Final Exam Review Key

Concepts Covered

- **Ch 16: EAS**
  - The 5 EAS rxns
  - Deactivating/Activating Groups
  - Ortho/Para-directing and Meta-directing groups
- **Ch 17: Carbonyl Chemistry**
  - Oxidation
  - Reduction
  - Organometallic reagents
    - MgBr--R, Li-R
    - LiCu--R₂
- **Ch 18: Ketones and Aldehydes**
  - Synthesis of ketones and aldehydes
  - Nucleophilic additions
    - Of H, R-group, and CN
  - Wittig Rxn
  - Addition of Amines
  - Hydration
  - Acetals/hemiacetals
- **Ch 19: Carboxylic Acids and Nitriles**
  - Synthesis of carboxylic acids
  - Acid-base rxns
    - Protonation of C=O oxygen, not the of the OH
  - Reduction, hydrolysis and organometallic addition of nitriles
- **Ch 20: Nucleophilic Acyl Substitution**
  - Structure, bonding, rates
  - Carbonyl Reactivity and L.G ability
  - Acyl Chloride Reactions
    - Mechanism
  - Acid Anhydrides
  - Fischer Esterification
    - Ester Hydrolysis
    - Saponification
  - Amide Hydrolysis
Ch. 21 Enol/Enolate Chemistry
  ○ Tautomerization
    ■ Acid-Catalyzed
    ○ Racemization of alpha-carbon
    ○ Halogenation at alpha-carbon and elimination
    ○ Kinetic vs Thermodynamic Enolates
    ○ Malonic/Acetoacetic Esters

Ch. 22 Aldol Reaction
  ○ The Claisen Reaction
  ○ Dieckmann Reaction
  ○ Michael Reaction
  ○ Robinson Annulation

Ch. 23 Amines
  ○ Acid-base equilibrium
  ○ Synthesis of amines
  ○ Reactions
    ■ As nucleophile
    ■ With NaNO₂ + HCl
    ■ Substitution of aryl diazonium ions

Peter’s Problems Here
1. (18.7) Synthesize m-bromoaniline from benzene. Structures are provided below.

   ![m-bromoaniline](image)

Solution:
It is very important to keep track of meta, ortho, and para directors and determine the sequences in which they were added on. NO₂ are meta directors, since we see the product has 2 substituents that are at meta from each other. Therefore, NO₂ is probably added first. Therefore, we first add the NO₂, then the bromine, and finally reduce the NO₂ into NH₂.
2. (18.5) Draw the products formed from nitration of each compound
A. 
B.
Solution:
In both of the structures, there is an OH and an alkyl group present. Between the two, the OH is a stronger activating group. Therefore, the new nitro group will be ortho, para with respect to the OH and not alkyl group. Always remember that no substitutions will occur between 2 meta groups. See note for Part B.

A.

Solution:
In both of the structures, there is an OH and an alkyl group present. Between the two, the OH is a stronger activating group. Therefore, the new nitro group will be ortho, para with respect to the OH and not alkyl group. Always remember that no substitutions will occur between 2 meta groups. See note for Part B.

B.

3. (18.11) Synthesize the structure below from benzene.
The most likely questions you will receive on your final for this chapter will be these synthesis problems that require you to form a complex structure. Always keep track of the meta, ortho/para directors, know which ones are added on first and which ones are added after. In this question, we see the product having 3 substituents: nitro, a strong deactivating meta director; a ketone, a meta director; an alkyl group, an ortho/para director. Remember that NO2 cannot undergo FC, therefore, however, both the ketone and alkyl group must be added on using FC pathways. Therefore, the NO2 is probably added last. Between the other 2 substituents, the alkyl and ketone, only the alkyl is an ortho/para director. Seeing that the alkyl group and the ketone are at ortho/para from each other, the alkyl is probably added first.

Therefore, the sequence of addition of these 3 substituents is: alkyl, ketone, finally nitro. We can take advantage of FC to add both of them.

A note: you may be wondering why did I not simply add the alkyl using 1 step FC, however, this is because if the one step pathway was used, rearrangement will occur. If we were to use the one step pathway, we would need to use a primary halide, which is prone to rearrangement. You can only use one step FC alkylation when the alkyl halide is tertiary.

My notes on rearrangement FC alkylation from VV lecture 2 years ago. Avoid
4. (20.2) Show 2 unique pathways to synthesize the structure below. You must use a Grignard reaction.

Solution:
A Grignard reagent has the general format of R-MgBr. Always remember that the starting material is always carbonyl because we are in 51C. Therefore, we will have 1 carbonyl molecule + Grignard reagent for each of the pathways here. Recall the reaction:

\[
\text{R} = \text{H or alkyl} \\
\text{[1]} \text{R''MgX or R'Li} \\
\text{[2]} \text{H}_2\text{O} \\
\text{R'} = \text{H or alkyl} \\
\text{1°, 2°, or 3° alcohol}
\]

Therefore, we can use either side of the product as the original aldehyde.
5. (20.54) Draw a stepwise mechanism for the following reaction. First, identify the reagents.

**Solution:**
A reduction reaction occurred.
Mechanism

[Image of energy diagram]

Luis’s Problems Here

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 ≅ 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 try to go from a less reactive carbonyl 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.

1. Predict the major product(s) of each reaction

   a.
For this instance, the reaction of primary amines will always result in an imine. Therefore, it is as if the C=O bond is replaced by an C=N bond with its corresponding carbon chains the primary amines have. For the mechanism, remember this:
- If you want to get rid of it, protonated
- If you want to keep it, deprotonated

b.
The addition of an organometallic reagent to nitrile results in the addition of carbon chains. However, the first step does provide an imine intermediate as shown above. The water added will turn that imine into a ketone. Even though Van Vranken does not require you to know the mechanism, it is important to understand that nitriles work in similar fashion to a Type I carbonyl. You will see this in chapter 19 & 22.
The reaction above demonstrates the **addition of an acetal protecting group**. **REMEMBER THAT THIS REACTION COULD ONLY OCCUR WITH KETONE AND ALDEHYDES**. Leave the ester alone. Like for many carbonyl reactions from Chapter 17-20, since the acetal is a weak nucleophile, the protonation of the ketone is necessary. As mentioned before:

- **If you want to get rid of it**, protonated
- **If you want to keep it**, deprotonated
This is an important reaction from Chapter 20 that could come useful when converting a lower energized type II carbonyl into a higher energy carbonyl (see my explanation at the beginning of my section). Nevertheless, SOCl\(_2\) with heat will convert ONLY CARBOXYLIC ACID into acid chloride. Important reaction to know for synthesis!

2. Suggest the starting material/s that would efficiently generate the product shown.
Now this is an example of a wittig reaction due to the presence of a phosphorus ylide as an reagent. Now typically you would want to break the double bond and replace it with a C=O bond. **However, there are two double bonds!** Which one do we break? Well **look at the reagent and see the carbon chain added, -CHCH₂CH₃, and only the double on the right matches the carbon chain.** Therefore, you only break that double bond.
Now the product here is an ester and the reagent is an alcohol, therefore, this should be an indication that the starting material is some sort of type II carbonyl. Now remember, the starting material cannot be a carbonyl lower energy than an ester, so amides are out. Now you have three
options: anhydride, carboxylic acid, and acid chloride. However, there is the presence of pyridine. Only one starting material requires pyridine: acid chloride.
Right off the bat, the presence of only DIBAL-H and HCl without any sort of organometallic should indicate a reaction from Chapter 19. The only starting material that could synthesize an aldehyde with those reagents is a nitrile. Now be careful and count carbons. It is as simple as cutting off the C=O and replacing it with a CN bond.
d. The product is an enamine and the starting material contains a secondary amine. Therefore, the starting material should be either a ketone or aldehyde. Now in this situation, you should cut the bond off the N(CH₃)₂ and replace it with a C=O bond. Additionally, remove the double and you get your answer.
3. Multi-step synthesis: Show any steps, reagents, and conditions necessary to efficiently carry out the following multi-step transformations from the starting material on the left to the product on the right.

a. 

\[
\begin{align*}
\text{C\equivN} & \quad ? \\
\text{C\equivN} & \quad ? \\
\text{C\equivN} \quad \text{Et-MgBr} \quad \text{Et-MgBr} \\
\text{Et-MgBr} \quad \text{Et-MgBr} \\
\text{H_2O} & \quad \text{H_2O} \\
\text{H_2O} & \quad \text{H_2O} \\
\text{Et-C(O)OEt} & \\
\text{Et-C(O)OEt} & \\
\text{Et-C(O)OEt} & \\
\text{Et-C(O)OEt} & \\
\text{Et-C(O)OEt} & \\
\text{Et-C(O)OEt} & \\
\text{Et-C(O)OEt} & \\
\text{Et-C(O)OEt} & \\
\end{align*}
\]
Many synthesis in the exam will require reagents from multiple chapters and this is no exception. Now you should notice that you add two -CH\(_2\)CH\(_3\) (-Et) groups from a nitrile. You know from chapter 19 that adding the organometallic reagent with water will do the job. However, you add two -Et groups so you add the reagent twice. Now your intermediate is an alcohol, but your product is an ester. Look at your intermediate as a reagent and with an addition of pyridine, you can make an ester. Now you can use a higher energy carbonyl such as acid chloride to complete synthesis.

\[
\text{\begin{align*}
\text{A} & \quad \text{B} \\
\text{\begin{array}{c}
H \quad \text{H} \\
\downarrow \quad \downarrow \\
\text{O} & \quad \text{O} \\
\text{CH}_3 & \quad \text{OH} \\
\text{H} & \quad \text{H} \\
\end{array}} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{OH} \\
\text{CH}_3 & \quad \text{OH} \\
\end{align*}}
\]

*hint: only a single reagent is needed*
A: The difference between the starting material and product is that there is an acetal protecting group and the ester has been reduced. Now that means that a strong reducing agent such as LiAlH₄ with water was used. However, it can also react with the aldehyde, therefore, HOCH₂CH₂OH with HCl should be added first before reducing the ester.

B: Now the ring product indicates that an intramolecular reaction occurred between two carbonyls, but the protecting group is still attached. How can you get rid of it? H₃O⁺ can get rid of the protecting group. ADDITIONALLY, IT CAN BE USED TO CONDUCT THE INTRAMOLECULAR REACTION because the -OH is a weak nucleophile, therefore, it must protonate the resulting aldehyde first.

1. Complete the following reactions by drawing the product. (Ch. 21)
   a. (Ignore stereochemistry)
LDA THF at -78 deg C deprotonates the **less substituted** alpha-carbon, this enolate can then perform Sn2 attack on the carbon adjacent to the Br, forming a new 7-membered ring.

b. (Ignore Stereochemistry)

NaOCH$_3$ with CH$_3$OH deprotonates the **more substituted** alpha-carbon, this enolate can then perform Sn2 attack on the carbon adjacent to the Br, forming a new 5-membered ring.

c.

When H$_3$O$^+$ is added to such a di-carbonyl with heat, hydrolysis and decarboxylation occurs. This gives us a racemic mixture of a ketone along with MeOH (from ester hydrolysis) and CO$_2$.

2. Complete the following reactions (Ch. 22)
   a.
NaOMe deprotonates the alpha carbon, allowing nucleophilic attack on the carbonyl C of another reactant molecule. Make sure to use the same alkoxide base as the ester (both OMe). Denote enantiomeric mixture due to formation of new stereocenter.

NaOEt deprotonates the alpha carbon of the di-carbonyl. This attacks the beta carbon of the other reactant, a beta-unsaturated carbonyl, forming carbon-carbon bonds

Robinson annulation mechanism is very complex. Best way to approach it is to arrange the reactants as shown below and proceed with a cyclization reaction. The final 6-membered ring replaces the right C=O with C=C and the C=C with a C–C.
3. Complete the following reactions (Ch. 23)
   a. 
   
   \[
   \begin{align*}
   &1. \text{NaOH} \\
   &2. \text{BrCH}_2\text{CH(CH}_3)_2 \\
   &3. \text{NaOH, H}_2\text{O, }\Delta \\
   \end{align*}
   \]

   1. NaOH deprotonates the reagent. 2. The phthalimide anion performs an Sn2 attack on the isobutyl bromide. 3. NaOH, H2O with heat ejects an amine with the same hydrocarbon structure as the bromide.

   b. 
   
   \[
   \begin{align*}
   &1. \text{LiAlH}_4 \\
   &2. \text{H}_2\text{O} \\
   \end{align*}
   \]

   LAH followed by water work-up reduces amides to amines.

   c. 
   
   \[
   \begin{align*}
   &\text{NaBH}_3\text{CN} \\
   \end{align*}
   \]

   The reagent NaBH₃CN denotes reductive amination. Simply replace the C=O bond with C–N. How the product amine looks depends on the nitrogen-based reagent.

4. Synthesize the following compounds from the starting material from benzene.
   a. 
   
   \[
   \begin{align*}
   \end{align*}
   \]
5. Draw the structure of the unknown compound based off of spectroscopy data.

IR Absorptions: 2981, 1731

Formula: C₅H₁₁BrO₂
Clues:

- C-NMR peak between 180-155 ppm indicates ester, amide, or acyl halide
- IR peaks show sp3-C-H’s (2981) and C=O (1731)
- 9H, s means a tert-butyl group
- 2H, s indicates a methylene group with no neighboring C-H’s
- No 10-12 ppm peak on H-NMR means no carboxylic acid or aldehyde