Exam II Study Guide

Section Agenda
1) Problem Set #5 will be graded by Wednesday
2) Handout: Exam II Study Guide
3) Handout: Practice Exam II
4) Handout: Practice Exam II Solutions

General Advice
- Do practice problems. Start with problems associated with the course (do the practice exam, redo the problem sets, do the section practice problems, do the problems in the lecture notes, do the problems on the database). Next, consider doing problems from the Chem 206 database. Problems from the book are good as skill drills for learning reactions.
- Consider reviewing the lecture slides from Chem 206. A number of problems from the last exam are basic/fundamental concepts covered in Chem 206. The lecture notes are posted online.

Common Errors
- Make sure that your mechanisms clearly indicate whether a process is stepwise or concerted. For instance, acetal opening is stepwise (1. protonation, 2. neutral alcohol leaves to form a resonance stabilized carbocation, 3. water attacks...). This is not a concerted $S_N2$ process, so draw out the intermediates.
- Make sure to protect all protic functionality (e.g. carboxylic acids, alcohols) when doing additions of Grignard and alkylthium reagents.
- As we discussed last week, make sure that your mechanisms are consistent with the conditions (acidic vs. basic). You will not have hydroxide or alkoxide leaving or attacking in acid.
- Do not use $H_2O$ as a reagent in a mechanism unless you are told it is in the reaction mixture.

Some Material (there is so much more than just this)
- Make sure you are familiar with diazotization of amines and the Sandmeyer reactions
- Make sure you are familiar with the Baeyer-Villiger oxidation and the Beckmann rearrangement
- In problems with a phosphine, look to form the oxide. In problems with hydrazines, look for an alkyl shift or a way to eliminate nitrogen.
- Axial (preferred unless nucleophile is bulky) vs. Equatorial attack of cyclohexanone.

Synthetic Strategy
1) See if the synthons you are given suggest an obvious forward step
2) Try “mapping” the synthons on to portions of the target. If you can figure out where a synthon “fits into the puzzle,” you can then worry about the proper reactions to establish the connectivity.
3) If these methods don’t work, take your target molecule and go back one reaction at a time. Upon going back, see if it is now more obvious how to work forward from the starting materials. Try to put the most complicated steps towards the end of your synthesis.
4) Practice! The best way to learn how to do these problems is to learn from mistakes.
Some Synthetic Transforms

These are some transforms that you may have forgotten about or never thought of. These routes are not necessarily the best way to make each class of target compounds.

**Symmetric Carboxylic Acid Derivatives**

\[
\begin{align*}
\text{RX} & \quad \overset{\text{O} \underset{\text{O}}{\text{O}}}{\text{n}} \quad \text{XR} \\
\rightarrow & \quad \Delta \\
\text{n} & \quad + \\
\end{align*}
\]

1) \(O_3\)  
2) \(\text{H}_2\text{O}_2, \text{NaOH}\)  
3) DCC, \(R \rightarrow \text{XH}\)

**Esters**

\[
\begin{align*}
\text{O} \quad \overset{\text{O} \underset{\text{X}}{\text{O}}}{\text{R}} \quad \text{R} \\
\rightarrow & \quad \text{R} \quad + \\
& \quad \text{RCO}_2\text{H} \\
& \quad \text{or} \\
\text{O} \quad \overset{\text{R} \underset{\text{X}}{\text{R}}}{\text{R}} \\
\end{align*}
\]

1) \(\text{R}^2\text{MgBr} (2 \text{ eq.})\)  
2) \(\text{H}_3\text{O}^+\)

**Substituted Alcohols**

\[
\begin{align*}
\text{HO} \quad \overset{\text{R} \underset{\text{R}}{\text{R}}}{\text{R}} \\
\rightarrow & \quad \text{O} \quad + \\
\text{R} \quad & \quad \text{CO} \quad \text{R} \\
\end{align*}
\]

1) \(\text{R}^2\text{MgBr}\)  
2) \(\text{H}_3\text{O}^+\)  
3) DMP

**Substituted Amines**

\[
\begin{align*}
\text{R}^3 \quad \text{N} \quad \text{CH}_2\text{R}^2 \\
\rightarrow & \quad \text{R}^1\text{-NH}_2 + \\
& \quad \text{R}^2\text{CHO, NaBH}_3\text{CN, pH 5} \\
& \quad \text{NaBH}_3\text{CN, pH 5} \\
\end{align*}
\]

1) \(\text{NH}_2\text{OH, pH 5}\)  
2) TsCl, pyridine

**Substituted Amides**

\[
\begin{align*}
\text{R}^1 \quad \text{NH} \quad \text{R}^2 \\
\rightarrow & \quad \text{R}^1\text{R}^2\text{R}^3 \quad + \\
& \quad \text{R}^3\text{MgBr} \\
& \quad \text{H}_3\text{O}^+ \\
& \quad \text{H}_3\text{O}^+ \\
\end{align*}
\]

1) \(\text{NH}_2\text{OH, pH 5}\)  
2) TsCl, pyridine

**Chiral Alcohols**

\[
\begin{align*}
\text{OH} \quad \overset{\text{O}}{\text{R}} \\
\rightarrow & \quad \text{O} \quad + \\
& \quad \text{Zn(BH}_4)_2 \\
\end{align*}
\]

1) E.A.S. w/ \(X^1\) (+)  
2) SnCl\(_2\)/HCl

**meta Substituted Benzene Derivatives**

\[
\begin{align*}
\text{X}^1 \quad \text{X}^2 \\
\rightarrow & \quad \text{NO}_2 \quad + \\
& \quad \text{X}^1 = \text{Br, Cl, COR} \\
& \quad \text{X}^2 = \text{Br, Cl, I, F, OH, H} \\
& \quad 1) \text{E.A.S. w/ X}^1\) (+) \\
& \quad 2) \text{SnCl}_2/\text{HCl} \\
& \quad 3) \text{NaNO}_2/\text{HCl} \\
& \quad 4) \text{Sandmeyer rxn for X}^2
\end{align*}
\]
Carboxylic Acids

\[
\begin{align*}
\text{R} & \quad \text{O} \\
\text{ROH} & \quad \text{R}_3\text{Br}
\end{align*}
\]

1) KCN 2) H$_3$O$^+$, heat

Substituted Amides

\[
\begin{align*}
\text{R}^1 & \quad \text{N} \quad \text{R}^2 \\
\text{R}^1\text{N} & \quad \text{R}^2
\end{align*}
\]

1) BuLi 2) R$_2$–I 3) BuLi 4) R$_3$–I

Amines

\[
\begin{align*}
\text{R}^1 & \quad \text{N} \quad \text{R}^2 \\
\text{R}^1\text{N} & \quad \text{R}^2
\end{align*}
\]

1) LiAlH$_4$ 2) H$_3$O$^+$, heat

Some Common Reduction-Oxidation (Redox) Reagents

Oxidants

- **DMP**: 2$^\circ$ alcohols → ketones, 1$^\circ$ alcohols → aldehydes
- **PCC or CrO$_3$**: 1$^\circ$ alcohols → aldehydes (basic, anhydrous conditions)
- **HCrO$_4$**: 1$^\circ$ alcohols → carboxylic acids, 2$^\circ$ alcohols → ketones (fairly harsh)
- **O$_3$**: olefins → aldehydes
  olefins → carboxylic acids (w/ DMS or Zn/AcOH workup)
  olefins → allylic bromides (w/ H$_2$O$_2$, NaOH workup)
- **NBS**: aryl hydrocarbons → benzyl bromides
  olefins → allylic bromides
- **RCOOOH**: olefins → epoxides
  ketones → esters (Baeyer-Villegar)

Reductants

- **NaBH$_4$**: ketones, aldehydes → alcohols (Felkin product)
- **Zn(BH$_4$)$_2$**: ketones, aldehydes → alcohols (chelation control product)
- **NaBH$_3$CN**: protonated imines (pH 5) → amines (used in reductive aminations)
- **DIBAL-H**: esters → aldehydes (relatively mild conditions)
- **LiAlH$_4$**: carboxylic acids → 1$^\circ$ alcohols
  amides, imines → amines (harsh conditions)
- **RLi**: aldehydes → 2$^\circ$ alcohols; esters, ketones → 3$^\circ$ alcohols (Grignard)
- **RMgBr**: aldehydes → 2$^\circ$ alcohols; esters, ketones → 3$^\circ$ alcohols (Grignard)
- **RZnCl**: acid chlorides → ketones (won’t add to ketones)
Protecting Groups

**Alcohols**

\[ R\text{OH} \xrightarrow{TsOH} R\text{-O\text{TsOH}} \xrightarrow{H_3O^+} R\text{OH} \]

\[ R\text{OH} \xrightarrow{TBSCI, pyridine} R\text{-OTBS} \xrightarrow{TBAF} R\text{OH} \]

**Glycols (1,2-Diols)**

\[ HO\text{-R-O-R-}OH \xrightarrow{TsOH} \xrightarrow{H_3O^+} \]

**Ketones and Aldehydes**

\[ \text{R-C=O} \xrightarrow{\text{HO-OR}} \xrightarrow{H_3O^+} \text{R-C=O} \]

**Hemiacetals**

\[ \text{OCH}_3 \xrightarrow{\text{TsOH}} \xrightarrow{H_3O^+} \text{OH} \]

**Carboxylic Acids**

\[ \text{RCOOH} \xrightarrow{\text{CH}_2\text{N}_2} \xrightarrow{\text{LiOH, MeOH/H}_2\text{O}} \text{RCOOH} \]

\[ \text{RCOOH} \xrightarrow{\text{Br, DBU}} \xrightarrow{H^+} \text{RCO}_2\text{Bu} \]

Take note of orthogonal protecting groups that are removed with different conditions so you can selectively deprotect one group at a time.