Principles of Organic Synthesis
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Lecture 19
Aromatic Diazonium Salts

Welcome you all to Principles of Organic Synthesis. So far, we had eighteen lectures where we studied the aliphatic C-C and C-N bond formation, electrophilic aromatic substitution and nucleophilic aromatic substitution. Today, we will start the new module in which we shall study the aromatic diazonium salts. In this module too we will have three lectures. In this lecture, we will study the formation and reaction of the aromatic diazonium salts.

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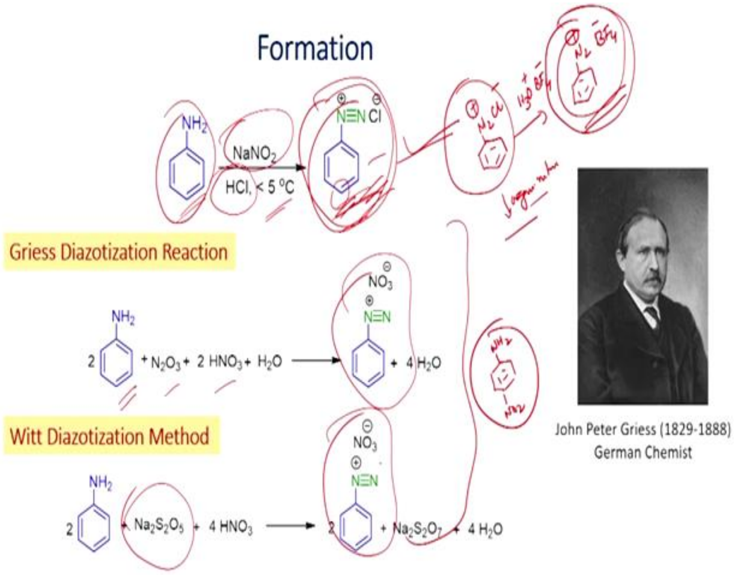
Formation



Griess Diazotization Reaction

Witt Diazotization Method

John Peter Griess (1829-1888)
German Chemist

All of you know well that primary amine with nitrous acid produces the diazonium salt. For example, aniline with $NaNO_2$ and HCl generates the phenyldiazonium salt. If you compare the stability of aliphatic and aromatic diazonium salts, the latter is more stable.

The other methods that are used for the preparation of the diazonium salts include the use of the combination of N_2O_3 and HNO_3 to produce phenyldiazonium nitrate. We can also utilize the combination of $Na_2S_2O_4$ with HNO_3 to prepare the phenyldiazonium nitrate.

Diazonium chloride can be reacted with fluoroboric acid to give tetraflouroborate, which is the stable salt that can be isolated and stored at room temperature. We can also react with organic nitrite in weak acid such as acetic acid and the salt can be precipitated using ether.

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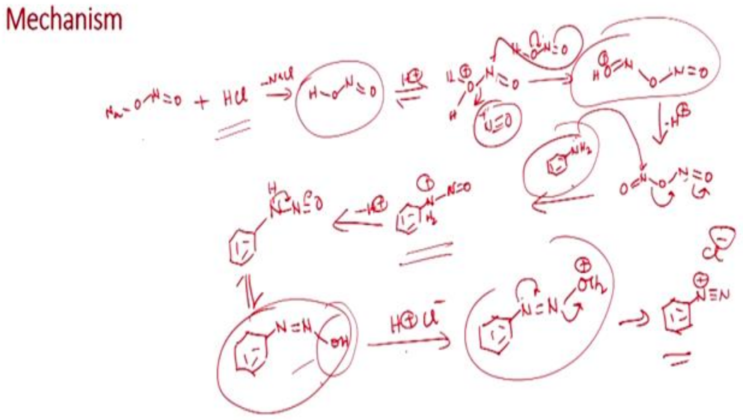
Mechanism

NaNO$_2$ in water is added to a solution of HCl and aniline. NaNO$_2$ with HCl produces HNO$_2$, which protonates and reacts with HNO$_2$ to give N$_2$O$_3$. Substitution with aniline followed by removal of water molecule produces the diazonium salt. Alternatively, protonation of HNO$_2$ followed by removal of water molecule can generate nitrosonium ion that reacts with aniline to give the diazonium salt.

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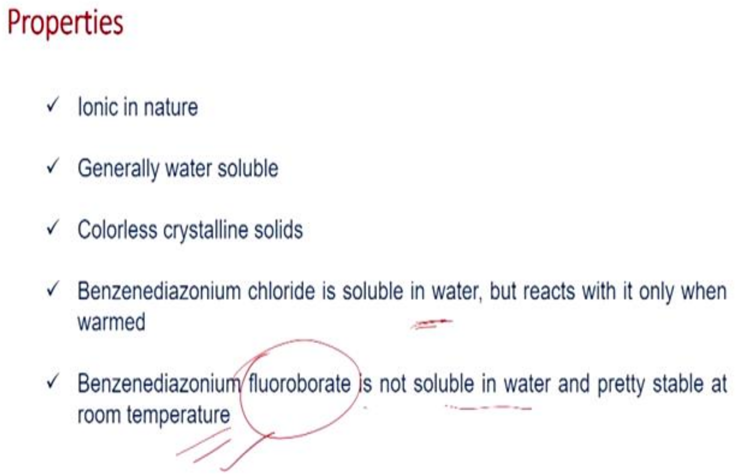
Properties

- ✓ Ionic in nature
- ✓ Generally water soluble
- ✓ Colorless crystalline solids
- ✓ Benzenediazonium chloride is soluble in water, but reacts with it only when warmed
- ✓ Benzenediazonium fluoroborate is not soluble in water and pretty stable at room temperature

Diazonium salts are crystalline and water soluble. If you look at the phenyldiazonium chloride, which is soluble in water and stable but reacts only when it is warmed. For example, when you heat, it converts to phenol.

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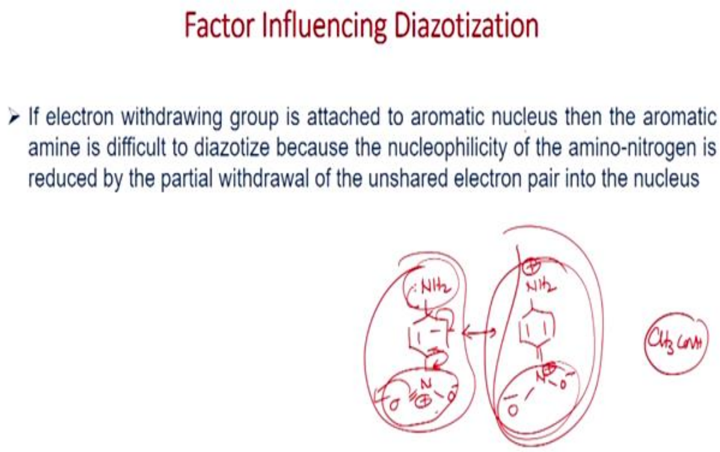

Factor Influencing Diazotization

- If electron withdrawing group is attached to aromatic nucleus then the aromatic amine is difficult to diazotize because the nucleophilicity of the amino-nitrogen is reduced by the partial withdrawal of the unshared electron pair into the nucleus

Now let us look at the effect of substituent in the formation of diazonium salt. If the electron withdrawing group is present in the aryl ring, which is difficult to diazotize. For example, nitroaniline in which the amine lone pair is delocalized towards the nitro group and thus the nucleophilicity of the amine is reduced. However, you can make diazonium salt using weak acid like acetic acid by modifying the reaction conditions.

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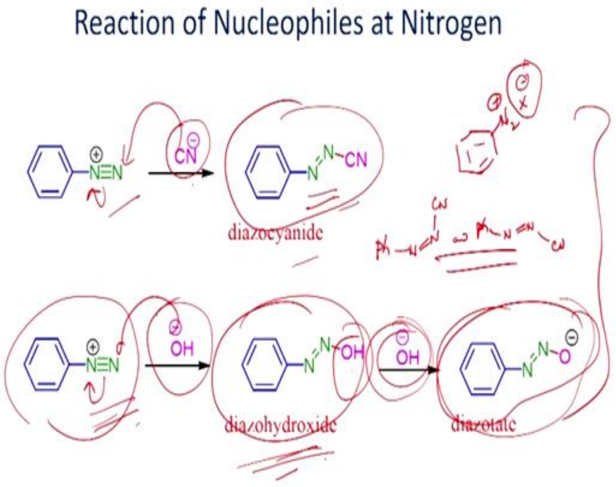

Reaction of Nucleophiles at Nitrogen

Now let us see the reaction of the diazonium salt. There are three types of reactions. Let us see the first type in which the diazonium salt bearing weak anion such as OAc^- undergoes reaction with strong nucleophile to give the addition product. For example, phenyldiazonium chloride reacts with cyanide ion to give diazocyanide. Similarly, hydroxide ion reacts to give diazohydroxide, which can convert to diazotate if the reaction medium is basic.

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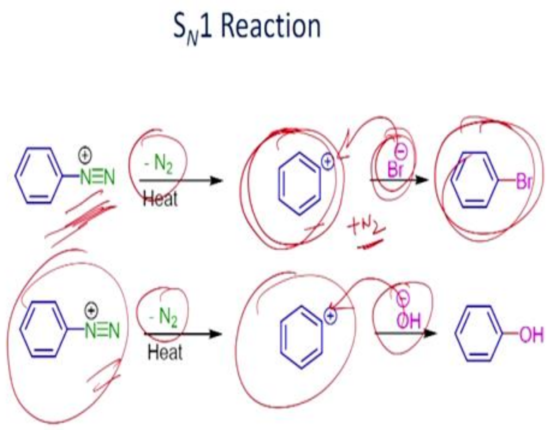

In the second type, the diazonium salt loses nitrogen molecule on heating and produces the aryl carbocation that reacts with nucleophile to give the substitution product. The first example involves the heating of phenyldiazonium salt, which loses nitrogen and the phenyl carbocation reacts with bromide anion to give bromobenzene. Similarly, phenyldiazonium salt reacts with water to give phenol via phenyl carbocation intermediate.

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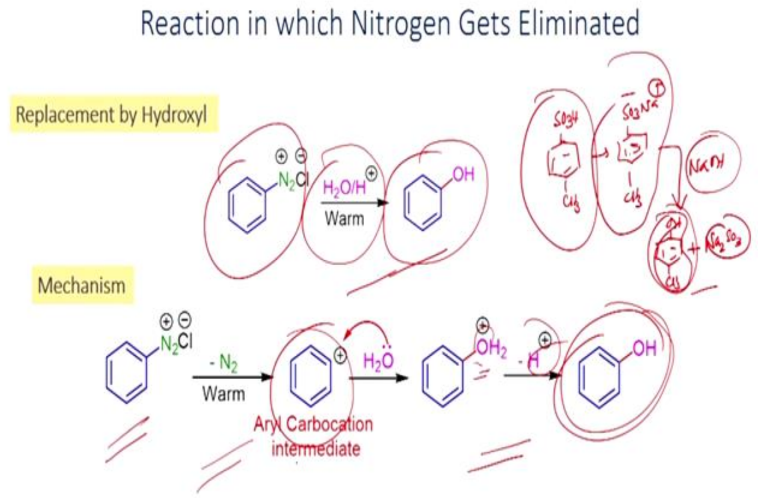

Here the reaction of phenyldiazonium chloride to phenol is shown. When you heat the diazonium salt, it loses nitrogen molecule to give the phenyl carbocation, which reacts with water to give phenol. Thus, if you have aniline, which can be converted to diazonium salt that can be further reacted with water to give phenol.

Normally, sulfonic acid is used as the substrate precursor to prepare phenol via sodium sulfonate, which with NaOH produces phenol. The conversion of diazonium salt to phenol is alternative approach, which can be utilized wherever, the sulfonic acid to phenol suffers.

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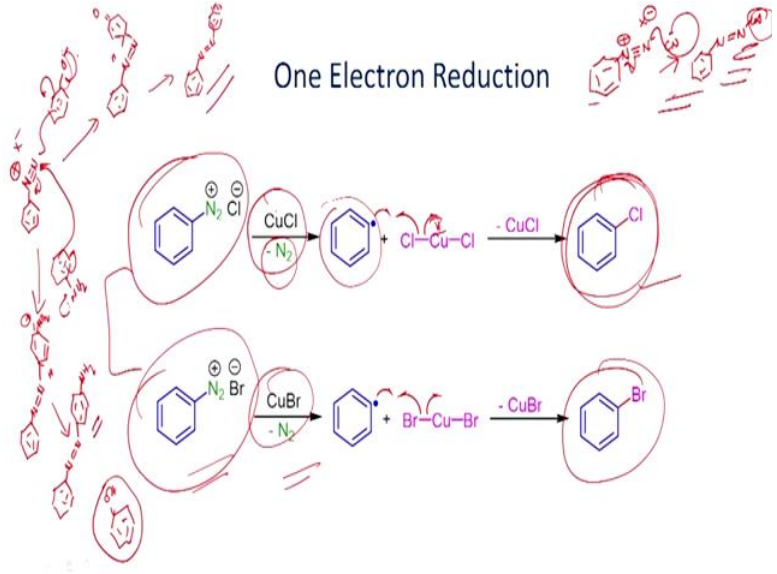

One Electron Reduction

Here is the third type of reaction. In this reaction, copper(I) chloride converts aryldiazonium salt to aryl radical by single electron transfer (SET) reduction. Copper(I) halide converts to copper(II) halide, which transfers halide to aryl radical to produce the aryl halide.

The first example involves the reaction phenyldiazonium chloride to chlorobenzene using CuCl. Similarly, phenyldiazonium bromide can be converted to bromobenzene using CuBr. These reactions are known as the Sandmeyer reaction.

So far, we have seen three types of reactions of aryldiazonium salts. First type involves the addition of strong nucleophile to produce azo derivative. The second type involves the decomposition of diazonium salt to aryl carbocation that reacts with nucleophile. The third type covers a SET process converting aryldiazonium salt to aryl radical, which is transformed to aryl halide.

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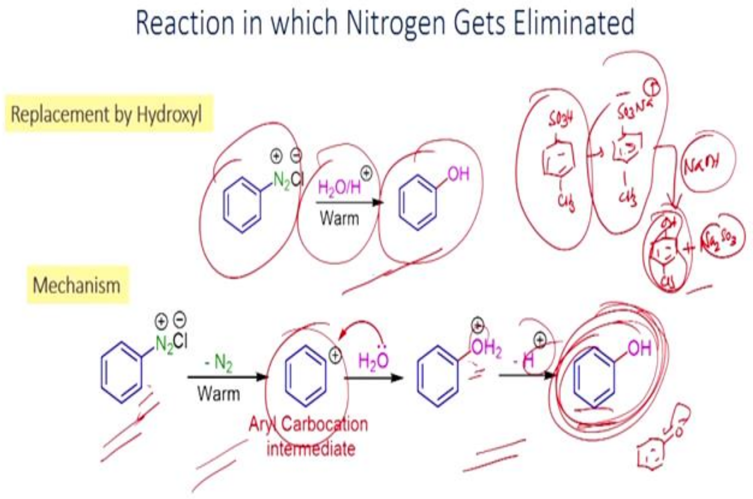

Reaction in which Nitrogen Gets Eliminated

Replacement by Hydroxyl

Mechanism

In the transformation of diazonium salt to phenol using water, the reaction medium is to be acidic. If it is basic, phenol will be converted to phenoxide that can further react with the diazonium salt. Therefore, pH of the reaction medium is crucial for the selectivity.

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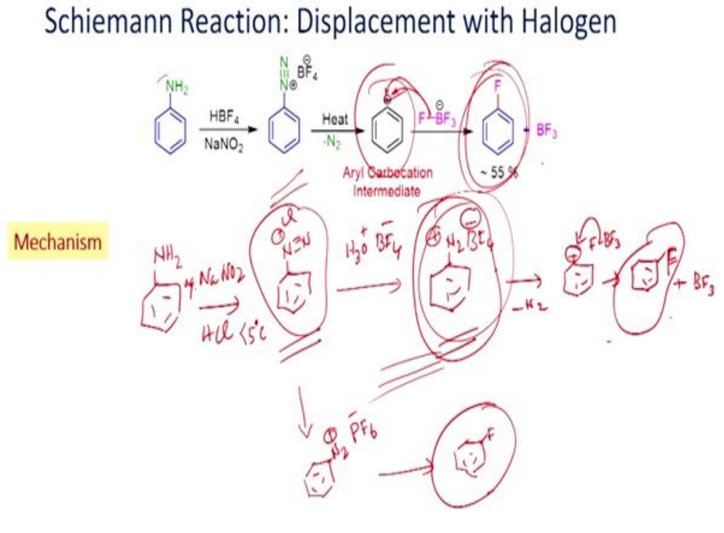

Schiemann Reaction: Displacement with Halogen

Mechanism

Here transformation of aniline to fluorobenzene is shown. Diazotization of aniline using $NaNO_2$ and HCl produces phenyldiazoninum chloride, which reacts with fluoroboric acid to give phenyldiazonium tetrafluoroborate. When you heat the salt, it loses nitrogen to give phenyl carbocation that reacts with tetrafluoroborate to give fluorobenzene. Similarly, phenyldiazonium chloride reacts with $NaPF_6$ to give phenyldiazonium hexafluoroborate that also on heating produces fluorobenzene. These reactions are known as the Schiemann reaction.

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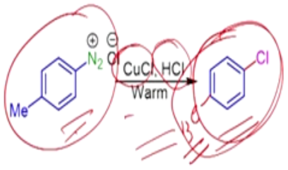
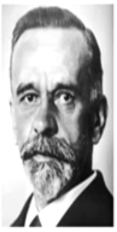
Replacement by Halogen : Sandmeyer Reaction



Mechanism



Traugott Sandmeyer (1854-1922)
German Chemist

Similarly, if you want to convert phenyldiazonium chloride to chlorobenzene by heating, the reaction is not successeful due to decomposition. Therefore, CuCl is essential to convert the diazonium salt to the aryl radical that is further reacted with $CuCl_2$ to give chlorobenzene.

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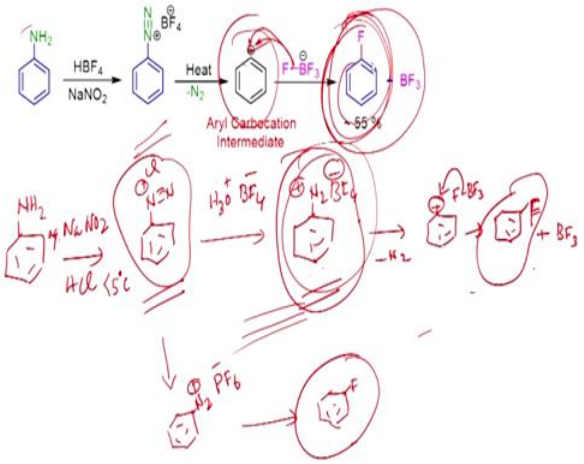
Schiemann Reaction: Displacement with Halogen



Mechanism

However, in case of phenyldiazonium tetrafluoroborate, you don’t have the problem as the salt is stable, which converts to phenyl carbocation on heating that reacts with tetrafluoroborate to give fluorobenzene.

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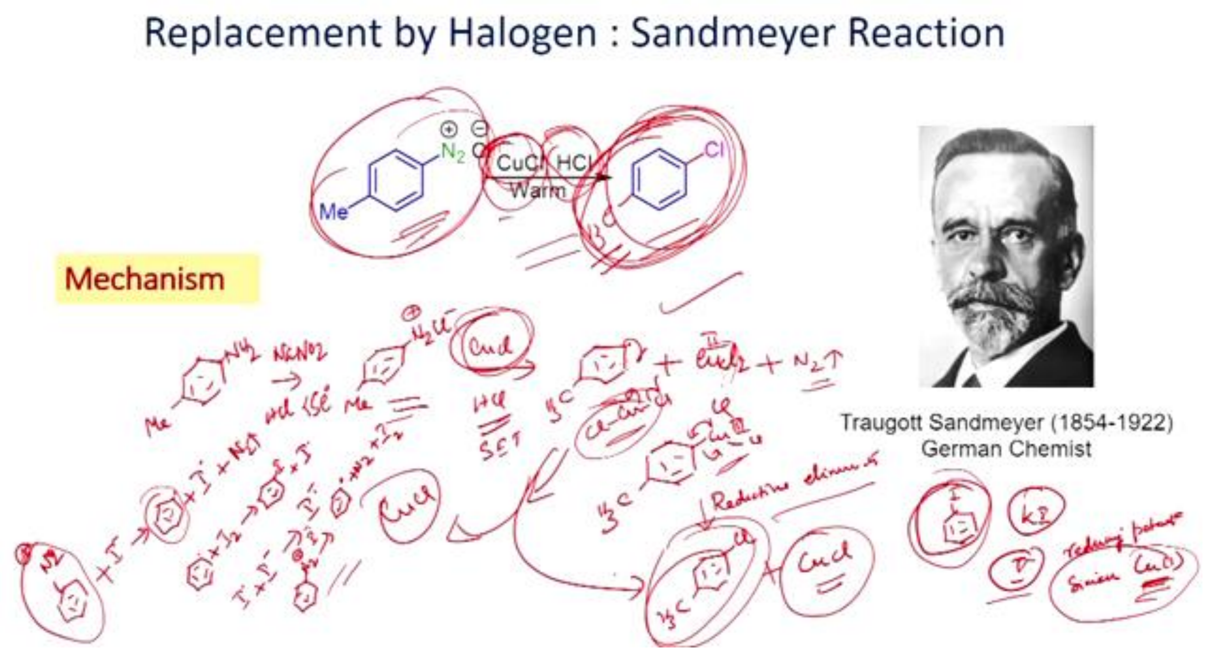
Replacement by Halogen : Sandmeyer Reaction

Mechanism

Traugott Sandmeyer (1854-1922)
German Chemist

Here is the mechanism for the Sandmeyer reaction. CuCl reduces phenyldiazonium chloride to phenyl radical, where CuCl is converted to $CuCl_2$. Reaction of phenyl radical with $CuCl_2$ produces copper(III) species, which give chlorobenzene via reductive elimination along with CuCl. Similarly, phenyldiazonium bromide can be converted to bromobenzene using CuBr.

In case of phenyldiazonium salt to iodobenzene, KI can be used. Iodide ion has reduction potential similar to copper(I). Thus, iodide ion can reduce the diazonium salt to phenyl radical that can react with iodine to give iodobenzene and iodine radical. Iodide ion can react with iodine radical to give iodide ion radical that can react with diazonium salt to give phenyl radical and iodine.

So far we have seen the transformation of aryldiazonium salt to aryl halide.

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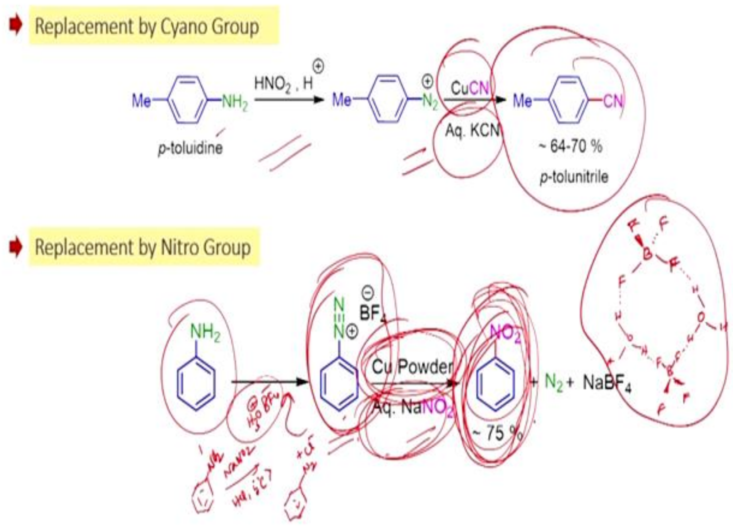

Replacement by Cyano Group

Replacement by Nitro Group

You can also react aryldiazonium salt with aq KCN using CuCN to produce the nitrile. For example, p-toluidine reacts with nitrous acid to produce the diazonium salt that reacts with aq KCN in the presence of CuCN to produce p-tolunitrile in 64-70% yields.

Similarly, aniline can be converted to phenyldiazonium fluoroborate, which reacts with aq $NaNO_2$ in the presence of Cu powder to produce nitrobenzene.

Fluoroboric acid exist with tetrahedral structure through hydrogen bonding.

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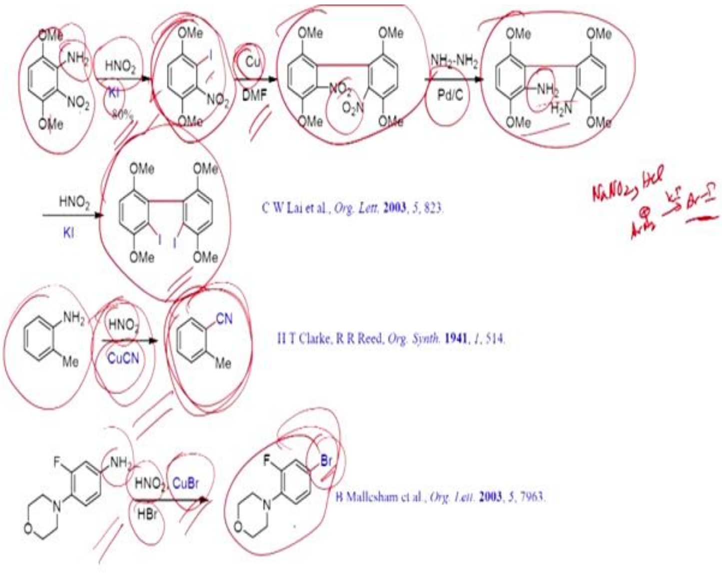

C W Lai et al., *Org. Lett.* **2003**, *5*, 823.

H T Clarke, R R Reed, *Org. Synth.* **1941**, *1*, 514.

B Mallesham et al., *Org. Lett.* **2003**, *5*, 7963.

Here first example involves the conversion of aryl amine to aryl iodide, which undergoes C-C coupling using Ullmann coupling to give the biaryl. Reduction of the nitro group using hydrogen produces the amine, which is diazotized and reacted with KI to give the aryl iodide.

The second example involves the diazodization followed by coupling with aq KCN in the presence of CuCN to produce the nitrile. Similarly, aryl amine can be reacted with $NaNO_2$ and HBr to produce aryldiazonium bromide, which converts to aryl bromide in the presence of CuBr.

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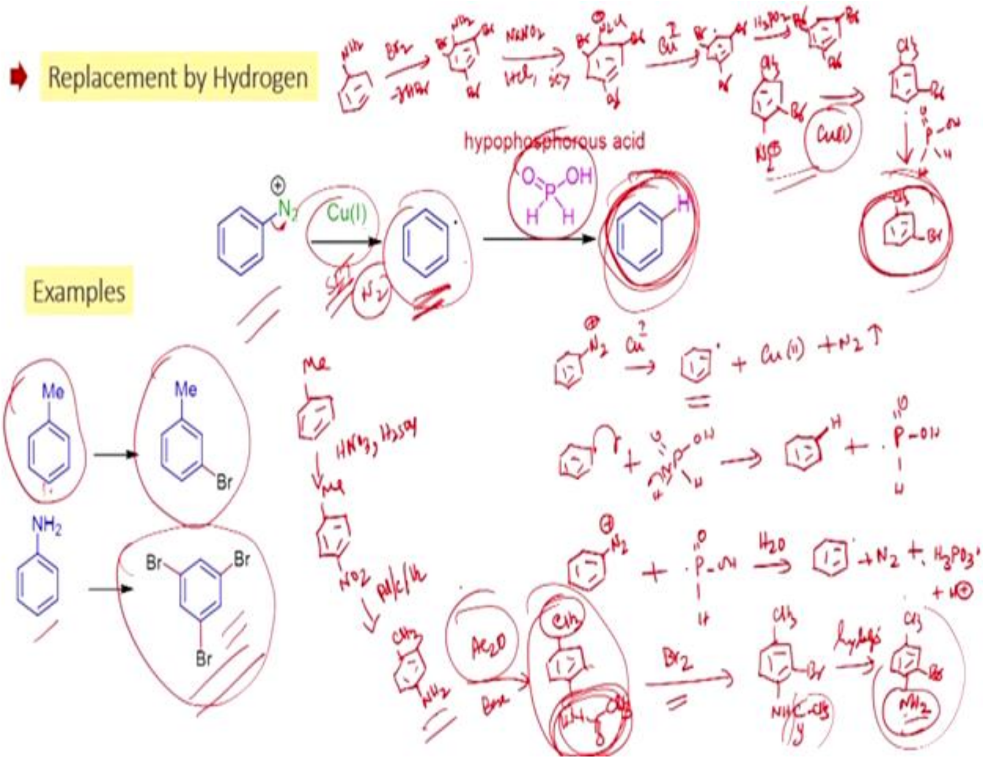

Replacement by Hydrogen

Examples

Here the first example involves the transformation of phenyldiazonium salt to benzene using hypophosphorous acid in the presence of Cu(I) halide. As we have seen, copper(I) halide can reduce the diazonium salt to phenyl radical, which reacts with hypophosphorous acid to give benzene and PH_2O_2 radical, which converts benzenediazonium salt to phenyl radical and transforms to phosphorous acid.

Using these reactions, we can transform toluene to 3-bromotoluene. Nitration of toluene can give 4-nitrotoluene, which can be reduced using hydrogen in the presence of Pd/C. Reaction of 4-methylaniline with Ac_2O produces 4-methylacetanilide, which with bromine followed by hydrolysis produces 2-bormo-4-methylaniline. Diazotization followed by treatment with Cu(I) halide and hyphophsphorous yields 3-bormotoluene.

Similarly, bromination of anline can give 2,4,6-tribromoaniline, which can be converted to diazonium salt. Which can react with copper(I) halide to give the aryl radical that can be reacted with hypophosphorous acid to furnish 1,3,5-tribromobenzene.

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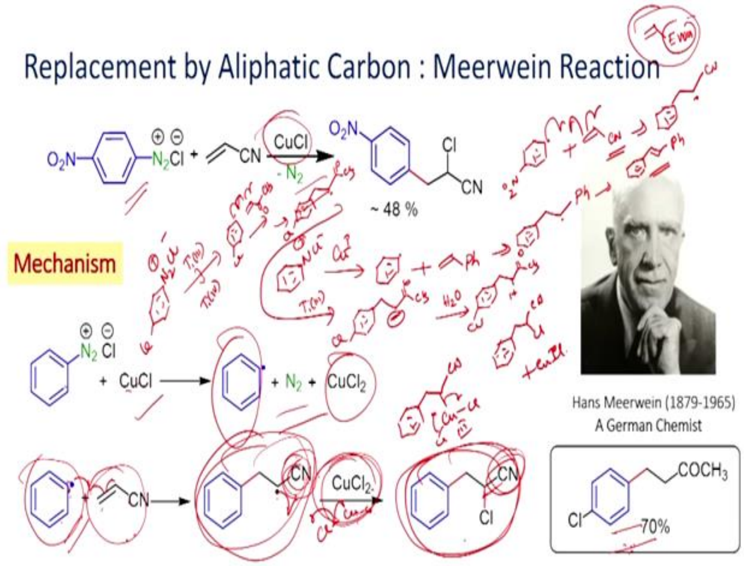

Replacement by Aliphatic Carbon : Meerwein Reaction

Hans Meerwein (1879-1965)
A German Chemist

The aryldiazonium salt can also be reacted with electron deficient alkenes. For example, 4-nitroaniline reacts with $NaNO_2$ and HCl to produce the aryldiazoniun salt, which with CuCl affords the aryl radical that adds to acrylonitrile. The radical further reacts with $CuCl_2$ to give copper(III) species, which leads to reductive elimination to give 3-aryl-2-chloropropionitrile.

Similarly, the phenyl radical can be reacted with methyl vinyl ketone to give the carbon radical intermediate that can be converted to carbanion using Ti(III). Protonation can give the ketone, while the addition of phenyl radical with styrene gives the carbon radical, which can be converted to stilbene

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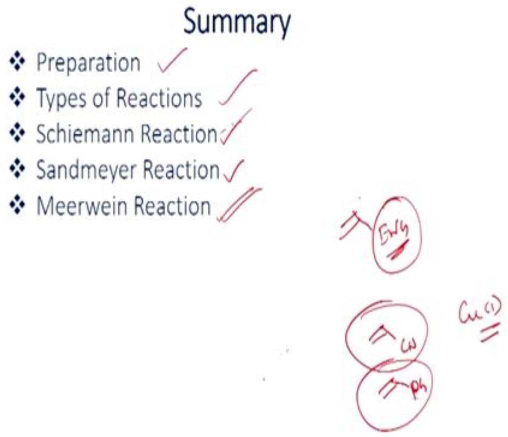

Summary

- Preparation ✓
- Types of Reactions ✓
- Schiemann Reaction ✓
- Sandmeyer Reaction ✓
- Meerwein Reaction //

In summary, we have seen the preparation and reaction of the diazonium salts. The reaction condition is crucial for the formation of the diazonium salt. Primary amine reacts with nitrous acid to give the diazonium salt. Aryldiazonium salt is more stable compared to alkyl one.

We have seen three types of the reaction of the salts. First one involves the addition reaction with strong nucleophile. The second type involves the carbocation intermediate, which reacts with nucleophile. The third type involves the radical intermediate by SET, which can be converted to aryl bromide/chloride as well as addition to electron deficient alkenes to give the alkylated compounds.

With this we conclude this lecture thank you very much.