# Enaminones

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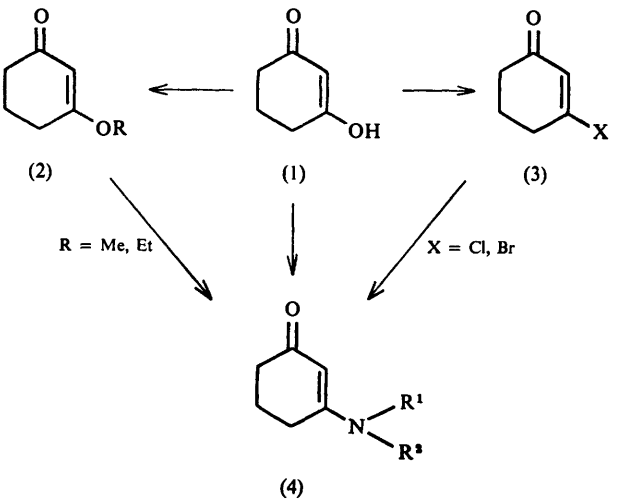
## 1 Introduction

The term enaminone is used to indicate any compound containing the conjugated system N—C=C—C=O. It may be a mono-enamine of a 1,3-diketone (vinylogous amide) or of a 3-keto-ester (vinylogous urethane). Designations sometimes used, such as enamino ketone or β-amino-α,β-unsaturated ketone, are misleading in that the compounds rarely show the physical or chemical properties normally associated with ketones.

This review covers the chemical and (briefly) physical properties of enaminones and attempts to demonstrate their potential uses in synthetic and medicinal chemistry.

## 2 Preparation

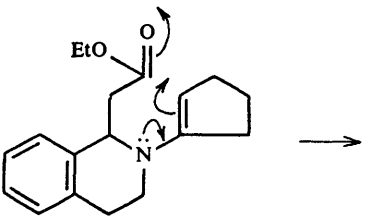
The most used general method for the synthesis of enaminones involves reaction between ammonia or a primary or secondary amine and a 1,3-diketone or 3-keto-ester[1] (Scheme 1). This occasionally fails, for example with the very weak




**Scheme 1**

[1] K. Dixon and J. V. Greenhill, *J.C.S. Perkin II*, 1974, 164.

bases *o*- and *p*-nitroaniline.[2] Conversion of the diketone into a vinylogous acid halide or vinylogous ester followed by reaction with the base often gives a kinetically favoured route[3] [*e.g.* (2) R = Me → (4) $R^1 = H$, $R^2 = p\text{-}NO_2C_6H_5$—]. The addition of a base to an acetylenic ester or ketone (when available) provides an excellent method of preparation.[4] The reactions of enamines with acid chlorides are sometimes employed,[5] as in the standard preparation of 2-propionyl cyclohexanone (Scheme 5). Similarly, the ring closure [(5) → (6)] is a general method for polycyclic compounds. With nitriles (7) ring closure is catalysed by magnesium perchlorate to give the amidine (8) which gives the enaminone (9) on basic hydrolysis.[6]

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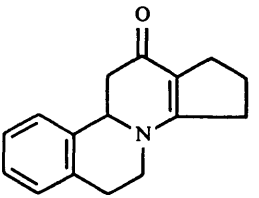


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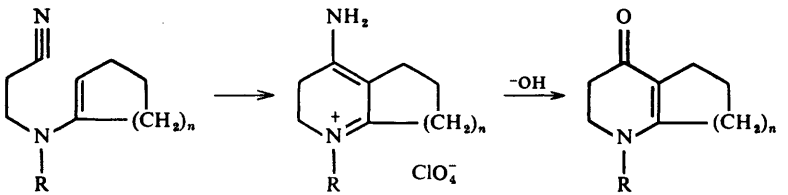


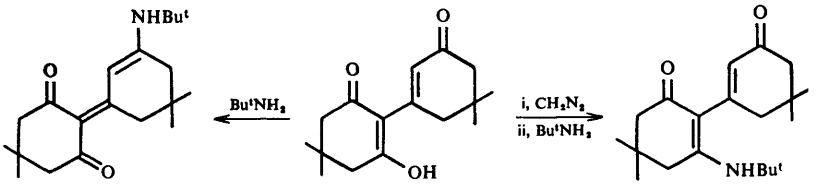

(7) (8) (9)

R = Me, $Et_2N(CH_2)_2$—, or $Et_2N(CH_2)_3$—, $n$ = 1, 2, 3, 4.

t-Butylamine reacts with dimedone in refluxing xylene to give, in addition to the expected enaminone, the dienamine-dione (11). This red compound ($\lambda_{max}^{H_2O}$ 286 nm, $\epsilon$ 14 200; $\lambda_{max}^{H_2O}$ 410 nm, $\epsilon$ 26 100) has coplanar rings.[7] The same compound is obtained from the trione (10). For confirmation, the alternative

[2] J. V. Greenhill, *J.C.S. Perkin I*, 1976, 2207.
[3] K. Dixon and J. V. Greenhill, *J.C.S. Perkin I*, 1976, 2211.
[4] E. Winterfeldt and J. M. Welke, *Chem. Ber.*, 1968, **101**, 2381; K. Bowden, E. A. Braude, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 1946, 45.
[5] S. Hunig, E. Benzing, and E. Lucke, *Chem. Ber.*, 1957, **90**, 2833.
[6] A. I. Meyers, A. H. Reine, J. C. Sircar, K. B. Rao, S. Singh, H. Weidmann, and M. Fitzpatrick, *J. Heterocyclic Chem.*, 1968, **5**, 151.
[7] J. V. Greenhill, *J. Chem. Soc.* (*C*), 1970, 1002.

structure (12) was prepared from the methoxy derivative of (10). The planes of the rings in this colorless 2-substituted enaminone were at an angle to each other[8] ($\lambda_{max}^{H_2O}$ 290 nm, $\epsilon$ 17 800). To avoid dimerization in this example, the diketone was converted into the vinylogous bromide (*c.f.* 3; X = Br) before reaction with t-butylamine to give [*c.f.* (4) $R^1$ = H, $R^2$ = Bu$^t$].

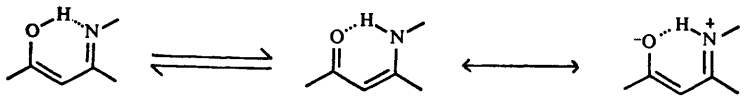



(11) (10) (12)

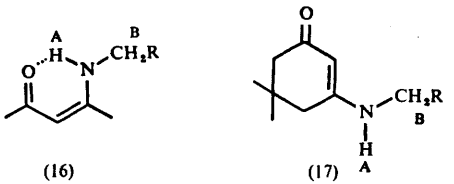
## 3 Tautomerism

It is well established that enaminones of all types exist predominantly in the carbonyl form (13). Undoubtedly this is stabilized by the contribution of the mesomer (15). Dipole moments have been reported[9] for two cyclohexanedione derivatives and in both cases are over 6 D. N.m.r. studies[10] have confirmed the contribution of zwitterionic forms.

The importance of the carbonyl tautomer for compounds derived from acetylacetone or dimedone and primary amines is clearly shown by analysis of the —NH—$CH_2$— spin–spin splitting. For example, compound (16; R = H) shows $J_{AB}$ 5.3 Hz, (16; R = Ph) $J_{AB}$ 6.8 Hz, and compound (17; R = Ph) $J_{AB}$ 5.3 Hz, all in deuteriochloroform.[11] In the case of compound (17; R = H) derived from [$^{15}$N]methylamine, the $^{15}$N–$H_A$ spin coupling is 94.3 Hz with a superimposed



(14) (13) (15)



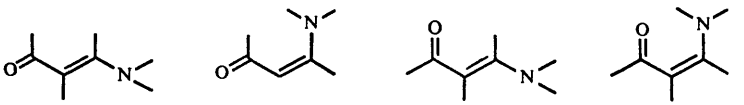

(16) (17)

[8] M. Ramli, Ph.D. Thesis, University of Bradford, 1973.
[9] D. Pitea and G. Favini, *J.C.S. Perkin II*, 1972, 142.
[10] E. J. Cone, R. H. Garner, and A. W. Hayes, *J. Org. Chem.*, 1972, **37**, 4436.
[11] G. O. Dudek and R. H. Holm, *J. Amer. Chem. Soc.*, 1962, **84**, 2691.

4.9 Hz coupling from the methyl group.[12] From p$K_a$ values of a series of 3-aminocyclohex-2-enones and their *O*- and *N*-methyl derivatives[13] it has been shown that the carbonyl form is favoured over the enol form by a factor of the order of $10^8$. A recent suggestion[14] that benzylamine and dimedone react together in hexane to give first the enol-imine tautomer is probably mistaken. It seems likely, from the data provided, that the compounds studied were amine salts of dimedone.

## 4 U.v., I.r., and N.M.R. Spectra

Four conformers of the enaminone system are possible (Scheme 2). For u.v. spectra to be compared they must be measured in solvents of similar polarity. Most are reported in water or alcohol which stabilize the charge separated form of the excited state.[13] In consequence, enaminones absorb at shorter wavelengths in non-polar solvents.[13,15]



*trans*-s-*trans* *cis*-s-*trans* *trans*-s-*cis* *cis*-s-*cis*

**Scheme 2**

Fixed *trans*-s-*trans* compounds[16,17] generally absorb in the range 285—305 nm with molecular extinction constants of 25 000 to 35 000 l mol$^{-1}$ cm$^{-1}$. *cis*-s-*cis* Systems[1,18] show longer wavelength absorption (300—320 nm) but, more important, lower $\epsilon$ values (10 000 to 20 000 l mol$^{-1}$ cm$^{-1}$). *cis*-s-*trans* Compounds could not be distinguished from *cis*-s-*cis* forms on these data.[15] The difficulty of designing enaminones with fixed *trans*-s-*cis* configurations has presumably prevented any reliable data for this type becoming available so far. The ranges quoted are for polar solvents and do not include compounds with aromatic ligands. Primary enaminones absorb at the lower ends and tertiary enaminones towards the higher ends of the wavelength ranges. Most of the acyclic compounds in this review are drawn in the s-*cis* form for convenience, but this is probably the major conformer only when stabilised by hydrogen bonding.

Enaminones derived from cyclohexane-1,3-dione[18,19] show two or three very strong i.r. absorption bands in the range 1540—1610 cm$^{-1}$. For acyclic compounds[19,20] the range is approximately 1540—1660 cm$^{-1}$. There are no other

[12] G. O. Dudek and E. P. Dudek, *J. Amer. Chem. Soc.*, 1964, **86**, 4283.
[13] J. V. Greenhill, *J. Chem. Soc.* (*B*), 1969, 299.
[14] E. J. Kikta and J. F. Bieron, *Org. Magnetic Resonance*, 1976, **8**, 192.
[15] C. Kashima, M. Yamamoto, and N. Sugiyama, *J. Chem. Soc.* (*C*), 1970, 111.
[16] K. Ramalingham, M. Balasubramanian, and V. Baliah, *Indian J. Chem.*, 1972, **10**, 62.
[17] J. V. Greenhill, *J. Chem. Soc.* (*C*), 1971, 2699.
[18] D. L. Ostercamp, *J. Org. Chem.*, 1970, **35**, 1632.
[19] J. Dabrowski and K. Kamienska-Trela, *Spectrochim. Acta*, 1966, **22**, 211 and references cited therein.
[20] N. J. Leonard and J. A. Adamcik, *J. Amer. Chem. Soc.*, 1959, **81**, 593.

bands in the double bond stretching region. Because of the strong mesomeric interactions these bands have been assigned to the whole of the C=C—C=O system rather than the separate units.[19] A recent, careful, examination of conformational effects treats the $\nu$(C=C) and $\nu$(C=O) vibrations as out-of-phase and in-phase coupled modes.[21]

Proton chemical shifts in enaminones generally show the expected values. The only difficulty lies in assigning the signals for protons adjacent to the carbonyl group and the double bond. For compounds derived from dimedone the higher field signal usually at about $\tau$ 7.7 to 7.9 is taken by most authors to represent the C-6 methylene group while another signal at about $\tau$ 7.5—7.7, which is sometimes broadened by allylic coupling to the vinyl C—H, represents the C-4 methylene group.[22] For acetylacetone derivatives of type (16; R = alkyl or arylalkyl) the methyl signals appear at $\tau$ 8.0 to 8.3 and $\tau$ 7.9 to 8.1 in $CDCl_3$.[11] The unequivocal assignment of these signals awaits further research.

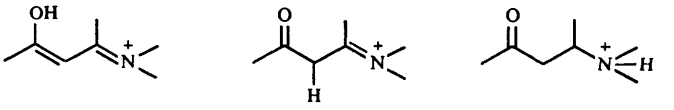
Only a few examples of $^{13}C$ n.m.r. spectra have so far appeared, but the technique seems to be insensitive to changes in configuration and conformation.[23] On the other hand, $^{14}N$ n.m.r. signals fall in a range close to that of amides, but slightly shifted towards the region characteristic of amines.[24]

## 5 Protonation

The p$K_a$ values of four 3-alkylaminocyclohex-2-enones range[13] from 2.96 to 3.10. Similarly for three tricyclic *cis*-s-*trans* enaminones [*e.g.* (25)] p$K_a$'s of 2.82 to 2.98 are reported.[25] Nevertheless, many vinylogous amides give stable salts with strong acids.[20,26] Invariably the system protonates on oxygen (18). In the u.v. spectra this is shown by a hypsochromic shift of 10—18 nm, although a few aromatic enaminones[27] show shifts as small as 4 nm. *C*-Protonation (19) would effectively remove the u.v. absorption and *N*-protonation (20) would give much larger hypsochromic shifts. To be sure such weak bases are fully protonated, the spectra must be measured in at least 0.1 M mineral acid.[27] Little or no shift is seen for solutions of salts in water or ethanol although this did not prevent some authors from reaching correct conclusions.[26,28] I.r.[20] (one or two strong bands near 1600 $cm^{-1}$) and n.m.r. studies[29] have confirmed the predominance of *O*-protonation.

In the one case studied of protonation of a vinylogous urethane, the strong u.v. absorption at 240 and 295 nm disappeared in acid solution,[30] clearly showing *C*-protonation.

[21] D. Smith and P. J. Taylor, *Spectrochim. Acta*, 1976, **32A**, 1477.
[22] C. Kashima, H. Aoyama, Y. Yamamoto, and T. Nishio, *J.C.S. Perkin II*, 1975, 665.
[23] G. R. Bedford and P. J. Taylor, *Org. Magnetic Resonance*, 1977, **9**, 49.
[24] J. Dabrowski, A. Skup, and M. Sonelski, *Org. Magnetic Resonance*, 1969, **1**, 341.
[25] A. I. Meyers, A. H. Reine, and R. Gault, *J. Org. Chem.*, 1969, **34**, 698.
[26] G. H. Alt and A. J. Speziale, *J. Org. Chem.*, 1965, **30**, 1407.
[27] J. V. Greenhill, *J.C.S. Perkin I*, 1976, 2207.
[28] W. Sobotka, W. N. Beverung, G. G. Munoz, J. C. Sircar, and A. J. Meyers, *J. Org. Chem.*, 1965, **30**, 3667.
[29] H. E. A. Kramer, *Annalen.*, 1966, **696**, 15.
[30] J. C. Powers, *J. Org. Chem.*, 1965, **30**, 2534.

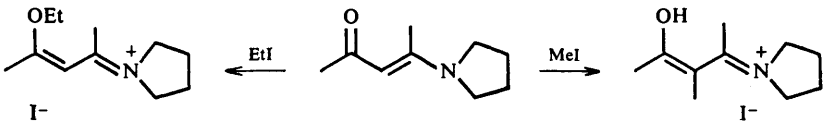


(18) (19) (20)

## 6 Alkylation

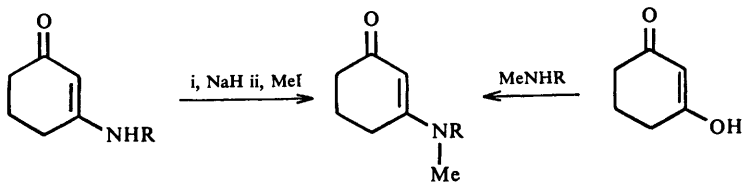
The alkylation of vinylogous urethanes which, after hydrolysis, gave α-alkylated β-keto esters usually offers no advantage over the direct alkylation of the β-keto-ester.[31] When the very reactive propargyl bromide is involved, however, the use of an enaminone prevents the dialkylation which occurs when ethyl acetoacetate is the substrate.[32]

Vinylogous amides derived from butane-1,3-dione and pentane-2,4-dione react with methyl iodide to give *C*-methyl derivatives.[33–35] 4-Pyrrolidinyl-3-penten-2-one (21) gives a *C*-methyl derivative (22) contaminated with some *O*-methyl salt. Ethyl iodide, on the other hand, gives the *O*-ethyl salt (23) in 31% pure yield.[20]



(23) (21) (22)

*Trans*-s-*trans* Enaminones derived from cyclohexane-1,3-diones give high yields of *O*-alkylated salts, even when methyl iodide is used.[13,15,25] *N*-Methylation has been achieved by preliminary de-protonation with sodium hydride followed by treatment with methyl iodide. The identity of the product has been confirmed by independent synthesis[13] (Scheme 3). This methylation of (24; R = $C_6H_{11}$)



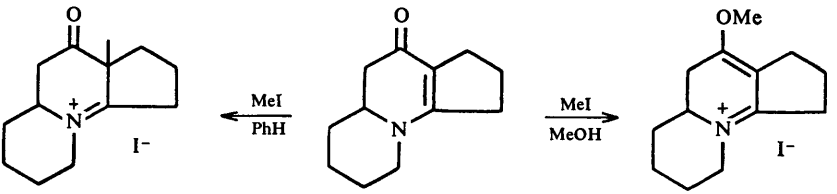
(24)

R = $-CH_2CH_2Ph$, $-C_6H_{11}$

**Scheme 3**

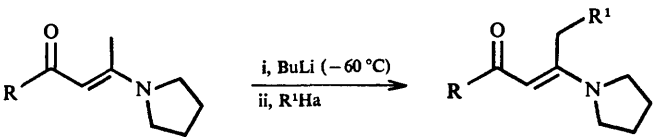
[31] W. M. Lauer and G. W. Jones, *J. Amer. Chem. Soc.*, 1937, **59**, 232.
[32] G. Eglington and M. C. Whiting, *J. Chem. Soc.*, 1953, 3052.
[33] A. Combes and C. Combes, *Bull. Soc. chim. France*, 1892, **7**, 778.
[34] N. K. Kochetkov, *Bull. Akad. Sci. U.S.S.R.*, 1953, 833.
[35] N. K. Kochetkov, M. G. Ivanova, and A. N. Nesmeyanov, *Bull. Akad. Sci. U.S.S.R.*, 1956, 687.

also gave a trace of 2-methyl derivative, detected by t.l.c.[36] Although potentially useful, only a few examples of *N*-alkylation of enaminone anions have been reported, and further developments may require the use of different basic catalysts. The *cis*-s-*trans* enaminone (25) reacts with methyl iodide[25] in non-polar solvents to give the *C*-methyl derivative (26), but in alcoholic solvent to give the *O*-methyl compound (27). In aprotic polar solvents (acetonitrile *etc.*) the ratio of (26):(27) increases with reaction time. It was shown that nucleophilic attack by the iodide ion can reverse the reaction (25) → (27) and allow the *C*-methyl derivative (26) to accumulate.[25]




(26) (25) (27)

A new technique for regiospecific alkylation at the $\gamma$ position of a tertiary enaminone involves de-protonation with butyl-lithium or lithium di-isopropylamide, followed by treatment with an alkyl halide[37] (Scheme 4). Compound (28)



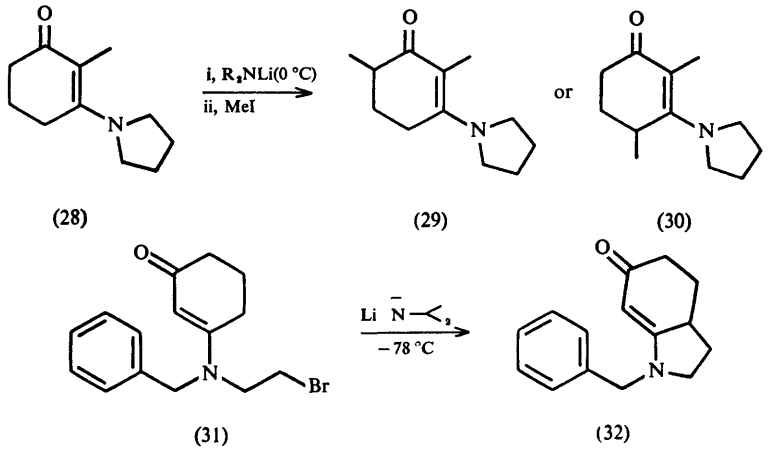

R = Me, Ph, —OMe
$R^1$ = Me, $Pr^n$, Bz, $—CH_2—CH=CH_2$, $—CH_2—COOEt$

**Scheme 4**

gives either the $\alpha'$ (29) or the $\gamma$ (30) derivative, depending on whether base or enaminone is in excess.[38] These methods may have useful synthetic applications; for example a recently reported ring closure [(31) → (32)] may have value in alkaloid synthesis.[37]

Quaternization of enaminones has not been achieved and only simple chlorovinyl ketones react with tertiary amines to give quaternary ammonium salts.[35]

[36] G. V. Kondrat'eva, V. I. Gunar, L. F. Ovechkina, S. I. Zav'yalov, and A. I. Krotov, *Bull. Akad. Sci. U.S.S.R.* 1967, 609.
[37] M. Yoshimoto, N. Ishida, and T. Hiraoka, *Tetrahedron Letters*, 1973, 39; T. A. Bryson and R. B. Gammill, *Tetrahedron Letters*, 1974, 3663.
[38] J. E. Telschow and W. Rensch, *J. Org. Chem.*, 1975, **40**, 862.



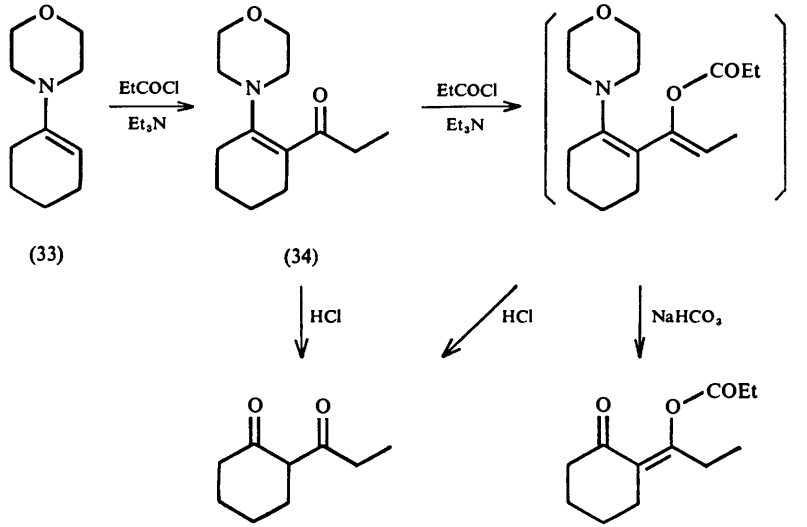

(28) (29) (30)

(31) (32)

## 7 Acylation

Acetylation or benzoylation of primary or secondary enaminones gives generally *N*-acyl derivatives.[16,18] From simple acyclic secondary enaminones mixtures of *N*- and α-*C*-acetylated derivatives are obtained in the presence of triethylamine; with pyridine traces of rather unusual *O*,*N*-diacetyl derivatives are reported, but these compounds have not yet been well characterised.[39]

An enamine from cyclohexanone (33) gives an enaminone with one equivalent of an acid chloride (34). With excess acid chloride *O*-acylation must occur because mild hydrolysis gives an enol ester[5] (Scheme 5).

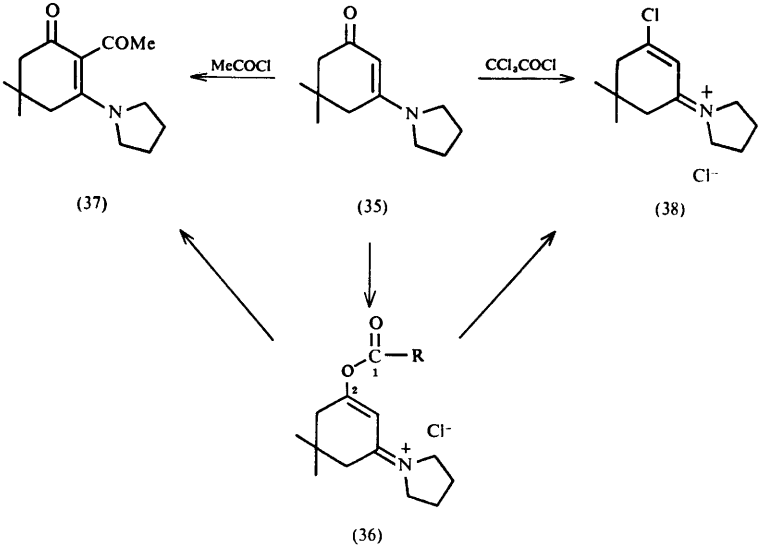



(33) (34)

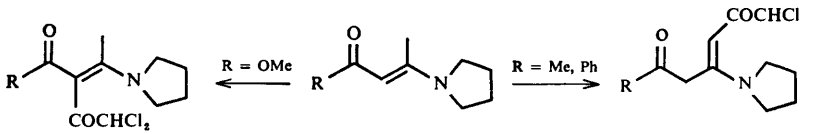
**Scheme 5**

[39] L. Kozerski, *Tetrahedron*, 1976, **32**, 1299.

The teritary enaminone (35) reacts with acetic anhydride or acetyl chloride to give the *C*-acetyl derivative (37) in good yield. Pivalyl chloride and several substituted benzoyl chlorides also give *C*-acyl derivatives, but trichloracetyl chloride gives a chloriminium salt (38). It was suggested that initial *O*-acetylation gave the unstable salt (36), but normally attack by the chloride ion at the carbonyl carbon (1) reformed the original reactants and the more slowly formed *C*-acetyl derivative (37) accumulated. When the alternative attack by chloride ion at ring carbon (2) could release a trichloracetate ion (better leaving group) the chloriminium salt (38) was formed.[40] Compound (38) is also formed when tosyl chloride, picryl chloride or, best, phosphorus pentachloride are used. These all give anions which are good leaving groups.




Acylation of a series of acyclic tertiary enaminones with dichloroketen gave α derivatives from vinylogous urethanes and γ derivatives from vinylogous amides[41] (Scheme 6).

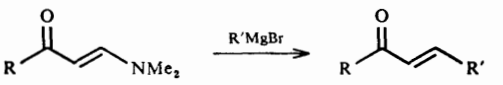



**Scheme 6**

[40] G. H. Alt and A. J. Speziale, *J. Org. Chem.*, 1964, **29**, 798.
[41] M. Yoshimoto, T. Hiraoka, and Y. Kishida, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 2469.

**8 Reactions with Grignard Reagents**

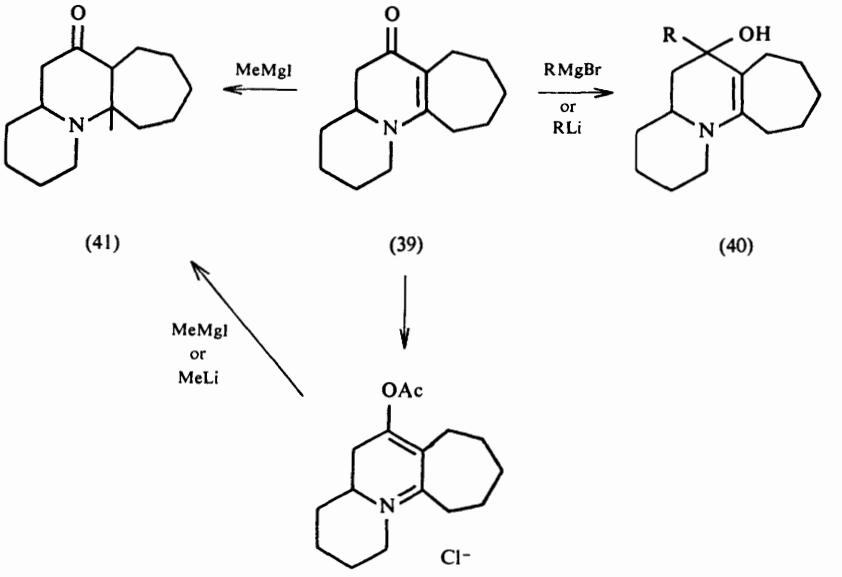
The Grignard reactions on acyclic enaminones, which have been reported, all give nitrogen-free products through 1,4 addition[42,43] (Scheme 7). The *cis*-s-*trans*




R = Ph, Me; R' = Ph, Me, Et

**Scheme 7**

compound (39) does give the enamine alcohol (40) in high yield, but with methyl magnesium iodide only 10% of the 1,4 addition product (41) is obtained together with unreacted starting material and a mixture of unidentified compounds. Preliminary conversion of the enaminone (39) to its *O*-acetyl iminium salt (42) allows preparation of the amino ketone (41) in a useful 60 to 65% yield.[44]




(42)

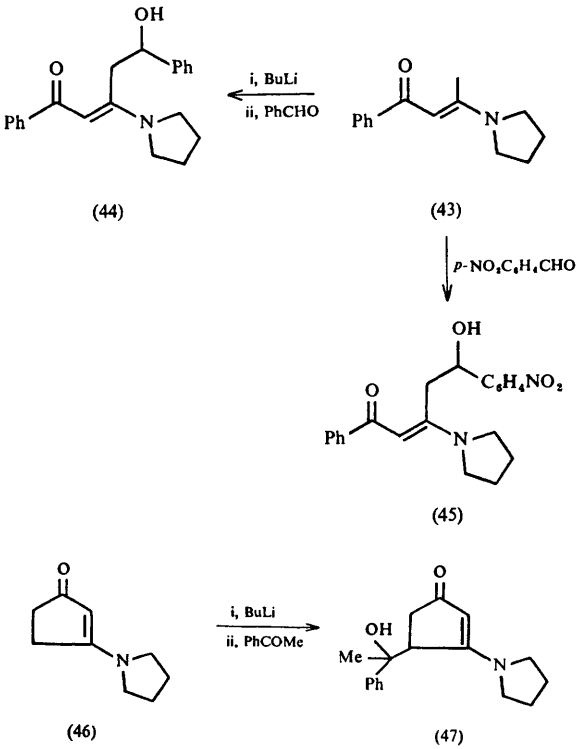
Organometallic reactions on acyclic or *cis*-s-*trans* enaminones clearly have synthetic potential, but several attempts in this laboratory to employ *trans*-s-*trans*

[42] E. Benary, *Chem. Ber.*, 1931, **64**, 2543.
[43] N. K. Kochetkov, *Bull. Akad. Sci. U.S.S.R. Div. Chem. Sci.*, 1954, 37.
[44] A. J. Meyers and S. Singh, *Tetrahedron Letters*, 1967, 5319.

enaminones derived from cyclohexane-1,3-diones have failed, good recovery of starting material always being made.[45]

**9 Reactions with Aldehydes and Ketones**

The anion of the acyclic enaminone (43) generated at −60 °C reacts with benzaldehyde to give the $\gamma$ substituted product[37] (44). However, the same enaminone reacts with *p*-nitrobenzaldehyde under catalysis by toluene-*p*-sulphonic acid, sodium ethoxide, triethylamine or 1,4-diazabicyclo-octane at reflux temperatures to give a similar $\gamma$ substituted product[41] (45). One example has been reported where an enaminone anion reacts with a ketone to give a tertiary alcohol[37] [(46) → (47)].

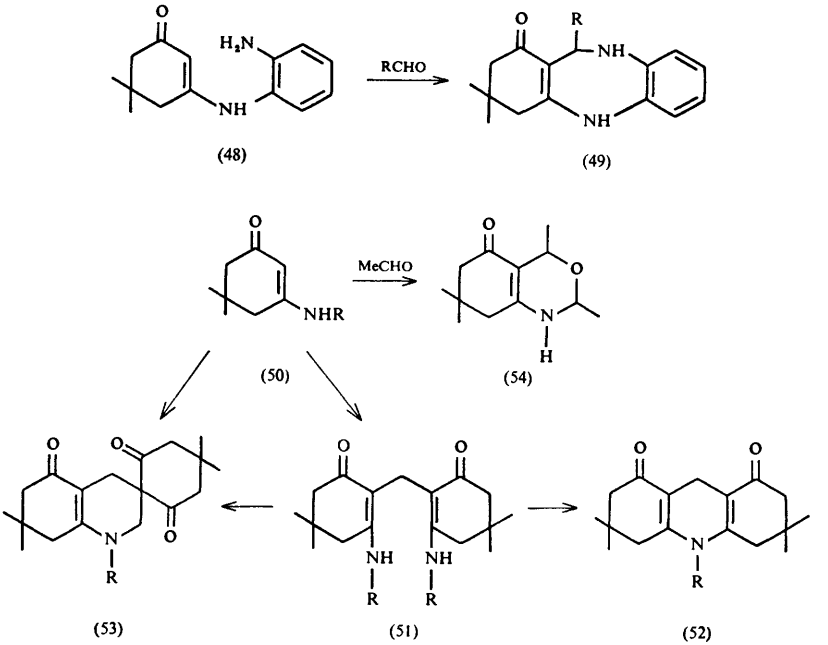



The derivative of *o*-phenylenediamine (48) reacts readily with aldehydes to give the hexahydrodibenzodiazepinones (49) in a Mannich-type reaction.[46]

Dimedone derivatives (50) react with formaldehyde under neutral conditions to give the methylenebisenaminones (51) which on heating with acid rapidly

[45] K. Dixon, Ph.D. Thesis, University of Bradford, 1976.
[46] S. Miyano and N. Abe, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 1588.

change to the hexahydroacridinediones (52). Either the original enaminones or the derivatives (51) react with aqueous acidic formaldehyde at room temperature to give the spiranes (53), again *via* an intramolecular Mannich-type reaction. Acetaldehyde under the same conditions converts the enaminone (50; R = H) into a tetrahydrobenzoxazinone (54).[17]



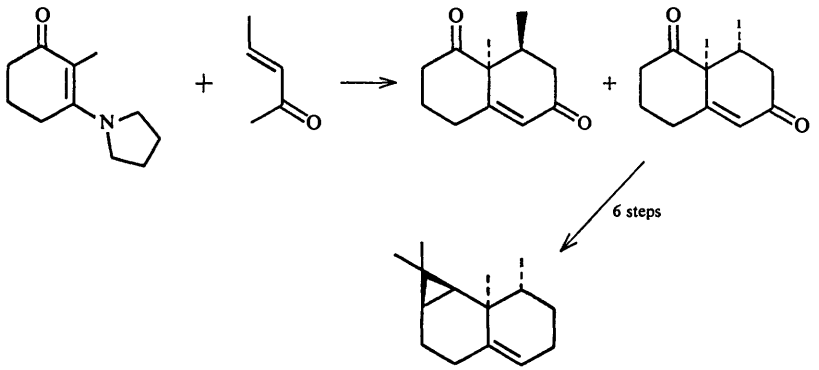

(48) (49) (50) (54) (53) (51) (52)

Robinson annelation of 2-methylcyclohexane-1,3-dione with pent-2-en-4-one was examined as the first stage of a total synthesis of calarene. Only a low yield of unwanted *trans*-isomer was obtained. Conversion of the dione to its enaminone before annelation gave an improved yield (27%) of a 1:1 mixture of isomers (Scheme 8) from which the *cis*-isomer was separated and the synthesis completed.[47] The reaction involved Michael addition of the vinyl ketone to the 2-position of the enaminone followed by hydrolysis of the immonium intermediate and aldol condensation.[38]

**10 Reactions with other Electrophiles**

Treatment with *N*-bromosuccinimide, *N*-chlorosuccinimide or 1 equivalent of molecular bromine generally gives the α substituted enaminone.[48,49] Dimedone has been used for *N*-protection in peptide synthesis and removed as 2,2-dibromo-

[47] R. M. Coates ane J. E. Shaw, *J. Amer. Chem. Soc.*, 1970, **92**, 5657.
[48] T. Tokumitau and T. Hayashi, *Nippon Kagaku Kaishi*, 1973, **11**, 2152.
[49] I. Jirkovsky, *Canad. J. Chem.*, 1974, **52**, 55.

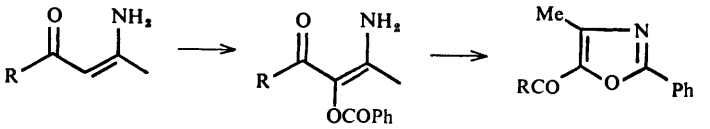



Calarene

**Scheme 8**

dimedone by treatment with excess bromine.[50] Primary and secondary enaminones react readily with isocyanates at elevated temperature to give vinylogous ureas by α substitution.[49] Tertiary acyclic compounds react even at room temperature to give 1:2 adducts in which both the α and γ positions are substituted.[51]

Acyclic enaminones give, with dibenzoylperoxide, α-benzoyl derivatives which are converted to oxazoles in refluxing acetic acid[52] (Scheme 9).



R = Me, —OEt

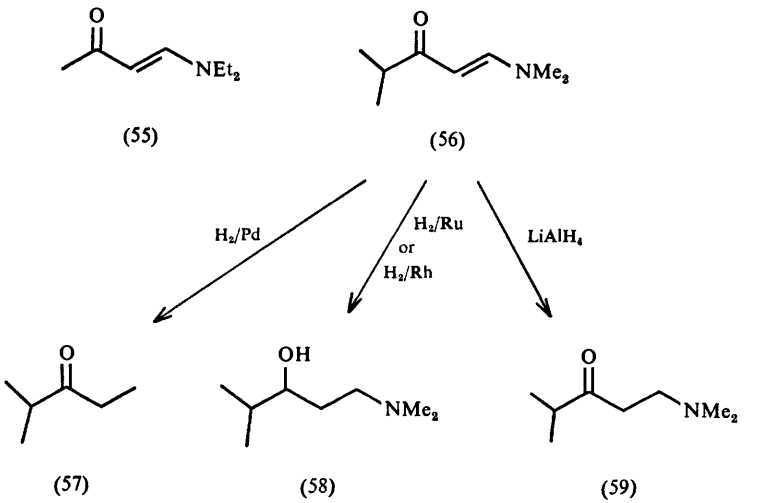
**Scheme 9**

## 11 Reduction

Selective reduction of the enaminone system could provide a source of β-aminoketones. In many examples investigated, however, the standard techniques fail to give any reaction and under more forcing conditions either nitrogen[43,53] or oxygen,[54] is split out of the molecule. On hydrogenation over platinum, the simpie enaminone (55) gives only butanone. It is suggested that hydrogenolysis removes the nitrogen atom first and then the olefin bond is saturated since Mannich bases give amino-alcohols on hydrogenation.[43] The closely related compound (56) also gives the neutral ketone (57) when hydrogenated over palladium. Over rhodium

[50] B. Halpern and L. B. Jones, *Nature*, 1964, **202**, 592.
[51] O. Tsuge and A. Inaba, *Bull. Chem. Soc. Japan*, 1973, **46**, 286; 2221.
[52] H. J. Jakobsen, E. H. Larsen, P. Madsen, and S. O. Lawesson, *Arkiv. Kemi.*, 1965, **24**, 519.
[53] J. C. Martin, K. R. Barton, P. G. Gott, and R. H. Meen, *J. Org. Chem.*, 1966, **31**, 943.
[54] J. V. Greenhill, M. Ramli, and T. Tomassini, *J.C.S. Perkin I*, 1975, 558.

or ruthenium, however, the saturated amino-alcohol (58) results and with lithium aluminium hydride the amino-ketone (59) is obtained.[53]




3-Aminocyclohex-2-enone is hydrogenated over Raney nickel at 70 °C to a mixture of the 3-aminocyclohexanols. The method gives a product considerably richer in the *trans*-isomer than the previously used procedure, reduction of 3-acetamidophenol.[54]

2-Acetyl cyclopentanone (60) reacts with ammonia to give only one product (61) which is unaffected by metal hydride reducing agents. Hydrogenation gives an amino-alcohol which can be converted to an amide and oxidised to the amido-ketone (62). The appearance of the methyl signal as a doublet in the n.m.r. spectrum confirms the structure of the enaminone (61). 2-Acetyl cyclohexanone (63) on the other hand, reacts with ammonia at the ring carbonyl group to give (64) so a similar series of reactions gives an amido-ketone (65) with a singlet methyl signal.[54]

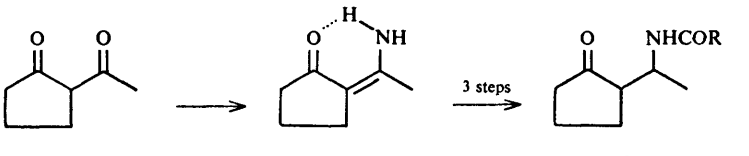
The resistance of the enaminone system to reduction is illustrated by the reaction of the vinylogous urethane (66) with excess lithium aluminium hydride or lithium borohydride. The non-conjugated ester group is reduced and the alcohol spontaneously ring closes to the furanone (67). Acid hydrolysis[54] gives tetronic acid (68).

Although *trans*-s-*trans* enaminones have not been reduced with metal hydrides, the *cis*-s-*trans* compound (39)[44] and some acyclic enaminones[55] are reduced to saturated amino-ketones.

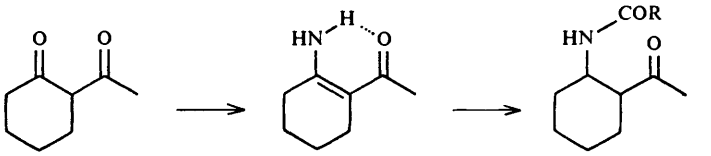
## 12 Heterocyclic Syntheses

Simple chlorovinyl ketones and their derived enaminones react together at room

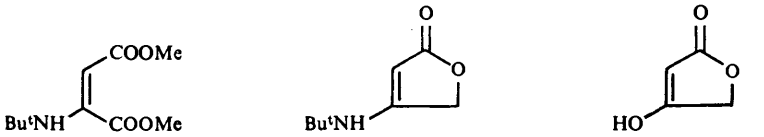
[55] G. N. Walker, *J. Org. Chem*, 1962, **27**, 4227.



(60) (61) (62)

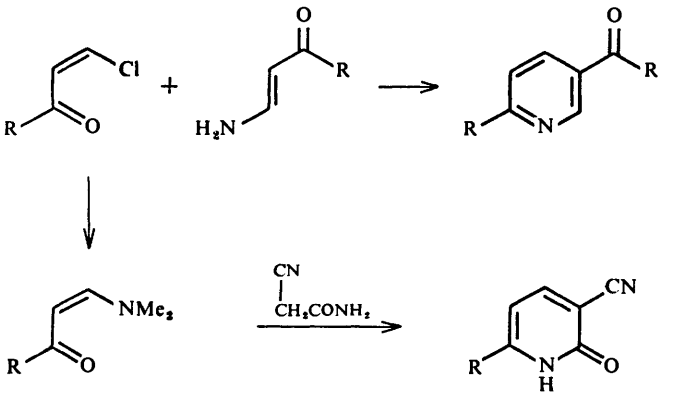


(63) (64) (65)



(66) (67) (68)

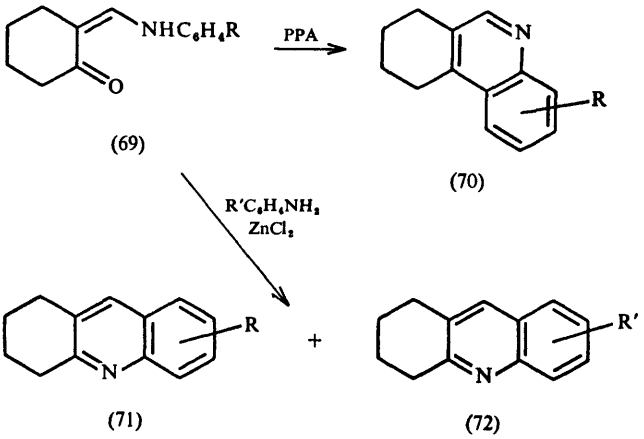
temperature to give pyridine derivatives in good yield. Tertiary enaminones prepared from these chlorovinyl ketones react with cyanoacetamide to give 6-alkyl-3-cyanopyrid-2-ones[43] (Scheme 10).



R = Me, Et, $Pr^n$, $Bu^i$, $nC_5H_{11}$

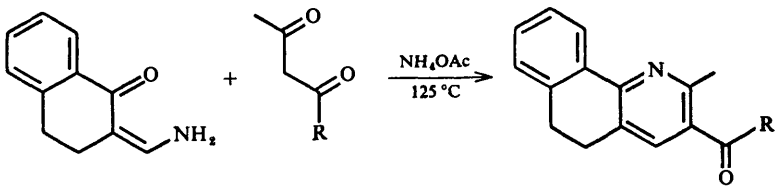
**Scheme 10**

Cyclodehydration of the enaminones (69) with polyphosphoric acid gives the expected tetrahydropenanthridines (70). When a different substituted aniline hydrochloride and zinc chloride are used a mixture of tetrahydroacridines is obtained (Scheme 11). The original arylamine moiety was retained afrer re-




**Scheme 11**

arrangement (71) or replaced by the reacting arylamine (72).[56] A similar rearrangement must be involved in the reaction of a 2-aminomethylene cycloalkanone with a 1,3-dione[57] (Scheme 12).



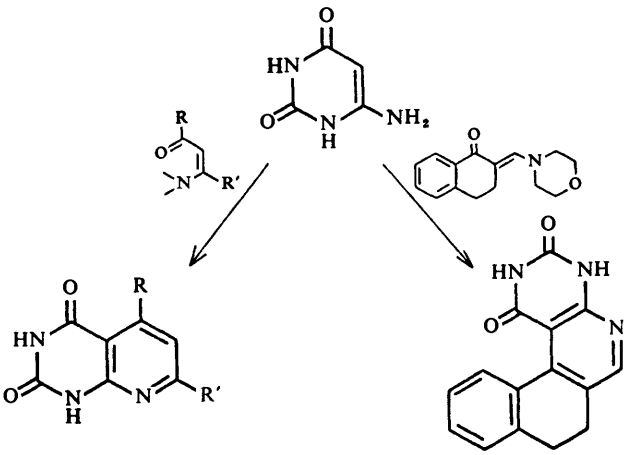

R = Me,—OEt

**Scheme 12**

4-Aminouracil reacts with a series of enaminones to give fused heterocycles (*e.g.* Scheme 13). Transamination precedes ring closure.[58]

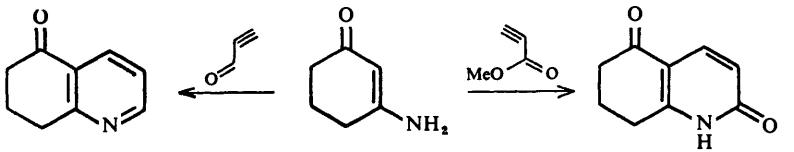
3-Aminocyclohex-2-enone (73) reacts with propynal to give the ketone (74) which can be reduced by the Huang–Minlon method to 5,6,7,8-tetrahydroquinoline.[59] With methyl propiolate the same enaminone gives the 5-oxotetra-

[56] B. D. Tilak, H. Berde, V. N. Gogte, and T. Ravindranathan, *Indian J. Chem.*, 1970, **8**, 1.
[57] G. Bouchon, K-H. Spohn, and E. Breitmaier, *Chem. Ber.*, 1973, **106**, 1736.
[58] W. Remp and H. Junek, *Monatash.*, 1973, **104**, 1101 and references cited therein.
[59] C. Ruangsiyanand, J. Rimek, and F. Zymalkowski, *Chem. Ber.*, 1970, **103**, 2403.



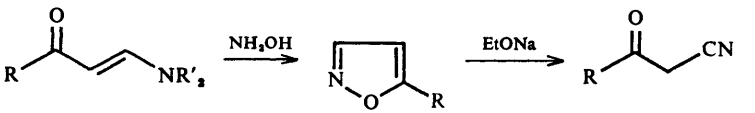
**Scheme 13**

hydroquinolone (75) which is an intermediate in the preparation of 4-azasteroids.[60]



(74) (73) (75)

Acyclic tertiary enaminones react with hydroxylamine to give high yields of 5-alkyl isoxazoles which are a source of β-keto-nitriles (Scheme 14). The parent chlorovinyl ketones give mixtures of 3-alkyl and 5-alkyl isoxazoles.[43]

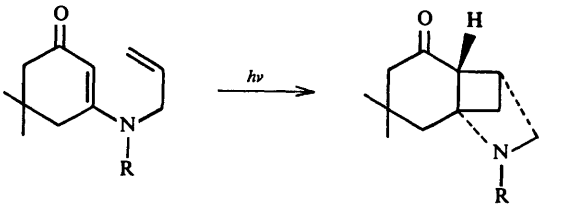


R = Me, Pr$^n$; R′ = Me, Et

**Scheme 14**

[60] M. A. T. Sluyter, U. K. Pandit, W. N. Speckamp, and H. O. Hiusman, *Tetrahedron Letters*, 1966, 87.

Irradiation of allylamine derivatives of dimedone gives bicyclo[2,1,1]hexanes[61] (Scheme 15).




R = Me, Ph, $-CH_2-CH=CH_2$

**Scheme 15**

## 13 Conclusion

The reactions of enaminones vary somewhat with conformation and nitrogen substitution, but the physical and chemical properties are sufficiently similar for the group to represent a class of organic compounds in its own right. With five positions vulnerable to electrophilic attack and two to nucleophilic attack, the enaminone system shows interesting and sometimes complicated reactivity.

Enaminones are already established as synthetic intermediates, particularly in heterocyclic chemistry, but, for many of the reactions mentioned in this review, only a few examples have been reported. Although it is not possible to comment on the generality of these, their wider use in synthetic schemes clearly merits investigation. In the future, they may be useful as protected amines. As pro-drugs their potential is considerable. An enaminone derivative of a physiologically active amine may well show improved transport across biological membranes and allow a high concentration of the amine to be released close to the site of action. Such derivatives have the added advantage, always attractive to medicinal chemists, that they may have physiological activity in their own right.

Recent years have seen a rapid rise of interest in this area, and we can look forward to a continuing expansion of the literature of enaminone chemistry.

[61] Y. Tamura, H. Ishibashi, M. Hirai, Y. Kita, and M. Ikeda, *J. Org. Chem.* 1975, **40**, 2702.