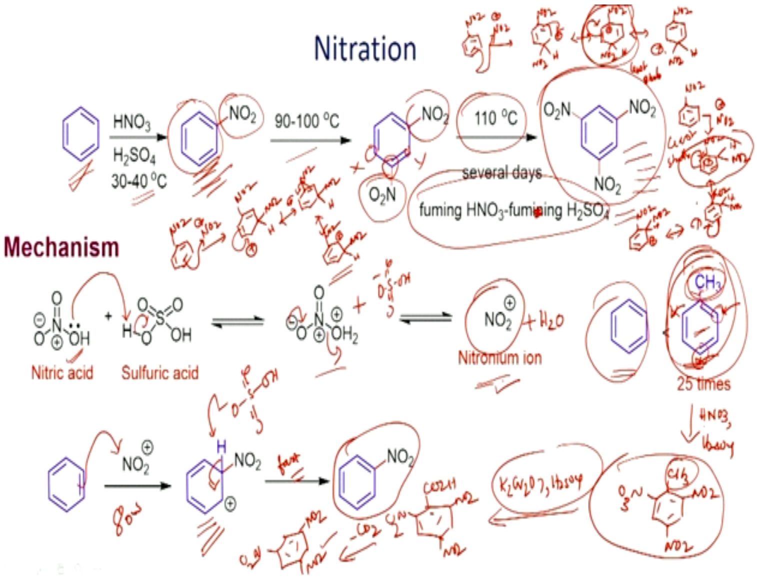
# Principles of Organic Synthesis
**Professor. T. Punniyamurthy**
**Department of Chemistry,**
**Indian Institute of Technology, Guwahati.**
**Lecture 15**
## Electrophilic Aromatic Substitution

Welcome you all to principles of organic synthesis. Presently, we study the electrophilic aromatic substitution. In this topic, so far we had two lectures. The first lecture focused on the principles of the electrophilic aromatic substitution and Fiedel-Crafts reactions, while the second lecture covered formylation, carboxylation, Mannich and isoquinoline synthesis. In this lecture, we will see the nitration, sulfonation and halogenation.

(Refer Slide Time: 1:30)



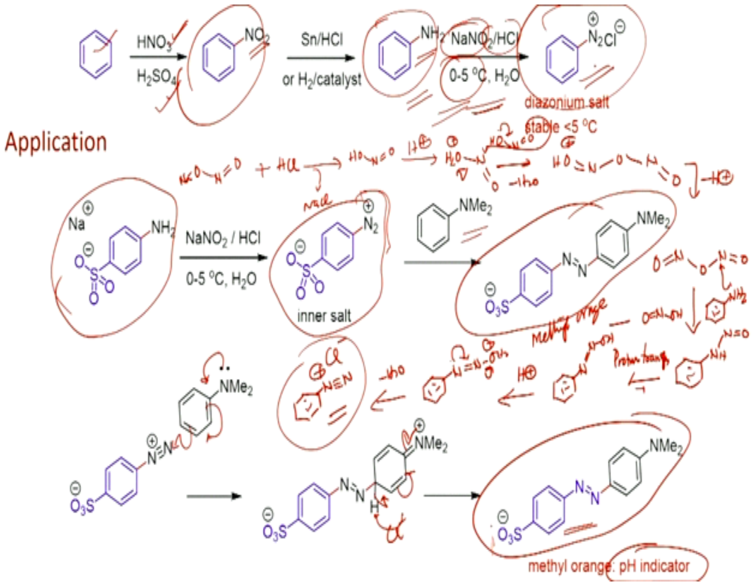
Here an example is shown for the nitration. Usually nitration is done using a mixture of nitric and sulfuric acids. If you carry out the reaction of benzene, you will be able to produce nitrobenzene at 30-40 °C. Nitrobenzene can further react to give 1,3-dinitrobenzene if we raise the temperature to 90-100 °C. If we increase the temperature to 110 °C, 1,3-dinitrobenzene can further react to produce trinitrobenzene. Because nitrobenzene is less nucleophilic compared to benzene. Similarly, dinitrobenzene is less nucleophilic compared to nitrobenzene. Therefore, vigorous condition is needed to have trinitrobenzene.

Nitrobenzene undergoes nitration at *meta*-position. Similarly, 1,3-dinitrobenzene undergoes nitration at *meta*-position. This can be understood by drawing the resonance structures as we have in the earlier lecture.  On the other hand, if it is *ortho* or *para* position, one of the resonance structures bears the carbocation where the nitro group is bonded. Therefore, this structure is less stable. This situation does not happen when the reaction takes place at *meta* position.

If you compare the rate of the nitration of benzene with toluene, toluene shows 25 times greater reactivity. Because of electron donating nature of methyl group. Therefore, toluene can be converted to trinitrotoluene, and the methyl group can then be oxidized to carboxylic acid using $K_2Cr_2O_7$. Dcarboxylation can produce the trinitrobenzene, which will be the best approach to make trinitrobenzene.

Let us see the mechanism. Protonation of nitric acid followed by removal of water molecule produces the nitronium ion, which acts as the electrophile. Reaction with aromatic ring gives the carbocation. Removal of the proton by $HSO_4^-$ produces nitrobenzene.

(Refer Slide Time: 12:45)



Nitro compounds are used as precursor to prepare diazonium salts. For example, nitrobenzene is reduced to aniline using Sn/HCl or hydrogenation, which can be further reacted with $HNO_2$ to produce the diazonium salt.

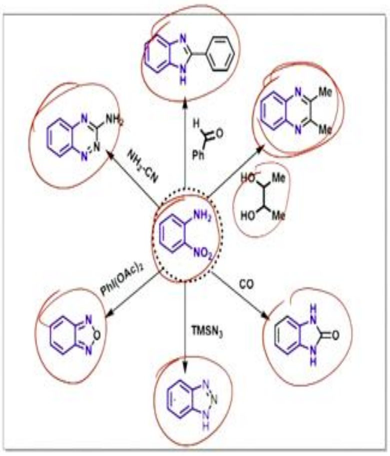
The mechanism starts with the reaction of $NaNO_2$ with HCl to produce $HNO_2$, which is converted to $N_2O_3$ that acts as the electrophile, undergoing addition reaction with amine to produce ArNHNO. Proton transfer generates ArN=NOH that protonates and loses water molecule to give the diazonium salt.

The application of diazonium salt in the preparation of methyl orange is shown. Aniline undergoes diazodizaton to give the diazonium salt, which can be reacted with *N,N-*

dimethylaniline at *para* position to give the methyl orange, which is used as the indicator in titration.

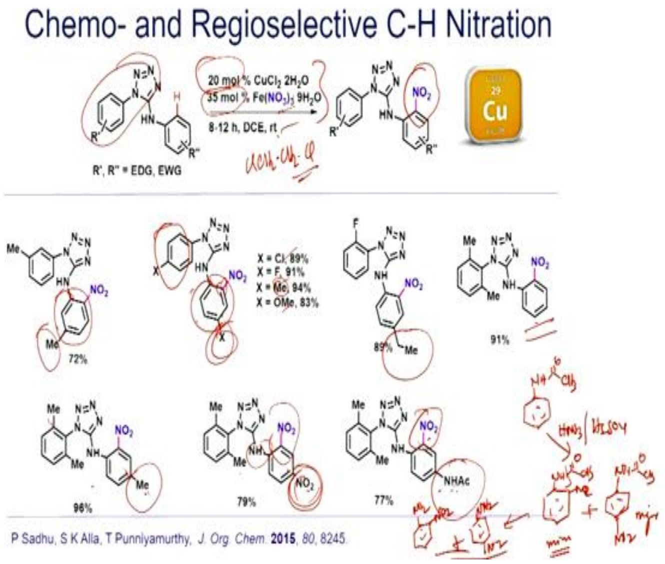
(Refer Slide Time: 17:57)

Importance of 2-Nitroanilines



Here the application of *ortho*-nitroaniline for the construction of diverse heterocyclic compounds is shown. For example, it can be reduced to 1,2-diaminobenzene, which can react with aldehyde via condensation followed by oxidative cyclization to produce benzimidazole. Similarly, reaction with $TMSN_3$ produces benzotriazole, while reaction with CO can give 1,3-dihyrobenzoimidazol-2-one. Likewise, reaction using $PhI(OAc)_2$ gives benzooxadiazole. Similarly, it can be utilized for the preparation of broad range of heterocyclic compounds.

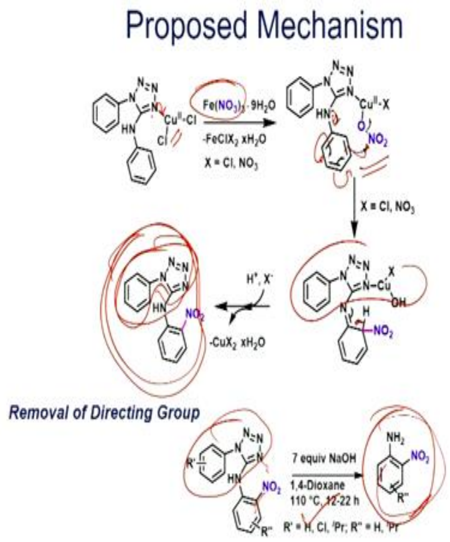
(Refer Slide Time: 18:23)


Chemo- and Regioselective C-H Nitration

P Sadhu, S K Alla, T Punniyamurthy, J. Org. Chem. 2015, 80, 8245.

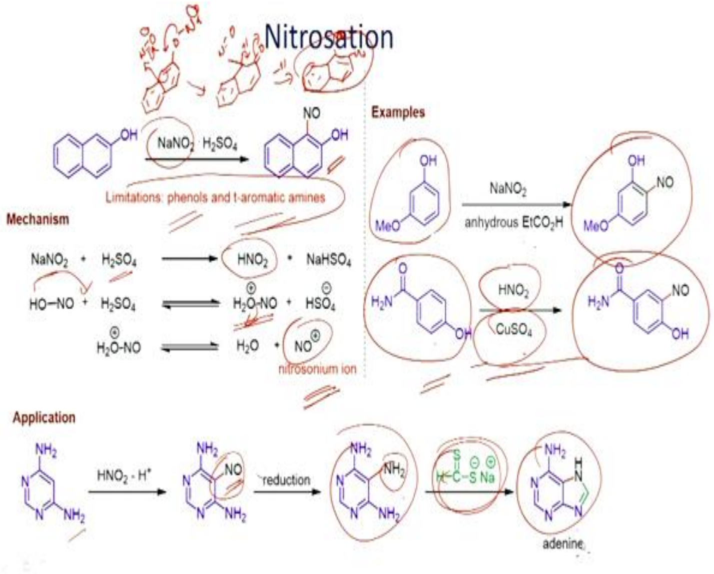
Now let us look at chemo- and regioselective nitration using transition-metal-catalysis. The reaction employs $Fe(NO_3)_3$ as nitro source in the presence of catalytic amount of copper(II) chloride, and the nitration takes place at *ortho* position. The reaction is general and broad range of substituents can be present. The tetrazole plays the crucial by chelating with catalyst that facilities the reaction at 5-aminoaryl ring.

(Refer Slide Time: 22:01)


Proposed Mechanism

Copper(II) chloride with $Fe(NO_3)_3$ gives an active Cu(II) complex, which makes chelation with tetrazoe. Which leads to aromatic electrophilic substitution at the *ortho* position. The tetrazole can be cleaved by base hydrolysis to produce *ortho* nitroaniline, which serves as precursor for the construction of diver nitrogen heterocycles.

(Refer Slide Time: 23:42)



Nitrosation

$\xrightarrow{NaNO_2 \cdot H_2SO_4}$

Limitations: phenols and t-aromatic amines

Examples

$\xrightarrow[\text{anhydrous } EtCO_2H]{NaNO_2}$

$\xrightarrow[CuSO_4]{HNO_2}$

Mechanism

$NaNO_2 + H_2SO_4 \longrightarrow HNO_2 + NaHSO_4$

$HO{-}NO + H_2SO_4 \rightleftharpoons H_2\overset{\oplus}{O}{-}NO + H\overset{\ominus}{S}O_4$

$H_2\overset{\oplus}{O}{-}NO \rightleftharpoons H_2O + NO^{\oplus}$

nitrosonium ion

Application

$\xrightarrow{HNO_2 \cdot H^+}$ $\xrightarrow{\text{reduction}}$

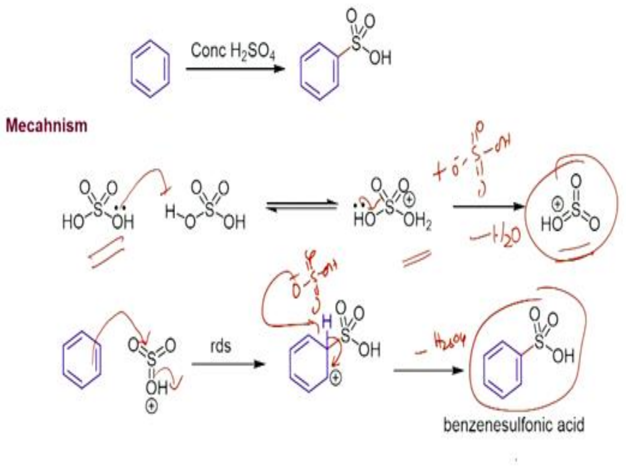
adenine

In place of nitro group, you can also use nitroso group. However, it has some limitations. For example, it works with phenols and anilines, however, simple substrate like benzene does not work. Thus, β-naphthol undergoes nitrosation using $NaNO_2$ in the presence sulfuric acid. $NaNO_2$ with $H_2SO_4$ generates $HNO_2$, which protonates and loses water molecule to afford nitrosonium ion that acts as the electrophile an undergoes reaction with the aryl ring to give the substitution product.

Similarly, 4-methoxyphenol undergoes nitrosation using $NaNO_2$ in the presence of propionic acid, while phenol having amide group at *para* position leads to nitrozation using $HNO_2$ in the presence of $CuSO_4$. The reaction has been applied for the synthesis of adenine. As above, nitrosation using $HNO_2$ in the presence of acid followed reduction give amino derivative, which is reacted thiocarbomate to produce adenine.

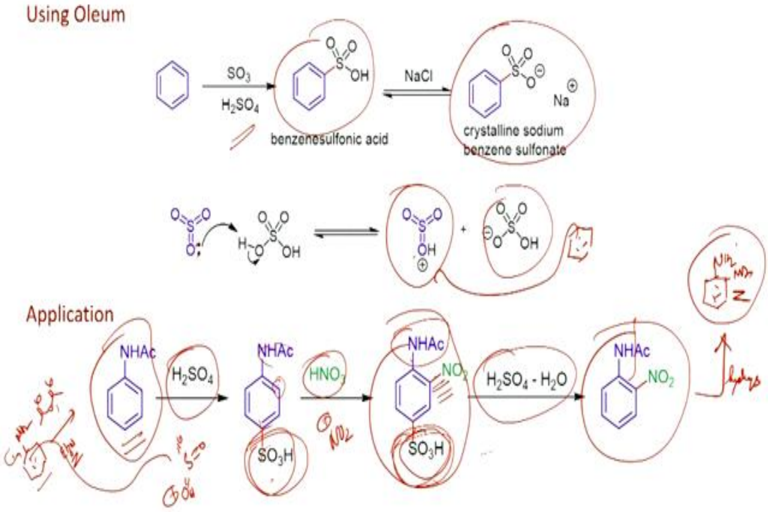
(Refer Slide Time: 27:49)

Sulfonation



Now let us look at sulfonation. Benzene with sulfuric acid readily reacts to produce benzenesulfonic acid. The mechanism starts with protonation of sulfuric acid followed by removal of water produces protonated sulfur trioxide, which acts as the electrophile. Reaction with aryl ring gives benzenesulfonic acid.

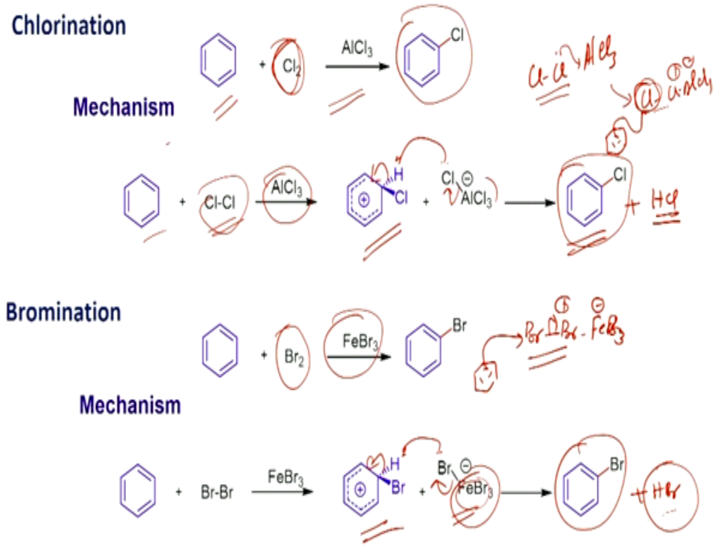
(Refer Slide Time: 29:07)



Sulfonation can be carried out using $SO_3$ in the presence of sulfuric acid. Sulfur trioxide undergoes protonation, which acts as the activated electrophile and reacts with aromatic system. For example, benzene reacts with $SO_3$ in the presence of sulfuric acid to give benzenesulfonic acid, which can be reacted with NaCl to give the crystalline sodium salt.

Acetanilide reacts with $H_2SO_4$ to give *para* sulfonic acid, which undergoes nitration using $HNO_3$. Desulfonation using $H_2SO_4$ followed by hydrolysis of amide produces *ortho*-nitroaniline.

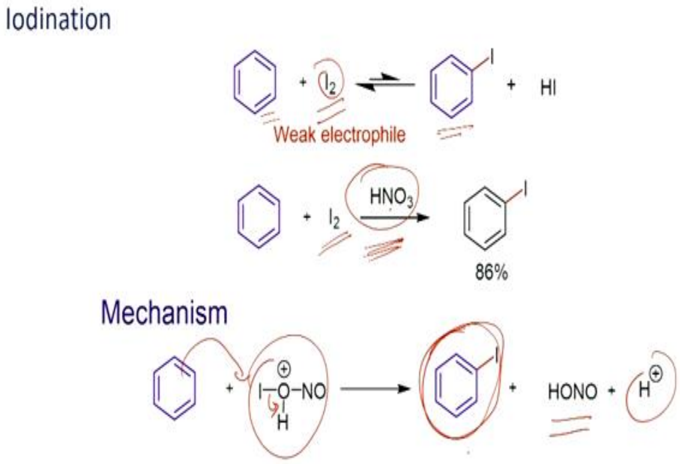
(Refer Slide Time: 32:32)



So far we have seen the nitration and sulfonation. Now let us look at the halogenation. The first example involves the reaction of $Cl_2$ with benzene to give the chlorobenzene. This can be carried out in the presence of aluminium(III) chloride, which activates $Cl_2$ that reacts with benzene to give the carbocation. Removal of proton gives chlorobenzene.

Similarly, benzene reacts with bromine in the presence of $FeBr_3$ to produce bromobenzene. $FeBr_3$ activates bromine, which reacts with benzene to produce the carbocation that loses proton to give bromobenzene.

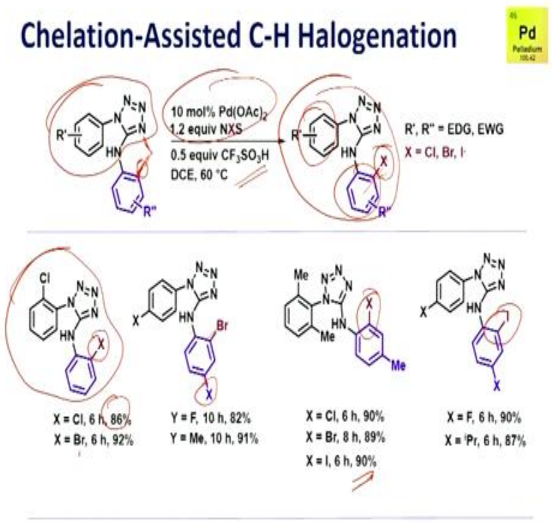
(Refer Slide Time: 35:09)


Iodination

Mechanism

When you go for the reaction with iodine, it is a weak electrophile compared to chlorine and bromine. Thus, the formation of iodobenzene and hydrogen iodide is less effective as the reaction is a reversible. Therefore, when we carry out the reaction using oxidising agent like $HNO_3$, it will react with iodine and generate an active species, which acts the electrophile to produce iodobenzene.

(Refer Slide Time: 36:12)


Chelation-Assisted C-H Halogenation

X = Cl, 6 h, 86%
X = Br, 6 h, 92%

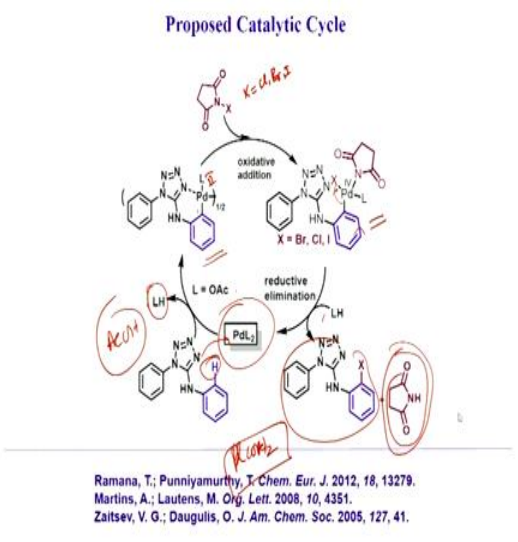
Y = F, 10 h, 82%
Y = Me, 10 h, 91%

X = Cl, 6 h, 90%
X = Br, 8 h, 89%
X = I, 6 h, 90%

X = F, 6 h, 90%
X = ⁱPr, 6 h, 87%

Here an example for the transition-metal-catalysed halogenation of arene is shown. The reaction is *ortho* selective and N-halosuccinimide is used as halogenating reagent in the presence of Pd-catalysis. The reaction is general and broad range of substrates react. The reaction works with chlorination, bromination and iodination. Triflic acid is utilized as an additive, which activates the Pd-catalyst.

(Refer Slide Time: 37:57)

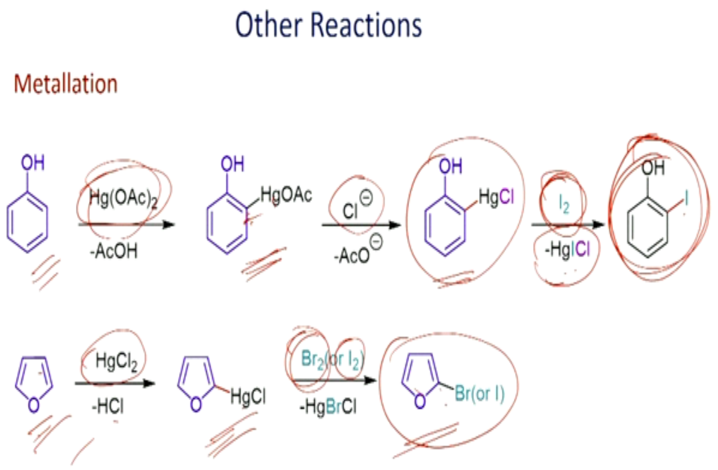


Proposed Catalytic Cycle

Ramana, T.; Punniyamurthy, T. *Chem. Eur. J.* 2012, *18*, 13279.
Martins, A.; Lautens, M. *Org. Lett.* 2008, *10*, 4351.
Zaitsev, V. G.; Daugulis, O. *J. Am. Chem. Soc.* 2005, *127*, 41.

Chelation of Pd(OAc)$_2$ with tetrazole followed by *ortho*-selective C-H activation takes place. Oxidative addition of N-halosuccinimide produces Pd(IV) complex, which gives the product by reductive elimination.

(Refer Slide Time: 39:48)



Other Reactions

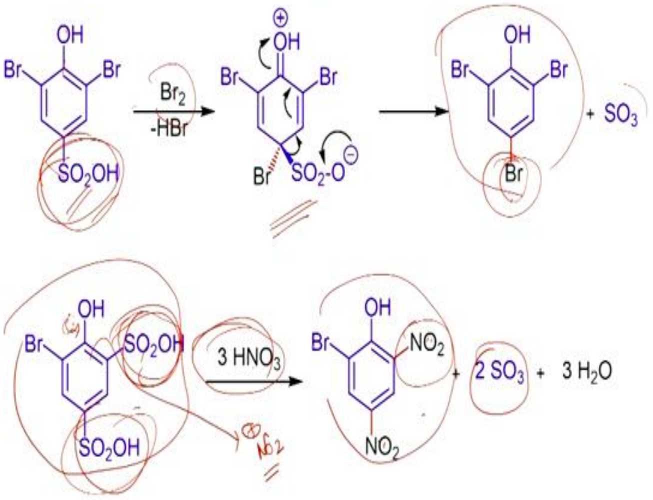
Metallation

Some other reactions are here shown. The first example involves the transformation of phenol to 2-iodophenol. The reaction of phenol with Hg(OAc)$_2$ produces Ar-HgOAc, which reacts with Cl$^-$ to produce ArHgCl. Reaction with iodine gives 2-iodophenol.

Similarly, furan can be converted to 2-bromo/2-iodofuran using bromine/iodine in the presence of $HgCl_2$.

(Refer Slide Time: 42:11)

Desulfonation



Here an example is shown for the desulfonation. For example, aryl sufonic acid undergoes substitution reaction with bromine. Desulfonation leads to bromo derivative.

The next example involves the substitution of sulfonic acid group with nitro group. In this way, we will be able to prepare substituted compound.

(Refer Slide Time: 43:50)

Summary

- Nitration
- Nitrosation
- Sulfonation
- Halogenation
- Desulfonation

In summary, we have seen the nitration. There are several approaches. One of the common methods that we use in the laboratory is the use of nitric acid in the presence of sulfuric acid to generate nitronium ion that reacts with aromatic system.

If you have the electron withdrawing group, the reaction is slow due to poor nucleophilicity of the aromatic ring. For example, nitration of nitrobenzene requires higher temperature. Moreover, electron withdrawing group facilities the nitration at *meta* position compared to *ortho* and *para* positions. These can be understood by drawing the resonance structures.

The reaction of aromatic system that has electron donating group is facilitated. For example, toluene shows 25 times greater reactivity compared to benzene.

We have seen the application of aromatic nitro compounds. We have seen for the formation diazonium salts and their application in the preparation of methyl orange indicator.

We also have seen introduction of nitroso function group. If you have sodium nitrite, which can convert to nitrosonium ion in the presence of acid that acts as the electrophile. We have seen the application of nitroso compound for the preparation of adenine.

We have seen sulfonation. This reaction can be accomplished using sulfuric acid or sulfur trioxde in the presence of acid. The is an important transformation, and finds application in dye industries. It also helps to introduce other functional groups regioselectively. After the reaction, sulfonyl group can be easily removed.

Then we have seen chlorination and bromination that can be carried out in the presence of Lewis acid. Whereas iodination is to be done in the presence of oxidizing reagent to push the reaction forward.

We have seen the recent development in the nitration and halogenation using transition-metal-catalysts. The regioselective C-H nitration can be accomplished using $CuCl_2$ with $Fe(NO_3)_3$ as the nitrating reagent.

Similarly, the chlorination, bromination and iodination can be regioselectively achieved via C-H activation using N-halosuccinimide in the presence of Pd-catalysis. These are important developments in the sustainable technologies. With this we conclude this lecture. Thank you very much.