**n - contg functional groups: diazonium salts**

**Diazonium Salts** —

**Introduction to Diazonium salts**:

The aliphatic diazo-compounds are characterized by the presence of the group ―



**Aliphatic Diazo Compounds**:

There are only **two important aliphatic diazo-compounds** —

1. Diazomethane, and
2. Diazo acetic ester or ethyl diazo acetate,

**General Strategy and Planning for Synthesis of Aliphatic Diazo Compounds** —

**Aliphatic diazo** compounds can be prepared from an - amino ester containing at least one -- atom. Under the following **three conditions**, amino acid ester can be converted into diazo compounds ―

1. Only **ester**, **cyano** or **acid chloride** of an amino compound can be converted to a diazo salt, free acid does not give the reaction.
2. Only the derivative of - amino acids can be converted to diazo salts but not - or - amino acids.
3. - Atom attached to the atom or group must contain at least one - atom.



**Preparation of Diazo Acetic Ester** —

When a cooled solution of hydrochloride of ethyl glycine ester is treated with cold and dilute solution in water, ethyl diazo acetate is formed.



**Preparation of Diazomethane** —

Diazomethane can be prepared by the following steps ―

1. **Urea** is treated with **methyl ammonium chloride** to get - methyl urea



1. - Methyl urea so formed is treated with to give - nitroso-- methyl urea



1. - Nitroso-- methyl urea so formed reacts with to form diazomethane.



Diazomethane is a yellow, gaseous, poisonous compound and generally used in ethereal solution. (IL FINAR – Page 392, Vol I)

**Synthetic Applications of Diazomethane** ―

All the reactions of diazomethane () are classified into two types ―

1. Reactions in which - gas is lost, and
2. Reactions in which - is retained

Diazomethane is best represented as a resonance hybrid derived from linear resonating structures with opposing dipoles (IL FINAR – Page 392, Vol I) ―



Under appropriate conditions, diazomethane can behave as an **electrophile** () or a **nucleophile** (), as a **- dipole** () or as a source of **methylene** ().

**Reactions of Diazomethane in which - gas is lost** ―

Most of the reactions of diazomethane are readily explained in terms of nucleophilic attack (structure ) on the substrate, followed by loss of nitrogen.

[] **Methylation of Active - atom containing compound** ―

Diazomethane reacts with all compounds containing an active - atom; such as halogen acids, - atom of ***acidic*** hydroxyl groups for example carboxylic acids, sulphonic acids, phenols and enols. Actually, diazomethane methylated the acidic or active - atom containing compounds and thereby, forming different types of compounds and hence, the reactions are called methylation reactions. For example, ―





**Mechanism**: A possible mechanism for methylation reaction of diazomethane is ― with halogen acids, for example, **with hydrochloric acid**―



Similarly, **with carboxylic acids** ―



[] **Methylation of Alcohols** ―

The - atom of alcoholic group being less acidic, an alcohol can’t ne methylated easily using diazomethane; however, in presence of aluminium alkoxide, which acts as a Lewis acid, methylation can be done.



[] **Reactions with Aldehydes & Ketones** ―

Diazomethane reacts with **aldehydes** to form methyl ketones along with the formation of some epoxides (oxiranes) as side products (may be the predominant product also).



Similarly, with ketones, diazomethane reacts to form higher homologue of the starting ketone along with the formation of some epoxides (oxiranes) as side products (may be the predominant product also).



[] **Ring Expansion or Enlargement Reactions** ―

() **Aromatic Ring Expansion reactions** (formation of bicyclic compounds) ―

An ethereal solution of an aromatic hydrocarbon with on irradiation with - light, a **carbene** is generated, which adds to the aromatic compound to form an alicyclic compound containing one - atom more. For example, with benzene, cyclobutene and cyclopropane ―



() **Reaction with Cyclic Ketones** ― Diazomethane reacts with **cyclic ketones** to form higher ketones along with the formation of some epoxides (oxiranes) as side products. For example, cyclopentanone reacts with to form cyclohexanone along with an epoxide in minor quantity.



Similarly, with cyclohexane ―



() **Reaction with Acetylenic Compounds** ― formation of pyrazole or its derivatives

Diazomethane adds to acetylenic compounds, to form pyrazole derivatives. For example, with acetylene, pyrazole is formed following a - dipolar addition ―



**Reactions of Diazomethane in which - atom is retained**:

**Reaction of Diazomethane with Alkyl halides ―Arndt-Eistert Synthesis**:

In this reaction an acid (aliphatic, aromatic, alicyclic or heterocyclic) is converted to its next higher homologue by treating it with diazomethane. In this reaction, first a **diazoketone** is formed, and this loses nitrogen to form a **ketene** by a rearrangement reaction called **Wolff rearrangement** in presence of moist as catalyst. Thus, ―



Both the **diazoketone** formed by the reaction of alkyl halide with diazomethane and **ketene** formed from diazoketone by Wolff rearrangement are very important intermediate for the synthesis of many organic compounds. For example, ―

() Hydrolysis of ketene yields higher homologue of carboxylic acid,



() Diazoketone reacts with alcohols and ammonia in presence of moist as catalyst to form esters and amides respectively via ketene intermediate ―



() Diazoketone reacts with water in presence of formic acid to yield hydroxy methyl ketone,



() Diazoketone reacts with  to form chloro methyl ketone ―



**Problem**: ***How will you convert benzoic acid to benzoyl acid***?

**Solution**:



**Problem**: What happens when diazomethane reacts with 1, 2 – dimethyl acetylene?

**Solution**: Diazomethane reacts with - dimethyl acetylene to form - dimethyl derivative of pyrazole,



**Problem**: ***How will you convert the following via diazomethane***?

1. A pyrazole derivative,
2. Pyrazole, and
3. Propanoic acid from acetic acid.

**Synthetic Applications of Diazo Acetic Ester or Ethyl Diazoacetate**:

Ethyl diazoacetate () is the resonance hybrid of the following structures ―



***Following are the important reactions of ethyl diazoacetate*** ―

[] **Reduction** ― Reduction by & acetic acid yields glycine and ammonia,

[] **Acid Hydrolysis**― Acid Hydrolysis of ethyl diazoacetate gives glycolic ester,

[] **Reaction with active - atom containing compound**― Ethyl diazoacetate replaces the active - atom of acids, phenols, alcohols, etc. to form the derivatives of glycolic ester,

**Mechanism**: With carboxylic acid, as an example ―



[] **Reaction with conc. halogen acid**― Diazoacetic ester when warmed with conc. halogen acid, ***ethyl halogeno-acetate*** is formed. For example, with ―

[] **Reaction with acetylenes and ethylenes**― Diazoacetic ester when treated with alkenes or alkynes results **pyrazole** and **pyrazoline** derivatives,





**Aromatic Diazo Compounds OR**

**Aromatic Diazonium Salts**



**Introduction:**

Each class of amine yields a different kind of product in its reaction with nitrous acid (). This unstable reagent is generated by the presence of the amine by the action of mineral acid on sodium nitrite, at low temperature.

Primary aromatic amines react with nitrous acid to yield ***diazonium salts***; this is one of the most important reactions in organic chemistry.

A diazonium salt

**Preparation of Aromatic Diazonium Compounds:**

The formation of aromatic diazonium salts from aromatic primary amines by the action of nitrous acid, at low temperature () in strong acid medium (usually conc. ) is called **diazotization reaction**, since two - atoms (nitrogen, ) are bonded to the nuclear carbon by this process.

Aromatic diazonium compounds are prepared by the action of nitrous acid, on aromatic primary amines. is prepared in the medium itself by the action of mineral acid on sodium nitrite, at low temperature.

If the amino compound containing two amino groups, , then a tetra-azotized compound is formed. For example, ―



**Mechanism**:



Now,



**Important Note**:

() Primary aliphatic amines also react with nitrous acid to yield diazonium salts; but aliphatic diazonium salts are quite unstable and immediately breaks into a mixture of alcohols and alkenes with the evolution of nitrogen gas ―hence, little or no synthetic utility.



() Both aliphatic and aromatic secondary amines react with nitrous acid to yield - nitroso-amines.



() Tertiary aromatic amines undergo ring substitution, to yield compounds in which a nitroso group, is joined to - atom. Thus, - dimethylaniline yields chiefly -nitroso-- dimethylaniline.



**Synthetic Applications of Aromatic Diazonium Salts**:

The aromatic diazonium salts are very important synthetic reagent, for the synthesis of various aromatic compounds such as, dyes and drugs. All the reactions of aromatic diazo compounds are classified into - categories ―

1. Reactions in which nitrogen is lost i.e. displacement of diazo group, by another univalent group, and
2. Reactions in which the nitrogen is retained.

**Following reactions are belonging to the 1st category, *i.e*.**

**Reactions where - gas is lost:**

[] **Synthesis of Benzene & its Derivatives** [Replacement of Group by Hydrogen]:

Replacement of diazonium group by can be brought about by number of reducing agents. For example, when diazonium salt is treated with hypo-phosphoric acid, [ethanol or sodium borohydride, may also be used] in presence of - ions, the diazonium group is replaced by - atom and an **arene** is obtained. Thus, ―



**Mechanism**: A highly favoured mechanism for this reaction involves a free radical chain:



***Chain Propagation***:



**Application**: The reaction of diazonium salt in which the group is replacement by - atom provides a good method for removing group from an aromatic ring and the process is found to be extremely useful in many organic syntheses. For example, ―

***Conversion of aniline to benzene***:



***Conversion of nitrobenzene to benzene***:



**Important Conversion**:



[] **Formation of Aromatic Halo- Compounds** [Replacement of Group by ]:

Aromatic halo compounds are prepared from aromatic diazonium salts by a number of ways by replacing group by halogen atom. Some important reactions are ―

**Sandmeyer Reaction**: Reaction of aromatic diazonium salts solution (freshly prepared) with cuprous halide (normally chloride and bromide: ) dissolves in corresponding halogen acid (*i.e*. ) to form aryl chloride or aryl bromide is generally referred to as the Sandmeyer reaction. Thus, ―



**Mechanism**: The mechanism of Sandmeyer reaction can be written as ―

Now, ―

**Gattermann Reaction**: Gattermann reaction is same as Sandmeyer reaction, except instead of using of cuprous halide; **Copper powder** is used followed by heating. Thus, in Gattermann reaction, ***aryl chloride or aryl bromide*** is prepared by warming the aromatic (or benzene) diazonium salts solution (freshly prepared) with Copper powder and hydrogen halide. For example, ―



**Modified Sandmeyer Reaction** ― **Formation of Iodo - Benzene**:

Aryl iodide or iodobenzene may be prepared by boiling the benzene diazonium salt solution with aqueous . Thus, for the replacement of diazo group by iodine not cuprous halide or Copper powder or halogen acid but requires aqueous solution only. Thus, ―



**Schiemann Reaction** ― **Formation of Fluoro-Benzene**:

When ***fluoroboric acid***, is added to a diazonium salts (aromatic) solution, the insoluble diazonium fluoroborate, is precipitate, which on gentle heating yields aryl fluoride. Thus, ―



[] **Formation of Cyano-Benzene [Special case of Sandmeyer & Gattermann Reaction]** [Replacement of Group by]:

Aryl or benzene diazonium salt can be **converted** into **aryl cyanides** by treating it with cuprous cyanide, dissolved in aqueous or with aqueous in presence of aqueous - powder. Thus, ―



**Application**: Since, the **hydrolysis** of nitriles (cyanides) yields carboxylic acids hence, this reaction provides a very good route for the synthesis of aromatic carboxylic acids from aryl cyanides; which in turn synthesised from diazonium salts.

For example, this method provides an excellent route for the conversion of **nitro compounds to carboxylic acids**.



[] **Formation of Biphenyl** ―[Replacement of Group by Group]:

Aryl diazonium salts on treatment with benzene or substituted benzene in presence of an aqueous alkali yields biphenyl or its derivatives (whatever the nature of the substituent in the 2nd component,  or substitution always occurs w.r.t. the diazonium group). For example, ―



[] **Formation of Nitrobenzene** ―[Replacement of Group by Group]:

Nitro group can be introduced in place of diazo group by the decomposition of the diazonium fluoroborate by aqueous containing - powder. Thus, ―



**Application**: This reaction is synthetically very important. Since, group is -directing *i.e*. **electron-withdrawing** group, hence it is very difficult to synthesis - dinitrobenzene by simple nitration method *i.e*. by using nitrating mixture (). However, indirectly we can prepare - dinitrobenzene using **diazonium salt**, starting from aniline. Thus, ―



[] **Formation of Aryl-ethers** ―[Replacement of Group by Group i.e. reaction with alcohols,]:

Most common phenyl ethers are **anisole** and **phenetole**, and these two can be synthesised *via* benzene diazonium salts as shown below ―



[] **Formation of Phenol** ―[Replacement of Group by Group]:

Benzene diazonium salts when hydrolysed or boiled with dilute  gives phenol. Thus,



**Following reactions are belonging to the 2nd category, i.e. Reactions where - is retained in the product formed** ―

Important examples belongs to this category are ―

[] **Reduction of Benzene Diazonium Salts** ―

With mild reducing agents, such as or aqueous followed by **dilute acid** () **hydrolysis** (***laboratory method***) benzene diazonium salts reduced to **phenyl hydrazine**. Thus, ―



**Mechanism**: Formation of phenyl hydrazine can be explained as ―



However, with **vigorous reducing** agents such as , the product is an amine ―



[] **Coupling Reactions or Diazo-coupling Reactions** ―

Under proper conditions, diazonium salts react with certain aromatic compounds to yield products of the general formula , called **azo compounds**. In this reaction, known as the **coupling reaction**, the nitrogen of the diazonium group is retained. Thus, ―

The aromatic ring () undergoing attack by the diazonium ion in general, contain a powerful electron-releasing group, generally .Substitution usually occurs - to the activating group. Typically, coupling with **phenols** is carried out in mildly **alkaline** solution, and with amines in mildly **acidic** solution. Thus, ―



**Some specific examples are** ―



Generally, the coupling reaction takes place at - position to the aromatic group; but if - position is blocked, the reaction takes place at - position of aromatic group. If - position is also blocked, the coupling reaction does not take place.

**For example**, - methyl aniline undergoes coupling reaction with benzene diazonium salt at - position w.r.t. group in acidic medium. But, -bromo--chloro--methyl phenol fails to undergo coupling reaction with benzene diazonium salt in basic medium.



If the compounds contain both groups then in acid medium coupling takes place - to and in basic medium - to group. For example, ―



All the above azo compounds are **- azo** compounds. Some **- azo** side products are also formed. For example, ―



If more than one - groups are present then -, - azo compounds will be formed. For example, ―



Similarly, if the compound containing more than one groups coupled with diazonium compounds then also -, - azo compounds are formed. For example, with - dihydroxy benzene, this undergoes diazo coupling reaction with benzene diazonium salt solution in alkaline medium to yield a series of coupling products. For example, ―



**Mechanism**: The diazo coupling reaction proceeds through electrophilic substitution pathways in which the electrophile being the diazonium cation and the substrate being the free amine or the phenoxide ion derived from the phenol in basic medium. Thus, ―



Similarly, with **phenoxide ion**, ―



Since, the structure () is the “***REACTIVE***” contributing resonating structure, any factor that increases its contribution will increase its contribution will increase the reactivity of the diazonium cation. It can be anticipated that electron-withdrawing groups (i.e. Gr, such as - Gr) would favour () and electron-releasing groups (i.e. Gr, such as - Gr) would favour (). This has been found to be in practice. For example, ―

1. The - nitrobenzene diazonium cation is more than times as reactive as the - methoxy ion under the identical reaction conditions.
2. The - trinitrobenzene diazonium cation is so reactive that it couples with certain hydrocarbons, for example mesitylene.

**Importance of Azo-compounds**:

Azo-compounds are strongly coloured, and they can be intensely yellow, orange, red, blue or even green, depending upon the exact structure of the molecule. Because of their colour, the azo compounds are of tremendous importance as dyes; about half of the dyes in industrial use today are azo dyes. Some of the acid-base indicators with which we are already familiar are azo compounds.



**Synthesis using Diazonium Salts**:

A few important example of synthesis showing the involvement of diazonium salts (aromatic) in organic synthesis are discussed below ―

To begin with, we might consider some rather simple compounds, the three isomeric **bromotoluenes**. The best way of synthesising for each isomer, diazotization technique may be employed, but not for the same purpose in the three cases. The - and - bromotoluenes are prepared from the corresponding - and -**nitrotoluene** ―



The advantage of these multi-step syntheses over direct bromination is, as we have seen, that a pure product is obtained. Separation of the - and -**bromotoluenes** obtained by direct bromination is not feasible.

Synthesis of **- bromotoluene** is a more complicated matter. The problem here is one of preparing a compound in which two -, - directing groups are situated - to each other. Bromination of toluene or methylation of **bromobenzene** would not yield the correct isomer. - Bromotoluene is obtained by the following sequence of reactions ―



The key to the synthesis is the introduction of a group that is a much stronger -, - director than , and that can be easily removed after it has done its job of directing bromine to the correct position. Such a group is group: it is introduced in the - position of toluene *via* nitration, reduction, and acetylation; it is easily removed by hydrolysis, diazotization, and reduction.

In the synthesis of bromotoluene, advantage was taken of the fact that the diazonium group is prepared from a group that is strongly directing. Ultimately, however, the diazonium group is prepared from  group, which is a strongly directing group. Advantage can be taken of this fact, too, as in the preparation of bromophenol:



Here, again there is the problem of preparing a compound with twodirectors situated to each other. Bromination at the nitro stage gives the necessary orientation.

As a final example, let us consider the preparation of 1,2,3 – tribromo benzene:



In this synthesis advantage is taken of the fact that thegroup is a stronglydirector, that the  group is andirector, and that each of them can be converted into a diazonium group. One diazonium group is replaced by , the other by . //

**Problem 1**: Outline the synthesis from benzene or toluene of the following compounds:

1. Nitro toluene,
2. Iodo toluene,
3. 3, 5 – Dibromo toluene,
4. 1, 3, 5 – Tribromo benzene,
5. The three toluic acids (),
6. The three methyl phenols (cresols),
7. Dibromo benzene,
8. Bromoiodo benzene.

**Problem 2**: How will you prepare:

1. An azobenzene derivative with benzene diazonium chloride,
2. Chlorobenzene by Sandmeyer reaction,
3. Fluorobenzene from benzene diazonium chloride.

**Problem 3**: ‘’Aliphatic diazonium compounds are less stable than aromatic diazonium compounds.” Explain the statement with suitable examples.

**Problem 4**: What will be the product when methylaniline is treated with  and  at low temperature? Give their structures. What happen when this product is treated with ―

1. Cuprous bromide, and
2. Hypo-phosphorous acid?

**Problem 5**: Starting from acetic acid, syntheses the following compounds:

1. Chloroacetic acid,
2. Propanoic acid,
3. Ethanol, and Methyl amine.

**Problem 6**: Starting from nitrobenzene, syntheses the following compounds:

1. Dinitrobenzene, and
2. Dinitrobenzene.

**Problem 7**: How will you transform a carboxylic acid to its next higher homologue by Arndt – Eistert synthesis?