

Organic Chemistry-4
Semester-4, CBCS
Course: CEMA CC-4-8-TH

Course taught by: Kaushik Basu, Department of Chemistry, SPCMC, Kolkata
email: chiralkaushik@gmail.com

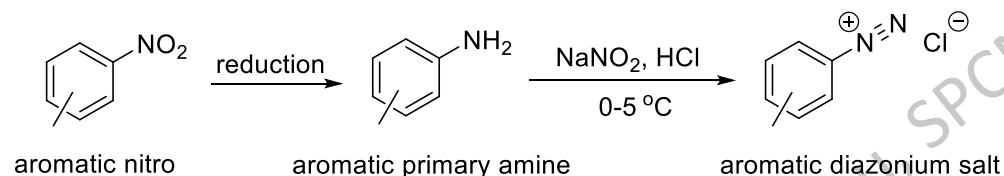
Recommended texts:

1. Study Guide to Organic Chemistry, Volume 4, by Saha, Chakraborty, Saha & Basu, Techno World, ISBN 9788192695259,
2. Organic Chemistry, Second Ed. by Clayden, Greeves & Warren, OUP, ISBN 9780198728719

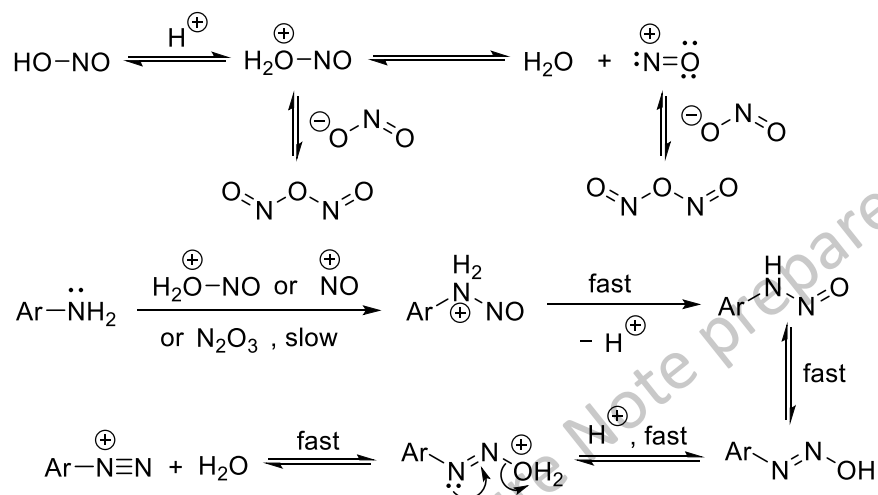
Organonitrogen Chemistry

Diazotization of primary aromatic amines: A versatile way to functionalize the aromatic ring:

Reduction of nitro compounds in strongly acidic medium affords aromatic primary amines, a versatile application of which in organic synthesis is through the formation of diazonium salt. When a primary aromatic amine is treated with nitrous acid under cold solution, the product is a relatively "unstable" compound known as a diazonium salt:



The formation of a diazonium compound by reaction of sodium nitrite, an inorganic acid (usually HCl) and a primary aromatic amine, in ice-cold solution, is known as diazotization.



Several factors, including the acidity of the solution, affect the rate law of diazotization.

In weakly aqueous acid solutions (and in more strongly acid solutions), the RDS is nitrosation of the free amine.

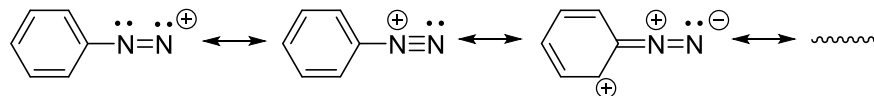
The effective nitrosation agent is probably not HNO₂ itself.

At relatively low acidity it is thought to be N₂O₃, while as the acidity is increased, a more effective species, protonated nitrous acid, and finally the nitrosonium ion starts to act as the nitrosating agent.

However, as the acidity of the solution is increased, the free amine concentration also decreases because it gets protonated and loses its nucleophilic activity.

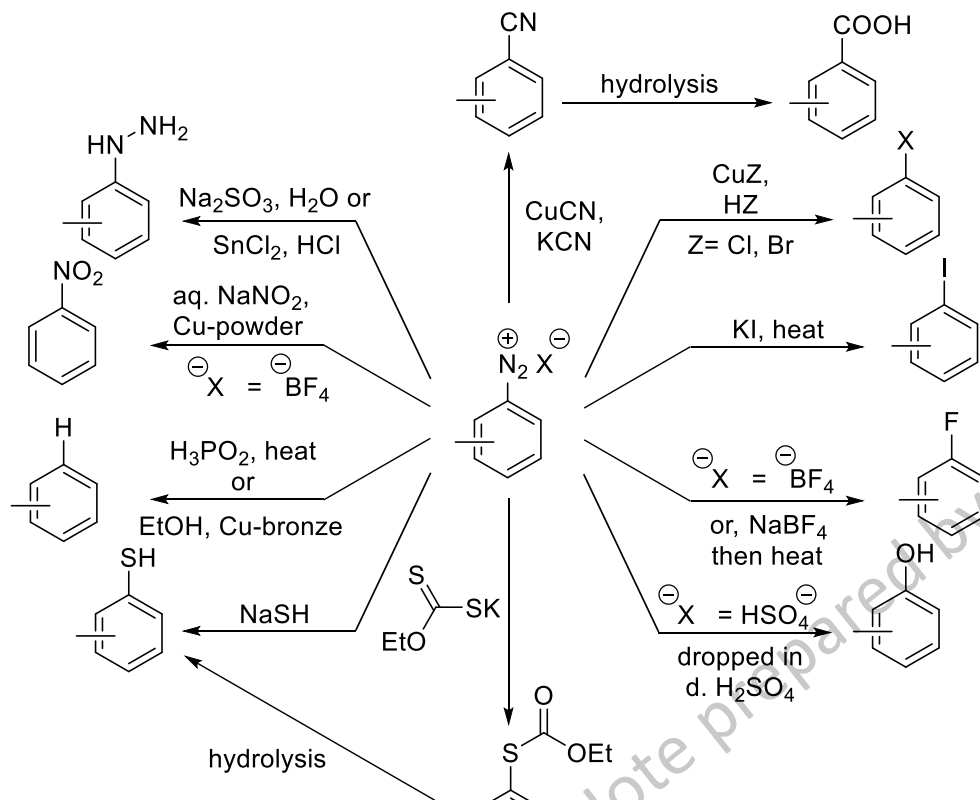
So, a compromise in terms of solution acidity has to be struck in nitrosation.

Compared to aliphatic diazonium salts, which tend to decompose extremely rapidly to various by-products with evolution of nitrogen gas, aromatic diazonium compounds are *relatively* more stable. This additional stability is attributed to the conjugation of -N₂⁺ with the aromatic ring:

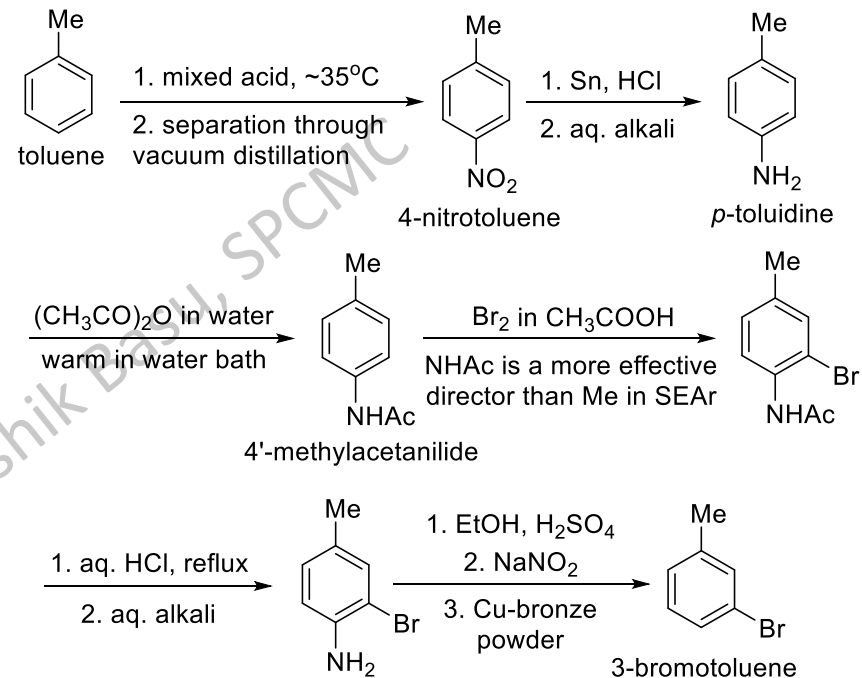
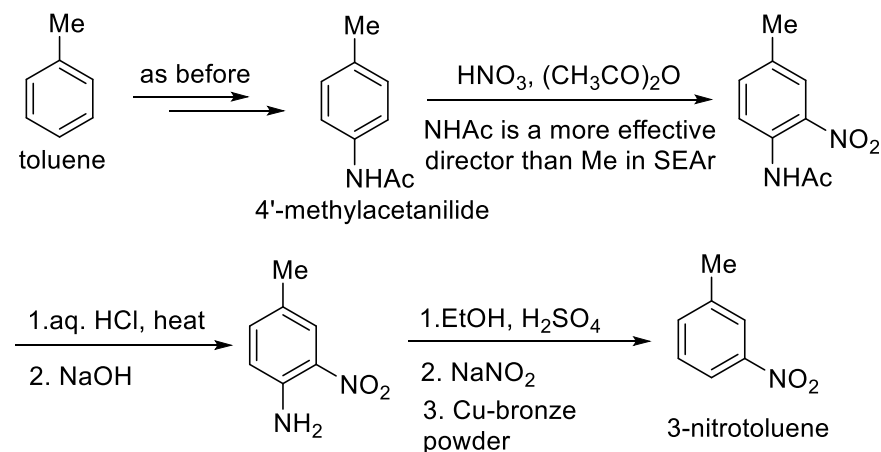


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Synthetic utility of the diazonium salt:



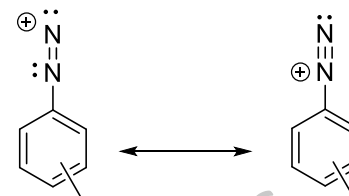
The problem of introducing a bromo or a nitro group at *meta*-position with respect to the *ortho*-/*para*-directing methyl group is solved by adding a 'dummy' amino group which is used to set up the required relationship and then removed by diazotization and reduction.

Synthesis of *m*-bromotoluene:Synthesis of *m*-nitrotoluene:

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Diazo-coupling and its applications:

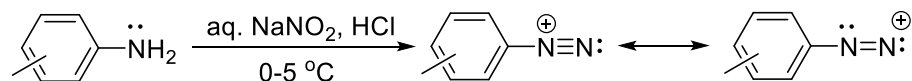
A classic aromatic electrophilic substitution is diazo-coupling, in which the effective electrophile has been shown to be the diazonium cation:



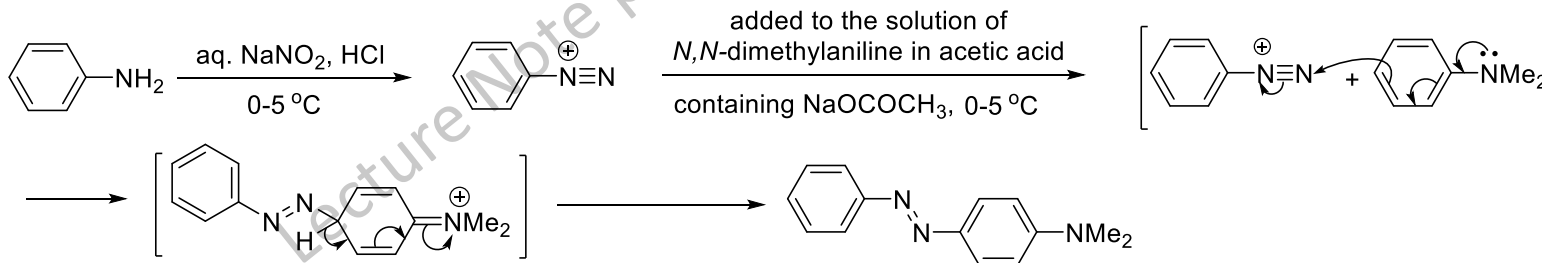
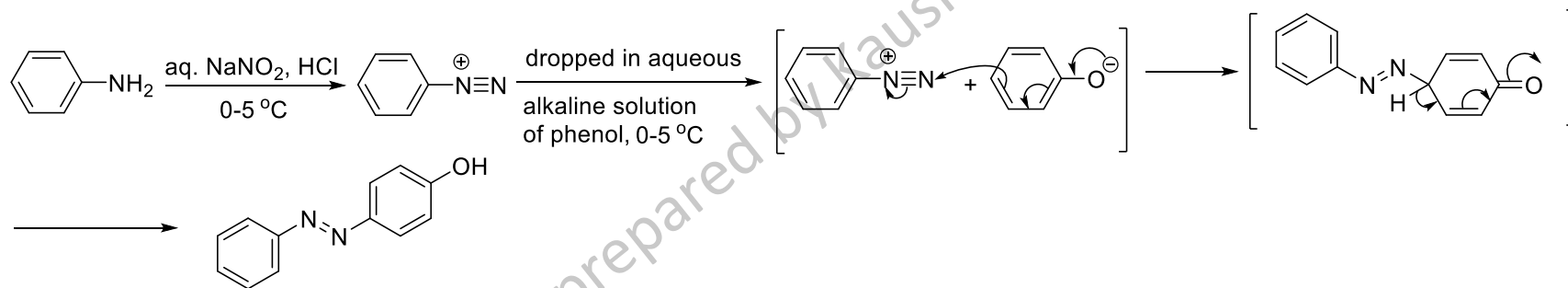
Greiss

J. P. Greiss
(1829-1888)

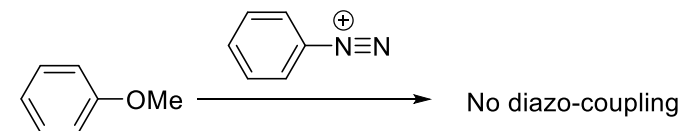
Diazonium salt is easily made through the diazotization of aromatic primary amines:



For the more contributing canonical form of the diazonium cation each element has an octet. Thus diazonium cation is a much weaker electrophile (as compared to NO_2^+). As a result, diazo-coupling proceeds only with highly activated aromatic substrates: such as *N,N*-dialkylanilines and phenols.



Even anisole which is usually considered to be a very much reactive substrate for $\text{S}_{\text{E}}\text{Ar}$ reactions, does not participate in diazo-coupling.

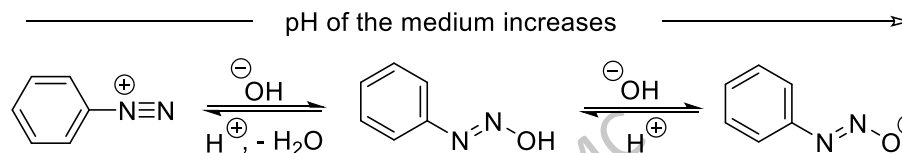


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Diazo-coupling and its applications:

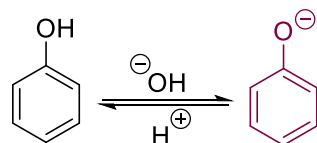
The pH dependence of diazo-coupling:

Depending on the pH of the medium, the diazonium salt may exist in one of the following forms in solution:



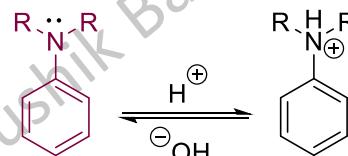
In the diazo-coupling reaction, diazonium salt is actually the electrophile. Thus, with respect to the diazonium salt a *lower pH will favour the diazo-coupling*.

Depending on the pH of the medium phenol can exist in the following two forms:



The phenoxide ion is more susceptible to electrophilic attack than phenol is. Thus with respect to phenol, a *higher pH will favour the diazo-coupling*.

Depending on the pH of the medium *N,N*-dialkylaniline will exist in the following two forms:



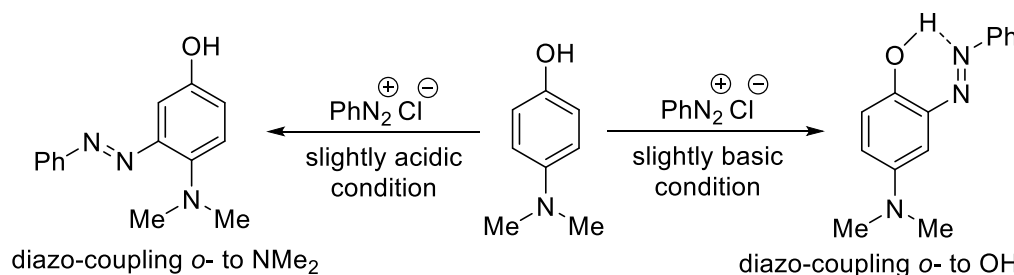
N,N-dialkylaniline is more susceptible to electrophilic attack than its conjugate acid. Thus, w.r.t. *N,N*-dialkylaniline, a *higher pH will again favour the diazo-coupling*.

Thus diazo-coupling reaction should be carried out at an optimum pH

This optimum pH is slightly alkaline with respect to phenol, as *under this condition it is converted into the more reactive phenoxide* ion which is also more soluble in the medium. That the neutral phenol is not effective for coupling is evident from the fact that even the usually highly reactive anisole, PhOCH_3 does not participate in diazo-coupling. Of course, there can be no phenoxide here!

This optimum pH is slightly acidic with respect to *N,N*-dialkylaniline, as *under this condition the compound exists in the salt form which is more soluble*. Diazo-coupling actually proceeds upon the non-protonated form which exists in equilibrium with its conjugate acid, the protonated, deactivated anilinium salt (pKa ca. 5.5). But as the diazotization proceeds, the non-protonated form is consumed and the equilibrium is shifted towards it till the reaction is complete (Le Chatelier's principle).

Thus we have the following observation:

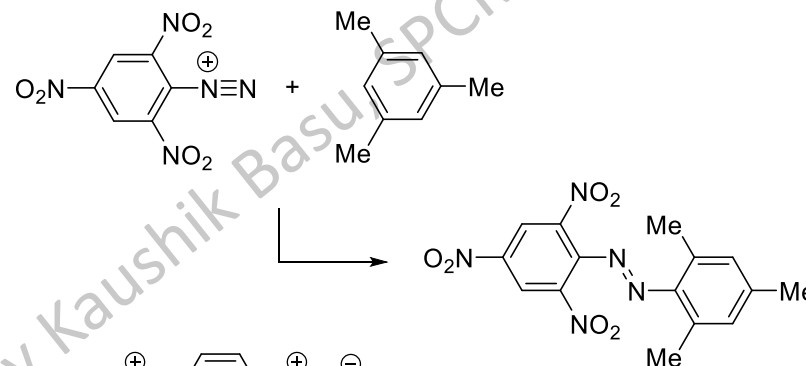


Diazo-coupling and its applications:

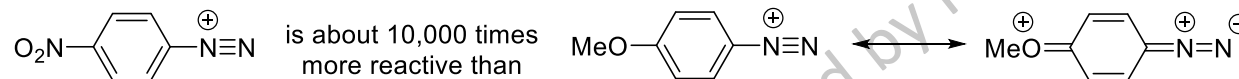
Diazonium cations are weak electrophiles and thus deactivated aromatic rings such as acylated aniline derivatives, phenolic ethers and esters are ordinarily not reactive enough for diazo-coupling.

However, it is sometimes possible to couple them as well as polyalkylated benzenes as mesitylene and pentamethylbenzene with diazonium salts when the latter is *exceptionally electrophilic* in nature.

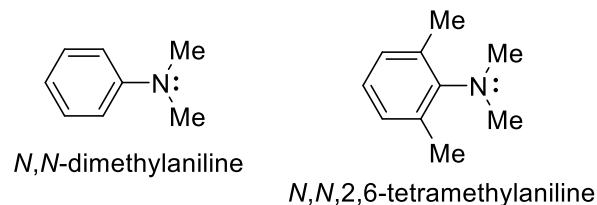
This is true for diazonium salts containing EWGs in the *para*-position, since such groups increase the concentrations of positive charge and thus electrophilicity of ArN_2^+ .



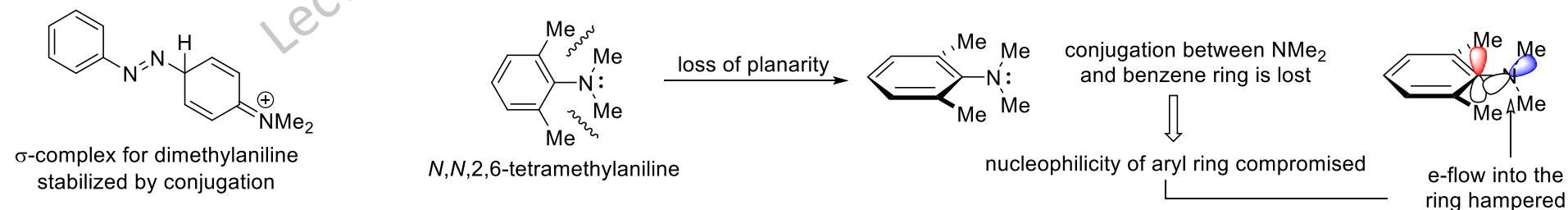
Similarly, by the introduction ERG, the electrophilicity of the diazonium salt is decreased. Thus, towards diazo-coupling:



The importance of keeping the nucleophilicity of the aromatic nucleus high in order to achieve a successful diazo coupling is demonstrated by the observation that while *N,N*-dimethylaniline undergoes diazo-coupling easily but *N,N*,2,6-tetramethylaniline, does not.

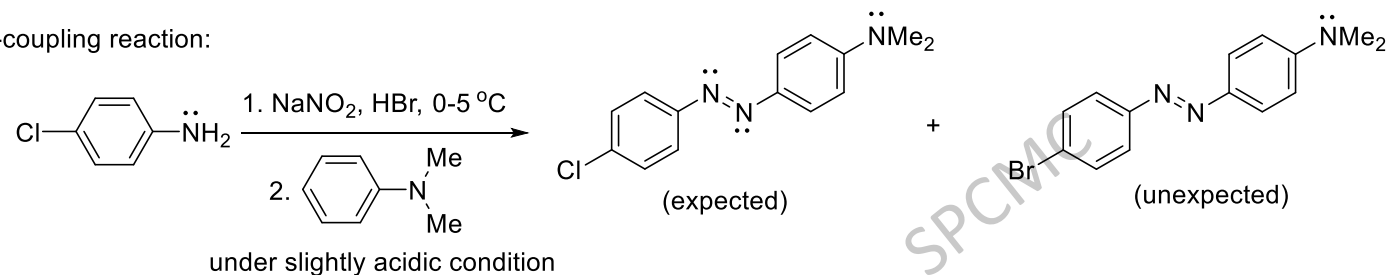


This is, undoubtedly, reflecting that the second molecule is less nucleophilic than the first. This is expected, considering the loss of planarity of the NMe_2 group w.r.t. the benzene nucleus to avoid steric clash with the *ortho*-methyls which results in its inability to properly stabilize the sigma-complex associated with the electrophilic attack.

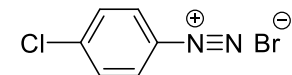


Diazo-coupling and its applications:

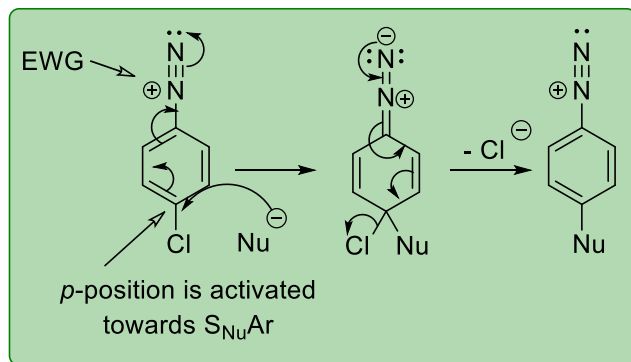
Unusual outcome of a diazo-coupling reaction:



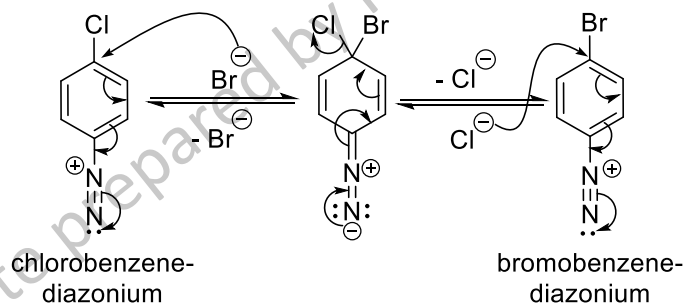
To explain the formation of the unexpected product, we need to look at the diazonium cation generated in situ:



It undergoes a nucleophilic substitution by the bromide ion present via the addition-elimination mechanism, as the diazonium salt is activated towards nucleophilic attack by the electron-withdrawing nature of the diazonium group.



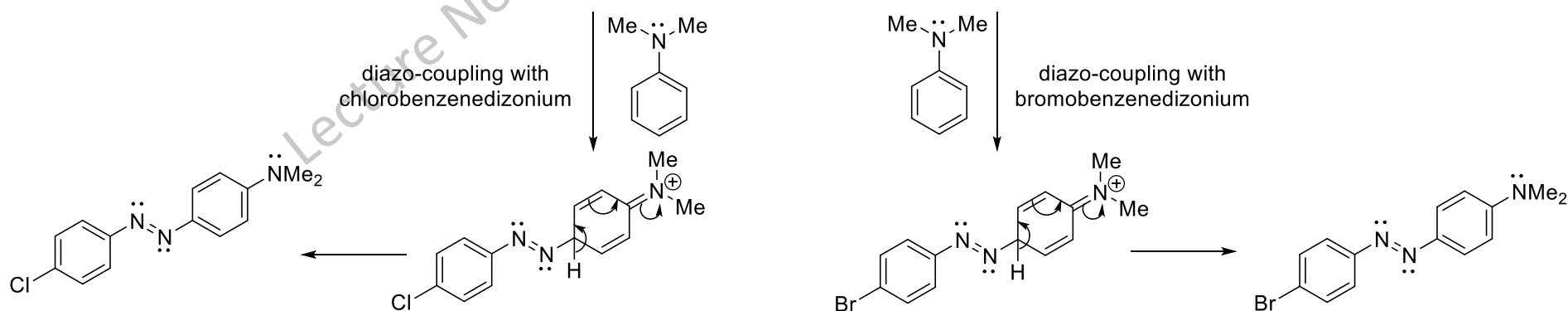
Thus, here, the Cl atom of chlorobenzene diazonium is replaced by Br via an S_{NuAr} :



This nucleophilic substitution reaction is faster than the rate at which the chlorobenzene diazonium is captured by the amine.

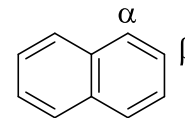
So there are two diazonium salts present in the medium both of which participate in the coupling with *N,N*-dimethylaniline.

As a result, we get two diazo-coupled products.



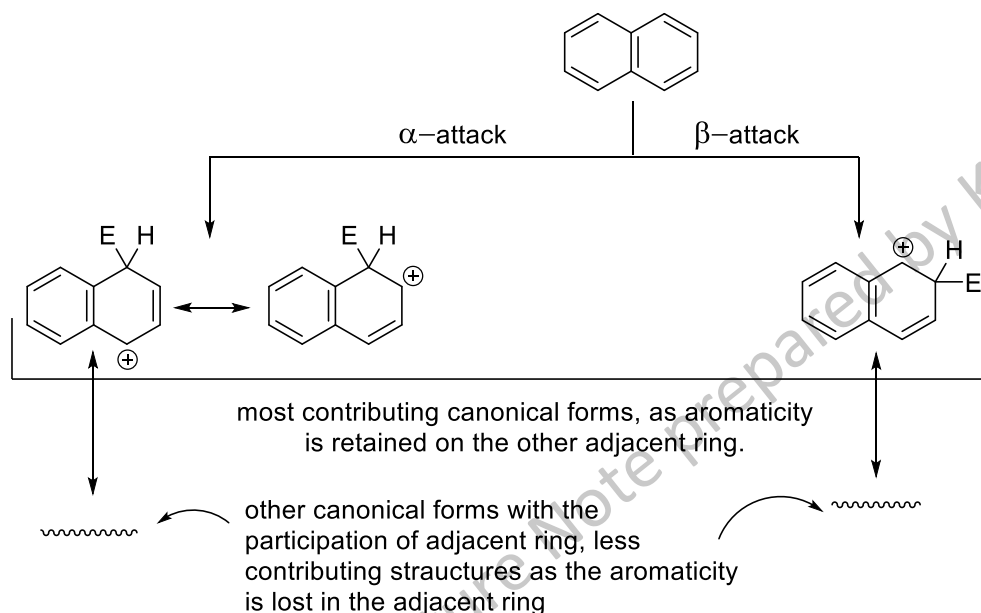
Diazo-coupling and its applications:

Let us consider the diazo-coupling reactions of α -naphthol and β -naphthol respectively. Recall that there are two possible positions, α and β , for the electrophilic substitution on naphthalene system:



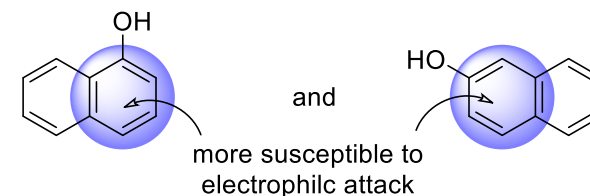
We know that the SEAr reaction on aromatic nucleus will regioselectively proceed at that site at a faster rate which leads to the formation of a more stable sigma-complex and the corresponding product will be the major product.

In case of naphthalene where we have the two possible sites available for electrophilic attack:



Thus, simply by counting the number of canonical forms we can say that the σ -complex for α -attack is more stable than that for β -attack. So, in case of naphthalene, α -attack is more favoured over β -attack.

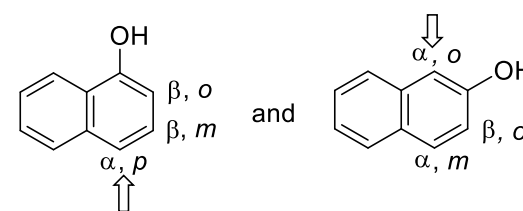
In the cases of α -naphthol and β -naphthol, the substituent, the hydroxyl group, is ER in nature (+R effect). Thus the ring containing the hydroxyl group is more susceptible to electrophilic attack i.e.



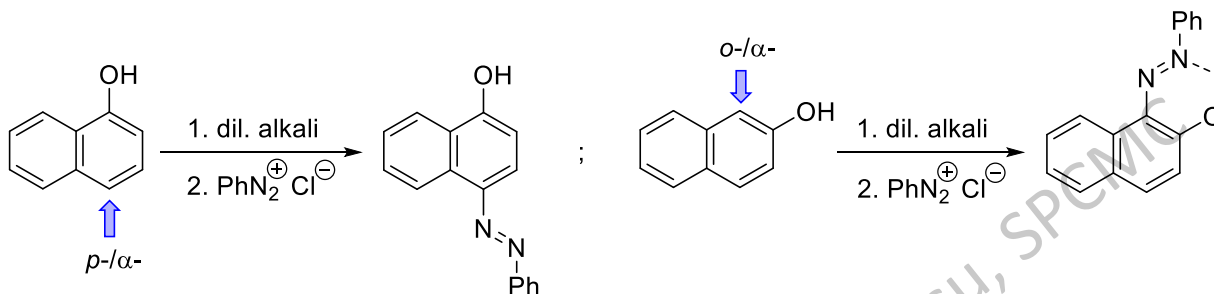
We know that electrophilic substitution will regioselectively proceed at that site at a faster rate where the σ -complex is more stable. Now we already have the following information:

The σ -complex for α -attack (with respect to naphthalene nucleus) is more stable than that of β -attack. The σ -complex for *ortho*- and *para*-attack (with respect to hydroxy group) is more stable than that for *meta*-attack.

The favoured positions of electrophilic substitution in the two ring systems can be marked by the arrows as shown below



Diazo-coupling and its applications: α -naphthol and β -naphthols

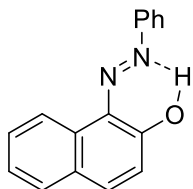


In fact, diazo-coupling with β -naphthol is used for the qualitative detection of aromatic primary amino groups.

The test requires diazotizing your sample in HCl medium and pouring the diazotized solution into the alkaline solution of β -naphthol in aqueous alcoholic medium. Appearance of a red or orange azo-dye confirms presence of amino group in your sample.

Why specifically use β -naphthol and why not the α -isomer? Consider the following points:

1. Considering the stabilities of σ -complexes through the loss of resonance energy it is expected that the naphthalene nucleus is more susceptible to electrophilic attack than the benzene nucleus, for which electrophilic substitution reaction is expected to take place more rapidly on naphthols, in comparison to common phenols.
2. The size of the hydrophobic part of the naphthol system is greater in comparison to common phenols. As a result, the diazo-coupled products of naphthols is expected to be less soluble in aqueous alkaline solution.
3. Through the following type chelation that exists in the diazo-coupled β -naphthol system, the acidity of the hydroxyl group decreases. As a result, it is expected that this product will be insoluble under the alkaline reaction condition



In consequence, the diazo-coupling product is expected to separate from the reaction medium in the form of a coloured precipitate, leading to a *much more discernible and vivid change* (compared to a colour change in solution).

In the case of α -naphthol, the coloured product is expected to be more acidic than the reactant (α -naphthol) and therefore it is expected to be more soluble in the alkaline reaction condition.

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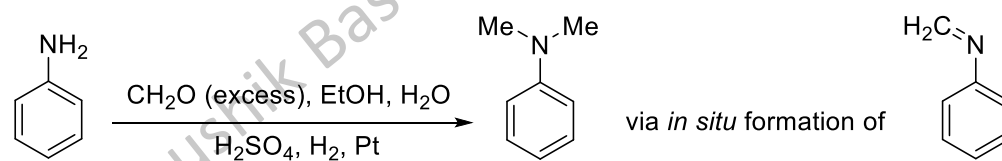
Synthesis of secondary and tertiary aromatic amines:

Methylation of aniline can be achieved to access either *N*-methylaniline or *N,N*-dimethylaniline by using methanol and sulphuric acid. The nature of the final product depends on the ratio of the substrate to methanol: using 1.2 equivalents of the alcohol affords the secondary amine, while large excess of methanol leads to the tertiary amine as the main product.

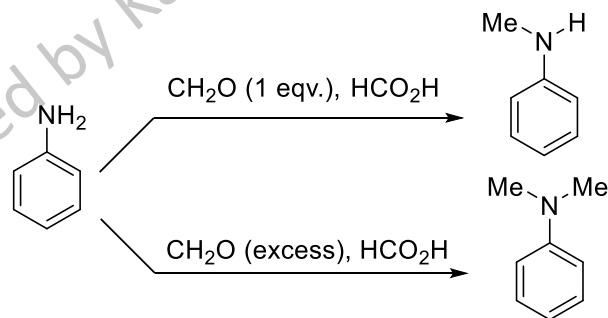


Alkylation with alkyl halides always runs the risk of over-alkylation, so a better alternative is reductive alkylation.

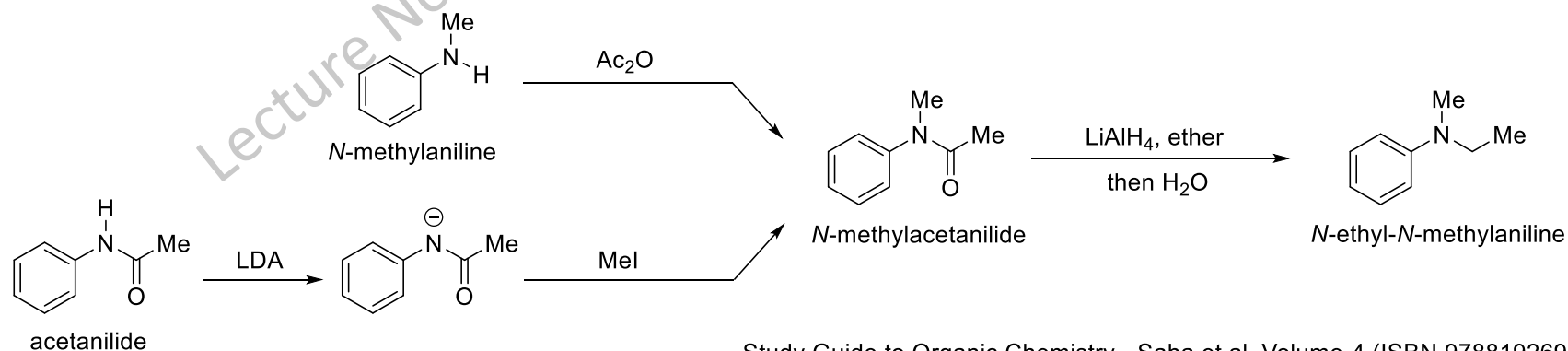
One example is synthesis of *N,N*-dimethylaniline through reductive methylation of aniline using formaldehyde:



Similarly, the Eschweiler-Clarke methylation can give access to both the secondary and the tertiary amine:



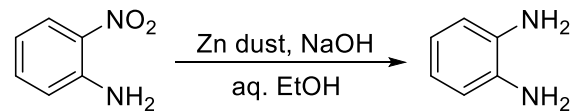
Reduction of amide is another way:



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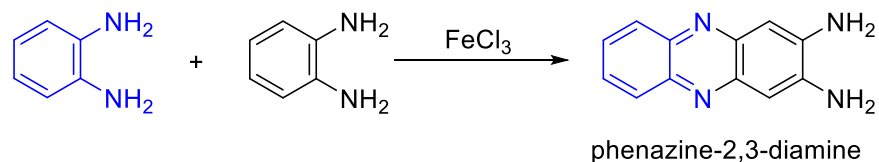
Formation and reactions of diphenyleneamines:

o-Phenylenediamine: It is prepared by reducing *o*-nitroaniline with zinc dust and aqueous ethanolic sodium hydroxide:

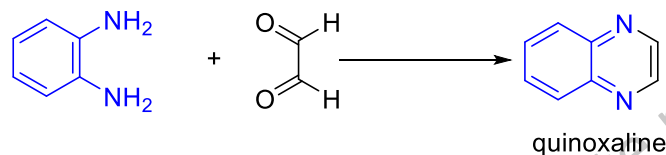


The most characteristic property of *o*-diamines is the ease with which they form heterocyclic compounds.

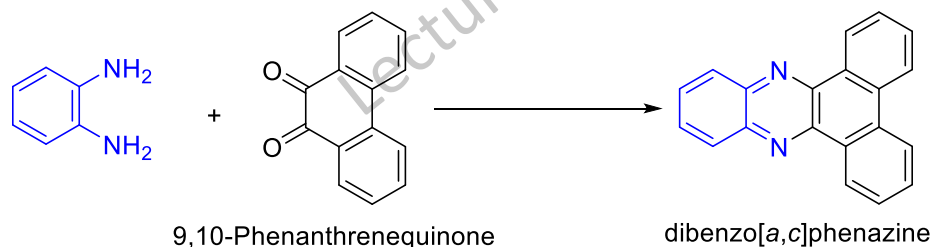
When *o*-phenylenediamine is treated with ferric chloride solution, a dark red colour is produced due to the formation of 2,3-diaminophenazine:



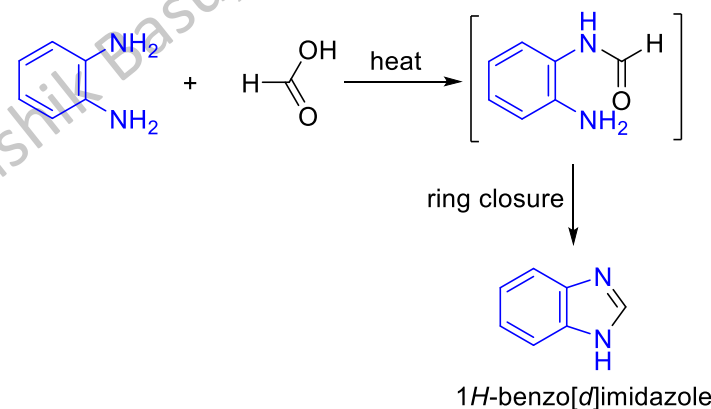
When *o*-phenylenediamine condenses with α -dicarbonyl compounds, quinoxalines are formed; e.g., with glyoxal, quinoxaline is the product:



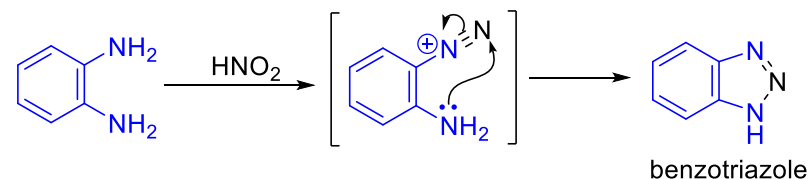
This reaction is used to identify *o*-diamines; the 1,2-dicarbonyl compound employed for this purpose is phenanthraquinone, which results in the formation of a sparingly soluble phenazine derivative:



Benzimidazoles are formed when *o*-phenylenediamine is heated with organic acids, e.g.,



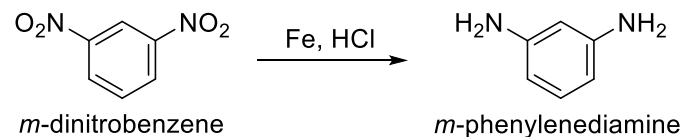
When *o*-phenylenediamine is treated with nitrous acid (best way: an acidic solution of the diamino compound is treated with aqueous sodium nitrite), benzotriazole is formed through an intramolecular reaction:



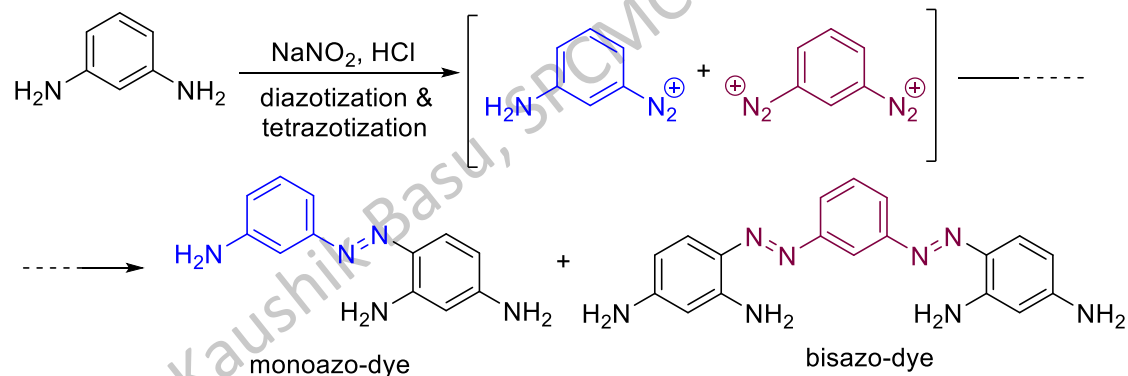
Note that the reactivity of the two amino groups are initially the same but after diazotization of one amino group, the reactivity of the other is reduced drastically in the intermediate. This promotes the intramolecular reaction at the expense of another diazotization and the benzotriazole results.

Formation and reactions of diphenyleneamines:

m-Phenylenediamine: This one is prepared by reducing *m*-dinitrobenzene:

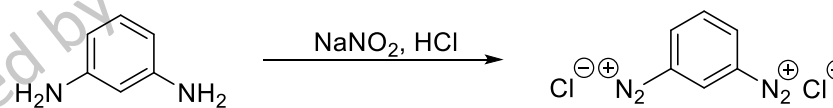


The most characteristic reaction of *m*-phenylenediamine when treated with nitrous acid is the formation of brown dyes - Bismarck Brown - a monoazo- and a bisazo-compound are formed:

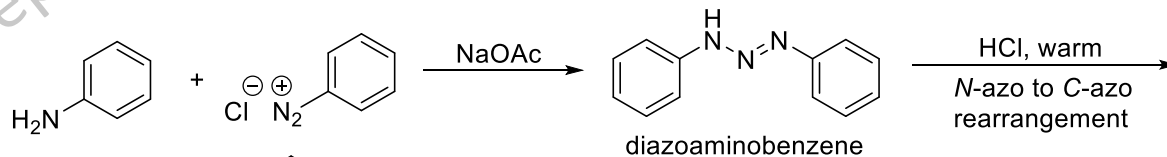


This reaction is used as a colorimetric method for the determination of nitrites in water; even when nitrites are present in traces, a yellow color is produced.

On the other hand, by dissolving *m*-phenylenediamine in concentrated hydrochloric acid, and keeping the nitrous acid always in excess, both amino-groups may be diazotized (double diazotization / tetrazotization) to give the tetrazo-compound):



p-Phenylenediamine: It is prepared by reducing *p*-nitroaniline or aminoazobenzene, e.g.



p-Phenylenediamine can be diazotized in the ordinary way, and during diazotization some *p*-benzoquinone is formed through oxidation:

