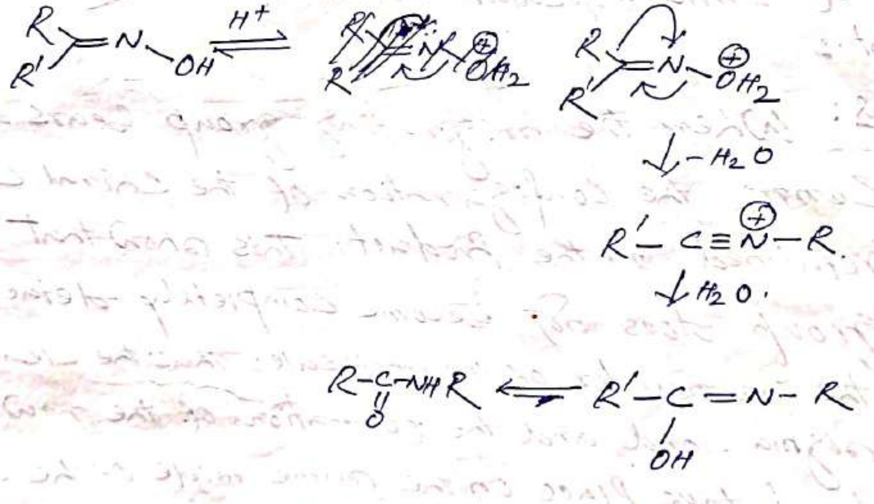
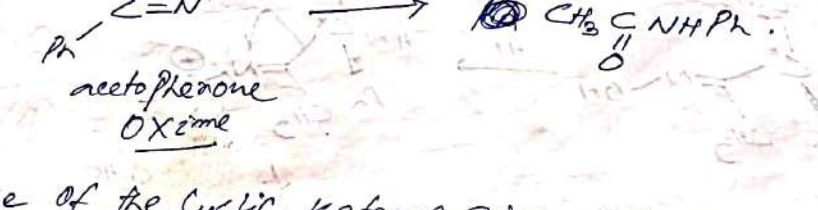
The Beckmann Rearrangement:

Under the influence of a variety of acidic reagents the oximes rearranges to substituted amides, a reaction termed as Beckmann rearrangement. The rearrangement is stereospecific and the group that normally migrates is one that is anti placed with respect to hydroxyl, and this method is often used to determine the configuration of the oxime. Acetophenone oxime gives only acetanilide. The intermediate formation of nitrilium ion has been confirmed by spectral methods. The rearrangement is intramolecular, since if the migration group is chiral it retains its configuration.

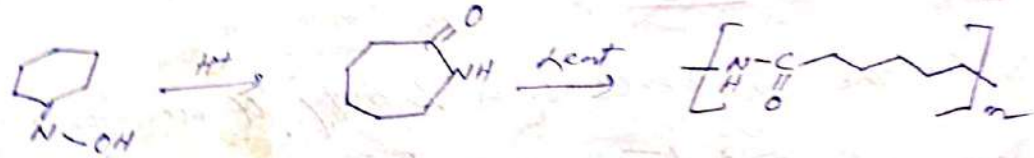
The function of the acidic reagents is to convert the hydroxyl group to a better leaving group.



Thus e.g. with H_2SO_4, this group is converted into $\overset{\oplus}{O}H_2$ and with PCl_5 it is the phosphate which is the leaving group.



The oxime of the cyclic ketones give ring enlargement. Caprolactam gives a polymer of the nylon group when heated.



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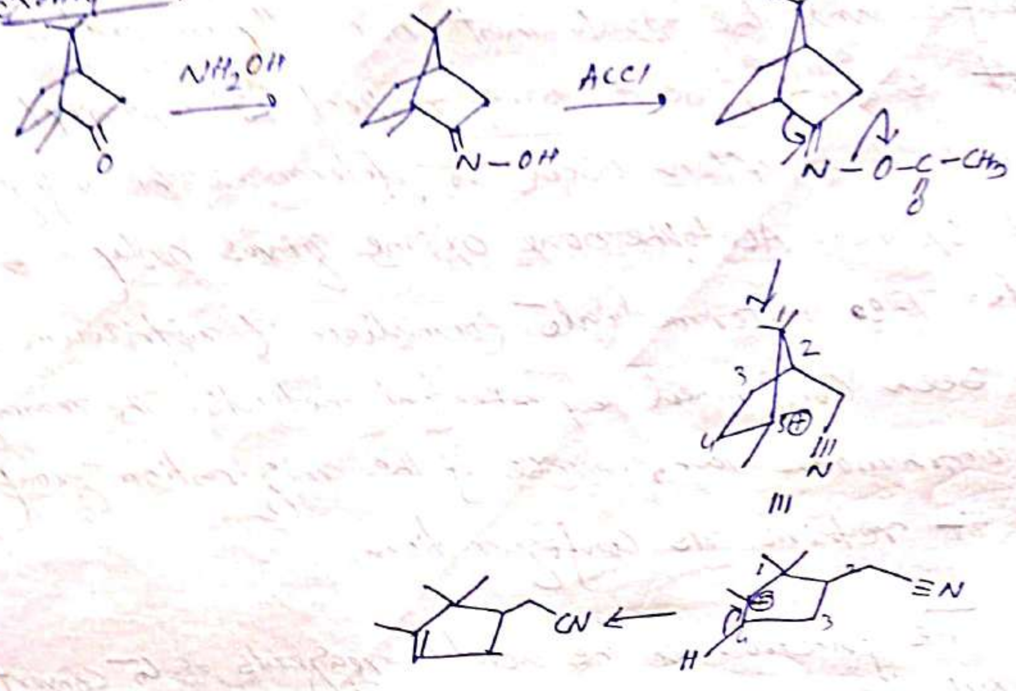
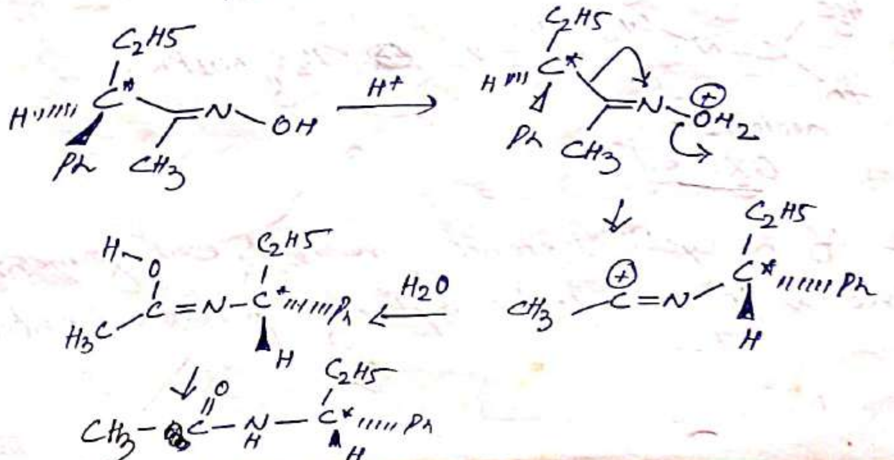
Examples.



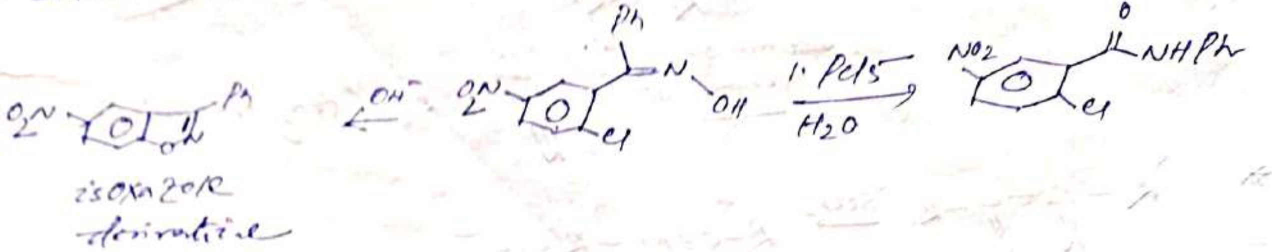
Prove of Intramolecular nature of Beckmann rearrangement:

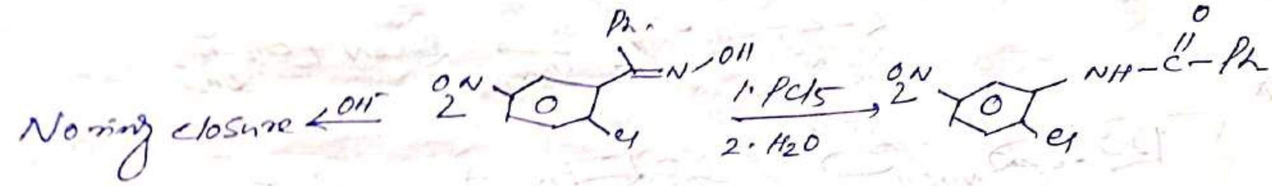
Ans: When the migrating group bears a chiral centre, the configuration of the chiral center is retained in the product. This show that migrating group does not become completely detached from the remainder of the molecule. Thus the cleavage of C-C sigma bond and the formation of the new C-N sigma bond take place on the same side of the chiral carbon in a synchronous manner. Discrete carbanion formation may lead to recemised Product.



Prove of anti migration:

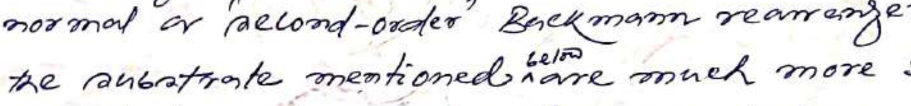
Migration group in this rearrangement approaches the nitrogen atom from the side opposite to the departing oxygen atom. Ring closer experiment confirms the configuration of Ketoxime as shown below:





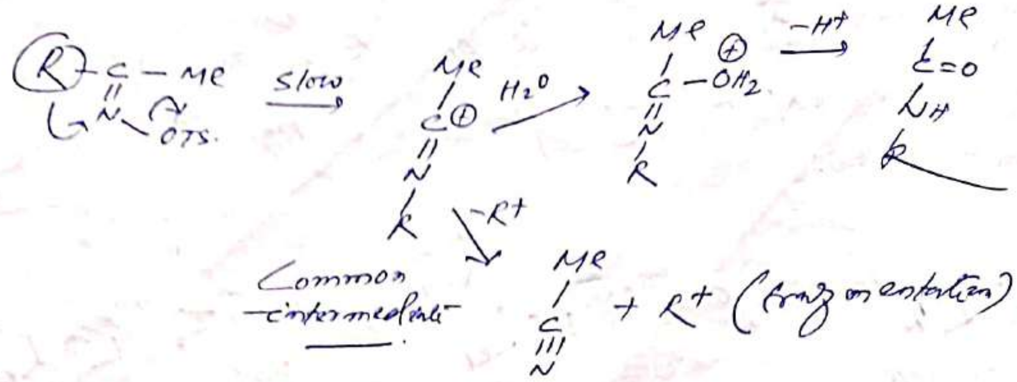
Abnormal Beckmann rearrangement:

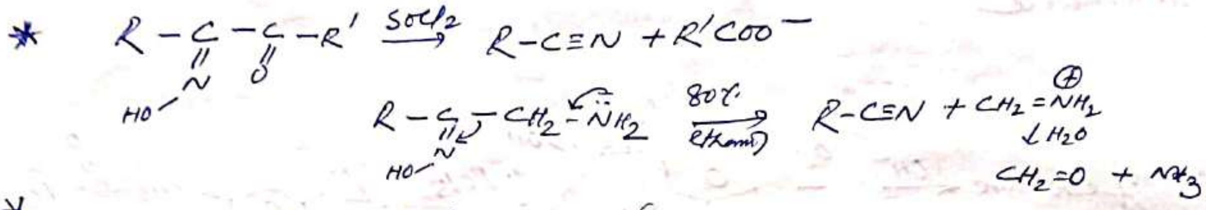
The reaction that normally occurs on treatment of a Ketoxime with a Lewis or proton acid is the Beckmann rearrangement; fragmentation are considered side reactions often called abnormal or 'second-order' Beckmann rearrangement. Obviously, the substrate mentioned below are much more susceptible to fragmentation than are ordinary ketoximes, since in each case an unshared pair is available to assist in removal of the group cleaving from the carbon. However, fragmentation is a side reaction even with ordinary ketoximes and in cases where a particularly stable carbocation can be cleaved, may be the main reaction;

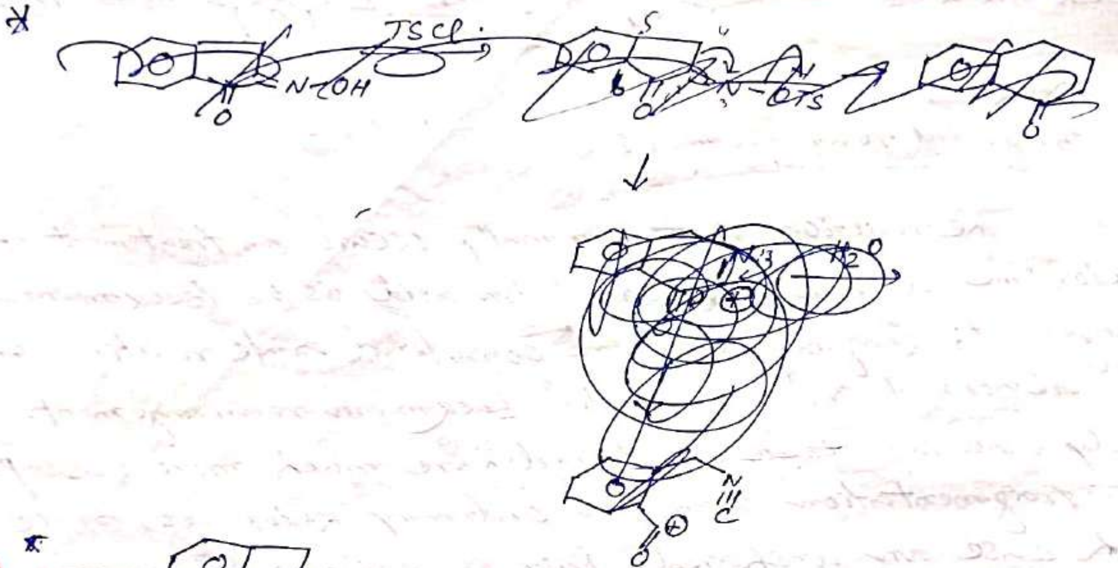


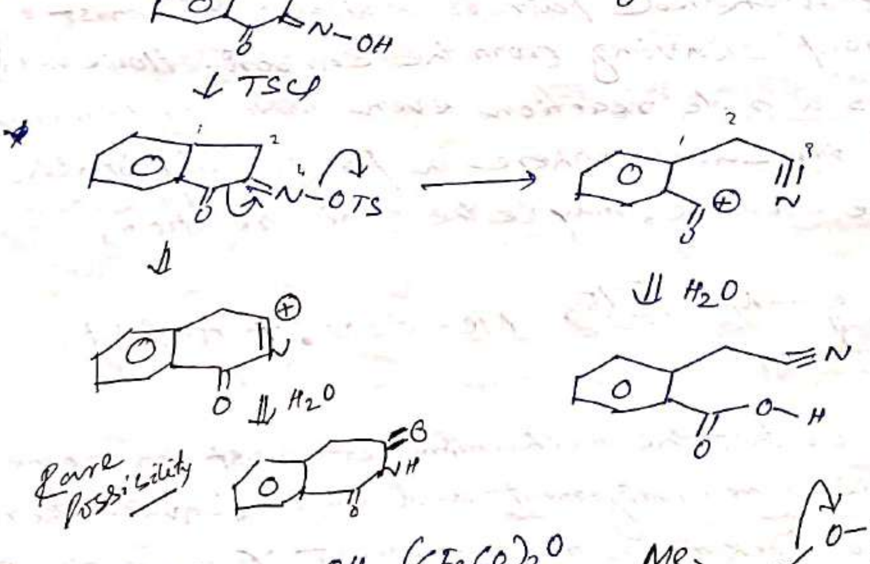
$$Ar_2CH-\underset{\underset{N-OH}{\|}}{C}-Me \xrightarrow{PCl_5} Me-C\equiv N + Ar_2CHCl$$

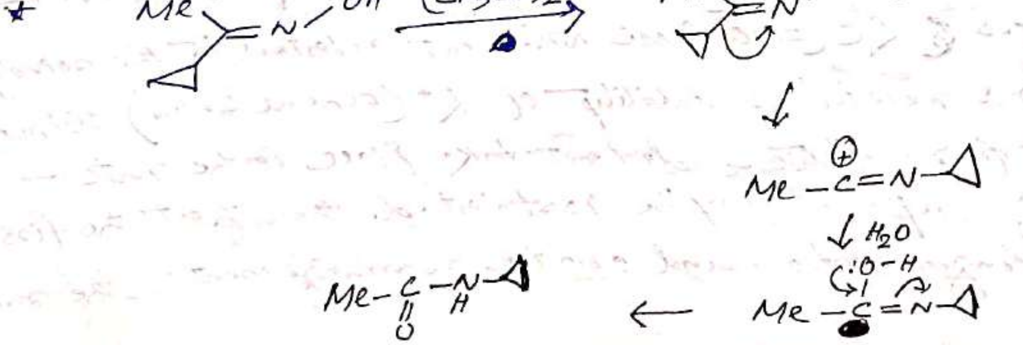
There are indication that the mechanism at least in some cases first involves a rearrangement and then cleavage. The ratio of fragmentation to Beckmann rearrangement of a series of oxime tosylates RC(=NOTs)Me was not related to the solvolysis rate but was related to stability of R^+ (scheme below) which showed that fragmentation did not take place in the rate-determining step. It may be postulated then that the first step in the fragmentation and in the rearrangement is the same-and that this is the rate-determining step. The product is determined in the second step.











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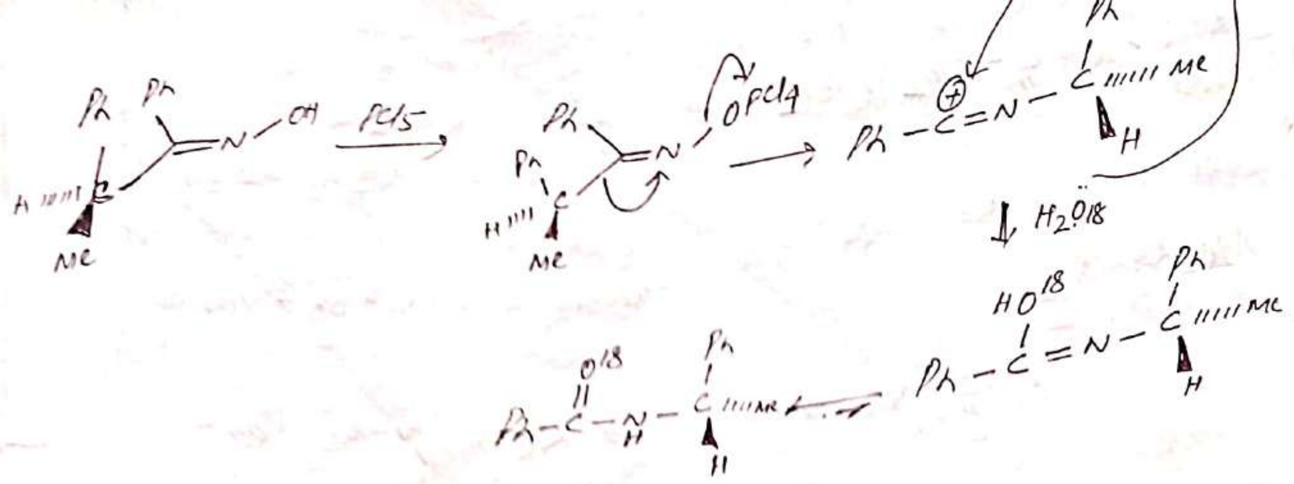

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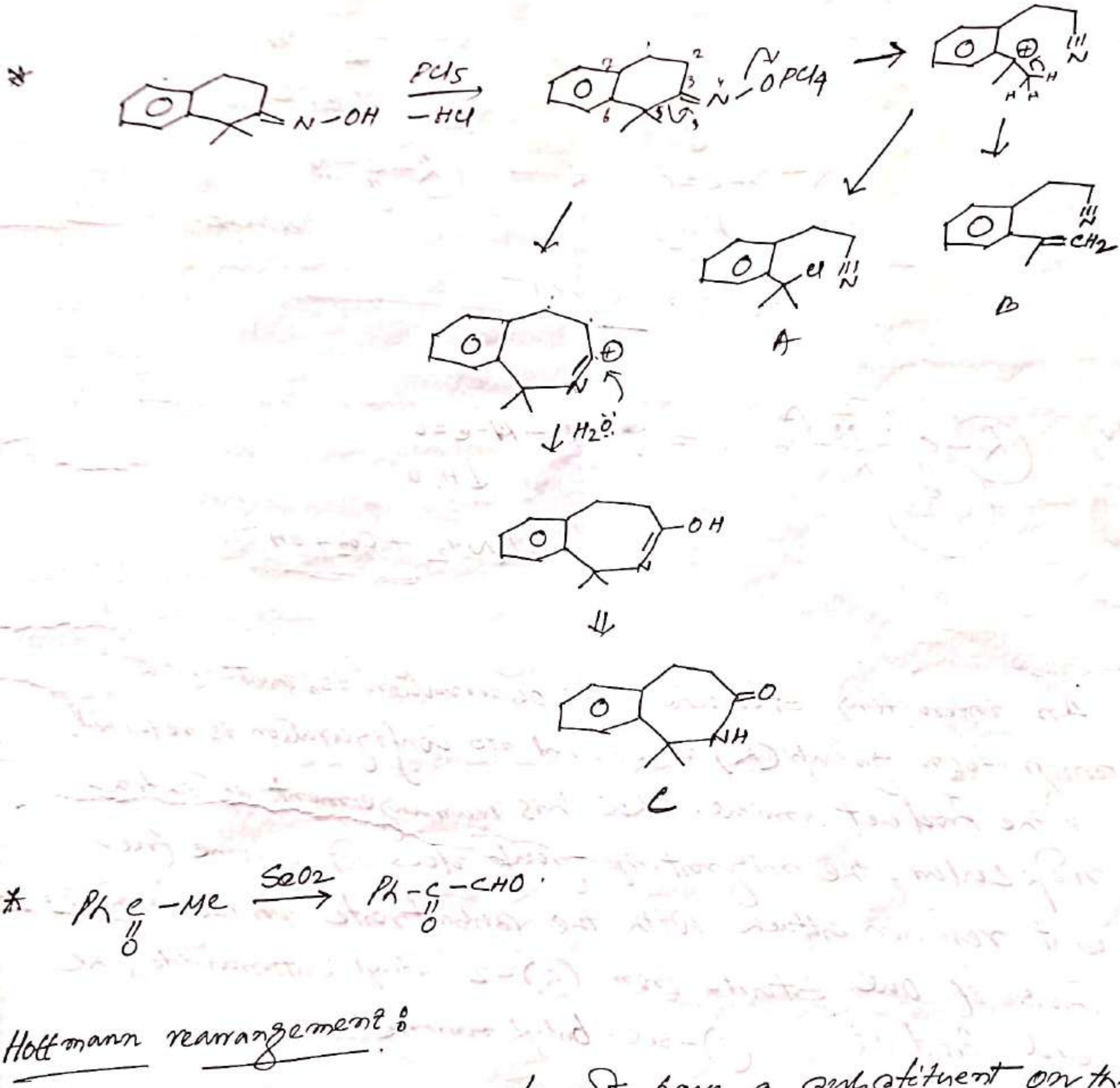

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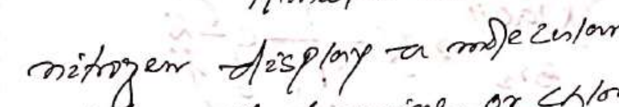
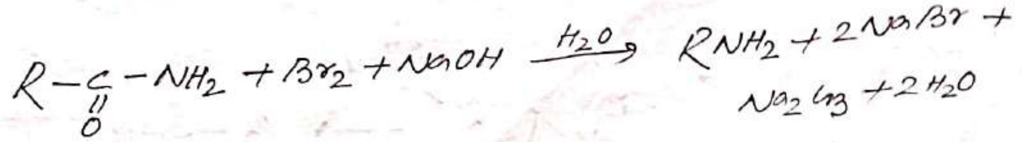


$Ph\underset{\overset{\parallel}{O}}{C}-Me \xrightarrow{SeO_2} Ph-\underset{\overset{\parallel}{O}}{C}-CHO$

Hoffmann rearrangement :

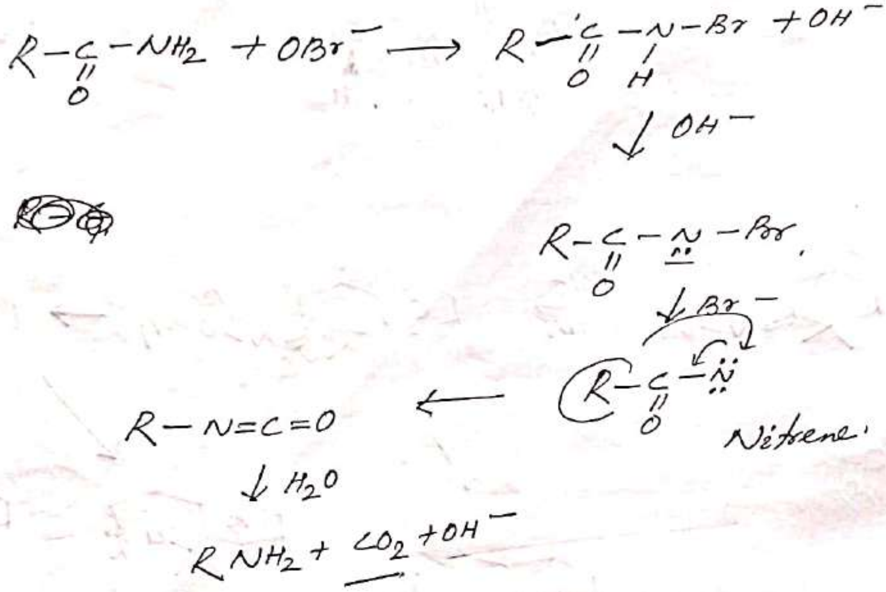
Amides which do not have a substituent on the nitrogen display a molecular rearrangement on treatment with solutions of bromine or chlorine (NaOH solⁿ) to give primary amines. In this rearrangement the carbonyl carbon atom of the amide is lost and the 'R' group of amide gets attached to the nitrogen of the amine.



$$R-\underset{\underset{O}{\|}}{C}-NH_2 + Br_2 + NaOH \xrightarrow{H_2O} RNH_2 + 2NaBr + Na_2CO_3 + 2H_2O$$

$NaOH + Br_2 \rightarrow NaOBr + HBr$

Mechanism



$$R-\underset{\underset{O}{\|}}{C}-NH_2 + OBr^- \longrightarrow R-\underset{\underset{O}{\|}}{C}-\underset{\underset{H}{|}}{N}-Br + OH^-$$

$$\downarrow OH^-$$

$$R-\underset{\underset{O}{\|}}{C}-\ddot{N}^{-}-Br$$

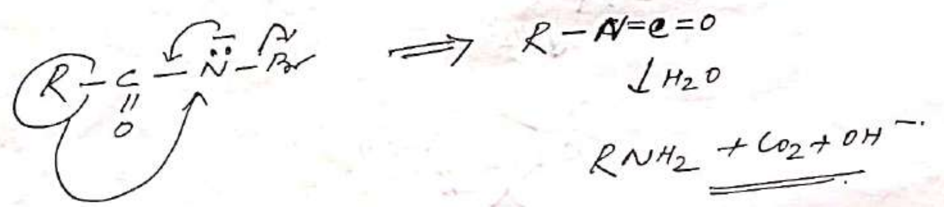
$$\downarrow Br^-$$

$$R-N=C=O \longleftarrow R-\underset{\underset{O}{\|}}{C}-\ddot{N}: \text{ Nitrene}$$

$$\downarrow H_2O$$

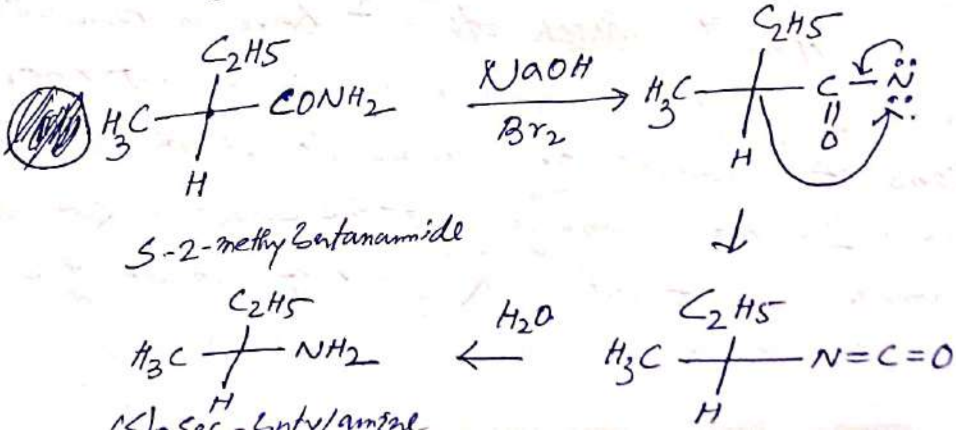
$$RNH_2 + CO_2 + OH^-$$

or,



$$R-\underset{\underset{O}{\|}}{C}-\ddot{N}^{-}-Br \Longrightarrow R-N=C=O \xrightarrow{H_2O} RNH_2 + CO_2 + OH^-$$

* An interesting stereochemical observation is, that if the migration group (R) is chiral its configuration is retained in the product amine. Thus this rearrangement is intra molecular, the migrating group does not become free but remain attach with the substrate in some way. Thus if one starts from (S)-2 methyl butanamide, the end product is (S)-sec-butyl amine.

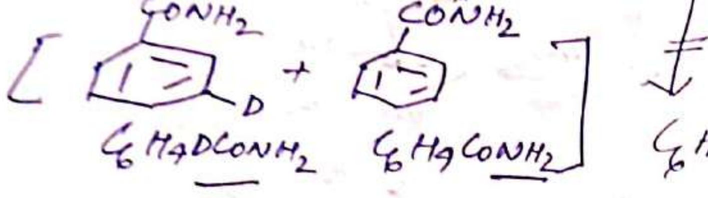


S-2-methylbutanamide

(S)-sec-butylamine

The intramolecular nature of the rearrangement was demonstrated by carrying out the reaction with a mixture of 3-deuteriobenzamide and ^{15}N-benzamide. Mixed anilines could not be isolated to indicate that the migrating group does not separate during the rearrangement.

$$C_6H_4DCONH_2 + C_6H_4CO\overset{*}{N}H_2 \xrightarrow{NaOBr} C_6H_4DNH_2 + C_6H_5\overset{*}{N}H_2$$

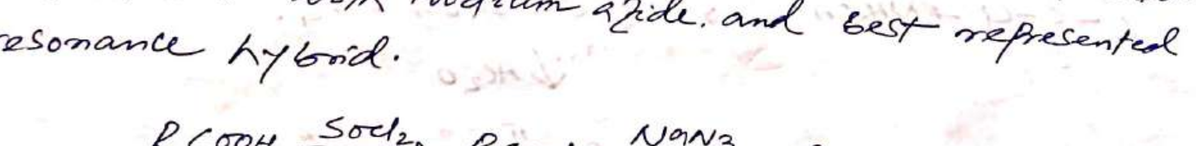


$C_6H_4D\overset{*}{N}H_2$ or $C_6H_5NH_2$.

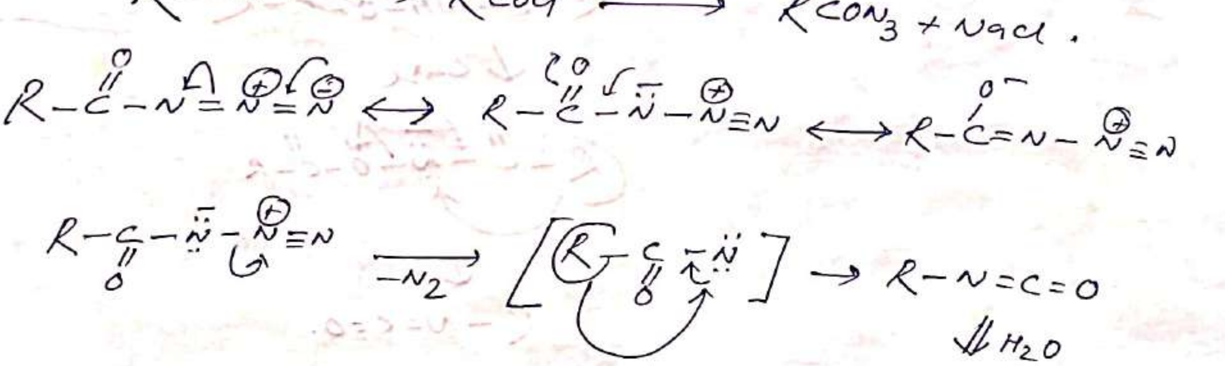
Curtius, Schmidt and Lossen rearrangement:

These rearrangement alongwith Hofmann rearrangement are closely related where a carbon migrates from carbon to nitrogen with the formation of an isocyanate. In these 1,2-shifts the migrating group is an alkyl or aryl group and the leaving group may be –Br (Hoffmann rearrangement); $-N_2$ (Curtius and Schmidt rearrangements) or $RCOO^-$ (Lossen rearrangement). The Curtius rearrangement involves the pyrolysis of acyl azides to give isocyanates. Acid azides are prepared from acid chlorides on treatment with sodium azide and best represented as a resonance hybrid.

$$RCOOH \xrightarrow{SOCl_2} RCOCl \xrightarrow{NaN_3} RCON_3 + NaCl.$$



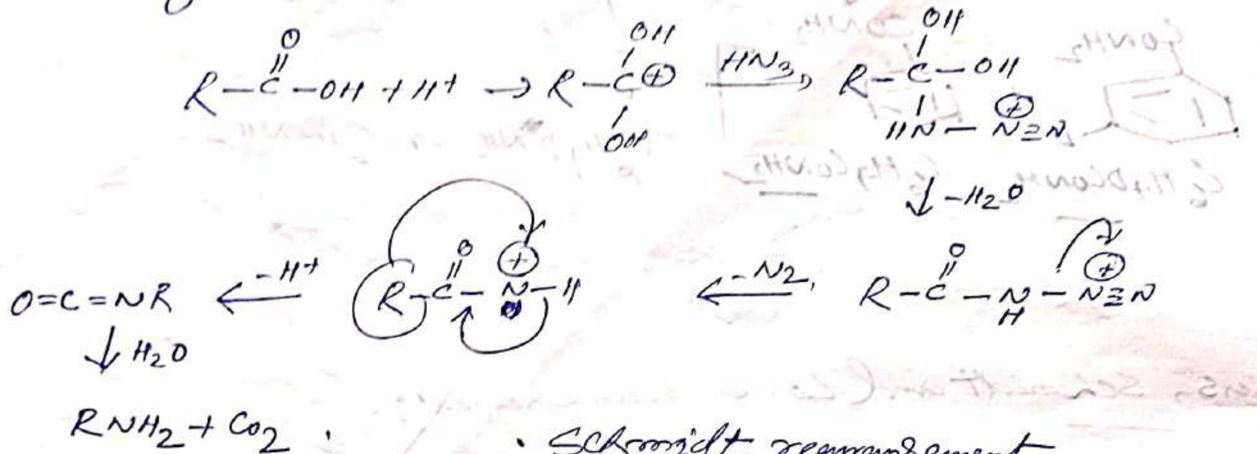
$$R-\overset{O}{\overset{\|}{C}}-N=\overset{\oplus}{N}=\overset{\ominus}{N} \longleftrightarrow R-\overset{O}{\overset{\|}{C}}-\ddot{\bar{N}}-\overset{\oplus}{N}\equiv N \longleftrightarrow R-\overset{O^-}{\overset{|}{C}}=N-\overset{\oplus}{N}\equiv N$$



$$R-\underset{O}{\underset{\|}{C}}-\ddot{\bar{N}}-\overset{\oplus}{N}\equiv N \xrightarrow[-N_2]{} \left[R-\underset{O}{\underset{\|}{C}}-\ddot{N}\right] \rightarrow R-N=C=O \xrightarrow{H_2O} R-NH_2 + CO_2 + OH^-$$

Curtius rearrangement

The Schmidt reaction involves the reactions of a carboxylic acid with hydrazoic acid in the presence of concentrated sulfuric acid to give isocyanates directly. The reaction occurs via the acid azide, however, under the strong acid conditions of the reaction it is present as its conjugate acid from which nitrogen is lost without heating.

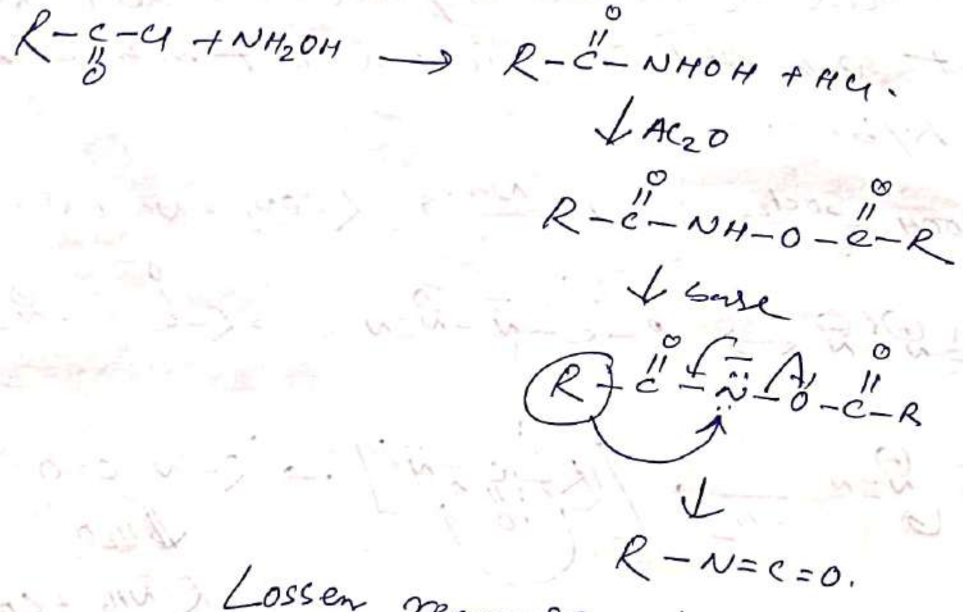


$R-\overset{O}{\overset{\|}{C}}-OH + H^+ \rightarrow R-\overset{OH}{\underset{OH}{C^{\oplus}}} \xrightarrow{HN_3} R-\overset{OH}{\underset{HN-\overset{\oplus}{N}\equiv N}{C}}-OH \xrightarrow{-H_2O} R-\overset{O}{\overset{\|}{C}}-\underset{H}{N}-\overset{\oplus}{N}\equiv N \xrightarrow{-N_2} R-\overset{O}{\overset{\|}{C}}-\overset{\oplus}{N}-H \xrightarrow{-H^+} O=C=NR$

$O=C=NR \xrightarrow{H_2O} RNH_2 + CO_2$

Schmidt rearrangement

The Lossen rearrangement occours when O-acyl-derivatives of hydroxamic acid are heated with base. The hydroxamic acids display tautomerism, the keto form is termed hydroxamic form while the enol form is called hydroxamic acid. Hydroxamic acid is prepared by the action of hydroxylamine on acid chloride.



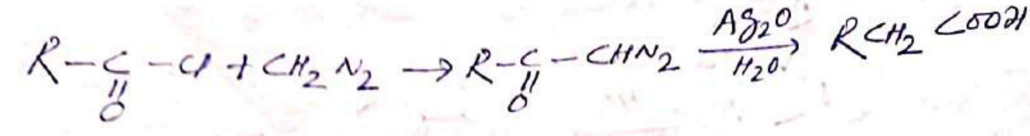
$R-\underset{\|}{\underset{O}{C}}-Cl + NH_2OH \rightarrow R-\overset{O}{\overset{\|}{C}}-NHOH + HCl$

$\xrightarrow{Ac_2O} R-\overset{O}{\overset{\|}{C}}-NH-O-\overset{O}{\overset{\|}{C}}-R \xrightarrow{base} R-\overset{O}{\overset{\|}{C}}-\ddot{N}^{-}-O-\overset{O}{\overset{\|}{C}}-R \rightarrow R-N=C=O.$

Lossen rearrangement

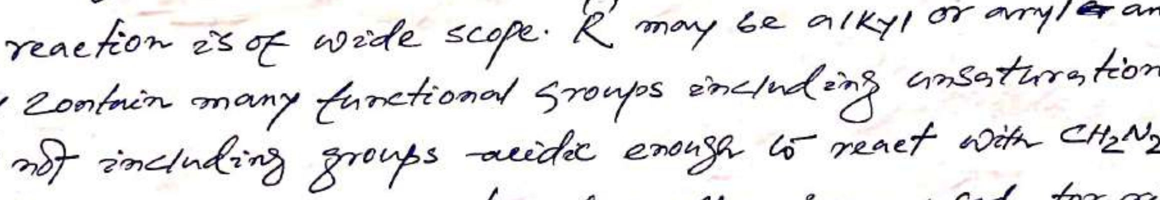
The Arndt - Eistert Synthesis:

In the Arndt-Eistert Synthesis an acyl halide is converted to a carboxylic acid with one additional carbon.



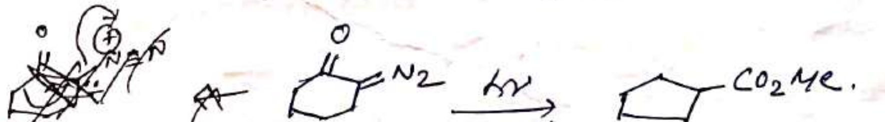
$$R-\underset{\underset{O}{\|}}{C}-Cl + CH_2N_2 \rightarrow R-\underset{\underset{O}{\|}}{C}-CHN_2 \xrightarrow[H_2O]{Ag_2O} RCH_2COOH.$$

The actual rearrangement occurs in the second step on treatment of the diazo ketone with water and silver oxide or silver benzoate and triethylamine. This rearrangement is called the Wolff rearrangement. It is the best method of increasing a carbon chain by one if a carboxylic acid is available. If an alcohol is used instead of water, the ester RCH_2COOR is isolated directly. Similarly ammonia gives an amide

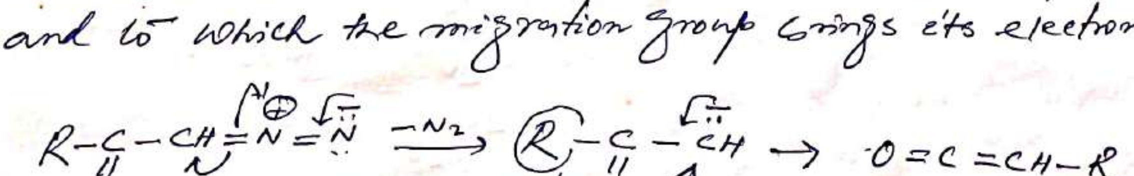


$$RCH_2CONH_2 \xleftarrow[Ag_2O]{NH_3} R-\underset{\underset{O}{\|}}{C}-CHN_2 \xrightarrow[Ag_2O]{R'OH} R-CH_2COOR'$$

The reaction is of wide scope. R' may be alkyl or aryl and may contain many functional groups including unsaturation, but not including groups acidic enough to react with CH_2N_2 or diazo ketones. The reaction has often been used for ring contraction of cyclic diazo ketone.



The mechanism is generally regarded as involving formation of a carbene. It is divalent carbon that has the open sextet and to which the migration group brings its electron pair.

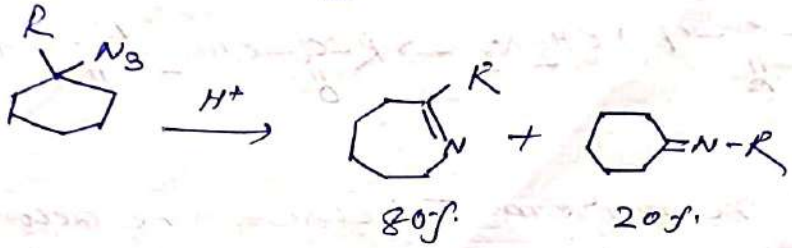


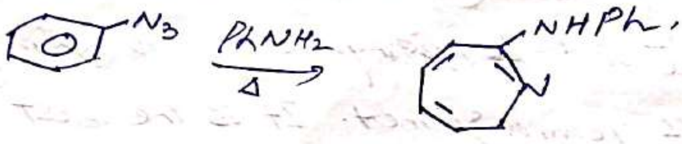
$$R-\underset{\underset{O}{\|}}{C}-CH\overset{\oplus}{=}N=\ddot{N} \xrightarrow{-N_2} R-\underset{\underset{O}{\|}}{C}-\ddot{C}H \rightarrow O=C=CH-R$$

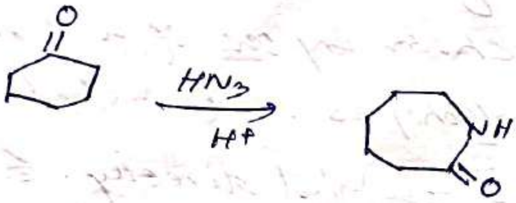
The actual product of the reaction is thus a ketene, which then reacts with water or alcohol or an amine.

Particularly Stable ketenes have been isolated and other have been ~~trapped~~ ~~in~~ isolated and other have been trapped in other ways.

Examples of Curtious rearrangement:







Hinsberg method's of detection of amines:

Hinsberg method is an excellent test for distinguishing Primary, secondary and tertiary amines. In this test, the amine is shaken well with Hinsberg reagent in the presence of aqueous alkali. A reagent containing aqueous sodium-hydroxide solution and benzene sulfonyl chloride is added to the substrate. A Primary amine will form a soluble sulfonamide salt which precipitates after addition of diluted HCl. A secondary amine in the same reaction will directly form an insoluble sulfonamide. A tertiary amine doesn't react with the sulfonamide but is insoluble. After adding dilute acid this insoluble amine is converted to a soluble ammonium salt. In this way the reaction can distinguish between the three types of amines.

Reaction Path Way

Amines serve as nucleophiles in attacking the sulfonyl chloride electrophile, displacing chloride. The sulfonamide resulting from primary and secondary amines are poorly soluble and precipitate as solids from solution:

$$PhSO_2Cl + 2RR'NH \xrightarrow{NaOH} PhSO_2NRR' + RR'NHCl$$

(Water insoluble)

For primary amines, the initially formed sulfonamide is deprotonated by base to give water soluble sulfonamide salt.

$$PhSO_2Cl + RNH_2 \xrightarrow{NaOH} PhSO_2N(H)R \xrightarrow{NaOH} Na^+[PhSO_2NR]^- + H_2O$$

Water soluble.

$\downarrow HCl$

$PhSO_2NHR \Rightarrow$ ppt.

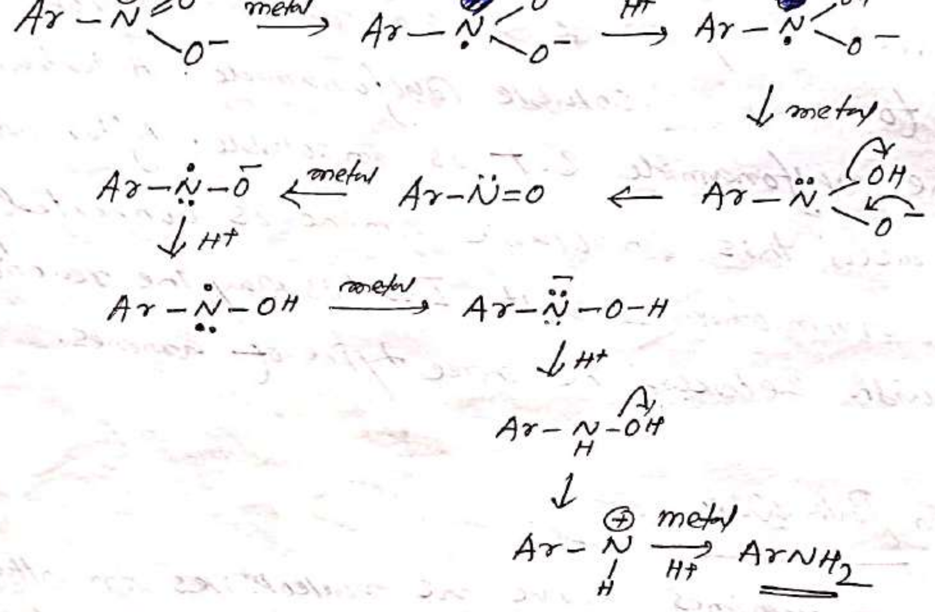
Tertiary amines promote hydrolysis of the sulfonyl chloride functional group, which affords water-soluble sulfonate salts

$$PhSO_2Cl + R_3N + H_2O \rightarrow R_3\overset{+}{N}H[PhSO_3^-]$$

Reduction of nitro group under acidic condition:

Both aliphatic and aromatic nitro compound can be reduced to amines, though the reaction has been applied much more often to aromatic nitro compounds, owing to their greater availability. Many reducing agents have been used to reduce aromatic nitro compounds, the most common being Zn, Sn or Fe and acid.

$$ArNO_2 \xrightarrow{Zn/HCl} ArNH_2$$



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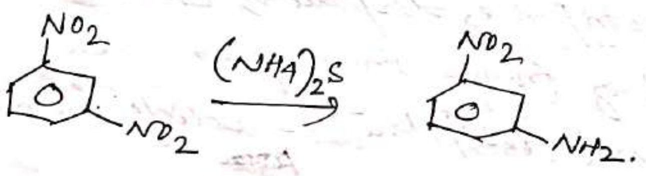


Reduction of nitro group under neutral condition:

When aromatic nitro groups are reduced with Zinc and Water under neutral conditions, hydroxyl amines are formed.

$$ArNO_2 \xrightarrow[H_2O]{Zn} ArNHOH$$

or $Zn-NH_4Cl$
H_2O.

Reduction of nitro group under basic condition:

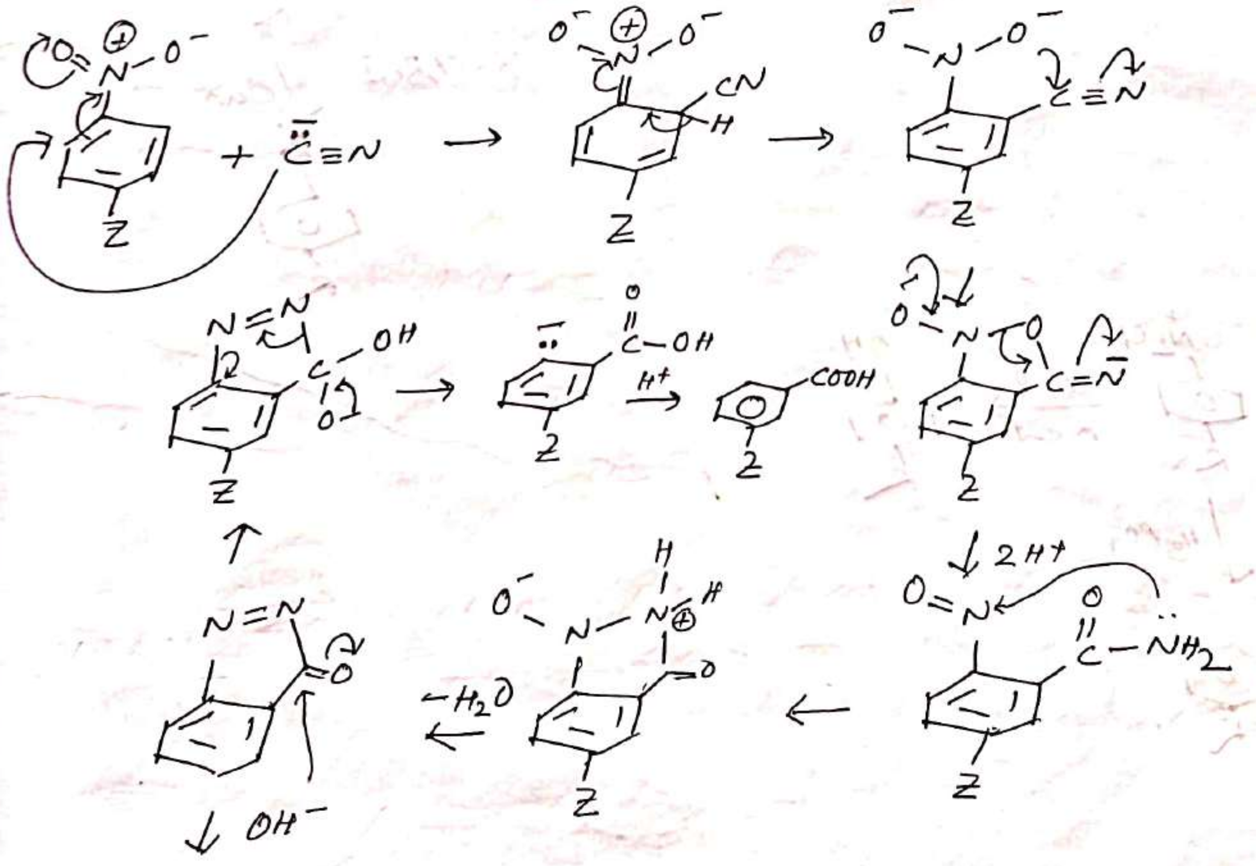
Nitro compounds can be reduced to hydrazo compounds with Zinc and Sodium hydroxide.

$$2\,ArNO_2 \xrightarrow{Zn/NaOH} Ar{-}NH{-}NH{-}Ar.$$

The von Richter Rearrangement:

When aromatic nitro compounds are treated with cyanide ion, the nitro group is displaced and a carboxyl group enters with cine substitution, always ortho to the displaced group, never meta or para. As with other nucleophilic aromatic substitution, the reaction gives best results when electron withdrawing groups are in ortho and para positions, but yields are low.

Mechanism



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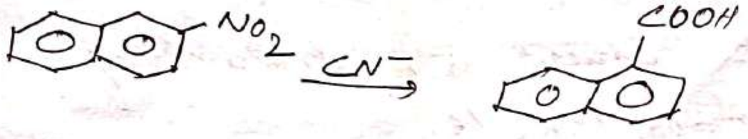
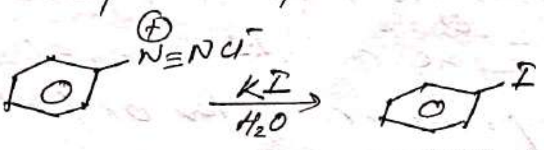
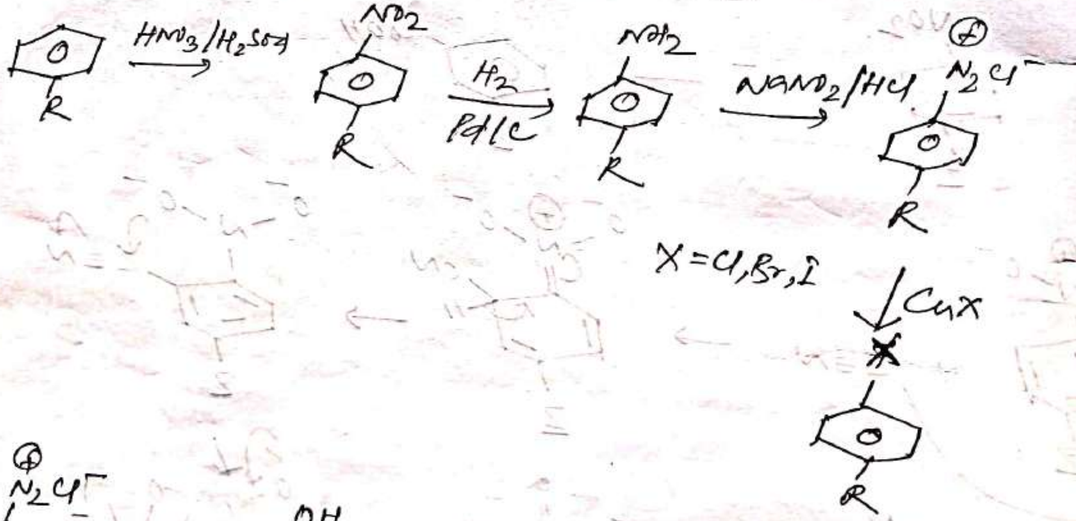


* Aryl iodide are not easy to make by electrophilic substitution as aryl chloride or bromide because - iodine is not reactive enough to attack benzene rings. But adding potassium iodide to diazonium salt gives an aryl iodide by nucleophilic aromatic substitution.



75% yield.

Other nucleophile, such as chloride, bromide and cyanide are best added as copper (I) salts. Since aromatic amines are usually made by reduction of nitro compounds, a common sequence of reactions goes like this:



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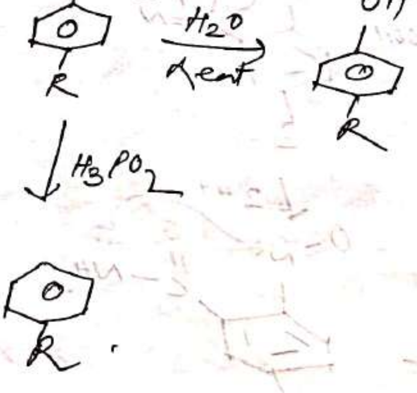

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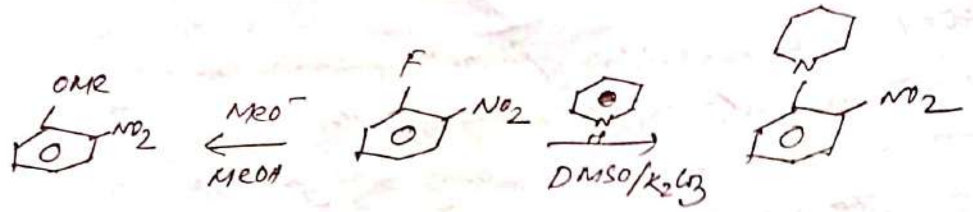
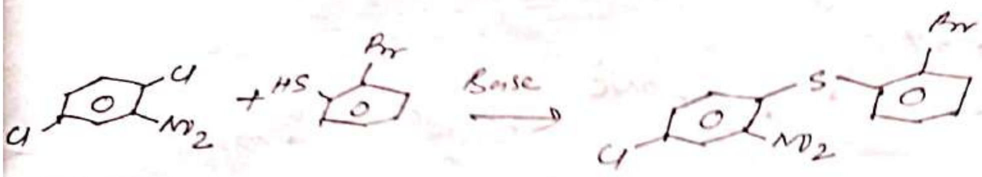
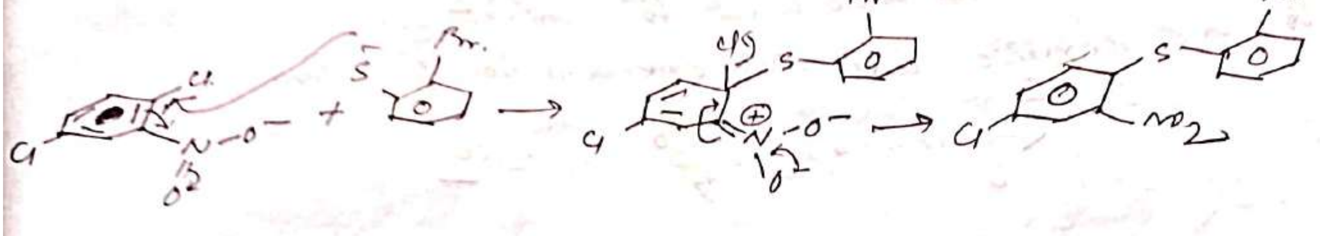




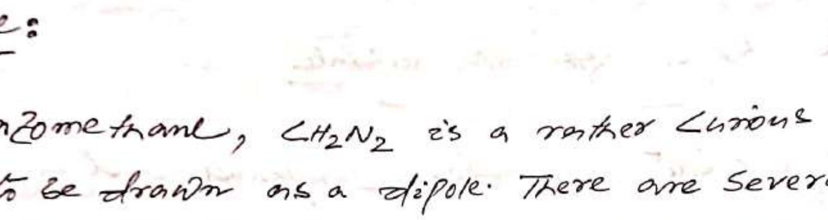


Diazomethane:

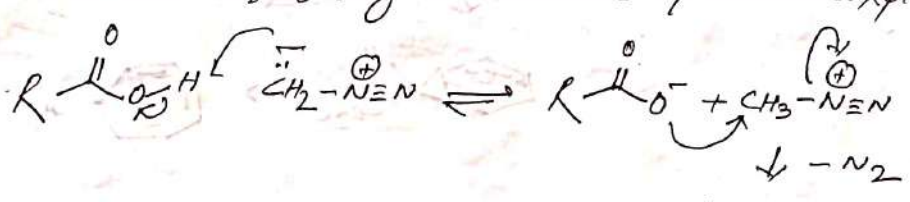
Diazomethane, CH_2N_2 is a rather curious compound that has to be drawn as a dipole. There are several different ways of expressing its structure.

$$H_2C=\overset{\oplus}{N}=\overset{-}{\ddot{N}} \longleftrightarrow H_2\overset{-}{\ddot{C}}-\overset{\oplus}{N}\equiv N \longleftrightarrow H_2\overset{-}{\ddot{C}}-N=\overset{\oplus}{N}$$

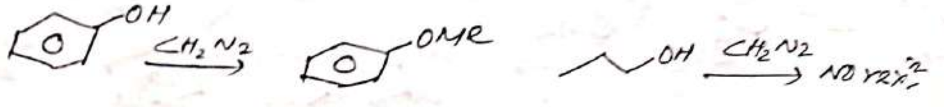
Diazomethane is prepared by hydrolysis of an ethereal solution. of an N-methyl nitrosamide with aqueous base. The traditional precursor is N-nitroso-N-methyl urea, but this compound is itself somewhat unstable, and nowadays compounds such as - nitroso-p-toluenesulfonamide are preferred.



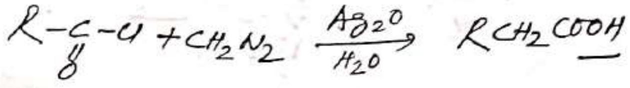
Diazomethane methylates carboxylic acid because carboxylic acid readily protonate it, giving an extremely unstable diazonium cation. This compound is desperate to lose N_2, ~~as~~ and so it does, with the 'N_2' being substituted by the carboxylate anion.



Diazomethane will also methylate phenols because they are acidic enough to protonate it. Ordinary alcohols, are not methylated because they are not strong enough acids to protonate diazomethane.

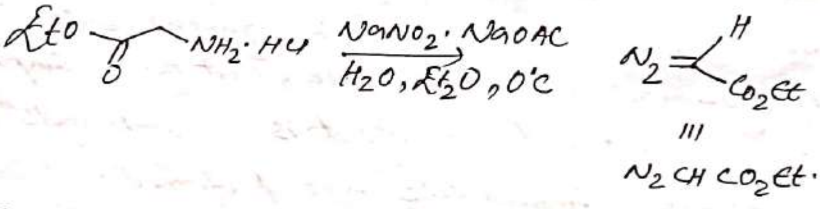


Diazomethane is also used to convert an acyl halide to a carboxylic acid with one additional carbon.

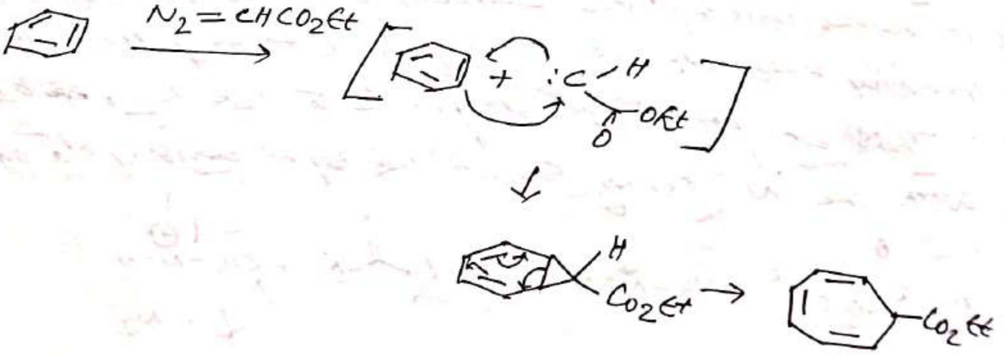

$$R-\underset{O}{\overset{}{C}}-Cl + CH_2N_2 \xrightarrow[H_2O]{Ag_2O} RCH_2COOH$$

Diazo acetic ester or Ethyl diazoacetate:

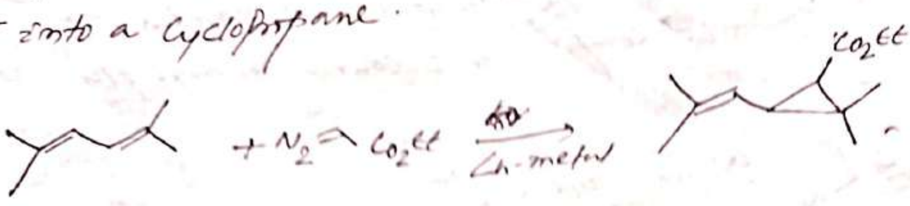
Ethyl diazoacetate is a diazo compound and a reagent in organic chemistry. The compound can be prepared by reaction of ethylester of glycine with sodium nitrite and sodium acetate in water.



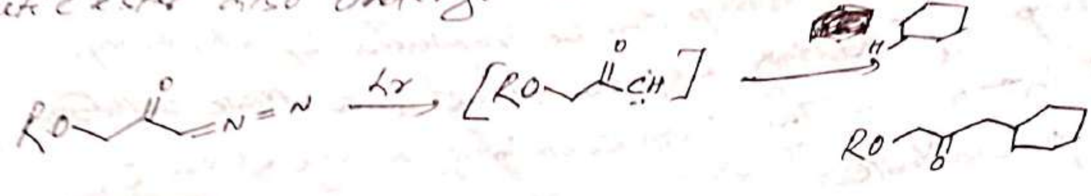
It is used for cyclopropanation of alkene. On heating it generates a carbene. Carbene like this, substituted with electron-withdrawing carboxylate group, are more powerful nucleophile than carbene like :CCl_2 and will even add to the double bond of benzene.



The carbene derived by metal-catalyzed ethyl diazoacetate attacks alkenes to introduce a two- fragment into a cyclopropane.

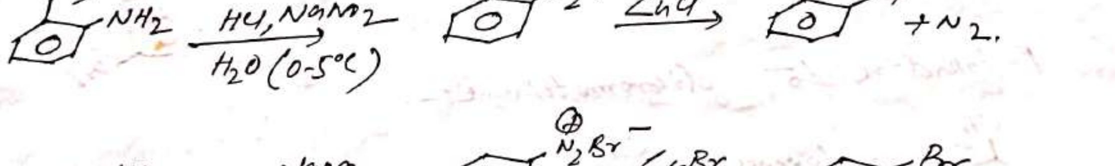


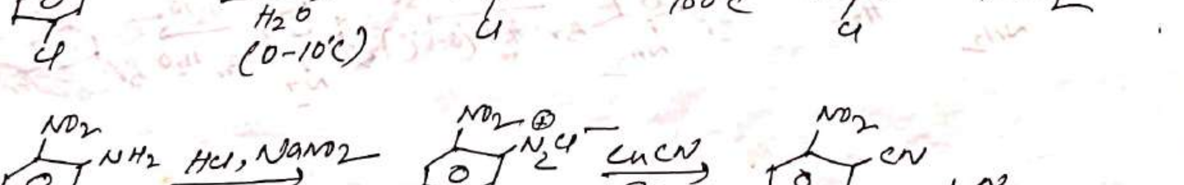
diazoacetic ester also undergo C-H insertion rex^n.

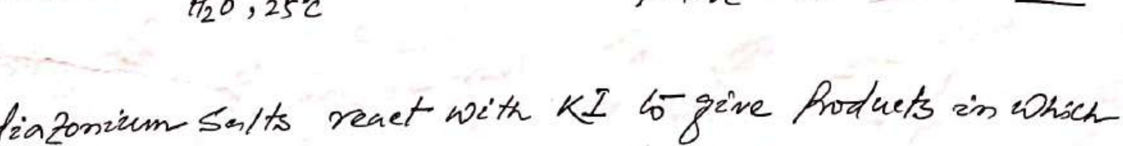


The Sandmeyer Reaction:

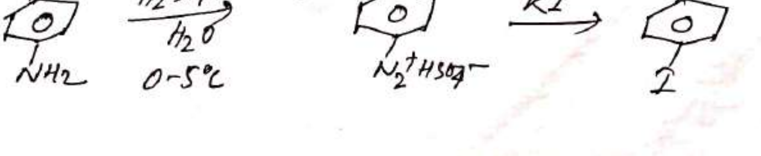
Arenediazonium salts with cuprous chloride, cuprous bromide and cuprous cyanide to give products in which the diazonium group has been replaced by -Cl, -Br and -CN respectively. These reactions are known generally as Sandmeyer reactions. The mechanism of these replacement are not fully understood; the reactions appear to radical in nature not ionic.



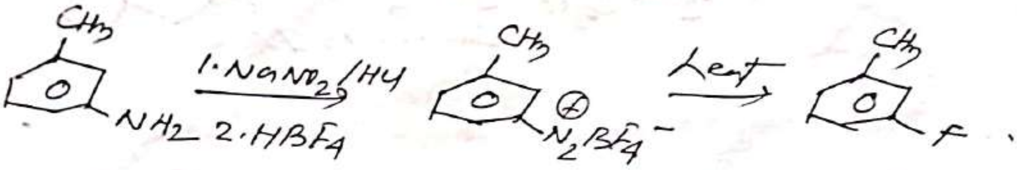




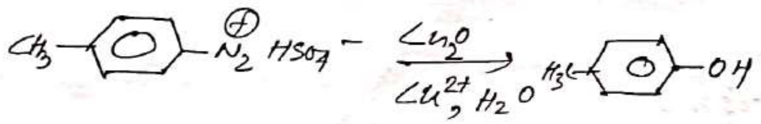
Arenediazonium salts react with KI to give products in which the diazonium group has been replaced by -I.



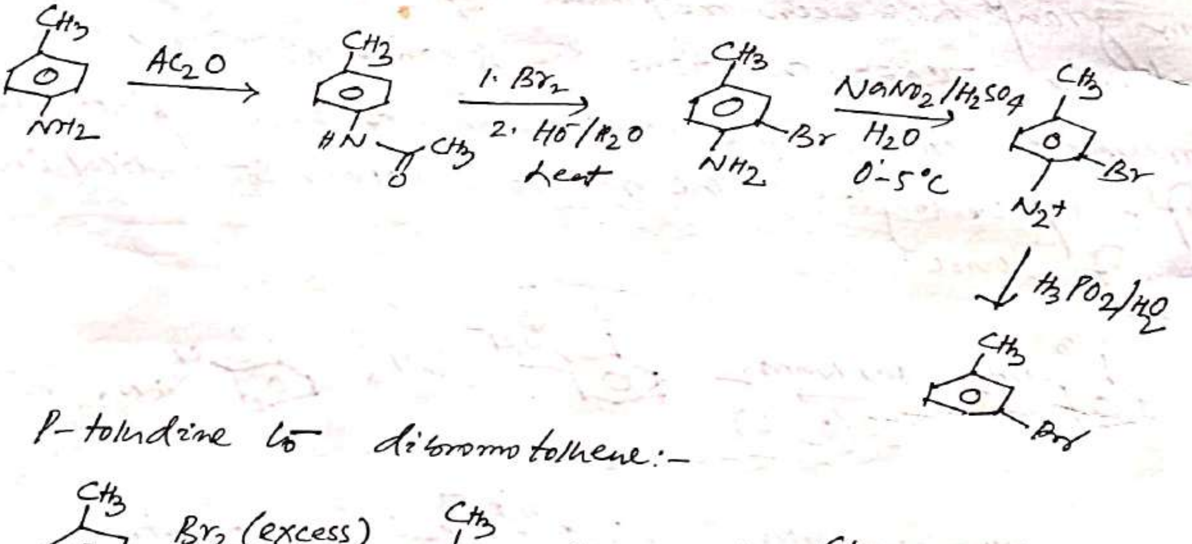
The diazonium group can be replaced by fluorine by treating the diazonium salt with fluoroboric acid (HBF_4). The diazonium fluoroborate that ppt. is isolated, dried and heated untill decomposition occour. An aryl fluoride is produced.



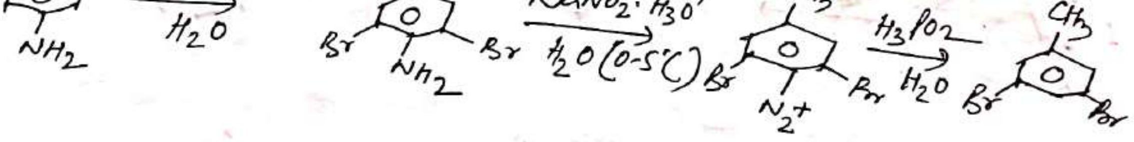
The diazonium group can be replaced by a hydroxyl group by adding cuprous oxide to a dilute solution of the diazonium salt containing a large excess of cupric nitrate



* Convert p-toluidine to m-bromotoluene:

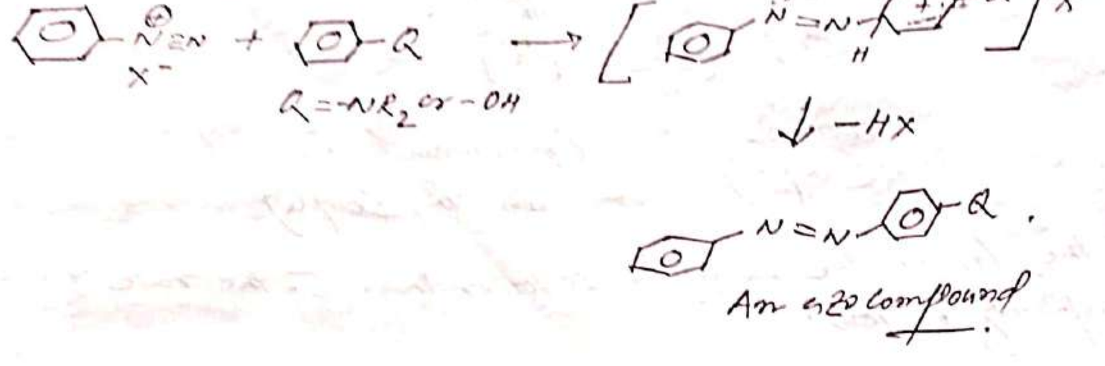


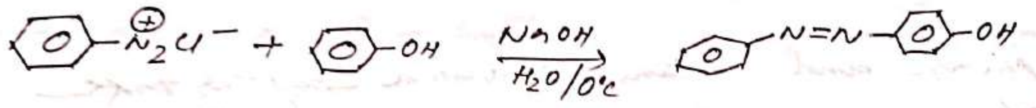
* p-toluidine to dibromotoluene:-

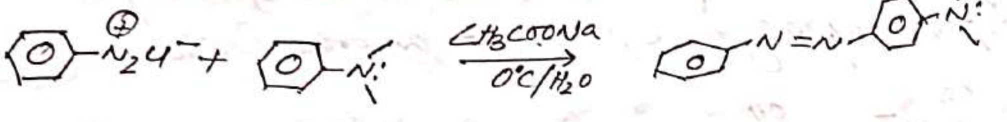


Diazo Coupling reaction:

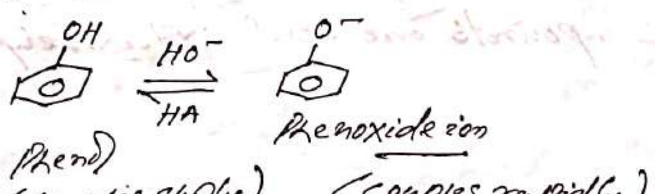
Arenediazonium ions are weak electrophiles; they react with highly reactive aromatic compounds - with phenols and tertiary arylamines to yield azo compounds. This electrophilic aromatic substitution is often called a diazo coupling reaction.







Couplings between arenediazonium cations and phenols take place most rapidly in slightly alkaline solution. Under these conditions an appreciable amount of the phenol is present as a phenoxide ion, ArO⁻, an phenoxide ions are even more reactive toward electrophilic substitution than are phenol themselves. If the solution is too alkaline (pH > 10), however, the arene diazonium salt itself reacts with hydroxide ion to form a relatively unreactive diazohydroxide or diazoate ion.

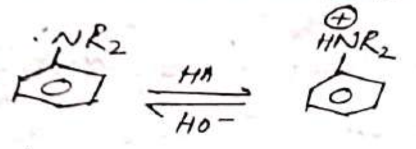


$$Ar-\overset{\oplus}{N}\equiv N \underset{HA}{\overset{HO^-}{\rightleftharpoons}} Ar-\ddot{N}=\ddot{N}-OH \underset{HA}{\overset{HO^-}{\rightleftharpoons}} Ar-N=N-O^-$$

(diazo hydroxide doesnot couple)

Diazotate ion (does not couple)

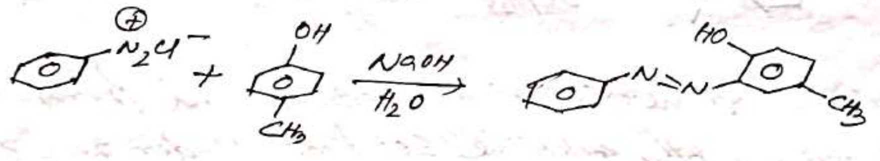
pling between arenediazonium Cations and amines ke place most rapidly in slightly acidic solution ($P_H = 5-7$). Under this Conditions the Concentration of the arenediazonium Cation is at maximum; at the same time an excessive amount of the amine has not been Converted to an unreactive aminium salt:



Amine (Couples) (Aminium Salt) (does not Couple)

If the P_H of the solution is lower than 5, the rate of amine Coupling is low.

* With phenols and aniline derivative Coupling take place almost exclusively at the para position if it is open. If it is not, Coupling take place at the ortho position.



Azo ~~Com~~ Compounds are usually intensely Colored because the azo linkage $-N=N-$, brings the two aromatic rings into Conjugation. This gives an extended system of delocalized π electrons and allows absorption of light in the visible region. Azo compounds, because of their intense colors and because they can be synthesized from relatively inexpensive compounds are used extensively as dyes.

Preparation of amines:

Nitriles, oximes and amides can be reduced to amines. Reduction of a nitrile or an oxime yields a primary amine, reduction of an amide can yield primary, secondary, or tertiary amines

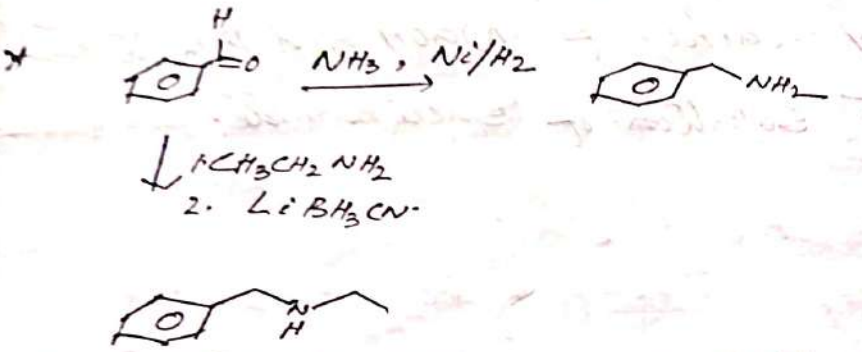
$R-C{\equiv}N \xrightarrow{[H]} RCH_2NH_2$

$R-CH{=}NOH \xrightarrow{[H]} RCH_2NH_2$

$R-CONR'R'' \xrightarrow{[H]} RCH_2NRR'$

B

$LiAlH_4$ can acts as a reducing agent

*


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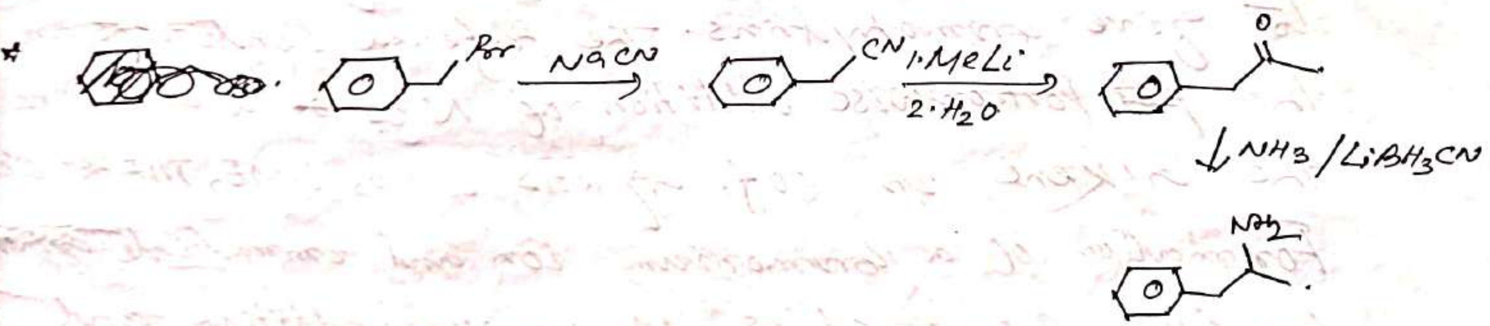

Amphetamine