## Midterm 2 Review Key

### Nucleophilic Acyl Substitution: Acid Chlorides

1) Can form anhydrides
   
   ![Anhydride Structure](image)

   a) Using carboxylate anion

2) Can form ester
   
   a) Using alcohols (HO-R), pyridine

3) Can form carboxylic acids
   
   a) H₂O, pyridine

4) Can form amides
   
   a) Using NH₃, NR₃, NHR₂, NH₂R (2 equiv)

### Nucleophilic Acyl Substitution: Anhydrides

1. WILL NOT form acid chlorides directly from anhydrides

2. Can form ester
   
   a. Using alcohols (HO-R), pyridine

3. Can form carboxylic acids
   
   a. H₂O, pyridine

4. Can form amides
   
   a. Using NH₃, NR₃, NHR₂, NH₂R (2 equiv)

### Nucleophilic Acyl Substitution: Esters

1. Can make carboxylic acids (acidic and basic conditions)
   
   a. (Acidic) Hydrolysis: H₃O⁺ or reverse of Fischer esterification
   
   b. (Basic) Saponification: using -OH
      
      i. This WILL NOT fully form the carboxylic acid
      
      ii. Ends at the carboxylate anion with an alcohol byproduct

2. Can make amides
   
   a. Using HNR₂
   
   b. Byproduct: Alcohol (CH₃OH)

3. Can make OTHER forms of esters (trans-esterification)
   
   a. Using other alcohols (ex: EtOH, propanol)

### Nucleophilic Acyl Substitution: Carboxylic Acids
5) Can form acid chlorides/bromide
   a) Using SOCl\(_2\) or PBr\(_3\)

6) Can form anhydrides
   a) ONLY for 5 or 6 membered rings

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{OH} \\
\text{w/ heat} \\
\text{O} \\
\text{OH}
\end{array}
\]

b) 

7) Can form ester
   a) Fischer esterification - Using alcohols (HO-R), H\(_2\)SO\(_4\)
   b) This can also make intramolecular reactions (a hydroxyl group to a carboxylic acid)

8) Can form amides
   a) Using NH\(_3\) with heat
   b) NR\(_3\), NHR\(_2\), NH\(_2\)R with DCC
   c) Very harsh conditions

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**Nucleophilic Acyl Substitution: Amides**

1. Can make carboxylic acids
   a. Using H\(_3\)O\(+\) with heat
   b. Using NaOH with heat
      i. WILL NOT fully form the carboxylic acid
      ii. Same as Saponification for esters
   c. Very harsh conditions (unfavorable)

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**Chapter 22: Nitriles**

1. Making nitriles
   a. Alkyl halides with NaCN
   b. Epoxides with NaCN
   c. Aldehydes and ketones with NaCN

2. Hydrolysis
   a. Using R-CN with H\(_3\)O\(+\) or -OH makes carboxylic acids

3. Reduction
   a. Using LiAlH\(_4\), then H\(_2\)O with R-CN makes amines
   b. Using DIBAL-H with R-CN makes aldehydes

4. Carbon addition
   a. Using organometallics (Grignard’s and Organolithiums)
   b. Makes ketones
Chapter 23: Enols and Enolates

1. Deprotonation
   a. Using strong bases to form enols and enolates

2. Unsymmetric ketones form
   a. Kinetic: less substituted side
      i. Using LDA
   b. Thermodynamic: more substituted side
      i. Using NaOCH₂CH₃ or KOTBu
      ii. Protic solvent and high temperature

3. Halogenation
   a. Using acidic conditions
      i. Cl₂ with HCl, H₂O
      ii. Stops after single addition (Monohalogenation)
      iii. Once monohalogenated, you can use
         1. Li₂CO₃, LiBr, DMF to make an elimination
         2. This makes an alpha-beta unsaturated carbonyl
         3. REMEMBER you can add cuprates to this
   b. Using basic conditions
      i. Br₂ with KOH
      ii. Stops after all acidic hydrogens are gone (perhalogenation)

4. Carbon additions
   a. Can add alkyl halides to enols/enolates
   b. Only works with primary or methyl carbons (SN2)

5. Other carbonyls
   a. enol/enolate formation can work with other carbonyls
      i. Examples: aldehydes, esters, nitriles

6. Beta-dicarbonyls
   a. Using NaOEt makes an enolate precursor
   b. Available for more carbon additions with alkyl halides (alkylation)

Chapter 24: Carbonyl Condensation Reactions

1. Aldol Addition & Aldol Condensation (aldehydes & ketones)
   a. Basic condition reagents: NaOH, H₂O
      i. Is the enol or enolate formed?
   b. Acidic condition reagents: H₃O⁺
      i. Is the enol or enolate formed?
ii. Product: alpha, beta-unsaturated carbonyl  
iii. Acidic conditions will not stop at the beta-hydroxy carbonyl!

2. Crossed Aldol Reactions  
   a. Reagents: 2 different aldehydes/ketones  
   b. Choose your reagents carefully:  
      i. One aldehyde/ketone does not have an alpha H  
         1. ex) benzaldehyde  
      ii. One aldehyde/ketone has much more acidic H than the other  
         1. ex) dicarbonyl

3. Directed Aldol Reactions  
   a. Step-wise reaction of adding 1 aldehyde/ketone with LDA, THF, -73dC; then,  
      add the other aldehyde/ketone  
   b. Product: beta-hydroxy carbonyl  
      i. Requires heat to drive to the Aldol condensation product

4. Intramolecular Aldol Reactions  
   a. Occurs when nucleophile (enol/enolate) is 2 or 3 carbons away from the  
      electrophile (aldehyde/ketone) on the same molecule  
   b. Product: 5 or 6 membered ring

5. E1Cb mechanism  
   a. Any reaction that produces an alpha, beta-unsaturated carbonyl will undergo an  
      E1Cb mechanism  
   b. This is a 2-step mechanism  
   c. Incorrect: using base to deprotonate acidic H and kicking off the -OH leaving  
      group in a E2 like mechanism  
   d. Correct:  
      i. Base deprotonates acidic H → pushes electron density up to the  
         carbonyl  
      ii. Enolate is regenerated in basic conditions  
      iii. Carbonyl is reformed → kicks off the -OH

6. Claisen Condensation  
   a. Reagents: enolate + ester  
   b. Product: beta-keto ester  
   c. Only basic conditions because you need something to drive this equilibrium  
      i. Formation of a stabilized enolate drives equilibrium  
      ii. If there is no stabilized enolate formed, your reaction will revert back to  
          starting materials  
          1. Why? Ketone is more reactive than ester

7. Dieckmann Reaction  
   a. Reagents: enolate + ester on the same molecule  
   b. Product: 5-6 membered ring  
   c. Also known as an intramolecular Claisen reaction

8. Michael Reaction
### Michael Reaction

- **Reagents:** stabilized enolate + alpha, beta-unsaturated carbonyl
- Unlike other previous reactions where a 1,2-addition was performed, the Michael reaction undergoes a **1,4-addition**
  - Adding to the C=C bond of an alpha, beta-unsaturated carbonyl
- **Product:** 1,5-dicarbonyl
- Michael product can be **decarboxylated** if malonic esters (beta-keto acid) are present
  - **Decarboxylation:** hydrolysis of ester → carboxylic acid → 1,5-dicarbonyl
    1. Produces CO2
    2. **Reagents:**
       - 1) basic: NaOH, H2O
       - 2) H3O+, heat
     - 2) acidic: H2O, H3O+, heat

### Robinson Annulation

- **Reagent:** 1,5-dicarbonyl (Michael product) + base + aldehyde/ketone
  - **Step 1:** Michael reaction (enolate + alpha, beta-unsaturated carbonyl)
  - **Step 2:** enolate (from the Michael product) + aldehyde/ketone on the same compound
- **Product:** 6 membered ring
- **Mechanism** include E1Cb (for Aldol condensation)

### Chapter 25: Amines

#### 1. Reduction of Amines

- **Nitro → amine**
  - **Reagents:** R-NO2 + H2, Pd/C
  - **Product:** R-NH2
- **Nitrile → amine**
  - **Reagents:** R-C≡N + LiAlH4 (followed by H2O workup)
  - **Product:** R-CH2-NH2
- **Amide → amine**
  - **Reagents:** amide + LiAlH4 (followed by H2O workup)
  - **Product:** R-CH2-NR2

#### 2. Reductive Amination

- **Addition to imines**
  - **Reagent:** NaCNBH3
    1. Acts very similar to NaBH4 except NaCNBH3 reduces imines → amine
    2. Recall how to generate imine
      1. **Reagents:** ketone/aldehyde + amine

#### 3. Strecker Reaction

- **Reagents:** imine + NaCN + NH4Cl
<table>
<thead>
<tr>
<th>Synthesis Tips for Claisen, Michael &amp; Robinson Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Claisen Reaction</td>
</tr>
<tr>
<td>a. Start counting from the ester</td>
</tr>
<tr>
<td>b. Break the alpha,beta-bond</td>
</tr>
<tr>
<td>c. Add base to the beta-position</td>
</tr>
<tr>
<td>i. Match up the base to the ester</td>
</tr>
<tr>
<td>d. Put negative charge in the alpha-position</td>
</tr>
<tr>
<td>2. Michael Reaction</td>
</tr>
<tr>
<td>a. Select one carbonyl to start from</td>
</tr>
<tr>
<td>b. Break beta-gamma bond</td>
</tr>
<tr>
<td>c. Put a double bond in the alpha,beta position</td>
</tr>
<tr>
<td>d. Put a negative charge in the gamma position</td>
</tr>
<tr>
<td>3. Robinson Reaction</td>
</tr>
<tr>
<td>a. Take apart Aldol Condensation product</td>
</tr>
<tr>
<td>i. break the alpha,beta-unsaturated bond</td>
</tr>
<tr>
<td>ii. This results in breaking the ring</td>
</tr>
<tr>
<td>b. Add a carbonyl to the beta position</td>
</tr>
<tr>
<td>c. Then, take apart the Michael product</td>
</tr>
<tr>
<td>i. Refer to #2</td>
</tr>
</tbody>
</table>
1.) Propose the reagents to complete the following reactions.

a.)
\[ \text{O} \quad \text{O} \quad \text{O} \quad \rightarrow \quad \text{O} \quad \text{O} \]

1.) NaOEt
2.) CH₃I
3.) NaOEt
4.) \( \equiv \text{Br} \)
5.) H₃O⁺

b.)
\[ \text{O} \]

1.) Br₂, HCl, H₂O
2.) OH\( \equiv \text{OH} \)
3.) NaCN
4.) H₃O⁺
5.) NaBH₄
6.) H₂O
2.) Provide the mechanism for the following reaction.

a) 

\[
\begin{align*}
\text{OH} & \quad \text{NH}_2\text{CH}_3 \\
\text{H} & \quad \text{NaCNBH}_3 \\
\text{mild acid} & \\
\end{align*}
\]

\[
\begin{align*}
\text{H} & \quad \text{N} \\
\text{H} & \quad \text{H} \\
\text{A} & \\
\text{aminal} & \\
\end{align*}
\]

\[
\begin{align*}
\text{H} \quad & \quad \text{H} \\
\text{N} & \quad \text{N} \\
\text{amine} & \\
\end{align*}
\]
3.) Predict the product of the following reactions.

1. 

\[
\text{HCO}_2\text{Et} \quad \text{NaOEt, HOEt}
\]

2. 

\[
\text{NH}_2 \quad \text{NaBH}_3\text{CN}
\]

3. 

\[
\text{NaOH, H}_2\text{O}
\]
-What is the most apparent reagent here? **NaBH₃CN**.
-Recall from the reagent table (from CH. 25) that **NaBH₃CN** is used to convert imines —> amines.
-Our product is already an amine, so would that mean our reagent in the box is an imine? Nope!
-You need to look at what other reagents are present: we have a **primary amine** (above the arrow).
-So, from this information, we need an **imine** to react with **NaBH₃CN**, but we have a **primary amine**.
-What is the relationship between an imine and a primary amine? **Ketone/aldehyde + primary amine —> imine**.

-Therefore, we need a ketone/aldehyde to react with the primary amine to form an imine. As a result, the formed imine will react with **NaBH₃CN** to produce the final amine.
-The entire reaction is essentially this:

-What **NaBH₃** essentially does is put H-H across the C=N bond. This results in a reaction called **reductive ammination**.
-How did I know that I should use that ketone instead of another ketone/aldehyde? Look at what the product is:
4.) For the following target molecules, predict the starting material(s) it came from.

Seeing that the target product is a $1,5$-dicarbonyl, you know this is a Michael Reaction. Therefore, you need an alpha-beta-unsaturated carbonyl and a stabilized enolate molecule. The enolate contains esters as opposed to carboxylic acids because acids are very problematic in basic conditions. Esters can be easily converted to carboxylic acids.
-Use the Synthesis Tips at the end of the reagent table in the beginning of this packet to help you solve this problem.
-What is the product? The product is a **1, 3-dicarbonyl with an ester**.
-What type of reaction does this imply? **Claisen Condensation**.
-What are the reagents used in a Claisen Condensation? **Ester + Ester OR Ester + Aldehyde/Ketone**. Putting it simply, reagents are an ester + enolate.

-Using the tips provided in the reagent table:
  - **a) Start counting from ester**.
  - **b) Break the alpha,beta bond**.
  - **c) Add base to the beta position. Match the base up with the -OR group present on the other ester**.
What is the product? **1,5-dicarbonyl compound.**
Which reaction do we know that produces a 1,5-dicarbonyl?
- **The Michael Reaction produces a 1,5-dicarbonyl.**
What are the reagents for a Michael Reaction?
  *Stabilized enolate + alpha-beta unsaturated ketone.*

Let's use the Synthesis Tips to help us with this problem:
- a) Select one carbonyl to start from.

- b) Break the beta-gamma bond.

- c) Put a double bond in the alpha-beta position.

- d) Put a negative charge in the gamma position.
-These are the two potential starting materials. What are some problems with these reagents?

Acidic H that will react in the presence of base. Solution: change to ester. Converting from ester -> carboxylic acid is easily done through hydrolysis reagents.

Need to make into stabilized enolate so 1,4-addition can occur.

-So which starting materials do we choose? **We will choose the right duo** since all modifications are present on one molecule. The left duo requires modifications from two compounds that might take more work to achieve.
5. Provide an arrow pushing mechanism for the following aldol reaction.

Below is a mechanism for the acidic reaction. Prof. Prescher may have not discussed this in class, but if she tries to throw any tricks your way on the exam, or if anyone is just curious about the acidic mechanism, here it is for reference :)!
6. Provide an arrow pushing mechanism for the following Claisen condensation reaction.
7. Provide an arrow pushing mechanism for the following Dieckmann reaction.
8. Provide an arrow pushing mechanism for the following Michael Reaction.
9. Provide an arrow pushing mechanism for the following Robinson Annulation reaction.