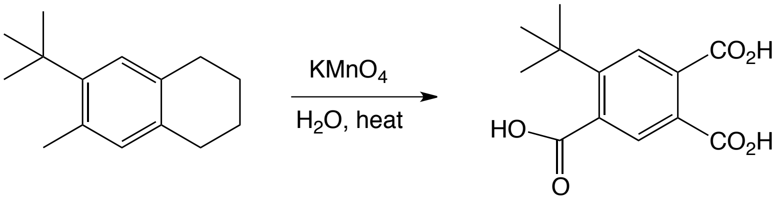
Chem 263 **Oct. 6, 2016**

Reaction of Side Chains of Aromatic Compounds:

1) Alkyl Side Chain Oxidation
2) Clemmensen Reduction
3) Nitro Reduction and Amino Diazotization

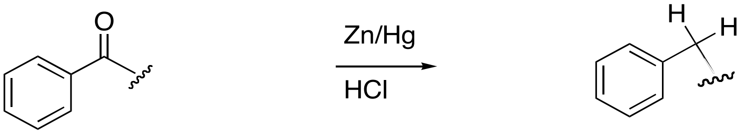
Alkyl Side Chain Oxidation Reaction (discussed last time)

Example:

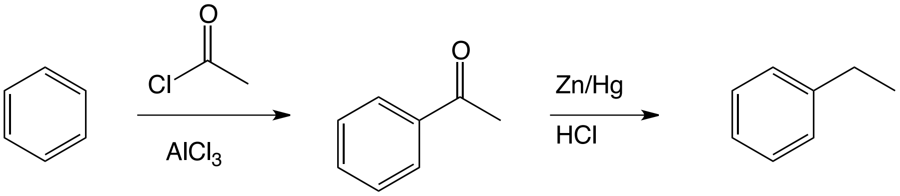


Clemmensen Side Chain Reduction Reaction

The Clemmensen reduction is an example of a reduction of a conjugated ketone to the alkyl chain using a zinc/mercury amalgam and an acid:

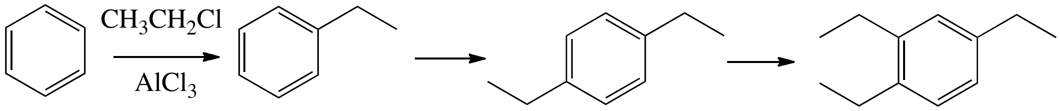


Sn (tin) can also be used instead of Zn/Hg amalgam



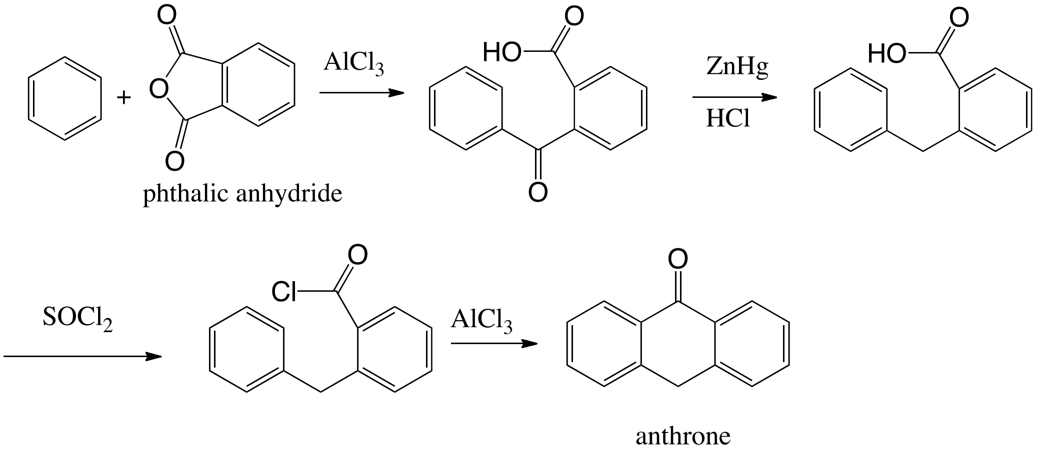
acetophenone

It may seem simpler to make ethyl benzene with ethyl chloride, BUT….

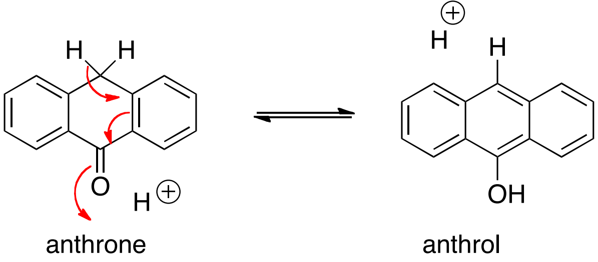


Ethyl benzene is more reactive than benzene (inductive effect): reacts faster
Acetophenone is less reactive than benzene (resonance effect): reacts slower

More examples:



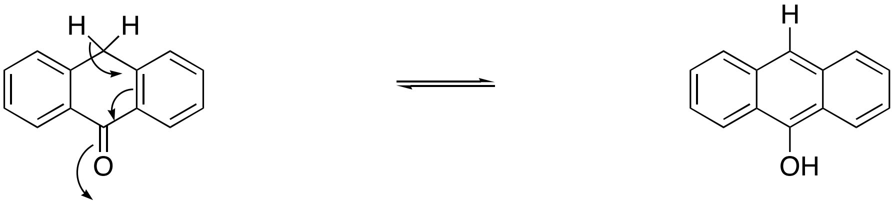
Keto-enol tautomerism:



Fluorescent

Keto $\rightleftharpoons$ Enol

Anthrone undergoes a keto to enol isomerization to anthrol, which is a fluorescent dye that absorbs UV light and emits in the visible.

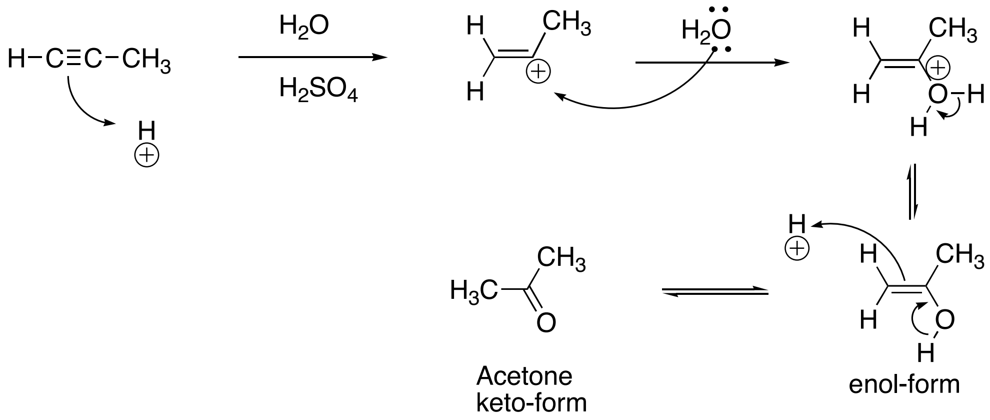


Anthrone (keto form)

Anthrol (enol form)

Anthrone and anthrol are **tautomers** (rapidly interconverting structural isomers).

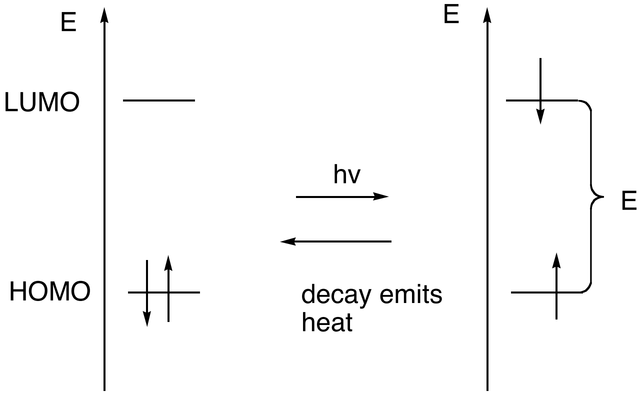
Review tautomerization from CHEM 261



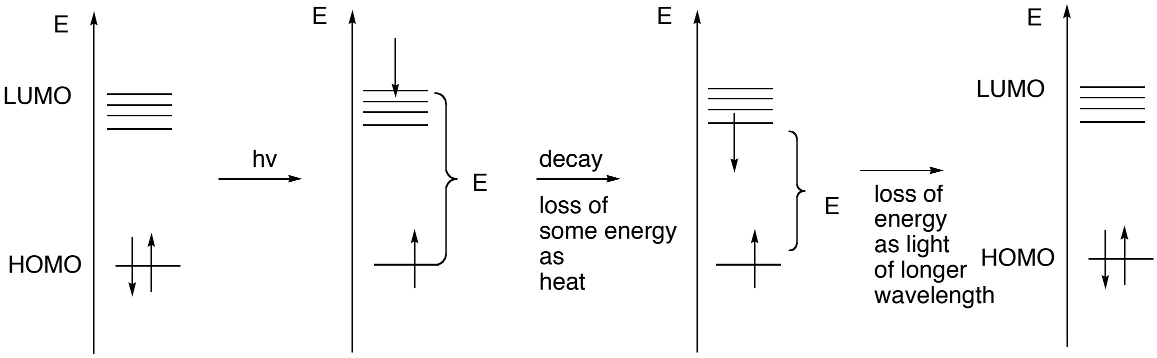
Fluorescence digression

Fluorescence is the emission of electromagnetic energy from an excited state (obtained by irradiation, normally in the ultraviolet) as light (usually visible wavelengths).

Commonly, electromagnetic radiation (light) is absorbed if it matches the difference between the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO). The promoted electron in the LUMO then decays back to the HOMO with loss of the energy as heat (molecular motion, collision with other molecules).



However, if a conjugated molecule absorbs a high-energy photon into a higher vibrational state of the LUMO or a higher unoccupied MO and then the electron goes into the lowest vibrational excited state of the LUMO (with the loss of energy as heat), the remaining energy to return to the ground state can be emitted as a lower-energy photon with a longer wavelength (visible).



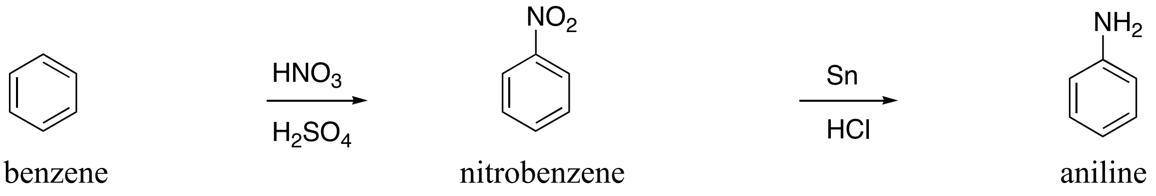
There are many natural conjugated molecules that exhibit fluorescence, for example, green fluorescence protein (GFP).

Phosphorescence also occurs for some natural compounds if the electrons become unpaired. Phosphorescence decay is slower than fluorescence, so it lasts longer than fluorescence; it can be seen in novelty items such as ‘glow in the dark’ stars that can be stuck to the wall.

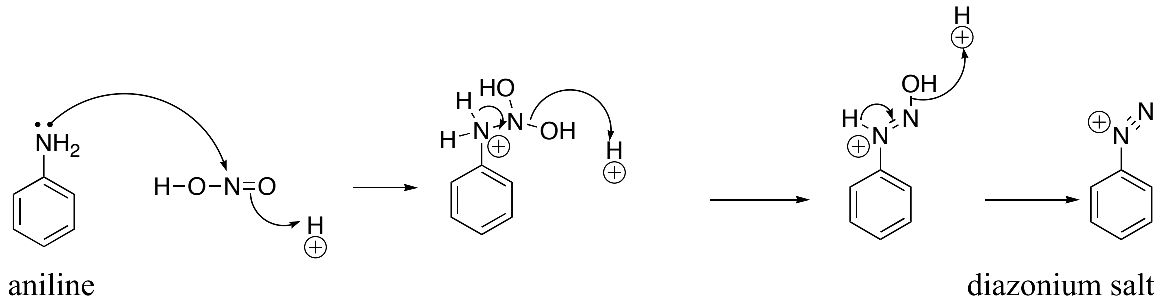
Chemiluminescence is the result of a reaction that emits energy as light. An example of chemiluminescence is seen in fireflies.

Nitro Reduction and Diazotization

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 (Sn) under acidic conditions to reduce the nitro group to an amine, forming aniline.

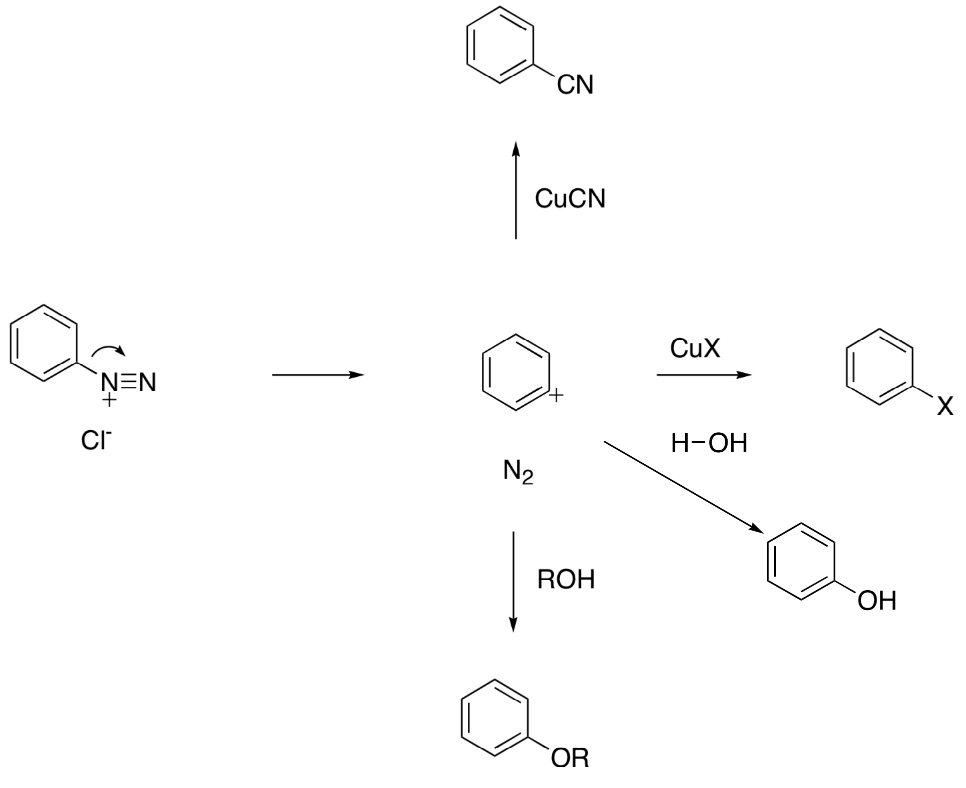


The aniline can then be reacted with nitrous acid to give a diazonium salt (explosive). Nitrous acid (HONO) is formed from the addition of sodium nitrite ($NaNO_2$) and hydrochloric acid (HCl). In a very abbreviated mechanism, the first step of the mechanism is the attack of aniline on nitrous acid to form the new nitrogen-nitrogen bond. This is followed by deprotonation and reprotonation to make the nitrogen-nitrogen double bond. 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. Examples include the addition of copper cyanide (CuCN) to give an aromatic cyanide, addition of CuX (where X is a halogen) to give a halogenated benzene, and the addition of alcohols to give ethers. Formally these reactions proceed via an S_N1 like mechanism.

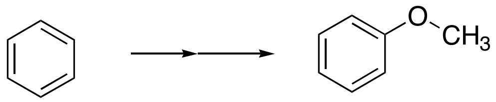


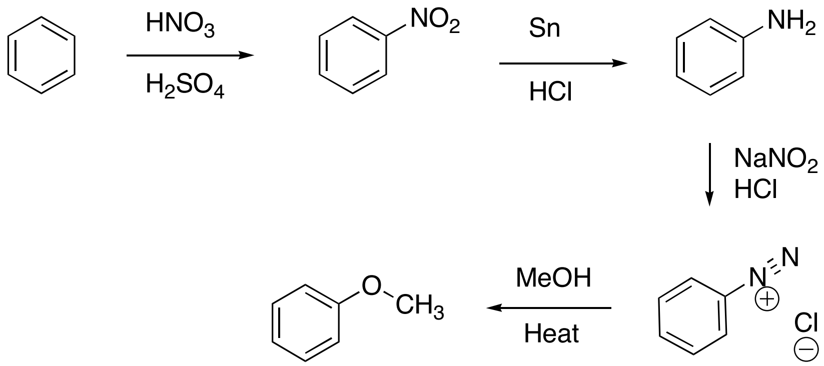
This is a very useful way to make phenols, which are difficult to make by other methods

Umpolung – Polarity inversion. Benzene usually behaves like a negative species that reacts with positive species. This reaction allows us to put negative species onto the benzene ring.

Example:

Make anisole (methoxybenzene)

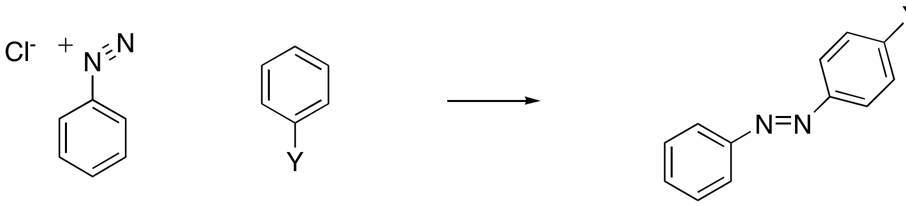




Diazonium Salts in Electrophilic Ar Substitution

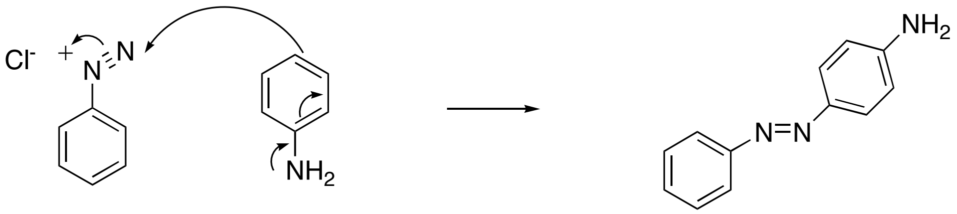
Diazonium Coupling: Requires phenol or aniline as a partner

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/emit in the visible region of the electromagnetic spectrum. As shown below, Y generally must be OH, NH_2 or NHR.

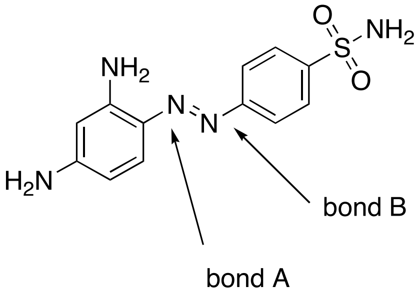


(E+) Y=OH, NHR Azo compound (Dye)

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.

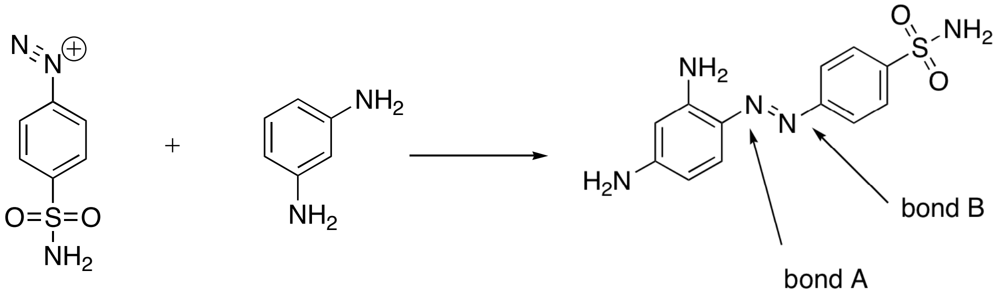


Aromatic azo compounds are valuable intermediates in the preparation of dyes and pharmaceuticals. For example, sulfa drugs such as Prontosil were the first useful antibiotics known and were found to have a broad spectrum of activity. Prontosil is prepared commercially by a process that uses a diazonium 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.

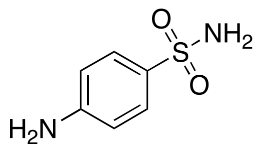


Prontosil

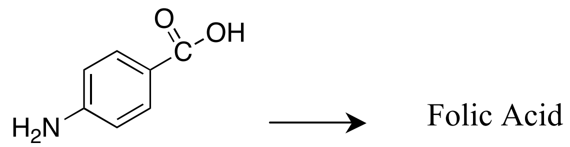
Bond A can also be seen to be formed last due to the nature of the groups on the aromatic rings. Amines are ortho/para directors where as sulfonamides are meta directors.



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 need to make folic acid. The bacteria mistakenly tries to use sulfanilamide (an enzyme inhibitor) and eventually dies.



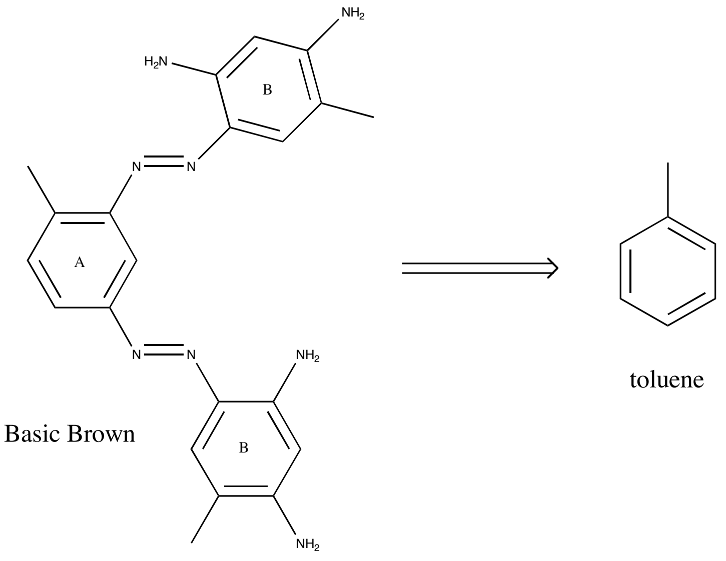
sulfanilamide



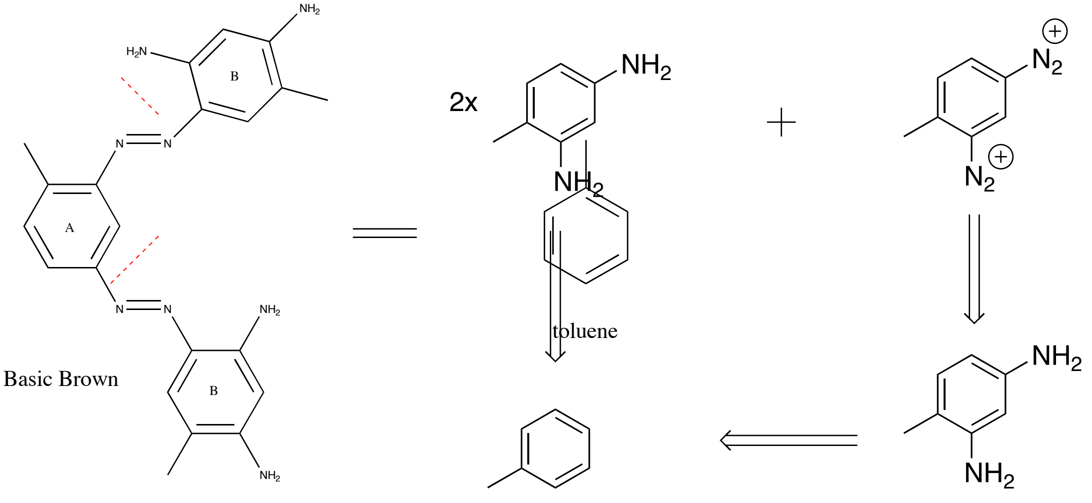
p-aminobenzoic acid

The process of predicting what starting materials could be used to synthesize a target molecule is known as **retrosynthesis**

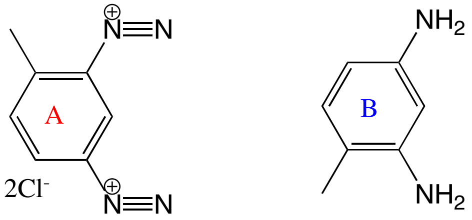
How can Basic Brown (shown below) be synthesized from toluene?



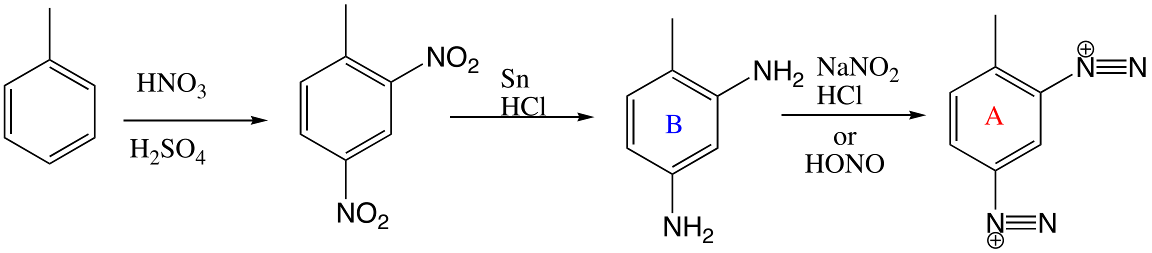
Using retrosynthesis we can break basic brown into intermediate compounds



It is easier to make the bond to the two B rings than it is to make the bond to ring A. The following rings (one of A and two of B) could be used to synthesize basic brown:



The forward reaction would be the following:



A and B will react with each other spontaneously to form basic brown.