enamine underwent alkylation. The degree of enantioselectivity was thereby substantially increased, but in the opposite chiral sense, using the cyclohexanone enamine **354** derived from (+)-trans-2,5-dimethylpyrrolidine (assumed to have the S,S-configuration based on the results of



354

Scheme 97. R = Me, n-Pr, $CH_2CH=CH_2$.

alkylation). Optical yields in excess of 80% were obtained (Scheme 97).[281] Also noteworthy is the low level of dialkylation (4–7%) produced during the alkylation of enamine **354**. Similar methodology has been applied to the alkylation of 4-substituted cyclohexanone enamines to give mainly the less stable trans disubstituted cyclohexanone (Scheme 98).[280]



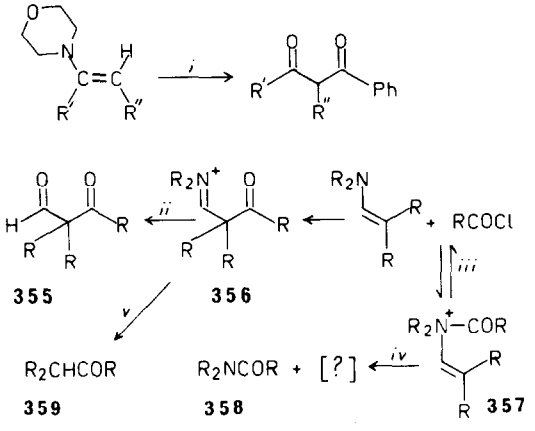
t°			
	20	17%	83%
	40	22%	78%
	78	32%	68%

Scheme 98. Reagents: (i) $CH_2=CHCN$, EtOH, 3 hr; (ii) H_3O^+.

C. *Acylation*

Several reviews on the acylation of enamines have appeared.[29a] The use of acid chlorides in the synthesis of carbocyclic systems will be dealt with in Part II of this report. Among new methods of acylation there may be mentioned the reaction of iodobenzene with nickel carbonyl in the presence of enamines to give β-diketones on hydrolysis in high yield.[282]

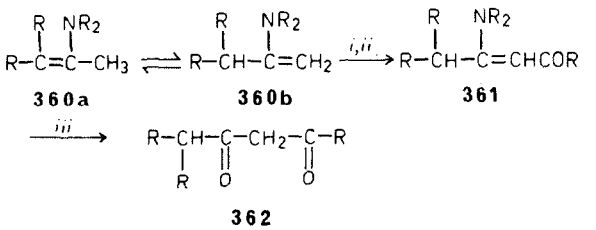
Although N-acylation of enamines is reversible at low temperatures, at high temperatures (i.e. boiling benzene) C–N heterolysis can occur to give the corresponding amide **358**, sometimes in quite high yield (30–60%),[283] particularly with morpholine enamines of aldehydes:



Scheme 99. Reagents: (i) PhI, $Ni(CO)_4$; (ii) aq. HCl; (iii) 20°; (iv) 80°; (v) conc. HCl or aq. NaOH; R',R'' = $(CH_2)_3$; $(CH_2)_4$; Ph, H; Et, n-Pr.

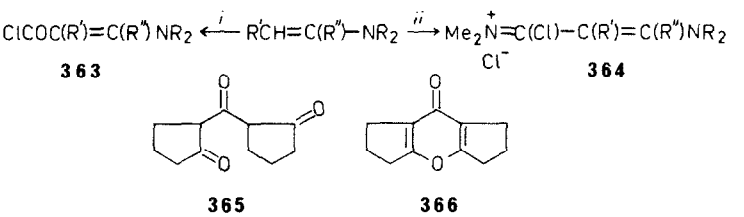
The use of hindered aldehyde enamines derived from di-isopropylamine, for example, prevents N-acylation and results in good yields of C-acylated aldehydes.[283] Otherwise, by working at room temperature or below, C-acylation occurs to give the iminium salt **356** which can be hydrolysed to the C-acylated aldehyde **355** in good yield, or deformylated to give the ketone **359**.[284,285]

With ketone enamines there is less tendency for amide formation and morpholine enamines often give better yields of C-acylated products than do the more reactive pyrrolidine enamines. Since enamines of unsymmetrical alkyl methyl ketones are now readily available via the titanium chloride method of White and Weingarten (Section 4) acylation of the pure regioisomer **360b** or the enamine mixture **360a, b** gives enamino ketones **361** and 1,3-dicarbonyl compounds **362** on hydrolysis in good yields (40–90%).[286]



Scheme 100. Reagents: (i) RCOCl; (ii) Et_3N; (iii) H_3O^+.

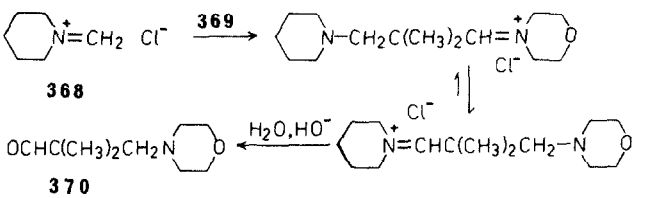
Phosgene and N-dichloromethylene-N,N-dimethylammonium chloride (**367**) react with enamines to give *β-(chlorocarbonyl) enamines* **363**[287] *and the amide chlorides* **364**.[288] *With cyclic ketone enamines* further reaction with phosgene occurs to give the triketone (i.e. **365**) and its cyclised derivative (**366**).[289]



Scheme 101. Reagents: (i) $COCl_2$; (ii) $Cl_2C=\overset{+}{N}Me_2Cl^-$ (**367**).

Analogues of 364 have also been obtained by reaction of enamines with other amide chlorides.[290]

An amusing little reaction in which the amine moiety of the enamine is retained involves the conversion of 1-morpholinoisobutene (**369**) to 2,2-dimethyl-3-morpholinopropanal **370** with methylene piperidinium chloride **368**.[292]

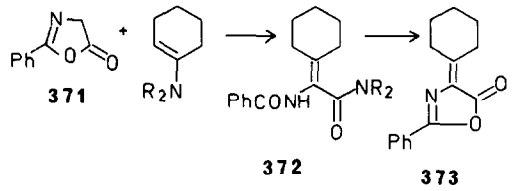


Scheme 102.

Reaction of enamines with 2-phenyloxazol-5(4H)-one **371** gives the corresponding amides of the alkylidenehippuric acid **372** which cyclise to the alkylidene oxazolone **373** on heating.[291]

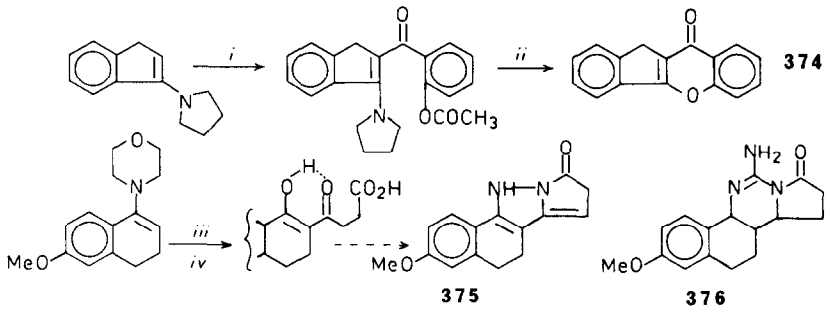
The reaction of aldehyde enamines with trichloroacetic anhydride proceeds with decarboxylation and results in β-trichloroacetylation and α-trichloromethylation of the enamine.[293]

Further applications of the Stork reaction include (i) the synthesis[294] of the annulated γ-pyrone **374** and (ii) the synthesis[295] of various hetero-steroids **375** and **376**.



371 372 373

Scheme 103.

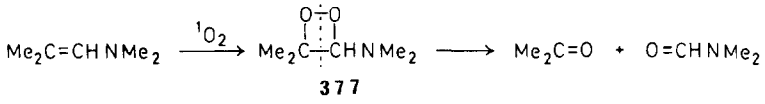


374 375 376

Scheme 104. Reagents: (i) o-acetoxybenzoyl chloride; (ii) NaOMe; (iii) $MeO_2CCH_2CH_2COCl$; (iv) H_3O^+.

D. *Oxidation*

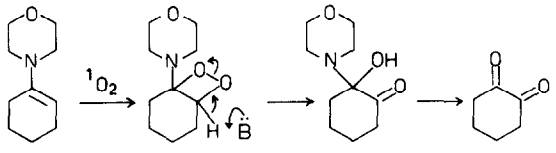
Photosensitized oxygenation of enamines has been shown to occur via 1,2-addition of singlet oxygen to the double bond. At low temperatures (−78°) the intermediate dioxetane **377** can be isolated.[296] At higher temperatures C–C bond cleavage to give the amide and ketone occurs. In some cases C–N bond cleavage has also been observed.[299] With cyclic enamines the dioxetane may undergo cleavage of the O–O bond by a β-elimination process to give an α-diketone.[297] Some controversy exists as regards the



377

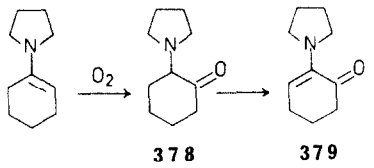
Scheme 105.

mechanism of the symmetry-forbidden cycloaddition process which may occur via perepoxide, zwitterion, or 1,4-diradical intermediates.[298]



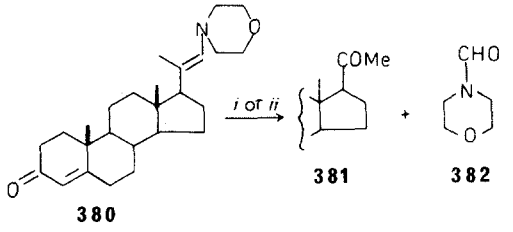
Scheme 106.

Non-sensitized oxygenation of some, but not all, enamines also occurs of course, merely by treatment with oxygen at room temperature or above, under anhydrous conditions.[300] For example reaction of 1-di-n-butylaminobut-1-ene with oxygen in benzene at 25 or 80° gave a mixture of di-n-butylamine (hydrolysis of the enamine), N,N-di-n-butylformamide (double bond cleavage) and 1-N,N-di-n-butylaminobutan-2-one. Similarly the reaction between 1-pyrrolidinocyclohexene and oxygen in dry ethyl acetate was virtually complete in 20 min at room temperature, giving α-pyrrolidinocyclohexanone **378** and 6-oxo-1-pyrrolidinocyclohexene **379**. Compound **378** itself rapidly absorbed oxygen to give **379**. The morpholine enamine failed to react under these same conditions, but oxidation occurred at 80° to give some α-morpholinocyclohexanone and tar.



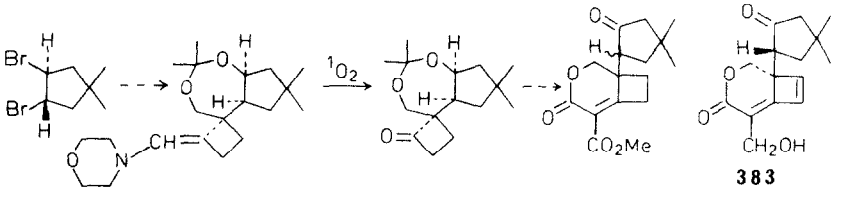
Scheme 107.

Aldehyde enamines such as **380** are reported to be stable to ground state oxygen.[301] However in the presence of cuprous chloride oxygen is rapidly absorbed and the double bond cleaved to give progesterone **381** and N-formylmorpholine **382** in quantitative yield.[302]



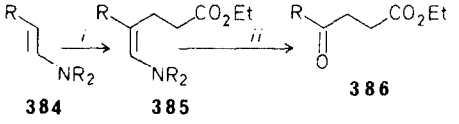
Scheme 108. Reagents: (i) CuCl, $CHCl_3$, O_2, O° 4.5 hr; (ii) $h\nu$, rose bengal sensitizer.

The same reaction occurs on photooxygenation[301] and has been utilised in a sequence of steps leading towards the synthesis of the active metabolite formannosin **383**.[303] The reaction has also been employed



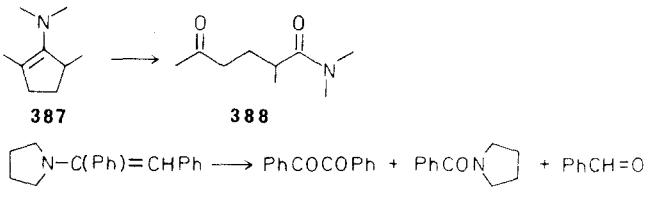
Scheme 109.

on the product derived from the alkylation of an aldehyde enamine,[304] and gives access to γ-ketoesters (**384**→**385**→**386**). Ketone enamines are similarly oxygenated (**387**→**388**) in the presence of cuprous



Scheme 110. Reagents: (i) ethyl acrylate; (ii) O_2, CuCl.

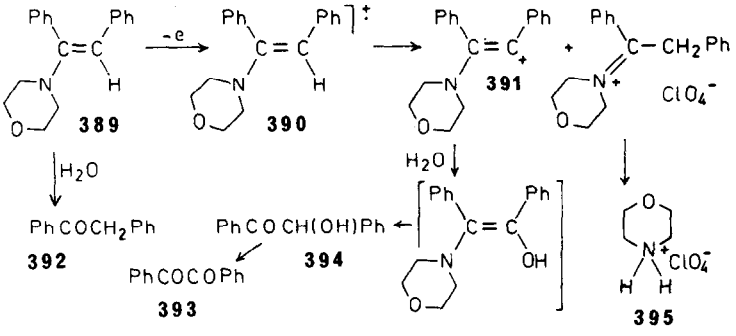
chloride. For enamines containing a β-hydrogen, diketone formation competes favourably with double-bond cleavage.



Scheme 111.

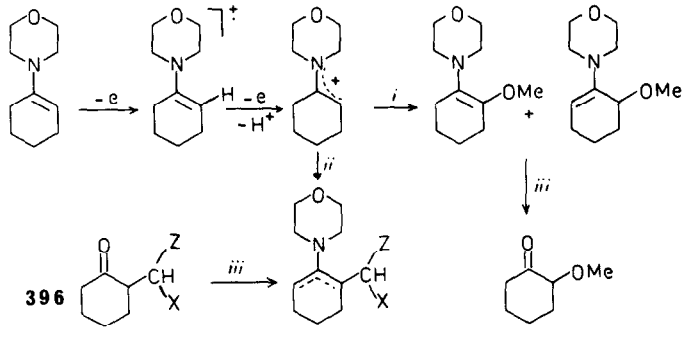
Similar oxygenation occurs in the presence of cupric chloride and the relative rates of oxygenation of isobutyraldehyde and cyclohexanone enamines has been correlated with the ionization potential (IP_1) of the enamine (Section 2).[70]

Electrochemical oxidation of enamines appears to occur via a vinyl cation intermediate **391** formed by disproportionation of a radical cation **390**.[305] For example anodic oxidation of **389** in t-butanol–water with lithium perchlorate as supporting electrolyte gave desoxybenzoin **392**, benzoin **394**, benzil **393**, and the morpholine salt **395** derived as follows:[306]



Scheme 112.

The vinyl cation can be trapped in the presence of nucleophiles other than water. For example anodic oxidation of 1-N-morpholinocyclohexene in methanol and sodium methoxide as supporting electrolyte gave the methoxy enamines and 2-methoxycyclohexanone on hydrolysis.[307] If a β-dicarbonyl compound is present the vinyl cation reacts preferentially with the carbanion to give α-substituted ketones **396** on hydrolysis.[308]

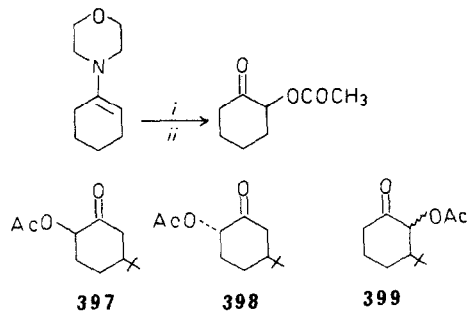


Scheme 113. Reagents: (i) NaOMe, MeOH; (ii) CH_2XZ, NaOMe; (iii) H_3O^+; X, Z = COMe, CO_2Me; COMe, COMe; CO_2Me, CO_2Me.

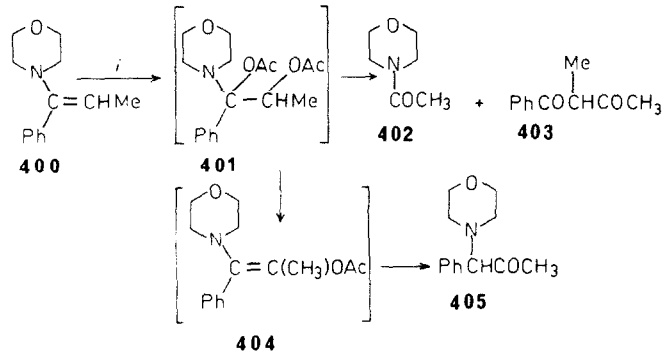
The oxidation potentials of N,N-dimethylaminoalkenes have been determined[309] and correlated with the ionization potentials[310] (Section 2).

Oxidation of the morpholine enamine of ketones with thallium acetate is a good method for the preparation of α-acetoxy ketones.[311] The reaction with the 3-t-butylcyclohexanone enamine gave the 2,5-disubstituted ketones **397** and **398** (ratio 7:1), little if any of the 2,3-disubstituted ketone **399** being formed. In contrast, 2-methylcyclohexanone enamines gave a mixture of cis-2-acetoxy-6-methylcyclohexanone (i.e. axial incorporation of the acetoxy group) and 2-acetoxy-2-methylcyclohexanone, the latter presumed to be formed via allylic rearrangement of the 2,6-disubstituted acetoxyenamine.[311] Oxidation with lead tetracetate is complex,[312] a typical reaction (under anhydrous conditions) being the conversion of **400** into **402**, **403** and **405**[313] presumably via intermediates such as **401** and **404**.

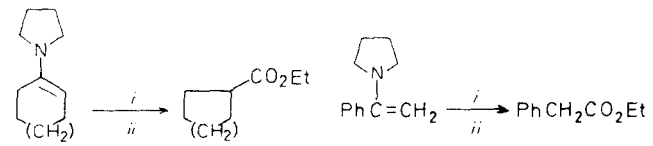
In the presence of boron trifluoride no α-acetoxylated products are formed. Instead a Favorski type rearrangement has been shown to occur to give a ring contracted ester.[314] Aryl methyl ketone enamines



Scheme 114. Reagents: (i) $Tl(OCOCH_3)_3$ (1 equiv.), gl. HOAc, R.T., 11 days; (ii) H_2O.



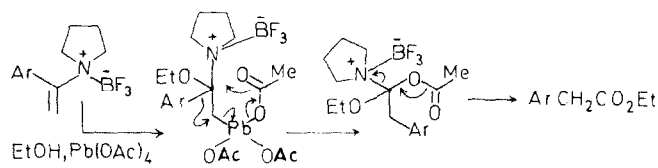
Scheme 115. Reagents: (i) $Pb(OAc)_4$.



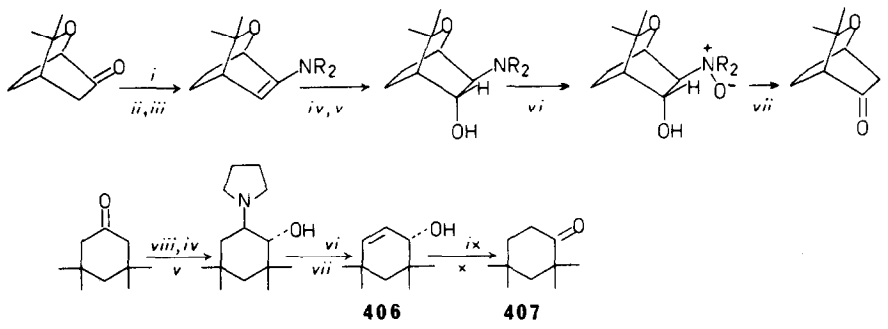
Scheme 116. Reagents: (i) $Pb(OAc)_4$, BF_3OEt_2, EtOH, C_6H_6, R.T., 30 hr; (ii) H_3O^+.

give arylacetic acid esters. The mechanism proposed involves alkoxyplumbation of the enamine–boron trifluoride double bond thus generating an intermediate which can undergo a concerted 1,2-migration of aryl (or alkyl) group and extrusion of lead(II) acetate (Scheme 117).

Hydroboration–oxidation of enamines gives 1,2-aminoalcohols. Cis-1,2-addition of BH_3 occurs to give the trans-β-aminocycloalkylborane. Peroxide oxidation of the borane from 1-morpholinocyclohexene gives trans-2-morpholinocyclohexanol.[315] Cope reaction of the derived N-oxide has been used for the 1,2-transposition of carbonyl groups[316] (Scheme 118). When hydrogen atoms are present on the α and α' carbons of the starting ketone, allylic alcohols are produced and the carbonyl transposition then requires an oxidation and reduction step[317] (**406** → **407**).

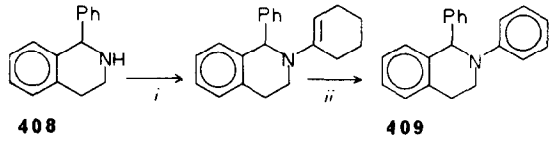


Scheme 117.



Scheme 118. Reagents: (i) NH_2OH; (ii) HNO_2; (iii) R_2NH; (iv) B_2H_6; (v) H_2O_2, NO^-; (vi) H_2O_2; (vii) 160°; (viii) pyrrolidine; (ix) CrO_3, 0°; (x) H_2, PtO_2.

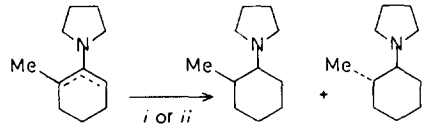
A method for the conversion of secondary amines such as **408** into the N-phenyl derivative **409** has been developed by palladium catalysed dehydrogenation of the intermediate enamine in the presence of a hydrogen acceptor such as styrene.[318]



Scheme 119. Reagents: (i) cyclohexanone, p-TSA, benzene; (ii) 10% Pd/C, styrene, xylene, Δ 20 hr.

E. *Reduction*

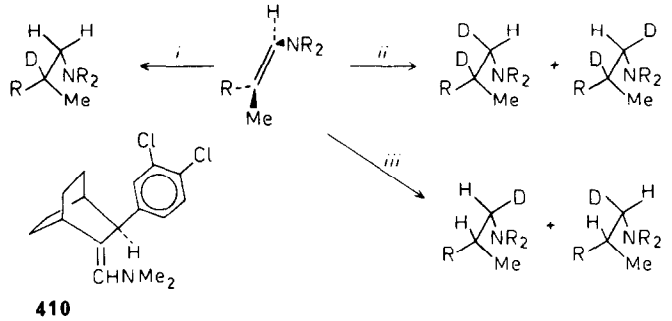
Both phosphorous acid[319] and formic acid[320] have been shown to reduce enamines with a high degree of stereoselectivity and in high yield.



Reagents: (i) H_3PO_3, 100°,	75,	25;
(ii) HCO_2H, Δ,	85,	15.

Scheme 120.

The use of deuterioformic acids leads to deuteriated amines and proves the intermediacy of an iminium salt in the reduction process:[321]

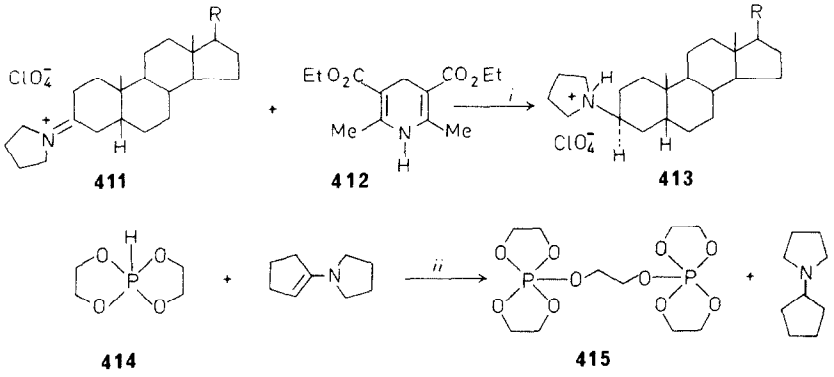


Scheme 121. Reagents: (i) HCO_2D; (ii) DCO_2D; (iii) DCO_2H.

Stereoselective reduction has been observed in the catalylic hydrogenation of enamine **410** to produce 2-(3,4-dichlorophenyl)-3-N,N-dimethylaminomethylbicyclo[2.2.2]octane. The trans isomer was obtained exclusively using palladium catalyst in benzene or ethanol and mainly the cis-isomer (98%) by using PtO_2 in isopropanol.[322] Reduction of enamines, and the reductive alkylation of sec-amines by ketones, has also been carried out with potassium hydridotetracarbonylferrate [$KHFe(CO)_4$] under carbon monoxide, to give the corresponding saturated tertiary amine.[323] A mercuration-reductive demercuration process has also been developed into a general synthesis of tertiary amines in high yield.[324] Mercuric chloride gives mainly the N-mercurated amine, whereas the more electrophilic mercuric acetate gives C-mercuration. The iminium salt thus formed can be reduced and demercurated with sodium borohydride. Preformed

Scheme 122. Reagents: (i) $HgCl_2$; (ii) $NaBH_4$; (iii) $Hg(OAc)_2$.

iminium salts have also been shown to be reduced to amine salts by 1,4-dihydropyridine derivatives[325] (i.e. the Hantzsch ester **412**) which have been taken as NADH models for pyridine nucleotide-mediated enzymatic reduction of the C=N linkage in biological systems.[326] This reaction can also occur with surprising stereoselectivity (**411** → **413**).

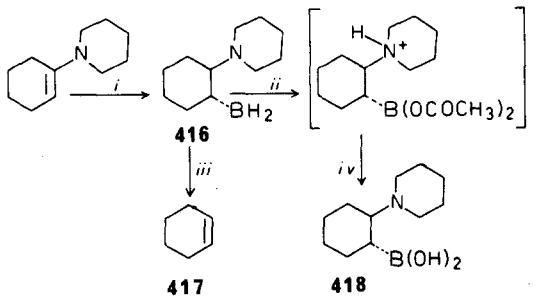


Scheme 123. Reagents: (i) CH_3CN, Δ; (ii) ethylene glycol; R = C_8H_{17}, OAc, Ac.

Reaction of spirophosphorane **414** containing a P–H bond with enamines in the presence of ethylene glycol yields the corresponding tertiary amine and pentaoxydispirophosphorane **415** by an oxidation–reduction condensation.[327]

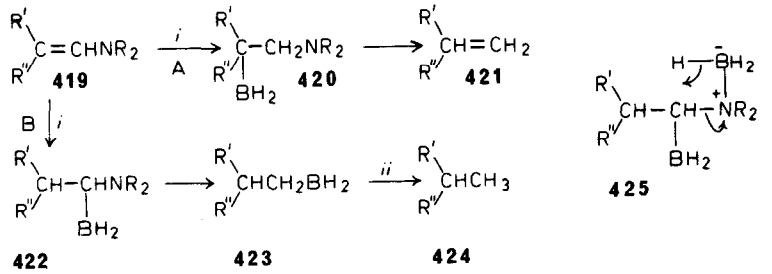
Hydrogenolysis of enamines by a hydroboration–protonolysis procedure has been extensively investigated by Lewis and collaborators and developed into a general synthesis of olefins **417**. With ketone enamines electrophilic attack at the β-carbon occurs to give a trans-β-aminoorganoborane **416**, by overall cis-addition to the double bond; this then undergoes easy trans-elimination of the boron group and the amine function on heating in the presence of acid (propionic acid in diglyme); at low temperatures a boronic acid **418** is formed.[328]

α-Substituted cyclohexanone enamines give only the 3-substituted cyclohexene, free of the 1-substituted isomer, hydroboration of the less reactive more substituted form of the enamine not occurring. In the case of 1-N-pyrrolidinocyclo-octene the hydroboration–protonolysis sequence gives the expected cis-cyclo-octene whereas reaction with aluminium hydride, which in other cases converts enamines into olefins,[329] gives cyclo-octane via trans-cyclo-octene as an intermediate. Similarly the pyrrolidine enamines of the acyclic ketones pentan-3-one and heptan-4-one gave high yields of the corresponding olefins, pent-2-ene (85%) and hept-3-ene (86%) respectively.[328] In contrast, 2-ethyl-1-N-pyrrolidinohex-1-ene **419** gave only 42% of the olefin **421** and 52% of the alkene **424**. This is attributed to



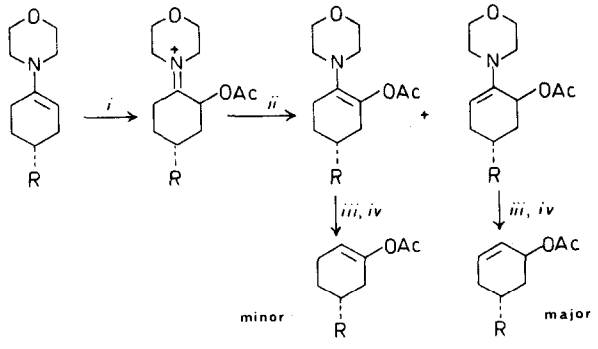
Scheme 124. Reagents: (i) B_2H_6, THF, 30 min R.T.; (ii) CH_3CO_2H in diglyme, 18 hr R.T.; (iii) propionic acid in diglyme, Δ 4 hr; (iv) H_2O.

competing initial attack at nitrogen, thus reversing the polarisation of the double bond ($\overset{\delta-}{C}=C-\ddot{N}\rightarrow\overset{\delta-}{C}=C-\overset{+}{N}-B$) and giving rise to the α-aminoorganoborane **422** (path b):



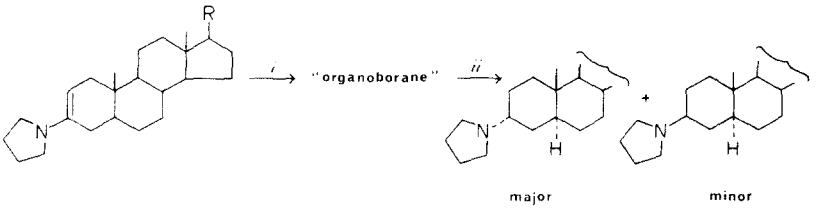
Scheme 125. Reagents: (i) BH_3; (ii) $EtCO_2H$; R′ = n-Bu; R″ = Et; R_2N = pyrrolidino.

The organoborane **423** could arise by intramolecular hydrogenolysis of the α-borane **422** via a second molecule of borane co-ordinated with the nitrogen atom as shown in **425**. Combination of this process with the thallium acetate acetoxylation of enamines[311] provides a means of converting enamines into acetoxycycloalkenes.[330]



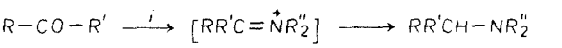
Scheme 126. Reagents: (i) $Tl(OAc)_3$, $CHCl_3$, 25°, 24 hr; (ii) 5% aq. Na_2CO_3, 2 min; (iii) BH_3, THF, 0°, 24 hr; (iv) 3N HOAc, diglyme, Δ, 12 hr; R = H, Me, t-Bu.

In sterically hindered situations there appears to be a tendency for the BH_2 group to be internally displaced by hydride anion, under vigorous conditions (boiling methanol), resulting in overall reduction of the enamine to the amine:[331,332]



Scheme 127. Reagents: (i) B_2H_6, THF: (ii) MeOH (with or without H_2O_2, HO^-), Δ.

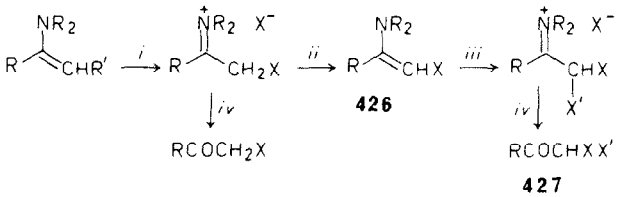
Enamines may also be reduced by lithium or sodium cyanoborhydride at pH 5.0. Since aldehydes and ketones are only reduced at lower pH (pH 3–4) the condensation of a carbonyl compound with an amine (primary or secondary) or ammonia can be carried out in the presence of $NaBH_3CN$ at pH ~ 6 and the intermediate iminium salt is reduced *in situ* to the tertiary amine. This provides an excellent method for the reductive amination of aldehydes and ketones.[333]



Scheme 128. Reagents: (i) R''_2NH, $LiBH_3CN$ or $NaBH_3CN$, HCl, MeOH, 25°, 72 hr; R, R', R'' = H, alkyl, aryl, cycloalkyl.

F. *Halogenation*

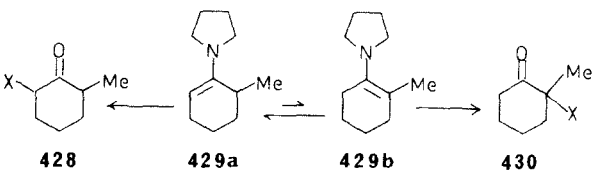
Step-wise halogenation of acyclic[334–337] and cyclic[338] enamines has been studied in some detail. Introduction of the halogen atom must be carried out at low temperature; treatment with base or ion-exchange resin then regenerates the halogeno-enamine system necessary for the introduction of the second halogen which can be the same or different.[336] Both the bromoenamine **426** (R = i-Pr, X=Br) and



Scheme 129. Reagents: (i) halogen (X_2), R' = H; (ii) base; (iii) halogen (X'_2); (iv) H_2O; R = t-Bu or i-Pr, R' = H;[334–336] R = H, R' = Et, C_5H_{11}, t-Bu;[335] R = R' = Ar[337].

the dibromoketone **427** (R=i-Pr, X=X'=Br) are unstable, the latter rearranging to the α,α'-dibromoketone.[334] Aldehyde enamines have also been reacted with N-halogenosuccinimides to give chloro, bromo, or iodo aldehydes on hydrolysis.[339]

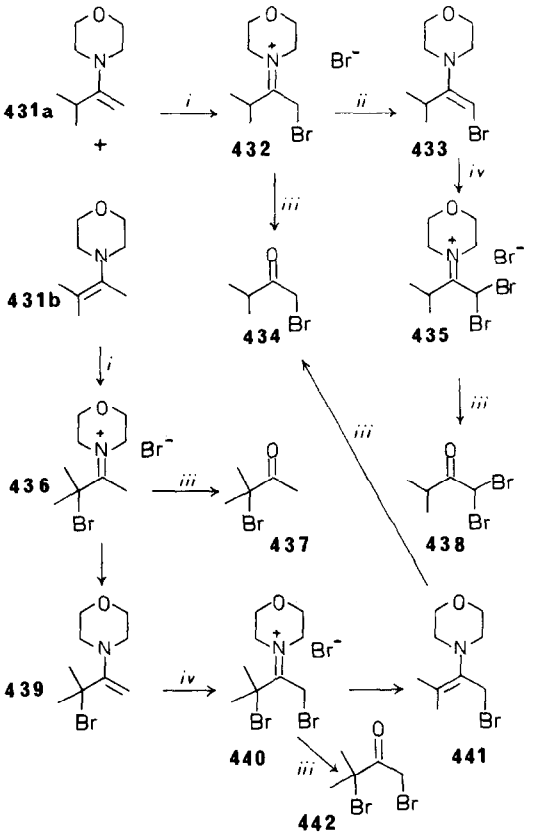
In principle the pyrrolidine enamine **429** of 2-methylcyclohexanone, existing primarily as **429a**, should be convertible by halogenation mainly to **428** with little if any **430**. In practice[340] several halogenation procedures (no experimental details given) are reported to give primarily **430** and only a little of **428**.



Scheme 130.

However bromination of **429** in acetic acid at 0–5° did give mainly 428, which rearranged slowly to **430** (complete in 24 hr at room temperature).[340] The bromination of methyl isopropyl ketone enamine is also

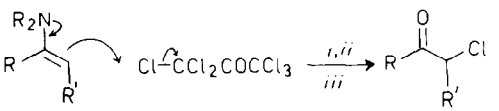
surprising. The morpholine enamine exists as a mixture of isomers (**431a** and **431b**) and it has been shown[341] that each isomer is brominated once, both individually and as a mixture, at −78°. The ketones **434** and **437** are obtained on hydrolysis. At room temperature the more substituted isomer reacts again to give the α,α′-dibromoketone **442** on hydrolysis. Where the product **434** from the less substituted isomer is obtained in amounts greater than the amount of **431a** originally present, this is attributed to debromination (**440**→**441**→**434**) rather than displacement of the enamine equilibrium (**431b**⇌**431a**).



Scheme 131. Reagents: (i) Br_2, −78°; (ii) Me_3N; (iii) H_2O; (iv) Br_2, ambient temperature.

Under conditions of reverse addition virtually no α,α-dibromoketone **438** is formed. If the bromine is added to the enamine, however, deprotonation of **432** presumably occurs and α,α-dibromination does occur. This can be made the exclusive product from isomer **431a** by subsequent addition of trimethylamine followed by further bromination[342] (**432**→**433**→**435**→**438**). These brominations occur with great rapidity and the products are formed reversibily; whether these reactions occur by normal enamine mechanisms or whether, in some cases, reactions occur by other mechanisms,[311,343] is not clear. Certainly the indications are that the transition states are reactant-like and that predictions based on consideration of $A^{1,3}$-interactions are not valid.†

A recent method which looks useful in view of the reactivity of enamines and inertness of alkenes and enol ethers, involves chlorination with hexachloroacetone.[344] Chlorination of 2-methylcyclo-

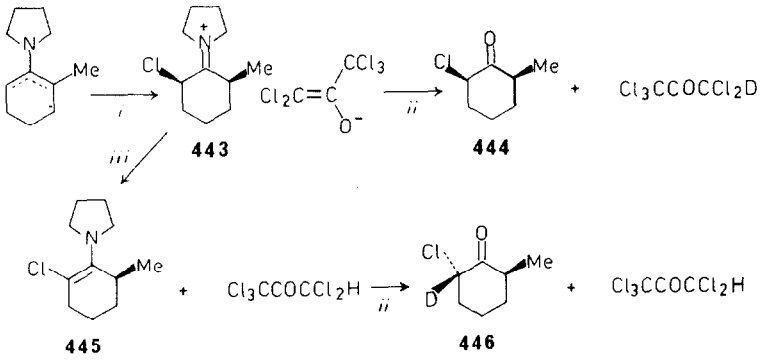


Scheme 132. Reagents: (i) hexachloroacetone, THF, −78°; (ii) H_3O^+; (iii) $NaHCO_3$.

hexanone enamine by this method gave a mixture consisting of 90% 2-chloro-6-methylcyclohexanone

†Preliminary studies show low stereoselectivity for the bromination of 4-t-butylcyclohexanone enamines, indicative of an early transition state (G. J. Davison and P. W. Hickmott, unpublished results).

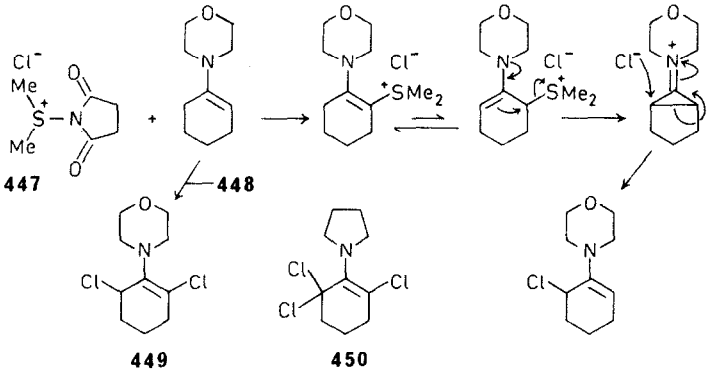
(cis and trans isomers) and only 10%, or less, of 2-chloro-2-methylcyclohexanone. The cis-isomer **444** was the main product at −78°, formed by direct hydrolysis of iminium salt **443**, whereas the trans-isomer **446** was the main product at −23°, formed by axial protonation (or deuteriation) of enamine **445**.[196]



Scheme 133. Reagents: (i) hexachloroacetone, −78°; (ii) D_2O; (iii) −23°.

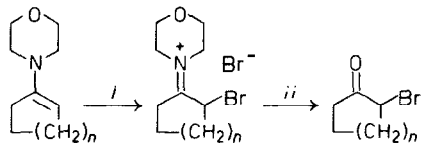
The reaction is therefore complimentary to the direct chlorination of 2-methylcyclohexanone with chlorine, or sulphuryl chloride, which gives mainly 2-chloro-2-methylcyclohexanone.[345] Application of the reaction to 3-methylcyclohexanone enamine gave a mixture of 77% 2-chloro-5-methylcyclohexanone (cis:trans ratio 64:13) and 23% 2-chloro-3-methylcyclohexanone (cis:trans ratio 15:8). Chlorination of 1-N-morpholinocyclohexene gave 6-chloro-1-morpholinocyclohex-1-ene.

Chlorocyclohexanone and cyclopentanone enamines have been obtained by reaction with dimethylsuccinimidosulphonium chloride **447** whereas 2,6-dichloro- and 2,2,6-trichloroenamines (**449** and **450**) are



Scheme 134.

formed with N-chlorosuccinimide **448**.[346] Another reagent recently used for bromination of enamines is bromodimethylsulphonium bromide.[347] Fluorinations have been carried out with N_2F_2.[348]

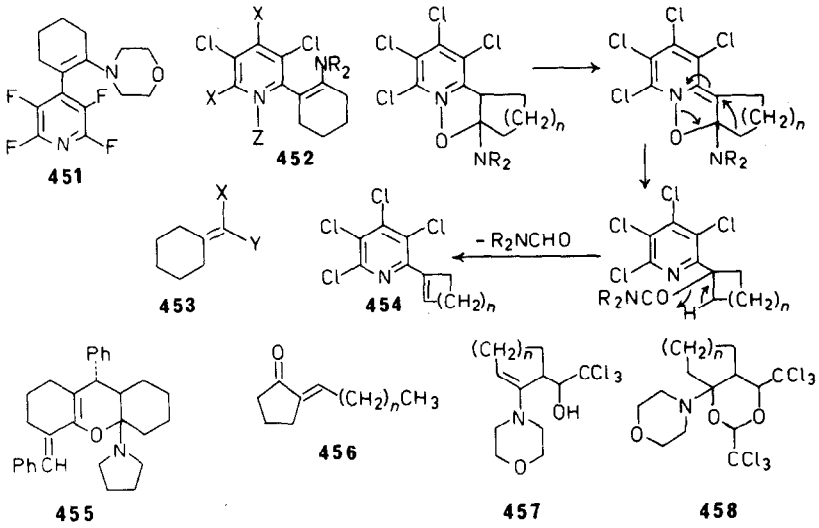


Scheme 135. Reagents: (i) $Me_2\overset{+}{S}Br$, Br^-, CH_2Cl_2, R.T.; (ii) aq. HCl, R. T. 15 min; n = 1–4.

Asymmetric induction has also been reported in the bromination of L-proline ester enamines of cyclohexanone, giving R-2-bromocyclohexanone[349] [e.e. 30–40%; see Section 5B(iii)].

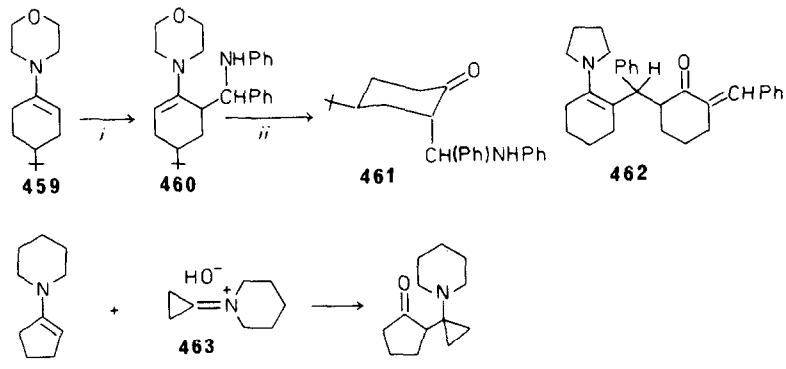
G. *Miscellaneous reactions*

Tetrahalogenopyridylenamines **451** and **452**, and the corresponding cycloalkanones, have been obtained by C-arylation of enamines with pentafluoropyridine, 3,5-dichlorotrifluoropyridine, and pentachloropyridine N-oxide. In the latter case ring-contraction leading to pyridylcycloalkenes **454** also occurred with extrusion of N-formylamine.[350]



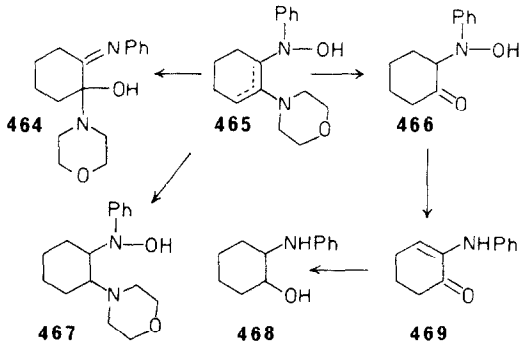
Scheme 136. (a) X = F, Z = • •; (b) X = Cl, Z = 0; n = 1, 2.

Condensation of 1-N-pyrrolidinocyclohexene with benzaldehyde in boiling ethanol gave 85% yield of the xanthene **455**.[351] With 2-morpholinoindene aromatic aldehydes gave mainly the more crowded (E)-1-benzylidene-2-indanone on hydrolysis.[352] Aliphatic aldehydes condense with 1-N-morpholinocyclopentene to give 2-alkylidenecyclopentanones **456**.[353] In the reaction with chloral the intermediate carbinolamine **457** can be isolated or hydrolysed to the corresponding β-hydroxyketone.[354] In the presence of two equivalents of chloral the 1,3-dioxane **458** is obtained. Enamines act as carbonyl equivalents in the Knoevenagel reaction with active methylene compounds to give cyclohexylidene derivatives **453** (X=CN, CO_2H; Y=CN, CO_2H, $CONH_2$, CO_2Et).[355] Enamines, such as **459**, also react with Schiff bases to give **460** which can be hydrolysed to the trans-β-aminoketone **461**, showing that axial attack had occurred on the enamine. The pyrrolidine enamine reacted further to give **462**.[356] A similar reaction occurs with the cyclopropyliminium salt **463**.[357]



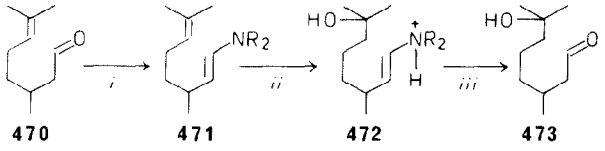
Scheme 137. Reagents: (i) benzylideneaniline, MeOH, R.T.; (ii) H_2O-silica gel.

Enamines react with nitrosobenzenes to give an unstable hydroxylamine (i.e. **465**) as the initial product. This rearranges to the imine **464**, and can be hydrolysed to the hydroxyamino-ketone **466**, or the amino-ketone **469**, and reduced to the hydroxylamine **467** or the hydroxyamine **468**.[358]



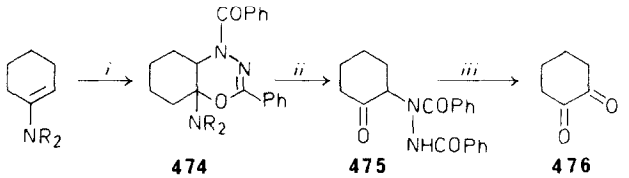
Scheme 138.

An improved route[359] to the synthetic perfume hydroxycitronellal **473** has made use of the reduced rate of hydrolysis of enamines in strongly acidic media [see Section 5A(iii)]. Hydration of **471** in strong acid presumably gives the hydroxy-N-protonated enamine **472** which is hydrolysed to **473** in weak acid. If the aldehyde function in **470** is not first protected before hydration, then cyclisation to hydroxycyclohexanes (isopulegol and menthoglycol) occurs.



Scheme 139. Reagents: (i) R_2NH (1 equiv), 15–25°, 30 min; (ii) 50% aq. H_2SO_4, 25–30°, 4 min; (iii) pH 6.5–7.0, <15°.

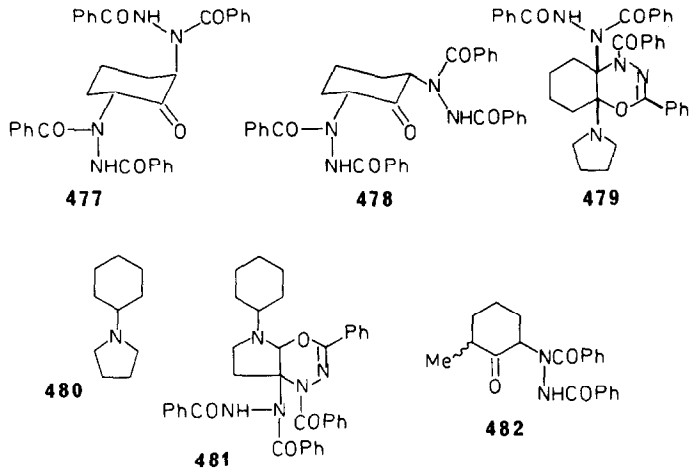
Dehydrogenation of tertiary amines $R_2N-\underset{|}{C}H-CH\diagdown$ with dibenzoyldi-imide (DBD) leads to the formation of enamines $R_2N-\underset{|}{C}=C\diagdown$, which further react with dibenzoyldiimide present in solution.[360] Reaction of DBD with 1-morpholino or 1-piperidinocyclohexene gives the 1,3,4-oxadiazine cycloadduct **474**, hydrolysis of which gives **475** or **476**.[361] The corresponding adduct **474** from the pyrrolidine enamine could only be isolated by working with an excess of enamine. Further reaction gave the products of



Scheme 140. Reagents: (i) PhCON = NCOPh (DBD), C_6H_6, R.T., 24 hr; (ii) H_3O^+, R.T.; (iii) H_3O^+, 100°.

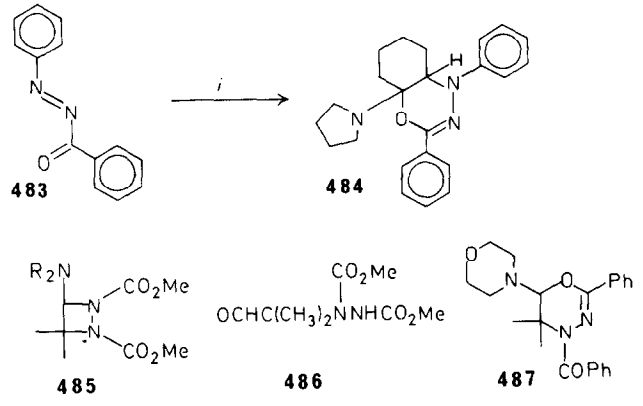
2,6-disubstitution **477** and **478** on hydrolysis, but the one from 2,2-disubstitution **479** was the main product, formed in 50–80% yield! The author does not suggest a reason for **479** being formed

preferentially. Except to note, in passing, that simply heating cyclohexanone with DBD alone gives **475**, and reaction of DBD with N-cyclohexylpyrrolidine **480** at room temperature gives **481**[360] in which the pyrrolidine ring has been attacked. This is in contrast to the corresponding reaction of diethyl-azodicarboxylate which dehydrogenates 480 to 1-N-pyrrolidinocyclohexene which then reacts to give the normal product of 2,6-disubstitution.[362] So we are dealing with a strange reagent. Surprisingly it behaves itself in reacting with 2-methylcyclohexanone enamines giving the product **482** of 2,6-disubstitution.[361]



Scheme 141.

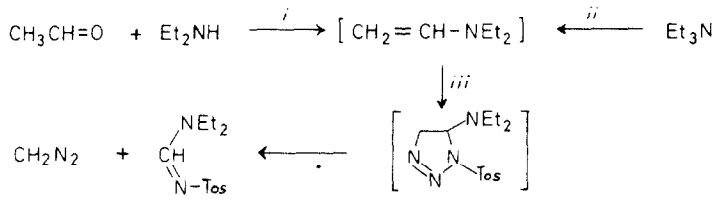
Preliminary investigations indicate that the mono-benzoyldi-imide **483** behaves in a relatively normal manner, reaction with 1-N-pyrrolidinocyclohexene giving only the oxadiazine derivative **484**.[363] Reaction of diethyl azodicarboxylate with β-disubstituted aldehyde enamines is reported to give the 1,2-diazetidine **485** and hence the aldehyde **486** on hydrolysis,[364] whereas dibenzoyldi-imide gives 1,3,4-oxadiazine **487**.[365]



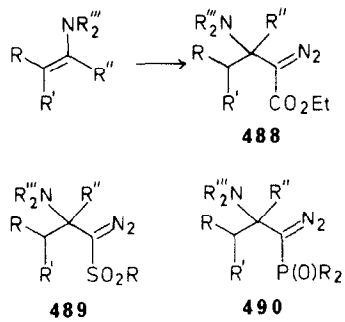
Scheme 142. Reagents: (i) 1-N-pyrrolidinocyclohexene.

The 1,3-dipolar cycloaddition of aryl azides to enamines gives aminotriazolines and triazoles.[23c] However tosyl azide gives an unstable triazoline which decomposes spontaneously to a diazoalkane and an amidine.[366] This provides a convenient alternative to the carcinogenic or neoplastic methyl-nitrosamides as a source of diazoalkanes. Acetaldehyde or triethylamine, for example, can be used as a source of diazomethane in a one-pot procedure.[366a]

The 1,3-dipolar cycloaddition of α-diazoesters to enamines, which normally leads to amino-dihydropyrazoles or pyrazoles,[23c] is inhibited by cuprous chloride, silver salts, and protic solvents; the

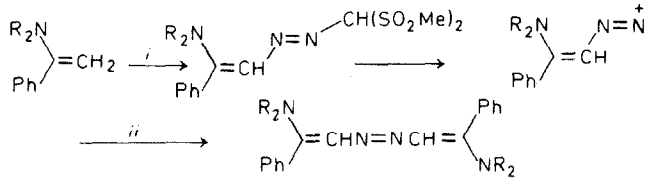


Scheme 143. Reagents: (i) anhydr. Na_2SO_4, C_6H_6, R.T., 10 min;[367] (ii) dibenzoylperoxide, R.T.;[368] (iii) p-toluenesulphonyl azide, R.T.



Scheme 144.

α-addition products **488** are obtained instead.[369] α-Diazosulphones react similarly, in the absence of catalysts or protic solvents. Iminium salt character is induced in the enamine by a hydrogen bonding interaction with the acidic α-CH of the diazosulphone, which thus allows nucleophilic attack by the diazo α-carbon on the α-carbon of the enamine to give **489**.[370] The presence of two sulphone groups in the diazo compound results in yet a further change in the course of the reaction (Scheme 145).[371] Phosphoryl diazomethanes give adducts **490**.[372]

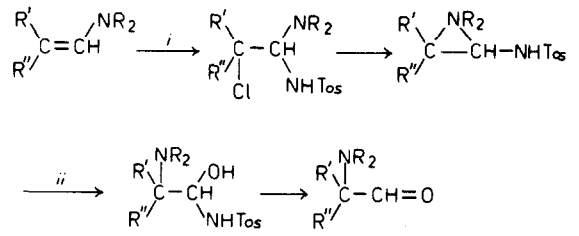


Scheme 145. Reagents: (i) $N_2C(SO_2Me)_2$; (ii) $R_2N(Ph)C=CH_2$.

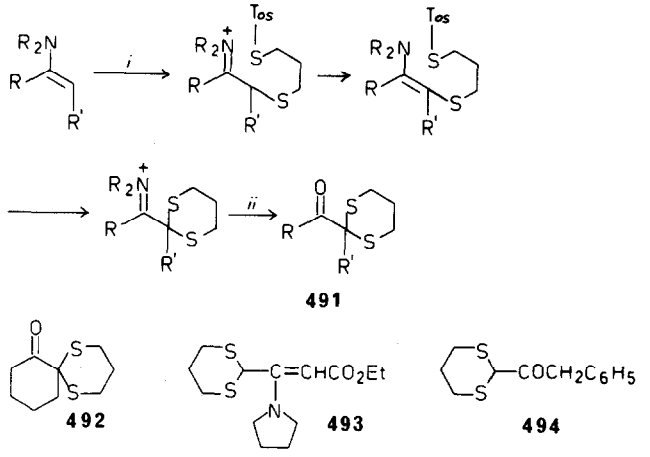
A remarkable reaction of enamines with Chloramine-T has been reported recently in which the secondary amine moiety migrates to the β-position of the enamine to give an α-dialkylaminoaldehyde in high yield (50–84%)[373] (Scheme 146).

Woodward *et al.*[374] have shown that trimethylene dithiotosylate reacts with enamines in the presence of triethylamine to give dithianes **491**. Thus 1-pyrrolidinocyclohexene gave **492**,[375] the pyrrolidine enamines of acetoacetic ester and phenylacetone reacted in their more reactive less substituted forms to give **493** and **494** respectively, but the pyrrolidine enamine of β-tetralone underwent aromatization to β-pyrrolidinonaphthalene. Since dithianes are stable to acid and base, and can be converted back to methylene compounds by reduction, this reaction provides a means for protecting a reactive α-methylene or methyl group while chemical transformations are carried out at less active sites of a molecule. The method has also been ingeniously utilised by van Tamelen *et al.*[376] for descending an homologous series of aldehydes (**495**→**496**).

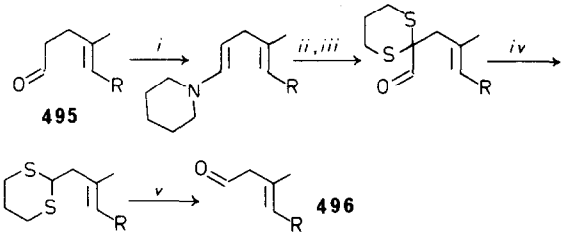
1,3-Dithiane itself has been widely exploited as a formyl anion equivalent and recently 2-chloro-1,3-



Scheme 146. Reagents: (i) Chloramine-T $3H_2O$, CH_2Cl_2, R.T., 3.5–20 hr; (ii) H_2O; R′,R″ = Me, Me; Et, Et; Me, Ph; $(CH_2)_5$; R_2N = piperidino, morpholino, pyrrolidino, dimethylamino.



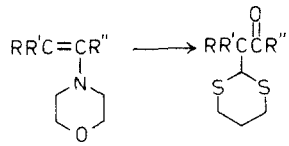
Scheme 147. Reagents: (i) $CH_3C_6H_4SO_2S(CH_2)_3S\ SO_2C_6H_4CH_3$, Et_3N,N_2, CH_3CN, Δ, 10–24 hr; (ii) H_3O^+.



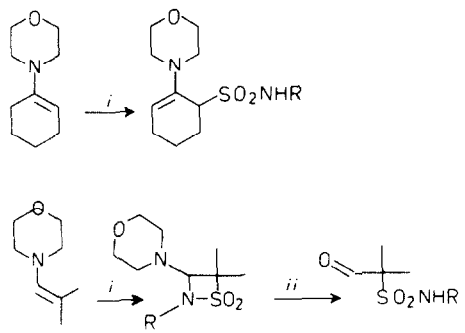
Scheme 148. Reagents: (i) piperidine; (ii) Tos $S(CH_2)_3S$ Tos, Et_3N; (iii) H_3O^+; (iv) NaOMe, Me_2SO, H_2O; (v) MeI, $CaCO_3$, H_2O, CH_3CN.

dithiane **497** has been introduced as a readily accessible synthetic equivalent to a formyl halide (i.e. a formyl cation equivalent). Reaction of **497** with aldehyde enamines gives half-protected malondialdehyde derivatives, and acyclic and cyclic ketone enamines can be α-formylated by this method[377] (Scheme 149).

N-Alkylsulphamoyl chlorides have been reported to react with enamines in the presence of triethylamine via the N-alkylsulphonyl imide ($RN{=}SO_2$). The products are either acyclic (sulphonamides) or cyclic (1,2-thiazetidine-1,1-dioxides) depending on the enamine used.[378]

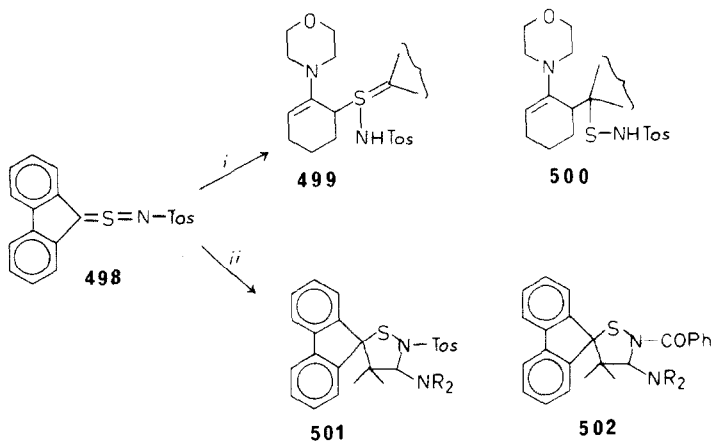


Sheme 149. R = R′ = Me, R″ = H; R = Me, R′ = R″ = H; R = Et, R′ = R″ = H; R = Me, R′ = H, R″ = Et; R, R″ = $(CH_2)_3$, R′ = H; R, R″ = $(CH_2)_4$, R′ = H.



Scheme 150. Reagents: (i) RNH SO_2Cl, Et_3N; (ii) H_2O.

Another new heterocumulene which has been shown to react with enamines is the thione-S-imide **498**. Again acyclic (**499** or **500**) or cyclic (1,2-thiazolidines **501**) products have been isolated depending on the enamine.[379] The benzoyl analogue of **498** similarly underwent 1,3-cycloaddition to give **502**.[380]

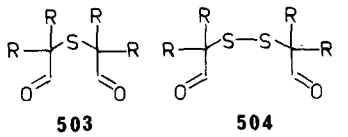


Scheme 151. Reagents: (i) 1-N-morpholinocyclohexene; (ii) 1-N-pyrrolidinoisobutene.

Treatment of 1-piperidinocyclohexene with N-phenylthiophthalimide gives 2-phenylthiocyclohexanone.[381] Thia and dithiadialdehydes **503** and **504** are obtained from the corresponding aldehyde enamine and SCl_2 or S_2Cl_2 respectively.[382]

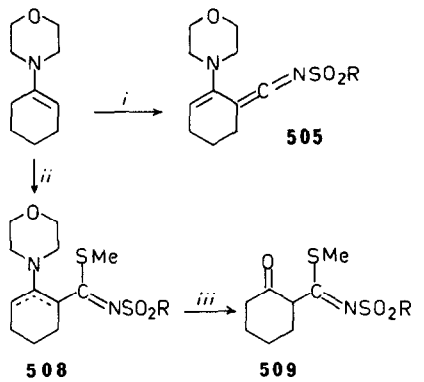
The reaction of N-sulphonylisonitrile dichlorides **506** with enamines is reported to give the heterocumulenes **505**.[383a] The methylmercapto analogue **507** gives **508** and **509**.[383b]

An important method has been developed for conversion of alkyl aryl ketones **510** into arylalkanoic acids **512** by means of the 1,3-dipolar addition of diphenyl phosphorazidate [DPPA, $(PhO)_2P(O)N_3$] to



503 504

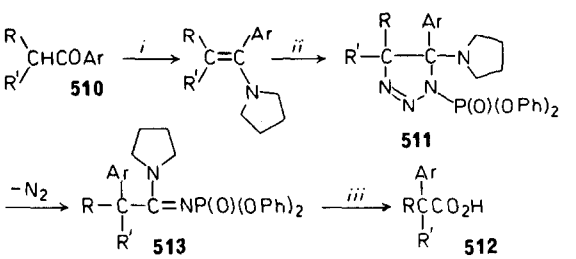
Scheme 152.



505 508 509

Scheme 153. Reagents: (i) $RSO_2N = CCl_2$ (**506**); (ii) $RSO_2N = C(Cl)SMe$ (**507**); (iii) H_2O.

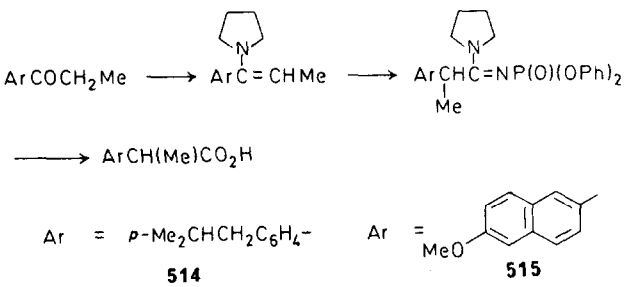
enamines. This gives a labile triazoline **511** which decomposes with evolution of nitrogen and migration of the aryl group onto what was the β-position of the enamine. The N-phosphorylated amidine **513** thus obtained can then be hydrolysed to the acid **512** in high yield.[384]



510 511 513 512

Scheme 154. Reagents: (i) pyrrolidine, BF_3-OEt_2; (ii) DPPA, THF, Δ, (iii) KOH, ethylene glycol.

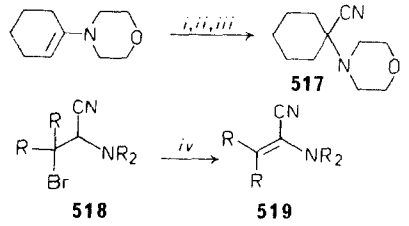
Application of the method to the efficient synthesis of two non-steroidal antiinflammatory agents ibuprofen **514** and naproxen **515** is given in Scheme **155**.



514 515

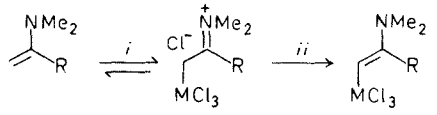
Scheme 155.

Diethyl phosphorocyanidate **516** has been used to convert enamines into α-aminonitriles **517** in a non-aqueous analogue of the Strecker synthesis. Decyanation to the amine occurs with lithium aluminium hydride.[385] Addition of cyanogen bromide to enamines gives α-amino-β-bromonitriles **518** which can be dehydrobrominated to α-cyanoenamines **519**.[386]



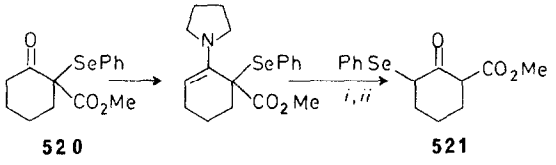
Scheme 156. Reagents: (i) $(EtO)_2P(O)CN$ (**516**), THF; (ii) HCl, $CHCl_3$; (iii) $NaHCO_3$; (iv) Et_3N.

Organometallic enamines and iminium salts are formed from enamines with Group IV halides:[387]



Scheme 157. Reagents: (i) MCl_4; (ii) base; M = Si, Ge, Sn; R = Ph, NMe_2.

A pyrrolidine-mediated rearrangement of a 2,2-disubstituted cyclohexanone **520** to the 2,6-disubstituted analogue **521** has been reported.[388]



Scheme 158. Reagents: (i) Δ; (ii) H_3O^+.

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