Nucleophilic Aromatic Substitution Reactions (SNAr)

Objective

Objective

After completing this section, you should be able to

- identify the conditions necessary for an aryl halide to undergo nucleophilic aromatic substitution, and give an example of such a reaction.
- write the detailed mechanism for a nucleophilic aromatic substitution reaction.
- compare the mechanism of a nucleophilic aromatic substitution reaction and the S_N1 and S_N2 mechanisms discussed earlier.
- identify the product formed when a given nucleophile reacts with a given aryl halide in a nucleophilic aromatic substitution reaction.

Nucleophilic Aromatic Substitution Reactions

- A nucleophilic aromatic substitution is
  - a substitution reaction in organic chemistry in which the **nucleophile** displaces a **good leaving group**, such as a **halide**, on an **aromatic ring**.
  - **nucleophilic addition** to an **aromatic ring (**which **destroys** the **ring's aromaticity),** followed by an **elimination step (**which **restores** the lost **aromaticity)**.
  - Aromatic rings are usually nucleophilic, but some aromatic compounds do undergo nucleophilic substitution.

nucleophilic substitution Reactions of Aryl halides

- The carbon-halogen bonds of aryl halides are like those of alkenyl halides in being much stronger than those of alkyl halides.
- The simple aryl halides generally are resistant to attack by nucleophiles in either S_N1 or S_N2 reactions.
- However, this low reactivity can be changed dramatically by changes in the reaction conditions and the structure of the aryl halide. In fact, nucleophilic displacement becomes quite rapid.

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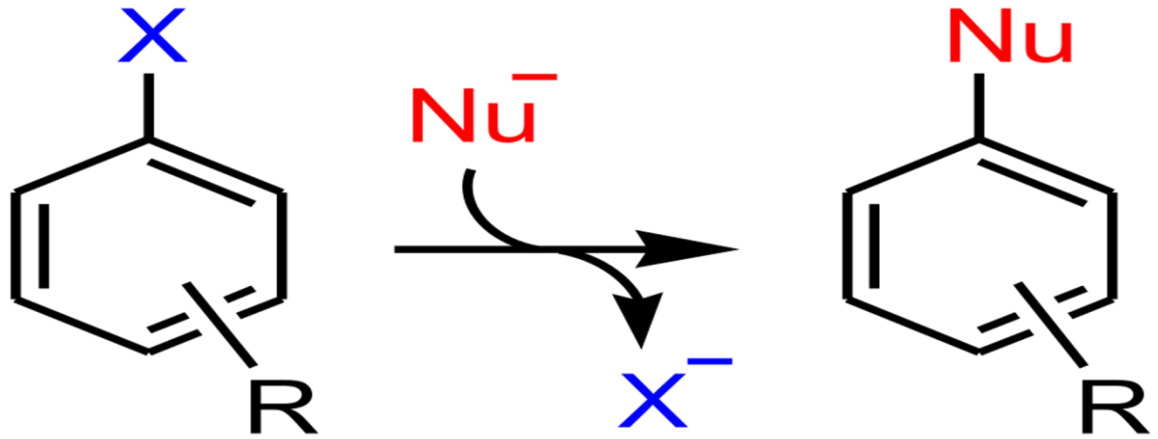
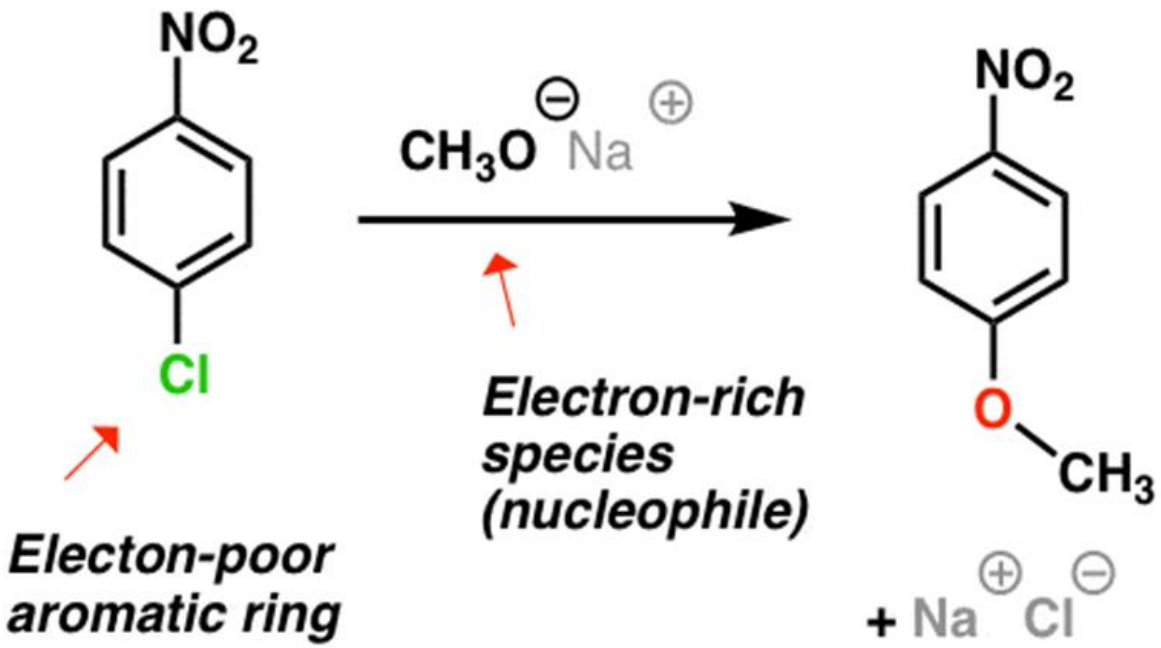
- when the aryl halide is activated by substitution with strongly electron-attracting groups such as NO_2, and when very strongly basic nucleophilic reagents are used.



X = halogen etc. Nu = nucleophile

Example

Would you believe..



Electon-poor aromatic ring

Electron-rich species (nucleophile)

Bonds formed	Bonds broken
C–O	C–Cl

a substitution reaction...

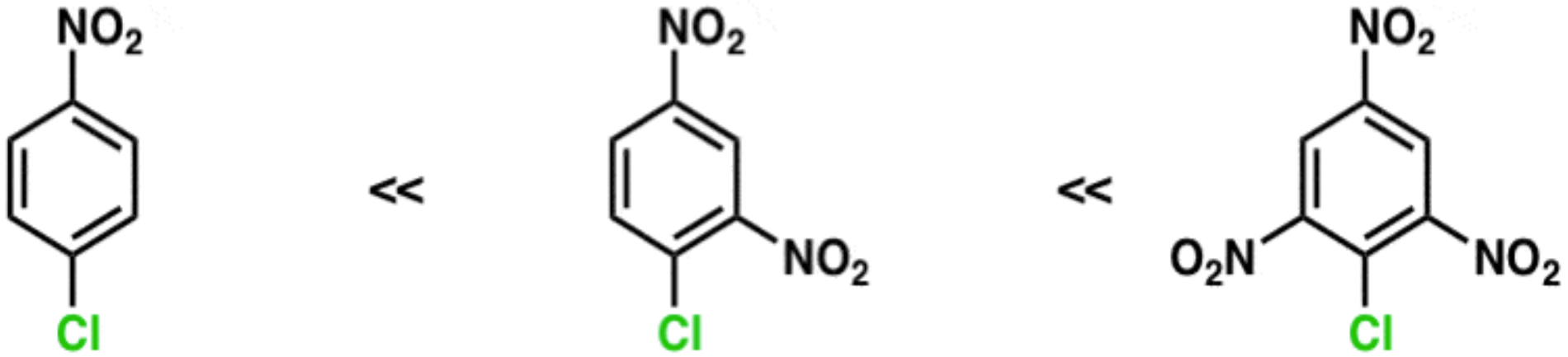
by a nucleophile !?

Cont'd

Electron-Withdrawing Groups in Nucleophilic Aromatic Substitution:

one EWG	two EWGs	*three EWGs*
slowest	**faster**	**fastest**

(by a factor of about 10^5)

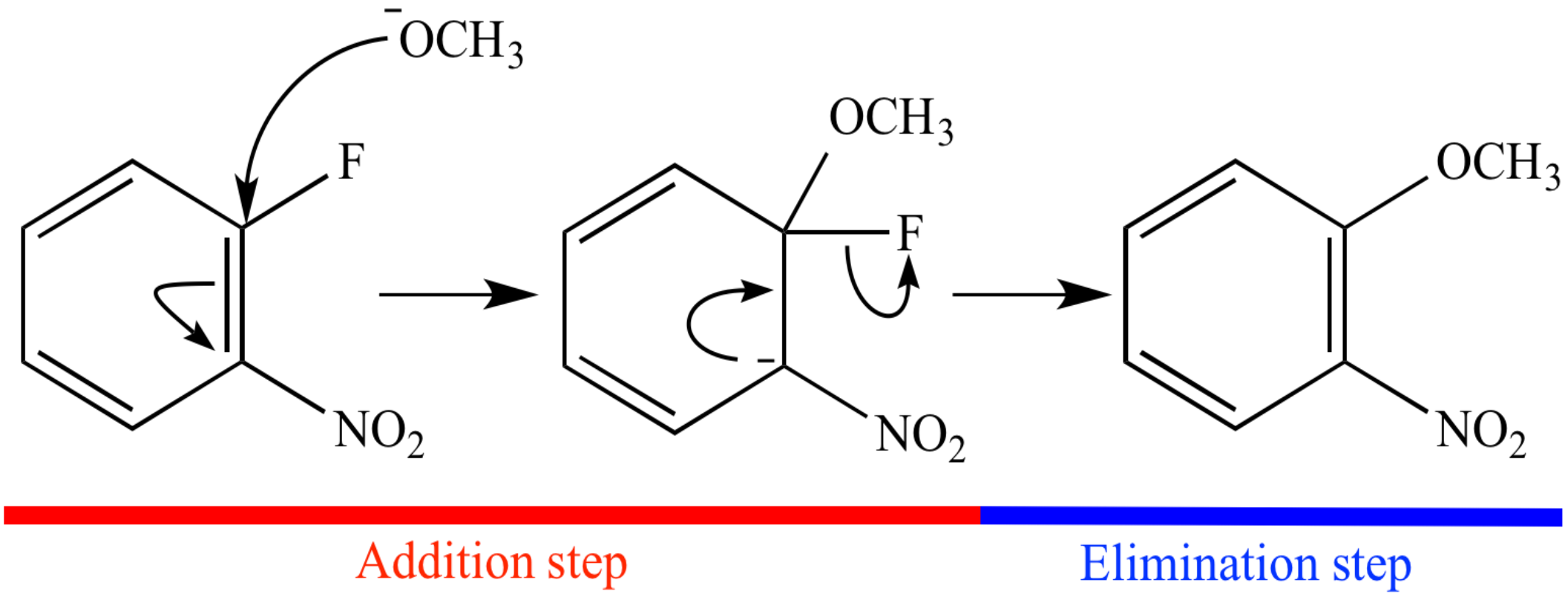


Nucleophilic Aromatic Substitution Reactions

- **Step [1] Addition of the nucleophile (:Nu–) to form a carbanion (meisenheimer intermediate or complex**
  - Addition of the nucleophile (:Nu–) forms a resonance-stabilized carbanion called with a new C – Nu bond— three resonance structures can be drawn.
  - This Step is rate-determining and Aromaticity of the benzene ring is lost
- **Step [2] loss of the leaving group re-forms the aromatic ring.**
  - This step is fast because the aromaticity of the benzene ring is restored.

Nucleophilic Aromatic Substitution Reactions

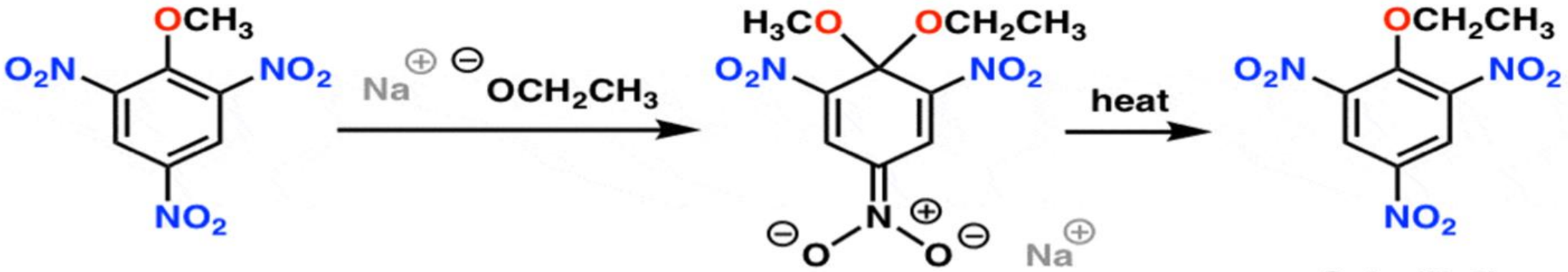
Mechanism



Nucleophilic Aromatic Substitution Reactions

The "Meisenheimer" Intermediate

Intermediates from nucleophilic aromatic substitution (called "Meisenheimer complexes" after their 1902 discovery) have been isolated.
Further heating of these products results in the substitution product.



"Meisenheimer complex "

(Can be isolated)

Substitution product

Pretty clear evidence for a two-step mechanism that proceeds through
1) attack of nucleophile on the ring
2) elimination of the leaving group

The Effect Of Substituents On The Ring

- In nucleophilic aromatic substitution (SNAr), all the trends you learned in electrophilic aromatic substitution operate, but in reverse.
- The first trend to understand is that electron withdrawing groups (EWG's) dramatically increase the rate of reaction, not decrease it.
- From this, it follows that the more EWG's there are, the faster the reaction.
- For example, the rate of SNAr for 2,4-dinitrophenyl chloride is about 105 times faster than for p-nitrophenyl chloride. [note] (I don't have a rate constant for 2,4,6-trinitrophenyl chloride readily available, but it is orders of magnitude faster still).

- According to the Hammond postulate, electronwithdrawing groups stabilize the intermediate carbanion by lowering the energy of the transition state.
- Interestingly, increasing the electronegativity of the halogen atom in substrates increases the reactivity of the aryl halide.
- **This trend is opposite to reactivity for aliphatic nucleophilic substitution, but the reason behind this is that a more electronegative halogen stabilizes the intermediate carbanion better by an inductive effect.**

- Thus, aryl fluorides (ArF) are much more reactive than other alkylyl halides, which contain less electronegative halogens

- The SNAr reactions follow a second order kinetics according to the following equation: ◦ Rate = k[aryl halide] [nucleophile] ◦ Following data illustrates the significant differences observed between reactivity of alkyl halides.

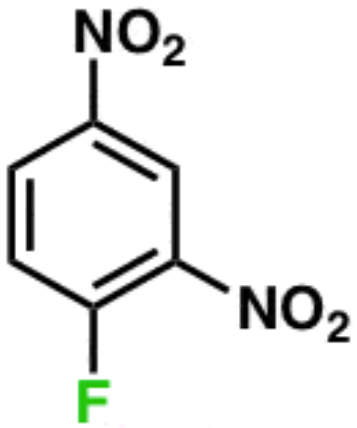
Effect Of The Leaving Group

- The Effect Of The Leaving Group One of the most eye-opening aspects of nucleophilic aromatic substitution is noting that fluorine is often used as a leaving group.
- This is seen in Sanger's reagent for sequencing peptides, to take one example (more on that below).
- After all, given the stern tones we instructors use in Org 1 on this subject, the words "FLUORINE IS NEVER A LEAVING GROUP IN SN2 AND SN1 REACTIONS" may as well have been carved on one of the stone tablets handed down to Moses on Mt. Sinai.

Effect Of The Leaving Group

- Here's a thought: if even a "bad" leaving group like fluorine works in nucleophilic aromatic substitution, then surely a "better" leaving group like bromine or iodine would work even better. Right?
- This is a good hunch. It is also wrong – which *does not make it a dumb idea*, only that organic chemistry is deep.

Fluorine is actually a better leaving group than Cl, Br, and I



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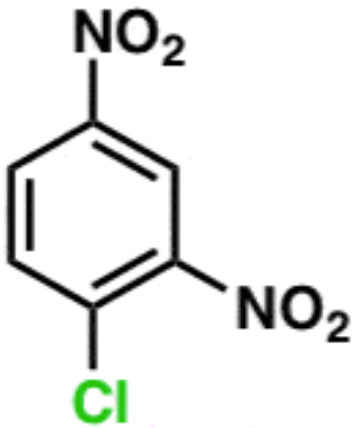

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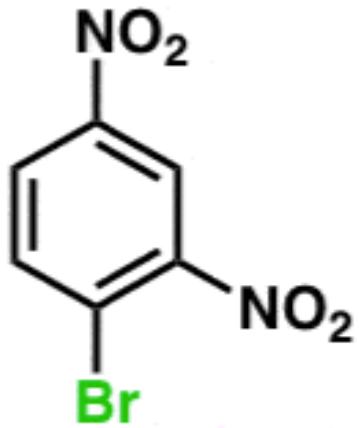

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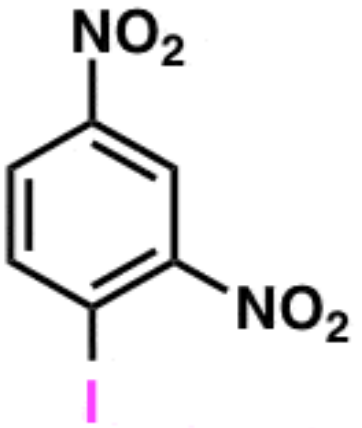


1

suggests that C–F bond cleavage is not involved in the rate-determining step!

Cont'd

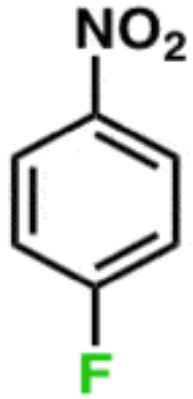
- So what could be different about nucleophilic aromatic substitution that makes the rate of reaction much less sensitive to the identity of the leaving group than the S_N1 and S_N2 reactions?
- Well, for one thing, this would suggest that, unlike the S_N1 and S_N2 reactions, C-F bond cleavage does not occur in the rate-determining step.
- This information is helpful in coming up with a mechanism for the reaction.

The Effect Of Substitution Pattern

- The position of substitution is controlled by the placement of the leaving group.
- However that isn't to say that the rate of the reaction isn't affected by the relative position of the leaving group and the electron-withdrawing group.
- For example, nucleophilic aromatic substitution of *p*-nitrophenyl fluoride is orders of magnitude faster than *m*-nitrophenyl fluoride, even though the NO2 is closer to the leaving group and should presumably exert more of an inductive effect.
- The *ortho* isomer is also faster than the *meta* by a large margin.

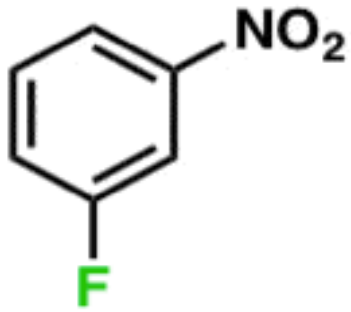
The effect of substitution pattern

Nucleophilic aromatic substitution on *p*-nitrofluorobenzene is faster than *m*-nitrofluorobenzene. **Why?**



p-fluoronitrobenzene

Fast



m-fluoronitrobenzene

Slow

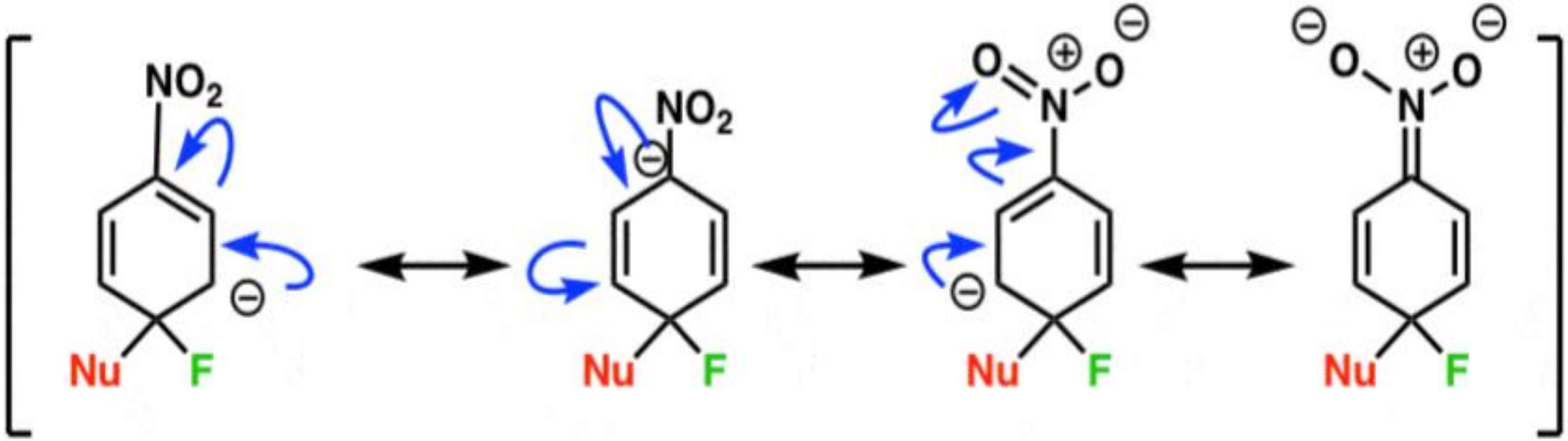
Cont'd

- **Why Is The *para*- Isomer Faster Than The *meta*- Isomer ? It's All About Stabilizing Negative Charge**
- This two-step mechanism where addition is the rate-determining step helps to explain our earlier puzzle of why the reaction with *para*-nitro is faster than the *meta*- isomer.
- Note how the anion in the *para*- intermediate can be delocalized to the oxygen on the nitro group, putting a negative charge on (more electronegative) oxygen.
- In the *meta*- intermediate, the negative charge cannot be delocalized to the nitro group, and is stuck on (less electronegative) carbon.

Cont'd

The negatively charged intermediate is stabilized by electron withdrawing groups (such as NO_2)

In the attack of a nucleophile on *p*-nitrophenyl fluoride, the negative charge can be delocalized to the oxygen of the nitro group;



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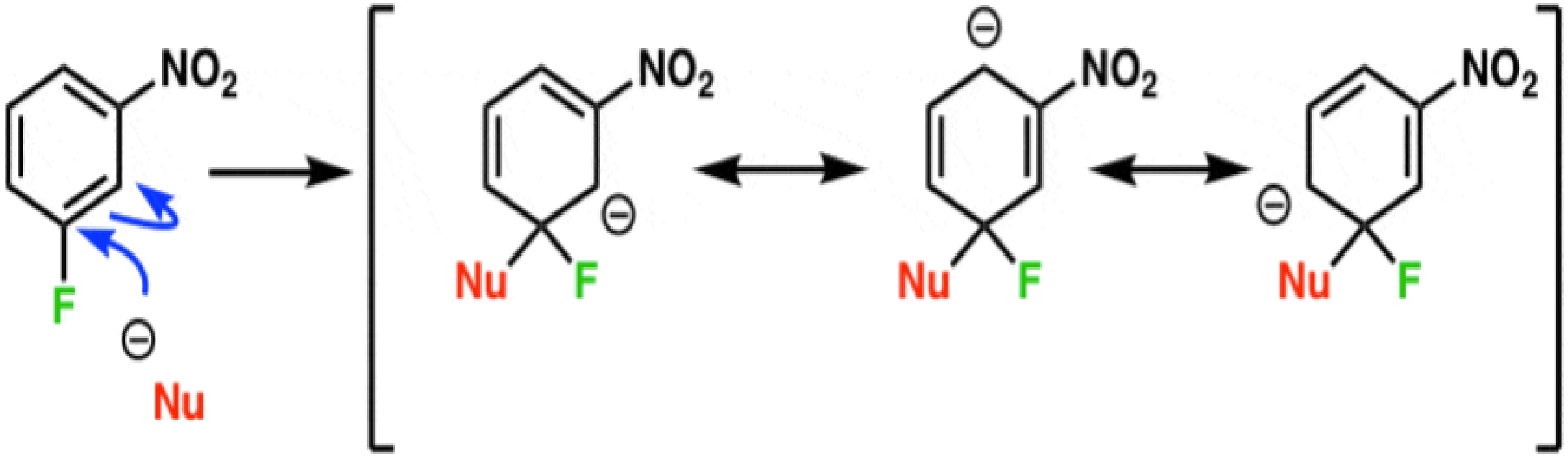
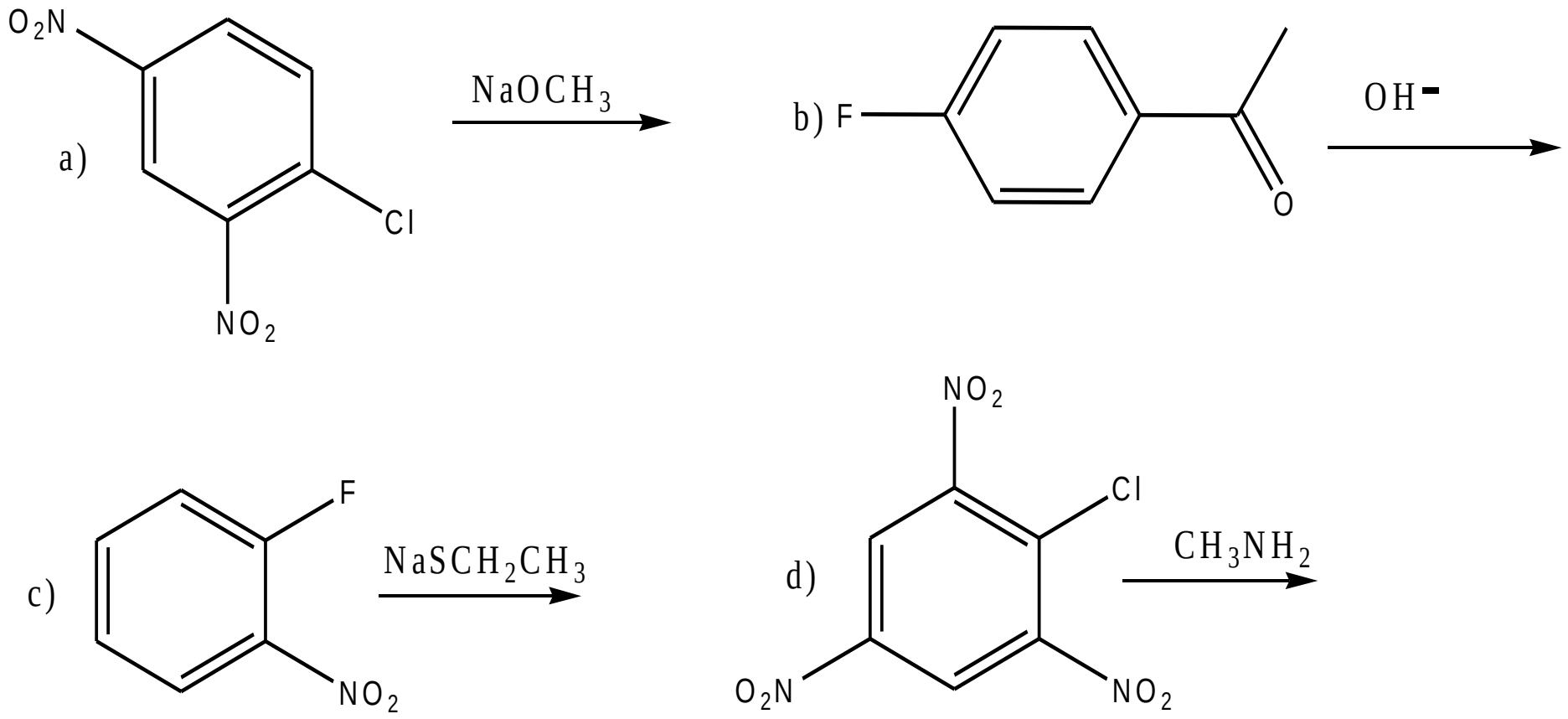
This isn't possible in the intermediate arising from attack on *m*-nitrophenyl fluoride:



This explains why the rate of nucleophilic aromatic substitution is much faster with the *para* than the *meta* isomer.

Nucleophilic Aromatic Substitution Reactions

❖ **Question # 1:-** Draw the product and write the mechanism of the reaction



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- **Question # 2:-** Explain why a methoxy group (CH3O) increases the rate of electrophilic aromatic substitution, but decreases the rate of nucleophilic aromatic substitution.

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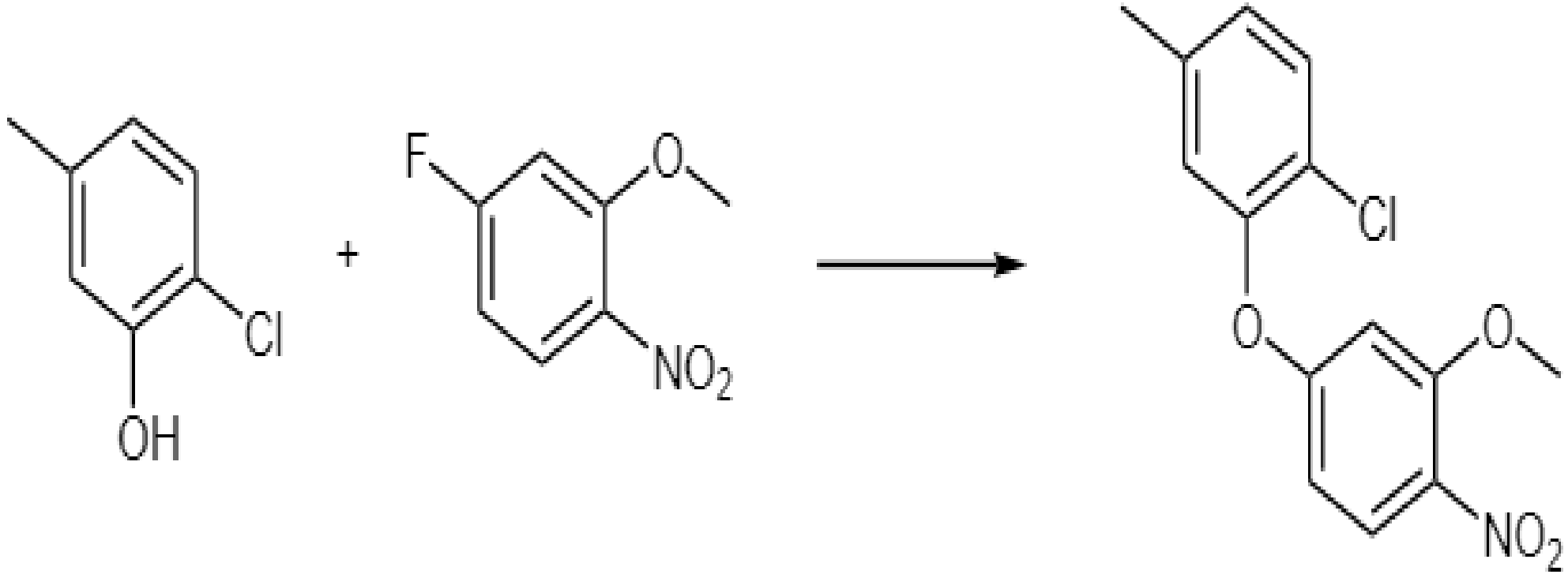
❖ Exercise 1:-



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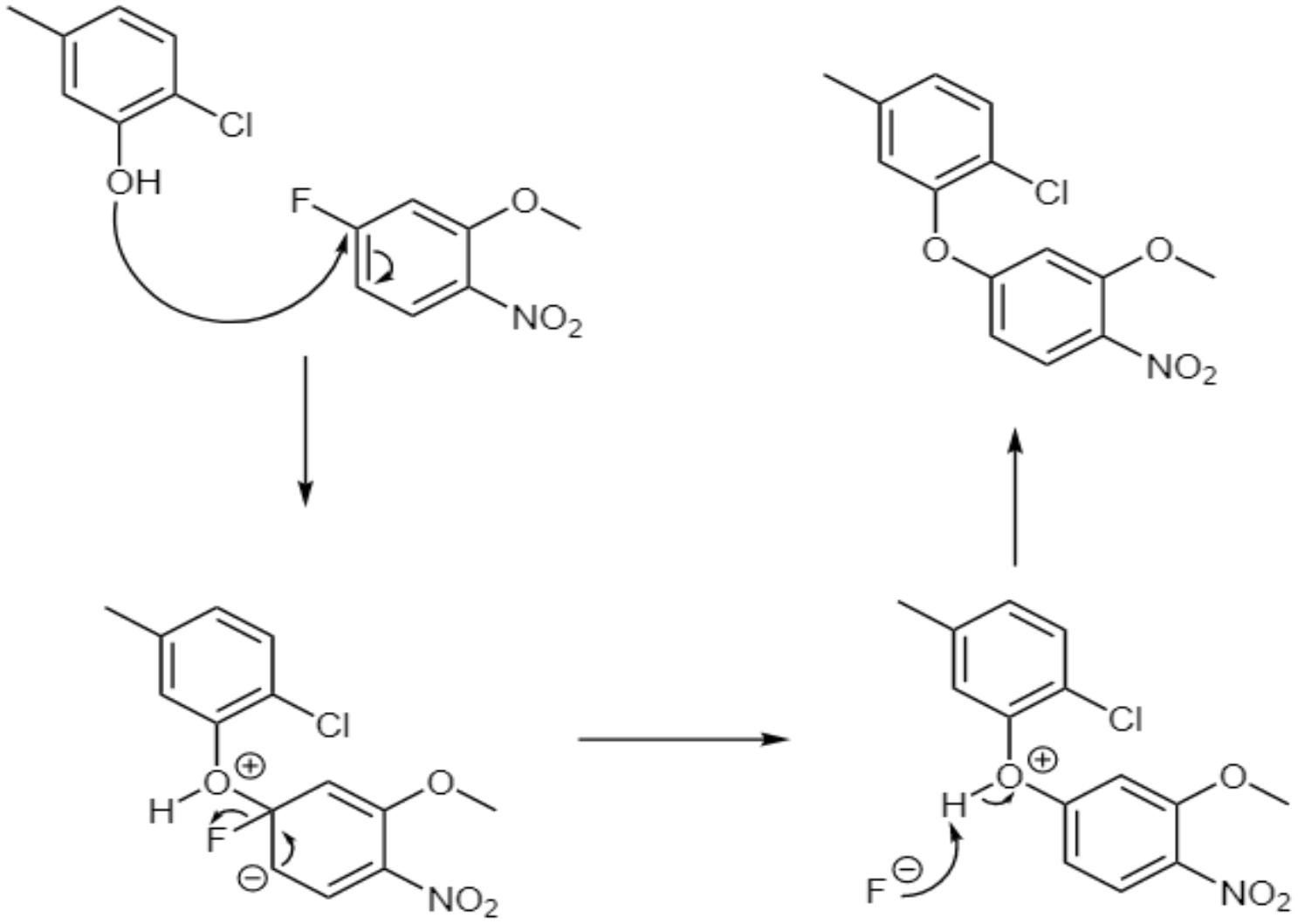
❖ Answer :-



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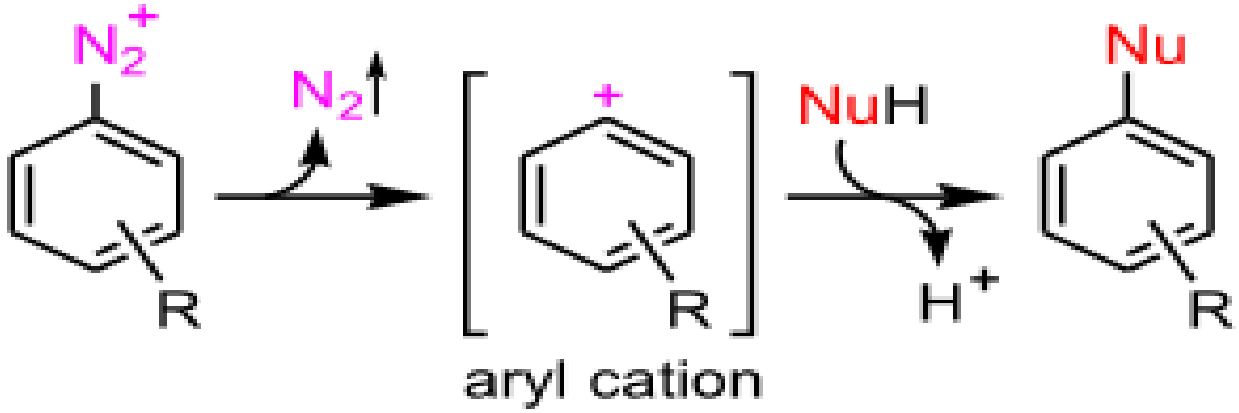
ArSN1 Mechanism- elimination /addition



- This mechanism operates in the reaction of diazonium salts with nucleophiles.
- The driving force resides in the strength of the bonding in the nitrogen molecule that makes it a particularly good leaving group.

Reactions of Aromatic Side Chains

Reactions of Aromatic Side Chains

- Aromatic side chain oxidation is an interesting reaction.
- Benzene is not easily oxidized, nor is an alkane.
- However, **when attached to a benzene ring the benzylic carbon is susceptible to a unique oxidation yielding a benzoic acid**.
- Benzene ring can activate the benzylic position of alkylbenzene toward oxidation with strong oxidants such as $KMnO_4$ and $Na_2Cr_2O_7$ to give benzoic acids.

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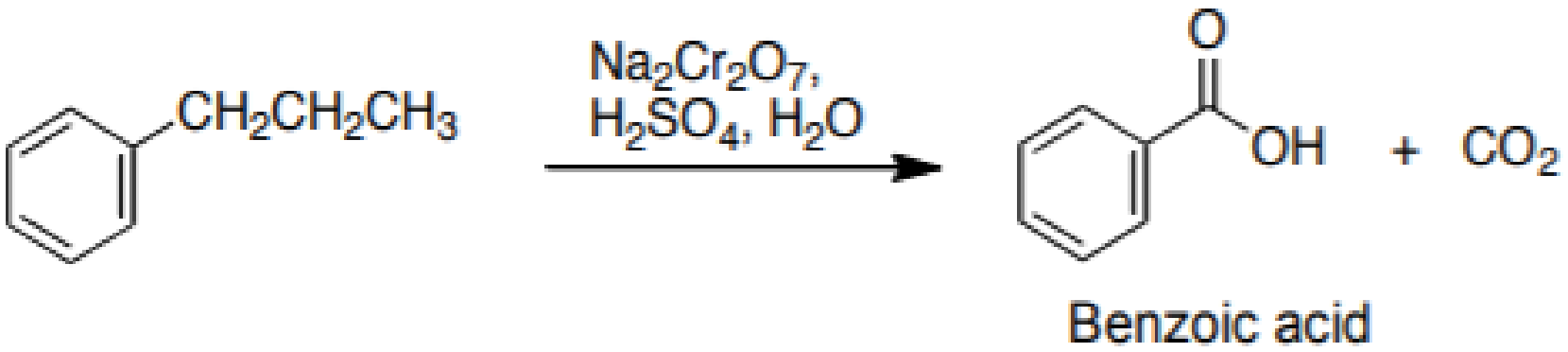
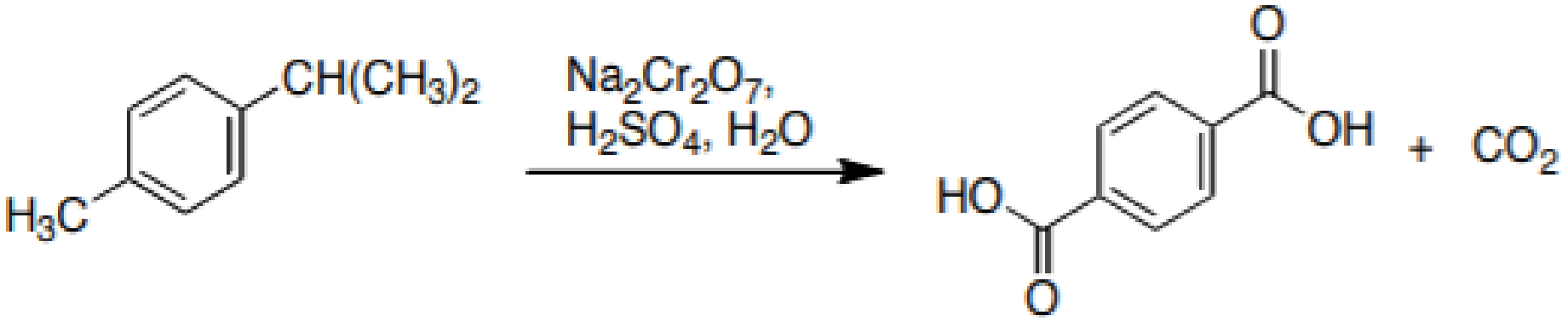
Example



Benzoic acid



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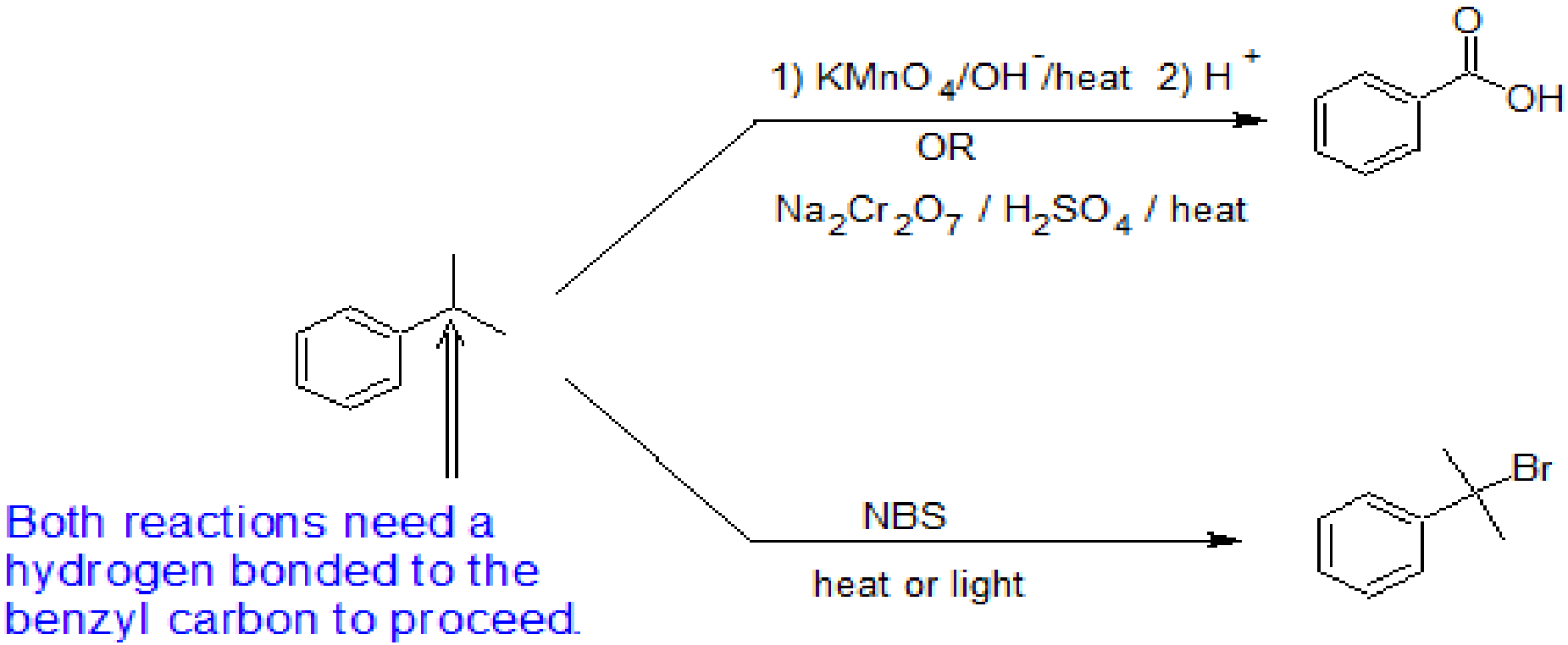
Example



Both reactions need a hydrogen bonded to the benzyl carbon to proceed.

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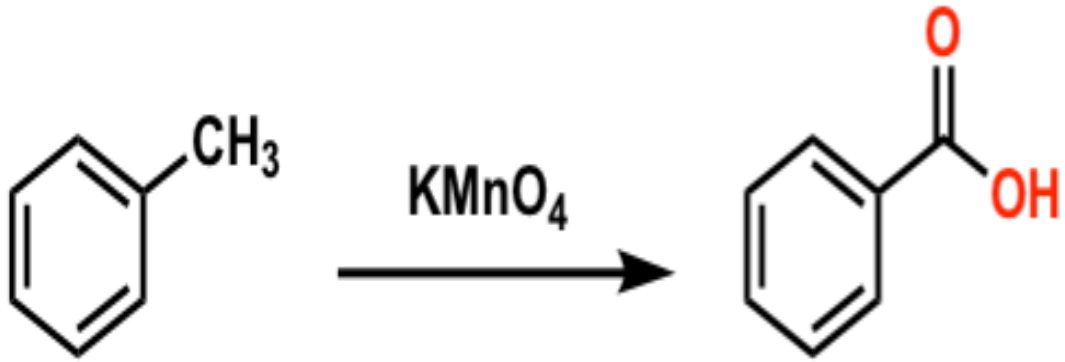
Conversion of alkylbenzenes to benzoic acids using $KMnO_4$

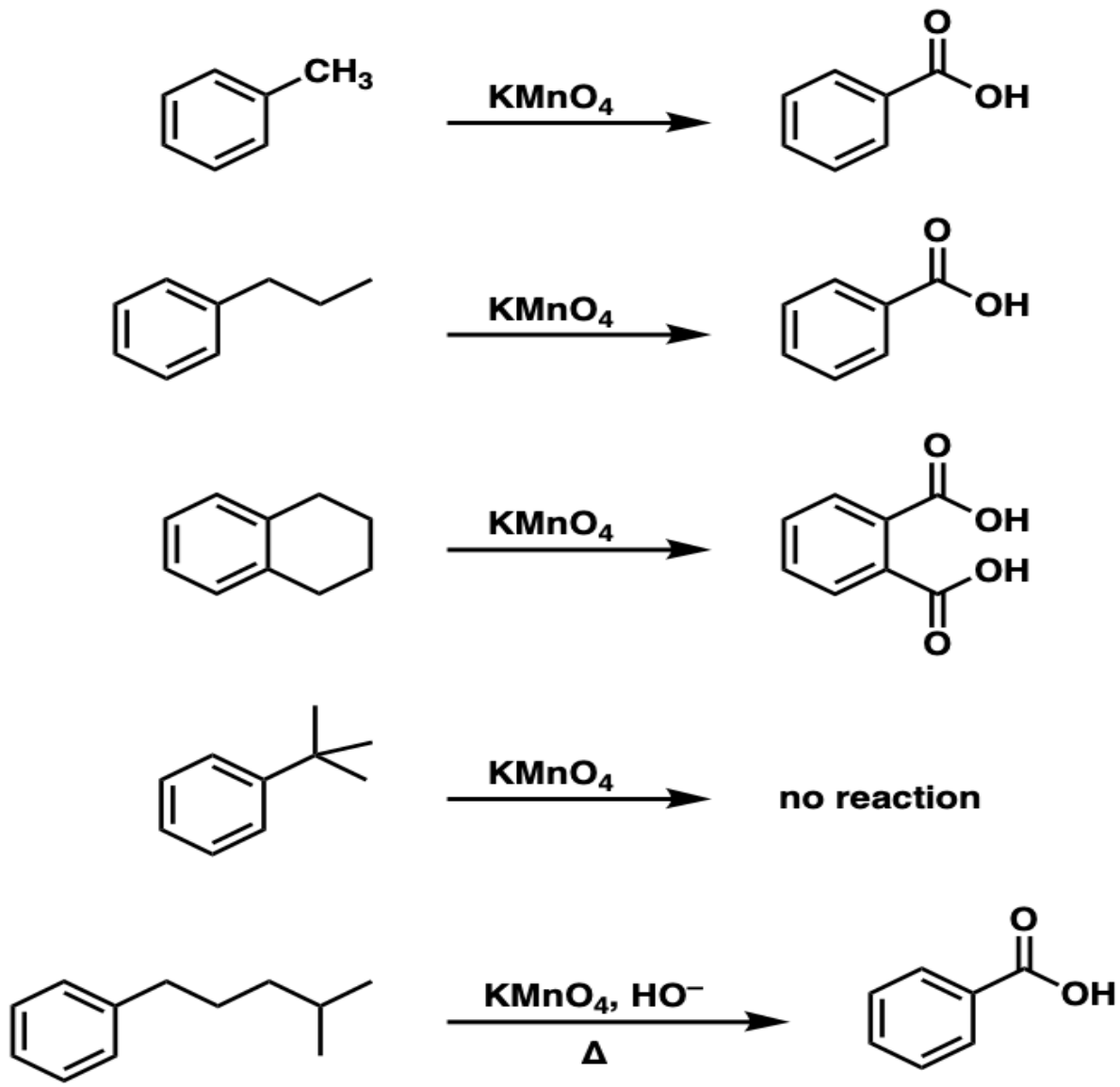


Alkylbenzene → *Benzoic acid*

Key bonds formed	Key bonds broken
C–O(π)	C–H
C–O	C–H
C–OH	C–H

Cont'd

Example



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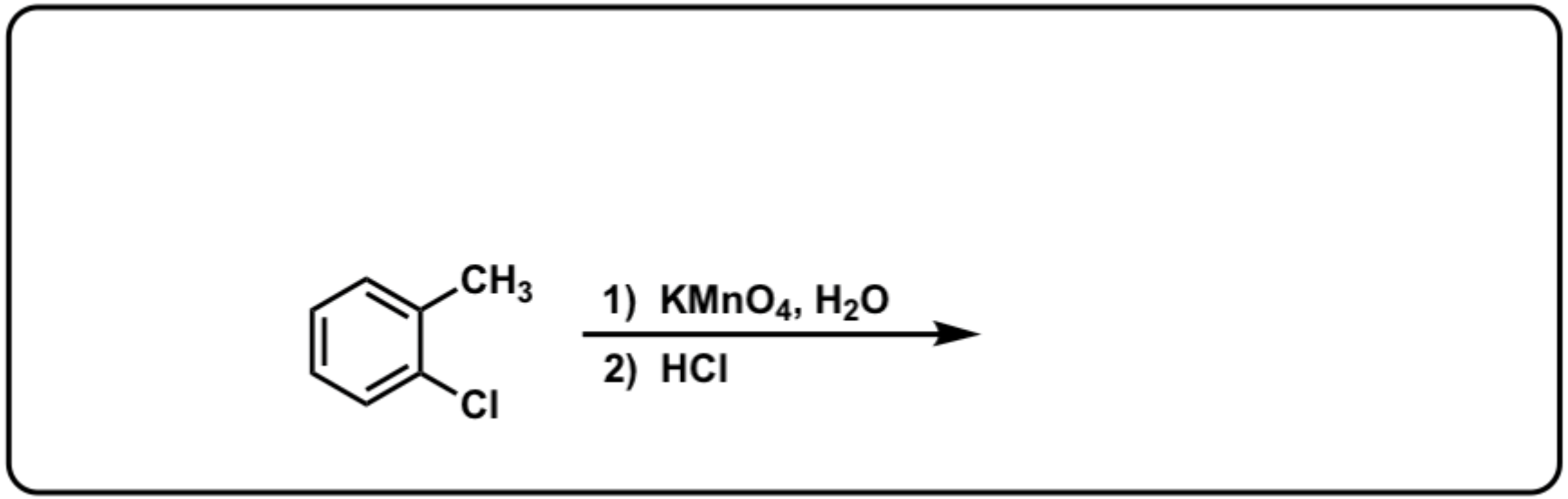
- **Question # 3 complete the reaction**



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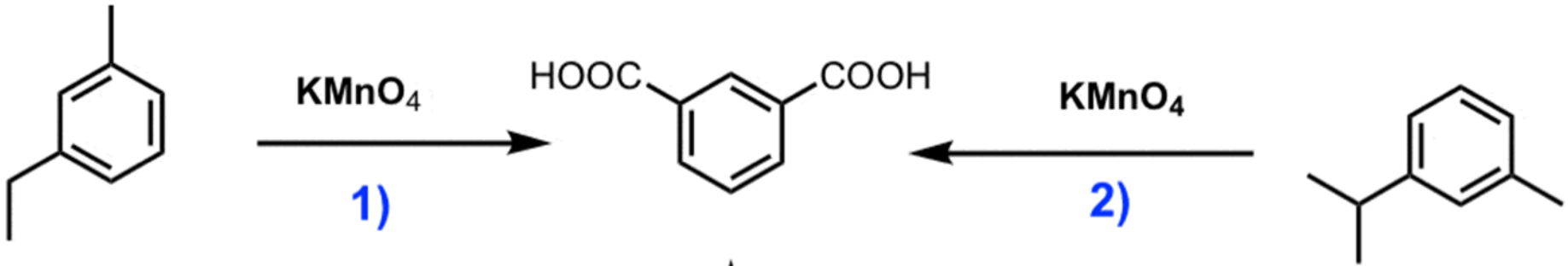
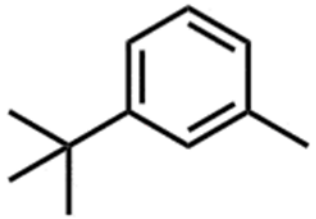
Question # 4



Which of the reactions 1) - 3) is correct?

a) 1)
b) 2)
c) 3)
d) 1) and 2)
e) all are correct



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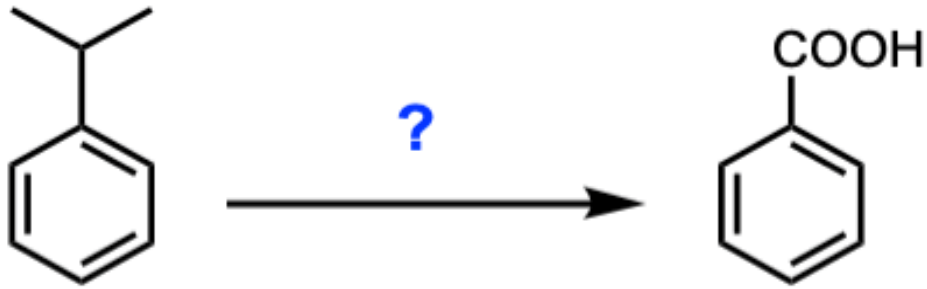
Question # 5



Choose a suitable reagent to carry out this reaction :

a) $NaBH_4$

b) H_2 , Pd-C

c) $KMnO_4$

d) H_2SO_3

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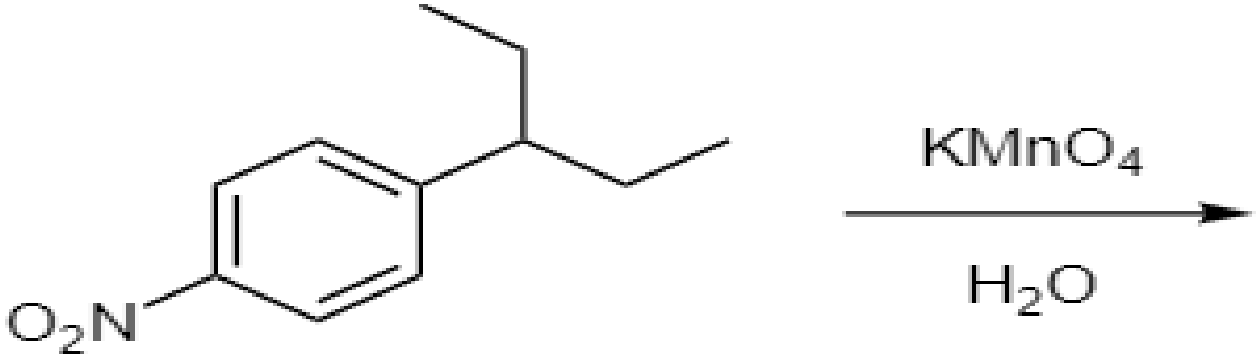
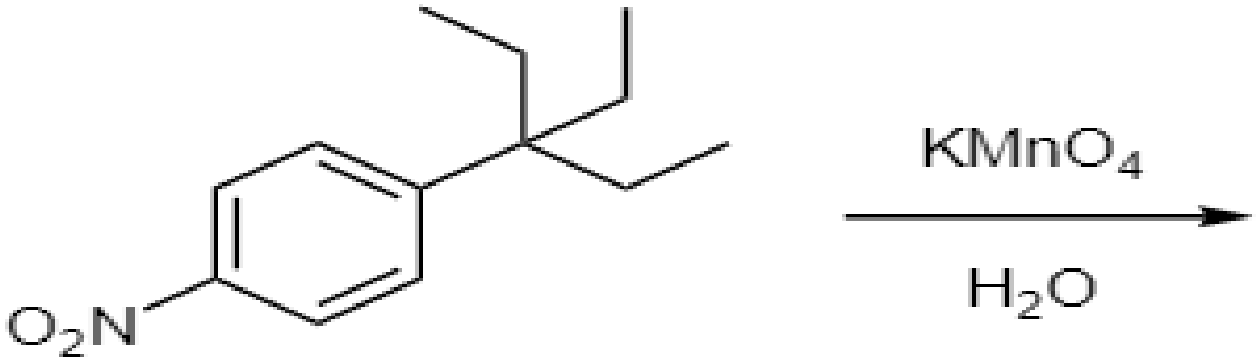
❖ **Class work:** Predict the products of the following two reactions.





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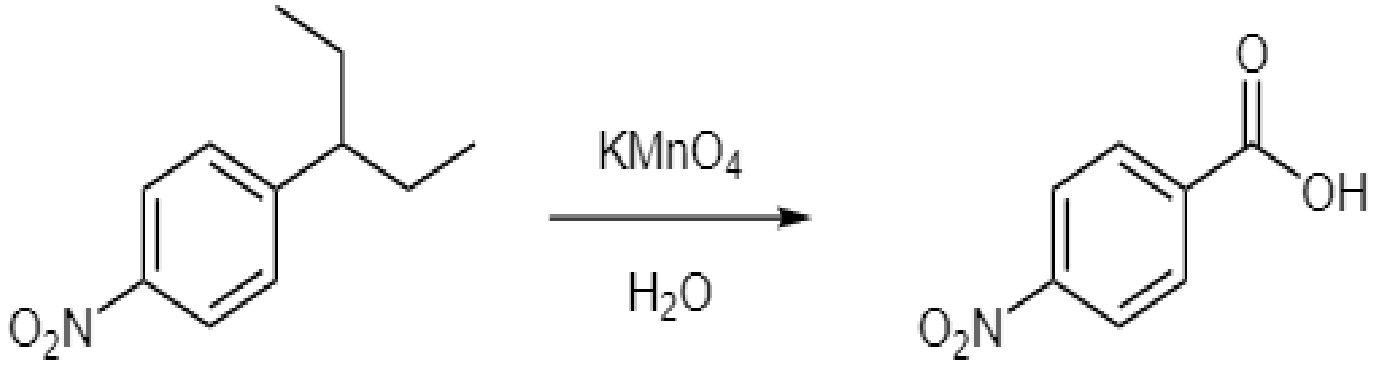
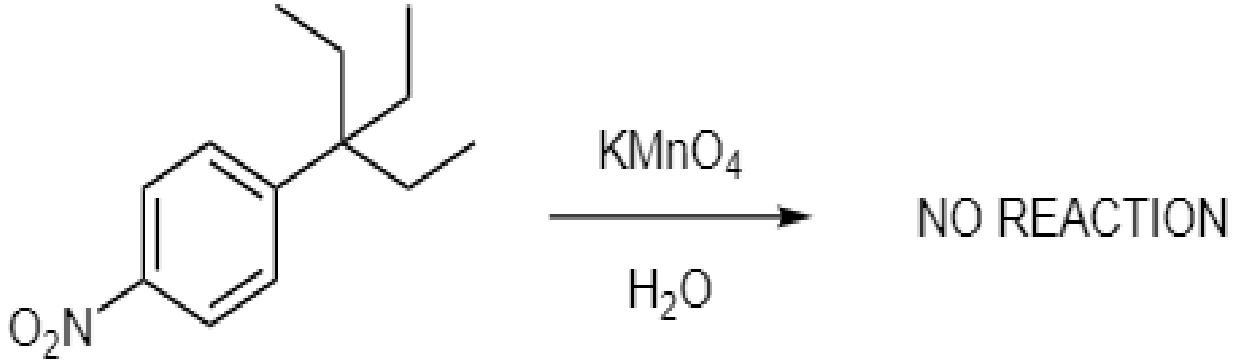
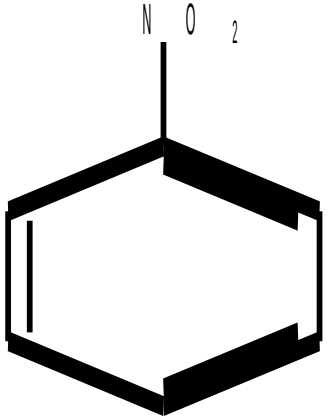
Answer



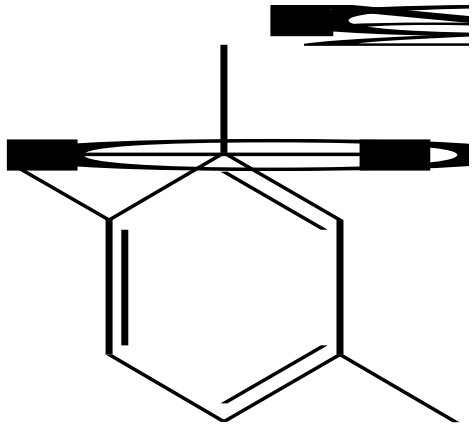


Reduction of Nitro Groups and Aryl Ketones

- Nitro compounds are an important class of organic compounds that are recognized by the presence of one of more nitro functional groups (NO2) bonded directly to the carbon of the hydrocarbon chain or aromatic ring.
- Nitro compounds are usually prepared by different synthetic techniques but a few of them are naturally occurring.
- **Example**



Nitrobenzene

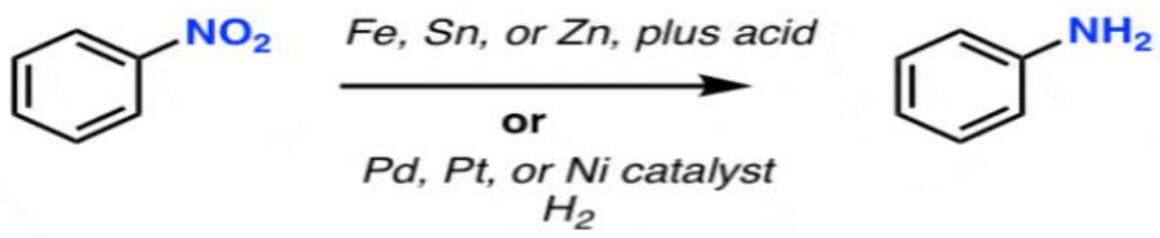


4-methyl-2-nitrophenol

- **Nitro group is very strong nucleophile and is readily converted to a series of functional groups of various degree of reduction.**
  - Very exceptionally to a nitroso group
  - More often to a hydroxylamino group

hydroxylamino group

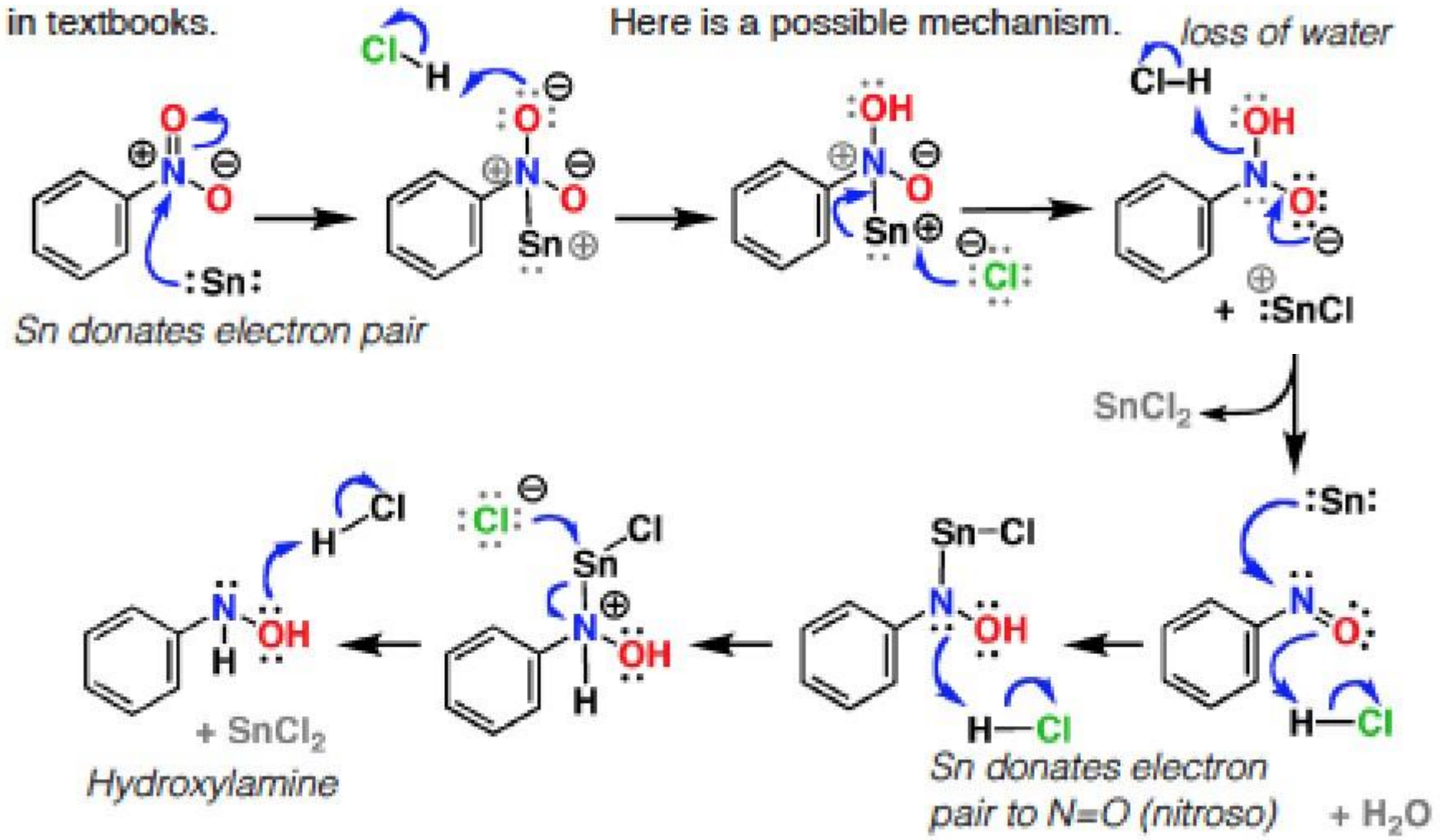
  - Most frequently to amino group

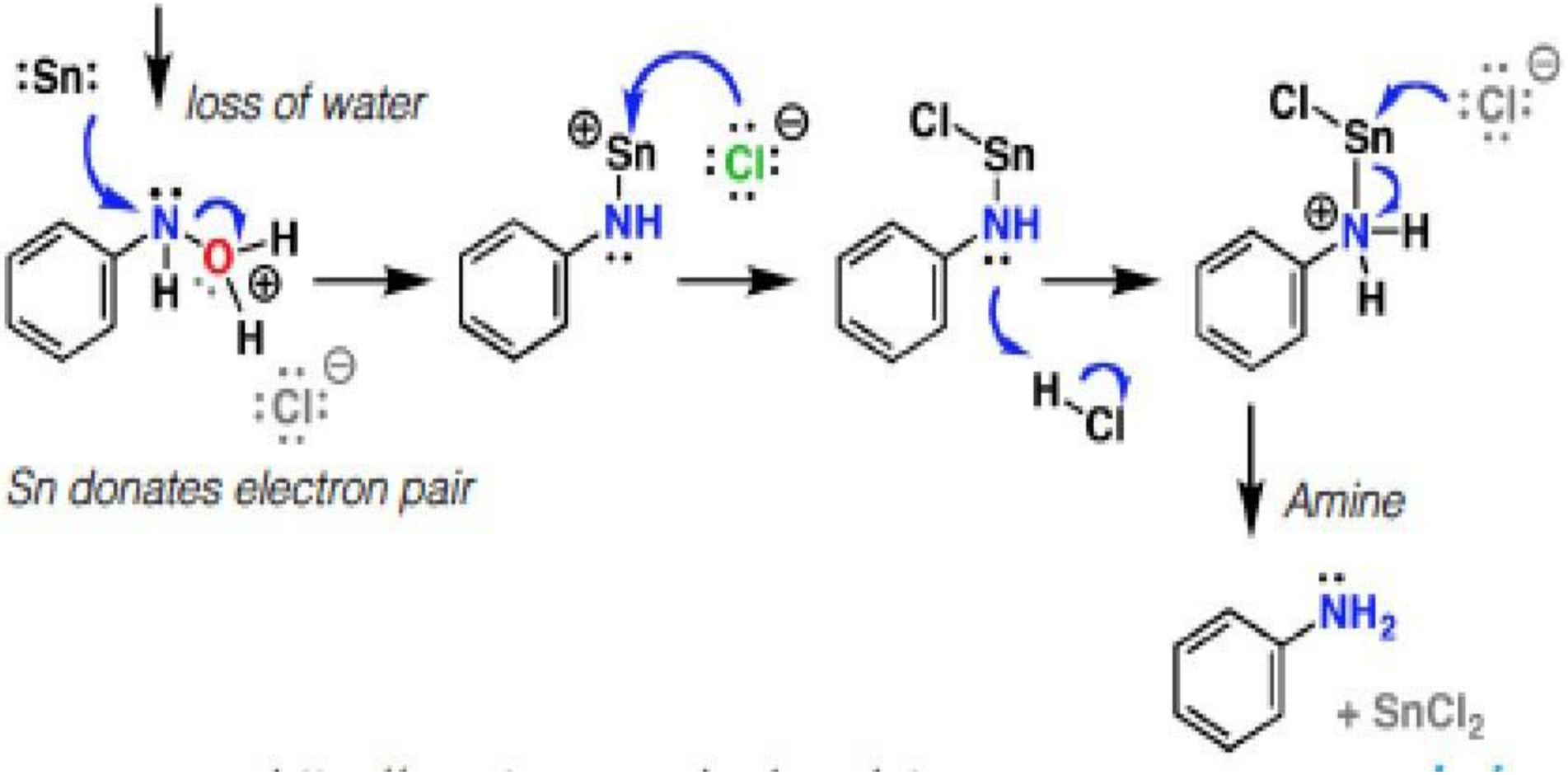


- **Reduction of nitro groups to amines can be done using two general methods:**

1. **Addition of an easily oxidized metal like iron (Fe), tin (Sn) or zinc (Zn) in the presence of acid, such as HCl (but often just written, "H+ ") will convert NO_2 to NH_2.**
2. **Hydrogenation over a palladium, platinum, or nickel catalyst will also convert NO_2 to NH_2.**

Mechanism


in textbooks.
Here is a possible mechanism.
loss of water
Sn donates electron pair
+ :SnCl
SnCl2
Sn donates electron pair to N=O (nitroso)
+ H2O
+ SnCl2
Hydroxylamine


:Sn:
loss of water
Sn donates electron pair
Amine
+ SnCl2

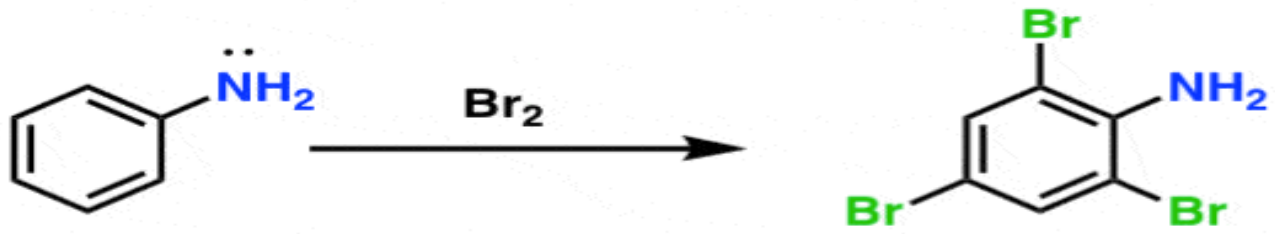
Protection of the Amino Group

- One of the most important features of the reduction of nitro groups to amines is that it converts a strongly deactivating, *meta*-directing substituent into a strongly activating, *ortho-, para*- directing substituent.
- As it turns out, however, this can actually introduce some new problems!
- First, the amino group is so activating that electrophilic aromatic substitution reactions can occur not just once, but *multiple* times, resulting in undesired products.

- Secondly, the lone pair on the amine is basic.
- Reactions that require a Brønsted or Lewis acid catalyst (such as the Friedel-Crafts reactions, sulfonylation, or nitration) don’t end up accelerating the reaction of the electrophile, but instead result in the coordination of the acid to the amine lone pair!

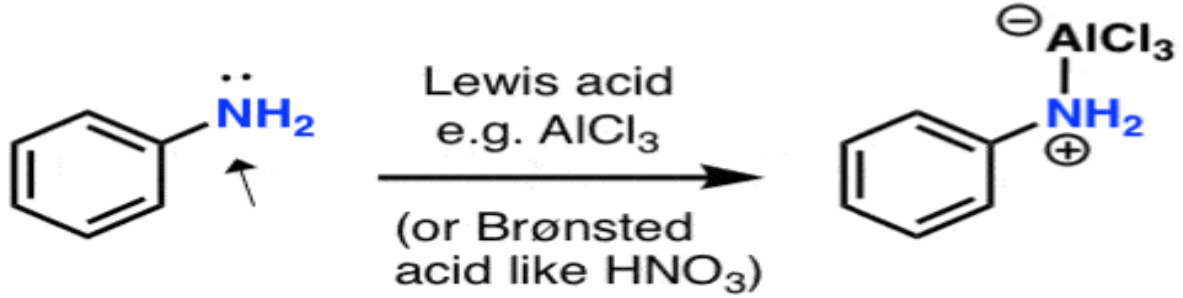
The problem with amino groups

Too activating! Hard to control reactions such that only one substitution occurs



Multiple substitutions (hard to control), even without a catalyst

Also incompatible with Bronsted and/or Lewis acids necessary for Friedel-Crafts, sulfonylation, nitration, etc. because of the basic amine lone pair



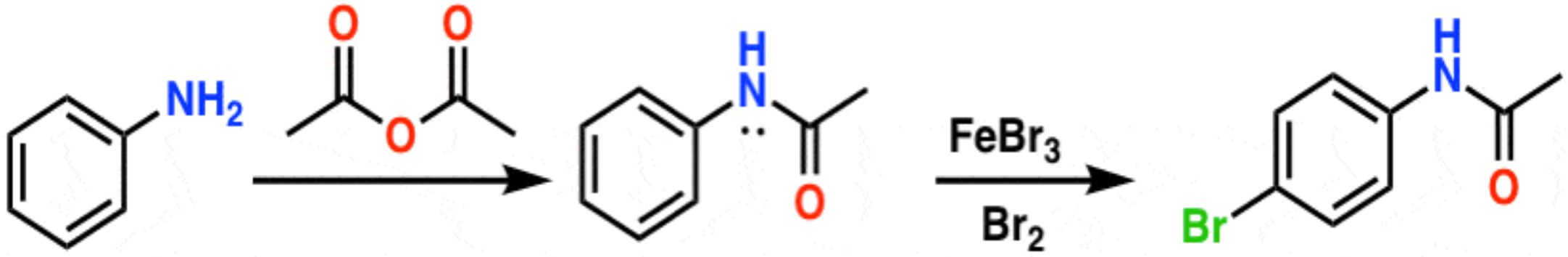
Also, the lone pair on nitrogen is no longer avaible to donate into the ring.

An amine coordinated to an acid becomes an electron-poor *meta* director!

the basic lone pair on nitrogen coordinates to the Lewis acid (or Bronsted acid), preventing acid "activation" of the electrophile

- Furthermore, this means that the lone pair on nitrogen is no longer able to donate into the aromatic ring (through “pi donation”).
- Since nitrogen is more electronegative than carbon, the nitrogen coordinated to an acid is electron-withdrawing and actually behaves as a *meta*– director!
- So how do we tame the “wild horse” that is a free amino substituent?
- Fortunately, it’s fairly easy. One common method is to convert the free amine into an *amide* with a reagent such as acetic anhydride (Ac_2O).

Solution: Convert the amine into an amide



strongly activating
***ortho-, para-* director**

moderately activating
***ortho-, para-* director**

- The resulting amide still an *ortho*- , *para*– director (note that lone pair on the nitrogen!) but not nearly as activating as the free amine.
- Furthermore, amides are much more compatible with Bronsted and Lewis acids than free amines.
- If the free amine is desired afterwards, it can be obtained by subjecting the amide to acidic hydrolysis (water, H_2SO_4, heat).

Organometallic compounds from aryl halides

- Alkyl halides , vinyl halides and aryl halides are can all be used to form organo-lithium and organo-magnisium compounds
- However , these organometallic compounds cannot be prepared from compounds containing acidic groups (OH,NH_2,NHR,SH,C=CH,CO_2H)

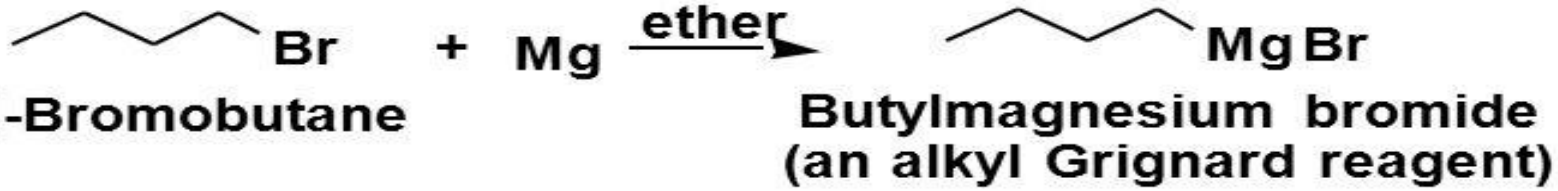
- The alkali metals (Li, Na, K etc.) and the alkaline earth metals (Mg and Ca, together with Zn) are good reducing agents, the former being stronger than the latter.
- Sodium, for example, reduces elemental chlorine to chloride anion (sodium is oxidized to its cation), as do the other metals under varying conditions.
- In a similar fashion these same metals reduce the carbon-halogen bonds of alkyl halides.

- The halogen is converted to halide anion, and the carbon bonds to the metal (the carbon has carbanionic character).
- Halide reactivity increases in the order: Cl < Br < I.
- The following equations illustrate these reactions for the commonly used metals lithium and magnesium (R may be hydrogen or alkyl groups in any combination).
- The alkyl magnesium halides described in the second reaction are called Grignard Reagents after the French chemist, Victor Grignard, who discovered them.

- The other metals mentioned above react in a similar manner, but the two shown here are the most widely used.
- Although the formulas drawn here for the alkyl lithium and Grignard reagents reflect the stoichiometry of the reactions and are widely used in the chemical literature, they do not accurately depict the structural nature of these remarkable substances.
- Mixtures of polymeric and other associated and complexed species are in equilibrium under the conditions normally used for their preparation.

A. Grignard Reagents

- **Grignard reagent:** An organomagnesium compound is a very versatile reagent:
  - prepared by addition of an alkyl, aryl, or alkenyl (vinylic) halide to Mg metal in diethyl ether or THF.



1-Bromobutane

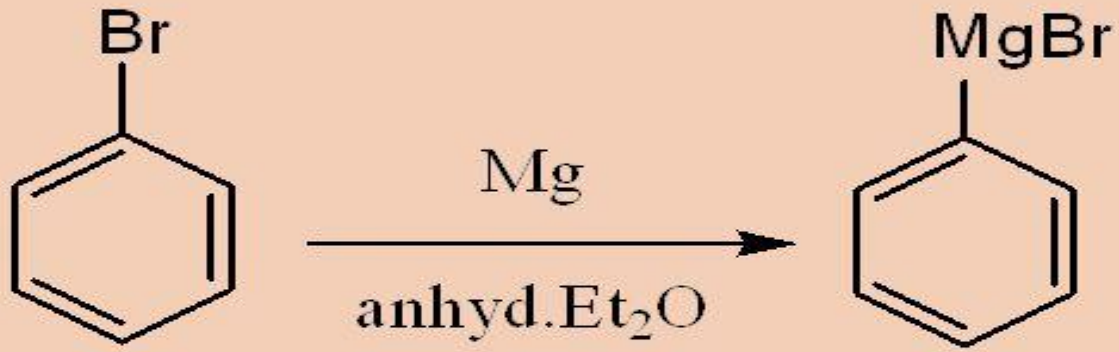
Butylmagnesium bromide
(an alkyl Grignard reagent)

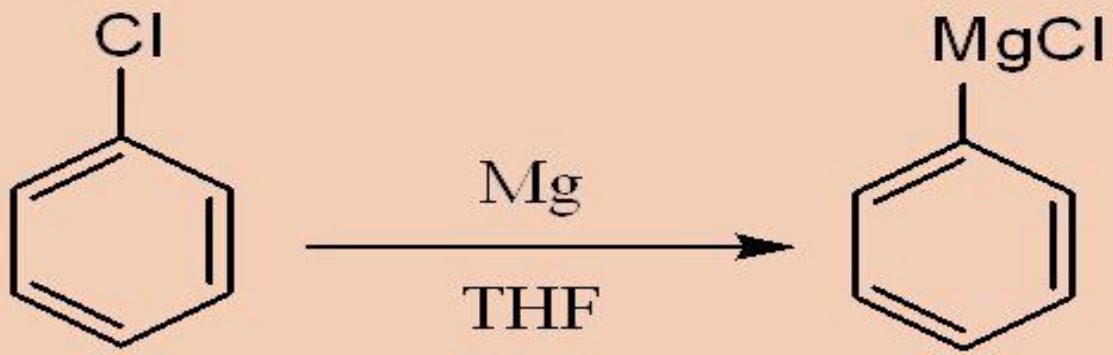
Bromobenzene

Phenylmagnesium bromide
(an aryl Grignard reagent)

Reactions of aryl halides:

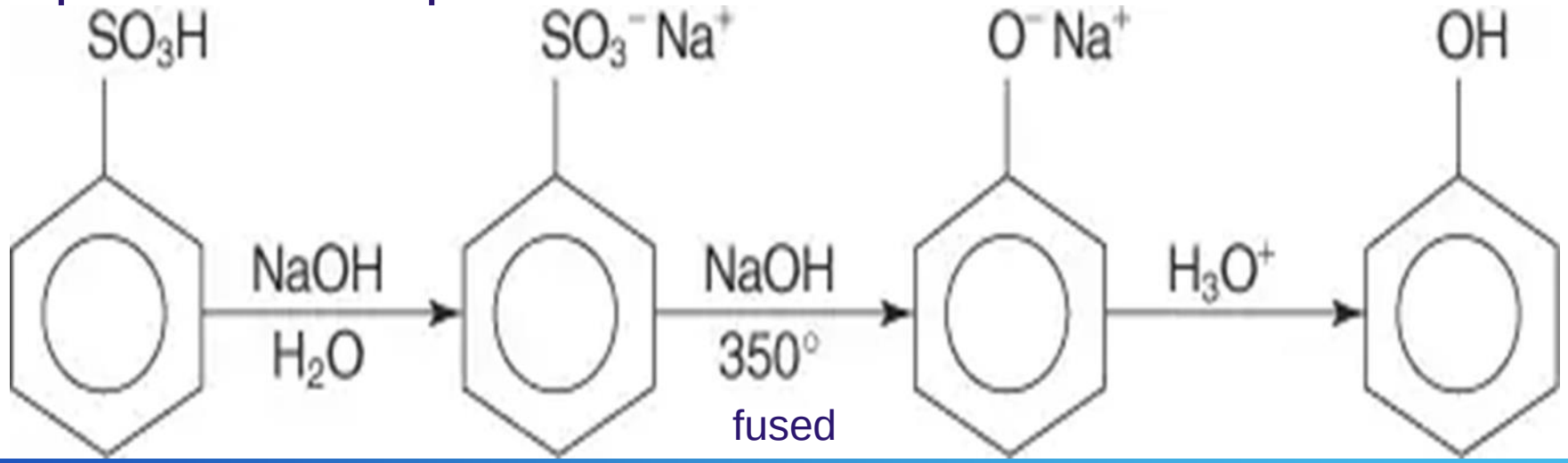
1. Formation of Grignard reagents





Hydrolysis and Fusion of Sulphonic Acids

- Hydrolysis. **Arylsulfonic acids are susceptible to hydrolysis, the reverse of the sulfonation reaction**.
- Whereas benzenesulfonic acid hydrolyzes above 200 °C, most related derivatives are easier to hydrolyze. Thus, heating aryl sulfonic acids in aqueous acid produces the parent arene.



Modifying the Influence of Strong Activating Groups

- The strongest activating and ortho/para-directing substituents are the amino (-NH_2) and hydroxyl (-OH) groups.
- Direct nitration of phenol (hydroxybenzene) by dilute nitric acid gives modest yields of nitrated phenols and considerable oxidative decomposition to tarry materials; aniline (aminobenzene) is largely destroyed.
- Bromination of both phenol and aniline is difficult to control, with di- and tri-bromo products forming readily.

Modifying the Influence of Strong Activating Groups

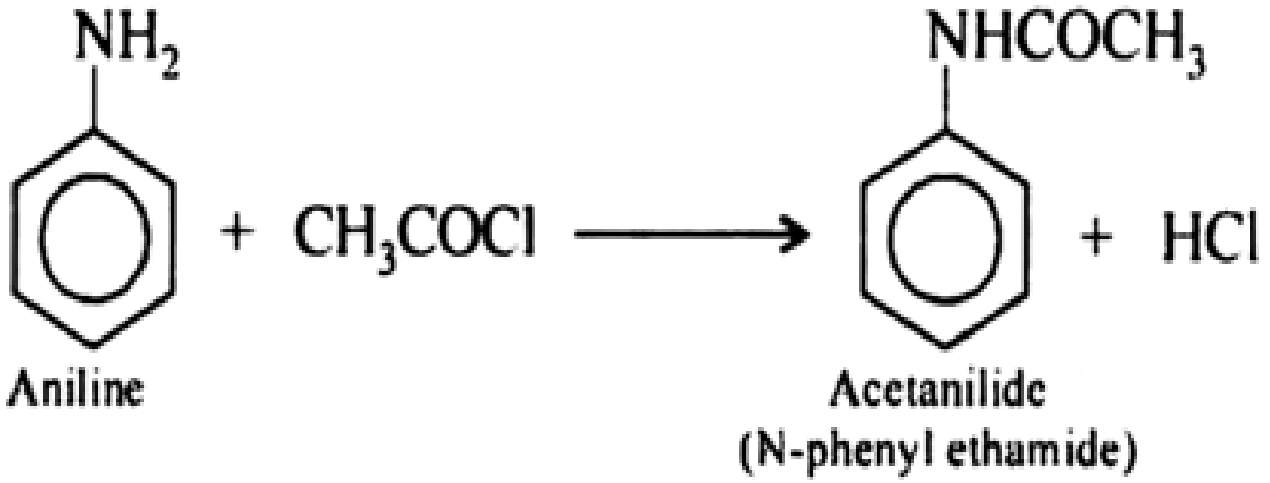
- Because of their high nucleophilic reactivity, aniline and phenol undergo substitution reactions with iodine, a halogen that is normally unreactive with benzene derivatives.
- The mixed halogen iodine chloride (ICl) provides a more electrophilic iodine moiety, and is effective in iodinating aromatic rings having less powerful activating substituents

Modifying the Influence of Strong Activating Groups

- By acetylating the heteroatom substituent on phenol and aniline, its activating influence can be substantially attenuated.
- For example, acetylation of aniline gives acetanilide (first step in the following equation), which undergoes nitration at low temperature, yielding the para-nitro product in high yield.
- The modifying acetyl group can then be removed by acid-catalyzed hydrolysis (last step), to yield para-nitroaniline.

Modifying the Influence of Strong Activating Groups

- Although the activating influence of the amino group has been reduced by this procedure, the acetyl derivative remains an ortho/para-directing and activating substituent.



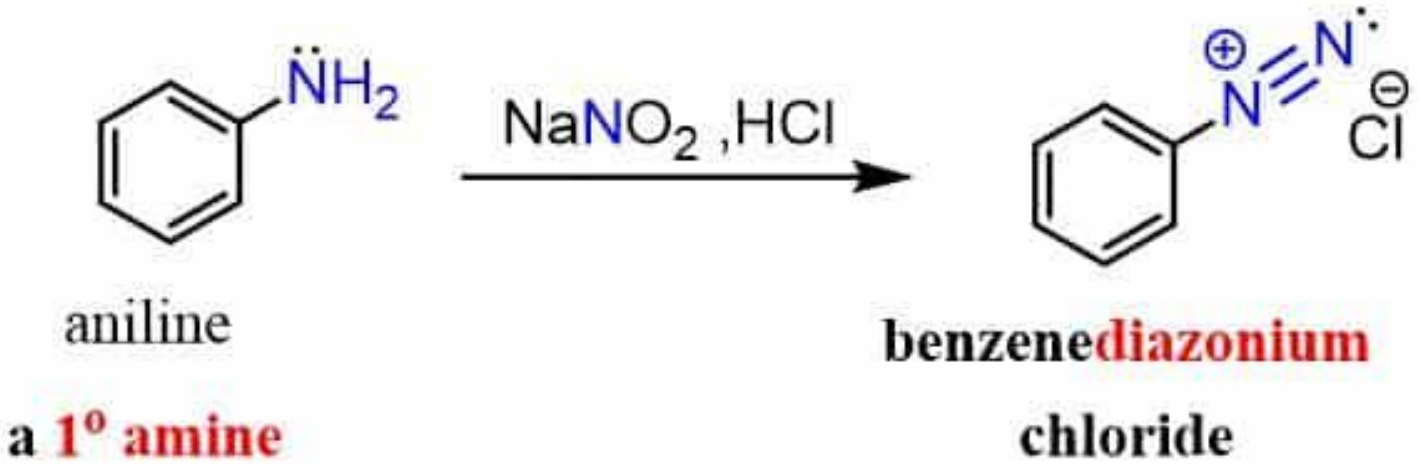
Aniline
strongly activated

acetanilide
less activated

Diazotization of Primary Aromatic Amines

- **The chemical process used in converting a primary aromatic amine into the corresponding diazonium salt of the amine** is commonly referred to as diazotization. This process is also known as 'diazotization.
- The German industrial chemist Peter Griess was the first person to report such a reaction in 1858.

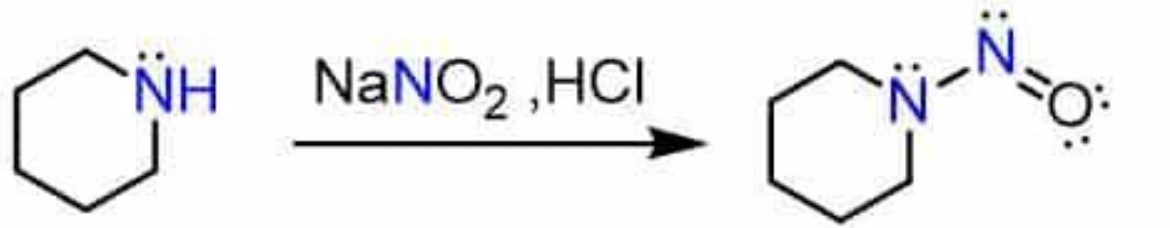
❖ Example



aniline

a 1° amine

benzenediazonium chloride



piperidine

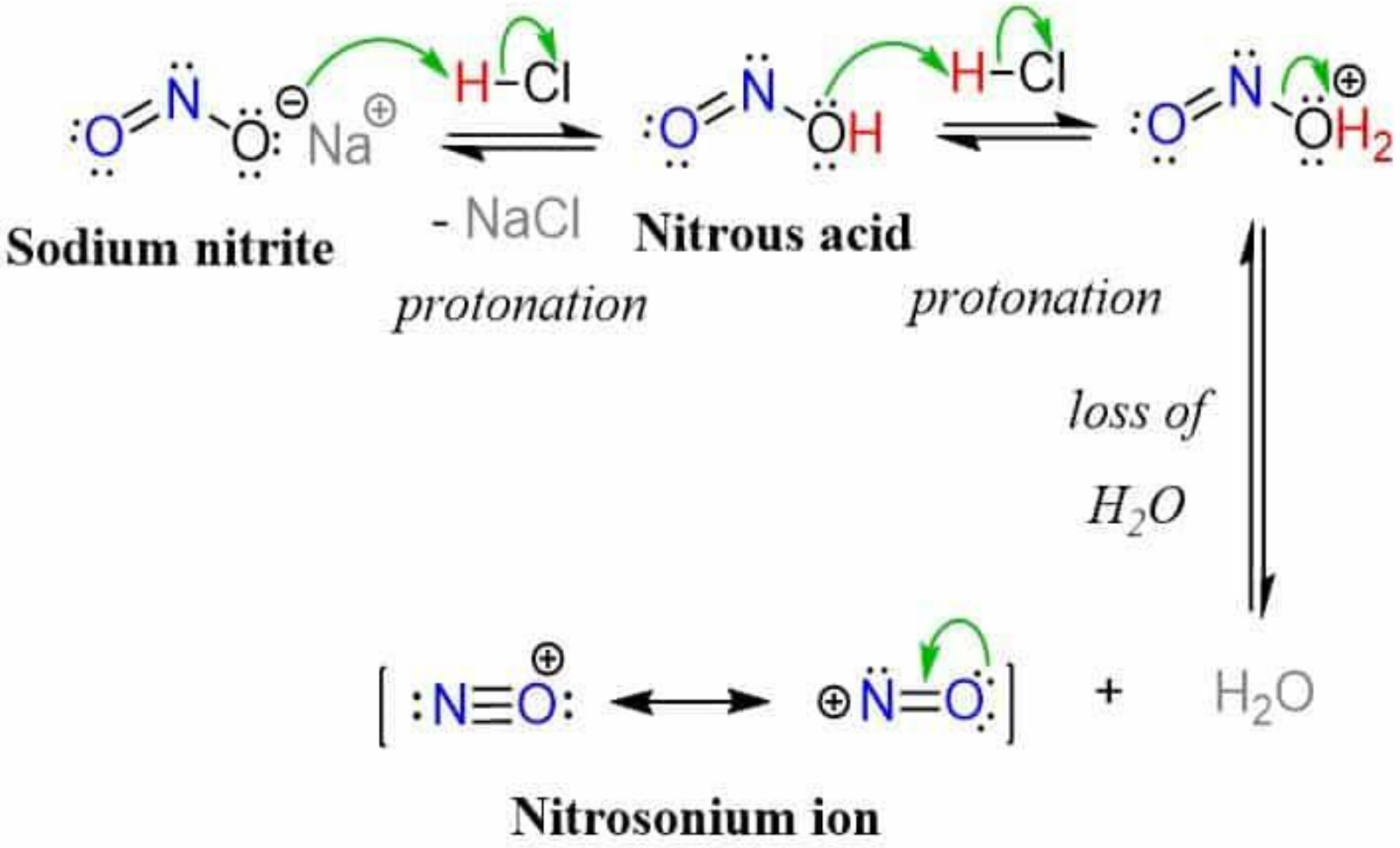
a 2° amine

An **N-nitrosamine**

Cont'd

❖ Mechanism

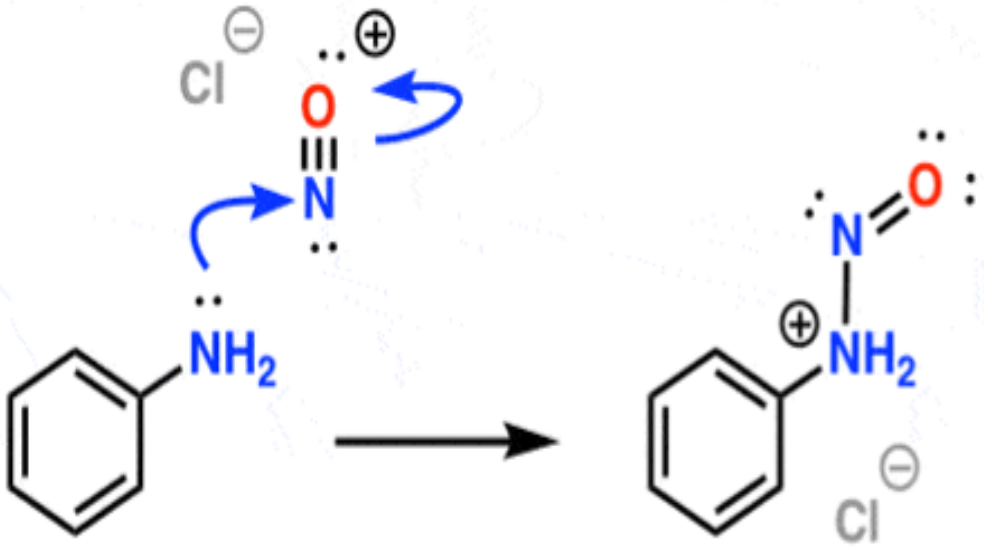
Formation of Nitrous Acid and Nitrosonium Ion



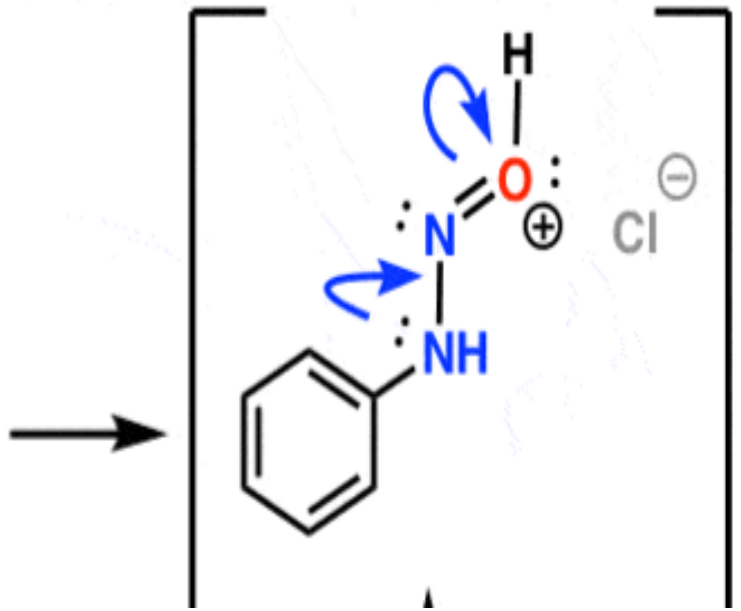
Nitrosonium ion

Mechanism: Formation of Diazonium Ions From Aromatic Amines

Step 1: Addition to nitrosonium ion



Step 2: Proton Transfer



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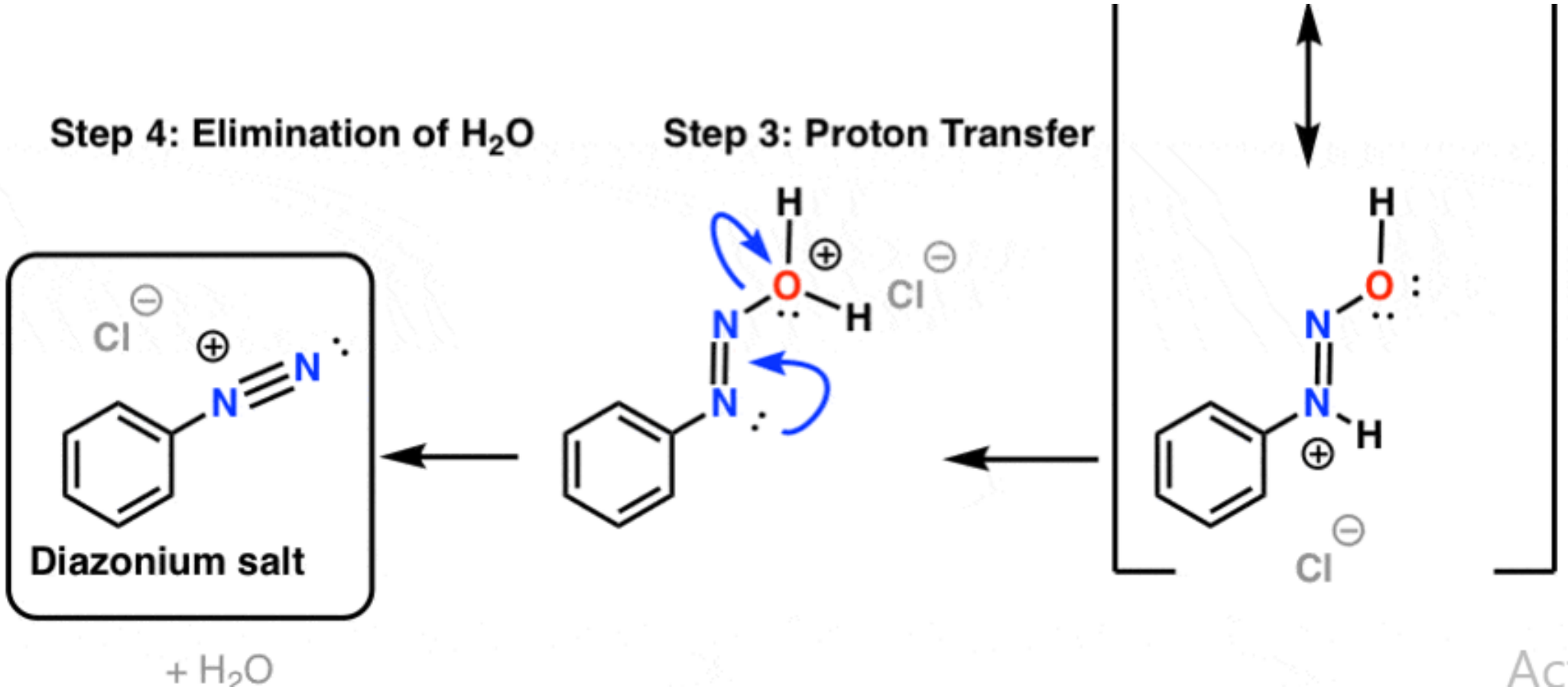
Step 4: Elimination of H_2O
Step 3: Proton Transfer
Diazonium salt
+ H_2O
Act

Cont'd

Uses of diazonium salt in Synthesis of Aromatic Derivatives

- Diazonium Salts are found to be useful in the Fischer Indole Synthesis process because they can be reduced to hydrazine derivatives with the help of stannous chloride.
- They are used as standard reagents while synthesizing organic compounds.
- Diazonium salts have the potential to have applications in the field of nanotechnology. They are useful in the efficient functionalization of single wall nanotubes.