

ORGANIC CHEMISTRY

ORGANOMETALLIC AND ORGANOSULPHUR COMPOUNDS

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Organometallic Compounds

The compounds in which metal is directly bonded to a carbon atom, is known as organometallic compounds and generally represented as R-M. Organometallic compounds of Li, Mg are some of the most important organometallic reagents. Many other metals such as B, Na, Cu, Zn, Pd etc also forms metal-carbon bond and are extensively used in the organic syntheses. Each kind of organometallic compound has its own sets of properties and its use depends on the property of each kind of organometallic compounds. In every case metal is less electronegative than carbon, as a result the carbon metal bond is highly polar. Ionic character of the carbon metal bond depends on the nature of the metal used, as for example ionic character order of common metal is: $\text{Na} > \text{Li} > \text{Mg} > \text{Al} > \text{Zn} > \text{Cd} > \text{Hg}$. The ionic nature of the carbon metal bond makes organometallic compounds as source of nucleophilic carbon which reacts with electrophilic carbon and forms a new carbon-carbon bond. The electrostatic potential maps show that the carbon atom is electron rich in the organometallic compounds while it is electron poor in the alkyl halide. To rationalize the general reactivity of organometallic compounds it is convenient to view them as ionic, so $\text{R-M} = \text{R}^-\text{M}^+$. In this chapter physical and chemical properties of organolithium (RLi), Grignard reagents (RMgX) and organozinc compounds will be discussed.

Nomenclature

Organometallic compounds are normally named as substituted metals, *e.g.* alkyl metal or alkyl metal halide. For examples:

CH_3Li = methyl lithium

CH_3MgBr = methyl magnesium bromide

$\text{C}_6\text{H}_5\text{MgBr}$ = phenyl magnesium bromide

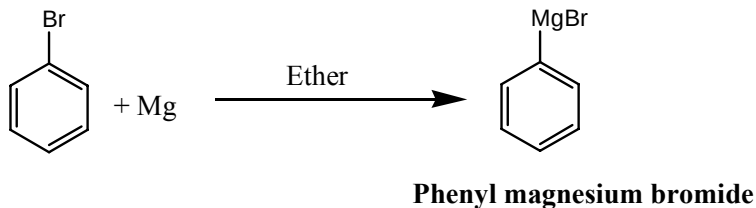
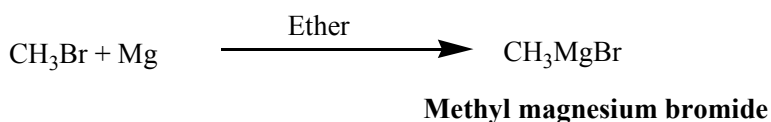
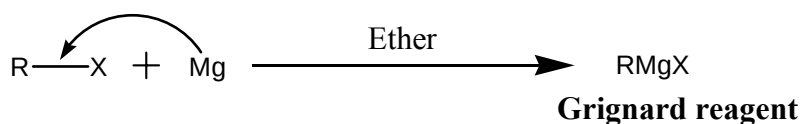
$\text{CH}_3(\text{CH}_2)_3\text{Li}$ = n-butyl lithium.

Physical properties

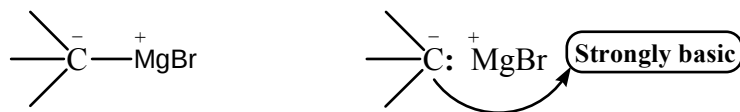
Due to high reactivity, organometallic compounds are kept in organic solvents under inert atmosphere. These reagents decompose very fast in the presence of trace amount of moisture or oxygen. Organometallic compounds are very polar and acts as a strong base.

Preparation and properties of organo magnesium compounds (Grignard reagent)

Organolithium and organomagnesium compounds are most important organometallic compounds of group IA and IIA. The compound with general formula RMgX is commonly known as Grignard reagent. The reaction of substituted halides (primary, secondary, tertiary, allylic, benzylic, aralkyl, and aryl) with magnesium metal in diethyl ether is a classical example of Grignard reagent, which was discovered by Francis August Victor Grignard (1871-1935). This reaction was discovered in 1900 and in next five years nearly 200 research papers were published on this reaction. In 1912 F. A. Victor Grignard was awarded Noble Prize in chemistry along with Paul Sabatier. In simple way of understanding Mg is oxidized to Mg^{+2} and is inserted between the carbon and the halogen.

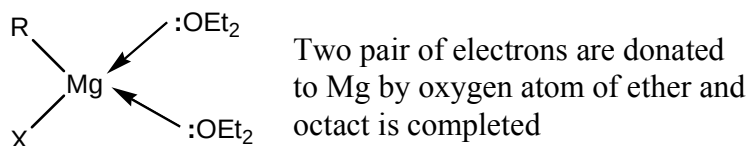


In Grignard reagent carbon bears high electron density as metal is more electropositive than carbon, so the carbon atom attached to Mg behaves as a nucleophile and acts as a strong base.

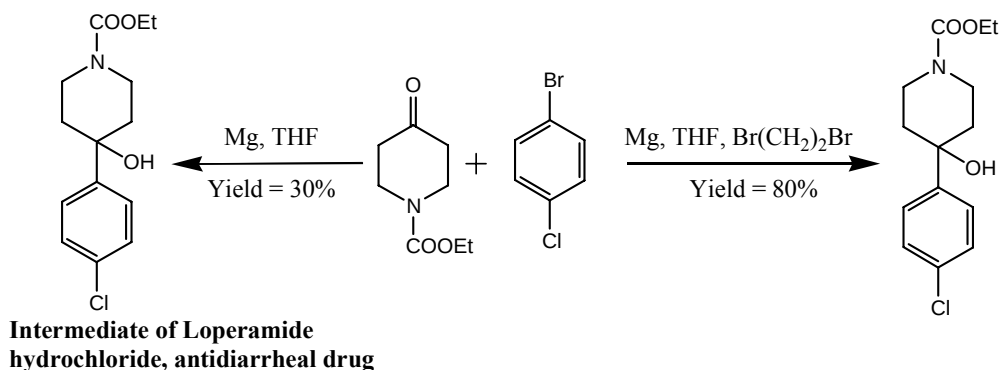


The Grignard reagents can not be used in the presence of compounds with acidic functionalities such as OH, NH, COOH or SH. Solution of some Grignard reagents methylmagnesium bromide (MeMgBr), ethylmagnesium bromide (C₂H₅MgBr), and phenyl magnesium bromide (PhMgBr) in ethereal solvents are commercially available.

Diethyl ether has been the solvent of choice for this reaction and plays a crucial role in the formation of a Grignard reagent. Magnesium atom of a Grignard reagent is surrounded by only four electrons and it requires two more pairs of electrons to form an octet. Solvent molecule (ether) provide these electrons by coordinating (supplying electron pairs) to the metal and forms lewis acid base complex between ether oxygen and magnesium atom.



Coordination allows the Grignard reagent to dissolve in the solvent and prevents the Grignard reagent from coating the magnesium shavings, which would make them unreactive. Tetrahydrofuran (THF) is another solvent that is commonly used for the synthesis of Grignard reagent since it has been found that it increases the reactivity of organic halides towards magnesium. In many cases where the synthesis of Grignard reagent is difficult, the addition of catalytic amount of methyl iodide may result in the formation of the Grignard reagent. This method is known as *entrainment method*. However, it was observed that addition of ethylene dibromide (3 moles or more) to excess of magnesium (6 moles or more) gives best results. The importance of this method can be realized in the synthesis of intermediate of loperamide hydrochloride (an antidiarrheal drug). In the absence of dibromoethane the yield of the desired product was 30% and addition of dibromoethane improved the yield to 80%.



Ease of formation of Grignard reagent depends on the following factors:

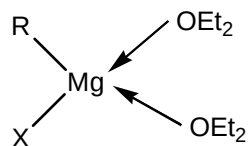
- The order of reactivity of halides is $\text{RI} > \text{RBr} > \text{RCl}$.
- Formation of Grignard reagent becomes increasingly difficult as the number of carbon atoms in the alkyl group increases i.e. the ease of formation is: $\text{CH}_3\text{X} > \text{C}_2\text{H}_5 > \text{C}_3\text{H}_7\text{X} > \dots$.
- Tertiary alkyl iodides readily eliminates hydrogen iodide with the formation of an alkene, tertiary alkyl chlorides are used for the preparation of Grignard reagents of tertiary alkyl halides.

Structure of Grignard reagent

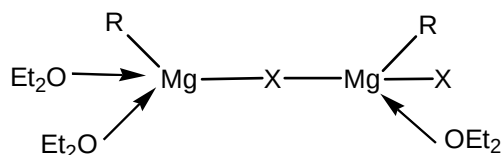
Structures of many Grignard reagents have been determined with the help of X-ray crystallography but this issue still has not been settled. According to Ashby the composition of Grignard reagents in ether may be represented by the following equilibrium:



The extent of association depends on the concentration of the Grignard reagent. Each molecule of Grignard reagent coordinate with one molecule of ether and the halogen atom of one molecule coordinates with the magnesium atom of another molecule. Structure of monomeric and dimeric Grignard reagent is shown below:



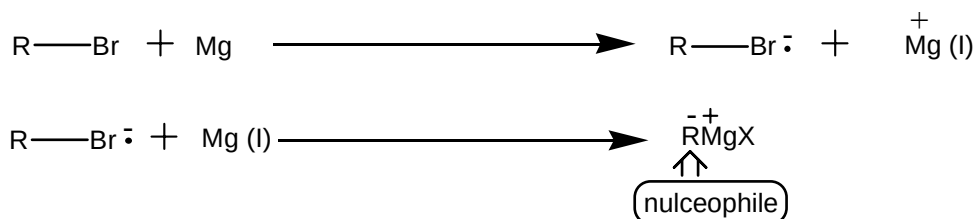
Monomer



Dimer

Mechanism of Grignard reaction

Mechanism of Grignard reaction has been a subject of debate. It is believed that the reaction takes place at the metal surface. Reaction probably takes place with an electron transfer, followed by rapid combination of organic groups with magnesium ion. The carbon-bromine bond breaks either prior to or during the formation of the carbon magnesium bond formation.

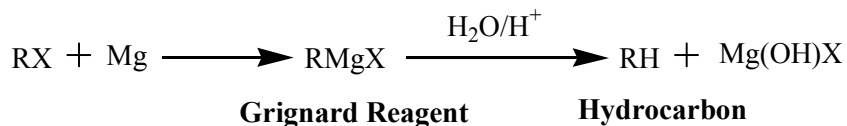


Synthetic uses of Grignard reagent

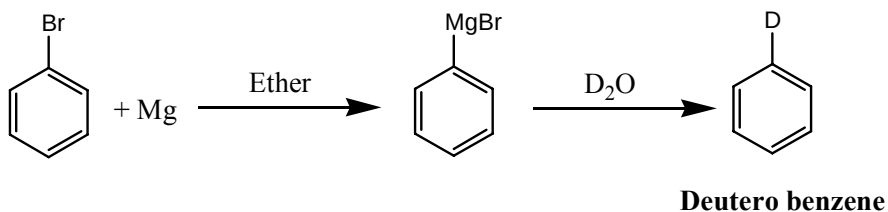
Grignard reagent can be used in the preparation of wide variety of organic compounds. Some of the important uses of Grignard reagent is discussed below.

Synthesis of hydrocarbons

Grignard reagent on reaction with a compound that contains active hydrogen or acidic hydrogen produces hydrocarbon. In practice, water or dilute acid is used in the preparation of hydrocarbons from Grignard reagents. Since the alkyl halides are readily prepared from alcohols, it is easy to convert an alcohol to the corresponding hydrocarbon.



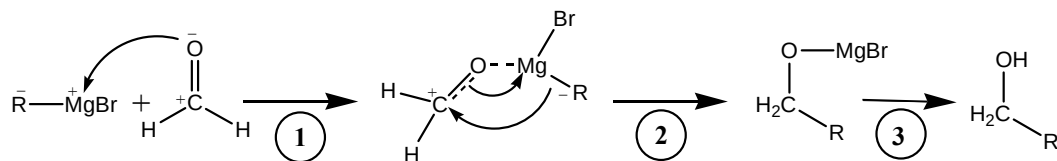
This reaction can be used to synthesize deuterated compounds. For example, reaction of phenyl magnesium bromide with D₂O resulted the formation of deuterobenzene.



Synthesis of alcohols

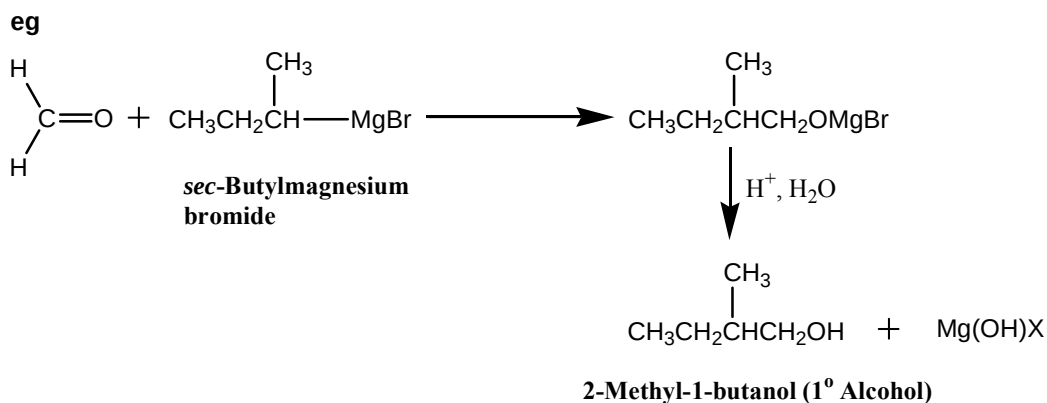
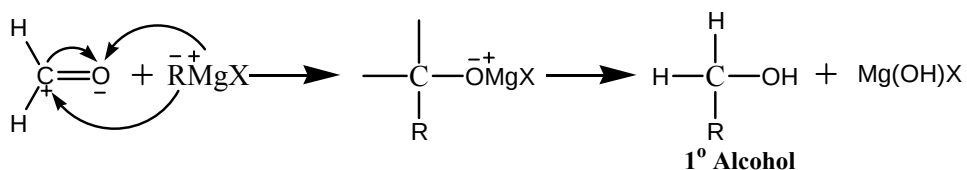
Reaction of Grignard reagent with carbonyl compounds is one of the most important synthetic uses of Grignard reagent. Carbonyl carbon being electron deficient reacts with negatively charged carbon of Grignard reagent and forms a new carbon-carbon bond. Hydrolysis of the resulted adduct lead the formation of alcohols. Depending on the

carbonyl compounds used in the reaction, one can get primary, secondary and tertiary alcohols.

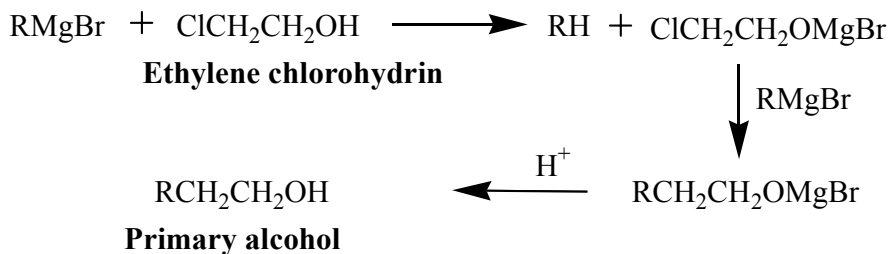


Synthesis of primary alcohols

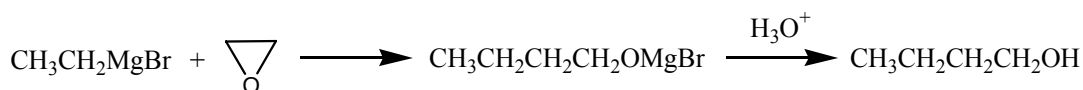
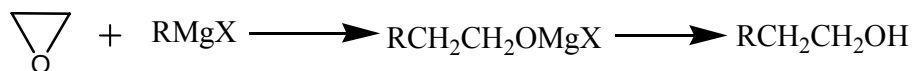
When Grignard reagent is treated with formaldehyde gas or with paraformaldehyde, a primary alcohol is obtained by decomposing the magnesium complex with dilute acid. In a simple way of understanding the reaction can be shown as below.



Primary alcohol containing two carbon atom more than the Grignard alkyl group can be prepared by adding one molecule of ethylene chlorohydrin to two molecules of Grignard reagent.



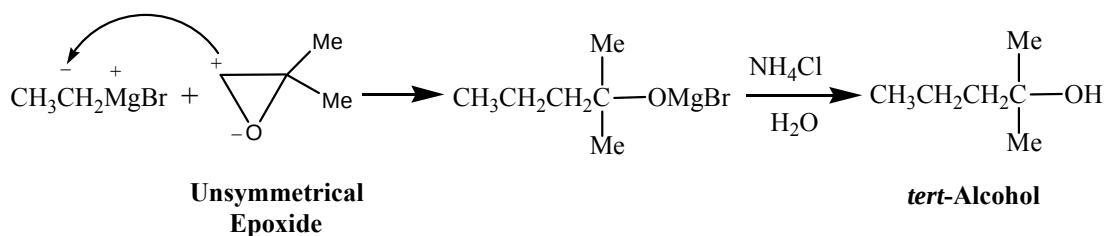
Epoxide ring being electrophilic in nature, is susceptible to reacts with Grignard reagents. The reaction of a Grignard reagent with ethylene oxide produces primary alcohol with two carbon atom more than the starting organohalide from which the Grignard reagent is prepared.



2 Carbon atom

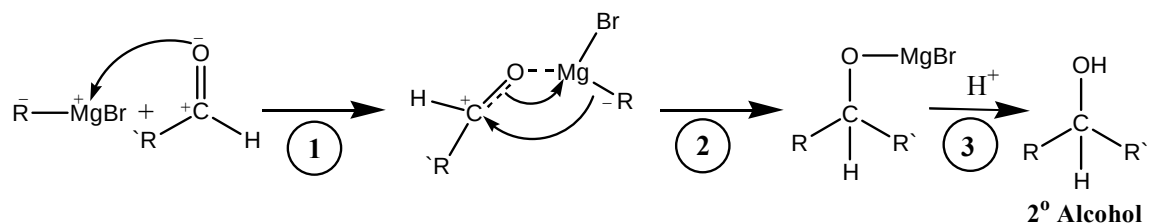
4 Carbon atom

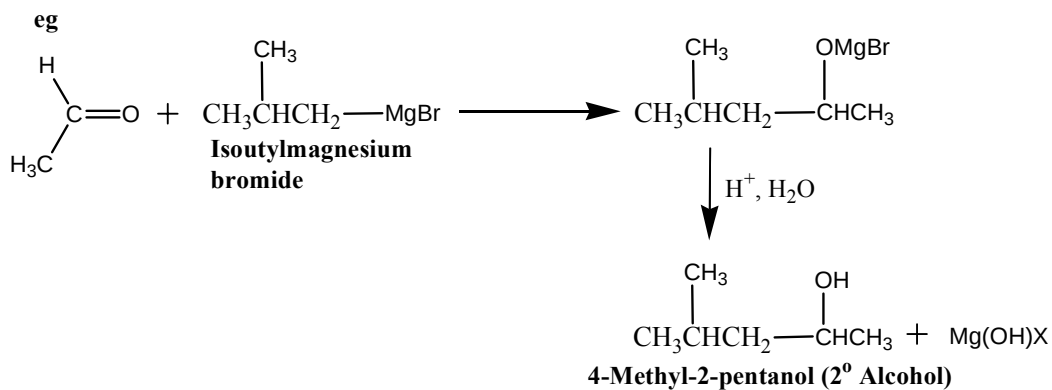
Unsymmetrical epoxide reacts with Grignard reagents at the less hindered carbon atom of the ring. Therefore, unsymmetrical epoxides produce 2° and 3° alcohols instead of primary alcohols.



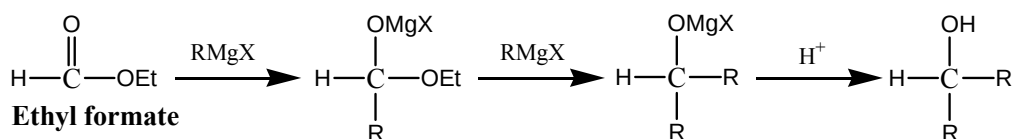
Synthesis of secondary alcohols:

When Grignard reagent is treated with aldehydes other than formaldehyde, a secondary alcohol is formed.



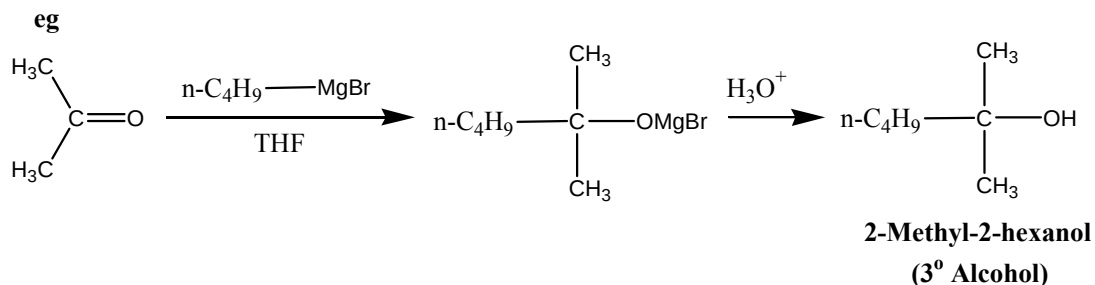
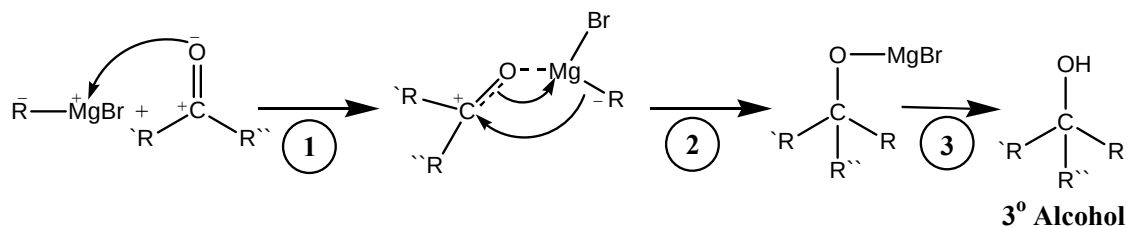


Secondary alcohols can also be prepared by the reaction of Grignard reagent (2 moles) and ethyl formate (1 mole).

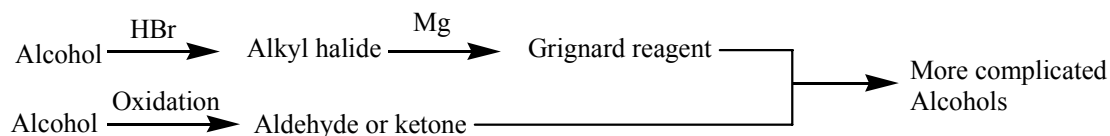


Synthesis of tertiary alcohols

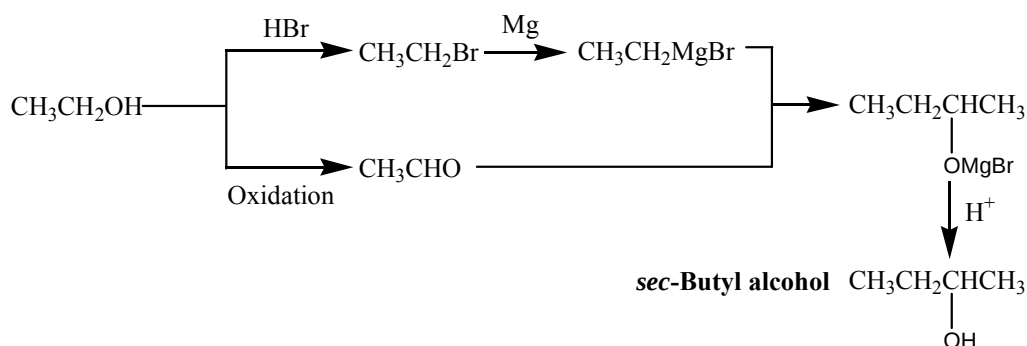
Reaction of Grignard reagent with ketones results in the formation of tertiary alcohols.



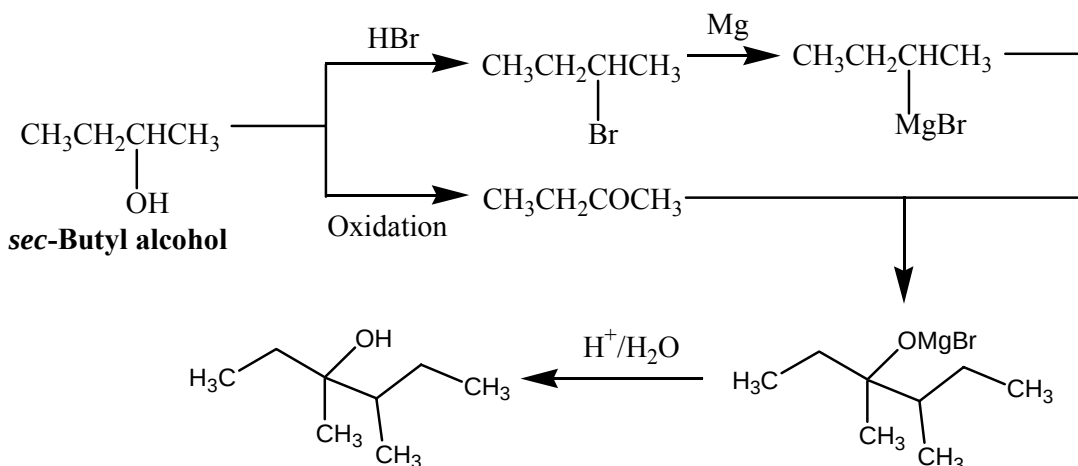
Halides and carbonyl compounds can easily be prepared from alcohols. So complicated alcohols can be prepared from simple alcohols as shown below:



For example using ethyl alcohol as a starting material one can prepare four carbon *sec*-butyl alcohol.

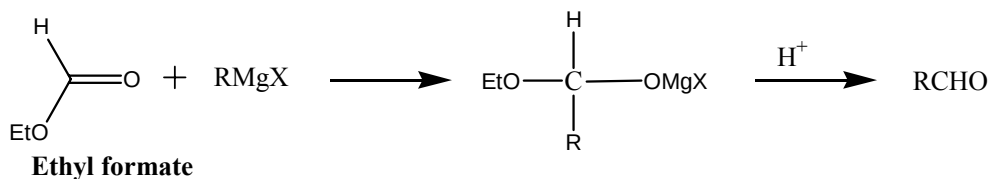


Using *sec*-butyl alcohol as a starting material one can synthesize even larger and more complicated alcohol.

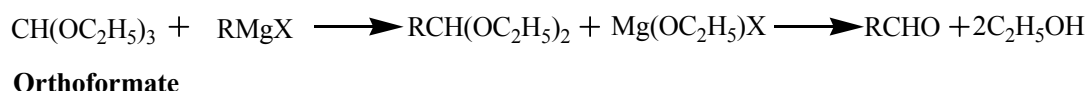


Synthesis of aldehydes:

Reaction of Grignard reagent (1 mole) and ethyl formate (2 mole) yields an aldehyde. If the Grignard reagent is used in excess, a secondary alcohol is formed. In a typical reaction conditions, the Grignard reagent is added to the ester.

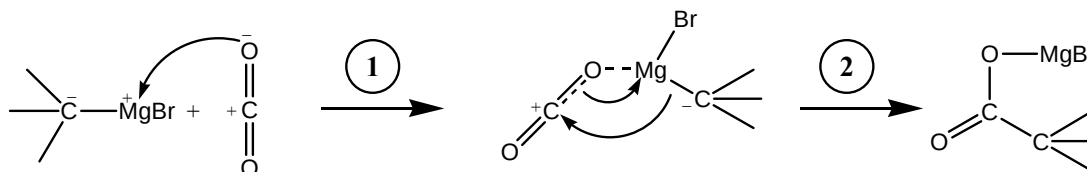


Yield of an aldehyde can be increased if orthoformate is used instead of ethyl formate. This is because of formation of secondary alcohol is prevented by the formation of an acetal.

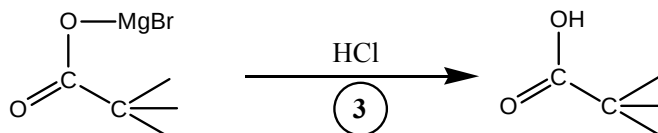


Synthesis of carboxylic acids:

Monocarboxylic acid can be prepared by the reaction of Grignard reagent with solid carbon dioxide followed by decomposition of complex with dilute acid. Carbon dioxide is polarized in such a way that its double bond connects an electrophilic carbon atom with a nucleophilic oxygen atom. Formally, the carbon atom of a Grignard reagent reacts as a nucleophile towards the carbon atom of CO_2 , producing halomagnesium salt of a carboxylic acid. The first step in this reaction is the attraction of carbonyl oxygen atom towards the electrophilic metal ion.



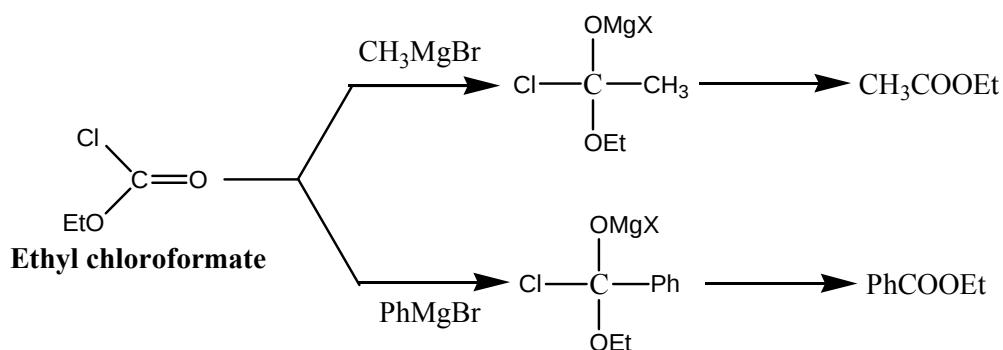
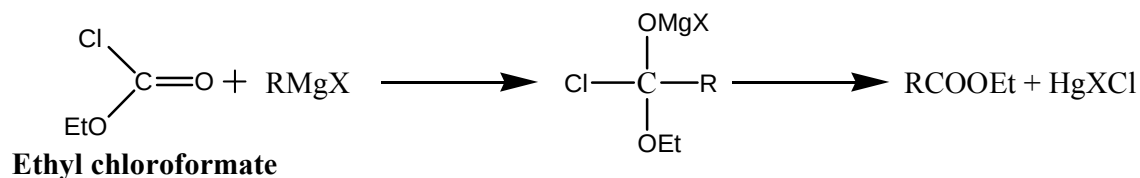
A separate hydrolysis step is required to liberate the free carboxylic acid. So treating the reaction mixture with dilute hydrochloric acid produces the carboxylic acid and magnesium halide. Magnesium halides are water soluble and can be washed away from the less polar organic molecules.



This method is very useful for the synthesis of hindered acids such as R_3CCOOH , which usually cannot be prepared by the cyanide synthesis using a tertiary alkyl halide.

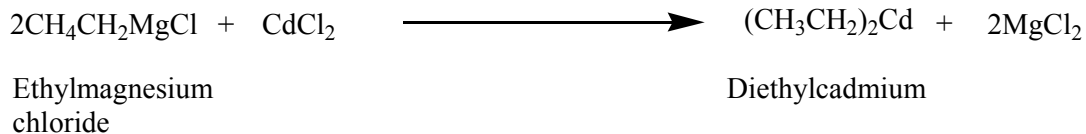
Synthesis of esters:

When one mole of Grignard reagent reacts with one mole of ethyl chloroformate, an ester is formed. In a typical reaction procedure, Grignard reagent is added to the ester in order to avoid the reaction with the carbethoxy group.



Transmetallation reaction:

Grignard reagent undergoes transmetallation (metal exchange) if it is added to a metal halide whose metal is more electronegative than magnesium. In other words, metal exchange will occur only if it results in a less polar carbon-metal bond. For example, carbon-cadmium bond is less polar than a carbon-magnesium bond, so metal exchange reaction takes place.



Limitation of Grignard reactions:

- Due to its highly basic character and reactivity towards many functional groups, Grignard reagent can't be prepared from any halide that contains an acidic hydrogen (alcohol, phenol, carboxylic acid, amine or thiol), or a reactive

functional group (carbonyl, nitrile, epoxide, nitro) even acetylenic hydrogen is acidic enough to decompose the Grignard reagent. Some of the examples of organic halides that can not form Grignard reagent are listed below (figure 1).

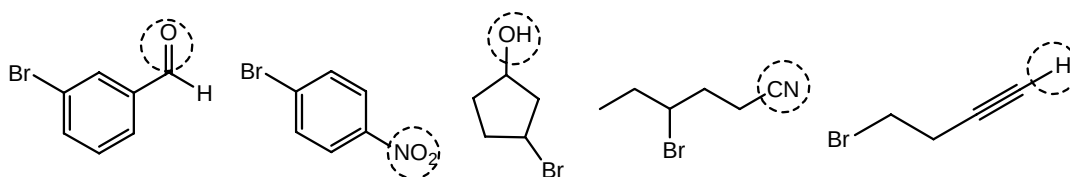
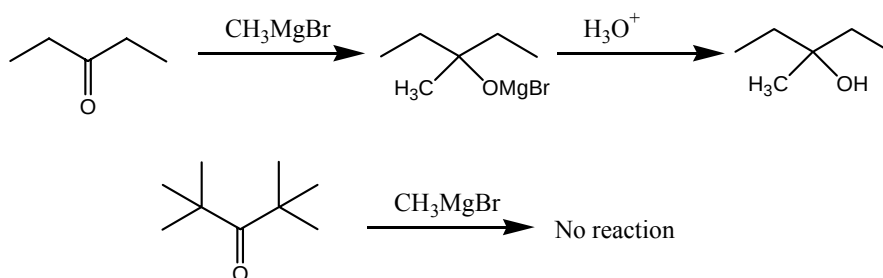
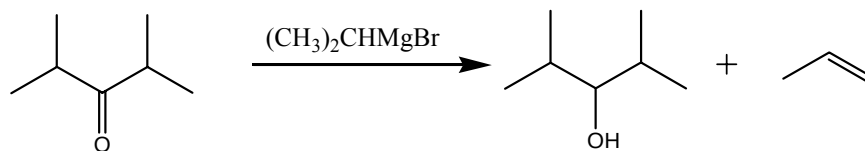


Figure 1: Organic halides that can not form Grignard reagent due to presence of acidic hydrogen or reactive functional group

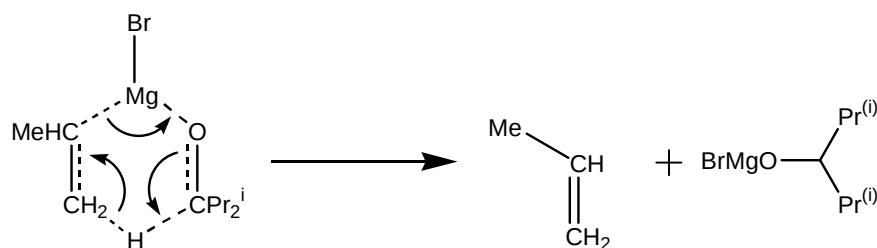
- Grignard reagent does not react with compounds that have branching at the functional group possibly due to steric hindrance. For example, methyl magnesium bromide reacts with $\text{CH}_3\text{CH}_2\text{COCH}_2\text{CH}_3$ while it does not react with $(\text{CH}_3)_3\text{CCOC}(\text{CH}_3)_3$.



- In another case when isopropyl magnesium bromide is added to di-isopropyl ketone, the expected tertiary alcohol is not formed, instead the secondary alcohol, di-isopropylcarbinol is obtained, resulting from the reduction of the ketone.

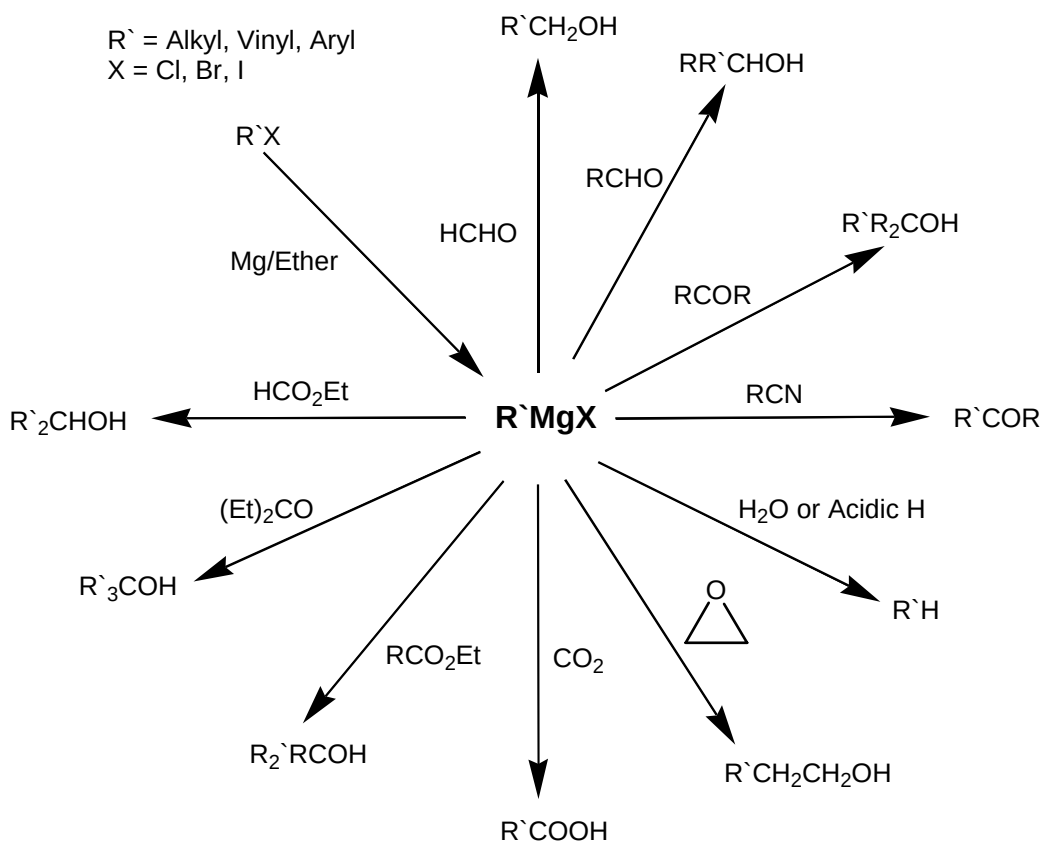


This abnormal reaction can be explained by the transfer of a hydride ion from the Grignard reagent via a cyclic transition state.



- The reaction of dihalides of the type $\text{Br}(\text{CH}_2)_n\text{Br}$ with magnesium depends on the value of n . For $n = 1-3$ no Grignard reagent is formed; eg ethylene dibromide ($n = 2$) gives ethylene; 1,3-dibromopropane ($n = 3$) gives propene, cyclopropane, and other products. When $n > 4$, the magnesium compound is obtained, but the yields are usually of the order of about 30%.

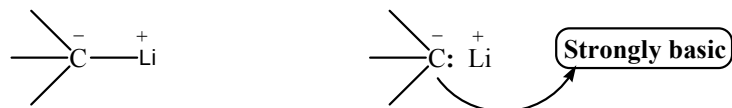
Overview of Grignard reactions:



Organolithium reagent:

Organolithium reagent is an organometallic compound in which carbon is bonded with a lithium atom. Due to strong electropositive nature of lithium the charge density of the bond lies on the carbon atom, effectively creating a carbanion. Organolithium compounds

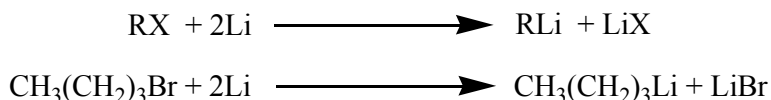
are strong bases and acts as a nucleophiles. Like organomagnesium compounds organolithium compounds are not monomeric but exist as tetrameric or hexameric species in solution as well as in solid state. Many organolithium compounds such as methyl lithium, butyl lithium, *sec*-butyl lithium, *tert*-butyl lithium are commercially available.



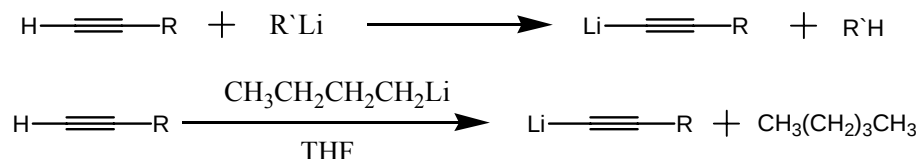
Preparation of organolithium compounds

Most commonly used methods for the preparation of organolithium compounds are discussed below:

1. Industrially organolithium reagents are prepared by the reaction of an organohalogen with lithium metal. Most of the halides such as alkyl, vinyl, and aryl halides can form organolithium compounds. Alkyl bromides are commonly used for this purpose because alkyl bromides are more reactive than alkyl chlorides and are less expensive than alkyl iodides. When alkyl iodide is used as a reactant, R-R coupled product (*Wurtz reaction*) is a side product of this reaction, which is formed by the reaction of R-Li species with an R-I. This side reaction can be almost completely avoided by using alkyl chlorides or bromides.

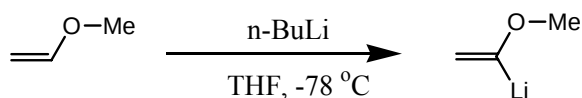
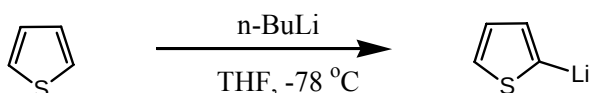
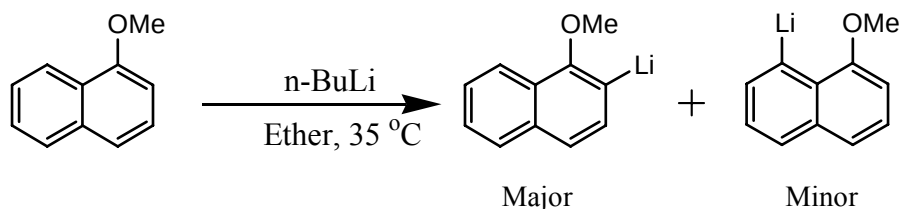


2. Another method which has limited utility is the hydrogen-metal exchange. This method is used for the synthesis of alkynyllithium reagents. The reaction proceeds smoothly because of the relative acidity of the hydrogen bounded to *sp* carbon.

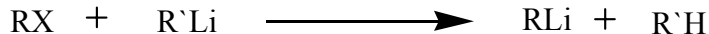


Metallation is an important reaction for the synthesis of organolithium compounds. The position of lithiation is determined by the relative acidities of the available hydrogen and the directing effect of the substituent groups. Benzylic and allylic hydrogen's are relatively reactive towards lithiation because of the resonance stabilization of the resulting anion. In heterocyclic compounds, the preferred site for lithiation is usually the adjacent to the heteroatom, while substituents that can co-ordinate (such as alkoxy,

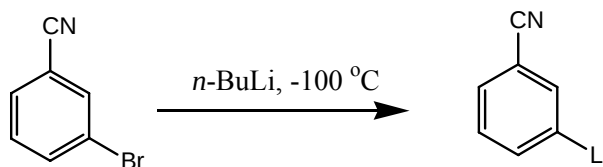
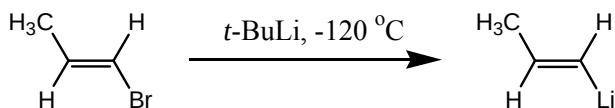
amido, sulfonyl) with lithium have powerful influence on the position and site of lithiation in the aromatic compounds.



3. Metal-halogen exchange is the another method for the synthesis of organolithium reagents. This reaction leads to the formation of more stable organolithium reagent that is the one derived from the more acidic organic structure.



4. By the use of the very basic organolithium compound *n*-butyl or *t*-butyllithium, halogen substituents at more acidic carbons are readily exchanged to give the corresponding lithium compounds. Halogen-metal exchange is particularly useful for converting aryl or alkenyl halides to the corresponding lithium compounds. The deriving force of the reaction is the greater stability of sp^2 carbanions in comparison with sp^3 carbanion.



Physical properties of organolithium compounds:

Organolithium compounds such as butyllithium are pyrophoric in nature so it is not feasible to determine chemical and physical properties such as melting point, boiling point, vapor pressure, water solubility and pK_a values of many organolithium compounds. An organolithium compound decomposes in presence of air and moisture, so any reaction that does not exclude air and moisture may not proceed. Butyllithium is extremely reactive towards air, moisture and is not stable in their presence. In fact butyllithium solutions are pyrophoric and catch fire if open to the air. Decomposition products are generally butane gas and corrosive hydroxide salts. It must be stored and handled in sealed systems under a dry inert gas (N_2 , argon) to prevent loss of activity.

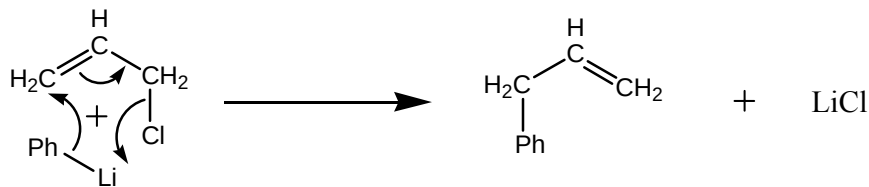
Organolithium compounds can deprotonate a large variety of organic compounds, with the exception of alkanes since they are highly basic in nature. Due to the extreme basicity of organolithium compounds, they are not commonly used for nucleophilic addition reactions, even though this can be a side reaction in deprotonation. The most commonly used organolithium reagents are methylolithium, *n*-butyllithium and *t*-butyllithium. As alkyl groups are weakly electron donating, the basicity of the organolithium compound increases with the number of alkyl substituents on the charge-bearing carbon atom. This makes *tert*-butyllithium the strongest commercially available deprotonating agent.

n-Butyllithium is the most prominent organolithium reagent. It has wide use as a polymer initiator in the production of thermoplastic elastomers (TPE) such as styrene. *n*-Butyllithium is also used as a strong base in organic synthesis. As it reacts violently with air and water, it is always used as a solution in an ether or hydrocarbon solvent. Annual worldwide production and consumption of *n*-butyllithium and other organolithium compounds is estimated at 1800 metric tones.

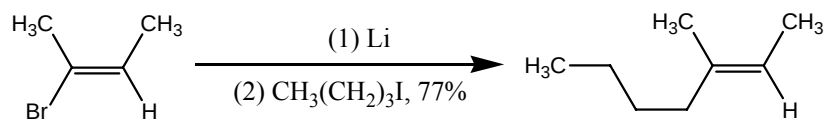
Chemical reactivity of organolithium compounds:

Reaction with alkylating agents:

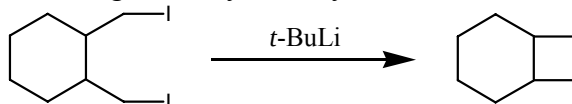
Although organolithium compounds are strongly basic and nucleophilic, but their use in the carbon-carbon bond formation is limited. Alkylation's of allylic halides is a more satisfactory reaction. Alkylations in this case proceed via a cyclic transition state.



Alkenyllithium reagents can be alkylated in good yields by alkyl iodides and bromides.

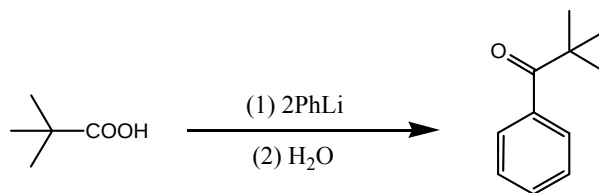
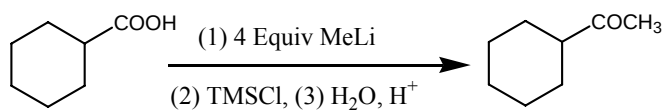
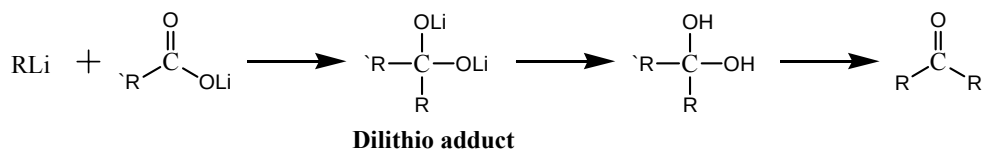


Reaction of 1,3-, 1,4-, and 1,5-diiodides with t-butyllithium is an effective method for the ring closure, but 1,6-diiodides gives very little cyclization.



Reaction with carboxylic acids:

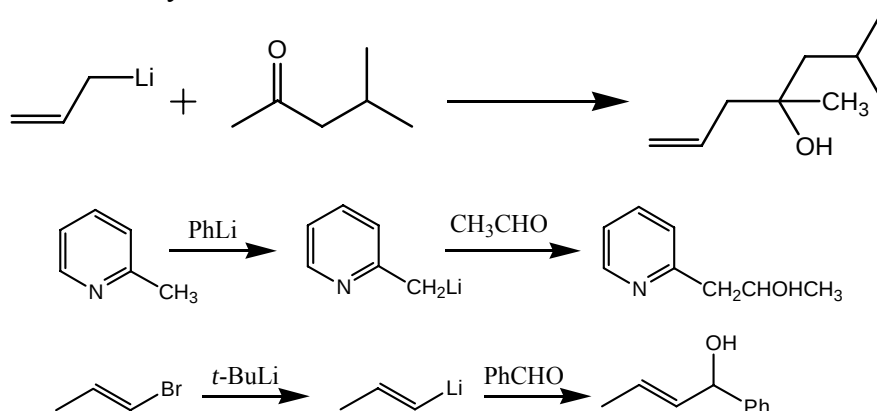
Reaction of alkyl lithium with lithium salts of carboxylic acid results in the formation of ketones. The success of this reaction depends on the stability of dilithio adduct thus formed during the reaction. The dilithio intermediate on hydrolysis generates ketone.



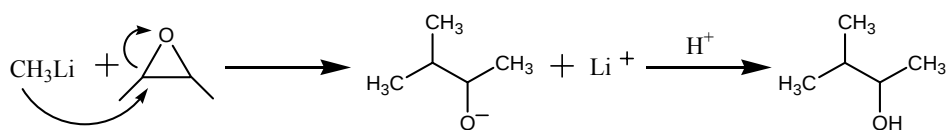
Reaction with carbonyl compounds:

Organolithium compounds are strongly polar compounds since lithium is electropositive in nature. They are therefore highly reactive nucleophiles and react with almost all types

of electrophiles. They are comparable to Grignard reagents, but are much more reactive. Due to this reactivity they are incompatible with water, oxygen and must be handled under inert atmosphere, preferably argon. Organolithium compounds on reaction with aldehydes and ketones yields alcohols.

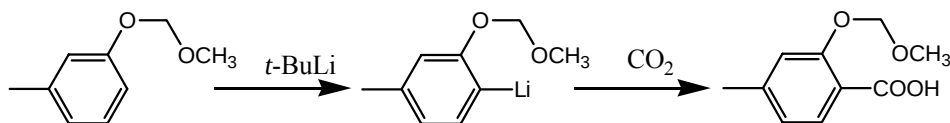


Organolithium reacts with epoxides and generates secondary alcohols.



Reaction with carbon dioxide:

Carbon dioxide on reaction with organolithium yields carboxylic acids.



Organozinc compounds

The reactivity of transition metal organometallic compounds depends on three properties of the metal viz. oxidation state of the metal, co-ordination number and its geometry. Zinc has filled *d* orbital (*d*¹⁰ electronic configuration) so +2 oxidation state of Zn is very stable. In most of the cases oxidation state or co-ordination number of the transition metal centre changes during the reaction but in case of zinc oxidation state remains same. This property makes the reactivity patterns of the group IIB organometallics more similar to those of the organometallics of groups IA and IIA than to those of organometallics of

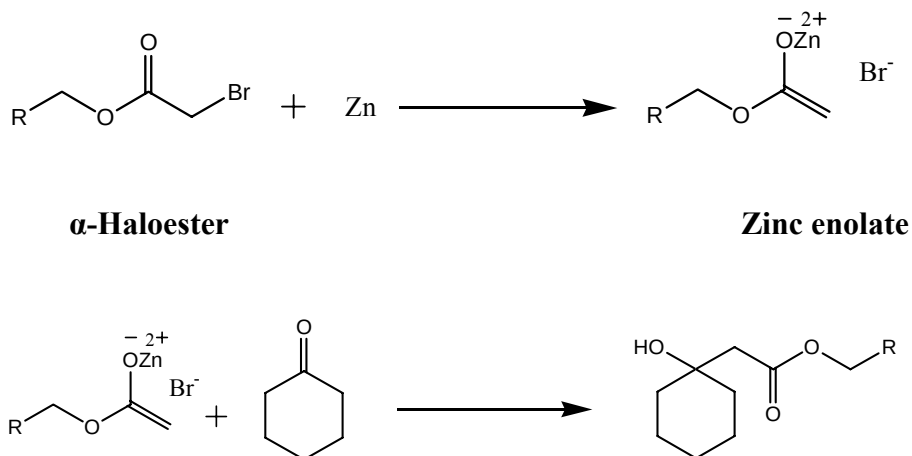
transition metals with vacant *d* orbital. Since zinc is much less electropositive than Li, or Mg metals, so the nucleophilicity of organozinc compounds is much less than organolithium or organomagnesium compounds.

Synthesis of organozinc compounds:

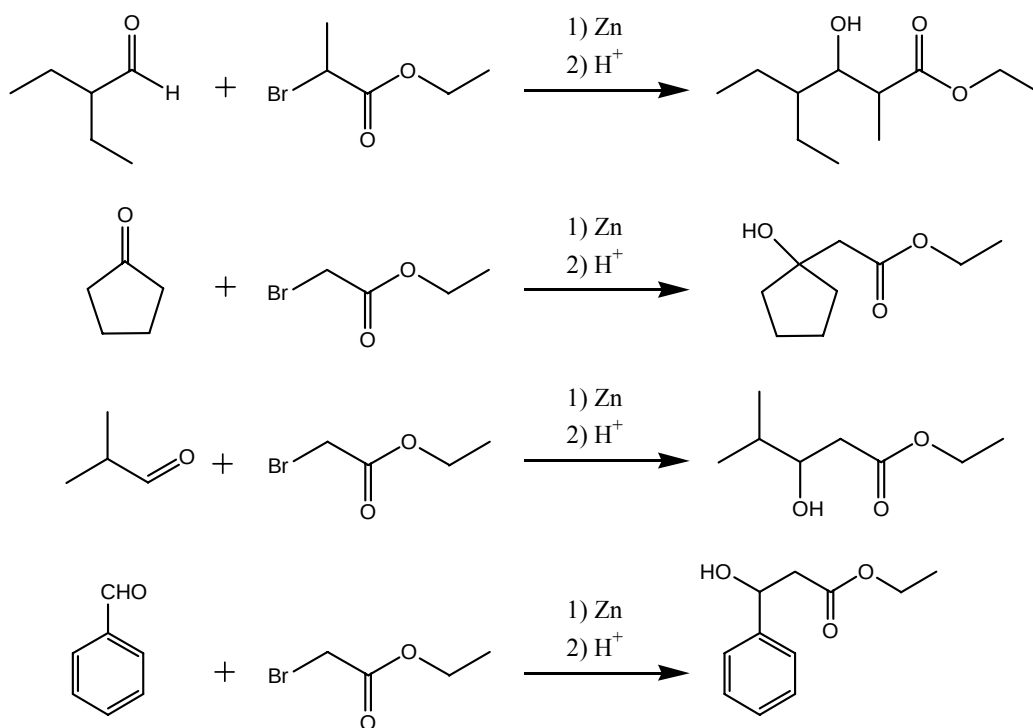
Organozinc compounds can be prepared by the reaction of Grignard or organolithium reagents with zinc salts. Sonication of organic halides, magnesium metals and zinc chloride has been a reliable method for the preparation of organozinc compounds.

Reaction involving Zn metal/salts:

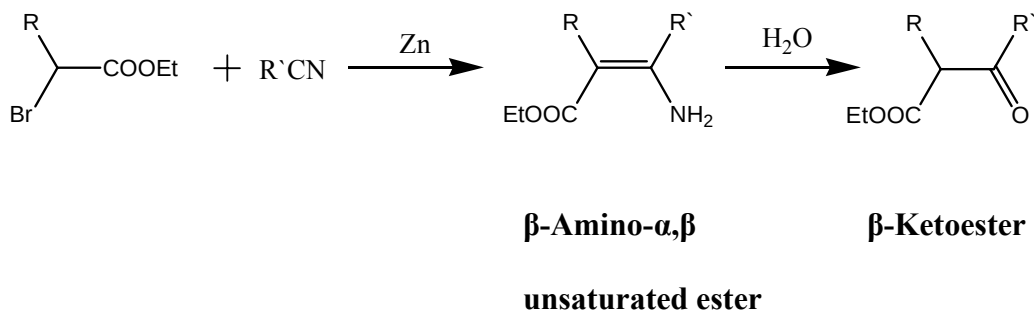
Reformatsky reaction: Reaction of zinc with α -haloester and carbonyl compounds yields a β -hydroxyester. This reaction is known as Reformatsky reaction. The reaction involves the formation of organozinc reagent, which is known as zinc enolate. The enolate carries out the nucleophilic attack on the carbonyl carbon.



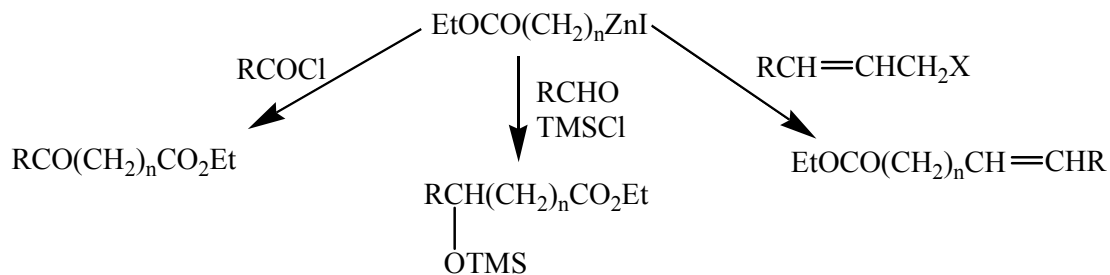
The yields of Reformatsky reaction can be improved by activating the zinc metal. Activation of zinc metal can be achieved by the pretreatment of zinc dust with a solution of copper acetate, or exposure of zinc metals to trimethylsilyl chloride. Some examples of Reformatsky reaction are listed below.



Zinc enolates some time undergo addition reaction with nitriles. The initial products are β -amino- α,β -unsaturated esters, which on hydroxylation yields β -ketoesters.



Organozinc compounds can react with various electrophiles such as acid chlorides, allyl tosylates and aldehydes in presence of tetramethyl silyl chloride (TMS-Cl) yielding different products.



Organosulphur compounds

Sulphur belongs to *p*-block and is located immediately below oxygen in the periodic table. Sulphur is less electronegative than oxygen and it possesses electronegativity characteristics comparable to carbon. Sulphur forms covalent bond with carbon and it is strong enough that the compounds can be isolated, however, carbon-sulphur bonds are weak enough to be efficiently and selectively cleaved in the presence of much stronger carbon-oxygen bonds. Sulphur also forms stable bonds to itself, with crystalline elemental sulphur being comprised of eight membered rings. Sulphur is an extremely versatile element, it can exist in a variety of oxidation states (+II, +IV and +VI) and it can behave as an electrophile and as a nucleophile. The common sulphur containing compounds are thiols, thioethers, thioacetals, thiocarbonyls, sulphoxides, sulphones, sulphonic acids and sulphonamides etc. According to IUPAC system of nomenclature the SH group is known as thiol group and suffix thiol is used for the naming these compounds. Compounds having SH group are also known as mercaptans, so common name of the SH containing compounds is alkyl mercaptans. Mercaptans are the sulphur analogues of the alcohols.

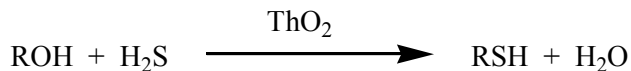
Structure	Common Name	IUPAC Name
CH_3SH	Methyl mercaptan	Methanethiol
$(\text{CH}_3)_2\text{CHCH}_2\text{SH}$	<i>Iso</i> -butyl mercaptan	2-Methylpropanethiol
$(\text{CH}_3)_3\text{CCH}_2\text{SH}$	<i>tert</i> -butyl mercaptan	3,3-Dimethylpropanethiol
$\text{CH}_3\text{CH}=\text{CHCH}_2\text{SH}$	Butenethiol	2-Butene-1-thiol

General methods of preparation:

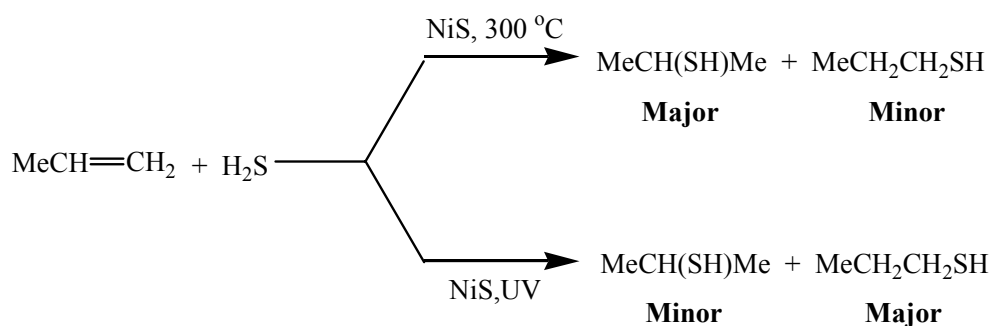
1. Thiols may be prepared by heating potassium or sodium hydrogen sulphide with an alkyl halide, a sodium alkyl sulphate or with a tosylate.



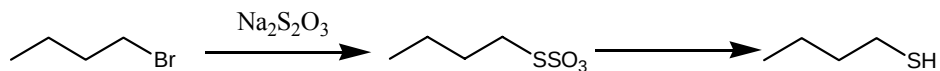
2. Another method for preparing thiols is to pass a mixture of alcohol vapour and hydrogen sulphide over a ThO_2 catalyst at 400°C .



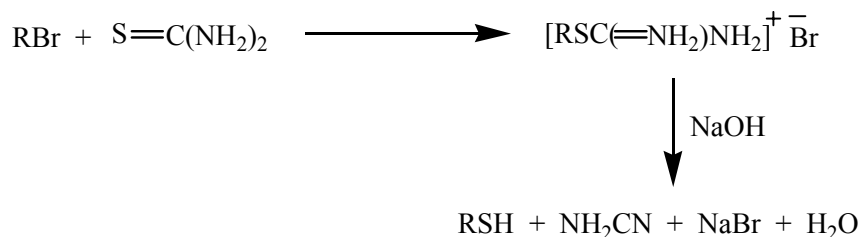
3. Reaction of alkenes with hydrogen sulphide in presence of nickel sulphide catalyst also leads to the formation of thiols. *Sec*-Thiol is the major product in this reaction and the reaction proceeds via Markonikoff polar addition mechanism. When UV light is used in this reaction, anti-Markonikoff product (primary thiol) is formed predominantly.



4. Aliphatic thiols can also be prepared *via* nucleophilic displacement of aliphatic halides with reagents such as H_2S , $\text{Na}_2\text{S}_2\text{O}_3$.



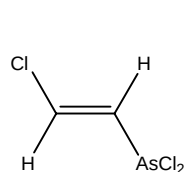
5. Decomposition of S-alkylisothiouranium salts with alkali is the best method of synthesizing thiols.



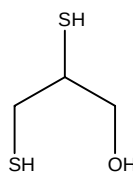
General properties:

Most of the thiols except methanethiol, are colorless volatile liquids with unpleasant smells. Since sulphur is less electronegative than oxygen, thiols do not form strong hydrogen bonds, and the boiling points of thiols are lower than the corresponding alcohols. The thiols are less soluble in water than the corresponding alcohols due to their lower ability to form hydrogen bond with water.

Thiols are more acidic than alcohols as SH bond is weaker (347.3 kJ) than OH bond (464.4 kJ). This difference can be accounted for the aromatic thiol/phenol pair by less effective resonance stabilization in the RS^- form. Therefore, thiols can easily be deprotonated under mild basic conditions (alkali hydroxides/alkoxides). In addition, sulphur possesses a very high affinity for metals such as mercury or silver and stable salts with these metals are easily formed. Thiols are also known as ‘**mercaptans**’ as a direct result of their ability to capture mercury. Since thiols complex with heavy metals, these are useful for making antidotes to heavy-metal poisoning. For example, during World War II the Allies were concerned that German would use lewisite (a volatile arsenic compound) as a chemical war fare agent. Since thiols complex strongly with arsenic, so British scientist developed dimercaprol (2,3-dimercapto-1-propanol) as an antidote.



Lewisite

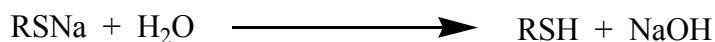
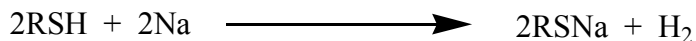


Dimercaprol
British anti-lewisite (BAL)

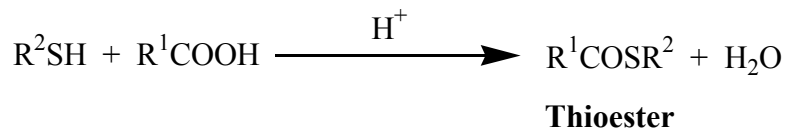
Chemical reactions:

Thiols resemble the alcohols in their chemical reaction except their behavior towards oxidizing agents is different.

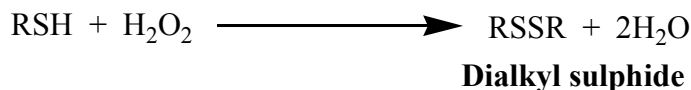
1. On reaction with alkali metals, thiols form mercaptides. Since alkali mercaptides are salts, so they can be decomposed by water.



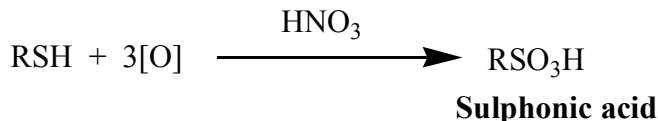
2. Reaction of thiols with carboxylic acids in presence of inorganic acids, results in the formation of thioester.



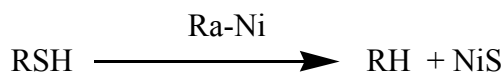
3. Thiols can be oxidized and the nature of the product formed depends in the nature of the oxidizing agents used. Mild oxidation with air, hydrogen peroxide, cupric chloride, or sodium hypochlorite results in the formation of dialkyl disulphides.



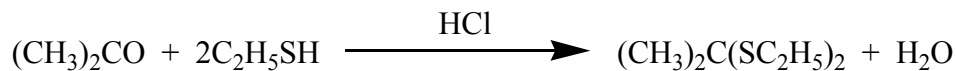
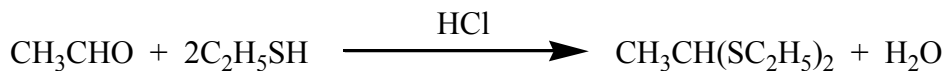
4. When oxidized with strong oxidizing agents, such as nitric or periodic acid, thiols can be converted into sulphonic acids.



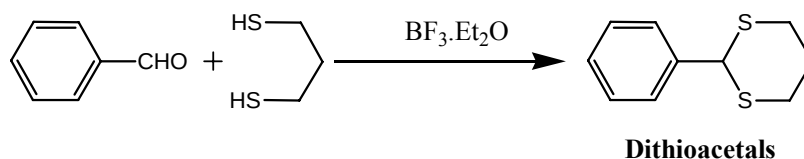
5. With Raney nickel, thiols undergo desulphurization.



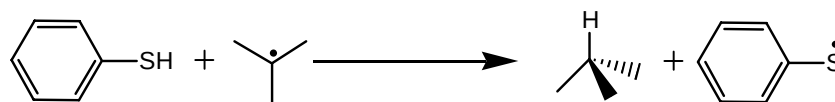
6. On reaction with aldehydes or ketones, thiols form mercaptals and mercaptols. This reaction takes place under acidic conditions.



7. Sulphur compounds are better nucleophiles than oxygen compounds towards saturated carbon atoms in $\text{S}_{\text{N}}2$ type reactions. Dithioacetals can easily be prepared by the reaction of aldehydes or ketones with thiols. Dithioacetal formation is favorable as a direct result of the enhanced nucleophilicity of the sulphur centre.



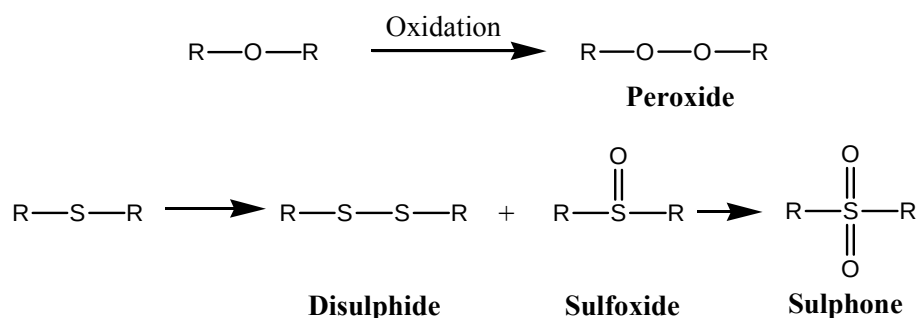
8. Since SH bond is weak, so thiols behave as hydrogen donor in free radical reactions. This type of reaction is exothermic in nature and requires a low activation energy and thus thiols are frequently employed in mechanistic studies as radical traps.



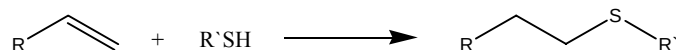
Thioether or alkyl sulphides:

The compounds having general formula R-S-R are known as thioethers, where R can be any organic group. A thioether is similar to an ether (R-O-R) except that it contains a sulfur atom in place of the oxygen. As both oxygen and sulphur are in the same group in the periodic table so the chemical properties of both atoms are similar and the chemical properties of the two functional groups are similar as well. Methionine, an amino acid is the most important example having thioether functional group. One characteristic feature of thioethers, like other sulfur containing compounds, is that simple volatile thioethers have foul odors.

The major difference between ether and thioether is the oxidation products one can obtain. Ethers (R-O-R) can easily be oxidized to peroxides, while thioethers can either be oxidized to disulphides or sulfoxides, which can themselves be oxidized to sulphones.



Biochemically, a thioether linkage is formed when a vinyl group reacts with a thiol/sulphydryl group, sulphur being attached to the less substituted carbon of the double bond.

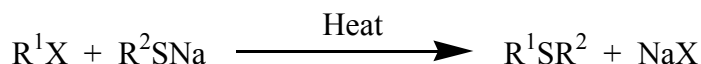


Preparation of thioethers:

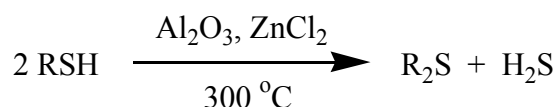
- Heating of an ether with phosphorous pentaoxide lead the formation of a thioether.



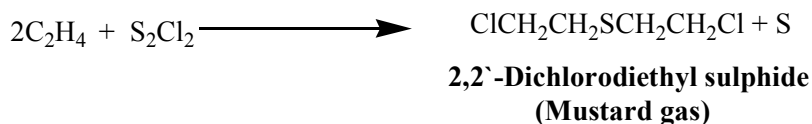
- By heating an alkyl halide with a sodium mercaptide. This method is known as Williamson's synthesis.

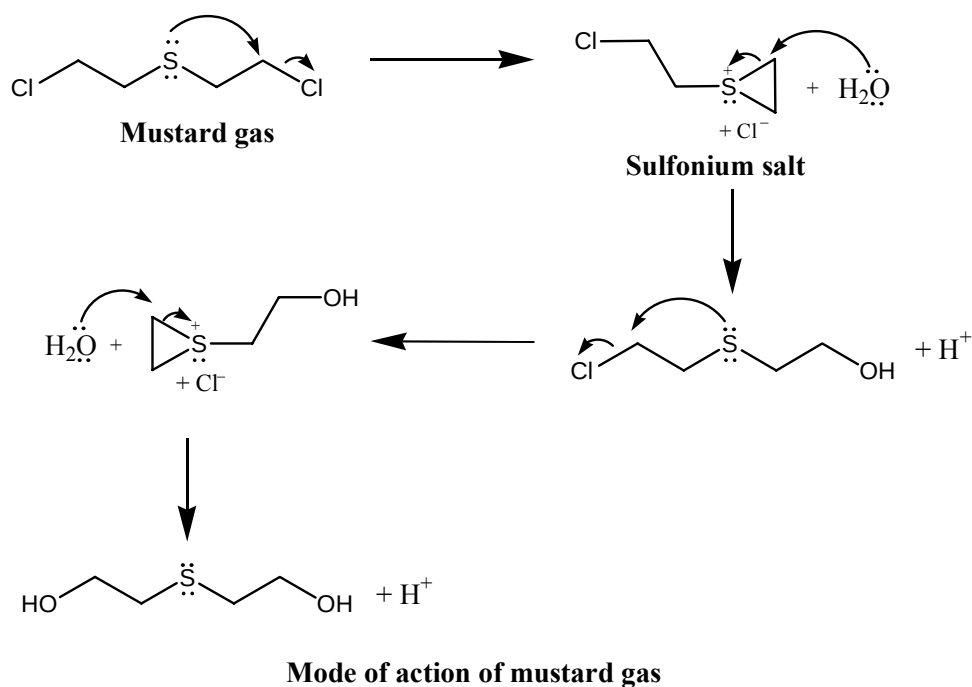


- By passing a thiol over a mixture of alumina and zinc chloride at 300 °C.

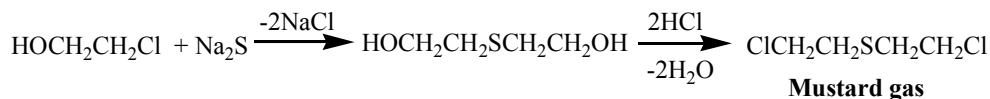


- 2,2'-Dichlorodiethyl sulphide or bis (2-chloroethyl) sulphide is known as mustard gas, which is a poison. It can be prepared easily by the reaction of sulphur monochloride on ethylene. Mustard gas is very toxic and produces blisters over the surface of the body. It is very reactive because of the formation of the strained three membered cyclic ring. The nucleophilic sulphur easily replaces chloride ion by intramolecular S_N2 reaction, forming cyclic sulfonium salt that readily reacts with a nucleophile. The toxicity of mustard gas is due to the high local concentration of HCl that is produced when water or any other nucleophile reacts with the gas when it comes into contact with the skin and/or lungs.



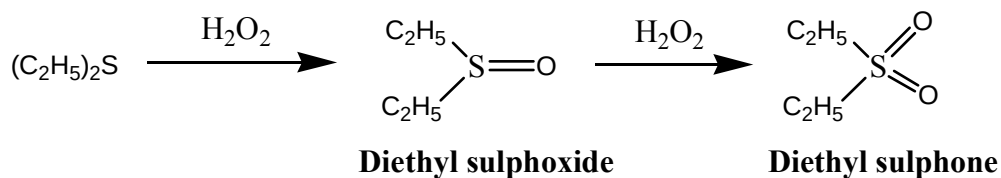


- Mustard gas can also be prepared by the heating of ethylene chlorohydrin with sodium sulphide, treating the resulting product with HCl.

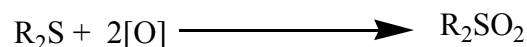


General properties and reactions of thioethers:

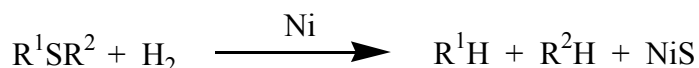
Thioethers are insoluble in water but soluble in common organic solvents. They behave as a weak bases. Thioethers can be oxidized to sulfoxides, which on further oxidation give sulphones. For example, ethyl sulphide on oxidation with hydrogen peroxide in glacial acetic acid gives first diethyl sulphoxide and then diethyl sulphone.



On oxidation with concentrated nitric acid, thioethers yield sulphone.

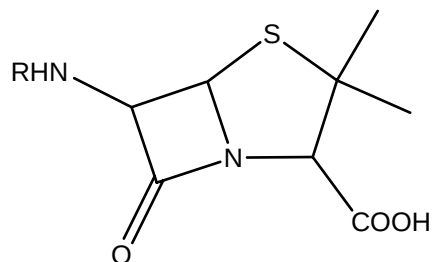


On treatment with Raney nickel, alkyl sulphides undergo desulphurization.



Penicillin is the most important example of thioesters, which exhibit potent antibacterial activity. The antibacterial effect of **penicillin** was discovered by Alexander Fleming in 1929. He noted that a fungal colony had grown as a contaminant on an agar plate streaked with the bacterium *Staphylococcus aureus*, and that the bacterial colonies around the fungus were transparent, because their cells were lysing. Fleming had devoted much of his career to find out the methods for treating wound infections, and immediately recognised the importance of a fungal metabolite that might be used to control bacteria. The substance was named penicillin, because the fungal contaminant was identified as ***Penicillium notatum***. Fleming found that it was effective against many Gram positive bacteria in laboratory conditions, and he even used locally applied, crude preparations of this substance, from culture filtrates, to control eye infections. However, he could not purify this compound because of its instability, and it was not until the period of the Second World War (1939-1945) that two other British scientists, Florey and Chain, working in the USA, managed to produce the antibiotic on an industrial scale for widespread use. All three scientists shared the Nobel Prize for this work, and rightly so - penicillin rapidly became the "wonder drug" which saved literally millions of lives. It is still a "front line" antibiotic, in common use for some bacterial infections although the development of penicillin-resistance in several pathogenic bacteria now limits its effectiveness.

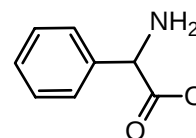
As shown in the diagram below, penicillin is not a single compound but a group of closely related compounds, all with the same basic ring-like structure (a **beta-lactam**) derived from two amino acids (valine and cysteine) via a tripeptide intermediate. Penicillin is a group of antibiotics that contain 6-aminopenicillanic acid with a side chain attached to the 6-amino group. The penicillin nucleus is the chief structural requirement for biological activity.



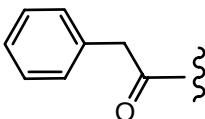
General Structure of Penicillin

R = H, 6-Aminopenicillanic acid

Ampicillin, R =



Penicillin G, R =



Sulphonic Acids

Compounds having the general formula RSO_3H are known as sulphonic acid where R being an alkyl or an aryl group. Sulphonic acids are named either as alkylsulphonic acids or as alkanesulphonic acids.



Methylsulphonic acid or methanesulphonic acid



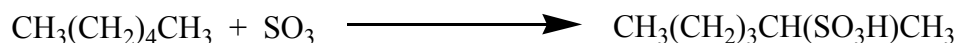
Isopropylsulphonic acid or propane-2-sulphonic acid



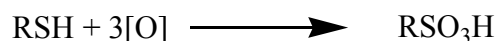
Benzenesulphonic acid

General methods of preparation:

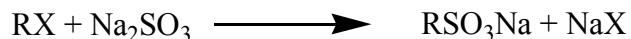
- Alkyl sulphonic acids are prepared by the reaction of sulphuric acid, oleum (fuming sulphuric acid) or chlorosulphonic acid with an alkane. The sulphonic acid group gets attached at the second carbon atom in the long chain alkane.



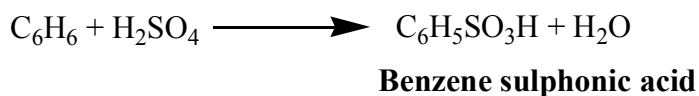
- Sulphonic acids can also be prepared by the oxidation of thiols with nitric acid or potassium permanganate or with sodium hypobromite.



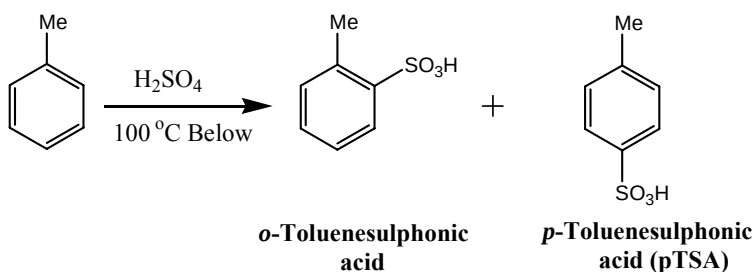
- Sodium salts of sulphonic acids can be prepared by heating an alkyl halide with sodium sulphite. This reaction is known as *Strecker reaction*.



- Sulphonation is a very common reaction in aromatic hydrocarbons and usually aromatic sulphonic acids are prepared by direct sulphonation of hydrocarbons with sulphonating agents such as concentrated sulphuric acid, sulphur trioxide in sulphuric acid i.e. oleum (fuming sulphuric acid). Benzenesulphonic acid can be prepared as shown below:



- Toluenesulphonic acid can be prepared by the reaction of concentrated sulphuric acid with toluene. When reaction is carried out below 100 °C, both *o* and *p* isomers formed in almost 1:1 ratio. However, at higher temperature *p*-isomer forms predominantly.



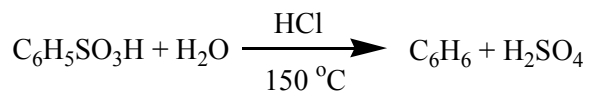
General properties

Sulphonic acids are very strong organic acids, possessing pK_a values comparable to sulphuric acid. Sulphonic acids are soluble in common organic solvents, so they are frequently used as an acid catalysts for reactions in aprotic solvents. In addition, they are non-oxidizing and unlike acids such as HCl, their conjugate bases are very poor nucleophiles. Camphorsulphonic acid (CSA) is used as an acid catalysts.

- Sulphonic acids when treated with PCl_5 yields acid chlorides.



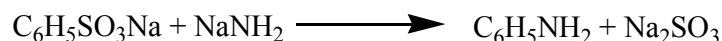
- Sulphonyl chlorides are hydrolyzed slowly by water. Sulphonic acids also on reaction with water at high temperature get hydrolyzed.



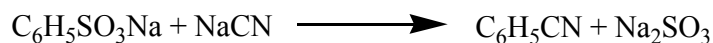
- Sulphonyl chloride reacts with concentrated aqueous ammonia to form sulphonamides and with alkoxides to form esters.



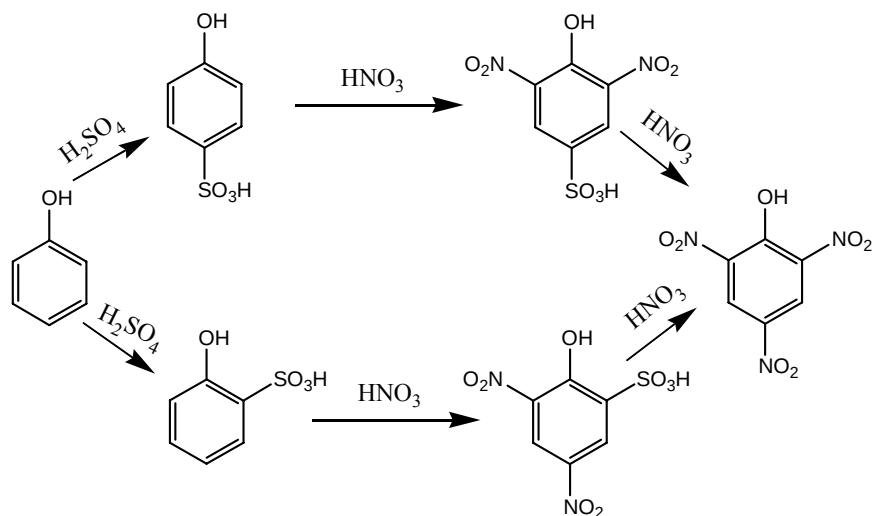
- Sodium benzenesulphonate on reaction with sodamide yields aniline.



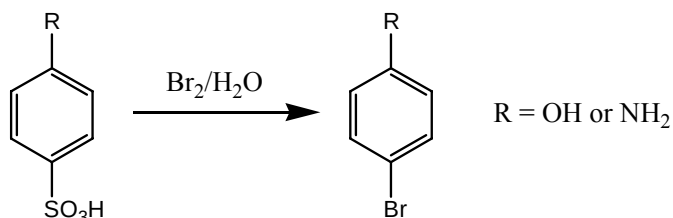
- When sodium benzenesulphonate is fused with sodium cyanide, phenyl cyanide is obtained.



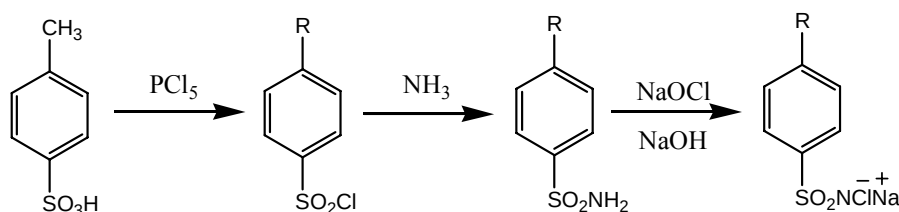
- Sulphonic acid group can easily be replaced by a nitro group. This offers a means of preparing nitro derivatives of compounds that are easily oxidized by nitric acid, as sulphonic acids are not easily oxidized. Using this methodology one can prepare picric acid from phenol.



- Sulphonic acid group *o* or *p* to hydroxyl or amino group can also be replaced by halogens.



- o*-Toluenesulphonyl chloride is used in the preparation of saccharin, *p*-toluenesulphonic acid (pTSA) is used for the preparation of chloramine T and dichloramine T which are antiseptics compounds. Chloramine T is the sodium salt of N-chloro-*p*-toluenesulphonate and can be prepared as shown below.



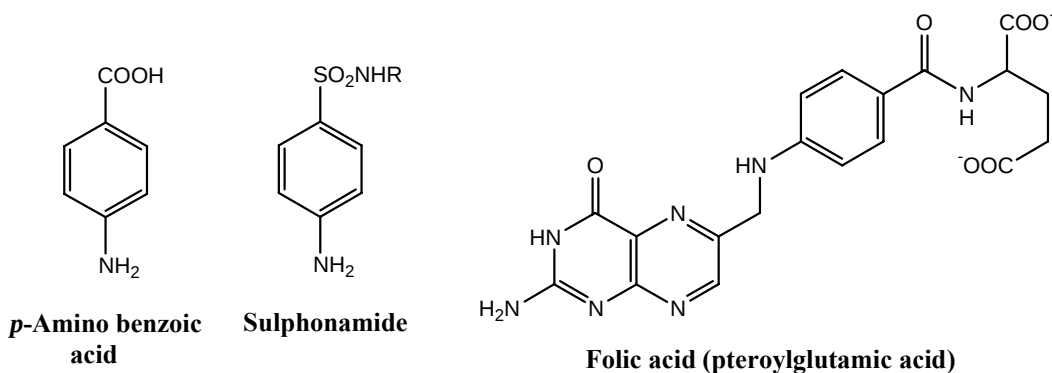
Sulpha Drugs

In the year 1932 Gerhard Domagk, noted German bacteriologist and pathologist observed the antibacterial effect of Prontosil (red dye) on streptococcal infections in mice. Later French investigators were the first to prove that sulfonamide was the active constituent responsible for the antibacterial activity of Prontosil. In subsequent years researchers created a rational basis for sulfonamide chemotherapy. Sulfonamides were the first chemical substances that were systematically used to cure and prevent bacterial infections in humans.

Sulfa drugs are assigned to four groups based on the rapidity with which they are absorbed and excreted. The most common side effects of sulfa drugs include nausea, vomiting and mental confusion. Other side effects include fever, skin eruptions, anemia, leukopenia and irritation of the liver or kidneys. More potent antibacterial drugs have largely replaced the sulfa drugs. However, they are still used in the treatment of urinary tract infection.

Sulphonamides:

Sulphonamides are therapeutically important molecules that exhibit potent antibacterial activity. Sulphonamides are not bactericidal which means in normal therapeutic concentrations sulphonamides do not kill the bacteria, but inhibit the growth and multiplication of the infectious organism and thus allow the host to eradicate the infection by normal defense mechanism. The bacteriostatic nature of sulphonamides is due to their similarity in structure with that of *p*-aminobenzoic acid. It has been observed that micro-organisms which are sensitive to sulphonamides require *p*-aminobenzoic acid as an essential nutrient. *p*-Aminobenzoic acid is an important precursor required for the synthesis of folic acid, which is an essential growth factor of some micro-organisms. When sulphonamides act on the susceptible organisms they compete with *p*-aminobenzoic acid and being similar in structure they are taken up by the bacteria by mistake. Thus, the enzymes required for the synthesis of folic acid are not available.

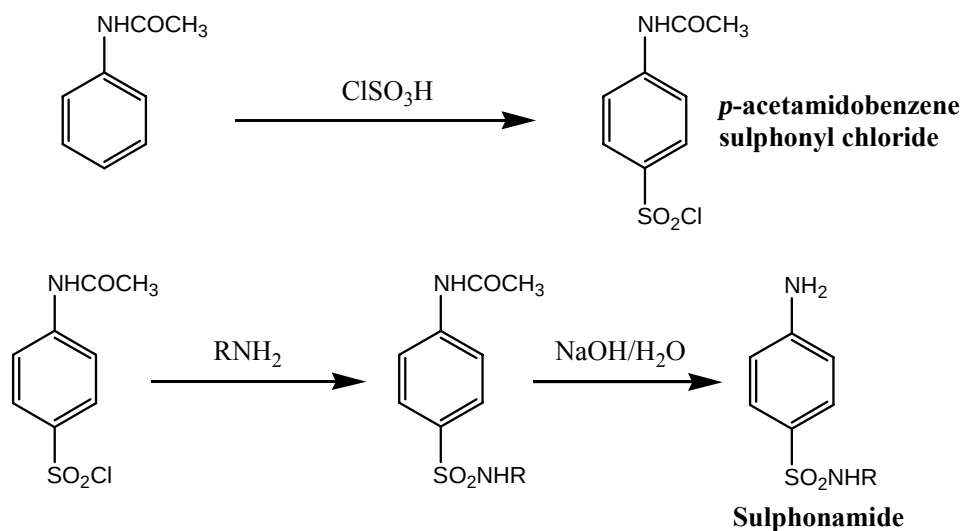


Therefore, sulphonamides act as inhibitors for the enzymes which incorporate *p*-aminobenzoic acid into folic acid. Once the synthesis of folic acid is stopped the micro-organisms cease to grow and multiply. The white blood corpuscles of the host then kill the infectious bacteria present and thus eradicate the infection.

The micro-organism which do not require *p*-aminobenzoic acid for their growth and multiplication or can use folic acid from some other source, are resistant to sulphonamides. Sulphonamides, in general, are not effective against viral infections. The most common sulphonamides are sulphanilamide, sulphapyridine, sulphaacetamide, and sulphadiazine.

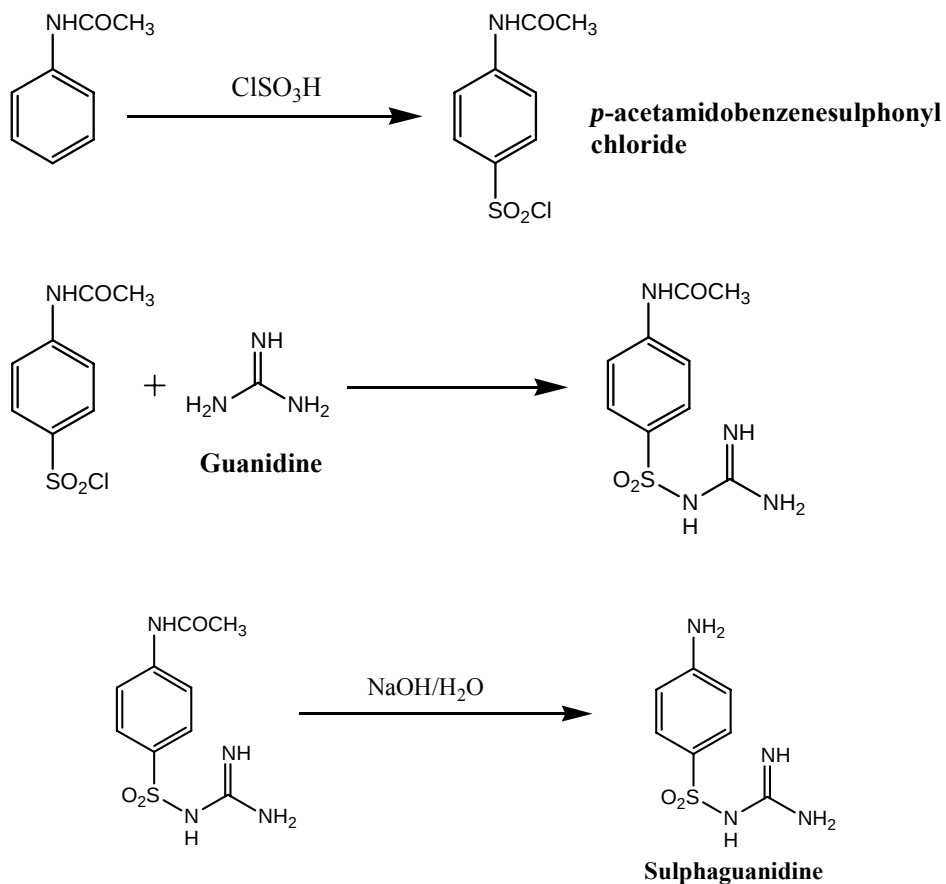
Synthesis of sulphonamides:

Sulphonamides are prepared in three steps. First step involved chlorosulphonation of acetanilide, which results in the formation of *p*-acetamidobenzenesulphonyl chloride. Next step is the condensation of this intermediate with appropriate compound, followed by the removal of acetyl group by hydrolysis with alkali.

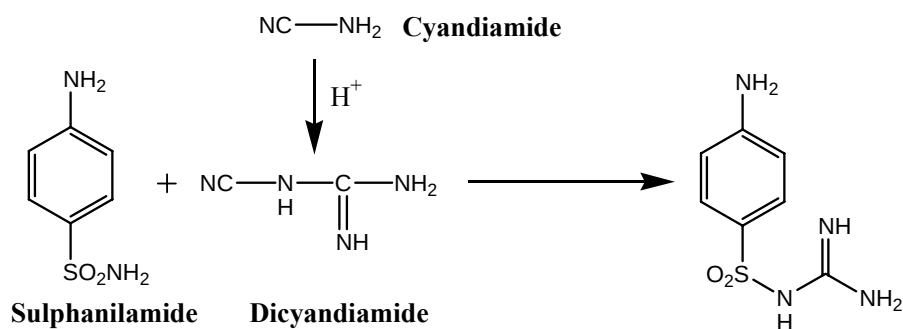


Sulphaguanidine:

Synthesis: Sulphaguanidine can be prepared by the condensation of *p*-acetamidobenzenesulphonyl chloride with guanidine followed by hydrolysis.

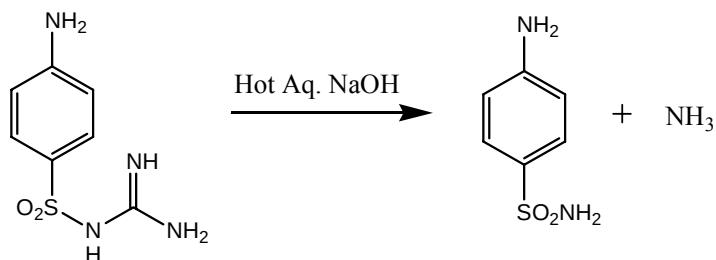


Alternatively sulphaguanidine can be prepared by the reaction of sulphanilamide with dicyandiamide. Dicyandiamide can be prepared by the acid catalyzed condensation of cyanamide.



General properties and uses:

Sulphaguanidine is a white, odorless, crystalline powder. It is stable in air but slowly darkens on exposure to light. It is slightly soluble in water, less soluble in hot alcohol and insoluble in benzene, ether and chloroform. Due to the presence of basic group sulphaguanidine is readily soluble in cold dilute mineral acids, but insoluble in cold dilute bases. In hot alkaline solutions, it decomposes to sulphanilamide with evolution of ammonia.



Sulphaguanidine is poorly absorbed by the intestinal mucosa. It can, therefore, be given in large doses without the development of high blood level and toxic side effects. As a result it can be used in the treatment of bacillary infections of the intestine.