

Molecular Rearrangements

Organic Chemistry (SEM IV)

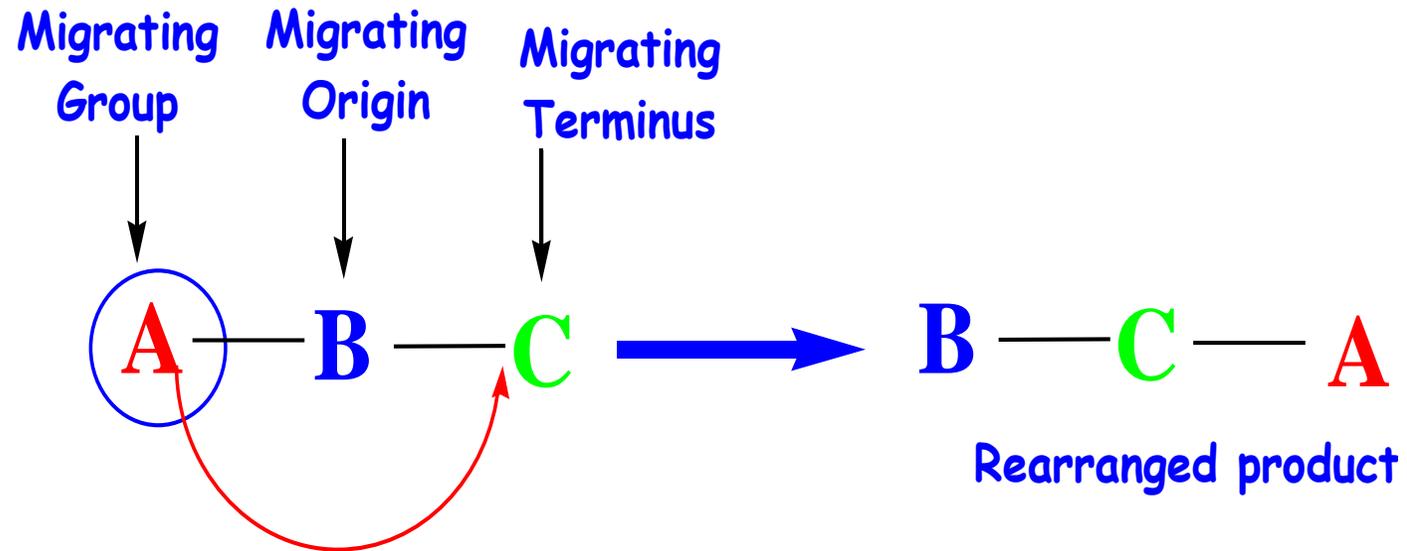
Prepared by

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Molecular Rearrangements

- Rearrangement reactions are an interesting class of reactions wherein a group or an atom migrates during the course of the reaction. While most of the rearrangements are designed in that fashion, it can also be undesirable in some cases. Depending on the reaction conditions, the nature of rearrangement (and the product) could also change.

- Rearrangement reactions involve the migration of a group or an atom from one center (migration origin) to another (migration terminus) within the same molecule.

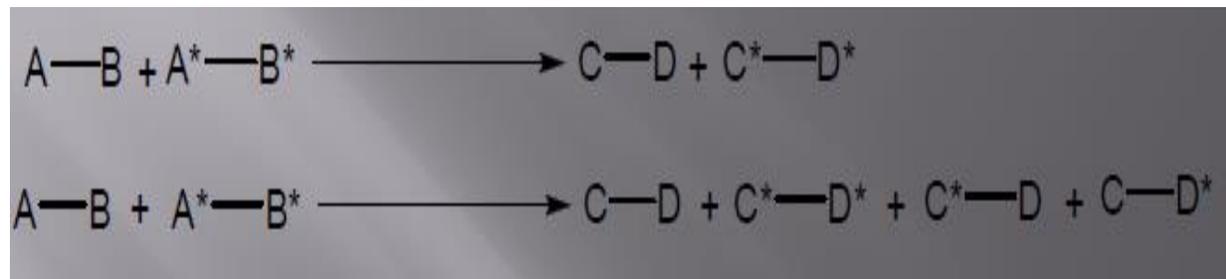


Crossover Experiments

The purpose of crossover experiment is to determine whether the given reaction takes place intermolecularly or intramolecularly i.e. whether reactant break apart to form intermediates, which diffuse away into solution before they combine to give product.

In this experiment two substrate differing in substituent are mixed together and are reacted under the same reaction condition and the product obtained is analyzed.

Illustration for cross-over experiments:
Consider, a simple reaction in which A-B reacts to give C-D.



There are two possible of outcomes for the above reaction, as A, A* are differently substituted (so are B and B*).

One in which no crossover of substituent is seen. This is possible if reaction is **intramolecular**.

The other possibility is that a mixture of products are obtained in the crossover reaction. This is possible in the case of **intermolecular** reaction.

Rearrangement reactions can be roughly classified on the basis of the migration origin and migration terminus.

1. Rearrangements to Electron Deficient Carbon
2. Rearrangements to Electron Deficient Nitrogen
3. Rearrangements to Electron Deficient Oxygen
4. Sigmatropic Rearrangements
5. Other Rearrangements

Rearrangements to Electron Deficient Carbon

1. Wagner-Meerwin Rearrangement
2. Pinacol-Pinacolone Rearrangement
3. Demjanov Rearrangement (Tiffeneau- Demjanov)
4. Benzil-Benzilic acid Rearrangement
5. Wolff Rearrangement (Arndt-Eistert Synthesis)
6. Dienone-Phenol Rearrangement

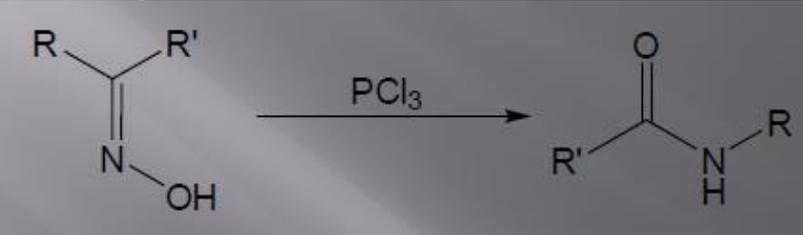
N.B: All these rearrangements are discussed in classes

Rearrangements to Electron Deficient Nitrogen

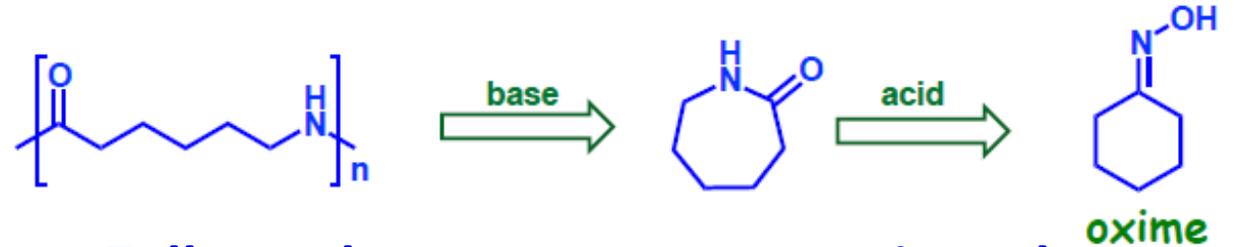
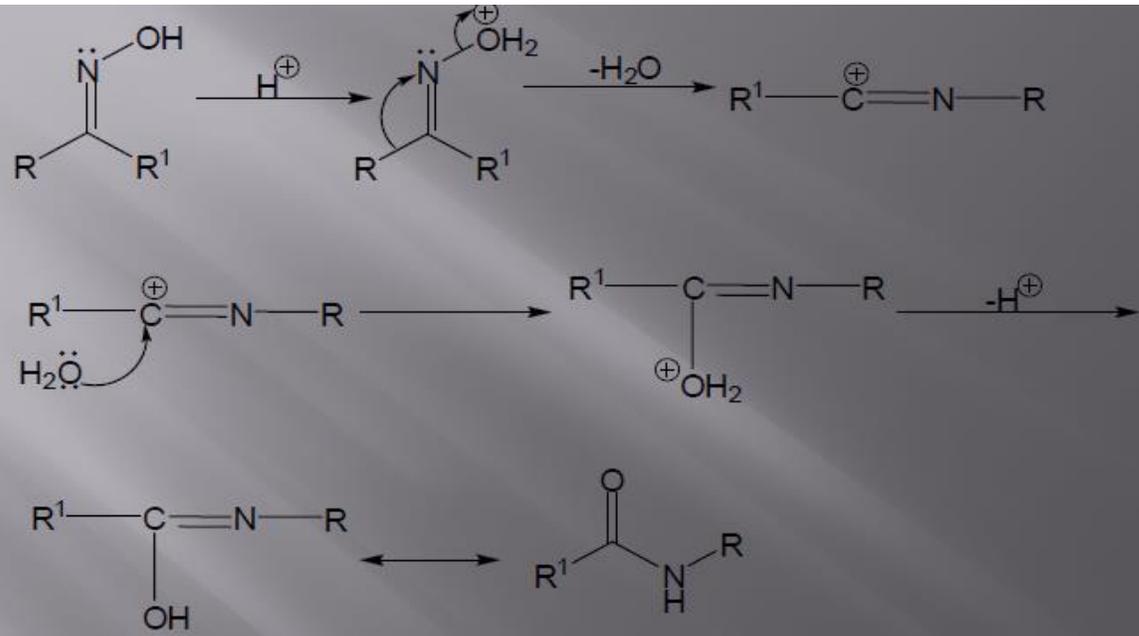
1. Beckmann Rearrangement
2. Hofmann Rearrangement
3. Curtius rearrangement
4. Lossen Rearrangement
5. Schmidt Rearrangement

Beckmann Rearrangement

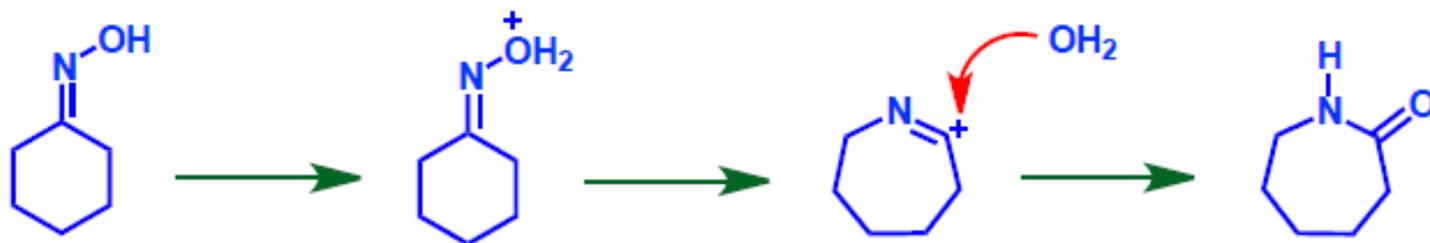
The industrial formation of nylon relies upon the alkaline polymerization of a acyclic amide known as caprolactam



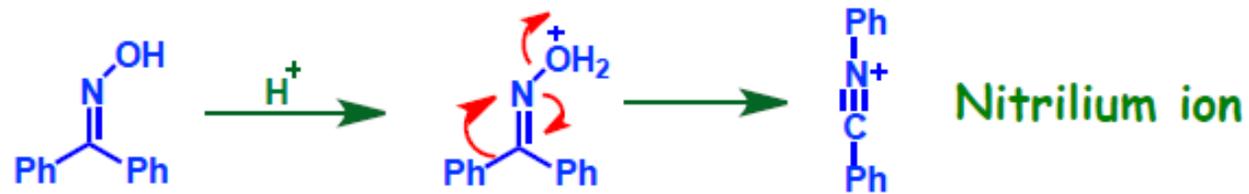
Mechanism:



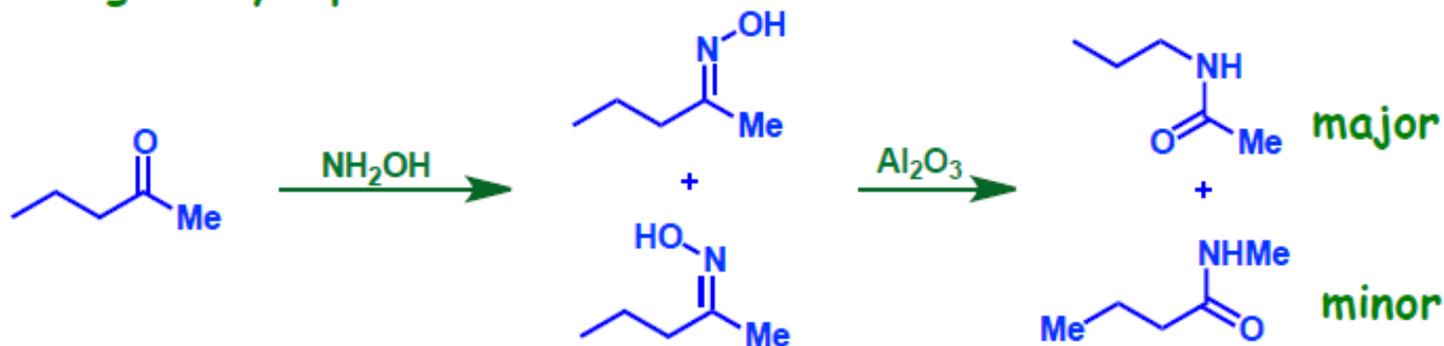
- Follows the same pattern as pinacol
- Converts the oxime into a good leaving group
- Alkyl/ Aryl group migrates on to nitrogen as water departs
- The product cation is then trapped by water to give an amide
- It can also work with acyclic oximes
- PCl_5 , SOCl_2 & other acyl or sulfonyl chlorides can be used instead of acid



Caprolactam can be produced by the action of sulfuric acid on the oxime of cyclohexanone in a rearrangement known as the Beckmann rearrangement

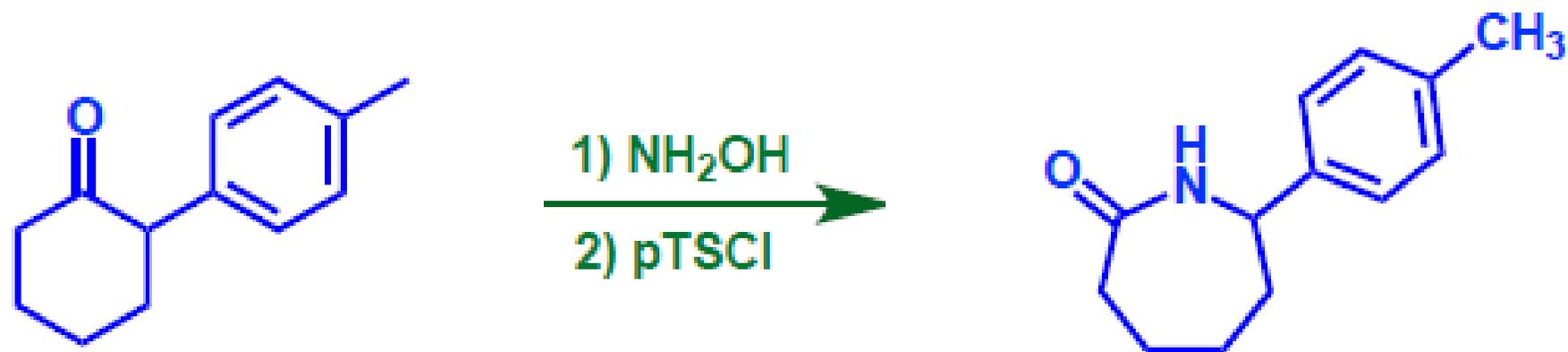
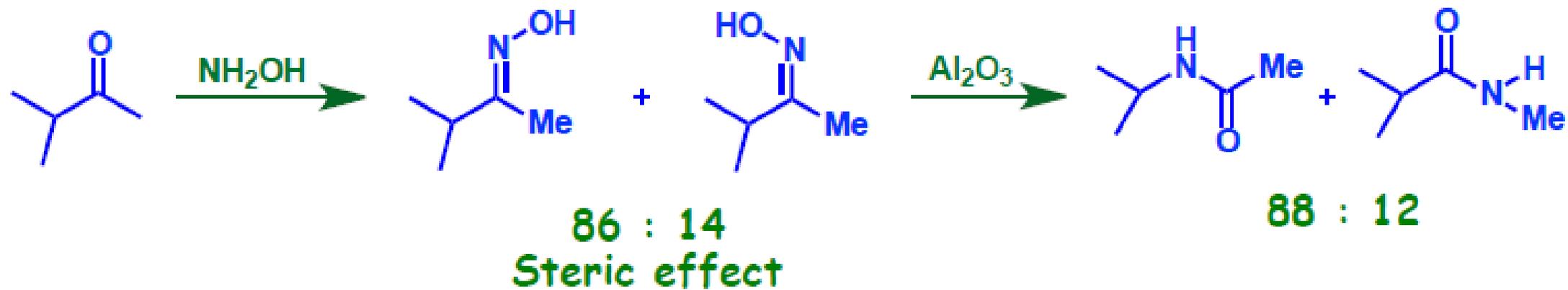


Migratory Aptitude:



In case of unsymmetrical ketone:

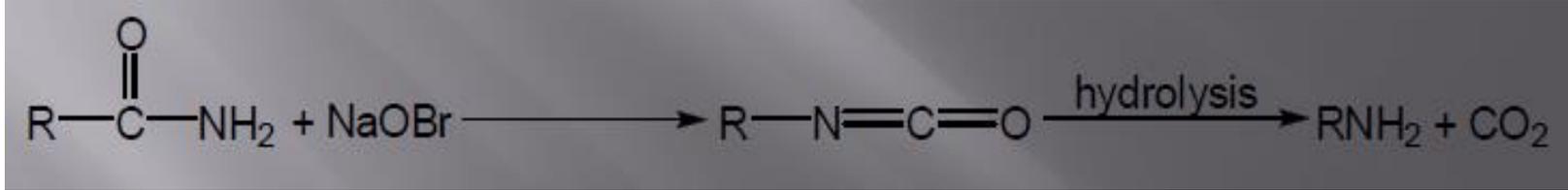
- There are two groups that could migrate
- There are two possible geometrical isomers of unsymmetrical oxime
- When the mixtures of geometrical isomer of oximes are rearranged, mixtures of products result
- Interestingly, the ratio of products mirrors exactly the ratio of geometrical isomers in the starting materials
- The group that has migrated, is trans to the -OH group



Hofmann rearrangement

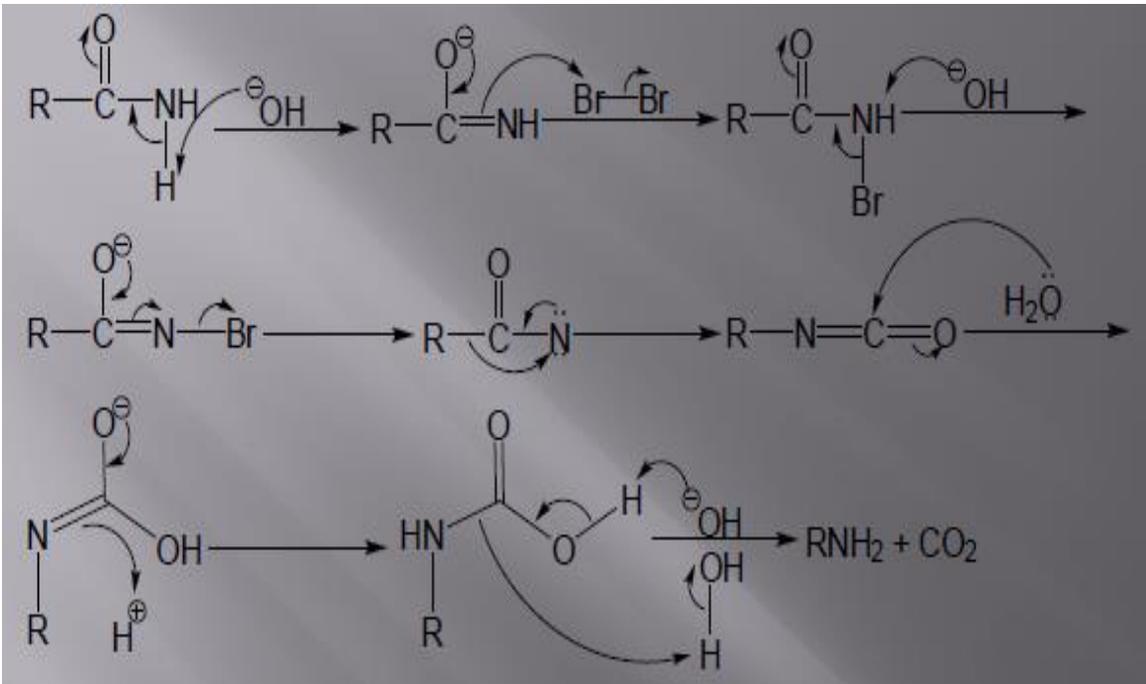
When an unsubstituted amide is treated with sodium hypobromite, corresponding primary amine with one carbon less is produced. This reaction involves Hofmann rearrangement.

Reaction



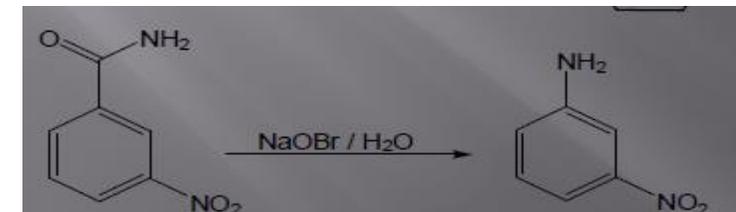
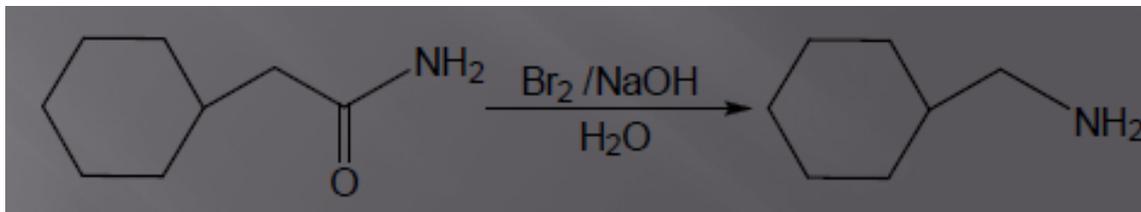
R in this reaction can be alkyl or aryl.

Mechanism

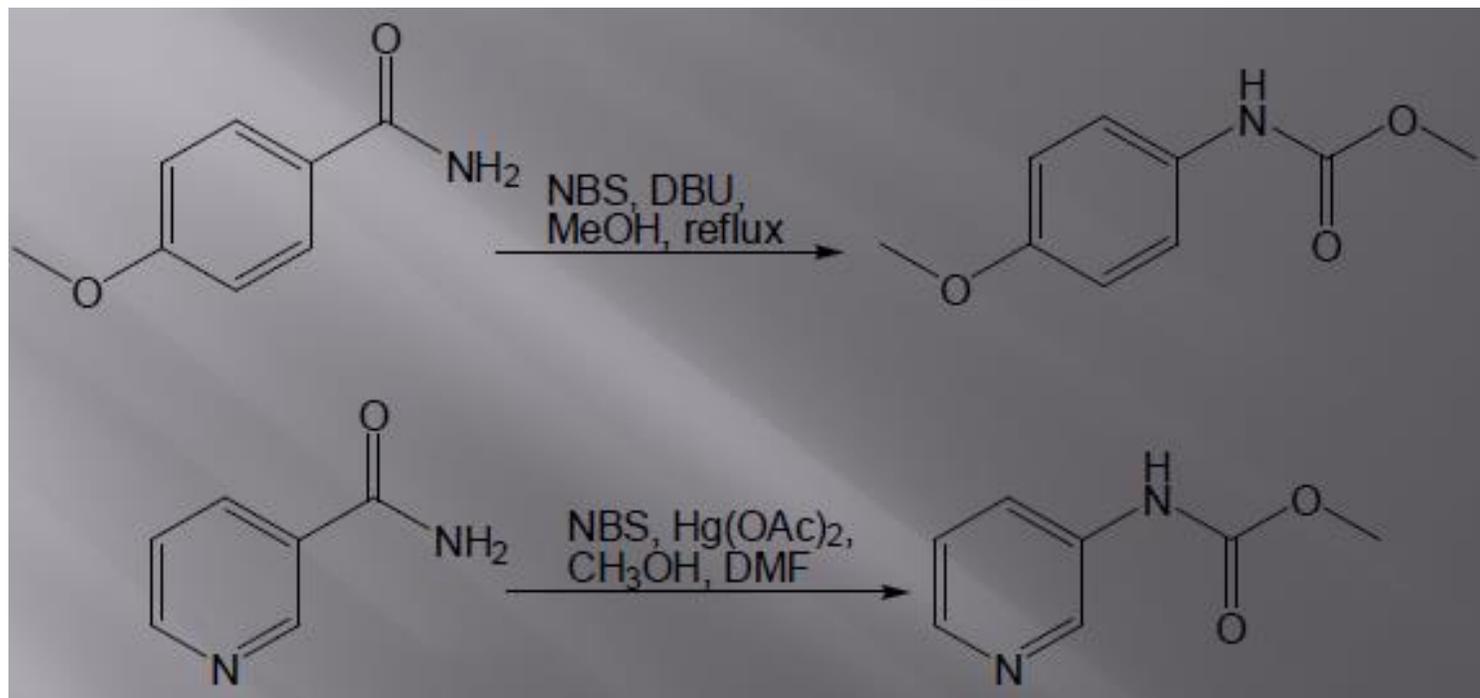


In the first step, base removes a proton from amide. The conjugate base of amide thus formed reacts with bromine to give N-bromoamide. Acidity of proton on nitrogen is increased by this bromine atom and its removal becomes easy toward generating nitrene intermediate (in which nitrogen is electron deficient). 1,2-shift of alkyl group in this nitrene intermediate gives corresponding isocyanate. This **isocyanate** on hydrolysis gives primary amine with one carbon less than starting material.

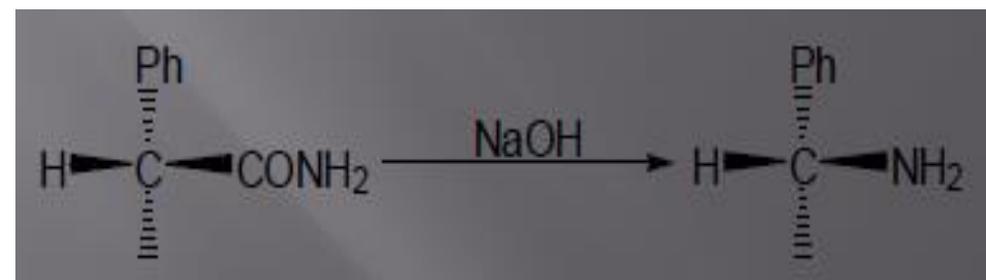
Other Examples



When methanol is used as a solvent instead of water, then the corresponding carbamate ester can be obtained.

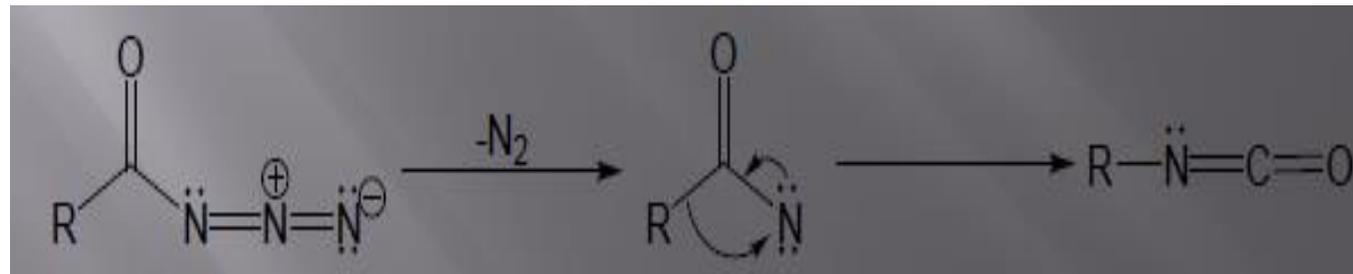
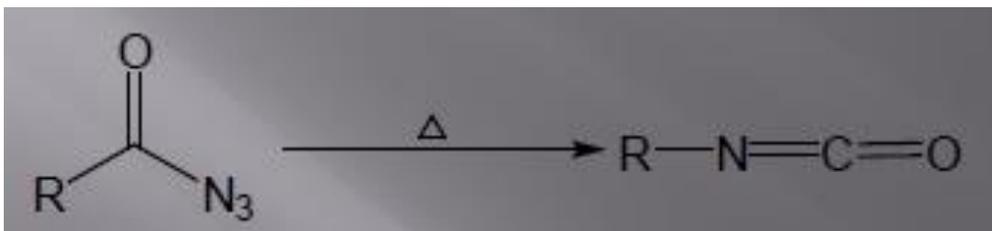


When optically active α -phenylpropionamide undergoes Hofmann degradation, α -phenylethylamine of same configuration and optical purity is obtained i.e. rearrangement proceeds with **retention of configuration**.

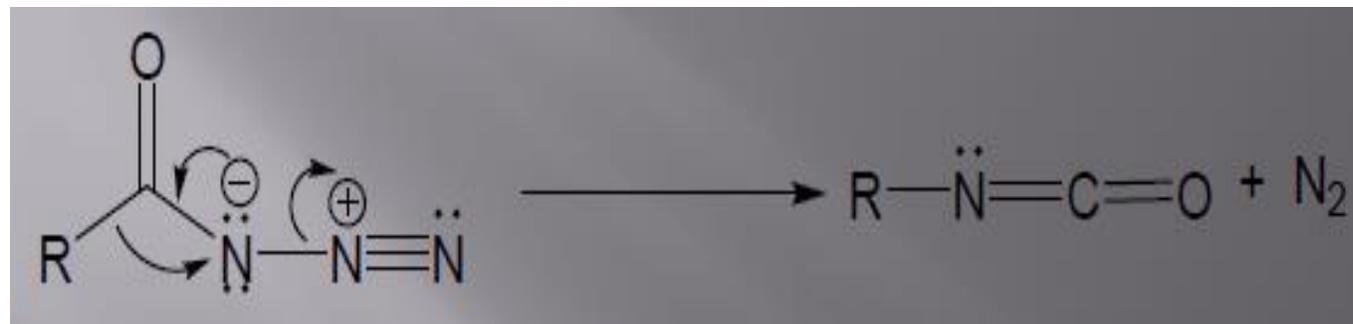


Curtius rearrangement:

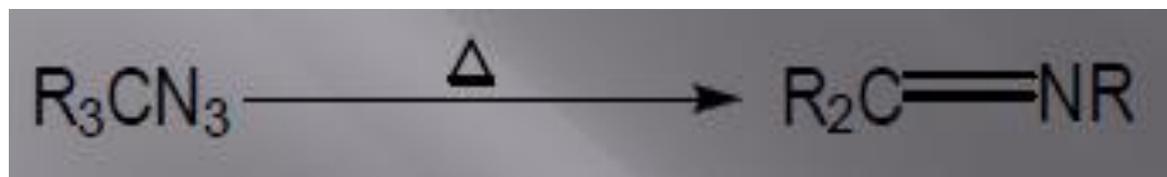
In Curtius rearrangement, acyl azide are pyrolysed into **isocyanate** which can be hydrolyzed to corresponding amines. Curtius rearrangement is catalyzed by protic or Lewis acids. Mechanism is similar to that of Hofmann



However, there is no evidence of existence of free **nitrene**. These two steps may be concerted.

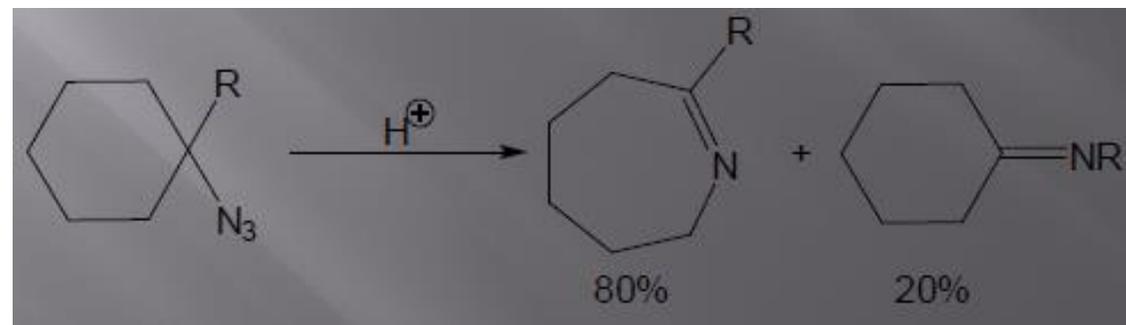


In a similar reaction, alkyl azides provide imines.

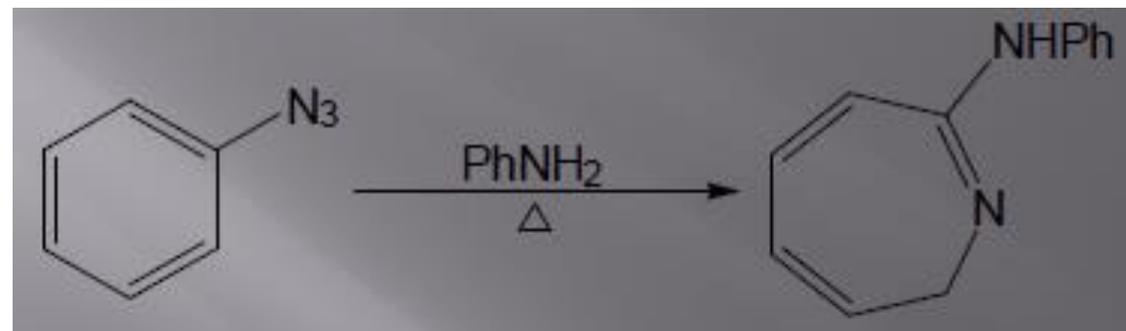


R may be alkyl, aryl or hydrogen. In the case of tertalkyl azides, there is evidence of existence of nitrene.

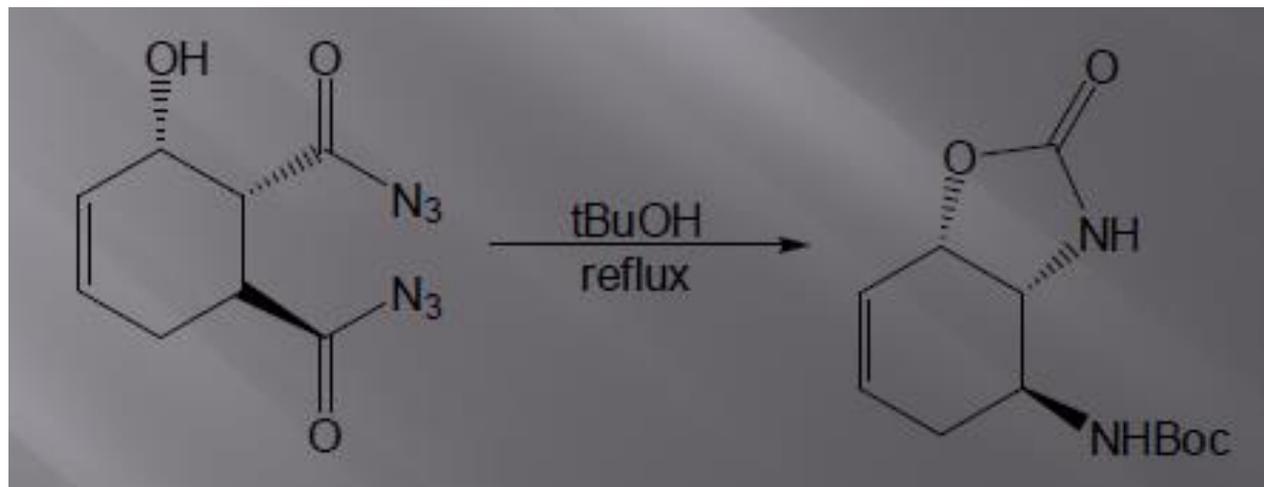
Cycloalkyl azides can yield ring expansion.



Aryl azides can also give ring expansion on heating.



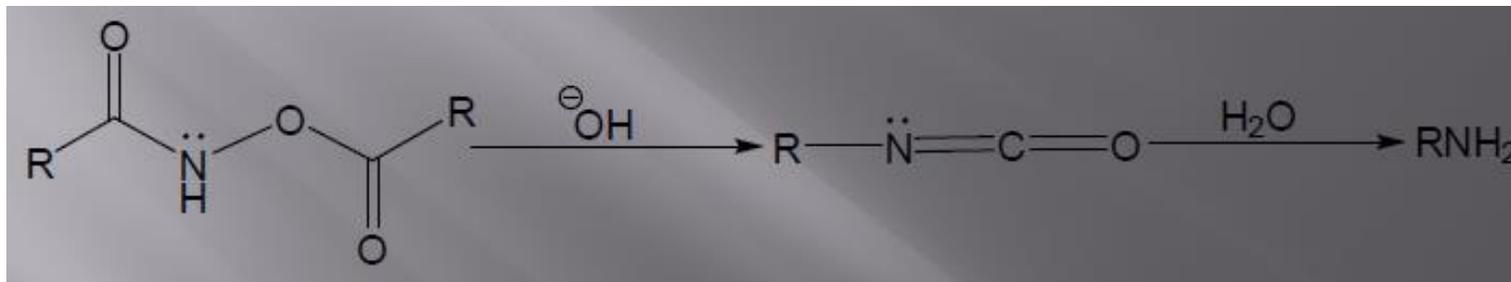
Home work: (Propose a mechanism for the following reaction)



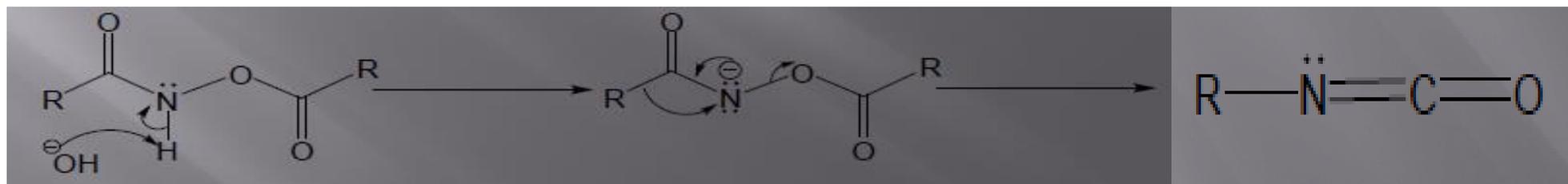
Lossen rearrangement:

O-acyl derivatives of hydroxamic acids on heating with a base converts to the corresponding **isocyanate**. This reaction is known as Lossen rearrangement. The isocyanate thus produced can be further hydrolyzed to corresponding amines.

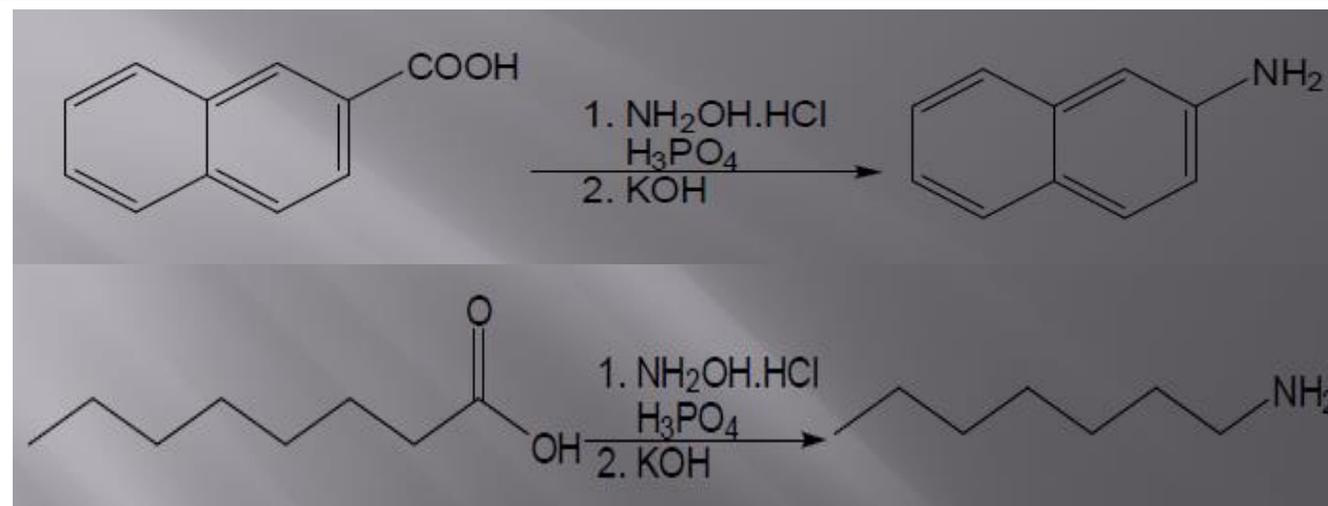
Reaction



Mechanism

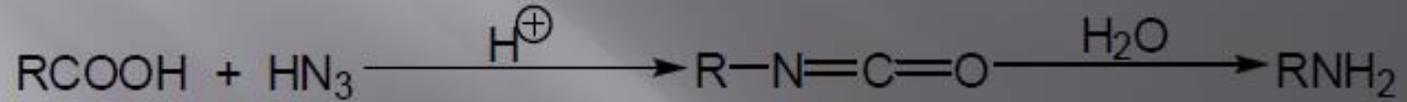


Other Examples



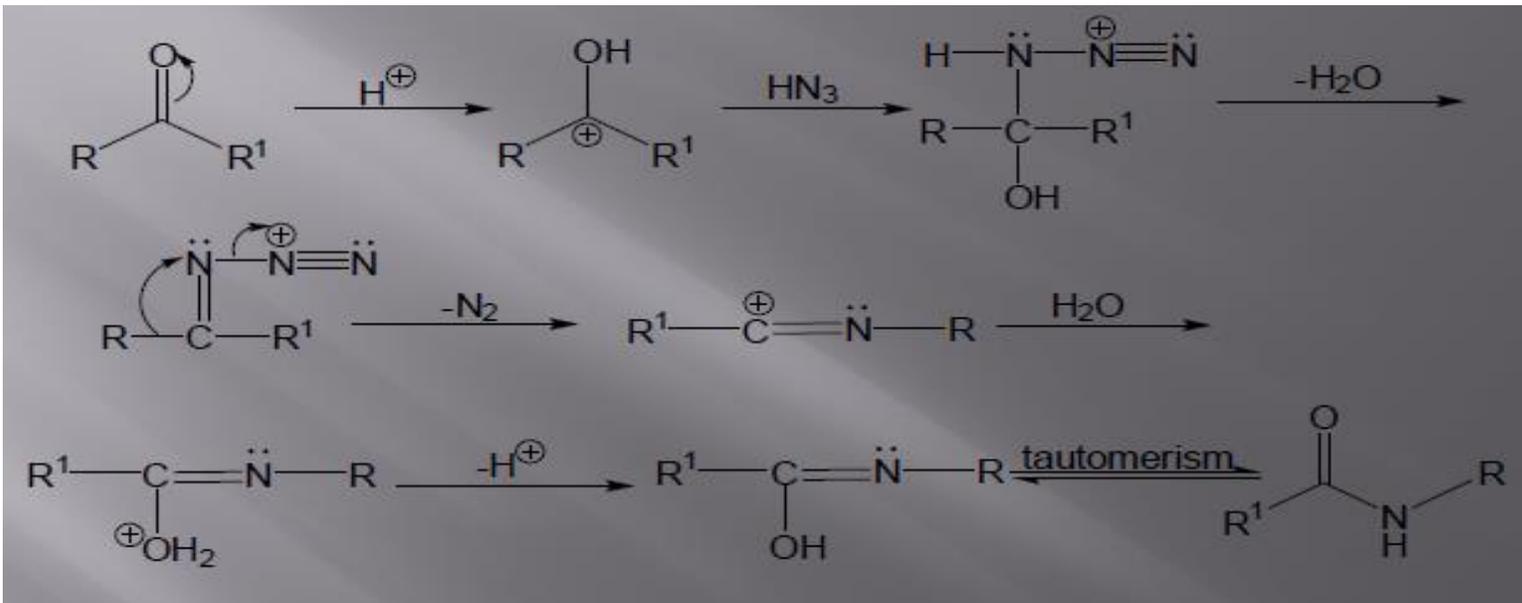
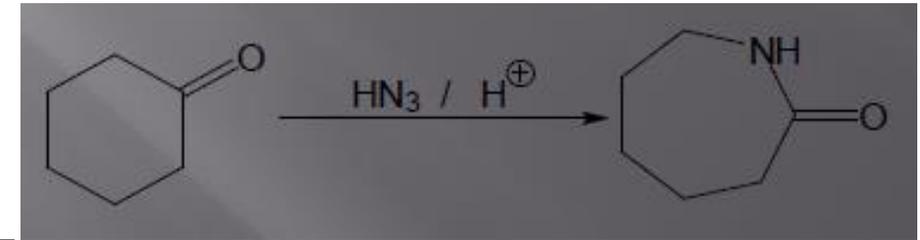
Schmidt rearrangement

Reaction of carboxylic acid or aldehyde or ketone with **hydrazoic acid** in the presence of mineral or Lewis acid to give corresponding primary amine or amide is known as Schmidt rearrangement.



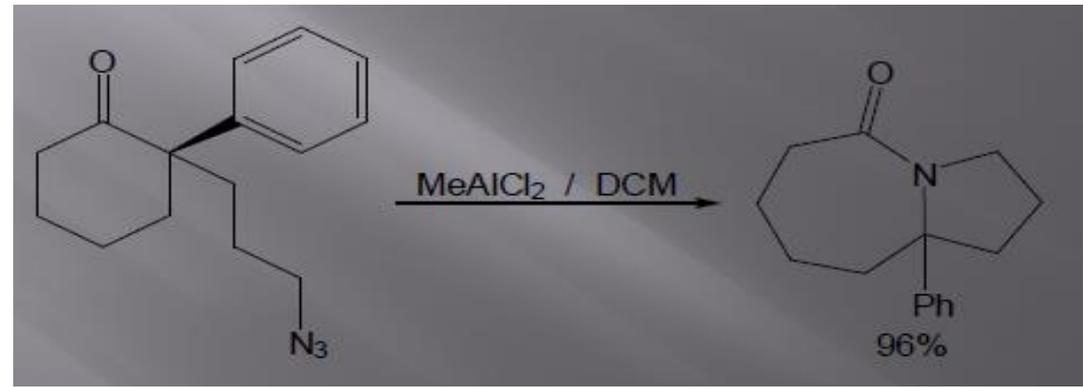
Cyclic ketones give lactams.

Mechanism is similar to that of Curtius rearrangement, except that protonated azide undergoes molecular rearrangement.

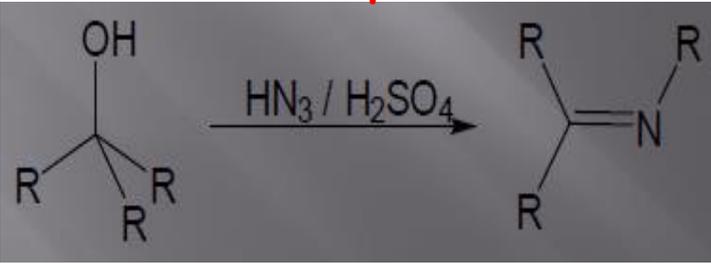


In reaction with ketone, ketone is activated by protonation for nucleophilic addition of azide group to it.

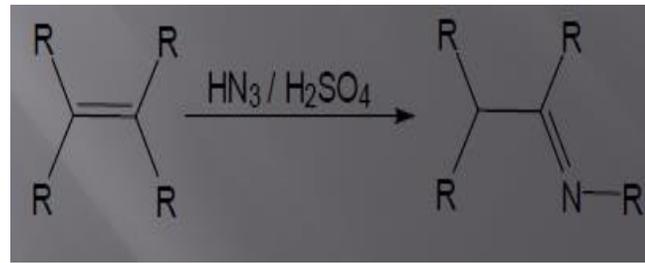
In the case of alkyl aryl ketone, the aryl group migrates preferentially except for bulky alkyl group. Intramolecular Schmidt reaction can be used for the preparation of bicyclic lactams.



Example 1

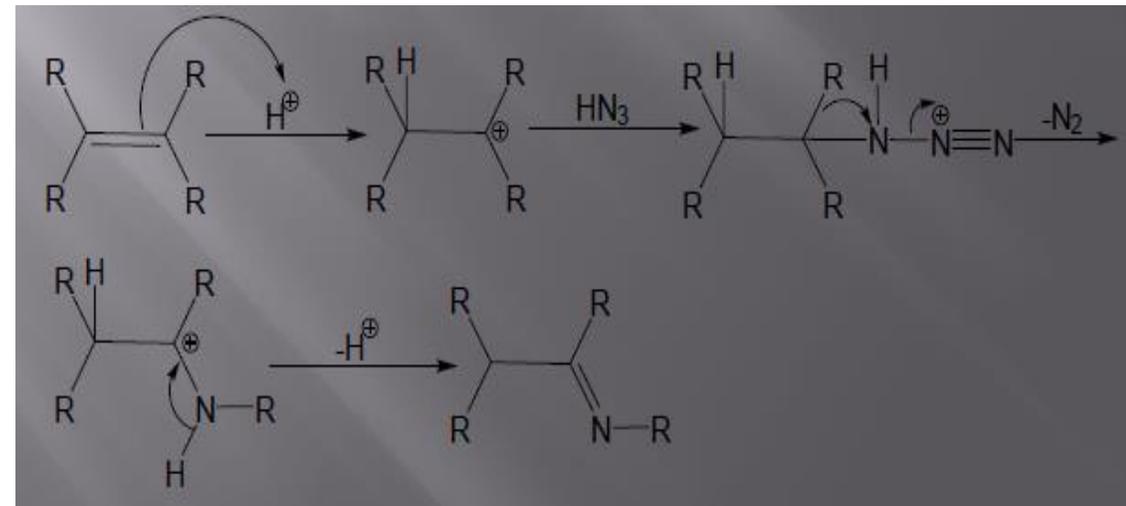
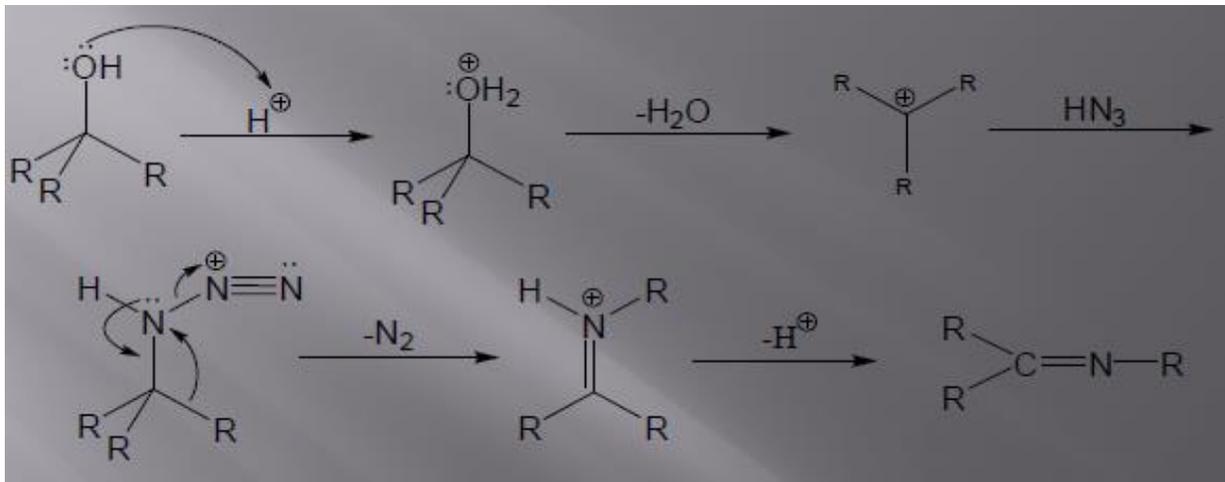


Example 2



Reaction of tert-alcohol (e.g.1) or olefin (e.g., 2) with hydrazoic acid under acidic condition to give substituted imines is also a form of Schmidt rearrangement
olefin

Mechanism of the reaction is as follows.
tert-alcohol



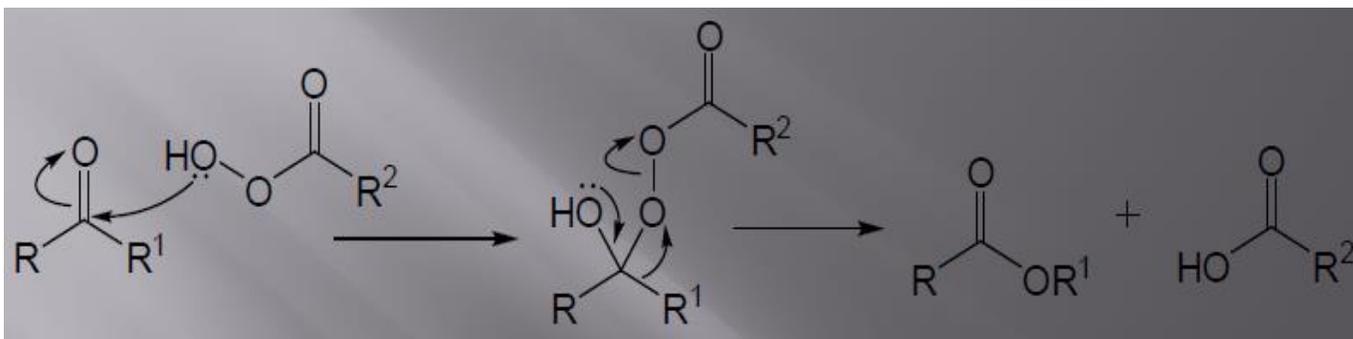
Rearrangements to Electron Deficient Oxygen

1. Baeyer Villiger Oxidation
2. Cumene hydroperoxide phenol
3. Dakin Reaction

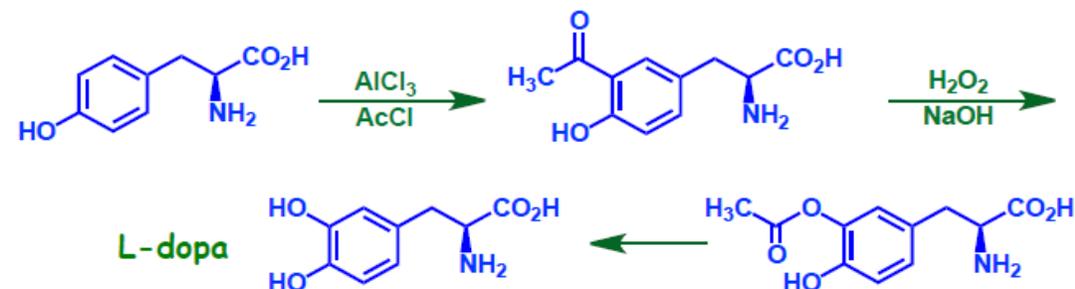
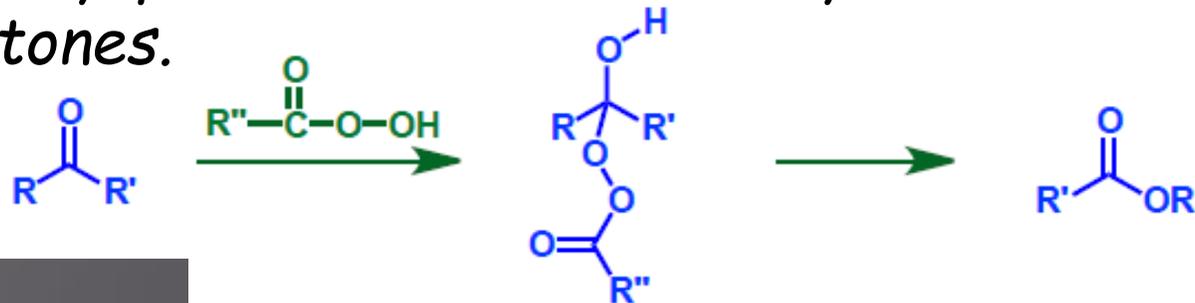
Baeyer Villiger Oxidation

In Baeyer-Villiger rearrangement, ketone on treatment with peracid gives ester by oxyinsertion. Reaction is catalyzed by presence of acid catalyst. Reaction is particularly useful for synthesis of lactones.

Mechanism



Reaction:



First step is the addition of peroxy acid to the carbonyl carbon leading to a tetrahedral intermediate. In next step, a concerted migration of the migrating group and loss of carboxylic acid provides the product.

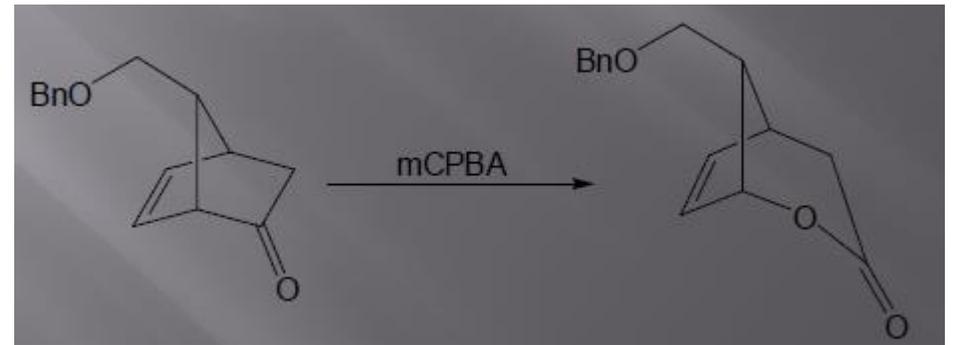
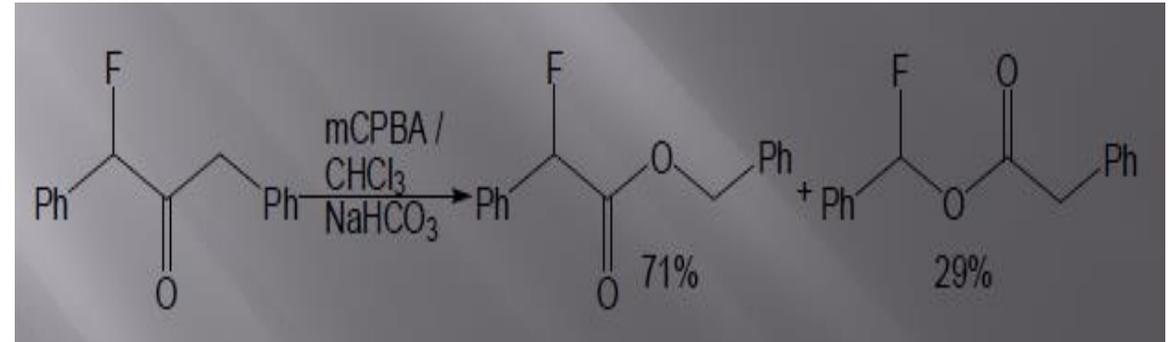
The mechanism is supported by fact that oxidation of Ph²C¹⁸O yields only PhC¹⁸OOPh (i.e. there is no scrambling of ¹⁸O label in the product Ester.)

The loss of carboxylates and migration of R is concerted, as the reaction is known to be faster when electron withdrawing substituents are present in the leaving group and electron donating substituents in migrating group.

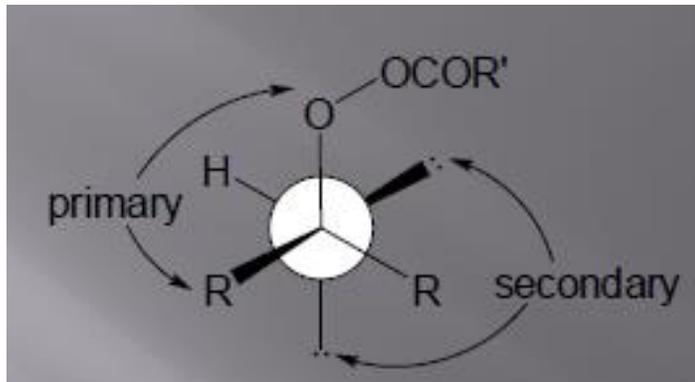
If the migrating group is chiral then its stereochemistry is retained.

Migratory aptitude in unsymmetrical ketones is as, $3^\circ > \text{cyclohexyl} > 2^\circ > \text{benzyl} > \text{aryl} > 1^\circ > \text{methyl}$. In case of aryl group, migrating ability is increased by electron donating groups present on ring.

Migration is favored when migrating group is antiperiplanar to the O-O bond of leaving group. This is known as primary stereoelectronic effect. Antiperiplanar alignment of lone pair of electrons on O2 with migrating group is termed as secondary stereoelectronic effect.



In the case of unsaturated ketones epoxidation is likely to be a competitive reaction. But, Baeyer-Villiger rearrangement is favored because ring strain can be relieved by oxy insertion and ring expansion.



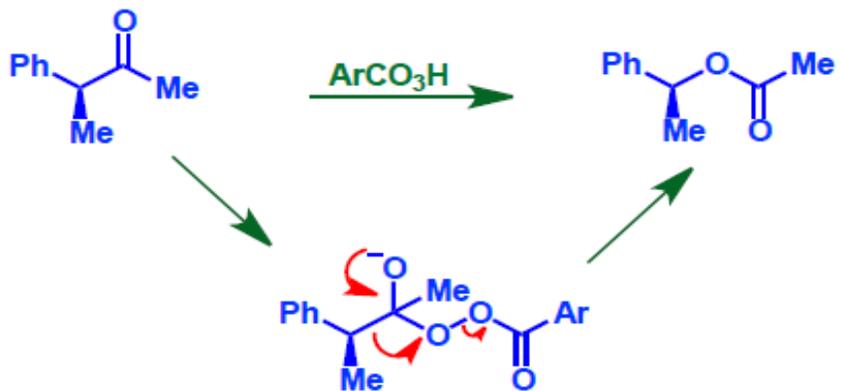
B.V.O. of Unsaturated Ketones:

There are three possibilities

- 1) Peracids can selectively epoxidize
- 2) Peracids can selectively carry out B.V.O
- 3) Can carry out both reactions

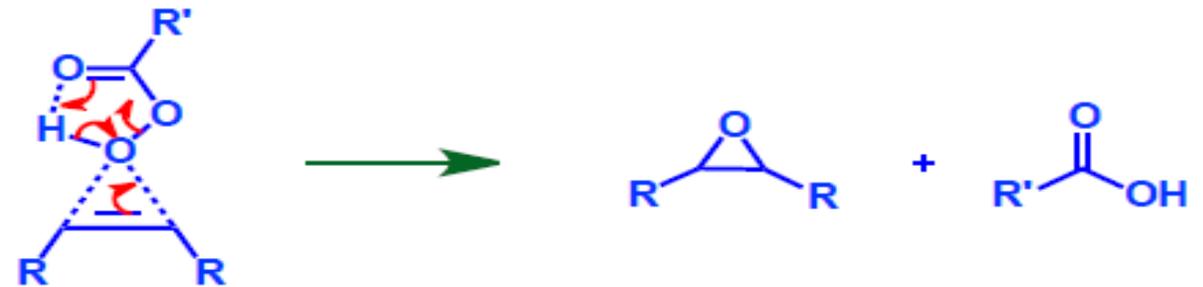
- Tertiary group migrates in preference of the secondary Group
- The alkene is not as reactive as expected because of steric crowding

Starting material configuration is retained in the product

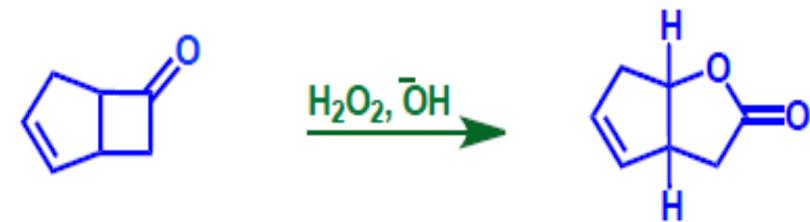


It is difficult to predict the outcome & it depends on-

- 1) Electrophilic nature of the ketone
- 2) Nucleophilic nature of the alkene

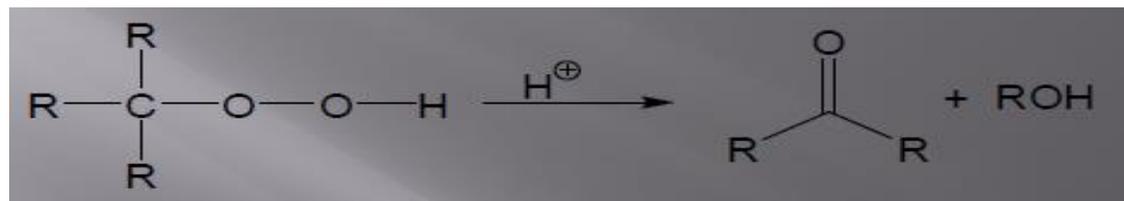


Small ring ketones will readily undergo B.V.O.

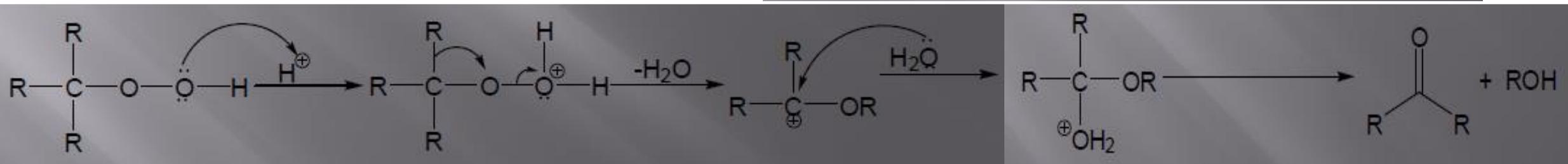


Rearrangement of hydroperoxide

Hydroperoxides can be cleaved in the presence of protic or Lewis acid. Reaction goes through rearrangement.

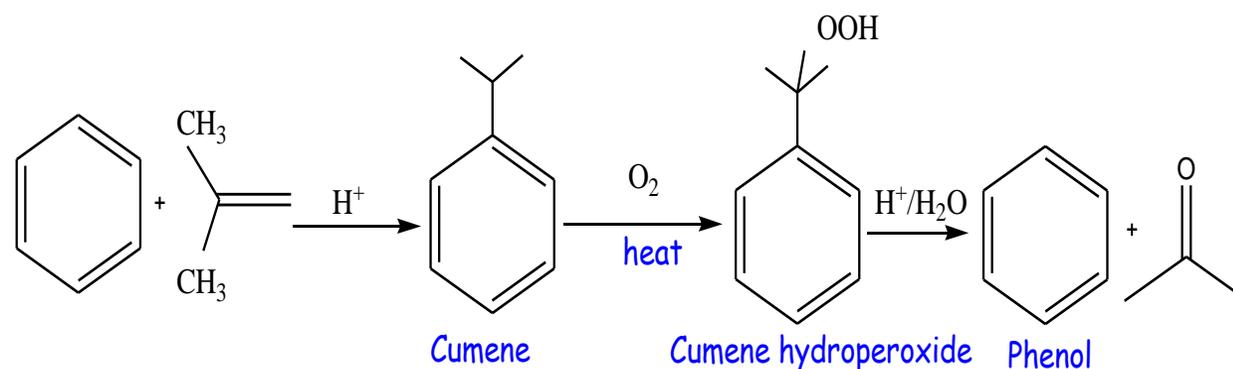
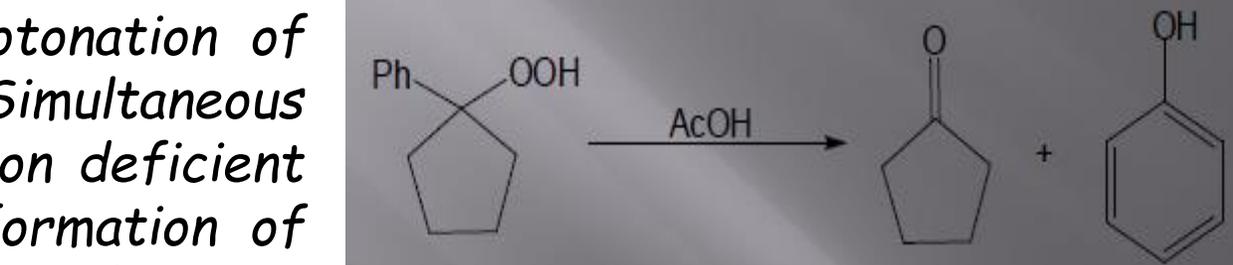


Mechanism



The important steps of the mechanism (a) Protonation of peroxide and removal of a molecule of water (b) Simultaneous shift of the migrating alkyl group to the electron deficient oxygen to give a rearranged carbocation (b) formation of hemiketal by the reaction of water, which then breaks down to give alcohol and ketone.

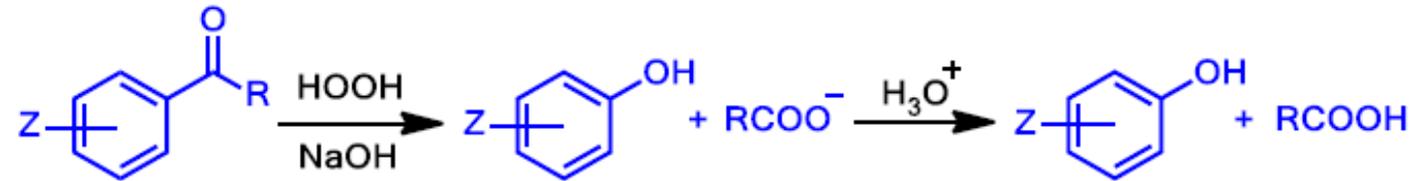
Alkyl group must be showing some sort of anchimeric assistance and the rearrangement must be going through benzenium ion in case of **cumene hydroperoxide-phenol rearrangement**.



Dakin Reaction

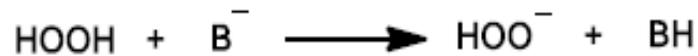
Benzaldehyde or acetophenone bearing **hydroxyl substituent in the ortho or para position** proceed rearrangement to give **catechol** or **quinol**, respectively known as Dakin Reaction. The reaction is performed in the presence of alkaline hydrogen peroxide and the mechanism is similar to that of Baeyer-Villiger reaction.

Reaction

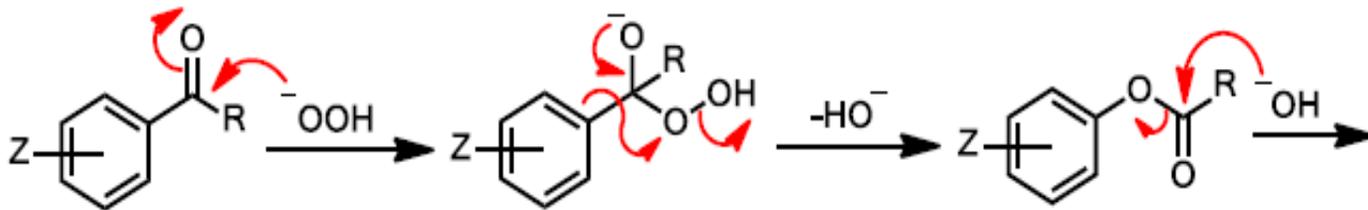


Mechanism:

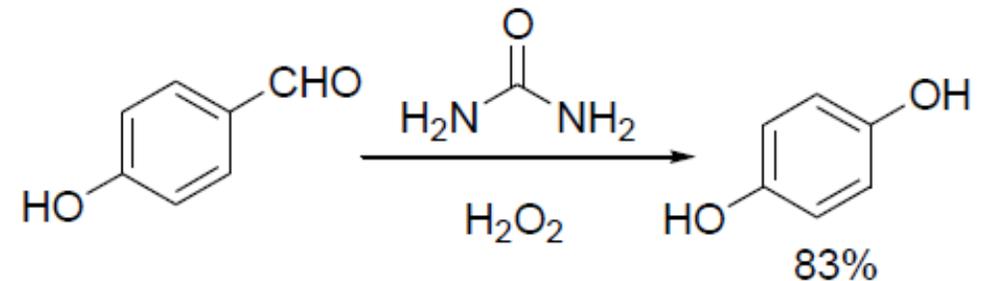
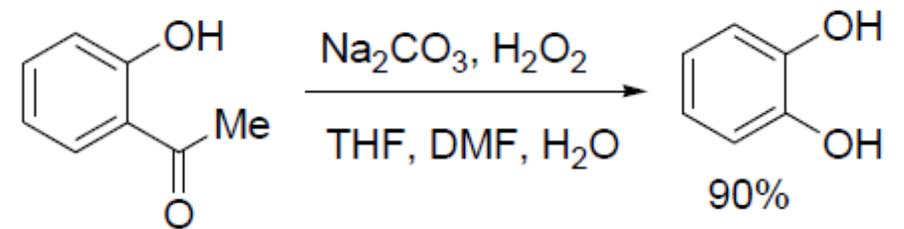
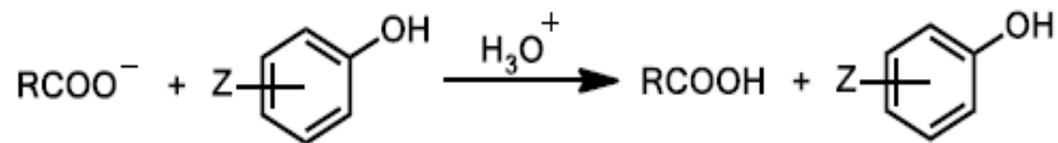
Examples:



Base source : NaOH
Base : HO⁻



Z : ortho/para-hydroxyl



Aromatic Rearrangement

1. Migration from oxygen to ring carbon

➤ Claisen rearrangement

➤ Fries rearrangement

2. Migration from nitrogen to ring carbon

✓ Hofmann-Martius rearrangement (N-Alkylanilines)

✓ Fisher-Hepp rearrangement (N-Alkyl-N-nitrosoanilines)

✓ Bamberger rearrangement (N-Arylhydroxylamines)

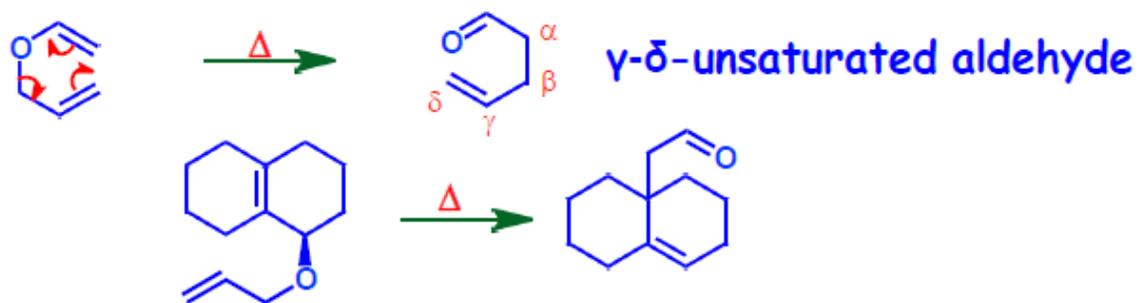
✓ Benzidine-Semidine rearrangement (Hydrazobenzenes)

✓ Orton Rearrangement (N-Haloanilides)

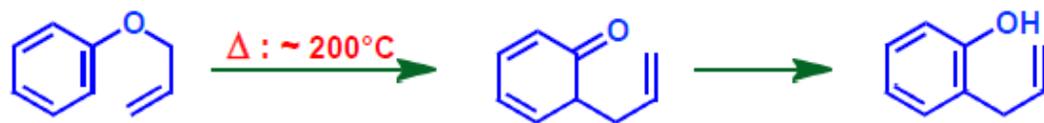
✓ N-azo to C-azo rearrangement

Claisen Rearrangement [3,3]-Sigmatropic Shift

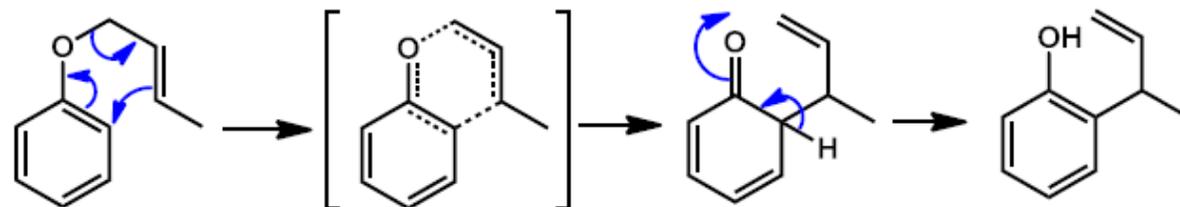
It is a [3,3]-sigmatropic rearrangement with only carbon atoms except one oxygen involved in a six membered transition state. Claisen Rearrangement are of two types: **1) Claisen Rearrangement of Allylvinyl Ethers:**



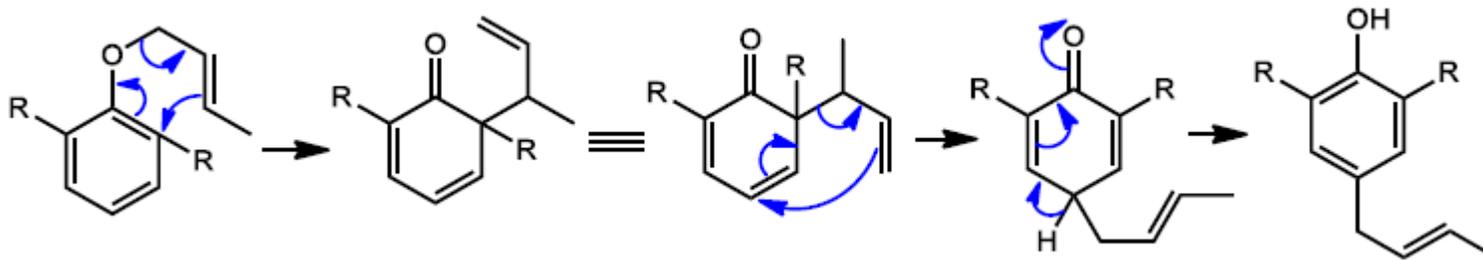
2) Claisen Rearrangement of Allylphenyl Ethers:



Mechanism

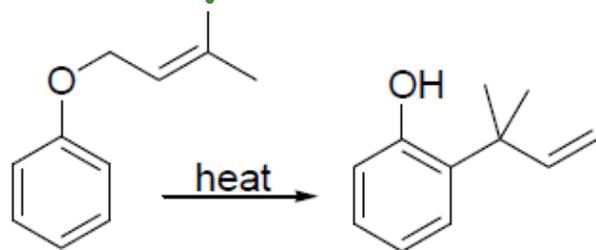


If ortho position is blocked, rearrangement continues to give para-product.

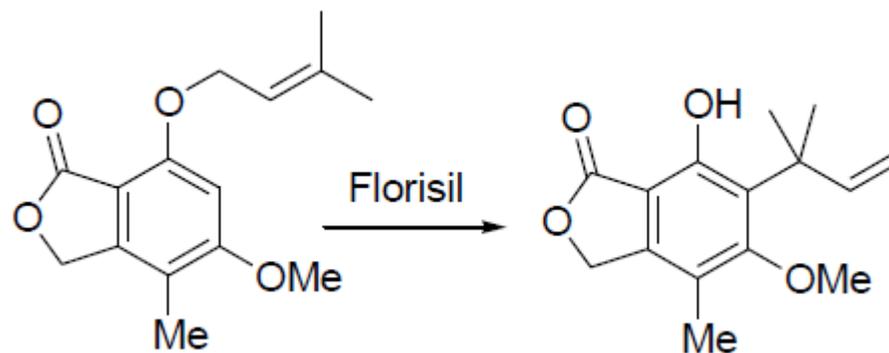


Other Examples

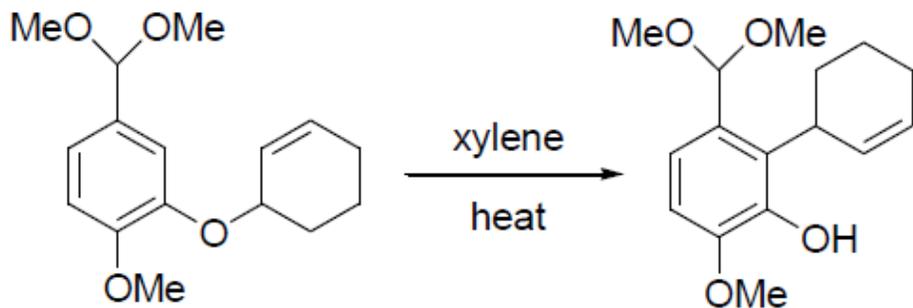
1.



2.



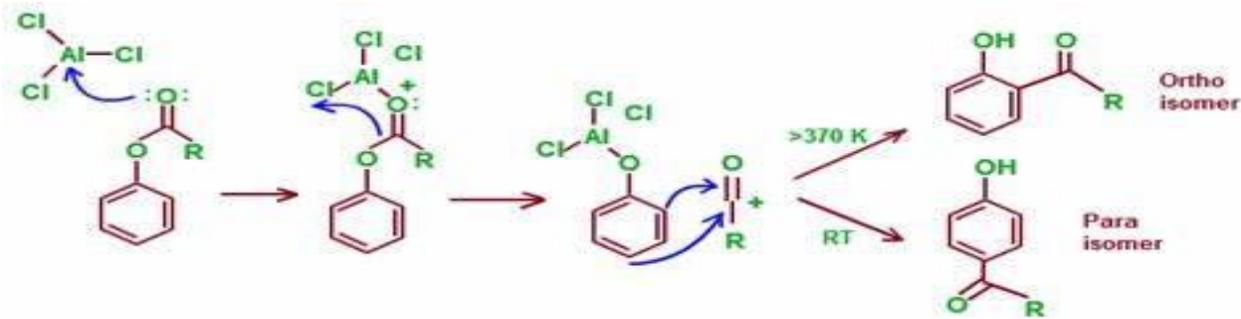
3.



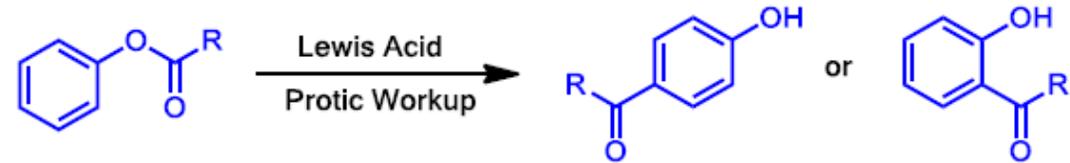
Fries rearrangement

Aryl esters with Lewis acid undergo rearrangement to give **ortho and para keto substituted phenols**. The complex between the ester and Lewis acid gives an **acylium ion** which reacts at the ortho and para positions as in Friedel-Crafts acylation.

Mechanism

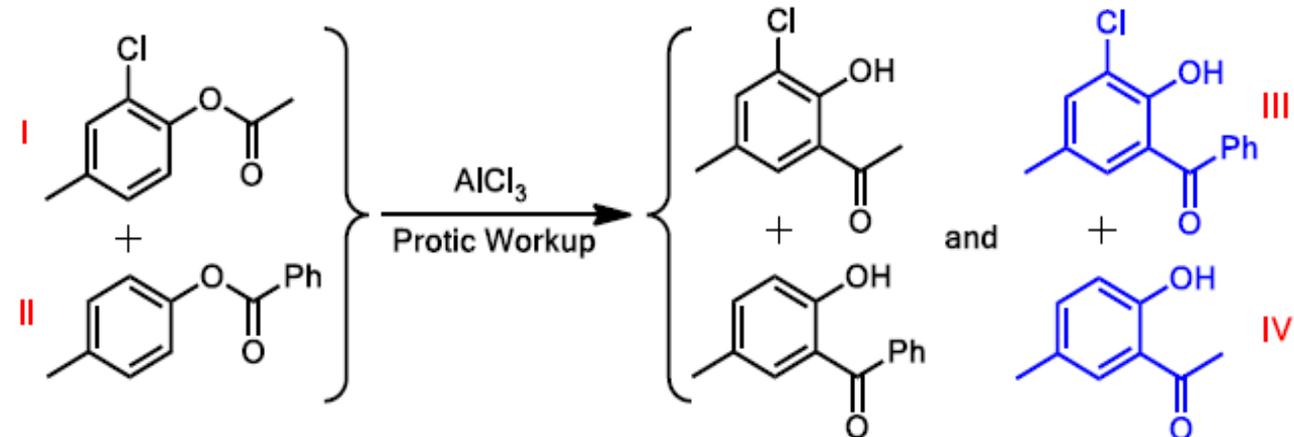
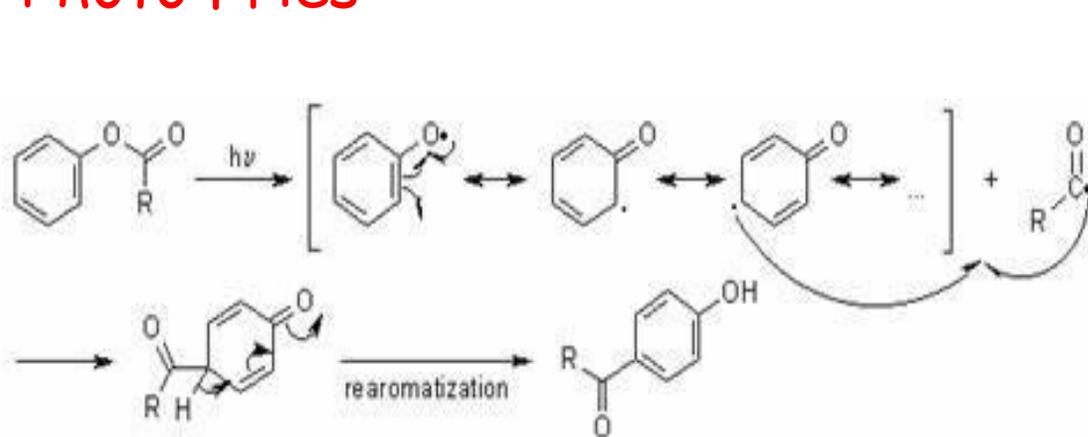


Reaction



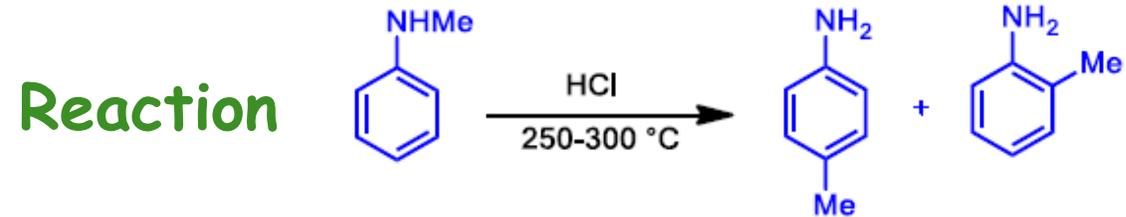
A mixture of aryl esters **I** and **II** reacted to form their corresponding keto substituted phenols along with crossover products **III** and **IV**.

Photo Fries

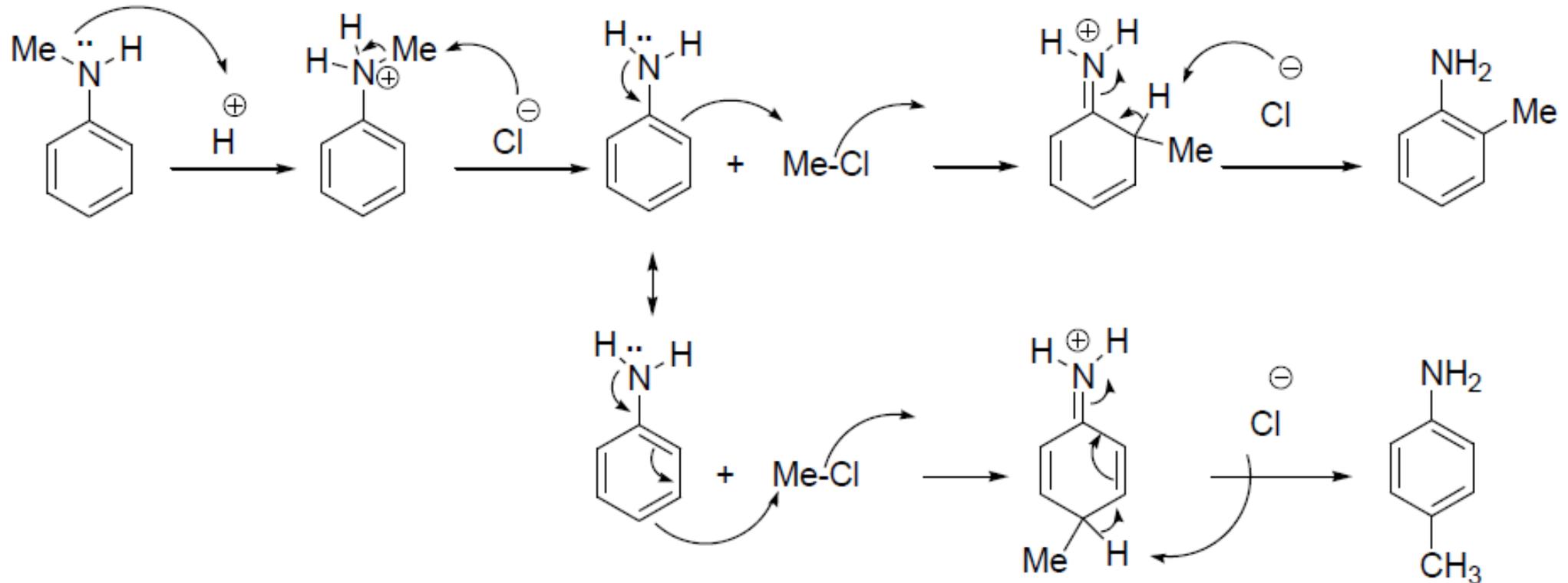


Hofmann-Martius rearrangement (Rearrangement of N-Alkylanilines)

N-alkylanilines in presence of acid at very high temperature rearranged to ortho and para alkylated products.



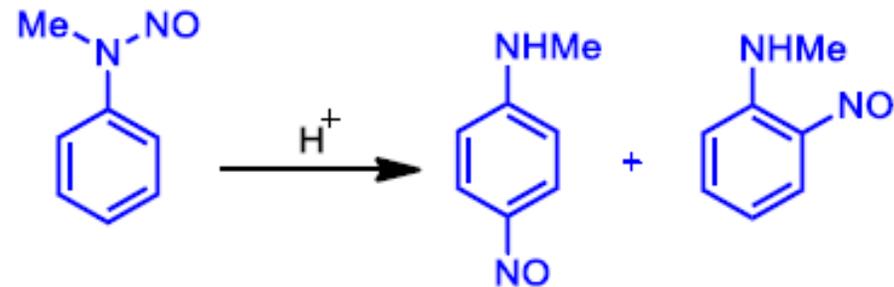
Mechanism



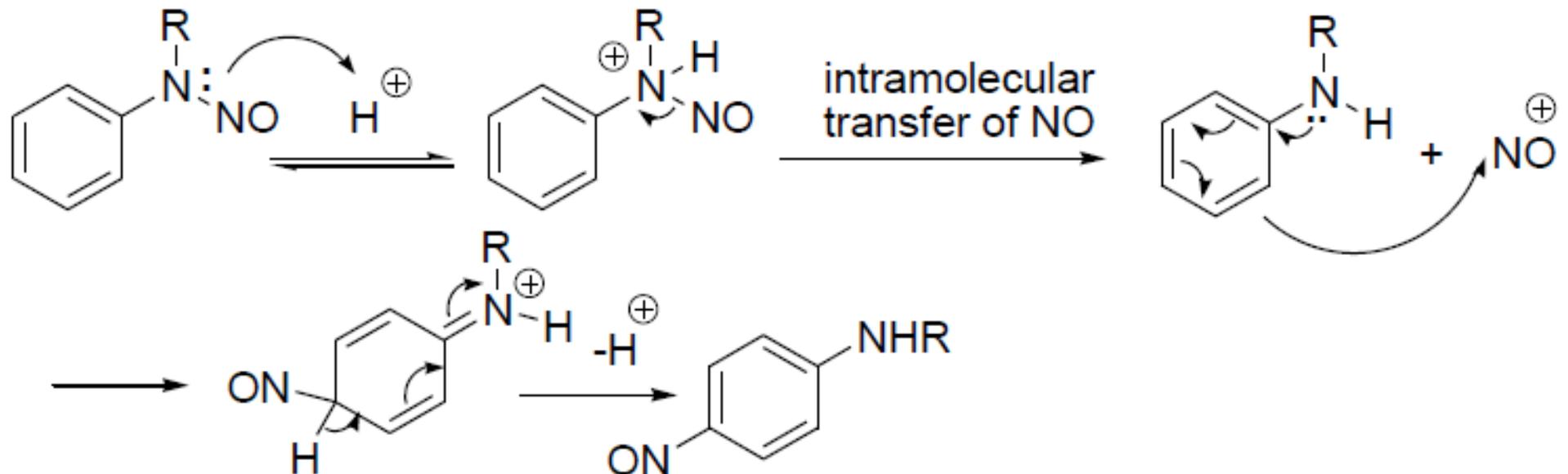
Fisher-Hepp Rearrangement (Rearrangement of N-Alkyl-N-nitrosoanilines)

The conjugate acid of the **N-Alkyl-N-nitrosoanilines** supply the nitrosonium ion which reacts mainly at the para-position in intramolecular fashion to give the p-nitroso product.

Reaction



Mechanism

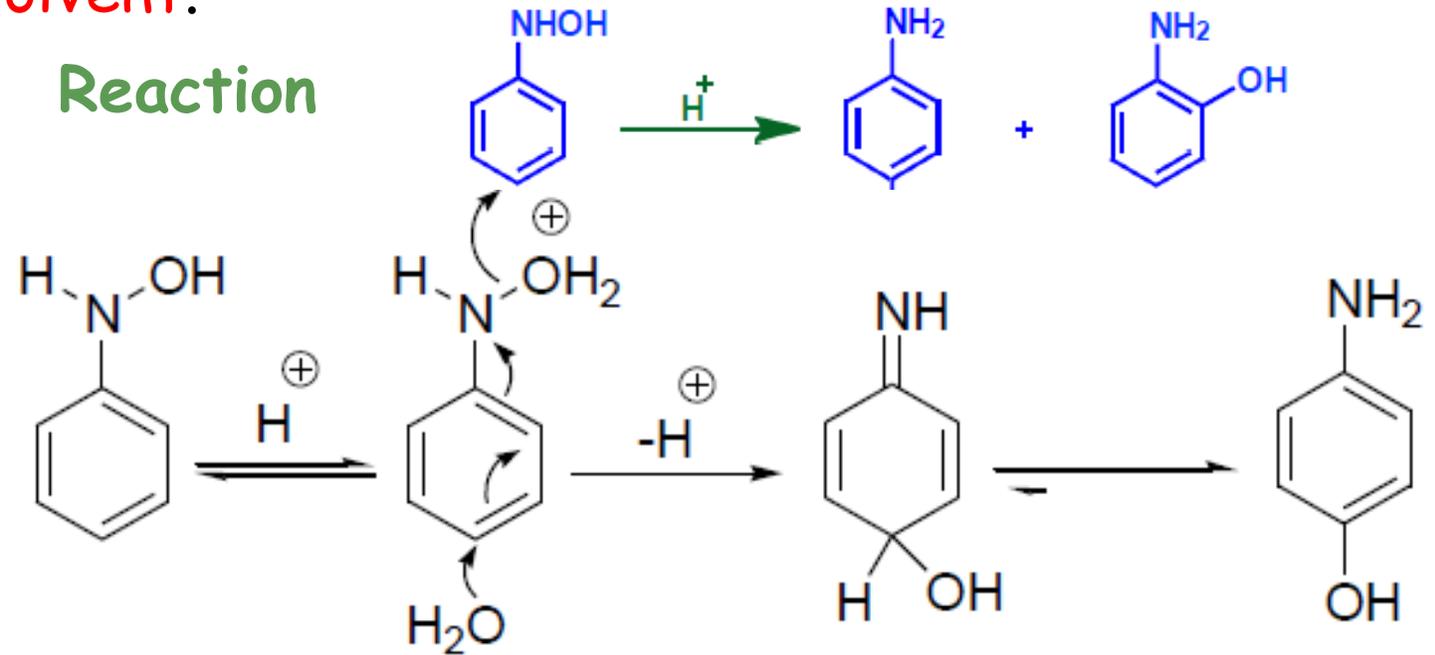


Bamberger Rearrangement

(Rearrangement of N-Arylhydroxylamines)

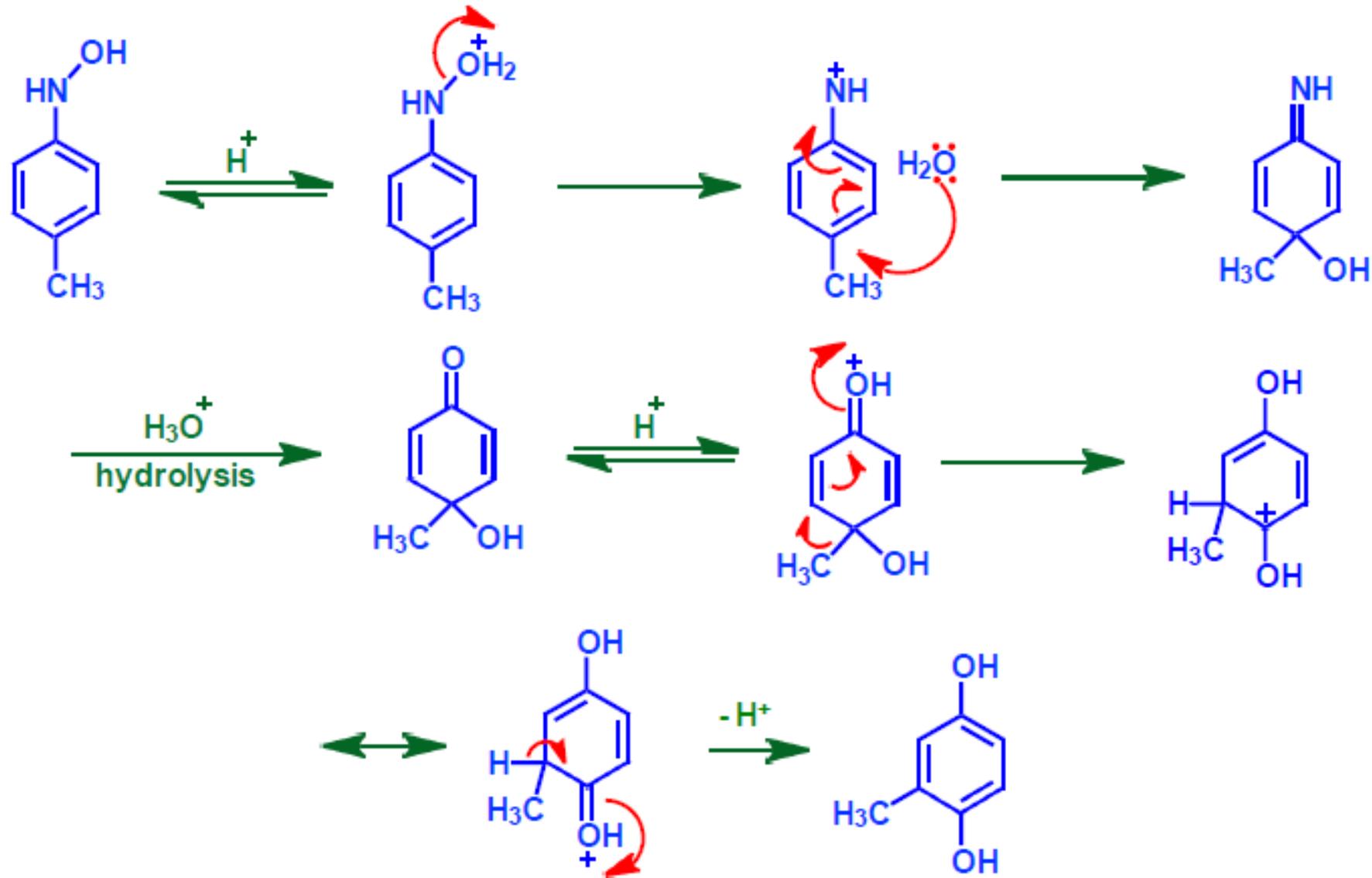
N-Arylhydroxylamines with **acid** undergoes rearrangement to give **aminophenols**. In this rearrangement, the conjugate acid of the hydroxylamine undergoes nucleophilic attack by the **solvent**.

Mechanism



When para-position is already occupied ???

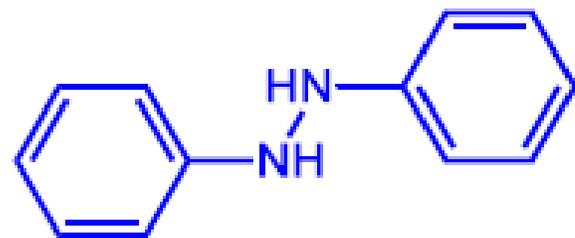
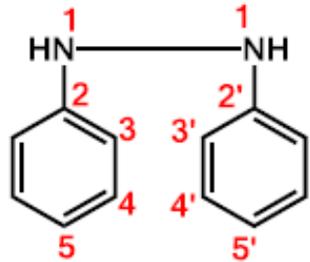
Hydrolysis followed by Dienone-phenol type of rearrangement occurs.



Benzidine-Semidine Rearrangement (Rearrangements of Hydrazobenzenes)

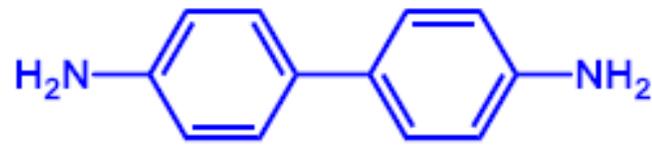
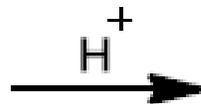
Hydrazobenzene undergoes [5,5]-sigmatropic rearrangement in the presence of acid to give **Benzidines**, **Diphenylene** and **Semidines**.

Structure of Benzidines

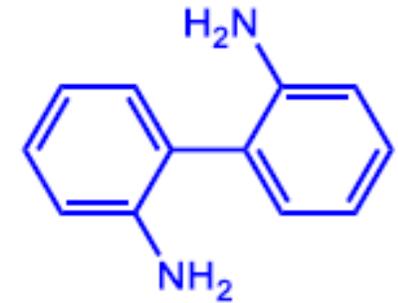


Hydrazobenzene

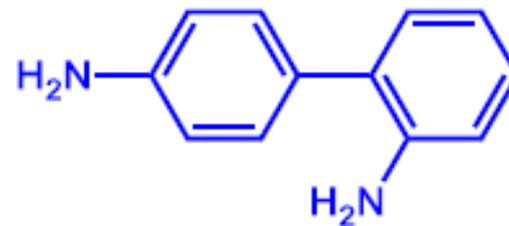
Reaction



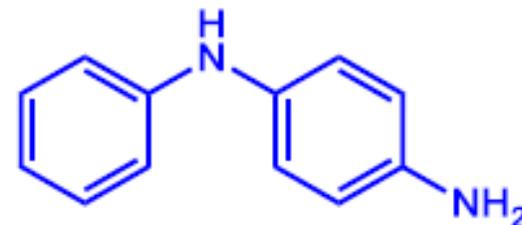
p-Benzidine



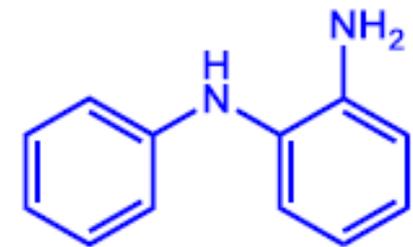
o-Benzidine



Diphenylene



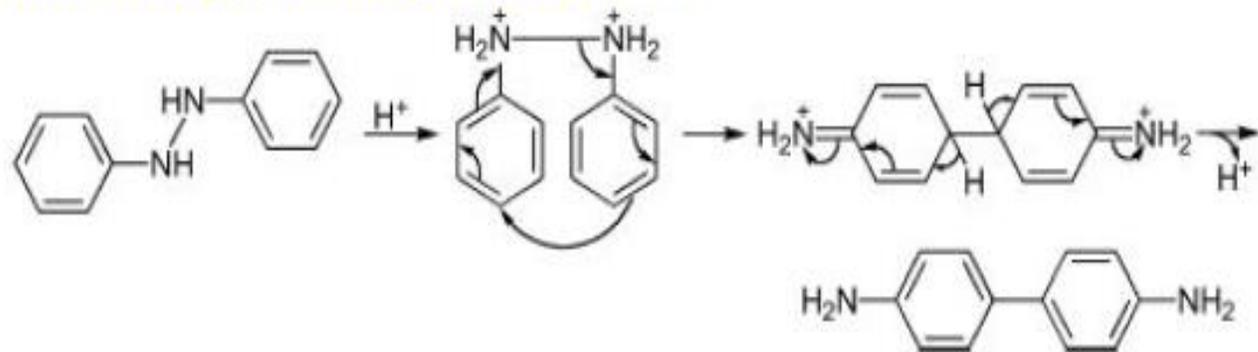
p-Semidine



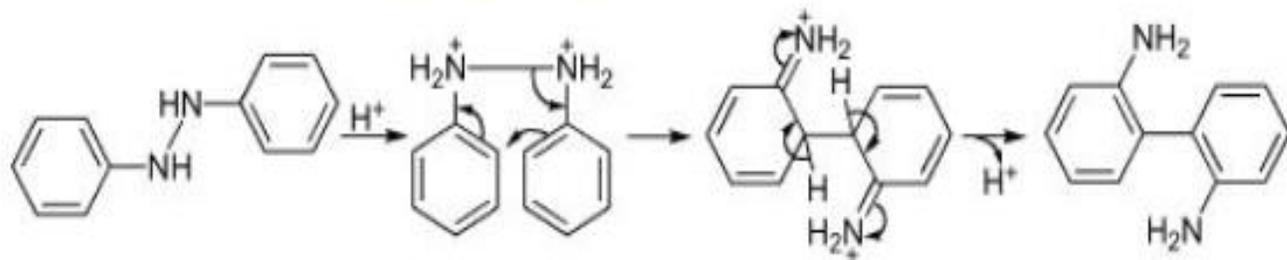
o-Semidine

Mechanism

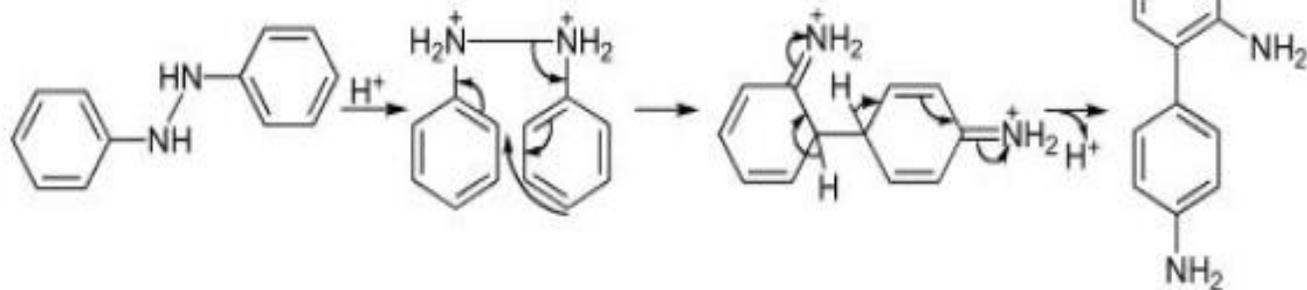
Formation of *p*-Benzidine: [5,5'] rearrangement



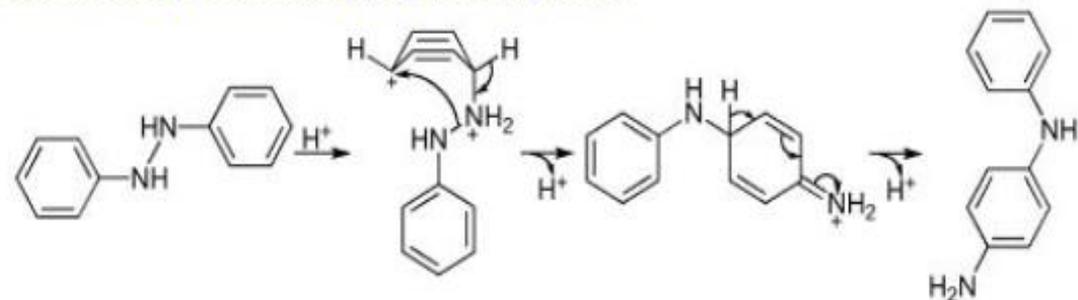
Formation of *o*-Benzidine: [3,3'] rearrangement



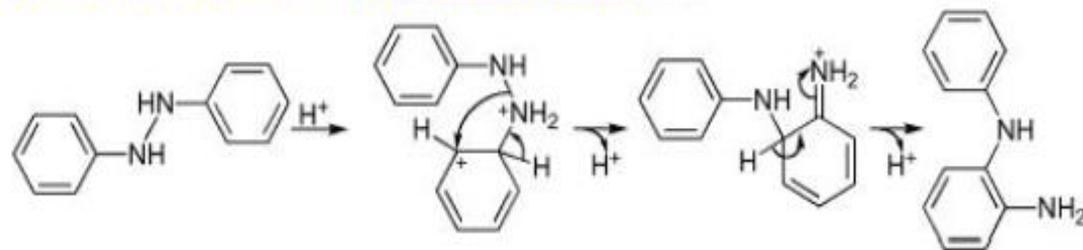
Formation of Diphenylene: [3,5'] rearrangement



Formation of *p*-Semidine: [1,5'] Rearrangement



Formation of *o*-Semidine: [1,3'] Rearrangement



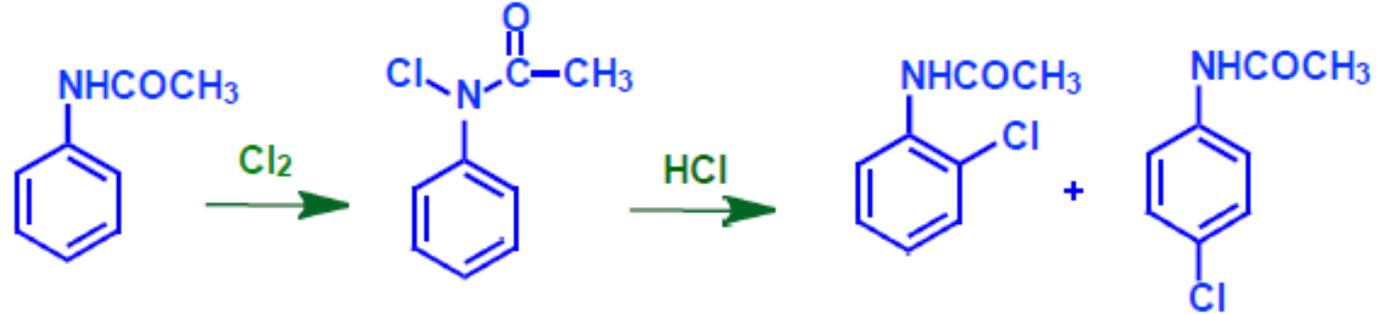
Other Examples

- Reaction 1: CN(C)c1ccccc1 reacts with SO_2 at 20°C for 48 h to yield CNc1ccc(cc1)-c2ccc(NC)cc2 in 75% yield.
- Reaction 2: CN(C)c1ccc(Br)cc1 reacts with HCl to yield Nc1ccc(Br)cc1-c2ccc(N)cc2 in 75% yield.

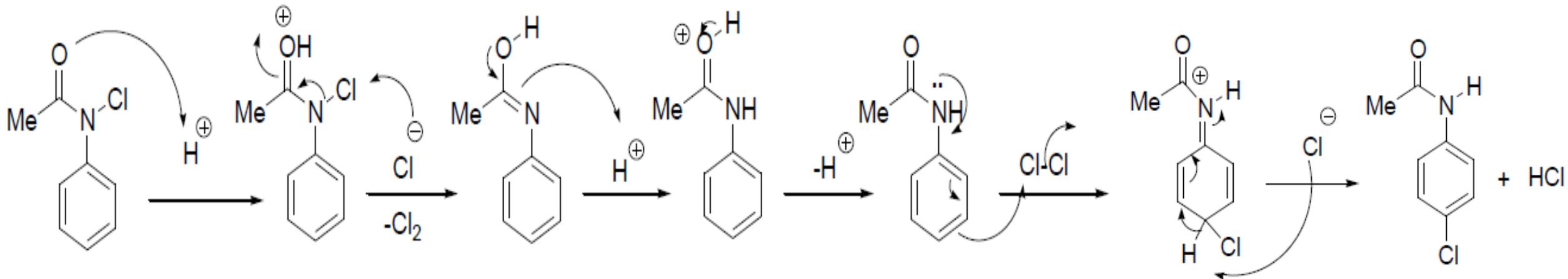
Orton Rearrangement (Rearrangements of N-Haloanilides)

Treatment of N-chloroacetanilide with hydrochloric acid affords a mixture of ortho and para-chloracetanilides in the same proportions as in the direct chlorination of acetanilide.

Reaction



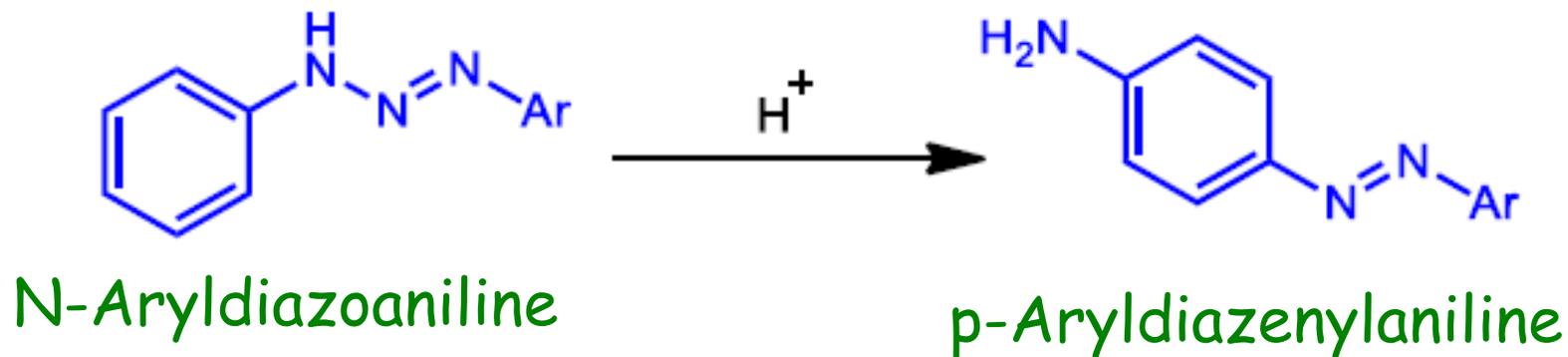
Mechanism



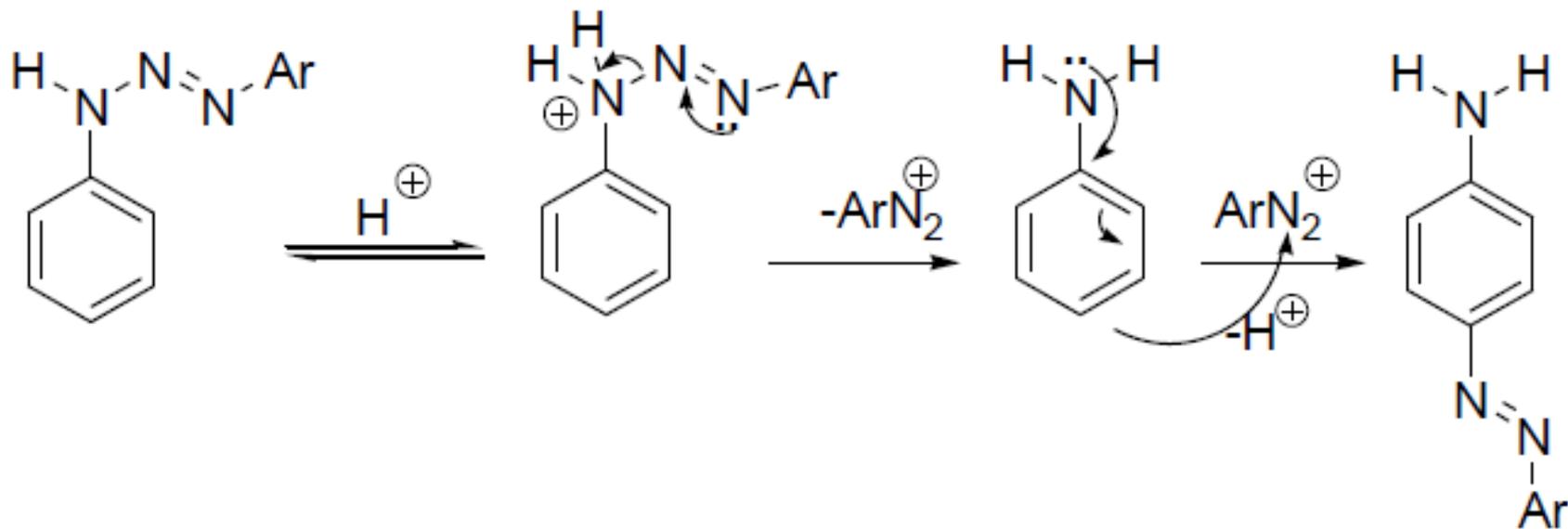
Rearrangements of N-Aryldiazoanilines

N-Aryldiazoanilines undergo rearrangement in presence of an acid to produce p-Aryldiazenylanilines. On treatment with acid, aryldiazonium ion is formed from the conjugate acid of amine, which migrates to the para position almost selectively.

Reaction



Mechanism



Text Books:

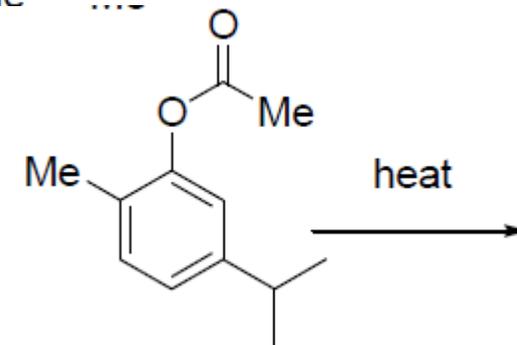
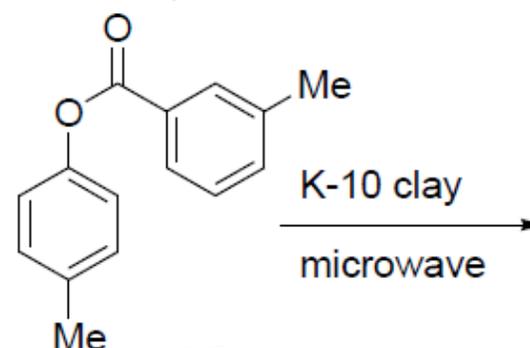
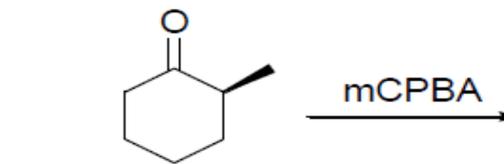
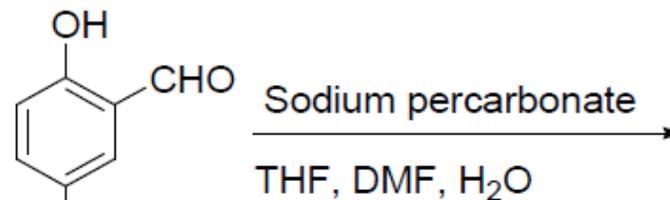
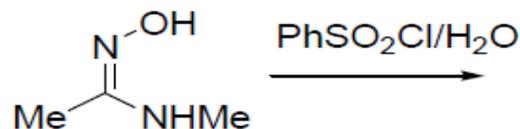
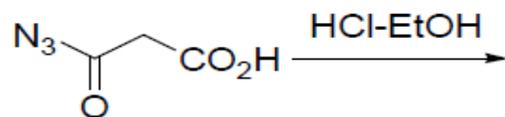
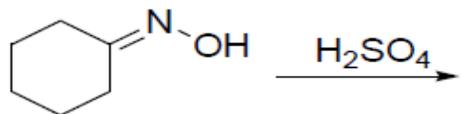
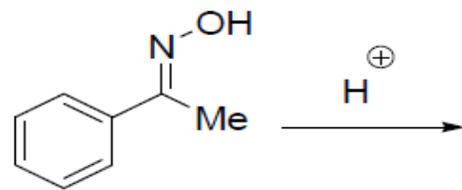
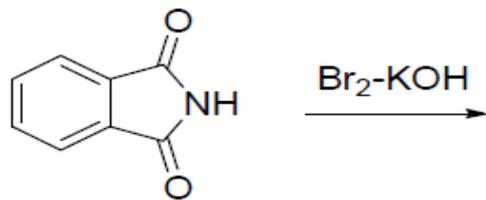
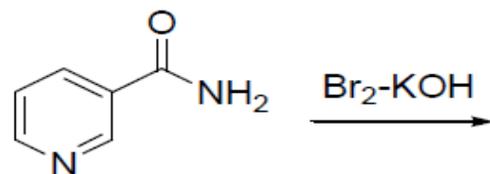
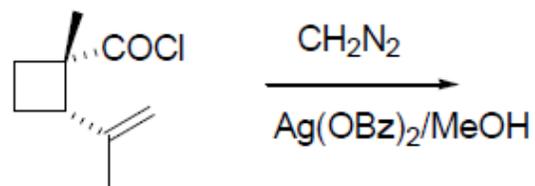
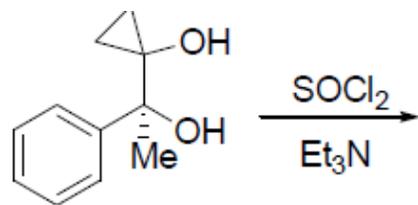
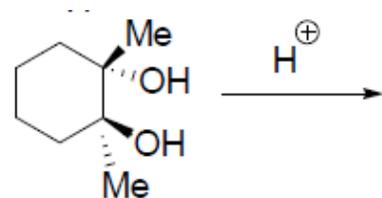
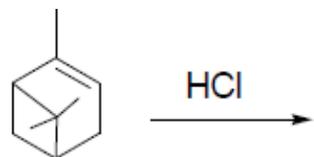
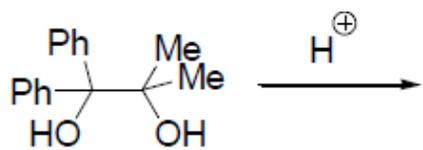
1. R.O.C. Norman and C. M. Coxon, *Principles of Organic Synthesis*, CRC Press, New York, 2009.
2. B. P. Mundy, M. G. Ellerdt, F. G. Favaloro Jr, *Name Reactions and Reagents in Organic Synthesis*, Wiley Interscience, New Jersey, 2005.
3. J. March, *Advanced Organic Chemistry*, 4th ed, Wiley Interscience, New York, 1992.

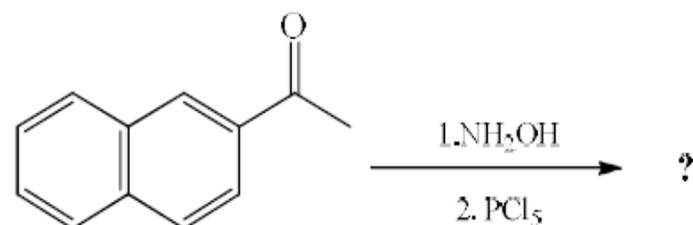
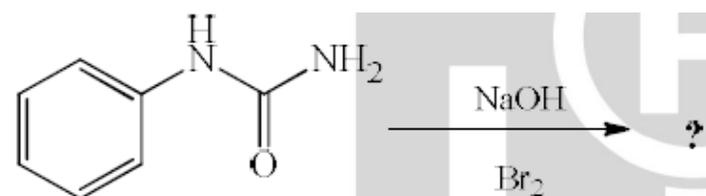
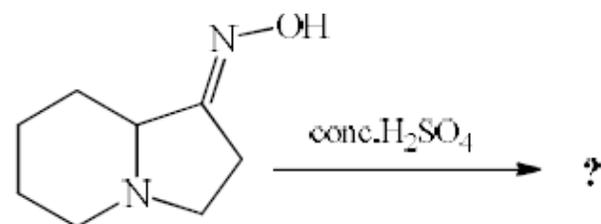
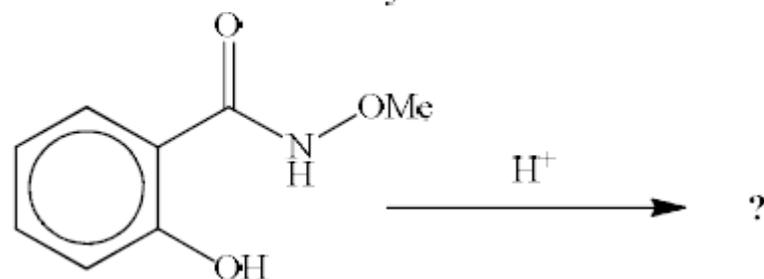
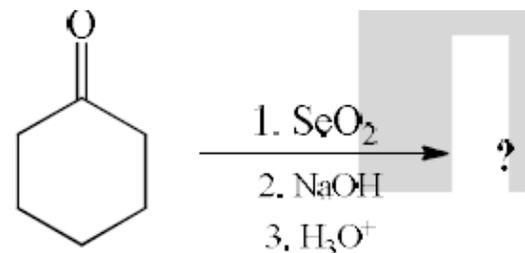
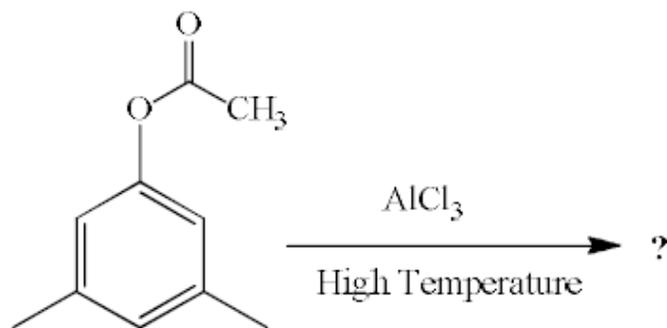
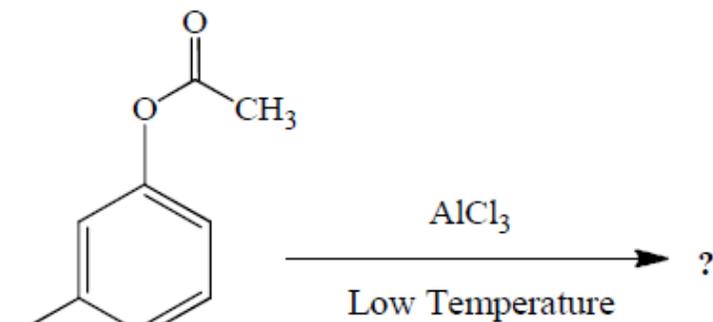
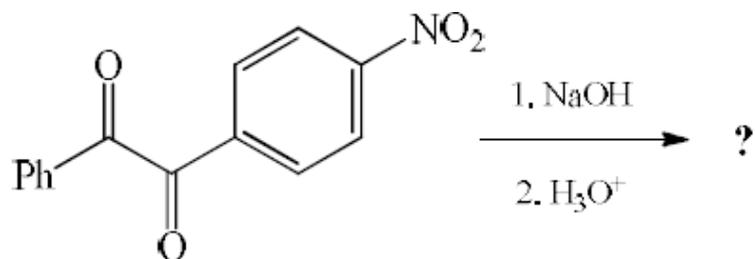
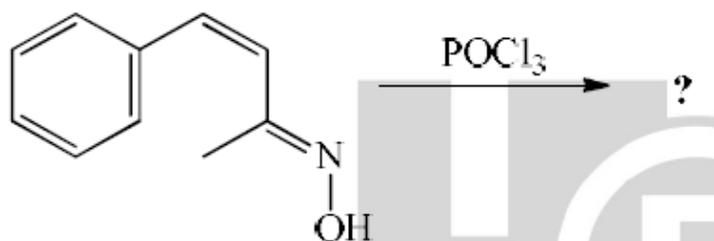
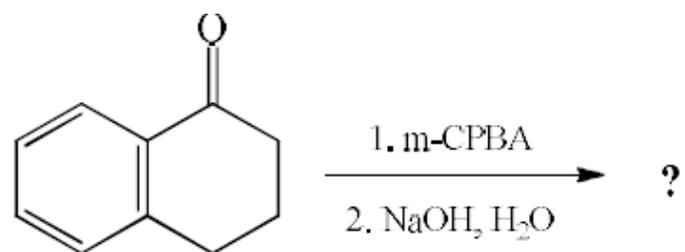
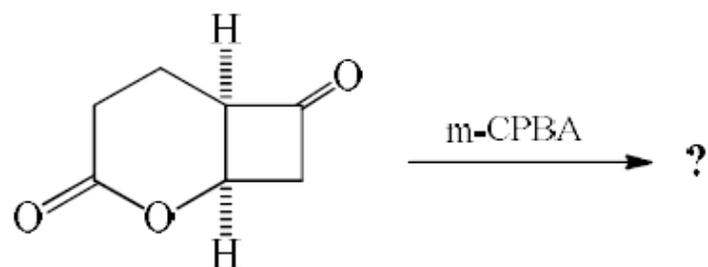
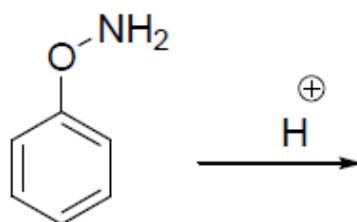
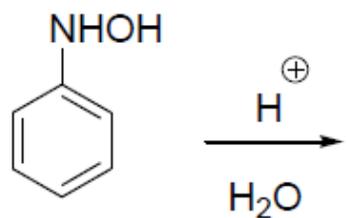
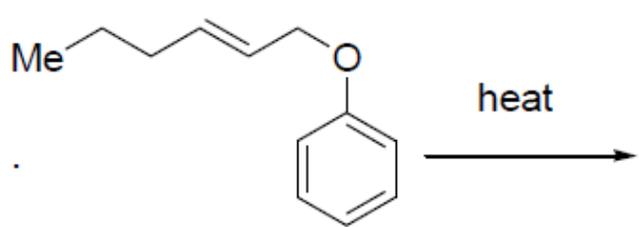
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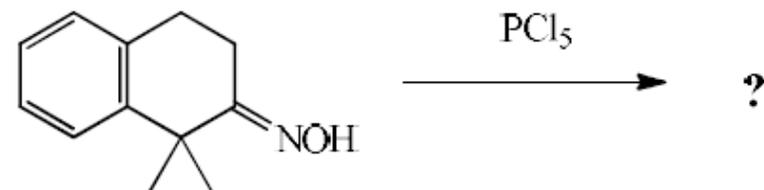
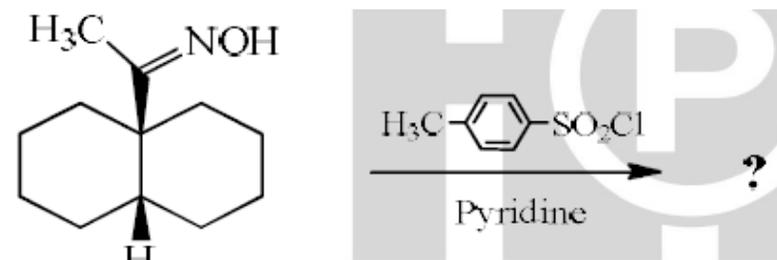
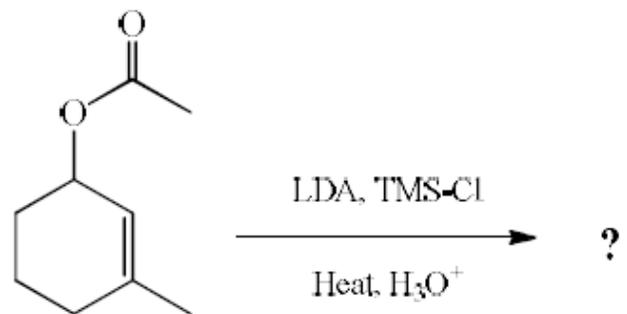
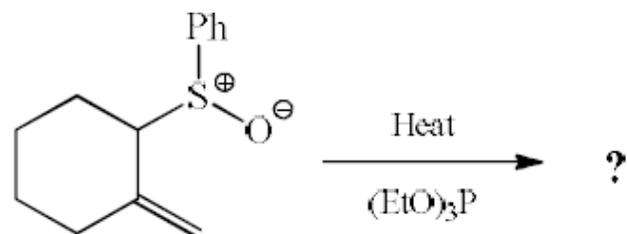
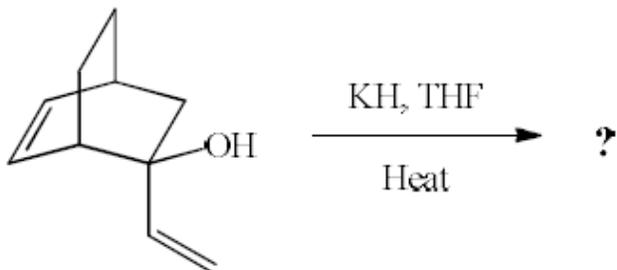
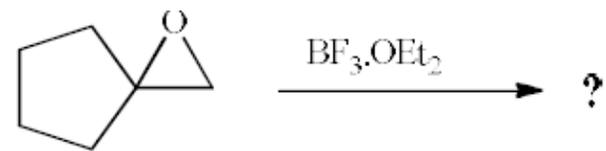
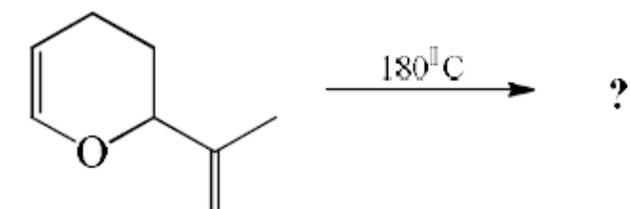
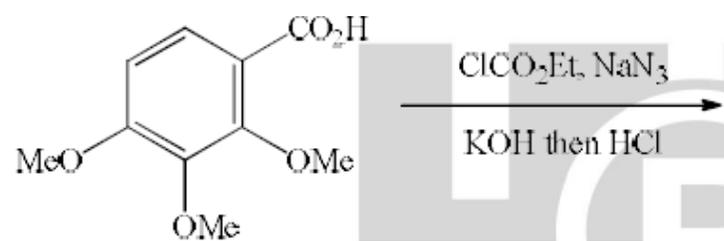
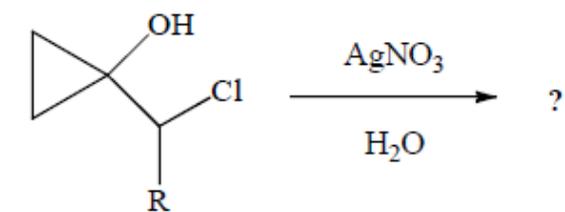
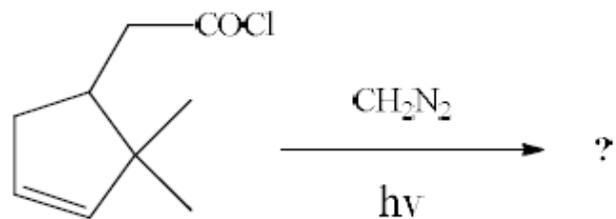
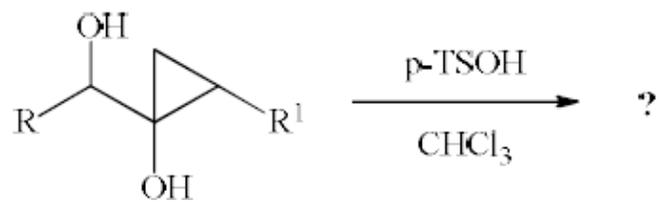
The material has been developed with the help of different text books, journal material and web help.

Problems

A. Predict the major products in the following reactions with mechanism.

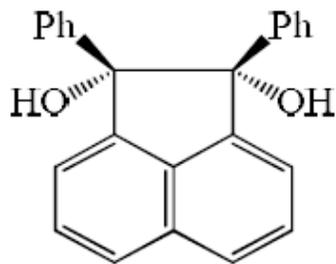




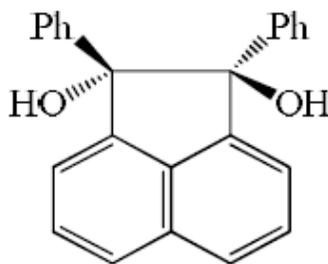


Explain each of the following observations.

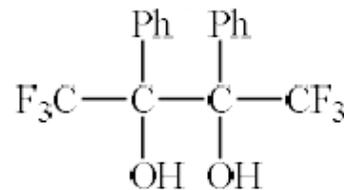
1. Cis- and trans-1,2- dimethylcyclohexane-1,2-diol give different products on treatment with concentrated sulfuric acid.
2. In the pinacol rearrangements of $\text{PhMeC(OH)-C(OH)PhMe}$ and $\text{Ph}_2\text{C(OH)-C(OH)Me}_2$, a phenyl group migrates in the former case but a methyl group migrates in the latter.



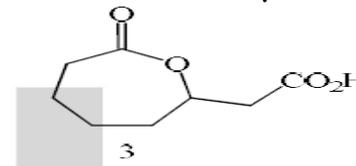
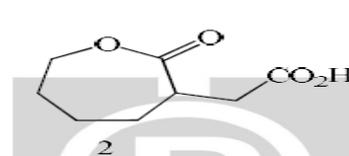
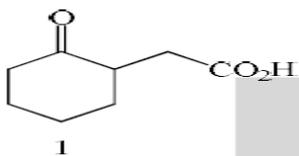
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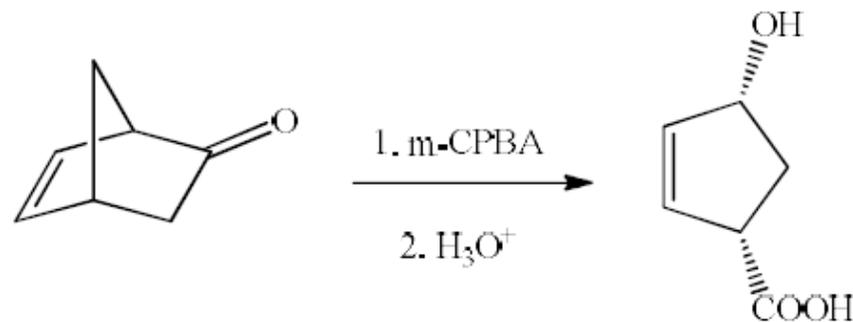
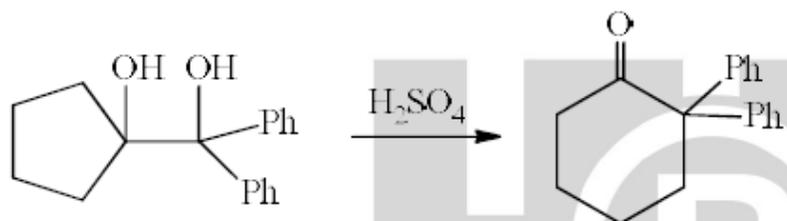
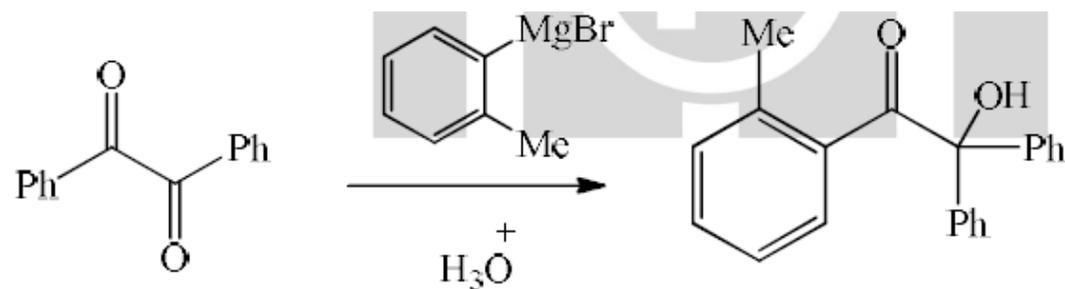
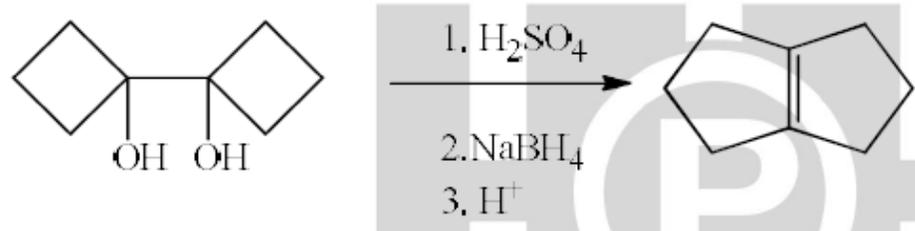
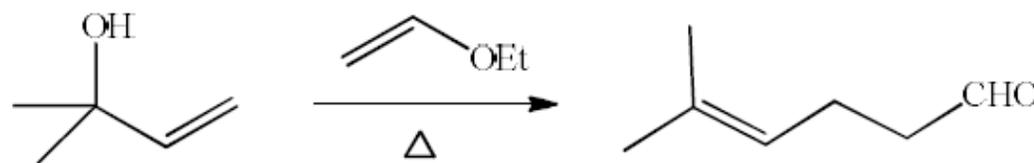
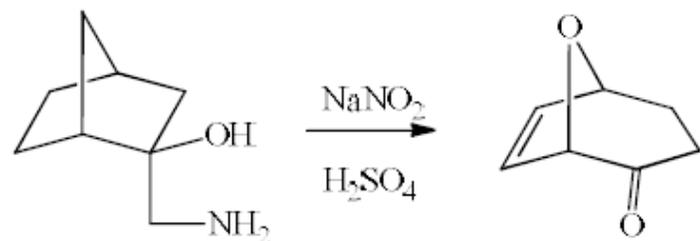
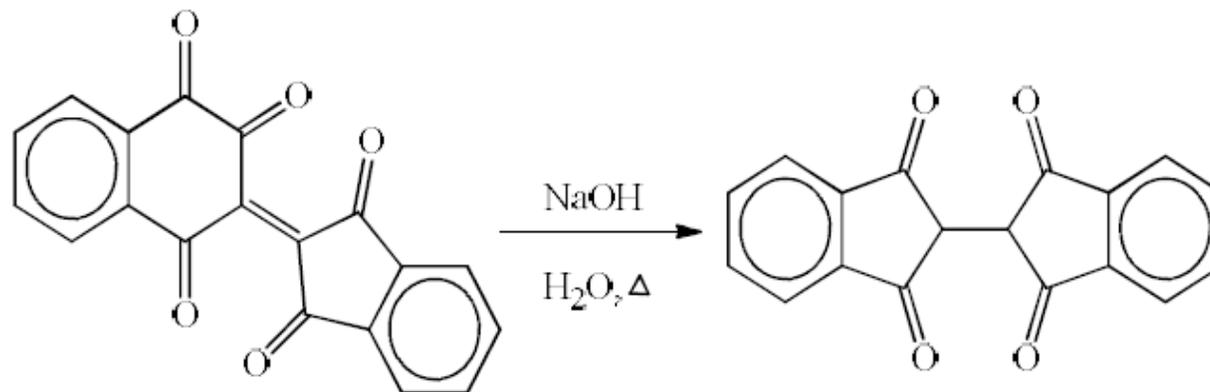
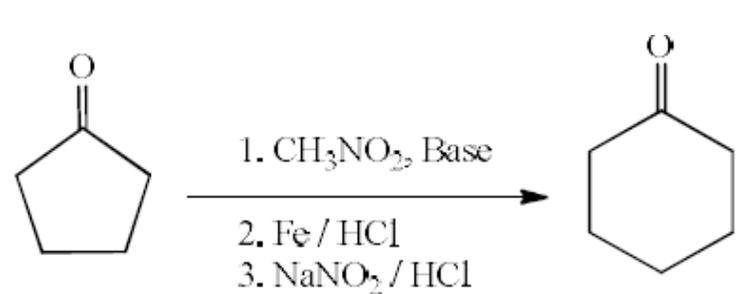
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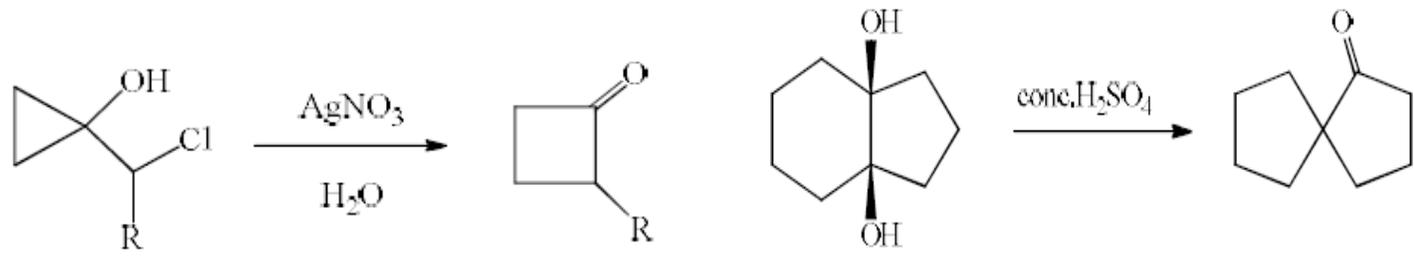
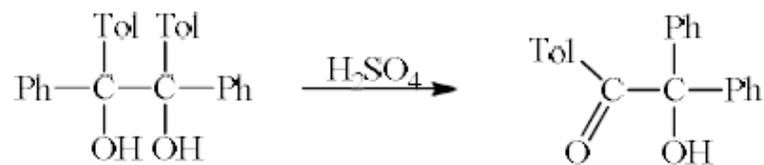
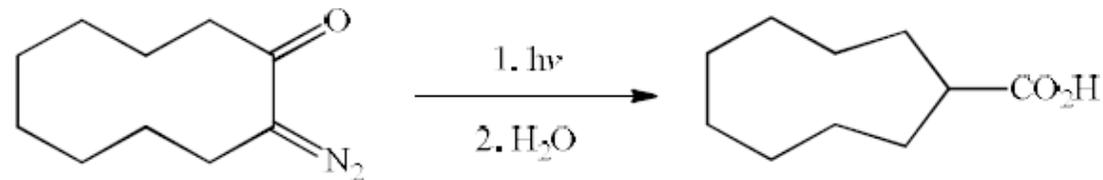
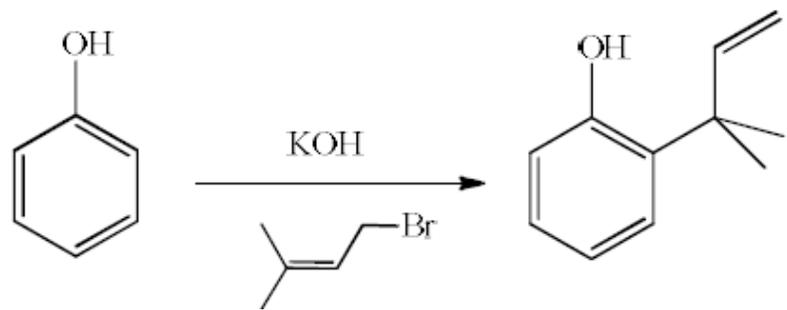


3. Compound given below does not undergo Pinacol-Pinacolone rearrangement.
4. Wolff rearrangement is used to prepare higher homologue of starting acid.
5. Pinacol rearrangement is used to prepare spiroketone.
6. Aldoximes are not suitable substrates for the Beckman rearrangement.
7. Fries rearrangement of Phenyl acetate gives o-hydroxy acetophenone at high temperature and p-hydroxy acetophenone at low temperature.
8. Ortho tolyl group is having less migratory aptitude than phenyl group in Benzil-Benzilicacid rearrangement.
9. N-Methyl benzamide does not give N-Methyl aniline when treated with Br_2/NaOH whereas benzamide gives aniline under similar reaction conditions.
10. Beckman rearrangement is used to prepare synthetic polymer.
11. In the Claisen rearrangement of β -phenyl allyl ether, the allyl group migrates to the 1 position and not to the 3 position.
12. In Baeyer-Villiger rearrangement, t-butyl group migrates in preference to phenyl group.
13. In the Baeyer-Villiger rearrangement of compound **1** with PhCO_3H , compound **2** is obtained and not compound **3**.



Provide suitable reaction pathways for following transformations and justify your answer.





where Tol = *o*-tolyl group

