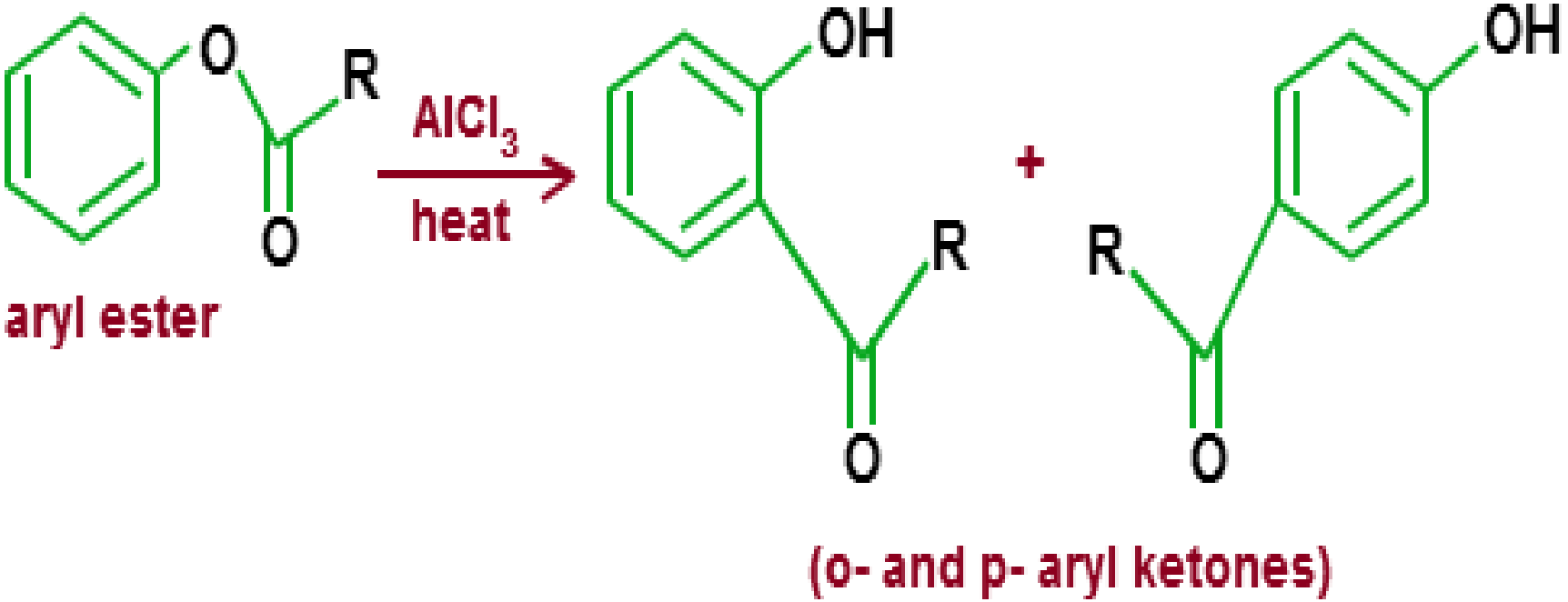
Aromatic Rearrangements

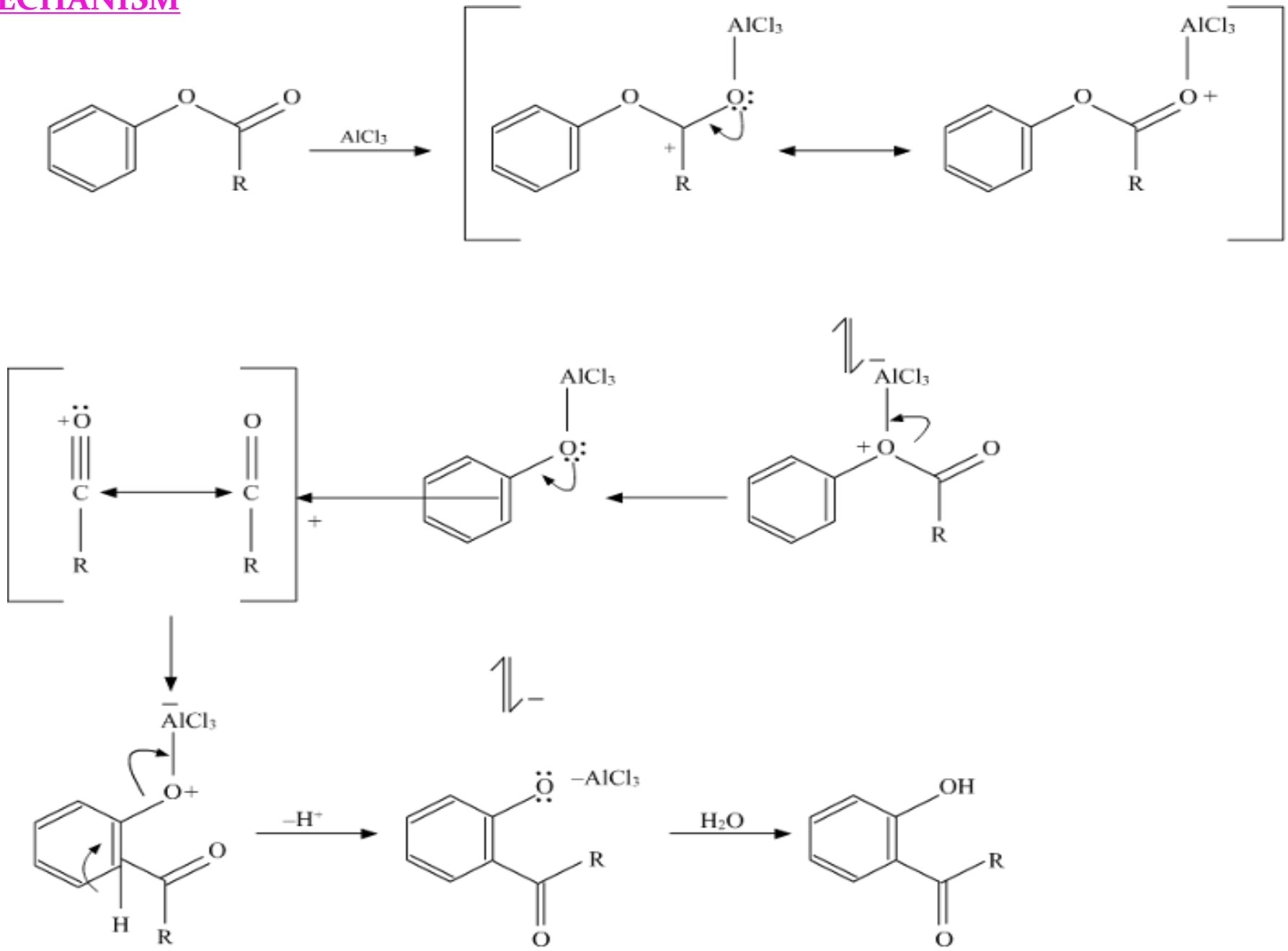
FRIES REARRANGEMENT

1. Intra molecular Friedal –Craft Acylation
2. Rearrangement of phenolic ester by heating it with Friedal –Craft catalyst.
3. The reaction is catalyzed by Brønsted or Lewis acids such as HF, $AlCl_3$, BF_3, $TiCl_4$ or $SnCl_4$. The acids are used in excess of the stoichiometric amount, especially the Lewis acids, since they form complexes with both the starting materials and products.



The conversion of phenolic esters to the corresponding ortho and/or para substituted phenolic ketones and aldehydes, in the presence of Lewis or Brönsted acids is called the Fries rearrangement.

MECHANISM



The Fries rearrangement has the following general features:

1. usually it is carried out by heating the phenolic ester to high temperatures (80-180 °C) in the presence of at least one equivalent of Lewis acid or Brönsted acid (e.g., HF, $HClO_4$)

2. Lewis acids that catalyze the Friedel-Crafts acylation are all active but recently solid acid catalysts (e.g., zeolites, mesoporous molecular sieves) and metal triflates have also been used

3. The rearrangement is general for a wide range of structural variation in both the acid and phenol component of phenolic Esters

4. yields are the highest when there are electron-donating substituents on the phenol, while electronwithdrawing substituents result in very low yields or no reaction;

5. with polyalkylated phenols alkyl migration is often observed under the reaction conditions

6. the selectivity of the rearrangement to give ortho or para- substituted products largely depends on the reaction conditions (temperature, type, and amount of catalyst, solvent polarity, etc.)

7. at high temperatures without any solvent the ortho-acylated product dominates (TEMP > 370 ^{O}C while low temperatures favor the formation of the para-acylated product

8. with increasing solvent polarity the ratio of the para-acylated product increases.

There are two main variants of the Fries rearrangement:

A. Upon irradiation with light phenolic esters undergo the same transformation, which is known as the photo-Fries rearrangement.

B. An anionic ortho-Fries rearrangement takes place when ortho-lithiated O-aryl carbamates undergo a facile intramolecular [1,3]-acyl migration to give substituted salicylamides at room temperature.

PHOTO -FRIES REARRANGEMENT

1.The photo-initiated rearrangement of phenyl or aryl esters is generally known as the photo-Fries rearrangement or photo-Fries reaction and usually carried out in an aprotic solvent.

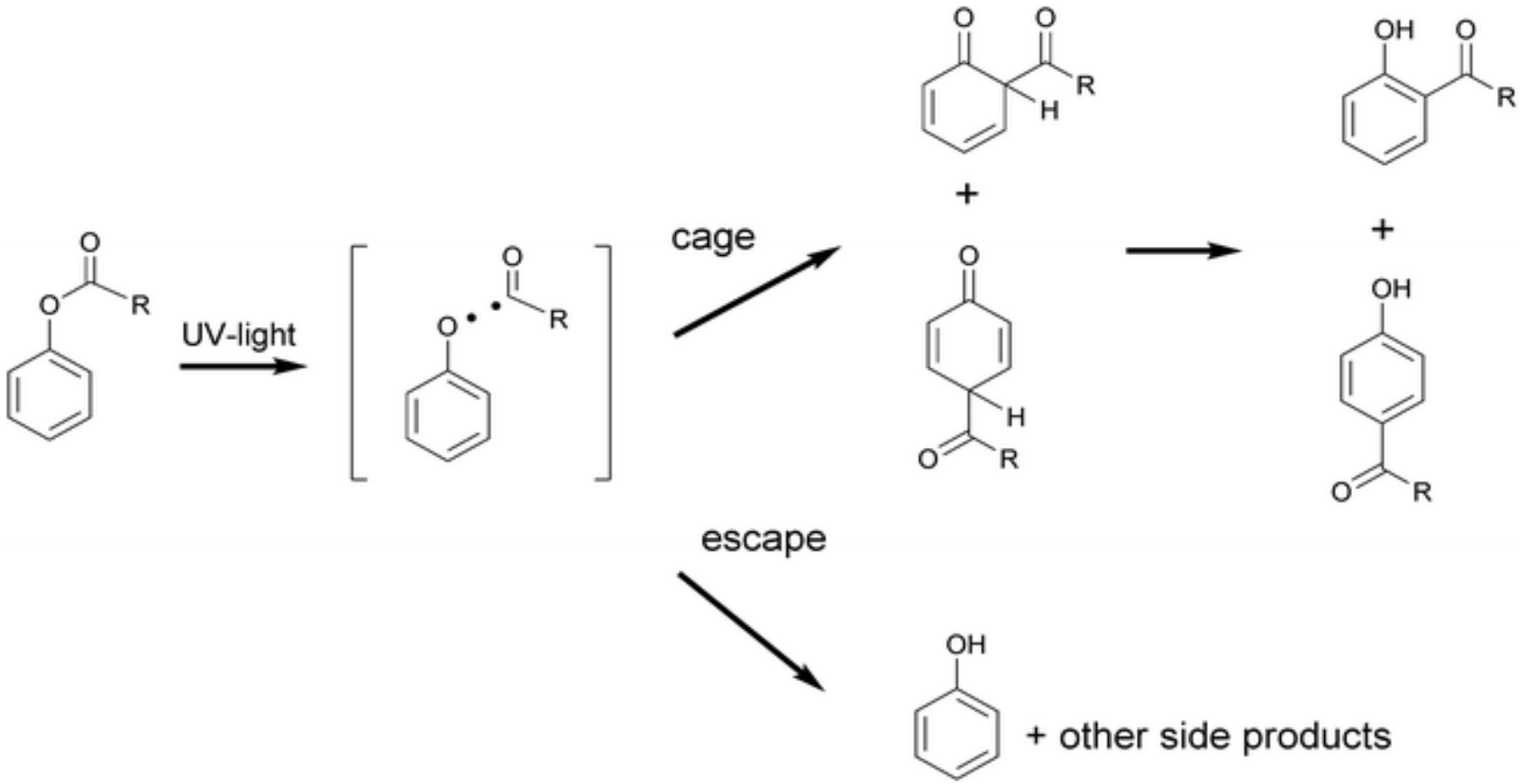
2.The mechanistic features of this rearrangement can be compared with the normal Fries rearrangement catalyzed by Lewis acid.

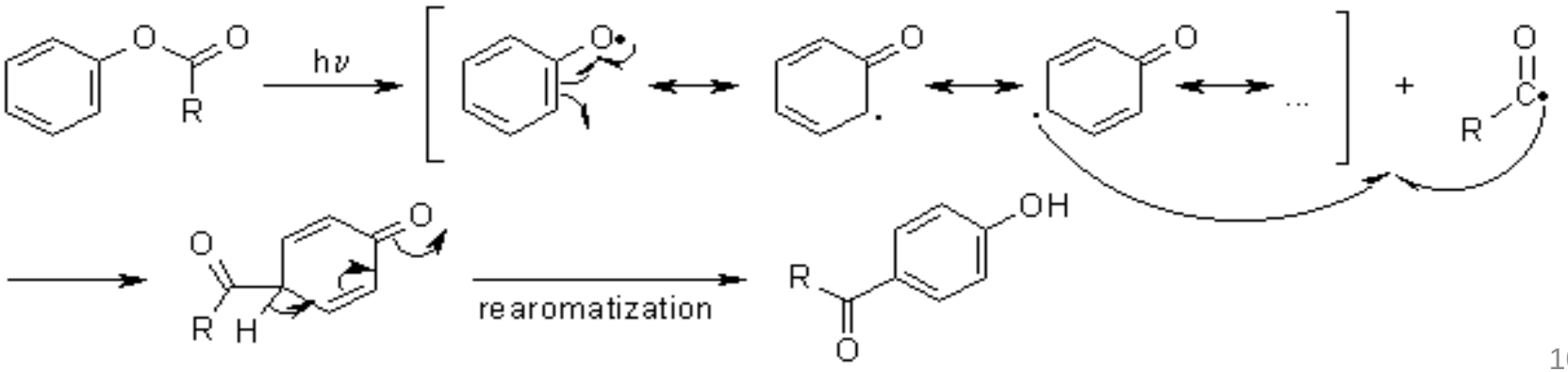
3.The study finds that regioselectivity can be further enhanced when the photo-Fries rearrangement is carried out in presence of zeolite. Besides phenyl and aryl esters, several other kinds of compounds can also undergo the hemolytic

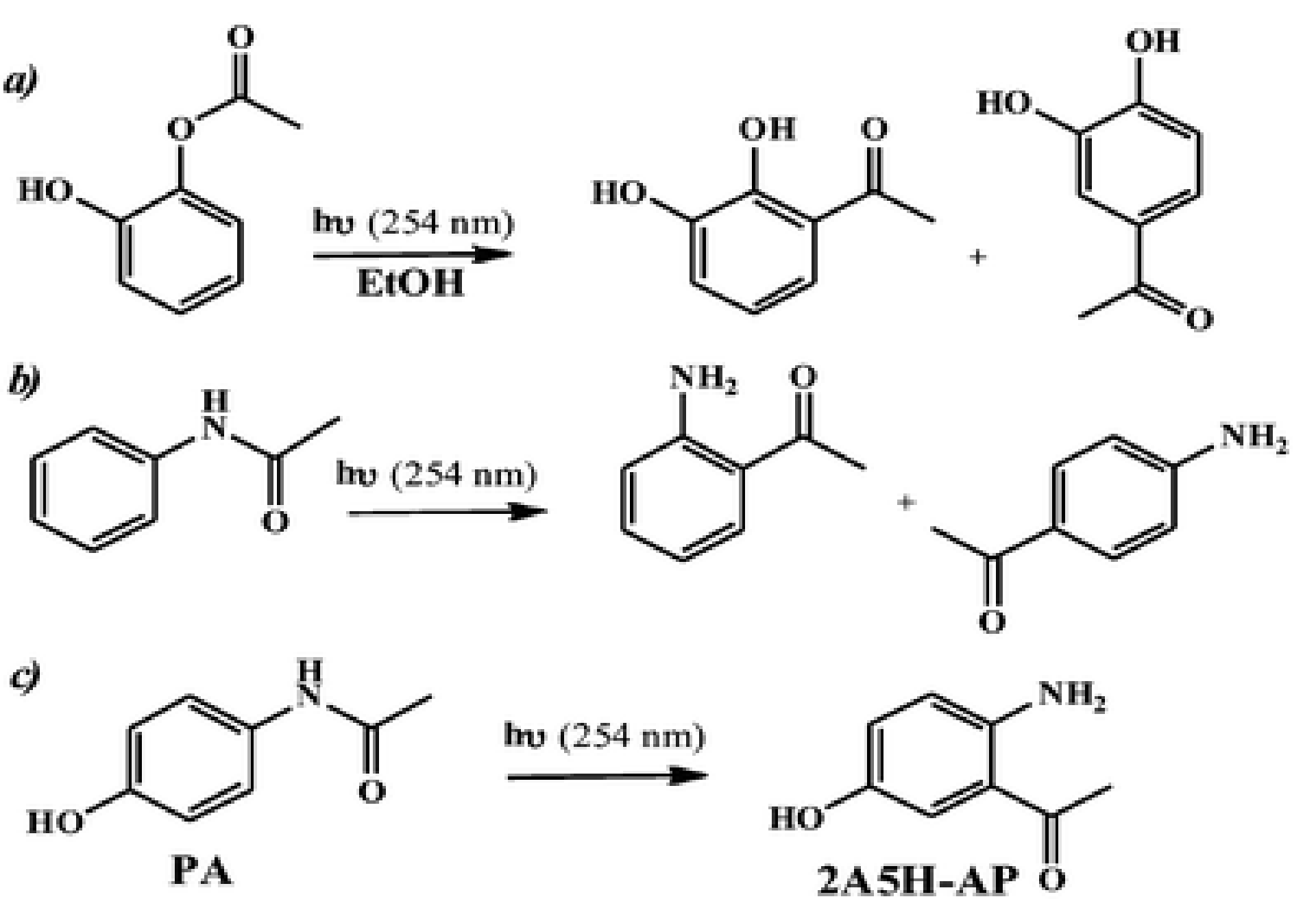
4.This reaction is not useful in actual organic synthesis because of its different by-products.

5. In the normal course of reaction when the reaction is irradiated under nirtogen atmosphere with UV light, the acyl group migrates from phenolic oxygen to the C atom at o- and p- positions to form o- and p- substituted products.

6. Its predominantaly an intra molecular free radical process hence both the o- and p- products are obtained.


UV-light
cage
escape
+ other side products


hν
rearomatization



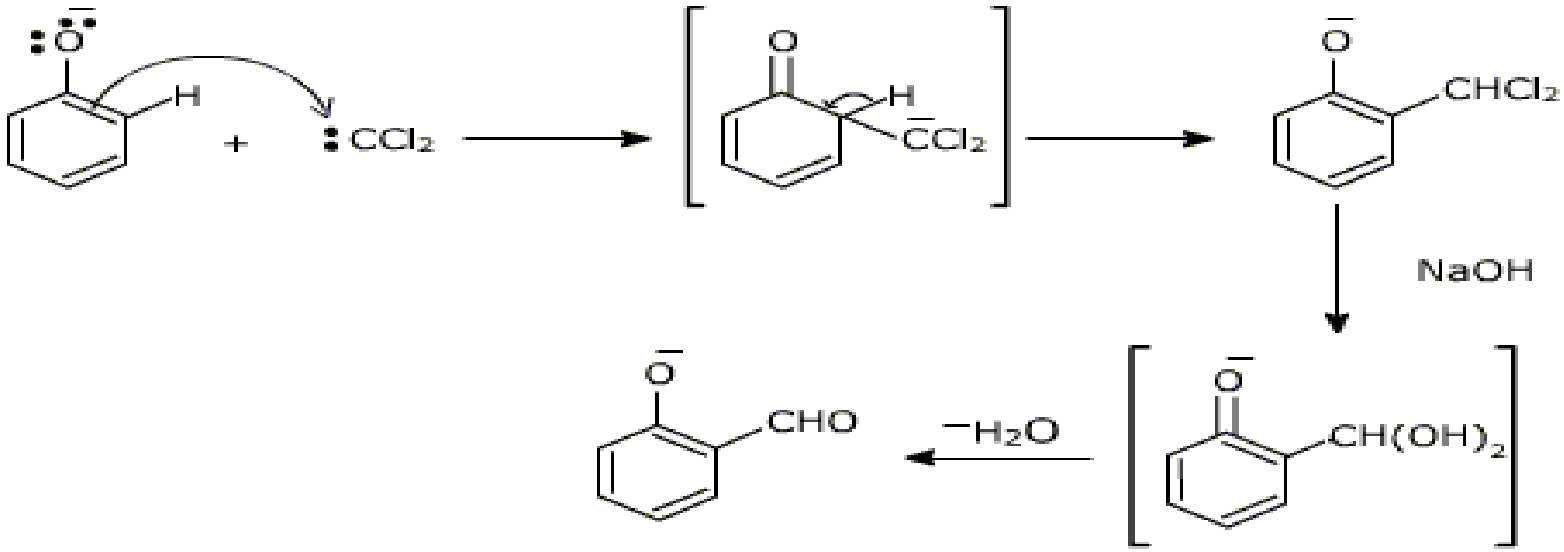
N-(4-hydroxyphenyl)ethanamide (paracetamol)

2′-amino-5′-hydroxyacetophenone

REIMER- TIEMANN REACTION (FROMYLATION)

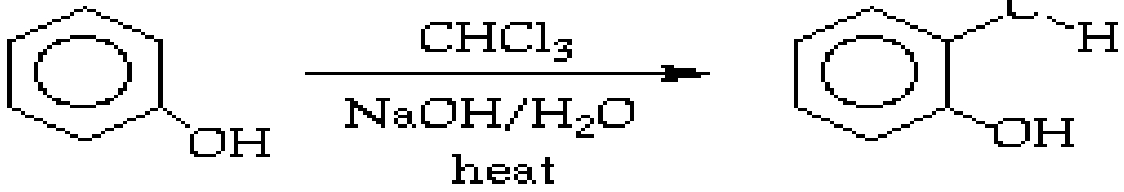
The Reimer-Tiemann reaction is an organic reaction used for ortho- formylation of phenol.

In the reaction a phenol is converted to an o-hydroxy benzaldehyde (salicyldehyde) using chloroform in basic medium.

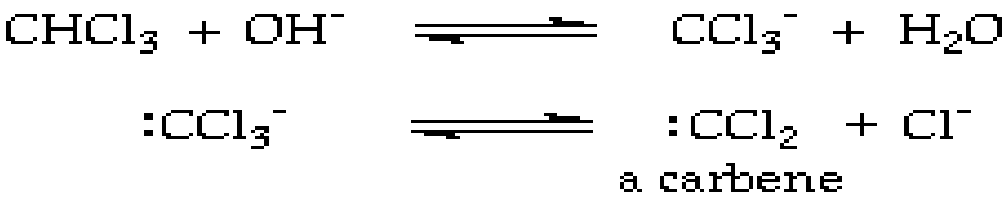


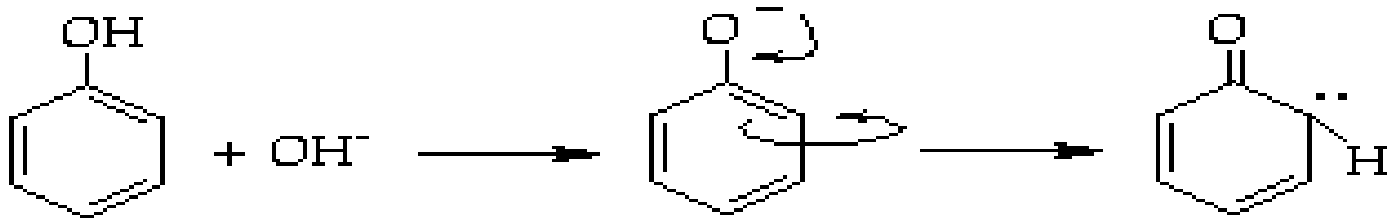
MECHANISM

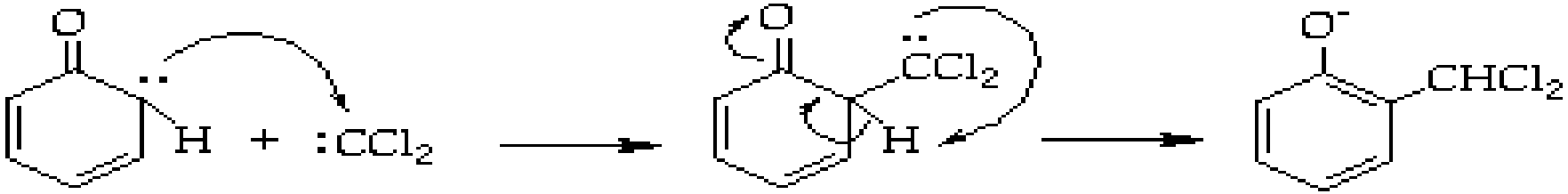
Overall:

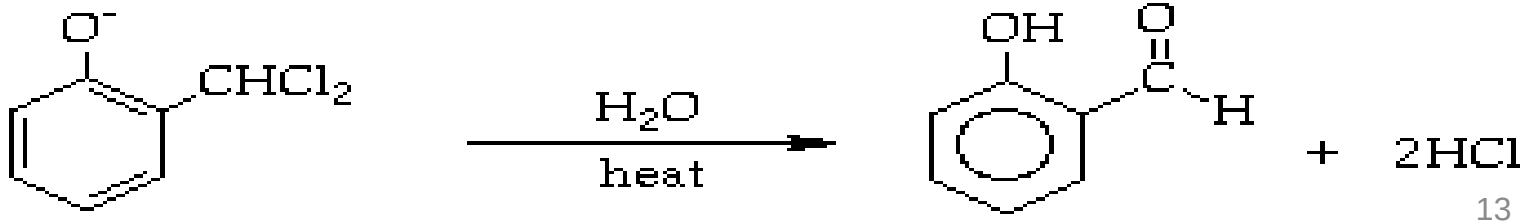


salicylaldehyde





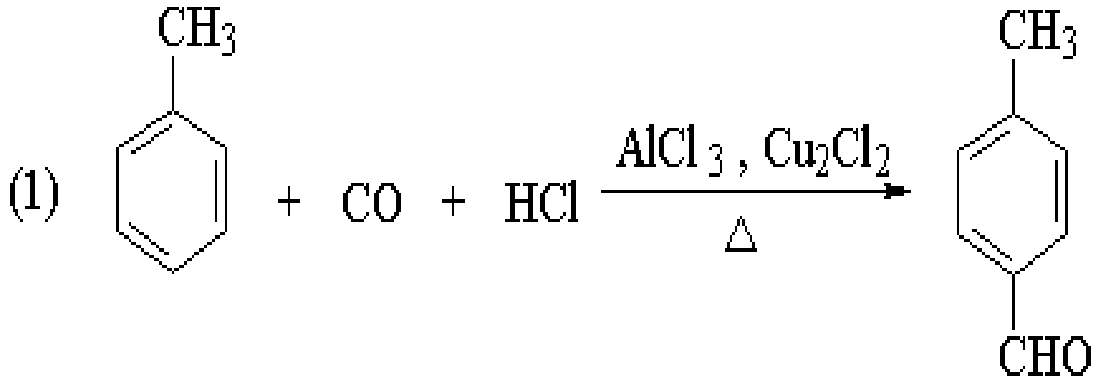


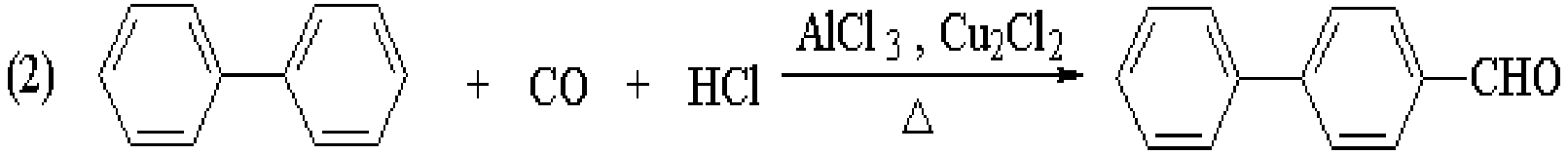


- **Chloroform is deprotonated by strong base (normally hydroxide) to form the chloroform carbanion. which will quickly alpha-eliminate to givedichlorocarbene which is principle reactive species.**
- **The hydroxide deprotonates the phenol to give a negatively charged phenolate.**
- **The negative charge is delocalised into the aromatic ring, making it far more nucleophilic and increases its ortho selectivity.**
- **Nucelophilic attack of the dichlorocarbene from the ortho position gives an intermediate dichloromethyl substituted phenol.**
- **After basic hydrolysis, the desired product is formed.**

GATTERMANN – KOCH REACTION (FROMYLATION)

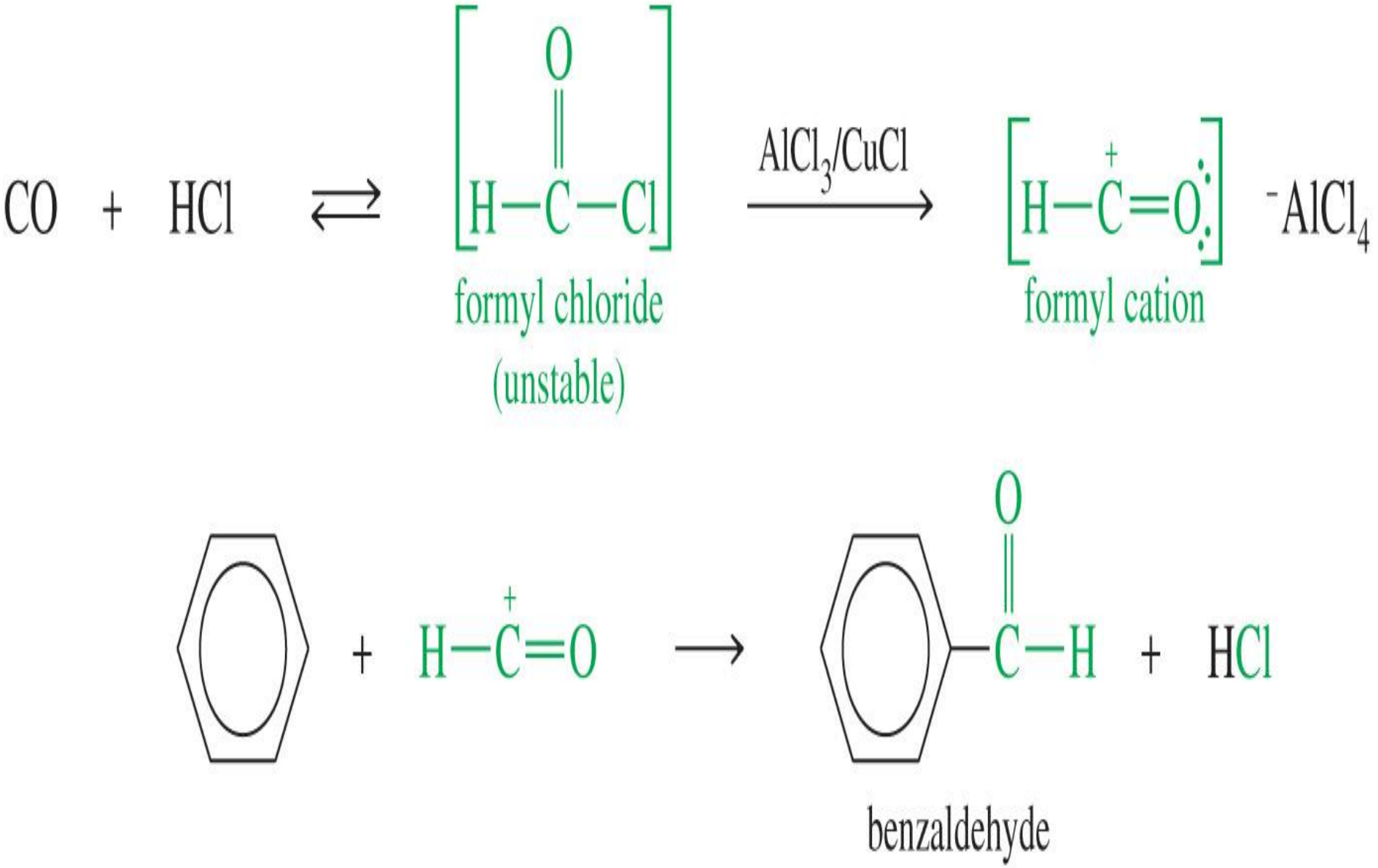
Formylation of aromatic hydrocarbon or polycyclic aromatic hydrocarbon with carbon monoxide and hydrogen chloride in the presence of $AlCl_3$ at high pressure is known as Gattermann-Koch reaction. The other catalysts used are cuprous chloride, HF, BF_3, trifluoro methane sulphonic acid. The reaction is less accessible due to toxicity of carbon monoxide and high pressure.





The catalyst commonly used is aluminum chloride with cuprous chloride as a carrier. The carrier is not necessary when high pressure is used

MECHANISM



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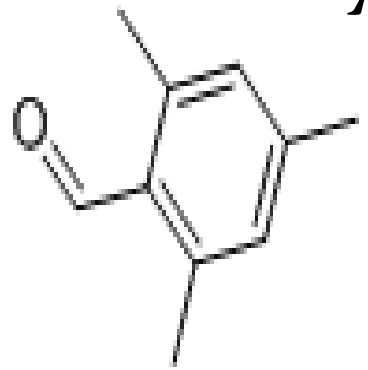
GATTERMANN–ALDEHYDE SYNTHESIS (FROMYLATION)

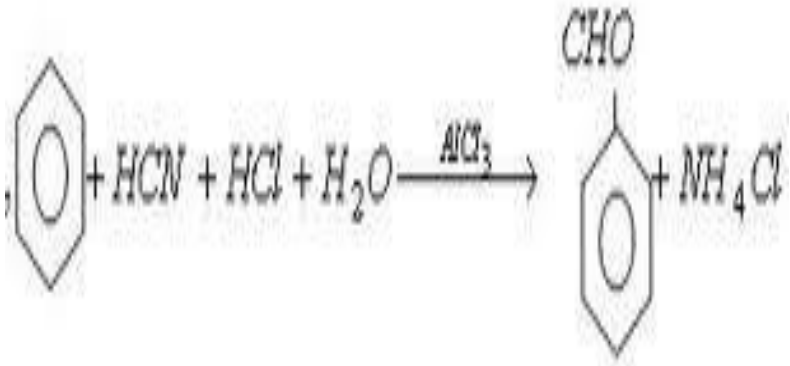
The preparation of aromatic aldehydes containing hydroxyl or alkyloxyl groups on the aromatic ring by treatment of the aromatics with hydrogen cyanide and hydrogen chloride in anhydrous solvent (e.g., ether) with or without the presence of a Lewis acid (e.g., $ZnCl_2$, $AlCl_3$) as a catalyst, in which aldimine hydrochloride functions as an intermediate, is generally referred to as the Gattermann aldehyde synthesis or simply as the Gatterman synthesis

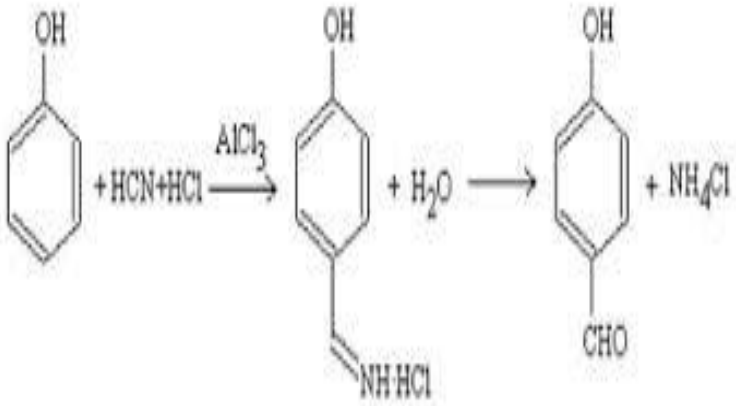
.

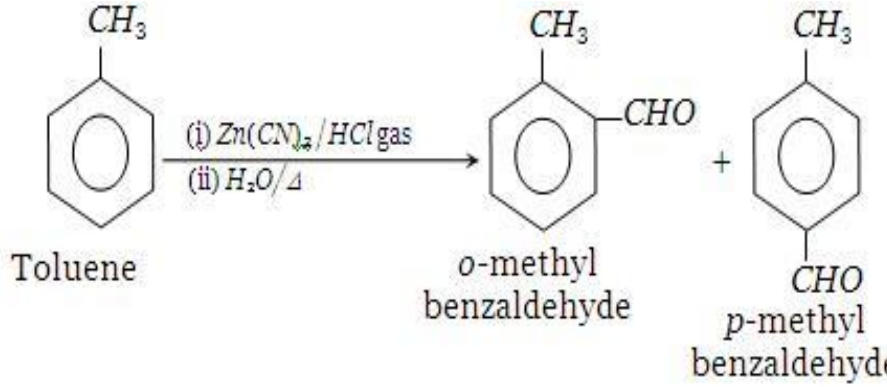
This is an alternative to Gattermann – Koch Reaction in which HCN in used instead of CO.

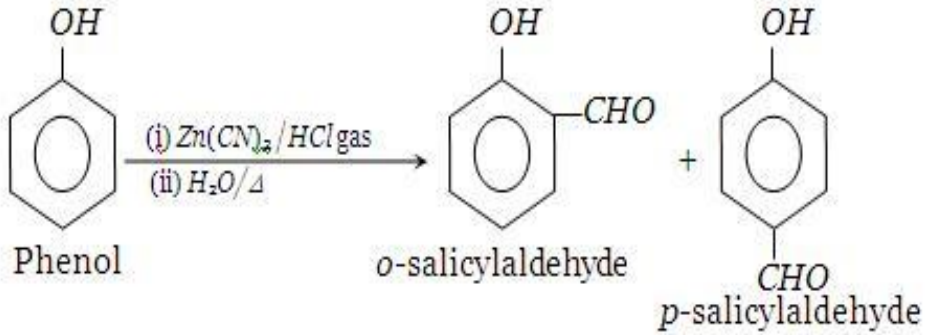
This reaction is useful in the preparation of aromatic aldehydes with hydroxy, alkoxy, and even mutli-alkyl groups, such as mesitaldehyde (2,4,6- tri methyl – benzaldehyde)

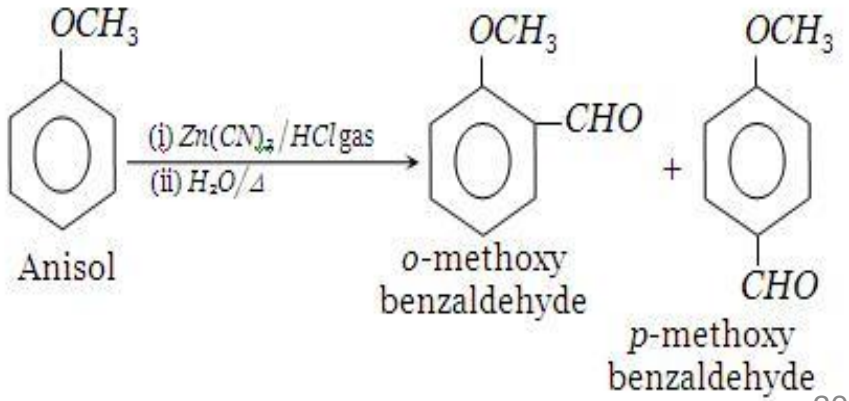



CHO
+ HCN + HCl + H2O
AlCl3
+ NH4Cl

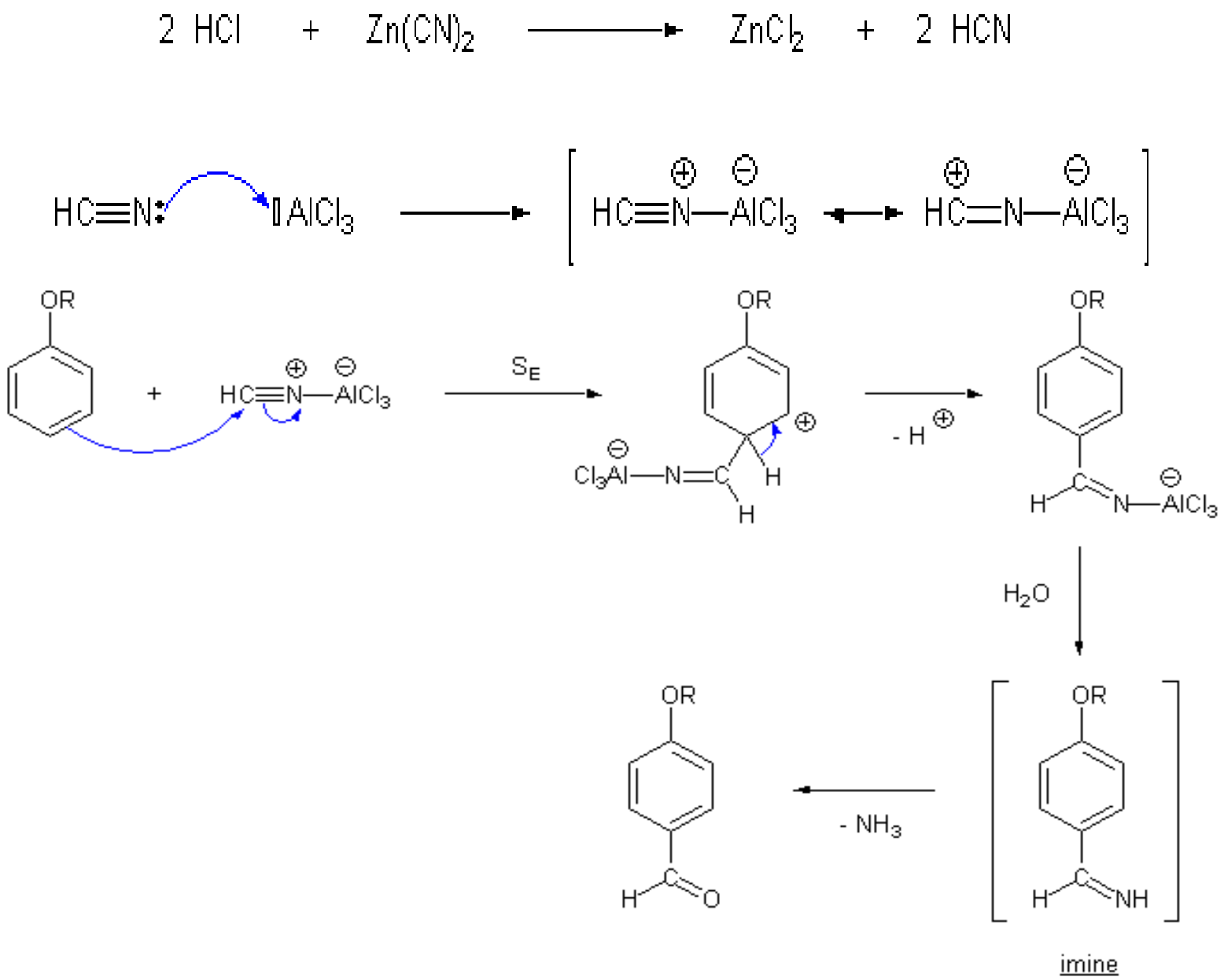

OH
OH
OH
+HCN+HCl
AlCl3
+ H2O
+ NH4Cl
CHO
NH·HCl


CH3
CH3
CH3
CHO
(i) Zn(CN)2 / HCl gas
(ii) H2O/Δ
+
CHO
Toluene
o-methyl benzaldehyde
p-methyl benzaldehyde


OH
OH
OH
CHO
(i) Zn(CN)2 / HCl gas
(ii) H2O/Δ
+
CHO
Phenol
o-salicylaldehyde
p-salicylaldehyde

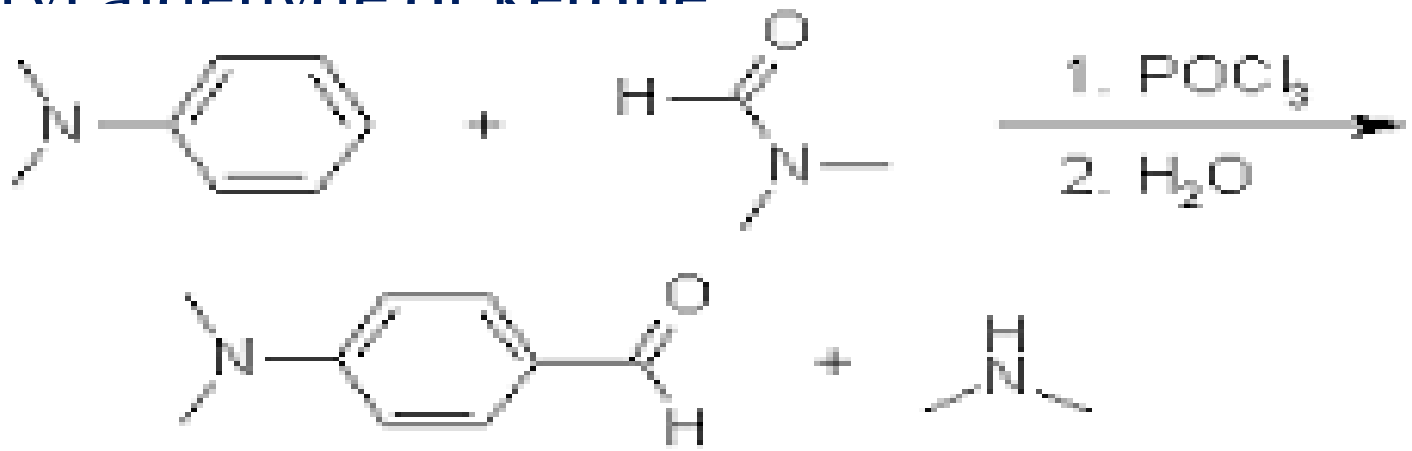

OCH3
OCH3
OCH3
CHO
(i) Zn(CN)2 / HCl gas
(ii) H2O/Δ
+
CHO
Anisol
o-methoxy benzaldehyde
p-methoxy benzaldehyde

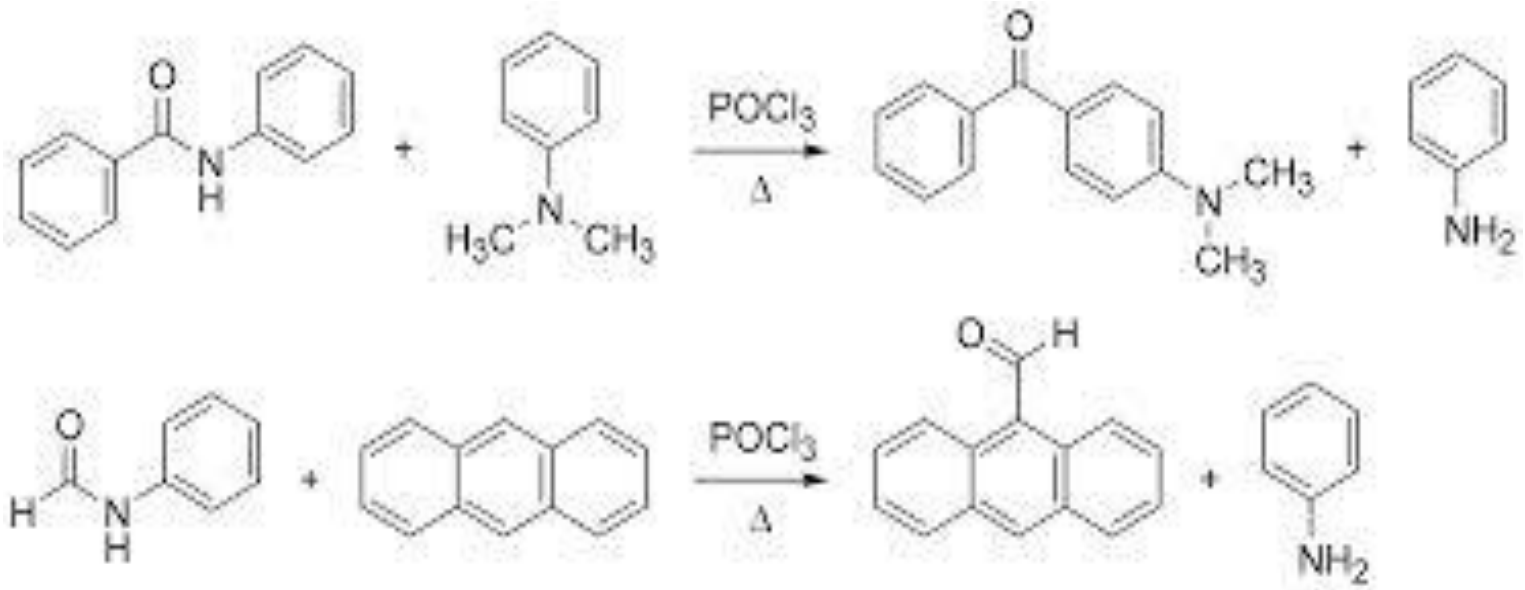
MECHANISM


2 HCl + Zn(CN)2 → ZnCl2 + 2 HCN
HC≡N: ⟦AlCl3 → [HC≡N—AlCl3 ↔ HC=N—AlCl3]
OR
+ HC≡N—AlCl3
SE
Cl3Al—N=C
H
H
- H⊕
H2O
- NH3
imine

VELSMEIER – HAACK REACTION (FROMYLATION)

The Vilsmeier-Haack reaction is an organic reaction used to convert an electron rich aromatic ring to an aryl aldehyde using DMF Dimethylformamide, an acid chloride (phosphorus oxychloride), and aqueous workup to produce an aryl aldehyde or ketone




O
N
H
+
H3C
N
CH3
POCl3
Δ
O
CH3
N
CH3
+
NH2
O
H
H
N
+
O
H
POCl3
Δ
+
NH2

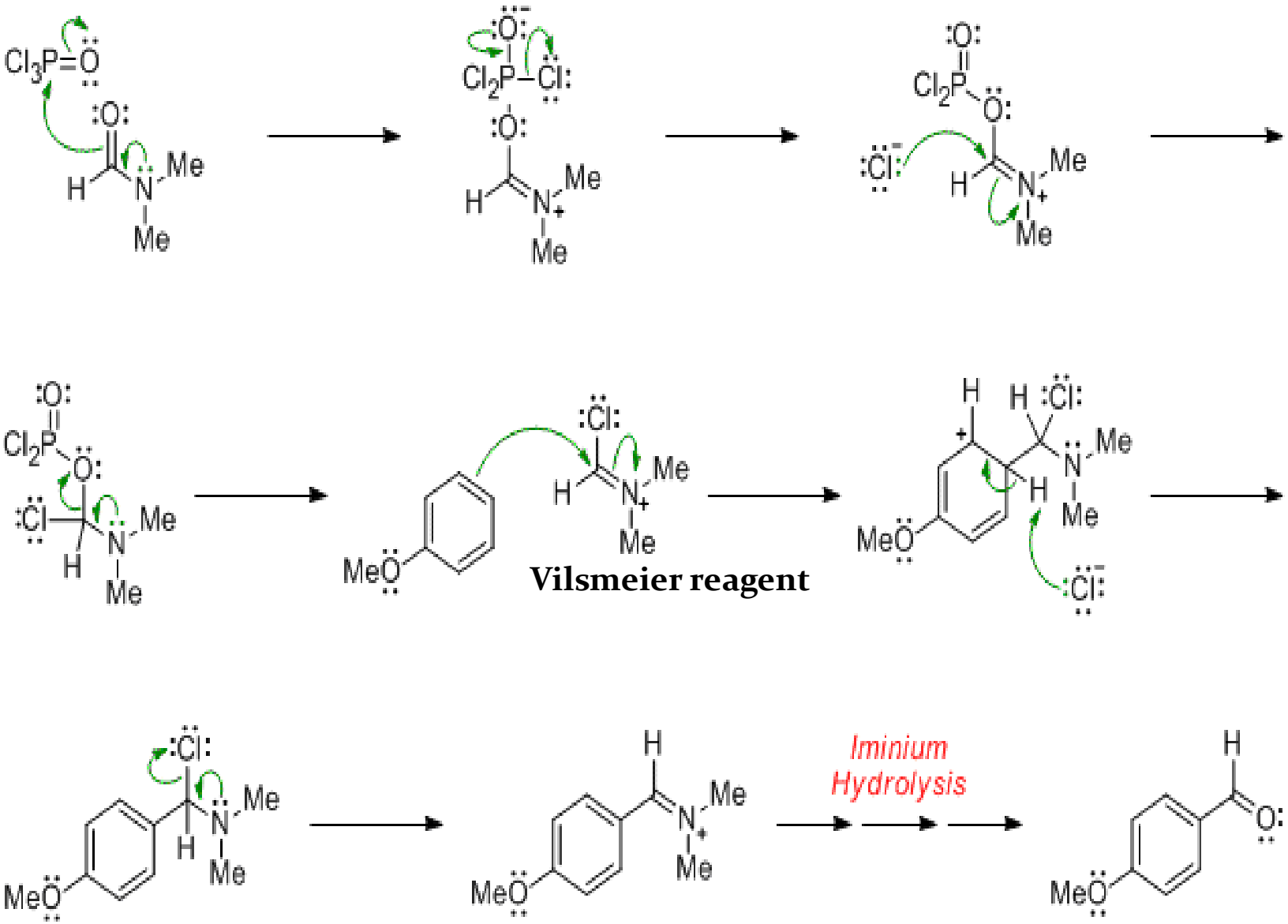
MECHANISM

The mechanism begins with the reaction of DMF with the acid chloride to form chloroiminium ion known as the "Vilsmeier reagent“. The amide O is replaced with Cl, (P-O bond being stronger).

The electron rich aromatic ring then attacks the iminium ion with loss of aromaticity.

A deprotonation step restores aromaticity, which is followed by the release of a chloride ion to form another iminium intermediate.

Aqueous work-up then leads to the aryl aldehyde final product


Vilsmeier reagent
Iminium
Hydrolysis