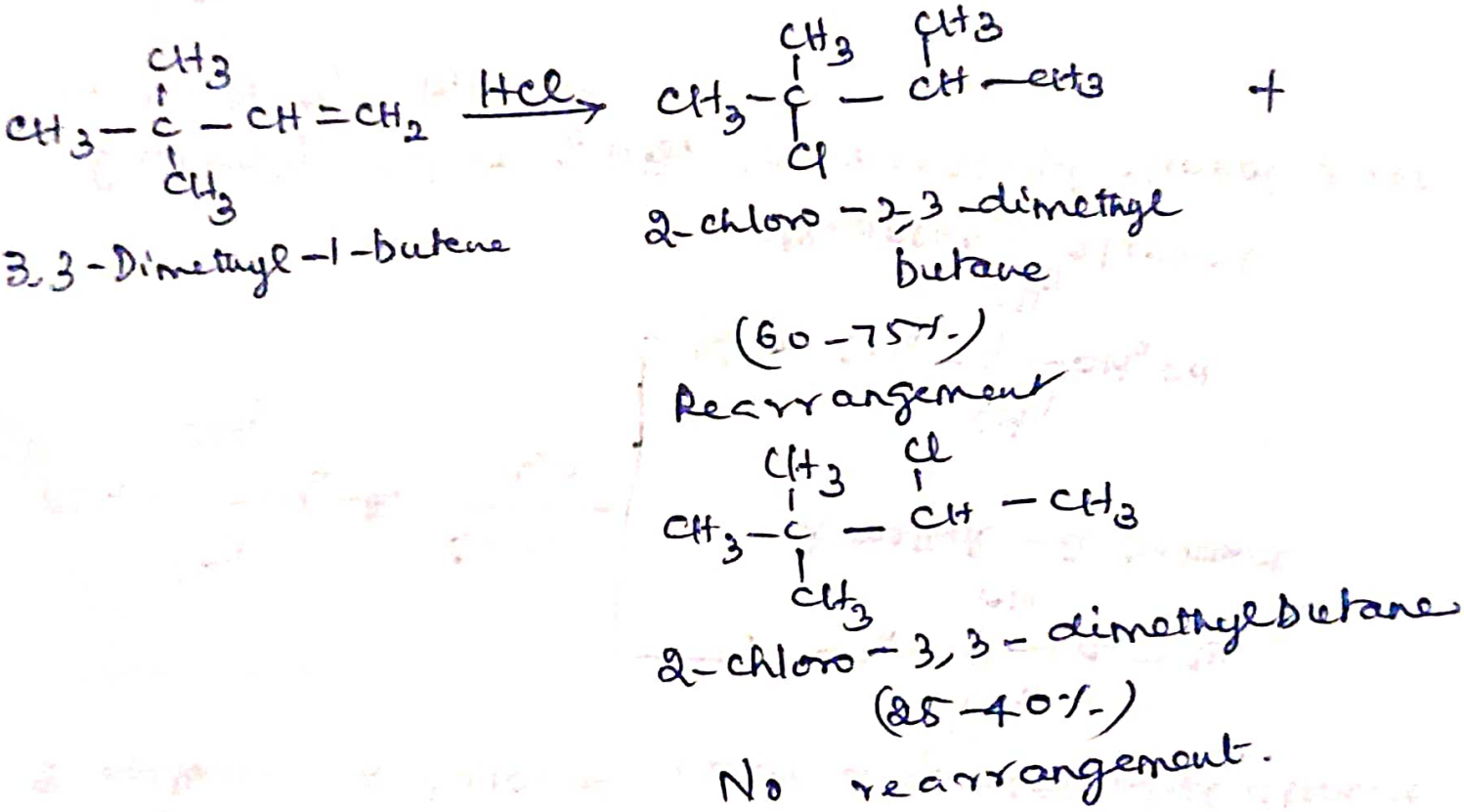
Wagner- Meerwein rearrangement

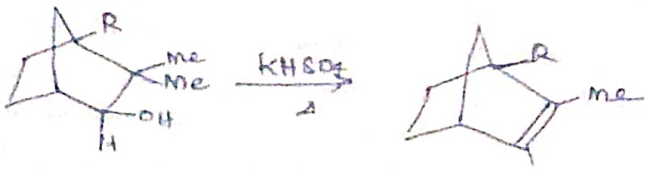
Rearrangements which occur during rxns. involving change in the carbon skeleton thro' rearrangement of carbocations as intermediates → W-M. rearrangement.

For ex,

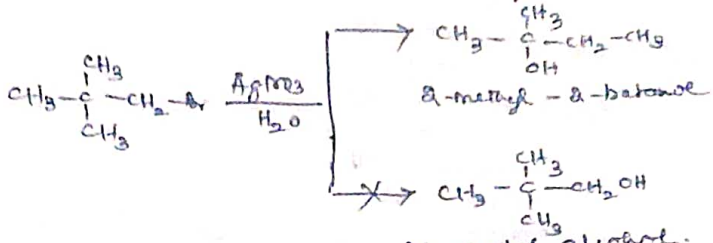


These rearrangements occur via an intermediate carbocation and involve the migration of alkyl group with its pair of e⁻s to an e⁻ deficient carbon atom. In terpenoids, these rearrangements involve a change in ring str or migration of methyl group which involves the migration of methyl group is a spl & case of W-M rearrangement - Nametkin rearrangement. for ex, 3,3-dimethyl [2.2.1] bicyclo heptan-2-ols such as camphenilol or 4-methyl camphenilol

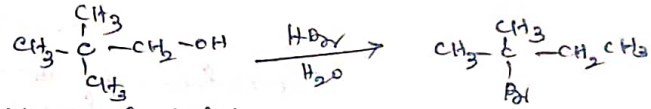
is treated with acid.



Solvolysis of neopentyl bromide or neopentyl alcohol reacts under conditions favouring the S_N1 mode. Solvolysis of neopentyl bromide in water leads to 2-methyl-2-butanol instead of the expected neopentyl alcohol.



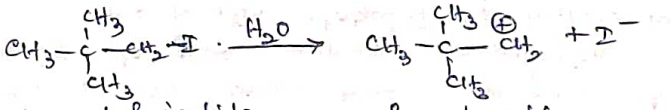
Similarly, action of HBr on neopentyl alcohol gives tert-pentyl bromide



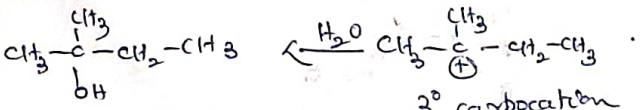
Neopentyl alcohol

Mechanism

N-M rearrangements are very common in rxns involving carbocation as intermediate.



Neopentyl iodide — 1° carbocation



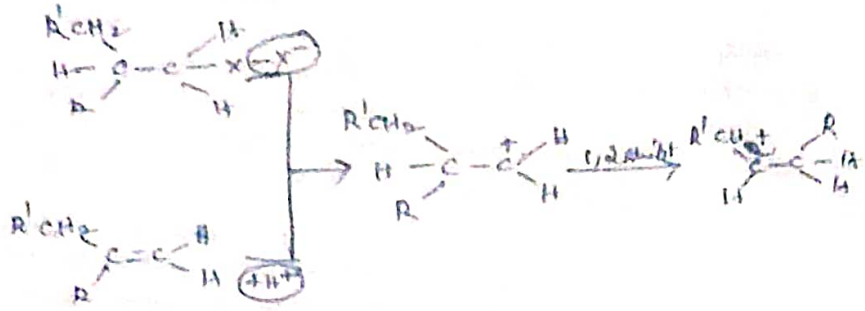
2-methyl-2-butanol — 3° carbocation

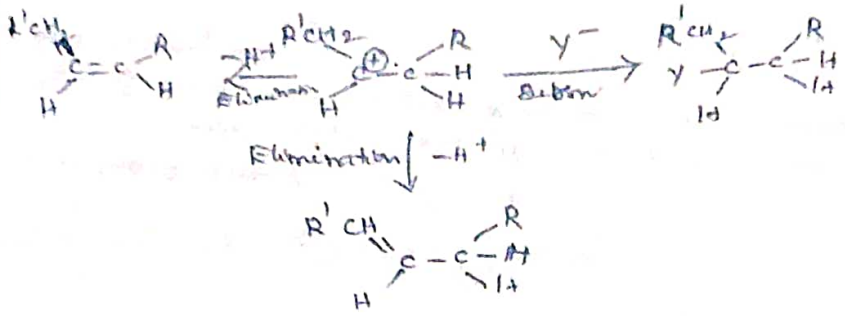
Unstable carbocation formed by the dissociation of C–I bond, rearranges to a much more stable tert. carbocation.

Step I: Generation of a carbocation, formed in the rxns where loss of a leaving group occurs. ex, loss of a water molecule from protonated alcohols, N_2 from aliphatic diazonium ions or halide ion from alkyl halides.

Step II: Shift of a group along with the pair of e^-s, occurs from one carbon atom to the adjacent cationic carbon atom.

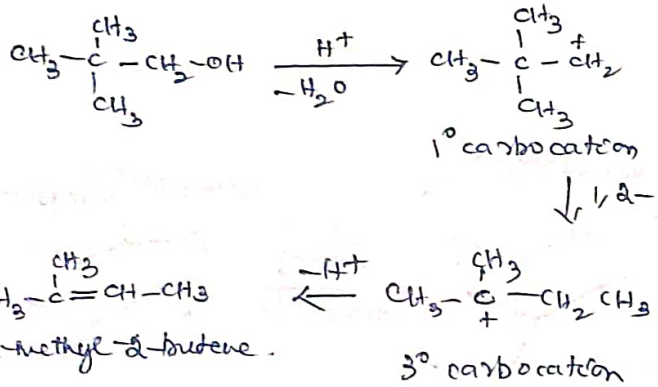
The resulting rearranged carbocation either combines with a nucleophile or loses proton to give alkene.





When neopentyl alcohol is heated with H_2SO_4, water is eliminated and neopentyl carbocation is formed. This carbocation undergoes 1/2 methyl shift to give tertiary carbocation.

The greater stability of tert. carbocation than pri. carbocation is the driving force for the shift of $-CH_3$ gp. Loss of proton from tert. carbocation results in 2-methyl-2-butene.



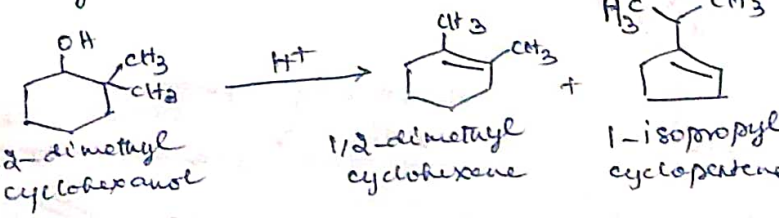
1° carbocation

1/2-CH_3 shift

2-methyl-2-butene.

3° carbocation

In alicyclic cpds, W-M. rearrangement leads to expansion or contraction of cycloalkane ring. In the dehydration of the cyclic sec. alcohol 2,2-dimethyl cyclohexanol in presence of acid leads to a mix. of 1,2-dimethyl cyclohexene and 1-isopropyl cyclopentene. In the alicyclic systems, the relieve of strain is the driving force for the rearrangement.



2,2-dimethyl cyclohexanol

1,2-dimethyl cyclohexene

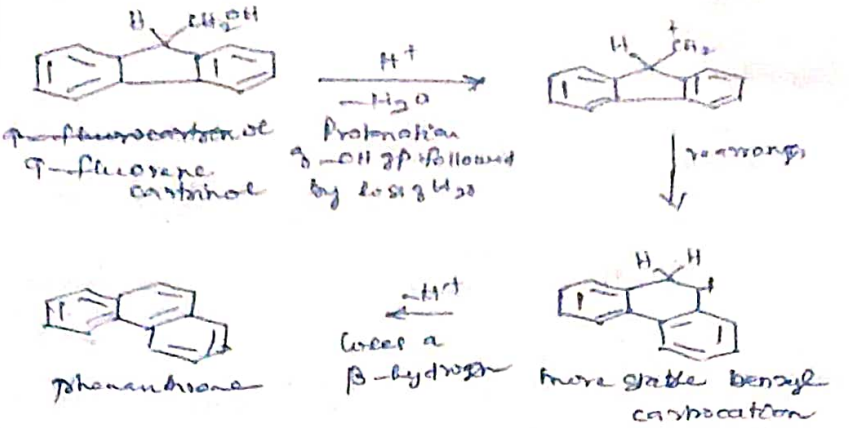
1-isopropyl cyclopentene.

Aryl groups have a far greater migratory aptitude than alkyl groups or hydrogen.

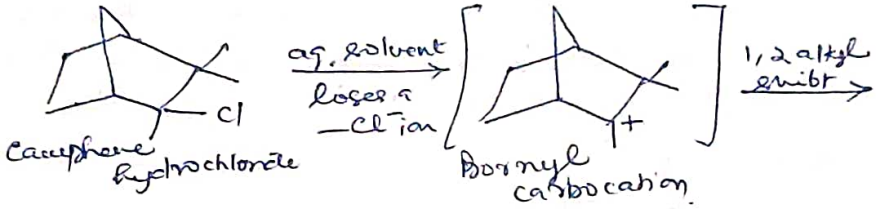
Electron releasing gp in the aryl gp increases the rate of migration while e⁻-withdrawing gp decreases the rate of migration.

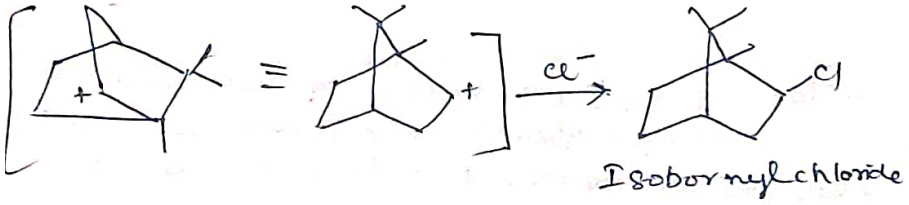
Applications

1. Conversion of 9-fluorenylcarbinol into phenanthrene.

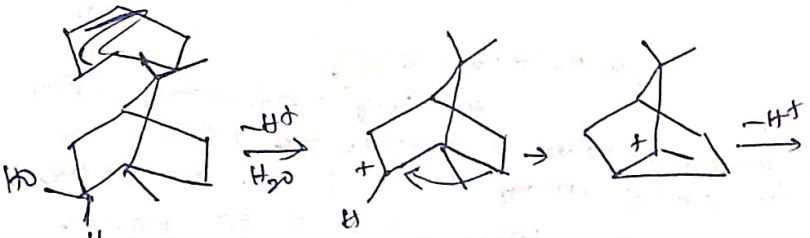


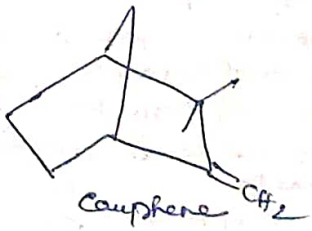
2. Camphene in terpenes.



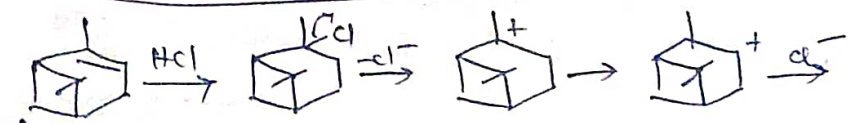


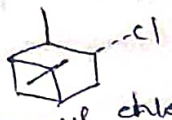
3. Dehydration of isoborneol to camphene





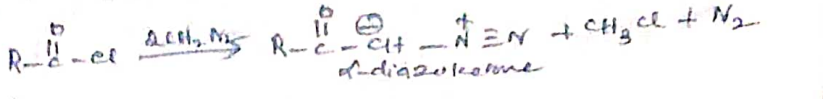
4. Bornyl chloride to α-pinene

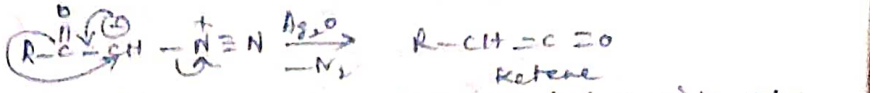




Wolff rearrangement

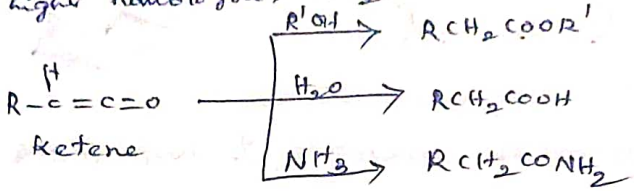
α-diazoketones undergo rearrangement with elimination of very stable N_2 molecule in presence of Ag_2O to form a ketone.





Ketene

Wolff rearrangement generates ketene in the absence of any nucleophile, and therefore it can be isolated as this rxn. When this rearrangement is carried out in the presence of H_2O, alcohol or amine, the ketene is converted into carboxylic acid, ester or amide. The overall rxn is called Arndt-Eistert synthesis. This is useful for converting an acid RCOOH into its higher homologue, RCH_2COOH



Wolff rearrangement can be brought about either thermally or by photolysis. Generally, thermal rxn is carried out in the presence of Ag_2O.

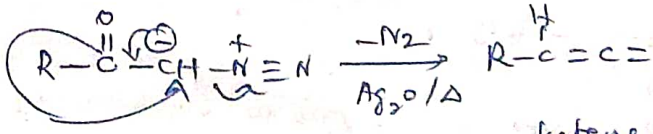
Mechanism

Loss of N_2 from the α-diazoketone is accompanied by 1,2 shift of the alkyl gp with e⁻ pair. The resulting ketene readily combines with the solvent molecule, with H_2O → acid, alcohol → ester, RNH_2 to give amide.

When rxn is brought about by photolysis, the Wolff rearrangement is believed to involve formn of a carbene. The migration of a group (alkyl or aryl) with its pair of e⁻s to e⁻ deficient carbon of carbene gives the ketene. The ketene then reacts with solvent to give the final pdt.

Ketene

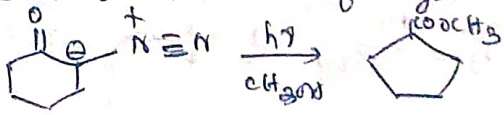
When rearrangement is carried out thermally in presence of Ag_2O, a concerted migration of alkyl group and expulsion of N_2 is involved and there is no clear evidence that carbene is formed as an intermediate.

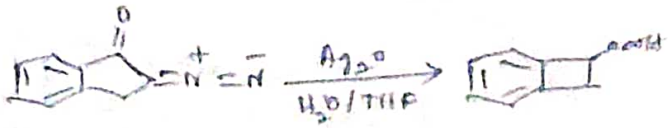


α-diazoketone

Ketene

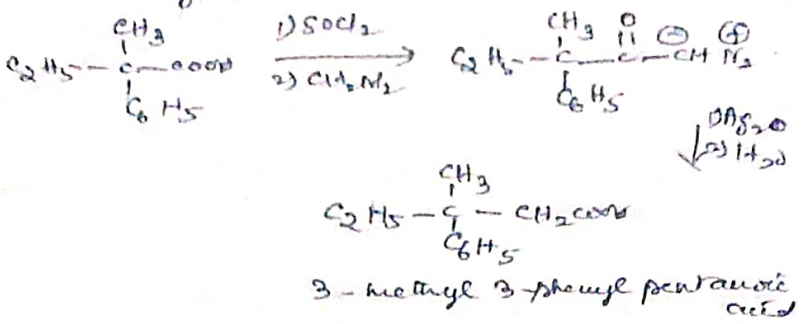
With cyclic α-diazoketones, the rearrangement leads to contraction of rings.





Application

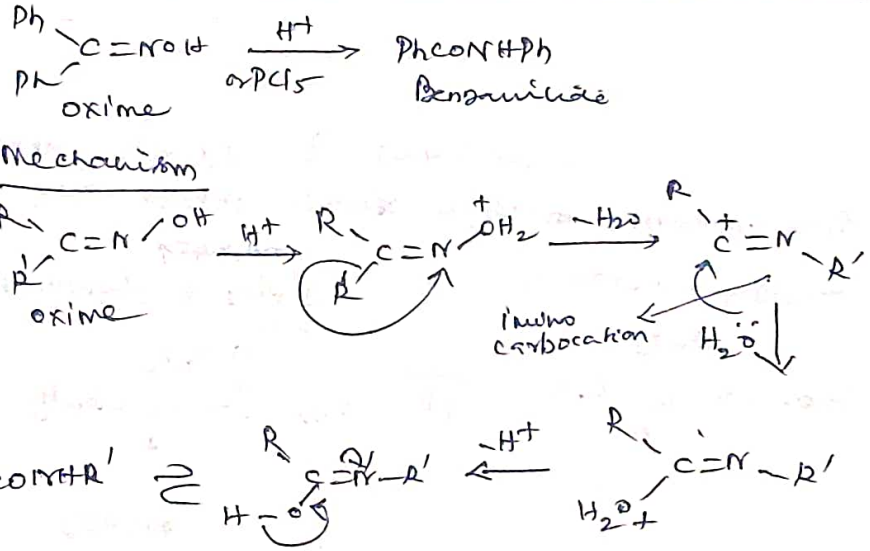
Wolff rearrangement is involved in an important method for converting an acid into its next higher homologue.



Beckmann rearrangement

Rearrangement of oximes under the influence of a variety of acidic reagents to N-substituted amides is called Beckmann rearrangement. PCl_5 is commonly used as a catalyst. But Conc. H_2SO_4, polyphosphonic acid, formic acid, $SOCl_2$ have been used.

Rearrangement of benzophenone oxime to benzanilide in the presence of PCl_5



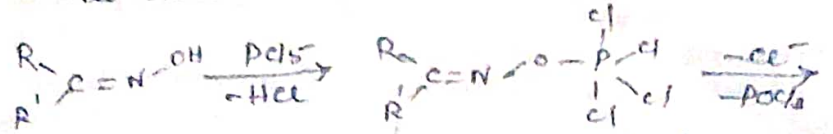
Mechanism

Treatment of oxime with acid generates a good leaving group on the nitrogen atom. Loss of the leaving group generates an e^- deficient species, which is accompanied by migration of a group from adjacent carbon to the e^- deficient nitrogen.

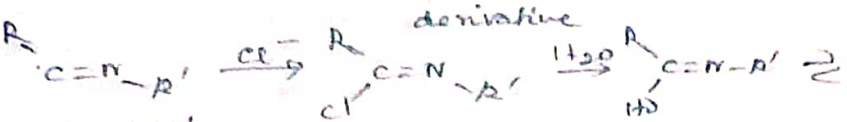
The resulting imino carbocation traps H_2O to give an amide on the final part. The driving force for the 1, 2-alkyl shift is the formn. of more stable carbocation.

When migrating group is aryl, the e^- withdrawing gps on the migrating group strongly retard rearrangement and e^- donating gps. strongly accelerate it.

When PCl_5 is used to effect rearrangement, a tetrachloro phosphoryl derivative is first produced which undergoes rearrangement with cleavage to $POCl_3$ and Cl^- ion. The Cl^- ion unites with imino carbonium cation to form the imidoyl chloride which reacts with H_2O to yield amide



tetrachloro phosphoryl derivative

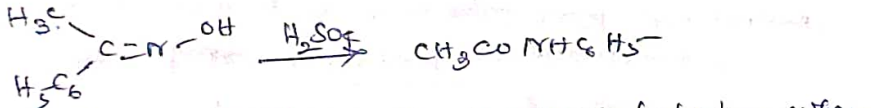


(+) methyl-3-heptyl ketoxime

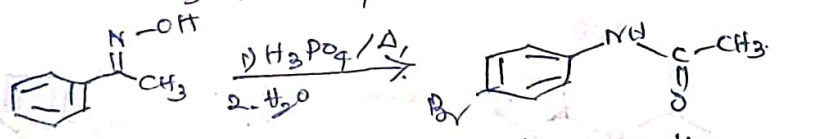
3-acetamidoheptane

Here chiral groups migrate intramolecularly with retention of configuration

The rearrangement is highly stereospecific, gp anti to the oxime -OH gp always migrates, regardless of relative migratory aptitude to the R gpp. In acetophenone oxime, it is the phenyl group which migrates and thus the product formed is acetanilide.



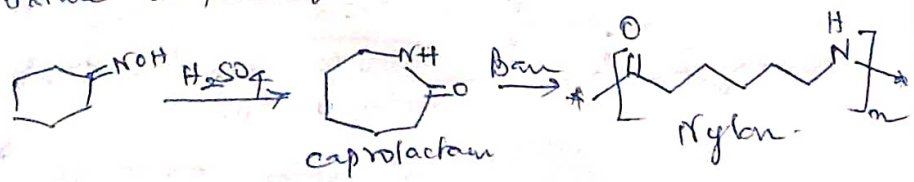
Ie, anti-H-bromophenyl methyl ketoxime when treated with H_3PO_4 gives p-bromoacetanilide.



Beckmann rearrangement involves the concerted stereoselective migration of the alkyl gp or aryl group anti to -OH group in the starting material.

Applications

1. Synthesis of caprolactam from cyclohexanone oxime in pres. of Conc. H_2SO_4.

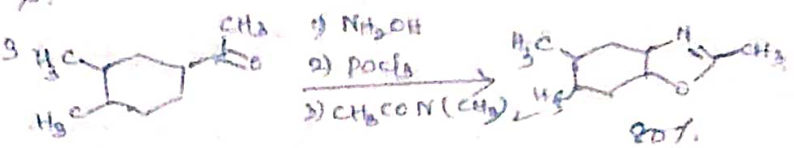


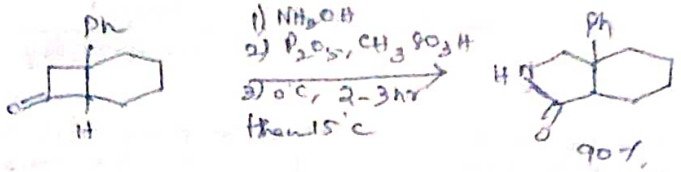
caprolactam

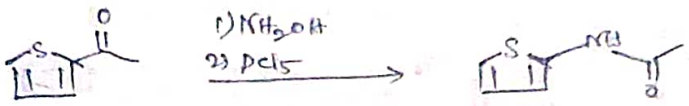
Nylon-

2. It establishes the stereochemistry of the oxime as it occurs by migration of a group anti to the oxime hydroxyl

3.

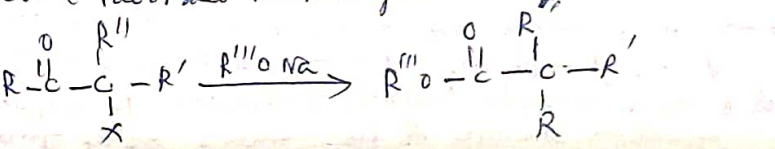




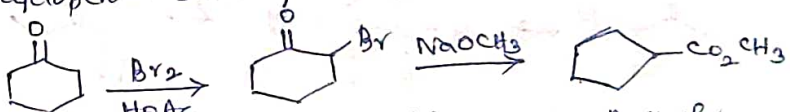


Favorskii rearrangement

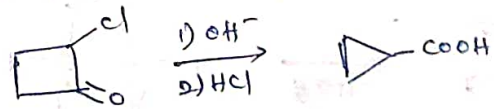
The base-catalysed rearrangement of α-haloketones to carboxylic acid derivatives is called Favorskii rearrangement.



The rearrangement of cyclic ketones involves ring contraction. 2-bromocyclohexanone when treated with CH_3ONa is converted into methyl ester of cyclopentanecarboxylic acid.



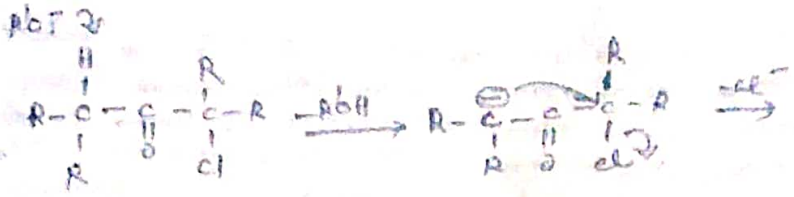
2-chlorocyclobutanone on treatment with CH_3ONa, followed by hydrolysis is converted to cyclopropanecarboxylic acid.



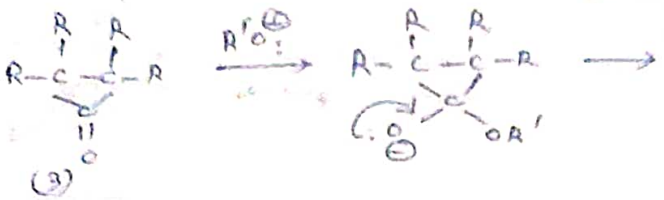
Mechanism

Generally accepted mechanism involves the reactive cyclopropanone intermediate.

Base abstracts the α-hydrogen from (1) to give the carbanion (2), which undergoes intramolecular S_N2 displacement of the halide ion. The resulting cyclopropanone intermediate (3) is opened under the reaction conditions to give more stable carbanion (4), which takes proton from solvent to furnish final product, ester (5).



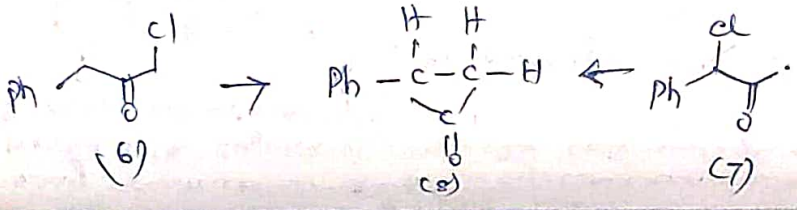
(1) (2)



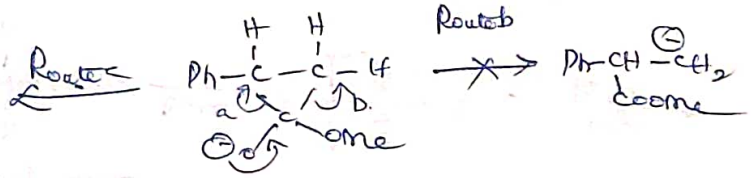
(3)

(4) (5)

The above mechanism is supported by the fact that same ester (10) is formed from the isomeric haloketones (6) and (7).



(6) (8) (7)



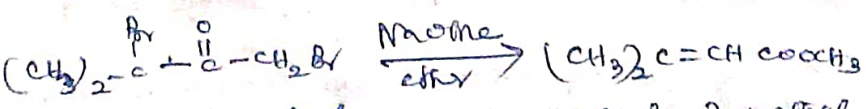
$Ph\overset{\ominus}{C}HCH_2COOMe$

(9)

$PhCH_2CH_2COOMe$

(10)

Favorskii rearrangement of α,α' and α,α dihaloketones leads to the formn. of α,β unsatd esters. In this case, ring opening involves elimination of halide ion.



1,3-dibromo 3-methyl butan-2-one

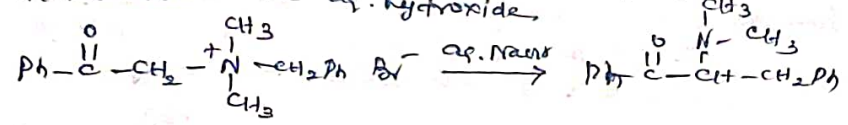
Methyl-3-methyl crotonate

Stevens rearrangement

A quartenary ammn. salt in which none of the alkyl gp's is having a β hydrogen atom, but one of the alkyl gp is has an e^- withdrawing gp β to the nitrogen atom, undergoes base catalysed rearrangement to yield a tertiary amine.

Rearrangement involves migration of a group, without pair of e's, from nitrogen to carbon having -ve charge

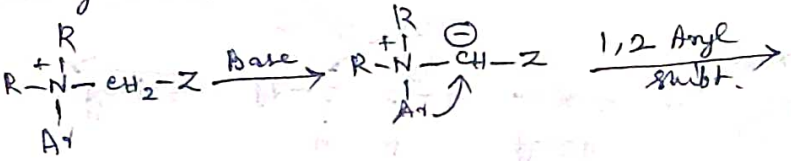
For ex, phenacyl benzyldimethylammonium bromide gives α-dimethylamino β-phenyl propiophenone on treatment with aq. hydroxide.

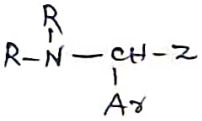


Mechanism

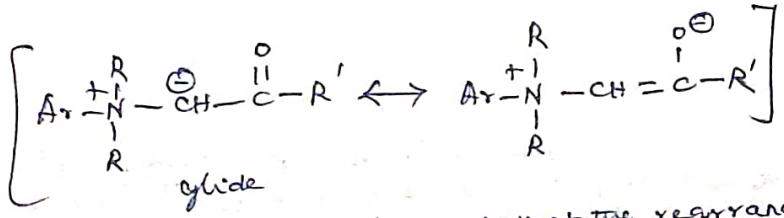
crossover expts showed the mechanism of Stevens rearrangement to be intramolecular.

The base abstracts the hydrogen from the ammn. salt to give the ylide, which rearranges to give the tertiary amine.



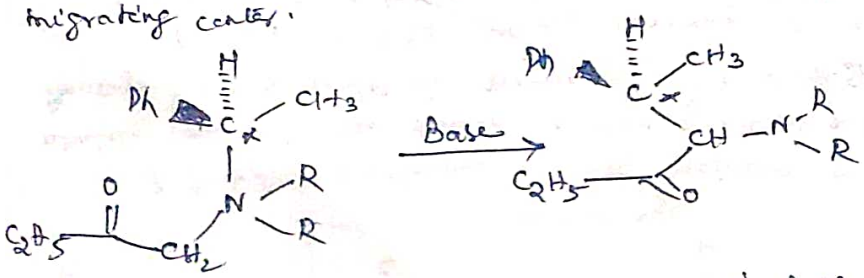


The role of e^--withdrawing gp, such as a carbonyl group, is to stabilise the ylide.



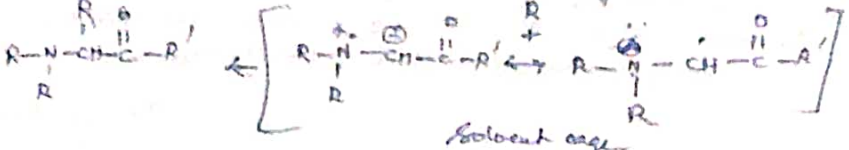
ylide

It was further observed that the rearrangement occurs with retention of absolute stereochemistry at the migrating center.



The radical pair mechanism involves deprotonation followed by homolytic fragmentation of ylide to produce a pair of radicals. The rapid recombination of pair of radicals, which remain together in a tight solvent ~~cage~~ cage, gives the final pdt. Formn. of small amt of coupling product R–R supports this mechanism

Ylide



Solvent cage

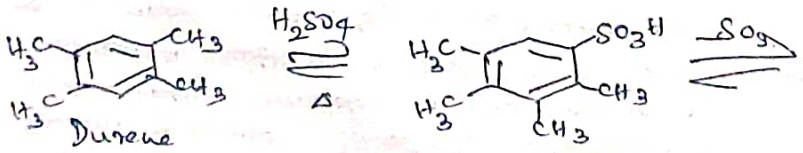
A third mechanism is also proposed, in which ion pairs are formed instead of radical pairs. Benzyl group migrates in preference to the alkyl gp.

A variant of the Stevens rearrangement is the rearrangement of sulphur ylides. For ex, sulphonium salt on deprotonation gives a sulphur ylide, which subsequently rearranges. Quartenary salts having β-hydrogen atom undergo elimination on the base to give alkene and tertiary amine.

Jacobsen rearrangement

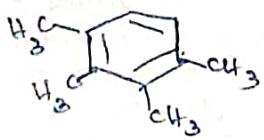
Alkyl gps attached to benzene ring can be migrated from one position to another. Migration of alkyl gp from one position to another in polyalkyl benzenes during sulphonation is known as Jacobsen rearrangement.

Durene on sulphonation yields a product prehnitenesulphonic acid, in which $-CH_3$ gp has migrated. Desulphonation of prehnitenesulphonic acid yields the hydrocarbon, prehnitene in 41% yield. The Jacobsen rearrangement followed by desulphonation sequence can be used as a means of rearranging polyalkylbenzenes.



Durene

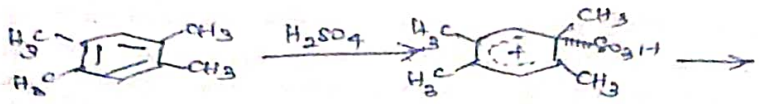
prehnitenesulphonic acid



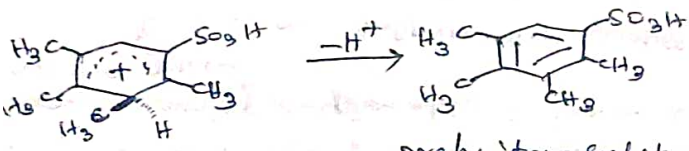
prehnitene

The mechanism involves ipso-sulphonation, followed by intramolecular migration of $-CH_3$ gp without pair of e⁻s to give most stable arenium ion. In the last step - H^+ is lost to regenerate the aromatic ring. The reaction is intramolecular, however, sulphonation of durene gives some trimethyl and pentamethyl benzene sulphonic acids.

formation of these products can be explained by the fact that methyl group migrates from one nucleus to another. Since the mechanism is undoubtedly intramolecular, the cross migration involves a shift of methyl from a benzenonium ion to another nucleus by an S_Ni^2 mechanism.



Durene

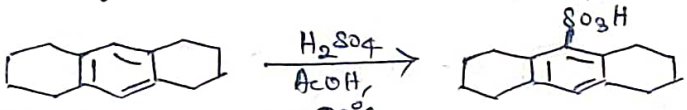


Stable arenium ion

prehnitenesulphonic acid

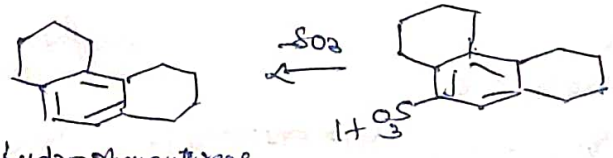
Applications

1) Imp. application is the isomerisation of octahydroanthracene to octahydrophenanthrene.



octahydroanthracene

octahydroanthracene-9-sulphonic acid.



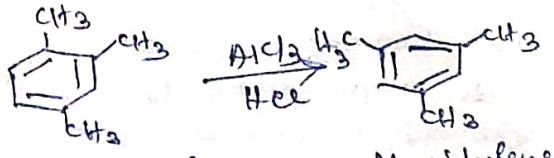
octahydrophenanthrene

2)

p-xylene

m-xylene.

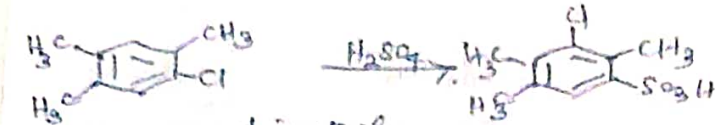
3)



1,2,4 trimethyl benzene

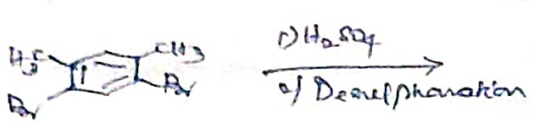
Mesitylene

4. Halogenated polyalkyl benzenes undergo isomerisation during sulphonation due to the migration of halogen atom. This rearrangement is also known as Jacobsen rearrangement.



5-chloro-1,2,4-trimethyl benzene

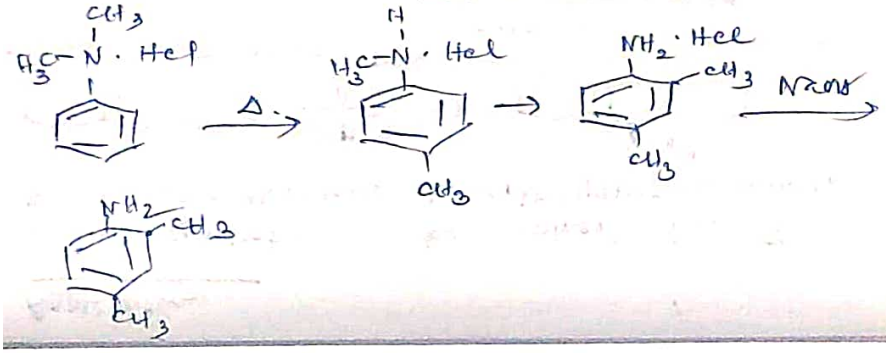
3-chloro-2,4,5-trimethyl benzene sulphonic acid



4,6-dibromo-m-xylene

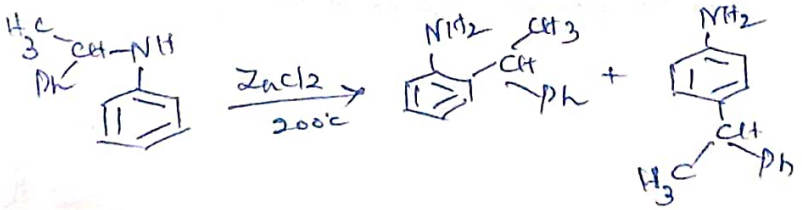
2,4-dibromo-m-xylene.

Hofmann-Martius rearrangement



Hofmann 44 & 933.

Thermal conv. of N-alkyl or N,N'-dialkyl aniline hydrochlorides to ortho and para alkylanilines via the intermolecular migration of alkyl groups. When N,N'-dimethylaniline hydrochloride is strongly heated, one methyl group migrates preferentially to the para position of the ring. The N-methylaniline hydrochloride so produced then undergoes migration of the remaining $-CH_3$ gp to the ortho position, since the para position has been blocked. The rxn is known Hofmann-Martius rearrangement & used for the prepn. of homologues of aniline.

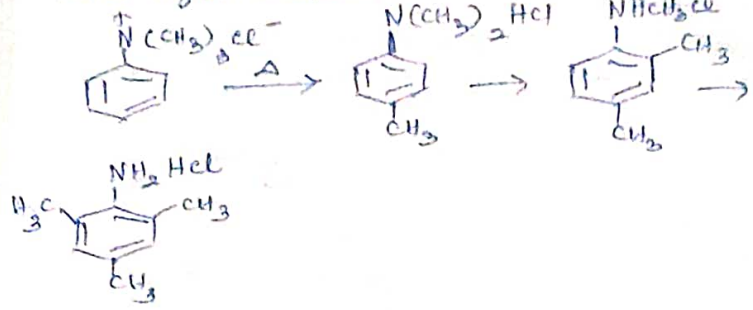


Mechanism

The mechanism of this rearrangement is intermolecular, and involves the formn. of RX by the S_N2 rxn. of mono N-alkylaniline salt with the Cl^-. Alkyl halide and aniline then undergo normal Friedel-Crafts alkylation process. However, with sec or tert. alkyl gp, the rxn. proceeds through the carbocations. give rearranged pdts

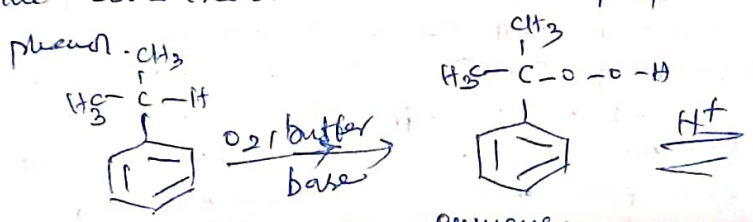
Applications

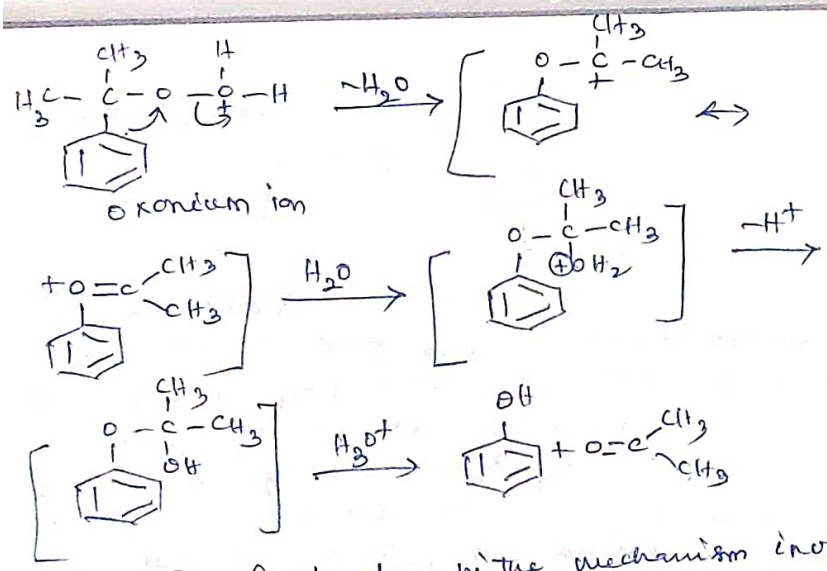
Phenyl trimethyl ammonium chloride when heated under pr. is converted to 2,4,6 trimethylaniline as its hydrochloride.



Hydroperoxide rearrangement

Cumene hydroperoxide when treated with H_2SO_4 gives hemiacetal. Hydrolysis of unstable hemiacetal gives phenol and acetone. The cumene hydroperoxide can be obtained by autooxidation of cumene. This is the commercial method for the preparation of phenol.



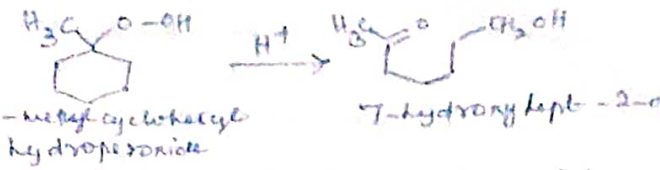


oxonium ion

The first step in the mechanism involves the protonation by acid at the oxygen atom of alkyl hydroperoxide. This is followed by the cleavage of the peroxide bond and migration of alkyl or aryl group from adjacent carbon to oxygen. The migration of phenyl group to the resulting e⁻ deficient oxygen atom is synchronous with the loss of water. The resulting carbocation intermediate is hydrated to give a hemiacetal.

Subsequently, hemiacetal under acidic conditions readily undergo hydrolysis to an alcohol and a carbonyl cpd.

1-methylcyclohexyl hydroperoxide rearranges to give 7-hydroxyhept-2-one.



1-methylcyclohexyl hydroperoxide — 7-hydroxyhept-2-one

Rearrangements in hydroperoxide can be catalysed by strong acids such as H_2SO_4, $HClO_4$ and also by Lewis acids

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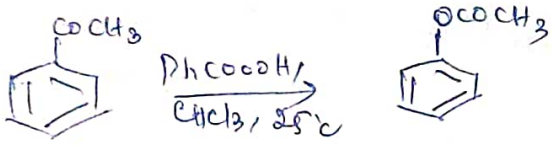
Baeyer–Villiger rearrangement

Oxidn. of ketones to esters with H_2O_2 or with peracids (RCO_3H) is Baeyer–Villiger oxidn. or rearrangement. The rxn can be brought about conveniently by H_2O_2 in weakly basic solns. Typical peracids used are peracetic acid, trifluoroperacetic acid, perbenzoic acid, performic acid and m-chloroperbenzoic acid (m-CPBA)

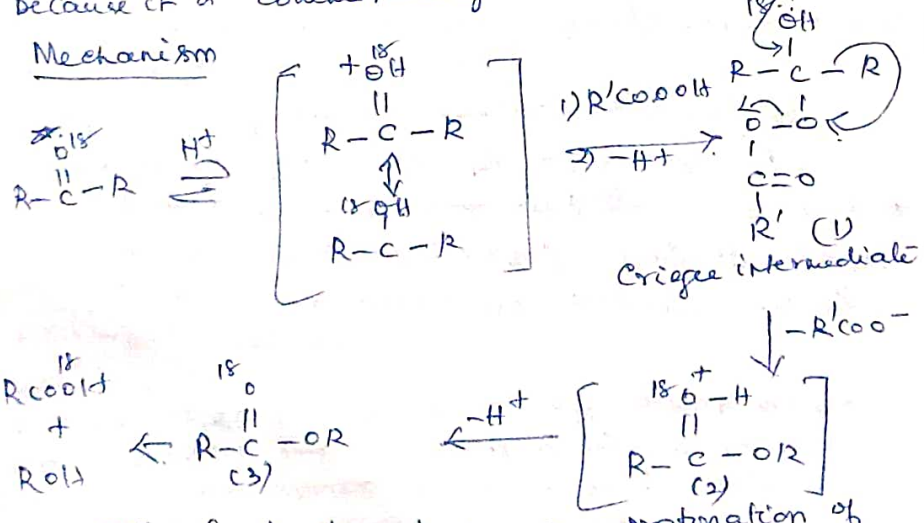


Acetophenone

With caro's acid, the rearrangement step is much faster than with peracetic acid because SO_4^{2-} is a better leaving gp than acetate. Trifluoroperacetic acid is the most efficient reagent for this rearrangement. For instance, cyclohexanone reacts 200 times faster with trifluoroperacetic acid than peracetic acid.

However, m-CPBA is the most common rgt because it is commercially available.

Mechanism



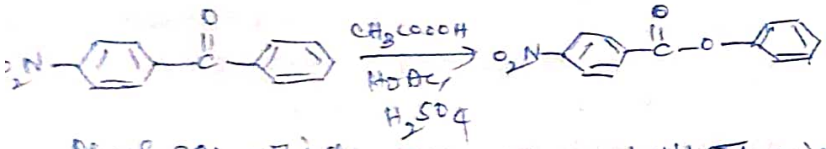
The first step involves the protonation of carbonyl oxygen. The addition of peracid to the initially protonated ketone gives a tetrahedral intermediate (1). Elimination of carboxylate anion and migration of R to the e⁻ deficient oxygen atom occur simultaneously. The resulting protonated form of ester (2)

loses a proton to yield ester(B). Thus, the rxn involves a migration of alkyl or aryl group from adjacent carbon to electrophilic oxygen. As the leaving group, carboxylate anion departs, partial positive charge develops at the oxygen atom and 1,2-alkyl shift from adjacent carbon to oxygen takes place. A mechanistic study using O^{18} labelled ketone has demonstrated that the carbonyl oxygen of the ketone becomes the carbonyl oxygen of the ester and the ester has the same O^{18} content as the ketone.

Migratory aptitude

The order of preference for migration among alkyl gps is $3^\circ > 2^\circ > 1^\circ >$ methyl. Aryl gp migrates in preference to $-CH_3$ and alkyl gps. In the aryl gp, migration is facilitated by e^- releasing para substituents. Migratory aptitude among aryl gps is $p\text{-}CH_3OC_6H_4 > C_6H_5 > p\text{-}O_2NC_6H_4$.

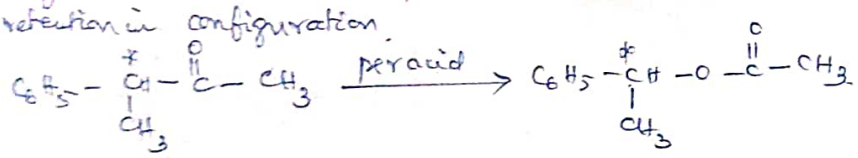
For ex, phenyl p-nitro phenyl ketone yields only phenyl p-nitrobenzene by migration of phenyl gp.



Phenyl gps which are ortho substituted migrate less readily than their para substituted counterparts

Stereochemistry

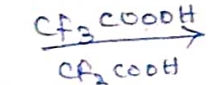
The ketone in which the migrating gp has an asymmetric center gives product / with complete retention in configuration.

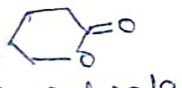


Applications

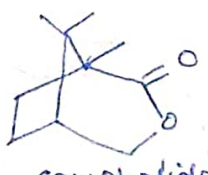
This rearrangement has great synthetic utility as it permits the transformation of ketones into esters. This rxn is applicable to both acyclic ketones and cyclic ketones.

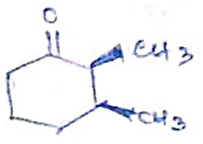

cyclopentanone

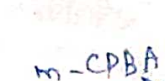


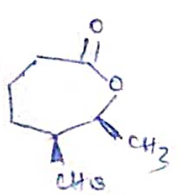

δ-valerolactone

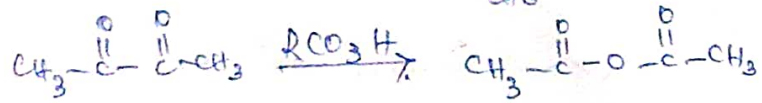

camphor

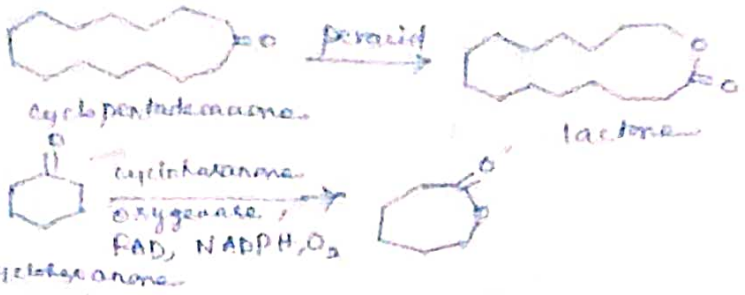

α-camphorlide

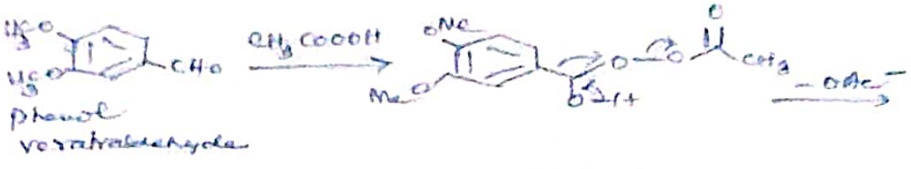


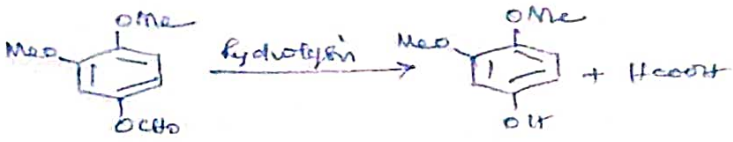




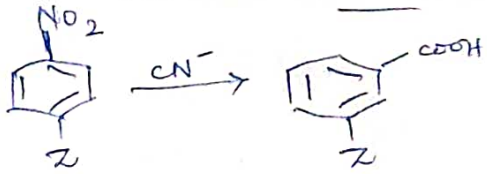






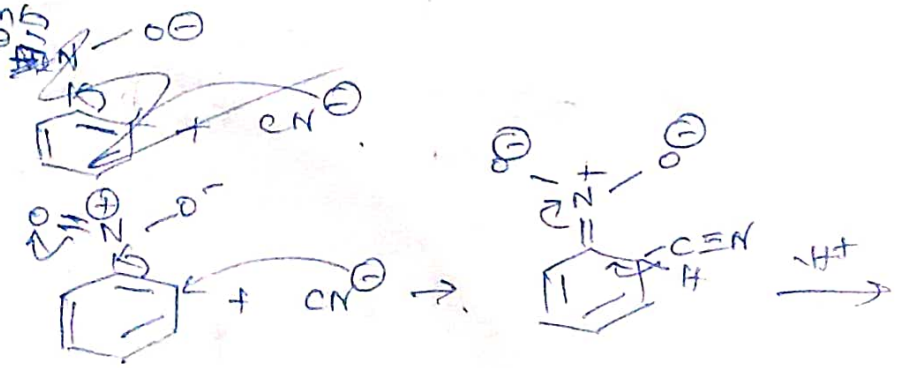


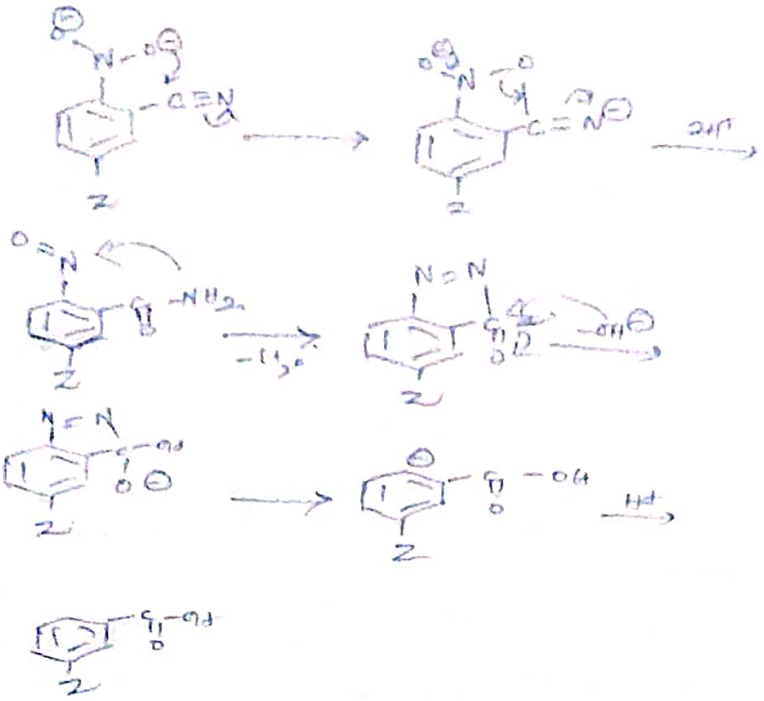
Von-Richter rearrangement



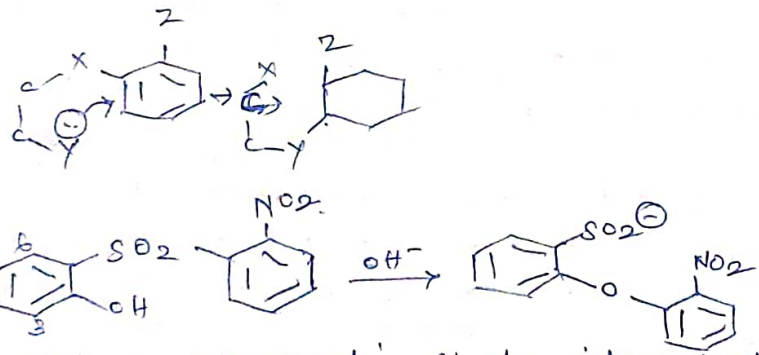
When aromatic nitro cpds are treated with CN^- ion, the nitro gp is displaced and a carboxyl gp enters into ~~ortho~~ cine substitution, always ortho to the displaced group, never meta or para. The rxn gives best results when e^- withdrawing gps are in ortho and para positions, but yields are low.

α-naphthyl cyanide is not hydrolysable to α-naphthoic acid under conditions at which β-nitronaphthalene undergoes the Von-Richter rearrangement to give α-naphthoic acid. This proved that nitrile cannot be an intermediate in this case. It was subsequently demonstrated that elemental nitrogen in the rxn was converted to ammonia, which would be compatible with a nitrile intermediate. Since ammonia is a hydrolysis product of nitriles. Formation of N_2 indicated that nitrogen-nitrogen bond must be formed during the course of the rxn.





Smiles rearrangement

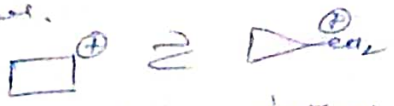


This rearrangement is simply intramolecular nucleophilic substitutions. In the above example, SO_2Ar is the leaving group and ArO^- the nucleophile, and the nitro gp serves to activate its ortho position. The ring at which the subsn takes place is nearly always activated, usually at ortho or para ~~position~~ nitro gps, X is usually S, SO, SO_2, O_2 or CO. Nu is usually the conjugate base of OH, NH_2, NHR or SH.

The rxn. rate is greatly enhanced by subsn in the 6 position of the attacking ring, for steric reasons. For example, a methyl, chloro or bromo group in the 6 position caused the rate to be about 10^7 times faster than when the same groups were in ~~4~~ the position.

Demyanov rearrangement

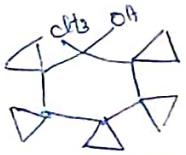
When a positive charge is formed on an alicyclic carbon, migration of an alkyl grp can take place to give ring contraction, producing a ring that is one carbon smaller than the original.



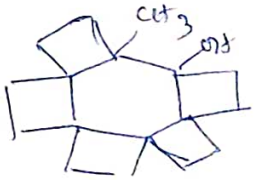
This change involves conversion of a secondary to a primary carbocation, when a positive charge is placed on a carbon α to an alicyclic ring, ring expansion take place. The new carbocation and the old one, may then give prdt by combination with a nucleophile or by elimination. For ex, cyclobutyl amine and cyclopropylmethylamine give similar mixtures of the 2 alcohols.

When the carbocation is formed by diazotisation of an amine, the rxn is called the Demyanov rearrangement.

The expansion rxn has been performed on rings C_3 to C_8, but yields are best with the smaller rings.



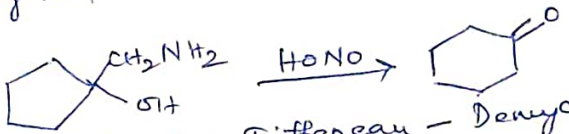
p-toluene sulphonic acid / acetic-H_2O.



16-methyl penta spiro[2.0, 2.0, 2.0, 2.0, 2.1] hexadecan-16-ol.

2-methyl hexacyclo [12.2, 0.0, 0, 0, 0, 0] hexadecan-1-ol

Ring expansion of hydroxyamine.



This rxn is called Tiffeneau – Demyanov ring expansion.