

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.

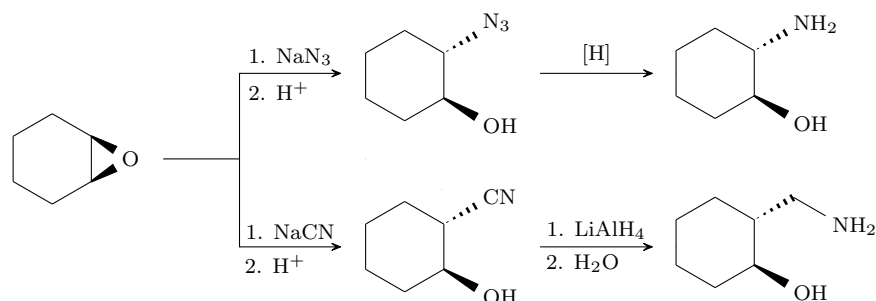


Figure 4.1: Aminoalcohol synthesis from epoxides.

- Recall from 5.12 that **epoxides** are essentially 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.
 - Introduction.
 - Synthesis of carboxylic acids.
 - Oxidation of alcohols and aldehydes.
 - Carboxylation of Grignard reagents.
 - Hydrolysis of nitriles.
 - Types of carboxylic acid derivatives.
 - Acyl transfer reactions.
 - Background.
- We'll begin with Topic 1: Introduction.
- Carboxylic acid derivative:** A compound of the following form, where $\text{X} \neq \text{H}, \text{R}$. *Structure*

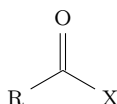


Figure 4.2: Carboxylic acid derivative.

- 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*

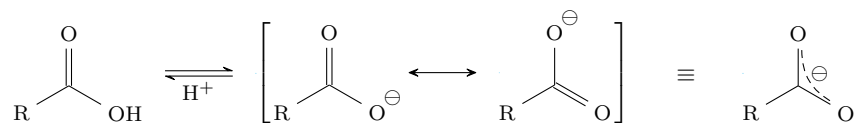


Figure 4.3: Carboxylic acid.

- $pK_a \approx 5$.
 - By comparison, $pK_a \approx 16$ for an alcohol.
 - Therefore, carboxylic 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*

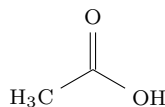
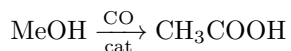


Figure 4.4: Acetic acid.

- 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?



- 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 biscalboxylic acids.

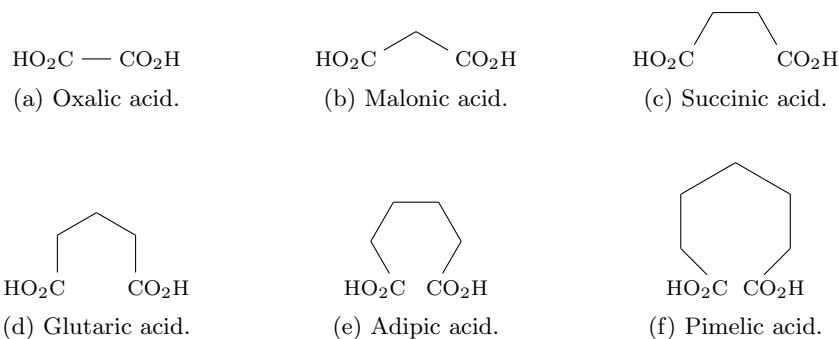


Figure 4.5: Biscalboxylic acids.

- **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.
 - CO₂'s central carbon has 4 bonds to oxygen.
 - Thus, we need to do a 2-electron reduction to turn CO₂ 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.

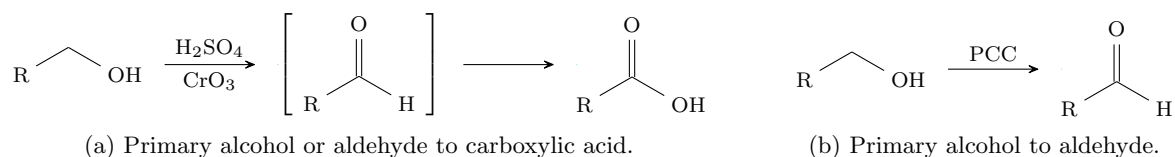


Figure 4.6: Oxidation of alcohols and aldehydes.

- 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 carboxylic 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 H₂SO₄ and CrO₃.
- We now discuss Subtopic 2.b: Carboxylation of Grignard^[1] reagents.

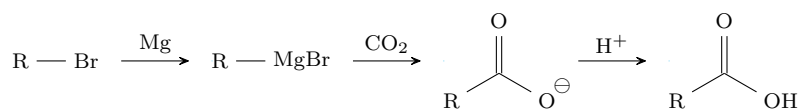


Figure 4.7: Carboxylation of Grignard reagents.

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.

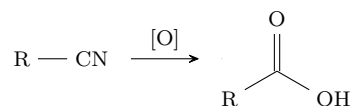


Figure 4.8: Nitrile hydrolysis.

- 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.

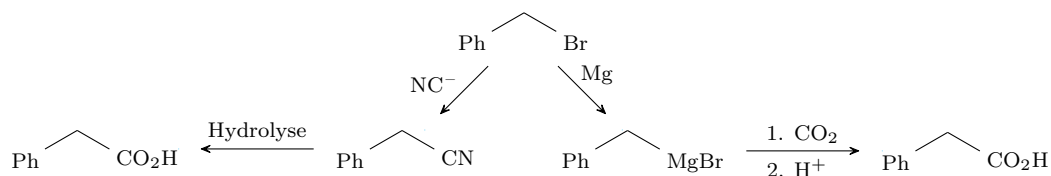


Figure 4.9: Typical test question: Multiple synthetic paths.

- First way: Make the Grignard and add CO_2 .
- Second way: Do an $\text{S}_{\text{N}}2$ 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 $\text{X} = \text{Cl}$. *Structure*

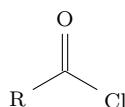


Figure 4.10: Acid chloride.

- 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 $\text{X} = \text{RCO}_2$. *Structure*

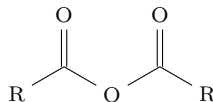


Figure 4.11: Acid anhydride.

- Synthesize these from two carboxylic acids that combine and release water.
- Example of an acid anhydride: Phthalic anhydride.

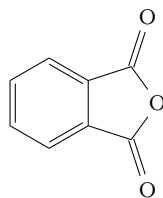


Figure 4.12: Phthalic anhydride.

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

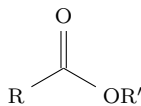


Figure 4.13: Ester.

- Esters are common in scents and smells.
- Example of an ester: Isoamyl acetate.

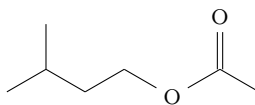


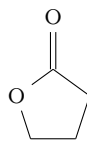
Figure 4.14: Isoamyl acetate.

- 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.

²Coincidentally, acid iodides are used in the Monsanto acetic acid process!

³See the 5.12 equation review sheet!!

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

Figure 4.15: γ -butyrolactone.

- **Amide:** A carboxylic acid derivative for which $X = \text{NR}'\text{R}''$. *Structure*

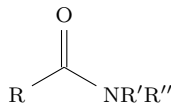


Figure 4.16: Amide.

- Example of a (poly)amide: Nylon.

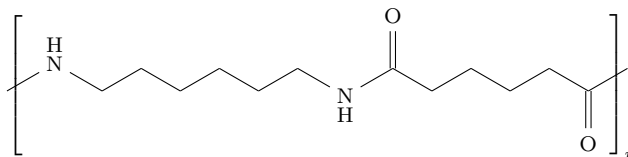


Figure 4.17: Nylon.

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

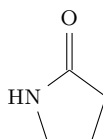


Figure 4.18: 2-Pyrrolidone.

- Lactams are incredibly important; many of us are only alive because of lactams.
- Examples of lactams: The penicillins, a class of molecules that changed the world.

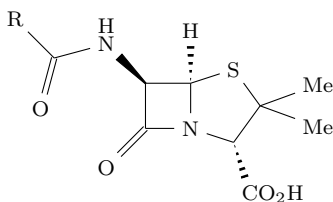


Figure 4.19: Penicillin core structure.

- 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.



- Example: $\text{HCl} + \text{H}_2\text{O} \rightleftharpoons \text{Cl}^- + \text{H}_3\text{O}^+$.
- Example: $\text{HO}^- + \text{H}_2\text{O} \rightleftharpoons \text{O}^{2-} + \text{H}_3\text{O}^+$.
- pK_a — a thermodynamic 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.

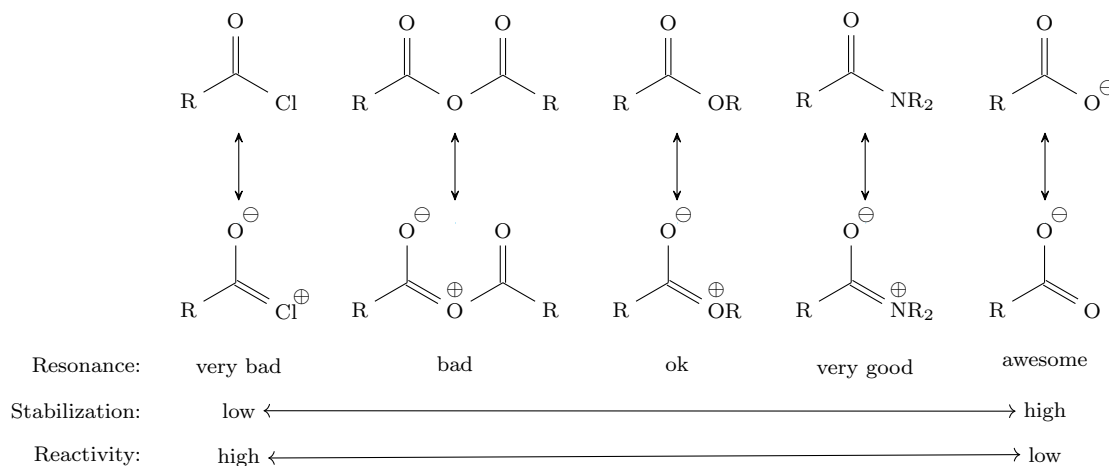


Figure 4.20: Resonance stabilization of carboxylic acid derivatives.

- 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!

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