Midterm 2 Review Packet Key

**Concepts Covered:**

**Ch. 17: Carbonyl Chemistry; Organometallics; Redox Reactions**
- Reduction of carbonyls
  - Stereochemistry
- Oxidation of alcohols and aldehydes
  - *No need to know mechanism
- Organometallic reactions
  - Making organometallic reagents
  - Stereochemistry
  - Protecting Groups
- Retrosynthesis of Grignard Products
- α,β-unsaturated carbonyls
  - 1,2-addition (MgBr/Li-R) v.s. 1,4-addition (Cuprates)

**Ch. 18: Aldehydes and Ketones**
- Adding to carbonyls in base and acids
- Cyanohydrins
- Hydrolysis of Nitriles
- Wittig Reaction
- Imines formation primary RNH2
- Emaines formation from secondary RNH2
- Hydrolysis of imines and enamines
- Other Nucleophilic Addition Reactions

**Ch. 19: Carboxylic Acids & Nitriles**
- Structure and properties of carboxylic acids
- Acidity trends
  - Inductive effect trend
  - Understand the stability of the conjugate base
  - Bases that deprotonate carboxylic acids
- Reaction of nitriles

**Ch. 20: Nucleophilic Acyl Substitution**
- Reactions of anhydrides & acid chloride
- Ester reactions
  - Hydrolysis
    - Acid catalyzed mechanism
    - Saponification and what product is formed (alkoxide as a leaving group)
- Carboxylic acid reactions
  - Fischer esterification
Use of SOCl₂ for conversion to acid chloride

Amide reactions
- Acid catalyzed hydrolysis
- Acid catalyzed esterification

1. State the reagents necessary to convert the molecule below to another functional group. When adding carbons, feel free to use the generic R-group to represent carbon chains.

![Molecule](image)

a. Primary Alcohol
   \[ \text{NaBH}_4, \text{CH}_3\text{OH}; 1. \text{LiAlH}_4 2. \text{H}_2\text{O} \]

b. Secondary Alcohol
   1. Li/BrMg-R 2.H₂O; 1. NaC≡C-R 2. H₂O CrO₃

c. Carboxylic Acid
   \[ \text{CrO}_3, \text{H}_2\text{SO}_4, \text{H}_2\text{O} \]

d. Imine
   \[ \text{R-NH}_2, \text{cat. CH}_3\text{COOH} \]

e. Alkene
   \[ \text{Ph}_3\text{P}═\text{C-(R)}_2 \]

f. Acetal
   2 equiv. R-OH, cat. TsOH

2. Complete the following reactions
   a. DIBAL-H reduction allows the reduction of esters to stop at the aldehyde step, rather than
b. To oxidize an alcohol to an aldehyde/ketone, use PCC.

\[
\text{OH} \quad \xrightarrow{\text{PCC}} \quad \text{CHO}
\]

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c. In step 1, we want to make a Grignard reagent from Pr-Br. To do so, add Mg and diethyl ether to make Pr-MgBr. Then, we do a Grignard reaction by reacting the Grignard reagent with a ketone, leading to the production of a tertiary alcohol. Make sure to draw both enantiomers because of the formation of a new stereocenter.

3. Draw out the electron-pushing mechanism of the following reaction.
4. Draw out every reaction pathway that leads to the product below that involves MgCl.
To tackle this retrosynthesis problem, visualize severing one of the C-C bonds adjacent to the C-OH bond into individual components of the Grignard reaction (R-MgCl and ketone).

The top pathway severs the ethyl group; this gives us cyclopentanone and Et-MgCl to work with, which reacts together—followed by H$_2$O work-up—to form the product.

The bottom pathway severs the cyclopentane ring (both these C-C bonds adjacent to the C-OH are equivalent because the molecule is symmetrical); this gives us one reactant that will undergo intramolecular Grignard reaction, giving us the product after H$_2$O work-up.

5. Predict the product when the reactant reacts with EtLi and Et$_2$CuLi.

As with previous examples, organolithium reagents perform 1,2-addition, meaning it predominantly attacks the C=O carbon. The reaction results in two enantiomers due to the EtLi being able to attack the C=O carbon from either the top face or the bottom face.
Cuprates, unlike organolithium/Grignard reagents, do 1,4-addition and attack the conjugated, more distant C=C double bond rather than the C=O Carbon. Two stereoisomers result because the nucleophile can attack the C=C carbon from either the top face or the bottom face.

6. (21.45) Draw the products of each reaction.

Solution:
Step 1a: Formation of Wittig Reagent, SN2

Step 1b: Formation of Wittig Reagent, deprotonation of phosphonium salt

Step 2: Wittig Reaction
7. (21.4) Draw a stepwise mechanism for the following reaction.

\[
\text{pentane-2,5-diol} + \text{H}_2\text{O} \xrightleftharpoons[\text{H}_2\text{SO}_4 \rightleftharpoons \text{pentane-2,5-dione} + 2\text{CH}_3\text{OH}
\]

**Solution:**

**Part 1: Conversion of acetal to hemiacetal**
Part 2: Conversion of hemiacetal to carbonyl compound

8. (21.62) Design a stepwise synthesis to convert the left to right.

Solution:
No need to worry about the mechanism for the protection. It was never shown in the book.
9. (21.26) Propose a stepwise mechanism for the following reaction.

\[ \text{Step 1: Protection} \]
\[ \text{Step 2: Reduction, Grignard reagent} \]
\[ \text{Step 3:} \]

Solution:
This reaction is an imine hydrolysis.

An imine:

\[ \text{Step 1: Imine acts as a base} \]
Step 2: Protonated imine acts as an electrophile

Step 3:

Step 4: Formation of aldehyde

10. (21.57) Show two different methods to carry out the following transformation: a one-step
method using a Wittig reagent, and a two-step method using a Grignard reagent. Which is preferred? Why?

Solution:
Using Wittig Reagent:

Using Grignard reagent:

For dehydration, you may use strong acids such as H2SO4 or TsOH, Heat, or POCl3+pyridine (Alcohols chapter)

Note that using the Grignard reagent, you will only get 1 product, versus if you used Grignard reagent, you will end up with 2 products. In chemistry, we always want to have
control over the product, the more specific, the less interfering products, the better.
Therefore, we would prefer the Wittig reagent product in this case.

11. Rank the following compounds in order of decreasing acidity:

1 = most acidic
5 = least acidic

The acidity of the carboxylic acid derivative is determined by the stability of the conjugate base. In all cases, there is a negatively charged oxygen that will instablized the compound without an electron withdrawing group (EWG) or something with a huge inductive effect. Therefore, the more electronegative atom, the stronger the inductive effect and the closer it is to the oxygen, the stronger the inductive effect. In that case, the fluoride is the most electronegative atom and more fluorides will add on the inductive effect. The EWG will withdraw electron density from the oxygen, stabilizing the compound, therefore, more acidic.
These are some fundamental concepts I picked up from my organic chemistry professor I believe all the students should know before diving into the next several problems.

Above is the energy diagram for all the type II carbonyl you will encounter throughout Chapter 20. The higher the energy, the more reactive the carbonyl is. Therefore, reactivity follows:

Acid Chloride > Anhydride > Ester \approx Carboxylic acid > Amide

The general rule is a more reactive carbonyl can produce a less reactive carbonyl. Therefore, it can go from more reactive to less reactive, but NOT VICE VERSA! That means you can go from an acid chloride to anhydride but not an anhydride to acid chloride. Here’s an example:
If you tried to go from a less reactive to more reactive carbonyl, it will not work because the most reactive carbonyl typically has a stronger leaving group therefore, you will get the same product.

12. Provide mechanisms for the following two reactions:

a. $$\text{CH}_3\text{CHOCH}_3 \quad \text{Na}^{18}\text{OH} \quad \text{H}_2^{18}\text{O} \quad \text{CH}_3\text{C}^{18}\text{O}^- + \text{CH}_3\text{OH}$$
Typical Type II Carbonyl Reaction:
1. Nucleophile attacks the carbonyl
2. Electrons come back down and the better leaving group is kicked out

*This is basically the steps involved in every type II reaction (There will be exceptions with protonation & deprotonation). REMEMBER THIS!*

What we have here is an example of saponification which is the transformation of an ester to carboxylate under basic conditions. **Hydroxide is a strong nucleophile, therefore, it can directly attack the carbonyl without any protonation of the carbonyl.** The electrons come back down and the -OCH₃ is kicked out. However, this is basic condition, anything acidic such as the carboxylic acid will be quickly deprotonated by OCH₃ or OH.
This is an example of an intramolecular esterification under acidic conditions. Here’s the difference from a reaction under basic conditions: Since it involves a weak nucleophile such as H₂O or ROH, the carbonyl needs to be protonated first to become more electrophilic for
the weak nucleophile to attack. As mentioned from my previous worksheets, whatever you want to keep, DEPROTONATE! If you want to get rid of it, PROTONATE! Protonating will make it more acidic, therefore, a better leaving group. Lastly, deprotonate the finishing carbonyl to get the product. Ester hydrolysis is the reverse reaction of esterification, so the mechanism is literally working backwards.

13. Predict the products or provide reagents in the following reactions. For reactions that require reagents, if more than one step is required, number individual steps.

a.
This is transforming an acid chloride to an ester. Since acid chloride is EXTREMELY REACTIVE, protonation of the carbonyl is not required so the oxygen will directly attack the carbonyl. Next, find which leaving group is better, which is Cl\textsuperscript{-}, so it gets kicked out. Again, if you want to keep it, deprotonate it.

b.

\[
\begin{align*}
13\text{CO}_2 & \quad \overset{1. \text{CH}_3\text{MgBr}}{\longrightarrow} & C & \overset{2. \text{H}_3\text{O}^+}{\longrightarrow} & D \\
13\text{C}_3\text{H}_3 & \quad & & & \quad \text{CH}_3\text{C} ^{13}\text{C} \quad \text{H}
\end{align*}
\]
C: One method of synthesizing a carboxylic acid is using carbon dioxide with a Grignard reagent, but don’t forget an acid to protonate the carboxylate. Now how do I go from carboxylic acid to imine.

D: One clue for this synthesis is the last reagent is a primary amine with CH₃ since ONLY PRIMARY sp CREATES AN IMINE (don’t forget the acid with it). Now think of the primary anime reaction as replacing the NCH₃ with O if you are working backwards so the previous product is an aldehyde. Now how do I go from carboxylic acid to aldehyde.
For this class sake, just remember adding acid to a nitrile will create a carboxylic acid. Don’t need to know the mechanism for it.
Another example of saponification where you transfer an ester to a carboxylate using basic conditions. Remember that you can never create a carboxylic acid under basic conditions because it will be easily deprotonated by both water and hydroxide.
14. Show how to synthesize the following compound from the given starting material. Provide the reagents and products for each step.

a. For this synthesis, you are going from the least reactive type II carbonyl to most reactive carbonyl. Therefore, it is impossible to directly add a Cl⁻ because Cl⁻ is definitely a better leaving group than NH₂ since it is more acidic. And it requires energy to synthesize a
compound of more reactivity or less stability than the starting material (essentially endothermic reaction). Nevertheless, you can make acid chloride by using $\text{SOCl}_2$, but only from carboxylic acid. So there is one reagent. Amide to carboxylic acid are the few cases where you can go from lower energy to higher energy but using heat (forcing conditions). There is the second and final reagent required.

b.
If you start with a bromine bonded to a benzene, just add an organometallic reagent, preferably Grignard reagent and ether. Your options of adding carbon chains and functional groups dramatically increase with -MgBr. Now you have an amide and you can synthesize it using more reactive carbonyl such as acid chloride, anhydride, or ester. Not carboxylic acid because it is extremely acidic so it will just get deprotonated by the RNH₂. However, with an organometallic reagent, the only possible type II carbonyl you can pick is carboxylic acid. Use CO₂ and H₂O⁺ to create the carboxylic acid and use SOCl₂ to create the acid chloride. For the last reagent, use two equivalents of amine to deprotonate the additional hydrogen in the final amide product.