Week 7

Nucleophilic Aromatic Substitution

7.1 Office Hours (Salinas)

2/21:

- Setup drawings points for Eucalyptus Oil and Bromination of Vanillin notebook pages? No new glassware setups so no drawings needed, right?
  - Nope, not needed — we can just refer back.
- Go over Eucalyptus Oil reagent table column entries; make sure I have everything I need.
  - Any hydrocarbon component.
- Crude yield and percent recovery calculations?
  - I did them correctly.
- Do we not need an entry for one of the substances this week? Perhaps EtOH in H_2O? Since there are only 15 points on Canvas, that leads me to think you're only looking for 5 entries.
  - Do all six reagents.
  - Just treat 50% EtOH in H_2O as EtOH (though there might be slight safety differences; check to make sure there isn't a separate MSDS for EtOH in H_2O).

7.2 Nucleophilic Aromatic Substitution

2/22:

- Office hours Wednesday/Thursday at 4:00 PM.
- 1 page notes sheet for the exam next week.
- Alkyl groups activate aromatic rings via induction.
- Halogens.
  - Electron-withdrawing due to induction.
  - Unlike alkyl groups, however, they have lone pairs that can contribute to resonance once the electrophile is added (i.e., in the carbocation intermediate).
  - Halogens with greater electronegativity are more strongly electron-withdrawing and thus more deactivating.
- Two major problems:
  1. Predicting the products based off of the substituents present on a ring.
  2. Synthesizing a ring with multiple substituents on it (the order you add them matters!).

- Practice problem takeaways.
  - When you have an ortho/para-directing substituent, you don't have to indicate major/minor products.
  - However, when doing a synthesis, try and make the reaction more selective by precluding one of the sites with another functional group. You could synthesize ortho/para products and then purify (throw away half of your yield), and while this is an acceptable answer, it is not the best answer when there are other options.
  - *t*-butyl groups generate significant steric hindrance, so groups will avoid adding ortho to them (even though *t*-butyl is an ortho/para-director by induction).
  - We will not see trick questions where something is so deactivating that we don't have a reaction; in these cases in reality, raising the temperature would suffice to force the reaction.
  - Resonance donation outcompetes induction donation.
- Rules.
  1. If all substituents direct to the same place, EAS happens there.
  2. If not, the strongest *activator* wins.
     - This is because deactivators slow everything down (but just the meta site less) whereas activators specifically accelerate particular sites.
  3. If one site is significantly more crowded than a second (out of two choices), sterics can play a role.
     - You do need a really big *t*-butyl group (or something larger) though to see this effect.
- Synthesis practice problem.
  - Benzene to 3-bromoaniline.
  - Preferentially use $H_2 + Pd/C$ to form an amine from a nitro group. The others are less common.
- **Nucleophilic aromatic substitution**. *Also known as* **NAS**, **S_NAr**.
- Reacting various aromatic compounds with methoxide and methanol.
  - Chlorobenzene: No reaction.
  - para-chloronitrobenzene: The methoxide substitutes the chloride (at high temperatures).
  - 1-chloro-2,4-dinitrobenzene: The methoxide substitutes the chloride (much faster at lower temperatures).
  - meta-chloronitrobenzene: No reaction.
- Mechanism.

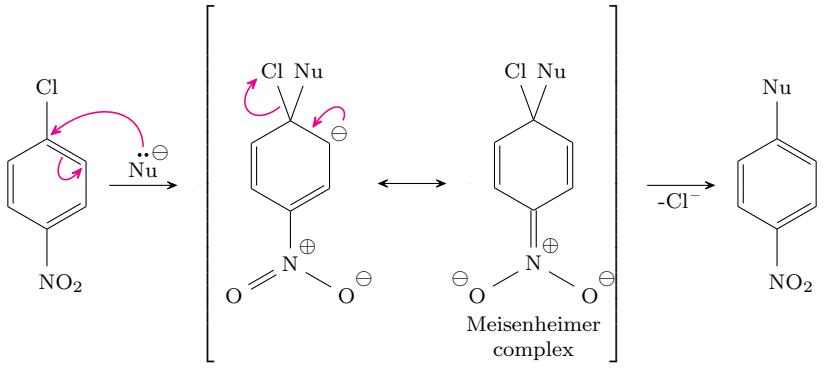
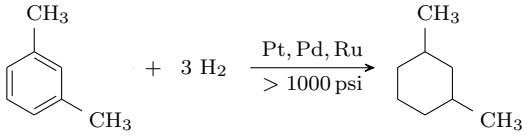


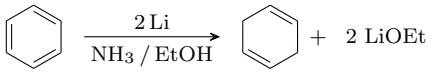
Figure 7.1: Nucleophilic aromatic substitution mechanism.

  - The driving force for the reaction is having the better leaving group leave.
    - Between methoxide and chloride, for example, chloride is the better LG.
  - To form the Meisenheimer complex, you need a strongly electron-withdrawing group (such as a nitro group) or an intramolecular kinetic driving force.
    - You also need the EWG in the right position to be able to accept electron density through resonance.

- **Meisenheimer complex**: The intermediate with a double-bonded nitrogen in a nitrobenzene derivative undergoing S_NAr.
  - Can be isolated at very low temperatures.
- 1,2-dichloro-4-nitrobenzene becomes 2-chloro-1-methoxy-4-nitrobenzene due to the para-activation of the nitro group.
- Reduction of aromatic compounds.
  - Useful when you want to create a cyclohexane derivative — you can put on functional groups with EAS and NAS, and then reduce at the end.
- High pressure catalyzed.
- General form.



  - Only one of the listed transition metals is needed.
  - This is not practical because you don't want such high pressure bombs in the lab.
- Birch reduction.
- General form.



  - Creates a singly-reduced, dearomatized system.
  - Sodium and potassium metals can also be used (in place of lithium).
  - This is similar to alkyne reduction.
- Mechanism.

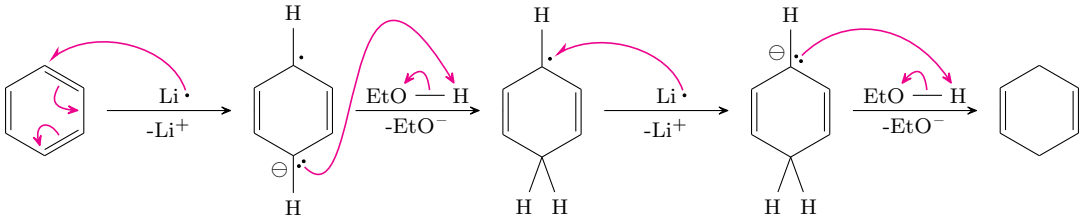


Figure 7.2: Birch reduction mechanism.

  - Although we draw the lithium radical directly attacking benzene, in reality, lithium gives up one of its electrons to become a cation, and this electron is solvated by NH_3.

- One more reaction.
- General form.

$$\mathrm{PhBr} \xrightarrow[\mathrm{NH_3}]{\mathrm{NaNH_2}} \mathrm{PhNH_2}$$

  - Also works with other alkali metals.

- A radiolabeling study.

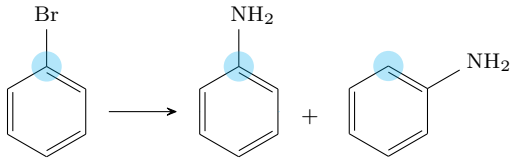


Figure 7.3: Radiolabeling bromobenzene and transforming it into aniline.

  - When we radiolabel the carbon to which bromine is initially bonded, we see that two products are formed in equimolar ratios.
  - This means that something other than S_NAr is occurring, and that whatever is happening is proceeding through some sort of symmetric intermediate.

- Mechanism.

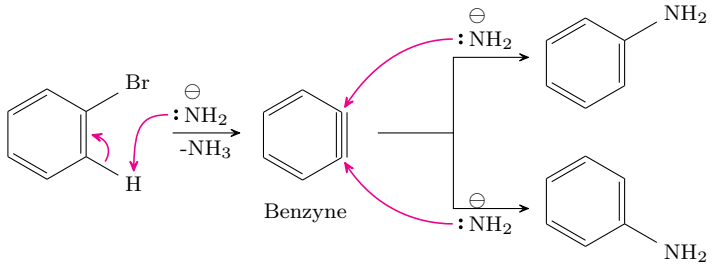


Figure 7.4: Bromobenzene to aniline mechanism.

  - With a strong enough base, we can formally abstract a hydrogen from benzene to create an alkyne-like species.
  - Orbitally, we can picture the triple bond in benzyne as a weak interaction (weak because of the nonlinearity/intense angle strain) between adjacent p orbitals in the molecular plane.

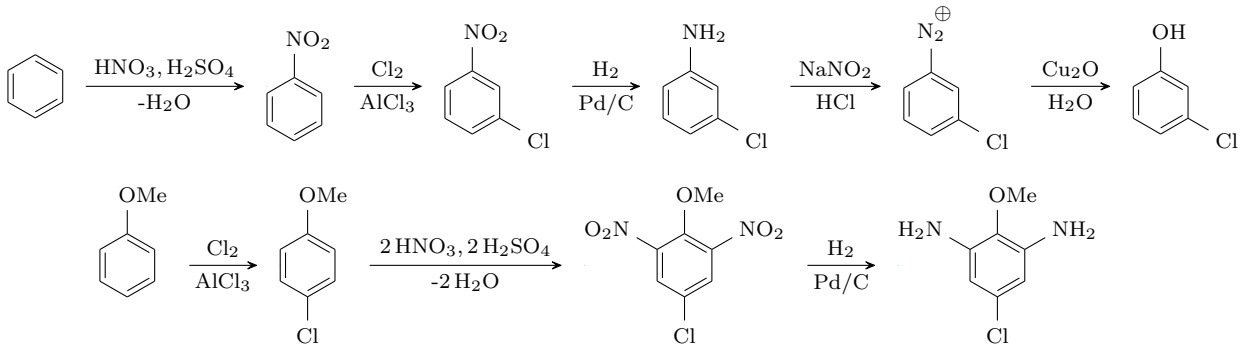
- Applications of this reaction and further mechanistic evidence.

  1. Using the strong base KNH_2, we can generate the benzyne intermediate and then trap it with other nucleophiles, leading to an equimolar mixture of products.
  2. We can also trap benzyne by using it as the dieneophile in a Diels-Alder reaction.
  3. Lastly, we note that 2-bromo-1,3-dimethylbenzene does not react under these conditions, confirming the need for an α-proton to make the benzyne intermediate.

7.3 Review / Alcohols

2/24:

- Practice synthesis problems.



- Takeaways.
  - Don't be afraid to get another isomer than what you need and chuck it out if you have to.
  - It's always better to activate first and deactivate later if possible.
- One new reaction.

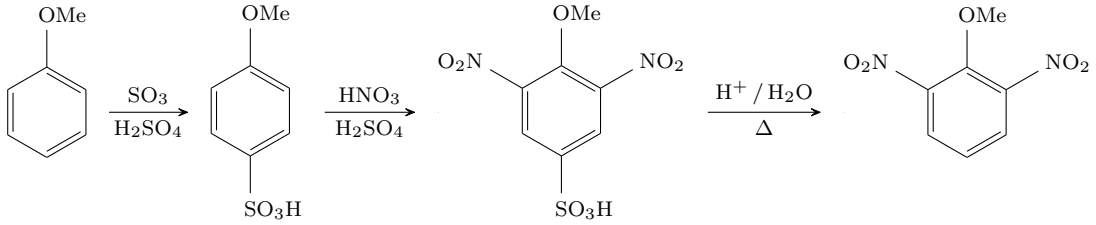


Figure 7.5: Protecting groups.

  - Make use of a protecting group.
  - Note that the sulfate group adds para due to sterics.
  - To finish the synthesis, just chlorinate para (Cl_2 / $AlCl_3$) and reduce the nitro groups ($H_2 + Pd/C$).
- If they want us to draw all of the resonance structures, they'll ask. Most likely yes in a mechanism but no in a synthesis.
- Answer to PSet 4, Q6 given.
- For PSet 4, Q7a, recall that you can't run F-C alkylation when you have EWGs on the ring.
- PSet 4, Q7b's issue is not the reactivity. Guessing the actual product is p-bromoisopropylbenzene.
- Hint for PSet 4, Q8: You can create an aromatic ring by brominating one of the alkenes in cyclohexa-1,4-diene and then doing E2 twice.
  - Looks like Dickinson may be asking us to invent new stuff on PSets and the exam.
- Synthesis and reactivity of alcohols.
- Alcohols have unique properties.
  - Boiling points: Alcohols significantly raise the boiling points of the compounds to which they're attached (because of hydrogen bonding).
- General reactivity of alcohols.
  - Adding acid to an alcohol makes water a leaving group, yielding an alkyl carbocation that can then react with nucleophiles.

  - Adding a very strong base/good nucleophile (a Grignard reagent) leads to the creation of an alkoxide (and the fully protonated Grignard species as a side product).

- Relative strengths of nucleophiles.

$$^{-}\mathrm{NRH} > \mathrm{RO}^{-} \,/\, \mathrm{HO}^{-} > \mathrm{Br}^{-} > \mathrm{NR}_3 > \mathrm{Cl}^{-} > \mathrm{F}^{-} > \mathrm{H_2O} \,/\, \mathrm{ROH} > \text{alkene} > \text{benzene}$$

- Acidity effects.
  - $1^\circ > 2^\circ > 3^\circ$.
  - More inductive donating effects (e.g., from alkyl groups) means more destabilization of the conjugate base.
  - On the other hand, $\mathrm{CF_3CH_2OH}$ has a much lower $\mathrm{p}K_\mathrm{a}$ because of the strong inductive withdrawing effects and resultant delocalization.
  - Similarly, phenoxide is stabilized via resonance.
  - At the extreme, $(\mathrm{CF_3})_3\mathrm{COH}$ is a true acid (will be predominantly deprotonated in water).
  - Inductive and resonance effects can be mixed, too: 2,4,6-trinitrophenol[1] is a very strong acid ($\mathrm{p}K_\mathrm{a} = 0.6$).

- Alkoxide generation.
  1. $\mathrm{EtOH} + \mathrm{NaOH} \rightleftharpoons \mathrm{NaOEt} + \mathrm{H_2O}$.
  2. $\mathrm{EtOH} + \mathrm{Na}^\circ \longrightarrow \mathrm{NaOEt} + \frac{1}{2}\mathrm{H_2}$.
     - Na° is sodium metal.
     - This is a strongly exothermic reaction and a dangerous one (since $\mathrm{H_2}$ is explosive).
     - It is common in laboratory use, though.
  3. $\mathrm{CyOH} + \mathrm{NaNH_2} \rightleftharpoons \mathrm{NaOCy} + \mathrm{NH_3}$.
     - A more common form of this reaction uses LDA (lithium diisopropylamine), a sterically hindered strong base, instead of $\mathrm{NaNH_2}$.
  4. $i\text{-BuOH} + \mathrm{NaH} \rightleftharpoons \mathrm{NaOBu}^i + \mathrm{H_2}$.
  5. $\mathrm{CH_3OH} + \mathrm{LiMe} \rightleftharpoons \mathrm{LiOMe} + \mathrm{CH_4}$.
     - We can also use LiBu, MeMgBr, etc. as other sources of carbanions.
  6. $\mathrm{PhOH} + \mathrm{NaOH} \rightleftharpoons \mathrm{NaOPh} + \mathrm{H_2O}$.

7.4 Office Hours (Dickinson)

- Is the order of the deactivating halogens reversed?
  - Yes — fluorine should be the most deactivating. The way I have it drawn in Figure 6.8 is correct.
- Why would the Clemmensen reduction work for reducing a nitro group to an amine — isn't it for carbonyls?
  - Don't get caught up on the name. The same reagents do the same thing in a few contexts; it's just using them to reduce ketones in particular that is termed the "Clemmensen reduction."
- Electron flow in Figure 7.4?
- Sulfonation vs. sulfation?
  - Would have to ask the IUPAC, but he could have it backwards. There probably isn't any issue though.

[1] Also known as picric acid.