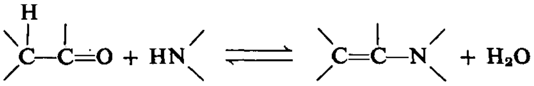
1 Preparation and some properties

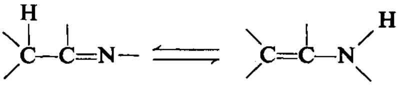
1.1. Preparation

1.1.1. From aldehydes and ketones. The most versatile, and most often used method of formation of enamines involves the condensation between an aldehyde or ketone and a secondary amine:



Primary amines, of course, also react with carbonyl compounds to form imines:

and whereas tautomerism is possible with the formation of the enamine:



the equilibrium is almost always in favour of the imine structure. This book will be concerned almost entirely with tertiary enamines, derived from secondary amines.

The commonest procedure for enamine formation, which was first used by Herr and Heyl in 1952, then exploited by Stork *et al.*, involved heating under reflux an equimolecular mixture of the carbonyl compound and the amine in a solvent such as anhydrous benzene, toluene or xylene, with azeotropic removal of the water. Usually a Dean and Stark trap is used, but a number of modifications have been made (e.g. other drying agents, molecular sieves, etc.). Slow reactions can be catalysed by acids, usually *p*-toluenesulphonic acid (*p*-TSA). However,

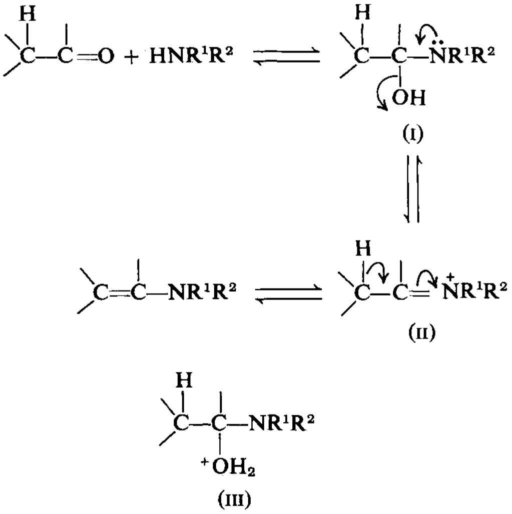
Cambridge University Press
978-0-521-09731-4 - The Chemistry of Enamines
S. F. Dyke
Excerpt
More information

in the original preparation of enamines, described in 1936 by Mannich and Davidson, anhydrous potassium carbonate was used as condensing agent. The mechanism of the reaction is usually expressed as shown in scheme 1.1. In the acid-catalysed reaction, presumably the *N*-hemiacetal (I) is protonated to (III). The actual rate of enamine formation depends in a complex way upon several factors:

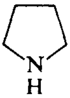
(i) the basicity of the amine;
(ii) the degree of steric hindrance in either the amine or the ketone, which affects the rate of formation of (I);
(iii) the rate of loss of the hydroxyl group from (I) or (III); and
(iv) the rate of loss of a proton from (II).

The enamine, once formed may be isolated, for example by distillation, or may be used *in situ* for subsequent reactions.

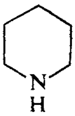
Scheme 1.1



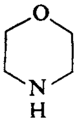
The secondary amine. The most commonly used compounds have been the cyclic amines pyrrolidine (IV), piperidine (V) and morpholine (VI), and open-chain amines such as *N*-methylaniline and diethylamine. The actual amine used does influence, to some extent, the reactivity of the enamine formed (see p. 11).



(IV)



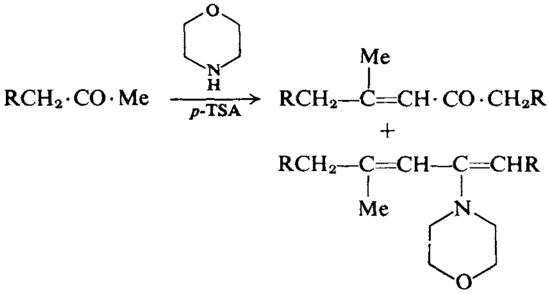
(V)



(VI)

The carbonyl compound. This may be an aldehyde or ketone, and the latter may be acyclic or cyclic. Most studies of enamine chemistry have involved the use of cyclohexanone and cyclopentanone, but some open-chain ketones have also been used. Cyclohexanones without α-alkyl substituents react with pyrrolidine very readily (room temperature in methanolic solution), but α-alkylcyclohexanones, cycloheptanones and linear ketones react less readily. More hindered ketones, for example, 2,6-dialkylcyclohexanones, cannot be converted into enamines by azeotropic removal of water.

Side reactions have been observed when some methyl ketones react with secondary amines, e.g.

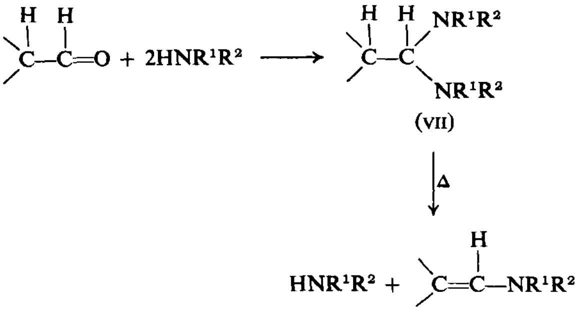


i.e. aldol condensation occurs to give the usual dimer, together with its enamine. The enamine of acetophenone is unstable and rapidly polymerises in the presence of a trace of acid. Other, less direct routes can be employed for the preparation of enamines from methyl ketones (see below).

The overall reaction scheme (scheme 1.2) for the formation of enamines of aldehydes is widely believed to involve the aminal (VII), but the evidence is conflicting. There is no doubt that aminals *are* produced, but it is not certain that they are the direct precursors in enamine formation.

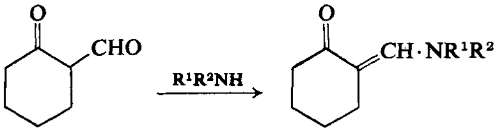
Enamines derived from simple aldehydes are often unstable, being easily hydrolysed, oxidised or polymerised. The simplest possible ena-

Scheme 1.2



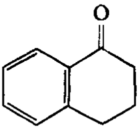
mine, that derived from acetaldehyde and dimethylamine, has been obtained by a modification of the method of Mannich and Davidson.

If a molecule contains both aldehydic and ketonic functions, e.g. (VIII), reaction with a secondary amine occurs at the former:



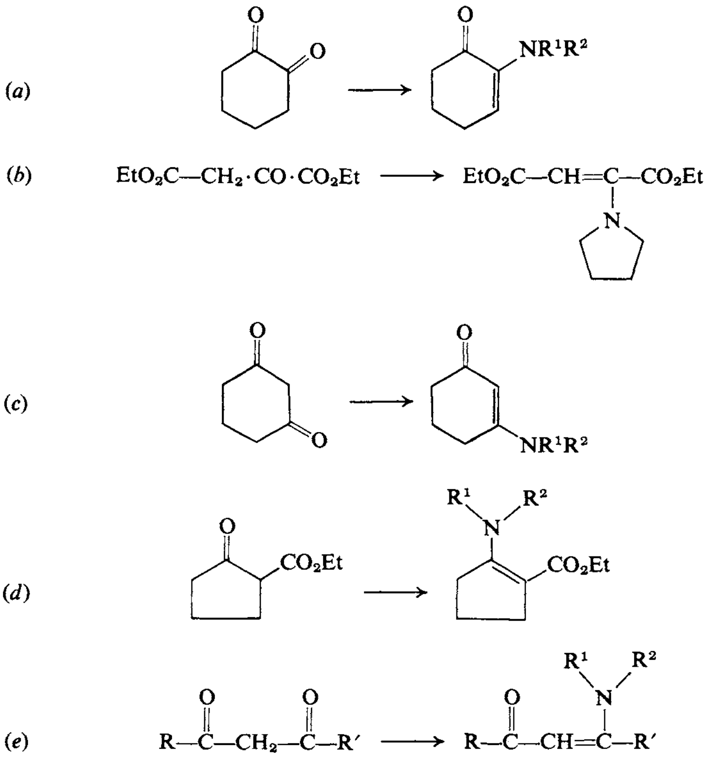
(VIII)

Recently a very effective modification to the general procedure for preparing enamines was described. A stoichiometric mixture of titanium tetrachloride, the secondary amine and the carbonyl compound is left for several hours at room temperature. High yields of enamines are realised, especially from methyl ketones, hindered ketones and other carbonyl compounds. α-Tetralone (IX), which reacts with difficulty under normal conditions is converted into its enamine using titanium tetrachloride. Some other examples of enamine formation are included in scheme 1.3.

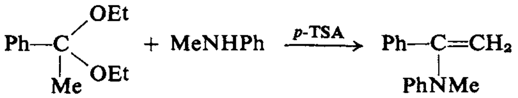


(IX)

Scheme 1.3



1.1.2. From ketals. Enamines have been obtained by heating secondary amines with ketals:



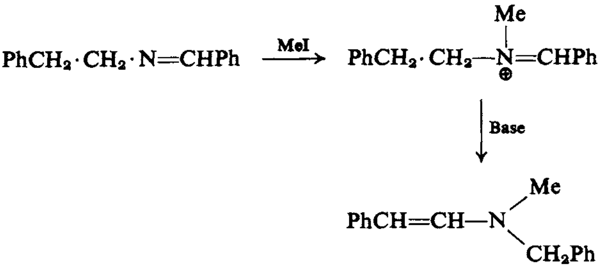
$$\mathrm{Ph{-}C(Me)(OEt)_2} + \mathrm{MeNHPh} \xrightarrow{p\text{-TSA}} \mathrm{Ph{-}C(NMePh){=}CH_2}$$

Although this method has not been studied very extensively, it has been used to obtain some enamines that are difficult to prepare by other methods.

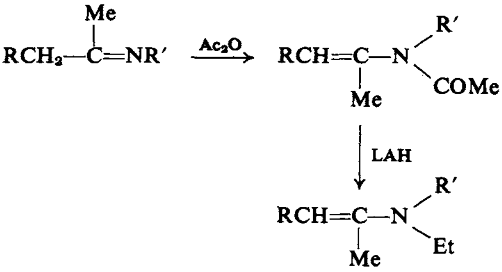
1.1.3. From imines. The imine, prepared in the usual way from a carbonyl compound and a primary amine, can be converted into the tertiary enamine by a variety of methods. For example, by direct *N*-alkylation with an alkyl halide or a dialkyl sulphate, or by the use of the Meerwein reagent ($[Et_3O]^+BF_4^-$):

CAMBRIDGE

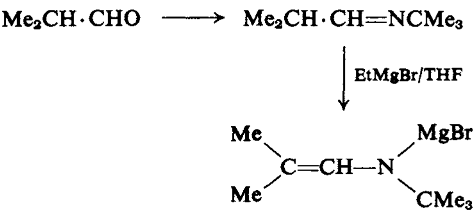
Cambridge University Press
978-0-521-09731-4 - The Chemistry of Enamines
S. F. Dyke
Excerpt
More information



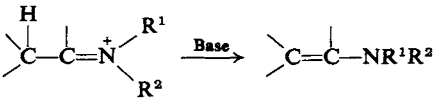
Alternatively, the imine may be *N*-acylated, and the amide formed reduced by lithium aluminium hydride:



Another modification involves the reaction of the imine with a Grignard reagent:

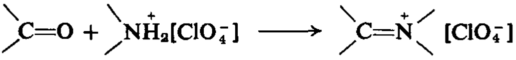


1.1.4. From iminium salts. Since tertiary iminium salts (x) can be converted into the corresponding enamines (xi) by base, methods of preparation of the former are equivalent to the formation of the latter. A very



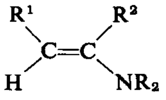
(x) (xi)

simple and effective method, developed by Leonard and his associates, involves heating a ketone with the secondary amine perchlorate:

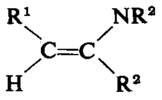


Three other useful methods exist for the preparation of enamines, but since they are of especial interest in the formation of heterocyclic enamines, discussion of them is deferred until Chapter 3. These methods involve: (*a*) oxidation of tertiary amines with mercuric acetate; (*b*) selective, partial reduction of aromatic nitrogen heterocycles; and (*c*) the reaction of lactams with Grignard reagents or with lithium aluminium hydride.

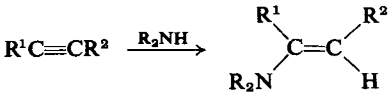
In the methods of formation of enamines described so far, a mixture of the two possible geometrical isomers (XII) and (XIII) is usually formed, often with the *trans* form predominating. It is, however, possible to prepare the *cis*-isomer in a pure state by the stereospecific addition of an amine to an alkyne:



(XII)

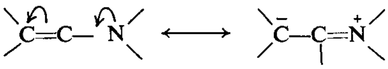


(XIII)



1.2. Some properties of enamines

1.2.1. Protonation and basicity. The structure of the enamine system may be regarded as a resonance hybrid to which the canonical forms (XIV) and (XV) are the important contributors. Hence, electrophilic reagents, including protons, may attack the system at either the nitrogen atom, to give the ammonium salt (XVI), or, more importantly, at

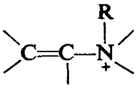


(XIV) (XV)

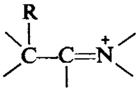
Cambridge University Press
978-0-521-09731-4 - The Chemistry of Enamines
S. F. Dyke
Excerpt
More information

the carbon atom β to the nitrogen to yield an iminium salt (XVII). It is now known that the protonation of an enamine occurs initially at nitrogen, and that this may be followed by a rearrangement, that is usually rapid, to the *C*-β-protonated form. Cases are known, for example for derivatives of dehydroquinuclidine (XVIII), where *C*-protonation cannot take place for steric reasons.

One direct synthetic application of protonation reactions is the preparation of deuterated ketones, for example (XIX) is formed when the pyrrolidine enamine of 2-methylcyclohexanone is treated with deuteroacetic acid in deuterium oxide (CH_3CO_2D/D_2O).

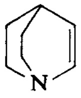


(XVI)

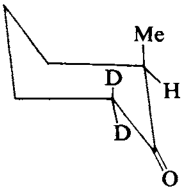


(XVII)

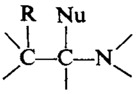
Of further interest is the fact that (XVII) is susceptible to attack by a nucleophilic reagent (Nu) to yield (XX). If R is a proton, the overall result is the addition of H—Nu to the carbon–carbon double bond of the enamine system.



(XVIII)



(XIX)

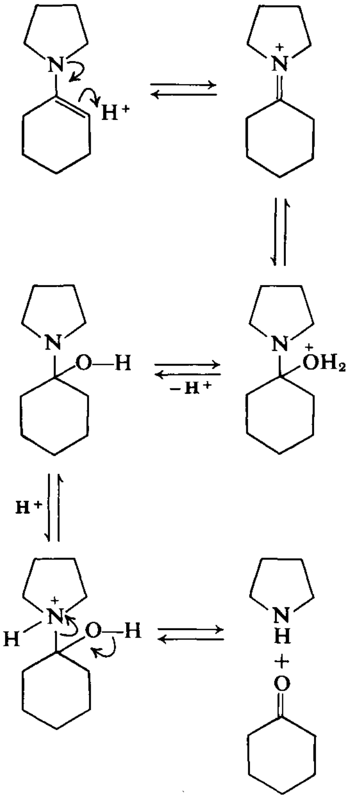


(XX)

Enamines possessing a tertiary nitrogen atom have often been stated to be more basic than the corresponding saturated amine, but recently this generalisation has been severely criticised. It seems that the presence or absence of an α-, or of a β-alkyl substituent in the enamine system will dictate the basicity. α-Alkyl substituents are base-strengthening whereas β-alkyl substituents are base-weakening. The question of base strength in the system under investigation is dependent upon the *position* of protonation. In some cases the *N*-protonated enamine formed initially does not rearrange to yield the *C*-protonated ion.

Enamines are usually easily hydrolysed by acids; the mechanism is often expressed (scheme 1.4) as a number of separate steps. The ratedetermining step depends very much upon the pH of the medium and upon the structure of the original enamine.

Scheme 1.4



1.2.2. Ultraviolet spectra. Enamines give rise to a band at 220–240 nm ($\epsilon_{\max}$ 5000–9000), depending upon the degree of p–π overlap between the nitrogen unshared electron pair and the carbon–carbon double bond.

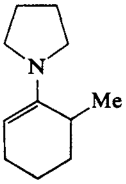
There is little difference between the ultraviolet spectra of the *C*-β-protonated form, and the enamine, but if protonation occurs at nitrogen this ion would be expected to exhibit end absorption only, due to the isolated double bond.

1.2.3. Infrared spectra. The carbon–carbon double bond of the vinylamine function absorbs at about 1630–1660 cm^{-1} giving a medium-to-strong band. When the enamine is converted into its iminium salt by *C*-β-protonation, a very characteristic shift of 20–50 cm^{-1} to higher frequency occurs, with an increase in the intensity of the absorption.

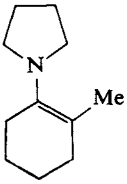
1.2.4. Nuclear magnetic resonance spectra. The chemical shift of the vinyl proton or protons of the enamine function is indicative of the degree of overlap in the *p*–π system (see below). The greater the overlap, the lower is the chemical shift from tetramethylsilane (TMS).

1.3. Structures of isomeric enamines

Some confusion exists in the literature concerning the structure of enamines derived from unsymmetrical ketones. In their original definitive paper, Stork *et al.* showed by nuclear magnetic resonance (n.m.r.) studies that the pyrrolidine enamine of 2-methylcyclohexanone has the structure (XXI), with the trisubstituted double bond, rather than the more stable structure (XXII) containing a tetrasubstituted double bond. Subsequent workers have extrapolated this observation to other ketones and other amines. It is now realised, however, that in the majority of cases a mixture of *both* isomeric (tautomeric) enamines is formed, the ratio depending upon a number of factors. It is postulated that the degree of *p*–π overlap between the nitrogen lone pair electrons and the double bond varies with the amine used to form the enamine of a given ketone, and is greater for the pyrrolidine enamine. This correlation is illustrated by the data collected into table 1.1. The first column of figures refers to the chemical shift of the olefinic proton in the cyclohexanone enamines formed from the amines indicated. The greater the degree of *p*–π overlap, the greater is the electron density at the β-carbon atom, and, consequently, the greater is the magnetic shielding of the vinylic proton. Thus, for 1-pyrrolidino-1-cyclohexene, the chem-



(XXI)



(XXII)