Srinivasan College of Arts and Science
Perambalur 621 212
Department of Chemistry

Course Material

For II M.Sc Students

Subject Code: P16CHE4A Subject: Green Chemistry

UNIT-1 **Introduction to Green Chemistry**

Green Chemistry: Green chemistry is defined as environmentally benign chemical synthesis. The synthetic schemes are designed in such a way that there is least pollution to the environment.

MOTO of Green Chemistry: It is best to carry out reactions in the aqueous phase. Synthetic methods should be designed in such a way that the starting materials are consumed to the maximum extent in the final product. The reaction should also not generate any toxic by-products.

***Twelve principles of Green Chemistry*:**

The following basic principles of green chemistry have been formulated:

- Prevention of waste/by-products.
- Maximum incorporation of the reactants (starting materials and reagents) into the final product.
- Prevention or minimization of hazardous products.
- Designing of safer chemicals.
- Energy requirement for any synthesis should be minimum.
- Selecting the most appropriate solvent.
- Selecting the appropriate starting materials.
- Use of the protecting group should be avoided whenever possible.
- Use of catalysts should be preferred wherever possible.
- Products obtained should be biodegradable.
- The manufacturing plants should be so designed as to eliminate the possibility of accidents during operations.
- Strengthening of analytical techniques to control hazardous compounds.

i) Prevention of Waste/By-Products

It is most advantageous to carry out a synthesis in such a way so that formation of waste (by-products) is minimum or absent. It is especially important because in most of the cases the cost involved in the treatment and disposal of waste adds to the overall production cost. Even the unreacted starting materials (which may or may not be hazardous) form part of the waste. Hence, the next basic principle is important and should carefully be considered as "prevention is better than cure" applies in this case also. In other words, the formation of the waste (or by-products) should be avoided as far as possible. The waste (or by-products) if discharged (or disposed off) in the atmosphere, sea or land not only causes pollution but also requires expenditure for cleaning-up.

ii) Maximum Incorporation of the Reactants (Starting Materials and Reagents) into the Final Product

Chemists globally consider that if the yield of a reaction is about 90%, the reaction is good. The percentage yield is calculated by

$$\%\ \text{yield} = \frac{\text{Actual yield of the product}}{\text{Theoretical yield of the product}} \times 100$$

In other words, if one mole of a starting material produces one mole of the product, the yield is 100%. Such synthesis is deemed perfectly efficient by this calculation. A perfectly efficient synthesis according to the percentage yield calculations may, however, generate significant amount of waste (or by-products) which is not visible in the above calculation. Such synthesis is not green synthesis. Typical examples like Wittig reaction and the Grignard reactions illustrate the above contention. Both these reactions may proceed with 100% yield but do not take into account the large amounts of by-products obtained.

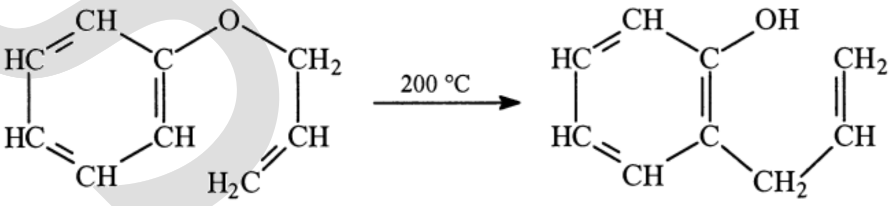
The reaction or the synthesis is considered to be green if there is maximum incorporation of the starting materials and reagents in the final product. We should take into account the percentage atom utilization, which is determined by the equation,

$$\%\ \text{atom utilization} = \frac{\text{MW of desired product}}{\text{MW of (desired product + waste products)}} \times 100$$

The concept of atom economy developed by B.M. Trost is a consideration of 'how much of the reactants end up in the final product'. The same concept determined by R.A. Sheldon is given as,

$$\%\ \text{atom economy} = \frac{\text{FW of atoms utilized}}{\text{FW of the reactants used in the reaction}} \times 100$$

a) Rearrangement Reactions: These reactions involve rearrangement ofthe atoms that make up a molecule. For example, allyl phenyl ether on heating at 200°C gives o-allyl phenol.



Allyl phenyl ether o-Allyl phenol

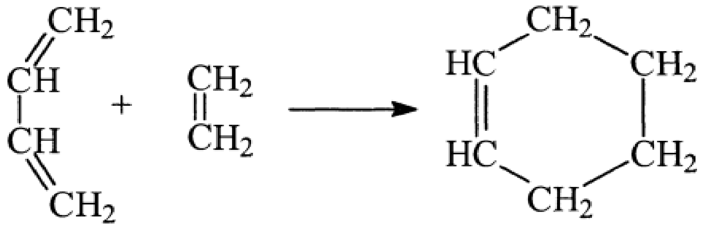
This is a 100% atom economical reaction, since all the reactants are incorporated into the product.

b) Addition Reactions: Consider the addition of hydrogen to an olefin.

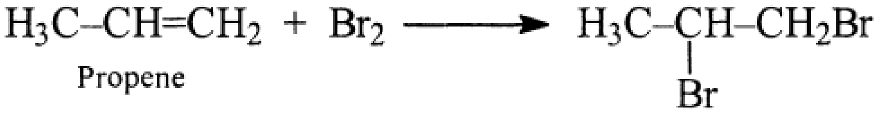
$$H_3C{-}CH = CH_2 + H_2 \xrightarrow{Ni} H_3C{-}CH_2{-}CH_3$$

Propene Propane

Here also, all elements of the reactants (propene and hydrogen) are incorporated in the final product (propane). The reaction is a 100% atom economical reaction. Similarly, cycloaddition reactions and bromination of olefins are 100% atom economical reactions.



Butadiene Cyclohexene

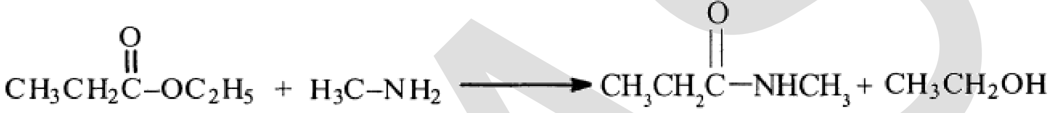


$$H_3C{-}CH{=}CH_2 + Br_2 \longrightarrow H_3C{-}CH(Br){-}CH_2Br$$

Propene

1,2-Dibromopropane

c) Substitution Reactions: In substitution reactions, one atom (or group of atoms) is replaced by another atom (or group of atoms). The atom or group that is replaced is not utilised in the final product. So the substitution reaction is less atom-economical than rearrangement or addition reactions. Consider the substitution reaction of ethyl propionate with methyl amine.



$$CH_3CH_2C(=O){-}OC_2H_5 + H_3C{-}NH_2 \longrightarrow CH_3CH_2C(=O){-}NHCH_3 + CH_3CH_2OH$$

Ethyl propionate Methyl amine Propionamide Ethyl alcohol

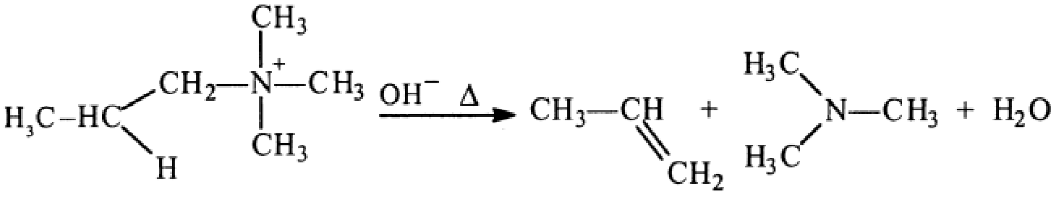
In this reaction, the leaving group (OC_2H_5) is not utilised in the formed amide. Also, one hydrogen atom of the amine is not utilised. The remaining atoms of the reactants are incorporated into the final product. The total of atomic weights of the atoms in reactants that are utilised is 87.106 g/mole, while the total molecular weight including the reagent used is 133.189 g/mole (see table). Thus, a molecular weight of 46.069 g/mole remains unutilised in the reaction.

	Reactants		Utilised		Unutilised	
	Formula	FW	Formula	FW	Formula	FW
	$C_5H_{10}O_2$	102.132	C_3H_5O	57.057	C_2H_5O	45.061
	CH_5N	31.057	CH_4N	30.049	H	1.008
Total	$C_6H_{15}NO_2$	133.189	C_4H_9NO	87.106	C_2H_5OH	46.069

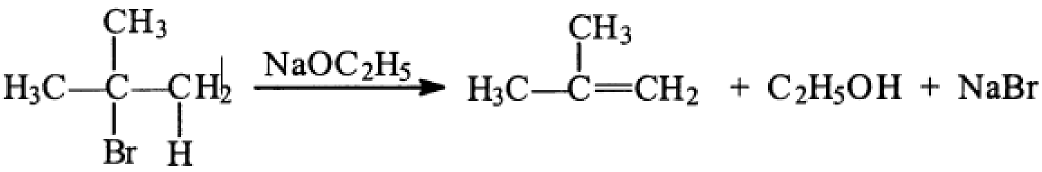
Therefore, the % atom economy = $\frac{87.106}{133.189} \times 100 = 65.40$ %.

d) Elimination Reactions: In an elimination reaction, two atoms or group of atoms are lost from the reactant to form a π-bond.

Consider the following Hofmann elimination,



The elimination reaction is not very atom-economical. The percentage atom economy is 35.30%. In fact this is least atom-economical of all the above reactions. Consider another elimination reaction involving the dehydrohalogenation of 2-bromo-2-methylpropane with sodium ethoxide to give 2-methylpropene.



$$H_3C-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle Br}{|}}{C}}-\underset{\underset{\displaystyle H}{|}}{CH_2} \xrightarrow{NaOC_2H_5} H_3C-\overset{\overset{\displaystyle CH_3}{|}}{C}=CH_2 + C_2H_5OH + NaBr$$

This dehydrohalogenation (an elimination reaction) is also not very atom-economical. The percentage atom economy or utilization is 27% which is even less atom-economical than the Hofmann elimination reaction.

iii) Prevention or Minimization of Hazardous Products

The most important principle of green chemistry is to prevent or at least minimize the formation of hazardous products, which may be toxic or environmentally harmful. The effect of hazardous substances if formed may be minimised for the workers by the use of protective clothing, engineering controls, respirator etc. This, however, adds to the cost of production. It is found that sometimes the controls can fail and so there is much more risk involved. Green chemistry, in fact, offers a scientific option to deal with such situations.

iv) Designing Safer Chemicals

It is of paramount importance that the chemicals synthesised or developed (e.g. dyes, paints, adhesives, cosmetics, pharmaceuticals etc.) should be safe to use. A typical example of an unsafe drug is thalidomide (introduced in 1961) for lessening the effects of nausea and vomiting during pregnancy (morning sickness). The children born to women taking the drug suffered birth defects (including missing or deformed limbs). Subsequently, the use of thalidomide was banned, the drug withdrawn and strict regulations passed for testing of new drugs, particularly for malformation-inducing hazards. With the advancement of technology, the designing and production of safer chemicals has become possible. Chemists can now manipulate the molecular structure to achieve this goal.

v) Energy Requirements for Synthesis

In any chemical synthesis, the energy requirements should be kept to a minimum. For example, if the starting material and the reagents are soluble in a particular solvent, the reaction mixture has to be heated to reflux for the required time or until the reaction is complete. In such a case, time required for completion should be minimum, so that bare minimum amount of energy is required. Use of a catalyst has the great advantage of lowering the energy requirement of a reaction.

In case the reaction is exothermic, sometimes extensive cooling is required. This adds to the overall cost. If the final product is impure, it has to be purified by distillation, recrystallisation or ultrafiltration. All these steps involve the use of energy. By designing the process such that there is no need for separation or purification, the final energy requirements can be kept at the bare minimum.

vi) Selection of Appropriate Solvent

The solvent selected for a particular reaction should not cause any environmental pollution and health hazard. The use of liquid or supercritical liquid CO_2 should be explored. Ifpossible, the reaction should be carried out in aqueous phase or without the use a of solvent (solventless reactions). A better method is to carry out reactions in the solid phase.

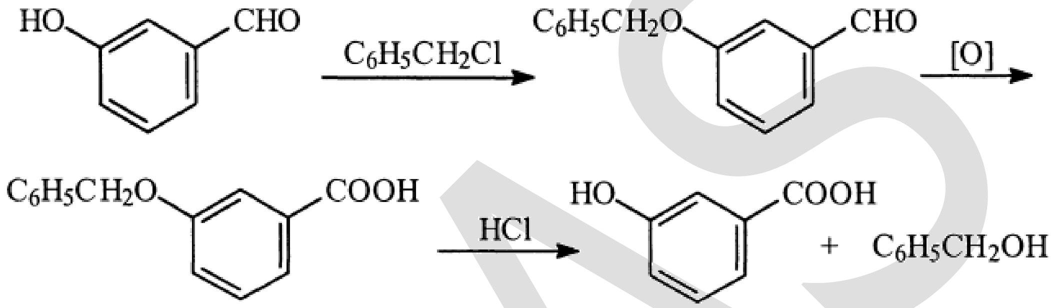
One major problem with many solvents is their volatility that may damage human health and the environment. To avoid this, a lot of work has been carried out on the use of immobilised solvents. The immobilised solvent maintains the solvency of the material, but it is non-volatile and does not expose humans or the environment to the hazards of that substance. This can be done by tethering the solid molecule to a solid support or by binding the solvent molecule directly on to the backbone of a polymer. Some new polymer substances having solvent properties that are non-hazardous are also being discovered.

vii) Selection of Starting Materials

Starting materials are those obtained from renewable or non-renewable material. Petrochemicals are mostly obtained from petroleum, which is a non-renewable source in the sense that its formation takes millions of years from vegetable and animal remains. The starting materials which can be obtained from agricultural or biological products are referred to as renewable starting materials. The main concern about biological or agricultural products however, is that these cannot be obtained in continuous supply due to factors like crop failure etc.

viii) Use of Protecting Groups

In case an organic molecule contains two reactive groups and you want to use only one of these groups, the other group has to be protected, the desired reaction completed and the protecting group removed. For example,



Reactions of this type are common in the synthesis of fine chemicals, pharmaceuticals, pesticides etc. In the above protection, benzyl chloride (a known hazard) and the waste generated after deprotection should be handled carefully.

Thus, we see that the protecting groups that are needed to solve a chemoselectivity problem should be added to the reaction in stoichiometric amounts only and removed after the reaction is complete. Since these protecting groups are not incorporated into the final product, their use makes a reaction less atom-economical. In other words the use of protective group should be avoided whenever possible. Though atom-economy is a valuable criteria in evaluating a particular synthesis as 'green', other aspects of efficiency must also be considered.

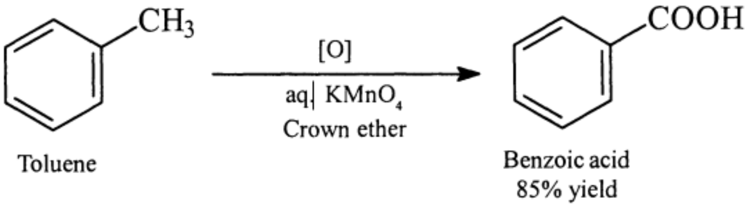
ix) Use of Catalyst

It is well known that use of a catalyst facilitates transformation without the catalyst being consumed in the reaction and without being incorporated in the final product. Therefore, use of catalyst should be preferred whenever possible. Some of the advantages are:

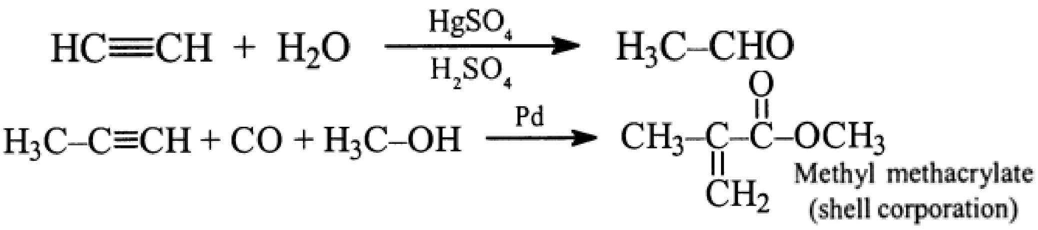
(a) Better yields. Hydrogenation or reduction of olefins in presence of nickel catalyst,

$$\underset{\text{Propene}}{H_3C{-}CH{=}CH_2} + H_2 \xrightarrow{Ni} \underset{\text{Propane}}{H_3C{-}CH_2{-}CH_3}$$

$$\underset{\text{Benzyl chloride}}{C_6H_5CH_2Cl} + \text{aqueous } KCN \xrightarrow[\text{Catalyst}]{\text{Phase transfer}} \underset{\text{Benzyl cyanide}}{\underset{\text{90\% yield}}{C_6H_5CH_2CN}}$$



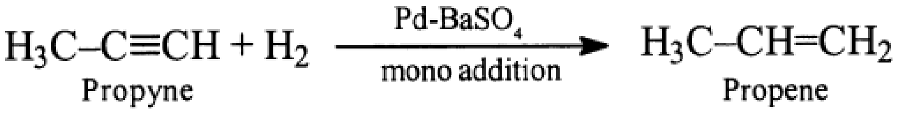
(b) The reaction becomes feasible in those cases where no reaction is normally possible



$$HC\equiv CH + H_2O \xrightarrow[H_2SO_4]{HgSO_4} H_3C-CHO$$

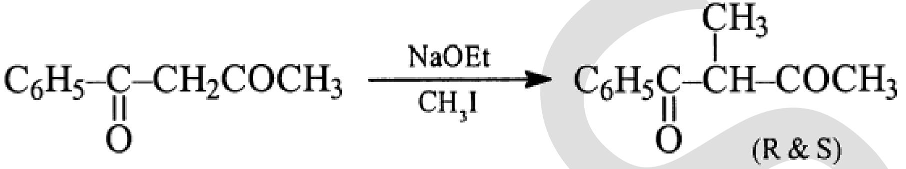
$$H_3C-C\equiv CH + CO + H_3C-OH \xrightarrow{Pd} CH_3-\underset{\underset{CH_2}{||}}{C}-\overset{\overset{O}{||}}{C}-OCH_3$$

(c) Selectivity enhancement



$$H_3C-C\equiv CH + H_2 \xrightarrow[\text{mono addition}]{Pd\text{-}BaSO_4} H_3C-CH=CH_2$$

Selectivity in C-methylation versus O-methylation



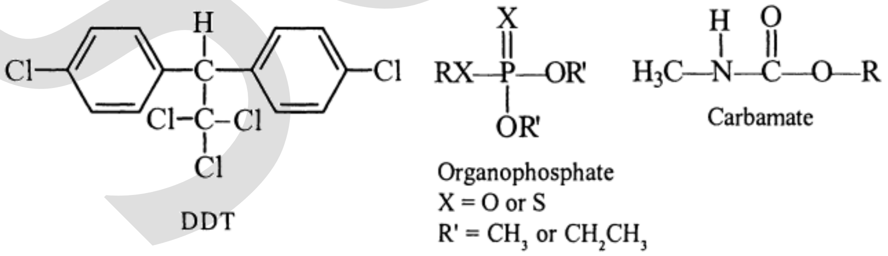
$$C_6H_5-\underset{\underset{O}{||}}{C}-CH_2COCH_3 \xrightarrow[CH_3I]{NaOEt} C_6H_5\underset{\underset{O}{||}}{C}-\overset{\overset{CH_3}{|}}{CH}-COCH_3$$

In addition to the above mentioned beneficial use of catalysts, there is significant advantage in the energy requirement. With advances in the selectivity of catalysts, certain reactions in green synthesis have become very convenient. A special advantage of the use of catalysts is better utilisation of starting materials and minimum waste product formation.

x) Products Designed should be Biodegradable

The problem of products not being biodegradable is encountered particularly in insecticides and polymers.

Insecticides: It is well known that farmers use different types of insecticides to protect crops from insects. The more widely used insecticides are organophosphates, carbamates and organochlorides. Of these, organophosphates and carbamates are less persistent in the environment compared to the organochlorides (for example aldrin, dieldrin and DDT). Though the latter are definitely effective but they tend to bioaccumulate in many plant and animal species and incorporate into the food chain. Some of the insecticides are also responsible for the population decline of beneficial insects and animals, such as honeybees, lacewings, mites, bald eagles etc.



Considering the above, it is of utmost importance that any product (e.g. insecticides) synthesised must be biodegradable. It is also equally important that during degradation the products themselves should not possess any toxic effects or be harmful to human health. It is possible to have a molecule (e. g. insecticide) which may possess functional groups that facilitate its biodegradation. The functional groups should be susceptible to hydrolysis, photolysis or other cleavage.

xi) Designing of Manufacturing Plants

The importance of prevention of accidents in manufacturing units cannot be over emphasised. A number of accidents have been found to occur in industrial units. The gas tragedy in Bhopal (December 1984) and several other places has resulted not only in loss of thousands of human lives but also rendered many persons disabled for the rest of their lives.

The hazards posed by toxicity, explosions, fire etc. must be looked into and the manufacturing plants should be so designed to eliminate the possibility of accidents during operation.

xii) Strengthening of Analytical Techniques

Analytical techniques should be so designed that they require minimum usage of chemicals, like recycling of some unreacted reagent (chemical) for the completion of a particular reaction. Further, placement of accurate sensors to monitor the generation of hazardous by-products during chemical reaction is also advantageous.

Planning/Designing a green synthesis

In any synthesis of a target molecule, the starting materials that are made to react with a reagent under appropriate conditions. Before coming to a final decision, consider all the possible methods that can give the desired product. The same product can also be obtained by modifying the conditions. The method of choice should not use toxic starting materials and should eliminate by-products and wastes.

Following are some of the important considerations.

Choice of Starting Materials: It is very important to choose the appropriate starting materials. The synthetic pathway will depend on this. Also consider the hazards that may be faced by the workers handling the starting materials.

Choice of Reagents: Selection of the right reagent for a reaction is made on the basis of efficiency, availability and its effect on environment. The selection of a particular reagent versus another reagent for the same transformation can effect the nature of by-products, percentage yield etc.

Choice of Catalysts: Certain reactions proceed much faster and at a lower temperature with the use of catalysts. Heavy metal catalysts should be avoided as they cause environmental problems and are toxic in nature. Use of visible light to carry out the required chemical transformation should be explored. Certain biocatalysts (enzymes) can also be used for various steps.

Choice of Solvents: Most of the common solvents generally used cause severe hazards. One of the commonly used solvents, benzene is now known to cause or promote cancer in humans and other animals. Some ofthe other aromatic hydrocarbons, for example toluene could cause brain damage, have adverse effect on speech, vision and balance, or cause liver and kidney problems. All these solvents are widely used because of their excellent solvency properties. These benefits nevertheless, are coupled with health risks.

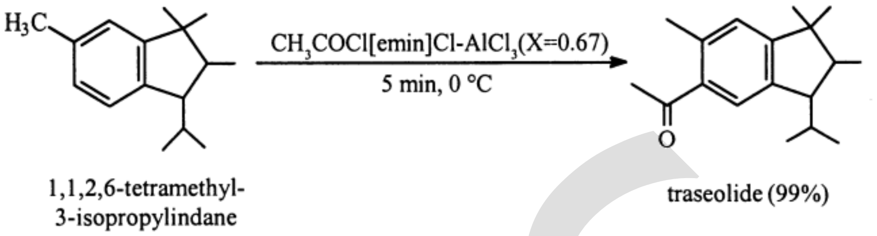
A versatile solvent, carbon dioxide is used as liquid CO_2 or supercritical CO_2 fluid (the states of CO_2 most commonly used for solvent use). A gas is normally converted to a liquid state by increasing the pressure exerted upon it. However, if the substance is placed at a temperature above its critical temperature Tc (31°C for CO_2) and critical pressure Pc (72.8 atm for CO_2), a supercritical fluid is obtained. The Tc of a substance is the temperature above which a distinct liquid phase of the substance cannot exist, regardless of the pressure applied. Pc is the pressure at which a substance can no longer exist in gaseous state. In a supercriticalliquid, the individual molecules are pressed so close together (due to high pressure) that they are almost in liquid state. Supercritical liquids have density close to that of the liquid state and viscosity close to that of gaseous state.

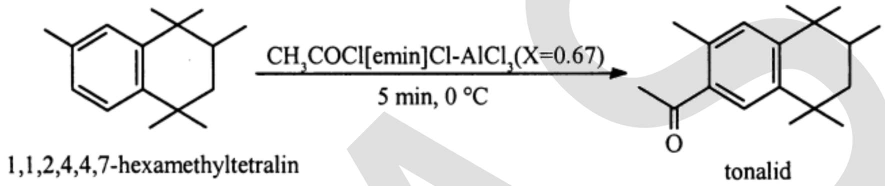
Reactions in Acidic Ionic Liquids

The chloroaluminate (III) ionic liquids (where X(AlCl) > 0.50) behave like powerful Lewis acid and promote reactions that are usually promoted by $AlCl_3$.

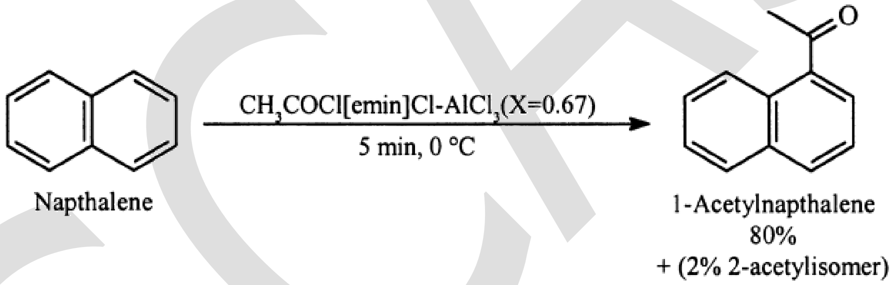
In fact, chloroaluminate ionic liquids are powerful solvents and can be prepared by mixing the appropriate organic halide salt with $AlCl_3$ and heating to form the ionic liquid. This synthesis should be performed in inert atmosphere.

The well-known Friedel-Crafts reaction works very well with the chloroaluminate (III) ionic liquids. Thus, using this methodology, traseolide (5-acyl-I,I,2,6-tetramethyl-3-isopropylindane) and tonalid (6-acetyl-1,1,2,4,4,7 -heaxmethyltetralin have been synthesised in high yield in the ionic liquid [emin]CI-AICI$_3$ (X = 0.67).

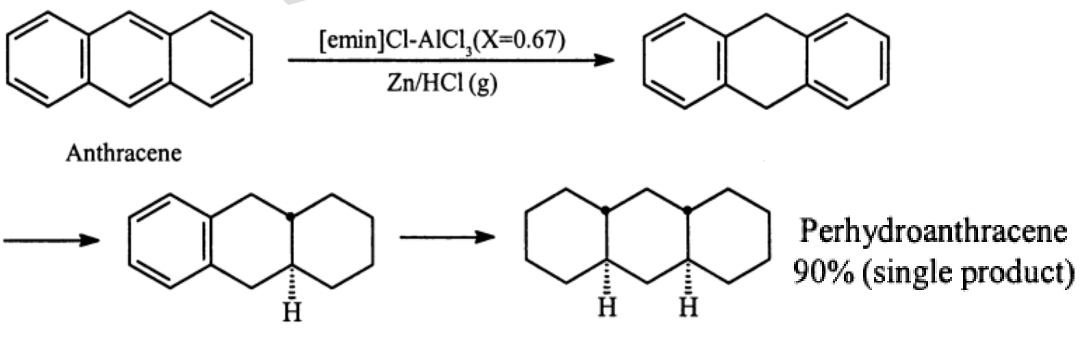




Similarly Friedel-Crafts reaction of naphthalene gives I-acetyl derivative as the major product

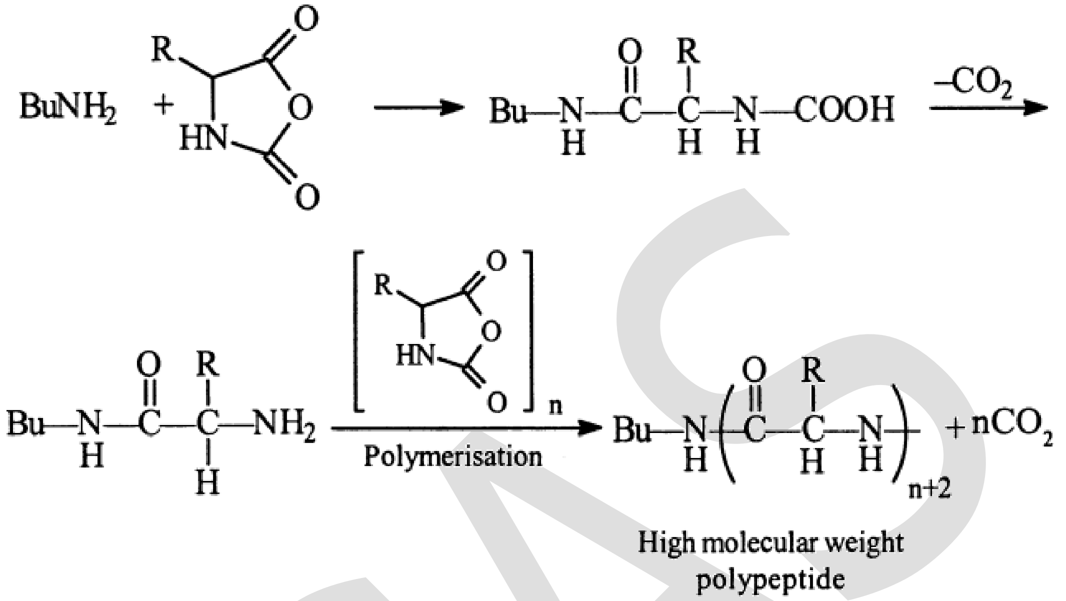


Another interesting application in the use of ionic liquids is in the hydrogenation of polycyclic aromatic hydrocarbons, 'which are soluble in chloroaluminate (III) ionic liquids to form highly coloured paramagnetic solutions, which on treatment with a reducing agent such as an electropositive metal and a proton source results in selective hydrogenation of the aromatic compound. Using this method, the anthracene can be reduced to perhydroanthracene at normal temperature and pressure to give the most stable isomer.



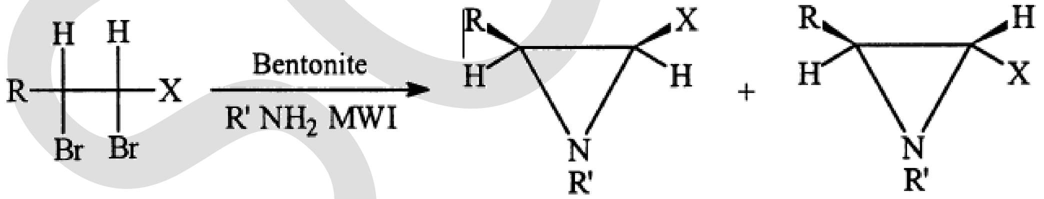
Solid Supported Organic Synthesis

In these reactions, the reactants are stirred in a suitable solvent (for example, water, alcohol, methylene chloride etc.). The solution is stirred thoroughly with a suitable adsorbent or solid support like silica gel, alumina, phyllosilicate (Mn+ -montomorillonite etc.). After stirring, the solvent is removed in vacuo and the dried solid support on which the reactants have been adsorbed are used for carrying the reaction under microwave irradiation.



Applications of solid support synthesis are given as follows.

Synthesis of Aziridines Dry media synthesis under focused microwave irradiation (MWI) by Michael addition has resulted in various substituted aziridines, though elimination predominates over the Michael addition under MWI when compared to classical heating under same condition.



Use of Microwaves

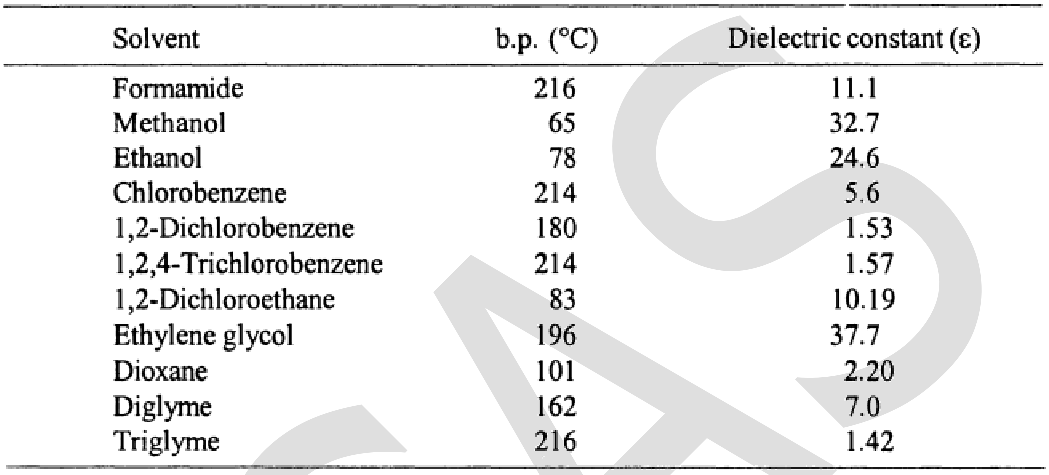
The microwaves, as we know, are used for heating purposes. The mechanism of how energy is given to a substance which is subjected to microwave irradiation is complex. One view is that microwave reactions involve selective absorption of electromagnetic waves by polar molecules, non-polar molecules being inert to microwaves. When molecules with a pennanent dipole are submitted to an electric field, they become aligned and as the field oscillates their orientation changes, this rapid reorientation produces intense internal heating.

The main difference between classical heating and microwave heating, lies in core and homogenous heating associated with microwaves, whereas classical heating is all about heat transfer by preheated molecules.

The preferred reaction-vessel for microwave induced organic reaction, is a tall beaker (particularly for small scale reactions in the laboratory), loosely covered and the capacity ofthe beaker should be much greater than the volume of the reaction mixture. Alternatively, teflon and polystyrene containers can be used. These materials are transparent to microwaves. Metallic containers should not be used as reaction vessels.

In microwave induced organic reactions, the reactions can be carried out in a solvent medium or on a solid support in which no solvent is used. For reactions in a solvent medium, the choice of the solvent is very important.

The solvent to be used must have a dipole moment so as to absorb microwaves and a boiling point at least 20-30 °e higher than the desired reaction temperature. An excellent solvent in a domestic microwave oven is N, N -dimethylformamide (DMF) (b.p. 160 °C, E = 36.7). The solvent can retain water formed in a reaction, thus, obviating the need for water separation. Some other solvents of choice are given as follows:



Solvent	b.p. (°C)	Dielectric constant (ε)
Formamide	216	11.1
Methanol	65	32.7
Ethanol	78	24.6
Chlorobenzene	214	5.6
1,2-Dichlorobenzene	180	1.53
1,2,4-Trichlorobenzene	214	1.57
1,2-Dichloroethane	83	10.19
Ethylene glycol	196	37.7
Dioxane	101	2.20
Diglyme	162	7.0
Triglyme	216	1.42

Hydrocarbon solvents, for example, hexane (Ɛ = 1.9), benzene (Ɛ = 2.3), toluene (Ɛ = 2.4) and xylene are unsuitable because of less dipole moment and also because these solvents absorb microwave radiations poorly. However, addition of small amounts of alcohol or water to these solvents can lead to dramatic coupling effects. Liquids which do not have a dipole moment cannot be heated by microwaves.

Microwaves may be considered as a more efficient source of heating than conventional steam (or oil heated vessels), since the energy is directly imparted to the reaction medium rather than through the walls of a reaction vessel. In fact, the rapid heating capability of the microwave leads to considerable saving in dissolution or the reaction time. The smaller volume of solvent required contributes to saving in cost and diminishes the waste disposal problem.

Applications

It is possible to carry out a number of microwave organic synthesis. These syntheses are grouped in the following three categories:

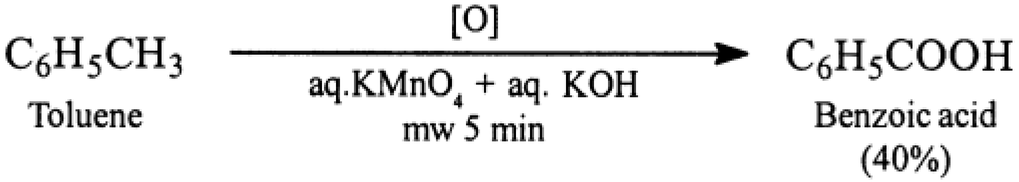
(i) Microwave-assisted reactions in water.

(ii) Microwave-assisted reactions in organic solvents.

(iii) Microwave solvent-free reactions (solid state reactions).

Microwave Assisted Reactions in Water

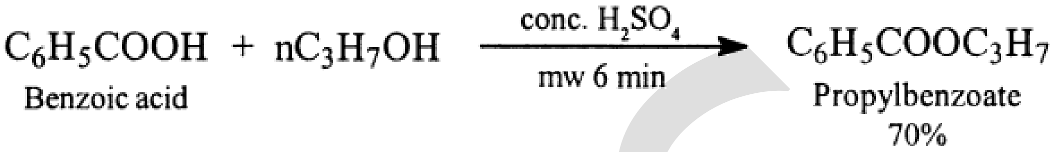
Oxidation of Toluene: Oxidation of toluene with KMn04 under normal conditions ofrefluxing takes 10-12 hr compared to reaction in microwave conditions, which takes only 5 min and the yield is 40%,



$$C_6H_5CH_3 \xrightarrow[\text{aq.KMnO}_4\text{ + aq. KOH, mw 5 min}]{[O]} C_6H_5COOH$$

<u>Microwave-Assisted Reactions in Organic Solvents</u>

Esterification: *Reaction of Carboxylic Acid and Alcohol* A mixture of benzoic acid and n-propanol on heating in a microwave oven for 6 min in presence of catalytic amount of cone. sulphuric acid gives propylbenzoate

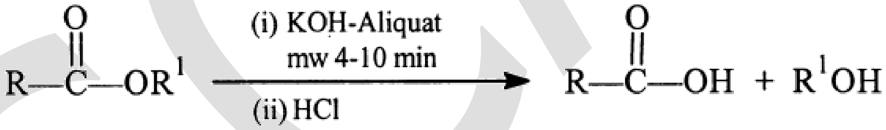


$$C_6H_5COOH + nC_3H_7OH \xrightarrow[\text{mw 6 min}]{\text{conc. }H_2SO_4} C_6H_5COOC_3H_7$$

<u>Microwave Solvent Free Reactions (Solid State Reactions</u>)

By the use of this technique, it is now possible to carry out reactions without the use of toxic or other solvents, which is one of the main problems associated with green synthesis. In these, the reactants are dissolved in a suitable solvent like water, alcohol, methylene chloride etc. and the solution stirred with a suitable adsorbent or solid support like silica gel, alumina or phyllosilicate (Mn+ -montomorillonite). After stirring, the solvent is removed in vacuo and the dried solid support on which the reactants have been adsorbed are used for carrying out the reaction under microwave irradiation.

Saponification of Esters: Hindered esters which take 5 hr under classical heating with alkali can be easily saponified under microwave irradiation using KOH-Aliquat,



$$R{-}\overset{O}{\overset{\|}{C}}{-}OR^1 \xrightarrow[\text{(ii) HCl}]{\text{(i) KOH-Aliquat, mw 4-10 min}} R{-}\overset{O}{\overset{\|}{C}}{-}OH + R^1OH$$

<u>**Use of Ultrasound:**</u>

When a sound wave, propagated by a series of compression and refraction cycles, pass through a liquid medium, it causes the molecules to oscillate around their mean position. During the compression cycle, the average distance between the molecules is reduced and during refraction, the average distance between the molecules is increased. In the refraction cycle, under appropriate conditions, the attractive forces of the molecules of the liquid may be overcome, causing formation of bubbles. In case the internal forces are great enough to ensure collapse of these bubbles, very high local temperature (around 5000°C) and pressure (over 1000 bar) may be created. It is this very high temperature and pressure that initiate chemical reactions.

The term 'sonochemistry' is used to describe the effect of ultrasound waves on chemical reactivity. A number of reviews on the chemical applications of ultrasound have been published.

Applications of Ultrasound

Following are some of the important applications of ultrasound in chemical synthesis. Most of the reactions/syntheses reported are carried out at room temperature unless otherwise specified. The symbol is used for reactions carried out on exposure to ultrasound.

Esterification: This is generally carried out in presence of a catalyst like sulphuric acid, p-toluenesulphonic acid, tosylchloride, polyphosphoric acid, dicyclo-hexylcarbodiimide etc. The reaction takes longer time and yields are low.

A simple procedure for the esterification of a variety of carboxylic acids with different alcohols at ambient temperature using ultrasound has been reported.

$$RCOOH + R^1OH \xrightarrow[)))]{H_2SO_4,\ R.T.} RCOOR^1$$

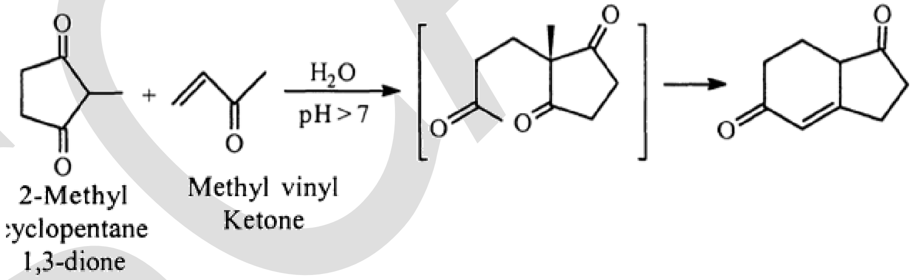
UNIT-II Addition and Condensation Reactions:

Michael Addition

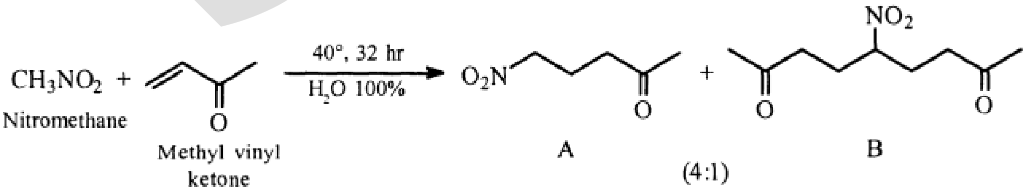
It is an addition reaction between an α, β-unsaturated carbonyl compound and a compound with an active methylene group (e.g., malonic ester, acetoacetic ester, cyanoacetic ester, nitroparaffins etc.) in presence of a base, e.g., sodium ethoxide or a secondary amine (usually piperidine).

In Aqueous Phase:

The first successful report of Michael reaction in aqueous medium was in the 1970s. 2-Methylcyclopentane-I,3-dione when reacted with vinyl ketone in water gave an adduct without the use of a basic catalyst (pH > 7). The adduct further cyclises to give a 5-6 fused ring system.



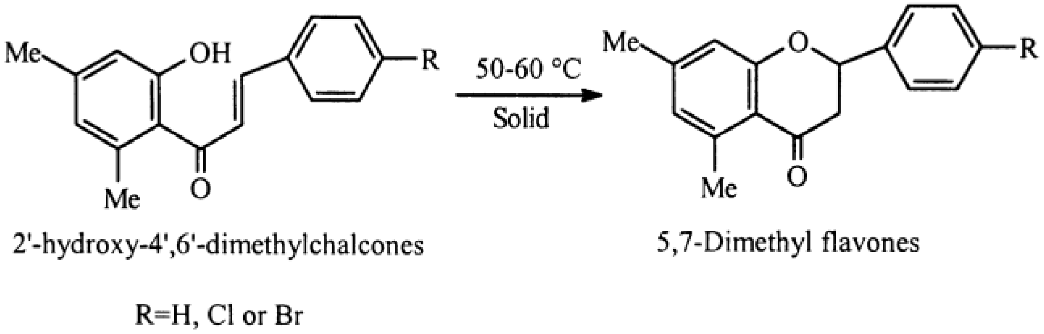
In this reaction, use of water as solvent gave better yields and pure compound compared to reaction with methanol in presence of a base.
The Michael addition of nitro methane to methyl vinyl ketone in water (in absence of a catalyst) gave 4: 1 mixture of adducts (A and B).



Use of methyl alcohol as a solvent (in place of H_2O) gave 1: 1 mixture of A and B. The above reaction does not occur in neat conditions or in solvents like THF, PhMe etc. in the absence of a catalyst**.**

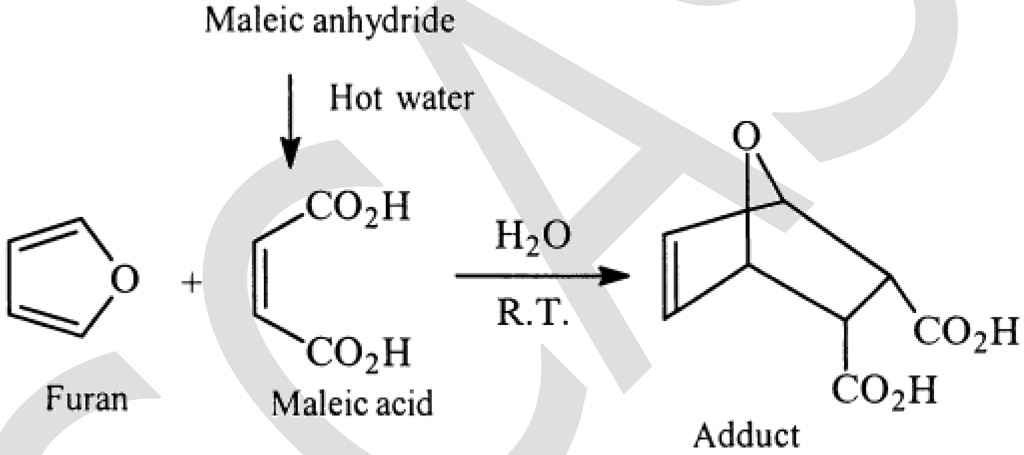
Solid state method:

A number of 2'-hydroxy-4',6'-dimethylcha1cones undergo a solid state intramolecular Michael type addition to yield the corresponding flavonones.



Diels-Alder Reaction

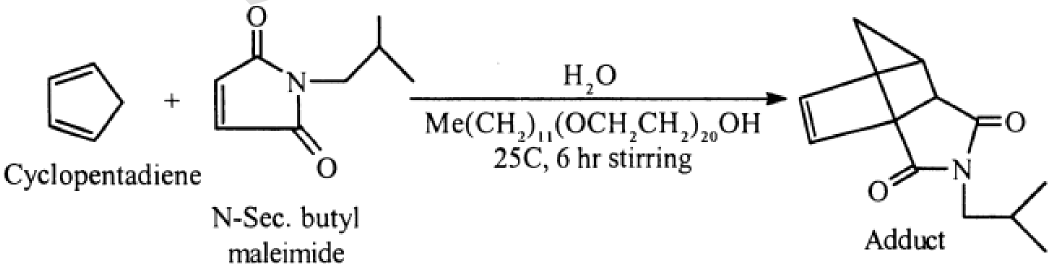
The most important method to form cyclic structures is the well-known Diels-Alder reaction. However, the first Diels-Alder reaction in aqueous media was carried out in the beginning of the 19th century. Thus, furan reacted with maleic anhydride in hot water to give the adduct.



The product obtained was a diacid showing that the reaction occurred via the formation of maleic acid from maleic anhydride.

In Aqueous phase:

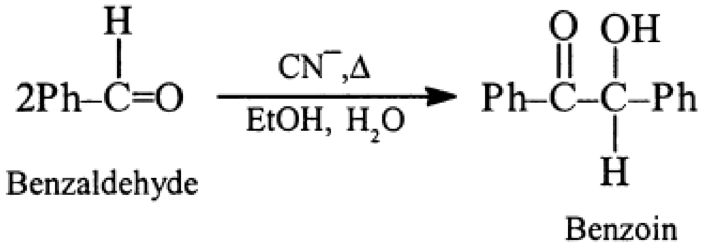
A typical reaction of cyclopentadiene with N-sec. butylmaleimide gave quantitative yield of the adduct.



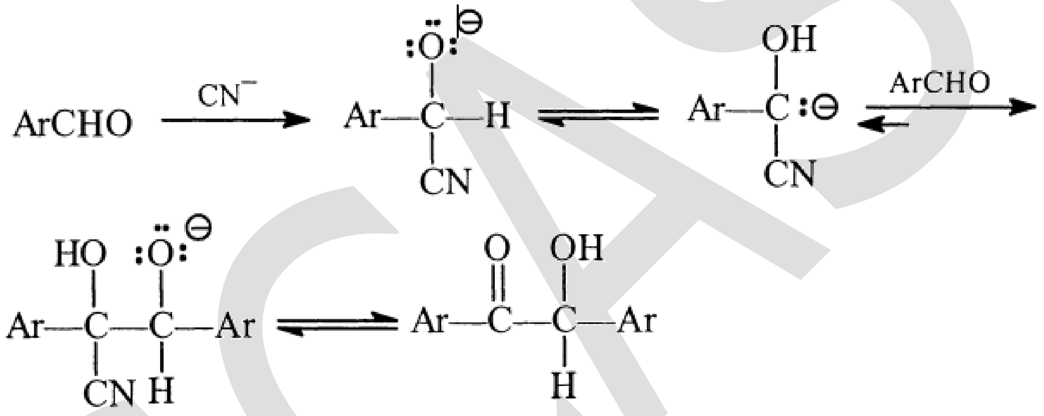
However, it was only in 1980 that Breslow observed that the Diels-Alder reaction of cyclopentadiene with butenone in water was more than 700 times faster than the same reaction in isooctane.

Benzoin condensation:

It consists in the treatment of aromatic aldehydes with sodium or potassium cyanide, usually in an aqueous ethanolic solution to give a-hydroxy ketones (benzoins).



Benzoin condensation can be considered to occur through a formal Knoevenagel type addition. The key step of the reaction is the loss of the aldehydic proton, which gives rise to the cyanohydrin anion. In this case the acidity of the proton is increased by the electron-withdrawing power of the cyano group.



It is found that benzoin condensation of aldehydes are strongly catalysed by a PTC (quaternary ammonium cyanide in a two phase system). In a similar way, acyloin condensations are easily effected by stirring aliphatic or aromatic aldehydes with a quaternary catalyst (PTC), N-laurylthiazolium bromide in aqueous phosphate buffer at room temperature. The aromatic aldehydes reacted in a short time (about 5 min). However, aliphatic aldehydes require longer time (5-10 hr) for completion. Mixtures of aliphatic and aryl aromatic aldehydes give mixed a-hydroxy ketones.

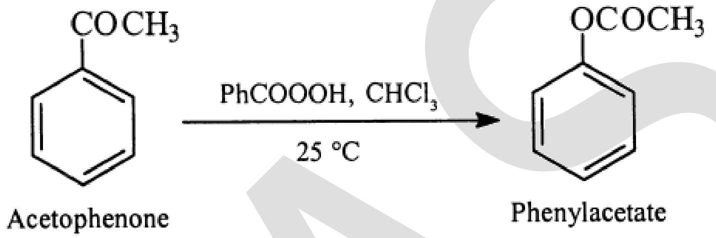
On the basis of extensive work, Breslow found that the benzoin condensation in aqueous media using inorganic salts (e.g., LiCl) is about 200 times faster than in ethanol (without any salt). The addition ofy-cyclodextrin also accelerates the reaction, whereas the addition of ~-cyclodextrin inhibits the condensation.

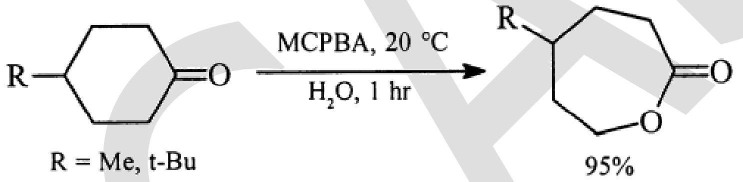
Oxidation Reactions

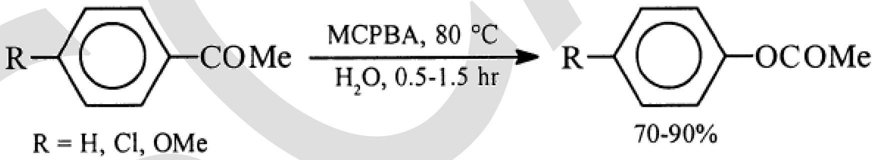
Baeyer -Villiger oxidation

The Baeyer -Villiger oxidation is well known for the conversion of aromatic ketones (e.g., acetophenone) into the corresponding esters. The common peracids used are perbenzoic acid, performic acid and m-chloroperbenzoic acid. The reaction is generally carried out in organic solvents.

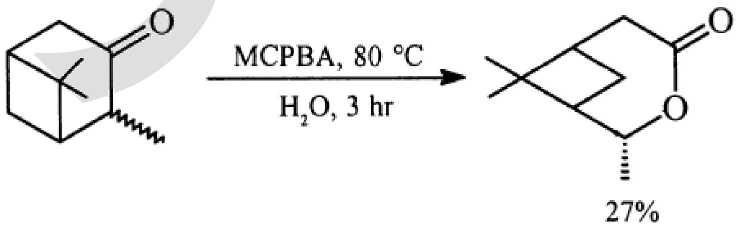
The Baeyer-Villiger oxidation of ketones has been satisfactorily carried out in aqueous heterogeneous medium with MCPBA at room temperature. 125 Some examples using the above methodology are given





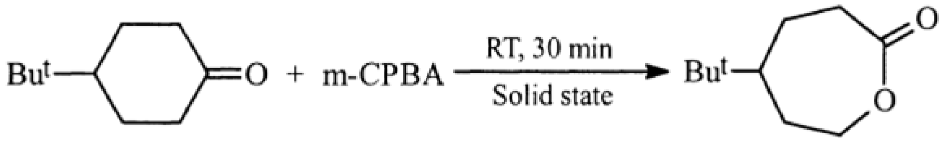


Using the above procedure, ketones, which are reactive (e.g. anthrone which usually gives anthraquinone) and ketones, which are unreactive or give the expected lactones in organic solvents with difficulty can also be oxidized,

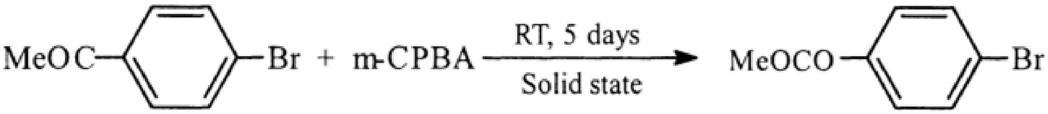


Baeyer -Villiger oxidation in Solid State Method:

Some Baeyer-Villiger oxidation of ketones with m-chloroperbenzoic acid proceeds much faster in the solid state than in solution. In this method, a mixture of powdered ketone and 2-mole equivalent of m-chloroperbenzoic acid is kept at room temperature to give the product. The yields obtained in solid state are much better than in $CHCl_3$. Some representative examples are given as follows,



95%
(94% in $CHCl_3$)



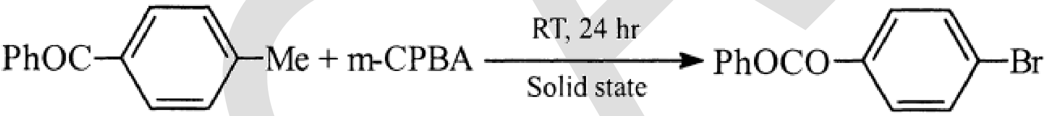
64%
(50% in $CHCl_3$)

$$\mathrm{PhCOCH_2Ph + m\text{-}CPBA \xrightarrow[\text{Solid state}]{\text{RT, 24 hr}} PhCOOCH_2Ph}$$

97%
(46% in $CHCl_3$)

$$\mathrm{PhCOPh + m\text{-}CPBA \xrightarrow[\text{Solid state}]{\text{RT, 24 hr}} PhCOOPh}$$

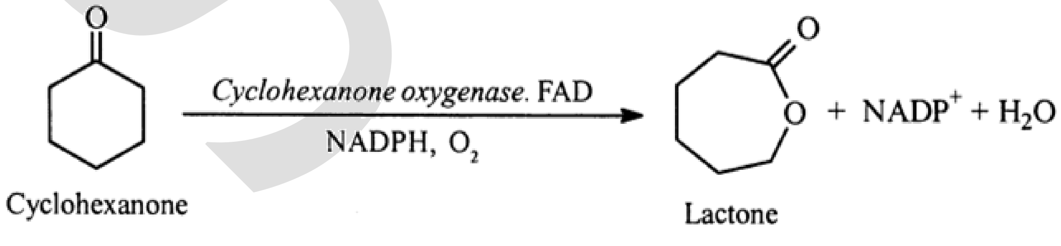
85%
(13% in $CHCl_3$)



50%
(72% in $CHCl_3$)

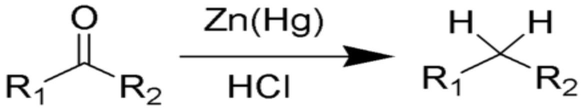
<u>Baeyer -Villiger oxidation in enzymatic condition:</u>

A typical transformation in the enzymatic Baeyer-Villiger oxidation, which converts cyclohexanone into the lactone using a purified cyclohexanone oxygenase enzyme.



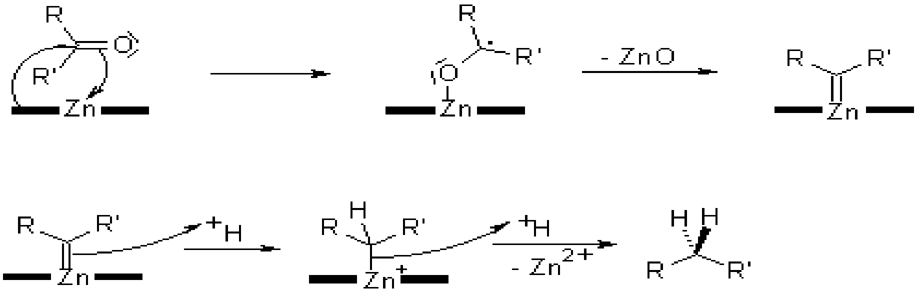
Clemmensen Reduction

Clemmensen reduction is a chemical reaction described as a reduction of ketones (or aldehydes) to alkanes using zinc amalgam and concentrated hydrochloric acid.



Mechanism of the Clemmensen Reduction

The reduction takes place at the surface of the zinc catalyst. In this reaction, alcohols are not postulated as intermediates, because subjection of the corresponding alcohols to these same reaction conditions does not lead to alkanes. The following proposal employs the intermediacy of zinc carbenoids to rationalize the mechanism of the Clemmensen Reduction:



APPLICATION

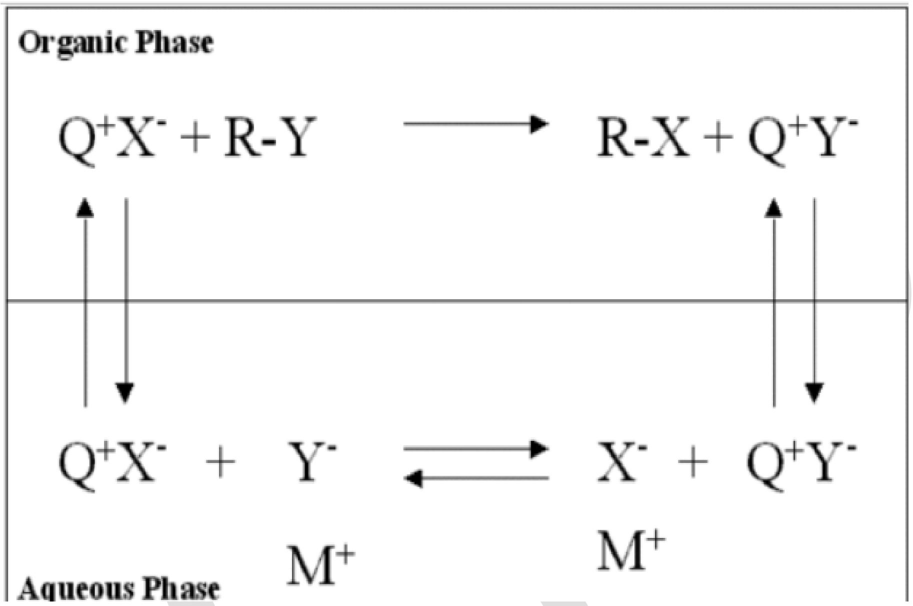
The original Clemmensen reduction conditions are particularly effective at reducing aryl-alkyl ketones, such as those formed in a Friedel-Crafts acylation. The two-step sequence of Friedel-Crafts acylation followed by Clemmensen reduction constitutes a classical strategy for the primary alkylation of arenes. With aliphatic or cyclic ketones, modified Clemmensen conditions using activated zinc dust in an anhydrous solution of hydrogen chloride in diethyl ether or acetic anhydride is much more effective.

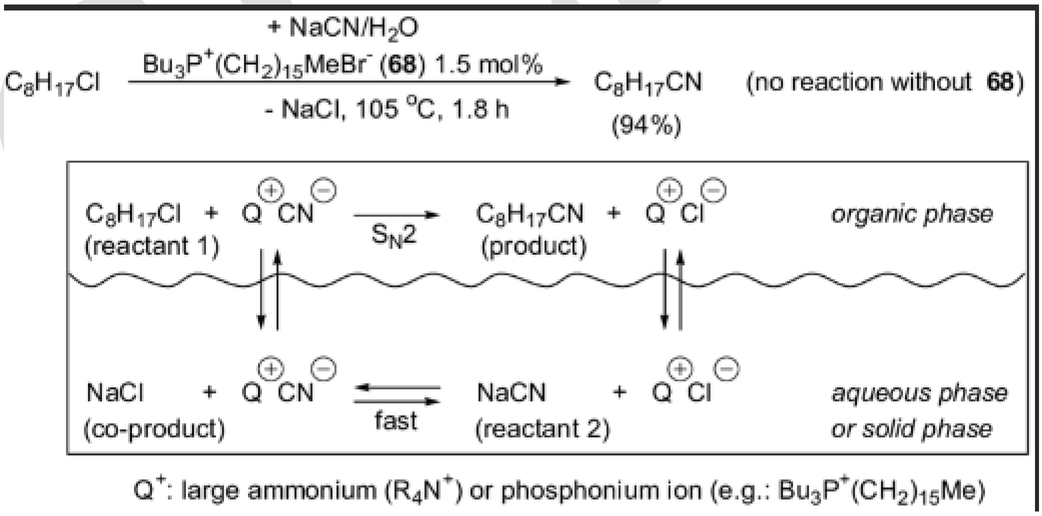
The substrate must be tolerant of the strongly acidic conditions of the Clemmensen reduction (37% HCl). Several alternatives are available. Acid-sensitive substrates that are stable to strong base can be reduced using the Wolff-Kishner reduction; a further, milder method for substrates stable to hydrogenolysis in the presence of Raney nickel is the two-step Mozingo reduction.

In spite of the antiquity of this reaction, the mechanism of the Clemmensen reduction remains obscure. Due to the heterogeneous nature of the reaction, mechanistic studies are difficult, and only a handful of studies have been disclosed. Mechanistic proposals generally invoke organozinc intermediates, sometimes including zinc carbenoids, either as discrete species or as organic fragments bound to the zinc metal surface. However, the corresponding alcohol is believed not to be an intermediate, since subjection of the alcohol to Clemmensen conditions generally does not afford the alkane product.

Phase-transfer catalyst

A phase-transfer catalyst or PTC is a catalyst that facilitates the migration of a reactant from one phase into another phase where reaction occurs. Phase-transfer catalysis is a special form of heterogeneous catalysis. Ionic reactants are often soluble in an aqueous phase but insoluble in an organic phase in the absence of the phase-transfer catalyst. The catalyst functions like a detergent for solubilizing the salts into the organic phase. Phase-transfer catalysis refers to the acceleration of the reaction upon the addition of the phase-transfer catalyst.



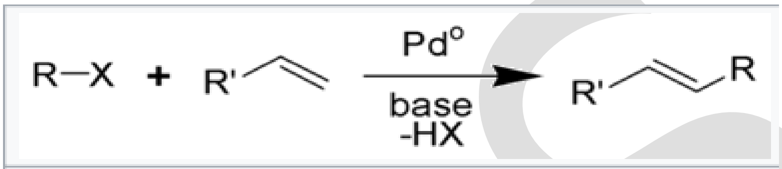


Applications

PTC is widely exploited industrially. Polyester polymers for example are prepared from acid chlorides and bisphenol-A. Phosphothioate-based pesticides are generated by PTC-catalyzed alkylation of phosphothioates. One of the more complex applications of PTC involves asymmetric alkylations, which are catalyzed by chiral quaternary ammonium salts derived from cinchona alkaloids.

Heck Reaction

The Heck reaction (also called the Mizoroki-Heck reaction) is the chemical reaction of an unsaturated halide (or triflate) with an alkene in the presence of a base and a palladium catalyst (or palladium nanomaterial-based catalyst) to form a substituted alkene. It is named after Tsutomu Mizoroki and Richard F. Heck. Heck was awarded the 2010 Nobel Prize in Chemistry, which he shared with Ei-ichi Negishi and Akira Suzuki, for the discovery and development of this reaction. This reaction was the first example of a carbon-carbon bond-forming reaction that followed a Pd(0)/Pd(II) catalytic cycle, the same catalytic cycle that is seen in other Pd(0)-catalyzed cross-coupling reactions. The Heck reaction is a way to substitute alkenes.



The Heck reaction

Catalyst and substrates

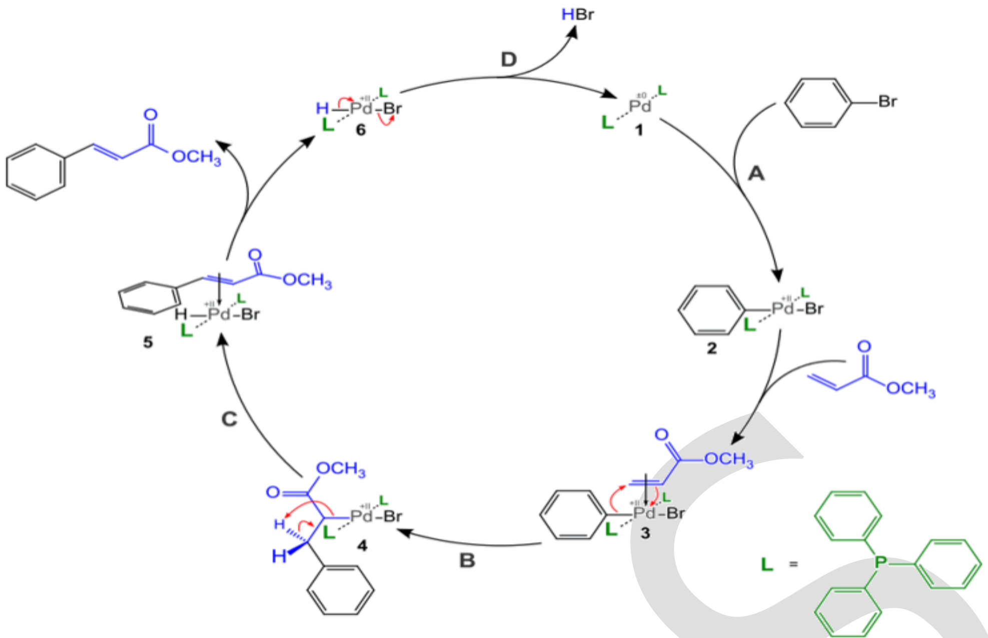
The reaction is catalyzed by palladium salts and complexes. Typical catalysts and precatalysts include tetrakis(triphenylphosphine)palladium(0), palladium chloride, and palladium(II) acetate. Typical supporting ligands are triphenylphosphine, PHOX and BINAP. Typical bases are triethylamine, potassium carbonate, and sodium acetate.

The aryl electrophile can be a halide (Br, Cl) or a triflate as well as benzyl or vinyl halides. The alkene must contain at least one sp^2-C-H bond. Electron-withdrawing substituents enhance the reaction, thus acrylates are ideal.

Reaction mechanism

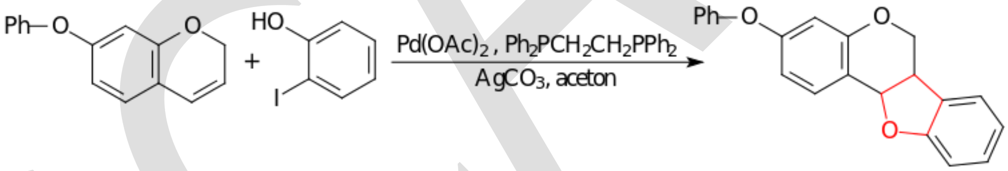
The mechanism involves organopalladium intermediates. The palladium(0) compound required in this cycle is generated in situ from a palladium(II) precursor.

For instance, palladium(II) acetate is reduced by triphenylphosphine to bis(triphenylphosphine)palladium(0) (**1**) and triphenylphosphine is oxidized to triphenylphosphine oxide. Step **A** is an oxidative addition in which palladium inserts itself in the aryl to bromide bond. Palladium then forms a π complex with the alkene (**3**) and in step **B** the alkene inserts itself in the palladium - carbon bond in a syn addition step. Then follows a torsional strain relieving rotation to the trans isomer (not shown) and step **C** is a beta-hydride elimination (here the arrows are showing the opposite) step with the formation of a new palladium - alkene π complex (**5**). This complex is destroyed in the next step. The palladium(0) compound is regenerated by reductive elimination of the palladium(II) compound by potassium carbonate in the final step, **D**. In the course of the reaction the carbonate is stoichiometrically consumed and palladium is truly a catalyst and used in catalytic amounts. A similar palladium cycle but with different scenes and actors is observed in the Wacker process



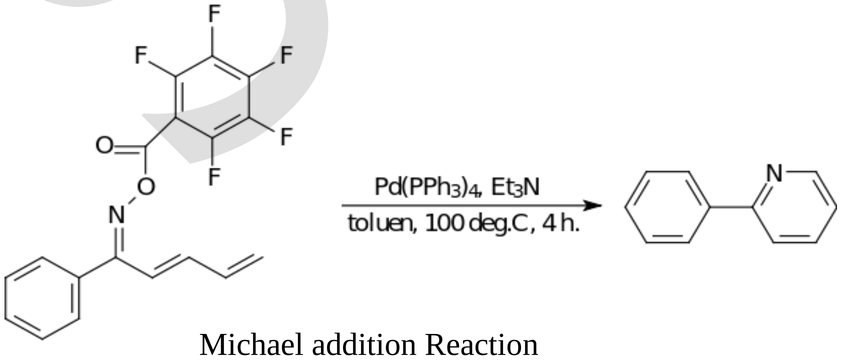
Heck oxyarylation

In the Heck oxyarylation modification the palladium substituent in the syn-addition intermediate is displaced by a hydroxyl group and the reaction product contains a dihydrofuran ring.



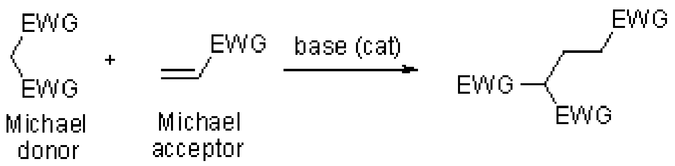
Amino-Heck reaction

In the amino-Heck reaction a nitrogen to carbon bond is formed. In one example, an oxime with a strongly electron withdrawing group reacts intramolecularly with the end of a diene to form a pyridine compound. The catalyst is tetrakis(triphenylphosphine)palladium(0) and the base is triethylamine.



Michael addition Reaction

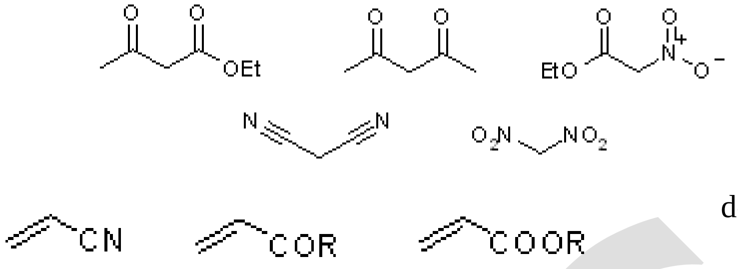
Michael



Addition

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

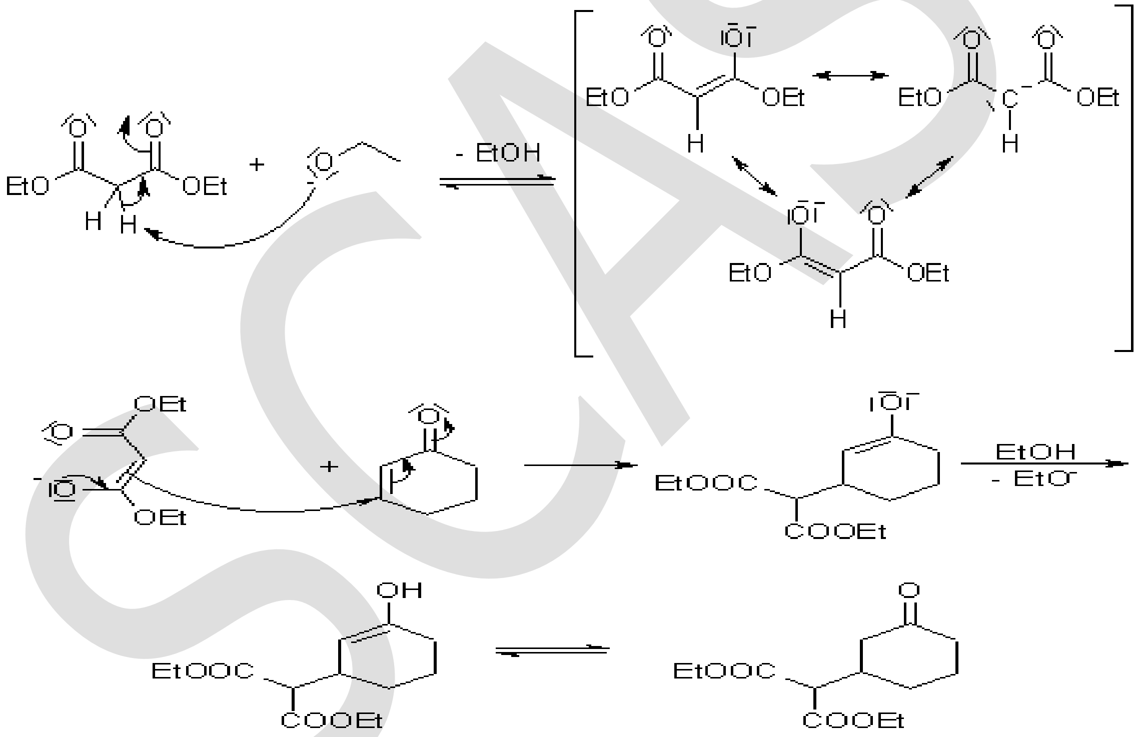
Examples:



donors

acceptors

Mechanism of the Michael Addition

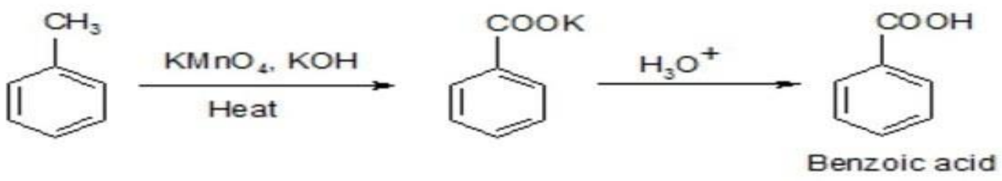


Oxidation of toluene to benzoic acid

The reaction of the oxidation of toluene to benzoic acid:

$$5\,C_6H_5CH_3 + 6\,KMnO_4 + 9\,H_2SO_4$$
$$\rightarrow 5\,C_6H_5COOH + 14\,H_2O + 3\,K_2SO_4 + 6\,MnSO_4$$

Benzoic acid can be prepared from toluene by oxidising it. Toluene is oxidised by alkaline $KMnO_4$ to get potassium benzoate, which on acid hydrolysis, benzoic acid is obtained.



Reimer–Tiemann reaction

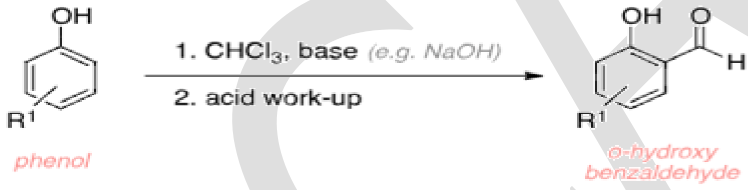
The Reimer–Tiemann reaction is a chemical reaction used for the ortho-formylation of phenols; with the simplest example being the conversion of phenol to salicylaldehyde. The reaction was discovered by Karl Reimer [de] and Ferdinand Tiemann.

Reimer Tiemann reaction is a type of substitution reaction, named after chemists Karl Reimer and Ferdinand Tiemann. The reaction is used for the ortho-formylation of C_6H_5OH (phenols).

Reaction: When phenols i.e. C_6H_5OH is treated with CHCl3 (chloroform) in the presence of NaOH (sodium hydroxide), an aldehyde group (-CHO) is introduced at the ortho position of benzene ring leading to the formation of o-hydroxybenzaldehyde. The reaction is popularly known as Reimer Tiemann reaction.

⇒ Jump to: Reimer Tiemann Reaction Mechanism

A common example of Reimer Tiemann reaction is the conversion of phenol to salicylaldehyde (2-hydroxy benzaldehyde) as shown below.



Reimer Tiemann reaction: Conversion of phenol to salicylaldehyde

Reimer Tiemann Reaction Mechanism

The mechanism of Reimer Tiemann reaction begins with the deprotonation of chloroform by a strong base to form a chloroform carbanion. This chloroform carbanion quickly undergoes alpha elimination and gives rise to dichlorocarbene – the principle reactive species for this reaction.

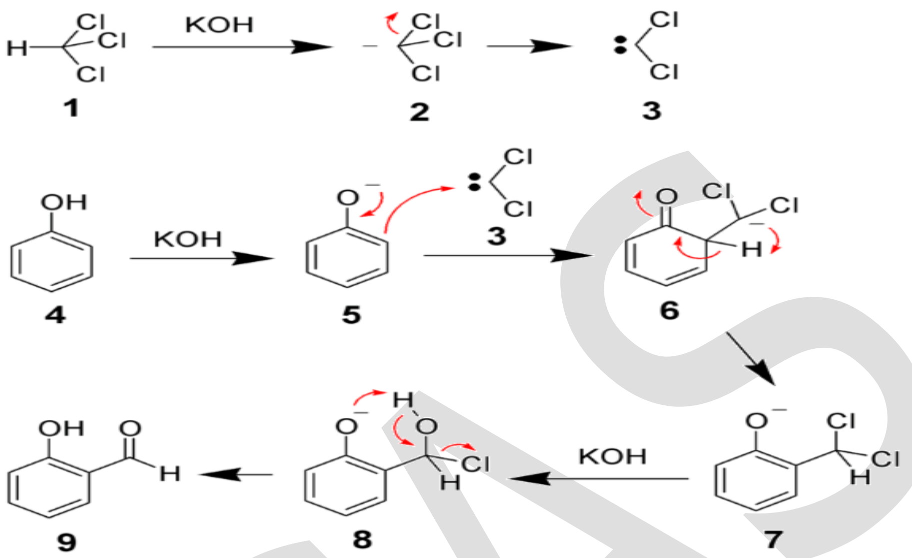
The Reimer Tiemann reaction is an organic chemical reaction where phenol is converted into an ortho hydroxy benzaldehyde using chloroform, a base, and acid workup. This name reaction can also be described as the chemical reaction used for the ortho-formylation of phenols.

The mechanism of Reimer Tiemann Reaction can be explained in 9 major steps:

- The chloroform is deprotonated by the strongly basic aqueous hydroxide solution, giving the chloroform carbanion.
- This chloroform carbanion readily undergoes alpha elimination, giving dichlorocarbene as the product. As mentioned earlier, the dichlorocarbene is the principle reactive species.
- The aqueous hydroxide also deprotonates the phenol reactant, yielding a negatively charged phenoxide.

- This negative charge is now delocalized into the benzene ring, causing it to be far more nucleophilic.
- This results in a nucleophilic attack on the dichlorocarbene, forming an intermediate dichloromethyl substituted phenol.
- This intermediate is subjected to basic hydrolysis to finally achieve the formation of the desired ortho-hydroxybenzaldehyde.

The illustration of the Reimer Tiemann reaction mechanism is given below:

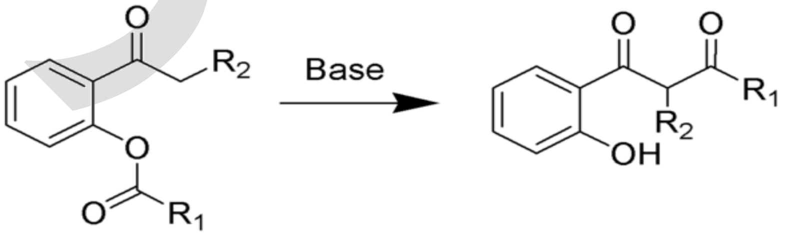


Thus, the given phenol is converted into an ortho-hydroxy benzaldehyde using chloroform, a base and acid workup. It can be noted that the carbene is highly electron-deficient due to the electron-withdrawing nature of its two chlorine groups. This is why it is strongly attracted to the phenoxide which is rich in electrons. The interaction favours ortho-formylation of a selective nature.

Baker–Venkataraman rearrangement

Jump to search

The Baker–Venkataraman rearrangement is the chemical reaction of 2-acetoxyacetophenones with base to form 1,3-diketones.

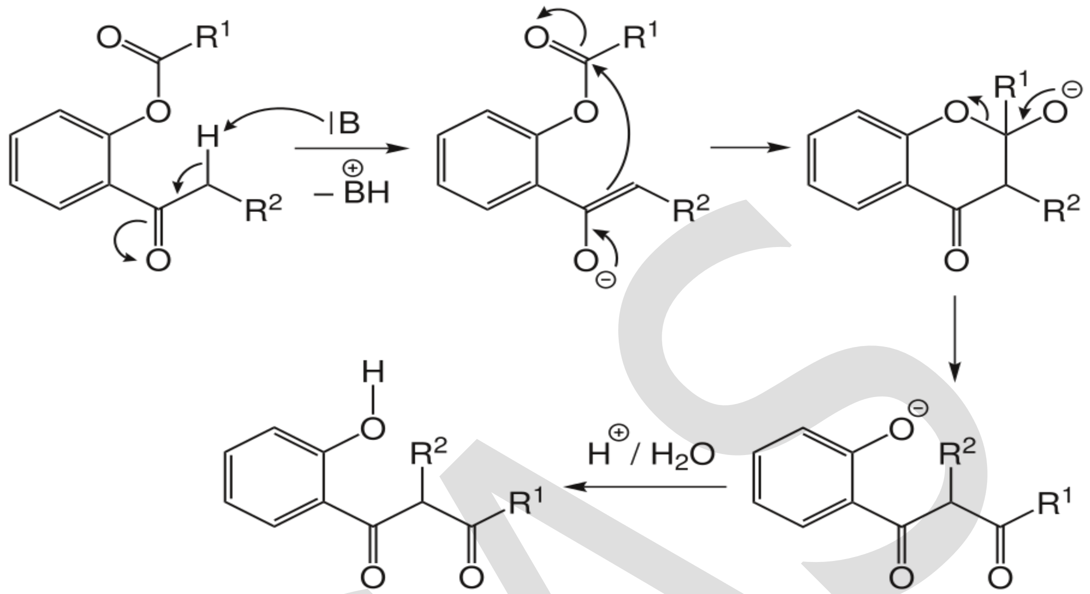


This rearrangement reaction proceeds via enolate formation followed by acyl transfer. It is named after the scientists Wilson Baker and K. Venkataraman.

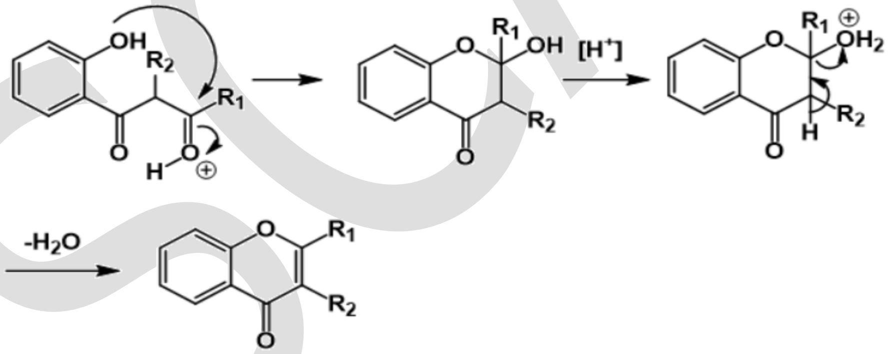
The Baker–Venkataraman rearrangement is often used in the synthesis of chromones and flavones. After the base-catalyzed rearrangement, treatment with acid generally affords the chromone or flavone core, though other milder methods have been reported

Mechanism

A base abstracts the hydrogen atom alpha to the aromatic ketone, forming an enolate. Then, the enolate attacks the ester carbonyl to form a cyclic alkoxide. The cyclic intermediate is opened up to form a more stable phenolate, which is protonated during acidic work-up to give the desired product.



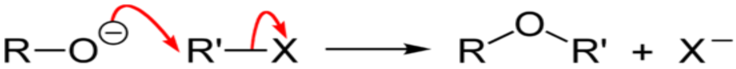
To complete the construction of the chromone or flavone core, cyclodehydration is required. This was commonly afforded by treatment with strong acid, however many milder conditions have now been developed. One proposed mechanism for this dehydration is as follows:



William Etherson synthesis

The Williamson ether synthesis is an organic reaction, forming an ether from an organohalide and a deprotonated alcohol (alkoxide). This reaction was developed by Alexander Williamson in 1850.[2] Typically it involves the reaction of an alkoxide ion with a primary alkyl halide via an S_N2 reaction. This reaction is important in the history of organic chemistry because it helped prove the structure of ethers.

The general reaction mechanism is as follows:



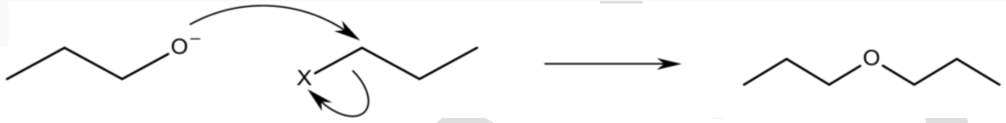
An example is the reaction of sodium ethoxide with chloroethane to form diethyl ether and sodium chloride:

$$[Na]^+[C_2H_5O]^- + C_2H_5Cl \rightarrow C_2H_5OC_2H_5 + [Na]^+[Cl$$

Mechanism

The Williamson ether reaction follows an S_N2 bimolecular nucleophilic substitution mechanism. In an S_N2 reaction mechanism there is a backside attack of an electrophile by a nucleophile and it occurs in a concerted mechanism (happens all at once). In order for the S_N2 reaction to take place there must be a good leaving group which is strongly electronegative, commonly a halide.

In the Williamson ether reaction there is an alkoxide ion (RO^-) which acts as the nucleophile, attacking the electrophilic carbon with the leaving group, which in most cases is an alkyl tosylate or an alkyl halide. The leaving site must be a primary carbon, because secondary and tertiary leaving sites generally prefer to proceed as an elimination reaction. Also, this reaction does not favor the formation of bulky ethers like di-tertbutyl ether, due to steric hindrance and predominant formation of alkenes instead.



An example for a Williamson ether synthesis to make dipropyl ether. X^- product is not shown.

The Williamson reaction often competes with the base-catalyzed elimination of the alkylating agent, and the nature of the leaving group as well as the reaction conditions (particularly the temperature and solvent) can have a strong effect on which is favored. In particular, some structures of alkylating agent can be particularly prone to elimination.

When the nucleophile is an aryloxide ion, the Williamson reaction can also compete with alkylation on the ring since the aryloxide is an ambident nucleophile

Sonication

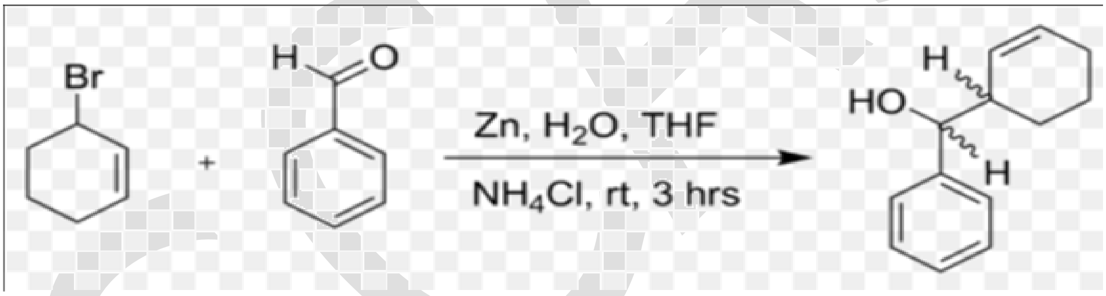
Even though the rate acceleration effect of **sonication** has been long known, its application to organic synthesis is becoming popular only relatively recently.

The development was slow because the early studies were limited to aqueous reactions and the equipment were not widely available. From the early 1980’s, synthetically relevant reports started to appear.

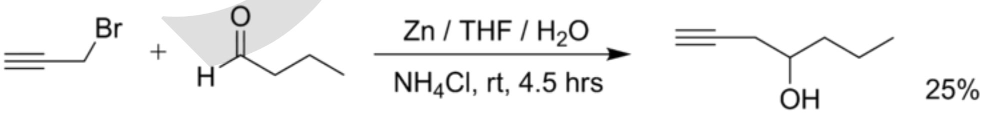
The field that focuses on the effect of sonication is called **sonochemistry.**

Barbier Reaction

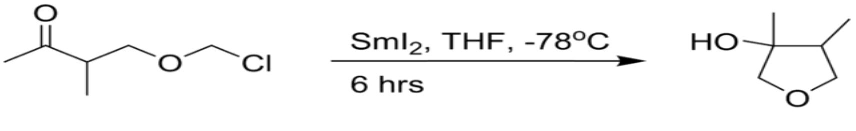
The Barbier reaction is an organic reaction between an alkyl halide and a carbonyl group as an electrophilic substrate in the presence of aluminium, zinc, indium, tin or its salts. The reaction product is a secondary or tertiary alcohol. The reaction is similar to the Grignard reaction but the crucial difference is that the Barbier reaction is a One-pot synthesis whereas a Grignard reagent is prepared separately before addition of the carbonyl compound. Barbier reactions are nucleophilic addition reactions that take place with relatively inexpensive and water insensitive metals or metal compounds in contrast to Grignard reagents or organolithium reagents. For this reason it is possible in many cases to run the reaction in water which makes the procedure part of green chemistry. The Barbier reaction is named after Victor Grignard’s teacher Philippe Barbier.



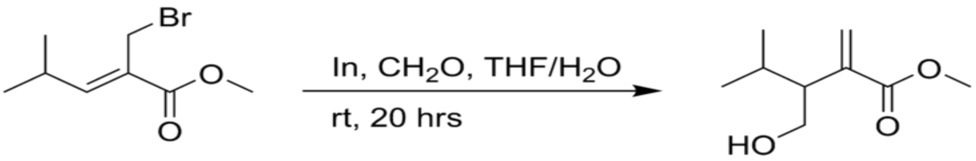
Examples of Barbier reactions are, the reaction of propargylic bromide with butanal with zinc metal (the reaction is carried out in THF, the saturated aqueous ammonium chloride solution added later to quench the reaction):



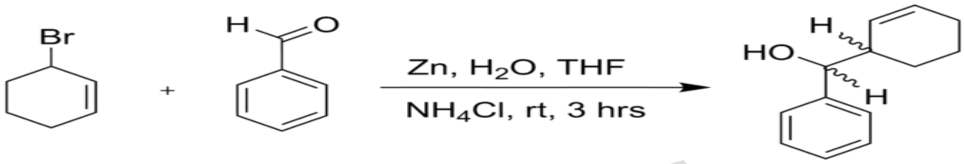
With a substituted <u>alkyne</u> instead of a <u>terminal alkyne</u> the <u>allene</u> product is favoured the <u>intramolecular</u> Barbier reaction with <u>samarium(II) iodide</u>:



The reaction of an <u>allyl</u> bromide with <u>formaldehyde</u> in THF with <u>indium</u> powder:



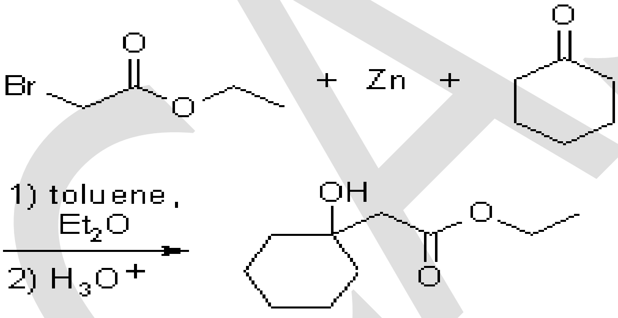
The Barbier reaction is accompanied by an allylic rearrangement to a terminal alkene or another allyl bromide in a reaction with benzaldehyde and zinc powder in water:



The observed diastereoselectivity for this reaction is erythro : threo = 83 : 17

Reformatsky Reaction

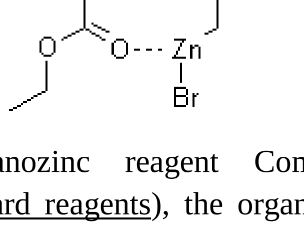
The Reformatsky reaction (sometimes spelled Reformatskii reaction) is an organic reaction which condenses aldehydes or ketones with α-halo esters using metallic zinc to form β-hydroxy-esters: The organozinc reagent, also called a 'Reformatsky enolate', is prepared by treating an alpha-halo ester with zinc dust.



The formation of ester-stabilized organozinc reagents and their addition to carbonyl compounds

Mechanism of the Reformatsky Reaction

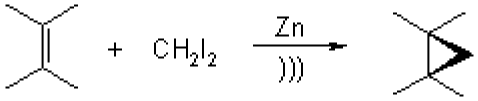
Organozinc compounds are prepared from α-halogenesters in the same manner as Grignard Reagents. This reaction is possible due to the stability of esters against organozincs. Due to the very low basicity of zinc enolates, there is hardly any competition from proton transfer, and the scope of carbonyl addition partners is quite broad. In presence of ketones or aldehydes, the organozinc compounds react as the nucleophilic partner in an addition to give β-hydroxy esters.



An ester-stabilized organozinc reagent Compared to organolithiums and organomagnesium halides (Grignard reagents), the organozinc halide reagents used in the Reformatsky Reaction are relatively stable, and many are available commercially.

Simmons-Smith Reaction

The Simmons–**Smith reaction** is an organic cheletropic **reaction** involving an organozinc carbenoid that reacts with an alkene (or alkyne) to form a cyclopropane.



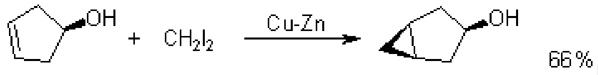
This reaction affords the cyclopropanation of olefins.

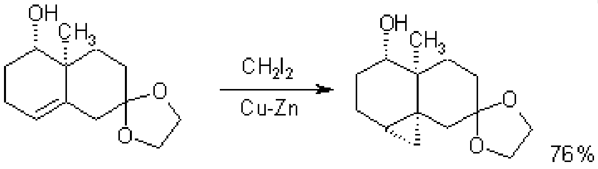
Mechanism of the Simmons-Smith Reaction

Ultrasonication improves the rate of formation of these organozinc compounds, as with many organometallic reactions occurring at a surface.

$$2\,CH_2I_2 + 2\,Zn \longrightarrow 2\,ICH_2ZnI \rightleftharpoons (ICH_2)_2Zn + ZnI_2$$

The mechanism has not been fully clarified, but pure carbenes can be excluded, and a metal carbenoid is likely to be involved. The following results may be interpreted to indicate a possible complexation of the active species by hydroxy groups leading to reaction on the same face as this substituent. This would only be possible if an organozinc reagent is present.

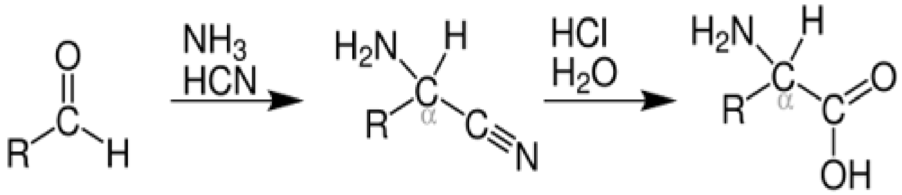




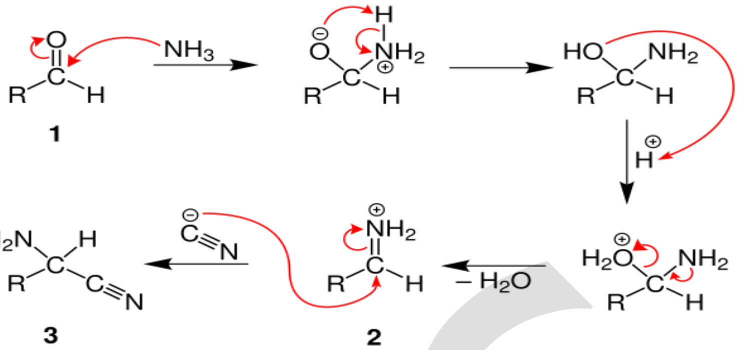
Various research groups have developed variants of the Simmons-Smith cyclopropanating reagent through the replacement of the iodide ligand on the zinc atom with a strongly electron-withdrawing substituent. Whereas the original reagent often requires a directing group such as the hydroxyl of an allylic alcohol, carbenoids such as $CF_3CO_2ZnCH_2I$ and $(PhO)_2P(O)OZnCH_2I$ enable a rapid cyclopropanation of alkenes without the need for such a directing group.

Strecker reaction

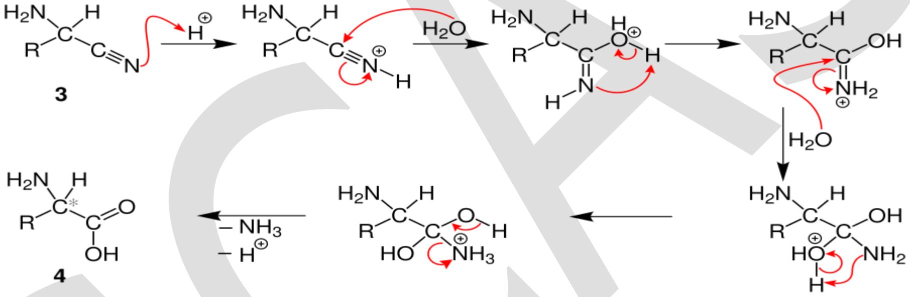
The Strecker amino acid synthesis, also known simply as the Strecker synthesis, is a method for the synthesis of amino acids by the reaction of an aldehyde with ammonium chloride in the presence of potassium cyanide. The condensation reaction yields an α-aminonitrile, which is subsequently hydrolyzed to give the desired amino acid. The method is used commercially for the production of racemic methionine from methional.



Reaction mechanism, In the first part of the reaction, the carbonyl oxygen of an aldehyde is protonated, followed by a nucleophilic attack of ammonia to the carbonyl carbon. After subsequent proton exchange, water is cleaved from the iminium ion intermediate. A cyanide ion then attacks the iminium carbon yielding an aminonitrile.



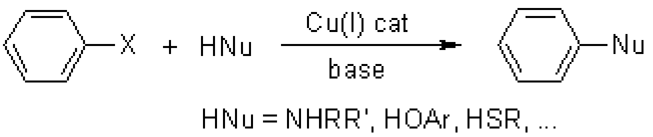
In the second part of the Strecker Synthesis the nitrile nitrogen of the aminonitrile is protonated, and the nitrile carbon is attacked by a water molecule. A 1,2-diamino-diol is then formed after proton exchange and a nucleophilic attack of water to the former nitrile carbon. Ammonia is subsequently eliminated after the protonation of the amino group, and finally the deprotonation of a hydroxyl group produces an amino acid.



Ullmann coupling reaction

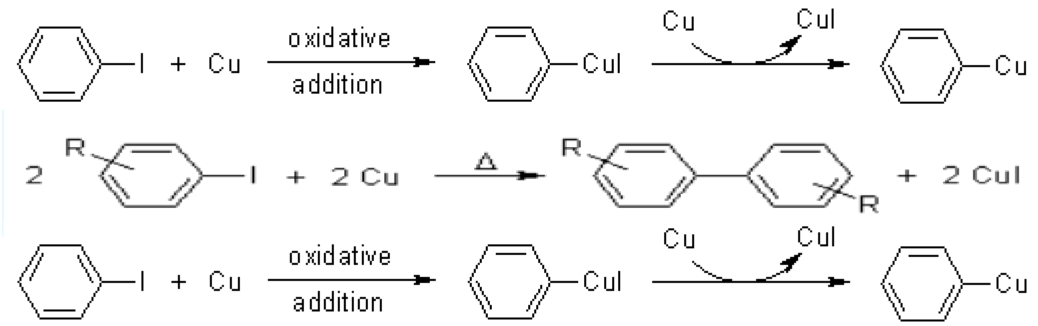
The Ullmann reaction or Ullmann coupling is a **coupling reaction between aryl halides and copper**.

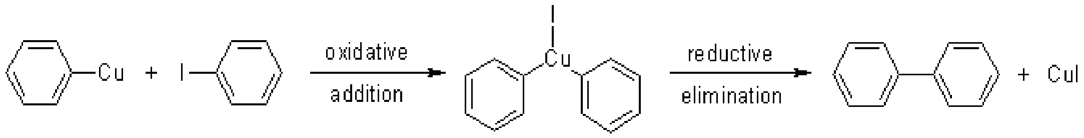
There are two different transformations referred as the Ullmann Reaction. The "classic" Ullmann Reaction is the synthesis of symmetric biaryls via copper-catalyzed coupling. The "Ullmann-type" Reactions include copper-catalyzed Nucleophilic Aromatic Substitution between various nucleophiles (e.g. substituted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



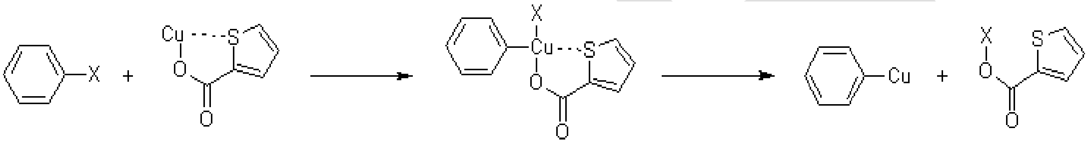
Mechanism of the Ullmann Reaction

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

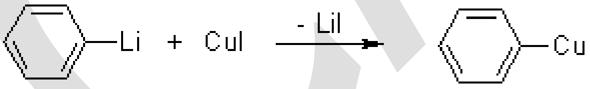




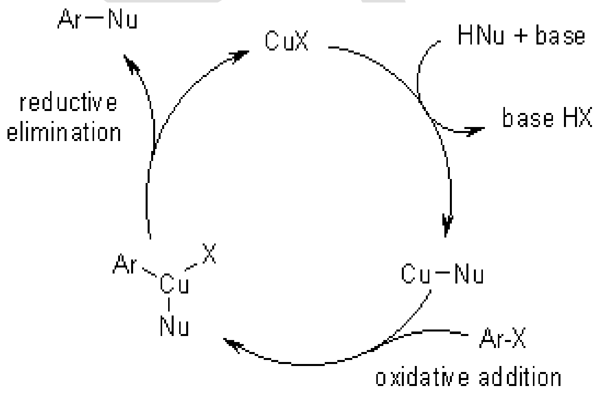
The organocopper intermediate can be generated at a more moderate 70 °C using a novel thiophenecarboxylate reagent. The reaction otherwise follows the same reaction path as above.

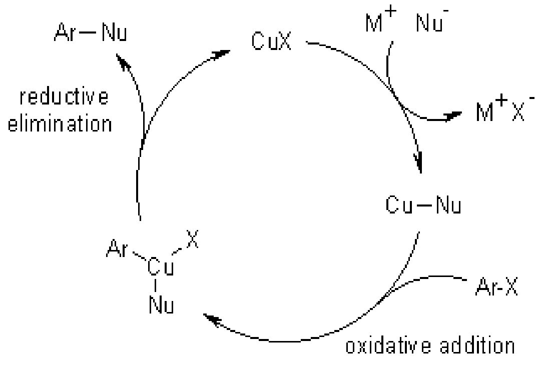


Another possibility is the use of Cu(I) for the oxidative coupling of aryllithium compounds at low temperatures. This method can also be used to generate asymmetric biaryls, after addition of the appropriate halide.



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





Wurtz Reaction

The Wurtz reaction, named after Charles Adolphe Wurtz, is a coupling reaction in organic chemistry, organometallic chemistry and recently inorganic main group polymers, whereby two alkyl halides are reacted with sodium metal in dry ether solution to form a higher alkane. In this reaction alkyl halides are treated with sodium metal in dry ethereal (free from moisture) solution to produce higher alkanes and it is also used for the preparation of higher alkanes containing even number of carbon atoms.

Wurtz Reaction Mechanism

The mechanism of the Wurtz reaction involves a free radical species denoted by R• which is a part of a halogen-metal exchange. This mechanism is somewhat similar to the formation of Grignard reagents. The carbon-carbon bond is formed in a nucleophilic substitution reaction in this reaction mechanism, which can be broken down into the following 3 steps:

Step 1: The transfer of an electron from the metal (sodium in this case) to the halogen leads to the formation of an alkyl halide along with the metal halide. This reaction can be written as follows.

$$\mathbf{R\text{-}X + Na \rightarrow R\bullet + Na^{+}R^{-}}$$

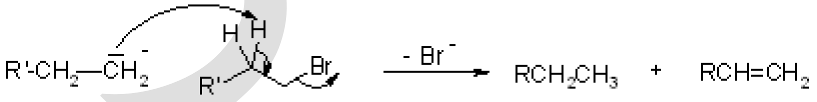
Step 2: A different sodium atom now donates a single electron to the alkyl radical, leading to the formation of an alkyl anion as shown below.

$$\mathbf{R\bullet + Na \rightarrow R\text{–}Na+}$$

Step 3: The carbon belonging to the alkyl anion having a nucleophilic nature proceeds to displace the halogen in the alkyl halide via an SN2 reaction and form a covalent bond with the carbon which was bonded with the halogen. The reaction detailing this step is given below.

$$\mathbf{R\text{–}Na^{+} + R\text{-}X \rightarrow R\text{-}R + Na^{+}X^{-}}$$

As discussed earlier, the free radical mechanism for the Wurtz reaction involves the possibility of an alkene being produced as a side product. This side reaction is explained via the reaction provided below.



Thus, the required alkane product is formed in the Wurtz reaction mechanism. It can be noted that the reaction has relatively low yields due to the formation of multiple products.

Limitations of the Wurtz Reaction

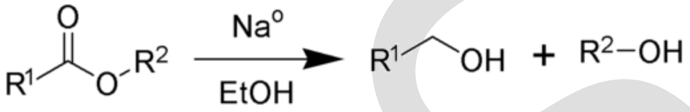
A few limitations of this reaction are listed below.

- Commonly, only symmetric alkanes can be synthesized via this method since a mixture of alkane products are formed when dissimilar alkanes are reacted (these mixtures are difficult to separate).

- There exists a side reaction via which an alkene product is formed. Should the alkyl halides be bulky in nature, especially at the halogen end, there is a greater amount of alkene formed.
- Methane cannot be synthesized via the Wurtz reaction since the product of an organic coupling reaction must have at least two carbon atoms.
- The Wurtz coupling method generally fails when tertiary alkyl halides are used

Bouveault reaction

The Bouveault–Blanc reduction is a chemical reaction in which an ester is reduced to primary alcohols using absolute ethanol and sodium metal. Bouveault and Blanc demonstrated the reduction of ethyl oleate and n-butyl oleate to oleyl alcohol.modified versions of which were subsequently refined and published in Organic Syntheses.

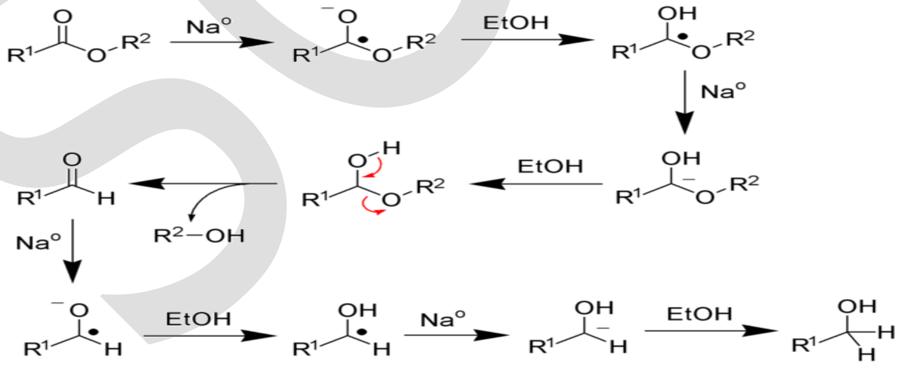


This reaction is used commercially although for laboratory scale reactions it was made obsolete by the introduction of lithium aluminium hydride.

Reaction mechanismSodium metal is a one-electron reducing agent. Four equivalents of sodium are required to fully reduce each ester. Ethanol serves as a proton source. The reaction produces sodium alcoxides, according to the following stoichiometry:

$$\mathrm{RCOOR'} + 6\ \mathrm{Na} + 4\ \mathrm{CH_3CH_2OH} \rightarrow \mathrm{RCH_2ONa} + \mathrm{R'ONa} + 4\ \mathrm{CH_3CH_2ONa}$$

In practice, considerable sodium is consumed by the formation of hydrogen. For this reason, an excess of sodium is often required. Because the hydrolysis of sodium is rapid, not to mention dangerous, the Bouveault-Blanc reaction requires anhydrous ethanol. The mechanism of the reaction follows:



Consistent with this mechanism, sodium-ethanol mixtures will also reduce ketones to alcohols.

This approach to reducing esters was widely used prior to the availability of hydride reducing agents such as lithium aluminium hydride and related reagents. It requires vigorous reaction conditions and has a significant risk of fires, explaining its relative unpopularity. One modification involves encapsulating the alkali metal into a silica gel, which has a safety and yield profile similar to that of hydride reagents. Another modification using a sodium dispersion.