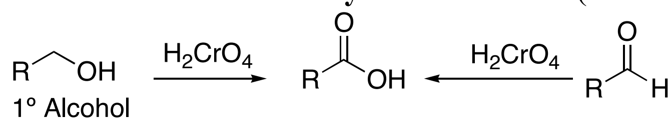
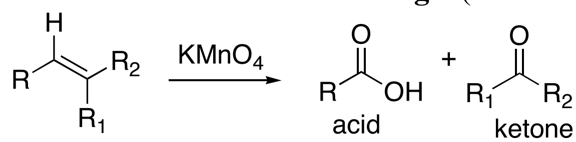
Synthesis of Carboxylic Acids

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



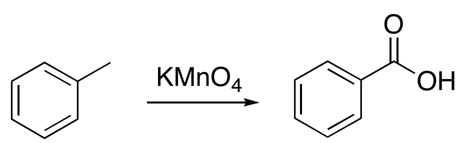
- No mechanism required for the reaction

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



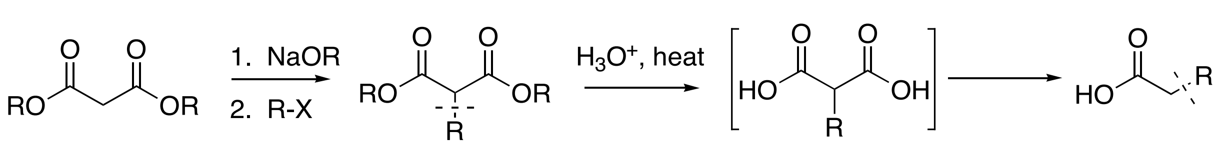
- No mechanism required for the reaction
- Where C=C begins, C=O ends. But where an attached H begins, an OH ends.
- RCH=CHR would give two acids; $RCH=CH_2$ would give an acid and carbonic acid (H_2CO_3), etc..

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.

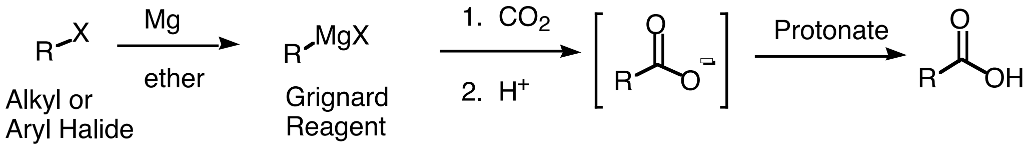
4. **From 1,3-Diesters: Via Hydrolysis/Decarboxylation**: (Chapter 22)



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

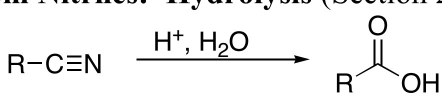
5. **From Grignard Reagents: Via Carboxylation**: (Section 20-8B)

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



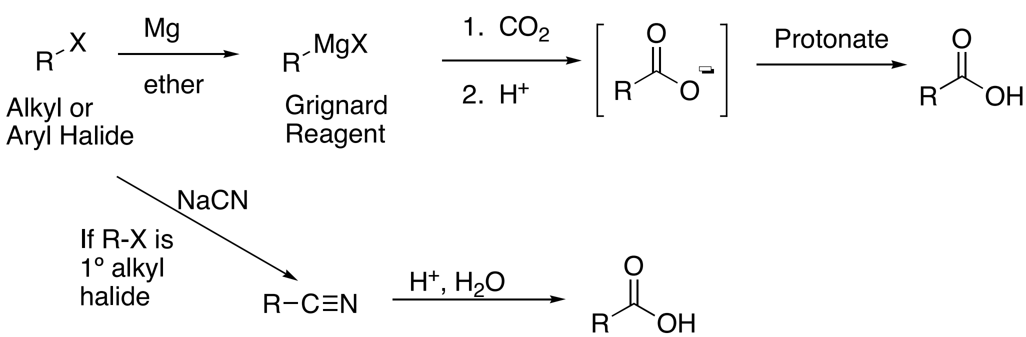
- Access: Alkyl or Aryl Acids
- Alkyl group can be 1°, 2°, or 3°
- Mechanism required. (From Grignard on.)

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)**

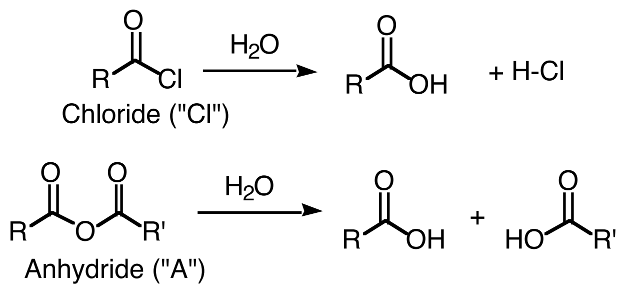


- Formation/Hydrolysis of Nitriles Requires a 1° Alkyl Halide to begin, since the formation of the nitrile proceeds via S_N2
- Reaction via the Grignard has no such limitation
- For 1° alkyl halides, the formation/hydrolysis of the nitrile is technically easier, since there is no need to handle air-sensitive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

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

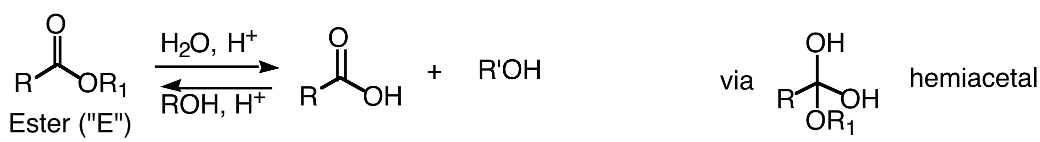
a) "Downhill" hydrolysis: From acids or anhydrides with NEUTRAL WATER alone

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



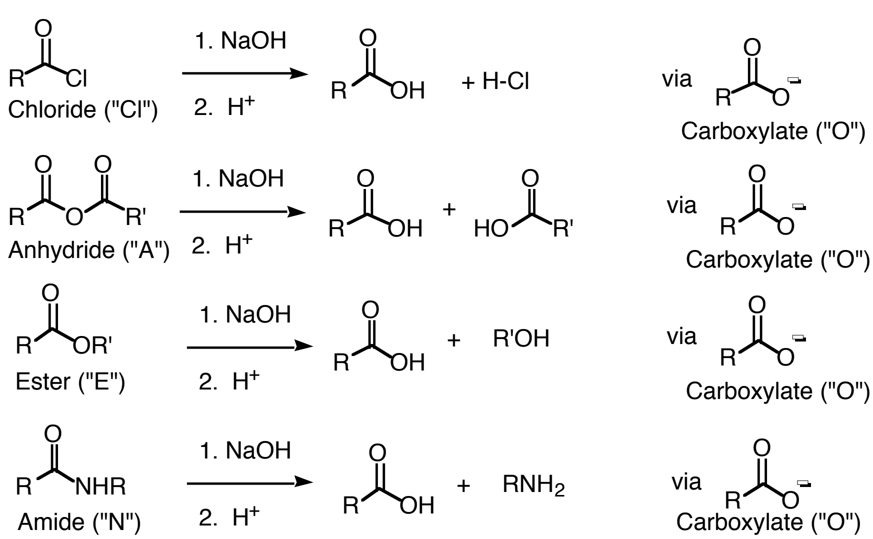
b) "Lateral" hydrolysis: From esters with water and acid catalysis (ACID WATER)

- **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



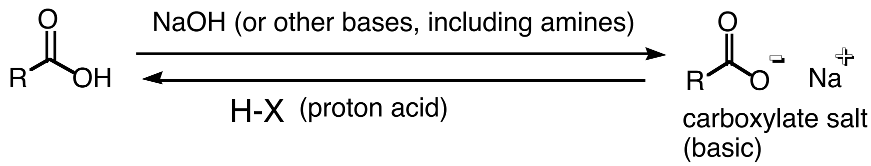
<u>**c) "Basic" hydrolysis using NaOH (BASIC WATER) (always downhill) followed by H$^+$ workup**</u>

- **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)

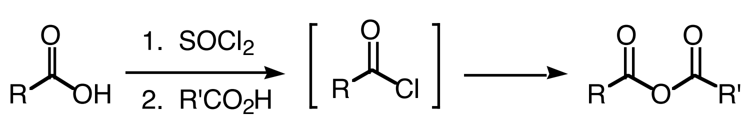


- Mechanism: Required (deprotonation)
- Reverse Mechanism: Required (protonation)
- Carboxylic acids are completely converted to carboxylate salts by base
- Carboxylate salts are completely neutralized back to carboxylic acids by strong acid
- The resonanance stabilization makes carboxylates much more 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
    - o Electron donors destabilize the carboxylate anion, so make the parent acid less acidic
    - o Electron withdrawers stabilize the carboxylate anion, so make the parent acid more acidic

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

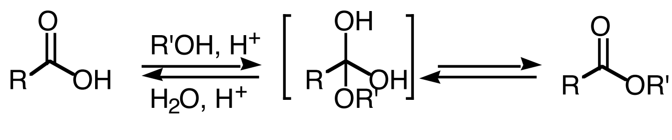
- Mechanism: Not Required
- Easy (but smelly) reaction. Side products HCl and SO_2 are gases, so can just evaporate away leaving clean, useful product. So no workup is required, nice!
- Extremely useful because the acid chlorides are so reactive, and can be converted into esters, anhydrides, or amides.

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



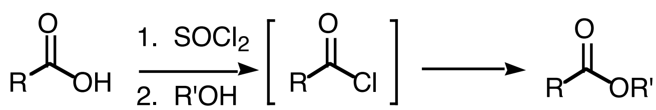
- mechanism required **for acid chloride to anhydride conversion: addition-elimination-deprotonation**
- Conversion of the acid chloride to the anhydride is a "downhill" reaction energetically.
- Conversion of the acid to the anhydride directly would be an "uphill" reaction

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



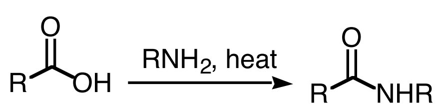
- **mechanism required: protonation-addition-deprotonation (to hemiacetal intermediate) followed by protonation-elimination-deprotonation (hemiacetal to ester)**
- These reactions are under equilibrium control. With excess water, you go to the acid. With removal of water and/or excess alcohol, the equilibrium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



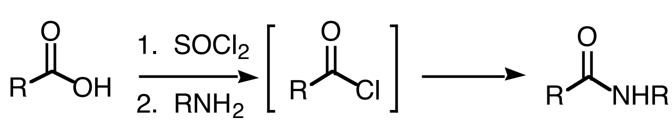
- mechanism required **for acid chloride to ester conversion: addition-elimination-deprotonation**
- Conversion of the acid chloride to the ester is a "downhill" reaction energetically.

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



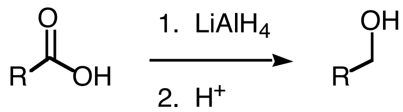
- **mechanism not required**
- This is a "downhill" reaction energetically, but is complicated and retarded by acid-base reactions. Normally the "indirect) conversion is more clean in the laboratory
- This reaction occurs routinely under biological conditions, in which enzymes catalyze the process rapidly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

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



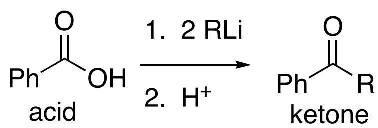
- mechanism required **for acid chloride to amide conversion: addition-elimination-deprotonation**
- This reaction sequence works very well in the laboratory

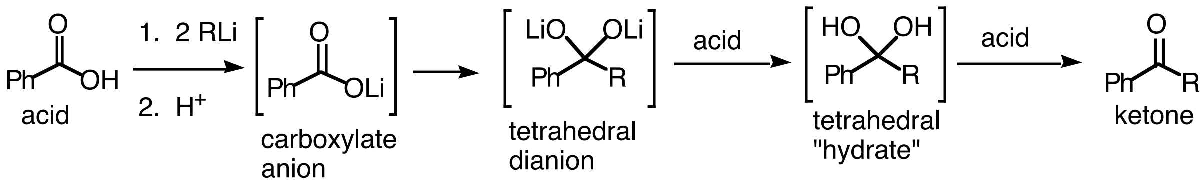
16. **Reduction to Primary Alcohol** (Sections 10-11, 20-14)



- **mechanism not required**

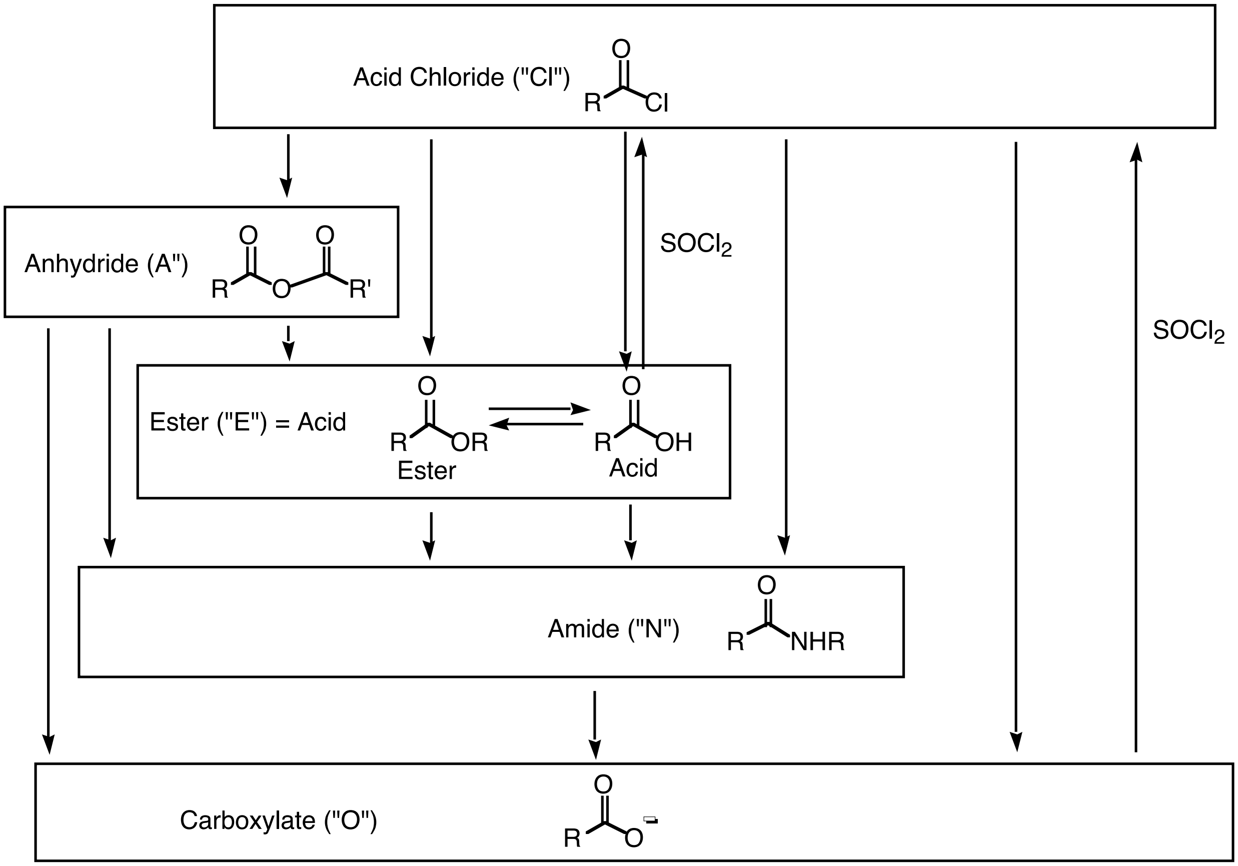
17. **Alkylation to Form Ketones** (Section 18-19, 20-15)





- **mechanism not required**

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

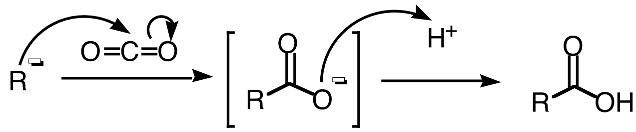


- "Cl-A-vE-N-O" Chlorides-Anhydrides-Esters (and Acids)-Amides-Carboxylates
- Any downhill step can be done directly
- Any "lateral" step (acid to ester or vice-versa) can be done with acid
- Any "uphill" sequence requires going up through the Acid Chloride, either directly (from an acid or a carboxylate) 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

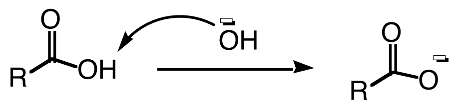
A. Miscellaneous

5. **From Grignard Reagents: Via Carboxylation**:



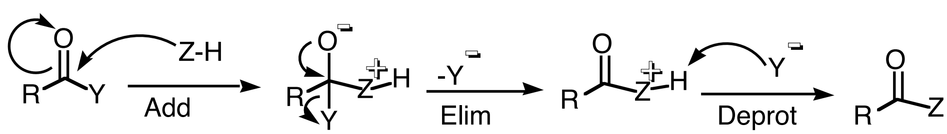
- exactly like any Grignard reaction

9. Reaction as a Proton Acid



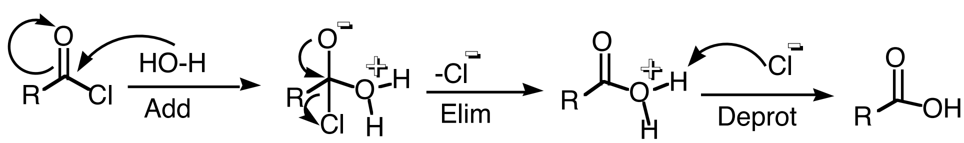
B. Any "Downhill" Interconversions (8a, 8c, 11, 13, 15, 18): All Proceed by Addition-Elimination-Deprotonation

General

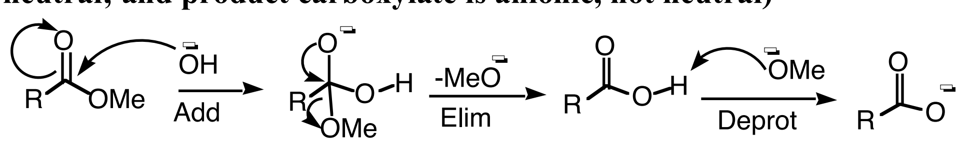


Examples

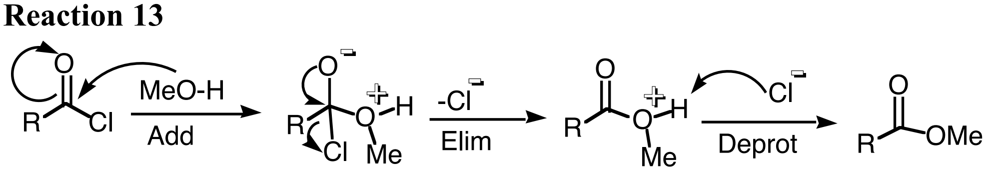
Reaction 8a



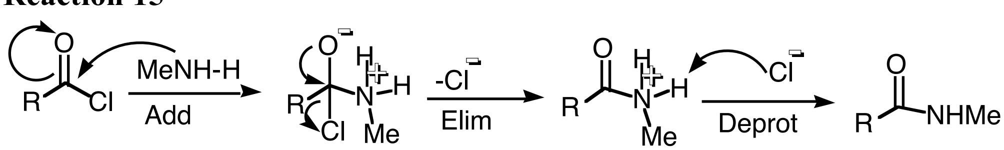
Reaction 8c (Note: Slightly different because hydroxide nucleophile is anionic, not neutral; and product carboxylate is anionic, not neutral)



Reaction 13



Reaction 15

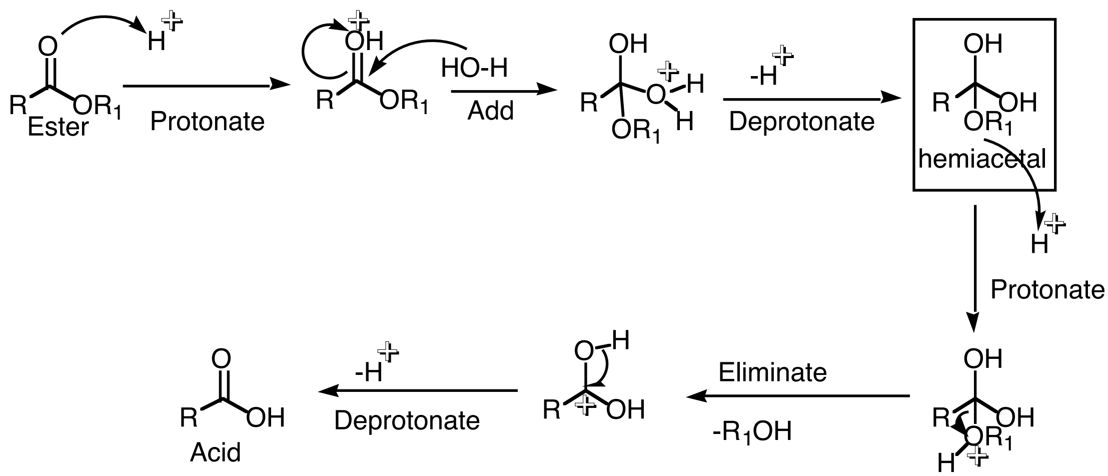


C. "Lateral" Interconversions (8b/12): Acid-Catalyzed conversion from Ester to Acid (8b) or From Acid to Ester (12): (ACID WATER)

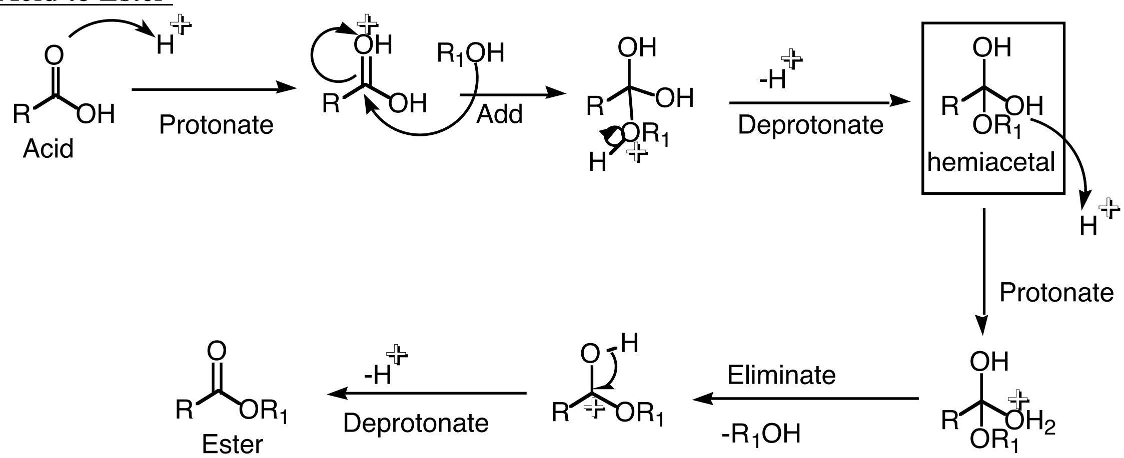
- **General Mechanism: protonation-addition-deprotonation (acid-catalyzed addition to a carbonyl to produce the tetrahedral hemiacetal intermediate) followed by protonation-elimination-deprotonation (acid catalyzed elimination)**

<u>Examples</u>

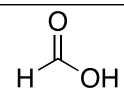
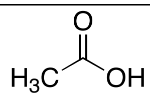
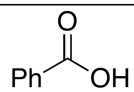
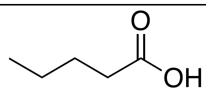
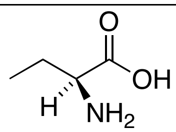
<u>Reaction 8b: Ester to Acid</u>



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



Nomenclature (20.2) Formal: alkanoic acid (space in between)
-highest priority of any functional group

	Formal	Common
	Methanoic acid	Formic acid
	Ethanoic acid	Acetic acid
	Benzoic acid	Benzoic acid
	Pentanoic acid	
	(S)-2-aminobutanoic acid	

1. Nomenclature. Provide names or structures for the following.

   a. 3-phenylbutanoic acid

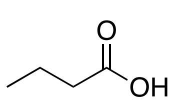
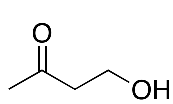
   b. 2,2-dichloropropanoic acid

   c. 2-hydroxy-3-propanoyl-4-ethoxy-5-amino-6-hydroxyheptanoic acid

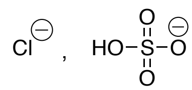
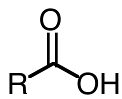
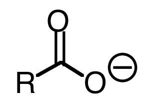
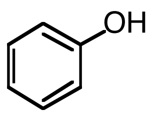
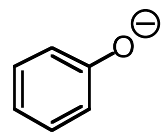
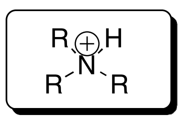
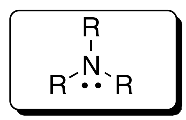
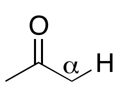
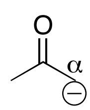
Physical Properties (Section 20.3)
Boiling Points: (weight being equal): acid > alcohol > 1,2º amines > non-H-bonders
- Acids boil about 20º higher than same-weight alcohols
- First four acids are completely water soluble

Water solubility (weight being equal): amines > acids ? ketones, alcohols, ethers >> alkanes
- Basicity is more important than acidity

2. Circle the one with higher boiling point, and square the one with the greater solubility in water.

Acidity/Basicity Table 19.2: With both Neutral and Cationic Acids and both Neutral and Anionic Bases (Section 20-4)

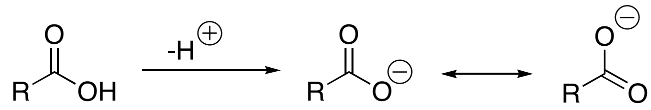
Class	Structure	Ka	Acid Strength	Base	Base Strength	
Strong Acids	H-Cl, H_2SO_4	10^{2}				**S**mell **A**wful!
Hydronium	H_3O^+, ROH^+ cationic	10^{0}		H_2O, HOR neutral		**H**umans
Carboxylic Acid		10^{-5}				**C**uz
Phenol		10^{-10}				**P**eople
Ammonium Ion (Charged)	 Charged, but only weakly acidic!	**10^{-12}**		 Neutral, but basic		**A**gainst
Water	HOH	10^{-16}		$HO^{\ominus}$		**W**orking
Alcohol	ROH	10^{-17}		$RO^{\ominus}$		**A**re
Ketones and Aldehydes		10^{-20}				**K**ingdoms
Amine (N-H)	$(iPr)_2N$-H	10^{-33}		$(iPr)_2N^{\ominus}Li^{\oplus}$		**A**nimal
Alkane (C-H)	RCH_3	10^{-50}		$RCH_2^{\ominus}$		**A**ll

Quick Checklist of Acid/Base Factors

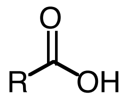
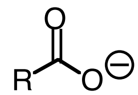
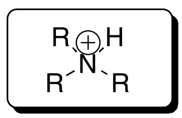
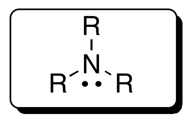
1. **Charge**
2. **Electronegativity**
3. **Resonance/Conjugation**
4. **Hybridization**
5. **Impact of Electron Donors/Withdrawers**
6. **Amines/Ammoniums**

- **When comparing/ranking any two acids or bases, go through the above checklist to see which factors apply and might differentiate the two.**
- **When A neutral acid is involved, it's often best to draw the conjugate anionic bases, and to think from the anion stability side.**

Acidity (20-4)



- Anion is stabilized by conjugation/resonance
- Charge dispersal
- Carboxylate is an anion, so is stabilized by electron withdrawing groups (increasing acidity) and destabilized by electron donating groups (decreasing acidity)

Carboxylic Acid		10^{-5}	
Ammonium Ion (Charged)	 Charged, but only weakly acidic!	**10^{-12}**	 Neutral, but basic
Alcohol	ROH	10^{-17}	$RO^{\ominus}$

- Acids are a million times more acidic than average ammoniums (despite charge)
- Acids are trillions more acidic than alcohols

Amino Acids:

- Which way does the equilibrium lie?
- Equilibrium always favors the weaker acid and weaker base?
- What happens under acid conditions, and what happens under base conditions?

38. Carboxylic Acids as Acids. Rank the acidity of the following groups, 1 being most acidic and 3 being least acidic. [Remember: the best guideline for acidity is the stability of the anion!]

a. acetic acid ethanol phenol

b. propanoic acid CH_3NH_3Cl $(CH_3)_3NHCl$

Substituent Effects (20.4B)

- Withdrawers stabilize anions, increase acidity
- Donors destabilize anions, reduce acidity
- Opposite from the effect of donors and withdrawers on amines and ammoniums

1. Carboxylic Acids as Acids. Rank the acidity of the following groups, 1 being most acidic and 3 being least acidic. [Remember: the best guideline for acidity is the stability of the anion!]

a. propanoc acid 3-Chloropropanoic acid 2-fluoropropanoic acid

b. benzoic acid p-methylbenzoic acid p-nitrobenzoic acid

2. For each of the following acid/base reactions, draw a circle around the weakest base, and draw an arrow to show whether the reaction would proceed from left to right, or from right to left.

a.

b. Ph−OH + NaOH Ph−ONa + HOH

c.

d.

$K_a=10^{-5}$ $K_a=10^{-7}$

20.5 Carboxylate Salts

RCO_2H + NaOH → RCO_2Na + H_2O Produces weaker acid and base

- Easy to make
- Ionic → water soluble

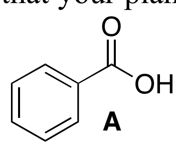
Acids are soluble in NaOH/water or $NaHCO_3/H_2O$

- Weak bases, react with HCl → RCO_2H
- Named: sodium alkanoate

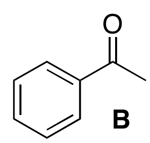
Purification Schemes for Acids from other Organics Based on Acidity

a. Dissolve acid and neutral organic in ether
b. Treat with NaOH/water
    - Neutral stays neutral, goes in ether layer
    - Acid is deprotonated to RCO_2Na, goes into water layer
c. Concentrate ether layer → pure neutral organic
d. Add HCl to aqueous layer, results in: RCO_2Na + HCl → RCO_2H
e. Neutral RCO_2H now has low solubility in water, so can be harvested by filtration (if solid) or by organic extraction

1. Design a solubility flow chart to separate benzoic acid ("**A**") from acetophenone $PhC(O)CH_3$ ("**B**"). Make sure that your plan enables you to isolate both **"A"** and "**B**".



A



B

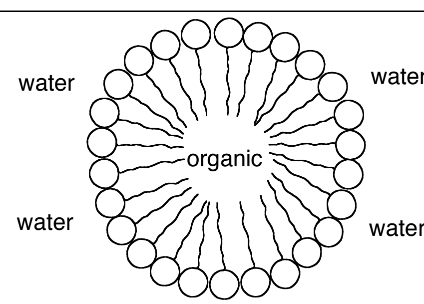
Soaps (20.6, 25.4) (not for test)

RCO_2Na with variable long alkyl chains

Ex: $C_{17}H_{35}CO_2^{\ominus}\ Na^{\oplus}$

Carboxylate head: hydrophilic → water soluble
Hydrocarbon tail: hydrophobic → can dissolve grease and organic materials

Form "micelles" in water

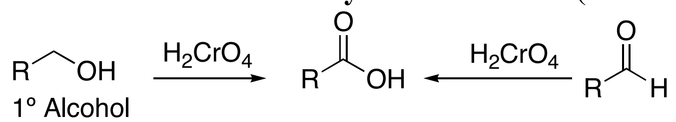
The hydrophobic hydrocarbon tails (strings) self-aggregate, while the ionic heads (circles) keep the microdroplet soluble in water. Organic materials can be dissolved inside the organic center, and carried through the water. Thus grease gets dissolved, and dirt protected by grease is freed.	

B. Synthesis of Carboxylic Acids

Synthesis of Carboxylic Acids

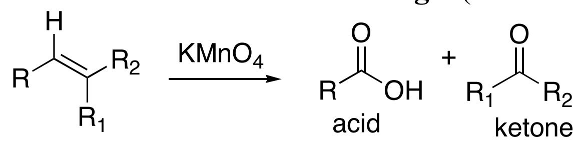
Review (20.8)

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



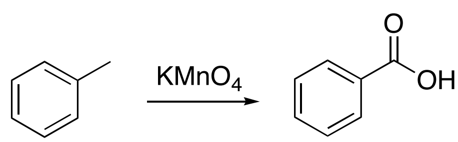
- No mechanism required for the reaction

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



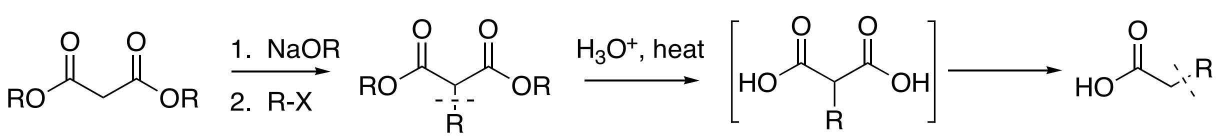
- No mechanism required for the reaction
- Where C=C begins, C=O ends. But where an attached H begins, an OH ends.
- RCH=CHR would give two acids; $RCH=CH_2$ would give an acid and carbonic acid (H_2CO_3), etc..

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.

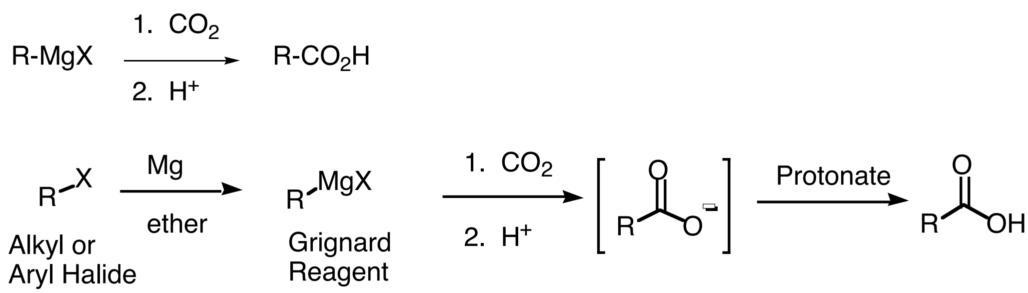
4. **From 1,3-Diesters: Via Hydrolysis/Decarboxylation**: (Chapter 22)



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

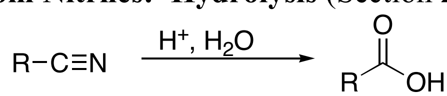
<u>New Routes</u>

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



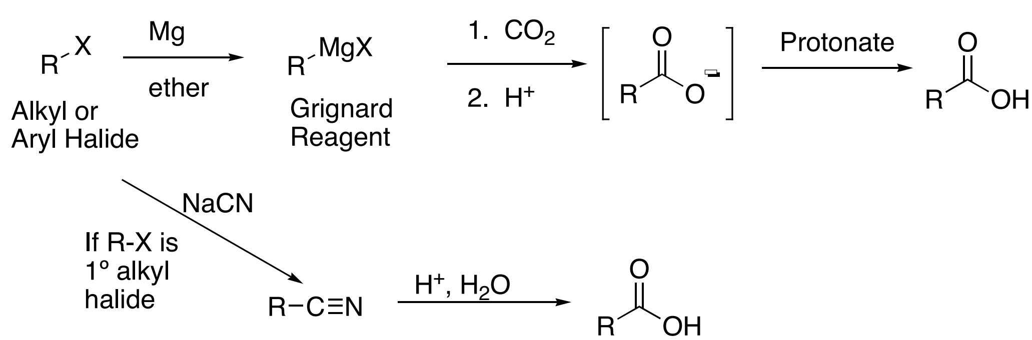
- Access: Alkyl or Aryl Acids
- Alkyl group can be 1°, 2°, or 3°
- Mechanism required. (From Grignard on.)

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



- Mechanism not required.

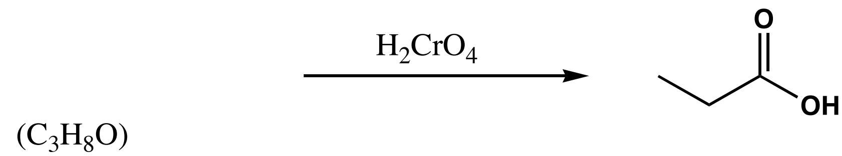
7. **From Halides: Either via Formation and Carboxylation of Grignards (Reaction 5) or via Formation and Hydrolysis of Nitriles (Reaction 6)**



- 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

Problems

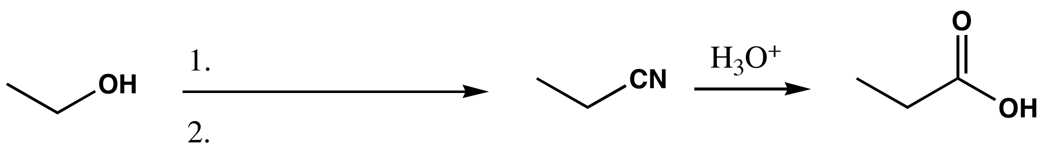
1. Preparation of Carboxylic Acids. Fill in the blanks for the following reactions.

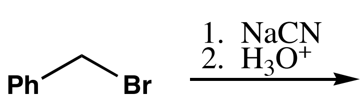
a. 

b. Bromobenzene $\xrightarrow{\text{1. Mg; 2. epoxide; } H_2O\text{; 3. } H_2CrO_4}$

c. 

d. Benzene $\xrightarrow{Br_2,\ FeBr_3}$ $\xrightarrow{Mg}$ $\xrightarrow{\text{1. } CO_2\text{; 2. } H^+}$

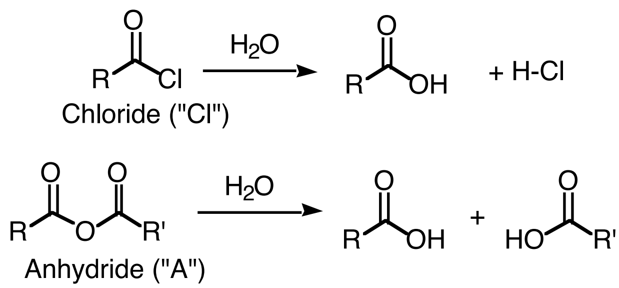
e. 

f. 

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

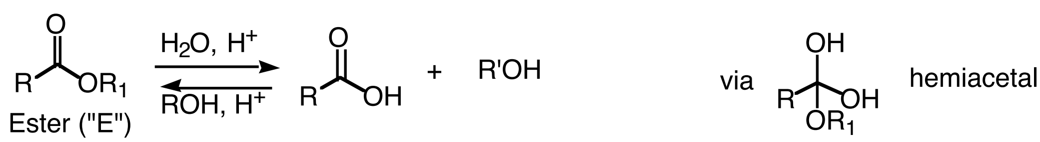
a) "Downhill" hydrolysis: From acids or anhydrides with NEUTRAL WATER alone

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



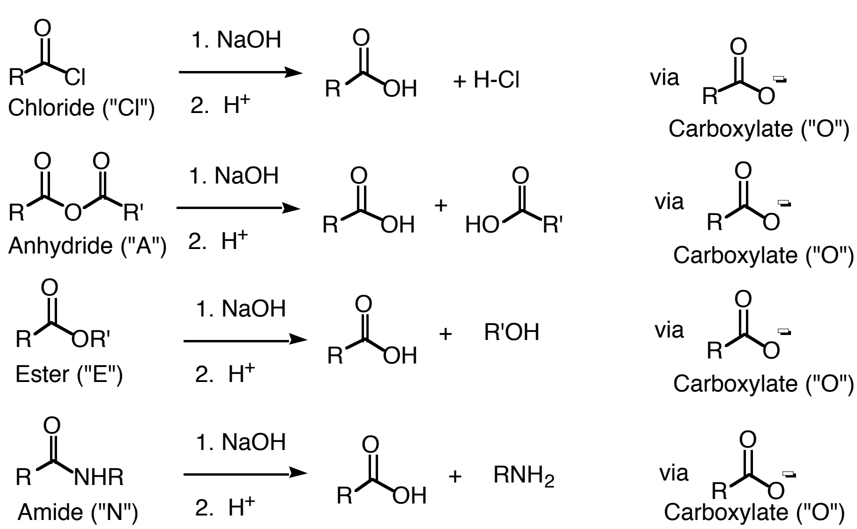
b) "Lateral" hydrolysis: From esters with water and acid catalysis (ACID WATER)

- **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

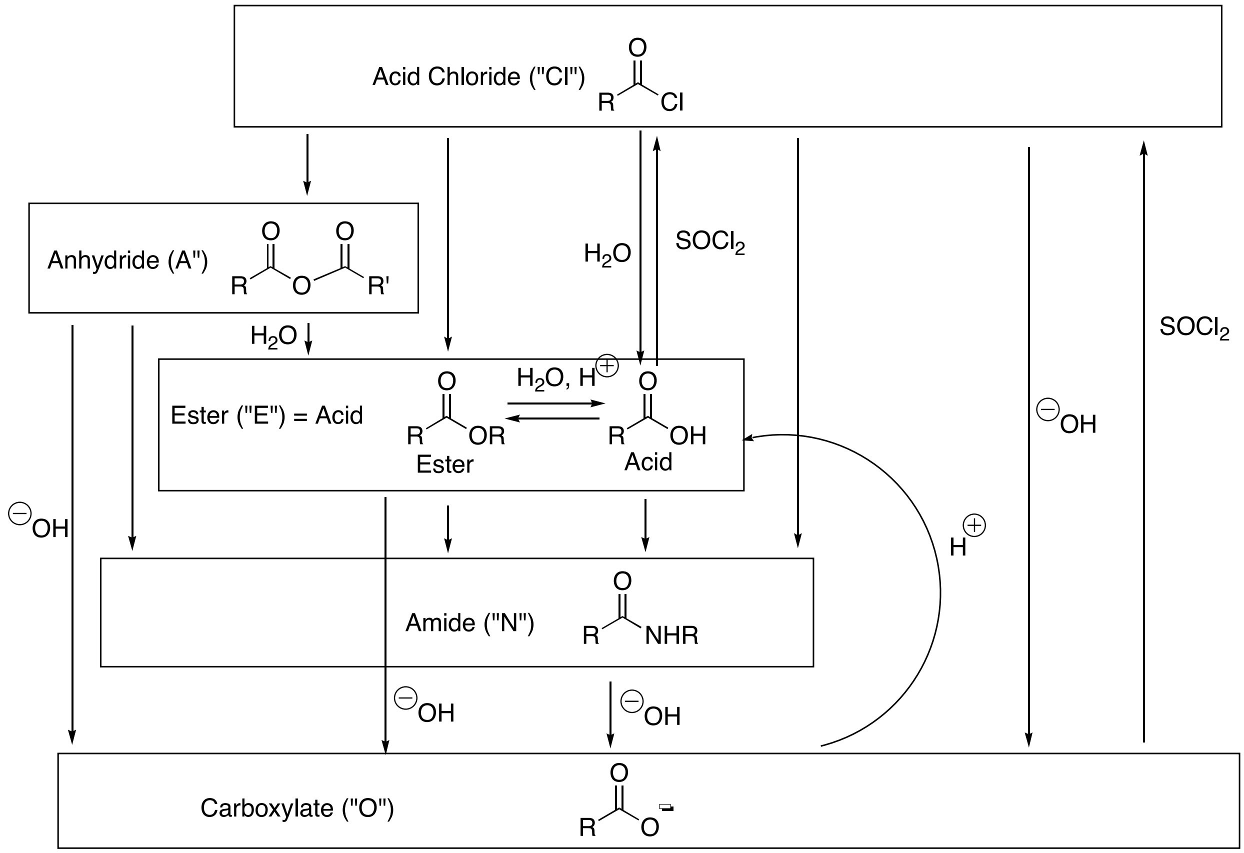


<u>**c) "Basic" hydrolysis using NaOH (BASIC WATER) (always downhill) followed by H$^+$ workup**</u>

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



Interconversions and Reactivity of Acids and Acid Derivatives (Section 21-5 and others)



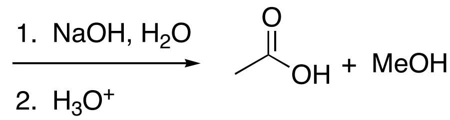
- "Cl-A-vE-N-O" Chlorides-Anhydrides-Esters (and Acids)-Amides-Carboxylates
- Any downhill step can be done directly
- Any "lateral" step (acid to ester or vice-versa) can be done with acid
- Any "uphill" sequence requires protonation or going up through the Acid Chloride, either directly (from an acid 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)

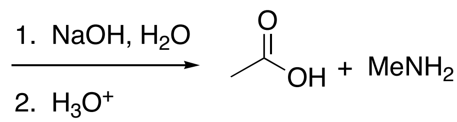
"Cl-A-vE-N-O" applied to Hydrolysis

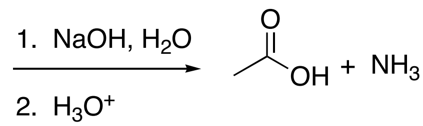
1. Chlorides and Anhydrides are "above" acids, so can be converted to acids by direct hydrolysis with neutral water
2. Esters are "lateral" to acids, so can be hydrolyzed to acids by acid-catalyzed hydrolysis
3. Chloride, anhydrides, esters, and amides can all be base-hydrolyzed (NaOH/water) to carboxylates.
   - Subsequent acid workup protonates the carboxylate and produces the acid
   - Base hydrolysis always works
4. For amides, basic hydrolysis is the only way to do it

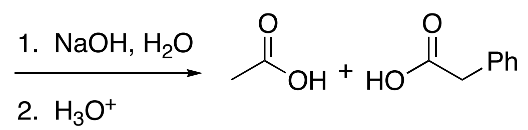
1. For the following problems, draw the starting materials that would give the indicated hydrolysis products.

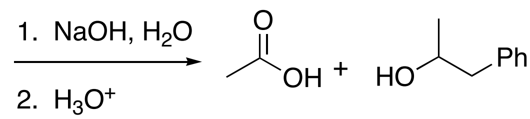
- Note: All of these are drawn as basic hydrolyses, but some could also be done using neutral water or acidic water. Mark which could proceed using neutral hydrolysis or acid-catalyzed hydrolysis in addition to via basic hydrolysis.







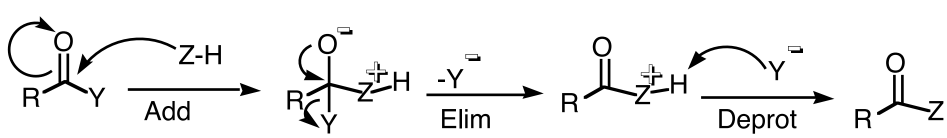




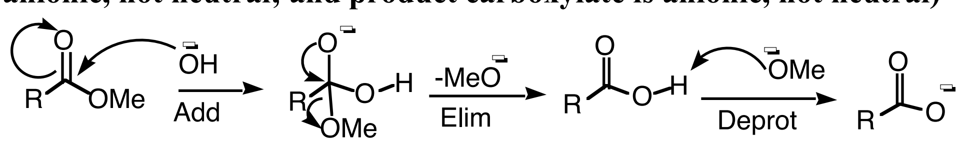
Mechanism: General Mechanism for Any "Downhill" Cl-A-vE-N-O Interconversions (8a, 8c, 11, 13, 15, 18):

All Proceed by Addition-Elimination-Deprotonation

General

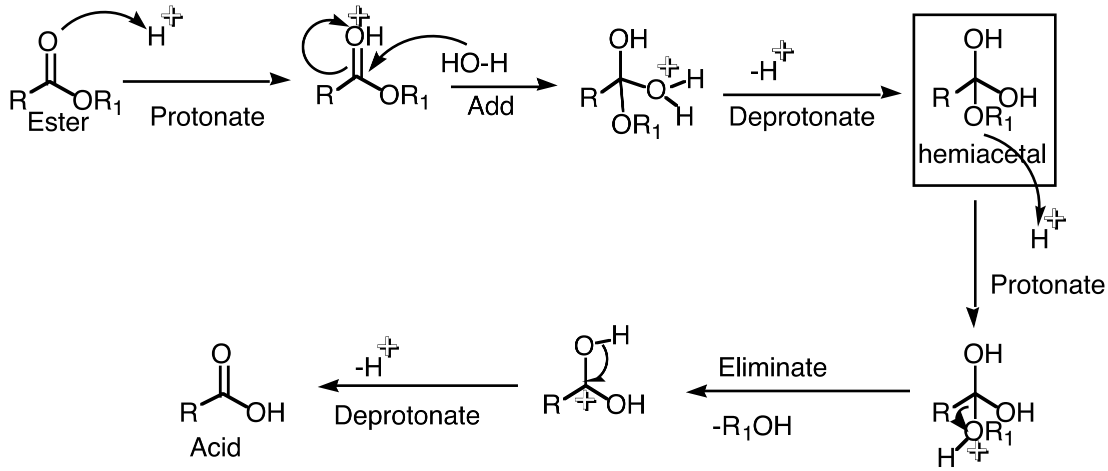


Base Case, Using Anionic Hydroxide: Slightly different because hydroxide nucleophile is anionic, not neutral; and product carboxylate is anionic, not neutral)

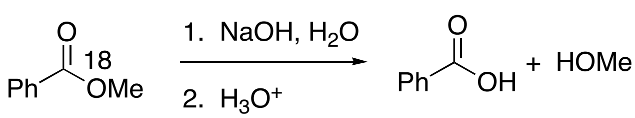


Acid-Catalyzed conversion from Ester to Acid (8b): (ACID WATER)

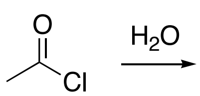
- **General Mechanism: protonation-addition-deprotonation (acid-catalyzed addition to a carbonyl to produce the tetrahedral hemiacetal intermediate) followed by protonation-elimination-deprotonation (acid catalyzed elimination)**

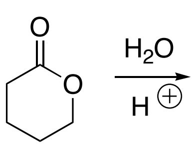


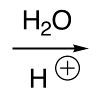
Draw the Mechanisms for the following Hydrolyses



Where will the O^{18} label end up?

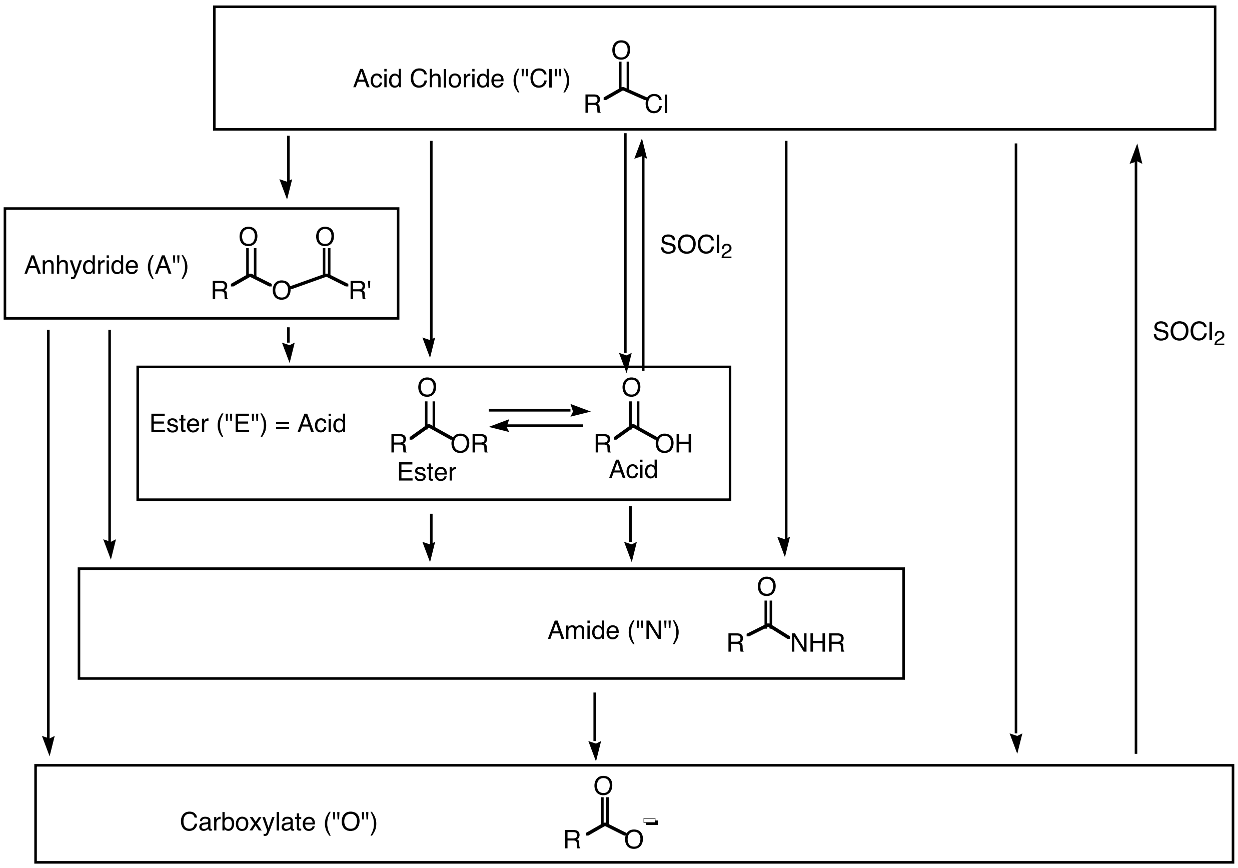






C. Reactions of Carboxylic Acids

20.9, 21.5 Interconversions with Derivatives: Cl-A-vE-N-O



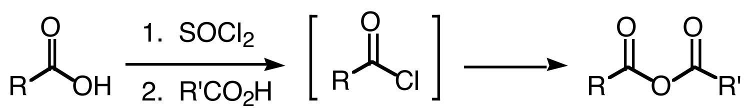
- "Cl-A-vE-N-O" Chlorides-Anhydrides-Esters (and Acids)-Amides-Carboxylates
- All can be interconverted by substitution procedures: 1, 2, or 3 steps
- Any downhill step can be done directly
- Any "lateral" step (acid to ester or vice-versa) can be done with acid
- Any "uphill" sequence requires going 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)

Acid Chlorides: Preparation and Uses (Sections 20.11 and 21.5)

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

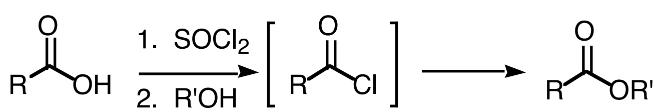
- Mechanism: Not Required
- Easy (but smelly) reaction.
  - Side products HCl and SO_2 are gases, so can just evaporate away leaving clean, useful product. So no workup is required, nice!
- Extremely useful because the acid chlorides are so reactive, and can be converted into esters, anhydrides, or amides.

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



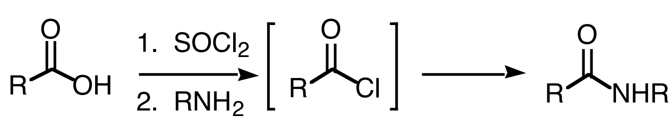
- mechanism required **for acid chloride to anhydride conversion: addition-elimination-deprotonation**
- Conversion of the acid chloride to the anhydride is a "downhill" reaction energetically.
- Conversion of the acid to the anhydride directly would be an "uphill" reaction
- Base often present to absorb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

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.
- Base often present to absorb the HCl

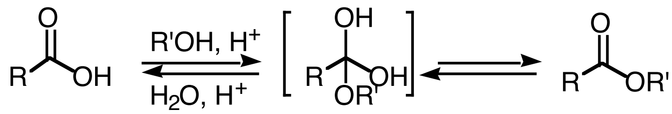
15. **Indirect Conversion to Amides** (Sections 20-11, 20-13, 21-5)



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

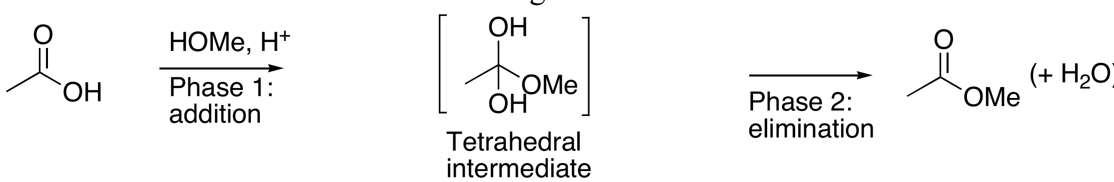
Condensation/Hydrolysis: Interconversions between Acids and Esters (20.10, 13, 21.7)

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

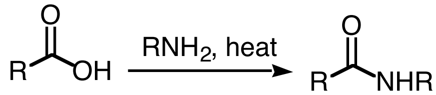


- **mechanism required: protonation-addition-deprotonation (to hemiacetal intermediate) followed by protonation-elimination-deprotonation (hemiacetal to ester)**
- These reactions are under equilibrium control.
    1. With excess water, you go to the acid.
    2. With removal of water and/or excess alcohol, the equilibrium favors the ester
- This is a "lateral" reaction, neither uphill nor downhill energetically
- This is the exact reverse of reaction 8b
- Under base conditions, the equilibrium always goes completely away from the ester and goes to the acid side
    1. The base deprotonates the carboxylic acid, so LeChatellier's principle says that the equilibrium keeps driving from ester towards acid to compensate

2. Draw the mechanism for the following reaction.



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

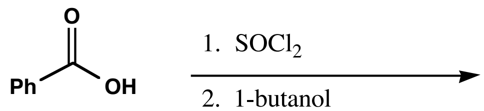


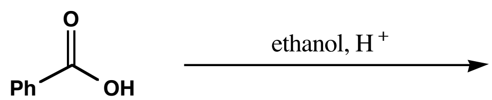
- **mechanism not required**
- This is a "downhill" reaction energetically, but is complicated and retarded by acid-base reactions. Normally the "indirect) conversion is more clean in the laboratory
- This reaction occurs routinely under biological conditions, in which enzymes catalyze the process rapidly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

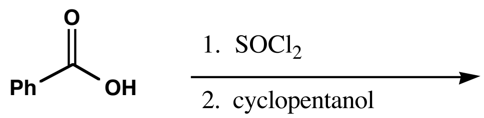
Problems

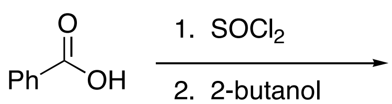
1. Synthesis of Acid derivatives. Draw the products for the following reactions.

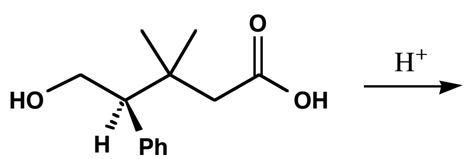
a. 

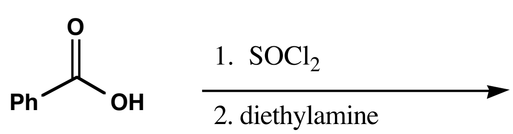
b. 

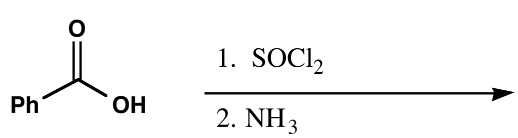
c. 

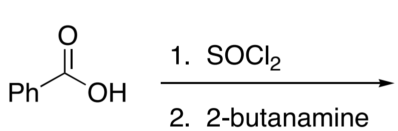
d. 

e. 

f. 

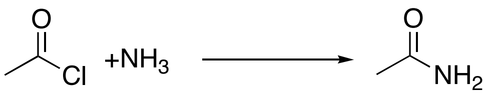
g. 

h. 

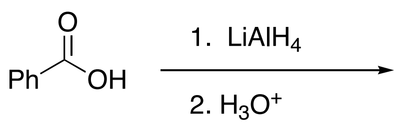
i. 

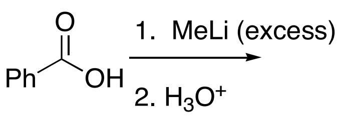
j. 

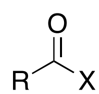
1. Draw the mechanism.

b. 

2. Draw the products for the following reactions.

a. 

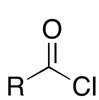
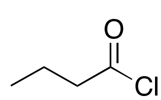
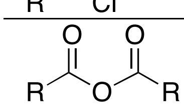
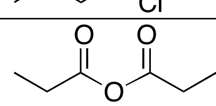
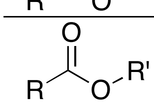
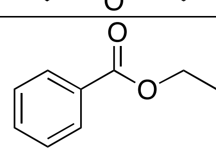
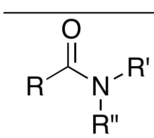
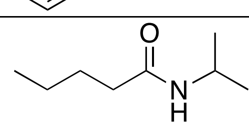
b. 

Ch. 21 Carboxylic Acid Derivatives: 

- Cl chloride
- A anhydride
- E ester
- N amide
- O: carboxylate

21.1,2 Structure, Names, Notes

- all are subject to hydrolysis
- All hydrolyze to acids (actually, to carboxylate anion) upon treatment with NaOH/H_2O
- Some (Cl and A) hydrolyze to acids under straight water treatment
- Esters hydrolyze to acids under acid catalysis

	General		Example	
	Alkanoyl chloride		Butanoyl chloride	• High reactivity • Named as if ionic
	Alkanoic Anhydride		Propanoic anhydride	
	Alkyl Alkanoate		Ethyl Benzoate	Named as if ionic
	Alkanamide		N-isopropyl pentanamide	

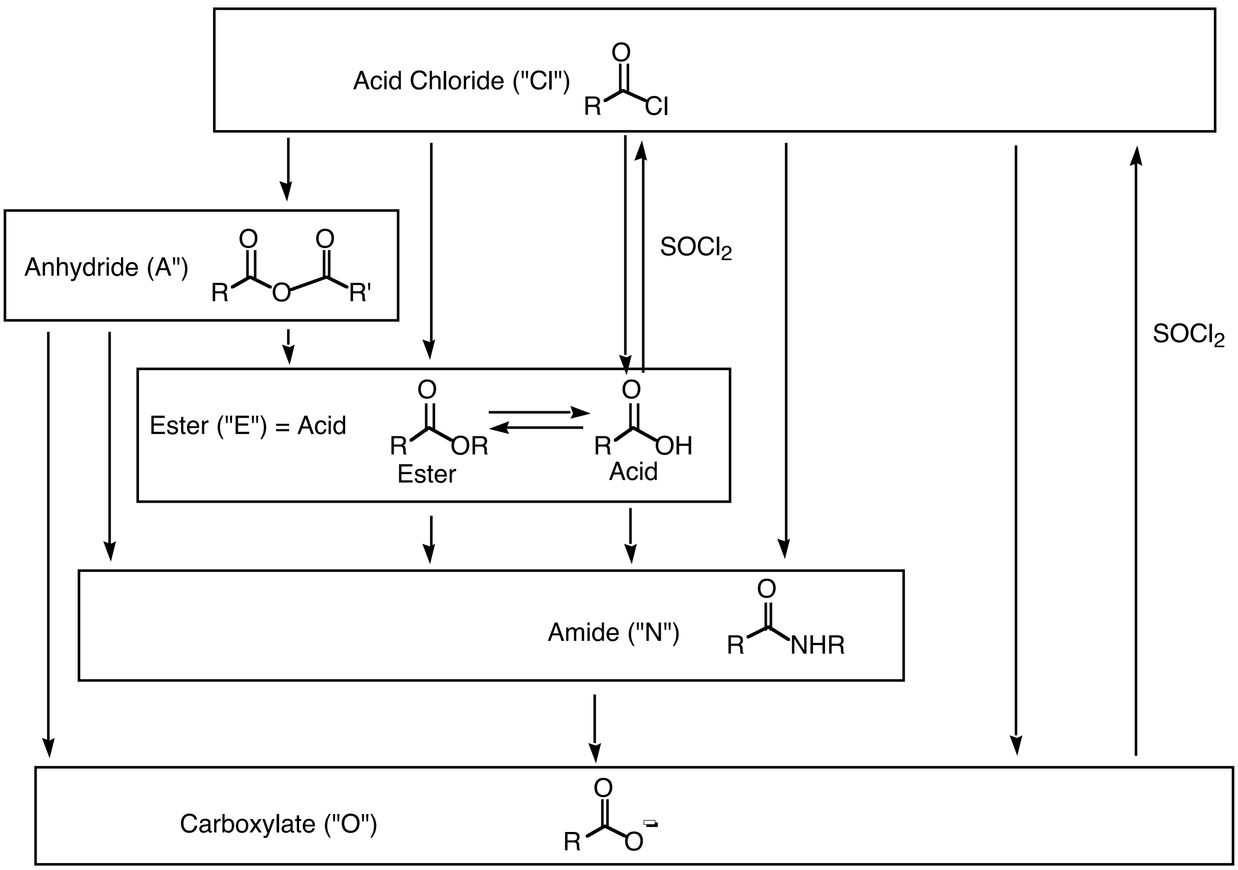
1. Draw the structures for the following esters.

a. propyl benzoate

b. methyl ethanoate

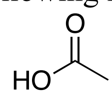
c. ethyl butanoate

21.5 Interconversion of Acid Derivatives: Cl-A-vE-N-O

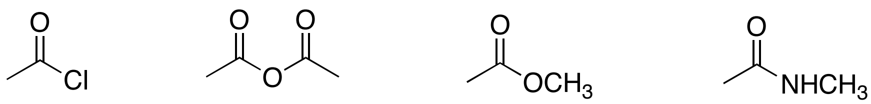


- "Cl-A-vE-N-O" Chlorides-Anhydrides-Esters (and Acids)-Amides-Carboxylates
- All can be interconverted by substitution procedures: 1, 2, or 3 steps
- Any downhill step can be done directly
- Any "lateral" step (acid to ester or vice-versa) can be done with acid
- Any "uphill" sequence requires going 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)

1. Rank the acidity of the following molecules, **1** being most acidic and **4** being least acidic.

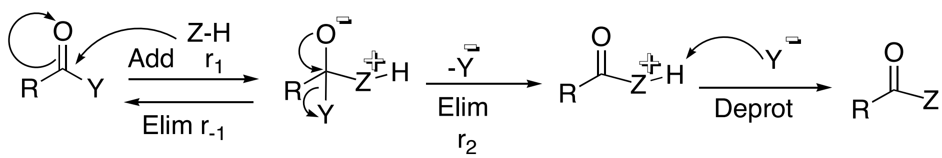
H–Cl  $HOCH_3$ NH_2CH_3

2. Rank the reactivity of the following toward hydrolysis. Do you see a similarity between your rankings for this question relative to your answers for question 8?



<u>Notes:</u>

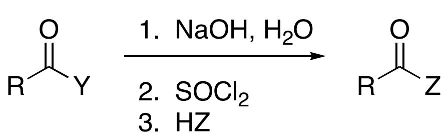
- Any "downhill" reaction can be done in one laboratory step
- Any "downhill" reaction involves a 3-step mechanism: addition-elimination-deprotonation



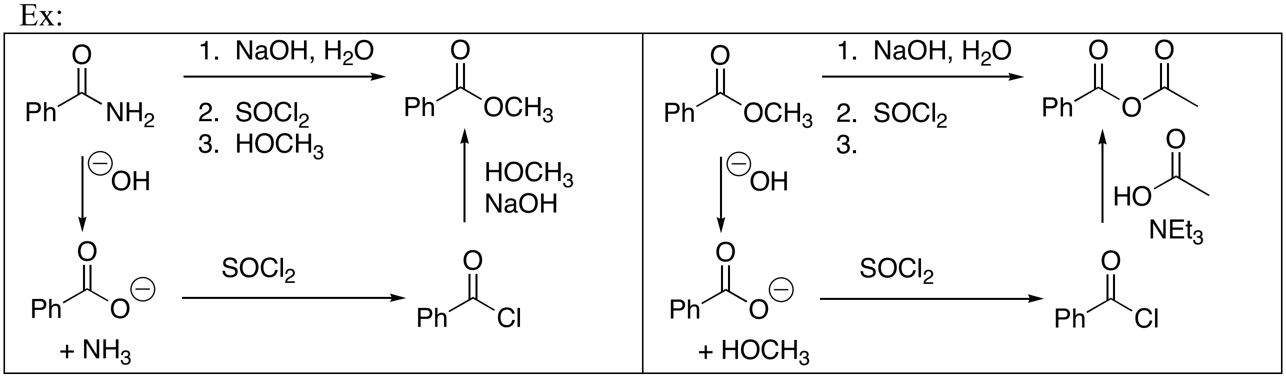
- The overall reactivity correlates the leaving ability of the Y ⊖ for two reasons
  1. This affects the kinetic r_2/r_{-1} partion. If r_2 is slow, the addition is simply reversible
  2. The same factors that make Y ⊖ a good leaving group also make the initial carbonyl more reactive toward addition (step 1, r_1).
  3. Thus good leaving groups have benefits at both r_1 and r_2

- Memory
  - Think anion stability
  - Cliff $\boxed{\text{Cl-A-vE-N-O}}$

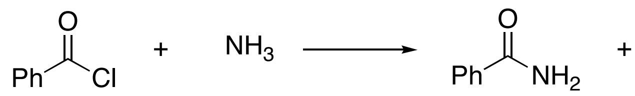
B. "Uphill" Reaction Sequences: 3-steps

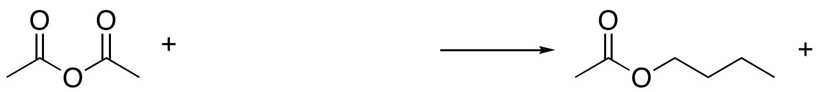


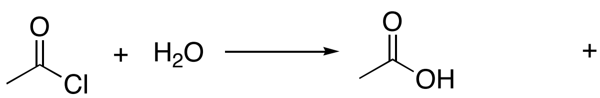
Ex:

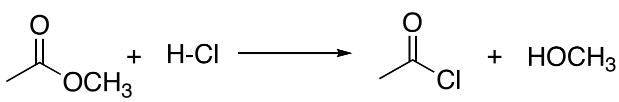


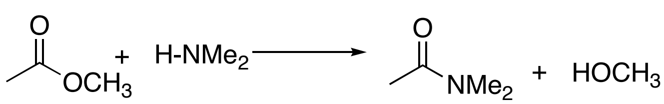
1. Which will proceed easily/directly? ("downhill"?) Add Appropriate Reactant(s) and Side Product. If it doesn't go directly, give indirect route.

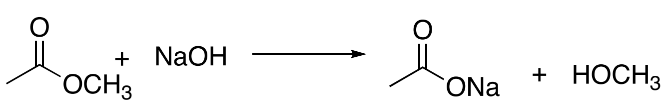
a. 

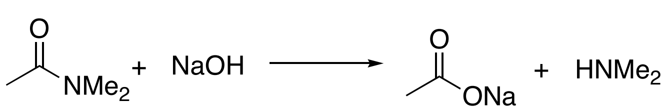
b. 

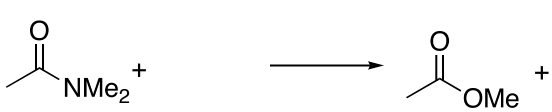
c. 

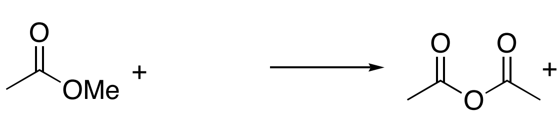
d. 

e. 

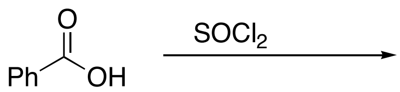
f. 

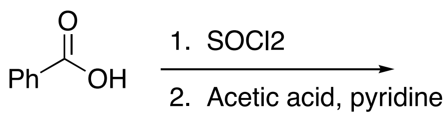
g. 

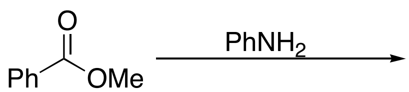
h. 

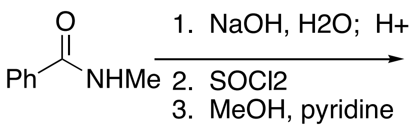
i. 

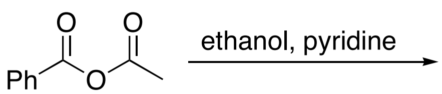
1. Provide products for the following transformations.

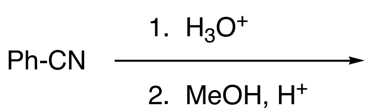
a. 

b. 

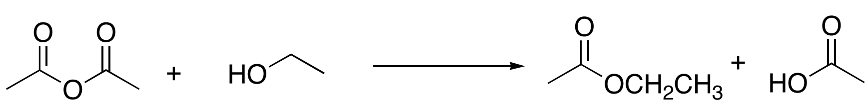
c. 

d. 

e. 

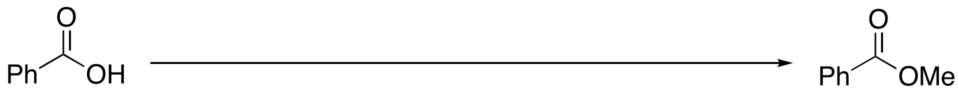
f. 

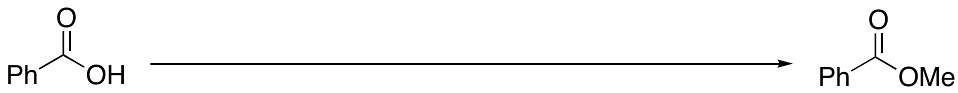
2. Draw the mechanism for the following reaction.

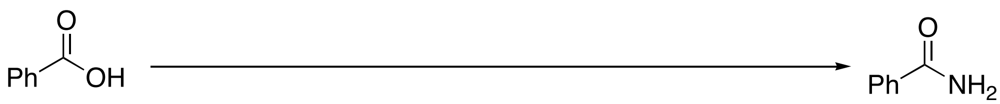


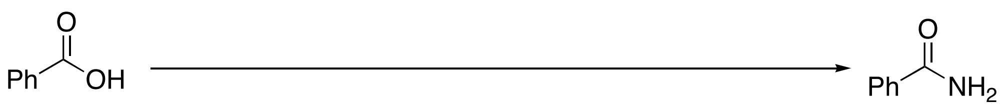
(3 steps)

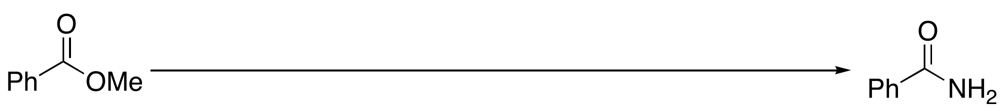
1. Provide reagents for the following transformations.

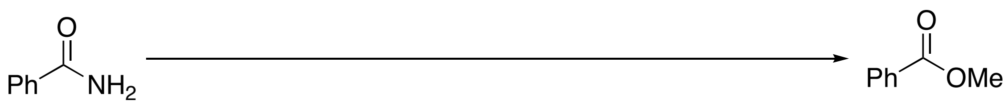
a.  (Method 1)

b.  (Method 2)

c.  (Method 1)

d.  (Method 2)

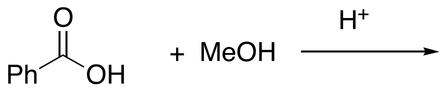
e. 

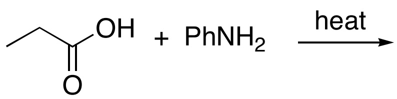
f. 

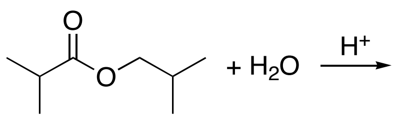
g. 

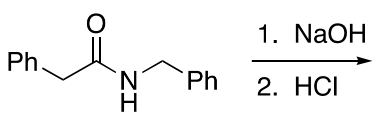
h. 

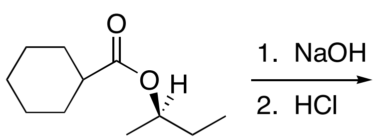
2. Provide products for the following condensation or hydrolysis transformations.

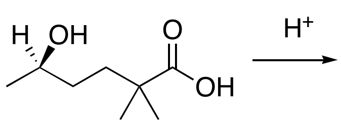
a. 

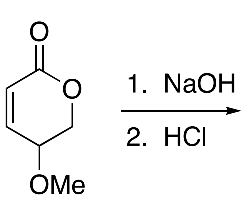
b. 

c. 

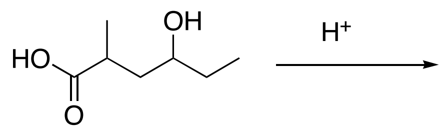
d. 

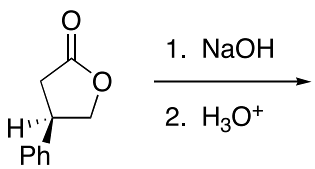
e. 

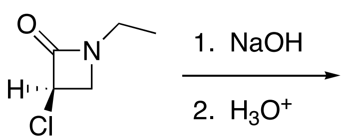
f. 

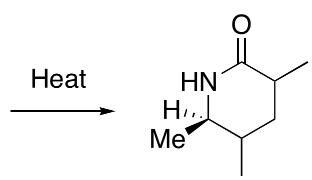
g. 

3. Cyclic Esters and Amides: Provide products or starting reactants for the following condensation or hydrolysis reactions involving cyclic esters or amides.

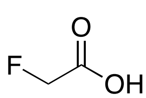
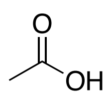
a. 

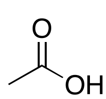
b. 

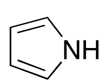
c. 

d. 

4. Rank the following as acids or bases.

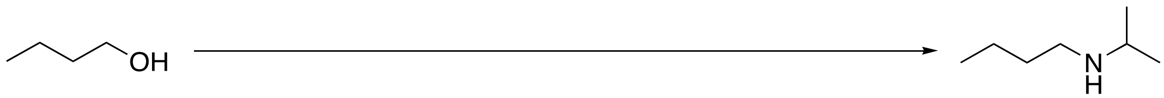
a.   $CH_3\overset{\oplus}{N}H_3$ NH_3

b. $(CH_3)_2\overset{\oplus}{N}H_2$ $Ph\overset{\oplus}{N}H_3$  H_2O

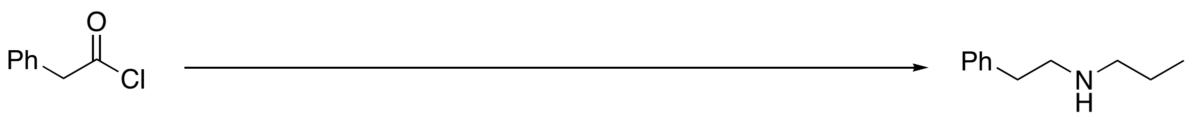
c. Et_3N $EtNH_2$  PhMgBr

5. Provide reagents for the following transformations. There may be more than one solution.

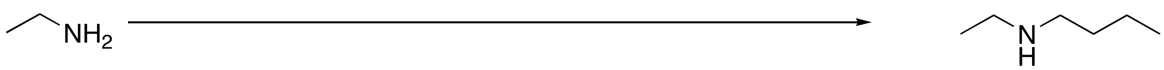
a.



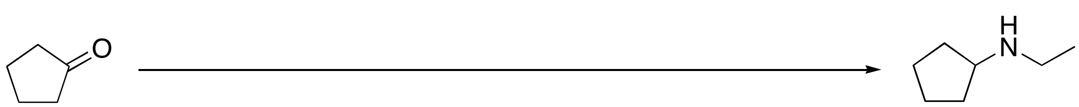
b.



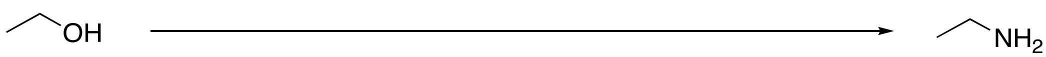
c.



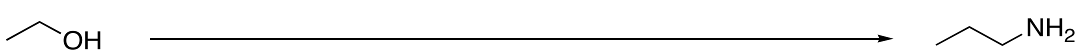
d.



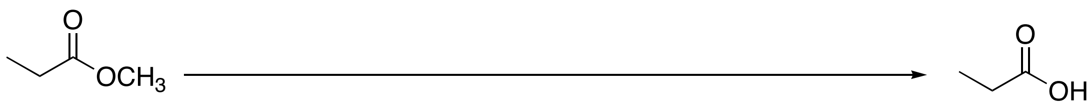
e.

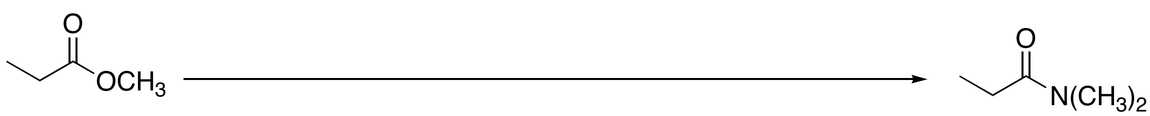


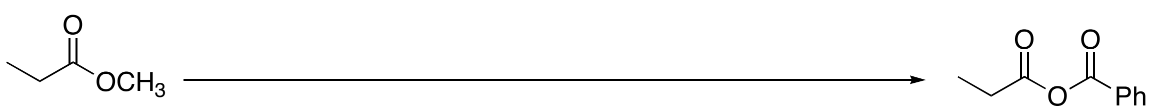
f.



6. Provide reagents for the following transformations. There may be more than one solution.

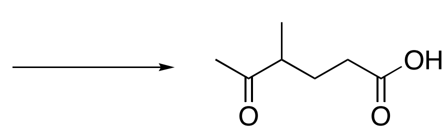
a. 

b. 

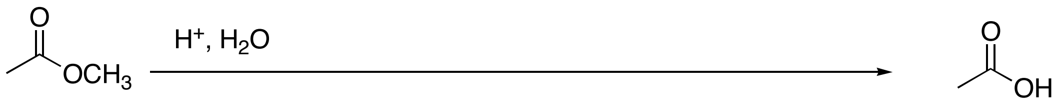
c. 

d. 

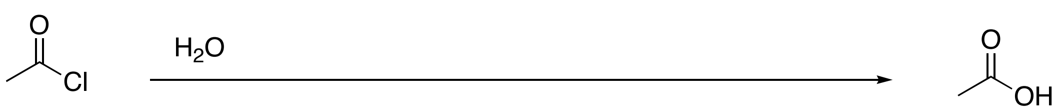
e. 

f. 

7. Provide mechanism for the following reactions.

a. 

b. 

c. 

d. $CH_3NH_2 \xrightarrow{3\ CH_3Br,\ NaOH} (CH_3)_4N^{\oplus}\ Br^{\ominus}$