Unit 4

Carboxylic Acids and Derivatives

4.23 Carboxylic Acids Intro

10/30:

- Lecture 22 recap.
  - A. Amine synthesis by direct S_N2 (of, for example, NH_3) leads to mixtures unless you use a very large excess of ammonia (Figure 3.13).
    - Alternative: Gabriel synthesis (Figure 3.14).
    - Alternative: Conversion of a primary or secondary alkyl halide to an azide and subsequent reduction (Figure 3.15).
  - B. Reductive amination is an incredibly powerful technique (Figures 3.16, 3.17, & 3.18).
    - It can build primary, secondary, and tertiary amines.
    - Be intimately familiar with this process for Exam 3!!
  - C. Acylation/reduction is also a great method (Figure 3.19).
    - Acylate the amine to give an amide intermediate, reduce with LAH, and quench with water.
  - D. Primary and secondary alkyl bromides, iodides, and tosylates can be substituted to the nitrile and reduced to an amine (Figure 3.21).
    - This is a 1-carbon homologation.
  - E. HONO (generated from $NaNO_2 + HCl$) converts aniline to an aryl diazonium salt (Figure 3.24).
- Announcement: The notes taken by the TFs are posted on Canvas (that's these!).
  - Consider referring to these even over the ones that Prof. Buchwald provides.
- Lecture 22 continued.
- Using the sequence of reaction in Figure 3.25, you can form an aryl diazonium salt.
  - Treating it with KI yields an aryl iodide.
  - Treating it with H_2O yields a phenol.
  - Treating it with hypophosphorus acid (H_3PO_2) yields benzene again.
    - Once again, you are not responsible for the name "hypophosphorus acid."
  - Treating it with CuX (where $X = Cl, Br, CN$) yields PhX.
- This is a great example of what we do with synthesis!
  - Synthesis is all about connecting compounds with transformations.
  - Breaking down the example in such a way is called **retrosynthetic analysis**.

- Recall from last time that azides are reduced to amines by $LiAlH_4$ and a subsequent water workup (Figure 3.15). Here's a further note on this.

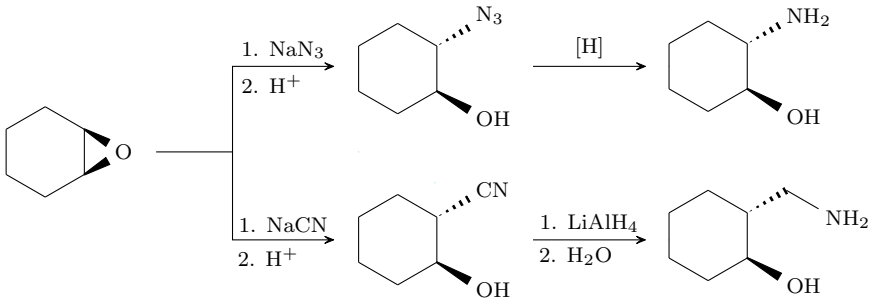


Figure 4.1: Aminoalcohol synthesis from epoxides.

  - Recall from 5.12 that **epoxides** are essentialy just reactive ethers, due to their ring strain.
  - Therefore, if we treat an epoxide with NaN_3, we'll get a backside attack that yields a certain intermediate.
  - Then upon reduction, we get a *trans*-1,2-aminoalcohol.
    - This is an important functional group for β-blockers in biology!
  - Alternatively, we can treat epoxides with CN^-, yielding the cyanoalcohol.
    - We can then reduce this to the 1,3-aminoalcohol.

- This concludes our discussion of amines.
- Today: Introduction to carboxylic acids and their derivatives.
  - Reading: Chapter 10 of Clayden et al. (2012).
- Lecture outline.
  1. Introduction.
  2. Synthesis of carboxylic acids.
     a. Oxidation of alcohols and aldehydes.
     b. Carboxylation of Grignard reagents.
     c. Hydrolysis of nitriles.
     d. Types of carboxylic acid derivatives.
  3. Acyl transfer reactions.
     a. Background.
- We'll begin with Topic 1: Introduction.
- **Carboxylic acid derivative**: A compound of the following form, where $X \neq H, R$. *Structure*

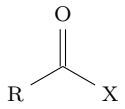


Figure 4.2: Carboxylic acid derivative.

  - Since X is *not* equal to H or R, we're not considering aldehydes or ketones.

- **Carboxylic acid**: A carboxylic acid derivative for which X = OH. *Structure*

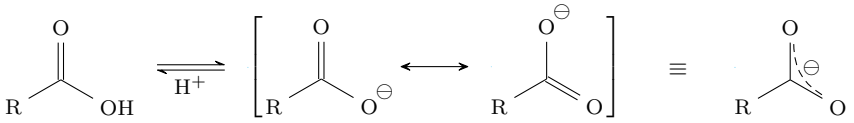


Figure 4.3: Carboxylic acid.

  - $pK_a \approx 5$.
    - By comparison, $pK_a \approx 16$ for an alcohol.
    - Therefore, carboylic acids are *eleven orders of magnitude* more acidic than alcohols.
  - Deprotonation gives us a resonance-stabilized **carboxylate**, which can be drawn either as resonance forms or as a delocalized anion.

- One of the simplest carboxylic acids is **acetic acid**.

- **Acetic acid**: The carboxylic acid for which R = Me. *Structure*

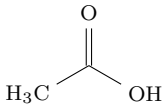


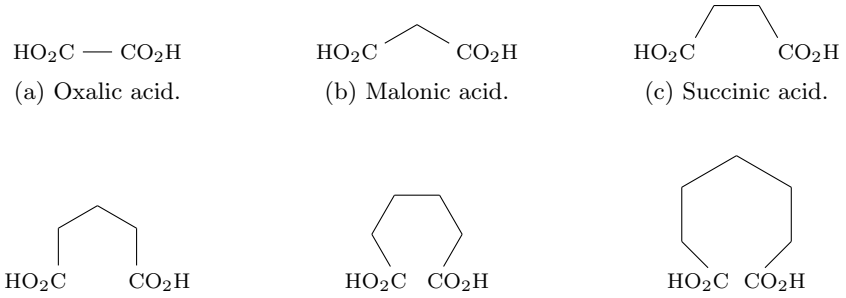
Figure 4.4: Acetic acid.

  - Acetic acid is in vinegar! In fact, vinegar is about 4-5% acetic acid in water.
  - Acetic acid is also used as an industrial solvent (in the 100% pure form, which is quite caustic).
  - How is acetic acid made?

$$\mathrm{MeOH} \xrightarrow[\text{cat}]{\mathrm{CO}} \mathrm{CH_3COOH}$$

    - Acetic acid is produced industrially via the Monsanto acetic acid process, which carries out the carbonylation of methanol using a rhodium catalyst.

- The first several biscarboxylic acids.



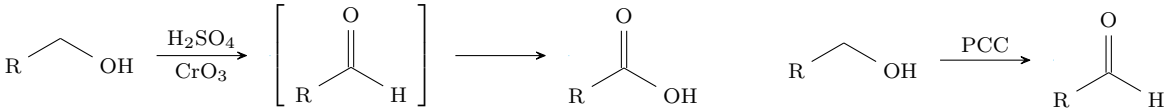
(a) Oxalic acid. (b) Malonic acid. (c) Succinic acid.

(d) Glutaric acid. (e) Adipic acid. (f) Pimelic acid.

Figure 4.5: Biscarboxylic acids.

  - **Oxalic**, **malonic**, **succinic**, **glutaric**, **adipic**, and **pimelic** acids.
  - Aside: Adipic acid is really important because it's involved in the manufacture of nylon.
  - How do you remember all these names? There's a neumonic: OMSGAP or "Oh My, Such Good Apple Pie."

- We now move onto Topic 2: Synthesis of carboxylic acids.
- Aside: A new definition of **oxidation** and **reduction**.
  - Notice that in a carboxylic acid (e.g., see Figure 4.4), the central carbon has 3 bonds to oxygen.
  - In contrast, a primary alcohol's central carbon has 1 bond to oxygen.
    - Thus, we need to do a 4-electron oxidation to turn an alcohol into a carboxylic acid.
  - An aldehyde's central carbon has 2 bonds to oxygen.
    - Thus, we need to do a 2-electron oxidation to turn an aldehyde into a carboxylic acid.
  - CO_2's central carbon has 4 bonds to oxygen.
    - Thus, we need to do a 2-electron reduction to turn CO_2 into a carboxylic acid.
  - This array of related compounds motivates the following two definitions.
- **Oxidation**: A chemical reaction that increases the number of carbon-oxygen bonds.
- **Reduction**: A chemical reaction that decreases the number of carbon-oxygen bonds.
- We now discuss Subtopic 2.a: Oxidation of alcohols and aldehydes.



(a) Primary alcohol or aldehyde to carboxylic acid. (b) Primary alcohol to aldehyde.

Figure 4.6: Oxidation of alcohols and aldehydes.

  - Suppose you have a primary alcohol.
    - To convert it into a carboxylic acid, treat it with **Jones reagent**.
      - ➢ The mechanism proceeds through the aldehyde.
      - ➢ However, it can't stop, so it goes all the way to carboylic acid.
    - To stop the oxidation at the aldehyde, use PCC!
  - Now suppose you're starting at the aldehyde.
    - To convert it to the carboxylic acid, just subject it to Jones reagent conditions! This is like picking up in the middle of the Figure 4.6a mechanism.
  - Relevant reading: Clayden et al. (2012, pp. 194–196).
- **Jones reagent**: The combination of excess H_2SO_4 and CrO_3.
- We now discuss Subtopic 2.b: Carboxylation of Grignard[1] reagents.

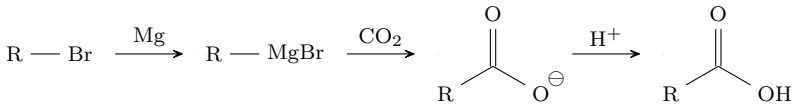


Figure 4.7: Carboxylation of Grignard reagents.

[1] "GRIN-yurd"

  - To make a Grignard reagent, react an alkyl bromide with magnesium.
    - Aside (chemis-tea): Victor Grignard won the Nobel Prize for Grignard reagents, even though his mentor invented them!
    - Note that Grignard reagents are very reactive! They are strong bases and strong nucleophiles, so if there's an acidic hydrogen in solution, it will get deprotonated.
      - ➢ Essentially, we have to consider the functional group tolerance of a method.
    - These reactions are fun to do in the lab!
  - Once you make the Grignard reagent, just throw dry ice (a source of CO_2) into the flask. There will be a bunch of bubbling, and we'll get our carboxylic acid.

- We now discuss Subtopic 2.c: Hydrolysis of nitriles.

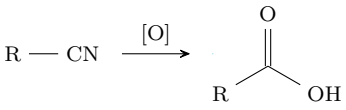


Figure 4.8: Nitrile hydrolysis.

  - Two ways to do this.
    - Acid (H_3O^+) and heat (Δ).
    - Base (HO^-), water (H_2O), and heat (Δ) followed by subsequent quenching with acid and heat.
  - Nitriles are *really, really, really* good intermediates (hint for Exam 3!!).

- We'll now look at how nitriles may come up in a typical test question.
- Typical test question (TTQ): Provide two ways to convert benzyl bromide into phenylacetic acid.

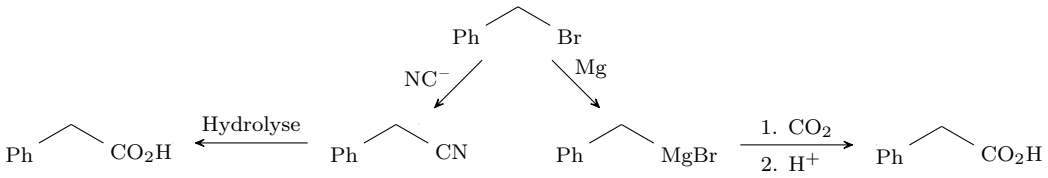


Figure 4.9: Typical test question: Multiple synthetic paths.

  - First way: Make the Grignard and add CO_2.
  - Second way: Do an S_N2 with CN^-, and then hydrolyze the nitrile.
  - Note that Prof. Buchwald uses checkmarks to denote the product on the board.

- If we're answering a test question like this, will you want two separate arrows, or is one arrow with "1. *reagent*" above and "2. *reagent*" below?
  - Either is good.

- We now discuss Subtopic 2.d: Types of carboxylic acid derivatives.
- **Acid chloride**: A carboxylic acid derivative for which X = Cl. *Structure*

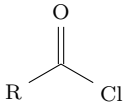


Figure 4.10: Acid chloride.

  - These are far more common than acid bromides or acid iodides.[2]
  - To convert a carboxylic acid into an acid chloride, use $SOCl_2$ and pyridine.[3]
  - Mechanism: Clayden et al. (2012, pp. 214–215).

- **Acid anhydride**: A carboxylic acid derivative for which $X = RCO_2$. *Structure*

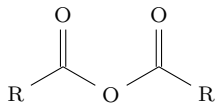


Figure 4.11: Acid anhydride.

  - Synthesize these from two carboylic acids that combine and release water.

- Example of an acid anhydride: Phthalic anhydride.

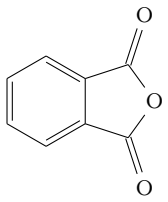


Figure 4.12: Phthalic anhydride.

- **Ester**: A carboxylic acid derivative for which $X = OR'$. *Structure*

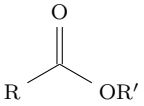


Figure 4.13: Ester.

  - Esters are common in scents and smells.

- Example of an ester: Isoamyl acetate.

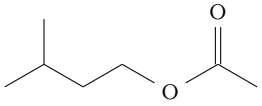


Figure 4.14: Isoamyl acetate.

  - This is the odor of banana oil! The infinite corridor smells like this because of the Banana Lounge.
  - There are easy ways to make this chemical that can legally be described as natural, even if it did not come from a banana.

[2] Coincidentally, acid iodides are used in the Monsanto acetic acid process!
[3] See the 5.12 equation review sheet!!

- **Lactone**: A cyclic ester. *Example*

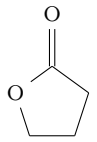


Figure 4.15: γ-butyrolactone.

- **Amide**: A carboxylic acid derivative for which X = NR′R″. *Structure*

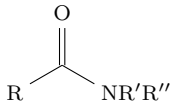


Figure 4.16: Amide.

- Example of a (poly)amide: Nylon.

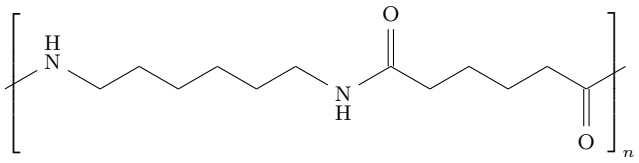


Figure 4.17: Nylon.

- **Lactam**: A cyclic amide. *Example*

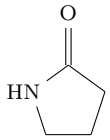


Figure 4.18: 2-Pyrrolidone.

  - Lactams are incredibly imporant; many of us are only alive because of lactams.

- Examples of lactams: The penicillins, a class of molecules that changed the world.

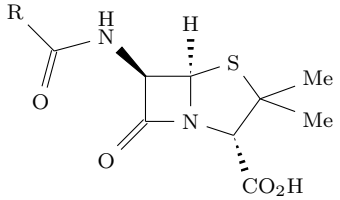


Figure 4.19: Penicillin core structure.

  - Varying R yields different penicillins; all penicillins share the core motif above, though.
  - Penicillins were discovered by Alexander Flemming and changed the course of the world wars.
  - Penicillin and amoxycillin are both β-lactam antibiotics.

- We now move onto Topic 3: Acyl transfer reactions.
- Subtopic 3.a: Background.
- For each X group in a carboxylic acid derivatives, let's see how good of a leaving group it is.

X	Cl	RCO_2	OR	NR_2	O^-
pK_a (HX)	-7	5	16	≈ 35	VERY HIGH

Table 4.1: Leaving groups in carboxylic acid derivatives.

  - To be clear, we're measuring the pK_a's of the following reactions.

$$HX + H_2O \rightleftharpoons X^- + H_3O^+ \qquad K_a = ?$$

    - Example: $HCl + H_2O \rightleftharpoons Cl^- + H_3O^+$.
    - Example: $HO^- + H_2O \rightleftharpoons O^{2-} + H_3O^+$.
  - pK_a — a theromodynamic parameter — is a good measure of how good of a leaving group something is.
    - Important because acyl transfer reactions involve an X group from Table 4.1 departing.
    - Thus, knowing how stable the X group is after leaving as a conjugate base in an acid reaction can help us predict how stable it will be as a departed nucleophile in an acyl transfer reaction, and hence how likely a proposed acyl transfer reaction is to proceed.
- Let's now investigate the resonance stabilization of each of our carboxylic acid derivatives.

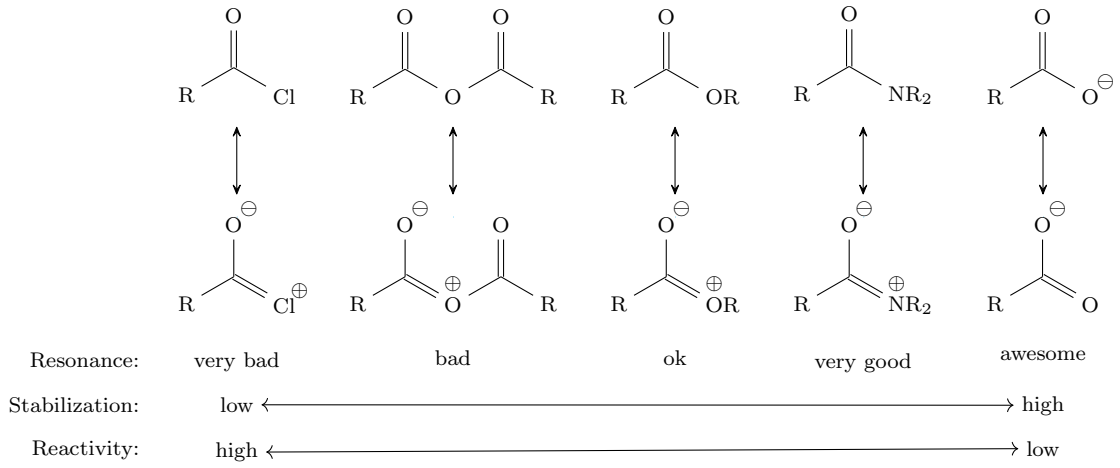


Figure 4.20: Resonance stabilization of carboxylic acid derivatives.

  - The lone pairs on chlorine are high energy, so we can get some degree of resonance, but the resonance structure is very bad.[4]
  - Keep in mind that we have "awesome" resonance *only* for the deprotonated, carboxylate form of a carboxylic acid; carboxylic acids, themselves, aren't nearly as stabilized.
  - Stability and reactivity are clearly inversely related; it should make sense that the less stable something is, the more reactive it is!
- From Table 4.1 and Figure 4.20, we can see that the better leaving groups form more reactive carboxylic acid derivatives, and vice versa!

[4]Think about MOs! Big energy difference means bad mixing and hence poor conjugation