ALDOL CONDENSATION

Aldehydes having α-hydrogen(s) undergo self-condensation on warming with dilute or mild base to give β-hydroxy aldehydes, called aldols (aldehyde + alcohol). This reaction is known as aldol condensation.

A typical example is the reaction of acetaldehyde with base under mild condition.

$$CH_3CHO + CH_3CHO \xrightleftharpoons{\ominus OH} \underset{\text{Acetaldol}}{CH_3CH(OH)CH_2CHO}$$

Various basic reagents such as dilute sodium hydroxide, aqueous alkali carbonate, alkali metal alkoxides, etc., may be used. The reaction is not favourable for ketones.

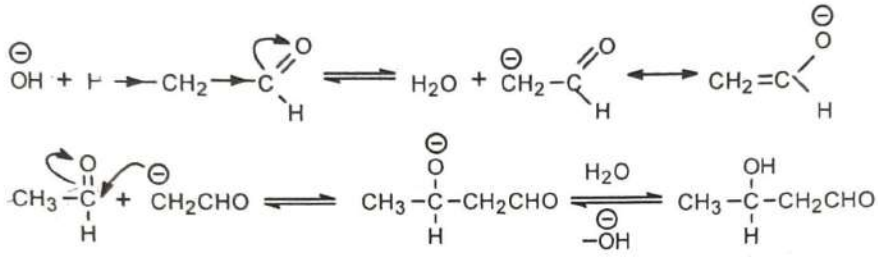
Aldol condensation has broad scope. It can occur between

(i) two identical or different aldehydes,
(ii) two identical or different ketones and
(iii) an aldehyde and a ketone.

When the condensation is between two different carbonyl compounds, it is called crossed aldol condensation.

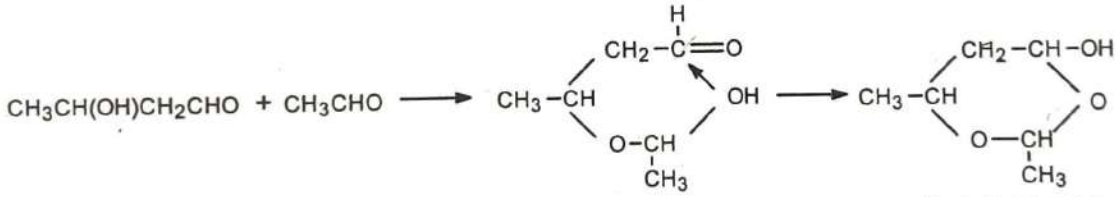
Mechanism

The first step involves the formation of a resonance-stabilized enolate anion by the removal of an α-hydrogen from the aldehyde by the base. In the second step the enolate anion attacks the carbonyl carbon of the second molecule of the aldehyde to form an alkoxide ion. The latter then takes up a proton from the solvent to yield aldol in the third step.



Thus, the overall reaction is an addition of enolate anion to the carbonyl double bond. [Recall that Michael reaction involves addition to an activated carbon–carbon double bond.]

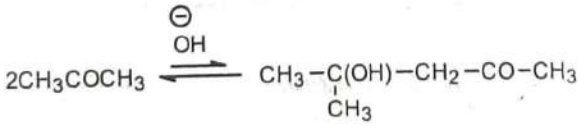
Usually aldol as such is not isolated, e.g., acetaldol is isolated as a cyclic hemiacetal.



Cyclic hemiacetal

Aldol is isolated under reasonable mild condition, i.e., using aqueous K_2CO_3 as base.

The reaction between two ketones is not very successful. The equilibrium is not favourable and lies far to the left.

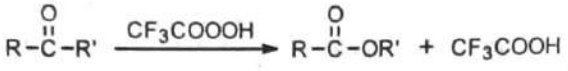


This is because the carbonyl carbon of ketone is less positive (due to +I effect) and more sterically hindered relative to aldehydes. This reduces the nucleophilic attack on the carbonyl carbon. However, it is possible to prepare diacetone alcohol in reasonable good yield by boiling acetone with solid $Ba(OH)_2$ in a specially devised apparatus.

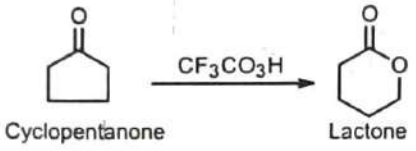
BAEYER–VILLIGER REARRANGEMENT

Baeyer–Villiger rearrangement is an example of the migration of a group from carbon to electron-deficient oxygen.

The reaction involves the oxidation of ketones to esters by the treatment with peracids such as peracetic acid, perbenzoic acid, pertrifluoroacetic acid, permonosulphuric acid, etc.



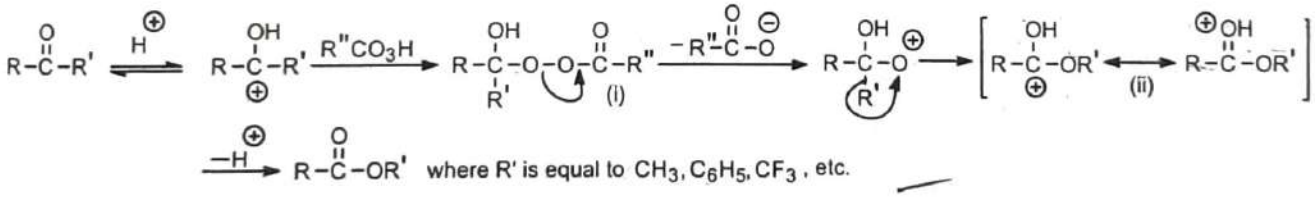
Cyclic ketones are converted to lactones with ring expansion.



The overall reaction is an insertion of oxygen atom between the carbonyl group and the adjacent carbon in ketone. Organic solvents which are inert under the conditions of reaction may be used. The choice of solvent depends upon the solubility of the reactants. Commonly used solvents are glacial acetic acid and chloroform.

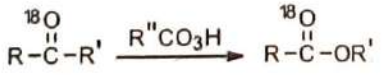
Mechanism

Nucleophilic attack of the peracid on the protonated ketone gives an intermediate peroxide (i). The peroxide then undergoes loss of carboxylate anion and migration of a group from carbon to electron deficient oxygen to yield the protonated ester (ii). Finally the loss of proton gives the ester.

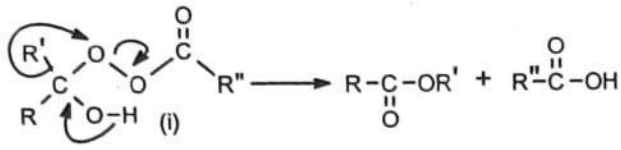


The reaction is catalysed by acids. Electron-releasing groups in the ketone and electron-withdrawing groups in peracids promote the reaction rate. Pertrifluoroacetic acid is very effective because trifluoroacetate ion is a good leaving group.

The mechanism is supported by the fact that the labelled oxygen atom of the ketone is entirely present in the carbonyl oxygen of the ester.



The loss of carboxylate anion and the migration of the group may be concerted. Syrkin has suggested that the peroxide (i) transforms into products by a cyclic mechanism, which shows that the last three steps may be concerted.



The migrating group retains its configuration as in other concerted reactions. For acylic compounds the migrating group, R′ must be 2°, 3° or vinylic. However, migration of 1° alkyl group may be brought about by using CF_3CO_3H or BF_3–H_2O_2 as reagent.

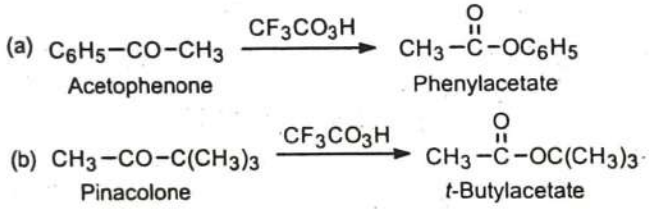
Baeyer–Villiger oxidation can be brought about with H_2O_2 and base also in some cases.

In unsymmetrical ketones, that group migrates which is more electron-releasing. Thus, the migratory aptitude of alkyl groups is in the order 3° > 2° > 1° > CH_3. Electron-releasing substituents in the aryl group facilitate migration. The migratory order of aryl groups is *p*-anisyl > *p*-tolyl > phenyl > *p*-chlorophenyl > *p*-nitrophenyl, etc. In case of alkyl aryl ketones, it is the aryl group which migrates (except in case of *t*-butyl group).

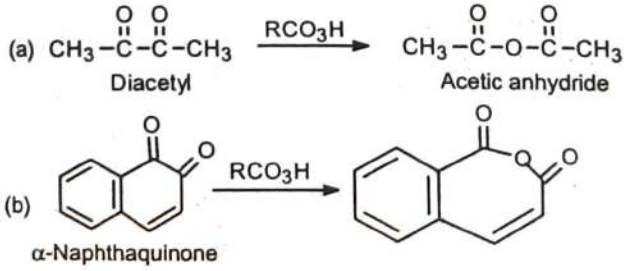
Applications

The reaction has valuable synthetic applications.

1. Esters Esters which are difficult to synthesize can be prepared by this method.

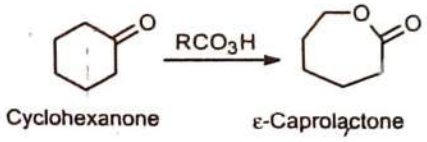


2. Anhydrides When 1, 2-diketones or *o*-quinones are subjected to Baeyer–Villiger rearrangement, anhydrides are produced.



The products can be converted to various types of compounds.

3. Lactones Cyclic ketones are converted to lactones with ring expansion.



Long-chain hydroxyesters can be prepared from large ring-size ketones.

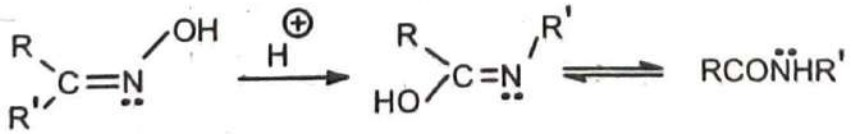
BECKMANN REARRANGEMENT

The acid-catalyzed conversion of ketoximes to *N*-substituted amides is known as Beckmann rearrangement. The reaction is catalysed by acidic reagents such as, H_2SO_4, $SOCl_2$, SO_3, P_2O_5, PCl_5, $C_6H_5SO_2Cl$, etc.

The reaction involves the migration of a group from carbon to electron-deficient nitrogen.

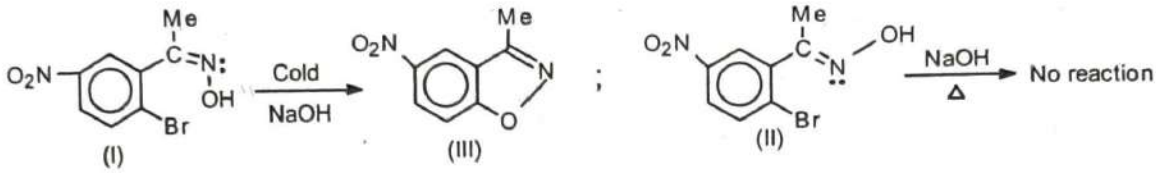
$$RR'C{=}NOH \xrightarrow{\oplus H} RCONHR' \quad \text{or} \quad R'CONHR$$

Some aldoximes undergo the rearrangement in the presence of polyphosphoric acid (PPA) but the reaction is not a general one. The migration of the group depends not on the migrational aptitude but upon the orientation of the group in relation to the OH group. It is found that the migrating group is always *anti* (i.e., *trans*) to the hydroxyl group. Thus, the reaction is stereospecific.



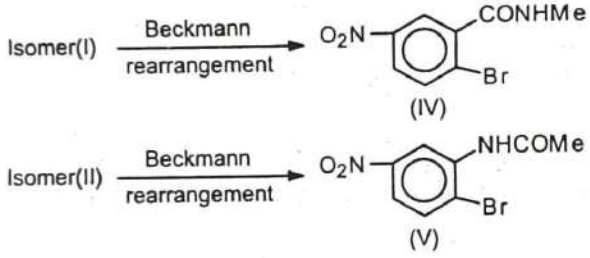
That it is always the antigroup which migrates has been confirmed by the rearrangements of the two isomeric oximes of 2-bromo-5-nitroacetophenone. The structures of the two isomeric oximes were first determined by an elegant method as given below.

On treatment with cold NaOH solution, one isomer (I) was cyclized to 3-methyl-5-nitrophenyl isooxazole (III) while the other isomer (II) remained unaffected even under drastic conditions.



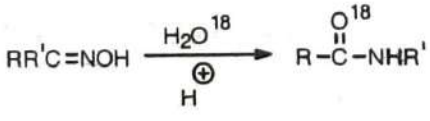
Obviously, the OH and Br groups in isomer (I) are close enough for reaction and cyclization. Hence, the Me and OH groups are *anti* (i.e., *trans*) to each other. In isomer (II), the OH and Br groups are far apart for reaction, i.e., the Me and OH groups are *syn* (i.e., *cis*) to each other. Thus, the structures of isomers (I) and (II) are confirmed.

Now, on subjecting the two isomers to Beckmann rearrangement it is found that (a) isomer (I) gives *N*-methyl-2-bromo-5-nitrobenzamide (IV) indicating the migration of the antigroup Me to the nitrogen atom and (b) isomer (II) gives *N*-(2-bromo-5-nitrophenyl)- acetamide (V) due to the migration of the *anti*-aryl group to the nitrogen atom.

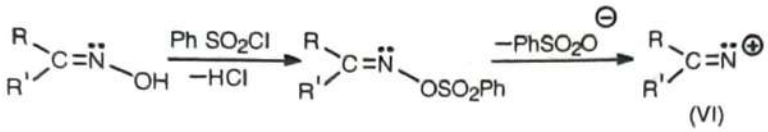


Oxime esters and ethers also undergo Beckmann rearrangement. The acidic reagents convert the OH group to a better leaving group—acids convert OH to H_2O, other reagents convert OH to an ester-leaving group, e.g., $OPCl_4$ from PCl_5, $OSO_2C_6H_5$ from $C_6H_5SO_2Cl$, etc. The reaction is facilitated by heat, polar solvents or an increase in the acid strength.

That direct interchange of the migrating group and OH does not occur is proved by the fact that ^{18}O is incorporated in the product in the presence of $H_2{}^{18}O$.



With other acidic reagents, e.g., $PhSO_2Cl$, the same intermediate (VI) is obtained.



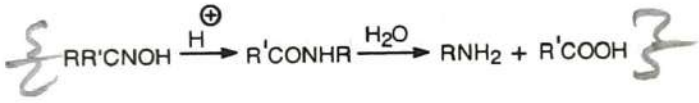
In strong acids, the reaction proceeds with the protonation of the OH group of the oxime with subsequent loss of water to yield the species (vi) with electron-deficient nitrogen which is also obtained with other acidic reagents by the loss of ester group. The migration of R then gives a carbocation. The attack of water molecule on the carbon followed by the loss of proton gives the amide.

The migrating group retains its configuration and hence the migrating group does not become completely free during the migration, otherwise the reaction cannot be stereospecific. Thus, the migration and the breaking of N–O bond may be concerted or at least very rapid. This has been supported by crossover experiments.

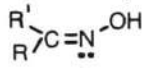
Applications

1. Configuration of ketoximes can be assigned A ketoxime gives an amide on Beckmann rearrangement. From the products of hydrolysis of the amide, the structure of the amide is known and for that matter, the configuration of the oxime is known.

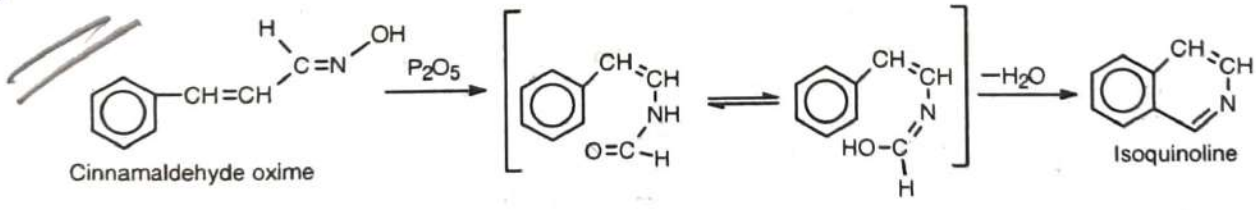
Thus,



Formation of RNH_2 indicates the migration of the group R to the nitrogen atom. The groups R and OH are, therefore, *anti* to each other, i.e., the structure of the oxime is

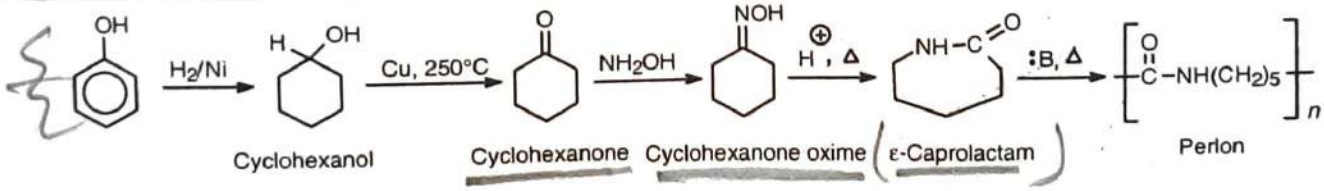


2. Synthesis of isoquinoline



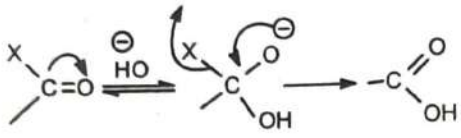
3. Synthesis of lactams Alicyclic ketones of all ring sizes undergo the Beckmann rearrangement of their oximes to yield lactams.

A product of considerable industrial importance is perlon (valuable textile polymer) which is prepared from ω-caprolactam. This is obtained by the Beckmann rearrangement of cyclohexanone oxime. It is synthesized from phenol as below.



BENZILIC ACID REARRANGEMENT

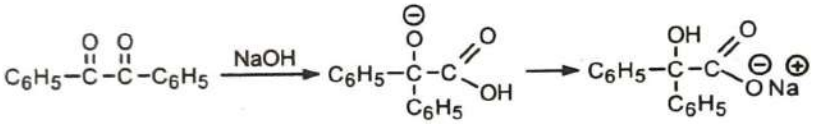
The addition of a strong base to a carbonyl group results in the formation of an anion. The reversal of the anionic charge may cause expulsion of the attached group, X, e.g.,



(cf. Hydrolysis of esters when X = OR)

However, in a 1:2-diketone the group X may migrate to the adjacent electron-deficient carbonyl carbon forming α-hydroxy acid.

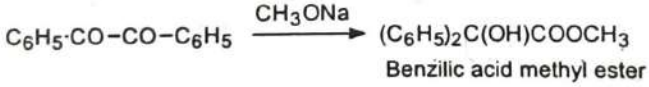
Thus, benzil on treatment with a strong base forms benzilic acid (salt), whence the name benzilic acid rearrangement.



Benzil

Sodium salt of benzilic acid

Barium and thallous hydroxides are more effective than sodium or potassium hydroxides. Alkoxide ions (methoxide, *t*-butoxide, etc.) in place of hydroxide ion give the corresponding esters.



Benzilic acid methyl ester

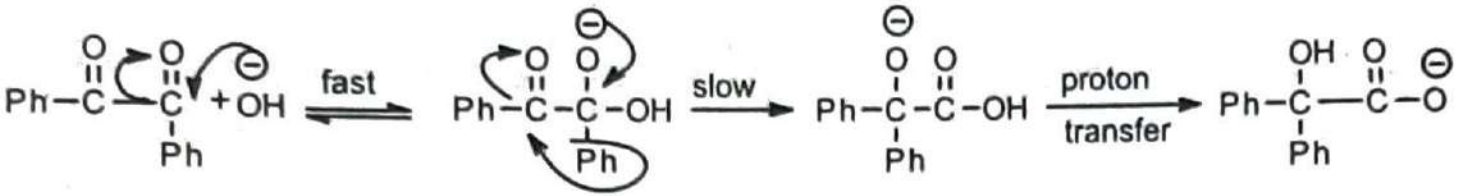
Phenoxide ions are too weak a nucleophile to attack. Besides aromatic 1, 2-diketones, aliphatic and heterocyclic diketones as also *o*-quinones undergo this rearrangement.

Mechanism

It has been seen that the rate of reaction is proportional to the concentrations of benzil and the hydroxide ion, i.e., rate $\propto [C_6H_5COCOC_6H_5][\bar{O}H]$

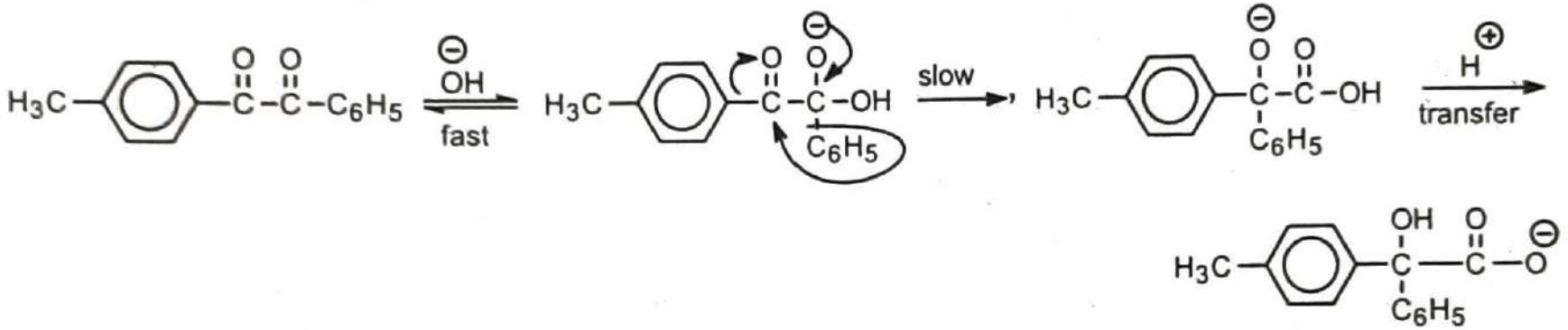
It has also been found that when the reaction is carried out in the presence of $H_2{}^{18}O$, benzil exchanges ^{18}O faster than it rearranges.

On the basis of the above observations, it has been suggested that a fast reversible nucleophilic attack occurs at the carbonyl carbon in the first step. The second step is the rate-determining step in which the migration occurs. Finally, a rapid proton transfer completes the process.



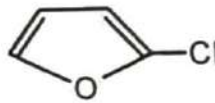
The rearrangement is analogous to intramolecular Cannizzaro reaction of glyoxal.

The carbonyl group which is attached to the less electron releasing of the two aryl groups is relatively more positively charged and, hence, is attacked by $\bar{O}H$. Consequently, the less electron-donating aryl group migrates to the other carbonyl group.



(*p*-Tolyl group is more electron-releasing than phenyl group)

CANNIZZARO REACTION

In the presence of a strong base, aldehydes without α-hydrogens, i.e., nonaldolizable aldehydes undergo self-oxidation–reduction i.e., disproportionation reaction, This is known as Cannizzaro reaction. Thus, aromatic aldehydes (ArCHO), formaldehyde (HCHO), trialkyl acetaldehydes (R_3CCHO), heterocyclic aldehydes,  etc., undergo Cannizzaro reaction, e.g.,

$$2C_6H_5CHO + NaOH \xrightarrow{\Delta} \underset{\text{Benzyl alcohol}}{C_6H_5CH_2OH} + \underset{\text{Sodium benzoate}}{C_6H_5COONa}$$

$$2HCHO + NaOH \xrightarrow{\Delta} \underset{\text{Methyl alcohol}}{CH_3OH} + \underset{\text{Sodium formate}}{HCOONa}$$

The reaction best proceeds with aromatic aldehydes. Although the reaction is characteristic of aldehydes without α-hydrogen, a few aldehydes with α-hydrogen are known which undergo Cannizzaro reaction.

$$\underset{\text{Dimethyl acetaldelyde}}{2(CH_3)2CHCHO} + NaOH \xrightarrow{200°C} \underset{\text{2-Methylpropanol-1.}}{(CH_3)_2CHCH_2OH} + \underset{\text{Sodium-2-methyl propanoate}}{(CH_3)_2CHCOONa}$$

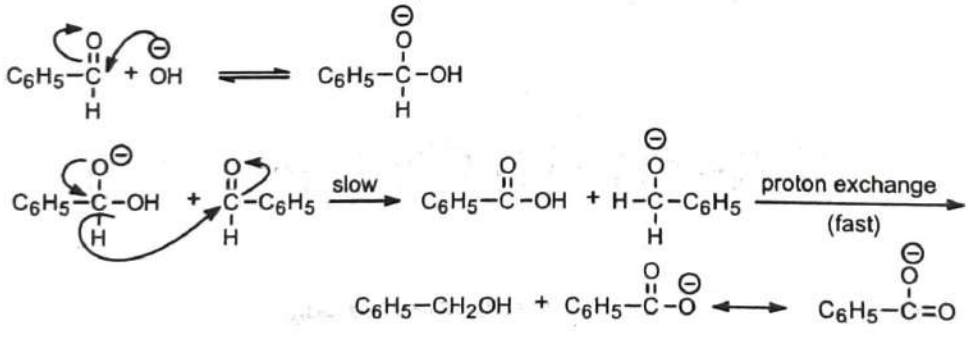
The reaction can also occur between two different aldehydes having no α-hydrogens when it is called crossed Cannizzaro reaction.

$$C_6H_5CHO + HCHO \xrightarrow[\Delta]{NaOH} C_6H_5CH_2OH + HCOONa$$

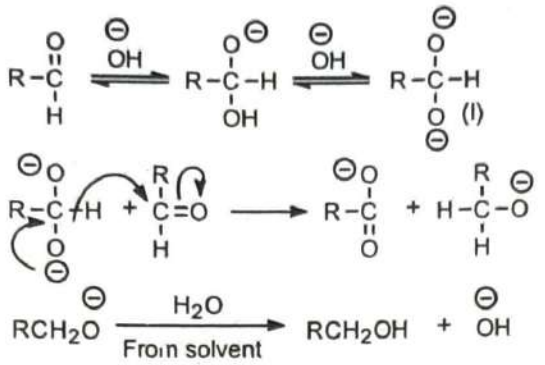
When formaldehyde undergoes crossed Cannizzaro reaction with other aldehydes without α-hydrogens, it is seen that formaldehyde is oxidized and the other is reduced. This is because the nucleophilic attack occurs more readily on formaldehyde than on other aldehydes.

Mechanism

Rapid addition of $\overset{\ominus}{O}H$ to one molecule of aldehyde results in the formation of a hydroxy alkoxide ion which like aluminium-isopropoxide acts as a hydride-ion donor to the second molecule of aldehyde. In the final step of the reaction, the acid and the alkoxide ion exchange proton for reasons of stability.



In the presence of a very strong concentration of alkali, aldehyde first forms a doubly charged anion (I) from which a hydride anion is transferred to the second molecule of the aldehyde to form acid and an alkoxide ion. Subsequently, the alkoxide ion acquires a proton from the solvent.



Evidence in support of the mechanism

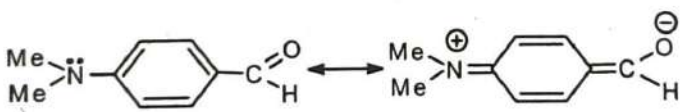
(i) The reaction follows third-order law (second order in aldehyde and first order in base), i.e., rate $\propto [Ald]^2[OH^-]$. This suggests the reaction between the first-formed anion (from base and aldehyde) and another molecule of aldehyde in the rate-determining step.

In the presence of a high concentration of base, the reaction follows fourth-order law (second order in both the aldehyde and base), i.e., rate $\propto [Ald]^2 [OH]^{2-}$

This suggests the reaction between the doubly charged anion (formed from one molecule of aldehyde and two molecules of base) and another molecule of aldehyde.

(ii) That the hydride ion is directly transferred from one molecule of the aldehyde to the other, and does not become free in solution has been proved by the observation that the recovered alcohol does not contain deuterium when the reaction is performed in the presence of D_2O.

It is seen that the reaction depends on the nucleophilic attack on the carbonyl carbon. Hence, factors which reduce the positive charge of the carbonyl carbon retard the reaction. In extreme cases the reaction may not occur, e.g., *p*-dimethylaminobenzaldehyde does not undergo Cannizzaro reaction.



Similarly, sterically hindered aldehydes do not undergo the reaction.

CLAISEN CONDENSATION

Esters having α-hydrogen on treatment with a strong base, e.g., C_2H_5ONa, undergo self-condensation to produce β-ketoesters

$$2\,CH_3COOC_2H_5 \xrightarrow[2.\ H^{\oplus}]{1.\ C_2H_5ONa} \underset{\text{Ethyl acetoacetate}}{CH_3COCH_2COOC_2H_5}$$

$$2\,R'CH_2COOC_2H_5 \xrightarrow[2.\ H^{\oplus}]{1.\ C_2H_5ONa} R'CH_2COCH(R')COOC_2H_5$$

This reaction is called Claisen condensation although there are several closely related reactions which follow the same mechanistic pattern.

Mixed or crossed Claisen condensation also occurs between two different esters or between an ester and a ketone.

Mechanism

The ethoxide ion abstracts a proton from the α-carbon of the ester to produce the anion (of the ester) which is a powerful nucleophile (Ist step). The nucleophilic attack of the anion on the carbonyl carbon of a second molecule of ester produces an oxonium ion (IInd step), which eliminates an ethoxide ion to give the β-ketoester (IIIrd step). The β-ketoester having an active methylene group is acidic and reacts with sodium ethoxide to form enolate salt (IVth step). Subsequent acidification with acetic acid (1 : 1) regenerates the β-ketoester.

$$C_2H_5O^{\ominus} + H{-}CH_2COOC_2H_5 \rightleftharpoons C_2H_5OH + {:}CH_2COOC_2H_5^{\ominus} \quad \ldots (I)$$

$$CH_3{-}\underset{\underset{OC_2H_5}{|}}{\overset{\overset{O}{\|}}{C}}{:}^{\ominus} + CH_2COOC_2H_5 \rightleftharpoons CH_3{-}\underset{\underset{OC_2H_5}{|}}{\overset{\overset{O^{\ominus}}{|}}{C}}{-}CH_2COOC_2H_5 \quad \ldots (II)$$

$$CH_3{-}\underset{\underset{OC_2H_5}{|}}{\overset{\overset{O^{\ominus}}{|}}{C}}{-}CH_2COOC_2H_5 \rightleftharpoons CH_3{-}\overset{\overset{O}{\|}}{C}{-}CH_2COOC_2H_5 + C_2H_5O^{\ominus} \quad \ldots (III)$$

$$CH_3{-}\overset{\overset{O}{\|}}{C}{-}CH_2COOC_2H_5 + C_2H_5O^{\ominus} \longrightarrow C_2H_5OH + \left[CH_3{-}\overset{\overset{O}{\|}}{C}{-}\overset{\ominus}{C}H{-}\overset{\overset{O}{\|}}{C}{-}OC_2H_5 \longleftrightarrow CH_3{-}\overset{\overset{O}{\|}}{C}{-}CH{=}\overset{\overset{O^{\ominus}}{|}}{C}{-}OC_2H_5\right.$$

$$\left. \longleftrightarrow CH_3{-}\overset{\overset{O^{\ominus}}{|}}{C}{=}CH{-}\overset{\overset{O}{\|}}{C}{-}OC_2H_5\right]^{\oplus}Na \equiv \left[CH_3{-}\overset{\overset{O}{\|}}{C}{-}CH{-}\overset{\overset{O}{\|}}{C}{-}OC_2H_5\right]^{\ominus}{}^{\oplus}Na \quad \ldots (IV)$$

$$\left[CH_3-\overset{O}{\overset{\|}{C}}-CH-\overset{O}{\overset{\|}{C}}-OC_2H_5 \right]^{\ominus}Na^{\oplus} \xrightarrow{CH_3COOH} CH_3-CO-CH_2-COOC_2H_5 + CH_3COONa$$

The first three steps are in unfavourable equilibrium state. Hence, excess sodium ethoxide is used to force the equilibrium to shift in the forward direction by the formation of a resonance-stabilized enolate anion (IVth step). This is substantiated by the fact that esters having only one α-hydrogen do not undergo Claisen condensation with C_2H_5ONa. This is because the ketoester formed (analogous to step III) cannot be converted to its enolate anion due to the absence of a second α-hydrogen, with the result that the equilibrium does not shift to the right.

However, in the presence of a very strong base such as triphenylmethyl sodium, such esters, e.g., ethyl isobutyrate, undergo Claisen condensation to give β-ketoesters. This is because the very strong base, $(C_6H_5)_3CNa$ acts in two ways.

(i) It withdraws the weakly acidic α-hydrogen irreversibly from the ester (analogous step I is highly reversible).

$$\underset{\text{Ethyl isobutyrate}}{CH_3-\overset{CH_3}{\overset{|}{C}}H-COOC_2H_5} + (C_6H_5)_3\overset{\ominus}{C} \rightleftharpoons CH_3-\overset{CH_3}{\overset{|}{\underset{\ominus}{C}}}-COOC_2H_5 + (C_6H_5)_3CH$$

(ii) It completely removes one of the equilibrium products, i.e., ethyl alcohol, so that the equilibrium shifts to the right. (Compare step III.)

$$\underset{\text{Ethyl isobutyrate}}{2(CH_3)_2CH-COOC_2H_5} \xrightleftharpoons{(C_6H_5)_3\overset{\ominus}{C}} \underset{\text{Ethyl isobutyrylisobutyrate}}{(CH_3)_2CH-\overset{O}{\overset{\|}{C}}-\overset{CH_3}{\overset{|}{C}}-COOC_2H_5} + C_2H_5OH$$

$$(C_6H_5)_3CNa + C_2H_5OH \rightleftharpoons (C_6H_5)_3CH + C_2H_5ONa$$

CLEMMENSEN REDUCTION

The reduction of carbonyl groups of aldehydes and ketones to methylene groups with amalgamated zinc and concentrated hydrochloric acid is known as Clemmensen reduction.

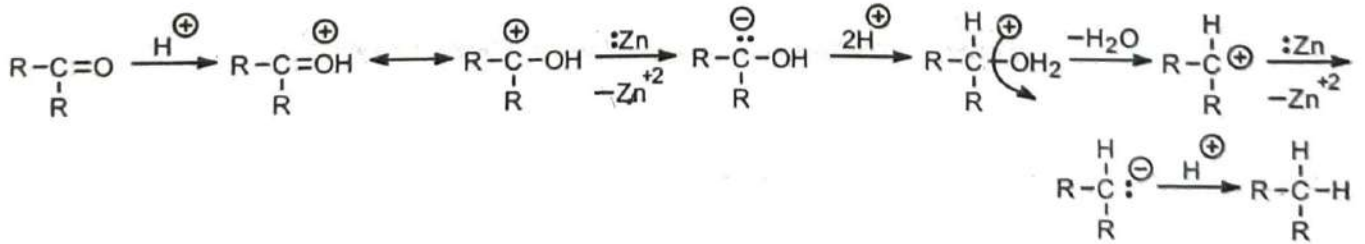
$$\underset{\text{Acetophenone}}{C_6H_5COCH_3} \xrightarrow[\text{Reflux}]{\text{Zn-Hg, HCl}} \underset{\text{Ethyl benzene}}{C_6H_5CH_2CH_3}$$

The reduction consists in refluxing the carbonyl compounds with amalgamated zinc and excess of concentrated hydrochloric acid. The reduction is useful especially for ketones containing phenolic or carboxylic groups which remain unaffected. Ketones are reduced more often than aldehydes. Such reduction is also observed in Wolff–Kishner reduction but Clemmensen reduction is easier to perform. The reduction, however, fails with acid-sensitive and high molecular weight substrates. The α, β-unsaturated ketones undergo reduction of both the olefinic and carbonyl groups. However, the reduction is specific for carbonyl groups of aldehydes and ketones containing other functional and reducible groups.

Mechanism

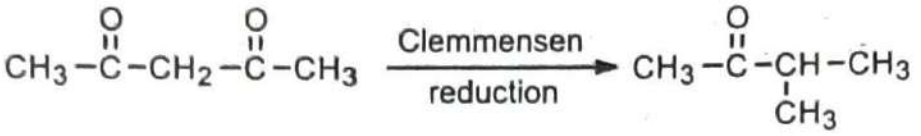
Various mechanisms have been suggested which are so contradictory that no conclusion can be drawn. A mechanism suggesting the intermediate formation of alcohol was rejected since the reagent fails to reduce most alcohols to hydrocarbons.

Nakabayaski has suggested a mechanism on the assumption that the reduction under acid condition involves protonated carbonyl group to which electrons are transferred from the metal.

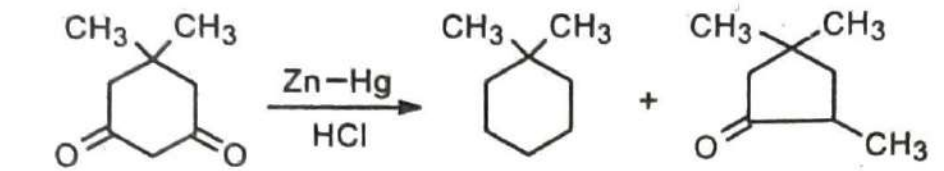


Certain types of aldehydes and ketones do not give the normal reduction products alone. Thus,

α-hydroxy ketones give either ketones through hydrogenolysis* of OH group or olefins and 1, 3-diketones give exclusively monoketones with rearrangement.

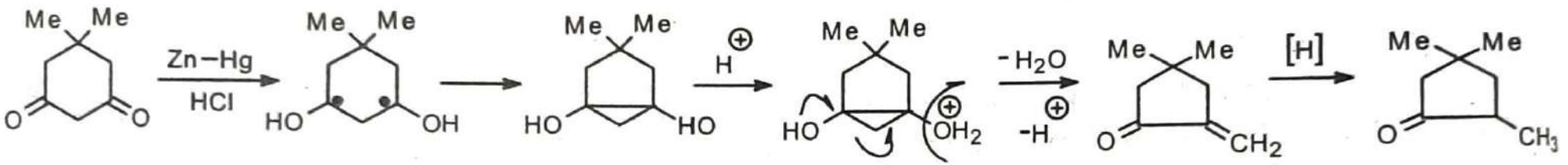


Certain cyclic 1, 3-diketones give under Clemmensen reduction a fully reduced product along with a monoketone with ring contraction.



5, 5-Dimethyl cyclohexane-1,3-dione — 1, 1-Dimethyl cyclohexane — 2, 4, 4-Trimethyl cyclopentanone

The latter probably is formed through a diradical with subsequent intramolecular C–C bond formation and pinacol-type rearrangement.



KNOEVENAGEL REACTION

Condensations of aldehydes and ketones with compounds having active methylene group in the presence of basic catalyst to form α, β-unsaturated compounds is called Knoevenagel reaction. The basic catalysts may be ammonia or its derivatives. Thus, primary, secondary or tertiary amines, e.g., aniline, di- or tri-alkyl amines, pyridine, piperidine, etc., are used.

$$C_6H_5CHO + \underset{\text{Malonic ester}}{H_2C(COOR)_2} \xrightarrow[\text{piperidine}]{\text{Pyridine-}} C_6H_5CH=C(COOR)_2 \xrightarrow[2.\Delta,-CO_2]{1.\ H_2O} \underset{\text{Cinnamic acid}}{C_6H_5-CH=CH-COOH}$$

Mechanism

The initial stage of the reaction is base-catalysed aldol condensation with subsequent dehydration.

In the first step the base removes a proton from the active methylene group to generate a carbanion. The carbanion then attacks the carbonyl carbon of the substrate to form an alkoxide ion which abstracts the proton from the protonated catalyst to form a hydroxy compound. Subsequent dehydration gives the α, β-unsaturated compound which is hydrolysed and decarboxylated to obtain α, β-unsaturated acid. The reaction with a malonic ester is as shown:

$$R_3\ddot{N} + H_2C(COOR)_2 \rightleftharpoons R_3\overset{\oplus}{N}H + \overset{\ominus}{H}C(COOR)_2$$

$$R'-\overset{O}{\overset{\|}{C}}-H + \overset{\ominus}{C}H(COOR)_2 \rightleftharpoons R'-\underset{H}{\overset{\ominus O}{\underset{|}{\overset{|}{C}}}}-CH(COOR)_2 \underset{-R_3N:}{\overset{\oplus}{R_3NH}} R'-\underset{H}{\overset{OH}{\underset{|}{\overset{|}{C}}}}-CH(COOR)_2 \xrightarrow{-H_2O}$$

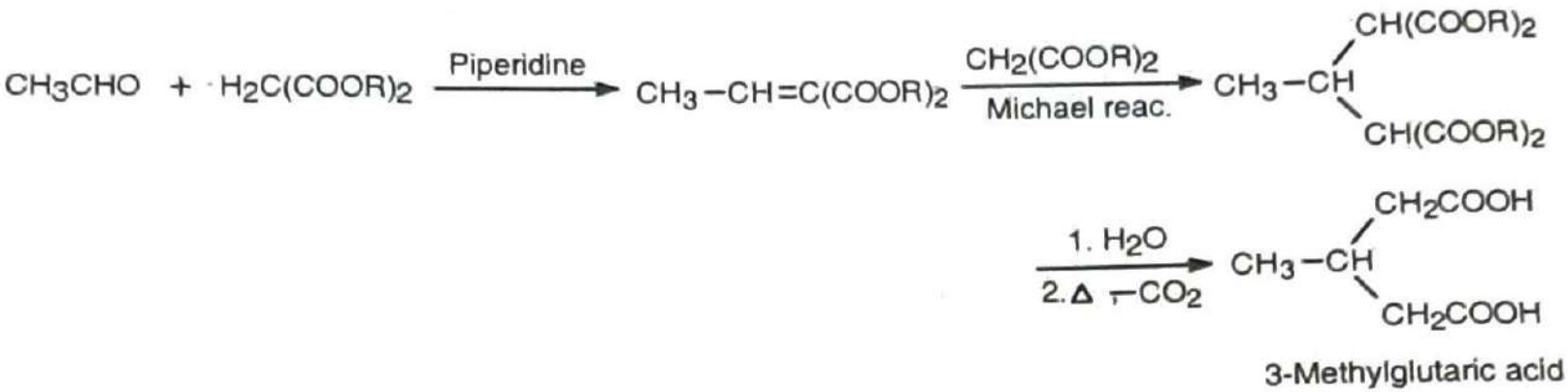
$$R'-CH=C(COOR)_2 \xrightarrow[2.\Delta,-CO_2]{1.\ H_2O} R'-CH=CHCOOH.$$

High reactivity of the methylene group of the active methylene compound prevents self-condensation of the aldehyde.

Both aromatic and aliphatic aldehydes give this reaction. For steric and electronic reasons ketones are less reactive than aldehydes. Hence, ketones react with compounds having powerful active methylene group only, e.g., ethyl acetoacetate, cyanoacetic acid and its ester but not usually with malonic ester for which stronger bases have to be used.

$$(CH_3)_2C=O + H_2\overset{CN}{\underset{COOR}{C}} \xrightarrow[CH_3COOH]{CH_3CONH_2} (CH_3)_2C=\overset{CN}{\underset{COOR}{C}} \xrightarrow[2.\Delta,-CO_2]{1.\ H_2O} \underset{\text{3-Methylcrotonic acid}}{(CH_3)_2C=CHCOOH}$$

The intermediate unsaturated product formed during the course of reaction with aldehydes tends further to undergo Michael reaction especially in the presence of excess of the active methylene compound. The Michael condensation product may be hydrolysed and decarboxylated to obtain dibasic acid.



3-Methylglutaric acid

Hence, Knoevenagel reaction best proceeds with aromatic aldehydes.

PERKIN REACTION

In Perkin reaction, condensation has been effected between aromatic aldehydes and aliphatic acid anhydrides in the presence of sodium or potassium salt of the acid corresponding to the anhydride, to yield α, β-unsaturated aromatic acids.

The acid anhydride should have at least two α-hydrogens.

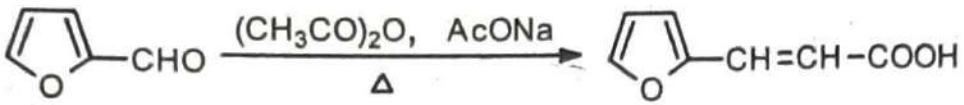
$$C_6H_5CHO + (CH_3CO)_2O \xrightarrow[170\text{—}180^\circ C,\ 5\ h]{AcONa} C_6H_5-CH=CH-COOH + CH_3COOH$$

Besides simple aromatic aldehydes, their vinylogs, heterocyclic aldehydes and even phathalic anhydride (as the carbonyl component) give this reaction.

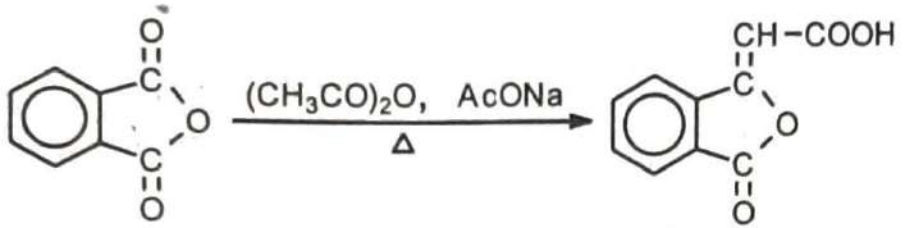
PERKIN REACTION

(a) $C_6H_5-CH=CH-CHO \xrightarrow[\Delta]{(CH_3CO)_2O,\ AcONa} C_6H_5-CH=CH-CH=CH-COOH$

5-Phenyl-pent-2,4-dienoic acid

(b) 

3-(α-Furyl)-acrylic acid

(c) 

Phthalylacetic acid

SCHMIDT REACTION

Carboxylic acids and hydrazoic acid react in the presence of sulphuric acid to give amines. This reaction is known as Schmidt reaction.

$$RCOOH + N_3H \xrightarrow{H_2SO_4} RNH_2 + CO_2 + N_2$$

Free hydrazoic acid is highly toxic and hence sodium azide is slowly added to the solution of the carboxylic acid in sulphuric acid when hydrazoic acid is liberated.

The reaction is closely related to Hofmann and Curtius reactions, all of which involve the formation of isocyanate intermediate through the migration of a group from carbon to nitrogen.

Schmidt reaction also occurs between ketones or aldehydes and hydrazoic acid when ketones give substituted amides and aldehydes give a mixture of nitriles and *N*-formyl derivatives.

$$R_2CO + N_3H \xrightarrow{H_2SO_4} RCONHR + N_2$$

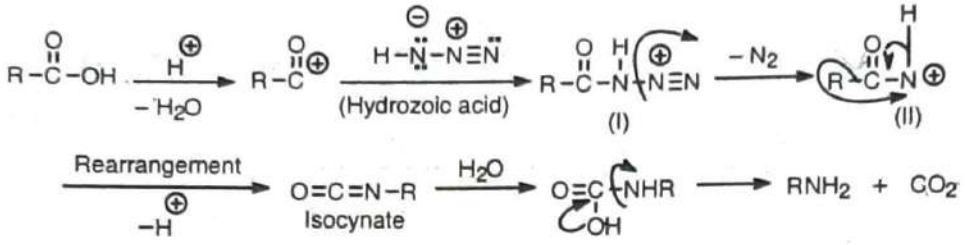
$$RCHO + N_3H \xrightarrow{H_2SO_4} \underset{\text{Nitrile (Major)}}{RCN} \text{ and } \underset{\text{}}{RNHCHO}$$

N-Formyl derivative (Minor)

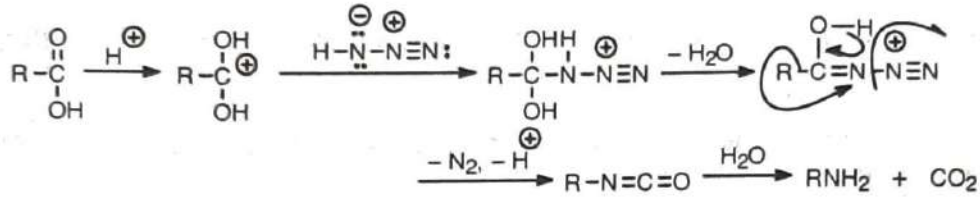
The rearrangements in these cases closely resemble the Beckmann rearrangement. Dialkyl and cyclic ketones react more readily than alkyl aryl ketones. With alkyl aryl ketones, it is the aryl group which migrates.

Mechanism

(a) Acids (i) It was found that the transformation occurs most rapidly without heating with sterically hindered acids (e.g., mesitoic acid) which readily form acyl cations in sulphuric acid. This clue led to suggest the formation of protonated acyl azide (I), in the first step, which eliminates nitrogen to form the intermediate (II). The intermediate (II) then undergoes rearrangement to form isocyanate which is hydrolysed under the reaction conditions to amine and carbon dioxide.

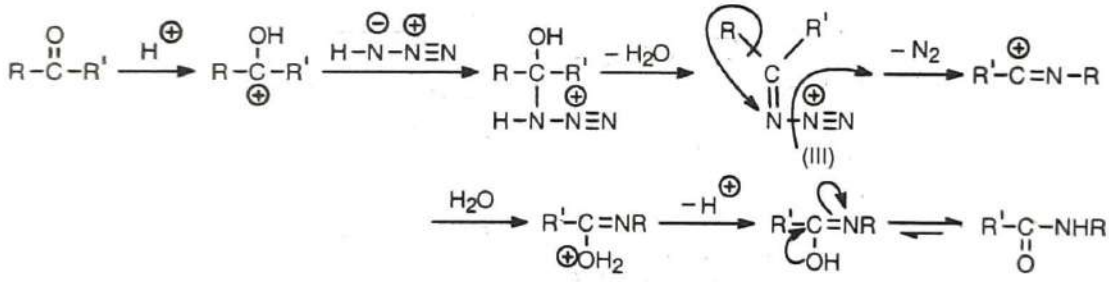


(ii) Acids which do not form acyl cation react through the protonated acid on heating as below.



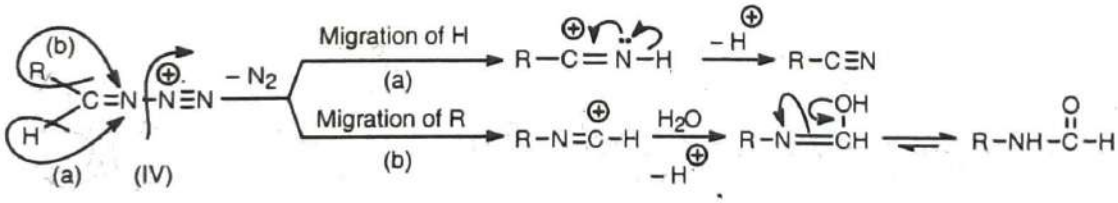
Isocyanate is not isolated under the acid condition although it has been isolated under anhydrous condition. The rearrangement is intramolecular since the migrating group never becomes free. This has been concluded from the crossover experiment and from the fact that the migrating group retains its configuration.

(b) Carbonyl compounds The mechanism for the reaction with ketones was suggested by Schmidt. The reaction proceeds through the protonated carbonyl compound.



Steps from (III) onwards resemble Beckmann rearrangement.

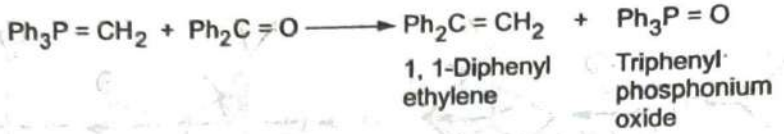
In the case of aldehyde the intermediate (III) will have the structure (IV) in which migration of H will give nitrile and migration of R will give formyl derivative.



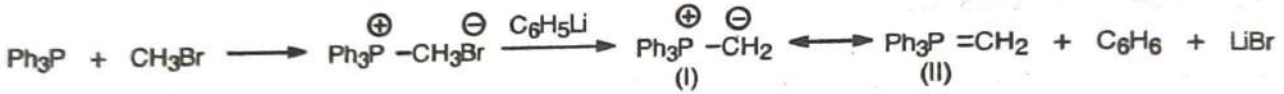
Sulphuric acid is the most common catalyst for Schmidt reaction but Lewis acids have also been used.

WITTIG REACTION

Wittig reacton affords an important and useful method for the synthesis of alkenes by the treatment of aldehydes or ketones with alkylidenetriphenylphosphorane ($Ph_3P{=}CR_2$) or simply known as phosphorane.



The Wittig reagent, alkylidenetriphenylphosphorane, is prepared by treating trialkyl or triarylphosphine usually the latter with an alkyl halide in ether solution. The resulting phosphonium salt is treated with a strong base (such as C_6H_5Li, BuLi, $NaNH_2$, NaH, C_2H_5ONa, etc.) which removes a halacid to give the reagent, methylenetriphenyl phosphorane (II).

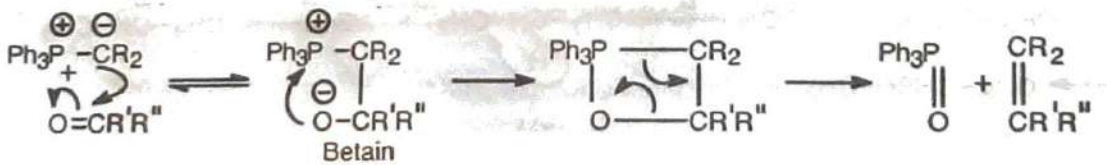


In the alkyl halide a hydrogen is necessary on the halogen-bearing carbon. Alkylidenetriphenylphosphoranes are also called ylids due to the presence of opposite formal charges on adjacent atoms as in one of the resonance structures (I). The methylene structure (II) has a $d\pi$-$p\pi$ bond between phosphorus and carbon. The ylid may be considered as a carbanion stabilized by the adjacent phosphonium cation.

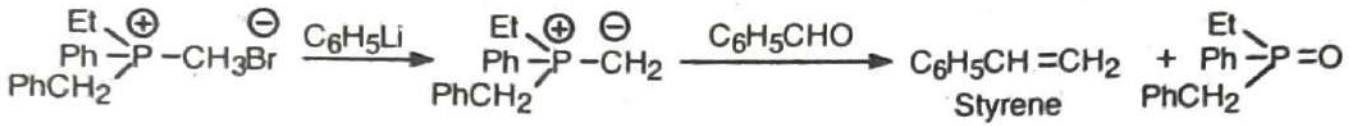
The carbonyl compound is directly treated with the ethereal solution of the reagent.

Mechanism

The reaction probably proceeds by the nucleophilic attack of the ylid on the carbonyl carbon. The dipolar complex (betain) so formed decomposes to olefine and triphenylphosphine oxide via a four-centred transition state.

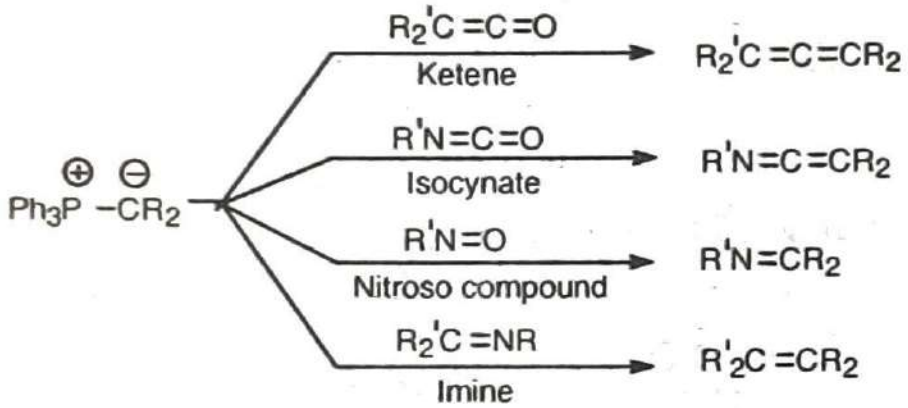


The mechanism is supported by the fact that an optically active phosphonium salt reacts to produce a phosphine oxide with retention of configuration.



Since desired alkyl groups can be introduced in the alkyl halide and the carbonyl compound, it is extremely useful for the synthesis of desired substituted alkenes. Double or triple bonds even when conjugated with the carbonyl group $\left(\diagup C{=}O\right)$ does not interfere. The reaction with the carbonyl group of esters is very slow and does not interfere.

Phosphorous ylids react in the same manner with the C=O groups of ketenes and isocyanates as also with the N=O and C=N groups of nitroso and imine compounds respectively.



WOLFF–KISHNER REDUCTION

Wolff–Kishner reduction involves the conversion of carbonyl groups of aldehydes and ketones to methylene groups by heating their hydrozones, semicarbazones or azines in the presence of strong base such as C_2H_5ONa or NaOH.

$$>C{=}O + H_2NNH_2 \longrightarrow >C{=}NNH_2 \xrightarrow[\Delta]{C_2H_5ONa \text{ or } NaOH} >CH_2 + N_2$$

Thus, ketones and aldehydes can be conveniently reduced to hydrocarbons by this method. Earlier method of heating the hydrozones of carbonyl compounds with C_2H_5ONa at 180°C in an autoclave has since been modified. In the modified procedure, hydrazine hydrate and the carbonyl compound are heated with KOH or NaOH in ethylene glycol for several hours. The water formed escapes and the temperature rises to 200°C when the hydrazone decomposes with the formation of hydrocarbon with evolution of nitrogen.

$$R_2C{=}O + H_2NNH_2 \longrightarrow R_2C{=}N{\cdot}NH_2 \xrightarrow[\Delta]{C_2H_5ONa,\ Glycol} R_2CH_2 + N_2$$

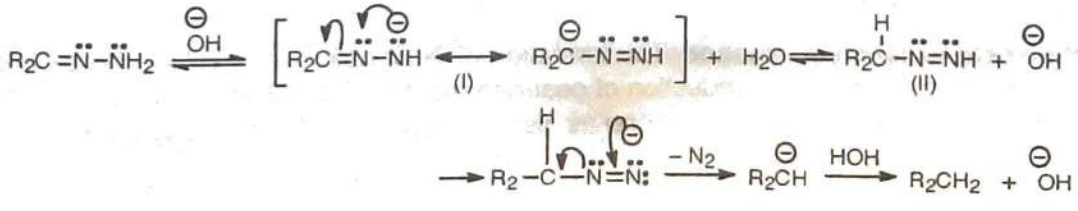
In a further modification, the reduction can be carried out at room temperature by using dimethyl sulphoxide as solvent and potassium tertiary butoxide as base. The yield is excellent. Thus, benzophenone gives diphenyl methane in high yield.

$$(C_6H_5)_2C{=}O \xrightarrow{H_2N{\cdot}NH_2} (C_6H_5)_2C{=}N{\cdot}NH_2 \xrightarrow[Me_2SO,\ 30°C]{Me_3COK,} \underset{\text{Diphenyl methane}}{C_6H_5{\cdot}CH_2{-}C_6H_5} + N_2$$

Unlike Clemmensen reduction, the reaction does not fail with acid-sensitive or high molecular weight substrates.

Mechanism

First step involves the formation of the anion of the hydrazone (I) which is protonated at the carbonyl carbon to form a substituted diimine (II). This is followed by simultaneous loss of nitrogen and formation of hydrocarbon. (Compounds of the type (II) are unstable and decompose to hydrocarbon and nitrogen probably through carbanion or free radical mechanism.)



During the course of reduction, semicarbazones and azines are first converted to hydrazones before reduction.

$$\underset{\text{Semicarbazone}}{R_2C{=}N{\cdot}NH{\cdot}CO{\cdot}NH_2} + H_2O \longrightarrow R_2C{=}N{\cdot}NH_2$$

$$\underset{\text{Azine}}{R_2C{=}N{-}N{=}CR_2} + 2NH_2{\cdot}NH_2 \longrightarrow 2R_2C{=}N{\cdot}NH_2$$

The method is specific for the reduction of carbonyl groups only, for other functional groups in the substrate remain unaffected. The method is, however, not suitable for α, β-unsaturated ketones.