Organic Chemistry-4

Semester-4, CBCS

Course: CEMA CC-4-8-TH

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Chemistry of diazonium salts:

Synthesis of aromatic diazonium sats: 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:

aromatic nitro   aromatic primary amine   aromatic diazonium salt
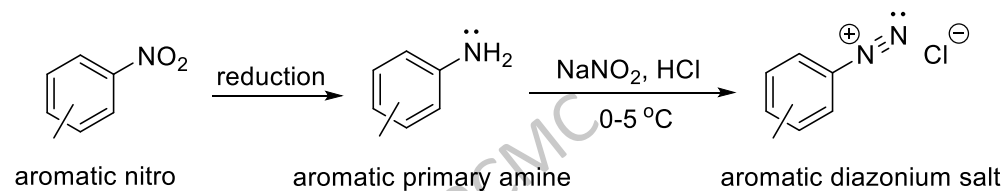
The formation of a diazonium compound by reaction of sodium nitrite, an inorganic acid (usually HCl) and a primary aromatic amine, in ice-cold solution, is known as diazotization.
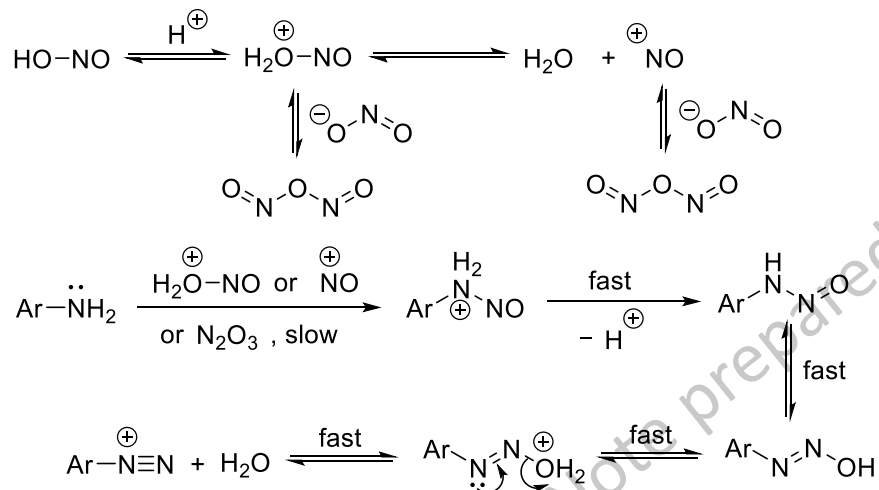
Several factors, including the acidity of the solution, affect the rate law of diazotization.

In weakly aqueous acid solutions (and in more strongly acid solutions), the RDS is nitrosation of the free amine.
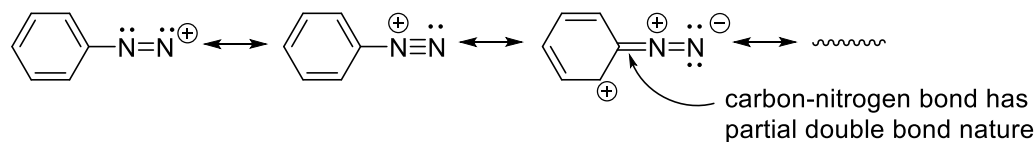
The effective nitrosation agent is probably not HNO_2 itself.

At relatively low acidity it is thought to be N_2O_3, while as the acidity is increased, a the 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 $-N_2^+$ with the aromatic ring:

carbon-nitrogen bond has partial double bond nature

The diazonium salts are very important synthetic intermediates, being the starting point in the preparation various aromatic compounds, oftentimes via loss of the nitrogen (dediazoniation). Recall the following chart:

Synthesis of *m*-bromotoluene:

Synthesis of *m*-nitrotoluene:

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.

Replacement of nitrogen: Aromatic Nucleophilic Substitution via Phenyl Cation from Diazonium Salts - the S_N1 like Mechanism:

Recall that phenyl chloride generally does not undergo nucleophilic substitution via the SN1-like mechanism as it involves formation of highly unstable phenyl cation and the reaction is thus associated with a large activation energy barrier. However, if there is an excellent leaving group attached with the phenyl nucleus, that may prompt the phenyl cation formation. A prime candidate for this sort of reaction is the diazonium salt as molecular nitrogen, a highly stable gaseous molecule, is one of the best leaving groups.

Thus we have several examples of nucleophilic substitution of diazonium ions proceeding via the S_N1 mechanism:
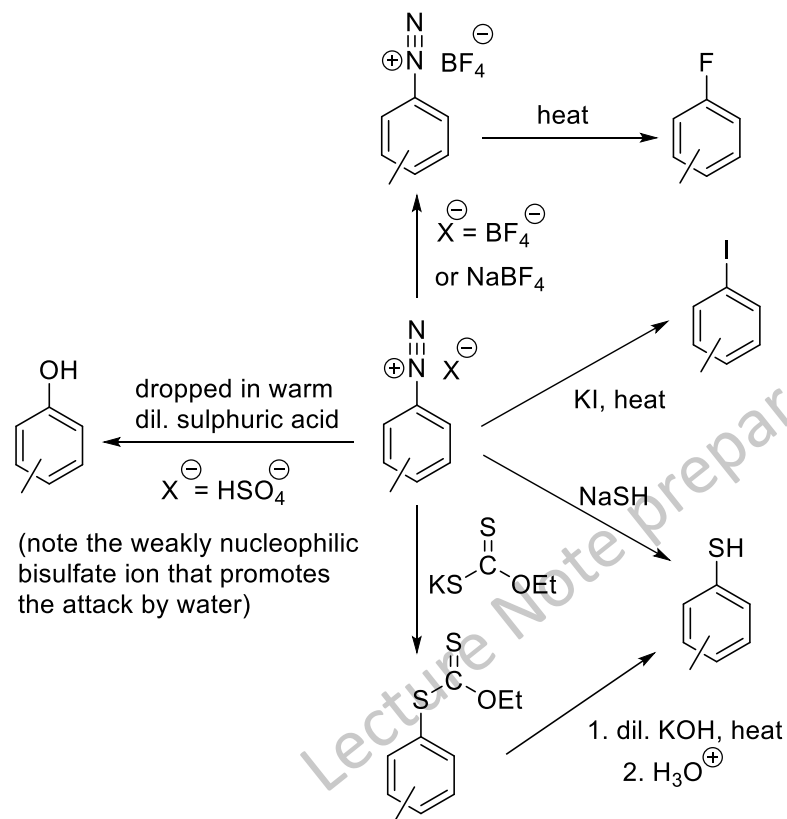
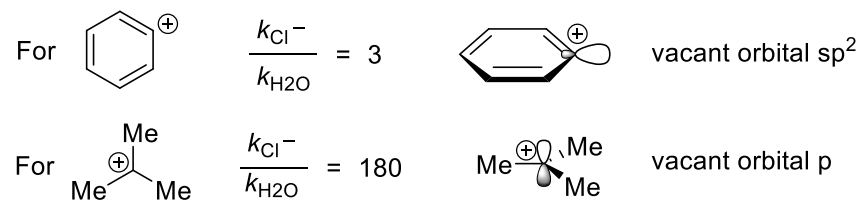All these reactions are believed to proceed through the following pathway:
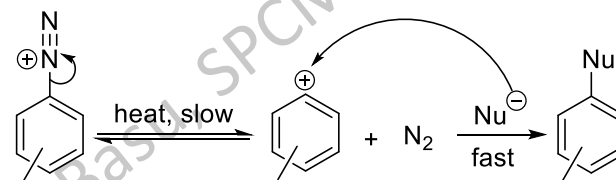
This mechanistic course is supported by the following facts:

a) These reactions are found to follow the rate law:
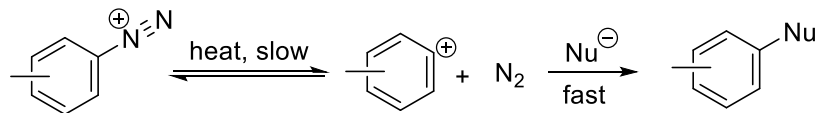
Rate of the reaction = k x [Ar-$N_2^{\oplus}$]

b) The rate of the reaction is independent on the concentration of nucleophile. This is analogous to an SN1 reaction. As in SN1 reactions, added nucleophiles like Cl⁻, CH_3OH etc. are found to affect the product composition but not the rate of the reaction.

c) The phenyl cation is very unstable and highly reactive. So it is expected to have poor selectivity towards nucleophiles. The low selectivity is demonstrated by the fact that the ratio of rate constants for its reaction with chloride ion and that with water is only 3, while the same is 180 for *t*-butyl carbocation, which is a much more stable species and thus more selective.


For (phenyl cation) $\dfrac{k_{Cl^-}}{k_{H2O}} = 3$ vacant orbital sp²

For (t-butyl cation) $\dfrac{k_{Cl^-}}{k_{H2O}} = 180$ vacant orbital p

(note the weakly nucleophilic bisulfate ion that promotes the attack by water)

Replacement of nitrogen: Aromatic Nucleophilic Substitution via Phenyl Cation from Diazonium Salts - the S_N1 like Mechanism:

These reactions are believed to proceed through the following pathway:


This mechanistic course is supported by the following facts (contd.):

Reversible first step indicates that molecular nitrogen is acting as a nucleophile!

d) The very high reactivity of phenyl carbocation is reflected in its ability to recombine with N_2, i.e. the decomposition of diazonium cation is reversible. This was demonstrated by observing the partial scrambling of ^{15}N in diazonium fluoroborate in the *recovered material,*

$[^{15}N = N]$

non-nucleophilic, non-basic counterion
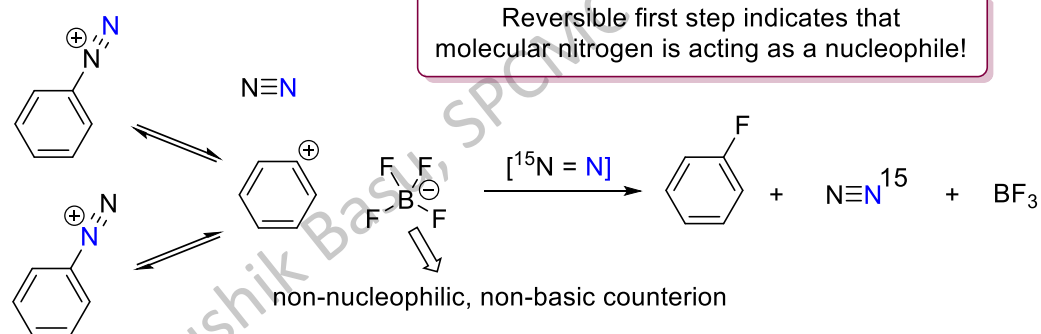
Synthesis of labelled dizonium salts:
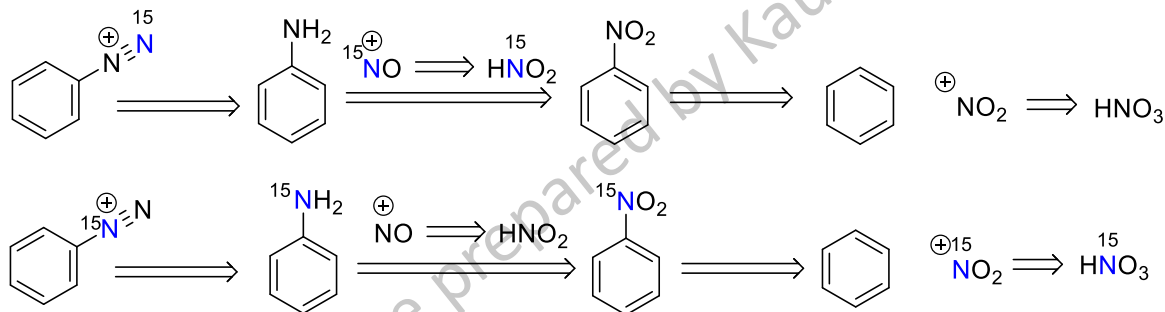


e) The SN1 reaction of substituted diazoniums show marked decrease in the rate *irrespective* of the electronic nature of the substituent, i.e. both 4-methoxy- and 4-nitrobenzenediazonium ions react slower than benzediazonium ion. This seems unusual as presence of ERG should facilitatethe cation formation and rate should increase.

Explanation of unusual behaviour:
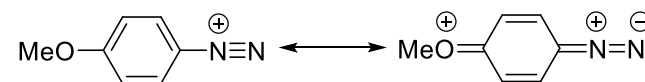
EWG like nitro destabilise the aryl cation:
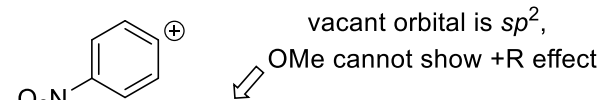
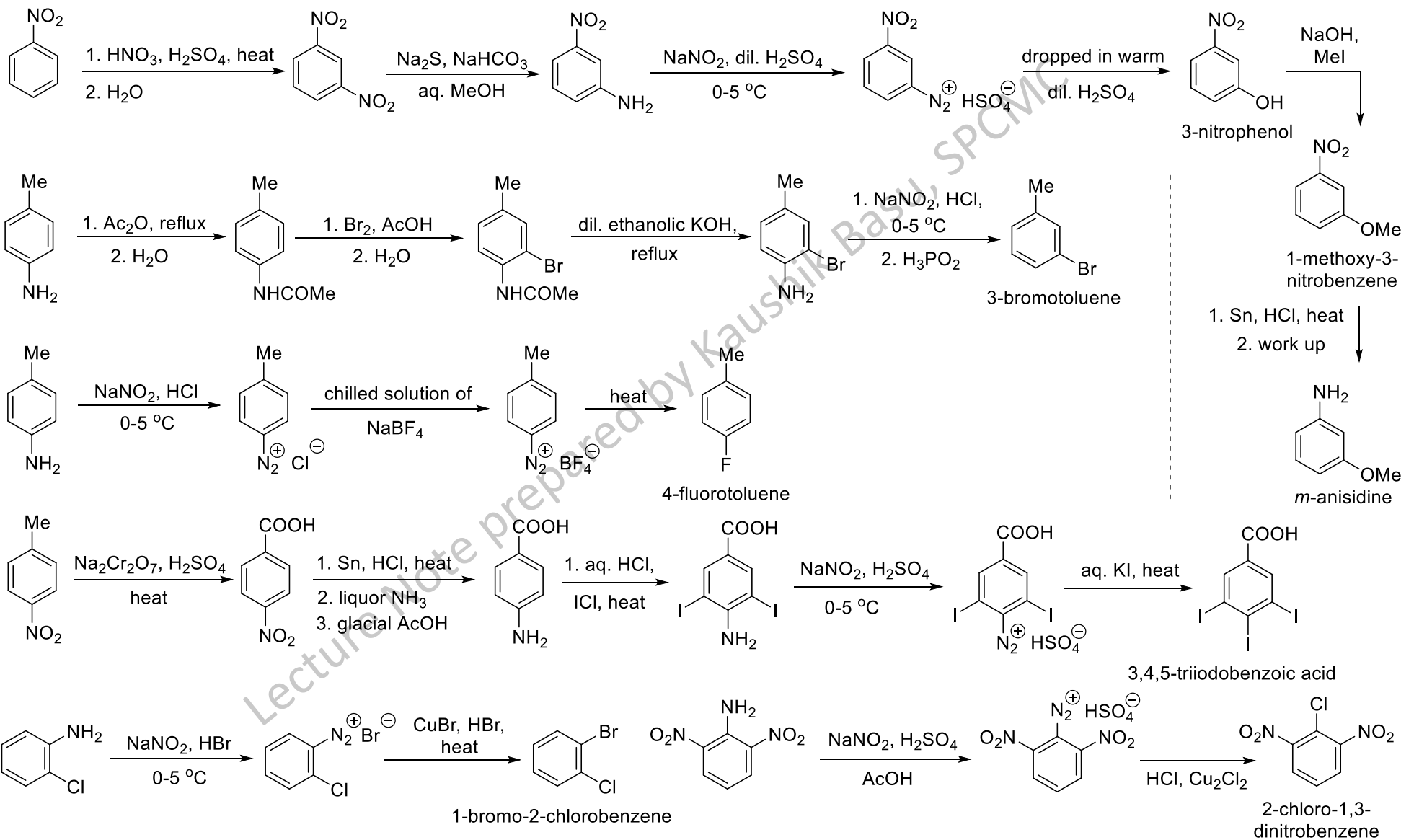ERG like OMe cannot stabilise the aryl cation:
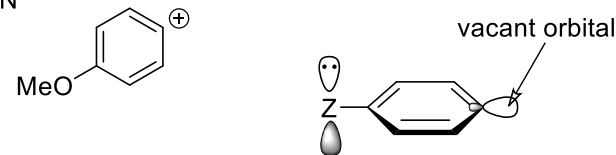
So OMe and NO_2 both display -I EW effect, so cation formation is difficult.

vacant orbital is sp^2, OMe cannot show +R effect

vacant orbital

In addition, for the methoxy derivative, the C-N bond in the diazonium salt has significant double bond nature, making it difficult to break.

Aromatic Nucleophilic Substitution via phenyl cation from
diazonium salts: The S_N1-like mechanism: Synthetic scope

3-nitrophenol

1-methoxy-3-nitrobenzene

3-bromotoluene

4-fluorotoluene

m-anisidine

3,4,5-triiodobenzoic acid
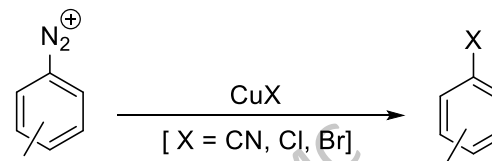
1-bromo-2-chlorobenzene
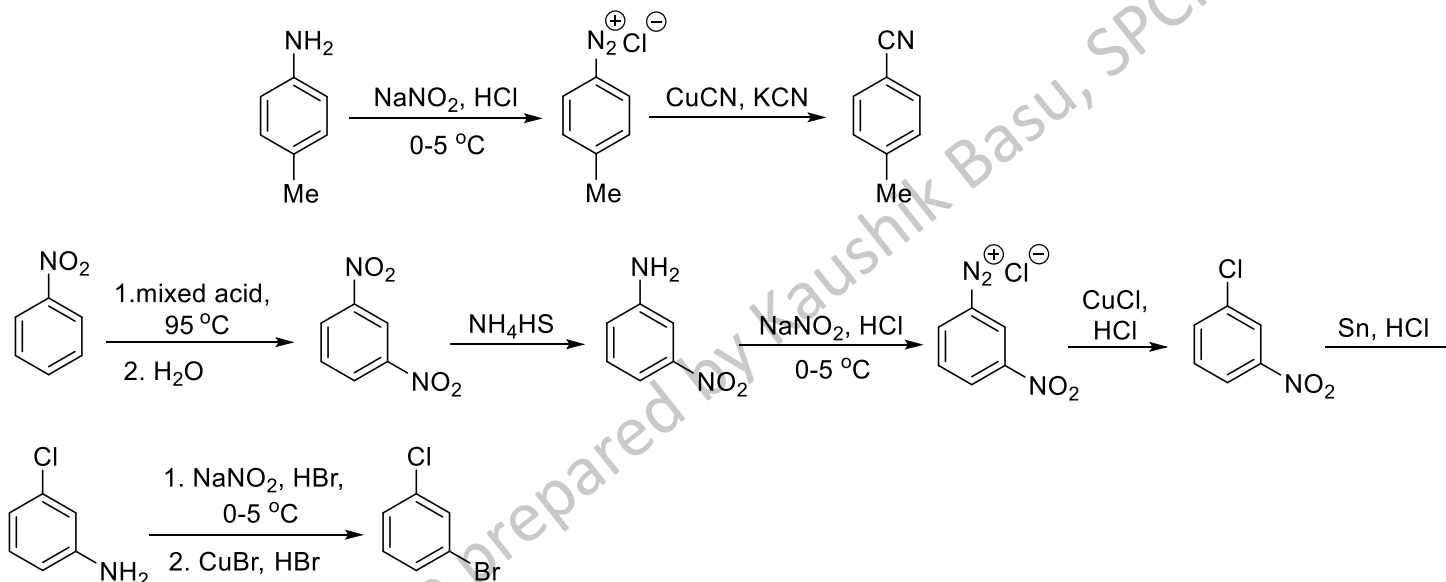
2-chloro-1,3-dinitrobenzene

Organonitrogen Chemistry

Reactions of diazonium ions: Replacement of nitrogen - aromatic nucleophilic substitution via aryl free radical formation:

Sandmeyer Reaction involves a copper(I)-catalyzed aromatic nucleophilic substitution of diazonium salt, where the negative part of the cuprous salt is introduced in the ring and nitrogen is replaced:
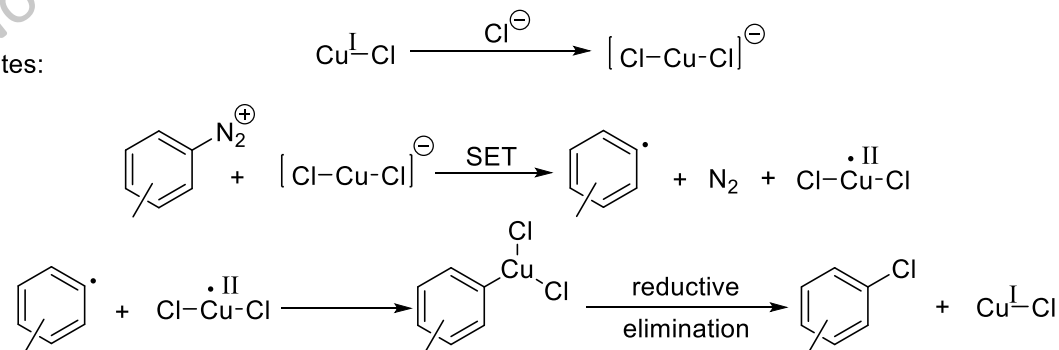

T. Sandmeyer
(1854-1922)

Let us consider the following examples:

All these reactions are believed to proceed via the formation of aryl free radical intermediates:

Reactions of diazonium ions: Replacement of nitrogen - aromatic nucleophilic substitution via aryl free radical formation:

The replacement of N_2 by H through a treatment of hypophophorous acid is substantially improved in the presence of Cu(I) catalyst.
The reaction is also a free radical process:
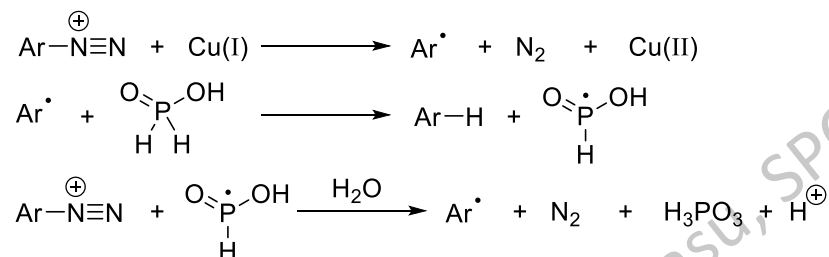
Such a reductive deamination can also be effected smoothly by ethanol in presence of copper powder or copper-bronze powder.
Thus, we have the classical synthesis of *m*-bromotoluene:


4'-methylacetanilide
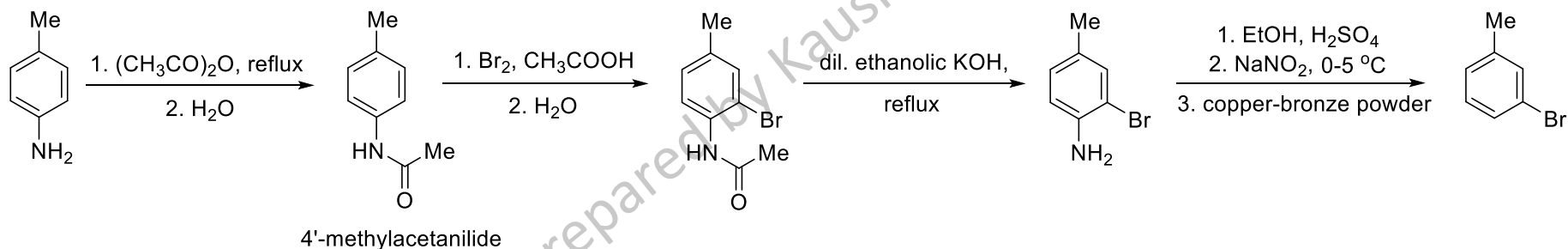
At the first sight it may seem rather strange to replace a reactive functional group such as an amine or a diazo with a hydrogen atom that offers no selectivity over the other C-H bonds to any attacking reagents, but this method of synthesis does offer a way of producing aromatics with *unusual substituion pattern*. For example, m-bromotoluene cannot be synthesised by either brominating toluene (Me being *o-/p*-orienting) or by Firiedel-crafts reaction on bromobenzene (Br also being *o-/p*-orienting). Another example is synthesis of 2,4,6-tribromobenzoic acid:
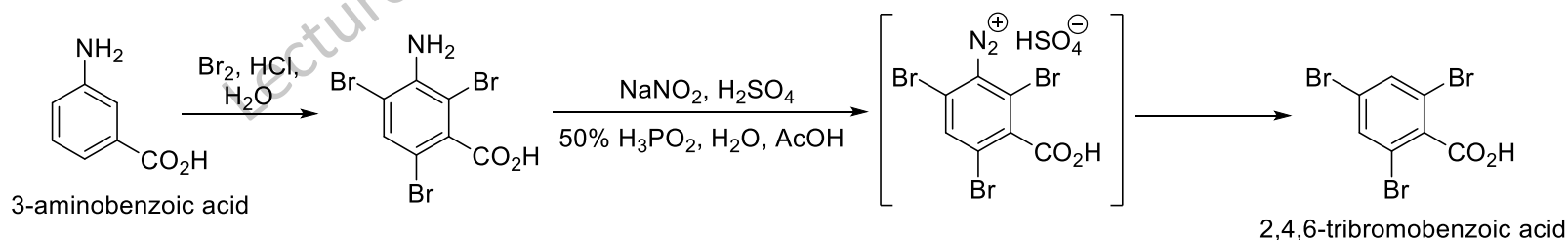
3-aminobenzoic acid

2,4,6-tribromobenzoic acid

Reactions of diazonium ions: Replacement of nitrogen - aromatic nucleophilic substitution via aryl free radical formation:

In the replacement reactions discussed above, a significant amount of biphenyl derivatives is frequently found to be present in the reaction product.
This gives a clue that by tinkering the reaction conditions we might manage to synthesise biphenyl derivatives using the coupling methodology.
This has been achieved by adding the aqueous diazonium salt solution to a liquid aromatic compound and then basifying the vigorously stirred two-phase system by adding sodium hydroxide or sodium acetate solution. Thus;

yield ~21% (low)

yield ~35% (low)
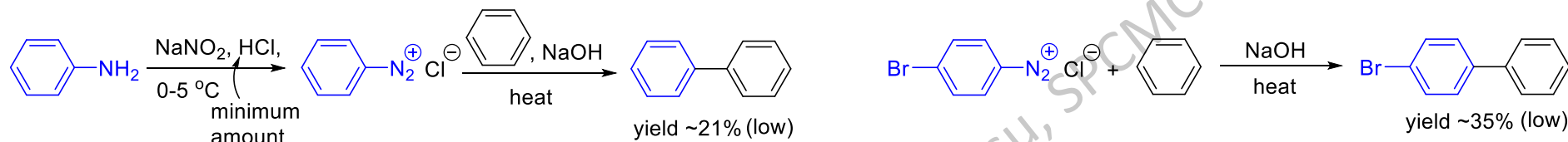
This is known as Gomberg-Bachmann reaction - a base-promoted radical coupling between an aryl diazonium salt and an arene to biphenyl derivatives.
This reaction is an example of free radical substitution on aromatic nucleus:

azenol - withdrawn in liquid hydrocarbon medium

N_2 + ·OH

·OH H_2O
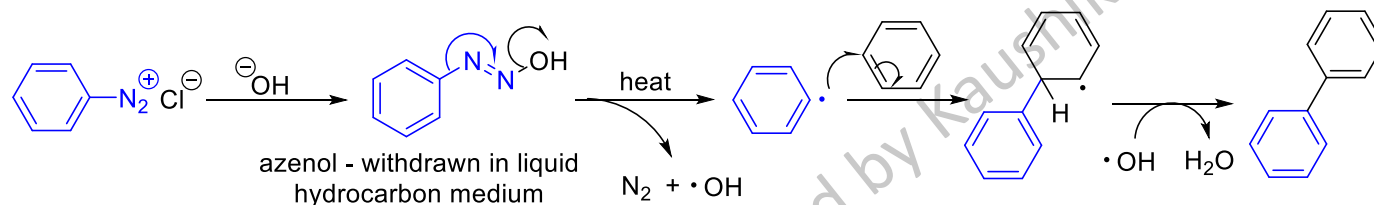
M. Gomberg
(1866-1947)

W. E. Bachmann
(1901-1951)

In our study so far we have considered the free radical substitution on benzene - a completely symmetrical substrate.
With a substituted benzene, there is a possibility of formation of a mixture of products, o-, m- and p-. However, irrespective of the nature of the substituents, we get mainly the o- and p- products. Let us consider the following examples:
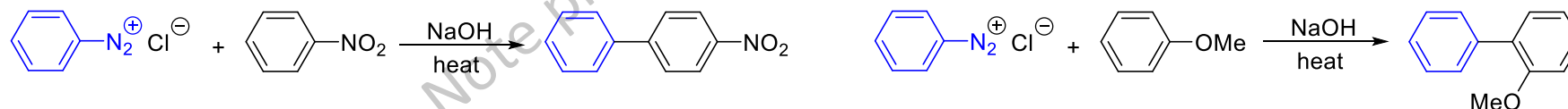
Thus to obtain substituted biphenyl we have to use a substituted aromatic primary amine and symmetrical aromatic substrate. For example, say we are in need of 4-methylbiphenyl. So we have to consider the following retrosynthetic analysis:
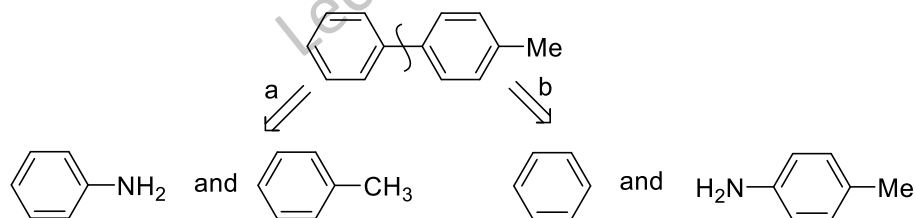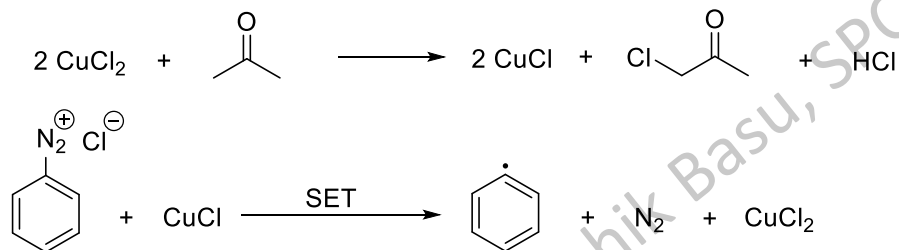

The second set of synthons (route b) is the better choice as that avoids the obvious regioselectivity problem associated with the first (route a).

Reactions of diazonium ions: Replacement of nitrogen - aromatic nucleophilic substitution *via* aryl free radical formation:

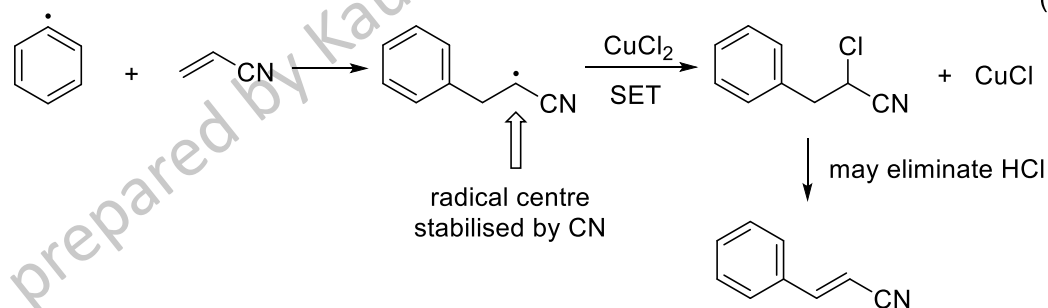The other carbon-carbon bond forming reaction using diazonium salt is known as Meerwein arylation.

It is the reaction between diazonium salts and activated ethylenic double bond to give arylated products. The reaction is carried out in acetone solution in the presence of a cupric salt, e.g. benzene diazonium chloride adds to vinyl cyanide with the elimination of nitrogen.

The mechanism is uncertain, it is generally accepted that cupric chloride is readily reduced by acetone to yield cuprous chloride and it is this Cu(I) species that is responsible to form phenyl radical from benzene diazonium chloride in the following way:
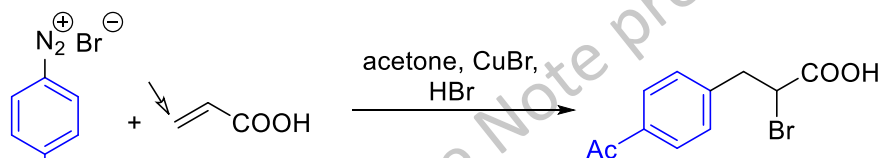
$$2 \ CuCl_2 \ + \ \text{(acetone)} \ \longrightarrow \ 2 \ CuCl \ + \ \text{(ClCH}_2\text{COCH}_3) \ + \ HCl$$

$$\text{PhN}_2^{\oplus} \ Cl^{\ominus} \ + \ CuCl \ \xrightarrow{SET} \ \text{Ph}^{\bullet} \ + \ N_2 \ + \ CuCl_2$$
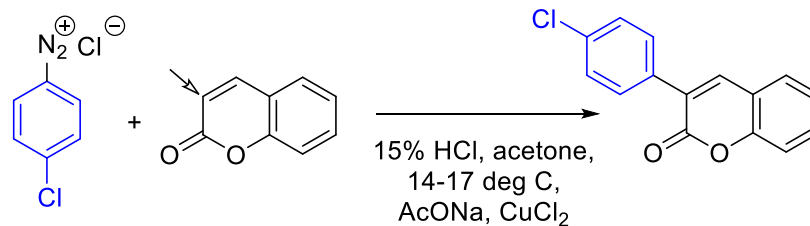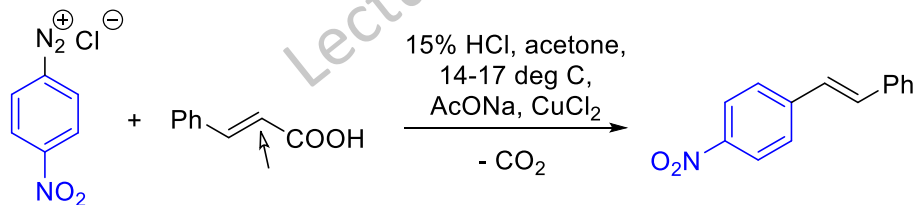
H. Meerwein
(1879-1965)

This phenyl radical undergoes regioselective addition via the attack at the α-carbon of the activated ethylenic compound to yield the more stable free radical and the reaction goes to completion with the transfer of chlorine radical from cupric chloride to yield cuprous chloride again:

$$\text{Ph}^{\bullet} \ + \ \text{(CH}_2=\text{CHCN)} \ \longrightarrow \ \text{Ph-CH}_2\text{-}\overset{\bullet}{\text{C}}\text{HCN} \ \xrightarrow[\text{SET}]{CuCl_2} \ \text{Ph-CH}_2\text{-CHClCN} \ + \ CuCl$$

radical centre stabilised by CN

may eliminate HCl

$$\text{Ph-CH=CH-CN}$$

Examples:

acetone, CuBr, HBr

→ coupling site

15% HCl, acetone, 14-17 deg C, AcONa, CuCl₂

- CO₂

15% HCl, acetone, 14-17 deg C, AcONa, CuCl₂

Reactions of diazonium ions: Japp-Klingemann Reaction:

Recall from our precious discussions on diazo-coupling reactions that diazonium salts are weak electrophiles that are attacked only by aromatic rings activated by electron-donor groups. Thus coupling with phenols and *N,N*-dimethylaniline is possible under respective optimum pH, but toluene does not undergo such a coupling. Enolic compounds, on the other hand are nucleophilic enough to react with diazonium electrophiles. In this connection the structural similarity between phenol and enol must be revisited:
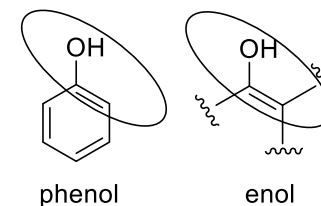
Recall, however, that it is the phenoxide ion, and not phenol that undergoes successful coupling with diazonium salts, so that the optimum pH for that coupling reaction is slightly alkaline. You might want to recall why that is so.

Enols, in the similar token, can couple with a diazonium electrophile in alkaline medium. If we can supply a precursor that can exist in the enol form in a significant amount (enter β-dicarbonyls!), we can achieve a coupling reaction. When the β-dicabonyl compound carries a substituent at the activated methylene carbon, the product of that coupling is an arylhydrzone, this reaction is known as Japp-Klingemann reaction.
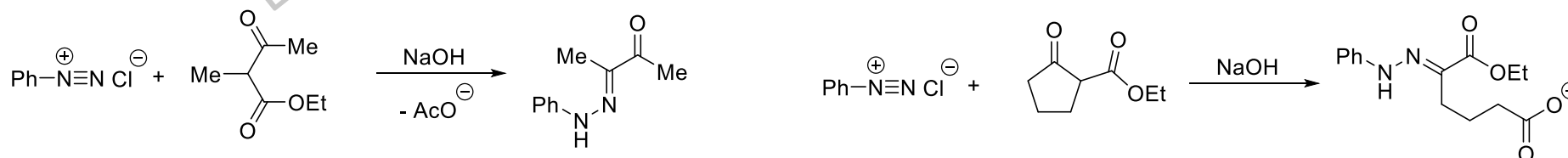

substituted
aceoacetic acid
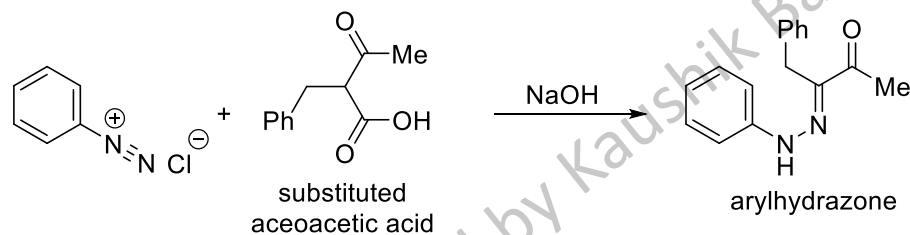
arylhydrazone

F. R. Japp
(1848-1925)

Clearly, here we have a coupling and a decarboxylation. A plausible mechanism for this reaction is outlined below:

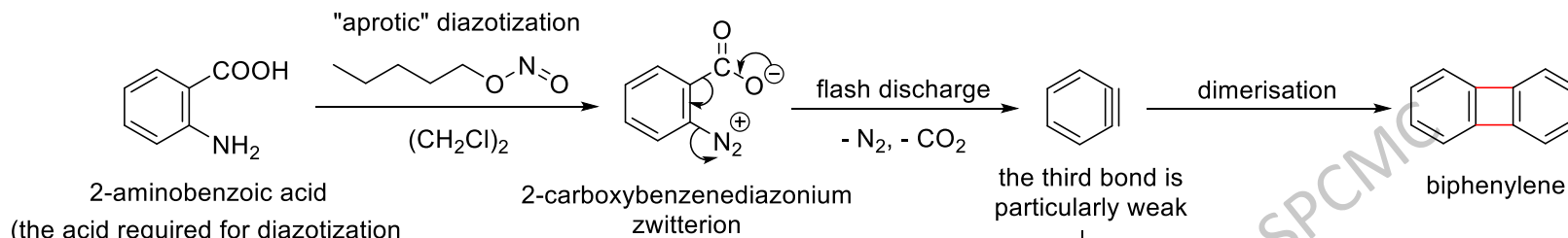more reactive anionic site of the
dianion makes the nucleophilic attack
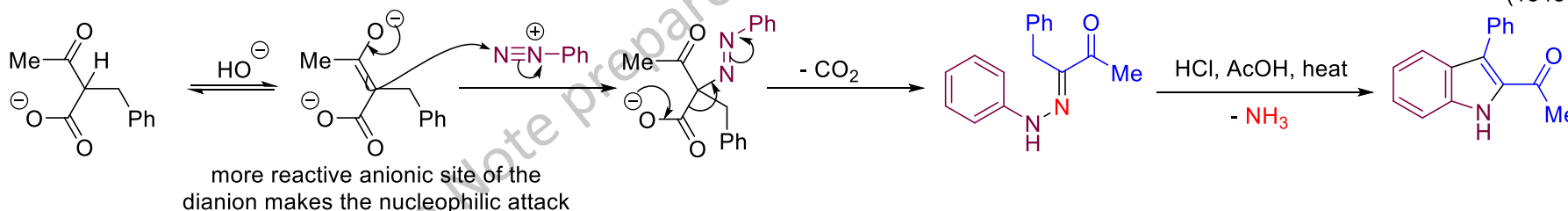
This arylhydrazone is an important precursor for
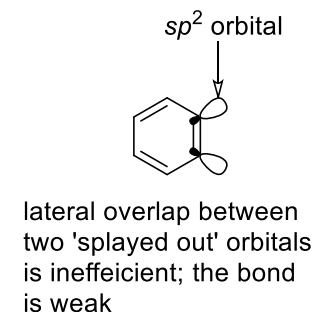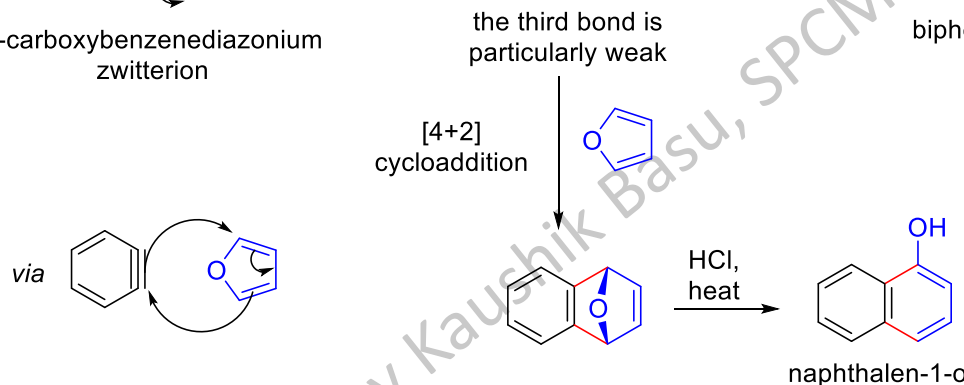indole nucleus synthesis (Fischer Indole synthesis).

In light of what we have discussed about the Japp-Klingemann reaction, explore the following two reactions and come up with a plausible mechanism for each:

Reactions of diazonium ions: Formation of benzyne by dediazoniation

2-aminobenzoic acid
(the acid required for diazotization
is present within the substarte)

2-carboxybenzenediazonium
zwitterion

the third bond is
particularly weak

biphenylene

sp^2 orbital

lateral overlap between
two 'splayed out' orbitals
is ineffeicient; the bond
is weak

The third bond of benzyne is very weak
and thus it is an excellent dienophile.

via

[4+2]
cycloaddition

HCl,
heat

naphthalen-1-ol

Hydrolysis of the Diels-Alder adduct
derived from furan and benzyne:

1-naphthol
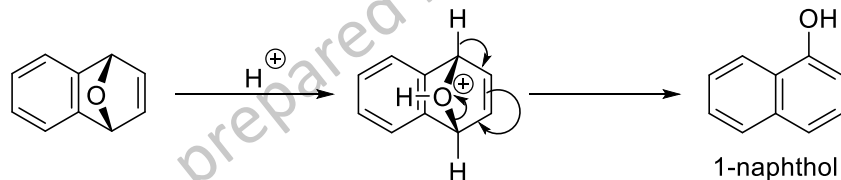
In rare cases, the H at *ortho* position of a diazonium group may act as an electrofuge and give rise to aryne intermediate in dediazoniation reaction:

3-nitroanisole
cine-substitution product,
can only form if a benzyne int. is involved

via

negative charge stabilised *o*- to NO_2,
as -NO_2 is an EWG;
attack of methoxide is regioselective