2.222 Practice Problems 2003

Set #1

1. Provide the missing starting compound(s), reagent/solvent, or product to correctly complete each of the following. Most people in the class have not done this type of problem very well this year, and you really must improve before the final. Try to do them first without using your book or notes, even though you will of course have your “cheat sheet” for the final.

(a) $\text{O} \quad \text{MeO} \quad \text{O} \quad \text{OMe}$
   1) NaOMe, MeOH, BrCH₂CH₂CH₂Br
   2) H₂SO₄, H₂O
      100 °C

(b) $n$-BuLi, THF

(c) reagent, solvent, workup

(d) $\text{CH₃CH₂MgBr}$
   Cul (cat.), Ether
   $\text{H}_2\text{O}^+$ workup
(e) 

(f) 

(g) 

(h)
(i) Toluene, reflux

(j) 1) Br₂, PBr₃, CH₂Cl₂
then add CH₃CH₂OH

(k)
2. Here are some mechanism problems based on chemistry from Chapters 10 through 14. Some of them are a bit complex, but all of them involve only steps we have explicitly discussed in class. In most cases the overall reaction involves a combination of ideas, possibly from different reactions. Work systematically and keep on track towards the product shown.

(a) \[
\begin{align*}
\text{H}_3\text{CO} & \quad \text{NaBH}_4, \text{MeOH} \\
\text{O} & \quad \text{quenched with aq. HCl}
\end{align*}
\]

(b) Why is the new ring formed with a cis junction, and why is the bromine trans?

(c) When a nitrile is treated with a Grignard reagent, followed by an acidic aqueous workup, the product is a ketone, as shown schematically below. Include what happens during the workup in your mechanism.

(d) We have seen several reactions in which electrophiles add to alkenes. These reactions can sometimes be “chained together” to product quite complicated products. This is actually how many complex natural products are formed in living systems, although Nature uses an enzyme instead of sulphuric acid as catalyst.
Recall that an electrocyclic reaction can form a 1,3-diene to create a mechanism for the following unusual process involving two sequential reactions.

The following is another process involving two types of reactions chained together in tandem to produce a moderately complex product. Note that there are at least two possible pathways consistent with this process.

The Pinacol rearrangement is driven by the formation of a carbonyl group. The following reaction is related to the Pinacol rearrangement.
1. I think many people have not been connecting the mechanisms with the overall reactions we have been discussing. When you look at a mechanism, make sure you can explain exactly what every component of the reaction is doing. This will help you to remember the overall “recipe” for the reaction, as well as clarifying the mechanism.

(a) Malonic ester synthesis followed by acidic decarboxylation

\[
\begin{align*}
\text{MeO} & \quad \text{O} \\
\text{\text{COOH}} & \\
\text{MeO} & \quad \text{O} \\
\text{OMe} & \\
\end{align*}
\]

1) \(\text{NaOMe} \quad \text{MeOH, BrCH}_2\text{CH}_2\text{CH}_2\text{Br} \)
2) \(\text{H}_2\text{SO}_4, \text{H}_2\text{O} \quad 100^\circ\text{C}\)

(b) Wittig reaction; note that the 3 carbons of acetone appear at the right of the product structure.

\[
\begin{align*}
\text{n-\text{BuLi, THF then}} & \\
\text{Ph} & \quad \text{O} \\
\text{P} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{Br} & \\
\end{align*}
\]

1) \(\text{B}_2\text{H}_6, \text{THF} \)
2) \(\text{H}_2\text{O}_2, \text{NaOH (aq.)} \)

(c) Hydroboration-oxidation. When you see anti-Markovnikov addition of \(\text{H}_2\text{O}\), always think hydroboration.
Remember that adding Cu(I) to Grignards or alkylithiums changes them into ‘soft’ nucleophiles. This leads to conjugate addition. The isolated alkene group is NOT influenced by nucleophiles under these conditions.

You did this reaction in lab!

Robinson annulation (sequential Michael-aldol). Notice where the methyl group ends up.

Ozonolysis of the alkene followed by reduction of the ozonide gives an aldehyde.
Reaction of the more-electrophilic ketone group with ethylene glycol forms the ketal, expelling water. If one let this reaction proceed for a long time, and with heating, one would see the methyl ester exchanging with the glycol as well.

Diels-Alder cycloaddition. Recall that these reactions work best when the dienophile is electron-poor.

Hell-Vollhard-Zelinsky bromination. The intermediate acid bromide can be quenched with alcohol rather than water, giving an ester product directly. Note that $S_N2$ displacement of the bromine would be much slower than reaction of the acid chloride.
Intramolecular aldol condensation. Since the product is a 5-membered ring, elimination occurs easily even at room temperature. You could also have used NaOMe in MeOH or NaOEt (k) in EtOH.
2. Here are some mechanism problems based on chemistry from Chapters 10 through 14. Some of them are a bit complex, but all of them involve only steps we have explicitly discussed in class. In most cases the overall reaction involves a combination of ideas, possibly from different reactions. Work systematically and keep on track towards the product shown.

(a) When the aldehyde is reduced, the intermediate is an alkoxide. Alkoxides are bases and nucleophiles, and there is a carboxylic ester located in the right place to undergo intramolecular attack to form a 5-membered ring. Recall that esters are not reduced by NaBH₄.
The bromine can coordinate to the alkene from either side, and in fact it does so. Only when the Br is trans to the alkyl chain is it possible for the bridged ion to be attacked by the hydroxyl. If you make a model, you will find that it is very difficult to bring the OH group in on the backside of the 3-membered bridged ion in any other way.
(c) When a nitrile is treated with a Grignard reagent, followed by an acidic aqueous workup, the product is a ketone, as shown schematically below. Include what happens during the workup in your mechanism.
(d) Remember that we saw carbocations adding to aryl rings in Chapter 11, and we noted that many kinds of cations and electrophiles added to alkenes in Chapter 10. This is just an extension of those ideas. The whole process is reversible, but I have written forward arrows for simplicity.
(e) Recall that an electrocyclic reaction can form a 1,3-diene to create a mechanism for the following unusual process involving two sequential reactions.
When an amine and an aldehyde are mixed in the presence of an acid catalyst, an imine can be formed. Under these conditions, the imine can be protonated and will be attacked by the enol nucleophile. Likewise, the aldehyde itself can be an electrophile, reacting with the enol to form a conjugated ketone. If this happens, the amine can attack in a Michael fashion. This will lead to the same product eventually. Since the reactions are all reversible, the process is thermodynamically driven towards the more stable product.
(g) The Pinacol rearrangement is driven by the formation of a carbonyl group. The following reaction is related to the Pinacol rearrangement.