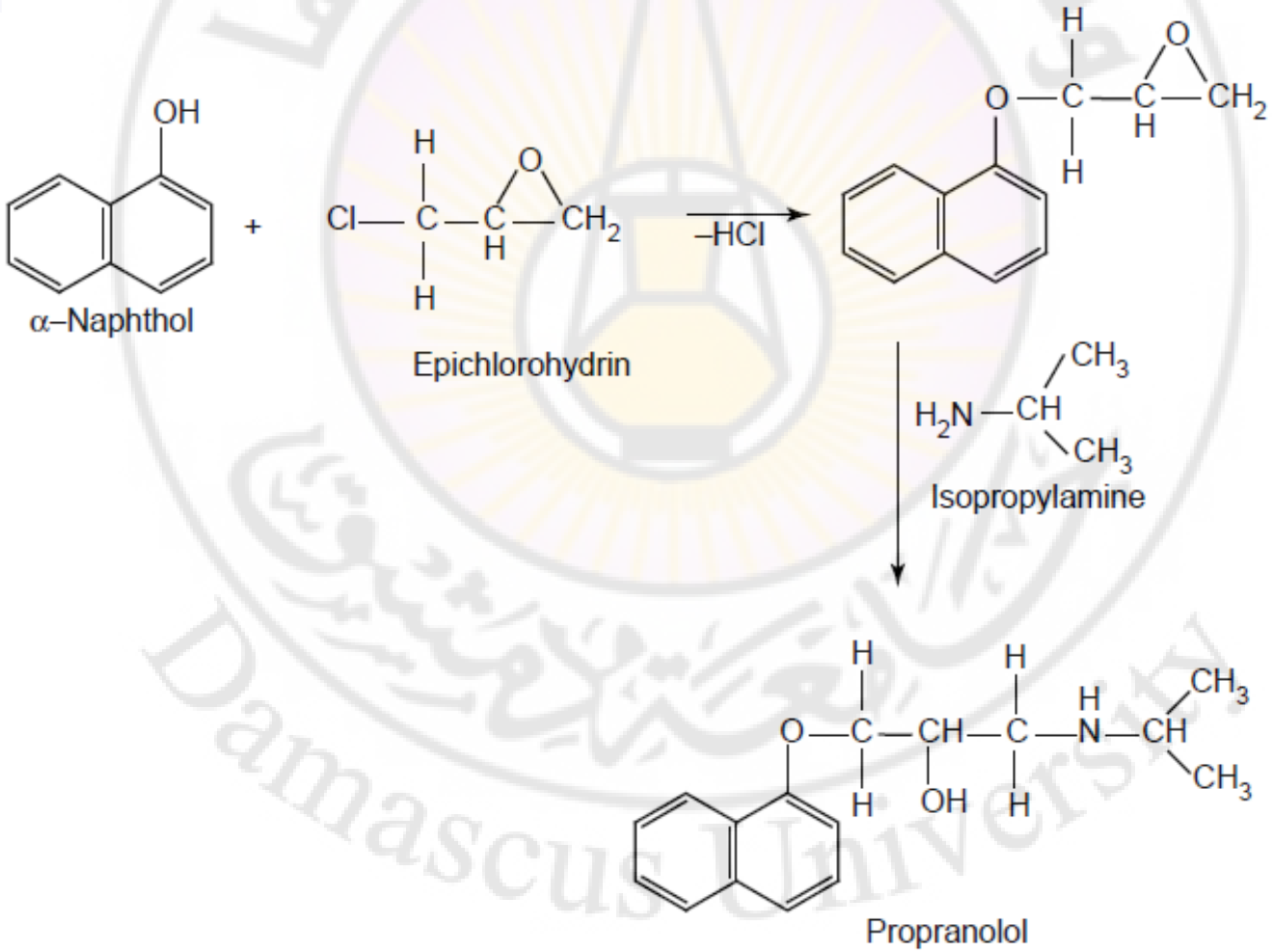
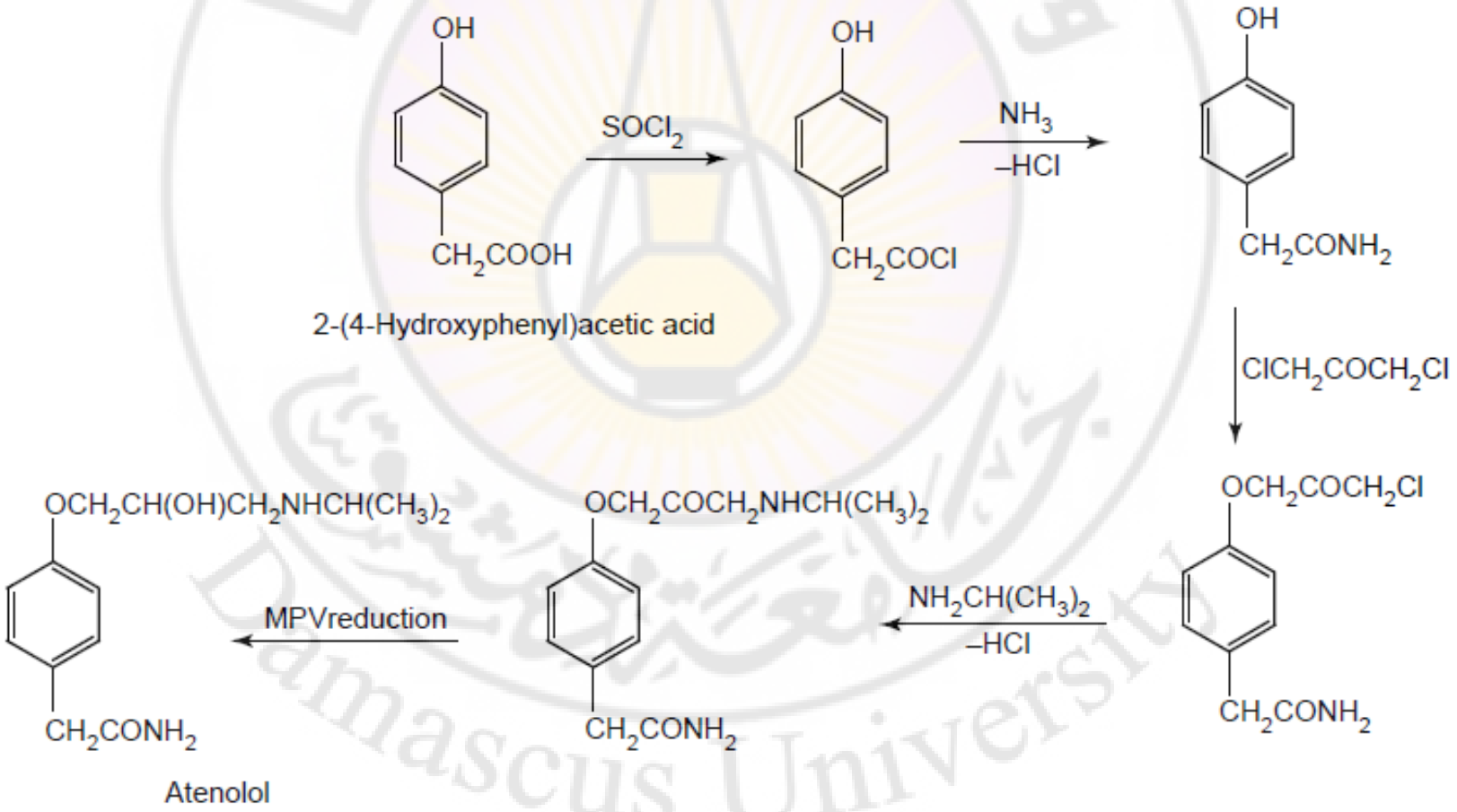
Drug Synthesis

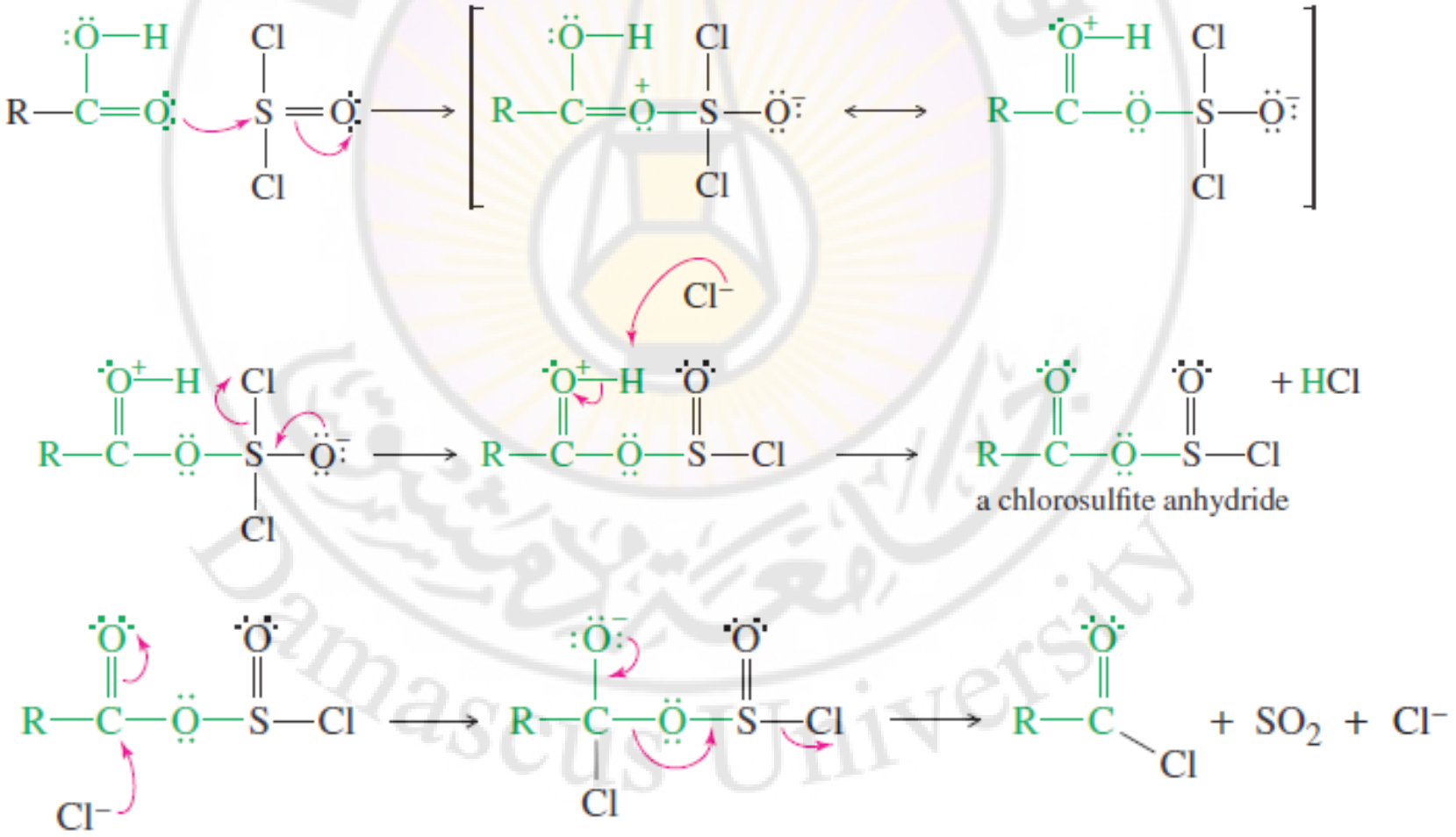
Propranolol Synthesis



Atenolol synthesis



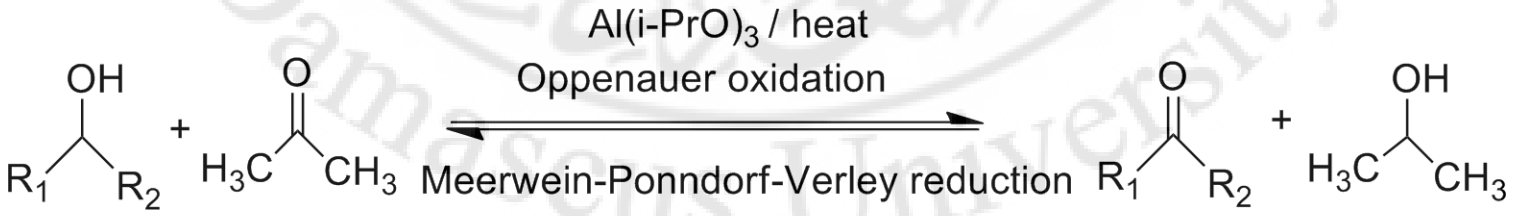
Atenolol synthesis



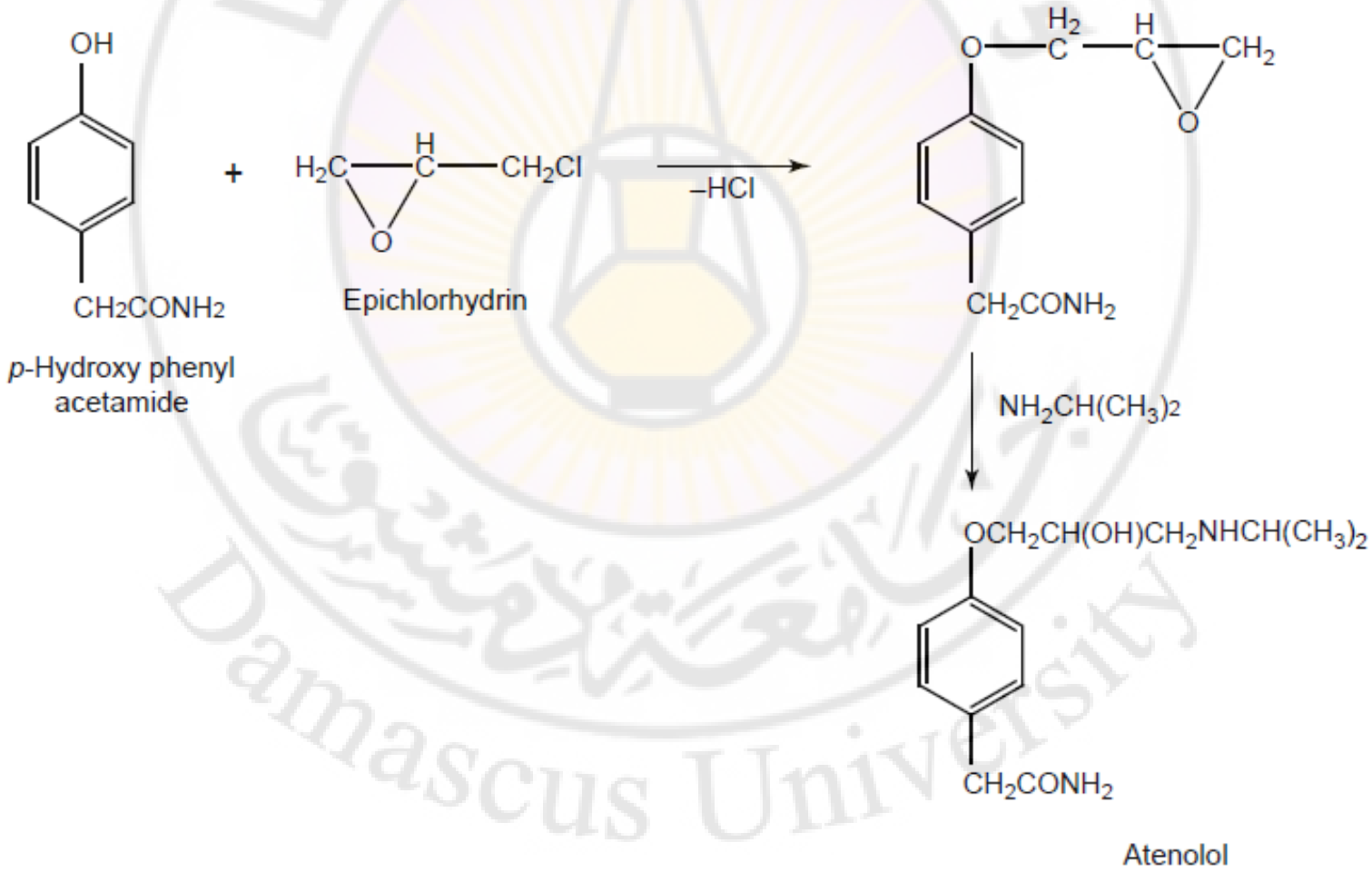
Atenolol synthesis

The MeerweinPonndorf Verley (MPV) reduction in organic chemistry is the reduction of ketones and aldehydes to their corresponding alcohols utilizing aluminium alkoxide catalysis in the presence of a sacrificial alcohol

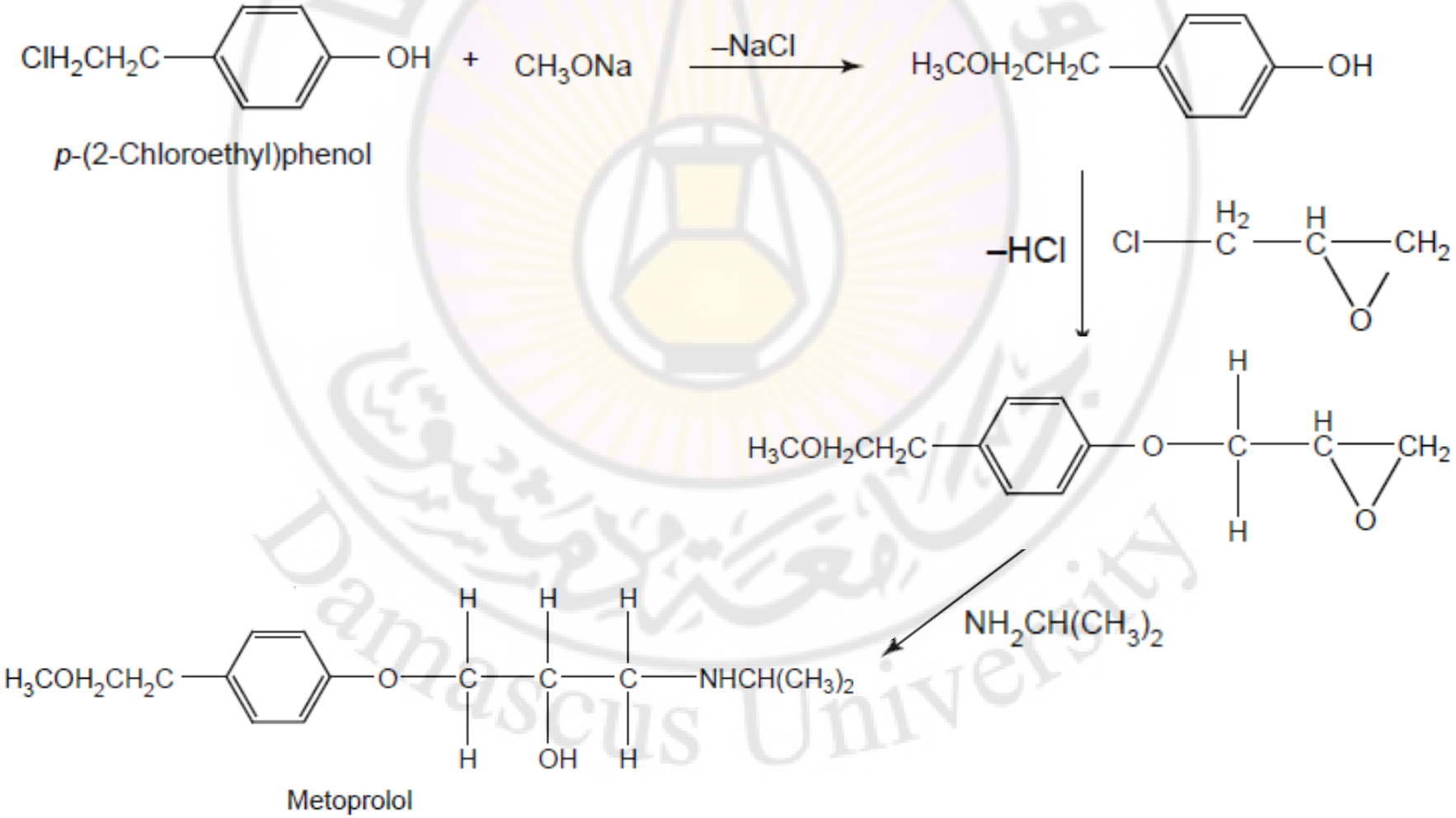
The advantages of the MPV reduction lie in its high chemoselectivity, and its use of a cheap environmentally friendly metal catalyst



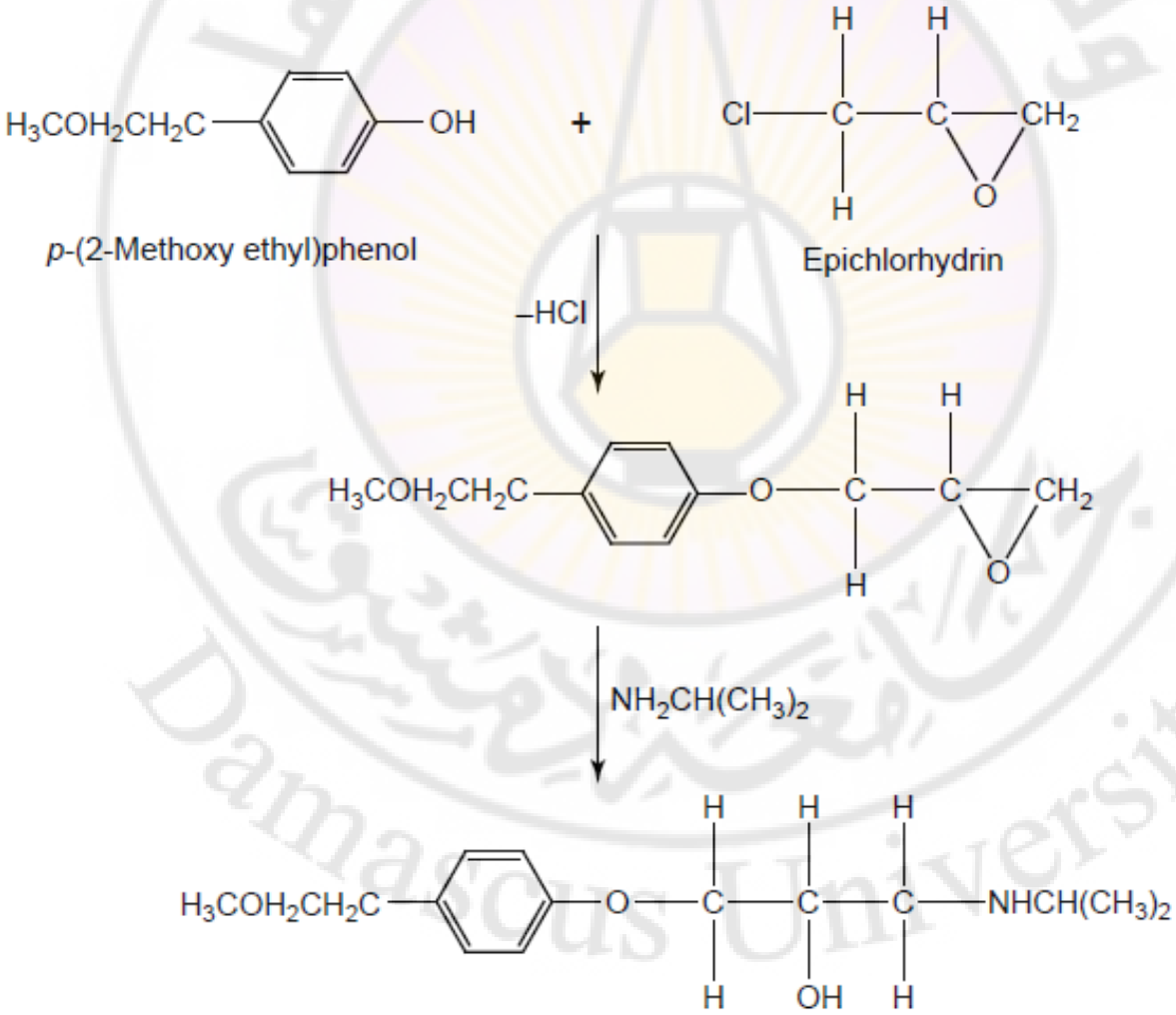
Atenolol synthesis



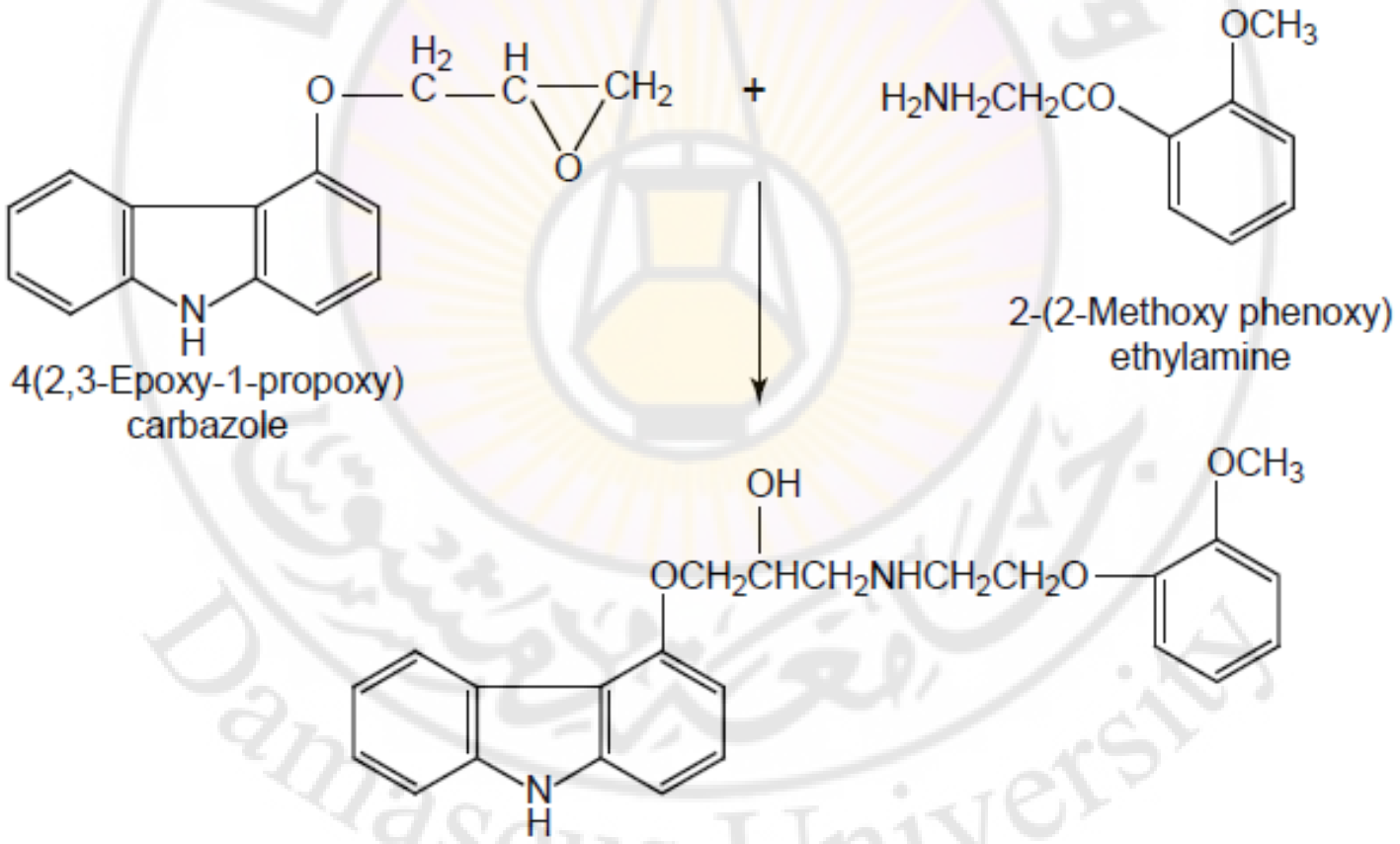
Metoprolol synthesis



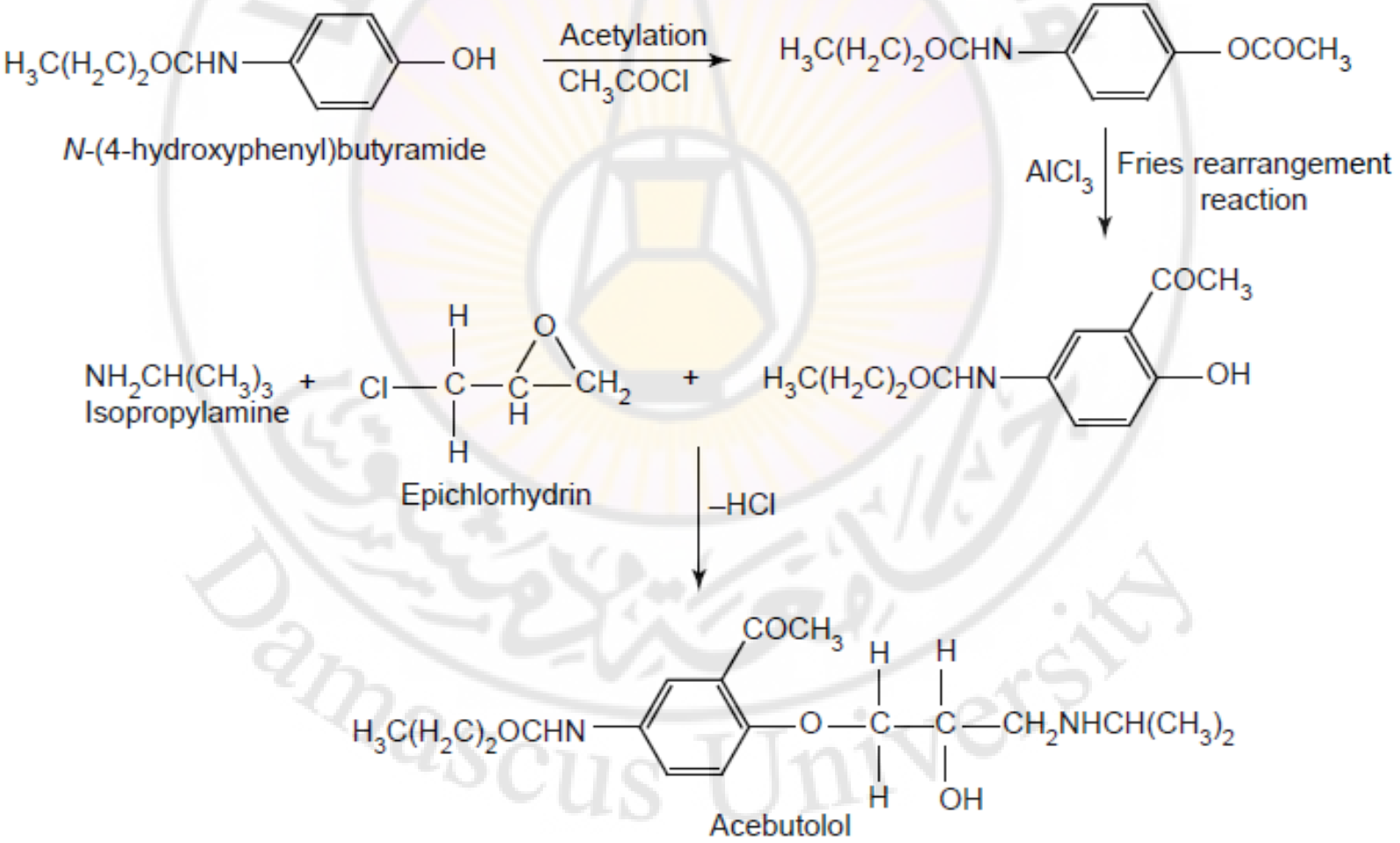
Metoprolol synthesis



Carvedilol synthesis

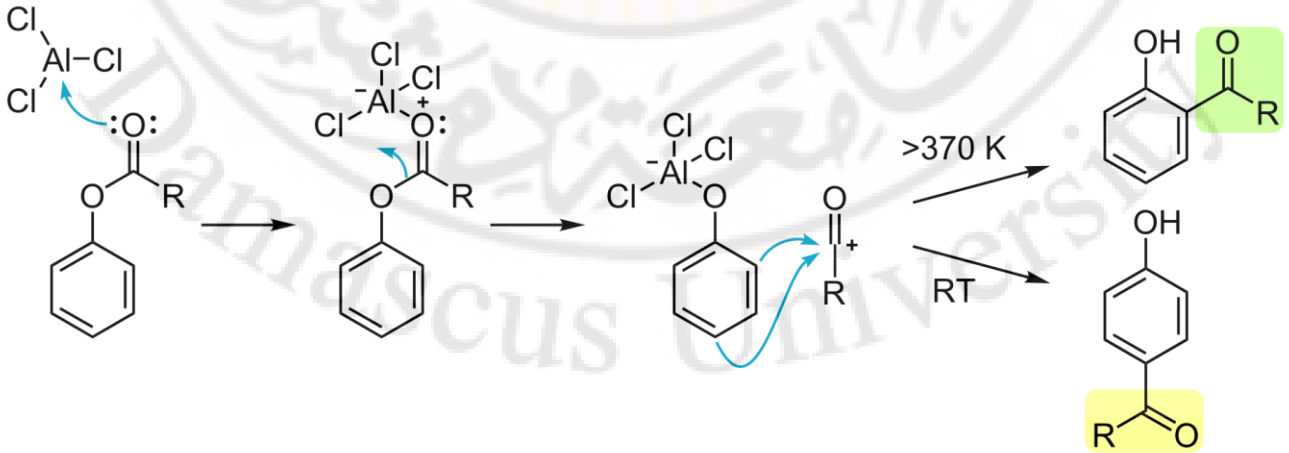


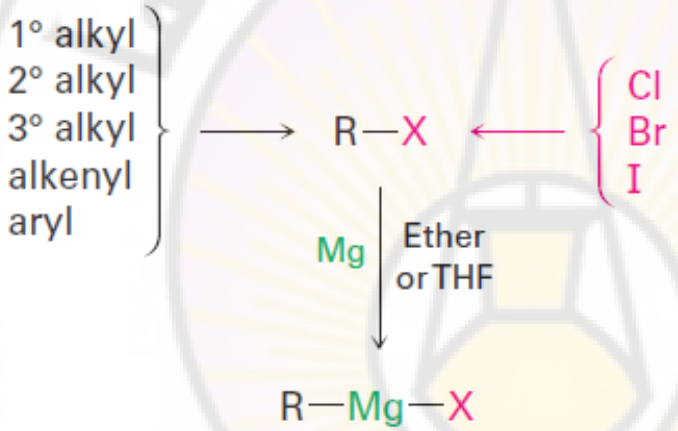
Acebutolol synthesis

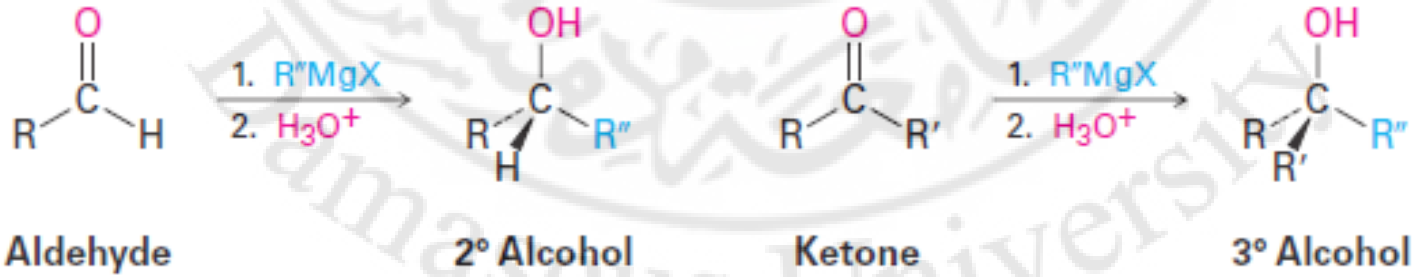


Fries rearrangement

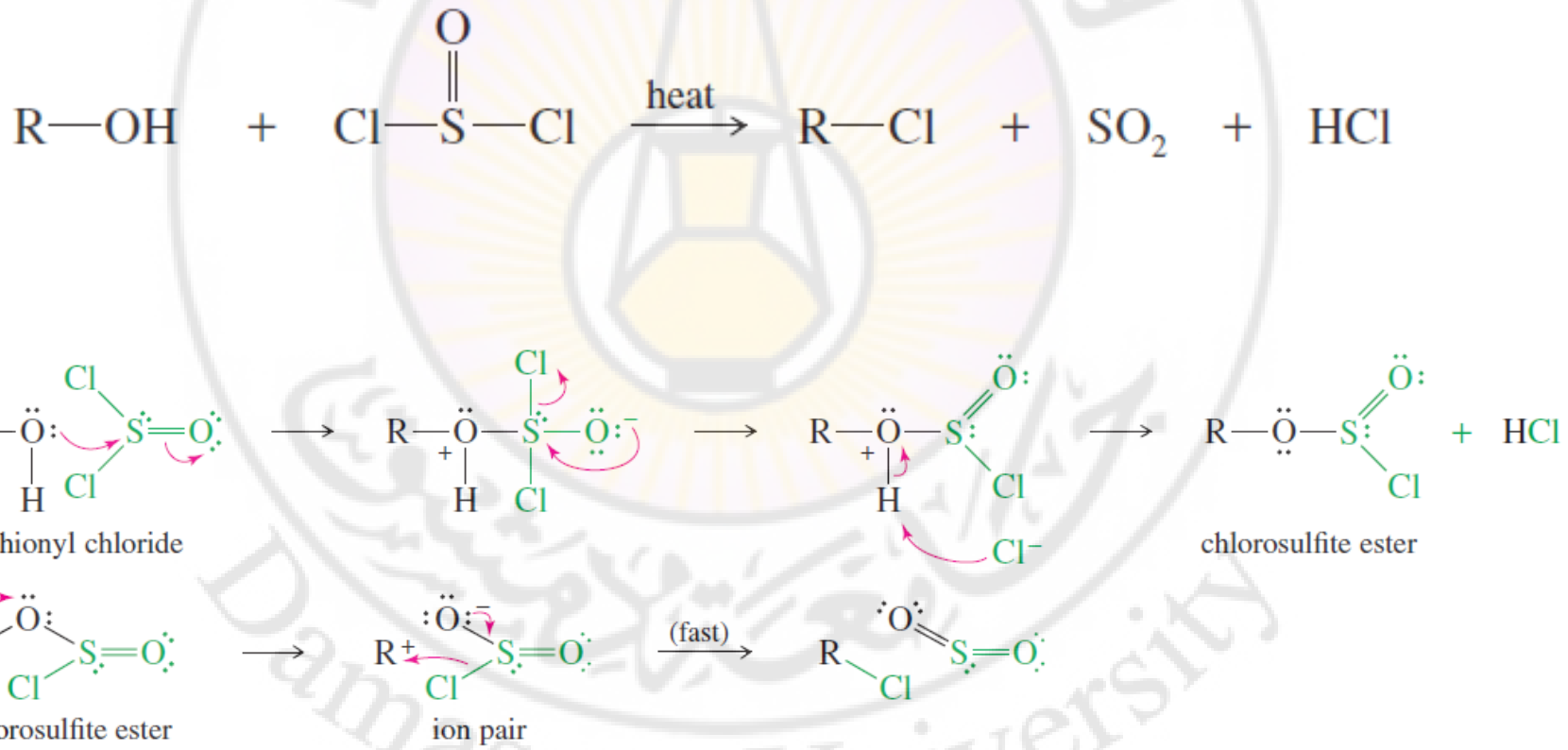
- The **Fries rearrangement** is a rearrangement reaction of a phenolic ester to a hydroxy aryl ketone by catalysis of Lewis acids.
- It involves migration of an acyl group of phenol ester to the aryl ring.
- The reaction is ortho and para selective and one of the two products can be favoured by changing reaction conditions, such as temperature and solvent.




1° alkyl
2° alkyl
3° alkyl
alkenyl
aryl
R—X
Cl
Br
I
Mg
Ether
or THF
R—Mg—X

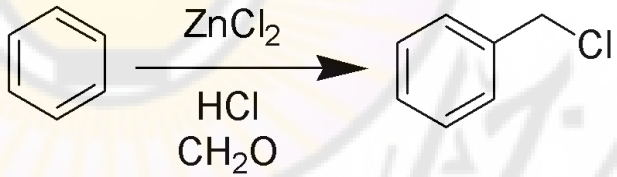

O
R
C
H
1. R″MgX
2. H3O+
OH
R″
Aldehyde
2° Alcohol
Ketone
R′
3° Alcohol

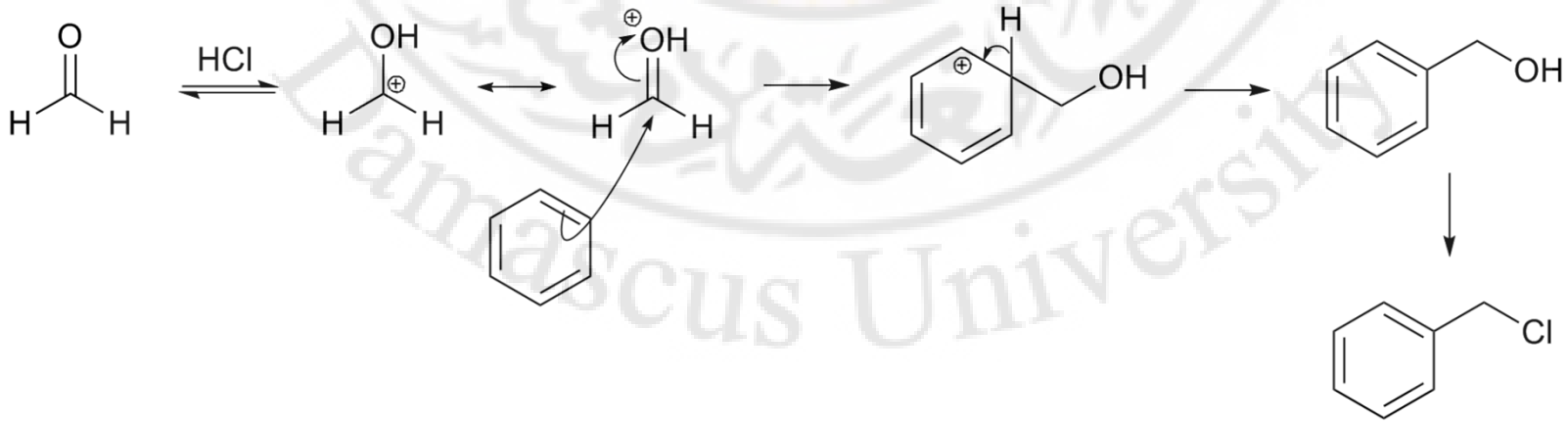
BromoDiphenhydramine ( ) synthesis

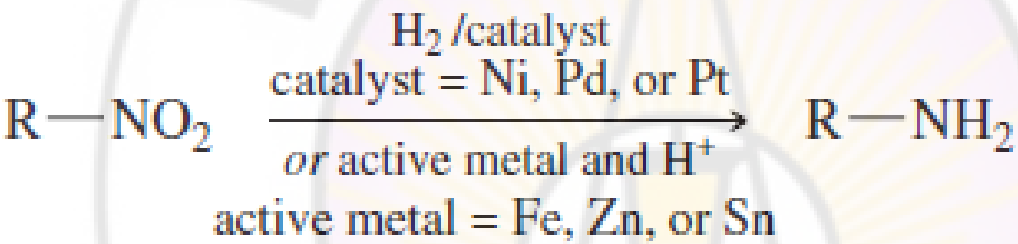


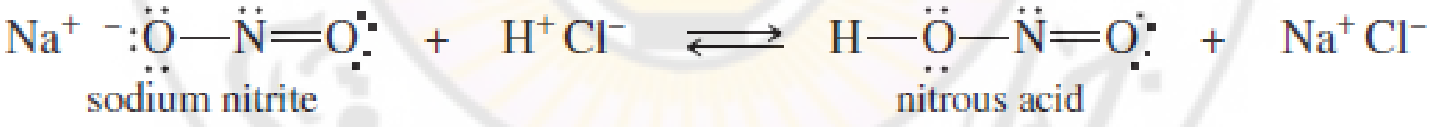
Blanc chloromethylation

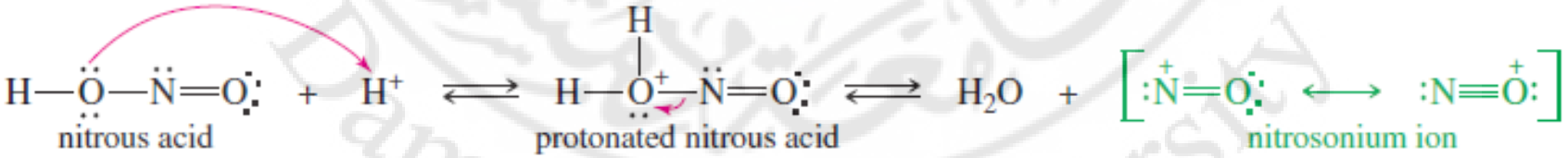
The **Blanc chloromethylation** (also called the **Blanc reaction**) is the chemical reaction of aromatic rings with formaldehyde and hydrogen chloride catalyzed by zinc chloride or other Lewis acid to form chloromethyl arenes. hydrogen chloride catalyzed by zinc chloride or other Lewis acid to form chloromethyl arenes

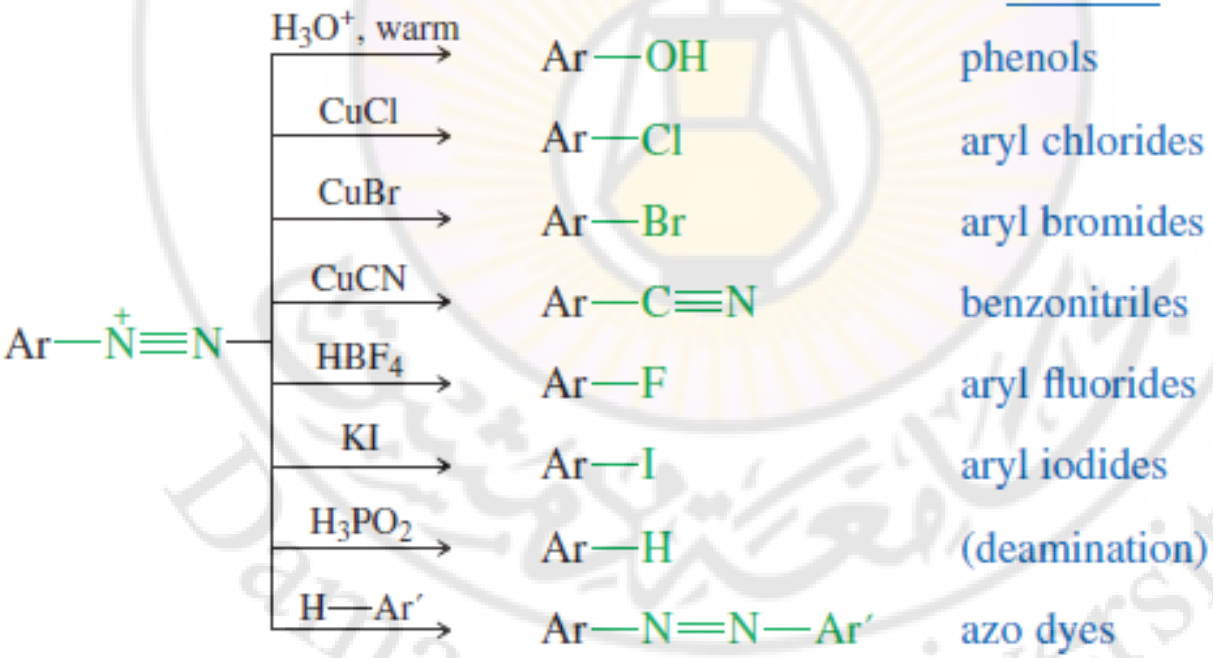





H2 /catalyst
catalyst = Ni, Pd, or Pt
or active metal and H+
active metal = Fe, Zn, or Sn
R—NO2
R—NH2


Na+ −:O—N=O:
sodium nitrite
+
H+ Cl−
H—O—N=O:
nitrous acid
+
Na+ Cl−

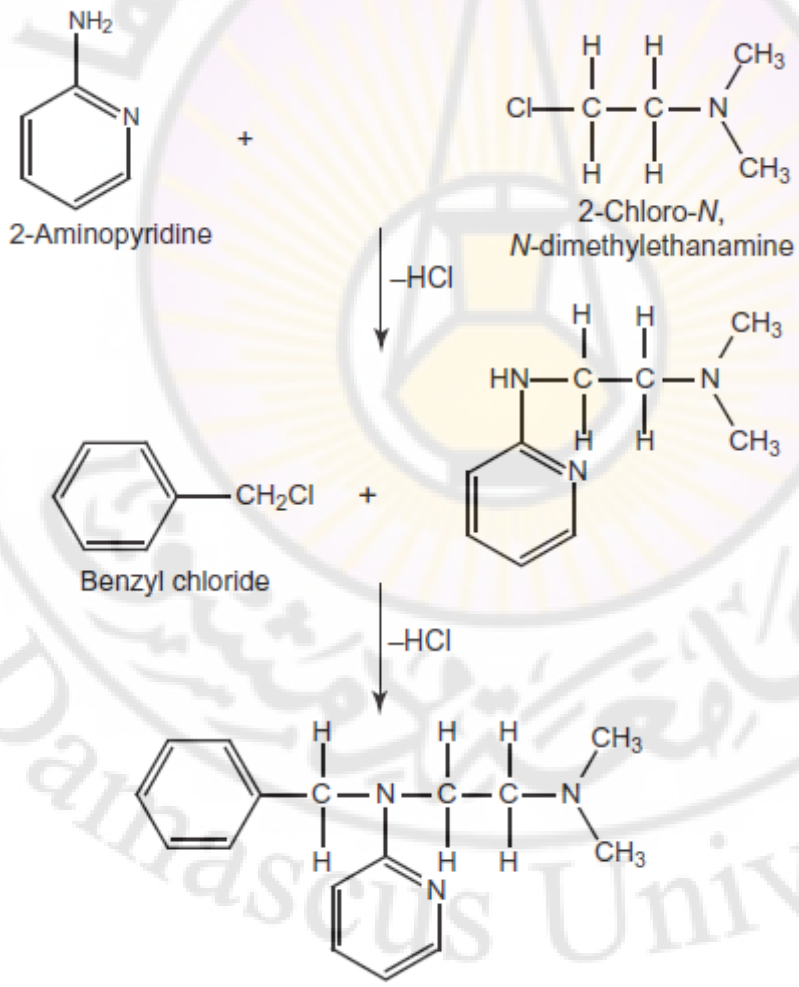

H—O—N=O:
nitrous acid
+
H+
H
H—O+—N=O:
protonated nitrous acid
H2O
+
:N=O:
:N≡O:
nitrosonium ion


Products
H_3O^+, warm
Ar—OH
phenols
CuCl
Ar—Cl
aryl chlorides
CuBr
Ar—Br
aryl bromides
CuCN
Ar—C≡N
benzonitriles
Ar—$\overset{+}{N}$≡N—
HBF_4
Ar—F
aryl fluorides
KI
Ar—I
aryl iodides
H_3PO_2
Ar—H
(deamination)
H—Ar′
Ar—N=N—Ar′
azo dyes

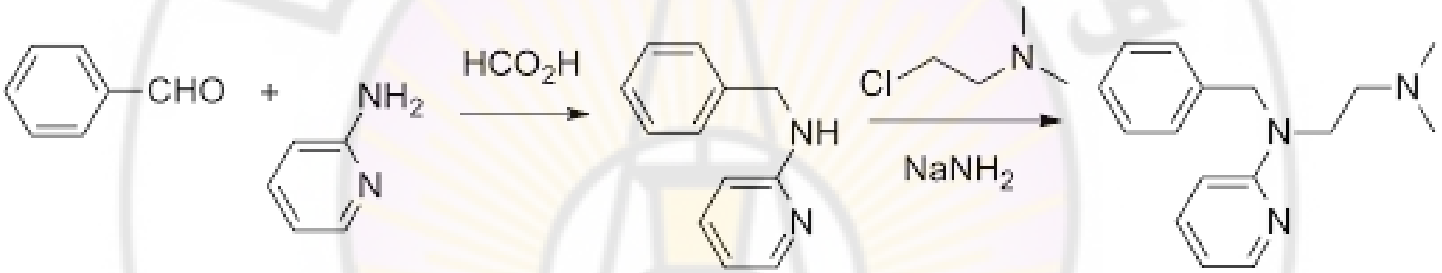
Drug Synthesis

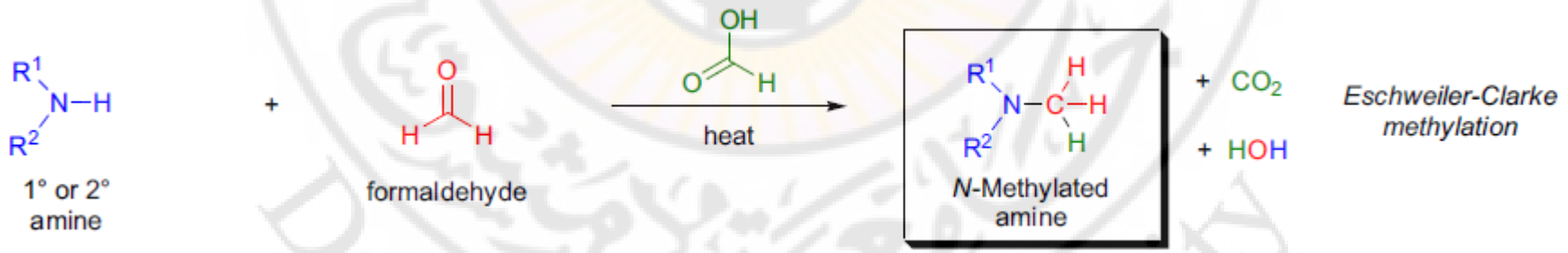
of Antihistamine

Tripelennamine (Pyribenzamine HCl) synthesis



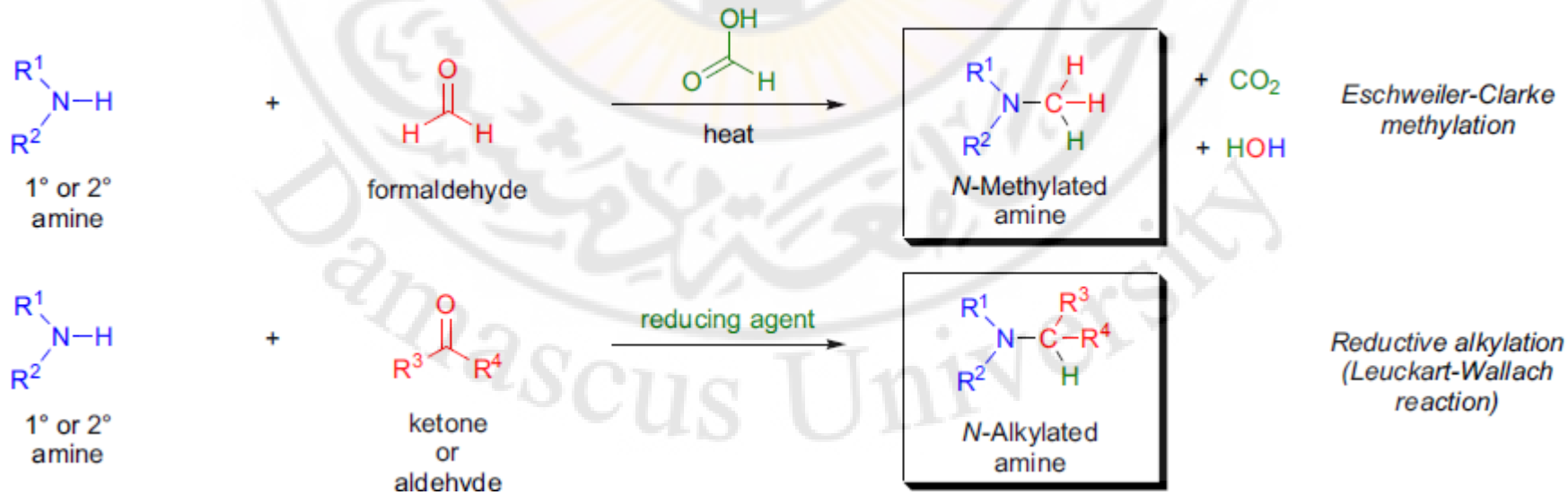
Tripelennamine (Pyribenzamine HCl) synthesis





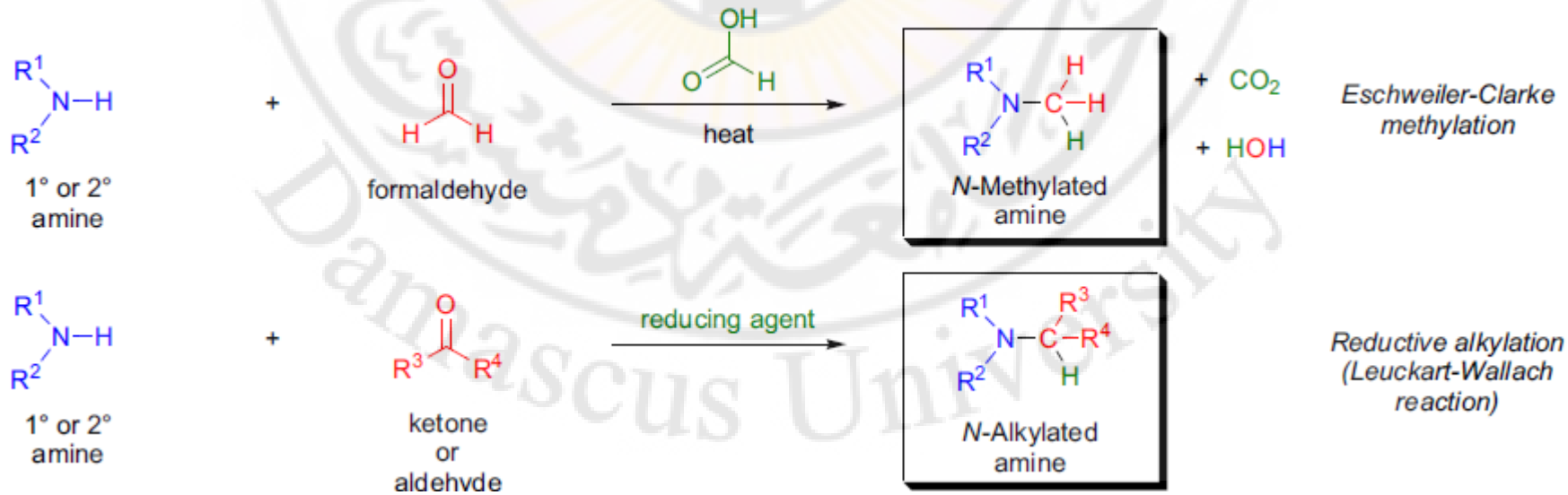
Eschweiler-Clarke methylation

The one-pot reductive methylation of primary and secondary amines to the corresponding tertiary amines is known as the Eschweiler-Clarke methylation. This reaction falls into the category of reductive alkylation of amines by carbonyl compounds (aldehydes and ketones), and it is considered as a modification of the Leuckart-Wallach reaction.



Eschweiler-Clarke methylation

Formic acid serves as a reducing agent (hydride donor), which reduces the Schiff base intermediate to the corresponding amine. Today, other reducing agents, such as sodium borohydride, sodium cyanoborohydride $NaBH_3CN$, sodium triacetoxyborohydride $[NaBH(OAc)_3]$



Eschweiler-Clarke methylation

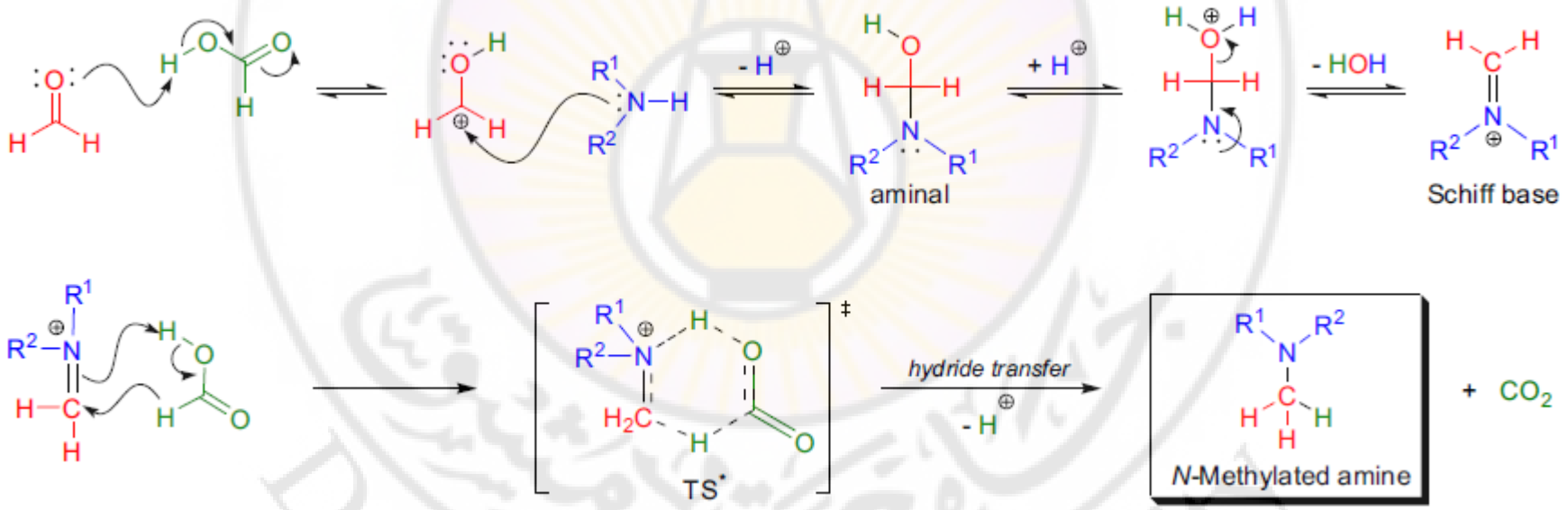
The following steps are believed to be involved in the Eschweiler-Clarkemethylation:

1) formation of a Schiff-base (imine) from the starting primary or secondary amine and formaldehyde via an aminoalcohol (aminal) intermediate

2) hydride transfer from the reducing agent (e.g., formic acid, cyanoborohydride, etc.) to the imine to get the corresponding N-methylated amine along with the loss of CO_2 .

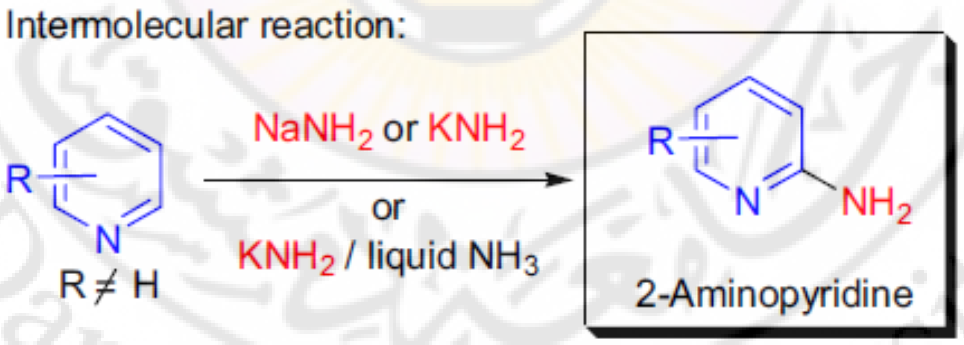
3) if the starting amine was primary, then steps 1 and 2 are repeated.

Eschweiler-Clarke methylation

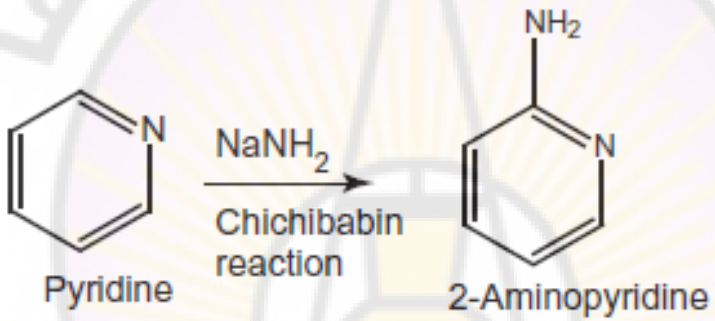


Chichibabin reaction

In the early 1900s, A.E. Chichibabin reacted pyridine with sodium amide (NaNH2) in dimethylamine at high temperature (110 °C). After aqueous work-up, he isolated 2-aminopyridine in 80% yield. A decade later, he added pyridine to powdered KOH at 320 °C, and after aqueous work-up 2-hydroxypyridine was isolated.



Chichibabin reaction

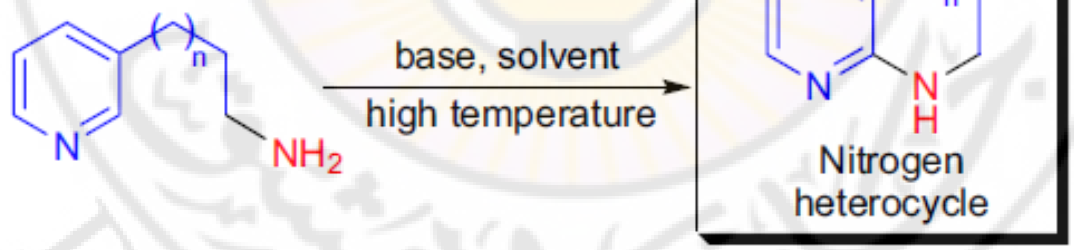


This reaction is also widely used for the direct introduction of an amino group into the electron-deficient positions of many azines and azoles (e.g., quinoline is aminated at C2 & C4, isoquinoline at C1, acridine at C9, phenanthridine at C6, quinazoline at C4).

Chichibabin reaction

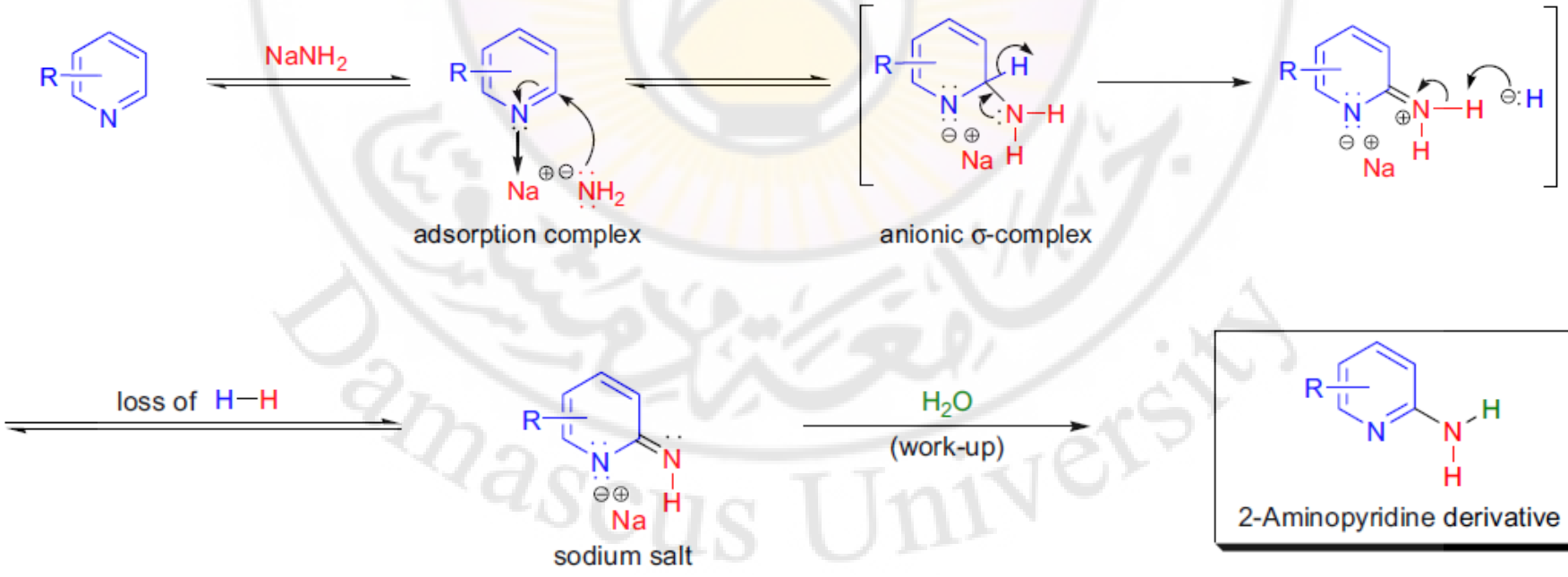
Similar reactions take place when pyridine or its derivatives are treated with strong nucleophiles such as alkyl- and aryllithiums to give 2-alkyl and 2-arylpyridines.

Intramolecular reaction:



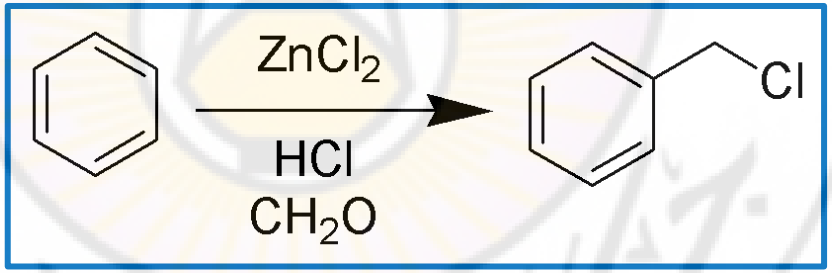
Chichibabin reaction

The direct amination of pyridine and its derivatives at their electron-deficient positions *via* Nucleophilic Aromatic Substitution (S_NAr) is known as the *Chichibabin reaction*.

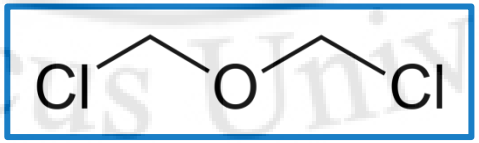


Blanc chloromethylation

The **Blanc chloromethylation** (also called the **Blanc reaction**) is the chemical reaction of aromatic rings with formaldehyde and hydrogen chloride catalyzed by zinc chloride or other Lewis acid to form chloromethyl arenes.



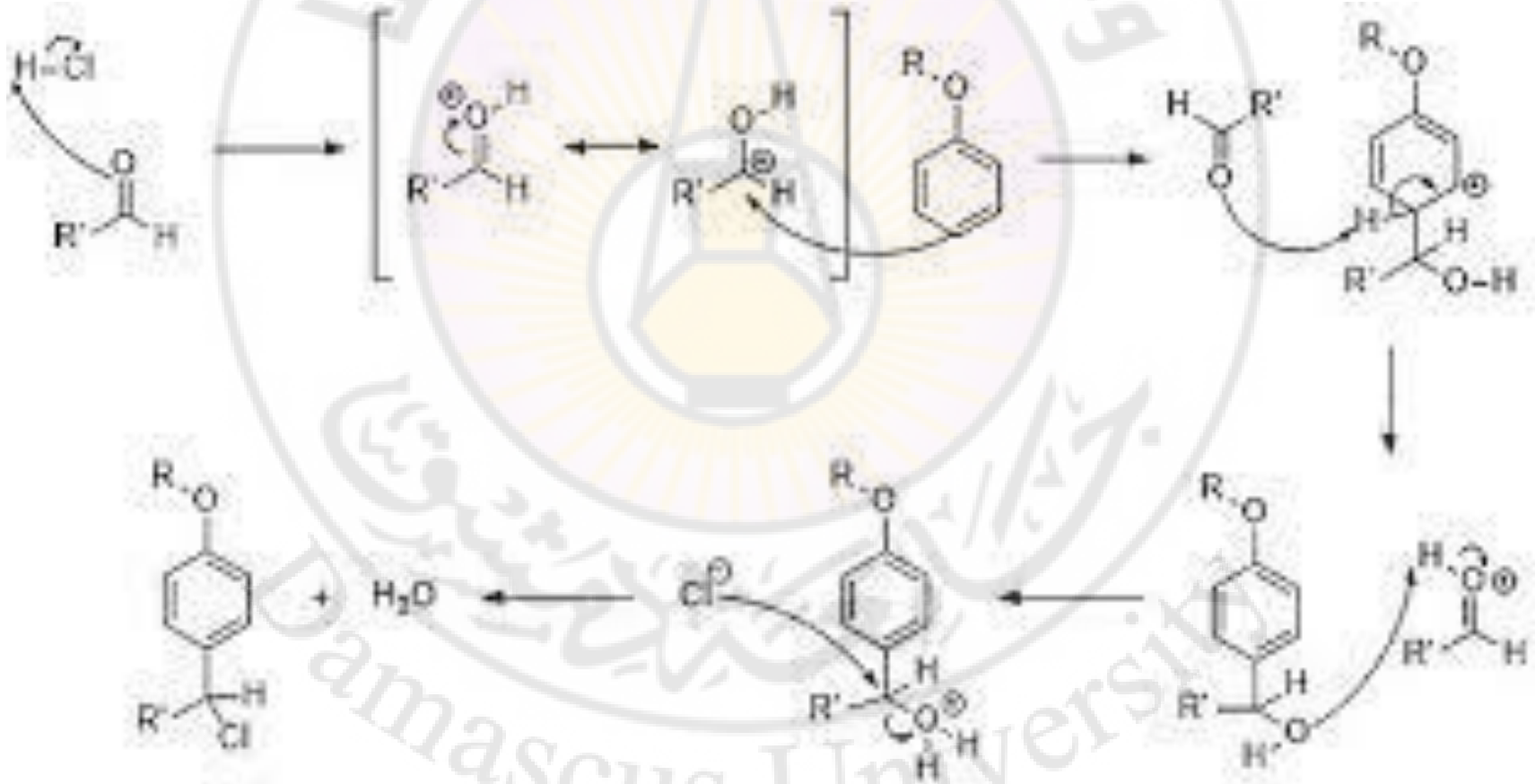
The reaction is performed with care as, like most chloromethylation reactions, it produces highly carcinogenic bis(chloromethyl) ether as a by-product.



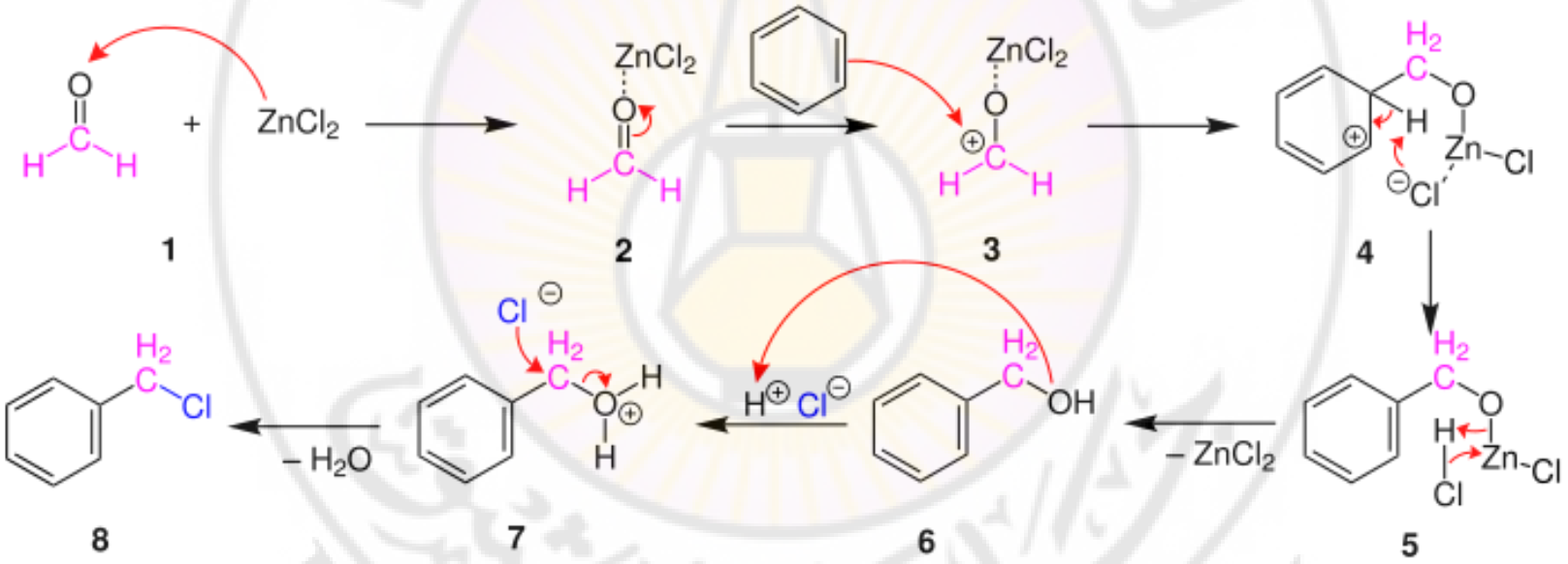
Blanc chloromethylation

- ✓ The reaction is carried out under acidic conditions and with a $ZnCl_2$ catalyst.
- ✓ These conditions protonate the formaldehyde carbonyl making the carbon much more electrophilic.
- ✓ The aldehyde is then attacked by the aromatic pi-electrons, followed by rearomatization of the aromatic ring.
- ✓ The benzyl alcohol thus formed is quickly converted to the chloride under the reaction conditions.

Blanc chloromethylation



Blanc chloromethylation



Blanc chloromethylation

- ✓ Highly activated arenes like phenols and anilines are not suitable substrates, since they undergo further electrophilic attack by Friedel-Crafts alkylation with the formed benzylic alcohol/chloride in an uncontrolled manner. In general, the formation of diarylmethane side product is a common outcome

- ✓ Although the reaction is an efficient means of introducing a chloromethyl group, the production of small amounts of highly carcinogenic bis(chloromethyl) ether is a disadvantage for industrial applications.

Blanc chloromethylation

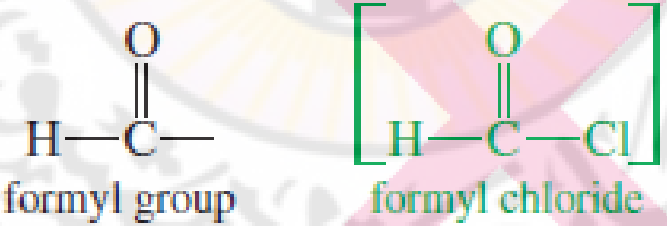
- ✓ moderately and strongly deactivated substrates that are inert to Friedel-Crafts reactions like acetophenone, nitrobenzene and p-chloronitrobenzene do show marginal reactivity of limited synthetic utility under chloromethylation conditions.

- ✓ Deactivated substrates give better results under modified chloromethylation conditions using chloromethyl methyl ether (MOMCl) in the presence of 60% H_2SO_4

- ✓ The corresponding fluoromethylation, bromomethylation and iodomethylation reactions can also be achieved, using the appropriate hydrohalic acid

The Gatterman–Koch Formylation: Synthesis of Benzaldehydes

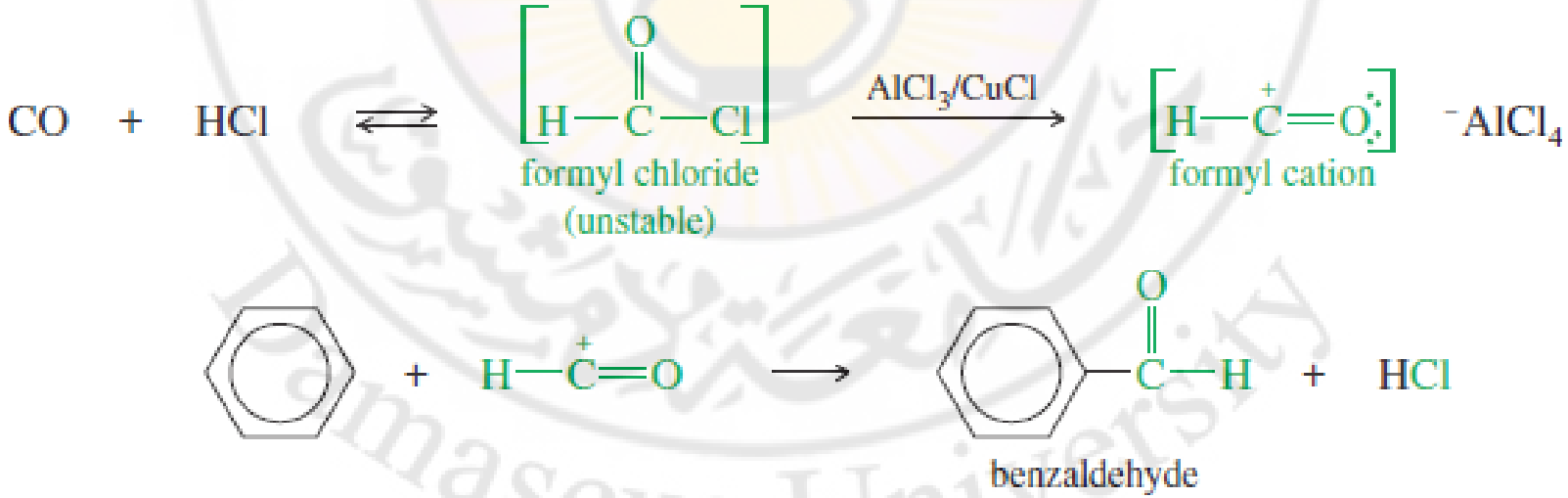
- ✓ We cannot add a formyl group to benzene by Friedel–Crafts acylation in the usual manner.
- ✓ The problem lies with the necessary reagent, formyl chloride, which is unstable and cannot be bought or stored.



The Gatterman–Koch Formylation: Synthesis of Benzaldehydes

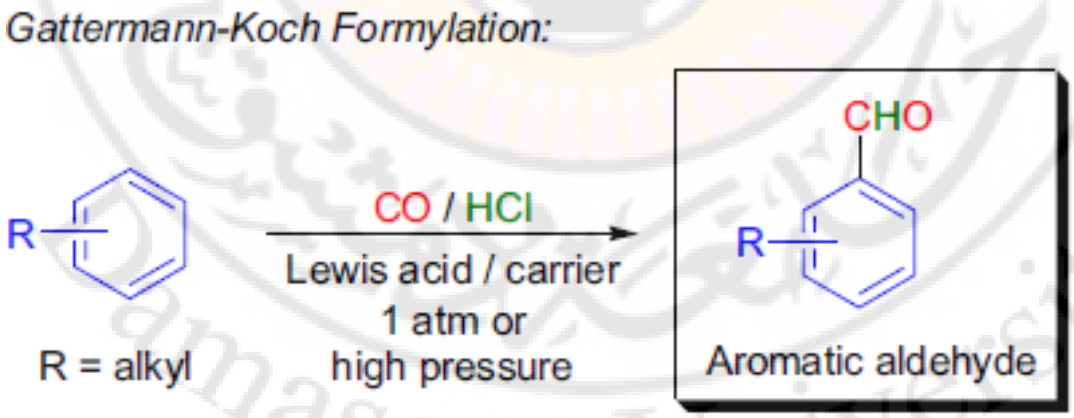
The reaction with benzene gives formyl benzene, better known as benzaldehyde.

This reaction, called the Gatterman–Koch synthesis, is widely used in industry to synthesize aryl aldehydes.



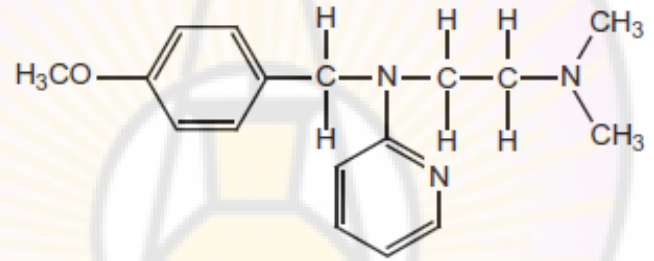
The Gatterman–Koch Formylation: Synthesis of Benzaldehydes

Formylation can be accomplished by using a high-pressure mixture of carbon monoxide and HCl together with a catalyst consisting of a mixture of cuprous chloride (CuCl) and aluminum chloride.
This mixture generates the formyl cation, possibly through a small concentration of formyl chloride.

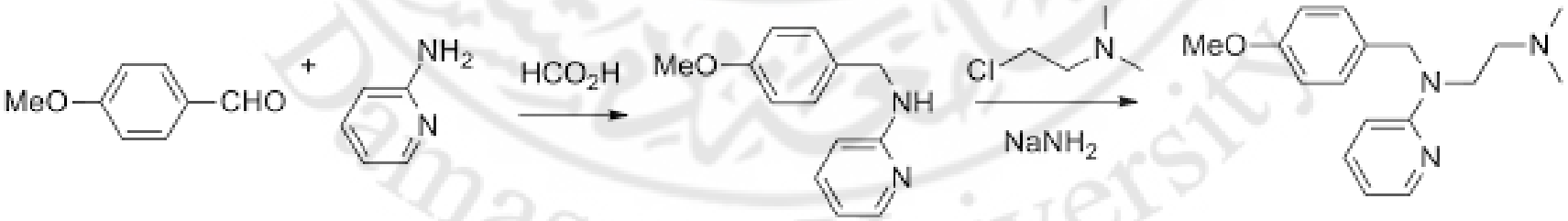


Mepyramine synthesis

ii. Pyrilamine (Mepyramine, Anthisan)



N-(4-Methoxybenzyl)-*N*-(2-(dimethylamino)ethyl)pyridin-2-amine

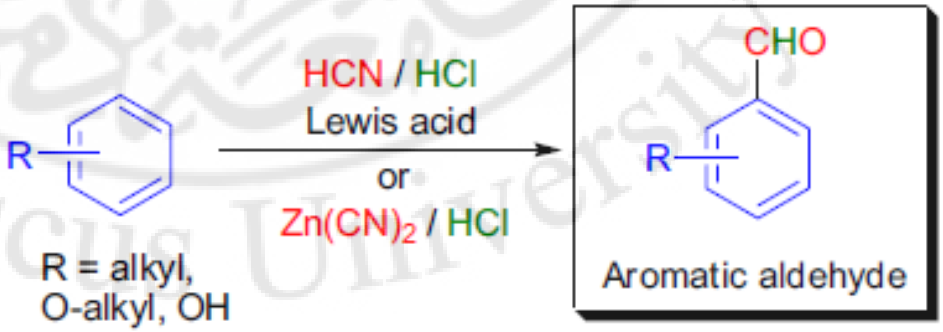


The Gatterman Formylation: Synthesis of Benzaldehydes

The scope of the *Gattermann-Koch reaction* in terms of suitable substrates is also limited, since it is mostly restricted to alkylbenzenes.

Gattermann introduced a modification where HCN is mixed with HCl in the presence of $ZnCl_2$ to formylate phenols, phenolic ethers and heteroaromatic compounds (e.g., pyrroles and indoles).
This modification is called the Gattermann formylation (or Gattermann synthesis)

Gattermann Formylation:



The Gatterman Formylation: Synthesis of Benzaldehydes

✓ The main drawback of the *Gattermann formylation* was that it called for the use of anhydrous HCN, which is a very toxic compound.

✓ To avoid the handling of HCN, R. Adams generated it *in situ* along with $ZnCl_2$ by reacting $Zn(CN)_2$ with HCl in the presence of the aromatic substrate (*Adams modification*).

✓ Other modifications used NaCN and CNBr successfully instead of HCN. Cyanogen bromide is hydrolyzed to release hydrogen cyanide and hypobromous acid

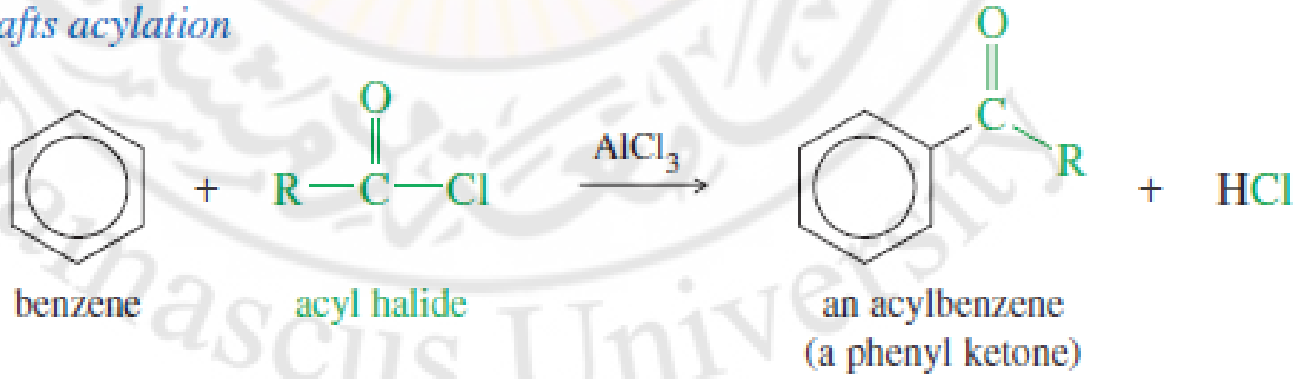
$(CN)Br + H_2O \rightarrow HCN + HOBr$

✓ A serious limitation of both title reactions is that they cannot be used for the formylation of aromatic amines due to numerous side reactions.

The Friedel–Crafts acylation

- ✓ In the presence of aluminum chloride, an acyl chloride reacts with benzene (or an activated benzene derivative) to give a phenyl ketone: an acylbenzene.
- ✓ The Friedel–Crafts acylation is analogous to the Friedel–Crafts alkylation, except that the reagent is an acyl chloride instead of an alkyl halide and the product is an acylbenzene (a "phenone") instead of an alkylbenzene.

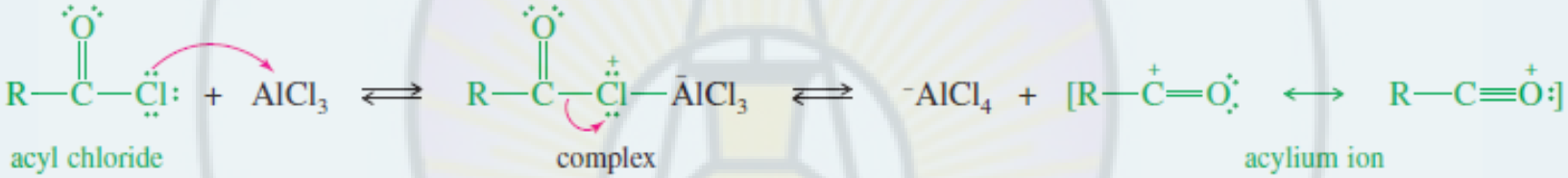
Friedel–Crafts acylation



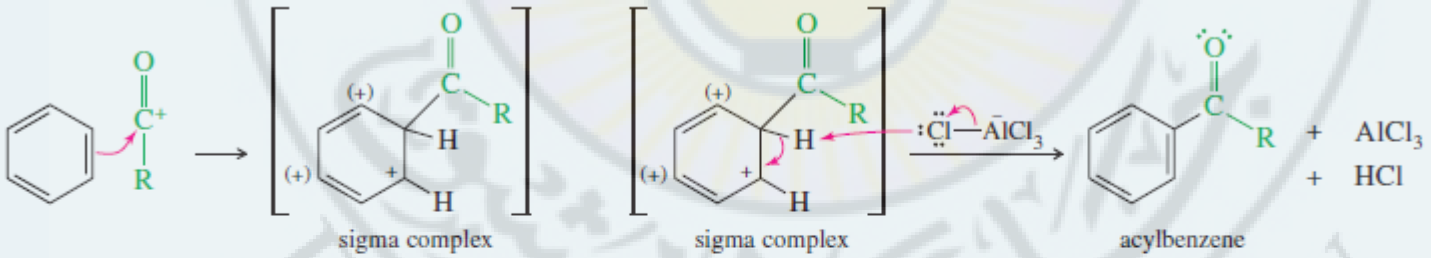
The Friedel–Crafts acylation

Friedel–Crafts acylation is an electrophilic aromatic substitution with an acylium ion acting as the electrophile.

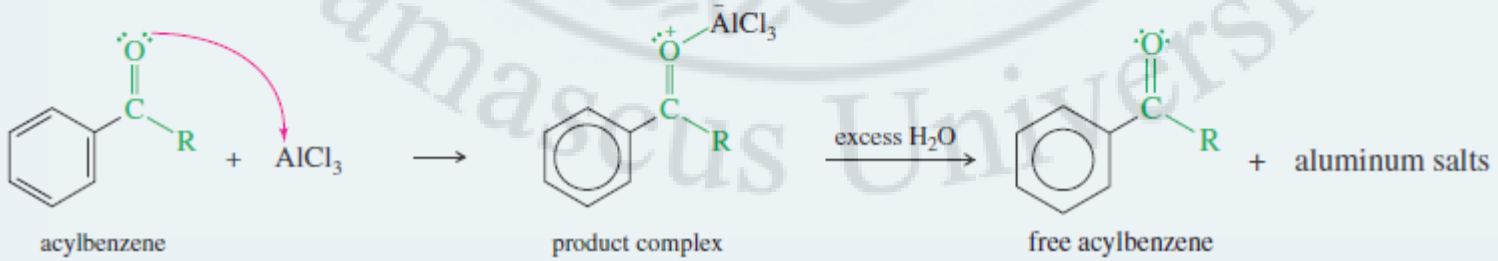
Step 1: Formation of an acylium ion.



Steps 2 and 3: Electrophilic attack forms a sigma complex, and loss of a proton regenerates the aromatic system.



Step 4: Complexation of the product. The product complex must be hydrolyzed (by water) to release the free acylbenzene.



The Friedel–Crafts acylation

- ✓ Friedel–Crafts acylation overcomes two of the three limitations of the alkylation:

1) The acylium ion is resonance-stabilized, so that no rearrangements occur;

2) and the acylbenzene product is deactivated, so that no further reaction occurs.

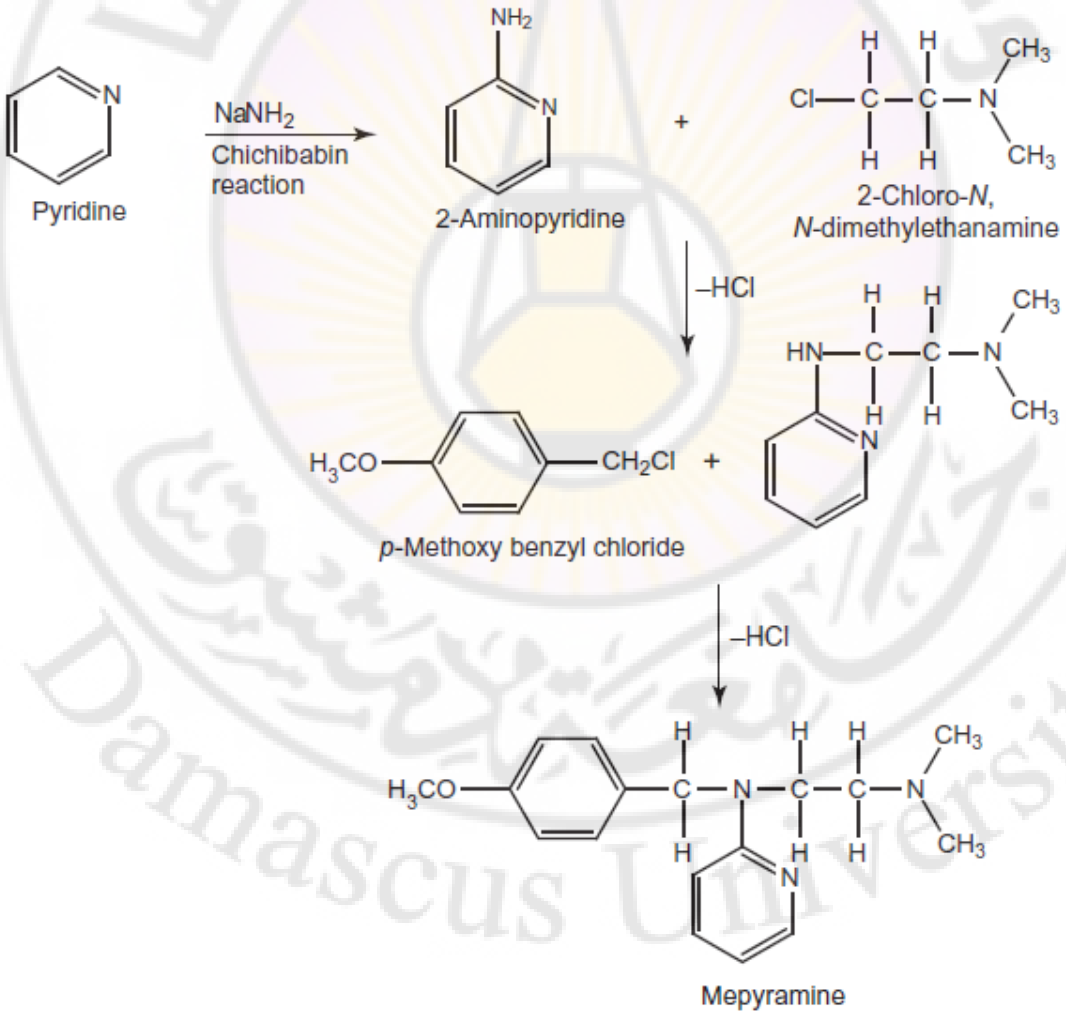
3) Like the alkylation, however, the acylation fails with strongly deactivated aromatic rings

The Friedel–Crafts acylation

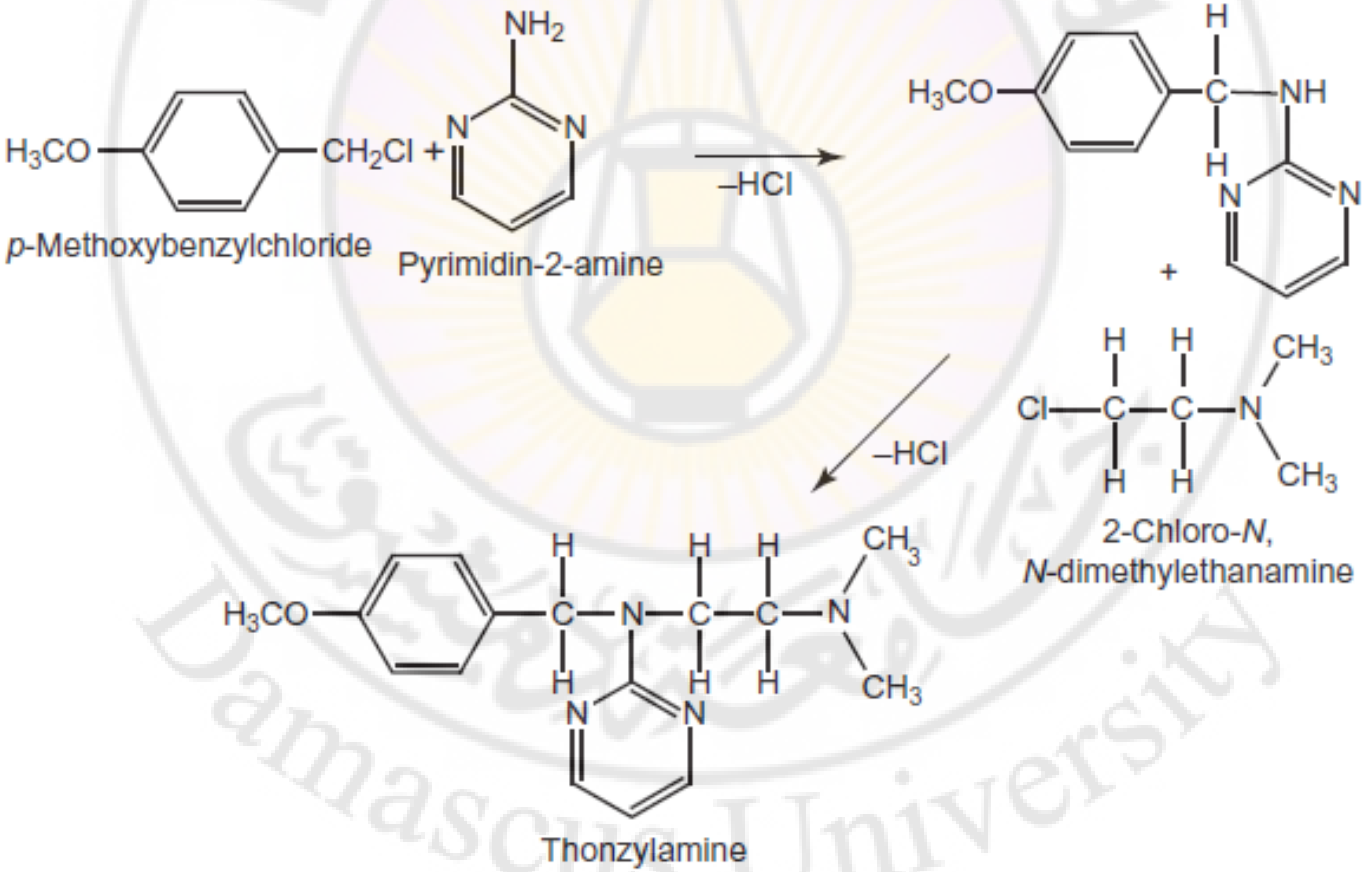
Alkylation
The alkylation cannot be used with strongly deactivated derivatives.
The carbocations involved in the alkylation may rearrange.
Polyalkylation is commonly a problem.

Acylation
Also true: Only benzene, halobenzenes, and activated derivatives are suitable.
Resonance-stabilized acylium ions are not prone to rearrangement.
The acylation forms a deactivated acylbenzene, which does not react further.

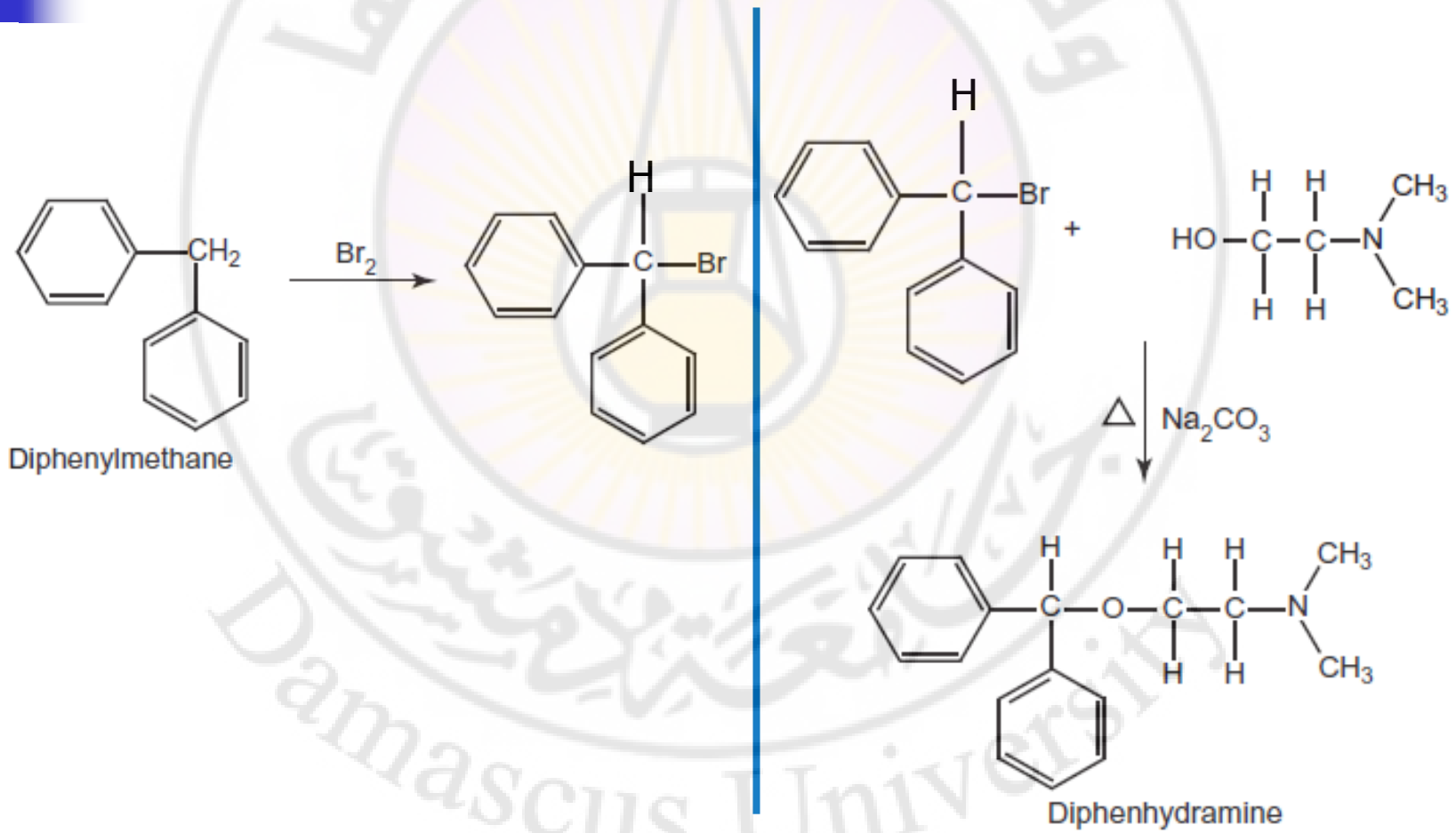
Mepyramine (Pyribenzamine HCl) synthesis



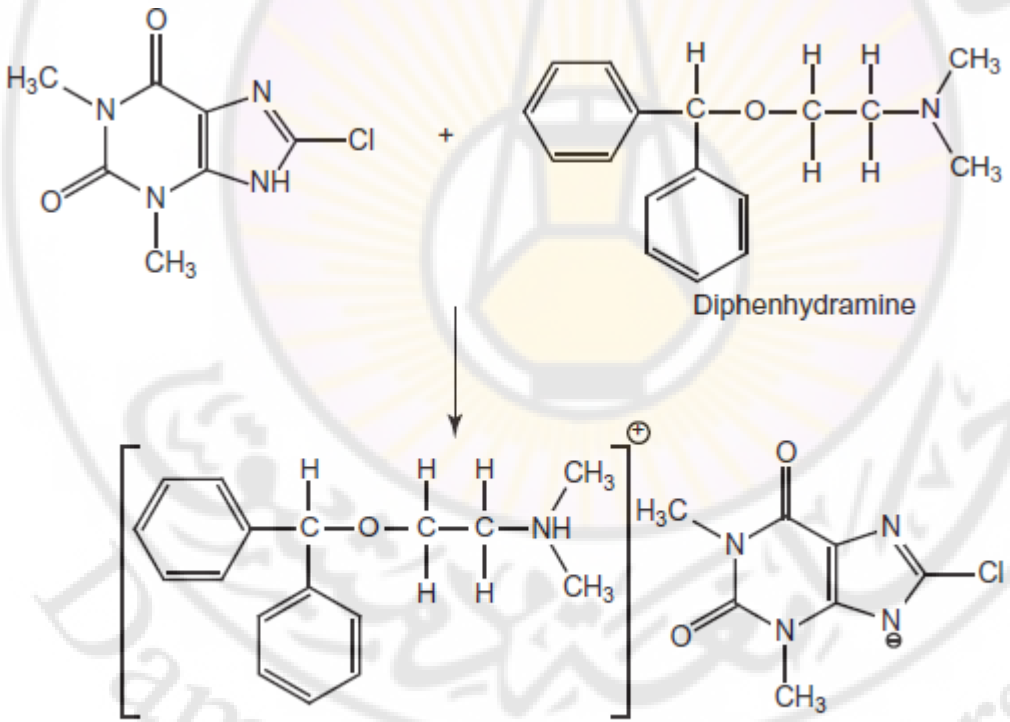
Tonzylamine synthesis



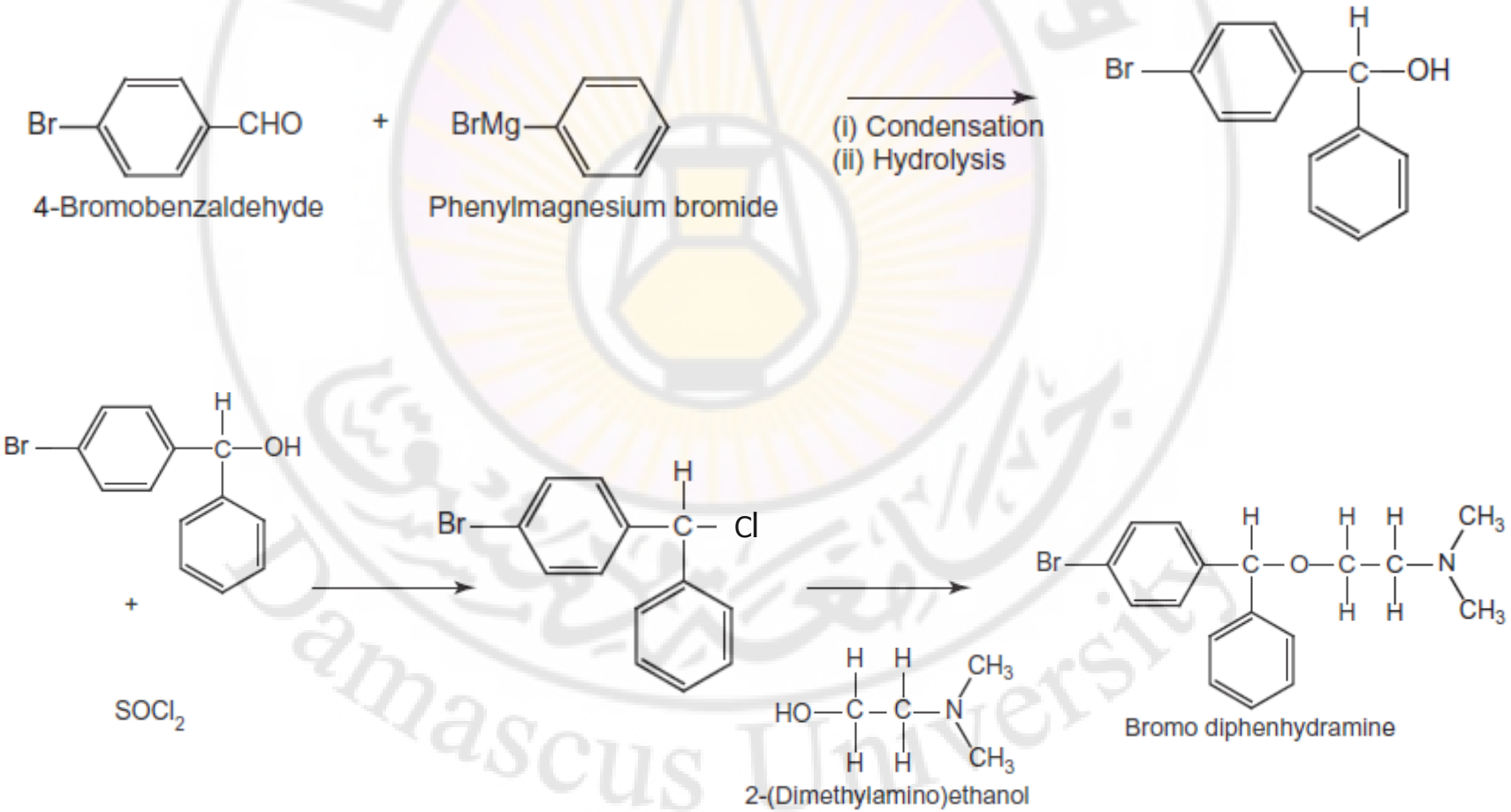
Diphenhydramine synthesis



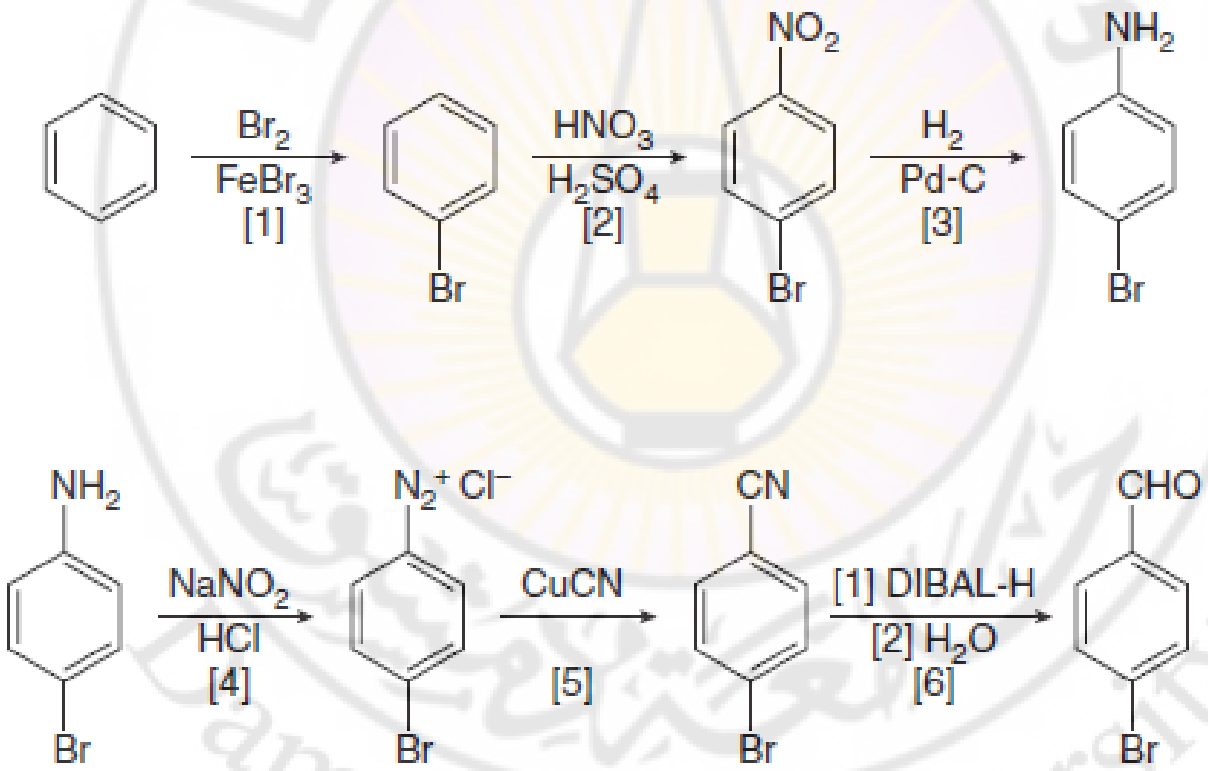
Diphenhydramine synthesis

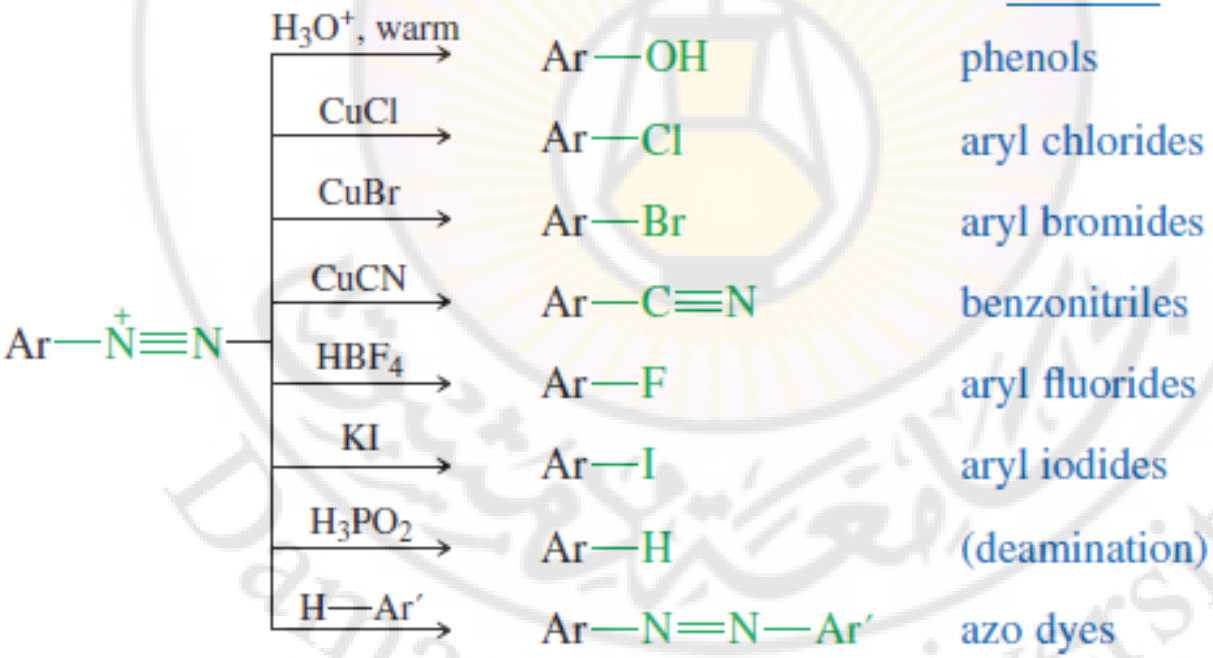


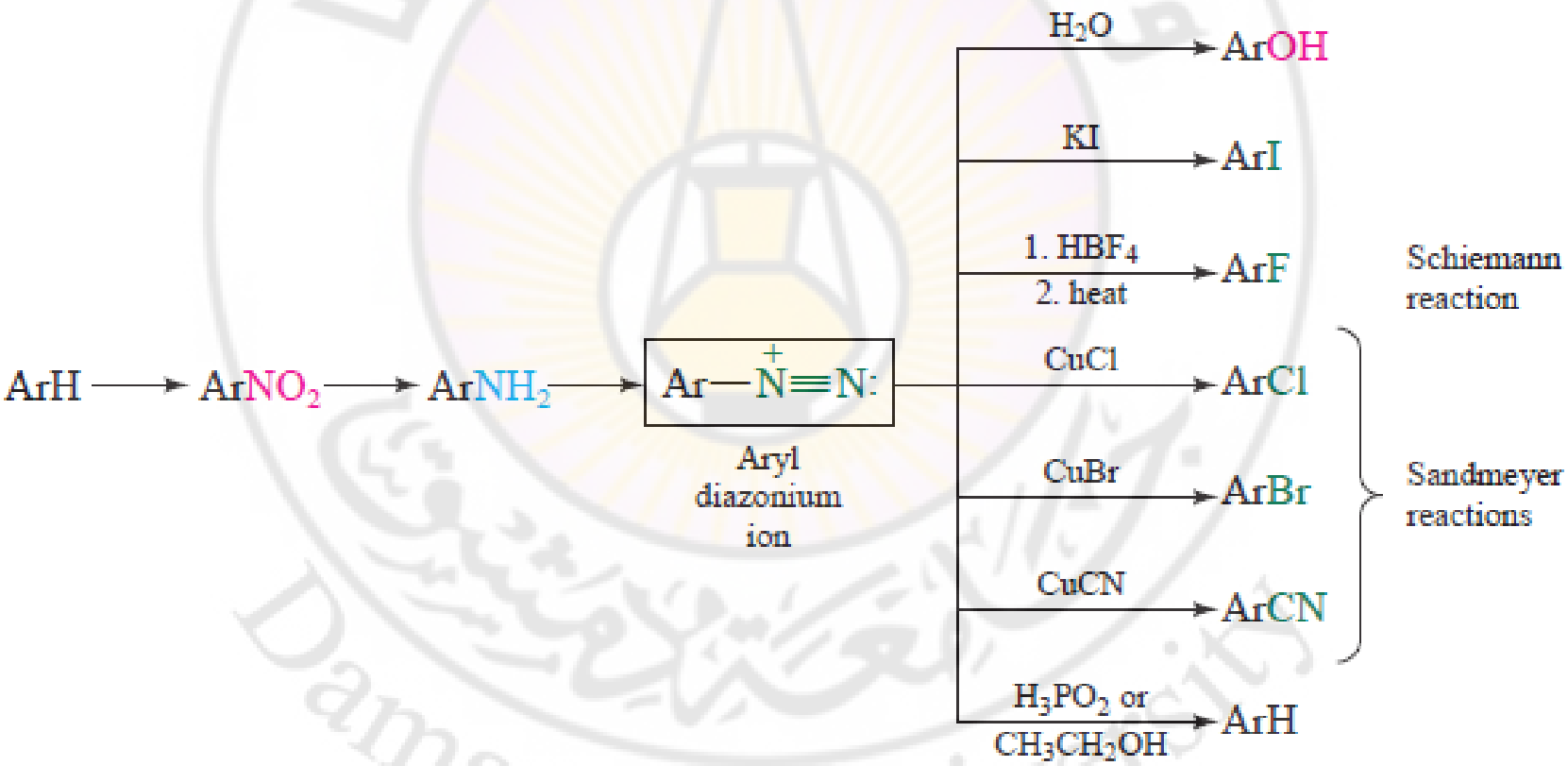
Bromodiphenhydramine synthesis



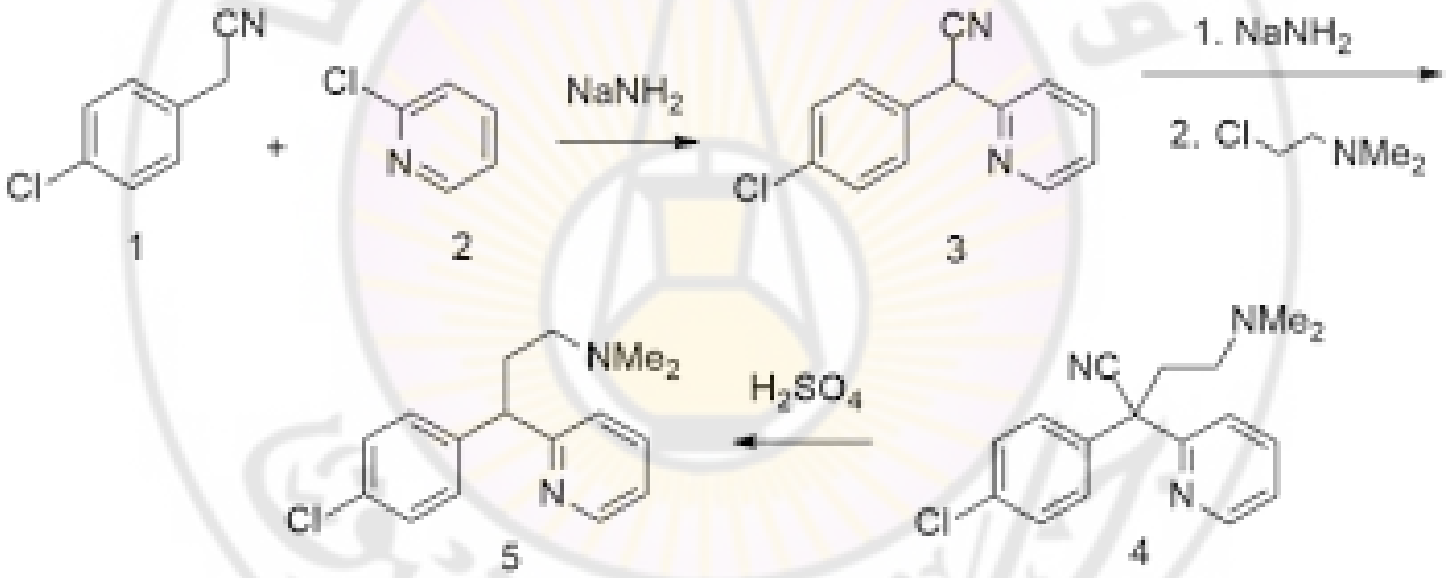
Bromodiphenhydramine synthesis



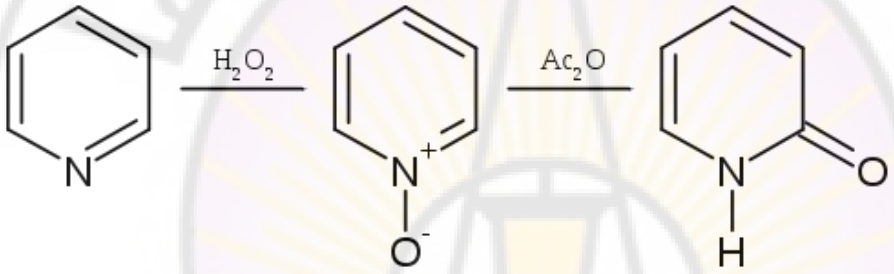

Products
H_3O^+, warm
Ar—OH
phenols
CuCl
Ar—Cl
aryl chlorides
CuBr
Ar—Br
aryl bromides
CuCN
Ar—C≡N
benzonitriles
Ar—$\overset{+}{N}$≡N—
HBF_4
Ar—F
aryl fluorides
KI
Ar—I
aryl iodides
H_3PO_2
Ar—H
(deamination)
H—Ar′
Ar—N=N—Ar′
azo dyes

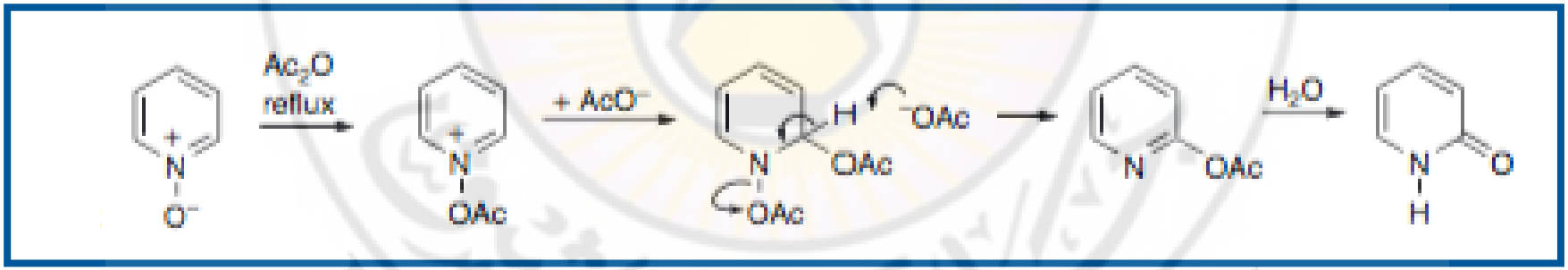

ArH
ArNO2
ArNH2
Ar—N≡N:
Aryl diazonium ion
H2O
ArOH
KI
ArI
1. HBF4
2. heat
ArF
Schiemann reaction
CuCl
ArCl
CuBr
ArBr
CuCN
ArCN
Sandmeyer reactions
H3PO2 or CH3CH2OH
ArH

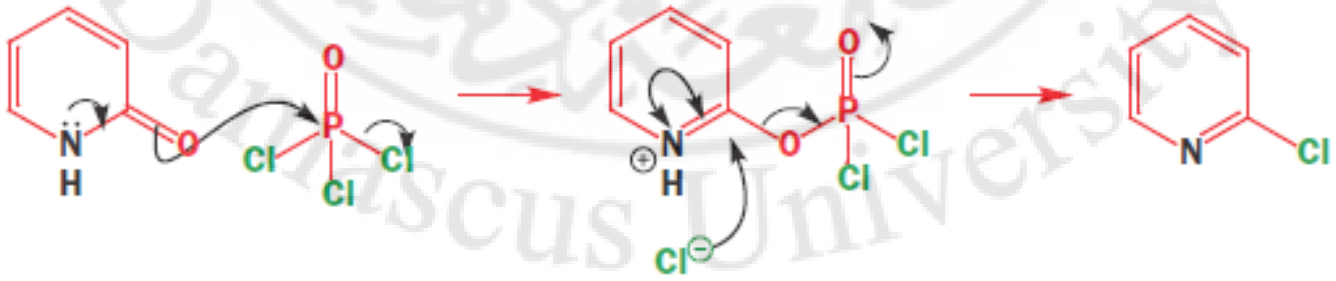
Diphenhydramine synthesis



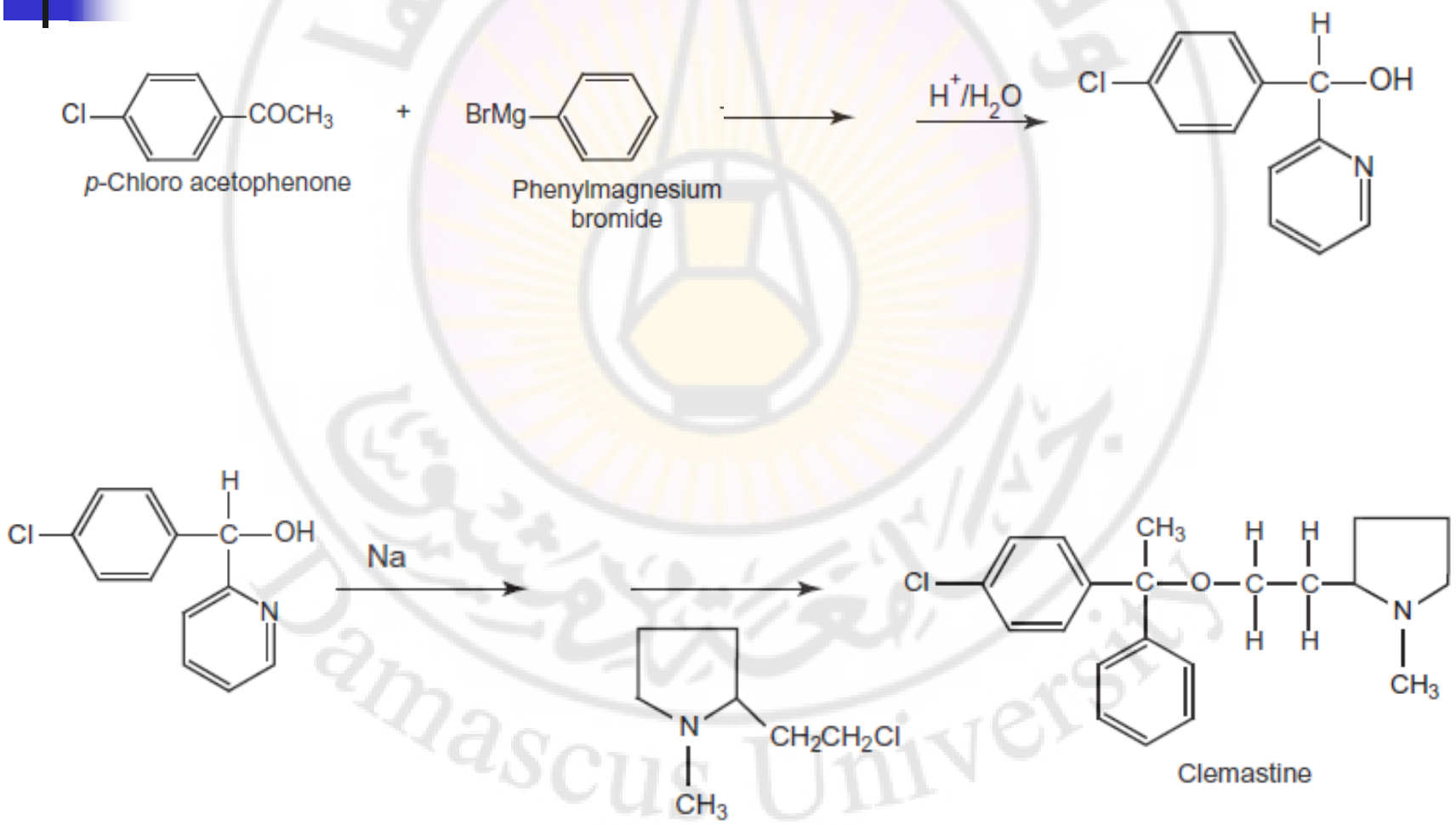
Diphenhydramine synthesis



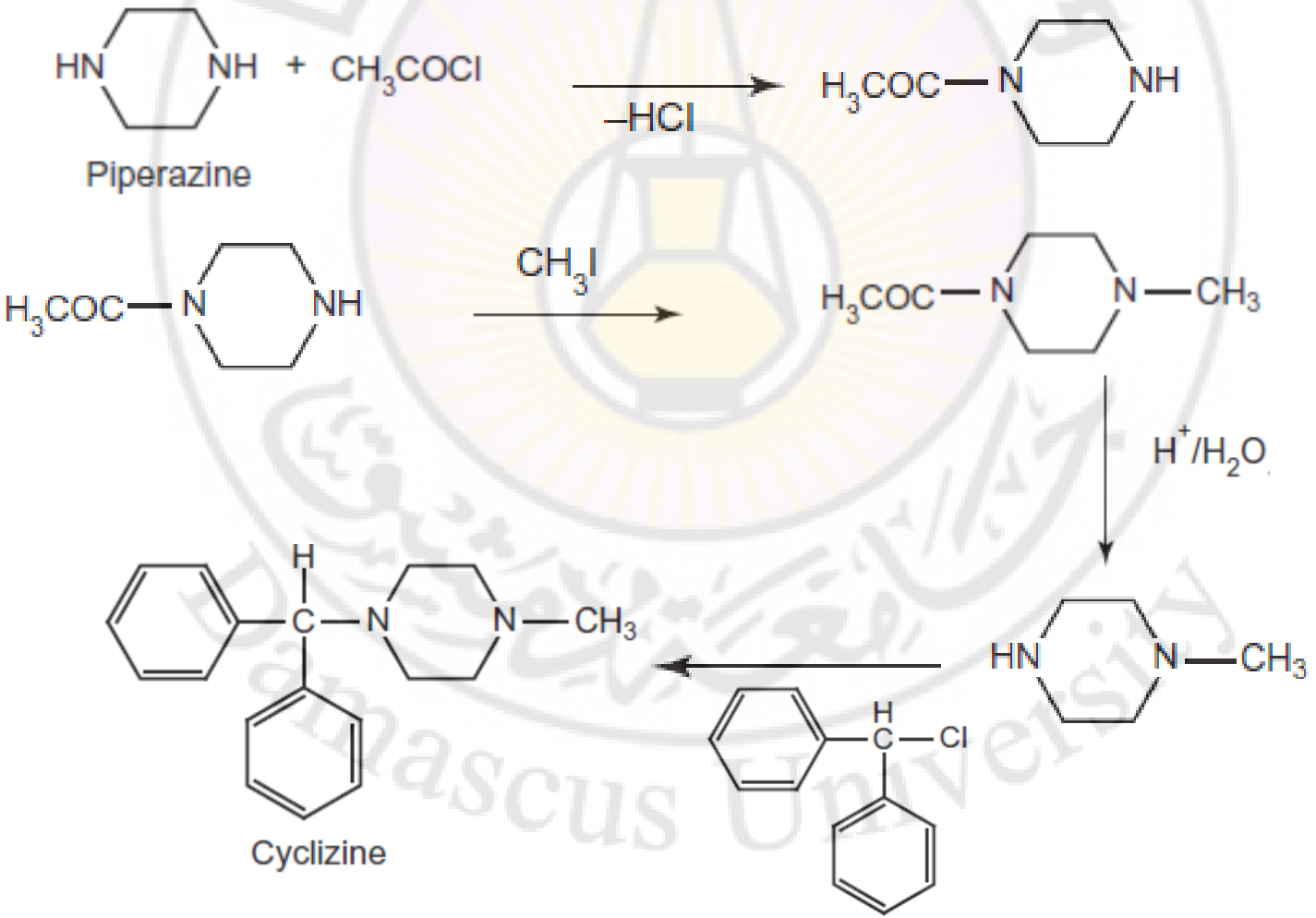




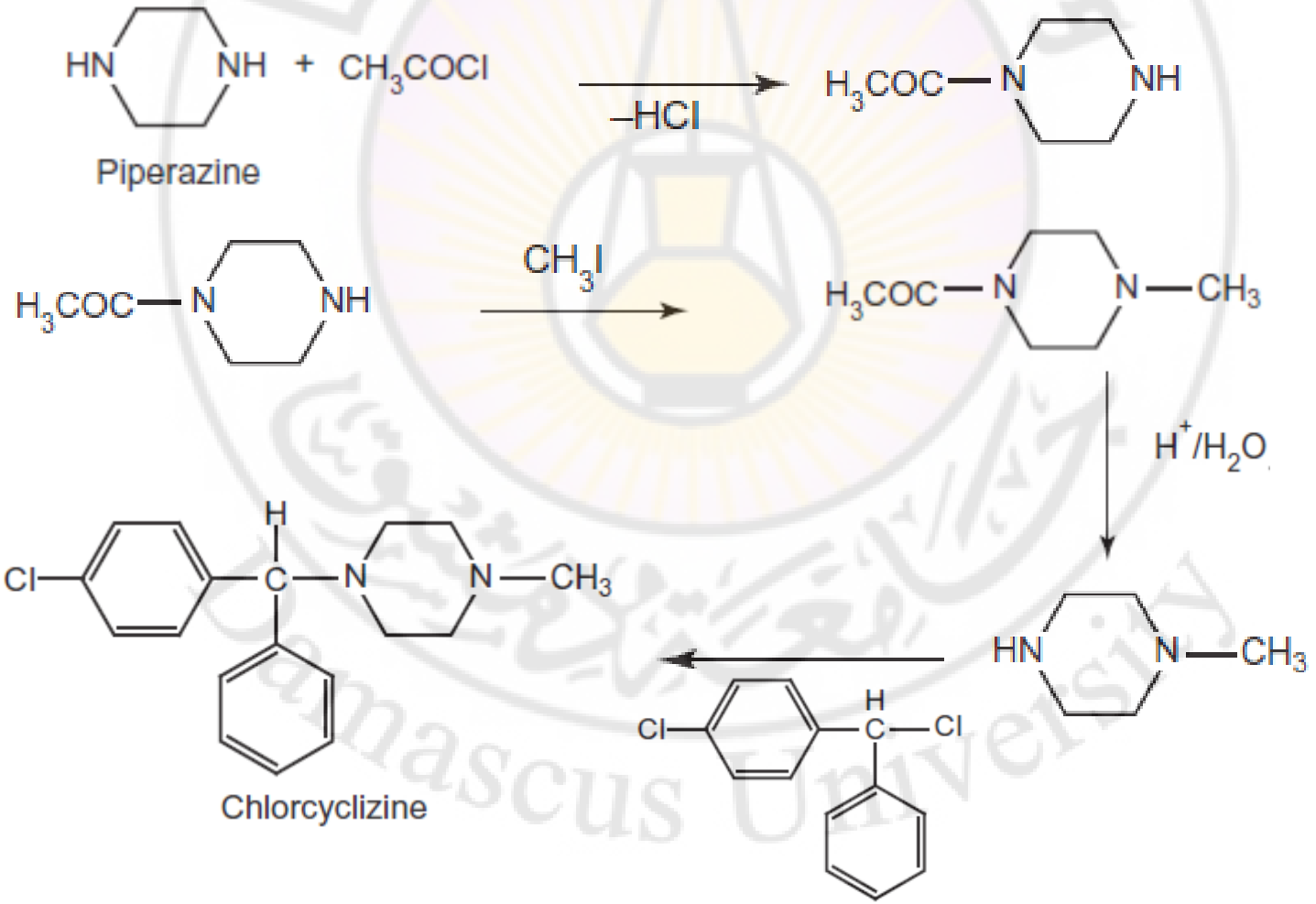
Climastine synthesis



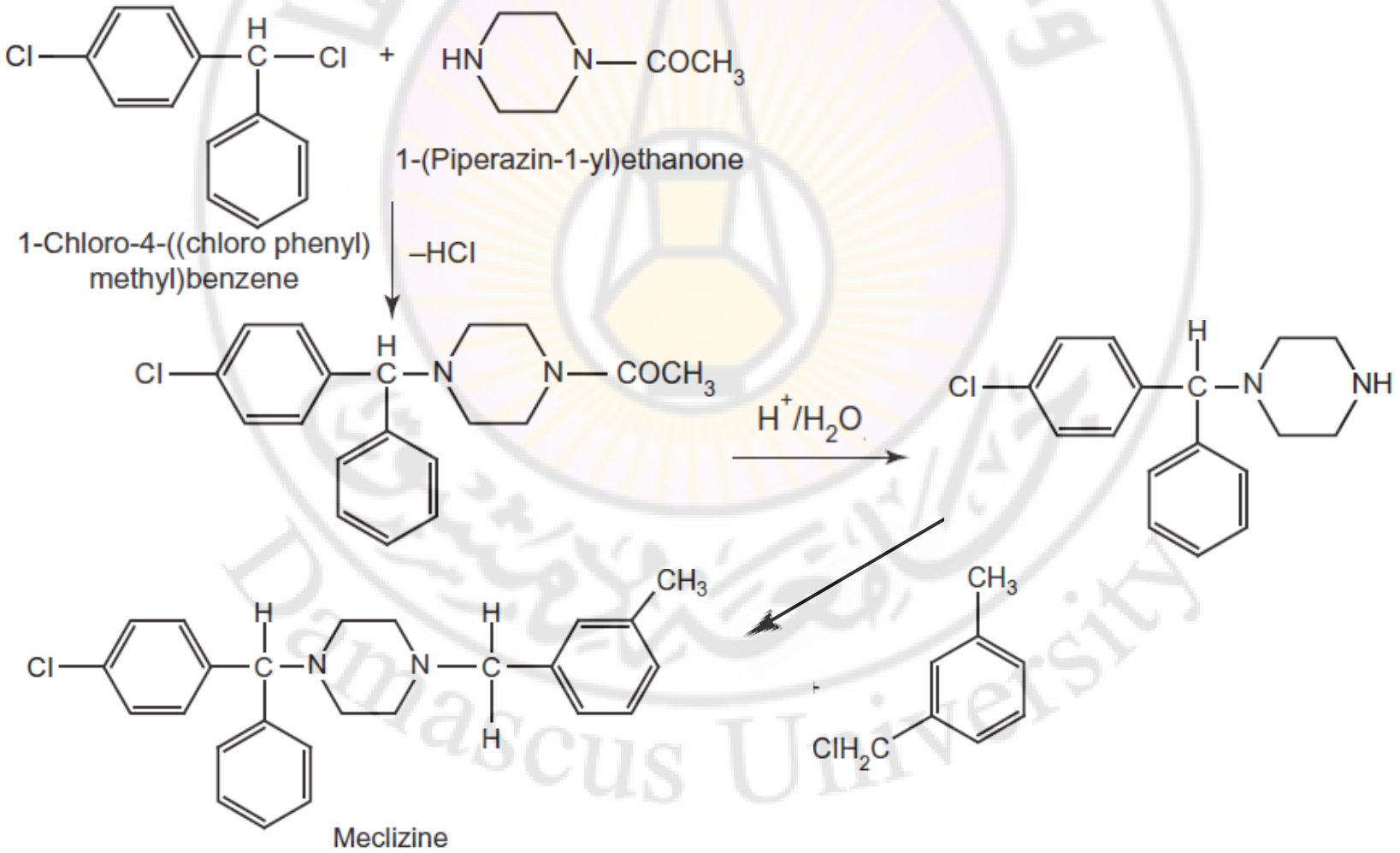
Cyclizine synthesis



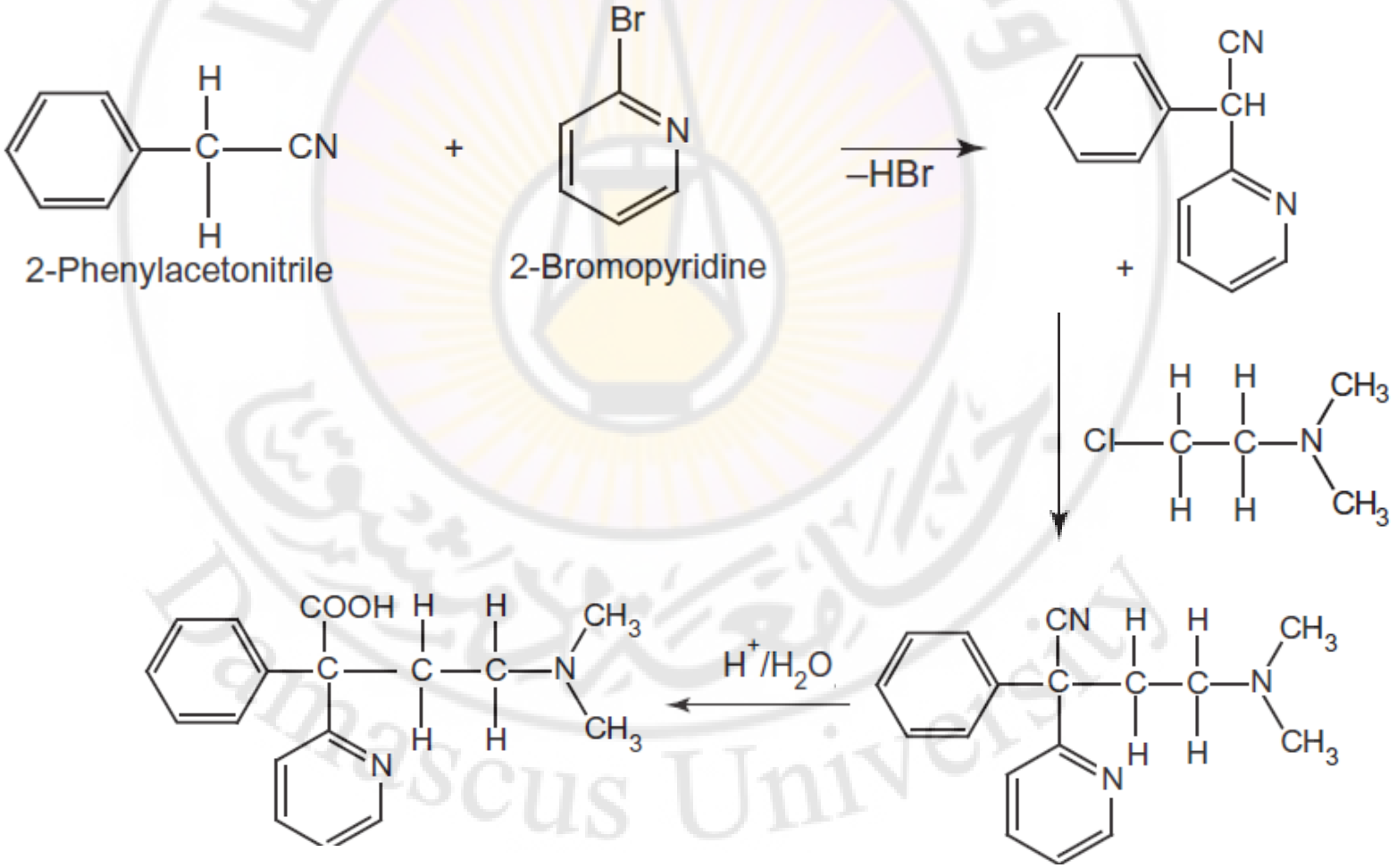
Chlorcyclizine synthesis



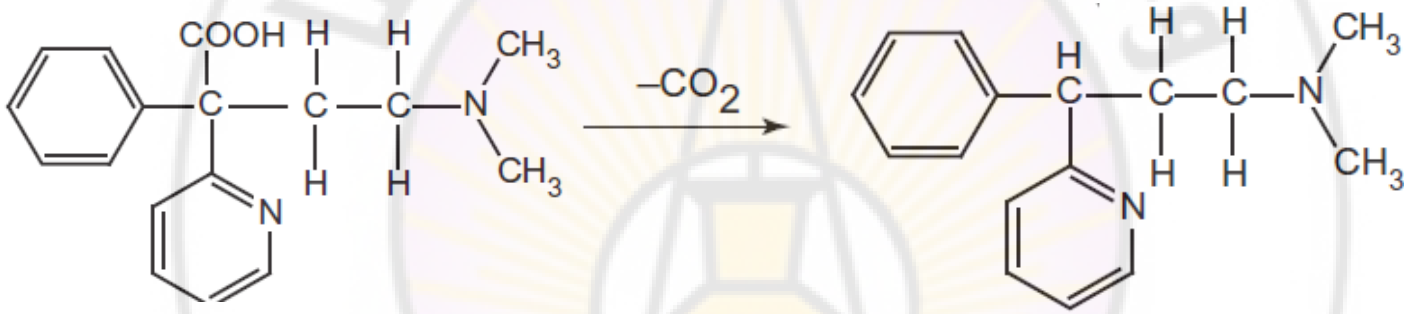
Meclizine synthesis



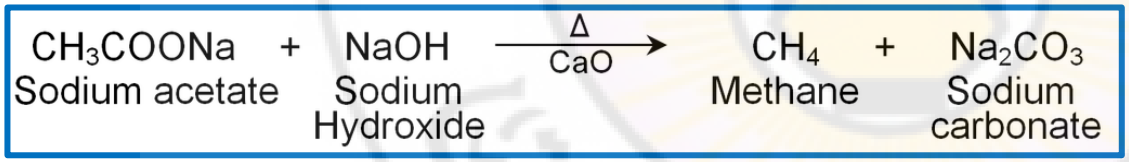
Pheniramine synthesis



Pheniramine synthesis

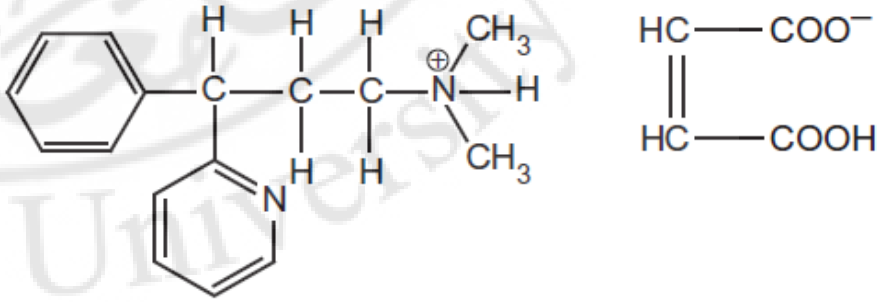


Pheniramine



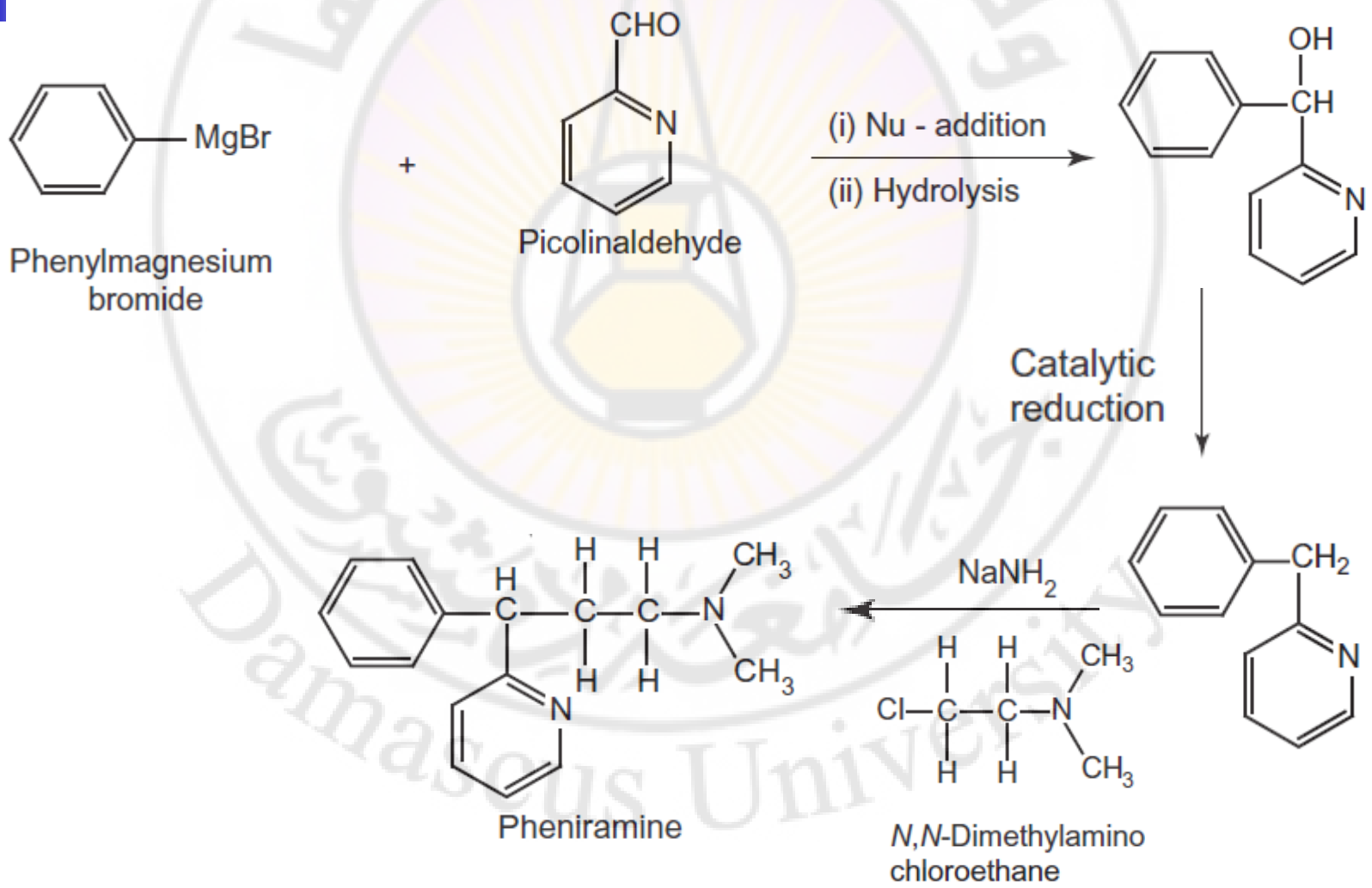
Sodalime decarboxylation

Maleic acid

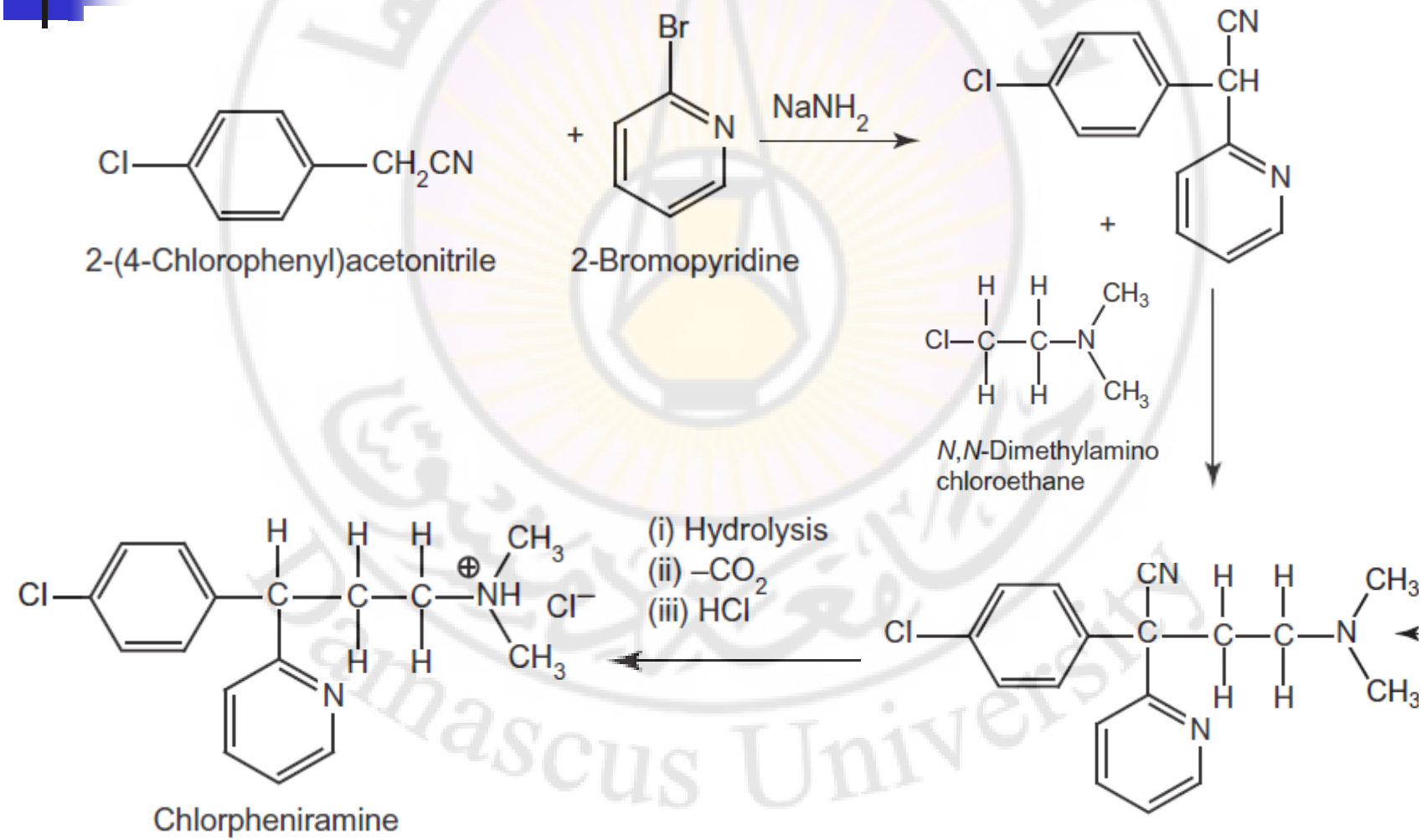


Pheniramine maleate

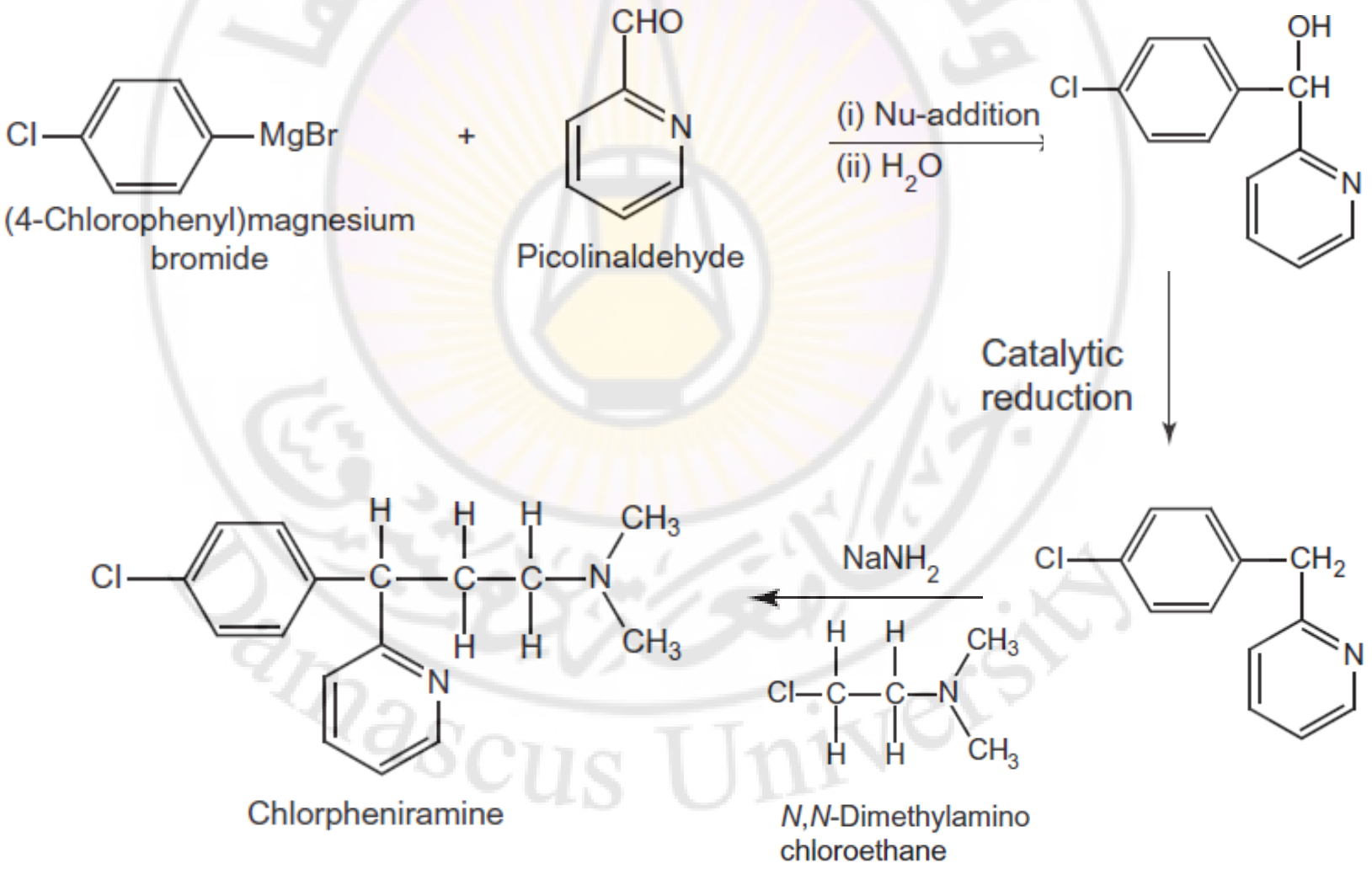
Pheniramine synthesis



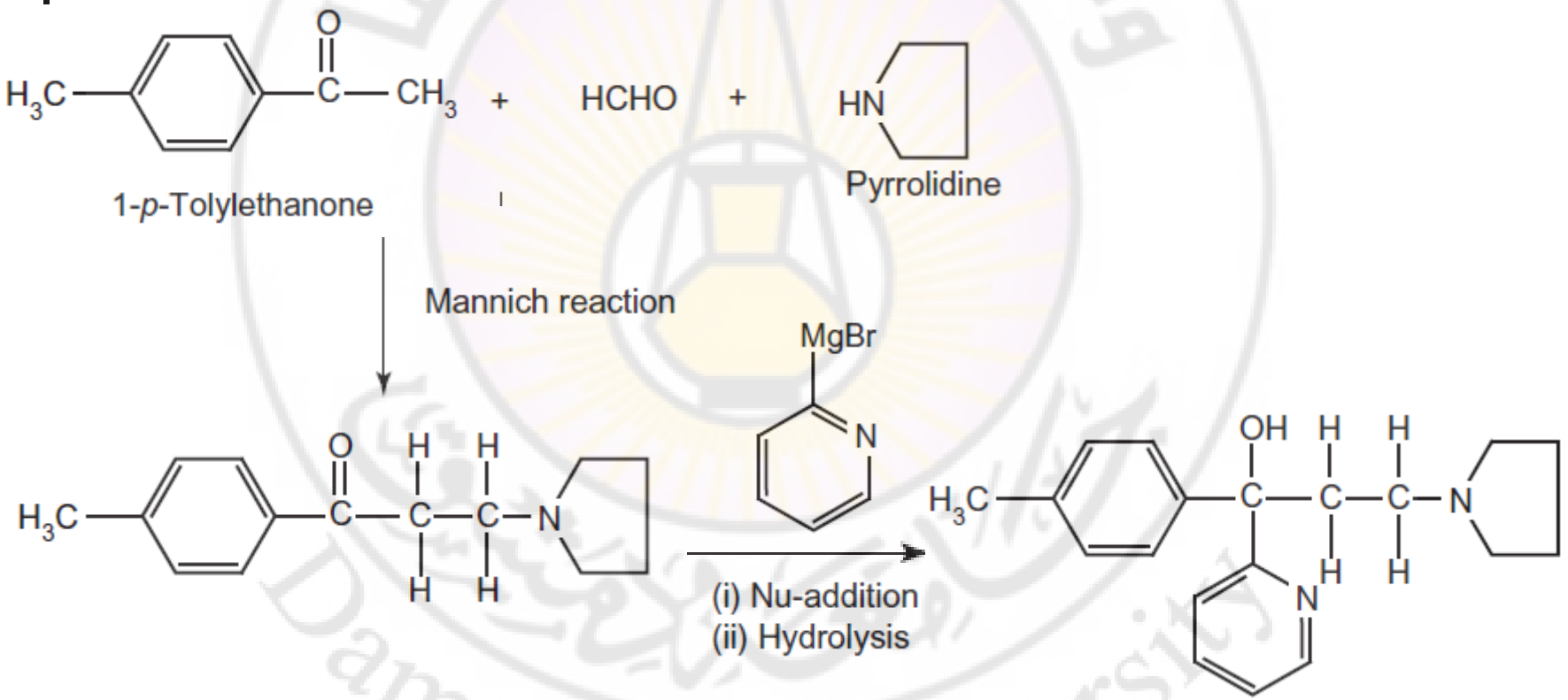
Chlorpheniramine synthesis



Chlorpheniramine synthesis



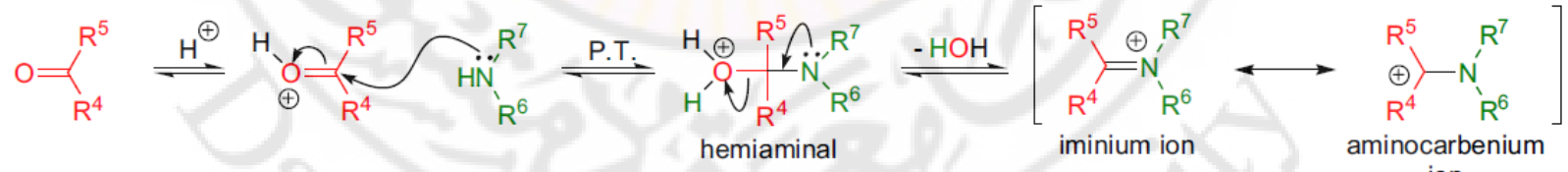
Triprolidine synthesis



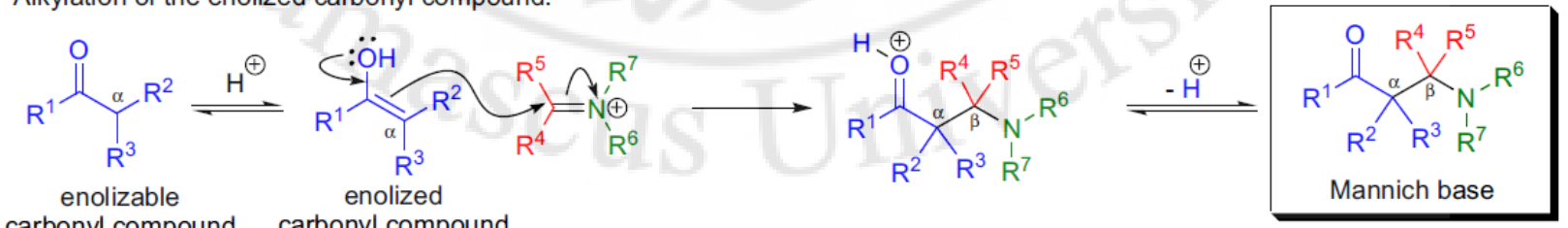
Mannich reaction

Under acidic conditions the first step is the reaction of the amine component with the protonated non-enolizable carbonyl compound to give a hemiaminal, which after proton transfer loses a molecule of water to give the electrophilic iminium ion. This iminium ion then reacts with the enolized carbonyl compound (nucleophile) at its α-carbon in an aldol-type reaction to give rise to the Mannich base.

Formation of the reactive iminium ion under acidic conditions:

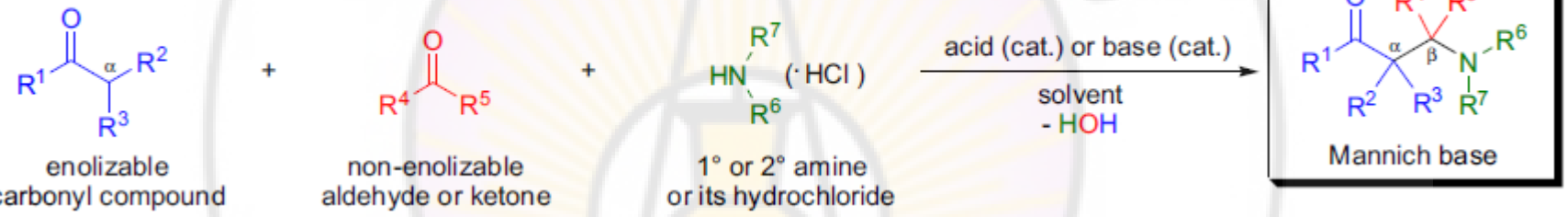


Alkylation of the enolized carbonyl compound:

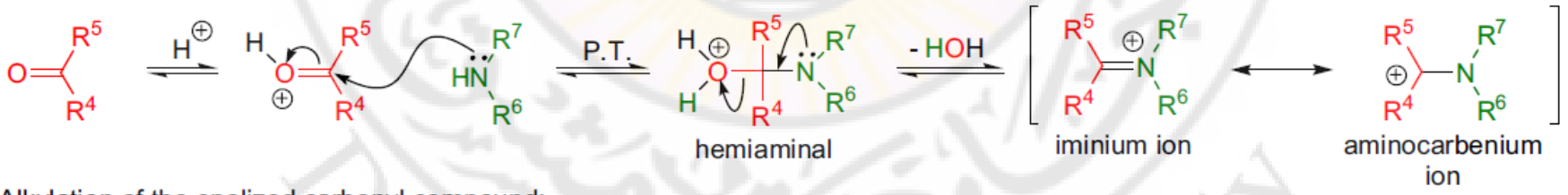


Mannich reaction

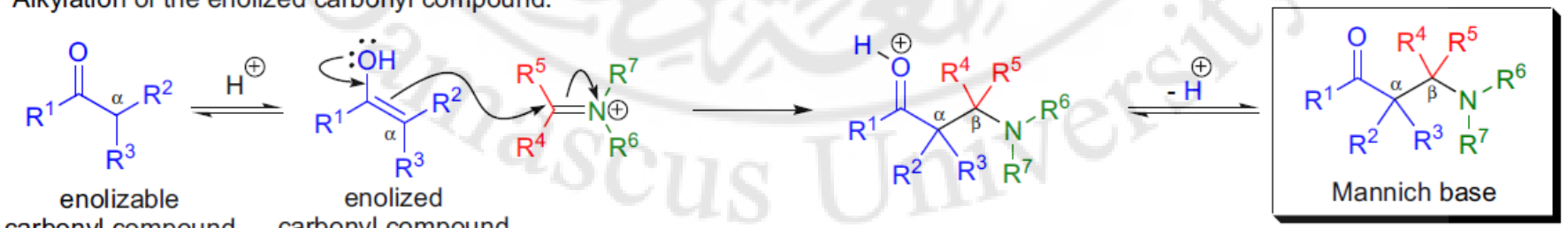
Mannich reaction:



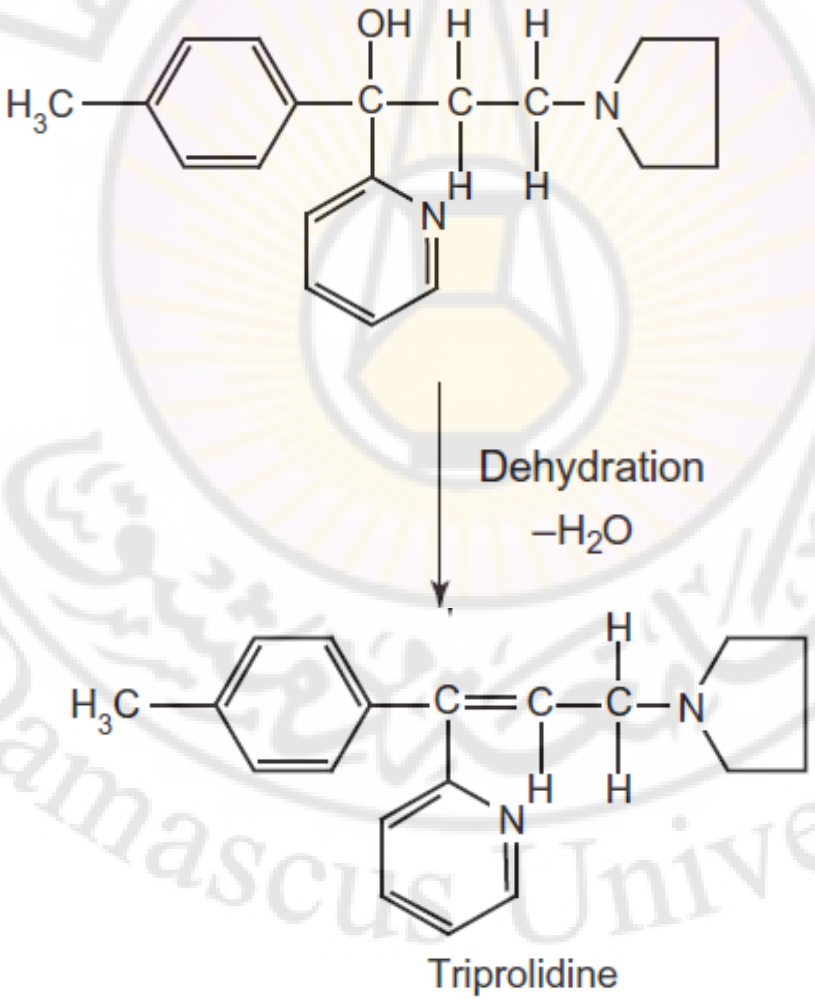
Formation of the reactive iminium ion under acidic conditions:



Alkylation of the enolized carbonyl compound:



Triprolidine synthesis

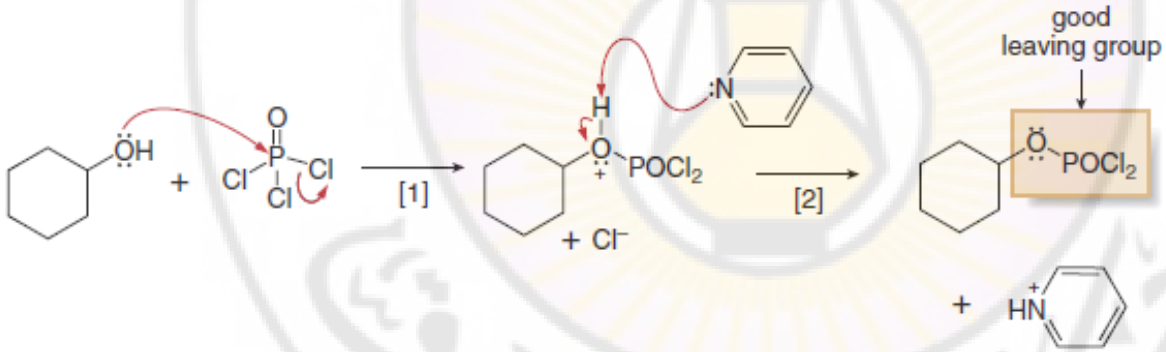


Triprolidine

Alcohol Dehydration

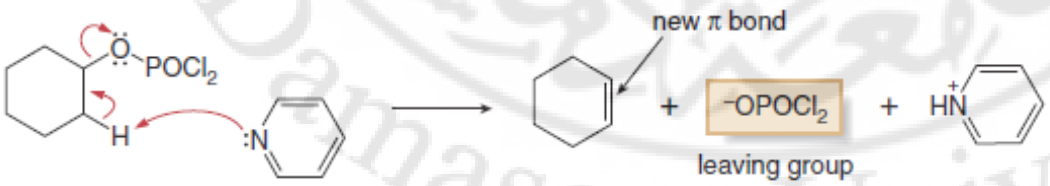
Mechanism 9.4 Dehydration Using $POCl_3$ + Pyridine—An E2 Mechanism

Steps [1] and [2] Conversion of OH to a good leaving group



- A two-step process converts an OH group into $OPOCl_2$, **a good leaving group:** reaction of the OH group with $POCl_3$ followed by removal of a proton.

Step [3] The C–H and C–O bonds are broken and the π bond is formed.

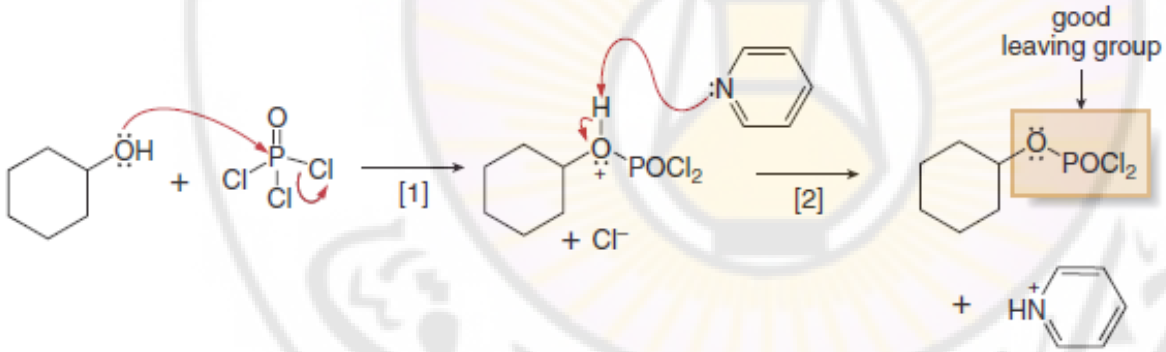


- **Two bonds are broken and two bonds are formed in a single step:** the base (pyridine) removes a proton from the β carbon; the electron pair in the β C–H bond forms the new π bond; the leaving group ($^-OPOCl_2$) comes off with the electron pair from the C–O bond.

Alcohol Dehydration

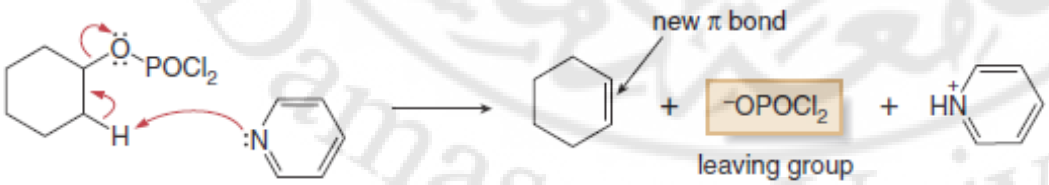
Mechanism 9.4 Dehydration Using $POCl_3$ + Pyridine—An E2 Mechanism

Steps [1] and [2] Conversion of OH to a good leaving group



- A two-step process converts an OH group into $OPOCl_2$, **a good leaving group:** reaction of the OH group with $POCl_3$ followed by removal of a proton.

Step [3] The C–H and C–O bonds are broken and the π bond is formed.

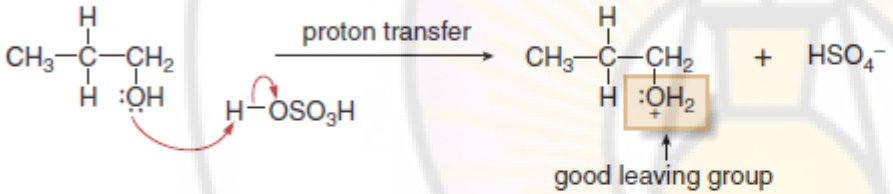


- **Two bonds are broken and two bonds are formed in a single step:** the base (pyridine) removes a proton from the β carbon; the electron pair in the β C–H bond forms the new π bond; the leaving group ($^-OPOCl_2$) comes off with the electron pair from the C–O bond.

Alcohol Dehydration

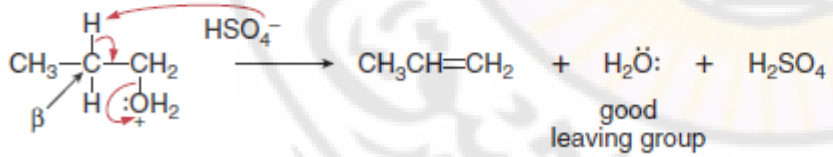
Mechanism 9.2 Dehydration of a 1° ROH—An E2 Mechanism

Step [1] The O atom is protonated.



- **Protonation of the oxygen atom** of the alcohol converts a poor leaving group (^-OH) into a good leaving group (H_2O).

Step [2] The C – H and C – O bonds are broken and the π bond is formed.

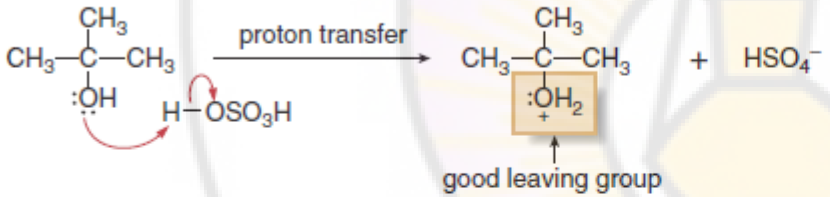


- **Two bonds are broken and two bonds are formed in a single step:** the base (HSO_4^- or H_2O) removes a proton from the β carbon; the electron pair in the β C – H bond forms the new π bond; the leaving group (H_2O) comes off with the electron pair in the C – O bond.

Alcohol Dehydration

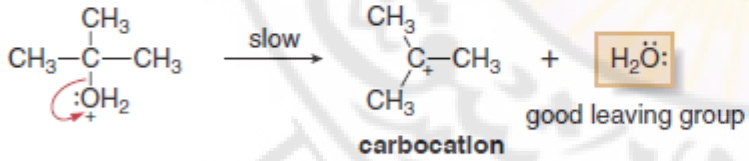
Mechanism 9.1 Dehydration of 2° and 3° ROH—An E1 Mechanism

Step [1] The O atom is protonated.



- **Protonation of the oxygen atom** of the alcohol converts a poor leaving group (^{-}OH) into a good leaving group (H_2O).

Step [2] The C – O bond is broken.

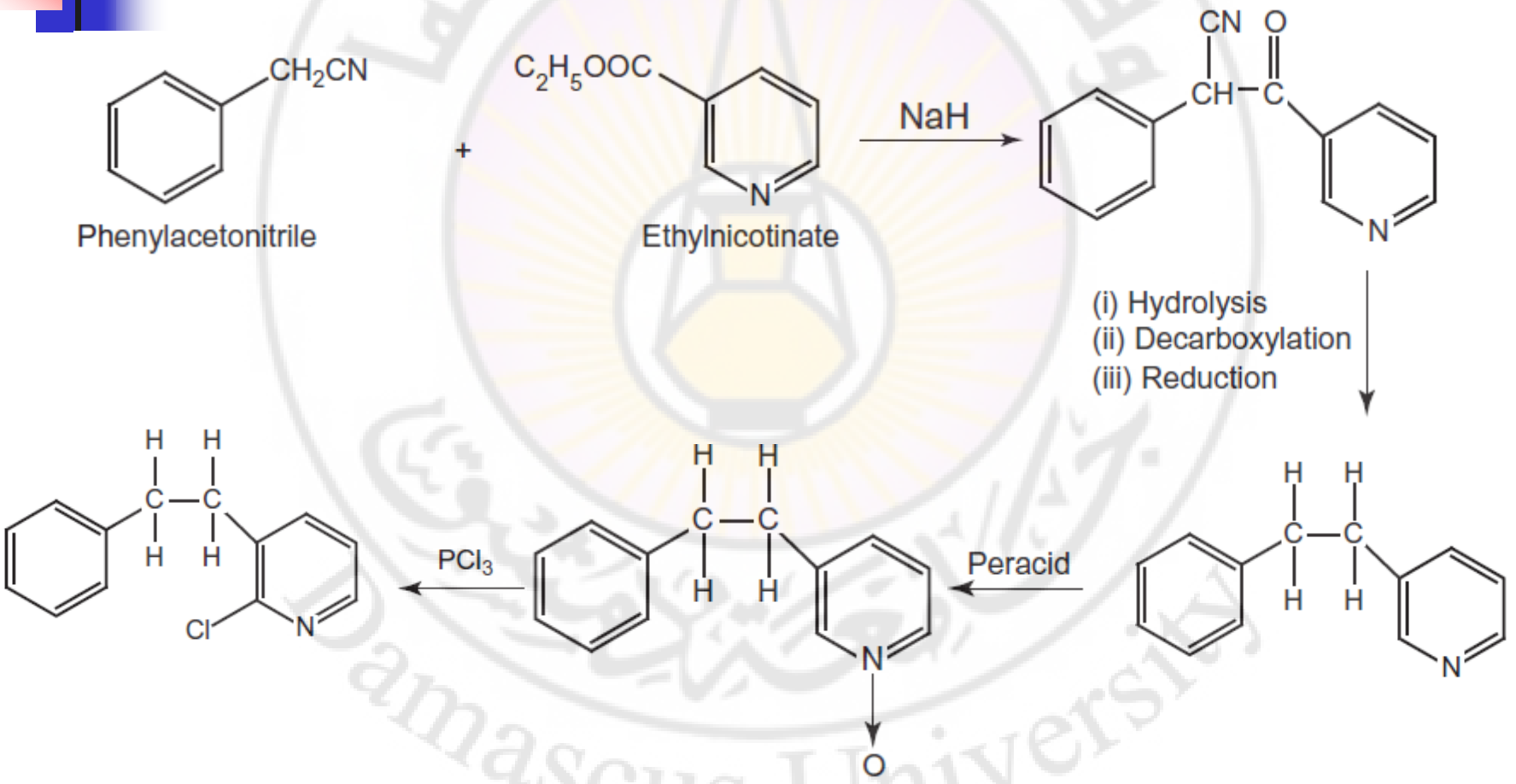


- **Heterolysis of the C – O bond forms a carbocation.** This step is rate-determining because it involves only bond cleavage.

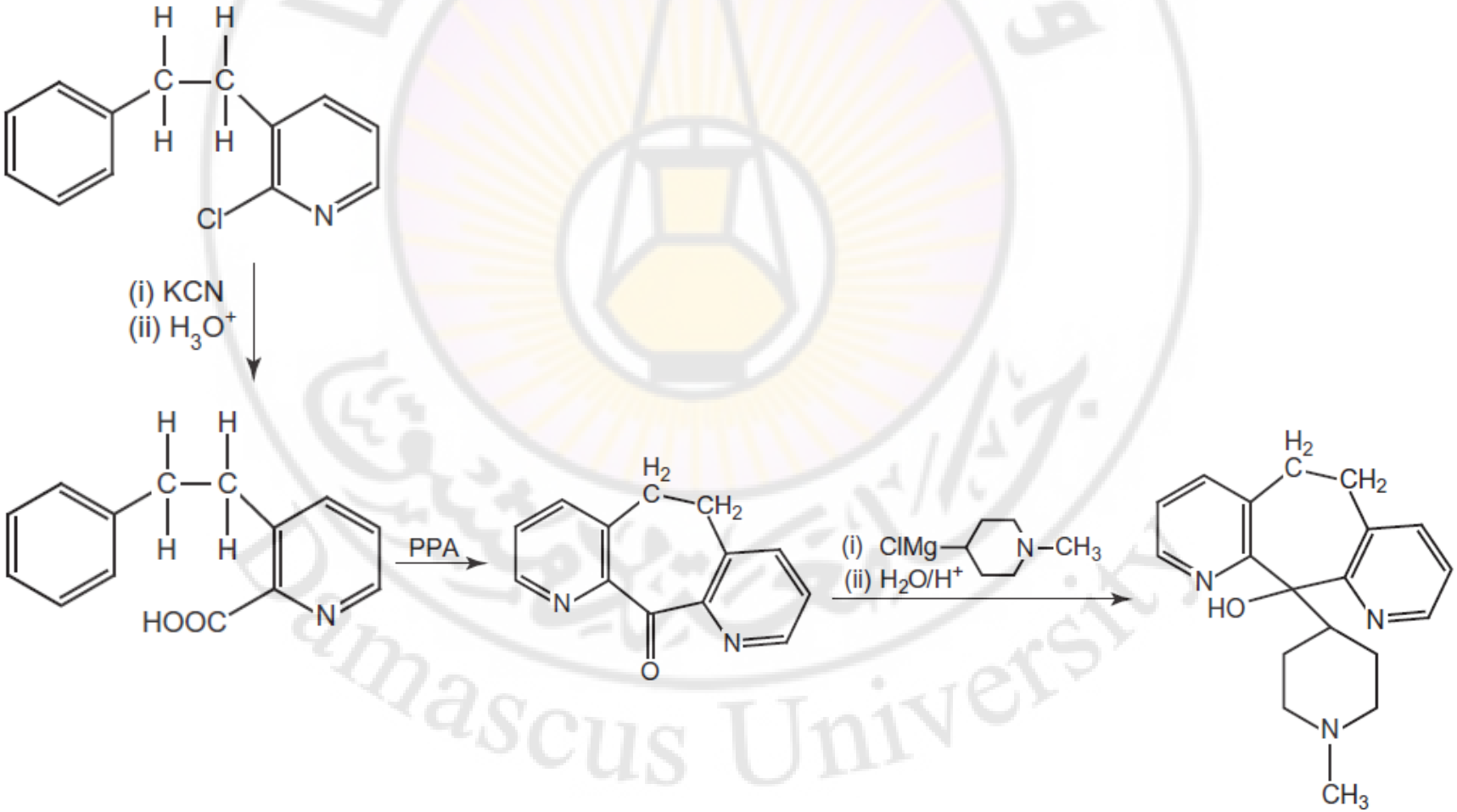
Step [3] A C – H bond is cleaved and the π bond is formed.

- **A base (such as HSO_4^- or H_2O) removes a proton** from a carbon adjacent to the carbocation (a β carbon). The electron pair in the C – H bond is used to form the new π bond.

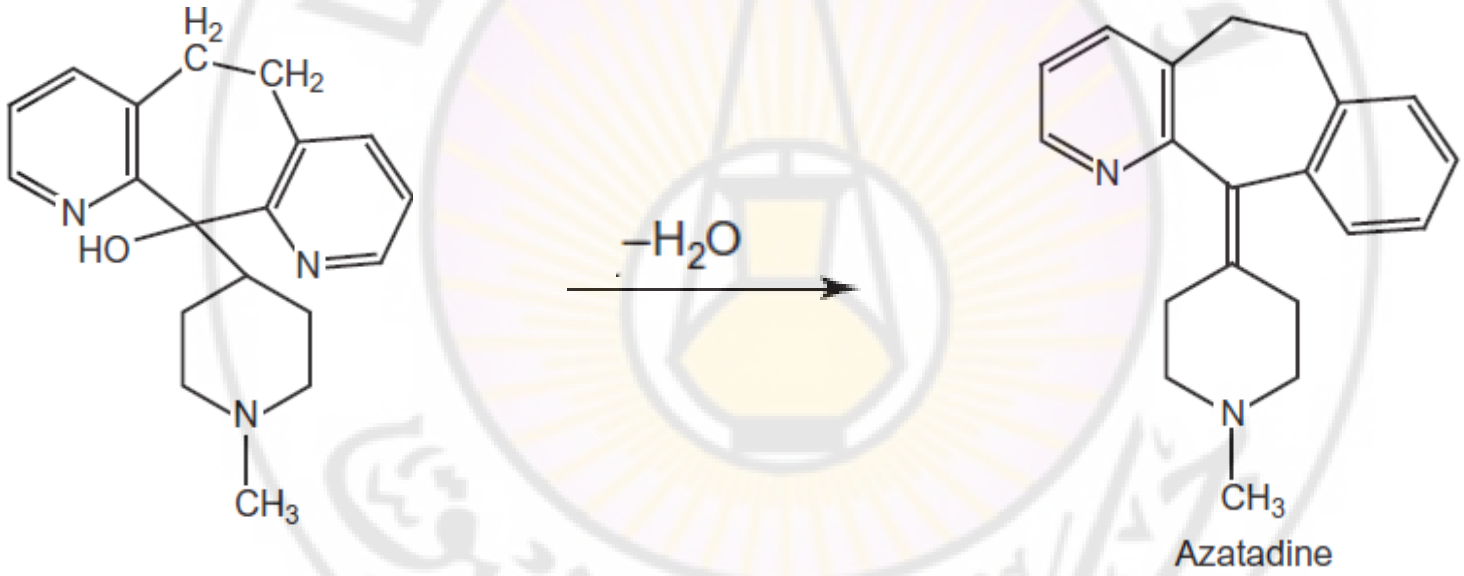
Azatidine synthesis



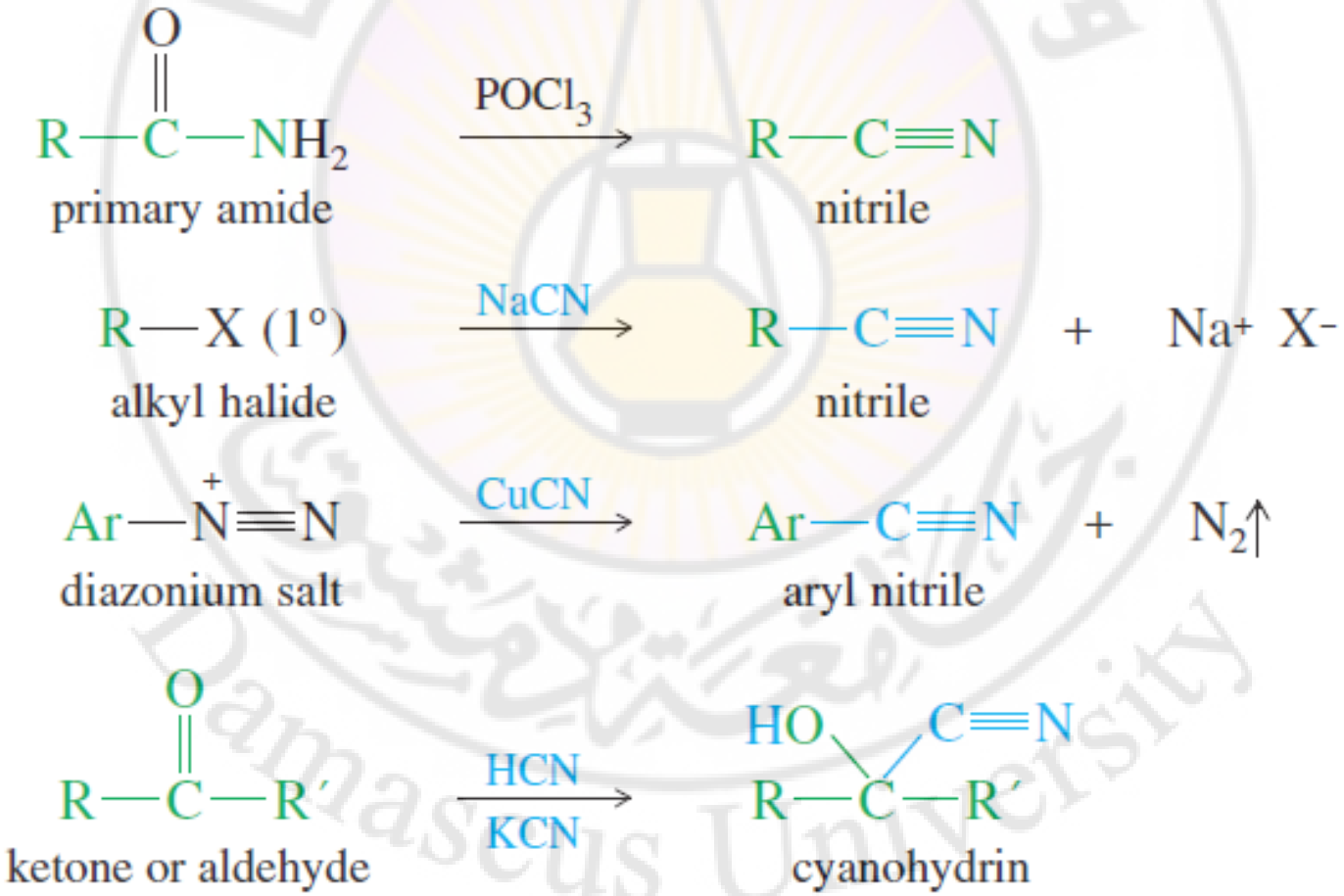
Azatidine synthesis



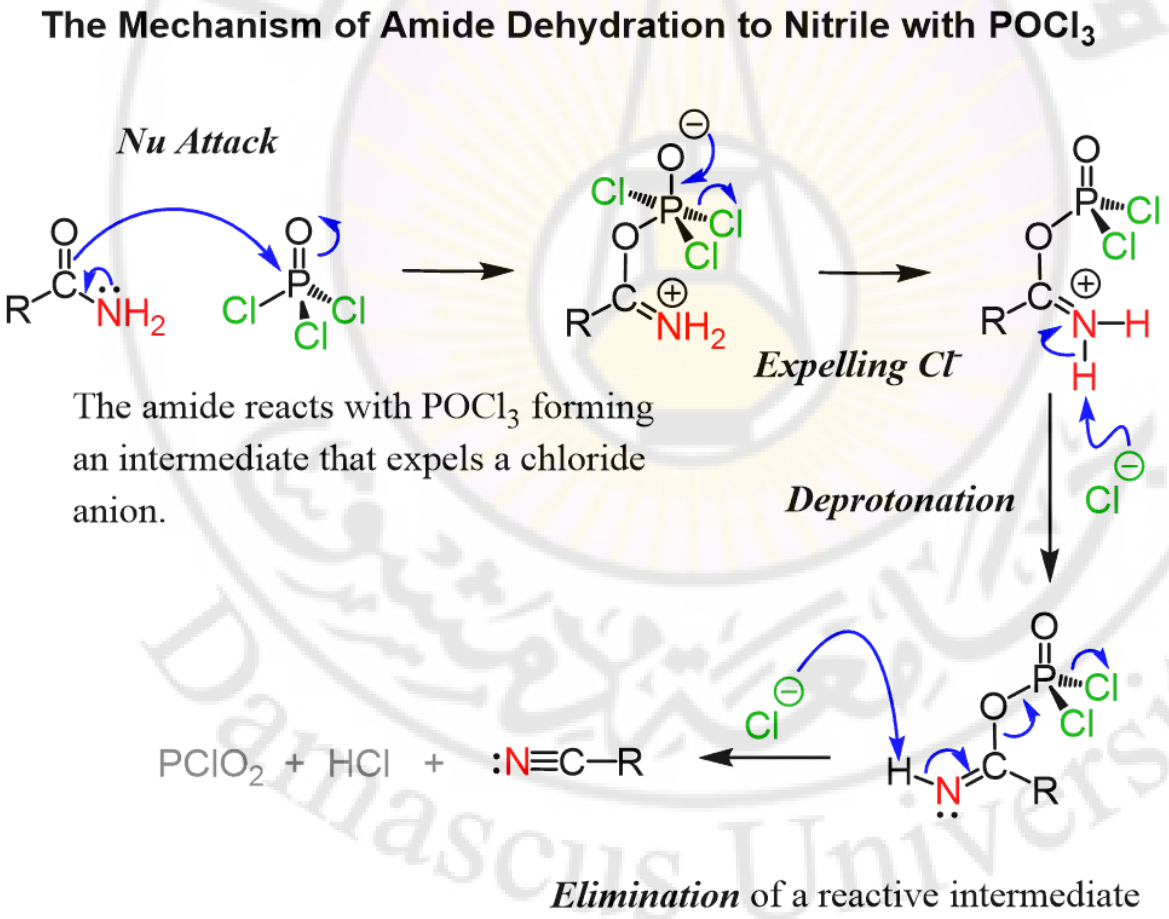
Azatidine( ) synthesis



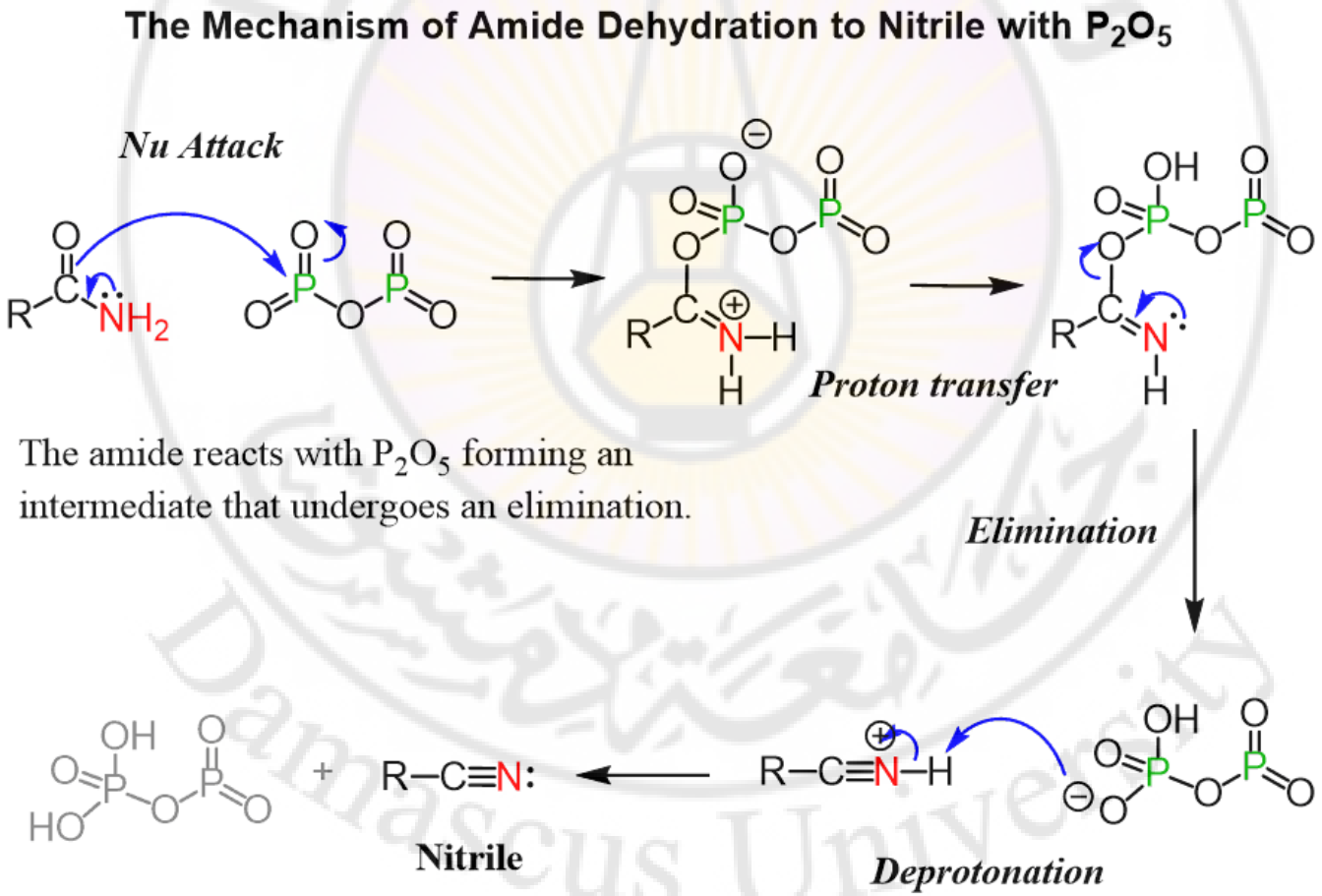
Nitrile synthesis



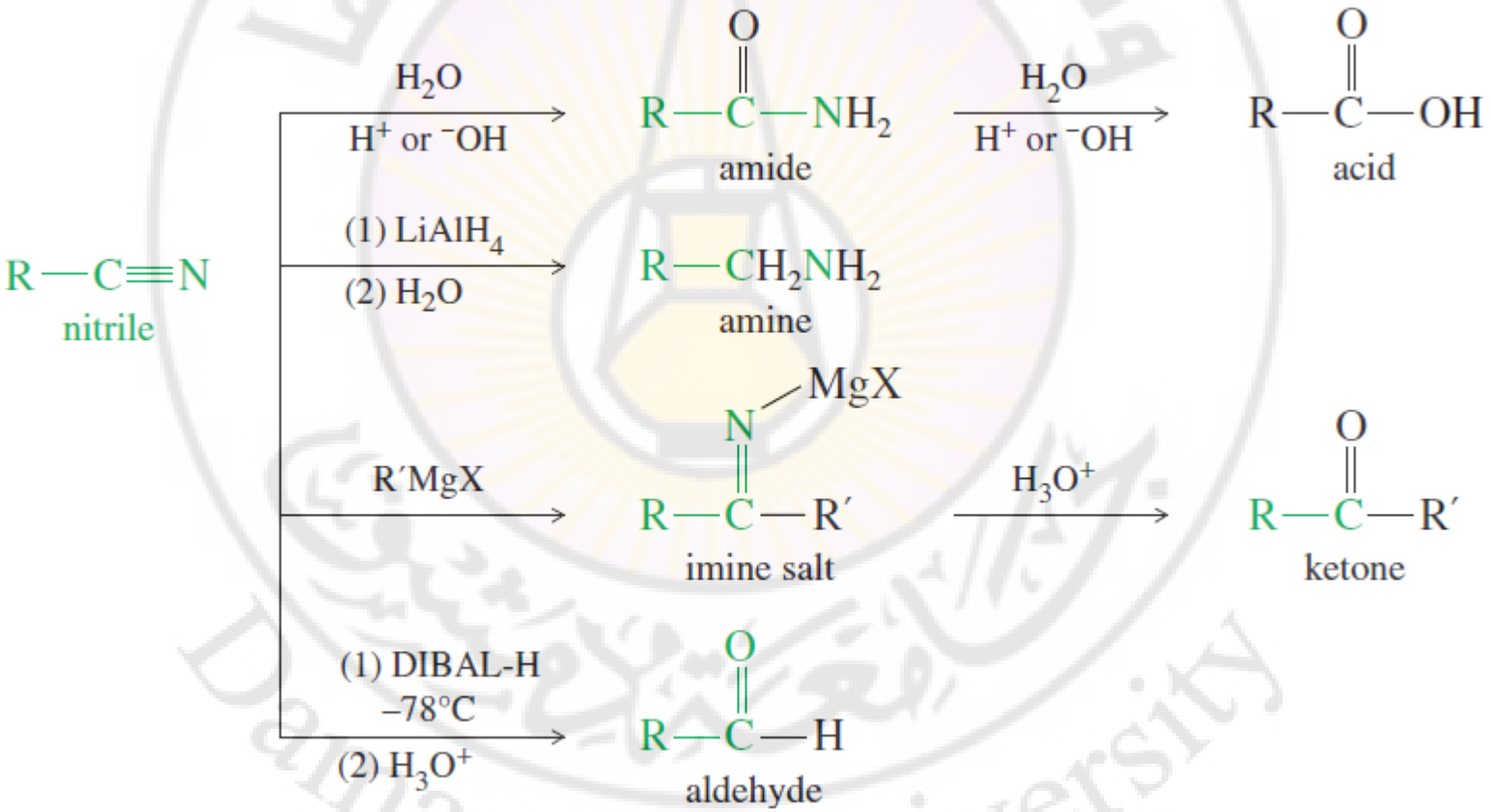
Nitrile synthesis



Nitrile synthesis



Nitrile reaction



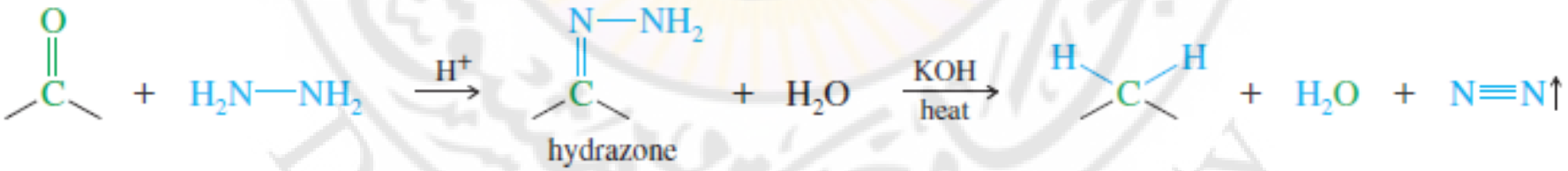
Clemmensen reduction

17-11B The Clemmensen Reduction: Synthesis of Alkylbenzenes

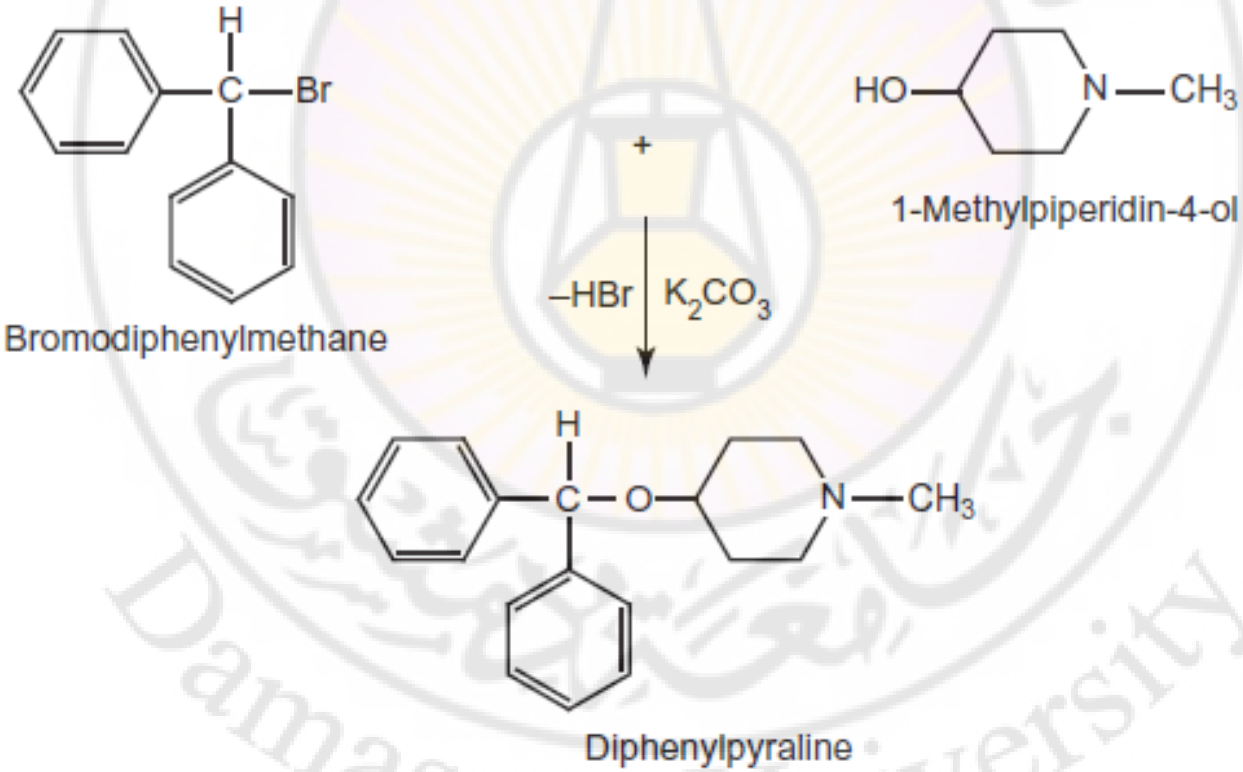
How do we synthesize alkylbenzenes that cannot be made by Friedel–Crafts alkylation? We use the Friedel–Crafts acylation to make the acylbenzene, then we reduce the acylbenzene to the alkylbenzene using the **Clemmensen reduction:** treatment with aqueous HCl and amalgamated zinc (zinc treated with mercury salts).

Wollf-Kishner reduction

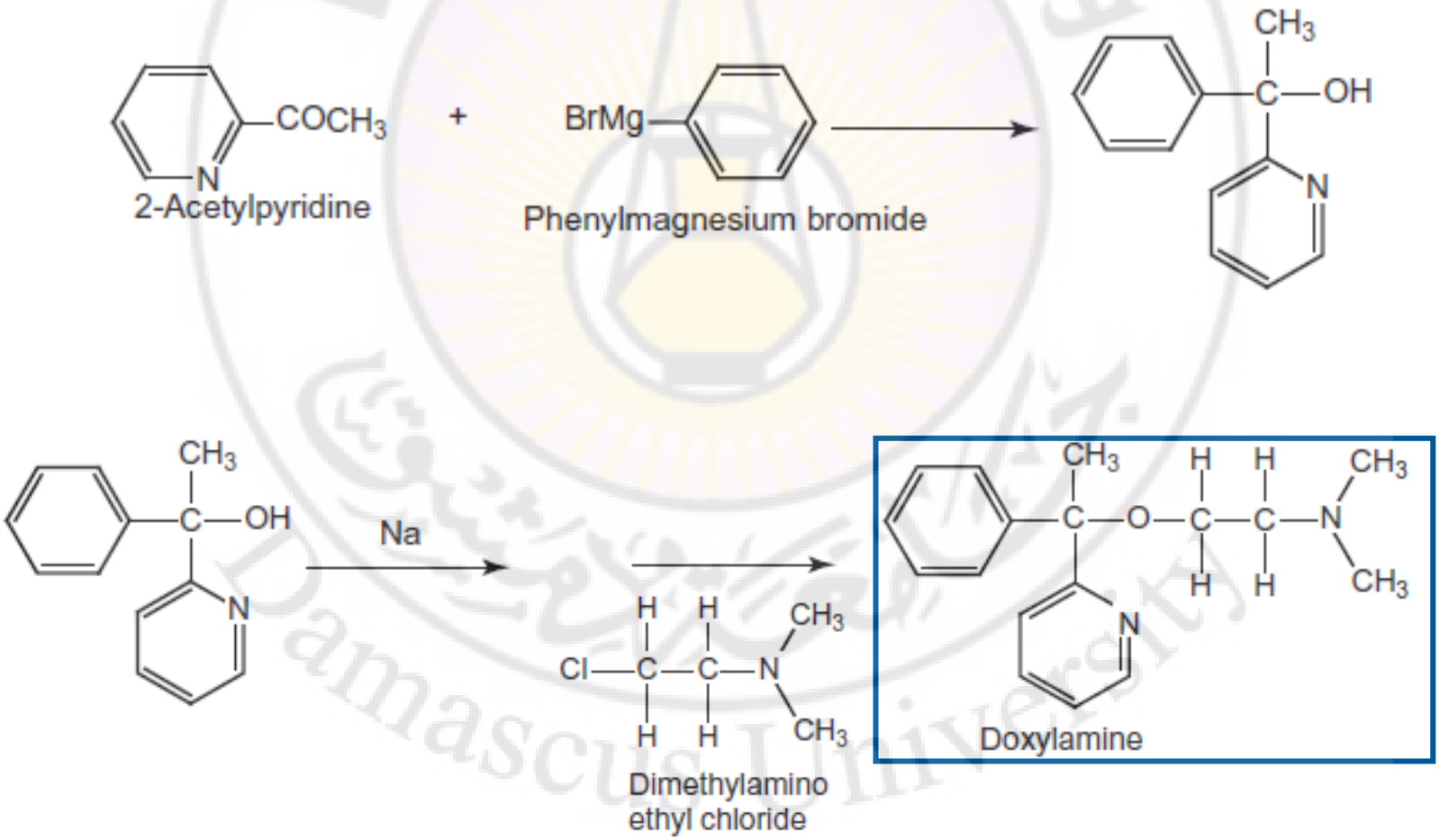
Wolff–Kishner Reduction Compounds that cannot survive treatment with hot acid can be deoxygenated using the **Wolff–Kishner reduction.** The ketone or aldehyde is converted to its hydrazone, which is heated with a strong base such as KOH or potassium *tert*-butoxide. Ethylene glycol, diethylene glycol, or another high-boiling solvent is used to facilitate the high temperature (140–200 °C) needed in the second step.



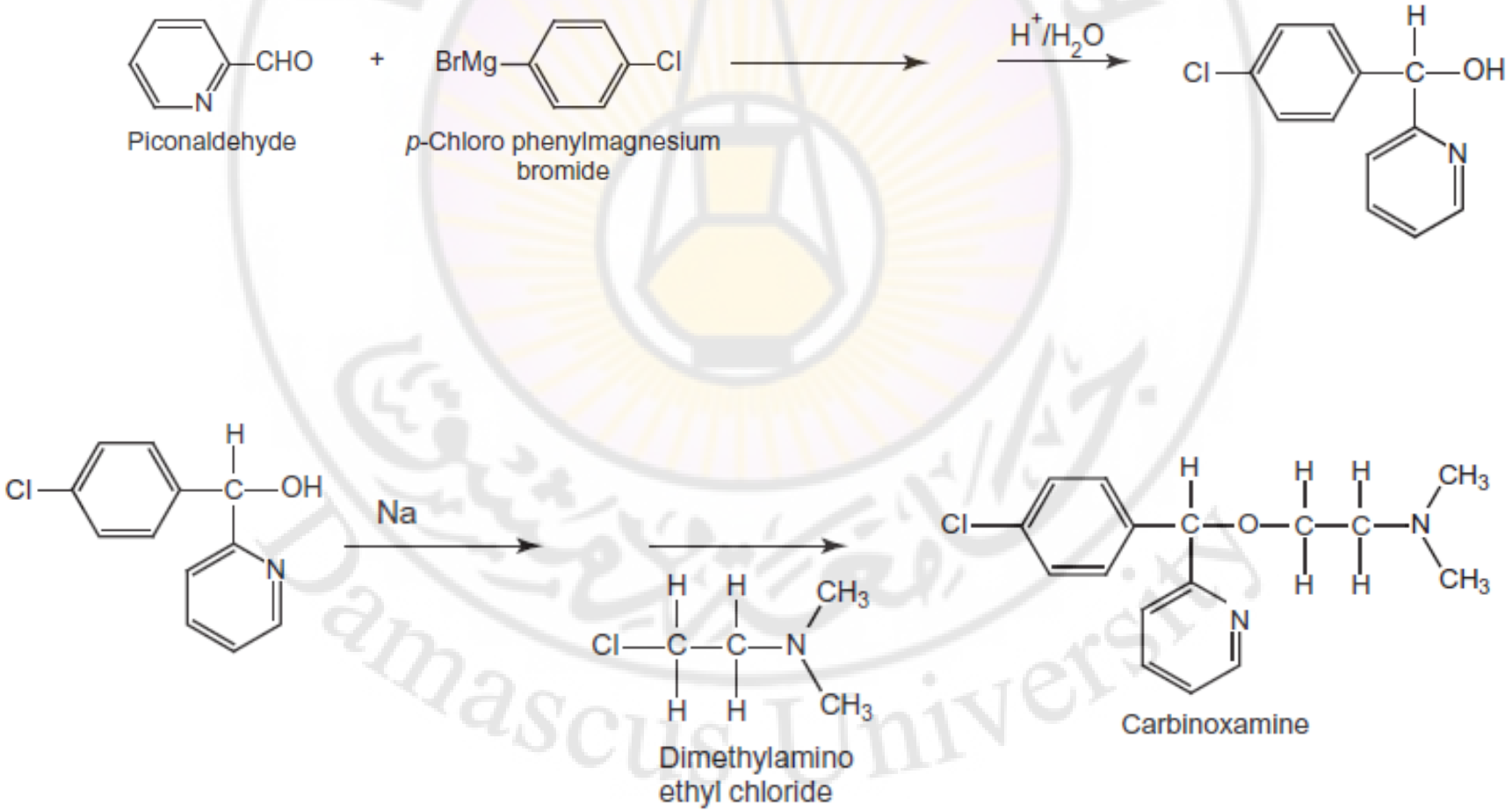
Diphenhylpyraline ( ) synthesis



Doxylamine synthesis

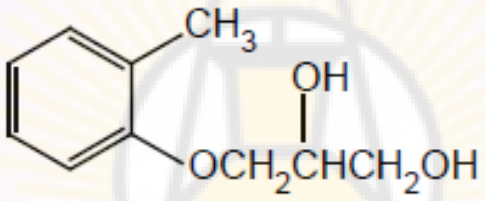


Carbinoxamine synthesis

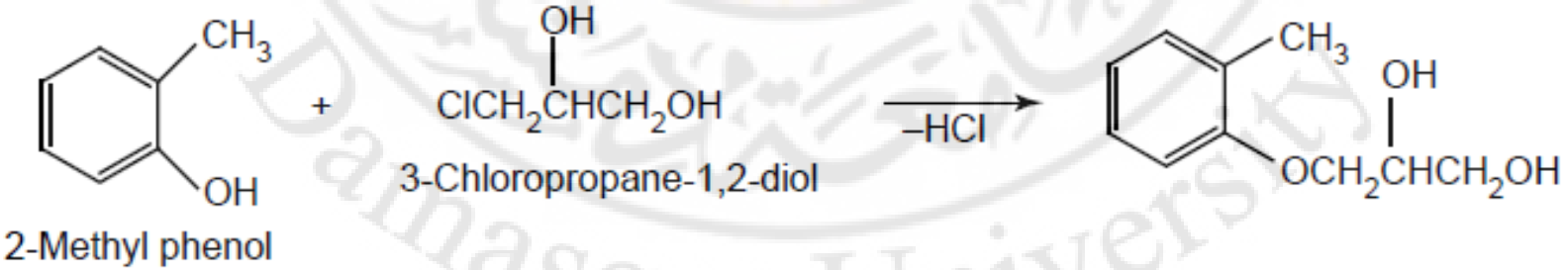


Drug Synthesis of Skeletal Muscle Relaxants

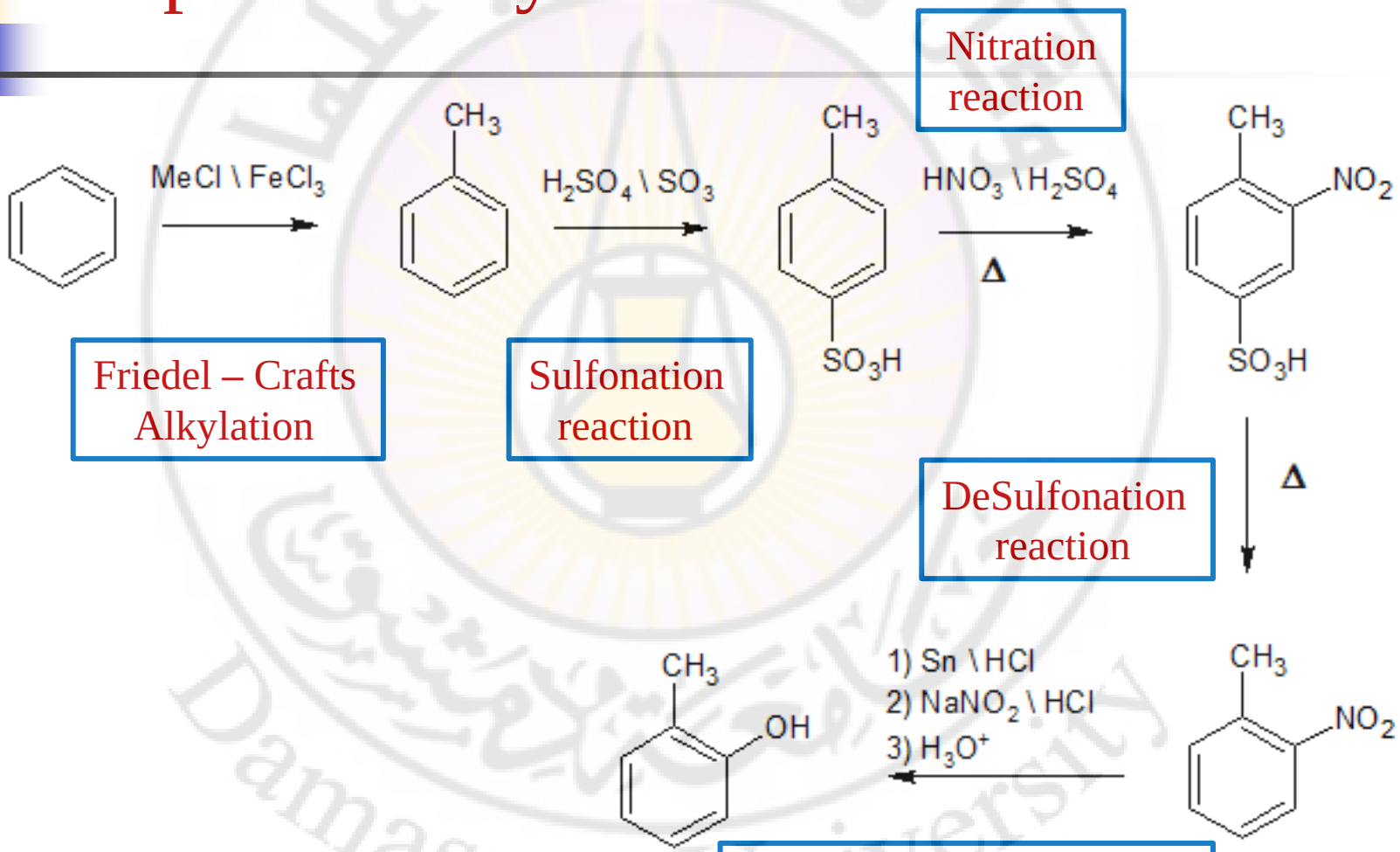
Mephenesin synthesis



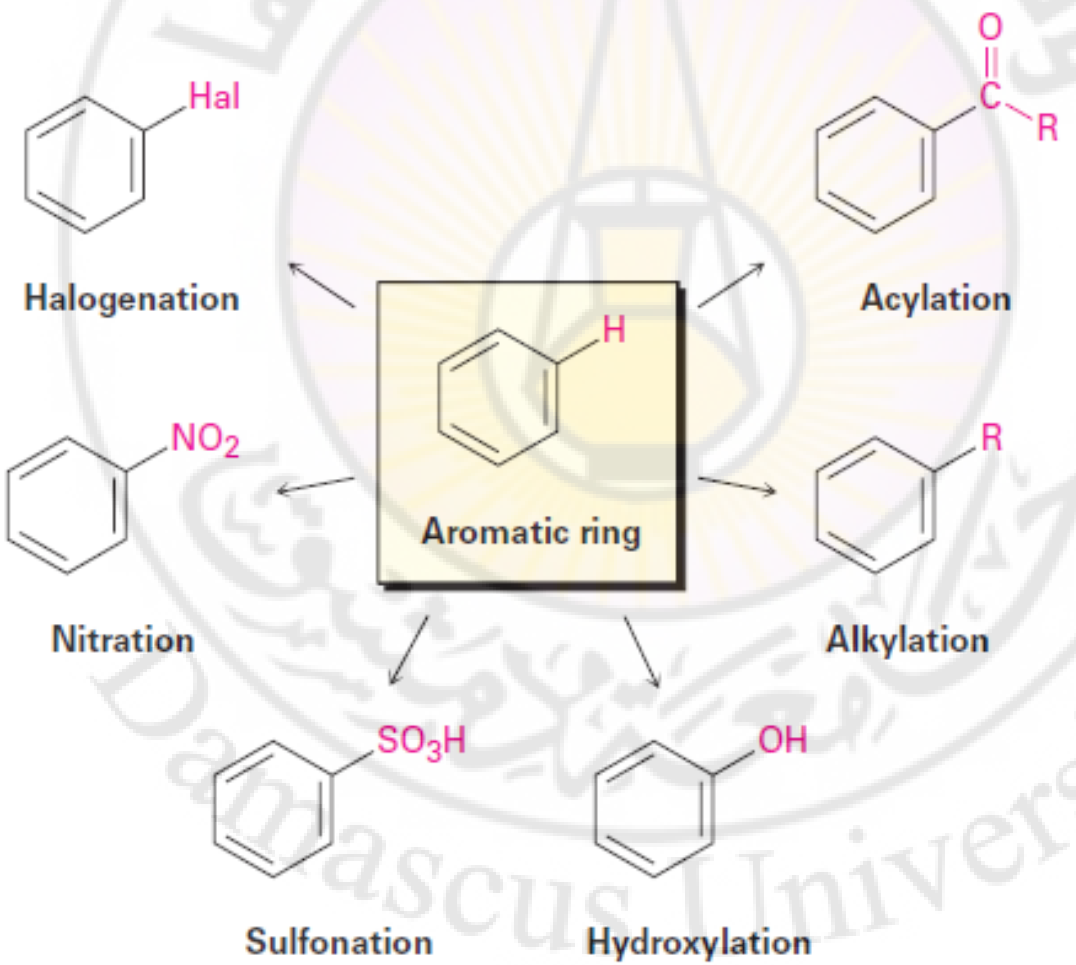
Mephenesin



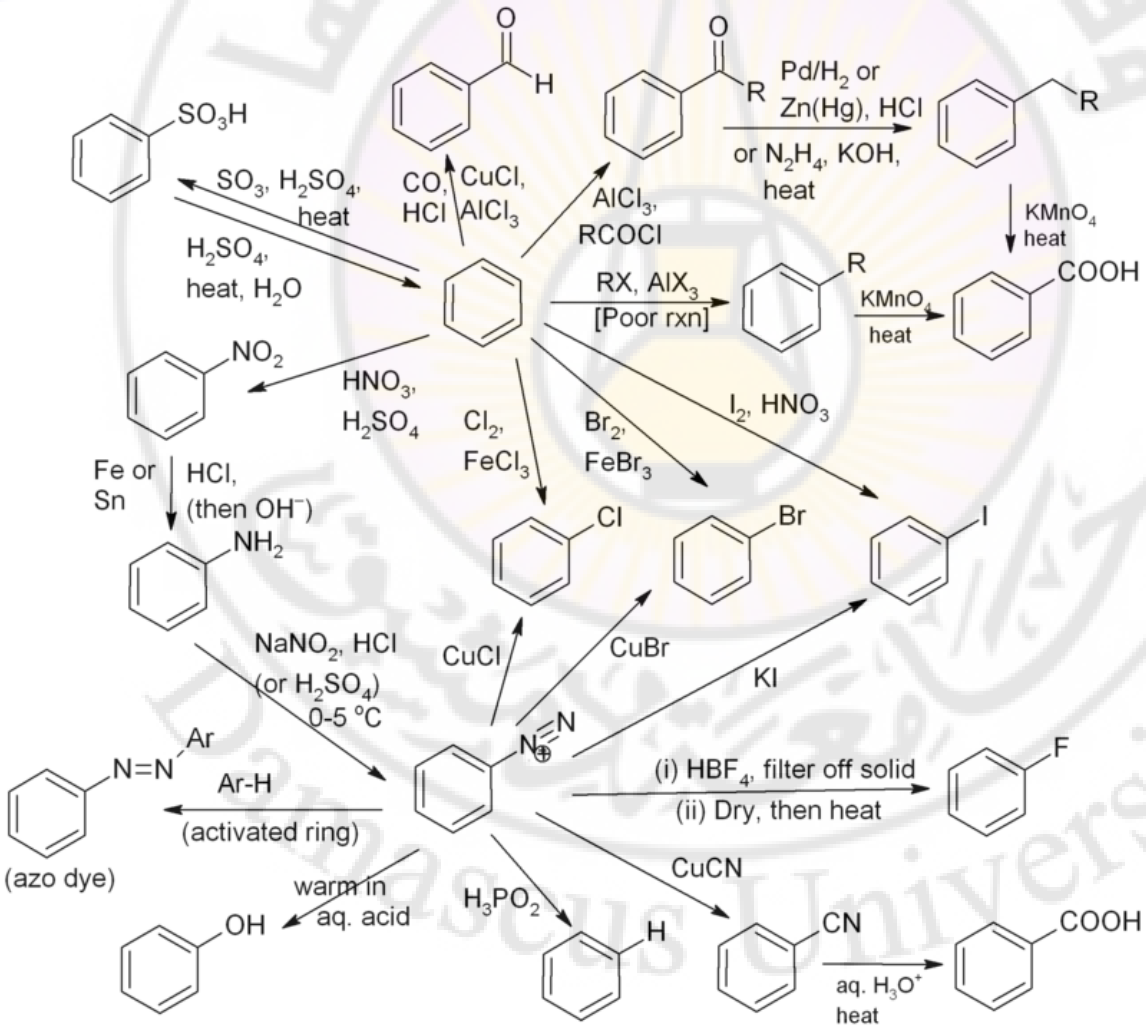
Mephenesin synthesis



Benzene reactions

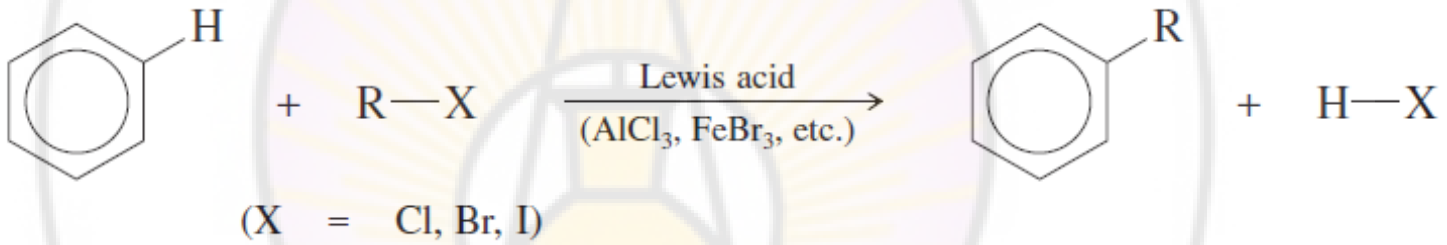


Benzene reactions



Friedel – Crafts Alkylation

Friedel–Crafts alkylation



The Friedel–Crafts alkylation has three major limitations

Limitation 1 Friedel–Crafts reactions work only with benzene, activated benzene derivatives, and halobenzenes.

They fail with strongly deactivated systems such as nitrobenzene, benzenesulfonic acid, and phenyl ketones.

In some cases, we can get around this limitation by adding the deactivating group or changing an activating group into a deactivating group *after* the Friedel–Crafts step.

Friedel – Crafts Alkylation

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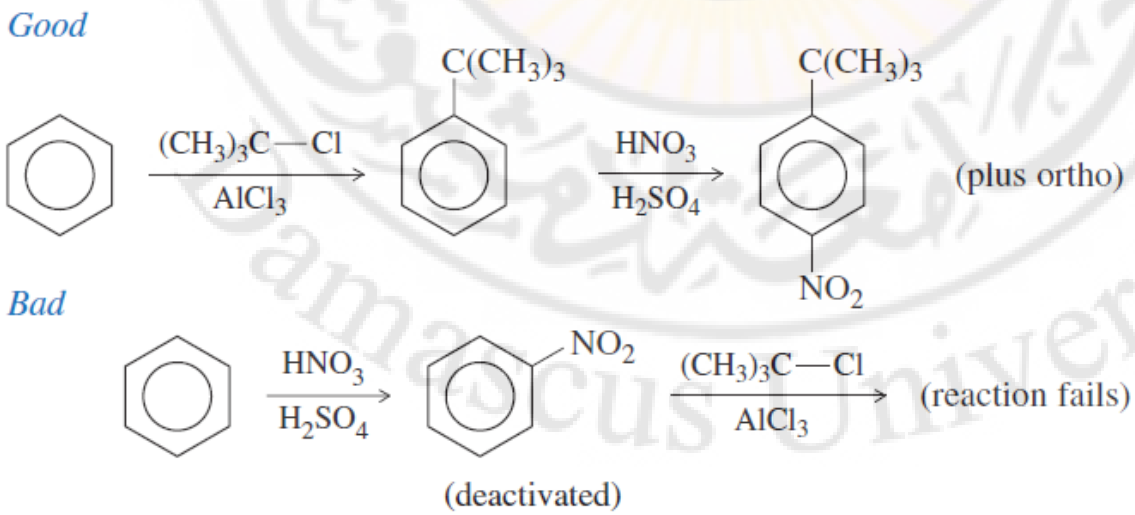


Friedel – Crafts Alkylation

The Friedel–Crafts alkylation has three major limitations

Limitation 2

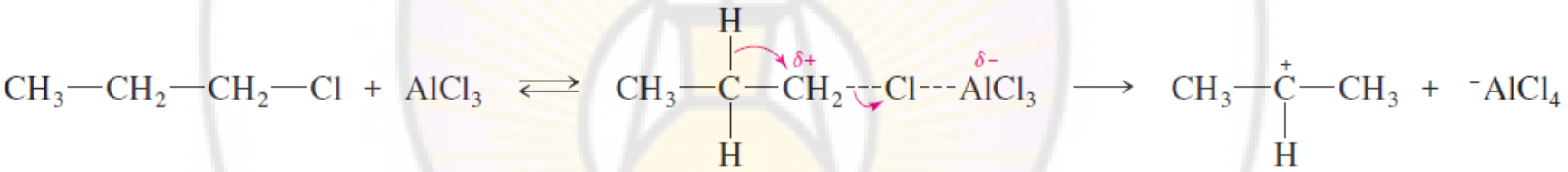
The Friedel–Crafts alkylation is susceptible to carbocation rearrangements.

As a result, only certain alkylbenzenes can be made using the Friedel–Crafts alkylation.

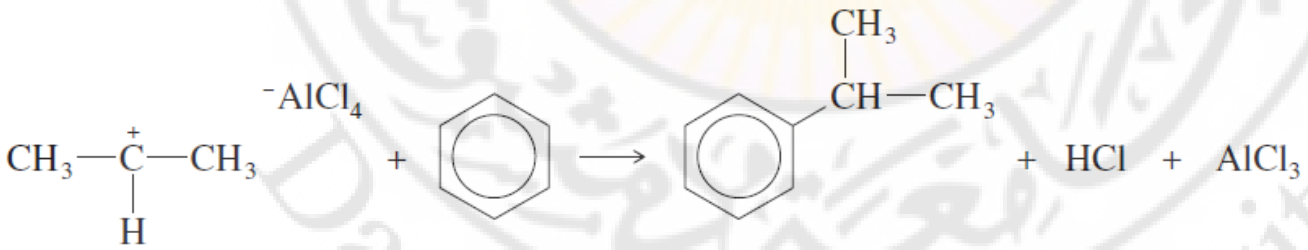
tert-Butylbenzene, isopropylbenzene, and ethylbenzene can be synthesized using the Friedel–Crafts alkylation because the corresponding cations are not prone to rearrangement.

Friedel – Crafts Alkylation

Ionization with rearrangement gives isopropyl cation



Reaction with benzene gives isopropylbenzene



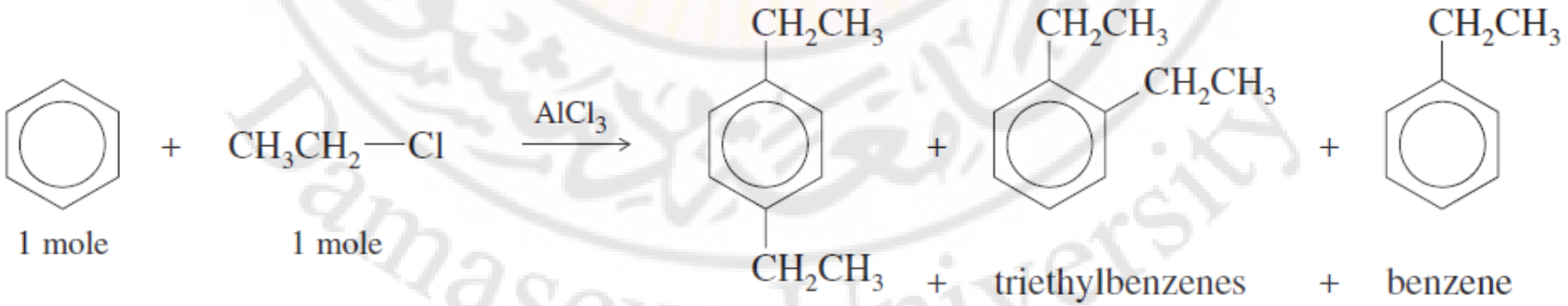
Friedel – Crafts Alkylation

The Friedel–Crafts alkylation has three major limitations

Limitation 3

Because alkyl groups are activating substituents, the product of the Friedel–Crafts alkylation is more reactive than the starting material.

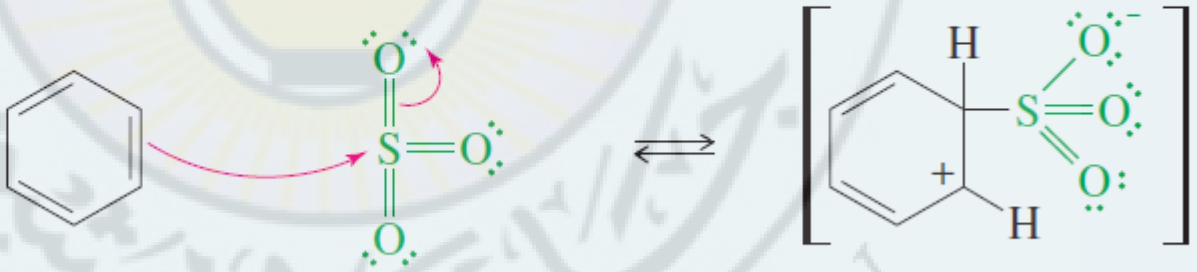
Multiple alkylations are hard to avoid. This limitation can be severe.



Sulfonation of Benzene

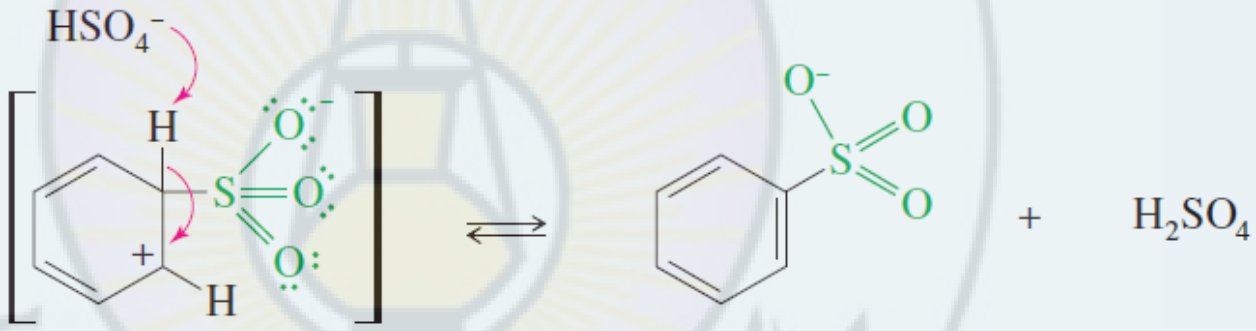
Sulfur trioxide is a powerful electrophile.

Step 1: Attack on the electrophile forms the sigma complex.



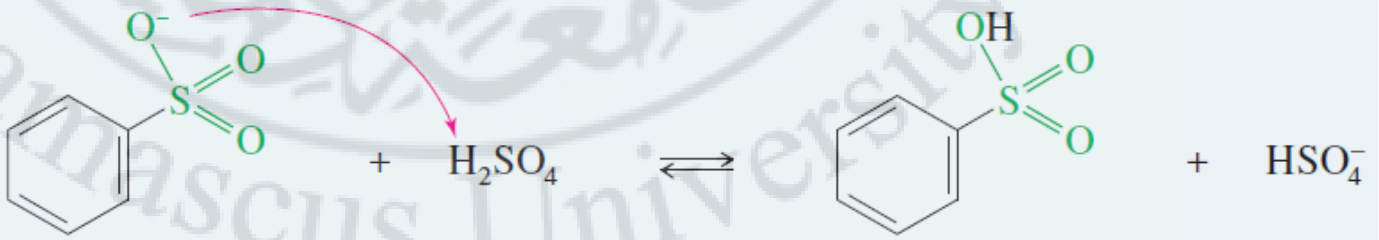
Sulfonation of Benzene

Step 2: Loss of a proton regenerates an aromatic ring.



sigma complex benzenesulfonate anion

Step 3: The sulfonate group may become protonated in strong acid.

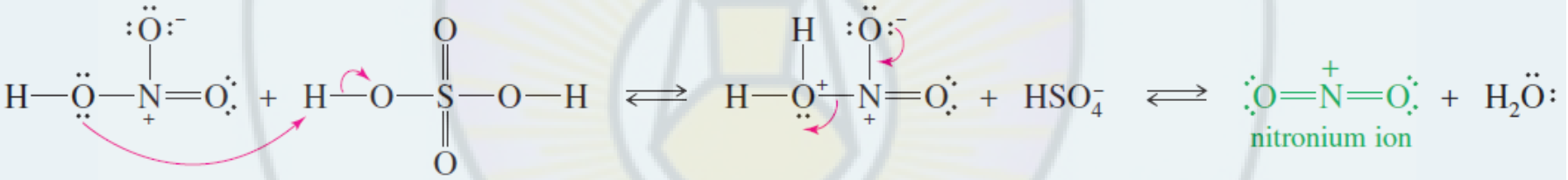


benzenesulfonic acid

Nitration of Benzene

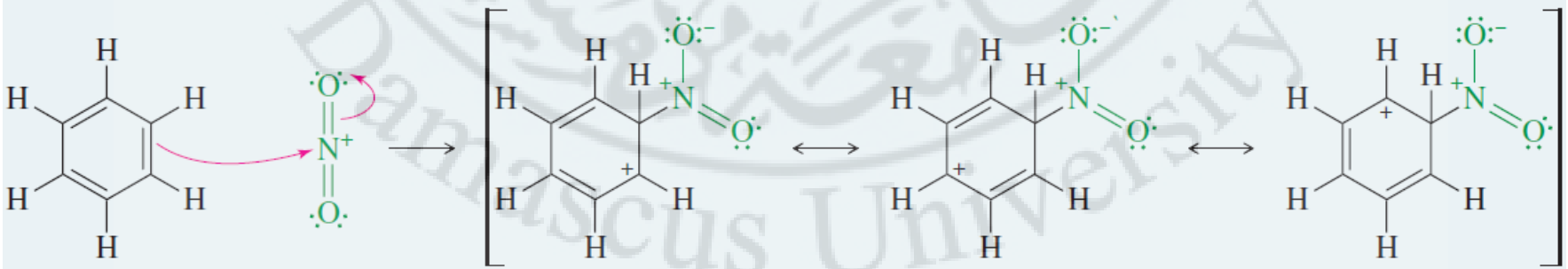
Preliminary steps: Formation of the nitronium ion, NO_2^+.

Nitric acid has a hydroxyl group that can become protonated and leave as water, similar to the dehydration of an alcohol.



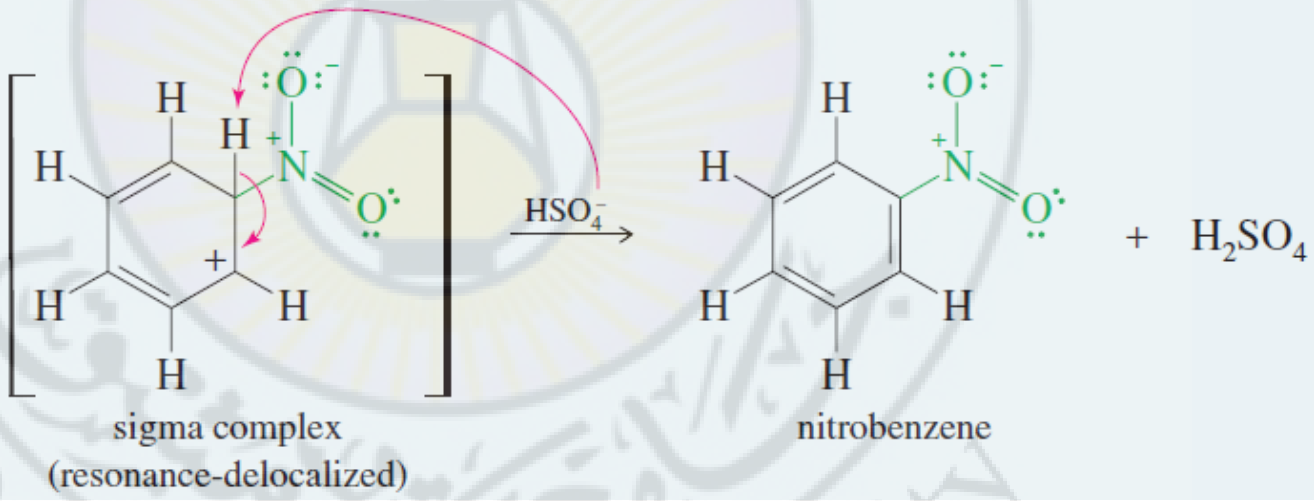
Electrophilic aromatic substitution by the nitronium ion gives nitrobenzene.

Step 1: Attack on the electrophile forms the sigma complex.



Nitration of Benzene

Step 2: Loss of a proton gives nitrobenzene.

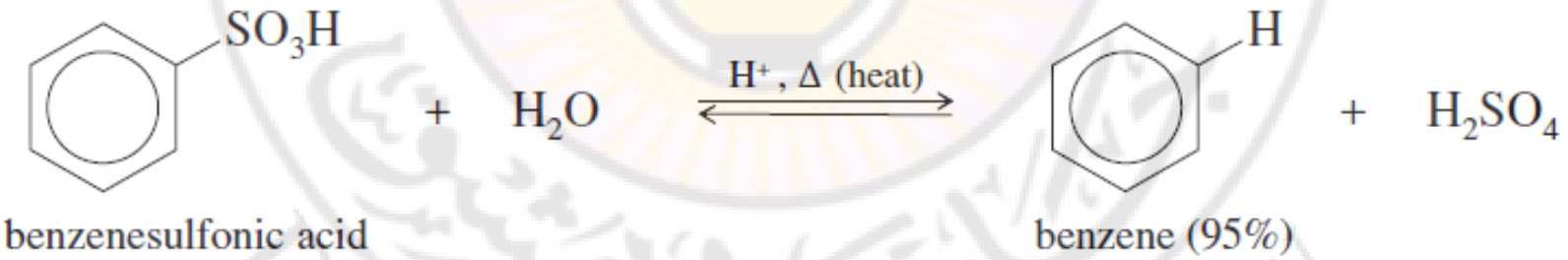


sigma complex
(resonance-delocalized)

nitrobenzene

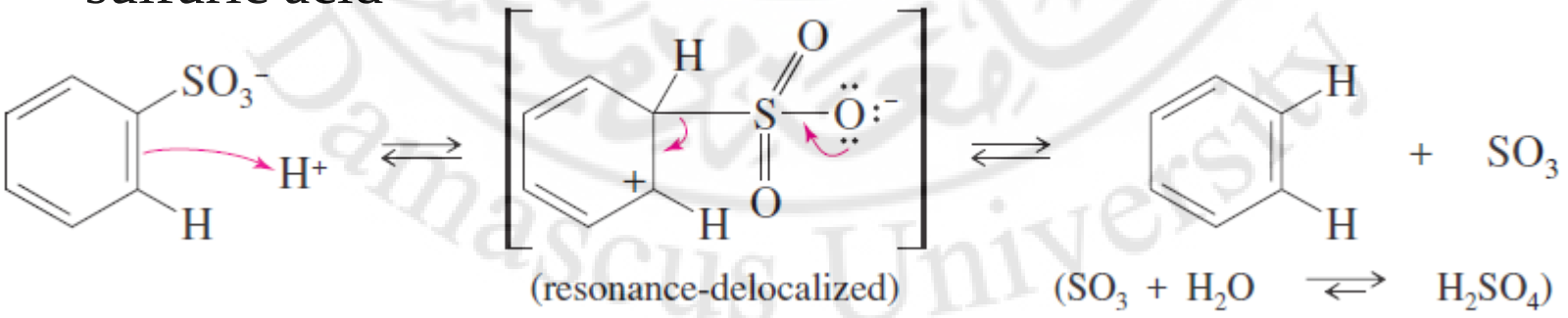
Desulfonation of Benzene

- ✓ Sulfonation is reversible, and a sulfonic acid group may be removed from an aromatic ring by heating in dilute sulfuric acid

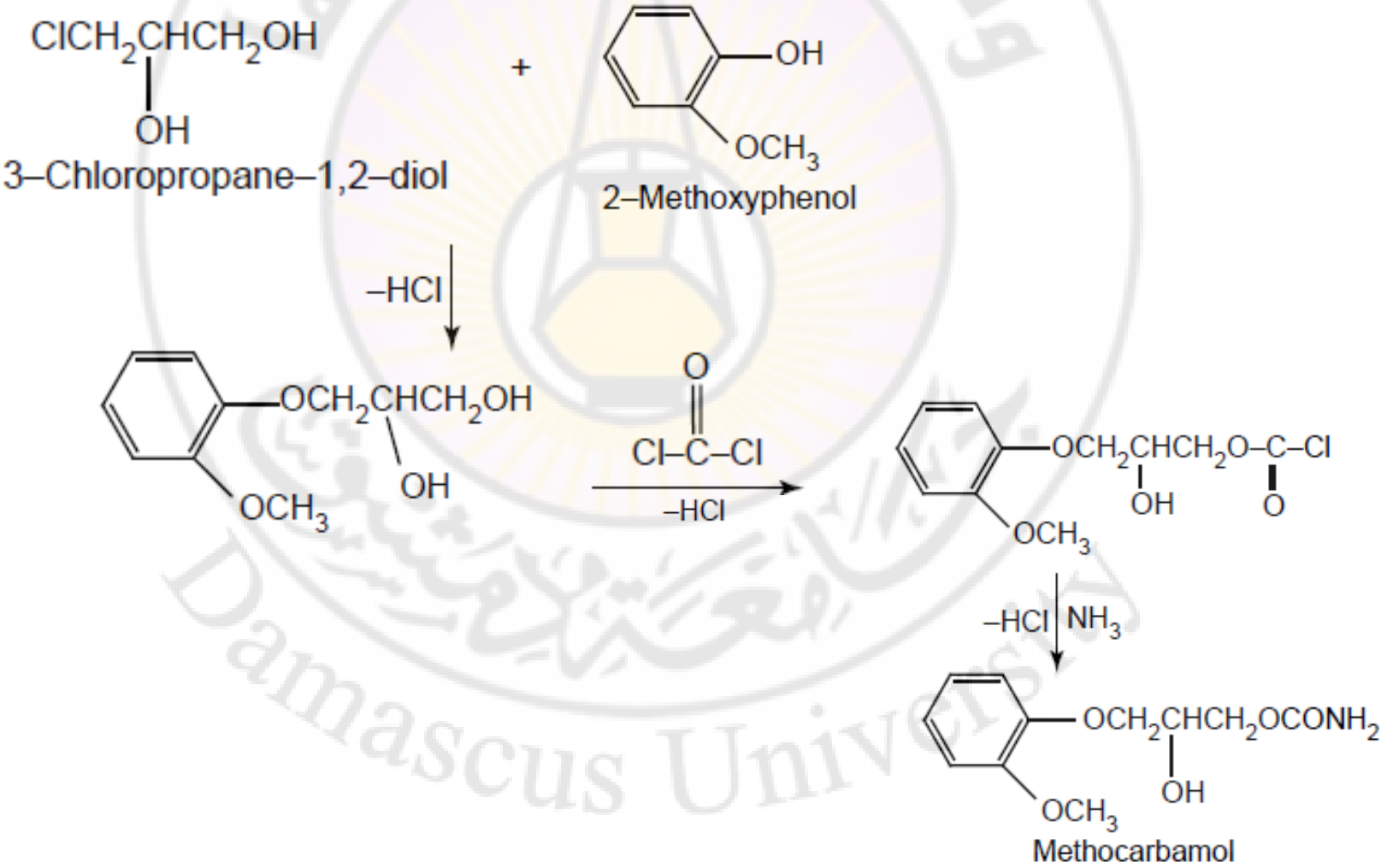


Desulfonation of Benzene

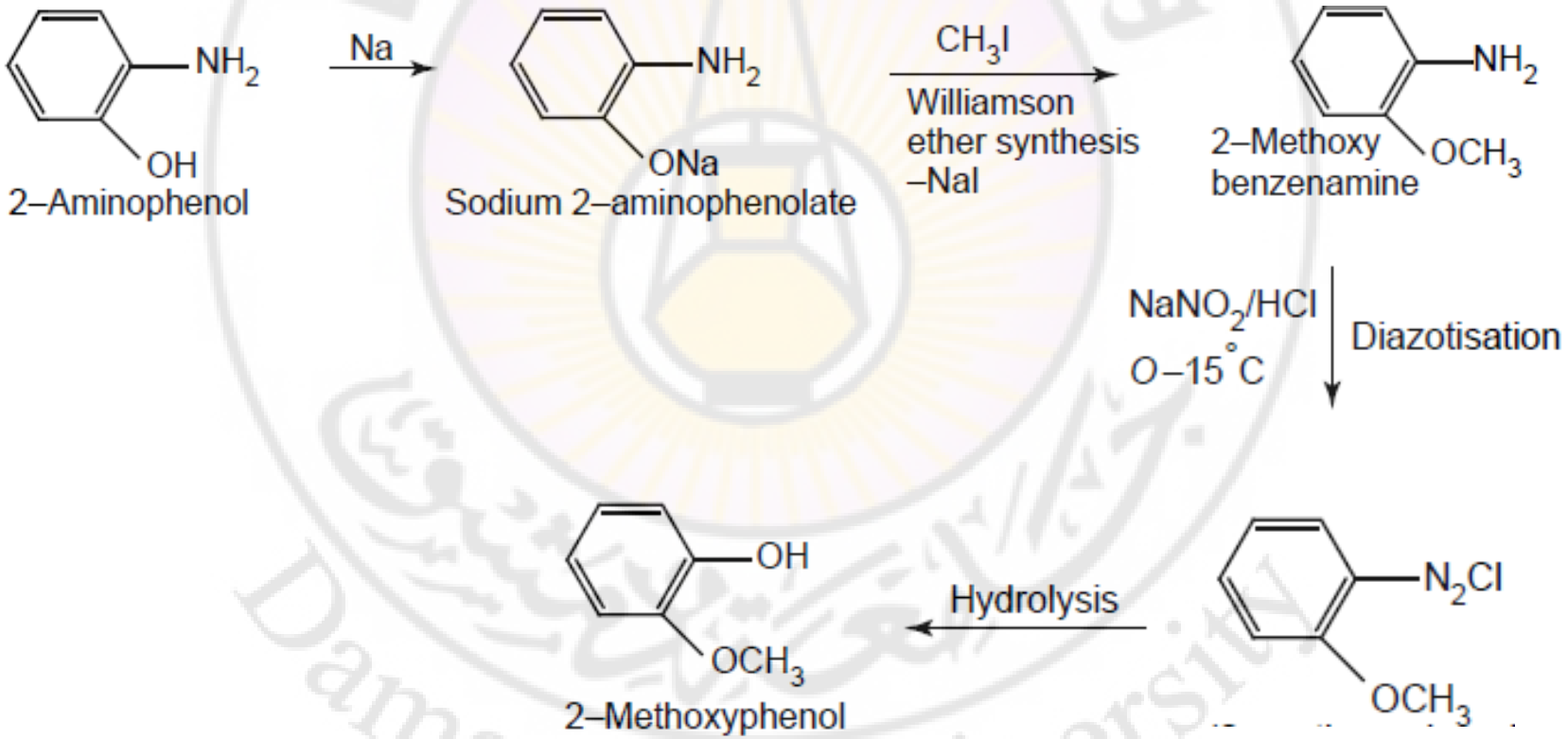
- ✓ Desulfonation follows the same mechanistic path as sulfonation, except in the opposite order.
- ✓ A proton adds to a ring carbon to form a sigma complex, then loss of sulfur trioxide gives the unsubstituted aromatic ring.
- ✓ Excess water removes from the equilibrium by hydrating it to sulfuric acid



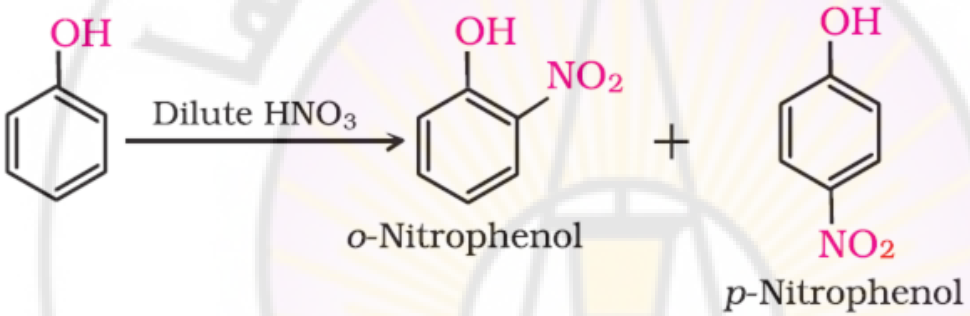
Methocarbamol synthesis



2-Methoxyphenol synthesis



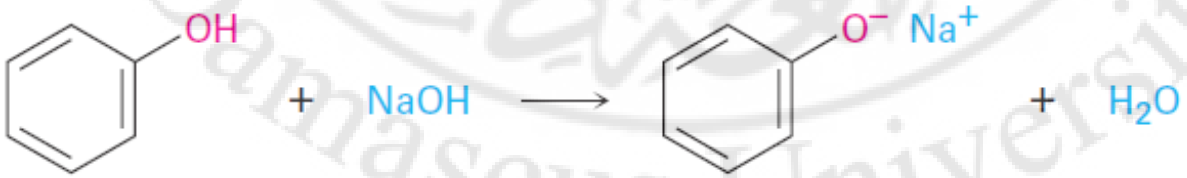
synthesis



$$R{-}NO_2 \xrightarrow[\text{catalyst} = \text{Ni, Pd, or Pt}]{H_2/\text{catalyst}} R{-}NH_2$$

or active metal and H^+

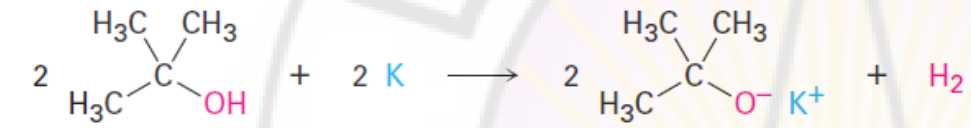
active metal = Fe, Zn, or Sn



Phenol

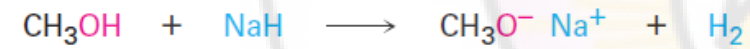
Sodium phenoxide (sodium phenolate)

synthesis



tert-Butyl alcohol (2-methyl-2-propanol)

Potassium *tert*-butoxide (potassium 2-methyl-2-propanolate)

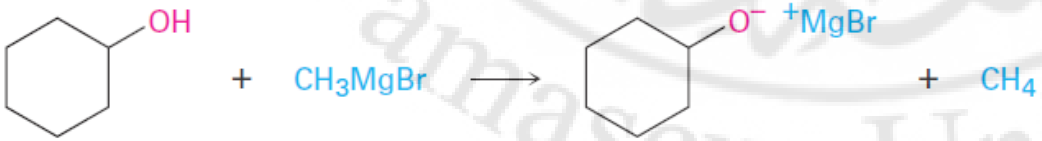


Methanol

Sodium methoxide (sodium methanolate)

Ethanol

Sodium ethoxide (sodium ethanolate)



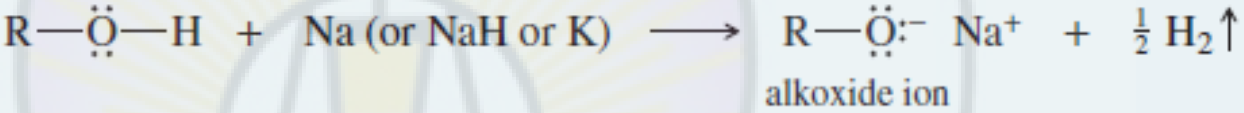
Cyclohexanol

Bromomagnesium cyclohexanolate

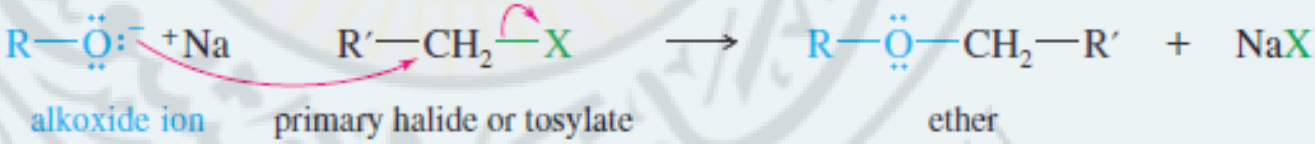
Compound	pK_a
$(CH_3)_3COH$	18.00
CH_3CH_2OH	16.00
H_2O	15.74
CH_3OH	15.54
Phenol	9.89
p-Chlorophenol	9.38
p-Nitrophenol	7.15

Williamson Ether Synthesis

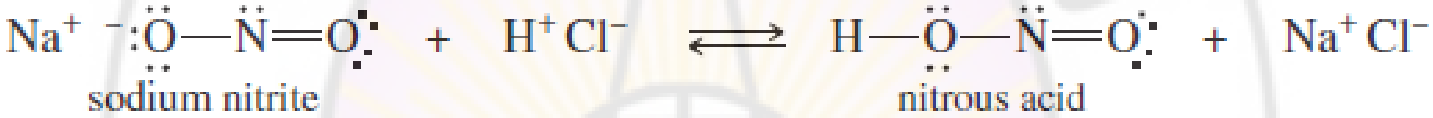
Step 1: Form the alkoxide of the alcohol having the more hindered group.

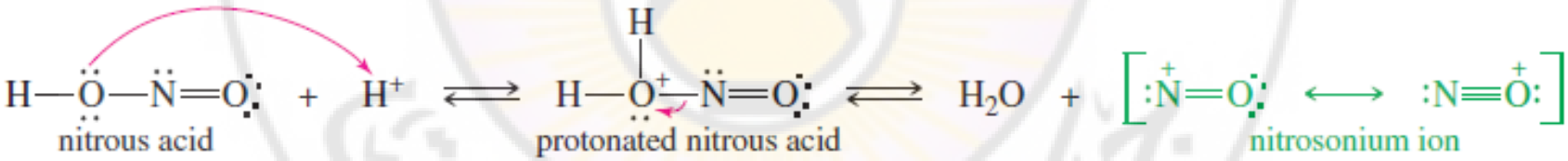


Step 2: The alkoxide displaces the leaving group of a good S_N2 substrate.



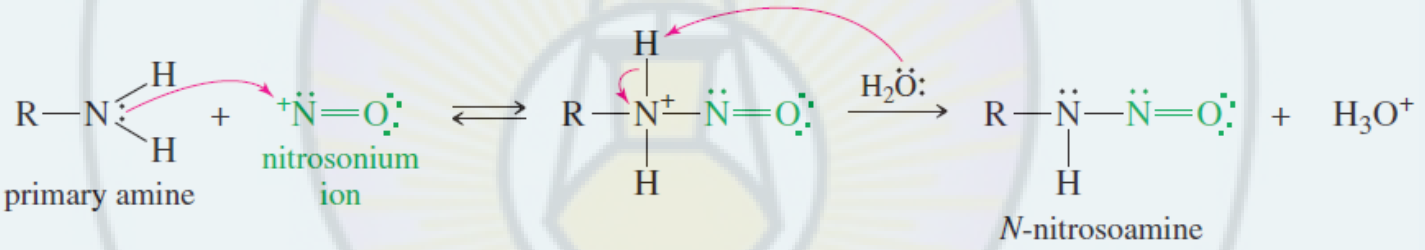
Diazotization reaction



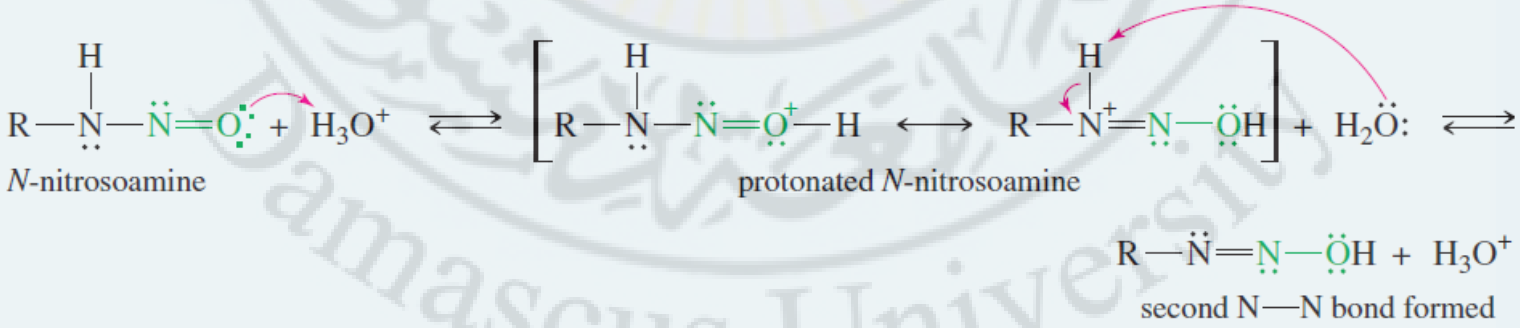


Diazotization reaction

Part 1: Attack on the nitrosonium ion (a strong electrophile), followed by deprotonation, gives an *N*-nitrosoamine.

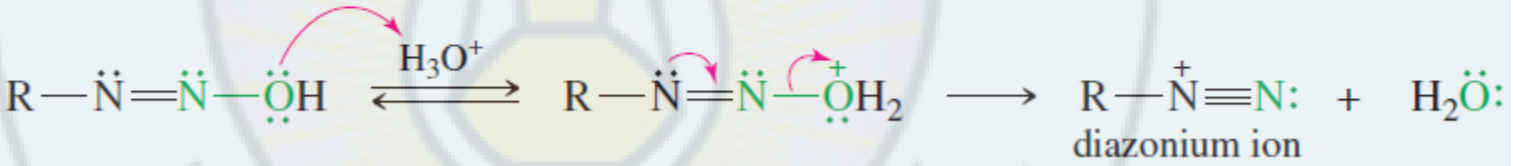


Part 2: A proton transfer (a tautomerism) from nitrogen to oxygen forms a hydroxyl group and a second N—N bond.

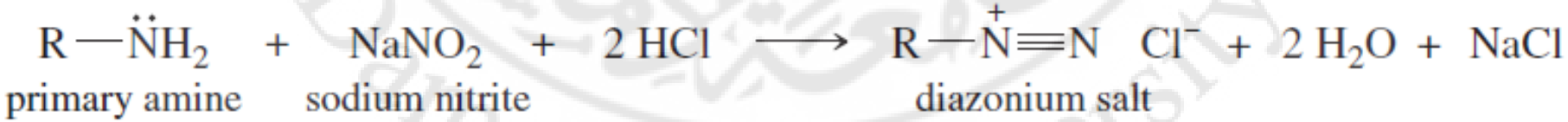


Diazotization reaction

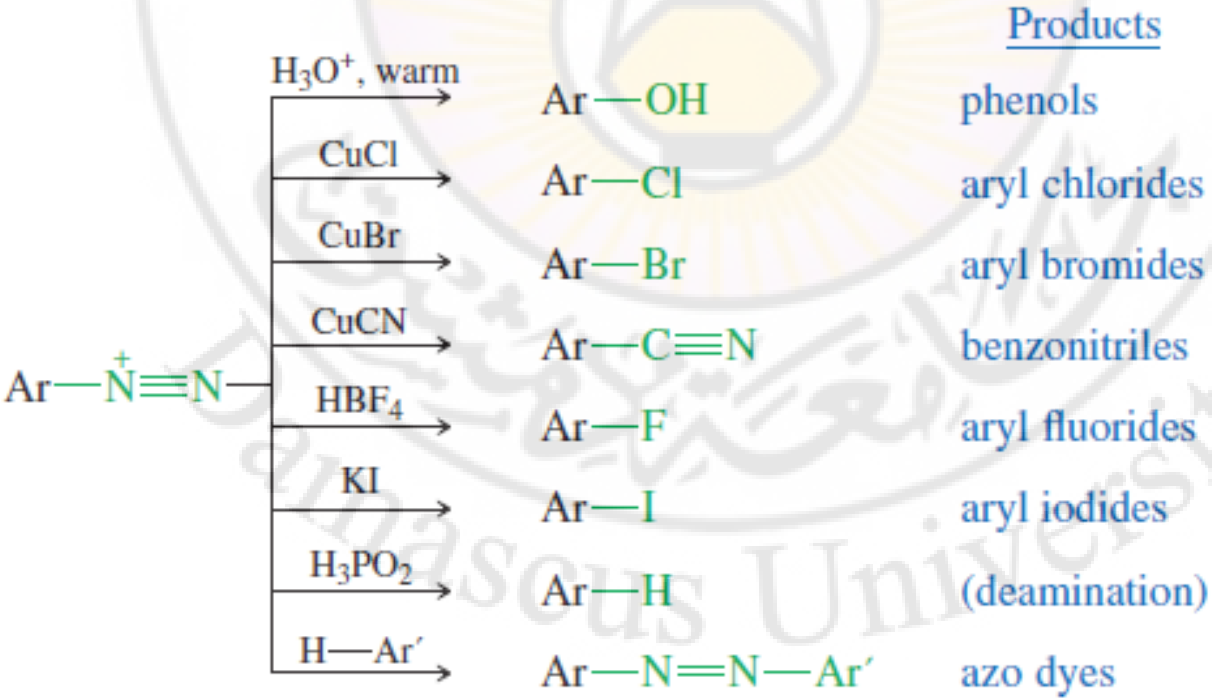
Part 3: Protonation of the hydroxyl group, followed by loss of water, gives the diazonium ion.

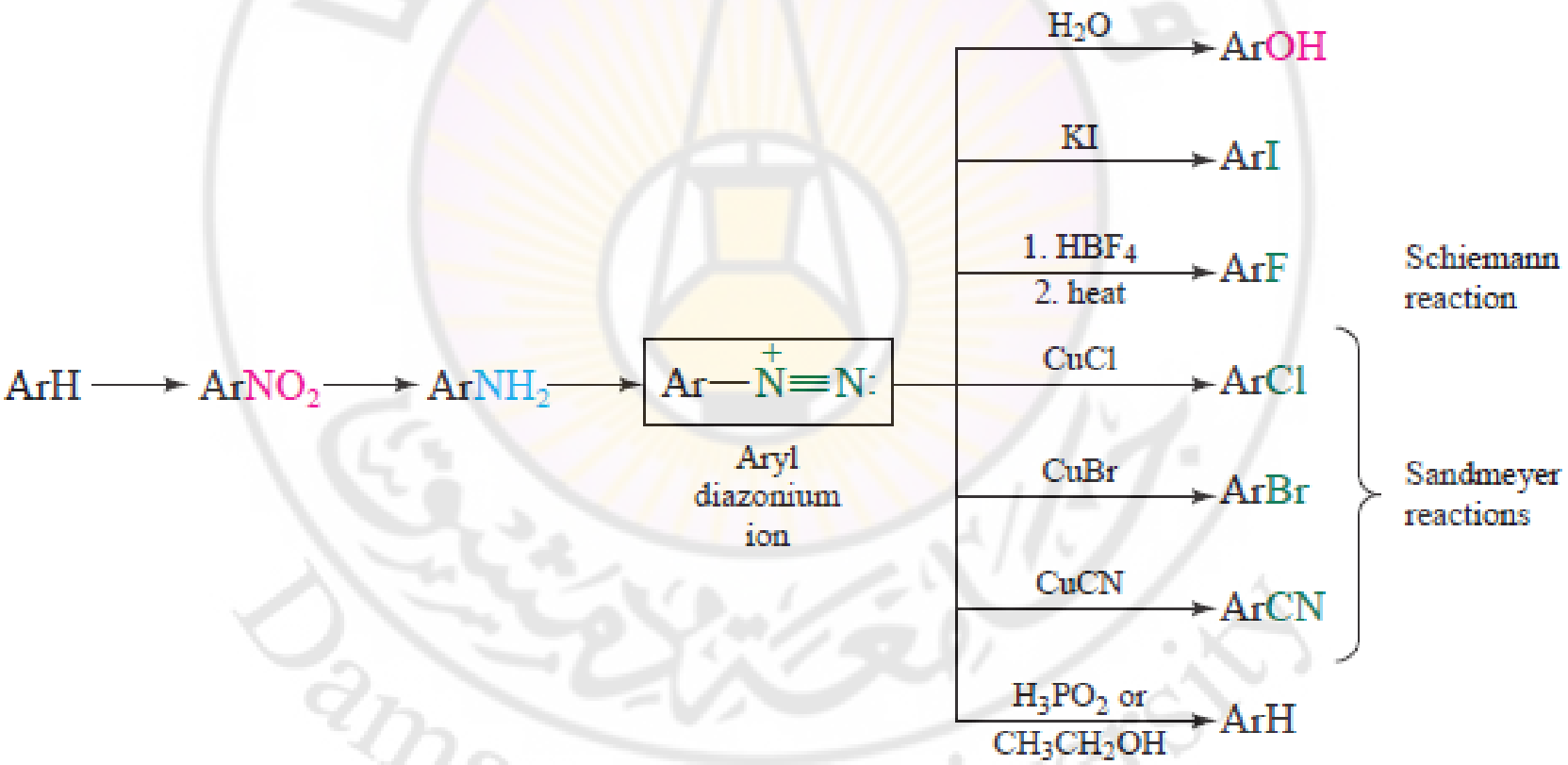


The overall diazotization reaction is

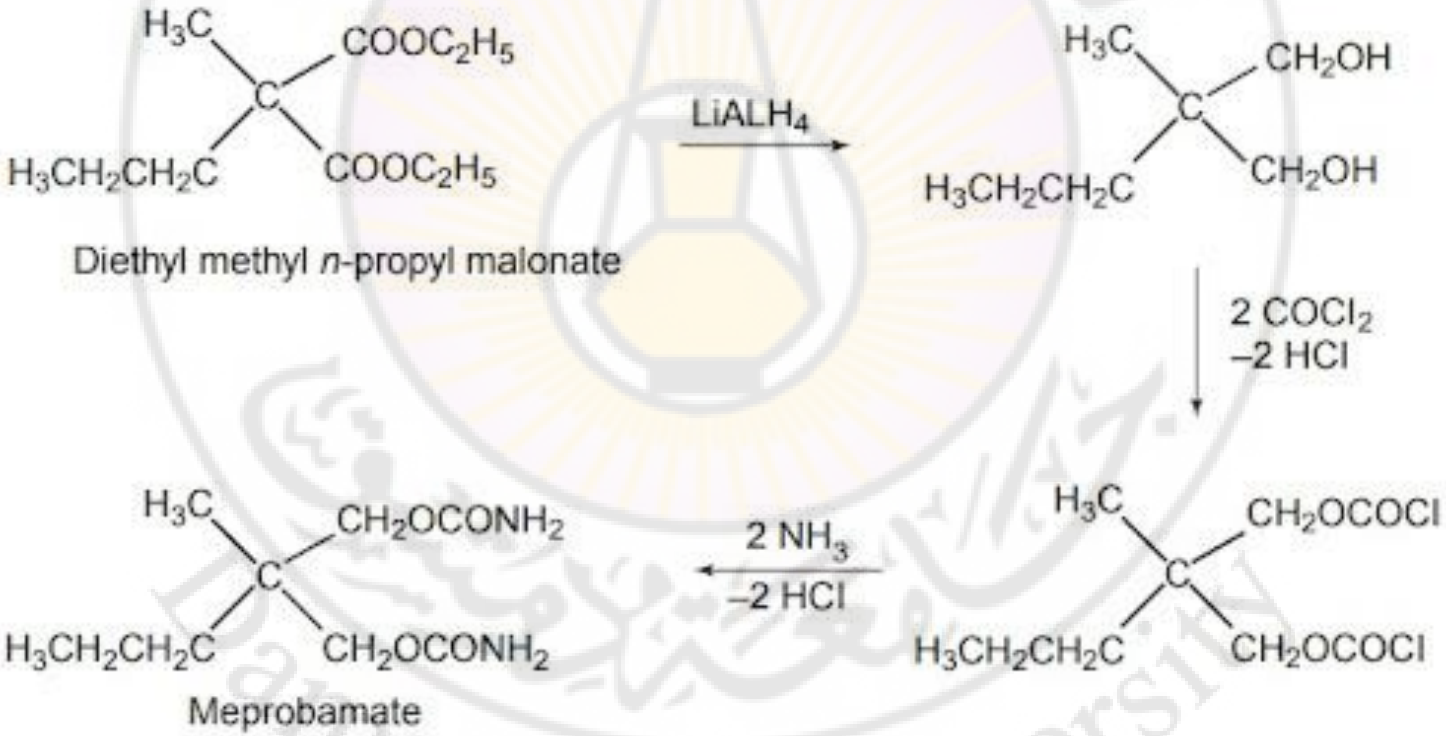


In contrast to alkanediazonium salts, arenediazonium salts are relatively stable in aqueous solutions around 0–10 °C.
The diazonium group can be replaced by many different functional groups, including -H, -OH, -CN and halogens (Cl, Br, I, F).

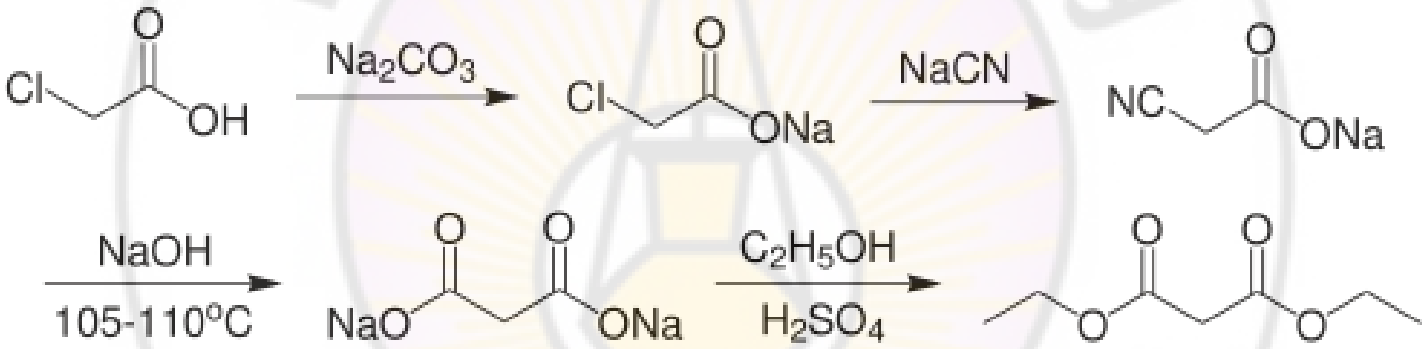



ArH
ArNO2
ArNH2
Ar—N≡N:
Aryl diazonium ion
H2O
ArOH
KI
ArI
1. HBF4
2. heat
ArF
Schiemann reaction
CuCl
ArCl
CuBr
ArBr
CuCN
ArCN
Sandmeyer reactions
H3PO2 or CH3CH2OH
ArH

Meprobamate synthesis



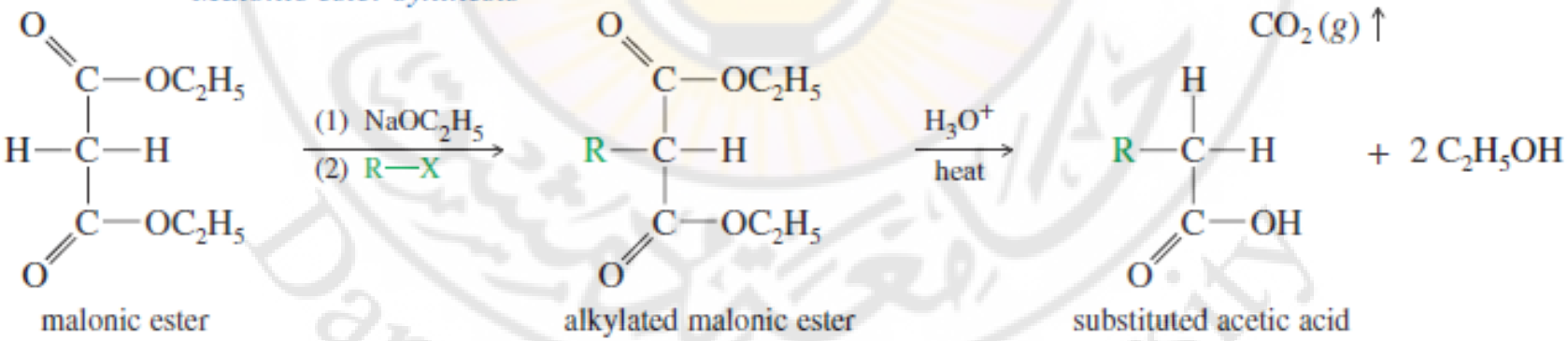
Malonic acid & Diethylmalonate synthesis



Malonic ester synthesis

The malonic ester synthesis makes substituted derivatives of acetic acid. Malonic ester (diethyl malonate) is alkylated or acylated on the more acidic carbon that is to both carbonyl groups, and the resulting derivative is hydrolyzed and allowed to decarboxylate

Malonic ester synthesis

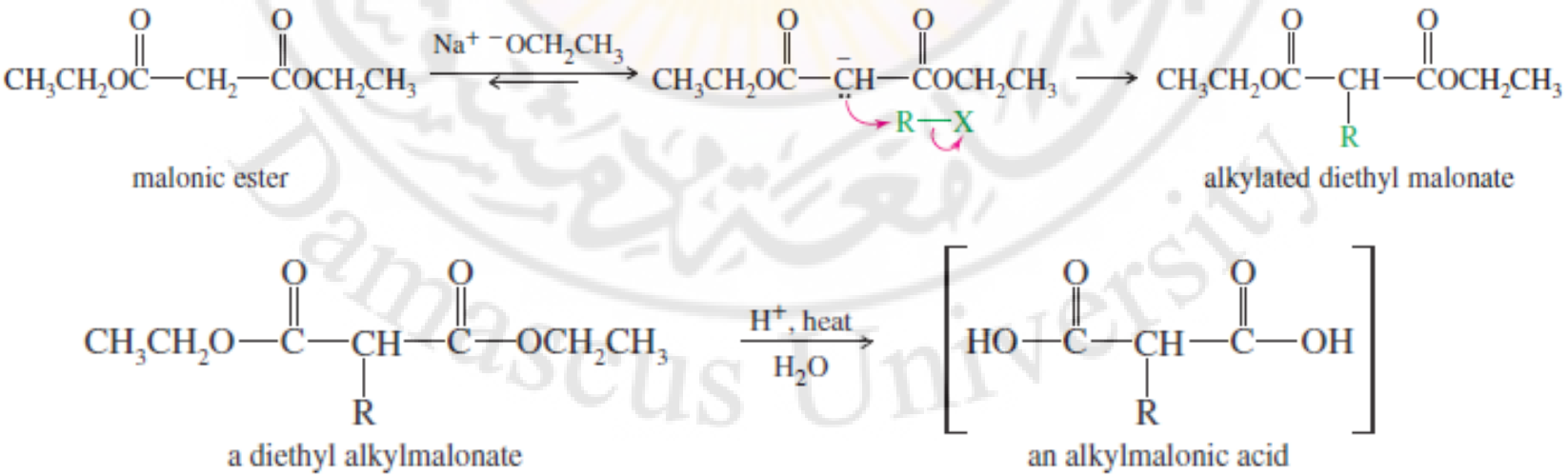


Malonic ester synthesis

Malonic ester is completely deprotonated by sodium ethoxide. The resulting enolate ion is alkylated by an unhindered alkyl halide, tosylate, or other electrophilic reagent.

This step is an S_N2 displacement, requiring a good SN2 substrate.

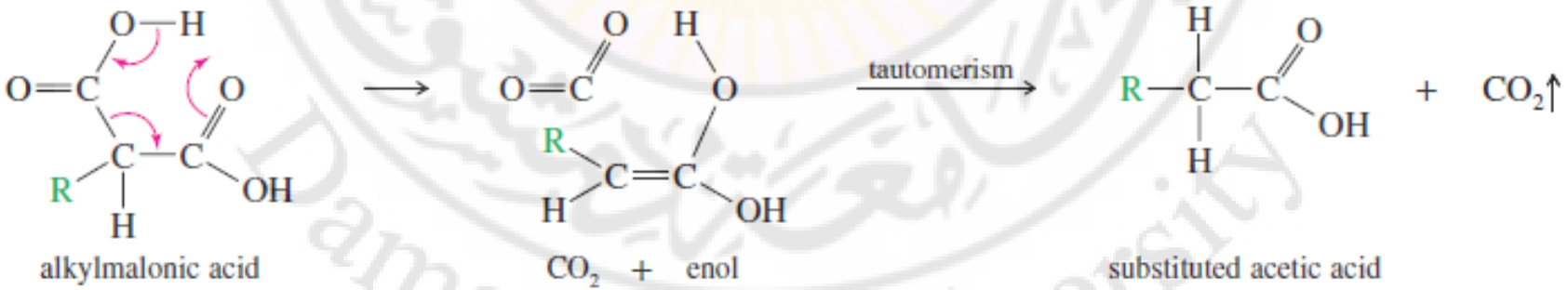
Hydrolysis of the alkylated diethyl malonate (a diethyl alkylmalonic ester) gives a malonic acid derivative.



Malonic ester synthesis

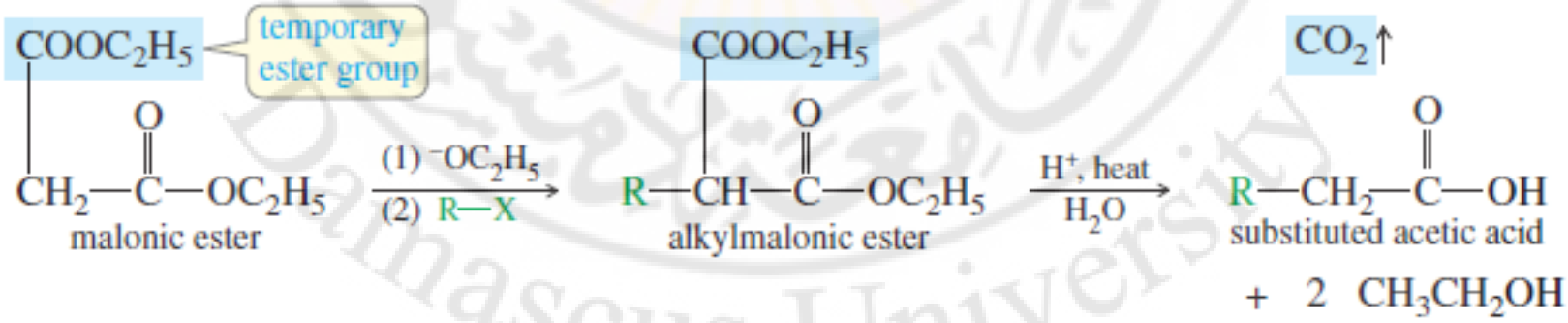
Any carboxylic acid with a carbonyl group in the β position is prone to decarboxylate.

At the temperature of the hydrolysis, the alkylmalonic acid loses to give a substituted derivative of acetic acid. Decarboxylation takes place through a cyclic transition state, initially giving an enol that quickly tautomerizes to the product, a substituted acetic acid.



Malonic ester synthesis

The product of a malonic ester synthesis is a substituted acetic acid, with the substituent
being the group used to alkylate malonic ester. In effect, the second carboxyl group is temporary, allowing the ester to be easily deprotonated and alkylated.
Hydrolysis and decarboxylation remove the temporary carboxyl group, leaving the substituted acetic acid.

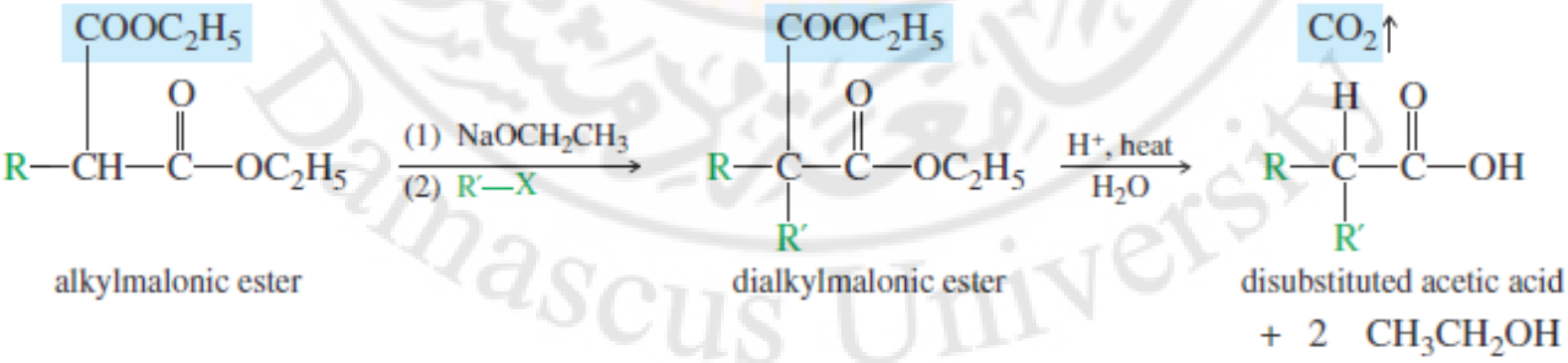


Malonic ester synthesis

The alkylmalonic ester has a second acidic proton that can be removed by a base.

Removing this proton and alkylating the enolate with another alkyl halide gives a dialkylated malonic ester.

Hydrolysis and decarboxylation lead to a disubstituted derivative of acetic acid.

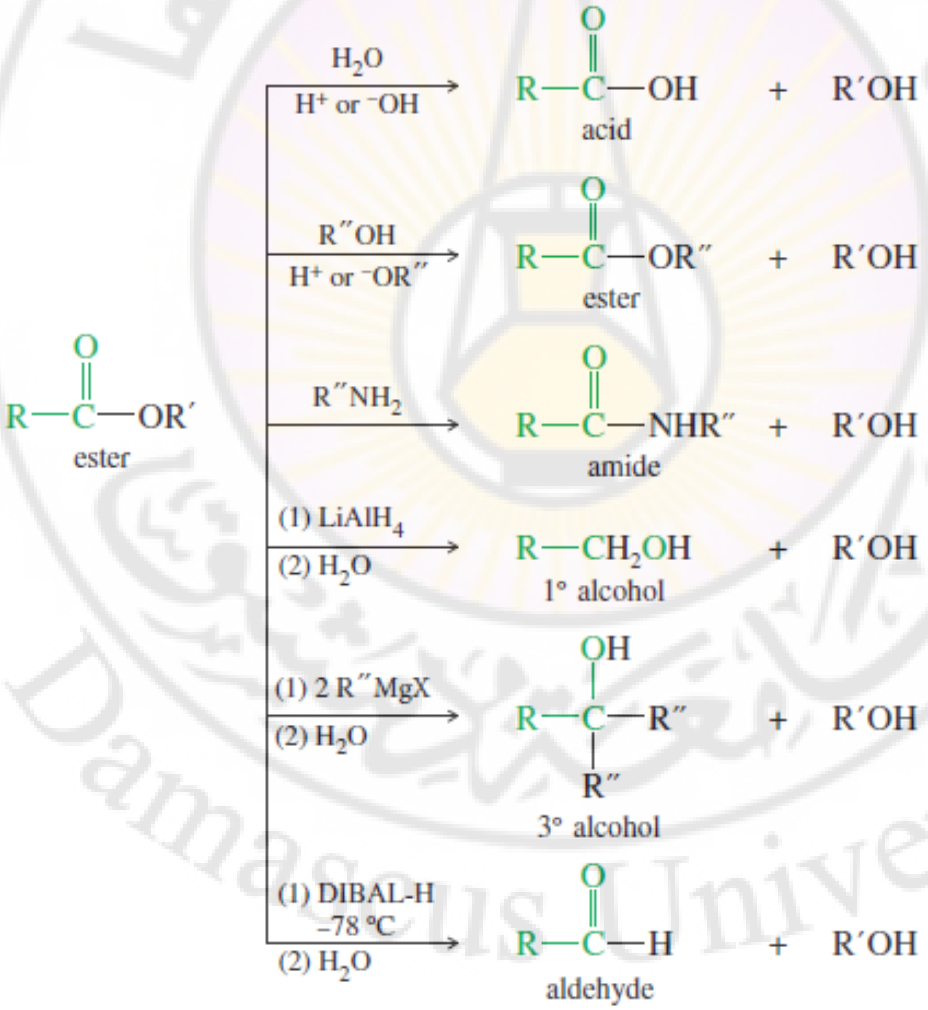


alkylmalonic ester

dialkylmalonic ester

disubstituted acetic acid

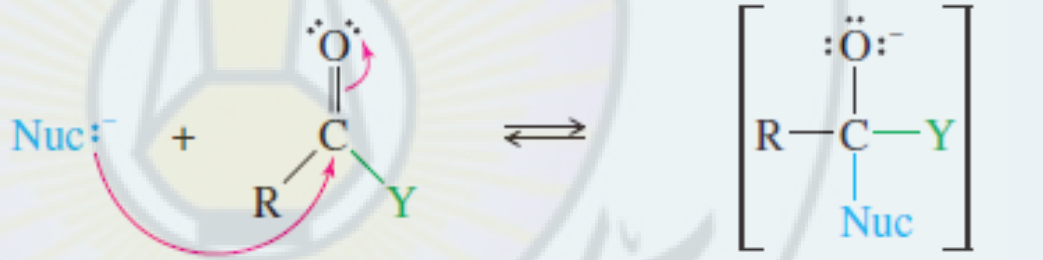
Reaction of Ester



Reaction of Ester

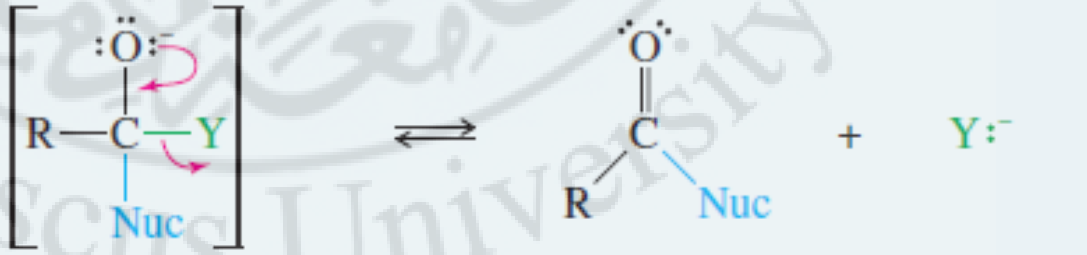
Addition–Elimination Mechanism of Nucleophilic Acyl Substitution

Step 1: Addition of the nucleophile gives a tetrahedral intermediate.



nucleophilic attack — tetrahedral intermediate

Step 2: Elimination of the leaving group regenerates the carbonyl group.

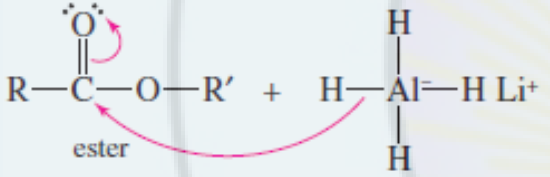


tetrahedral intermediate — products — leaving group

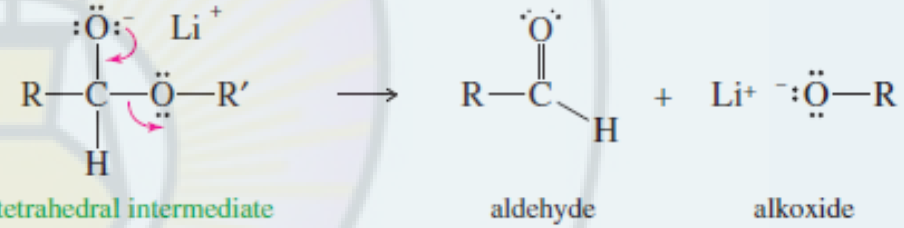
Reduction of Ester

Nucleophilic acyl substitution gives an aldehyde, which reduces further to an alcohol.

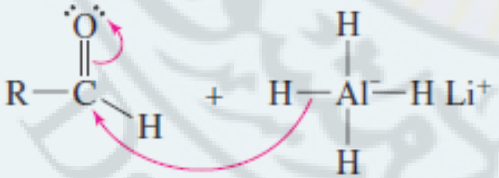
Step 1: Addition of the nucleophile (hydride).



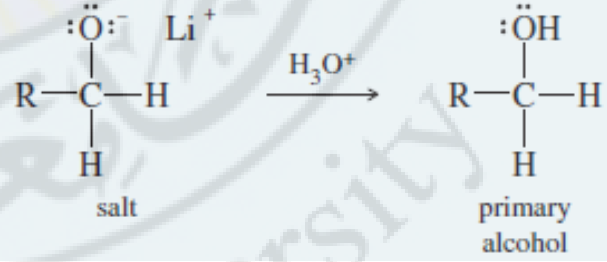
Step 2: Elimination of alkoxide.



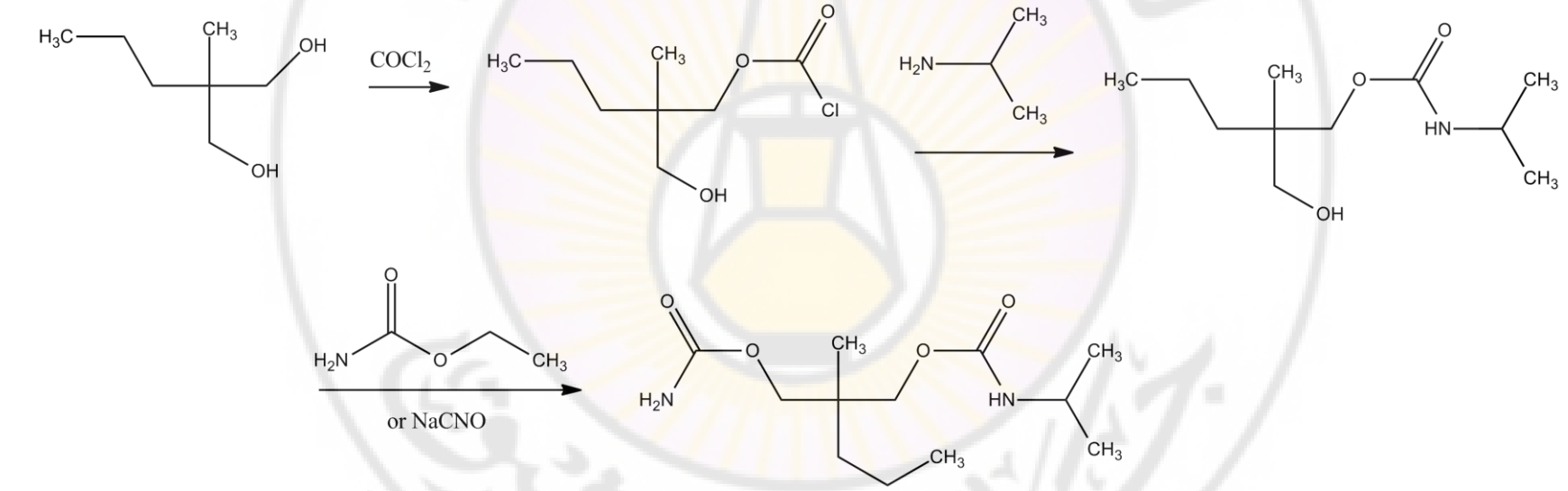
Step 3: Addition of a second hydride ion.

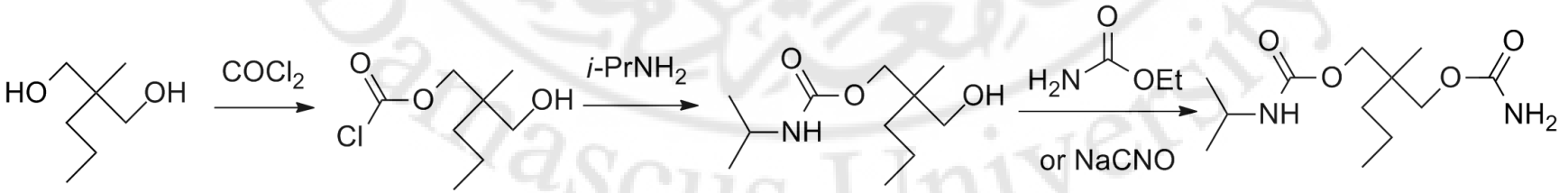


Step 4: Add acid in the workup to protonate the alkoxide.

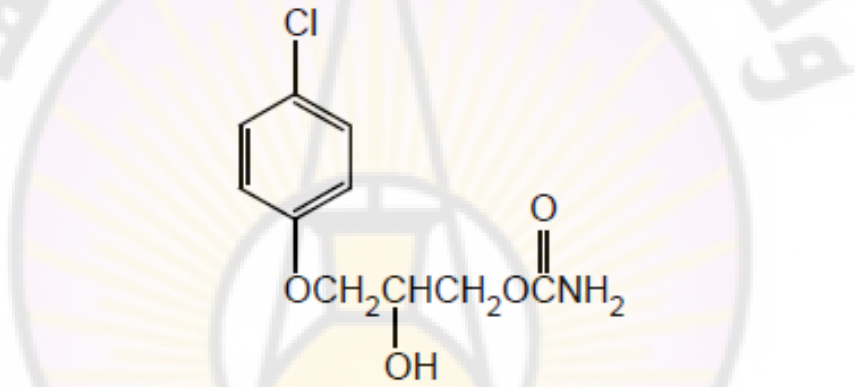


Carisoprodol synthesis

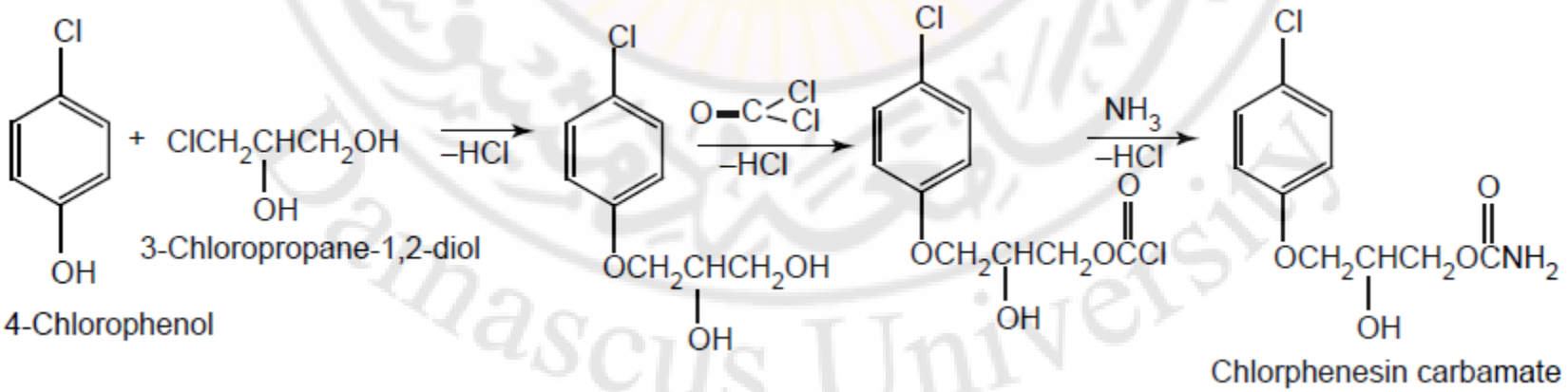




Chlorphenesin Carbamate synthesis



3-(*p*-Chloro phenoxy)-1,2-propanediol-1-carbamate

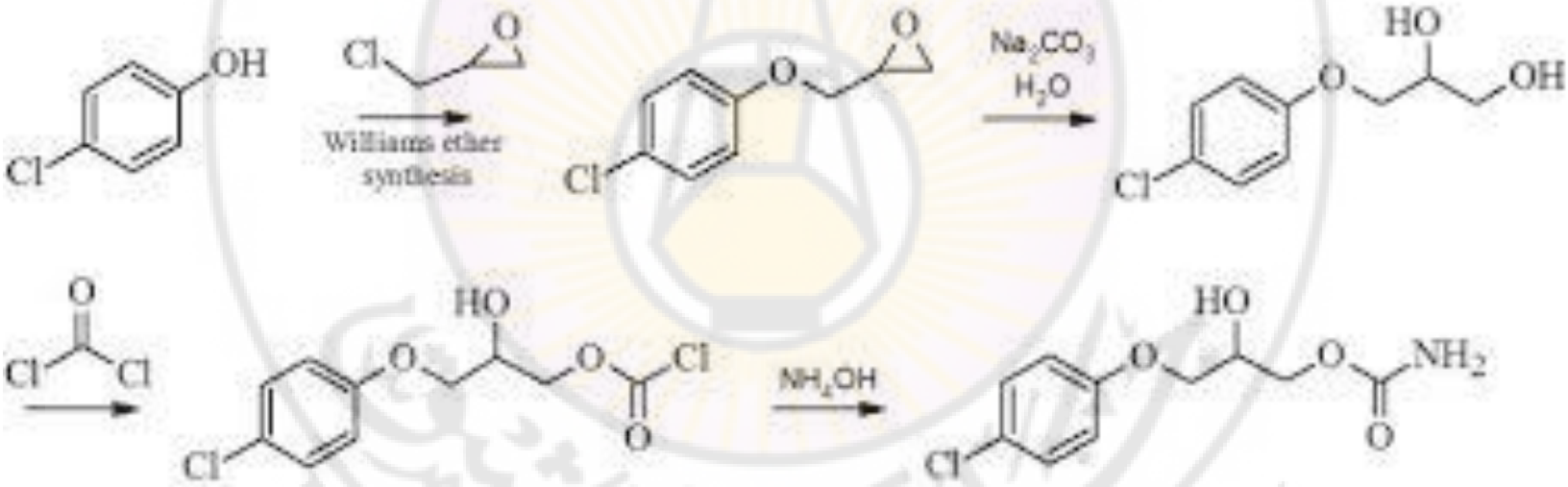


4-Chlorophenol

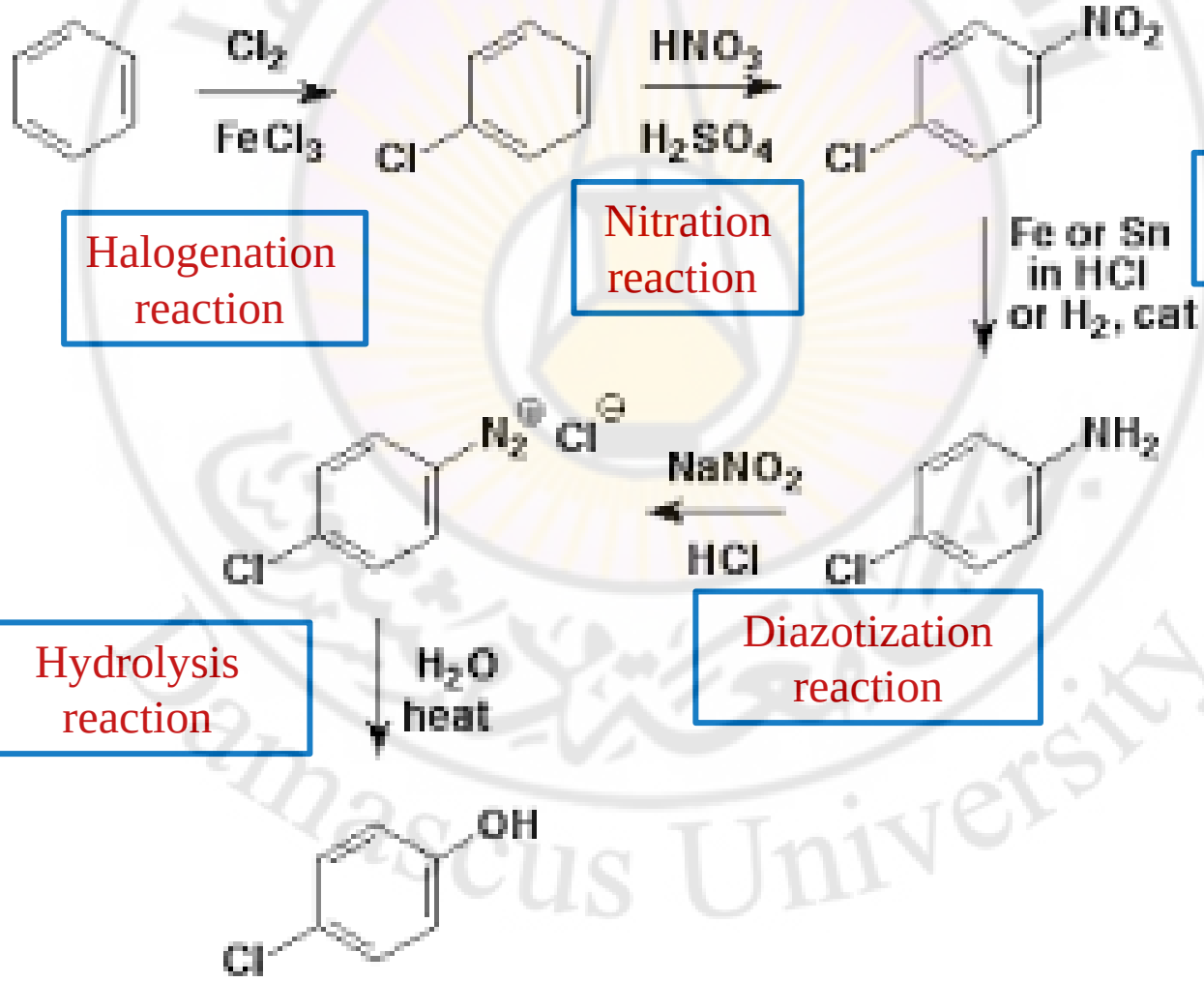
3-Chloropropane-1,2-diol

Chlorphenesin carbamate

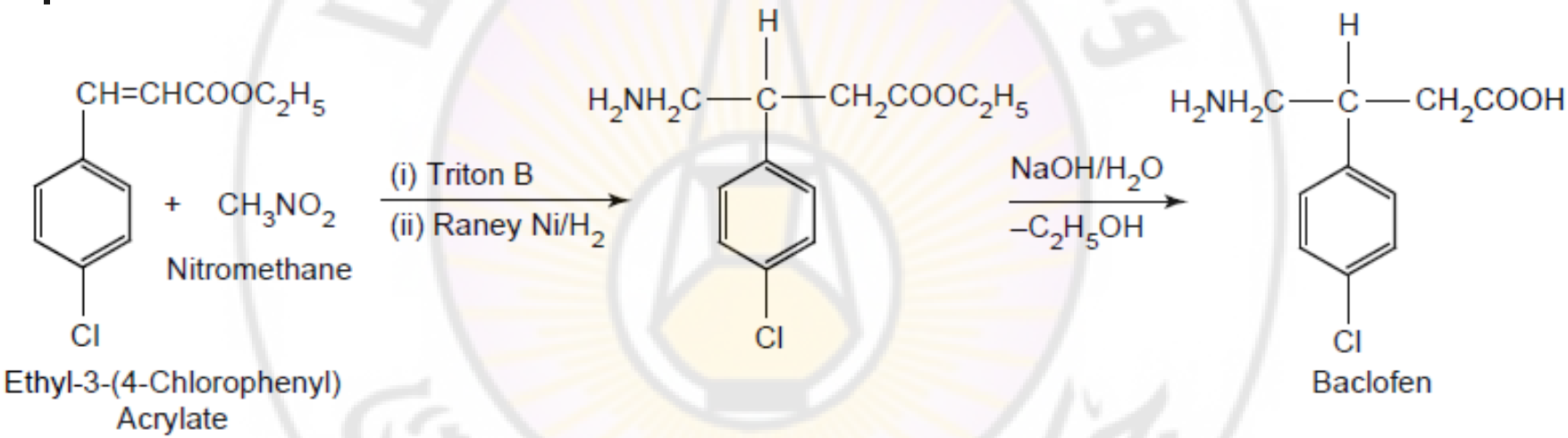
Chlorphenesin Carbamate synthesis



Chlorphenesin Carbamate synthesis

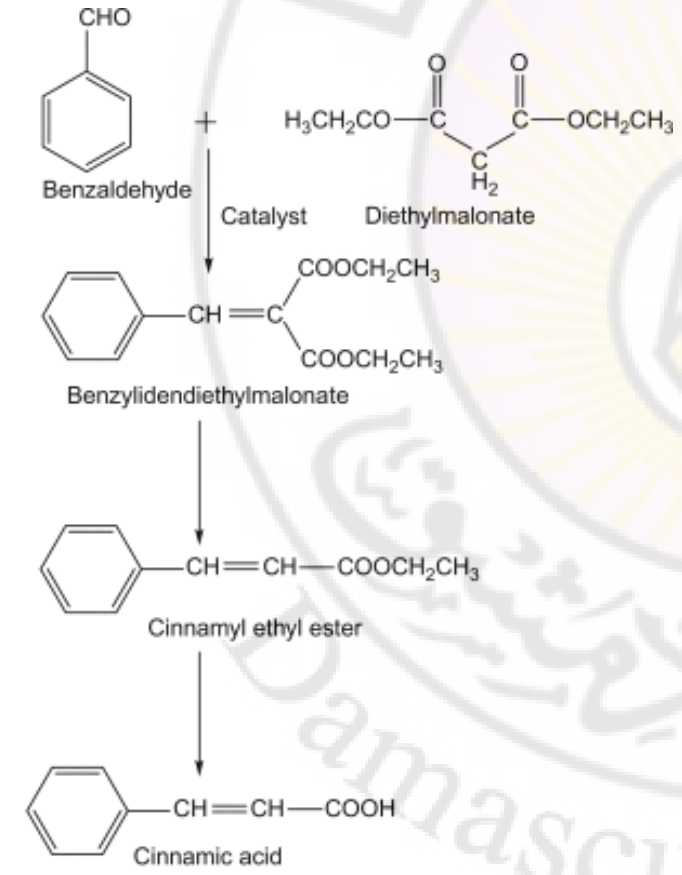


Baclofen synthesis



Benzyltrimethylammonium hydroxide, also known as Triton B or trimethylbenzylammonium hydroxide, is a quaternary ammonium salt that functions as an organic base.

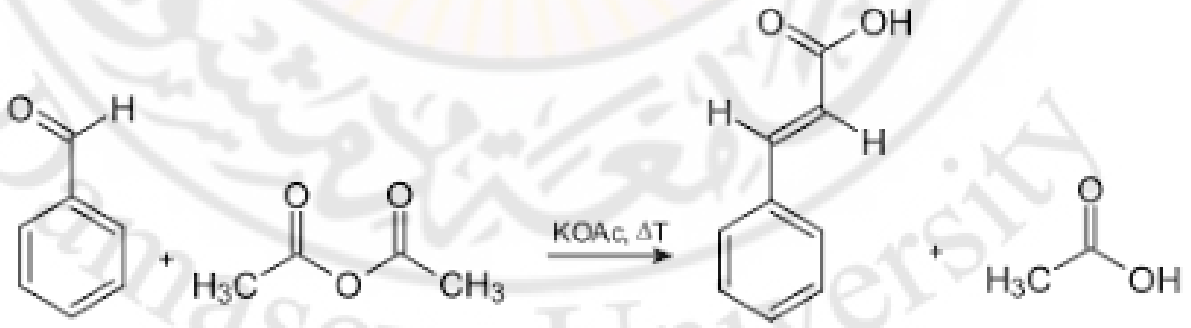
Cinnamic acid and Ethyl cinnamate ester synthesis by Knoevenagel condensation



One of the simplest and most efficient and environmentally benign methods for cinnamic acid synthesis is based on the Knoevenagel condensation of diethylmalonate with benzaldehyde

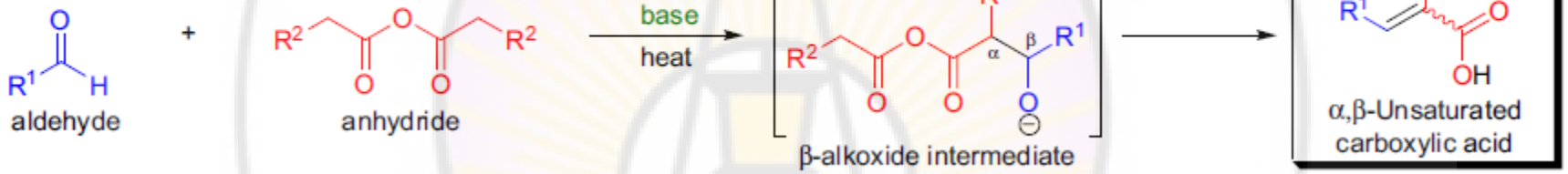
Cinnamic acid synthesis by Perkin reaction

- ✓ The Perkin reaction is an organic reaction developed by English chemist William Henry Perkin that is used to make cinnamic acids.
- ✓ It gives an α,β-unsaturated aromatic acid or α-substituted β-aryl acrylic acid by the aldol condensation of an aromatic aldehyde and an acid anhydride, in the presence of an alkali salt of the acid.
- ✓ The alkali salt acts as a base catalyst, and other bases can be used instead

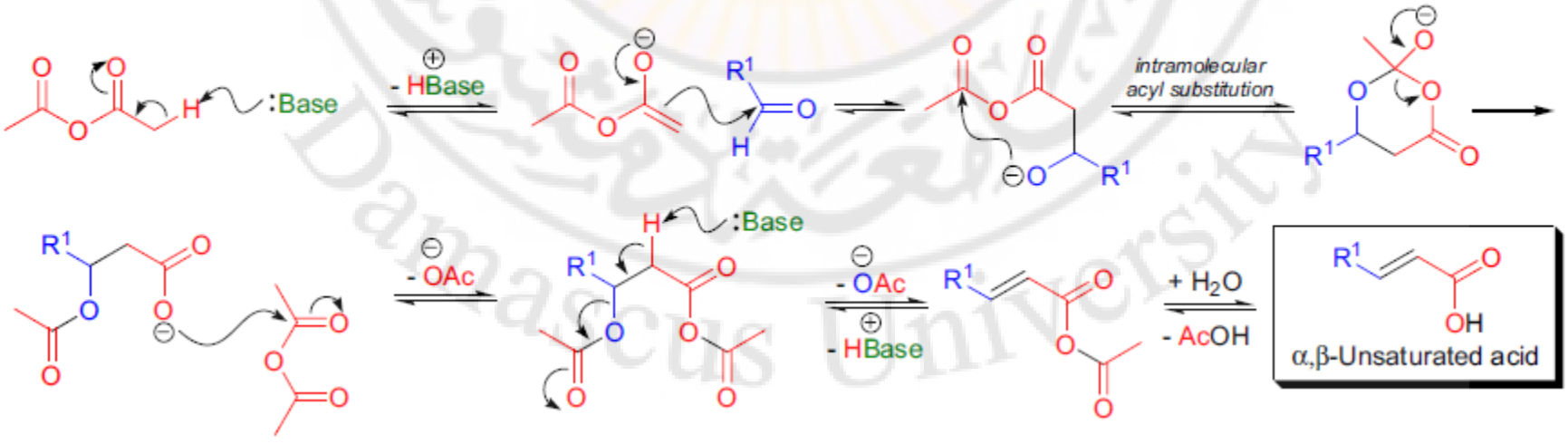


Cinnamic acid synthesis by Perkin reaction

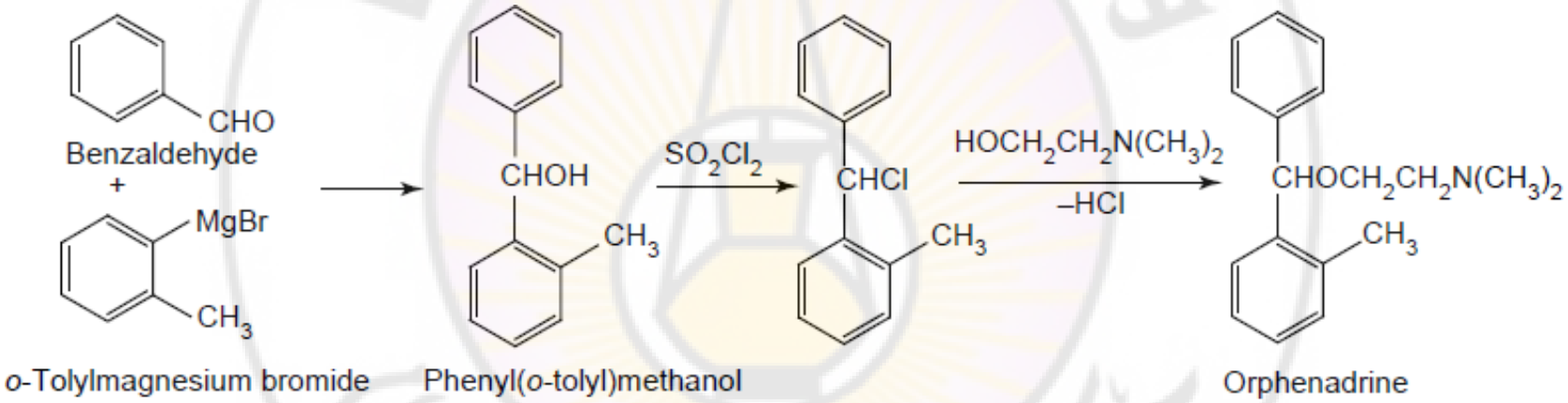
Perkin reaction:



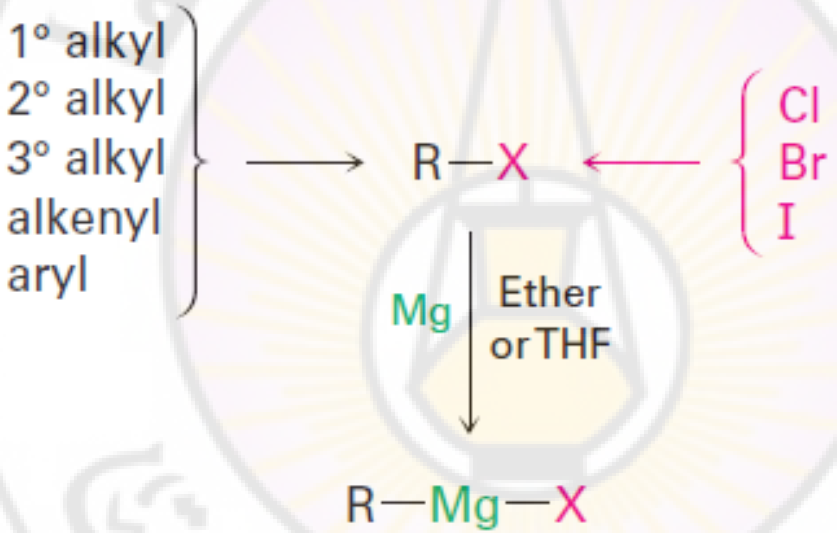
Mechanism: [23,3,24-31,4,32-35]

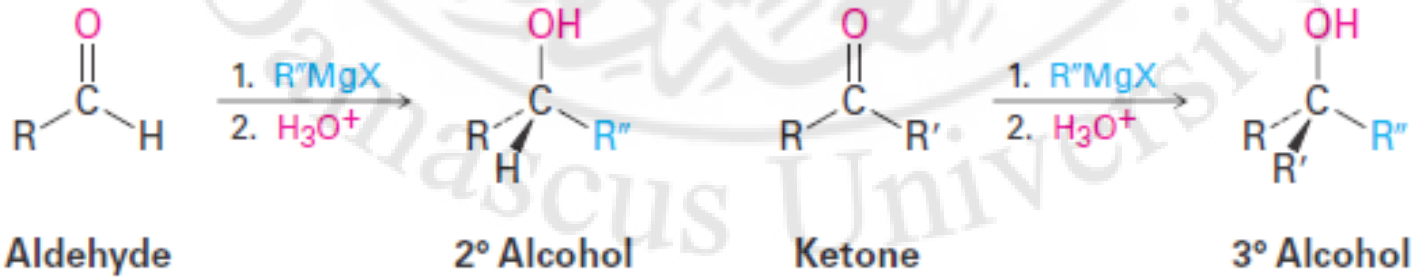


Orphenadrine synthesis



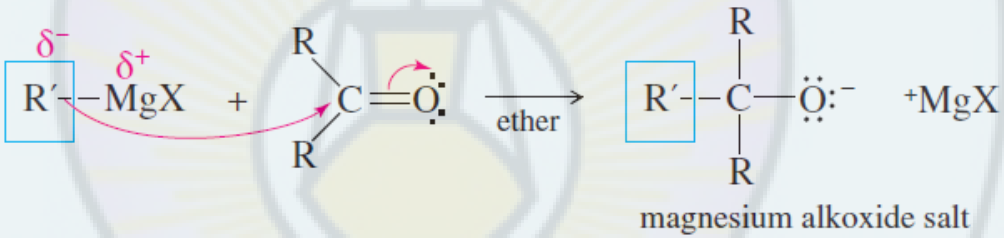
Grignard reagents



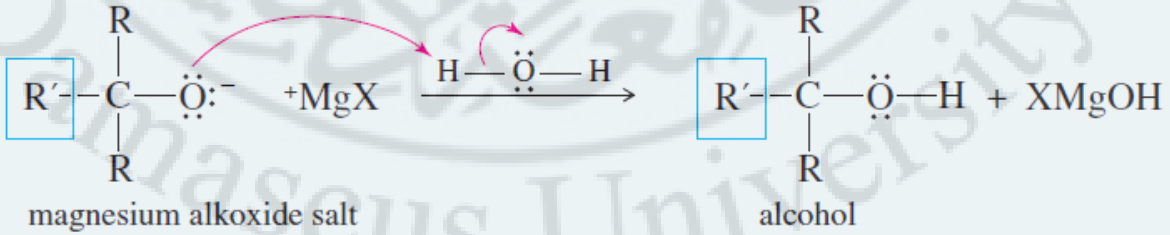


Grignard reagents

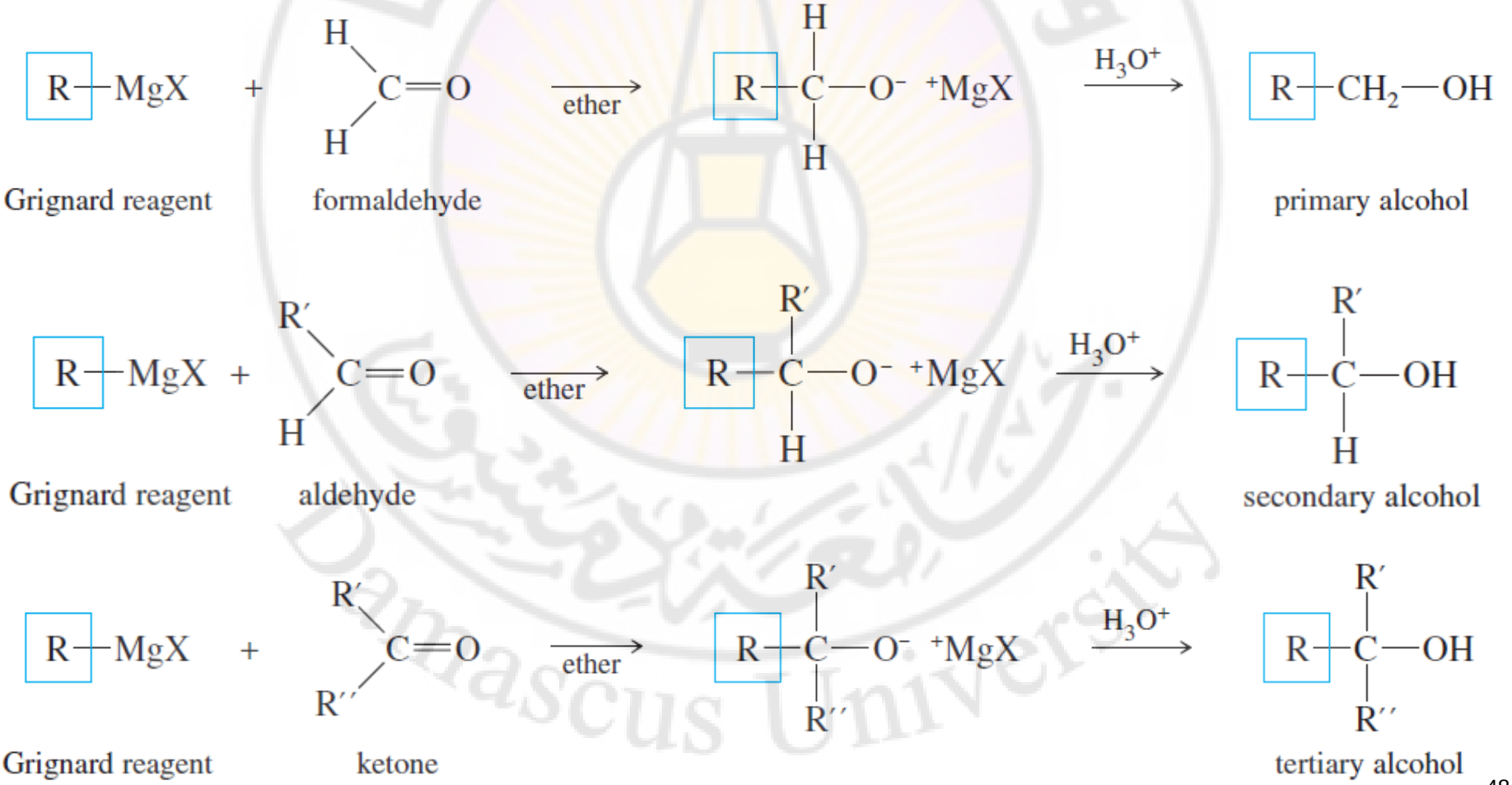
Reaction 1: The Grignard reagent attacks a carbonyl compound to form an alkoxide salt.



Reaction 2: After the first reaction is complete, water or dilute acid is added to protonate the alkoxide and give the alcohol.

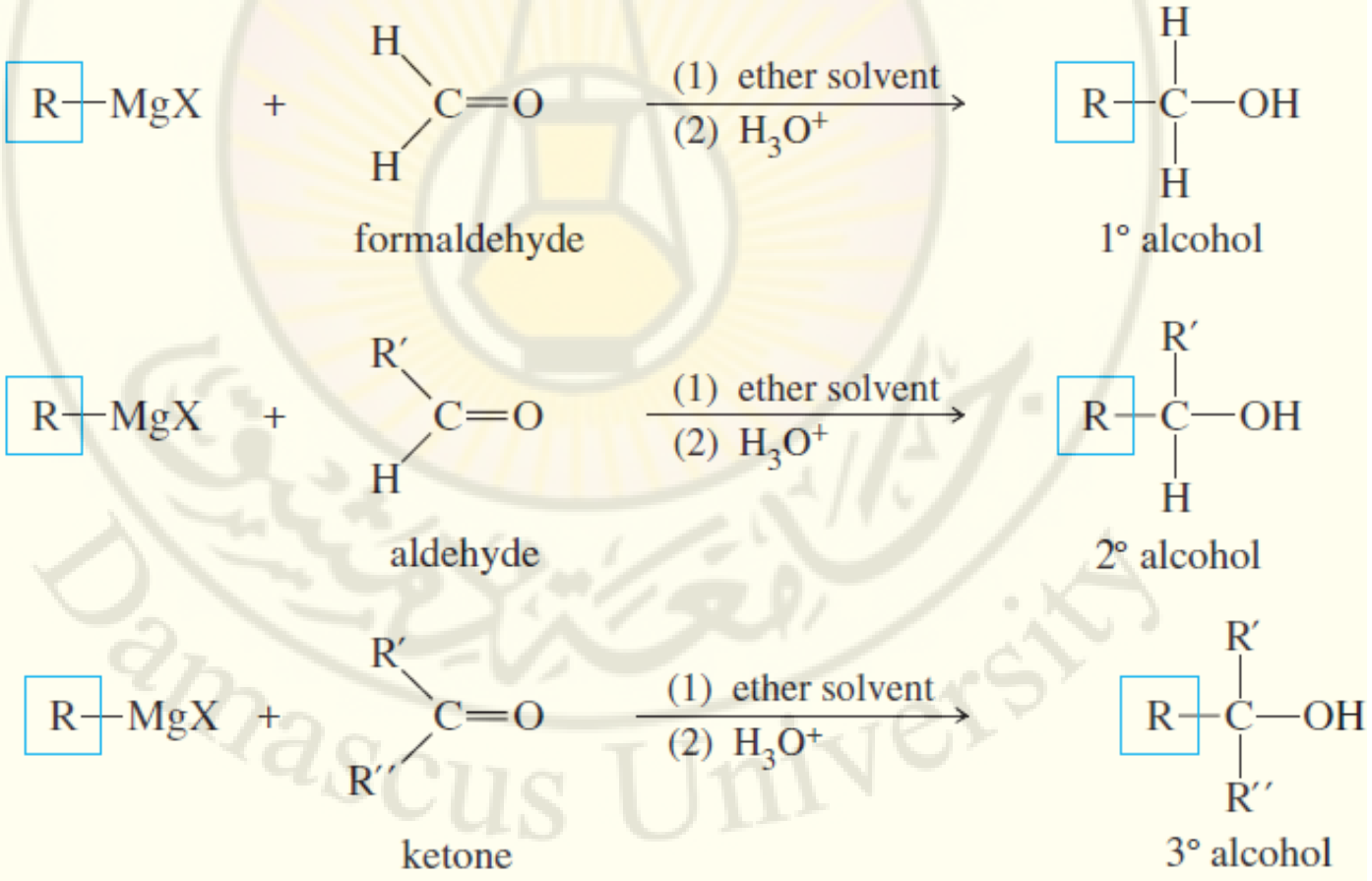


Grignard reagents

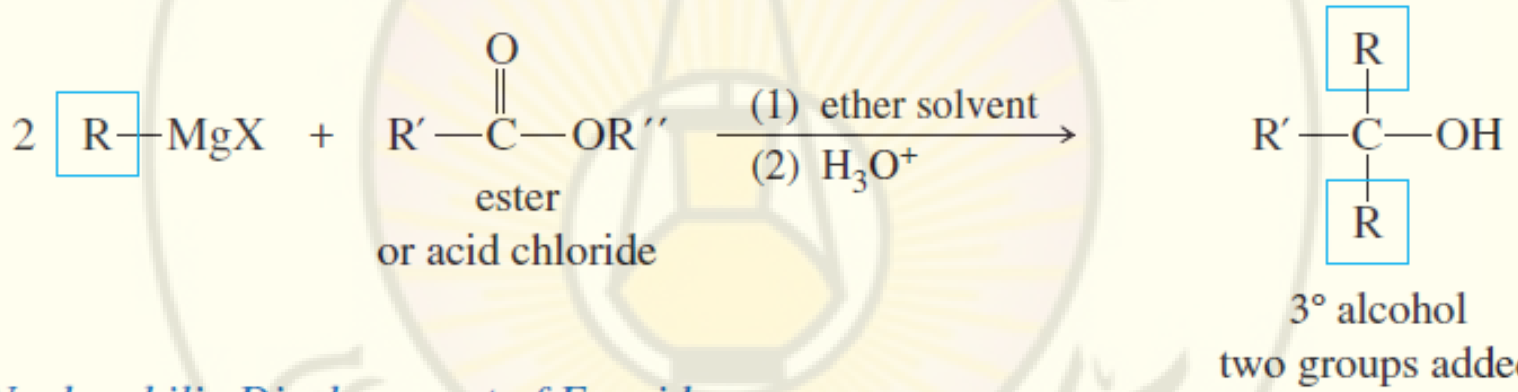


Grignard reagents

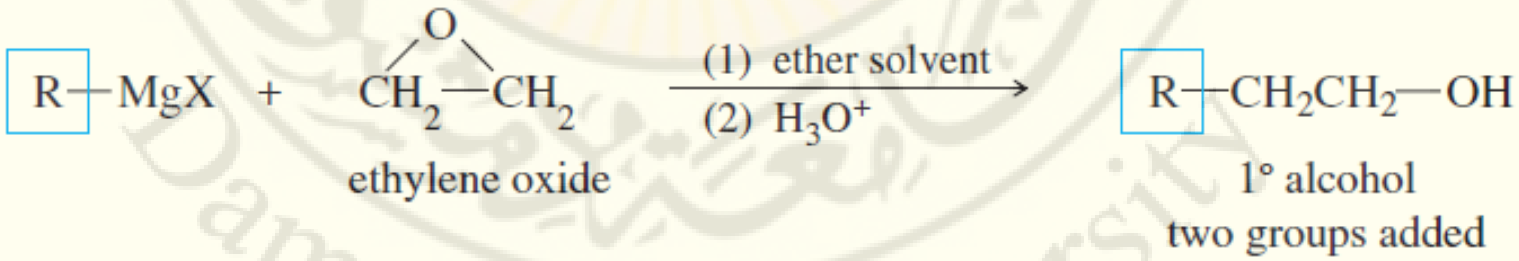
1. Nucleophilic Additions to Carbonyl Compounds



Grignard reagents



2. Nucleophilic Displacement of Epoxides



Converting Alcohols to alkyl halides

$$3\,R{-}OH + PCl_3 \longrightarrow 3\,R{-}Cl + P(OH)_3$$

$$3\,R{-}OH + PBr_3 \longrightarrow 3\,R{-}Br + P(OH)_3$$

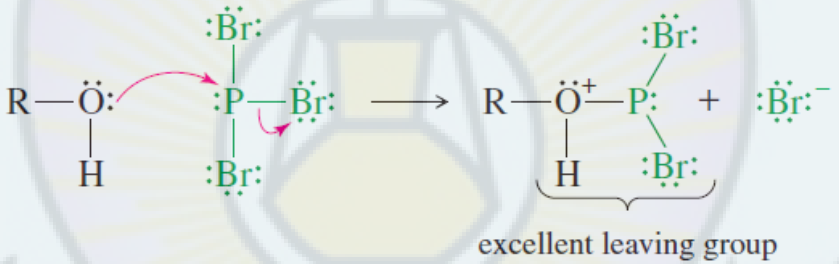
$$R{-}OH + PCl_5 \longrightarrow R{-}Cl + POCl_3 + HCl$$

$$2\,P + 3\,I_2 \rightleftharpoons 2\,PI_3$$

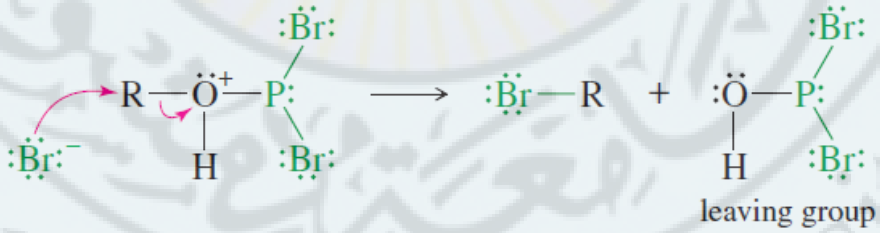
$$6\,R{-}OH + 2\,P + 3\,I_2 \longrightarrow 6\,R{-}I + 2\,P(OH)_3$$

Converting Alcohols to alkyl halides

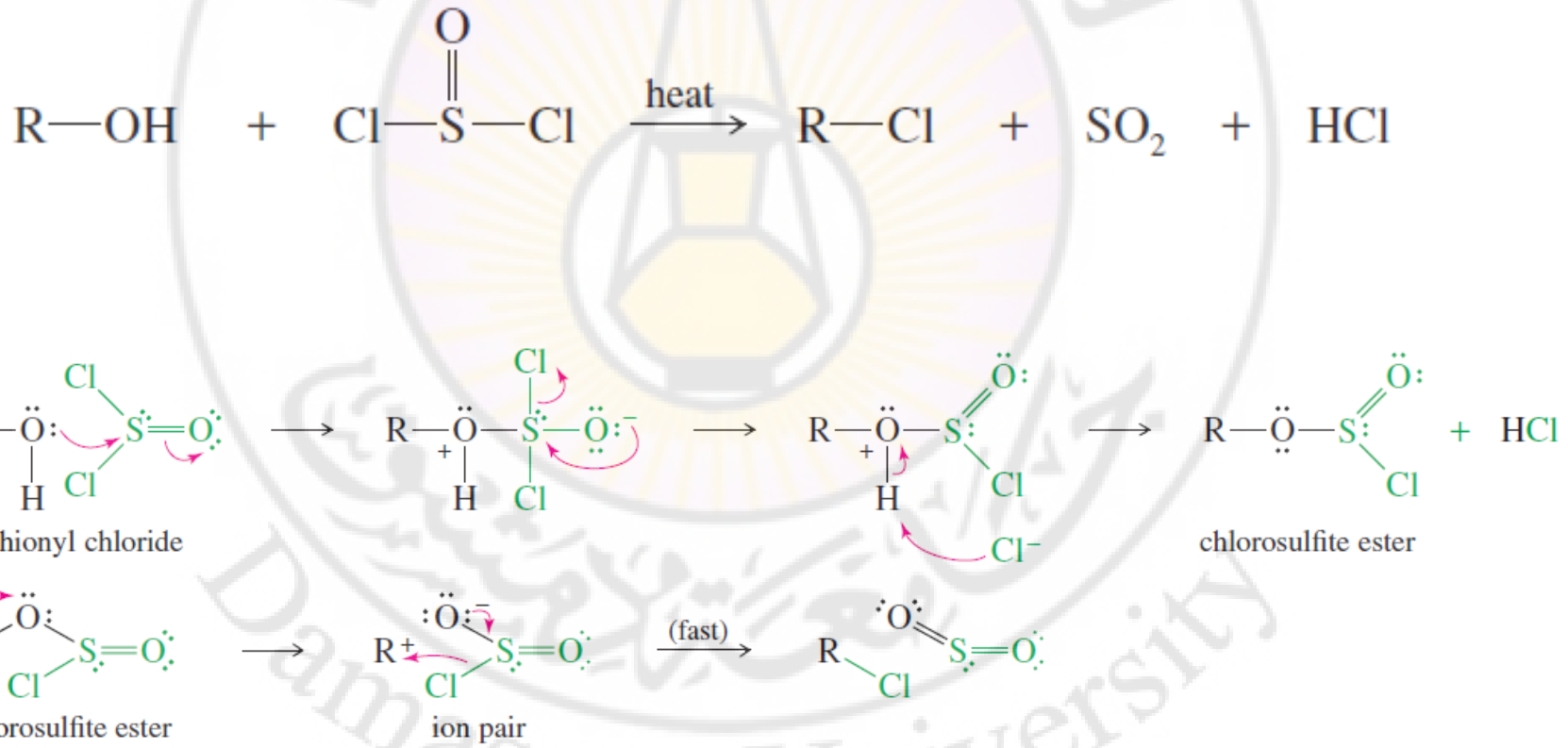
Step 1: PBr_3 is a strong electrophile. An alcohol displaces bromide ion from PBr_3 to give an excellent leaving group.



Step 2: Bromide displaces the leaving group to give the alkyl bromide.



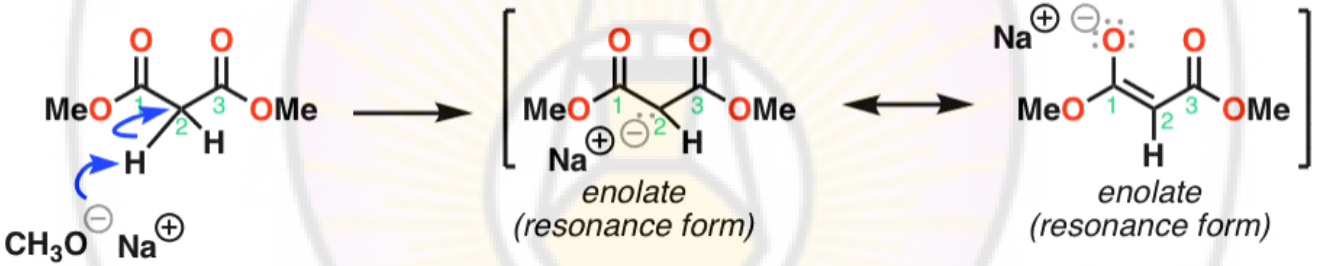
Converting Alcohols to alkyl halides



Converting Alcohols to alkyl halides

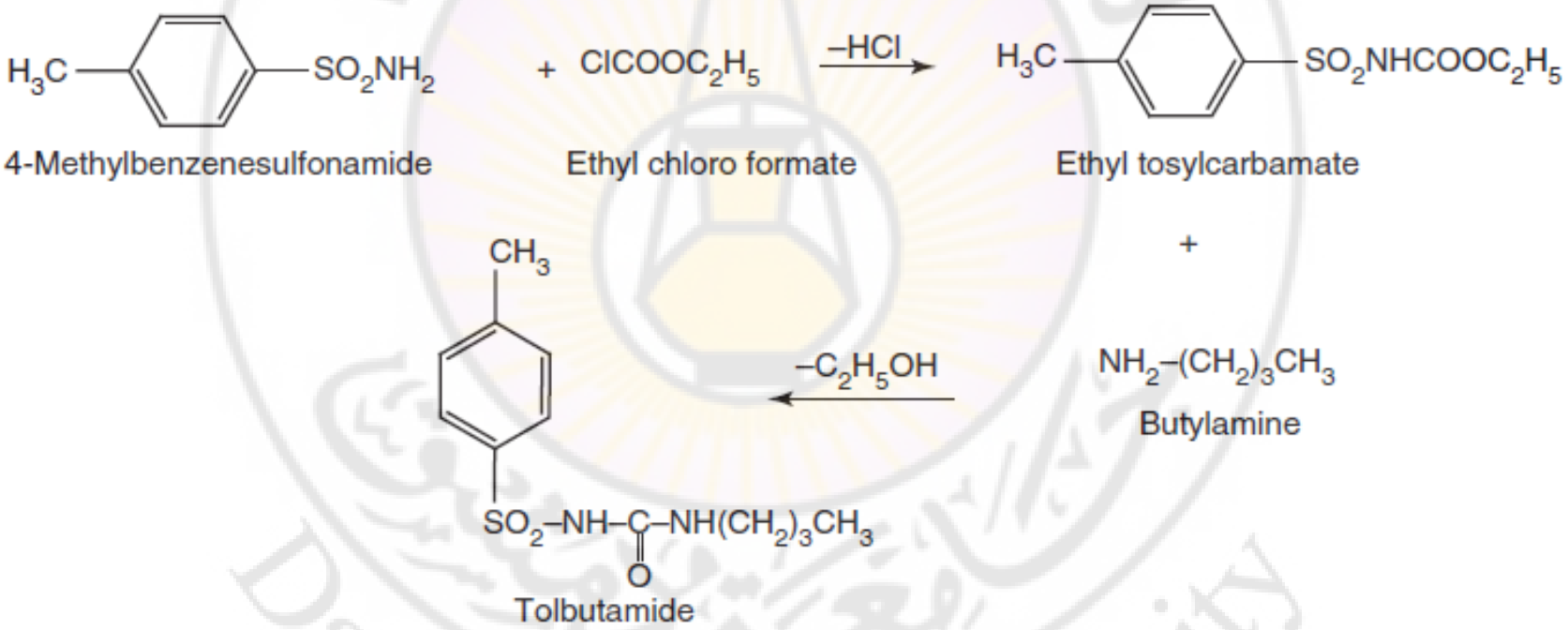
The Malonic Ester Synthesis: Mechanism

In step 1, the $CH_3O^{\ominus}$ acts as a base to remove the most acidic proton (on C_2) to make an enolate

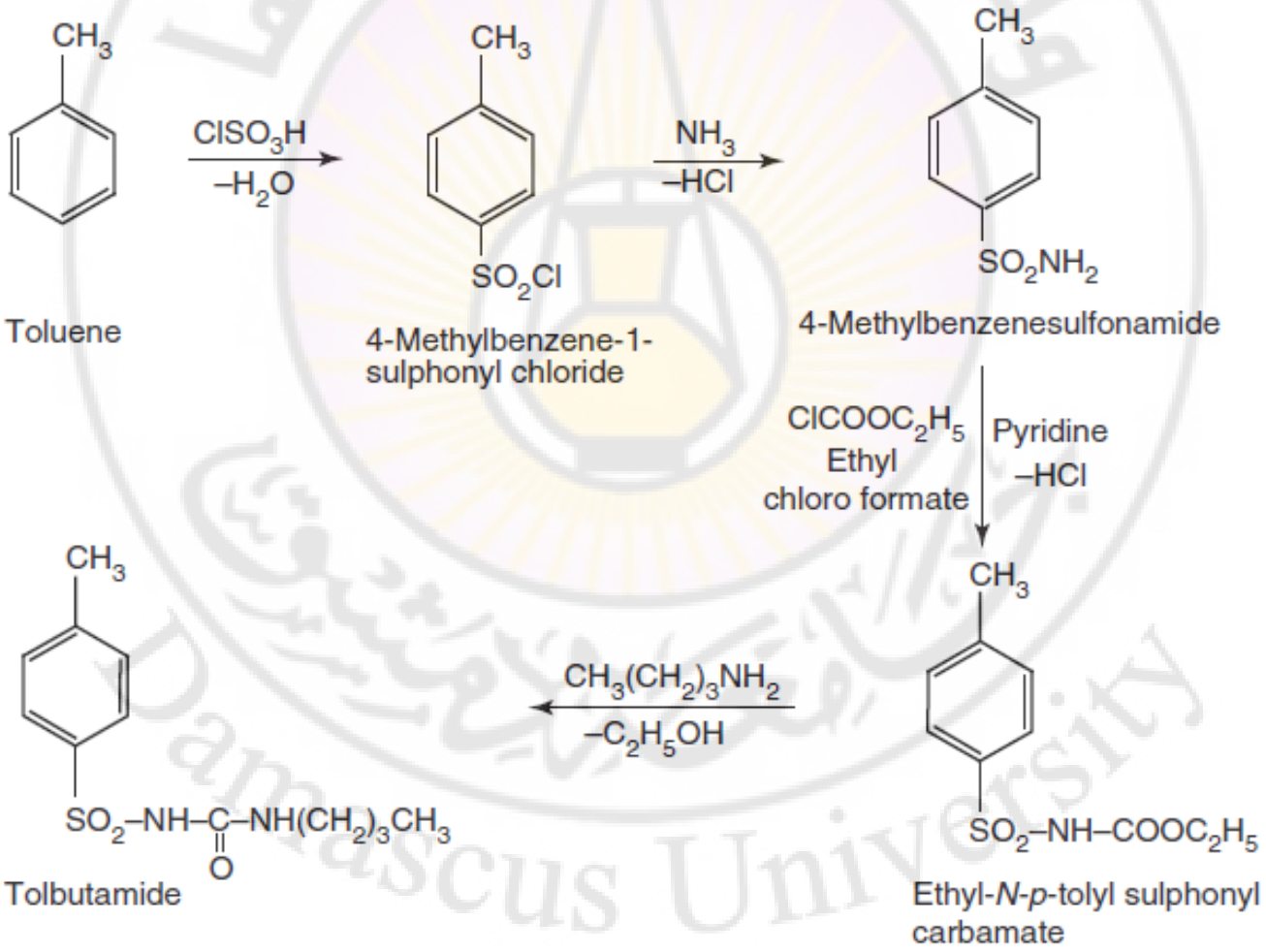


Drug Synthesis
Hypoglycaemic drugs

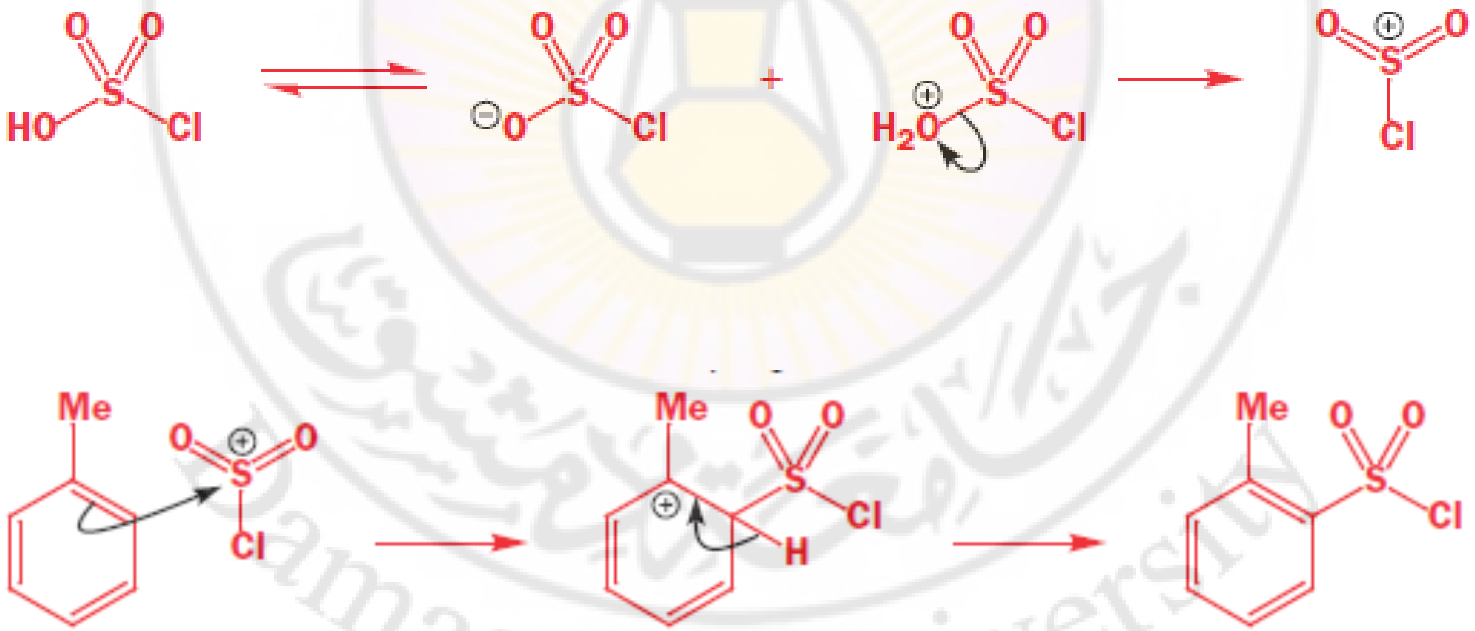
Tolbutamide Synthesis



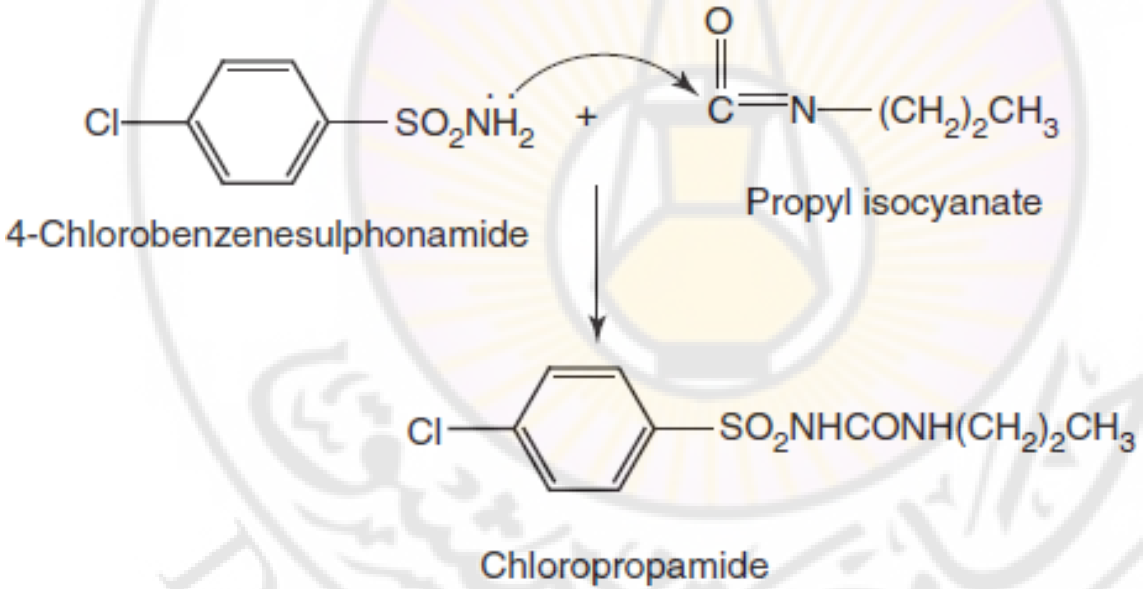
Tolbutamide synthesis



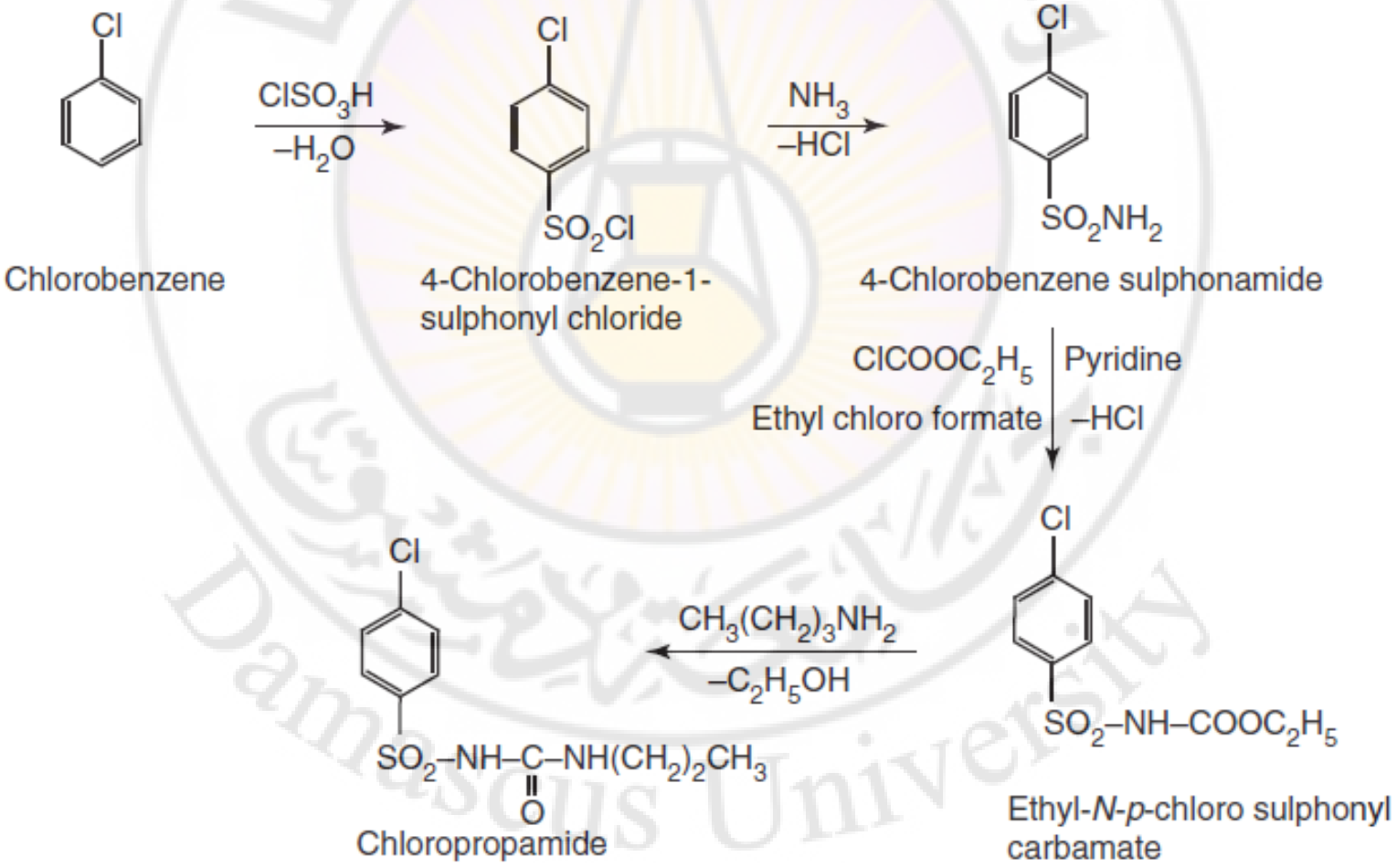
Tolbutamide synthesis

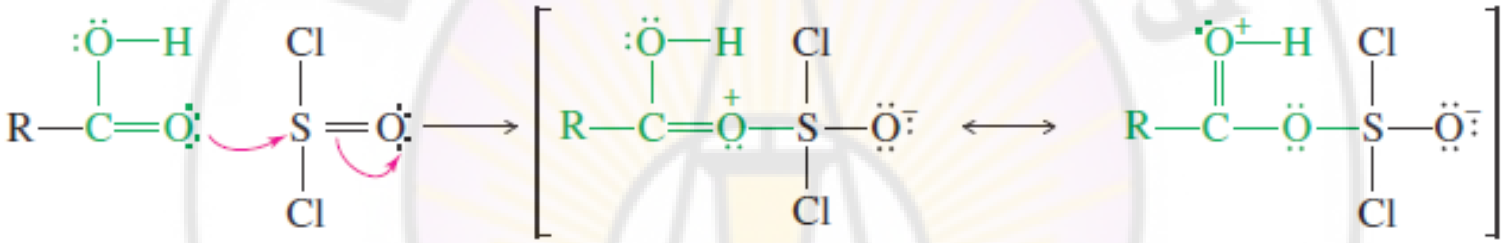


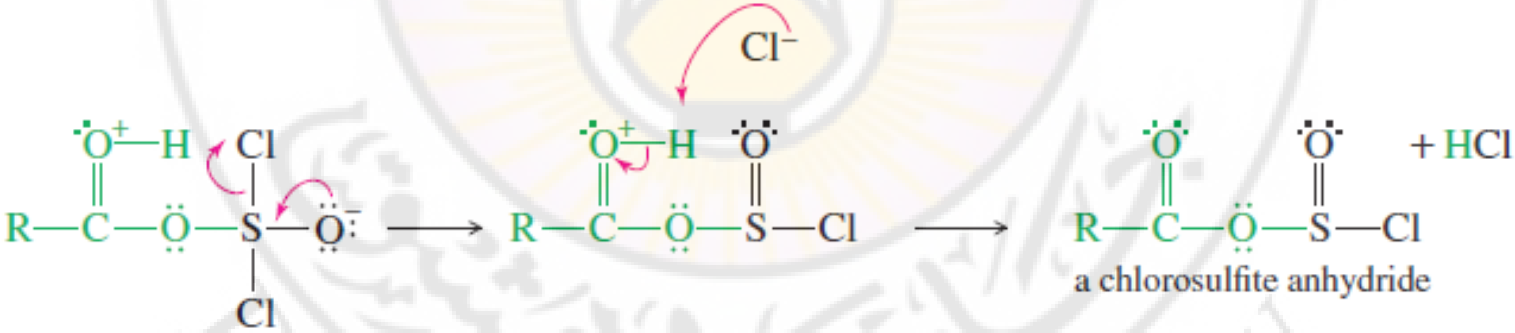
Chloroproamide synthesis

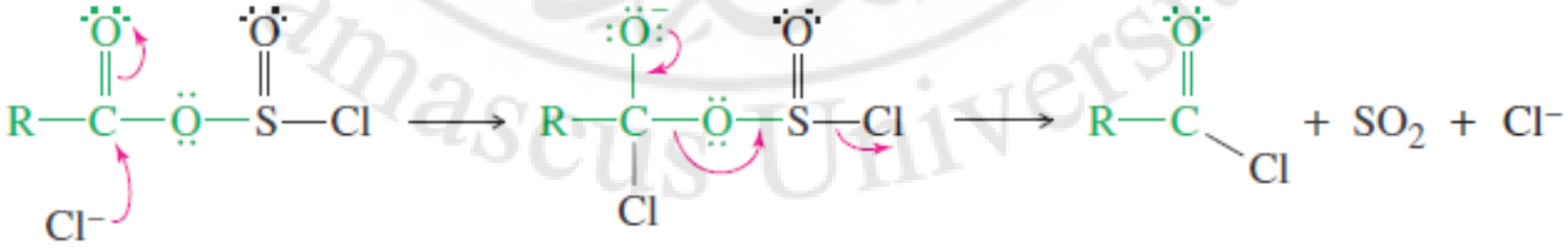


Chloroproamide synthesis

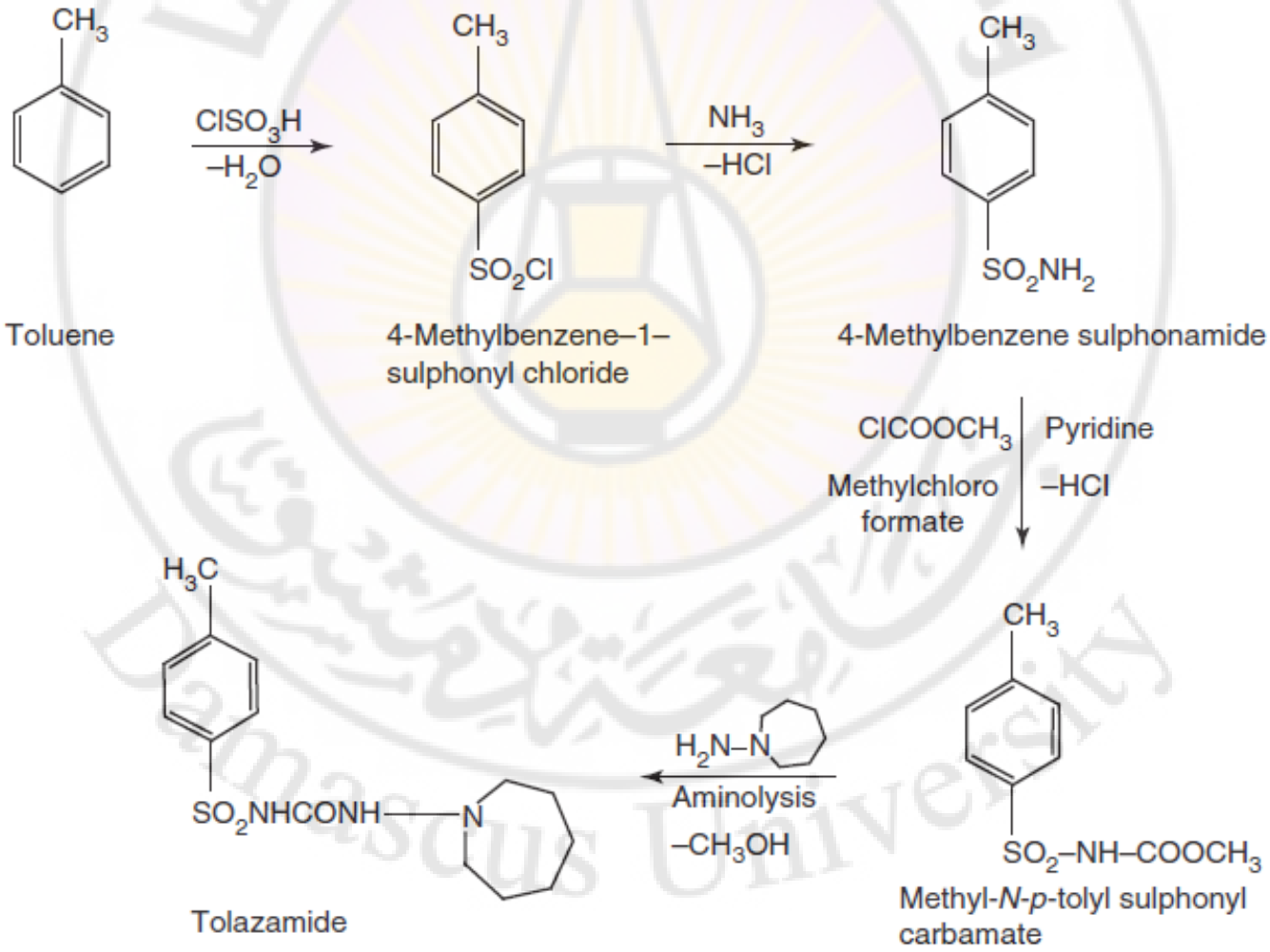




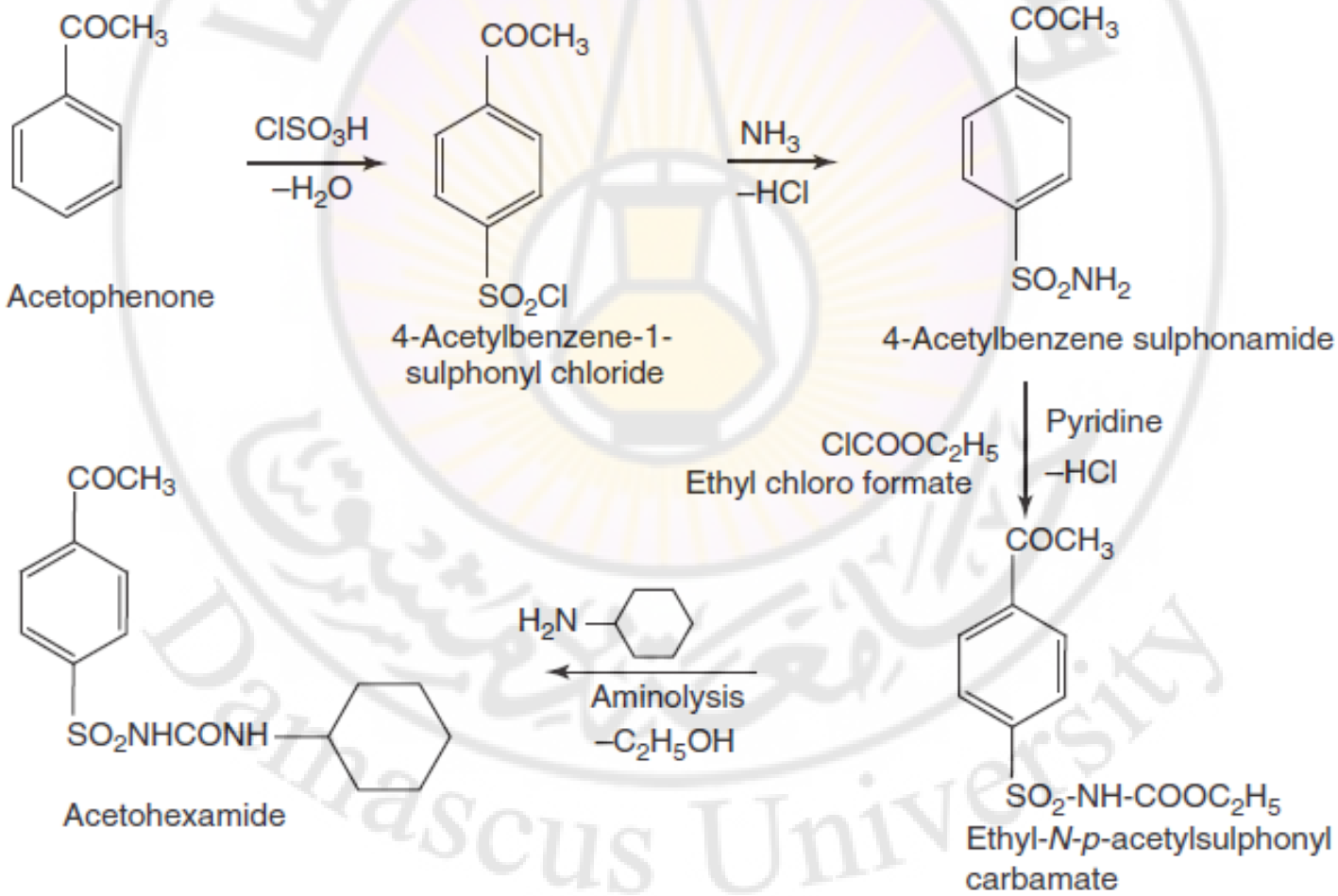

Cl⁻
+ HCl
a chlorosulfite anhydride


Cl⁻
+ SO2 + Cl⁻

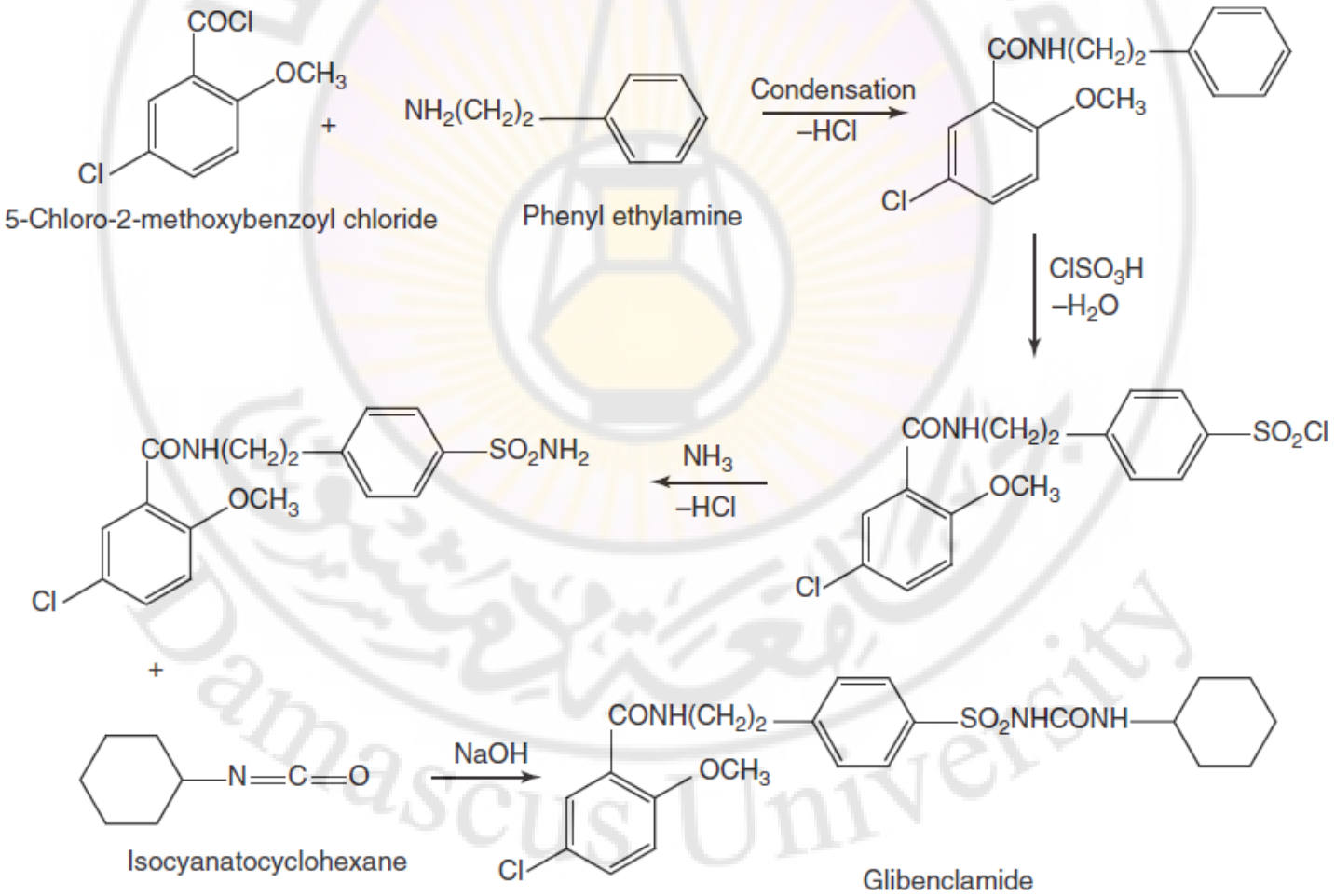
Tolazamide synthesis



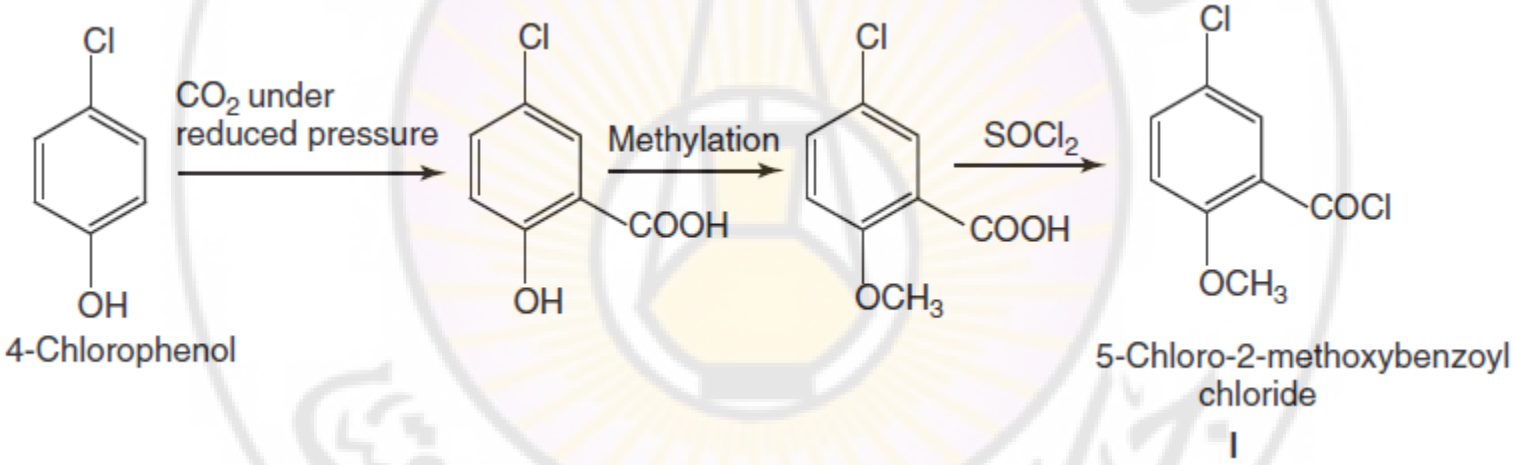
Acetohexamide synthesis



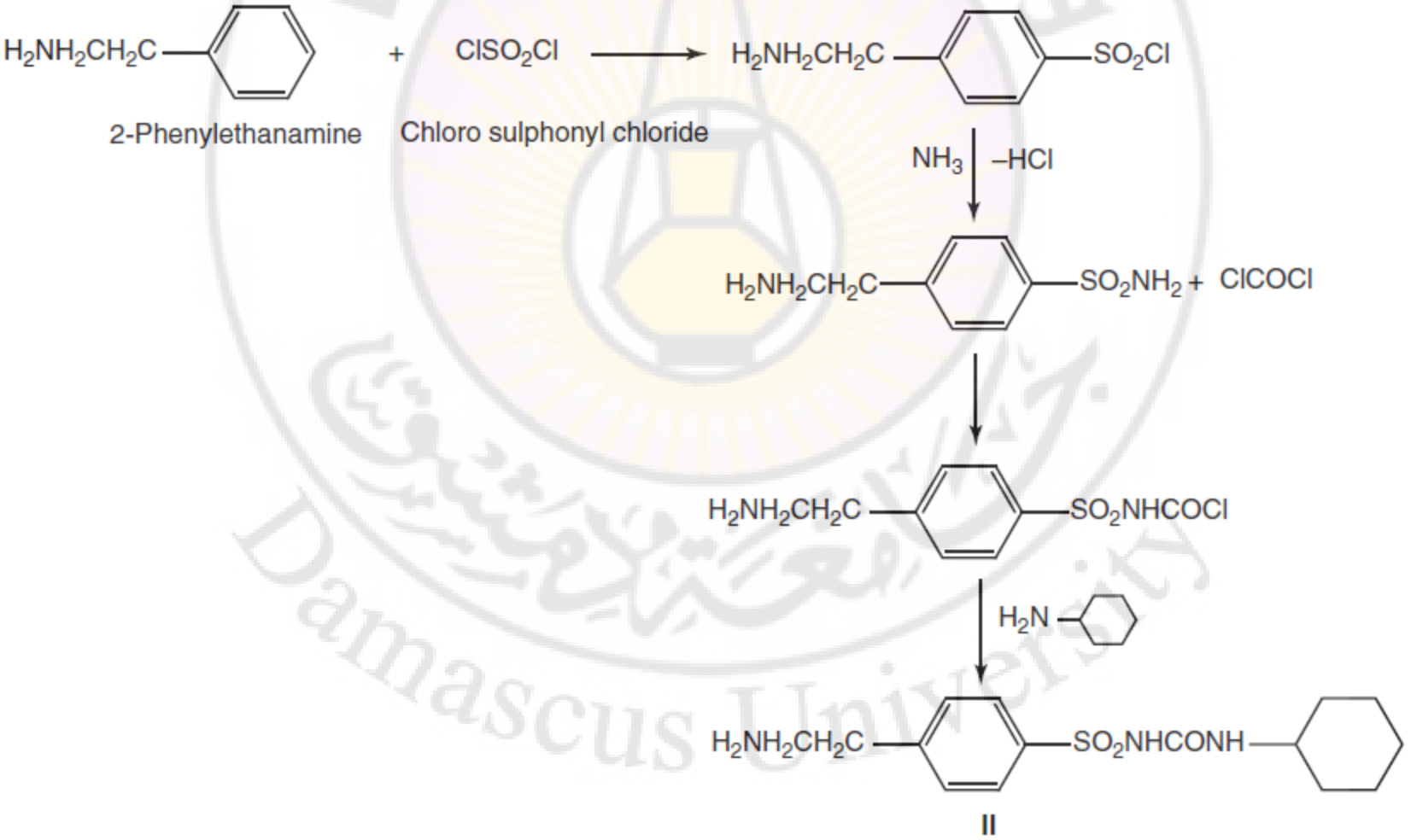
Glibenclamide synthesis



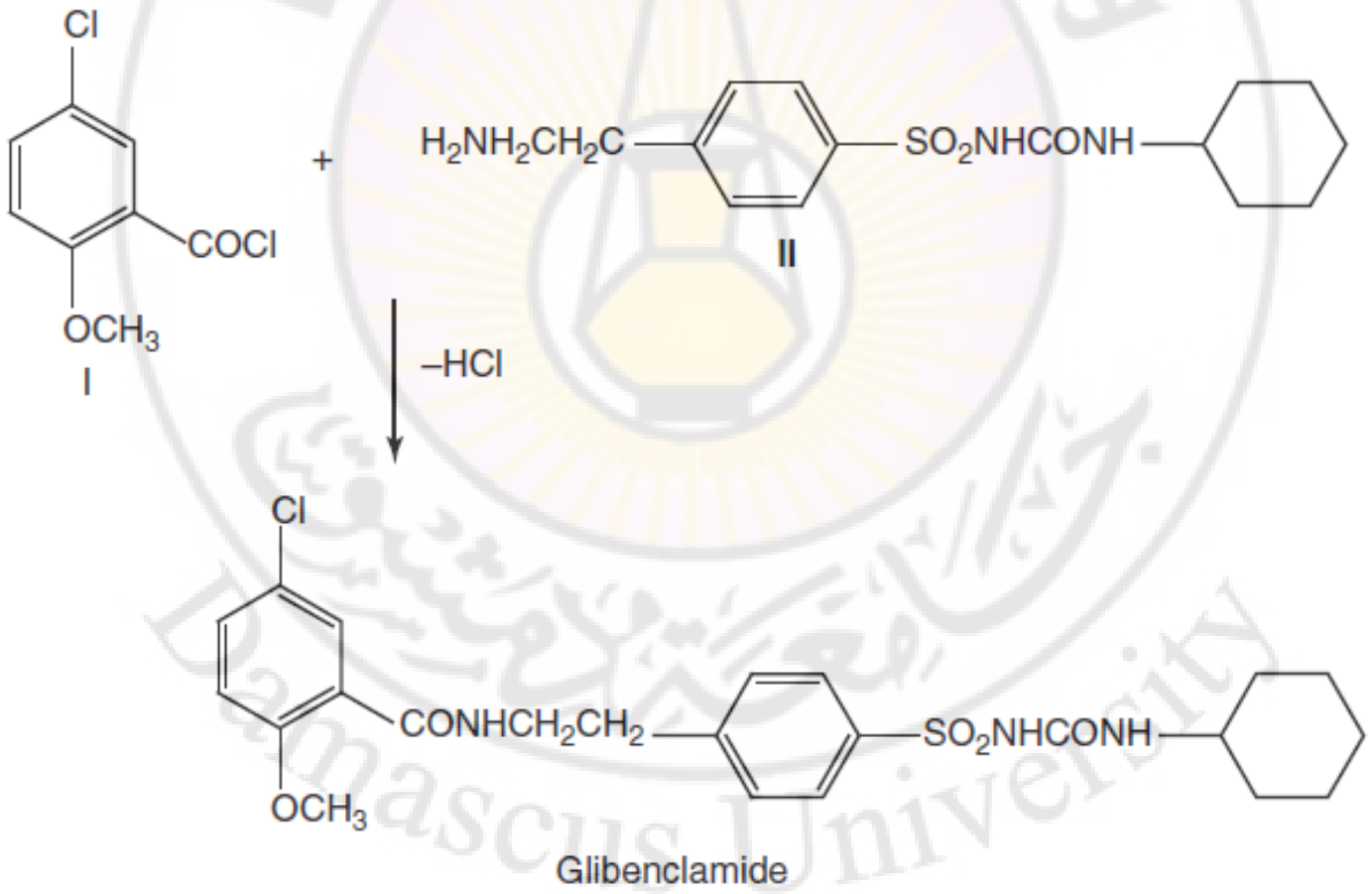
synthesis



synthesis


H2NH2CH2C
+
ClSO2Cl
H2NH2CH2C
SO2Cl
2-Phenylethanamine
Chloro sulphonyl chloride
NH3
–HCl
H2NH2CH2C
SO2NH2 + ClCOCl
H2NH2CH2C
SO2NHCOCl
H2N
H2NH2CH2C
SO2NHCONH
II

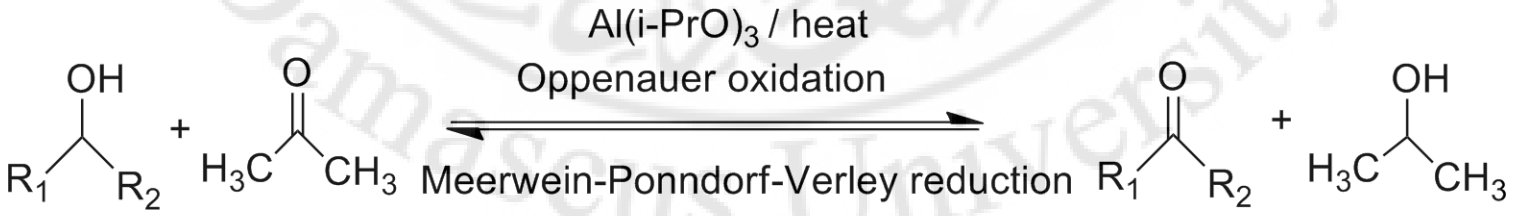
synthesis


Cl
COCl
OCH3
I
+
H2NH2CH2C
SO2NHCONH
II
–HCl
Cl
CONHCH2CH2
SO2NHCONH
OCH3
Glibenclamide

MeerweinPonndorf Verley

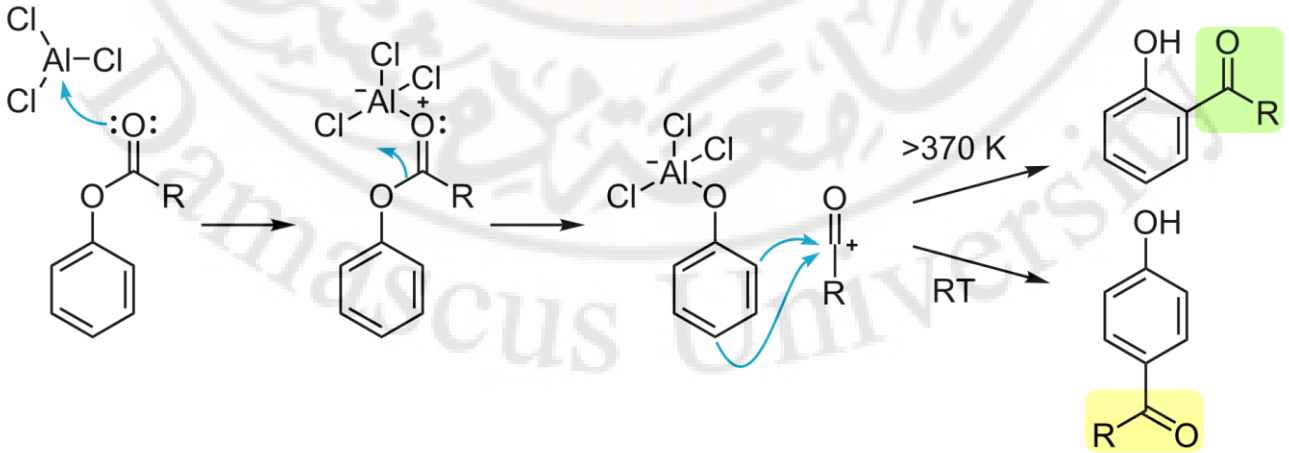
The **MeerweinPonndorf Verley** (MPV) reduction in organic chemistry is the reduction of ketones and aldehydes to their corresponding alcohols utilizing aluminium alkoxide catalysis in the presence of a sacrificial alcohol

The advantages of the MPV reduction lie in its high chemoselectivity, and its use of a cheap environmentally friendly metal catalyst

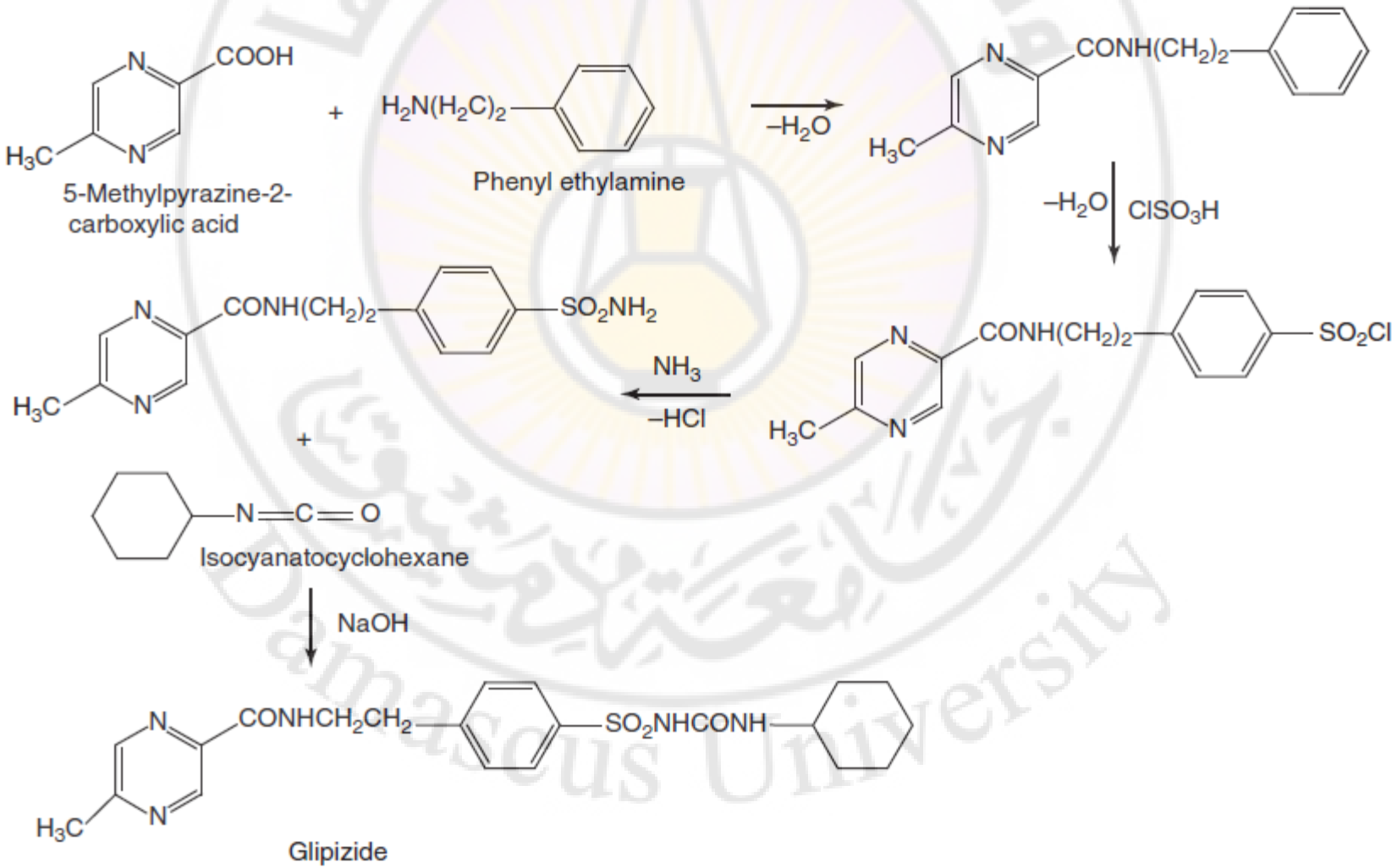


Fries rearrangement

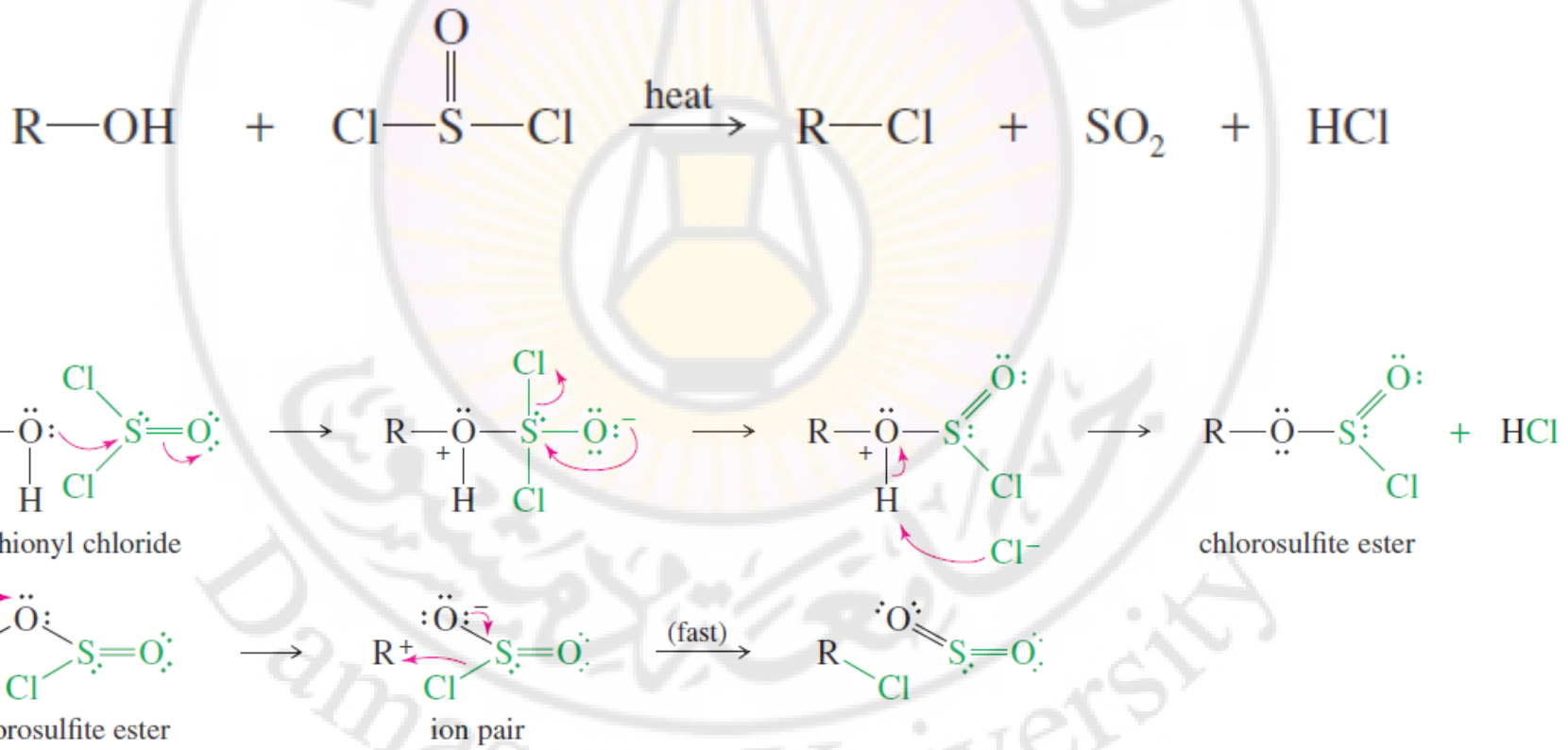
- ✓ The **Fries rearrangement** is a rearrangement reaction of a phenolic ester to a hydroxy aryl ketone by catalysis of Lewis acids.
- ✓ It involves migration of an acyl group of phenol ester to the aryl ring.
- ✓ The reaction is ortho and para selective and one of the two products can be favoured by changing reaction conditions, such as temperature and solvent.

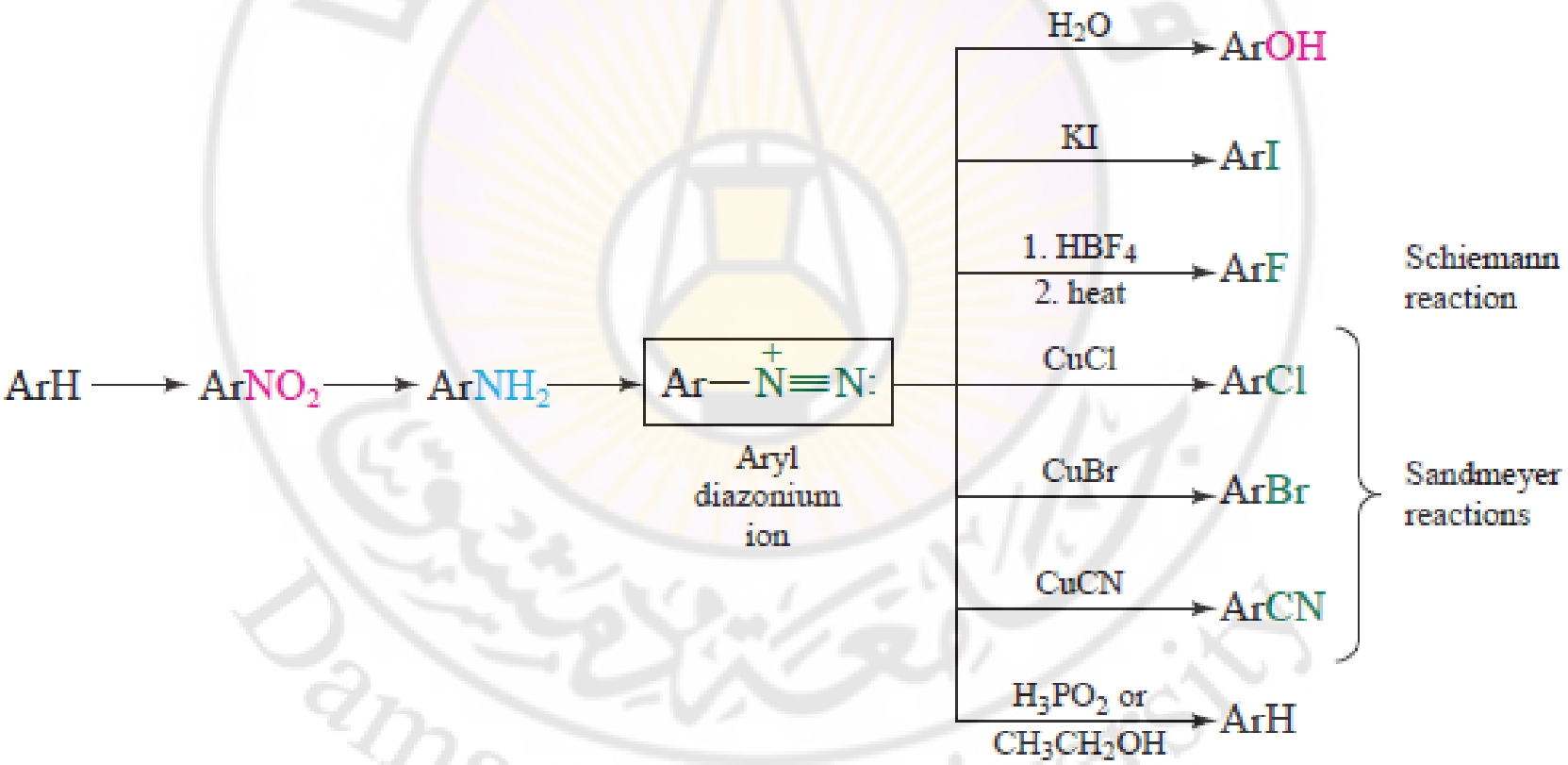


Glipizide synthesis



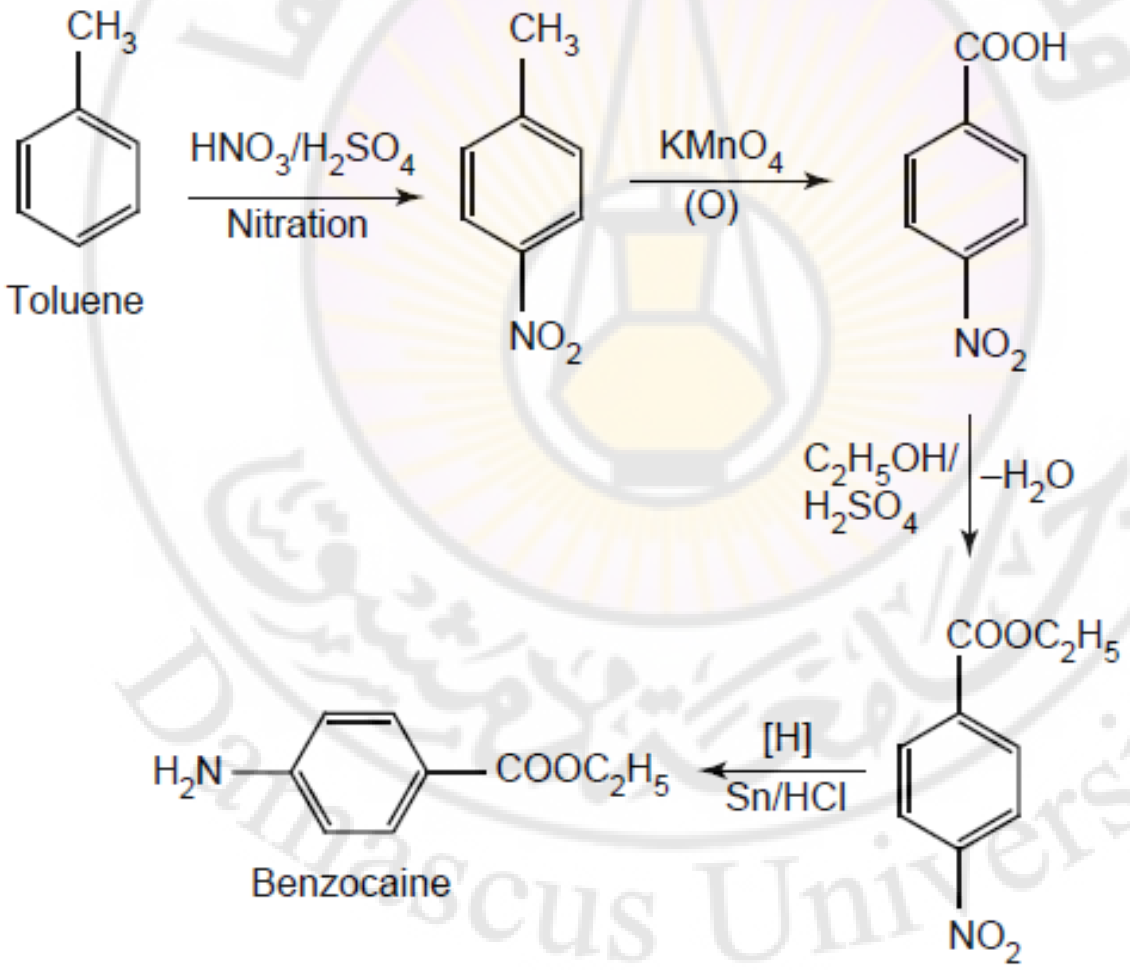
synthesis


R—OH + Cl—S(=O)—Cl heat R—Cl + SO2 + HCl
thionyl chloride
chlorosulfite ester
HCl
chlorosulfite ester
ion pair
(fast)

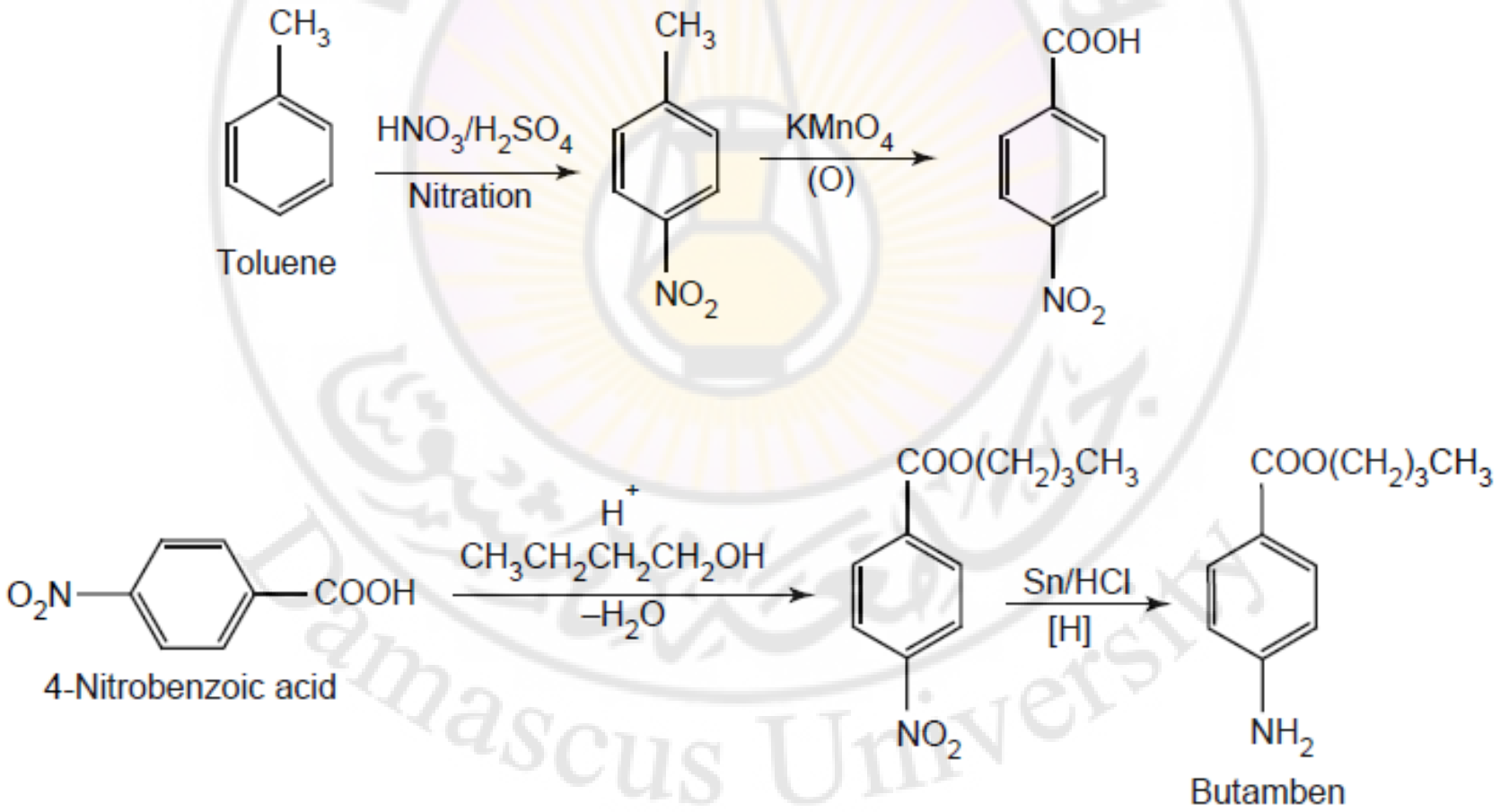

ArH
ArNO2
ArNH2
Ar—N≡N:
Aryl diazonium ion
H2O
ArOH
KI
ArI
1. HBF4
2. heat
ArF
Schiemann reaction
CuCl
ArCl
CuBr
ArBr
CuCN
ArCN
Sandmeyer reactions
H3PO2 or CH3CH2OH
ArH

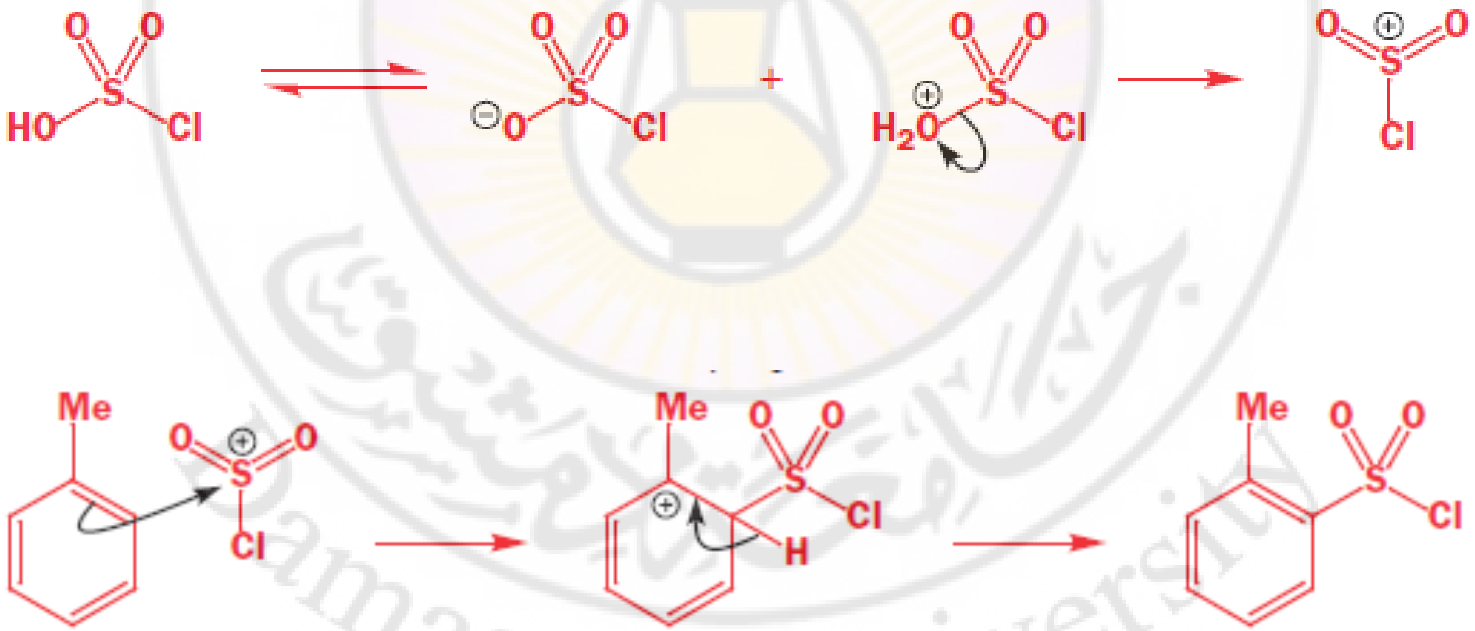
Drug Synthesis
Local Anaesthetics drugs

Benzocaine Synthesis

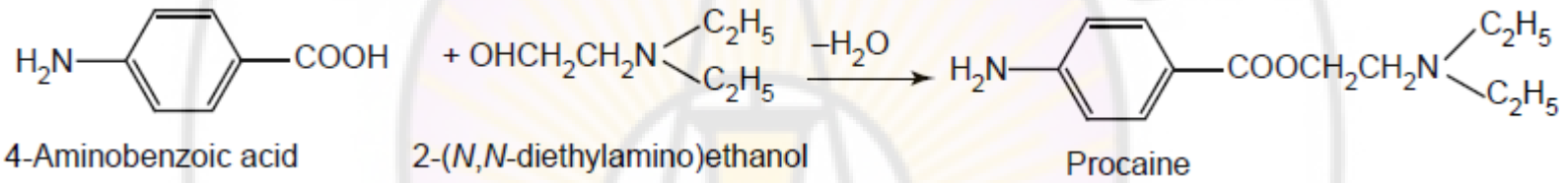


Butamben synthesis




HO
Cl
H2O
Me
H

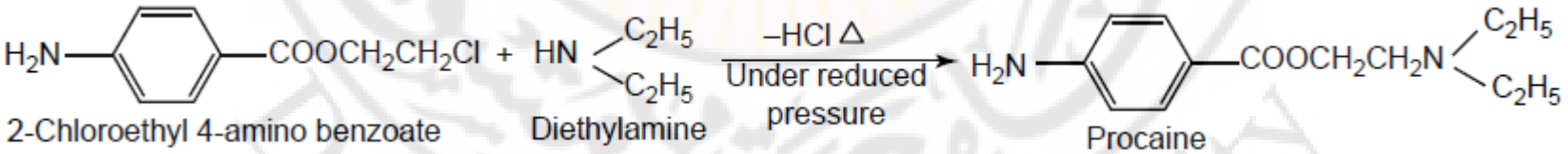
Procaine synthesis



4-Aminobenzoic acid

2-(*N*,*N*-diethylamino)ethanol

Procaine

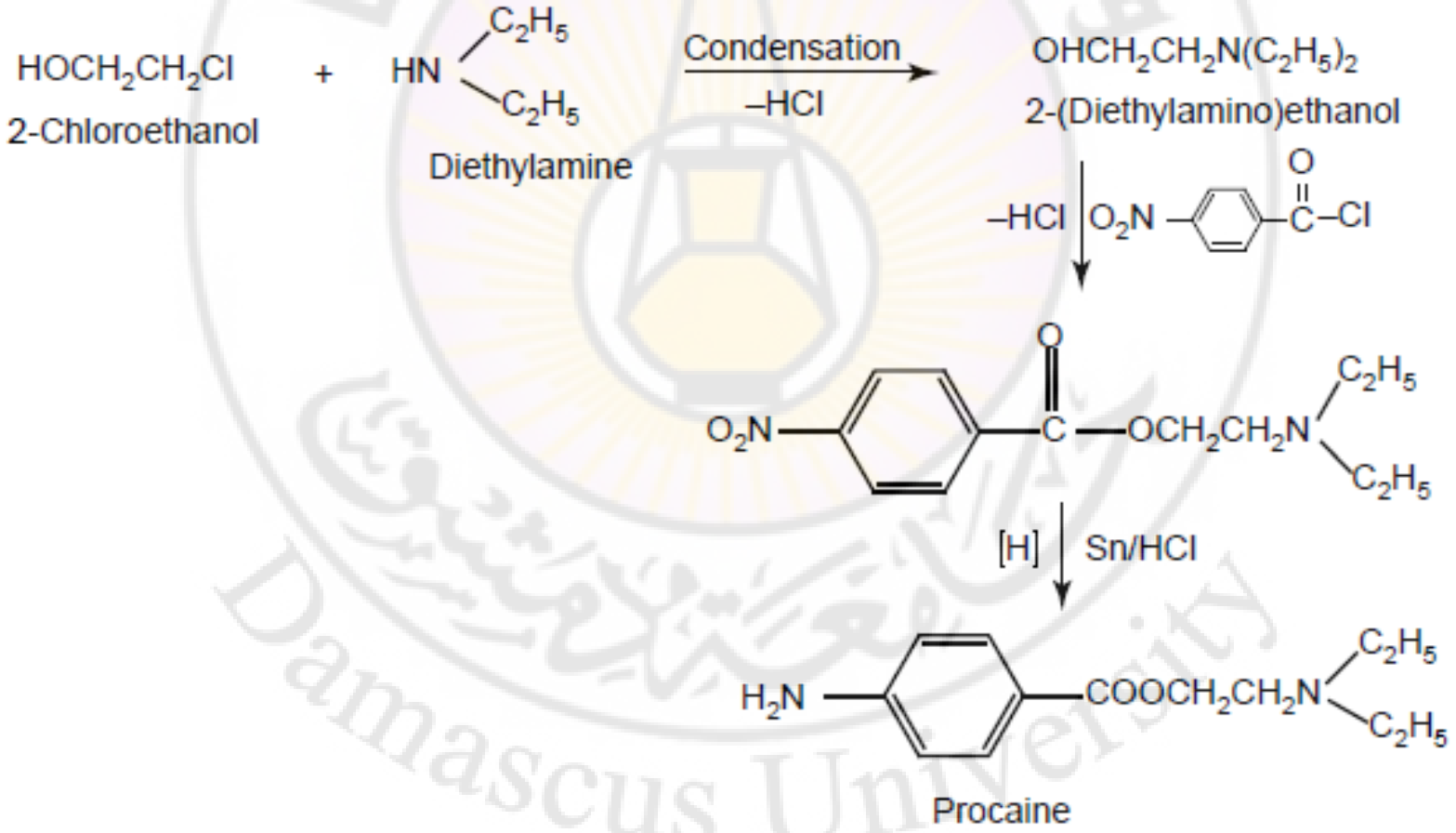


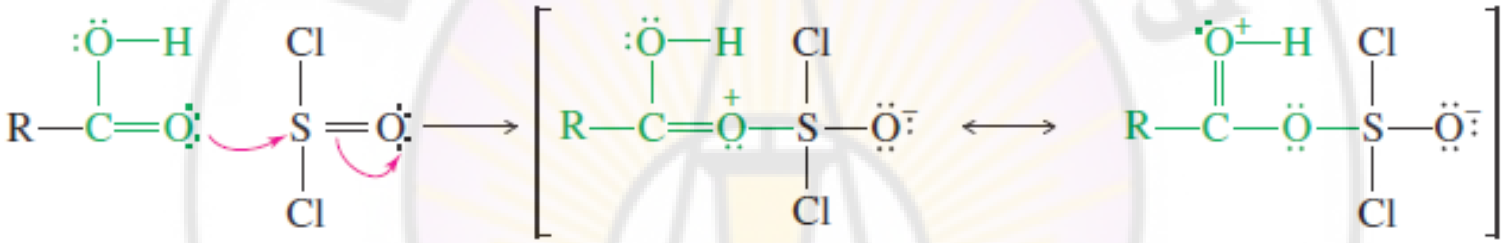
2-Chloroethyl 4-amino benzoate

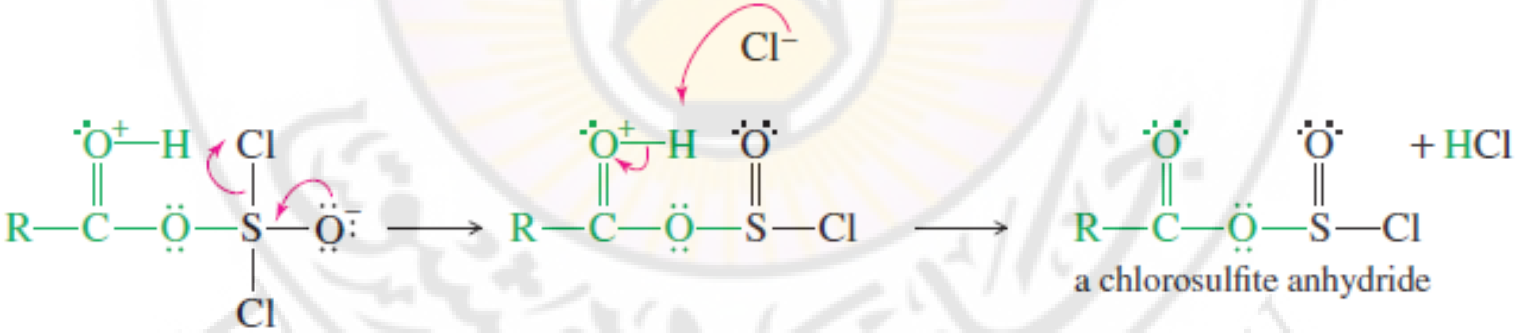
Diethylamine

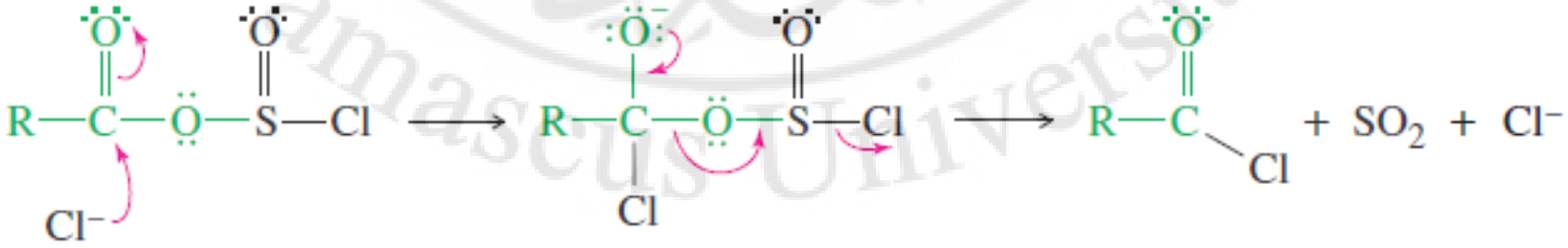
Procaine

Procaine synthesis

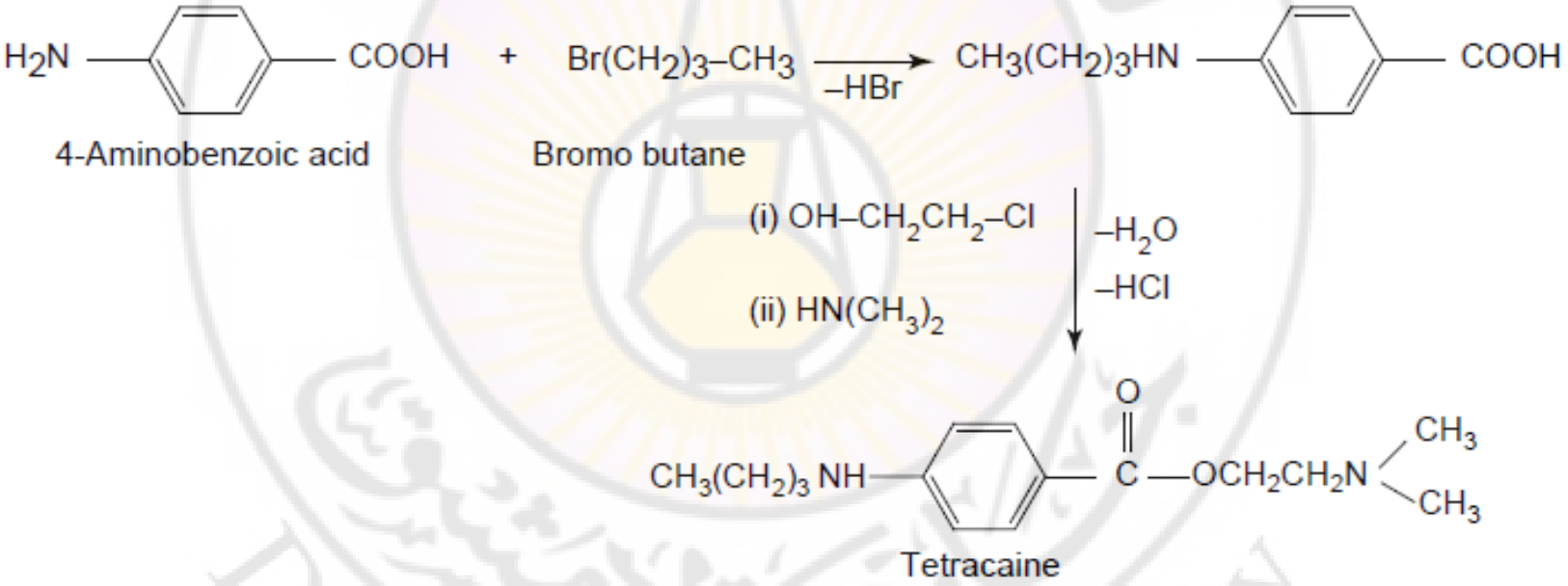




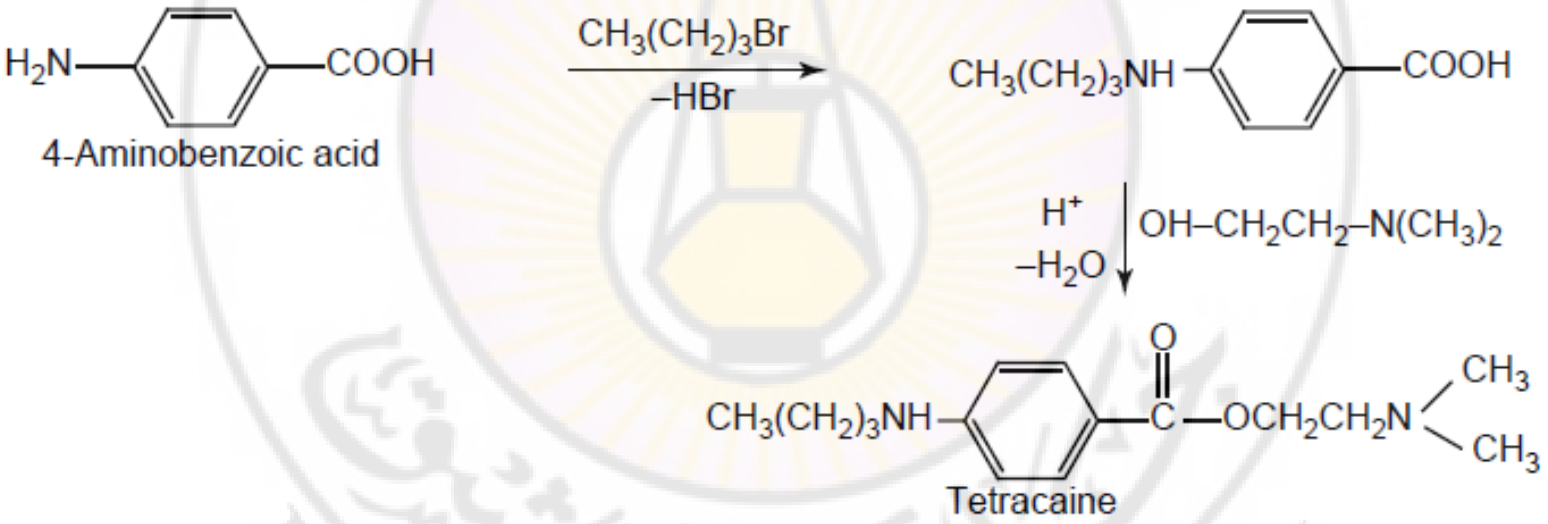

Cl⁻
+ HCl
a chlorosulfite anhydride


Cl⁻
+ SO2 + Cl⁻

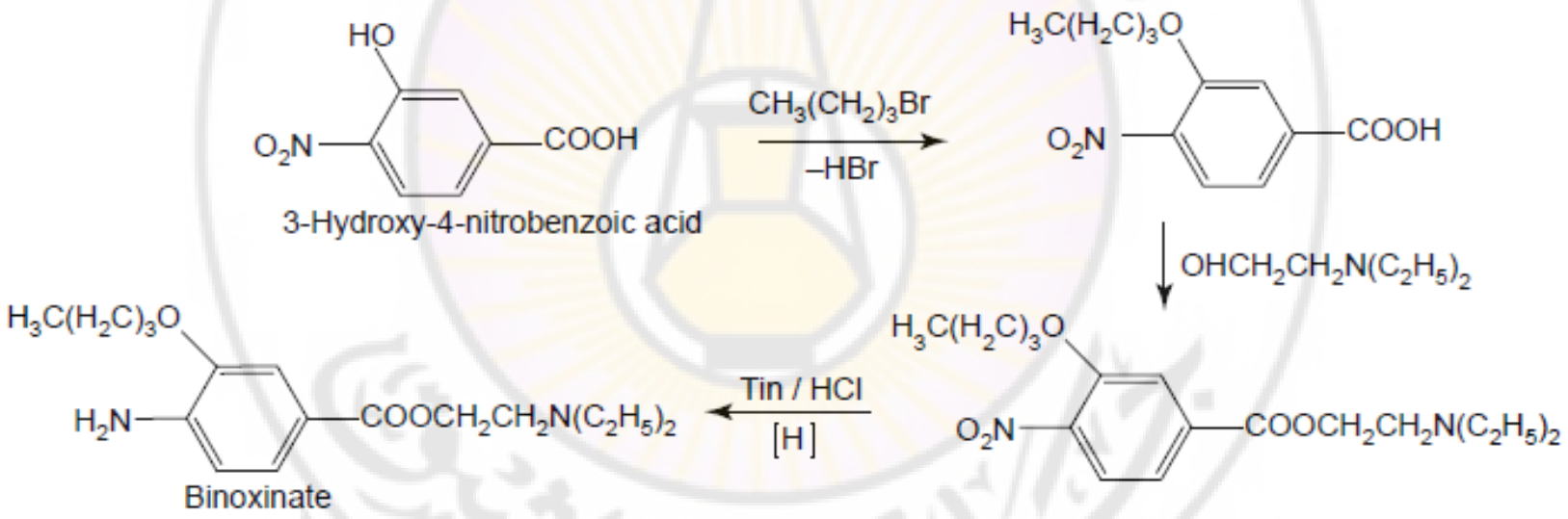
Tetracaine synthesis



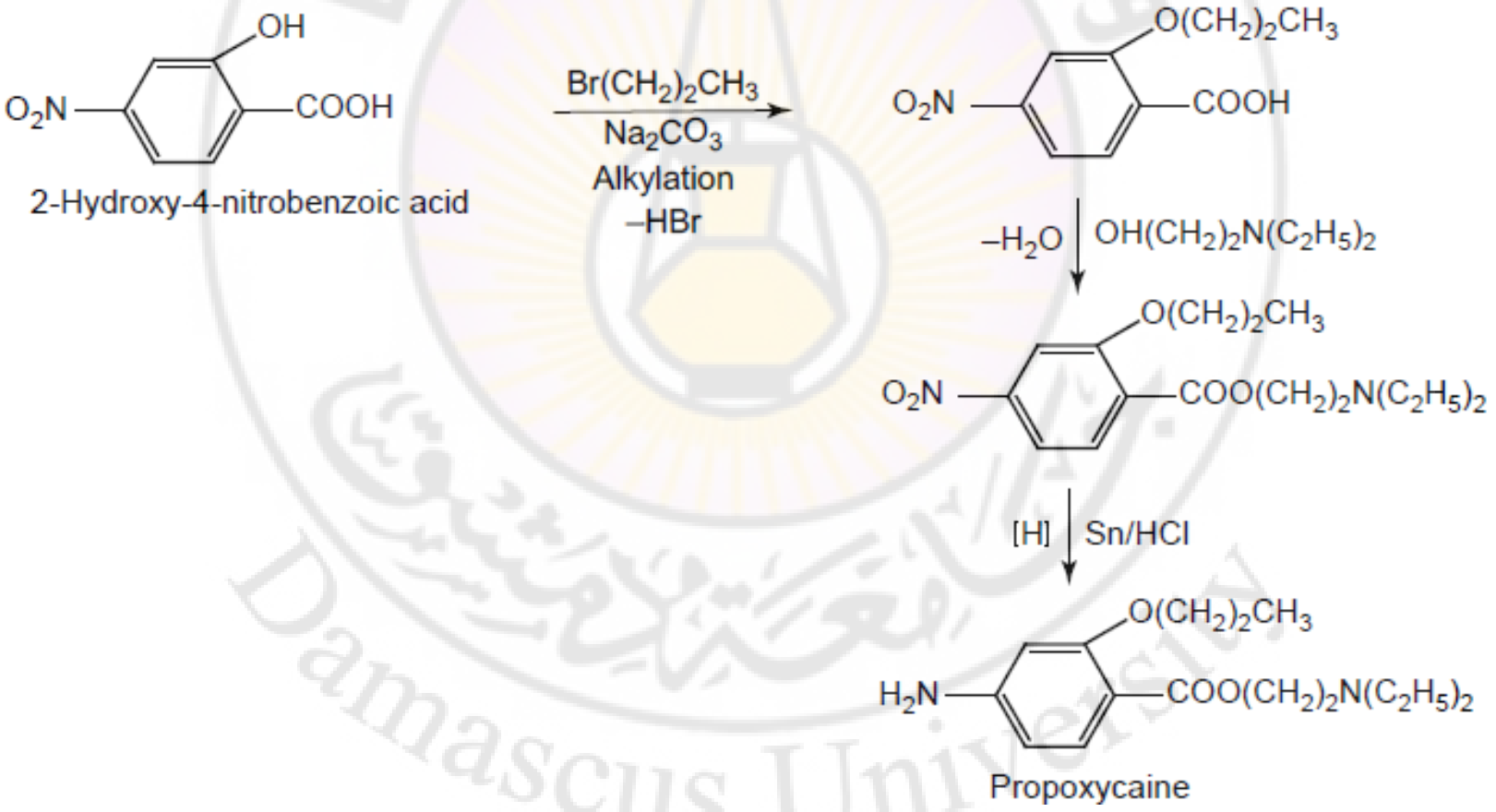
Tetracaine synthesis



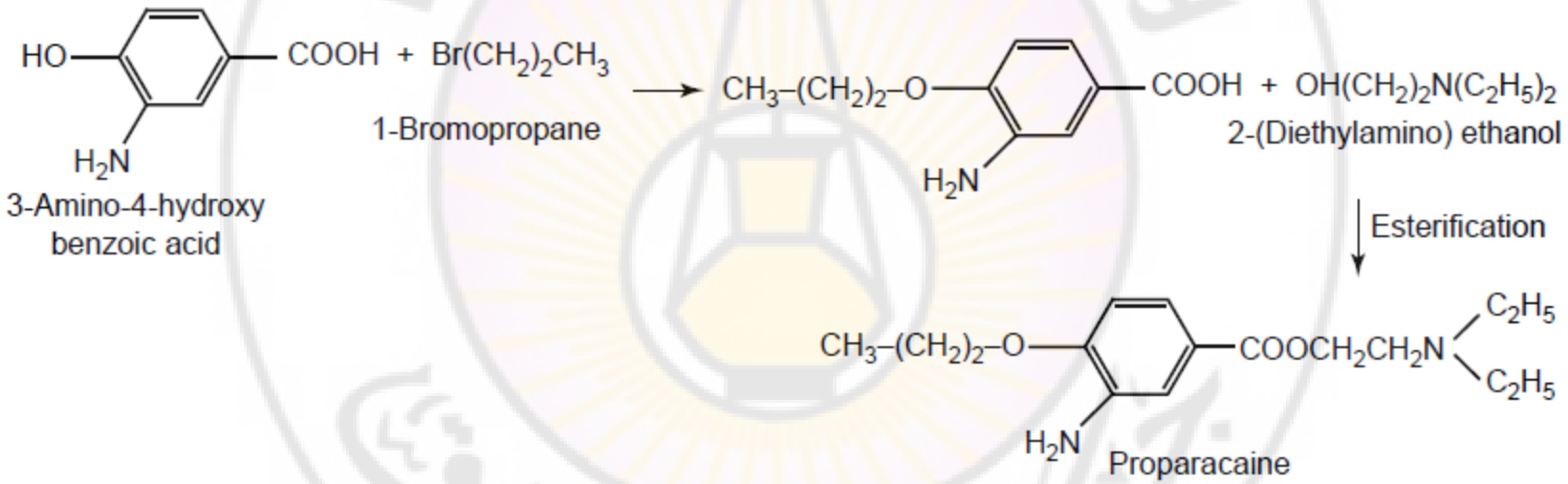
Binoxinate synthesis



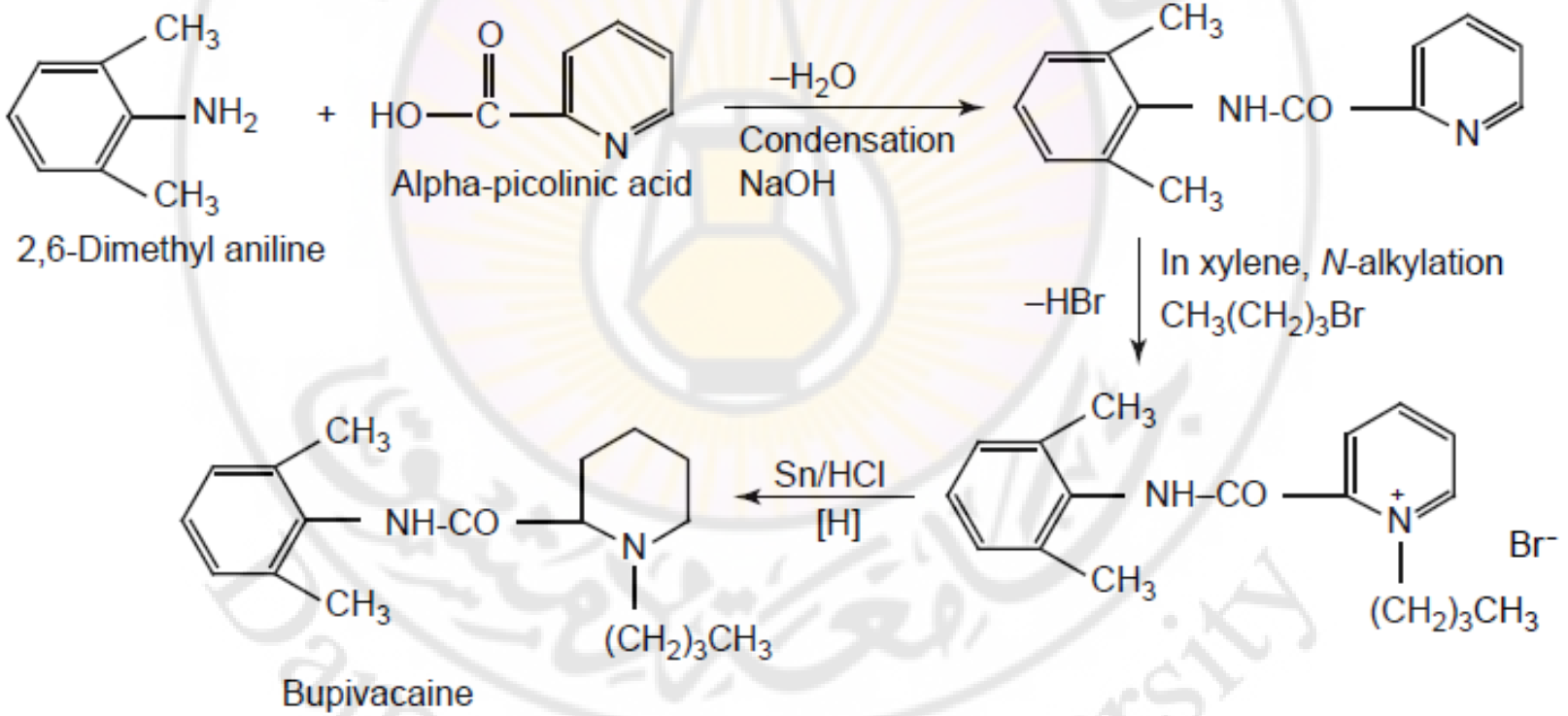
Propoxycaine synthesis



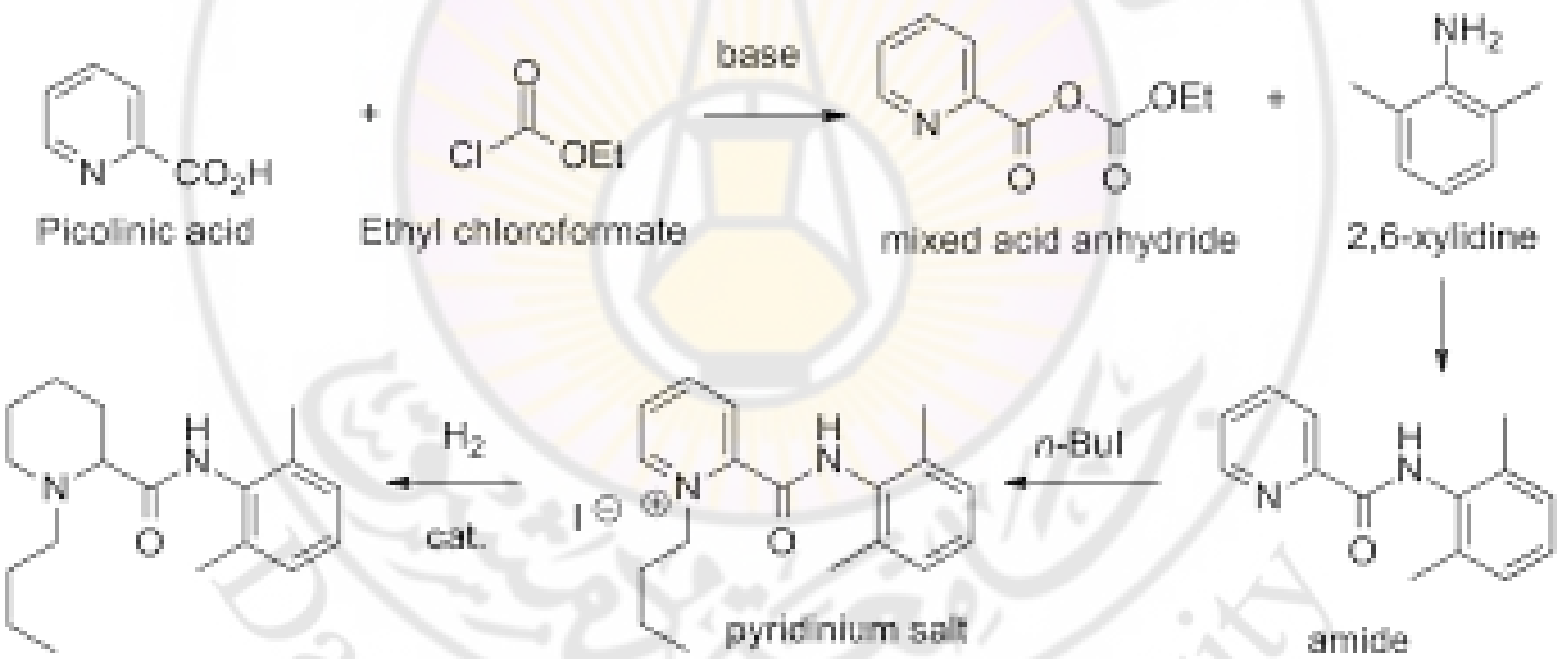
Proparacaine synthesis



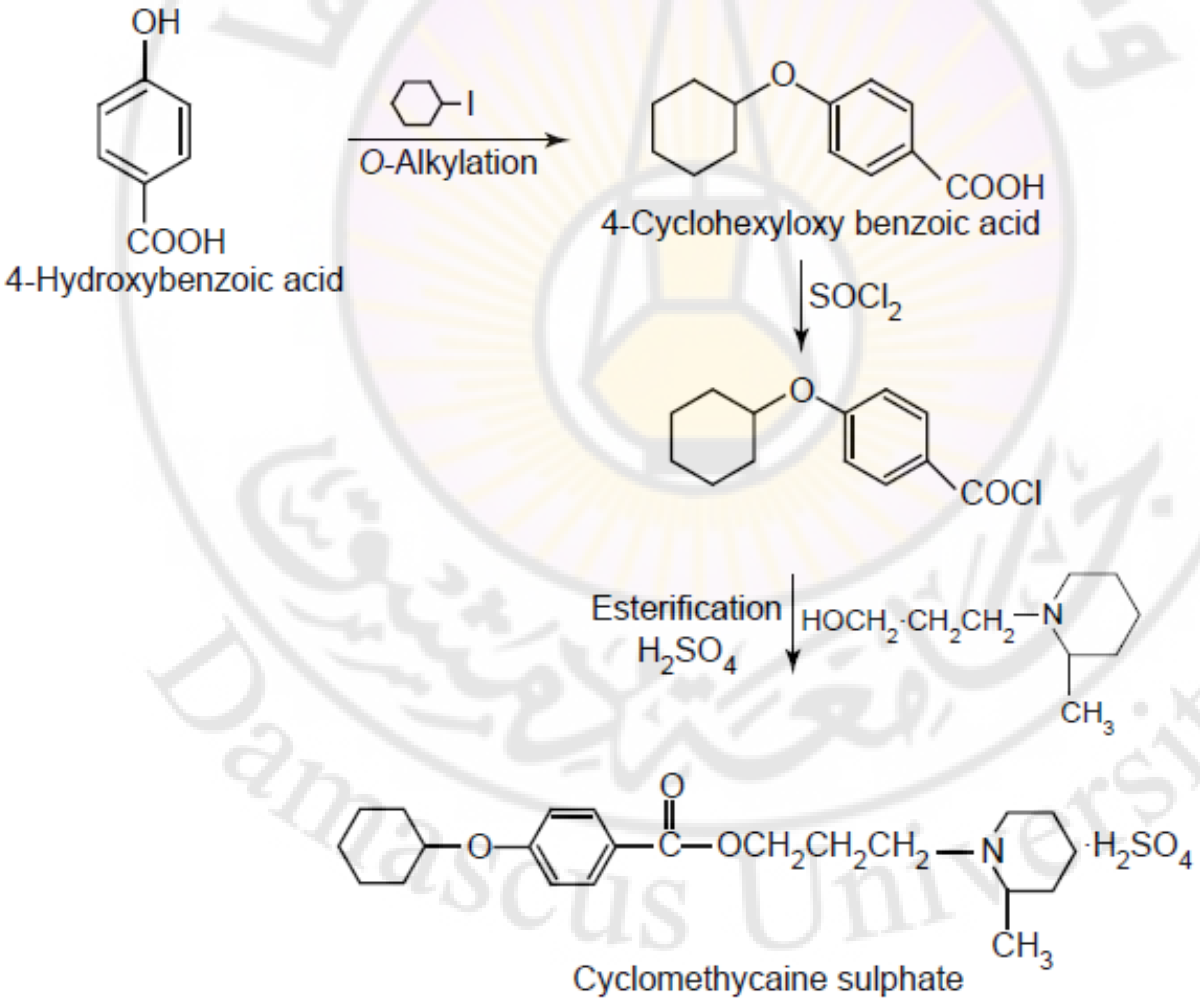
Bupivacaine synthesis



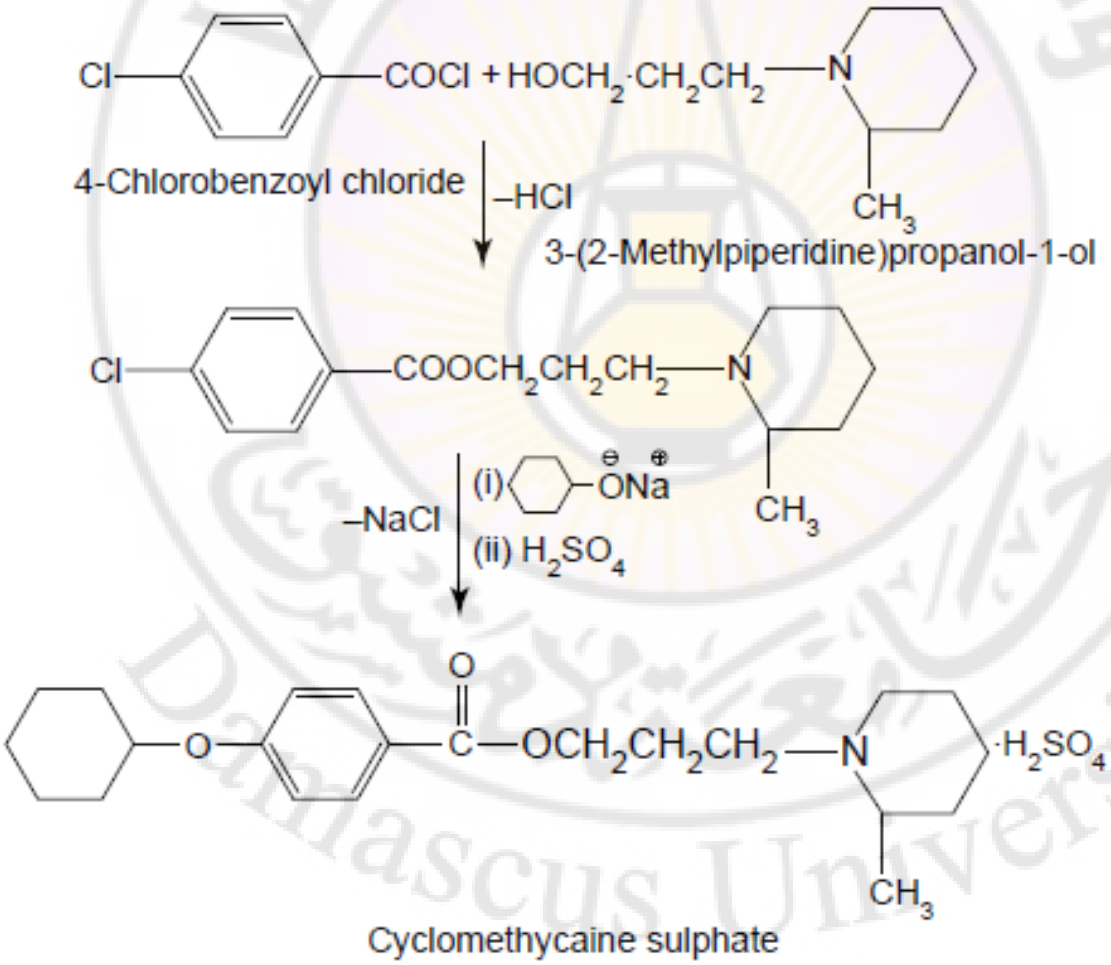
Bupivacaine synthesis



Cyclomethycaine synthesis



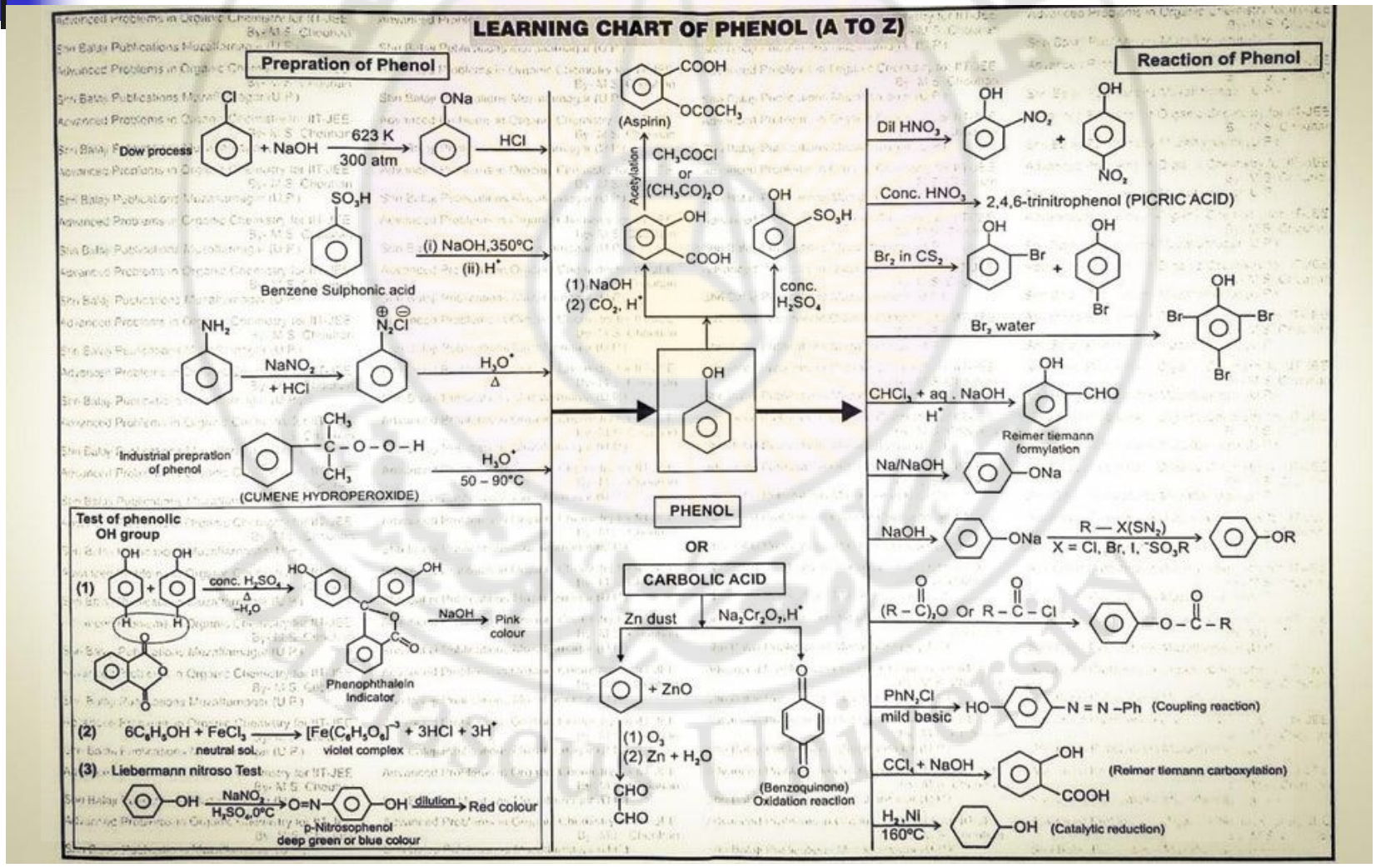
Cyclomethycaine synthesis



Cyclomethycaine sulphate

Drug Synthesis of α agonists

Phenol reactions



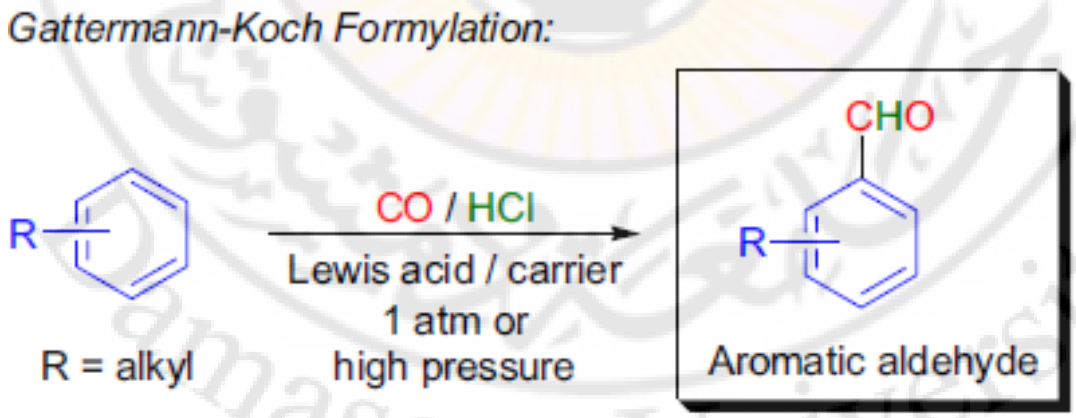
Phenol reactions

The direct formylation of aromatic compounds can be accomplished by various methods such as the :

1) Gattermann reaction
2) Gattermann–Koch reaction
3) Vilsmeier–Haack reaction
4) Duff reaction
5) Reimer–Tiemann reaction

The Gatterman–Koch Formylation: Synthesis of Benzaldehydes

Formylation can be accomplished by using a high-pressure mixture of carbon monoxide and HCl together with a catalyst consisting of a mixture of cuprous chloride (CuCl) and aluminum chloride.
This mixture generates the formyl cation, possibly through a small concentration of formyl chloride.

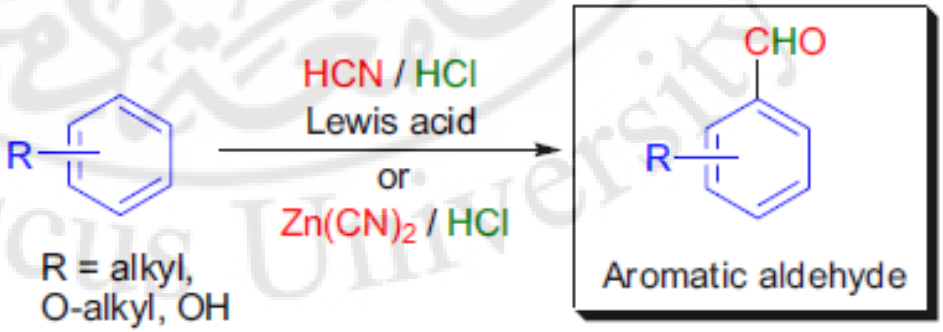


The Gatterman Formylation: Synthesis of Benzaldehydes

The scope of the *Gattermann-Koch reaction* in terms of suitable substrates is also limited, since it is mostly restricted to alkylbenzenes.

Gattermann introduced a modification where HCN is mixed with HCl in the presence of $ZnCl_2$ to formylate phenols, phenolic ethers and heteroaromatic compounds (e.g., pyrroles and indoles).
This modification is called the Gattermann formylation (or Gattermann synthesis)

Gattermann Formylation:



The Gatterman Formylation: Synthesis of Benzaldehydes

✓ The main drawback of the *Gattermann formylation* was that it called for the use of anhydrous HCN, which is a very toxic compound.

✓ To avoid the handling of HCN, R. Adams generated it *in situ* along with $ZnCl_2$ by reacting $Zn(CN)_2$ with HCl in the presence of the aromatic substrate (*Adams modification*).

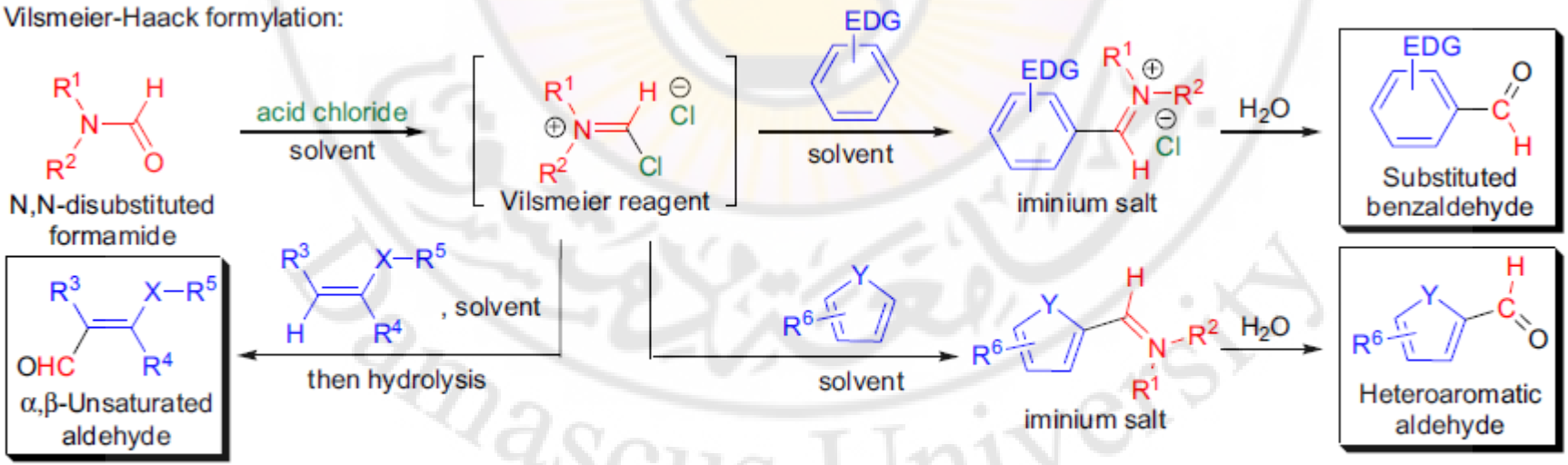
✓ Other modifications used NaCN and CNBr successfully instead of HCN. Cyanogen bromide is hydrolyzed to release hydrogen cyanide and hypobromous acid

$(CN)Br + H_2O \rightarrow HCN + HOBr$

✓ A serious limitation of both title reactions is that they cannot be used for the formylation of aromatic amines due to numerous side reactions.

Phenol reactions
Vilsmeier–Haack reaction

- ✓ The Vilsmeier–Haack reaction (also called the Vilsmeier reaction) is the chemical reaction of a substituted amide with phosphorus oxychloride and an electron-rich arene to produce an aryl aldehyde or ketone



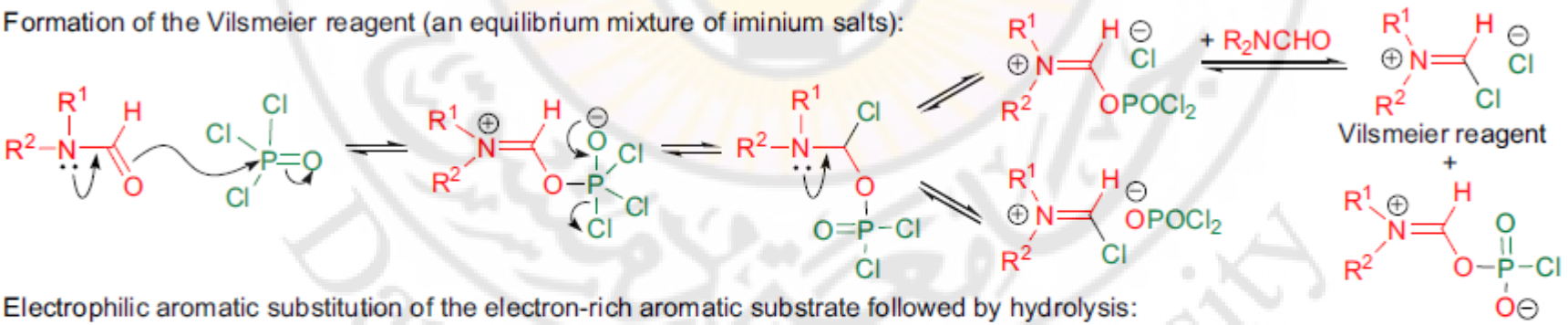
R^{1-2} = alkyl, aryl; acid chloride: $POCl_3$, $SOCl_2$, $COCl_2$, $(COCl)_2$, Ph_3PBr_2, 2,4,6-trichloro-1,3,5-triazine; solvent: DCM, DMF, $POCl_3$; EDG = OH, *O*-alkyl, *O*-aryl, NR_2; R^{3-4} = H, alkyl, aryl; R^5 = alkyl, aryl; X = O, NR, CH_2, CR_2; Y = O, S, NR, NH; R^6 = H, alkyl, aryl

Phenol reactions
Vilsmeier–Haack reaction

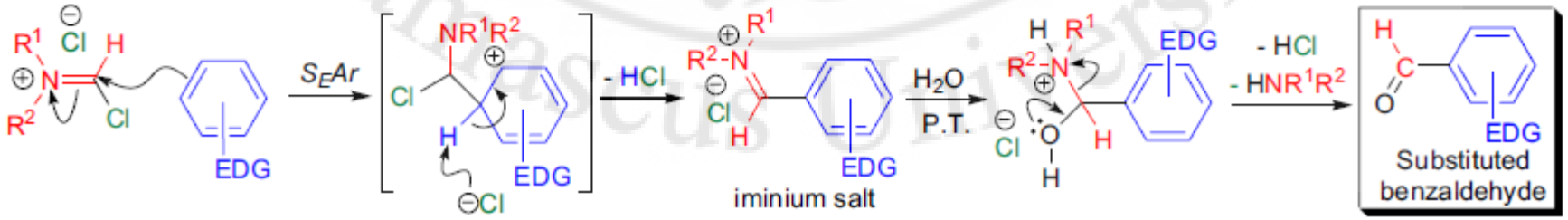
- ✓ The Vilsmeier–Haack reaction (also called the Vilsmeier reaction) is the chemical reaction of a substituted amide with phosphorus oxychloride and an electron-rich arene to produce an aryl aldehyde or ketone

Mechanism: [34-41,8,42,11]

Formation of the Vilsmeier reagent (an equilibrium mixture of iminium salts):

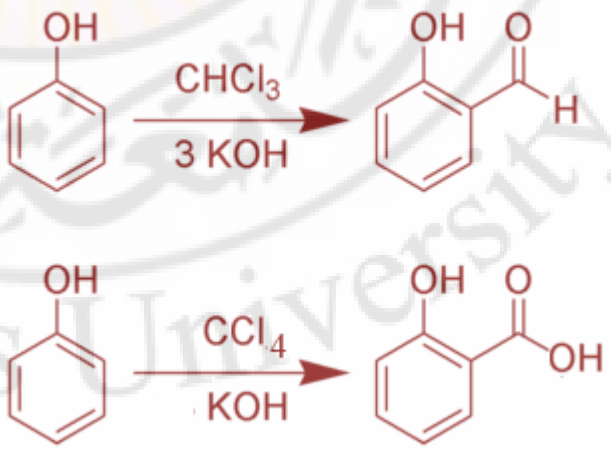


Electrophilic aromatic substitution of the electron-rich aromatic substrate followed by hydrolysis:



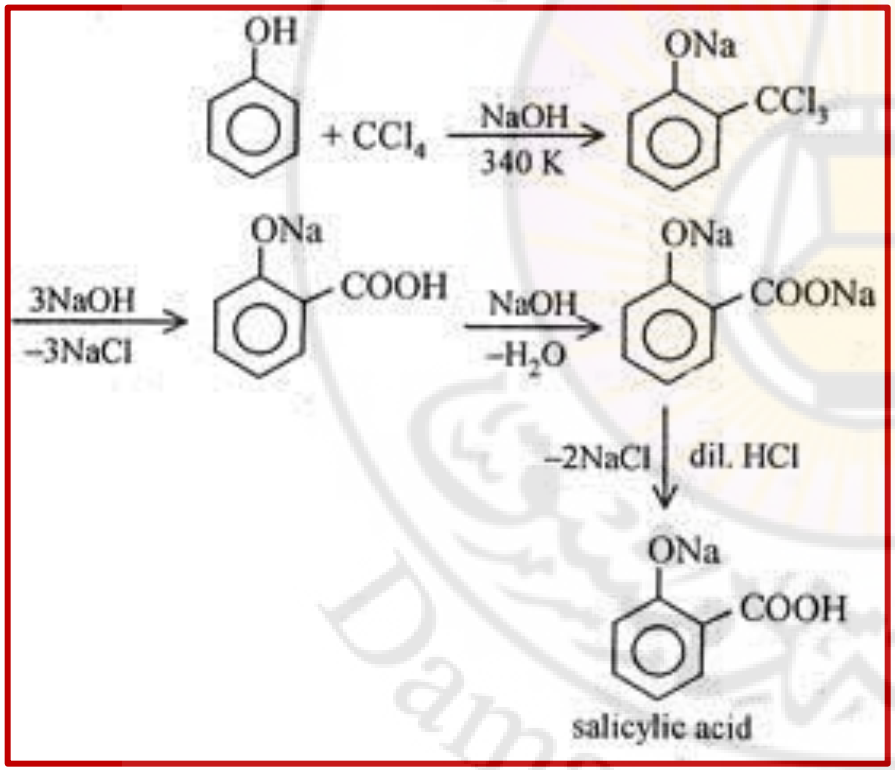
Phenol reactions
Reimer–Tiemann reaction

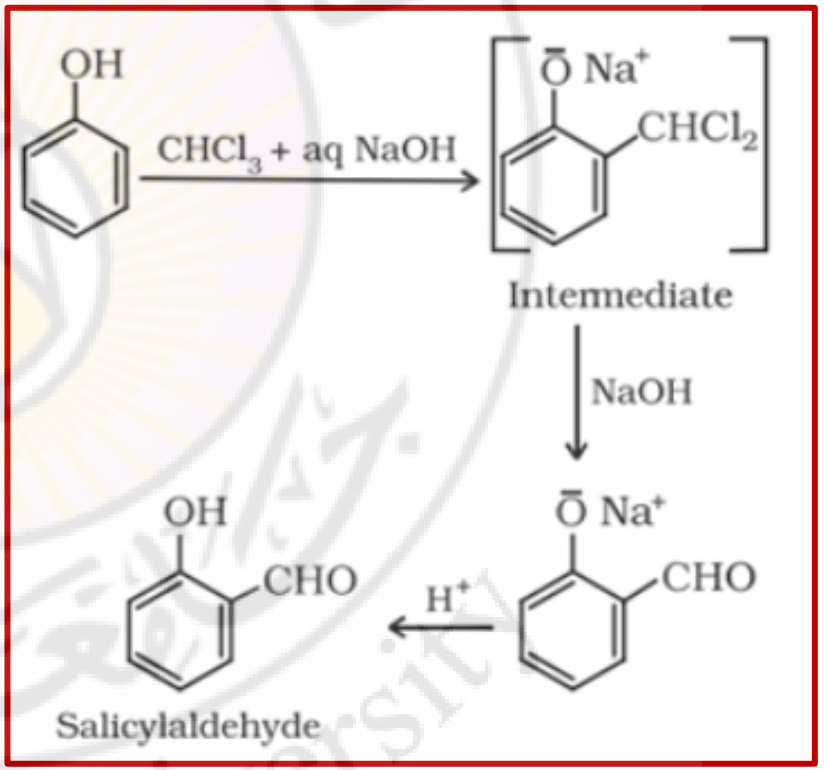
- ✓ The Reimer–Tiemann reaction is a chemical reaction used for the ortho-formylation of phenols; with the simplest example being the conversion of phenol to salicylaldehyde.
- ✓ The Reimer–Tiemann reaction can be altered to yield phenolic acids by substituting the chloroform with carbon tetrachloride. For instance, the altered reaction with phenol would yield salicylic acid rather than the expected product, salicylaldehyde



Phenol reactions

Reimer–Tiemann reaction

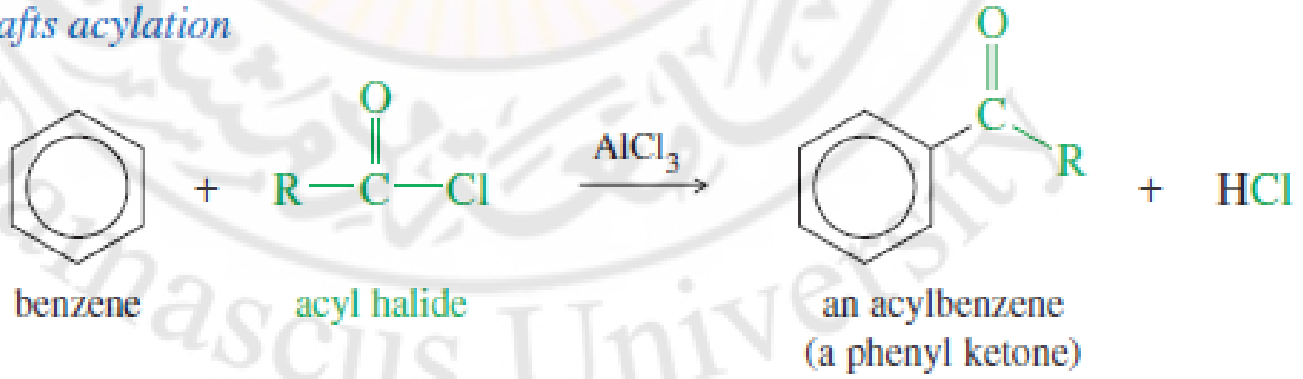




The Friedel–Crafts acylation

- ✓ In the presence of aluminum chloride, an acyl chloride reacts with benzene (or an activated benzene derivative) to give a phenyl ketone: an acylbenzene.
- ✓ The Friedel–Crafts acylation is analogous to the Friedel–Crafts alkylation, except that the reagent is an acyl chloride instead of an alkyl halide and the product is an acylbenzene (a "phenone") instead of an alkylbenzene.

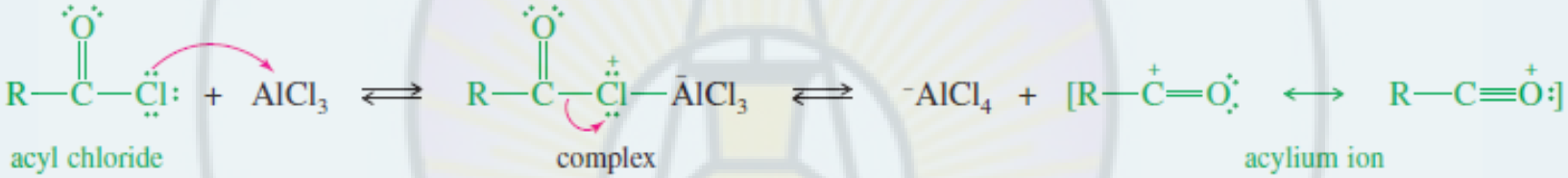
Friedel–Crafts acylation



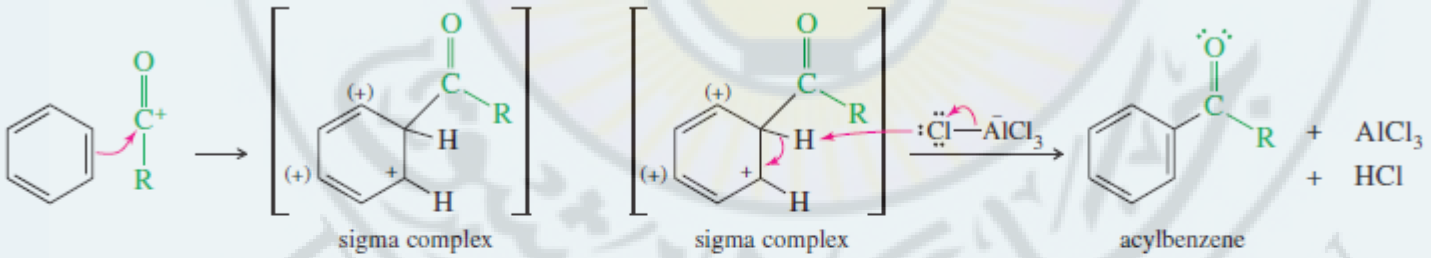
The Friedel–Crafts acylation

Friedel–Crafts acylation is an electrophilic aromatic substitution with an acylium ion acting as the electrophile.

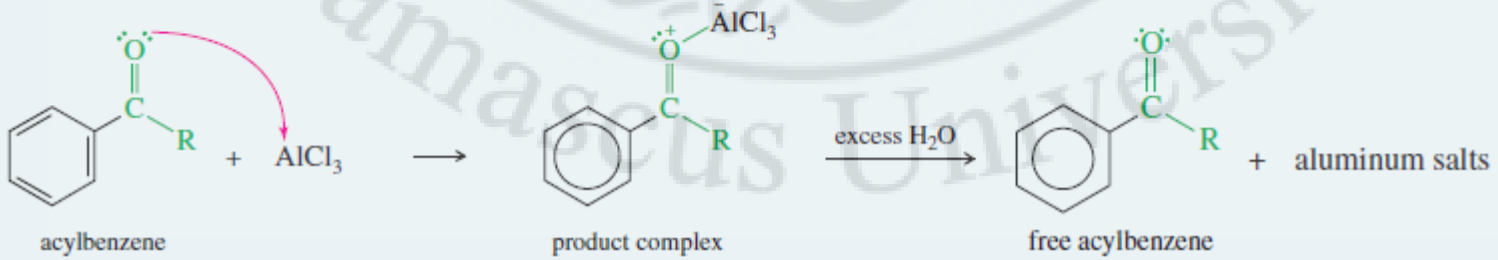
Step 1: Formation of an acylium ion.



Steps 2 and 3: Electrophilic attack forms a sigma complex, and loss of a proton regenerates the aromatic system.



Step 4: Complexation of the product. The product complex must be hydrolyzed (by water) to release the free acylbenzene.



The Friedel–Crafts acylation

- ✓ Friedel–Crafts acylation overcomes two of the three limitations of the alkylation:

1) The acylium ion is resonance-stabilized, so that no rearrangements occur;

2) and the acylbenzene product is deactivated, so that no further reaction occurs.

3) Like the alkylation, however, the acylation fails with strongly deactivated aromatic rings

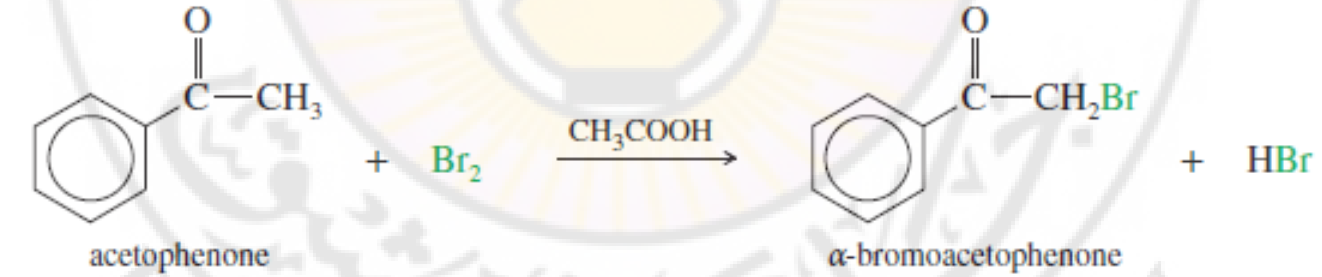
The Friedel–Crafts acylation

Alkylation
The alkylation cannot be used with strongly deactivated derivatives.
The carbocations involved in the alkylation may rearrange.
Polyalkylation is commonly a problem.

Acylation
Also true: Only benzene, halobenzenes, and activated derivatives are suitable.
Resonance-stabilized acylium ions are not prone to rearrangement.
The acylation forms a deactivated acylbenzene, which does not react further.

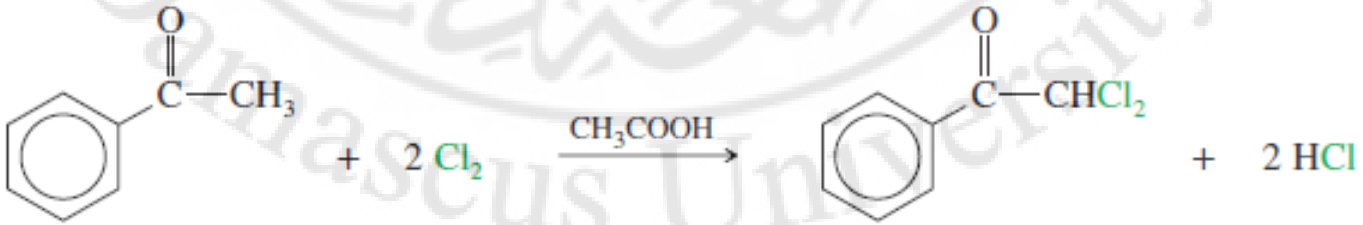
Acid-Catalyzed Alpha Halogenation

The α halogenation of ketones can also be catalyzed by acid. One of the most effective procedures is to dissolve the ketone in acetic acid, which serves as both the solvent and the acid catalyst. In contrast with basic halogenation, acidic halogenation can selectively replace just one hydrogen or more than one, depending on the amount of the halogen added.



acetophenone

α-bromoacetophenone
(70%)



acetophenone

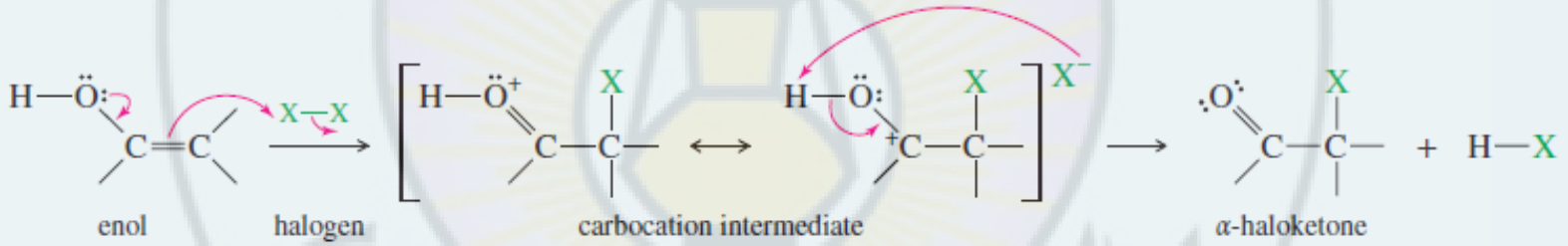
α,α-dichloroacetophenone

Acid-Catalyzed Alpha Halogenation

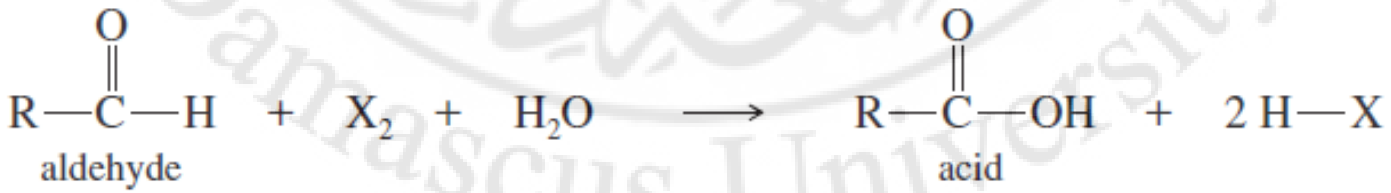
Acid-catalyzed halogenation results when the enol form of the carbonyl compound serves as a nucleophile to attack the halogen (a strong electrophile). Deprotonation gives the α-haloketone.

Step 1: The enol attacks the halogen.

Step 2: Deprotonation.

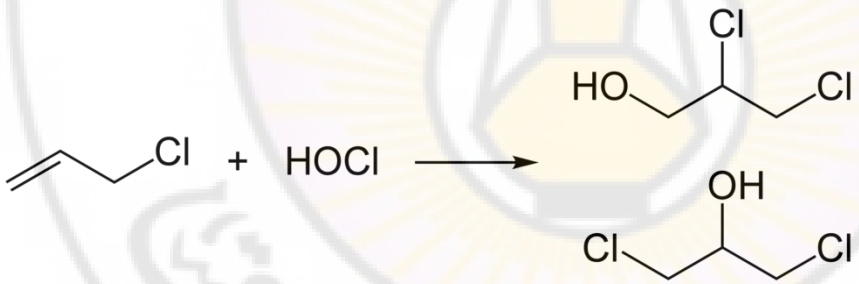


Unlike ketones, aldehydes are easily oxidized, and halogens are strong oxidizing agents. Attempted halogenation of aldehydes usually results in oxidation to carboxylic acids.

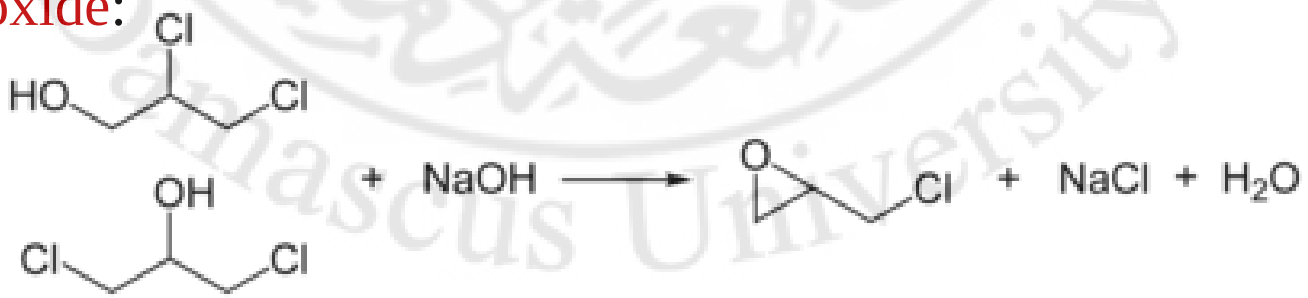


Epichlorohydrin Synthesis

Epichlorohydrin is traditionally manufactured from allyl chloride in two steps, beginning with the addition of hypochlorous acid, which affords a mixture of two isomeric alcohols



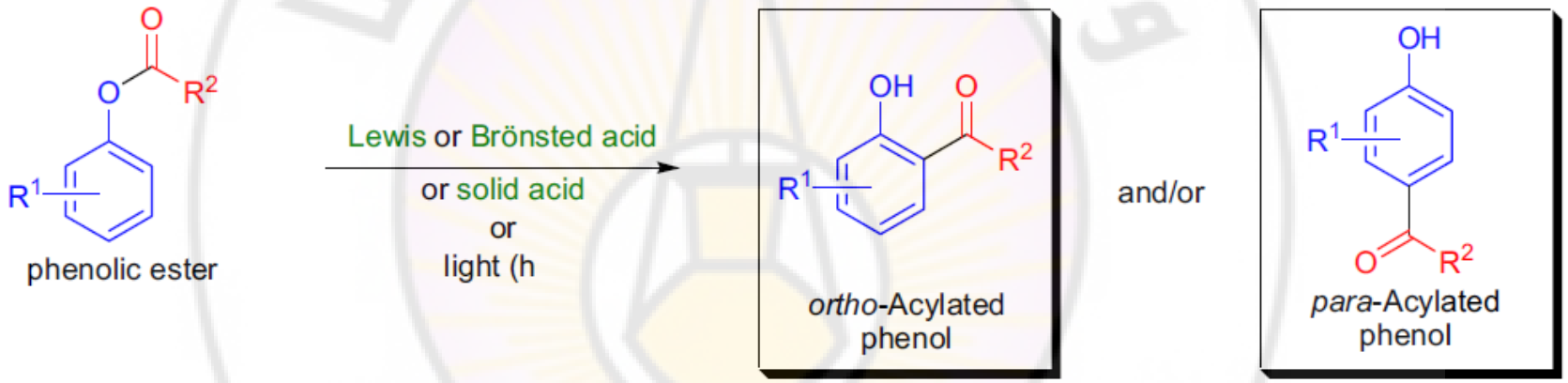
In the second step, this mixture is treated with base to give the epoxide:

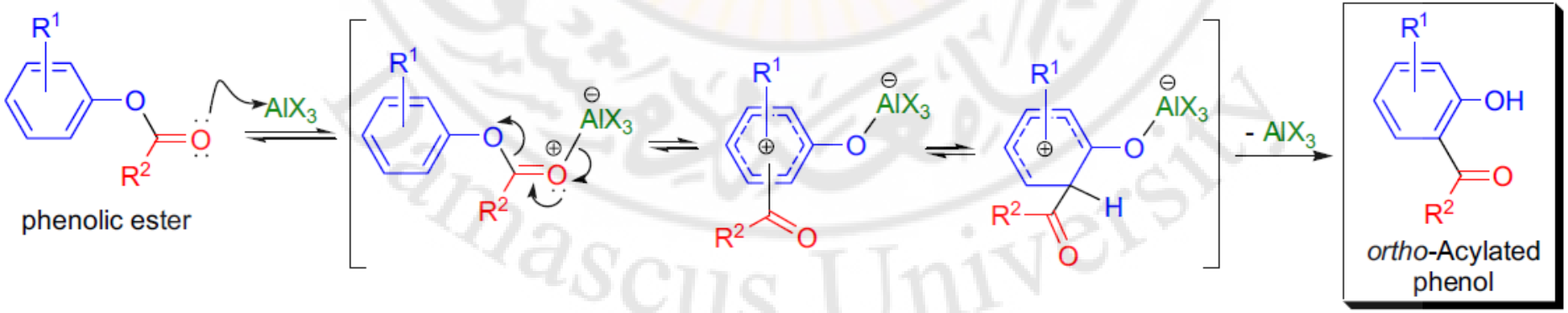


Fries rearrangement

- 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*.
- 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, HClO4, PPA)
- the *Friedel-Crafts acylation* of phenols is usually a two-step process: formation of a phenolic ester followed by a *Fries rearrangement*

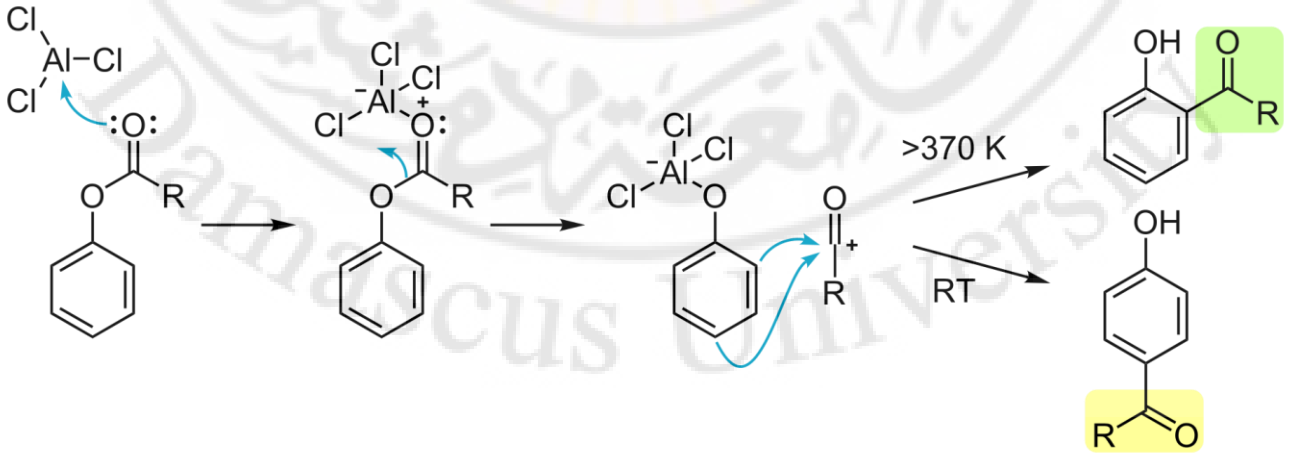
Fries rearrangement





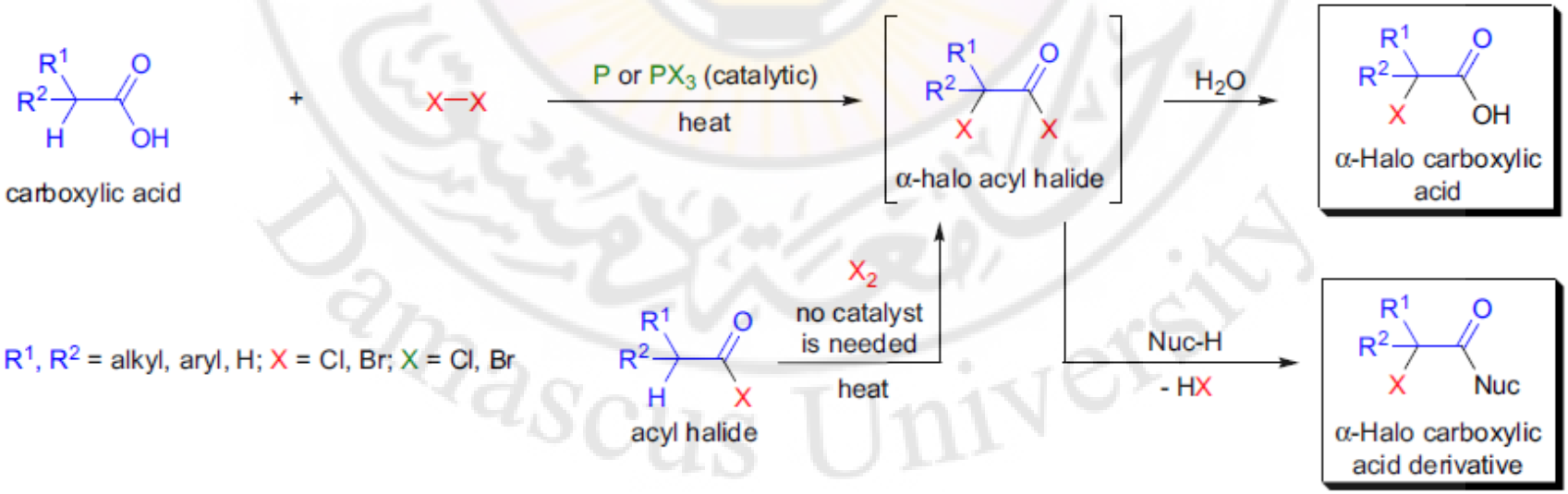
Fries rearrangement

- ✓ The Fries rearrangement is a rearrangement reaction of a phenolic ester to a hydroxy aryl ketone by catalysis of Lewis acids.
- ✓ 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 favored by changing reaction conditions, such as temperature and solvent.



Hell-Volhard-Zelinsky Reaction
HVZ reaction

The preparation of α-halo carboxylic acids by treating the corresponding carboxylic acid with elemental halogen (Cl2 or Br2) at elevated temperatures in the presence of catalytic amounts of red phosphorous (P) or phosphorous trihalide (PCl3 or PBr3) is known as the *Hell-Volhard-Zelinsky reaction* (*HVZ reaction*).



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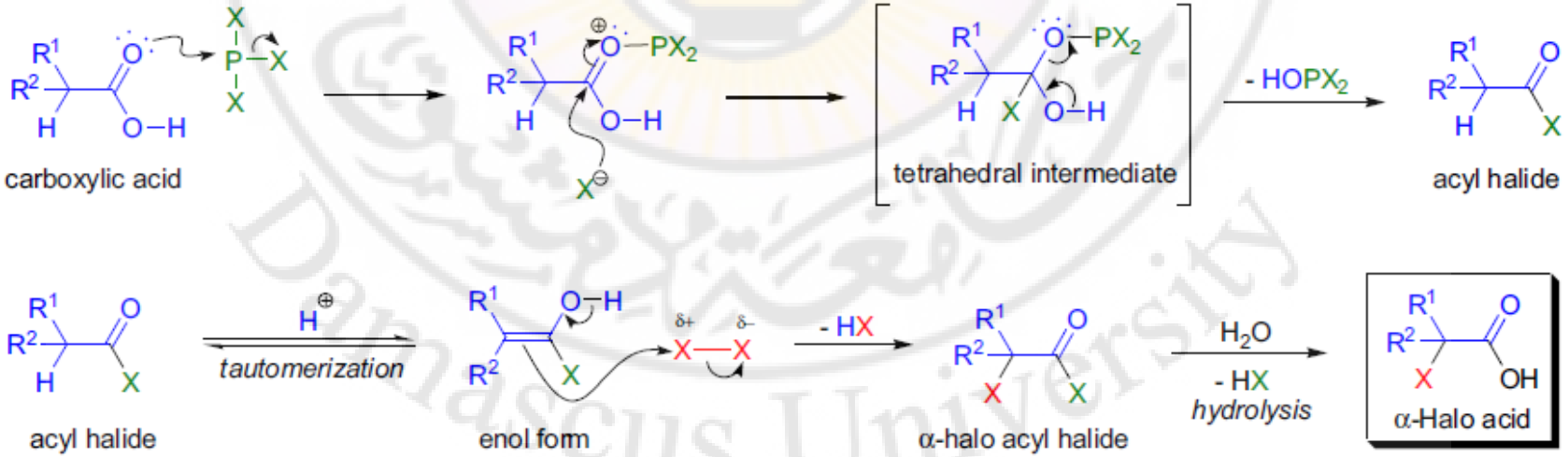
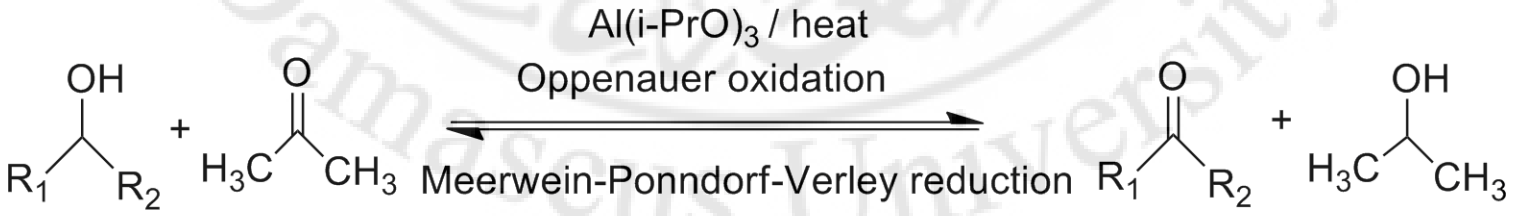


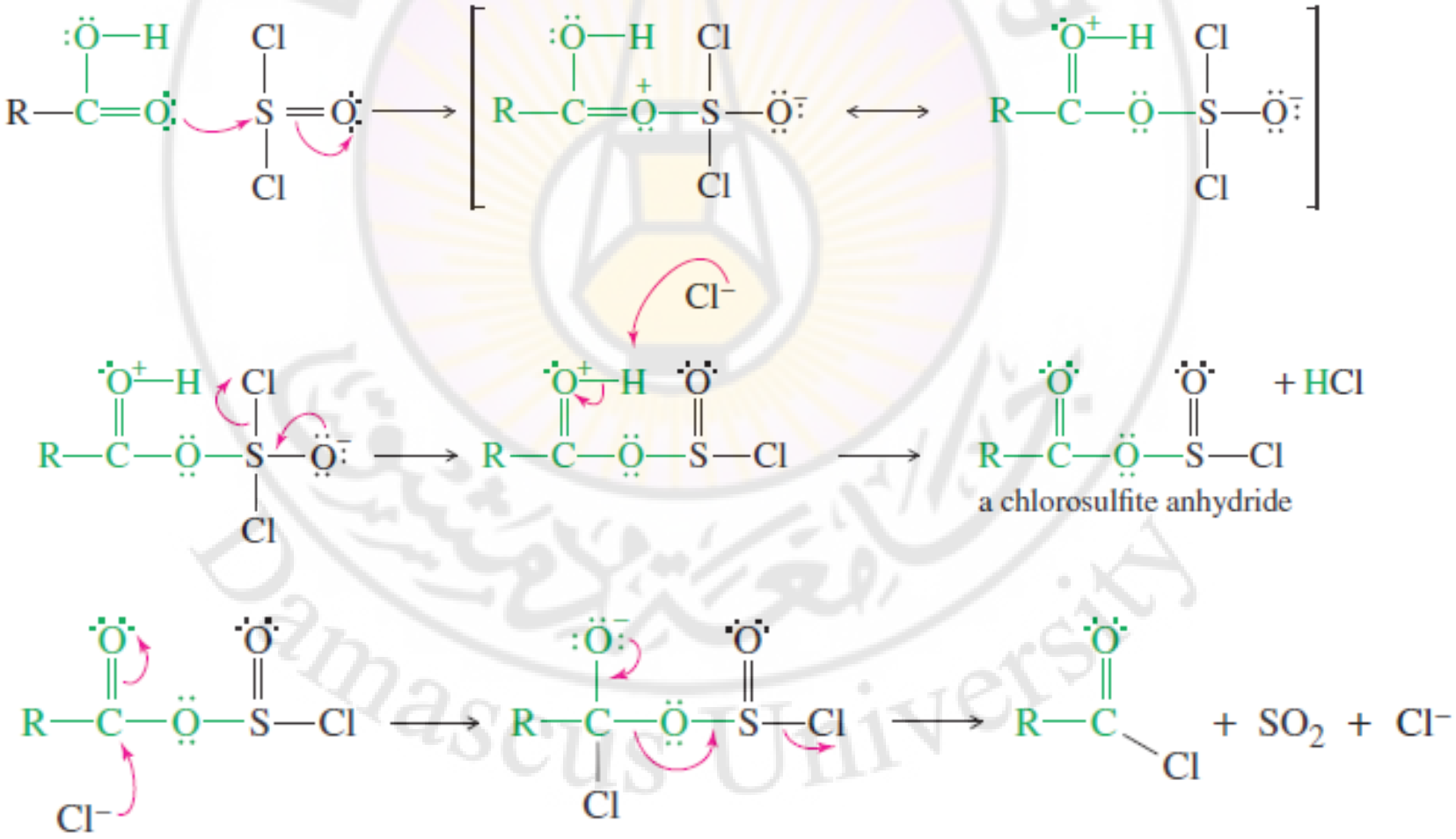
Meerwein Ponndorf Verley (MPV) reduction

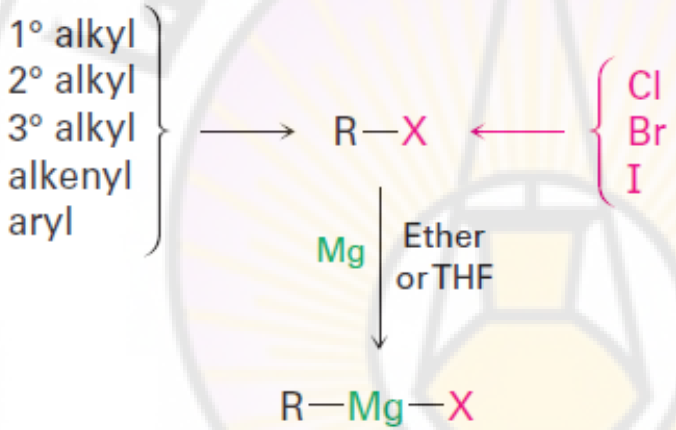
The Meerwein Ponndorf Verley (MPV) reduction in organic chemistry is the reduction of ketones and aldehydes to their corresponding alcohols utilizing aluminium alkoxide catalysis in the presence of a sacrificial alcohol

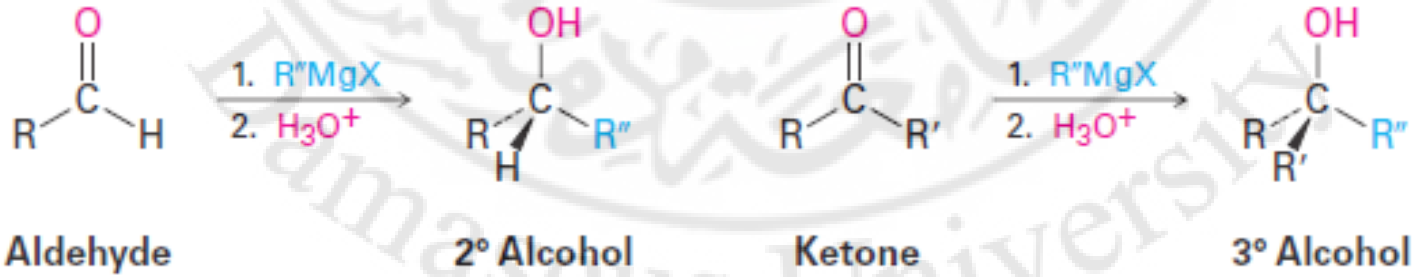
The advantages of the MPV reduction lie in its high chemoselectivity, and its use of a cheap environmentally friendly metal catalyst



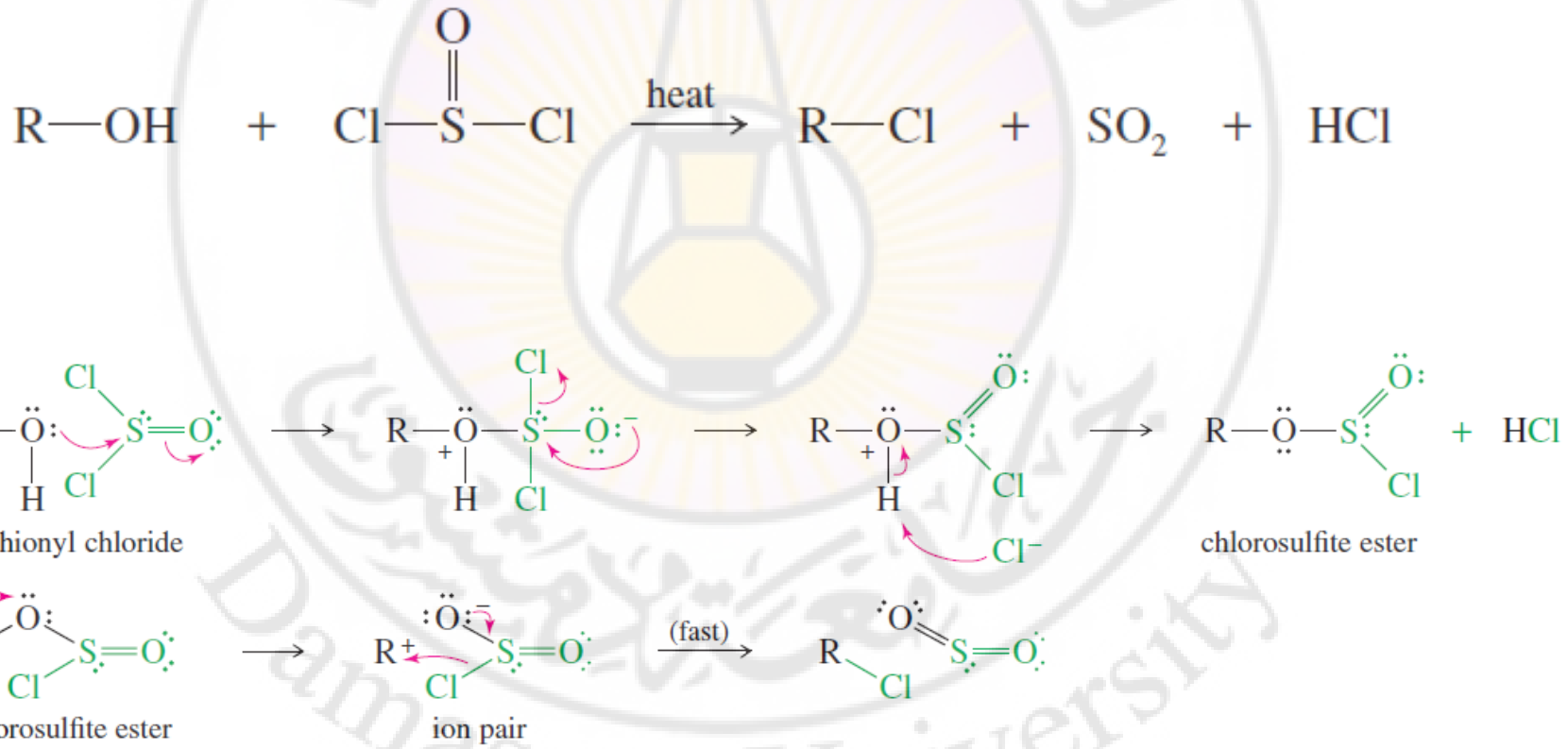
Converting Carboxylic Acid into Acid Chloride




1° alkyl
2° alkyl
3° alkyl
alkenyl
aryl
R—X
Cl
Br
I
Mg
Ether
or THF
R—Mg—X

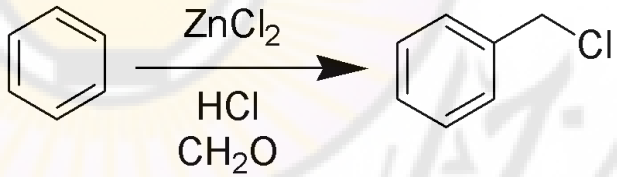

O
R
C
H
1. R″MgX
2. H3O+
OH
R″
Aldehyde
2° Alcohol
Ketone
R′
3° Alcohol

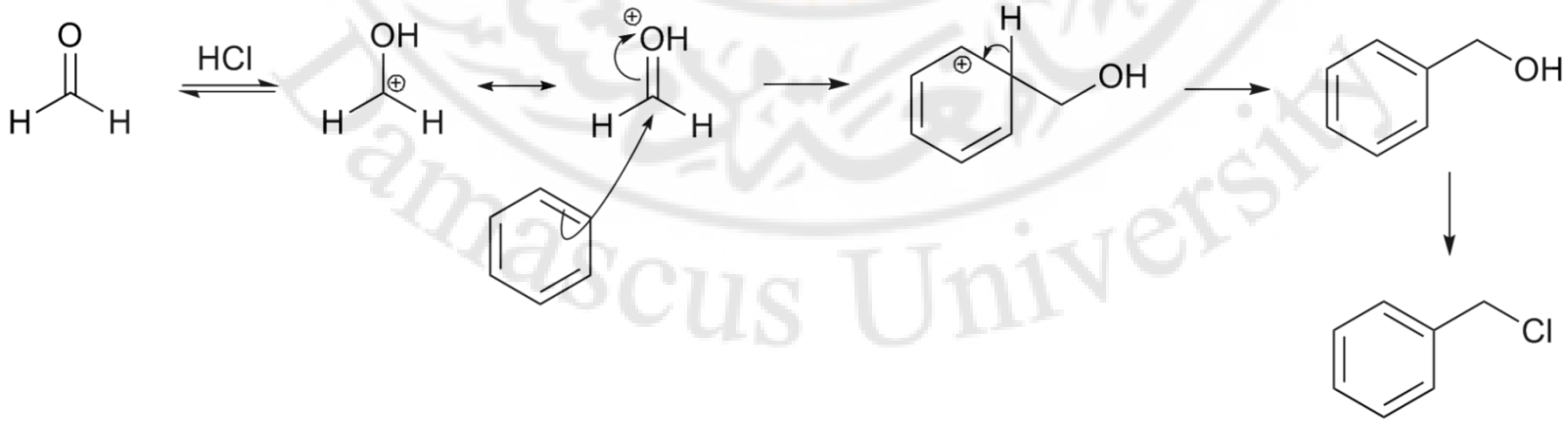
Converting alcohol into alkyl halide

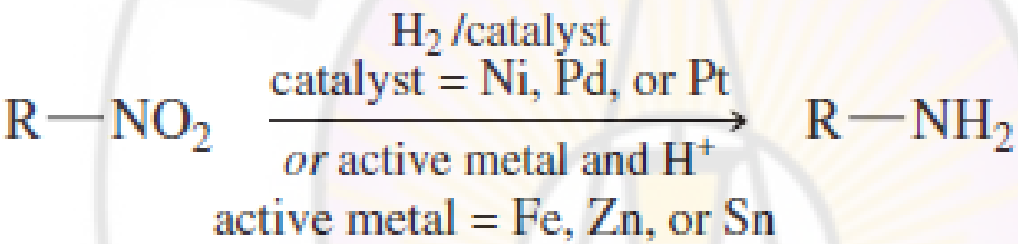


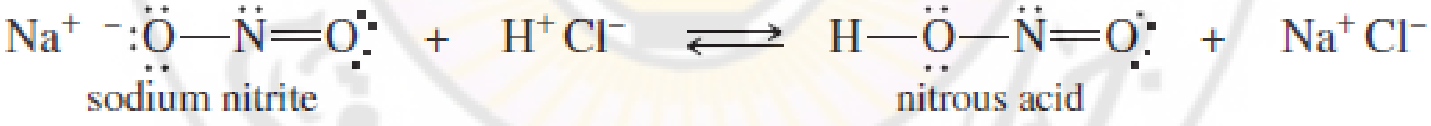
Blanc chloromethylation

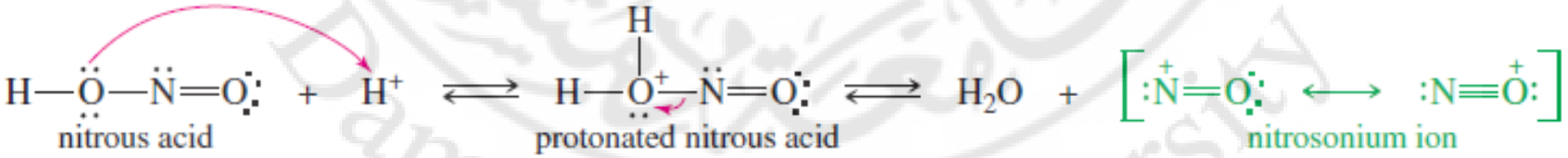
The Blanc chloromethylation (also called the Blanc reaction) is the chemical reaction of aromatic rings with formaldehyde and hydrogen chloride catalyzed by zinc chloride or other Lewis acid to form chloromethyl arenes. hydrogen chloride catalyzed by zinc chloride or other Lewis acid to form chloromethyl arenes

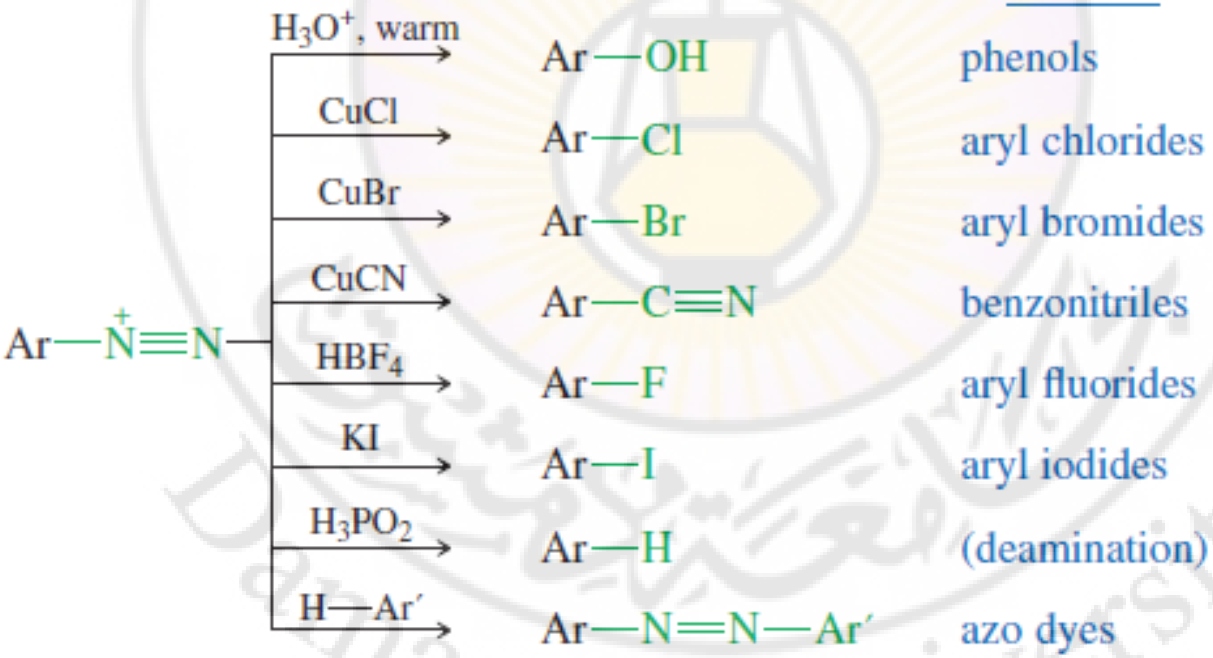


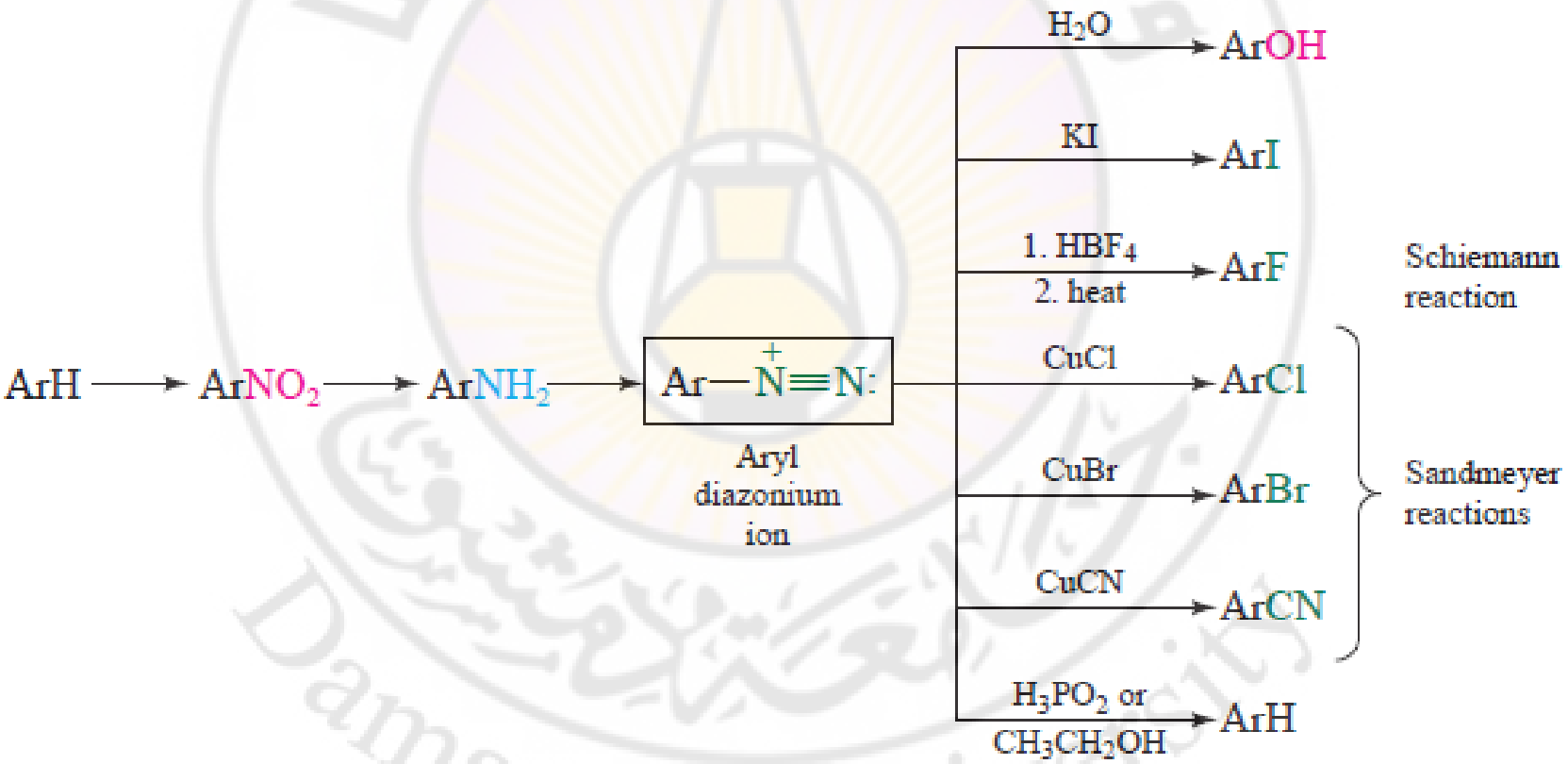



H2 /catalyst
catalyst = Ni, Pd, or Pt
or active metal and H+
active metal = Fe, Zn, or Sn
R—NO2
R—NH2


sodium nitrite
nitrous acid

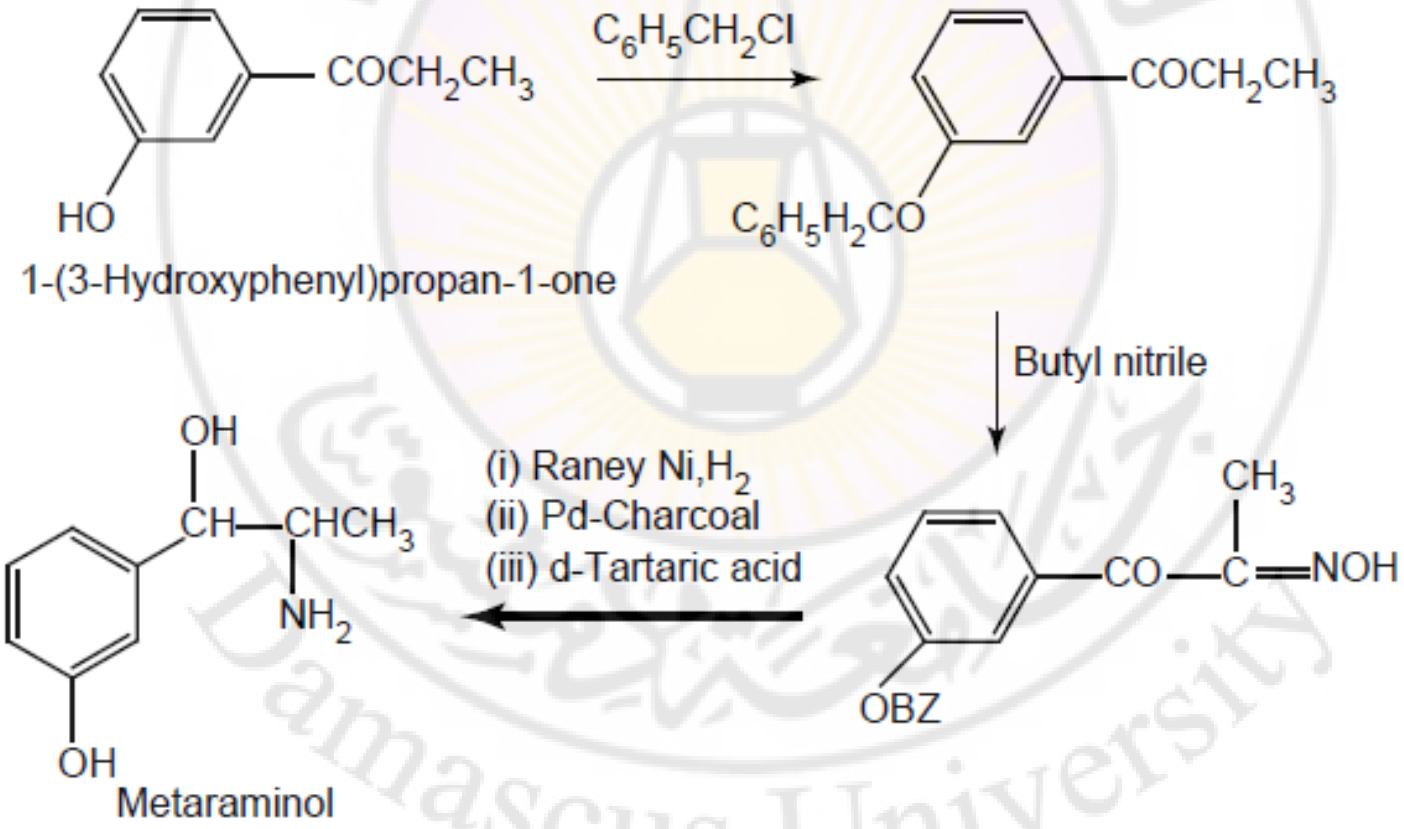

nitrous acid
protonated nitrous acid
nitrosonium ion


Products
H_3O^+, warm
Ar—OH
phenols
CuCl
Ar—Cl
aryl chlorides
CuBr
Ar—Br
aryl bromides
CuCN
Ar—C≡N
benzonitriles
Ar—$\overset{+}{N}$≡N—
HBF_4
Ar—F
aryl fluorides
KI
Ar—I
aryl iodides
H_3PO_2
Ar—H
(deamination)
H—Ar′
Ar—N=N—Ar′
azo dyes

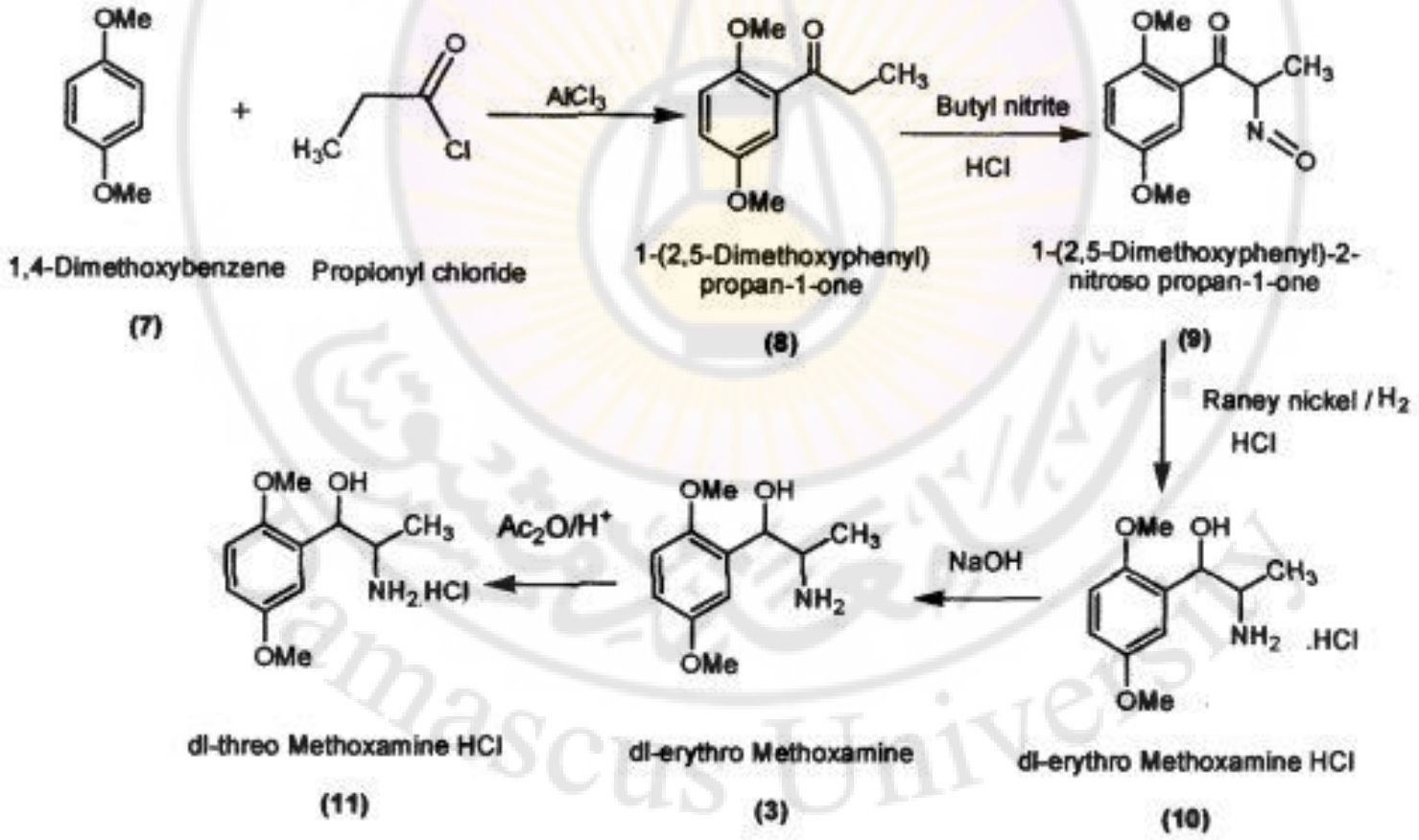

ArH
ArNO2
ArNH2
Ar—N≡N:
Aryl diazonium ion
H2O
ArOH
KI
ArI
1. HBF4
2. heat
ArF
Schiemann reaction
CuCl
ArCl
CuBr
ArBr
CuCN
ArCN
Sandmeyer reactions
H3PO2 or CH3CH2OH
ArH

Drug Synthesis of α agonists

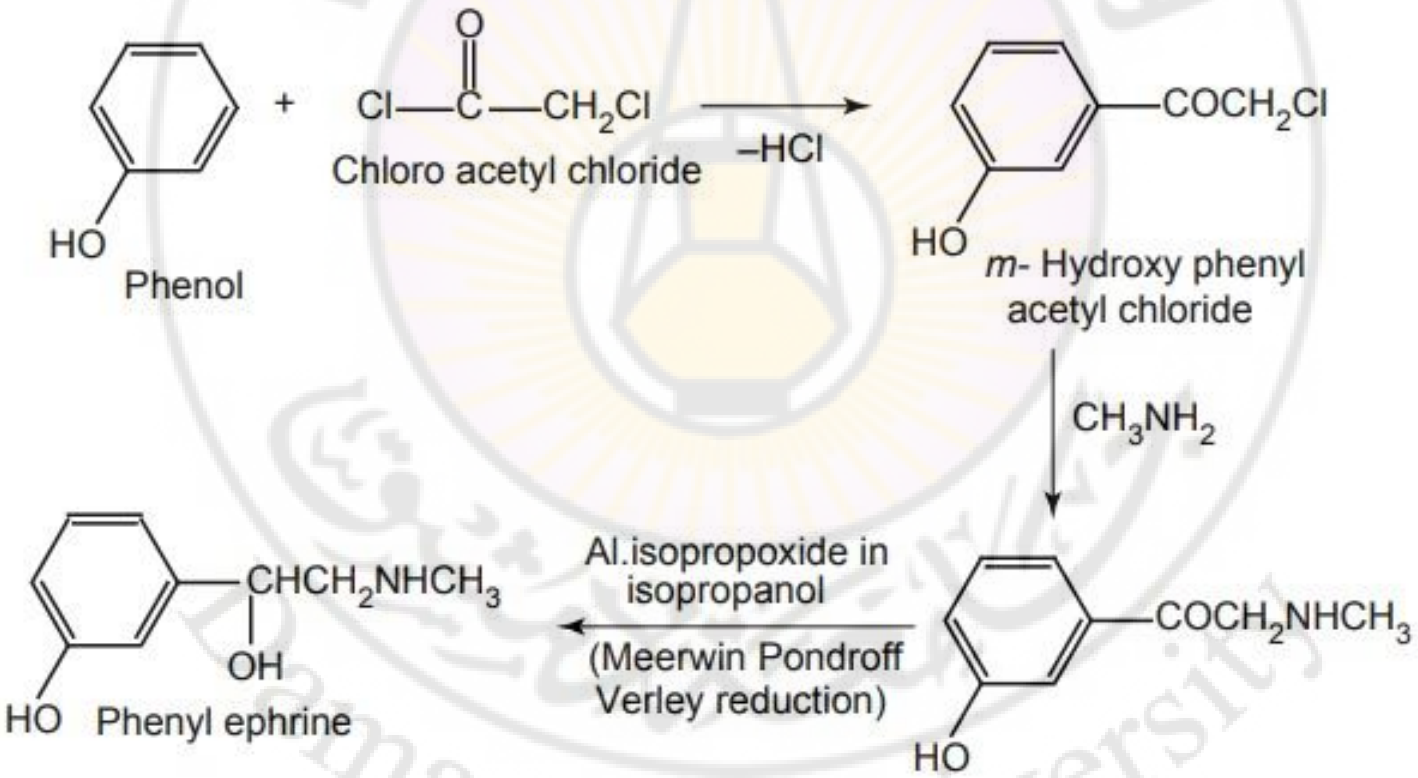
Metaraminol synthesis



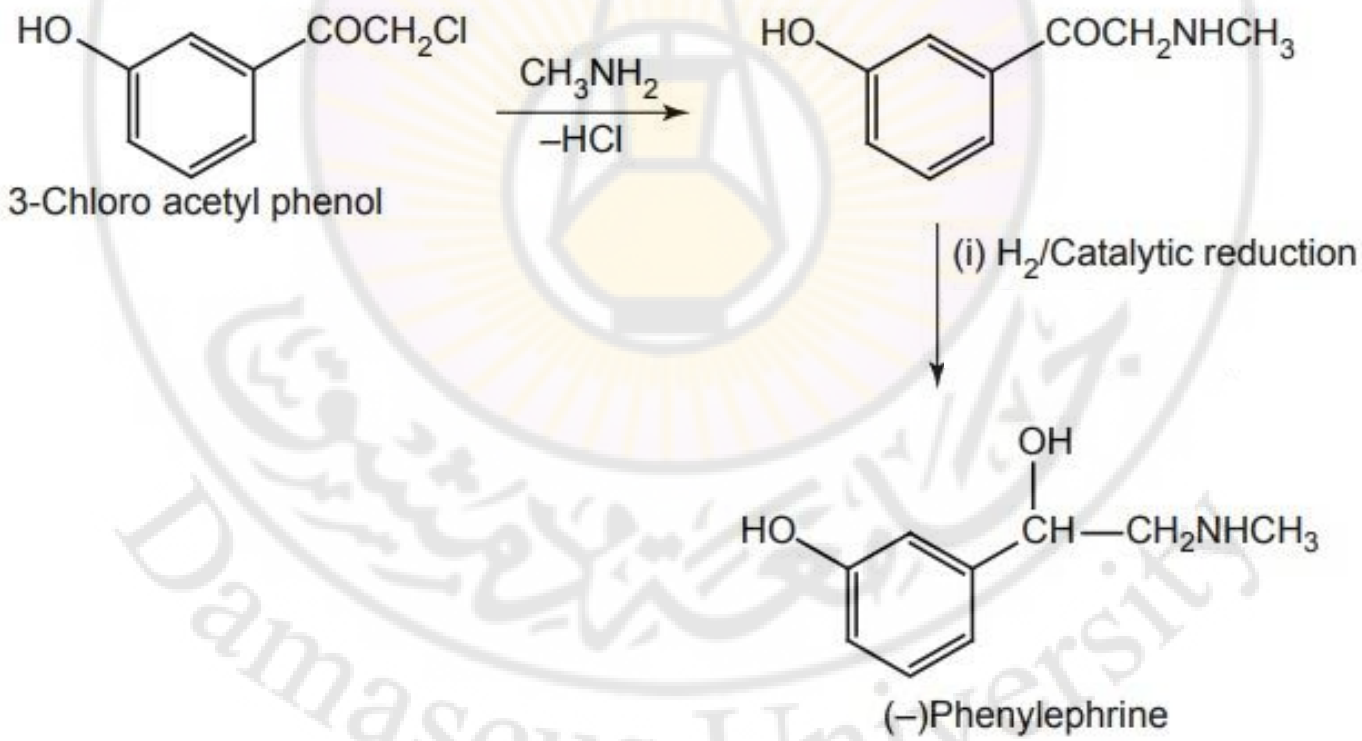
Metoxamine synthesis



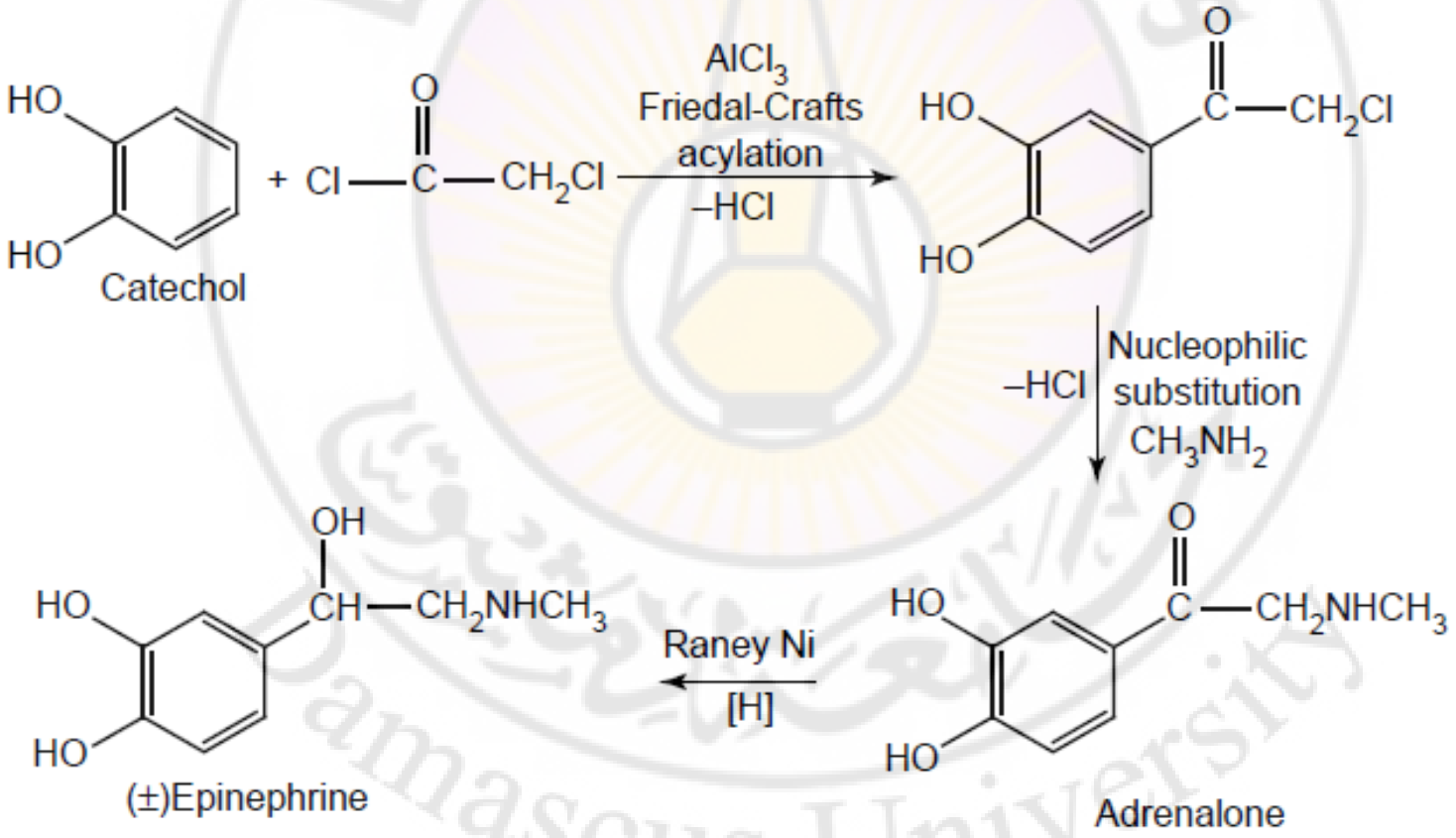
Phenylephrine synthesis



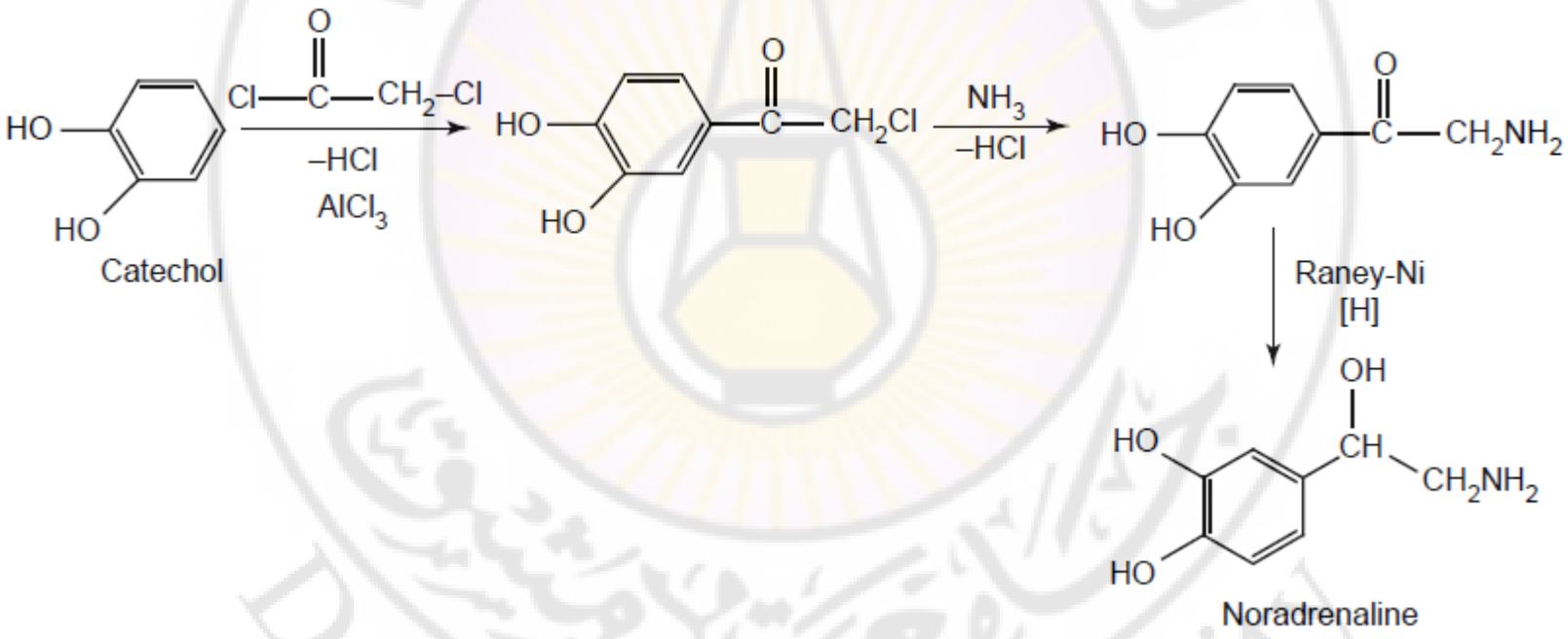
Phenylephrine synthesis



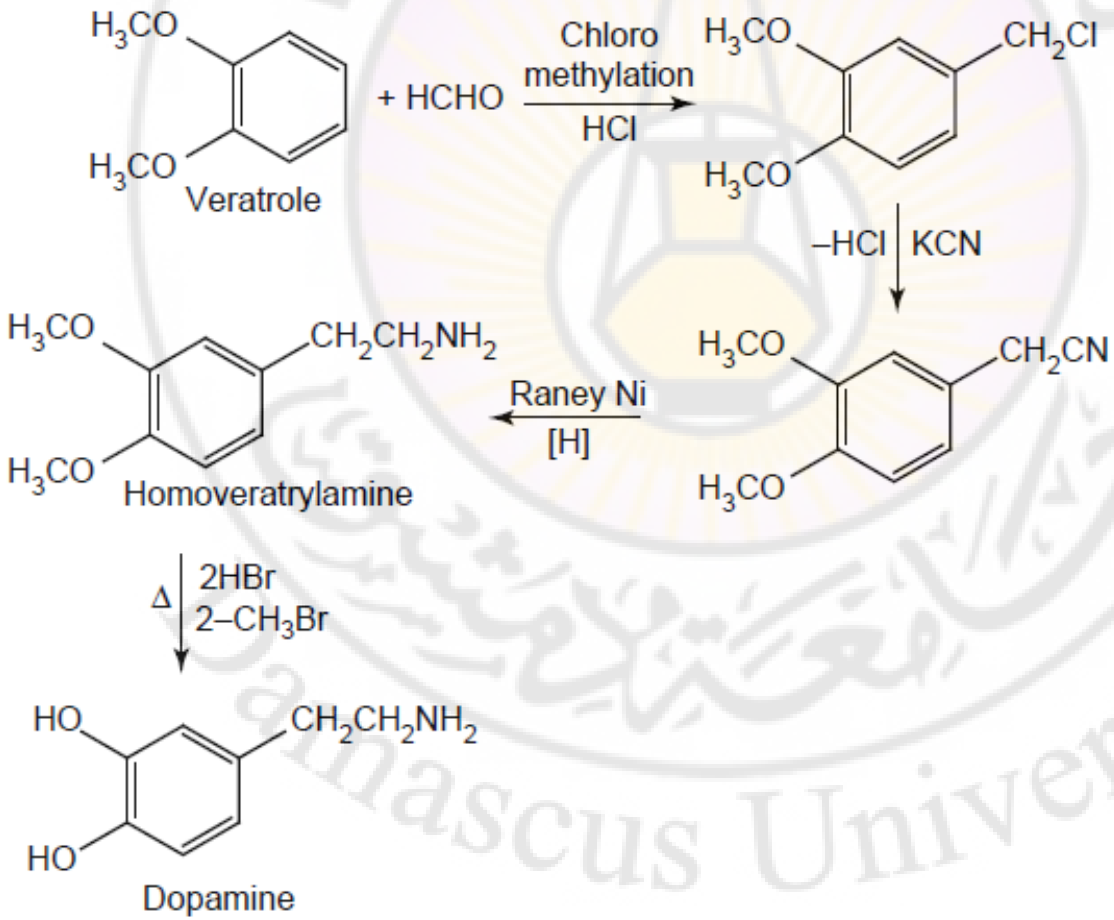
Adrenaline synthesis



Noradrenaline synthesis

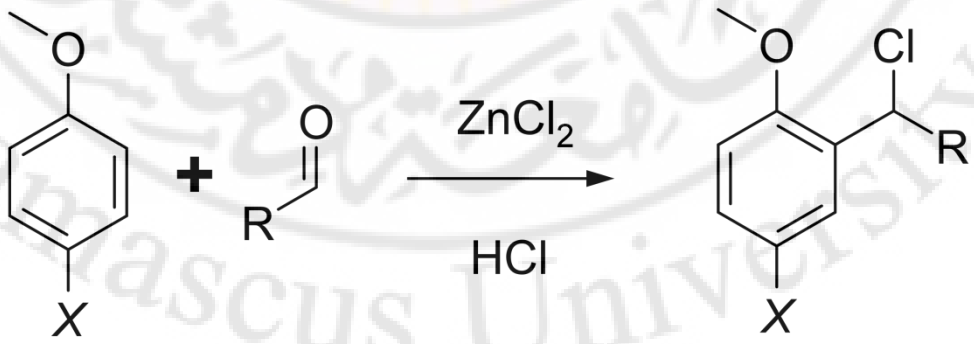


Dopamine synthesis

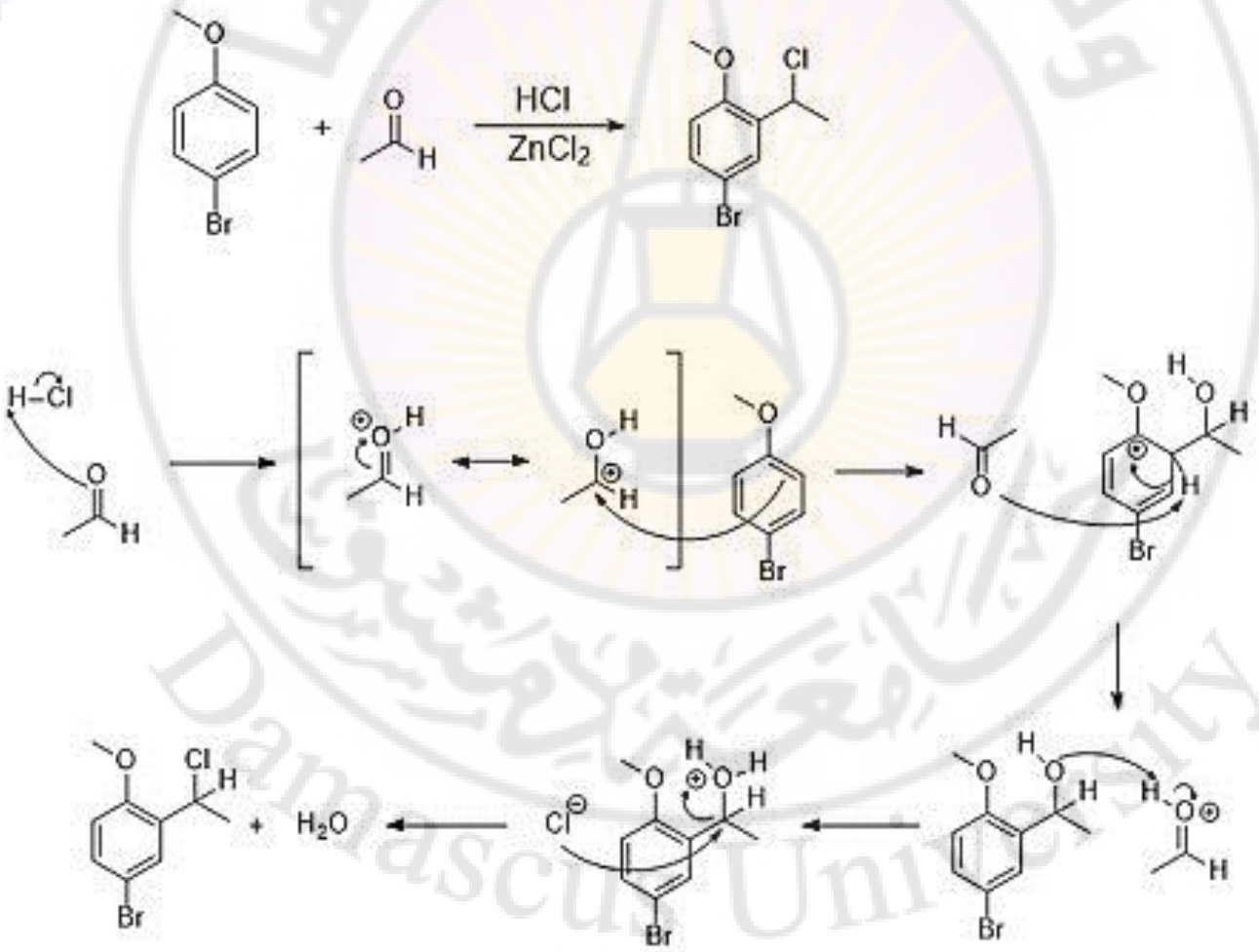


Quelet reaction

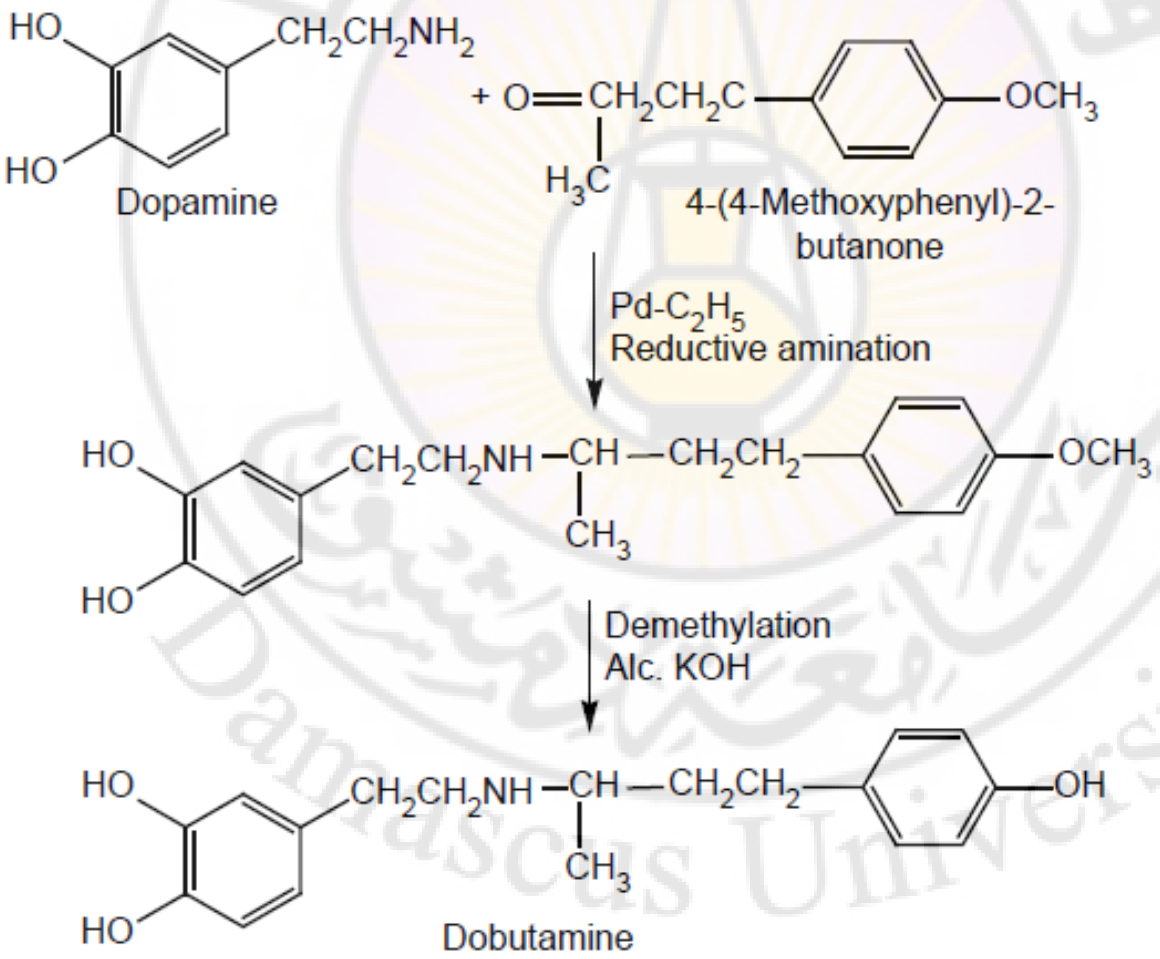
- ✓ The Quelet reaction (also called the Blanc–Quelet reaction) is an organic coupling reaction in which a phenolic ether reacts with an aliphatic aldehyde to generate an α-chloroalkyl derivative.
- ✓ The Quelet reaction is an example of a larger class of reaction, electrophilic aromatic substitution.
- ✓ The reaction requires a strong acid catalyst, but both Lewis acids and Brownsted-Lowry acids can be used in the Quelet reaction



Quelet reaction



Dubotamine synthesis



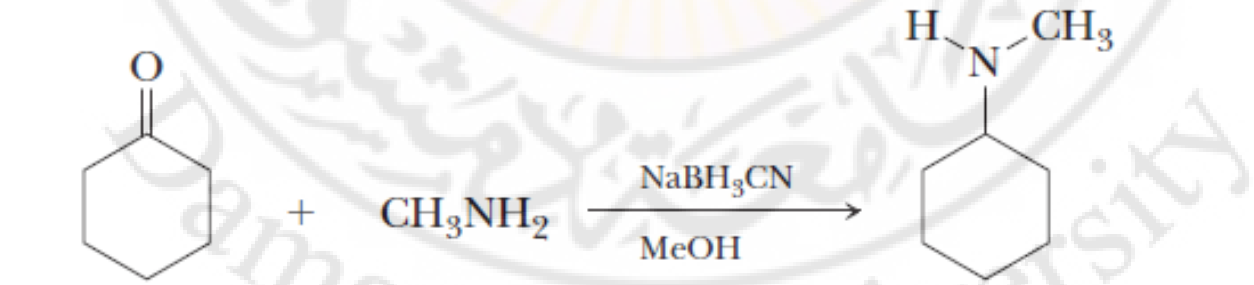
reductive amination

- ✓ One of the chief values of imines is that the carbon-nitrogen double bond can be reduced by hydrogen in the presence of a nickel or other transition metal catalyst to a carbon-nitrogen single bond.
- ✓ By this two-step reaction, called **reductive amination**, a primary amine is converted to a secondary amine by way of an imine as illustrated by the conversion of cyclohexylamine to dicyclohexylamine.

Cyclohexanone **Cyclohexylamine** (an imine intermediate) **Dicyclohexylamine**

reductive amination

- ✓ It is possible to carry out reductive amination in a single step by using a reducing agent that is not powerful enough to reduce the starting aldehyde or ketone, but is strong enough to reduce the more easily reduced imine that is formed.
- ✓ The reducing agent usually used for this purpose is sodium cyanoborohydride, NaBH3CN.



Cyclohexanone **N-Methylcyclohexylamine**