Final Exam Worksheet KEY

**Chapter 16 Concepts: Reactions of Aromatic Compounds**
- mechanisms (2-step) of electrophilic aromatic substitutions
- effects of aromatic substituents on regioselectivity
  - ortho, para, meta
  - inductive, resonance, reactivity
- types of electrophilic aromatic substitutions
  - halogenation
  - nitration
  - sulfonation
  - friedel-crafts alkylation
  - friedel-crafts acylation
- reactions of other benzene derivatives

**Chapter 17 Concepts: Introduction to Carbonyl Chemistry, Organometallic Reagents, and Oxidation and Reduction**
- Types of Carbonyl Compounds and General Reactions
  - nucleophilic addition: aldehydes and ketones
  - nucleophilic substitution: carbonyl compounds with leaving groups
- Reactivity of Aldehyde vs Ketone
- Oxidation Reactions
  - def) an increase in the number of C–Z bonds (usually C–O bonds)
    - ex. aldehydes to carboxylic acids
- Reduction Reactions
  - def) a decrease in the number of C–Z bonds
  - Hydride reduction via nucleophilic addition (LiAlH4, NaBH4)
    - aldehydes and ketones
  - Catalytic hydrogenation to 1° and 2° alcohols (H2, Pd-C)
    - α,β-unsaturated aldehydes and ketones
  - Enantioselective reduction (S-CBS, R-CBS)
    - ketones
  - other reactions of acid chlorides, esters, carboxylic acids to 1° alcohols, amides to amines
- Preparation and Reactions with Organometallic Reagents
- Protecting Groups

**Chapter 18 Concepts: Aldehydes and Ketones - Nucleophilic Addition**
- Nucleophilic Addition Reactions
  - Addition of Hydride (H-) (18.7)
  - Addition of organometallic reagents (R-) (18.7)
  - Addition of cyanide (CN-) (18.8)
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- Wittig reaction (18.9)
- Addition of 1° amines (18.10)
- Addition of 2° amines (18.11)
- Addition of H2O - Hydration (18.12)
- Addition of alcohols (18.13)

- Other reactions
  - Synthesis of wittig reagents (18.9A)
  - Conversion of cyanohydrins to aldehydes and ketones (18.8)
  - Hydrolysis of nitriles (18.8)
  - Hydrolysis of imines and enamines (18.11)
  - Hydrolysis of acetals (18.13)

Chapter 19 Concepts: Carboxylic Acids and Nitriles
- pKa and effects of resonance, inductive effects, etc on pKa
- Protonation of carbonyl O
- Hydrolysis of Nitriles
- Reduction of Nitriles
- Addition of Nitriles to Organometalllics

- Nucleophilic Acyl Substitution
  - Acid chlorides, anhydrides, carboxylic acids, esters, amides
- Nitrile Synthesis
- More Reaction of Nitriles
  - Hydrolysis, reduction, reaction with organometallic reagents
  - Nucleophilic Acyl Substitution
  - Structure, bonding, rates
  - Carbonyl Reactivity and L.G ability
  - Acyl Chloride Reactions
    - DCC, Et3N, and pyridine as solvents
    - Mechanism
- Acid Anhydrides
- Fischer Esterification
  - Ester Hydrolysis
- Saponification
- Hydrolysis of Amides
- Multistep Synthesis
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Chapter 21 Concepts: Enols and Enolates
- 21.1-4 Enol/Enolate Chemistry
  - Tautomerization
    - Acid-Catalyzed
  - 21.5 Racemization of alpha-carbon
  - 21.7 Halogenation at alpha-carbon
    ○ Subsequent elimination of halogen
  - 21.8 Kinetic vs Thermodynamic Enolates
  - 21.9-10 Malonic/Acetoacetic Esters

Chapter 22 Concepts: Carbonyl Condensation Reactions
- The aldol reaction
- Crossed aldol reactions
- Directed aldol reactions
- Intramolecular aldol reactions
- The Claisen reaction
- The crossed Claisen and related reactions
- The Dieckmann reaction
- The Michael reaction
- The Robinson annulation

Chapter 23 Concepts: Amines
- Properties of amines (basicity) and other compounds
- Synthesis reactions
  - Direct nucleophilic substitution with NH3 and amines
  - Gabriel synthesis
  - Reduction methods
  - Reductive amination
- Reactions of amines
  - Reaction as a base
  - Nucleophilic addition to aldehydes and ketones
  - Nucleophilic substitution with acid chlorides and anhydrides
  - Hofmann elimination
  - Reaction with nitrous acid
- Reactions of diazonium salts
1. What starting material(s) is (are) needed to synthesize each compound using an aldol or similar reaction? (3rd Ed 24.33)

a.

b.

c.
d. Locate the α’ and β C’s to the carbonyl group, and break the molecule into two halves at this bond. The α C and all of the atoms bonded to it belong to one carbonyl component. The β C and all the atoms bonded to it belong to the other carbonyl component. Aldol reactions with dicarbonyl compounds can be used to make five- and six-membered rings. The enolate formed from one carbonyl group is the nucleophile, which attacks the electrophilic carbonyl carbon in the same molecule to generate a more stable five-or six-membered ring over the much less stable three-membered ring. Additionally, reactions that synthesize larger rings from smaller ones are called ring expansion reactions (eg. 5-membered ring to 6-membered ring via a two-step sequence using an intramolecular aldol reaction).
2. What crossed Claisen product is formed from each pair of compounds? (3rd Ed 24.16)

a. CH3CH2COOEt and HCO2Et

\[
\text{CH}_3\text{CH}_2\text{CO}_2\text{Et and } \text{HCO}_2\text{Et} \rightarrow \text{H} \quad \text{OEt}
\]

b. CH3(CH2)5CO2Et and HCO2Et

\[
\text{CH}_3(\text{CH}_2)_5\text{CO}_2\text{Et and } \text{HCO}_2\text{Et} \rightarrow \text{H} \quad \text{COEt}
\]

c. (CH3)2C – O and CH3CO2Et

\[
\text{CH}_3\text{C} \quad \text{CH}_3 \quad \text{and} \quad \text{CH}_3\text{C}\text{OEt} \rightarrow \text{O} \quad \text{O}
\]

d. 

\[
\text{O} \quad \text{and} \quad \text{O} \quad \text{COEt} \rightarrow \text{O} \quad \text{O}
\]

In the Claisen reaction, two molecules of an ester react with each other in the presence of an alkoxide base to form a β-keto ester. Because the generation of a resonance-stabilized enolate from the product β-keto ester drives the Claisen reaction, only esters with two or three hydrogens on the α carbon undergo this reaction; that is, esters must have the general structure CH3CO2R' or RCH2CO2R'. A Claisen reaction between two different carbonyl compounds is called a crossed Claisen reaction. In a crossed Claisen reaction between an ester and a ketone, the enolate is formed from the ketone, and the product is a β-dicarbonyl compound (Arrows indicate compounds that form the enolate).
3. Draw a stepwise mechanism for the formation of one C–C bond in polytulipalin (3rd Ed 24.57)

In the Michael reaction, the nucleophile is an enolate. Enolates of active methylene compounds are particularly common. The α,β-unsaturated carbonyl component is often called a Michael acceptor in which the nucleophile attacks at the β carbon. The Michael reaction always forms a new carbon–carbon bond on the α carbon of the Michael acceptor—Polymerization occurs by repeated these reactions.

4. Octinoxate is an unsaturated ester used as an active ingredient in sunscreens. (a) What carbonyl compounds are needed to synthesize this compound using a condensation reaction? (b) Devise a synthesis of octinoxate from the given organic starting materials and any other needed reagents
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a. To determine the two starting carbonyl compounds, identify the α’s and β C’s to the carbonyl group.

```
[1] NaH
[2] CH₃Cl
CH₃O
CH₃OH

[1] Mg
[2] H₂CO

CH₃OH
```

b. Phenol is methylated with methyl chloride (source of good LG) to make anisole. To add a -CHO (aldehyde) para to -OCH₃ (methoxy group), bromination is done followed by the Grignard reaction with a ketone derived from primary alcohol and oxidation as the last step. For the other ester compound, secondary alcohol is oxidized to carboxylic acid (CrO₃) in the presence of
5. Treatment of the amino alcohol $X$ with diethyl carbonate forms the heterocycle $Y$. Draw a stepwise mechanism for this process. (3rd Ed 22.65)

\[
\begin{align*}
\text{X} & \quad \overset{\text{diethyl carbonate}}{\longrightarrow} \quad \text{Y} \\
\text{NH}_2 & \quad \overset{\text{any base} \quad B^+}{\longrightarrow} \quad \text{NH}_2 \\
\text{OH} & \quad \overset{\text{diethyl carbonate}}{\longrightarrow} \quad \text{OH} \\
\text{Y} & \quad \overset{\text{HB}^+}{\longrightarrow} \quad \text{CH}_3\text{CH}_2\text{OH} \quad \text{+ B}^+ \\
\end{align*}
\]

5. (a) Both monomers needed for the synthesis of nylon 6,6 can be prepared from 1,4-dichlorobutane. Write out the steps illustrating these syntheses. (b) Devise a synthesis of adipic acid from cyclohexene. (3rd 22.77)

\[
\begin{align*}
\text{Cl} & \quad \overset{?}{\longrightarrow} \quad \text{H}_2\text{N} \quad \overset{\text{hexamethylenediamine}}{\longrightarrow} \quad \text{amino acid} \\
\text{Cl} & \quad \overset{?}{\longrightarrow} \quad \text{HO} \quad \overset{\text{adipic acid}}{\longrightarrow} \\
\end{align*}
\]
6. Draw the product of each reductive amination reaction (3rd Ed 25.57)

a.  
\[
\begin{align*}
\text{C}_6\text{H}_5\text{CH}_2\text{O} & \xrightarrow{\text{NaBH}_3\text{CN}} \text{C}_6\text{H}_5\text{CH}_2\text{NH} \\
\text{C}_6\text{H}_5\text{CH}_2\text{OH} & \xrightarrow{\text{NaBH}_3\text{CN}} \text{C}_6\text{H}_5\text{CH}_2\text{NH}
\end{align*}
\]

b.  
\[
\begin{align*}
\text{C}_6\text{H}_5\text{CH}_2\text{CHO} & \xrightarrow{(\text{CH}_3)_2\text{NH} \text{ NaBH}_3\text{CN}} \text{C}_6\text{H}_5\text{CH}_2\text{N(}\text{CH}_3\text{)}_2 \\
\text{C}_6\text{H}_5\text{CH}_2\text{CHO} & \xrightarrow{(\text{CH}_3)_2\text{NH} \text{ NaBH}_3\text{CN}} \text{C}_6\text{H}_5\text{CH}_2\text{N(}\text{CH}_3\text{)}_2 \\
\text{C}_6\text{H}_5\text{CH}_2\text{CHO} & \xrightarrow{\text{NH}_3 \text{ NaBH}_3\text{CN}} \text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{NH}_2
\end{align*}
\]
Reductive amination of an aldehyde or ketones adds one alkyl group (from an aldehyde or ketone) to a nitrogen nucleophile. Primary (1°), 2°, and 3° amines can be prepared. Reductive amination replaces a C=O by a C–H and C–N bond in which with a 1° or 2° amine as starting material, reductive amination is used to prepare 2° and 3° amines, respectively. The final product is a more substituted amine.

7. A chiral amine A having the R configuration undergoes Hofmann elimination to form an alkene B as the major product. B is oxidatively cleaved with ozone, followed by CH₃SCH₃, to form CH₂=O and CH₃CH₂CH₂CHO. What are the structures of A and B? (3rd Ed 25.70)

Because –NH₂ is a strong base, elimination wouldn’t happen. Instead, we use the Hofmann elimination to convert an amine into an alkene. In Step [1], the amine reacts as a nucleophile in an SN2 reaction with excess CH₃I to form a quaternary ammonium salt. The N(CH₃)₃ group thus formed is a much better leaving group than –NH₂. Step [2] converts one ammonium salt into another one with a different anion. The silver(I) oxide, Ag₂O, replaces the I– anion with –OH, a strong base. When the ammonium salt is heated in Step [3], –OH removes a proton from the beta carbon atom, forming the new π bond of the alkene. This is the E2 elimination that forms the new π bond.

8. Draw a stepwise mechanism for the following reaction. (3rd Ed 25.72)
Make sure to show all charges and lone pairs when drawing the mechanism.

9. Complete the following reactions. **Consider Stereochemistry.**

a. 

Cyanohydrin formation reaction: nucleophilic substitution attack followed by a deprotonation by HCl

b. 
Wittig reaction: ylide carbon attack on carbonyl then oxygen attacks phosphorus followed by a reverse $[2+2]$ cycloaddition.

10. Complete the following oxidation/reduction reactions in a single step.

a. PCC oxidizes a primary alcohol into an aldehyde by the oxygen of the alcohol attacking the chromium of the PCC which then displaces the chlorine. The chlorine then acting as a base oxidizes the alcohol and reduces the chromium.

b. CrO$_3$ with H$_2$SO$_4$, H$_2$O performs an oxidation reaction converting a primary alcohol into a carboxylic acid by means of adding water to an aldehyde and then oxidizing for a second time to produce a carboxylic acid.

c. 1. LiAlH$_4$
2. H$_2$O
LiAlH₄ is a strong reducing agent that will completely reduce all carbonyls and carboxylic acids. In this mechanism, there is a nucleophilic attack from the hydride anion and then the alkoxide is protonated.

11. Draw the correct product(s).

a. 

\[ \text{Nitration reaction: Nitro group (NO}_2\text{) is added to the benzene through the use of nitric acid (HNO}_3\text{) in the presence of sulfuric acid (H}_2\text{SO}_4\text{). The acid activates the electrophile which then gets attacked by the benzene and then the ring is deprotonated to restore aromaticity and regenerate the acid catalyst.} \]

b. 

\[ \text{Sulfonation reaction: Sulfonic acid (SO}_3\text{H) is added to the benzene through the use of sulfur trioxide (SO}_3\text{) in the presence of sulfuric acid (H}_2\text{SO}_4\text{). The acid activates the electrophile which then gets attacked by the benzene and then the ring is deprotonated to restore aromaticity and regenerate the acid catalyst.} \]
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Sulfonation reaction: Sulfonyl group (SO3H) is added to the benzene through the use of sulfur trioxide (SO3) in the presence of sulfuric acid (H2SO4). Works similarly to the nitration reaction in that it proceeds by the following steps: The acid activates the electrophile which then gets attacked by the benzene and then the ring is deprotonated to restore aromaticity and regenerate the acid catalyst.

12. Draw the organic products formed in each reaction. (20.40 a,b,e)
   a. Nucleophilic Aeryl Substitution with Acid Chloride reacting with an amine: N attacks carbonyl carbon, chlorine gets kicked off, deprotonates the amine.

   ![Nucleophilic Aeryl Substitution](image)

   b. Acetal Mechanism: protonate, loss of ROH, nucleophilic attack, proton transfer makes hemiacetal, proton transfer, loss of ROH, proton transfer.

   ![Acetal Mechanism](image)


   ![Ester Hydrolysis](image)

13. Draw the enol tautomers for each compound (21.32a,b,c)
14. Draw the organic products formed in each reaction (22.48a,b,c,d,e,f)

a. **Aldol**

\[
\begin{align*}
\text{Ketone} & \quad \text{Ketone} \\
\rightarrow & \quad \text{Enol} + \text{Enol} \\
\end{align*}
\]

(based on the conjugation of the enol form, the more stable form)

b. 

\[
\begin{align*}
\text{Ketone} & \quad \text{Ketone} \\
\rightarrow & \quad \text{Enol} + \text{Enol} \\
\end{align*}
\]

14. Draw the organic products formed in each reaction (22.48a,b,c,d,e,f)

a. **Aldol**

\[
\begin{align*}
\text{Ketone} & \quad \text{Ketone} \\
\rightarrow & \quad \text{Enol} + \text{Enol} \\
\end{align*}
\]

(based on the conjugation of the enol form, the more stable form)
b. Aldol

\[
\text{NC}_3\text{H}_7\text{C}=\text{O} + \text{EtOH} \xrightarrow{\text{NaOEt, EtOH}} \text{CN}_{2}\text{H}_{10}\text{O}_{2}\text{Et}
\]


c. Aldol reaction

\[
\text{O} \xrightarrow{[1]} \text{LDA} \xrightarrow{[2]} \text{CH}_3\text{CH}_2\text{CHO} \xrightarrow{[3]} \text{H}_2\text{O}
\]

Robinson Annulation

\[
\text{C}_3\text{H}_5\text{O} + \text{C}_7\text{H}_8\text{CH}=\text{CH}_2 \xrightarrow{\text{NaOCH}_3, \text{CH}_3\text{OH}} \text{C}_9\text{H}_{16}\text{O}
\]
Aldol Condensation

\[
\text{CHO} + \text{H}_2\text{O} \rightarrow \text{C}_{10}\text{H}_{18}\text{O}_2
\]  
\((E\text{ and }Z)\)

e.

Intramolecular Aldol

\[
\text{EtCO} + [1\text{ NaOEt, EtOH}] \rightarrow \text{C}_{10}\text{H}_{18}\text{O}_2
\]  
\[\text{[2]H}_2\text{O}^{+}\]

f.

15. Draw the organic products formed in each reaction (23.56a,b,c,d,g)
a. **Sn2**

\[
\text{CH}_2\text{Cl} \rightarrow \text{NH}_2
\]

excess

 excess
b. KOH reacts to make potassium phthalimide where water is eliminated. Then, haloalkene is added and the alkyl group is attached to the phthalimide part where the potassium halide is eliminated.

\[
\begin{align*}
\text{[1] KOH} \\
\text{[2] (CH}_2\text{CHCH}_2\text{Cl)} \\
\text{[3] } \text{OH, H}_2\text{O}
\end{align*}
\]

\[\text{O} \quad \text{H} \quad \text{NH}_2 \quad \text{CO}_2 \quad \text{CO}_2\]

\[\text{b. KOH reacts to make potassium phthalimide where water is eliminated. Then, haloalkene is added and the alkyl group is attached to the phthalimide part where the potassium halide is eliminated.}\]

\[
\begin{align*}
\text{c. Reduction of NO}_2 \text{ to NH}_2 \\
\text{Br} \\
\text{Br} \\
\text{NO}_2 \\
\text{Br} \\
\text{NH}_2
\end{align*}
\]

\[\text{c. Reduction of NO}_2 \text{ to NH}_2\]

\[\text{d. Reduction of Nitrile Triple Bonds (CN to CH}_2\text{NH}_2)\]

\[\text{e. Diazonium salt formation: diazonium salts are produced by taking an alkyl or aryl primary amine and adding to it with sodium nitrite.}\]
Extra Practice:

16. Synthesize each compound from benzene. (3rd Ed 18.34)

a.

b.

Both are o,p directors, but they are meta to each other. The alkyl group must be obtained by reduction of a carbonyl.

c.
Most Friedel–Crafts reactions (alkylation and acylation) involve carbocation electrophiles to form new carbon–carbon bonds. Note that the carbocations derived from vinyl halides and aryl halides do not undergo Friedel-Crafts alkylation since they are highly unstable and do not readily form.

17. Explain why the pKa of compound A is lower than the pKa's of both compounds B and C. (3rd Ed 19.45)

The O in A is more electronegative than the N in C so there is a stronger electron-withdrawing inductive effect. This stabilizes the conjugate base of A, making A more acidic than C. Since the O in A is closer to the COOH group than the O atom in B, there is a stronger electron-withdrawing inductive effect. This makes A more acidic than B.