Chemical Reactions

(Reaction mechanism – Named reactions – Chromatography)

3rd Year Students – Chemistry Group

Faculty of Education

First Term – 2022/2023

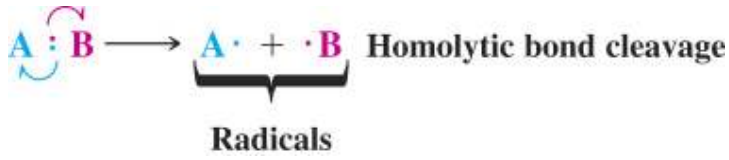
Dr./ Ibrahim Abdul-Motaleb Mousa

Chemical reaction (التفاعل الكيميائى)

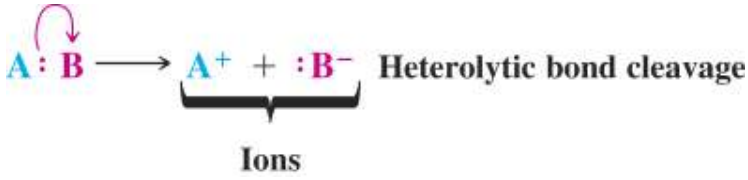
بصفة عامة التفاعل الكيميائى فى مجمله عبارة عن كسر روابط كيميائية وتكوين روابط جديدة. ولذا يجب توضيح الكيفية التى يتم بها تكسير رابطة او تكوين رابطة أخرى.

Cleavage of Covalent Bonds (كيفية تكسير رابطة تساهمية)

a- Homolytic bond Cleavage: تكسير متماثل للرابطة



b- Heterolytic bond Cleavage: تكسير غير متماثل للرابطة



Bond making (كيفية تكوين رابطة)

a- Homogenic bond making (تكوين متماثل للرابطة)

أمثلة: تفاعلات جذور حرة

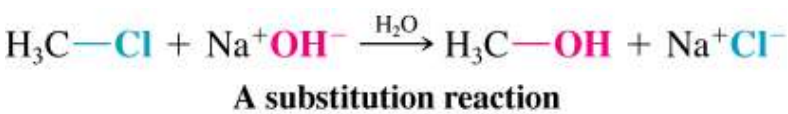
b- Heterogenic bond making (تكوين غير متماثل للرابطه)

أمثلة: تفاعلات قطبية أو قطبية نسبية

Types of Reactions and Their Mechanisms

بصفة عامة يمكن تقسيم التفاعلات العضوية الى أربع أنواع من التفاعلات.

1- Substitution reactions تفاعلات استبدال

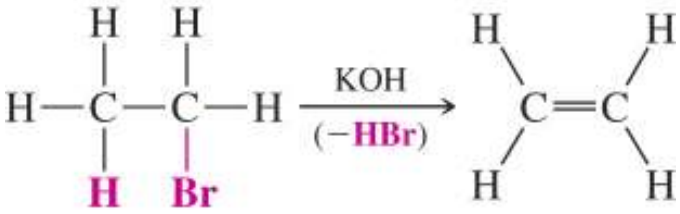


A substitution reaction

2- Addition reactions تفاعلات اضافة

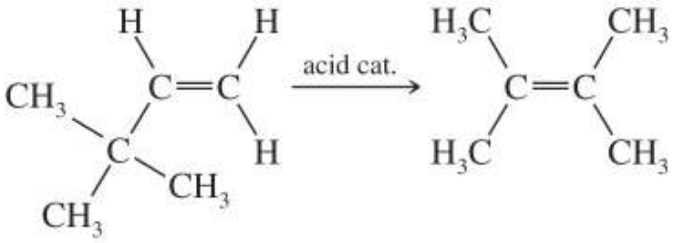
An addition reaction

3- Elimination reactions تفاعلات نزع



An elimination reaction

4- Rearrangement reactions تفاعلات اعادة ترتيب



A rearrangement

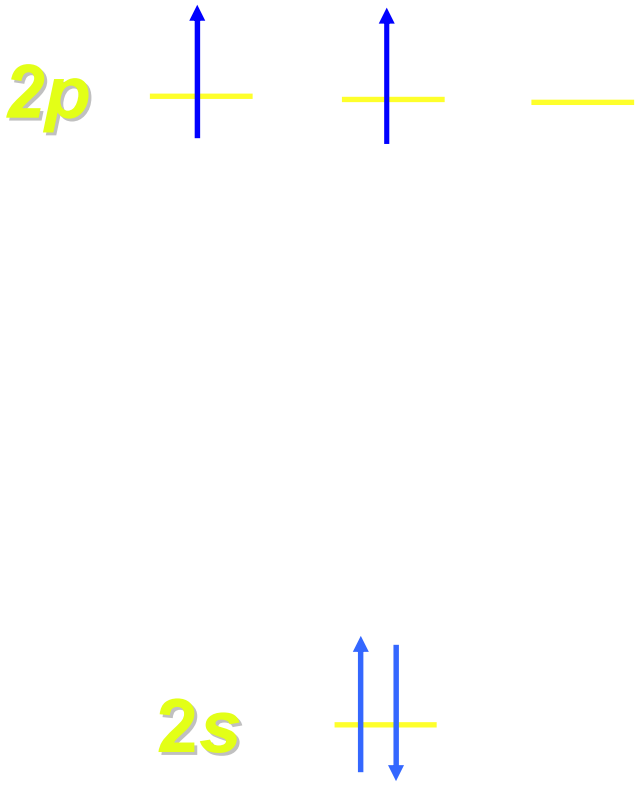
تهجين المدارات وتكوين الروابط فى الميثان، الأيثان، الأيثيلين، الأسيتيلين

التركيب الألكترونى للكربون

- فقط عدد ٢ الكترون غير مزدوج

- لذا المقدره على الأرتباط بعدد ٢ ذرة هيدروجين فقط

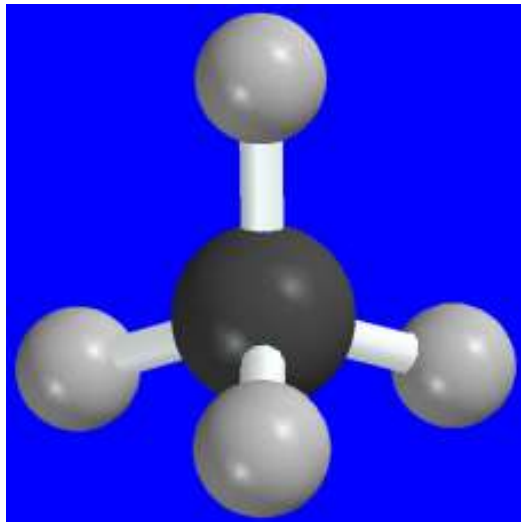
- هل الكربون ثنائى التكافؤ!!!!

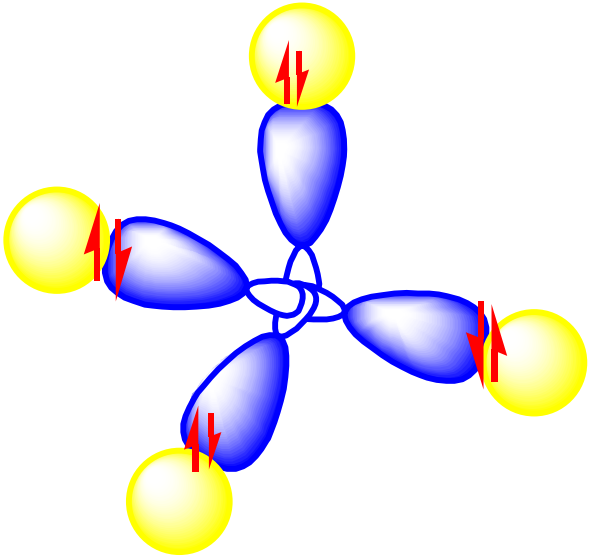


التركيب الفراغى للميثان

- الشكل الفراغى: رباعى السطوح هرمى الشكل
- مقدار الزاوية = 109.5°
- طول الرابطه C—H = 110 pm
- هذا يدلل على ان الكربون رباعى التكافؤ.

وهذا يعزى الى التهجين.

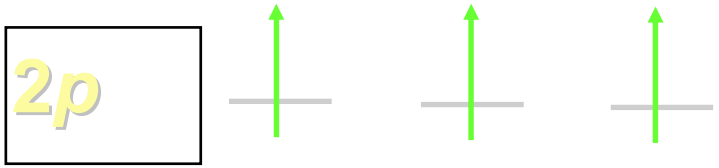




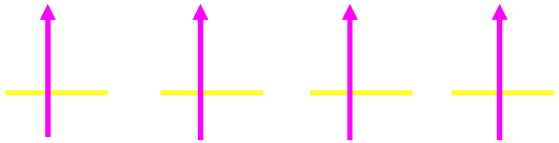
مدارات مهجنه من نوع sp^3

اثارة الكترون من المدار 2s الى المدار 2p

مدارات مهجنه من نوع sp^3



تهجين عدد واحد مدار من 2s مع عدد ثلاثة مدارات من 2p



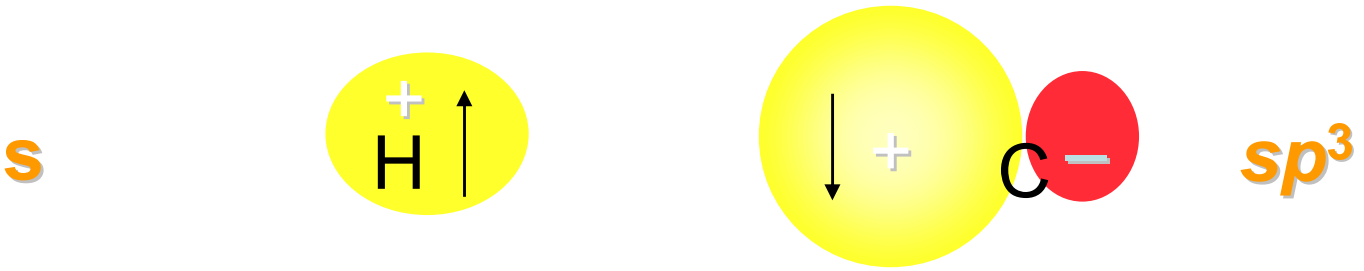
الناتج: هو أربع مدارات مهجنه (متكافئه) من نوع sp^3

شكل المدارات المهجنه من نوع sp^3

p s	خذ مدار s وضعه على قمة مدار p s + p	(هجين) sp وفقا لعدد مدارات p يكون نوع الهجين sp, sp^2 or sp^3

الرابطة سيجما C—H

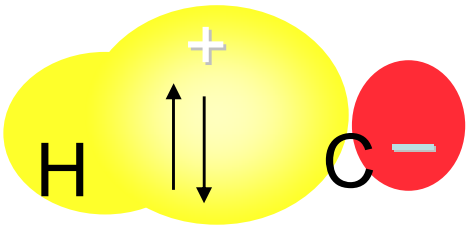
- تداخل مدار نصف ممتلىء من s مع مدار نصف ممتلىء من هجين sp^3



يعطى:

H—C σ bond

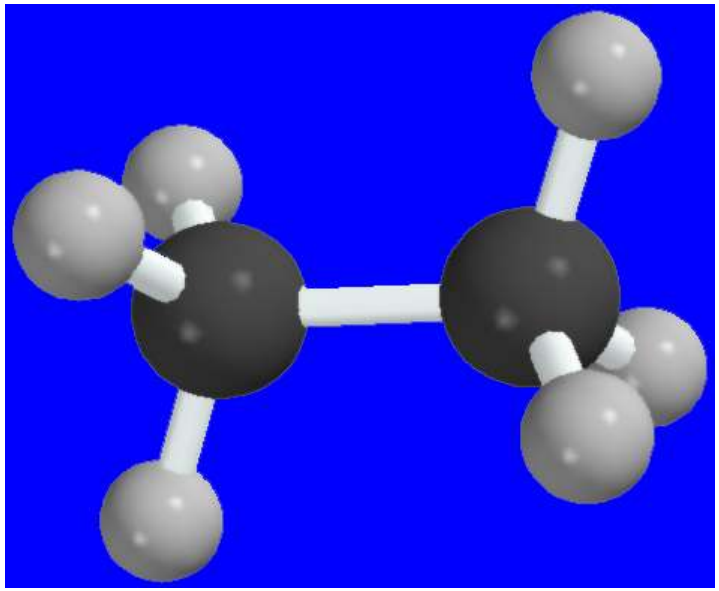
هجين من نوع $s\text{-}sp^3$



التركيب الفراغى للأيثان

C_2H_6

CH_3CH_3

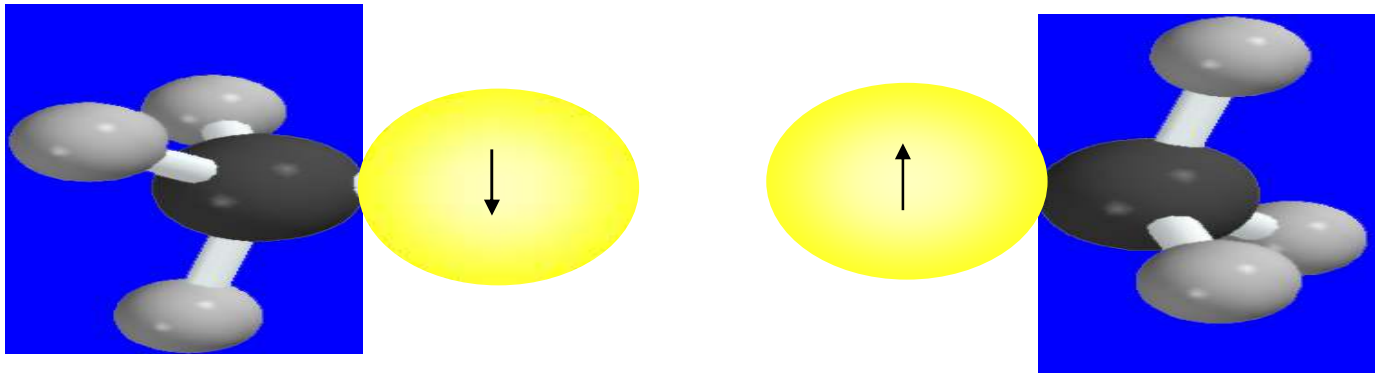


- الشكل الفراغى: رباعى السطوح هرمى الشكل عند ذرات الكربون

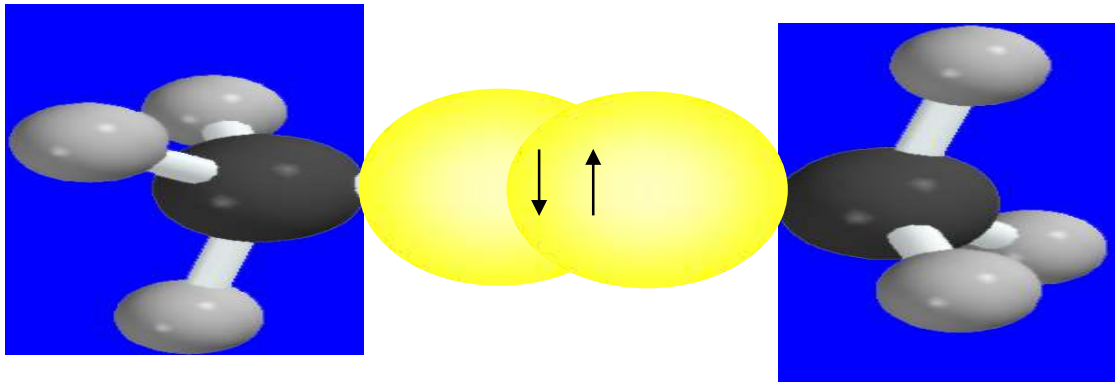
طول الرابطه C—H = 110 pm

طول الرابطه C—C = 153 pm

الرابطة سيجما C-C



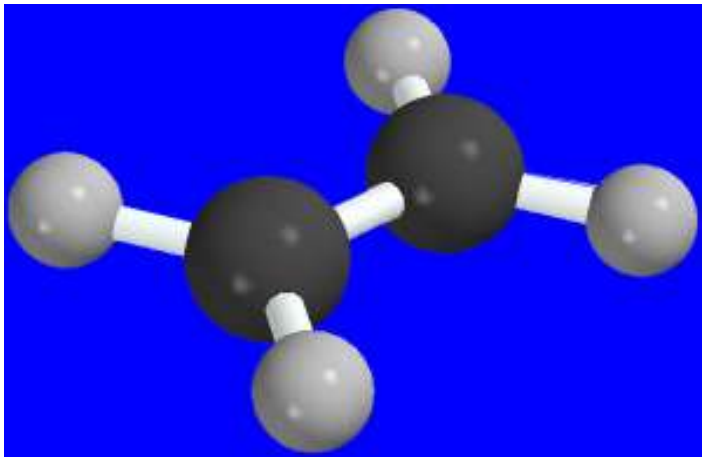
C—C σ bond, sp^3-sp^3 هجين من نوع



التركيب الفراغى للأيثيلين

C_2H_4

$H_2C=CH_2$



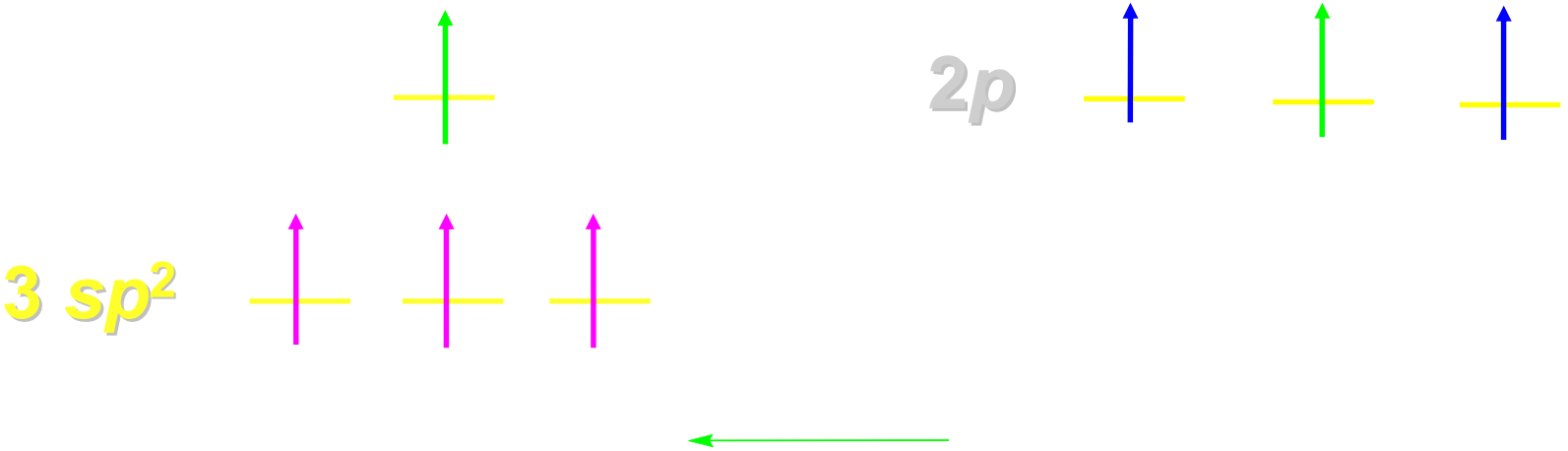
مستو الشكل

زوايا الرابطة : تقارب 120°

أطوال الروابط : C-H = 110 pm

C=C = 134 pm

هجين من نوع sp^2



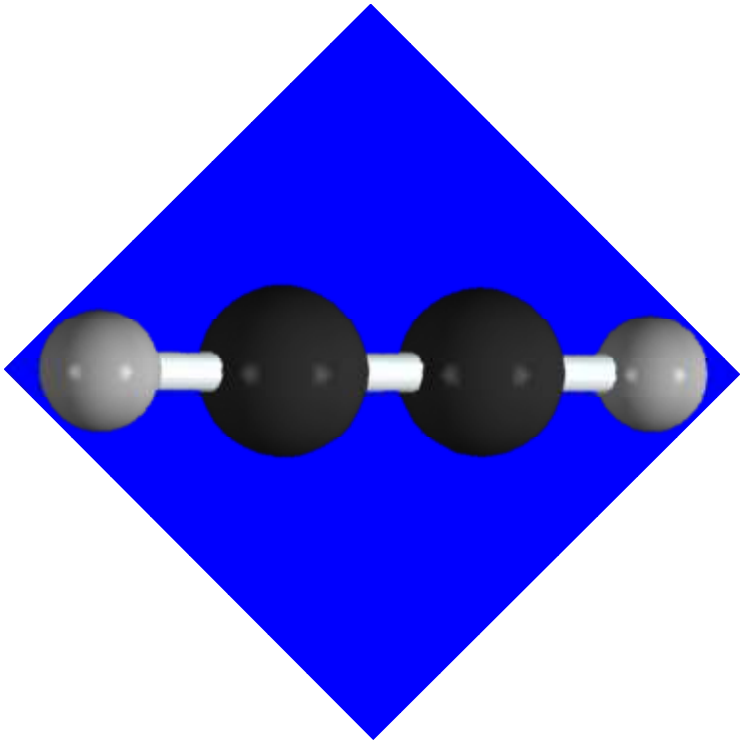
الناتج: هو ثلاث مدارات مهجنه (متكافئه) من نوع sp^2

بالأضافه الى عدد واحد مدار p لم يدخل فى التهجين (حيث انه مشترك فى تكوين عدد واحد رابطة ثنائه من نوع π)

التركيب الفراغى للأسيتيلين

C_2H_2

$HC \equiv CH$



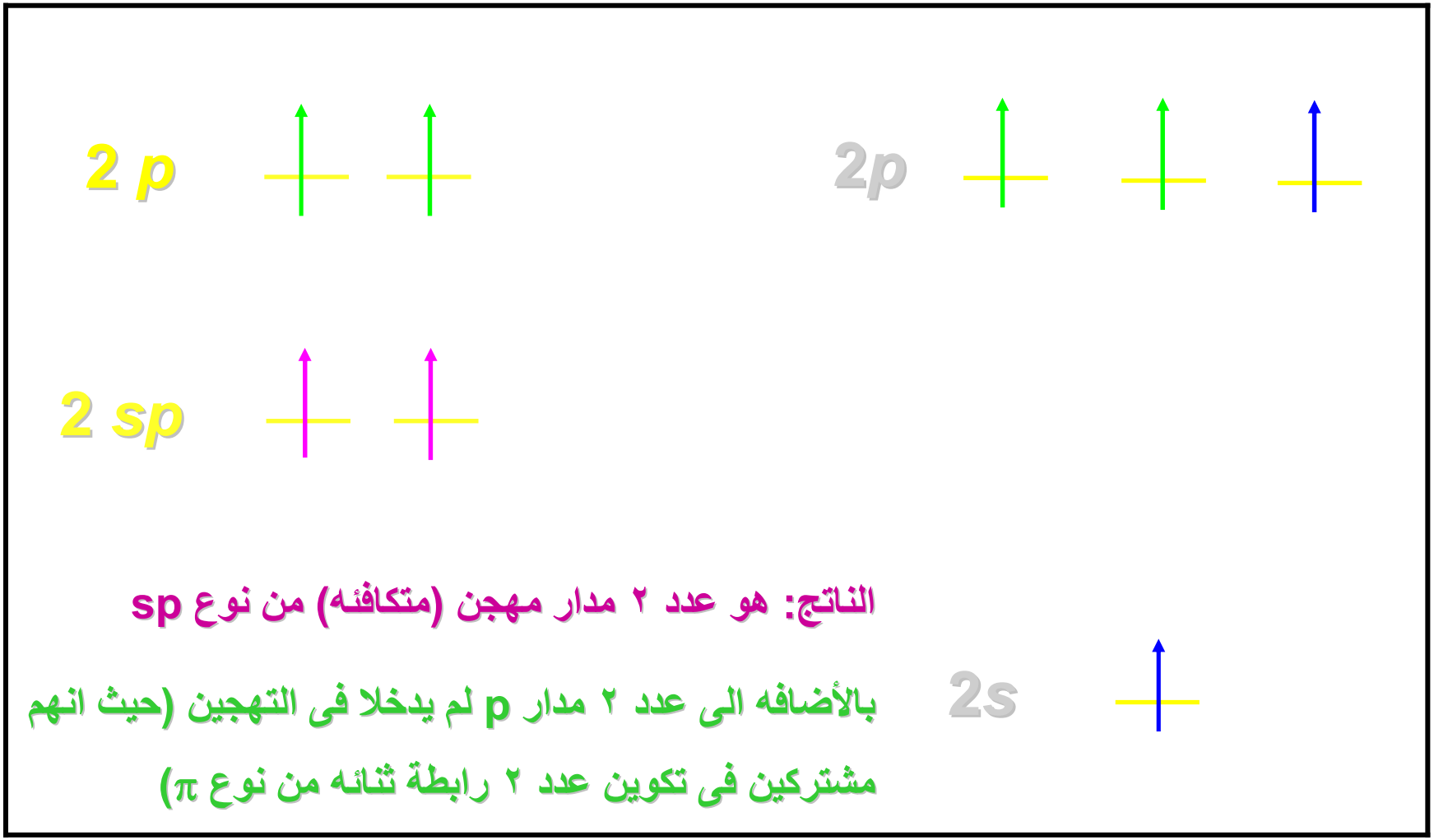
خطى الشكل

زوايا الرابطة: 180°

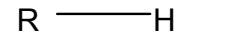
أطوال الروابط: C—H = 106 pm

C≡C = 120 pm

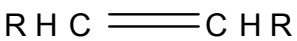
هجين من نوع sp



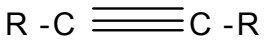
Common Functional Groups (المجموعات الفعاله)



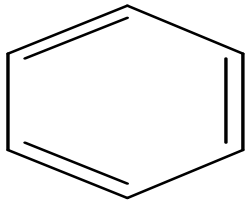
alkane



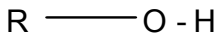
alkene



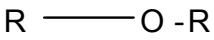
alkyne



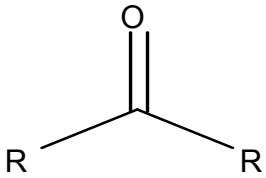
aromatic



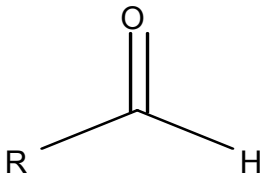
alcohol



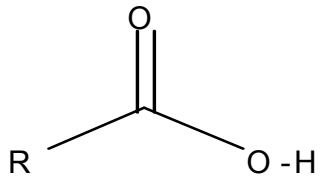
ether



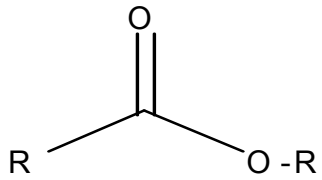
ketone



aldehyde



carboxylic acid



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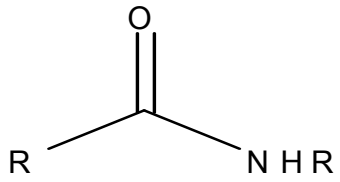
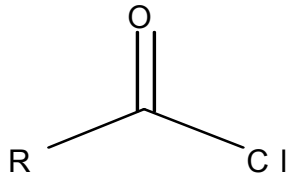
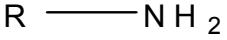


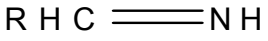
amide



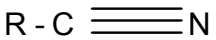
acid chloride



amine



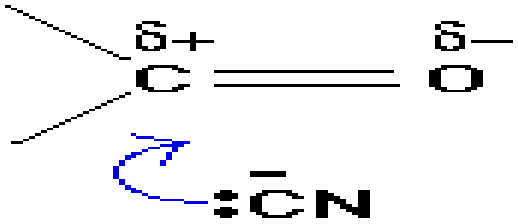
imine

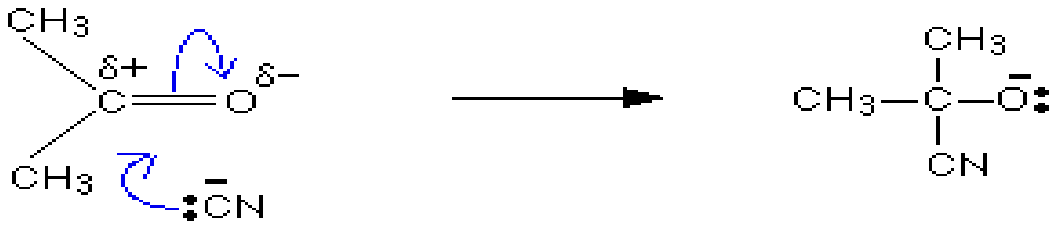


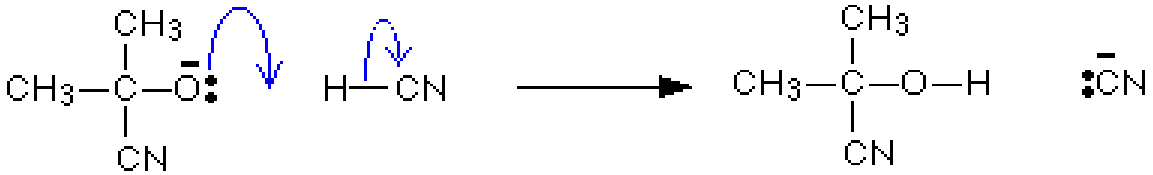
nitrile

Nucleophilic Addition Reaction

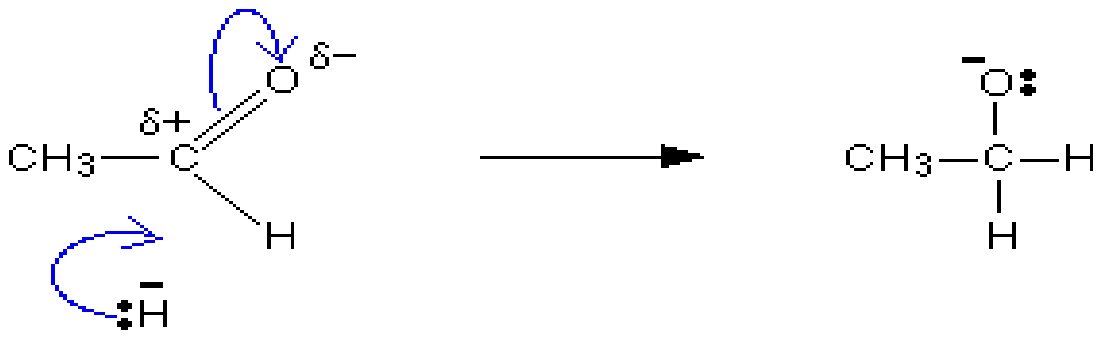
1- Addition of HCN:

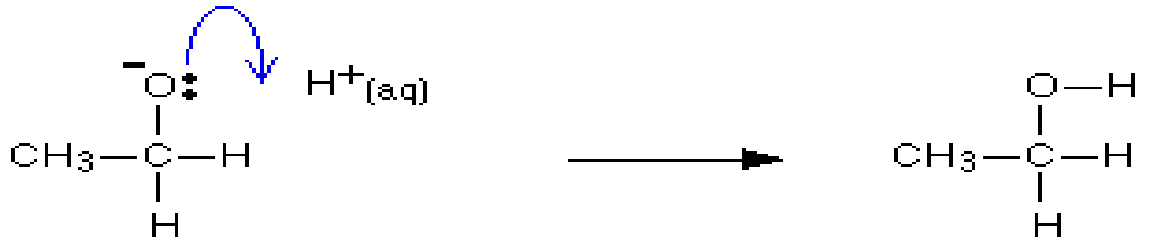




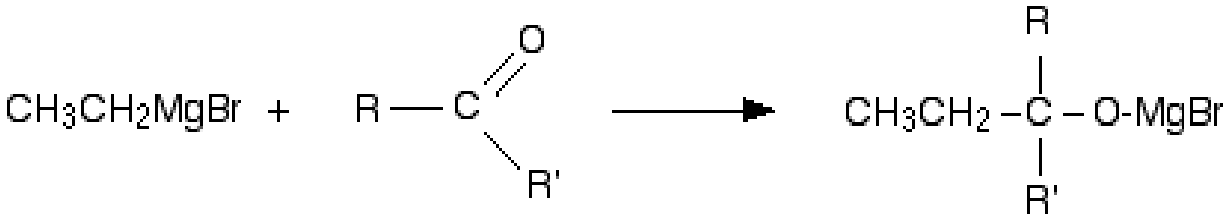


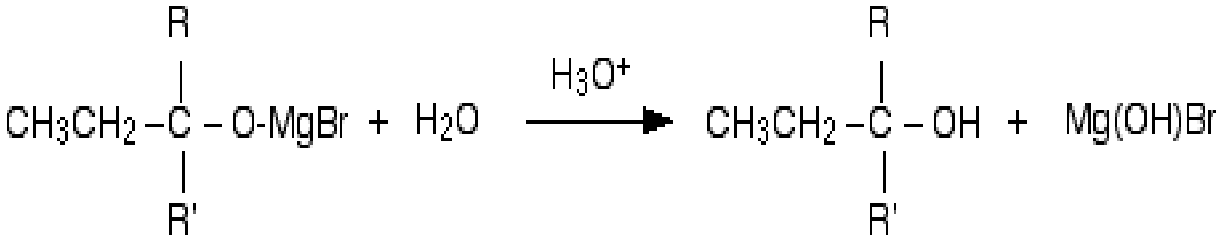
2- Reduction of aldehydes and Ketones:

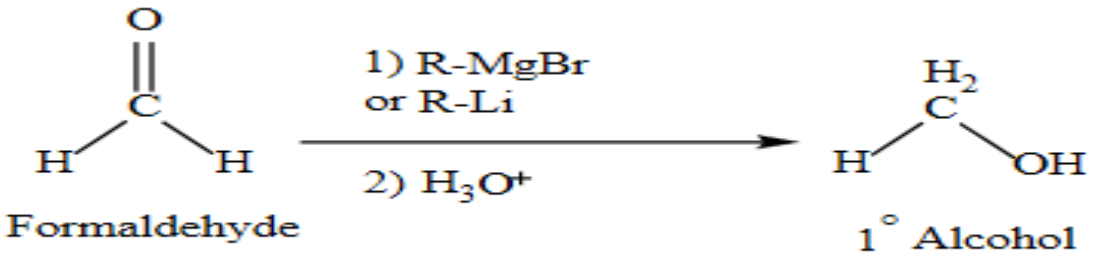


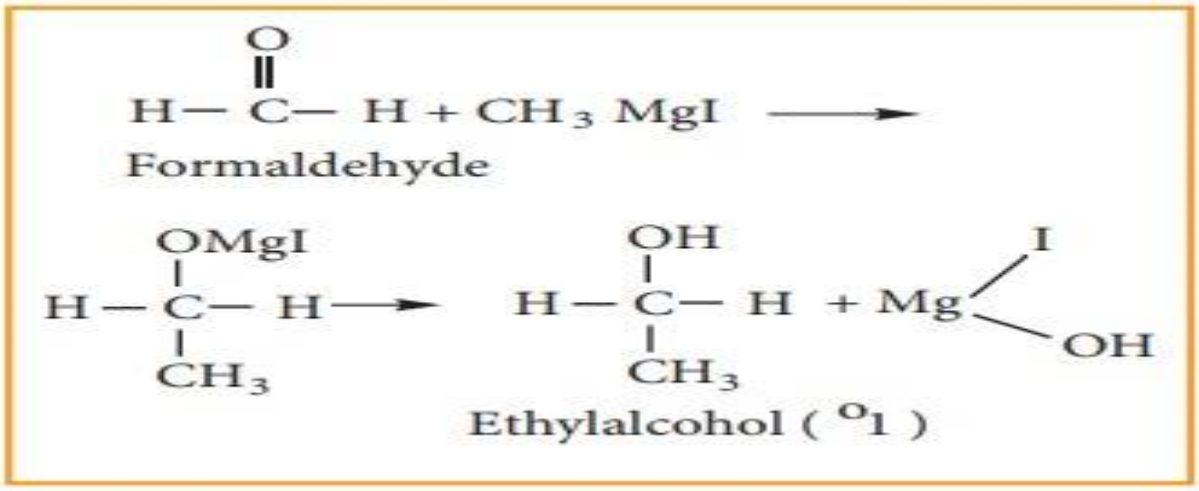


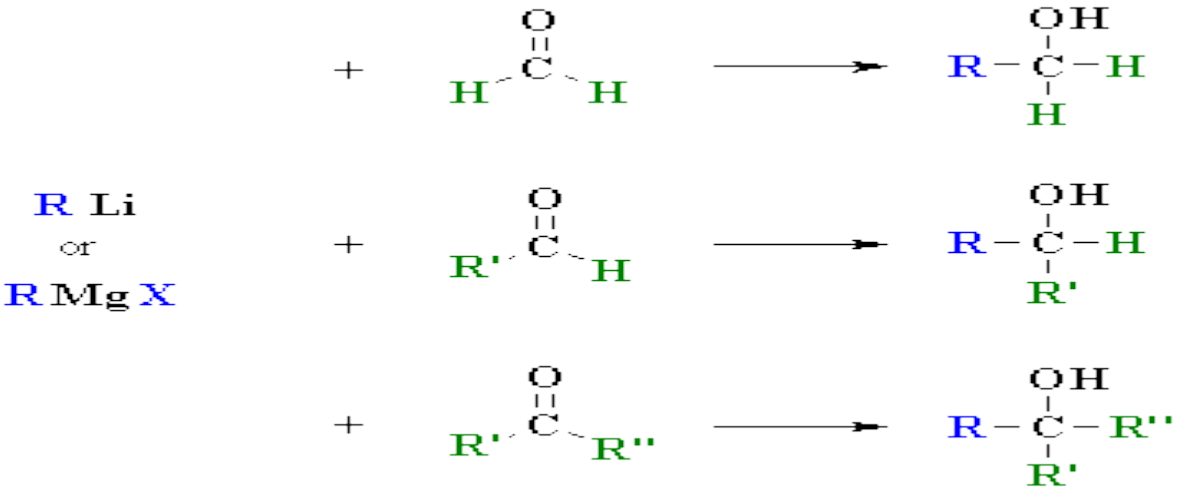
3- Addition of Grignard Reagents:

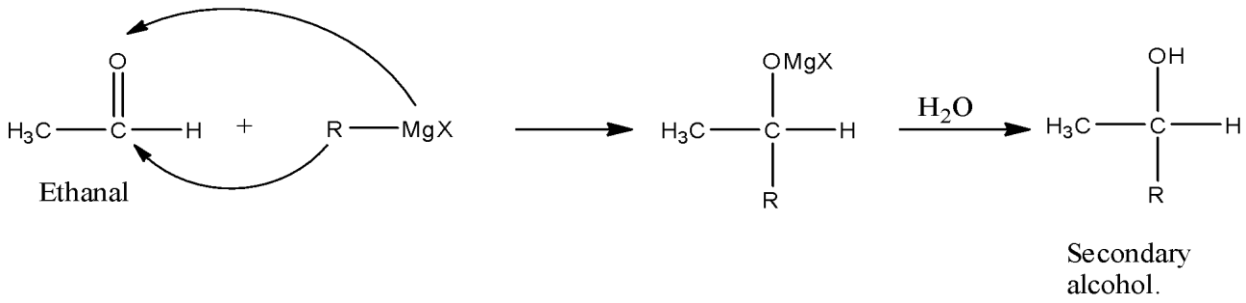




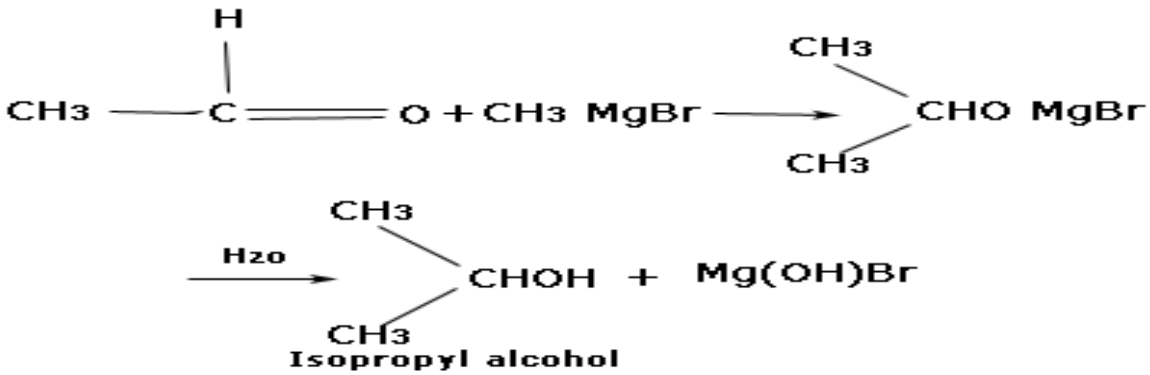


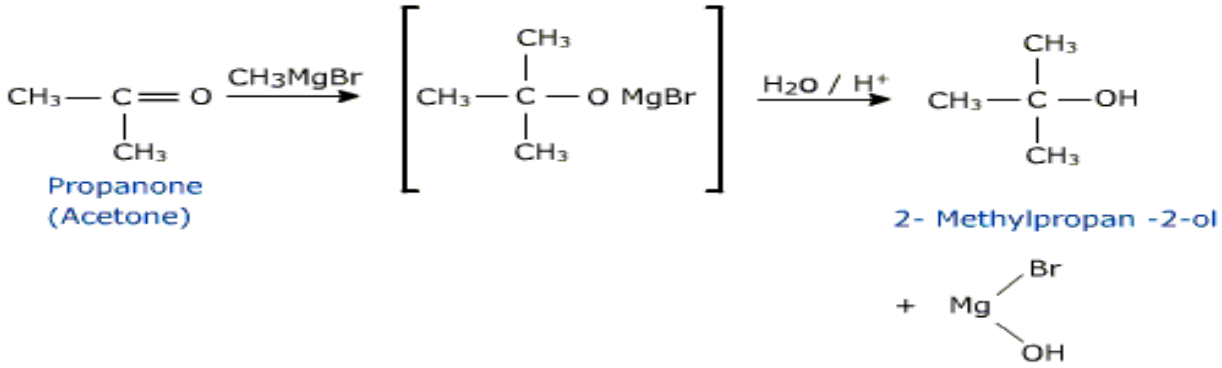




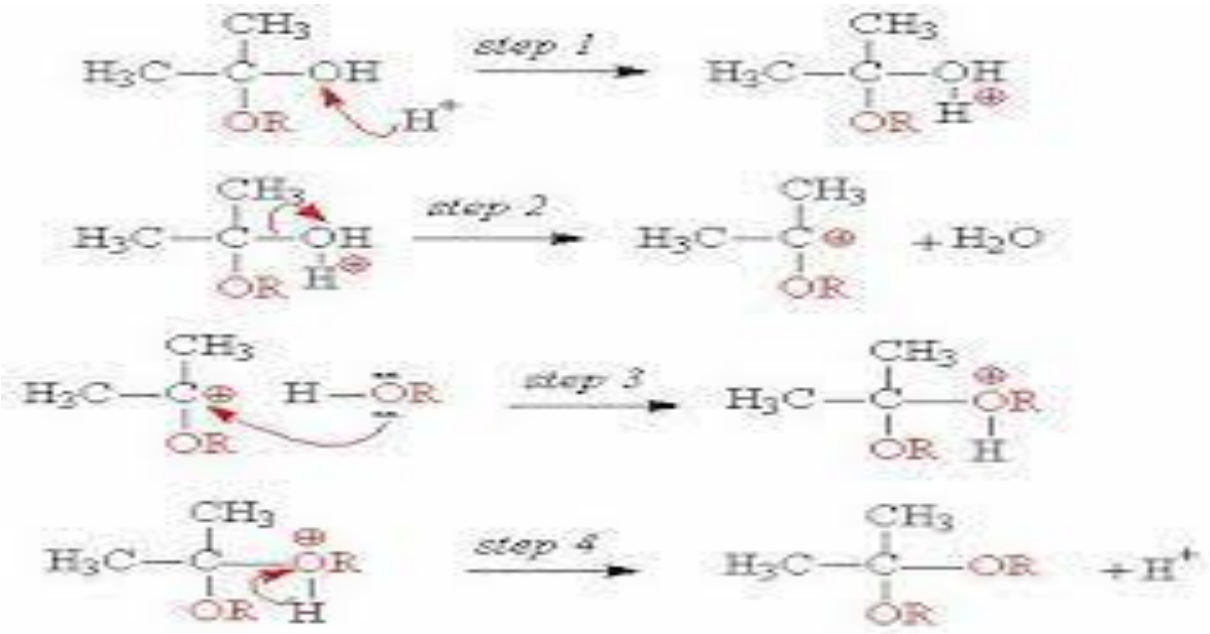


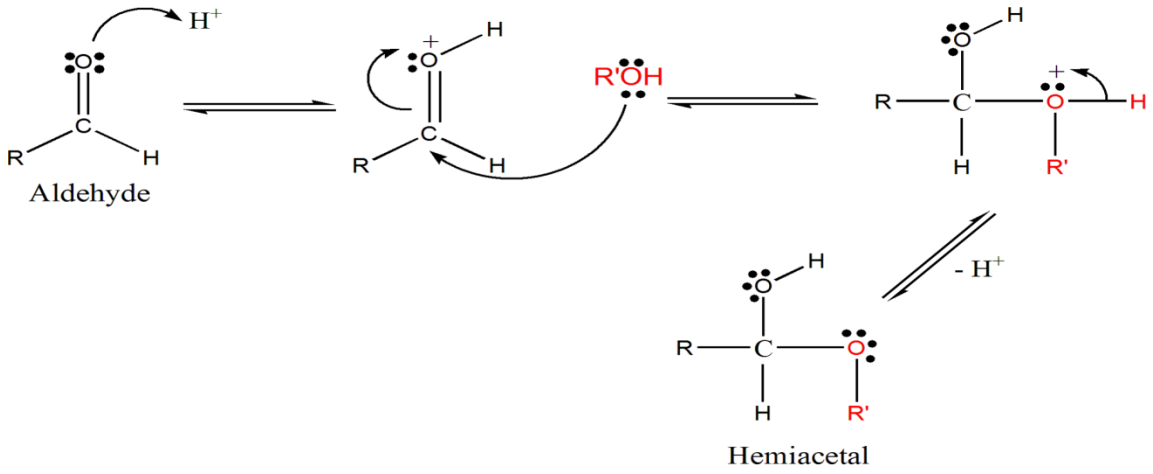
Secondary alcohol.



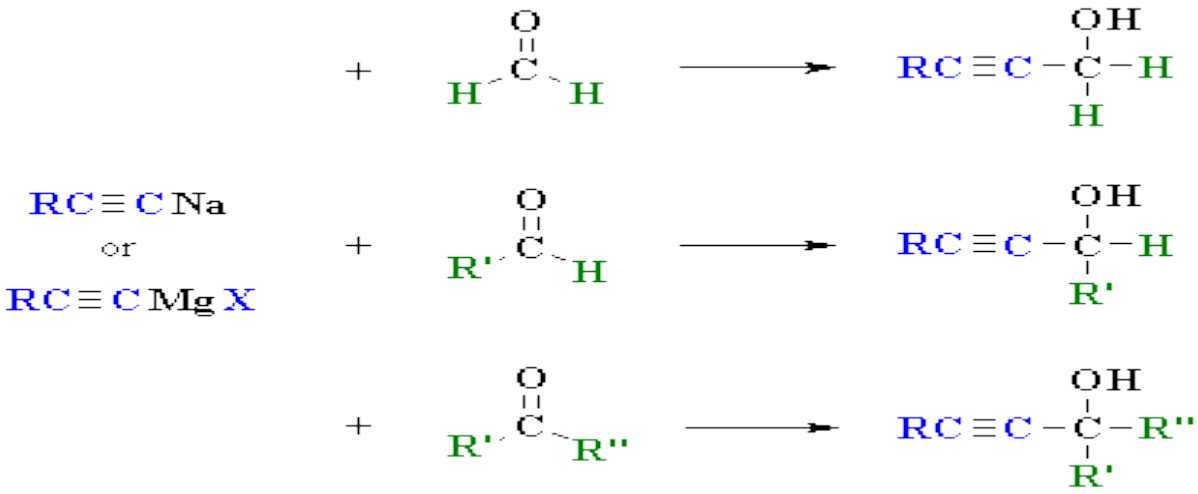


4- Addition of alcohols (formation of hemiacetal and acetal):





5- Addition of acetylene:

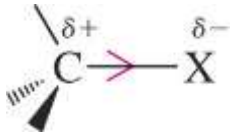


Ionic Reactions-Nucleophilic Substitution and Elimination Reactions of Alkyl Halides

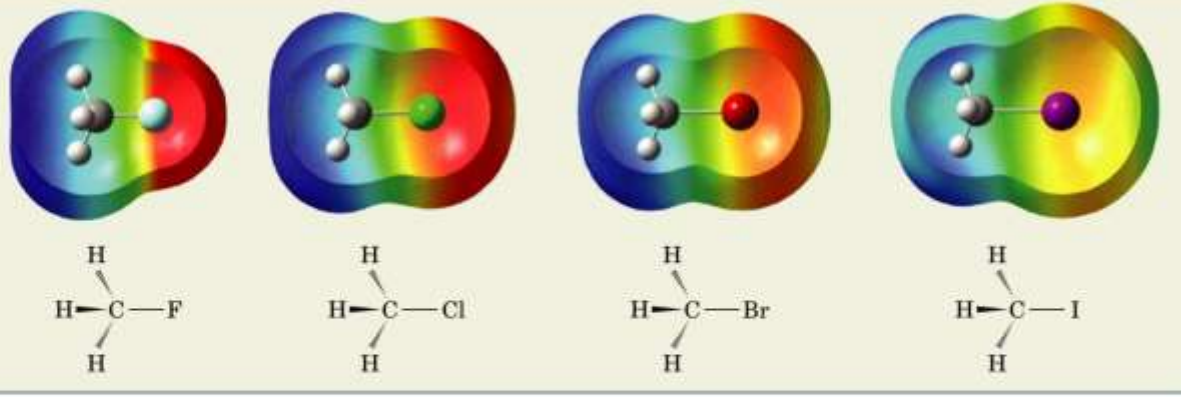
♦ Introduction

➔ **The polarity of a carbon-halogen bond leads to the carbon having a partial positive charge**

- **In alkyl halides this polarity causes the carbon to become activated to substitution reactions with nucleophiles**



➔ **Carbon-halogen bonds get less polar, longer and weaker in going from fluorine to iodine**

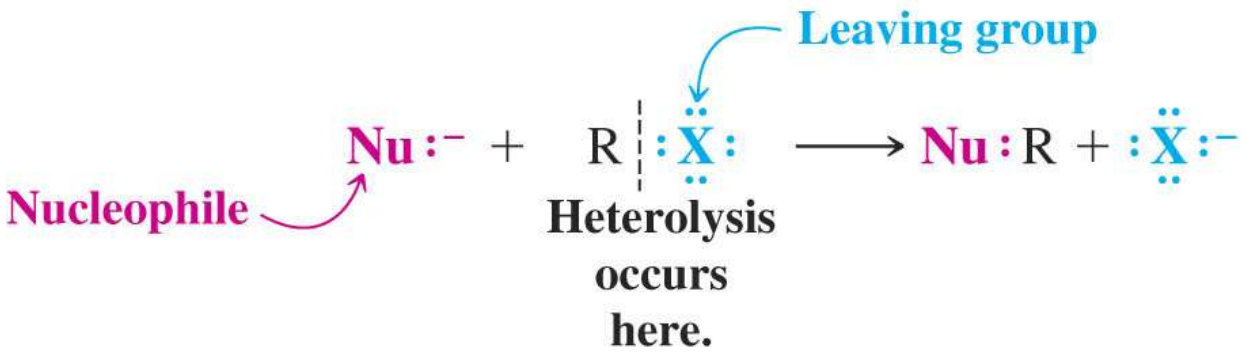


C—X Bond length (Å)	1.39	1.78	1.93	2.14
C—X Bond strength (kJ mol^{-1})	472	350	293	239

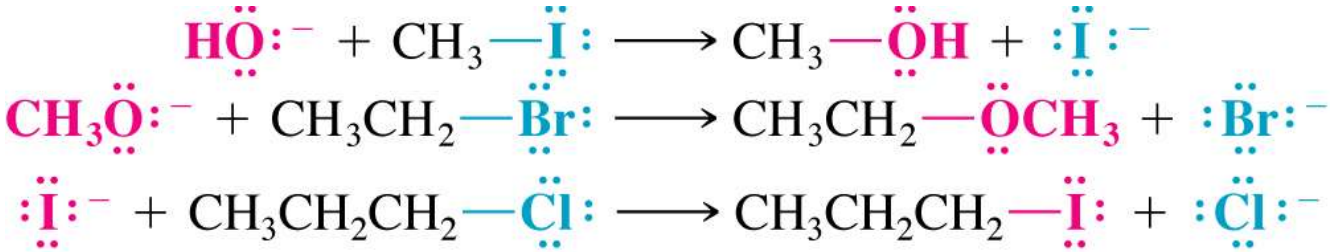
♦ Nucleophilic Substitution Reactions

➔ **In this reaction a nucleophile is a species with an unshared electron pair which reacts with an electron deficient carbon**

➔ **A leaving group is substituted by a nucleophile**

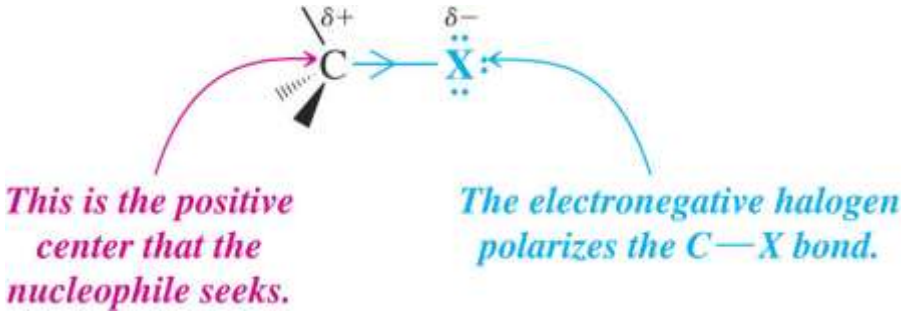


➔ **Examples of nucleophilic substitution**

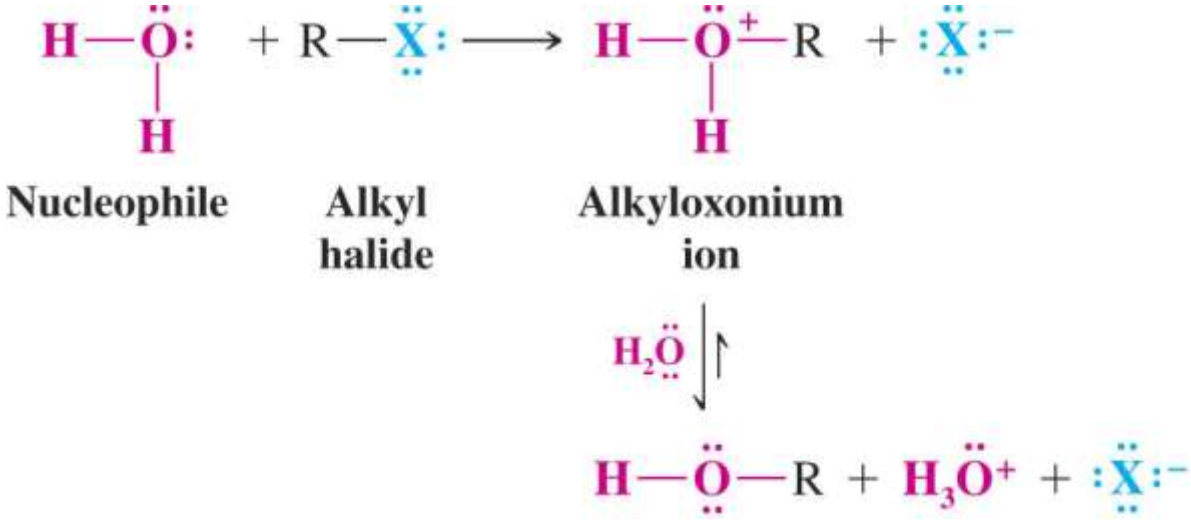


♦ Nucleophile

➔ **The nucleophile reacts at the electron deficient carbon**



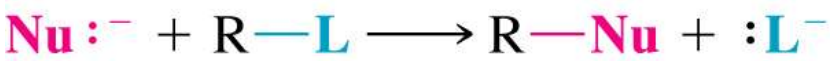
➔ **A nucleophile may be any molecule with an unshared electron pair**

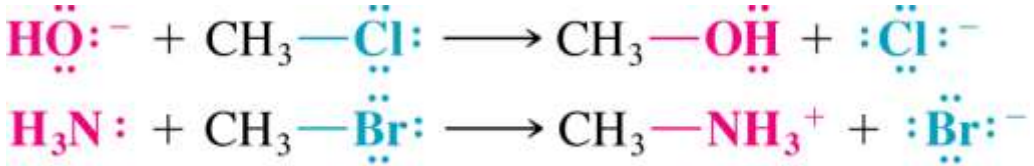


♦ Leaving Group

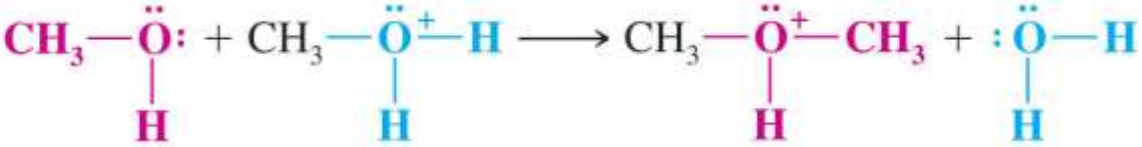
➔ **A leaving group is a substituent that can leave as a relatively stable entity**

➔ **It can leave as an anion or a neutral species**



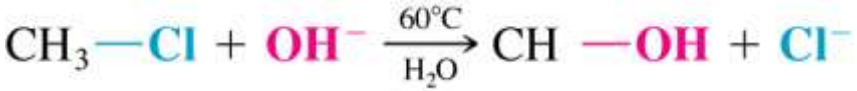


Specific Example



♦ Kinetics of a Nucleophilic Substitution Reaction: An S_N2 Reaction

➔ **The initial rate of the following reaction is measured**



➔ **The rate is directly proportional to the initial concentrations of both methyl chloride and hydroxide**

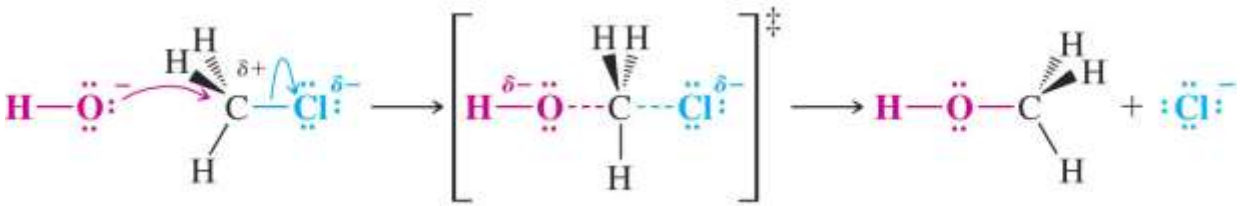
Experiment Number	Initial $[CH_3Cl]$	Initial $[OH^-]$	Initial Rate (mol L^{-1} s^{-1})
1	0.0010	1.0	4.9×10^{-7}
2	0.0020	1.0	9.8×10^{-7}
3	0.0010	2.0	9.8×10^{-7}
4	0.0020	2.0	19.6×10^{-7}

➔ **The rate equation reflects this dependence**

$$\text{Rate} = k[CH_3Cl][OH^-]$$

➔ **S_N2 reaction: substitution, nucleophilic, 2nd order (bimolecular)**

♦ A Mechanism for the S_N2 Reaction



Transition state

The negative hydroxide ion brings a pair of electrons to the partially positive carbon from the back side with respect to the leaving group. The chlorine begins to move away with the pair of electrons that bonded it to the carbon.

In the transition state, a bond between oxygen and carbon is partially formed and the bond between carbon and chlorine is partially broken. The configuration of the carbon atom begins to invert.

Now the bond between the oxygen and carbon has formed and the chloride ion has departed. The configuration of the carbon has inverted.

➔ **A *transition state* is the high energy state of the reaction**

- **It is an unstable entity with a very brief existence (10^{-12} s)**

➔ **In the transition state of this reaction bonds are partially formed and broken**

- **Both chloromethane and hydroxide are involved in the transition state and this explains why the reaction is second order**

♦ Transition State Theory: Free-Energy Diagrams

➔ **Exergonic reaction: negative ΔG^o (products favored)**

➔ **Endergonic reaction: positive ΔG^o (products not favored)**

➔ **The reaction of chloromethane with hydroxide is highly exergonic**

$$CH_3{-}Cl + OH^- \longrightarrow CH_3{-}OH + Cl^- \qquad \Delta G^\circ = -100 \text{ kJ mol}^{-1}$$

➔ **The equilibrium constant is very large**

$$\Delta G^\circ = -RT \ln K_{eq}$$

$$\ln K_{eq} = \frac{-\Delta G^\circ}{RT}$$

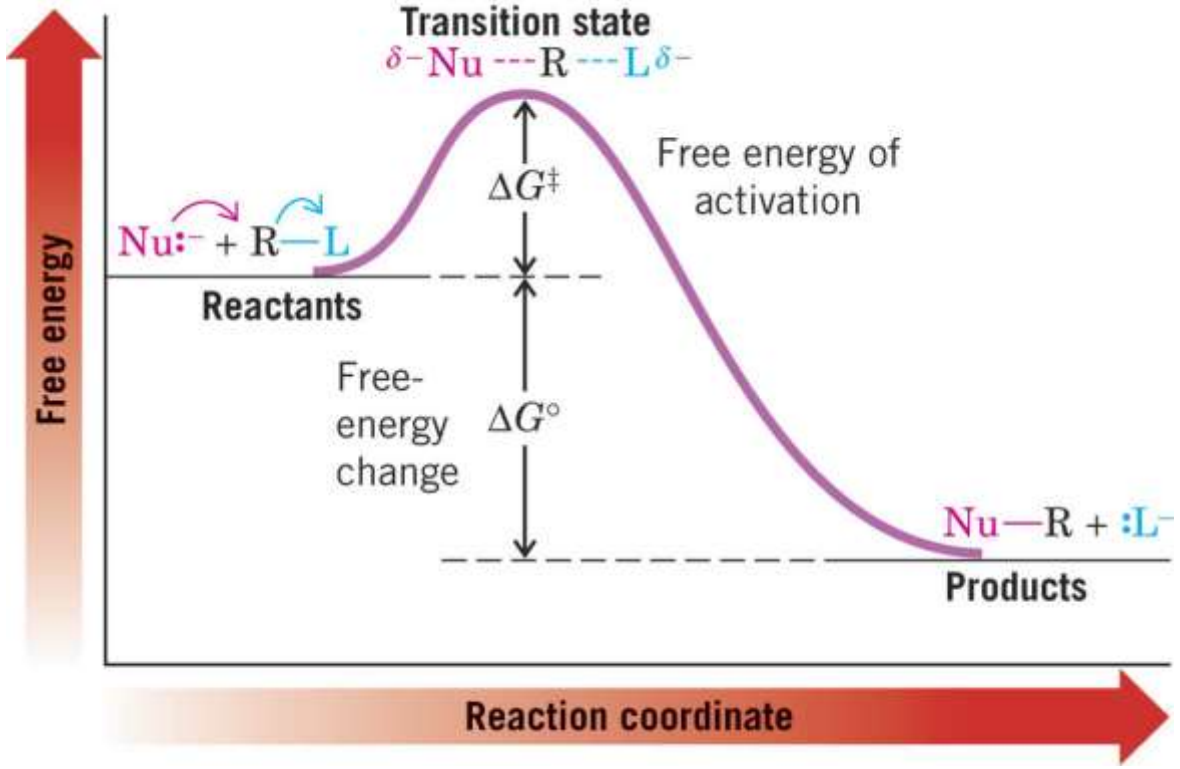
$$\ln K_{eq} = \frac{-(-100 \text{ kJ mol}^{-1})}{0.00831 \text{ kJ K}^{-1} \text{ mol}^{-1} \times 333 \text{ K}}$$

$$\ln K_{eq} = 36.1$$

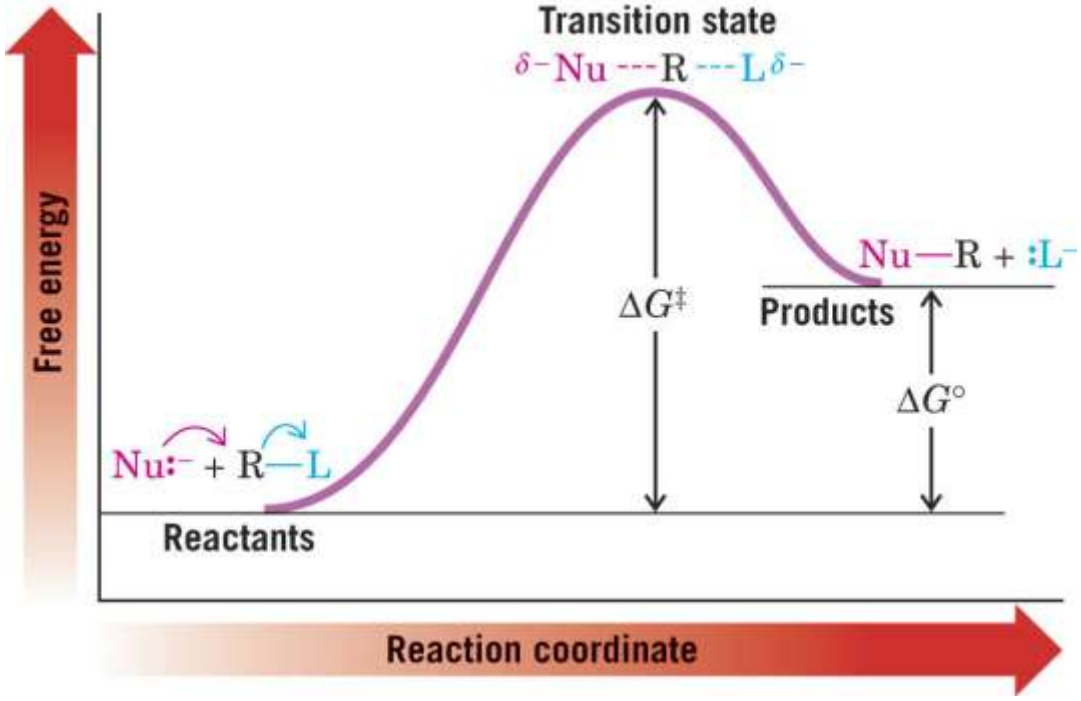
$$K_{eq} = 5.0 \times 10^{15}$$

➔ An energy diagram of a typical S_N2 reaction

- An energy barrier is evident because a bond is being broken in going to the transition state (which is the top of the energy barrier)
- The difference in energy between starting material and the transition state is the free energy of activation ($\Delta G^{\ddagger}$)
- The difference in energy between starting molecules and products is the free energy change of the reaction, ΔG^{o}



➔ **In a highly endergonic reaction of the same type the energy barrier will be even higher ($\Delta G^{\ddagger}$ is very large)**



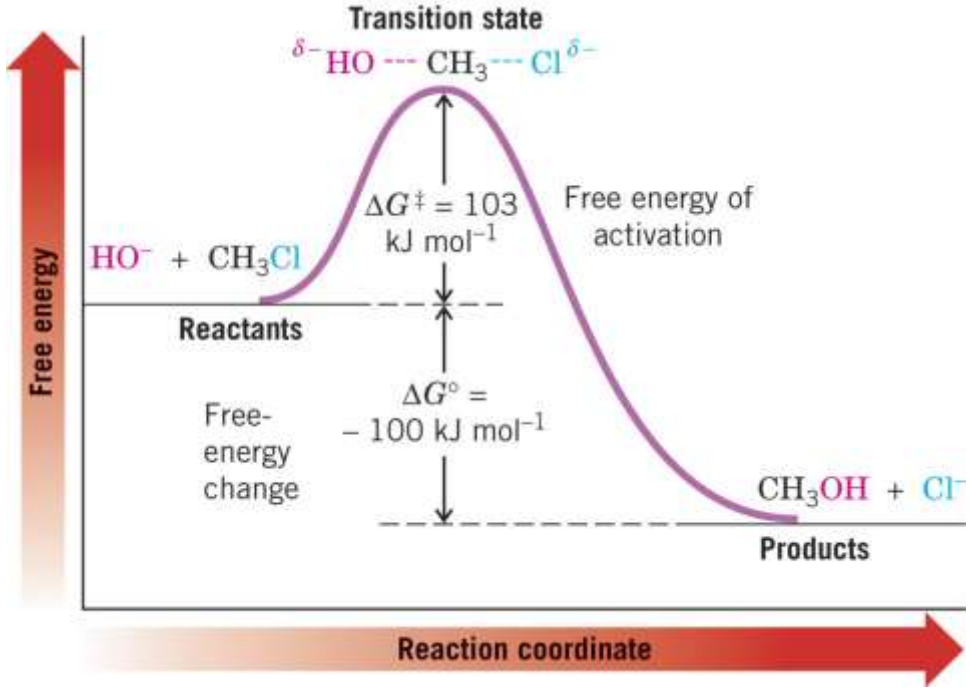
➔ **There is a direct relationship between $\Delta G^{\ddagger}$ and the temperature of a reaction**

- **The higher the temperature, the faster the rate**

$$k = k_0 e^{-\Delta G^{\ddagger}/RT}$$

- **Near room temperature, a 10°C increase in temperature causes a doubling of rate**
- **Higher temperatures cause more molecules to collide with enough energy to reach the transition state and react**

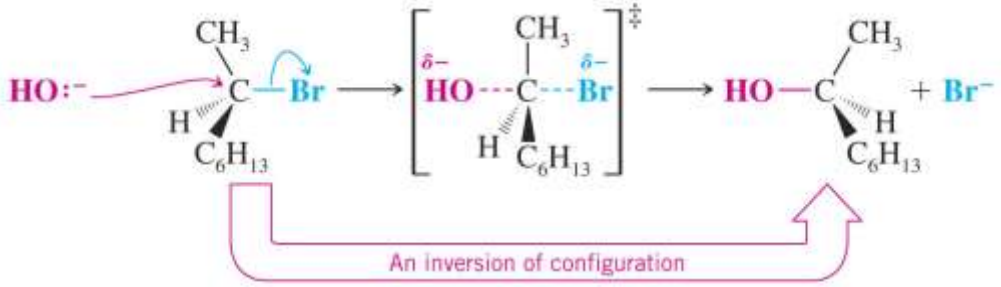
➔ **The energy diagram for the reaction of chloromethane with hydroxide:**



- **A reaction with $\Delta G^{\ddagger}$ above 84 kJ mol^{-1} will require heating to proceed at a reasonable rate**
- **This reaction has $\Delta G^{\ddagger}$ = 103 kJ mol^{-1} so it will require heating**

♦ The Stereochemistry of S_N2 Reactions

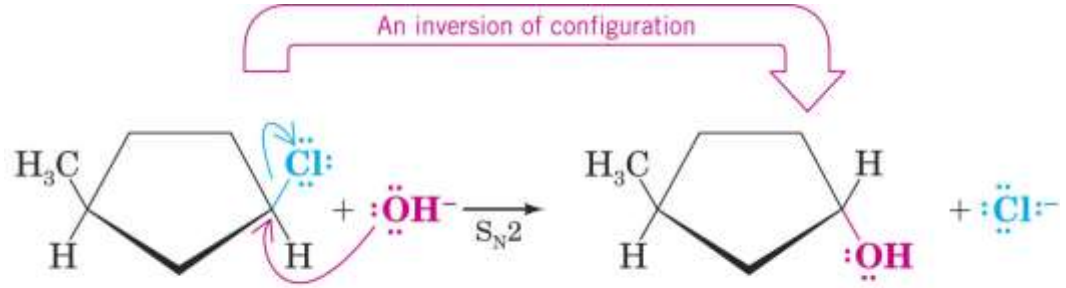
➔ **Backside attack of nucleophile results in an inversion of configuration**



(*R*)-(−)-2-Bromooctane
$[\alpha]_D^{25} = -34.25°$
Enantiomeric purity = 100%

(*S*)-(+)-2-Octanol
$[\alpha]_D^{25} = +9.90°$
Enantiomeric purity = 100%

➔ **In cyclic systems a cis compound can react and become trans product**



cis-1-Chloro-3-methylcyclopentane

trans-3-Methylcyclopentanol

♦ The Reaction of *tert*-Butyl Chloride with Hydroxide Ion: An S_N1 Reaction

➔ ***tert*-Butyl chloride undergoes substitution with hydroxide**

➔ **The rate is independent of hydroxide concentration and depends only on concentration of *tert*-butyl chloride**

$$(CH_3)_3C{-}Cl + OH^- \xrightarrow[H_2O]{\text{acetone}} (CH_3)_3C{-}OH + Cl^-$$

$$\text{Rate} \propto [(CH_3)_3CCl]$$

$$\text{Rate} = k[(CH_3)_3CCl]$$

➔ **S_N1 reaction: Substitution, nucleophilic, 1st order (unimolecular)**

- **The rate depends only on the concentration of the alkyl halide**
- **Only the alkyl halide (and not the nucleophile) is involved in the transition state of the step that controls the rate**

♦ Multistep Reactions and the Rate-Determining Step

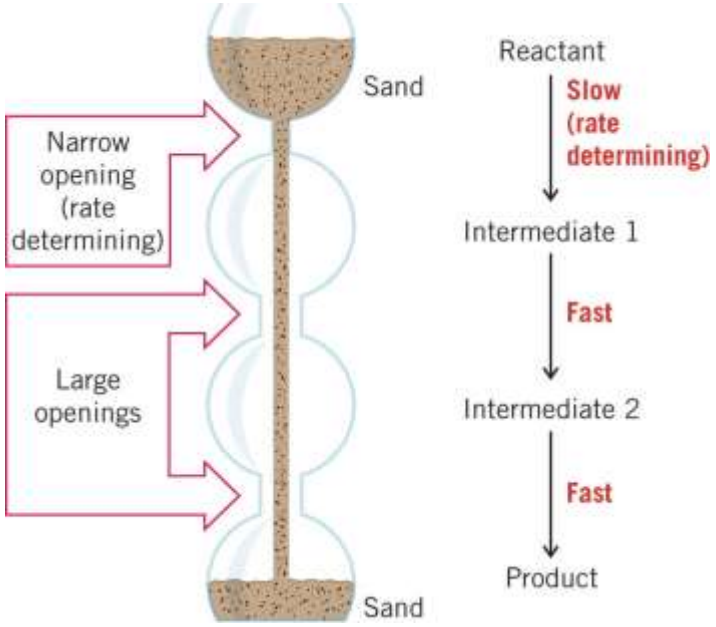
➔ In multistep reactions, the rate of the slowest step will be the rate of the entire reaction

➔ This is called the rate determining step

➔ In the case below $k_1 << k_2$ or k_3 and the first step is rate determining

$$\text{Reactant} \xrightarrow[\text{(slow)}]{k_1} \text{intermediate 1} \xrightarrow[\text{(fast)}]{k_2} \text{intermediate 2} \xrightarrow[\text{(fast)}]{k_3} \text{product}$$

Step 1 *Step 2* *Step 3*



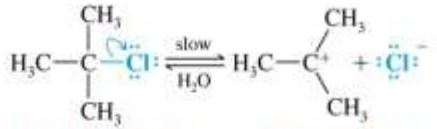
- **A Mechanism for the S_N1 Reaction (next slide)**
  - ➔ **Step 1 is rate determining (slow) because it requires the formation of unstable ionic products**
  - ➔ **In step 1 water molecules help stabilize the ionic products**

Reaction:

$$(CH_3)_3CCl + 2\,H_2O \longrightarrow (CH_3)_3COH + H_3O^+ + Cl^-$$

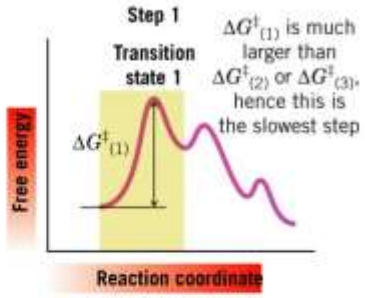
Mechanism:

Step 1

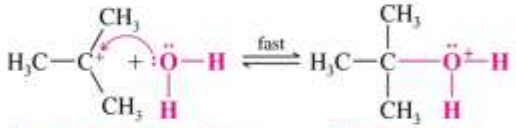


Aided by the polar solvent a chlorine departs with the electron pair that bonded it to the carbon.

This slow step produces the relatively stable 3° carbocation and a chloride ion. Although not shown here, the ions are solvated (and stabilized) by water molecules.

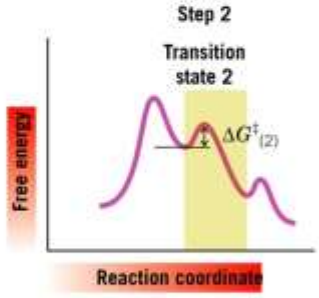


Step 2

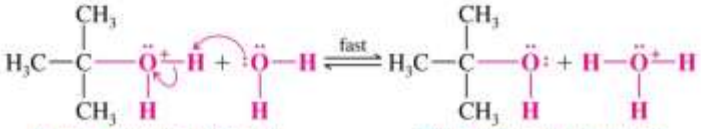


A water molecule acting as a Lewis base donates an electron pair to the carbocation (a Lewis acid). This gives the cationic carbon eight electrons.

The product is a *tert*-butyloxonium ion (or protonated *tert*-butyl alcohol).

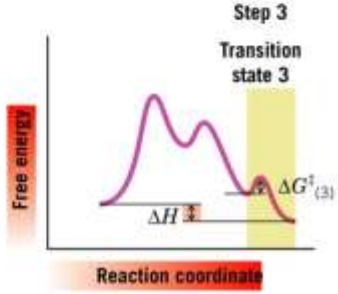


Step 3



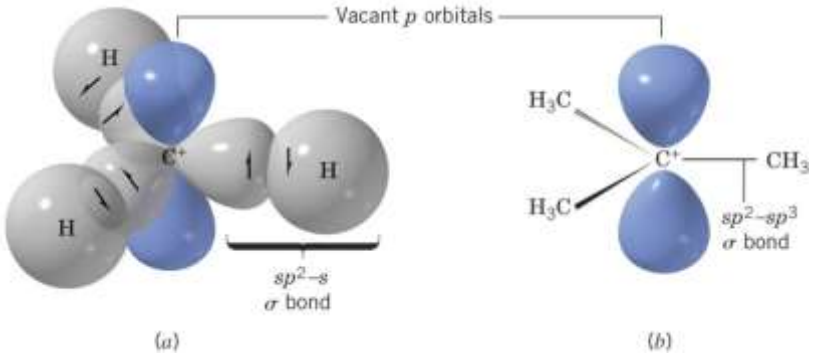
A water molecule acting as a Brønsted base accepts a proton from the *tert*-butyloxonium ion.

The products are *tert*-butyl alcohol and a hydronium ion.



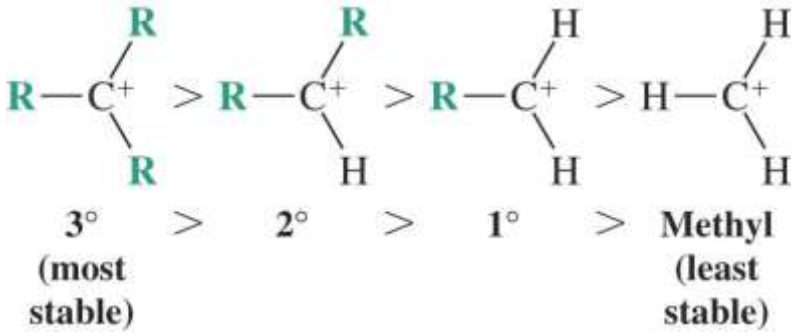
♦ Carbocations

➔ **A carbocation has only 6 electrons, is *sp*^{2} hybridized and has an empty *p* orbital**



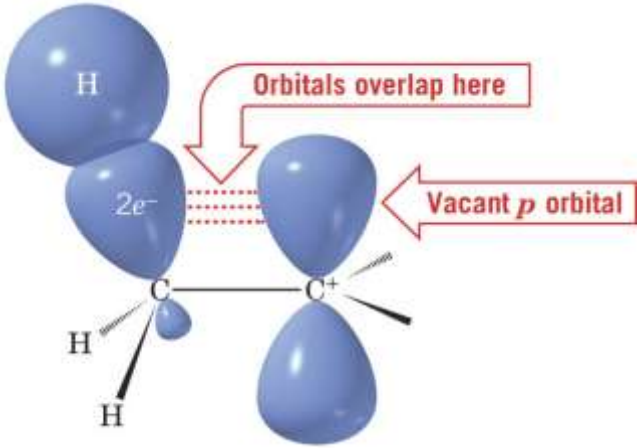
➔ **The more highly substituted a carbocation is, the more stable it is**

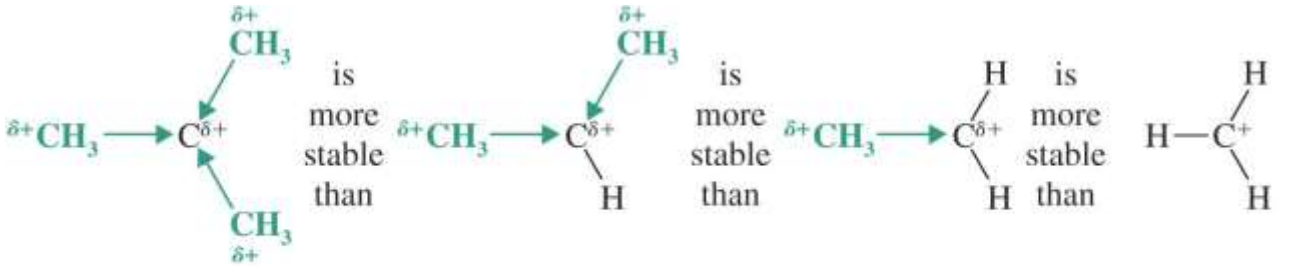
- **The more stable a carbocation is, the easier it is to form**



➔ **Hyperconjugation stabilizes the carbocation by donation of electrons from an adjacent carbon-hydrogen or carbon-carbon σ bond into the empty *p* orbital**

- **More substitution provides more opportunity for hyperconjugation**





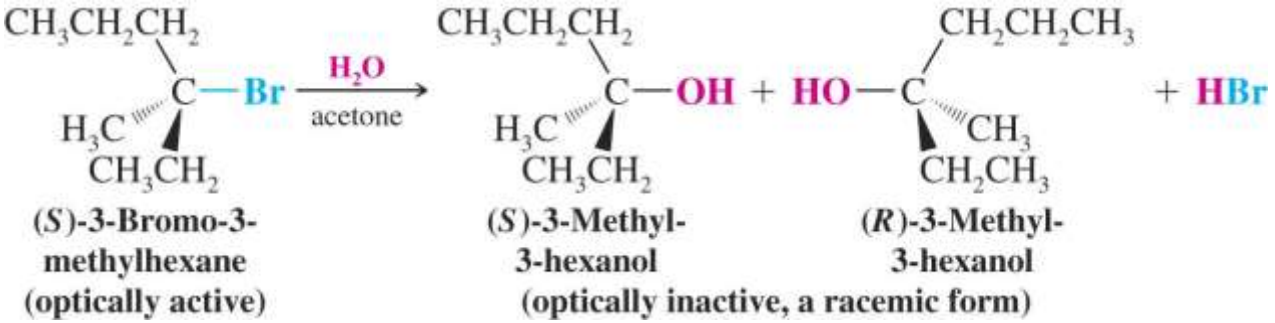
***tert*-Butyl cation (3°) (most stable)** | **Isopropyl cation (2°)** | **Ethyl cation (1°)** | **Methyl cation (least stable)**

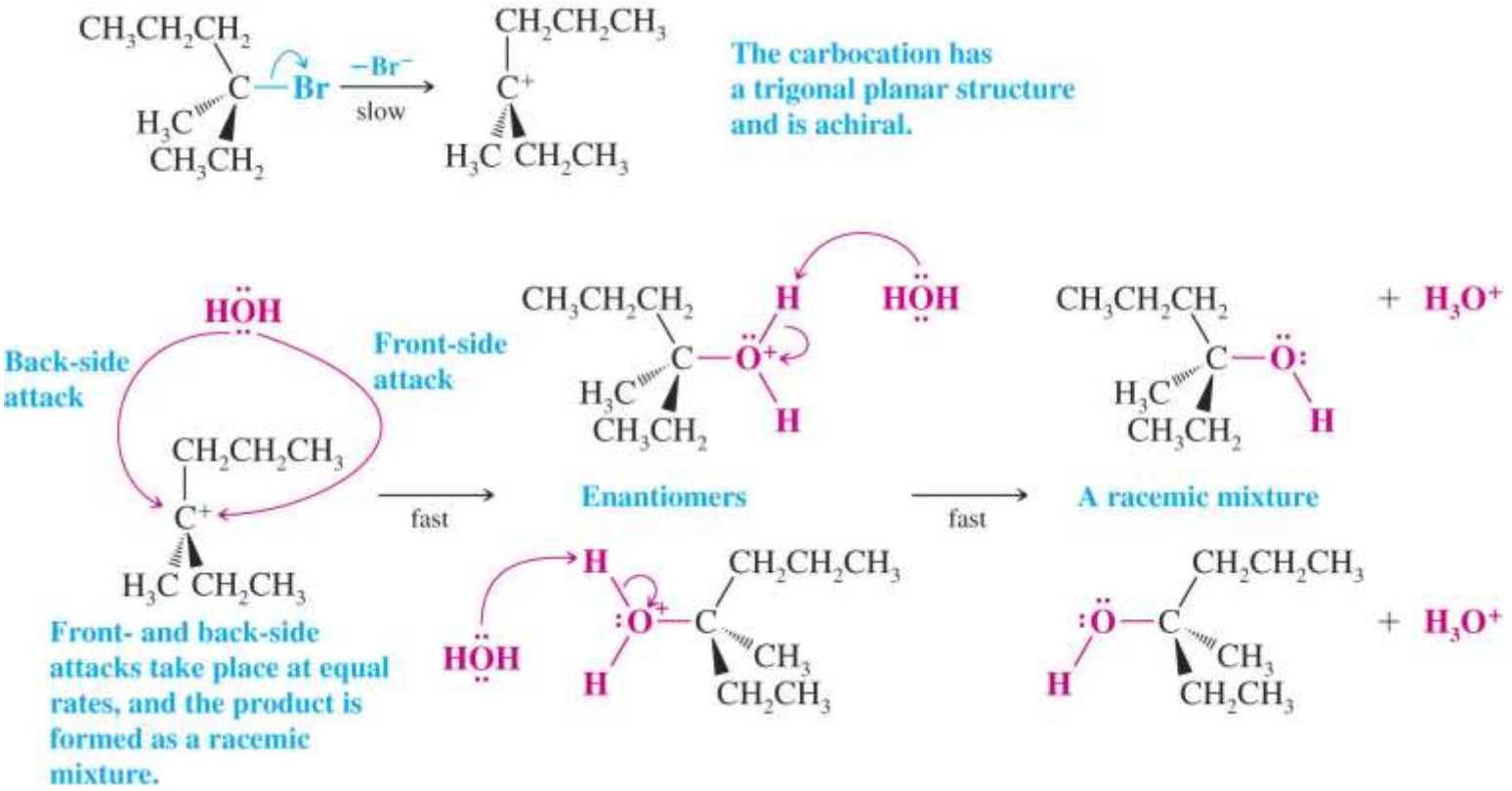
♦ The Stereochemistry of S_N1 Reactions

➔ **When the leaving group leaves from a stereogenic center of an optically active compound in an S_N1 reaction, racemization will occur**

- **This is because an achiral carbocation intermediate is formed**

➔ **Racemization: transformation of an optically active compound to a racemic mixture**

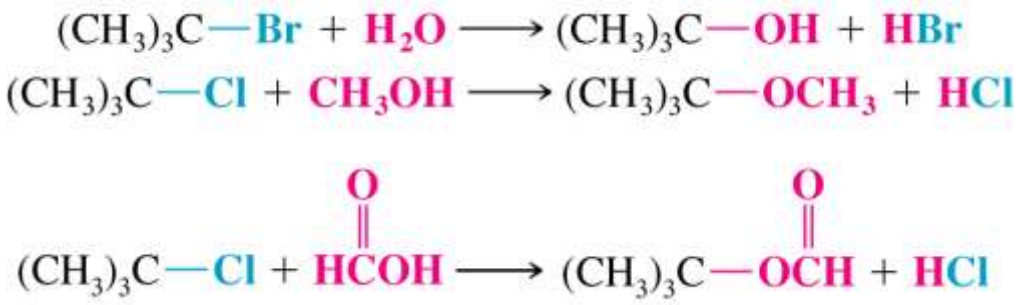



The carbocation has a trigonal planar structure and is achiral.
Back-side attack
Front-side attack
Front- and back-side attacks take place at equal rates, and the product is formed as a racemic mixture.
fast
Enantiomers
fast
A racemic mixture

♦ Solvolysis

➔ **A molecule of the solvent is the nucleophile in a substitution reaction**

- **If the solvent is water the reaction is a hydrolysis**



♦ Factors Affecting the Rate of S_N1 and S_N2 Reactions

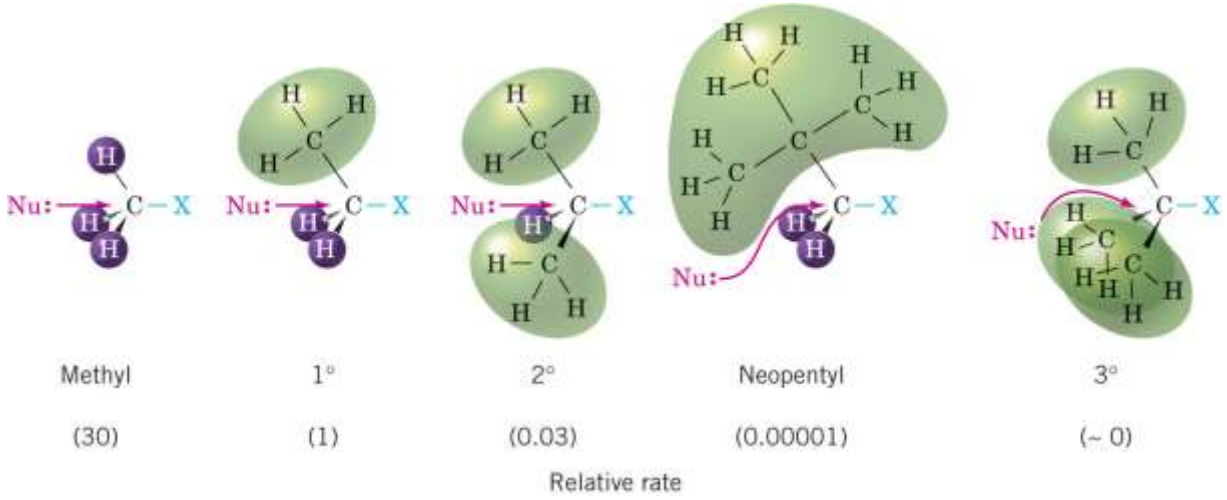
- **The Effects of the Structure of the Substrate**
- ***S_N2 Reactions***

➔ **In S_N2 reactions alkyl halides show the following general order of reactivity**

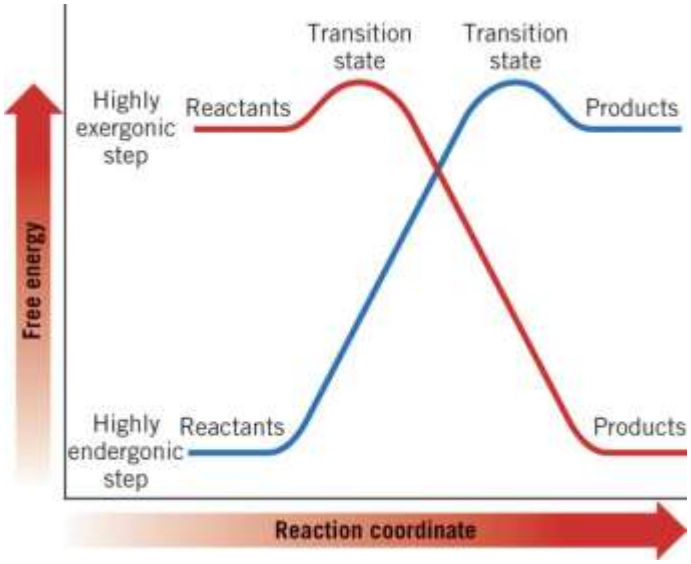
Methyl > primary > secondary ≫ (tertiary — unreactive)

➔ **Steric hinderance: the spatial arrangement of the atoms or groups at or near a reacting site hinders or retards a reaction**

- **In tertiary and neopentyl halides, the reacting carbon is too sterically hindered to react**

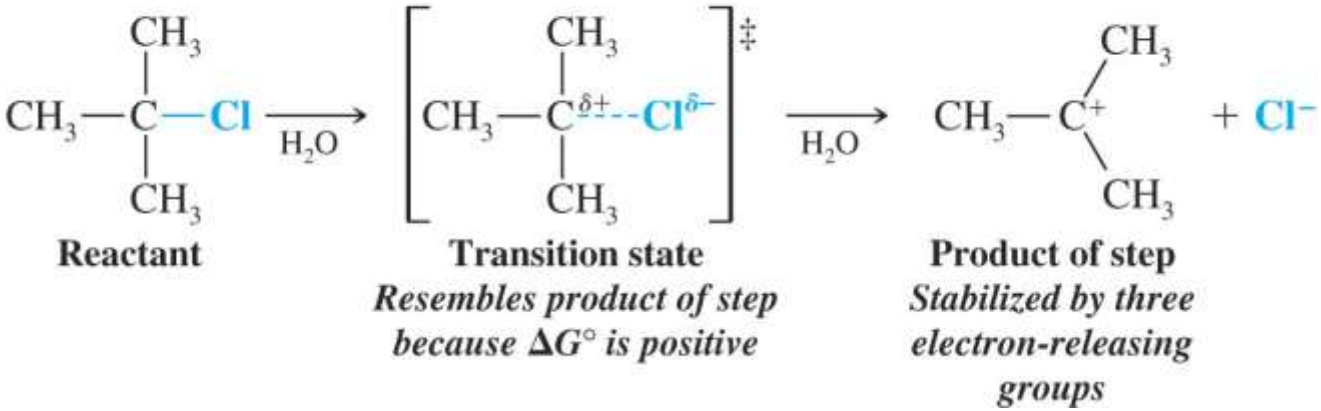


- ***S_N1 reactions***
  - ➔**Generally only tertiary halides undergo S_N1 reactions because only they can form relatively stabilized carbocations**
- ***The Hammond-Leffler Postulate***
  - ➔**The transition state for an exergonic reaction looks very much like starting material**
  - ➔**The transition state for an endergonic reaction looks very much like product**
  - ➔**Generally the transition state looks most like the species it is closest to in energy**



- ➔ **In the first step of the S_N1 reaction the transition state looks very much like carbocation**
- ➔ **The carbocation-like transition state is stabilized by all the factors that stabilize carbocations**
- ➔ **The transition state leading to tertiary carbocations is much more stable and lower in energy than transition states leading to other carbocations**

Ionization of the Leaving Group



Reactant

Transition state
Resembles product of step because ΔG° is positive

Product of step
Stabilized by three electron-releasing groups

- **The Effects of the Concentration and Strength of Nucleophile**
- ***S_N1 Reaction***
  - ➔**Rate does not depend on the identity or concentration of nucleophile**
- ***S_N2 Reaction***
  - ➔**Rate is directly proportional to the concentration of nucleophile**
  - ➔**Stronger nucleophiles also react faster**
    - **A negatively charged nucleophile is always more reactive than its neutral conjugate acid**
    - **When comparing nucleophiles with the same nucleophilic atom, nucleophilicities parallel basicities**

$$RO^- > HO^- \gg RCO_2^- > ROH > H_2O$$

  - ➔**Methoxide is a much better nucleophile than methanol**

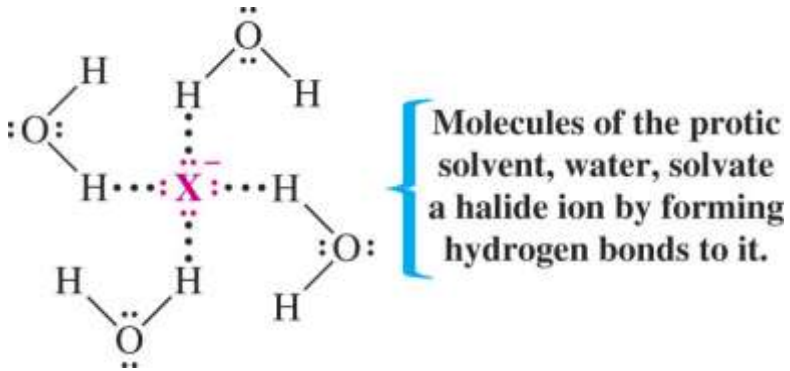
$$CH_3O^- + CH_3I \xrightarrow{\text{rapid}} CH_3OCH_3 + I^-$$

$$CH_3OH + CH_3I \xrightarrow{\text{very slow}} CH_3\overset{+}{O}(H)CH_3 + I^-$$

- **Solvent Effects on S_N2 Reactions: Polar Protic and Aprotic Solvents**

  ➔Polar Protic Solvents

  - **Polar solvents have a hydrogen atom attached to strongly electronegative atoms**
  - **They solvate nucleophiles and make them less reactive**



  - **Larger nucleophilic atoms are less solvated and therefore more reactive in polar protic solvents**

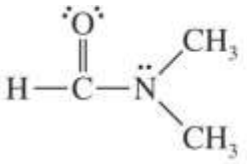
$$I^- > Br^- > Cl^- > F^-$$

  - **Larger nucleophiles are also more polarizable and can donate more electron density**
  - **Relative nucleophilicity in polar solvents:**

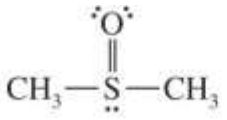
$$SH^- > CN^- > I^- > OH^- > N_3^- > Br^- > CH_3CO_2^- > Cl^- > F^- > H_2O$$

➔Polar Aprotic Solvents

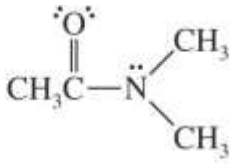
- **Polar aprotic solvents do not have a hydrogen attached to an electronegative atom**



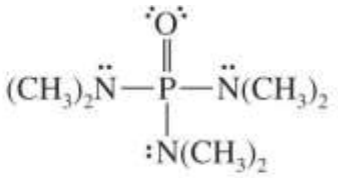
***N*,*N*-Dimethylformamide (DMF)**



Dimethyl sulfoxide (DMSO)

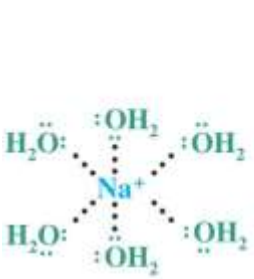


Dimethylacetamide (DMA)

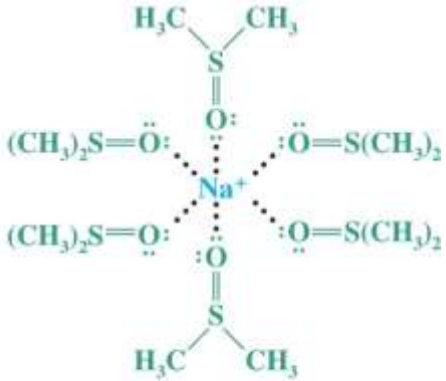


Hexamethylphosphoramide (HMPA)

- **They solvate cations well but leave anions unsolvated because positive centers in the solvent are sterically hindered**



A sodium ion solvated by molecules of the protic solvent water

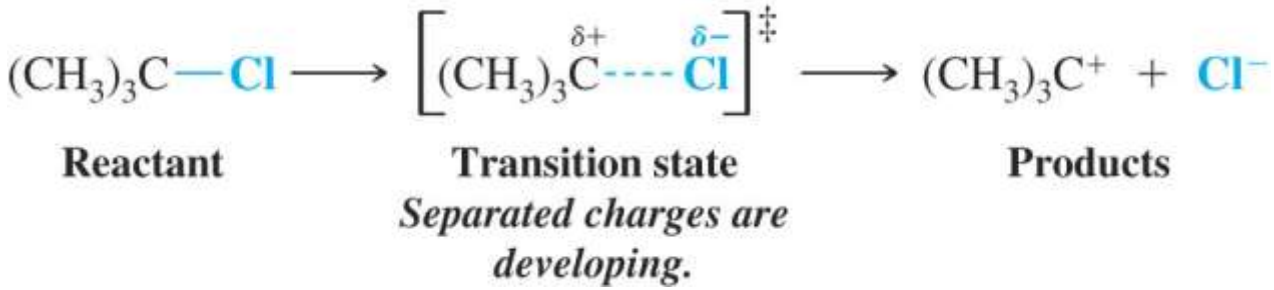


A sodium ion solvated by molecules of the aprotic solvent DMSO

- **Polar protic solvents lead to generation of "naked" and very reactive nucleophiles**
- **Trends for nucleophilicity are the same as for basicity**
- **They are excellent solvents for S_N2 reactions**

$$F^- > Cl^- > Br^- > I^-$$

- **Solvent Effects on S_N1 Reactions: The Ionizing Ability of the Solvent**
  - ➔ **Polar protic solvents are excellent solvents for S_N1 reactions**
  - ➔ **Polar protic solvents stabilize the carbocation-like transition state leading to the carbocation thus lowering $\Delta G^{\ddagger}$**
  - ➔ **Water-ethanol and water-methanol mixtures are most common**



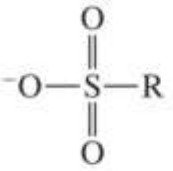
- **The Nature of the Leaving Group**
  - ➔ **The best leaving groups are weak bases which are relatively stable**
    - **The leaving group can be an anion or a neutral molecule**
  - ➔ **Leaving group ability of halides:**

$$I^- > Br^- > Cl^- \gg F^-$$

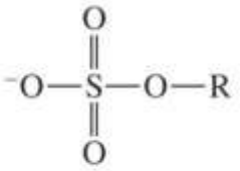
  - ➔ **This trend is opposite to basicity:**

$$F^- \gg Cl^- > Br^- > I^-$$

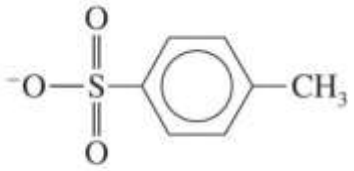
  - ➔ **Other very weak bases which are good leaving groups:**



An alkanesulfonate ion

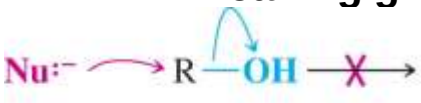


An alkyl sulfate ion



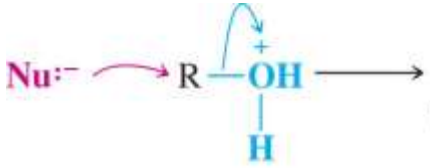
p-Toluenesulfonate ion

  - ➔ **The poor leaving group hydroxide can be changed into the good leaving group water by protonation**



$R-Nu + OH^-$

This reaction does not take place because the leaving group is a strongly basic hydroxide ion.



$R-Nu + H_2O$

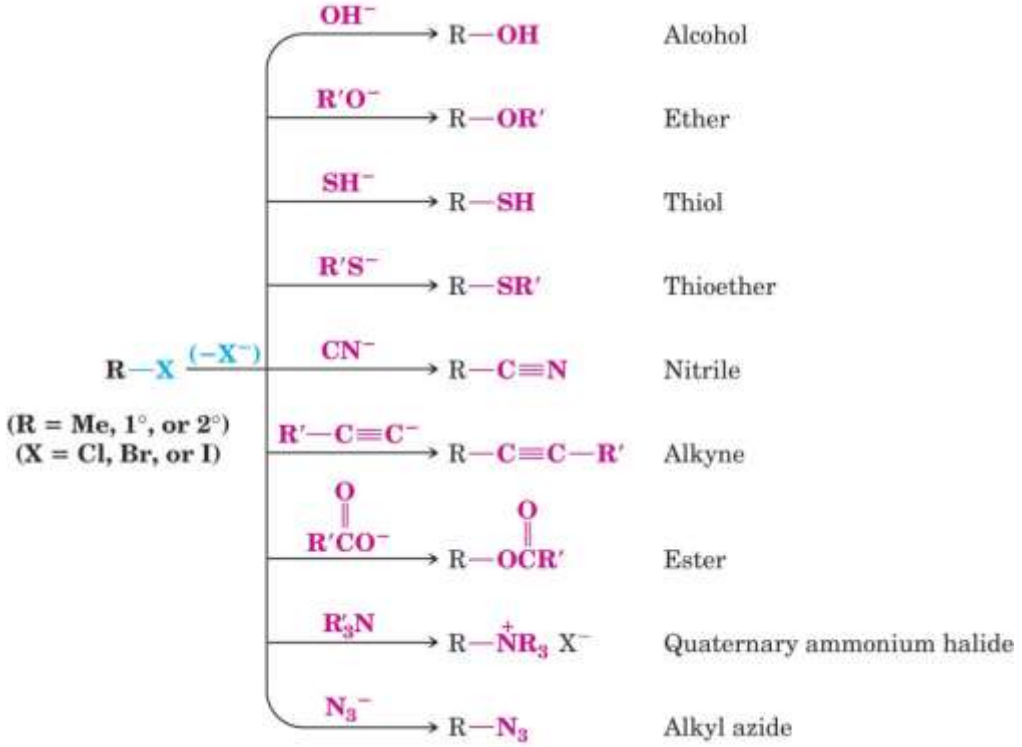
This reaction takes place because the leaving group is a weak base.

- **Summary S_N1 vs. S_N2**
  - **➔In both types of reaction alkyl iodides react the fastest because of superior leaving group ability**

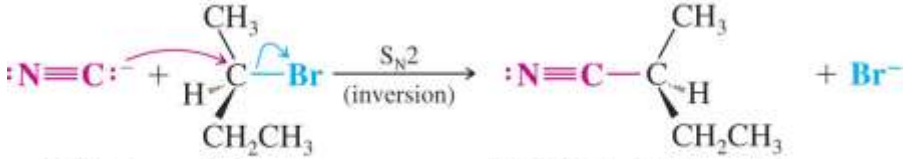
$$R—I > R—Br > R—Cl \qquad S_N1 \text{ or } S_N2$$

Factor	S_N1	S_N2
Substrate	3° (requires formation of a relatively stable carbocation)	Methyl > 1° > 2° (requires unhindered substrate)
Nucleophile	Weak Lewis base, neutral molecule, nucleophile may be the solvent (solvolysis)	Strong Lewis base, rate favored by high concentration of nucleophile
Solvent	Polar protic (e.g., alcohols, water)	Polar aprotic (e.g., DMF, DMSO)
Leaving group	I > Br > Cl > F for both S_N1 and S_N2 (the weaker the base after the group departs, the better the leaving group)	

♦ Organic Synthesis: Functional Group Transformations Using S_N2 Reactions



➔ **Stereochemistry can be controlled in S_N2 reactions**



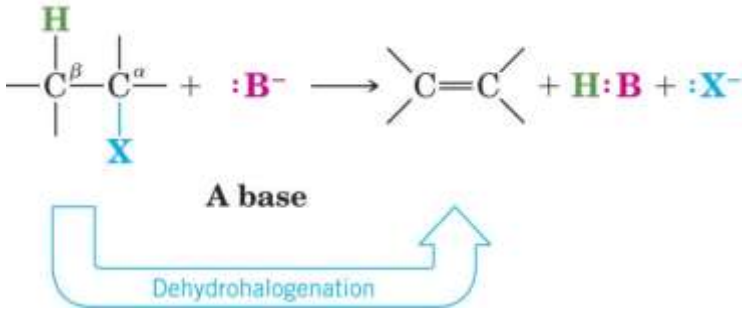
(*R*)-2-Bromobutane (*S*)-2-Methylbutanenitrile

♦ Elimination Reactions of Alkyl Halides

● Dehydrohalogenation

➔Used for the synthesis of alkenes

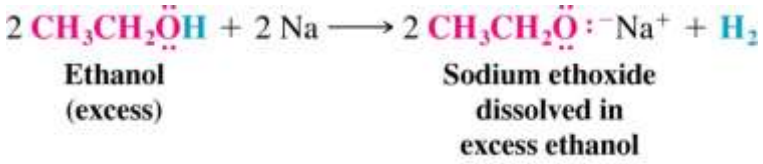
- Elimination competes with substitution reaction
- Strong bases such as alkoxides favor elimination

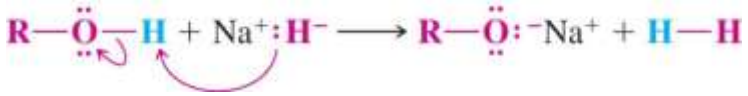


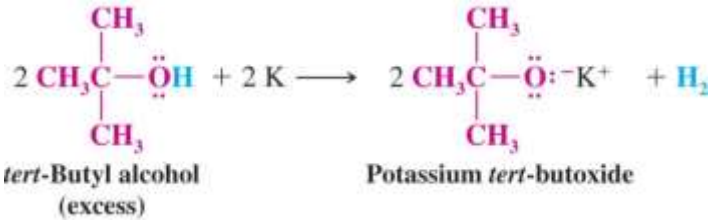
$$CH_3CHCH_3 \xrightarrow[C_2H_5OH,\ 55°C]{C_2H_5ONa} CH_2{=}CH{-}CH_3 + NaBr + C_2H_5OH$$
Br — (79%)

$$CH_3{-}\underset{CH_3}{\overset{CH_3}{C}}{-}Br \xrightarrow[C_2H_5OH,\ 55°C]{C_2H_5ONa} \underset{CH_3}{\overset{CH_3}{C}}{=}CH_2 + NaBr + C_2H_5OH$$
(91%)

➔**The alkoxide bases are made from the corresponding alcohols**







♦ The E2 Reaction

- ➔ **E2 reaction involves concerted removal of the proton, formation of the double bond, and departure of the leaving group**
- ➔ **Both alkyl halide and base concentrations affect rate and therefore the reaction is 2nd order**

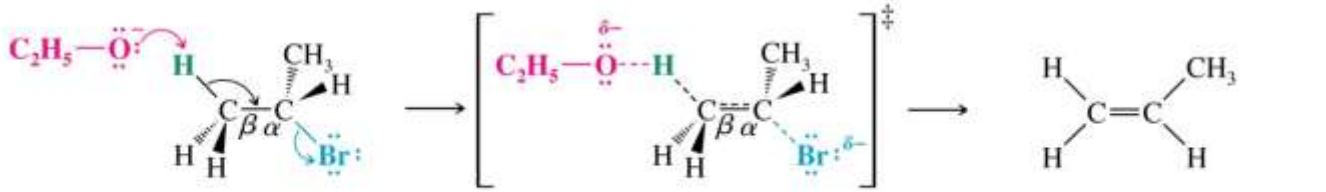
$$\text{Rate} \propto [CH_3CHBrCH_3][C_2H_5O^-]$$

$$\text{Rate} = k[CH_3CHBrCH_3][C_2H_5O^-]$$

Reaction:

$$C_2H_5O^- + CH_3CHBrCH_3 \longrightarrow CH_2{=}CHCH_3 + C_2H_5OH + Br^-$$

Mechanism:



The basic ethoxide ion begins to remove a proton from the β carbon using its electron pair to form a bond to it. At the same time, the electron pair of the β C—H bond begins to move in to become the π bond of a double bond, and the bromine begins to depart with the electrons that bonded it to the α carbon

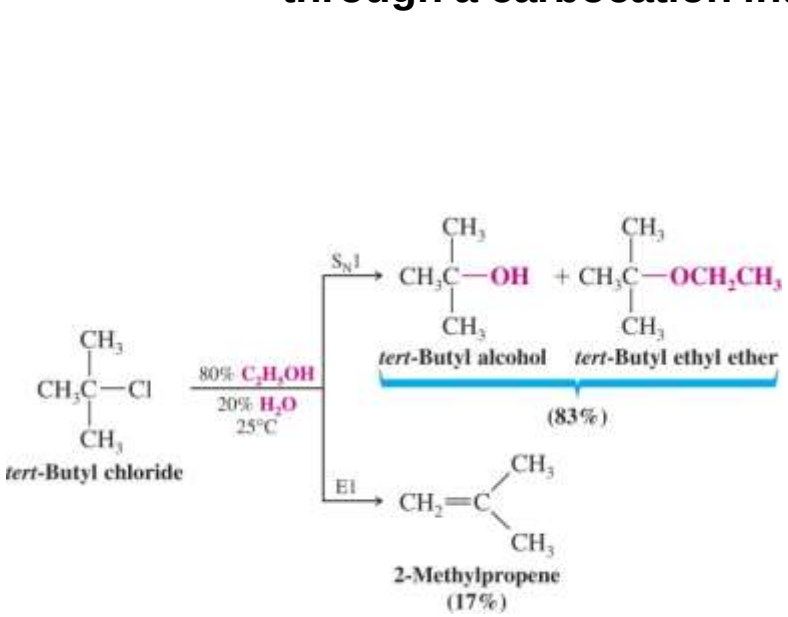
Transition state

Partial bonds in the transition state extend from the oxygen atom that is removing the β hydrogen, through the carbon skeleton of the developing double bond, to the departing leaving group. The flow of electron density is from the base toward the leaving group as an electron pair fills the π bonding orbital of the alkene.

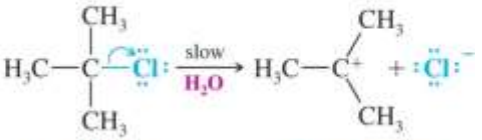
At completion of the reaction, the double bond is fully formed and the alkene has a trigonal planar geometry at each carbon atom. The other products are a molecule of ethanol and a bromide ion.

♦ The E1 Reaction

➔ **The E1 reaction competes with the S_N1 reaction and likewise goes through a carbocation intermediate**



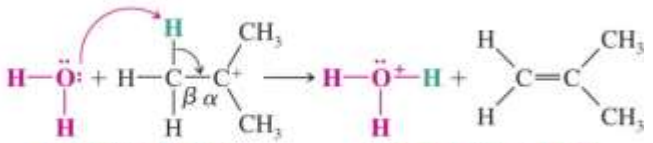
Step 1



Aided by the polar solvent, a chlorine departs with the electron pair that bonded it to the carbon.

This slow step produces the relatively stable 3° carbocation and a chloride ion. The ions are solvated (and stabilized) by surrounding water molecules.

Step 2

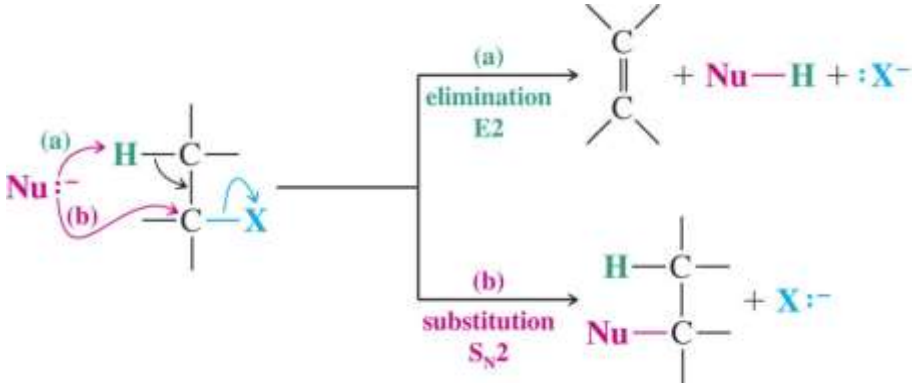


A molecule of water removes one of the hydrogens from the β carbon of the carbocation. These hydrogens are acidic due to the adjacent positive charge. At the same time an electron pair moves in to form a double bond between the α and β carbon atoms.

This step produces the alkene and a hydronium ion.

♦ Substitution versus Elimination

● S_N2 versus E2



➔Primary substrate

- **If the base is small, S_N2 competes strongly because approach at carbon is unhindered**

$$CH_3CH_2O^-Na^+ + CH_3CH_2Br \xrightarrow[55°C]{C_2H_5OH} \underset{S_N2\ (90\%)}{CH_3CH_2OCH_2CH_3} + \underset{E2\ (10\%)}{CH_2{=}CH_2}$$
$$(-NaBr)$$

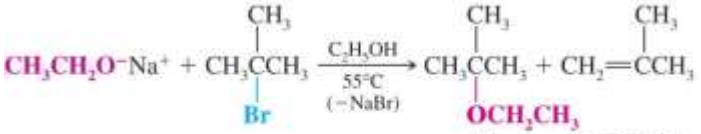
➔Secondary substrate

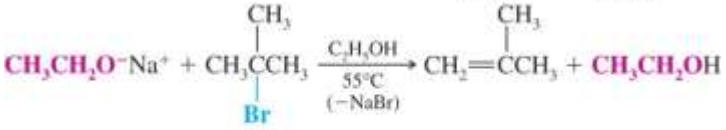
- **Approach to carbon is sterically hindered and E2 elimination is favored**

$$CH_3CH_2O^-Na^+ + \underset{Br}{CH_3CHCH_3} \xrightarrow[55°C]{C_2H_5OH} \underset{S_N2\ (21\%)}{\underset{OCH_2CH_3}{CH_3CHCH_3}} + \underset{E2\ (79\%)}{CH_2{=}CHCH_3}$$
$$(-NaBr)$$

➔Tertiary substrate

- **Approach to carbon is extremely hindered and elimination predominates especially at high temperatures**



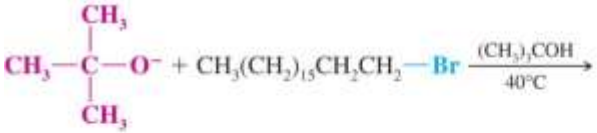


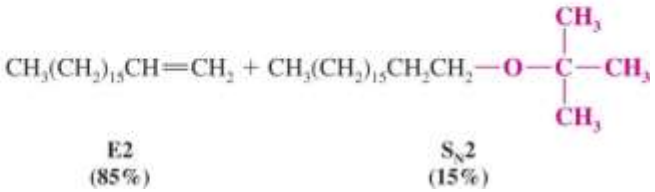
➔Temperature

- **Increasing temperature favors elimination over substitution**

➔Size of the Base/Nucleophile

- **Large sterically hindered bases favor elimination because they cannot directly approach the carbon closely enough to react in a substitution**
- **Potassium *tert*-butoxide is an extremely bulky base and is routinely used to favor E2 reaction**





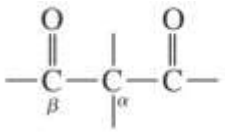
♦ Overall Summary

Factor	S_N1	S $_N2$
Substrate	3° (requires formation of a relatively stable carbocation)	Methyl > 1° > 2° (requires unhindered substrate)
Nucleophile	Weak Lewis base, neutral molecule, nucleophile may be the solvent (solvolysis)	Strong Lewis base, rate favored by high concentration of nucleophile
Solvent	Polar protic (e.g., alcohols, water)	Polar aprotic (e.g., DMF, DMSO)
Leaving group	I > Br > Cl > F for both S_N1 and S_N2 (the weaker the base after the group departs, the better the leaving group)	

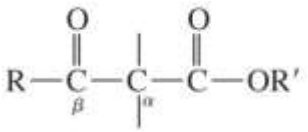
Synthesis and Reactions of β-Dicarbonyl Compounds: More Chemistry of Enolate Anions

♦ Introduction

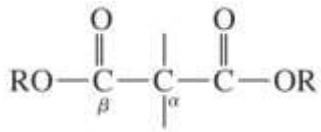
➔ β-Dicarbonyl compounds have two carbonyl groups separated by a carbon



The β-dicarbonyl system



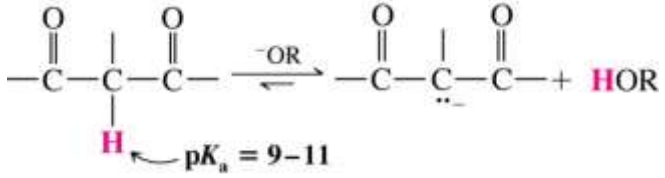
A β-keto ester (Section 19.2)

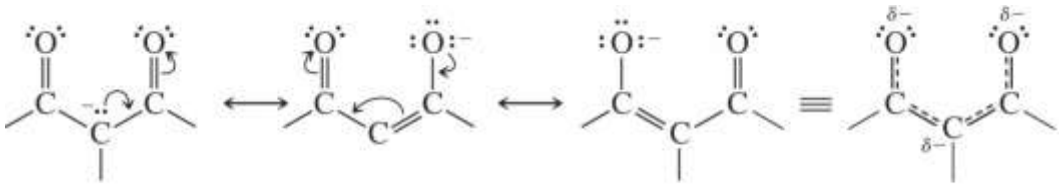


A malonic ester (Section 19.4)

➔ Protons on the α-carbon of β-dicarbonyl compounds are acidic (pK_a = 9-10)

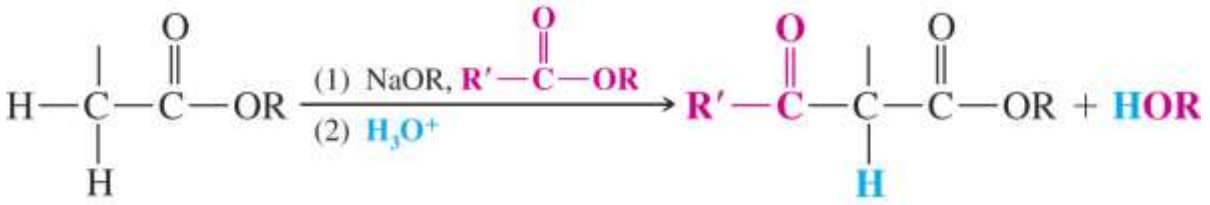
- The acidity can be explained by resonance stabilization of the corresponding enolate by two carbonyl groups



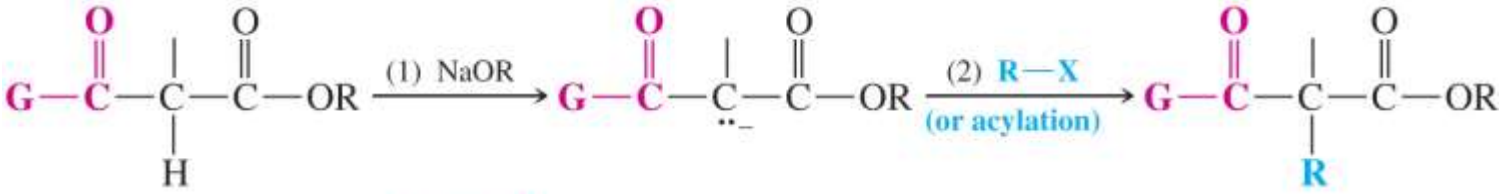


Contributing resonance structures Resonance hybrid

➔ β-Dicarbonyl compounds can be synthesized by the Claisen condensation

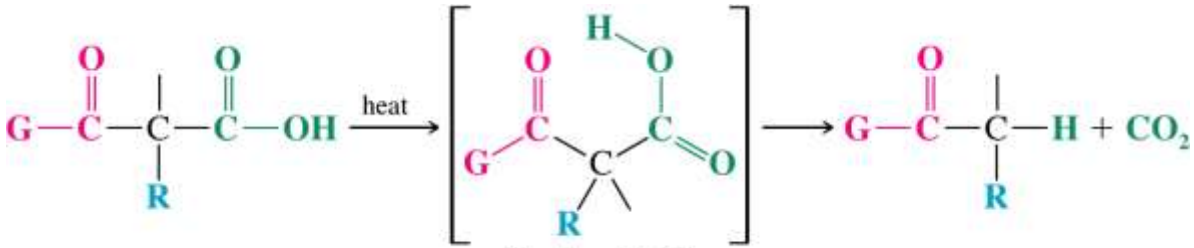


➔ The acetoacetic ester and malonic acid syntheses use β-dicarbonyl compounds for carbon-carbon bond forming reactions



Acetoacetic ester synthesis, G = CH_3
Malonic ester synthesis, G = RO

➔ The acetoacetic ester and malonic ester syntheses usually conclude with decarboxylation of a β-keto acid

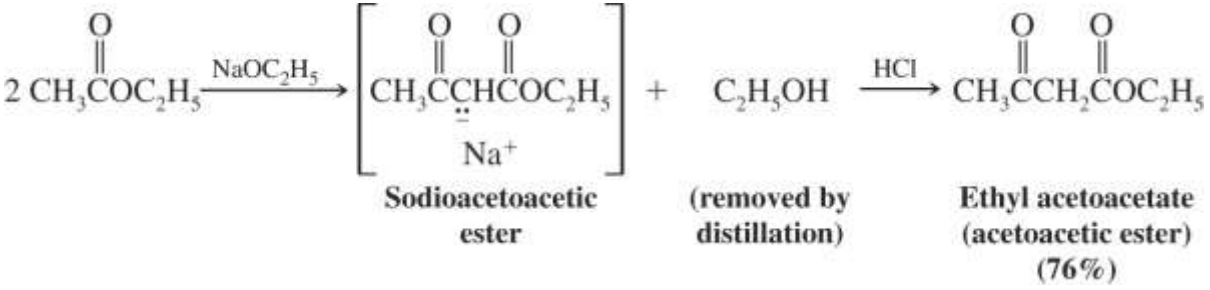


(Section 18.10)

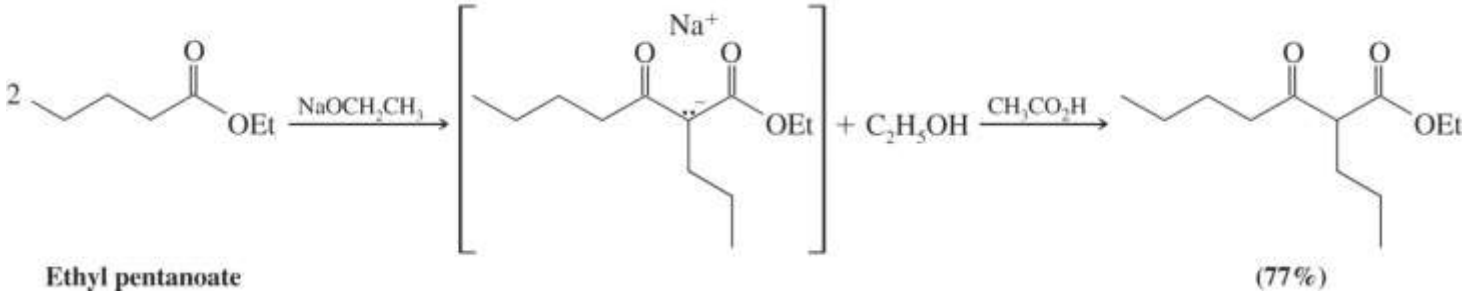
♦ The Claisen Condensation: Synthesis of β-Keto Esters

➔ **Ethyl acetate undergoes a Claisen condensation when treated with sodium ethoxide**

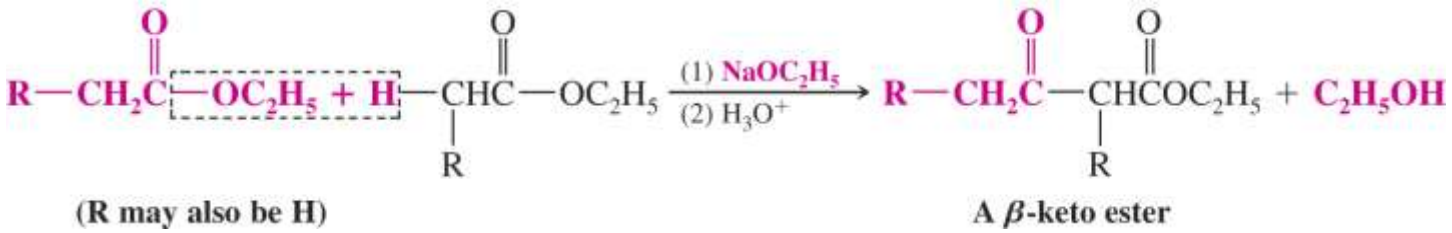
- **The product is commonly called an acetoacetic ester**



➔ **Ethyl pentanoate undergoes an analogous reaction**

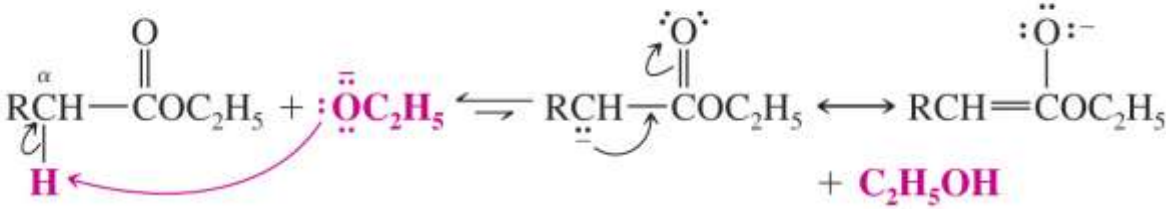


➔ **The overall reaction involves loss of an α hydrogen from one ester and loss of ethoxide from another**

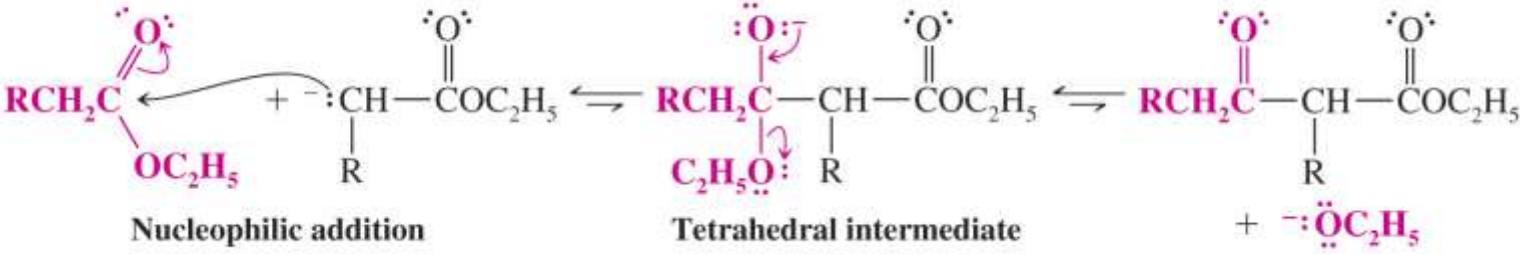


➔ **The mechanism is an example of the general process of nucleophilic addition-elimination at an ester carbonyl**

Step 1

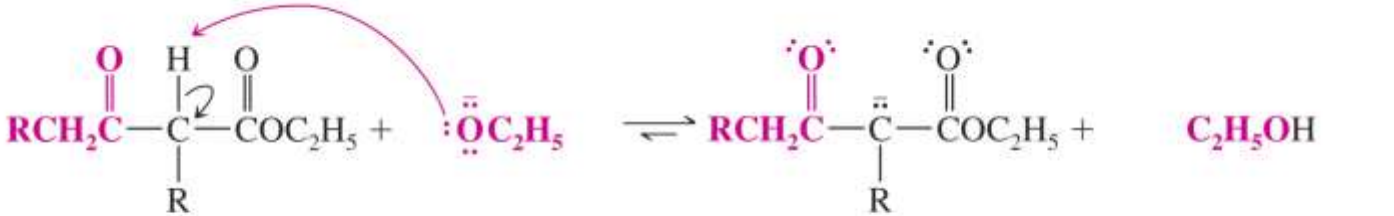


Step 2



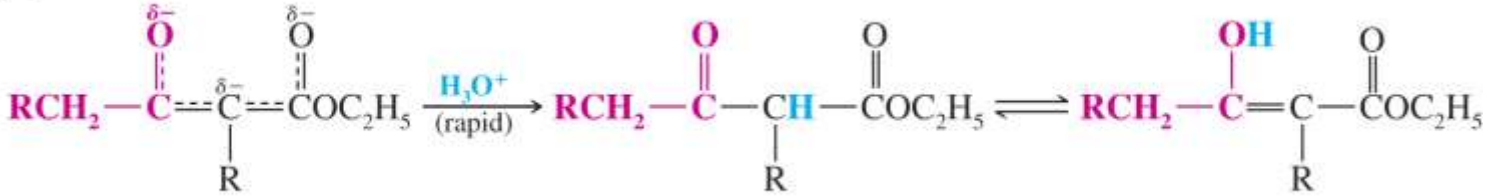
Nucleophilic addition | **Tetrahedral intermediate and elimination**

Step 3



β-Keto ester (pK_a ~ 9; stronger acid) | **Ethoxide ion** (stronger base) | **β-Keto ester anion** (weaker base) | **Ethanol** (pK_a 16; weaker acid)

Step 4



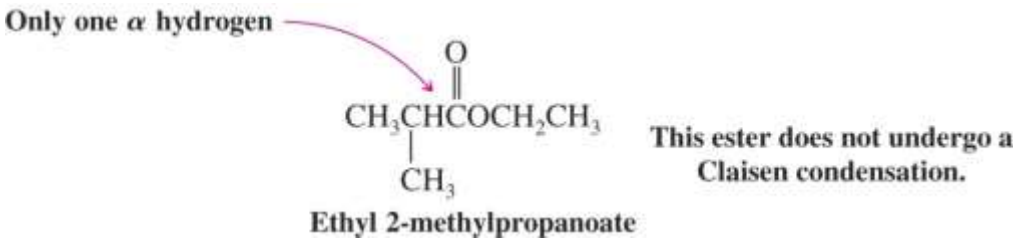
Keto form | **Enol form**

➔ **The alkoxide base must have the same alkyl group as the alkoxyl group of the ester**

- **The use of a different alkoxide would result in formation of some transesterification products**

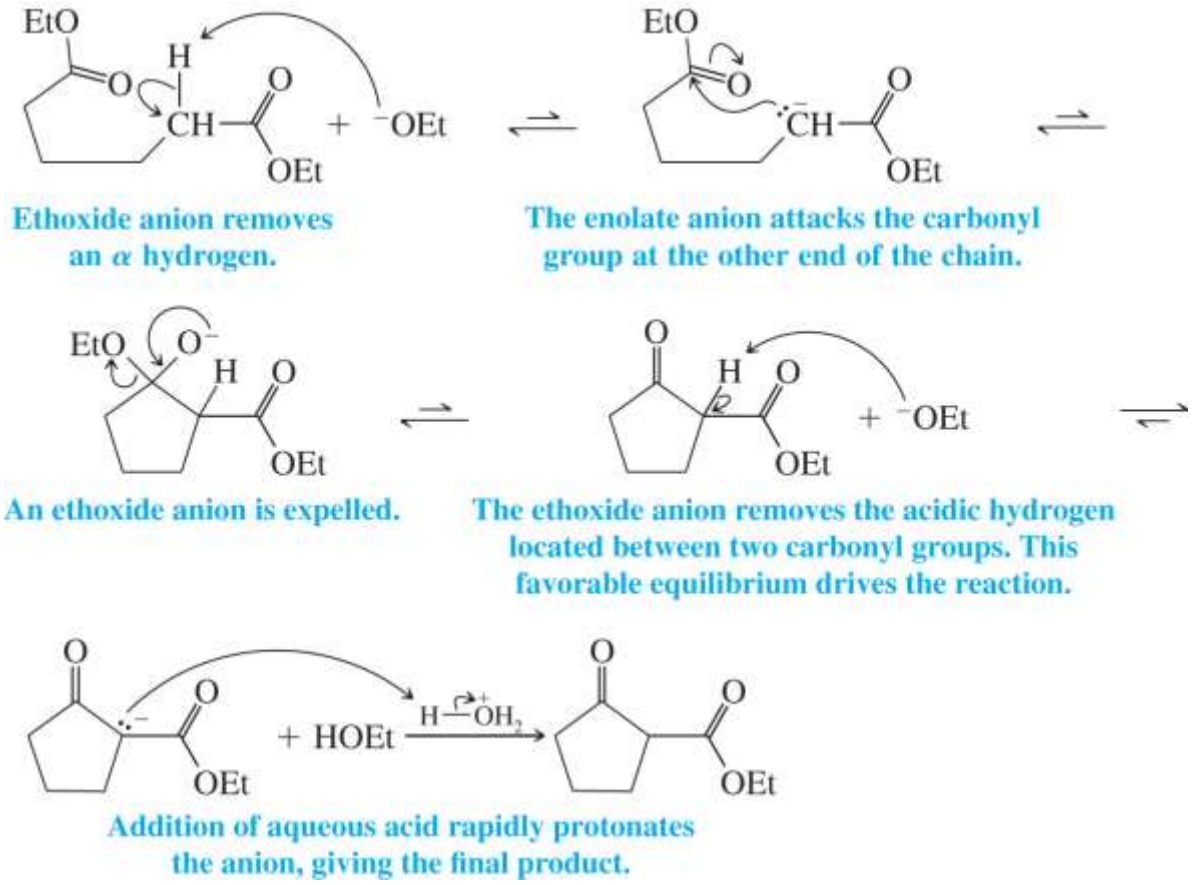
➔ **Esters with only one α hydrogen do not undergo Claisen condensation**

- **A second hydrogen on the α carbon is necessary so that it can be deprotonated in Step 3**
- **This deprotonation drives the reaction to completion**

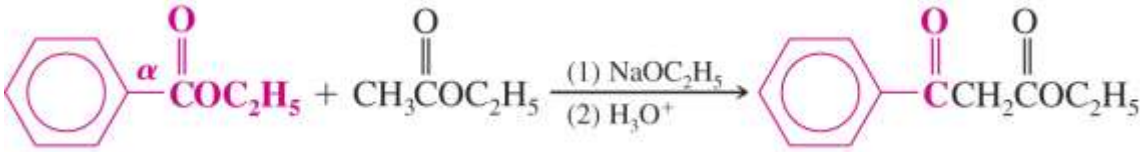


➔ **The Dieckmann condensation is an intramolecular Claisen condensation**

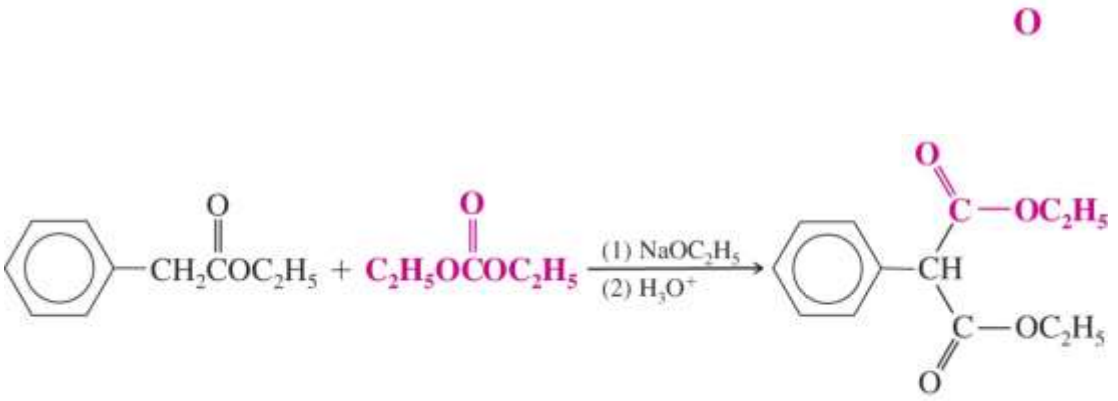
- **Only 5- and 6-membered rings may be prepared in this way**



- **Crossed Claisen Condensations**
  - ➔**Crossed Claisen condensations can lead to one major product when one of the two esters has no α hydrogen**

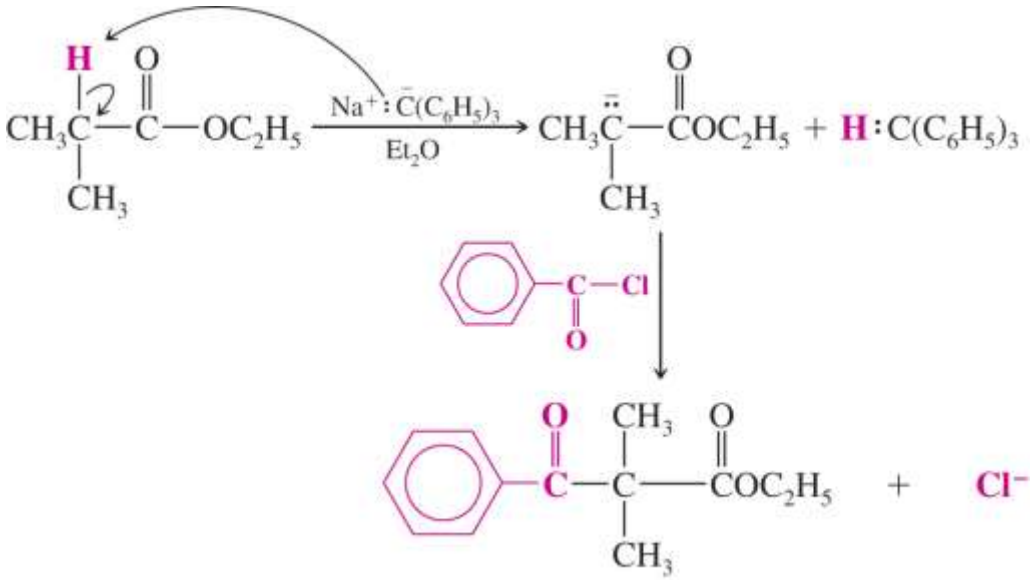


Ethyl benzoate (no α hydrogen) — **Ethyl benzoylacetate (60%)**



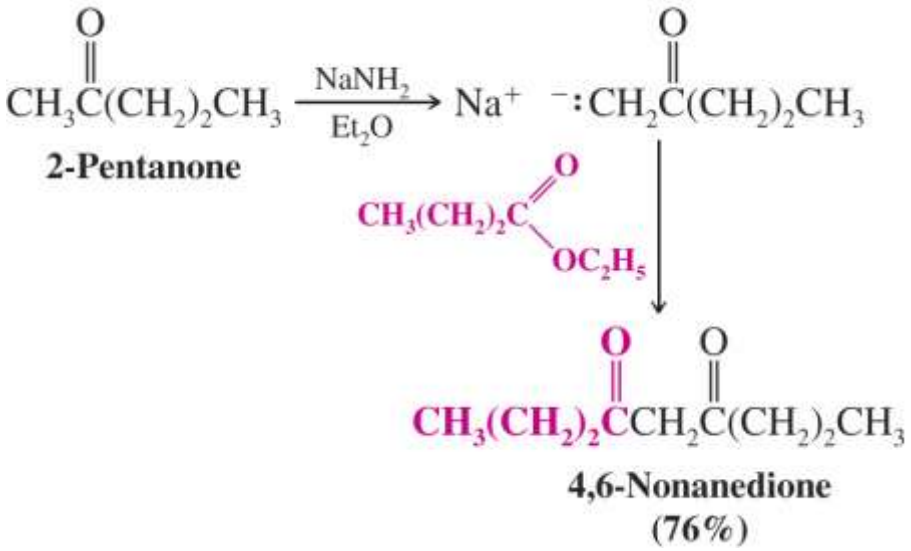
Ethyl phenylacetate — **Diethyl carbonate (no α carbon)** — **Diethyl phenylmalonate (65%)**

➔ **Esters with one α hydrogen can react in Claisen condensations if they are deprotonated with a strong base and acylated with an acyl chloride**



Ethyl 2,2-dimethyl-3-oxo-3-phenylpropanoate

- **Acylation of Other Carbanions**
  - ➔ **Ketone enolates formed with strong bases can also be acylated to form β-dicarbonyl compounds**
  - ➔ **Addition of strong base to 2-pentanone results in formation of the kinetic enolate which can be acylated with an ester**

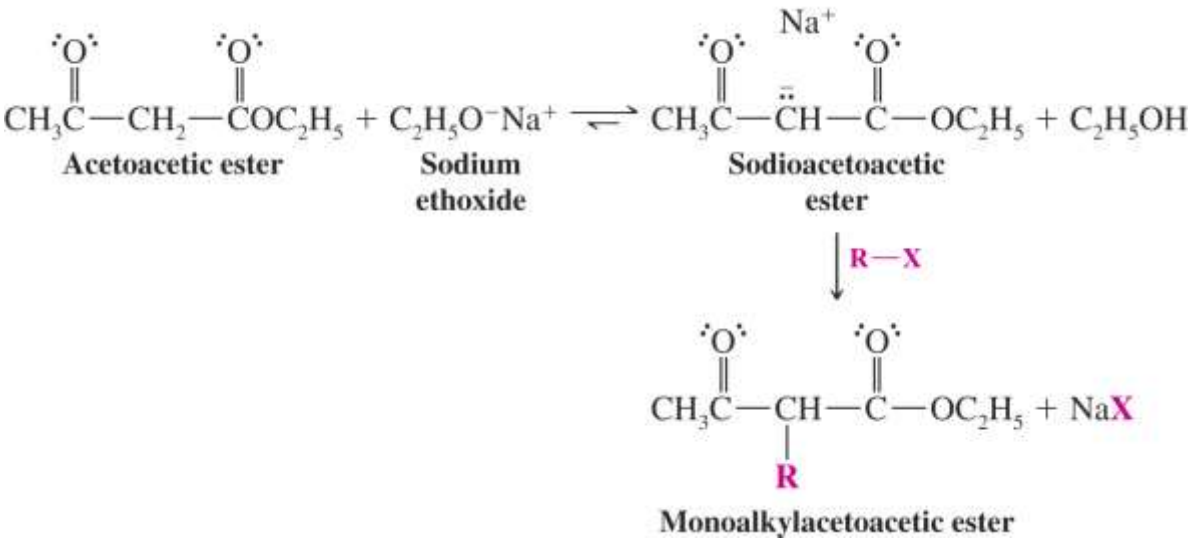


♦ The Acetoacetic Ester Synthesis: Synthesis of Methyl Ketones (Substituted Acetones)

- **Alkylation**

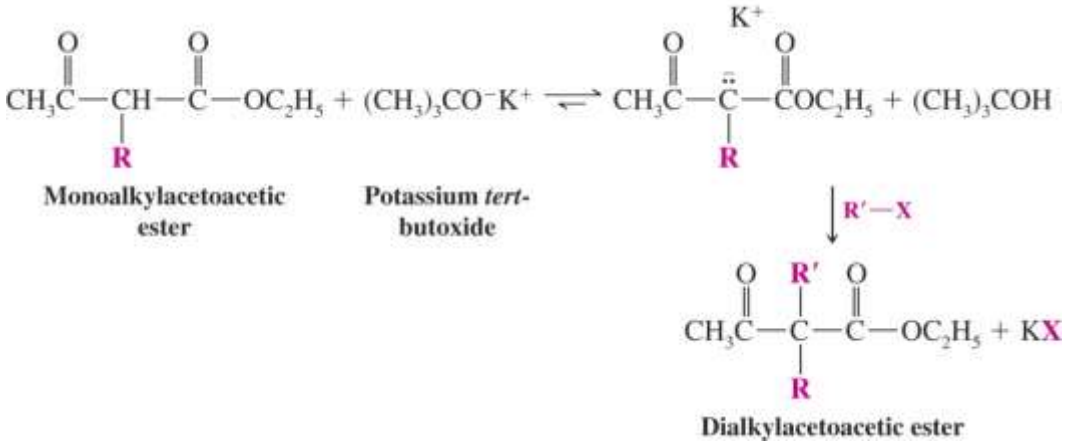
  ➔ Alkylation of the enolate derived from acetoacetic ester is called the acetoacetic ester synthesis

  - **This is an S_N2 reaction with the ethyl acetoacetate enolate acting as the nucleophile**



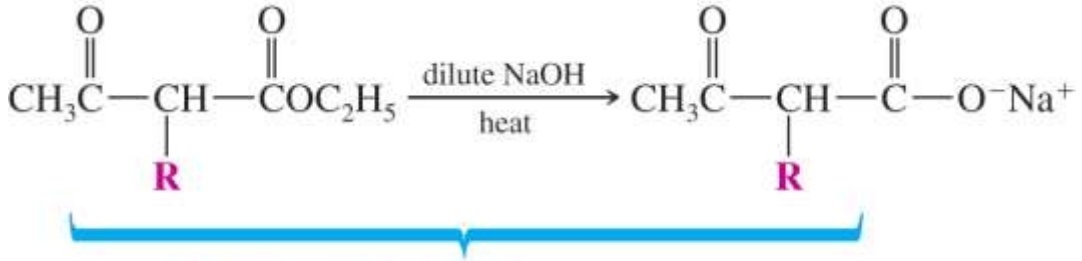
➔A second alkylation can be performed

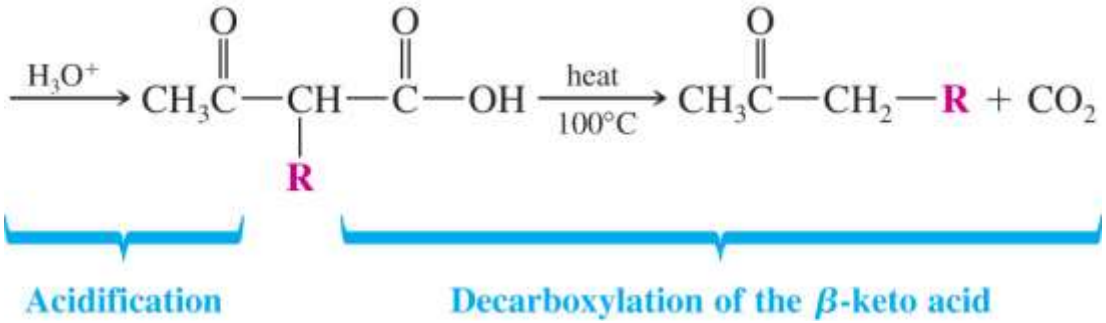
- **A stronger base such as potassium *tert*-butoxide must be use to deprotonate the monoalkyl ester**



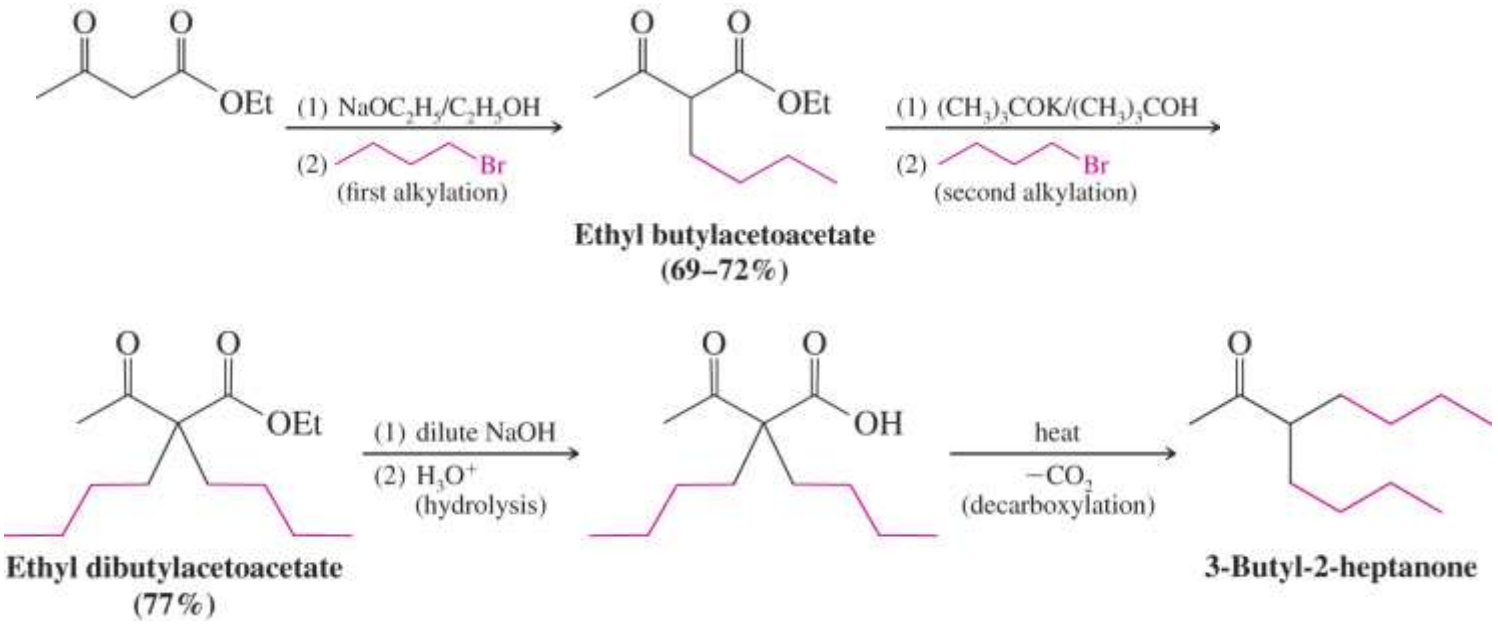
➔ **Hydrolysis of the ester and heating of the resultant β-ketoacid causes decarboxylation**

- **The product is a substituted acetone derivative**



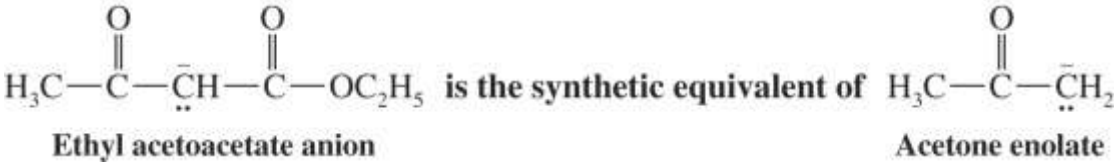


➔ **Example:**

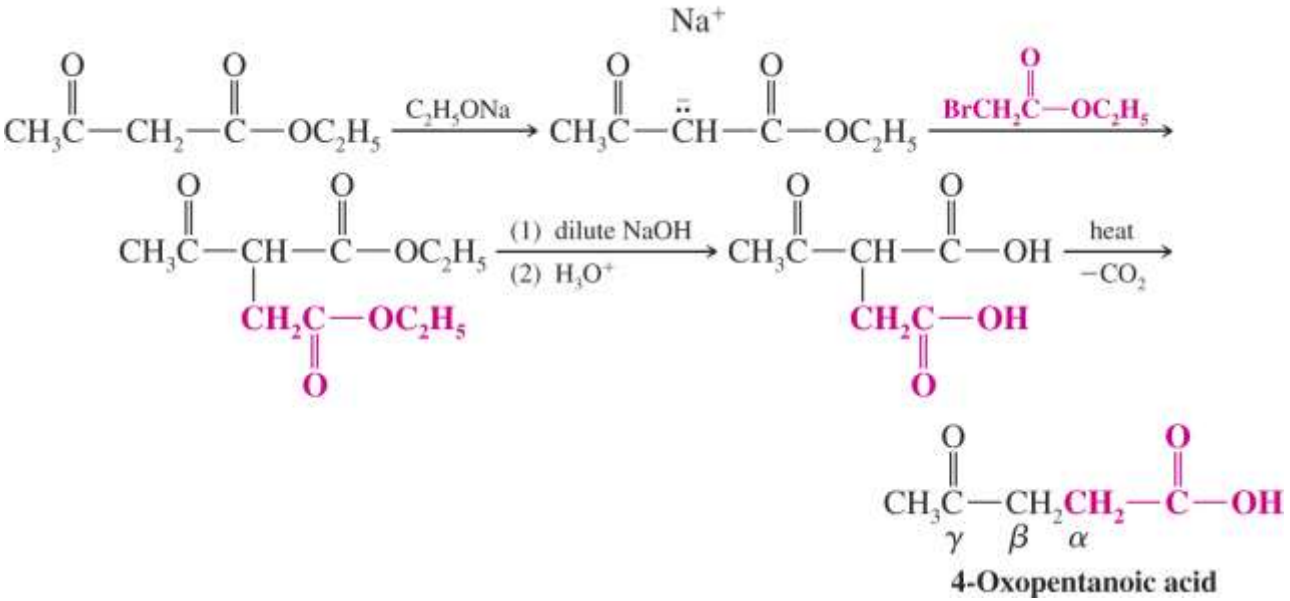

OEt
(1) $NaOC_2H_5/C_2H_5OH$
(2)
Br
(first alkylation)
OEt
Ethyl butylacetoacetate
(69–72%)
(1) $(CH_3)_3COK/(CH_3)_3COH$
(2)
Br
(second alkylation)
OEt
Ethyl dibutylacetoacetate
(77%)
(1) dilute NaOH
(2) H_3O^+
(hydrolysis)
OH
heat
$-CO_2$
(decarboxylation)
3-Butyl-2-heptanone

➔ **Ethylacetoacetate serves as a *synthetic equivalent* of the acetone enolate**

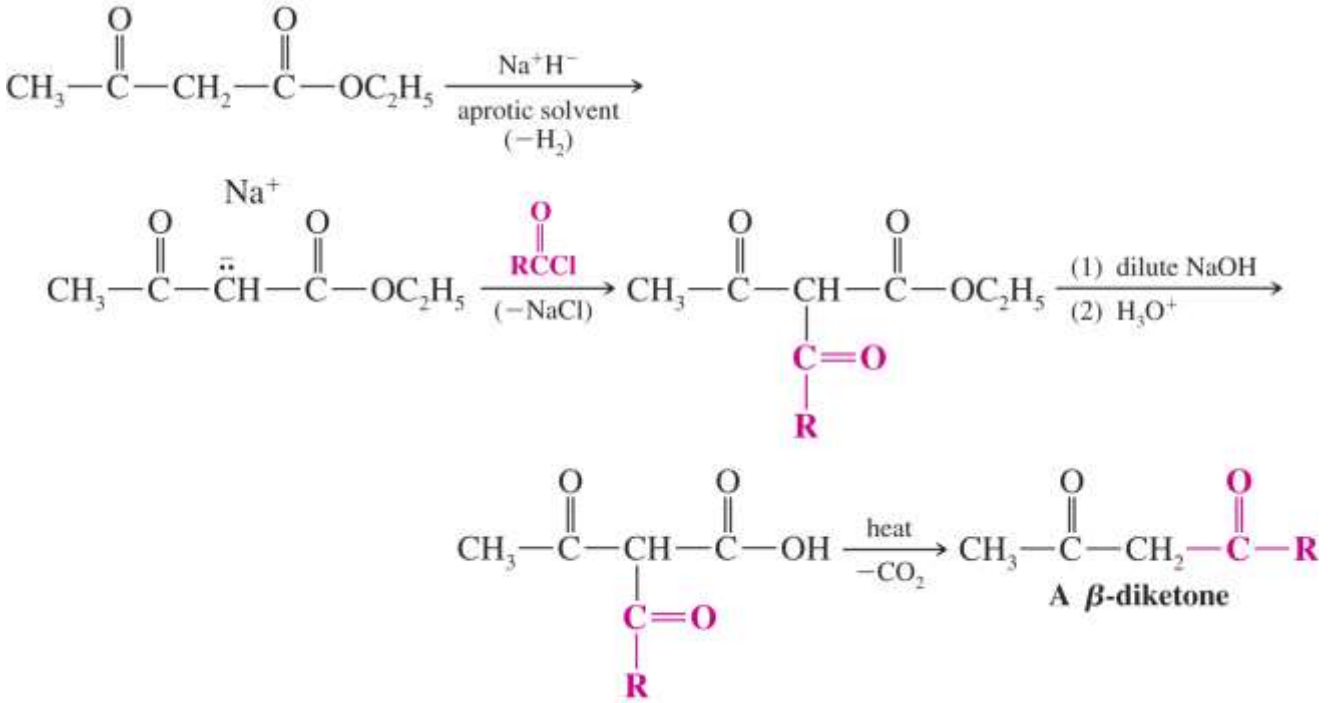
- **It is possible to use acetone enolate directly, but this would require a much stronger base and special reaction conditions**



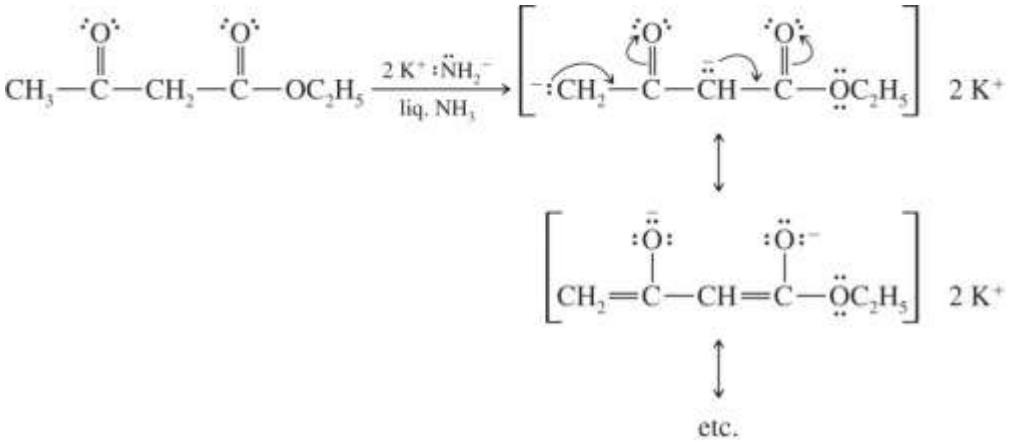
➔ **If α-halo esters are used to alkylate the enolate, γ-keto acids are obtained**



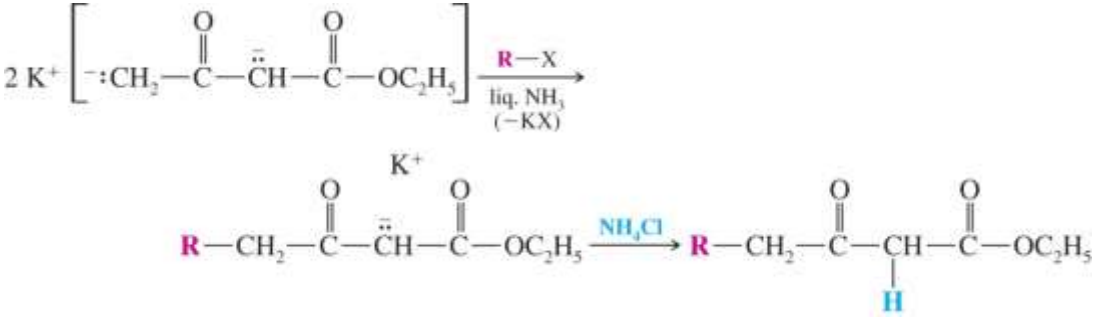
- **Acylation**
  - **➔Acetoacetic ester anion can also by acylated with acyl halides or anhydrides**
    - **The reaction is carried out in aprotic solvents such as DMF or DMSO because these will not destroy the acylating reagents**



- **Acetoacetic Ester Dianion: Alkylation at the Terminal Carbon**
  - ➔ **Treating acetoacetic ester with two equivalents of a very strong base produces the dianion**



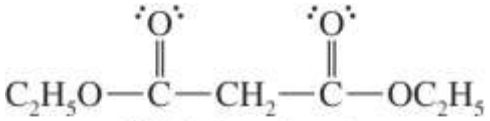
  - ➔ **Alkylation of the dianion occurs first at the terminal carbon**
    - **The terminal carbanion is more nucleophilic and more basic because it is stabilized by only one carbonyl group**



♦ The Malonic Ester Synthesis: Synthesis of Substituted Acetic Acids

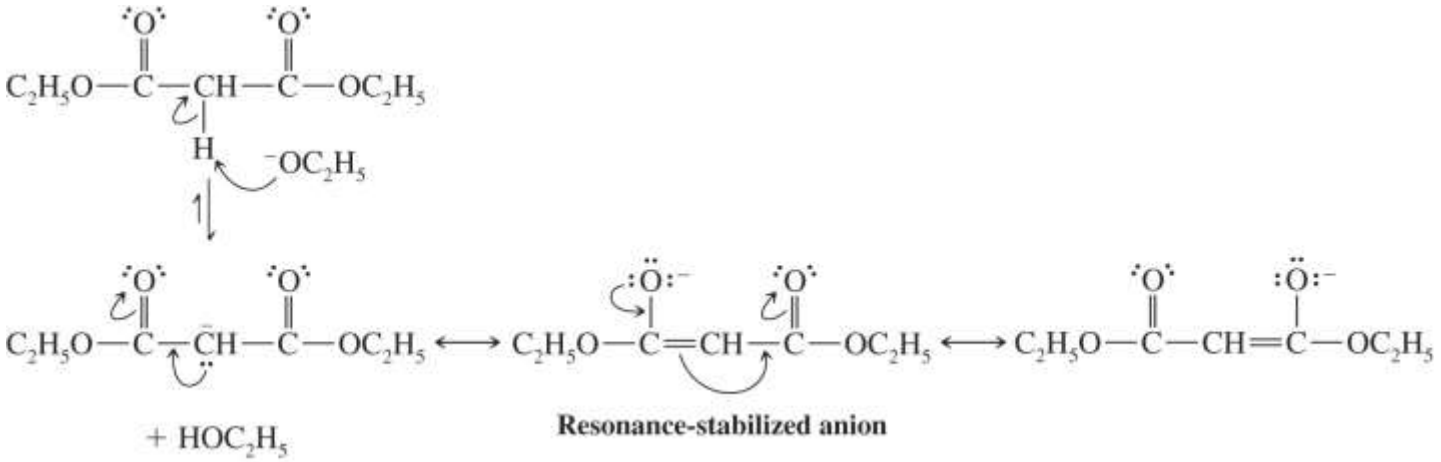
➔ **Alkylation of diethylmalonate, hydrolysis of the diester to the β-dicarboxylic acid, and decarboxylation can be used to synthesize mono- and disubstituted acetic acids**

- **The mechanism is analogous to that for the acetoacetic ester synthesis**



Diethyl malonate
(a *β*-dicarboxylic acid ester)

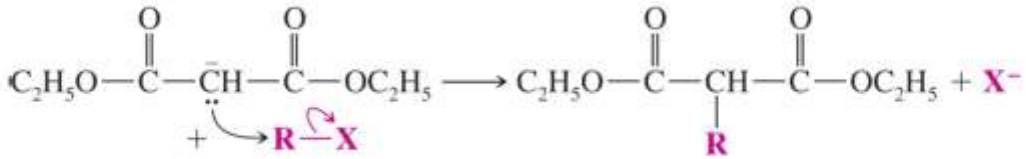
➔ **In step 1 the stabilized anion is formed**



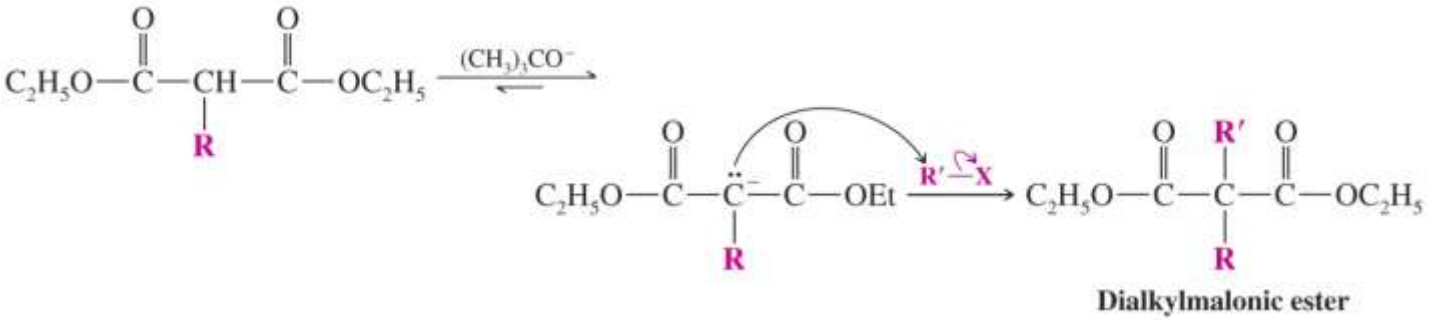
Resonance-stabilized anion

➔**In step 2 the anion is mono- or dialkylated using S_N2 reactions**

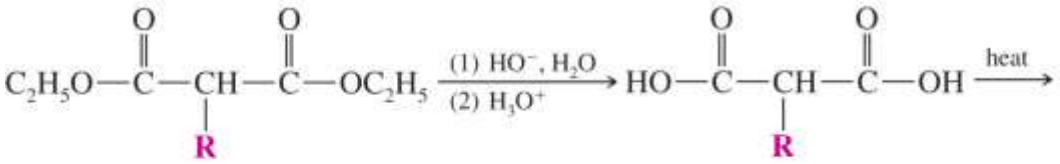
Step 2 This enolate anion can be alkylated in an S_N2 reaction,



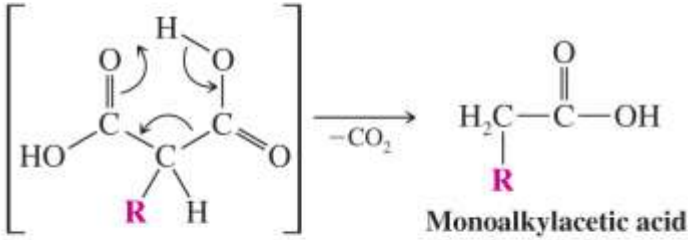
and the product can be alkylated again if our synthesis requires it:



➔ **In step 3 the mono- or dialkylated product is hydrolyzed and decarboxylated**

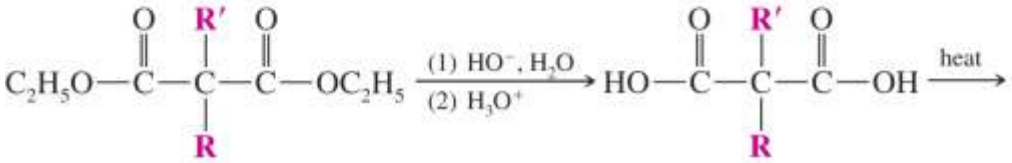


Monoalkylmalonic ester

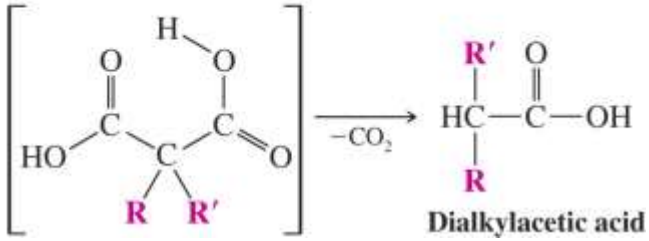


Monoalkylacetic acid

or after dialkylation,

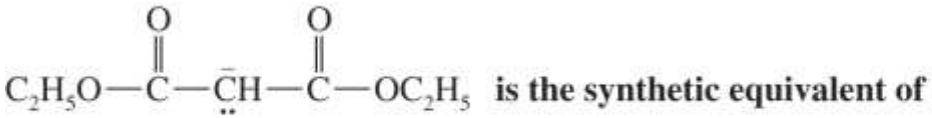


Dialkylmalonic ester

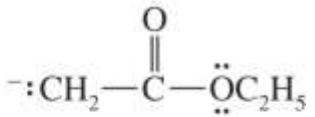


Dialkylacetic acid

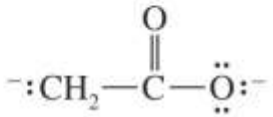
➔ **Diethylmalonate anion is the synthetic equivalent of acetic acid dianion**



Diethyl malonate anion **is the synthetic equivalent of**

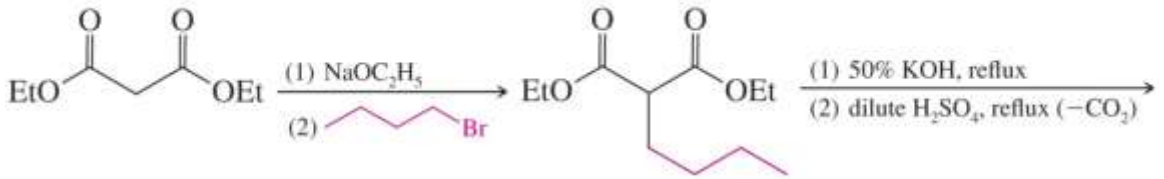


and



➔Examples

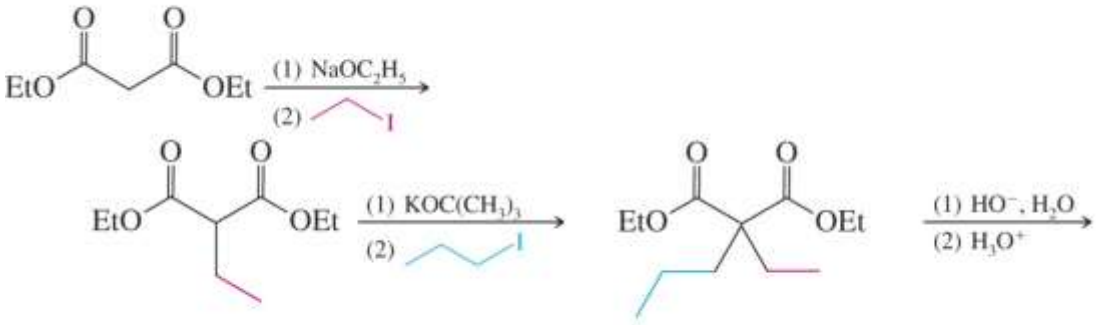
A Malonic Ester Synthesis of Hexanoic Acid



Diethyl butylmalonate (80–90%)

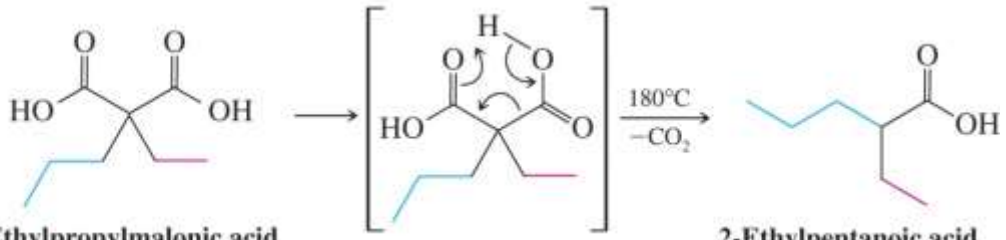
Hexanoic acid (75%)

A Malonic Ester Synthesis of 2-Ethylpentanoic Acid



Diethyl ethylmalonate

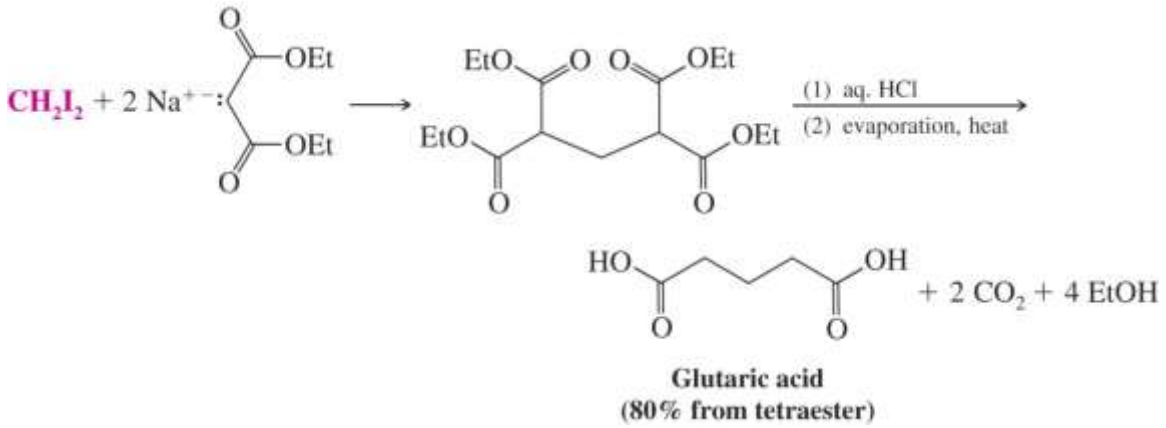
Diethyl ethylpropylmalonate



Ethylpropylmalonic acid

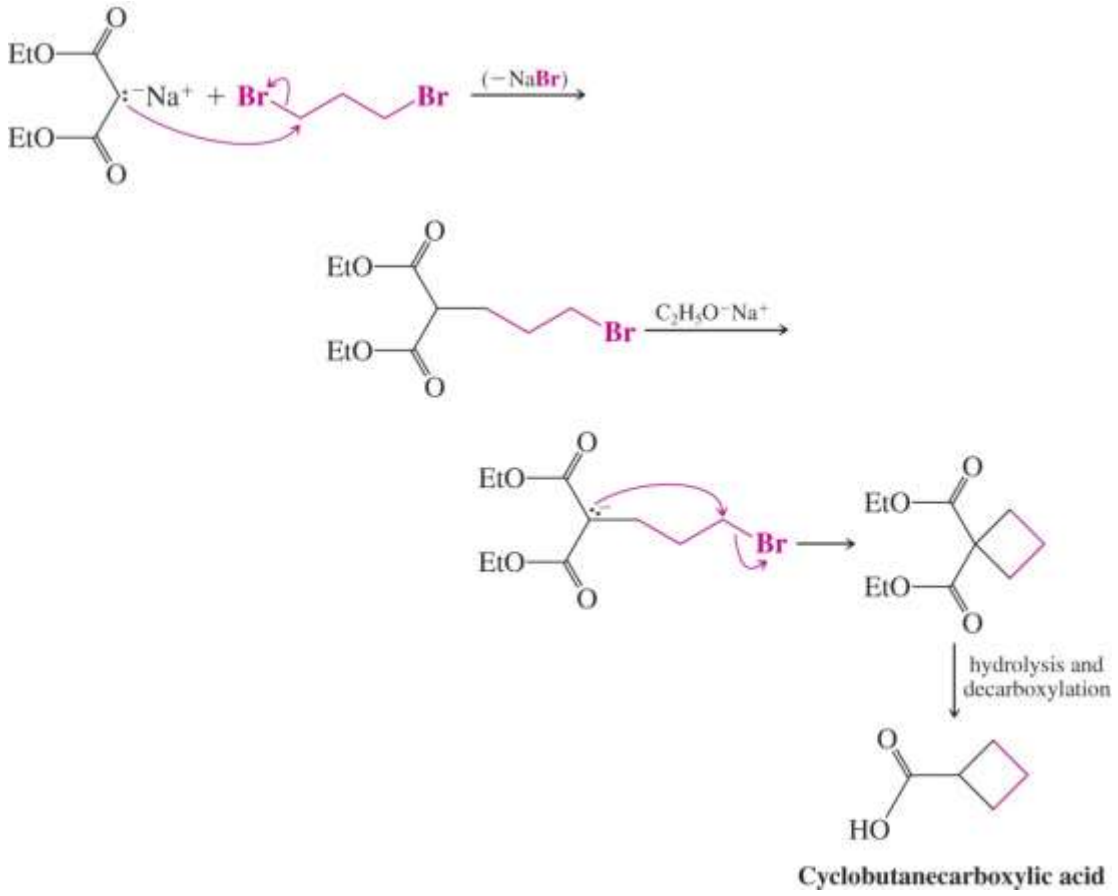
2-Ethylpentanoic acid

➔ **By using two molar equivalents of malonate anion and a dihalide, the dicarboxylic acid is obtained**



Glutaric acid
(80% from tetraester)

➔ **C2 through C5 terminal dihalides can react to form rings by dialkylation of one molar equivalent of malonate**



Cyclobutanecarboxylic acid

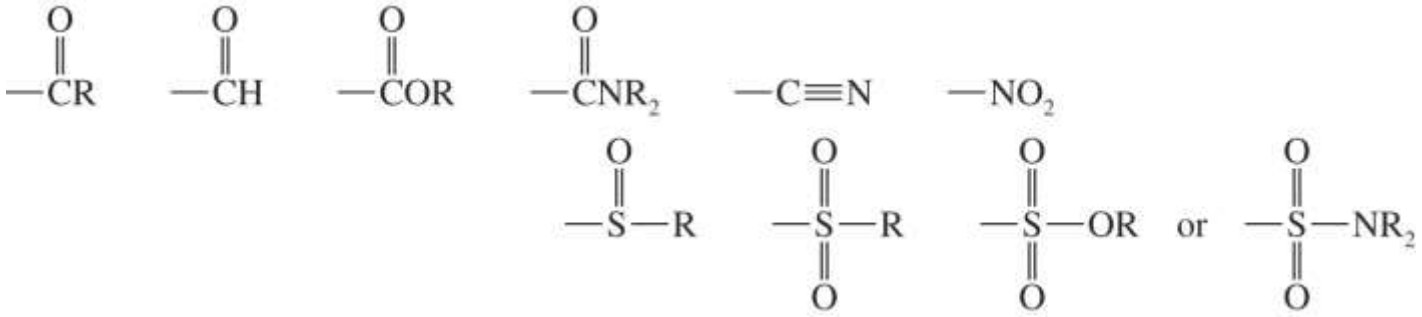
♦ Reactions of Other Active Hydrogen Compounds

➔ **Compounds in which the hydrogen atoms of a methylene (-CH_2-) group are made acidic by two attached electron-withdrawing groups are called *active hydrogen compounds* or *active methylene compounds***

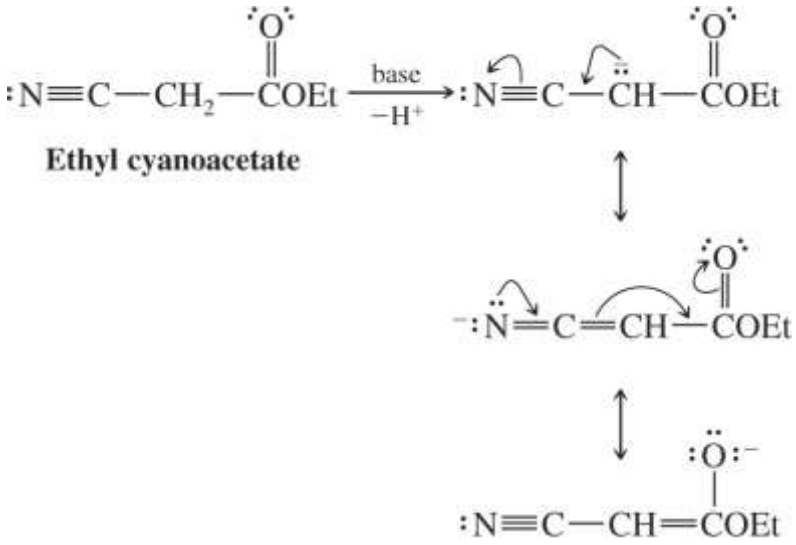
- **A variety of electron-withdrawing groups can produce enhanced α hydrogen acidity**

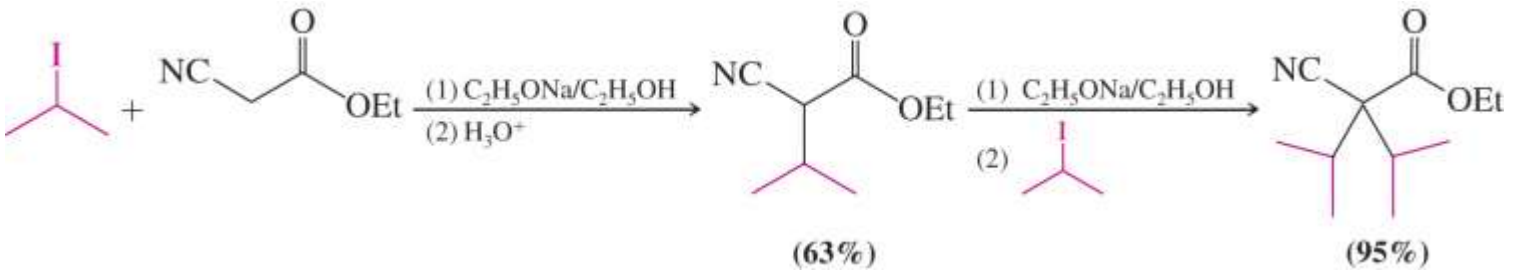
$$Z—CH_2—Z'$$

Active hydrogen compound
(Z and Z′ are electron-withdrawing groups.)



➔ **Example: Deprotonation of ethyl cyanoacetate forms a resonance-stabilized anion, which can then undergo alkylation**

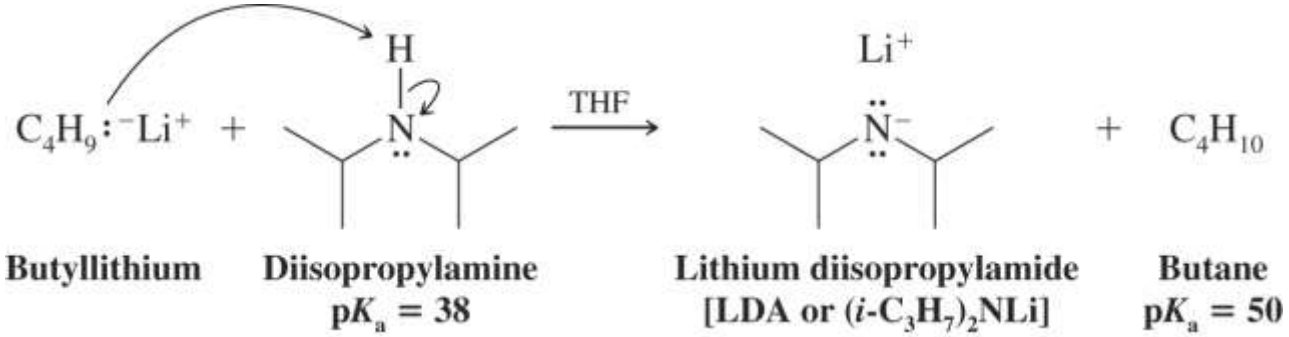


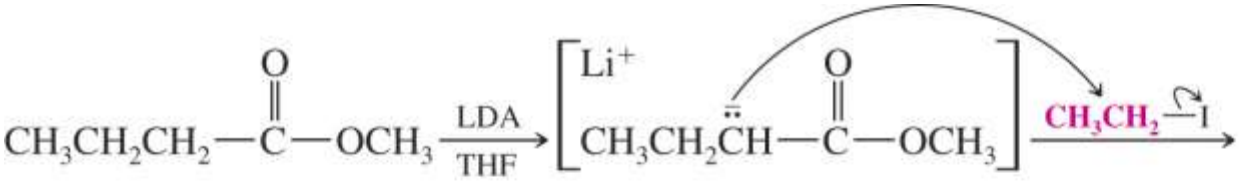


♦ Direct Alkylation of Esters and Nitriles

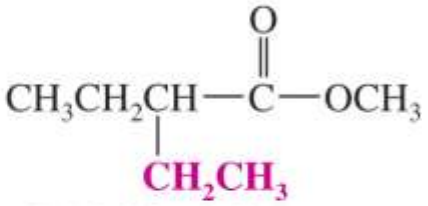
➔ **A strong and bulky base such as lithium diisopropyl amide (LDA) must be used to directly alkylate esters and nitriles**

- **A strong base rapidly converts all of the ester or nitrile molecules into enolates so that they will not undergo Claisen condensation**
- **A bulky base will not react as a nucleophile at the ester carbonyl or nitrile carbon**

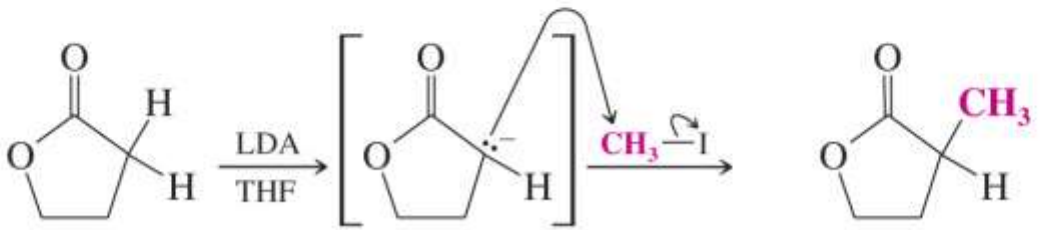




Methyl butanoate



Methyl 2-ethylbutanoate
(96%)



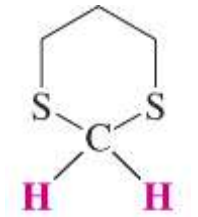
Butyrolactone

2-Methylbutyrolactone
(88%)

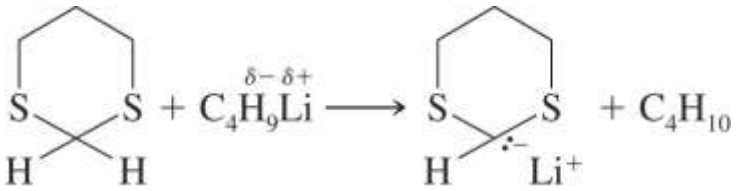
♦ Alkylation of 1,3-Dithianes

➔ **Protons on the carbon between the sulfur atoms of a 1,3-dithiane are acidic**

- **Strong bases convert the dithiane to its anion**

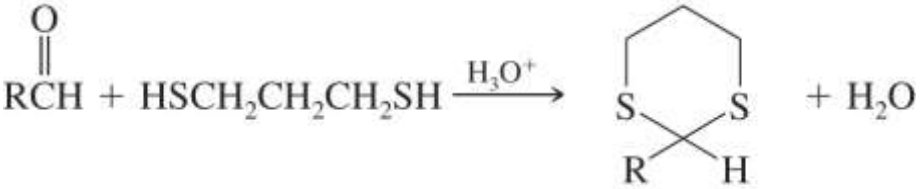


1,3-Dithiane
pK_a = 32



➔ **Dithianes are 6-membered ring thioacetals**

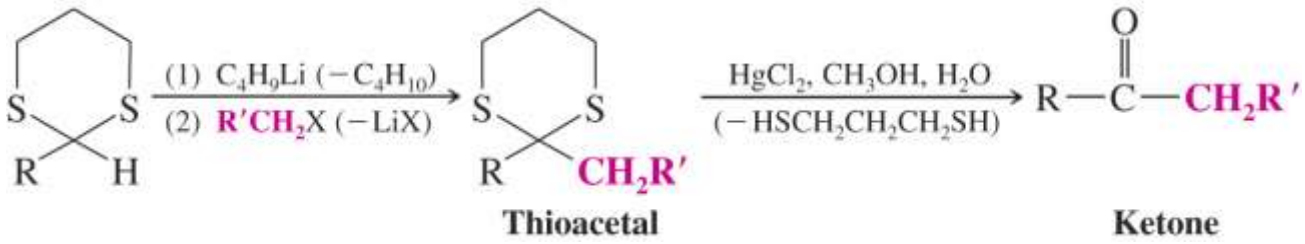
- **These can be prepared from an aldehyde and the 1,3- dithiol**



A 1,3-dithiane

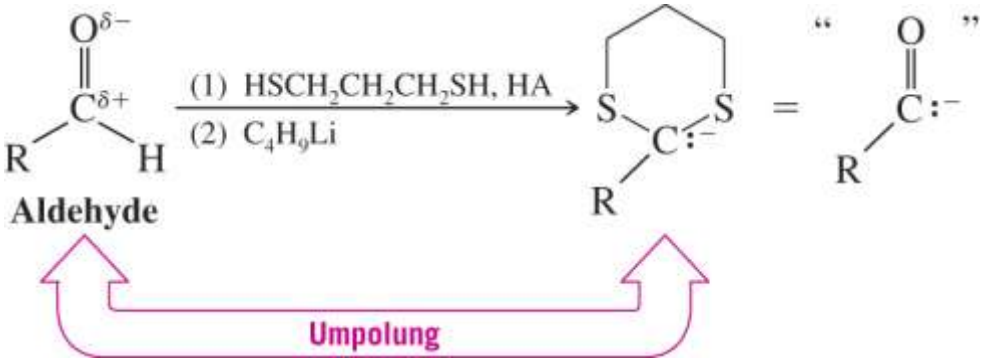
➔ **A dithioacetal anion is the synthetic equivalent of an aldehyde carbonyl anion**

- **An aldehyde can be converted to a ketone by preparing the thioacetal from the aldehyde, alkylating the corresponding 1,3-dithiane anion, and hydrolyzing the thioacetal**



➔ **The reversal of the polarity of the carbonyl carbon in this series of reactions is called *umpulong***

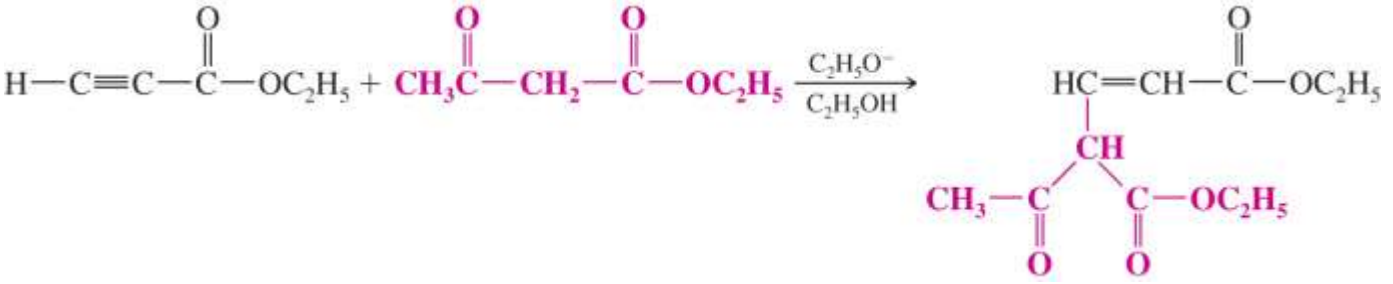
- **An aldehyde carbonyl carbon normally has a δ+ charge and is electrophilic**
- **In dithioacetal alkylation, the equivalent of the aldeyhde carbon is nucleophilic**



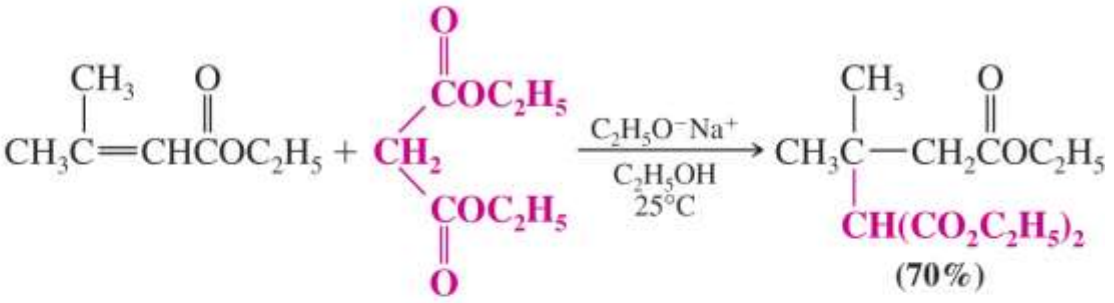
♦ Michael Additions

➔ **A Michael addition involves conjugate addition of the anion derived from an active hydrogen compound *(e.g.*, an enolate) to an α,β-unsaturated carbonyl compound (see next slide)**

➔ **Michael additions take place with a wide variety of α,β-unsaturated compounds**

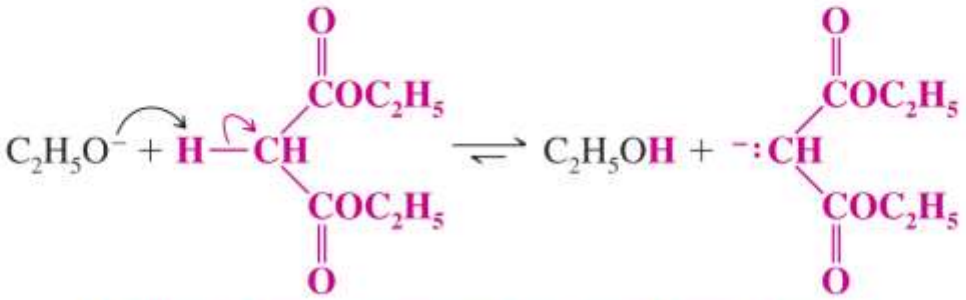


Overall Reaction:



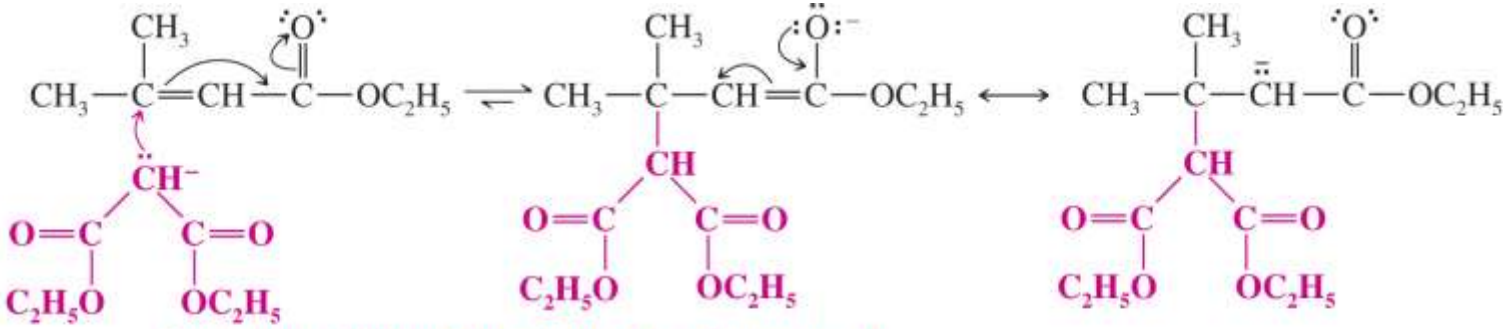
Mechanism:

Step 1



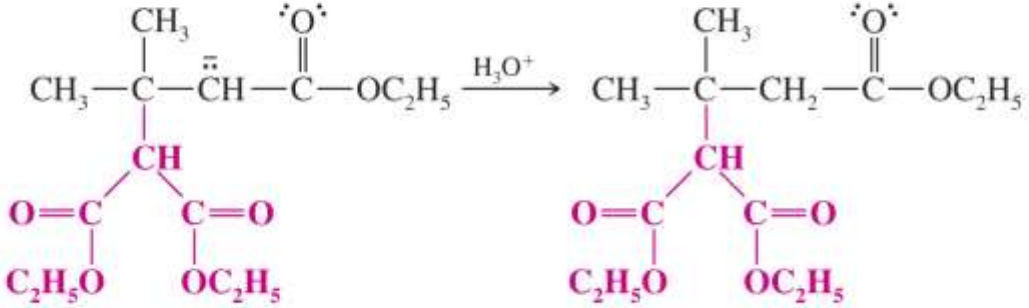
An alkoxide anion removes a proton to form the anion of the active methylene compound.

Step 2



Conjugate addition of the anion to the α,β-unsaturated ester leads to a new enolate anion.

Step 3

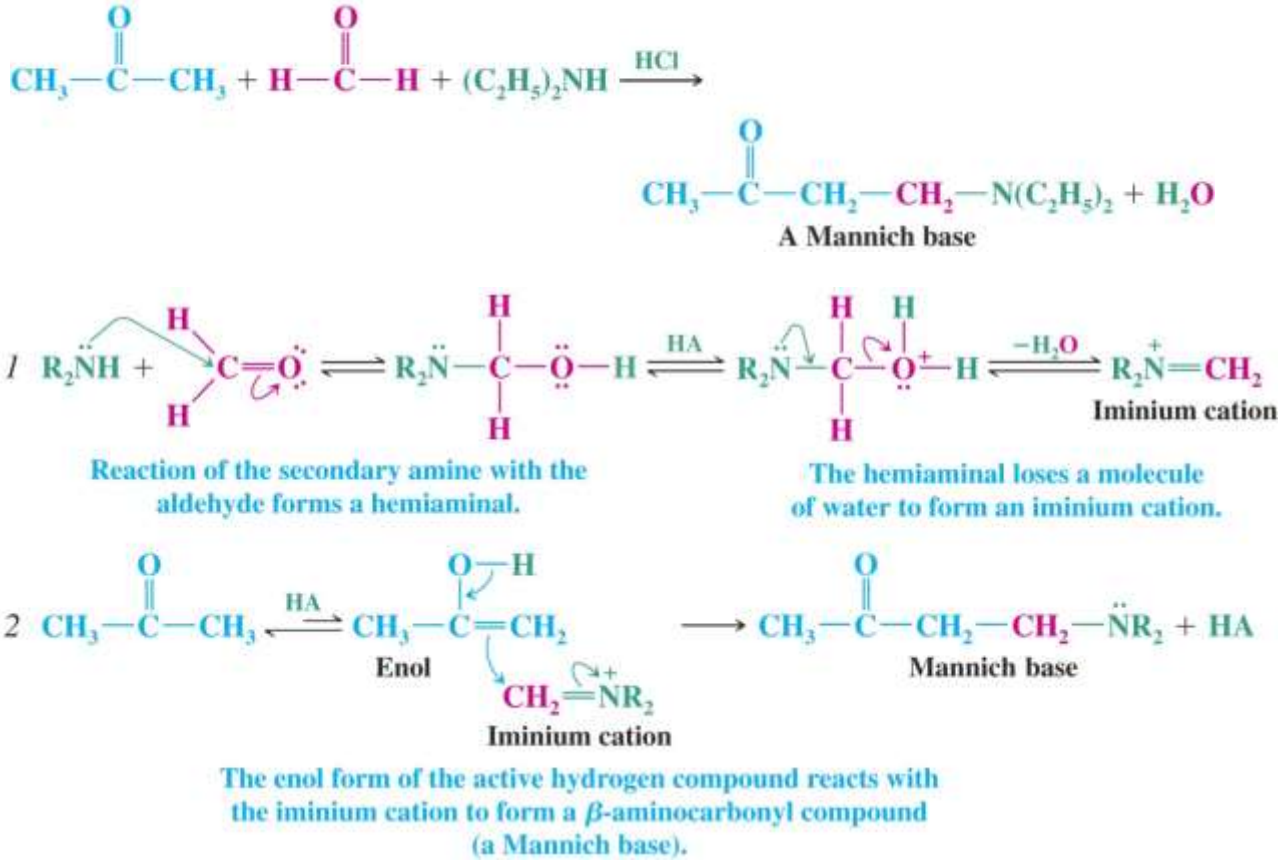


The enolate anion is protonated by an acid during the workup of the reaction.

♦ The Mannich Reaction

➔ **Compounds which can form enols react with imines or iminium ions derived from formaldehyde**

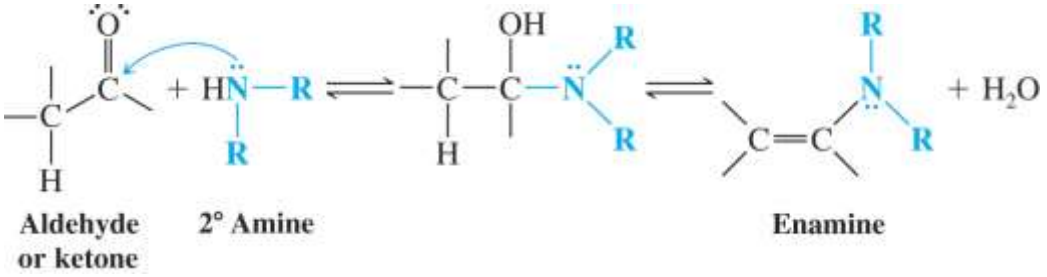
- **Primary or secondary amines can be used to form the corresponding formaldehyde imines or iminium ions**

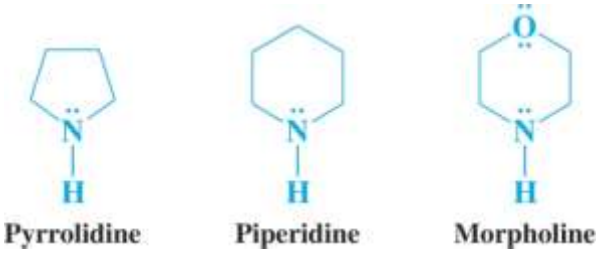


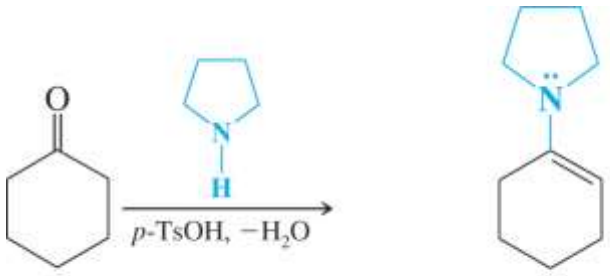
♦ Synthesis of Enamines: Stork Enamine Reactions

➔ **Aldehydes and ketones react with secondary amines to form enamines (see Section 16.8C)**

- **Cyclic amines are often used**
- **The reaction is catalyzed by acid**
- **Removal of water drives enamine formation to completion**



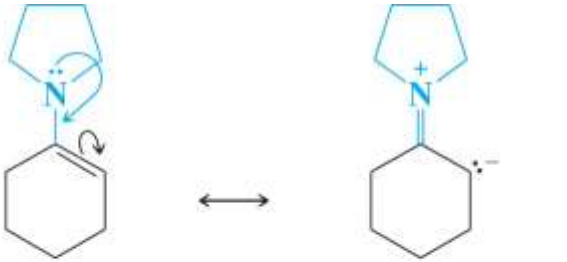




N-(1-Cyclohexenyl)pyrrolidine
(an enamine)

➔**Enamines have a nucleophilic carbon and are the equivalent of ketone and aldehyde enolates**

- **The nitrogen of enamines is also nucleophilic**



Contribution to the hybrid made by this structure confers nucleophilicity on nitrogen.

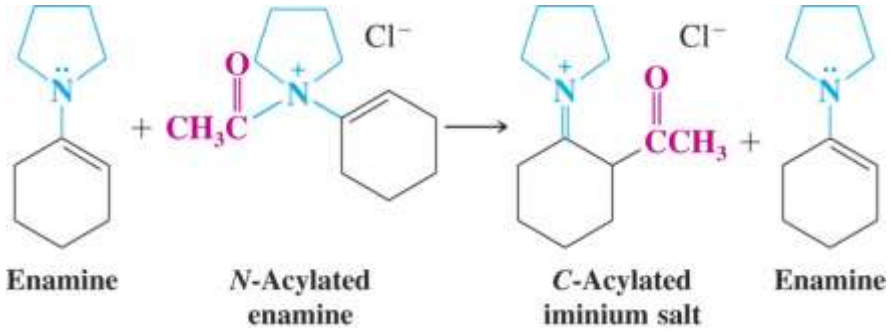
Contribution to the hybrid made by this structure confers nucleophilicity on carbon and decreases nucleophilicity of nitrogen.

➔ **Enamines can be acylated, alkylated, and used in Michael reactions**

- **The iminium intermediate is hydrolyzed when water is added**

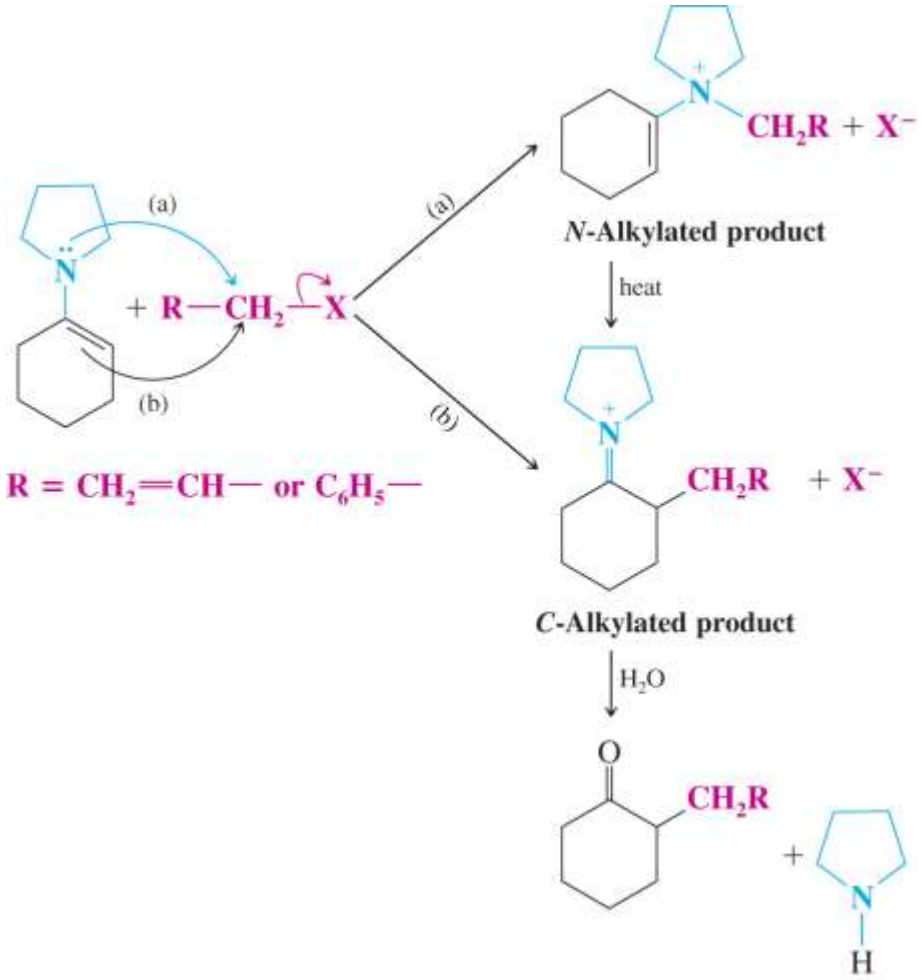
➔ ***C*-Acylation leads to β-diketones**

- ***N*-acylated products can be formed, but they are unstable and act as acylating agents themselves**



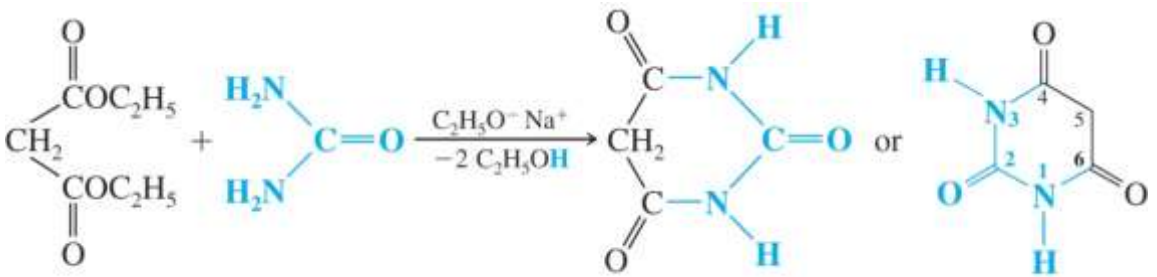
➔ Alkylation of enamines can lead to some *N*-alkylation

- **The *N*-alkylated product can often be converted to the *C*-alkylated product by heating**



♦ Barbiturates

➔ **Reaction of diethyl malonate with urea in the presence of sodium ethoxide produces barbituric acid**



Barbituric acid

➔ **Barbiturates are substituted derivatives of barbituric acid**

- **Barbiturates are used in medicine as soporifics (sleep inducers)**

Veronal
(5,5-diethylbarbituric acid)

Seconal
[5-allyl-5-(1-methylbutyl) barbituric acid]

Phenobarbital
(5-ethyl-5-phenylbarbituric acid)

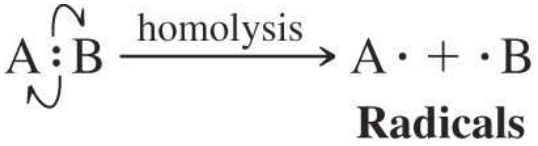
Radical Reactions

♦ Introduction

➔ **Homolytic bond cleavage leads to the formation of radicals (also called free radicals)**

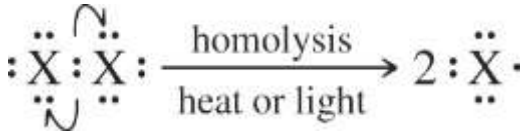
➔ **Radicals are highly reactive, short-lived species**

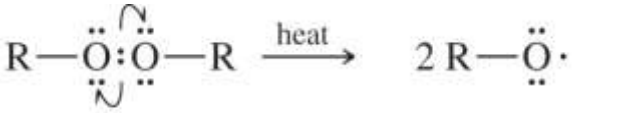
- **Single-barbed arrows are used to show the movement of single electrons**



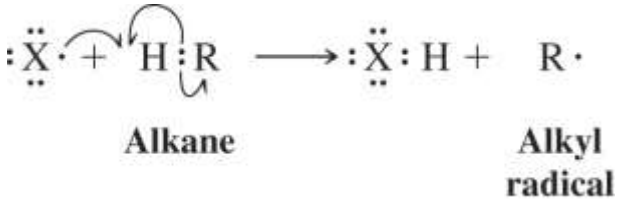
● Production of Radicals

➔ **Homolysis of relatively weak bonds such as O-O or X-X bonds can occur with addition of energy in the form of heat or light**





- **Reactions of Radicals**
  - **➔Radicals tend to react in ways that lead to pairing of their unpaired electron**
    - **Hydrogen abstraction is one way a halogen radical can react to pair its unshared electron**



♦ Homolytic Bond Dissociation Energies

➔ **Atoms have higher energy (are less stable) than the molecules they can form**

- **The formation of covalent bonds is exothermic**

➔ **Breaking covalent bonds requires energy (*i.e.* is endothermic)**

$$H—H \longrightarrow H\cdot + H\cdot \qquad \Delta H° = +436 \text{ kJ mol}^{-1}$$

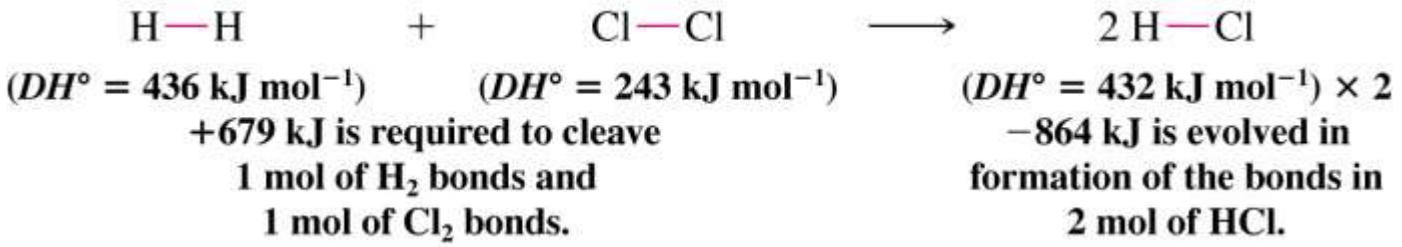
$$Cl—Cl \longrightarrow Cl\cdot + Cl\cdot \qquad \Delta H° = +243 \text{ kJ mol}^{-1}$$

- **The homolytic bond dissociation energy is abbreviated *DH°***

$$H—H \qquad (DH° = 436 \text{ kJ mol}^{-1})$$

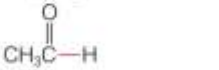
$$Cl—Cl \qquad (DH° = 243 \text{ kJ mol}^{-1})$$

- **Homolytic Bond Dissociation Energies and Heats of Reaction**
  - ➔ **Homolytic Bond Dissociation energies can be used to calculate the enthalpy change (ΔH^o) for a reaction**
  - ➔ **DH^o is positive for bond breaking and negative for bond forming**
  - ➔ **Example**
    - **This reaction below is highly exothermic since ΔH^o is a large and negative**
    - **ΔH^o is not dependant on the mechanism; only the initial and final states of the molecules are considered in determining ΔH^o**



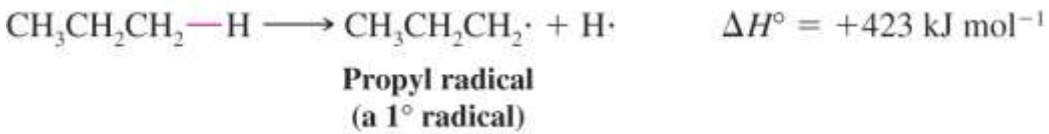
$$\Delta H^\circ = (-864\ \text{kJ} + 679\ \text{kJ}) = -185\ \text{kJ} \quad \text{for 2 mol HCl produced}$$

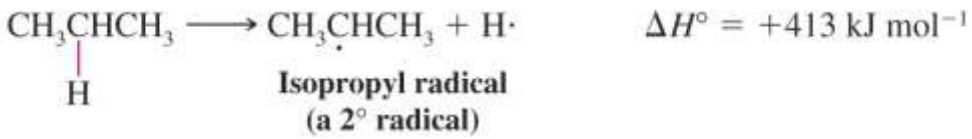
A:B ⟶ A· + B·

Bond Broken (shown in red)	kJ mol^{-1}	Bond Broken (shown in red)	kJ mol^{-1}
H—H	436	$(CH_3)_2CH$—Br	298
D—D	443	$(CH_3)_2CH$—I	222
F—F	159	$(CH_3)_2CH$—OH	402
Cl—Cl	243	$(CH_3)_2CH$—OCH_3	359
Br—Br	193	$(CH_3)_2CHCH_2$—H	422
I—I	151	$(CH_3)_3C$—H	400
H—F	570	$(CH_3)_3C$—Cl	349
H—Cl	432	$(CH_3)_3C$—Br	292
H—Br	366	$(CH_3)_3C$—I	227
H—I	298	$(CH_3)_3C$—OH	400
CH_3—H	440	$(CH_3)_3C$—OCH_3	348
CH_3—F	461	$C_6H_5CH_2$—H	375
CH_3—Cl	352	CH_2=$CHCH_2$—H	369
CH_3—Br	293	CH_2=CH—H	465
CH_3—I	240	C_6H_5—H	474
CH_3—OH	387	HC≡C—H	547
CH_3—OCH_3	348	CH_3—CH_3	378
CH_3CH_2—H	421	CH_3CH_2—CH_3	371
CH_3CH_2—F	444	$CH_3CH_2CH_2$—CH_3	374
CH_3CH_2—Cl	353	CH_3CH_2—CH_2CH_3	343
CH_3CH_2—Br	295	$(CH_3)_2CH$—CH_3	371
CH_3CH_2—I	233	$(CH_3)_3C$—CH_3	363
CH_3CH_2—OH	393	HO—H	499
CH_3CH_2—OCH_3	352	HOO—H	356
$CH_3CH_2CH_2$—H	423	HO—OH	214
$CH_3CH_2CH_2$—F	444	$(CH_3)_3CO$—$OC(CH_3)_3$	157
$CH_3CH_2CH_2$—Cl	354		
$CH_3CH_2CH_2$—Br	294		139
$CH_3CH_2CH_2$—I	176	CH_3CH_2O—OCH_3	184
$CH_3CH_2CH_2$—OH	395	CH_3CH_2O—H	431
$CH_3CH_2CH_2$—OCH_3	355		
$(CH_3)_2CH$—H	413		364
$(CH_3)_2CH$—F	439		
$(CH_3)_2CH$—Cl	355		

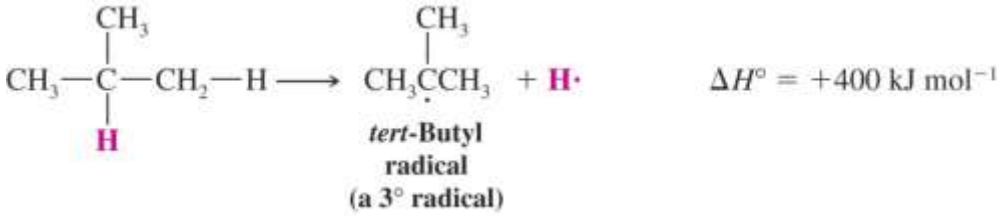
[a]Data compiled from the *National Institute of Standards (NIST) Standard Reference Database Number 69*, July 2001 Release, accessed via *NIST Chemistry WebBook* (http://webbook.nist.gov/chemistry/) and the *CRC Handbook of Chemistry and Physics*, 3rd Electronic Edition (updated from content in the 81st print edition), accessed via Knovel Engineering and Scientific Online References (http://www.knovel.com). $DH°$ values were obtained directly or calculated from heat of formation (H_f) data using the equation $DH°[A—B] = H_f[A\cdot] + H_f[B\cdot] - H_f[A—B]$.

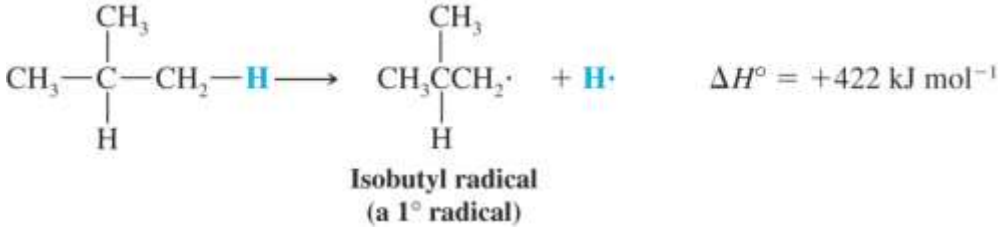
- **Homolytic Bond Dissociation Energies and the Relative Stabilities of Radicals**
  - ➔ **The formation of different radicals from the same starting compound offers a way to estimate relative radical stabilities**
  - ➔ **Examples**
    - **The propyl radical is less stable than the isopropyl radical**



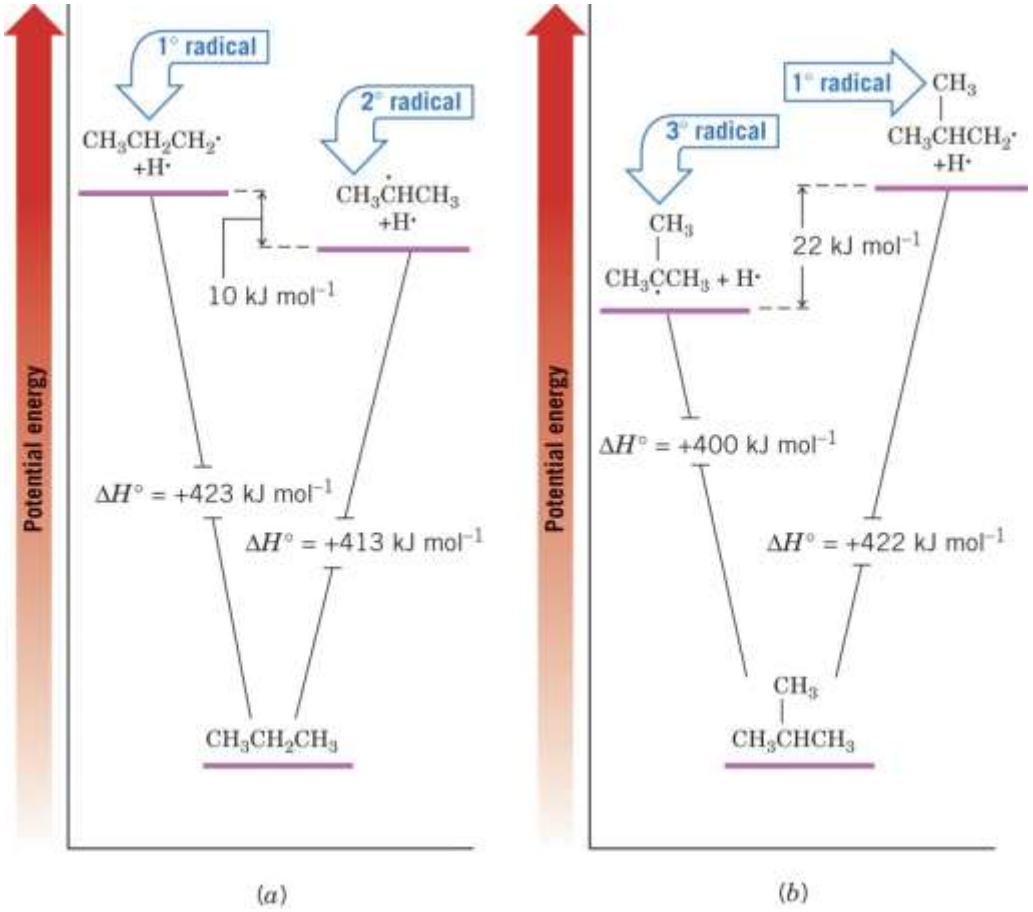


    - **Likewise the *tert*-butyl radical is more stable than the isobutyl radical**





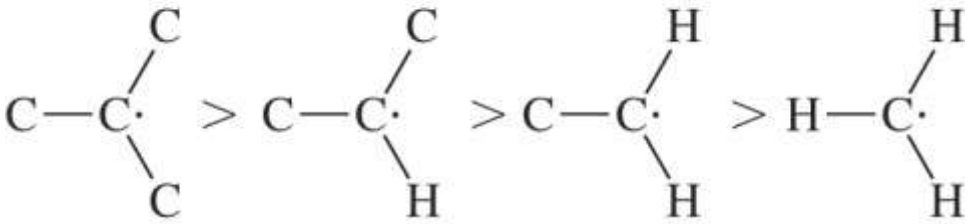
➔**The energy diagrams for these reactions are shown below**



➔ **The relative stabilities of radicals follows the same trend as for carbocations**

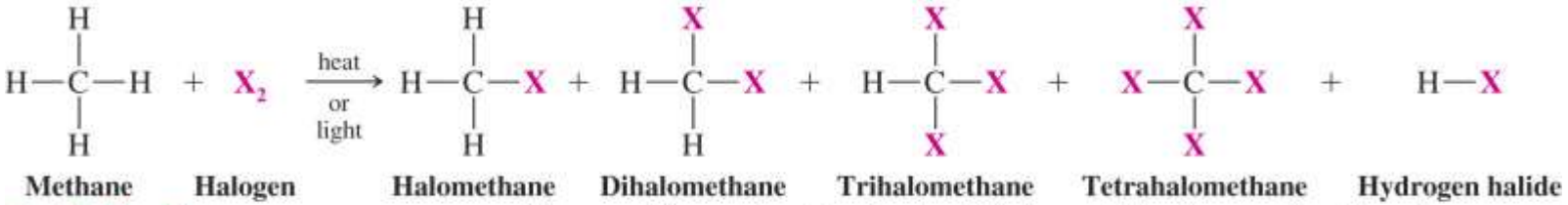
- **The most substituted radical is most stable**
- **Radicals are electron deficient, as are carbocations, and are therefore also stabilized by hyperconjugation**

Tertiary > Secondary > Primary > Methyl



♦ The Reactions of Alkanes with Halogens

➔ **Alkanes undergo substitution reactions with halogens such as fluorine, bromine and chlorine in the presence of heat or light**



- **Multiple Substitution Reactions versus Selectivity**

  ➔ **Radical halogenation can yield a mixture of halogenated compounds because all hydrogen atoms in an alkane are capable of substitution**

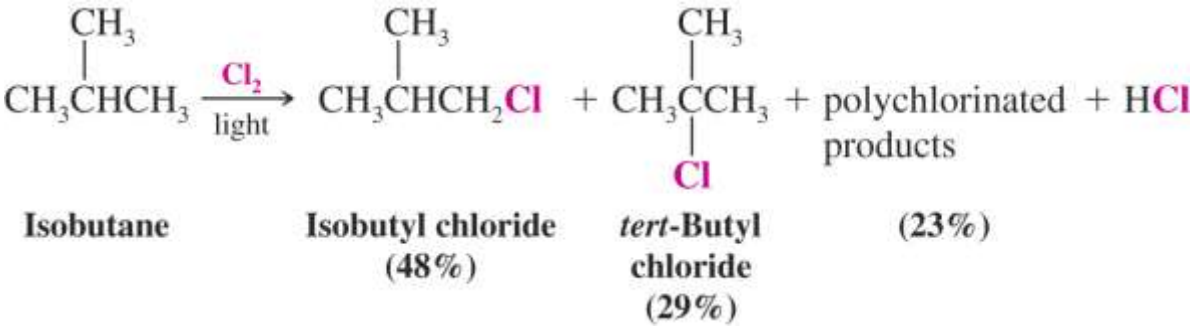
  - **In the reaction above all degrees of methane halogenation will be seen**

  ➔ **Monosubstitution can be achieved by using a large excess of the alkane**

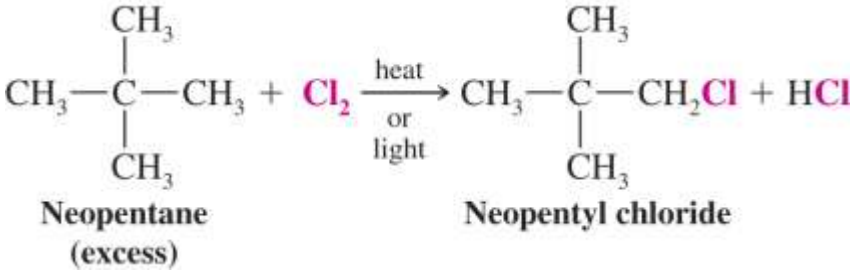
  - **A large excess of methane will lead to predominantly monohalogenated product and excess unreacted methane**

➔ **Chlorination of higher alkanes leads to mixtures of monochlorinated product (and more substituted products)**

- **Chlorine is relatively unselective and does not greatly distinguish between type of hydrogen**



➔ **Molecular symmetry is important in determining the number of possible substitution products**



➔ **Bromine is less reactive but more selective than chlorine (Sec. 10.6A)**

♦ Chlorination of Methane: Mechanism of Reaction

➔ **The reaction mechanism has three distinct aspects: Chain initiation, chain propagation and chain termination**

➔ **Chain initiation**

- **Chlorine radicals form when the reaction is subjected to heat or light**
- **Chlorine radicals are used in the chain propagation steps below**

Chain Initiation

$$\textit{Step 1}\quad Cl_2 \xrightarrow[\text{or light}]{\text{heat}} 2\,Cl\cdot$$

Chain Propagation

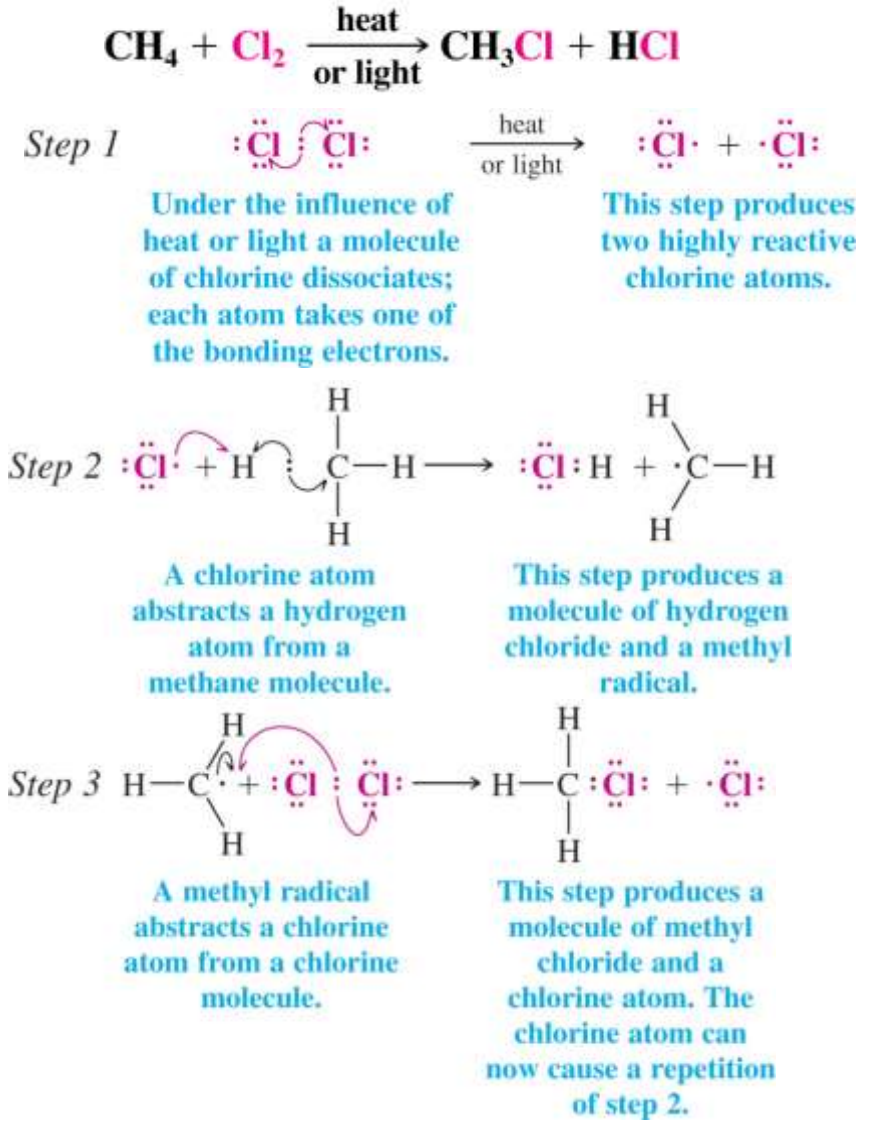
$$\textit{Step 2}\quad CH_4 + Cl\cdot \longrightarrow CH_3\cdot + H{-}Cl$$

$$\textit{Step 3}\quad CH_3\cdot + Cl_2 \longrightarrow CH_3Cl + Cl\cdot$$

➔ **Chain propagation**

- **A chlorine radical reacts with a molecule of methane to generate a methyl radical**
- **A methyl radical reacts with a molecule of chlorine to yield chloromethane and regenerate chlorine radical**
- **A chlorine radical reacts with another methane molecule, continuing the chain reaction**
- **A single chlorine radical can lead to thousands of chain propagation cycles**

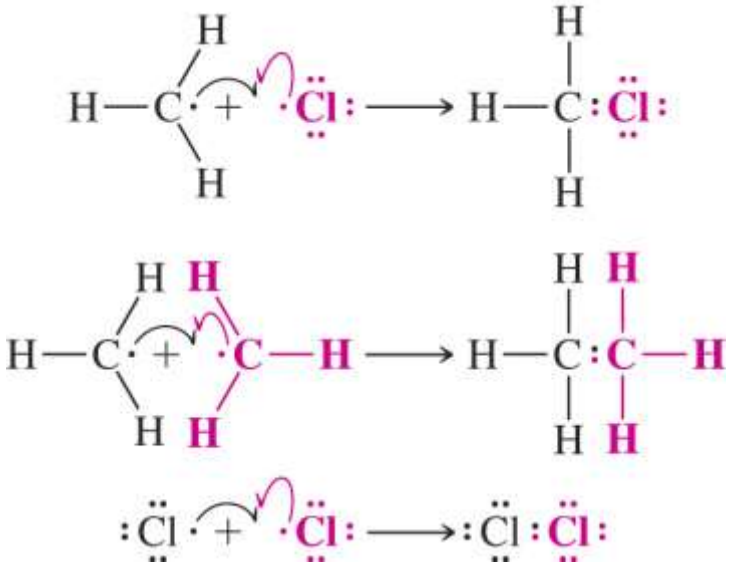
➔**The entire mechanism is shown below**



➔ **Chain reaction: a stepwise mechanism in which each step generates the reactive intermediate that causes the next cycle of the reaction to occur**

➔ **Chain termination**

- **Occasionally the reactive radical intermediates are quenched by reaction pathways that do not generate new radicals**
- **The reaction of chlorine with methane requires constant irradiation to replace radicals quenched in chain-terminating steps**



♦ Chlorination of Methane: Energy Changes

Chain Initiation

Step 1 $\mathrm{Cl{-}Cl \longrightarrow 2\,Cl\cdot}$ $\Delta H^\circ = +243\ \mathrm{kJ\ mol^{-1}}$

(*DH*° = 243)

Chain Propagation

Step 2 $\mathrm{CH_3{-}H + Cl\cdot \longrightarrow CH_3\cdot + H{-}Cl}$ $\Delta H^\circ = +8\ \mathrm{kJ\ mol^{-1}}$

(*DH*° = 440) **(*DH*° = 432)**

Step 3 $\mathrm{CH_3\cdot + Cl{-}Cl \longrightarrow CH_3{-}Cl + Cl\cdot}$ $\Delta H^\circ = -109\ \mathrm{kJ\ mol^{-1}}$

(*DH*° = 243) **(*DH*° = 352)**

Chain Termination

$\mathrm{CH_3\cdot + Cl\cdot \longrightarrow CH_3{-}Cl}$ $\Delta H^\circ = -352\ \mathrm{kJ\ mol^{-1}}$

(*DH*° = 352)

$\mathrm{CH_3\cdot + \cdot CH_3 \longrightarrow CH_3{-}CH_3}$ $\Delta H^\circ = -378\ \mathrm{kJ\ mol^{-1}}$

(*DH*° = 378)

$\mathrm{Cl\cdot + Cl\cdot \longrightarrow Cl{-}Cl}$ $\Delta H^\circ = -243\ \mathrm{kJ\ mol^{-1}}$

(*DH*° = 243)

➔ **The chain propagation steps have overall ΔH^o= -101 kJ mol^{-1} and are highly exothermic**

$\mathrm{Cl\cdot + CH_3{-}H \longrightarrow CH_3\cdot + H{-}Cl}$ $\Delta H^\circ = +8\ \mathrm{kJ\ mol^{-1}}$

$\mathrm{CH_3\cdot + Cl{-}Cl \longrightarrow CH_3{-}Cl + Cl\cdot}$ $\Delta H^\circ = -109\ \mathrm{kJ\ mol^{-1}}$

$\mathrm{CH_3{-}H + Cl{-}Cl \longrightarrow CH_3{-}Cl + H{-}Cl}$ $\Delta H^\circ = -101\ \mathrm{kJ\ mol^{-1}}$

- **The Overall Free-Energy Change: $\Delta G^o = \Delta H^o - T(\Delta S^o)$**
  - ➔ **In radical reactions such as the chlorination of methane the overall entropy change (ΔS^o) in the reaction is small and thus it is appropriate to use ΔH^o values to approximate ΔG^o values**
    - **ΔG^o = -102 kJ mol^{-1} and ΔH^o = -101 kJ mol^{-1} for this reaction**
- **Activation Energies**
  - ➔ **When using enthalpy values (ΔH^o) the term for the difference in energy between starting material and the transition state is the energy of activation (E_{act})**
    - **Recall when free energy of activation (ΔG^o) values are used this difference is $\Delta G^{\ddagger}$**
  - ➔ **For the chlorination of methane the E_{act} values have been calculated**

Chain Initiation

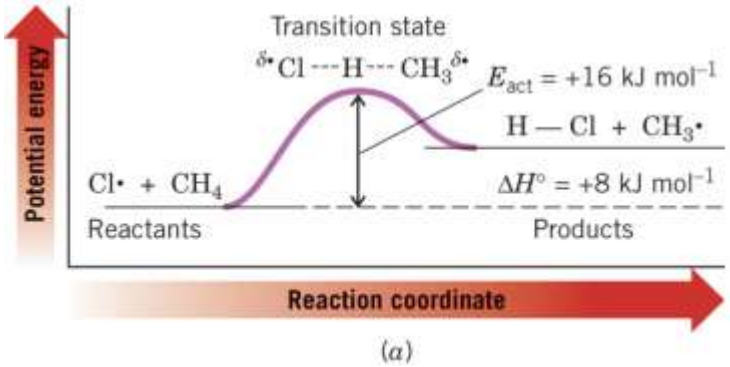
Step 1 $Cl_2 \longrightarrow 2\ Cl\cdot$ $\qquad E_{act} = +243\ kJ\ mol^{-1}$

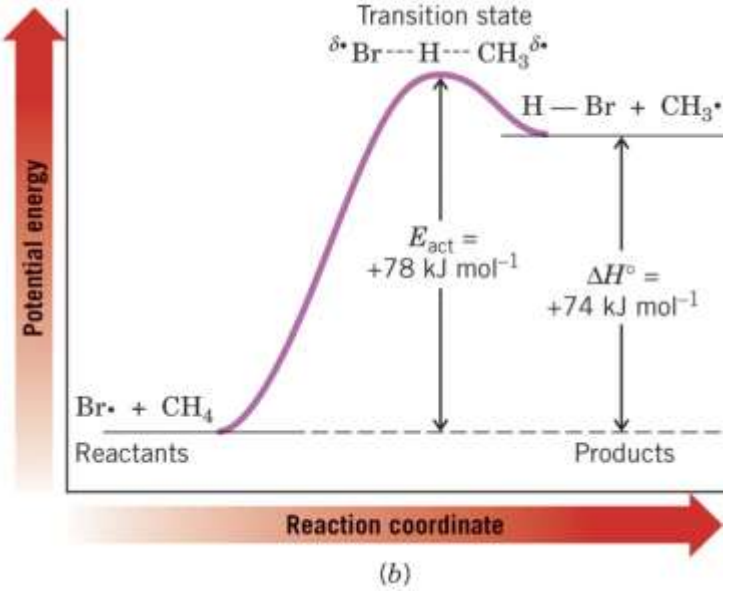
Chain Propagation

Step 2 $Cl\cdot + CH_4 \longrightarrow HCl + CH_3\cdot$ $\qquad E_{act} = +16\ kJ\ mol^{-1}$

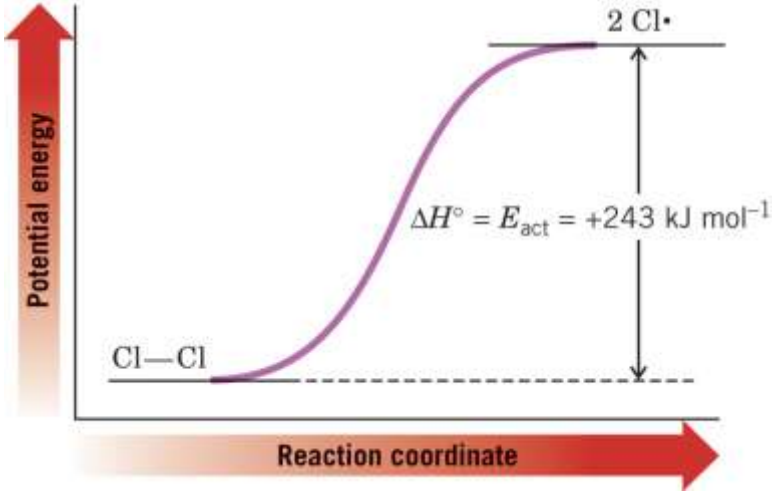
Step 3 $CH_3\cdot + Cl_2 \longrightarrow CH_3Cl + Cl\cdot$ $\qquad E_{act} = \sim 8\ kJ\ mol^{-1}$

- **Energy of activation values can be predicted**
  - ➔ **A reaction in which bonds are broken will have $E_{act} > 0$ even if a stronger bond is formed and the reaction is highly exothermic**
    - **Bond forming always lags behind bond breaking**
  - ➔ **An endothermic reaction which involves bond breaking and bond forming will always have $E_{act} > \Delta H^o$**

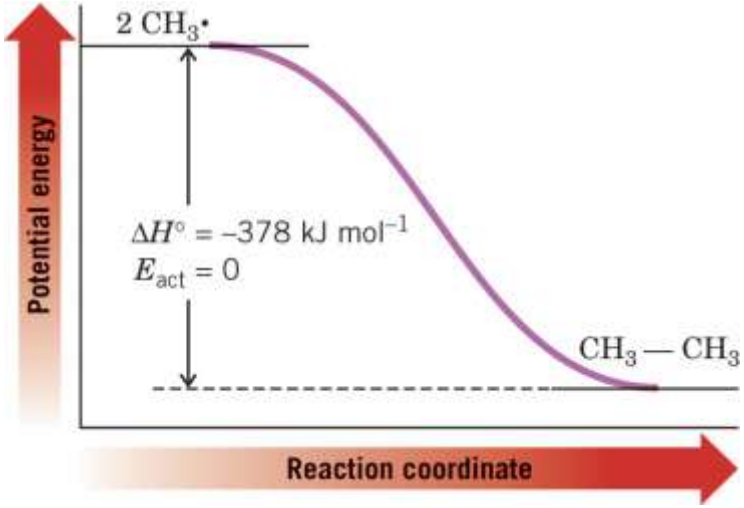




➔ **A gas phase reaction in which only bond homolysis occurs has $\Delta H^o = E_{act}$**



➔ **A gas phase reaction in which small radicals combine to form a new bond usually has $E_{act} = 0$**



- **Reaction of Methane with Other Halogens**
  - ➔ **The order of reactivity of methane substitution with halogens is: fluorine > chlorine > bromine > iodine**
  - ➔ **The order of reactivity is based on the values of E_{act} for the first step of chain propagation and ΔH^o for the entire chain propagation**
    - **Fluorination has a very low value for E_{act} in the first step and ΔH^o is extremely exothermic therefore fluorination reactions are explosive**
    - **Chlorination and bromination have increasingly higher values of E_{act} and lower overall ΔH^o values which makes these halogenation reactions less vigorous**
    - **Iodinination has a prohibitively high value for E_{act} of the first step and the reaction does not occur**
  - ➔ **The energy values of the initiation step are unimportant since they occur so rarely**
    - **On the basis of ΔH^o values for the initiation step iodination should be most rapid**

FLUORINATION

	$\Delta H°$ (kJ mol^{-1})	E_{act} (kJ mol^{-1})
Chain Initiation		
$F_2 \longrightarrow 2\ F\cdot$	+159	+159
Chain Propagation		
$F\cdot + CH_4 \longrightarrow HF + CH_3\cdot$	−130	+5.0
$CH_3\cdot + F_2 \longrightarrow CH_3F + F\cdot$	−302	Small
Overall $\Delta H°$ =	−432	

CHLORINATION

	$\Delta H°$ (kJ mol^{-1})	E_{act} (kJ mol^{-1})
Chain Initiation		
$Cl_2 \longrightarrow 2\ Cl\cdot$	+243	+243
Chain Propagation		
$Cl\cdot + CH_4 \longrightarrow HCl + CH_3\cdot$	+8	+16
$CH_3\cdot + Cl_2 \longrightarrow CH_3Cl + Cl\cdot$	−109	Small
Overall $\Delta H° = -101$		

BROMINATION

	$\Delta H°$ (kJ mol^{-1})	E_{act} (kJ mol^{-1})
Chain Initiation		
$Br_2 \longrightarrow 2\ Br\cdot$	+193	+193
Chain Propagation		
$Br\cdot + CH_4 \longrightarrow HBr + CH_3\cdot$	+74	+78
$CH_3\cdot + Br_2 \longrightarrow CH_3Br + Br\cdot$	−100	Small
Overall $\Delta H° = -26$		

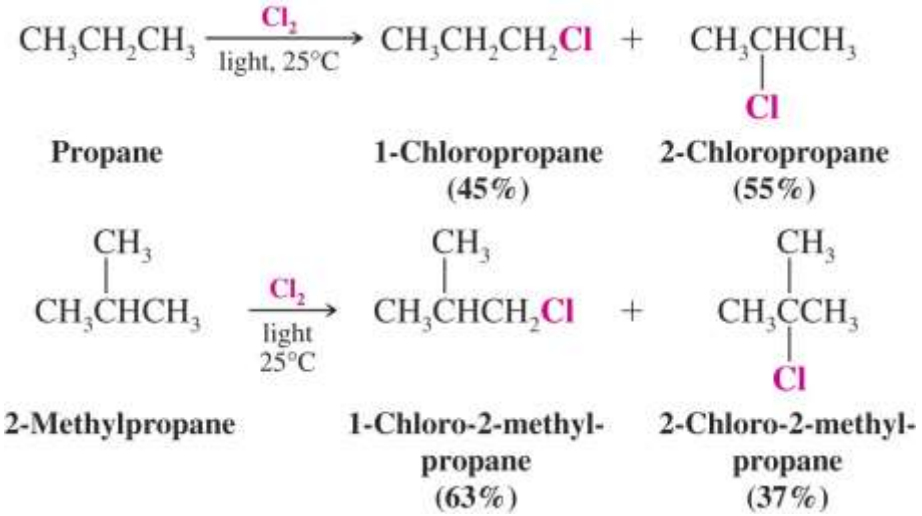
IODINATION

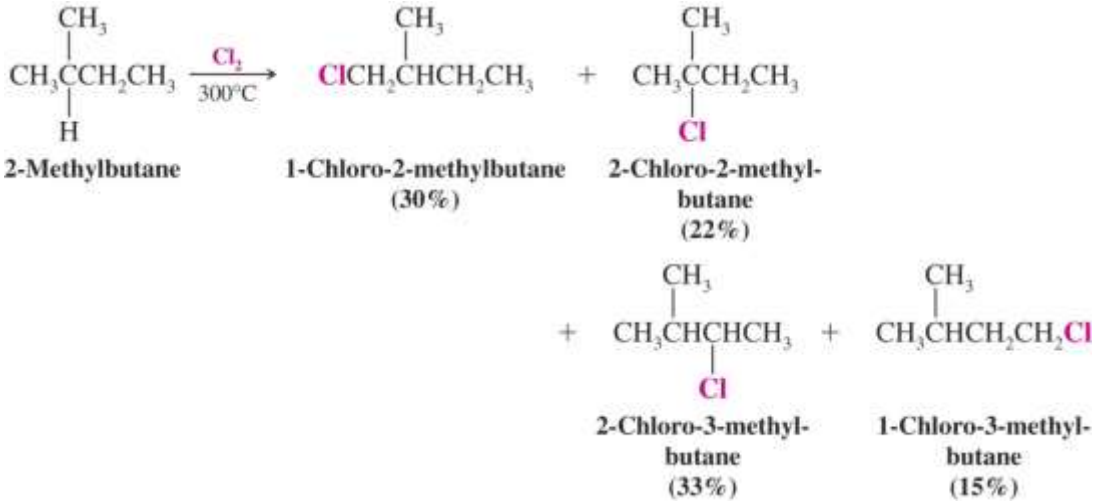
	$\Delta H°$ (kJ mol^{-1})	E_{act} (kJ mol^{-1})
Chain Initiation		
$I_2 \longrightarrow 2\ I\cdot$	+151	+151
Chain Propagation		
$I\cdot + CH_4 \longrightarrow HI + CH_3\cdot$	+142	+140
$CH_3\cdot + I_2 \longrightarrow CH_3I + I\cdot$	−89	Small
Overall $\Delta H° = +53$		

♦ Halogenation of Higher Alkanes

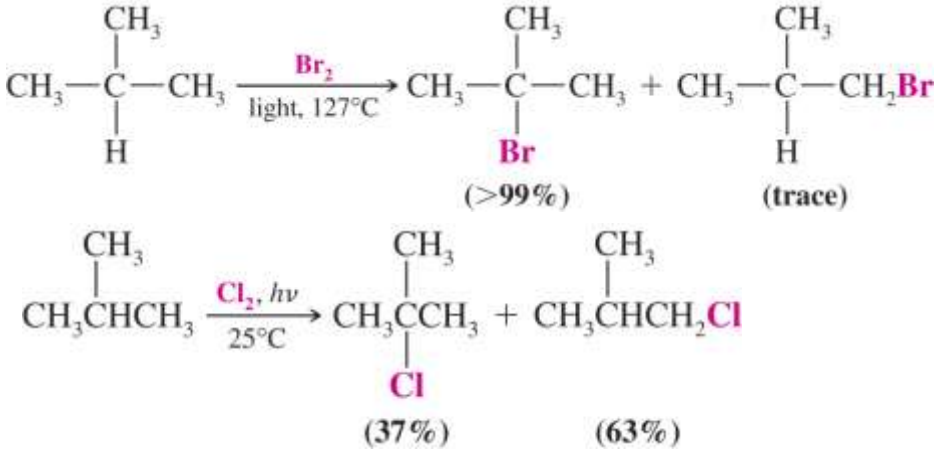
➔Monochlorination of alkanes proceeds to give some selectivity

- Teritiary hydrogens are somewhat more reactive than secondary hydrogens which are more reactive than primary hydrogens
- E_{act} for abstraction of a tertiary hydrogen is lower because of increased stability of the intermediate tertiary radical
- The differences in rate of abstraction are not large and chlorination occurs so rapidly it cannot distinguish well between classes of hydrogen and so is not very selective



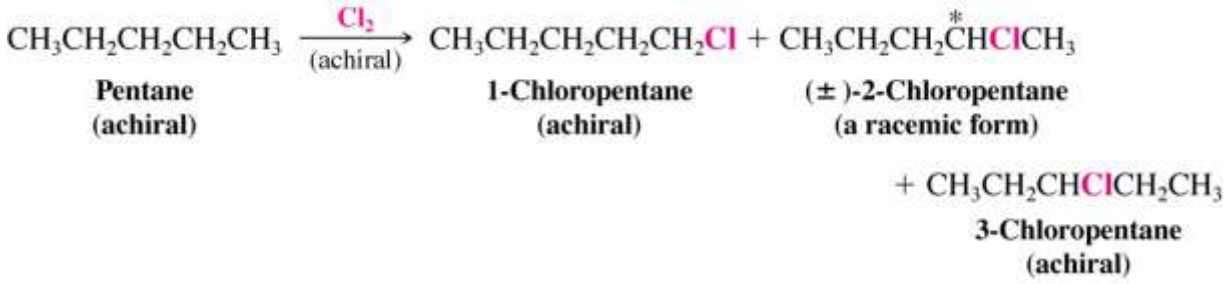


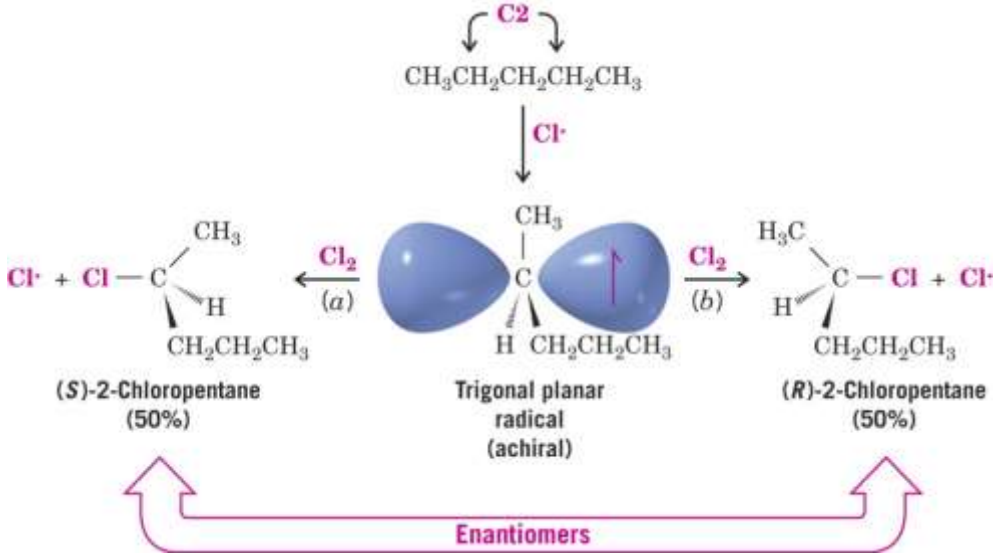
- **Selectivity of Bromine**
  - **➔Bromine is much less reactive but more selective than chlorine in radical halogenation**
    - **Fluorine shows almost no discrimination in replacement of hydrogens because it is so reactive**



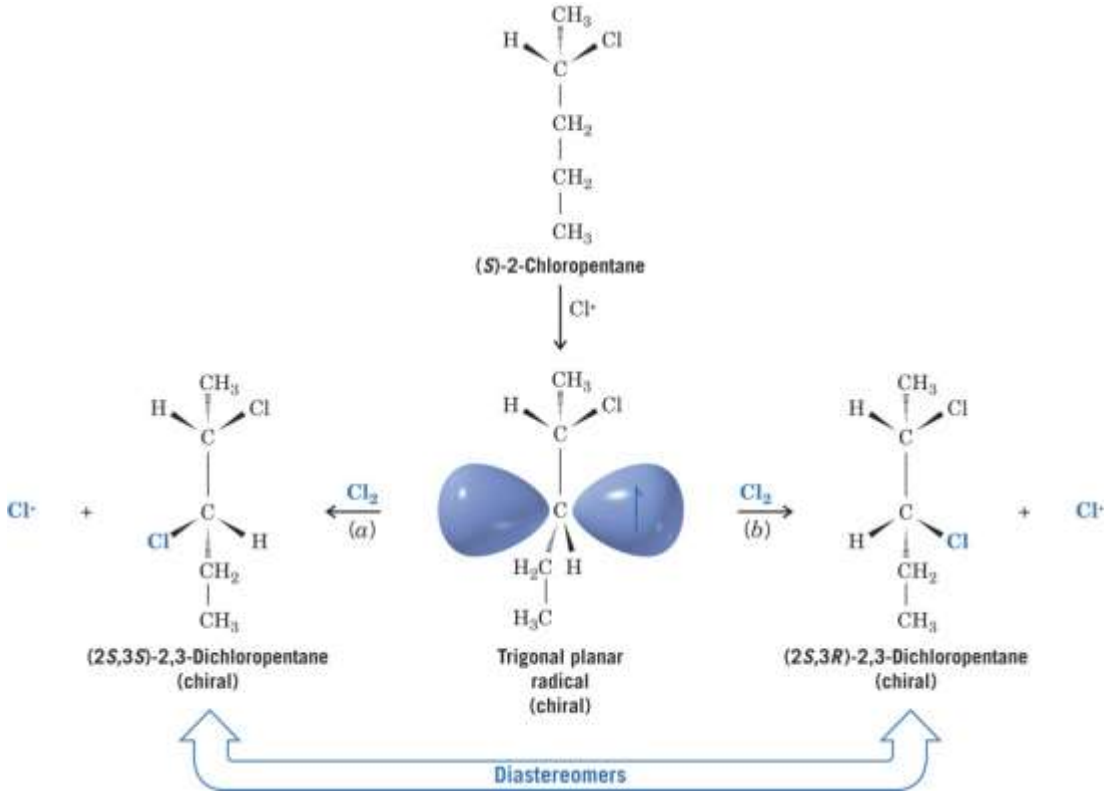
♦ Reactions that Generate Tetrahedral Stereogenic Carbons

➔ **A reaction of achiral starting materials which produces a product with a stereogenic carbon will produce a racemic mixture**





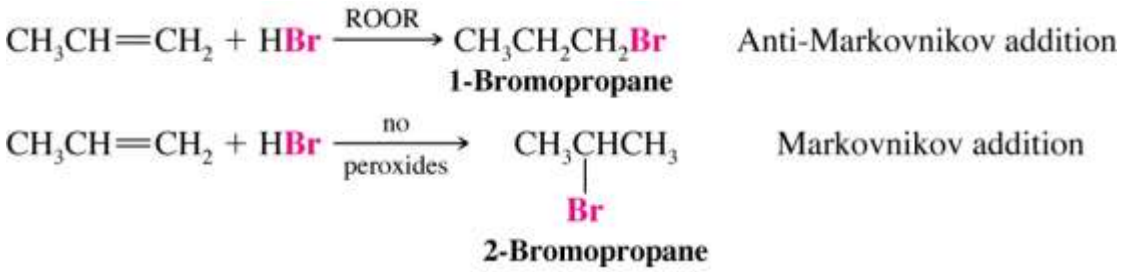
- **Generation of a Second Stereogenic Carbon in a Radical Halogenation**
  - ➔**When a molecule with one or more stereogenic carbons undergoes halogenation to create another stereogenic carbon, the two diastereomeric products are not produced in equal amounts**
    - **The intermediate radical is chiral and and reactions on the two faces of the radical are not equally likely**



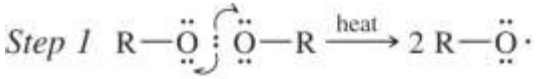
♦ Radical Addition to Alkenes: The anti-Markovnikov Addition of Hydrogen Bromide

➔ **Addition of hydrogen bromide in the presence of peroxides gives anti-Markovnikov addition**

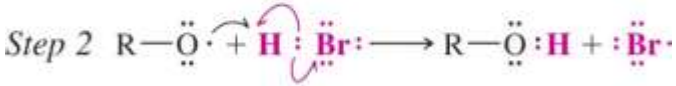
- **The other hydrogen halides do not give this type of anti-Markovnikov addition**



➔ **Steps 1 and 2 of the mechanism are chain initiation steps which produce a bromine radical**



Heat brings about homolytic cleavage of the weak oxygen–oxygen bond.



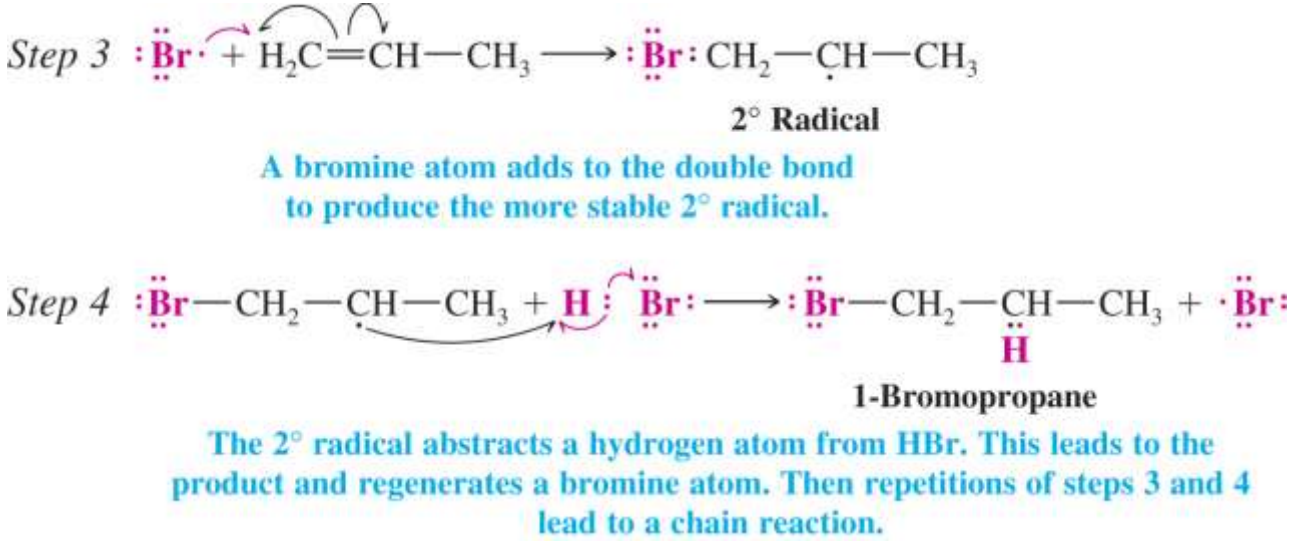
The alkoxyl radical abstracts a hydrogen atom from HBr, producing a bromine atom.

➔ **In step 3, the first step of propagation, a bromine radical adds to the double bond to give the most stable of the two possible carbon radicals (in this case, a 2° radical)**

- **Attack at the 1° carbon is also less sterically hindered**

➔ **Step 4 regenerates a bromine radical**

- **Bromine radical reacts with another equivalent of alkene**



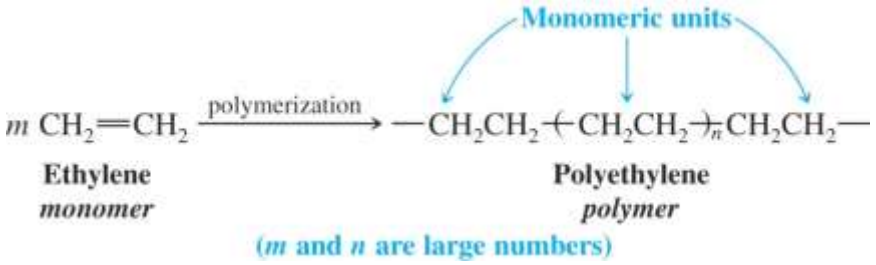
♦ Radical Polymerization of Alkenes: Chain-Growth Polymers

➔ **Polymers are macromolecules made up of repeating subunits**

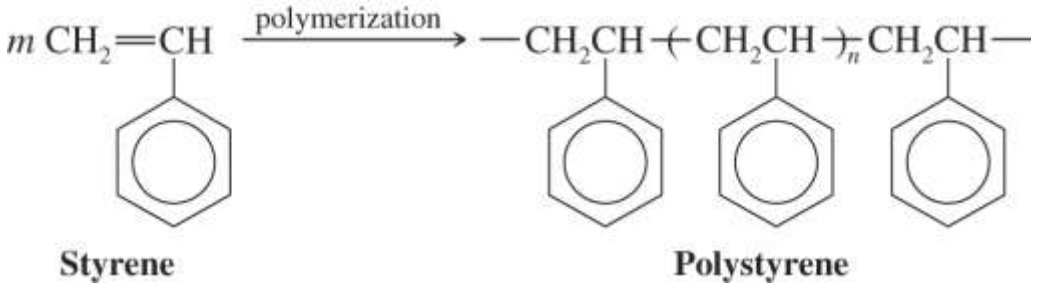
- **The subunits used to synthesize polymers are called monomers**

➔ **Polyethylene is made of repeating subunits derived from ethylene**

- **Polyethylene is called a chain-growth polymer or addition polymer**

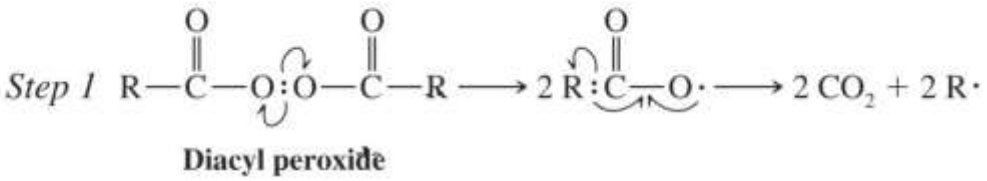


➔ **Polystyrene is made in an analogous reaction using styrene as the monomer**



➔ **A very small amount of diacyl peroxide is added in initiating the reaction so that few but very long polymer chains are obtained**

Chain Initiation



The diacyl peroxide dissociates and releases carbon dioxide gas. Alkyl radicals are produced, which in turn initiate chains.

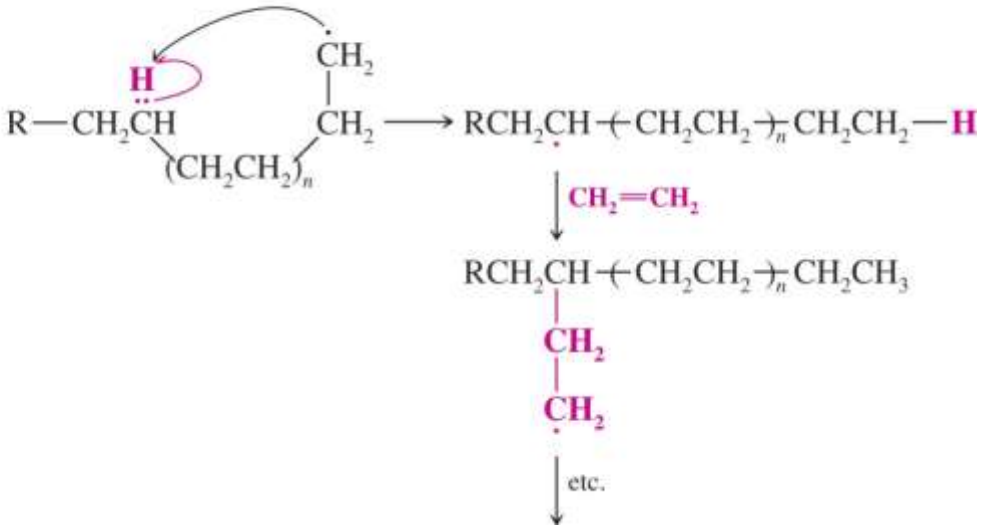
➔ **The propagation step simply adds more ethylene molecules to a growing chain**

Chain Propagation

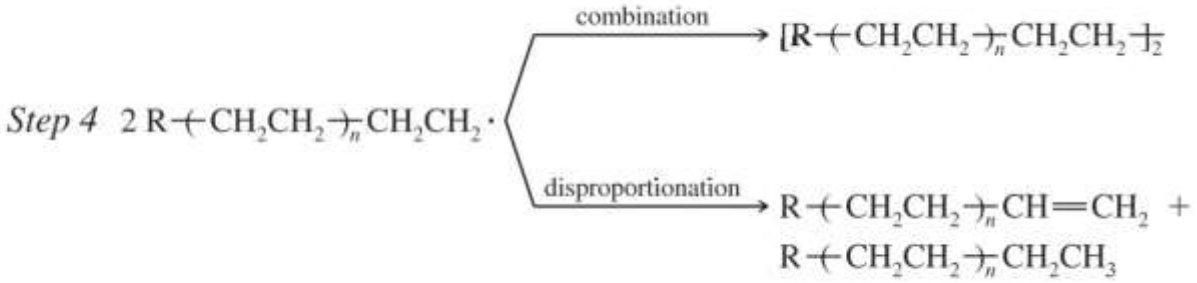
Chains propagate by adding successive ethylene units, until their growth is stopped by combination or disproportionation.

➔**Chain branching occurs by abstraction of a hydrogen atom on the same chain and continuation of growth from the main chain**

Chain Branching



Chain Termination



The radical at the end of the growing polymer chain can also abstract a hydrogen atom from itself by what is called "back biting." This leads to chain branching.

Monomer	Polymer	Names
$CH_2{=}CHCH_3$	$+CH_2-CH(CH_3)+_n$	Polypropylene
$CH_2{=}CHCl$	$+CH_2-CH(Cl)+_n$	Poly(vinyl chloride), PVC
$CH_2{=}CHCN$	$+CH_2-CH(CN)+_n$	Polyacrylonitrile, Orlon
$CF_2{=}CF_2$	$+CF_2-CF_2+_n$	Polytetrafluoroethene, Teflon
$CH_2{=}C(CH_3)CO_2CH_3$	$+CH_2-C(CH_3)(CO_2CH_3)+_n$	Poly(methyl methacrylate), Lucite, Plexiglas, Perspex

South Valley University

Faculty of Science

Chemistry Department

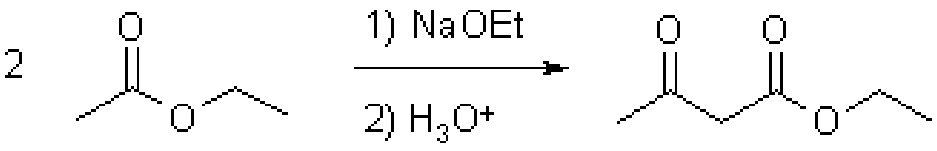
Named Reactions

By

Staff Members of Organic Chemistry

Acetoacetic-Ester Condensation

Claisen Condensation



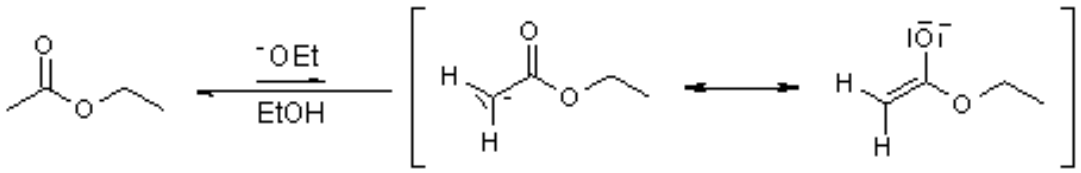
The Claisen condensation between esters containing α-hydrogens, promoted by a base such as sodium ethoxide, affords β-ketoesters. The driving force is the formation of the stabilized anion of the β-keto ester. If two different esters are used, an essentially statistical mixture of all four products is generally obtained, and the preparation does not have high synthetic utility.

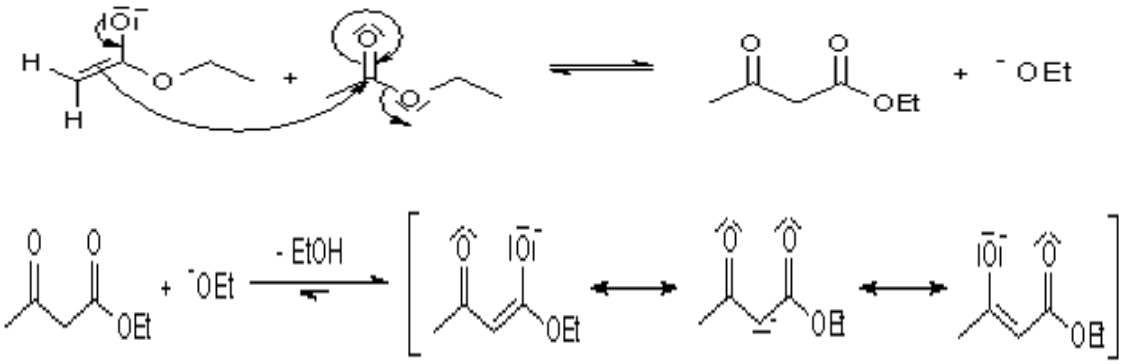
However, if one of the ester partners has enolizable α-hydrogens and the other does not (e.g., aromatic esters or carbonates), the mixed reaction (or crossed Claisen) can be synthetically useful. If ketones or nitriles are used as the donor in this condensation reaction, a β-diketone or a β-ketonitrile is obtained, respectively.

The use of stronger bases, e.g. sodium amide or sodium hydride instead of sodium ethoxide, often increases the yield.

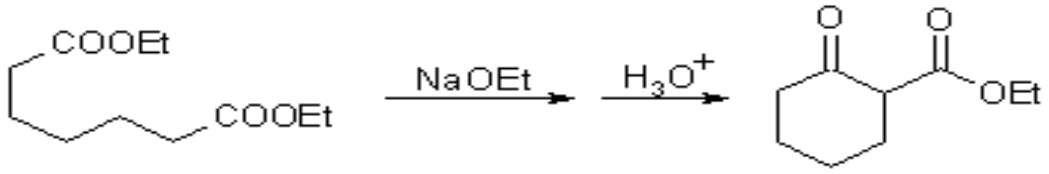
The intramolecular version is known as Dieckmann Condensation.

Mechanism of the Claisen Condensation





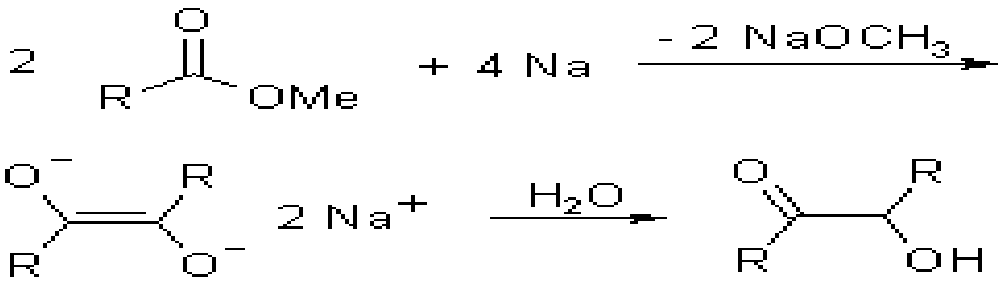
Dieckmann Condensation



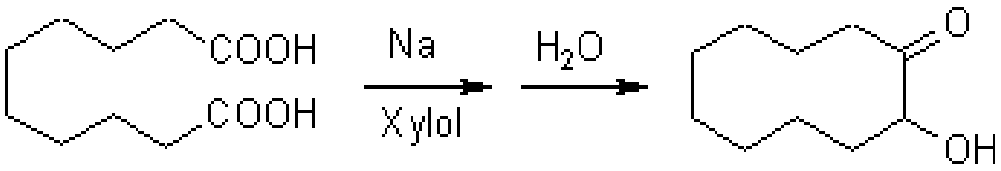
The base-catalyzed intramolecular condensation of a diester. The Dieckmann Condensation works well to produce 5- or 6-membered cyclic ß-keto esters, and is usually effected with sodium alkoxide in alcoholic solvent.

The yields are good if the product has an enolizable proton; otherwise, the reverse reaction (cleavage with ring scission) can compete

Acyloin Condensation



The bimolecular reductive coupling of carboxylic esters by reaction with metallic sodium in an inert solvent under reflux gives an α-hydroxyketone, which is known as an acyloin. This reaction is favoured when R is an alkyl. With longer alkyl chains, higher boiling solvents can be used. The intramolecular version of this reaction has been used extensively to close rings of different sizes, e.g. paracyclophanes or catenanes.

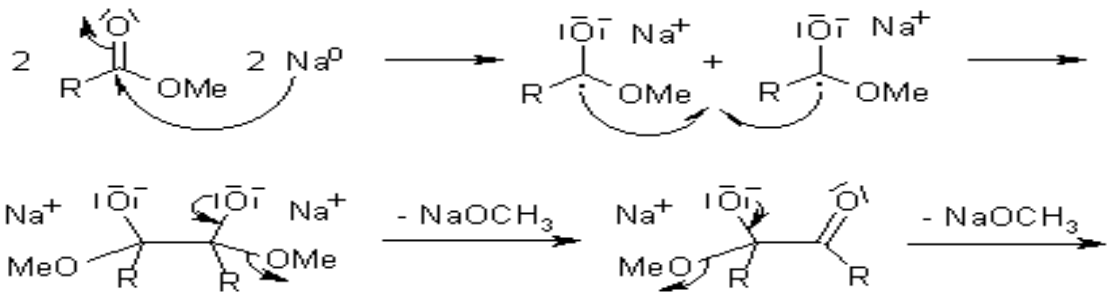


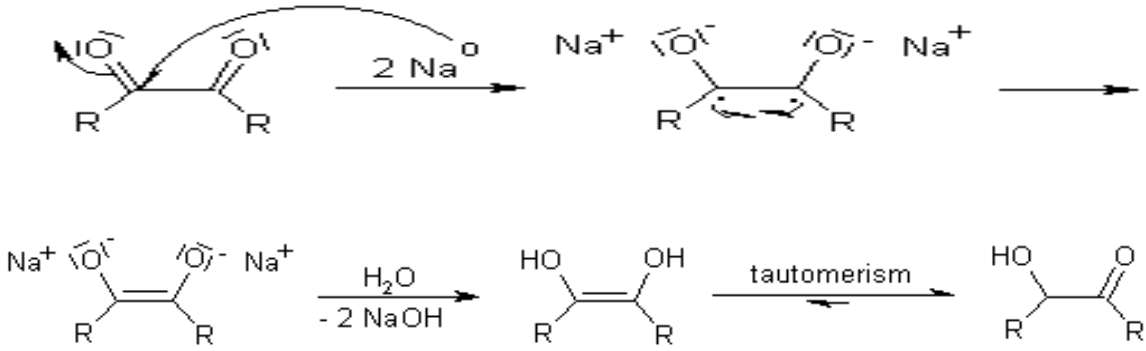
If the reaction is carried out in the presence of a proton donor, such as alcohol, simple reduction of the ester to the alcohol takes place (Bouveault-Blanc Reduction).

The Benzoin Condensation produces similar products, although with aromatic substituents and under different conditions.

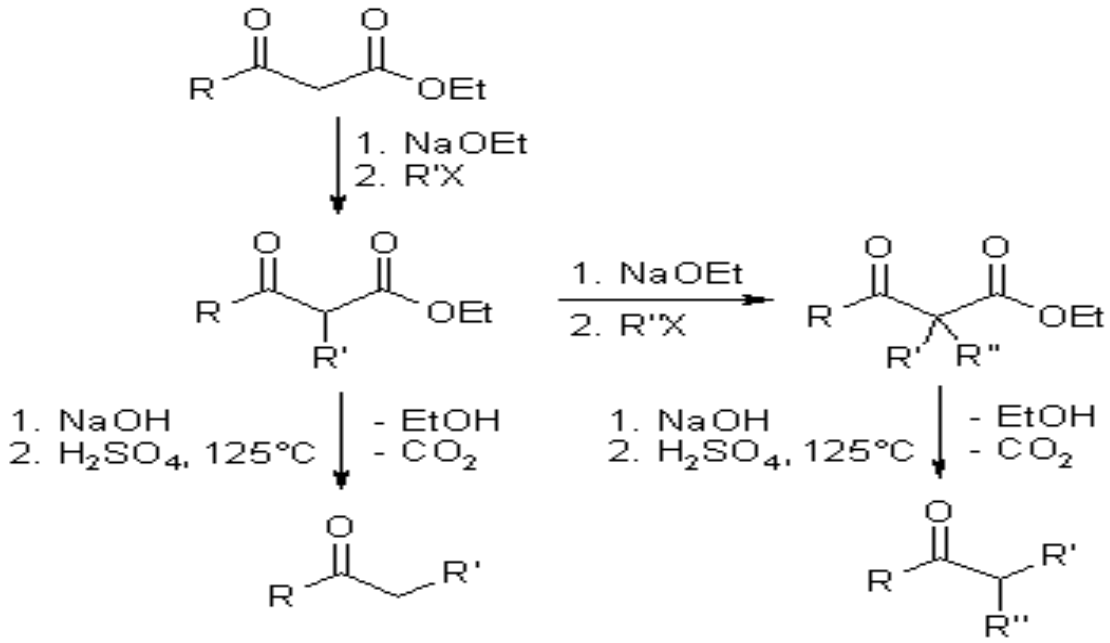
When the acyloin condensation is carried out in the presence of chloro-trimethylsilane, the enediolate intermediate is trapped as the bis-silyl derivative. This can be isolated and subsequently is hydrolysed under acidic condition to the acyloin, which gives a better overall yield.

Mechanism of Acyloin Condensation



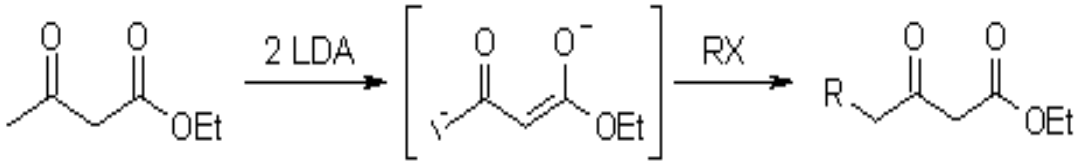


Acetoacetic Ester Synthesis



When α-keto acetic acid is treated with one mole of a base, the methylene group which is more acidic reacts with the base. And the reaction with an alkylation reagent gives alkyl products attached to methylene. When this reaction is repeated in the next step, the other hydrogen can also react to a dialkyl product. The two alkylation agents may be the same or different (R',R'').

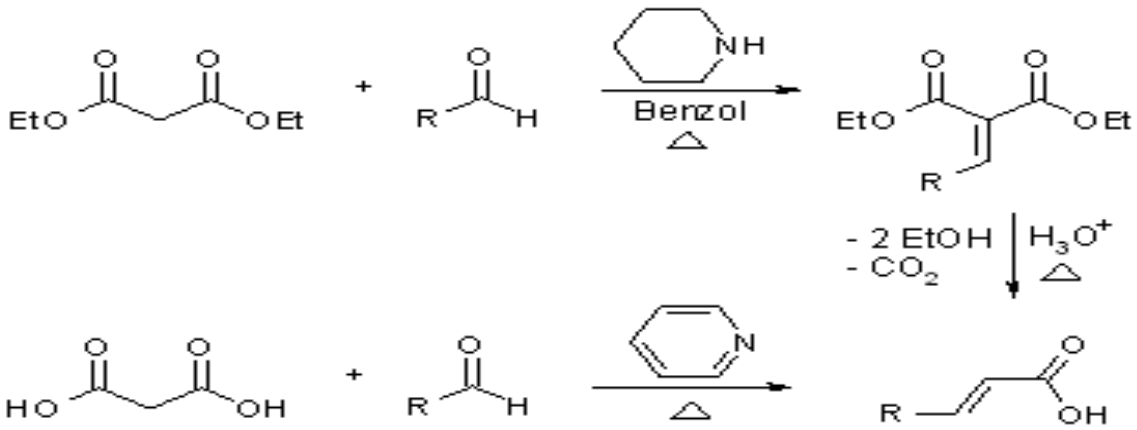
β-Keto esters tend to decarboxylate after hydrolysation to β-keto carboxylic acid and heating to give one or two alkyl-substituted ketones, respectively.



If two equivalents of a strong base are added in the first step, the hydrogen of the more acidic methylene group, and in the next step the hydrogen of the methyl group (ambident nucleophiles), reacts with the base. The hydrogenated methyl group is, however, more acidic than the hydrogenated methylene group. The reaction with alkylation agent in the following step gives a product substituted at methyl group. This can be synthetically used to prepare selectively ketones of different types.

Knoevenagel Condensation

Doebner Modification

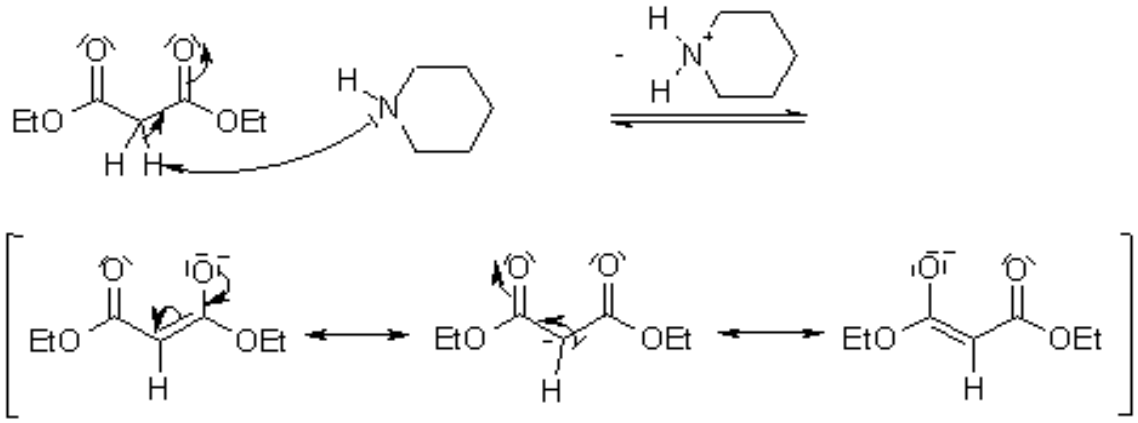


The condensation of carbon acid compounds with aldehydes to afford α,β-unsaturated compounds.

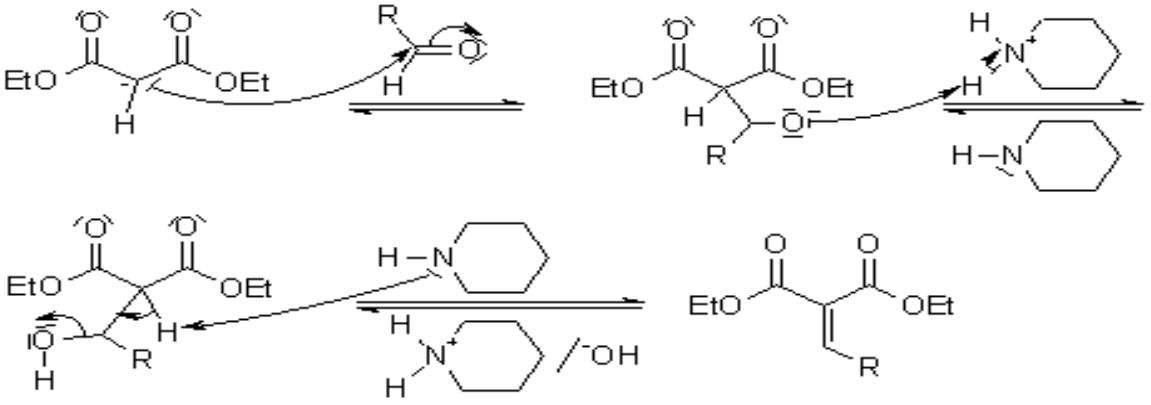
The Doebner Modification, which is possible in the presence of carboxylic acid groups, includes a pyridine-induced decarboxylation.

Mechanism of the Knoevenagel Condensation

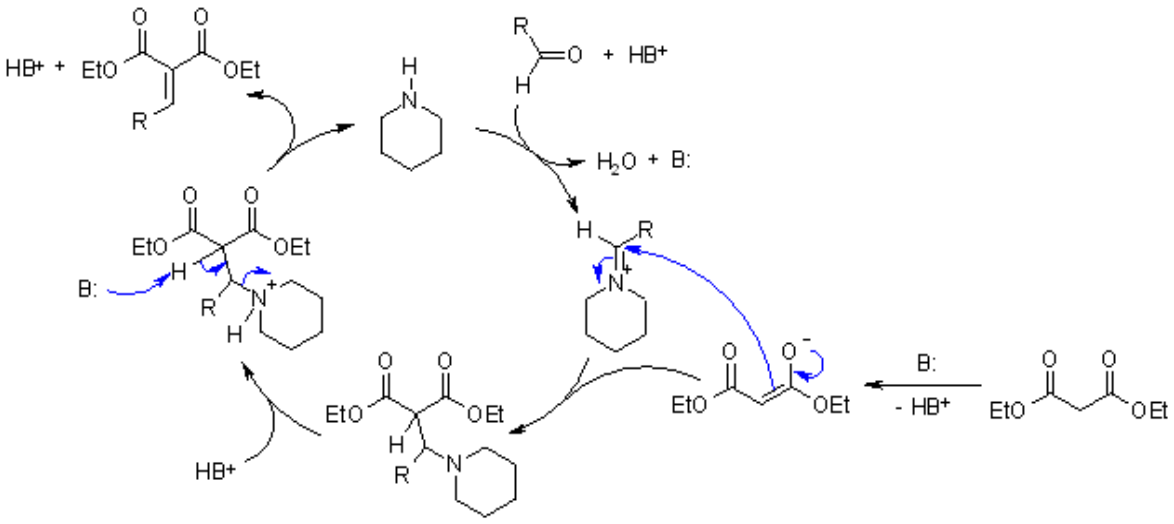
An enol intermediate is formed initially:



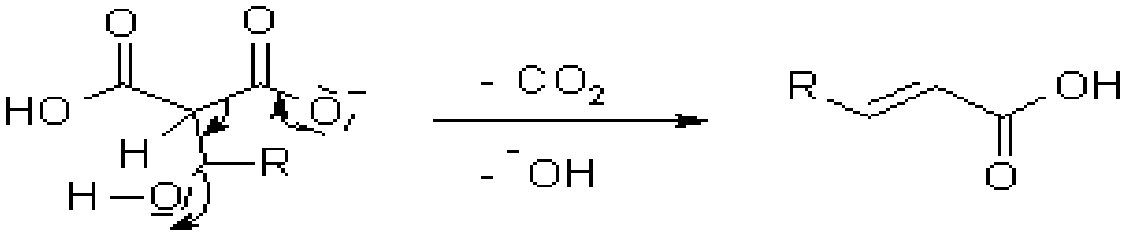
This enol reacts with the aldehyde, and the resulting aldol undergoes subsequent base-induced elimination:

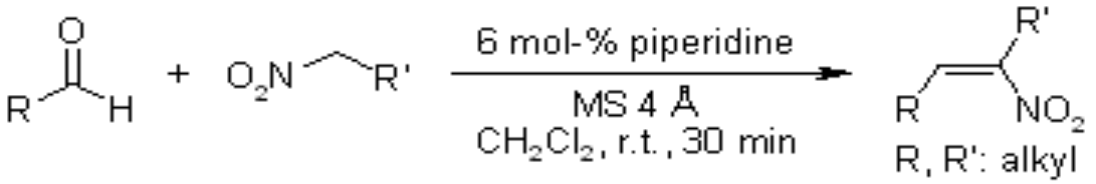


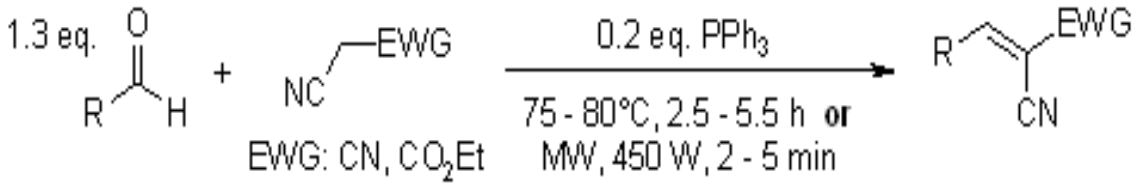
A reasonable variation of the mechanism, in which piperidine acts as organocatalyst, involves the corresponding iminium intermediate as the acceptor:



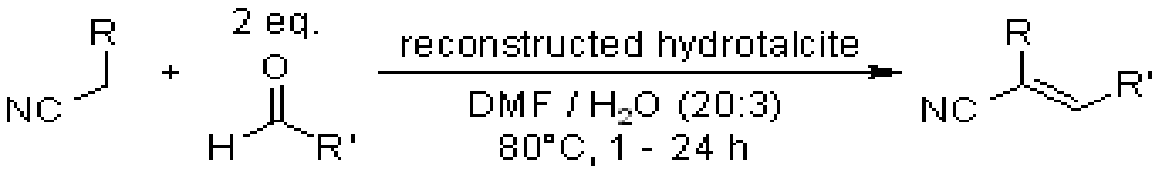
The Doebner-Modification in refluxing pyridine effects concerted decarboxylation and elimination:



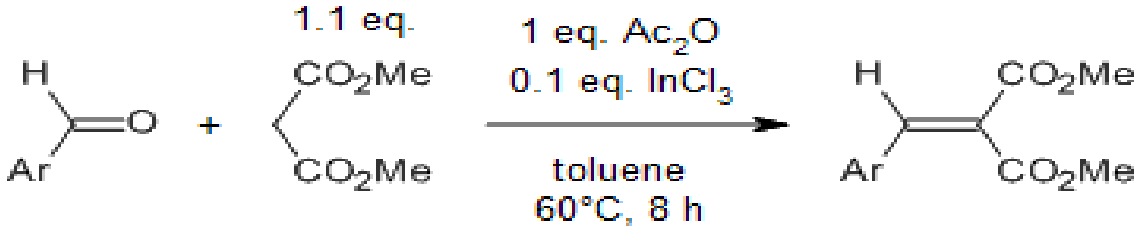




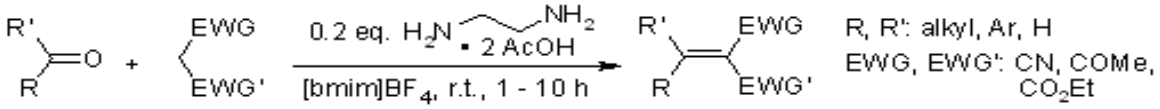
Phosphane-Catalyzed Knoevenagel Condensation: A Facile Synthesis of α-Cyanoacrylates and α-Cyanoacrylonitriles



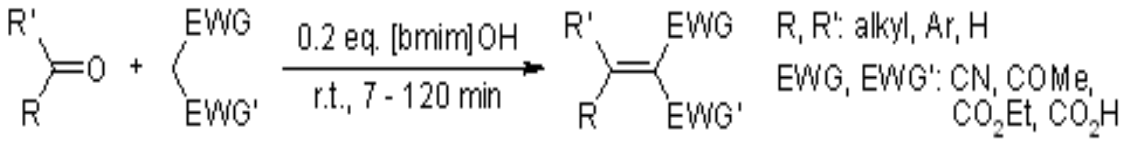
Reconstructed Hydrotalcite as a Highly Active Heterogeneous Base Catalyst for Carbon-Carbon Bond Formations in the Presence of Water



Indium(III)-Catalyzed Knoevenagel Condensation of Aldehydes and Activated Methylenes Using Acetic Anhydride as a Promoter

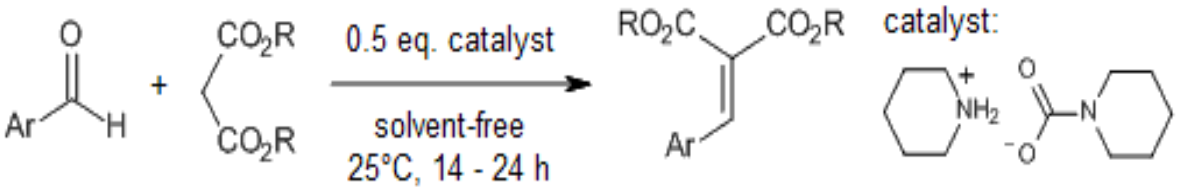


The ionic liquid 1-butyl-3-methylimidazonium tetrafluoroborate [bmim]BF_4 was used for ethylenediammonium diacetate (EDDA)-catalyzed Knoevenagel condensation between aldehydes or ketones with active methylene compounds. Catalyst and solvent can be recycled.

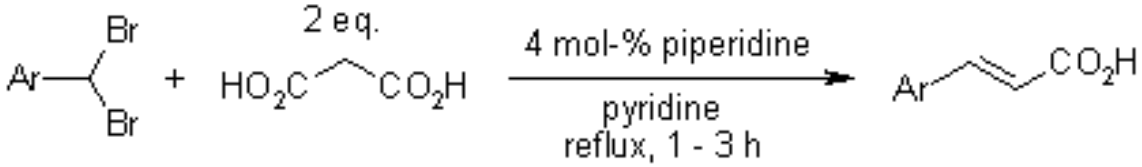


Ionic Liquid as Catalyst and Reaction Medium - A Simple, Efficient and Green Procedure for Knoevenagel Condensation of Aliphatic and Aromatic Carbonyl Compounds Using a Task-Specific Basic

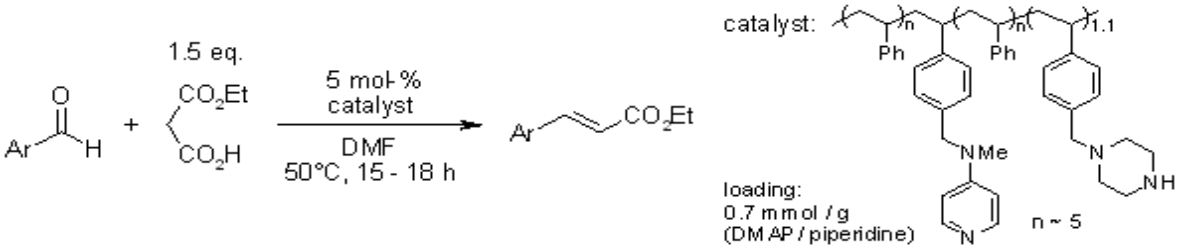
Ionic Liquid



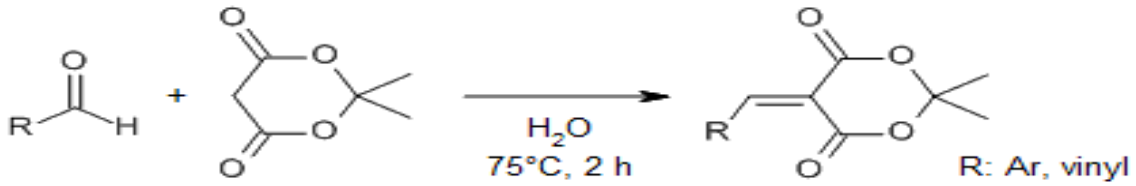
Organocatalytic Knoevenagel Condensations by Means of Carbamic Acid Ammonium Salts



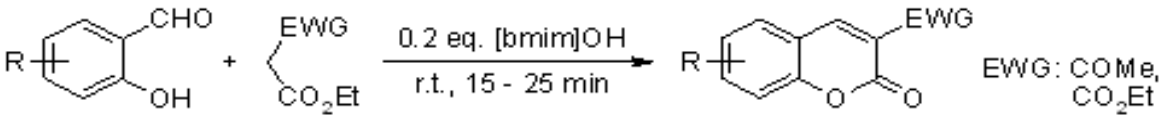
***gem*-Dibromomethylarenes: A Convenient Substitute for Noncommercial Aldehydes in the Knoevenagel-Doebner Reaction for the Synthesis of α,β-Unsaturated Carboxylic Acids**



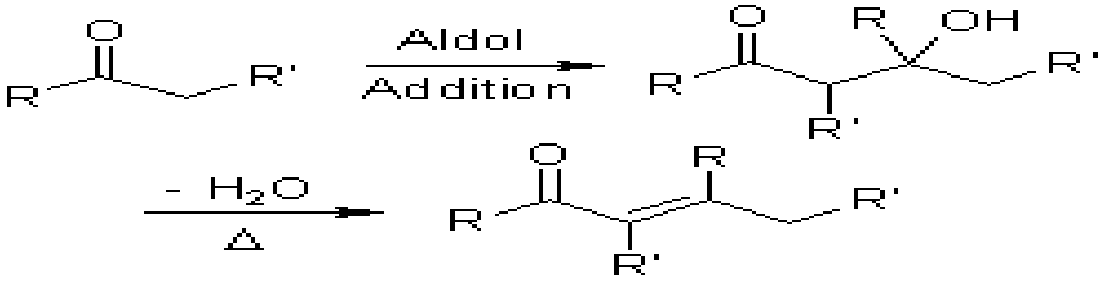
A bifunctional polystyrene bearing both DMAP and piperidine groups is an effective organocatalyst for decarboxylative Doebner-Knoevenagel reactions of arylaldehydes and monoethyl malonate to give *E*-cinnamates in high yields. A synergistic effect obtained by co-locating the two different catalytic amine groups on the same polymer backbone has been detected.



The use of $FeCl_3$ as catalyst enables a rapid decarboxylation of methylene tethered cyclic 1,3-diesters in the presence of water to yield α,β-unsaturated acids with high *E*-stereoselectivity under both microwave and conventional heating conditions. This powerful approach proved to be scalable to gram scale synthesis.



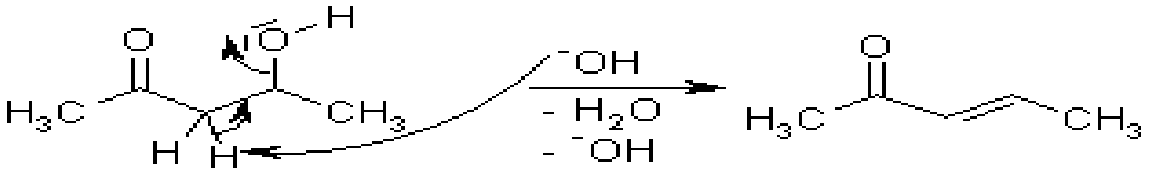
Aldol Condensation



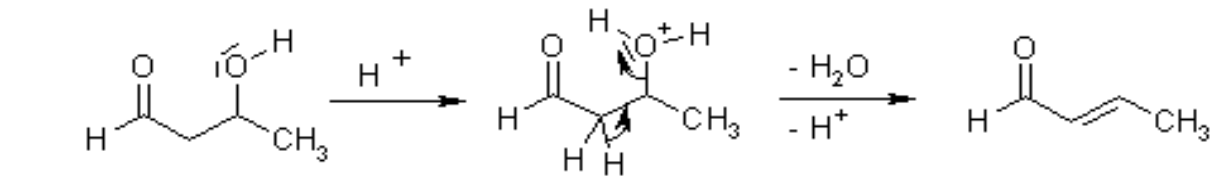
In some cases, the adducts obtained from the Aldol Addition can easily be converted (in situ) to α,β-unsaturated carbonyl compounds, either thermally or under acidic or basic catalysis. The formation of the conjugated system is the driving force for this spontaneous dehydration. Under a variety of protocols, the condensation product can be obtained directly without isolation of the aldol.

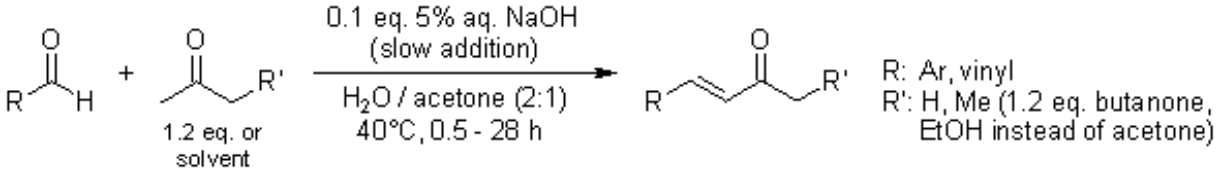
Mechanism of the Aldol Condensation

Base catalyzed condensation :



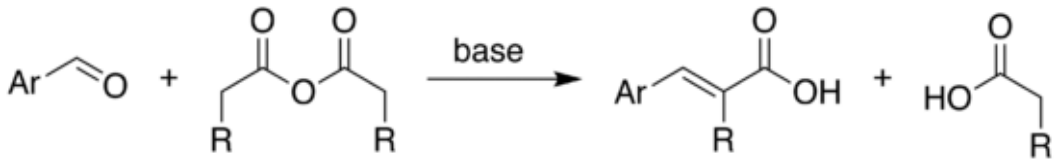
Acid catalyzed condensation :

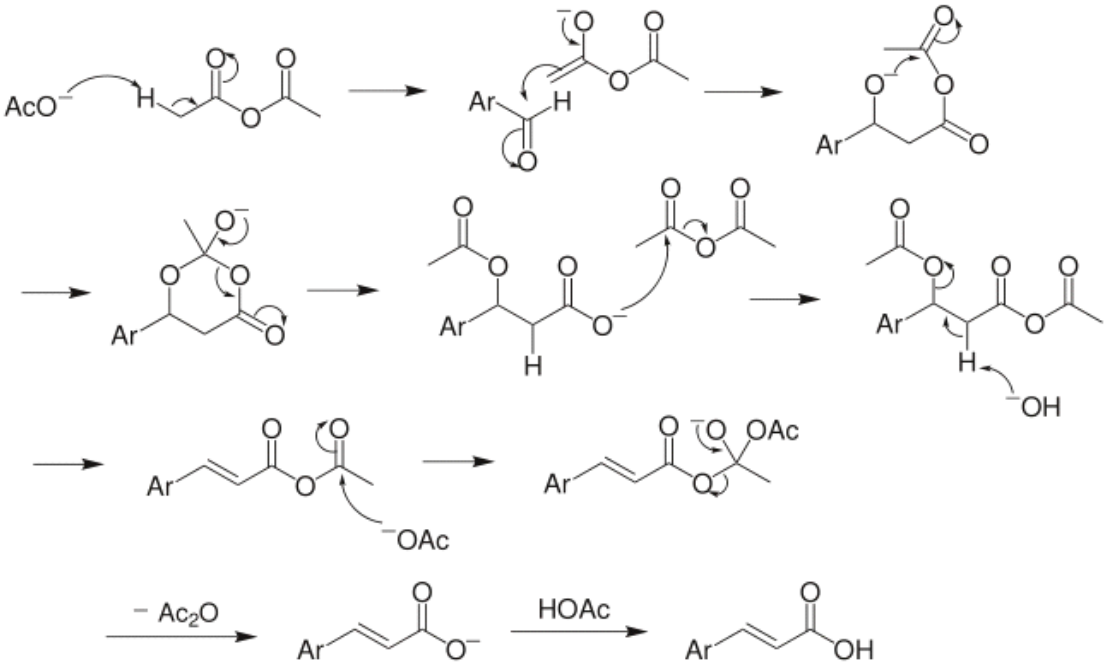




Perkin reaction

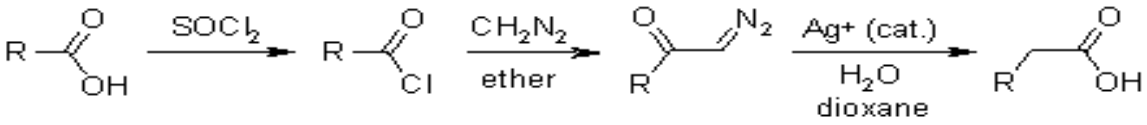
The Perkin reaction is an organic reaction developed by William Henry Perkinthat is used to make cinnamic acids. It gives an α,β-unsaturated aromatic acid by the aldol condensation of an aromatic aldehyde and an acid anhydride, in the presence of an alkali salt of the acid.[1][2] The alkali salt acts as a base catalyst, and other bases can be used instead.[3]





The above mechanism is not universally accepted, as several other versions exist, including decarboxylation without acetic group transfer

Arndt-Eistert Synthesis

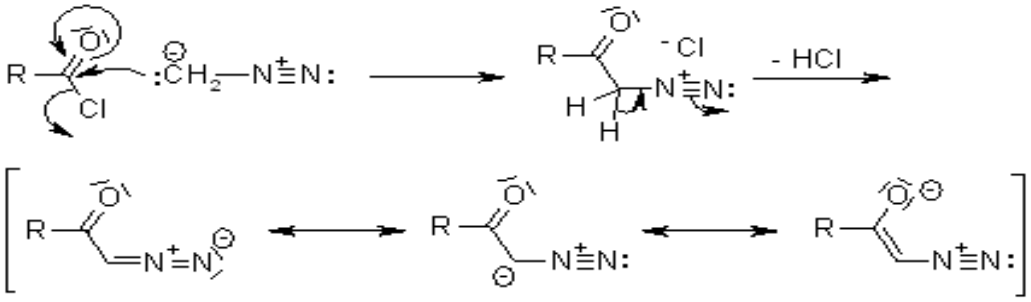


The Arndt-Eistert Synthesis allows the formation of homologated carboxylic acids or their derivatives by reaction of the activated carboxylic acids with diazomethane and subsequent Wolff-Rearrangement of the intermediate diazoketones in the presence of nucleophiles such as water, alcohols, or amines.

Mechanism of the Arndt-Eistert Synthesis

In the first step of this one-carbon homologation, the diazomethane carbon is acylated by an acid chloride or mixed anhydride, to give an 2α-diazoketone. The excess diazomethane can be destroyed by

addition of small amounts of acetic acid or vigorous stirring. Most α-diazoketones are stable and can be isolated and purified by column chromatography (see recent literature for specific methods).



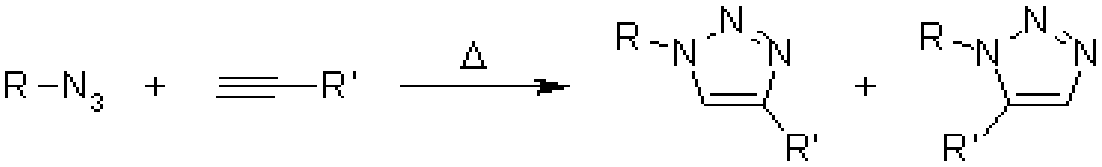
The key step of the Arndt-Eistert Homologation is the Wolff-Rearrangement of the diazoketones to ketenes, which can be accomplished thermally (over the range between r.t. and 750°C

Azide-Alkyne Cycloaddition

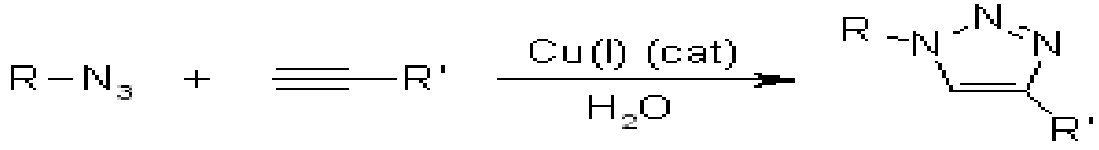
"Click Chemistry" is a term that was introduced by K. B. Sharpless in 2001 to describe reactions that are high yielding, wide in scope, create only byproducts that can be removed without chromatography, are stereospecific, simple to perform, and can be conducted in easily removable or benign solvents. This concept was developed in parallel with the interest within the pharmaceutical, materials, and other industries in capabilities for generating large libraries of compounds for screening in discovery research. Several types of reaction have been identified that fulfill these criteria, thermodynamically-favored reactions that lead specifically to one product, such as nucleophilic ring opening reactions of epoxides and aziridines, non-aldol type carbonyl reactions, such as formation of hydrazones and heterocycles, additions to carbon-carbon multiple

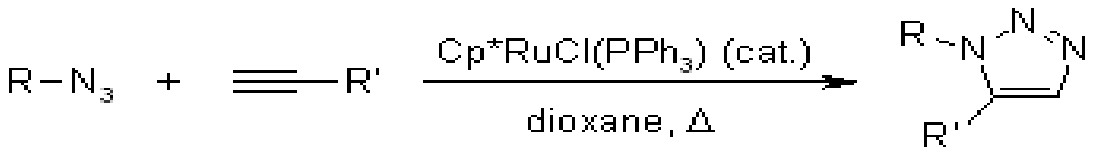
bonds, such as oxidative formation of epoxides and Michael Additions, and cycloaddition reactions.

For example, an examination of the azide-alkyne cycloaddition shows that it fulfills many of the prerequisites. Many of the starting monosubstituted alkynes and organic azides are available commercially, many others can easily be synthesized with a wide range of functional groups, and their cycloaddition reaction selectively gives 1,2,3-triazoles.



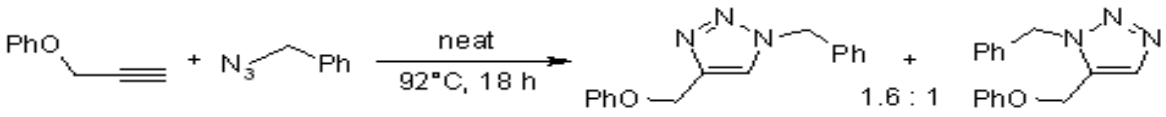
Unfortunately, the thermal 13Huisgen 1,3-Dipolar Cycloaddition of alkynes to azides requires elevated temperatures and often produces mixtures of the two regioisomers when using asymmetric alkynes. In this respect, the classic 1,3-dipolar cycloaddition fails as a true click reaction. A copper-catalyzed variant that follows a different mechanism can be conducted under aqueous conditions, even at room temperature. Additionally, whereas the classic Huisgen 1,3-dipolar cycloaddition often gives mixtures of regioisomers, the copper-catalyzed reaction allows the synthesis of the 1,4-disubstituted regioisomers specifically. By contrast, a later developed ruthenium-catalyzed reaction gives the opposite regioselectivity with the formation of 1,5-disubstituted triazoles. Thus, these catalyzed reactions comply fully with the definition of click chemistry and have put a focus on azide-alkyne cycloaddition as a prototype click reaction.





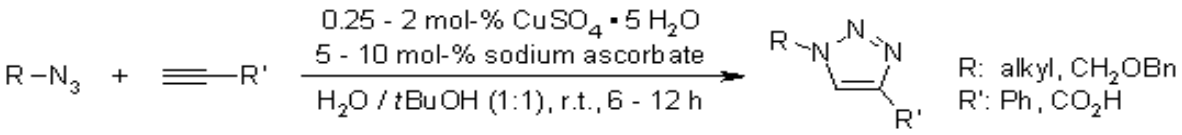
Mechanism of the Huisgen Azide-Alkyne 1,3-Dipolar Cycloaddition

For the mechanism, please refer to the text on 131,3-dipolar cycloaddition. This reaction is highly exothermic, but the high activation barrier is responsible for a very low reaction rate, even at elevated temperature. Another drawback is the formation of regioisomers, as the two possible HOMO-LUMO interactions of the substrates are closely related in terms of energy. The thermal reaction therefore often gives approximately 1:1 mixtures of both the 1,4-substituted and the 1,5-substituted regioisomers.



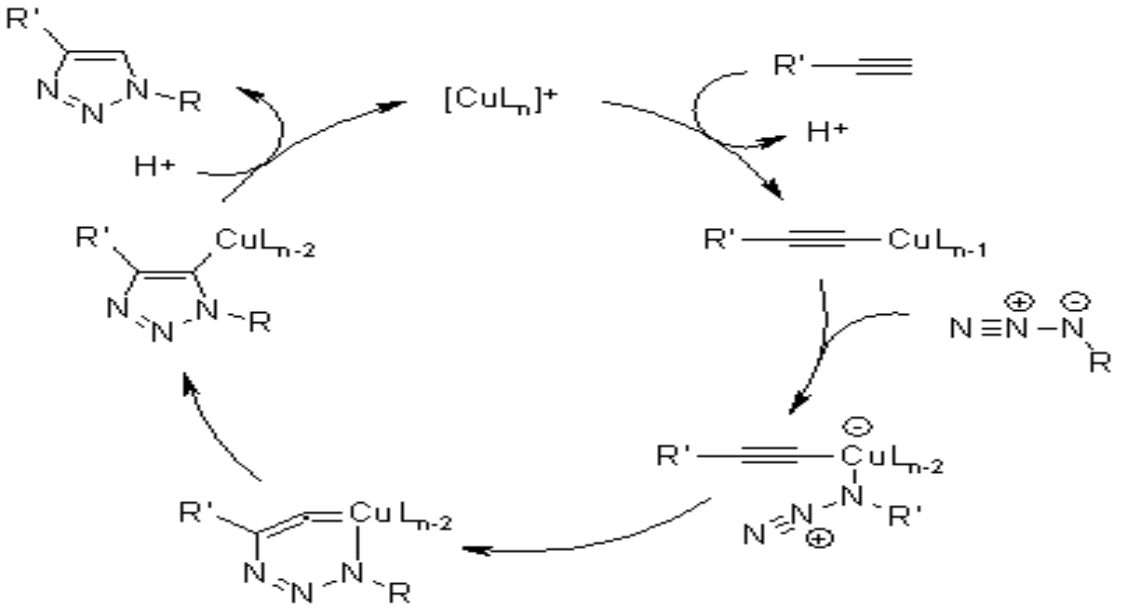
Mechanism of the Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC)

As one of the best click reactions to date, the copper-catalyzed azide-alkyne cycloaddition features an enormous rate acceleration of 10^7 to 10^8 compared to the uncatalyzed 1,3-dipolar cycloaddition. It succeeds over a broad temperature range, is insensitive to aqueous conditions and a pH range over 4 to 12, and tolerates a broad range of functional groups. Pure products can be isolated by simple filtration or extraction without the need for chromatography or recrystallization.



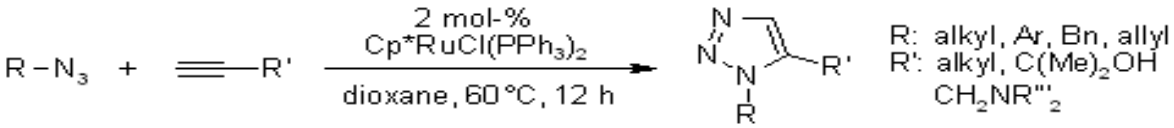
The active Cu(I) catalyst can be generated from Cu(I) salts or Cu(II) salts using sodium ascorbate as the reducing agent. Addition of a slight excess of sodium ascorbate prevents the formation of oxidative homocoupling products. Disproportionation of a Cu(II) salt in presence of a Cu wire can also be used to form active Cu(I).

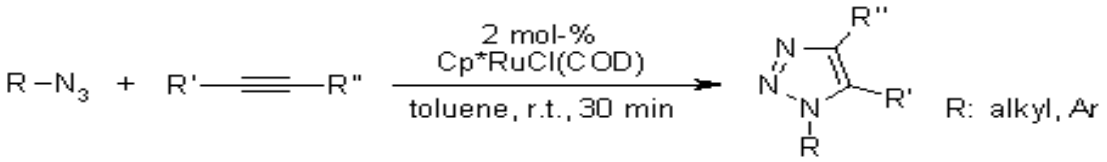
DFT calculations have shown that coordination of Cu(I) to the alkyne is slightly endothermic in MeCN, but exothermic in water, which is in agreement with an observed rate acceleration in water. However, coordination of Cu to the acetylene does not accelerate a 1,3-dipolar cycloaddition. Such a process has been calculated to be even less favorable than the uncatalyzed 1,3-dipolar cycloaddition. Instead, a copper acetylide forms, after which the azide displaces another ligand and binds to the copper. Then, an unusual six-membered copper(III) metallacycle is formed. The barrier for this process has been calculated to be considerably lower than the one for the uncatalyzed reaction. The calculated rate at room temperature is 1 s^{-1}, which is quite reasonable. Ring contraction to a triazolyl-copper derivative is followed by protonolysis that delivers the triazole product and closes the catalytic cycle.



Mechanism of the Ruthenium-Catalyzed Azide-Alkyne Cycloaddition (RuAAC)

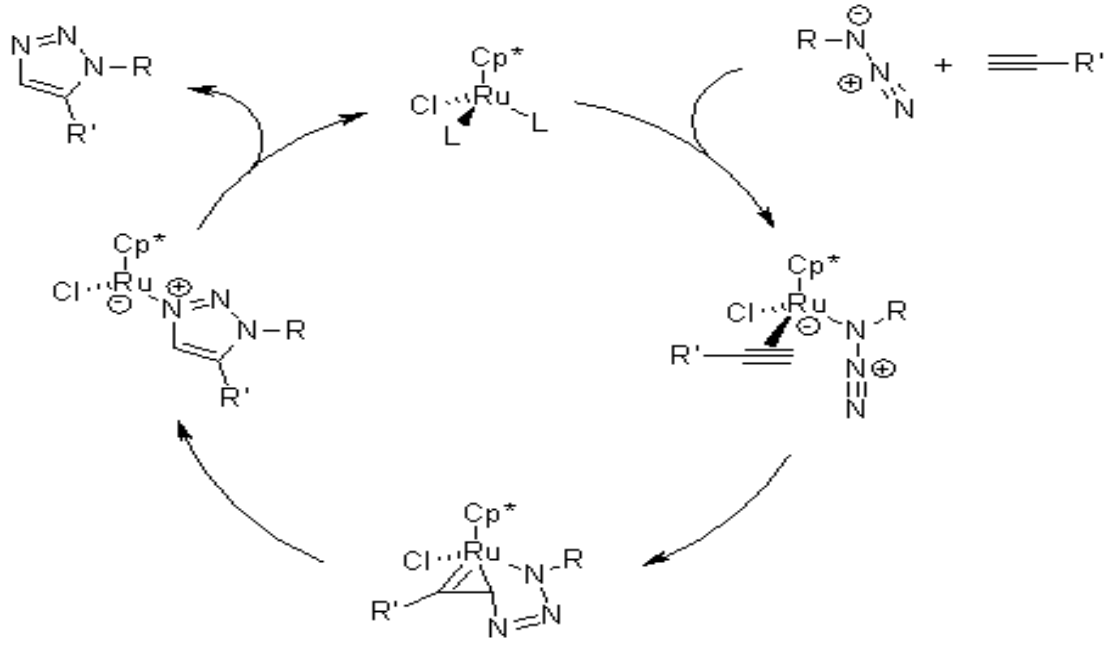
A search for catalysts revealed that pentamethylcyclopentadienyl ruthenium chloride [Cp*RuCl] complexes are able to catalyze the cycloaddition of azides to terminal alkynes regioselectively leading to 1,5-disubstituted 1,2,3-triazoles. In addition, RuAAC can also be used with internal alkynes, providing fully substituted 1,2,3-triazoles, which contrasts with CuAAC.



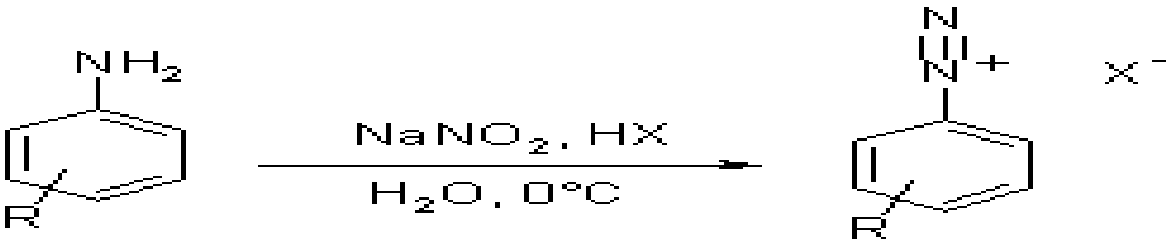


The ruthenium-catalyzed azide-alkyne cycloaddition (RuAAC) appears to proceed via oxidative coupling of the azide and the alkyne to give a six-membered ruthenacycle, in which the first new carbon-

nitrogen bond is formed between the more electronegative carbon of the alkyne and the terminal, electrophilic nitrogen of the azide. This step is followed by reductive elimination, which forms the triazole product. DFT calculations support this mechanistic proposal and indicate that the reductive elimination step is rate-determining..



Diazotisation

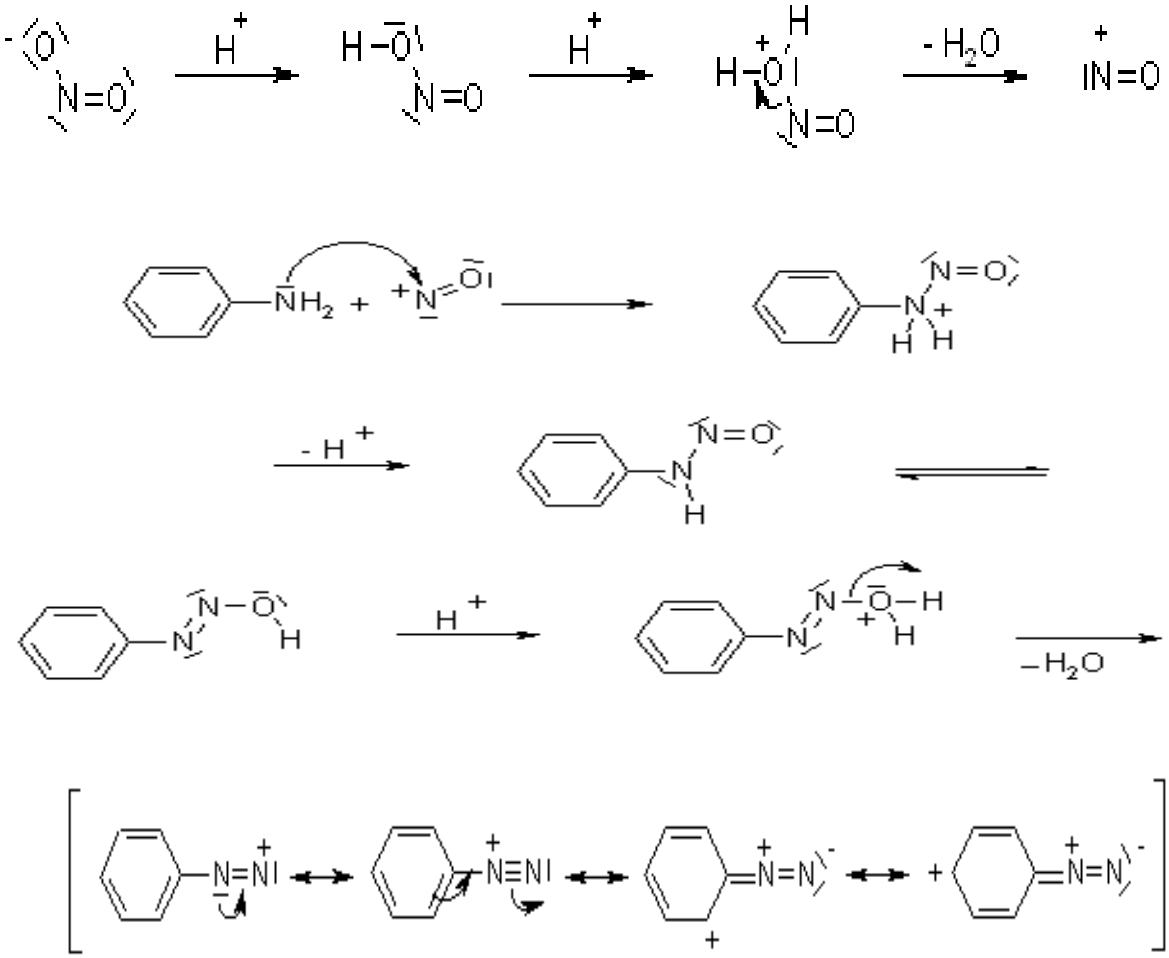


The nitrosation of primary aromatic amines with nitrous acid (generated in situ from sodium nitrite and a strong acid, such as hydrochloric acid, sulfuric acid, or HBF_4) leads to diazonium salts, which can be isolated if the counterion is non-nucleophilic.

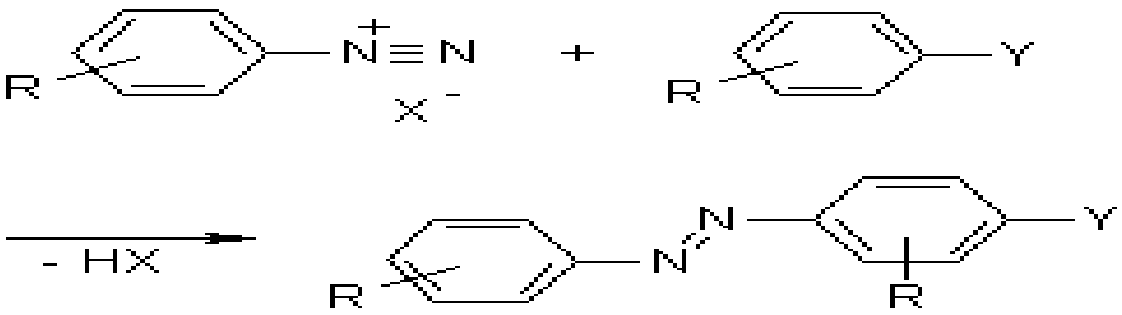
Diazonium salts are important intermediates for the preparation of halides (Sandmeyer Reaction, Schiemann Reaction), and azo compounds. Diazonium salts can react as pseudohalide-type electrophiles, and can therefore be used in specific protocols for theHeck Reaction or Suzuki Coupling.

The intermediates resulting from the diazotization of primary, aliphatic amines are unstable; they are rapidly converted into carbocations after loss of nitrogen, and yield products derived from substitution, elimination or rearrangement processes.

Mechanism of Diazotisation

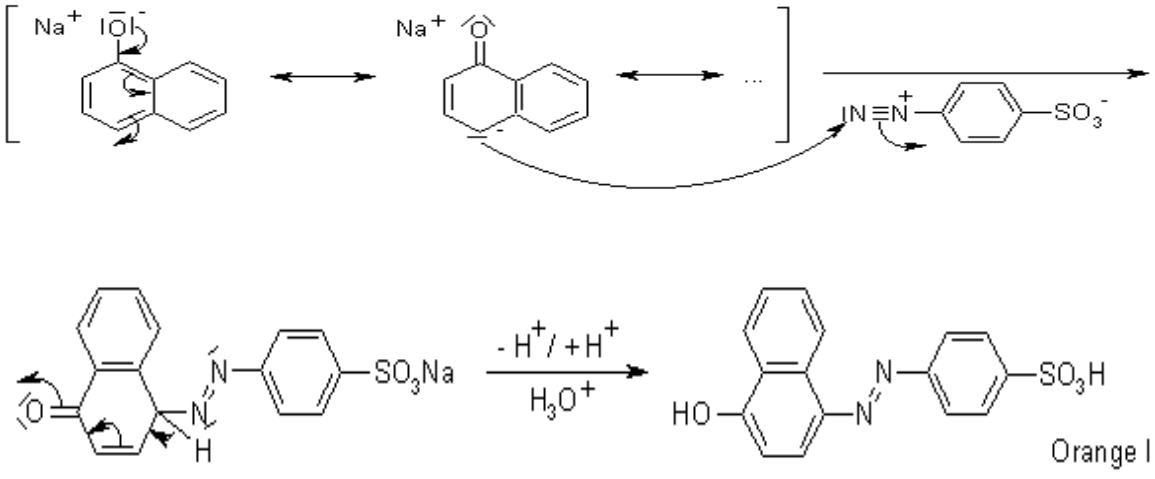


Azo Coupling

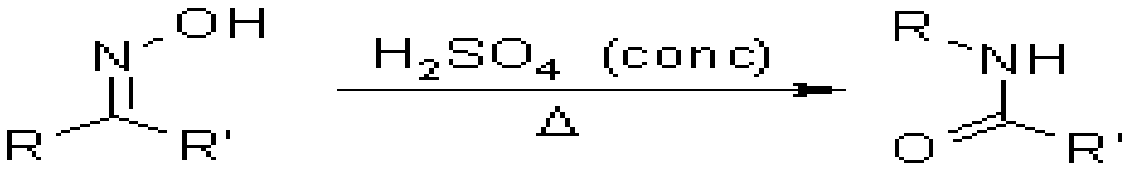


Azo coupling is the most widely used industrial reaction in the production of dyes, lakes and pigments. Aromatic diazonium ions acts as electrophiles in coupling reactions with activated aromatics such as anilines or phenols. The substitution normally occurs at the para position, except when this position is already occupied, in which case *ortho* position is favoured. The pH of solution is quite important; it must be mildly acidic or neutral, since no reaction takes place if the pH is too low

Mechanism of Azo Coupling



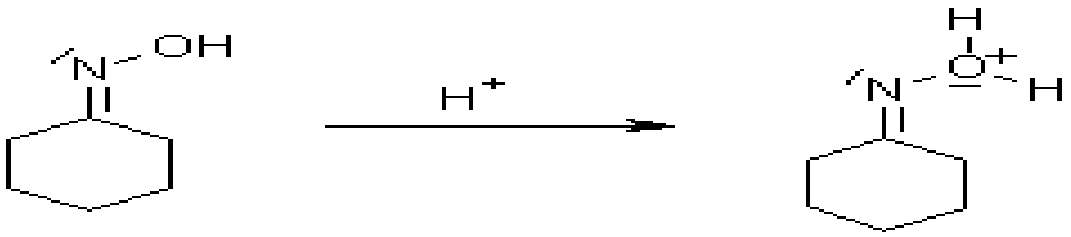
Beckmann Rearrangement



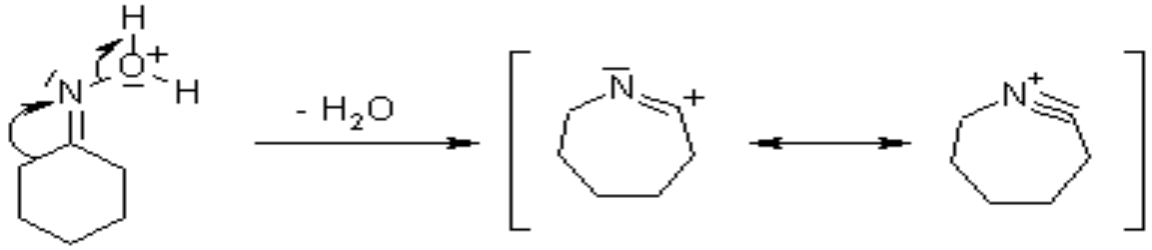
An acid-induced rearrangement of oximes to give amides.

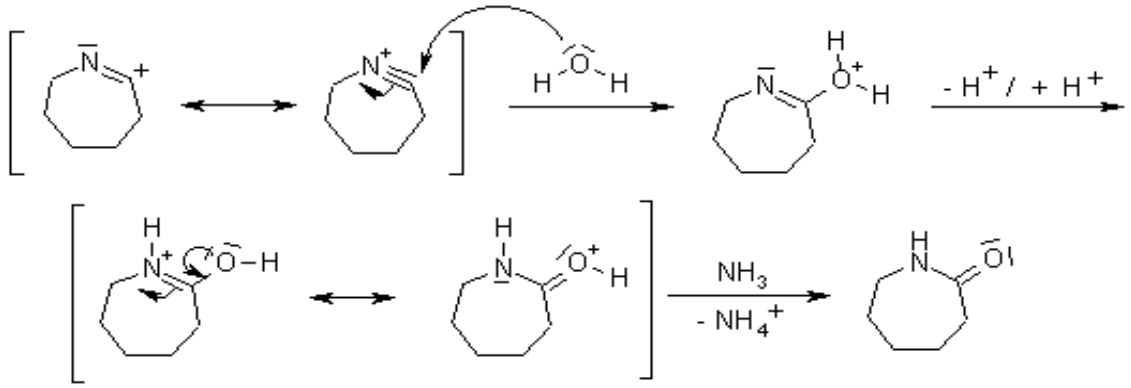
This reaction is related to the Hofmann and Schmidt Reactions and theCurtius Rearrangement, in that an electropositive nitrogen is formed that initiates an alkyl migration.

Mechanism of the Beckmann Rearrangement

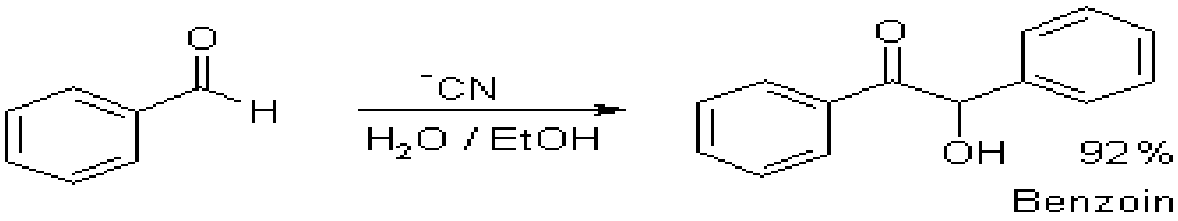


Oximes generally have a high barrier to inversion, and accordingly this reaction is envisioned to proceed by protonation of the oxime hydroxyl, followed by migration of the alkyl substituent "*trans*" to nitrogen. The N-O bond is simultaneously cleaved with the expulsion of water, so that formation of a free nitrene is avoided.





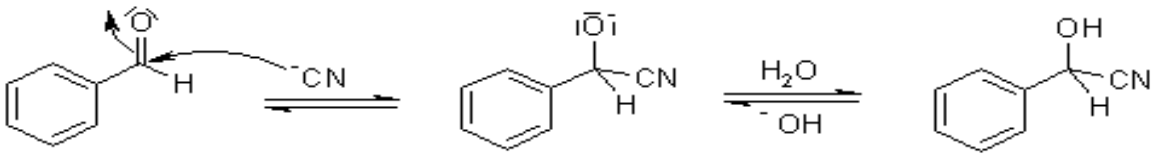
Benzoin Condensation



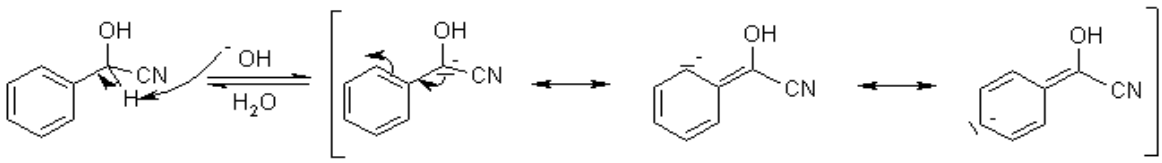
The Benzoin Condensation is a coupling reaction between two aldehydes that allows the preparation of α-hydroxyketones. The first methods were only suitable for the conversion of aromatic aldehydes.

Mechanism of Benzoin Condensation

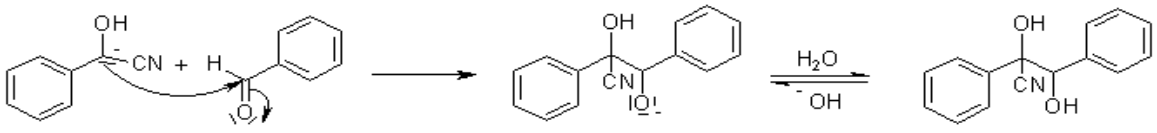
Addition of the cyanide ion to create a cyanohydrin effects an umpolung of the normal carbonyl charge affinity, and the electrophilic aldehyde carbon becomes nucleophilic after deprotonation: A thiazolium salt may also be used as the catalyst in this reaction (see Stetter Reaction).

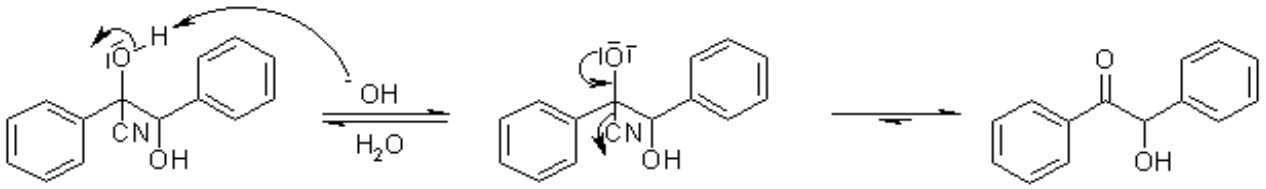


A strong base is now able to deprotonate at the former carbonyl C-atom:



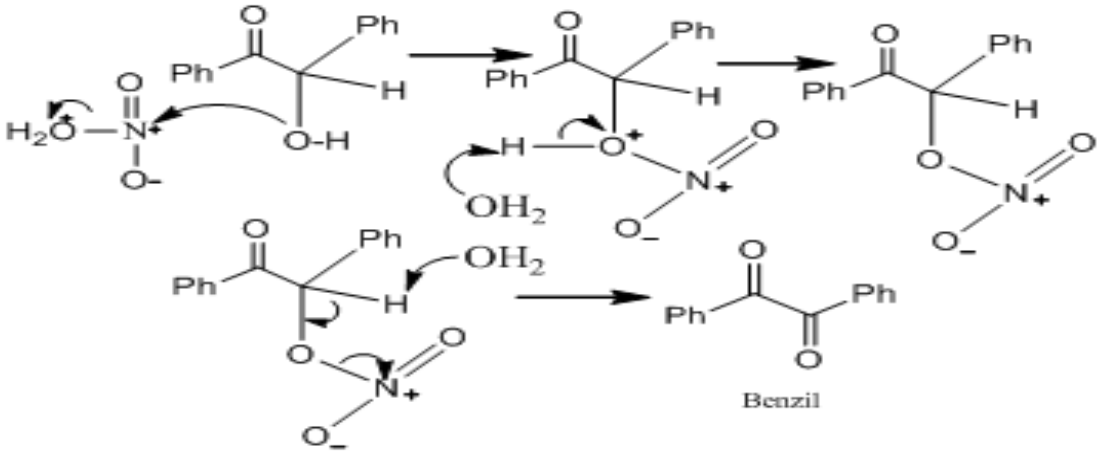
A second equivalent of aldehyde reacts with this carbanion; elimination of the catalyst regenerates the carbonyl compound at the end of the reaction:





Benzil

The alcohol group of benzoin must be oxidized. By utilizing the mild oxidizing agent of nitiric acid, benzoin was oxidized to produce benzil through the mechanism.

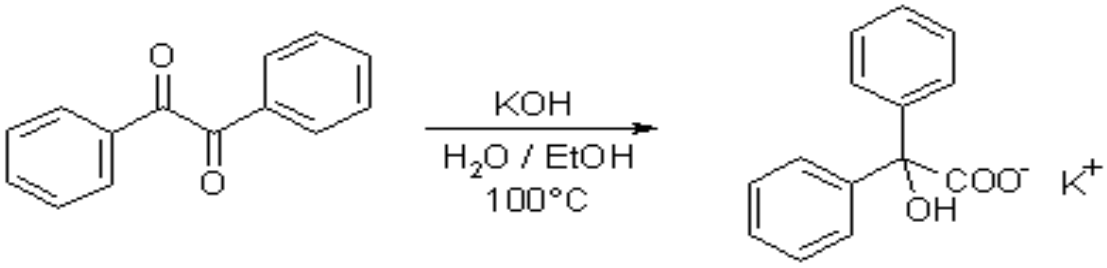


Scheme 2: The reaction of benzoin and nitric acid to form benzil.

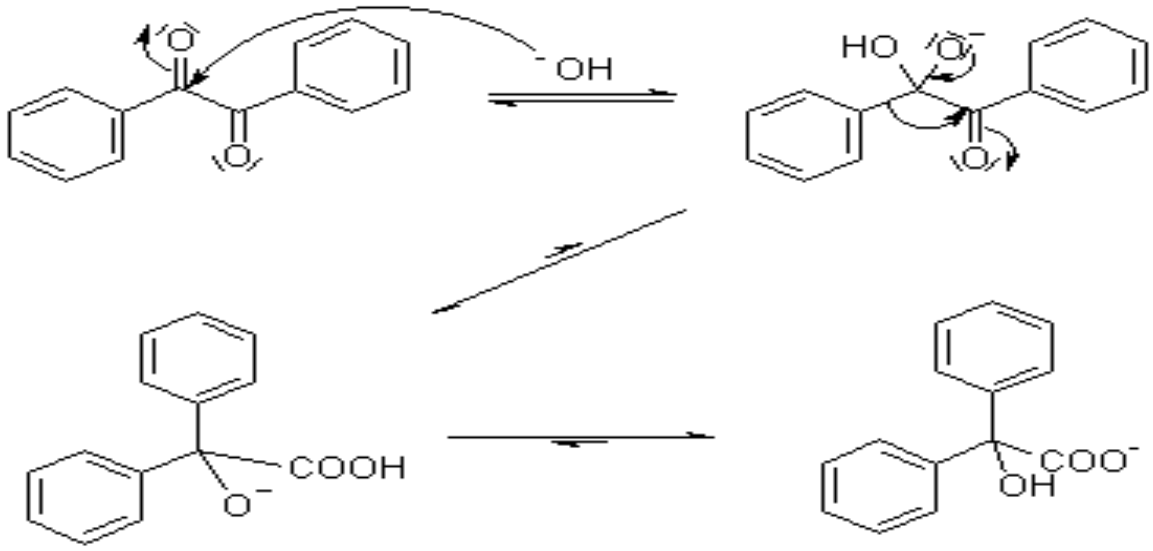
The final mechanism, involves the synthesis of the carboxylate salt intermediate, potassium benzilate, which drives the reaction to produce benzilic acid through workup.

Benzilic Acid Rearrangement

1,2-Diketones undergo a rearrangement in the presence of strong base to yield α-hydroxycarboxylic acids. The best yields are obtained when the subject diketones do not have enolizable protons.

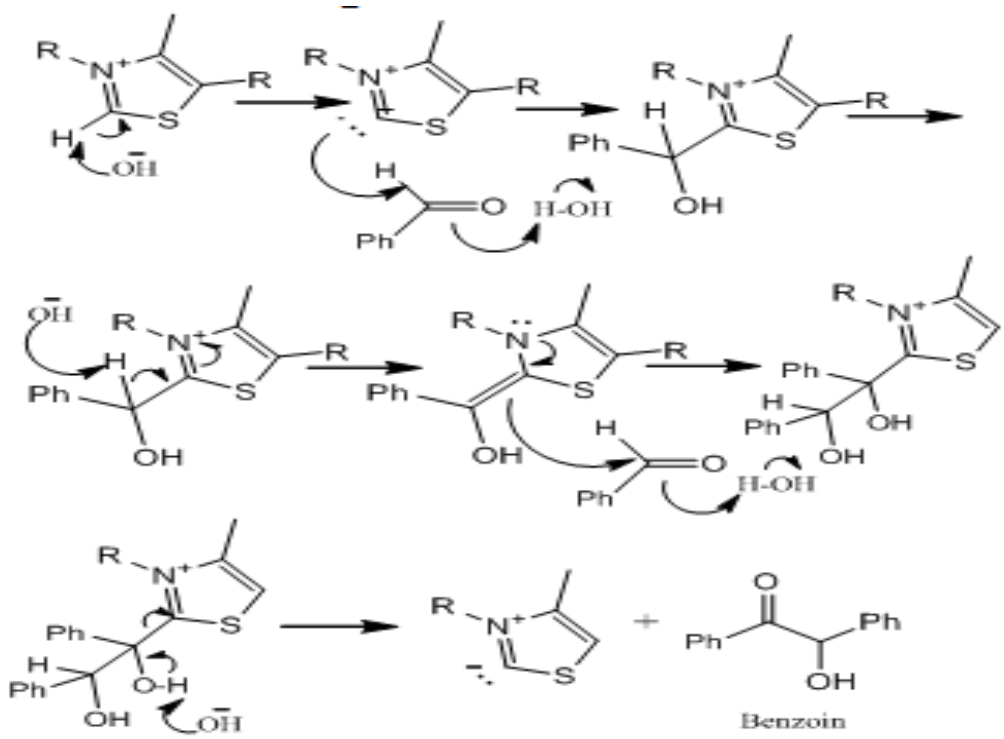


Mechanism of Benzilic Acid Rearrangement



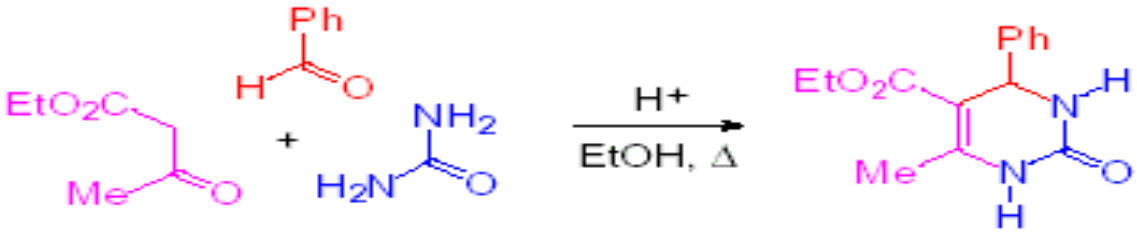
Reaction Mechanisms

it depicts the reaction between the catalyst thiamine hydrochloride and two equivalents of benzaldehyde. Once a proton was removed from thiamine hydrochloride, forming ylide, it acted as a nucleophile that allowed for the addition of the carbonyl group of benzaldehyde. A proton is removed from the intermediate and the new alkene bond attacks the carbonyl group of the second benzaldehyde. The ultimate products of ylide and benzoin are produced. The ylide is the regenerated catalyst and performs the mechanism again.



Scheme 1: The production of benzoin through the combination of thiamine hydrochloride and benzaldehyde.

Biginelli Reaction

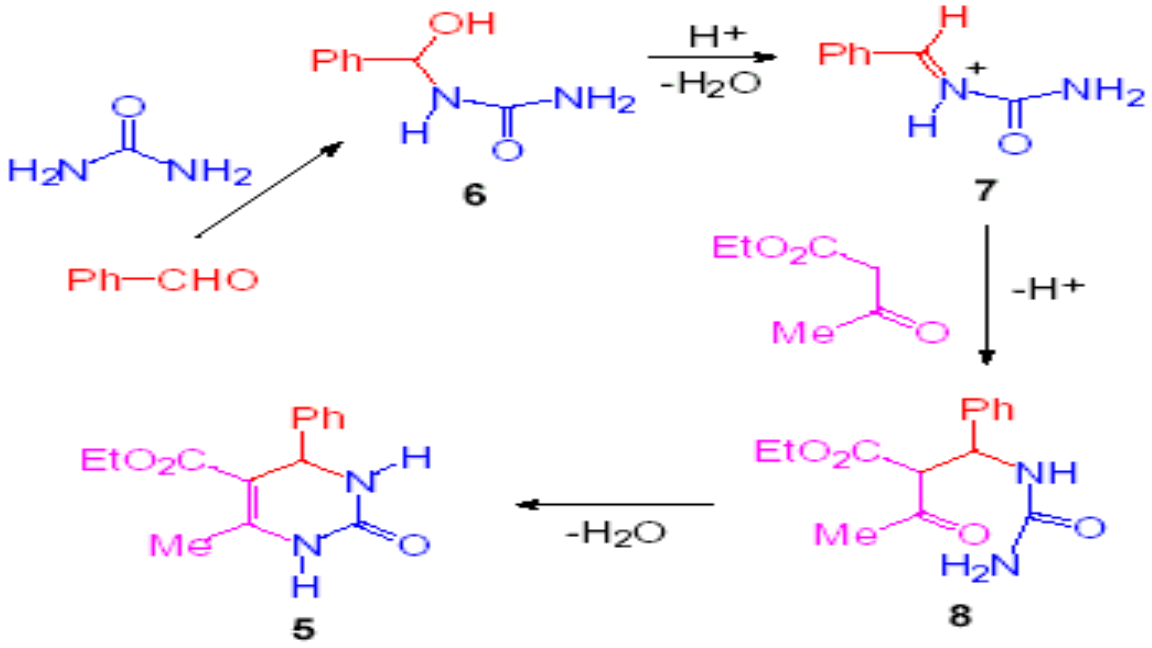


This acid-catalyzed, three-component reaction between an aldehyde, a ß-ketoester and urea constitutes a rapid and facile synthesis of dihydropyrimidones, which are interesting compounds with a potential for pharmaceutical application.

Mechanism of the Biginelli Reaction

The first step in the mechanism is believed to be the condensation between the aldehyde and urea, with some similarities to the Mannich Condensation. The iminium intermediate generated acts as

an electrophile for the nucleophilic addition of the ketoester enol, and the ketone carbonyl of the resulting adduct undergoes condensation with the urea NH_2 to give the cyclized product.



Bischler-Napieralski Reaction

Bischler-Napieralski Cyclization

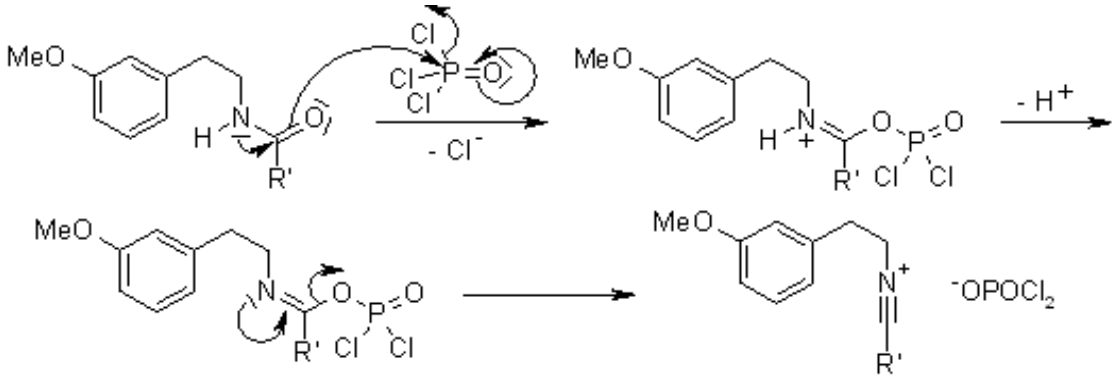
The Bischler-Napieralski Reaction allows the synthesis of 3,4-dihydroisoquinolines from the β-ethylamides of electron-rich arenes using condensation reagents such as P_2O_5, $POCl_3$ or $ZnCl_2$.

Mechanism of the Bischler-Napieralski Reaction

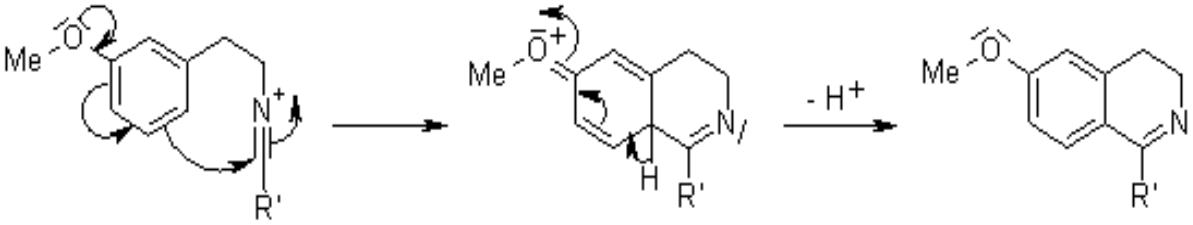
According to detailed studies by Fodor and Nagubandi, the Bischler-Napieralski Reaction involves an initial dehydration step of the amide followed by a cyclization. Fodor was able to prepare stable imidoyl salts at room temperature that formed nitrilium salts upon mild heating, whereas the Bischler-Napieralski Reaction required elevated temperatures to form dihydroisoquinolines. A mechanism

that includes nitrilium salts also accounts the occurrence of styrenes as side products as will be explained later.

In the dehydration, reagents such as PCl_5, $POCl_3$, $SOCl_2$, $ZnCl_2$ can be used to promote loss of the carbonyl oxygen. Use of $POCl_3$leads first to formation of imidoyl phosphates in which phosphate is a good leaving group. Use of P_2O_5 or addition of P_2O_5 to a reaction with $POCl_3$ leads to pyrophosphates, which are even better leaving groups.

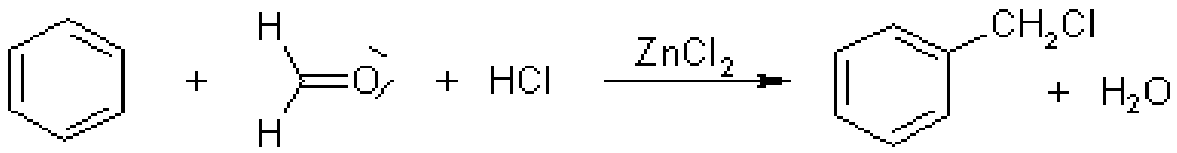


For the cyclization, an activated arene is needed to effect ring closure at reflux temperature if the solvent is toluene. Alternatively, xylene can be used, and microwave-assisted chemistry in superheated solvents is also a viable solution.



One of the most important side reactions is the retro-Ritter reaction forming styrenes, which is also evidence for nitrilium salts as intermediates:

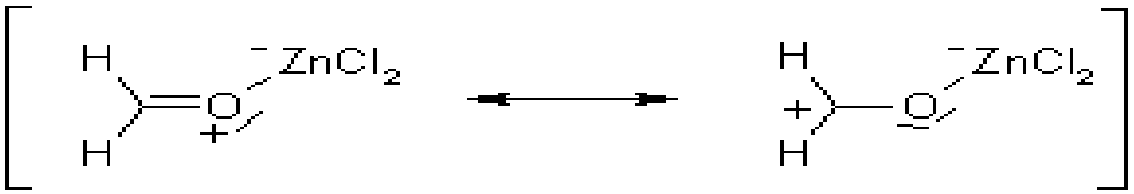
Blanc Reaction

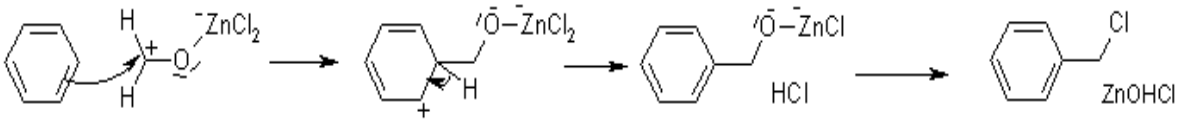


This reaction, which is comparable to a Friedel-Crafts Alkylation, is useful for the preparation of chloromethylated arenes (for example, the Merrifield resin based on polystyrene) from the parent arene with formaldehyde, HCl, and $ZnCl_2$.

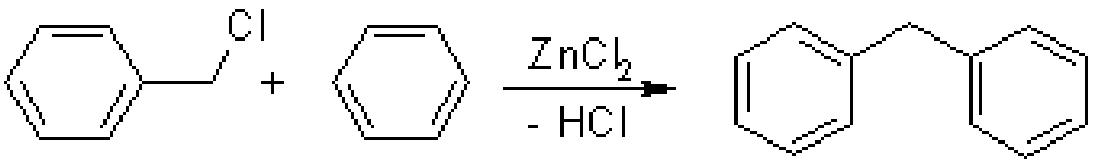
Mechanism of the Blanc Reaction

The Lewis acid $ZnCl_2$ effects formation of an oxonium ion which is reactive in electrophilic aromatic substitution. The intermediate zinc alkoxide reacts with the arene to form the chloromethylated product and zinc oxides:

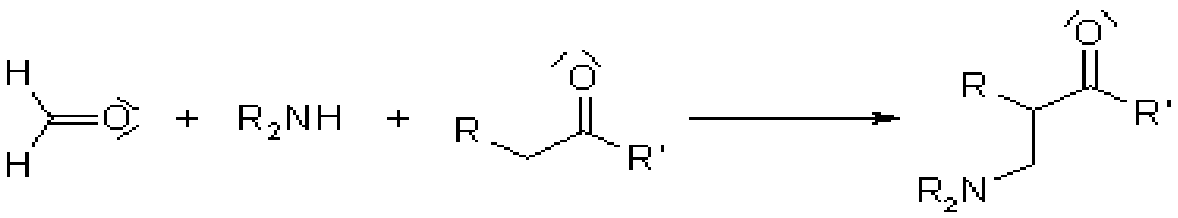




When the concentration (or, effective concentration in the case of polymer residues) is high, the formation of side products due to a second addition are observed:



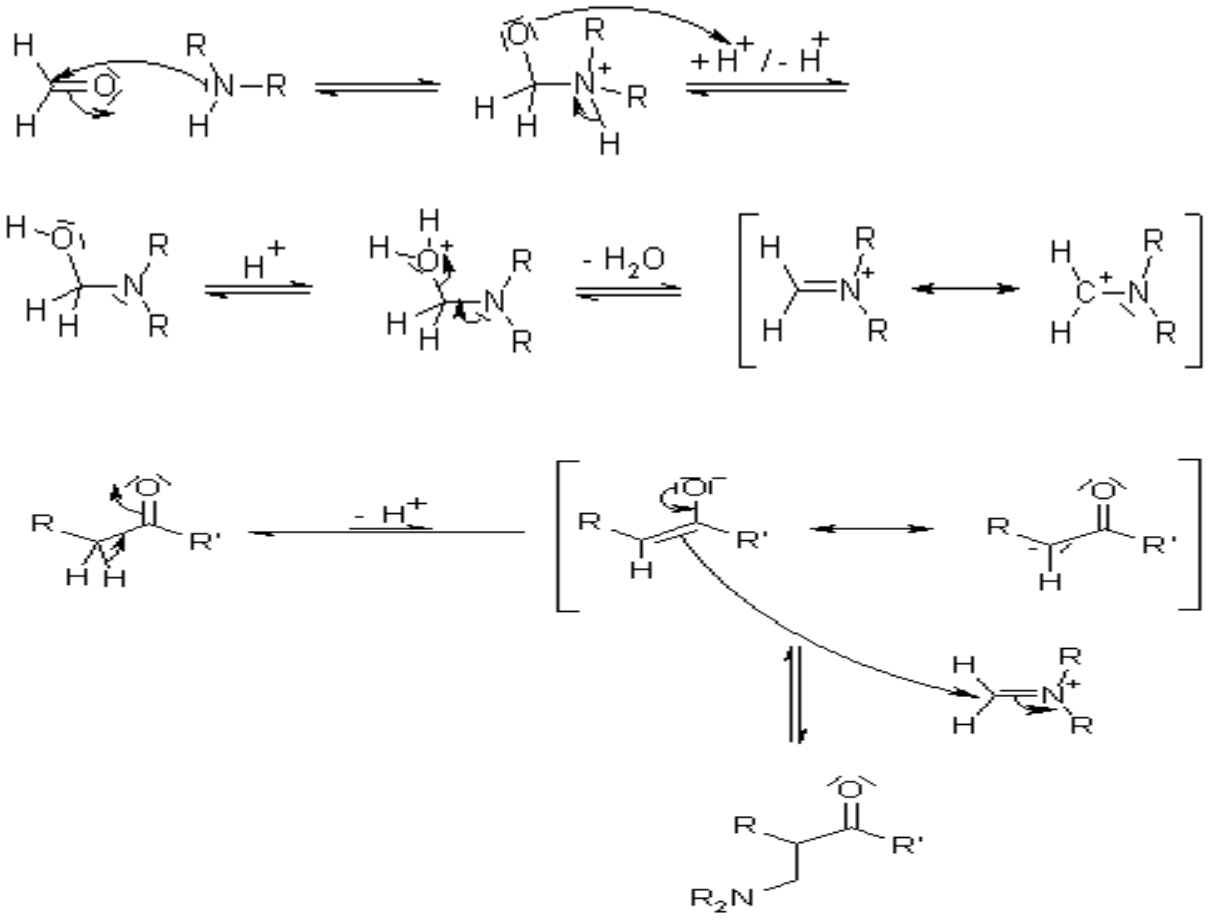
Mannich Reaction



This multi-component condensation of a nonenolizable aldehyde, a primary or secondary amine and an enolizable carbonyl compound affords aminomethylated products. The iminium derivative of the aldehyde is the acceptor in the reaction.

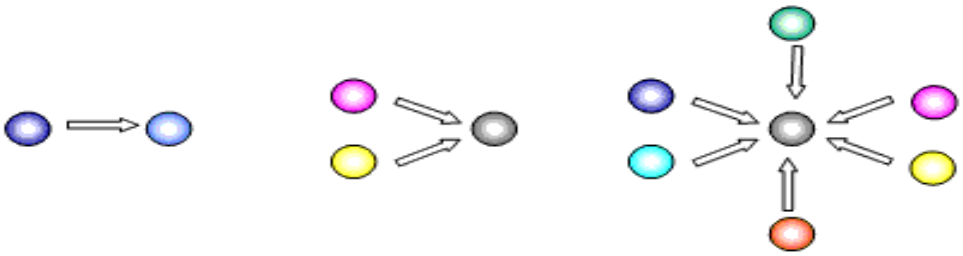
The involvement of the Mannich Reaction has been proposed in many biosynthetic pathways, especially for alkaloids

Mechanism of the Mannich Reaction



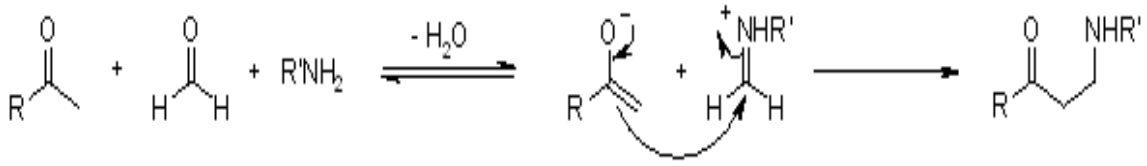
Multicomponent Reactions

Multicomponent Reactions (MCRs) are convergent reactions, in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed product. In an MCR, a product is assembled according to a cascade of elementary chemical reactions. Thus, there is a network of reaction equilibria, which all finally flow into an irreversible step yielding the product. The challenge is to conduct an MCR in such a way that the network of pre-equilibrated reactions channel into the main product and do not yield side products. The result is clearly dependent on the reaction conditions: solvent, temperature, catalyst, concentration, the kind of starting materials and functional groups. Such considerations are of particular importance in connection with the design and discovery of novel MCRs.



Multicomponent Reactions with Carbonyl Compounds

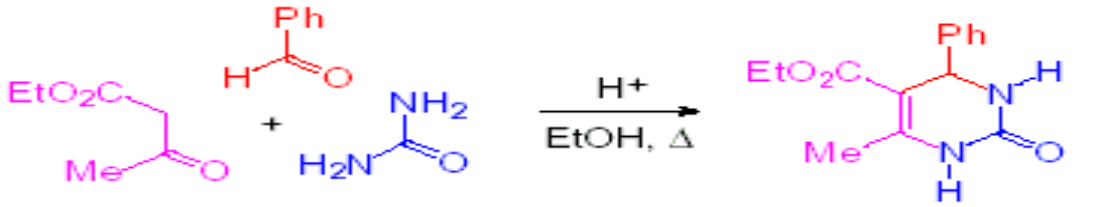
Some of the first multicomponent reactions to be reported function through derivatization of carbonyl compounds into more reactive intermediates, which can react further with a nucleophile. One example is the Mannich Reaction:



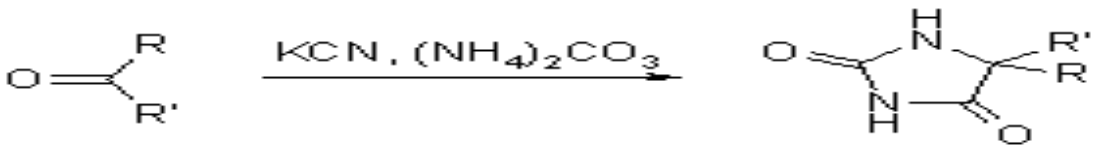
Mannich Reaction

Obviously, this reaction only proceeds if one carbonyl compound reacts faster with the amine to give an imine, and the other carbonyl compound plays the role of a nucleophile. In cases where both carbonyl compounds can react as the nucleophile or lead to imines with the same reaction rate, preforming the intermediates is an alternative, giving rise to a standard multistep synthesis.

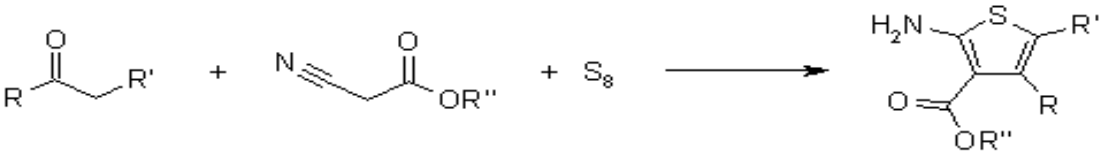
Carbonyl compounds played a crucial role in the early discovery of multicomponent reactions, as displayed by a number of name reactions:



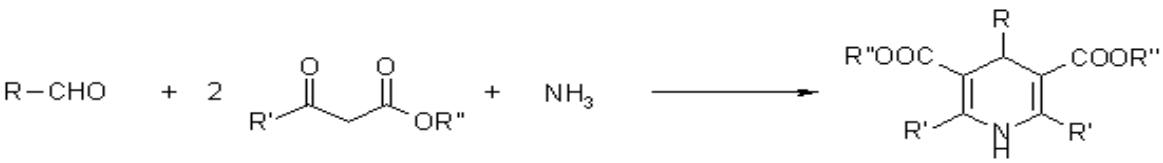
Biginelli Reaction



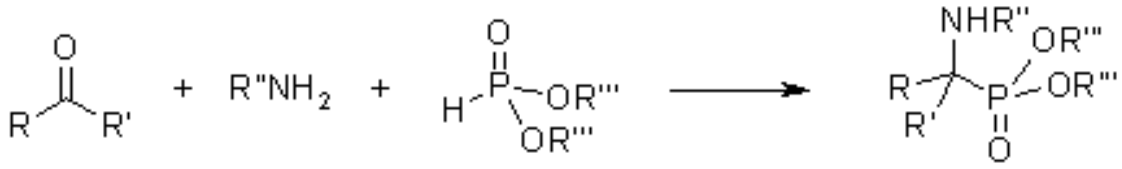
Bucherer-Bergs Reaction



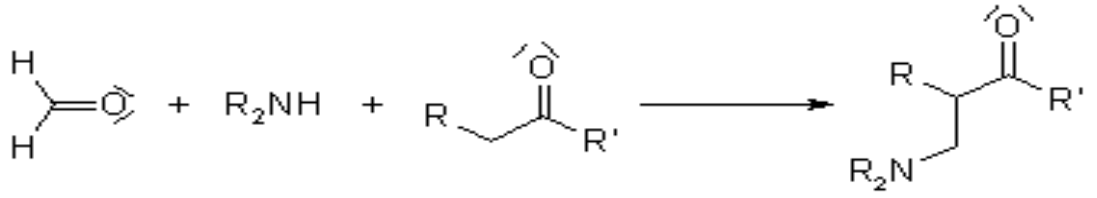
Gewald Reaction



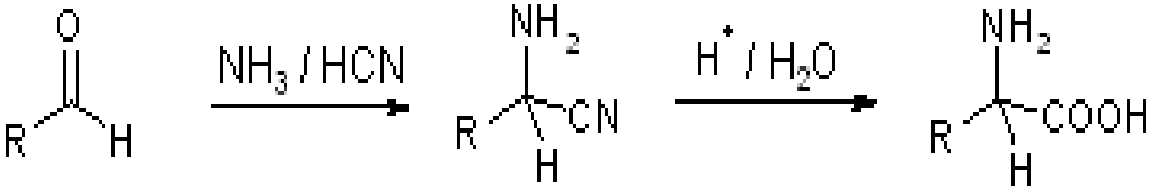
Hantzsch Dihydropyridine (Pyridine) Synthesis



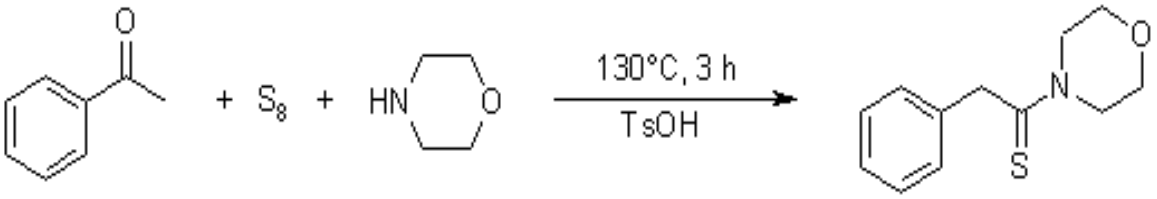
Kabachnik-Fields Reaction



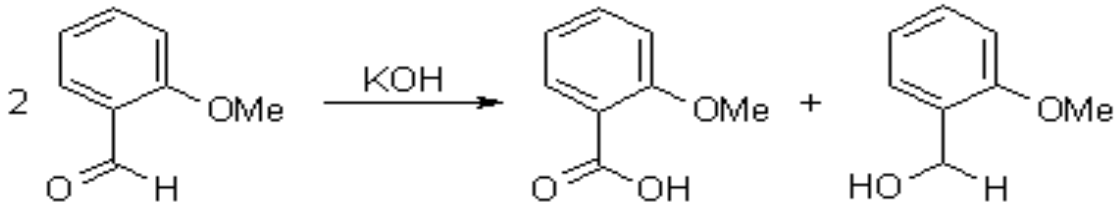
Mannich Reaction



Strecker Synthesis

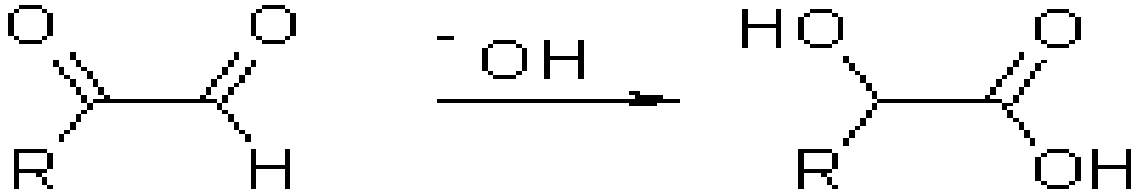


Cannizzaro reaction

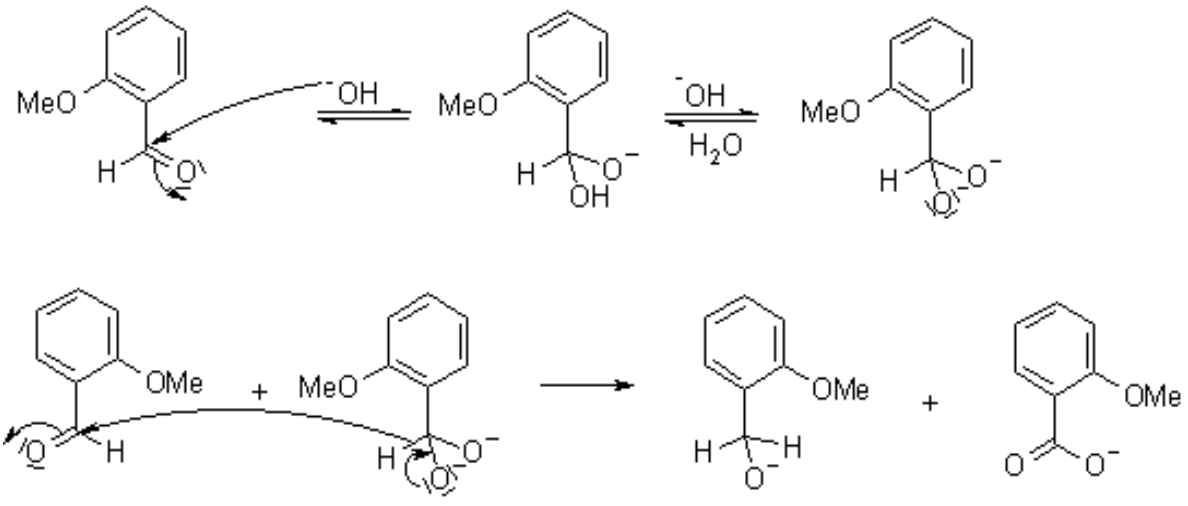


This redox disproportionation of non-enolizable aldehydes to carboxylic acids and alcohols is conducted in concentrated base.

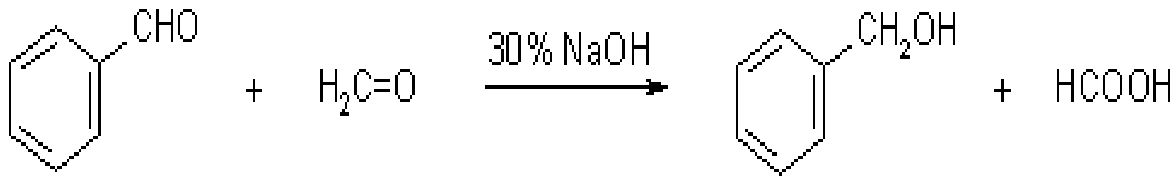
α-Keto aldehydes give the product of an intramolecular disproportionation in excellent yields.



Mechanism of the Cannizzaro Reaction



An interesting variant, the Crossed Cannizzaro Reaction, uses formaldehyde as reducing agent:



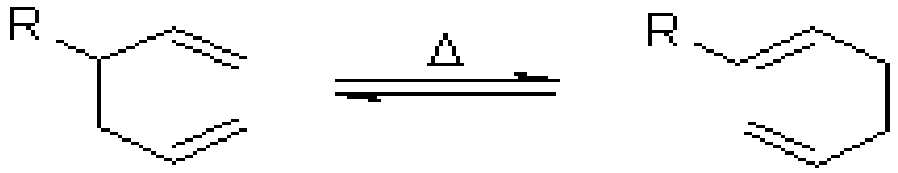
At the present time, various oxidizing and reducing agents can be used to carry out such conversions (with higher yields), so that today the Cannizzaro Reaction has limited synthetic utility except for the abovementioned conversion of α-keto aldehydes.

The Cannizzaro Reaction should be kept in mind as a source of potential side products when aldehydes are treated under basic conditions.

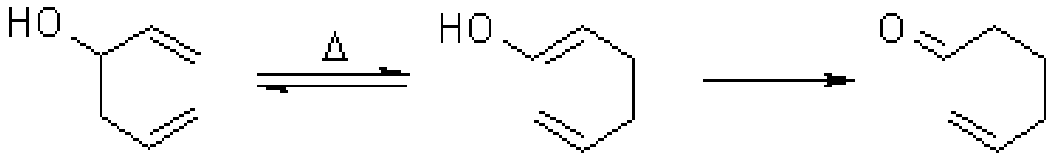
Cope Rearrangement

(Anionic) Oxy-Cope Rearrangement

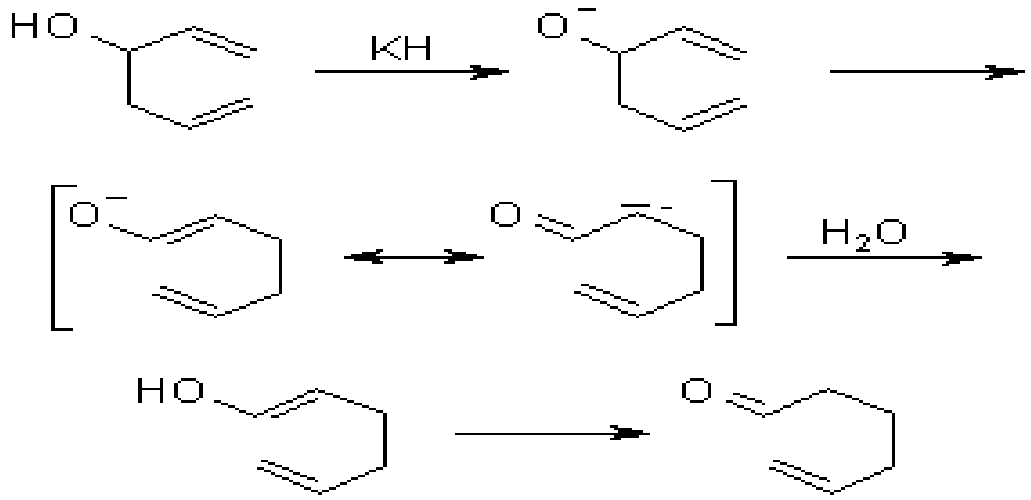
The Cope Rearrangement is the thermal isomerization of a 1,5-diene leading to a regioisomeric 1,5-diene. The main product is the thermodynamically more stable regioisomer. The Oxy-Cope has a hydroxyl substituent on an sp^3-hybridized carbon of the starting isomer.



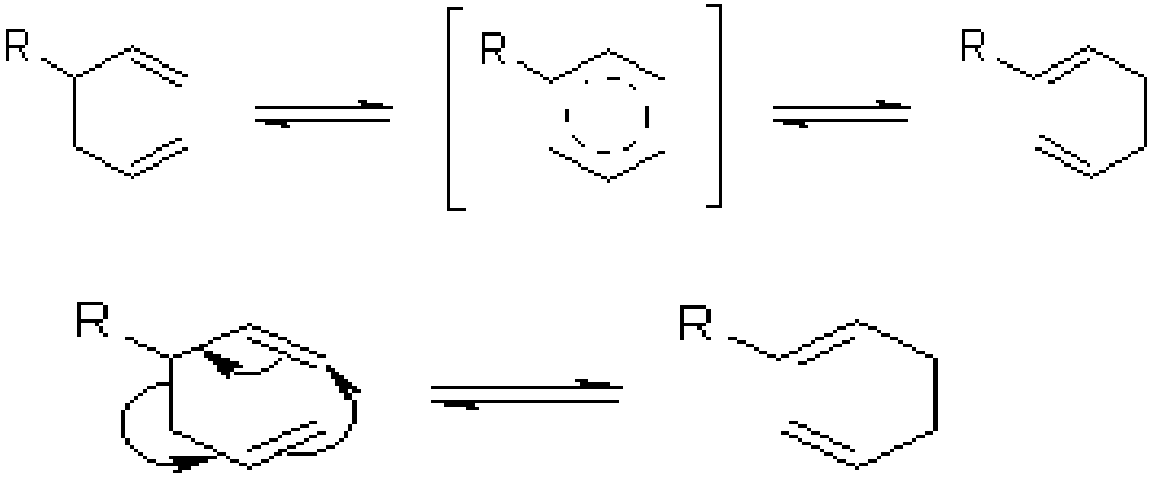
The driving force for the neutral or anionic Oxy-Cope Rearrangement is that the product is an enol or enolate (resp.), which can tautomerize to the corresponding carbonyl compound. This product will not equilibrate back to the other regioisomer.



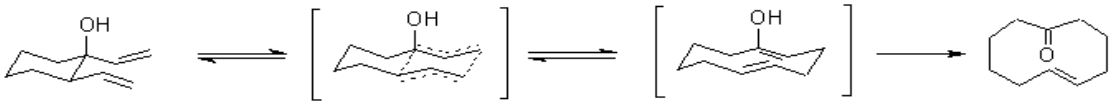
The Oxy-Cope Rearrangement proceeds at a much faster rate when the starting alcohol is deprotonated, e.g. with KH. The reaction is then up up to 10^{17} times faster, and may be conducted at room temperature. Aqueous work up then gives the carbonyl compound.

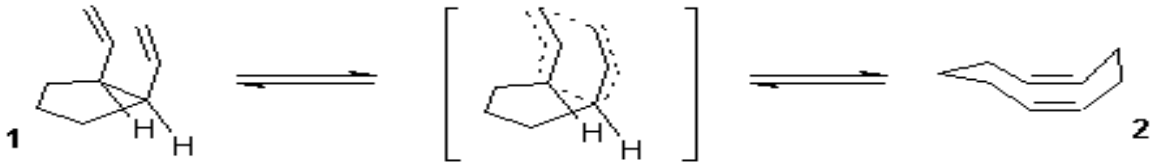


Mechanism of the Cope Rearrangement



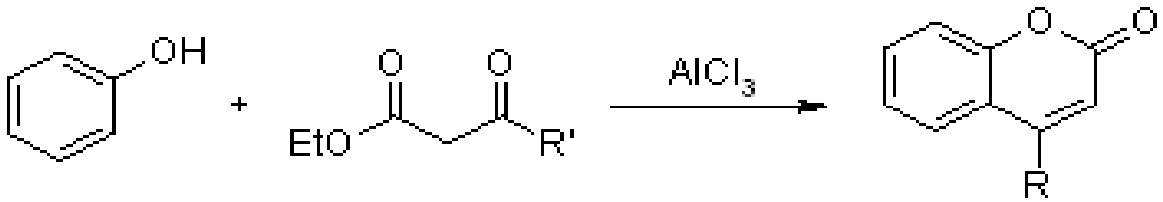
Two transition states are possible, and the outcome of the reaction can be predicted on the basis of the most favorable overlap of the orbitals of the double bond, as influenced by stereoelectronic factors:





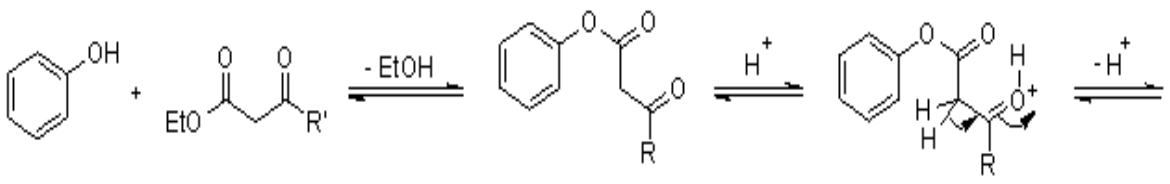
Pechmann Condensation

Coumarin Synthesis

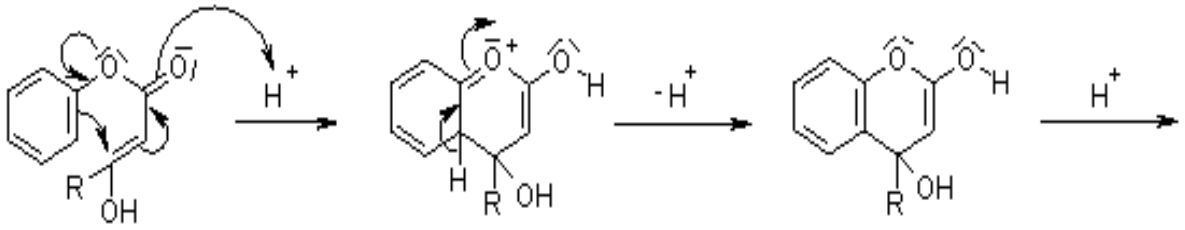


The Pechmann Condensation allows the synthesis of coumarins by reaction of phenols with β-keto esterMechanism of the Pechmann Condensation

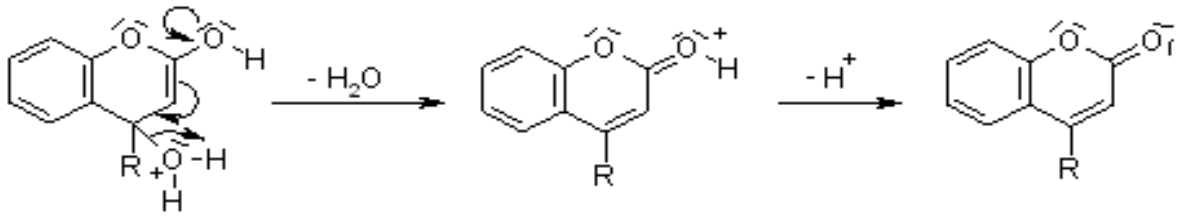
The reaction is conducted with a strong Brønstedt acid such as methanesulfonic acid or a Lewis acid such as $AlCl_3$. The acid catalyses transesterification as well as keto-enol tautomerisation:



A Michael Addition leads to the formation of the coumarin skeleton. This addition is followed by rearomatisation:

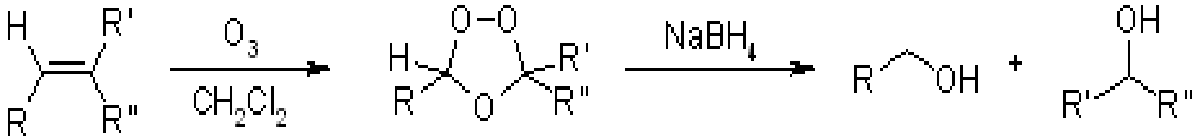


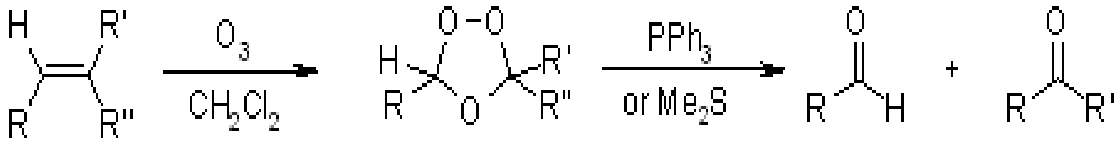
Subsequent acid-induced elimination of water gives the product:

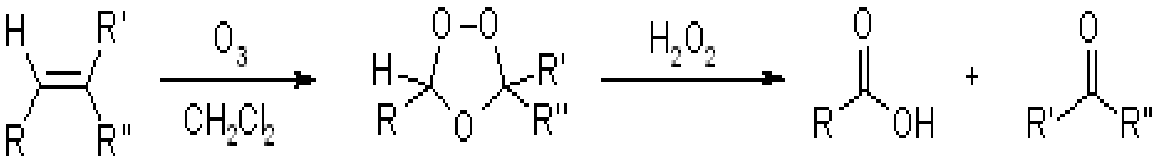


Ozonolysis

Criegee Mechanism





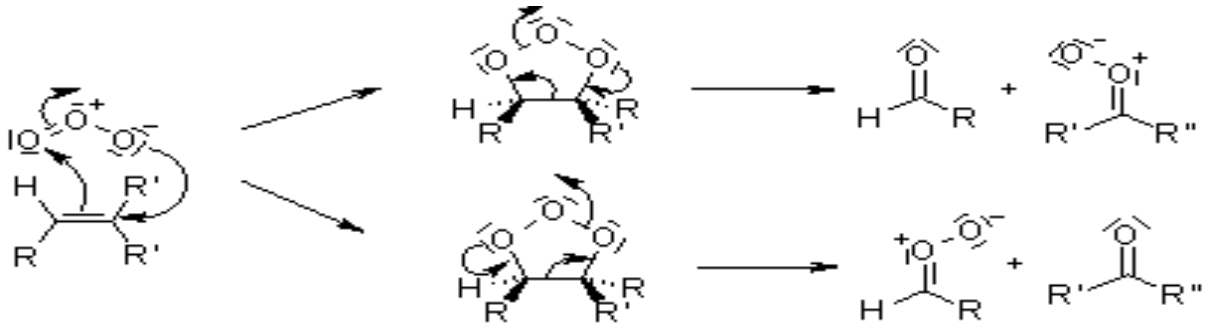


Ozonolysis allows the cleavage of alkene double bonds by reaction with ozone. Depending on the work up, different products may be isolated: reductive work-up gives either alcohols or carbonyl compounds, while oxidative work-up leads to carboxylic acids or ketones.

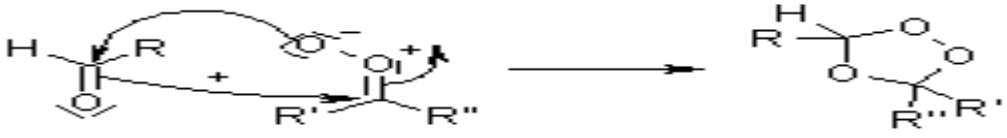
Mechanism of Ozonolysis

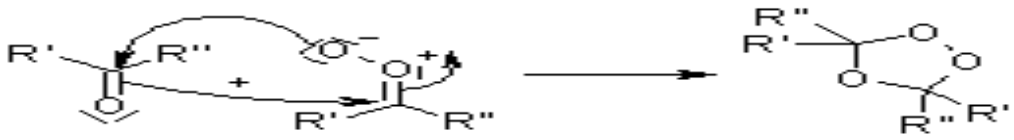
The mechanism was suggested by Criegee and has been recently revisited using ^{17}O-NMR Spectroscopy by the Berger Group

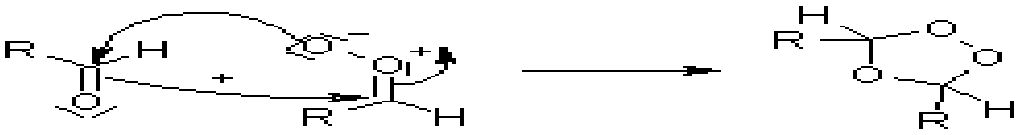
First step is a 1,3-dipolar cycloaddition of ozone to the alkene leading to the primary ozonide (molozonide, 1,2,3-trioxolane, or Criegee intermediate) which decomposes to give a carbonyl oxide and a carbonyl compound:



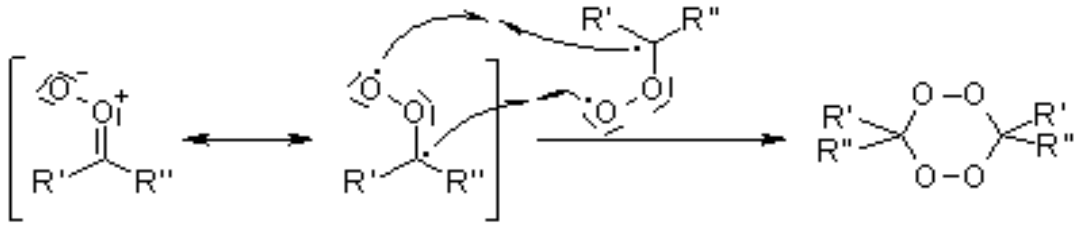
The carbonyl oxides are similar to ozone in being 1,3-dipolar compounds, and undergo 1,3-dipolar cycloaddition to the carbonyl compounds with the reverse regiochemistry, leading to a mixture of three possible secondary ozonides (1,2,4-trioxolanes):



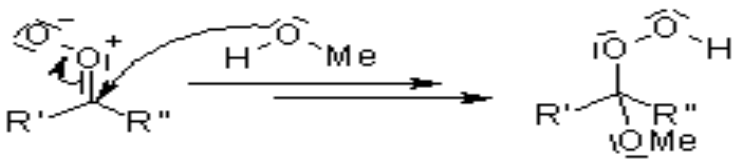




These secondary ozonides are more stable than primary ozonides. Even if the peroxy bridge is shielded by steric demanding groups leading to isolable products, they should not be isolated from an unmodified ozonolysis, because still more explosive side products (tetroxanes) may have been formed:



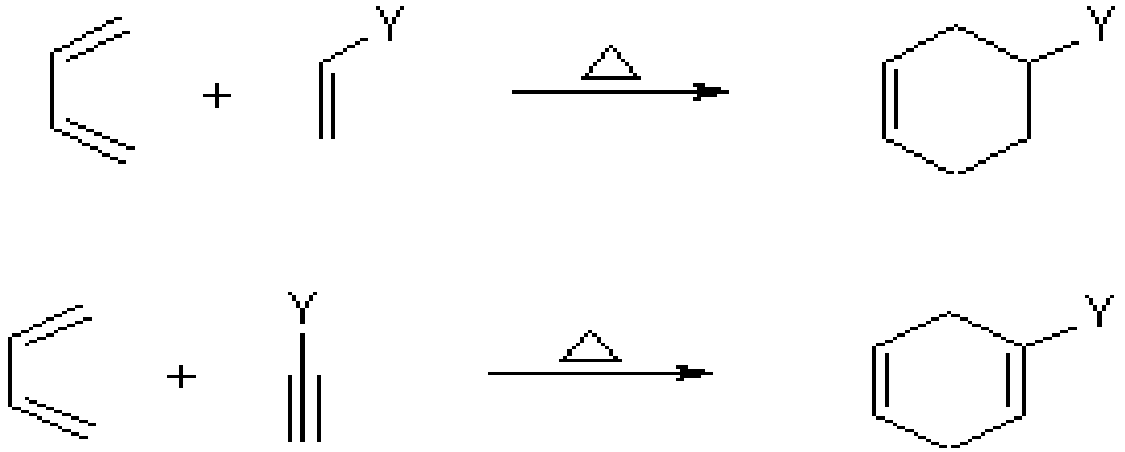
As endoperoxides are investigated as antimalarial compounds, more selective methods have been developed for their preparation (for example the Griesbaum Coozonolysis). Some reactions can be found here: The Criegee mechanism is valid for reactions in hydrocarbons, CH_2Cl_2, or other non-interactive solvents. Alcohols react with the carbonyl oxide to give hydroperoxy hemiacetals:



The synthetic value lies in the way the complex mixtures of intermediates can be worked up to give a defined composition of products and a clean conversion of all peroxide species. The three

main possibilities are given above, along with examples for the reagents used.

Diels-Alder Reaction



The [4+2]-cycloaddition of a conjugated diene and a dienophile (an alkene or alkyne), an electrocyclic reaction that involves the 4 π-electrons of the diene and 2 π-electrons of the dienophile. The driving force of the reaction is the formation of new σ-bonds, which are energetically more stable than the π-bonds.

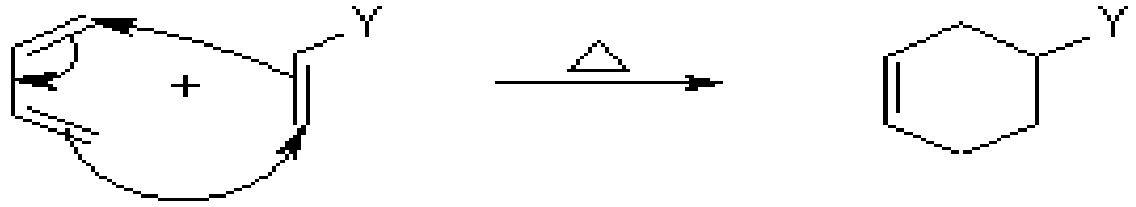
In the case of an alkynyl dienophile, the initial adduct can still react as a dienophile if not too sterically hindered. In addition, either the diene or the dienophile can be substituted with cumulated double bonds, such as substituted allenes.

With its broad scope and simplicity of operation, the Diels-Alder is the most powerful synthetic method for unsaturated six-membered rings.

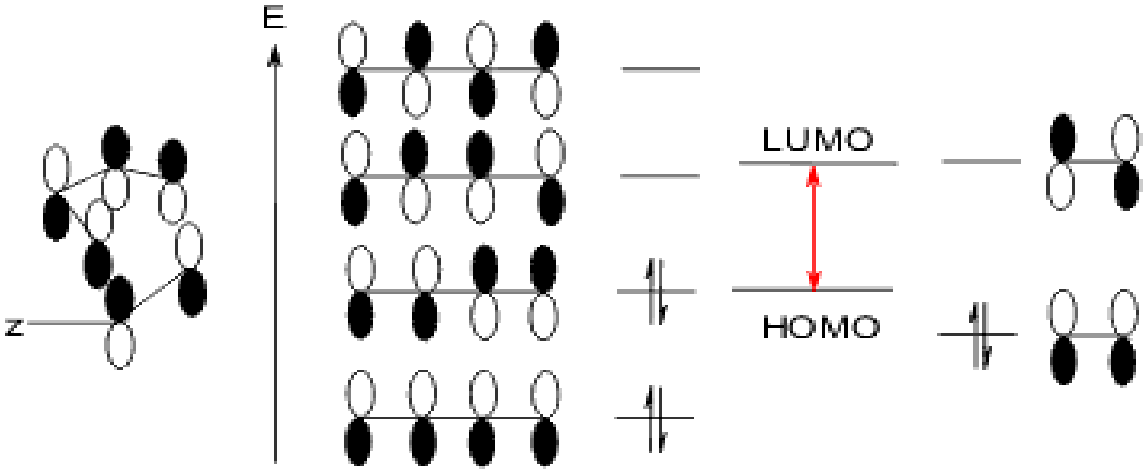
A variant is the hetero-Diels-Alder, in which either the diene or the dienophile contains a heteroatom, most often nitrogen or oxygen.

This alternative constitutes a powerful synthesis of six-membered ring heterocycles

Mechanism of the Diels-Alder Reaction



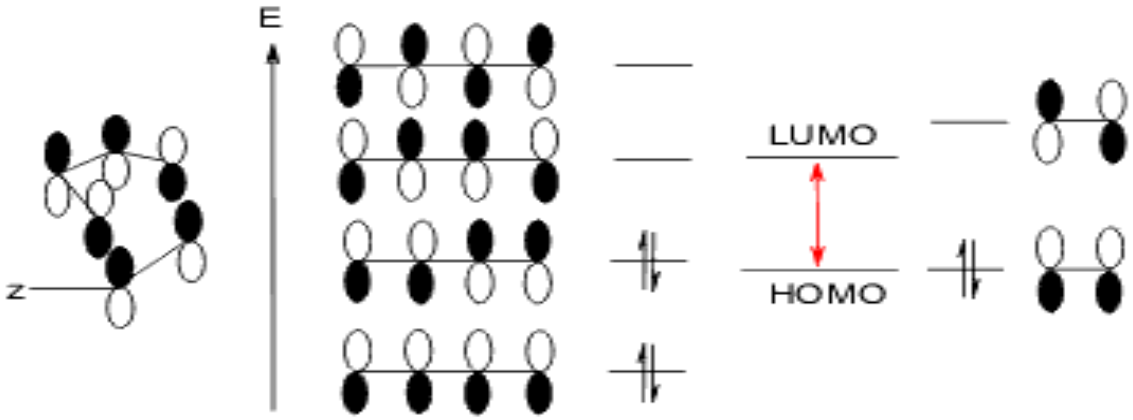
Overlap of the molecular orbitals (MOs) is required:



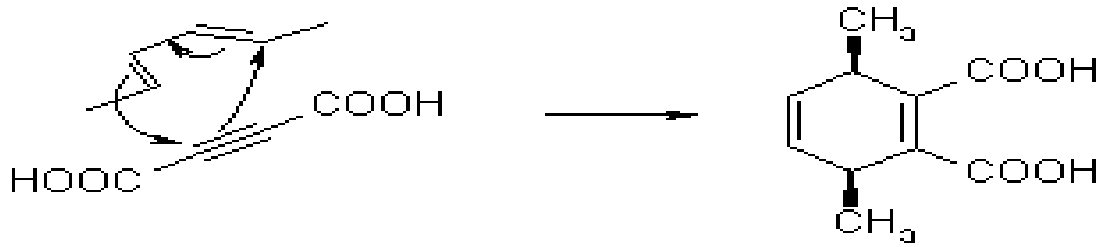
Overlap between the highest occupied MO of the diene (HOMO) and the lowest unoccupied MO of the dienophile (LUMO) is thermally allowed in the Diels Alder Reaction, provided the orbitals are of similar energy. The reaction is facilitated by electron-withdrawing groups on the dienophile, since this will lower the energy of the LUMO. Good dienophiles often bear one or two of the following substituents: CHO, COR, COOR, CN, C=C, Ph, or halogen. The diene component should be as electron-rich as possible.

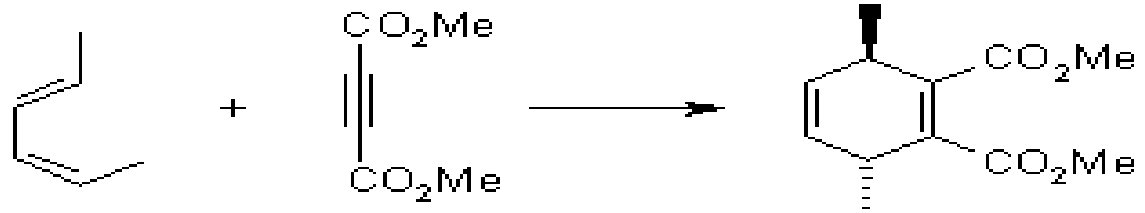
There are "inverse demand" Diels Alder Reactions that involve the overlap of the HOMO of the dienophile with the unoccupied MO of the diene. This alternative scenario for the reaction is favored by

electron-donating groups on the dienophile and an electron-poor diene.

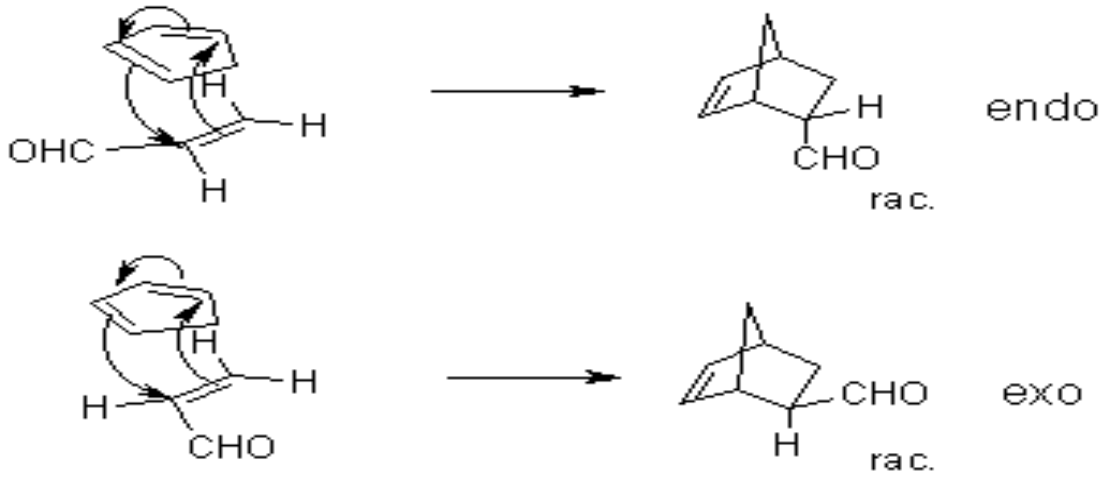


The reaction is diastereoselective.



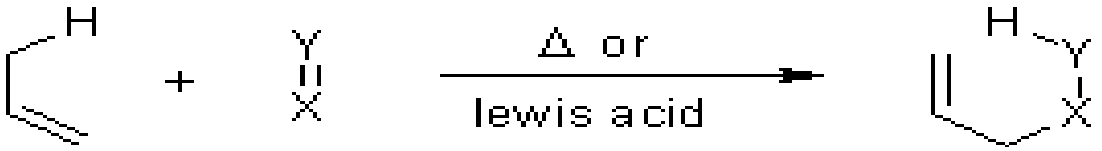


Cyclic dienes give stereoisomeric products. The endo product is usually favored by kinetic control due to secondary orbital interactions.



Alder-Ene Reaction

Ene Reaction



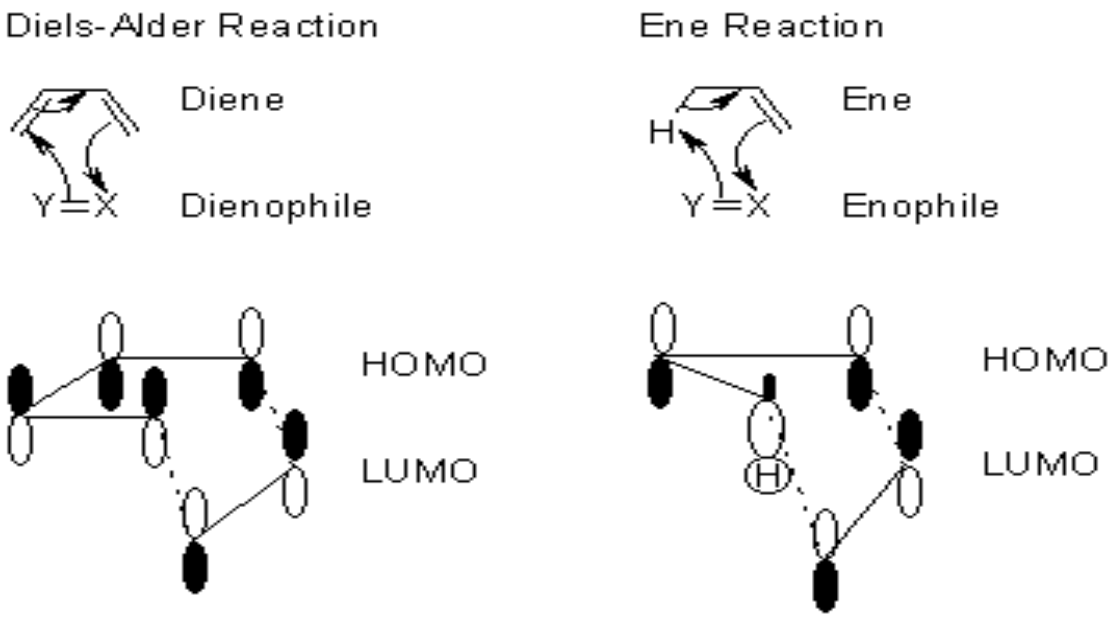
The four-electron system including an alkene π-bond and an allylic C-H σ-bond can participate in a pericyclic reaction in which the double bond shifts and new C-H and C-C σ-bonds are formed. This allylic system reacts similarly to a diene in a Diels-Alder Reaction, while in this case the other partner is called an enophile, analogous to the dienophile in the Diels-Alder. The Alder-Ene Reaction requires

higher temperatures because of the higher activation energy and stereoelectronic requirement of breaking the allylic C-H σ-bond.

The enophile can also be an aldehyde, ketone or imine, in which case β-hydroxy- or β-aminoolefins are obtained. These compounds may be unstable under the reaction conditions, so that at elevated temperature (>400°C) the reverse reaction takes place - the Retro-Ene Reaction.

While mechanistically different, the Ene reaction can produce a result similar to the Prins Reaction.

Mechanism of the Alder-Ene Reaction



Also like the Diels-Alder, some Ene Reactions can be catalyzed by Lewis Acids. Lewis-Acid catalyzed Ene Reactions are not necessarily concerted (for example: Iron(III) Chloride Catalysis of the Acetal-Ene Reaction).

Fischer Esterification

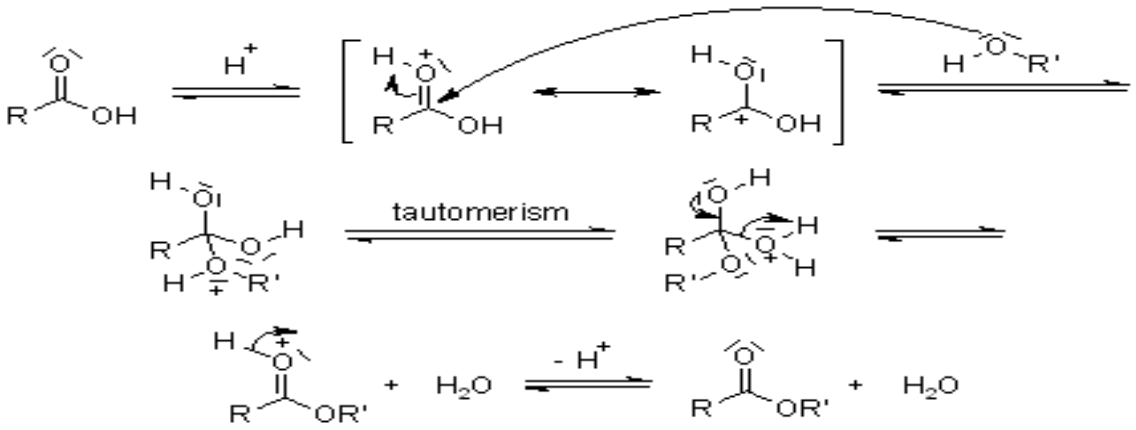
Fischer-Speier Esterification

The Lewis or Brønstedt acid-catalyzed esterification of carboxylic acids with alcohols to give esters is a typical reaction in which the products and reactants are in equilibrium.

The equilibrium may be influenced by either removing one product from the reaction mixture (for example, removal of the water by azeotropic distillation or absorption by molecular sieves) or by employing an excess of one reactant.

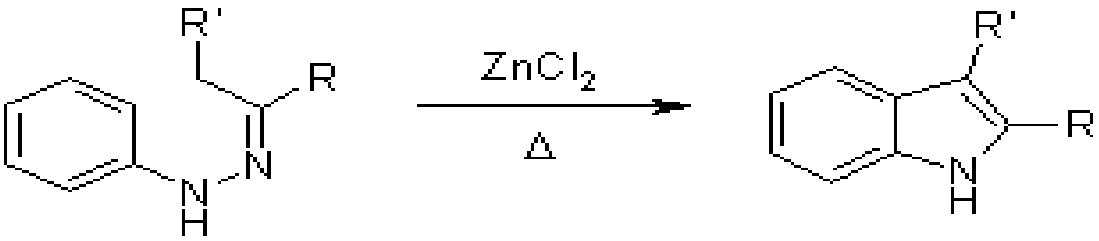
Mechanism of the Fischer Esterification

Addition of a proton (e.g.: *p*-TsOH, H_2SO_4) or a Lewis acid leads to a more reactive electrophile. Nucleophilic attack of the alcohol gives a tetrahedral intermediate in which there are two equivalent hydroxyl groups. One of these hydroxyl groups is eliminated after a proton shift (tautomerism) to give water and the ester.

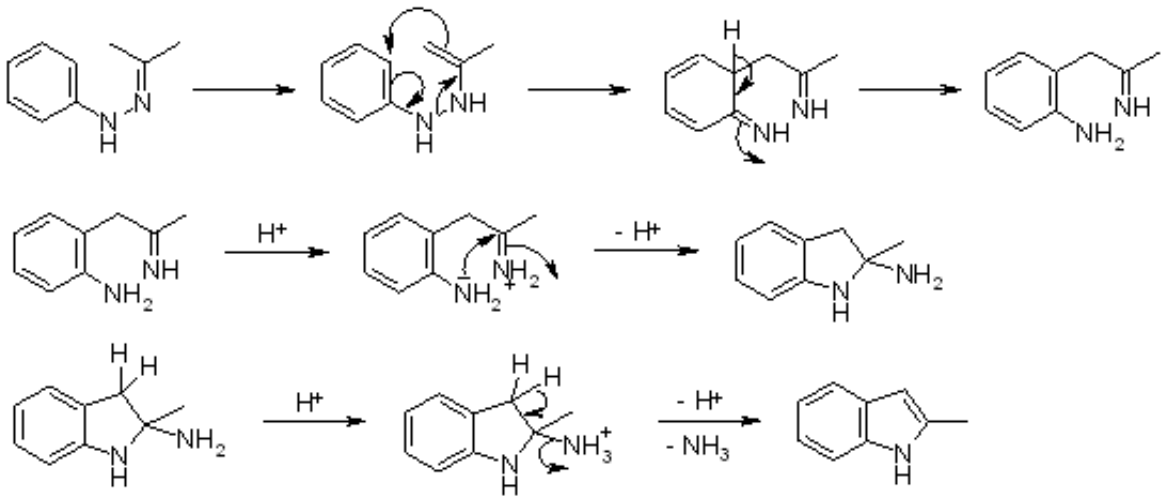


Alternative reactions employ coupling reagents such as DCC (Steglich Esterification), preformed esters (transesterification), carboxylic acid chlorides or anhydrides (see 1overview). These reactions avoid the production of water. Another pathway for the production of esters is the formation of a carboxylate anion, which then reacts as a nucleophile with an electrophile (similar reactions can be 12found here). Esters may also be produced by oxidations, namely by the Baeyer-Villiger oxidation and 1oxidative esterifications.

Fischer Indole Synthesis

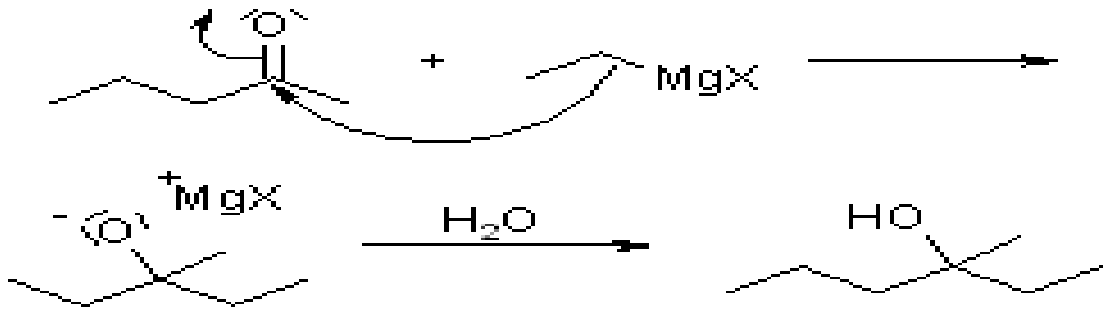


The conversion of aryl hydrazones to indoles; requires elevated temperatures and the addition of Brønsted or Lewis acids. Some interesting enhancements have been published recently; for example a milder conversion when *N*-trifluoroacetyl enehydrazines are used as substrates. Mechanism of the Fischer Indole Synthesis



Grignard Reaction

Grignard Reagents

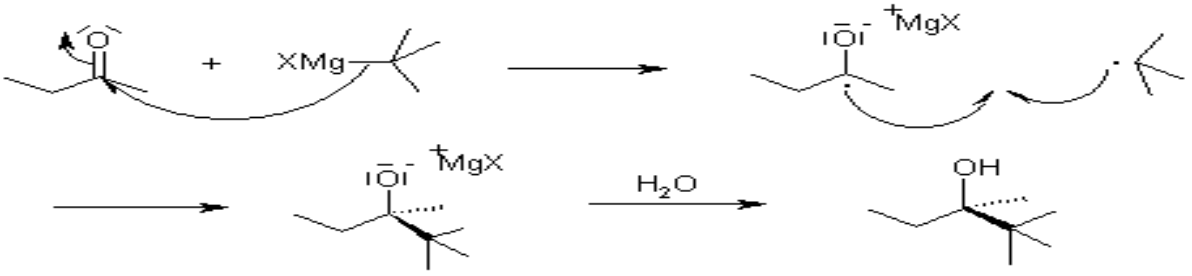


The Grignard Reaction is the addition of an organomagnesium halide (Grignard reagent) to a ketone or aldehyde, to form a tertiary or secondary alcohol, respectively. The reaction with formaldehyde leads to a primary alcohol.

Grignard Reagents are also used in the following important reactions: The addition of an excess of a Grignard reagent to an ester or lactone gives a tertiary alcohol in which two alkyl groups are the same, and the addition of a Grignard reagent to a nitrile produces an unsymmetrical ketone via a metalloimine intermediate. (Some more reactions are depicted below)

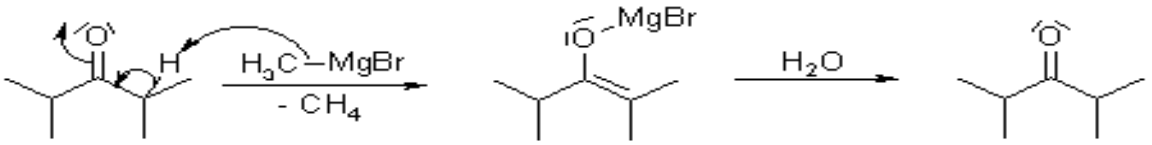
Mechanism of the Grignard Reaction

While the reaction is generally thought to proceed through a nucleophilic addition mechanism, sterically hindered substrates may react according to an SET (single electron transfer) mechanism:

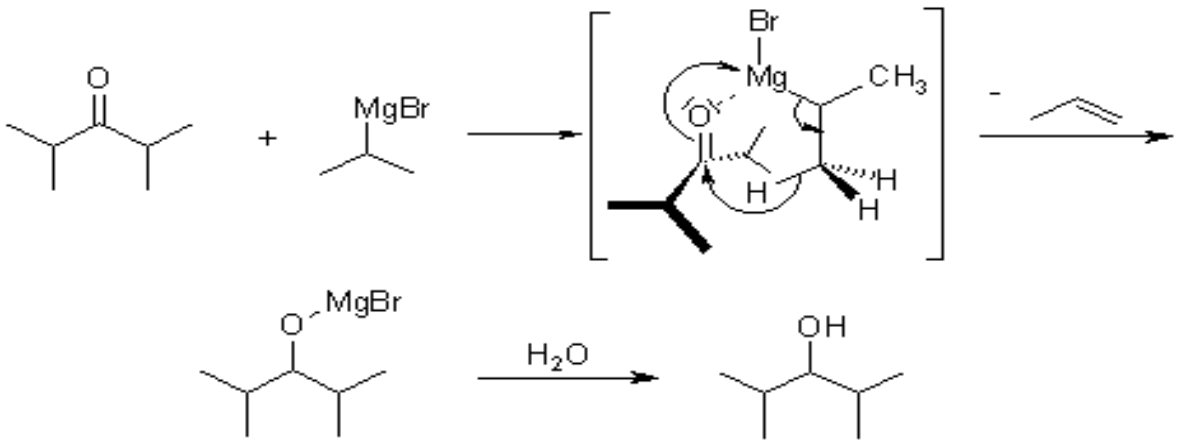


With sterically hindered ketones the following side products are received:

The Grignard reagent can act as base, with deprotonation yielding an enolate intermediate. After work up, the starting ketone is recovered.

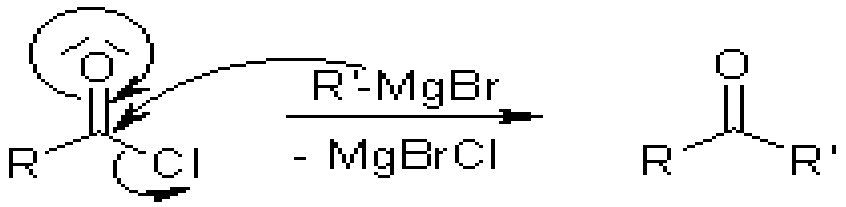


A reduction can also take place, in which a hydride is delivered from the β-carbon of the Grignard reagent to the carbonyl carbon via a cyclic six-membered transition state.

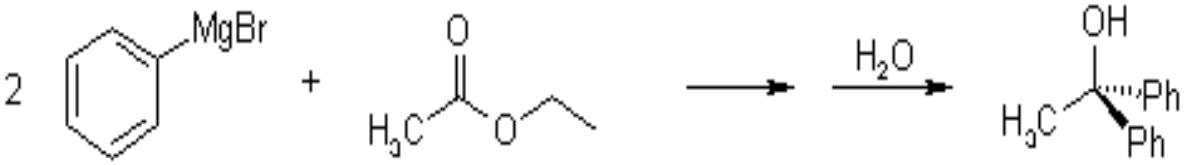


Additional reactions of Grignard Reagents:

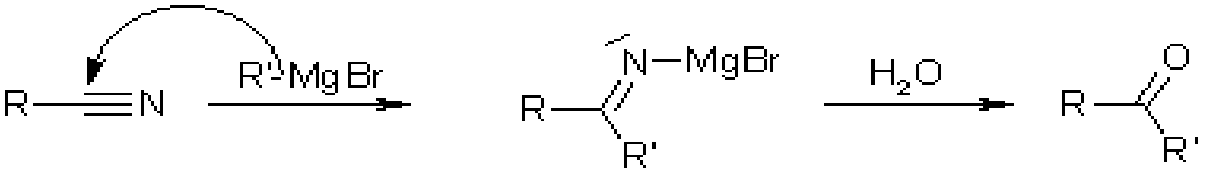
With carboxylic acid chlorides:



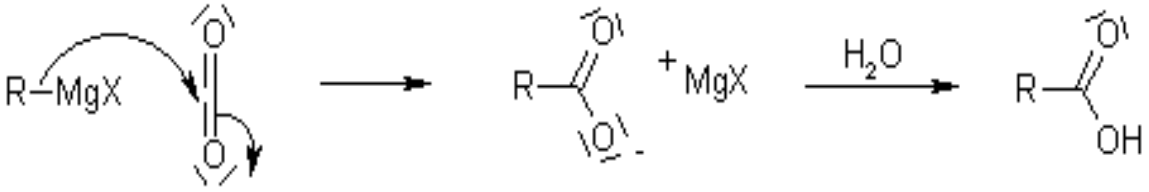
Esters are less reactive than the intermediate ketones, therefore the reaction is only suitable for synthesis of tertiary alcohols using an excess of Grignard Reagent:



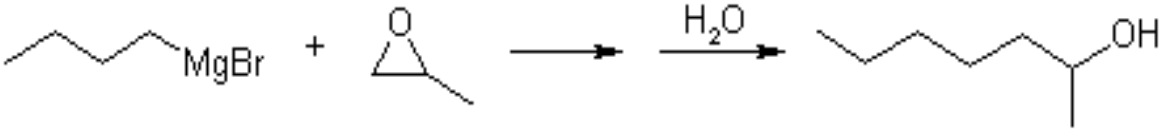
With nitriles:



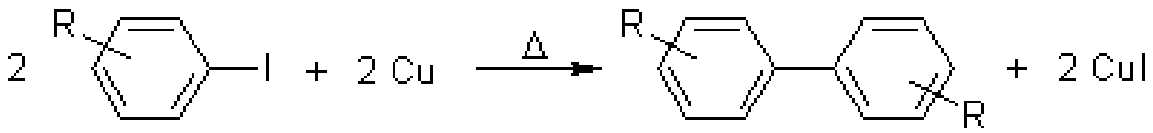
With CO_2 (by adding dry ice to the reaction mixture):



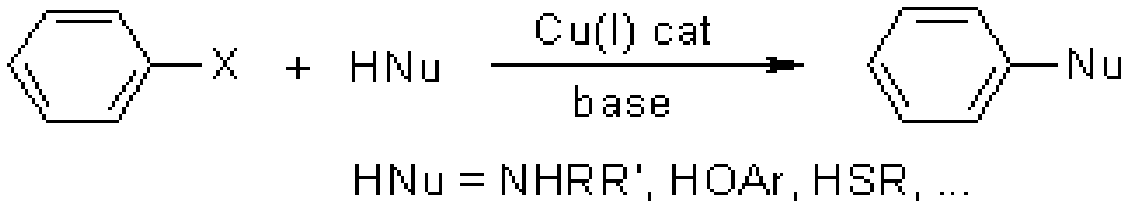
With oxiranes:



Ullmann Reaction

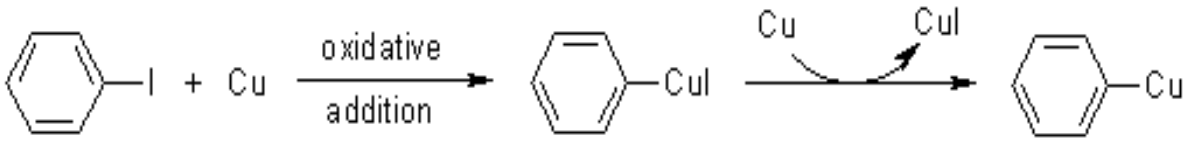


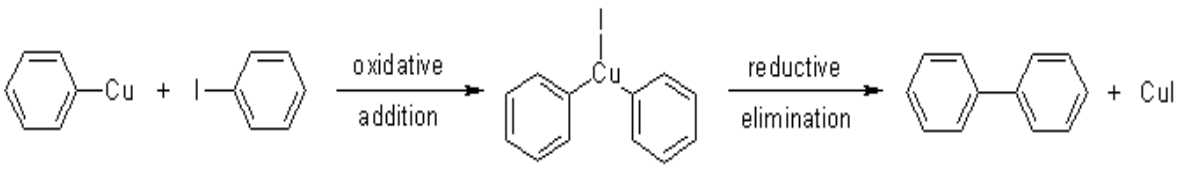
There are two different transformations referred as the Ullmann Reaction. The "classic" Ullmann Reaction is the synthesis of symmetric biaryls via copper-catalyzed coupling. The "Ullmann-type" Reactions include copper-catalyzed Nucleophilic Aromatic Substitution between various nucleophiles (e.g. substituted phenoxides) with aryl halides. The most common of these is the Ullmann Ether Synthesis.



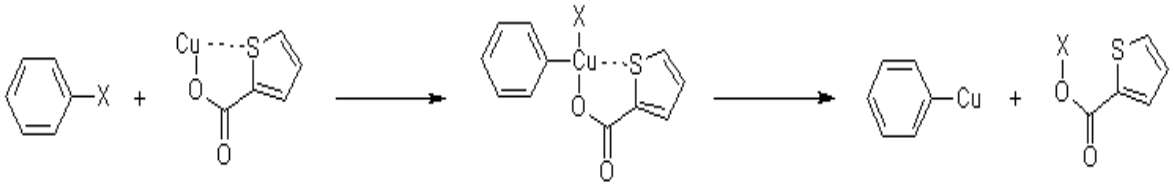
Mechanism of the Ullmann Reaction

Biaryls are available through coupling of the aryl halide with an excess of copper at elevated temperatures (200 °C). The active species is a copper(I)-compound which undergoes oxidative addition with the second equivalent of halide, followed by reductive elimination and the formation of the aryl-aryl carbon bond.

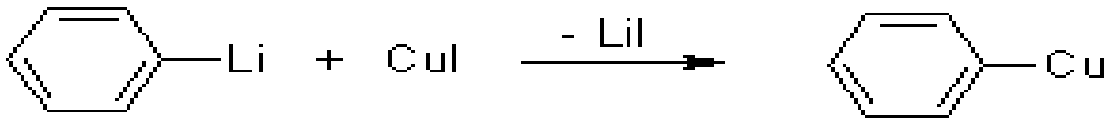




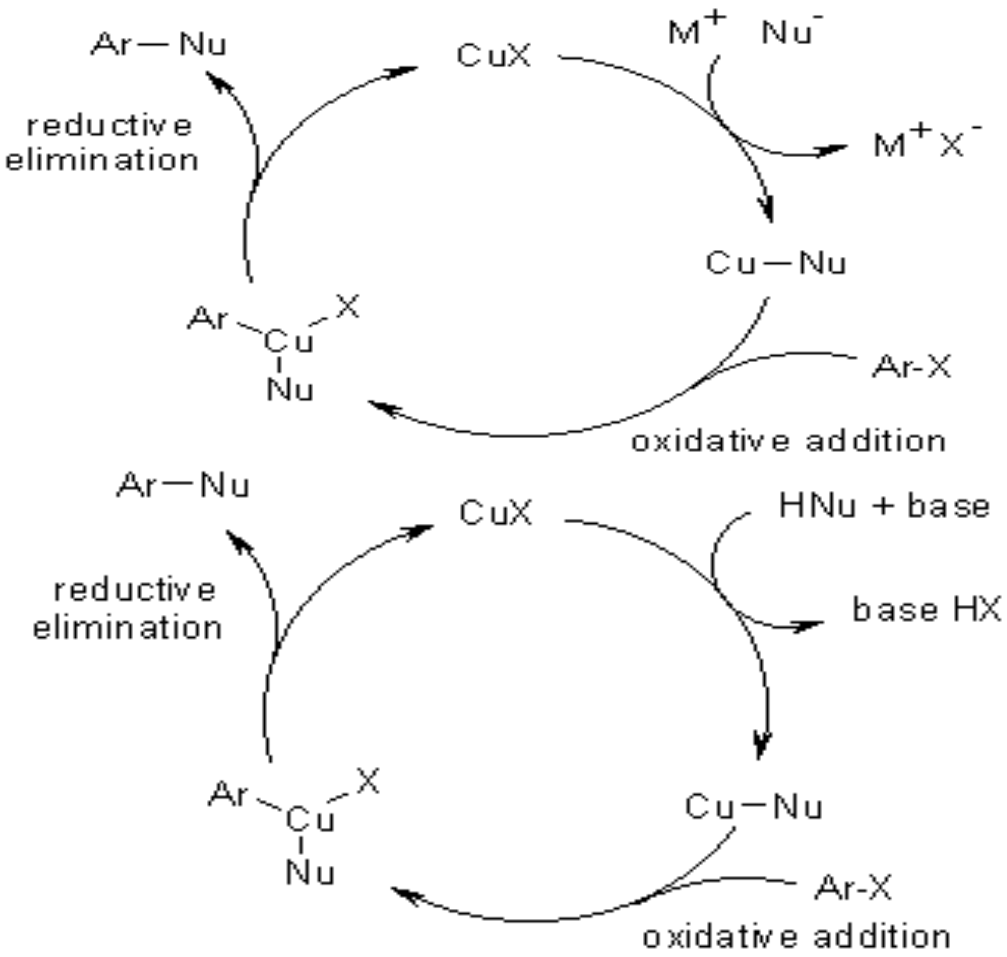
The organocopper intermediate can be generated at a more moderate 70 °C using a novel thiophenecarboxylate reagent. The reaction otherwise follows the same reaction path as above.



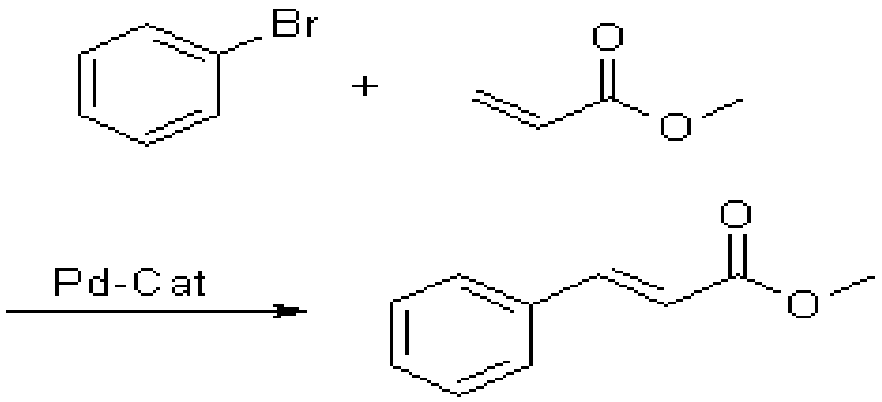
Another possibility is the use of Cu(I) for the oxidative coupling of aryllithium compounds at low temperatures. This method can also be used to generate asymmetric biaryls, after addition of the appropriate halide.



Ullmann-type reactions proceed through a catalytic cycle, and in one mechanism the copper is postulated to undergo oxidation to Cu(III). As some Cu(III) salts have been prepared, the suggestion for the mechanism is intriguing.


Ar—Nu
CuX
M+ Nu-
M+X-
reductive elimination
Cu—Nu
Ar
Cu
X
Nu
Ar-X
oxidative addition
Ar—Nu
CuX
HNu + base
base HX
reductive elimination
Ar
Cu
X
Nu
Cu—Nu
Ar-X
oxidative addition

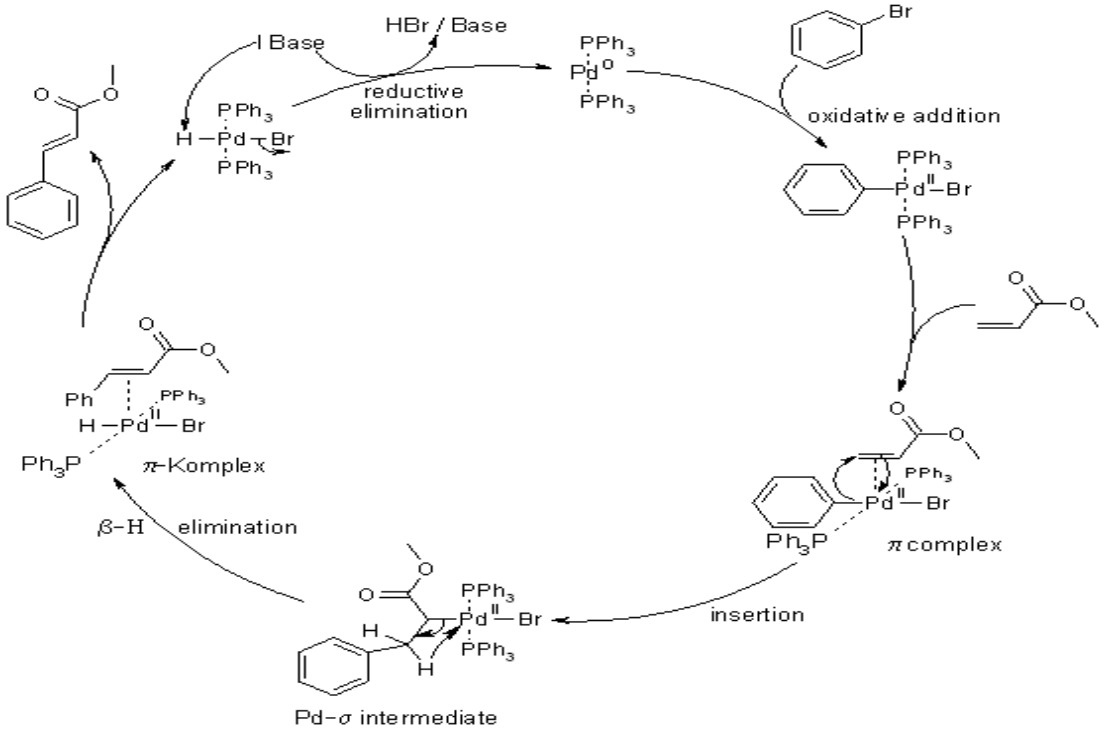
Heck Reaction



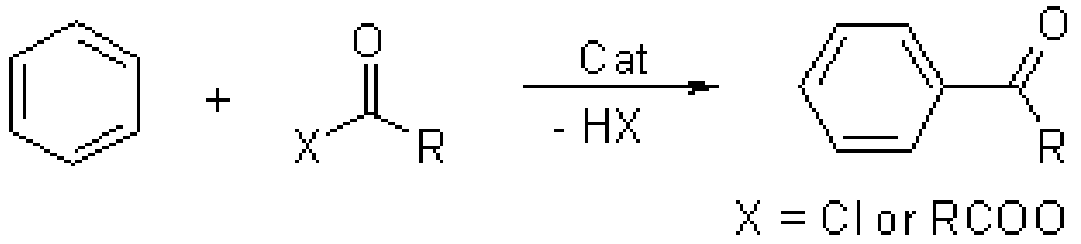
The palladium-catalyzed C-C coupling between aryl halides or vinyl halides and activated alkenes in the presence of a base is referred as the "Heck Reaction". Recent developments in the catalysts and reaction conditions have resulted in a much broader range of donors and acceptors being amenable to the Heck Reaction.

One of the benefits of the Heck Reaction is its outstanding *trans* selectivity.

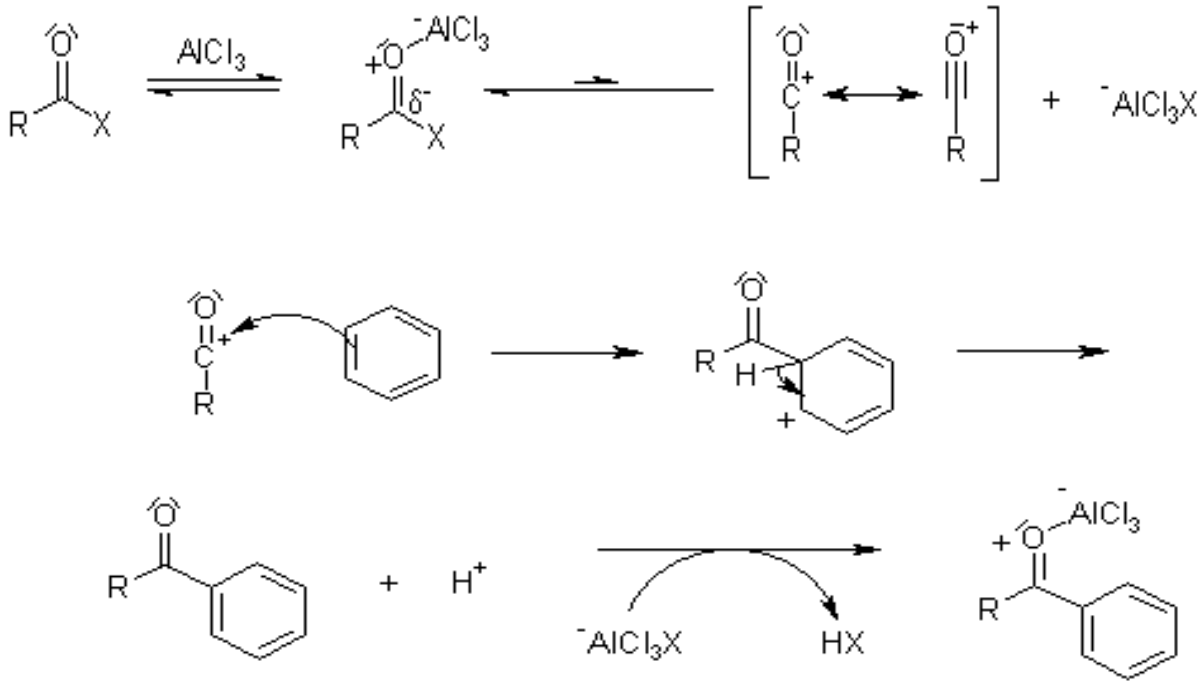
Mechanism of the Heck Reaction

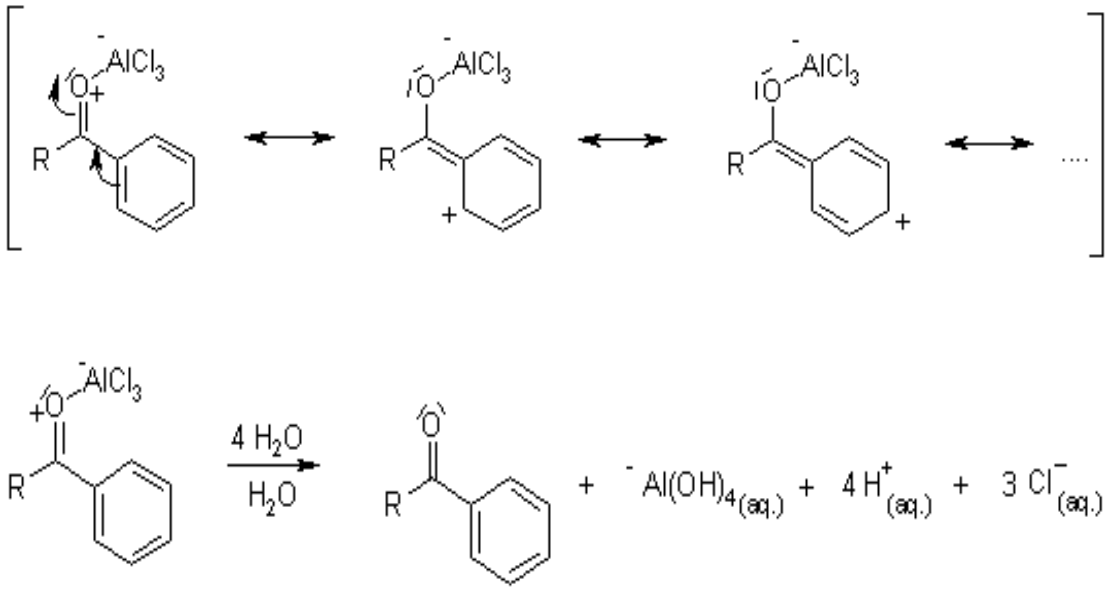


Friedel-Crafts Acylation

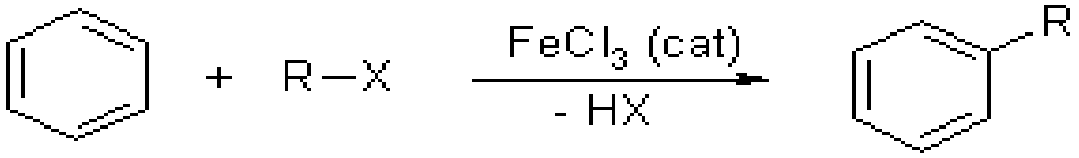


This electrophilic aromatic substitution allows the synthesis of monoacylated products from the reaction between arenes and acyl chlorides or anhydrides. The products are deactivated, and do not undergo a second substitution. Normally, a stoichiometric amount of the Lewis acid catalyst is required, because both the substrate and the product form complexesMechanism of the Friedel-Crafts Acylation



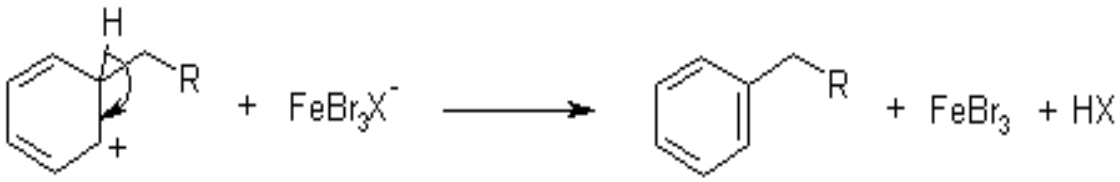


Friedel-Crafts Alkylation

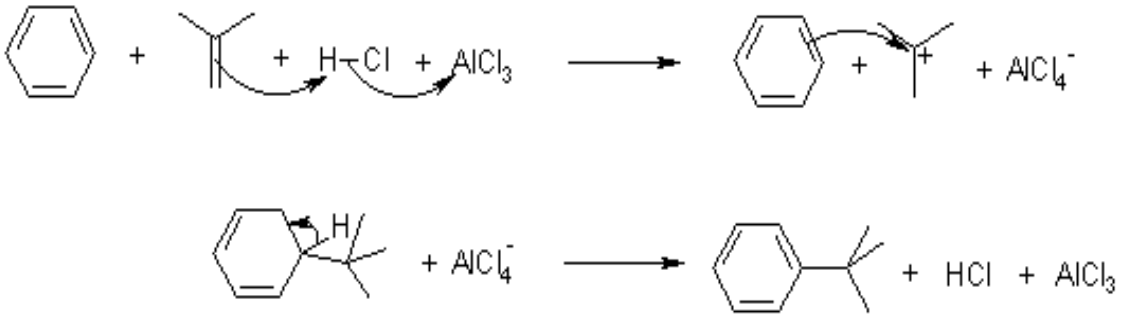


This Lewis acid-catalyzed electrophilic aromatic substitution allows the synthesis of alkylated products via the reaction of arenes with alkyl halides or alkenes. Since alkyl substituents activate the arene substrate, polyalkylation may occur. A valuable, two-step alternative is Friedel-Crafts Acylation followed by a carbonyl reduction.

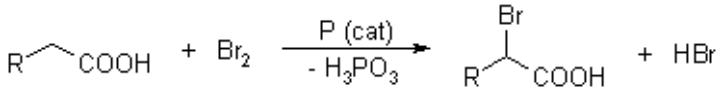
Mechanism of the Friedel-Crafts Alkylation



Using alkenes :

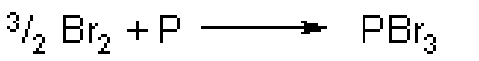


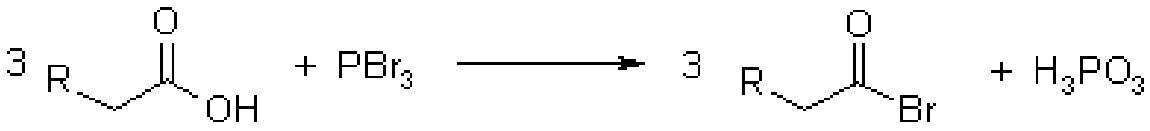
Hell-Volhard-Zelinsky Reaction



Treatment with bromine and a catalytic amount of phosphorus leads to the selective α-bromination of carboxylic acids Mechanism of the Hell-Volhard-Zelinsky Reaction

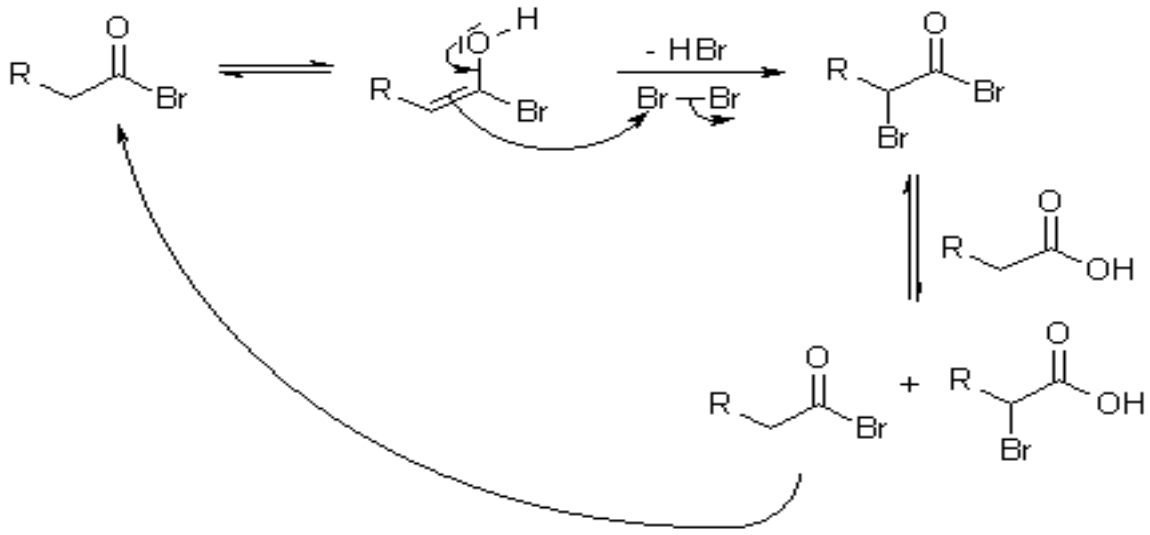
Phosphorus reacts with bromine to give phosphorus tribromide, and in thefirst step this converts the carboxylic acid into an acyl bromide.



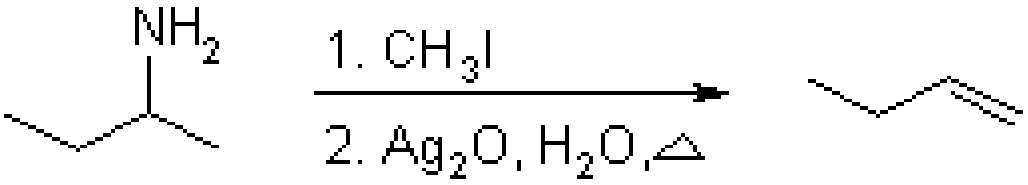


An acyl bromide can readily exist in the enol form, and this tautomer is rapidly brominated at the α-carbon. The monobrominated compound is much less nucleophilic, so the reaction stops at this

stage. This acyl intermediate compound can undergo bromide exchange with unreacted carboxylic acid via the anhydride, which allows the catalytic cycle to continue until the conversion is complete.

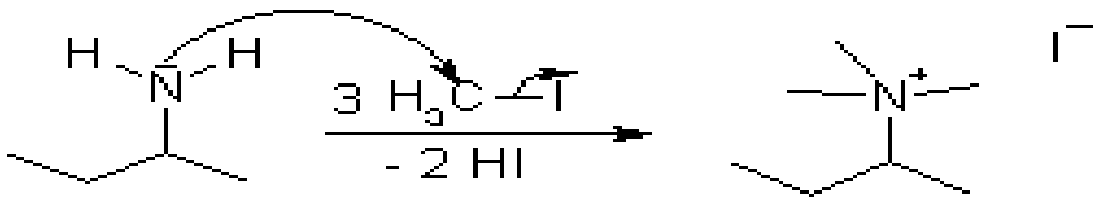


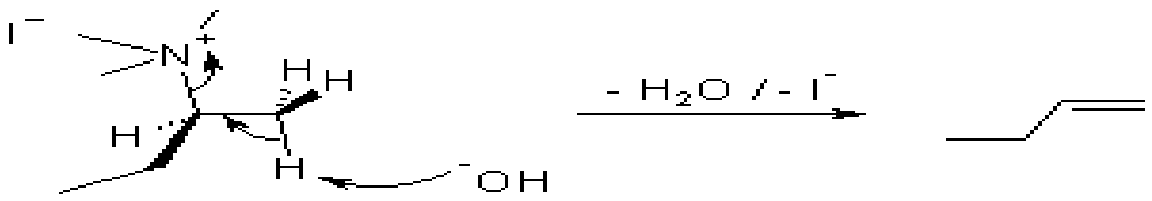
Hofmann Elimination



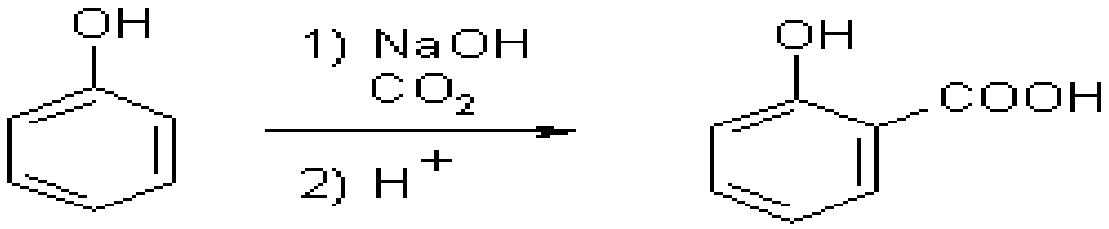
Sometimes referred to as the Hofmann Degradation. This elimination reaction of alkyl trimethyl amines proceeds with *anti*-stereochemistry, and is generally suitable for producing alkenes with one or two substituents. The reaction follows the Hofmann Rule

Mechanism of the Hofmann Elimination



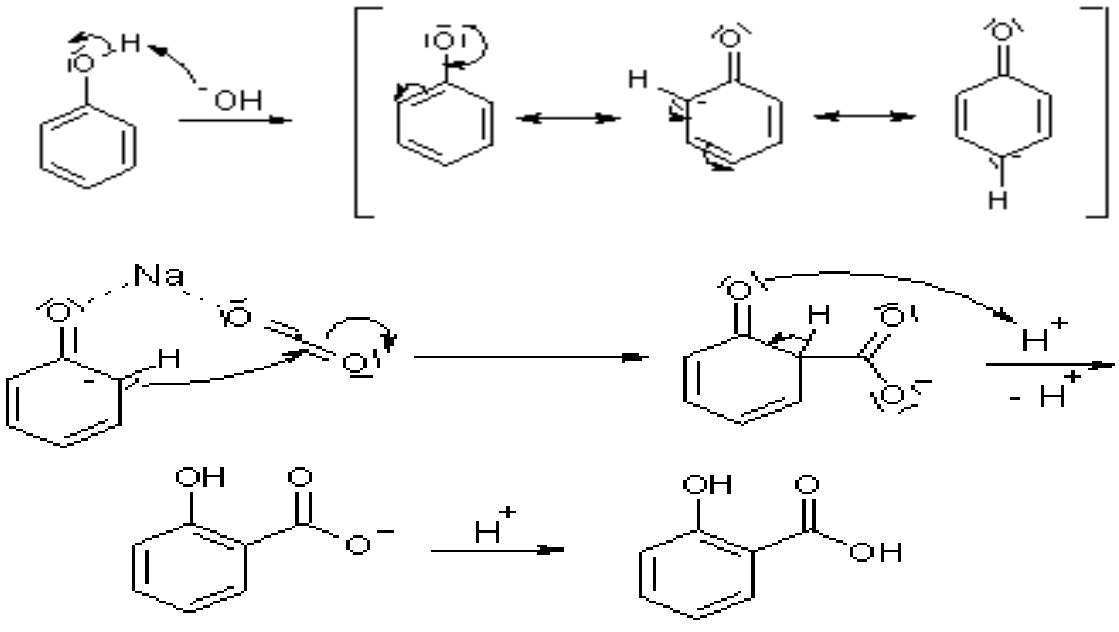


Kolbe-Schmitt Reaction

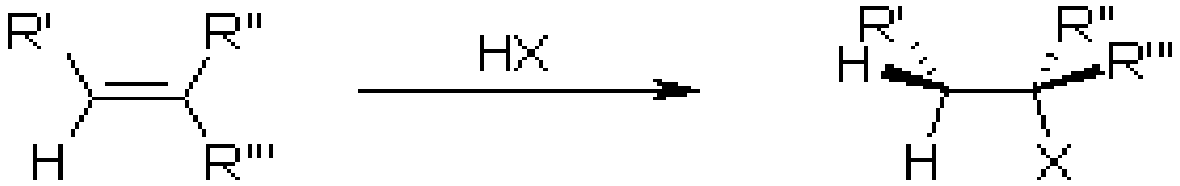


A base-promoted carboxylation of phenols that allows the synthesis of salicylic acid derivatives.

Mechanism of the Kolbe-Schmitt Reaction



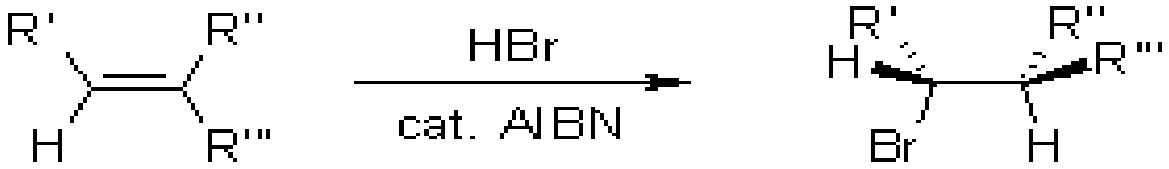
Markovnikov's Rule



Markovnikov Rule predicts the regiochemistry of HX addition to unsymmetrically substituted alkenes.

The halide component of HX bonds preferentially at the more highly substituted carbon, whereas the hydrogen prefers the carbon which already contains more hydrogens.

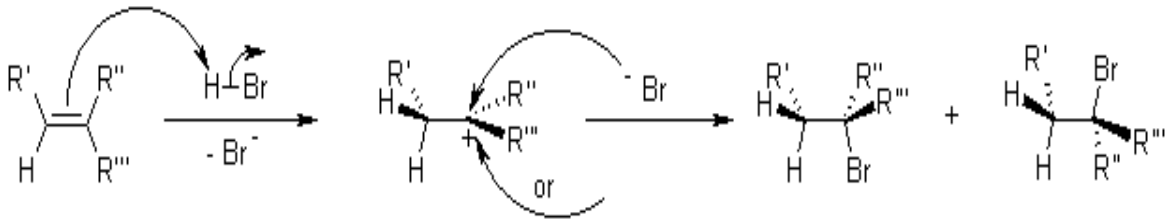
***Anti*-Markovnikov**



Some reactions do not follow Markovnikov's Rule, and *anti*-Markovnikov products are isolated. This is a feature for example of radical induced additions of HX and of Hydroboration.

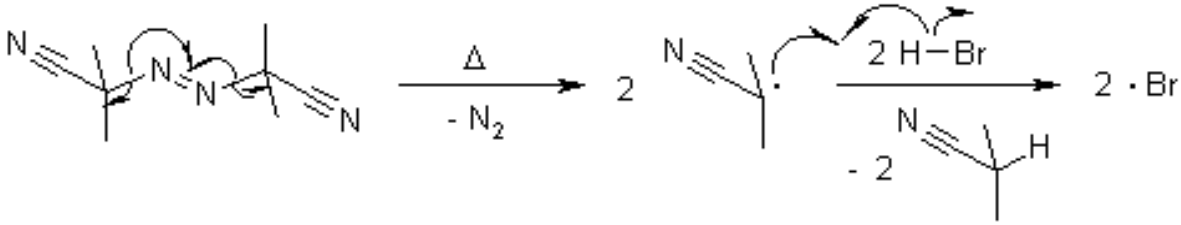
Mechanism

The proton adds first to the carbon-carbon double bond. The carbon bearing more substituents forms a more stable carbenium ion; attack of bromide ion follows in a second step:

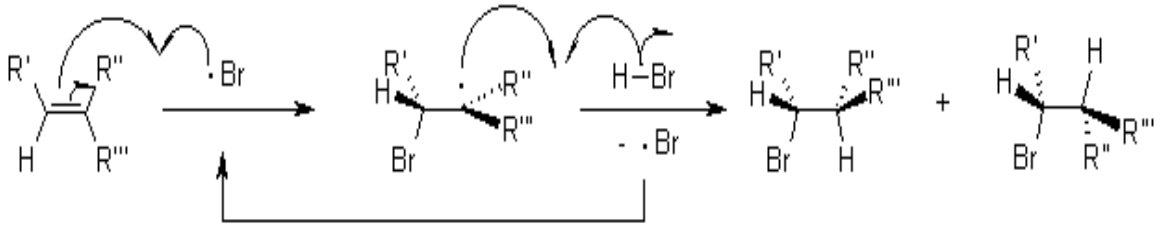


Markovnikov

Radical reactions require an initiation step. In this example, a bromo radical is formed.



The reversal of the regiochemistry of addition is the result of the reversal of the order in which the two components add to the alkene. Radical addition leads to the formation of the more stable radical, which reacts with HBr to give product and a new bromo radical:



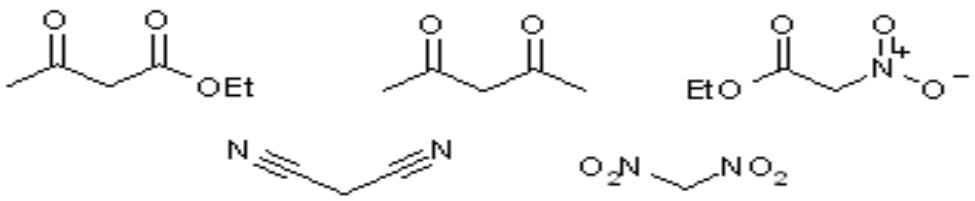
***Anti*-Markovnikov**

Michael Addition

The 1,4-addition (or conjugate addition) of resonance-stabilized carbanions. The Michael Addition is thermodynamically controlled; the reaction donors are active methylenes such as malonates and nitroalkanes, and the acceptors are activated olefins such as α,β-unsaturated carbonyl compounds.

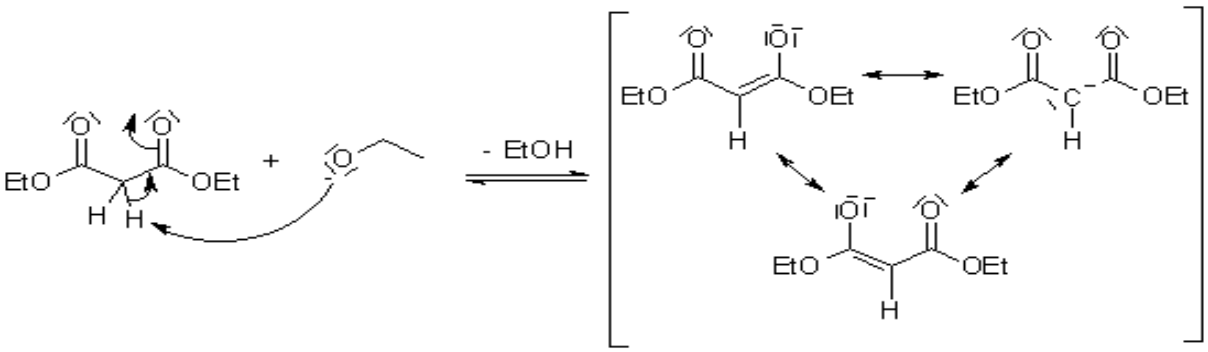
Examples:

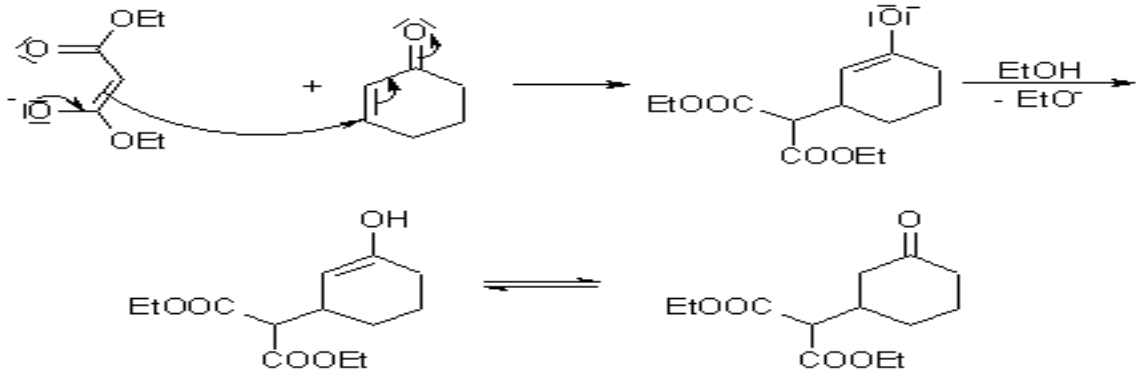
donors



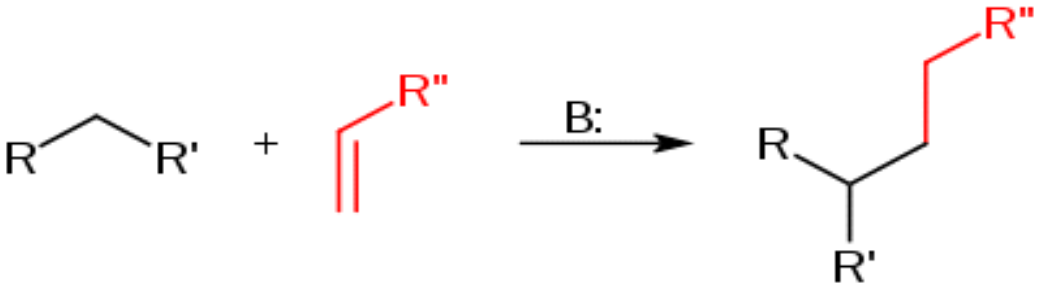
acceptors

Mechanism of the Michael Addition





The Michael reaction or Michael addition is the nucleophilic addition of a carbanion or another nucleophile to an2α,β-unsaturated carbonyl compound. It belongs to the larger class of conjugate additions. This is one of the most useful methods for the mild formation of C–C bonds.[3] Many asymmetric variants exist.



In this scheme the R and R' substituents on the nucleophile (a Michael donor) are electron-withdrawing groups such asacyl and cyano making the methylene hydrogen acidic forming the carbanion on reaction with base B:. The substituent on the activated alkene, also called a Michael acceptor, is usually a ketone making it an enone, but it can also be a nitrogroup.

As originally defined by Arthur Michael, the reaction is the addition of an enolate of a ketone or aldehyde to an α,β-unsaturated carbonyl compound at the β carbon. A newer definition, proposed by Kohler, is the 1,4-addition of a doubly stabilized carbon nucleophile to an α,β-unsaturated carbonyl compound. Some examples of nucleophiles include beta-ketoesters, malonates, and beta-cyanoesters. The resulting product contains a highly useful 1,5-dioxygenated pattern.

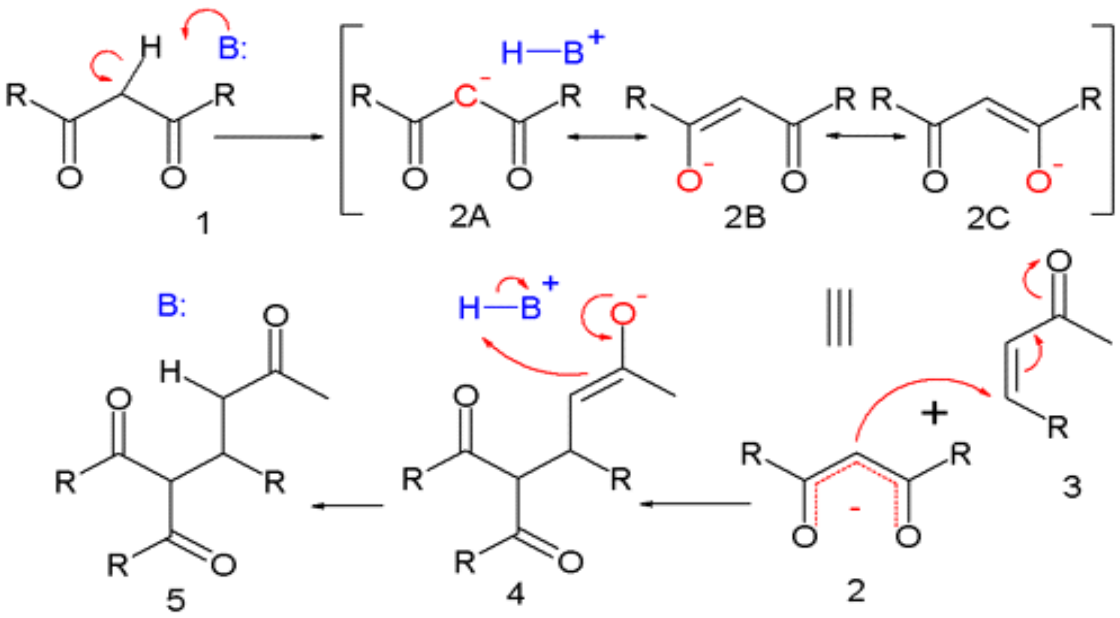
Classical examples of the Michael reaction are the reaction between diethyl malonate (Michael donor) and 1diethyl fumarate(Michael acceptor),that of mesityl oxide and diethyl malonate, that of diethyl malonate and 1methyl crotonate, that of22-

nitropropane and **methyl acrylate**,[12] that of *ethyl phenylcyanoacetate* and **acrylonitrile** and that of **nitropropane** and**methyl vinyl ketone**.[14]

The Michael addition is an important atom-economical method for diastereoselective and enantioselective C–C bond formation. A classical tandem sequence of Michael and aldol additions is the Robinson annulation.

Mechanism

The reaction mechanism is 1 (with R an alkoxy group) as the nucleophile:



Deprotonation of 1 by base leads to carbanion 2 stabilized by its electron-withdrawing groups. Structures 2a to 2c are threeresonance structures that can be drawn for this species, two of which have enolate ions. This nucleophile reacts with the electrophilic alkene 3 to form 4 in a conjugate addition reaction. Proton abstraction from protonated base (or solvent) by the enolate 4 to 5 is the final step.

The course of the reaction is dominated by orbital, rather than electrostatic, considerations. The HOMO of stabilizedenolates has a large coefficient on the central carbon atom while the LUMO of many alpha, beta unsaturated carbonyl compounds has a large coefficient on the beta carbon. Thus, both reactants can be considered soft. These polarizedfrontier orbitals are of similar energy, and react efficiently to form a new carbon–carbon bond.

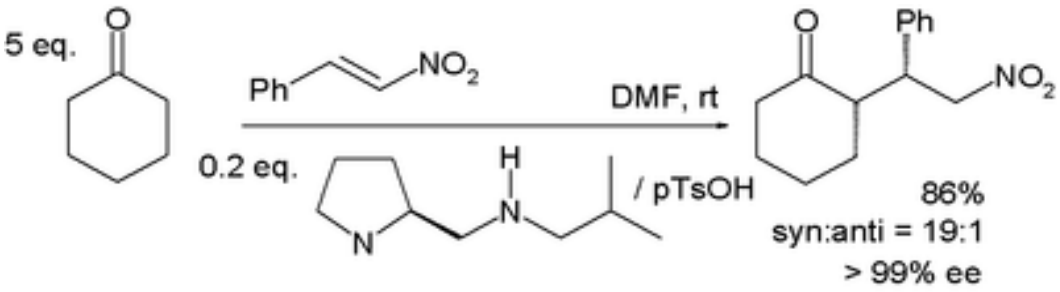
Like the aldol addition, the Michael reaction may proceed via an enol, silyl enol ether in the Mukaiyama-Michael addition, or more usually, enolate nucleophile. In the latter case, the stabilized carbonyl compound is deprotonated with a strong base (hard enolization) or with a Lewis acid and a weak base (soft enolization). The resulting enolate attacks the activated olefinwith 1,4-regioselectivity, forming a carbon–carbon bond. This also transfers the enolate to the electrophile. Since the electrophile is much less acidic than the nucleophile, rapid proton transfer usually transfers the enolate back to the nucleophile if the product is enolizable; however, one may take advantage of the new locus of nucleophilicity if a suitable electrophile is pendant. Depending on the relative acidities of the nucleophile and product, the reaction may be catalytic in base. In most cases, the reaction is irreversible at low temperature.

Asymmetric Michael reaction

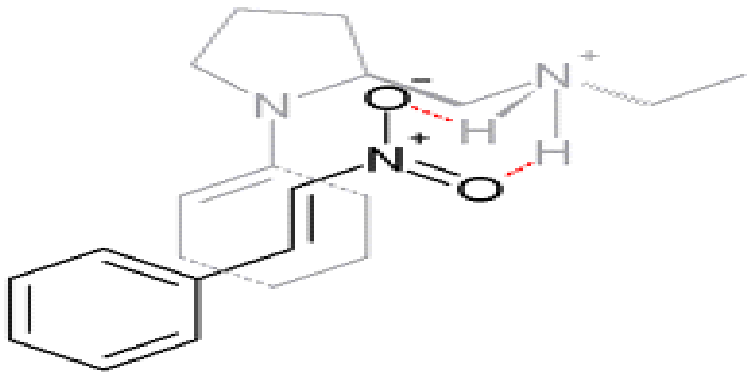
Recent research has focused on expanding the scope of asymmetric Michael additions. The most common methods involvechiral phase transfer catalysis, such as asymmetric quaternary ammonium salts derived from the Cinchona alkaloids; ororganocatalysis, which

uses enamine or iminium activation with chiral secondary amines, usually derived fromproline.

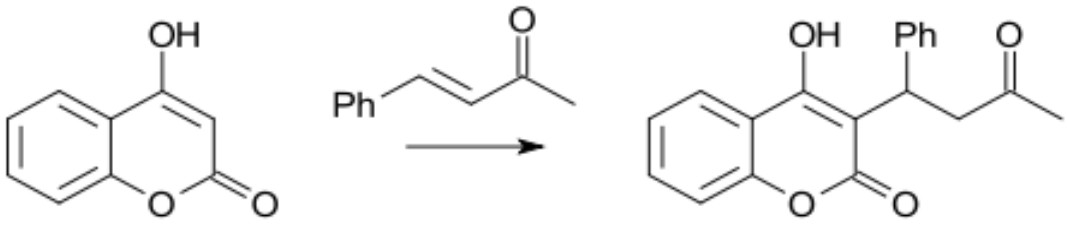
In the reaction between cyclohexanone and β-nitrostyrene sketched below, the base proline is derivatized and works in conjunction with a protic acid such as *p*-toluenesulfonic acid:



Syn addition is favored with 99% ee. In the transition state believed to be responsible for this selectivity, the enamine(formed between the proline nitrogen and the cycloketone) and β-nitrostyrene are co-facial with the nitro group hydrogen bonded to the protonated amine in the proline side group.

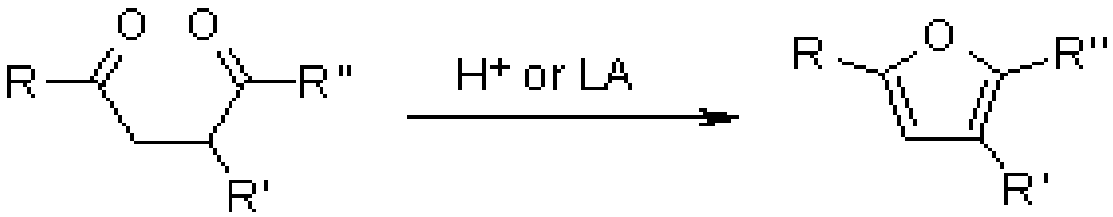


A well-known Michael reaction is the synthesis of warfarin from 44hydroxycoumarin and benzylideneacetone first reported by Link in 1944:



Several asymmetric versions of this reaction exist using chiral catalysts.

Paal-Knorr Furan Synthesis

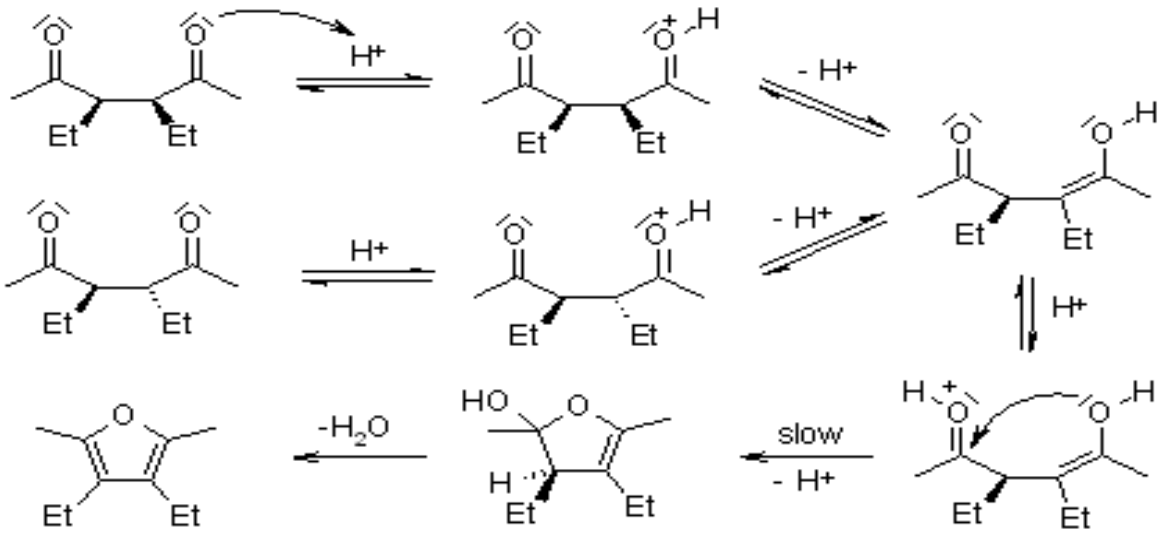


The acid-catalyzed cyclization of 1,4-dicarbonyl compounds known as the Paal-Knorr synthesis is one of the most important methods for the preparation of furans. As many methods for the synthesis of 1,4-diones have recently been developed, the synthetic utility of the Paal-Knorr reaction has improved.

Mechanism of the Paal-Knorr Furan Synthesis

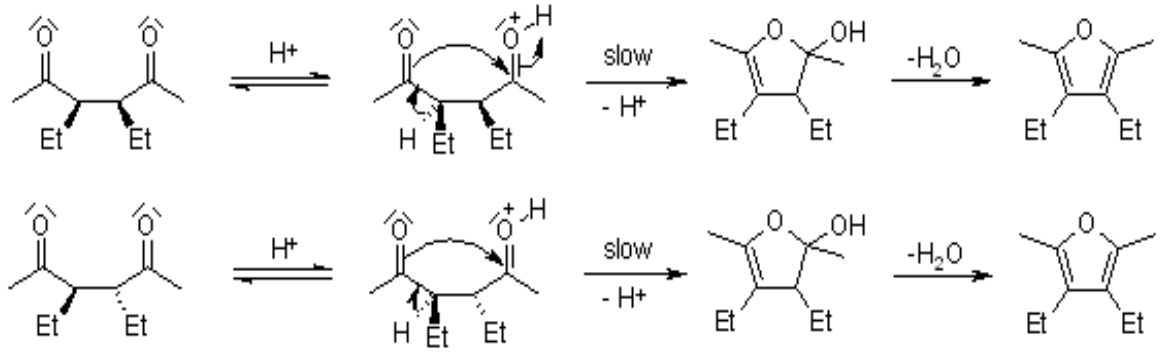
A comparison of the cyclizations of *meso*- and *dl*-3,4-diethyl-2,5-hexanediones showed that these compounds cyclize at unequal rates, and that the stereochemical configuration of unchanged dione is

preserved during the reaction. These findings are at odds with the commonly accepted mechanism shown here that involves the ring closure of a rapidly formed monoenol.

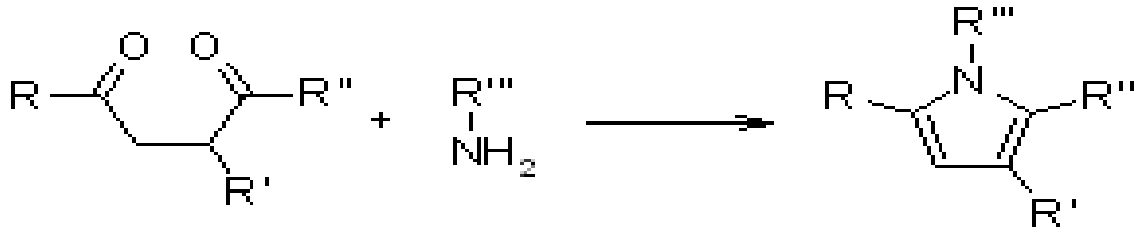


The rate of acid-catalyzed enolization is known not to be very sensitive to the structure of the ketone. Since the rate-determining step would be the same for both substrates, the differences in the reaction rate cannot be explained by this mechanism.

A mechanism in which the substituents would interfere differently in the rate-determining step is shown below. The ease of achieving a suitable conformation for the cyclization is not the same for both molecules:



Paal-Knorr Pyrrole Synthesis

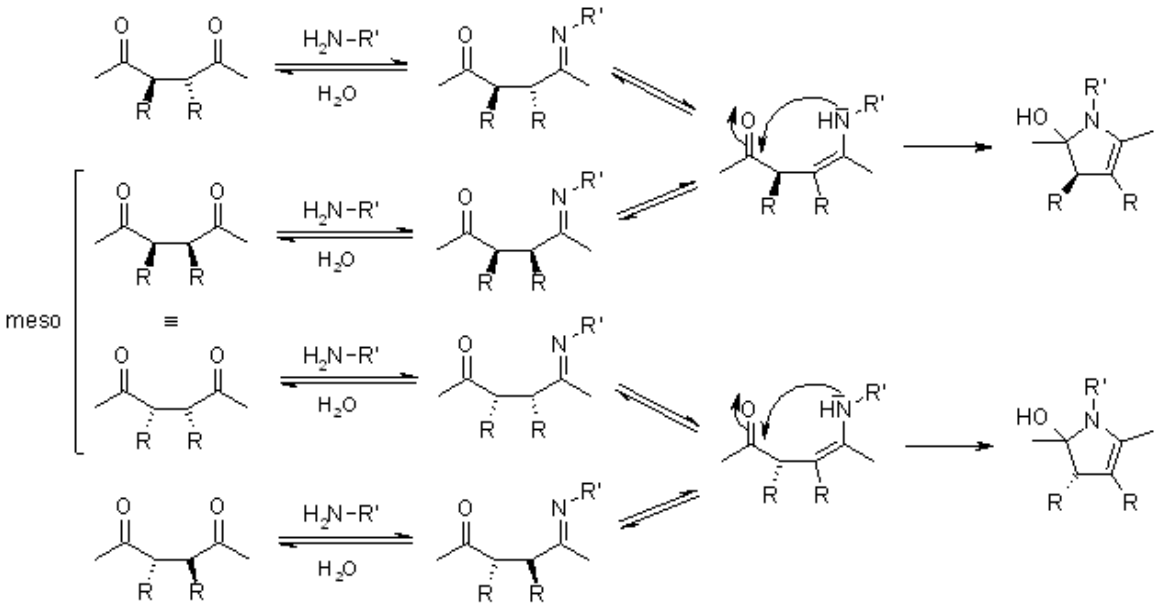


The Paal-Knorr Pyrrole Synthesis is the condensation of a 1,4-dicarbonyl compound with an excess of a primary amine or ammonia to give a pyrrole.

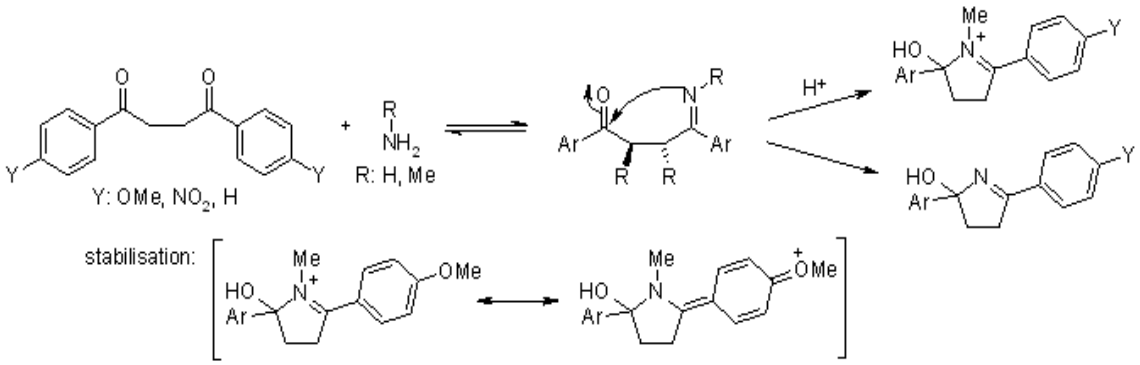
The reaction can be conducted under neutral or weakly acidic conditions. Addition of a weak acid such as acetic acid accelerates the reaction, but the use of amine/ammonium hydrochloride salts or reactions at pH < 3 lead to furans as main products (Paal-Knorr Furan Synthesis).

Mechanism of the Paal-Knorr Pyrrole Synthesis

Venkataraman Amarnath has shown that *meso*- and *dl*-3,4-diethyl-2,5-hexanediones cyclize at unequal rates, and that the stereochemical configuration of the unchanged dione is preserved during the reaction. Any mechanism such as the following one that involves the formation of an enamine before the rate-determining step - the cyclization - must be ruled out.



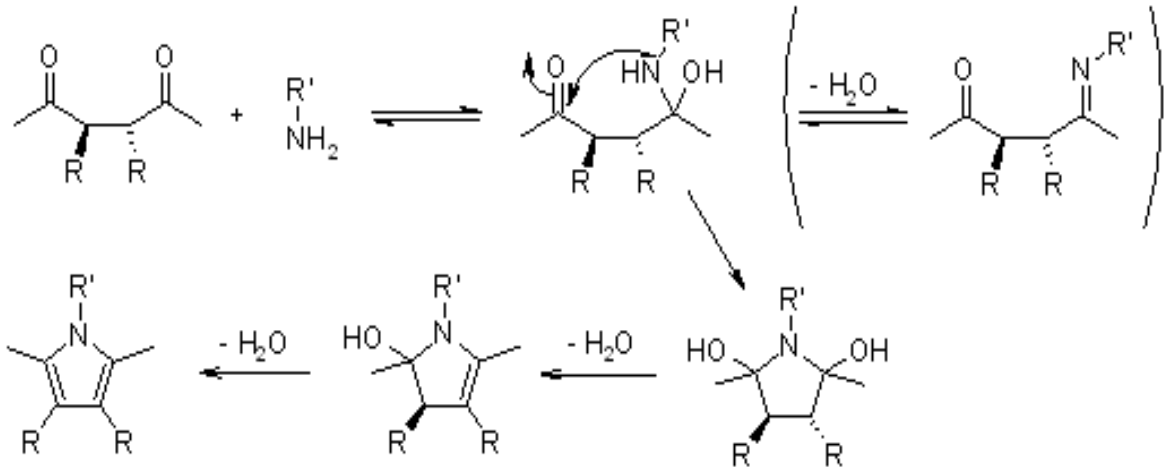
If the ring is formed from an imine that is generated from a primary amine, a charged immonium ion must be an intermediate. Amarnath tried to stabilize or destabilize the immonium ion with different aryl groups as substituents:



The use of ammonia should give an uncharged intermediate and is therefore less affected by the choice of substitutents. The substituents also influence the basicity of the imine, with the nitro group leading to a more basic nucleophile. The rates of cyclization have been compared using ammonia and methylamine. The nitro group has in every situation had a positive effect on the reaction rate. The methoxy group has a negative effect on the cyclization rate in each

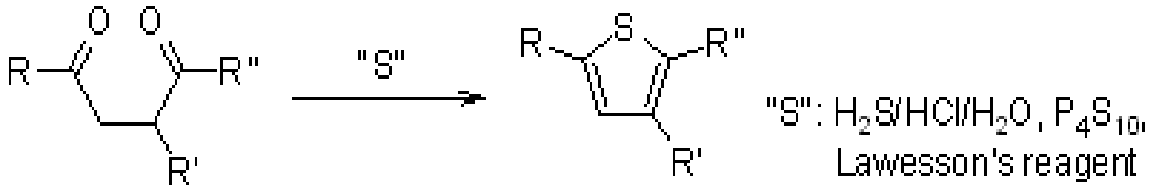
case. Comparison of the relative reaction rates of all substrates (R: H, Me) showed no specific stabilization/destabilization effect for a possible mechanism involving an immonium ion.

A mechanism that accounts for the influence of different substitution patterns (*meso*, *dl*) and explains the influence of a *p*-nitrophenyl group making a nucleophile more reactive (although not as the imine) includes the cyclization of a hemiacetal which is followed by different dehydration steps:



Paal-Knorr Thiophene Synthesis

Paal Thiophene Synthesis

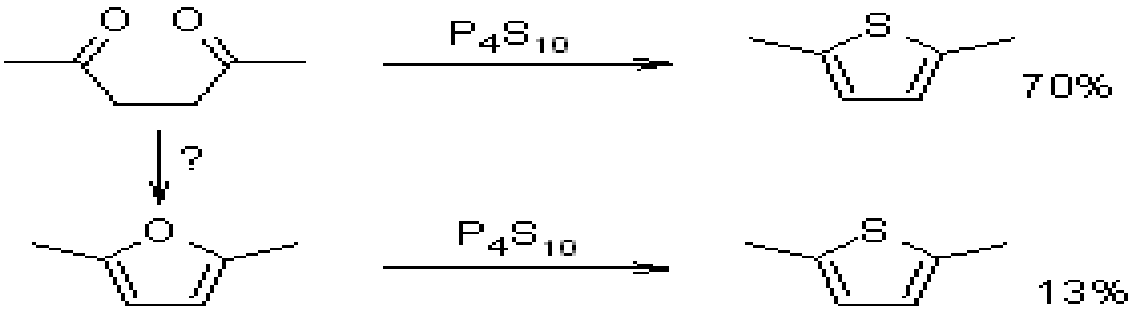


The Paal-Knorr Thiophene Synthesis allows the generation of thiophenes by condensation of a 1,4-dicarbonyl compound in the presence of an excess of a source of sulfur such as phosphorous pentasulfide or Lawesson's reagent.

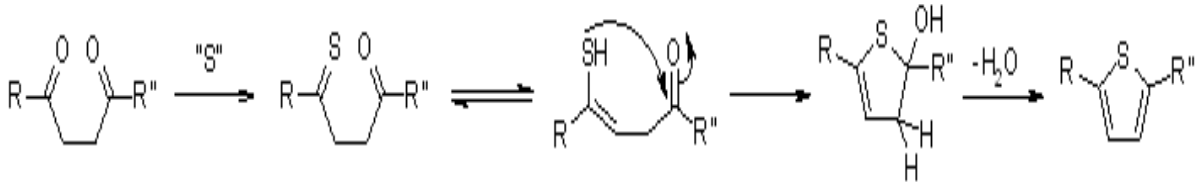
Attention: some toxic H_2S is formed as a side product regardless of the sulfur source.

Mechanism of the Paal-Knorr Thiophene Synthesis

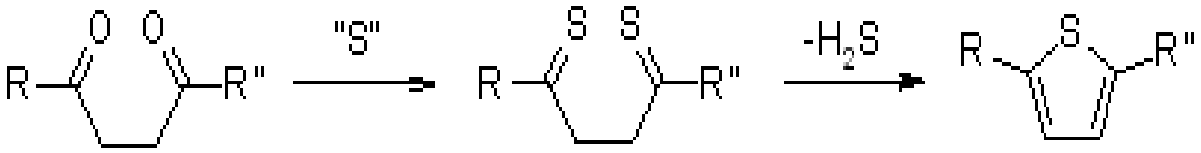
Reagents such as phosphorus pentasulfide or Lawesson's reagent act as sulfurizing agents as well as dehydrating agents, allowing a reaction pathway that could lead first to the formation of furans. This hypothesis was tested by Foye by treatment of different 1,4-dicarbonyl compounds and the corresponding possible furan intermediates (such as acetonylacetone and 2,5-dimethylfuran) with phosphorus pentasulfide. Using the same reaction conditions, the differences in the yields of 2,5-dimethylthiophene excludes the possibility that a predominant reaction pathway could lead through furan intermediates:



Foye suggested the following reaction pathway:



Today, the occurrence of a bis-thioketone intermediate is assumed to be possible but not necessary (J. Schatz, *Science of Synthesis*,

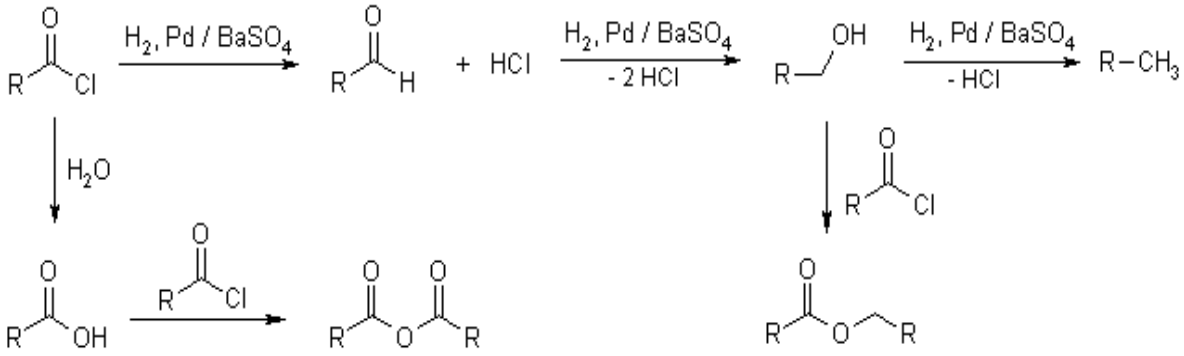


The reaction mechanism still needs further elucidation before it is fully understood.

Rosenmund Reduction

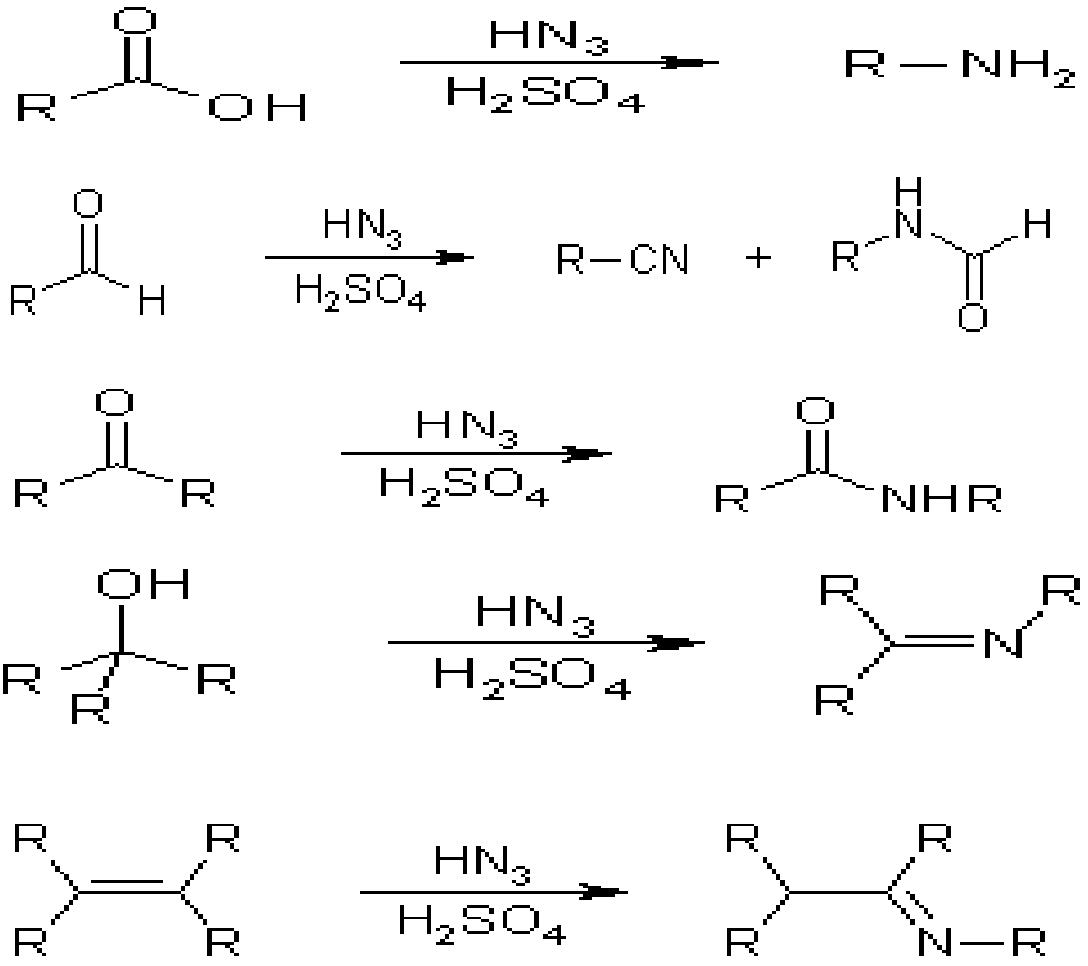
The catalytic hydrogenation of acid chlorides allows the formation of aldehydes

Mechanism of the Rosenmund Reduction



The Pd catalyst must be poisoned, for example with $BaSO_4$, because the untreated catalyst is too reactive and will give some overreduction. Some of the side products can be avoided if the reaction is conducted in strictly anhydrous solvents.

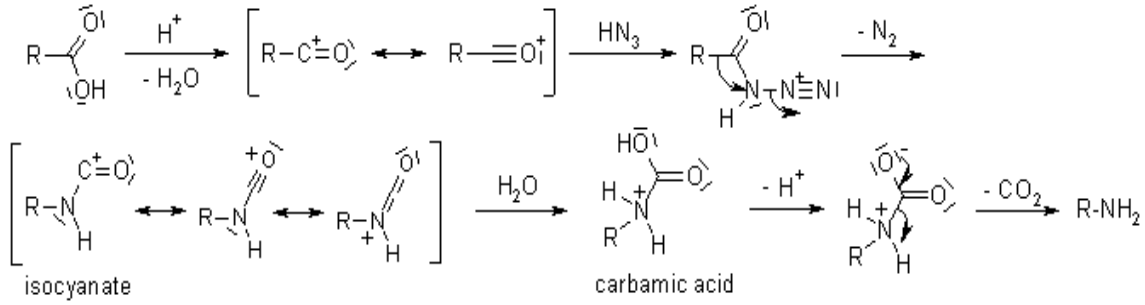
Schmidt Reaction



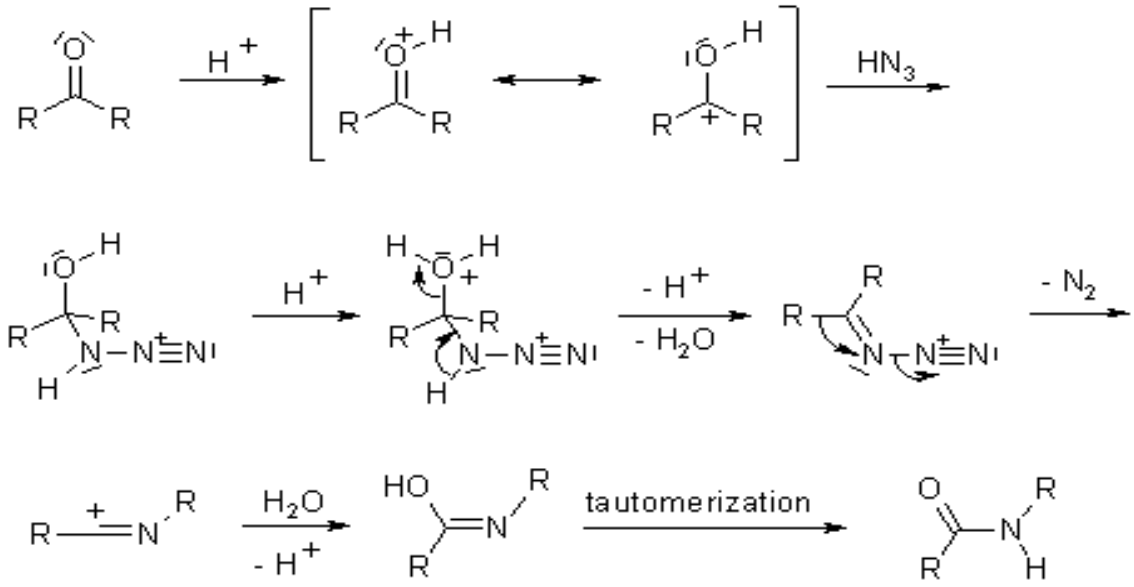
The acid-catalysed reaction of hydrogen azide with electrophiles, such as carbonyl compounds, tertiary alcohols or alkenes. After a rearrangement and extrusion of N_2, amines, nitriles, amides or imines are produced.

Mechanism of the Schmidt Reaction

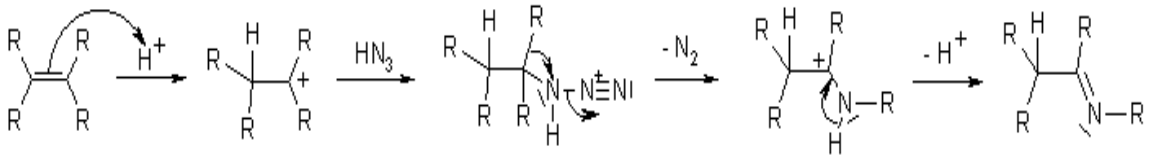
Reaction of carboxylic acids gives acyl azides, which rearrange to isocyanates, and these may be hydrolyzed to carbamic acid or solvolysed to carbamates. Decarboxylation leads to amines.



The reaction with a ketone gives an azidohydrin intermediate, which rearranges to form an amide:



Alkenes are able to undergo addition of HN_3 as with any HX reagent, and the resulting alkyl azide can rearrange to form an imine:

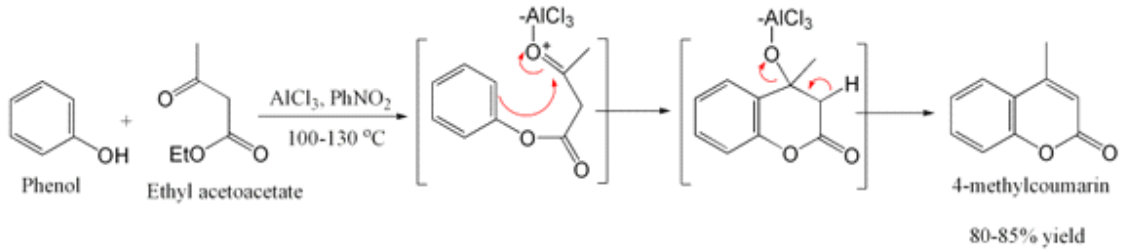


Tertiary alcohols give substitution by azide via a carbenium ion, and the resulting alkyl azide can rearrange to form an imine.

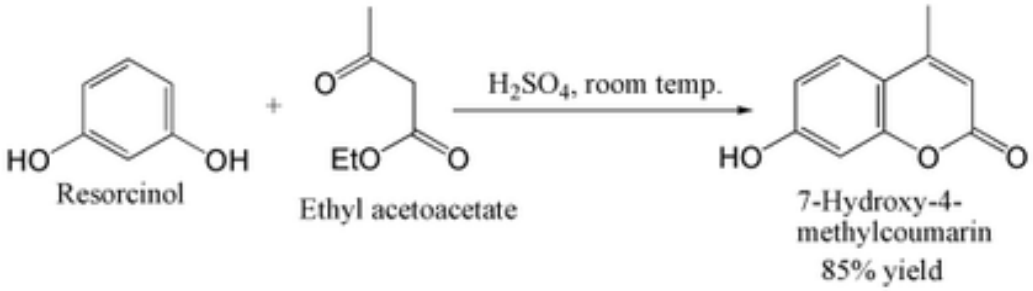
Pechmann condensation

The Pechmann condensation is a synthesis of coumarins, starting from a phenol and a carboxylic acid or ester containing a β-carbonyl group.The condensation is performed under acidic conditions. The mechanism involves an esterification/transesterification followed by attack of the activated carbonyl ortho to the oxygen to generate the new ring. The final step is a dehydration, as seen following an aldol condensation. It was discovered by the German chemist Hans von Pechmann.

With simple phenols, the conditions are harsh, although yields may still be good.

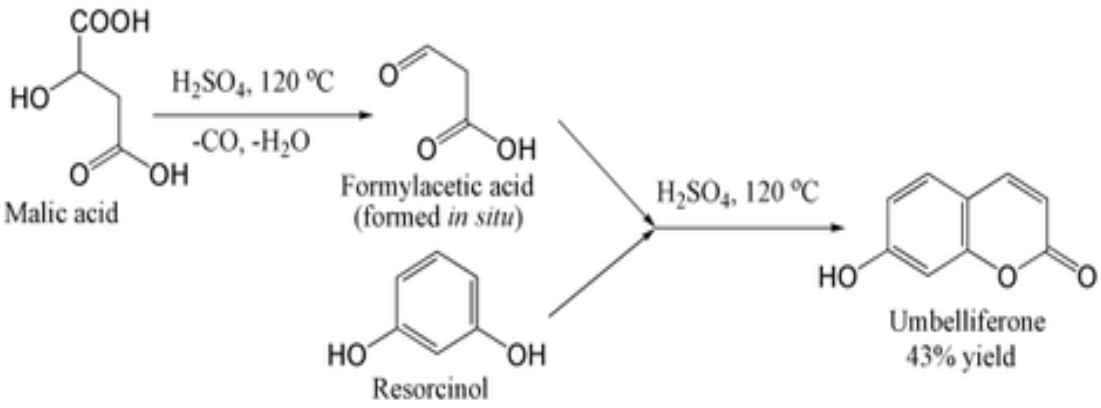


With highly activated phenols such as resorcinol, the reaction can be performed under much milder conditions. This provides a useful route to umbelliferone derivatives:



For coumarins unsubstituted at the 4-position, the method requires the use of formylacetic acid or ester. These are unstable and not

commercially available, but the acid may be produced *in situ* from malic acid and sulfuric acid above 100 °C. As soon as it forms, the formylacetic acid performs the Pechmann condensation. In the example shown, umbelliferone itself is produced, albeit in low yield:

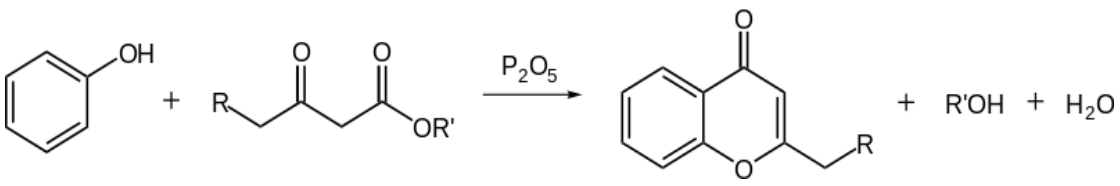


The mechanism of the reaction has been studied in details with theoretical treatment.

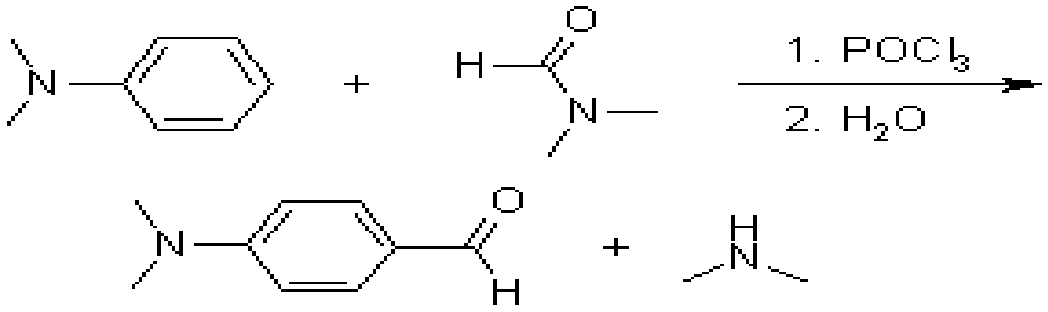
The study shown that reaction takes place on oxo-form, and not on enolic-form. Three different oxo-routes have been proposed.

Simonis chromone cyclization

In a variation the reaction of phenols and beta-ketoesters and phosphorus pentoxide yields a chromone. This reaction is called Simonis chromone cyclization. The ketone in the ketoester is activated by P_2O_5 for reaction with the phenol hydroxyl group first, the ester group in it is then activated for electrophilic attack of the arene.



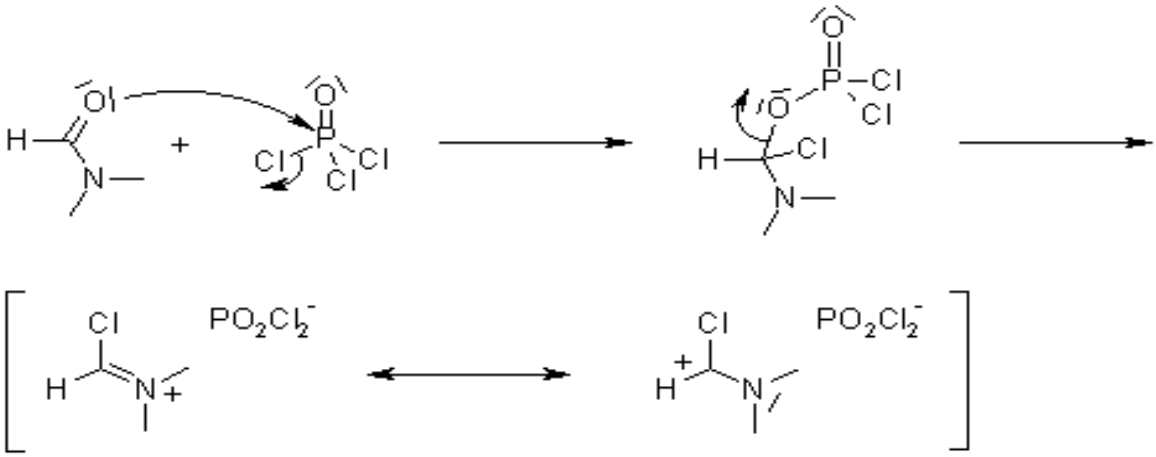
Vilsmeier-Haack Reaction



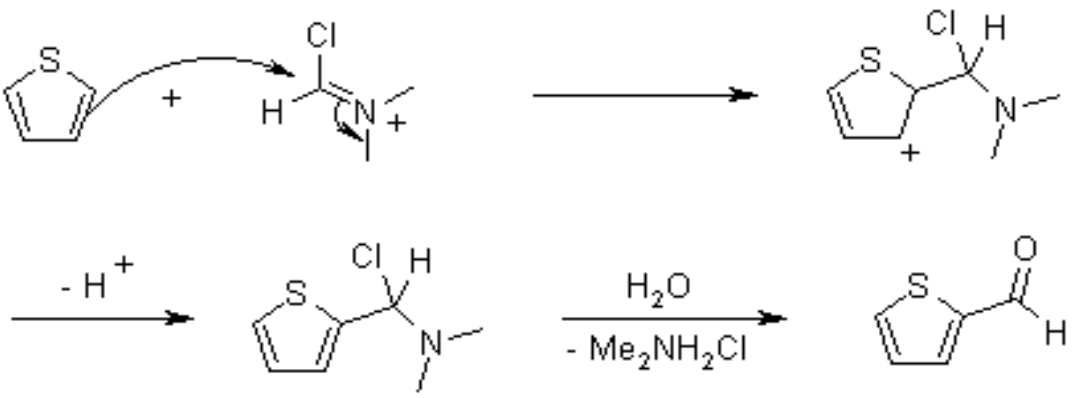
The Vilsmeier Reaction allows the formylation of electron-rich arenes.

Mechanism of the Vilsmeier-Haak Reaction

The formylating agent, also known as the Vilsmeyer-Haack Reagent, is formed *in situ* from DMF and phosphorus oxychlorid:

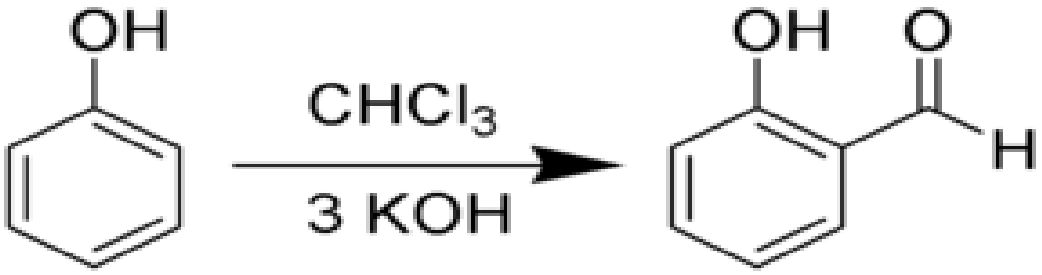


An electrophilic aromatic substitution leads to α-chloro amines, which are rapidly hydrolyzed during work up to give the aldehyde:

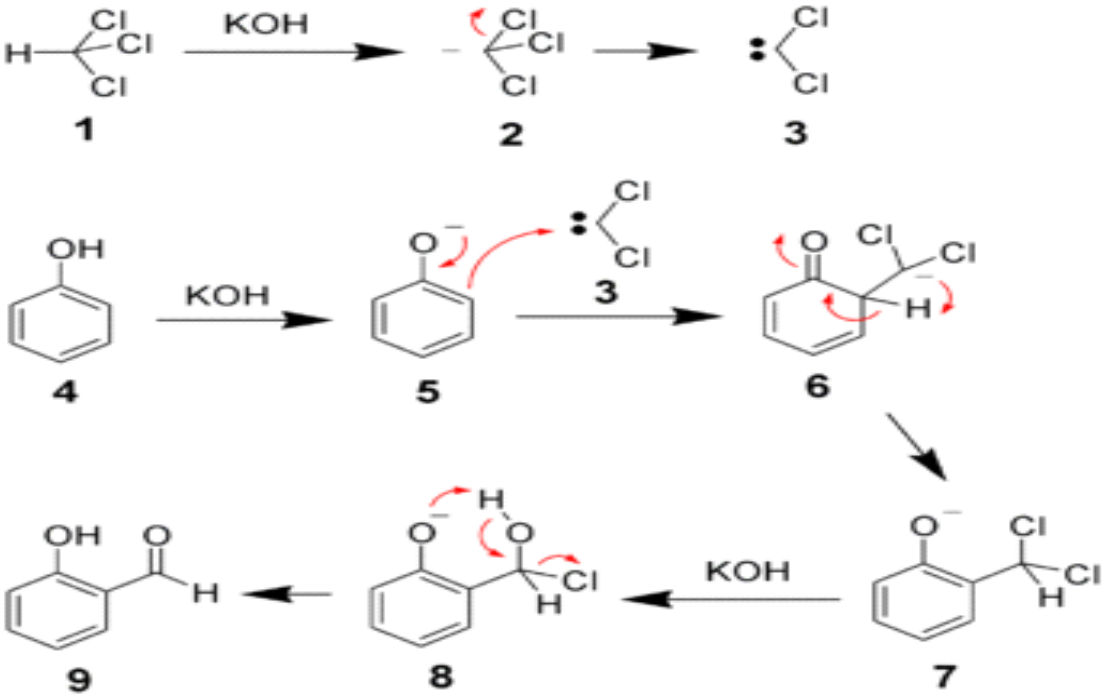


The Reimer–Tiemann reaction

The Reimer–Tiemann reaction is a chemical reaction used for theortho-formylation of phenols with the simplest example being the conversion of phenol to salicylaldehyde. The reaction was discovered by 1Karl Reimer and Ferdinand Tiemann. The Reimer in question was Karl Reimer (1845-1883) not the less known Carl Ludwig Reimer (1856-1921).



Reaction mechanism



The mechanism of the Reimer-Tiemann reaction

Chloroform (1) is deprotonated by strong base (normallyhydroxide) to form the chloroform carbanion (2) which will quickly alpha-eliminate to give dichlorocarbene (3); this is the principal reactive species. The hydroxide will also deprotonate the phenol (4) to give a negatively charged phenoxide (5). The negative charge is delocalised into the aromatic ring, making it far more nucleophilic and increases its ortho selectivity. Nucelophilic attack of the dichlorocarbene from the ortho position gives an intermediate dichloromethyl substituted phenol (7). After basic hydrolysis, the desired product (9) is formed.

Reaction conditions

Hydroxides are not readily soluble in the chloroform, thus the reaction is generally carried out in a biphasic solvent system. In the simplest sense this consists of an aqueous hydroxide solution and an organic phase containing the chloroform. The two reagents are therefore separated and must be brought together for the reaction to

take place. This can be achieved by rapid mixing, phase-transfer catalysts, or an emulsifying agent (the use of 141,4-Dioxane as a solvent is an example).

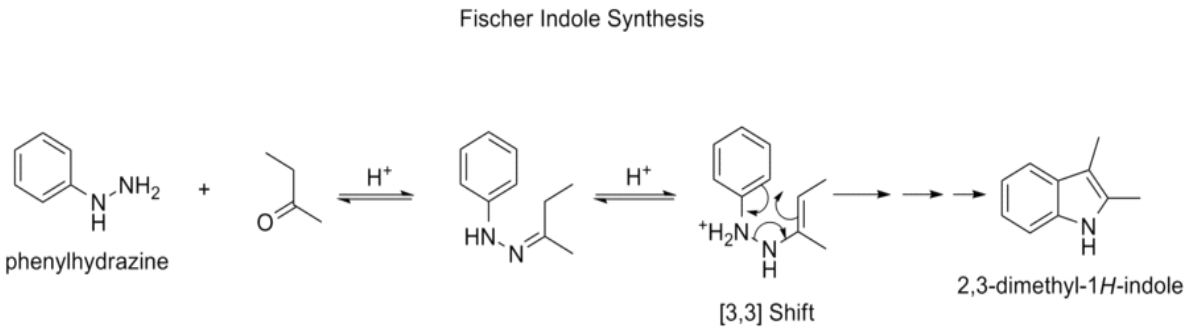
The reaction typically needs to be heated to initiate the process, however once started the Reimer-Tiemann Reaction can be highly exothermic; this combination makes it prone to thermal runaways.

Dichlorocarbenes can also react with alkenes and amines to form dichlorocyclopropanes and isocyanides, respectively. As such the Reimer-Tiemann reaction may be unsuitable for substrates bearing these functional groups. In addition, many compound can not withstand being heated in the presence of hydroxide.

The direct formylation of aromatic compounds can be accomplished by various methods such as the Gattermann reaction,2%Gattermann–Koch reaction, 2%Vilsmeier–Haack reaction, or Duff reaction; however, in terms of ease and safety of operations, the Reimer–Tiemann reaction is often the most advantageous route chosen in chemical synthesis. Of the prior mentioned reactions, the Reimer–Tiemann reaction is the only route not requiring acidic and/or anhydrous conditions.2%[3]Additionally the Gattermann-Koch and 2%Vilsmeier–Haack reactions are not applicable to phenol substrates.

Fischer indole synthesis

The Fischer indole synthesis is a chemical reaction that produces the aromatic heterocycle indole from a (substituted)phenylhydrazine and an aldehyde or ketone under acidic conditions.[18][19] The reaction was discovered in 1883 by Hermann Emil Fischer.



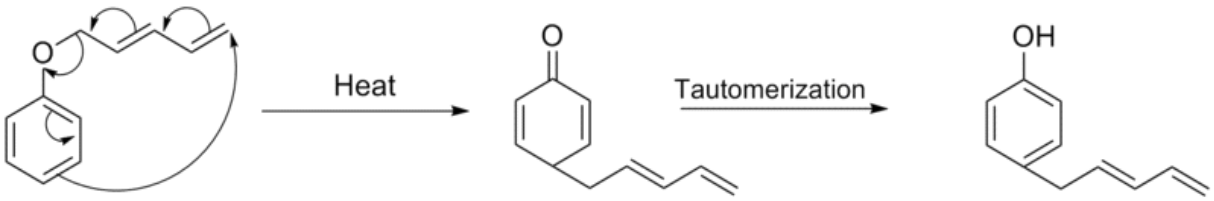
The choice of acid catalyst is very important. Bronsted acids such as HCl, H_2SO_4, polyphosphoric acid and p-toluenesulfonic acid have been used successfully. Lewis acids such as boron trifluoride, zinc chloride, iron(III) chloride, and aluminium chloride are also useful catalysts.

Several reviews have been published.

[5,5] Shifts

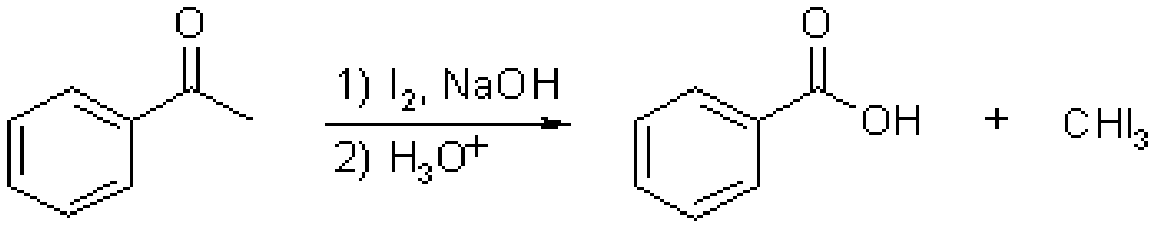
Similar to [3,3] shifts, the Woodward-Hoffman rules predict that [5,5] sigmatropic shifts would proceed suprafacially, Huckel topology transition state. These reactions are rarer than [3,3] sigmatropic shifts, but this is mainly a function of the fact that molecules that can undergo [5,5] shifts are rarer than molecules that can undergo [3,3] shifts.

[5,5] Shift of Phenyl pentadienylether



[2,3] shift

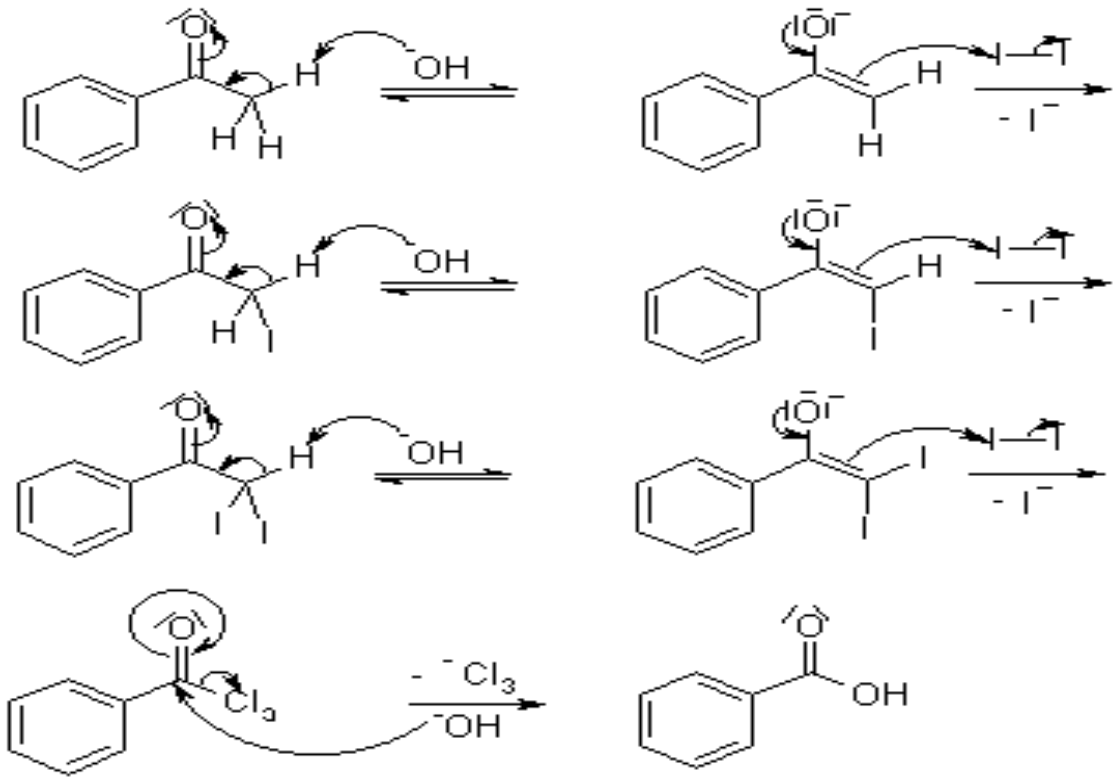
Haloform Reaction



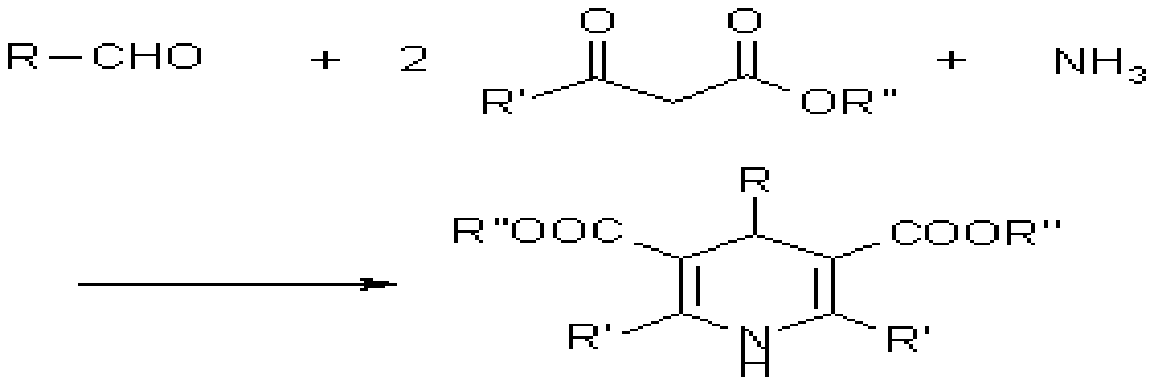
This reaction has been used in qualitative analysis to indicate the presence of a methyl ketone. The product iodoform is yellow and has a characteristic odour. The reaction has some synthetic utility in the oxidative demethylation of methyl ketones if the other substituent on the carbonyl groups bears no enolizable α-protons.

Mechanism of the Haloform Reaction

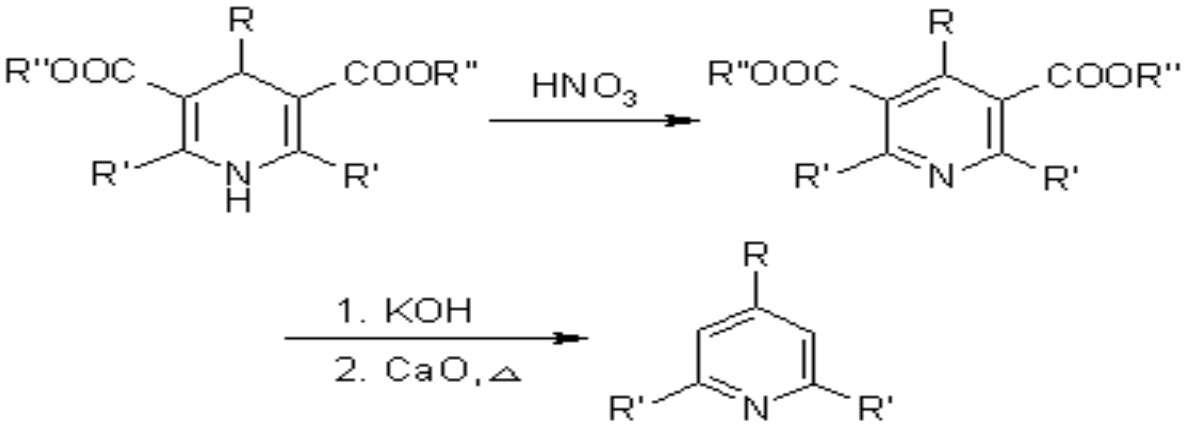
The reaction readily proceeds to completion because of the acidifying effect of the halogen substituents.



Hantzsch Dihydropyridine (Pyridine) Synthesis

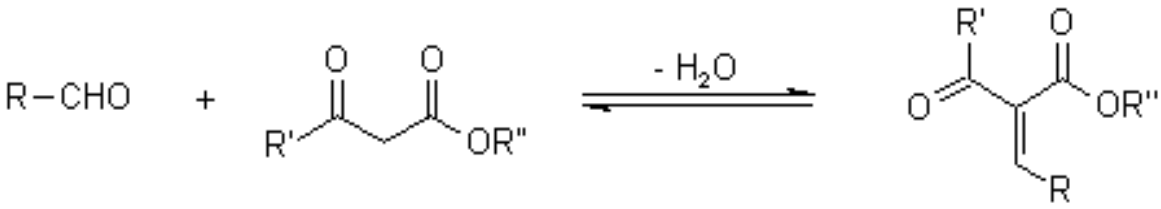


This reaction allows the preparation of dihydropyridine derivatives by condensation of an aldehyde with two equivalents of a β-ketoester in the presence of ammonia. Subsequent oxidation (or dehydrogenation) gives pyridine-3,5-dicarboxylates, which may also be decarboxylated to yield the corresponding pyridines.

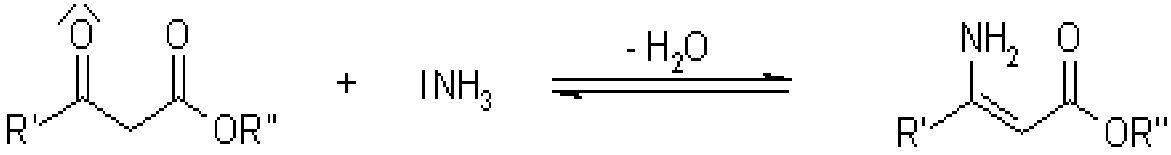


Mechanism of the Hantzsch Dihydropyridine Synthesis

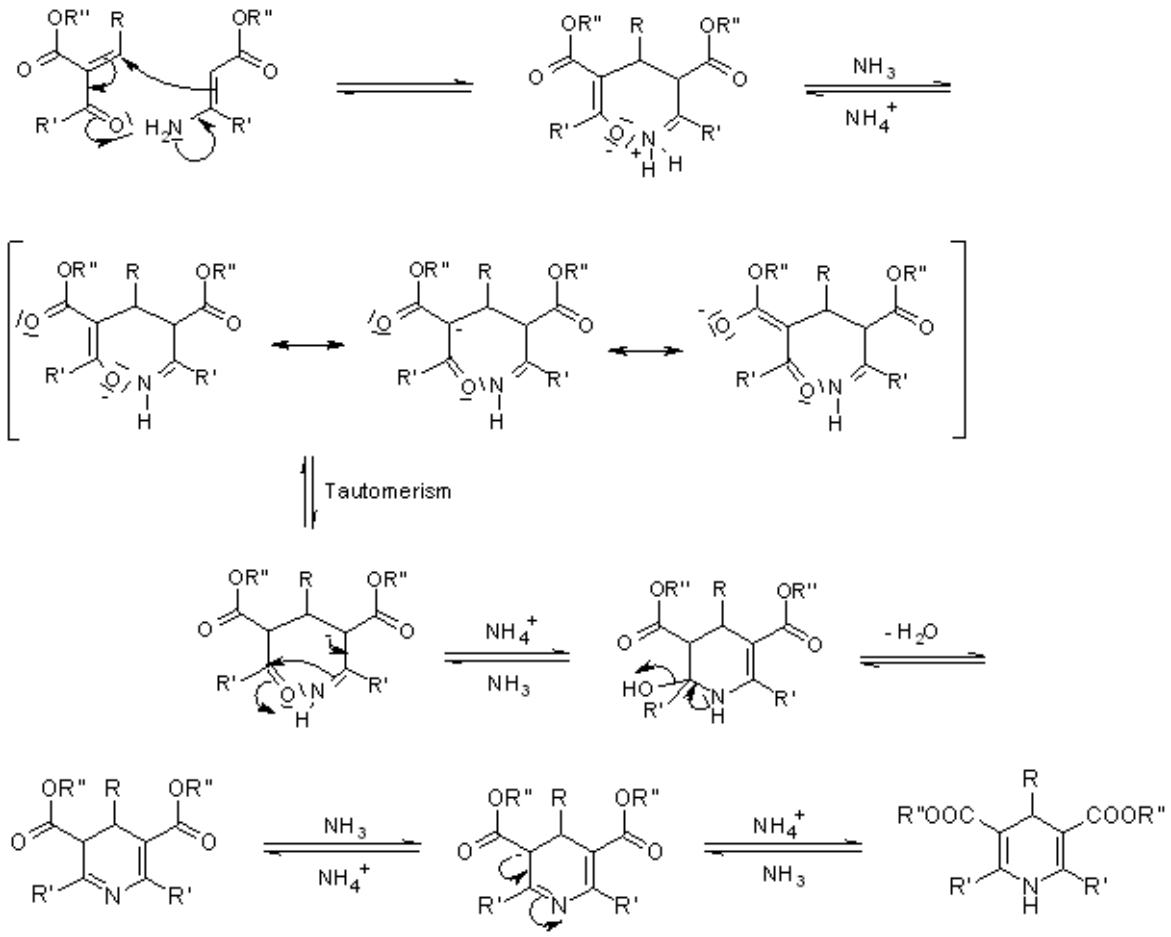
The reaction can be visualized as proceeding through a Knoevenagel Condensation product as a key intermediate:



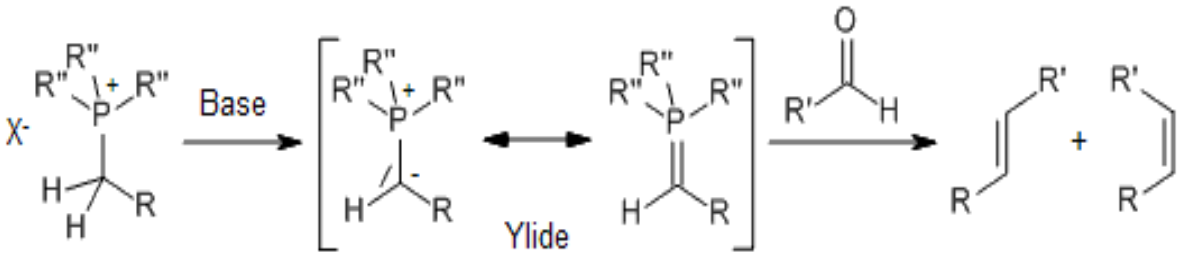
A second key intermediate is an ester enamine, which is produced by condensation of the second equivalent of the β-ketoester with ammonia:



Further condensation between these two fragments gives the dihydropyridine derivative:



Wittig Reaction

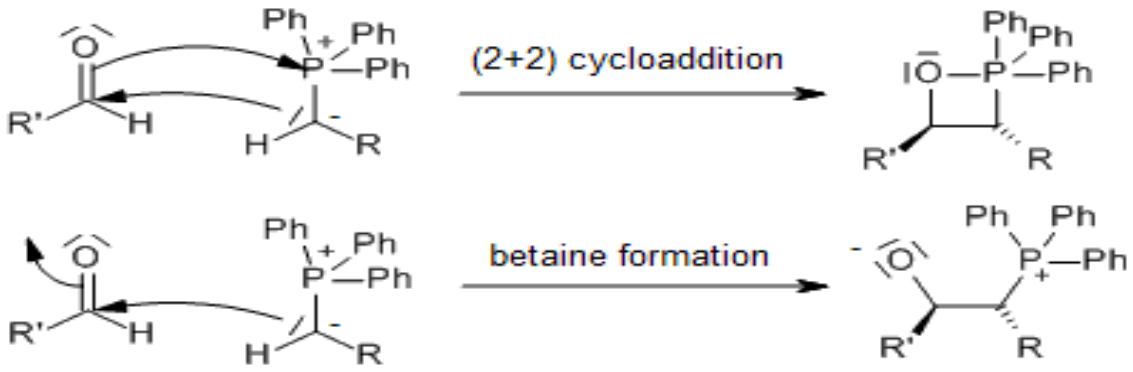


The Wittig Reaction allows the preparation of an alkene by the reaction of an aldehyde or ketone with the ylide generated from a phosphonium salt. The geometry of the resulting alkene depends on the reactivity of the ylide. If R'' is Ph or R is an electron withdrawing group, then the ylide is stabilized and is not as reactive as when R''

and R are alkyl. Stabilized ylides give (*E*)-alkenes whereas non-stabilized ylides lead to (*Z*)-alkenes (see also Wittig-Horner Reaction).

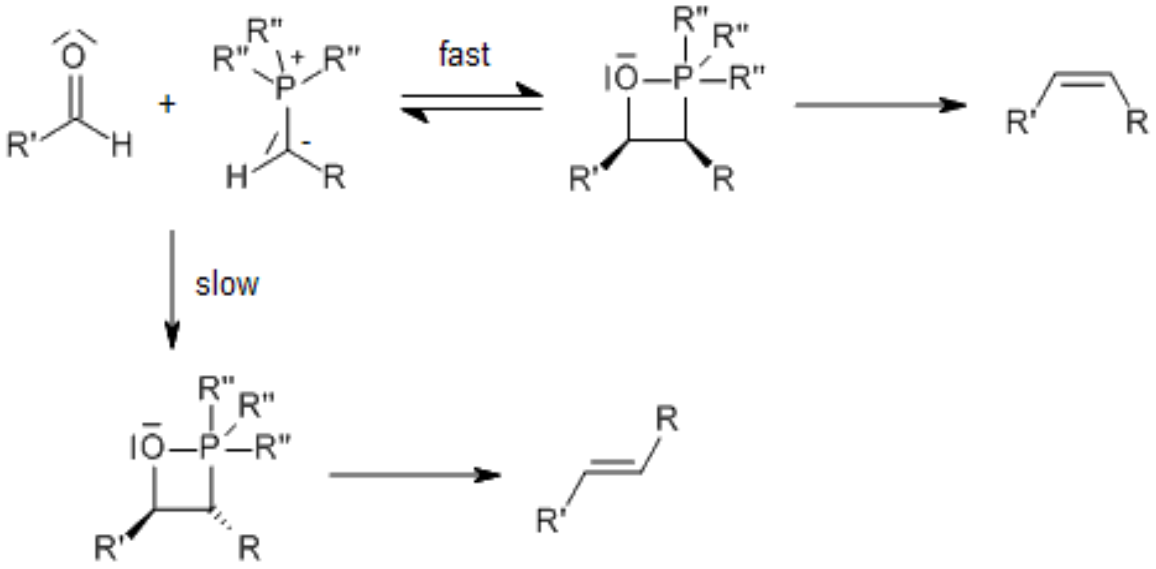
Mechanism of the Wittig Reaction

(2+2) Cycloaddition of the ylide to the carbonyl forms a four-membered cyclic intermediate, an oxaphosphetane. Preliminary posultated mechanisms lead first to a betaine as a zwitterionic intermediate, which would then close to the oxaphosphetane. The intermediacy of such betaines plays an important role in the Schlosser Modification. Betaines may be stabilized by lithium salts leading to side products; therefore, suitable bases in the Wittig Reaction are for example: NaH, NaOMe, NEt_3.

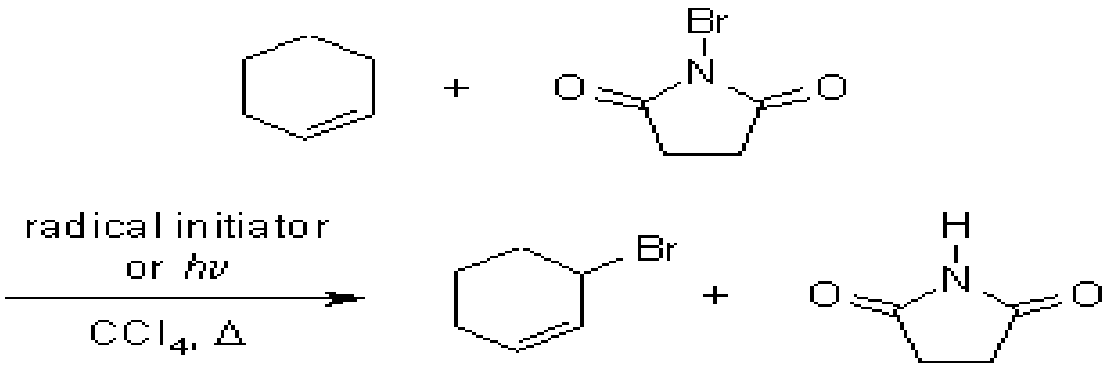


The driving force is the formation of a very stable phosphine oxide:

Reactive ylides give rapid reaction and subsequent rapid ring opening to give the (*Z*)-alkene:



Wohl-Ziegler Reaction

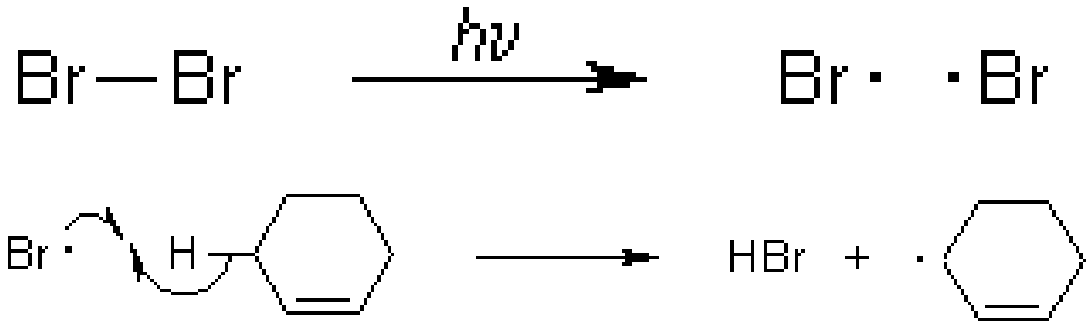


The bromination of allylic positions with *N*-bromosuccinimide (NBS) follows a radical pathway.

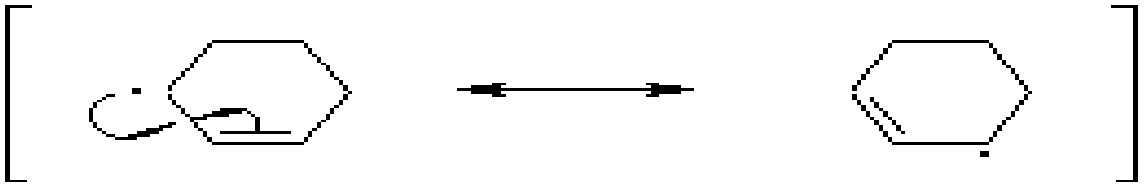
Mechanism of the Wohl-Ziegler Reaction

It is very important to keep the concentration of Br_2 and HBr low to prevent side reactions derived from simple ionic addition with the alkene. These reagents are therefore generated in situ from NBS. The catalytically active species is Br_2, which is almost always present in NBS samples (red colour).

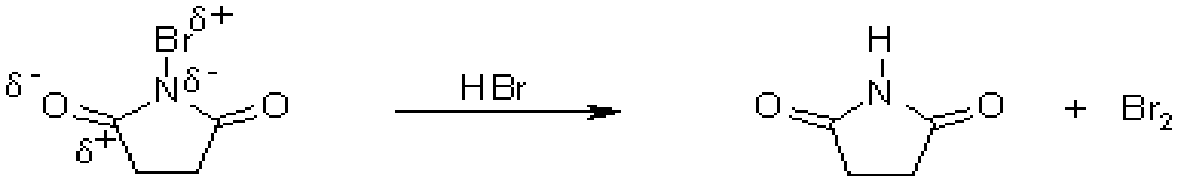
A radical initiator (UV, AIBN) is needed for the homolytic bond cleavage of Br_2 :



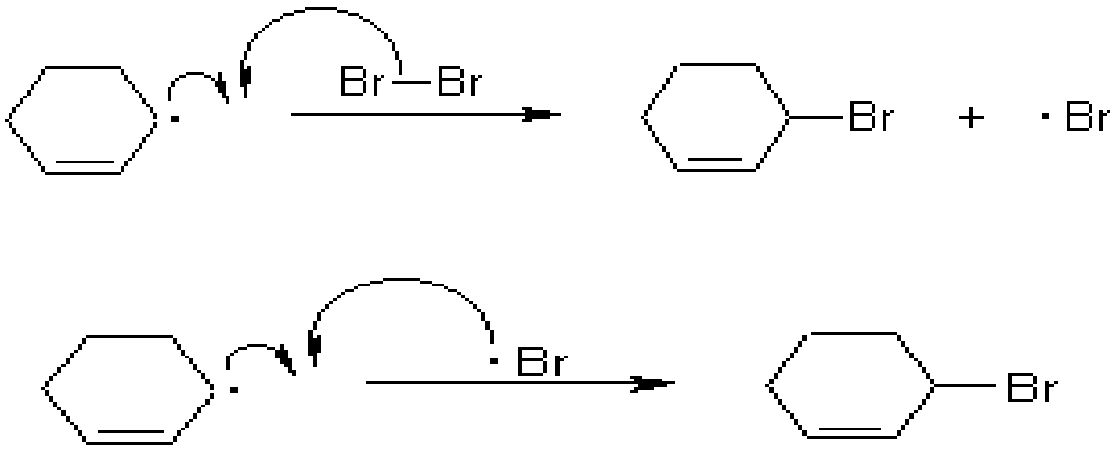
The allylic position is favoured for hydrogen abstraction, because the resulting radical intermediate is resonance stabilized:



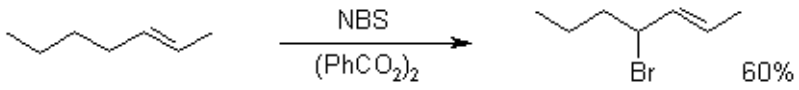
Regeneration of Br_2:



Bromination:



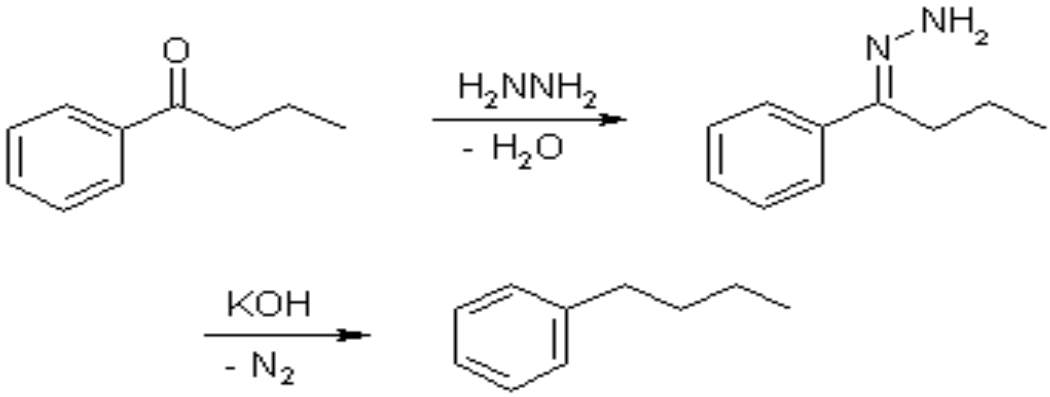
Bromination is favored to occur at the more highly substituted position, because the corresponding intermediate radicals are better stabilized.



CCl_4 is the solvent of choice, because NBS is poorly soluble and resulting succinimide is insoluble and floats at the surface. This keeps the concentration of reagents low and is a signal that the reaction is finished.

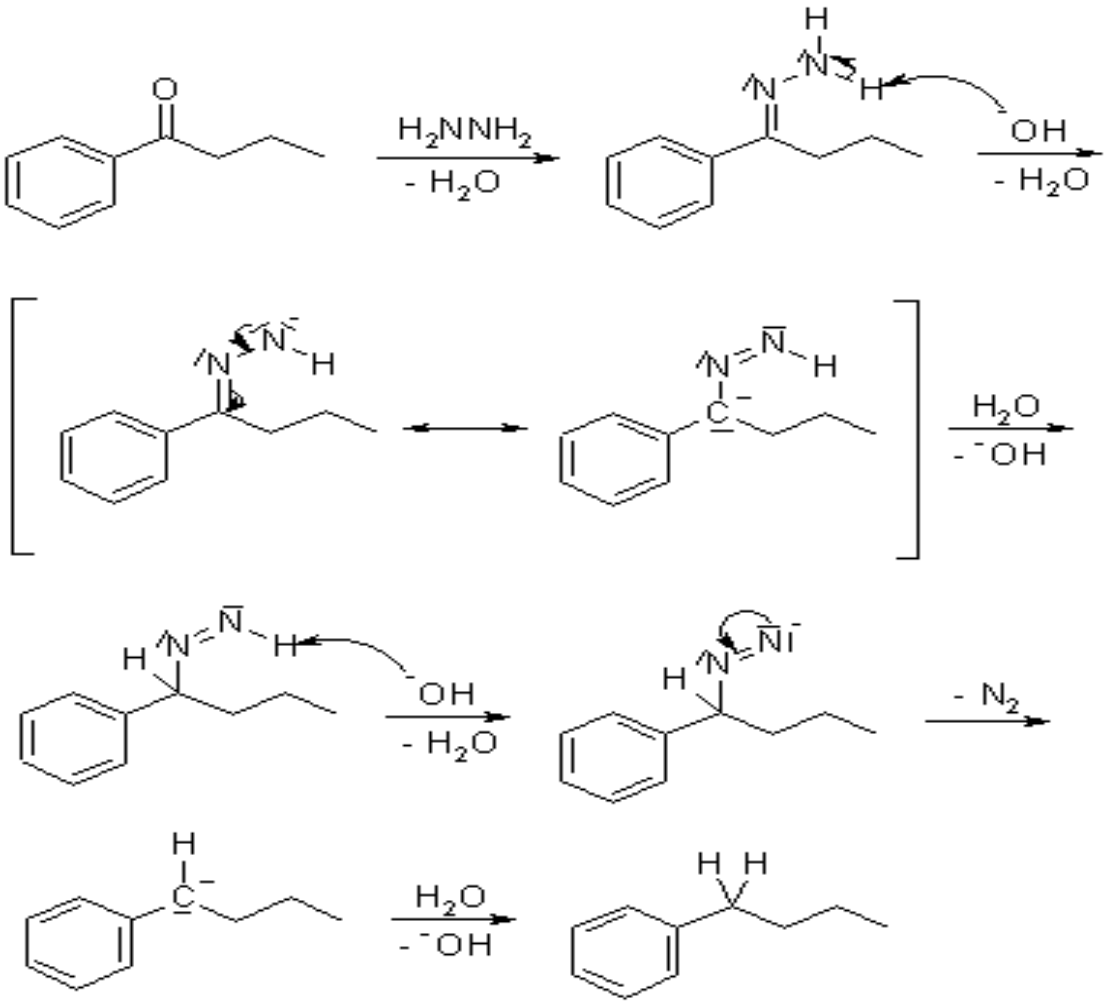
However, environmental concerns have all but eliminated the use of CCl_4, and its replacement, CH_2Cl_2, is being restricted as well. Many other solvents are reactive toward NBS, and are thus unsuitable, but acetonitrile can be used to good effect

Wolff-Kishner Reduction

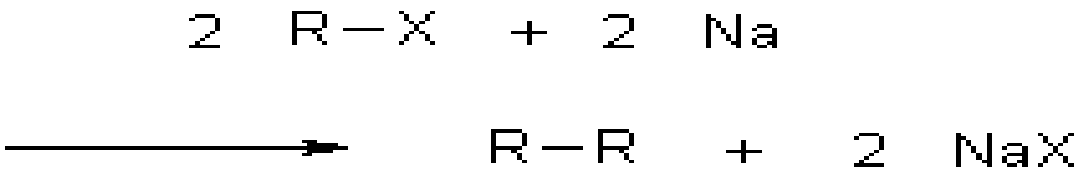


The reduction of aldehydes and ketones to alkanes. Condensation of the carbonyl compound with hydrazine forms the hydrazone, and treatment with base induces the reduction of the carbon coupled with oxidation of the hydrazine to gaseous nitrogen, to yield the corresponding alkane.

The Clemmensen Reduction can effect a similar conversion under strongly acidic conditions, and is useful if the starting material is base-labile

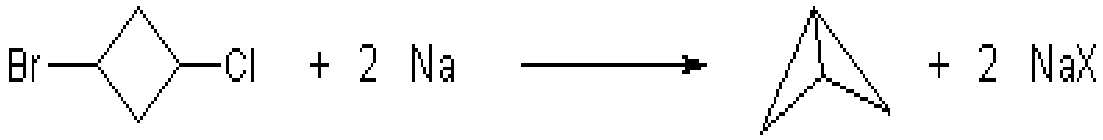


Wurtz Reaction



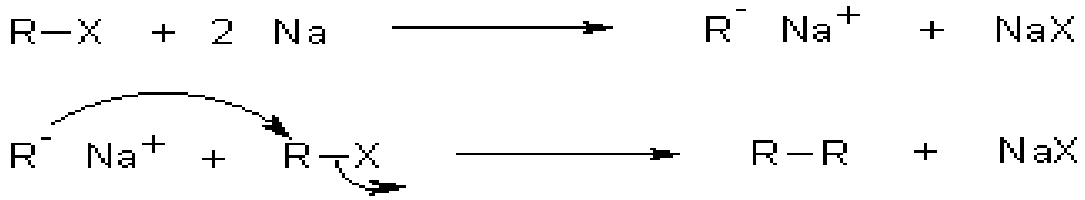
The Wurtz Coupling is one of the oldest organic reactions, and produces the simple dimer derived from two equivalents of alkyl

halide. The intramolecular version of the reaction has also found application in the preparation of strained ring compounds:

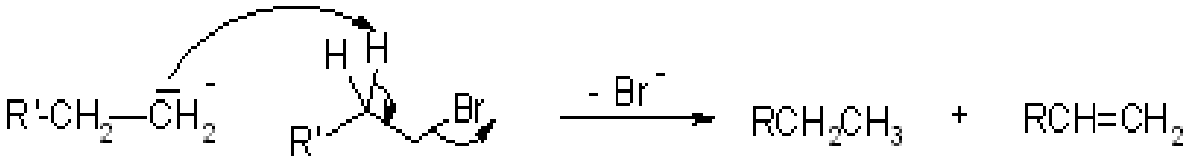


Using two different alkyl halides will lead to an approximately statistical mixture of products. A more selective unsymmetric modification is possible if starting materials have different rates of reactivity (see Wurtz-Fittig Reaction).

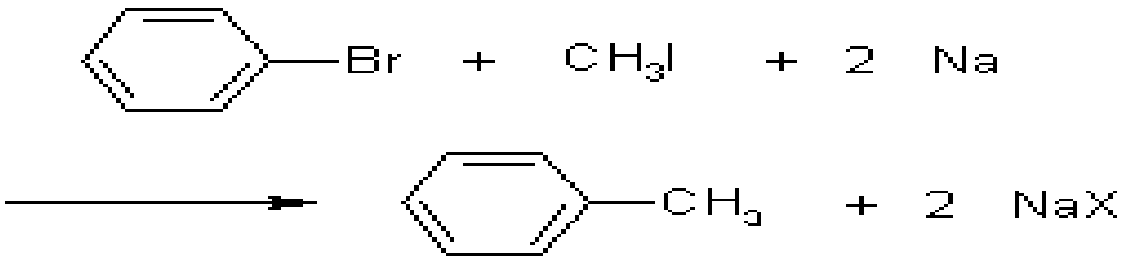
Mechanism of the Wurtz Reaction



Side products:



Wurtz-Fittig Reaction



This reaction allows the alkylation of aryl halides. The more reactive alkyl halide forms an organosodium first, and this reacts as a nucleophile with an aryl halide as the electrophile. Excess alkyl halide and sodium may be used if the symmetric coupled alkanes formed as a side product may be separated readily.

Chromatography

3rd Year Students – Chemistry Group – Faculty of Education

First Term 2022/2023

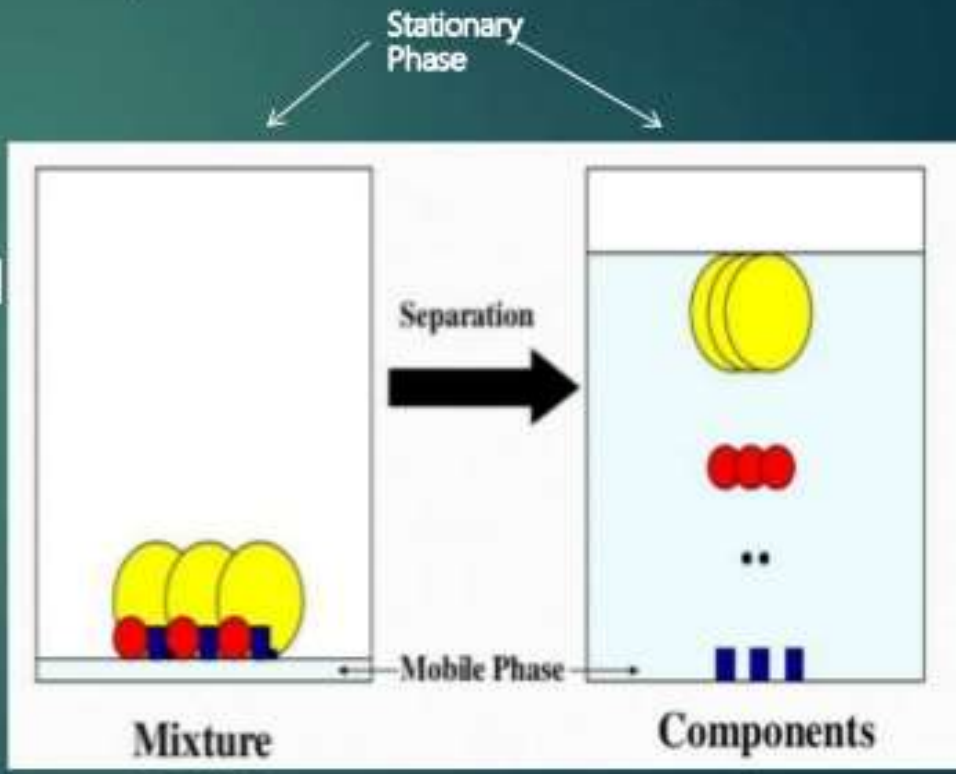
Dr/ Ibrahim Abdul-Motaleb Mousa

Contents

- Introduction to chromatographic techniques
- Chromatogram
- Classification of chromatography
- Paper chromatography
- Thin layer chromatography
- Rf value
- Column chromatography
- Gas chromatography
- HPLC chromatography

INTRODUCTION

- Chromatography is a physical process where the components (solutes) of a sample mixture are separated as a result of their differential distribution between stationary and mobile phases.



- Greek *chroma* meaning 'color' and *graphein* meaning 'writing'

HISTORY

- **Tswet**, Russian botanist (referred to *as Father of chromatography*) is credited for the development of chromatography.

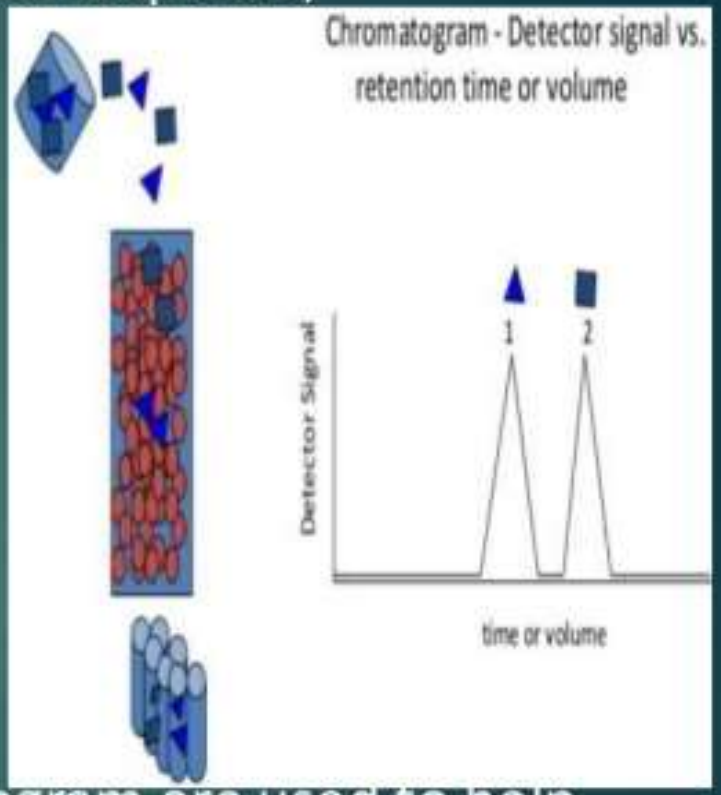
Principle -

- Chromatography is usually based on principle of partition of solute between two phases. It usually consists of a Mobile Phase and a Stationary Phase.

- **The Mobile Phase** usually refers to the mixture of the substances to be separated dissolved in a liquid or a gas .
- **The Stationary Phase** is a porous solid matrix through which the sample contained in the mobile phase percolates.

CHROMATOGRAM

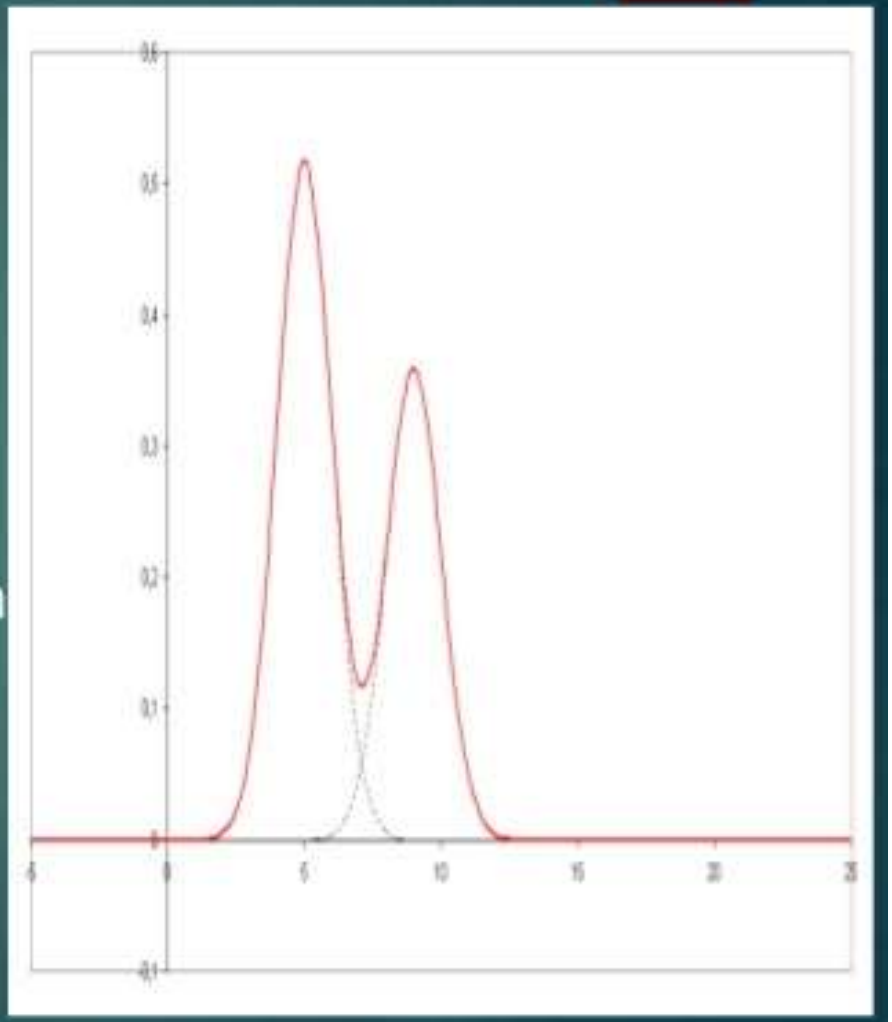
- A graphical presentation of detector response, concentration of analyte in the effluent, or other quantity used as a measure of effluent concentration.



- The retention time or volume is when a solute exits the injector and passes through the column and the detector .

- Data represented by the chromatogram are used to help identify and quantify the solute(s).

- Because eluting solutes are displayed graphically as a series of peaks, they are frequently referred to as chromatographic peaks.
- These Peaks are described in terms of peak (1) width, (2)height, (3)area



CLASSIFICATION

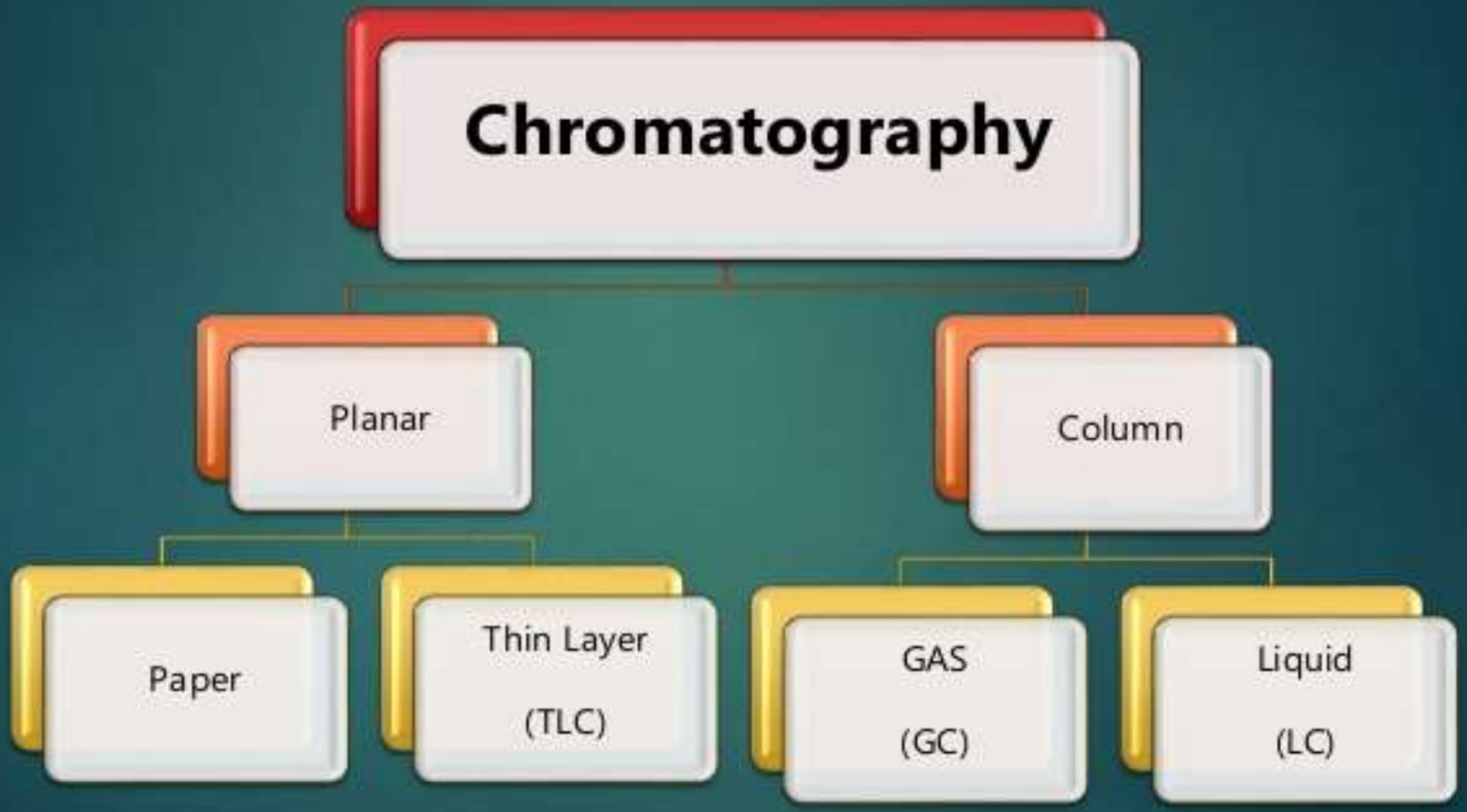
Chromatographic methods can be classified in three different ways :-

a) Based on shape of chromatographic beds .e.g.- Planar and column Chromatography

b) Based on the physical state of mobile and stationary phase. e.g- Gas and liquid chromatography

c) Based on mechanism of separation. e.g.-Ion-exchange chromatography, partition , affinity and adsorption chromatography

Based on shape of chromatographic beds



Planar Chromatography

- In Planar Chromatography stationary phase is present on a plane.
- The Plane can be a paper impregnated by a substance acting as a stationary phase- **Paper Chromatography** OR a Thin layer of a substance acting as a stationary phase spread on a glass, metal or plastic plate- **Thin Layer Chromatography.**
- Planar chromatography is also termed as **Open Bed Chromatography.**

Paper Chromatography

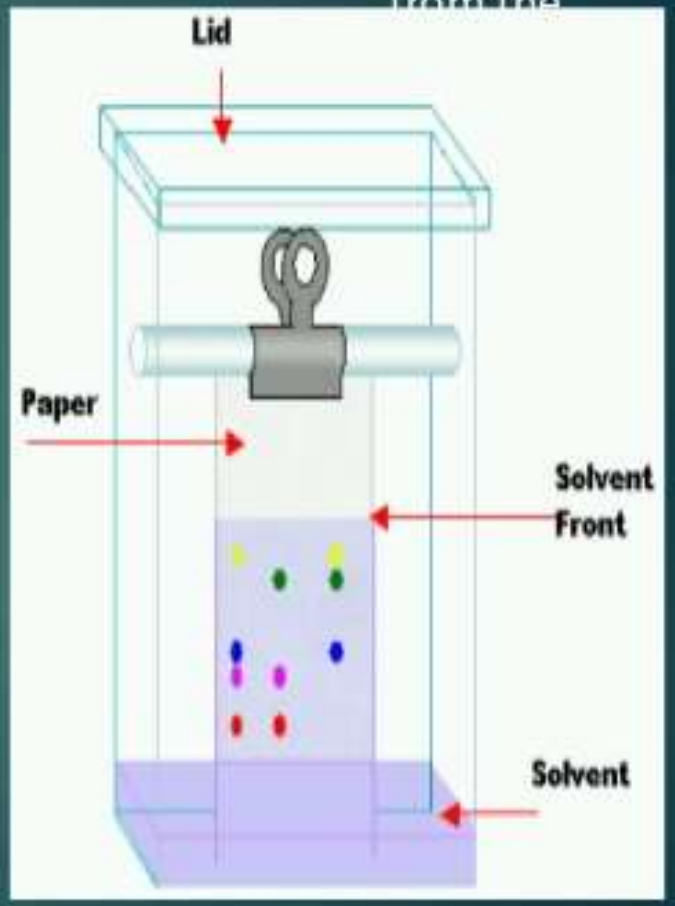
- Paper chromatography is a liquid partition chromatography.
- In paper chromatography, the end of the paper is dipped in solvent mixture consisting of aqueous and organic components.
- The solvent soaks in paper by capillary action because of fibrous nature of paper.
- The aqueous component of the solvent binds to the cellulose paper and thereby forms stationary phase with it .
- The organic component of the solvent binds continues migrating, thus forming the mobile phase.

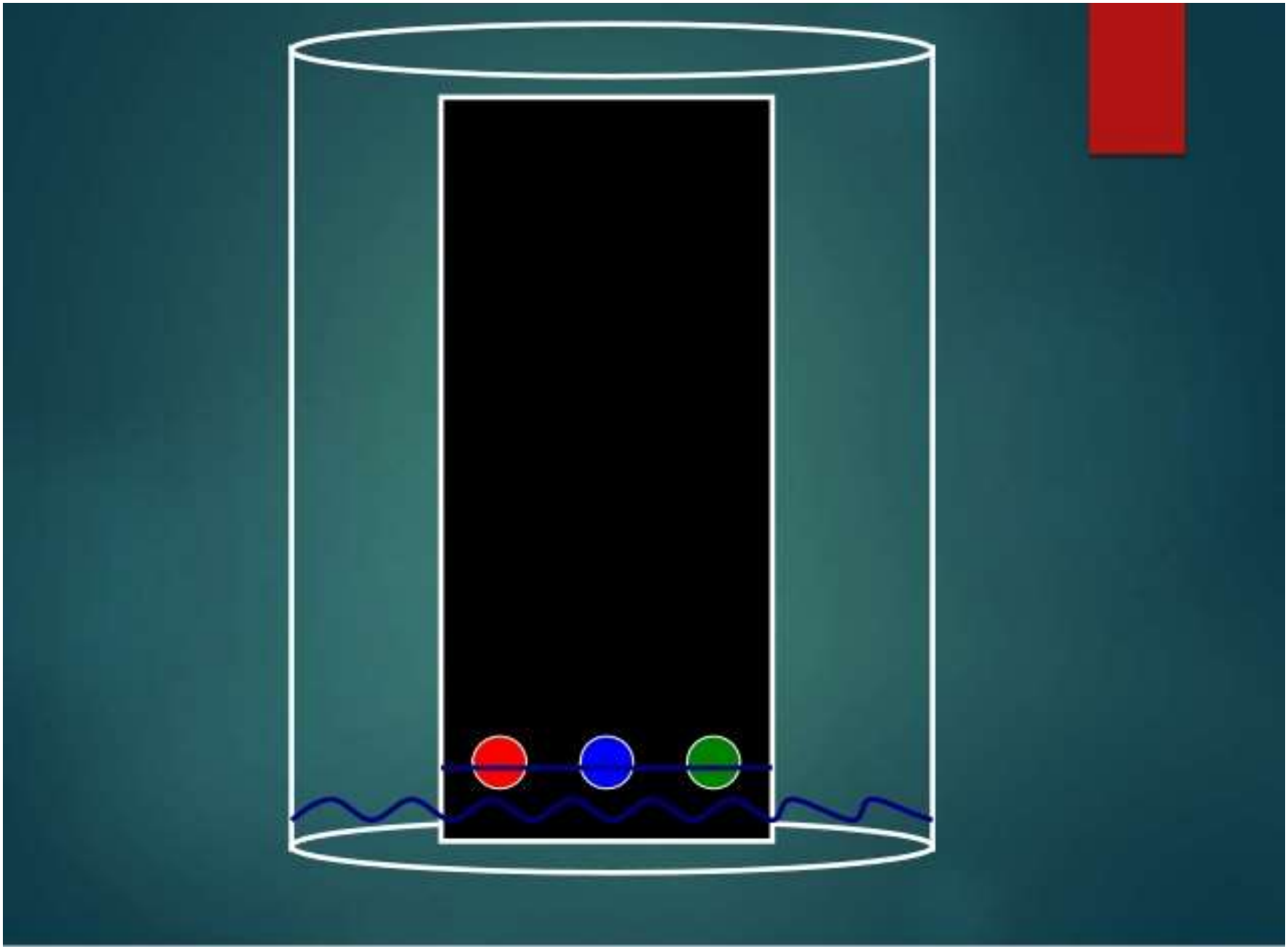
Mechanism of Separation

- Mobile Phase rises up by capillary action.
- Testing sample is concentrated as a minute spot at the bottom of the filter paper.
- Sample mixture gradually rises up with the mobile phase which is liquid.
- Compounds in the mixture will be separated according to their ability of solubility.
- More Polar substances will move slower and less polar substances will travel faster.

Procedure

- A small spot of sample is applied to a strip of chromatography paper about two centimeters away from the base of the plate.
- This sample is absorbed onto the paper and may form interactions with it.
- The paper is then dipped into a solvent, such as ethanol or water, taking care that the spot is above the surface of solvent , and placed in a sealed





- The solvent moves up the paper by capillary action and dissolves the sample mixture, which will then travel up the paper with the solvent solute sample.
- Different compounds in the sample mixture travel at different rates .
- It takes several minutes to several hours.
- **Analysis-** Spots corresponding to different compounds may be located by their color, UV light, Ninhydrin or by treatment with iodine vapors.

Ascending and Descending Paper chromatography

Ascending Chromatography- In this method, the solvent is in pool at the bottom of the vessel in which the paper is supported.

It rises up the paper by capillary action against the force of gravity.

Descending Chromatography- In this method , the solvent is kept in a trough at the top of the chamber and is allowed to flow down the paper .

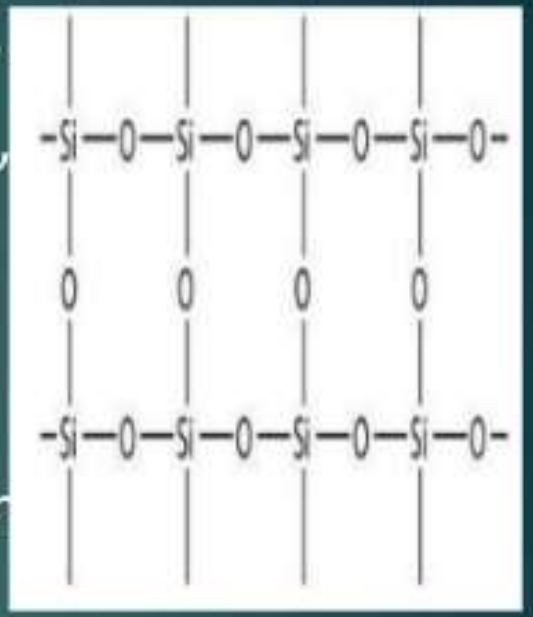
The liquid moves down by capillary action as well as by the gravitational force.

Significance of Paper Chromatography

- It is very easy, simple , rapid and highly efficient method of separation.
- Can be applied in even in micrograms quantities of the sample.
- Can also be used for the separation of a wide variety of material like amino acids , oligosaccharides, glycosides, purines and pyrimidines, steroids, vitamins and alkaloids like penicillin , tetracyclin and streptomycin.

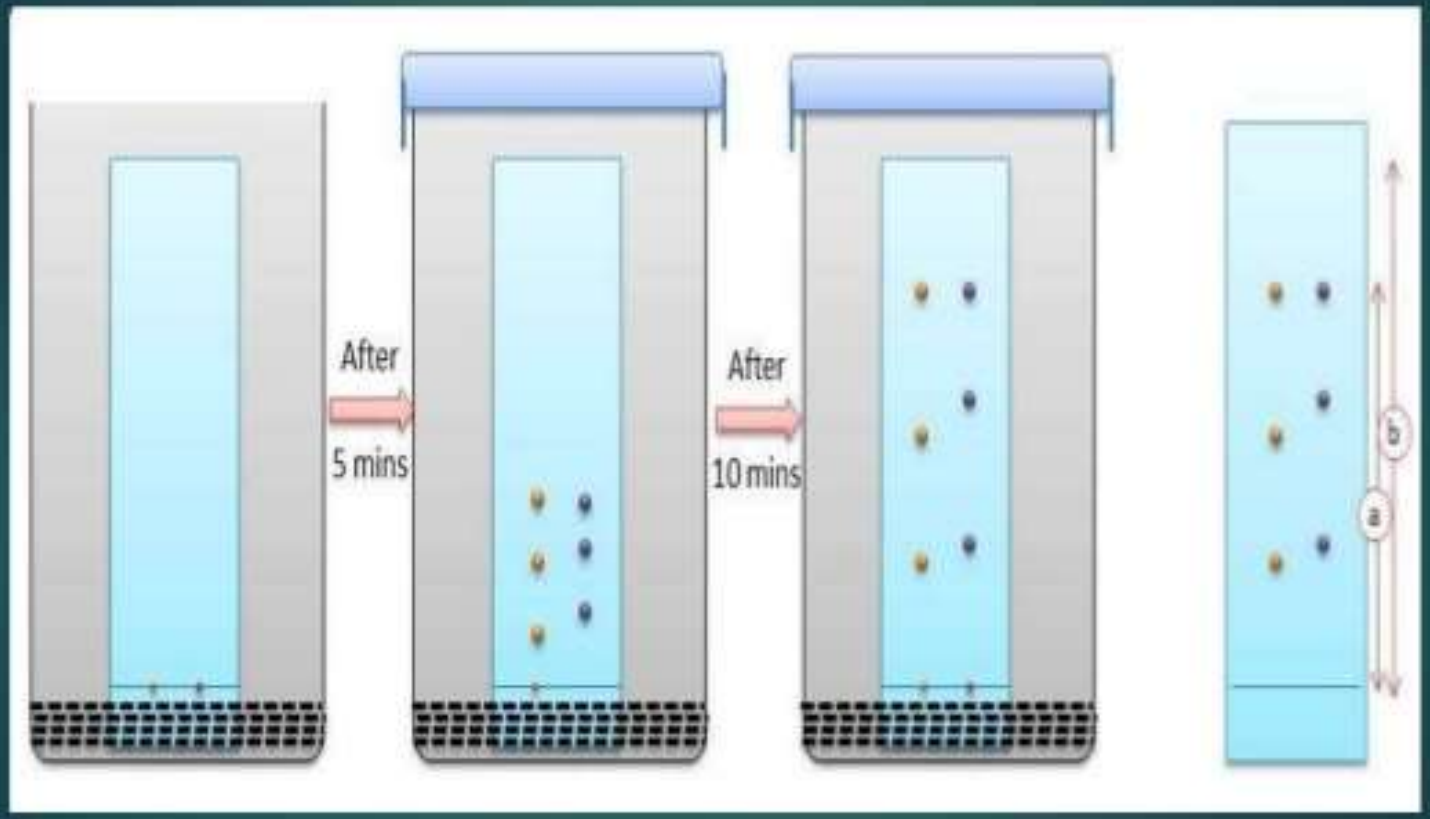
Thin Layer Chromatography (TLC)

- Stationary Phase consists of a thin layer of adsorbent material, usually silica gel , aluminium oxide, or cellulose immobilized onto a flat carrier sheet.



- A Liqiud Phase consisting of the solution to be separated which is dissolved in an appropriate solvent and is drawn up the plate via capillary action , separating the solution based on the polarity of the compound.

Steps of TLC



Significance

Its wide range uses include -

- Determination of the pigments a plant contains.
- Detection of pesticides or insecticides in food .
- Identifying compounds present in a given substance.
- Monitoring organic reaction.

Advantages Of TLC over Paper Chromatography

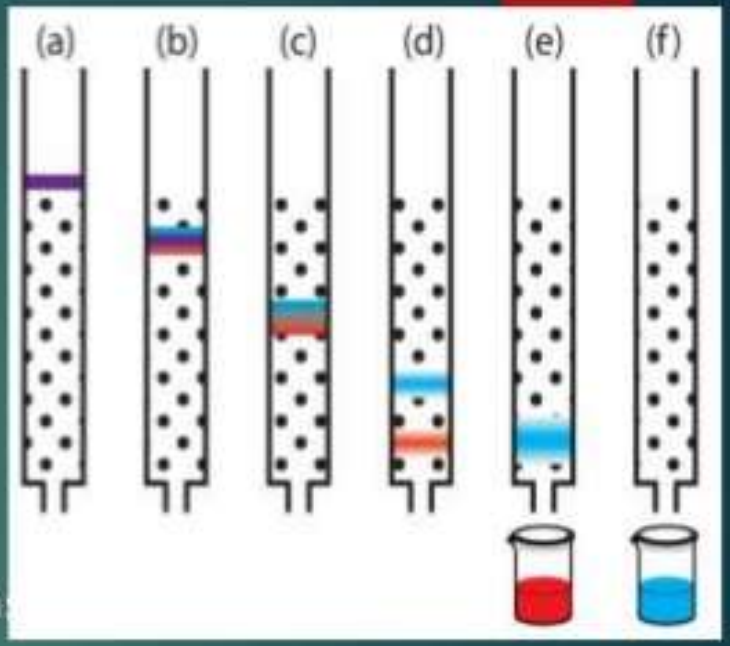
- In case of Paper Chromatography, it takes 14- 16 hrs for the separation of the components, but in TLC , it takes only 3-4 hrs.
- TLC has the advantage that the corrosive reagents like sulphuric acid can also be used which pose a limitation for the paper chromatography.
- It is easier to separate and visualise the components by this method.
- It has capacity to analyse multiple samples in a single run.
- It is relatively a low cost.

R_F value -

- The rate of migration of the various substances being separated are governed by their relative solubilities in the polar stationary phase and non polar mobile phase.
- The migration rate of a substances usually expressed as R_f (relative front).
- R_f = Distance travelled by the substance / Distance travelled by the solvent front

Column Chromatography

- The Stationary bed is within the tube.
- In column Chromatography the stationary Phase may be pure silica or polymer, or may be coated onto , chemically bonded to, support particles.
- Depending on whether mobile phase is a ga Chromatography or liquid Chromatography.
- When the Stationary phase in LC consists of small-diameter particles, the technique is High Performance Liquid Chromatography (HPLC).



Gas Chromatography

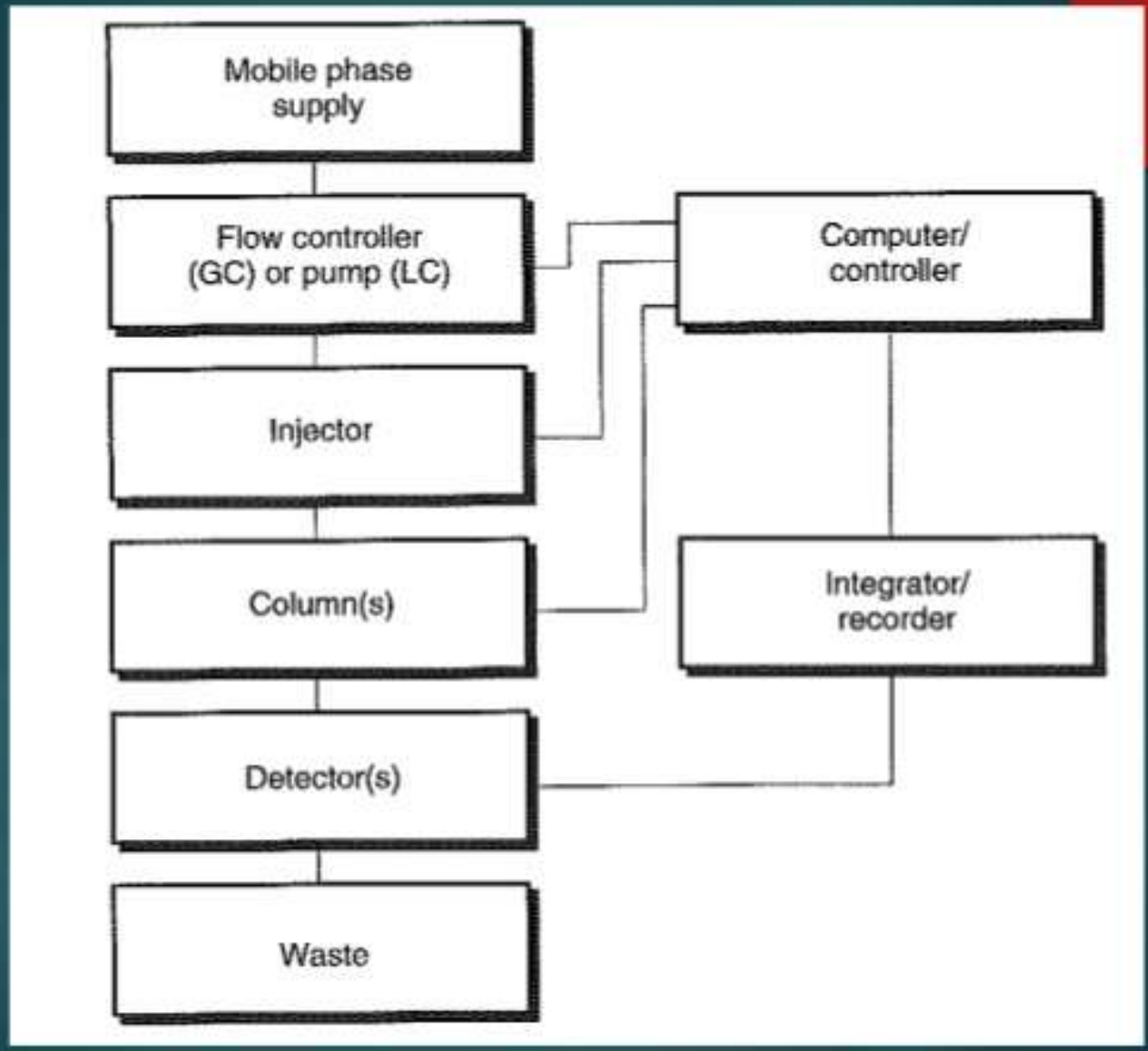
- Gas mobile phase is used to pass a mixture of volatile solutes through a column containing the stationary phase.
- The mobile phase often referred to as the carrier gas , is typically an inert gas such as nitrogen, helium ,or argon.
- Solute separation is based on the relative differences in the solutes vapor pressures and interactions with the stationary phase.
- Thus more volatile solute elutes from the column

- A solute that selectively interacts with the stationary phase elutes from the column after with lesser degree of interaction.
- The column effluent carries separated solutes to the detector in order of their elution.
- Solutes are identified qualitatively by their retention times.
- Peak size is proportional to the amount of solute detected and is used to quantify it.

Instrumentation

A basic gas Chromatograph consists of the following:-

- A chromatographic column to separate the solutes
- A supply of carrier gas and flow- control apparatus to regulate the flow of carrier gas through the system.
- An injector to introduce an aliquot of sample or derivatized analytes as they elute from the column.
- A computer to control the system and process data.


Mobile phase supply
Flow controller (GC) or pump (LC)
Injector
Column(s)
Detector(s)
Waste
Computer/ controller
Integrator/ recorder

Liquid Chromatography

- Separation by LC is based on the distribution of the solutes between a liquid mobile phase and a stationary phase.
- When particles of small diameter are used as stationary phase support, the technique is HPLC.
- Most widely used form of LC.

Instrumentation

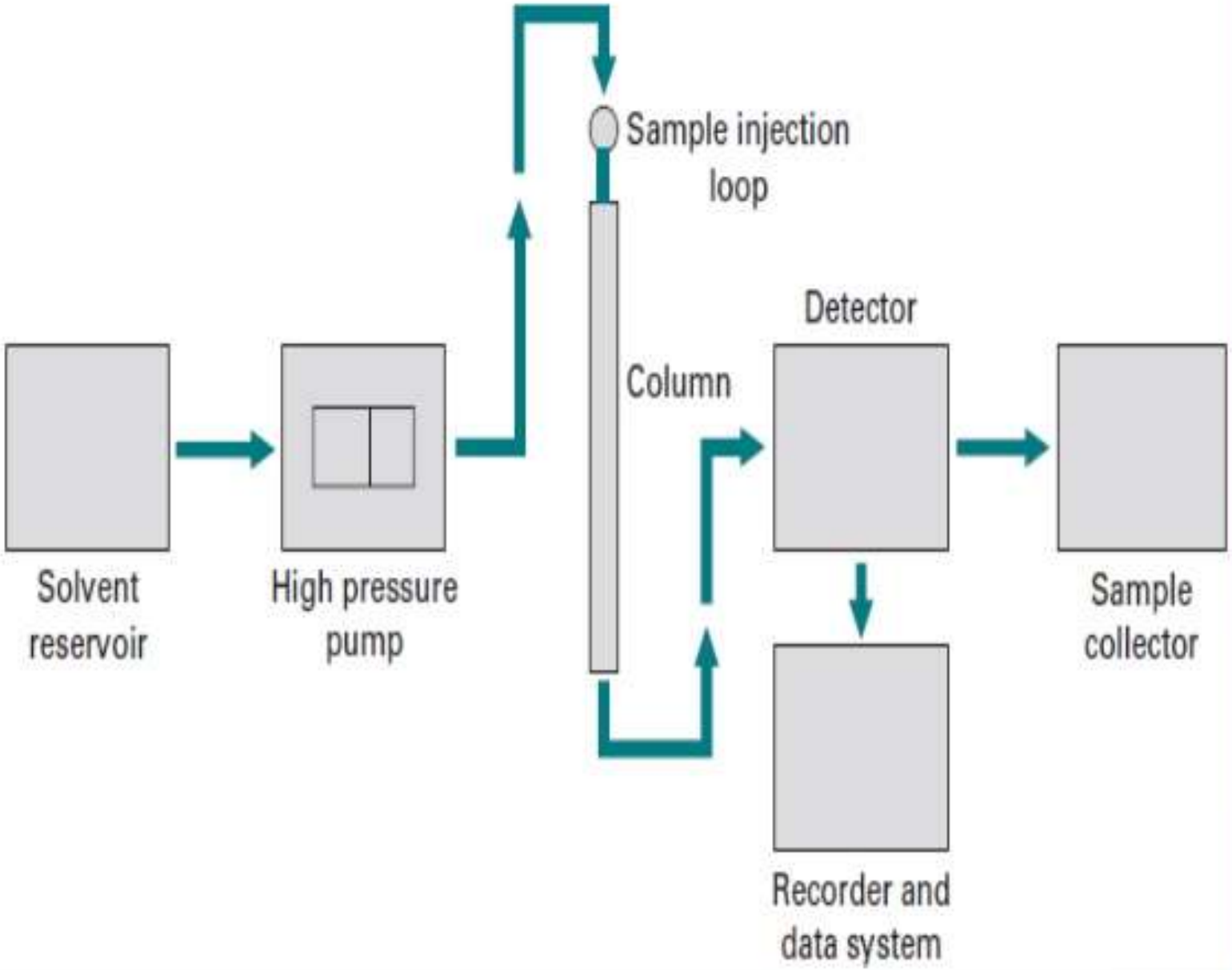
A basic Liquid chromatograph consists of following elements :-

- A solvent reservoir to hold the mobile phase through the system.
- An injector to introduce sample into the column.
- A chromatographic column to separate the solutes.
- Detector to detect the separated analytes as they elute from the column.
- A computer that processes the system and processes data.

HPLC

- HPLC is basically a highly improved form of Liquid Chromatography.
- Instead of a solvent (mobile phase) being allowed to drip through the column under gravity, it is forced through under high pressure.
- Yeilds high performance and high speed as compared with traditional column chromatography.

- The parameters used to describe a HPLC column refer to the nature, type and size of its packaging material, and the dimensions of the column used.
- Increased flow rates are obtained by applying a pressure difference across the column.
- A combination of high pressure and adsorbents of small particle size leads to the high resolving power and short analysis time characteristic of HPLC


Sample injection loop
Detector
Column
Solvent reservoir
High pressure pump
Sample collector
Recorder and data system

The advantages of HPLC are the result of two major advances :-

- The development of stationary supports with very small particle sizes and large surface areas .
- The improvement of elution rates by applying high pressure to the solvent flow.

Applications

Pharmaceutical- Tablet dissolution of pharmaceutical dosages

- Shelf life determination of pharmaceutical products
- Identification of counterfeit drug products
- Pharmaceutical quality control

Forensics- On site identification and quantification of the drug Ecstasy.

- Identification of anabolic steroids in serum, urine, sweat and hair
- Forensic determination of textile dyes.
- Simultaneous quantification of psycotherapeutic drugs in human plasma

Clinical-

- Analysis of antibiotics.
- Detection of endogenous neuropeptides in brain extracellular fluids.

Food and Flavour-

- Ensuring soft drink consistency and quality
- Analysis of vicinal diketones in beer.
- Sugar analysis in fruit juices.

- Trace analysis of military high explosives in agricultural crops.

Based on Separation Mechanisms

- Chromatographic separations are classified by the chemical or physical mechanisms used to separate solutes.

- These include-

1. Ion- exchange
2. Partition
3. Adsorption
4. Size exclusion
5. Affinity mechanisms

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