Synthesis of Aldehydes And Ketones

To Oxidate of the **1°alcohol** to **Aldehyde only** , and not to the Carboxylic Acid we should use **PCC** as the oxidating Reagant

[o]= $KCr0_7$, $KCrO_4$, $NaCrO_4$

Reaction of carbon a

Tautomerisation Keto-Enol

The Ketone form is the favorite form

Oxygen replacement

Reactions with Alcohols

Synthesis of Imine

Reactions whit Derivatives of Amonia

Phenyl-hydrazine

Phenyl-hydrazone

Grignard reagnt reaction

X=Cl,Br,I

Triphenyl-phosphine

Wittig Reaction

Triphenyl-phosphine-oxide

Betain

Aldol Condensetion

Aldol

We can get 4 different products: A & B can react with themselves or with each other- A attacks B or B attacks A.

Benzaldehyde

Cinnamaldehyde

Only 1 option because there is no H on C alpha

in this kind of reactions we will get rings of 5 to 7 Carbons depending on the starting material

Not stable

cis 10%

trans 90%

Oxidation

[o]= $KMnO_4$,CrO_3,Cr^{VI},H_2O_2,RCOOOH (peroxy acids)

[o] = CF_3COOOH (Peroxide)

Mechanism is in Bayer Viliger

Bayer Villiger

Clemmensen

Wolf Kishner

B: =KOH, R-ONa, R-OK

Carboxylic Acid Synthesis

Acid ==>Ester

Reaction with Diazomethane

Diazomethane

Reaction with Thionylchloride ($SOCl_2$)

Acid ==> Acyl

Acid ==> Amide

Hunsdiecker Reaction (chain reaction)

Esters synthesis

Esters Reactions

Acid Mechanism

Different mechanisem for 3° Carbon on the Ester

Base mechanisem for the same reaction (better than the Acid mechanisem if there are no halogens)

because of pKa differrences

Amide ==>Acid

Acylhalide ==>Acid

Acid <==>Acid Anhydride

Acid Anhydride

succinic acid

Trans-esterification

Acylhalide ==> Amides

Acid Derivatives

Intermdiate - Will react with another Grignard Reagent

Reduction of Acid Derivatives

LAH

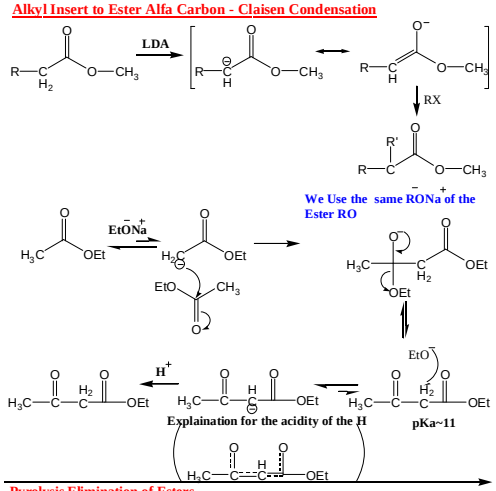
$LiAlH(OR)_3$

H_2/Pd/$BaSO_4$ Quinoline (Poisoned Catalyzator)

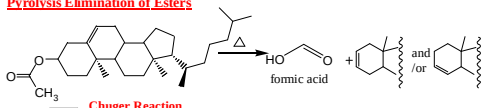
$LiAlH_4$ > $LiBH_4$ > $NaBH_4$ > $LiAlH(OR)_3$

All N=C HN-CH | Esters Ketones Aldehydes | Ketones Aldehydes Not Acids | Acyl Halides

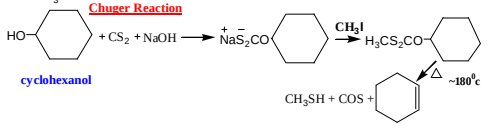
Alkyl Insert to Ester Alfa Carbon - Claisen Condensation



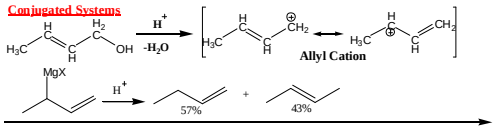
Pyrolysis Elimination of Esters



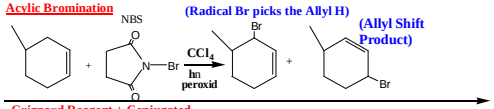
Chuger Reaction



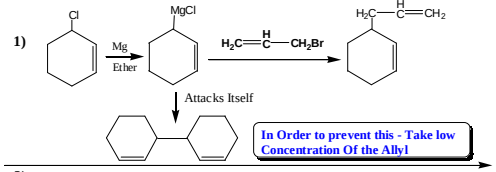
Conjugated Systems

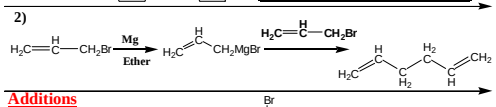


Acylic Bromination

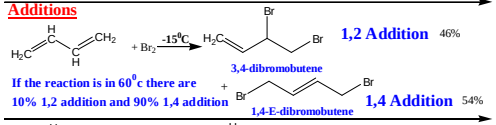


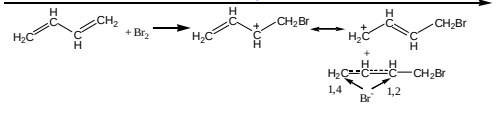
Grignard Reagent + Conjugated





Additions



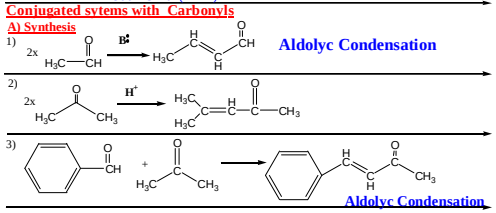


Allenes

N - No. Of C atoms
Even - A-Chiral (2N)
Odd - Chiral (2N+1)
(Just A Possibility)

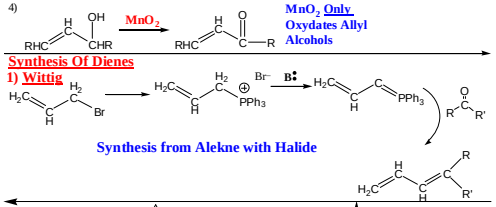
Conjugated sytems with Carbonyls

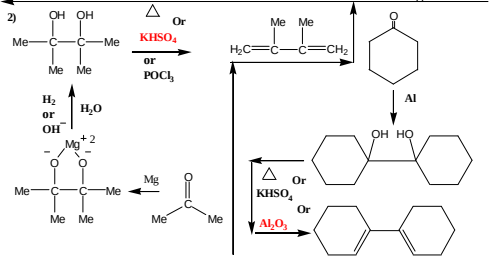
A) Synthesis



Synthesis Of Dienes

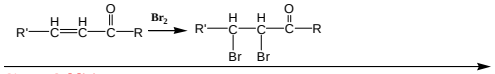
1) Wittig



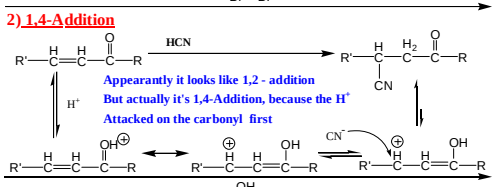


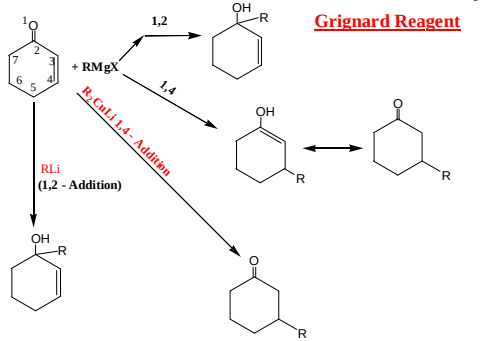
Reactions with conjugated Carbonyl

1) 1,2-Addition



2) 1,4-Addition

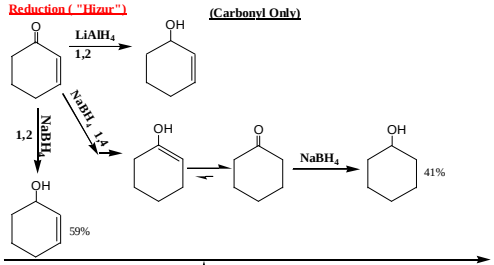




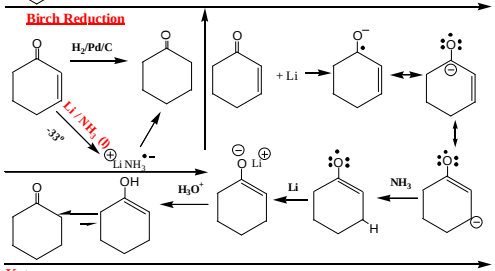
It seems like ordinary 1,2-addition to double bond but it's a delicate reduction reagant for carbonyl conjugated sytems

Reduction ("Hizur")

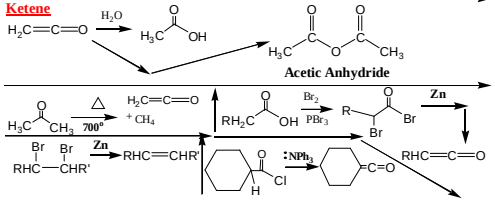
(Carbonyl Only)



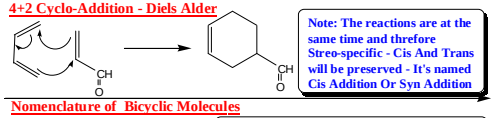
Birch Reduction



Ketene

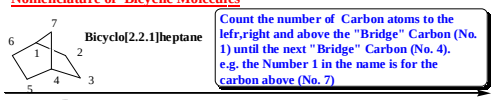


4+2 Cyclo-Addition - Diels Alder

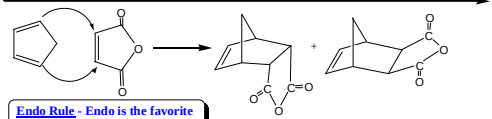


Note: The reactions are at the same time and threfore Streo-specific - Cis And Trans will be preserved - It's named Cis Addition Or Syn Addition

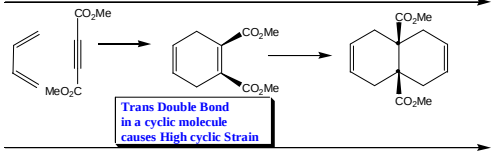
Nomenclature of Bicyclic Molecules



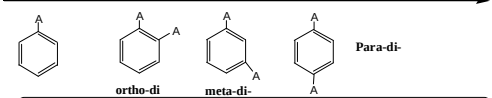
Count the number of Carbon atoms to the lefr,right and above the "Bridge" Carbon (No. 1) until the next "Bridge" Carbon (No. 4). e.g. the Number 1 in the name is for the carbon above (No. 7)



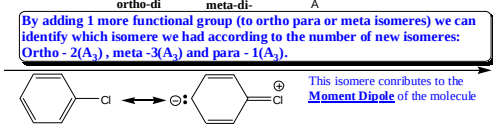
Endo Rule - Endo is the favorite Isomer and in low Temp. we'll get only Endo



Trans Double Bond in a cyclic molecule causes High cyclic Strain



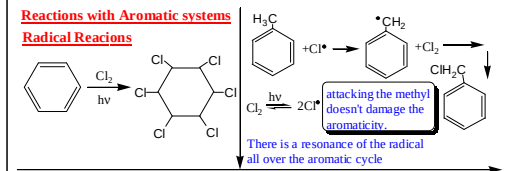
By adding 1 more functional group (to ortho para or meta isomeres) we can identify which isomere we had according to the number of new isomeres: Ortho - 2(A_3) , meta -3(A_3) and para - 1(A_3).



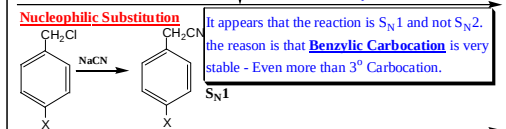
This isomere conributes to the Moment Dipole of the molecule

Reactions with Aromatic systems

Radical Reacions

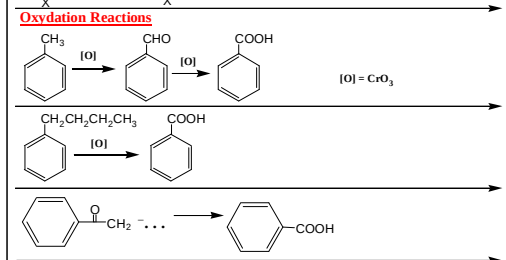


Nucleophilic Substitution

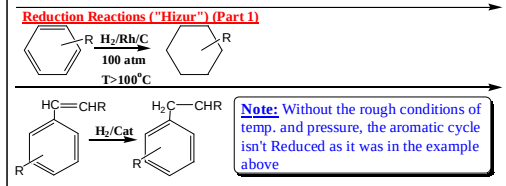


It appears that the reaction is S_N1 and not S_N2. the reason is that Benzylic Carbocation is very stable - Even more than 3° Carbocation.

Oxydation Reactions



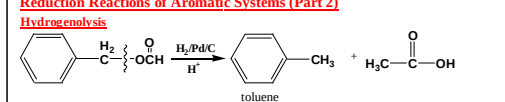
Reduction Reactions ("Hizur") (Part 1)

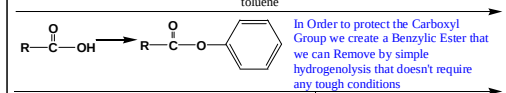


Note: Without the rough conditions of temp. and pressure, the aromatic cycle isn't Reduced as it was in the example above

Reduction Reactions of Aromatic Systems (Part 2)

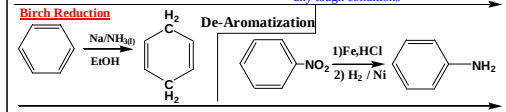
Hydrogenolysis

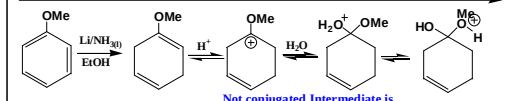




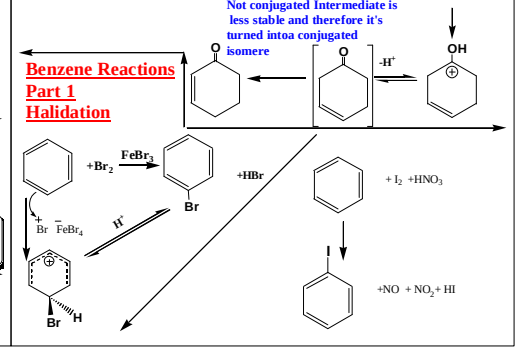
In Order to protect the Carboxyl Group we create a Benzylic Ester that we can Remove by simple hydrogenolysis that doesn't require any tough conditions

Birch Reduction

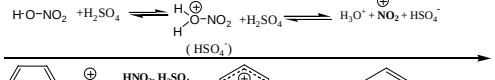


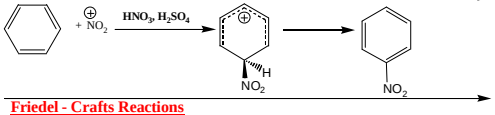


Benzene Reactions Part 1 Halidation



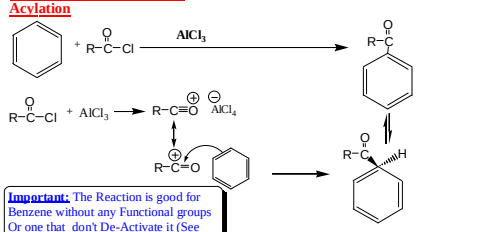
Benzene Reactions (Part 2)





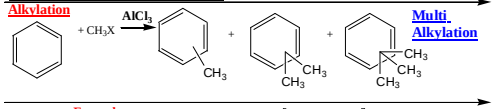
Friedel - Crafts Reactions

Acylation



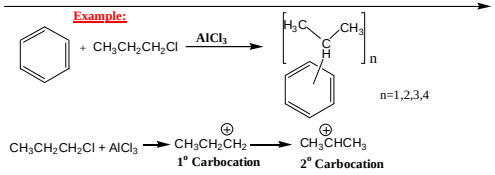
Important: The Reaction is good for Benzene without any Functional groups Or one that don't De-Activate it (See effects of functional groups on Benzene)

Alkylation

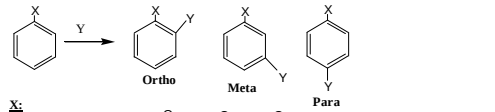


Multi Alkylation

Example:



Multiple Electrophilic Aromatic Reactions



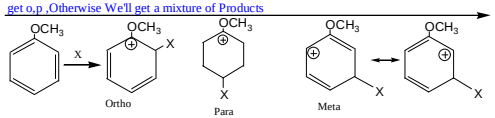
X:

Meta - NO_2, -C(=O)-R, -C(=O)-OR, -C(=O)-NR, -C(=O)-OH, CN, CF_3 ⟹ **De-Activation**

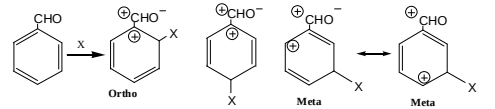
Ortho, Para -C(=O)-O-, -C(=O)-N-, NH_2, -OR, -R ⟹ **Activation**

Hallogenes ⟹ **Activation (Weak)**

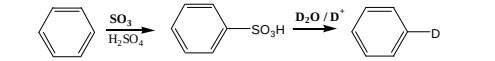
Note: For 3rd Subtitution - If one of the 2 functional groups leads strongly to o,p we'll get o,p ,Otherwise We'll get a mixture of Products

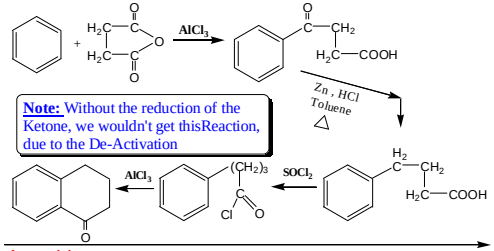


The Resonance of the + charge can give a form with the + on the carbon attached to the Electron Drawing group and stabilizes it. This can't happen on the Meta isomere and therefore Para and Ortho are the favorite isomere.
The **Activation** is resolved by the Electron Donation to the Aromatic system.



The + charge will never be on the Electron Donating group in Meta Isomere, but on Ortho and Para Isomere it can be. Therefore it De-stabilizes these 2 isomeres and the Meta Isomere is the favorite one.
The **De-Activation** is resolved of the Electron drawing from the Aromatic system.

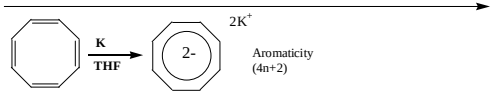


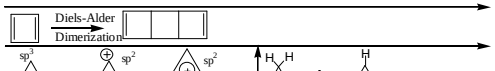


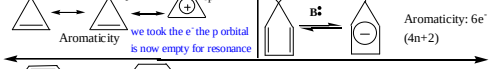
Note: Without the reduction of the Ketone, we wouldn't get thisReaction, due to the De-Activation

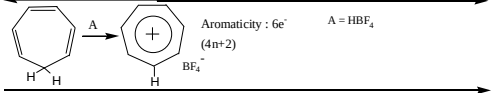
Aromaticity

Huckel Rule: Number of π Electrons: 4n+2 ⟹ **Aromaticity**
4n ⟹ **Anti-Aromatic**







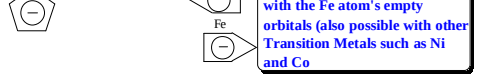


The p Electrons are shared with the Fe atom's empty orbitals (also possible with other Transition Metals such as Ni and Co

Amines

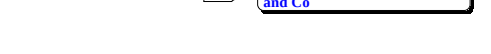
pKa

Electron drawing Functional groups such as NO_2,Cl,Br make the Amine to be Less Base and to have a lower pKa

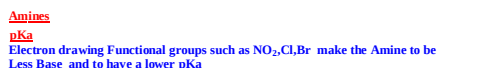


This is a good way to make rings with 3 carbons. However th problem is that NaOH is not soluable in Chloroform. And we need the Amine.

Synthesis of Amines

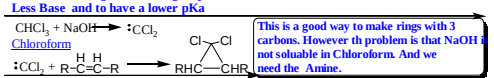


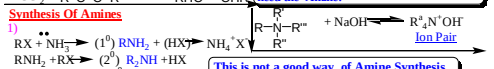
This is not a good way of Amine Synthesis because it creates a mixture of Amines

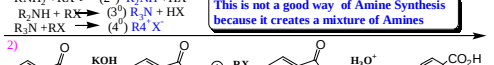


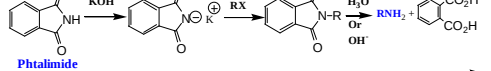
Phtalimide

Reduction

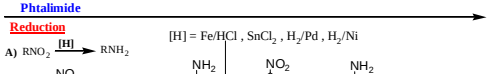


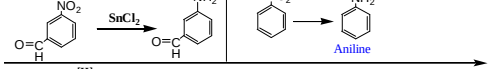


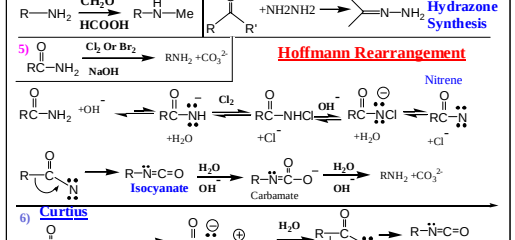




Schiff's Base





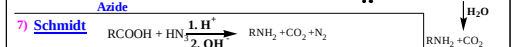


Hydrazone Synthesis

Hoffmann Rearrangement

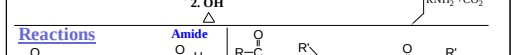
Nitrene

Isocyanate



Carbamate

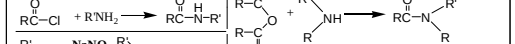
6) Curtius



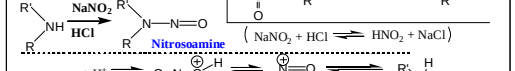
Azide

Isocyanate

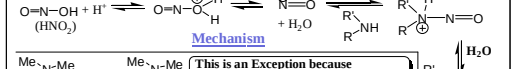
7) Schmidt



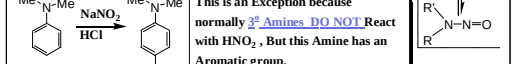
Reactions



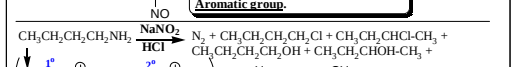
Amide



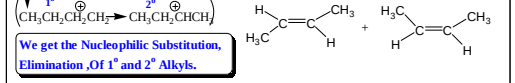
Nitrosoamine



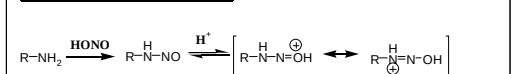
Mechanism



This is an Exception because normally 3° Amines DO NOT React with HNO_2 , But this Amine has an Aromatic group.



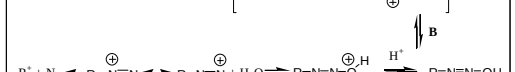
We get the Nucleophilic Substitution, Elimination ,Of 1° and 2° Alkyls.



Diazonium Salt

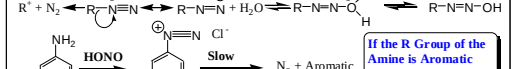
If the R Group of the Amine is Aromatic then the Diazonium Salt is stable

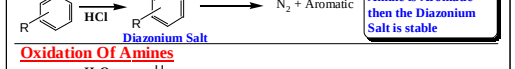
Oxidation Of Amines

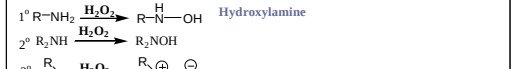


Hydroxylamine

Nitroxide







In case we have a Cyclic Amine:

Hoffmann Degradation

By the number of the double bonds after the degradation we can determine: 1 - Chain Amine, 2 -Cyclic Amine , 3 - Bicyclic Amine

We get the **Anti-Zeizev Product**

Cope Reaction

(For the following Reaction)

Enamine

DiazoAlkanes Derivatives

Diazomethane

This is a good way to add Carbon atoms to Carboxylic acids

(Works in the same mechanism)

Carbene

This is the mechanism of the Reaction above

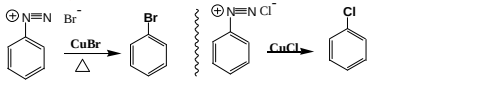
Phenol

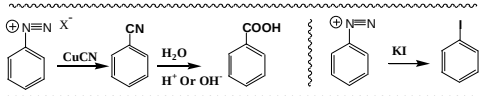
Chlorobenzene

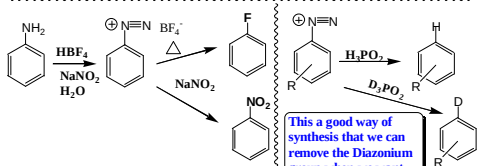
Phenol

Synthesis of only the Phenol

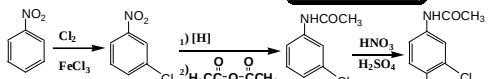
Sandmeyer Reaction



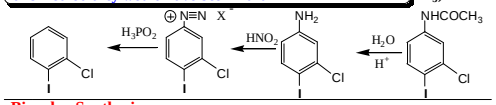




This a good way of synthesis that we can remove the Diazonium group when we want

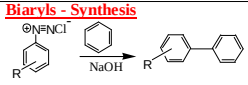


This is an example how we can use Sandmeyer Reaction in order to insert 2 Halogene groups in desired positions. In this case we put them in Ortho and without this method they would have been Para

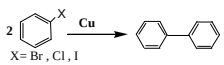


Biaryls - Synthesis

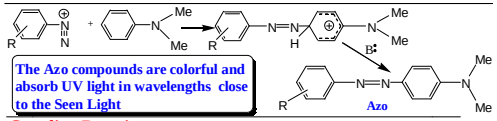
1) Gomberg - Bachman



2) Ulmann



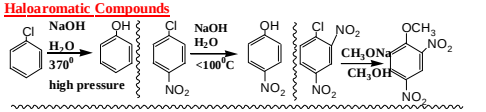
Electrone Drawing groups (like NO_2) or Simetric materials help this Reaction

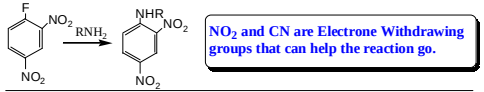


The Azo compounds are colorful and absorb UV light in wavelengths close to the Seen Light

Coupling Reactions

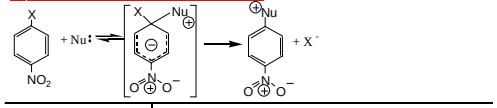
Haloaromatic Compounds

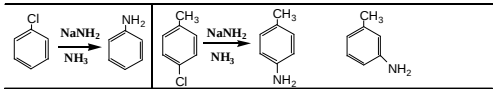


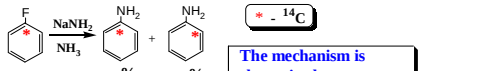


NO_2 and CN are Electrone Withdrawing groups that can help the reaction go.

Mechanism For Coupling Reactions

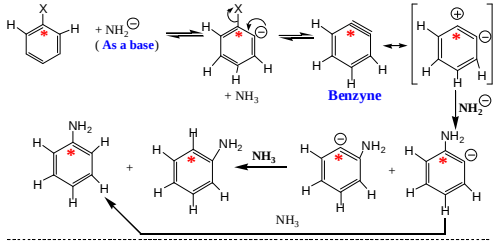


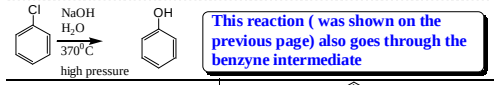




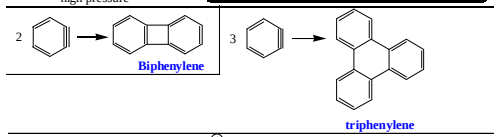
The mechanism is shown in the next page

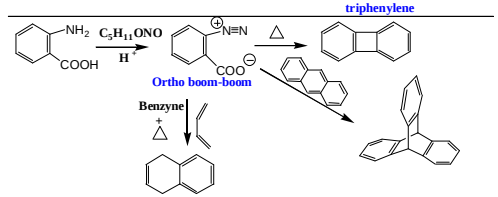
Mechanism for the coupling reaction from the previous page

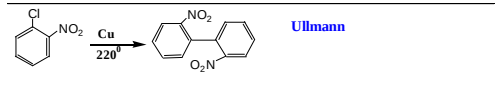


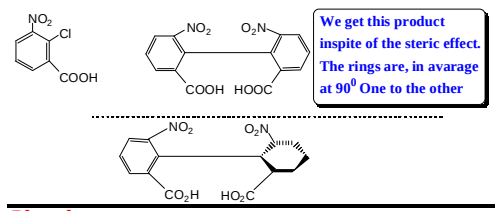


This reaction (was shown on the previous page) also goes through the benzyne intermediate



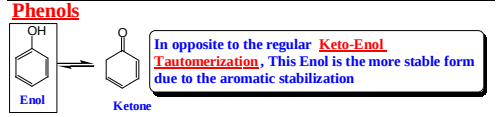






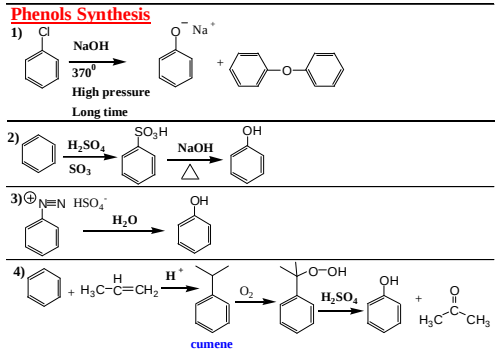
We get this product inspite of the steric effect. The rings are, in avarage at 90^0 One to the other

Phenols



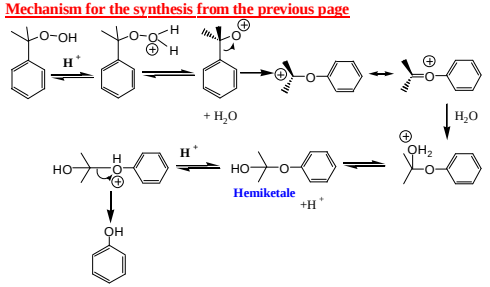
In opposite to the regular Keto-Enol Tautomerization , This Enol is the more stable form due to the aromatic stabilization

Phenols Synthesis



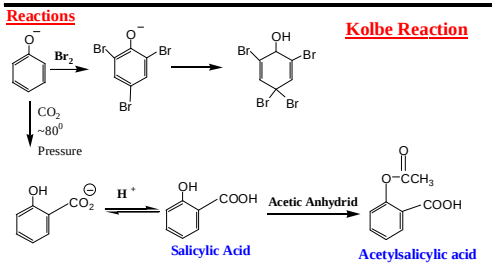
The Mechanism will be shown in the next page

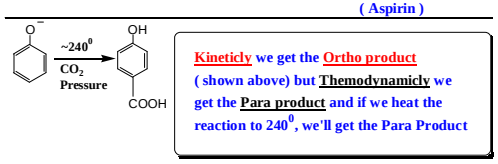
Mechanism for the synthesis from the previous page



Reactions

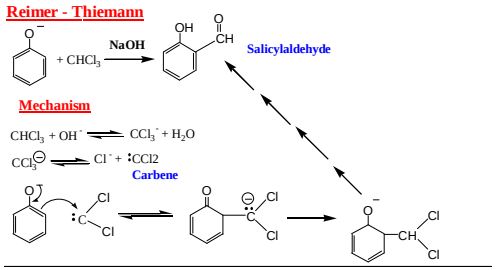
Kolbe Reaction





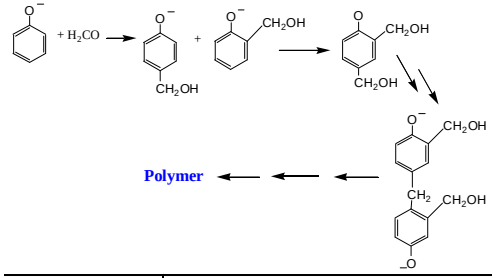
Kineticly we get the Ortho product (shown above) but Themodynamicly we get the Para product and if we heat the reaction to 240^0, we'll get the Para Product

Reimer - Thiemann

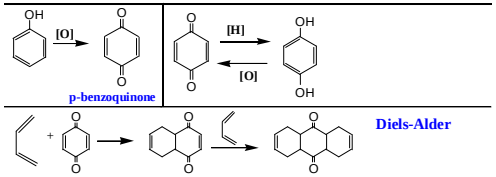


Salicylaldehyde

Mechanism

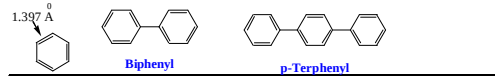


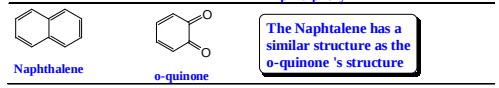
Polymer



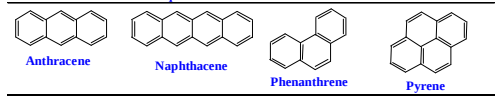
Diels-Alder

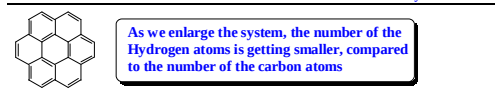
Polycyclic Aromatic Hydrocarbons



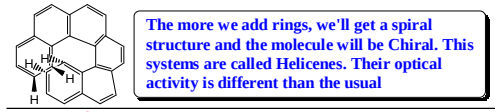


The Naphtalene has a similar structure as the o-quinone 's structure



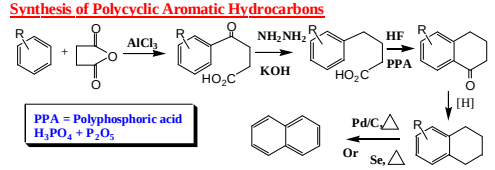


As we enlarge the system, the number of the Hydrogen atoms is getting smaller, compared to the number of the carbon atoms

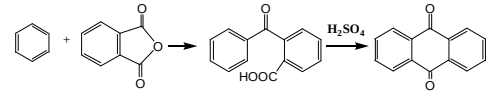


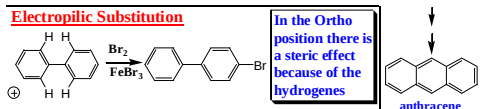
The more we add rings, we'll get a spiral structure and the molecule will be Chiral. This systems are called Helicenes. Their optical activity is different than the usual

Synthesis of Polycyclic Aromatic Hydrocarbons



PPA = Polyphosphoric acid $H_3PO_4 + P_2O_5$

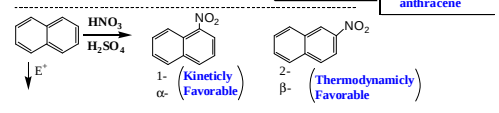




anthracene

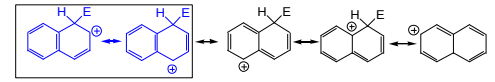
Electropilic Substitution

In the Ortho position there is a steric effect because of the hydrogenes

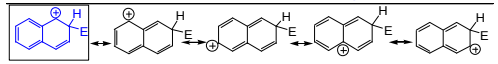


1- α- (Kineticly Favorable)

2- β- (Thermodynamicly Favorable)



There are 2 Resonance forms that have one benzene ring



There is only 1 resonanace form with one benzene ring

Reactions

Sulfunations

2) Friedle-Crafts

Guidance in Naphtalene

1) Meta guiding group : a position on the other ring

2) Ortho,Para guiding group in No.1 Position: Para is favorable because it's a Primary

3) Ortho,Para guiding group in No.2 Position:

Difunctional Compounds

Examples

1,2 - Diols

Synthesis

pinacol

We can see that with OsO_4 and $KMnO_4$ we get the Cis Product. This happens due the formation of the ring.

Pinacole Rearrangement

pinacol

pinacolone

Bicyclic compounds having one carbon common to both rings are spiro compounds

Spiro[5.6]dodecane

Oxidation

Aldehyde

Ketone

Another Reagent is Lead tetracetate

HIO_4 is specific to 1,2 Diols and doesn't oxidate other groups

Diacids

Malonic Acid

Diethyl Malonate pKa ~ 10

Decarboxylation

This is Specific for b Diacids Only

The overall process is a way to add 2 carbons to the chain - RX → RCH_2COOH

Knnovenagel Reaction

Synthesis of Conjugated Carboxylic Acids

Ethylcyanoacetate

Michael Addition

1,4-addition

a,b-unsaturated Ketone

This is a good way for Cyclization

Dieckmann Reaction

We can Synthesis 5or 6 carbons rings.For larger rings we need low concentrations to prevent Dimerization

Acyloinic Cyclization

(Here we don't need low concentrations)

Acyloin

o,p,m Xylene

Mechanism

Acyloin

Hydroxyacids

a- b- g-hydroxyacid d-hydroxyacid

g-Lactone

d-Lactone

d-hydroxyacid

Cyclic "Hemiacetal"

Amino-Acids , Peptides , Proteins

a-Amino acids

Zwitterion

pKa = 9.8

pKa=2.35

Gives Purple color

ninhydrin

Synthesis

Double substitution by the NH_3

In order to Synthesis all kinds of Amino Acids , all we need is to use another RX

Shtraker Reaction

Amide

Esetrification

With Amino Acids we get polymerization

Polymer

Protection for Amino Acids

Protection For The Amino side

1) Cbz

Carbobenzoxy- Cbz-

2) Boc

Boc On

Protection For The Carboxylic side

For the protection we create the Ester (Me,Et or Ph) with the Carboxylic Acid and when we want to remove it there are 2 options:

1) We can use this method to remove Et Ester and we'll get EtOH

2) OBn-

The OBn Protection doesn't fall in Hydrolysis , which could be very useful

dicyclohexylcarbodiimide

DCC- A catlyst for the condensation of 2 Amino Acids into a Peptide

Good for Dipeptides ONLY

Merrifield

Peptide

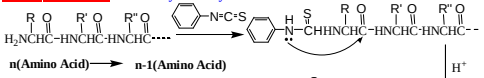
In order to add more A.Acids we need to add another A. Acid with Boc.It's Important to wash and Filter after every time.

Sanger Method

Sanger Method can determine what kind of A.Acid is in the N-Terminal part of the Peptide

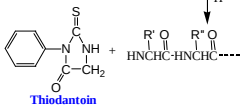
Edman Method

Phenylisothiocyonate



n(Amino Acid) → n-1(Amino Acid)

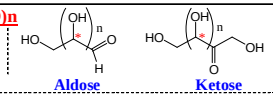
We can repeat it many times and determine the Sequence of the Amino Acids in the Peptide



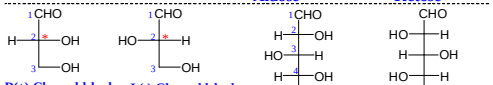
Thiodantoin

Carbohydrates - Cn(H2O)n

1) Monosacharides
2)Oligosacharides - 2-7 monomers
3)Polysacharides -7+ monomers



Aldose Ketose

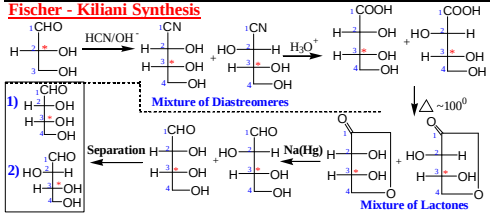


D(+)-Glyceraldehyde L(-)-Glyceraldehyde

We determine L or D by the Chiral Carbon with the highest number - If it's on the Right -D , and if it's on the Left -L

D-Glucose L-Glucose

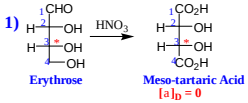
Fischer - Kiliani Synthesis



Mixture of Diastreomeres

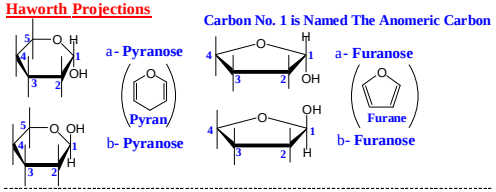
Separation Na(Hg)

Mixture of Lactones

1) 

2)

Haworth Projections

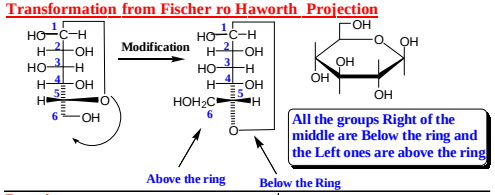


a- Pyranose b- Pyranose Pyran

a- Furanose b- Furanose Furane

Carbon No. 1 is Named The Anomeric Carbon

Transformation from Fischer ro Haworth Projection



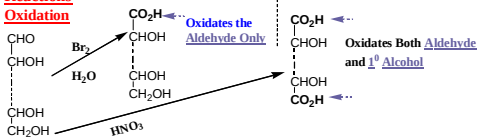
Modification

Above the ring Below the Ring

All the groups Right of the middle are Below the ring and the Left ones are above the ring

Reactions

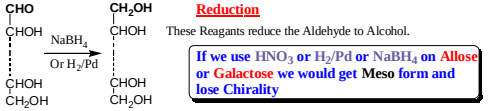
Oxidation



Oxidates the Aldehyde Only

Oxidates Both Aldehyde and 1⁰ Alcohol

Reduction



These Reagants reduce the Aldehyde to Alcohol.

If we use HNO_3 or H_2/Pd or $NaBH_4$ on Allose or Galactose we would get Meso form and lose Chirality

1)

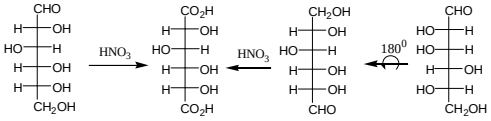
Erythrose Meso-tartaric Acid $[a]_D = 0$

2)

Threose $[a]_D \neq 0$

HNO_3 oxidates only 1⁰-Alcohols and Aldehydes to Carboxylic Acids. This helps the separation process, because here we get a Chiral product and an a-Chiral product.

Identifying Glucose and Manose



D-Glucose L-Gulose

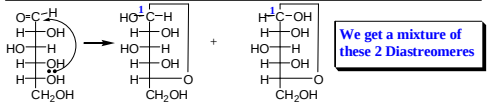
If we have L-Gulose we can oxidate it and then if we oxidate Glucose and Mannose -Only Glucose will give the same product as the L-Gulose

If we Crystalize Glucose from an H_2O solution we'll get 2 Different materials:

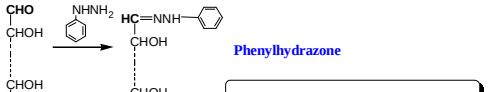
1) $[a]D = 112^0$ → Equlibration Time → $[a]D = 52^0$

2) $[a]D = 19^0$ → Equlibration Time → $[a]D = 52^0$

Appearantly these 2 materials are shifting from one form to the other until they reach Equlibrium and we get the 52^0. This lead to the conclusion that glucose is mostly in a Cyclic Form:



We get a mixture of these 2 Diastreomeres

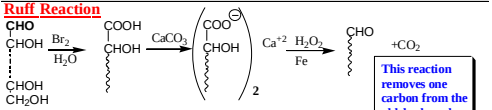


Phenylhydrazone

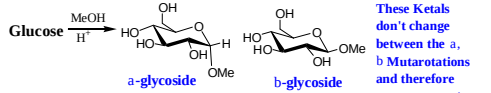
This reaction occurs only on carbons 1 & 2.It helps us to identify the Carbohydrates that have a difference only in carbon No. 2, because they'll give the same Osazone

Osazone

Ruff Reaction

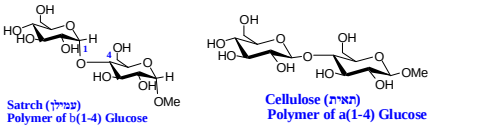


This reaction removes one carbon from the aldehyde end



a-glycoside b-glycoside

These Ketals don't change between the a, b Mutarotations and therefore we can seperate them



Satrch (עמילן) Polymer of b(1-4) Glucose

Cellulose (תאית) Polymer of a(1-4) Glucose