CHAPTER 1

Basic Aspects of Organic Chemistry

The chemistry of organic substances is known as organic chemistry. Carbonaceous resources such as coal, natural gas, and petroleum, as well as plants, are the main natural sources of organic compounds. The unique feature of organic substances is that they have a considerably higher number of carbon-containing compounds than non-carbon-containing molecules. These substances may be big and intricate. It is also possible for the arrangement of carbon atoms to be complex. Aside from that, biology and medicine depend heavily on organic chemistry. It serves as the foundation for technological advancement and is crucial to many businesses.

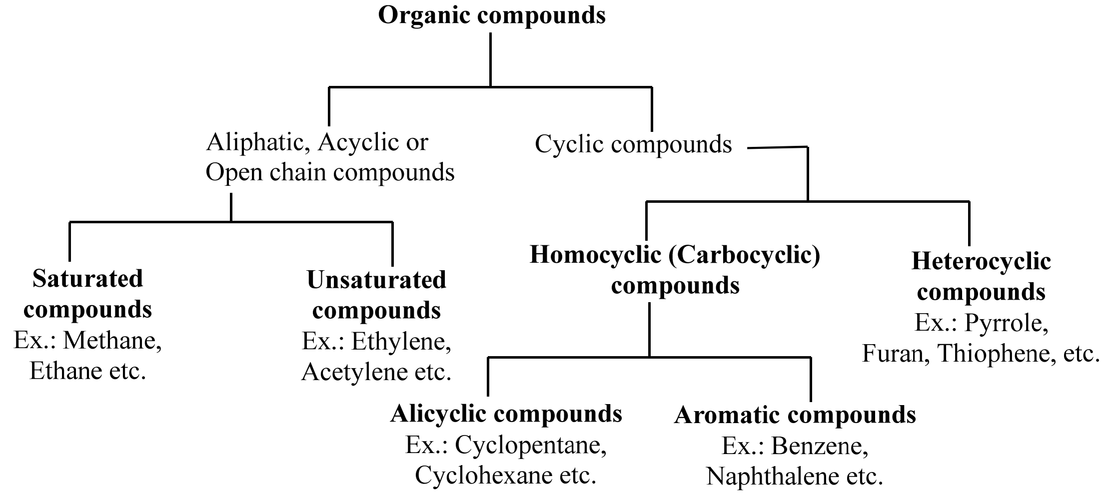
Agrochemicals, plastics, dyes, pigments, textiles, biochemicals, medications, vitamins, and many more materials are all made possible by organic chemistry, which is also essential to human life. Although prehistoric cultures were aware of numerous organic substances, such as sugar, lipids, starches, indigo, and alcohol, modern organic chemistry was founded in the 18th century when natural products were isolated from a variety of natural sources. From natural sources, Scheele separated malic acid, tartaric acid, and citric acid. He also created lactic acid, oxalic acid, and glycerol. The phrase "organic compounds" was created by Berzelius to describe substances that came from plants and animals. He stated that the area of chemistry that deals with organic chemicals is called organic chemistry. The branch of chemistry known as inorganic chemistry studies compounds derived from minerals. Vital Force Theory believes that organic chemicals were made from nature by the operation of vital force, inherent in living cells. With the synthesis of urea from ammonium cyanate by Wöhler in 1828, the era of synthetic organic chemistry started.

The important features of organic compounds:

1. The carbon atoms can bind to each other carbon atoms by stable covalent bonds; these can form chains, branched chains or rings. These are also capable of forming complex molecules. This kind of self-linking is called Catenation.
2. These are non-ionic in nature.
3. These form bonds to a limited number of other elements like H2, halogens, oxygen, nitrogen, sulfur, selenium, silicon, phosphorus, boron, etc.
4. These can form isomers.
5. These are generally insoluble in water but soluble in organic solvents.
6. These are highly volatile and flammable.
7. These have characteristic odor and color.
8. These have low melting point and boiling point.

9. These can be classified based on various functional groups which attribute special properties particular to that class.

Classification of organic compounds:



Types of bonds:

Three types of bonds are known:

a) **Ionic or Electrovalent Bond:**

The bond is formed due to the electrostatic attraction between the reacting oppositely charged ions. The electrons are completely transferred to the other reacting ion. Ex.: NaCl, KCl.

b) **Covalent Bond:**

Here the bond is formed due to the mutual sharing of electrons between two reacting species. Ex.: CH_4, C_2H_6.

c) **Coordinate Covalent Bond:**

It is formed by the donation of a pair of electrons to other deficient reacting species. Ex.: NH^+4, O3.

General properties of Inorganic and Organic compounds:

S. No.	Inorganic compounds	Organic compounds
1.	These are ionic molecules	These are covalent molecules
2.	These undergo ionic reactions	These undergo covalent bonding and related to molecules
3.	Isomerism is not exhibited	These molecules show isomerism
4.	These exist as acids, bases and salts	These are classified depending on the functional group like alcohols, amines, aldehydes, ketones, carboxylic acids, esters, amides etc.
5.	These exhibit high melting point and boiling point	These have low melting point and boiling point
6.	These are generally colorless and odourless	These possess characteristic color and odour
7.	These are generally water soluble	These are generally water insoluble, but soluble in organic solvents
8.	These have less volatility and flammability	These are highly volatile and flammable

Sources of organic compounds:

These can be obtained both from natural and synthetic sources. From nature, these can be isolated from plants and animals.

Important applications of organic compounds in daily life:

We depend every day on many organic compounds for our use. Apart from several complex molecules like amino acids, peptides, proteins, DNA, RNA, enzymes, lipids and hormones, Compounds, play a significant role in keeping us in good health

Foods: Glucose, Sucrose, Starch, Fats, Proteins, Vitamins, etc.

Clothes: Cotton, Wool, Silk, Nylon, Terylene, etc.

Fuels: Coal, Kerosene, Petrol, Diesel

Dyes: Indigo, Congo-Red, Malachite Green, etc.

Rubbers, Polymers, Plastics: Bakelite, Melamine, Teflon, Polyethylene, Polypropylene, Polystyrene, Polyvinyl chloride, etc.

Paints, Varnishes, Enamels:

Agrochemicals, Pesticides, Pheromones and Fertilizers: Urea, DDT, Malathion, Boric acid, Acephate, Diazinon, Glyphosate, Gammaxene, etc.

Stationery: Inks, Papers, etc.

Refrigerants:

Cosmetics and Perfumes: Parabens, Phthalates, Lanolin, Triclosan, Hydroquinone, Ammonium lauryl sulphate, Propylene glycol, Isopropanol, Phenoxyethanol, Vanillin, Camphor, etc.

Medicines: Aspirin, Penicillin, Sulfonamide, Streptomycin, Cortisone, Cephalosporin, Penams, Propranolol, Tetracyclines, etc.

Disinfectants: Ethyl Alcohol, Chlorine compounds, Formaldehyde, Peracetic acid, Phenols, *ortho*-phthalaldehyde, Glutaraldehyde, Iodophors, etc.

Explosives: TNT, Picric acid, Nitroglycerin, etc.

Composition of organic compounds:

The principal elements present in organic compounds, in general, are carbon, hydrogen, oxygen, nitrogen, sulfur, fluorine, chlorine, bromine, iodine, phosphorus, boron, etc.

Structure of organic molecules:

Tetracovalency of Carbon: The atomic number of carbon is six. C = $1s^2$, $2s^2$, $2p^2$.

Ground state = $1s^2$, $2s^2$, $2p_x^1$, $2p_y^1$, $2p_z^0$. Excited state = $1s^2$, $2s^1$, $2p_x^1$, $2p_y^1$, $2p_z^1$. Carbon can complete octet by sharing one electron each with four atoms with mono-valency such as hydrogen. Ex.: CH_4; One important characteristic of carbon is that it can form covalent bonds with other carbon atoms. Catenation is the name given to this characteristic. This characteristic leads to the formulation of both straight and branched carbon chains. It may also create cyclic formations that resemble rings. Many naturally occurring compounds, often known as natural products, are examples of the complex molecules that carbon may make. Synthetic substances are molecules or compounds that humans have created in a lab. Covalent bonds are formed when the electron of one bonding atom fills the half-filled orbital of another atom. They may alternatively be described as the increasing overlapping of bonding or combining atomic orbitals. The original orbitals merge to form new molecular or hybrid orbitals, and this merging is known as hybridization. The effective overlap takes place when (a) Two combining orbitals are half-filled, (b) When both bonding orbitals approach closer with proper alignment, (c) When the electrons of bonding orbitals move in opposite direction (spin). Greater is the overlap, greater is the energy released and higher is the bond strength, lower is the bond length.

Type of bond	Bond energies (kcal/mol)	Bond length (Å)
H-H	103.2	0.74
C-H	98.7	1.12
C-C	83.0	1.54
C-N	148.1	1.47
C-O	84.0	1.43
C-Cl	83.0	1.77

Types of covalent bonds:

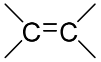
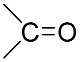
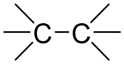
Covalent bond can be formed by the s-s overlap and s-p overlap, p-p overlap (linear or sidewise). These overlaps form different molecular orbitals with shapes and energies. Two main types of molecular orbitals are formed depending on directional dispositions. Two types of covalent bonds are formed σ-sigma and π-pi bonds.

Sigma bond (σ): When the overlapping bonding orbitals form a molecular orbital, which is symmetrically distributed along the nuclear axis, the bond is called σ-sigma bond. These are formed by overlap of (a) 2-s orbitals or (b) one s- and one p-orbital or (c) one p-orbital and one p-orbital-overlap in linear direction. Ex.: H_2 (s-s); H-F (s-p); F_2 (p-p).

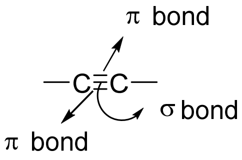
Pi bond (π): Lateral or sideways overlap of bonding p-orbitals of two atoms results in pi-(π) bond formation. Such bond is weaker than sigma bond and there is no free rotation of atom about the nuclear axis, the rotation about the bond axis of a π bond will be restricted. Ex.: O_2- $1s^2$, $2s^2$, $2p_x^2$, $2p_y^1$, $2p_z^1$ (one σ bond and one π bond); N_2- $1s^2$, $2s^2$, $2p_x^1$, $2p_y^1$, $2p_z^1$ (one σ bond and two π bonds).

With four half-filled atomic orbitals ready to overlap carbon can form 4 sigma bonds such as in CH_4 resulting in 1 s-s, 3 s-p bonds. As the experimental data indicate that all four bonds are equivalent, the concept of hybridization explains that all the bonding atomic orbitals merge and redistribute. Their energy and shape, forming entirely "new", symmetrically four equivalent sp3 orbitals. The hybrid orbitals are equal in number to merging atomic orbitals. The orbitals have two electrons with opposite spin. The hybridization can be explained based on tetra covalency of carbon.

Types of Hybrid Orbitals:

Mixing orbitals	Hybrid orbitals	Types of hybridization	Shape	Bond angle	Example
1s and 1p	2-sp	sp	Linear	180°	$—C\equiv C—$
1s and 2p	3-sp^2	sp^2	Trigonal	120°	 
1s and 3p	4-sp^3	sp^3	Tetrahedral	109°28'	

In ethylene molecule two sp^2 hybridized carbon atoms form one sigma-bond by head-on overlap of two sp^2 orbitals and the remaining two sp^2 hybrid orbitals of carbon form two sigma bonds with two hydrogen atoms. The unhybridized $2p_z$ orbitals of two carbons form sidewise overlap forming π bond- a part of C=C bond. Similarly, in acetylene molecule, 2sp orbitals of two carbons each form a sigma bond between two carbons. The remaining sp orbital overlap with s orbital of hydrogen atom. The two unhybridized 2py, 2pz orbitals of two carbon atoms form sideways overlap resulting in two π bonds – part of C≡C.



The resonance can be defined as the concept of delocalization of electrons across multiple conventional Lewis structures to form a more stable hybrid structure with lower energy. The amount of difference of energy between the real conjugated molecule and hypothetical resonance structures is called resonance energy.

Bond angle: It is the angle between the direction of two covalent bonds.

Bond energy: It is the average value of all bonds' dissociation energies of a molecule.

Bond order: Number of covalent bonds in the molecule H2=1; O2=2; N_2=3"

Bond dissociation energy: It is the amount of energy required to break a particular bond in a polyatomic molecule in the gaseous state into free radicals or neutral fragments in the gaseous state.

Hybridization: Linus Pauling in 1931 defined hybridization as the combination inter-mixing of atomic orbitals or slightly different energies to form a new set of equivalent orbitals of equivalent energies and shapes.

The important criteria for hybridization are:

- **a)** The orbitals undergoing hybridization must have nearly equal energy.
- **b)** Valence shell orbitals are to be hybridized.
- **c)** Both filled or partly filled orbitals can participate in hybridization.
- **d)** The hybridized orbitals are equivalent in shape and energies.
- **e)** These hybridized orbitals can form stable bonds.
- **f)** The number of resultant hybrid orbitals after hybridization is equal to the number of orbitals undergoing hybridization.
- **g)** The hybridized orbitals direct into characteristic geometric patterns to have minimum repulsion between electron pairs and to have a stable arrangement.

Nomenclature of organic compounds:

The following are some of the important rules for naming the organic compounds under IUPAC system:

1. Longest chain rule: In the given compound, the longest carbon chain of the molecule is identified and named as the derivative of that alkane.
2. Lower number of substituent rules: While numbering the longest chain, the number should start from the end so as to give the lowest number to the substituent.
3. Arrangement of prefixes: In a given compound, when more than two groups are there, these groups are numbered in alphabetical order. When the same group is present more than one time, they are prefixed as di, tri, tetra, etc.

4. Lowest number for the functional group: Double or triple bonds are also considered as functional groups. Violating rule 2, when a functional group is also present, numbering is to be done so as to give first preference to the functional group.

5. The order of preferences in numbering: 1) Principal functional groups, 2) double bond or triple bond, 3) Substituent groups or atoms. Among these, the priority order is: a) carboxylic acid, b) acid derivatives, c) aldehydes, d) nitriles, e) ketones, f) alcohols, g) amines, h) ethers, i) olefins, j) acetylenes.

Some functional groups are mentioned as prefixes and some as suffixes.

6. Writing for compounds having more than one functional group: when more functional groups are present, the names are combined in endings, or the important functional group is mentioned as a a substituent.

7. Considering groups of one kind of a single molecule as same and numbering as well as naming are preferentially given.

8. Selected chain to include maximum number of functional groups. This can sometimes violate longest chain rule (rule 1).

Steps in writing IUPAC name of a given compound:

a) Locate largest chain, write functional group including multiple bonds.

b) Select the root word for the carbon chain according to the number of carbons present.

c) Number the longest possible chain from the end nearest to the functional group.

d) Depending on the carbon chain, carbon bonds are given suffixes like ane, ene, yne.

e) Add suffixes or prefixes with numerals indicating the number and position of all important attachments to the main chain, placing the numerals before the functional group or unsaturation.

f) Add hyphens to connect numbers and letters to connect prefixes with the main compound name.

g) Commas are used to separate the individual numbers.

h) Parentheses and square brackets are used to demarcate certain locants.

Organic reactions are chemical reactions taking place between organic compounds. Basically, these are: 1. Addition reactions, 2. Elimination reactions, 3. Substitution reactions, 4. Rearrangement reactions. Apart from these photochemical, pericyclic and redox reactions are also familiar in organic synthesis. These play significant role in the preparation of simple to complex organic molecules. Many name reactions are known by their inventors' names and are applicable both in basic and industrial research as well as manufacturing sectors. These make use of various organic and inorganic reagents. Polar reactions are characterized by the movement of electron pairs from sources like nucleophiles or lone pairs to electrophiles. Radical reactions are known by single electron transfers or movements and participated by radicals. These reactions may proceed by chain or non-chain processes. Pericyclic reactions are concerted reactions involving cyclic rearrangement of atoms/groups and redistribution of chemical bonds, as well as a cyclic transition state. These require continuous overlap of participating orbitals and are governed by orbital symmetry considerations. Generally, organic reaction can be represented by

$$\begin{array}{c} \text{Organic molecule or substrate + Attacking reagent} \\ \downarrow \\ \text{Transition state or Transitionary Intermediate} \\ \downarrow \\ \text{Products or Byproducts} \end{array}$$

Substrate is the reactant that contains carbon atoms some of whose bonds with other atoms are broken and some new bonds are formed due to the reaction between substrate molecule and attacking reagent. Organic reaction mechanism depicts the total steps involved in breaking of bonds and making of bonds, resulting in the formation of product molecules. Through the transitionary intermediates, including the details of electron movements, are explained. The reaction is made possible by the displacement of bonding electrons, resulting in polarity in the reacting molecules due to electron displacement effects. Four important effects are generally observed in the organic molecules.

1. **Inductive Effect:** It can be defined as the local change in the electron density due to the electron donating or electron withdrawing groups attached in the molecule. It results in the permanent dipole in the bond (sigma bond). This permanent effect of polarity caused by minor displacement of electrons can be a -I effect or a +I effect depending on the polarity of the substituent attached to the parent carbon chain.

When a halogen atom is attached to a carbon atom as in an alkyl halide, the shared electrons between the C-X bond are moved or displaced towards the more electronegative X atom (Cl, Br, I). The positive charge is relayed towards down the chain. This is known as -I effect. In case of electron releasing (Y) substituent attached to carbon, negative charge is relayed down the chain. This is known as +I effect. Both these -I and +I effect decrease slowly from α, β, γ-carbon atoms. The effect falls rapidly in the carbon chain as the distance from the functional group increases.

$$\mathrm{C} \longrightarrow \mathrm{X}$$

(-I effect)

$$\begin{array}{ccccccc} \mathrm{C} & \longrightarrow & \mathrm{C} & \longrightarrow & \mathrm{C} & \longrightarrow & \mathrm{X} \\ \delta{+}{+}{+} & & \delta{+}{+} & & \delta{+} & & \delta{-} \end{array}$$

$$\mathrm{C} \longleftarrow \mathrm{X}$$

(-I effect)

$$\begin{array}{ccccccc} \mathrm{C} & \longleftarrow & \mathrm{C} & \longleftarrow & \mathrm{C} & \longleftarrow & \mathrm{Y} \\ \delta{-}{-}{-} & & \delta{-}{-} & & \delta{-} & & \delta{+} \end{array}$$

a) **-I effect groups (electron attracting)**

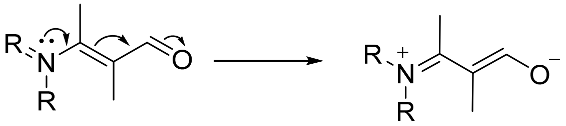
$$-NO_2 > F > CO_2H > Cl > Br > I > OH > C_6H_5$$

b) **+I effect groups (electron releasing or donating)**

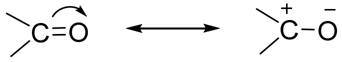
$(CH_3)_3C- > (CH_3)_2\text{-}CH- > CH_3CH_2- > CH_3-$ or $3^o > 2^o > 1^o$

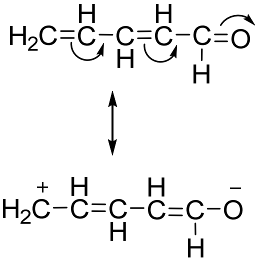
tert-butyl > Isopropyl > Ethyl > Methyl

2. **Electromeric Effect:** It is the temporary molecular polarizability caused by the intramolecular electron displacement in the substrate molecule by the shift of an electron pair from one atom to another under the influence of an electrophilic reagent, usually when a double bond or triple bond is expose dually when a double bond or triple bond is exposed.



3. **Mesomeric Effect:** When an electron withdrawing or electron releasing group is conjugated with a π-bond or a set of alternatively positioned σ or π bonds, the electron displacement is transmitted through the π electrons in the chain of the substrate molecule. π-electrons get delocalized as a consequence of mesomeric effect, resulting in a number of resonance structures of the molecule.

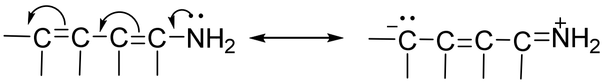


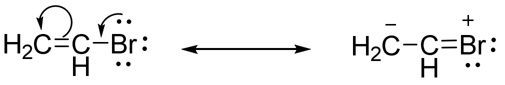


Just like the inductive effect, the mesomeric effect can also be shown as a +M effect or a -M effect, depending on the electron displacement direction. Greater the degree of delocalization, greater is the stability.

+M effect: direction of electrons away from the group. Ex.: -OH; -OR; $-NH_2$; -SR

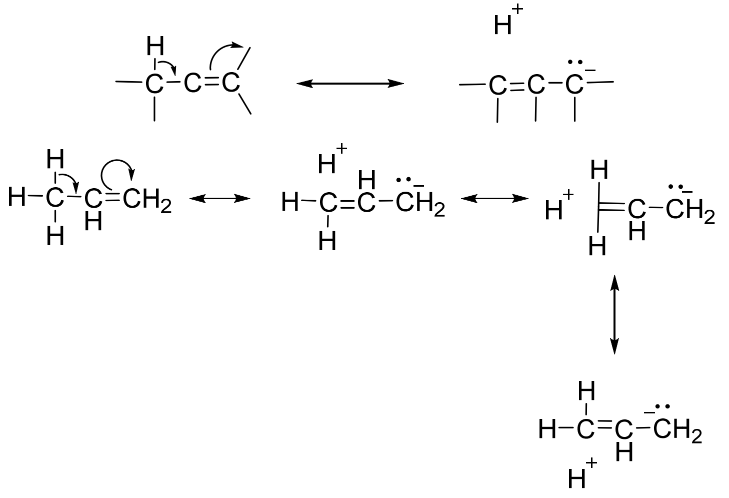
-M effect: direction of electrons towards the group. Ex.: -C(O)-; $-NO_2$; -CN; $-SO_3H$



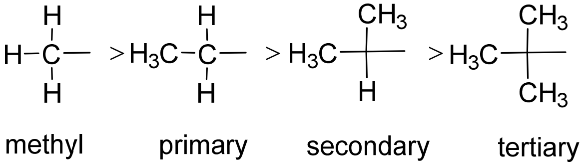


Both these electromeric effects and mesomeric effects are combinedly known as resonance effects.

4. **Hyperconjugation:** It is the delocalization of electrons with the participation of bonds of primarily σ character. This is also known as no-bond resonance or σ-conjugation. It involves the electrons of σ-orbitals such as those of C-C or C-H bonds; increased electrons delocalization due to hyperconjugation increases the stability of the system in the substrate molecule. It affects bond lengths, dipole moments, heat of formation of molecules, as well as the stability of carbocations According to Baker and Nathan, the hyperconjugation effect takes place through the interaction of σ electrons of C-H with π electrons of C=C.



The hyperconjugative effect depends on the number of C-H bonds at the α-carbon to the unsaturated system. It would be maximum with a CH3 group at the α-position, followed by an isopropyl group. As there is no C-H bond at the α-position, a tert-butyl group shows zero effect. The order of release of electrons for the alkyl group is as follows:



Bond Fission:

A covalent bond is formed due to the sharing of a pair of electrons. Bond fission separates these two atoms. The process can take place in two ways. When each electron of the shared pair is taken away by each atom symmetrically it is called homolytic fission or homolysis. Such single-electron species are called free radicals, and these are not charged. These are transitory and react immediately to gain stability, by pairing up with another electron of the available species.

$$\underset{\text{Molecule}}{A : B} \longrightarrow \underset{\text{Free radicals}}{A^{\bullet} + B^{\bullet}}$$

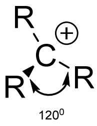
$$Cl : Cl \xrightarrow[\text{light or heat}]{} \underset{\text{Chlorine free radicals}}{Cl^{\bullet} + Cl^{\bullet}}$$

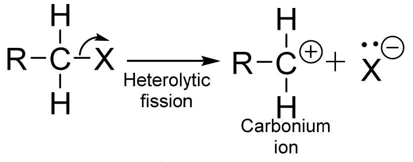
When a covalent bond breaks in such a way that both the bonding electrons go to only one of the bonded atoms, forming one negatively charged and one positively charged species, determined by the electronegativities of the two atoms. The process is called heterolytic fission. It is most common in organic reactions conducted in solution phase. The progress of this process depends on the nature of the solvent. Polar solvents and ionic catalysts contribute significantly for the progress of the heterolytic fission of covalent bonds. The energy required to break the bond is partly taken from the energy of solution of the ions generated.

$$\underset{\text{Molecule}}{A : B} \longrightarrow \underset{\text{Anion}}{A^{\ominus}} + \underset{\text{Cation}}{B^{\oplus}}$$

Reactive intermediates:

1. **Carbocation:** It can be defined as the ion containing positively charged carbon species. As the carbon of a carbocation has only 6 electrons (six). It is very reactive and unstable. It will have a tendency to gain an octet. It will be ready to react with any species that can donate a pair of electrons. It is a flat structure with all three bonds in one plane. Bonding is 120° between all three bonds.



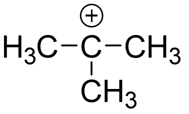


$$R-CH_2-X \xrightarrow[\text{fission}]{\text{Heterolytic}} R-\overset{\oplus}{C}H_2 + \ddot{X}^{\ominus}$$

Ex. $\underset{\text{Primary}}{\overset{\oplus}{C}H_3}$, $\underset{\text{Primary}}{CH_3\overset{\oplus}{C}H_2}$, $\underset{\text{Secondary}}{(CH_3)_2\overset{\oplus}{C}H}$, $\underset{\text{Tertiary}}{(CH_3)_3C^{\oplus}}$

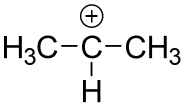
Ex. $\overset{\oplus}{C}H_3$ Methyl carbonium ion

$CH_3\overset{\oplus}{C}H_2$ Ethyl carbonium ion



$$H_3C-\overset{\oplus}{\underset{CH_3}{C}}-CH_3$$

tert-butyl carbonium ion



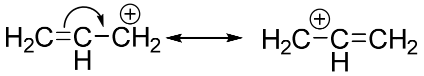
$$H_3C-\overset{\oplus}{\underset{H}{C}}-CH_3$$

Isopropyl carbonium ion

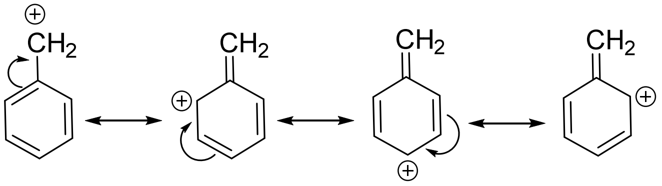
The stability of carbonium ion follows-

Tertiary carbonium ion > Secondary carbonium ion > Primary carbonium ion

Electron-withdrawing groups such as -NO2, -C(O)- attached to the carbon reduce the carbocation stability by withdrawing electrons through the connecting bond and enhancing the positive charge on the carbon. Electron donating groups (+I effect) release electrons through the connecting bond and make the carbonium ion more stable.

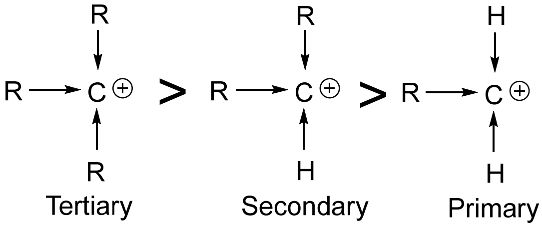


Allyl carbonium ion hybrid



Benzyl carbonium ion hybrid

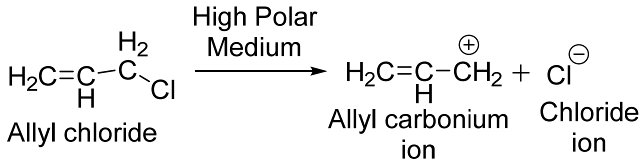
Allyl and benzyl carbocation hybrids are stabilized by resonance and are depicted by canonical structures. These are more stable than an isopropyl carbocation due to the resonance effect. Resonance, hyperconjugation, and inductive effects influence the carbocation stability.



Formation of Carbocations:

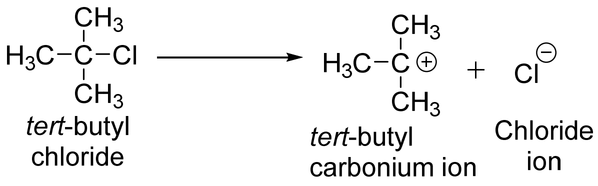
1. Direct ionization of alkyl and aryl halides in polar medium

a)



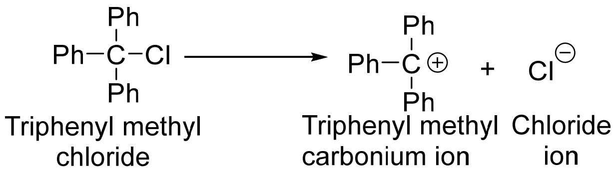
$$H_2C=CH-CH_2-Cl \xrightarrow{\text{High Polar Medium}} H_2C=CH-\overset{\oplus}{C}H_2 + Cl^{\ominus}$$

b)



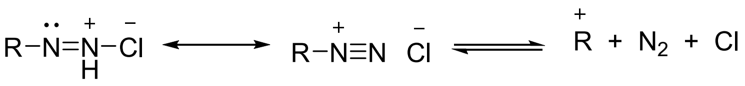
$$(CH_3)_3C-Cl \longrightarrow (CH_3)_3C^{\oplus} + Cl^{\ominus}$$

c)



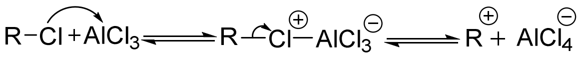
$$Ph_3C-Cl \longrightarrow Ph_3C^{\oplus} + Cl^{\ominus}$$

2. By the decomposition of diazonium salts

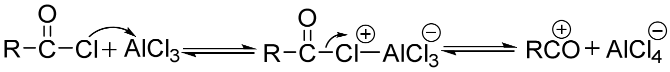


$$R-\overset{\cdot\cdot}{N}=\underset{H}{\overset{+}{N}}-\overset{-}{Cl} \longleftrightarrow R-\overset{+}{N}\equiv N\ \overset{-}{Cl} \rightleftharpoons \overset{+}{R} + N_2 + Cl$$

3. By the protonation of alkyl or aryl halides in the presence of Lewis acid or proton donating solvent

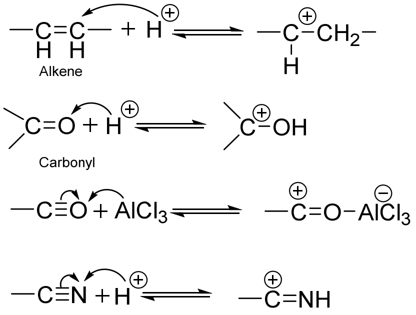


$$R-Cl + AlCl_3 \rightleftharpoons R-\overset{\oplus}{Cl}-AlCl_3^{\ominus} \rightleftharpoons \overset{\oplus}{R} + AlCl_4^{\ominus}$$

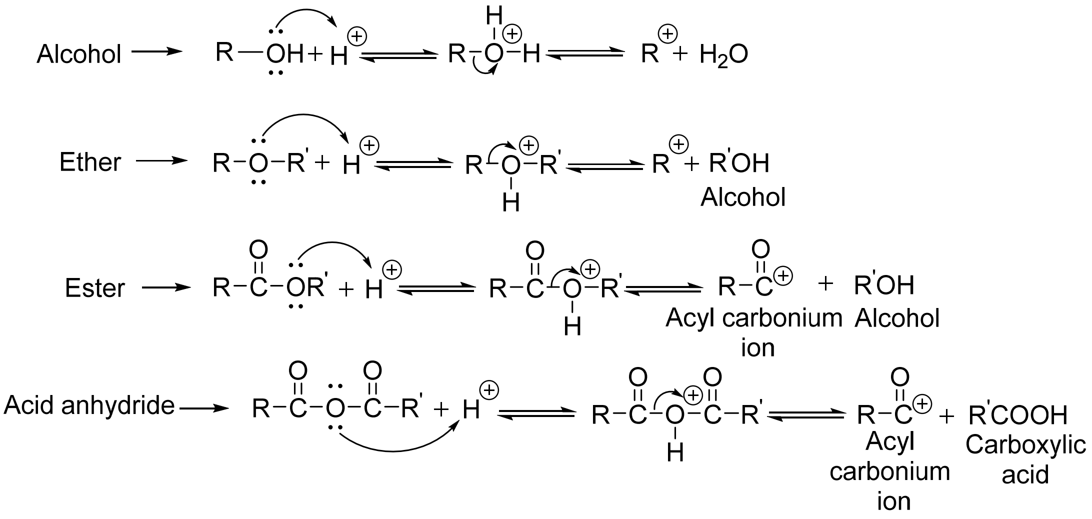


$$R-\overset{O}{\overset{\|}{C}}-Cl + AlCl_3 \rightleftharpoons R-\overset{O}{\overset{\|}{C}}-\overset{\oplus}{Cl}-AlCl_3^{\ominus} \rightleftharpoons R\overset{\oplus}{C}O + AlCl_4^{\ominus}$$

4. **By the protonation of unsaturated compounds such as alkenes carbonyl compounds and nitriles in the presence of a Lewis acid or proton donating solvent**



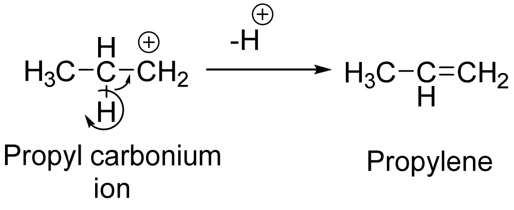
5. **By the deprotonation of an atom with lone pair of electrons in the presence of an acid**



Reactions of Carbocations:

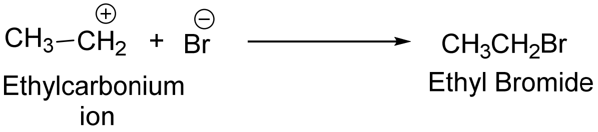
Carbonium ions react or participate in the following reactions:

a) **It may lose a proton to form an alkene**



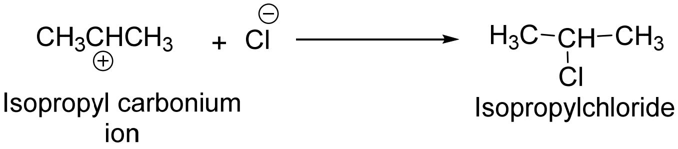
b) Carbocation may combine with nucleophiles by accepting a pair of electrons and forming a bond. Nucleophiles such as H2O, NH3, or available anions such as X-, OH-, CN- may react with carbocations

i)



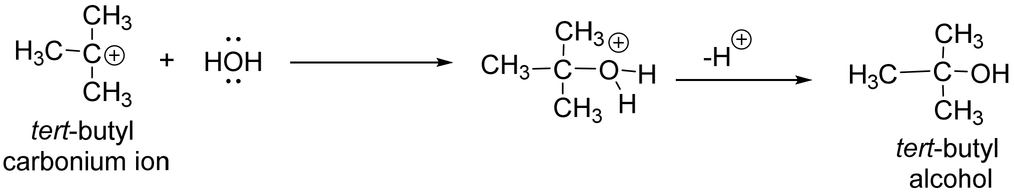
$CH_3-\overset{\oplus}{C}H_2 + \overset{\ominus}{Br} \longrightarrow CH_3CH_2Br$

ii)



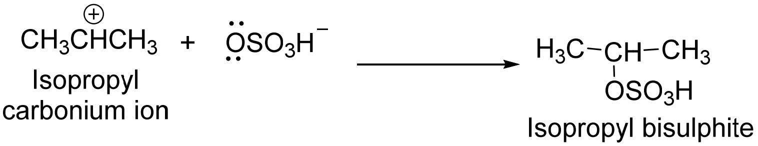
$CH_3\underset{\oplus}{C}HCH_3 + \overset{\ominus}{Cl} \longrightarrow H_3C-\underset{Cl}{\underset{|}{C}H}-CH_3$

iii)



$H_3C-\overset{CH_3}{\underset{CH_3}{C}}\oplus + H\ddot{\underset{\cdot\cdot}{O}}H \longrightarrow CH_3-\overset{CH_3}{\underset{CH_3}{C}}-\overset{\oplus}{O}(H)-H \xrightarrow{-H^{\oplus}} H_3C-\overset{CH_3}{\underset{CH_3}{C}}-OH$

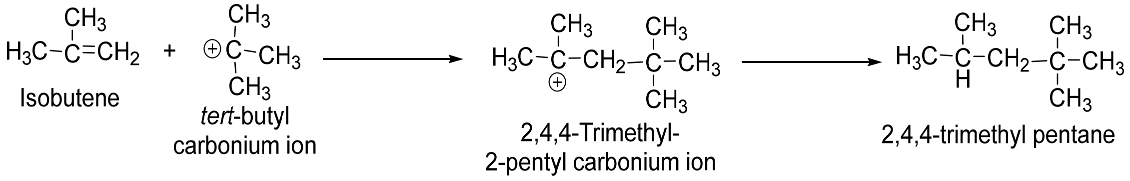
iv)



$CH_3\overset{\oplus}{C}HCH_3 + \ddot{\underset{\cdot\cdot}{O}}SO_3H^- \longrightarrow H_3C-\underset{OSO_3H}{\underset{|}{C}H}-CH_3$

c) Addition to an Olefin

The carbocation adds to an alkene forming a bigger carbocation.



$H_3C-\overset{CH_3}{C}=CH_2 + \oplus\overset{CH_3}{\underset{CH_3}{C}}-CH_3 \longrightarrow H_3C-\overset{CH_3}{\underset{\oplus}{C}}-CH_2-\overset{CH_3}{\underset{CH_3}{C}}-CH_3 \longrightarrow H_3C-\overset{CH_3}{\underset{H}{C}}-CH_2-\overset{CH_3}{\underset{CH_3}{C}}-CH_3$

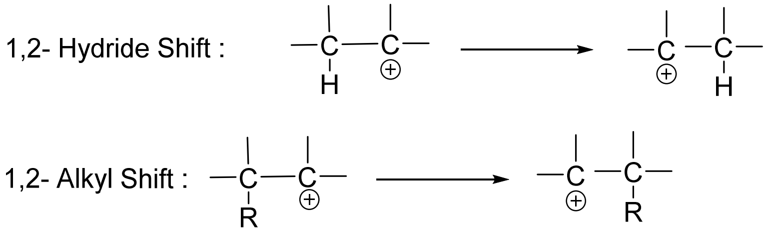
d) Molecular rearrangements

A carbocation can undergo rearrangements to produce more stable molecular species. Stability of the carbocation follows the order.

tertiary > secondary > primary

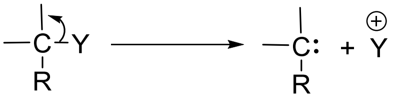
3° > 2° > 1°

These rearrangements take place by the migration of a hydrogen atom (hydride shift) or an alkyl group (alkyl shift), with a pair of bonding electrons. These rearrangements are known as 1,2-shifts.



2. Carbanions

Carbanions are defined as negatively charged species containing a carbon atom with three bonds along with an unshared pair of electrons.

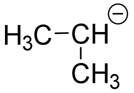


Y = Less electronegative atom than carbon

$$R{-}CH_2{-}X \ + \ \underset{\bullet\bullet}{B} \longrightarrow R{-}\overset{\ominus}{C}HX \ + \ BH$$

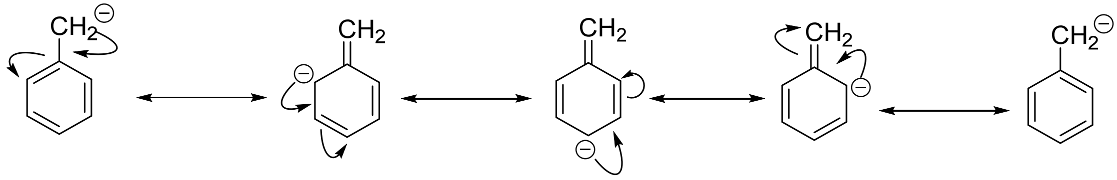
These are formed as electron rich fragments from heterolytic fission. These are highly reactive intermediates and react readily with electrophiles. Even though these are unstable, they can be stabilized by the attached electron-attracting groups like carbonyl and nitrile groups. However, the presence of electron-releasing groups such as alkyl groups increases the negative charge on the carbon atom, making the carbanion unstable.

$H_3C{-}\overset{\ominus}{C}H_2$ ethyl carbanion

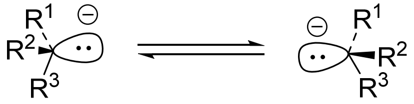


$H_3C{-}\underset{CH_3}{C}H^{\ominus}$ Isopropyl carbanion

Carbanions can also be stabilized by means of resonance. Ex.: Benzyl carbanion.

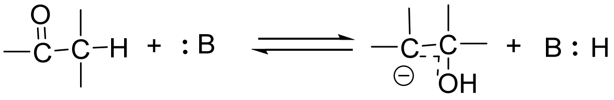


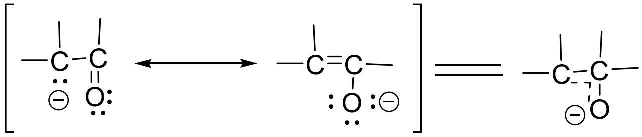
The carbanion carbon atom is sp3 hybridized. It has a pyramidal shape. In this, three sp3 hybrid orbitals form three covalent bonds with other atoms, and the fourth sp3 orbital contains an unshared pair of electrons. But when the carbanion is in conjugation, it is planar with sp2 hybridization.



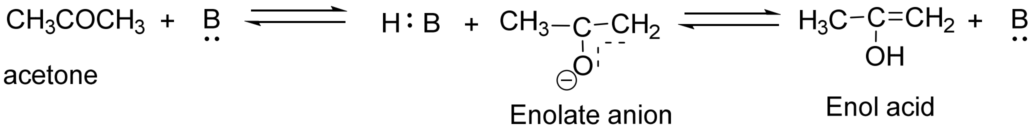
Formation of Carbanion:

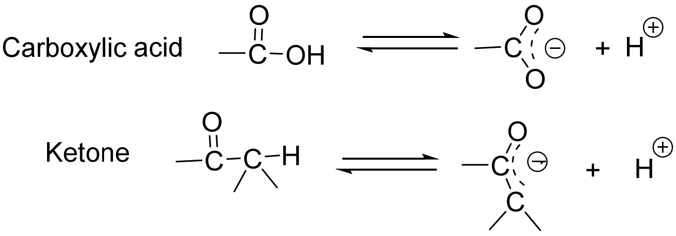
1. By the ionization of an α-hydrogen: In the case of carbonyl compounds, the α-hydrogens are acidic, and the negative charge generated on the α-carbon caused by the loss of a proton is stabilized by the carbonyl group, just as in the case of carboxylic acids.





Example:



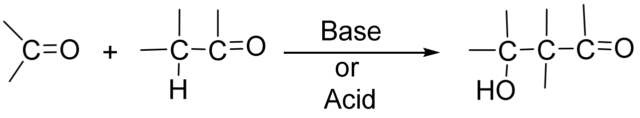


Reactions of carbanions:

Carbanions are electron-rich and act as potential nucleophiles. These actively participate in many addition and substitution reactions.

1. Addition reactions (Nucleophilic addition to carbonyl compounds)

a) Aldol condensation



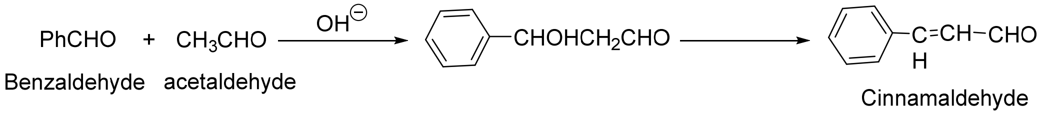
Compounds containing carbonyl groups like aldehydes, ketones, anhydrides, and esters can be used. The abstraction of α-hydrogen from carbonyl groups can be performed by the use of different bases like NaOH, NaOEt, CH_3COONa, amines, etc.

Examples:

a) Aldol reaction

$$\underset{\text{acetaldehyde}}{CH_3CHO + CH_3CHO} \xrightarrow{OH^{\ominus}} \underset{\text{3-OH-butanal}}{CH_3CHOHCH_2CHO} \xrightarrow[\text{Heat}]{NaHSO_4} \underset{\substack{\text{crotonaldehyde}\\ \text{or}\\ \text{2-butenal}}}{H_3CHC{=}CH{-}CHO + H_2O}$$

Crossed aldol condensation between two different aldehydes



b) Perkin reaction

$$\underset{\text{Benzaldehyde}}{PhCHO} + \underset{\text{Acetic anhydride}}{(CH_3CO)_2O} \xrightarrow{CH_3CO_2Na} \underset{\text{Cinnamic acid}}{PhHC{=}CH{-}CO_2H}$$

c) Knoevenagel condensation

$$PhCHO + CH_2(CO_2Et)_2 \xrightarrow[\text{2° amine}]{} PhHC{=}C(CO_2Et)_2$$

d) Claisen reaction

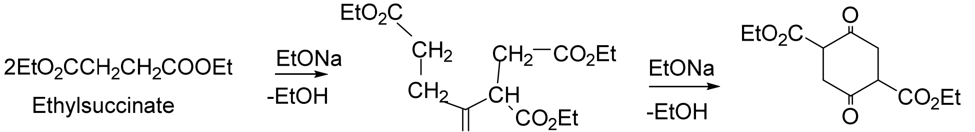
$$\underset{\text{Ethylacetate}}{2CH_3CO_2Et} \longrightarrow \underset{\text{Ethyl acetoacetate}}{CH_3COCH_2CO_2Et}$$

Crossed Claisen condensation with different Carbonyl Compounds

$$HCO_2Et + CH_3CO_2Et \xrightarrow[OEt^{\ominus}]{} HCOCH_2CO_2Et + EtOH$$

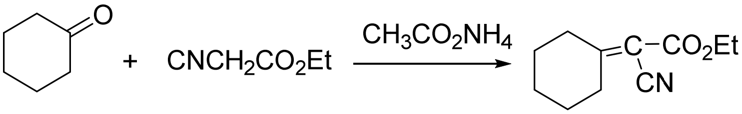
Ethylformylacetate

e) Dieckmann reaction

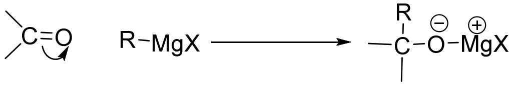


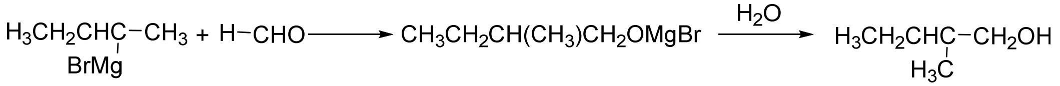
Cyclohexane
2,5-dione-1,4-dicarboxylic ester

f) Cope reaction



g) Addition of Grignard reagent





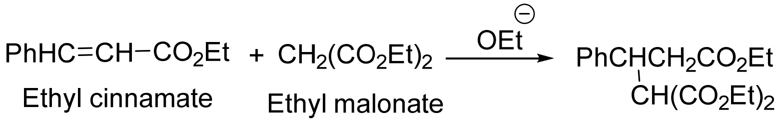
$$\underset{BrMg}{H_3CH_2CHC}-CH_3 + H-CHO \longrightarrow CH_3CH_2CH(CH_3)CH_2OMgBr \xrightarrow{H_2O} \underset{H_3C}{H_3CH_2CHC}-CH_2OH$$

sec-butyl magnesium bromide

2-Methyl-1-Butanol

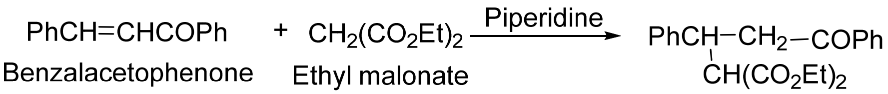
h) Michael addition

Addition of carbanion to α, β-unsaturated carbonyl compounds



$$PhHC{=}CH-CO_2Et + CH_2(CO_2Et)_2 \xrightarrow{OEt^{\ominus}} \underset{CH(CO_2Et)_2}{PhCH}CH_2CO_2Et$$

Ethyl cinnamate   Ethyl malonate

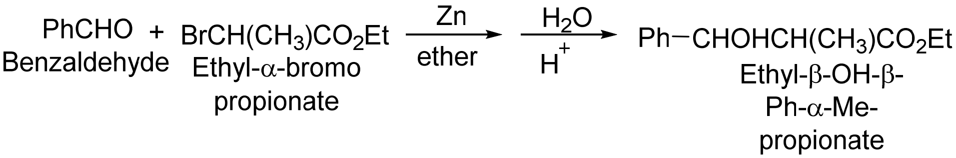


$$PhCH{=}CHCOPh + CH_2(CO_2Et)_2 \xrightarrow{Piperidine} \underset{CH(CO_2Et)_2}{PhCH}-CH_2-COPh$$

Benzalacetophenone   Ethyl malonate

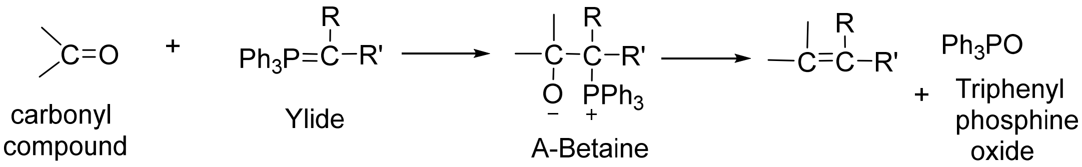
i) Reformatsky reaction – Preparation of β-OH esters

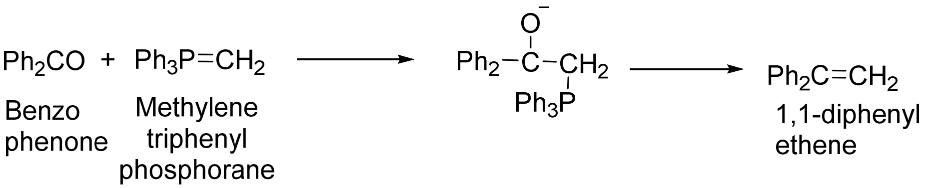
When an α-bromo ester is treated with metallic zinc in the presence of an aldehyde or ketone, a β-OH ester is formed.



$$\text{PhCHO} + \text{BrCH(CH}_3\text{)CO}_2\text{Et} \xrightarrow[\text{ether}]{\text{Zn}} \xrightarrow[\text{H}^+]{\text{H}_2\text{O}} \text{Ph–CHOHCH(CH}_3\text{)CO}_2\text{Et}$$

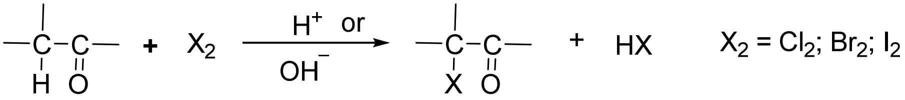
j) Wittig reaction

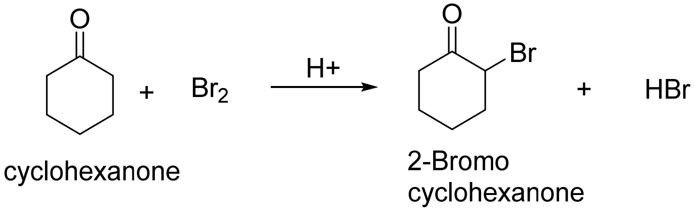




2. Substitution reactions

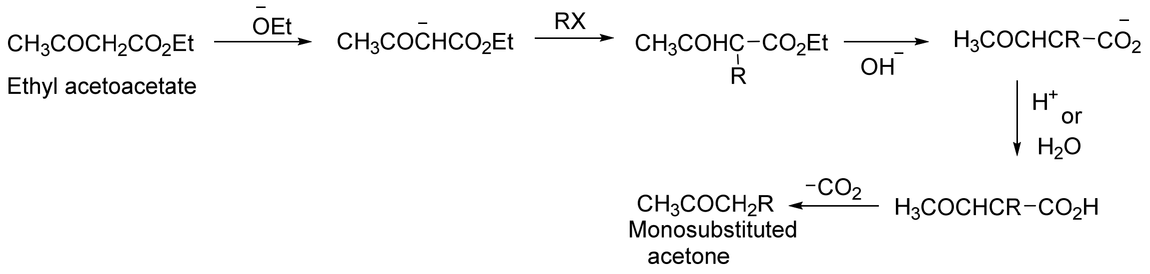
a) Halogenation of ketones





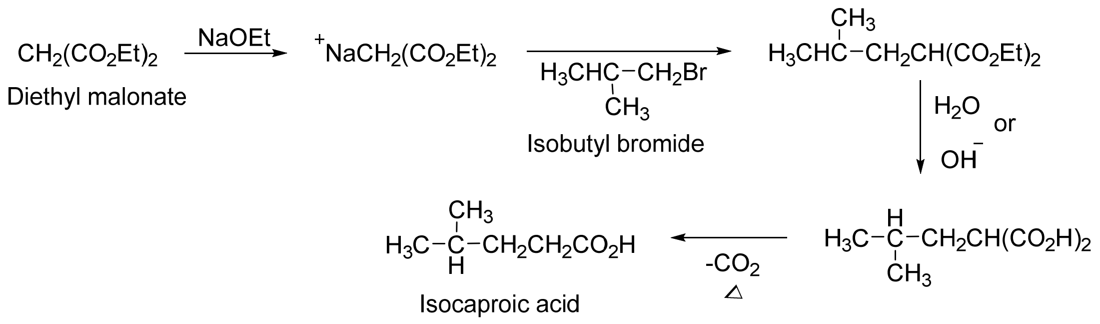
b) Acetoacetic ester; synthesis of ketones

In this reaction, a hydrogen atom is replaced by an alkyl group.



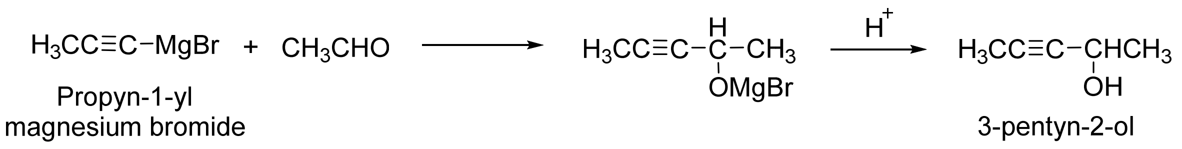
c) Malonic ester; synthesis of carboxylic acids

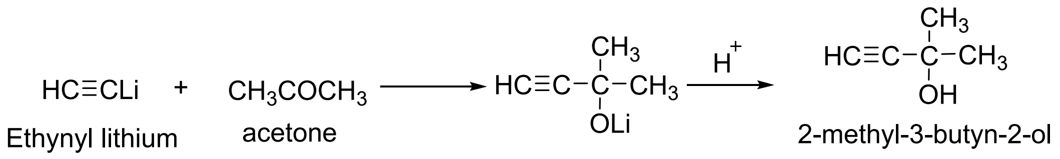
The synthesis provides acetic acid derivatives in which one or two hydrogens are replaced by the alkyl groups.



d) Synthesis of acetylides

A A carbon-carbon triple bond is an important building block in organic synthesis. The acidity of a terminal alkyne allows easy conversion of the triple bond to a metal acetylide. It is allowed to be introduced easily into molecules.





e) **Coupling of alkyl halides with organometallic compounds:** The alkyl group in organometallic compounds can be primary, secondary, or tertiary. Primary halides give good yields.

$$\underset{\text{Methyl bromide}}{CH_3Br} \longrightarrow \underset{\text{Methyl lithium}}{CH_3Li} \xrightarrow{CuI} \underset{\text{Lithium dimethyl copper}}{(CH_3)_2CuLi} \xrightarrow[\text{iodide}]{n\text{-octyl}} \underset{n\text{-nonane}}{CH_3(CH_2)_7CH_3}$$

3. **Free radicals**

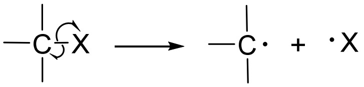
Free radicals can be defined as an atom or a group of atoms having an odd or unpaired electron and acting as neutral species. In the example below, a chlorine molecule underwent homolysis to form a chlorine radical, with cleavage in a symmetrical manner. Homolytic cleavage takes place when both bonded atoms have similar electronegativities. Ease of formation of free radicals and also stability of free radicals follows the order-

$$\text{allyl} > 3° > 2° > 1° > \dot{C}H_3 > \text{Vinyl}$$

Formation of free radicals:

1) By Homolysis:

$$\underset{\text{chlorine molecule}}{Cl_2} \xrightarrow[\text{light}]{\text{heat or}} \underset{\text{chlorine radical}}{2\dot{Cl}}$$



2) By abstraction

$$CH_4 + {}^{\bullet}Cl \longrightarrow HCl + \underset{\text{Methyl radical}}{CH_3^{\bullet}}$$

In the above equation, it is shown that Cl° abstracts hydrogen atom with an electron to form HCl and a methyl radical.

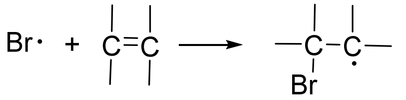
Ease of abstraction follows an order-

$$\text{allylic} > 3° > 2° > 1° > CH_4 > \text{Vinylic}$$

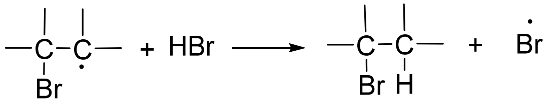
3) **By addition:** In the presence of peroxides, HBr adds to alkenes followed by the peroxide initiated free radical reaction. This is also known as peroxide effect or Kharasch effect. The mechanism is as follows-

i) $\text{peroxides} \longrightarrow \text{radical}^{\bullet}$

ii) $\text{radical}^{\bullet} \xrightarrow{HBr} \text{rad}:H + Br^{\bullet}$

iii 

chain initiation

iv 

chain propagation

4) **By photochemical fission:** Electromagnetic radiation causes bond fission, forming free radicals. Ex: Cl_2, Br_2, peroxides, acetone etc.

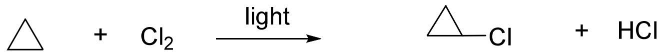
5) **Thermal fission:** Pyrolysis of organic compounds result in free radical formation. Heating of lead tetraethyl leads to free radical formation.

$$(C_2H_5)_4Pb \longrightarrow Pb + \text{Ethane} + Me\cdot$$

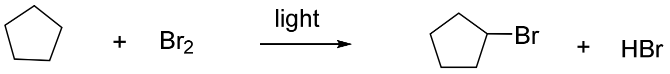
Organic peroxides undergo decomposition to give free radicals. Methyl free radical is obtained when azomethane is decomposed at 570K.

6) **Oxidation or reduction of inorganic ions and metals form free radicals:** Oxidation of ferrous ion with H2O2 in the presence of Fenton's reagent and Kolbe electrolysis of an aqueous solution of an alkali salt of a fatty acid are some examples.

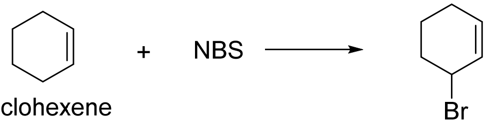
Reactions of free radicals: Generally, free radicals undergo a) Combination i.e., dimerization of two free radicals to yield bigger products, b) Abstraction- Abstraction of an atom from saturated organic compounds, c) Fragmentation- Some types of free radicals undergo fission resulting in a radical or non-radical fragments, d) Addition- Some free radicals add on to multiple bonds like double or triple bonds, e) Substitution reactions- Cycloalkanes undergo chiefly free radical substitution reactions.



Chlorocyclopropane

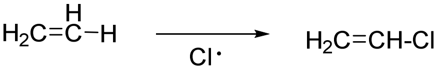


Bromocyclopentane



Cyclohexene

3-Bromocyclohexene



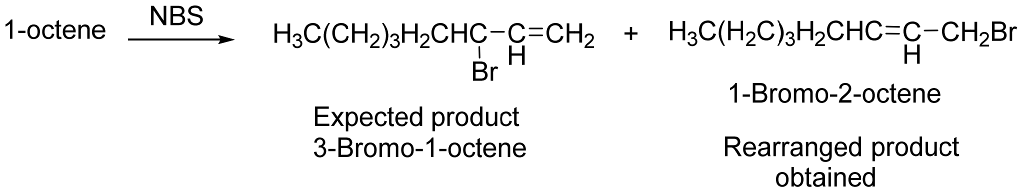
$$H_2C=\overset{H}{C}-H \xrightarrow[Cl\cdot]{} H_2C{=}CH{-}Cl$$

vinyl chloride

Tert-butyl peroxide is a stable and easy to handle liquid. It is a good source of free radicals.

$$(CH_3)_3COOC(CH_3)_3 \xrightarrow[\text{Heat or light}]{} 2(CH_3)_3CO^{\bullet} \xrightarrow[\text{CCl}_4,\ 130^{\circ}\text{C}]{\text{Isobutane}} \textit{tert}\text{-butylchloride} + CHCl_3$$

Free radical substitution leads to allylic rearrangements in alkenes.



$$\text{1-octene} \xrightarrow{\text{NBS}} H_3C(CH_2)_3H_2CH\underset{Br}{C}-\underset{H}{C}=CH_2 + H_3C(H_2C)_3H_2CHC=\underset{H}{C}-CH_2Br$$

Expected product
3-Bromo-1-octene

1-Bromo-2-octene

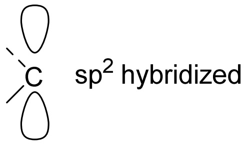
Rearranged product
obtained

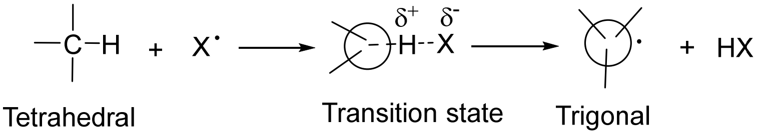
In conjugated alkenyl benzenes such as 1-phenyl propene, bromination in the absence of peroxides goes to the benzylic carbon, and in the presence of peroxides, bromide is attached to the carbon adjacent to the benzylic carbon.

$$PhHC{=}CHCH_3 \xrightarrow[\text{2.}Br^{\ominus}]{\text{1.HBr}} PhCHBrCH_2CH_3$$

$$PhHC{=}CHCH_3 \xrightarrow[\text{Peroxide}]{Br^{\bullet}} Ph\underset{\bullet}{C}HCHBrCH_3 \xrightarrow{\text{HBr}} PhCH_2CHBrCH_3$$

Structure of free radical: In carbon free radical, three sigma bonds are formed with three sp^2 hybrid orbitals and the odd electron is in the half-filled p orbital which exists above and below the plane of sigma bonds. These highly reactive species are generally named after the parent alkyl group or by their systematic names. These are obtained by the homolytic fission of alkanes. A decrease in the dissociation energy of the bond increases the stability of the free radical.



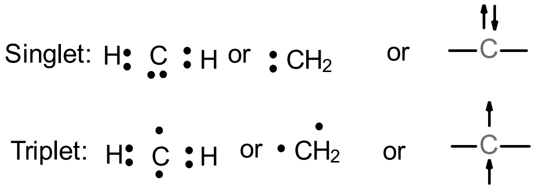


4. Carbene:

Carbenes are neutral carbon species with two bonds and two electrons. These behave as electrophiles in order to complete the octet state and gain the stability. Two states of carbenes known to exist are-

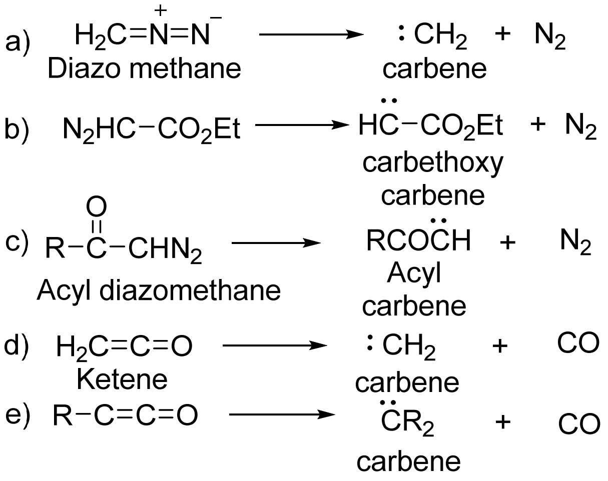
a) **Singlet state:** In this, both the electrons are present in the same orbital and move in anti-parallel and opposite spins.

b) **Triplet state:** In this, the two electrons stay in two different orbitals with parallel spins.



Formation of carbenes:

1) By the pyrolysis or photolysis of aliphatic diazo compounds or ketenes



2) Reaction of poly halogen compounds with base

a) $$CH_2Cl_2 + LiR \xrightarrow[-RH]{} [LiCHCl_2] \xrightarrow[-LiCl]{} :CHCl$$

dichloro methane; chloro carbene

b) $$(CH_3)_3C\bar{O} + CHCl_3 \rightleftharpoons (CH_3)_3COH + :\bar{C}Cl_3$$

tert-butoxide ion; *tert*-butanol

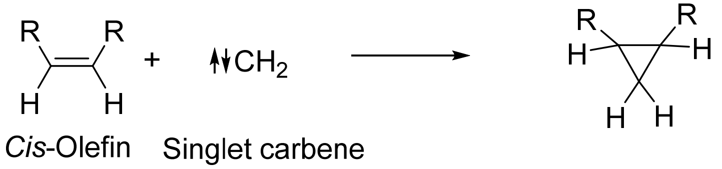
$$:\bar{C}Cl_3 \longrightarrow :CCl_2 + \bar{Cl}$$

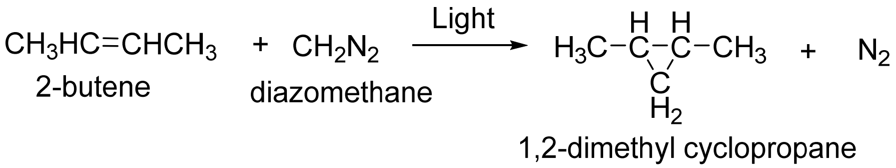
dichloro carbene

Reaction of carbenes:

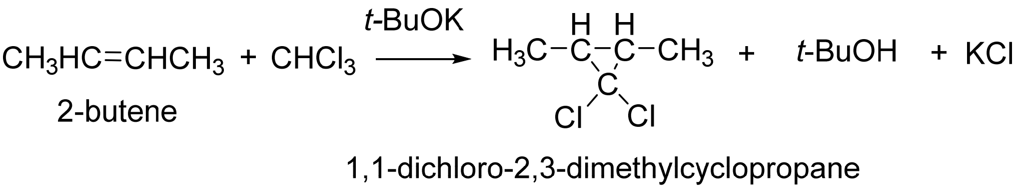
1) Addition to alkenes (Cycloaddition)

Singlet methylene undergoes cyclopropane stereospecific cycloaddition and triplet methylene undergoes non-stereospecific cycloaddition.

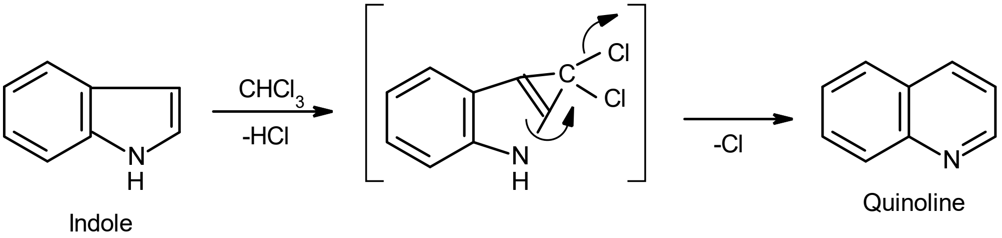




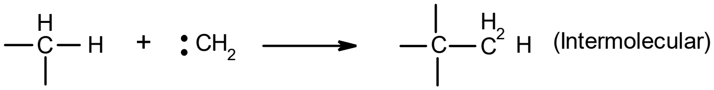
Addition of dihalocarbenes like singlet methylene is also stereospecific reaction.



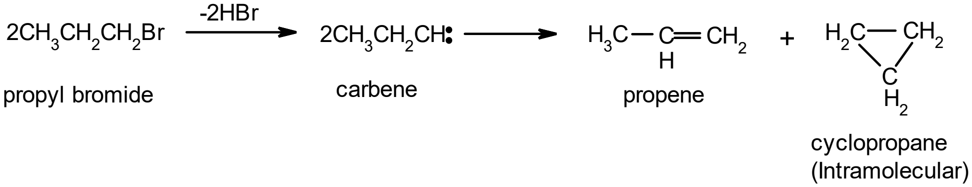
2) Ring expansion reactions



3) Insertion reactions

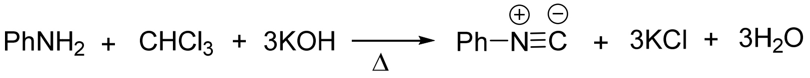


$$-\overset{H}{\underset{|}{C}}-H \;+\; :CH_2 \longrightarrow -\overset{|}{\underset{|}{C}}-\overset{H_2}{C}\,H \quad \text{(Intermolecular)}$$



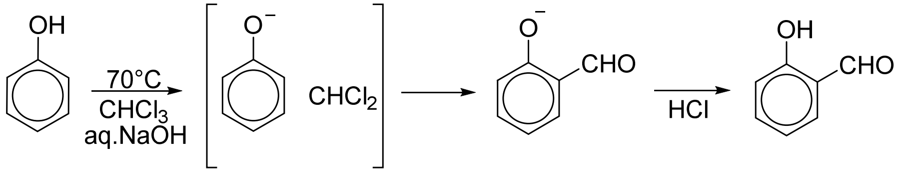
Applications- some examples:

1. Carbylamine reaction

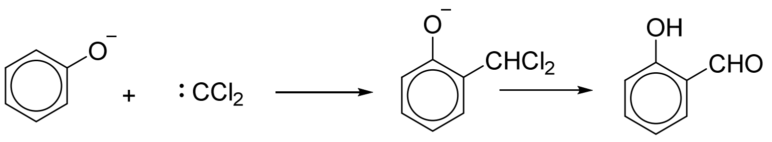


$$PhNH_2 + CHCl_3 + 3KOH \xrightarrow[\Delta]{} Ph-\overset{\oplus}{N}\equiv\overset{\ominus}{C} + 3KCl + 3H_2O$$

2. Reimer-Tiemann reaction



$$OH^- + CHCl_3 \rightleftharpoons H_2O + :\bar{C}Cl_3 \longrightarrow Cl^- + :CCl_2$$



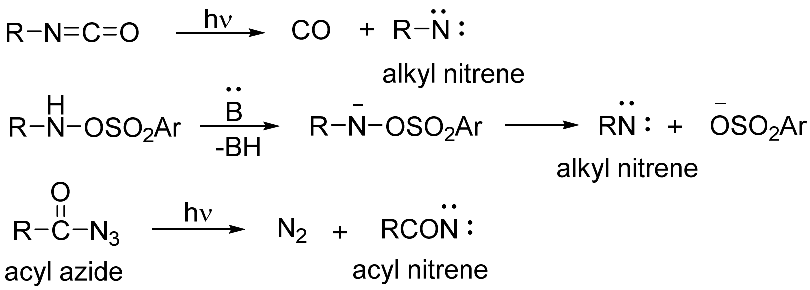
3. Synthesis of alkanes
4. Synthesis of spiro compounds
5. Wittig reaction
5. **Nitrenes:** Nitrenes are nitrogen-containing, electron-deficient species with a sextet of electrons. These are highly reactive and tend to complete octet to get stabilization.

Formation of Nitrenes:

1. Photolysis of N_3H

$$N_3H \xrightarrow{h\nu} N_2 + \ddot{\underset{\cdot\cdot}{N}}H$$

2. Generation of alkylated acyl nitrenes by the photolysis of isocyanates and acyl azides.



$$R{-}N{=}C{=}O \xrightarrow{h\nu} CO + \underset{\text{alkyl nitrene}}{R{-}\ddot{N}:}$$

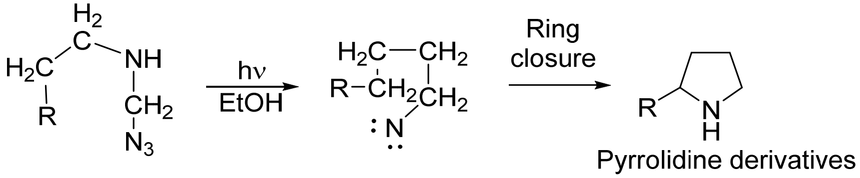
$$R{-}\overset{H}{N}{-}OSO_2Ar \xrightarrow[-BH]{\ddot{B}} R{-}\overset{-}{N}{-}OSO_2Ar \longrightarrow \underset{\text{alkyl nitrene}}{R\ddot{N}:} + \overset{-}{O}SO_2Ar$$

$$\underset{\text{acyl azide}}{R{-}\overset{O}{\overset{\|}{C}}{-}N_3} \xrightarrow{h\nu} N_2 + \underset{\text{acyl nitrene}}{RCO\ddot{N}:}$$

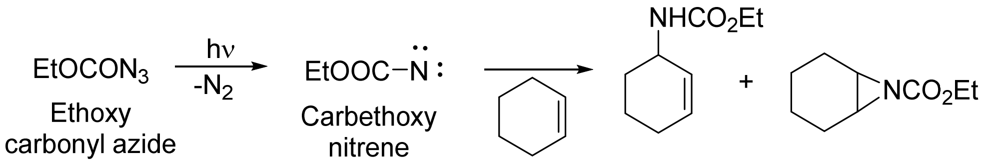
Reactions involving nitrenes:

1. Abstraction of hydrogen

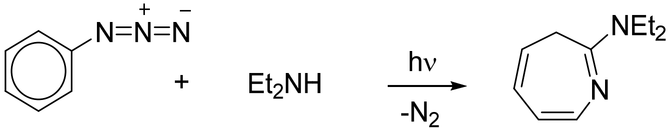
This process can be observed in the preparation of pyrrolidines and piperidines.



2. Addition to Olefins: These add to olefins

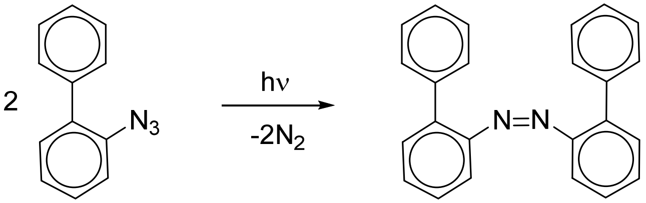


3. Ring enlargement reactions



Phenyl azide diethylamine Azepine

4. Combination of two nitrenes

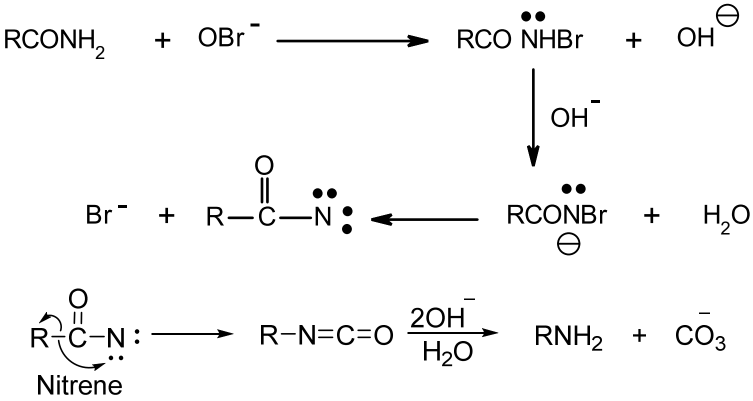


2-azido biphenyl 2,2-azido biphenyl

5. Rearrangement of reactions involving nitrenes

Rearrangements *via* migration to electron deficient nitrogen on treatment with base gets converted to amines *via* nitrene intermediate.

a) **Hoffmann rearrangement:** Primary amides on treatment with hypohalites result in primary amines with one less carbon via isocyanates involving a nitrene intermediate.



R-migration is like SN^2 and involves a 1,2-shift as an intramolecular rearrangement. It proceeds with complete retention of configuration at the chiral center of the migrating group. Here, the loss of Br and the migration of R in N-bromamide anion are concerted. Mostly, Br_2 is used in the reaction for *N*-bromamide formation. It is also known as Hoffmann bromamide reaction.

Examples:

a)

$$RCONH_2 + Br_2 + 4NaOH \longrightarrow RNH_2 + 2NaBr + Na_2CO_3 + 2H_2O$$

(R= aliphatic, aromatic, heterocyclic)

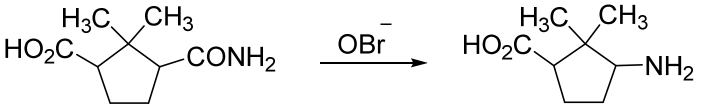
b)

$$\underset{\text{Caproamide}}{CH_3(CH_2)_4CONH_2} \xrightarrow[\text{KOBr}]{} \underset{n\text{-pentylamine}}{H_3C(H_2C)_4-NH_2}$$

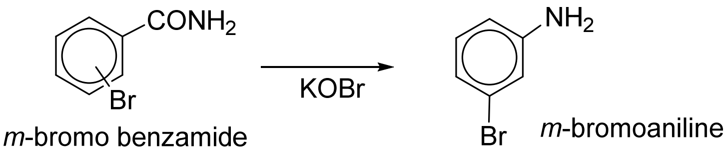
c)

$$\underset{\text{Urea}}{H_2NCONH_2} \xrightarrow[Br_2 / KOH]{} \underset{\text{Hydrazine}}{NH_2NH_2}$$

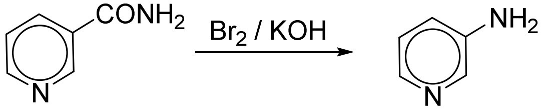
d)



e)

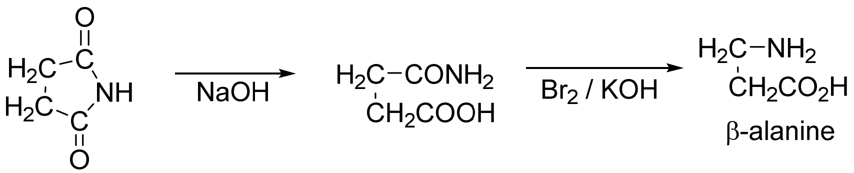


f)



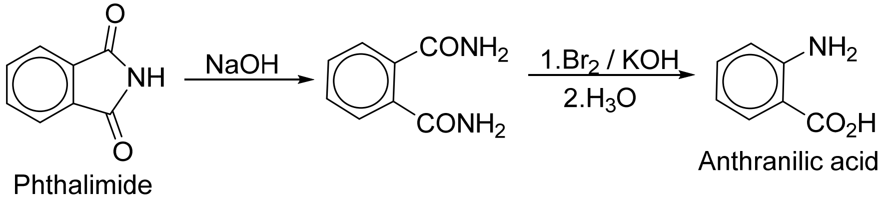
Nicotinamide β-aminopyridine

g)

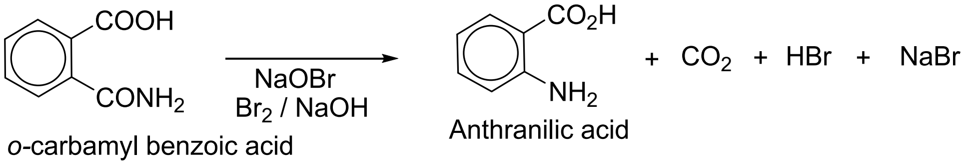


Succinimide

h)



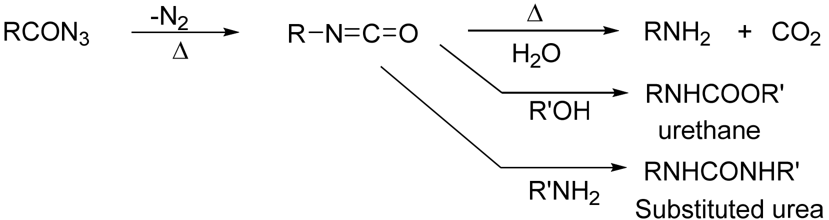
i)



b) Curtius reaction or Curtius rearrangement

The decomposition of acylazides in inert solvent to isocyanate is called Curtius rearrangement. If the reaction is conducted in an aqueous medium or alcohol, isocyanate forms an amine or urethane, or if an amine is present, it forms substituted urea. The reaction involves the formation of electron-deficient nitrogen species with the loss of N_2. All the steps are concerted.

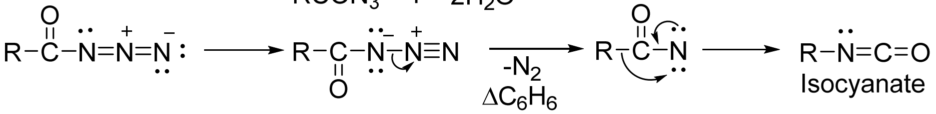
$$RCOCl + NaN_3 \xrightarrow[-NaCl]{} RCON_3 \xrightarrow[-N_2]{} RNCO + N_2$$

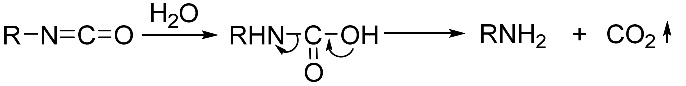


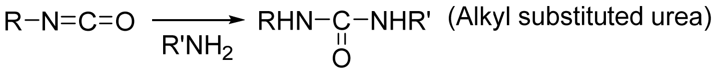
$$RCO_2Et \xrightarrow{NH_2NH_2} RCONHNH_2 \text{ (Acyl hydrazide)}$$

$$\downarrow HNO_2$$

$$RCON_3 + 2H_2O$$



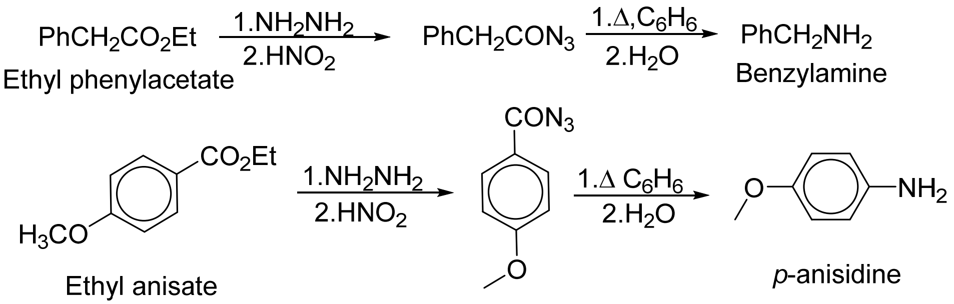




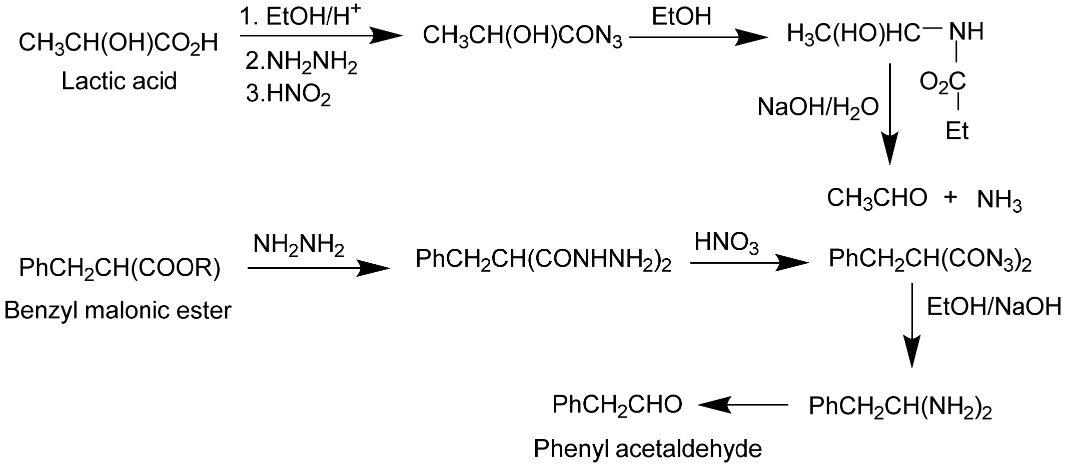
$$R{-}N{=}C{=}O \xrightarrow[R'NH_2]{} RHN{-}\underset{\underset{O}{\|}}{C}{-}NHR' \text{ (Alkyl substituted urea)}$$

Examples and applications:

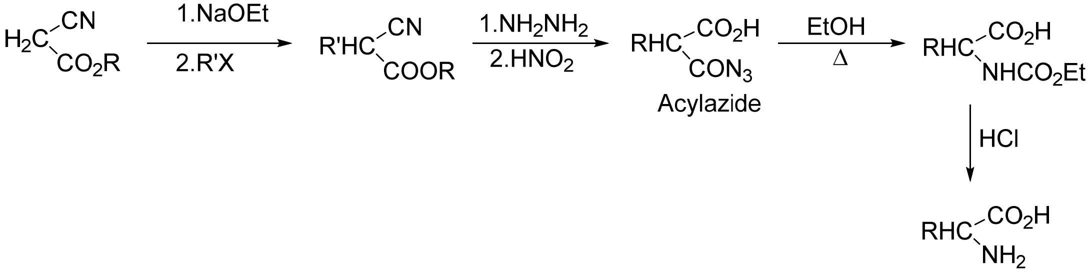
(i) Preparation of primary amines



(ii) Preparation of aldehydes

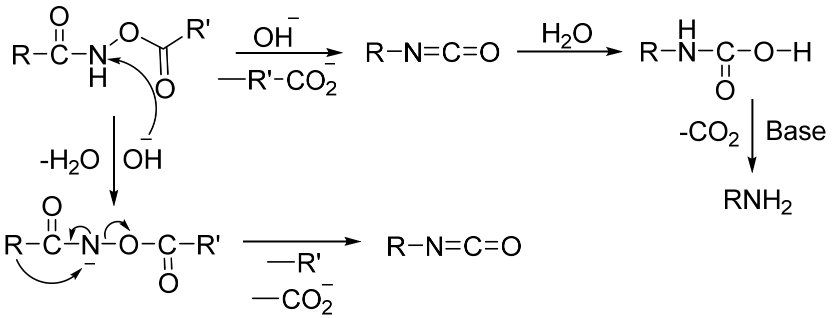


(iii) Preparation of α-amino acids



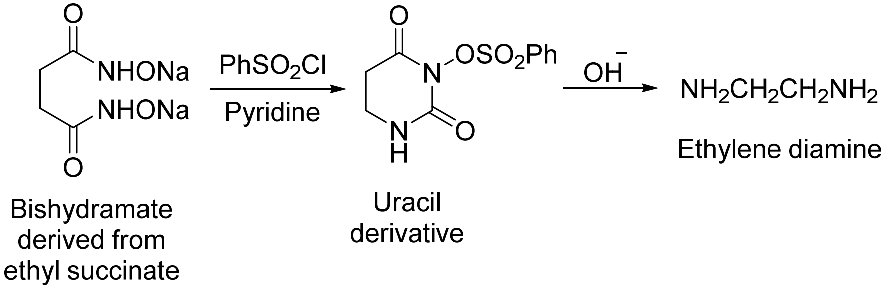
c) Lossen reaction

It is an intramolecular rearrangement, where o-acyl derivatives of free hydroxamine acids yield electron deficient nitrogen species which finally get converted to amines. O-Acyl, sulfonyl, or phosphonyl derivatives can be used in this reaction as substrates. The isocyanate obtained can be further converted to urea in the presence of amines or produce amines in the presence of water. It is named after Wilhelm Lossen.

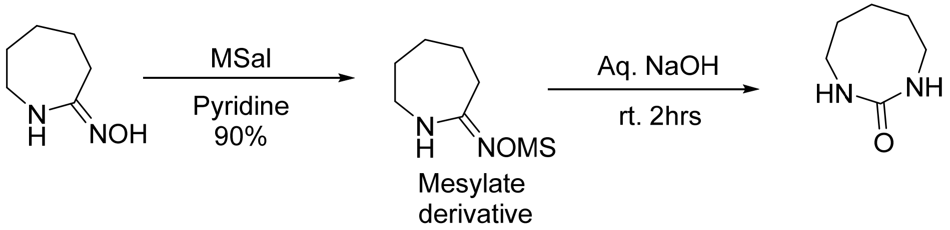


O-Acylated hydroxamic acid derivative on treatment with base produces isocyanate, which when treated with water loses CO2 to generate an amine. The reaction is initiated by the abstraction of a proton by a base. Spontaneous cycle of events releases carboxylate anion, forming an isocyanate intermediate. The rate of Lossen rearrangement is directly proportional to the acidity of the leaving groups or their conjugate acids.

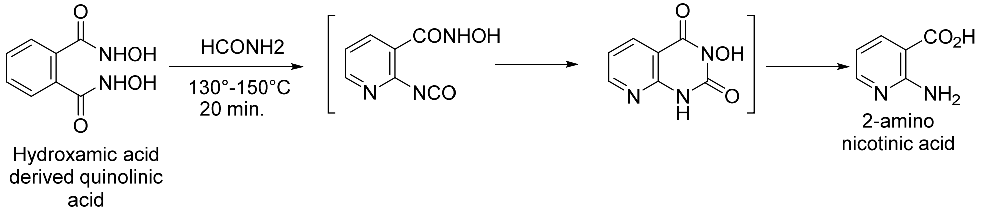
i)



ii)



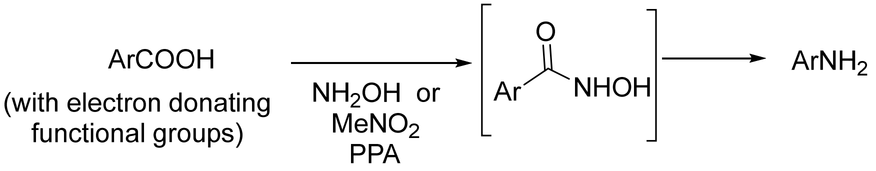
iii)



iv)

$$CH_3(CH_2)_4CO_2H \xrightarrow[\substack{170°\text{-}80°C\\ 2\text{-}5\ \text{min.}}]{\substack{NH_2OSO_3H\\ \text{(Hydroxylamine } o\text{-}\\ \text{sulfonic acid)}\\ \text{mineral oil}}} H_3C{-}(CH_2)_4{-}NH_2$$

v)



Types of reactions

Types of chemical reactions

1. Addition reaction
2. Elimination reaction
3. Substitution reaction
4. Rearrangement reaction

1. Addition reaction

An addition reaction can be defined as the reaction in which two molecules combine to form a single molecule as the product. Compounds that contain atoms sharing more than one pair of electrons or multiple bonded atoms can act as substrates in these reactions. In these types of reactions multiple bonds are converted to single bonds. The phenomenon is opposite to elimination reactions where multiple bonds are created. In addition, reactions a reagent is added to the substrate. The multiple bonds act as a source of electrons as well as base in these reactions. The electron-deficient or acidic reagents act as reagents. Therefore, these are called electrophilic reagents and the reaction is called electrophilic addition. When a free radical is involved in the reaction the reaction is called the free radical addition.

Let us examine some important addition reactions.

1. Addition of hydrogen or catalytic hydrogenation

Two kinds of hydrogenations are known.

a) Homogeneous hydrogenation

The reaction takes place in a single phase or solution phase. In this separation of catalyst is difficult. Hydrogenation is qualitative and reveals the number of unsaturation's present in the substrate molecule. Generally, organic complexes of rhodium, iridium, or other transition metals which are soluble in organic solvents act as reagents.

b) Heterogeneous hydrogenation

It is classical and widely used method wherein the reaction is conducted in two phases. Finely divided metals like palladium, nickel, or platinum are used as reagents. Reaction occurs rapidly and easily. The product is filtered and separated easily from the catalyst.

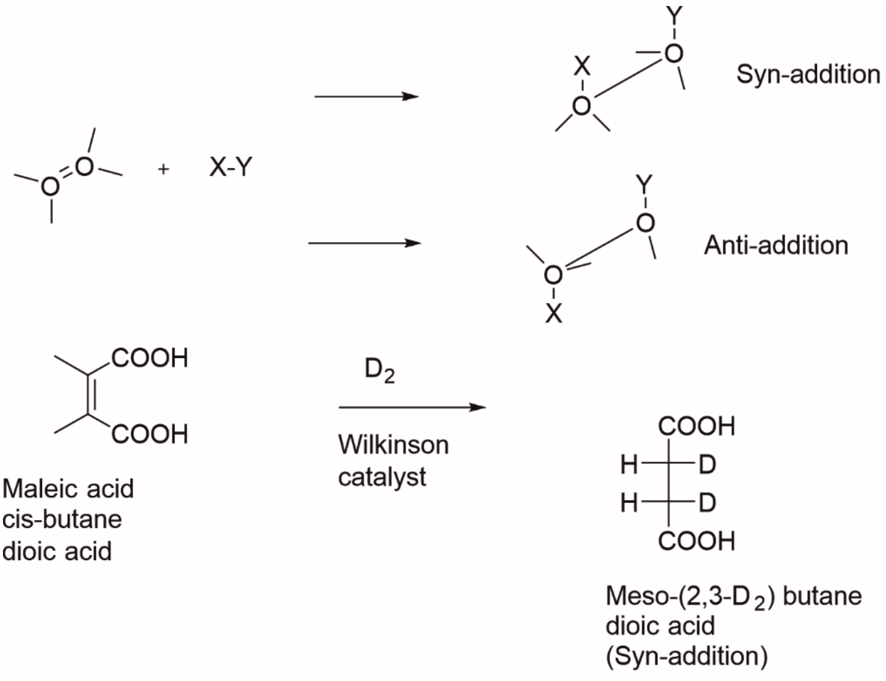
Hydrogenation is an exothermic reaction and the quantity of heat evolved when a mole of compound is hydrogenated is known as heat of hydrogenation. Hence, the function of the catalyst is to lower the activation energy (Eact). The catalyst speeds up the reaction but does not shift the position of equilibrium. Hydrogenation gives information about the relative stability of the unsaturated compounds. The greater the number of alkyl groups attached to the alkene carbon atom the more stable is the alkene.

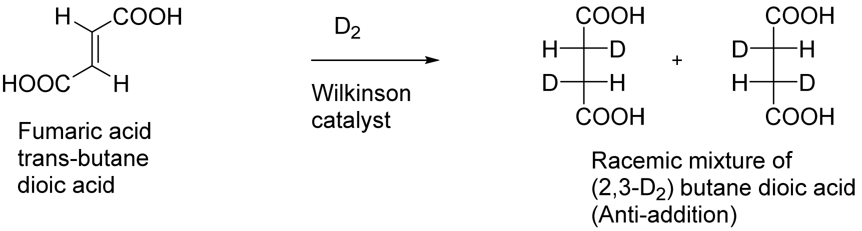
Stability of alkenes

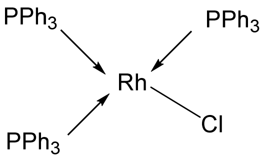
$$R_2C{=}CR_2 > R_2C{=}CHR > R_2C{=}CH_2,\ RCH{=}CHR > RCH{=}CH_2 > CH_2{=}CH_2$$

Stereochemistry of homogeneous hydrogenation

The alkenes exist as geometric isomers like cis and trans isomers. For example, in butane dioic acid, cis acid is maleic acid and trans acid is fumaric acid Therefore, stereochemically different substrates react differently, producing stereochemically different products. Thus, the reaction is not only stereoselective but also stereospecific. If the added groups are attached to the same face, it is "syn-addition," and if the groups are added on opposite faces, it is called "anti-addition". Deuterium addition experiments across the double bond clearly revealed the mechanism.





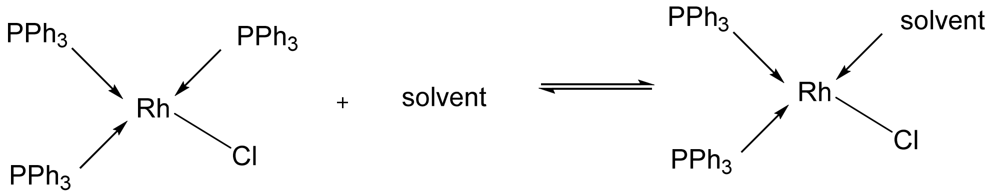


Tris (triphenyl phosphine) chloro rhodium (I)

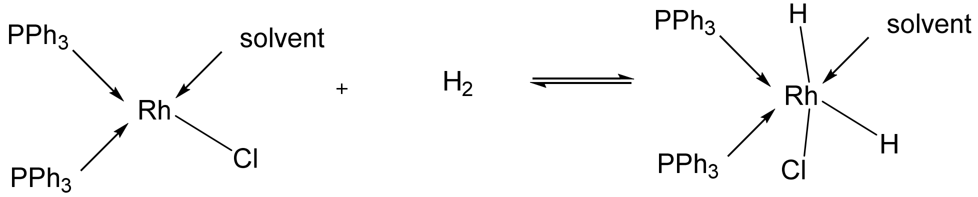
Wilkinson catalyst

Steps of hydrogenation by Wilkinson's catalyst.

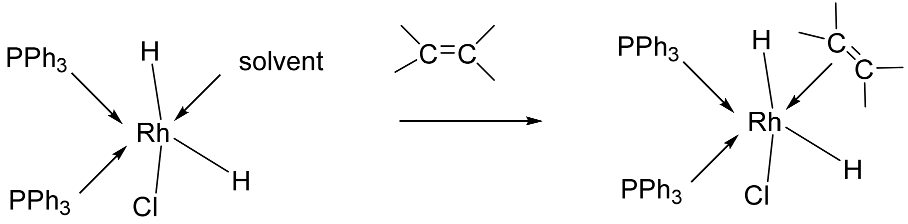
a) xchange of one PPh_3 for solvent molecule



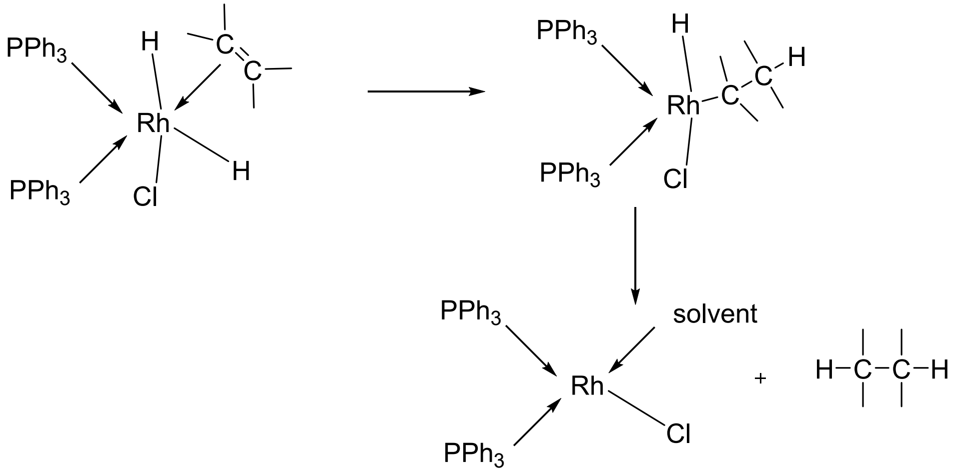
b) Reaction with H_2 molecule



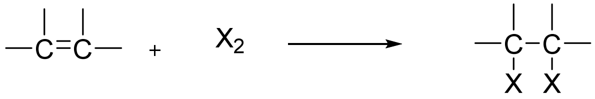
c) Reaction with alkene



d) Migration of hydrogen from the metal to double-bond



2. Addition of halogen



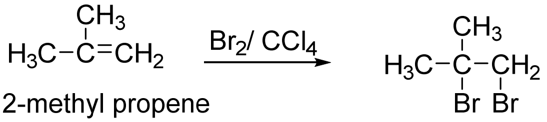
$$>C=C< + X_2 \longrightarrow -\underset{X}{C}-\underset{X}{C}-$$

X_2= Cl_2 or Br_2

Ex a) $CH_3CH{=}CH_2 \xrightarrow{Br_2/\ CCl_4} CH_3CHBrCH_2Br$

1,2-dibromopropane
(propylene bromide)

b)



$$H_3C-\overset{CH_3}{C}{=}CH_2 \xrightarrow{Br_2/\ CCl_4} H_3C-\underset{Br}{\overset{CH_3}{C}}-\underset{Br}{CH_2}$$

2-methyl propene
(isobutylene)

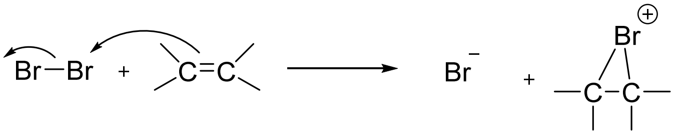
1,2-dibromo-2-methyl propane

The electrophilic addition of a halogen molecule goes by two steps.

a) Formation of halonium ion

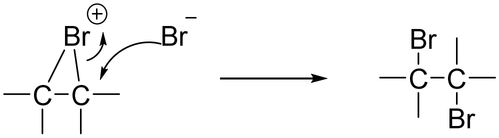
b) Addition of second ion of halogen.

a)



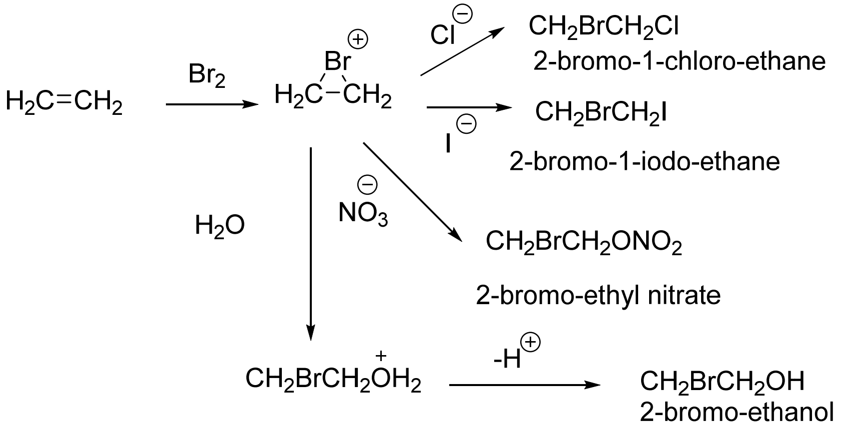
bromonium ion

b)

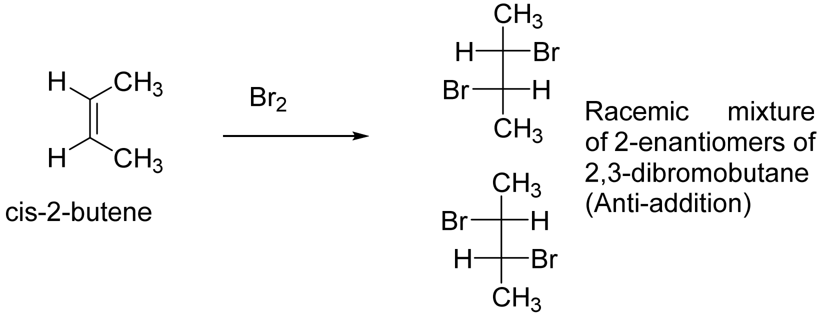


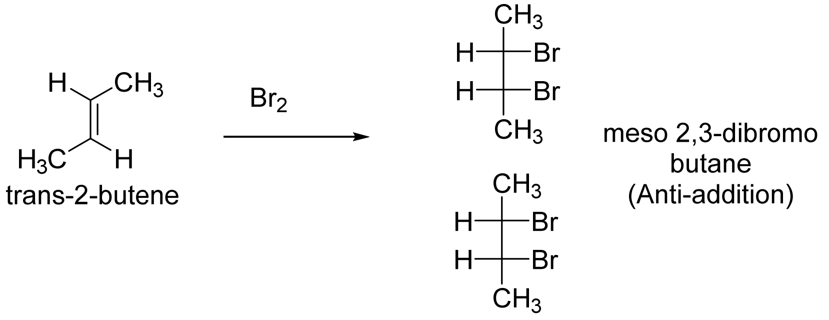
The bromonium ion formation initially is supported by the fact that when ethylene is brominated in the presence of other nucleophiles, the other nucleophile is also added onto the alkene as the other group. The bromonium or halonium ion bridge prevents free rotation of the C-C bond.

Example:

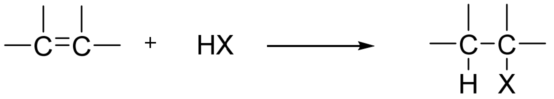


The reaction is completely stereo specific and stereo selective. Cis 2-butene on bromination yields racemic mixture of 2,3- dibromo butane whereas with trans 2- butene meso-product is obtained. The chlorination or bromination of alkene goes by anti-addition.





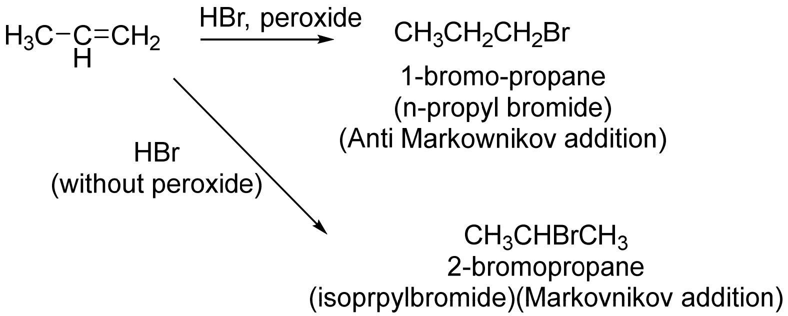
3. Addition of hydrogen halides



$$-\overset{|}{C}=\overset{|}{C}- \; + \; HX \longrightarrow -\underset{H}{\overset{|}{C}}-\underset{X}{\overset{|}{C}}-$$

HX: HCl, HBr, HI

EX:



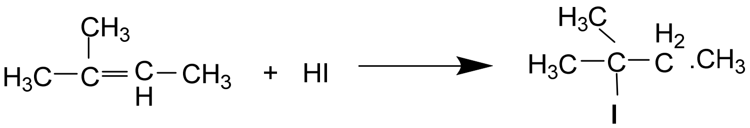
Vladimir Markovnikov observed that in the addition of an acid to the C=C double bond, the hydrogen of an acid attaches to the carbon that holds a more number of hydrogens. This is known as Markovnikov's rule.

a) $CH_3CH_2CH{=}CH_2 + HI \longrightarrow CH_3CH_2CHICH_3$

1-Butane

sec butyl iodide
2-iodo butane

b)



$$H_3C-\overset{CH_3}{\overset{|}{C}}=\underset{H}{C}-CH_3 \; + \; HI \longrightarrow H_3C-\underset{I}{\overset{H_3C}{C}}-\overset{H_2}{C}.CH_3$$

2-Methyl-2-butane

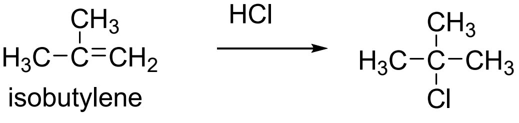
2-iodo-2-methyl butane

c) $CH_3CH_2CH{=}CHCH_3 + HI \longrightarrow CH_3CH_2CHICH_2CH_3$

2-pentene

3-iodopentane
\+ $CH_3CH_2CH_2CHICH_3$
2-iodo pentane

d)

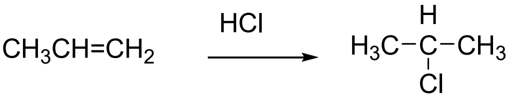


$$H_3C-\overset{CH_3}{\overset{|}{C}}=CH_2 \xrightarrow{HCl} H_3C-\underset{Cl}{\overset{CH_3}{C}}-CH_3$$

isobutylene

tertiary butyl chloride

e)

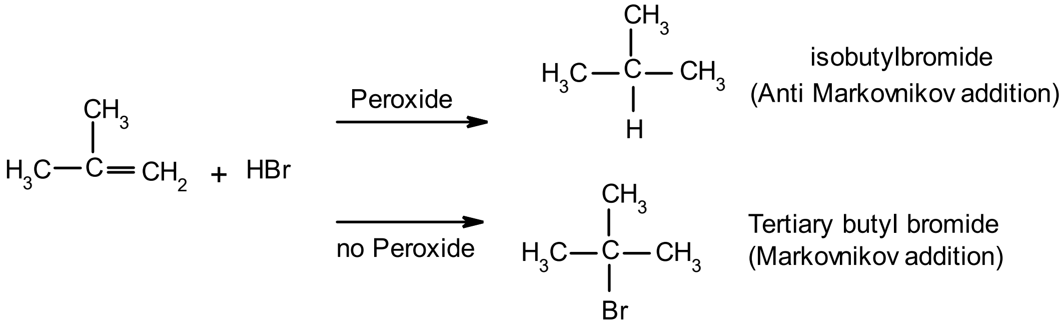


$$CH_3CH{=}CH_2 \xrightarrow{HCl} H_3C-\underset{Cl}{\overset{H}{C}}-CH_3$$

propylene

isopropyl chloride

M.S. Kharash and F.R. Mayo discovered that the orientation of the addition of HBr to C=C is determined solely by the presence or absence of peroxides. Organic peroxides containing -O-O- linkage such as in tertiary butyl peroxide or benzoyl peroxide bring about the peroxide effect, generating anti-Markovnikov addition products. However, the addition of inhibitors like hydroquinone or bisphenol amine influence Markovnikov addition.

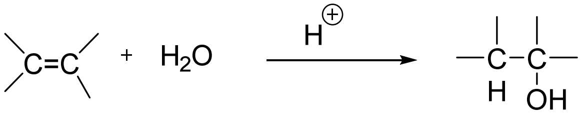


In all these reactions secondary carbonium ion is formed faster than primary and tertiary faster than secondary carbonium ion. This follows the rate of formation of carbonium ions as tertiary> secondary> primary>methyl carbonium ion. Same as that of stability of carbonium ions. Therefore, Markovnikov's rule can be interpreted as electrophilic addition to C=C involving the intermediate formation of a more stable carbocation. Therefore, the rate of addition of hydrogen ion to the double bond depends on the stability of the carbonium ion formed.

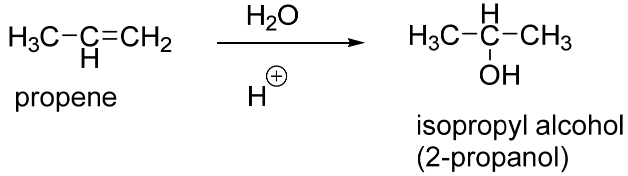
Order of reactivity of alkenes towards acids.

$$(C(CH_3)_2{=}CH_2 > CH_3CH{=}CHCH_3,\ CH_3CH_2CH{=}CH_2 >$$
$$CH_3CH{=}CH_2 > CH_2{=}CH_2 > CH_2{=}CHCl$$

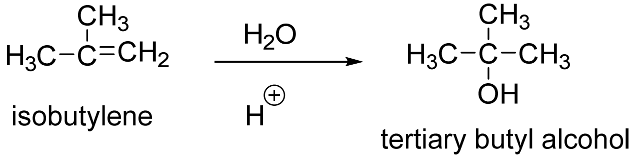
4. Addition of water-Hydration



Ex a)

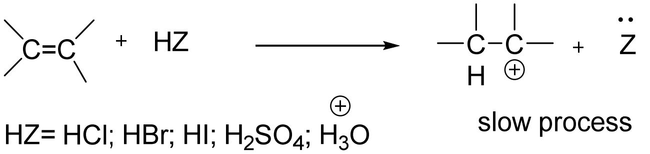


b)

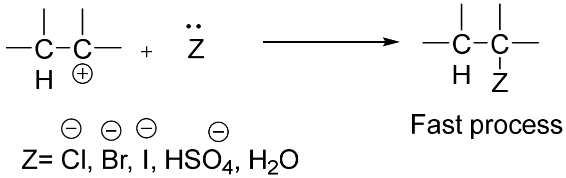


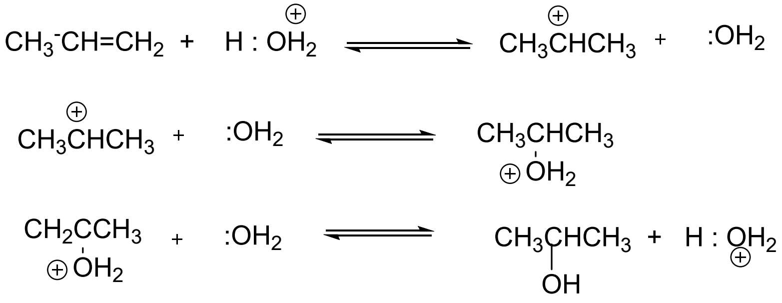
The reaction is a two-step process and consistent with Markovnikov's rule. When the hydration of alkenes via alkyl hydrogen sulphates-

a)



b)





$$CH_3CH{=}CH_2 + H:\overset{\oplus}{O}H_2 \rightleftharpoons CH_3\overset{\oplus}{C}HCH_3 + :OH_2$$

$$CH_3\overset{\oplus}{C}HCH_3 + :OH_2 \rightleftharpoons \underset{\oplus OH_2}{CH_3CHCH_3}$$

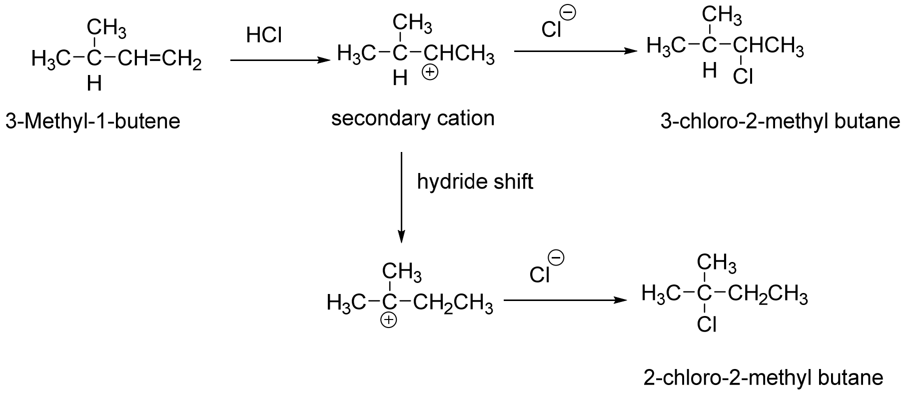
$$\underset{\oplus OH_2}{CH_2CCH_3} + :OH_2 \rightleftharpoons \underset{OH}{CH_3CHCH_3} + H:\underset{\oplus}{O}H_2$$

Hydrogen is transferred as a proton or electrophilic or acidic reagent.

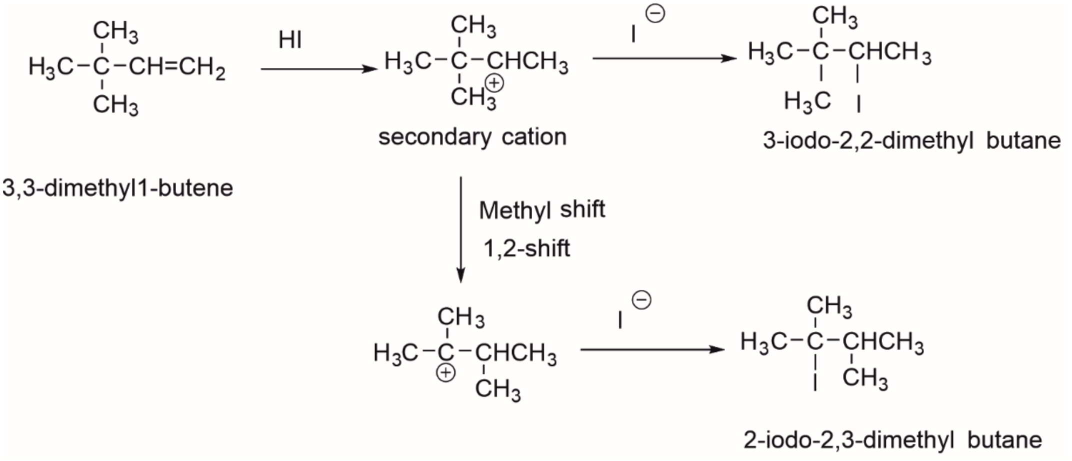
In these reactions depending on the alkene structures, some rearrangements follow to yield more stable cations.

Examples:

a)

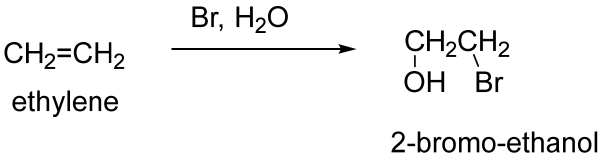


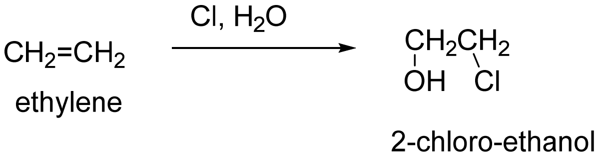
b)



5. Addition of halogen and -OH groups-halohydrin formation

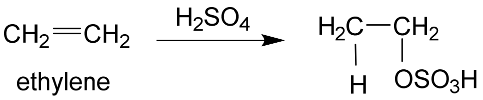
Addition of chlorine or bromine in the presence of water forms halohydrins i.e. chlorohydrins or bromohydrins.



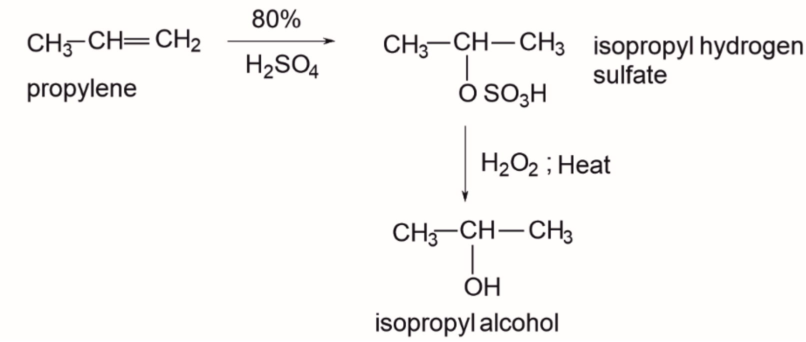


The reaction also goes by the formation of halonium ion

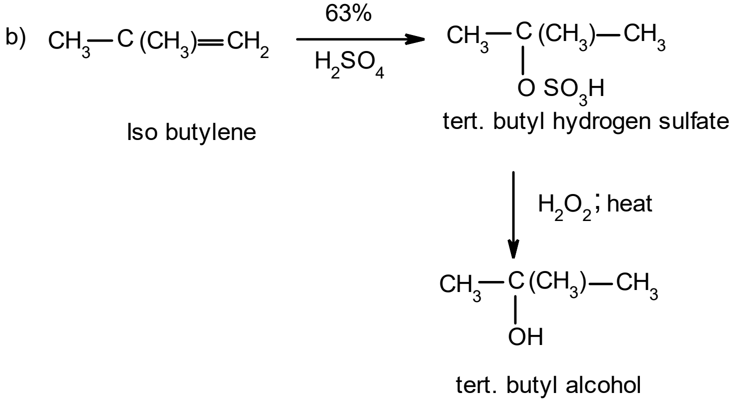
6. Addition of sulfuric acid



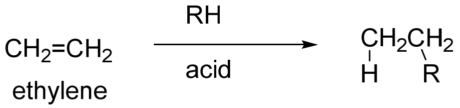
Ex : a)



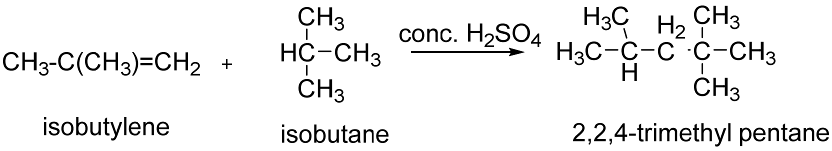
b)



7. Alkylation



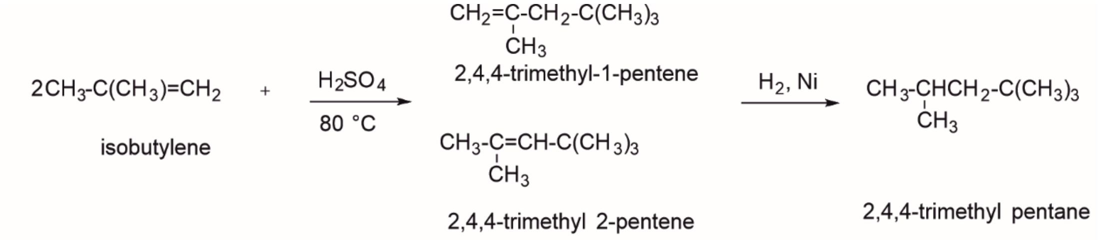
Ex:



8. Dimerization

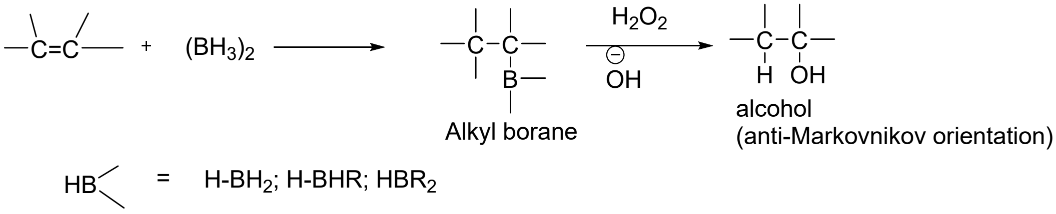
Two molecules of an alkene undergo acid catalyzed dimerization to provide a dimer of the same alkene.

Example:

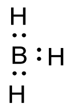


9. Hydroboration-Oxidation

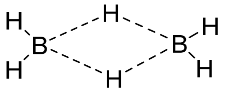
Alkenes undergo hydroboration with diborane reagent $(BH_3)2$ generating alkyl boranes R_3B. These on oxidation yield alcohols. This is a simple two step high yielding reaction. The reaction was invented by Professor Herbert. C. Brown in late 1950s., for which he was awarded Nobel Prize in Chemistry in 1979.



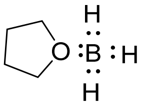
The reaction is commonly conducted in ether, tetrahydrofuran or diethylene glycol methyl ether (diglyme). Diborane is the dimer of BH3 (Borane) and is generally available in THF solution. The reagent is present in monomer form in THF as a complex.



Borane



Diborane

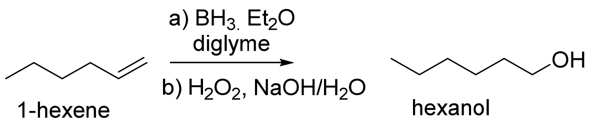


Borane-THF complex

The borane group of BH3 will go on adding until all hydrogens are transferred. Generally, the reaction is initiated by the hydrogen addition to olefinic carbon followed by alkyl borane formation. The alkyl borane undergoes oxidation to give alcohol by an anti-Markovnikov orientation. The products are obtained by the anti-Markovnikov addition of water to the C=C double bond. Hydroboration does not involve any rearrangement as there is no involvement of carbonium ion.

Examples:

a)

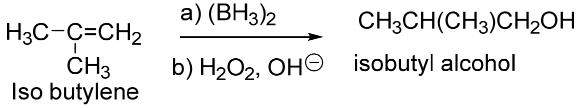


b)

$$CH_3CH{=}CH_2 \xrightarrow[\text{b) } H_2O_2,\ OH^{\ominus}]{\text{a) } (BH_3)_2} CH_3CH_2CH_2OH$$

propylene → n-propyl alcohol

c)



$$H_3C-\underset{CH_3}{C}{=}CH_2 \xrightarrow[\text{b) } H_2O_2,\ OH^{\ominus}]{\text{a) } (BH_3)_2} CH_3CH(CH_3)CH_2OH$$

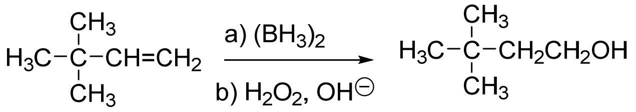
Iso butylene → isobutyl alcohol

d)

$$CH_3CH_2CH{=}CH_2 \xrightarrow[\text{b) } H_2O_2,\ OH^{\ominus}]{\text{a) } (BH_3)_2} CH_3CH_2CH_2CH_2OH$$

1-butene → n-butyl alcohol

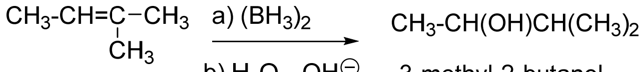
e)



$$H_3C-\overset{CH_3}{\underset{CH_3}{C}}-CH{=}CH_2 \xrightarrow[\text{b) } H_2O_2,\ OH^{\ominus}]{\text{a) } (BH_3)_2} H_3C-\overset{CH_3}{\underset{CH_3}{C}}-CH_2CH_2OH$$

3,3-dimethyl-1-butanol

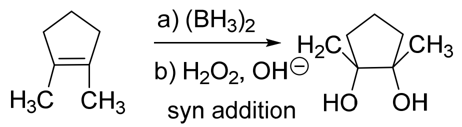
f)



$$CH_3\text{-}CH{=}\underset{CH_3}{C}-CH_3 \xrightarrow[\text{b) } H_2O_2,\ OH^{\ominus}]{\text{a) } (BH_3)_2} CH_3\text{-}CH(OH)CH(CH_3)_2$$

2-methyl-2-butene → 3-methyl-2-butanol

g)



1,2-dimethyl cyclopentene

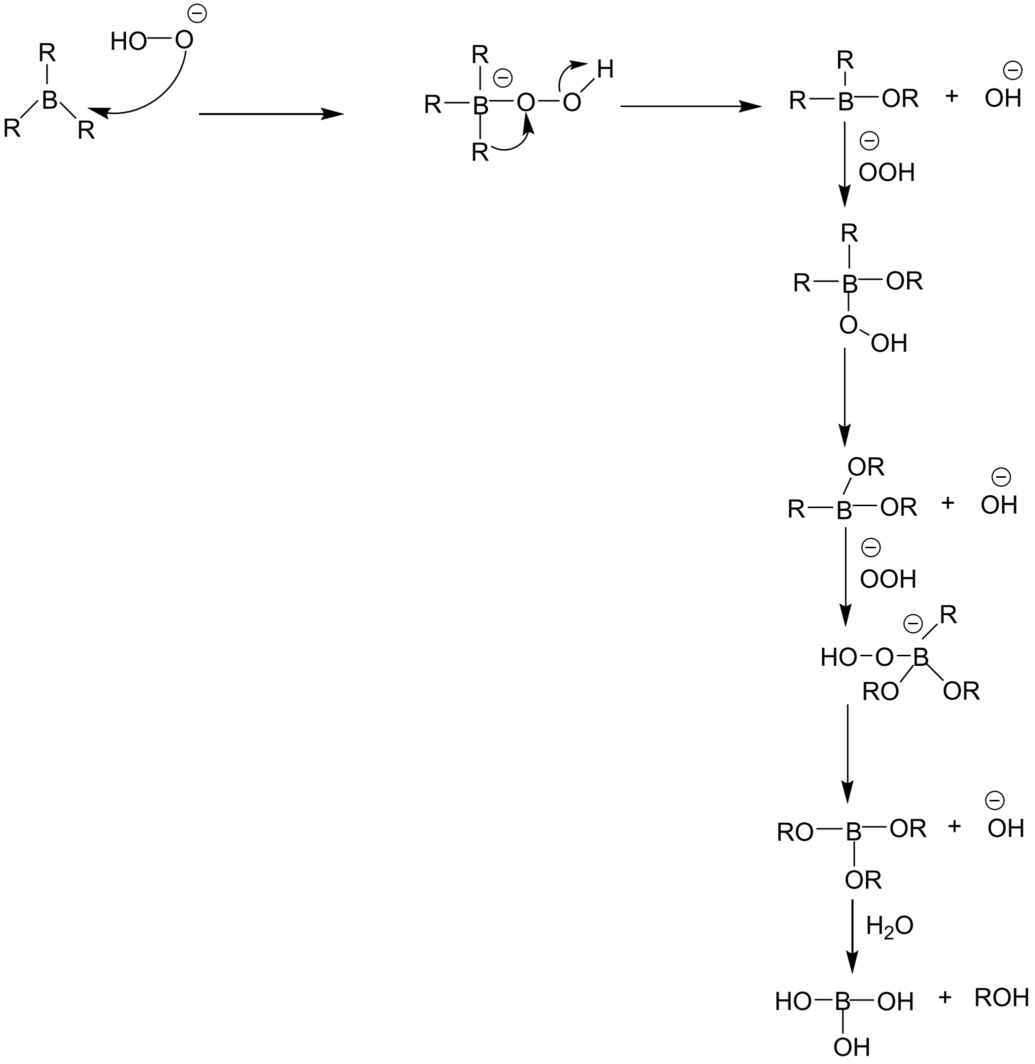
cis-1,2-dimethyl cyclopentanol

Hydroboration-Oxidation, the two-step process is a widely used reaction of importance since the

Products are not obtained by other methods from alkenes. It is the most convenient approach with great synthetic utility. Many modified hydroboration agents are reported like 9-BBN Borabicyclo (3.3.1.) nonane), catecholborane or disiamylborane.

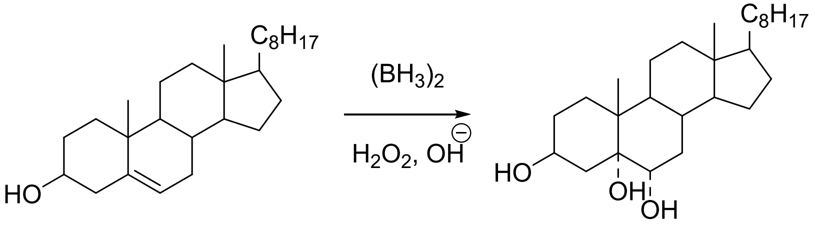
Hydroboration - Oxidation mechanism

Oxidation mechanism involves the nucleophilic hydroperoxide anion attack on Boran followed by alkyl migration to oxygen producing alkyl borane with retention of stereo chemistry.



Other oxidizing agents like N- methyl morpholine N-oxide in the presence of tetra propyl ammonium perruthenate converts alkyl borane into carbonyl compound. Terminal alkenes with dichromates are reacted with chromium agents (VI) that produce carboxylic acids.

Example:



Cholesterol

Cholestane-3-β,6α-diol

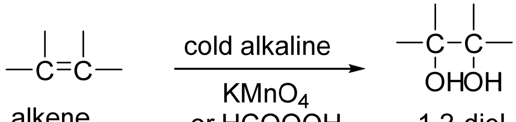
10. Hydroxylation

Preparation of glycols:

There are many oxidizing agents like potassium permanganate or peroxy acids like peroxy formic acid to convert alkenes into 1,2-diols.

Examples:

a)

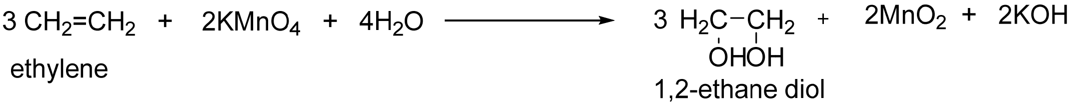


$$\underset{\text{alkene}}{>C=C<} \xrightarrow[\text{KMnO}_4 \text{ or HCOOOH}]{\text{cold alkaline}} \underset{\text{1,2-diol}}{-\underset{OH}{\overset{|}{C}}-\underset{OH}{\overset{|}{C}}-}$$

alkene

1,2-diol

b)



$$\underset{\text{ethylene}}{3\,CH_2=CH_2} + 2KMnO_4 + 4H_2O \longrightarrow \underset{\text{1,2-ethane diol}}{3\,H_2\underset{OH}{C}-\underset{OH}{C}H_2} + 2MnO_2 + 2KOH$$

$$CH_3\text{-}CH=CH_2 \xrightarrow[H_2O]{HCOOOH} CH_3CH(OH)CH_2(OH)$$

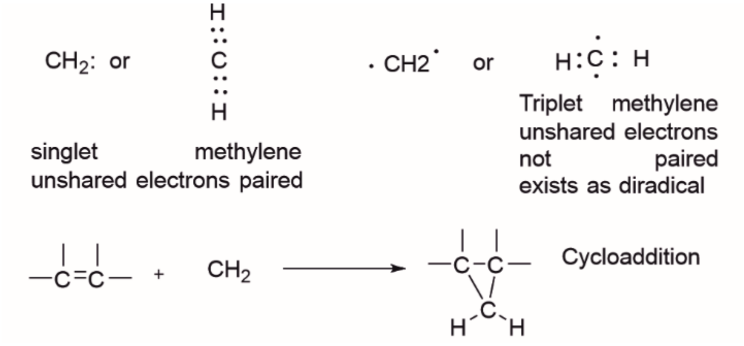
11. Addition of carbenes

Carbene or methylene addition to C=C generating a ring is called cycloaddition. Methylene is produced by the photolysis of diazomethane (CH2N2) or ketene (CH2=C=O).

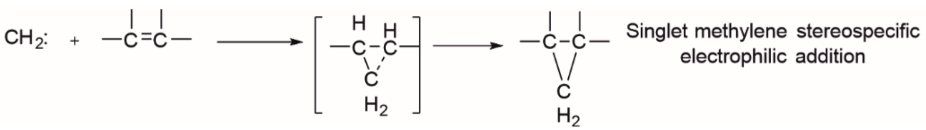
$$\underset{\text{diazomethane}}{CH_2=\overset{+}{N}=\overset{-}{N}} \xrightarrow{\text{UV light}} \underset{\text{methylene}}{CH_2} + N_2$$

$$\underset{\text{ketene}}{CH_2=C=O} \xrightarrow{\text{UV light}} \underset{\text{methylene}}{CH_2} + CO$$

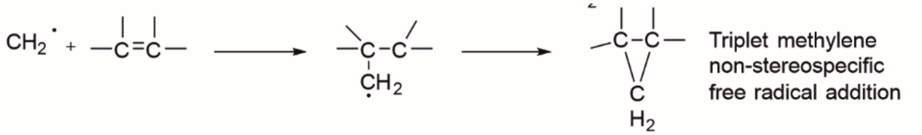
Methylene is a highly reactive entity and it exists in two different forms. Singlet methylene is less stable. Triplet methylene with unshared electrons not paired exist as a diradical. Singlet methylene undergoes stereo specific electrophilic addition and triplet methylene undergoes non stereo specific free radical addition. Singlet methylene is electron deficient and acts as an electrophile whereas triplet methylene being a di radical adds by a two-step free radical mechanism.



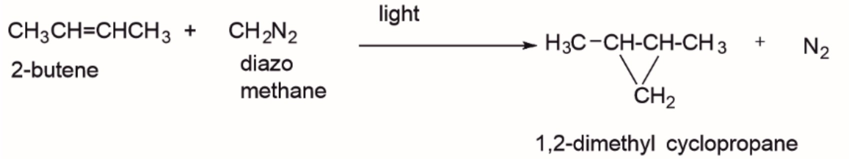
a)



b)



ex:



12. Addition of free radicals

To account for anti -Markovnikov addition across C=C in the presence of peroxides, Kharash and Mayo interpreted and proposed free radical mechanism for the addition reaction. The peroxides initiate the reaction by generating the radicals. Therefore, the addition does not involve carbonium ions and the reagents hydrogen and bromine in the reaction add on to the C=C homolytically and goes by the chain mechanism.

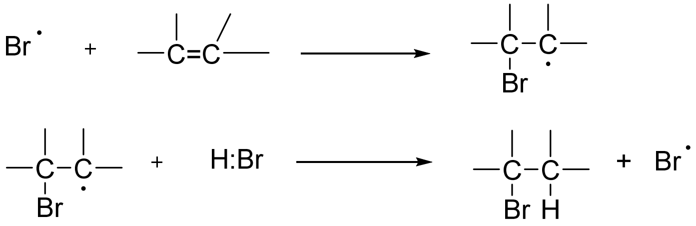
Mechanism:

a) $\text{peroxides} \longrightarrow \text{radical}$

b) $\text{Radical}^{\bullet} + \text{H: Br} \longrightarrow \text{Radical:H} + \text{Br}^{\bullet}$

c)

d)



$$Br^{\bullet} + -C{=}C- \longrightarrow -\underset{Br}{C}-\dot{C}-$$

$$-\underset{Br}{C}-\dot{C}- + H{:}Br \longrightarrow -\underset{Br}{C}-\underset{H}{C}- + Br^{\bullet}$$

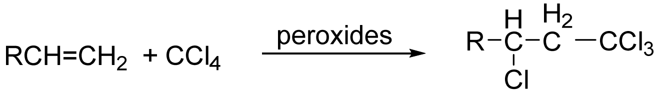
Steps a and b consist of chain initiation and c and d belong to chain propagation.

Example:

$$\underset{\text{3-propylene}}{CH_3CH{=}CH_2} \xrightarrow{Br^{\bullet}} CH_3\text{-}\dot{C}H\text{-}CH_2Br \xrightarrow{HBr} \underset{\text{n-propyl bromide}}{CH_3CH_2CH_2Br}$$

As secondary free radical is formed faster than primary free radical and n-propyl bromide is formed as against the electrophilic addition product of isopropyl bromide. The stability of the free radical formed, polar factors and steric factors influence the outcome of free radical addition.

Ability to accommodate partial positive charge as well as odd electron in the transition state, less hindered addition of free radical in the transaction state accounts for the stability of the transition state. As the hydrogen adds first in the electrophilic addition and bromine adds first in the free radical addition orientation of addition is reversed.

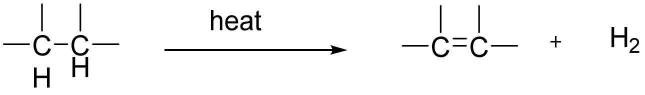


$$RCH{=}CH_2 + CCl_4 \xrightarrow{\text{peroxides}} R-\overset{H}{\underset{Cl}{C}}-\overset{H_2}{C}-CCl_3$$

2. Elimination reactions

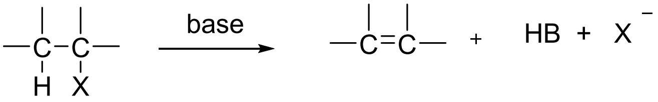
The elimination reaction can be defined as a reaction where in different atoms either in pairs or in groups are removed from a molecule by a one step or two step mechanism. Thus, it is a reversal of addition reaction.

a)



$$-\underset{H}{C}-\underset{H}{C}- \xrightarrow{\text{heat}} -C{=}C- + H_2$$

b)

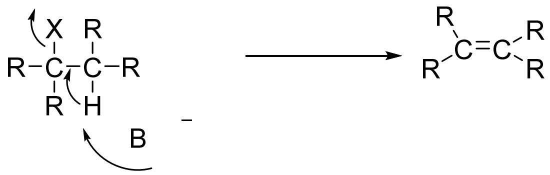


$$-\underset{H}{C}-\underset{X}{C}- \xrightarrow{\text{base}} -C{=}C- + HB + X^-$$

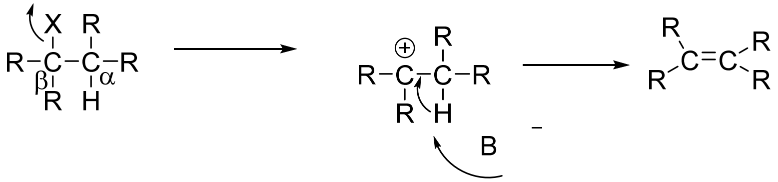
When a proton is abstracted at C and at the same time C -X is removed simultaneously in a concerted way such elimination is known as E2 elimination.

In E1 -elimination reaction which is a two-step process C-X bond is cleaved first forming a carbonium ion intermediate followed by the proton abstraction at C resulting in the formation of C=C bond.

E2 Elimination by concerted process



E1-Elimination by a 2 step process



According to Hughes and Ingold, the elimination reactions like nucleophilic substitutions proceed by two different mechanisms. E1 and E2 mechanisms.

The E1 is a unimolecular elimination reaction and follows first order kinetics. It is unimolecular as the rate determining step involves only one molecule of substrate. Out of two steps, in E1, carbonium ion formation is slow and rate determining. It depends on the concentration of the substrate. Therefore, the rate of E1 reaction is independent of base concentration.

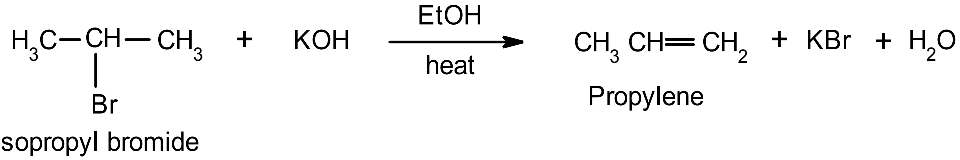
The E2 is a bimolecular elimination reaction and proceeds by second order kinetics. The rate determining step involves reaction of alkyl halide and base. Therefore, the rate of elimination reaction is proportional to the concentration of both substrate and the base.

Rate = K [RX] -E1-First order kinetics

Rate = K [RX] [B] -E2-Second order kinetics

Examples:

a)



$$H_3C-\underset{\displaystyle Br}{\underset{|}{CH}}-CH_3 + KOH \xrightarrow[\text{heat}]{\text{EtOH}} CH_3\,CH{=}CH_2 + KBr + H_2O$$

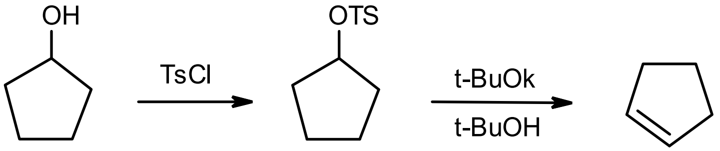
b) $CH_3CH_2CH_2CH_2Br \xrightarrow{\text{KOH alc}} CH_3CH_2\,CH{=}CH_2$

n-butyl bromide → 1-butene

c) $CH_3CH_2CHBrCH_3 \xrightarrow{\text{KOH alc.}} CH_3CH{=}CHCH_3 + CH_3CH_2CH{=}CH_2$

sec butyl bromide → 2-butene (major) + 1-butene (minor)

d)



cyclo pentanol

cyclopentyl tosylate

cyclopentene

e) $CH_3CH_2OH \xrightarrow{\text{acid}} CH_2{=}CH_2 + H_2O$

Dehydrohalogenation is a typical 1,2- elimination and is brought about by strong basic anions like hydroxide or alkoxide from alcohol (EtO,t.BuO). In these reactions the leaving group is a weekly basic halide ion or tosylates, brosylates, mesylates or triflates.

Evidences for the E2 mechanism

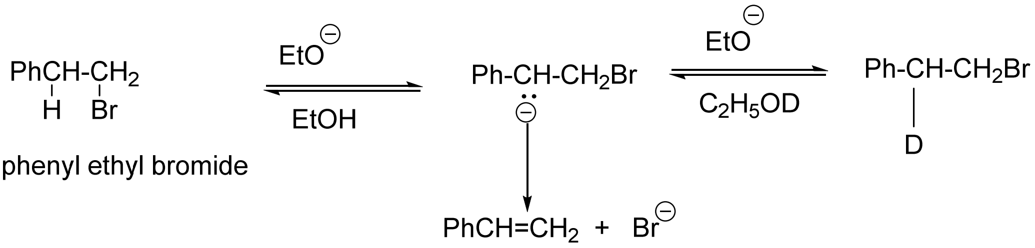
a) Second order kinetics

b) Absence of any rearrangement

c) Exhibition of large hydrogen isotope effects i.e. during isotope experiments bond to hydrogen atom is broken more rapidly than the bond to deuterium.

d) These reactions are not followed by any hydrogen atom exchange.

e) Exhibit element effect



2 phenyl ethyl bromide

styrene
phenyl ethylene

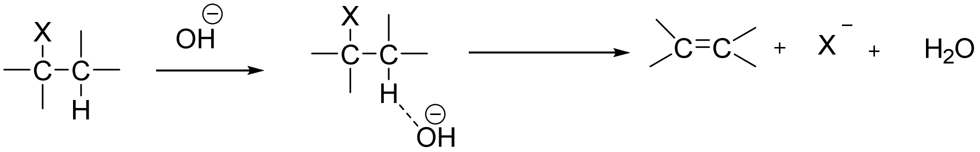
Heterolytic bond dissociation energy in these reactions follows the sequence

$$\text{R-F} > \text{R-Cl} > \text{R-Br} > \text{R-I}$$

Alkyl bromides react 25 -50 times rapidly than alkyl chlorides. These element effects are greater than isotope effects. Rate of breaking a carbon -halogen bond effect the rate of elimination reaction. The rate of reactivity of alkyl halides follows the sequence-

$$\text{R-I} > \text{R-Br} > \text{R-Cl} > \text{R-F}$$

Overall, alkyl iodides undergo elimination reaction 25000 times faster than alkyl fluorides. The stability of alkenes controls the ease of formation of alkenes. Russian scientist Alexander Saytzeff, in 1875 proposed that "in dehydrohalogenation, the preferred product is the alkene that has the greater number of alkyl groups attached to the double bonded carbon atoms." This is well known as Saytzeff's rule. Therefore, the orientation is determined by the more stable alkene, the faster it is formed. It also decides a more stable isomer. The transition state in the E2- reaction contains partly broken bonds to hydrogen and the leaving groups rendering alkene character to it.



Ease of formation of alkenes

$$R_2C=CR_2 > R_2C=CHR > R_2C=CH_2 > RCH=CHR > RCH=CH_2 > CH_2=CH_2$$

Stability of alkenes

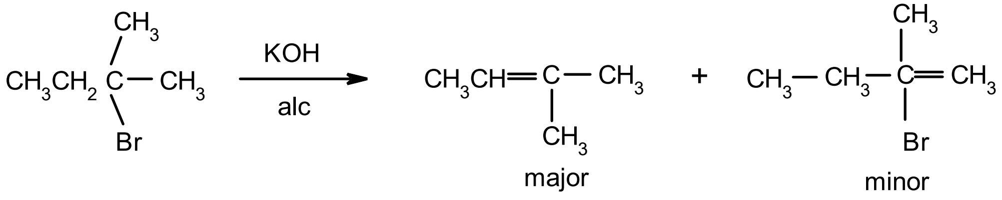
$$R_2C=CR_2 > R_2C=CHR > R_2C=CH_2 > RCH=CHR > RCH=CH_2 > CH_2=CH_2$$

Examples:

a)

$$CH_3CH_2CHBrCH_3 \xrightarrow[\text{alc}]{\text{KOH}} \underset{\text{major}}{CH_3CH=CHCH_3} + \underset{\text{minor}}{CH_3CH_2CH=CH_2}$$

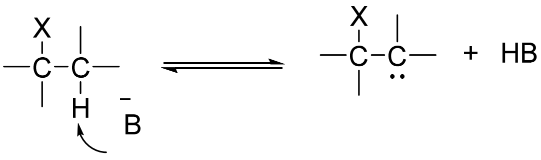
b)



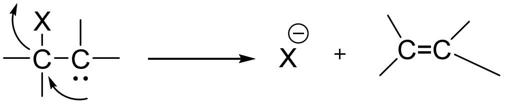
The order of the reactivity of alkyl halides in E2 dehydrohalogenation is tertiary > secondary > primary.

When elimination takes place via carbanion formation it is called E1cB elimination, the more stable the carbanion the faster will be the reaction. Electron withdrawing groups attached to the carbon disperses the negative charge and carbanion will be stabilized. Energy of the activation is lowered and the reaction becomes faster. Electron withdrawing tendency follows the order- F > Cl > Br > I.

a)

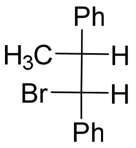


b)

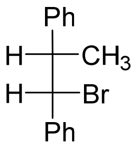


Stereochemistry of -E2 reaction

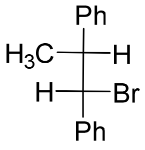
Examine the case of 1-bromo1,2-diphenyl propane, which exists as two pairs of enantiomers. Both pairs are diastereomers. On dehydrohalogenation



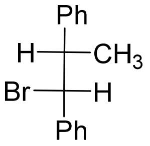
I



II



I

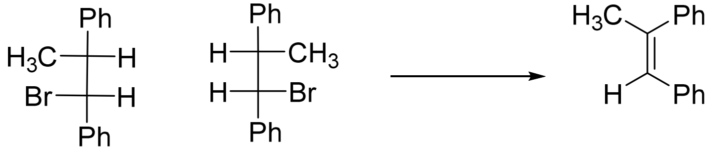


II

Erythro

Threo

Erythro compound gives Z-alkene and threo compound forms E-alkene. Hence it is a stereo selective and the stereo specific reaction.

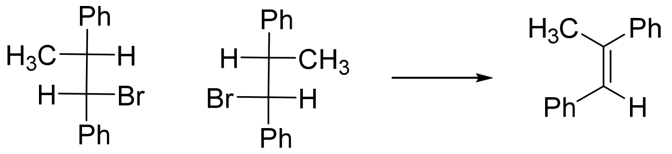


I II

Erythro

1-Bromo-1,2-diphenyl propane

(Z)-1,2-diphenyl propene



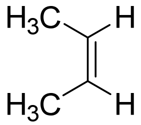
I II

Threo

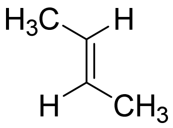
1-Bromo-1,2-diphenyl propane

(E)-1,2-diphenyl propene

When eliminated groups are from the same face it is called “syn elimination” and when eliminated groups are from opposite faces it is known as “anti-elimination.” E2 elimination involves anti-elimination. Conformationally, more trans isomer is formed than cis product in these E2 reactions. Trans isomer is more stable than cis isomer due to less Vander Waals strain encountered and trans product is formed faster than cis isomer.



cis-2-butene

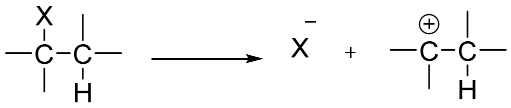


Trans-2-butene
more stable due to
less Vander Waals
strain

In the case of E1- the mechanism follows first order kinetics and involves two step unimolecular elimination as well as carbonium ion formation.

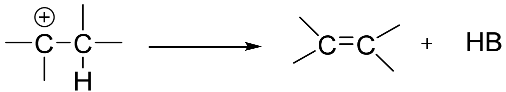
E1-Unimolecular elimination

a)



slow heterolysis
Rate determining step

b)



fast

alkene formation
First order kinetics

$$\text{Rate} = K[RX]$$

Evidences for E1- mechanism are as follows:

a) First order kinetics,

b) Do not show hydrogen isotope effect,

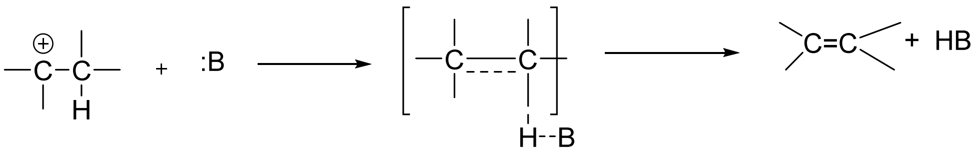
c) Accompanied by rearrangements,

d) Effect of the structure on the reactivity same as in SN1 reactions.

Order of reactivity of alkyl halides follows-

Tertiary > Secondary > Primary

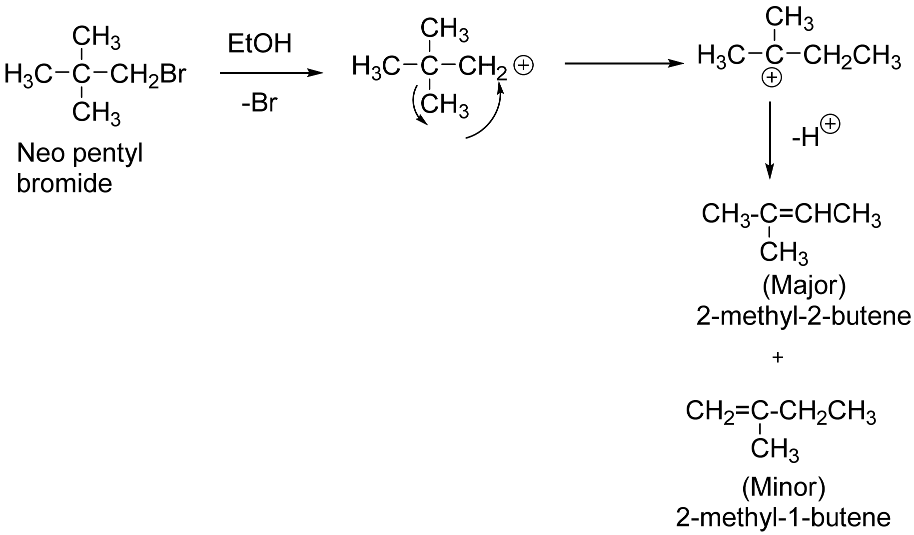
E1 process follows Saytzeff's rule. In the case of highly branched substrates the more stable compound is formed.



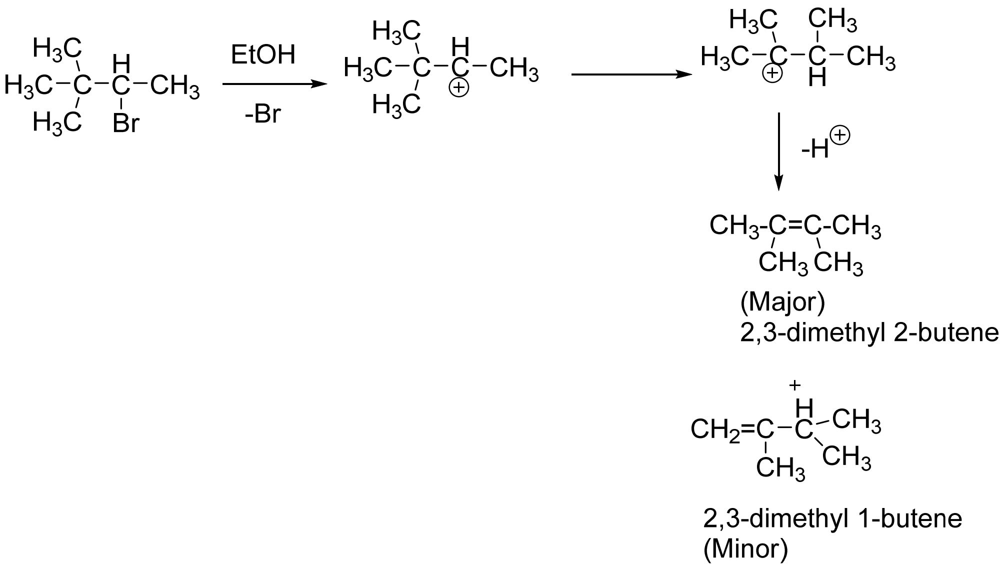
In both E1, and E2 it can be observed reactivity increases along - primary secondary tertiary. In E1, due to the greater stability of the carbonium ion formed in the rate determining step, the reactivity increases along the above lines. In E2 the reactivity increases because of the higher stability of the highly branched alkene formed.

Example:

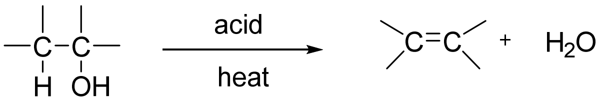
a)


Neo pentyl bromide
EtOH
-Br
$-H^{\oplus}$
(Major)
2-methyl-2-butene
+
(Minor)
2-methyl-1-butene

b)

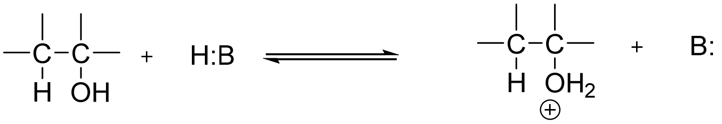

EtOH
-Br
$-H^{\oplus}$
(Major)
2,3-dimethyl 2-butene
+
2,3-dimethyl 1-butene
(Minor)

During dehydration of alcohols an elimination of water molecule takes place as 1,2- elimination.

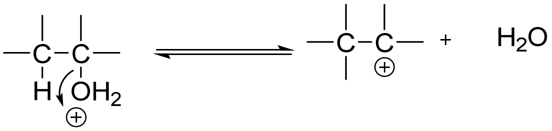


The reaction can be conducted in the presence of an acid and under heating conditions. Acid can be H_2SO_4, H_3PO_4 etc., The reaction can be performed by passing alcohol vapour over Alumina catalyst at higher temperatures. Here alumina acts as Lewis acid and Lowry Bronsted acid. The rate of reaction follows the order- tertiary secondary primary.

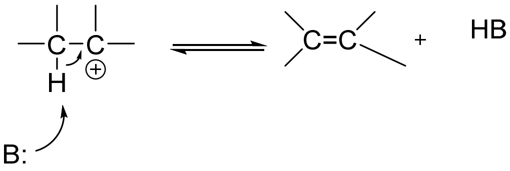
a)



b)



c)



The reaction strongly follows Saytzeff's rule and a more stable carbonium ion is formed, while producing alkene molecule.

a)

$$CH_3CH_2OH \xrightarrow[170\ °C]{95\ \%\ H_2SO_4} CH_2{=}CH_2$$

ethyl alcohol ethylene

b)

$$CH_3CH_2CH_2OH \xrightarrow[140\ ^oC]{75\%\ H_2SO_4} H_3CCH{=}CH{-}CH_3$$

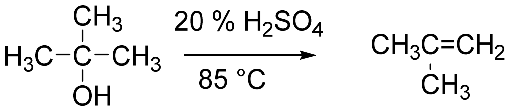
n-butyl alcohol 2-butene (major)

c)

$$CH_3CH_2CHOHCH_3 \xrightarrow[100\ °C]{60\ \%\ H_2SO_4} CH_2CH{=}CHCH_3$$

sec. butyl alcohol → 2-butene (major)

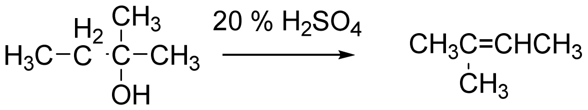
d)



$$H_3C-\overset{CH_3}{\underset{OH}{C}}-CH_3 \xrightarrow[85\ °C]{20\ \%\ H_2SO_4} CH_3\underset{CH_3}{C}{=}CH_2$$

tert.butyl alcohol → isobutylene

e)



$$H_3C-\overset{H_2}{C}-\overset{CH_3}{\underset{OH}{C}}-CH_3 \xrightarrow{20\ \%\ H_2SO_4} CH_3\underset{CH_3}{C}{=}CHCH_3$$

tert.pentyl alcohol → 2-methyl-2-butene (major)

3. Substitution reactions

When an electron rich reagent or nucleophile attacks the carbon nucleus resulting in the change of functional group, it is called substitution reaction or nucleophilic substitution reaction. Ex: Conversion of alcohols to alkyl halides.

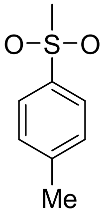
$$R\text{-}OH \xrightarrow{HX\ \text{or}\ PX_3} RX$$

Nucleophilic Substitution

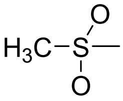
$$\underset{\text{Substrate}}{R{:}\,X} + \underset{\text{nucleophile}}{{:}Z} \longrightarrow R{:}Z + \bar{X}{:}$$

In the case of aliphatic compounds generally alcohols are good substrates for conversion.

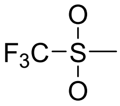
Nucleophilic substitution is the most widely practised and popular method in organic synthesis. Generally, the components of the reaction are substrates, containing good leaving groups, nucleophile and solvent. The nucleophile should be more powerful so that it can attack carbon faster. A large number of substitution reactions are known. In the above general equation, Z can be OH (alcohols), OR (ethers), CN (nitriles), NH_3 (primary amines), RNH_2 (secondary amines), R2 NH (tertiary amines), SH (thiols or mercaptans), SR (thioethers), ArH (in the presence of $AlCl_3$), I (alkyl iodides), C=C (forms alkynes), etc., Alkyl halides can also be converted to organometallic compounds with the help of lithium, magnesium, or copper metals. Apart from alkyl halides alkyl esters of sulfonic acids ($ArSO_2OR$) are commonly used in the synthesis. The following sulfonate esters are good leaving groups.



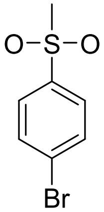
Tosyl
(TS)



Mesyl
(Ms)



Triflyl
(Tf)



Brosoyl
(Bs)

According to E.D. Hughes and Sir Christopher Ingold, the nucleophilic aliphatic substitution proceeds by two different mechanisms.

SN1-substitution nucleophilic, unimolecular,

SN2- substitution nucleophilic bimolecular

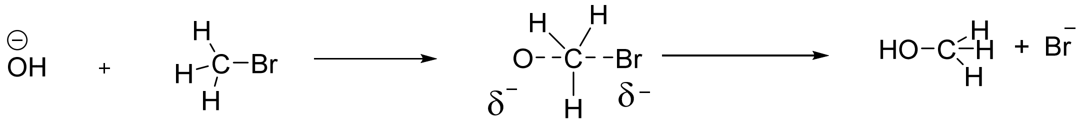
While proposing the theory in 1935, these scientists considered kinetic order and relative reactivities.

SN1-mechanism increases from primary alkyl halides to secondary to tertiary halides.

SN2- mechanism increases from tertiary, to secondary, to primary alkyl halides.

SN ^{1} increases
→
RX= CH_3X, primary alkyl halides, secondary alkyl halides, tertiary alkyl halides
←
SN ^{2} increases

In the case of methyl bromide hydrolysis, the rate of reaction depends both on the concentrations of methyl bromide and hydroxide ion and the reaction goes with complete inversion of configuration or opposite configuration.



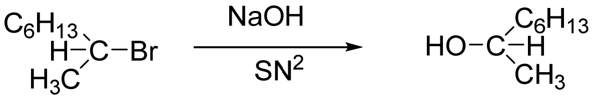
Transition state
Rate determining

Rate= $K[CH_3Br][OH^-]$

Better leaving group speeds up both SN1, and SN2 mechanisms. In the case of SN2 reaction, it occurs in a single step. Bond breaking and bond forming occur simultaneously in a concerted fashion. Bulky electron releasing functional groups facilitate back side attack, accommodating positive charge, increases hydrolysis, making reaction faster.

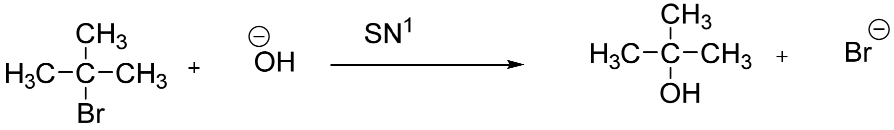
In the case of SN1-reaction unimolecular, the rate of reaction is independent of OH ion concentration and depends only on concentration of RBr.

Hydrolysis of methyl bromide follows second order kinetics whereas hydrolysis of tertiary butyl bromide follows first order kinetics.



(-) 2-bromo octane

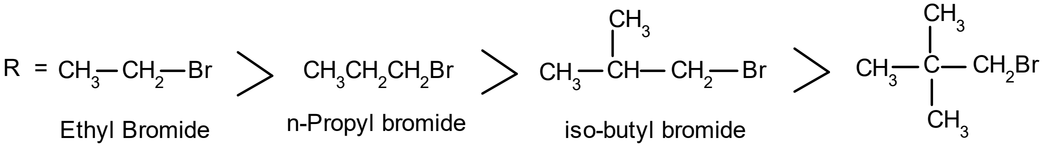
(+) 2-octanol



Rate= K[RBr]

$$RBr + Cl^{\ominus} \xrightarrow{DMF} R\text{-}Cl + Br^{\ominus}$$

Overall, we can observe that as the number of substituents attached to carbon with halogen group increases the reactivity towards SN2 substitution decreases. Therefore, more than polar factors steric factors are influencing the course of the reaction.



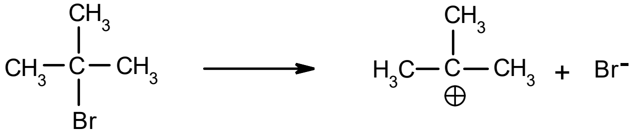
Ethyl Bromide

n-Propyl bromide

iso-butyl bromide

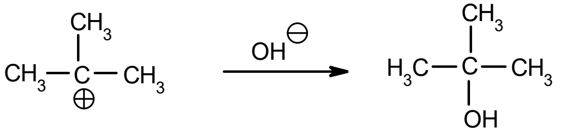
neo-pentyl bromide

a)



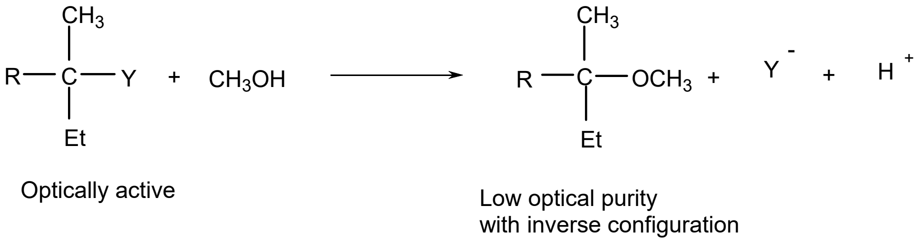
slow (Rate determining)

b)



faster

The rate determining step is the step whose rate controls overall rate of the reaction. Here in SN1 mechanism the rate of entire reaction is determined by the rapidity with which alkyl halide ionizes. It depends on the concentration of alkyl halide. When we carry out the reaction with optically pure substrates the end product will be a mixture of inverted compound and racemic compound. Thus, the reaction ends up with partial racemization plus inversion.



The difference between SN1 and SN2 is that an SN2 reaction proceeds with complete inversion and an SN1 reaction ends up with racemization. Complete stereo specificity in the SN2 process indicates concerted bond breaking and bond making in one step. Absence of complete stereo specificity among SN1 reactions show a stepwise completion.

Relative reactivities-SN1 VS SN2

As postulated by Hughes and Ingold reactivity towards SN2 decreases while going from CH3X, primary, secondary, and tertiary substrates.

Whereas, in the case of SN1 the reactivity order of the substrates is as follows:

Tertiary butyl > Isopropyl > Ethyl > Methyl

The stability of carbonium ion governs the reactivity and orientation in the reactions where carbonium ion is involved. The carbonium ion stability follows the order-

Tertiary > Secondary > Primary > Methyl

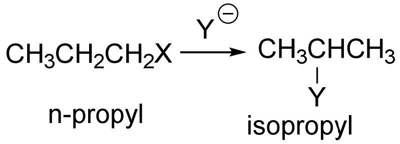
The stability of carbonium ion also depends on polar effects like resonance and inductive effects of the attached groups like dispersal of the charge, and ease of carbonium ion formation etc., A substrate can undergo SN1 faster when a carbonium ion can be formed faster as the rate determining step in SN1 involves the formation of carbonium ion. The more stable is a carbonium ion, the faster it can be formed.

Rearrangement of carbonium ions:

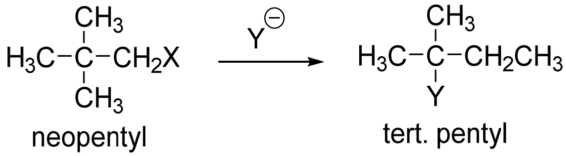
Sometimes nucleophilic substitutions accompany formation of rearranged products;

Examples:

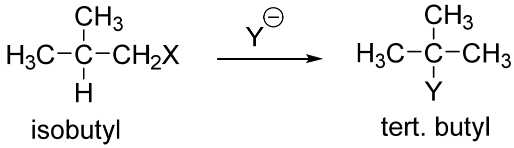
a)



b)



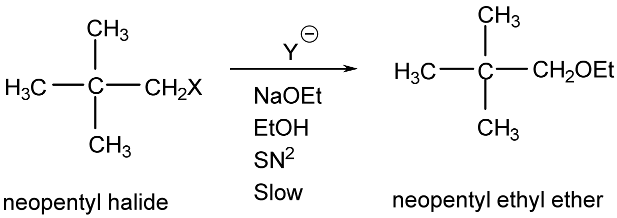
c)



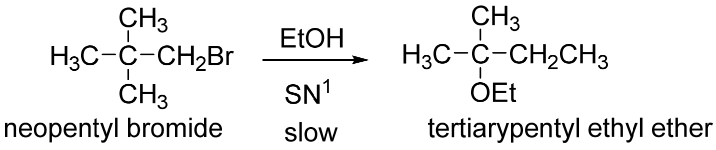
Typically, only reactions proceeding by SN1 mechanism are accompanied by rearrangements. Possibilities for such rearrangements are not there in the case of single step, concerted SN2 reactions. This is because of carbonium ion intermediate, in the slow first order reactions.

Examples:

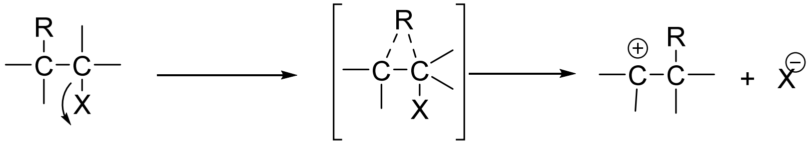
a)



b)

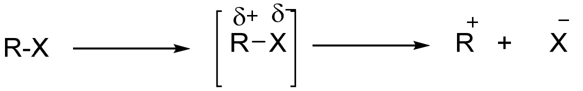


The examples illustrate that rearrangements take place to form a more stable carbonium ion. These also involve 1,2- shift of hydride or alkyl group.



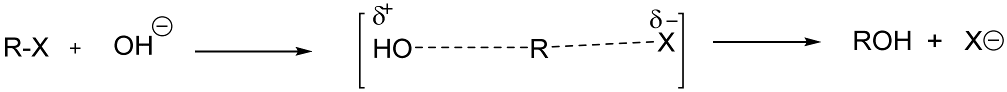
R= H, alkyl

The differences between reactivities of different substrates like primary, secondary, or tertiary compounds are also related to the lower energy of activation [Eact]. The lower the Eact the more stable will be the intermediate transition state. Moreover, the dipole-diplole interactions also play a role in the solution phase. More polar the reactant, stabilization will be more by the solvation.



Transition state

Solvents help in lowering the Eact by stabilizing the transition state. Therefore, SN1 reactions of neutral substrates tend to complete faster in water and alcohols, than in aprotic solvents such as DMF, DMSO etc., HCO_2H, CF_3CO_2H, CF_3CH_2OHetc., act as excellent ionizing solvents, as they can stabilize the transition state, prompting heterolysis involved in the reaction. Whereas, in the case of SN2 reactions two reactants such as alkyl halides and OH are involved in the rate determining step. Both differ in forming dipole-ion bonds with the solvent. Substrates are more stabilized than transition state in the solvent.



The strength of solvation and degree of deactivation of nucleophile differs from anion to anion in the case of SN2. Moreover, the effect differs from solvent to solvent. The greater the polarity of solvent, the slower will be SN2 reaction. Ideal solvent will be nonpolar solvent. Phase transfer catalysts play significant role in these reactions, minimizing two deactivating forces, solvation and ion pairing, acting on the anion.

Salient features:

S N1	SN2
1. First order kinetics	1. Second order kinetics
2. Racemization	2. Complete stereo chemical inversion
3. Rearrangement	3. Absence of rearrangement
4. Reactivity sequence Tert > Sec > Prim.> Methyl	4. Reactivity sequence Methyl> Prim>Sec>Tert
5. Step wise reaction	5.Concerted reaction

Examples:

a)

$$CH_3CH_2CH_2CH_2OH \xrightarrow[H_2SO_4]{NaBr} CH_3CH_2CH_2CH_2Br$$

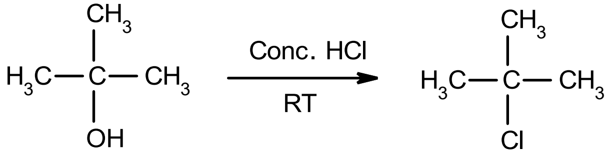
n-butyl alcohol → n-butyl bromide

b)

$$CH_3CH_2CH_2OH \xrightarrow[ZnCl_2]{HCl} CH_3CH_2CH_2Cl$$

n-propyl alcohol → n-propyl chloride

c)

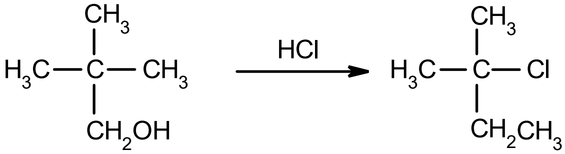


$$(CH_3)_3C{-}OH \xrightarrow[RT]{Conc.\ HCl} (CH_3)_3C{-}Cl$$

tert butyl alcohol

tert butyl chloride

d)

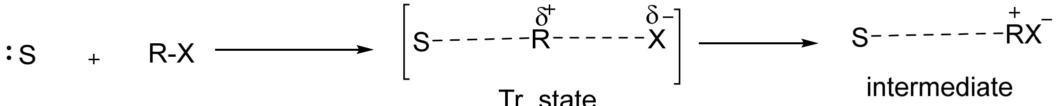


$$(CH_3)_3C{-}CH_2OH \xrightarrow{HCl} (CH_3)_2C(Cl){-}CH_2CH_3$$

neopentyl alcohol

tert. pentyl chloride

We can conclude that primary substrates undergo single step SN2 and tertiary substrates follow two step SN1 mechanism. In the case of secondary substrates, these may followSN1 like a two-step process or may involve nucleophilic assistance from the solvent (known as SN2i or SN2 intermediate). In the latter case, the intermediate is a nucleophilically solvated carbonium ion or encumbered carbo cation. This differs from SN2 kind of attack by a nucleophile. In this case, a single solvent molecule attacks the substrate from back side as a nucleophile and pushes out the leaving group from front side.



Tr. state nucleophilic assistance by solvent molecule

intermediate nucleophilically solvated carbonium ion

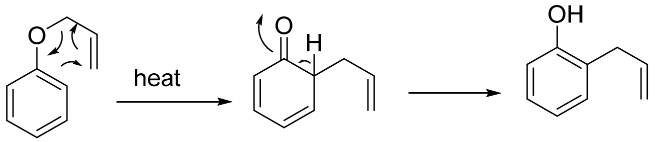
Alcohols also undergo SN1 or SN2 reactions just as alkyl halides, but needs strong acidic medium to protonate -OH group to make it ROH_2 as H_2O is a good leaving group than OH, which is a strong base. Protonation plays an important role in many kinds of substrates having N, O, or S, to make reaction faster.

4. Rearrangement reactions

Rearrangement reactions belong to a wide class of organic reactions in which the carbon skeleton of the substrate molecule undergoes rearrangement generating a new structural isomer of the substrate. These, which involve movement of an atom or a group of atoms, may be intramolecular or intermolecular. There are several rearrangements like 1,2- rearrangements, 1,3- rearrangements, olefin-metathesis, pericyclic reactions etc., Many name reactions come under rearrangements. These are discussed at various places in the book under the respective sections.

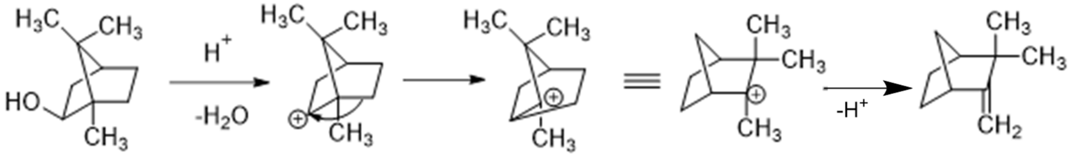
Examples:

a)



Aromatic claisen rearrangement

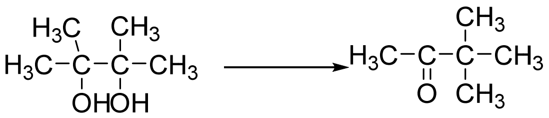
b)



Wagner-Meerwein rearrangement

camphene

c)



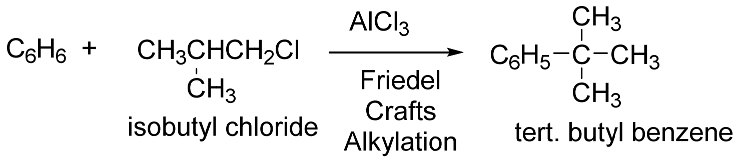
$$H_3C-\underset{OH}{\overset{H_3C}{C}}-\underset{OH}{\overset{CH_3}{C}}-CH_3 \longrightarrow H_3C-\underset{\overset{\|}{O}}{C}-\underset{CH_3}{\overset{CH_3}{C}}-CH_3$$

Pincol rearrangement

Pinacol
2,3-dimethyl
2,3-butanediol

Pinacalone
methyl tert.butyl ketone
3,3-dimethyl-2-butanone

d)



$$C_6H_6 + CH_3\underset{CH_3}{C}HCH_2Cl \xrightarrow[\text{Friedel Crafts Alkylation}]{AlCl_3} C_6H_5-\overset{CH_3}{\underset{CH_3}{C}}-CH_3$$

isobutyl chloride

tert. butyl benzene

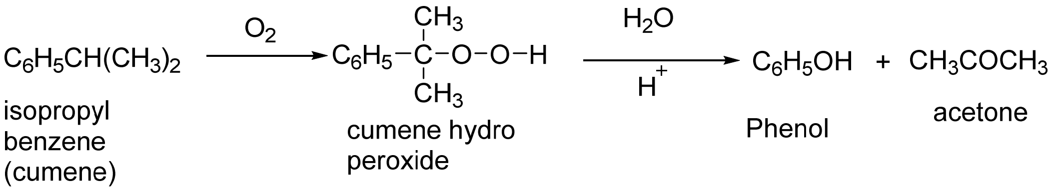
e)

$$C_6H_5COCOC_6H_5 \xrightarrow{OH^{\ominus}} (C_6H_5)_2C(OH)COO^- \xrightarrow[H^+]{} (C_6H_5)_2C(OH)COOH$$

Benzil

Benzilic acid

f)



$$C_6H_5CH(CH_3)_2 \xrightarrow{O_2} C_6H_5-\overset{CH_3}{\underset{CH_3}{C}}-O-O-H \xrightarrow[H^+]{H_2O} C_6H_5OH + CH_3COCH_3$$

isopropyl benzene (cumene)

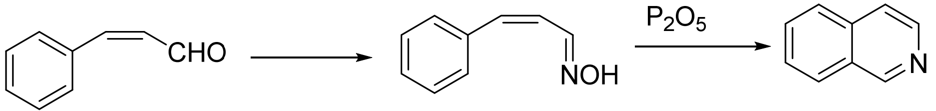
cumene hydro peroxide

Phenol

acetone

Rearrangement of hydroperoxide and migration to electron deficient oxygen species

g)

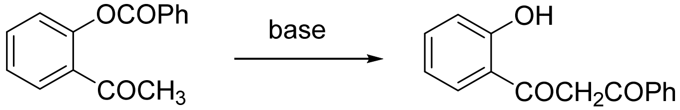


cinnamaldehyde

isoquinoline

Beckmann rearrangement

h)

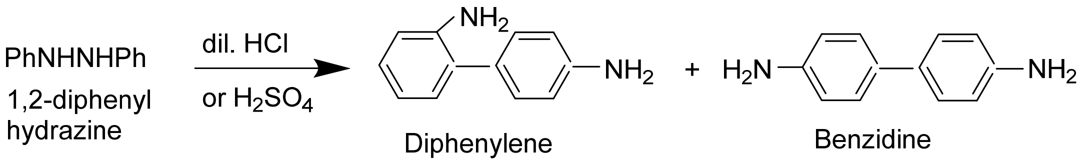


2-acetyl phenyl benzoate

1-(2-hydroxyphenyl)-3-phenylpropane-1,3-dione

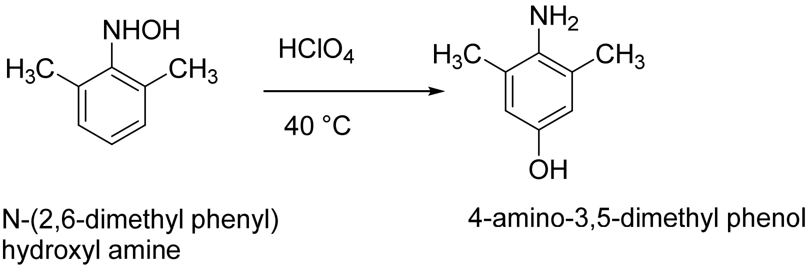
Baker-Venkataraman rearrangement

i)



Benzidine rearrangement

j)



Bamberger rearrangement

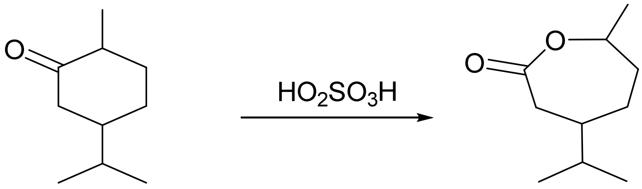
CHAPTER 2

Name Reactions

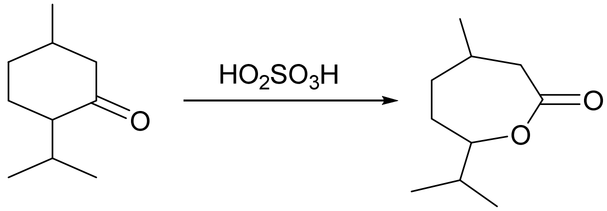
2.1 Baeyer-Villiger Oxidation

It was first reported by Adolf von Baeyer, a German chemist, who synthesized indigo, and Victor Villiger, another German chemist in 1899.

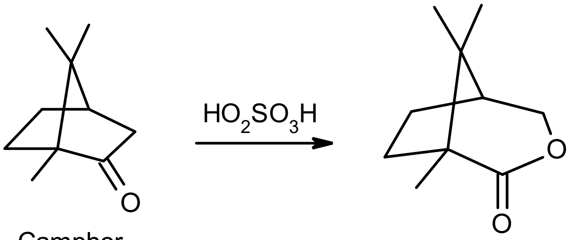
In this reaction an ester or a lactone are formed from a ketone or a cyclic ketone respectively, catalyzed by oxidants like peroxyacids or peroxides like peracetic acid, perbenzoic acid, pertrifluoroacetic acid, permonosulphuric acid or BF_3-H_2O_2 etc., Cyclic ketones can be converted to lactones with ring expansion. Long chain hydroxy esters can be prepared from large ring size ketones.



Tetrahydrocarvone



Menthone

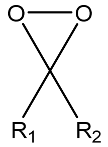


Camphor

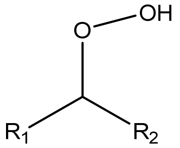
General reaction:

Mechanism:

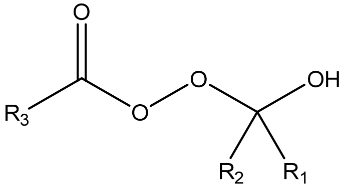
About three mechanisms involving the formation of three different intermediates followed by two modes of attacks of peroxyacid attack – on either the oxygen or the carbon of the carbonyl group are suggested. Attack on oxygen forms two possible intermediates, a) a dioxirane intermediate as suggested by Baeyer and Villiger, b) a peroxide as suggested by Georg Wittig and Gustav Pieper, and c) attack on carbon as suggested by Rudolf Criegee producing Criegee intermediate. However, oxygen-18 labelling concluded that the correct pathway involves the formation of the Criegee intermediate.



Baeyer and Villiger Intermediate



Wittig and Pieper Intermediate



Criegee Intermediate

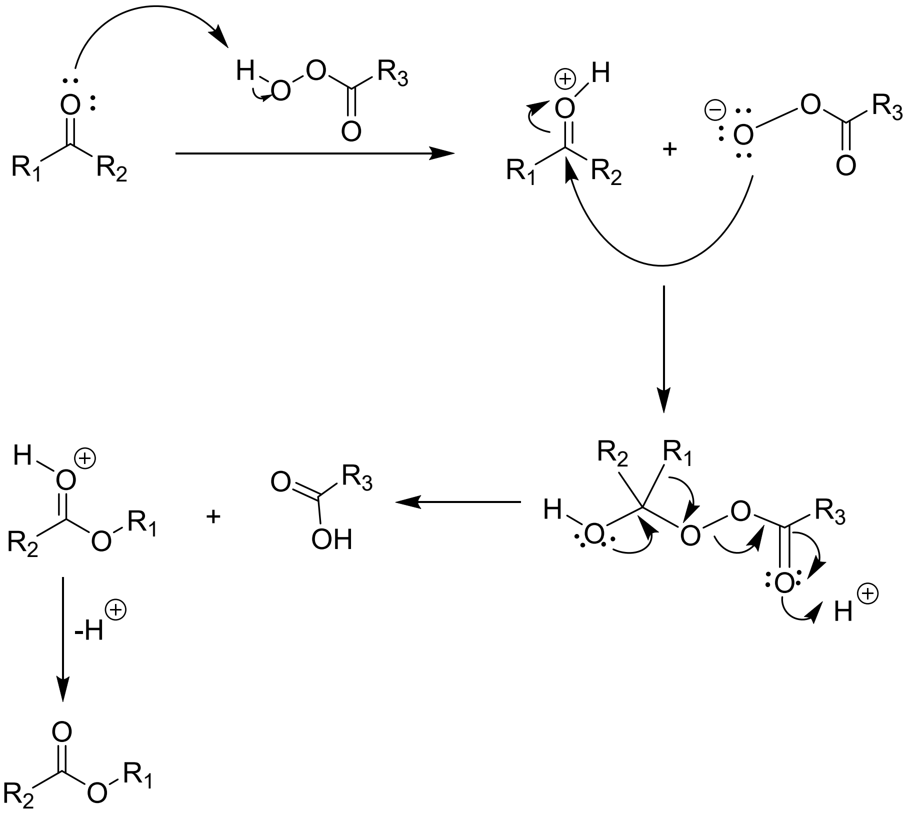
Now in the actual mechanism the initial protonation of the carbonyl group by peroxyacid, is followed by the attack of peroxyacid on the carbonyl carbon forming the Criegee intermediate. Next one of the substituents on the ketone group migrates to the oxygen of the peroxide group and the carboxylic acid leaves. The ester is formed by the deprotonation of the oxocarbenium ion. This migration is the rate determining step. Migratory group retains its configuration as in any other concerted mechanisms. The migratory aptitude of alkyl group follows the order tertiary>secondary>primary>methyl. Electron releasing substituents favour migration. In aryl groups the order is p-anisyl>p-tolyl>phenyl>p-chlorophenyl>p-nitrophenyl.

Both primary and secondary stereoelectronic effects control the outcome of the products.

a) The oxygen-oxygen bond in the peroxide group should be antiperiplanar to the group that migrates, making optimum overlap of the **σ** orbital of the migrating group to the σ* orbital of the peroxide group.

b) The lone pair on the oxygen of the hydroxyl group should be antiperiplanar to the migrating group, making optimum overlap of the oxygen nonbonding orbital with the σ* orbital of the migrating group.

Trifluoroperacetic acid (TFPAA), 4-nitroperbenzoic acid, *meta*-Chloroperoxybenzoic acid (mCPBA), performic acid, peracetic acid, hydrogen peroxide, tert-butyl hydroperoxide are some of the important oxidant catalysts useful in the Baeyer–Villiger oxidation reaction. In this the lower is the pK_a of the carboxylic acid or alcohol (in the case of the peroxides) the higher is the reactivity. The peroxyacids are more reactive than the peroxides. However, sometimes the Baeyer–Villiger oxidation can cause the undesirable oxidation of other functional groups.e.g., alkenes/amines. Hydrogen peroxide is known to be environmentally benign as the byproduct is only water.

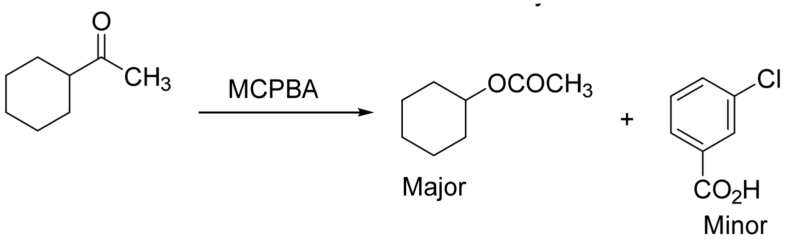


1. Preparation of esters from ketones

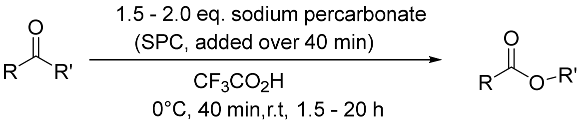
a) $\underset{\text{acetophenone}}{PhCOCH_3} \xrightarrow{CF_3CO_2H} \underset{\text{Phenylacetate}}{CH_3COOPh}$

b) $CH_3COC(CH_3)_3 \xrightarrow{CF_3CO_2H} \underset{\text{t-butylacetate}}{CH_3COOC(CH_3)_3}$

c)



d) Sodium percarbonate in trifluoroacetic acid was employed as an effective reagent for the Baeyer-Villiger oxidation of ketones to esters[1].



EX:

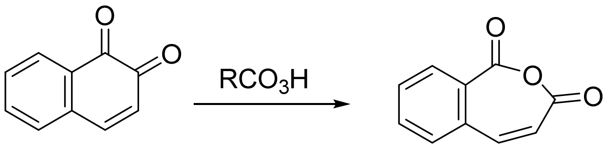
$$\text{PhCOPh} \dashrightarrow \text{PhCOOPh} \quad (Na_2CO_4, CF_3CO_2H,\ 0°C, 40\ \text{min, rt 1-4 hrs, 76\%})$$

2. Preparation of anhydrides

a) $CH_3COCOCH_3 \xrightarrow{RCO_3H} CH_3COOCOCH_3$

acetic anhydride

b)

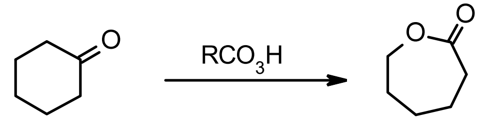


3. Preparation of epoxides

The epoxidation of various olefinic substrates and the Baeyer-Villiger oxidation of aldehydes and ketones with hydrogen peroxide was reported using aryl benzyl selenoxides[2].

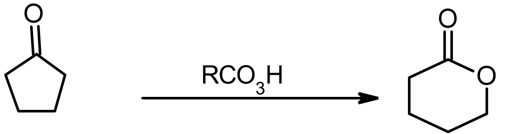
4. Preparation of lactones

a)



Cyclohexanone E-caprolactone

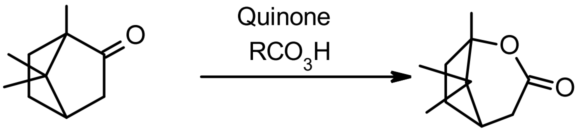
b)



Cyclopentanone

Tetrahydro
2H- pyran-2-one

c)



Camphor Major

5. Preparation of hydroxy alkyl esters

Hydroxy alkyl esters are also reportedly generated by the oxidation of cyclic acetals in the presence of MCPBA.

6. Microwave-assisted Baeyer–Villiger Oxidation

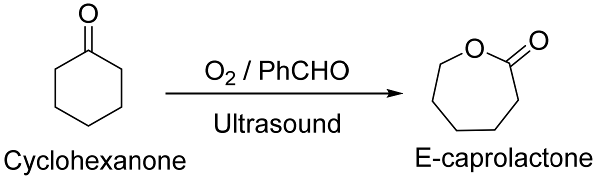
Preparation of lactones by the oxidation of cyclic ketones. The Baeyer–Villiger oxidation of cyclic ketones to the corresponding lactones was improved with *m*-CPBA under microwave irradiation.

Ex: Cycloheptanone into oxocan-2-one.

7. Ultrasound-assisted Baeyer–Villiger oxidation

Ex: Preparation of ε-caprolactone**.**

Baeyer–Villiger oxidation of cyclohexanone to ε-caprolactone was studied in a new sonochemical reactor. Ultrasound intensified the rates of reactions and also increased the yield of product. Facile oxidative conversion of cyclohexanone to yield ε-caprolactone using molecular oxygen and benzaldehyde was developed[3].

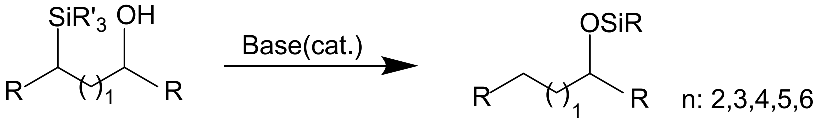


2.2 Brook rearrangement

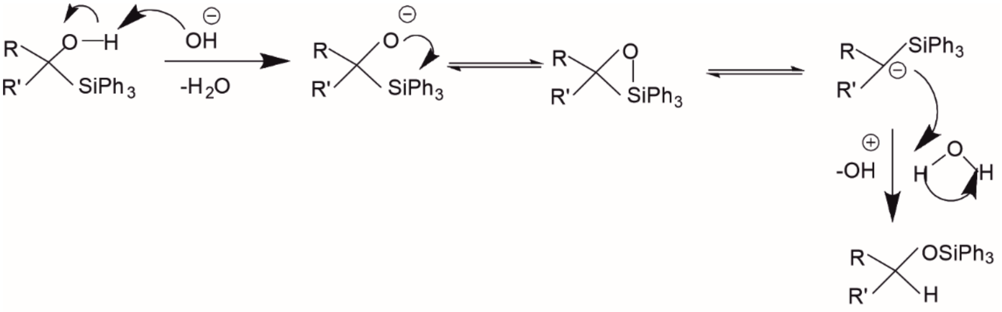
The Brook rearrangement introduced by Adrian Gibbs Brook, involves rearrangement of any [1,*n*] carbon to oxygen silyl migration producing silyl ethers as products which is driven by the stability of the oxygen-silicon bond. They can take place under basic/acidic conditions or thermally or photolytically. Anionic rearrangements are most common. It is an intramolecular 1,2-anionic migration of a silyl group with the formation of a cyclic pentavalent silicon species in the transition state. The rearrangement is known to occur with retention of configuration at the silicon.

The silyl substituents can be aliphatic or aromatic. An electron-withdrawing R group facilitates the reaction. Analogous Brook rearrangements are known including nitrogen, phosphorus, and sulfur as the nucleophilic components. When an intramolecular migration of a silyl group from oxygen to carbon take place, it is known as retro-Brook rearrangement.

General Reaction:

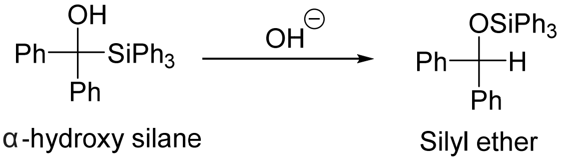


Mechanism:



Applications and examples:

1. Preparation of silyl ether



2. Allylation of β-Triphenyl silyl Allylic Alcohols

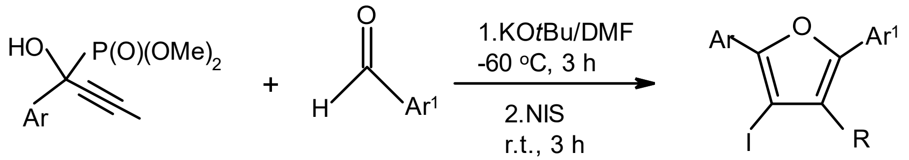
Copper(I) *tert*-butoxide and allylic halides are efficiently used in the preparation of β-triphenylsilyl allylic alcohols[4].

3. Preparation of α-Hydroxy Acid Derivatives

A wide range of α-substituted α-siloxy silanes were carboxylated under CO_2 atmosphere *via* Brook rearrangement, in the presence of CsF[5].

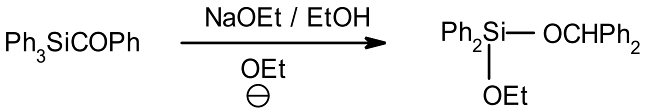
4. Synthesis of tetrasubstituted furans via [1,2]-phospha Brook rearrangement

Tetrasubstituted furan derivatives were prepared by utilizing the [1,2]-phospha-Brook rearrangement under Brønsted base catalysis. The two step one-pot [3 + 2] cycloaddition involves the nucleophilic addition of a propargyl anion, generated through the [1,2]-Phospha-Brook rearrangement, to an aldehyde followed by an intramolecular cyclization promoted by *N*-iodosuccinimide (NIS) to afford 2,4,5-trisubstituted-3-iodofurans[6].



R : alkyl

5. Conversion of silyl ketones to silyl ethers

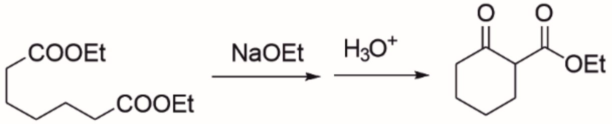


$$Ph_3SiCOPh \xrightarrow[\underset{\ominus}{OEt}]{NaOEt / EtOH} Ph_2\underset{OEt}{\underset{|}{Si}}—OCHPh_2$$

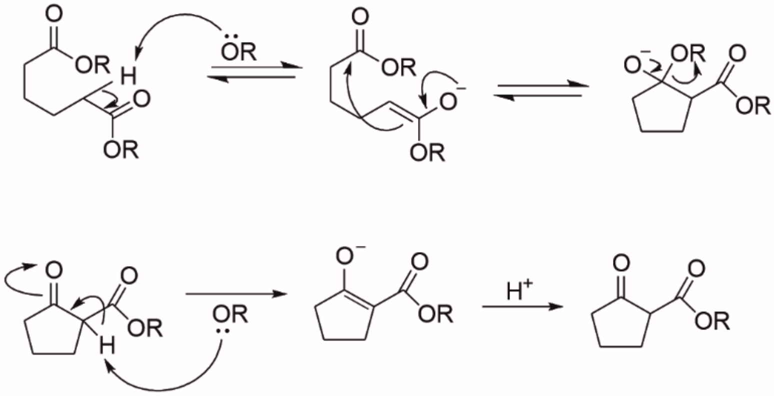
2.3 Dieckmann Reaction

It is the intramolecular conversion of diesters to β-keto esters in the presence of a base and is named after the German chemist, Walter Dieckmann. The Dieckmann condensation along with its intermolecular version are classic and interesting reactions studied because of their great importance in organic synthesis and biochemical transformations. An enolate ion is formed by the deprotonation of an ester at the α-position. It undergoes a 5-exo-trig nucleophilic attack to give a cyclic enol. A Bronsted-Lowry acid protonates (H_3O^+ for example) to form the β-keto ester. Five-membered and six-membered β-keto esters are formed from 1,6 diesters and 1,7 diesters respectively. Bases like tBuOK, tBuONa, EtOK, and EtONa etc., can be used as catalysts.

General reaction

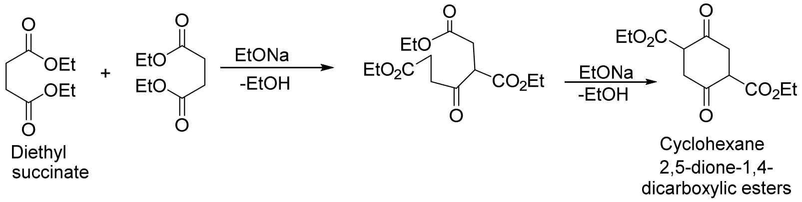


Mechanism:

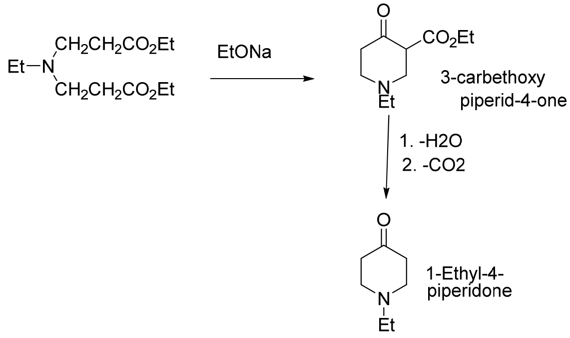


Applications and examples:

1.



2.



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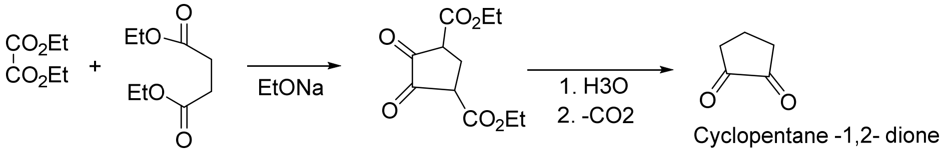

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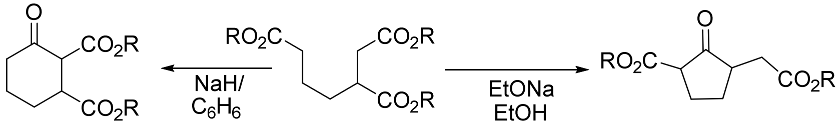
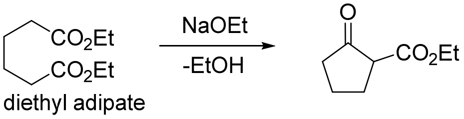
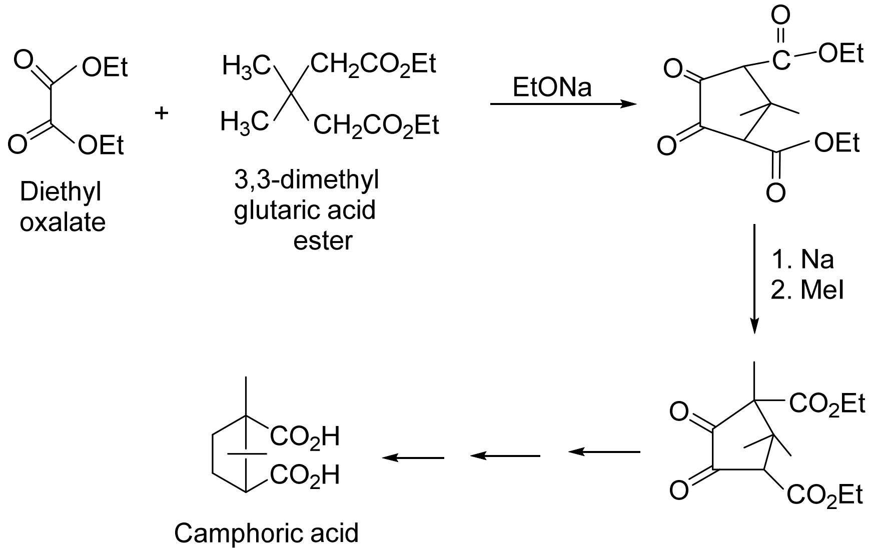


5.



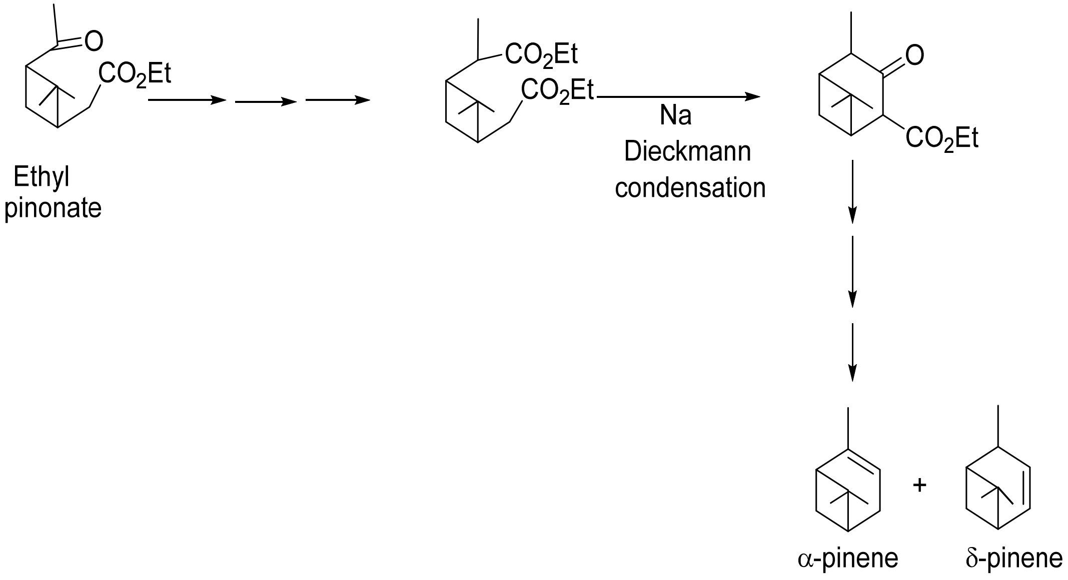
From Synthesis of Camphoric Acid

6.

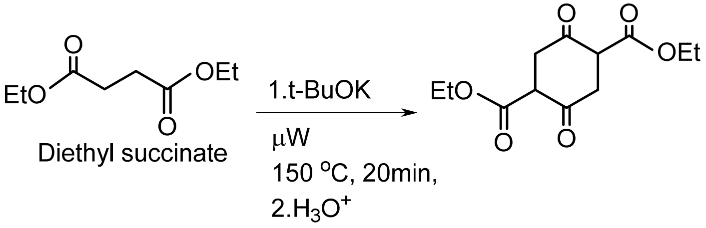


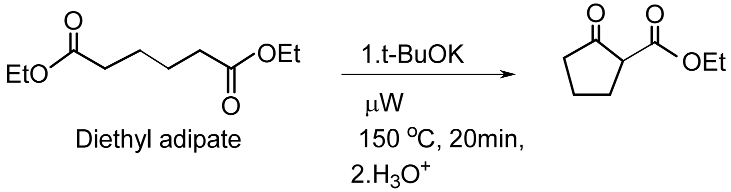
From Total Synthesis of α–pinene

7.

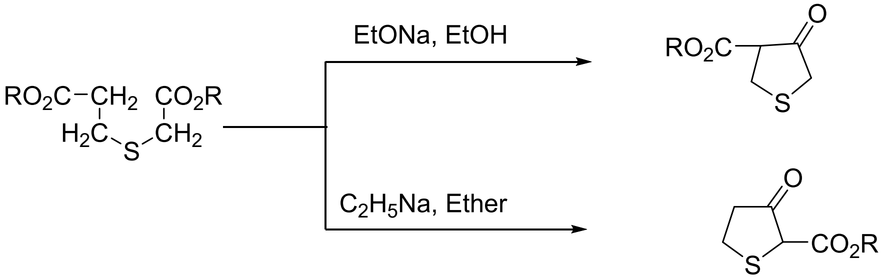


8. Conversion of diethyl succinate and diethyl adipate by microwave irradiation[7]



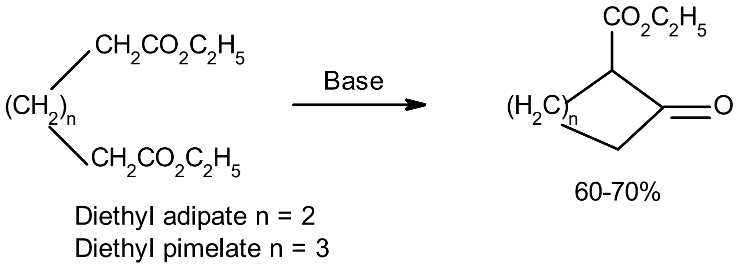


9. Preparation of thiophene derivatives promoted by base catalysis[8]



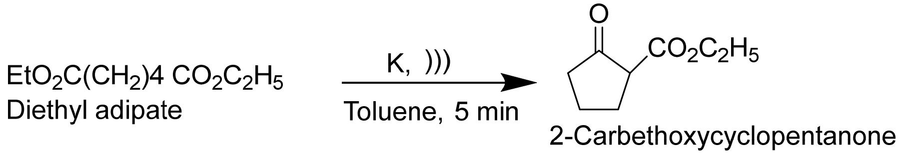
10. Solid-state Dieckmann condensation reaction[8]

Diethyl adipate and diethyl pimelates can be easily prepared by green methods like solid state reaction in the absence of any solvent in the presence of a base from powdered reaction mixture.



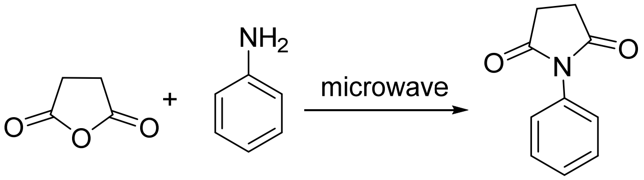
11. Dieckmann condensation under sonication[8]

The reaction took place well under the influence of sonication and dispersed potassium in toluene catalyzed the reaction efficiently.



12. Microwave assisted synthesis of *N*-phenylsuccinimide[9]

By heating a mixture of aniline and succinic anhydride in a domestic microwave oven for four minutes, *N*-phenylsuccinimide is obtained in moderate yields.



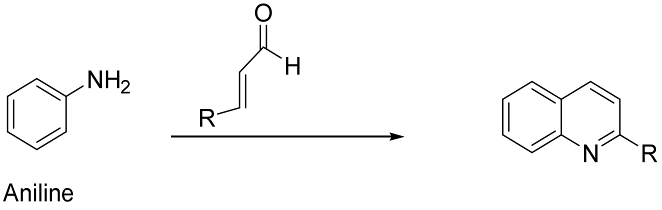
2.4 Doebner-Miller Reaction

Named after the Czech chemist Zdenko Hans Skraup and the German chemists Oscar Döbner (Doebner) and Wilhelm von Miller, this reaction is also known as Skraup-Doebner-Von Miller quinoline synthesis. This reaction is also a variant of the Skraup quinoline synthesis.

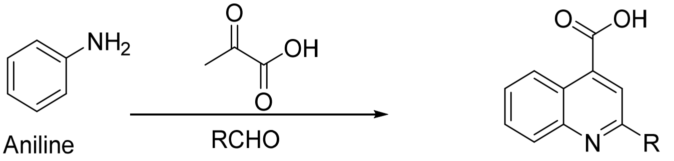
Primary aromatic amines (e.g., anilines) and α, β-unsaturated carbonyl compounds (mostly α, β-unsaturated aldehydes) undergo condensation to afford 2,3-disubstituted quinolines, catalyzed by Lewis acids or Brønsted acids. It can also be performed from primary aromatic amines, aldehydes and α-keto acids like 2-oxopropanoic acid or pyruvic acid. In such cases the reaction proceeds through three steps. **1.** Formation of β, γ-unsaturated alpha keto acid **2.** Michael addition with primary aromatic amine **3.** Air oxidation. Different catalysts like tin tetrachloride ($SnCl_4$), scandium (III) triflate $Sc(OTf)_3$, Ytterbium (III) trifluoromethanesulfonate (Yb (OTf)3), Zinc chloride ($ZnCl_2$), Indium (III) chloride ($InCl_3$), p-toluenesulfonic acid ($CH_3C_6H_4SO_3H$- PTSA or *p*-TsOH), perchloric acid ($HClO_4$), amberlite or iodine can be used. Moreover, microwave irradiation with the assistance of Lewis acid activators like montmorillonite K-10 is also reportedly employed to achieve this reaction.

General reaction:

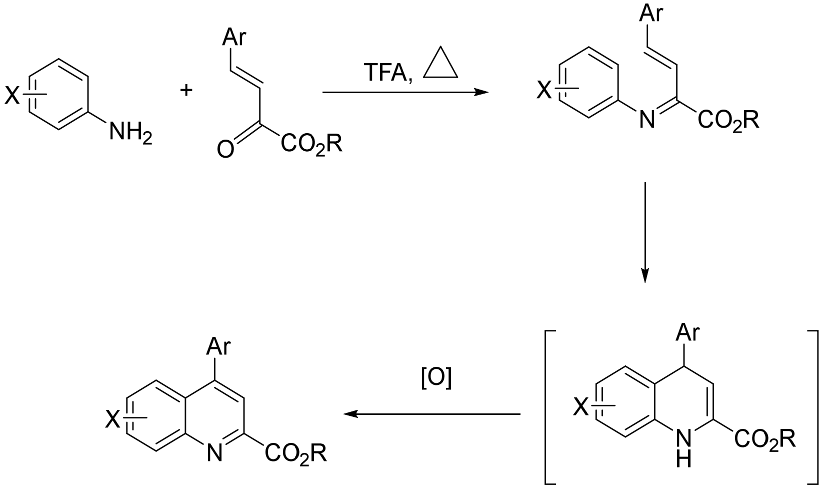
a)



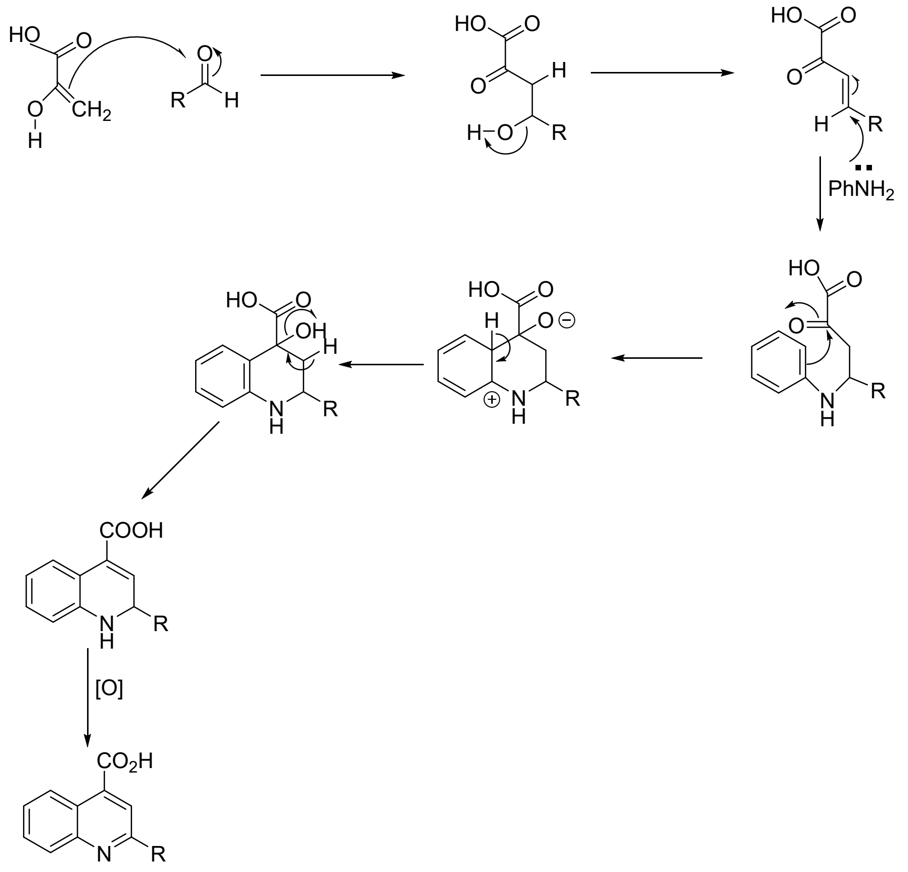
b)



c)

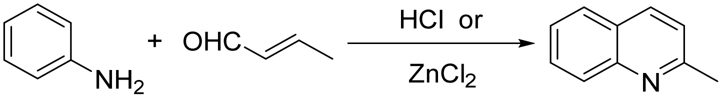


Mechanism:



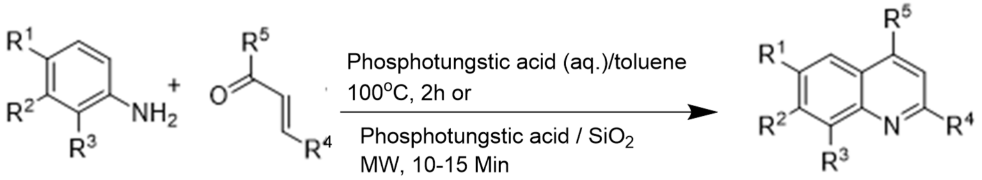
Applications and examples:

1.



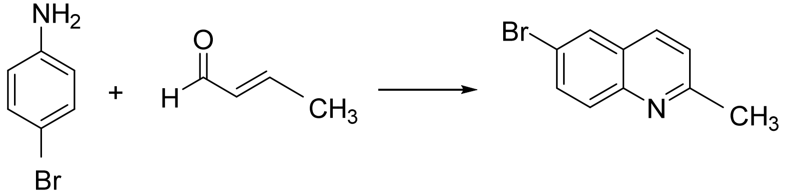
2. Synthesis of quinaldines and lepidines under thermal and microwave irradiation[10]

Quinaldines and lepidines can be produced by a one-pot reaction of anilines with crotonaldehyde or methyl vinyl ketone using phosphotungstic acid, a Keggins-type heteropoly acid, under both thermal and microwave irradiation conditions.



3. Preparation of Quinoline Derivatives[11]

Various substituted quinoline derivatives can be prepared from anilines and both aromatic and aliphatic α, β-unsaturated aldehydes catalyzed by recyclable Ag(I)-exchanged Montmorillonite K10.

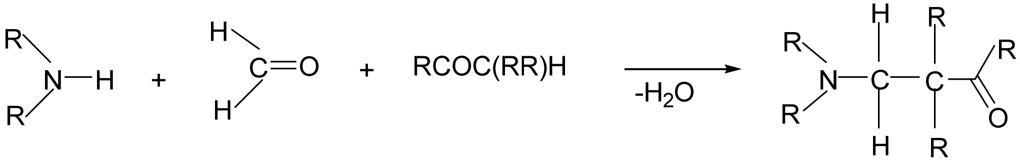


2.5 Mannich Reaction

This multicomponent condensation reaction, developed by Carl Mannich, involves the aminoalkylation of an acidic proton next to a carbonyl group by formaldehyde and a primary or secondary amine or ammonia. The product is a β-amino-carbonyl compound, known as Mannich base. Tertiary amines cannot participate in this reaction as these do not have N–H proton. Aryl amines generally do not participate in the reaction. Apart from carbonyl compounds phenols, nitriles, acetylenes, aliphatic nitro compounds, α-alkyl-or γ-alkyl pyridines or α-alkyl-or γ alkyl quinolines, imines can also react with Schiff base. Others like activated phenyl groups and electron-rich heterocycles such as furan, pyrrole, thiophene and indole derivatives also participate in this reaction. If the compound possesses more than one active hydrogen, all of them can be substituted by amino methyl groups. This reaction can be catalyzed by acid or base. It is extensively studied and applied.

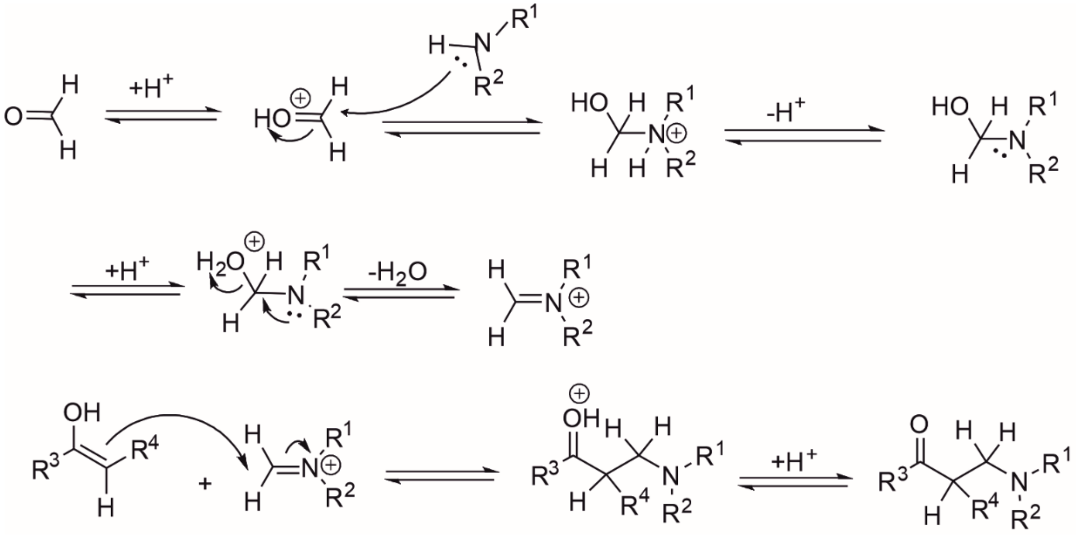
The Mannich reaction is applied in many areas like agrochemicals, alkaloids, organic intermediates, catalysts, nucleotides, peptides, pharmaceuticals (in the production of fluoxetine, a powerful antidepressant, and nonsteroidal anti-inflammatory drug tolmetin), polymers, and soap and detergents etc., It is involved in many biological pathways.

General reaction



Mechanism

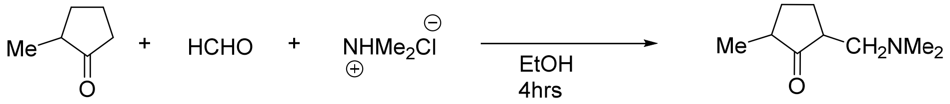
The reaction is initiated by the nucleophilic addition of an amine to a carbonyl group, via the formation of an iminium ion from the amine and formaldehyde, followed by dehydration to the Schiff base. The enol formed from the carbonyl compound containing an acidic α-proton undergoes electrophilic addition with the Schiff base.



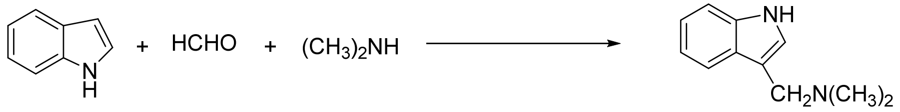
Applications and examples

1. $PhCOCH_3 + HCHO + (CH_3)_2NH.HCl \longrightarrow PhCOCH_2CH_2N(CH_3)_2.HCl + H_2O$

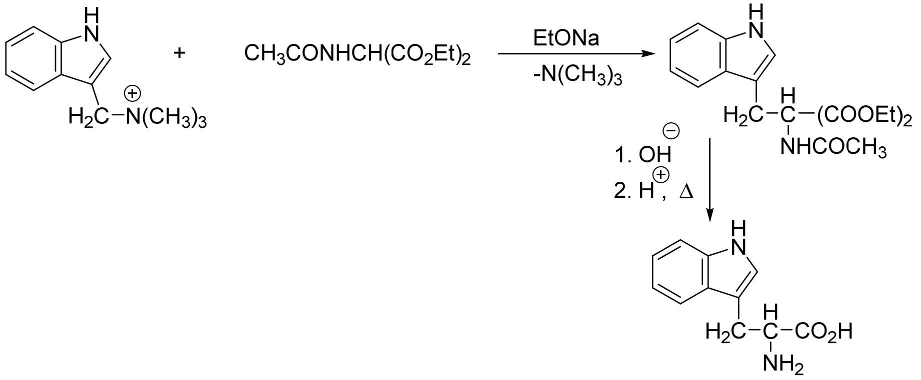
2.



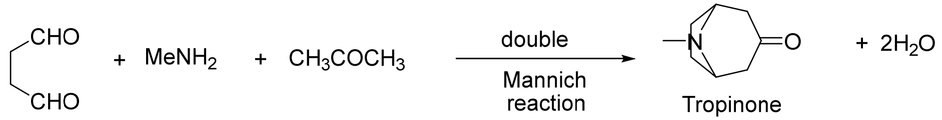
3.



4.



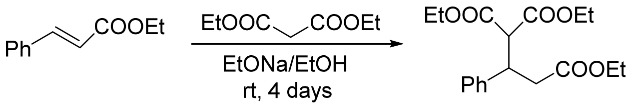
5.



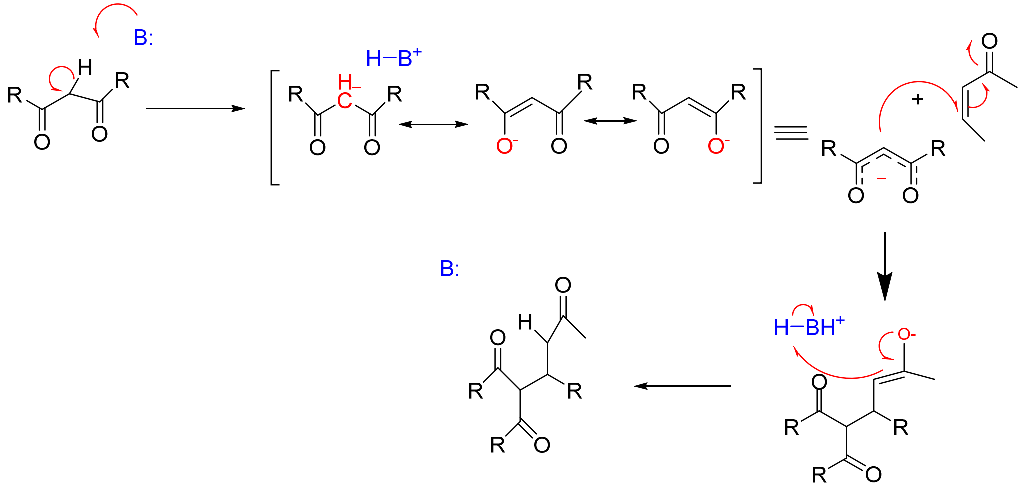
2.6 Michael Addition Reaction

The Michael reaction, invented by Arthur Michael, is the addition of an enolate of a ketone or aldehyde to an α,β-unsaturated carbonyl compound at the β carbon., or the 1,4-addition of a doubly stabilized carbon nucleophile to an α,β-unsaturated carbonyl compound. It can also be viewed as an addition reaction between α,α-disubstituted carbonyls, nitriles, sulfones, etc., called Michael donors and α,β-unsaturated carbonyls, nitriles, nitro, etc., called Michael acceptors. It is an important, widely applicable and atom-economical conjugate addition reaction, leading to the formation of C-C bonds (Michael adducts). These reactions can be enantioselective or/and diastereoselective. Tandem sequence of Michael and aldol additions is called the Robinson annulation.

General reaction:



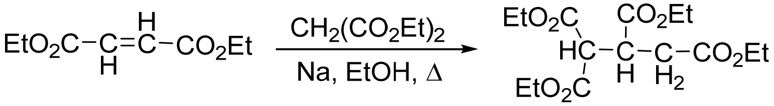
Mechanism



Applications and examples:

1. Preparation of ethyl propane-1,1,2,3-tetracarboxylate[12]

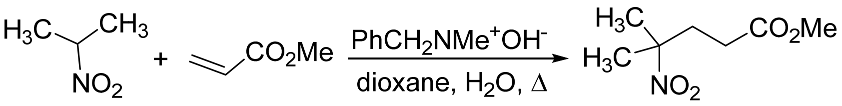
The addition reaction between diethyl malonate (Michael donor) and diethyl fumarate (Michael acceptor) in the presence of Na/EtOH under reflux generates the title compound.



$$EtO_2C{-}\underset{H}{C}{=}\overset{H}{C}{-}CO_2Et \xrightarrow[\text{Na, EtOH, }\Delta]{CH_2(CO_2Et)_2} \begin{matrix} EtO_2C \\ EtO_2C \end{matrix}\!\!>\!HC{-}\underset{H}{\overset{CO_2Et}{C}}{-}\underset{H_2}{C}{-}CO_2Et$$

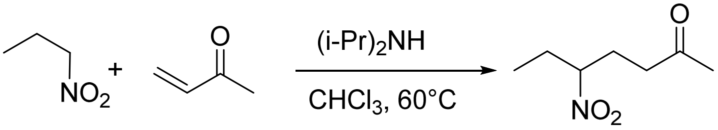
2. Preparation of methyl γ-methyl-γ-nitro valerate[13]

The reaction between and 2-nitropropane and methyl acrylate in the presence of 40% aqueous solution of benzyl trimethylammonium hydroxide (Triton B) in dioxane under reflux conditions forms the product.



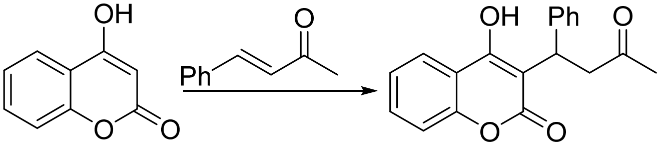
3. Preparation of 5-nitroheptan-2-one[14]

Methyl vinyl ketone reacts with 1-nitropropane catalyzed by diisopropylamine in CHCl3 under reflux to generate the product.

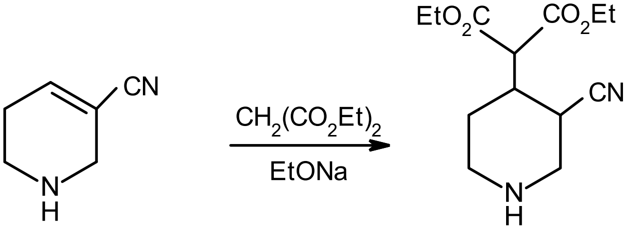


4. Preparation of warfarin[15]

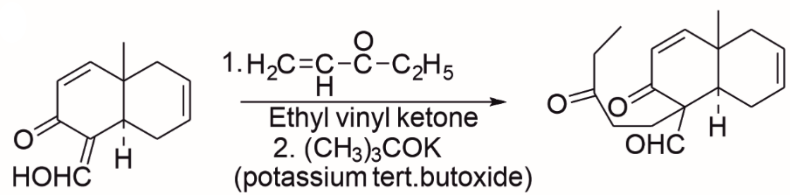
The addition reaction between 4-hydroxycoumarin and benzylideneacetone produces Warfarin by Michael reaction.



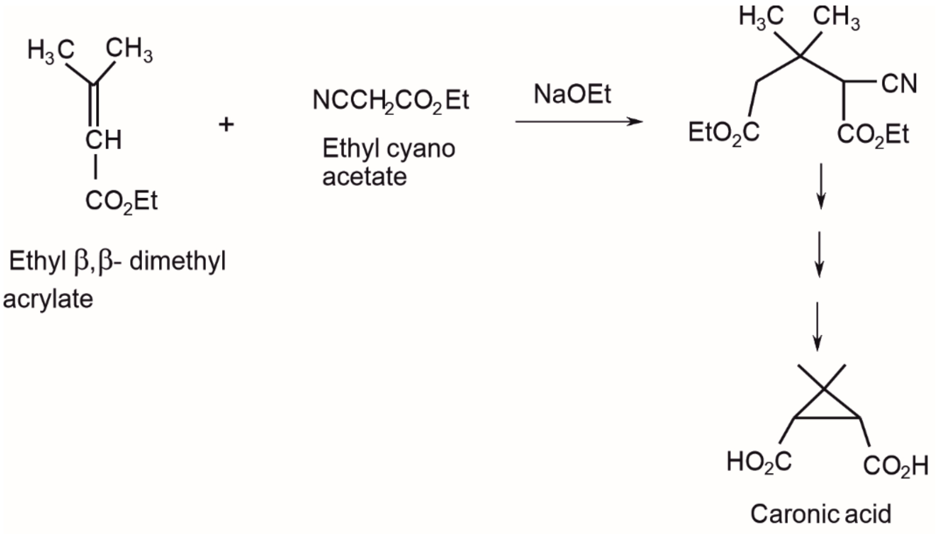
5. A step from the synthesis of cincholoiponic acid



6. An example from the total synthesis of Cholesterol by Woodward.

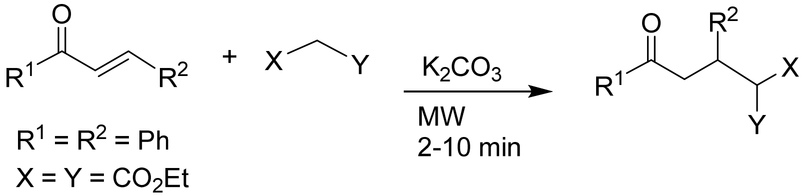


7. **Perkin and Thorpe employed Michael condensation as a step in the synthesis of caronic acid from ethyl cyanoacetate and ethyl β, β dimethyl acrylate.**



8. **Michael addition reaction mediated by microwave irradiation**[16]

Michael addition of active methylene compounds to, α,β -unsaturated carbonyl compounds take place on the surface of potassium carbonate under solvent-free microwave irradiation conditions.

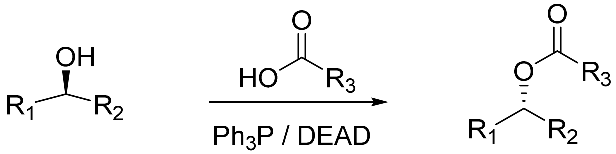


2.7 Mitsunobu reaction

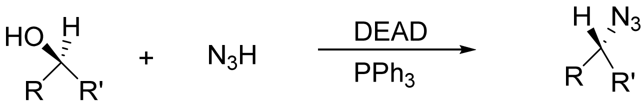
Discovered by Oyo Mitsunobu, the reaction deals with the conversion of primary and secondary alcohols into a variety of functional groups, such as an ester, phenyl ethers, thioethers, etc., using triphenyl phosphine and an azodicarboxylate like diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD). Apart from DEAD, DIAD some other azodicarboxylates also facilitate the reaction. Apart from carboxylic acids, imides, phenols, hydrazoic acid, arylsulfonylhydrazine and sulfonamides can also act as nucleophiles. Many variations and modifications as well as applications of this reaction are in practice. When a nitrogen nucleophile is involved, it is known as a Fukuyama–Mitsunobu reaction.

General reaction:

a)

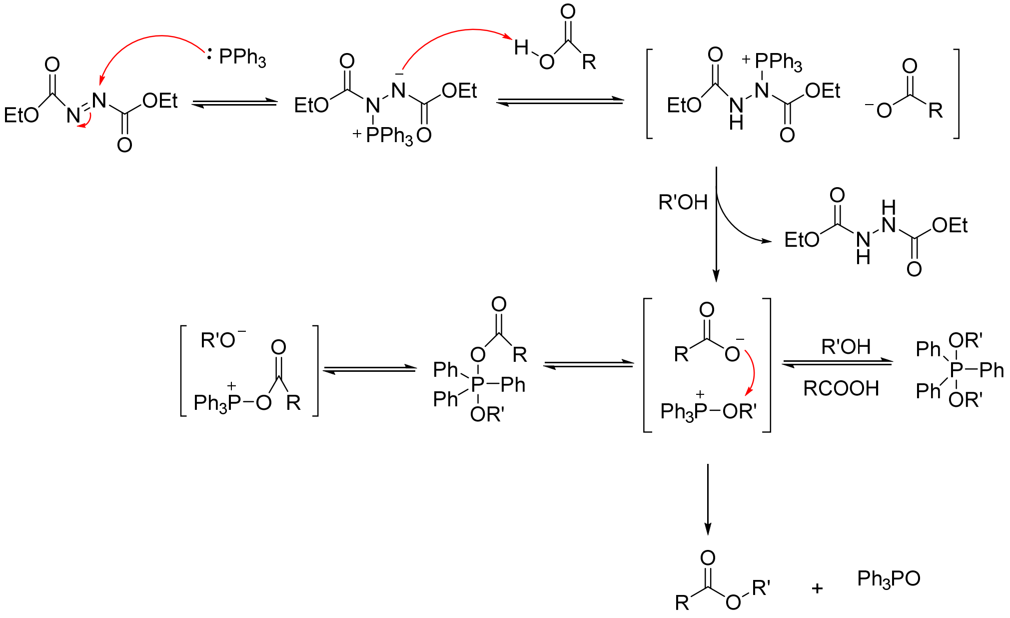


b)



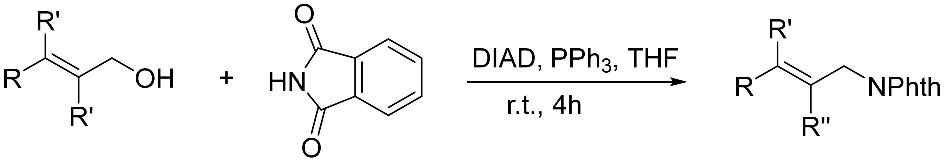
Mechanism:

Initially, a betaine intermediate is formed by the nucleophilic attack of triphenyl phosphine upon diethyl azodicarboxylate. This deprotonates the carboxylic acid to form the ion pair. The key oxophosphonium ion is formed by the alkoxide, which is produced by the deprotonation. The desired product is generated by the attack of the carboxylate anion on key oxophosphonium ion. The alcohol reacts with the phosphine and undergoes an inversion of stereochemistry in classic S_N2 mode.



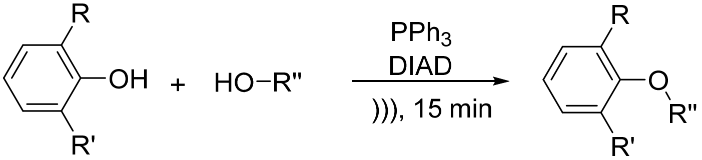
Applications and examples:

1. The Synthesis of Substituted Allylic Amines from Allylic Alcohols



2. Mitsunobu Reaction under sonication[17]

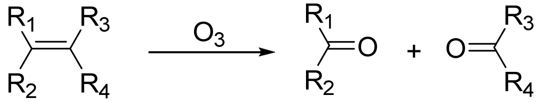
The research scientists observed that the coupling reaction of sterically hindered phenols and alcohols is greatly accelerated by the use of high reaction concentrations under sonication. The mono- and di-o-substituted phenols were reacted with cyclohexanol and neopentyl alcohol successfully.

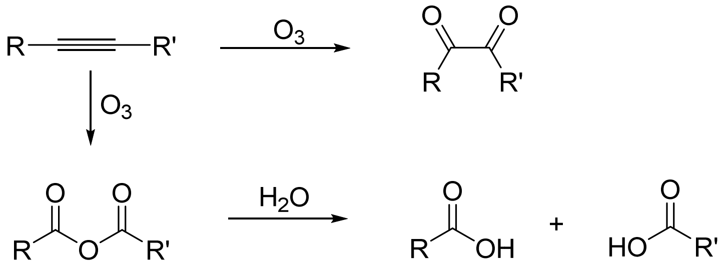


2.8 Ozonolysis Reaction

Ozonolysis is a chemical reaction where ozone is used to cleave the unsaturated bonds like alkene (C=C), alkyne, and azo compounds to determine the position of unsaturation. Ozone is a very reactive allotrope of oxygen and reacts readily with unsaturated compounds. It is discovered in 1845 by Christian Friedrich Schönbein, who discovered ozone in 1840. It is used extensively in the determination of the structure of natural products and aromatic compounds. It leads to the formation of ozonides. On hydrogenation or treatment with acid, ozonide forms a mixture containing aldehydes, ketones, or carboxylic acids. The azo compounds on ozonation give nitrosamines (N–N=O). Alkynes generally give an acid anhydride or diketone product and the anhydride hydrolyzes to give two carboxylic acids in the presence of water. The products depend on the type of multiple bonds being oxidized and the workup conditions. Ozonolysis is considered an organic redox reaction. It is conducted by bubbling ozone through the reaction medium generally in methanol at −78 °C until the solution turns to blue due to unreacted ozone. The completion of the reaction can be ascertained by the use of indicators. The ozonide is further worked up by reduction or oxidation. Reaction with NaBH4 produces alcohols. Aldehydes or ketones are produced on treating with of triphenylphosphine, thiourea, zinc dust, or dimethyl sulfide. Treatment with hydrogen peroxide generates carboxylic acid.

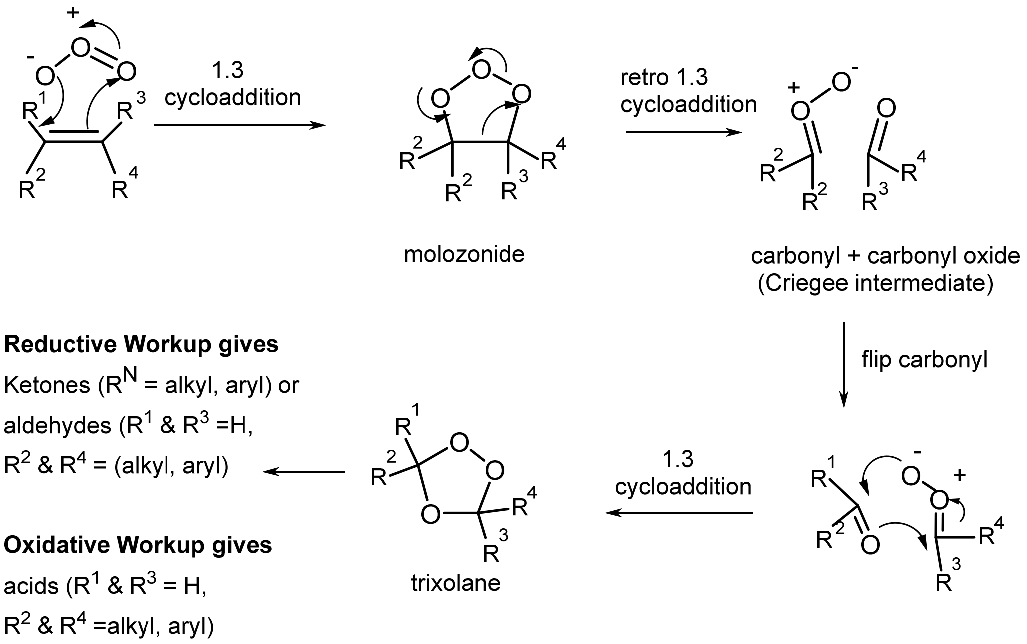
General reaction:





Mechanism:

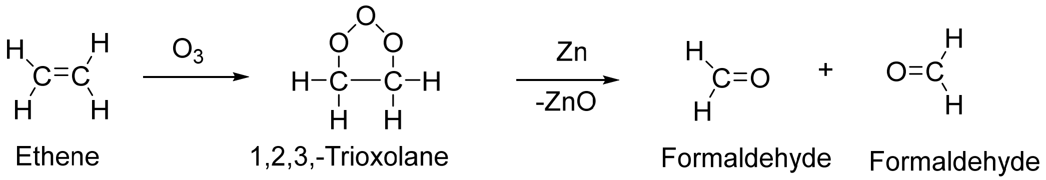
Rudolf Criegee in 1953 proposed reaction mechanism. The reaction follows 1,3-dipolar cycloadditions. Initially an intermediate molozonide is formed in a 1,3-dipolar cycloaddition, followed by reversion to the Criegee intermediate or Criegee zwitterion. Stable ozonide intermediate called trioxolane is formed by further 1,3-dipolar cycloaddition.



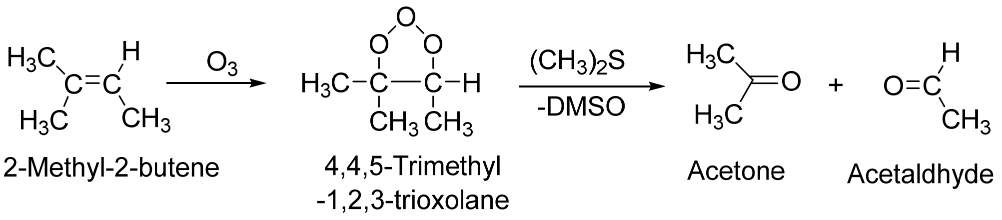
Applications and examples:

Reductive Workup

1.



2.



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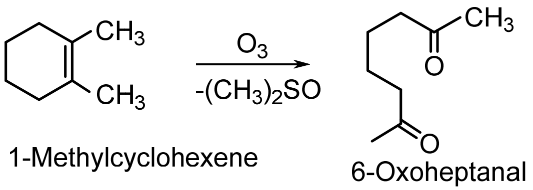
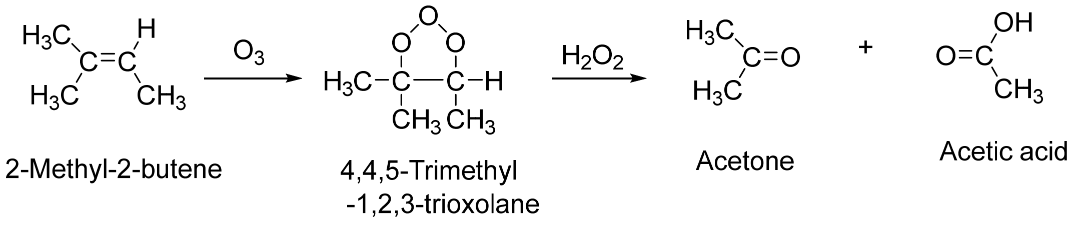


Oxidative workup (Aldehyde get oxidized to carboxylic acid)

4.

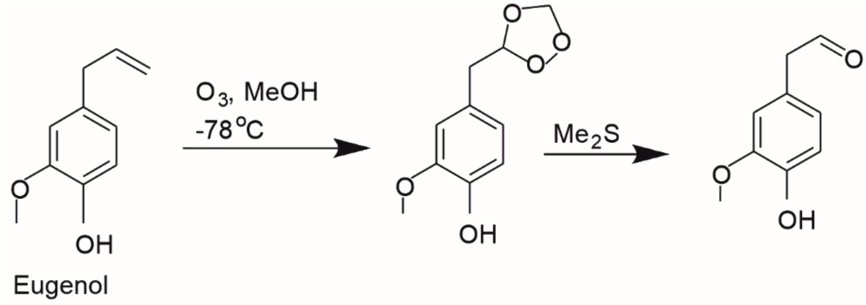


5. Ozonolysis of oleic acid

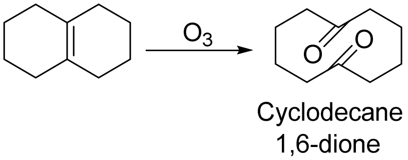
$C_8H_{17}CH{=}CHC_7H_{14}CO_2H + 4\ O_3 \longrightarrow HO_2C{-}C_7H_{14}{-}CO_2H + C_8H_{17}{-}CO_2H$

Azelaic acid Nonanoic acid

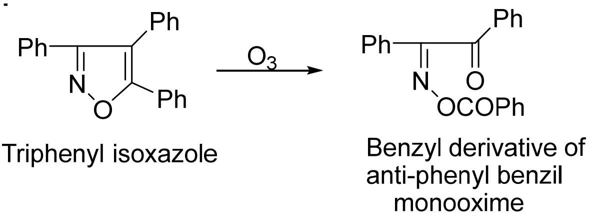
6.


O₃, MeOH
-78 °C
Me₂S
OH
OH
OH
Eugenol

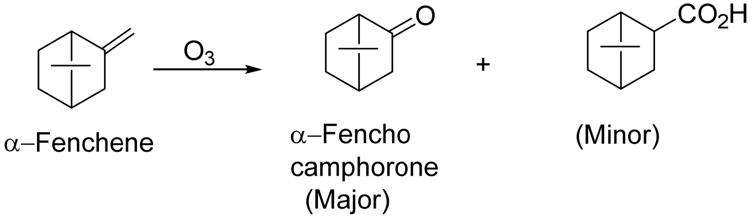
7.


O₃
O
O
Cyclodecane
1,6-dione

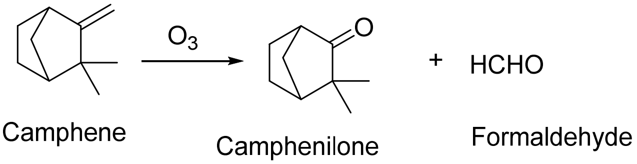
8.


Ph
Ph
N
O
Ph
O₃
Ph
Ph
N
O
OCOPh
Triphenyl isoxazole
Benzyl derivative of
anti-phenyl benzil
monooxime

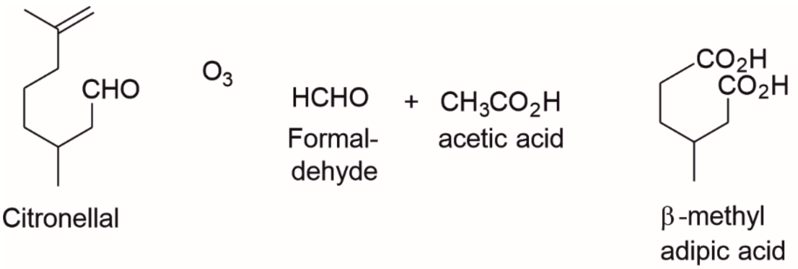
9.


O₃
O
+
CO₂H
α–Fenchene
α–Fencho
camphorone
(Major)
(Minor)

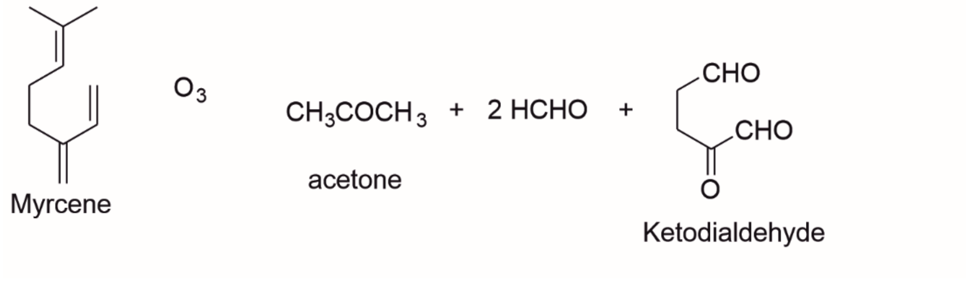
10.


O₃
O
+ HCHO
Camphene
Camphenilone
Formaldehyde

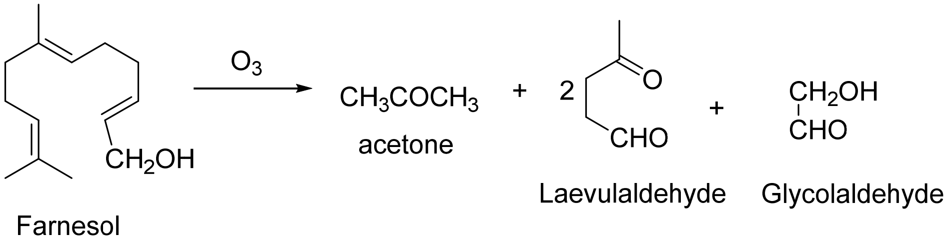
11



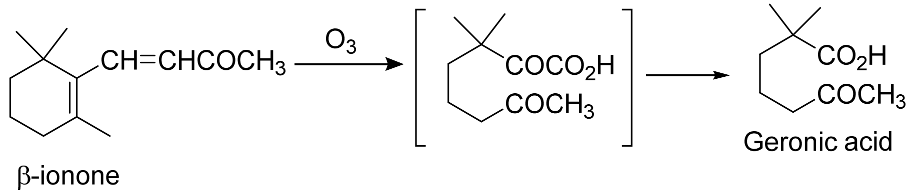
12



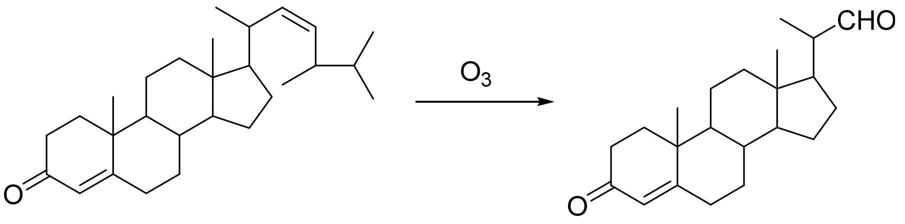
13



14



15 **From Progesterone Synthesis**

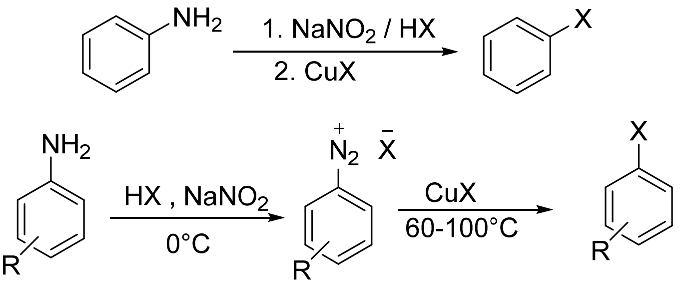


2.9 Sandmeyer reaction

The Sandmeyer reaction was first discovered in the year 1884 by Traugott Sandmeyer, a Swiss chemist. When he was carrying out a reaction to prepare phenylacetylene from benzenediazonium chloride and cuprous acetylide, he obtained phenyl chloride as the main product. This is widely used for the synthesis of aryl halides from aryl diazonium salts. In this reaction the amino group attached to an aromatic ring is converted into a diazonium salt by the treatment with nitrous acid in the presence of mineral acids (HCl or H_2SO_4) at low temperatures (0-5°C). The diazonium salt can be transformed into various functional groups. The diazonium salt is decomposed by heating with CuCl or CuBr in the presence of excess HCl or HBr resulting in aryl chlorides or bromides. In this the diazonium group acts as an excellent leaving group facilitating substitution.

It has wide utility and applicability in the organic transformations. Many variations and adaptations were developed over the original reaction leading to the generation of phenols, aryl thioethers, aryl nitriles and aryl fluorides (the Schiemann reaction). It can be categorized as a substitution reaction and an example of radical-nucleophilic aromatic substitution ($S_{RN}Ar$). Copper salts like Copper chloride, Copper bromide or Copper iodide are used as catalysts. The reaction is a two-step process, a). the formation of diazonium salts, b). conversion of diazo intermediates into aryl halides. Here N2 acts as an excellent leaving group. However, presently any reaction displacing diazo group by any nucleophile in the presence of catalytic copper(I) salts can be referred as Sandmeyer reaction. Apart from copper salts other transition metal salts like iron (III) and cobalt (III) have also been used. By virtue of the wider applicability, variations and importance this reaction is treated as complementary to electrophilic aromatic substitution.

General reaction:



X= CN, Br, Cl,SO_3H

Mechanism:

Copper has the ability to reduce the diazonium salt into aryl radical by oxidation-reduction sequence involving single electron transfer. It first reduces and then oxidizes. The formation of aryl halide by cupric ion may proceed either through carboniumion or organocopper compound.

Step I - Formation of diazonium salt.

Step II – Decomposition of diazonium salt and substitution.

Extensions of the reaction

Gattermann reaction

It uses copper bronze or copper powder in place of cuprous chloride.

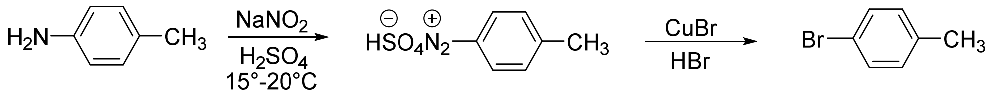
Schiemann reaction

Aryl fluorides can be prepared by reacting diazonium salt with fluoroboric acid or fluoroborate salt.

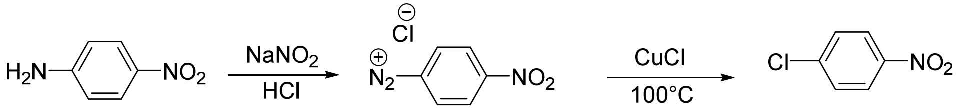
Applications and examples:

1. Preparation of aryl halides.

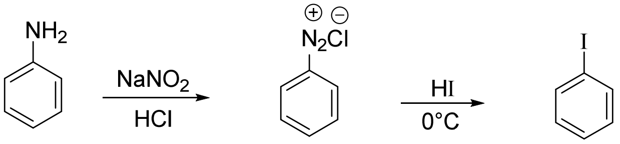
a)



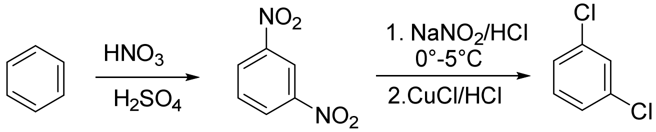
b)



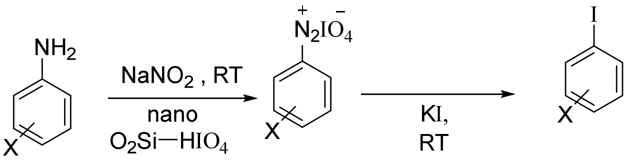
c)



d)



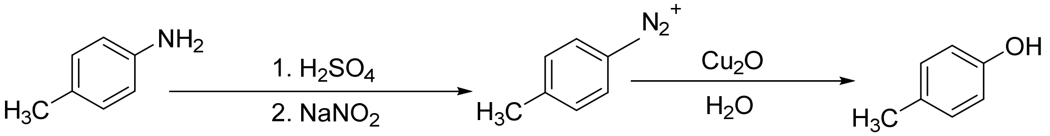
e)



X= Cl; Br; Me;
NO_2; H

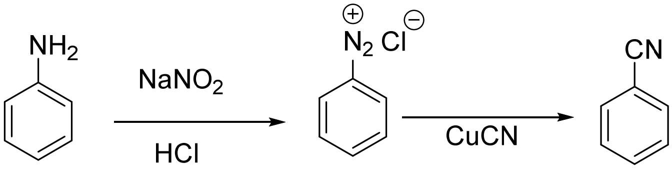
2. Preparation of phenols[18]

Aryl amines are converted to phenols at room temperature proceeding through the formation of an aryl diazonium salt, in the presence of copper catalyst.

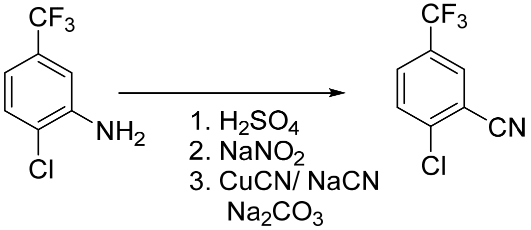


3. Preparation of benzonitriles

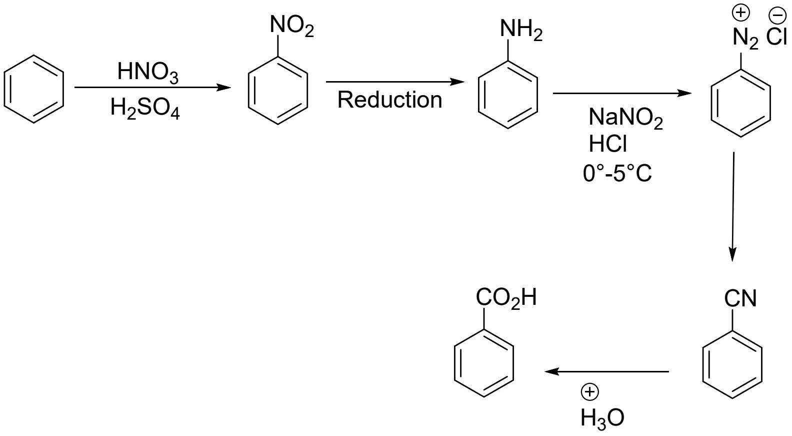
a)



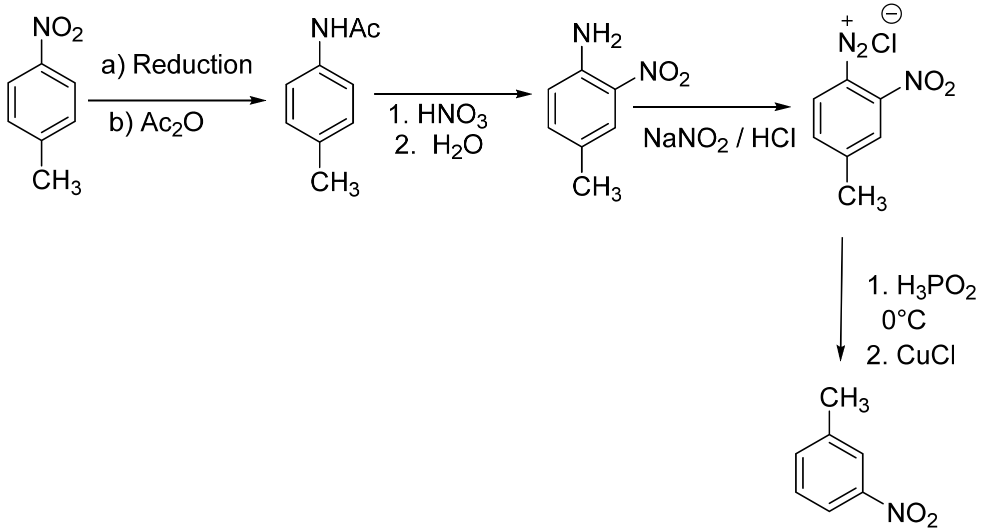
b) A new process was developed for the production of 2-chloro-5-trifluoromethyl-benzonitrile by the Sandmeyer reaction of 2-chloro-5-trifluoromethylaniline employing copper cyanide/sodium cyanide[19].



4. Preparation of benzoic acid



5. Preparation of 3- nitro toluene



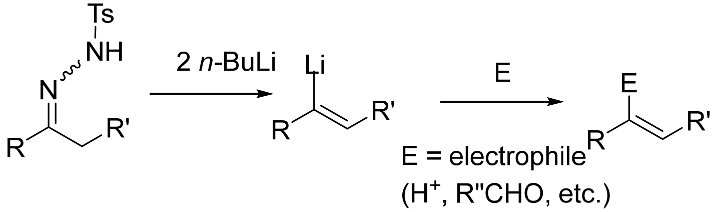
2.10 Shapiro Reaction

The Shapiro reaction, reported by Robert H. Shapiro in 1967 is a variant of the Bamford-Stevens reaction which was first reported in 1952.

These two are convenient methods for synthesizing olefinic compounds from ketones and aldehydes via sulfonyl hydrazones. In Bamford and Stevens reaction strong bases such as NaOMe, NaH, LiH, $NaNH_2$, etc. are used, whereas in the Shapiro reaction the bases like alkyllithiums and Grignard reagents are used. Both the reactions have similar mechanistic pathways. Highly substituted olefins are produced as thermodynamic products in the Bamford Stevens reaction. But in the Shapiro reaction less substituted olefins are generated because kinetic products are formed preferentially. These reactions are of interest as from simple molecules to biologically active complex molecules with double bond can be produced with the application of these reactions. Thus, Shapiro reaction involves the conversion of aryl sulfonyl hydrazones of aldehydes and ketones into olefins by reacting with alkyl lithium reagent, Grignard reagent, or alkali metal amide i.e. the basic decomposition of tosyl hydrazones. This reaction was applied in the total synthesis of Taxol reported by Prof. Nicolaou.

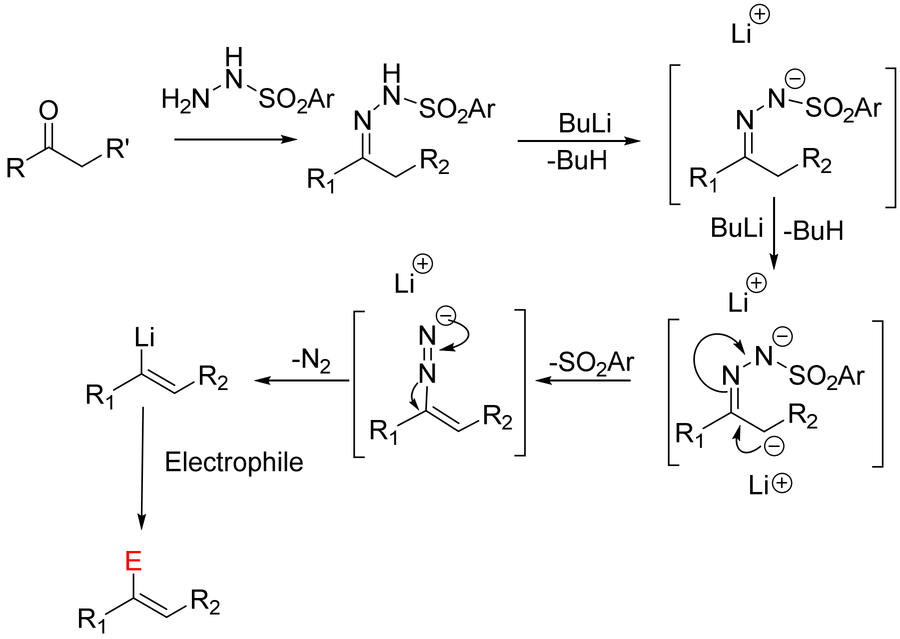
Shapiro suggested that the Shapiro reaction proceeded by a carbanion mechanism involving the approach of the alkyl lithium reagent at the least hindered and most acidic proton.

General reaction:



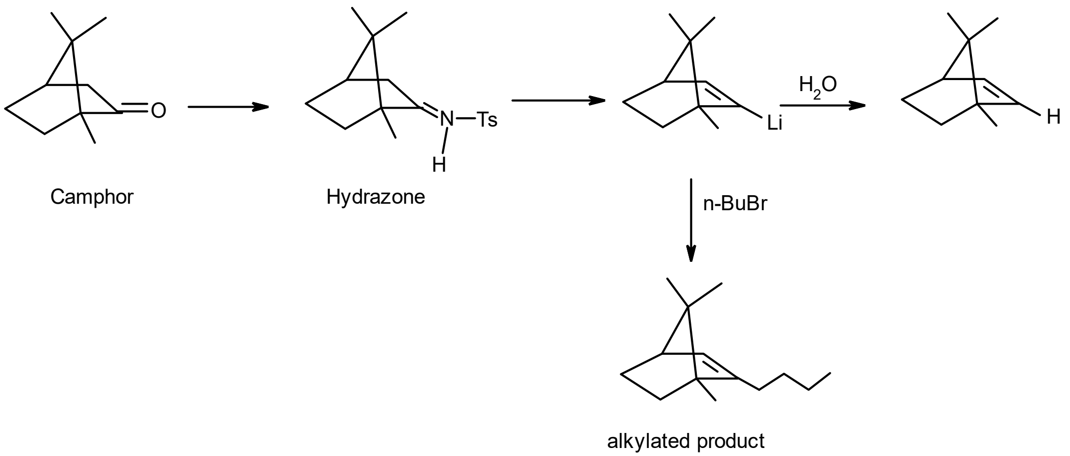
Mechanism:

Initially, a ketone / aldehyde reacts with p-toluenesulfonyl hydrazide generating tosylhydrazone. The proton from the hydrazone is abstracted by using two equivalents of strong base such as n-butyllithium followed by the less acidic proton α to the hydrazone carbon, resulting in a carbanion. This undergoes an elimination reaction affording a carbon–carbon double bond losing the tosyl anion leading to a diazonium anion. This with a loss of nitrogen molecule forms a vinyllithium species, which reacts with an electrophile or simple neutralization with water or an acid.

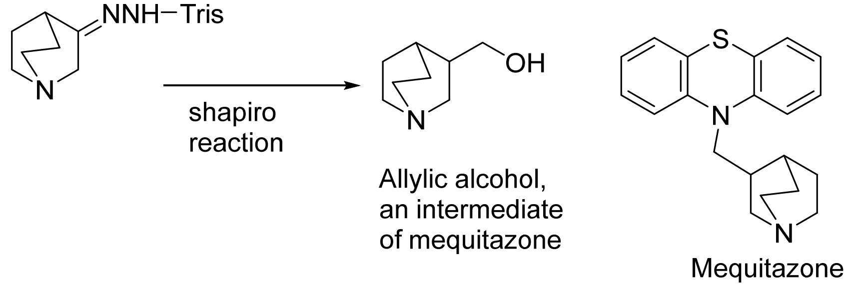


Applications and Examples:

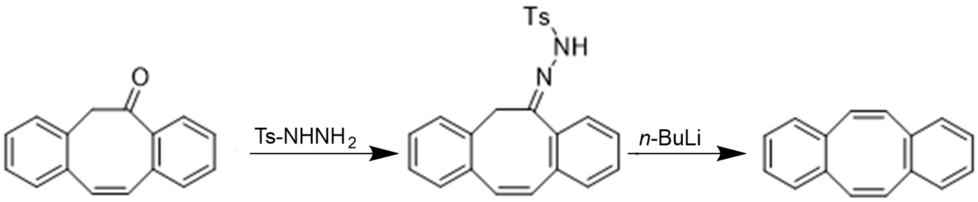
1. **Camphor forms the intermediate hydrazone which on Shapiro reaction gives the Vinyl lithium:** Addition of water results in 2-bornene and with addition of an *n*-butyl bromide affords the alkylated product.



2. **Synthesis of an intermediate of Mequitazine, an antihistamine drug:** The intermediate can be efficiently generated via the Shapiro reaction, from trisylhydrazone with excess n-BuLi followed by reacting the nucleophilic vinyl lithium reagent with paraformaldehyde.



3. **A structurally challenging polycyclic olefin was synthesized by Maier et al. by Shapiro reaction:** The ketone was converted to hydrazone, which was reacted with n-BuLi in THF affording tricyclic olefin[20].



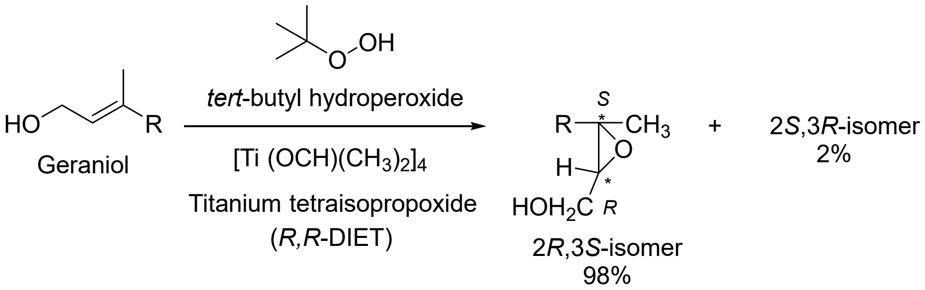
4. **Shapiro-Suzuki reaction:** The Shapiro reaction can also be combined with the Suzuki reaction to generate different olefin compounds. Keay and co-researchers developed a methodology combining both Shapiro reaction and Suzuki reaction in a one-pot process avoiding the isolation of the boronic acid. This application has a broad scope, substrate tolerance for a wide spectrum of tosylhydrazones and aryl halides, as well as several solvents and Pd sources.

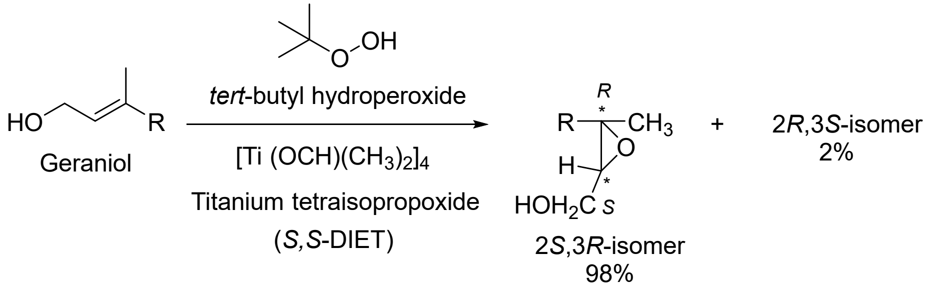
2.11 Sharpless Asymmetric Epoxidation

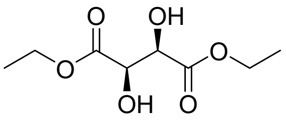
When a reaction occurs between two achiral agents, the chiral product formed consists of both enantiomers in equal amounts and called a racemic mixture. The formation of exclusively one enantiomer is very difficult. Developing enantioselective methods for the synthesis of biologically potent molecules is a challenging task.

William S. Knowles, K. Barry Sharpless, and Ryoji Noyori in their pioneering work developed in 1980-this enantioselective asymmetric epoxidation and 2001 Nobel Prize in Chemistry was awarded to them. When a chiral catalyst is used it temporarily holds the substrate molecule in an unsymmetric environment, as the nature does in case of enzymatic catalysis in biochemical reactions. When the substrate is open to a reaction to only one side, an excess of only one enantiomer is formed. Sharpless epoxidation is most popular and widely applicable to induce asymmetry in synthetic design for chiral target molecules.

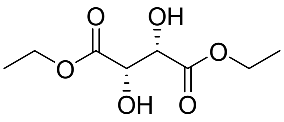
General reaction:







(*R*,*R*)-Diethyl tartarate (DIET)



(S,S)-Diethyl tartarate (DIET)

2.12 Suzuki Reaction

The Suzuki reaction, first published in 1979 by Akira Suzuki, is a cross-coupling reaction between a boronic acid and an organohalide catalyzed by a palladium(0) complex in the presence of base.

Suzuki shared the 2010 Nobel Prize in Chemistry with Richard F. Heck and Ei-ichi Negishi for the discovery and development of palladium-catalyzed cross-coupling reactions in organic synthesis. It is extensively used to prepare polyolefins, styrenes, and substituted biphenyls. It is also known as the Suzuki coupling or Suzuki–Miyaura reaction. In this reaction a new C-C bond is formed by the coupling reaction of a halide with organoboran compound catalyzed by a palladium catalyst and a base.

The advantages of Suzuki coupling are mild reaction conditions, availability of common less toxic boronic acids, use of wide variety of reagents including water-soluble reagents, as well as economical, eco-friendly, practicable nature and overall flexibility of methodology. The reagents include aryl- or vinyl-boronic acids and aryl- or vinyl-halides, pseudohalides such as triflates (OTf), as replacements for halides, Boronic esters and organtrifluoroborate salts in place of boronic acid. Frequently used solvent systems for Suzuki coupling are toluene, dioxane, THF, and DMF. The most frequently used bases are NaOH, K_2CO_3, KOtBu, K_3PO_4, Cs_2CO_3, and NEt_3. The Suzuki coupling reaction is scalable, cost-effective and widely applicable in the synthesis of intermediates for pharmaceuticals or fine chemicals and also many complex compounds. Various catalytic uses of metals other than palladium (especially nickel) have been developed. Percec and co-workers in 1995 reported the first nickel catalyzed cross-coupling reaction using aryl mesylates and boronic acids.

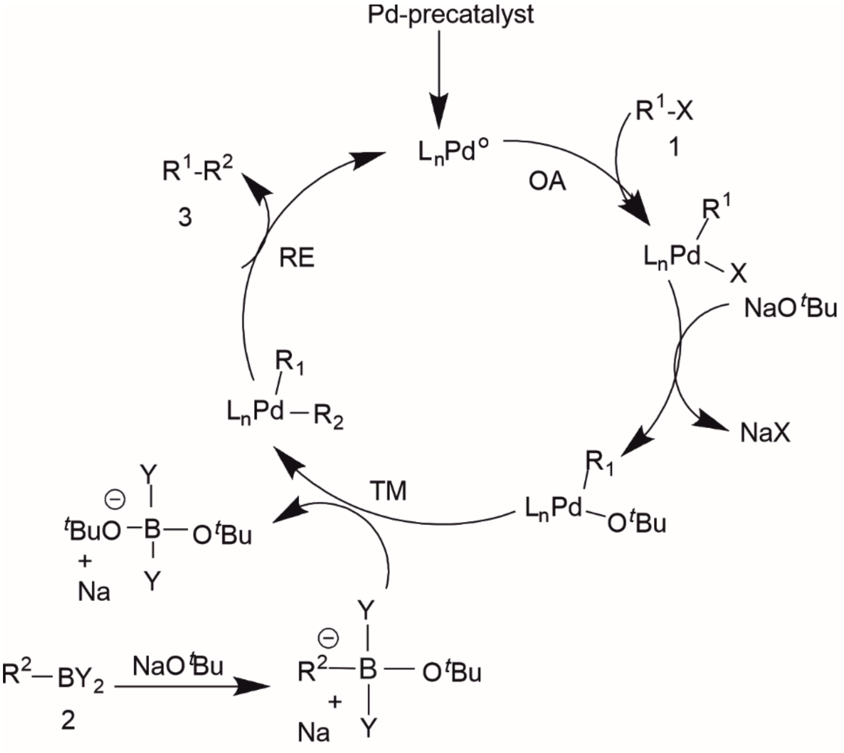
The use of nickel catalysts made the reaction possible for other substrates such as phenols, aryl ethers, esters, phosphates, and fluorides. Even though initially nickel catalyzed reactions required high catalyst loadings (3-10%), excess ligand (1-5 equivalents) and remained sensitive to air and moisture, many advancements and variations are reported making this reaction a very potential player in the development of synthetic organic chemistry.

General reaction:

$$R^1{-}X + R^2{-}BY_2 \xrightarrow{\text{[Pd]cat., base}} R^1\text{-}R^2$$

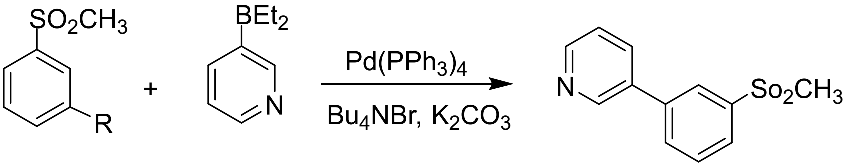
Mechanism:

The reaction is initiated by the formation of an active Pd(0) catalytic species, **A**, which forms the organopalladium intermediate B, by the oxidative addition of palladium to the halide reagent. The oxidative addition step breaks the carbon-halogen bond where the palladium is now bound to both the halogen (X) as well as the R^1 group. Oxidative addition proceeds with the retention of stereochemistry with vinyl halides. But in the case of allylic and benzylic halides it results in the inversion of stereochemistry. Even though, the cis–palladium complex is formed initially, it isomerizes to the trans-complex. This, with base gives intermediate, which via trans metalation with the boron-ate complex (produced by reaction of the boronic acid reagent with base) forms the transient organopalladium species. The product is formed by the reductive elimination, releasing the palladium catalyst. This completes a catalytic circle. Transmetalation is an organometallic reaction where ligands are transferred from one species to another. The base activates the organoboron compound and facilitates the formation of R^1-Pd^{II}-O^tBu intermediate from oxidative addition product R^1-Pd^{II}-X. The phosphine ligand is used in the Suzuki reaction. This increases the electron density at the metal center of the complex and helps in the oxidative addition step.

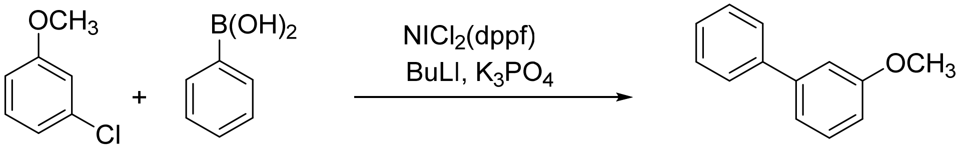


Applications

1. Coupling of 3-pyridylborane and 1-bromo-3-(methylsulfonyl)benzene.



2. Reaction of 3-chloro anisole with phenyl boronic acid



3. Preparation of Aryltrifluoroborate salts from boronic acids and potassium hydrogen fluoride, followed by the Suzuki coupling reaction.

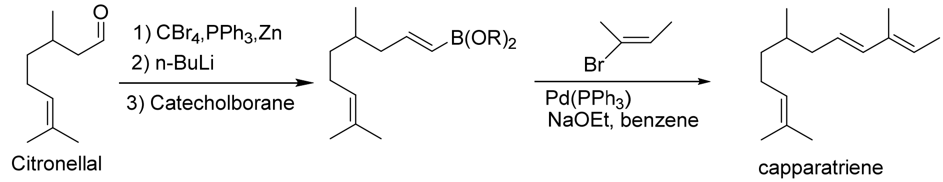
a) Aryltrifluoroborate synthesis

$$R{-}B(OH)_2 \xrightarrow{KHF_2} R{-}\overset{-}{B}F_3\ \overset{+}{K}$$

b) Aryltrifluoroborates in Suzuki reaction

$$Ar{-}Br \;+\; R{-}BF_3K \xrightarrow{\text{[Pd] cat., base}} Ar{-}R$$

4. Synthesis of capparatriene, an active compound against leukemia, from citronellal derivative[21].

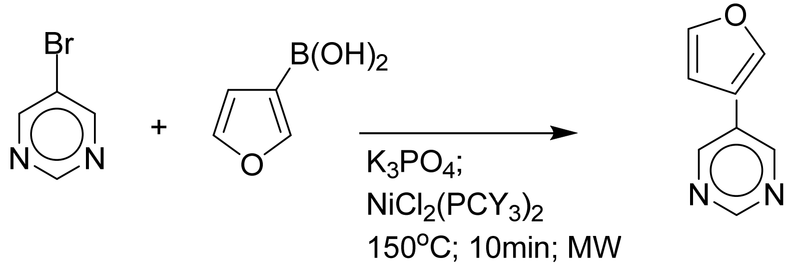


5. Suzuki-Miyaura Cross–Coupling reactions under ligand-free conditions using Pd (OAc)$_2$/TBAB/PEG-400 system as a reusable system was developed[22].

$$ArX \;+\; Ar'B(OH)_2 \xrightarrow[\text{Pd(OAc)}_2\text{;TBAB; K}_2\text{CO}_3\text{/PEG.400}]{110°\text{C; 4-24 h}} Ar{-}Ar'$$

6. Reaction of 5-bromopyrimidine with furanylboronic acid/pyridylboronic acid under microwave conditions.

a)



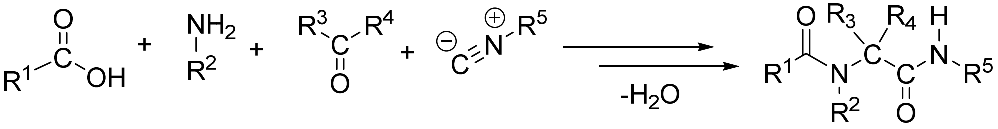
2.13 Ugi reaction

Ivar Karl Ugi first reported this reaction in 1959. It is an important, atom-economical, eco-friendly, four component condensation reaction in which an amine, aldehyde/ketone, a carboxylic acid and an isocyanide react to form a highly substituted bis-amide or α-aminoacyl amide with a loss of water molecule. The products are structurally similar to peptides. These can be called protein mimics or peptidomimetics. This isocyanide-based strategy allows multi-bond formations in a single step with wide applications. Large diversified chemical libraries can be generated using this reaction. By changing the reactants with diversified substitutions on the reactants many new biologically active compounds can be prepared. Ugi reaction can also be conducted combining with other reactions contributing for a broad range of structurally interesting compounds. This reaction is potentially applicable for pharmaceutical domain and combinatorial chemistry. Diversified molecules can be generated in minimum timeframe and energy requirements. It is also suitable to conduct under microwave, ultrasound, solvent- free conditions and also at room temperature as well as on-water. Polar protic solvents such as MeOH, EtOH, 2,2,2- trifluoroethanol (TFE) can be used as solvents. The Ugi as well as Passerini reactions are known to be accelerated in aqueous solutions, with an advantage of direct isolation by precipitation. The reaction can be conducted with high flexibility employing reactants with varied functional groups. Many natural products, macrocyclic molecules, linear and cyclic peptides and drug molecules can be generated employing the Ugi process. Merck applied this in the synthesis of an important HIV protease inhibitor-Crixivan (Indinavir-MK 639). Furanomycin isolated from *Streptomyces threomyceticus* was also prepared using Ugi method.

This reaction can also be applied in combination with other reactions like intramolecular Diels - Alder reaction, Smiles reaction, Heck reaction, Buchwald-Hartwig reaction etc.

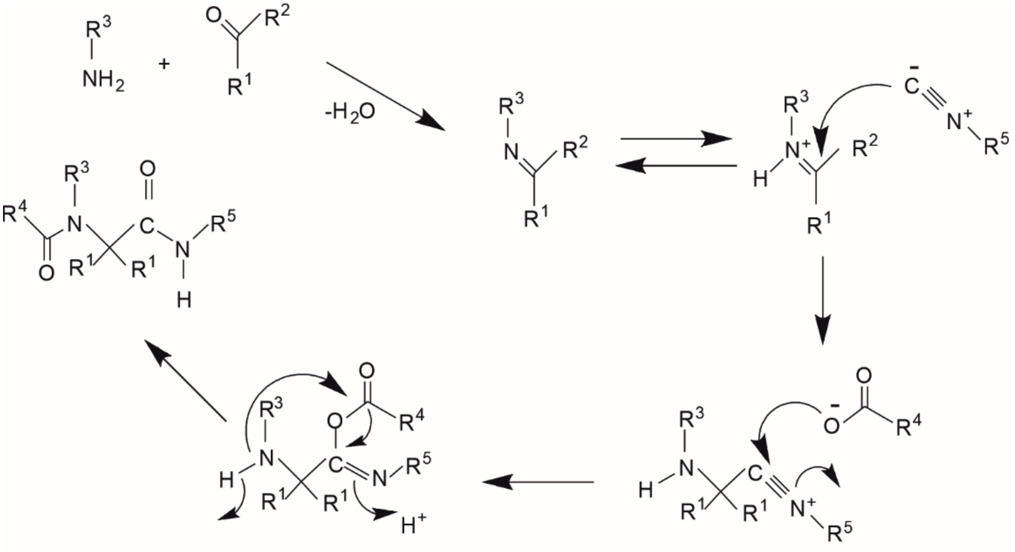
The Passerini reaction reported by Mario Passerini in 1921 involving the condensation of aldehyde or ketone, carboxylic acid and isocyanide affording α-acyloxyamide is also related to the Ugi reaction mechanistically. The Passerini reaction is a three-component reaction but does not involve amine component. Many green methods were developed such as microwave assisted and ultrasound promoted protocols for Ugi reaction.

General reaction:



Reaction Mechanism:

Initially, amine reacts with the ketone with a loss of water molecule. An iminium ion is formed by the proton exchange with carboxylic acid. Nucleophilic attack of isocyanide on the iminium ion forms nitrilium ion. Carboxylic acid anion attacks the imino carbon producing acylated isoamide. This rearranges by acyl transfer producing bis-amide.



Applications and Examples

1. Ugi-Smiles reaction

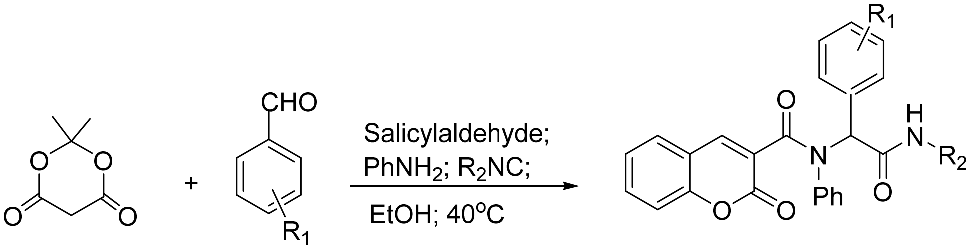
The Ugi-Smiles reaction is a powerful and widely applied strategy to get N-arylamines from phenolic substrates. In this reaction amines, carbonyl compounds, isocyanides and phenols with withdrawing groups are used as reactants. Here carboxylic acid of Ugi reaction is replaced by a o-nitrophenol, p-nitrophenol or a salicylate. It is useful in the preparation of N-aryl primary amines. The Smiles reaction takes place in the last step. Different post-condensation strategies of this reaction result in the generation of various fused heterocyclic systems such as quinoxalines, benzimidazoles, benzotriazoles, azepines etc.,

2. Ugi-Diels -Alder reaction

A one-pot, four-component approach involving Ugi reaction followed by an intramolecular Diels–Alder reaction for the preparation of arene-fused iso indolinones is developed[23].

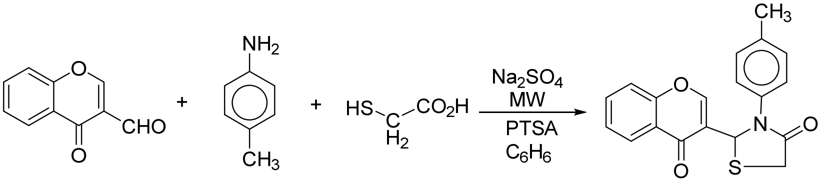
3. Knoevenagel-Ugi reaction

An efficient one-pot multicomponent Knoevenagel-Ugi condensation reaction was carried out by S. Kumar et al. From salicylaldehyde, aniline, benzaldehyde derivatives, isonitrile and 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrums acid) at 40ºc in EtOH affording coumarin based Knoevenagel-Ugi adducts by the sequential reactions. This method offers atom-economic, operationally facile process under mild reaction conditions[24].



4. Ugi reaction by Microwave irradiation

2-(4-Oxo-4H-1- benzopyran-3yl)-4-thiazolidinones were produced by Zhong-Zheng Zhou et al., using microwave-assisted parallel syntheses following combinatorial approach[25].

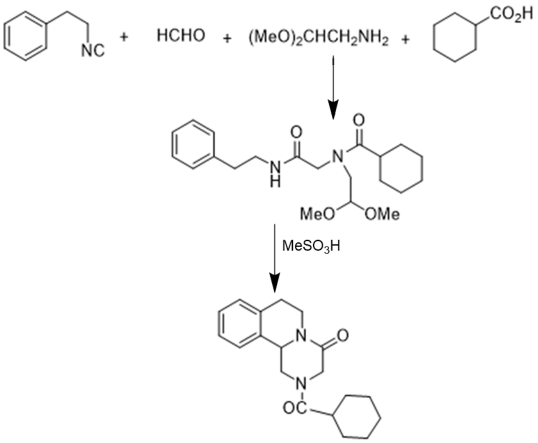


5. Ultrasound-assisted Ugi reaction

Some 2,5-diketopiperazine linked 1,4-disubstituted 1,2,3-triazole derivatives were prepared via the Ugi-4CR/lactamization/click sequence under mild, atom-economical, and ultrasound conditions[26].

6. Synthesis of Praziquantel

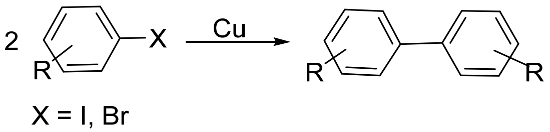
With a pyrazonoisoquinoline ring system, the compound is widely used as a drug for schistosomiasis. It is prepared via Ugi reaction under mild conditions[27].



2.14 Ullmann Coupling Reactions

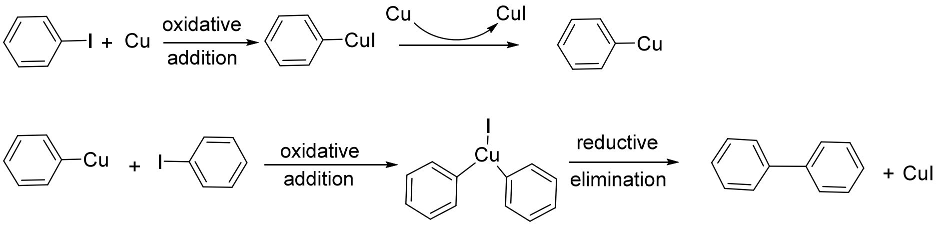
Ullmann cross-coupling reaction, or Ullmann coupling reaction or Ullmann reaction involves the coupling of two aryl halides into a biaryl product in the presence of finely divided copper or copper bronze at elevated temperatures (100-350 °c). It is named after Fritz Ullmann, a German chemist who reported this in 1901. Original Ullmann reaction requires harsh reaction conditions, but over the years many improvements were made and variations of the reaction were reported. Even though traditionally copper was used as catalyst, the use of palladium and nickel as catalysts widened the scope of the reaction. It is the most important and widely applied reaction. The mechanism and reaction conditions of the reaction were extensively studied. Copper-assisted cross-coupling reactions of aryl halides to aryl ethers or aryl thioethers, or aryl nitriles and aryl amines also come under this class of reactions. Generally, the reaction requires higher reaction temperatures and higher boiling polar solvents. Aryl iodides react with ease than aryl chlorides and bromides which require activation by an electronegative group placed on the aromatic ring. In the "classic" Ullmann reaction symmetric biaryls are produced from aryl halides via copper-catalyzed coupling. Ullmann-type" reactions cover the nucleophilic aromatic substitutions between different nucleophiles (e.g. substituted phenoxides) and aryl halides catalyzed by copper. Large number of biaryl and polyaryl compounds can be prepared by this method. Nitro group strongly activates the aryl halides particularly from ortho position whereas alkyl and alkoxy groups activate from any position.

General reaction:



Mechanism:

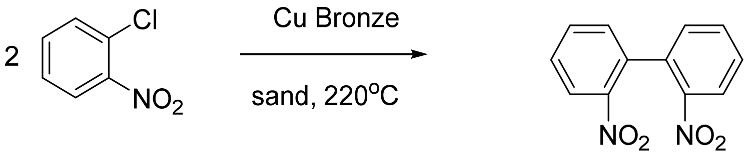
Copper reacts with aryl halide oxidatively to form Cu(I) compound by the elimination of CuI, which undergoes second oxidative addition with aryl halide followed by reductive elimination affording symmetrical biaryl. The reaction is more similar to Wurtz reaction. In most of the cases the yields are high.



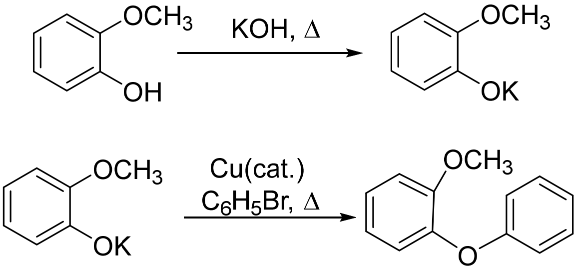
Applications and examples:

1. Preparation of 2,2'-Dinitrobiphenyl

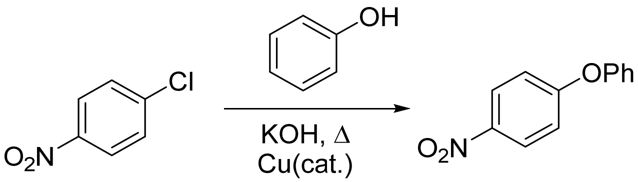
o-Chloronitrobenzene and copper bronze are heated in clean dry sand at 215–225 °C to afford the product.



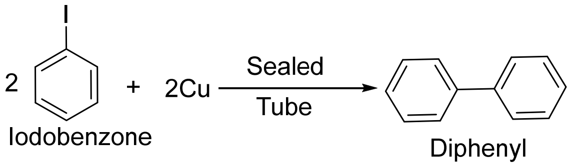
2. Preparation of 2-Methoxy diphenyl ether



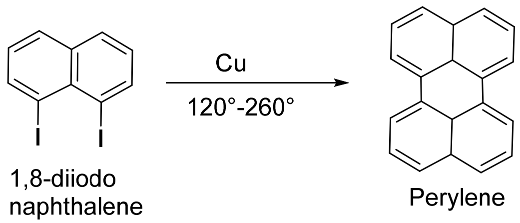
3. Preparation of 4-Nitro diphenyl ether



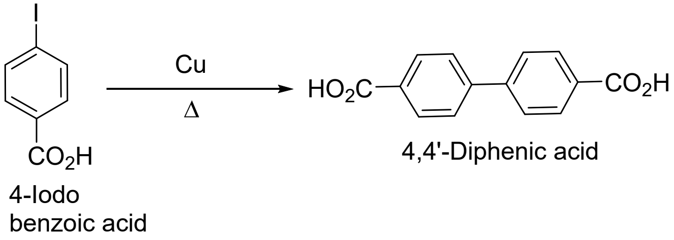
4. Preparation of diphenyl



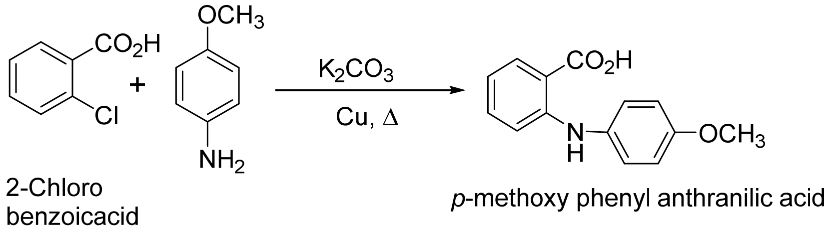
5. Preparation of perylene



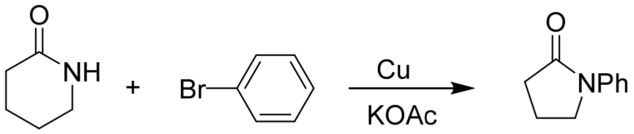
6. Preparation of 4,4- diphenic acid



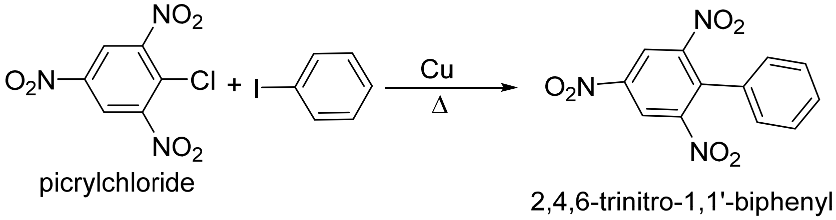
7. Preparation of 4-methoxyphenyl anthranilic acid



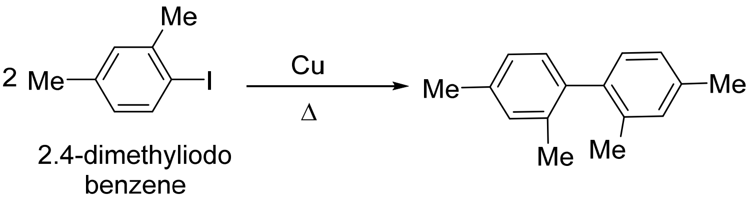
8. Preparation of 2-oxo-1-phenyl tetrahydropyrrole



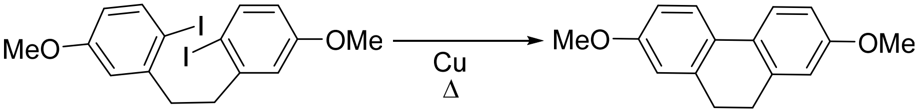
9. Preparation of 2,4,6- trinitro biphenyl



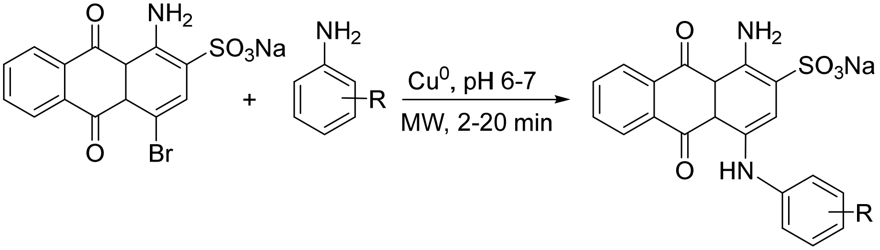
10. Preparation of 2,2,4,4 –tetramethyl biphenyl



11. Preparation of 2,7-dimethoxy-9,10-dihydro phenanthrene



12. Microwave-assisted Ullmann coupling reaction[28]

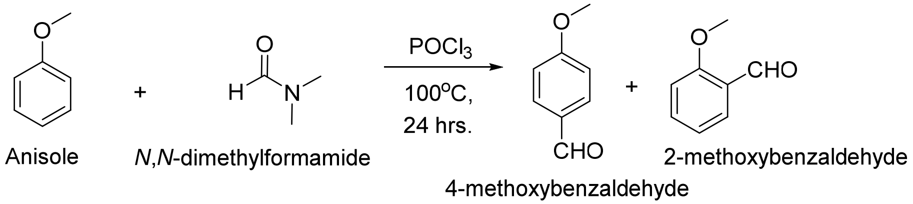


2.15 Vilsmeyer-Haack Reaction

In 1927, Vilsmeier and Haack reported the formylation of electron-rich aromatic or heterocyclic compounds. Dimethylformamide is used as an acylating agent. Activating agents such as phosphorus oxychloride or cobalt chloride are used. The iminium salt complex which is formed between DMF and activating agent is known as Vilsmeier-Haack reagent.

This is very useful reaction for reactive aromatics and heterocycles such as thiophenes, pyrroles, indoles, acridines, carbazoles and ferrocenes. Similar to Friedel-crafts acylation, in this also regioselectivity plays significant role and depends on the electron density of the attacked position in the reactant molecule.

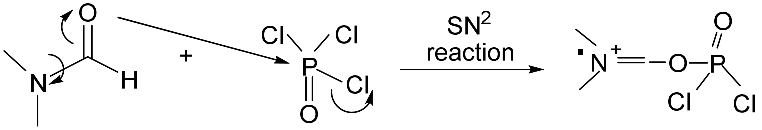
General reaction:



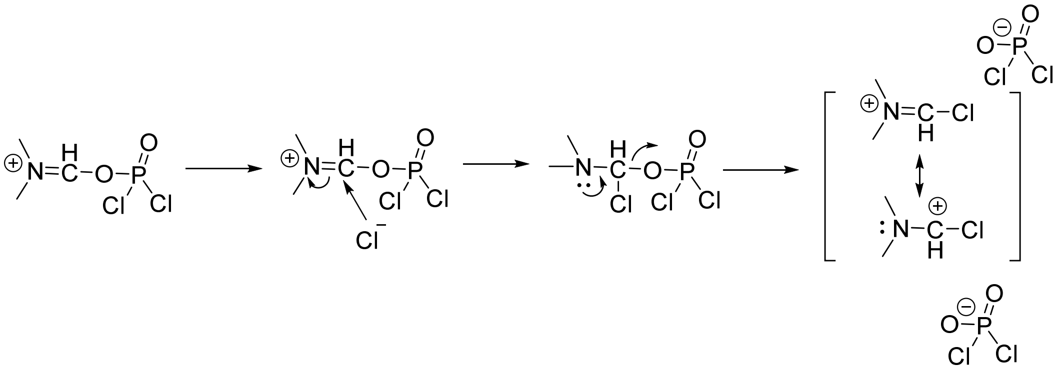
Mechanism:

Step 1: Nucleophilic substitution

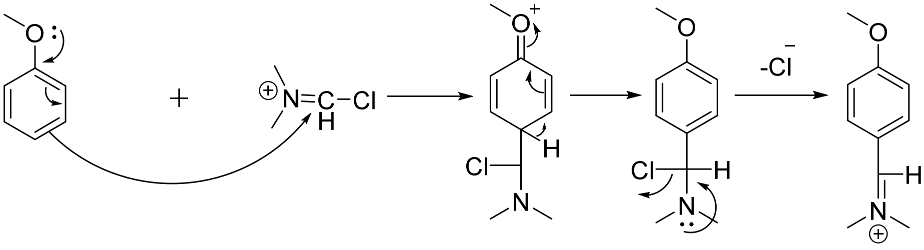
Reaction between phosphorus oxychloride and *N*,*N*-dimethylformamide



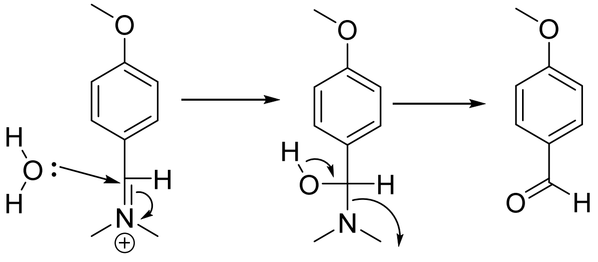
Step 2: Formation of Vilsmeier-Haack reagent



Step 3: Reaction between reactant and Vilsmeier-Haack reagent

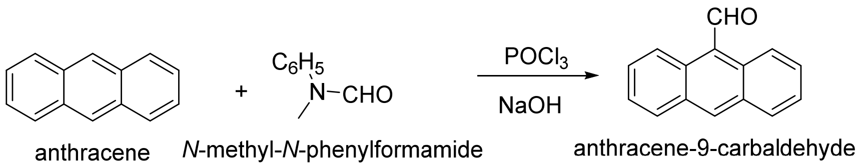


Step 4: Workup

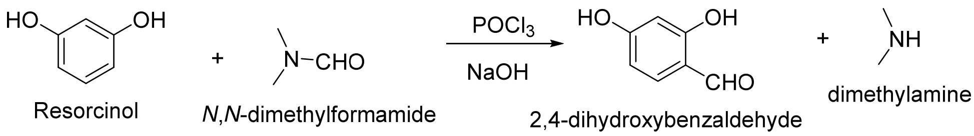


Applications:

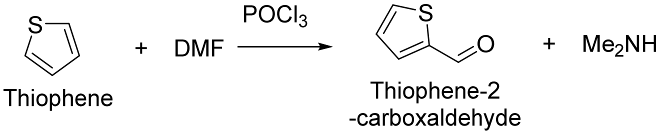
1.



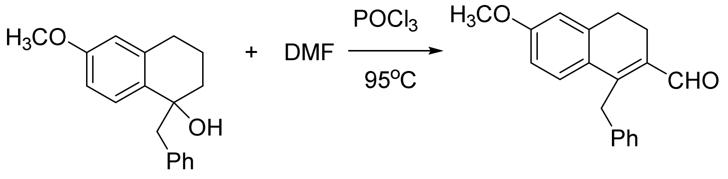
2.



3.



4.



5. Under the microwave irradiation[29].