Aldehyde and Ketone Chemistry:
Electrophilic at the carbonyl carbon, basic on oxygen
Hydride reducing agents
LiAlH$_4$, NaBH$_4$
Nucleophiles add to the carbonyl carbon
Carbanions: Grignards, alkyl lithuims, others
Amines: Formation of imines and enamines
Alcohols: Formation of acetals, hemiacetals
Review Chapter 19.
Review Chapter 20, sections 20.7 and 20.13.
Read Chapter 22. The first several sections are ‘general interest’ reading.
Interesting esters and amides

Nylon 6-6

Kevlar

Nomex
Interesting esters and amides

Aspartame

Met-enkephalin
Interesting lactones and lactams

Erythromycin

Penicillin G

Cefradine
Some ‘issues’

The question of the nucleophilic (or basic) oxygen in an ester or acid – what is acceptable?
Carboxylic Acid Derivatives, including acid chlorides, anhydrides, esters, amides, and nitriles.

Recognize that these same kinds of derivatives can be made from many other acids, including sulfur-based acids (sulfates, sulfonates), and phosphoric acids (phosphates).
What you should remember from the last lecture

The reactivity of different carboxylic acid derivatives toward nucleophilic acyl substitution: Acid chlorides (most reactive), Anhydrides, Esters, Amides (least reactive)

Fisher Esterification – Acid catalyzed condensation of an acid and an alcohol to form an ester.
What you should remember from the last lecture

- **Nucleophilic Acyl Substitution.** This process adds an acyl group (RC=O) to a nucleophile.
- **Ester formation from alcohols and acids** is reversible under acidic condition. Base hydrolysis is **saponification**.
- **Formation of Acid Chlorides.** Reaction of an acid with thionyl chloride (SOCl₂) produces an acid chloride.
- **Formation of esters and amides from acid chlorides,** and formation of amides with diimides.
Read Chapter 23 through section 23.8
Clarification from the last lecture

Dicyclohexylurea (DCU)
Some ‘issues’

The question of the mechanism of amide formation using carbodiimides (like DCC)....

Design an experiment that will distinguish between these two pathways.
Putting it into practice....

1. Reaction 1: 
   - **Starting Materials:** Cyclohexanone and 2-propanol. 
   - **Catalyst:** $\text{H}_2\text{SO}_4$. 
   - **Product:** Esterification of cyclohexanone with 2-propanol.

2. Reaction 2: 
   - **Starting Materials:** 2-Methylbutan-2-one and 2-propanol. 
   - **Catalyst:** DCC (Dicyclohexylcarbodiimide) and $\text{CH}_3\text{NH}_2$. 
   - **Product:** Esters of 2-Methylbutan-2-one with 2-propanol.

3. Reaction 3: 
   - **Starting Materials:** 2-Methylpentan-2,4-diol. 
   - **Catalyst:** $\text{SOCl}_2$. 
   - **Product:** Chlorinated esters of 2-Methylpentan-2,4-diol.

4. Reaction 4: 
   - **Starting Materials:** An unknown diol. 
   - **Product:** An unknown compound, possibly involving cyclic hexanone.

Chemical Structures:
- Cyclohexanone
- 2-Propanol
- 2-Methylbutan-2-one
- 2-Methylpentan-2,4-diol
- Dicyclohexylcarbodiimide (DCC)
- $\text{CH}_3\text{NH}_2$ (Methylamine)
- $\text{SOCl}_2$ (Sulfuryl Chloride)
What you should remember from the last lecture

Reactions of Acids, Esters, and Amides:

**Fisher Esterification** – Acid catalyzed condensation of an acid and an alcohol.

**Saponification** – Hydrolysis of esters under basic conditions.

**Hydrolysis** of amides, esters, and nitriles under acidic and under basic conditions.

**Transesterification** and **ester-amide exchange**
Putting it into practice....
Putting it into practice....

[Chemical structures and reactions depicted in the image]
Putting it into practice....

Amino acid esters are rarely stored as the free amines, but instead as the amine hydrochloride salt. Why?
Fisher Esterification of the hydroxy acid below could result in cyclization or in polymerization. What conditions would favor each pathway?

Cyclization: *Low concentration (to slow down bimolecular reactions).*
Polymerization: *High concentration.*
Where would you rank a thioester?

Acetyl-CoA (Acetyl-SCoA)
Some reactions of Acetyl-CoA

Acetyl-CoA (Acetyl-SCoA) → Choline synthase (an acetyl transferase) → Acetyl Choline (a neurotransmitter)

Oxaloacetate → Citrate synthase → Citrate (+ HS-CoA)

Key step in the Tricarboxylic acid cycle (aka the Krebs cycle) that is fundamental to aerobic metabolism.
What you should remember from the last lecture

**Enols and Enolates.** Formation, mechanism, acid strengths. pKa (for a ketone) is ~ 20.

**Halogenation of enols and enolates.** Monohalogenation occurs under acid (enol) conditions, but polyhalogenation tends to occur under basic (enolate) conditions.

**Enolates are ambident nucleophiles,** but are typically more nucleophilic at carbon than at oxygen, even if the oxygen has more negative charge in the hybrid.
What you should remember from the last lecture

Formation of Enols and Enolates by deprotonation of carbonyl compounds.

Thermodynamic (more highly substituted) enolates: Favored by strong bases (NaOEt), protic solvents (EtOH), and warm temperatures (25 °C)

Kinetic (less substituted) enolates: Favored by strong, hindered bases (LDA), aprotic solvents (THF) and low temperatures (-78 °C)
What you should remember from the last lecture

**Thermodynamic and Kinetic Enolates.** Moderate base/protic solvents/warm temperatures favor the thermodynamic enolate. Strong base (LDA), aprotic solvent (THF), and low temperatures favor the kinetic enolate.

**Alkylation of enolates with alkyl halides**
- C-alkylation rather than O-alkylation.

**Acetoacetic Ester Syntheses**
- Equivalent to alkylation of acetone. Uses very mild conditions.
Putting it into practice....
Putting it into practice....

\[ \text{CO}_2\text{Et} \quad \text{is} \quad \text{EtO} \quad \text{is} \]

1. NaOH, H\(_2\)O
2. HCl, H\(_2\)O
Putting it into practice....
Putting it into practice....

1. $\text{NaOH}$
2. $\text{HCl}, \text{H}_2\text{O}$
Putting it into practice....
Putting it into practice....

How could this compound be made?

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Practice! How could this be made?

1. **SOCl₂**
   2. **NH₃**

1. **NaOEt**
2. **EtBr**

1. **NaOH, H₂O**
2. **HCl, H₂O**

Putting it into practice....

1. NaOEt, EtOH
2. Et-Br

1. LDA, THF, -78˚
2. Et-Br

1. NaOEt, EtOH
2. Et-Br

cat. TsOH
Something to think about....

1. PhCH₂Br
2. H₃O⁺
What you should remember from the last lecture

Malonic Ester and Acetoacetic Ester Syntheses
Equivalent to alkylation of acetic acid and to alkylation of acetone, respectively. Uses very mild conditions.
Exam 3 is Wednesday

Every exam is cumulative.

This exam will cover material through the end of Chapter 23.
Something to think about....
Putting it into practice....

Will this work?

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\begin{align*}
\text{EtO}_2\text{C} - \text{CO}_2\text{Et} & \quad \text{Br} \quad \text{NaOEt} \quad \text{EtO}_2\text{C} - \text{CO}_2\text{Et} \\
\text{O} & \quad \text{Br} & \quad \text{NaOEt} & \quad \text{Br} & \quad \text{NaOEt} & \quad \text{Br} & \quad \text{NaOEt} & \quad \text{Br} & \quad \text{NaOEt} & \quad \text{Br} & \quad \text{NaOEt}
\end{align*}
\]

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\begin{align*}
\text{YES} & \quad \text{Ugh}....
\end{align*}
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\begin{align*}
\text{EtO}_2\text{C} - \text{CO}_2\text{Et} & \quad \text{Br} \quad \text{NaOEt} \quad \text{EtO}_2\text{C} - \text{CO}_2\text{Et} \\
\text{O} & \quad \text{Br} & \quad \text{NaOEt} & \quad \text{Br} & \quad \text{NaOEt} & \quad \text{Br} & \quad \text{NaOEt} & \quad \text{Br} & \quad \text{NaOEt} & \quad \text{Br} & \quad \text{NaOEt}
\end{align*}
\]

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\begin{align*}
\text{E}_{1_{\text{CB}}}
\end{align*}
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Putting it into practice....
Practiced!
What’s the product, and how?

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\text{CH}_3\text{OH, cat. TsOH} \rightarrow \text{CH}_3\text{O} - \text{C} - \text{CH}_3\text{OH}
\]
Why do diet sodas go bad?

Aspartame

Acid-catalyzed hydrolysis of the methyl ester!

Solvent: Water with Phosphoric Acid......
Synthesis practice

Target:

Requirements: any inorganic reagents, ethyl acetoacetate, any organic reagents of 4 C’s or less.

Immediately the problem is simplified to the question of how do you make this acid and this amine.
Synthesis practice

1. Mg
2. CO$_2$
3. HCl, H$_2$O

1. NaOH, H$_2$O
2. HCl, H$_2$O

EtNH$_2$, cat TsOH

NaBH$_4$
What you should remember from the last lecture

Malonic Ester and Acetoacetic Ester Syntheses
Equivalent to alkylation of acetic acid and to alkylation of acetone, respectively. Uses very mild conditions.
Changes to the Grading Scale

The cutoffs for A’s and B’s remains the same. The cutoff for earning a C has been changed to 55% (from 60%), and for passing it is now set at 40% (from 50%).