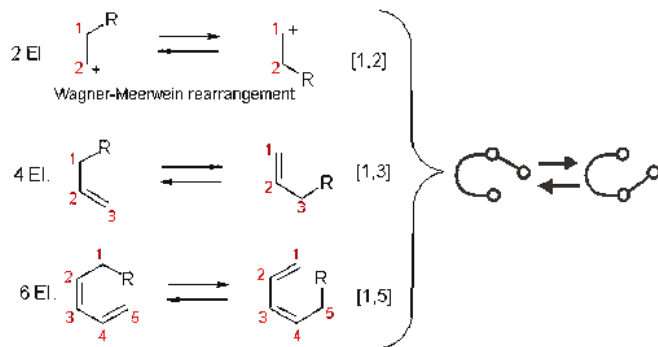


REARRANGEMENTS

Rearrangements: A rearrangement reaction is a broad class of organic reactions where the carbon skeleton of a molecule is rearranged to give a structural isomer of the original molecule



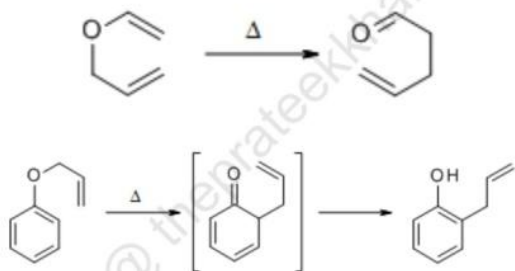
Intramolecular rearrangement

rearrangement in which a group or atom migrates from one position to another position within the molecule

GENERAL REACTION

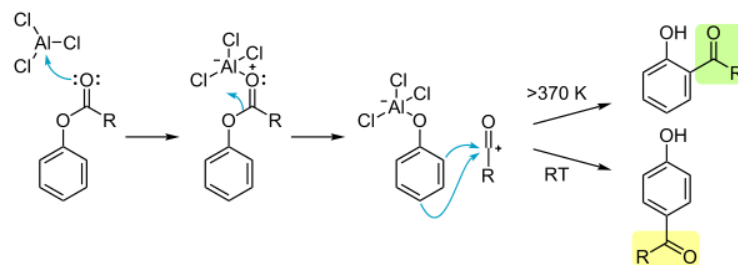
Compiled by: Pratik, Khanna

The Claisen rearrangement is an organic reaction where an allyl vinyl ether is converted into a γ,δ -unsaturated carbonyl compound with the input of heat or a Lewis acid.



Intermolecular rearrangement

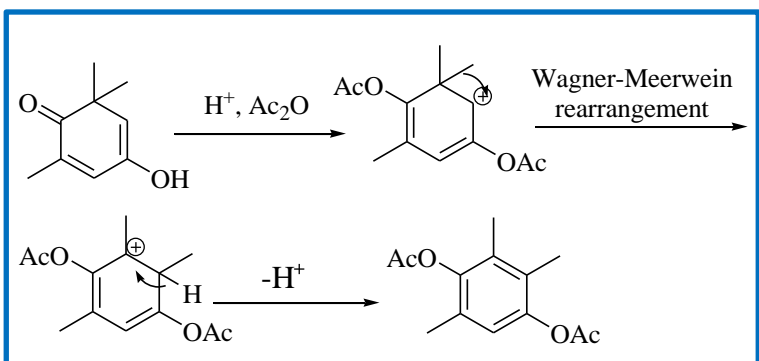
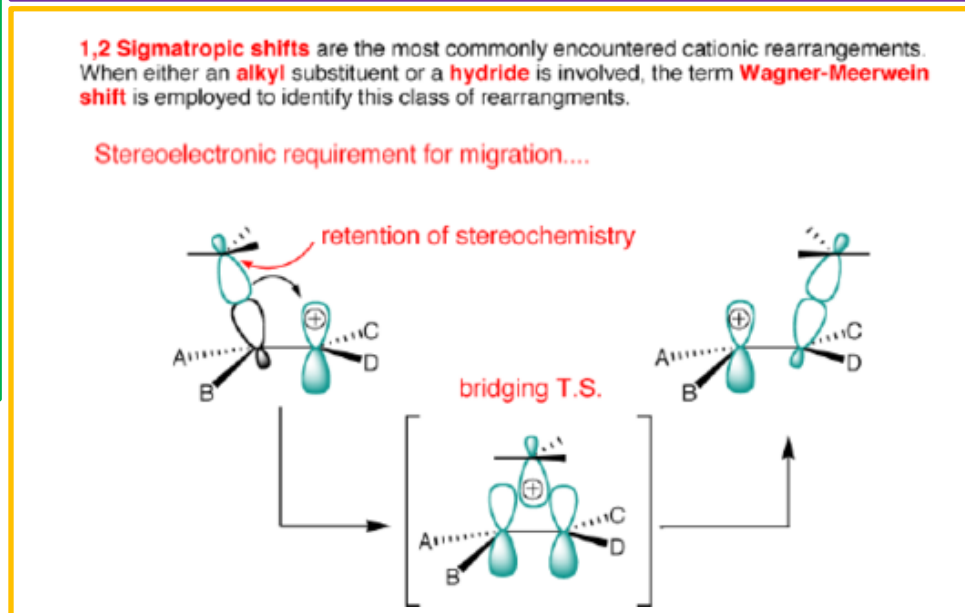
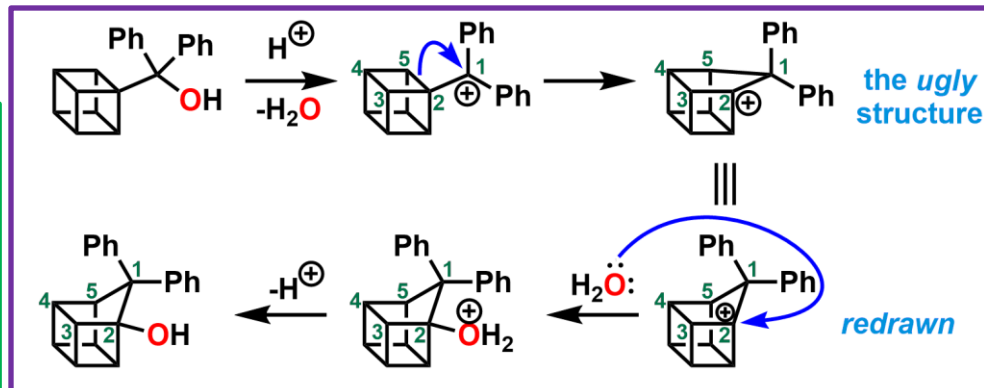
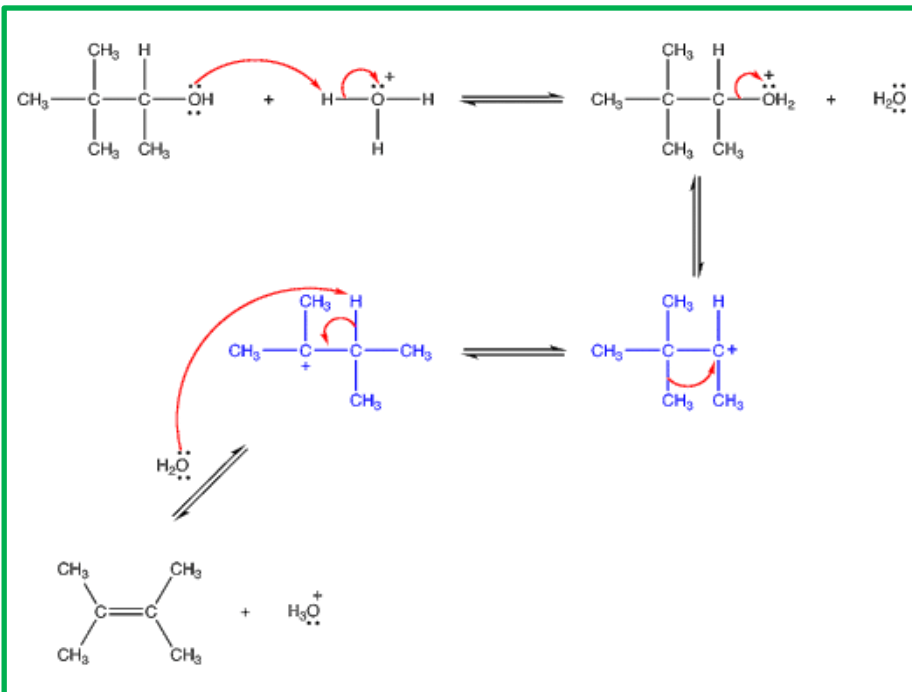
group becomes completely free during the migration



Rearrangement to electron-deficient carbon

Wagner-Meerwein rearrangement

- ❖ Class of [carbocation 1,2-rearrangement reactions](#)
- ❖ [hydrogen](#), [alkyl](#) or [aryl](#) group migrates from one carbon to a neighbouring carbon.
- ❖ Cationic [1,2]-sigmatropic rearrangements, proceeding suprafacially and with stereochemical retention.



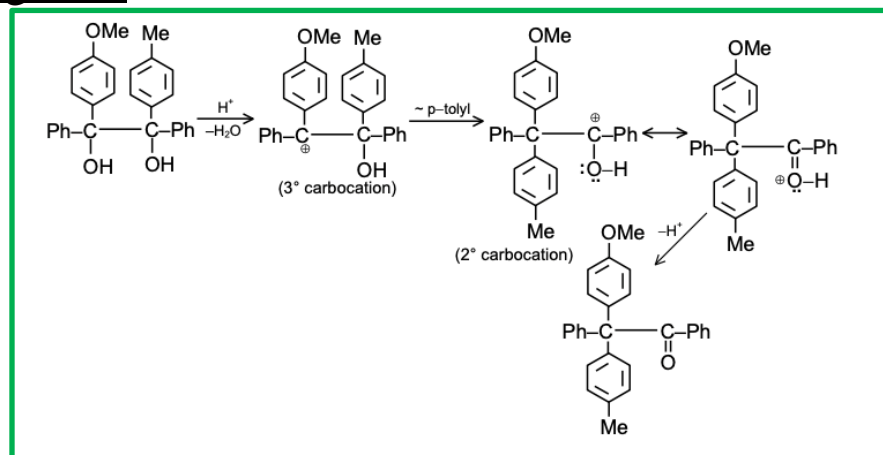
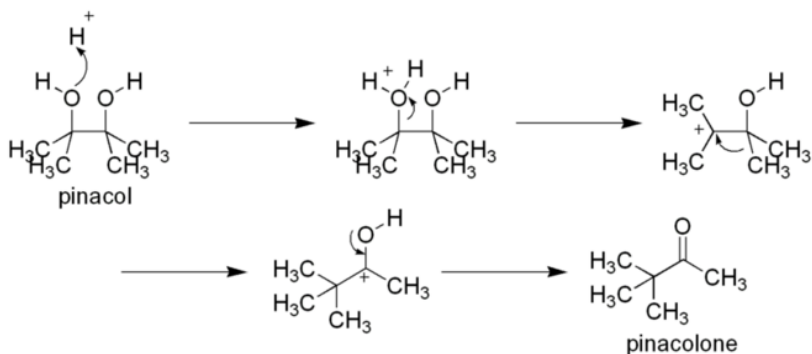
- The relationship is *suprafacial* when the same face of the π system or isolated orbital are involved in the process
- The relationship is *antarafacial* when opposite faces of the π system or isolated orbital are involved in the process

Pinacol-pinacolone rearrangement

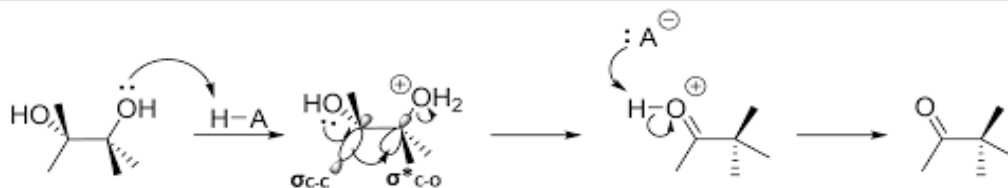
- Conversion a 1,2-diol to a carbonyl compound.
- The 1,2-rearrangement takes place under acidic conditions.
- The name comes from the rearrangement of pinacol to pinacolone

Mechanism

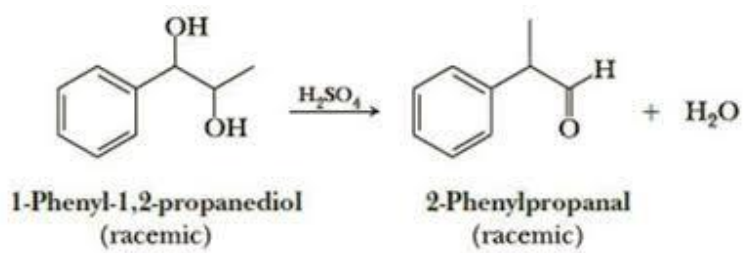
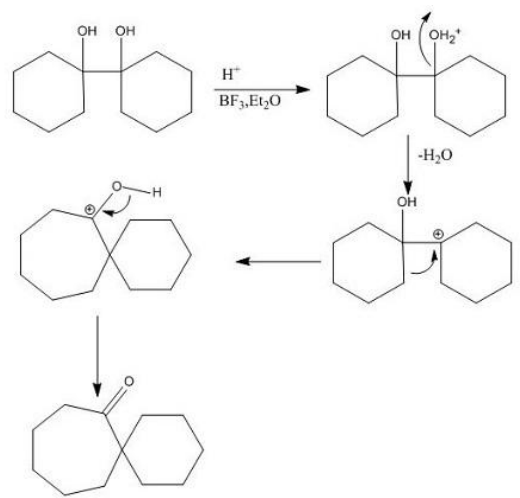
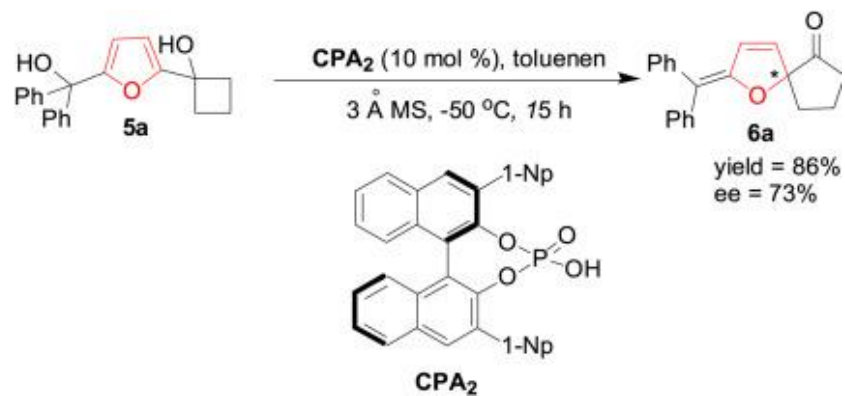
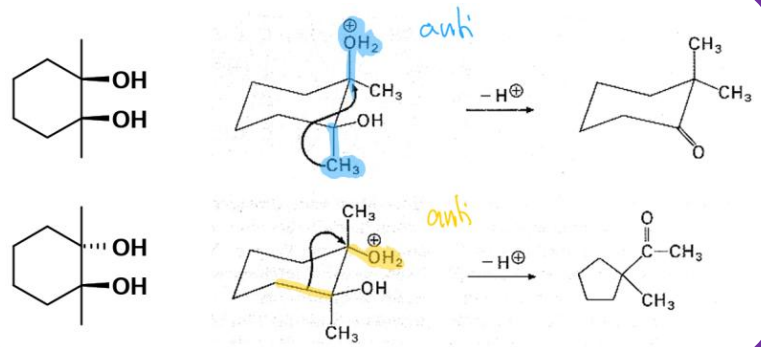
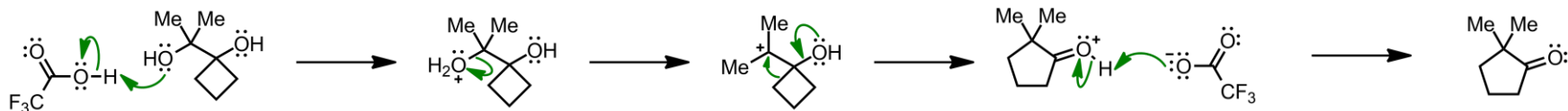
- ❖ If both the -OH groups are not alike, then the one which yields a **more stable carbocation** participates in the reaction
- ❖ driving force for this rearrangement step is believed to be the relative stability of the resultant oxonium ion
- ❖ Migratory aptitude, phenyl carbanion > tertiary carbanion (if formed by migration) > secondary carbanion (if formed by migration) > methyl carbanion > hydride, group which stabilizes the carbocation more effectively is migrated



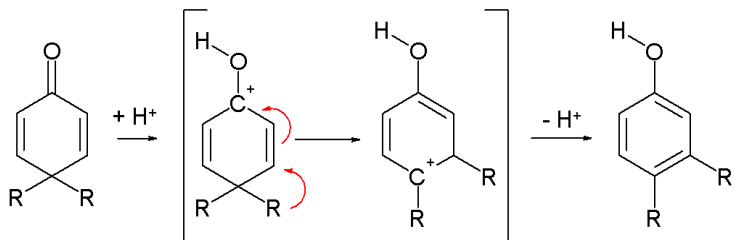
Configuration of chiral center is *retained*



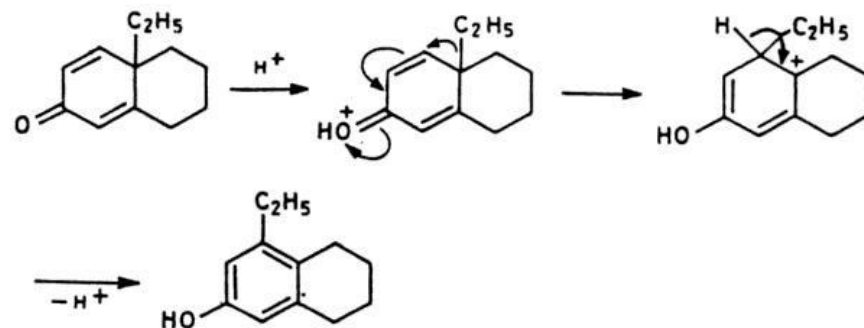
More examples of Pinacol-pinacolone rearrangement



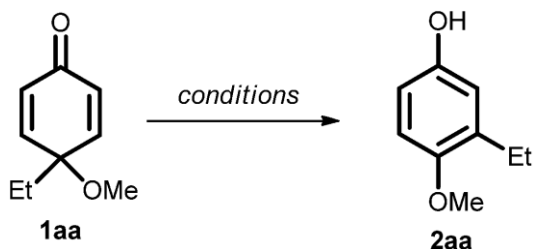
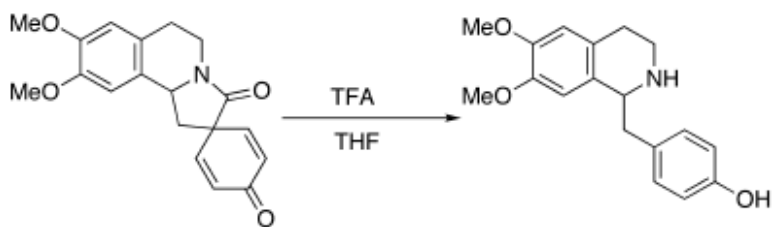
Dienone Phenol Rearrangement: Conversion of dienone to phenol in presence of acid as known as the Dienone Phenol Rearrangement



are employed. Thus, when $R = C_2H_5$ the reaction assumes the course shown in below to give a different product due to migration of the ethyl group.



Anamolous products are also obtained occasionally in this reaction.



Driving force is aromatisation

b. The aryl-migration in dienone-phenol rearrangement of spirocyclohexadienone

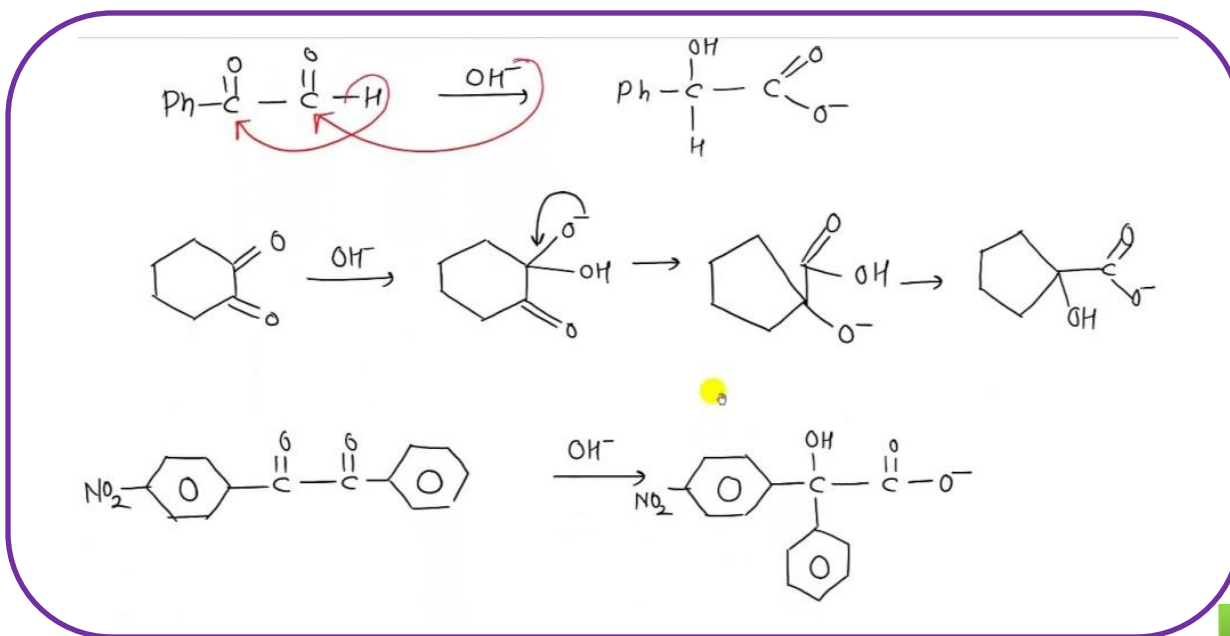
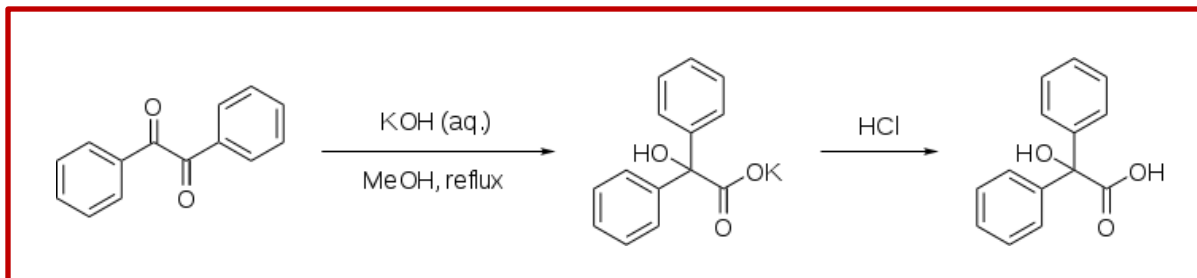
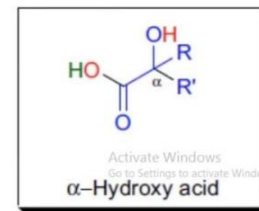
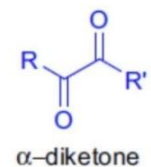


c. Initially postulated dienone-phenol rearrangement of spirooxindole involving the migration of the aryl moiety

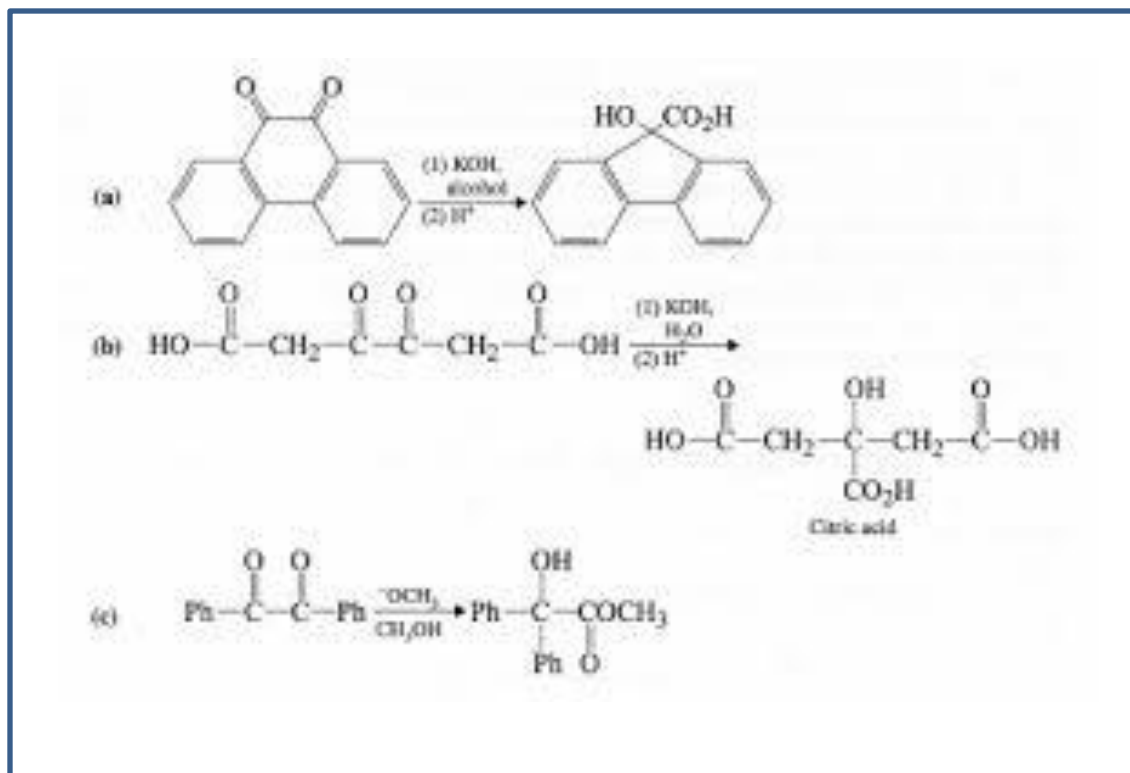


Benzil-benzilic acid rearrangement

- 1,2-rearrangement of 1,2-diketones to form α -hydroxy-carboxylic acids
- work in aromatic, semi-aromatic, aliphatic, and heterocyclic substrates
- Should not have adjacent enolizable protons, as this allows aldol condensation

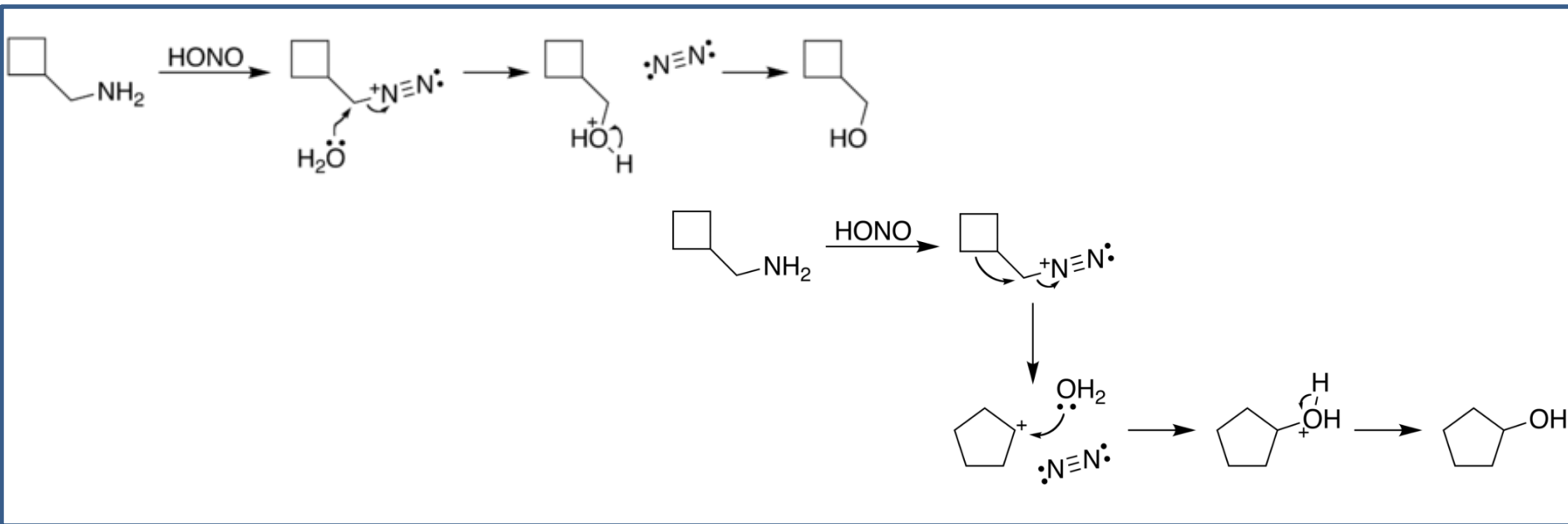


More examples of Benzil-benzilic acid rearrangement



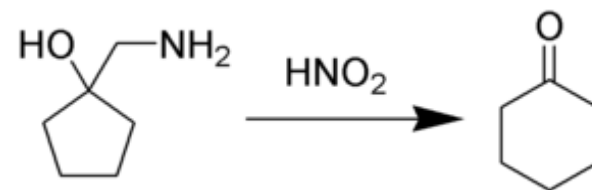
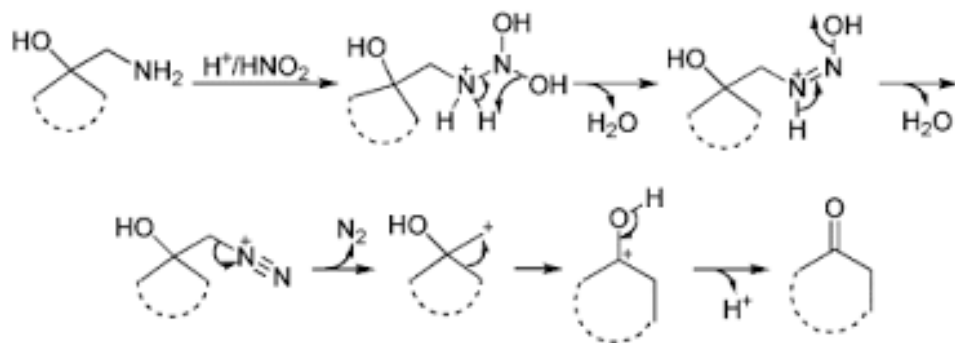
Demjanov rearrangement

➤ chemical reaction of primary amines with nitrous acid to give rearranged alcohols. It involves substitution by a hydroxyl group with a possible ring expansion.



Tiffeneau-Demjanov rearrangement

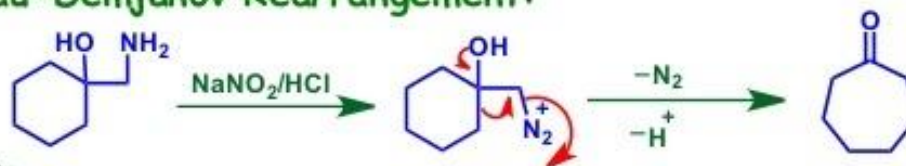
- ❖ Chemical reaction of a 1-aminomethyl-cycloalkanol with nitrous acid to form an enlarged cycloketone
- ❖ TDR is for synthesis of five, six, and seven member rings



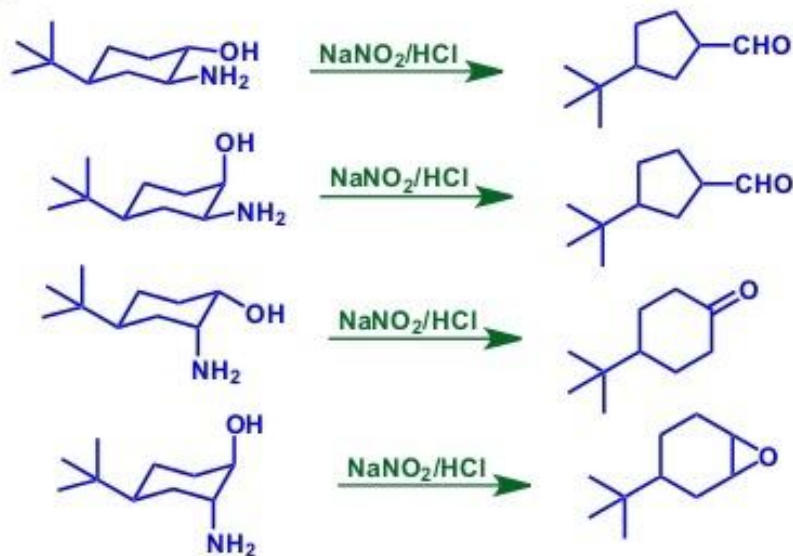
Molecular Rearrangements

Diazonium salts

Tiffeneau-Demjanov Rearrangement:



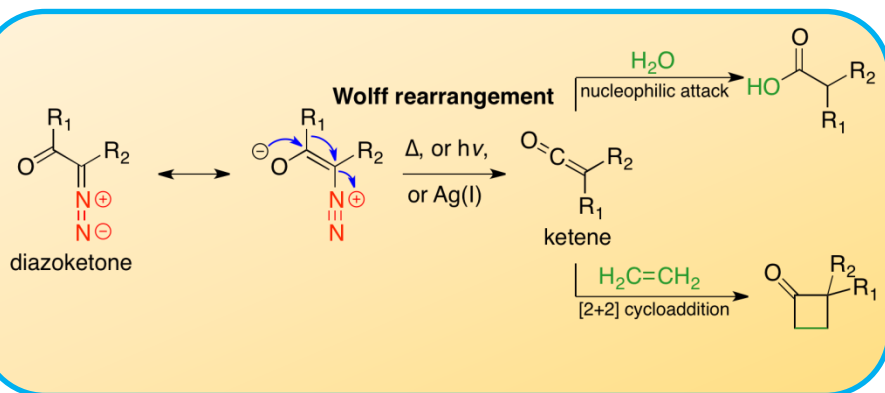
Selectivity :



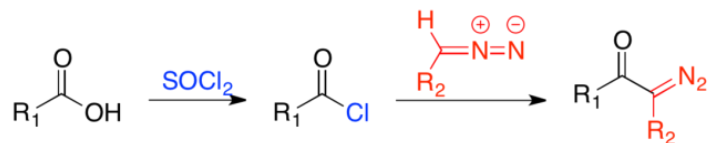
Rearrangement to electron-deficient carbon

Wolff rearrangement in Arndt-Eistert synthesis

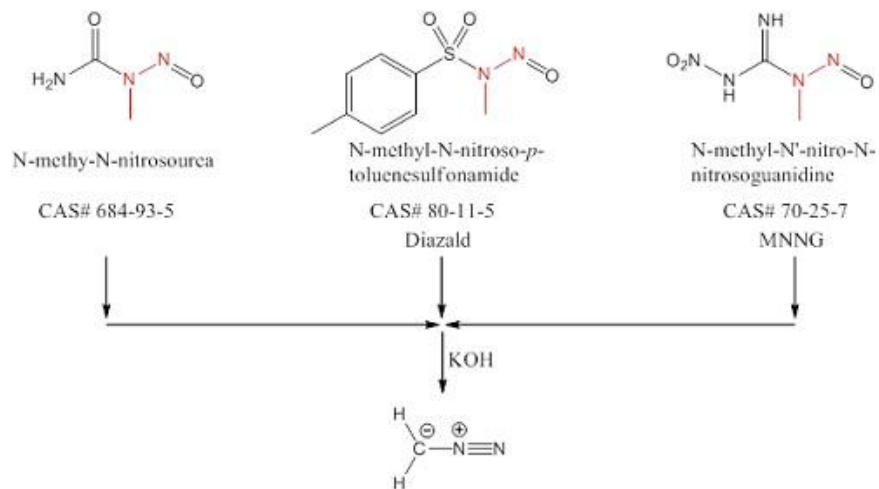
- ❖ Conversion of α -diazocarbonyl compound into a ketene by loss of dinitrogen with accompanying 1,2-rearrangement
- ❖ Yields ketene as an intermediate, undergoes nucleophilic attack with water, alcohols, and amines or undergo [2+2] cycloaddition
- ❖ Reaction is catalysed by Ag_2O , Δ or $h\nu$
- ❖ Stereochemical retention of the migrating group



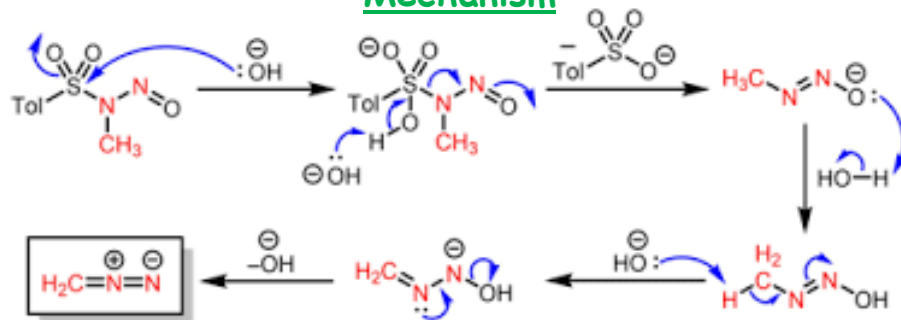
Synthesis of α -diazocarbonyl compound



Synthesis of diazomethane

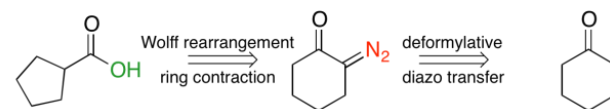
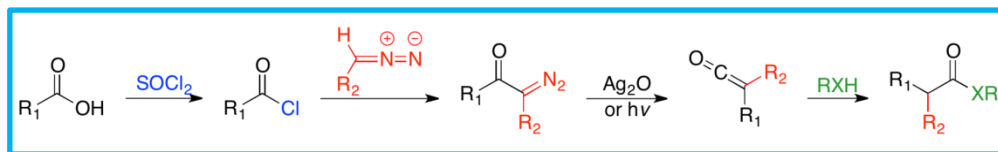
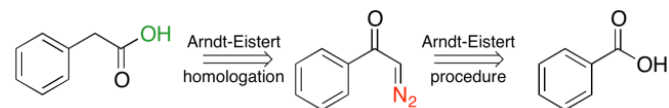


Mechanism

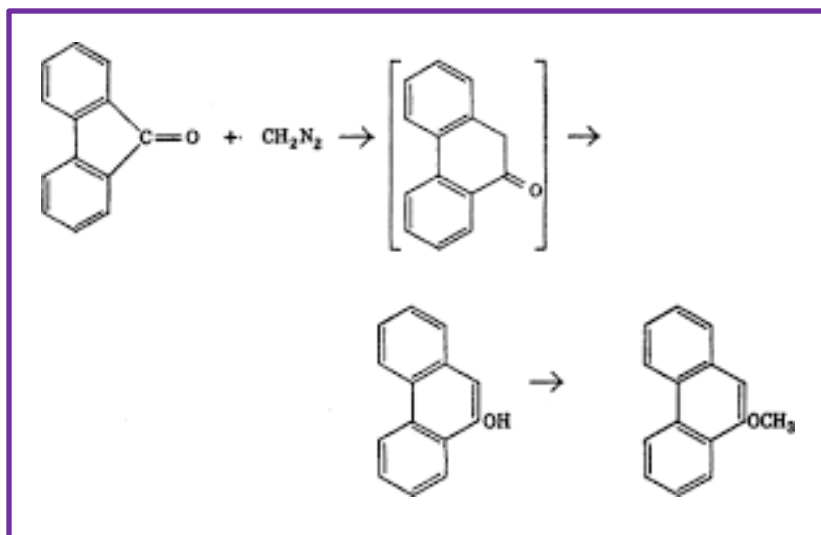
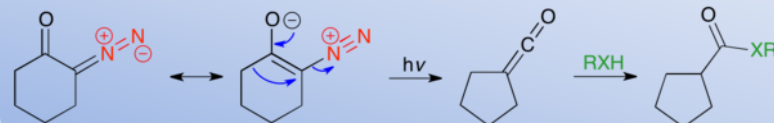


Wolff rearrangement in Arndt-Eistert synthesis

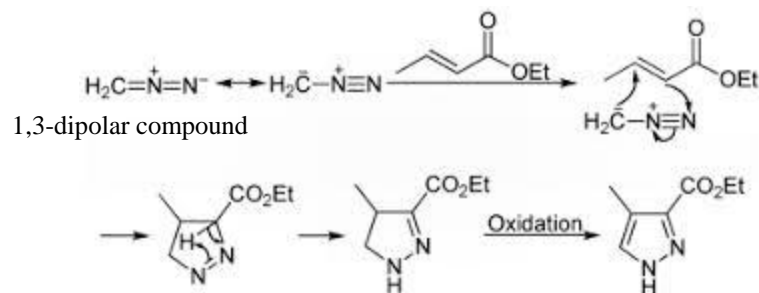
Arndt-Eistert reaction is the conversion of a carboxylic acid to its homologue



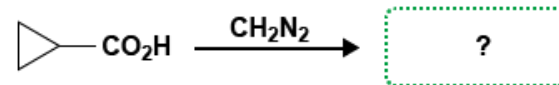
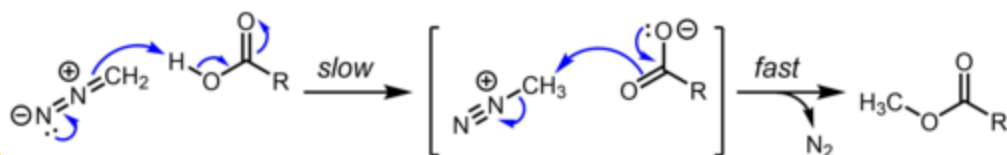
Ring contractions

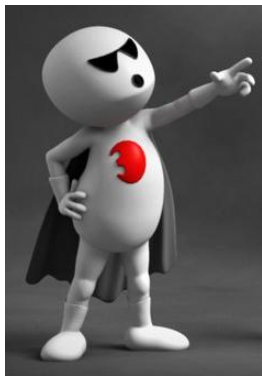


1,3-dipolar cycloaddition

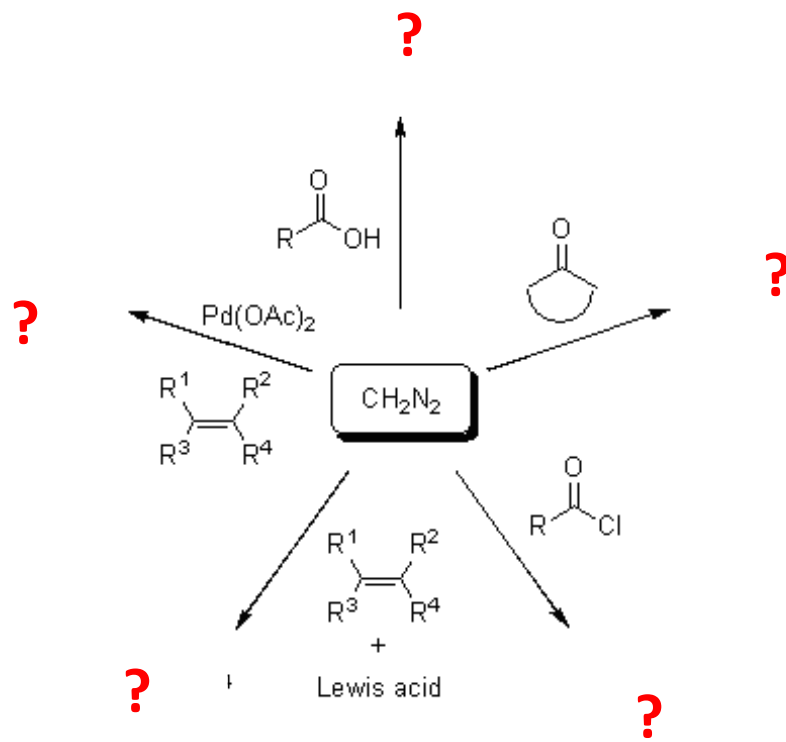


Reaction of diazomethane with carboxylic acid

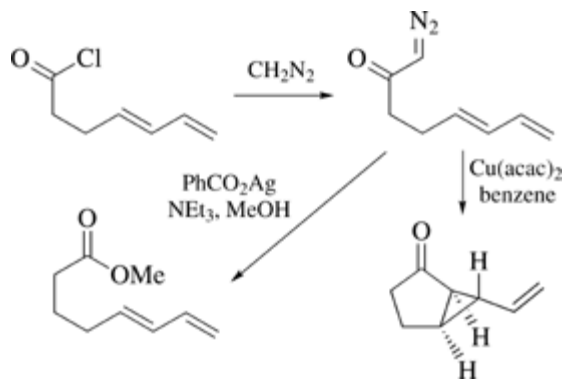




Solve the problems

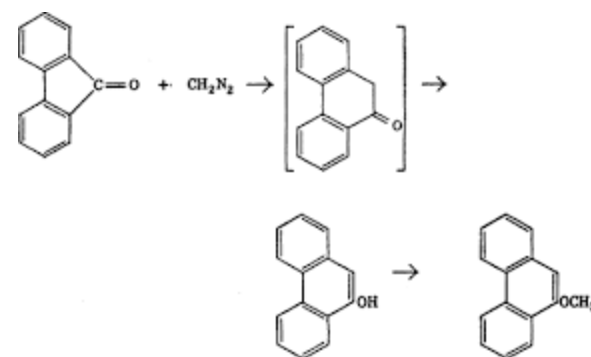
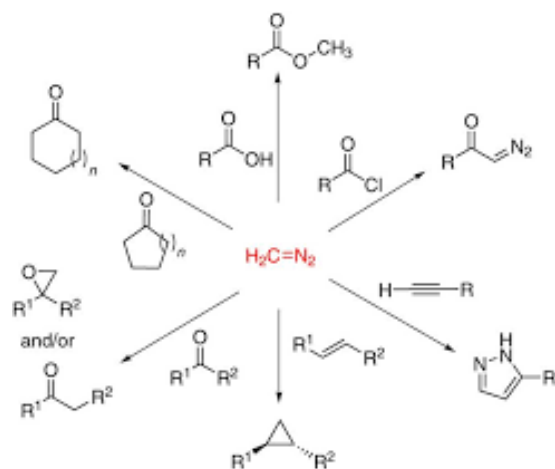
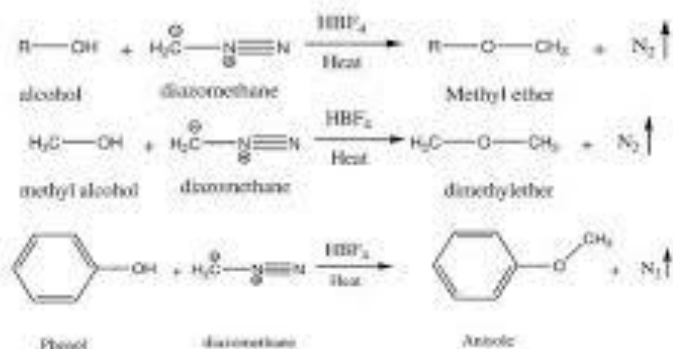


Scheme 1

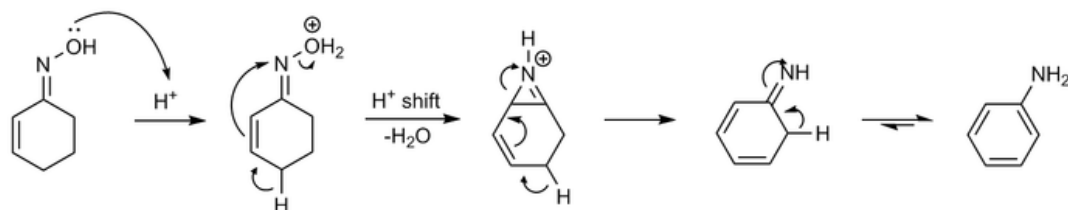


•Diazomethane method:

This method is used to prepare methyl ether only. When alcohol or phenol is heated with diazomethane in the presence of Fluoroboric acid, give methyl ether.



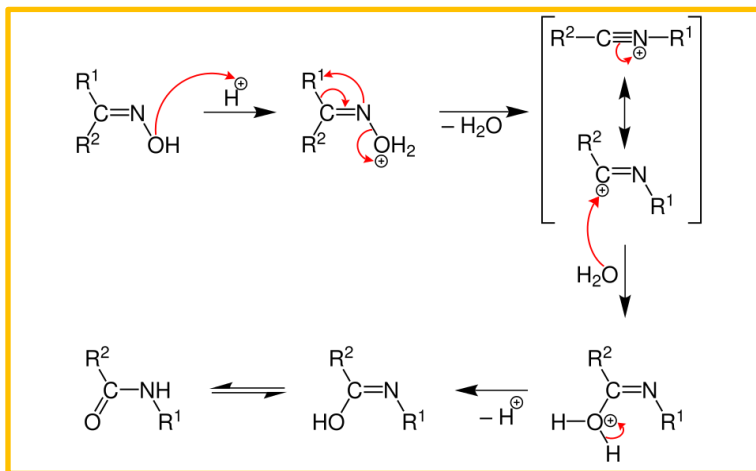
Semmler-Wolff reaction



Rearrangement to electron-deficient nitrogen

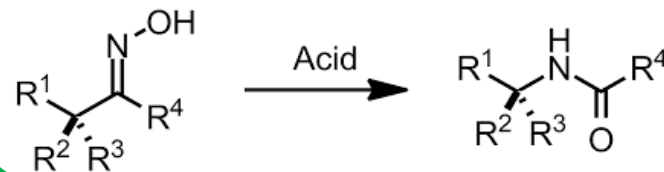
Beckmann rearrangements

- ❖ Rearrangement of an oxime functional group to give substituted amides.
- ❖ Catalyzed by acid tosyl chloride, thionyl chloride, phosphorus pentachloride, phosphorus pentoxide
- ❖ Migrating group being anti-periplanar to the leaving group on the nitrogen

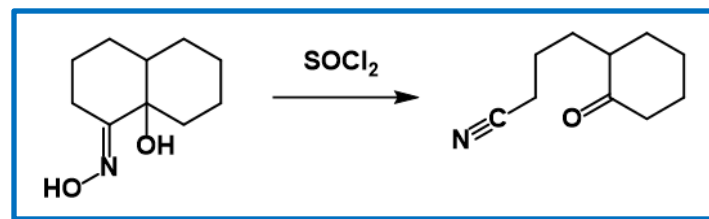
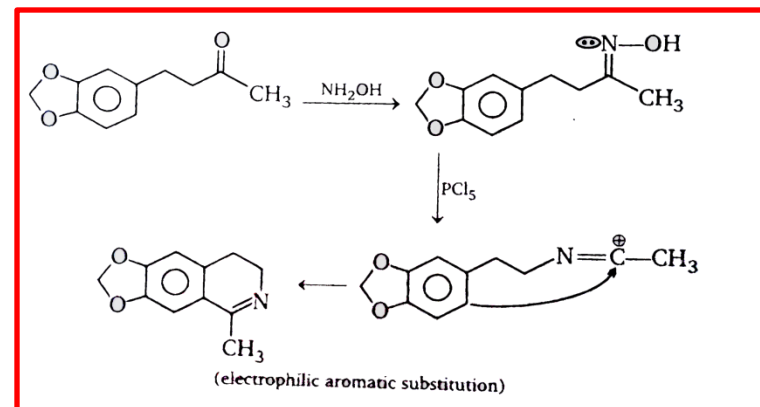
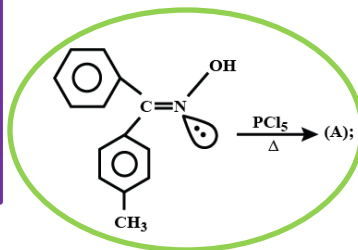
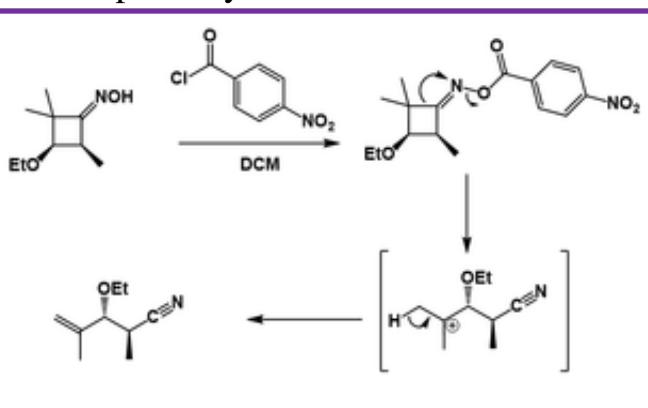


Reagents:-

Conc. H₂SO₄, HCl, PCl₅, PCl₃, SOCl₂, ZnO, SiO₂, PPA (Poly phosphoric acid) etc., are commonly employed in Beckmann rearrangement.

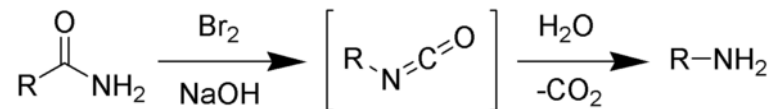


➤ Group α to the oxime is capable of stabilizing carbocation formation, the fragmentation becomes a viable reaction pathway

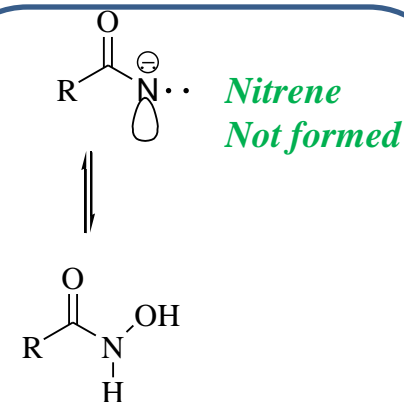
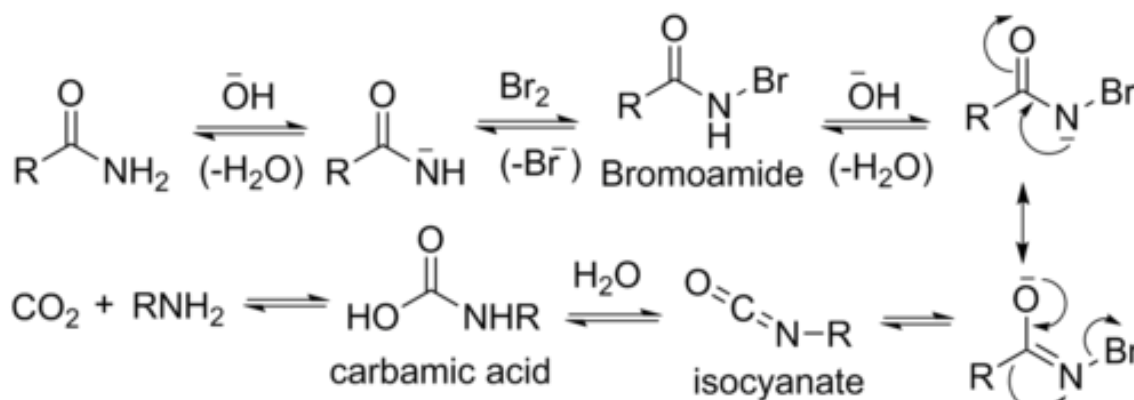


Hofmann rearrangement

Hofmann rearrangement is the [organic](#) reaction of a primary [amide](#) to a primary [amine](#) with one fewer [carbon](#) atom

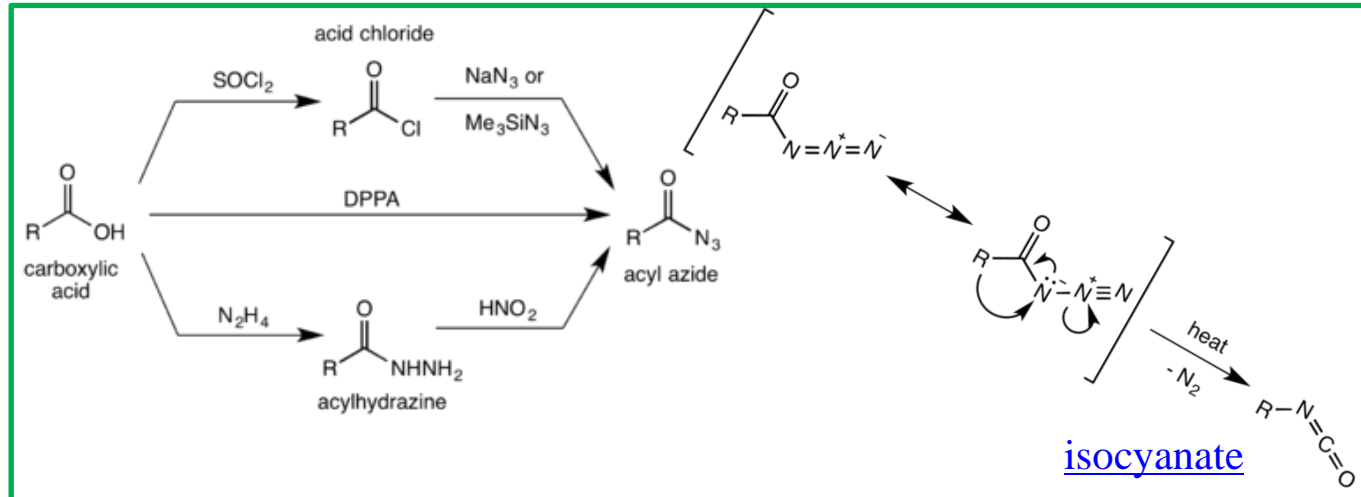


Mechanism: The reaction of [bromine](#) with [sodium hydroxide](#) forms [sodium hypobromite *in situ*](#), which transforms the primary [amide](#) into an intermediate [isocyanate](#). The formation of an intermediate [nitrene](#) is not possible because it implies also the formation of a [hydroxamic acid](#) as a byproduct, which has never been observed. The intermediate [isocyanate](#) is hydrolyzed to a primary amine, giving off [carbon dioxide](#)

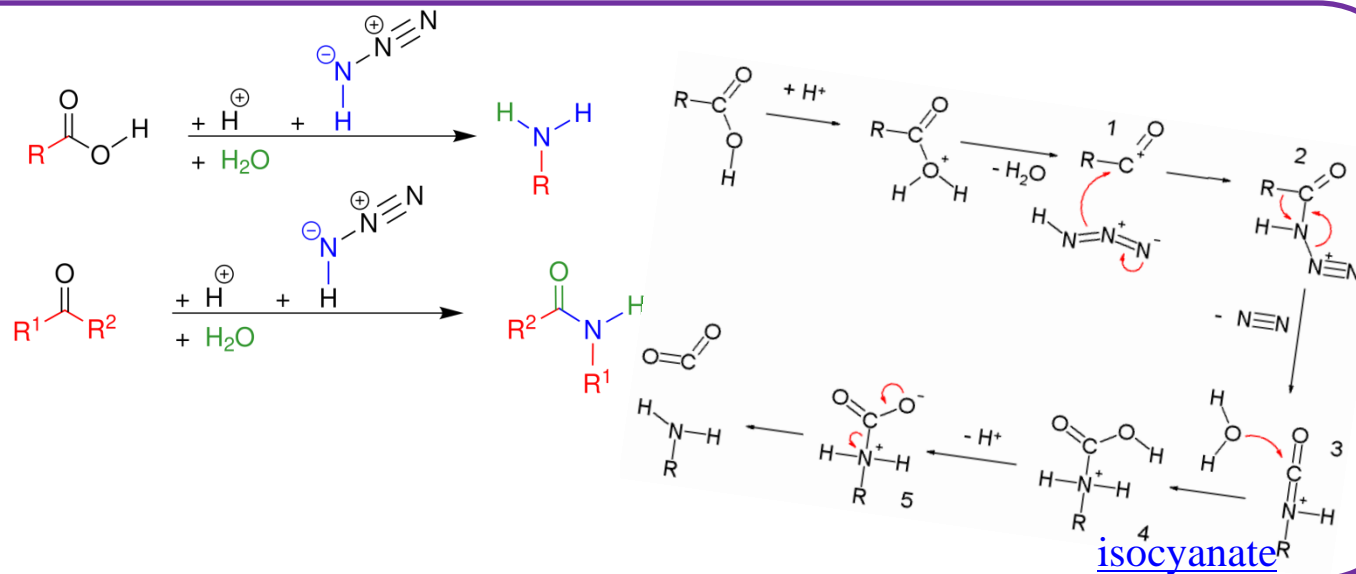


If nitrene is formed as intermediate, then hydroxamic acid could be the side product (which actually doesn't form)

Curtius rearrangement

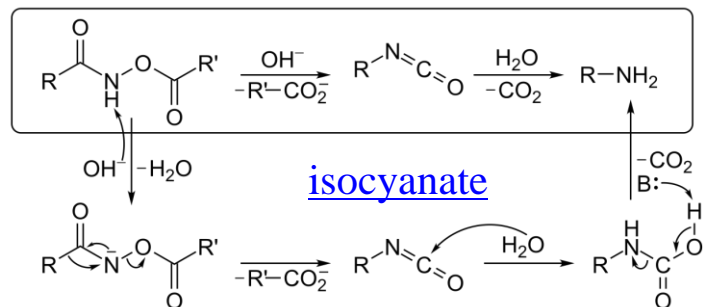


Schmidt reaction



Lossen rearrangement

O-acylated hydroxamic acid derivative



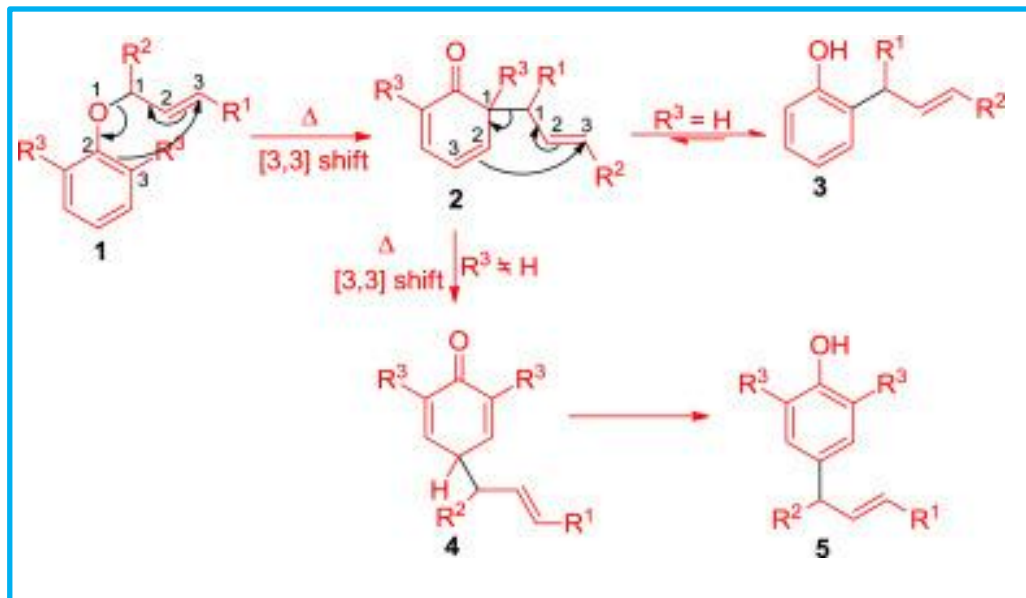
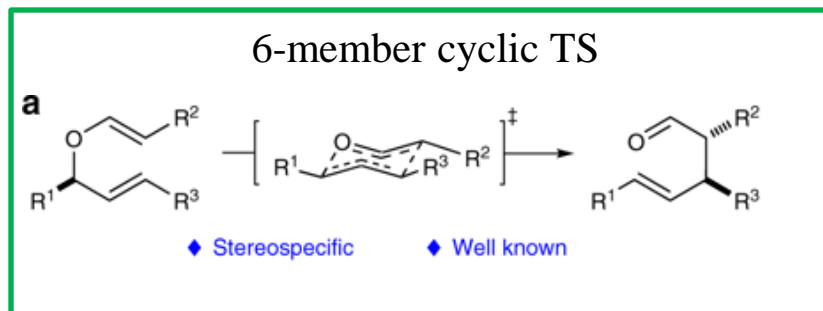
Aromatic rearrangements: Migration from oxygen to ring carbon

Claisen rearrangement

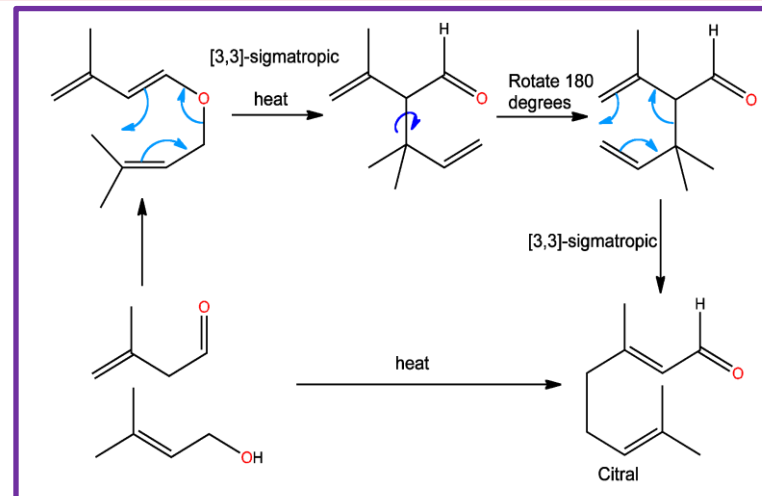
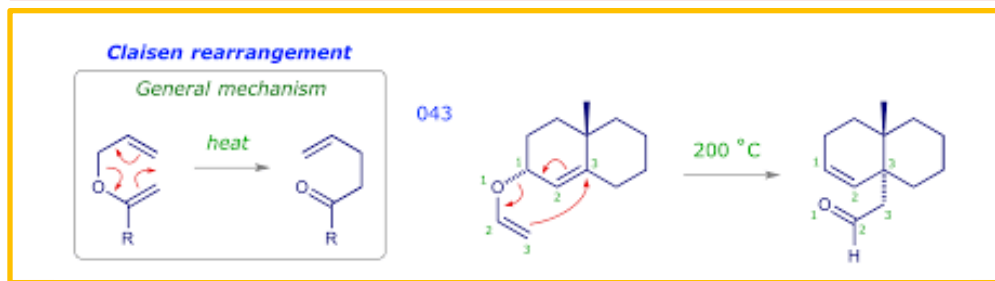
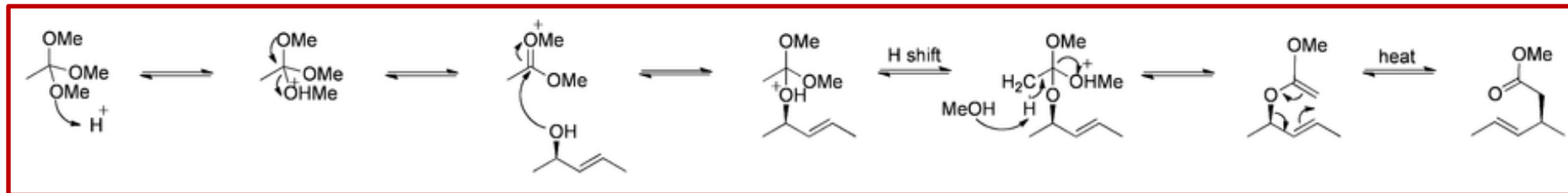
Claisen rearrangement is a powerful carbon–carbon bond-forming chemical reaction. heating of an allyl vinyl ether will initiate a [3,3]-sigmatropic rearrangement to give a γ,δ -unsaturated carbonyl

Mechanism:

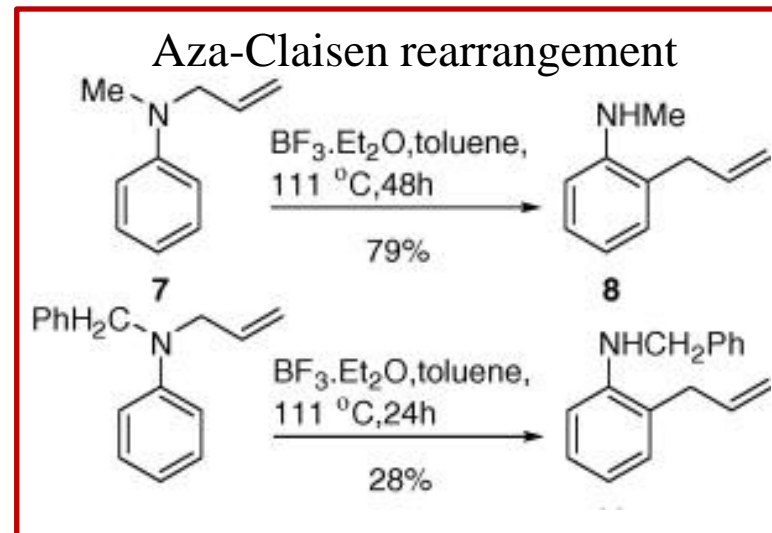
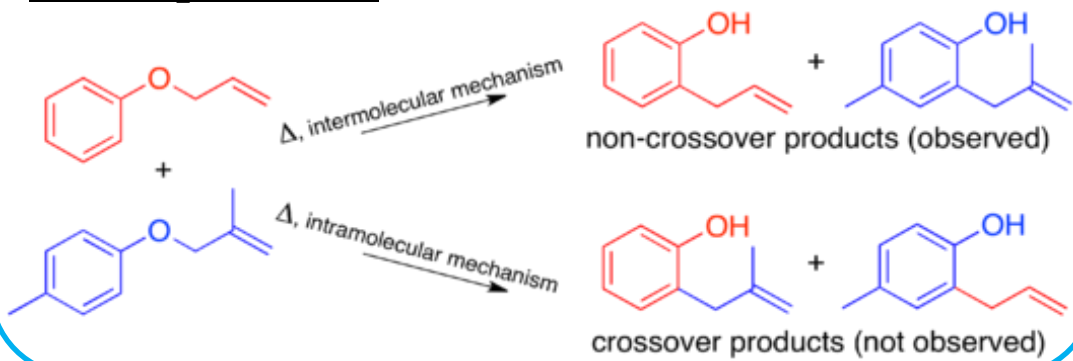
- ❖ exothermic, concerted (bond cleavage and recombination) pericyclic reaction (Cyclic TS & concerted path way)
- ❖ Suprafacial, stereospecific reaction pathway
- ❖ transformation proceeds through a highly ordered cyclic transition state
- ❖ Intramolecular reaction



More examples of Claisen rearrangement



evidence for the intramolecular pathway (Cross over experiment)



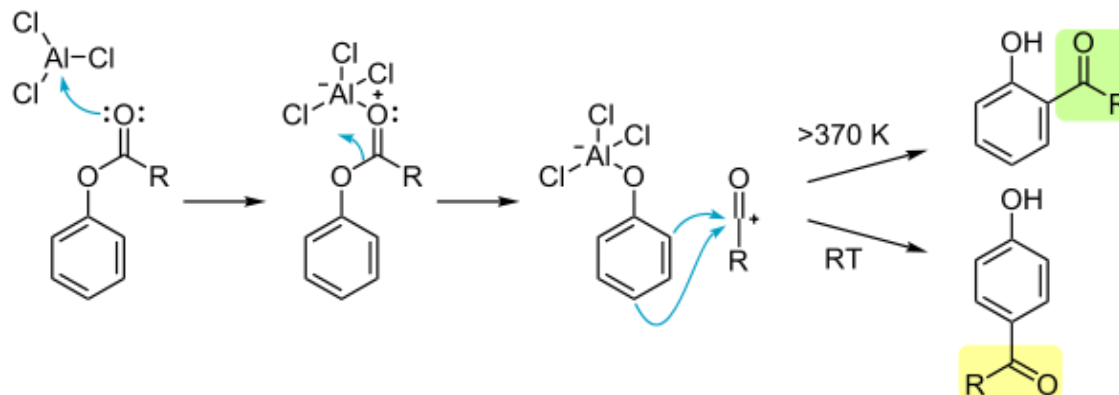
Fries rearrangement

Fries rearrangement: It is a rearrangement of a **phenolic ester** to a hydroxy aryl ketone by Lewis acids catalyst

It involves migration of an acyl group of phenol ester to the aryl ring. The reaction is ortho and para selective and one of the two products can be favoured by changing reaction conditions, such as temperature and solvent

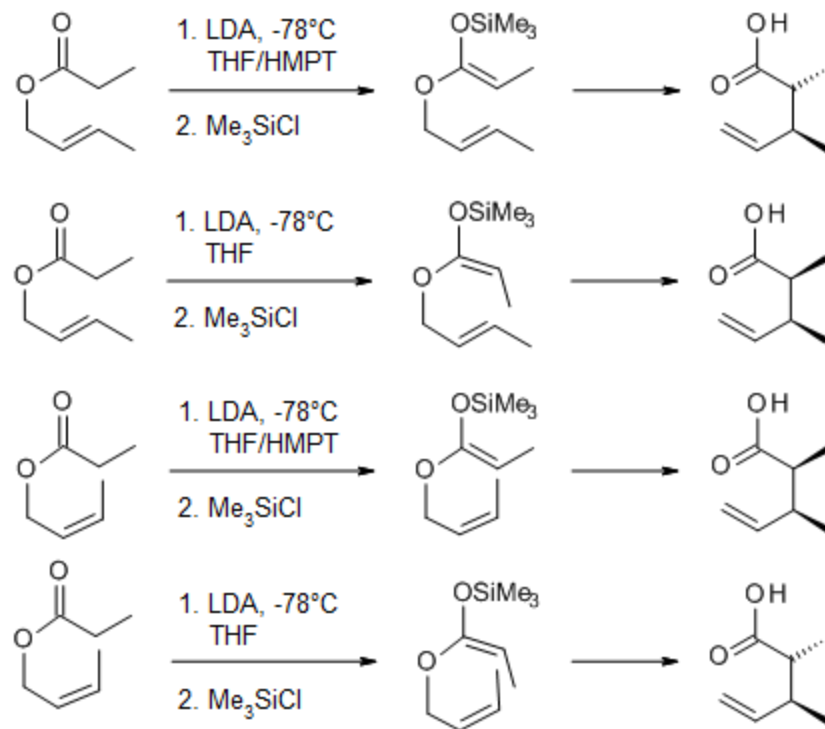
Evidence for inter- and intramolecular mechanisms have been obtained by crossover experiments with mixed reactants

A widely accepted mechanism involves a carbocation intermediate

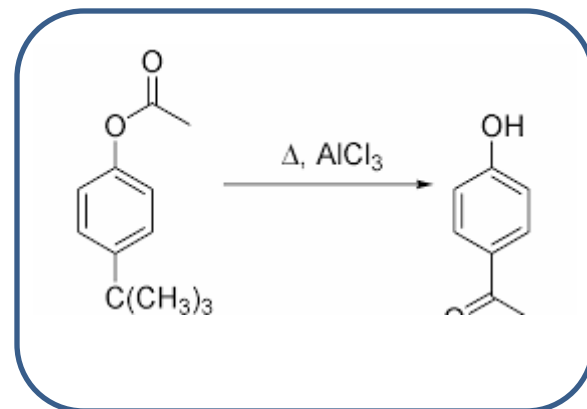
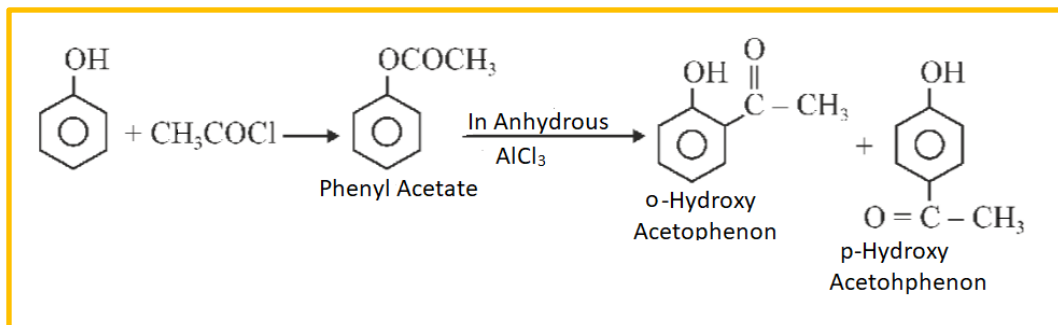


A low reaction temperature favors para substitution and with high temperatures the ortho product

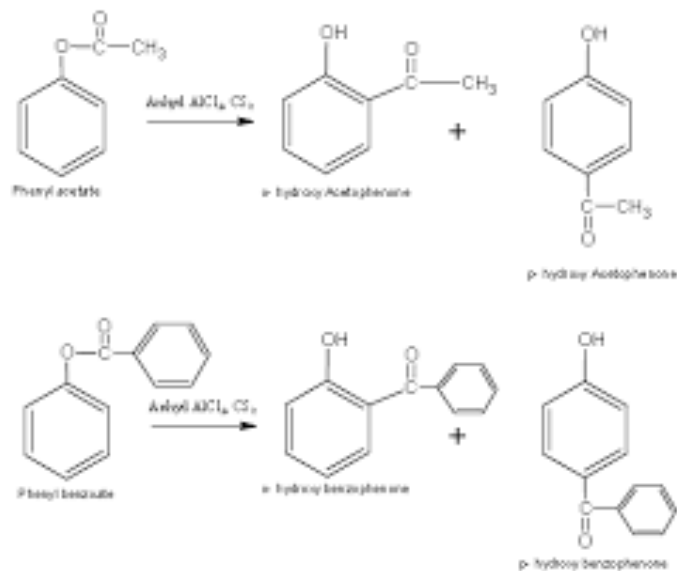
Cross over experiments (evidence for the intramolecular rearrangement)



Few examples of Fries rearrangement

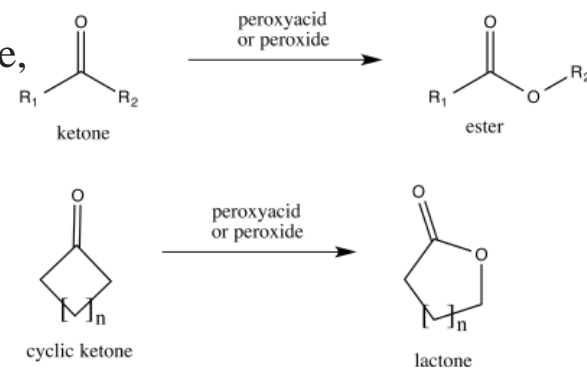


evidence in favour of intermolecular pathway (Cross over experiment)

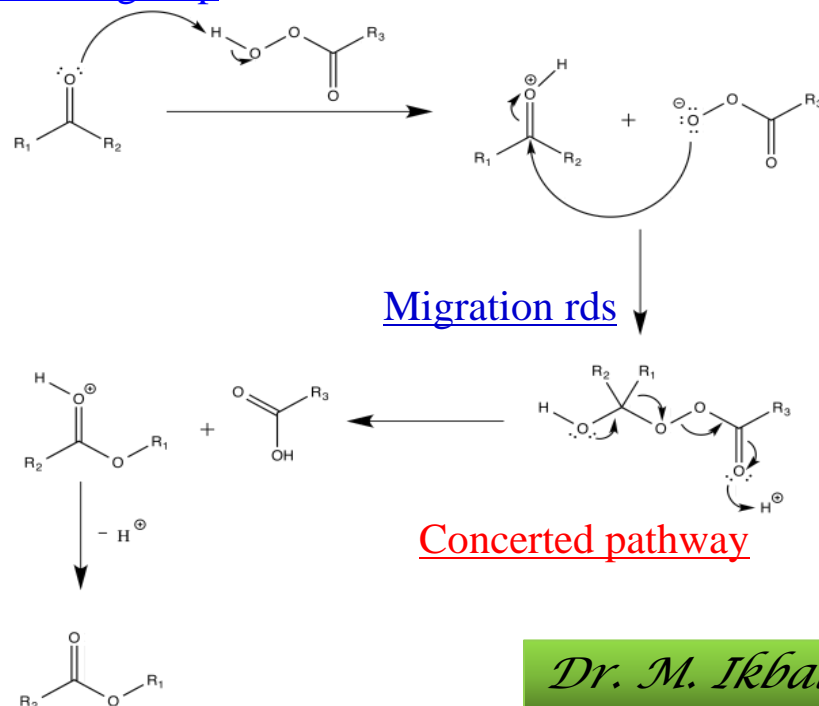


Rearrangement to electron-deficient oxygen

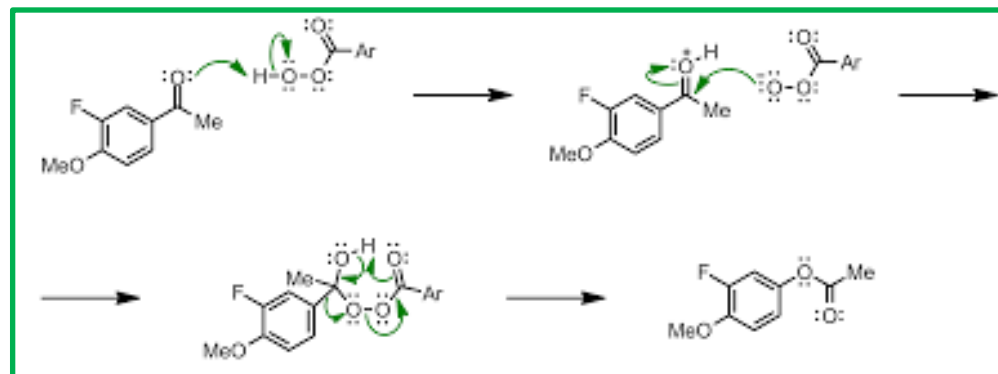
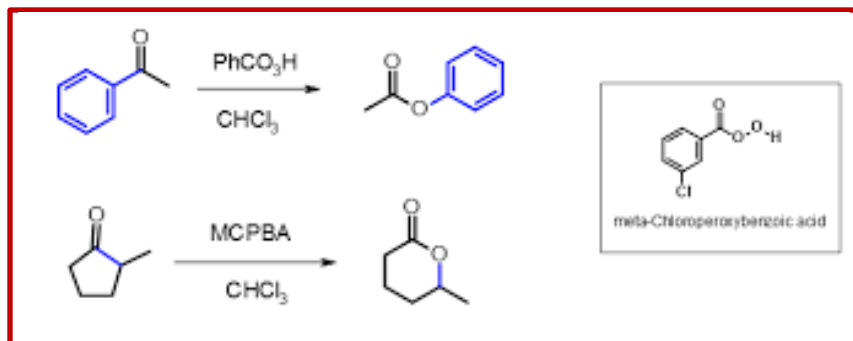
Baeyer–Villiger oxidation: Baeyer–Villiger oxidation is an [organic reaction](#) that forms an [ester](#) from a [ketone](#) or a [lactone](#) from a cyclic ketone, using [peroxyacids](#) or [peroxides](#) as the [oxidant](#)



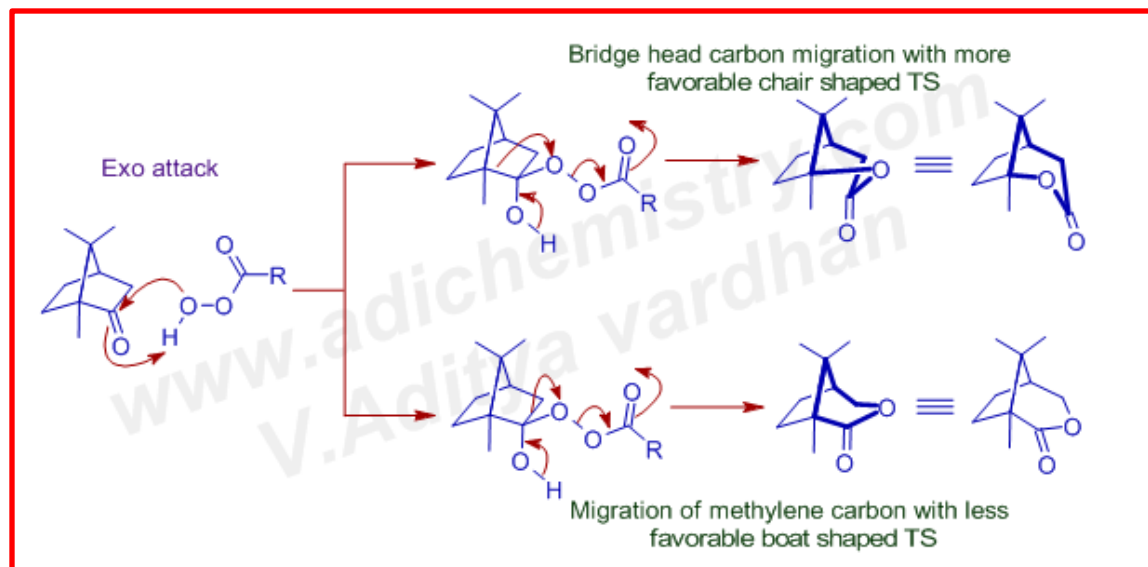
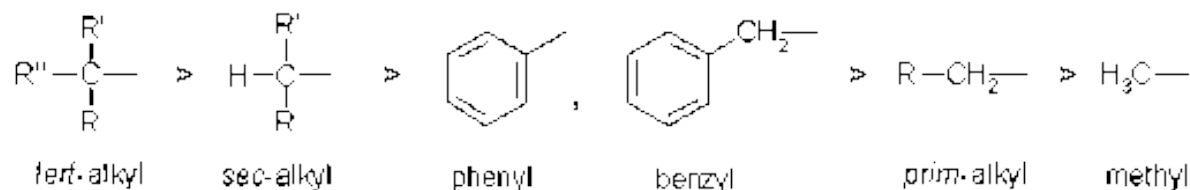
Mechanism: In the first step of the [reaction mechanism](#), the [peroxyacid](#) protonates the oxygen of the [carbonyl group](#). Next, the peroxyacid attacks to the carbonyl group forming [Criegee intermediate](#). Through a [concerted mechanism](#), one of the substituents on the [ketone](#) migrates to the oxygen of the [peroxide group](#). This migration step is thought to be the [rate determining step](#)



Baeyer-Villiger oxidation

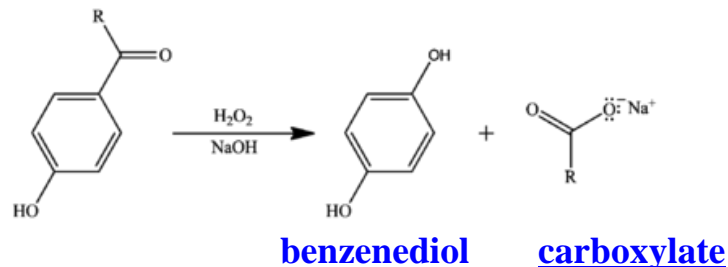


The migratory ability is ranked **tertiary > secondary > aryl > primary**



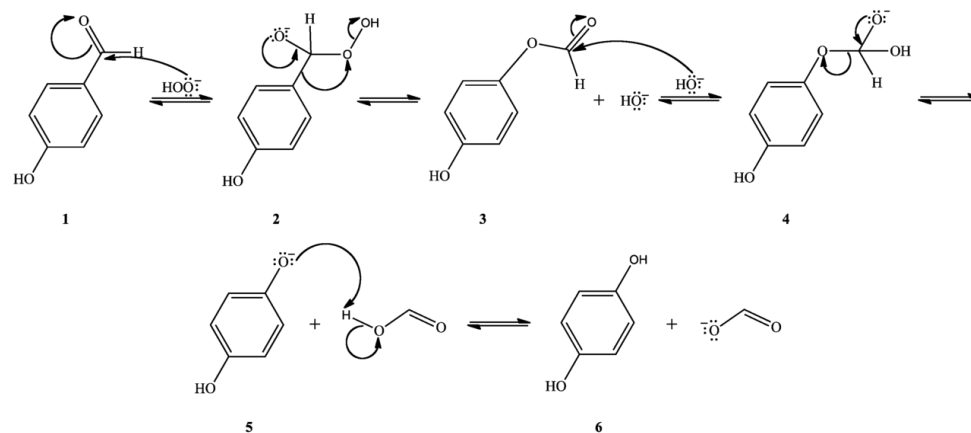
Dakin reaction: It is an organic redox reaction in which an *O* or *P*-hydroxylated phenyl aldehyde or ketone reacts with hydrogen peroxide in base to form a benzenediol and a carboxylate. Overall, the carbonyl group is oxidized, and the hydrogen peroxide is reduced.

O or *P*
hydroxylated phenyl aldehyde or
ketone



Mechanism: The Dakin oxidation starts with nucleophilic addition of a hydroperoxide anion to the carbonyl carbon, forming a tetrahedral intermediate (2), then [1,2]-aryl migration, and formation of a phenyl ester (3) hydroxide elimination. phenyl ester on basic hydrolysi gives phenoxide and carboxylic acid

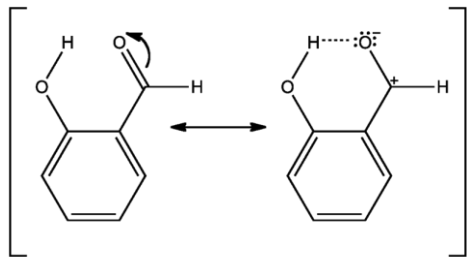
two rate-limiting steps, Nu⁻ addition of OH⁻ to the carbonyl carbon and aryl migration.



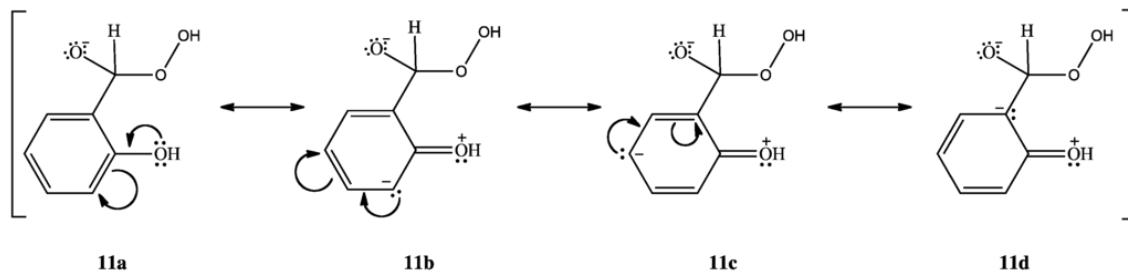
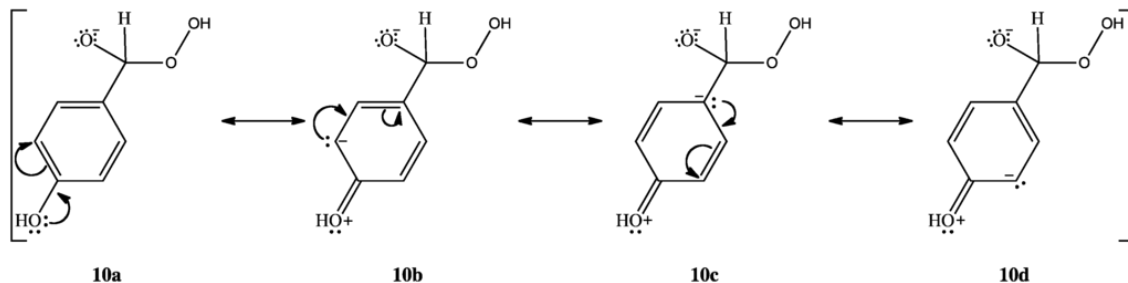
Factors affecting reaction kinetics:

i) relative positions of the hydroxyl, ii) presence of other functional groups on the ring, iii) alkyl substituents on the carbonyl carbon and iv) reaction mixture pH

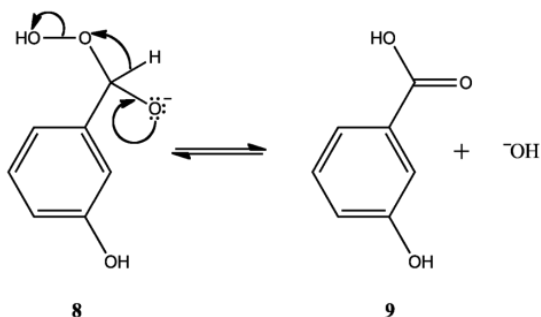
Dakin reaction



Lacking this ⁷stabilization, of **P-isomer**, it is less electrophilic and less reactive



Hydroxyl groups *O* or *P* to the carbonyl group increase the electron density at the aryl carbon bonded to the carbonyl carbon (**10c**, **11d**), increases migratory aptitude



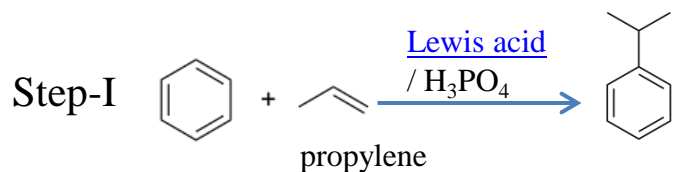
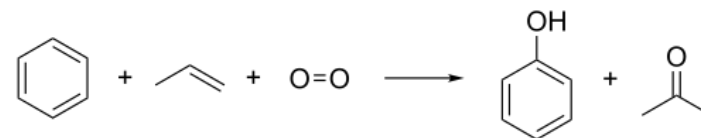
oxidation accelerates as pH increases toward the pK_a of hydrogen peroxide

Alkyl substituents

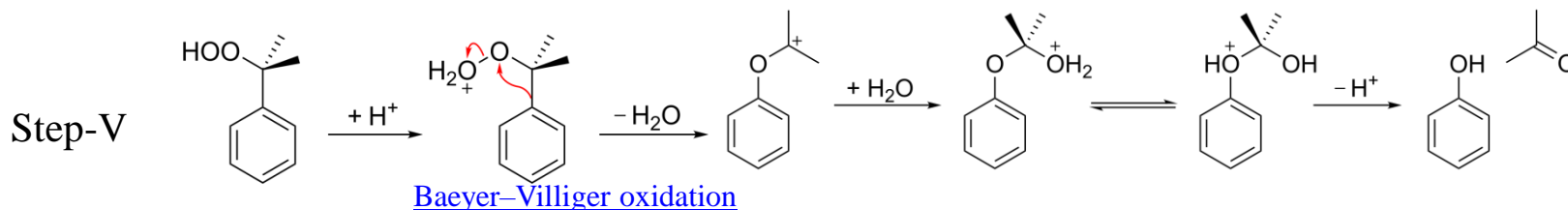
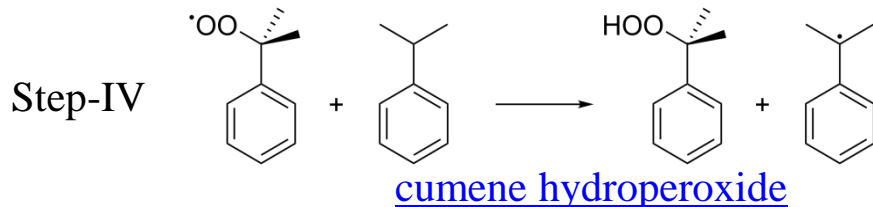
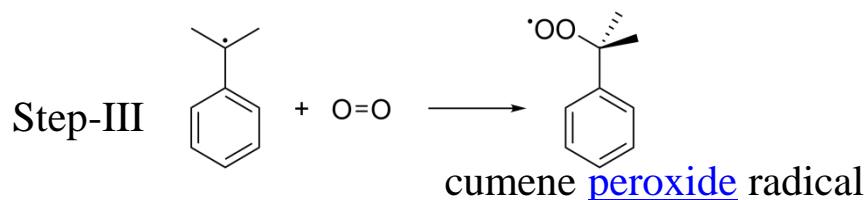
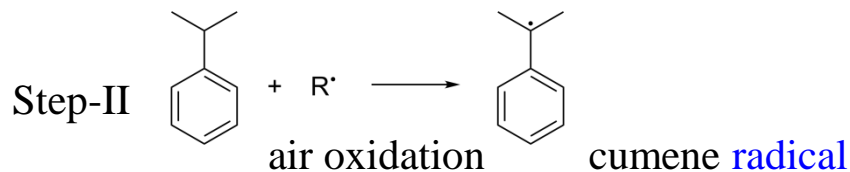
In general, PhCHO are more reactive than PhCOR, because the ketone carbonyl carbon is less electrophilic than the aldehyde carbonyl carbon

Cumene hydroperoxide-phenol rearrangement

Oxidation of **cumene** yields **cumene hydroperoxide**, which undergoes acid-catalyzed **rearrangement** to **phenol** and acetone

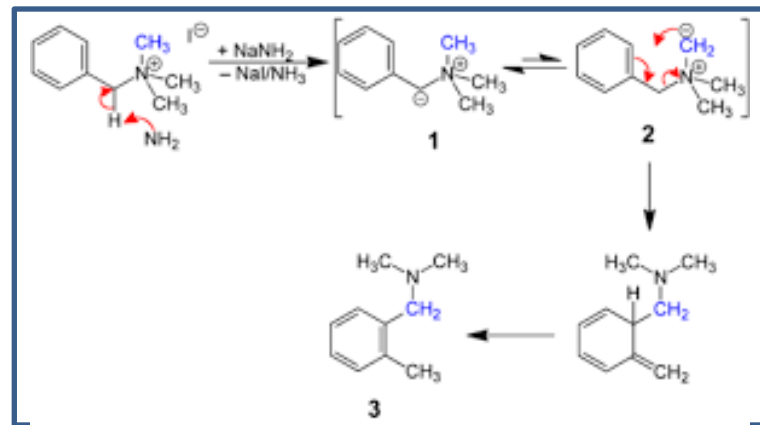
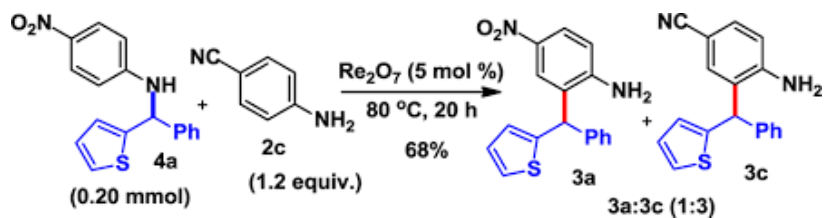
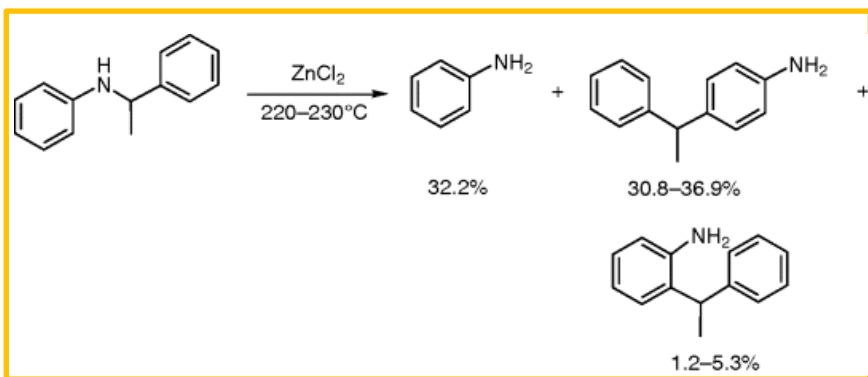
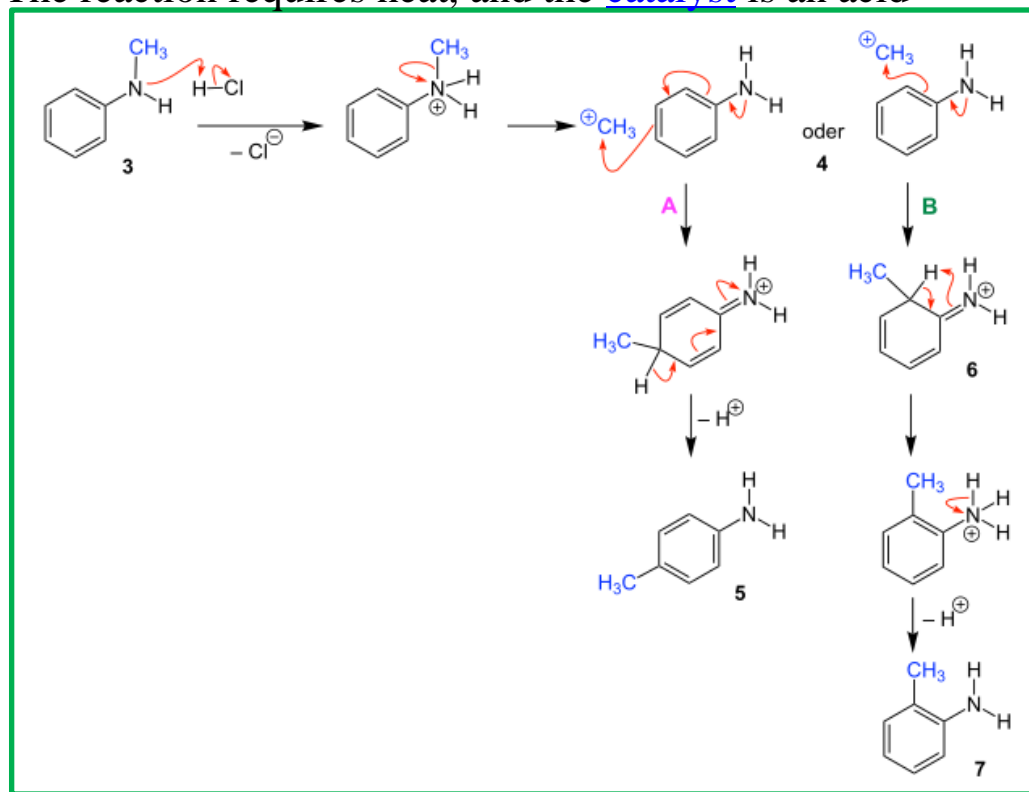
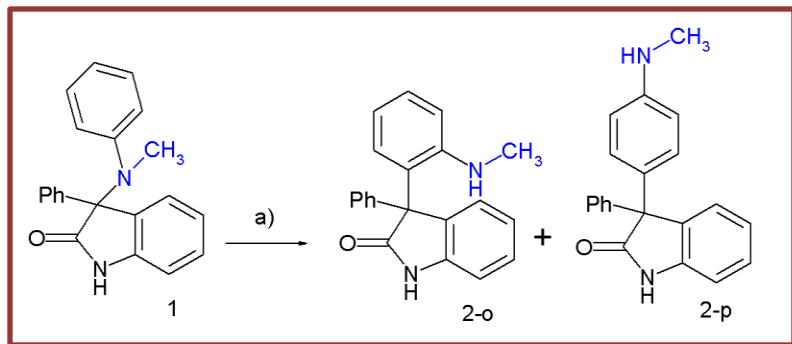


compressed together to a pressure of 30 standard atmospheres at 250 °C (482 °F) in presence of a H₃PO₄ or catalytic Lewis acid

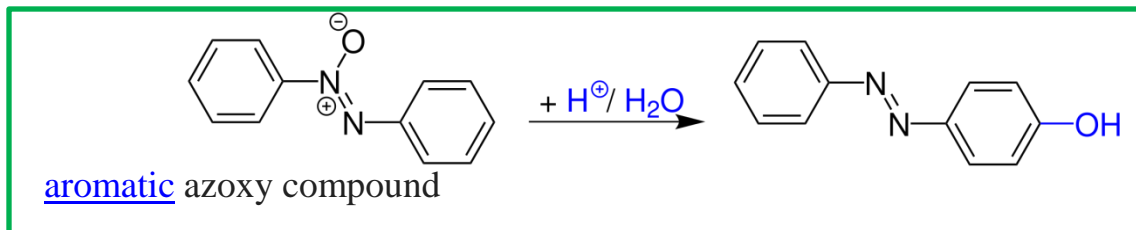


Migration from nitrogen to ring carbon

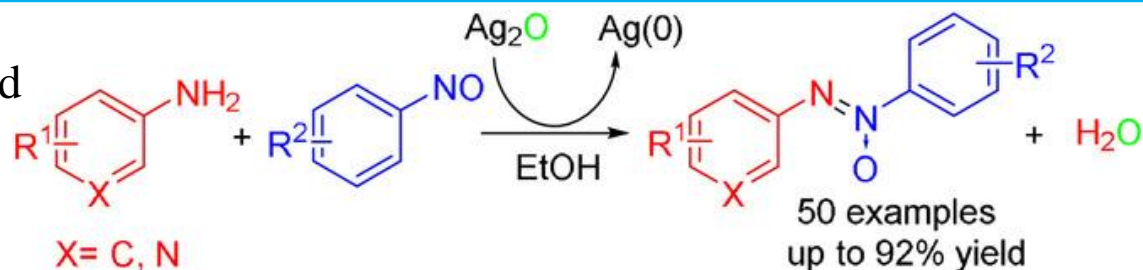
Hofmann-Martius rearrangement: It is a rearrangement reaction converting an N-alkylated aniline to the corresponding *O* and / or *P* aryl-alkylated aniline. The reaction requires heat, and the catalyst is an acid like hydrochloric acid



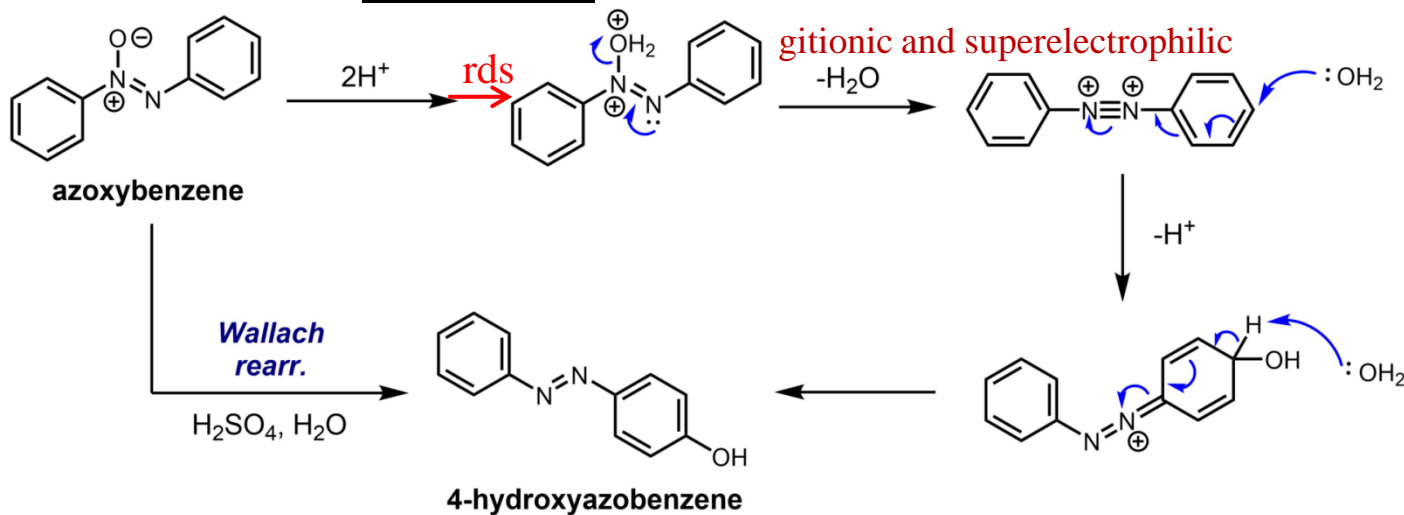
N-azo to C-azo rearrangement: The Wallach rearrangement is an organic reaction converting an aromatic azoxy compound with sulfuric acid or other strong acids to an azo compound with one arene ring substituted by a hydroxyl group in the aromatic para position.



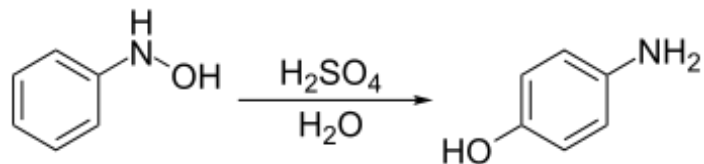
Preparation of azoxy compound



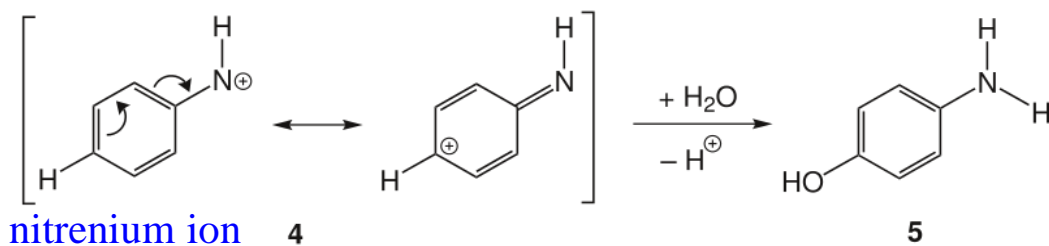
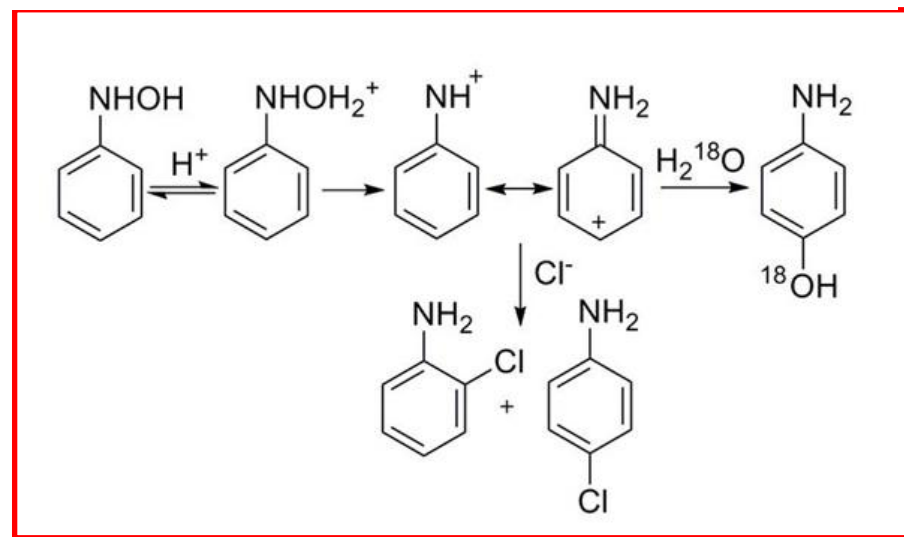
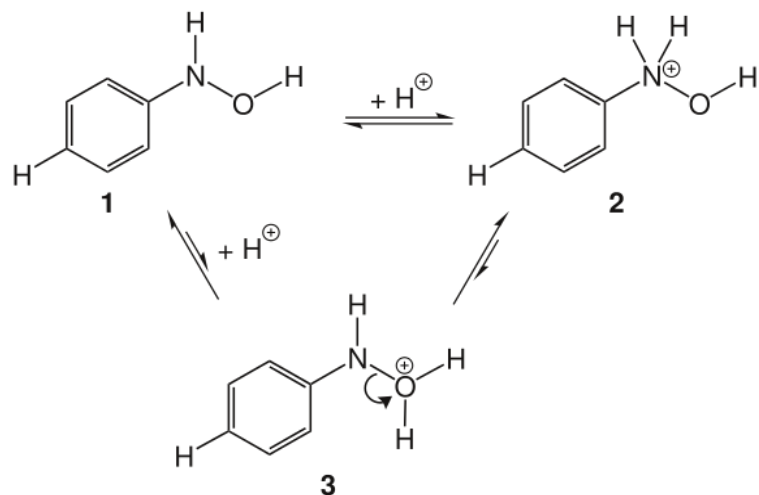
mechanism



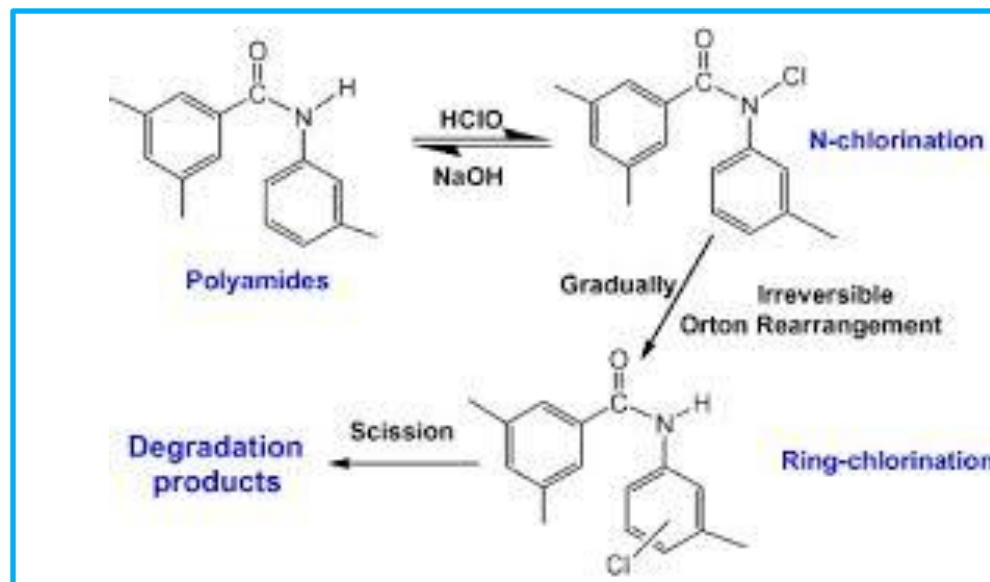
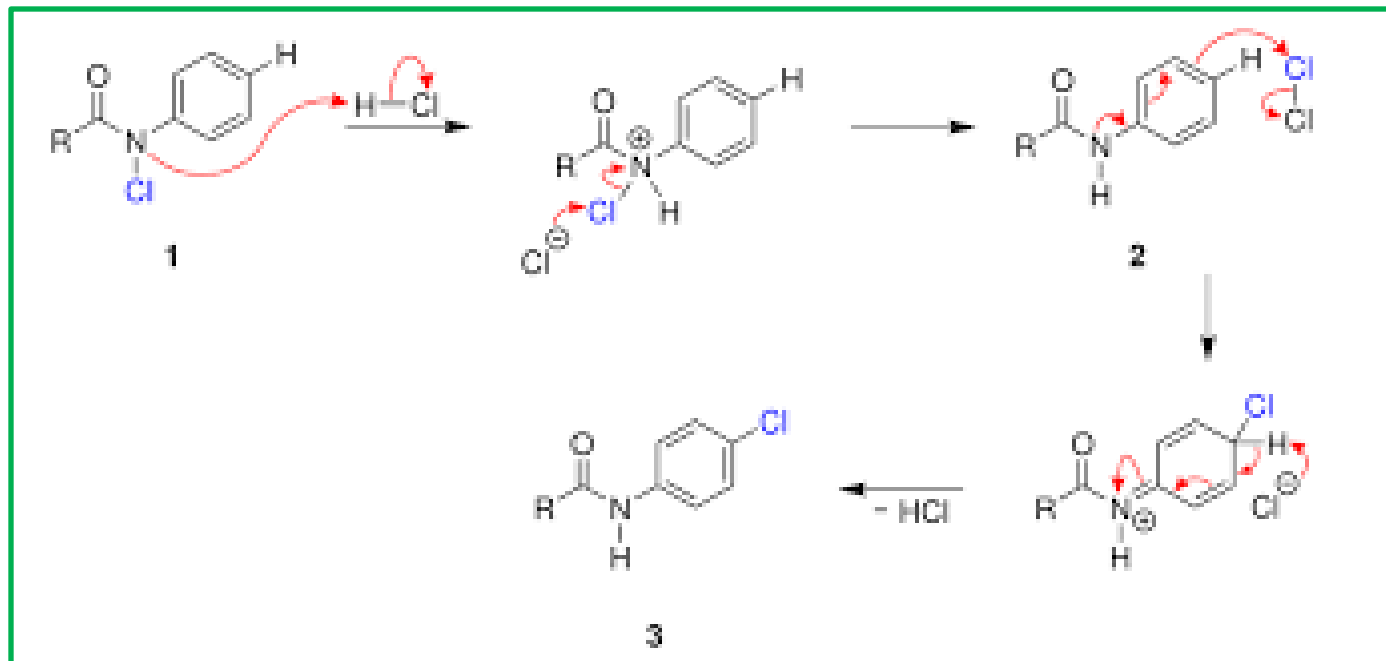
Bamberger rearrangement: [chemical reaction](#) of [phenylhydroxylamines](#) with strong [aqueous acid](#), which will [rearrange](#) to give 4-aminophenols.



Mechanism: Mechanism of the Bamberger rearrangement proceeds from the monoprotection of N-phenylhydroxylamine **1**. N-protonation **2** is favored, but unproductive. O-protonation **3** can form the [nitrenium ion](#) **4**, which can react with nucleophiles ([H₂O](#)) to form the desired 4-aminophenol **5**.

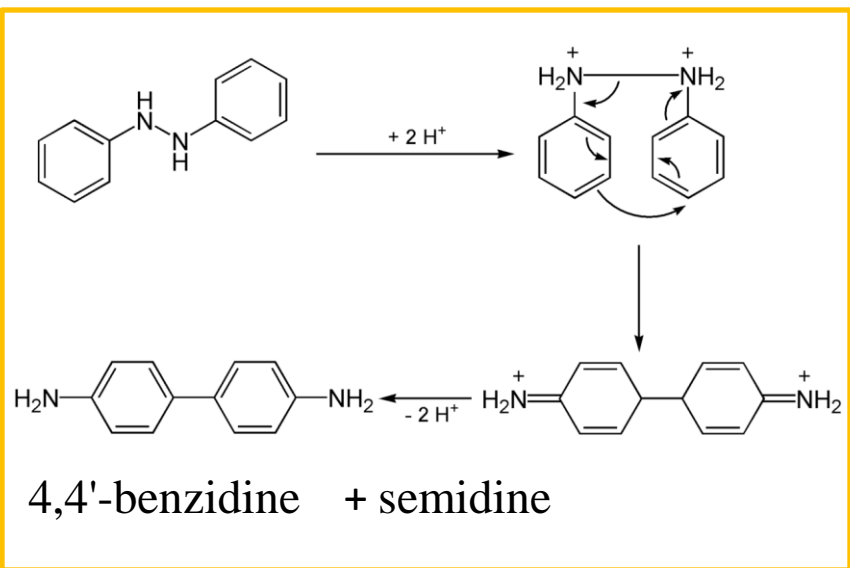
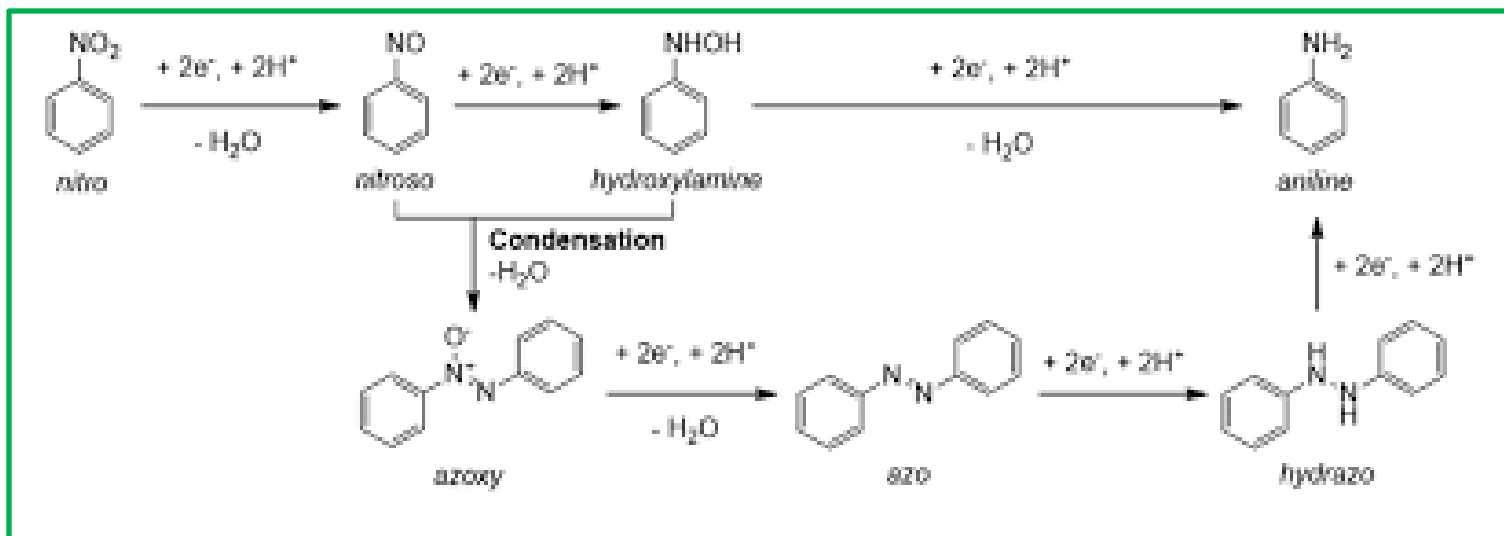


Orton rearrangement



Benzidine rearrangement

Benzidine also called **1,1'-biphenyl-4,4'-diamine**. It is an [aromatic amine](#). Related derivatives are used in the [production](#) of [dyes](#). Benzidine has been linked to [bladder](#) and [pancreatic cancer](#)

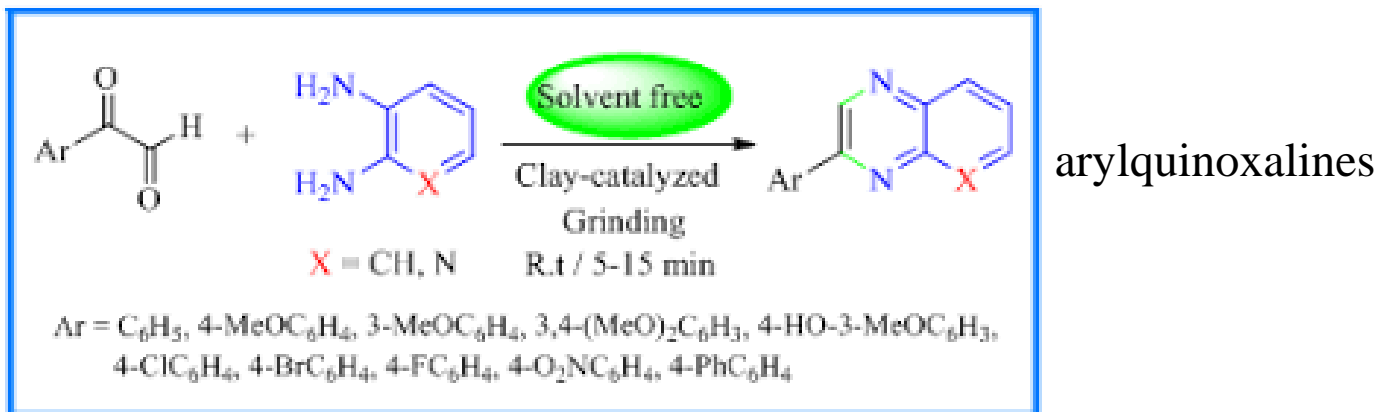


Treatment of this hydrazine with [mineral acids](#), undergoes a [rearrangement reaction](#) to 4,4'-benzidine. Smaller amounts of other isomers are also formed. The **benzidine rearrangement**, which proceeds intramolecularly.

The conversion is described as a [5,5][sigmatropic reaction](#).

Green chemistry: Green chemistry, also called sustainable chemistry, is an area of chemistry and chemical engineering focused on the designing of products and processes that minimize or eliminate the use and generation of hazardous substances

Design of chemical products and processes that reduce or eliminate the use or generation of substances hazardous to humans, animals, plants, and the environment.

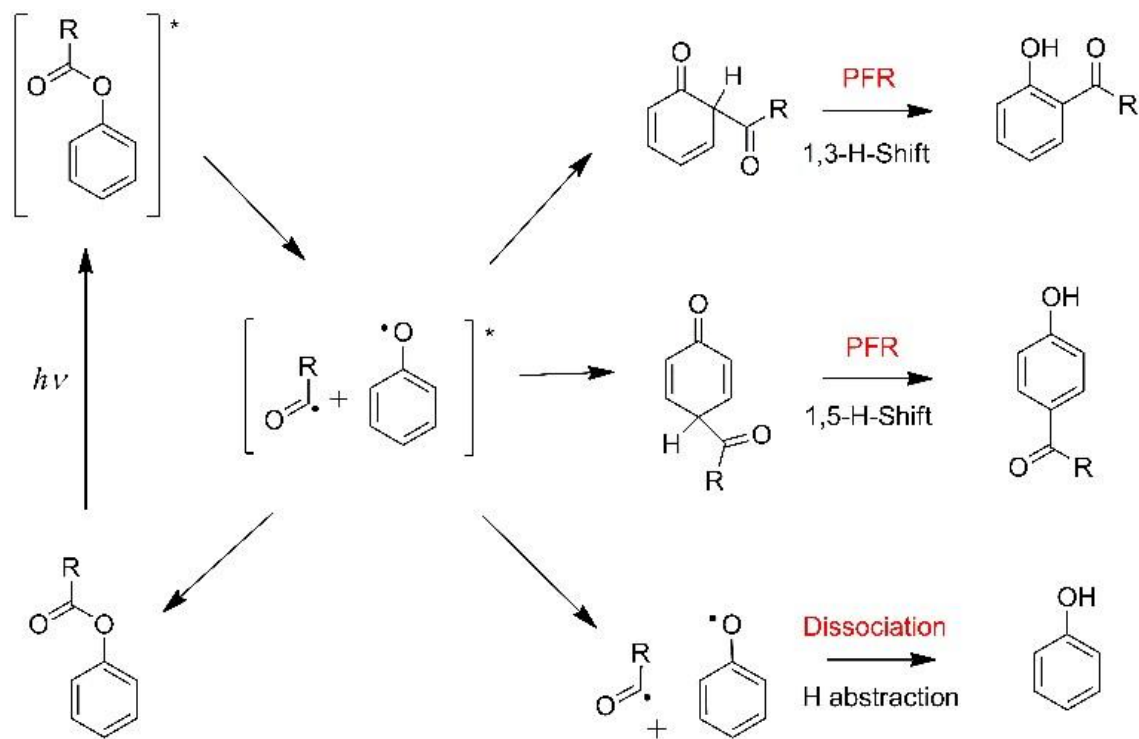


aromatic 1,2-diamines with arylglyoxals under clay-catalyzed

Clay is a finely-grained natural [rock](#) or [soil](#) material that combines one or more [clay minerals](#) with possible traces of [quartz](#) (SiO₂), [metal oxides](#) (Al₂O₃, MgO etc.) and [organic matter](#).

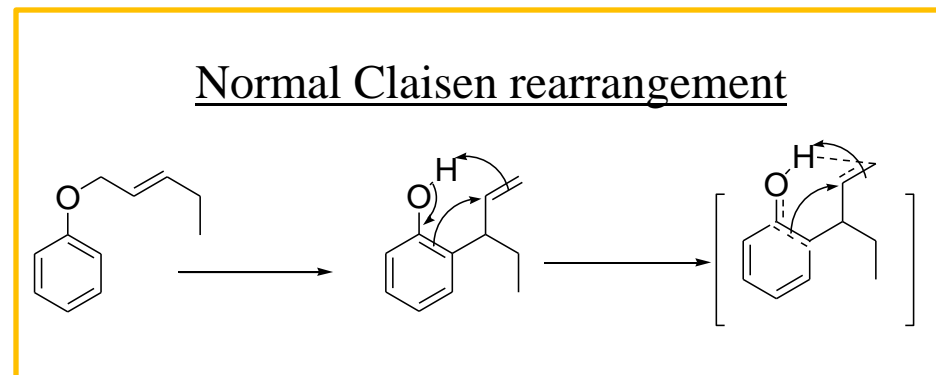
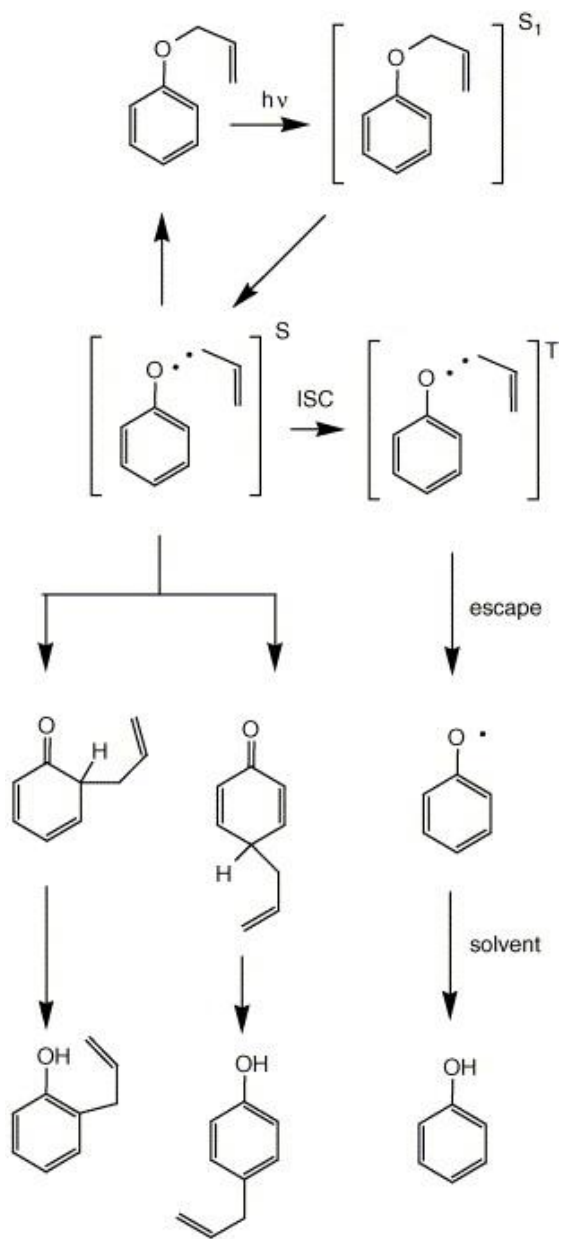
Photo Fries rearrangement

Fries Rearrangement is photochemical excitation, but this method is only feasible in the laboratory



UV light at a wavelength of about 310 nm, if the plastic has been heated to 40° Celsius

Photo Claisen rearrangement



Beckmann rearrangement by green approach

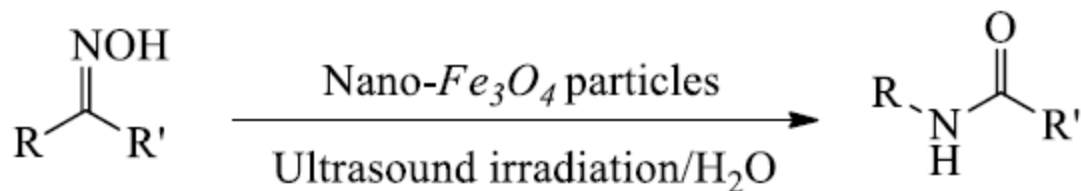
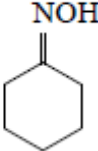
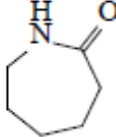
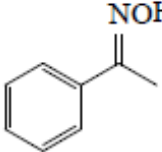
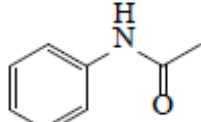
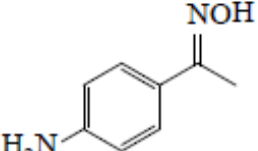
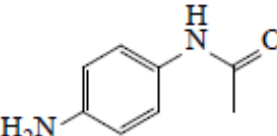
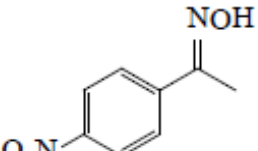
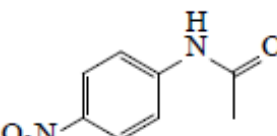
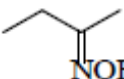
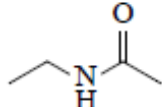
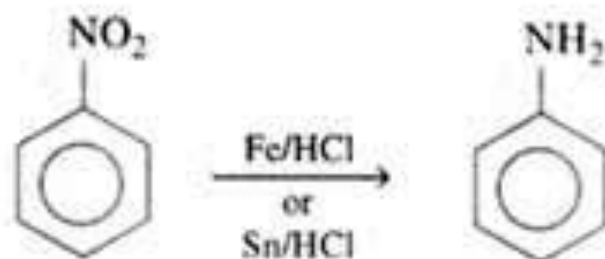
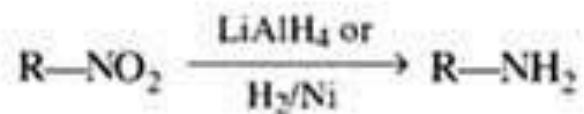
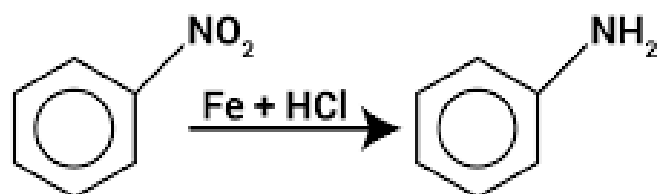
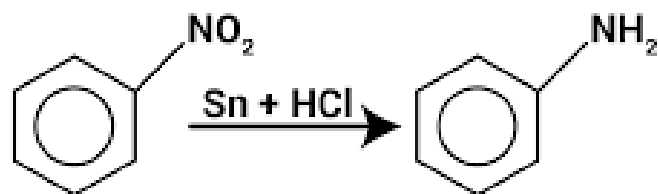


TABLE 2. Beckmann rearrangement of ketoximes with nano Fe₃O₄ system.^a

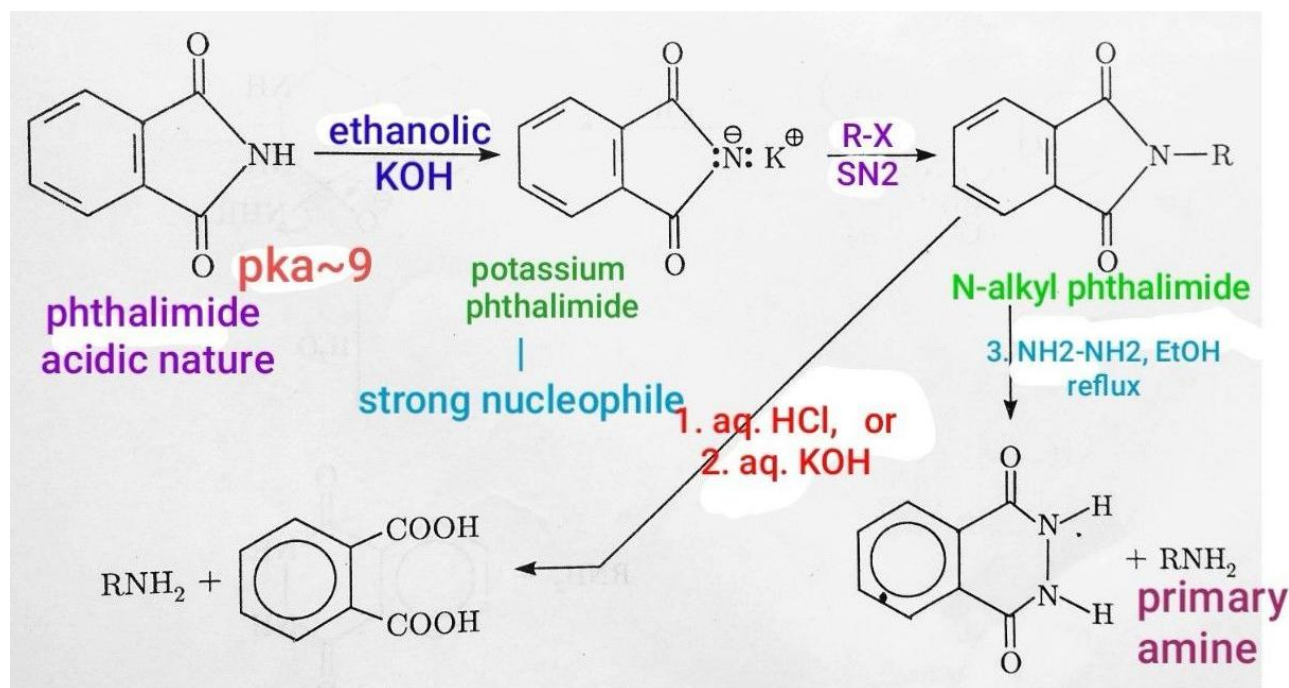
En	Substrate	Product	Molar ratio ^b	Time, min	Conversion ^c , %	Yield ^d , %	Yield ^e , %	Mp/°C (Lit.) ^f
1			1/0.5	45	100	98	97	70(71)
2			1/0.5	50	100	97	97	114(114-115)
3			1/0.5	50	100	97	95	165(163-166)
4			1/0.5	50	100	95	95	215(215)
5			1/0.5	35	100	95	95	-

reduction of nitro compounds

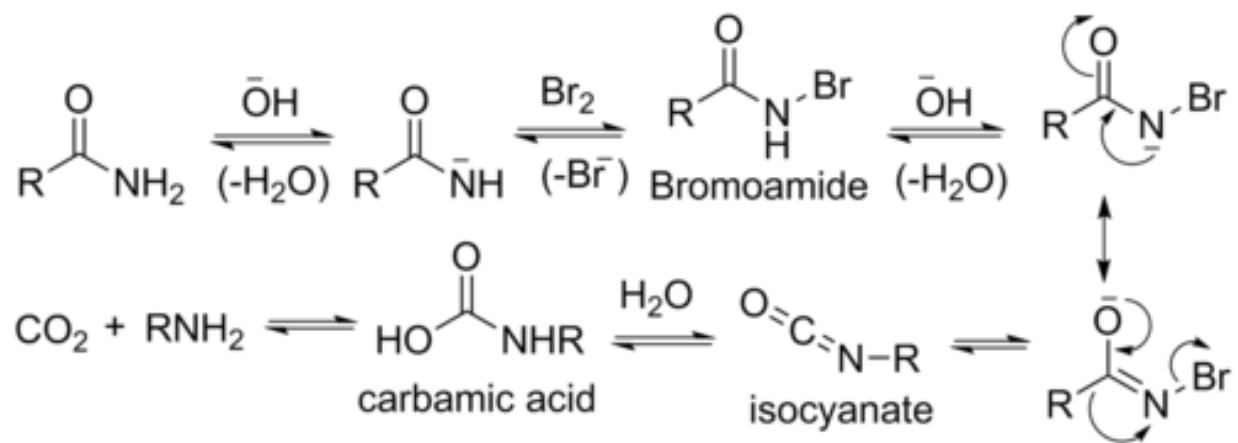


Preparation amines by Gabriel synthesis

Gabriel synthesis is a [chemical reaction](#) that transforms primary [alkyl halides](#) into primary [amines](#). Traditionally, the reaction uses [potassium phthalimide](#). The reaction is named after the German chemist Siegmund Gabriel.

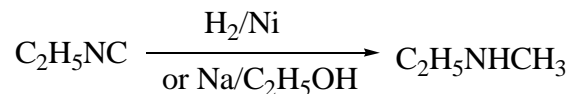


Preparation amines by Hofmann reaction

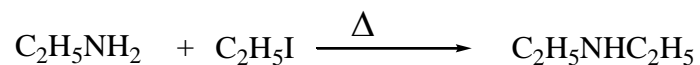


Preparation of Secondary amines

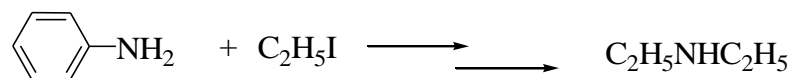
1. Reduction of isocyanides



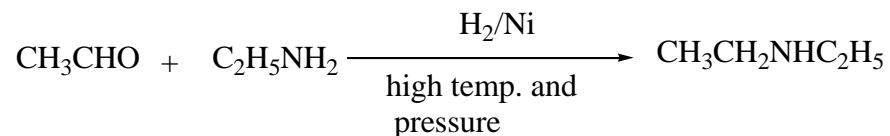
2. Alkylation of Primary amines



3. Using aniline and alkyl halides

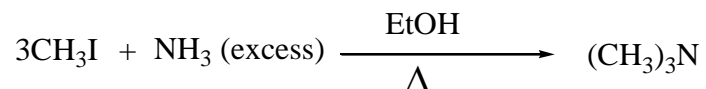


4. Reduction of imines

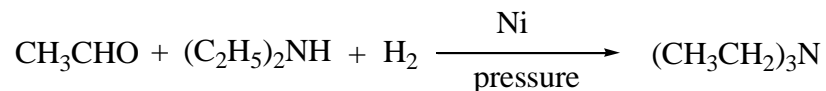


Preparation of Tertiary amines

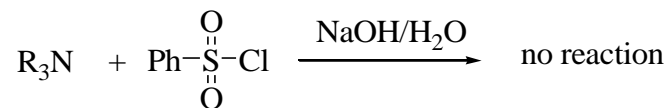
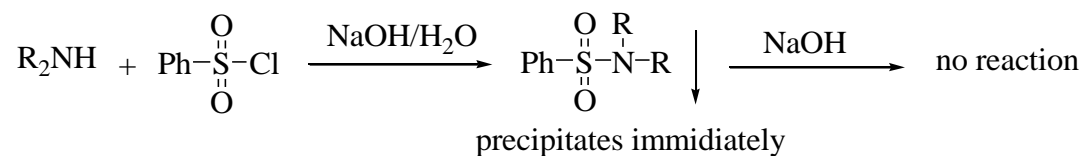
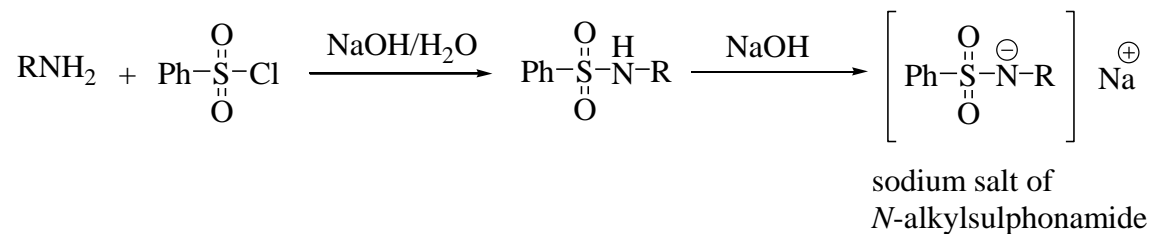
1. By Alkylation of ammonia



3. Reductive alkylation of secondary amines using carbonyl compound



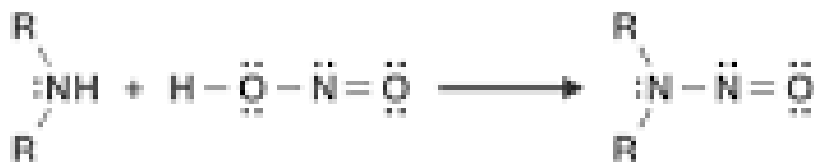
Distinction of 1°, 2° and 3° amines (Hinsberg test)



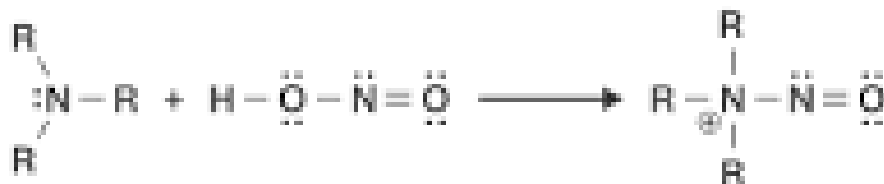
Reactions with HNO_2 (aliphatic amines)



Primary amine

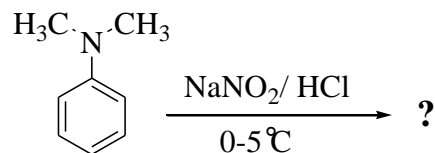
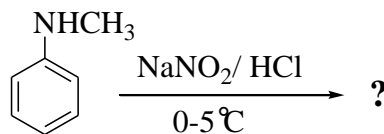
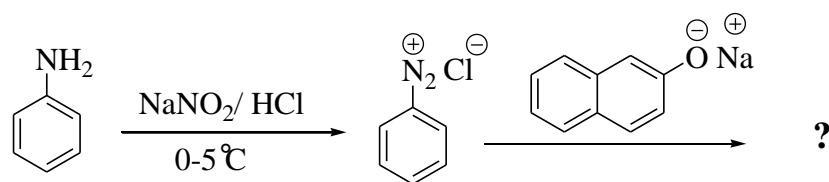


Secondary amine

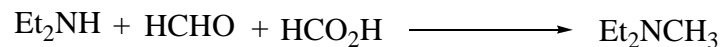
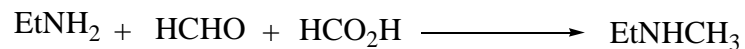


Tertiary amine

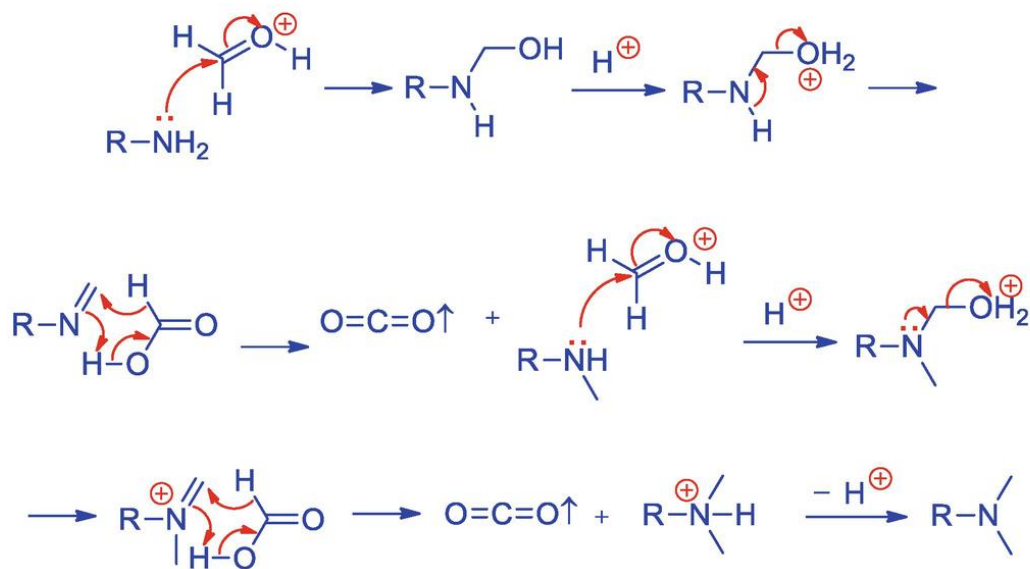
Reactions with HNO_2 (aromatic amines)



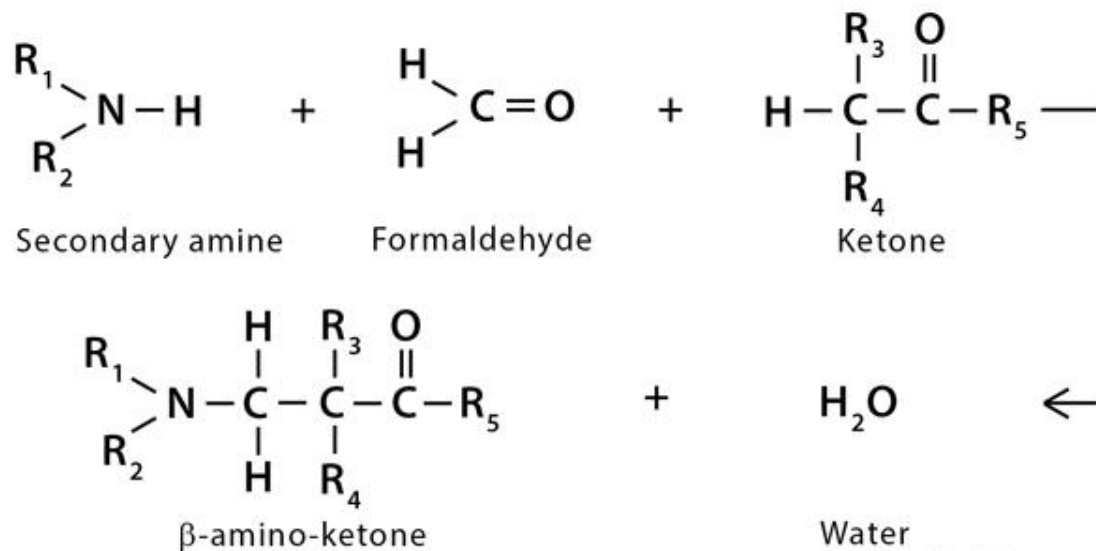
Eschweiler-Clarke methylation



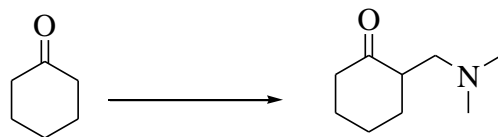
formic acid is the hydride source, serving as a reducing agent



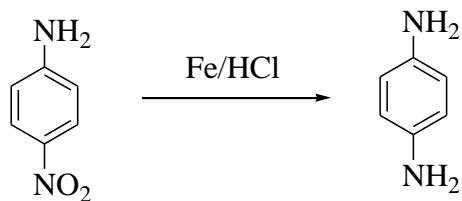
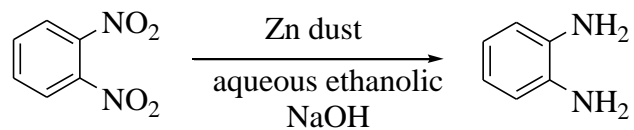
Mannich Reaction



Reaction of Enolizable carbonyl compound with HCHO and NH₃ or 1° 2° amine



Phenylenediamines preparation and their important reactions



Diazomethane

