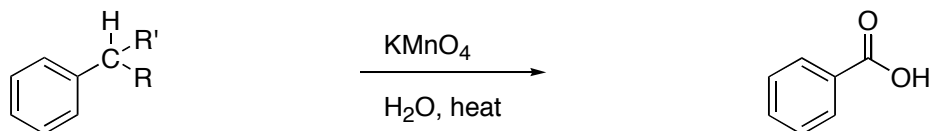
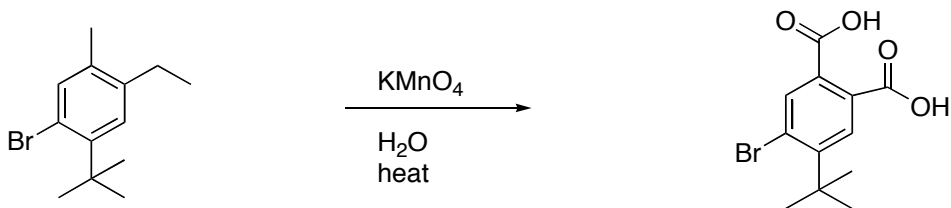


Review from last class**Alkyl Side Chain Oxidation Reaction**

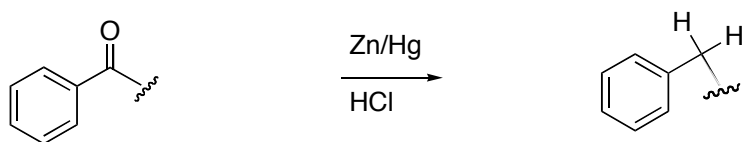
If the carbon directly attached to the aromatic ring has ≥ 1 hydrogen attached to it, it can be oxidized to the carboxylic acid with hot aqueous potassium permanganate (KMnO_4) as shown below.



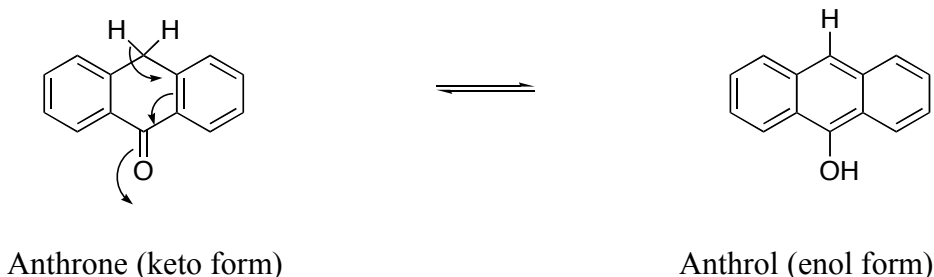
In the below example 1-bromo-2-*tert*-butyl-4-ethyl-5-methylbenzene is oxidized using potassium permanganate. Note that only the ethyl and methyl side chains have a hydrogen on the adjacent carbon to the aromatic ring and therefore are the only ones that are oxidized.

**Clemmensen Side Chain Reduction Reaction**

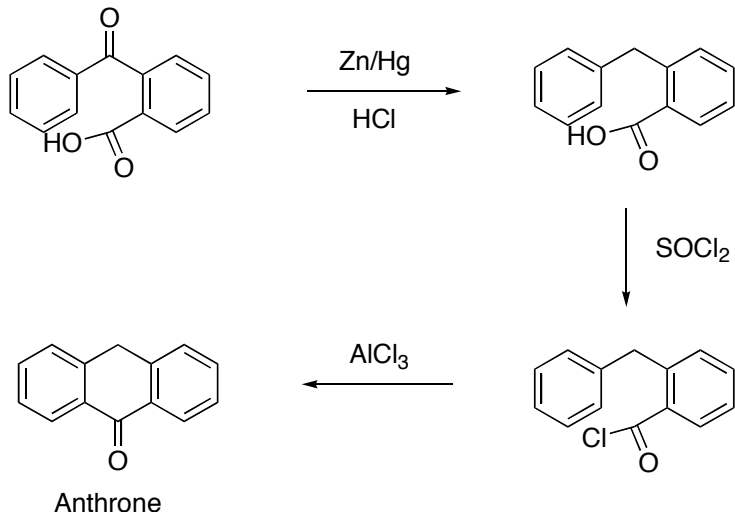
The Clemmensen reduction is an example of a reduction of a conjugated ketone to the alkyl chain using a zinc/mercury and an acid as shown below.



This reaction could in principle be used to reduce anthraquinone to anthrone. Anthrone undergoes a keto to enol isomerization to anthrol, which is a fluorescent dye that absorbs UV light and emits in the visible (remember the demo in class).

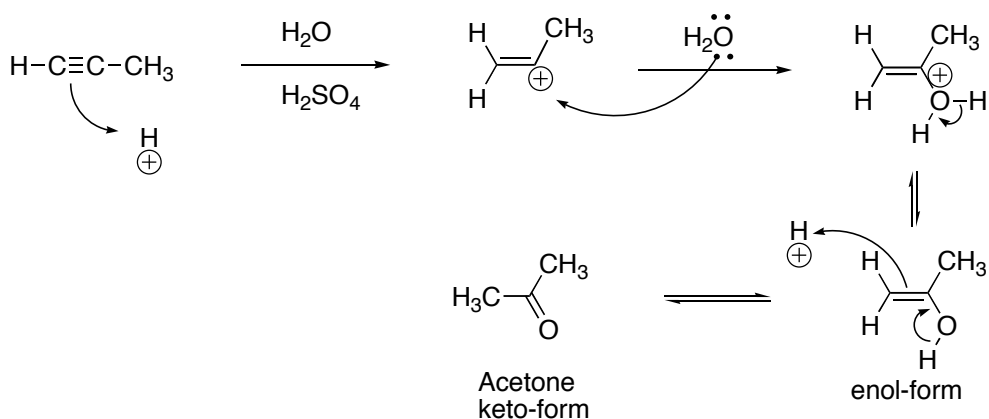


Anthrone can be made by following route:



Anthrone and Anthrol are tautomers (interconverting structural isomers).

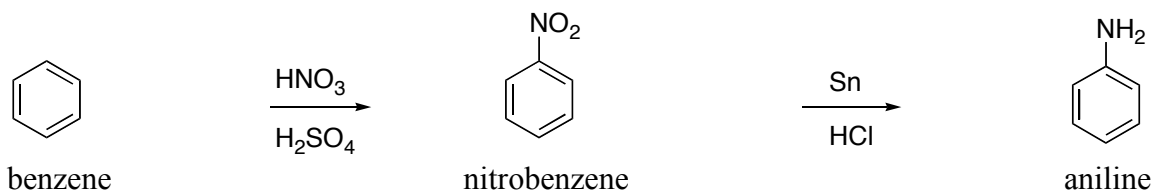
Review tautomerization from CHEM 261



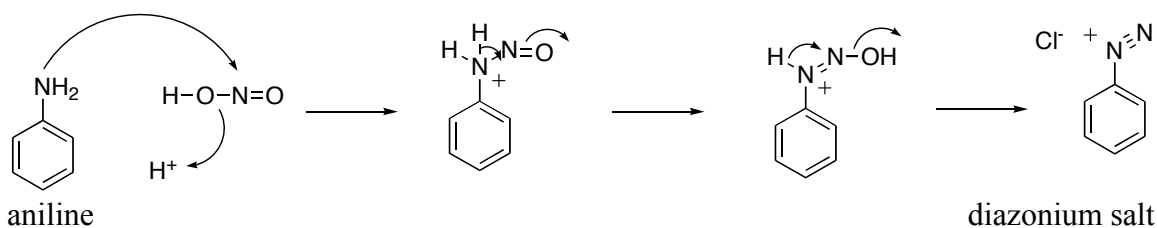
Reduction of Nitrobenzenes to Anilines and Nitrosation

Example:

For example, aniline can be formed from benzene by nitration followed by reduction of the nitro group. The first step involves the nitration of benzene to form nitrobenzene. The next step uses tin under acidic conditions to reduce the nitro group to an amine and form aniline.

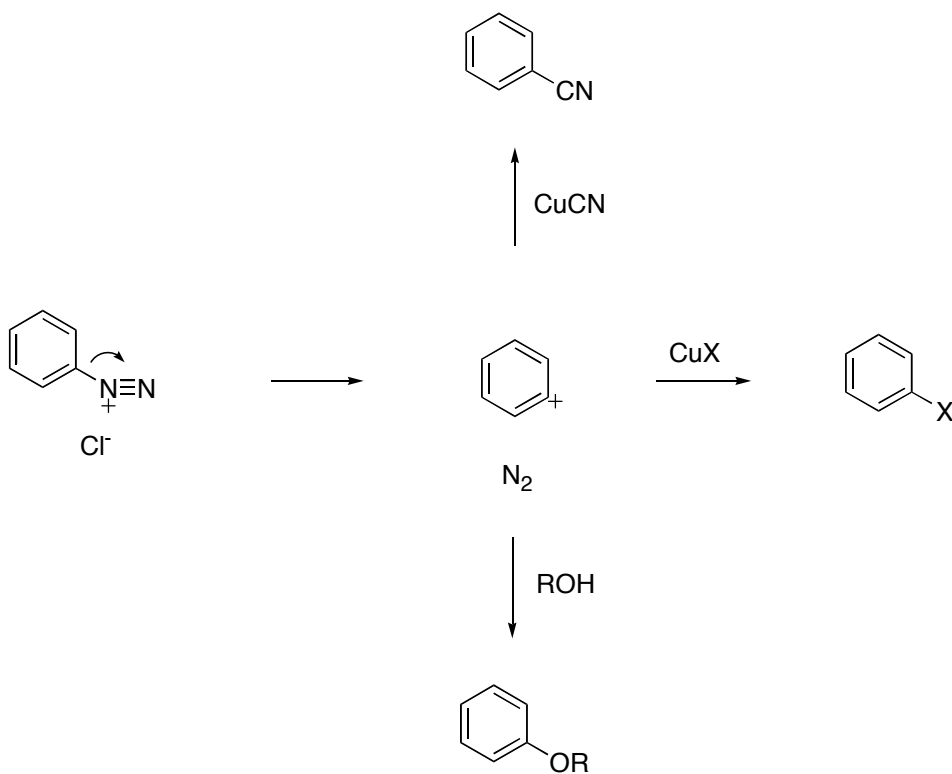


The aniline can then be reacted with nitrous acid to give the explosive diazonium salt. Nitrous acid is formed from the addition of sodium nitrite (NaNO_2) and hydrochloric acid (HCl). In a very abbreviated mechanism, first step of the mechanism is attack of the aniline on nitrous acid to form the new nitrogen-nitrogen bond. This is followed by deprotonation and reprotonation to make the nitrogen-nitrogen double bond. The loss of water then forms the diazonium species. The chloride counter ion is from the initial formation of nitrous acid with HCl .

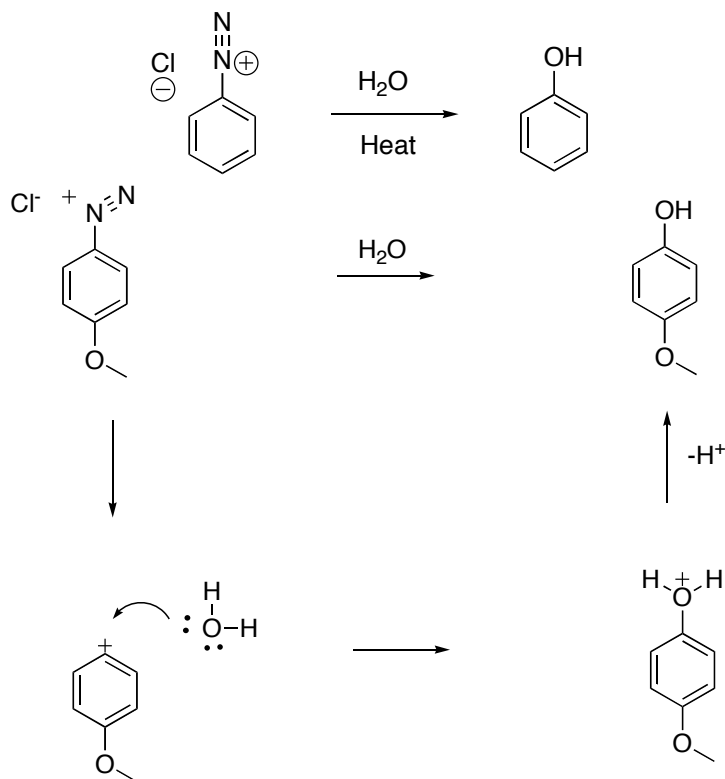


Replacement of N_2 of Diazonium salts

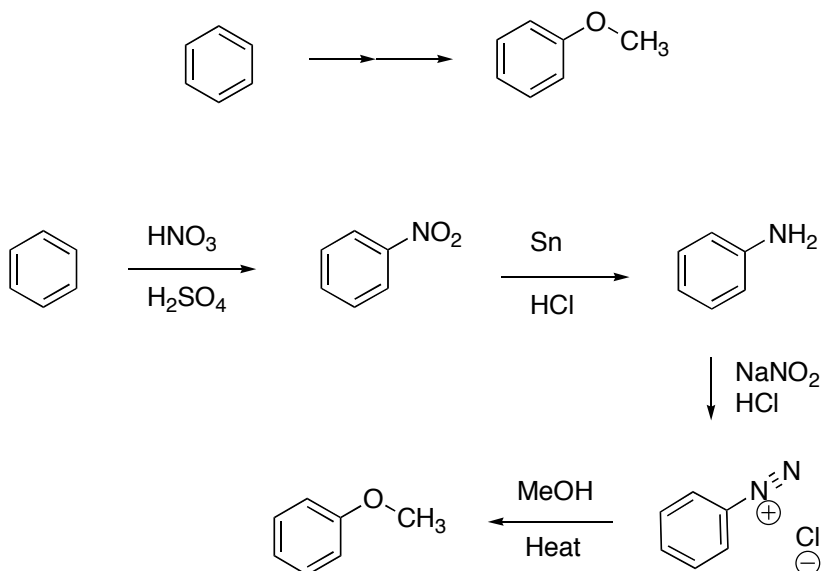
Diazonium salts are extremely useful in organic synthesis, because the diazonium group (N_2) can be replaced by nucleophiles. The diazonium salt behaves like a phenyl cation and can undergo a variety of nucleophilic aromatic substitutions such as the addition of copper cyanide (CuCN) to give an aromatic cyanide, addition of CuX (where X is a halogen) to give a halogenated benzene, or addition of alcohols to give ethers.



Example: The diazonium salt can also be replaced by a hydroxyl group to form phenols. This reaction is especially useful because few other general methods exist for introducing an -OH group onto an aromatic ring. For example, treatment of the *p*-methoxy diazonium salt with a hot water yields *p*-methoxyphenol. The mechanism of this reaction can be visualized as formation of the phenyl cation by loss of nitrogen gas (N_2). The lone pair of electrons on the water attacks the carbocation followed by deprotonation to yield *p*-methoxyphenol.

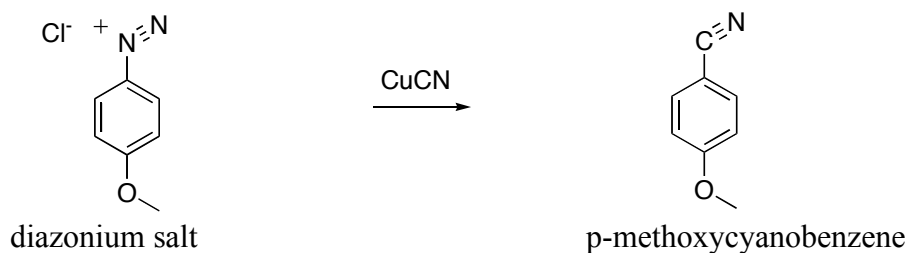


Example: make anisole (methoxybenzene)

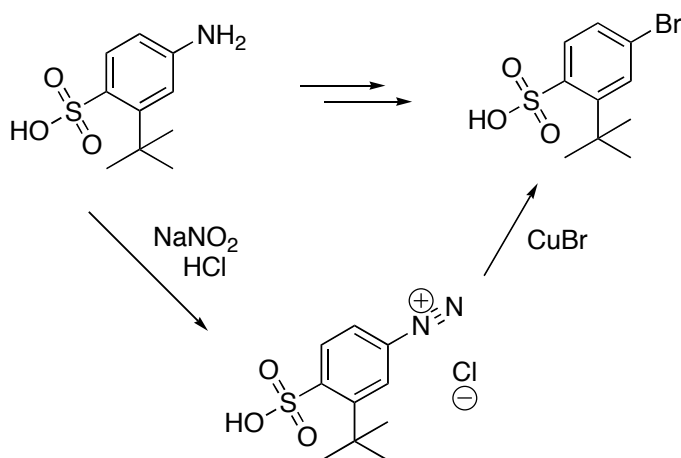


Example:

Treatment of the diazonium salt with cuprous cyanide (CuCN) yields the aryl nitrile, ArCN . Nitrogen gas is the leaving group. This reaction is useful because it allows replacement of the nitrogen substituent with by a carbon substituent. For example, treatment of the p-methoxy diazonium salt with CuCN forms p-methoxycyanobenzene (4-methoxybenzonitrile, 4-cyanoanisole).

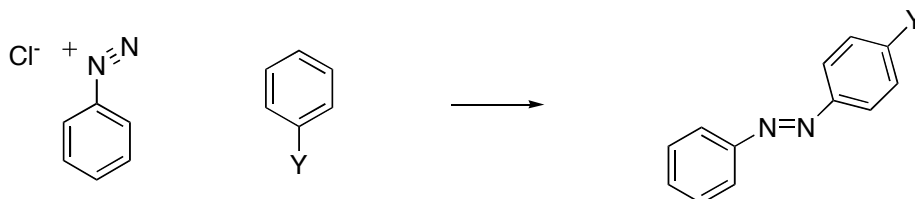


Example:

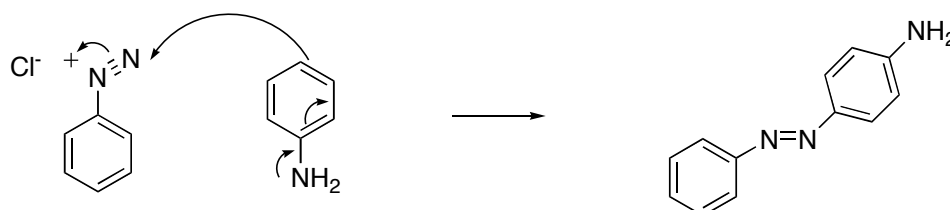


Diazonium Coupling

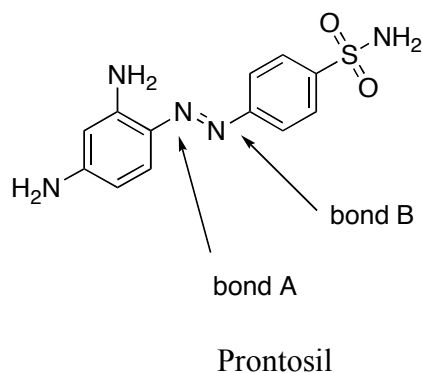
Diazonium salts undergo a coupling reaction with activated aromatic rings to yield very highly colored azo compounds with the general formula Ar-N=N-Ar as shown below. These azo coupled products are widely used as dyes because their extended conjugated pi (π) electron systems cause them to absorb in the visible region of the electromagnetic spectrum. As shown below, Y must be OH, NH_2 or NHR or the reaction will generally not work.



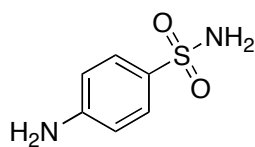
Diazonium couplings are typically electrophilic aromatic substitutions in which the positively charged diazonium ion is the electrophile that reacts with the electron rich ring of a phenol or arylamine. Diazonium coupling often takes place at the *para* position, although *ortho* attack can take place if the *para* position is blocked. An example is the formation of an azo aniline derivative. Attack of the aniline from *para* position on the diazonium salt, followed by loss of a proton forms the product.



Aromatic azo compounds are valuable intermediates in the preparation of dyes and pharmaceuticals. For example, the sulfa drugs, such as Prontosil, were the first useful antibiotics known and were found to have a broad range spectrum. Prontosil is prepared commercially by a process that uses a diazonium ion. The diazonium coupling requires the use of a diazonium salt and a highly activated aromatic compound. For this reason, bond A (not bond B) is the bond formed in the diazonium coupling reaction. The aniline is highly reactive and would make a good coupling partner to the diazonium salt.



Prontosil is an effective antibacterial agent because the human body readily converts it to sulfanilamide, which is the active drug. Sulfanilamide resembles the structure of para-aminobenzoic acid, which bacteria use to make folic acid. The bacteria mistakenly tries to use sulfanilamide (an enzyme inhibitor) and eventually dies.



sulfanilamide