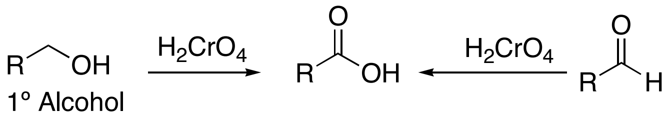
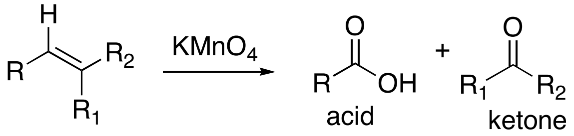
Synthesis of Carboxylic Acids

1. **From 1° Alcohols and Aldehydes: Oxidation** (Section 11-2B and 18-20)



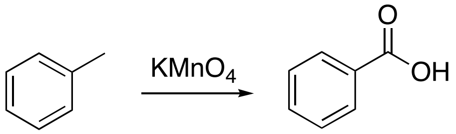
- No mechanism required for the reaction

2. **From Alkenes: Oxidative Cleavage**: (Section 8-15A and 9-10)



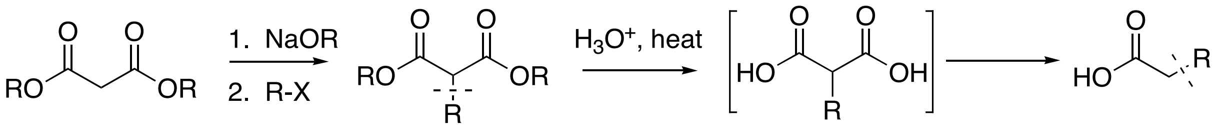
- No mechanism required for the reaction
- Where C=C begins, C=O ends. But where an attached H begins, an OH ends.
- RCH=CHR would give two acids; RCH=CH$_2$ would give an acid and carbonic acid (H$_2$CO$_3$), etc..

3. **From Aromatics**: **Oxidation of Alkylbenzenes** (Section 17-14A)



- No mechanism required for the reduction
- While toluenes (methylbenzenes) oxidize especially well, other alkyl benzenes can also be oxidized in this way.

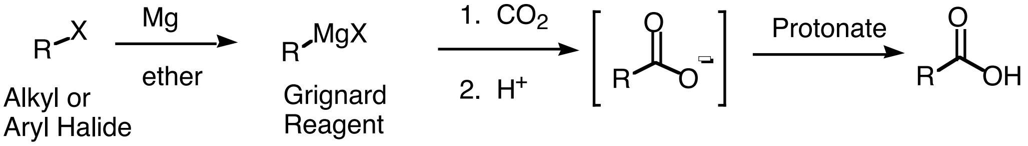
4. **From 1,3-Diesters: Via Hydrolysis/Decarboxylation**: (Chapter 22)



- Mechanism: Deprotation/Alkylation covered previously. The hydrolysis of the esters to acids will be required (see reaction 8b)

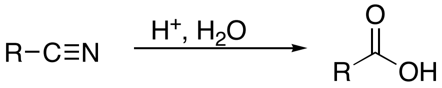
5. **From Grignard Reagents: Via Carboxylation**: (Section 20-8B)

$$\text{R-MgX} \xrightarrow[\text{2. } H^+]{\text{1. } CO_2} \text{R-}CO_2H$$



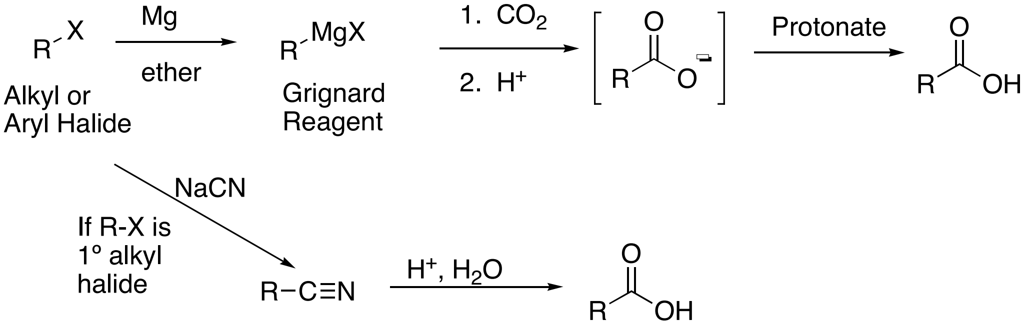
- Access: Alkyl or Aryl Acids
- Alkyl group can be 1°, 2°, or 3°
- Mechanism required. (From Grignard on.)

6. **From Nitriles: Hydrolysis** (Section 20-8C)



- Mechanism not required.

7. **From Halides: Either via Formation and Carboxylation of Grignards (Reaction 5) or via Formation and Hydrolysis of Nitriles (Reaction 6)**

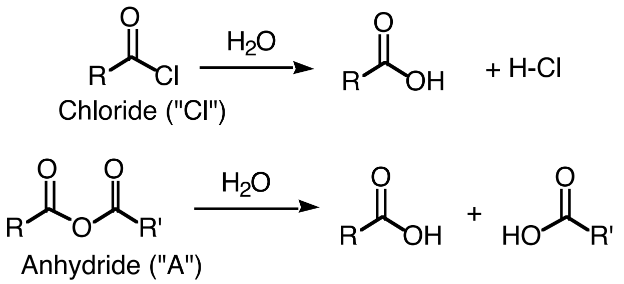


- Formation/Hydrolysis of Nitriles Requires a 1° Alkyl Halide to begin, since the formation of the nitrile proceeds via S_N2
- Reaction via the Grignard has no such limitation
- For 1° alkyl halides, the formation/hydrolysis of the nitrile is technically easier, since there is no need to handle air-sensitive Grignard reagents

8. **From Acid Chlorides, Anhydrides, Esters, or Amides: Hydrolysis** (Section 20-8C)

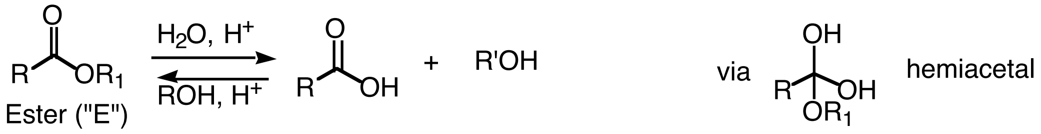
a) "Downhill" hydrolysis: From acids or anhydrides with NEUTRAL WATER alone

- **mechanism required: addition-elimination-deprotonation**



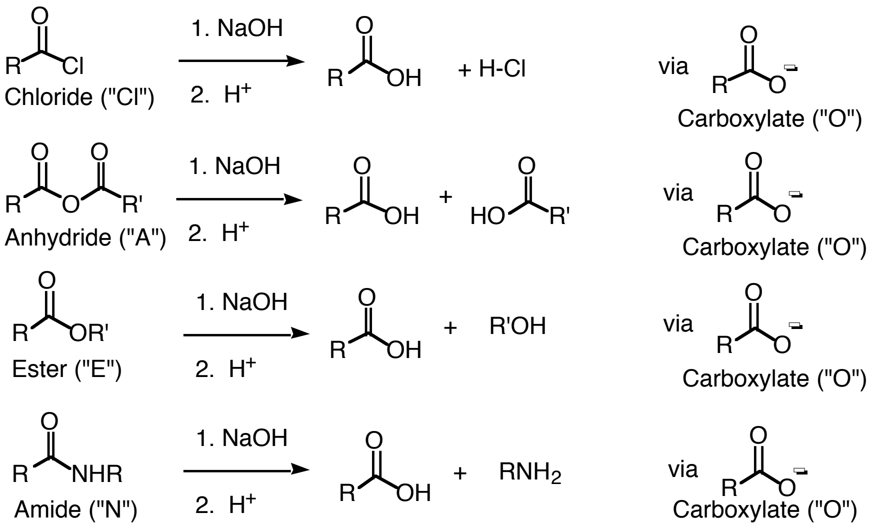
b) "Lateral" hydrolysis: From esters with water and acid catalysis (ACID WATER)

- **mechanism required: protonation-addition-deprotonation (to hemiacetal intermediate) followed by protonation-elimination-deprotonation (hemiacetal to acid)**
- These reactions are under equilibrium control. With excess water, you go to the acid. With removal of water and/or excess alcohol, the equilibrium favors the ester



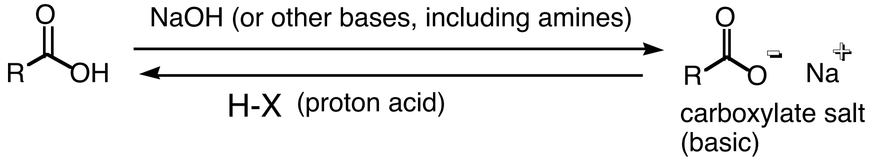
<u>c) "Basic" hydrolysis using NaOH (BASIC WATER) (always downhill) followed by H^+ workup</u>

- **mechanism required: addition-elimination-deprotonation (to carboxylate intermediate) followed by protonation**
- Since the reaction with NaOH is always downhill, all of these reactions work



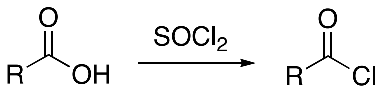
Reactions of Carboxylic Acids

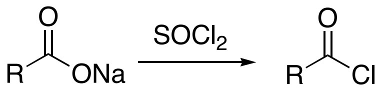
9. **Reaction as a proton Acid** (Section 20-4, 20-5)



- Mechanism: Required (deprotonation)
- Reverse Mechanism: Required (protonation)
- Carboxylic acids are completely converted to carboxylate salts by base
- Carboxylate salts are completely neutralized back to carboxylic acids by strong acid
- The resonanance stabilization makes carboxylates much more stable than hydroxide or alkoxide anions, which is why the parents are carboxylic "acids"
- Carboxylic acids are more acidic than ammonium salts
- Patterns in acid strength: Reflect stabilization/destabilization factors on the carboxylate
    - Electron donors destabilize the carboxylate anion, so make the parent acid less acidic
    - Electron withdrawers stabilize the carboxylate anion, so make the parent acid more acidic

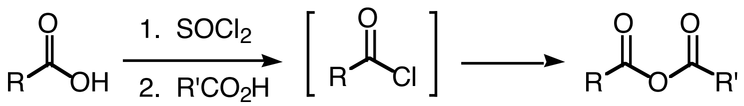
10. **Conversion to Acid Chlorides** (Section 20-11, 21-5)





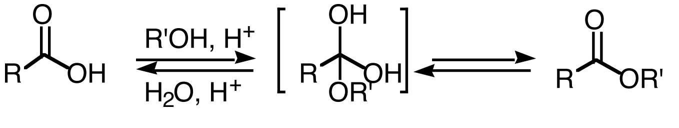
- Mechanism: Not Required
- Easy (but smelly) reaction. Side products HCl and SO_2 are gases, so can just evaporate away leaving clean, useful product. So no workup is required, nice!
- Extremely useful because the acid chlorides are so reactive, and can be converted into esters, anhydrides, or amides.

11. **Indirect Conversion to Anhydrides** (Section 21-5)



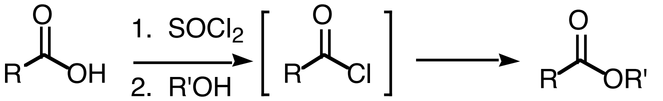
- mechanism required **for acid chloride to anhydride conversion: addition-elimination-deprotonation**
- Conversion of the acid chloride to the anhydride is a "downhill" reaction energetically.
- Conversion of the acid to the anhydride directly would be an "uphill" reaction

12. **Direct Conversion to Esters** (Sections 20-10-12, 21-5)



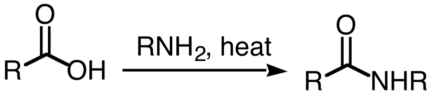
- **mechanism required: protonation-addition-deprotonation (to hemiacetal intermediate) followed by protonation-elimination-deprotonation (hemiacetal to ester)**
- These reactions are under equilibrium control. With excess water, you go to the acid. With removal of water and/or excess alcohol, the equilibrium favors the ester
- This is a "lateral" reaction, neither uphill nor downhill energetically
- This is the exact reverse of reaction 8b

13. **Indirect Conversion to Esters via Acid Chlorides** (Sections 20-10-12, 21-5)



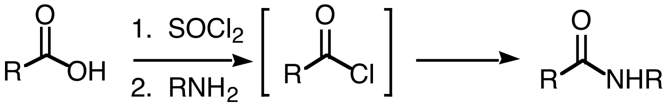
- mechanism required **for acid chloride to ester conversion: addition-elimination-deprotonation**
- Conversion of the acid chloride to the ester is a "downhill" reaction energetically.

14. **Direct Conversion to Amides** (Sections 20-11, 20-13, 21-5)



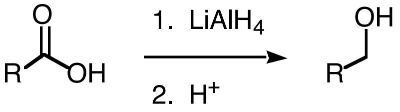
- **mechanism not required**
- This is a "downhill" reaction energetically, but is complicated and retarded by acid-base reactions. Normally the "indirect) conversion is more clean in the laboratory
- This reaction occurs routinely under biological conditions, in which enzymes catalyze the process rapidly even at mild biological temperatures.

15. **Indirect Conversion to Amides** (Sections 20-11, 20-13, 21-5)



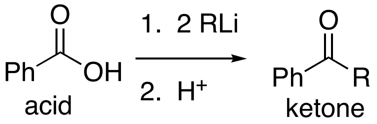
- mechanism required **for acid chloride to amide conversion: addition-elimination-deprotonation**
- This reaction sequence works very well in the laboratory

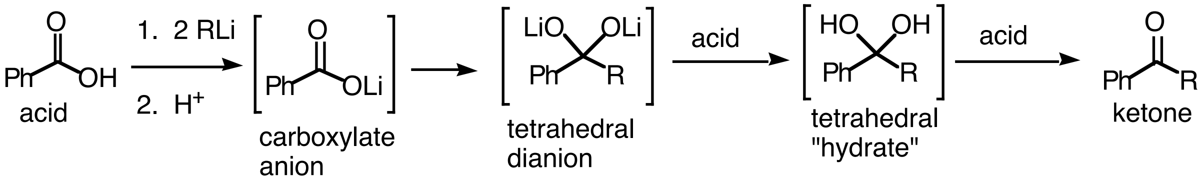
16. **Reduction to Primary Alcohol** (Sections 10-11, 20-14)



- **mechanism not required**

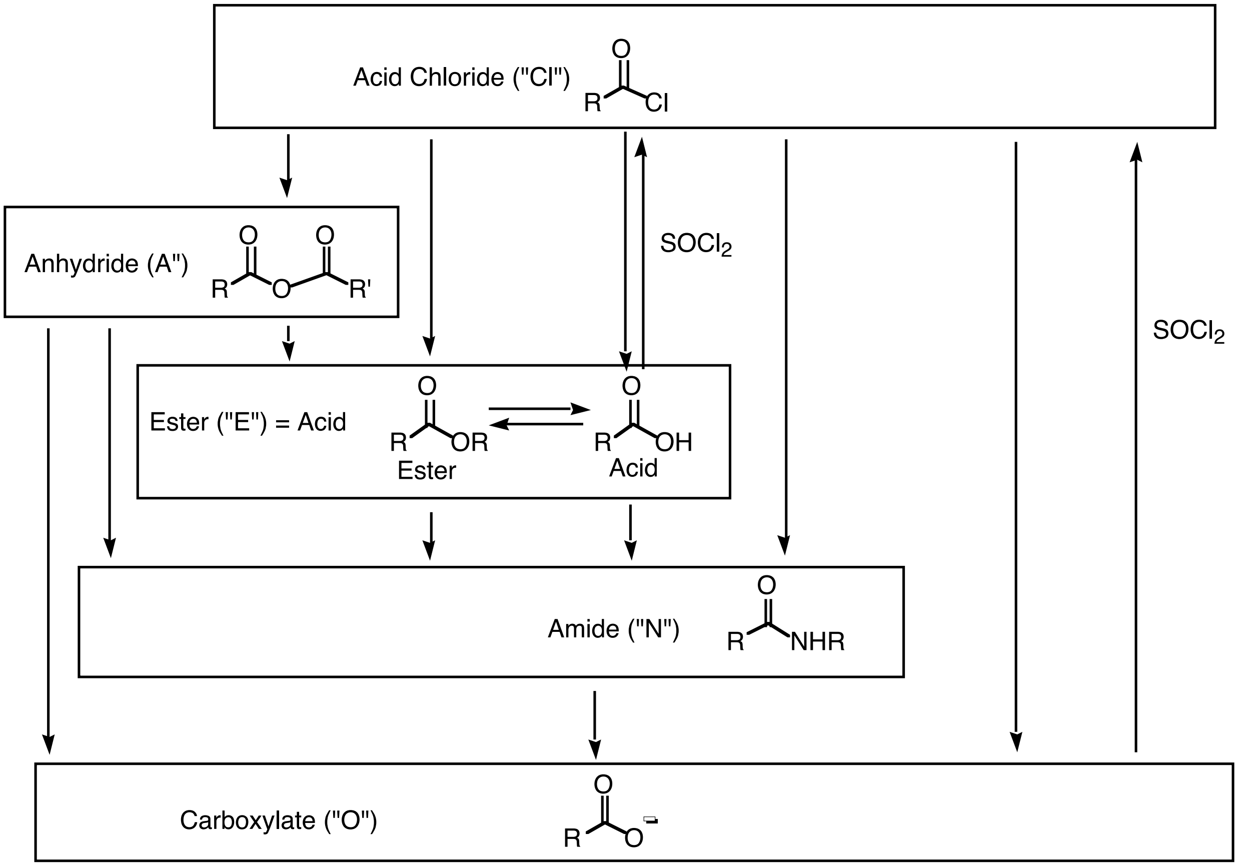
17. **Alkylation to Form Ketones** (Section 18-19, 20-15)





- **mechanism not required**

18. **Interconversions of Acids and Acid Derivatives** (Section 21-5 and many others)

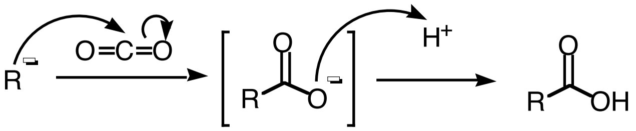


- "Cl-A-vE-N-O" Chlorides-Anhydrides-Esters (and Acids)-Amides-Carboxylates
- Any downhill step can be done directly
- Any "lateral" step (acid to ester or vice-versa) can be done with acid
- Any "uphill" sequence requires going up through the Acid Chloride, either directly (from an acid or a carboxylate) or indirectly (conversion to carboxylate; react with $SOCl_2$ to get to the top; then go downhill from there.)
- Mechanism is required for any downhill conversion and is the same: protonation-addition-deprotonation (addition to produce the hemiacetal intermediate) followed by protonation-elimination-deprotonation (elimination)

Mechanisms

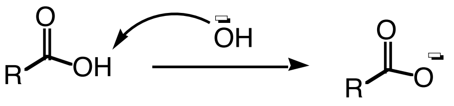
A. Miscellaneous

5. From Grignard Reagents: Via Carboxylation:



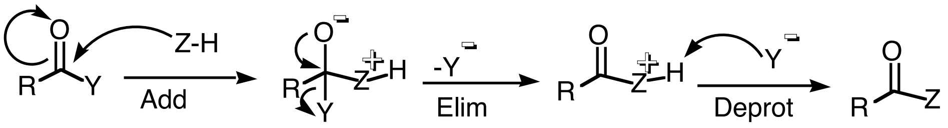
- exactly like any Grignard reaction

9. Reaction as a Proton Acid



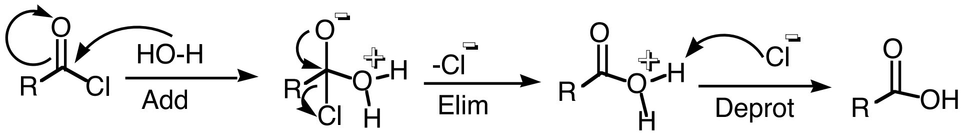
B. Any "Downhill" Interconversions (8a, 8c, 11, 13, 15, 18): All Proceed by Addition-Elimination-Deprotonation

General

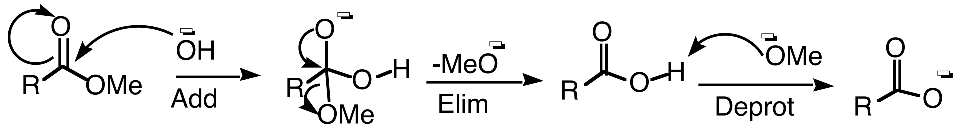


Examples

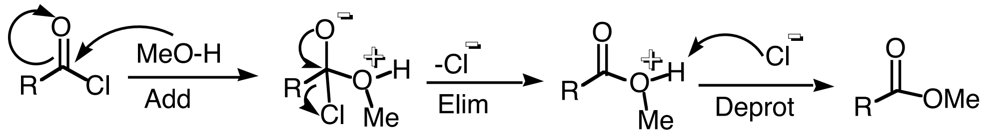
Reaction 8a



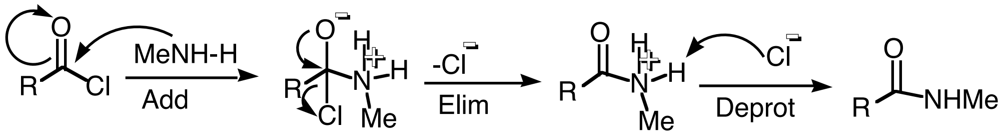
Reaction 8c (Note: Slightly different because hydroxide nucleophile is anionic, not neutral; and product carboxylate is anionic, not neutral)



Reaction 13



Reaction 15

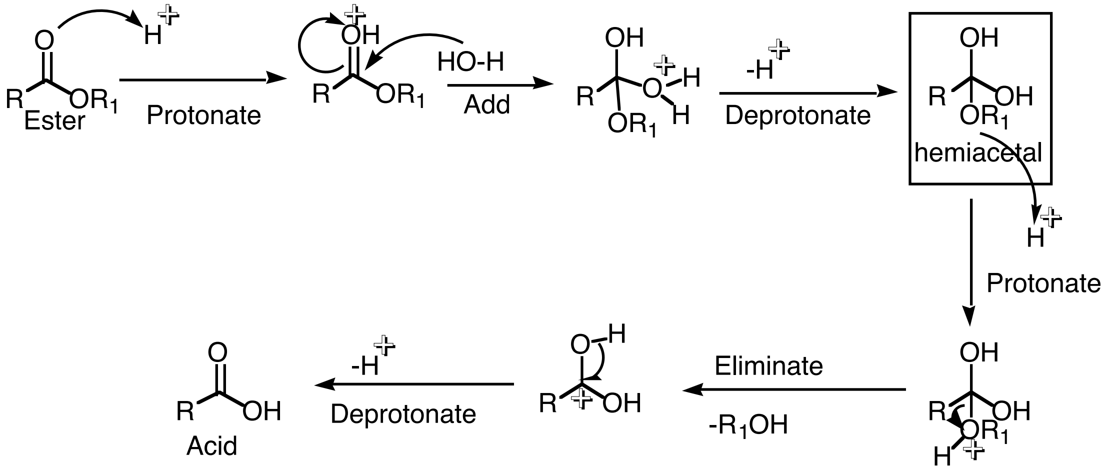


C. "Lateral" Interconversions (8b/12): Acid-Catalyzed conversion from Ester to Acid (8b) or From Acid to Ester (12): (ACID WATER)

- **General Mechanism: protonation-addition-deprotonation (acid-catalyzed addition to a carbonyl to produce the tetrahedral hemiacetal intermediate) followed by protonation-elimination-deprotonation (acid catalyzed elimination)**

<u>Examples</u>

<u>Reaction 8b: Ester to Acid</u>



<u>Reaction 12: Acid to Ester</u>