Principles of Organic Synthesis
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Lecture 20
Aromatic Diazonium Salts

Welcome you all to Principles of Organic Synthesis. At present, we study the aromatic diazonium salts. In this module, we had one lecture, where we studied the preparation and reaction of the diazonium salts. There are three types of reactions. First type involves the addition reaction of the strong nucleophile, whereas the second type focuses on the aryl carbocation intermediate, which reacts with the nucleophile and the third type covers the aryl radical intermediate that can be converted to aryl halide or alkylated products. In this lecture, we will continue with the reaction of diazonium salts.

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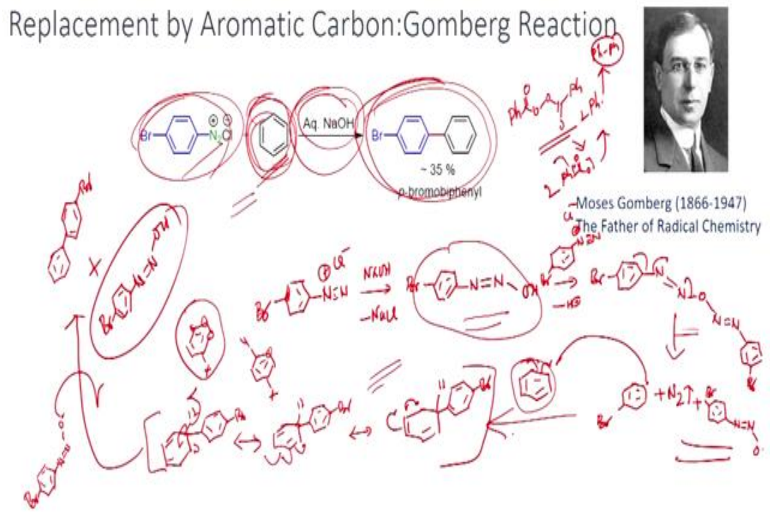

Replacement by Aromatic Carbon:Gomberg Reaction

Moses Gomberg (1866-1947)
The Father of Radical Chemistry

Aryldiazonium salt reacts with benzene in the presence of aqueous sodium hydroxide to give biaryl compound, which is known as the Gomberg reaction. Addition of hydroxide ion to the diazonium salt gives diazohydroxide, which converts to diazotate ion since the reaction is basic. Homolytic cleavage of 2,2’-oxybis(1-aryldiazene) can give the aryl radical, nitrogen molecule and diazotate radical. Addition of the aryl radical to benzene gives the biaryl radical, which reacts with diazotate radical to produce the biaryl compound and diazohydroxide. The reaction will be useful to prepare unsymmetrical biaryl compounds as benzoyl peroxide based reaction gives to the symmetrical biaryl compounds. However, with substituted aryl ring, we will end up with a mixture of compound as the reaction can take place at *ortho*, *para* or *meta* position with respect to the substituent. Further, the reaction is carried out in biphase system. For example, we have to take the diazonium salt in aqueous sodium hydroxide that reacts with benzene.

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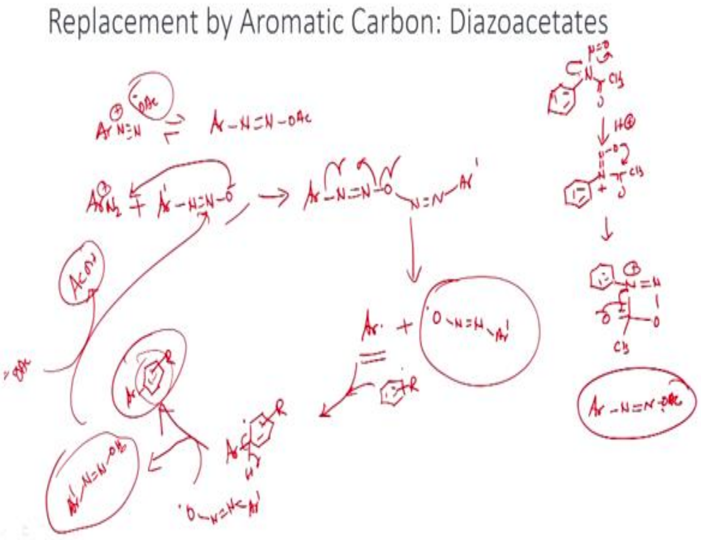

Replacement by Aromatic Carbon: Diazoacetates

Here the reaction of diazonium acetate with benzene provides the biaryl compound. N-Nitroso-N-arylacetamide rearranges to 1-actoxy-2-aryldiazene in the presence of acid, which exists in equilibrium with the aryldiazonium acetate. As we have seen in the Gomberg reaction, diazotate reacts with diazonium salt to form 2,2’-oxybis(1-aryldiazene), which leads to homolytic cleavage to produce diazotate radical and aryl radical. Addition of the aryl radical to benzene gives the biaryl radical, which reacts with diazotate radical to produce biaryl compound and diazohydroxide. Deprotonation using acetate ion lead to diazotate ion and acetic acid. As we have seen above, the yield is less and produces a mixture of biaryl compounds if the substituted aromatic system is used as the substrate.

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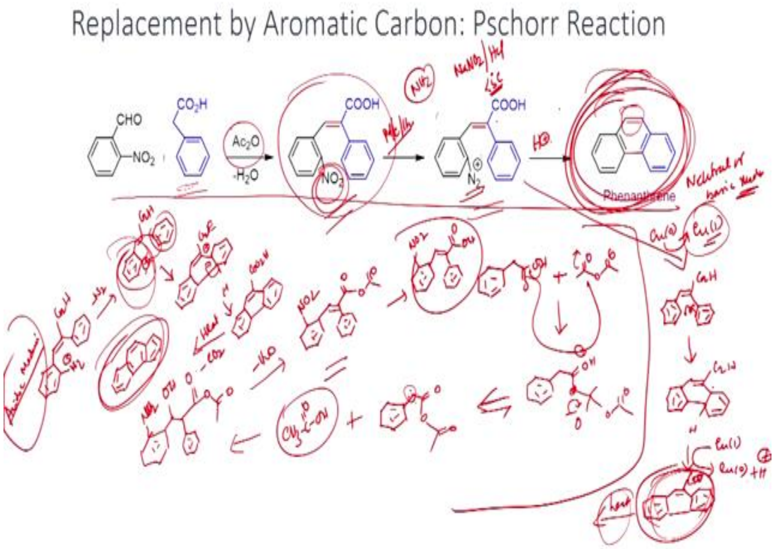

Replacement by Aromatic Carbon: Pschorr Reaction

Here is an application of the diazonium salt for phenanthrene synthesis. Condensation of phenylacetic acid with 2-nitrobenzaldehyde using Ac_2O produces 2,3-diarylacrylic acid. Reduction of the nitro group and diazotization using nitrous acid gives the aryldiazonium salt. It can lose nitrogen molecule in acidic solution to give the aryl carbocation, which can be reacted by the other aryl ring via an electrophilic aromatic substitution to furnish phenanthrene. Alternatively, the aryldiazonium salt can be converted to the aryl radical using copper powder via the single electron transfer (SET) under neutral or basic conditions. The aryl radical can undergo intramolecular reaction with the other aryl ring to produce phenanthrene. Depends on the nature of the reaction medium, aryldiazonium salt can thus be converted to the aryl carbocation or aryl radical, which can cyclize with other aryl ring, which is known as the Pschorr reaction. These reactions are also often difficult to control due to the formation many side reactions.

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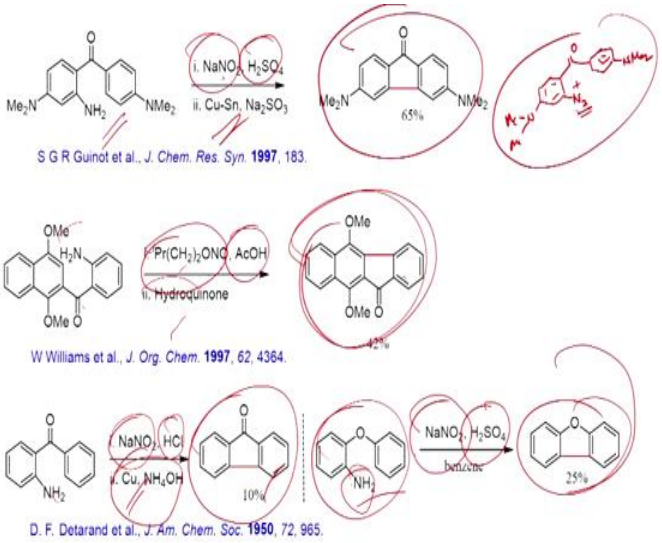

S G R Guinot et al., *J. Chem. Res. Syn.* **1997**, 183.

W Williams et al., *J. Org. Chem.* **1997**, *62*, 4364.

D. F. Detarand et al., *J. Am. Chem. Soc.* **1950**, *72*, 965.

Here the first example involves the diazotization of 2-aminobenzophenone derivative using $NaNO_2$ and H_2SO_4, which is reacted by reductive cyclization using Cu-Sn to give the fluoren-9-one derivative. In this reaction, the diazonium salt is converted to the aryl radical that undergoes intramolecular addition reaction with the other aryl ring to give the cyclic compound.

Likewise, the diazotization of the aniline derivative using the organic nitrite with AcOH followed by the reductive cyclization using hydroquinone gives the polycyclic ketone. Further, the diazotization of 2-aminobenzophenone using $NaNO_2$ and HCl and the reductive cyclization with Cu gives the fluoren-9-one derivative, while 2-phenoxyalniline diazotizes using $NaNO_2$ and H_2SO_4, which can be cyclized to yield dibenzofuran. Thus, Pschorr reaction has wide applications to construct functionalized aromatic compounds.

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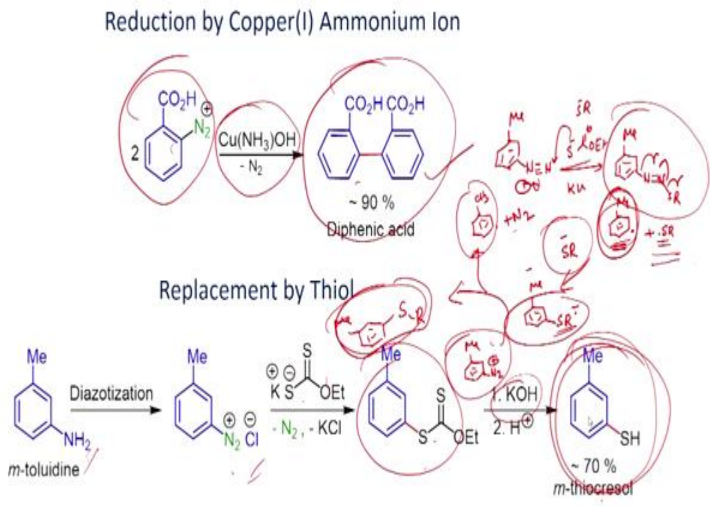

Reduction by Copper(I) Ammonium Ion

Replacement by Thiol

Here the diazonium salt of anthranilic acid reacts with Cu(NH$_3$)OH to produce benzoic acid radical that dimerizes to yield diphenic acid. Likewise, the diazotization of *m*-toluidine using nitrous acid and HCl, followed by reductive coupling with potassium salt of ethyl xanthate produces aryl ethyl xanthate. Hydrolysis using KOH produces *m*-thiocresol. This reaction involves the reductive coupling vis the aryl radical intermediate.

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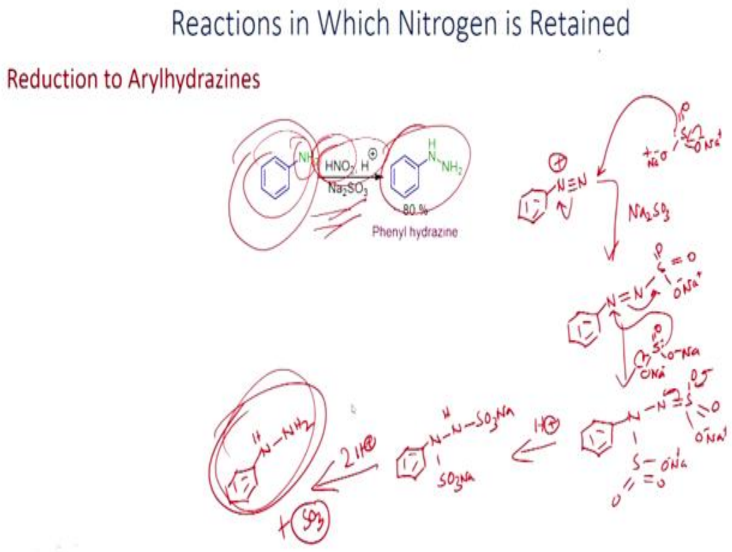

Reactions in Which Nitrogen is Retained

Reduction to Arylhydrazines

So far we have seen the reaction that involves the replacement of nitrogen mostly by aromatic carbons. Now, let us look at the reactions where the nitrogen is retained. Here the diazotization of aniline using nitrous acid gives the phenyldiazonium salt, which undergoes reduction using an excess of Na_2SO_3 to give phenylhydrazine. In this reaction, sodium sulfite adds to the diazonium salt to produce phenylhydrazine sulfonic acid salt, which is hydrolyzed using acid, which is known as Fischer phenylhydrazine synthesis.

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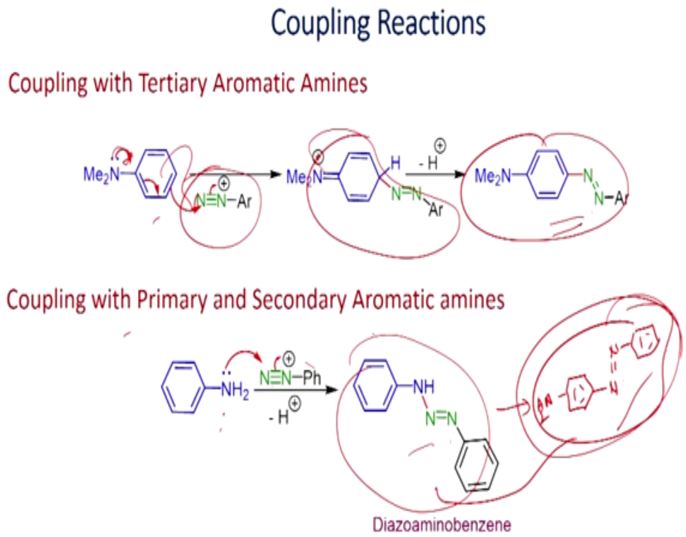

Coupling Reactions

Coupling with Tertiary Aromatic Amines

Coupling with Primary and Secondary Aromatic amines

Diazoaminobenzene

Here the C-N coupling of dimethylaniline with the aryldiazoniuim salt is presented. The electron rich dimethylaniline acts as the nucleophile and leads to addition to the diazonium ion to produce the diazo compound. In case of primary and secondary amines, the amino group adds to the diazonium ion. For example, aniline adds to the diazonium salt to give the diazoamino compound that further rearranges to give the diazo compound.

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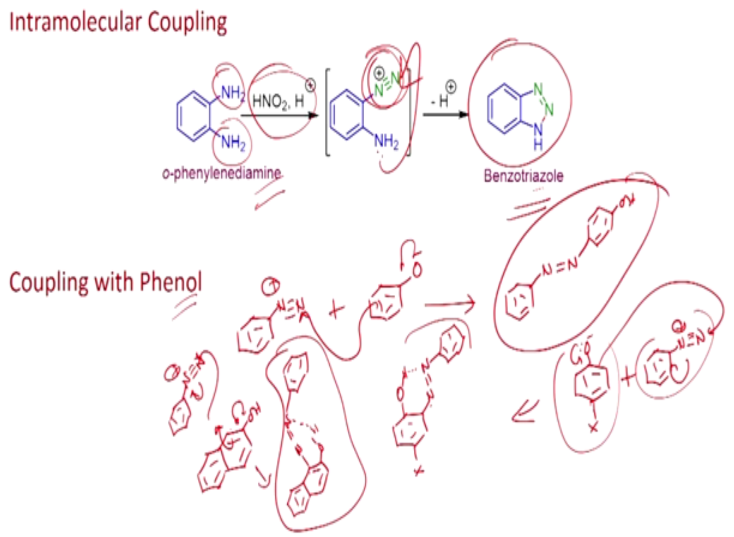
Intramolecular Coupling

Coupling with Phenol

In case of 1,2-diaminobenzene, one of the amino group undergoes diazotization, which reacts with the other amino group to give benzotrizole. Intramolecular addition of the amino group to the diazonium salt is more favoured compared to the intermolecular reaction. Likewise, phenol adds to the diazonium salt to produce a mixture of *ortho* as well as *para* compounds. Similarly, β-naphthol reacts with the diazonium salt to give the azo compound.

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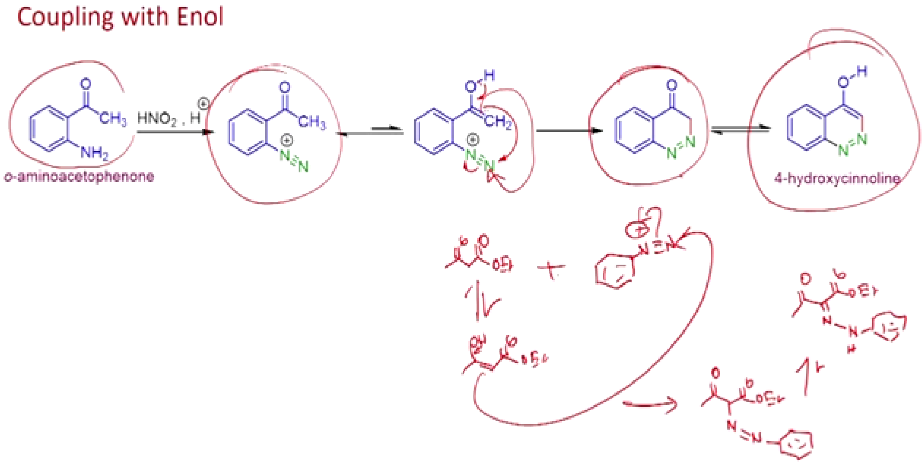
Coupling with Enol

In this reaction, diazotization of 2-aminoacetophenone produces the diazonium salt. Since the diazonium salt is under acidic conditions, acetyl group exits as enol, which undergoes intramolecular addition to the diazonium ion to produce hydroxycinnoline. Similarly, enol of ethyl acetoacetate can undergo addition reaction with the diazonium salt to produce the corresponding azo compound.

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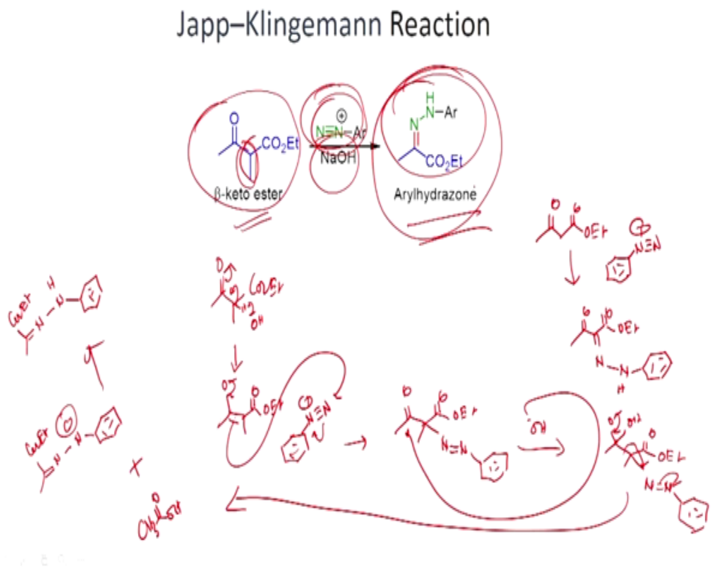

Japp–Klingemann Reaction

Now let us look at the reaction of other active methylene compounds with diazonium salts, which is known as Japp-Klingemann reaction. For example, ethyl acetoacetate with phenyldiazonium salt gives ethyl 3-oxo-2-(2-phenylhydrazineylidene)butanoate, whereas ethyl 2-methylacetoacetate with phenyldiazonium salt using base gives ethyl 2-(2-phenylhydrazineylidene)propanoate. Deprotonation followed by the addition of the enolate with the diazonium salt gives the phenyldiazenyl derivative. Addition reaction of the keto group with hydroxide ion followed by elimination of AcOH produces the respective arylhydrazone.

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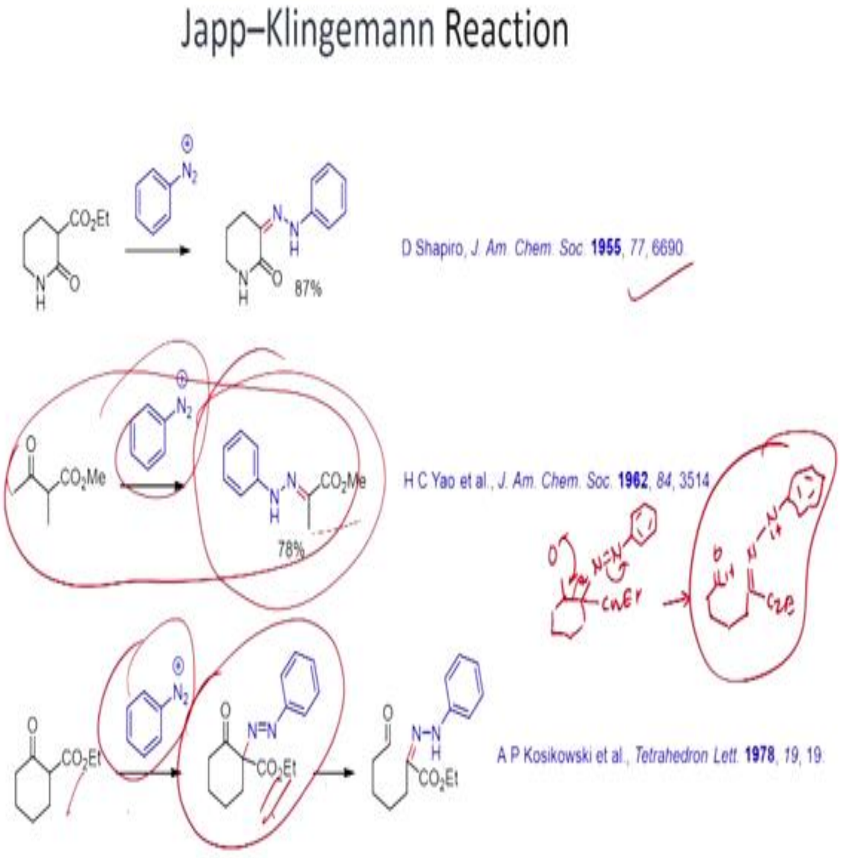

Japp–Klingemann Reaction

D Shapiro, *J. Am. Chem. Soc.* **1955**, *77*, 6690

H C Yao et al., *J. Am. Chem. Soc.* **1962**, *84*, 3514

A P Kosikowski et al., *Tetrahedron Lett.* **1978**, *19*, 19

Here the first example shows the addition of 3-carbethoxy-2-piperidone with the diazonium salt to produce 3-(2-phenylhydrazineylidene)piperidin-2-one. In this reaction, first the ester group hydrolyzes, which then adds to the diazonium salt to give the hydrazone. The next example involves the reaction of methyl 2-(methyl)acetoacetate with the phenyldiazonium salt to give hydrazone, which can be understood as we have seen for the reaction of ethyl 2-(methyl)acetoacetate. The third example deals with ethyl cyclohexanone carboxylate with the phenyldiazonium salt to produce the azo derivative. Reduction of the keto group gives the secondary alcohol that opens up to give the hydrazone derivative bearing aldehyde.

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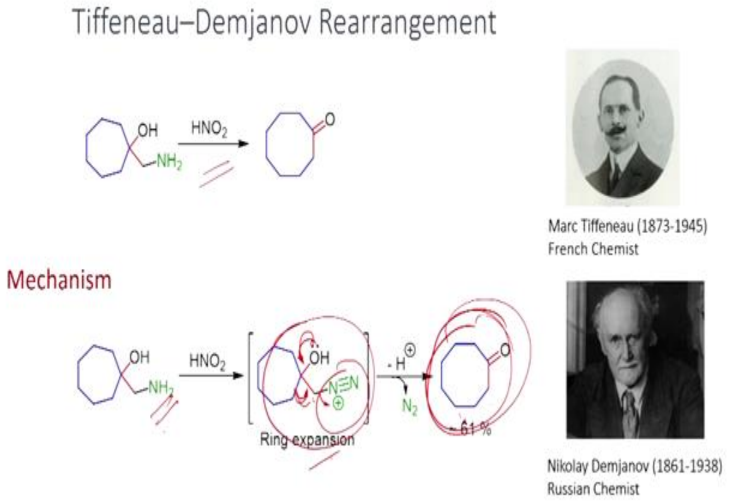
Tiffeneau–Demjanov Rearrangement

Mechanism

Marc Tiffeneau (1873-1945)
French Chemist

Nikolay Demjanov (1861-1938)
Russian Chemist

Here is an amino alcohol, which with nitrous acid gives the diazonium salt that undergoes an intramolecular rearrangement to form cyclooctanone. Alternatively, the diazonium salt may onvert to the carbocation that can undergo the rearrangement to give cyclooctanone, which is known as the Tiffeneau-Demjanov rearrangement.

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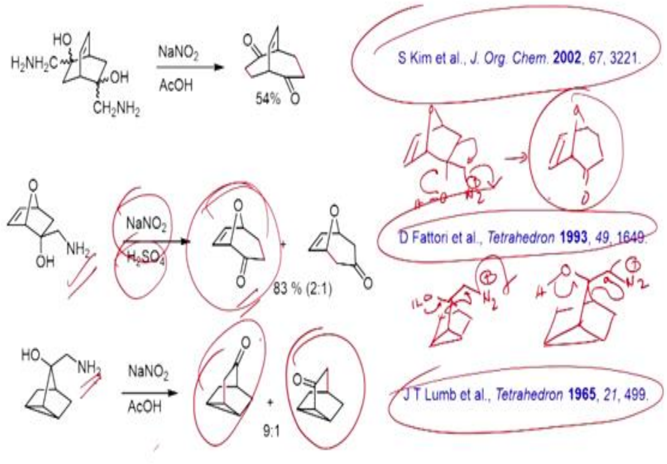

S Kim et al., *J. Org. Chem.* **2002**, *67*, 3221.

D Fattori et al., *Tetrahedron* **1993**, *49*, 1649.

J T Lumb et al., *Tetrahedron* **1965**, *21*, 499.

Here are some examples. Let us look at the first example where both the amine groups are converted to the diazonium salts, which rearrange to the diketone. The next example involves the formation of the diazonium salt followed by the rearrangement to give a mixture of bicyclic ketones. Similarly, the bicyclic amino alcohol can be converted to a mixture of the bicyclic ketones via the diazotization followed by rearrangement.

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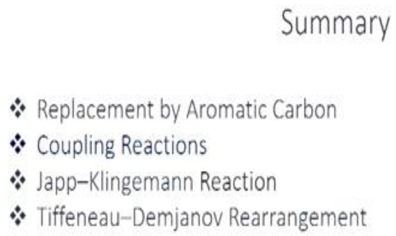

Summary

- ❖ Replacement by Aromatic Carbon
- ❖ Coupling Reactions
- ❖ Japp–Klingemann Reaction
- ❖ Tiffeneau–Demjanov Rearrangement

In summary, we have seen the transformation of the aryldiazonium salt to the aryl radical, which reacts with benzene to produce the biaryl compounds. Then, we have seen the transformation of the diazonium salt to the aryl carbocation, which reacts with aryl ring via the intramolecular electrophilic aromatic substitution. Following these reactions, we have seen the addition of the electron rich aromatic rings to the diazonium salts where the nitrogen is retained. Subsequently, we have discussed the addition of carbanion as well as enols to the diazonium salts to give hydrazones. Finally, we have seen the transformation of amino alcohol to ketone vis the formation of the diazonium salt and rearrangement. With this we conclude this lecture, thank you very much.