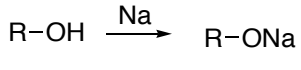
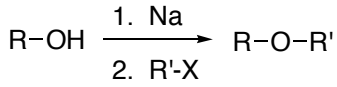
Summary of Alcohol Syntheses, Ch. 10 (and Review of Old Ones).

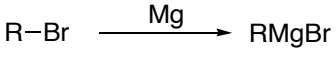
1 

- Potassium (K) analogous.
- Key way to convert alcohol to alkoxide, reactive as S_N2 nucleophile and E2 base.

2 

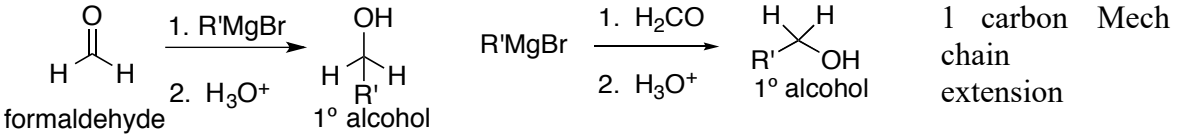
- Alkoxide formation-S_N2 route to ether
- The electrophile R'-X must be S_N2 reactive, preferably 1º with a good leaving group

Mech?

3 

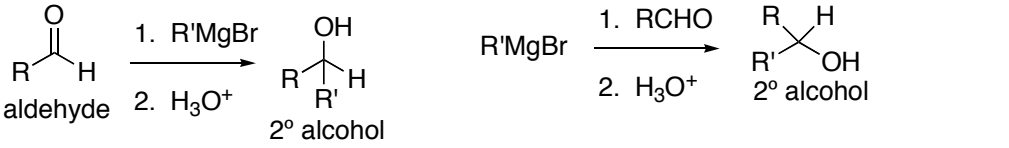
-Li is analogous for making RLi, which also act analogously.

-MgBr is spectator: $R^{\ominus}$ is key.

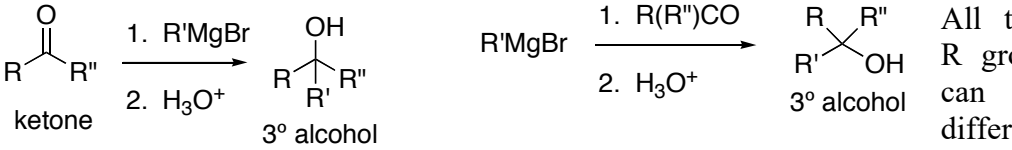
4 

1 carbon chain extension

Mech

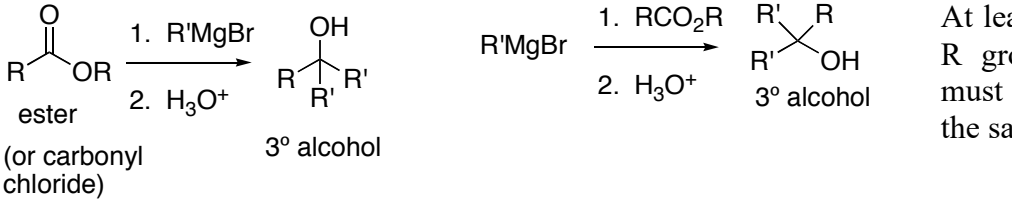
5 

Mech

6 

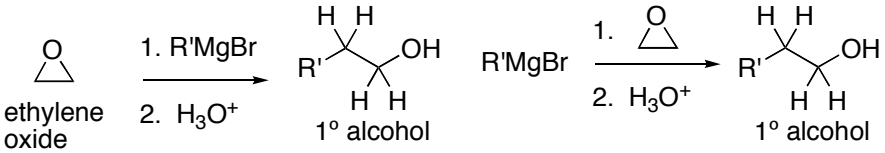
All three R groups can be different.

Mech

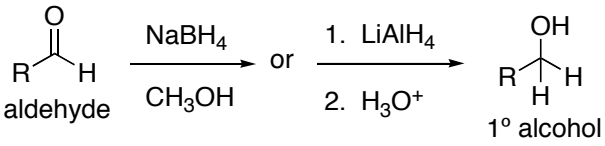
7 

At least 2 R groups must be the same

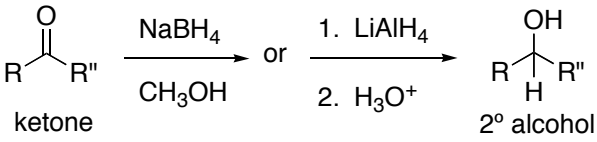
Mech

8 

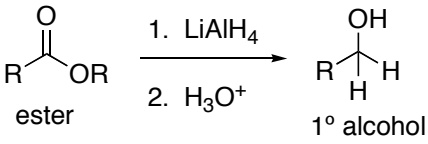
2-Carbon chain extension Mech

9 

Mech

10 

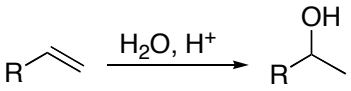
Mech

11 

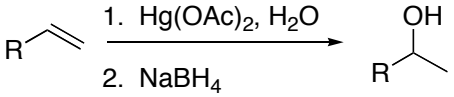
$NaBH_4$ will not react with esters

Mech

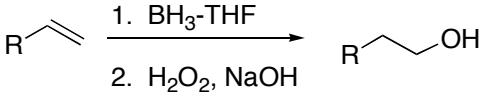
Review Routes to Alcohols

10 

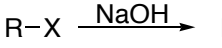
Markovnikov

11 

Markovnikov

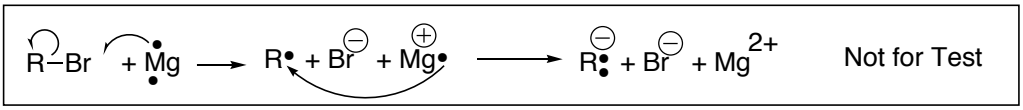
12 

anti-Markovnikov

13 

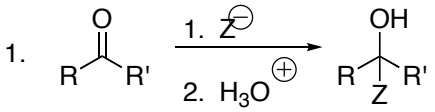
S_N2 mech, needs 1° or 2° system and an excellent leaving group

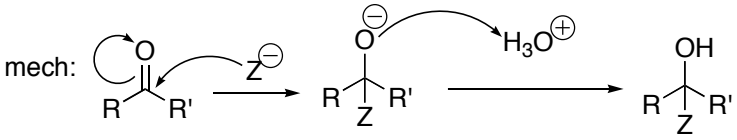
Summary of Mechanisms, Ch. 10



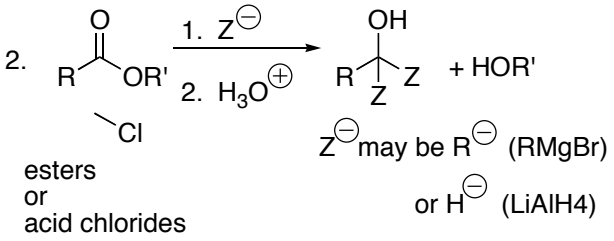
For Test:

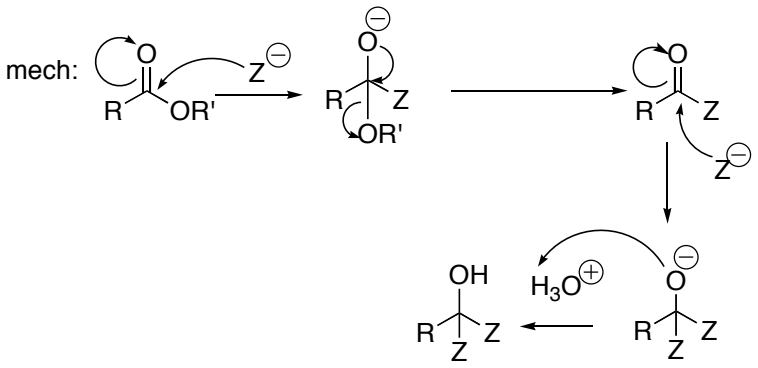
Aldehydes, Ketones, and Formaldehyde



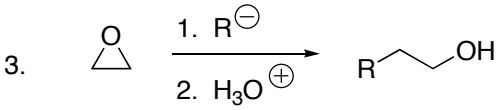


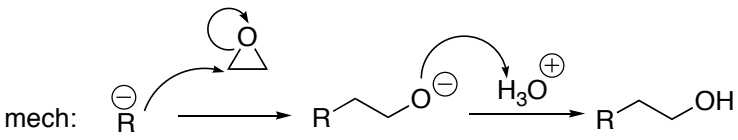
Esters





Epoxides

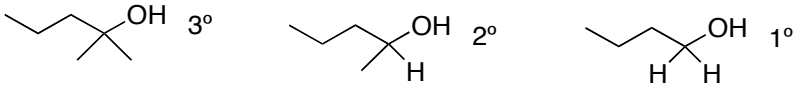




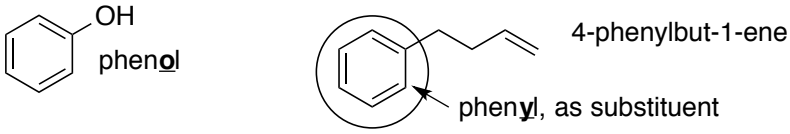
10.1,2 Intro, Classification

"**Alcohol**": OH attached to a saturated, sp^3, "alkyl" carbon

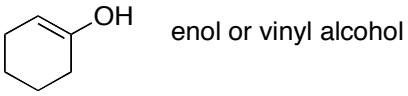
1º, 2º, 3º Alcohols: based on whether the carbon with the OH is 1º, 2º, or 3º



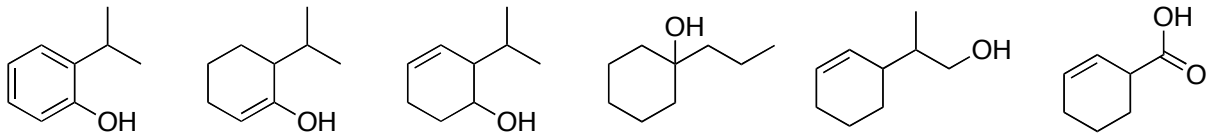
"**Phenol**": OH attached to an aromatic
-Note: phen**o**l, not phen**y**l



"Enol" or "vinyl alcohol": OH attached to an alkene



Problem: Classify each of the following either as a phenol, as a carboxylic acid, or as a 1º, 2º, 3º, or vinyl alcohol:

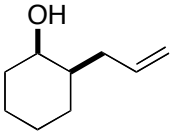


10.3 Nomenclature

A. IUPAC, when alcohol is priority functional group and is part of the core name: alkan-x-**ol**

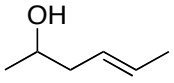
- Choose longest carbon chain **that has the OH attached**
- Remember to number! (including if it's on carbon number 1)
- The oxygen itself does not count as a number

B. Cycloalkanols: The OH-carbon is automatically Number 1. Don't need "-1-" in front of "ol".

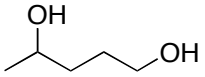


C. **Alk-**x-**en-z-ol**. When an alkene is in the main carbon chain, you need two number descriptors, one for the alkene, the second for the alcohol.

- The OH still dictates the numbering. Number from end nearest the OH.
- The OH number right before the "ol"
- The alkene number in front of the "en"



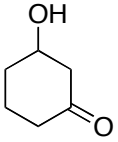
D. Diols: alkane-x,y-**diol**



E. Functional Group Priority: CO_2H > C=O > OH > amine > alkene > halide

- When you have more than one functional group, the higher priority dictates the numbering
- **The higher priority is used in the "core name"**
- **The lower priority group may be forced to be named as a substituent**

F. OH as a Substituent: "**Hydroxy**"

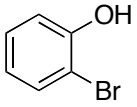


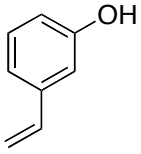
G. Common Names: Alkyl alcohol

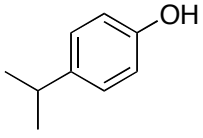
CH_3OH 

H. Substituted Phenols

- IUPAC: use numbers, with OH carbon #1
- Common:
  - **Ortho: 2-position, adjacent**
  - **Meta: 3-position, two carbons away**
  - **Para: 4 position**
- Skill: be able to use or recognize either system





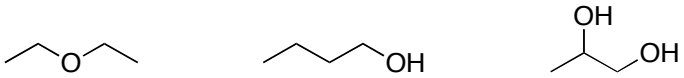


IUPAC:

Common:

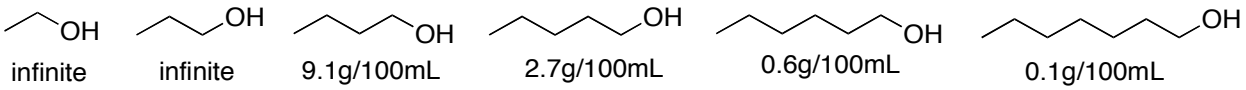
10.4 Physical Properties: Dominated by H-Bonding

BP: Match the boiling point for the following structures: 35º, 137º, 187º



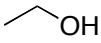
Water solubility: water solubility decreases as hydrophobic R gets longer

- In general,
  - R ≤ 4 carbons, ROH substantially water soluble
  - R ≥ 5 carbons, ROH minimal water solubility



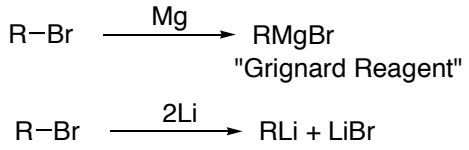
10.5 Commercially Important Alcohols

- Toxic: All alcohols are "toxic" if swallowed in sufficient quantities

CH_3OH		
• Cheap • Solvent • Fuel • 100 mL → death • 15 mL → blindness	• 200 mL (7 oz) → death • Least toxic alcohol • Alcoholic beverages • Fermentation • Solvent	• Rubbing alcohol • 100 mL → death • Kills germs on skin, but not absorbed

10.7 Synthesis of Alcohols: Review: See p. 2, from Alkyl Halides (S_N2) and Alkenes

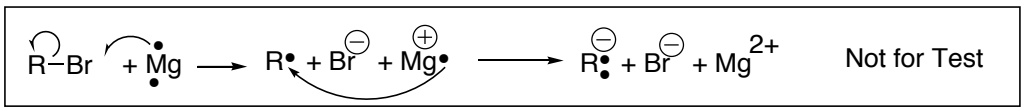
10.8 Organometallics: RM (M = Metal) = $R^{\ominus}$ $M^{\oplus}$



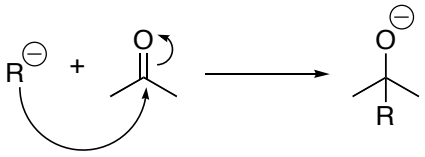
-Li is analogous for making RLi, which also act analogously.

-MgBr is spectator: $R^{\ominus}$ is key.

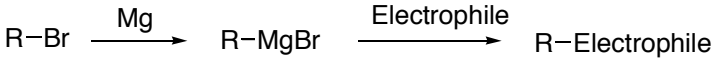
1. We will focus on the magnesium reagents RMgBr
2. RMgBr = "Grignard Reagents" (Victor Grignard)
3. Key: This is the way to make $R^{\ominus}$, strong nucleophiles/bases
4. RMgBr are formed via redox reaction.
   - Mg gives up two electrons, is oxidized
   - Bromine is reduced to bromide anion
   - Carbon is reduced to carbanion



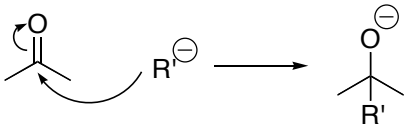
5. The formation of Grignard Reagents is completely general for all R-Halides:
   - 3º, 2º, and 1º alkyl halides all work well
   - Aryl and Vinyl halides as well as alkyl halides work well
   - RCl, RBr, and RI all work well
   - For class, we will normally use bromides, due to synthetic accessibility
6. **<u>View as carbanions: RMgBr = $R^{\ominus}$ Super Strong Bases and Nucleophiles</u>**
   - The counterion metal is a spectator
   - Stability-reactivity principle: very unstable → very reactive
   - This great reactivity is very useful (as nucleophile)
   - This great reactivity (as base) has implication for proper technical use (see following)
7. Solvent and handling: Grignard reactants RMgBr must be made, stored, and handled in special solvents under special conditions:
   - No water allowed
     - $R^{\ominus} + H_2O \rightarrow R\text{-}H + HO^{\ominus}$ Destroys carbanion
   - No alcohol or amines or acids allowed either, or carbanion will just deprotonate them too
   - If any chemicals with carbonyls are present, they too will react with the carbanion by nucleophile/electrophile reaction



   - Grignards and other organometallics are made in either alkane or ether solvents.
     - These don't have any acidic hydrogens that protonate carbanions.
     - These don't have any carbonyls that react with carbanions
8. Two perspectives for dealing with organometallics in general and RMgBr in particular
   - Mechanistic Thinking: $R^{\ominus}$
   - Predict-the-product thinking: R-MgBr: easier to see source and substitution product.



10.9 Addition of RMgBr to Carbonyl Compounds: Alcohols are Produced



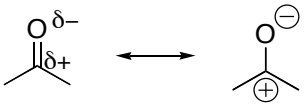
Exothermic Addition of Carbon or Hydrogen Anions:

- σ bond (made) stronger than π bond (broken)
- oxygen anion more stable than carbanion

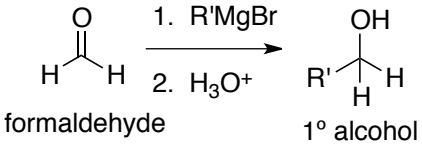
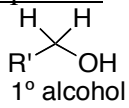
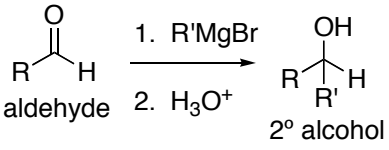
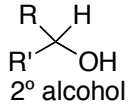
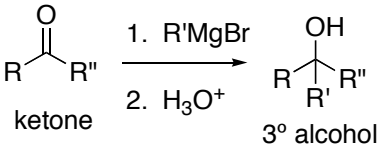
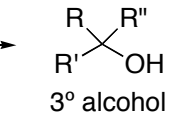
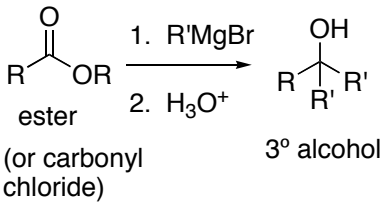
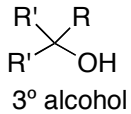
Carbonyl is strongly electrophile

-much stronger even than a 1º alkyl iodide!

1. Breakable π bond
2. Carbonyl polarity



Additions of Grignard Reagents to Carbonyl Compounds

	From Carbonyl's Perspective		From Grignard's Perspective			
4	 formaldehyde → 1º alcohol		R'MgBr	 1º alcohol	1 carbon chain extension	Mech
5	 aldehyde → 2º alcohol		R'MgBr	 2º alcohol		Mech
6	 ketone → 3º alcohol		R'MgBr	 3º alcohol	All three R groups can be different.	Mech
7	 ester (or carbonyl chloride) → 3º alcohol		R'MgBr	 3º alcohol	At least 2 R groups must be the same	Mech

Pattern:

1. After reaction, the original carbonyl carbon will have one and only one C-O single bond
2. For formaldehyde, aldehydes, and ketones, one R group adds (reactions 4-6)
3. For esters or carbonyl chlorides ("acid chlorides"), two R groups add
   - Replace not only the carbonyl p-bond, but also the "extra" C-O or C-Cl single bond
4. Product output:
   - Formaldehyde (2 H's) → 1º alcohol
   - Aldehyde (1 H) → 2º alcohol
   - Ketone (0 H) → 3º alcohol. No need for all 3 attachments to be the same.
   - Ester (0 H) → 3º alcohol. At least two common attachments at end.

Predicting Grignard Reaction Products

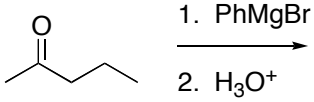
1. From carbonyl perspective:
   - The carbanion R' adds to the carbonyl carbon
   - The carbonyl =O gets replaced by –OH
   - For formaldehyde, aldehydes, and ketones: the two attachments on the original carbonyl carbon remain attached as spectators
   - For esters or acid chlorides: the one non-heteroatom attachment on the original carbonyl carbon remain attached as spectators.
     - The "extra" heteroatom gets replaced by a second carbanion R'

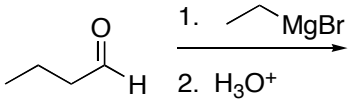
2. From Grignard perspective:
   - Where R-MgBr begins, R-C-OH ends.
     - In other words, the MgBr gets replaced by the carbonyl carbon

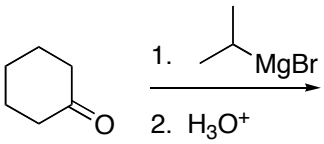
Note: Be sure that in the product, no carbon has more than one C-O bond

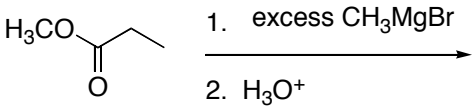
Draw products from the following reactions.

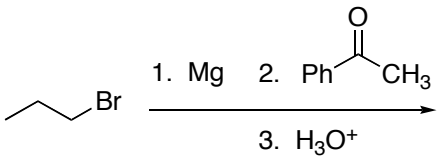
1º, 2º or 3º?

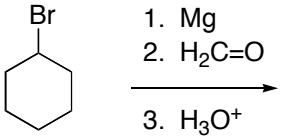
1 

2 

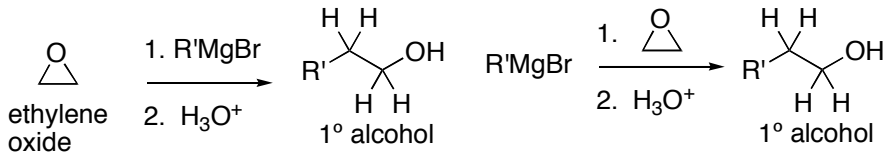
3 

4 

5 

6 

10.9E Grignard Reaction with Ethylene Oxide (Simplest Epoxide)

8 

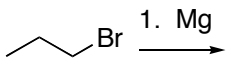
2-Carbon chain extension Mech

Notes

1. Results in a 1° Alcohol
2. **Predicting product: Two carbons end up in between the carbanion R' and the OH**
3. Ethylene oxide and formaldehyde are complementary Grignard acceptors leading to 1° alcohols
   - Ethylene oxide extends the carbon chain by two (relative to the original RMgBr)
   - Formaldehyde extends the carbon chain by one (relative to the original RMgBr)
4. 2-Carbon ethylene oxide and 2-carbon ethanal give different products
   - Ethylene oxide → the OH is 1° and the OH is two carbons removed from the carbanion R
   - Ethanal→ the OH is 2° and the OH and carbanion R are both connected to the same carbon

Draw products from the following reactions.

1

2 

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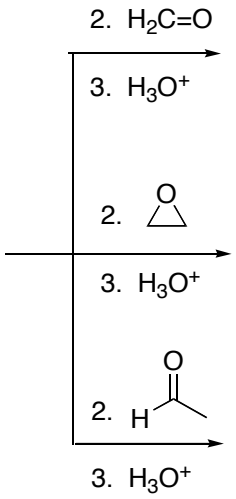
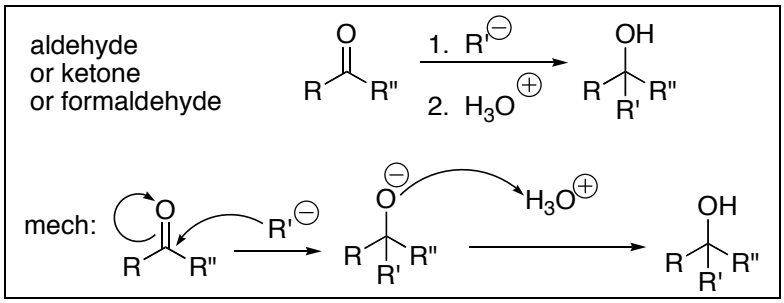


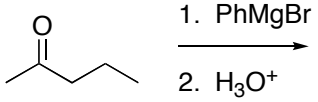
Reaction Mechanisms for Grignard Reactions

Formaldehyde, Aldehyde, or Ketone as Carbonyl Compound (Reactions 4, 5, and 6)



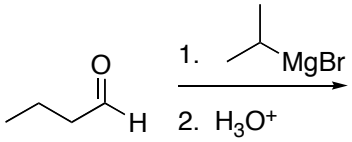
1. Two simple steps:
   - **a. Addition**
   - **b. Protonation**
2. Timing:
   - a. The carbanion is added first, at one step in time, under strongly anionic conditions
   - b. Later acid is added, in a second laboratory step. This provides a cationic environment
3. RMgBr = R-MgBr = R$^{\ominus}$ carbanion
   - a. The $^{\oplus}$ MgBr stuff is spectator, doesn't need to be drawn in
   - b. Ignore in mechanisms
   - c. In reality, it actually does play a nontrivial role, but we'll save that for grad school!

Draw mechanisms for the following reactions:

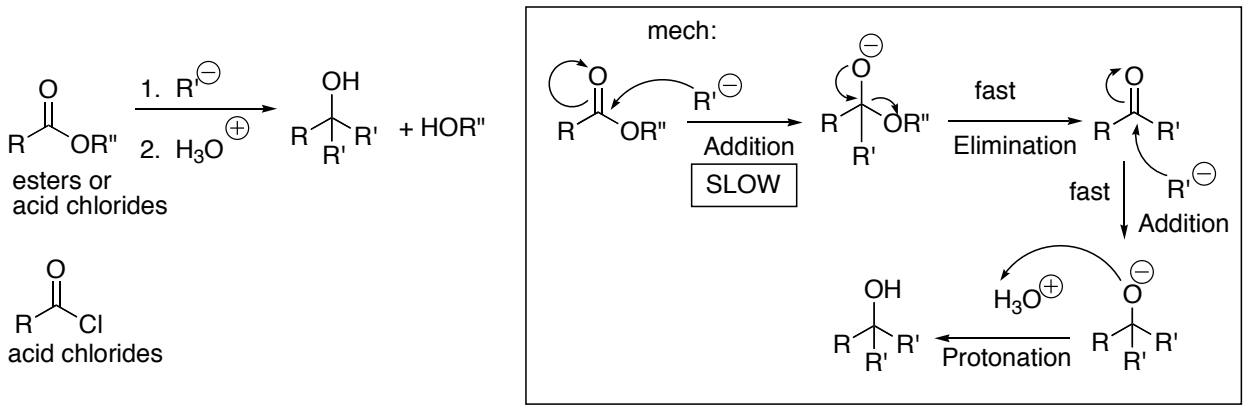
1 

Standard Simple Grignard Mechanism:
1. Add Anionic Nucleophile, to produce an oxyanion
2. Protonate

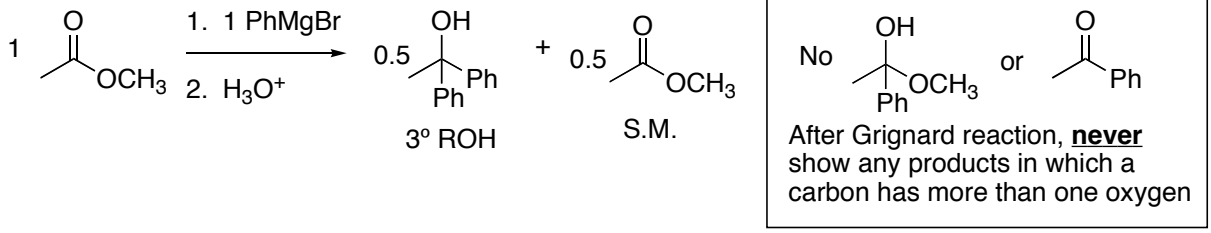
Mechanism requirement notes. Must:
1. draw intermediate(s)
2. show correct electron/arrow flow
3. Specific arrow source and target
4. MgBr can be left out (convenience)
5. Anion produces anion
6. H+ changes anion/cation conditions

2 

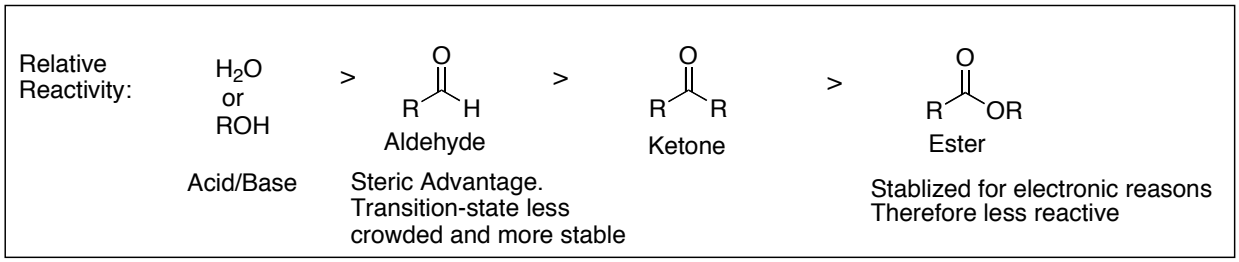
Esters or Acid Chlorides: More Complex, Needs to Explain Two Additions and More Bond Breakings



1. Four Step Mechanism:
   a. **Addition**
   b. **Elimination**
   c. **Addition**
   d. **Protonation**
2. Timing:
   a. The carbanion is added first, at one point in time, under strongly anionic conditions
      - The first three steps all occur under these anionic conditions
   b. Acid is only added much later, in a second laboratory step. This gives a cationic environment.
   c. Why don't you just protonate after the first step?
      - There is no proton source available, and the elimination proceeds instead!
3. What if I add only one RMgBr?

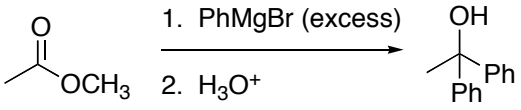


Why? Kinetics and Reactivity. **MEMORIZE**.



- Large differences in reactivity, with ketone > ester
- Elimination step 2 is also very fast
- Thus, under the anionic conditions, the addition is the slow step
  - After it does happen, elimination and another addition happens bang-bang.

Draw Mechanism:

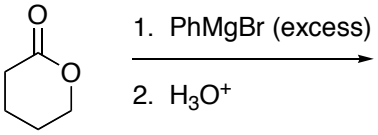


Ester Mechanism:

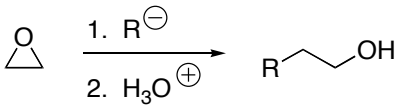
1. Add
2. Eliminate
3. Add Again
4. Protonate

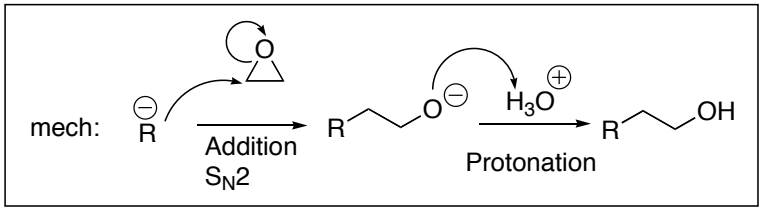
Cyclic Ester: The O-Carbonyl single bond breaks, but the other C-O single bond does **not** break -the result is formation of a dialcohol

Draw product and mechanism for the following:

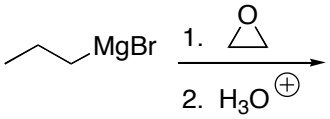


Ethylene Oxide Mechanism





Draw product and mechanism for the following:

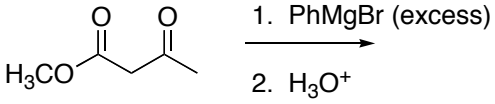


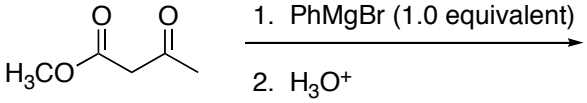
Mechanism:

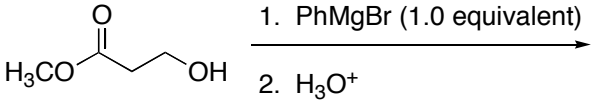
1. Add
2. Protonate

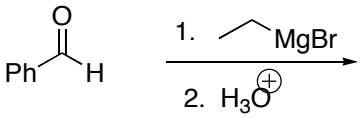
- Very Similar to the ketone/aldehyde mechanism, except you break a sigma rather than a pi bond.

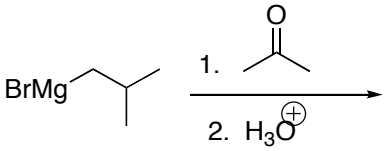
More Grignard Practice. Including polyfunctional Molecules: (Know relative reactivity)

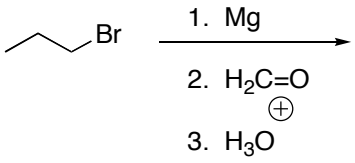
1 

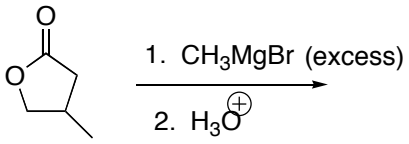
2 

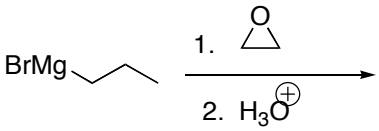
3 

4 

5 

6 

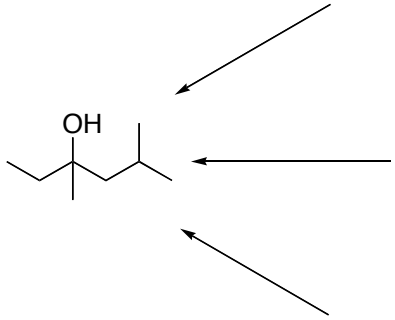
7 

8 

Grignards in Synthesis: Provide Precursors.

- **Think backwards from Targets to Reactants.**
- Identify possible Grignards and Grignard acceptors
- **Pattern:**
  - **3º alcohol, all three attachments different ← Ketone Precursor**
  - **3º alcohol, two (or more) of the attachments identical ← Ester**
  - **2º alcohol ← Aldehyde**
  - **1º alcohol ← Formaldehyde or ethylene oxide**

a.



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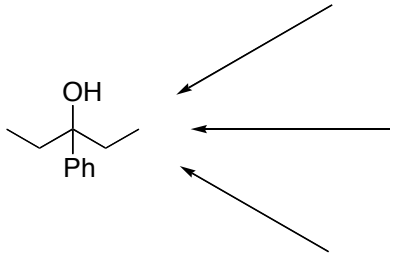

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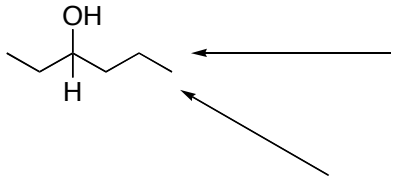
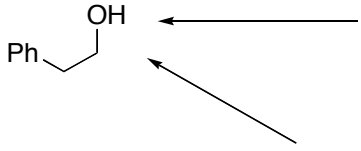
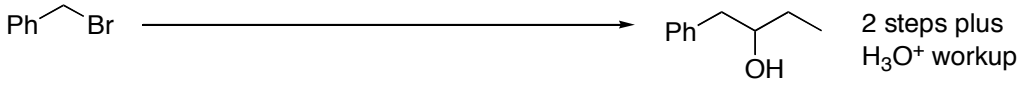


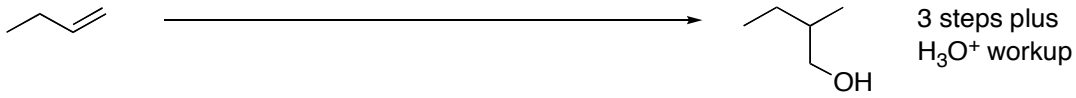
d.

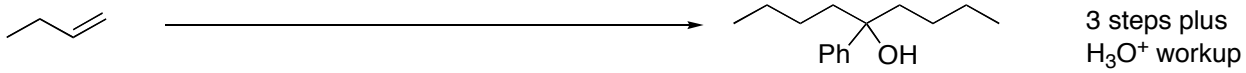


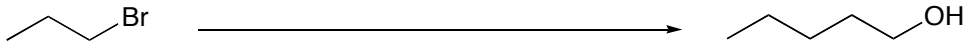
Provide Reagents for the Following Transformations. You may use whatever reagents, including ketones or aldehydes or Grignards or esters, that you need.

- Key: Try to identify key C-C connection in the product that wasn't present to start with
- Try to identify the where the reactant carbons are in the final product
- Numbering your carbon chains is very helpful.
- Usually best to work backwards from the product

a. 

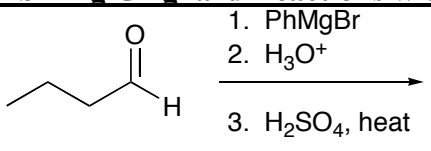
b. 

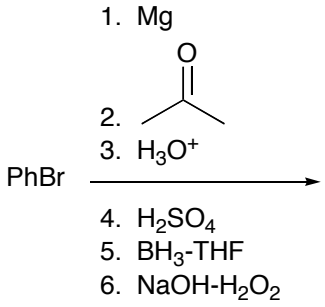
c. 

d. 

e. 

Combining Grignard Reactions with Other Reactions

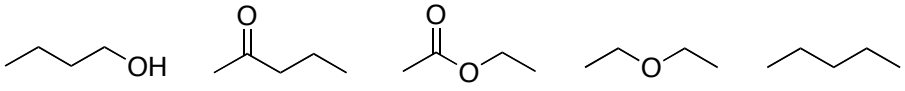
a. 

b. 

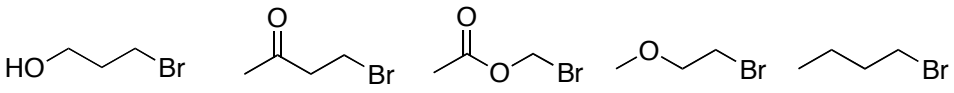
10.10 Restrictions on Grignard Reactions

- RMgBr = $R^{\ominus}$ carbanion, highly unstable, highly reactive.
- Unstable in the presence of:
  1. OH's (get proton transfer reaction)
  2. Carbonyls (get Grignard-type nucleophilic addition)

1. Solvent limitations. RMgBr cannot be formed and used in the presence of
   - H2O
   - ROH
   - Any solvent with a C=O

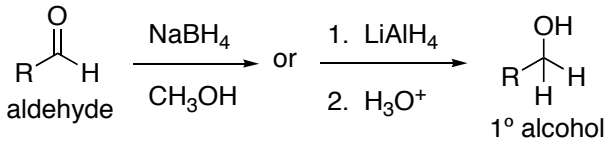
Which Solvents (if any) Would be OK for Handling RMgBr?, 

2. Substrate limitations. Any organohalide that also contains an OH or C=O bond can't be converted into a useful RMgBr, because it will self-destruct.

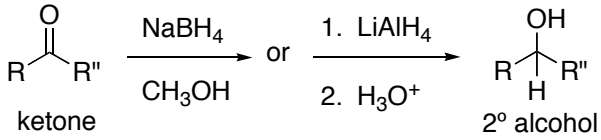
Which substrates could be converted into RMgBr, and subsequently reacted with CH_3CHO? 

3. Atmosphere/Glassware/Storage limitations. Make, store, and use in:
   - water-free dried glassware
   - moisture-free atmosphere. (Dried air, or else under nitrogen or argon atmosphere)
   - When stored for extended periods, must have very good seals so that no air can leak in.

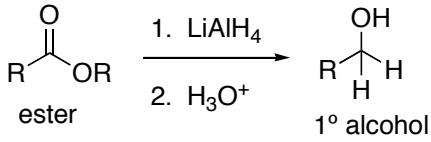
10.11 Alcohols by Reduction of Carbonyls: H $^{\ominus}$ Addition

9 

Mech

10 

Mech

11 

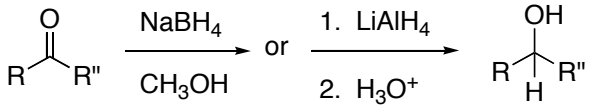
$NaBH_4$ will not react with esters

Mech

Mechanism

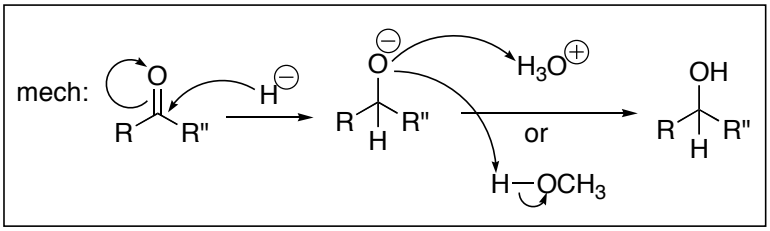
Aldehydes and Ketones

aldehyde
or ketone
or formaldehyde

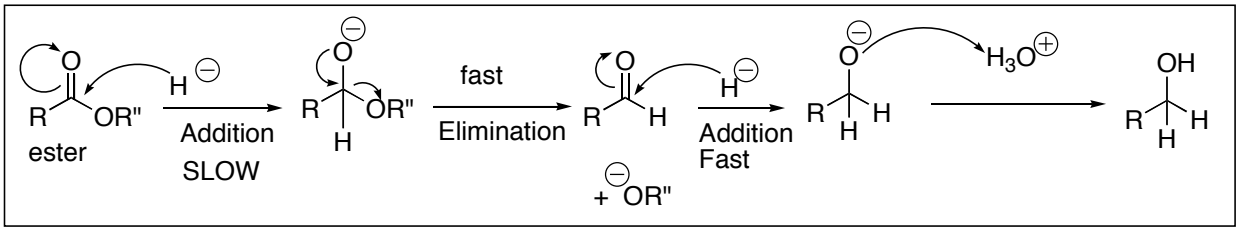


$NaBH_4 = H^{\ominus}$

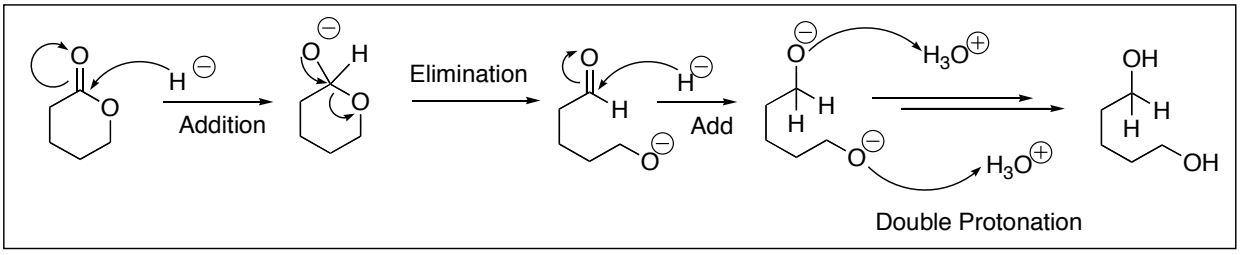
$LiAlH_4 = H^{\ominus}$



Esters

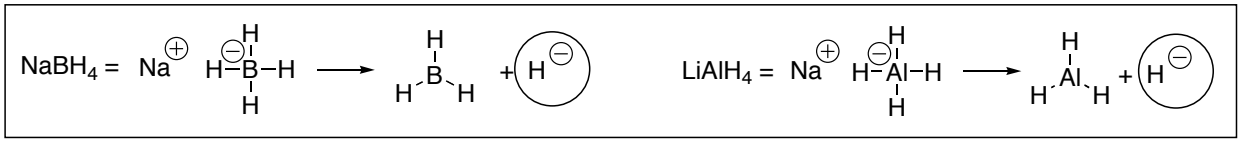


Cyclic Esters



Notes:

- Mechanisms are exactly like with Grignard reactions
- $LiAlH_4$ and $NaBH_4$ function as hydride anions $H^{\ominus}$
- For mechanisms, just draw $H^{\ominus}$ rather than trying to involve the Li and Al and Na and B…



- Boron is one row higher than aluminum, and in keeping with normal periodic patterns is more electronegative
  - Because boron is more electronegative, the $BH_4^{\ominus}$ anion is more stable, and less reactive.
    - The boron holds the $H^{\ominus}$ more tightly.
  - Aluminum being less electronegative doesn't attract and hold the $H^{\ominus}$ as well, and thus is considerably more reactive.

Reactivity

	Aldehydes	Ketones	Esters
$LiAlH_4$	Yes	Yes	Yes
$NaBH_4$	Yes	Yes	No

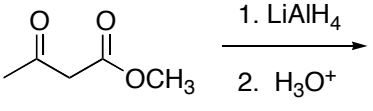
$LiAlH_4$ is much stronger, $NaBH_4$ much weaker

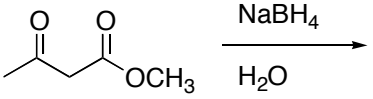
1. $LiAlH_4$ is strong enough to react with esters, $NaBH_4$ isn't
2. **Selective reduction**: if both an ester and an aldehyde/ketone are present:
   - $LiAlH_4$ reduces both
   - $NaBH_4$ selectively reduces the aldehyde/ketone but leaves the ester untouched
3. **$LiAlH_4$ is strong enough to react with and be destroyed by water or alcohol; $NaBH_4$ isn't**

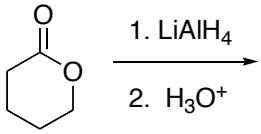
$$LiAlH_4 + H_2O \rightarrow H_2(gas) + LiOH + AlH_3 + heat$$

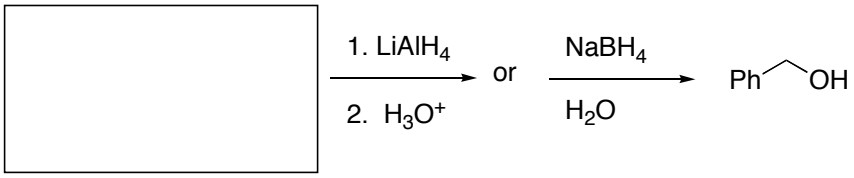
   a. As a result, $LiAlH_4$ is harder to use and store
   b. Acid has to be added in a subsequent step with the $LiAlH_4$; (thus, 2-step recipe)
   c. $NaBH_4$ can be run in alcohol solvent which serves as a proton source for protonating alkoxide
   d. Solvent restrictions, glassware must be dry, wet air must be excluded, etc.
   e. Because $NaBH_4$ is stable to water, it's easier to handle in air, easier to store, much easier to work with
   f. Default: for a simple aldehyde or ketone reduction, normally use $NaBH_4$ because it's so much easier
4. $LiAlH_4$ is strong enough to react with esters, $NaBH_4$ isn't

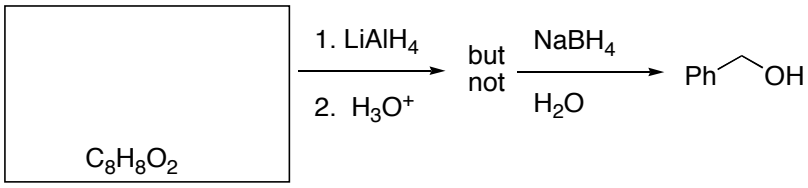
Draw the products for the following reactions.

1. 

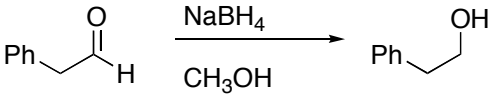
2. 

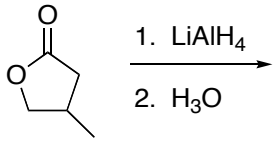
3. 

4. 

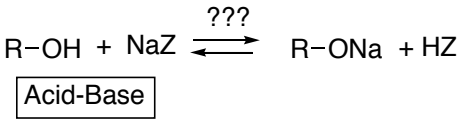
5. 

Draw the mechanism for the following reaction.

6. 

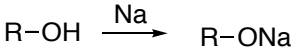
7. 

Summary of Alcohol Reactions, Ch. 11.

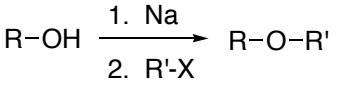
1 

Acid-Base

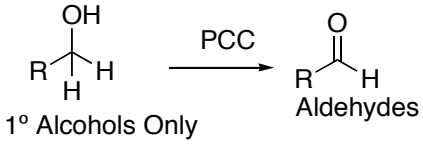
- Deprotonation by a base.
- Controlled by relative stability of RO $^{\ominus}$ versus Z $^{\ominus}$.
- Consider relative electronegativity and whether either anion is resonance stabilized.

2 

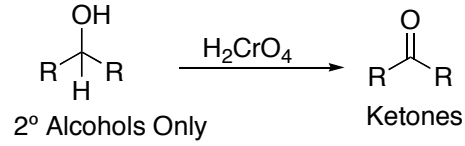
- Potassium (K) analogous.
- Key way to convert alcohol to alkoxide, reactive as S_N2 nucleophile and E2 base.

3 

- Alkoxide formation-S_N2 route to ether
- The electrophile R'-X must be S_N2 reactive, preferably 1º with a good leaving group

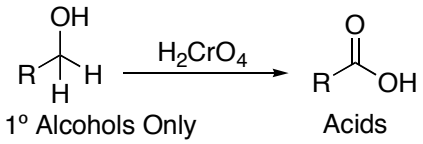
4 

- Key access to aldehydes, which are useful for more Grignard chemistry.
- Note difference between PCC and H_2CrO_4
- PCC does not react with 2º alcohols very rapidly

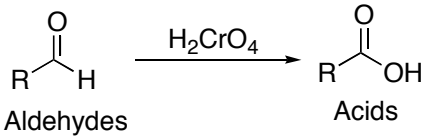
5 

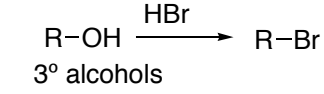
H_2CrO_4 = $Na_2Cr_2O_7$, H_2SO_4 or CrO_3/H_2O

- Key access to ketones.
- PCC does not react very fast with 2º alcohols

6 

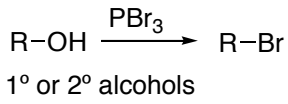
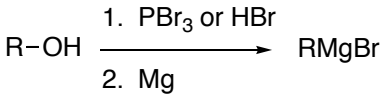
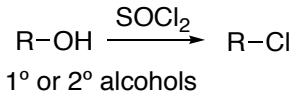
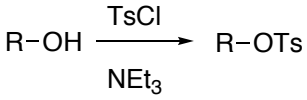
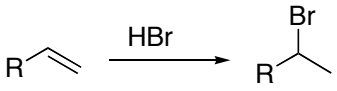
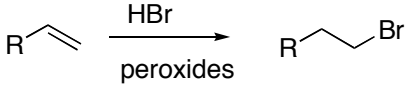
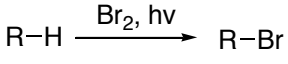
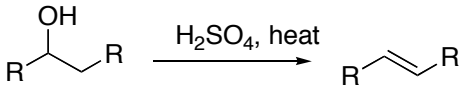
- Note difference between
- PCC and H_2CrO_4 when reacting with 1º alcohols.

7 

8 

Mech: Be able to draw!

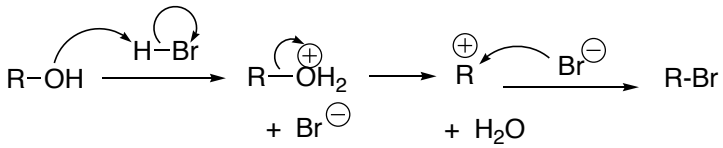
- HI, HCl analogous
- Converts alcohol into a bromide that can be used in Grignards, E2 reactions
- Cation mechanism
- Usually not method of choice for 1º, 2º alcohols

9		• Converts alcohol into a bromide that can be used in Grignards, E2, S_N2 reactions • Inversion of stereochem • Not good for 3º alcohols
10		• Quick 2-step conversion of alcohol into a nucleophilic Grignard
11		• Retention of stereo!
12		• Tosylates are super leaving groups, better even than iodides. • Tosylates are well suited to S_N2 and E2 reactions.
	Review Reactions	•
13		• Markovnikov addition
14		• anti-Markovnikov addition
15		• Radical mechanism, 3º > 2º > 1º
16		• Zaytsev elimination

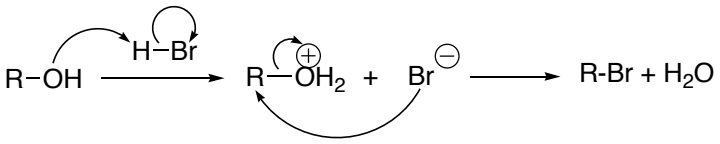
Mechanisms for ROH →RBr Reactions

R-OH (3°) $\xrightarrow{HBr}$ R-Br 3° mostly, sometimes 1°

HBr Mech for 3° ROH:

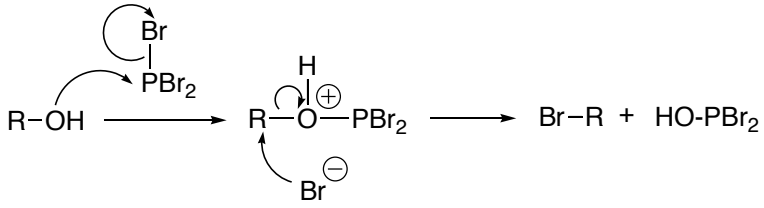


HBr Mech for 1° ROH:



R-OH (1°, 2°) $\xrightarrow{PBr_3}$ R-Br 1°, 2°

Mech:



Ch. 11 Reactions of Alcohols

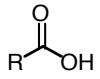
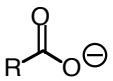
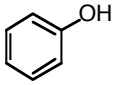
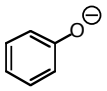
A. Conversion to Alkoxides. Acidity of Alcohols and Phenols (10.6)

"alkoxide" = $RO^{\ominus}$ anion

1	$R{-}OH + NaZ \underset{}{\overset{???}{\rightleftharpoons}} R{-}ONa + HZ$ Acid-Base	1. Deprotonation by a base. 2. Controlled by relative stability of $RO^{\ominus}$ versus $Z^{\ominus}$. 3. Consider relative electronegativity and whether either anion is resonance stabilized.

- Alcohols are weak acids → can be ionized by stronger bases
- goes to the right (alkoxide) only if resulting $RO^{\ominus}$ is more stable than $B^{\ominus}$
- ex. $^{\ominus}NH_2$, $^{\ominus}CH_3$ (nitrogen or carbon anions)
- ex. If a <u>less</u> stable oxygen anion can produce a <u>more</u> stable oxygen anion

Acidity Table

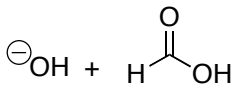
Class	Structure	Ka	Acid Strength	Anion	Base Strength	Base Stability
Strong Acids	H-Cl	10^{2}		$Cl^{\ominus}$		
Carboxylic Acid		10^{-5}				
Phenol		10^{-10}				
Water	H_2O	10^{-16}		$HO^{\ominus}$		
Alcohol	ROH	10^{-18}		$RO^{\ominus}$		
Amine (N-H)	RNH_2	10^{-33}		$RNH^{\ominus}$		
Alkane (C-H)	RCH_3	10^{-50}		$RCH_2^{\ominus}$		

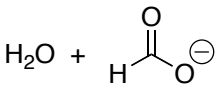
<u>Notes/skills:</u>

1. Be able to rank acidity.
2. Memorize/understand neutral OH acidity ranking: $RCO_2H > H_2O > ROH$
   - Reason: **<u>resonance</u>** stabilization of the **<u>anion</u>**
   - Alkoxide is **<u>destabilized</u>** relative to hydroxide by **<u>electron donor</u>** alkyl group
3. Predict deprotonation (acid/base) reactions
   - Any weak acid **<u>will be</u>** deprotonated by a **<u>stronger base (lower</u>** on table)
   - Any weak acid **<u>will not be</u>** deprotonated by a **<u>weaker base (higher</u>** on table)
4. Predict ether/water extraction problems
   - If an organic chemical is neutral and stays neutral, it will stay in ether layer
   - If an organic chemical is ionized (by an acid-base reaction), it will extract into the aqueous layer_____

Problems

1. Draw arrow to show whether equilibrium favors products or reactants. (Why?)





Key: a proton transfer will happen only if it results in a more stabilized anion

Key anion stability factors:

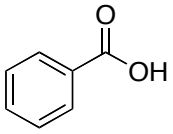
- Electronegativity (oxygen > nitrogen > carbon)
- Resonance. Carboxylate, phenoxide yes > hydroxide, alkoxide no
- Donor/withdrawer factor: hydroxide > alkoxide (electron donor destabilizes anion)

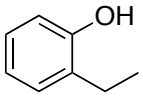
2. Which of the following will deprotonate methanol?

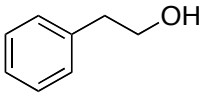
H_2O CH_3CO_2Na PhONa NaOH $NaNH_2$ CH_3MgBr

- Using the chart, an acid (left side) will only be deprotonated by an anion/base that is **lower** on the right side, because that will result in a more stable anion.
- Charge: neutral species aren't as basic as anionic analogs (H_2O versus NaOH)

3. When the following are dissolved in ether and then treated with NaOH/water, which would extract out of the ether layer into the water layer?







- Neutral species will stay in organic solvent (ether); only ionized species will extract into the water
- Thus the question of whether something will extract into the aqueous phase is really a question of whether there is something present that will cause an acid-base reaction
- NaOH is strong enough to ionize carboxylic acids and phenols, but not alcohols.

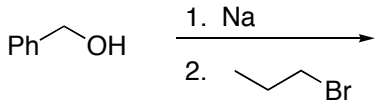
A2. Alkoxide formation by redox reaction with sodium or potassium (or other metals) (10.6B)

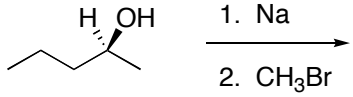
2	R–OH $\xrightarrow{Na}$ R–ONa R–OH $\xrightarrow{K}$ R–OK } R–O$^{\ominus}$	• Potassium (K) analogous. • Key way to convert alcohol to alkoxide, reactive as S_N2 nucleophile and E2 base.

- Key source of nucleophilic/basic alkoxides
- Alkoxides are used all the time as S_N2 nucleophilies and E2 bases

B. **<u>2-Step Conversion of Alcohols into Ethers via the Alkoxides (10.6B)</u>**

3	R–OH $\xrightarrow[2.\ R'\text{-}X]{1.\ Na}$ R–O–R'	• Alkoxide formation-S_N2 route to ether • The electrophile R'-X must be S_N2 reactive, preferably 1° with a good leaving group

1. 

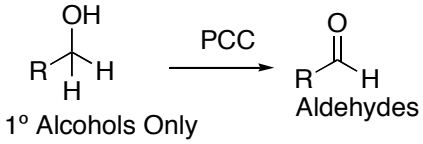
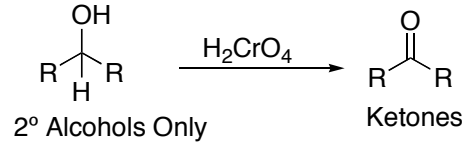
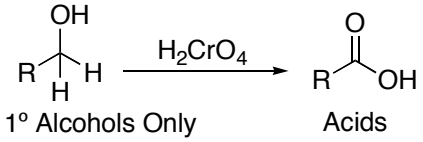
2. 

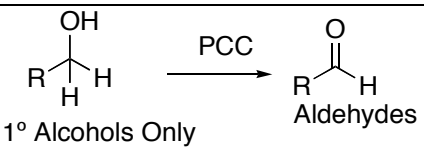
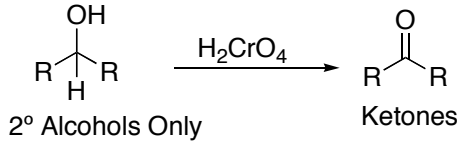
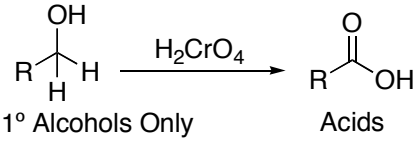
3. 

C. Oxidation of Alcohols to Carbonyl Compounds (11.1-4)
Summary: 2 Oxidants

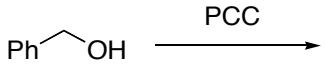
1. **PCC = mild 1º alcohols → aldehydes**
   - "**P**yridinium **c**hloro**c**hromate": soluble in water-free dichloromethane
   - Mild, selective for 1º over 2º alcohols, and when 1º alcohols are used stops at aldehyde

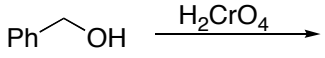
2. **H_2CrO_4 = strong**
   a. **2º alcohols → ketones**
   b. 1º alcohols → carboxylic acids
   c. 3º alcohols → no reaction
   d. aldehydes → carboxylic acids
   - $H_2CrO_4 = CrO_3 + H_2O$ or $Na_2Cr_2O7 + H_2SO_4$ (make in the reaction flask)
   - Always made and used in the presence of some water
   - Very strong, when 1º alcohols are used goes 1º RCH_2OH → RCHO → RCO_2H without stopping at aldehyde

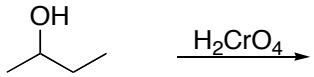
4		• Key access to aldehydes, which are useful for more Grignard chemistry. • Note difference between PCC and H_2CrO_4 • PCC does not react with 2º alcohols very rapidly
5	 $H_2CrO_4 = Na_2Cr_2O_7, H_2SO_4$ or CrO_3/H_2O	• Key access to ketones. • PCC does not react very fast with 2º alcohols
6		• Note difference between • PCC and H_2CrO_4 when reacting with 1º alcohols.

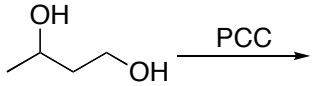
4		• Key access to aldehydes, which are useful for more Grignard chemistry. • Note difference between PCC and H_2CrO_4 • PCC does not react with 2º alcohols very rapidly
5	 H_2CrO_4 = $Na_2Cr_2O_7$, H_2SO_4 or CrO_3/H_2O	• Key access to ketones. • PCC does not react very fast with 2º alcohols
6		• Note difference between • PCC and H_2CrO_4 when reacting with 1º alcohols.

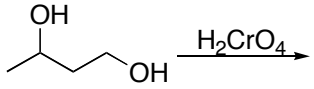
<u>Draw the products for the following oxidation reactions.</u>

1 

2 

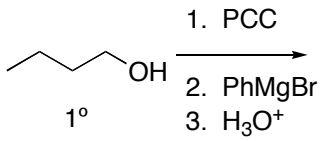
3 

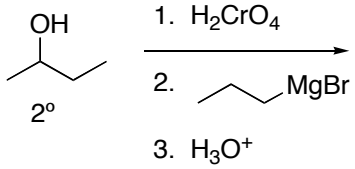
4 

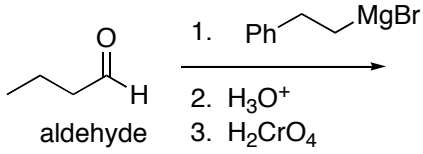
5 

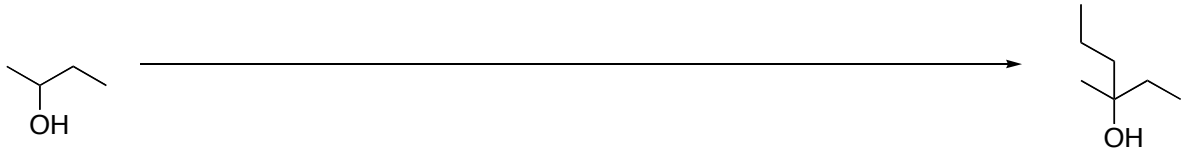
Oxidation Combined with Grignard Reactions (in either order): Indirectly Enables Substitution of Carbon for Hydrogen

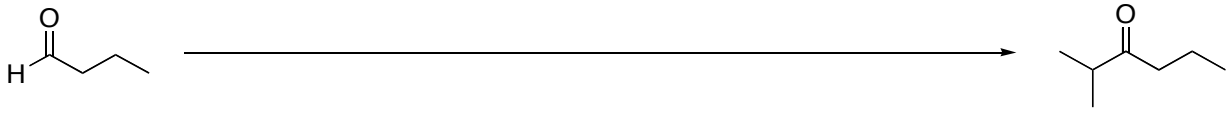
1. **1º alcohol** + PCC → aldehyde + RMgBr → **2º alcohol**
2. **2º alcohol** + H_2CrO_4 → ketone + RMgBr → **3º alcohol**
   - Oxidation followed by Grignard reaction essentially substitutes a carbon group for a hydrogen
3. **Aldehyde** + RMgBr → 2º alcohol + H_2CrO_4 → **ketone**
   - Grignard reaction followed by oxidation essentially substitutes a carbon group for a hydrogen

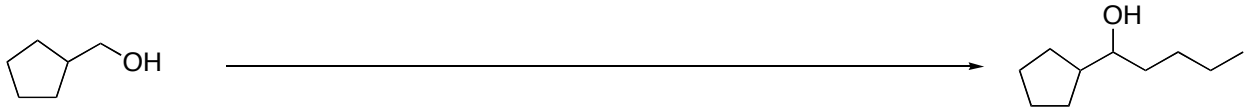
1 

2 

3 

4 

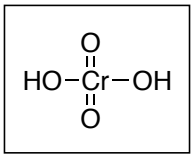
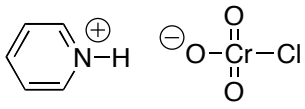
5 

6 

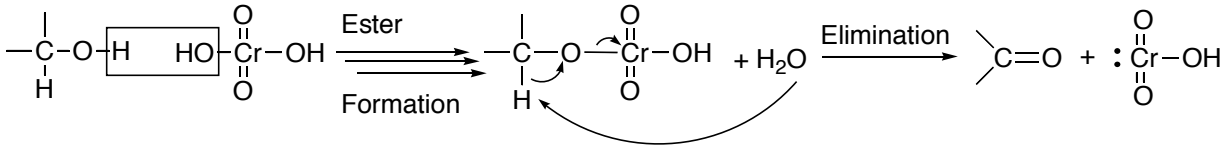
Jones Test H_2CrO_4 for Alcohols (11-2C) (test responsible)

- H_2CrO_4 (Jones Reagent) is clear orange
- Treatment of an unknown with Jones reagent:
  - Solution stays clear orange → no 1º or 2º alcohol present (negative reaction)
  - Solution gives a green/brown precipitate → 1º or 2º alcohol present (positive reaction)
  - 3º, vinyl, and aryl alcohols do not react. Nor do ketones, ethers, or esters.

Structure and Mechanism (not test responsible)

H_2CrO_4 = chromic acid = $Na_2Cr_2O_7$ = CrO_3/H_2O = Cr^{+6} oxidation state • Water soluble	
Pyridinium carbons renders PCC soluble in organic solvents, thus it is functional in organic solvent and in the absence of water	 PCC = Pyridinium Chloro**C**hromate

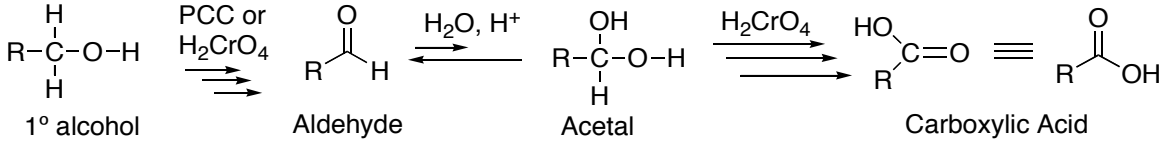
General Mechanism (not test responsible)



- PCC operates analogously

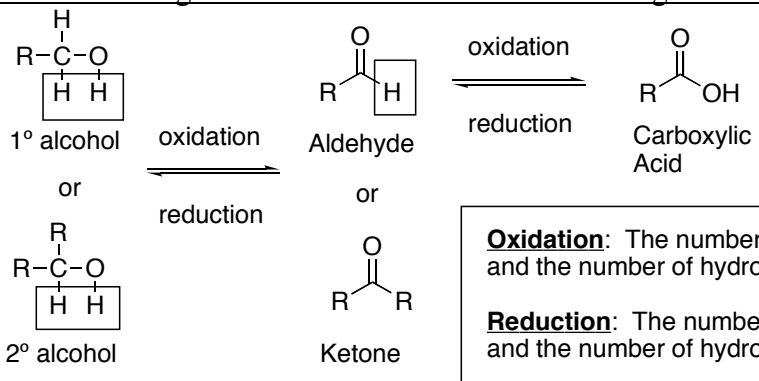
1º Alcohols, Aldehydes, and the Presence or Absence of Water: PCC vs H_2CrO_4

Q: Why does Anhydrous PCC stop at Aldehyde but Aqueous H_2CrO_4 Continues to Carboxylic Acid?



1. Both PCC and H_2CrO_4 convert 1º alcohols to aldehydes
2. In the presence of acidic water, aldehydes undergo an equilibrium addition of water to provide a small equilibrium population of acetal
3. The acetal form gets oxidized (very rapidly) to carboxylic acid
   - The aldehyde form cannot itself get oxidized to carboxylic acid
   - Since PCC is used in absence of water, the aldehyde is <u>not able</u> to equilibrate with acetal and simply stays aldehyde.
     - Since it can't convert to acetal, therefore no oxidation to carboxylic acid can occur
4. Chromic acid, by contrast, is in water
   - Therefore the aldehyde <u>is able</u> to equilibrate with acetal
   - The acetal is able to be oxidized.
   - Thus, the aldehyde via the acetal is able to be indirectly oxidized to carboxylic acid, and in fact does so very rapidly.

General Recognition of Oxidation/Reduction in Organic Chemistry

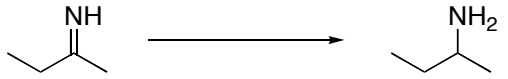


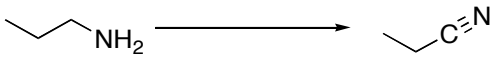
Oxidation: The number of oxygen bonds to a carbon increases, and the number of hydrogens bonded to a carbon decreases

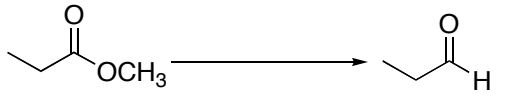
Reduction: The number of oxygen bonds to a carbon is reduced, and the number of hydrogens bonded to a carbon increases.

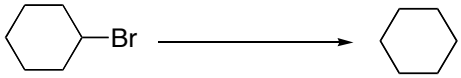
More General: # of bonds to heteroatoms versus to hydrogens

Classify the following transformations as "oxidations" or "reductions"

1. 

2. 

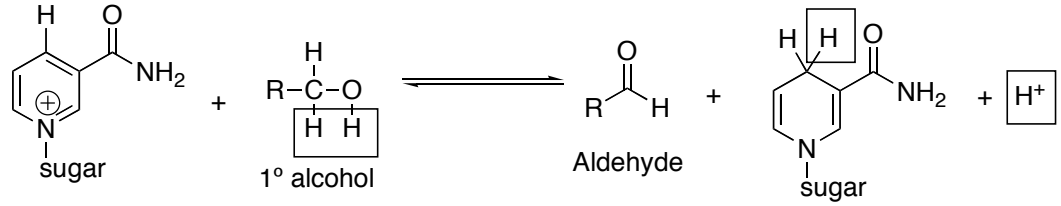
3. 

4. 

11.3, 11.4 Other methods for Oxidizing Alcohols. (No test)

There are lots of other recipes used for oxidizing alcohols (and for other oxidation reactions)

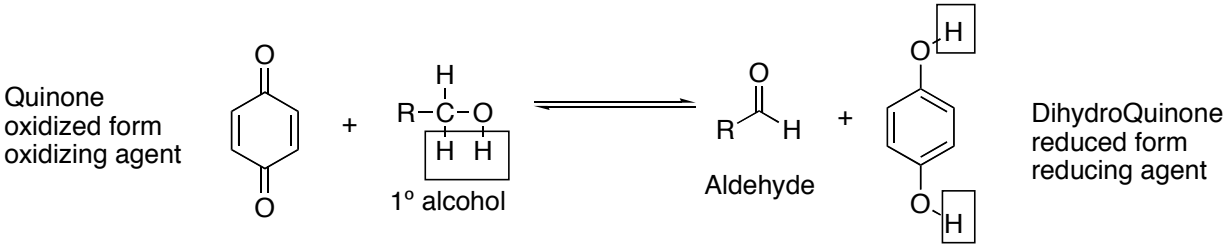
1. $KMnO_4$
2. CuO
3. "Jones": H_2CrO_4 with acetone added to temper reactivity
4. Collins: H_2CrO_4 with pyridine added to temper reactivity
5. "Swern": $(COCl)_2$ and $(CH_3)_2S{=}O$ then NEt_3
6. HNO_3
7. Biological Oxidant 1: "NAD^+" "nictonamide adenine dinucleotide"



NAD^+
oxidized form
oxidizing agent

NAD
reduced form
reducing agent

8. Biological Oxidant 2: "Quinones and hydroquinones" (Ch. 17-15)



In General: Recognizing Oxidizing versus Reducing Agents

Oxidizing Agents: Often have:

- Highly Oxidized Metals or Nonmetals
- Extra Oxygen

OsO_4 (+8)
$KMnO_4$ (+7)
CrO_3 (+6)
H_2CrO_4 (+6)
HNO_3 (+5)
$H_2O_2 \rightarrow H_2O$
$RCO_3H \rightarrow RCO_2H$
$O_3 \rightarrow O_2$

Reducing Agents: Often involve:

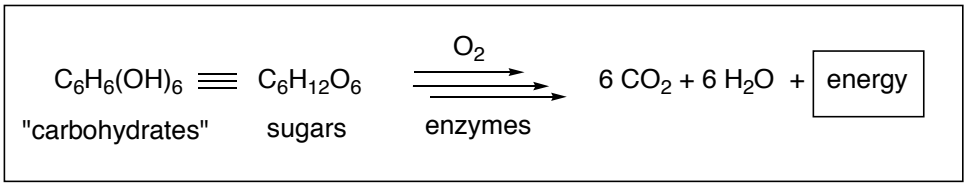
- Hydrides in Formulas
- Highly Reduced Metals
- Metals + H_2
- Metals + acid

$LiAlH_4$
$NaBH_4$
Li, Na, K, Mg, Zn, Al, etc.
Pd/H_2, Pt/H_2, Ni/H_2 etc.
Zn/HCl, Fe/HCl, Zn/Hg/HCl, etc..

- The ability to qualitatively recognize when a transformation involves an oxidation or reduction can be very helpful.
- The ability to recognize a reactant as an oxidizing agent or a reducing agent can be very helpful
- Often on standardized tests!

Some Biological Alcohol Oxidations (Not for Test)

1. Oxidation of "carbohydrates" or "sugars" is the primary source of bioenergy
   - multiple enzymes are involved for the many steps
   - A "carbohydrate" basically has a formula with one OH per carbon



2. Most alcohols are biooxidized to give toxic carbonyl derivatives ("intoxication")
   - the presence of substantial aldehydes and especially ketones in the blood is symptomatic of various problems
     - intoxication
     - alcoholism
     - uncontrolled diabetes
     - etc (other metabolic disorders)

11.7-9 Conversion of Alcohols to Alkyl Halides

8 $R-OH \xrightarrow{HBr} R-Br$ (3º alcohols)

Mech: Be able to draw!

- HI, HCl analogous
- Converts alcohol into a bromide that can be used in Grignards, E2 reactions
- Cation mechanism
- Usually not method of choice for 1º, 2º alcohols

9 $R-OH \xrightarrow{PBr_3} R-Br$ (1º or 2º alcohols)

- Converts alcohol into a bromide that can be used in Grignards, E2, S_N2 reactions
- **Inversion of stereochem**
- Not good for 3º alcohols

10 $R-OH \xrightarrow[2.\ Mg]{1.\ PBr_3 \text{ or } HBr} RMgBr$

- Quick 2-step conversion of alcohol into a nucleophilic Grignard

11 $R-OH \xrightarrow{SOCl_2} R-Cl$ (1º or 2º alcohols)

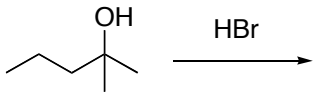
- Retention of stereo!
- Section 11-9

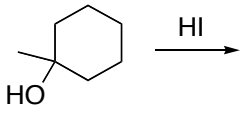
Summary:

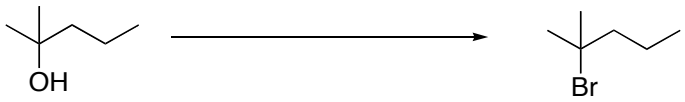
Class	**R-Br**	R-Cl
1º ROH	**PBr_3**	$SOCl_2$
2º ROH	**PBr_3**	$SOCl_2$
3º ROH	**HBr**	**HCl**
Vinyl or Aryl	Nothing works	Nothing works

Straight Reaction with H-X (Section 11.7)

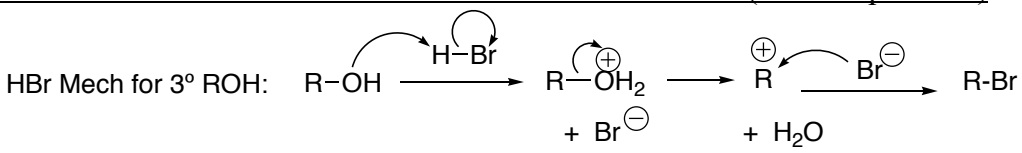
- Ideal only for 3º ROH,
- sometimes works with 1º alcohols, with a complex mechanism
- Only occasionally for 2º alcohols
- **Method of choice for 3º, but not for 1º or 2º**

1 

2 

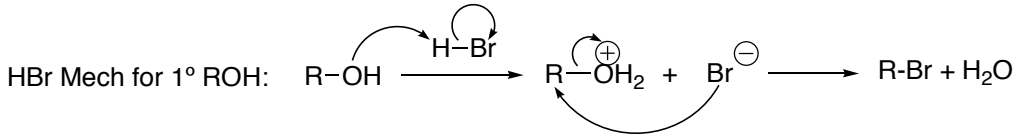
3 

Mechanism for H-X reactions with 3º Alcohols: Cationic (Test Responsible)



Notes:

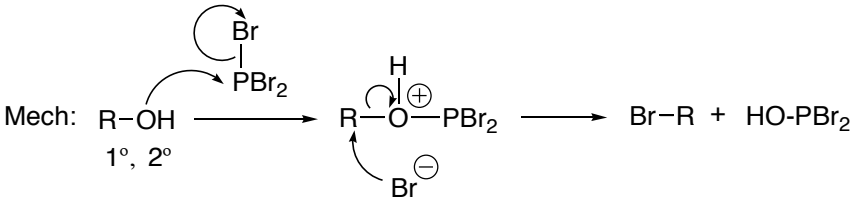
1. Memorize the 3º alcohol mechanism (test responsible)
   a. Protonate
   b. Leave to give Cation. This is the slow step for 3º alcohols
   c. Capture
2. Analogous with HI or HCl
   - HCl slower, normally enhanced with $ZnCl_2$, which enhances rate of cation formation (Lucas test, see later)
   - Outside of 3º systems, side reactions are common and yields aren't often very good
3. Outside of 3º alcohols, side reactions are common and yields aren't often very good
   - Elimination reactions and cation rearrangements…
4. S_N1 type: carbocation-forming step is the rate-determining step, so R+ stability key
   - 3º alcohols fastest
   - 2º alcohols are way slower
   - 1º alcohols can't react at all via this mechanism, because 1º R+ are too unstable.
   - Ditto for vinyl or aryl alcohols
5. HBr can also react with 1º ROH to give 1º RBr, although it is not often the method of choice
   - The mechanism is different, but rather interesting (not test responsible)



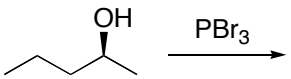
   - carbocation formation never occurs
   - bromide ion simply does S_N2 on the protonated alcohol, with water as an excellent leaving group
   - yields tend to be pretty inconsistent

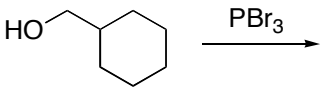
Reaction of 1º and 2º Alcohols with PBr_3 (Section 11-8)

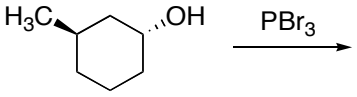
- Default recipe for 1º and 2º alcohols



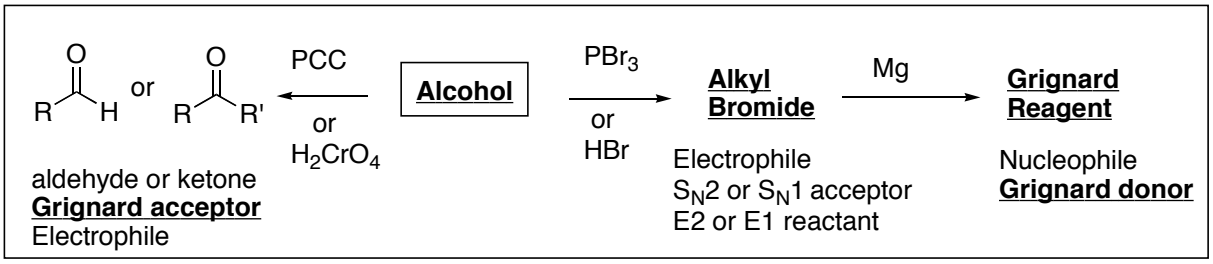
   - PBr_3 is an exceptional electrophile, and reacts even with neutral alcohols
   - The first step activates the oxygen as a leaving group.
   - The second step involves an S_N2 substitution
     - **stereochemical inversion occurs if chirality is present (common for 2º alcohols)**
   - Because the second step is an S_N2 substitution, the reaction fails for 3º ROH
   - PCl_3 does not react as well, and is not useful for making chlorides
   - PI_3 is not stable and can't be stored in a bottle. However, the combination of 1P + 1.5 I_2 → PI_3 in the reaction container (*in situ*)
     - Thus P/I_2 essentially provides the PI_3 that does the job

1 

2 

3 

Conversions of Alcohols into Other Reactive Species in Multi-Step Syntheses

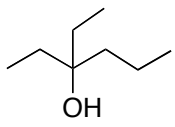


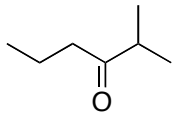
1. oxidation can convert an alcohol into a carbonyl = **Grignard acceptor (electrophile)**
2. PBr_3/Mg or HBr/Mg can convert an alcohol into RMgBr = **Grignard donor (nucleophile)**
3. PBr_3 or HBr can convert an alcohol into RBr, capable of normal substitution and elimination reactions.

Retrosynthesis Problems (In which you decide what to start from): Design syntheses for the following.

Allowed starting materials include:
Bromobenzene cyclopentanol any acyclic alcohol or alkene with ≤4 carbons
any esters ethylene oxide formaldehyde (CH_2O)
any "inorganic" agents (things that won't contribute carbons to your skeleton)

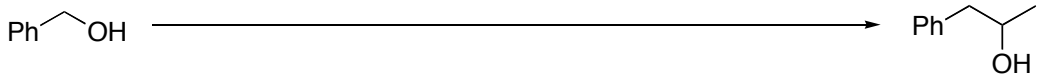
Tips:
1. Focus on the functionalized carbon(s)
2. Try to figure out which groups of the skeleton began together, and where new C-C bonds will have been formed
3. When "breaking" it up into sub-chunks, try to make the pieces as large as possible (4 carbon max, in this case, for acyclic pieces)
4. Remember which direction is the "true" laboratory direction.
5. Be careful that you aren't adding or substracting carbons by mistake

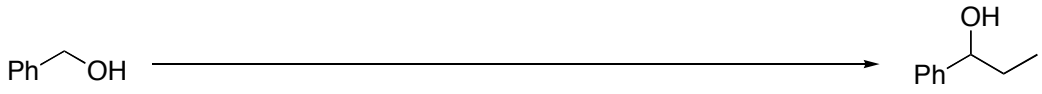
1 

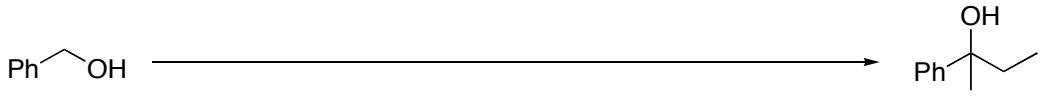
2 

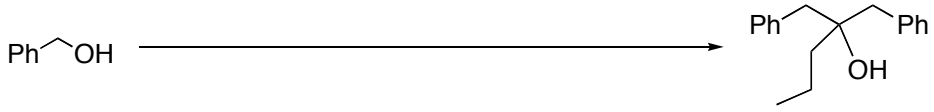
Normal Synthesis Design: In which you are given at least one of the starting Chemicals.
Provide Reagents. You may use whatever reagents, including ketones or aldehydes or Grignards or esters, that you need. **Tips**:

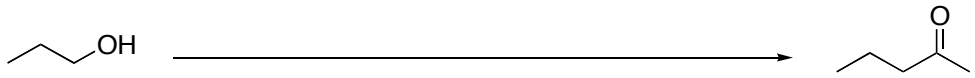
- Identify where the reactant carbons are in the product
- Is the original carbon still oxygenated? → SM should probably react via a Grignard acceptor
- Is the original carbon not still oxygenated? → SM should probably react as Grignard donor
- Working backwards helps.

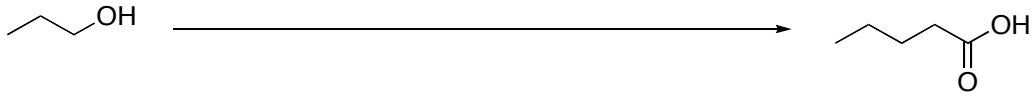
a. 

b. 

c. 

d. 

e. 

f. 

More Retrosynthesis Problems: Design syntheses for the following.

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1. Focus on the functionalized carbon(s)
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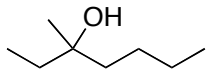
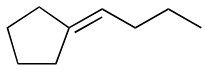
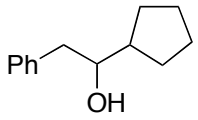
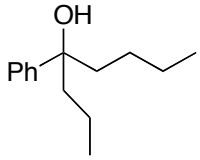
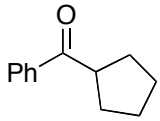
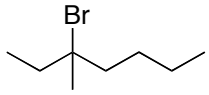
1 

2 

3 

4 

7 

5 

Unknowns and Chemical Tests (Sections 11-2C, 11-7)

1. H_2/Pt test for alkenes
2. Br_2 test for alkenes
3. **Jones reagent (H_2CrO_4) Test for 1º or 2º alcohols**
   - 3º alcohols do not react
   - 2º alcohols keep the same number of oxygens but lose two hydrogens in the formula
   - 1º alcohols lose two H's but also add one oxygen
4. **Lucas Test: HCl/$ZnCl_2$ for 3º or 2º alcohols**

R-OH $\xrightarrow{HCl/ZnCl_2 \text{ in water}}$ R-Cl via $R^{\oplus}$ 3º > 2º >>>> 1º

3º >	2º >>>	1º
<1 min	1-5 min	never

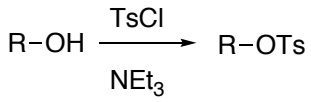
Why? $R^{\oplus}$ stability: 3º $R^{\oplus}$ > 2º $R^{\oplus}$ >>> 1º $R^{\oplus}$

- 3º alcohols are fastest
- 1º alcohols don't react at all
- $R^{\oplus}$ stability is the key

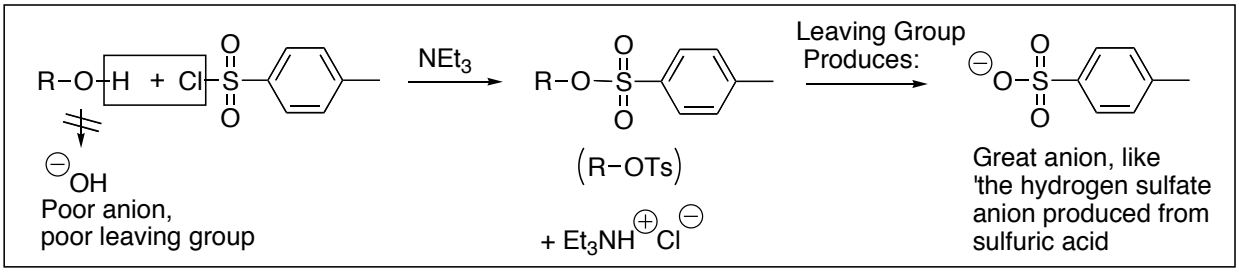
- Test is based on **solubility**: The R-Cl product is nonpolar and water insoluble, so it separates out from water. Alcohols are quite soluble especially in highly acidic water.
- Test fails is useless for alcohols with so many carbons that it doesn't even dissolve in the original HCl/$ZnCl_2$/water solution

		Jones (H_2CrO_4)	Lucas (HCl/$ZnCl_2$)	H_2/Pt	Required Facts	Possible Answers
1	$C_5H_{10}O$	Yes	No	Yes		
2	$C_6H_{12}O$	Yes	Yes, 1-5 min	No		
3	$C_6H_{12}O$	No	Yes	Yes		
4	$C_7H_{12}O$	Yes	Yes	Yes, Produces $C_7H_{14}O$		
5	C_3H_6O	No	No	Yes		
6	C_3H_6O	No	No	No		
7	C_3H_6O	Yes	No	Yes		
8	C_3H_6O	Yes,	Yes	No		

Section 11-5 Conversion of Alcohols to "Tosylates", and their use as Exceptional Leaving Groups in S_N2, S_N1, E2, and E1 Reactions

12 

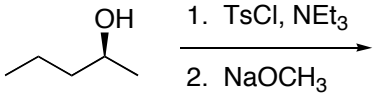
- Tosylates are super leaving groups, better even than iodides.
- Tosylates are well suited to S_N2 and E2 reactions.

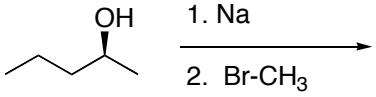


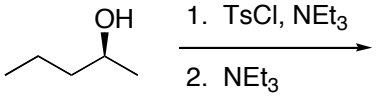
Notes:

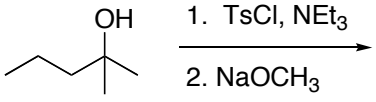
1. Tosylates are easy to form
2. "Toluene sulfonate"
3. Tosylate anion is really stable, comparable to the anion from sulfuric acid
   - Thanks to electronegative sulfur and the resonance/charge sharing with the other oxygens
4. Whereas a normal OH has a poor leaving group (hydroxide anion), conversion to the tosylate provides a super good leaving group.
5. Leaving Group Reactivity: Better than the best of the halides
   - OTs >> I > Br > Cl
6. Tosylates are highly reactive toward S_N2, S_N1, E2, and E1 Reactions
7. Triethylamine is used as an HCl scavenger in the tosylate formation
   - Often a weaker amine base called pyridine is used, to avoid unintentionally providing E2 on the tosylate

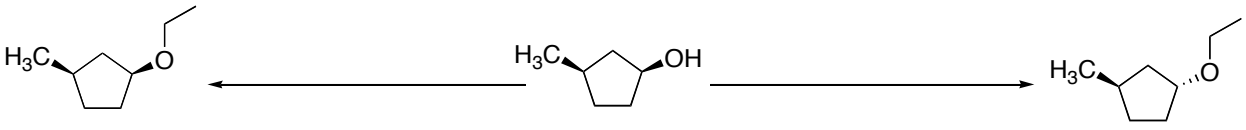
Draw Products

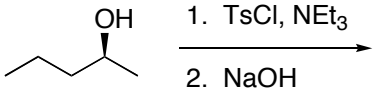
1 

2 

3 

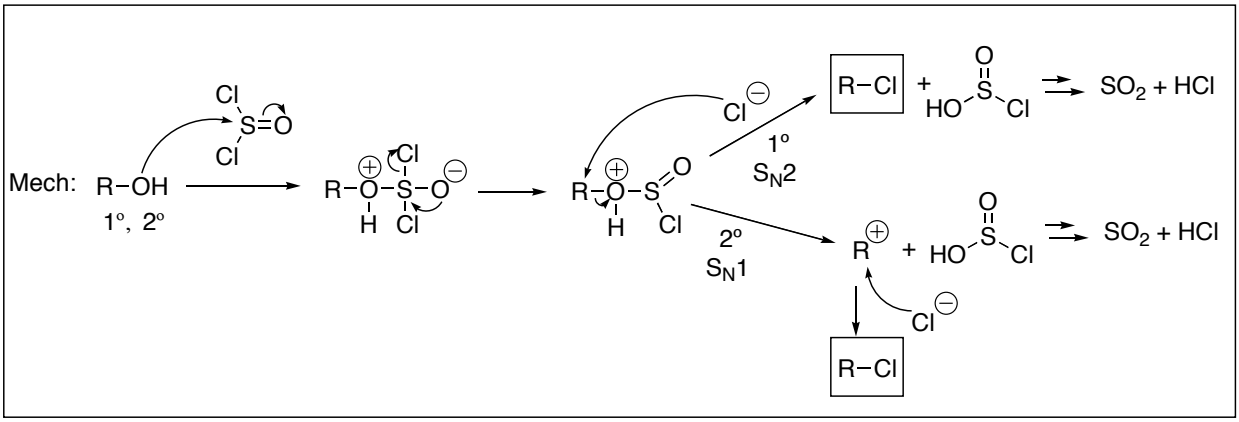
4 

5 

6 

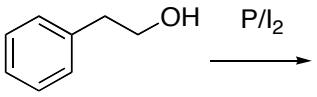
Reaction of 1º and 2º Alcohols with $SOCl_2$ (Section 11-9)

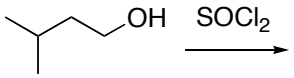
- Default recipe for chlorination of 1º and 2º alcohols

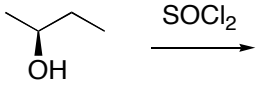


- Mechanism: Not for test responsibility
- Mechanism differs for 1º and 2º alcohols
- 1º involve an S_N2 substitution
- 2º involve an S_N1 type substitution
- The chloride that captures the cation is normally on the same side of the molecule on which the oxygen began, and often captures the cation very rapidly from that same side
- This results in a very unusual **retention of stereochemistry.**
- When they work, these reactions are convenient because the side products, SO_2 and HCl, are both gases. So workup is really easy. Simply rotovap the mixture down, and everything except for product is gone.

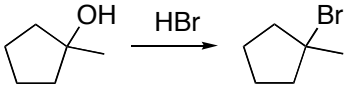
Draw Products or Provide Appropriate Reactants for the following Transformations

4 

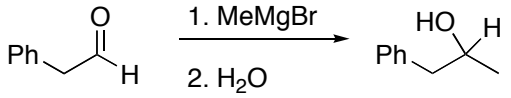
5 

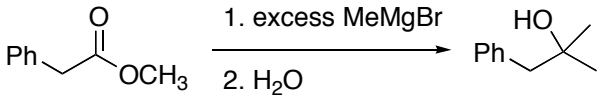
6 

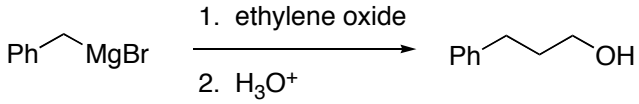
Draw the Mechanism:

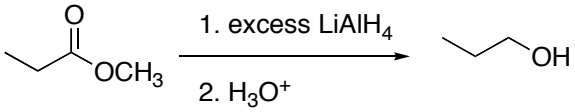


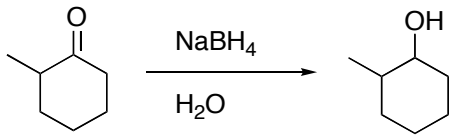
Draw the mechanisms for the following reactions.

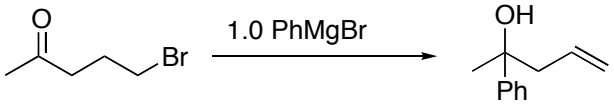
1 

2 

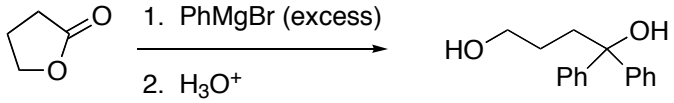
3 

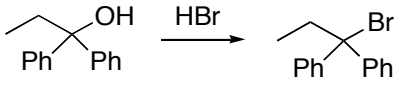
4 

5 

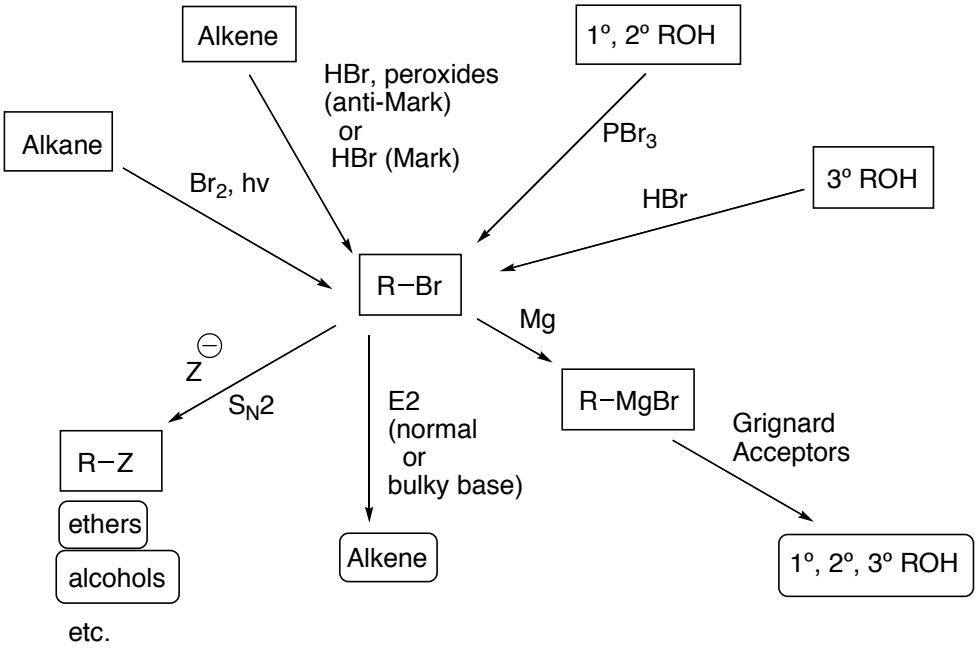
6 

Tricky combo

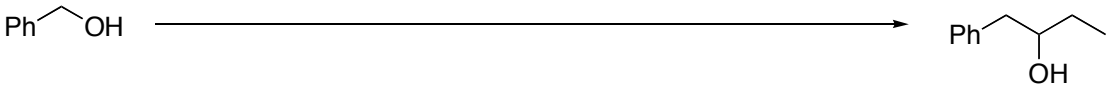
7 

8 

REVIEW. To make organometallic reagents, you must have RBr compounds (or RCl or RI).



a.



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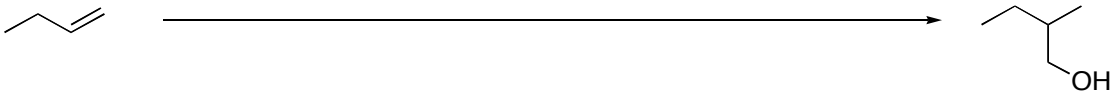

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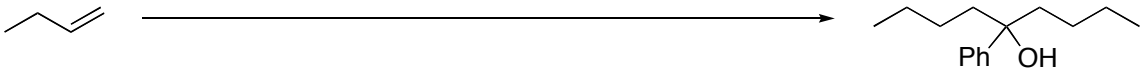
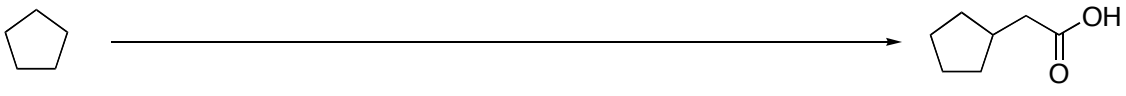
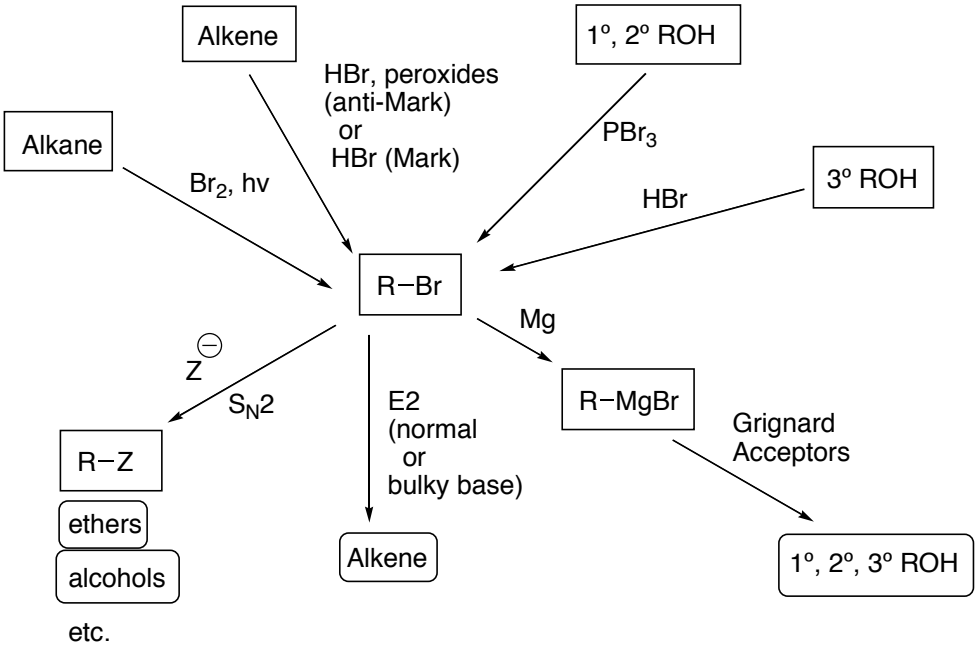


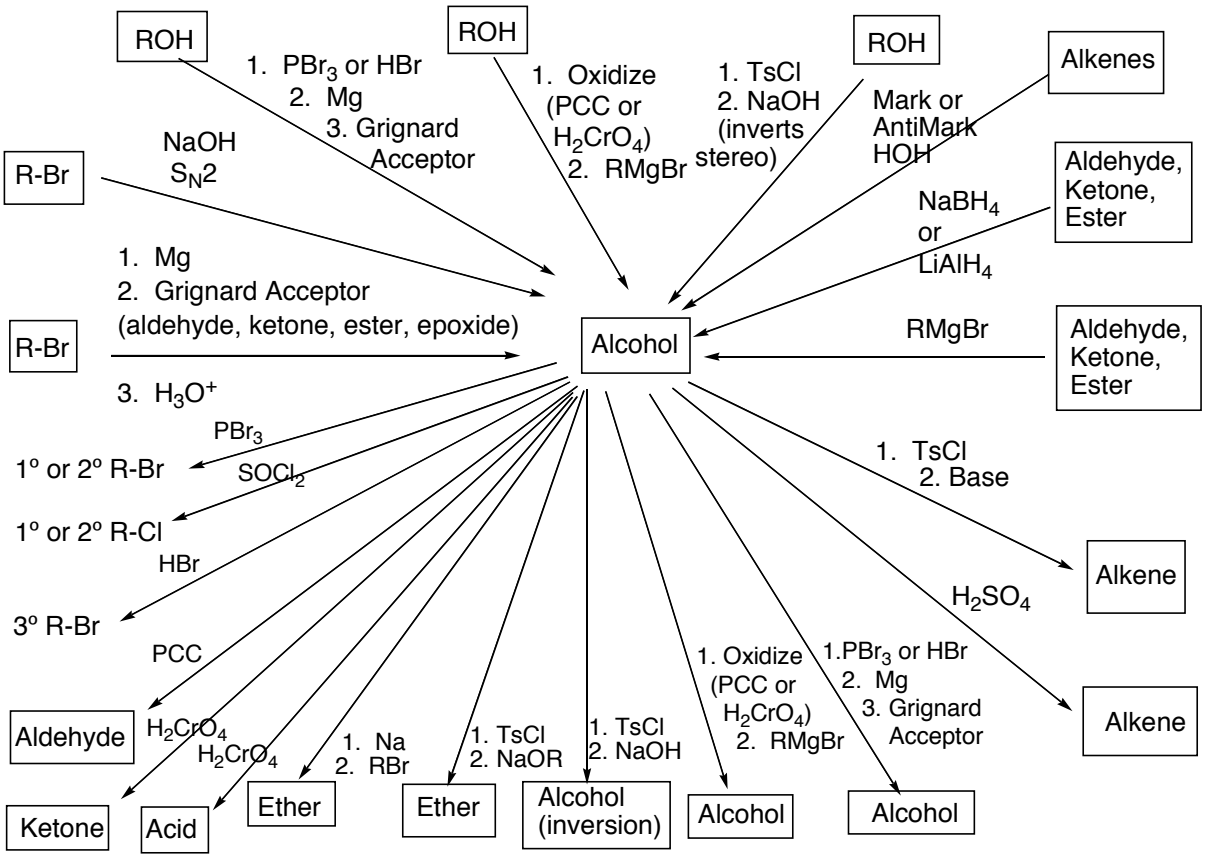
d.



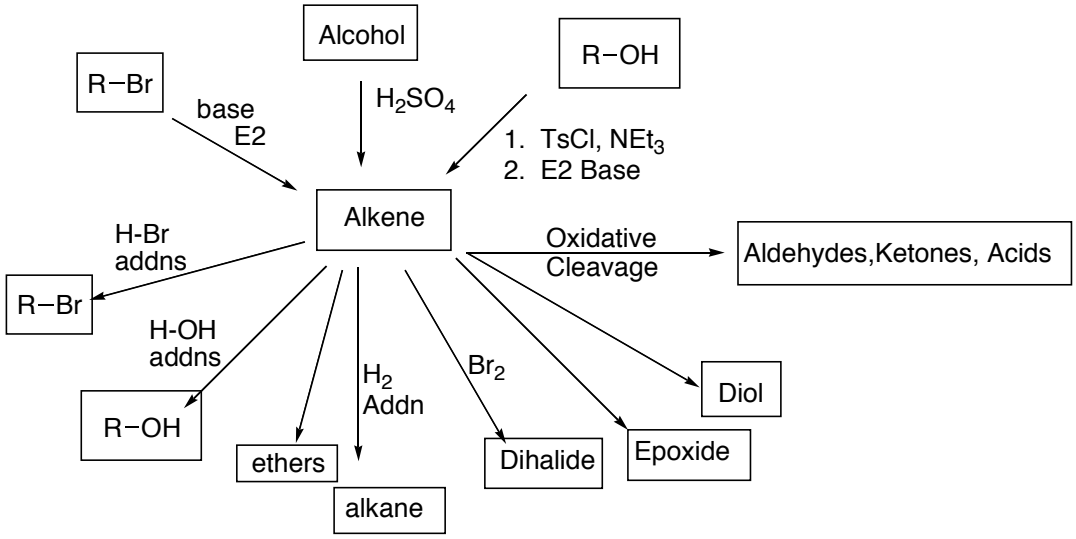
Bromoalkane Concept Map



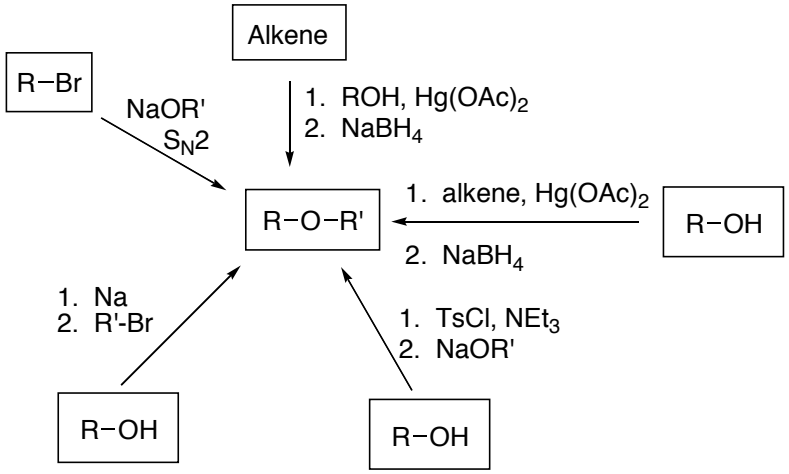
Alcohol Concept Map



Alkene Concept Map



Ether Concept Map



Short Summary of 1H-NMR Interpretation

For fuller explanation, see: http://web.mnstate.edu/jasperse/Chem355/H-NMR.doc.pdf

I. Number of Signal Sets

II. Integration These **must be simple whole-number ratios** (2:1, 3:1, 3:2, etc..)

III. "Chemical Shifts" of the Signal Sets

9's (9.0-10.0)	**Aldehyde** sp^2 hybridized C-H's
7's (6.5-8.4)	**Aromatic** sp^2 hybridized C-H's
5's (4.8-6.8)	**Alkene** sp^2 hybridized C-H's
3's (2.8-4.5)	**Oxygenated** or **Halogenated** sp^3 hybridized C-H's (halogenated and nitrogenated alkyl C-H's will also come in this window, although no candidates for today's lab). Oxygenated sp^3–carbons are routinely present for the following functional groups that contain oxygen single bonds: a. **alcohols**, b. **ethers**, or c. **esters**
2's (1.8-2.8)	**Allylic** sp^3 hybridized C-H's (sp^3 hybridized C-H's that has a double bond attached to the sp^3 hybridized C). Allylic signals routinely appear when one of the following double-bonded functional groups is present: a. **carbonyls**, (ketones, esters, aldehydes, acids, amides) b. **alkenes**, or c. **aromatics**
1's (0.7-2.0)	sp^3 hybridized C-H's, with **no attached Functional Groups** a. **Note:** Many molecules with non-functional alkyl portions will give a lot of signal in this area.
0-12 (anywhere!)	**Alcohol/Acid** O-H hydrogens (N-H hydrogens likewise) a. **alcohols**, b. **carboxylic acids**

1. Recognize OH's..
2. Check each of the zones. Each one gives you a yes or no answer about the presence of absence of the featured group.
3. End-Check: Check that the functional groups indicated by your chemical shift information match with the structure you believe you actually have! If not, structure needs correction!
4. The regions are somewhat approximate, and have some spillover.
5. For multi-functional complex molecules, there are more complex ways for a C-H to come in some of the above window. For example, an sp^3-hybridized C-H with two attached oxygens can come in the 5's, or an sp^3-hybridized C-H that is doubly allylic can come in the 3's. In other words, the impact of functional groups is roughly additive.

IV. Splitting

- **N-1 Rule: N lines → N-1 neighbor H's** (H's directly attached to carbons attached to the C-H group causing the signal)
  - The N-1 Rule is useful when working from spectrum to actual structure
- **N+1 Rule: N neighbor H's → N+1 lines**
  - The N+1 Rule is useful when working from structure to actual spectrum

Note: OH hydrogens don't participate in splitting (normally)

Short Summary of C13-NMR Interpretation

1. **Count how many lines** you have. **This will tell you how many types of carbons** you have. (Symmetry equivalent carbons will give a single line.)
   a. Each "unique"carbon gives a separate line.
   b. Symmetry duplicates give the same line.
   c. If there are more carbons in your formula than there are lines in your spectrum, it means you have symmetry.

2. **Check diagnostic frequency windows** ("chemical shift windows") of the lines **to provide yes-or-no answers regarding the presence or absence of key functional groups** in your molecule.

220-160	C=O carbonyl carbons, sp^2 hybridized
160-100	C alkene or aromatic carbons, sp^2 hybridized
100-50	C-O oxygen-bearing carbons, single bonds only, sp^3 hybridized
50-0	C alkyl carbons, no oxygens attached, sp^3 hybridized

3. **Check Splitting**. C13 NMR's are often acquired as "decoupled" spectra, in which each carbon signal appears as a singlet. However, at the cost of extra time and/or complexity it is also possible to get "coupled" C13 NMR's with splitting. These splitting values are very useful, and follow the N+1/N-1 rules (the number of lines is one greater than the number of attached H's). (Other experimentally preferable but conceptually complex "HSQC" two-dimensional NMR experiments can provide the same information more quickly.)

Quartert (q)	CH_3
Triplet (t)	CH_2
Doublet (d)	CH
Singlet (s)	C (no attached hydrogens).

- Note: The use of DEPT NMR or other techniques can also be used to establish whether carbons are CH_3, CH_2, CH, or carbons without any attached hydrogens.

4. **Signal Height/Size**
   a. Carbons without any attached H's are short. This is common for carbonyls (aldehydes are the only carbonyl carbons that have hydrogens attached) and for substituted carbons in a benzene ring.
   b. Symmetry duplication multiplies signal height (if you have two copies of a carbon, the line will probably be taller than normal!)

5. **Aromatics, Symmetry, and C-13 Signals**. Most aromatics have symmetry, and both the number of aromatic lines and the splitting of the aromatic lines can be indicative of the substitution pattern on a benzene. Mono- and para-disubstituted benzenes have symmetry.

4 lines	s, d, d, d	Monosubstituted benzene. (Has symmetry).
4 lines	s, s, d, d	Para-disubstituted benzene. (Has symmetry).
6 lines	s, s, d, d, d, d	Ortho- or meta-disubstituted benzene. (Has no symmetry).

Summary of IR (Infrared) Interpretation

1. **Check for Diagnostic Signals**

3500-3200	OH or NH
1800-1640	C=O
3500-2500 + 1800-1640	CO_2H

2. **Further Information in the "Carbonyl Zone"**

<1700	Unsaturated C=O
>1700	Saturated C=O
1720-1700	Saturated ketones, aldehydes, acids
1750-1735	Saturated ester

Hundreds of Practice Problems, and Thousands of Spectra.

- Looking at spectra and practicing NMR problems helps. There are many opportunities.

Here are several:

1. **Jasperse practice problems**:
   - Problems: http://web.mnstate.edu/jasperse/Chem360/NMR-Problems-Jasperse.pdf
   - Answers: http://web.mnstate.edu/jasperse/Chem360/NMR%20Problem%20Answers.pdf
   - The above site is linked from both the Jasperse Chem 342 and Chem 360 websites.
   - Some of these we will work in class together for practice, but there will be lots more you can practice on.
   - Even if I do work them in class, doing it fresh a day or more later may be much like working it fresh.

2. **Jasperse practice-test problems**:
   - http://web.mnstate.edu/jasperse/Chem360/Practice%20Tests/Chem360PracticeTests.html
   - These will the four versions of "test 2" practice tests linked.
   - Included will be links to the practice test movie sessions that I recorded in which I discuss some of the logic.

3. **Web Spectra site** (UCLA): Has about 75 problems of varying level of difficulty. Formulas are provided.
   - **www.chem.ucla.edu/~webspectra**

4. **Organic Structure Elucidation site** (Notre Dame): (64 problems)
   - http://www.nd.edu/~smithgrp/structure/workbook.html
   - Click the "Do the Problems" link on the left to access the problems page.

5. **NMR's for over 14,000 chemicals**. (These aren't problems, but if you enter the name or formula or CAS number for something,

- **http://riodb01.ibase.aist.go.jp/sdbs/cgi-bin/cre_index.cgi?lang=eng**

The four facets of 1H NMR spectroscopy:

1. The number of signal sets (Section 13.6)
   - The number of signal sets tells how many types of symmetry-unique hydrogen are present
   - Symmetry-duplicate hydrogens give the same signal sets

2. The chemical shifts (where the signals appear) (Most complex facet) (Section 13.5)
   - The chemical shifts reflect the chemical environment of each type of hydrogen
     a. Whether attached to an sp^3 or and sp^2 carbon
     b. What kind of functional groups might be attached to the carbon on which the hydrogen is attached.
     c. Whether attached to carbon versus to oxygen or nitrogen

3. The integration (size/area) of each signal set (Simplest facet, once you know how) (Section 13.7)
   - The integrated area for each signal set reflects how many hydrogens are responsible.
     a. 3H → CH_3 group (or 2H and 1H groups superimposed)
     b. 2H → CH_2 group (or two nonequivalent 1H groups superimposed)
     c. 1H → CH or OH group

4. The splitting (number of lines) in each signal set (Section 13.8)
   - The splitting provides information about what is connected to a given carbon
     a. N lines → N-1 "neighbor" H's (when working from spectrum to structure)
     b. N neighbors → N+1 lines (when predicting spectrum from structure)

Summary of Steps in Beginner 1H NMR Interpretation:

1. If provided with a chemical formula, calculate elements of unsaturation
   - This helps to put you on the alert for the presence of double bonds, rings, or aromatics
2. **Count how many signal sets** you have.
- **This will tell you how many types of hydrogen-bearing carbons** you have.
- Hydrogens attached to symmetry-equivalent carbons will give equivalent signals)
- Asymmetric signals indicate two or more overlapping signal sets
3. Check the **integration** of each signal set.
   - 3H → CH_3 group 2H → CH_2 group 1H → CH or OH group
   - The above are true if there isn't any accidental overlapping
   - Clean CH_3 or CH_2 signal sets will normally have reasonable shape symmetry
     a. Ex, if you have a nice symmetric 3H signal, conclude you have a CH_3
     b. But if you have a complex, unsymmetric 3H, do not assume it's really a CH_3.
   - Effective recognition and integration of signal sets can help you know how many CH_3's and CH_2's you have in your molecule
4. **Check diagnostic "chemical shift" windows** of the lines
   - Use yes-or-no checklist regarding the presence of key functional groups
   - Things can get more complicated if two or more functional groups are both affecting a common signal set.
   - Chemical shift information can quickly tell you whether hydrogens are attached to arenas or alkenes, and tell whether a CH_2 or CH_3 or CH signal set is attached to a single-bond oxygens or a carbonyl or an aromatic.

5. Check the **splitting** of each signal set.
   - A signal set with N lines means that there are N-1 hydrogens attached to carbons directly connected to the carbon that holds the signal set hydrogens
   - The splitting tells you nothing about the signal set itself (for example, whether it is a CH_3 or a CH_2 group). But it can tell you for example whether a CH_3 group (for example) is connected to a CH_2 group or a CH group, or perhaps to an oxygen or a carbonyl carbon that doesn't have any directly attached hydrogens.
   - Etc.
6. Try to find any sure things that you can as soon as you can.
7. Try to use integration to find any clean 3H signals that indicate CH_3 groups. Then use splitting and/or chemical shifts to track down what the CH_3 group is connected to, etc..

Other Practical Tips

1. Try to recognize any easy and obvious sure-thing components, for example:
   a. Aryl groups (chemical shift in the 7's, a 4H or 5H integral depending on whether di- or mono-substituted)
   b. CH_3 methyl groups (based on clean 3H integration)
   c. Isopropyl groups (6H doublet)
   d. Alcohol OH: integrates for only 1H, and normally doesn't have the splitting that a CH hydrogen does
2. Try to work from end(s) toward the middle
   - If you know you have a CH_3 group, you can write it down for sure, and then try to figure out via splitting and/or chemical shifts what it's connected to, etc.
3. Recognizing "end groups" can give you an idea whether you have a straight chain or have branching
   - CH_3
   - Cl, Br
   - OH
   - C_6H_5

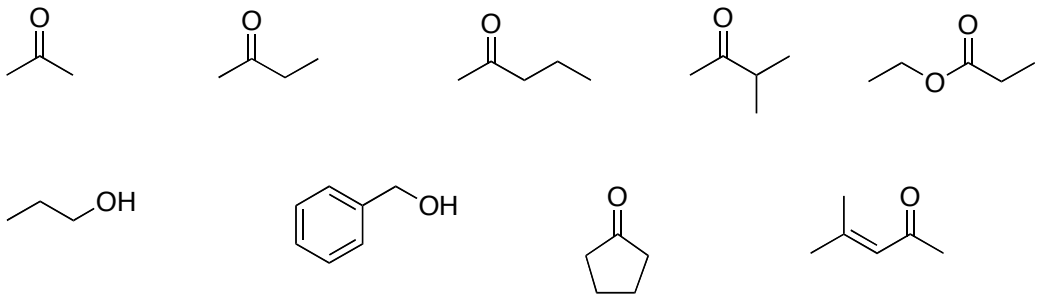
The Number of Signal Sets (Section 13-6)

1. Nonequivalent H's have different chemical environments and give different signals

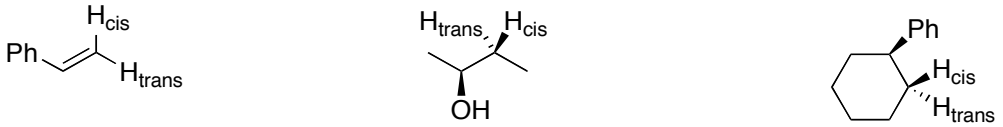
2. Symmetry-equivalent H's have the same chemical environment and give the same signal
   - Thus the number of signal sets tells you how many different types of hydrogens are present

3. On an **achiral** molecule (alkenes and rings excepted), hydrogens on a common carbon will be equivalent.
   - all three H's on a CH_3 group will be equivalent
   - both H's on a CH_2 group will be equivalent.

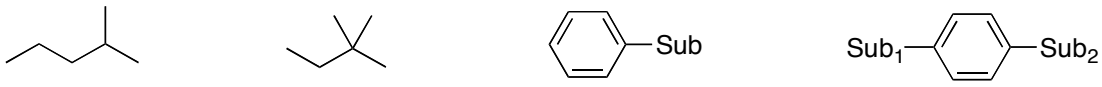
Example: How many H-NMR Signal Sets Would each of the following produce?



4. For chiral molecules, substituted rings, and alkenes, cis-trans relationships can often make the two hydrogens in a CH_2 group non-equivalent



5. **Beware of overlaps!**
   - Often two signal sets will show at about the same place. If you think you have a CH_3 group when in fact it's overlapping CH_2 and CH signals, you can get very confused…
   - Overlaps normally don't have the clean symmetry that a clean signal set has
6. **Beware of Symmetry Duplication**
   - Isopropyl groups are most common, and t-butyl groups on occasion
     - Integrations of 6H or 9H can help recognize these



Integration (Section 13-7)

1. All hydrogens give an equal amount of signal
   - The area produced is measured or "integrated" by the spectrometer
   - The measured area is normally referred to as the "integral"
2. When there is symmetry duplication of a hydrogen, the resulting signal will be multiplied accordingly!
   - Since all three H's on a CH_3 group are equivalent, they will sum to provide a signal set that integrates for 3H
3. Technical notes:
   a. The key is not the signal height, but rather the signal **area**.
   b. The signal **area** is measured by "integration lines". Make sure to differentiate integration marks, and what they mean, from signal lines themselves.

4. The relative areas of the signal-set integrals directly correlates the ratios of H's

- The integrals **must be simple whole-number ratios** (2:1, 3:1, 3:2, etc..)
- You can't have half a hydrogen or one-third of a hydrogen atom!

5. Clean sets involving equivalent H's give clean, symmetric signal sets:
   a. 1H → CH or OH
   b. 2H → CH_2
   c. 3H → CH_3
   d. 6H → 2 equivalent CH_3 groups
   e. 5H in aryl region → monosubstituted benzene (even if not clean set)
   f. 4H in aryl region → disubstituted benzene (even if not clean set)
6. Unsymmetrical messy sets involving overlapping signal sets: (these will routinely not look nice and symmetric…)
   a. 3H → CH_2 overlapping an OH or CH
   b. 4H → two overlapping but not exactly equivalent CH_2 groups; or a CH_3 overlapping an OH or CH
   c. 5H → common in the 7's, for 5 overlapping arene H's; also common in the 1's, when a CH_3 and CH_2 overlap
7. Recognizing 3H → methyl groups, or 6H → isopropyl groups is really helpful

Ways to Determine the Integration (Focus on the types of spectra that you'll see for test)

- Identify the integration line as opposed to the actual spectrum itself

1. Measure the raw areas for each signal set
   a. For class/test problems, use the grid lines
   b. For lab, the spectrometer will often measure an integral number for you
   c. For class or lab, if you prefer to use a ruler to measure, that's common to
2. Convert the raw areas into relative area ratios (Example, Handout problem 1)

Raw areas:

Three Ways to do this:

1. Divide any raw area by the smallest raw area

Ratio	Means	Ratio	Means	Ratio	Means	Ratio	Means
1		1.5		2		3	

2. Since all of our class/test NMR's will have 10 gridlines, you can take 10 gridlines/actual number of hydrogens (if formula is provided) to figure out the gridlines-per-hydrogen ratio

- You can then use this to convert your raw integrals into actual Hydrogen counts

Ex: 10 grids/7 H's = 1.4 grids/1 H

3. Since all of our class/test NMR's will have 10 gridlines, you can set up a ratio to solve for actual H's in a given signal set:

Ex: $$\frac{2.9 \text{ grids}}{10 \text{ grids}} = \frac{x \text{ H's}}{7 \text{ H's}}$$

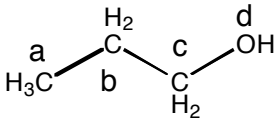
Splitting (Section 13.8)

- The number of lines in a signal set tell us nothing about the C-H's themselves that cause the signal (whether it's a CH_3 or CH_2 group, whether it's an sp^3 or sp^2 carbon, whether it's allylic or oxygenated…).
- But the splitting tells us something else that is really useful: what kind of CH groups are attached to the group of interest! Splitting tells us nothing about the group itself, but it does provide great information about neighbor groups.

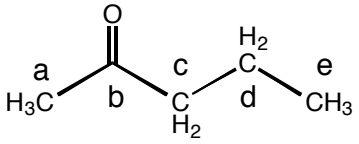
Rules of "Splitting"

- **N-1 Rule: N lines → N-1 neighbor H's** (H's directly attached to carbons attached to the C-H group causing the signal)
  - The N-1 Rule is useful when working from spectrum to actual structure
- **N+1 Rule: N neighbor H's → N+1 lines**
  - The N+1 Rule is useful when predicting a spectrum for a structure

N+1 Rule (Given structure, how many lines a spectrum should give)



Neighbors	2	3+2	2	0	
Lines	3	6	3	1	



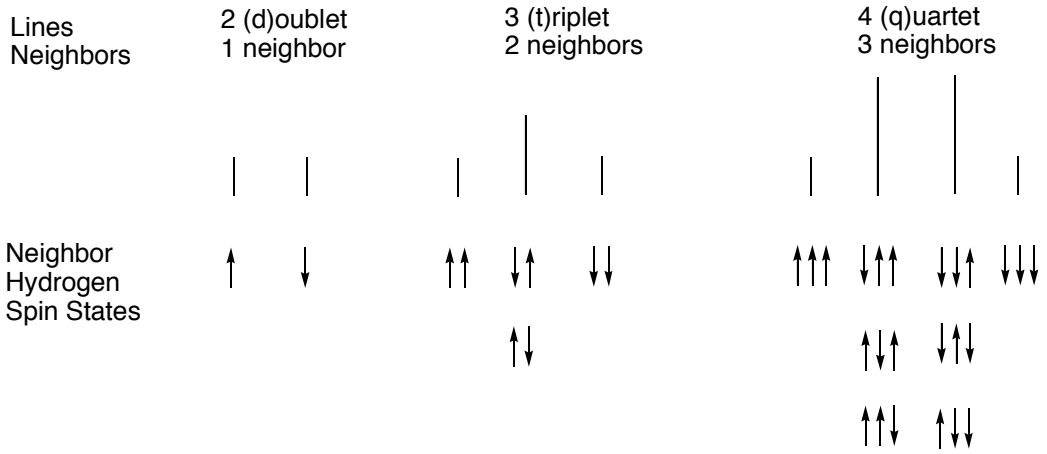
Neighbors	0	-	2	2+3	2	
Lines	1	-	3	6	3	

(Notice: OH doesn't split...)

N-1 Rule (Given spectrum, how many neighbors a structure should have)

Lines	1 (s)inglet		Lines	2 (d)oublet	
Neighbors	0		Neighbors	1	
Lines	3 (t)riplet		Lines	4 (q)uartet	
Neighbors	2		Neighbors	3	etc.

1. Physics Origin: hydrogens are quantized little magnets. Having neighbor hydrogens is equivalent to having local magnets that can either reinforce the external field (spin up) or counteract the external magnetic field (spin down).
   - The number of lines and the relative intensity of the lines reflects simple statistical possibilities in terms of neighbor hydrogen magnets being spin up or spin down.
     - With one neighbor magnet, the probability of spin up vs spin down is comparable → 1:1 doublet
     - With two neighbor magnets, they can be spin up/down in three different arrangements of 1:2:1 probability → 1:2:1 triplet
     - Etc.



2. Neighbor C-H hydrogens participate in splitting (always)
3. Neighbor OH hydrogens usually don't participate in splitting (~75% of the time). But sometimes they do (about 25% of the time).
   - They can have widely varying and rapidly changing hydrogen-bonding arrangements
4. Splitting from H's further distant than neighbor carbons sometimes occurs, but usually the amount of splitting is too small to worry about
5. Splitting nicknames:
   - 1 line = singlet (s) 2 lines = doublet (d) 3 lines = triplet (t)
   - 4 lines = quartet (q) 5 lines = pentet (p) >5 lines = multiplet (m)
6. Limitation to the N-1/N+1 rules: it is only reliable if all of the neighbor hydrogens are equivalent. However, the rules actually are accurate only if the neighbor H's are equivalent.
   - The rule can break down when some of the neighbor H's differ significantly from each other
   - The more nonequivalent the neighbor hydrogens, the less the N-1/N+1 rules apply
     - Neighbor hydrogens on acyclic and sp^3 carbons tend to be pretty similar
     - Alkenes or aldehyde hydrogens (on sp^2 carbons) tend to split rather differently than hydrogens on sp^3 carbons
     - Splitting involving cis versus trans hydrogens on rings or alkenes tend to split rather differently from each other and from hydrogens on acyclic sp^3 systems.
     - Chiral centers can mess up the splitting even on acyclic systems

"Chemical Shifts" of the Signal Sets (Section 13.5)

- The following apply when only one functional group is impacting
- If two or more are impacting, then signal sets can appear outside of these windows

1's (0.7-2.0) sp^3 hybridized C-H's, with **no attached Functional Groups**

- **Note:** Many molecules with non-functional alkyl portions will give a lot of signal in this area.
- **This is the default place for sp^3 C-H's, when no functional group is shifting them to higher number**

2's (1.8-3.1) **Allylic** sp^3 hybridized C-H's (sp^3 hybridized C-H's that has a double bond attached to the sp^3 hybridized C). Allylic signals routinely appear when one of the following double-bonded functional groups is present:

- +1 Adjustment factor
- **carbonyls**, (ketones, esters, aldehydes, acids, amides)
- **alkenes**, or
- **aromatics**

3's (2.8-4.5) **Oxygenated** sp^3 hybridized C-H's (halogenated and nitrogenated alkyl C-H's will also come in this window, although no candidates for today's lab). Oxygenated sp^3–carbons are routinely present for the following functional groups that contain oxygen single bonds:

- +2 Adjustment factor
- **alcohols**, (usually signal in 3's)
- **ethers**, (usually signal in 3's) or
- **esters** (usually signal in low 4's)
- **More general: heteroatom substituents (O, Cl, Br, I) usually have a +2 adjustment factor, N a +1.5-2.0 adjustment factor.**

5's (4.8-6.8) **Alkene** sp^2 hybridized C-H's

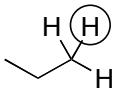
7's (6.5-8.4) **Aromatic** sp^2 hybridized C-H's

9's (9.0-10.0) **Aldehyde** sp^2 hybridized C-H's

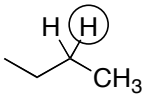
0-12 (anywhere!) **Alcohol/Acid** O-H hydrogens (N-H hydrogens likewise)

- **alcohols**, (normally 1.5-3.0)
- **carboxylic acids** (usually 10-12)

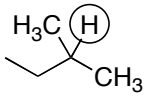
1. Replacement of H by more electronegative atom/group "deshields" a proton and moves it "downfield", to a higher number
   a. "methine" (CH) → "methylene" (CH_2) → "methyl" (CH_3) (case "a" vs "b" vs "c")
      - sequential replacement of hydrogens by more electronegative carbons moves the signal "downfield"
   b. See the electronegativity pattern as you go from: H (0.9) – C (1.2) – N (2.6) – I (3.2) – Br (3.3) – Cl (3.4) to O (3.5) (case "a" vs "b" vs "g" vs "i-l")
      - sequential replacement of hydrogens (or carbons) by any more electronegative substituents moves a signal "downfield"
   c. See the electronegativity pattern between amine (2.7) versus amide (3.2) (case "g" vs "h"), and alcohol/ether oxygen (3.5) versus ester oxygen (4.1) (case "l" vs "m")
      - the electron-withdrawing carbonyl attachment on the nitrogen or oxygen makes it effectively more electronegative and moves the signal "downfield"



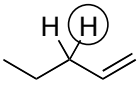
a. 0.90



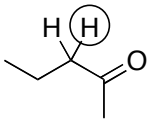
b. 1.20



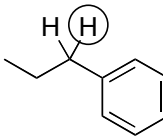
c. 1.50



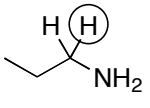
d. 2.00



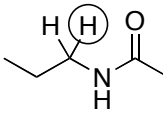
e. 2.45



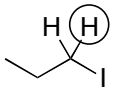
f. 2.55



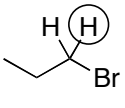
g. 2.65



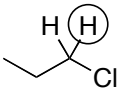
h. 3.20



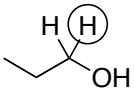
i. 3.15



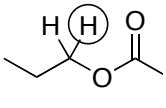
j. 3.35



k. 3.40

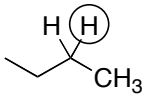


l. 3.53

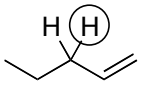


m. 4.08

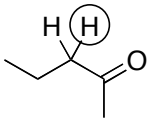
2. The allylic factor has the same basis: sp^2 carbons are more electronegative than sp^3 carbons, so replacing an sp^3 with an sp^2 "deshields"



1.20

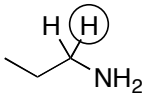


2.00

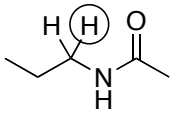


2.45

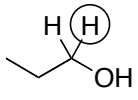
3. An electron-withdrawing carbonyl on a heteroatom makes the heteroatom effectively more electronegative. So ester versus ether and amide versus amine has the same electronegativity basis.



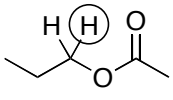
2.65



3.20



3.53



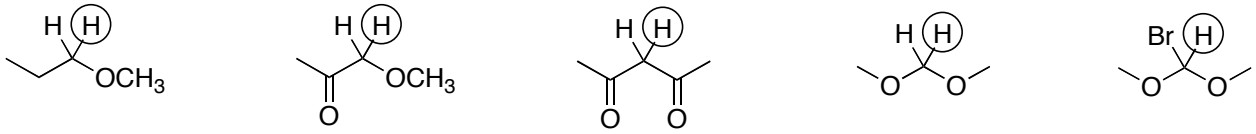
4.08

4. <u>Additivity values can be used to predict chemical shifts when two or more functional groups are acting</u>

Vinyl	Carbonyl ("Acyl")	Aryl	Amino	Amido	Halo	Hydroxy/ Alkoxy	Carbonyloxy
0.8	1.2	1.3	1.5	2	2.2	2.3	2.8

- Default reference points: CH_3 0.90 CH_2 1.20 CH 1.50
- Memorize the following qualitative additivity values:
  a. Double-bonded carbons (vinyl, acyl, aryl) → +1
  b. Oxygen or Halogen → +2

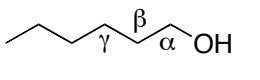
<u>Predict the chemical shifts for the circled hydrogens, using the specific chart additivity values and using the qualitative memorized ones:</u>



5. Strong hybridization effect: hydrogens on sp^2 carbons routinely above 5, those on sp^3 carbons normally come below 5.

1.20 5.4 7.1 9.7

6. Functional Groups further away have reduced but sometimes significant impact.
   - Direct "α" attached functional groups have a large impact
   - When the functional group is "β" it makes a difference, but not large
   - When the functional group is "γ" or further, it makes no difference
   - Sometimes a couple of "β" substituents can add up and push a signal set out of it's normal window



α-CH_2 3.5
β-CH_2 1.3
γ-CH_2 1.2

Key: The impact of two or more functional groups can sometimes deceptively push a signal into a window that you assume means something else

- A signal in the 3's normally implies an oxygenated (or halogenated) carbon. But it could also result from a double allylic carbon with two carbonyls attached.
- A signal in the 5's is normally implies an alkene, but it might also result from an sp^3-hybridized carbon that has two oxygen attachments.
- Etc.

7. **Recognize OH's.**.
   a. An OH can come anywhere, and can easily cause you to make a mistaken conclusion about a feature group. For example, if you have an OH and it comes in the 2's, and you conclude that you have an allylic C-H, that might send you down a bad blind alley. Or if you have an OH that appears in the 5's, you might falsely deduce that you have an alkene, etc.. Thus it is really helpful to recognize OH's when they appear so that they don't confuse you.
   b. Three recognition factors for OH signals:
      1. They always **integrate for 1H**, never for 2H or 3H
      2. They **lack sharp splitting**, and often **appear as singlets, often somewhat broad**. C-H signals tend to be sharper, and any C-H signal set that integrates for 1H will have significant splitting. The only way to have a 1H that doesn't split is for it to be an OH.
      3. They come anywhere, but often in the 1.5-3.0 range
      4. If you have an OH signal, of course you will also have some C-H signals in the 3.0-4.5 area.

8. **Check each of the zones. Each one gives you a tentative yes or no answer about the presence of absence of the featured group**.
   - Do I have something in the 9's? If yes → aldehyde
   - Do I have something in the 7's? (Other than a solvent singlet…)? If yes → aromatic
   - Do I have something in the 5's? If yes → alkene
   - Do I have something in the 3's? If yes → alcohol, ether, or ester (or OH)
   - Do I have something in the 2's? If yes → ketone, aromatic, or alkene (or OH)
   - Do I have something in the 1's? If yes → some nonfunctional alkyl carbons (or OH)

Caution: Mistaken conclusions can sometimes be drawn from two sources:

a. An OH in the 2's or 3's or 5's, from which you falsely conclude that you be allylic or oxygenated of vinylic
b. A signal that appears where it does because of the effect of two (or more) functional groups, rather than just one.

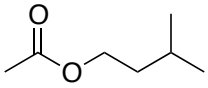
Standard Summary Format and Predicting H-NMR's There is a standard summary report format for H-NMR's which addresses **chemical shift, integration, and splitting**. Normally an **interpretation**/correlation with the actual structure is also included.

Ex: $CH_3OCH_2CH_2CH_2C(O)CH_3$ (I'll number the carbons from left to right…)

Standard report format (approximate chemical shift range, integration, splitting, and interpretation of which signal correlates to which group in the structure…)

3's, 3H, s (CH_3-1)
3's, 2H, t (CH_2-2)
1's, 2H, p (CH_2-3)
2's, 2H, t (CH_2-4)
2's, 3H, s (CH_3-6)

Predict the NMR for the Following Structure, Using the Standard Summary Format



Review + Summary

1. Use your formula to count elements of unsaturation
2. Count **how many signal sets** you have.
3. Check the **integration** of each signal set.
   - 3H → CH_3 group 2H → CH_2 group 1H → CH or OH group
4. Check the **splitting** of each signal set.
   - N lines → N-1 neighbor hydrogens
5. Check **"chemical shift" windows** of the lines to provide information regarding the **presence or absence of key functional groups** in your molecule.
   - Beware of misinterpreting overlapping signals
   - Beware of being confused by signal sets caused by OH's or caused by two or more functional groups impacting chemical shift
   - Steps 4 and 5 are definitely interchangeable
6. **Use "tracking" to work from known components (normally CH_3 end groups, or C_6H_5 end group, or OH end groups) down the chain**
   - **Integration** can tell whether it's a CH_3, CH_2, or CH causing a particular signal set
   - **Chemical shift** and/or **splitting** can then tell you what else may be **attached**
     a. **Chemical shift** tells if a **functional group** is attached
     b. **Splitting** tells what **CH, CH2, or CH3** groups are attached
7. **End-Check: Check that the structure you believe you actually have would give the number of signal sets you have, the chemical shifts you have, the integrations you have, and the splittings that you have. If not, your structure needs to be corrected!**

^{13}C NMR (Sections 13.13,14)

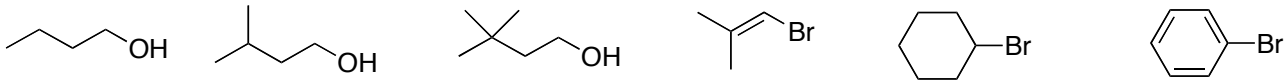
- ^{13}C is NMR active, ^{12}C is not
- Signals are much weaker, C-13 spectra are harder to get
  - C-13 gives about 1/10,000th as strong a signal as H-NMR
  - Because the natural abundance is only 1%, and the inherent sensitivity is only 1%
- A result is that for C-13 NMR, one or more of the following is usually true:
  1. Take longer
  2. Not as clean a baseline
  3. Higher sample/solvent concentration used
  4. Data processing tricks used in order to shorten the process. These often result in:
     - Loss of splitting information ("decoupled" C-13 NMR's in lab…)
     - Loss of integration information (our C-13 NMR's in lab…)

Summary of C-13 NMR Interpretation:

1. **Count how many lines** you have in a decoupled carbon spectrum. **This will tell you how many types of carbons** you have. (Symmetry equivalent carbons can at times cause the number of lines to be less than the number of carbons in your structure.)
2. **Check diagnostic frequency windows** ("chemical shift windows") of the lines **to provide yes-or-no answers regarding the presence or absence of key functional groups** in your molecule.
3. If **splitting** information is provided via a coupled carbon spectrum, or a DEPT NMR spectrum is provided, or a phase-sensitive 2-dimensional NMR is provided, use tools like these to decide which carbons are CH_3, CH_2, CH, and no-H C's.

1. **Count how many lines** you have. **This will tell you how many types of carbons** you have.
   1. Each "unique" carbon gives a separate line.
   2. Symmetry duplicates give the same line.
   3. If there are more carbons in your formula than there are lines in your spectrum, it means you have some symmetry.

Q: How many lines would show in the C-13's for the following?



2. Chemical Shifts: Where do the Lines Come?

220-160 C=O carbonyl carbons, sp^2 hybridized

160-180 → typically ester
- for formulas that have two oxygens, being able to recognize ester group helps a ton

180-220 → other carbonyls (ketone, aldehyde, carboxylic acid, amide)

160-100 C alkene or aromatic carbons, sp^2 hybridized
- If a molecule has alkene or aromatic, it's usually easy to tell which it is based on chemical formula or on the number of lines in the 100-160 zone (2 for alkene, usually more for aromatics

100-50 C-O oxygen-bearing carbons, single bonds only, sp^3 hybridized

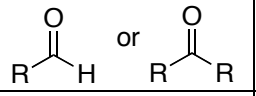
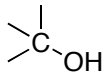
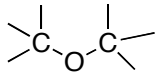
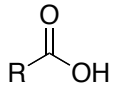
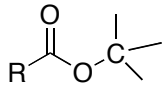
80-30 C-N nitrogen bearing carbons, single bonds only, sp^3 hybridized

80-30 C-X halogen bearing carbons, single bonds only, sp^3 hybridized

50-0 C alkyl carbons, no oxygens attached, sp^3 hybridized
- This is the default zone for sp^3 carbons with no attached heteroatoms
- Allylic carbons still fall into the 50-0 zone, unlike in H-NMR where allylic hydrogens are distinct

- Halogens or nitrogens complicate things a bit, because they can appear on either side of the 50-divider.
- But for formulas involving only C, H, and O, the 50-divider is very, very useful.

Using the "Oxygen Zones" for Oxygenated Systems

			220-160 Zone	100-50 Zone
One-Oxygen Formulas	Ketone, Aldehyde		180-220	
	Alcohol			One
	Ether			Two
Two-Oxygen Formulas	Acid		180-220	
	Ester		160-180	One
	Aldehyde/Ketone And Alcohol		180-220	One
	Aldehyde/Ketone And Ether		180-220	Two

3. **Splitting** in a coupled carbon NMR spectrum.
   - C13 NMR's are normally acquired as "decoupled" spectra, in which each carbon signal appears as a singlet, for reasons of speed and simplicity.
   - However, at the cost of extra time and at the expense of some simplicity, it is also possible to get "coupled" C13 NMR's with splitting. The C-13 atoms are split by directly attached hydrogens.
   - These splitting values are very useful, and follow the N+1/N-1 rules (the number of lines is one greater than the number of attached H's).

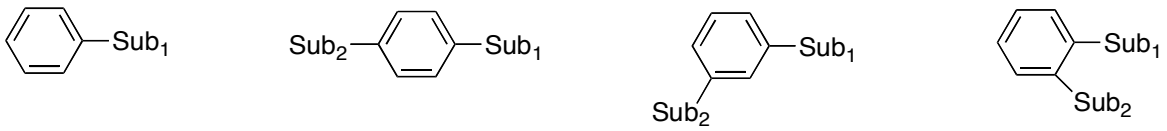
Quartert (q)	CH_3
Triplet (t)	CH_2
Doublet (d)	CH
Singlet (s)	C (no attached hydrogens)

   - Coupled C-13 has at last two drawbacks:
     1. The signal to noise ratio and thus the sensitivity is a lot worse.
     2. Overlap: With coupled C-13 NMR, there are a lot more lines, and overlapping of lines becomes normal and confusing for non- simple molecules.

4. **DEPT NMR.**
   - "Distortionless Enhanced Polarization Transfer" is another technique that can unambiguously assign carbons as methyl (CH_3), methylene (CH_2), methyne (CH), or quaternary (no attached hydrogens).
   - One or two DEPT experiments are done in conjunction with a decoupled C-13 NMR.
   - DEPT 90: only methine (CH) carbons show, and they point up
   - DEPT 135: both methine (CH) and methyl (CH_3) carbons point up, and methylene (CH_2) carbons point down.
   - Quaternary carbons won't appear in DEPT 90 or DEPT 135.
   - By combining information from a decoupled, DEPT90, and DEPT135 NMR, you can unambiguously identify which carbons are of which type.

5. **Aromatics, Symmetry, Splitting**. Most aromatics have symmetry, and both the number of aromatic lines and the splitting of the aromatic lines can be indicative of the substitution pattern on a benzene. Mono- and para-disubstituted benzenes have symmetry.

4 lines	s, d, d, d	Monosubstituted benzene. (Has symmetry)
4 lines	s, s, d, d	Para-disubstituted benzene. (Has symmetry)
6 lines	s, s, d, d, d, d	Ortho- or meta-disubstituted benzene. (Has no symmetry)



6. **Signal Height/Size** Unlike 1H-NMR, where integration is really important, signal size is not very important in C-13 NMR.
   a. Signal amplification tricks (to save time) compromise accurate integration
   b. Even when lines have equal area, a narrower one looks much taller than a fatter one
   c. Two patterns that can be somewhat helpful.
      1. Carbons without any attached H's are short. Common in:
         a. carbonyls (aldehydes are the only carbonyl carbons that have hydrogens attached)
         b. substituted carbons in aromatic rings.
         c. T-butyl carbons
      2. Symmetry duplication multiplies signal height (if you have two copies of a carbon, the line will probably be taller than normal!)

Problem Solving and C-13

Alone	In Support with H-NMR
1. Calculate EU 2. Symmetry? Check lines versus formula 3. Look for Obvious Things • Oxygen zones, aryl zone… 4. Use Splitting 5. Look for ends groups • Methyl, phenyl, OH, halogen	Look for obvious things 1. Carbonyls? (any, and if so ester or aldehyde?) 2. Oxygen zones? 3. Aromatic or alkene, and if so with what kind of substitution pattern? 4. Symmetry? 5. CH_3, CH_2, CH count

2-Dimensional NMR (Carey section 13.19)

1. In a 2-D NMR experiment, one spectrum gets plotted on the x-axis, another on the y-axis, and atoms that are coupled to each other give "cross peaks".
   - This enables you to tell which atoms are connected or coupled to each other
   - This is sometimes a faster or easier way to establish chain connectivity than simply relying on splitting to figure out which groups are neighbors.

2. Hydrogen-Hydrogen 2D ("COSY"): the hydrogen NMR of the sample is printed on both axes, but you can use the cross-peaks to identify which hydrogens are split by which other hydrogens

3. Carbon-Hydrogen 2D ("HSQC" or "HMQC"): the hydrogen NMR is plotted on one axid, the carbon NMR on the other. A hydrogen signal will give a cross peak with the carbon to which it is attached.
   - A phase-sensitive version can differentiate methylene (CH_2) carbons from methyl (CH_3) or methine. Experiments like these are often faster and more informative than DEPT or coupled carbon NMR's.

Infrared Spectroscopy (Chapter 12, Nice Summary in Section 12-11)

- Examples, Contrast to NMR
- Much more complex than NMR
    - In NMR, we expect to explain everything, and we can solve full structures
- In IR, two typical uses:
  a. Functional Group Identification: focus on a few key zones (our use)
  b. "Fingerprint" matchups of unknowns to knowns (we won't do)

Major overall zones:
1600-3600 useful (stretching, useful for functional group ID)
1600-600 vibrations "fingerprint", always busy, not very useful for function group ID

Major Bands that are of some Functional Group Interest

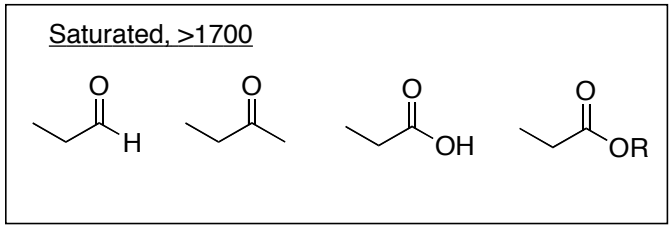
3500-2700	N-H, O-H, C-H single bonds
2300-2100	CN, CC triple bonds
1800-1580	C=O, C=N, C=C double bonds

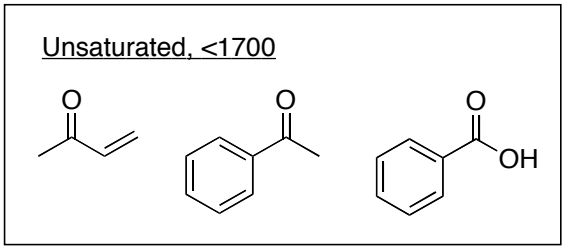
Practical Feature Groups

1. O-H/N-H Zone (except when O-H is a carboxylic acid O-H): 3500-3200
    - **Alcohol Recognition**
    - Amines or amides
    - Signals are sometimes rather broad due to hydrogen-bonding
    - Note: when looking at an actual spectrum, focus in specifically on the 3500-3200 range, don't just look generally around 3000
        - Because every organic molecule will have a big C-H signal around 2900-3000
        - That is ***not*** interesting or informative, and should ***not*** be mistaken for proof of alcohol
    - In contrast to alcohol O-H, carboxylic acid O-H signals are extremely broad, ranging somewhere within 3500-2200

2. Carbonyl Zone: Around 1710 ± 80
    - Very strong signal
    - First thing to check

    1700 rule
    - carbonyls >1700 are "saturated": no attached double-bonded carbons
    - carbonyls <1700 are "unsaturated": an sp^2 attached carbon (i.e. alkene or aromatic)



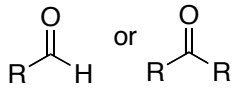
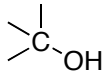
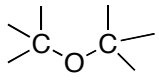
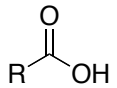
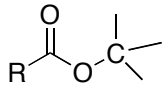


Esters versus Ketones/Aldehydes/Acids
- Saturated esters 1735-1750
- Saturated ketones/aldehydes/acids: 1700-1720
- Very useful for recognizing when a two-oxygen formula contains an ester

Carboxylic Acids (versus hydroxy ketones)

- Acid has both a carbonyl in the ~1700 zone and a broad hydroxyl spread somewhere in the 3500-2200 zone
- A formula with two oxygens that has one as ketone and one as alcohol would give a carbonyl in the ~1700 zone but a tighter alcohol O-H in the 3500-3200 zone
- Very useful for quick recognition of carboxylic acids

Using the "Oxygen Zones" for Oxygenated Systems

			Carbonyl Zone	Hydroxyl Zone
One-Oxygen Formulas	Ketone, Aldehyde		1700-1720 (if saturated, <1700 if not)	
	Alcohol			3500-3200
	Ether			
Two-Oxygen Formulas	Acid		1700-1720 (if saturated, <1700 if not)	3500-3200 (**broad**)
	Ester		1735-1750 (if saturated)	
	Aldehyde/Ketone And Alcohol		1700-1720 (if saturated, <1700 if not)	3500-3200 (**broad**)
	Aldehyde/Ketone And Ether		1700-1720 (if saturated, <1700 if not)	

Practical Use for IR: Fast recognition of key functional group information
-helpful support for an NMR solution, if you know what functionality is present.

Summary of IR (Infrared) Interpretation

Check for Diagnostic Signals

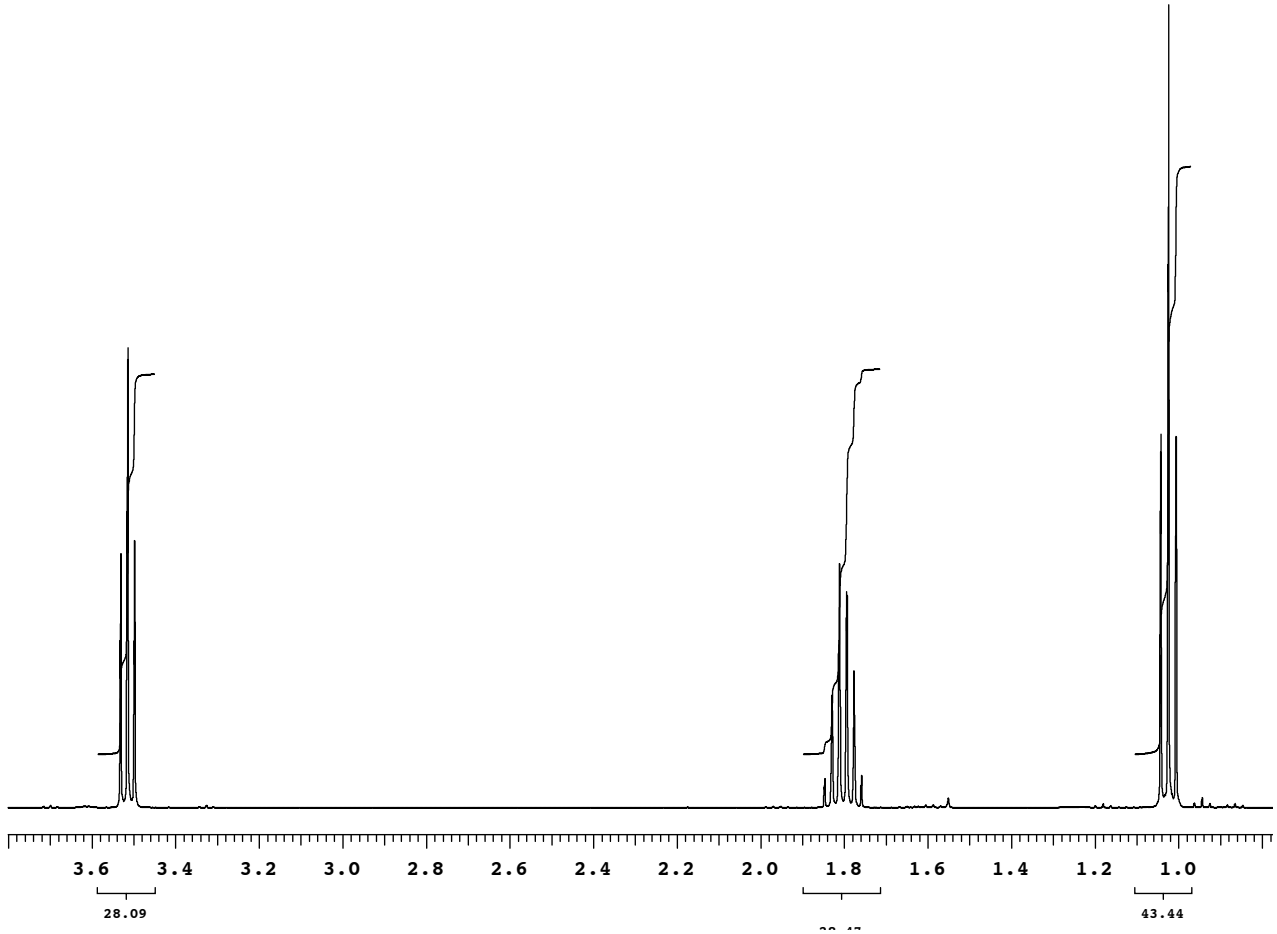
3500-3200	OH or NH
1800-1641	C=O
3500-2500 + 1800-1640	CO_2H

Further Information in the "Carbonyl Zone"

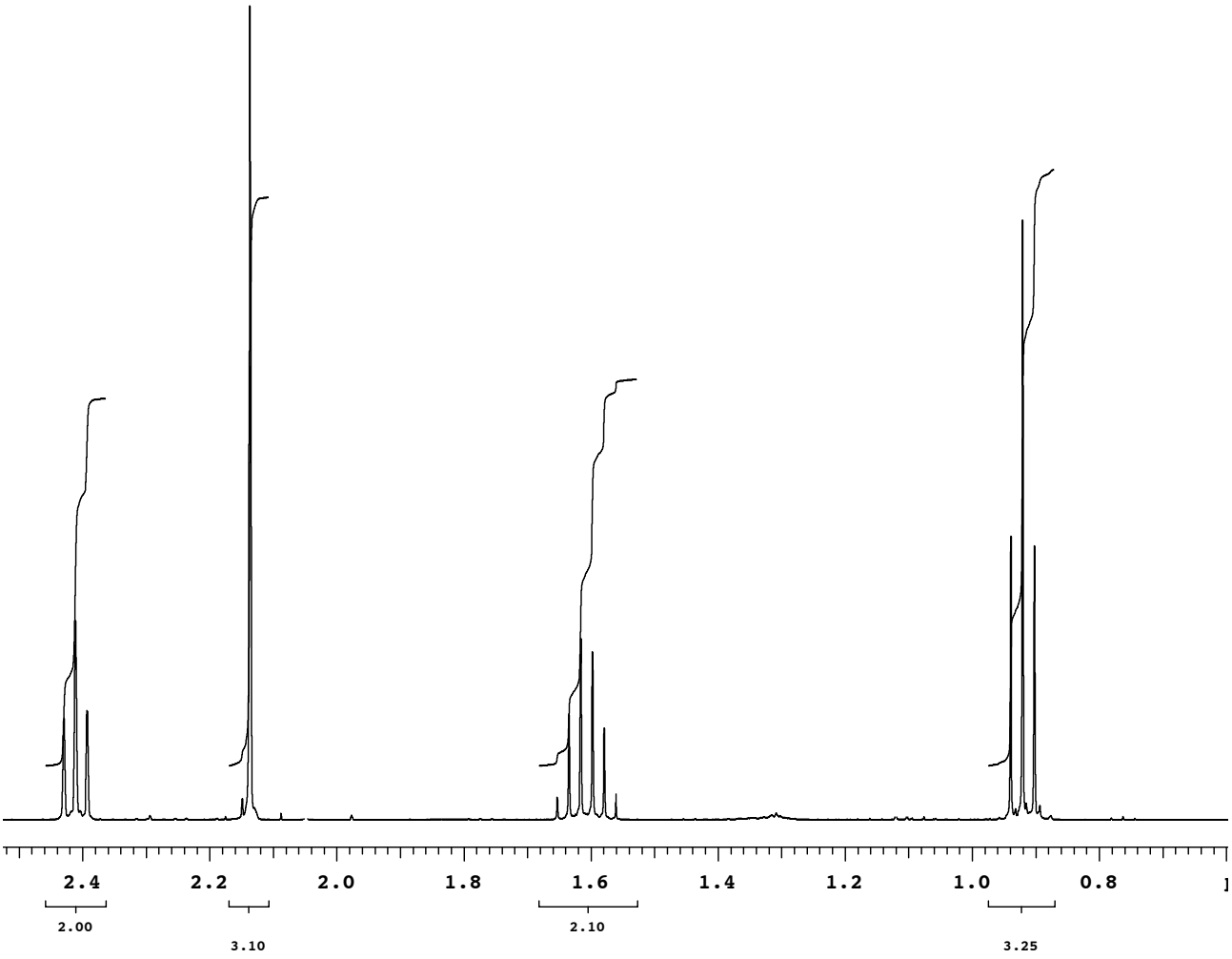
<1700	Unsaturated C=O
>1700	Saturated C=O
1720-1701	Saturated ketones, aldehydes, acids
1750-1735	Saturated ester

Jasperse Organic II NMR Problems

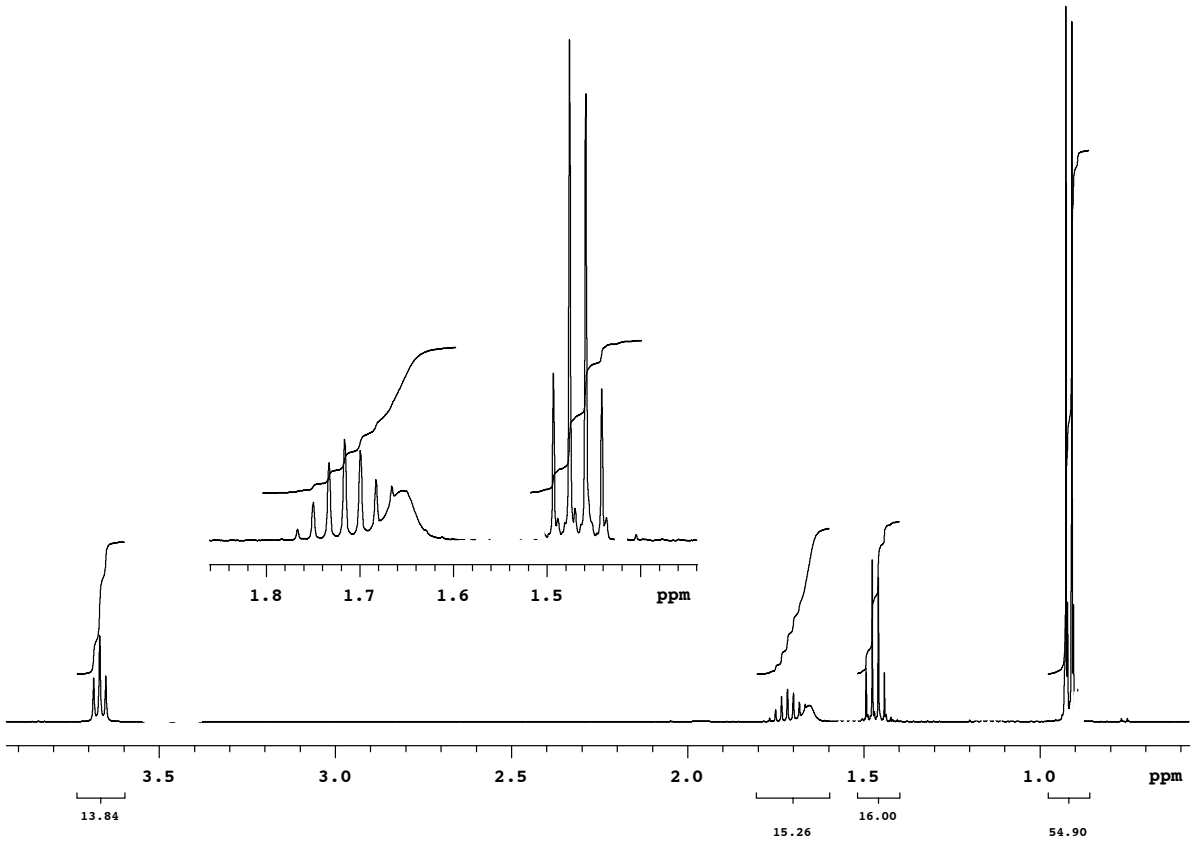
1. C_3H_7Cl



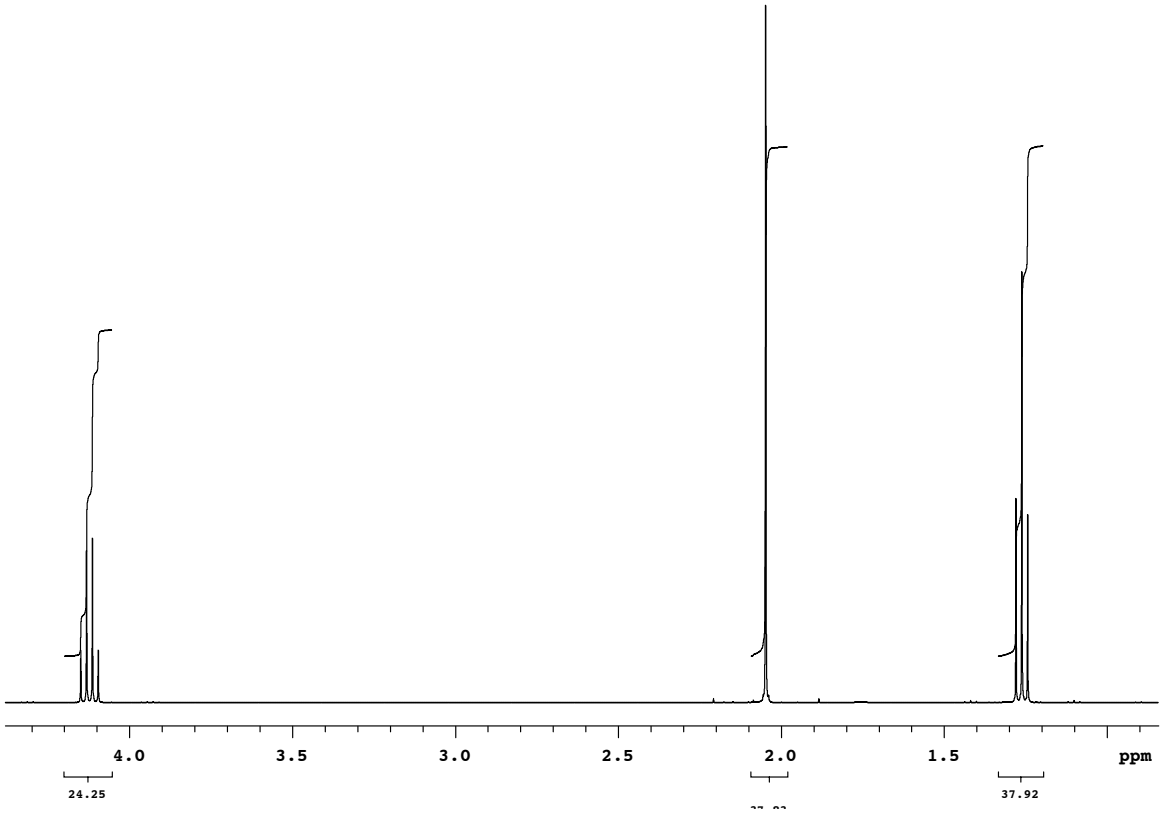
2. $C_5H_{10}O$



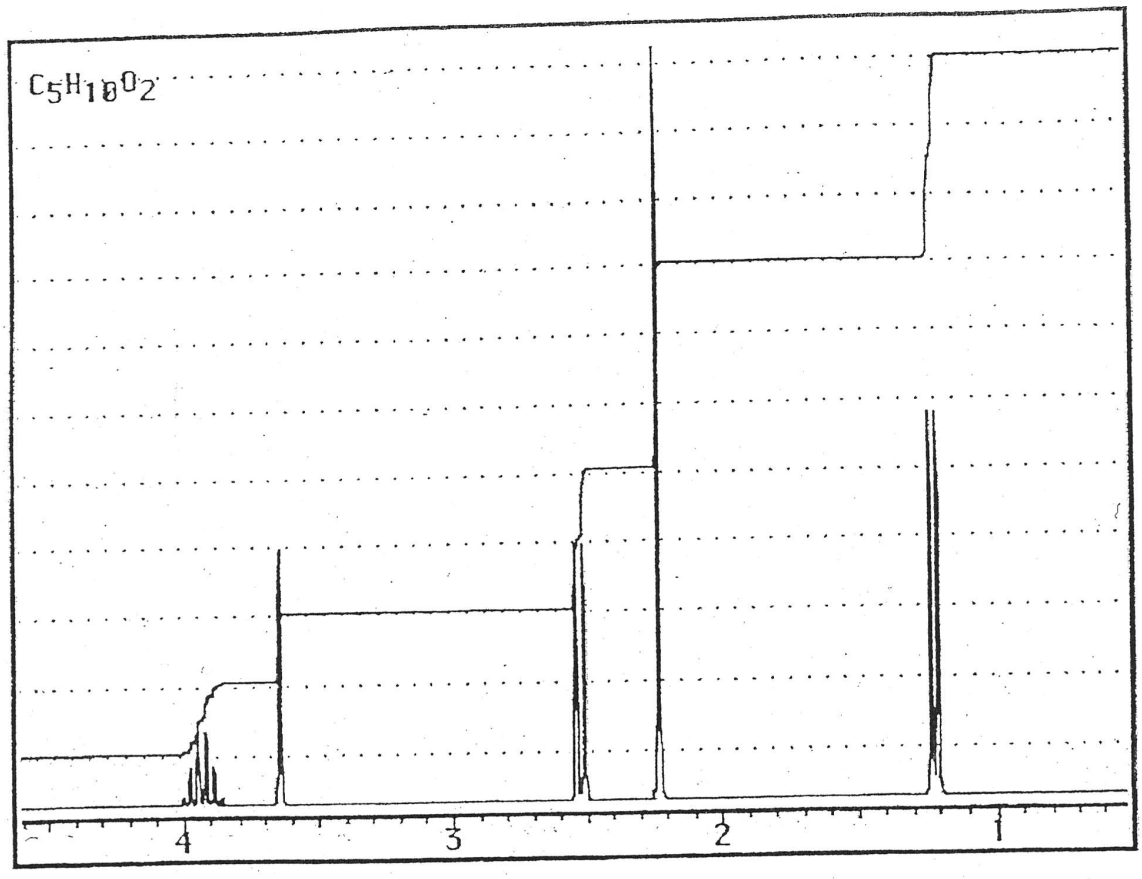
3. $C_5H_{12}O$



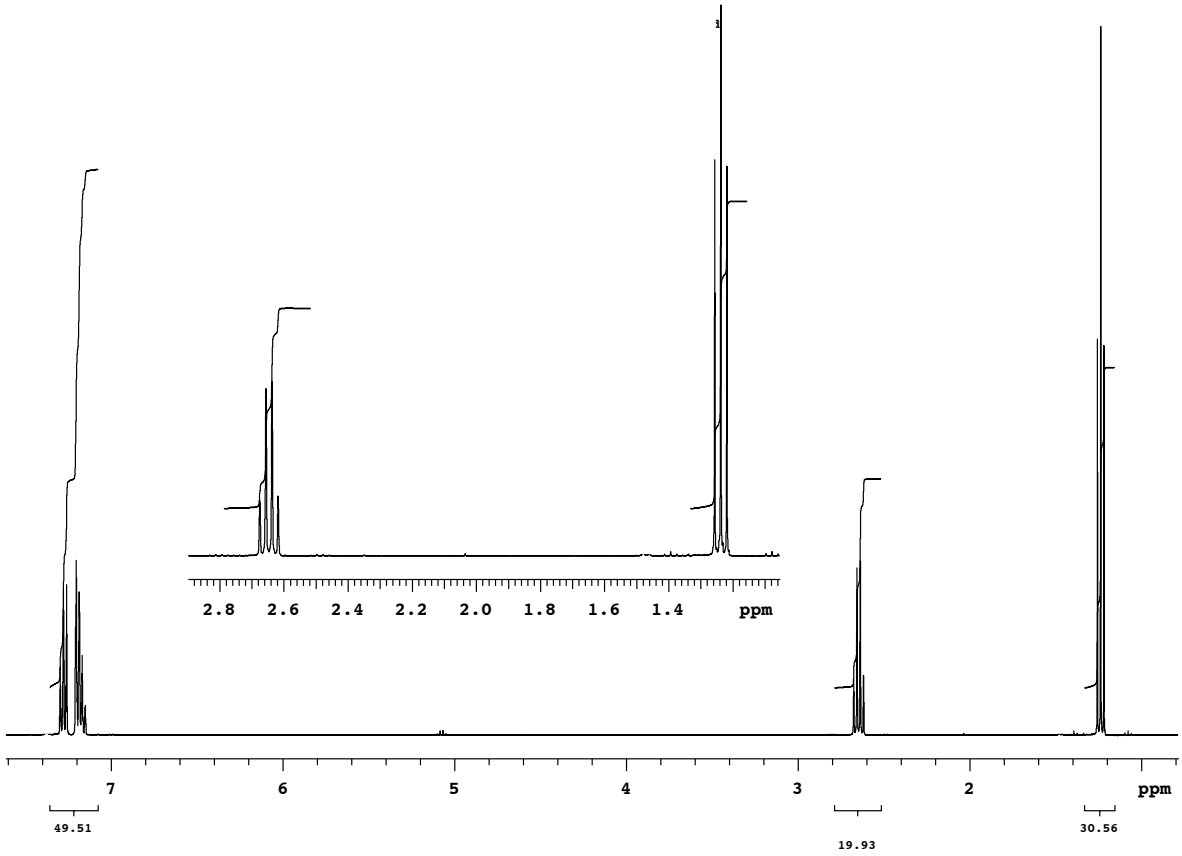
4. $C_4H_8O_2$



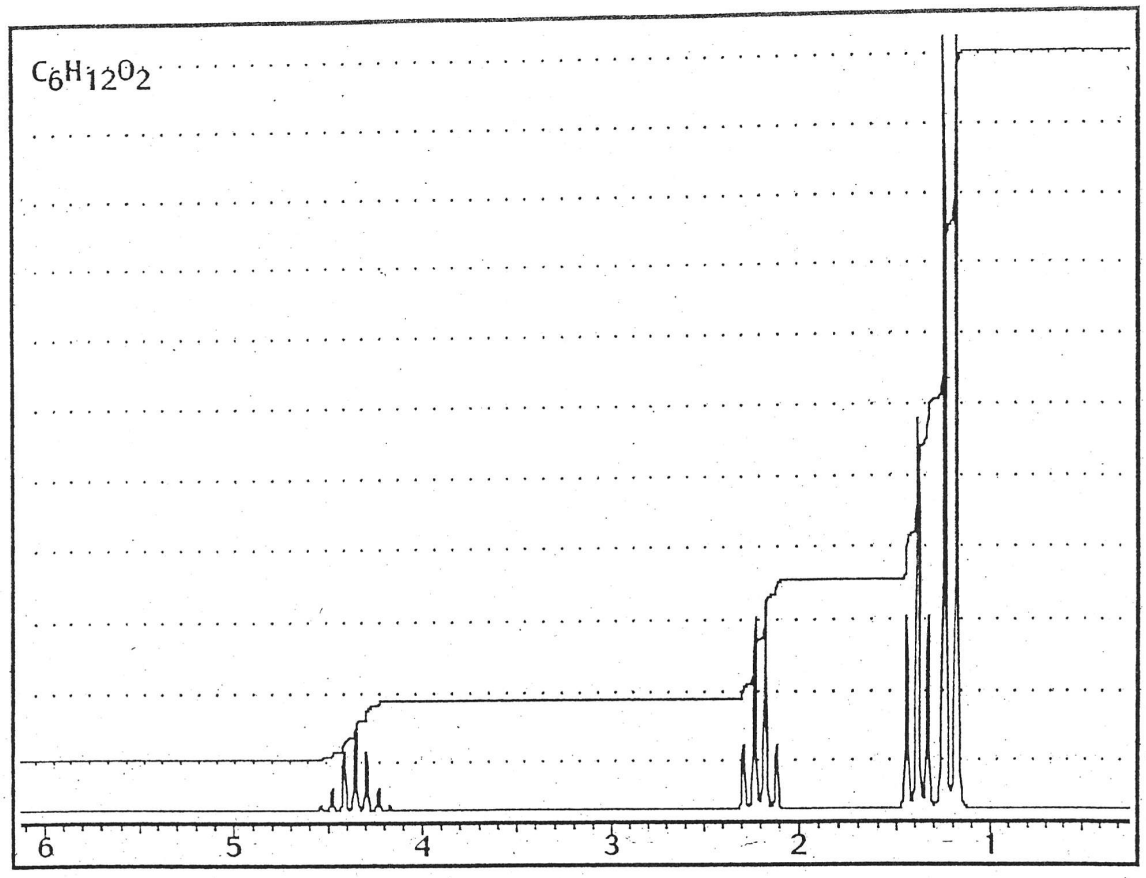
5. $C_5H_{10}O_2$



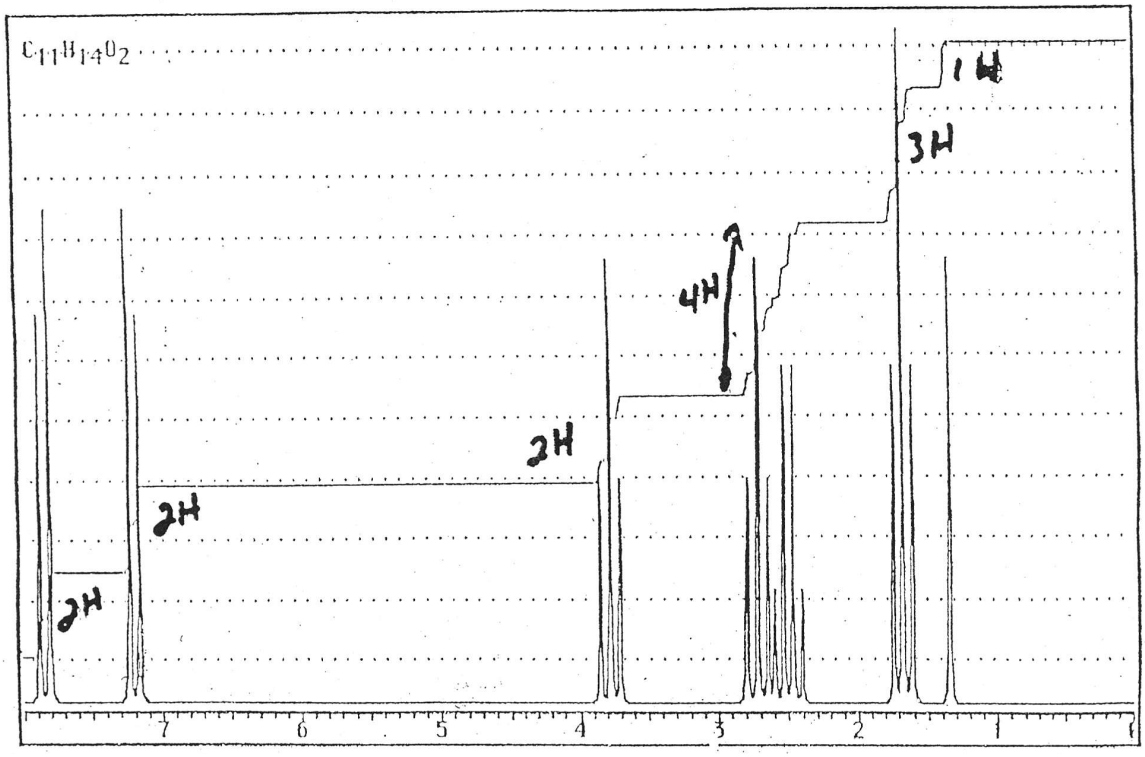
6. C_8H_{10}



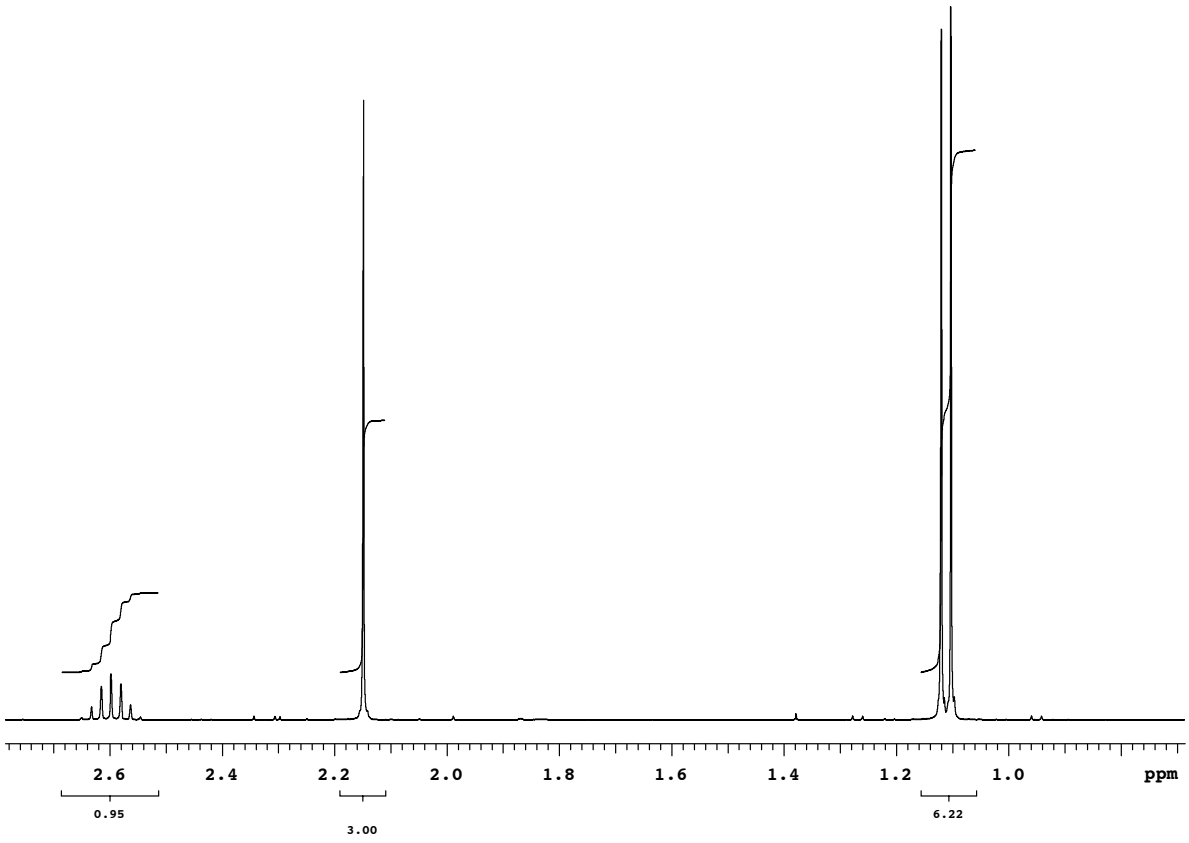
7. $C_6H_{12}O_2$



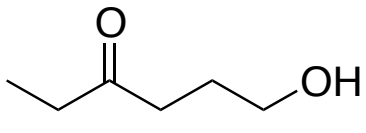
8. $C_{11}H_{14}O_2$

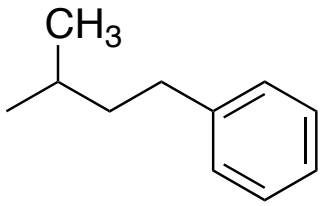


9. $C_5H_{10}O$



10. Predict the Spectrum for:

a. 

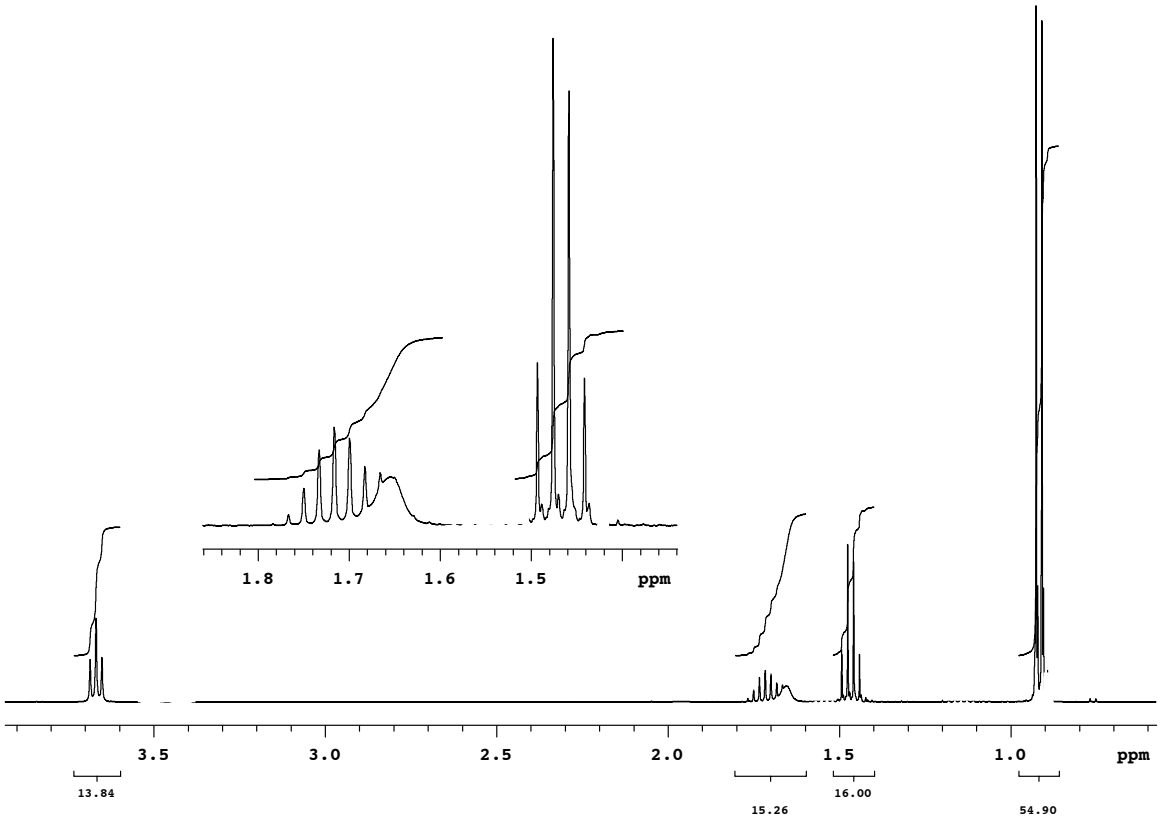
b. 

c. Identify the Structure from the Shorthand NMR (nongraphic)

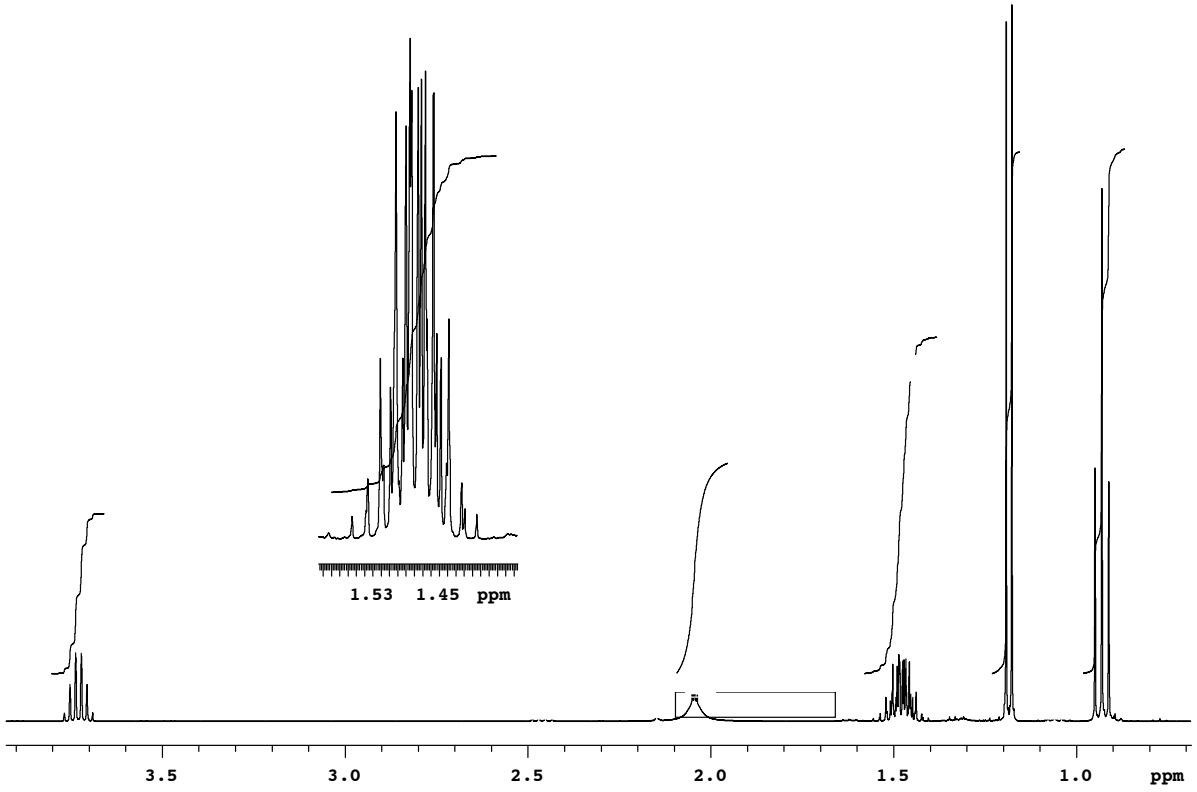
C_4H_8O

1.05, triplet, 3H
2.13, singlet, 3H
2.47, quartet, 2H

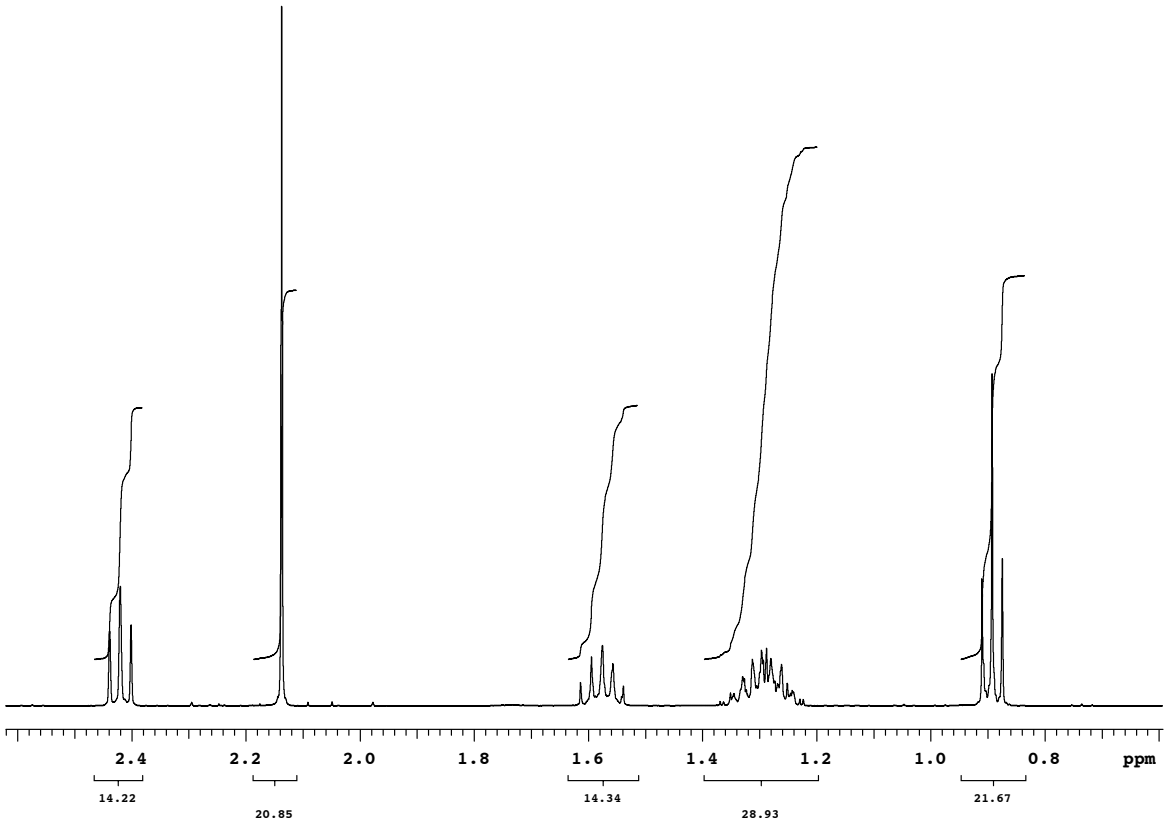
11.$C_5H_{12}O$



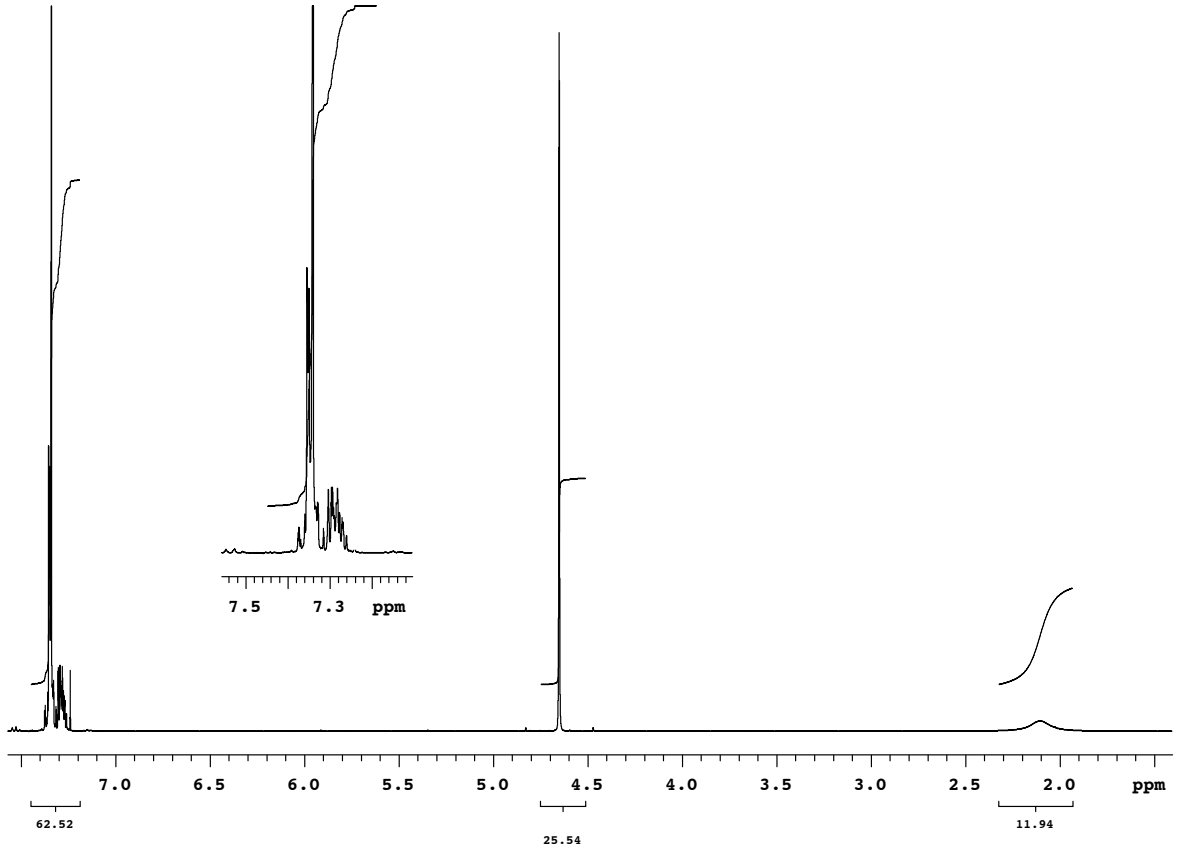
12. $C_4H_{10}O$ (somewhat contaminated. Ignore the non-integrated sets at 1.05 and 2.45).



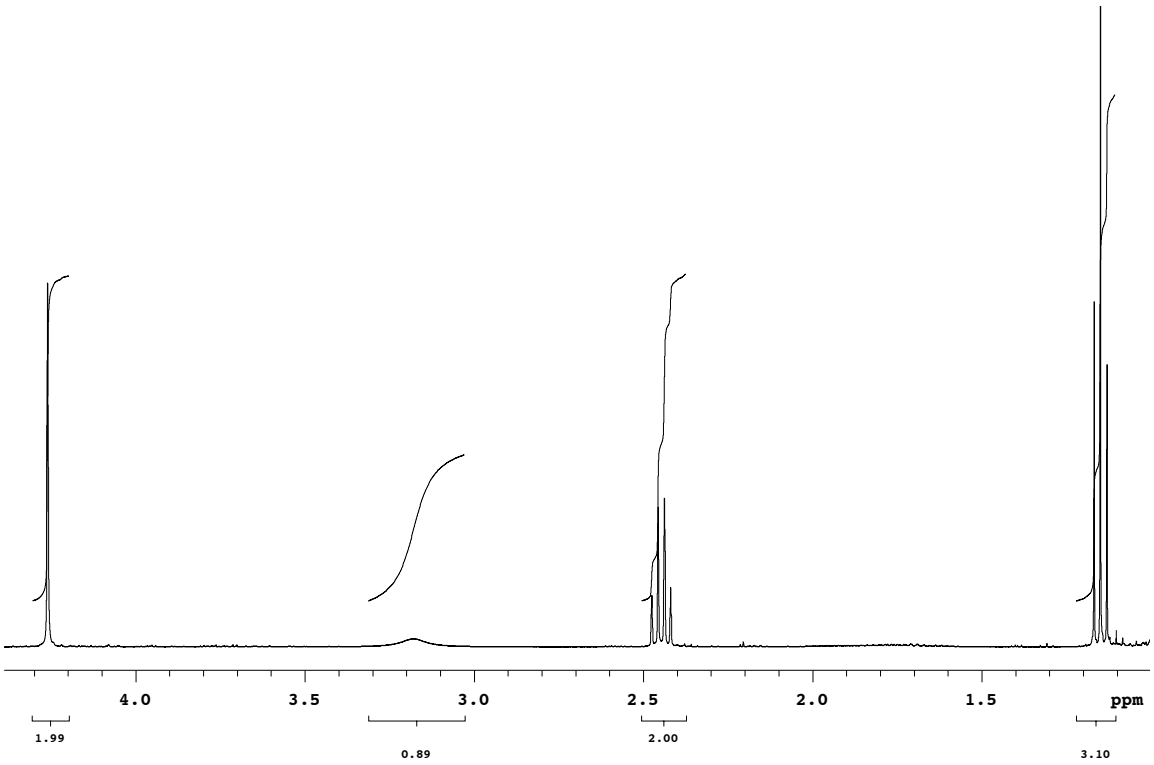
13. $C_7H_{14}O$



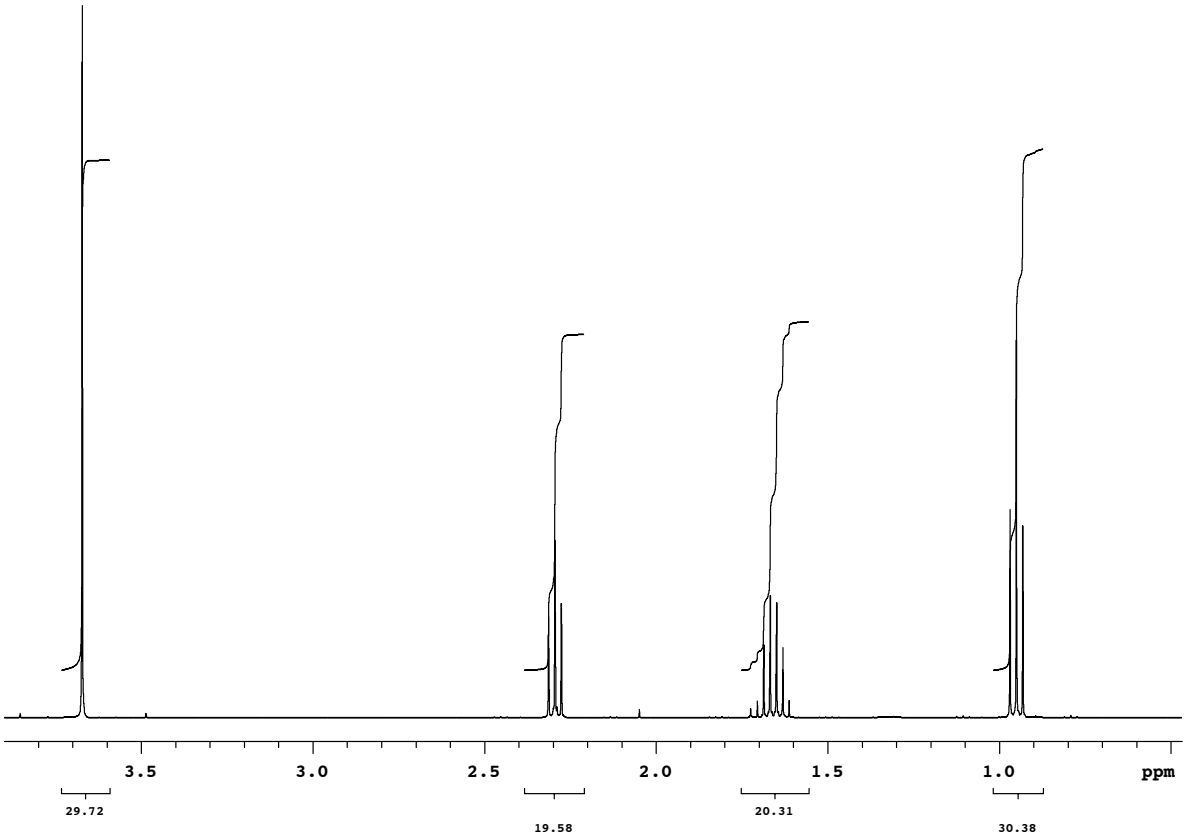
14. C_7H_8O



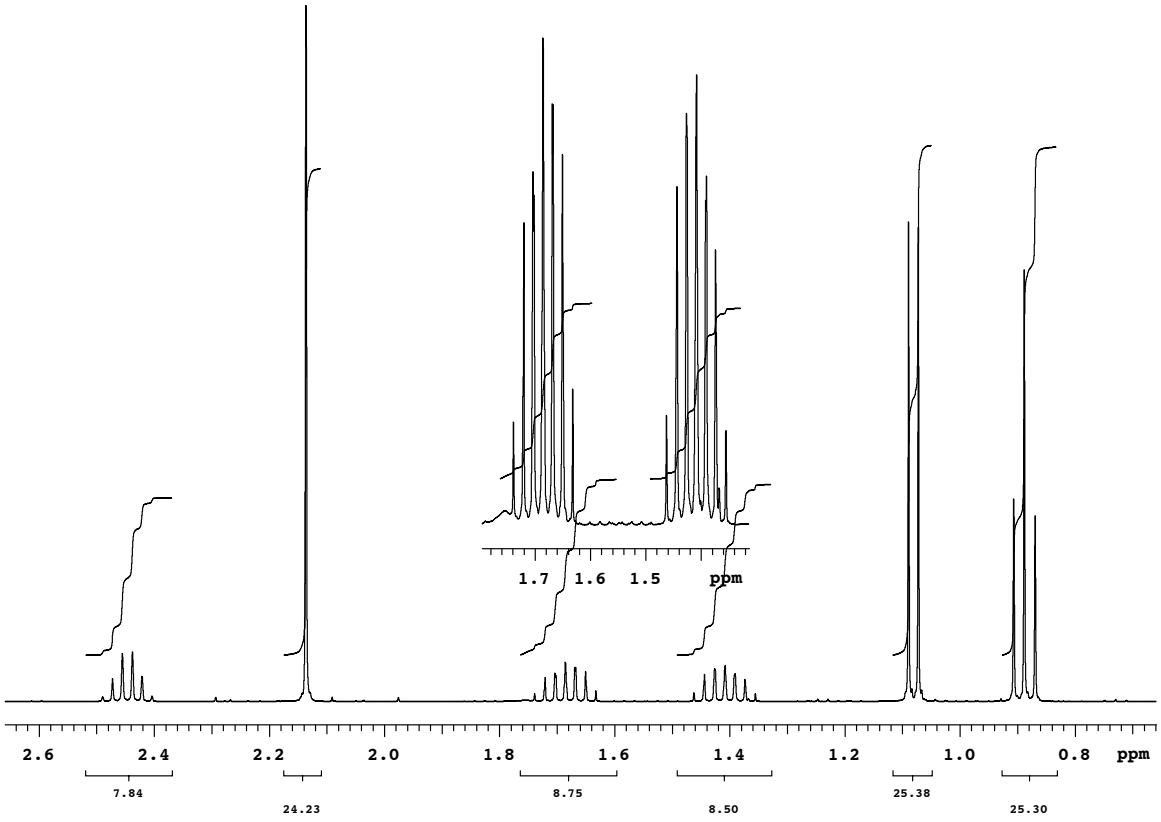
15. $C_4H_8O_2$



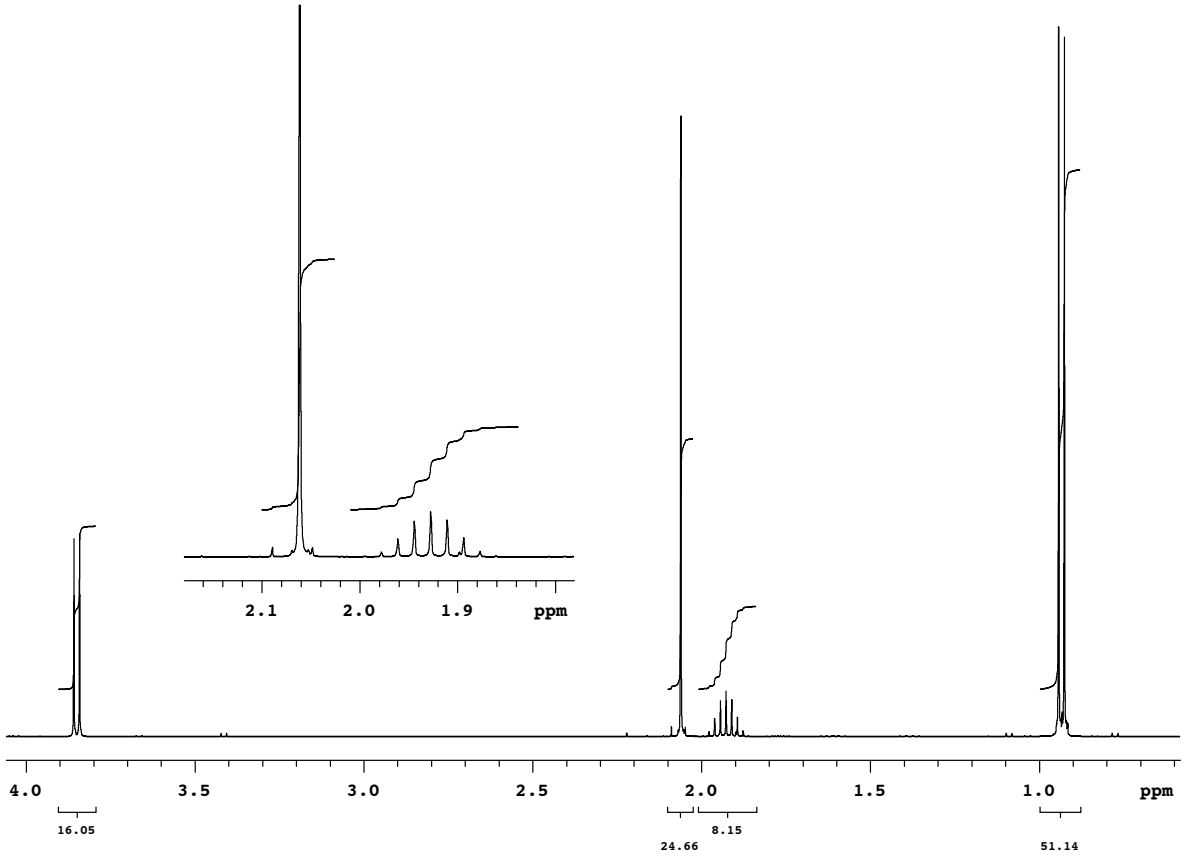
16. $C_5H_{10}O_2$



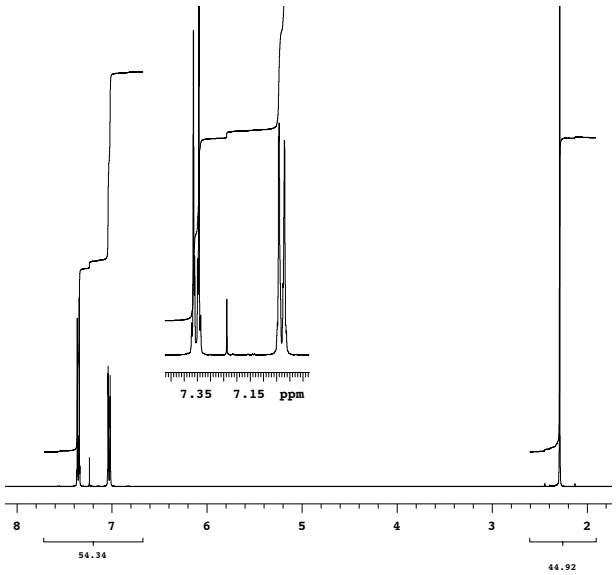
17. $C_6H_{12}O$

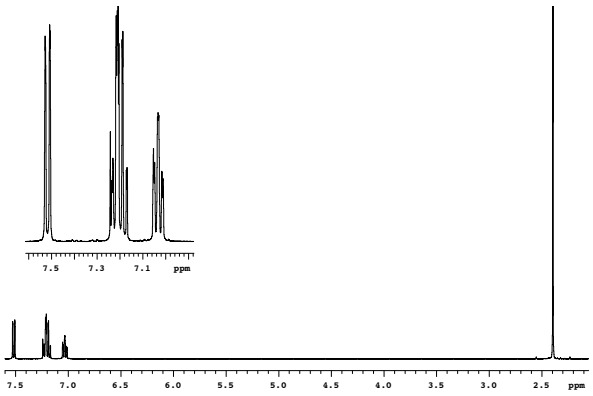

1.7
1.6
1.5
ppm
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
ppm
7.84
24.23
8.75
8.50
25.38
25.30

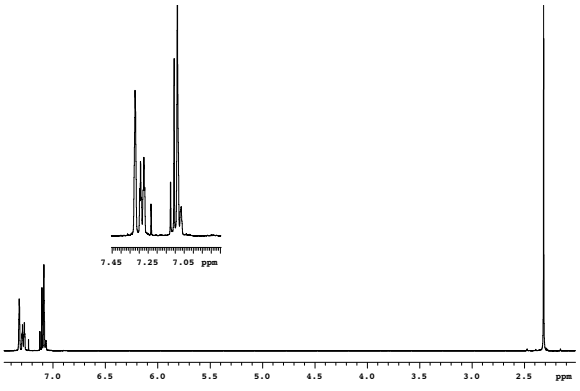
18. $C_6H_{12}O_2$



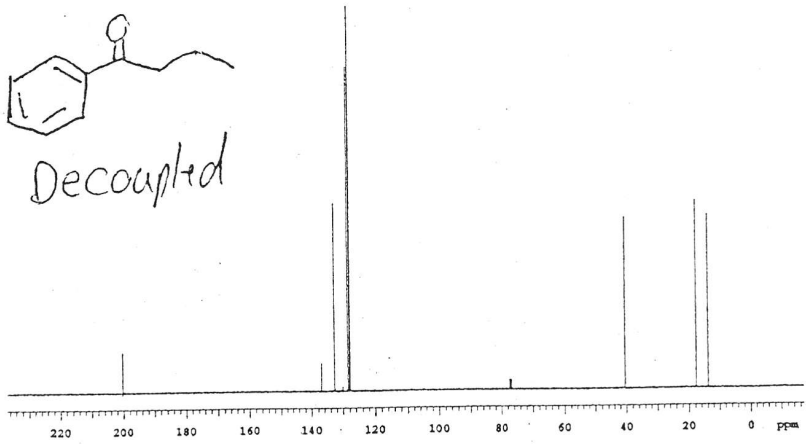
19. C_7H_7Br. Isomers of Bromotoluene

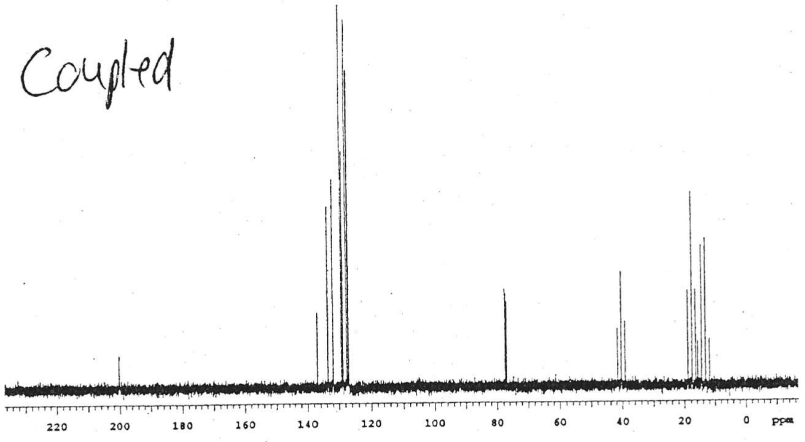


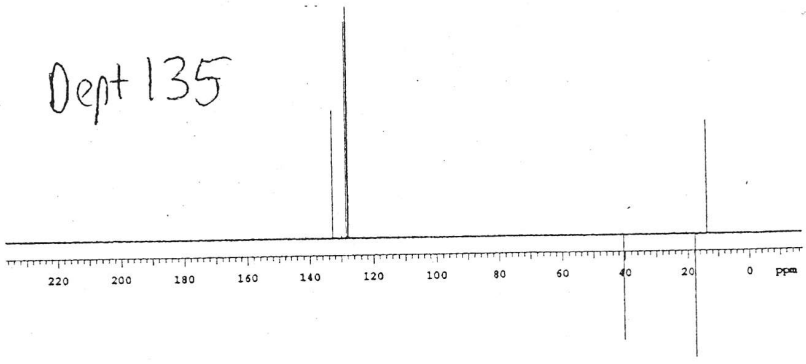




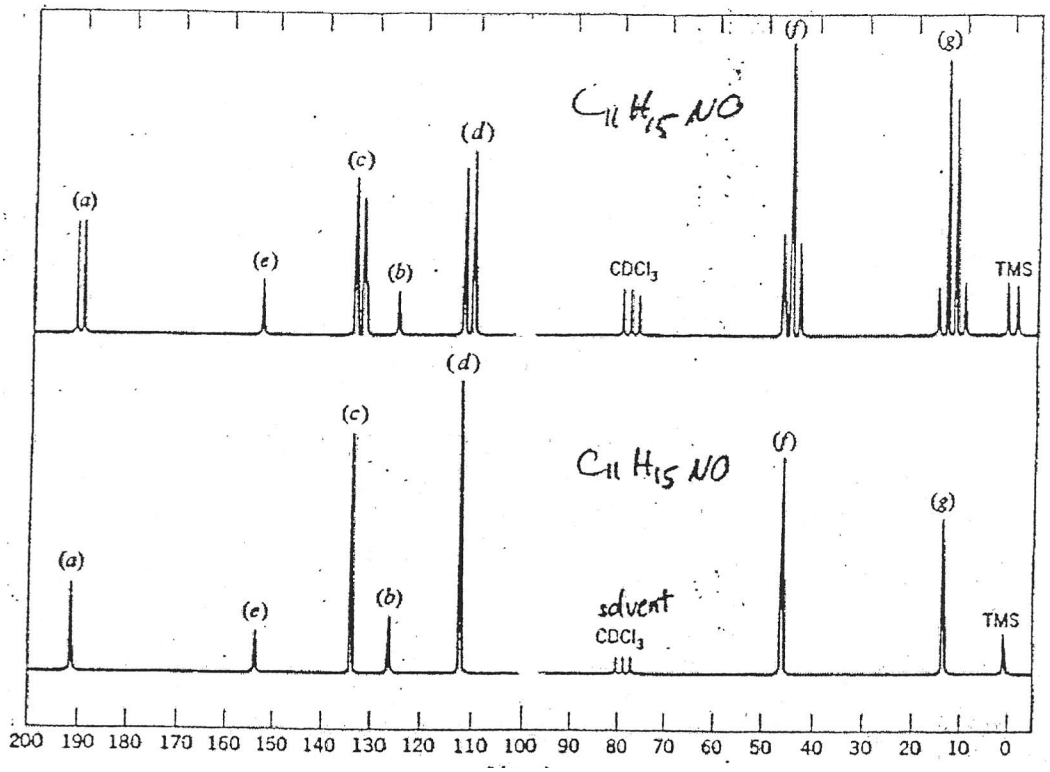
20. $C_{10}H_{12}O$ Carbon NMR Spectra: Decoupled, Coupled, DEPT 135

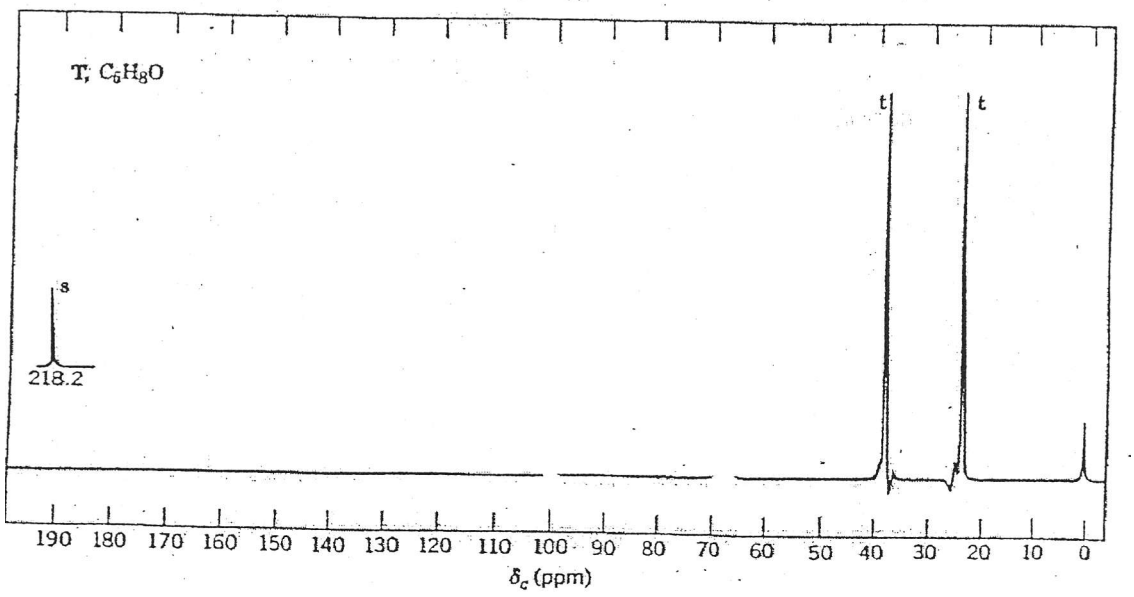




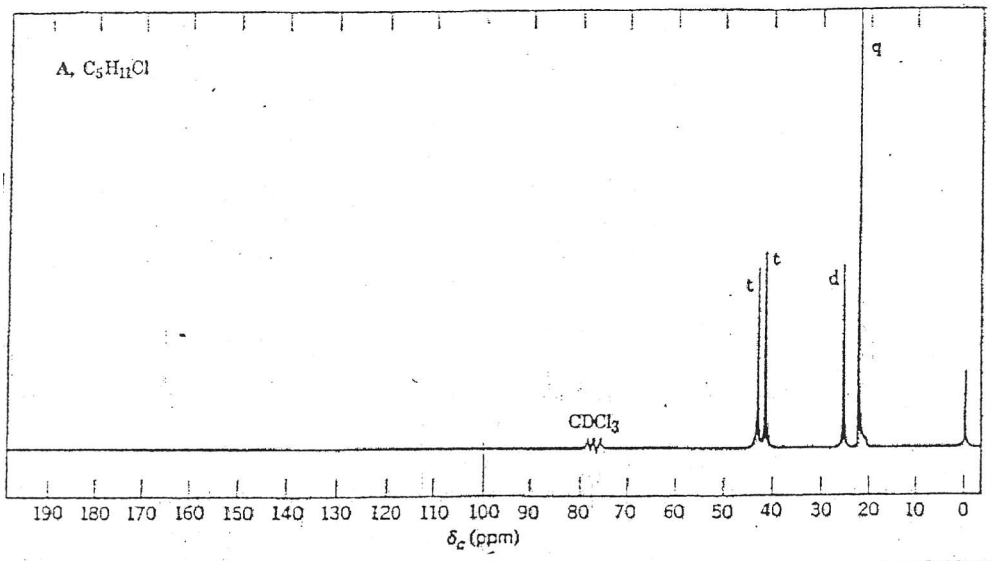


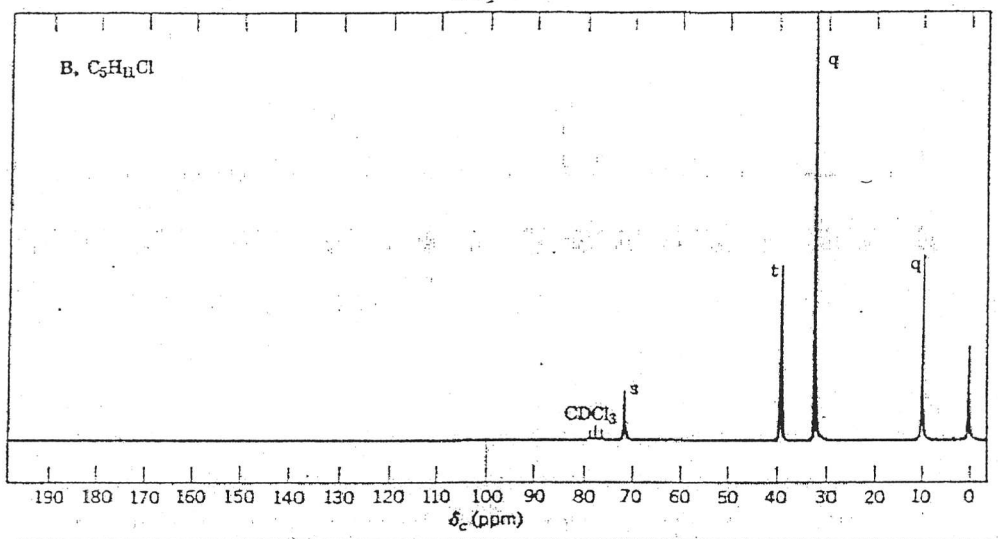
21. Carbon NMR Spectra Problems.

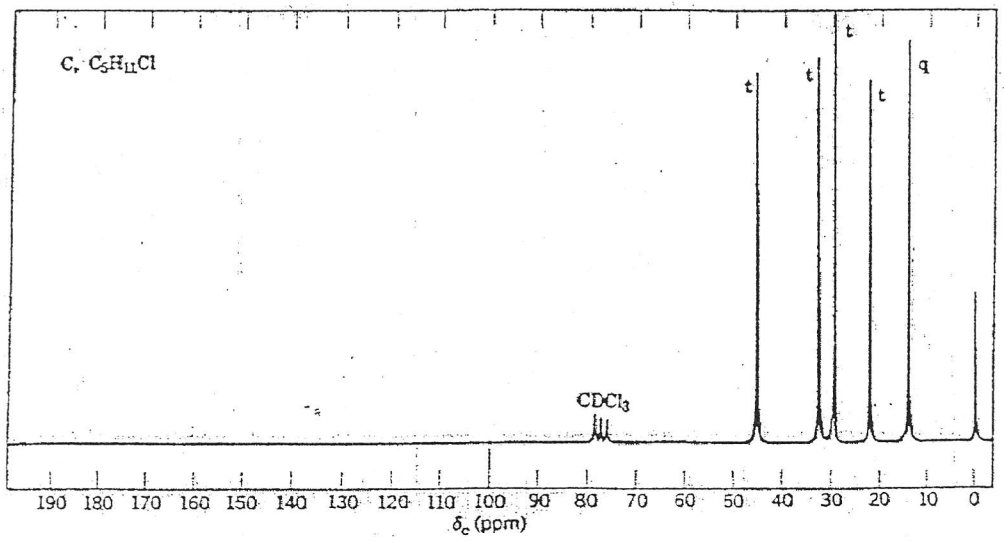




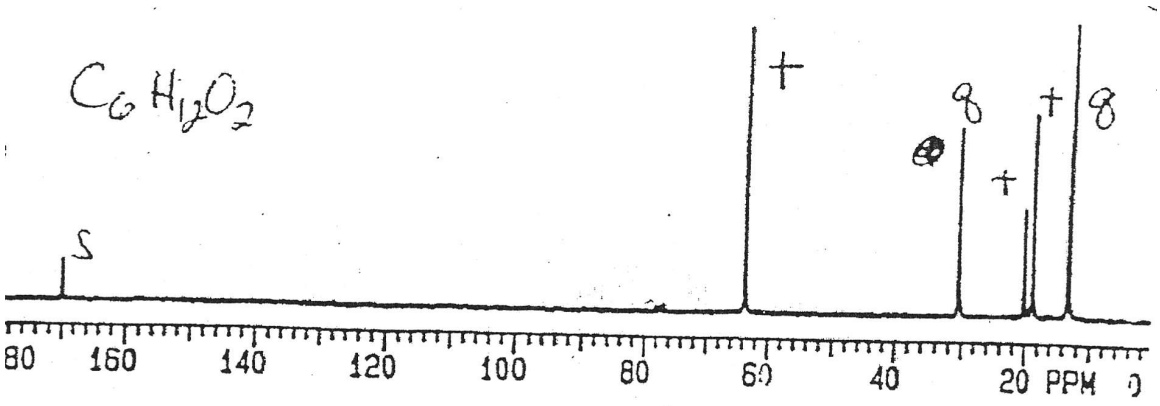
22. Carbon NMR Spectra Problems.

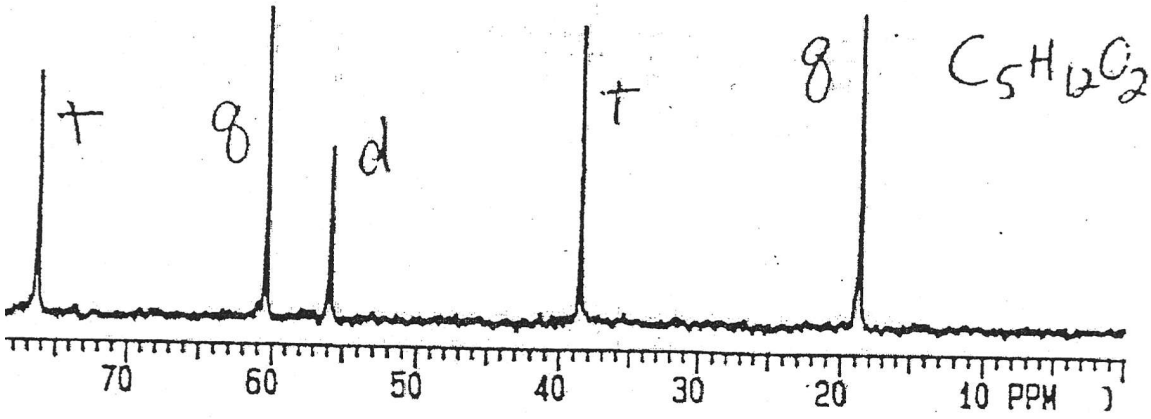




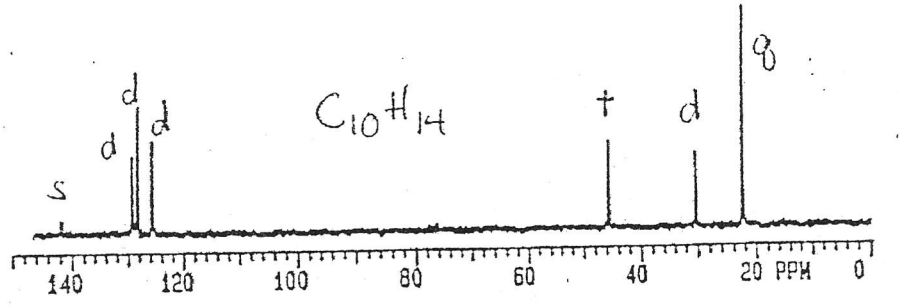


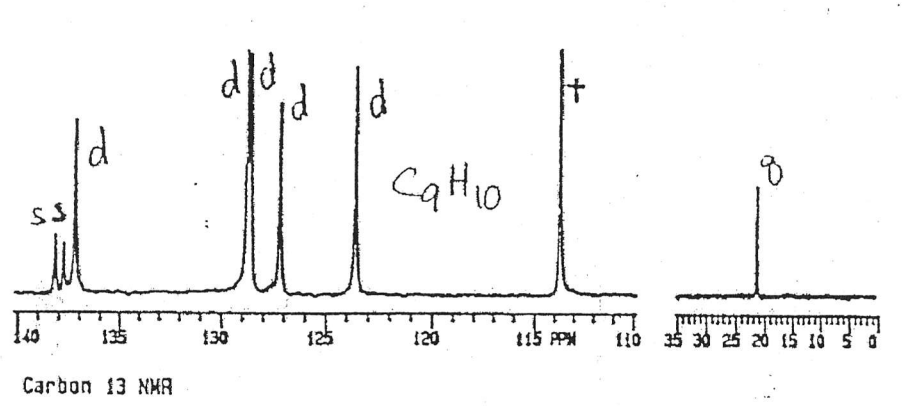
23. Carbon NMR Spectra Problems.



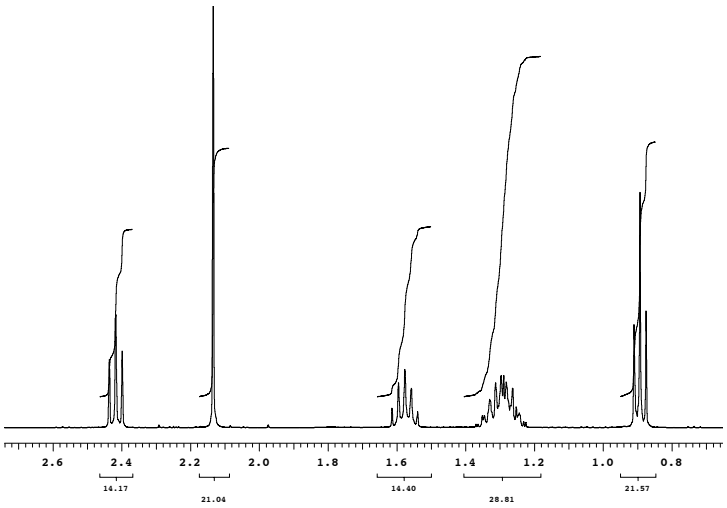


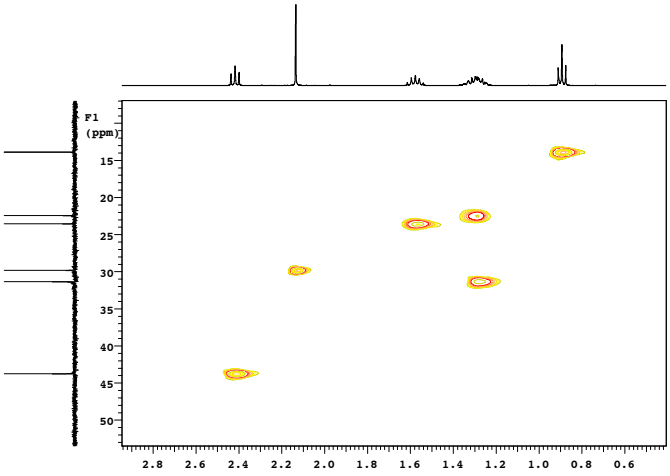
24. Carbon NMR Spectra Problems.

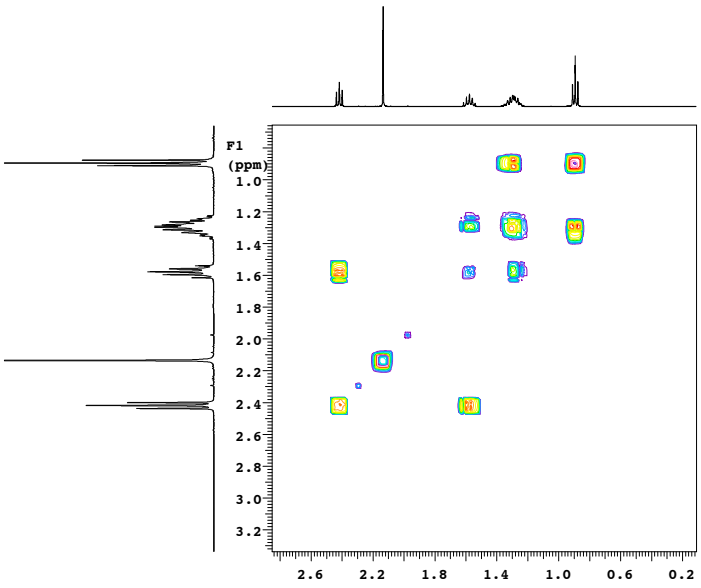




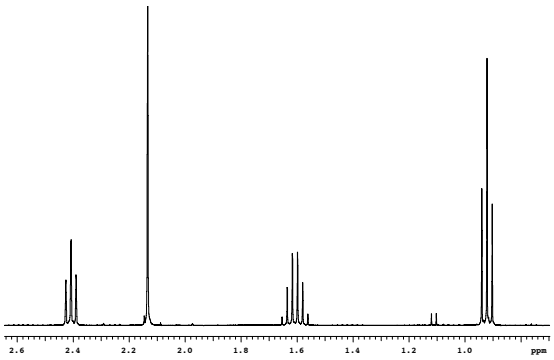
25. Carbon NMR: 2D Carbon-Hydrogen (HSQC) and 2D Hydrogen-Hydrogen (COSY) spectra. $C_7H_{14}O$

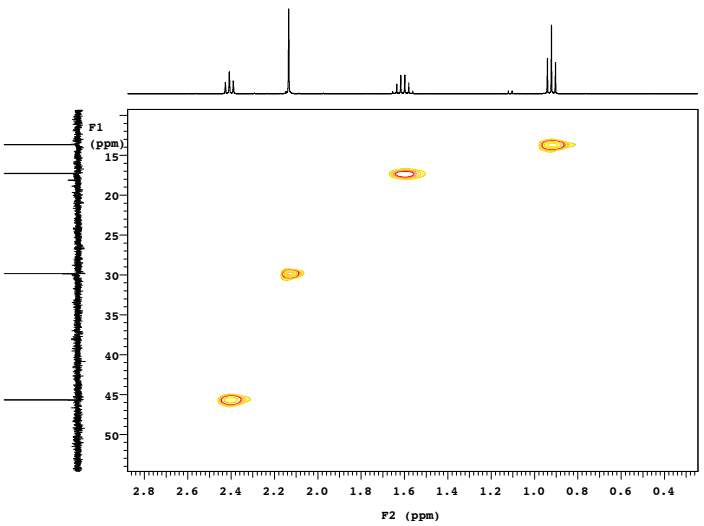


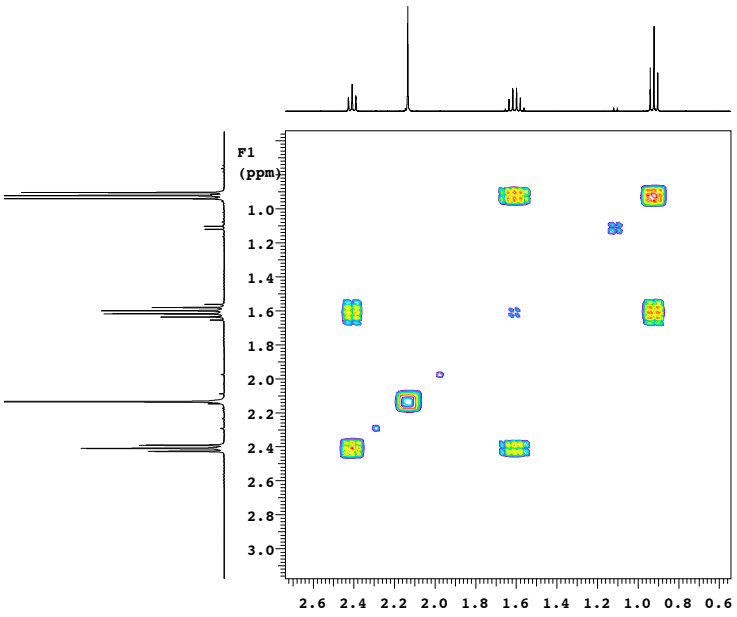




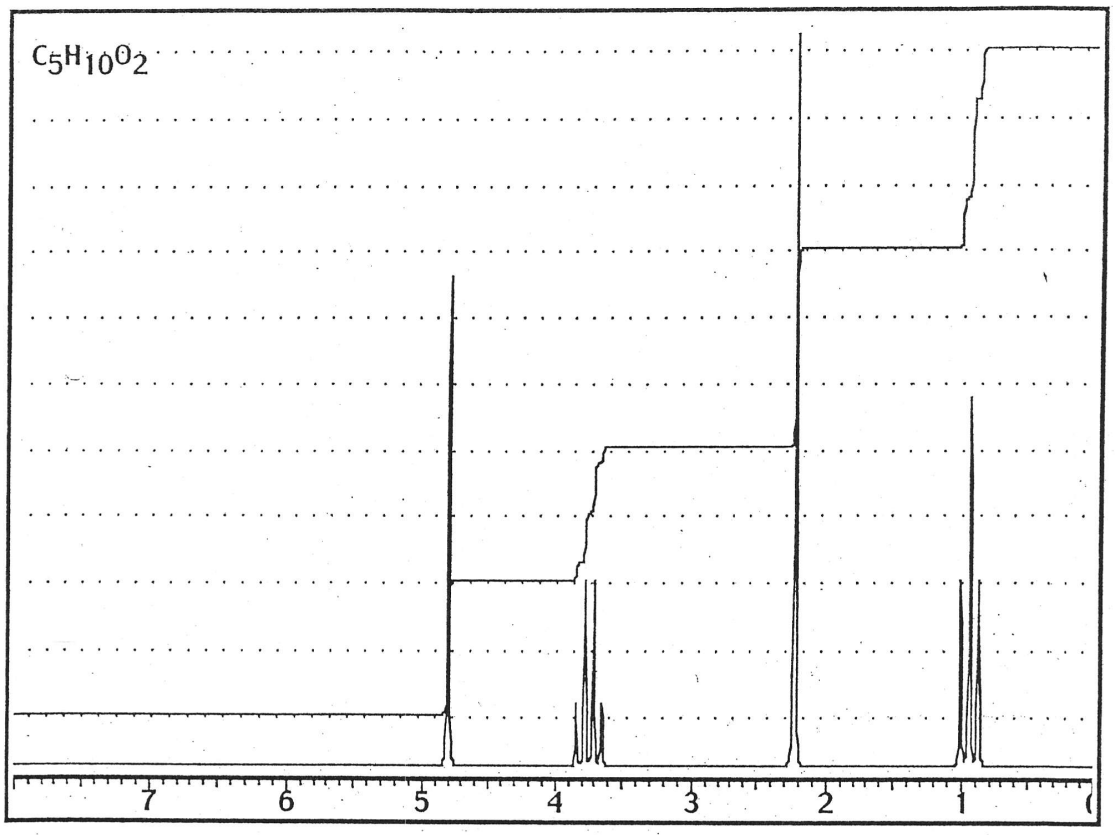
26. Carbon NMR: 2D Carbon-Hydrogen (HSQC) and 2D Hydrogen-Hydrogen (COSY) spectra. $C_5H_{10}O$



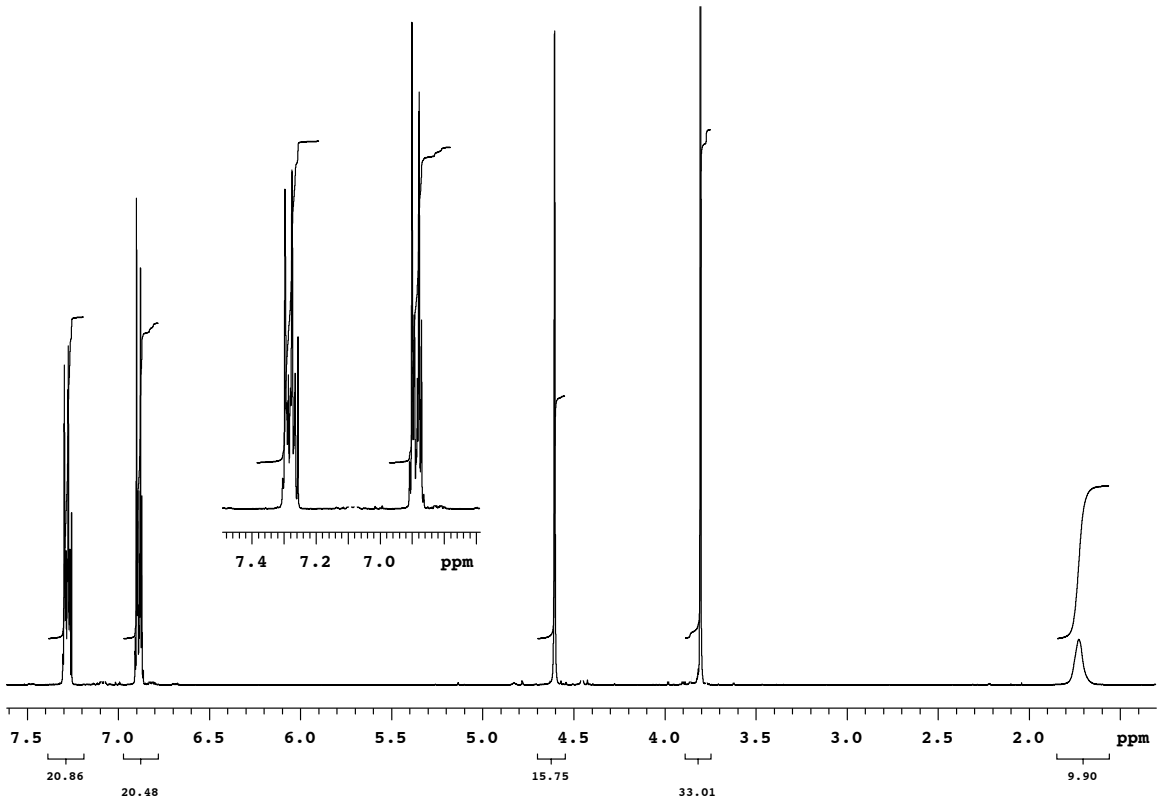




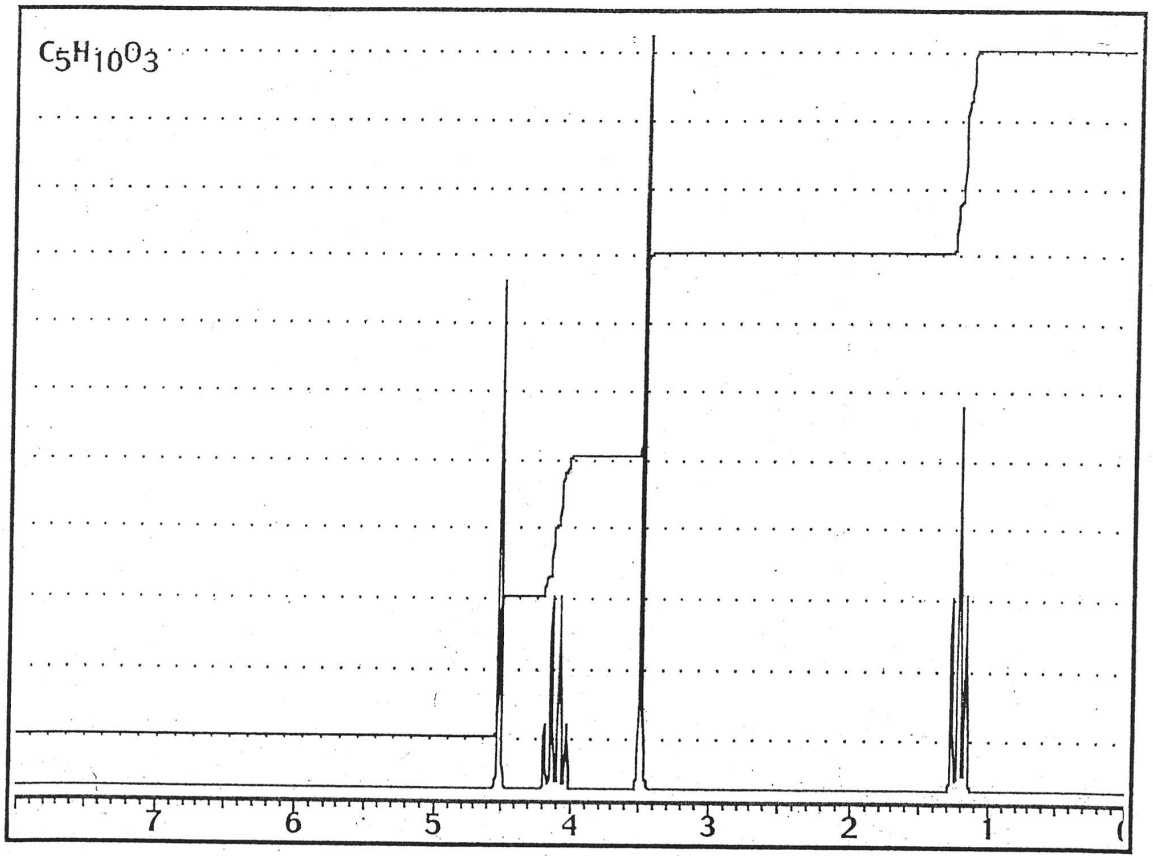
27. $C_5H_{10}O_2$



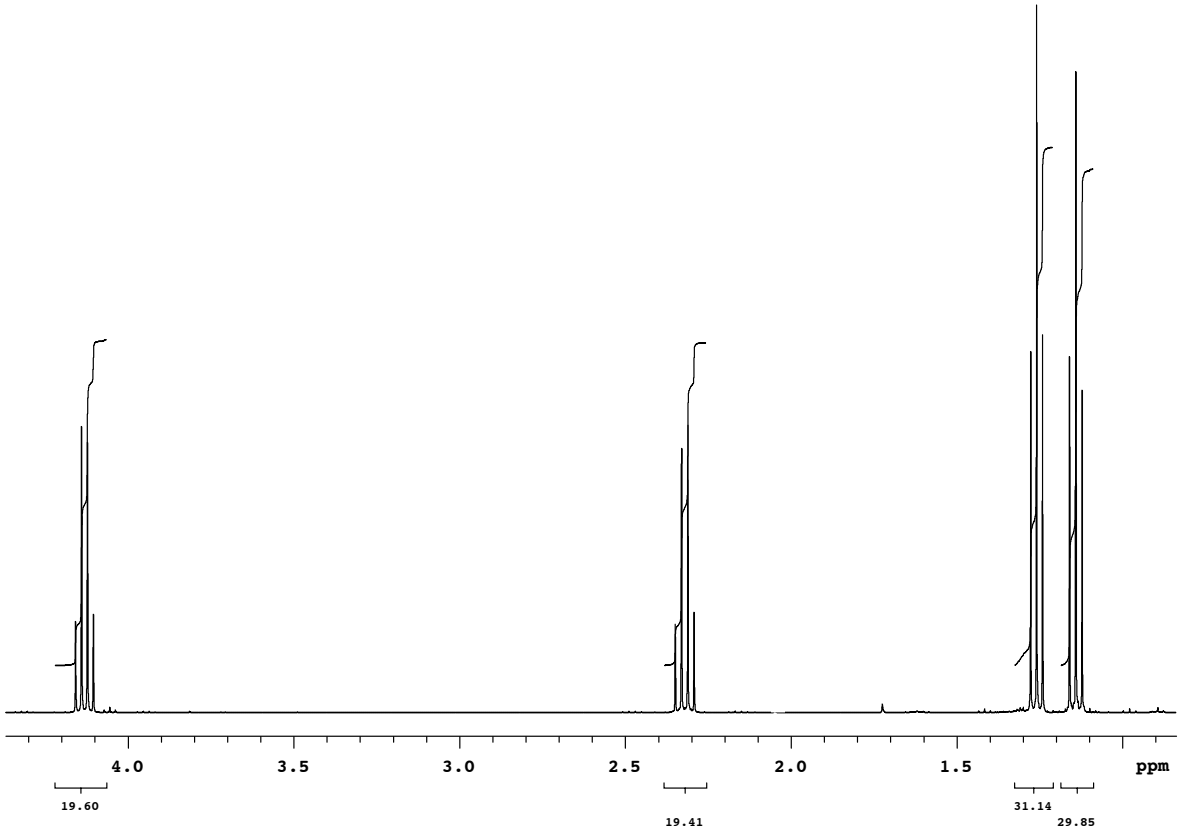
28. $C_8H_{10}O_2$


7.4
7.2
7.0
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
20.86
20.48
15.75
33.01
9.90

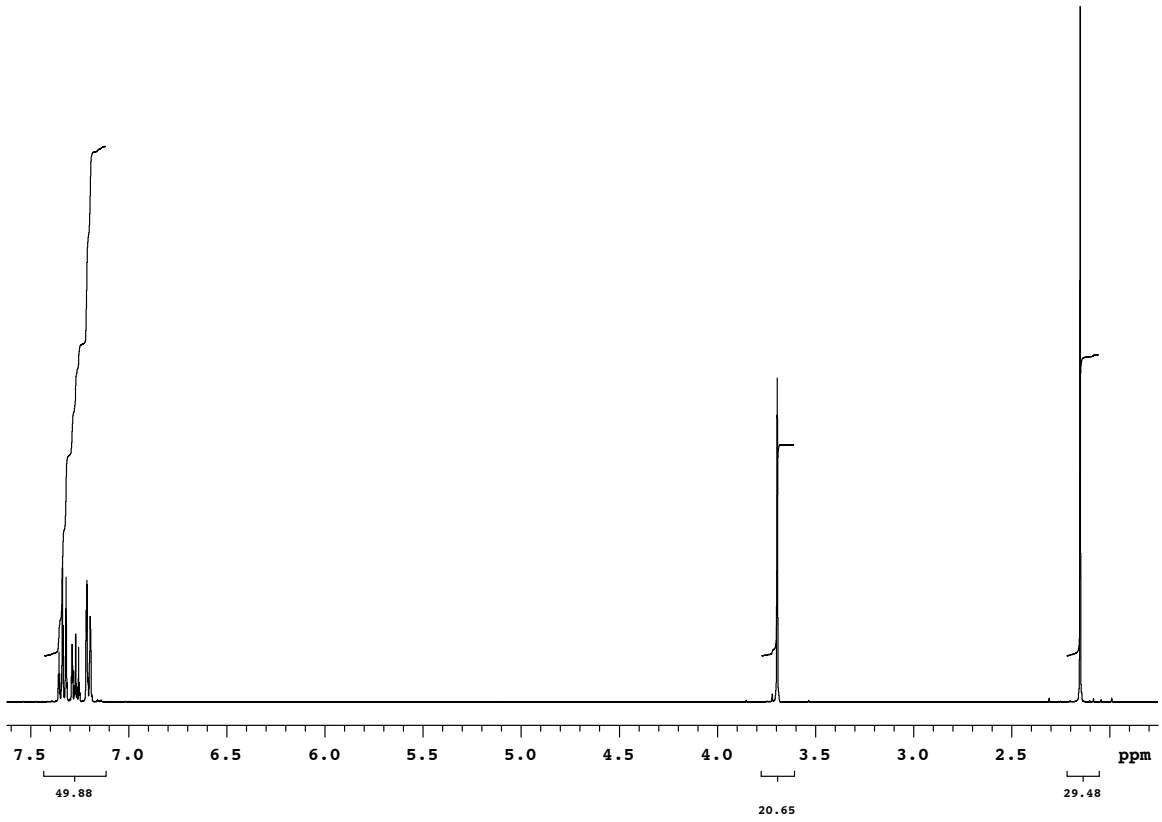
29. $C_5H_{10}O_3$



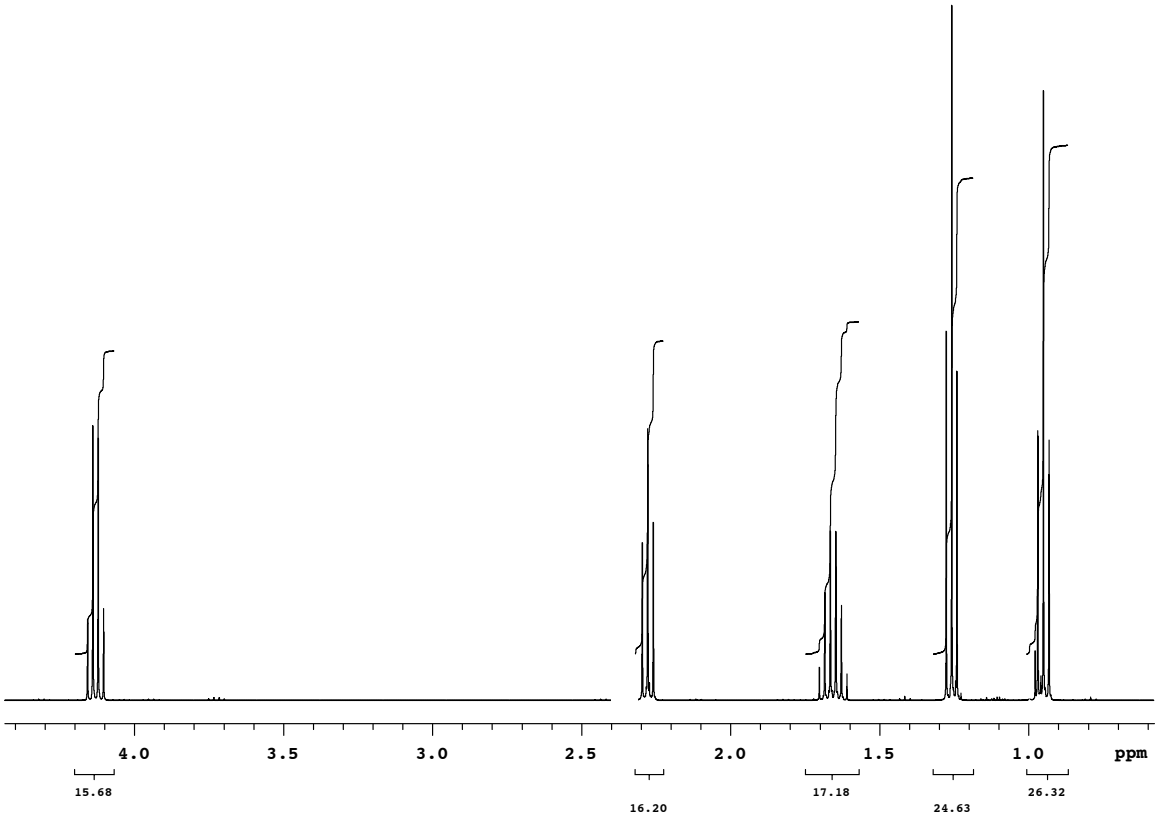
30. $C_5H_{10}O_2$



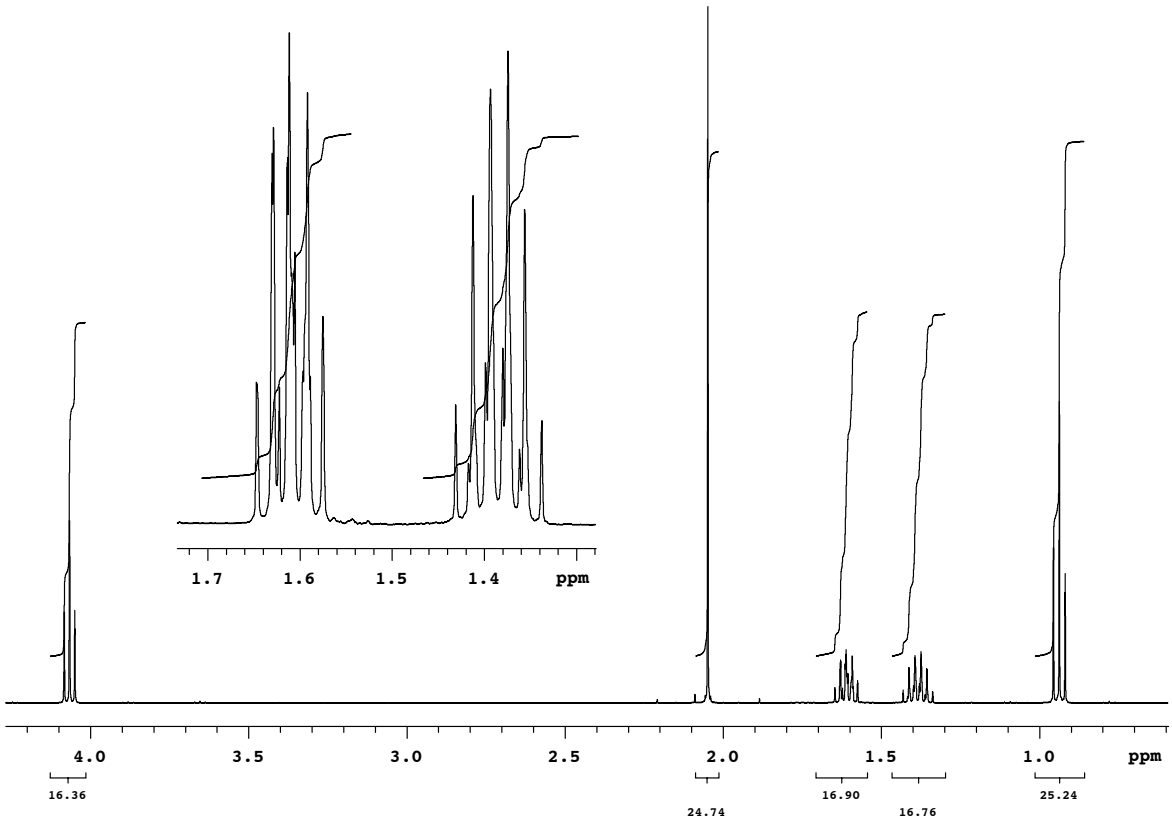
31. $C_9H_{10}O$



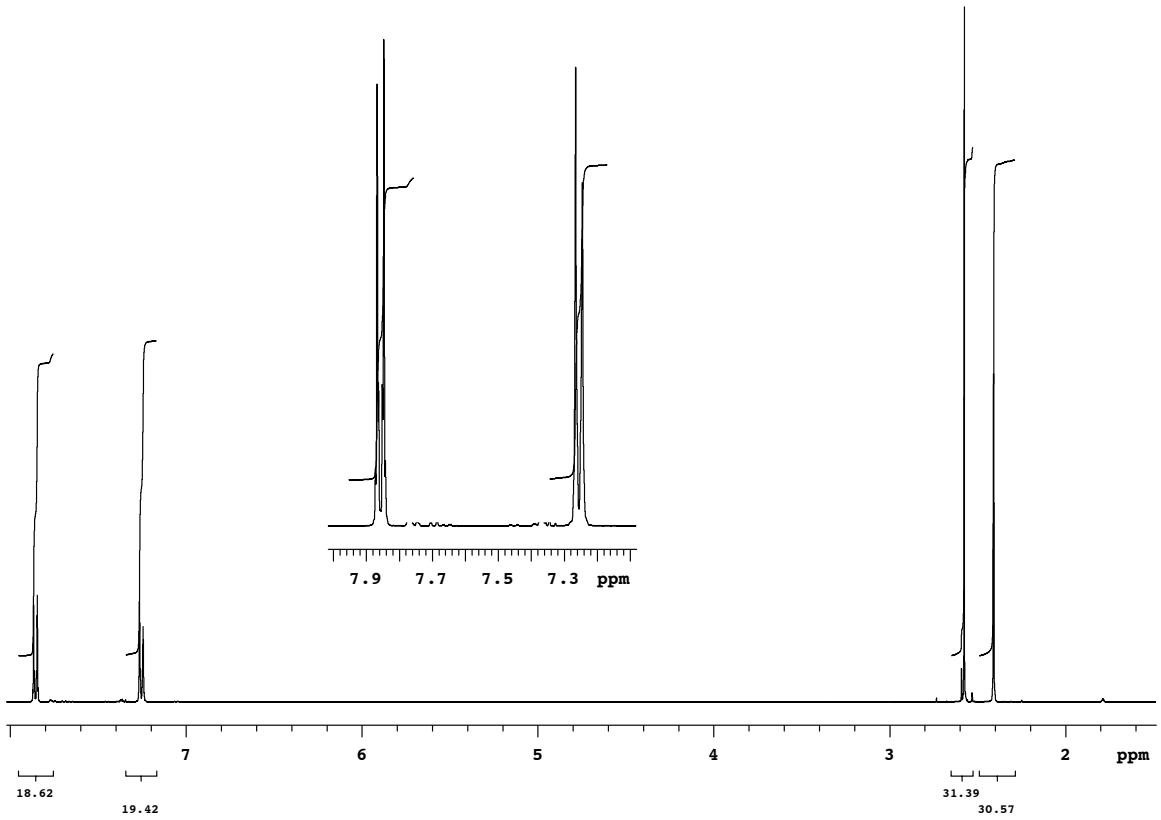
32. $C_6H_{12}O_2$



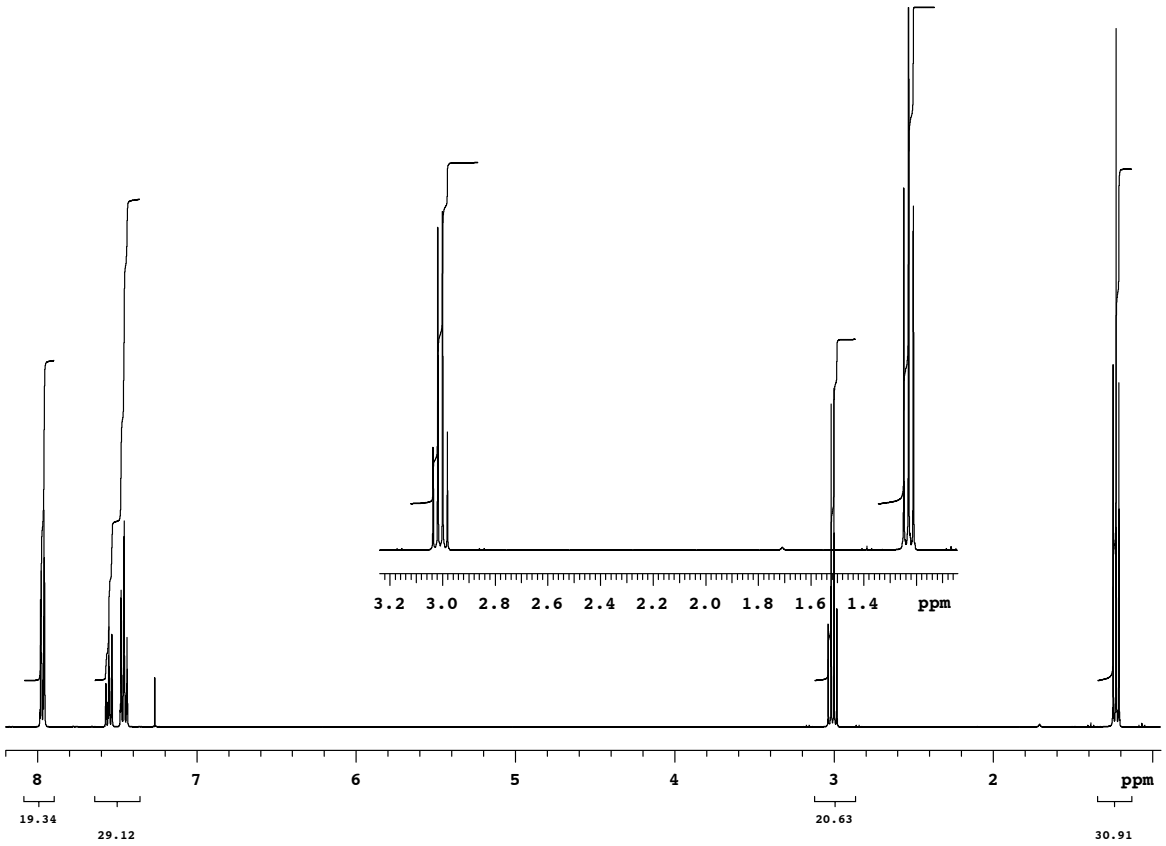
33. $C_6H_{12}O_2$



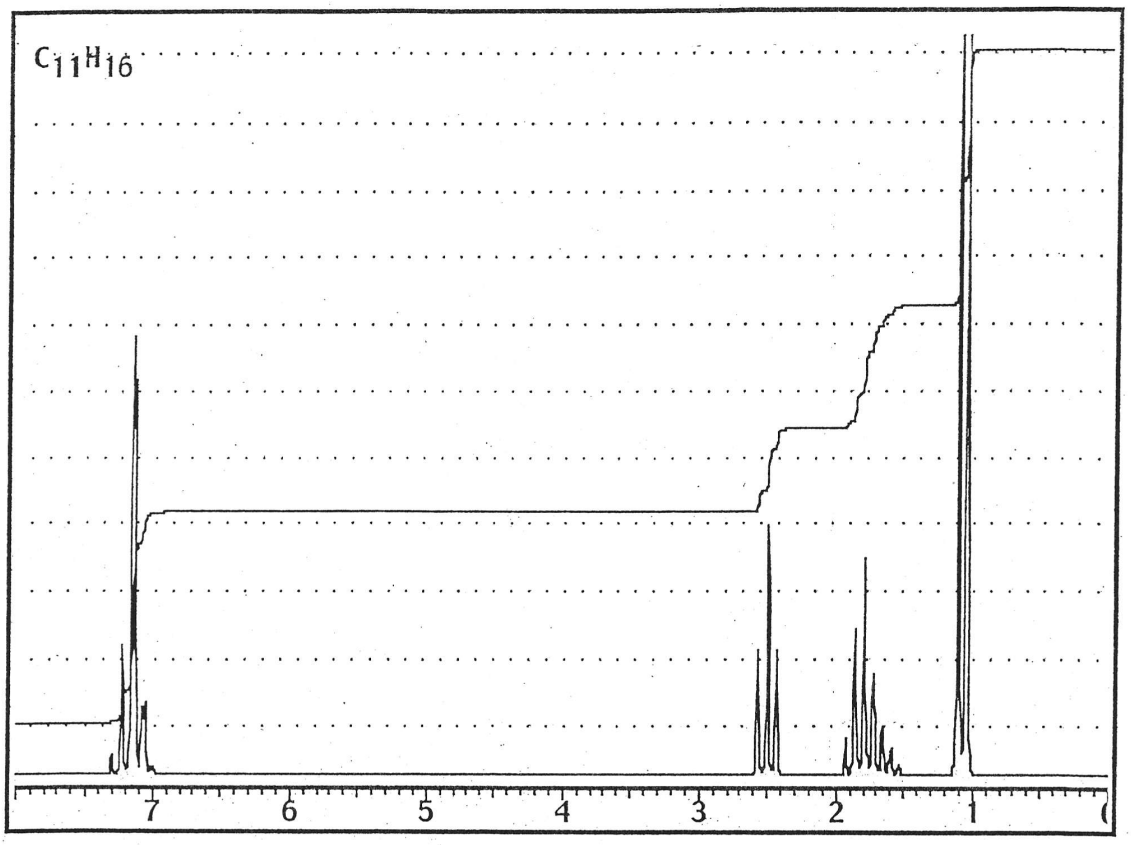
34. $C_9H_{10}O$



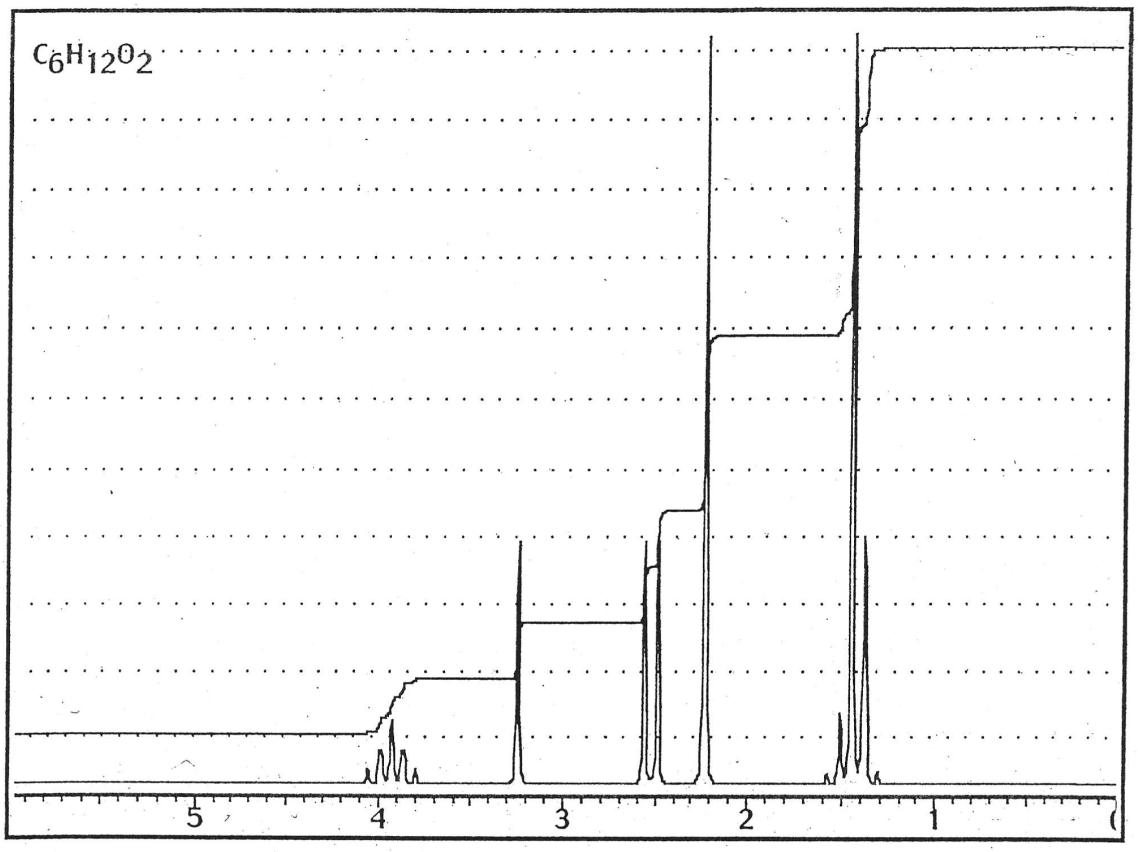
35. $C_9H_{10}O$



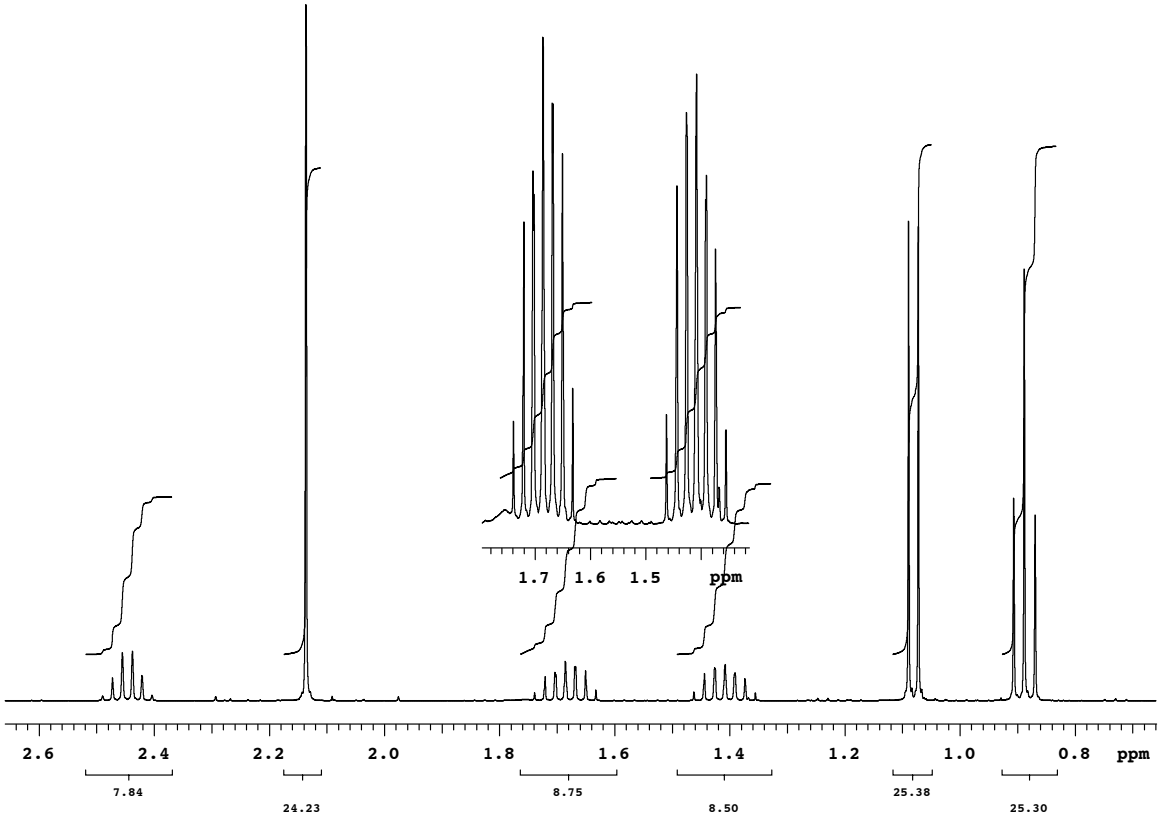
36. $C_{11}H_{16}$



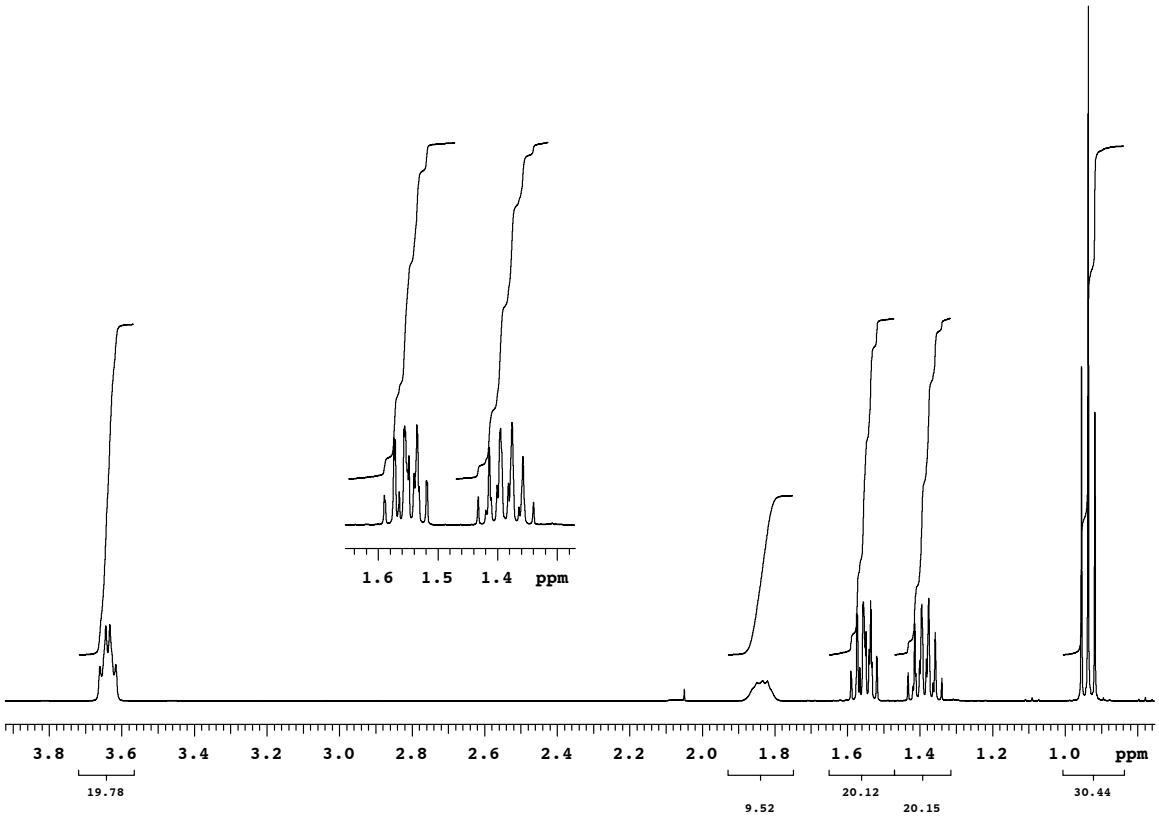
37. $C_6H_{12}O_2$



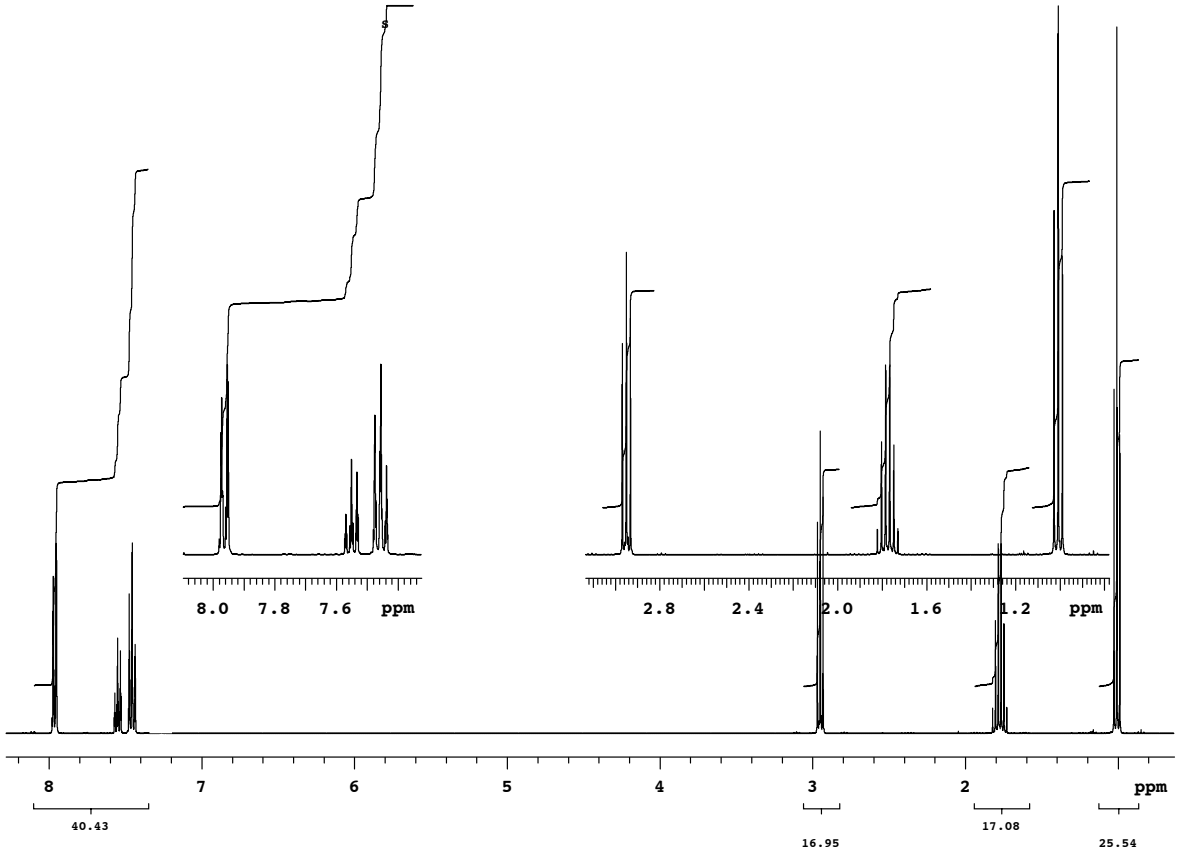
38. $C_6H_{12}O$


1.7
1.6
1.5
ppm
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
ppm
7.84
24.23
8.75
8.50
25.38
25.30

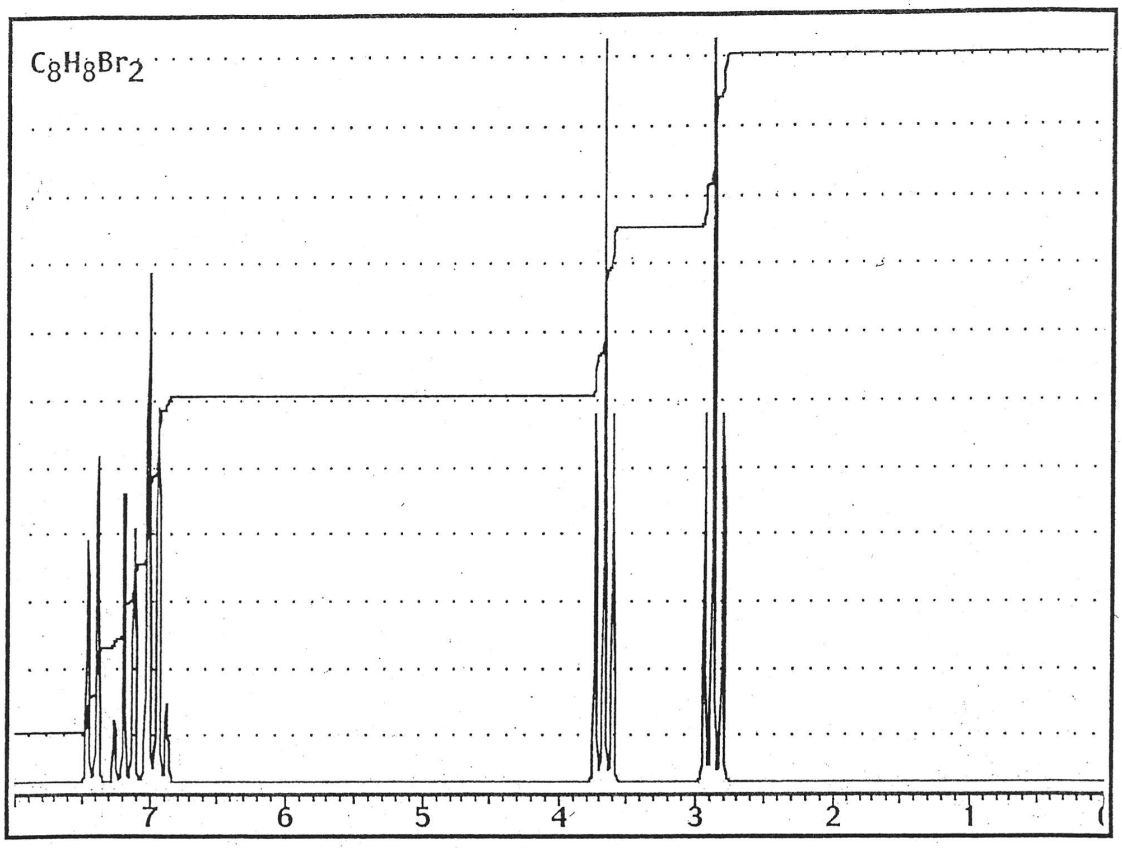
39. $C_4H_{10}O$


1.6 1.5 1.4 ppm
3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 ppm
19.78
9.52
20.12
20.15
30.44

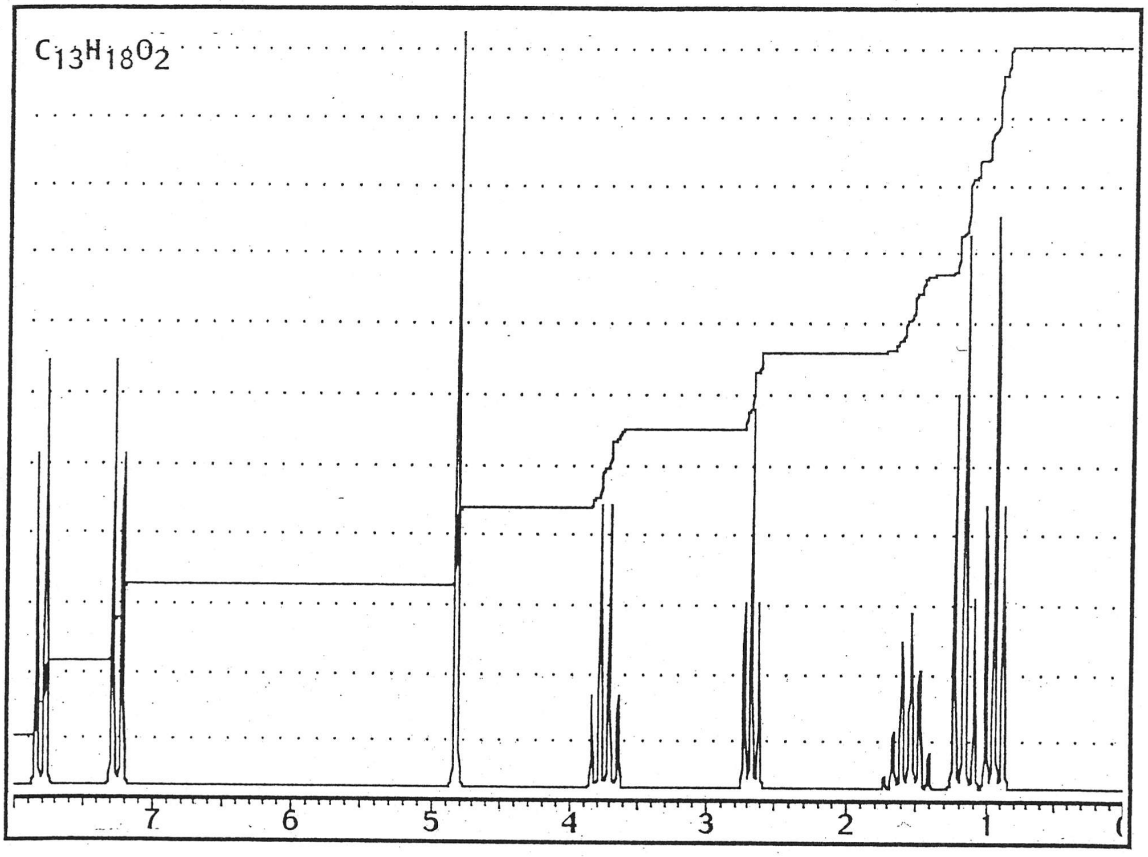
40. $C_{10}H_{12}O$



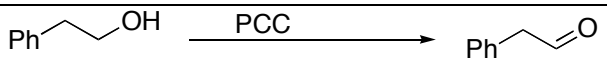
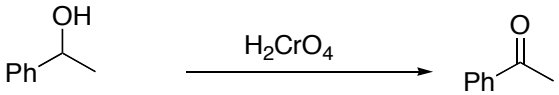
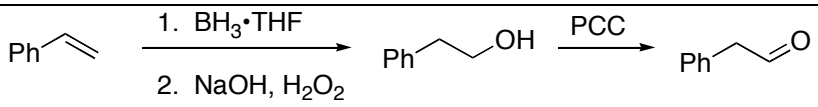
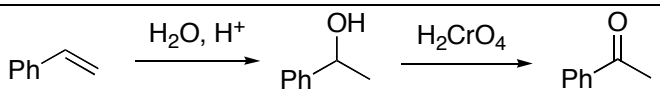
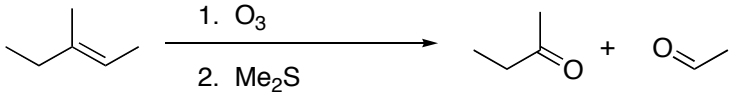
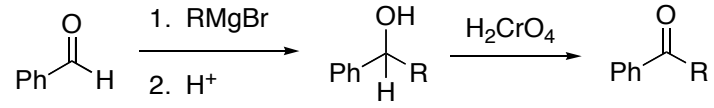
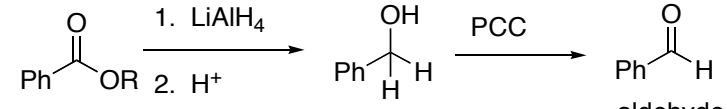
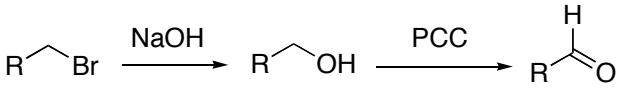
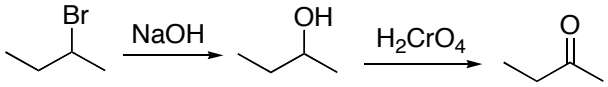
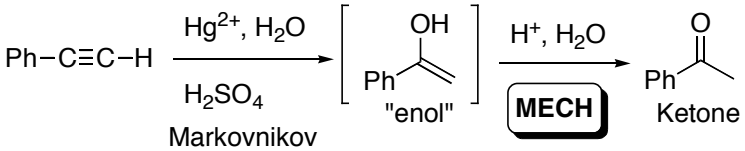
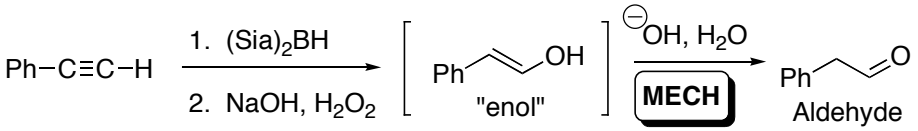
41. $C_8H_8Br_2$

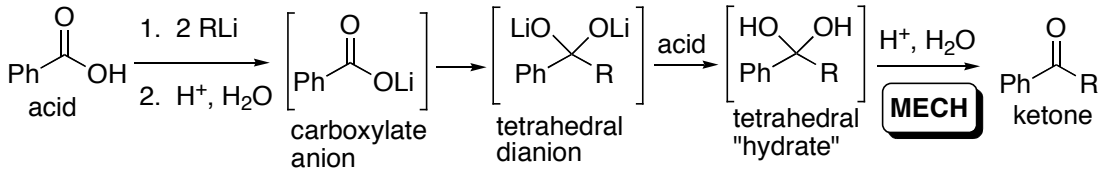
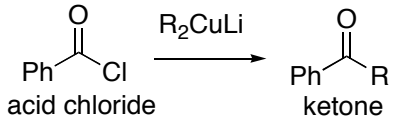
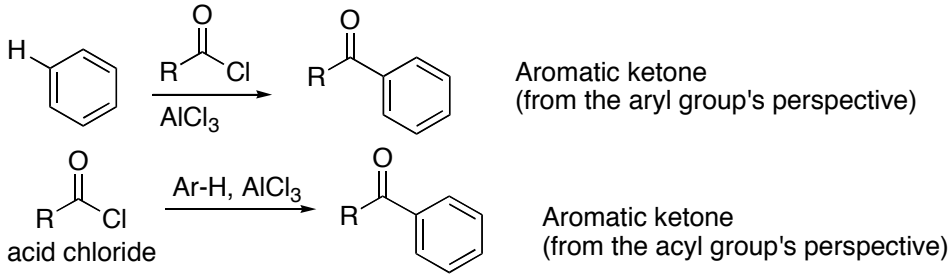
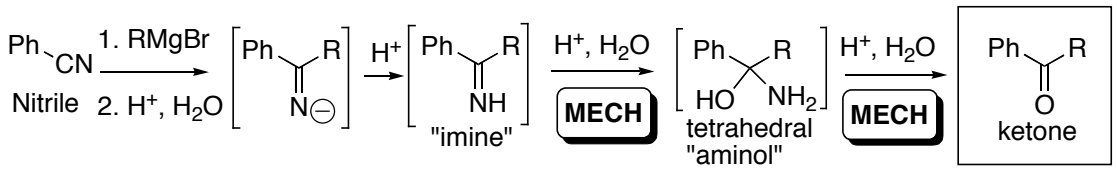
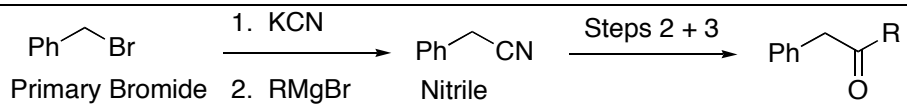


42. $C_{13}H_{18}O_2$

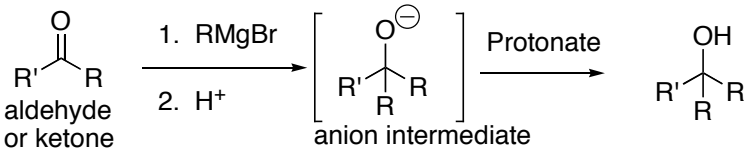
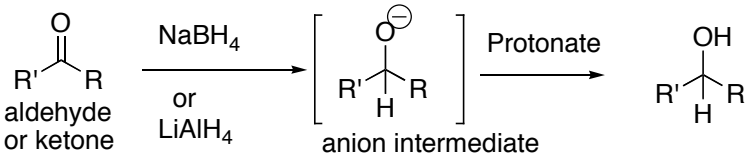
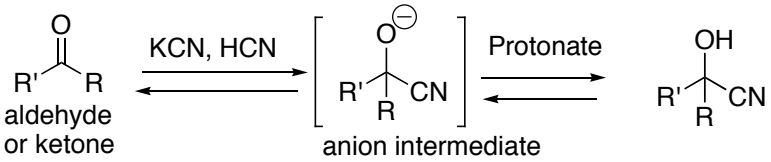
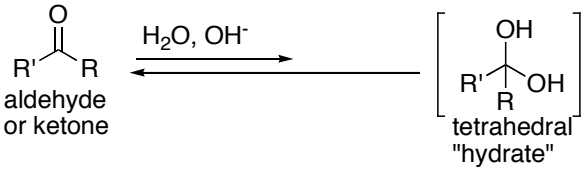
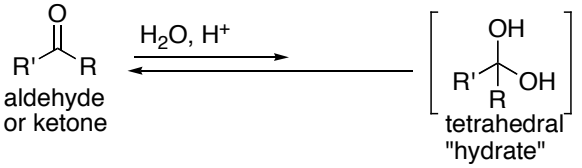


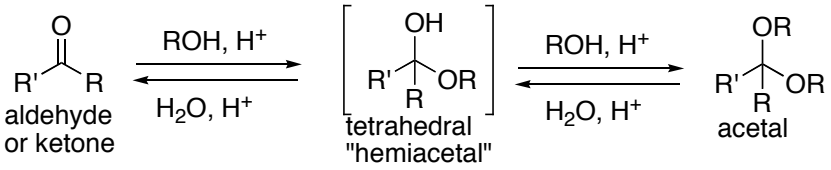
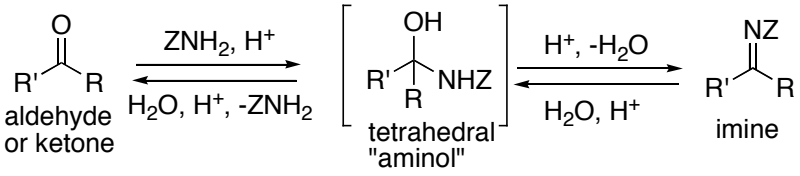
Synthesis of Ketones and Aldehydes

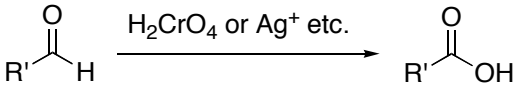
1		11.2
2		11.2
3		8.7
4		8.4
5		8.15
6	 Aldehyde Ketone	10.9
7	 acid or ester aldehyde	10.11
8		6.8
9		6.8
10		9.9
11		9.9

12		18.8
13		18.10
14		18.10
15		18.9
16		18.9

Reactions of Ketones and Aldehydes

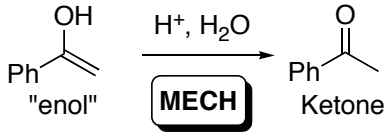
19	 **Anionic** Mech: Addition-Protonation. Strong nucleophile, Strongly anionic. Irreversible.	18.11, 10.9
20	 **Anionic** Mech: Addition-Protonation. Strong nucleophile, Strongly anionic. Irreversible.	18.11, 10.11
21	 **Anionic** Mech: Addition-Protonation. Medium nucleophile, Weakly anionic; literally buffered. Reversible.	18.13
22	 "Hydrates" are present only as transient equilibrium species. They never form to 100% and are never isolable. Always in equilbrium their aldehyde or ketone. **Anionic** Mech Forward: Addition-Protonation. Nucleophile, anionic mechanism. Reversible. Mech Reverse: Deprotonation-Elimination. Anionic mechanism. Reversible.	18.12
23	 "Hydrates" are present only as transient equilibrium species. They never form to 100% and are never isolable. Always in equilbrium with their aldehyde or ketone. **Cationic** Mech Forward: Protonation-Addition-deprotonation. Weakly nucleophile, cationic mechanism. Reversible. Mech Reverse: Protonation-Elimination-deprotonation. Cationic E1-type mechanism. Reversible.	18.12

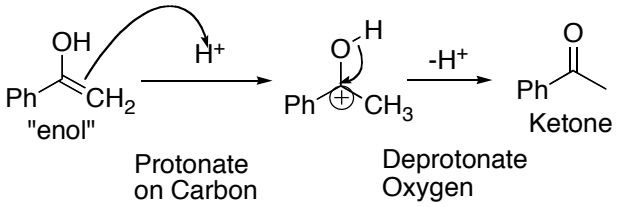
24	 **<u>Cationic</u>** Mech Forward: Protonation-Addition-deprotonation (hemiacetal) Protonation-elimination-addition-deprotonation (acetal). Weak nucleophile, cationic mechanism. Reversible. Mech Reverse: Protonation-Elimination-Addition-deprotonation. (hemiacetal) protonation-elimination-deprotonation (aldehyde or ketone). Reversible. Notes: • Reactions are reversible • The "hemiacetal" is an intermediate, and can never be isolated • The acetal <u>can</u> be isolated. • Equilibrium considerations (LeChatelier's principle) apply. When water is plentiful, things go to the left. When water is scarce or removed, and alcohol is abundant, things drive to the right. • Use H_2O/H^+ to hydrolyze an acetal back to an aldehyde or ketone • Use $MeOH/H^+$ to convert an aldehyde to an acetal • Use $HOCH_2CH_2OH/H^+$ to convert a ketone to an acetal • Aldehydes or ketones can be temporarily "protected" as their acetals, then later "deprotected" by hydrolysis	18.16, 18.17
25	 **<u>Cationic</u>** Mech Forward: Protonation-Addition-deprotonation (aminol) Protonation-elimination- deprotonation (imine). Mild nucleophile, cationic mechanism, buffered conditions. Reversible. Note: sometimes addition precedes protonation, or is concerted with protonation. Mech Reverse: Protonation-Addition-deprotonation (aminol) Protonation-elimination- deprotonation (aldehyde or ketone). Reversible. Notes: • "Z" can be a carbon, nitrogen, oxygen, or hydrogen atom/group. • The "aminol" can't be isolated, it's only present at equilibrium. Equilibrium factors apply. Water drives to the carbonyl side; removal of water drives to the imine side.	18.14, 18.15

26	 No Mech Responsibility "Tollens test" is a common chemical test for aldehydes. Ag^+ undergoes redox reaction with aldeydes to produce shiny Ag metal, or a "silver mirror".	18.19

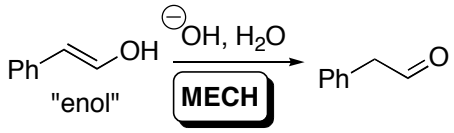
Ch. 18 Mechanisms

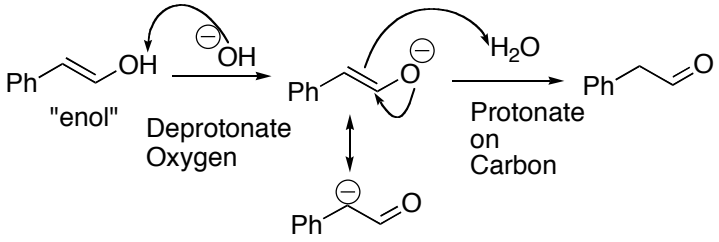
Some New Mechanisms Associated with the Syntheses of Aldehydes and Ketones

10 

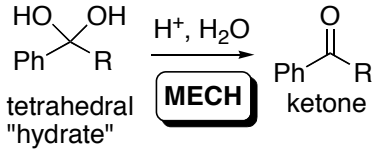


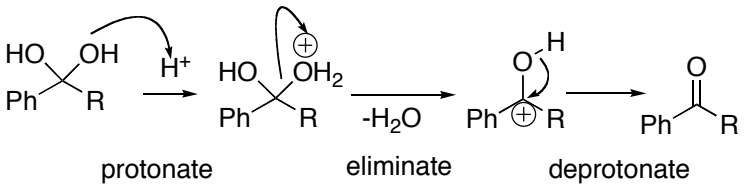
Enol to Carbonyl, Acid Catalyzed

11 

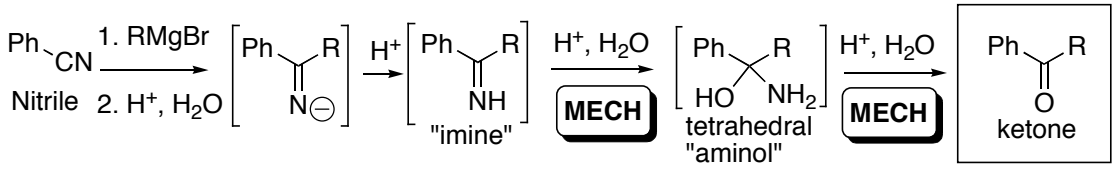


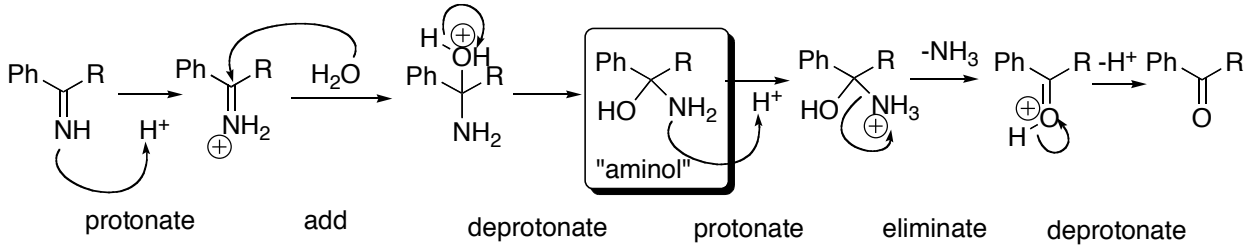
Enol to Carbonyl, Base Catalyzed

12 

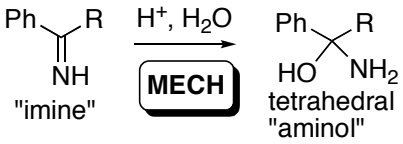


Acid-catalyzed elimination of a hydrate to a carbonyl

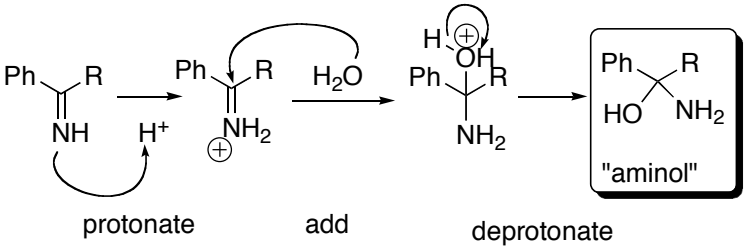
15 



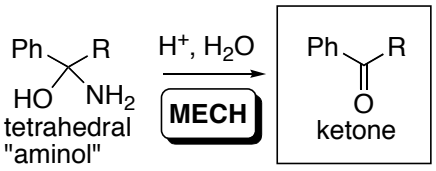
15 phase 1



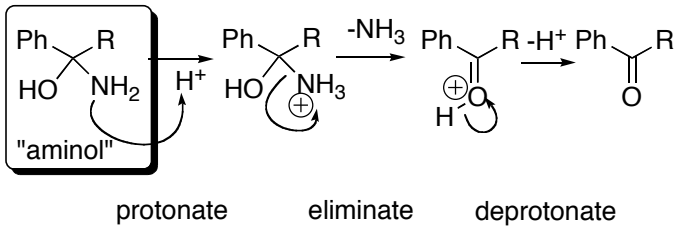
Acid-catalyzed addition of water to an imine



15 phase 2



Acid-catalyzed elimination of amine from an aminol to give a carbonyl



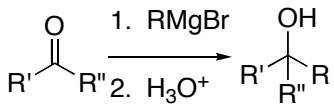
Review: Several Pertinent Mechanistic Principles

1. **Recognize anionic mechanisms** (when a strong anion is involved)
   - In an anionic mechanism, a strong anion will drive the first step
   - In an anionic mechanism, intermediates should avoid positive charges
   - Recognize anionic species even when they are disguised by a cationic metal counterion.

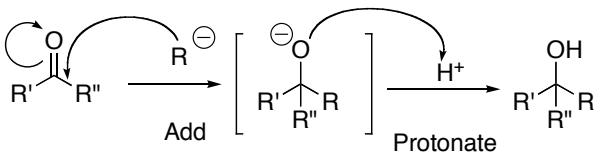
2. **Recognize cationic mechanisms**
   - Recipes that involve acid will be cationic
   - In a cationic mechanism, the first step will routinely involve protonation
   - In a cationic mechanism, the last step will frequently involve deprotonation to return to neutral
   - Normally the main step or steps are sandwiched in between the protonation and deprotonation events

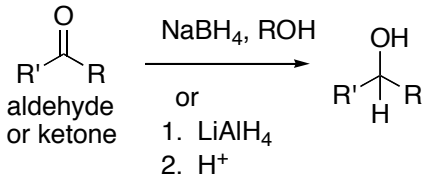
3. Focus on bonds made and broken
4. Draw in hydrogens on carbons whose bonding changes
5. Keep track of lone pairs on reacting centers (in your head if not on paper)
6. Always draw in formal charges where appropriate
7. Arrows show electron flow, from giver to receiver
8. A good mechanism illustrates not only where electrons go as bonds change, but also the timing of bond changes. Avoid drawing bond changes that occur at different times as if they occur in the same step, i.e. as if they were concerted.

Some Mechanisms Associated with the Reactions of Aldehydes and Ketones

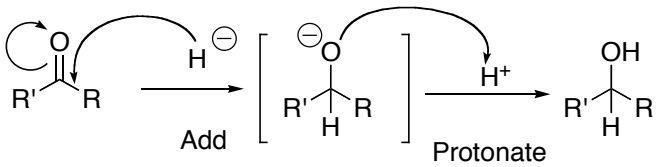
19 

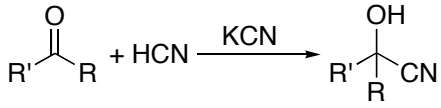
Grignard Addition of a Carbanion



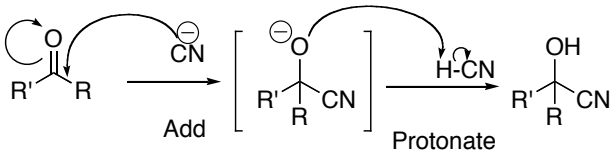
20 

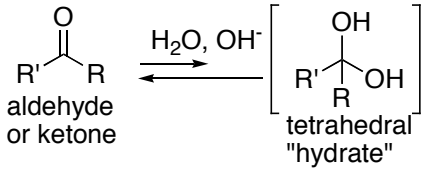
Hydride addition.



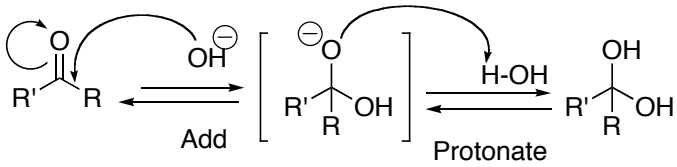
21 

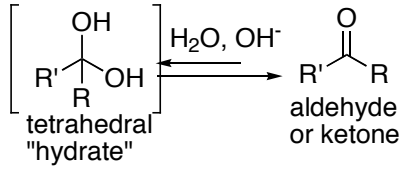
HCN addition, anionic mech.

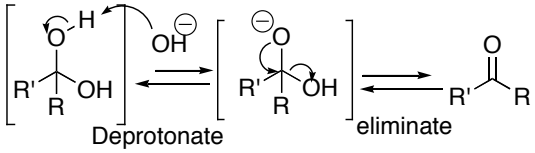


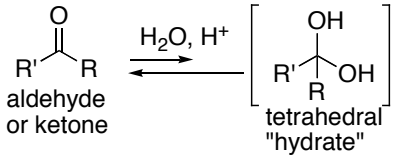
22 

Water addition, anionic mech.

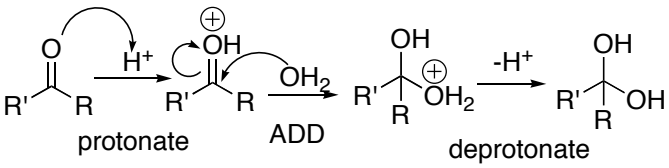


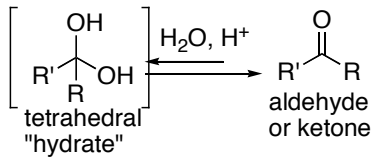
22r 

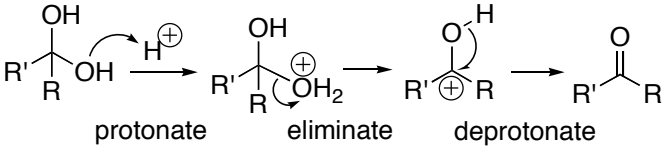


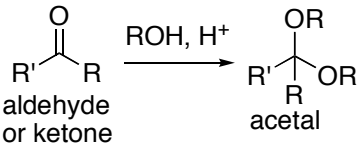
23 

Water addition, cationic mech.

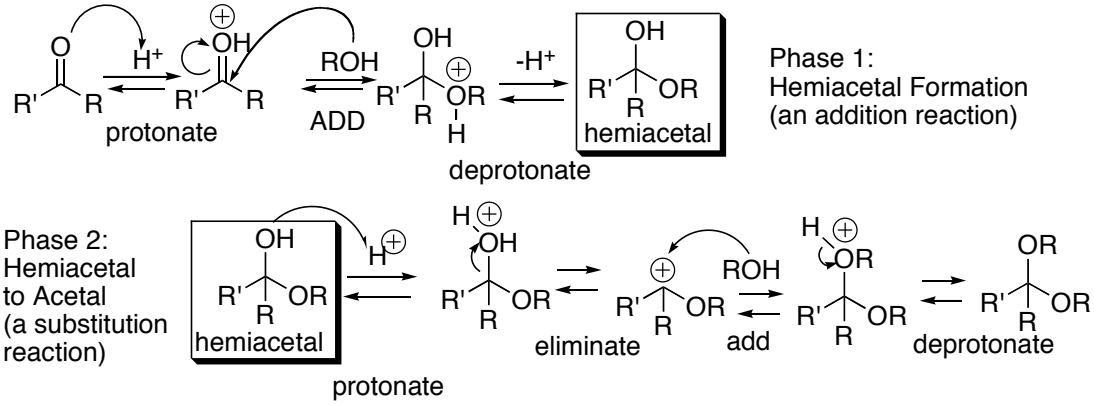


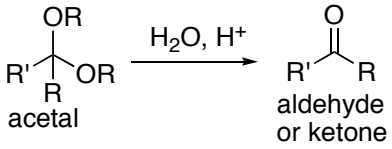
23r 



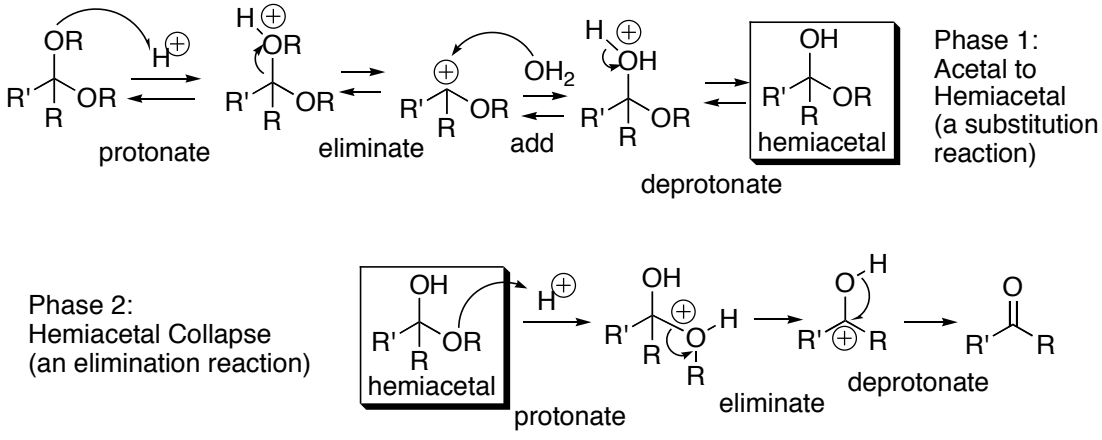
24 

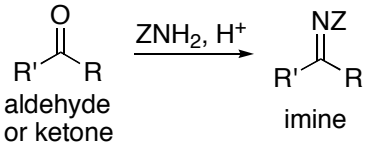
Acetal formation



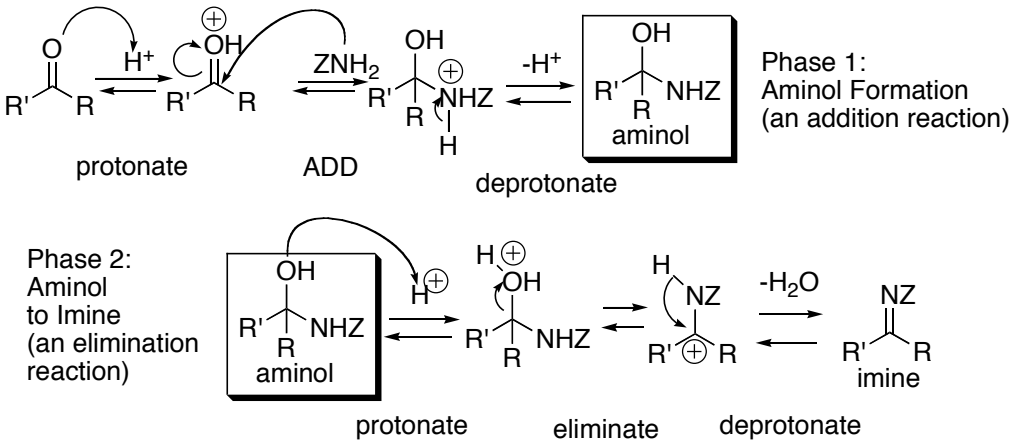
24r 

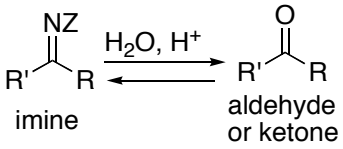
Acetal hydrolysis.



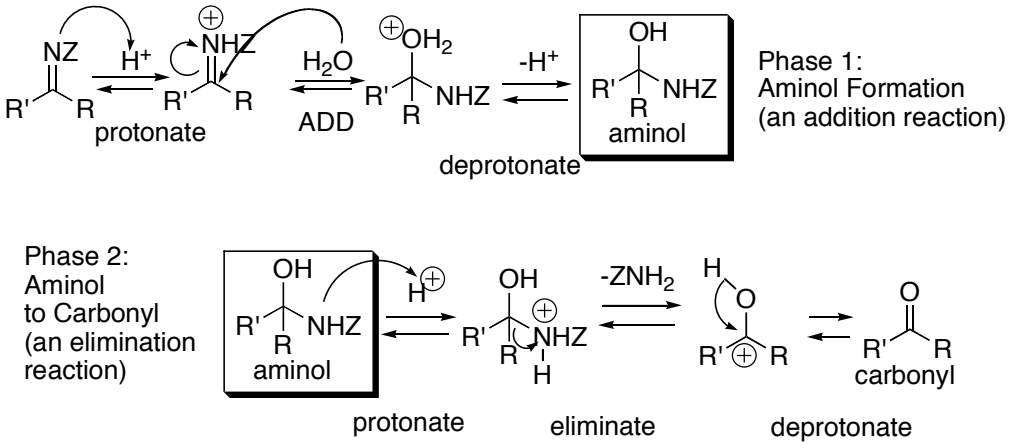
25 

Imine Formation



25r 

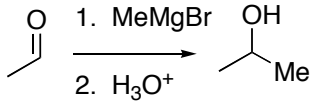
Imine Hydrolysis



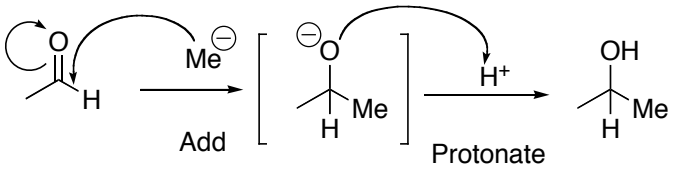
Classification of Mechanisms Associated With Ketone/Aldehyde Reactions.

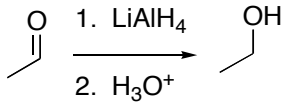
- There may seem to be a dizzying number of mechanisms this chapter. But all of them simplify into some combination of acid- or base-catalyzed **addition reaction**, **elimination reaction** and/or **substitution reaction**.
- To predict what product forms that can be isolated, you will need to know when an addition is all that happens, and when an addition is followed by elimination or substitution.
- Many reactions are reversible, and are controlled by equilibrium principles, so you ought to be able to go in either direction.
- The sequencing of many of the mechanistic steps is dependent on whether you are under acidic (cationic) conditions or basic (anionic) conditions.

ADDITION REACTIONS.

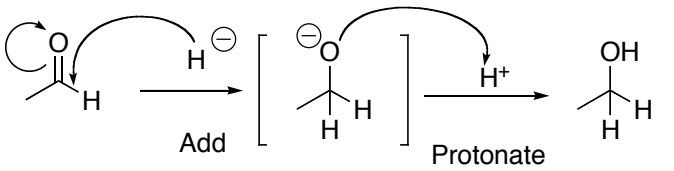
19 

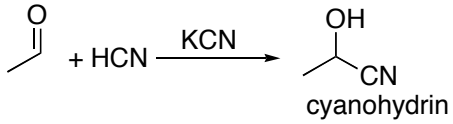
Grignard Addition of a Carbanion



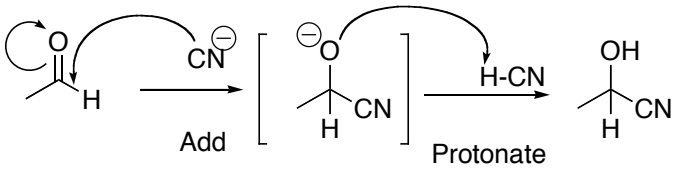
20 

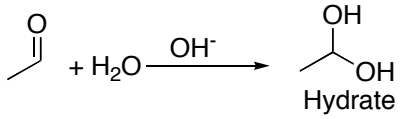
Hydride addition.



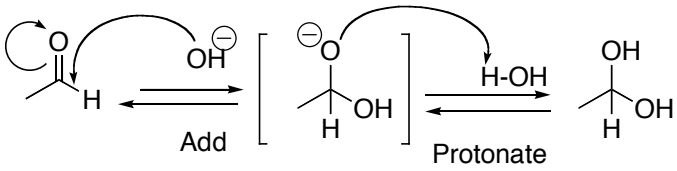
21 

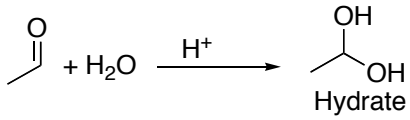
HCN addition, anionic mech.



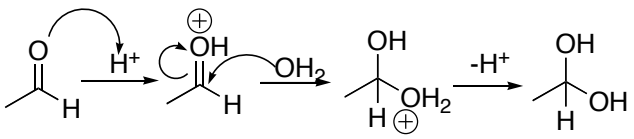
22 

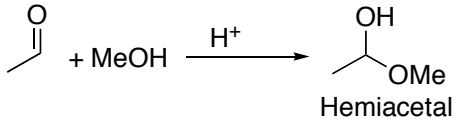
Water addition, anionic mech.



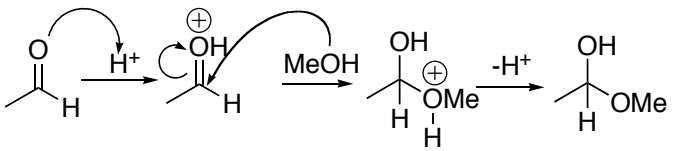
23 

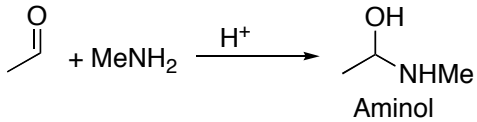
Water addition, cationic mech.



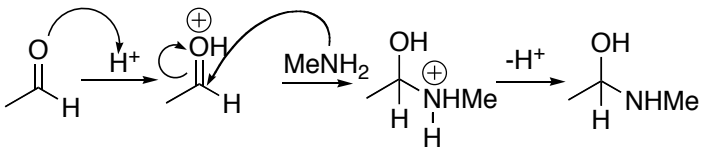
24 

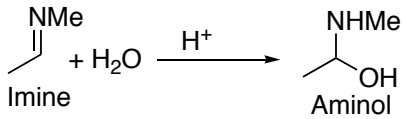
Alcohol addition, cationic mech.



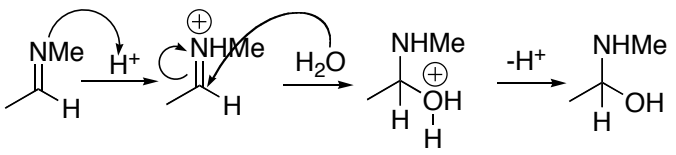
25 

Amine addition, cationic mech.

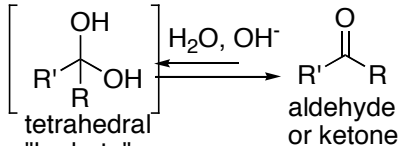
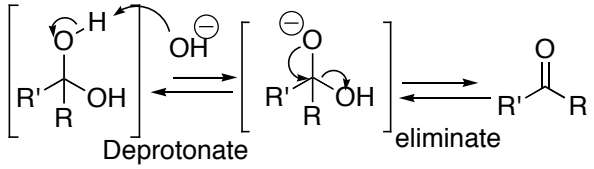
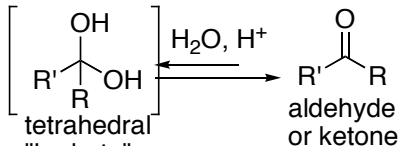
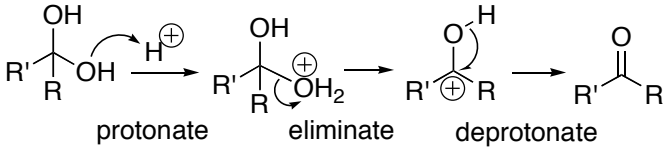
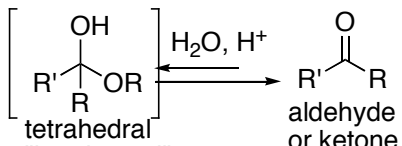
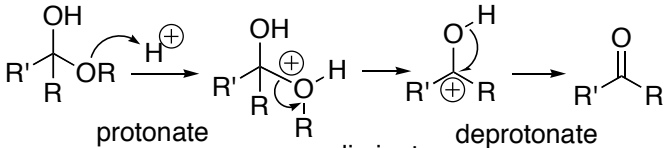
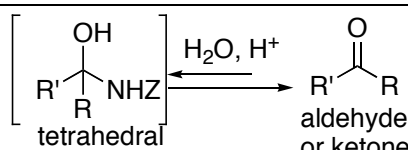
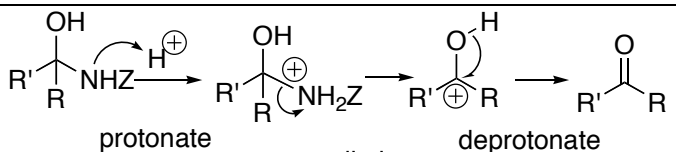
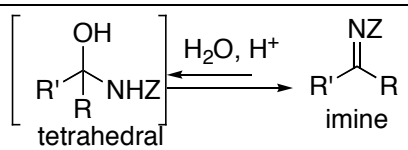
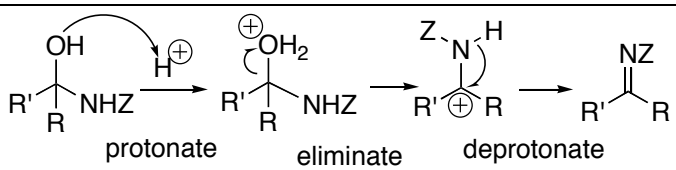


25r 

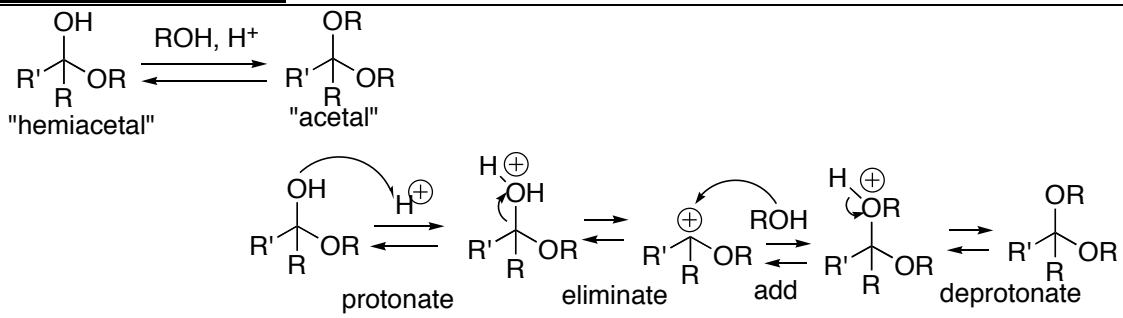
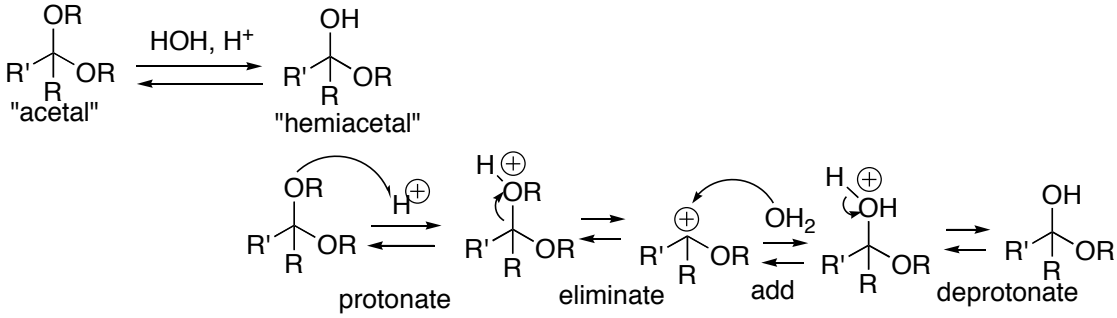
Water addition to imine, cationic mech



Elimination Reactions.

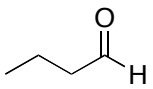
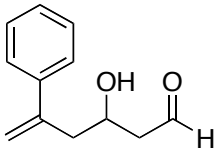
22r		
23r		
24r		
25r		
25b		

Substitution Reactions.

24b	
24r	

A. Nomenclature (Section 18-3)

1. Aldehydes:
   a. IUPAC: Alkan**al**

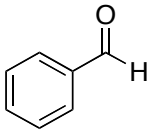
- Note: carbonyl takes precedence over alcohols (hydroxy), aromatics, alkenes, halides.
- Aldehyde carbon is always #1, so needs no number (don't forget to count that carbon!)

b. Aldehydes are often written as RCHO

CH_3CHO PhCHO

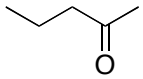
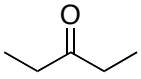
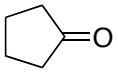
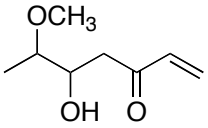
c. Common Names: (Memorize)


Formaldehyde

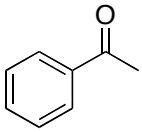
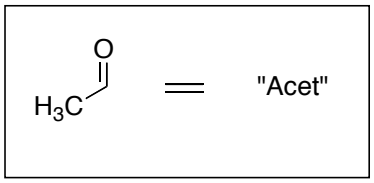
Acetaldehyde

Benzaldehyde

2. Ketones:
   a. IUPAC: alkan-x-**one**

Need number, remember to number!!

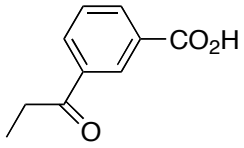
b. Common Names: (Memorize)

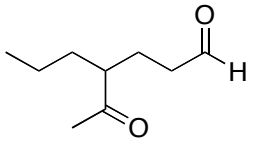

Acetone

Acetophenone


Acetone
Acetophenone
Acetaldehyde
Acetic Acid
Acetic Anhydride

3. Carbonyls as Substituents: **Alkanoyl**

- needed when there are higher priority functional groups present, such as carbonylic acids
- alkanoyl assumes the carbonyl is on the 1st, connecting carbon of the alkyl substituent
- Not for test: (x-oxoalkyl) when the carbonyl is not on the connecting carbon.





Common Names:

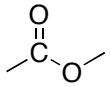
formyl

acetyl

B. General Review of Basic Nomenclature Principles

1. **Core name versus Substituents.** Which part of the molecule can be included in the core name, and which parts need to treated as substituents?

2. **Ranking of Functional Group Priority.**
   - when 2 or more functional groups are present, the priority functional group is included in the core name, and the core numbering is based on the priority group
   - Many common names incorporate two functional groups (benzoic acid, phenol, etc..)
   -

			OH	NH_2	Aryl	Alkene
Families	Acids Esters	Ketones Aldehydes				
Core Name	Alkanoic acids	alkan**al** alkan- x-**one**	alkan-x-**ol**	alkan-x-**amine**		alk-x-**ene**
Substituent		alkanoyl or (x-oxoalkyl)	hydroxy	amino	Phenyl	

   -

3. **Remember Descriptors**
   - Position of functional groups
   - Position of substituents
   - Stereochemical descriptors (cis/trans, E/Z, R/S)

4. **Punctuation**
   - Hyphenate numbers and stereochemical descriptors
   - Parenthesize stereochemical descriptors: (R)/(S), (E)/(Z)
   - Do not put any spaces for molecular-style names
   - Do put spaces for ionic style names

Ionic style:

NaCl: $PhCO_2H$: $PhCO_2CH_3$

C. **Properties of Carbonyls (Sections 18.2, 4)**

	• Strongly polar • Sp^2, flat, ~120° angles • Can H-bond water (impacting water solubility) • But cannot H-bond self (impacting boiling point)

For molecules of similar weight:

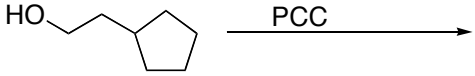
1. Boiling Point: Alcohols (H-bonding) >>> ketones (polar) > ethers (less polar) > alkanes (nonpolar)
   - Large difference between alcohols and ketones because of H-bonding
2. Water solubility: Alcohols > ketones > ethers >>> alkanes (nonpolar)
   - The difference between alcohols and ketones is much smaller, since both can H-bond to water's hydrogens

(Section 18-6) Many Ketones and Aldehydes have Famous, Nice Smells

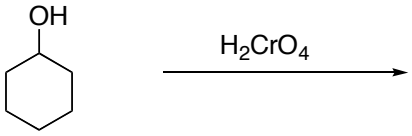
- Vanilla, almond extract, cinnamon, spearmint, pistachio, butter, camphor, etc.

D. **Synthesis of Ketones/Aldehydes: Review Routes, Handout Reactions 1-9 (Sections 18.7 and earlier book sections)**

From Alcohols

1 

11.2

2 

11.2

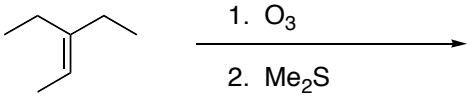
From Alkenes via Alcohols or Oxidative Cleavage

3 

8.7

4 

8.4

5 

8.15

From Carbonyl via Alcohols

6  10.9

7  10.11

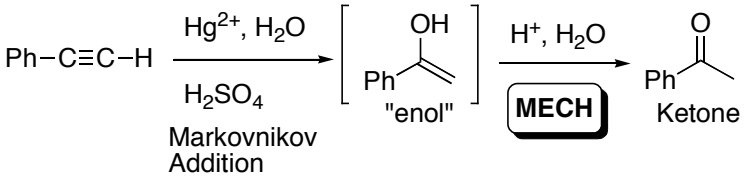
From Halides via Alcohols

8  6.8

9  6.8

E. **New Syntheses of Ketones/Aldehydes: Handout Reactions 10-18 (Sections 18.8-10 and earlier book sections)**

From Alkynes (Section 9.9F)

10  9.9F

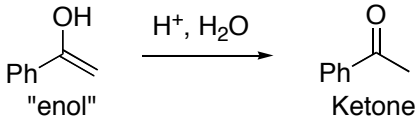
Two Phases:

1. The first phase is analogous to oxymercuration of an alkene
    a. It involves Hg^{2+} and water
    b. H-OH adds across the π-bond
    c. Markovnikov addition: OH adds to the more substituted end of alkyne
    d. $NaBH_4$ is actually not required
2. Phase 2: The "enol" produced in the first phase is unstable and rapidly converts to the carbonyl

- Phase 2: Mechanism Responsible.

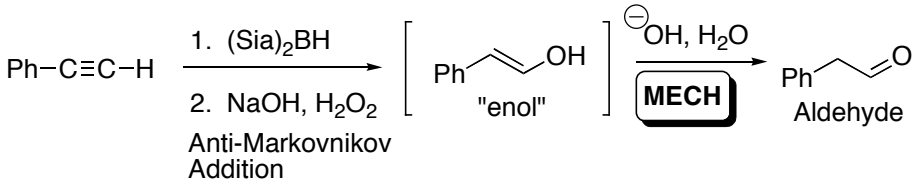
Mechanism: (Acid-Catalyzed enol → carbonyl)

New Bonds Broken Bonds



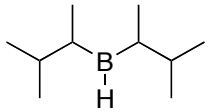
Acid Conditions:
1. Use H+ in first step
2. Cationic intermediates
3. At some point deprotonate to return to neutral.

11



Two Phases:

1. The first phase is analogous to hydroboration of an alkene
    a. H-OH adds across the π-bond
    b. It involves a borane
    c. Anti-Markovnikov addition: OH adds to the less substituted end of alkyne
    d. $(Sia)_2BH$ ~ BH_3-THF, but is much bulkier in order to ensure high anti-Markovnikov orientation and to ensure that it stop after one addition and leaves the second π-bond untouched. (BH_3 works but is less selective)

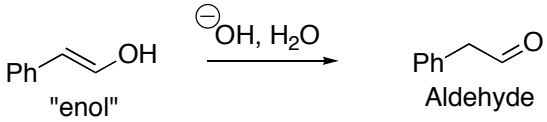


2. Phase 2: The "enol" produced in the first phase is unstable and rapidly converts to the carbonyl

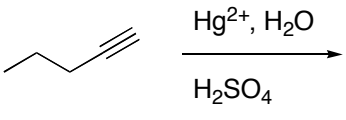
- Phase 2: Mechanism Responsible.

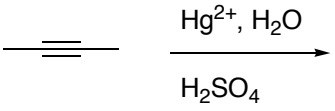
Mechanism: (Base-Catalyzed enol → carbonyl)

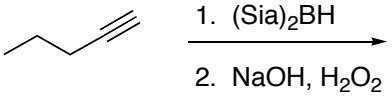
New Bonds Broken Bonds

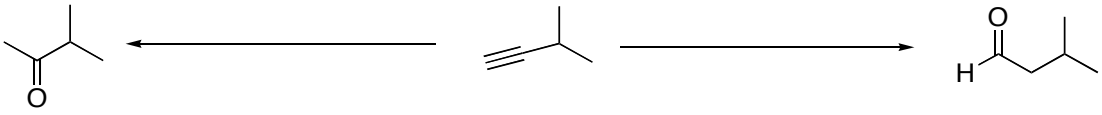


Base Conditions:
1. Use base (hydroxide) in first step
2. Cationic intermediates
3. At some point deprotonate to return to neutral.

a. 

b. 

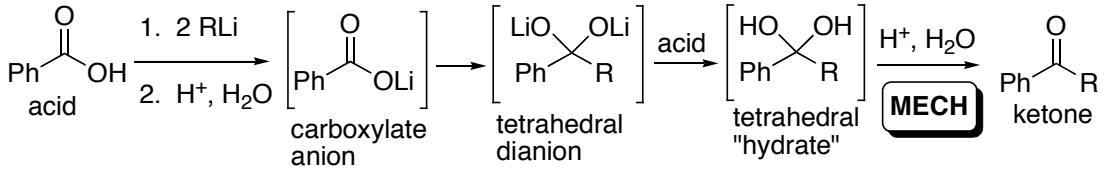
c. 

d. 

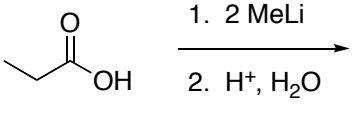
Remember:

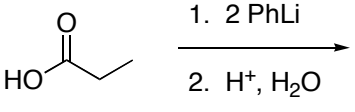
1. Enols quickly convert to carbonyls
2. Remember these two reactions mainly as Markovnikov or anti-Markovnikov addition of H-OH addition to alkyne

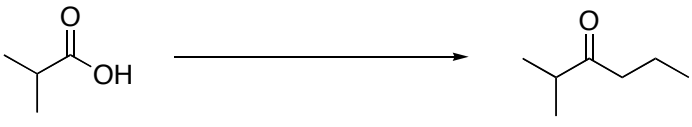
From Carboxylic Acids

12 

18.9

a. 

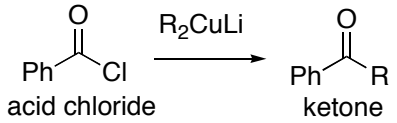
b. 

c. 

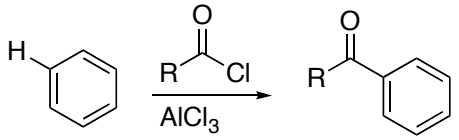
Mechanism: Key new Mechanism Step is the **<u>acid-catalyzed hydrolysis of the tetrahedral hydrate</u>** to the ketone

- Tetrahedral anion is stable until acid/water is added
- Tetrahedral hydrate rapidly "dehydrates" to ketone

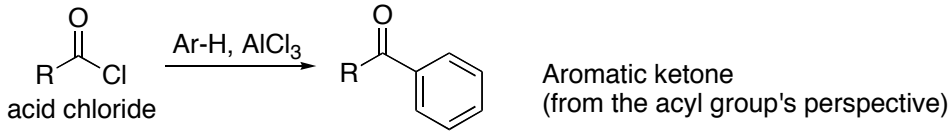
From Acid Chlorides (Section 18.10)

13 

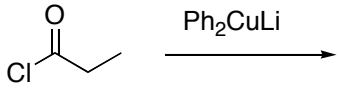
18.11

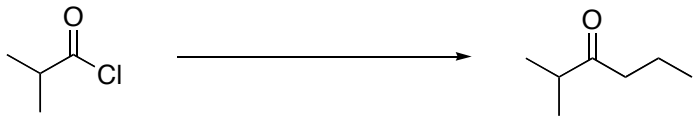
14 

18.11

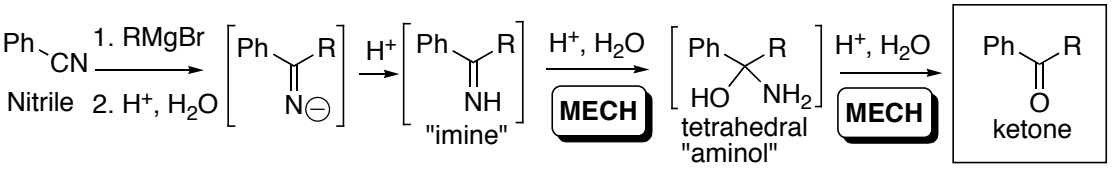


- No mechanism responsibility for reaction 13
- Reaction 14, mechanisms from chapter 17, Semester 1, Test 4
- R_2CuLi is a special, mild carbanion equivalent. Some special properties enable it to stop at ketone. (RMgBr would not stop at ketone, but would add again to give 3º alcohol)

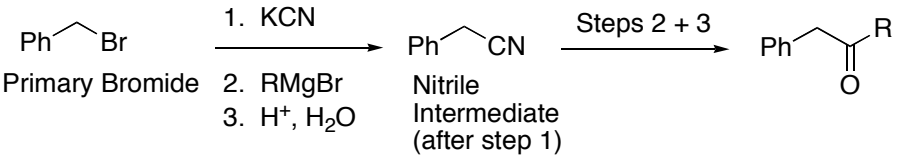
a. 

b. 

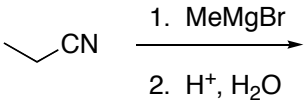
From Nitriles (Section 18-9)

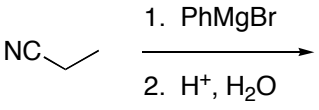
15 

18.10

16 

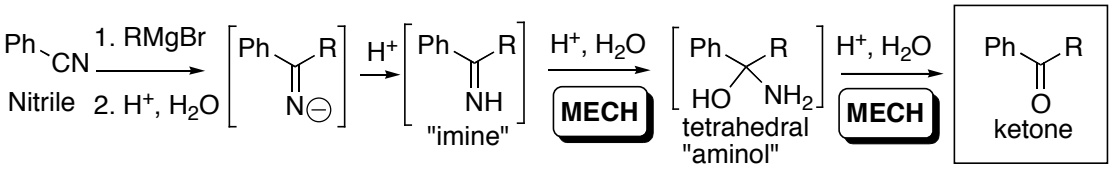
18.10

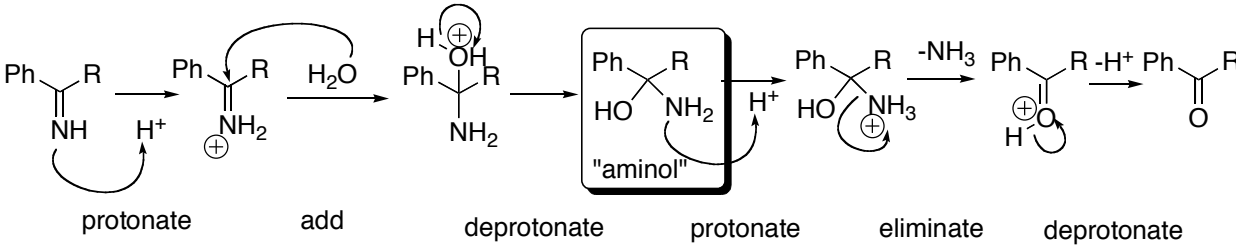
a. 

b. 

c. 

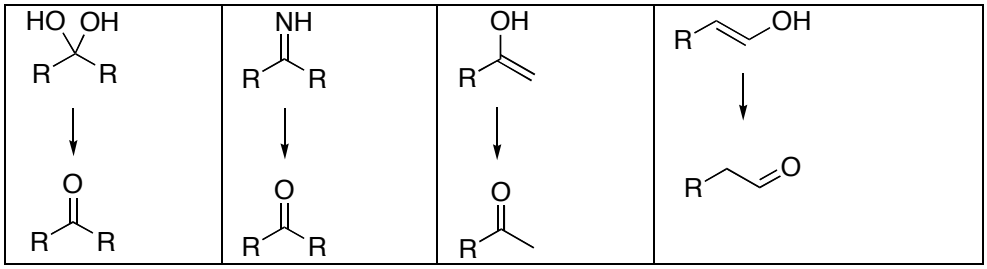
Mechanism: Acid-Catalyzed Hydrolysis of C=NH





Note: Many groups can "hydrolyze" to carbonyls

- A carbon with two heteroatoms attached, single-bonded or double-bonded
- A carbon with one heteroatom and one π-bond
- Often base or acid or some special acid assistant helps

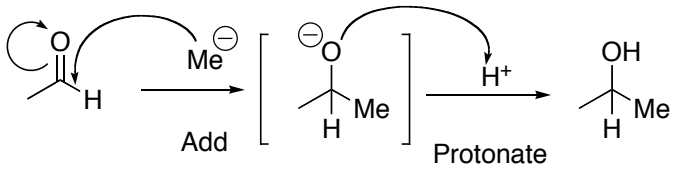


F. General Reactivity of Ketones and Aldehydes: Addition Reactions (Section 18.11)

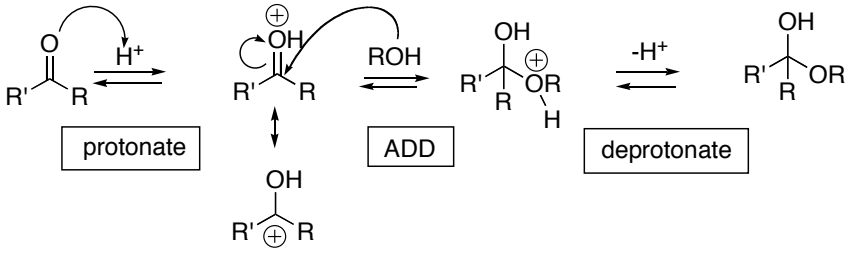
Key: Are reaction conditions anionic/basic or cationic/acidic (or perhaps buffered in between?)

1. **Anionic Conditions** (when a strong anion is involved)
   a. General principles review for strongly anionic/basic conditions apply
      1. In an anionic mechanism, a strong anion will drive the first step
      2. In an anionic mechanism, intermediates should avoid positive charges
      3. Recognize anionic species even when they are disguised by a cationic metal counterion.

   b. Anionic additions to ketones
      1. Strong nucleophile required ($R^{\ominus}$, $H^{\ominus}$, $HO^{\ominus}$, …)
         - Intermediates have negative charge
      2. **Addition first, protonation second**
      3. Addition is normally irreversible
         - Addition is often strongly exothermic
         - The proton source is often added in a separate laboratory step, because often the anion and the proton are incompatible



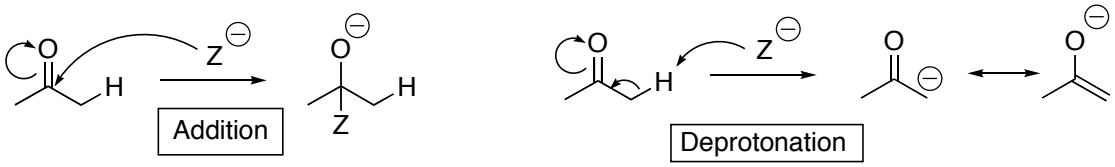
2. **Cationic Conditions** (acid is involved)
   a. General principles review for acid/cartionic conditions apply
      - Recipes that involve acid will be cationic
      - In a cationic mechanism, the first step will routinely involve protonation
      - In a cationic mechanism, the last step will frequently involve deprotonation to return to neutral
      - Normally the main step or steps are sandwiched in between the protonation and deprotonation events



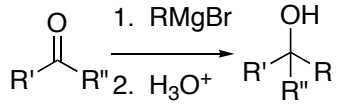
   b. Cationic additions to ketones
      1. Weak, neutral nucleophile involved (ROH, HOH…)
      2. Intermediates have positive charge
      3. **Protonation first, addition second**
         - Weak nucleophile is not strong enough to add to neutral carbonyl
         - Protonation activates the carbonyl as an electrophile
      4. A deprotonation step is routinely required following addition, to get back to neutral
      5. Addition is normally reversible
         - Nucleophile can come back off
         - Nucleophile is normally a reasonable leaving group

3. **Buffer Conditions** (both weak acid and weak base/nucleophile are present at same time)
   - RNH_2/H^+, KCN/HCN…
   - Reversibility again applies
   - Whether addition comes before protonation, or protonation precedes addition depends on the exact case

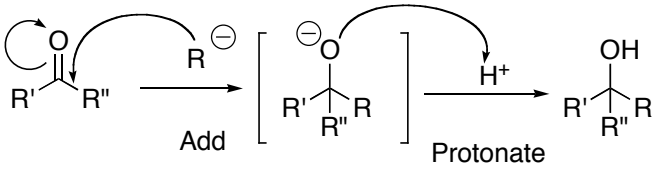
4. **Anion Conditions**: Nucleophilic addition versus deprotonation
   - Sometimes an anion will function as a base and remove a proton rather than functioning as a nucleophile and adding to the carbonyl
   - Comparable to S_N2 versus E2 reactions
   - Anion size will again factor, with bulky bases more likely to deprotonate and smaller ones to add
   - Chapter 22 will deal with the deprotonation pathway, followed by nucleophilic attack on electrophiles

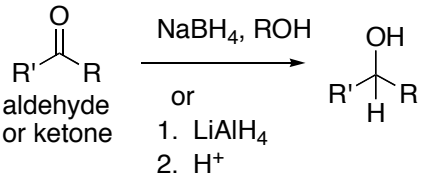


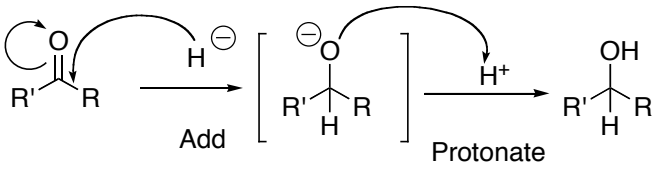
Addition of R$^{\ominus}$ (RMgBr) and H$^{\ominus}$ (NaBH$_4$, LiAlH$_4$) (Review, Section 18.11, Ch. 10)

19 

Grignard Addition of a Carbanion



20 

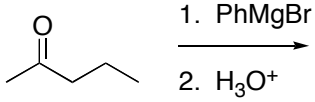


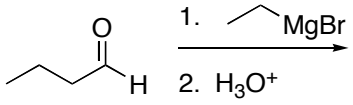
Hydride addition.

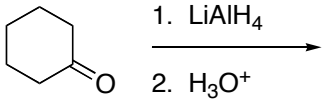
Note: For RMgBr and LiAlH$_4$, the basicity of the reagent is too strong to permit a proton source to be present at the same time. Thus the proton source must be added in a subsequent laboratory step. The NaBH$_4$ is weaker, both as a nucleophile but also as a base.

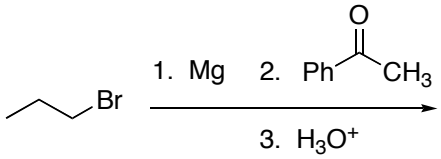
Draw products from the following reactions.

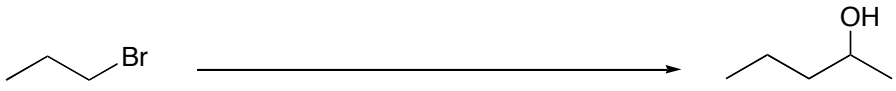
1º, 2º or 3º?

1 

2 

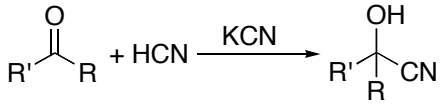
3 

4 

5 

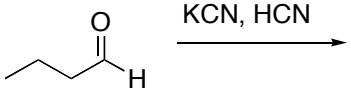
6. Draw the mechanism for reaction 1 above.

Addition of HCN to make "Cyanohydrins" (Section 18-13): Anionic Mechanism

21 

HCN addition, anionic mech.

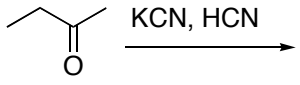
Draw the product and mechanism for the following:

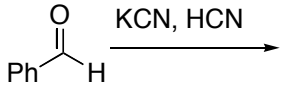


Mechanistic notes

1. Addition first, protonation second
2. $^{\ominus}$CN is a good nucleophile, HCN a decent acid
3. KCN/HCN represents a **buffer situation**: weak base/weak acid, not obvious which dominates. But in this case the anion does and it proceeds via anionic mechanism.
4. $^{\ominus}$CN is actually used as a catalyst: after the HCN donates proton, the $^{\ominus}$CN is regenerated
5. In reality, KCN/HCl or KCN/H_2SO_4 is often used
   - Easier to put together and handle
6. Reaction is reversible
   - Strongly favors product cyanohydrin, unless a strongly hindered ketone is used

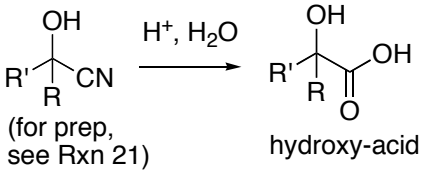
Draw products

a. 

b. 

c.

Key Application (not tested)

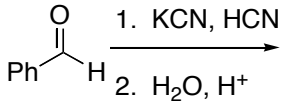
29 

(for prep, see Rxn 21)

hydroxy-acid

- Unique access to 2-hydroxyacids..
- Indirect provides the equivalent ("Synthon") for a $^{\ominus}CO_2H$ anion

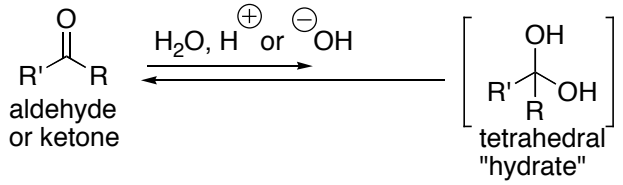
Draw Products

1. 

Reversible Addition of H_2O (H-OH) to Make Hydrates: Addition (and elimination) under Acidic or Basic Conditions (Section 18.12).

- Know mechanism under either base or acid
- Know mechanism for the reverse direction (hydrate to carbonyl) as well

22, 23



"Hydrates" are present only as transient equilibrium species. They never form to 100% and are never isolable. Always in equilbrium with their aldehyde or ketone.

Anionic

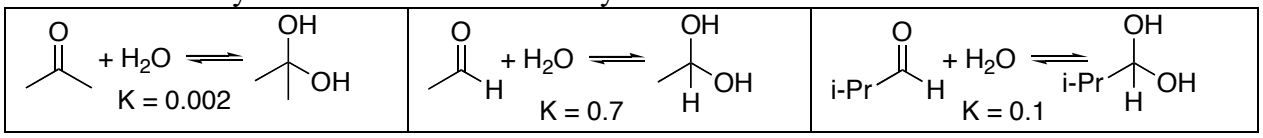
Mech Forward: Addition-Protonation. Nucleophile, anionic mechanism. Reversible.
Mech Reverse: Deprotonation-Elimination. Anionic mechanism. Reversible.

Cationic

Mech Forward: Protonation-Addition-deprotonation. Weakly nucleophile, cationic mechanism. Reversible.
Mech Reverse: Protonation-Elimination-deprotonation. Cationic E1-type mechanism. Reversible.

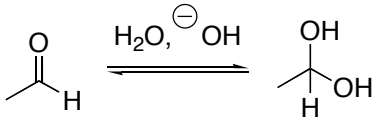
Notes:

1. True equilibrium.
2. Super unfavorable for ketones, moderately unfavorable for aldehydes
   - Ketone is stabilized more by the two alkyl donors
   - Ketone hydrate is destabilized more by sterics

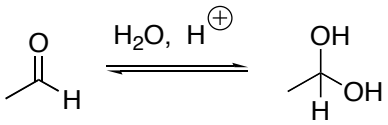


3. Hydrates can never be isolated, because as soon as you try to take them out of water, the drives back to the carbonyl side (LeChatelier's Principle)
4. While the hydrate is not present in high concentration, it is often a crucial intermediate in a variety of biological processes
   - We've also seen its importance in the oxidation of 1º alcohols to carboxylic acids using H_2CrO_4 in water.

Draw the **ANIONIC addition** mechanism



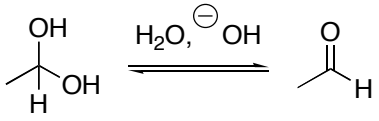
Draw the **CATIONIC addition** mechanism



Hydrate Hydrolysis (Elimination of Water from Hydrate to Generate Carbonyl)

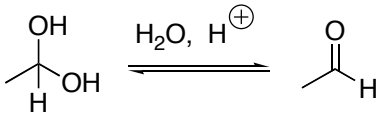
Draw the **ANIONIC elimination** mechanism

- Deprotonation precedes elimination
- E2-like



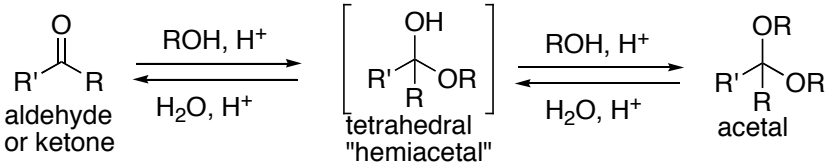
Draw the **CATIONIC elimination** mechanism

- Elimination precedes deprotonation
- E1-like



Reversible Reaction of ROH to Make Acetals via Hemiacetals. (Section 18.16, 17). Addition/Substitution under Acidic Conditions
Also know the reverses process, substitution/elimination under acid conditions

24



Cationic

Mech Forward: Protonation-Addition-deprotonation (hemiacetal) Protonation-elimination-addition-deprotonation (acetal). Weak nucleophile, cationic mechanism. Reversible.

Mech Reverse: Protonation-Elimination-Addition-deprotonation. (hemiacetal) protonation-elimination-deprotonation (aldehyde or ketone). Reversible.

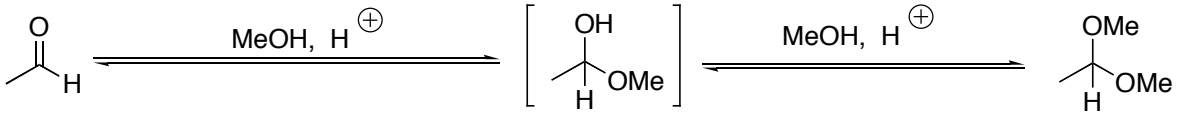
Notes:

- Reactions are reversible
- The "hemiacetal" is an intermediate, and can never be isolated
- The acetal can be isolated. (It is stable in absence of water)
- Equilibrium considerations (LeChatelier's principle) apply. When water is plentiful, things go to the left. When water is scarce or removed, and alcohol is abundant, things drive to the right.
- Use H_2O/H^+ to hydrolyze an acetal back to an aldehyde or ketone
- Use $MeOH/H^+$ to convert an aldehyde to an acetal
- Use $HOCH_2CH_2OH/H^+$ to convert a ketone to an acetal
- Aldehydes or ketones can be temporarily "protected" as their acetals, then later "deprotected" by hydrolysis

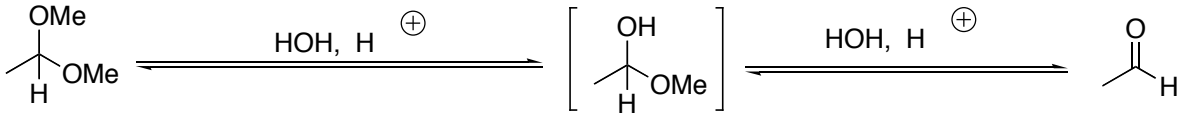
Notes:

1. While the acetal can be isolated, the hemiacetal cannot
2. Four reactions, each with their own mechanism:
   a. Carbonyl to hemiacetal = acid-catalyzed addition reaction.
   b. Hemiacetal to acetal = acid-catalyzed substitution reaction (S_N1-type)
   c. Acetal back to hemiacetal = acid-catalyzed substitution reaction (S_N1-type)
   d. Hemiacetal back to carbonyl = acid-catalyzed elimination (E1-type)

Draw the mechanism



Draw the mechanism

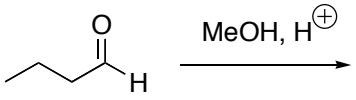


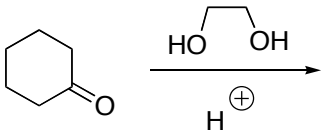
We have now seen three major acid-catalyzed reaction types in this chapter

1. Additions (protonate-**add**-deprotonate)
2. Eliminations (protonate-**eliminate**-deprotonate)
3. Substitutions (protonate-**eliminate-add**-deprotonate)

Notice that a protonation/deprotonation sandwiches the key step(s) in each of them

Draw the products for the following reactions

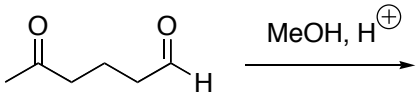
1 

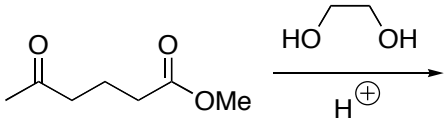
2 

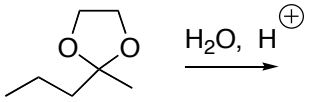
"Cyclic Acetal"

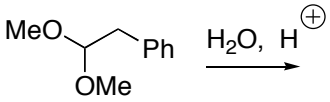
Key Synthetic Notes:

1. **Ethylene glycol** works well for making acetals from aldehydes or ketones. Use **ethylene glycol for KETONES.**
   a. Once the first oxygen adds, the second oxygen is always close by and ready to add
   b. The cyclic acetal is more stable; even if one oxygen comes off, it can come right back on.
   c. The cyclic acetal formation is actually more favorable energetically (enthalpy)
   d. The cyclic acetal also has entropy advantages (entropy)
2. Methanol is simpler for making acetals from aldehydes, but often has problems for ketones. Use **methanol for ALDEHYDES**
3. **Selective protection**:
   a. Methanol can be used to protect an aldehyde, while a ketone or ester will go untouched.
   b. Ethylene glycol can be used to protect a ketone, while an ester will be untouched.

3 

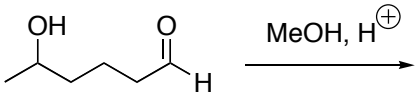
4 

5 

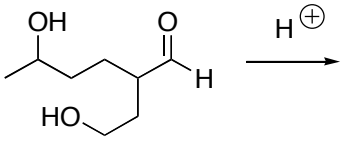
6 

Equilibrium and Acetals

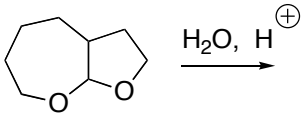
1. Normally favors the carbonyl, especially for ketones
2. Push to the acetal side by using excess alcohol
3. Push to carbonyl side by using excess water
4. **Equilibrium improves greatly for cyclic acetals.**
5. **Hemiacetals have a favorable equilibrium if and only if a 5- or 6-ring hemiacetal can form.** (This is central to carboyhydrate/sugar chemistry.)

7 

"Mixed Acetal"

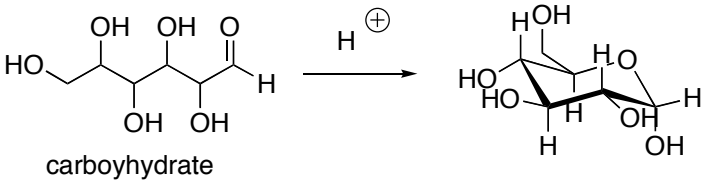
8 

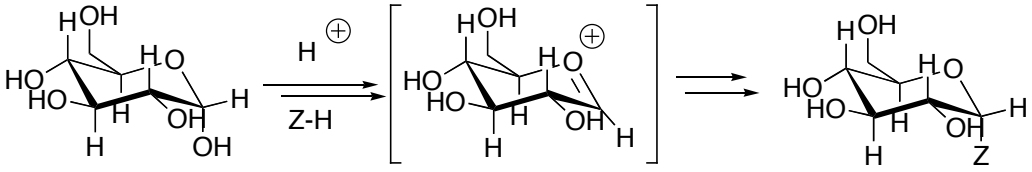
"Cyclic Acetal"

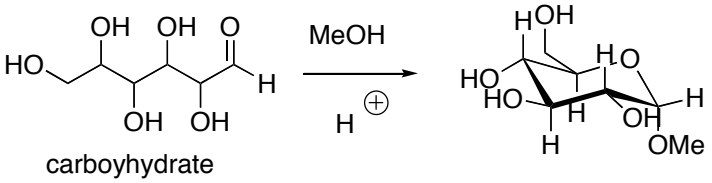
9 

Hydrolysis Of cyclic acetal

<u>Hemiacetals, mixed acetals, polymers, and Sugar/Carbohydrate Chemistry</u>

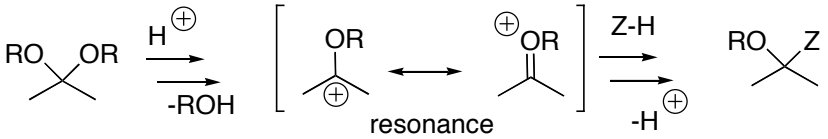
10 

11 

12 

<u>Notes:</u>

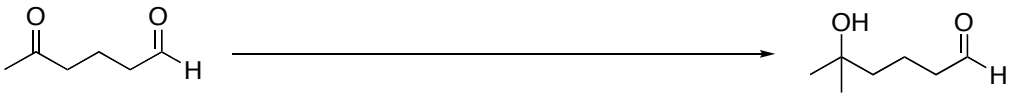
1. Acetal or hemiacetal carbons have two single-bond oxygens
2. When thinking about an acetal being hydrolyzed, the carbon with two single-bond oxygens hydrolyzes to a carbonyl
3. Acetal or hemiacetal carbons are **highly reactive as S_N1 substrates** thanks to cation stabilization by oxygen donor

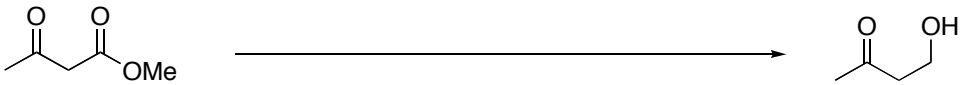


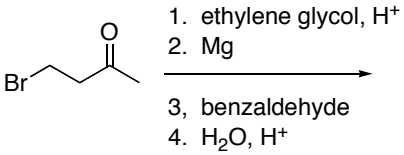
4. Carbohydrates exist as hemiacetals or acetals
5. Carbohydrates can polymerize or make complex derivatives via substitution at their acetal carbons

Acetals as Protecting Groups in Synthesis (Section 18-17)

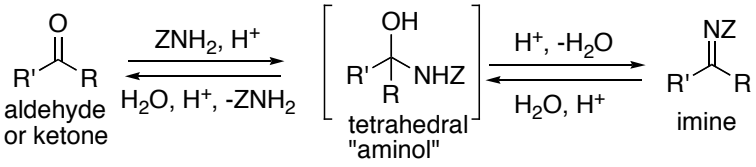
1. Reactivity: Aldehydes > Ketones >> Esters
   a. Aldehydes versus Ketones Why:
      - Sterics, ketones are more cluttered and additions make things worse
      - Electronics, ketones are more stable with two electron-donating groups
   b. Ketones versus Esters Why:
      - Electronics, the conjugation stabilizes esters
2. **Selective protection**:
   a. Methanol can be used to protect an aldehyde, while a ketone or ester will go untouched.
   b. Ethylene glycol can be used to protect a ketone, while an ester will be untouched.

13 

14 

15 

Addition of H_2N-Z Reagents (Sections 18-14,15)

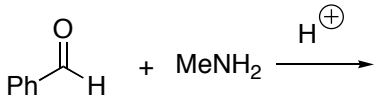
25 

Cationic

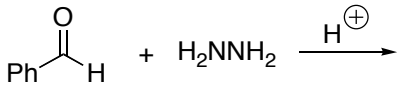
- Mech Forward: Protonation-Addition-deprotonation (aminol) Protonation-elimination- deprotonation (imine). Mild nucleophile, cationic mechanism, buffered conditions. Reversible.
- Note: sometimes addition precedes protonation, or is concerted with protonation.
- Mech Reverse: Protonation-Addition-deprotonation (aminol) Protonation-elimination- deprotonation (aldehyde or ketone). Reversible.

Notes:

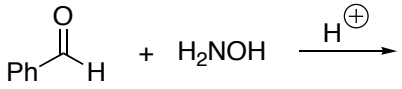
- "Z" can be a carbon, nitrogen, oxygen, or hydrogen atom/group.
- The "aminol" can't be isolated, it's only present at equilibrium.
- Equilibrium factors apply. Water drives to the carbonyl side; removal of water drives to the imine side.

1 

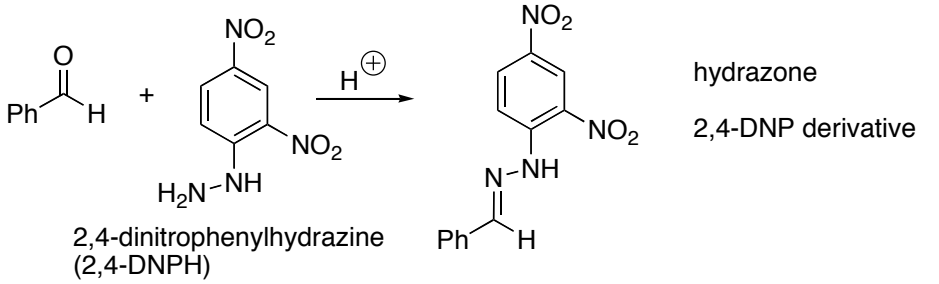
"Imine"
(Z = alkyl)

2 

Hydrazone
(Z = Nitrogen)

3 

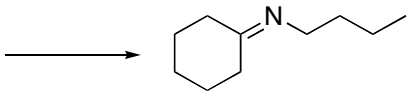
Oxime
(Z = Oxygen)

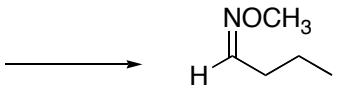
4 

2,4-DNP

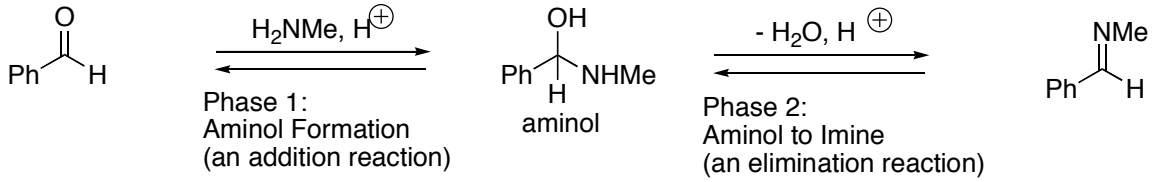
Notes:

1. C=N species can sometimes be hydrolyzed back to carbonyls by H_2O/H^+
2. "Imines" are frequent biology intermediates
3. 2,4-DNP derivatives are easily made and usually crystalline
   a. reaction of an unknown with DNPH to make a solid DNP-derivative is proof of aldehyde or ketone
   b. The melting point of DNP-derivatives permits identification

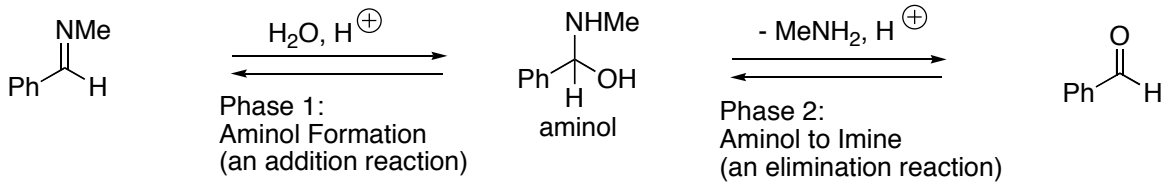
5 

6 

Draw the mechanism for the following:



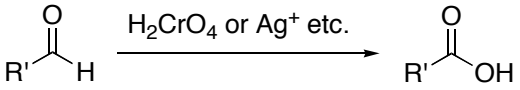
Draw the mechanism for the following:



Notes:

1. All steps are reversible, under equilibrium control
2. I'm writing these as cationic, acid-catalyzed steps
   a. Conditions are actually buffered;
   b. 1 RNH_2 + 0.5 H^+ → 0.5 RNH_2 + 0.5 RNH_3^+ → a buffer system.
   c. In some cases, nucleophilic addition addition by the neutral but reactive amines (to give oxyanions) may actually precede protonation

Oxidation of Aldehydes (Section 18.19)

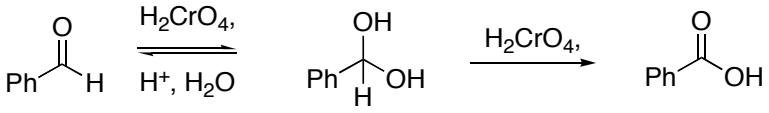
26 

18.20

No Mech Responsibility

"Tollens test" is a common chemical test for aldehydes. Ag^+ undergoes redox reaction with aldeydes to produce shiny Ag metal, or a "silver mirror".

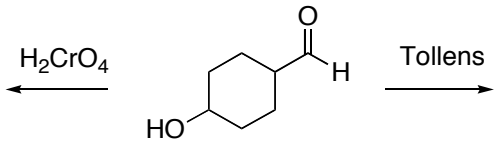
Review: Chromic Acid Oxidation proceeds in water via hydrate



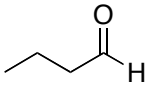
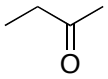
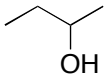
New: Ag^+ salts oxidize aldehydes in presence of alcohols, ketones

Tollens reagent: $Ag(NH_3)_2^+$ Chemical test for **aldehydes**

- A silver mirror forms



Chemical Tests

Class		DNP	Tollens	H_2CrO_4
Aldehydes				
Ketones				
Alcohols				

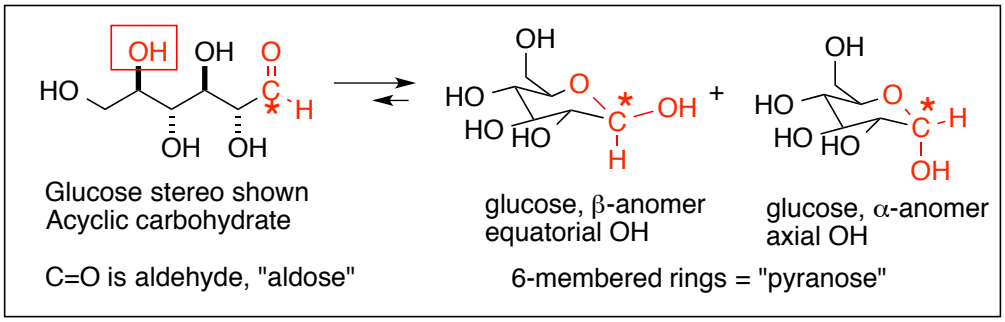
Hemiacetals, mixed acetals, polymers, and Sugar/Carbohydrate Chemistry (Ch 23)

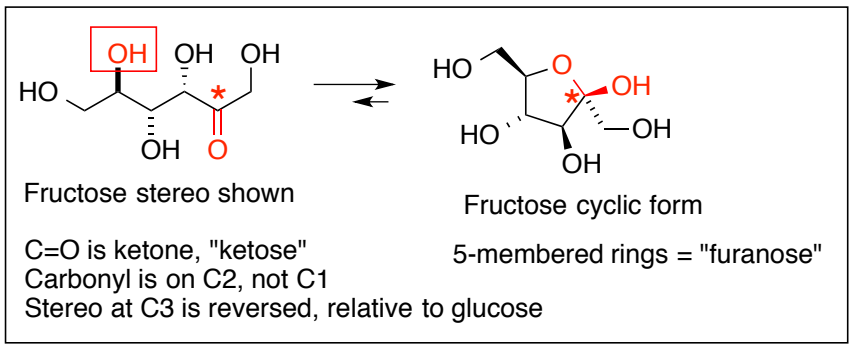
"Carbohydrate": most sugars have formula $C_N(H_2O)_N$

- Glucose: $C_6H_{12}O_6 = C_6(H_2O)_6$
- Fructose: $C_6H_{12}O_6 = C_6(H_2O)_6$
- Sucrose: $C_{12}H_{24}O_{12} = C_{12}(H_2O)_{12}$
- Lactose: $C_{12}H_{24}O_{12} = C_{12}(H_2O)_{12}$

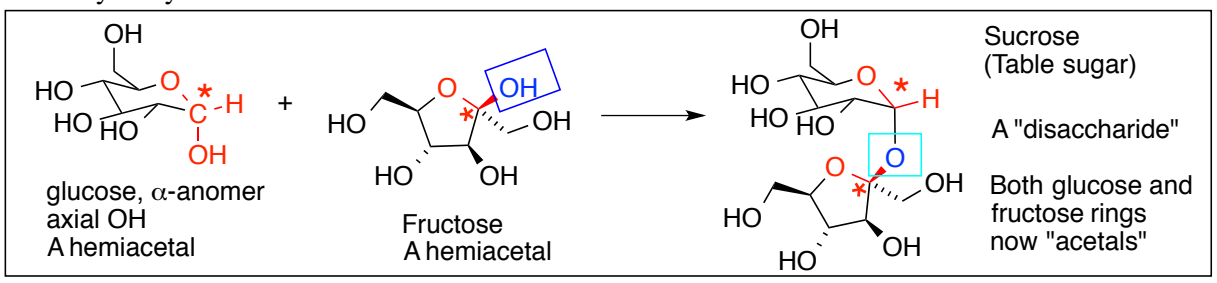
Monosaccharides: (23:3-7)

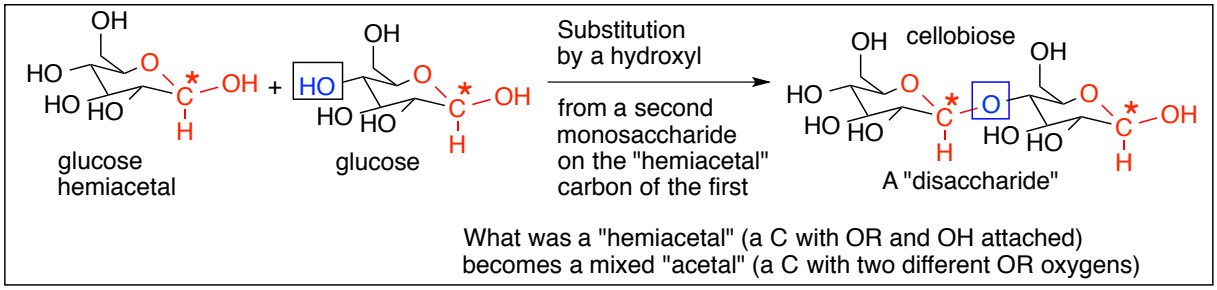
1. Has a carbonyl and multiple hydroxyls
2. Can reversibly interconvert between acyclic and cyclic versions
   - One of the hydroxyls adds to the carbonyl to make a hemiacetal
   - Typically use the OH that produces a 6-membered ring ("pyranose") (ex. Glucose)
   - Sometimes use an OH that produces 5-membered ring ("furanose") (ex. Fructose)
   - DNA and RNA skeletons use 5-membered "furanose" rings
3. Glucose is most famous and abundant monosaccharide
   - Stereochem is such that all of the ring-substituents can be equatorial
   - Other monosaccharides such as mannose, galactose, etc. have some axial substituents
4. Ring forms can have two stereoisomer forms:
   a. When the alcohol oxygen adds to the carbonyl carbon, that becomes a chiral center,
   b. The OH on the newly chiral center can be equatorial ("β") or axial ("α")
   c. The two isomers are called "anomers"





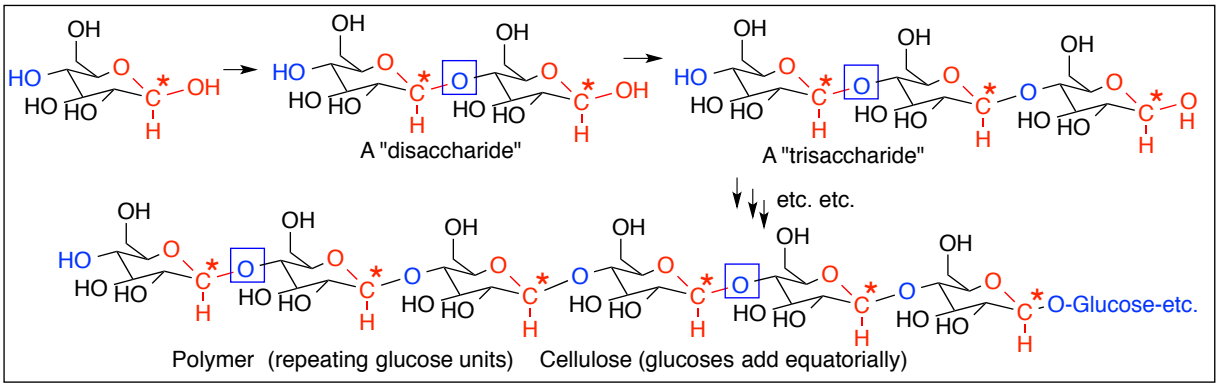
Disaccharides (23.17): Two units combine, by substitution of a hydroxyl from one monosaccharide for the hydroxyl on the hemiacetal carbon of the other. The hemiacetal carbon becomes "acetal"

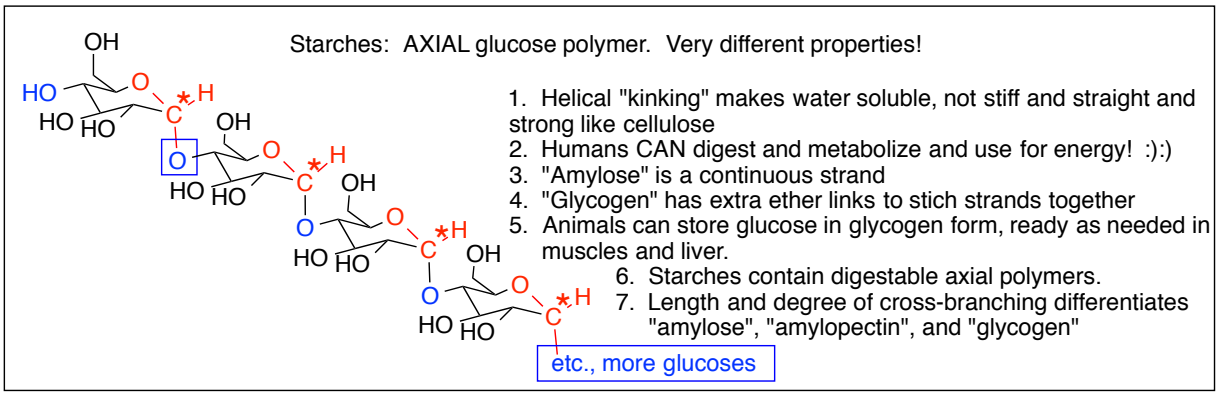




Polysaccharades: Saccharide polymers. (23.18)

1. The hemiacetal carbons are highly subject to SN1 substitution
2. Just as we could add on to convert a monosaccharide into a disaccharide, so we can continue to extend longer and longer, so long as their remains a hemiacetal on the end.
3. Cellulose: equatorial glucose string
4. These can be long, straight, and strong
5. Provide the stiff structural stuff of wood and plant stems
6. Humans lack enzyme to digest and break down into digestable, usable glucose
   - Plant-eating animals do have the enzymes needed!
7. "Starches" are polymers that ARE digestible to release glucose, due to axial substitution

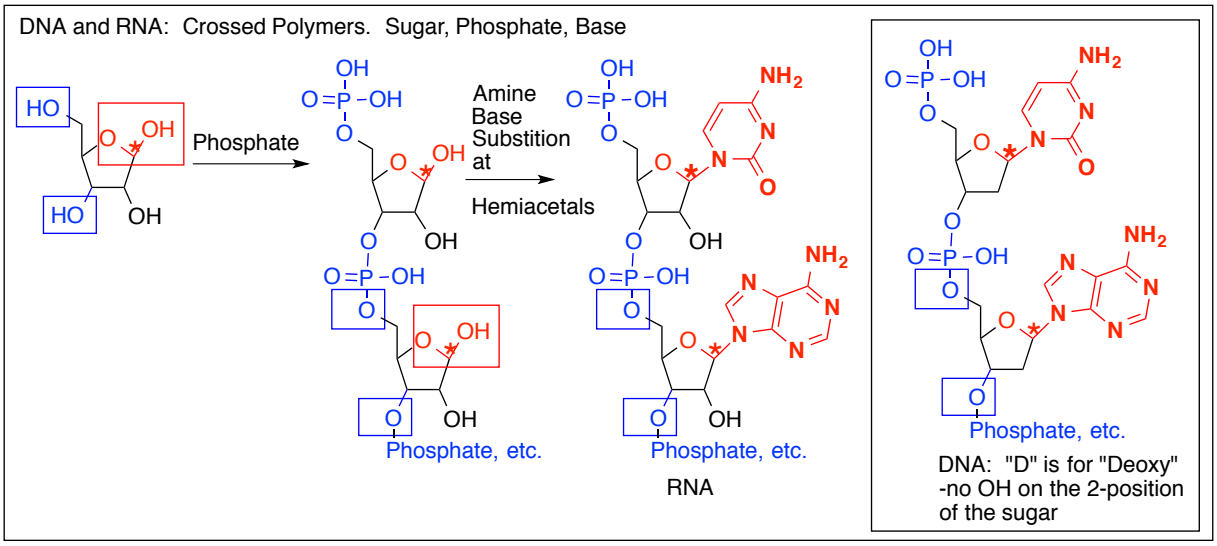




DNA and RNA: More Polymers involving sugars/carbohydrates (23.19-21)

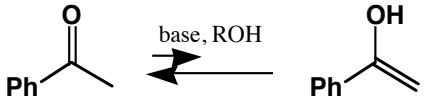
1. DNA and RNA are the stuff of genetics and cell reproduction!
2. Both involve carbohydrates
3. More complex biopolymers than cellulose and starches
   - Instead of simple sugar-sugar-sugar polymer, the sugars are instead connected by phosphate bridges
   - Main strand is sugar-phosphate-sugar-phosphate-sugar-phosphate, etc..
4. The sugars are 5-membered furanose sugars.
5. Sugar uses the hydroxyls at C3 and C5 to to connect to phosphate linkers
6. The structural different between RNA and DNA is that DNA doesn't have the hydroxyl group at the C2 position of the sugar.
   - Thus called "deoxy", which is where the "D" in "DNA" comes from!
7. Amine bases SN1 substitute for hydroxyls on the hemiacetal carbons of the sugars
   - These would then be referred to as mixed "aminals"

8. 4 different bases are used in DNA; 4 bases in RNA
   a. **C**ytosine, **A**denine, **G**uanine: both RNA and DNA
   b. **U**racil in DNA; **T**hymine in DNA. (Thymine is uracil with an extra methyl)
9. The sugar-phosphate-sugar-phosphate skeleton is common to both RNA and DNA; the bio-informatics coding comes from the specific sequene of the amine bases.
10. DNA has a beautiful curling helical structure. Two DNA strands wrap together, with hydrogen-bonding connections between complementary amine-base pairs from opposite strands.
11. During cell reproduction, the two strands unwind, then the "other" strand builds back into place in each cell to recreate the two-strand "double-helix"

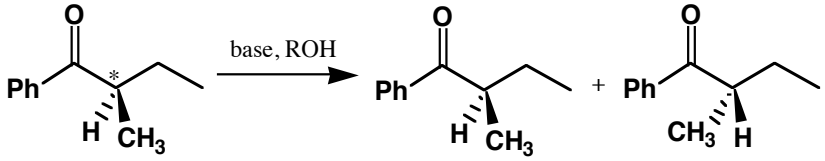


Chem 360-Jasperse **Chapter 22 (Enolate Chemistry) Reaction Summary**

PROTON as ELECTROPHILE

1. 

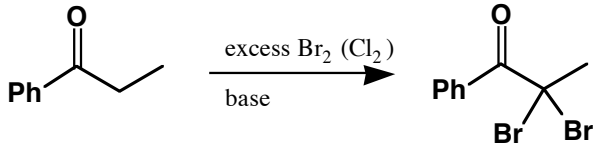
-Base-catalyzed keto-enol equilibrium
-know mech (either direction)
-know impact of substituents on enol concentration

2. 

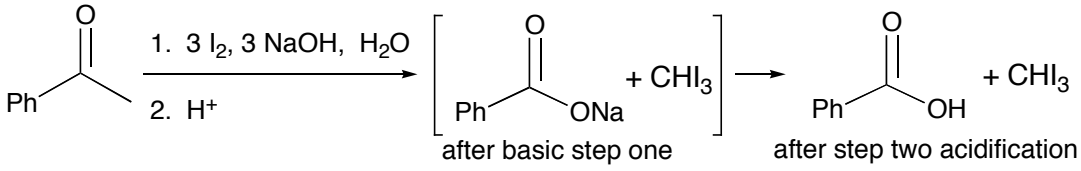
optically active racemic

-Racemization of α-chiral optically active carbonyls
-Mech

HALOGEN as ELECTROPHILE

3. 

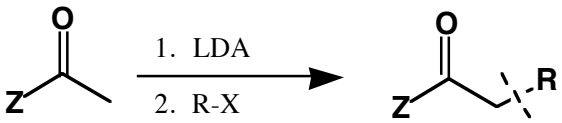
-Base catalyzed halogenation
-with excess halogen, all α-hydrogens get replaced
-Mech

4. 

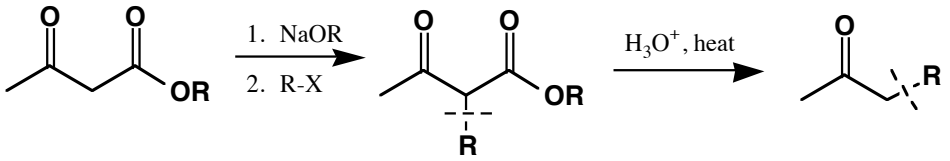
after basic step one after step two acidification

-Iodoform reaction.
-chemical test for methyl ketones

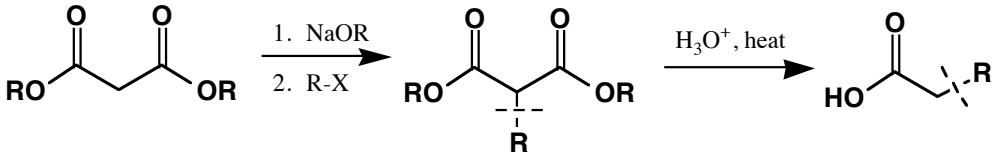
ALKYL HALIDE as ELECTROPHILE

6. 

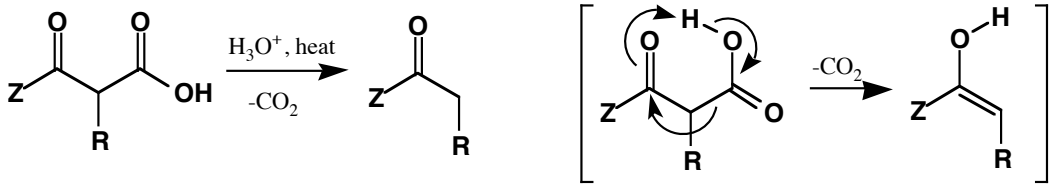
-Enolate alkylation
-strong LDA base required to completely deprotonate carbonyl
-Mech
-Ketones, Esters, Amides, Aldehydes: doesn't matter which kind of carbonyl
-unsymmetrical ketones give isomer problems
-S_N2 alkylation restricts R-X to active ones

7. 

-Enolate alkylation of 1,3-ketoester
-alkoxide base strong enough to completely generate enolate
-Mech for alkylation
-S_N2 alkylation restricts R-X
-position of alkylation is unambiguous
-acid-catalyzed hydrolysis/decarboxylation

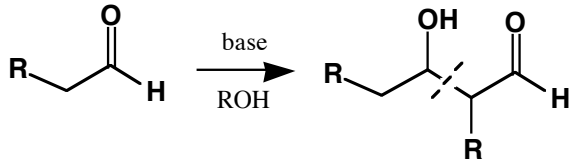
8. 

-Enolate alkylation of 1,3-diester
-alkoxide base strong enough to completely generate enolate
-Mech for alkylation
-S_N2 alkylation restricts R-X
-acid catalyzed hydrolysis/decarboxylation
-Final product is an ACID (Diester →Acid)

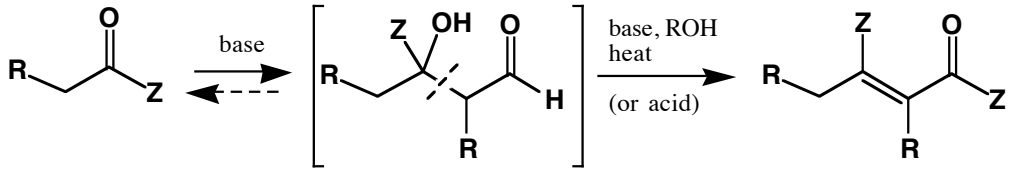
9. 

-decarboxylation of a 1,3-carbonyl acid
-"Z" can be anything so that you end with a ketone, aldehyde, or acid at the end
-know the mechanism for the decarboxylation, and acid-catalyzed enol to carbonyl isomerization
-rate will be impacted by stability of the enol intermediate

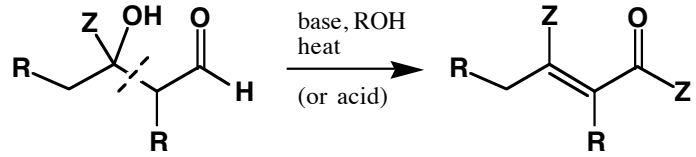
ALDEHYDE/KETONE as ELECTROPHILE

10. 

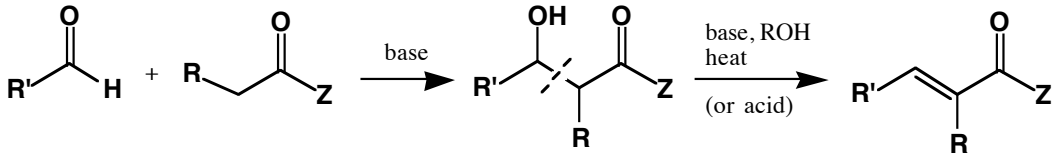
-Aldol Reaction
-Mech

11. 

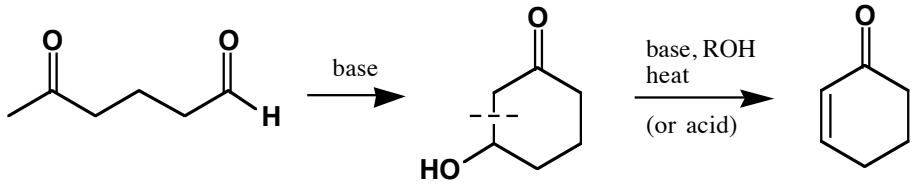
-Aldol Condensation
-Ketones as well as Aldehydes can be used
-In ketone case, unfavorable aldol equilibrium is still drawn off to enone
-In Aldehyde case, can stop at aldol if you don't heat
-Mech

12. 

-Aldol dehydration
-Mech under basic conditions

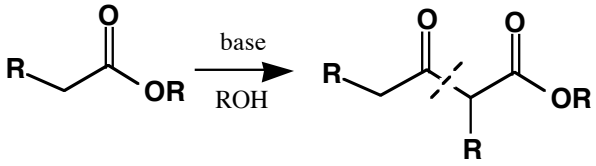
13. 

-Crossed Aldol (2 different carbonyls)
-Many variations, but there must be some differentiation so that one acts selectively as the enolate and the other as the electrophile
-Mech

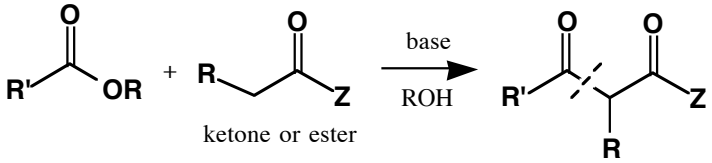
14. 

-Intramolecular aldol
-Mech
-many variations
-Normally only good for 5, 6-membered rings

ESTER as ELECTROPHILE

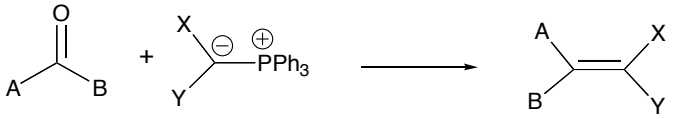
15. 

-Claisen Reaction
-Mech
-Produces 1,3-ketoester

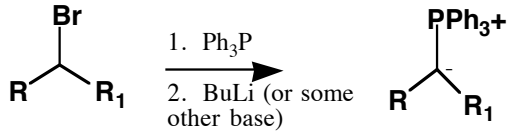
16. 

-Crossed Claisen
-May include cyclic Claisen reactions
-If the "enolate" carbonyl is a ketone, get a 1,3-diketone
-If the "enolate" carbonyl is an ester, get a 1,3-ketoester
-Mech

WITTIG REACTION

19. 

-Mech

20. 

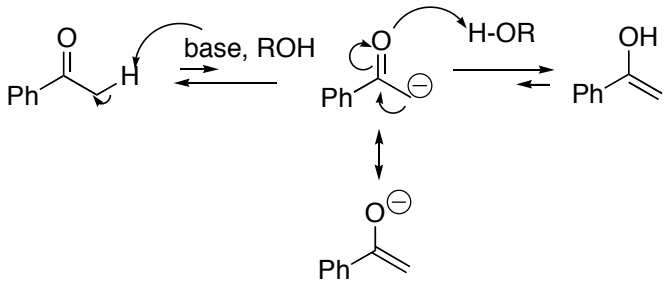
-Mech

Chem 360-Jasperse **Chapter 22 (Enolate Chemistry) Reaction Mechanisms Summary**

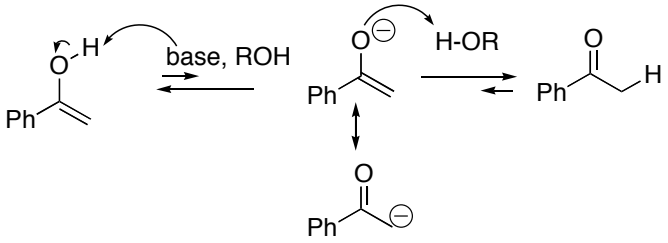
- Note: in many of these reactions, I simply write in "base". But for specific reactions, you need to recognize and specify the actual base that does the work.

PROTON as ELECTROPHILE

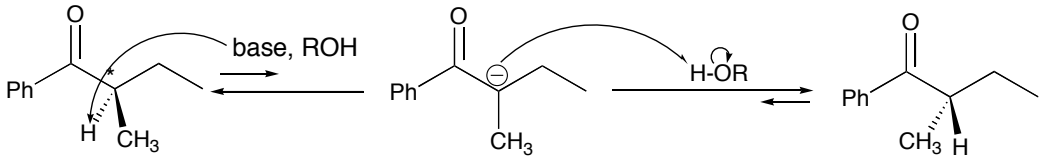
Ketone to Enol

1. 

Enol Back to Ketone:

1.-reverse 

Deprotonation/Reprotonation to Racemize an optically active α-chiral center

2. 

optically active

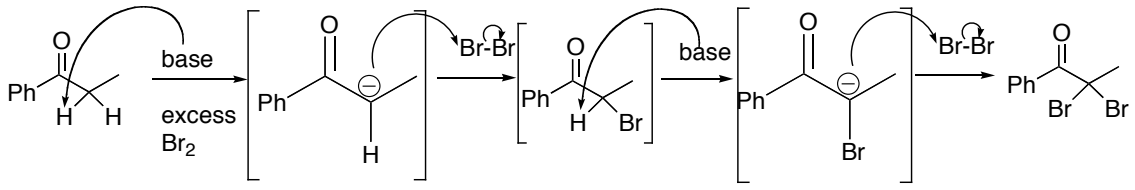
racemic

enantiomer or original. Protonation from the front gives enantiomer, from the back gives the original. The result is a 50/50 racemic mixture.

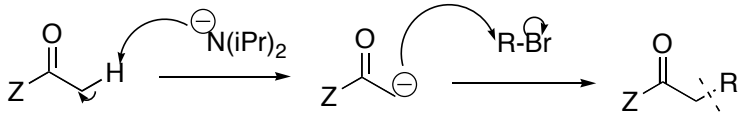
HALOGEN as ELECTROPHILE

Base catalyzed halogenation. Sequential deprotonation/halogenation until all the α-hydrogens are replaced.

- Note: addition of an electronegative, electron-withdrawing halogen stabilizes subsequent anion formation. As a result, the bromoketone formed after the first substitution is actually more acidic and therefore more reactive than the original ketone. For this reason you can't just stop with a single halogenation under base conditions. (But you can under acid conditions, via an enol rather than enolate mechanism.)

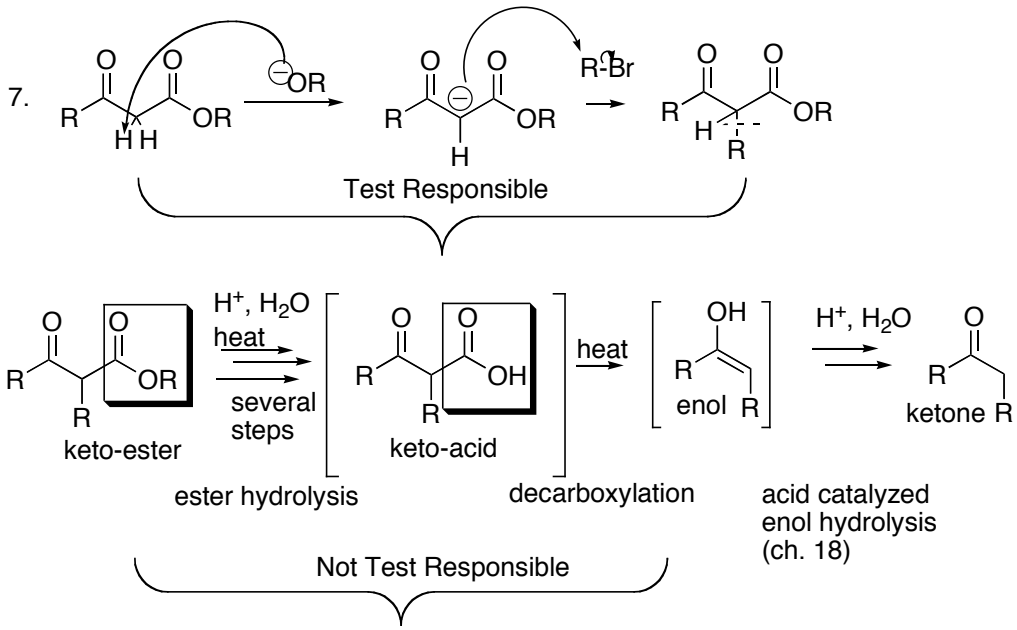
3. 

ALKYL HALIDE as ELECTROPHILE
With Strong LDA as Base, using a Monocarbonyl

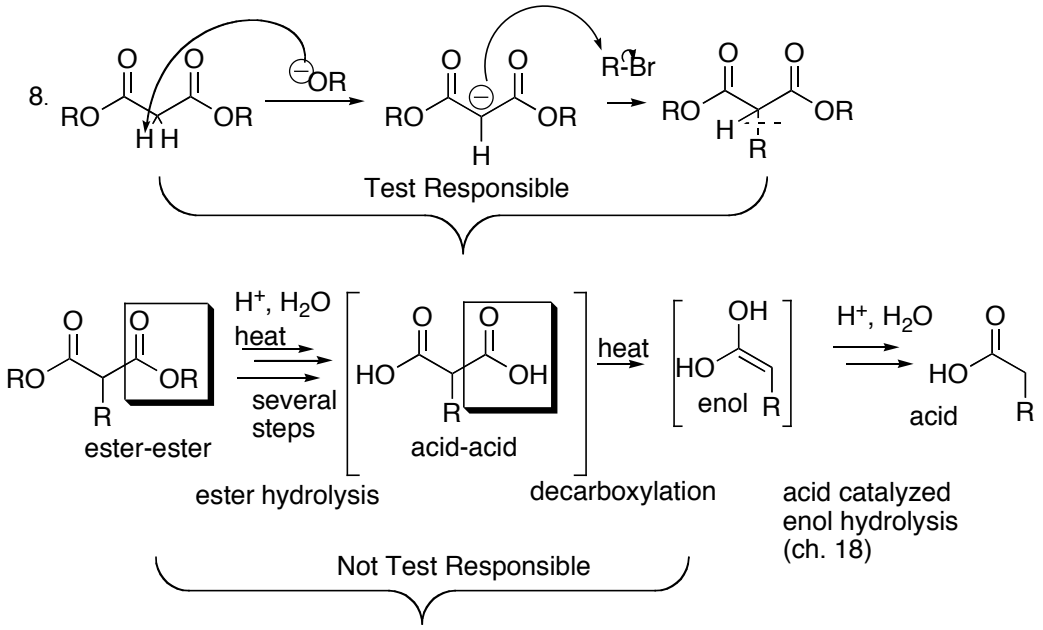
6. 

1. Z can be anything: works for ketones, esters, aldehydes, esters,…
2. "LDA" is lithium diisopropylamine, provides the nitrogen anion shown
3. strong LDA base required to completely deprotonate carbonyl. The base strength enables the enolate to form completely, no equilibrium or reversibility issues.
4. unsymmetrical ketones give isomer problems. If there are α-hydrogens on both left and right side of ketone, which will get deprotonated selectively?
5. S_N2 alkylation restricts R-X to active ones (ideally primary or allylic/benzylic…)
6. Sequencing: the LDA must be added first, allowing the enolate to form completely; then the alkyl halide is added subsequently. If you add the halide at the beginning, it reacts with LDA
7. LDA deprotonates the carbonyl rather than adding to the carbonyl carbon for steric reasons

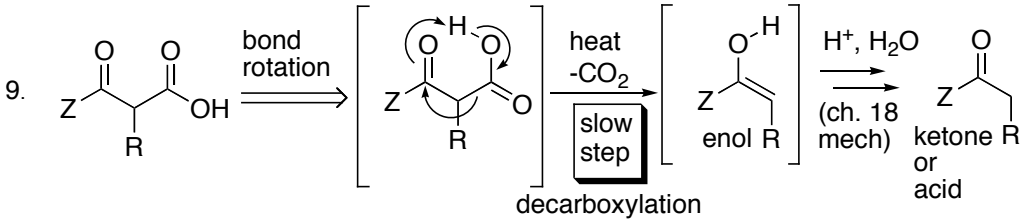
Using 1,3-Dicarbonyls, Such that Weaker Oxygen Bases are Strong Enough
Strong LDA as Base, using a Monocarbonyl

7. 

-alkoxide base strong enough to completely generate enolate
-S_N2 alkylation restricts R-X
-acid-catalyzed hydrolysis/decarboxylation
-not test responsible for the acid/catalyzed ester hydrolysis or the keto-acid decarboxylation mechanisms
-you are responsible for the acid-catalysis enol hydrolysis (not detailed here, but was in Ch. 18)



-alkoxide base strong enough to completely generate enolate
-S_N2 alkylation restricts R-X
-acid-catalyzed hydrolysis/decarboxylation
-not test responsible for the acid/catalyzed ester hydrolysis or the keto-acid decarboxylation mechanisms
-you are responsible for the acid-catalysis enol hydrolysis (not detailed here, but was in Ch. 18)

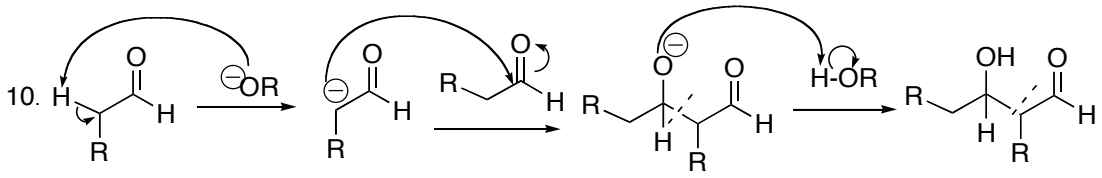


Not Fully Test Responsible. But must know that ENOL is key intermediate that forms in the slow step.
What is good for the enol (and it's alkene) accelerates the decarboxylation

-decarboxylation of a 1,3-carbonyl acid
-"Z" can be anything so that you end with a ketone, aldehyde, or acid at the end
-rate will be impacted by stability of the enol intermediate (more highly substituted enol alkene is better; conjugated enol alkene will form faster….)
-since the mechanism depends on the conversion of the left carbonyl into an enol, decarboxylations are limited to 1,3-carbonyl acids. If you have a 1,2-carbonyl acid or a 1,4-carbonyl acid (etc), the formation of an enol will not be possible and the decarboxylation will not occur

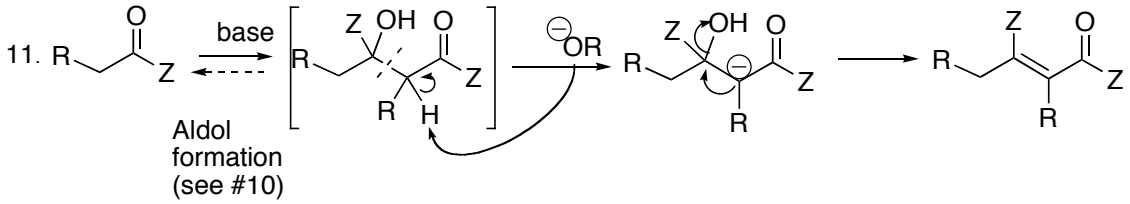
ALDEHYDE/KETONE as ELECTROPHILE

Simple Aldol Reaction, giving a β-hydroxy-carbonyl. In which the same carbonyl functions as both enolate precursor and electrophile.



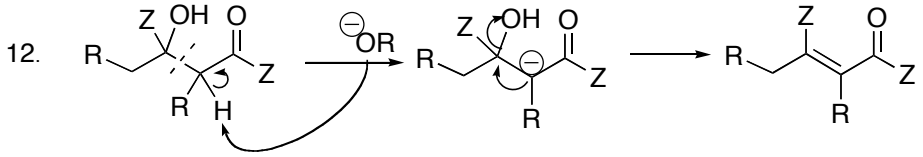
-Deprotonate-react-protonate
-Notice in this case that it's the same carbonyl that functions as both the enolate precursor but also as the electrophile.

Aldol Condensation, giving an enone. In which the initial aldol product undergoes dehydration.



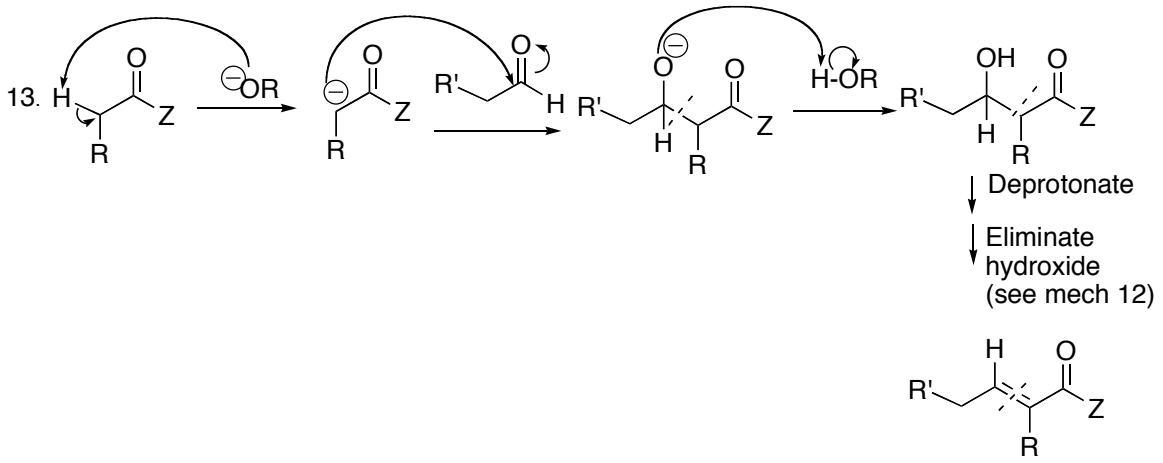
-The aldol product is formed as shown in mechanism 10. But under extended opportunity or heat, the product β-hydroxy group is eliminated to give the enone.
-The elimination mechanism involves deprotonation to enolate, followed by hydroxide extrusion
-Ketones as well as Aldehydes can be used
-In ketone case, unfavorable aldol equilibrium is still drawn off to enone
-In Aldehyde case, can stop at aldol if you don't heat and/or if you stop quickly enough

General Dehydration of β-hydroxy Carbonyls to Give α,β-unsaturated carbonyls



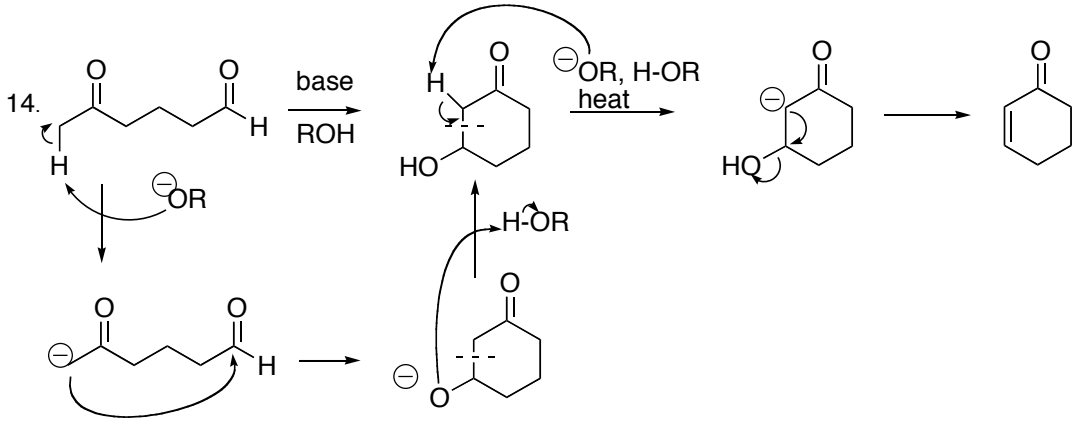
-Aldol dehydration
-Mech under basic conditions
- β-hydroxy Carbonyls can also eliminate water to give enones under acid conditions, via a different mechanism.

Crossed Aldol Reaction, in Which One carbonyl compound serves selectively as the Enolate Precursor and a different one (usually aldehyde) as the electrophile



-Crossed Aldol (2 different carbonyls)
-Many variations, but there must be some differentiation so that one acts selectively as the enolate and the other as the electrophile
-because aldehydes are so much more reactive as electrophiles, and because ketones are so much weaker as electrophiles and even when they do function as electrophiles the addition is reversible, crossed aldols between ketones and aldehydes work well, with the ketone reacting as the enolate and the aldehyde as the electrophile.
-The mechanisms for the addition and also the subsequent possibly dehydration are essentially the same as for reactions 10-12.

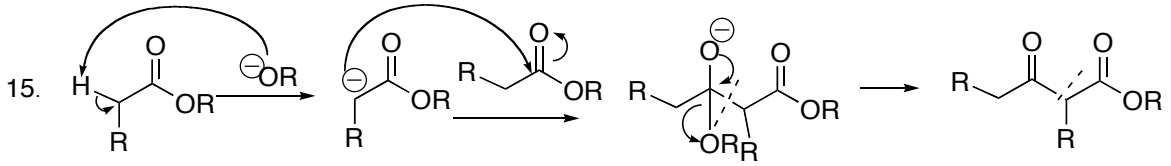
Aldol Cyclization: Basically a crossed aldol reaction in which both carbonyls are tied together, and in which aldol reaction results in formation of a cyclic rather than an acylic β-hydroxy carbonyl



-Intramolecular aldol
-many variations
-Normally only good for 5, 6-membered rings
-There are often multiple α-hydrogens that can give multiple different enolates. But since enolate formation is reversible, reaction proceeds via the enolate that can:
react with the best electrophile. (Aldehyde rather than a ketone), and react to give the best ring size (5 or 6 membered rings >>> 7-membered rings >> 3-, 4-, or ≥8-membered rings)

ESTER as ELECTROPHILE

Simple Claisen Reaction, giving a β-ketoester. In which the same ester functions as both enolate precursor and electrophile.

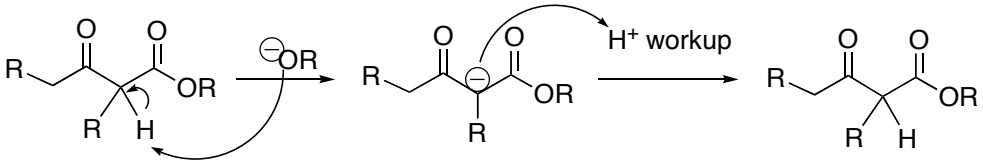
15. 

-Produces 1,3-ketoester

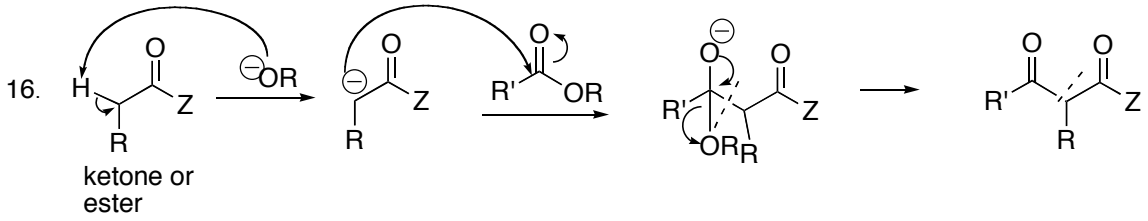
-The alkoxide used as base should match the R-group found in the ester. For example, if the ester OR group is OMe, then the base should be NaOMe/MeOH. If the ester OR group is OEt, then NaOEt/EtOH should be used, etc.

-Following enolate addition, the tetrahedral intermediate is *not* stable, and eliminates alkoxide to regenerate the carbonyl.

-Note: Under basic reaction conditions, the keto-ester is normally deprotonated to a stabilized enolate. Following acidic workup, the enolate is reprotonated to give the actual keto-ester product. The enolate formation is actually crucial, because it "protects" the ketone from nucleophilic attack.



Crossed Claisen Reaction, giving either a β-ketoester or a 1,3-diketone. In which either a ketone or an ester functions as the enolated precursor, and a different ester functions as electrophile.

16. 

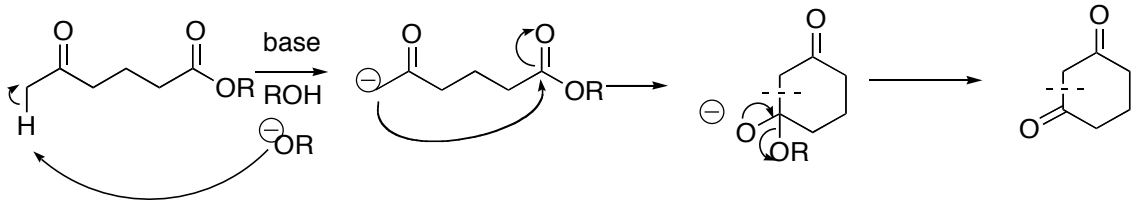
-Crossed Claisen

-If the "enolate" carbonyl is a ketone, get a 1,3-diketone

-When ketones and esters are mixed, the ketone usually functions as the enolate and the ester as the electrophile, because a) the ketone is more acidic, so makes enolate more easily, and b) addition/elimination to the ester is irreversible, whereas addition to ketone is reversible

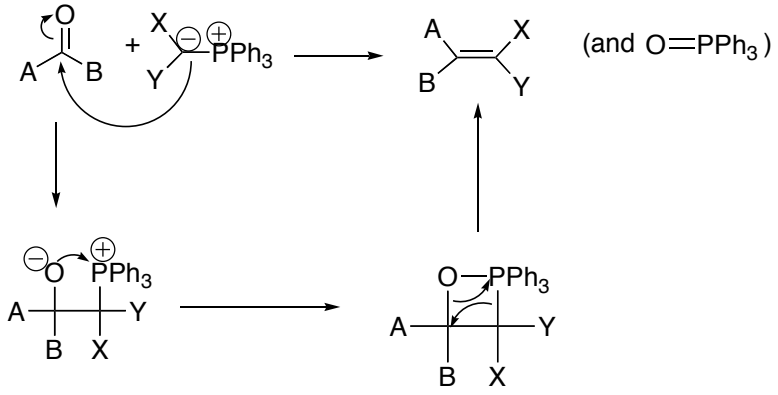
-If the "enolate" carbonyl is an ester, get a 1,3-ketoester. These work best if only one of the esters has α-hydrogens, so that you have just one enolate available.

-May include cyclic Claisen reactions (see example below)

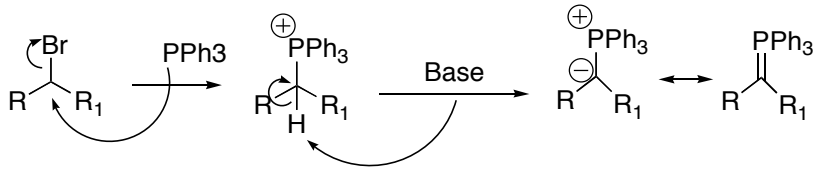


WITTIG REACTION

19.



20.

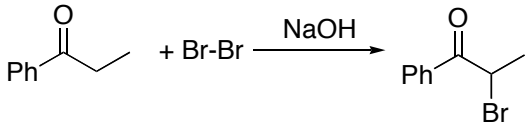


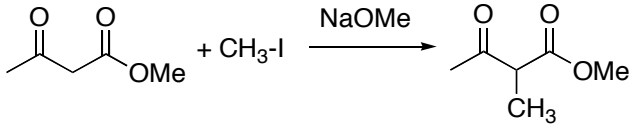
Ch. 22 Additions and Condensations of Enols and Enolate Ions

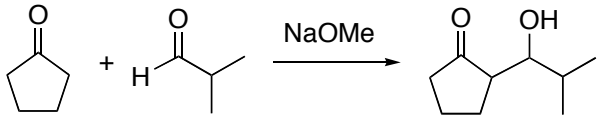
A. Intro: What is in Common for the Following Reactions, and How Do They Work?

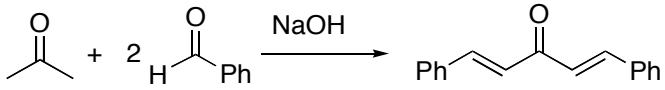
- **You should eventually be able to draw the mechanism for these (and other) reactions…**

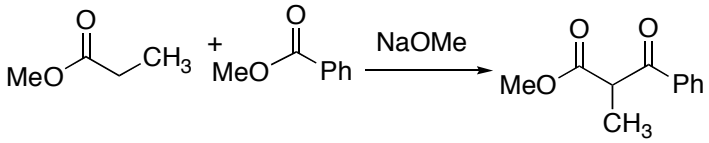
Key Intermediate

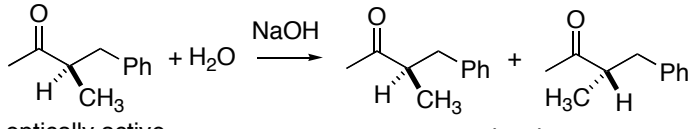
1 

2 

3 

4 

5 

6 

optically active racemic mixture

Things in Common **KEY:**

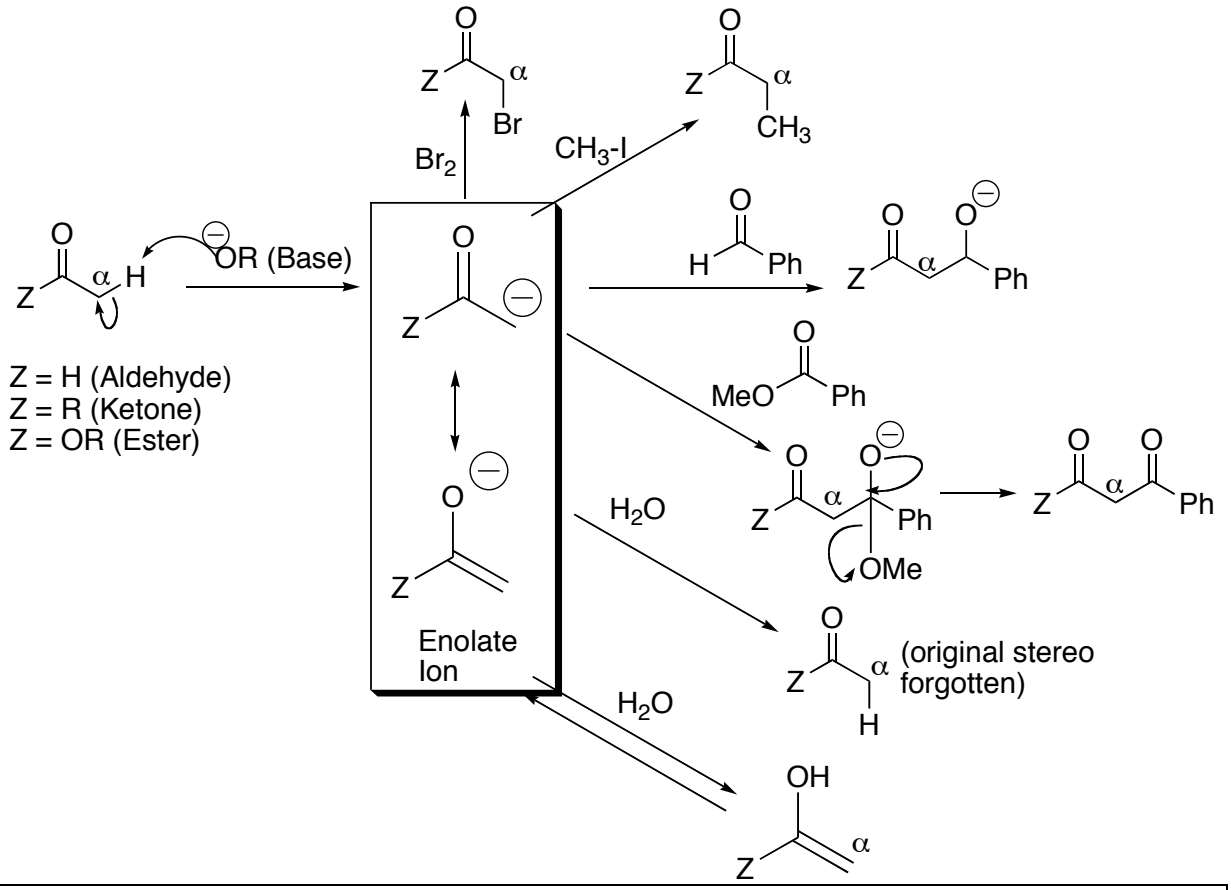
1.

2.

3.

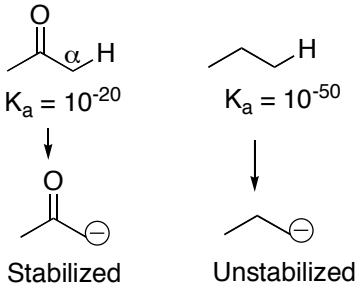
4.

TYPICAL MECHANISM: Via ENOLATE Anion



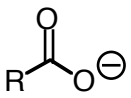
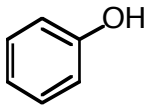
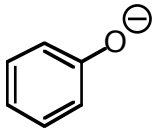
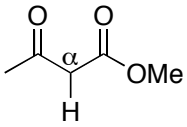
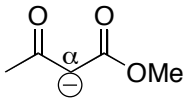
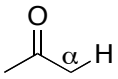
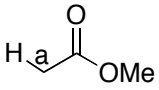
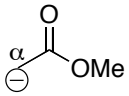
Under base conditions, a carbonyl compound with an α-hydrogen can be deprotonated to give a resonance-stablized, delocalized "enolate" anion, which is nucleophilic at the α-carbon.

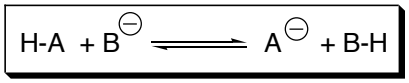
- Normal C-H bonds are very non-acidic. But C-H bonds α to a carbonyl are much more acidic because the resulting anion is resonance stabilized and is shared by the oxygen.



- The α-carbon has two other attachments in addition to the carbonyl and the H shown in this page. The other attachments will remain attached as spectators, and need to be accounted for in drawing products.
- α-Hydrogens are only slightly less acidic than is water or alcohol hydrogens

- **B: Acid/Base Considerations (Sections 22.2, 15) Acidity Table**

Class	Structure	Ka	Acid Strength	Anion	Base Strength
Strong Acids	H-Cl	10^{2}		$Cl^{\ominus}$	
Carboxylic Acid		10^{-5}			
Phenol		10^{-10}			
1,3-Dicarbonyl		10^{-12}			
Water	HOH	10^{-16}		$HO^{\ominus}$	
Alcohol	ROH	10^{-17}		$RO^{\ominus}$	
Ketones and Aldehydes		10^{-20}			
Ester		10^{-24}			
Amine (N-H)	$(iPr)_2N$-H	10^{-33}		$(iPr)_2N^{\ominus}Li^{\oplus}$ "LDA"	
Alkane (C-H)	RCH_3	10^{-50}		$RCH_2^{\ominus}$	

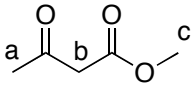


Relative stability of anions dictates equilibrium

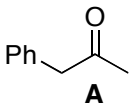
Notes to remember

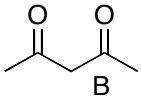
1. Carbonyls acidify α-H's (anion stabilized)
2. 1,3-Dicarbonyls are much more acidic than monocarbonyls (anion is more stabilized)
3. Ketones are more acidic than esters
4. A "lower" anion on the chart can favorably deprotonate any acid that's "higher" on chart. Because any acid-base equilibrium will always favor the more stable anion.
5. "LDA" is strong enough to **completely** deprotonate **ketones**, **esters**, or 1,3-dicarbonyls
6. NaOH, NaOR can **completely** deprotonate a 1,3-dicarbonyl (but not ketones or esters)
7. NaOH, NaOR do **not** completely deprotonate ketones or esters, but do provide a usable equilibrium supply of the enolate that can procede to product in some reactions.

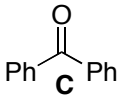
1. Rank the acidity of the hydrogens at the labeled positions, 1 being most acidic. Draw the three anions that would result from deprotionation at the three spots, and any pertinent resonance structures.

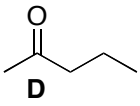


2. For the following compounds, record to what degree they would be deprotonated by $NaOCH_3$ or LDA [$LiN(iPr)_2$] respectively. The basic choices are "totally" (>98%), "zero" (no enolate whatsoever) or "slightly" (definitely some equilibrium amount, but <10%).







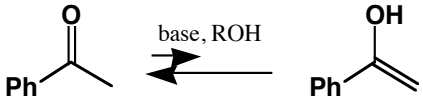


LDA:

NaOMe:

C. Enolates and Enols: Protons as Electrophile (22.2)

PROTON as ELECTROPHILE

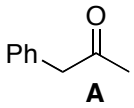
1. 

-Base-catalyzed keto-enol equilibrium
-know mech (either direction)
-know impact of substituents on enol concentration

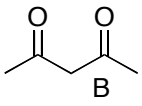
Notes:

1. Rapid equilibrium exists between the keto and the enol form
2. Both acid and base catalyze the equilibrium
3. All carbonyls with α-hydrogens can equilibrate with enols
   - But if there are no α-hydrogens, a carbonyl can **not** have any enol (or enolate!)
4. Ranking the population of enol:
   a. Normally, <5% enol will be present in solution, and >95% will be in the ketone form
   b. No α-hydrogens → no enol
   c. Two factors can stabilize enols and enrich the equilibrium enol population
      - Hydrogen bonding of the enol O-H to some other heteroatom (stabilizing)
      - Conjugation of the enol alkene (stabilizing)

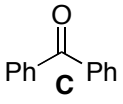
1. For the following compounds, draw the best possible enol (if any) rank them according to which would have the greatest amount of **enol isomer** present at equilibrium, 1 being most.



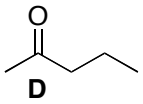
A



B



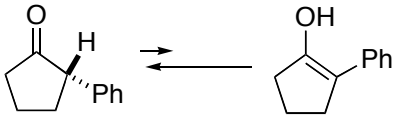
C



D

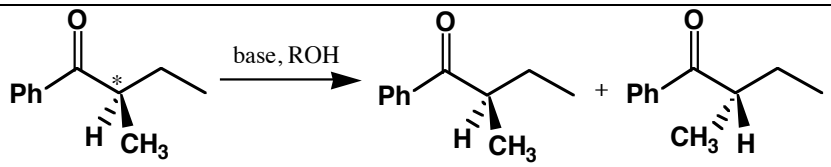
Mechanism for Base-Catalyzed Keto-Enol Equilibration:

2. Keto-Enol Mechanisms (use hydroxide as base, but many bases will do…)
   a. Draw the mechanism for conversion of the keto form to the enol form

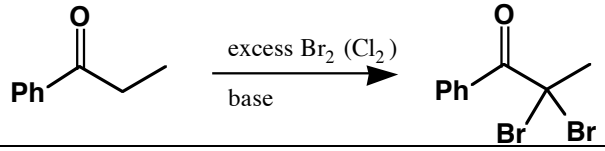


   b. Draw the mechanism for conversion of the enol form to the ketone

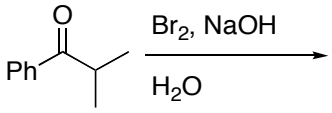
Racemization of α-chiral Compounds via Enolates

2.  optically active racemic	-Racemization of α-chiral optically active carbonyls -Mech

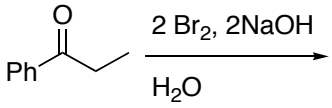
D. Halogen Electrophiles (22.3) (Skip 22.4)

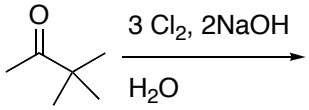
HALOGEN as ELECTROPHILE	-Base catalyzed halogenation -with excess halogen, all α-hydrogens get replaced -Mech
3. 	

1. Draw the product and mechanism for the following



2. Draw products for the following reactions





<u>Polyhalogenation versus monohalogenation</u>

- Under base conditions, if you add only one equivalent of Br_2 (or Cl_2) when an α-carbon has more than one α-hydrogen, clean mono-halogenation (product **B**) does not occur
- Instead messy mixtures result
- The major product is polyhalogenated (**C**), combined with a bunch of unreacted starting material (**A**)
- Why? Because the electron-withdrawing halogen makes product **B** more acidic (resulting in faster enolate formation) than the starting material **A**

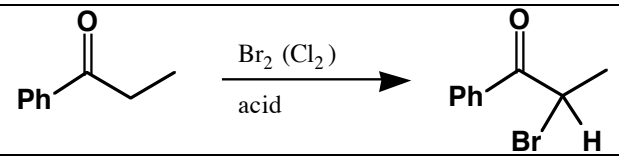
less reactive toward enolate formation

A
45%
less reactive toward enolate formation

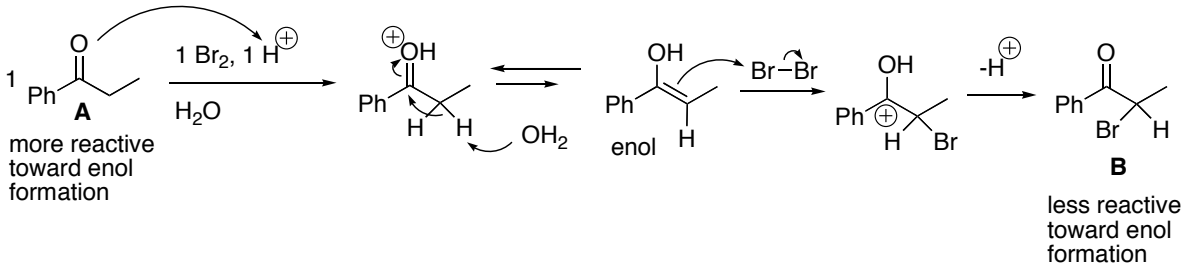
B
10%
more reactive toward enolate formation

C
45%

Acid-Catalyzed Monohalogenation (not for test)

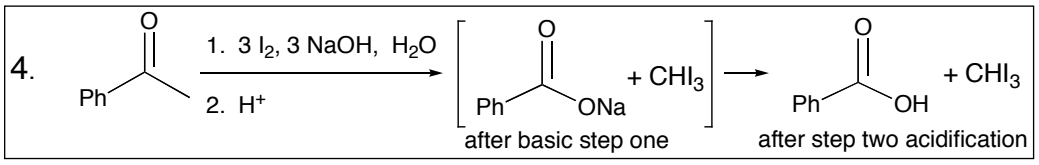
5. 		-Acid-catalyzed halogenation -can achieve selective mono-halogenation -No Mech required

- Under acid conditions, a very different mechanism takes place which allows clean mono-halogenation to proceed
- Enol mechanism (not for test)
- Cationic mechanism
- An electron-withdrawing anion stabilizes and accelerates enolate formation, but destabilizes and decelerated enol formation

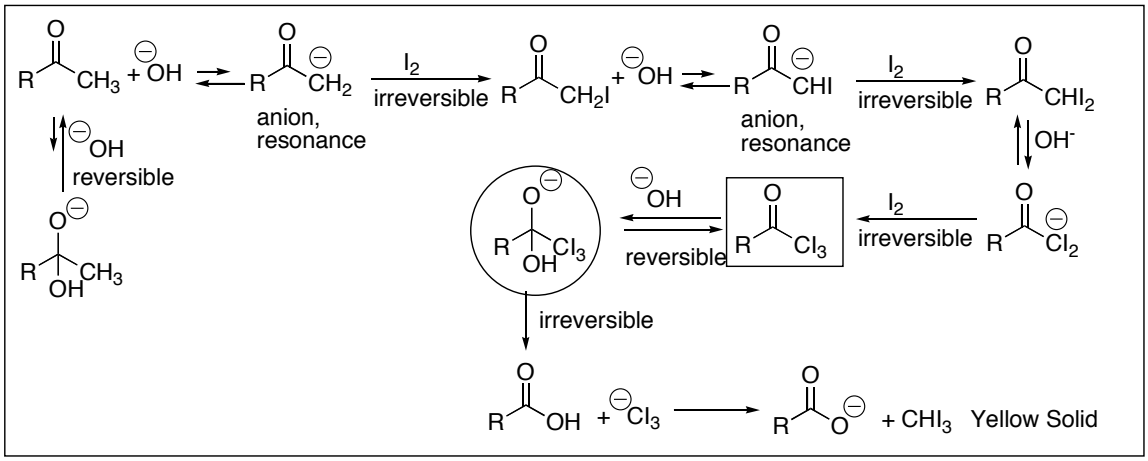


The Iodoform Reaction:

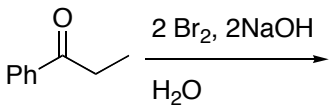
- A Chemical Test for methyl ketones (unknowns problems)
- A synthetic technique for converting methyl ketones to carboxylic acids

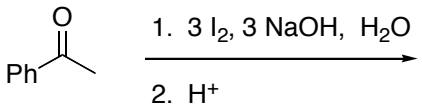


- You lose one carbon
- This only works for methyl ketones
- The chemical test involves formation of CHI_3 (iodoform), which is a yellow precipitate (and smelly)
- Mechanism (not for test):



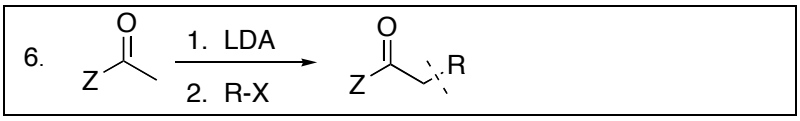
1. Draw products for the following reactions





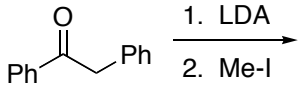
E. Enolate Alkylation: Alkyl Halides or Tosylates as Electrophiles

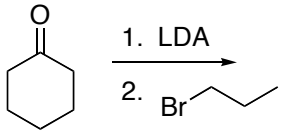
Alkylation of Monocarbonyls: Use strong, bulky LDA [$LiN(iPr)_2$] as base

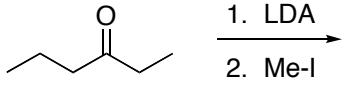


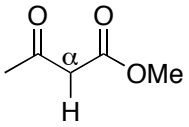
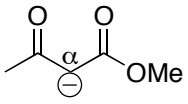
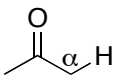
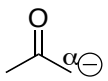
1. S_N2 alkylation reaction restricts R-X (or ROTs) to active, 1º electrophile
2. Ketones, Esters, Amides, Aldehydes all work, so long as they have an α-hydrogen that can be deprotonated
   - For unsymmetrical ketones, isomer problems can occur (which enolate forms?)
3. Predict the products: Attach the electrophile R group to the α-carbon
   - This is a substitution reaction: α-C-H + R-X → α-C-R
4. Mechanism: Deprotonate first, add the electrophile second
   - Treat LDA as $\ominus NR_2$

Practice: Draw products and mechanisms for the following alkylation reactions.

1. 

2. 

3. 

Class	Structure	Ka	Acid Strength	Anion	Base Strength
1,3-Dicarbonyl		10^{-12}			
Water	HOH	10^{-16}		$HO^{\ominus}$	
Alcohol	ROH	10^{-17}		$RO^{\ominus}$	
Ketones and Aldehydes		10^{-20}			
Amine (N-H)	$(iPr)_2N$-H	10^{-33}		$(iPr)_2N^{\ominus}Li^{\oplus}$ "LDA"	

For Monocarbonyls, why must we use LDA as base, rather than a normal oxygen base (NaOH or $NaOCH_3$) or a simpler Nitrogen base ($NaNH_2$)?

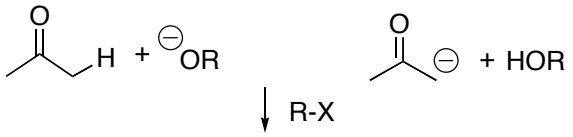
LDA is strong and bulky

1. Base Strength: the LDA base must be strong enough to **completely** deprotonate the carbonyl before the electrophile is added

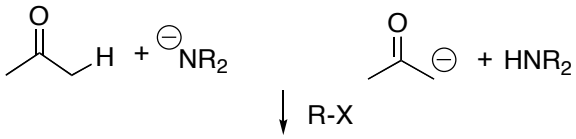
- With oxygen bases, the equilibrium favors the oxygen anion rather than the enolate, and it's just the oxygen anion which attacks the electrophile

For the following, which side would the equilibrium favor, and what product(s) would form?

Oxygen Base



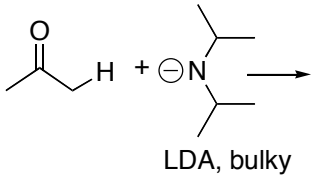
Nitrogen Base



2. Base size: A bulky base favors deprotonation over nucleophilic attack

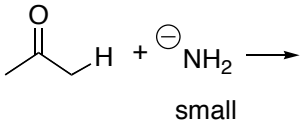
- Comparable to E2 versus S_N2 competition

Bulky Base (LDA)



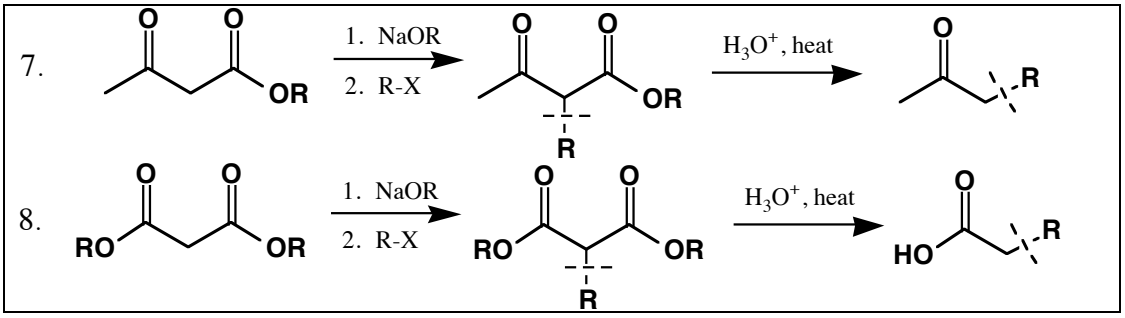
LDA, bulky

Small Base



small

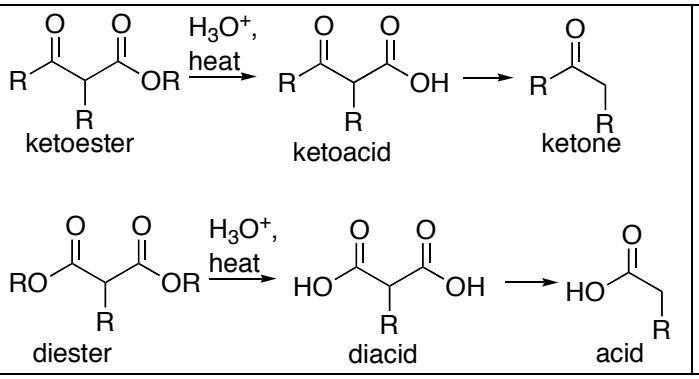
Alkylation of 1,3-dicarbonyls: Now oxygen bases are fine



Stage One: Alkylation of a 1,3-Dicarbonyl

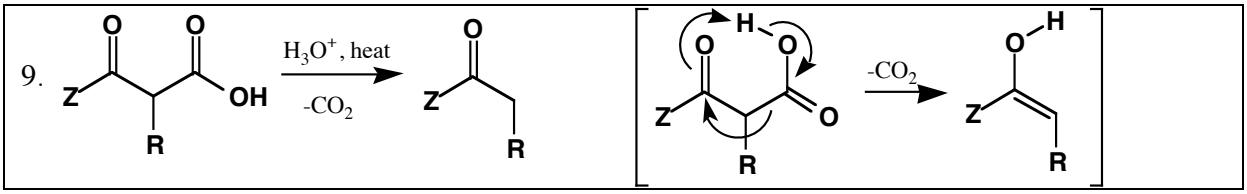
1. S_N2 alkylation reaction restricts R-X (or ROTs) to active, 1º electrophile
2. The dicarbonyl can be a 1,3-diketone, a 1,3 ketoester, or a 1,3-diester
3. Predict the products: Attach the electrophile R group to the α-carbon
4. Position of alkylation is unambiguous: in between the two carbonyls
5. Mechanism: Deprotonate first, add the electrophile second
   - $\ominus$ OR bases are fine, no need for LDA

Stage Two: Acid/water hydrolysis of any esters, and decarboxylation of 1,3-carbonyl acids



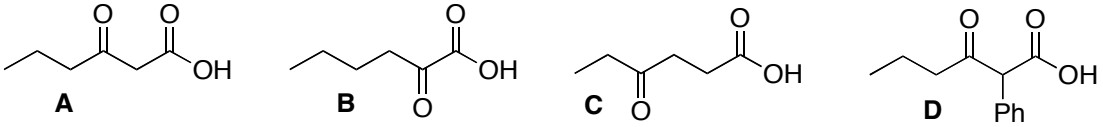
1. Upon treatment with H_2O/H^+, any esters hydrolyze to carboxylic acids

2. Under heat conditions, a 1,3-carbonyl acid (whether ketoacid or diacid) loses one CO_2 via an enol mechanism

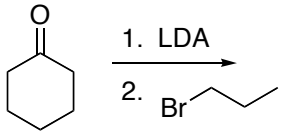


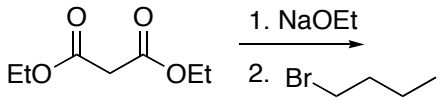
1. Decarboxylation of a 1,3-carbonyl acid
2. "Z" can be anything so that you end with a ketone, aldehyde, or acid at the end
3. Mechanism responsibility
   a. Be able to write the acid-catalyzed enol to carbonyl isomerization (see chapter 18)
   b. Know that an enol is involved in the rate-determining step
      - -rate will be impacted by stability of the enol intermediate
        1. conjugation of the enol alkene will help
        2. hydrogen-bonding of the enol O-H will help

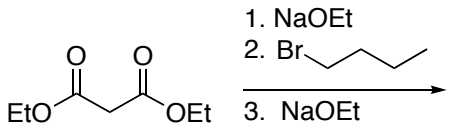
1. Which of the following would undergo decarboxylation? And which would go fastest?

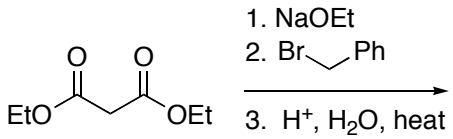


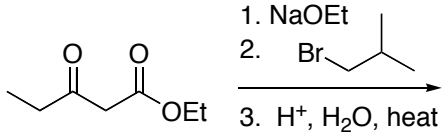
Draw products for the following alkylation reactions, often involving ester hydrolyses and thermal decarboxylations.

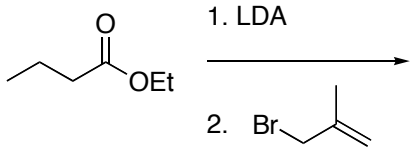
2. 

3. 

4. 

5. 

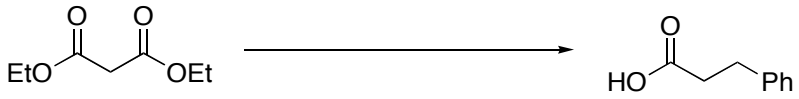
6. 

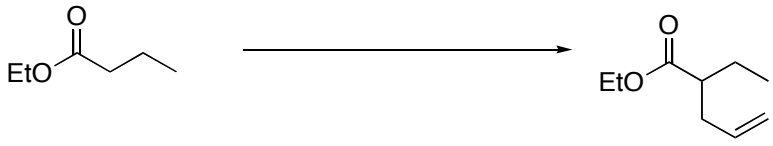
7. 

Some Synthetic Strategy Tips

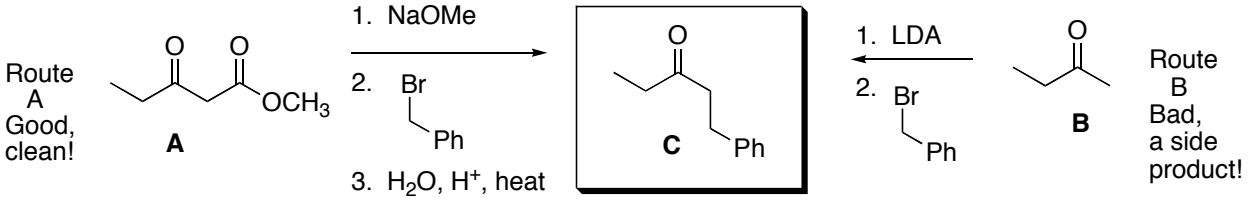
- Alkylation resulting eventually in an **acid**: from 1,3-diester, via NaOR, then subsequent ester hydrolysis/decarboxylation
- Alkylation resulting eventually in a **mono-ester**: from ester using LDA
- Alkylation resulting eventually in a **mono-ketone**, where unambiguous deprotonation was possible: from ketone using LDA
- Alkylation resulting in a **mono-ketone**, where unambiguous LDA deprotonation would not have been possible: from keto-ester using NaOR, then subsequent ester hydrolysis/decarboxylation

Provide reagents for the following:

8. 

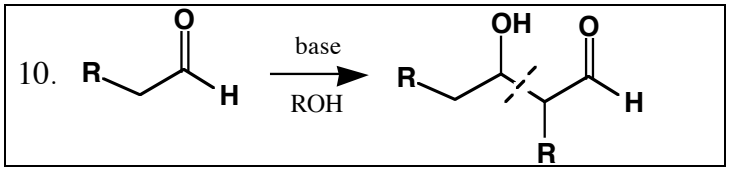
9. 

10. Shown below are two possible precursors **A** and **B** for making target ketone **C**. One works well, the other has a problem. Which is the good precursor, and which precursor/route will have problems?

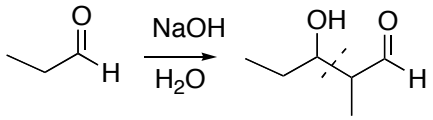


F. Aldehydes or Ketones as Electrophiles: The Aldol Reaction (22.7-11)

The basic aldol reaction: in which the same aldehyde functions as both enolate and electrophile, and in which a β-hydroxyaldehyde is produced.



1. Try to draw the mechanism for the following.

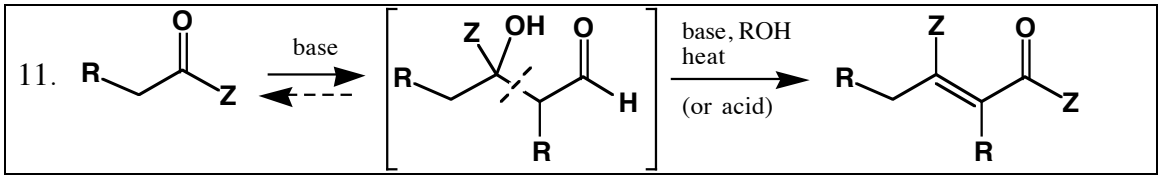


Notes:

a. Product: β-hydroxycarbonyl
b. One carbonyl converts to an enolate, another in its neutral form functions as electrophile
   - with oxygen anion as base, most carbonyl is in neutral form, only a small equilibrium population of enolate anion at any time.
c. Products and spectators: The α-carbon loses an H to make the enolate, but otherwise both the enolate and the electrophile retain all their spectator attachments
d. 3-step mechanism: deprotonate (to make enolate) – react (with electrophile) – protonate
   - the react-protonate steps are like normal Grignard addition-protonation
e. Aldol formation is reversible: favorable equilibrium for aldehydes, not for ketone

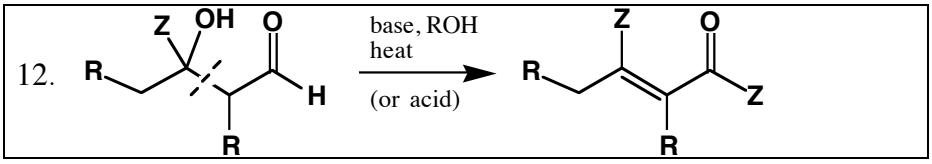
- With ketones, either you don't isolate β-hydroxycarbonyl. Either you proceed on to alkene (see below) or else you just recover starting ketone

Aldol Condensation: In which a β-hydroxycarbonyl is formed but then is pushed on via loss of H and OH to produce an "enone" (α,β-unsaturated carbonyl)



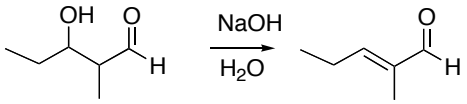
a. Elimination is irreversible
b. Ketones as well as Aldehydes can be used
   - In ketone case, unfavorable aldol equilibrium is still drawn off to enone
c. In Aldehyde case, can stop at aldol if you don't heat
   - To force toward the enone, give extra time or extra heat
d. Two a-hydrogens must be available for removal; otherwise product retains all spectators
e. Mechanism required

General Process for Dehydration of β-Hydroxy Carbonyl Compounds

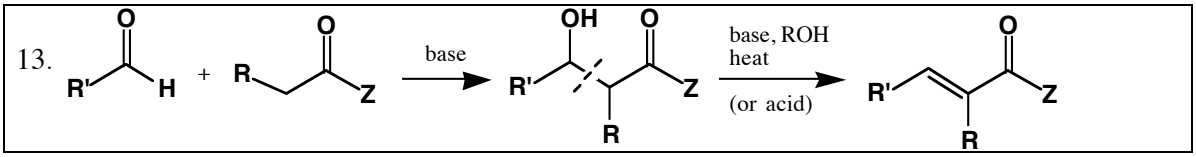
12. 

- We will focus on the base/enolate mechanism
- But this elimination is also possible using acid catalysis, via a different mechanism

1. Try to draw the mechanism for the following.

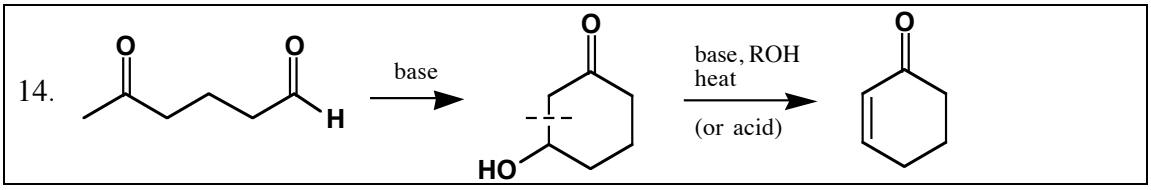


Crossed Aldol Reactions: Using 2 Different Carbonyls, One of Which Functions as Neutral Electrophile (normally an aldehyde) and the Other as the Nucleophilic Enolate

13. 

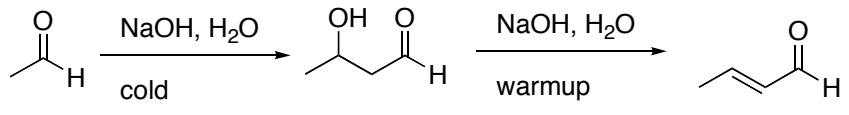
a. Mechanisms required
b. Many variations, but there must be some differentiation so that one carbonyl acts selectively as the enolate and the other as the electrophile
    1. If one carbonyl lacks any α-hydrogens, it can't be converted to nucleophile and can only function as electrophile
    2. Aldehydes are much better electrophiles than ketones
        - When ketones do function as electrophiles in aldol reactions, the reactions usually just reverses itself anyway
    3. Sometimes conjugation favors formation of one enolate over another

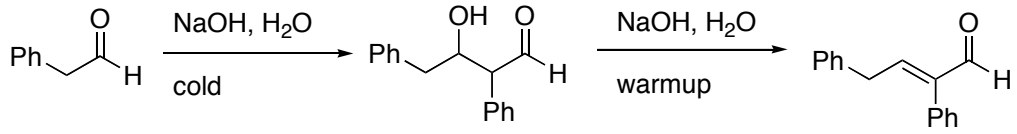
Ring-Forming Aldol Reactions

14. 

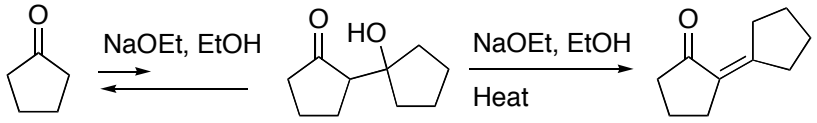
a. Intramolecular crossed aldol reactions
b. Electrophile: if one of the carbonyls is an aldehyde, it will function as the electrophile
c. Normally only good for 5, 6-membered rings
    - If more than one enolate can form, use the one that could produce a 5- or 6-ring

Aldol Examples: Aldehydes/Ketones as Electrophiles

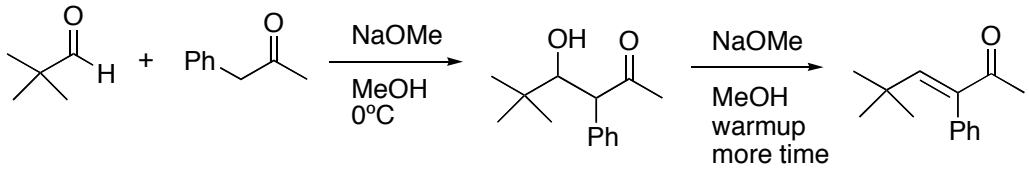
1. 

2. 

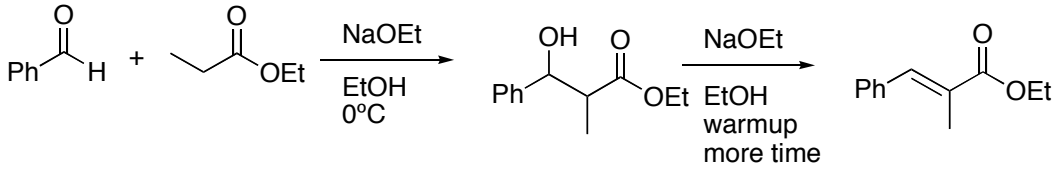
- With aldehydes, you can usually stop at the β-hydroxy carbonyl stage or proceed on to the α,β-unsaturated carbonyl, depending on time and temperature.

3. 

- With ketones as electrophiles, the aldol reaction to give the β-hydroxy carbonyl is normally reversible with an unfavorable equilibrium. However, while it is not possible to isolate high yields of the β-hydroxy ketone, further dehydration to give the enone is irreversible and can give good yields of the enone.

4. 

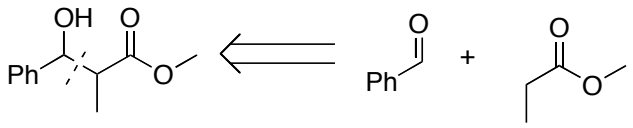
- With two different carbonyl compounds, one must function selectively as the enolate precursor, and the other as the electrophile.
- Since aldehydes are much more electrophilic, when mixed with a ketone **<u>the aldehyde will always be the electrophile</u>**
- If there are more than one site where an enolate might form, the most acidic site that would give a stabilized anion will form preferentially

5. 

<u>Comments</u>

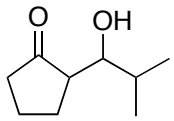
- Basic
- One carbonyl functions as the enolate nucleophile, a second carbonyl as the neutral electrophile. The enolate precursor and the electrophile carbonyl may be the same (examples 1-3) or different (examples 4 and 5)
- Loss of an α-H, replaced by an α,β C-C bond.

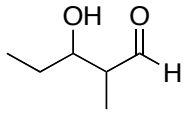
All of the following molecules can be made by an aldol-type reaction or an aldol-type condensation (aldol followed by loss of H_2O). Draw the carbonyl compound or compounds from which each is derived.

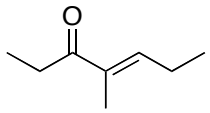
example: 

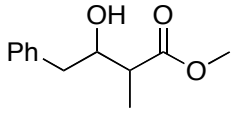
Strategy:

- Identify the carbonyl in the product, and mark off which are the α and β carbons. **The key bond connection will have been between the α and β carbons**.
- β was originally a carbonyl (the electrophile carbonyl)
- α originally had H's (it was the enolate carbanion)
- Note: **any attachments on the α and β carbons are spectators**. If they are there at the end, they must have been attached at the beinning!

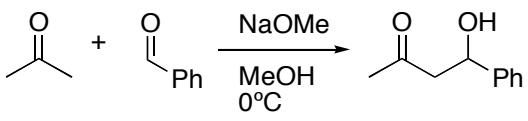
2. 

3. 

4. 

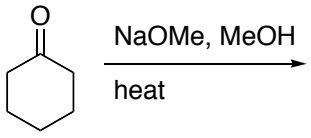
5. 

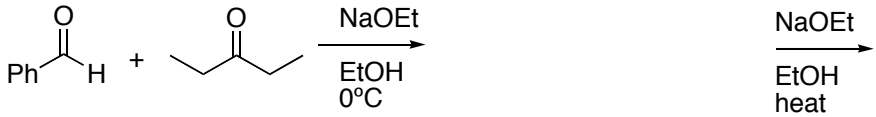
6. Draw the mechanism for the following reaction.

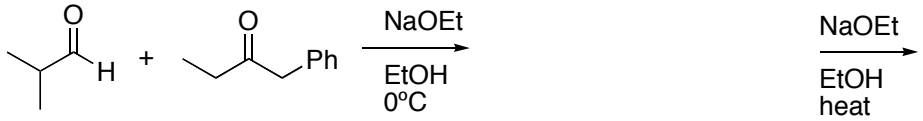


Provide products for the following aldol reactions.

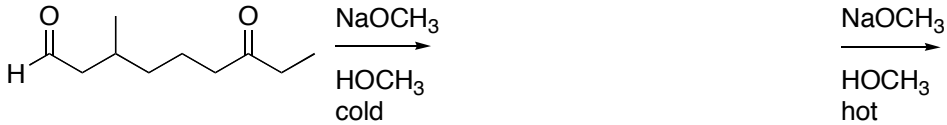
7. 

8. 

9. 

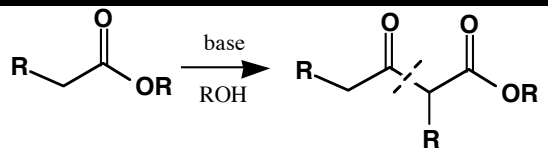
10. 

11. 

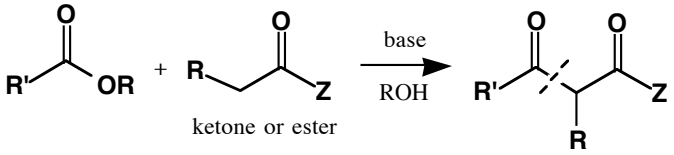
12. 

13. Draw the mechanism for phase one and then phase two of the reaction in problem 10.

G. Esters as Electrophiles. The Claisen Reaction. (22.12-14)

15. 

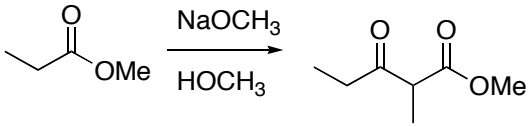
-Claisen Reaction
-Mech
-Produces 1,3-ketoester

16. 

-Crossed Claisen
-May include cyclic Claisen reactions
-If the "enolate" carbonyl is a ketone, get a 1,3-diketone
-If the "enolate" carbonyl is an ester, get a 1,3-ketoester
-Mech

Mechanism: enolate formation – addition to ester carbonyl – elimination of alkoxy anion

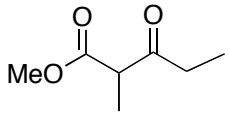
1. Draw the mechanism for the following reaction. (Claisen reaction).

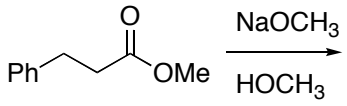


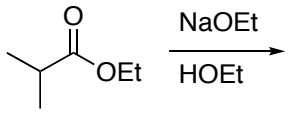
Notes

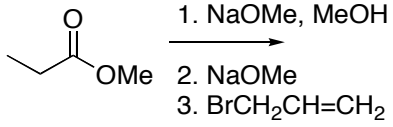
a. Product: β-keto ester (or ketone). The β-carbonyl was an ester, and the α-carbon was enolate
b. In actual laboratory, an acid workup is always required
   - The product, which has a 1,3-dicarbonyl, is actually more acidic than anything else, so it also gets deprotonated to the enolate; acid required to reprotonate it
   - The enolate of a 1,3-dicarbonyl is too stable to attack esters, so it doesn't compete as a nucleophile
c. Mechanism: does **not** involve direct S_N2 displacement on ester; addition to the carbonyl first to make a tetrahedral carbon (just like a Grignard addition) is followed by rapid fragmentation of the alkoxy group
d. In crossed Claisens that involve ketones, why does the ketone function as enolate nucleophile and the ester as the electrophile, even though ketones are normally better electrophiles?
   - Ketones are more acidic, so are more easily converted to enolates
   - While ketones are more reactive as electrophiles, addition to ketones is reversible and doesn't lead to product; whereas addition to esters leads irreversibly to product

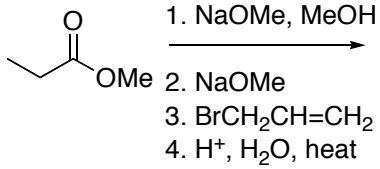
Provide products or reactants for the following Claisen reactions.

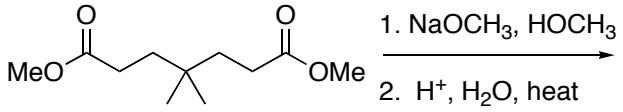
1. 

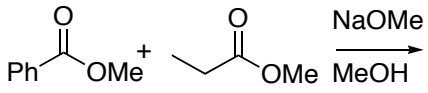
2. 

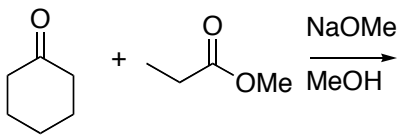
3. 

4. 

5. 

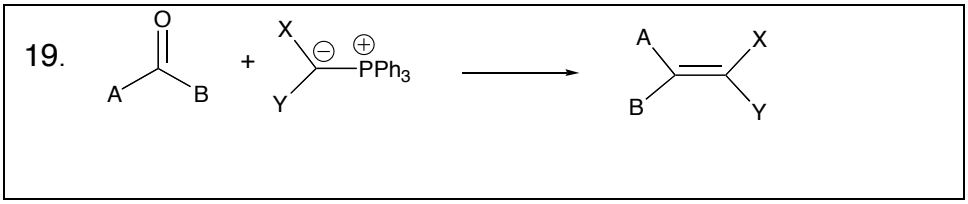
6. 

7. 

8. 

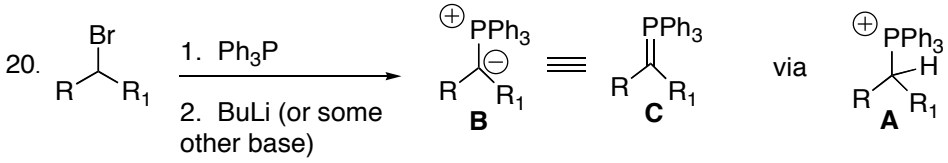
H. The WITTIG REACTION. A process involving carbonyls for coupling carbons to make alkenes. (18.18)

- No enolate chemistry is involved
- But this is process is complementary to the aldol condensation for making alkenes
- Very Powerful route to alkene synthesis

19. 

a. The carbonyl can be an aldehyde or a ketone
b. Phosphorus "ylide": a molecule with adjacent positive and negative charge, but overall neutral
c. The ylide carbon is strongly nucleophilic

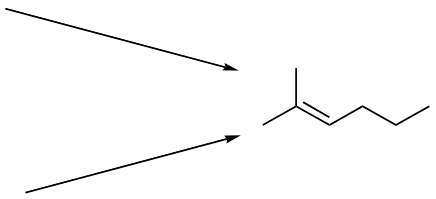
Ylide Preparation:

20. 

a. PPh_3 is a decent nucleophile, produces phosphonium salt (**A**)
b. Alkyl bromide is best 1º (S_N2 mechanism), but 2º can also work
c. The phosphonium salts **A** are weakly acidic and can be deprotonated by strong base (LDA also works) to produce Wittig reagent **B**
d. Wittig Reagent B is really in resonance with version C
   - **B** helps explain why the carbon is so nucleophilie
   - **C** is good for predicting alkene products
e. Bromide precursors for Wittig reagents are often available from alcohols, via PBr_3
   - PBr_3 – PPh_3 - BuLi is a common sequence for converting alcohols into Wittig reagents
   - PCC or H_2CrO_4 is a common conversion for alcohols into aldehydes or ketones (Wittig acceptors)

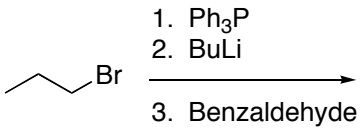
Draw the product, reagent, or starting material for the following Wittig reactions.

Combo 1:

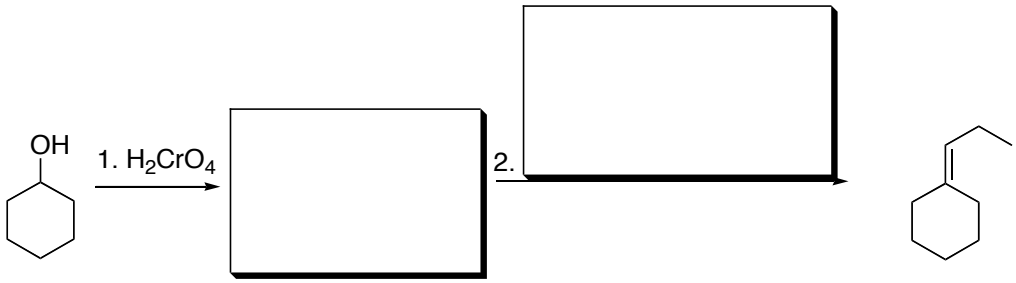


Combo 2:

1.



2.

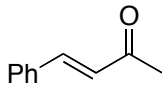


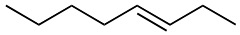
3.

General Routes to Make Alkenes

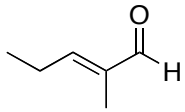
- **Wittig Reactions**.
  - Very general
  - Useful for making more elaborate organics, because two subcomponents can be coupled to make a larger product.
  - Technically longer and more difficult than an aldol condensation, so should not be used to make enones when an aldol condensation could be used instead.
- **Aldol Condensations**.
  - Great for making enones (α,β-unsaturated carbonyls). But limited to making enones.
  - If you see an enone target, make via aldol condensation.
  - Useful for making more elaborate organics, because two subcomponents can be coupled to make a larger product.
- **Elimination reactions** (from either halides or alcohols).
  - Not useful for building up carbon chain lengths. Simply involves transforming one functional group into another.

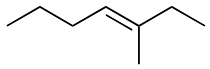
4. For the following alkenes, which method should you use, and what would be the immediate precursors that would be suitable?





5. Synthesis design. Design syntheses of the following products, starting from **alcohols of 4 carbons or less**. Some key reminder reactions:
   - PCC for oxidizing 1º alcohols to aldehydes
   - H_2CrO_4 for oxidizing 2º alcohols to ketones
   - PBr_3 for converting 1º or 2º alcohols to bromides needed for making Wittig reagents

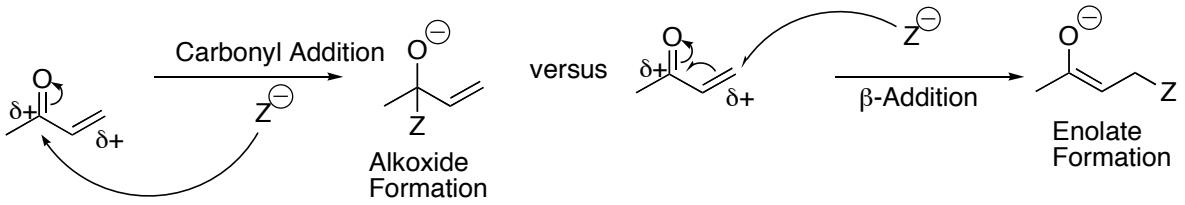
a. 

b. 

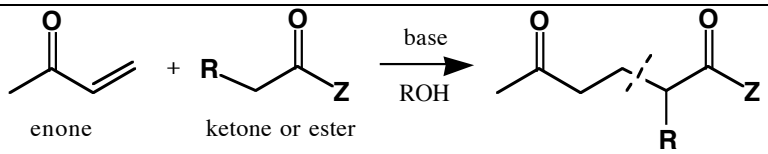
I. Enones as Electrophiles (22.18-19) Michael Reactions/β-Addition (Not for Test)

General: Enones as Electrophiles. Nucleophiles that attack enones must choose between:

- Carbonyl addition
- β-Addition
    - this isn't bad, as it results in enolate formation



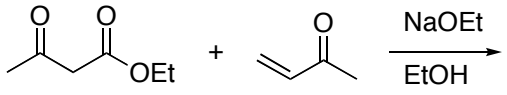
Carbonyl addition normally dominates with:	β- addition normally dominates with:
• RMgBr • RLi • $NaBH_4$ • $LiAlH_4$ • LiCCR	• enolates of dicarbonyls • sometimes enolates of monocarbonyls (but not always) • Cuprates (R_2CuLi) Prep: 2RBr $\xrightarrow[2.\ 1\ CuI]{1.\ 4\ Li}$ R_2CuLi

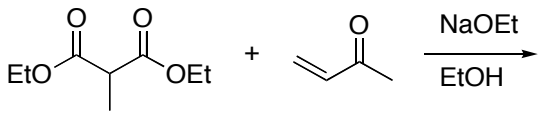
17. 

-"Michael Addition

-1,5 dicarbonyls are well suited for ring-forming aldol or Claisen reactions

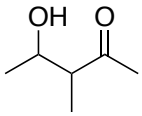
Draw the Products for the following Michael reactions

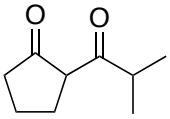
1. 

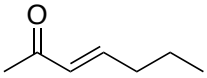
2. 

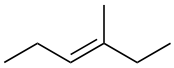
Retrosynthesis Practice: Design syntheses for the following targets, starting FROM ALCOHOLS WITH NO MORE THAN 5 CARBONS.

- Cyclopentanol is allowed.
- Esters may be used.
- Aldehydes, ketones, or Wittig reagents must be built from ≤5-carbon alcohols.

1. 

2. 

3. 

4. 

Chemical Tests Practice Problems. For each of the formulas provided, provide a possible structure given the chemical test results.

Common Chemical Tests, for this chapter:

	DNP	Tollens	Iodoform	H_2/Pt	Jones
Tests for:					

Problems:

DNP	Tollens	Iodoform	H_2/Pt	Jones
Yes	No	No	Yes, gives $C_6H_{12}O$	No

$C_6H_{10}O$

DNP	Tollens	Iodoform	H2/Pt	Jones
Yes	Yes	No	Yes, gives $C_6H_{10}O$	Yes

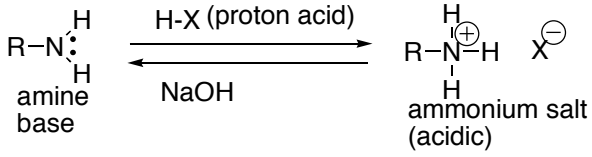
C_6H_8O

DNP	Tollens	Iodoform	H2/Pt	Jones
Yes	No	Yes	Yes, gives $C_6H_{12}O$	No

C_6H_8O

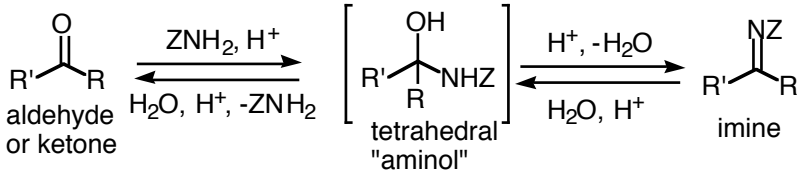
Reactions of Amines

1. **Reaction as a proton base** (Section 19-5 and 19-6)



- Mechanism: Required (protonation)
- Reverse Mechanism: Required (deprotonation)
- Amines are completely converted to ammonium salts by acids
- Ammonium salts are completely neutralized back to amines by bases
- Patterns in base strength: Reflect stabilization/destabilization factors for both the amine and the ammonium
    - N lone pair: $sp^3 > sp^2 > p$
    - For sp^3 nitrogens, $3^o > 2^o > 1^o$

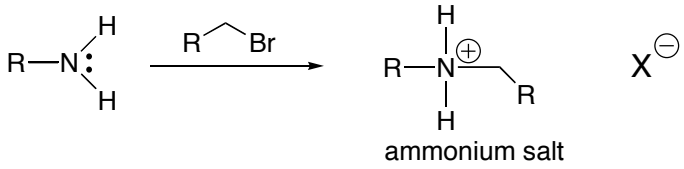
2. **Reaction with Ketones or Aldehydes** (Section 18-16,17 and 19-10)



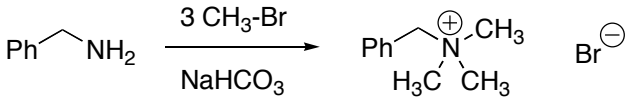
Notes:

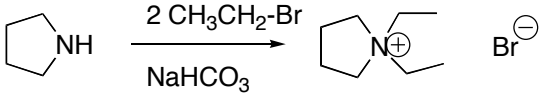
- "Z" can be a carbon, nitrogen, oxygen, or hydrogen atom/group.
- The "aminol" can't be isolated, it's only present at equilibrium.
- Equilibrium factors apply. Water drives to the carbonyl side; removal of water drives to the imine side.
- Mechanism: Learned for last test (not tested this time)
- Must have at least 2 H's on nitrogen → 2º, 3º amines can't do this

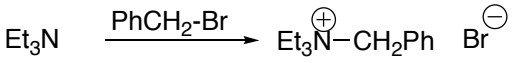
1. **Alkylation of 1º Alkyl Halides** (Section 19-12, 19-21A)



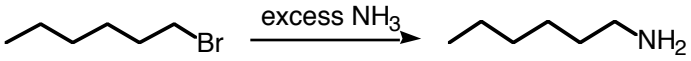
- **3a. Polyalkylation** is routine.
  - With excess alkyl halide and base, keep on alkylating until it becomes the quaternary ammonium salt (no surviving H's on nitrogen, examples below) .
  - Mechanism required for polylalkylations. The mechanism involves repetitive sequential S_N2 alkylation-deprotonations.



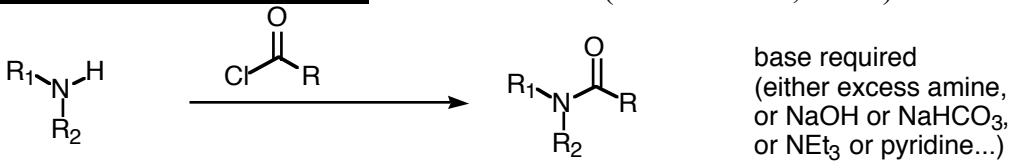




- **3b. Monosubstitution** is possible when excess ammonia (or other cheap amines) is used.
  - Mechanism for monosubstitution required. This involves simple S_N2, followed by deprotonation by the excess amine.

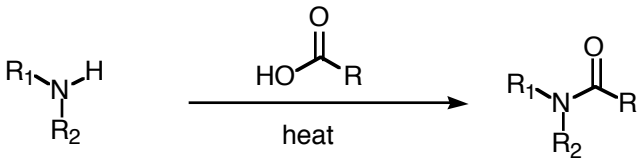


2. **Acylation with Acid Chlorides** to From Amides: (Section 19-13, 20-15)



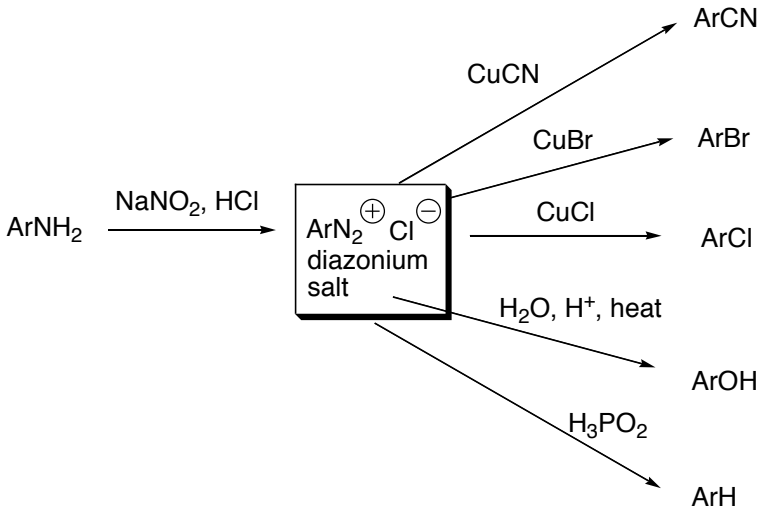
- Mechanism: Required (addition-elimination-deprotonation)
- Amine must have at least one hydrogen to begin. But 1º, 2º, or NH_3 all react well.
- But 3º amines can't work.
- Some base is required for the deprotonation step and to absorb the HCl. For cheap amines, excess amine can simply be used. Alternatively, amines with no H's (triethylamine, pyridine) can be used. Or else NaOH or $NaHCO_3$ can be used.

4b. **Acylation with Carboxylic Acids** to From Amides: (Section 20-12)



- Mechanism: Not Required
- Fairly high temperatures often required, and yields aren't as good as with acid chlorides
- Biologically amine + acid → amide is routine, and is facilitated by complex enzyme mechanisms

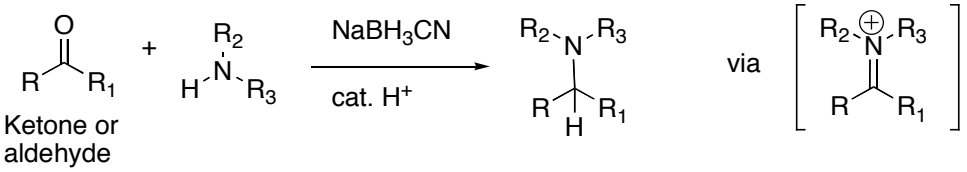
3. **Substitution for Aromatic Amines via the Diazonium Salts** ("The Sandmeyer Reaction") (Section 19-17, 18)



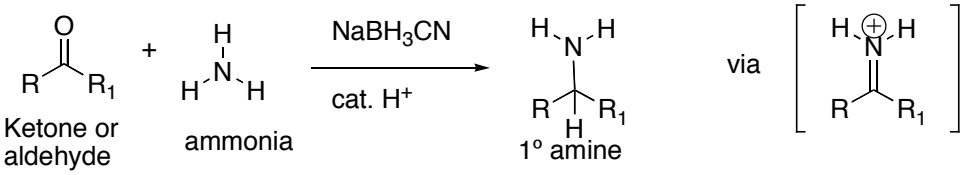
- Mechanism: Not Required
- Qualitatively, can think of this as a nucleophilic substitution: a nucleophile replaces N_2, a premier leaving group. The actual mechanism is probably radical, however.
- Application in synthesis: The amine (an o/p director) is often derived from a nitro (a meta director). Using the nitro group to direct meta, then reducing and converting the nitrogen into CN, Br, Cl, OH, or H, provides products we haven't been able to make before.

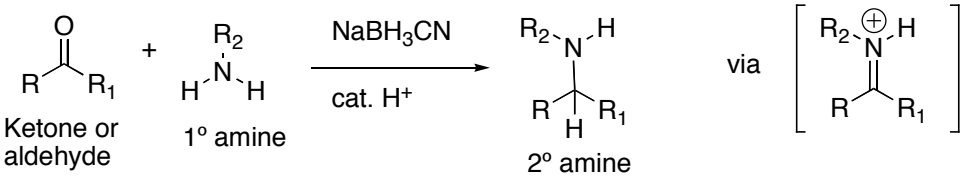
Synthesis of Amines

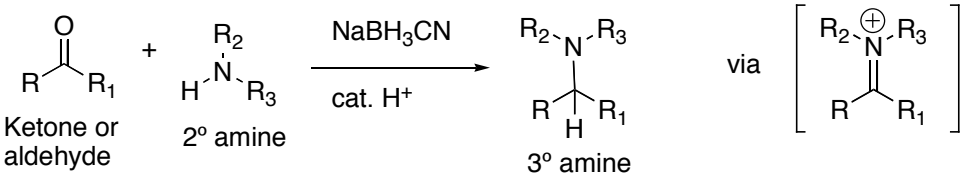
6. **From Aldehydes or Ketones: Reductive Amination** (Section 19-19)



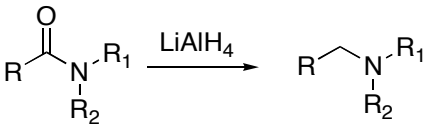
- Access: 1º, 2º, or 3º Amines
- Mechanism: Not required. (Basic workup)
- The carbonyl reactant can be an aldehyde or a ketone
- The amine reactant must have at least one hydrogen, as shown above; but R_2 and/or R_3 can be either a carbon or a hydrogen. Thus:
  - NH_3 → 1º RNH_2
  - 1º RNH_2 → 2º R_2NH
  - 2º R_2NH → 3º R_3N
  - 3º R_3N don't react





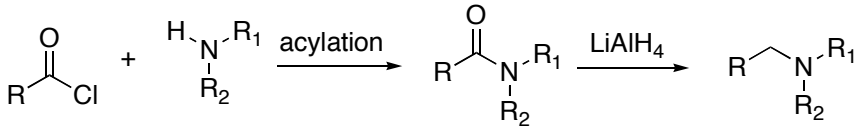


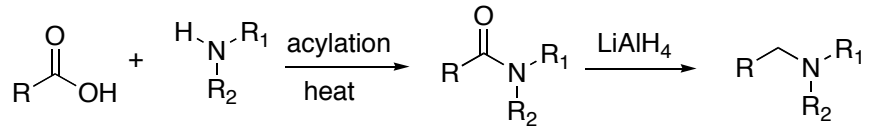
7. **Via Amides**: (Section 19-20)



- No mechanism required for the reduction
- Access: 1º, 2º, or 3º Amines.
- R_1 and R_2 can be either H or C. Thus, you can produce either 1º, 2º, or 3º amines in this way:
  - $RCONH_2$ → 1º RCH_2NH_2
  - $RCONHR$ → 2º RCH_2NHR
  - $RCONR_2$ → 3º RCH_2NR_2

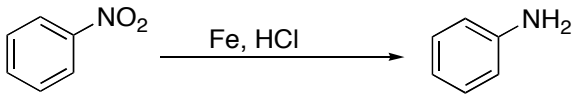
8. **From Amines via Amides**: (Section 19-20)





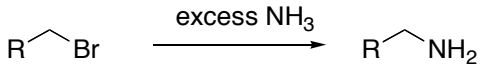
- Access: 1º, 2º, or 3º Amines
- Acylation mechanism required (see reaction 4) but reduction mechanism not required.

9. **Reduction of nitro compounds**: (section 19-21C)



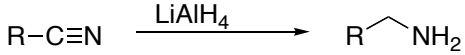
- Access: 1º Amines only (especially aromatic amines)
- No mechanism required.
- There are many other recipes for reduction of nitro compounds:
  - Pd/H_2, Ni/H_2, Pt/H_2,
  - Fe/HCl, Zn/HCl, Sn/HCl

10. **From 1º Alkyl Halides: Alkylation of Ammonia** (Section 19-12, 19-21A) (See reaction 3).



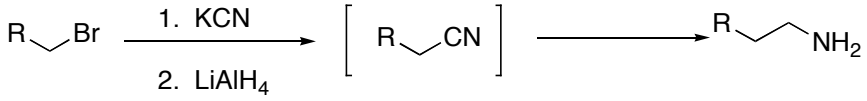
- Access: 1º Amines only
- Mechanism required. (see reaction 3b)
- No change in number of carbons.
- Excess NH_3 prevents polysubstitution.

11. **From Nitriles: Reduction of Nitriles** (Section 19-21B)



- Access: 1º amines
- Mechanism not required.

12. **From Alkyl Halides: Via the Nitrile** (Section 19-21B)



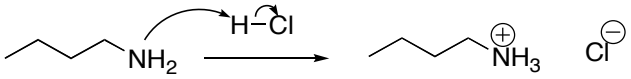
- Access: 1º Amines only
- Mechanism not required.
- One-Carbon chain extension!

Summary of Amine Syntheses

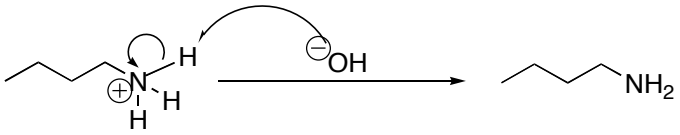
Route	Reaction Number	Source/ Precursor	Reagent	Available Amines	Comments
1	#6	Aldehydes or Ketones	R_2NH, H^+ $NaBH_3CN$,	1º, 2º, or 3º Amines	
2	#7, #8	Amides	$LiAlH_4$	1º, 2º, or 3º Amines	
3	#7, #8	Amines (via Amide)	1. RCOCl (or RCO_2H, heat) 2. $LiAlH_4$	1º $ArNH_2$	
4	#7, #8	Acid Chlorides or Acids (via Amide)	1. RNH_2 2. $LiAlH_4$		
5	#9	$ArNO_2$	Fe/HCl	1º $ArNH_2$	
6	#10	1º RCH_2Br	NH_3 (excess)	1º only, with CH_2 next to nitrogen	Original carbon chain is not extended
7	#12	1º RCH_2Br (via nitrile)	1. KCN or NaCN 2. $LiAlH_4$	1º only, with CH_2 next to nitrogen	Original carbon chain is extended by one carbon
8	#11	RCH_2CN	$LiAlH_4$	1º only, with CH_2 next to nitrogen	

Mechanisms

1. **Protonation**

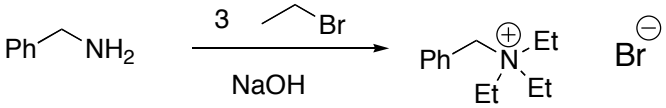


1.-**Reverse. Deprotonation**

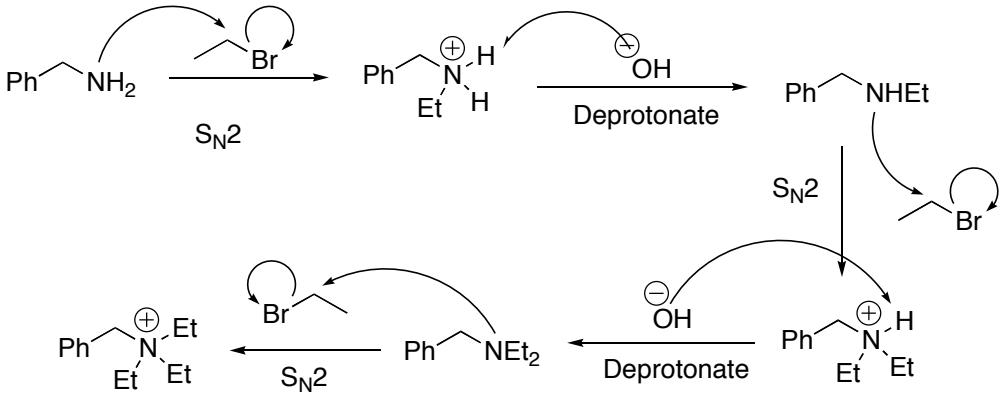


3. Polyalkylation

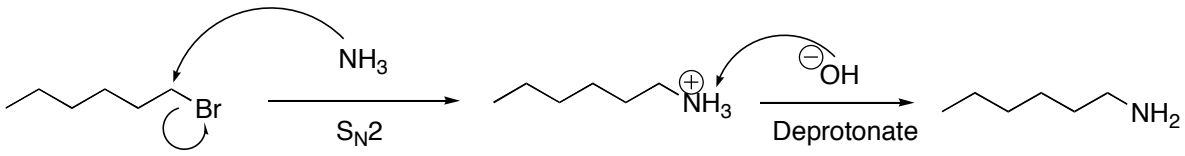
Ex:



Mech:

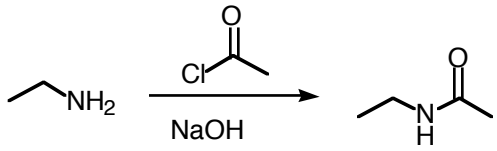


3b. Monoalkylation

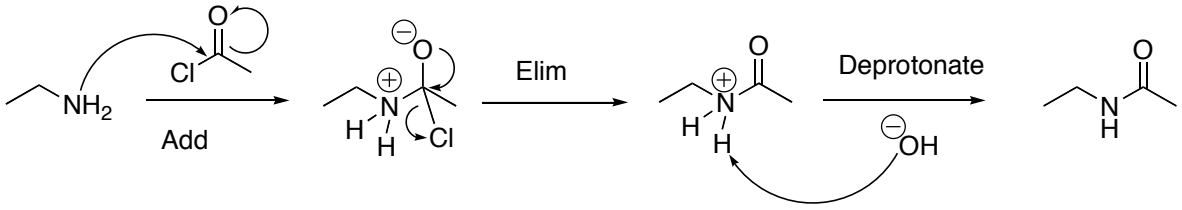


4. Acylation

Ex:



Mech: 3 steps: Addition-Elimination-Deprotonation



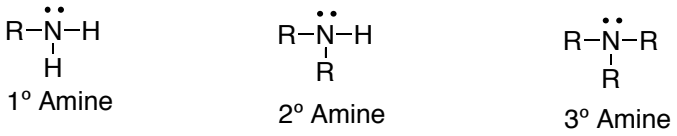
Chapter 19 Amines

A. Miscellaneous

19.1 Intro, Terms

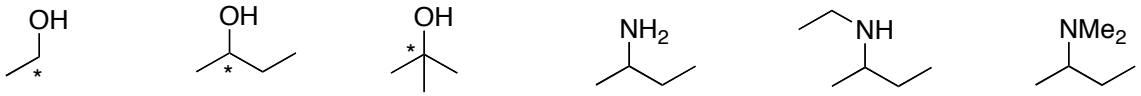
Amines versus Amides

1º, 2º, 3º classification: based on how many of the three nitrogen attachments are carbons:

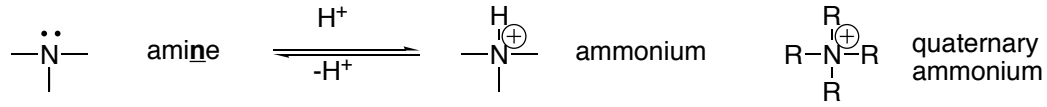


Note: 1º, 2º, 3º has a different sense than with alcohols.

1. In an alcohol, it's based on how many carbon groups are attached to the hydroxy-bearing carbon.
   - The alcohol oxygen always has one carbon group.
2. But in amines, it's how many carbon groups are attached to the nitrogen itself.
   - Because the nitrogen could have 0, 1, 2, or 3 carbon groups attached.



Amines versus Ammoniums: Neutral versus protonated/cationic



19.2 Formal **Amine Nomenclature**: alkan-x-amine, N-alkylalkan-x-amine, etc.

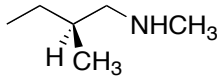
1. For core name, choose longest C-chain to which nitrogen is attached, and call it alkan-x-amine (including for alkan-1-amines)
   - Number from end nearer N
   - Be sure to specify with a number which **carbon** has the nitrogen
     - The nitrogen does ****not**** count as a number itself.
2. Substituents on the nitrogen (rather than on carbon) are designated as "N-"
   - Unlike substituents on a carbon, which are always designated by the carbon's number
   - The "N-" does not factor into alphabetizing. Ex: "N-ethyl" goes before "3-methyl"
3. NH_2 as a Substituent: "Amino"

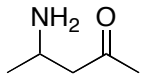
Draw the structure or provide the name for the following.

1. N-methyl-3-phenyloctan-2-amine

2. (Z)-pent-3-en-1-amine

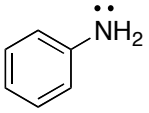
3. hexan-3-amine

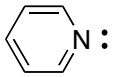
4. 

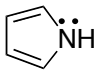
5. 

Common Naming (for simple amines): Alkylamine, dialkylamine, trialkylamine….

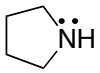
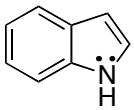
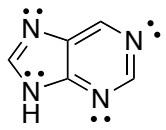
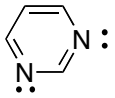
Three Common Amine Names to Memorize (Review from Aromatics Chapter)

Aniline 

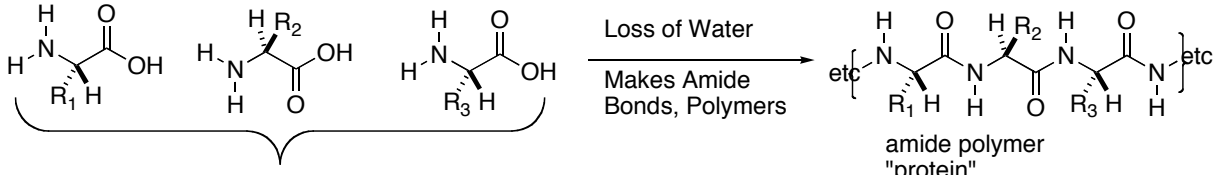
Pyridine 

Pyrrole 

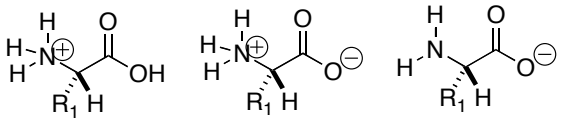
Some Other Famous Common Amine Names (No memory requirement)

Name	Structure	Name	Structure	
Pyrrolidine		Indole		
Purine		Pyrimidine		RNA, DNA, ATP, and ADP are made from derivatives of Purine and Pyrimidine

"Amino Acids"



-The major natural amino acids all have "S" configuration
-20 major natural amino acids
-Under neutral conditions, the amine actually deprotonates the acid to give not an "amino acid" but actually an "ammonium carboxylate"
-The side groups "R" can be acid, basic, hydrophilic, or hydrophobic.
-The sequence or R groups on thepolymer essentially spells out the biological activity of the protein.



Test Keys:

1. Understand that amino acids are the building blocks for polymeric proteins, and that the biological information is specified by the identity and sequence of the side groups

2. Understand what form an "amino acid" exists in, depending on whether the conditions are acidic, neutral, or basic pH
   - Is the nitrogen neutral (base form) or protonated and cationic (acid form)?
   - Is the carboxylic acid anionic (base form) or protonated and neutral (acid form)?

   a. Acidic pH: both are in protonated acid forms Overall Charge: POSITIVE
      - nitrogen is cationic and carboxylic acid is neutral

   b. Neutral pH: one in acid form, the other in base form Overall Charge: NEUTRAL
      - One acidic H between the two of them
      - The amine is in its acid form (protonated, cationic); while the carboxylic acid is in its base form (deprotonated, anionic)
      - The amine is more basic than the carboxylate, the carboxylic acid more acidic than the ammonium cation. Acid base drives the equilibrium to the ammonium carboxylate form

   c. Basic pH: both are in deprotonated base form Overall Charge: NEGATIVE
      - Nitrogen is neutral, carboxylic acid is anionic

Structure and Hybridization

1. **N <u>atoms</u>** are typically either sp^3 hybridized (normal) or sp^2 hybridized
    a. sp^3 is the default (when no double bonds/conjugation require a p orbital)
    b. sp^2 in either of two cases:
        - N atom is itself double bonded
        - N atom is conjugated to a double bond

2. **<u>N lone pair</u>** is either:
    a. sp^3 is the default (when no double bonds/conjugation require a p orbital)
    b. sp^2 when the N atom is itself double bonded
        - the p orbital is used to make the double bond
        - the lone pair is left in an sp^2 hybrid
    c. p when the N atom is conjugated to a double bond but is not itself double bonded
        - the lone pair sits in the p orbital so that it can overlap with the adjacent p orbital/π bond

<u>Practice</u>: For the nitrogens on page 10, identify the lone pair hybridization and bond angles.

19.3 Physical Properties

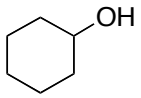
Key: hydrogen bond strength depends on acidity of the hydrogen and basicity of the N or O

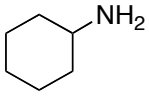
1. **Water Solubility**: All amines hydrogen-bond water → impacts solubility
   a. Because R_3N---HOH bond is stronger (due to amine lone-pair basicity) than ROH---HOH, amines tend to better H-bond water and are more soluble than oxygen analogs
   b. Based on basicity of substate (the acidity of water's hydrogen is common)

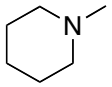
2. **Boiling Point:** 1º and 2º amines hydrogen bond themselves, but 3º amines don't
   a. Boiling point for similar mw amines: 1º, 2º amines > 3º amines
   b. amines generally have lower boiling points than analogous oxygen compounds
      - Boiling point for similar mw: RCO_2H > RCH_2OH > RCH_2NH_2
   c. for boiling point, the weaker acidity of the N-H hydrogens weakens the hydrogen-bonding strength more than the greater basicity of the Nitrogen lone pair.

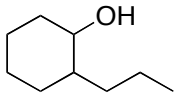
3. Amines stink! (ammoniums don't)

1. Boiling Points. Rank the following in terms of boiling point, 1 being highest, 4 being lowest.

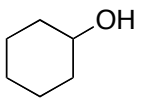


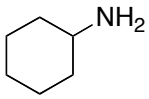


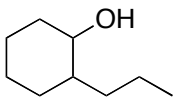


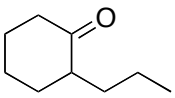


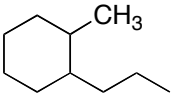
2. Water Solubility. Rank the following in terms of water solubility, 1 being most water soluble, 5 being least water soluble.







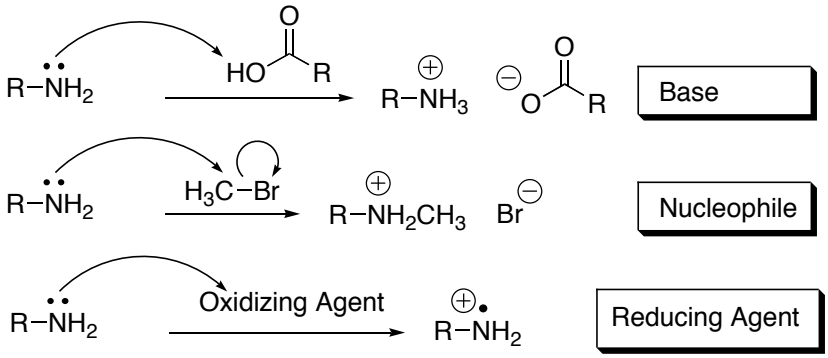




Keys:
1. H-bonding: Is there any at all?
2. How relatively strong is the H-bonding?
3. What impacts H-bonding strength?

What impact will extra carbons have?

B. Basicity of Amines: Reactivity of the Nitrogen Lone Pair (19.5,6)



•The nitrogen lone pair dominates amine reactivity

•Trends in base strength, nucleophile strength, and redox strength follow similar patterns, based on lone pair stability/reactivity

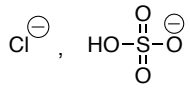
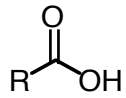
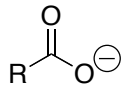
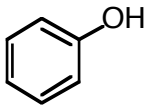
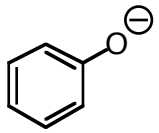
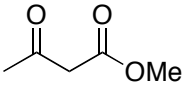
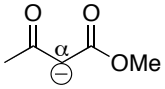
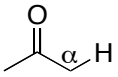
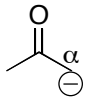
Neutral amine bases are stronger than:

1. Neutral oxygens (water, alcohol, ketones…)
2. Carboxylate anions (resonance stabilized)

Neutral amine bases are weaker than:

1. Anionic hydroxide or alkoxides
2. Anionic nitrogen or carbon bases

Acidity/Basicity Table 19.1: Neutral Acids and Anionic Bases

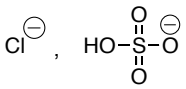
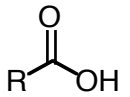
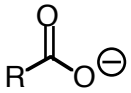
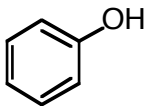
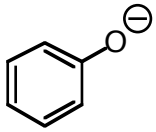
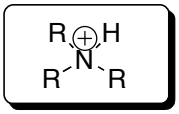
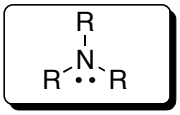
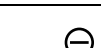
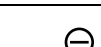
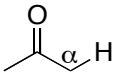
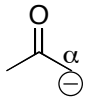
Class	Neutral Acid Structure	Ka	Acid Strength	Anion Base	Base Strength	Base Stability
Strong Acids	H-Cl, H_sSO_4	10^2				
Carboxylic Acid		10^{-5}				
Phenol		10^{-10}				
1,3-Dicarbonyl		10^{-12}				
Water	HOH	10^{-16}				
Alcohol	ROH	10^{-17}				
Ketones and Aldehydes		10^{-20}				
Amine (N-H)	$(iPr)_2N$-H	10^{-33}		$(iPr)_2N^{\ominus}Li^{\oplus}$		
Alkane (C-H)	RCH_3	10^{-50}		$RCH_2^{\ominus}$		

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 acids are involved, it's often best to draw the conjugate anionic bases, and to think from the anion stability side.**

Acidity/Basicity Table 19.2: With both Neutral and Cationic Acids and both Neutral and Anionic Bases

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}				**W**orking
Alcohol	ROH	10^{-17}				**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

Notes to remember

1. Average neutral amine a thousand billion times **more basic than a neutral oxygen** (**electronegativity** factor)
2. An average neutral amine is thousands of times **less basic than** non-resonance stabilized **hydroxide or alkoxide anions** (**charge** factor)
3. But average neutral amine **millions** of times **more basic** than highly resonance-stabilized **carboxylate anion** (**resonance** factor trumps charge factor in this case)
4. **Ammonium cations** are million of times **less acidic than** neutral **carboxylic acids**, but are **more acidic than neutral water/alcohol**!
5. Neutral amine can completely deprotonate carboxylic acids, but not water or alcohols.
6. Therefore hydroxide can deprotonate ammoniums, but carboxylates cannot.

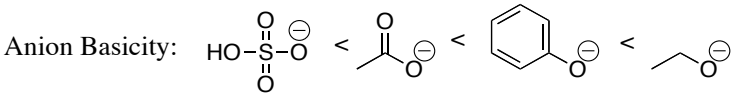
More Detailed Discussion of Acid/Base Patterns/Factors to remember

1. Charge

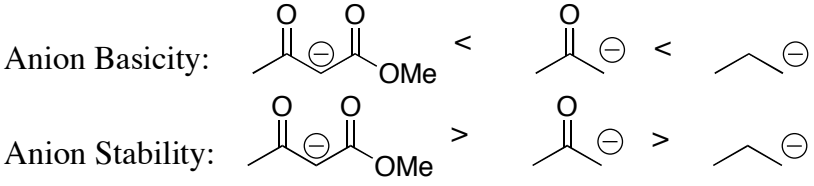
- **All else equal, cations are more acidic than neutrals, and anions more basic than neutrals. (See Table 19.2)**
- Nonfactor on Table 19.1, since all of the "acids" have the same charge (neutral), and all of the "bases" have the same charge (anions)

2. Electronegativity:
   - Acidity: H-C < H-N < H-O < H-X (halogen)
   - Basicity: $C^{\ominus}$ > $N^{\ominus}$ > $O^{\ominus}$ > $X^{\ominus}$
   - Anion Stability: $C^{\ominus}$ < $N^{\ominus}$ < $O^{\ominus}$ < $X^{\ominus}$

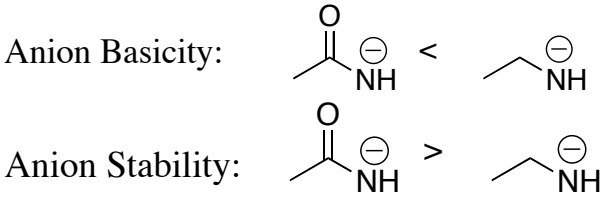
3. Resonance/Conjugation:
   - Oxygen Series:
     Acidity: sulfurice acid > carboxylic acid > phenol > alcohol



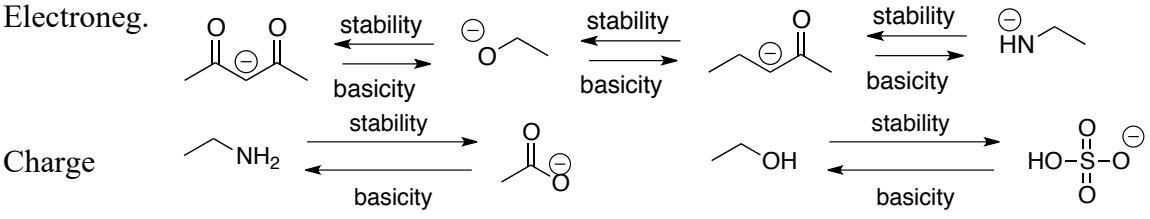
   - Carbon Series:
     - Acidity: 1,3-dicarbonyl > ketone (monocarbonyl) > alkane



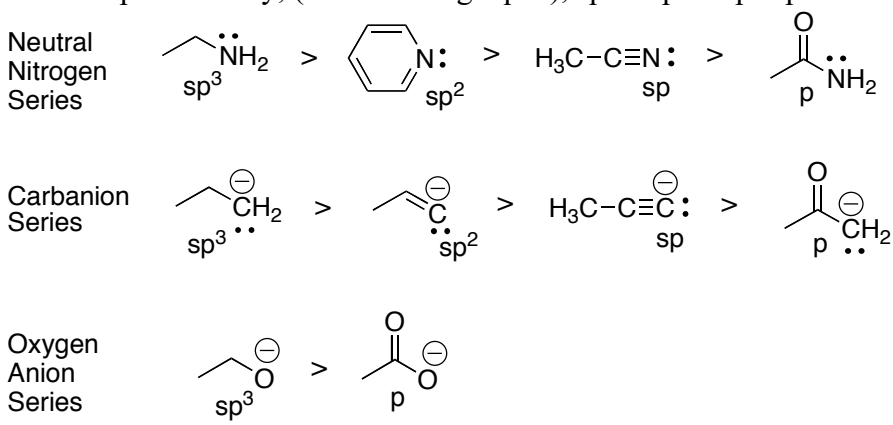
   - Nitrogen Series:
     - Acidity: amide > amine



- Note: Resonance is often useful as a tiebreaker (oxyanion versus oxyanion, etc.)
- NOTE: Resonance can sometimes (not always) trump electronegativity or charge.

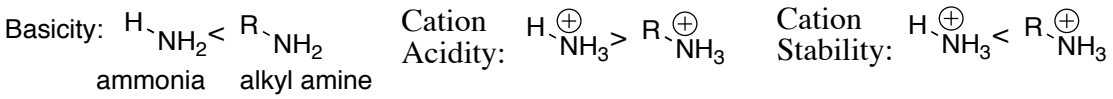


4. Hybridization:
   - For lone-pair basicity, (all else being equal), $sp^3 > sp^2 > sp > p$

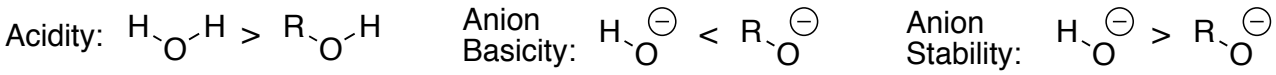


   - This means that for acidity, alkynes > alkenes > alkanes

5. Electron donating/electron withdrawing substituents:
   - Electron withdrawing substituents will stabilize negatively charged anions, but will destabilize positively charged cations.
     - This means a withdrawer will increase the acidity of a neutral acid because it will stabilize the resulting anion.
     - This means a withdrawer will decrease the basicity of a neutral base because it will destabilize the resulting cation
   - Electron donating substituents will stabilize positively charged cations, but will destabilize negatively charged anions.
     - This means a donor will increase the basicity of a neutral base because it will stabilize the resulting cation. The resulting cation will be less acidic.

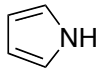
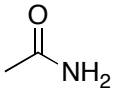
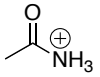
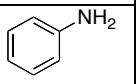
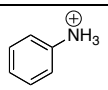
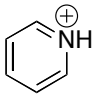


     - This means a donor will decrease the acidity of a neutral acid because it will destabilize the resulting anion, and will increase the basicity of the anion



6. Ammonium Cations as Acids and Neutral Amines as Bases
   - Neutral amines are more basic than any neutral oxygen (electronegativity factor)
   - Neutral amines are less basic than most anionic oxygens, including alkoxides, hydroxides (charge factor)
   - However, neutral amines are more basic than highly resonance-stabilized carboxylate anions (in this case, resonance factor trumps the charge factor).

Table 9.3 Relative Basicity of Different Classes of Neutral Nitrogen Compounds.

Entry	Structure of Amine Base	Base Strenth	Lone Pair Hybrid		Impact On Base Strength	Structure of Ammonium Acid	K_a	Acid Strenth
1			P	Aromatic, Conjugated	Decrease		10^{1}	
2			P	Conjugated, Electron-Withdrawing Carbonyl	Decrease		10^{0}	
3			P	Conjugated	Decrease		10^{-4}	
4			sp^2				10^{-5}	
5	**NH_3**		**sp^3**	**Reference**		$\oplus NH_4$	**$10^{-9.3}$**	
6	$EtNH_2$		sp^3	Alkyl Donor	Increase	$EtNH_3^{\oplus}$	$10^{-10.6}$	
7	Et_2NH		sp^3	Alkyl Donor	Increase	$Et_2NH_2^{\oplus}$	$10^{-10.8}$	
8	Et_3N		sp^3	Alkyl Donor	Increase	$Et_3NH^{\oplus}$	$10^{-11.0}$	

General Amine Basicity Patterns.

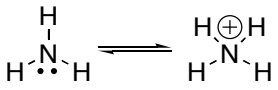
a. Relative basicity correlates Lone pair hybridization: sp^3 (entries 5-8) > sp^2 (entry 4) > p (entries 1-3) (hybridization factor)
b. Within the sp^3 amines, increasing alkyl substitution increases basicity (entries 5-8): 3º > 2º > 1º > NH_3 (electron donating group factor)

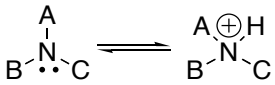
Note: patterns (a) and (b) essentially cover everything.

c. Amides are much less basic than amines, or even other nitrogens with p-lone pairs (less than amines reflects hybridization and conjugation; amides are less basic than other p-hybrid conjugated lone pairs because or the electron-withdrawing group factor).
d. Conjugated nitrogens are in general less basic than isolated nitrogens (both hybridization and conjugation factors)

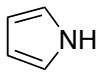
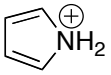
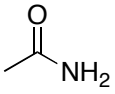
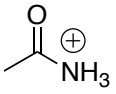
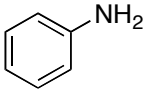
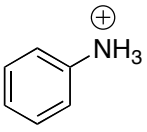
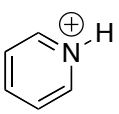
- Note: The **acidity of conjugate ammonium cations (conjugate acids relative to the amines) is directly and inversely related to the basicity of the neutral amines**.
- Key: remember patterns (a) and (b) above. That should help you solve relative basicity problems. If given ammoniums, draw the related conjugate neutral amines, rank them as bases, and realize that the strongest amine base relates to the weakest ammonium acid.
- You should be able to handle any ranking problems involving either amines as bases or their conjugate ammoniums as acids. This should include relative to non-nitrogen acids and bases.

Explanation for Basicity Pattern: Acidity/Basicity is an equilibrium measurement, and thus reflects both product stability and starting material stability.

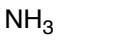


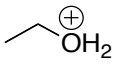
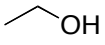


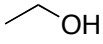
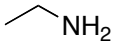
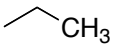
- Anything that **stabilizes the cation increases the basicity** of the nitrogen
- Anything that **destabilizes the cation decreases the basicity** of the nitrogen
- Anything that **stabilizes the amine decreases the basicity** of the nitrogen (especially if that stabilizing factor is sacrificed upon protonation)
- Anything that **destabilizes the amine** increases it's basicity
- When lone pair is p, that always reflects stabilizing conjugation and reduced basicity. This is the origin of both the p-hybridization factor and the resonance/conjugation factor.

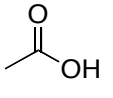
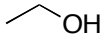
Entry	Base	Conjugate Cation	Substituent And it's Impact	Why: Which Side Is Stabilizied or Destabilized?
5	NH_3	NH_4^+	Reference	
6-8	Et_3N	Et_3NH^+	Alkyl Groups Increase Basicity	**Cation** side stabilized by alkyl groups (electron donors, cation stabilizers)
1			Being part of Aromatic ring Reduces Basicity	**Neutral** side is stabilized by aromaticity. (Aromaticity is lost following protonation.)
2			Acyl/Amide Conjugated To Carbonyl	**Neutral** side is stabilized by conjugation to the carbonyl. That conjugation is lost following protonation. Second, the **cation side is destabilized** by the strongly electron withdrawing carbonyl group.
3			Conjugated To Aromatic	**Neutral** side is stabilized by conjugation. (That conjugation is lost following protonation.)
5			Shorter, more stable lone pair	**Amine** side is stabilized by the sp^2 hybridization of the lone pair. An sp^2 lone pair is shorter than an sp^3 orbital. The shorter sp^2 orbital means the electrons are nearer and held more tightly by the nitrogen nucleus, and are thus more stable.

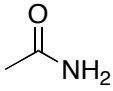
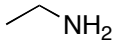
Choose the More Acidic for Each of the Following Pairs: Single Variable Problems

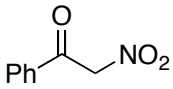
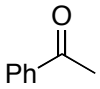
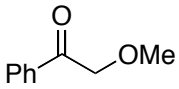
1.  

2.  

3.   

4.  

5.  

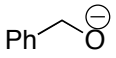
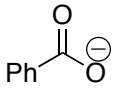
6.   

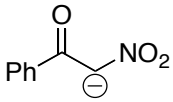
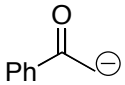
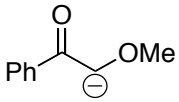
Choose the More **Basic** for Each of the Following Pairs (Single Variable)

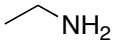
7. NH_3 $NaNH_2$

8. NaOH H_2O

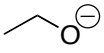
9. NH_3 H_2O

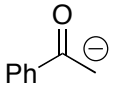
10.  

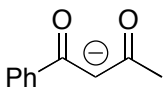
11.   

12.  NH_3 O_2N-NH_2

Choose the More **Basic** for Each of the Following (Multiple Variables, apples and oranges…)

13. NH_3 

14.  

15.  

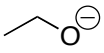
Choose the More Basic for Each of the Following Pairs

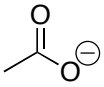
16. NH_3 $NaNH_2$

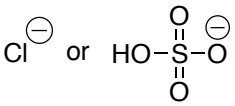
17. NH_3 $NaOH$

18. NH_3 H_2O

19. NH_3 CH_3OH

20. NH_3 

21. NH_3 

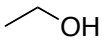
22. NH_3 

23. NH_3 CH_3MgBr

24. NH_3 CH_3NH_2

25. For the following sets of bases, rank them, 1 being the most basic.

a. CH_3MgBr CH_3NHNa CH_3NH_2 CH_3OH

b.   CH_3NH_2 

26. Amine Basicity. For the following pairs or sets of bases, rank them, 1 being the most basic.

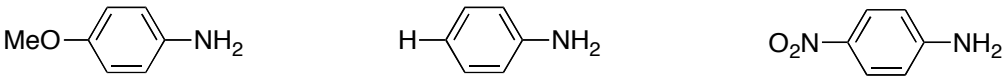
a. 

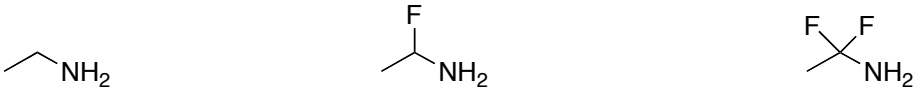
b. 

c. benzamide [$PhC(O)NH_2$] aniline ($PhNH_2$) pyridine triethylamine

d. triethylamine ethylamine ammonia

e. dimethylamine methylamine aniline ($PhNH_2$)

f. 

g. 

h. triethylamine NaOH

i. methanol methylamine methane

j. CH_3MgBr CH_3NHNa CH_3ONa CH_3NH_2 CH_3CO_2Na CH_3OH

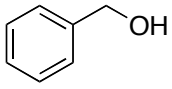
27. Rank the <u>acidity</u> of the following compounds, 1 being most acidic.

a. H_3O^+ $NH_4^+Cl^-$ water acetic acid (CH_3CO_2H) NH_3

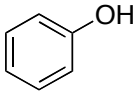
b. H_3O^+ acetic acid (CH_3CO_2H) $Me_3NH^+Cl^-$ ethanol

c. $NH_4^+Cl^-$ $Me_3NH^+Cl^-$ $PhNH_3^+Cl^-$

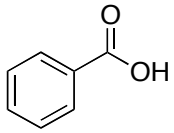
28. Suppose all of the molecules **A-D** are dissolved in diethyl ether.



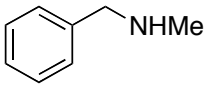
A



B



C



D

a. Which one or ones will extract (dissolve) into aqueous sodium hydroxide? (And why?)

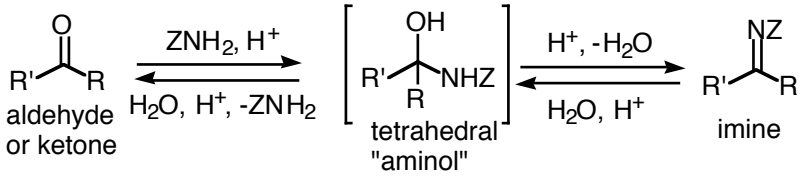
b. Which, if any, will extract into aqueous hydrochloric acid? (And why?)

c. Which, if any, will extract into neutral water? (Why or why not?)

d. Explain how you could use an extraction scheme to separate **D** from **A.**

C. Reactions of Amines (other than as bases)

2. Reaction with Ketones or Aldehydes (Section 19.10)



Notes:

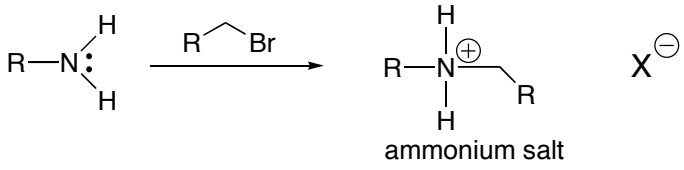
- "Z" can be a carbon, nitrogen, oxygen, or hydrogen atom/group.
- The "aminol" can't be isolated, it's only present at equilibrium.
- Equilibrium factors apply. Water drives to the carbonyl side; removal of water drives to the imine side.
- Mechanism: Learned for last test (not tested this time)
- Must have at least 2 H's on nitrogen → 2º, 3º amines can't do this

Draw the Products of the following Amine reactions.

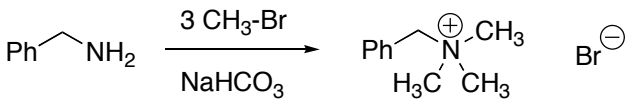
1. $PhNH_2$ —(4-phenyl-2-hexanone, H^+)→

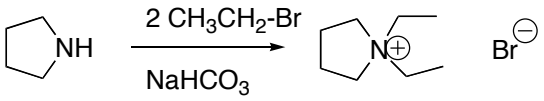
2. Cyclohexanone + H_2NNH_2 →

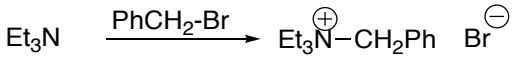
3. Alkylation of 1º Alkyl Halides (Section 19.12)



- **3a. Polyalkylation** is routine.
  - With excess alkyl halide and base, keep on alkylating until it becomes the quaternary ammonium salt (no surviving H's on nitrogen, examples below) .
  - Mechanism required for polylalkylations. The mechanism involves repetitive sequential S_N2 alkylation-deprotonations.



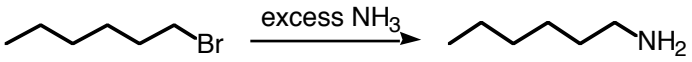




Notes

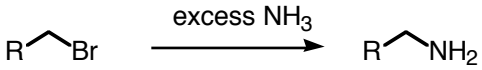
1. All amines are nucleophilic
   - $3^o > 2^o > 1^o > NH_3$
   - structural effects parallel basicity
2. Limited synthetic utility, due to frequent overalkylation
3. Due to S_N2 mechanism, limited to alkylation of 1^o R-X

- **3b. Monosubstitution** is possible when excess ammonia (or other cheap amines) is used.
  - Mechanism for monosubstitution required. This involves simple S_N2, followed by deprotonation by the excess amine.



Synthetically Useful Alkylation Scenarios:

1. Exhaustive Alkylation to Intentionally produce quaternary ammonium salts
2. Reaction 10. **From 1^o Alkyl Halides: Alkylation of Ammonia** (Section 19-12, 19-21A)

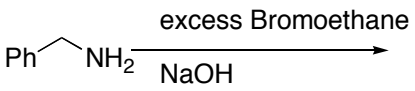


   - Access: 1^o Amines only
   - Mechanism required. (see reaction 3b)
   - No change in number of carbons.
   - Excess NH_3 prevents polysubstitution.

3. Cyclization reactions in which a 5 or 6-membered ring can form.

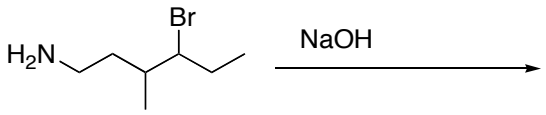
Draw the Products and mechanisms of the following Amine reactions.

1. $Me_3N + PhCH_2I \longrightarrow$

2. 

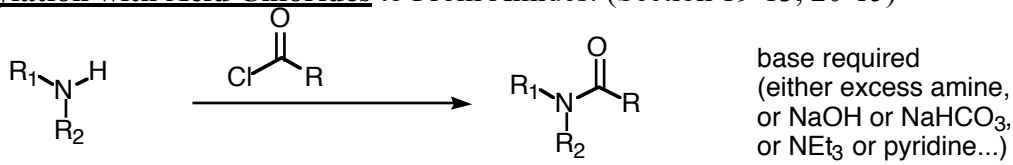
Draw the Products and mechanisms of the following Amine reactions.

1. $PhCH_2Br$ —(Excess NH_3)→

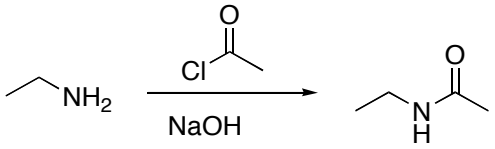
2. 

Why do you **not** get clean monoalkylation if you do a 1:1 mixture of RNH_2 and R-X?

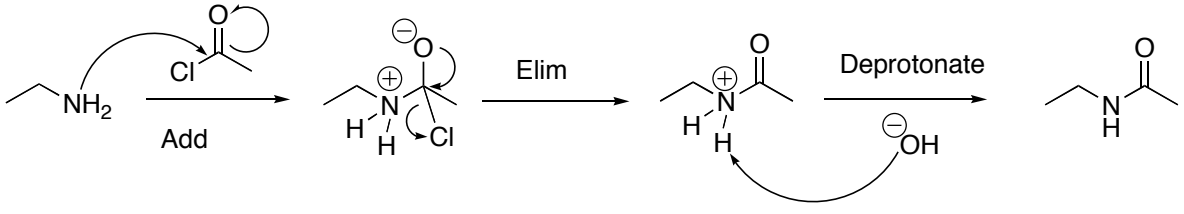
4. **Acylation with Acid Chlorides** to From Amides: (Section 19-13, 20-15)



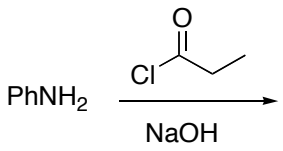
- Mechanism: Required (addition-elimination-deprotonation)
- Amine must have at least one hydrogen to begin. But 1º, 2º, or NH_3 all react well.
- But 3º amines can't work.
- Some base is required for the deprotonation step and to absorb the HCl. For cheap amines, excess amine can simply be used. Alternatively, amines with no H's (triethylamine, pyridine) can be used. Or else NaOH or $NaHCO_3$ can be used.

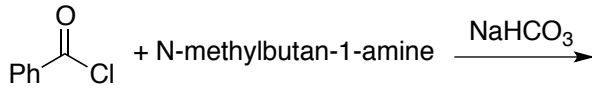


Mech: 3 steps: Addition-Elimination-Deprotonation

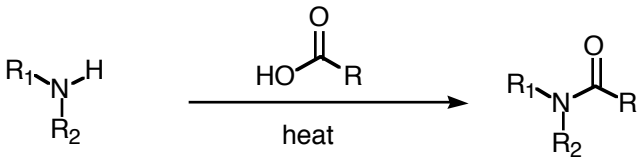


Draw the Products of the following Amine reactions, and the mechanism for the first one.

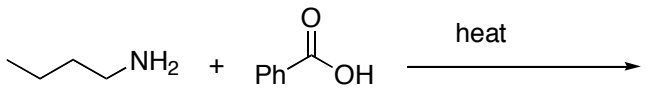
1. 

2. 

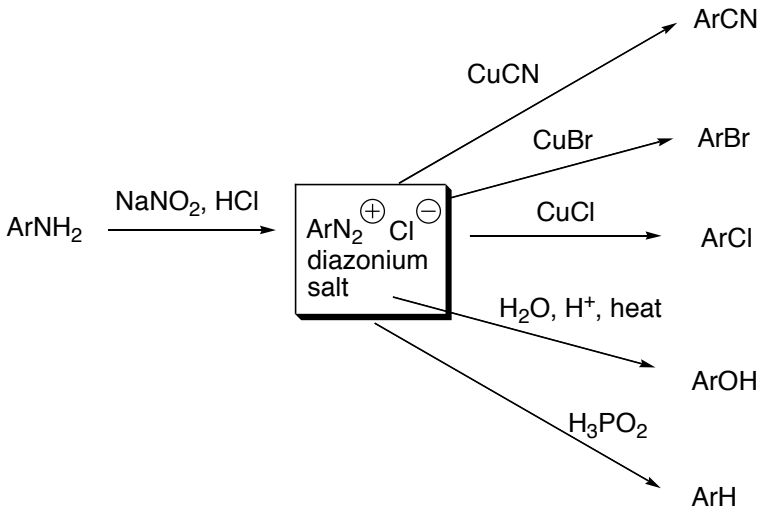
4b. **Acylation with Carboxylic Acids** to Form Amides: (Section 20-12)



- Mechanism: Not Required
- Fairly high temperatures often required, and yields aren't as good as with acid chlorides
- Biologically amine + acid → amide is routine, and is facilitated by complex enzyme mechanisms

1. 

5. Substitution for Aromatic Amines via the Diazonium Salts ("The Sandmeyer Reaction") (Section 19-17, 18)



- Mechanism: Not Required
- Qualitatively, can think of this as a nucleophilic substitution: a nucleophile replaces N_2, a premier leaving group. The actual mechanism is probably radical, however.
- Application in synthesis: The amine (an o/p director) is often derived from a nitro (a meta director). Using the nitro group to direct meta, then reducing and converting the nitrogen into CN, Br, Cl, OH, or H, provides products we haven't been able to make before.

Lewis bases (lone pair electron donors) all function as:

1. Bases (give electrons to H^+)
2. Nucleophiles (give electrons to some other electrophile)
3. Reducing agents (give electrons to oxidizing agents)

Amines can be oxidized

$NaNO_2$/HCl is a strong oxidizing agent, converts RNH_2 to RN_2^+, and $ArNH_2$ to ArN_2^+

- "Diazonium salts"

RN_2^+ has the best leaving group known, because the leaving group is highly stable, neutral N_2 gas

1. Alkyl RN_2^+ are highly unstable, give cations, and usually give mixtures of E1, S_N1, and cation rearrangement product mixtures
2. Not much use synthetically
3. However, N_2 is such a great leaving group that even 1º carbocations can be formed/studied

Reactivity: $RN_2^+ > ROH_2^+ > ROTs >$ RI > RBr > RCl Leaving group ability: N_2 > H_2O > TsO anion > Iodide anion > Bromide anion > Chloride anion

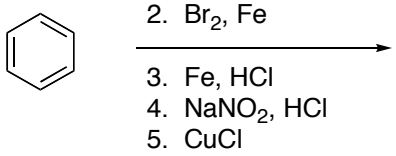
1. Unlike Alkyl diazoniums RN_2^+, aryl ArN_2^+ are very useful
2. A variety of substitutions for the nitrogen can be done
3. While the reactions look like ionic substitutions, most are really complex radical mechanisms

Synthetic Use:

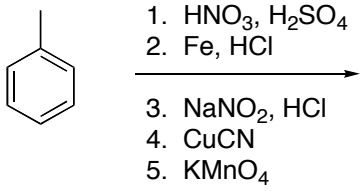
1. NO_2 (meta director) → NH_2 → N_2^+ → Cl, Br, OH, CN, H
2. Easy to get meta relationships, even when you end with things that are not meta directors

Draw the products

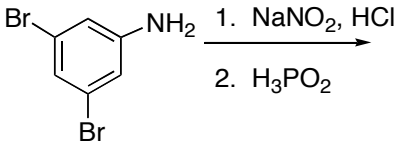
1.



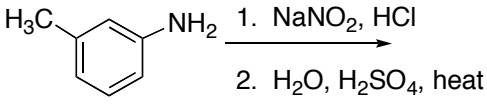
2.



3.

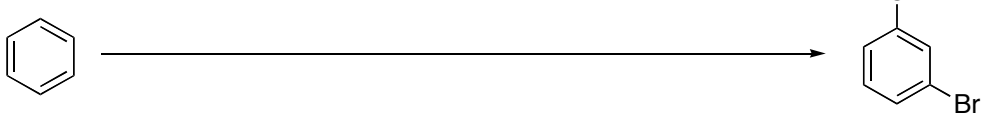


4.

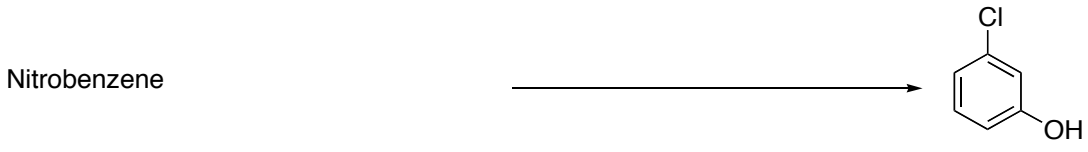


Design Synthesis

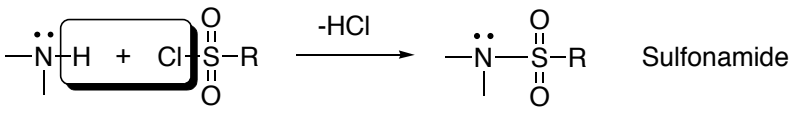
5.



6.



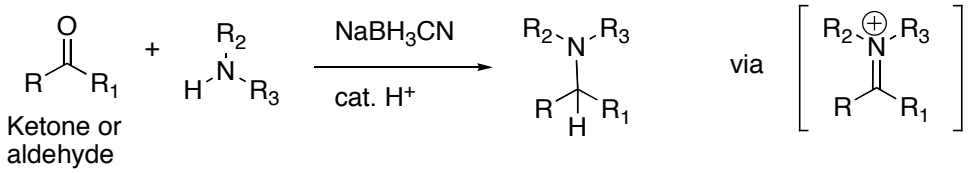
19.14 Reaction with Sulfonyl Chlorides (Not tested)



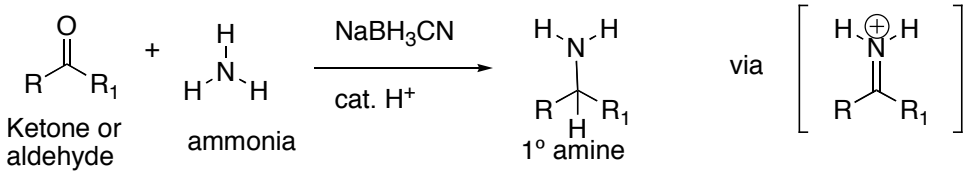
- Exactly as for amide formation
- Many antibiotic drugs: sulfonamides are so similar to amides that they occupy enzyme active sites → prevent bacterial growth

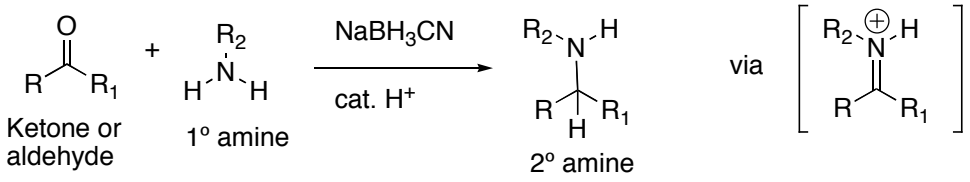
D. Synthesis of Amines

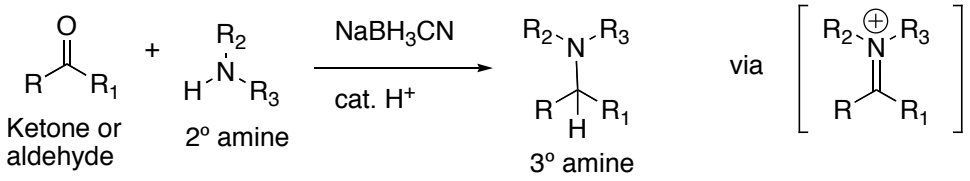
6. **From Aldehydes or Ketones: Reductive Amination** (Section 19-19)



- Access: 1º, 2º, or 3º Amines
- Mechanism: Not required. (Basic workup)
- The carbonyl reactant can be an aldehyde or a ketone
- The amine reactant must have at least one hydrogen, as shown above; but R_2 and/or R_3 can be either a carbon or a hydrogen. Thus:
  - $NH_3 \rightarrow$ 1º RNH_2
  - 1º $RNH_2 \rightarrow$ 2º R_2NH
  - 2º $R_2NH \rightarrow$ 3º R_3N
  - 3º R_3N don't react

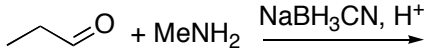


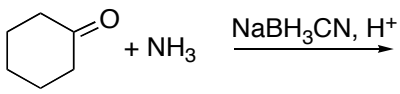


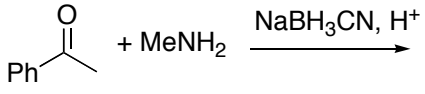


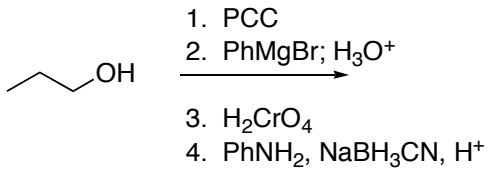
Note: book gives several other variants, but this is really the one universal method, and the one I'll use for my tests.

Synthesis of Amines: Draw the products for the following reactions.

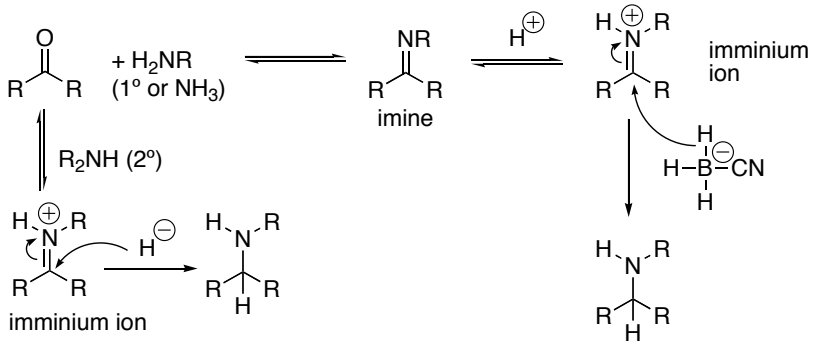
1. 

2. 

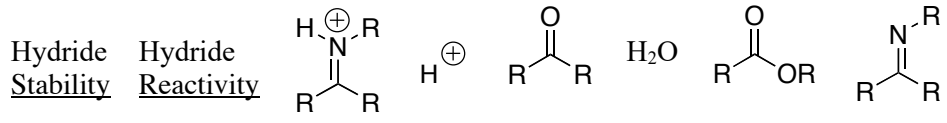
1. 

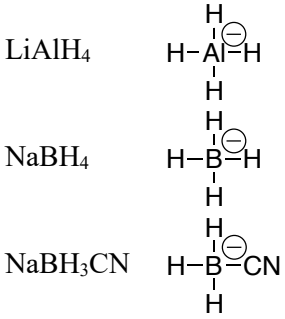
2. 

Mechanism (not for test) and some related notes

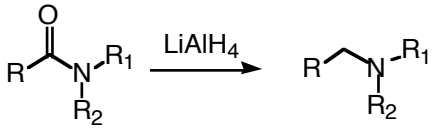


1. $NaBH_3CN$ functions as a hydride $H^{\ominus}$ source, similar to $NaBH_4$ and $LiAlH_4$
2. Formation of imminium cation is key
   - Highly electrophilic, much more so than neutral imine
3. $NaBH_3CN$ is a special, mild $H^{\ominus}$ source, much more stable and less reactive than $NaBH_4$ and $LiAlH_4$
   - So much so that it can coexist with acid (thus enabling imminium ion formation)
   - So much so that it does not reduce neutral ketones and aldehydes (thus allowing the aldehydes and ketones to sit around and equilibrate with imminium ion)



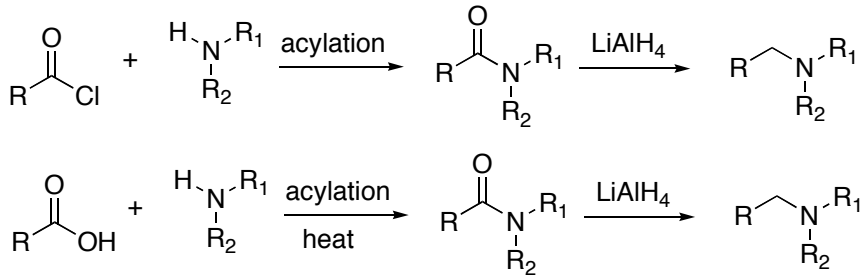


7. **Via Amides**: (Section 19-20)

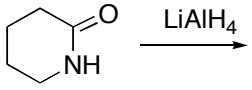


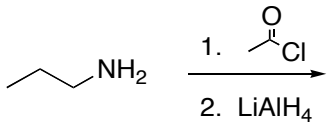
- No mechanism required for the reduction
- Access: 1º, 2º, or 3º Amines.
- R_1 and R_2 can be either H or C. Thus, you can produce either 1º, 2º, or 3º amines in this way:
  - $RCONH_2 \rightarrow$ 1º RCH_2NH_2
  - $RCONHR \rightarrow$ 2º RCH_2NHR
  - $RCONR_2 \rightarrow$ 3º RCH_2NR_2

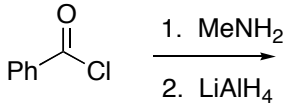
8. **From Amines via Amides**: (Section 19-20)



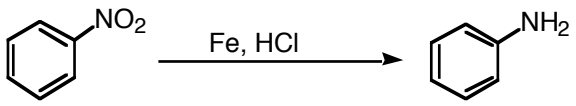
- Access: 1º, 2º, or 3º Amines
- Acylation mechanism required (see reaction 4) but reduction mechanism not required.

1. 

2. 

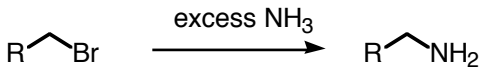
3. 

9. **Reduction of nitro compounds**: (section 19-21C)



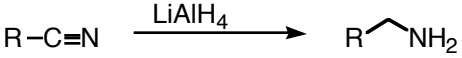
- Access: 1º Amines only (especially aromatic amines)
- No mechanism required.
- There are many other recipes for reduction of nitro compounds:
  - Pd/H_2, Ni/H_2, Pt/H_2,
  - Fe/HCl, Zn/HCl, Sn/HCl

10. **From 1º Alkyl Halides: Alkylation of Ammonia** (Section 19-12, 19-21A) (See reaction 3).



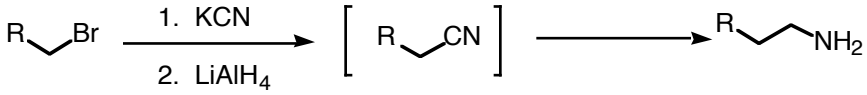
- Access: 1º Amines only
- Mechanism required. (see reaction 3b)
- No change in number of carbons.
- Excess NH_3 prevents polysubstitution.

11. **From Nitriles: Reduction of Nitriles** (Section 19-21B)

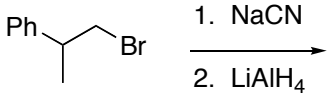


- Access: 1º amines
- Mechanism not required.

12. **From Alkyl Halides: Via the Nitrile** (Section 19-21B)



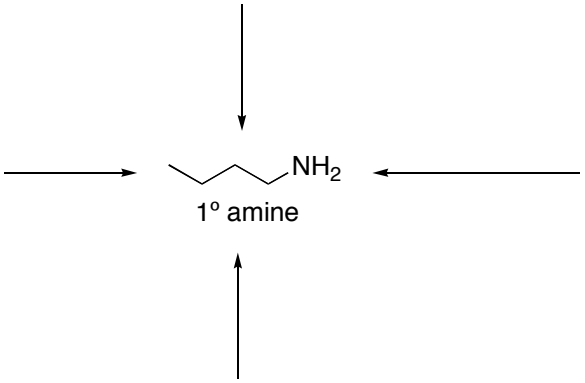
- Access: 1º Amines only
- Mechanism not required.
- One-Carbon chain extension!



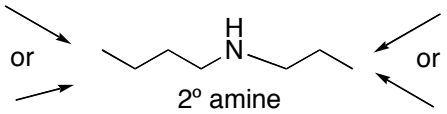
Summary of Amine Syntheses

Route	Reaction Number	Source/ Precursor	Reagent	Available Amines	Comments
1	#6	Aldehydes or Ketones	R_2NH, H^+ $NaBH_3CN$,	1º, 2º, or 3º Amines	
2	#7, #8	Amides	$LiAlH_4$	1º, 2º, or 3º Amines	
3	#7, #8	Amines (via Amide)	3. RCOCl (or RCO_2H, heat) 4. $LiAlH_4$	1º $ArNH_2$	
4	#7, #8	Acid Chlorides or Acids (via Amide)	3. RNH_2 4. $LiAlH_4$		
5	#9	$ArNO_2$	Fe/HCl	1º $ArNH_2$	
6	#10	1º RCH_2Br	NH_3 (excess)	1º only, with CH_2 next to nitrogen	Original carbon chain is not extended
7	#12	1º RCH_2Br (via nitrile)	3. 4. KCN 5. $LiAlH_4$	1º only, with CH_2 next to nitrogen	Original carbon chain is extended by one carbon
8	#11	RCH_2CN	$LiAlH_4$	1º only, with CH_2 next to nitrogen	

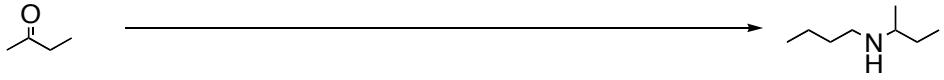
1. Come up with various pathways (4 good ones) to the following 1º amine:

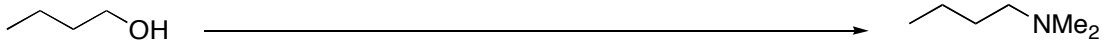


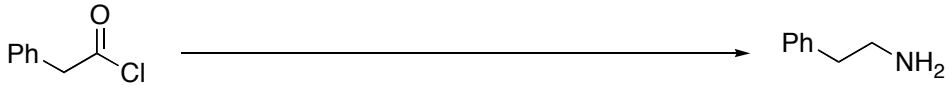
2. Come up with pathways (4 good ones) to the following 2º amine:

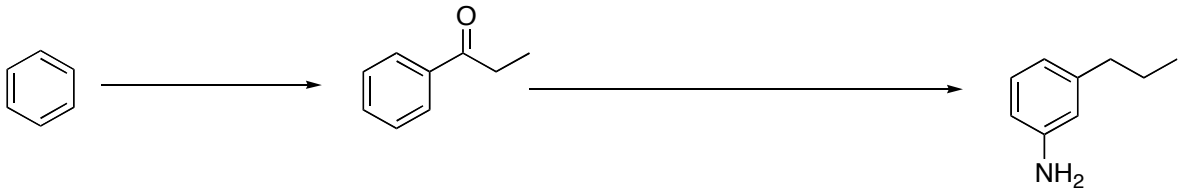


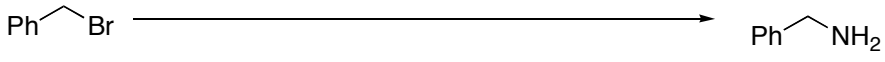
Provide Reagents for the following Transformations.

1. 

2. 

3. 

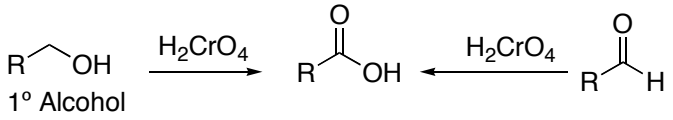
4. 

5. 

6. 

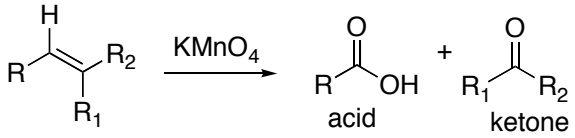
Synthesis of Carboxylic Acids

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



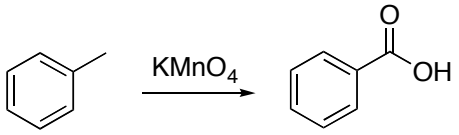
- No mechanism required for the reaction

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



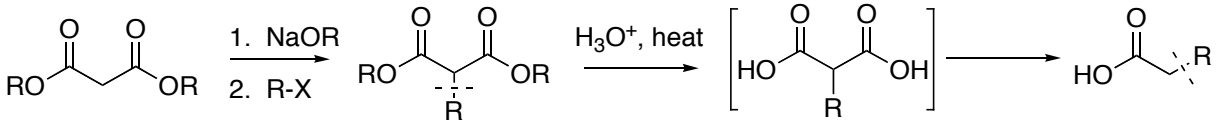
- No mechanism required for the reaction
- Where C=C begins, C=O ends. But where an attached H begins, an OH ends.
- RCH=CHR would give two acids; RCH=CH_2 would give an acid and carbonic acid (H_2CO_3), etc..

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



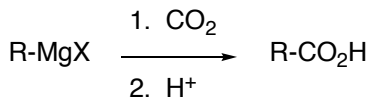
- No mechanism required for the reduction
- While toluenes (methylbenzenes) oxidize especially well, other alkyl benzenes can also be oxidized in this way.

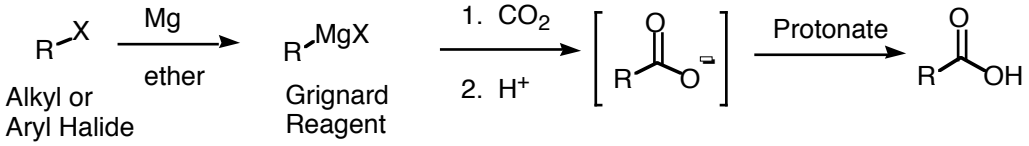
4. **From 1,3-Diesters: Via Hydrolysis/Decarboxylation**: (Chapter 22)



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

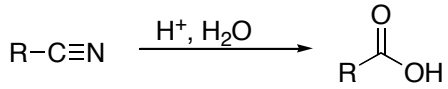
5. **From Grignard Reagents: Via Carboxylation**: (Section 20-8B)





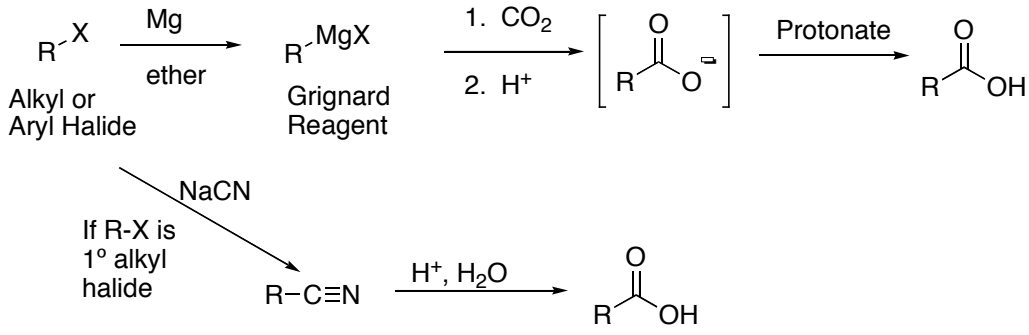
- Access: Alkyl or Aryl Acids
- Alkyl group can be 1º, 2º, or 3º
- Mechanism required. (From Grignard on.)

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)**

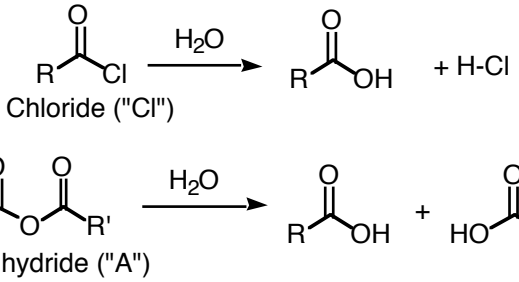


- Formation/Hydrolysis of Nitriles Requires a 1º Alkyl Halide to begin, since the formation of the nitrile proceeds via S_N2
- Reaction via the Grignard has no such limitation
- For 1º alkyl halides, the formation/hydrolysis of the nitrile is technically easier, since there is no need to handle air-sensitive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

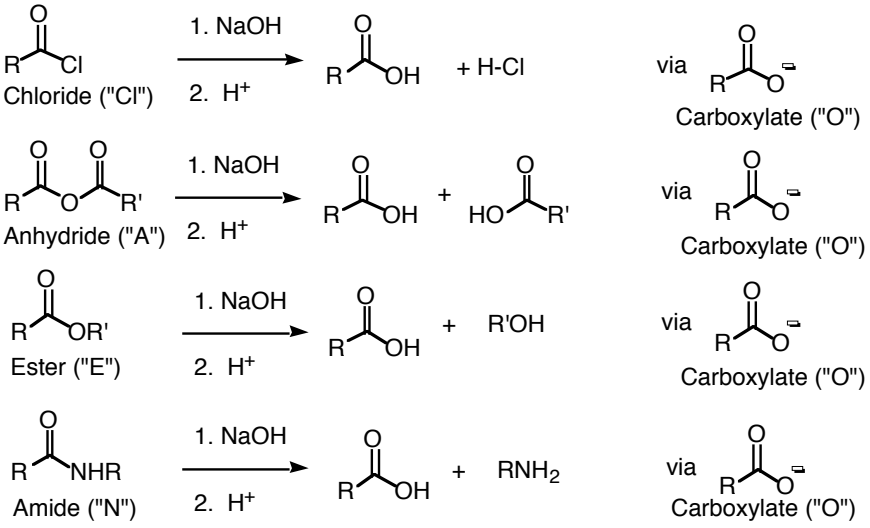


b) "Lateral" hydrolysis: From esters with water and acid catalysis (ACID WATER)

- **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

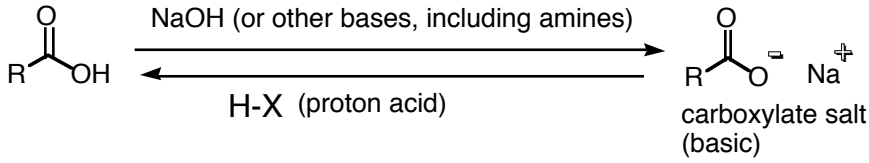
<u>c) "Basic" hydrolysis using NaOH (BASIC WATER) (always downhill) followed by H^+ workup</u>

- **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)

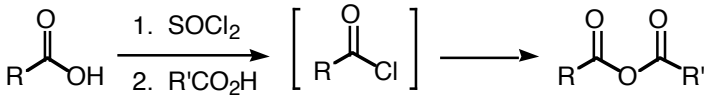


- Mechanism: Required (deprotonation)
- Reverse Mechanism: Required (protonation)
- Carboxylic acids are completely converted to carboxylate salts by base
- Carboxylate salts are completely neutralized back to carboxylic acids by strong acid
- The resonanance stabilization makes carboxylates much more 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)

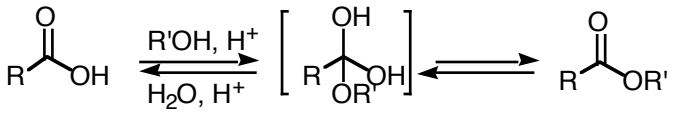
- Mechanism: Not Required
- Easy (but smelly) reaction. Side products HCl and SO_2 are gases, so can just evaporate away leaving clean, useful product. So no workup is required, nice!
- Extremely useful because the acid chlorides are so reactive, and can be converted into esters, anhydrides, or amides.

11. **Indirect Conversion to Anhydrides**



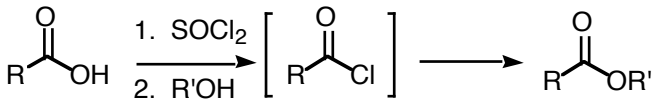
- mechanism required **for acid chloride to anhydride conversion: addition-elimination-deprotonation**
- Conversion of the acid chloride to the anhydride is a "downhill" reaction energetically.
- Conversion of the acid to the anhydride directly would be an "uphill" reaction

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



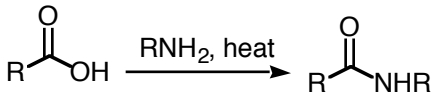
- **mechanism required: protonation-addition-deprotonation (to hemiacetal intermediate) followed by protonation-elimination-deprotonation (hemiacetal to ester)**
- These reactions are under equilibrium control. With excess water, you go to the acid. With removal of water and/or excess alcohol, the equilibrium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



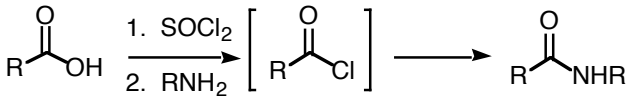
- mechanism required **for acid chloride to ester conversion: addition-elimination-deprotonation**
- Conversion of the acid chloride to the ester is a "downhill" reaction energetically.

14. **Direct Conversion to Amides**



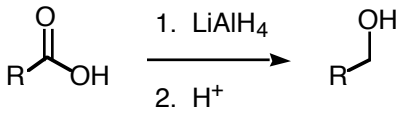
- **mechanism not required**
- This is a "downhill" reaction energetically, but is complicated and retarded by acid-base reactions. Normally the "indirect) conversion is more clean in the laboratory
- This reaction occurs routinely under biological conditions, in which enzymes catalyze the process rapidly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

15. **Indirect Conversion to Amides**



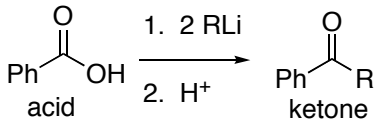
- mechanism required **for acid chloride to amide conversion: addition-elimination-deprotonation**
- This reaction sequence works very well in the laboratory

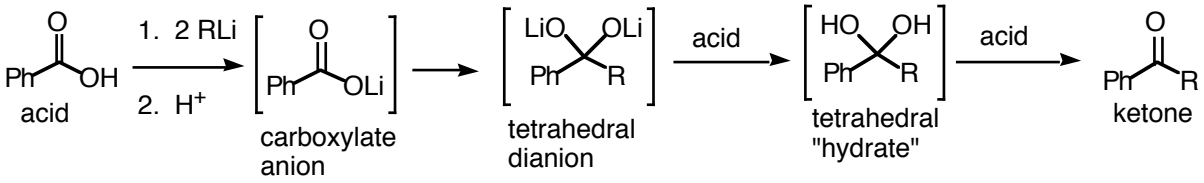
16. **Reduction to Primary Alcohol** (Sections 10-11, 20-14)



- **mechanism not required**

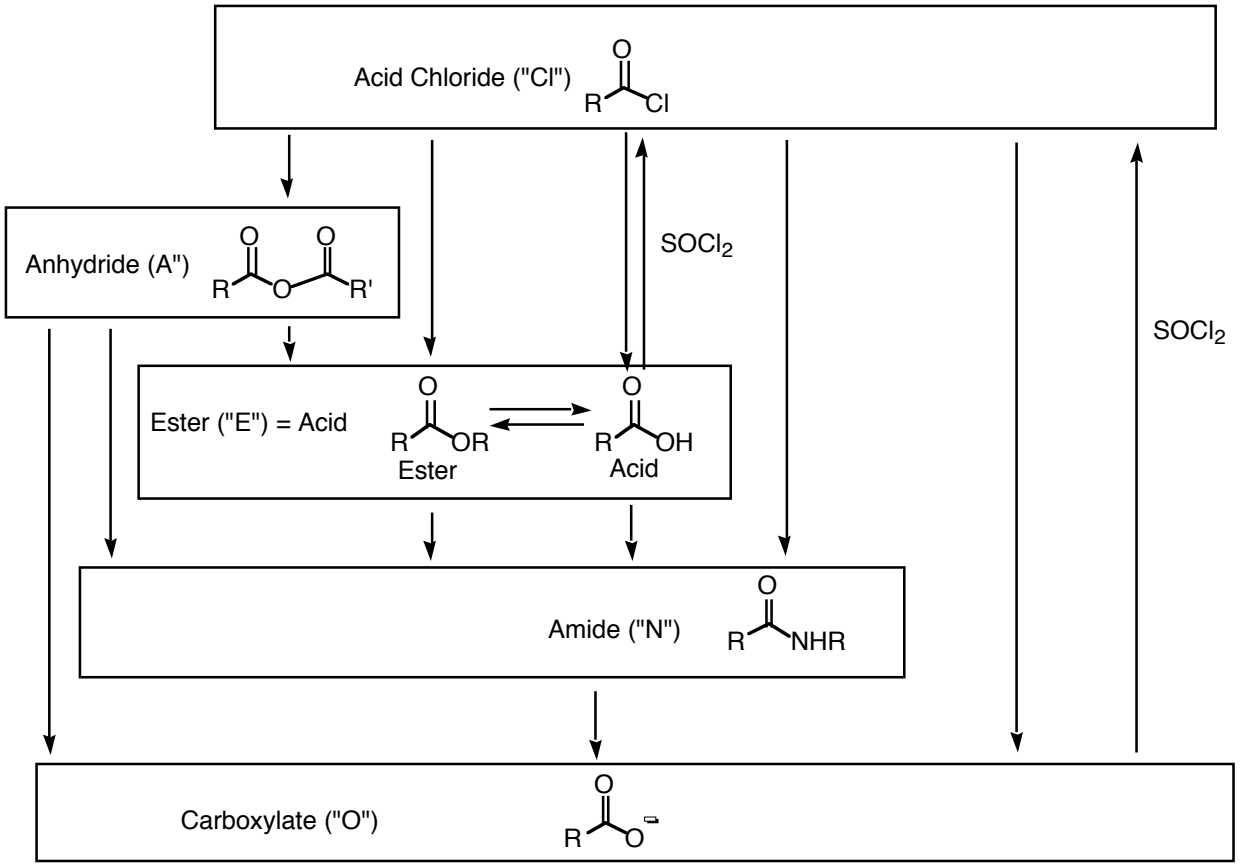
17. **Alkylation to Form Ketones** (Section 18-19, 20-15)





- **mechanism not required**

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

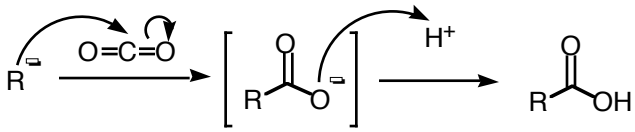


- "Cl-A-vE-N-O" Chlorides-Anhydrides-Esters (and Acids)-Amides-Carboxylates
- Any downhill step can be done directly
- Any "lateral" step (acid to ester or vice-versa) can be done with acid
- Any "uphill" sequence requires going up through the Acid Chloride, either directly (from an acid or a carboxylate)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

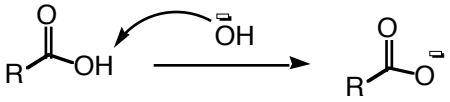
A. Miscellaneous

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



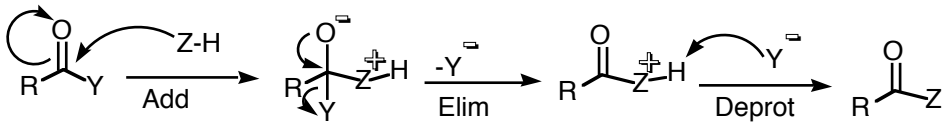
- exactly like any Grignard reaction

9. Reaction as a Proton Acid



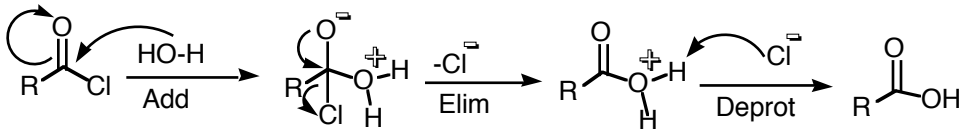
B. Any "Downhill" Interconversions (8a, 8c, 11, 13, 15, 18): All Proceed by Addition-Elimination-Deprotonation

General

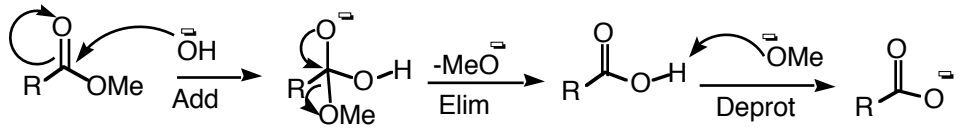


Examples

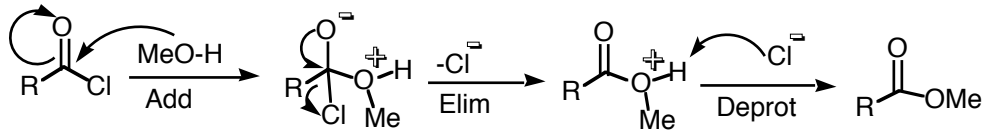
Reaction 8a



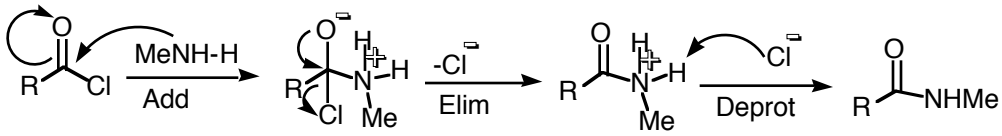
Reaction 8c (Note: Slightly different because hydroxide nucleophile is anionic, not neutral; and product carboxylate is anionic, not neutral)



Reaction 13



Reaction 15

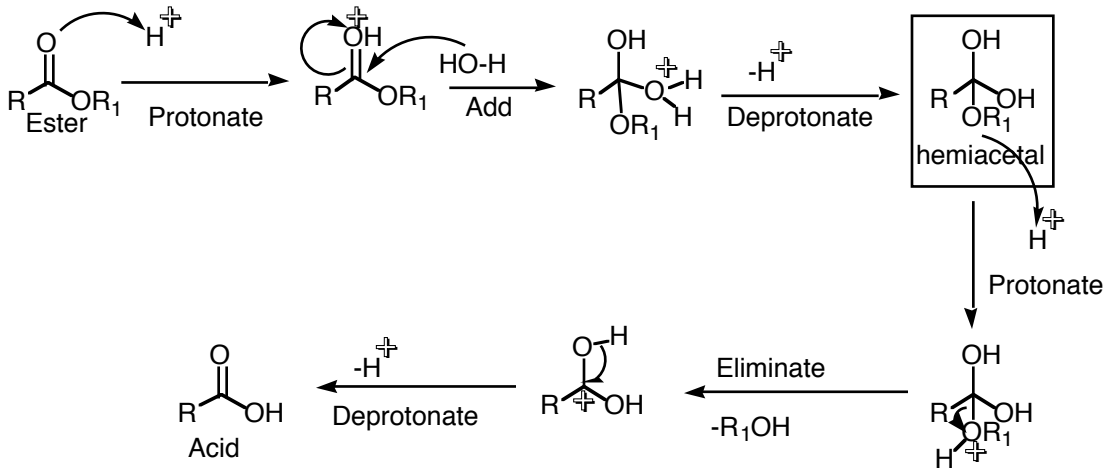


C. "Lateral" Interconversions (8b/12): Acid-Catalyzed conversion from Ester to Acid (8b) or From Acid to Ester (12): (ACID WATER)

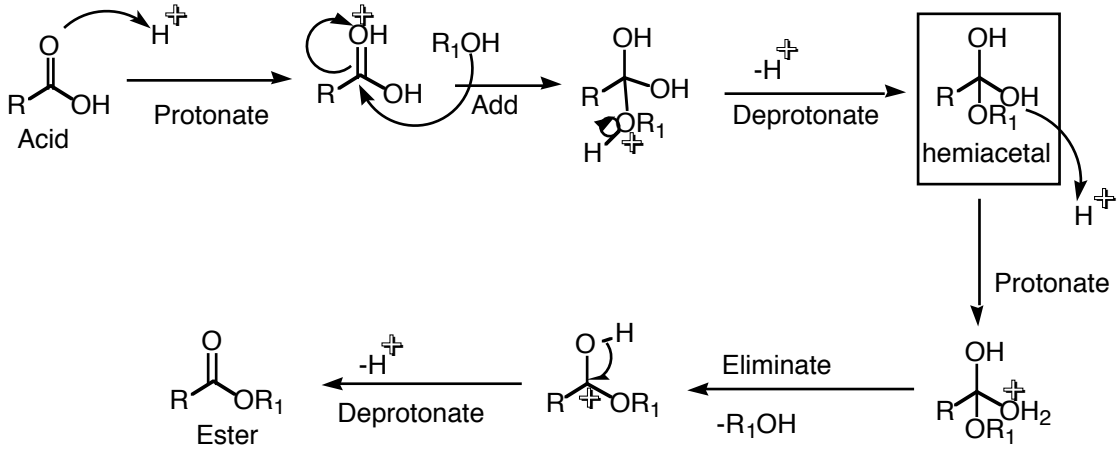
- **General Mechanism: protonation-addition-deprotonation (acid-catalyzed addition to a carbonyl to produce the tetrahedral hemiacetal intermediate) followed by protonation-elimination-deprotonation (acid catalyzed elimination)**

Examples

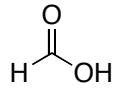
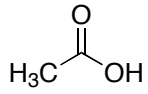
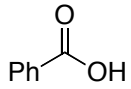
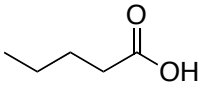
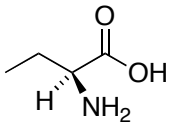
Reaction 8b: Ester to Acid



Reaction 12: Acid to Ester



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-oxoheptanoic acid

Physical Properties (Section 18.3)

Boiling Points: (weight being equal): acid > alcohol > 1,2º amines > non-H-bonders

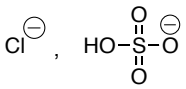
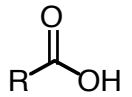
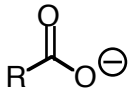
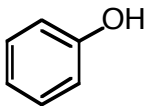
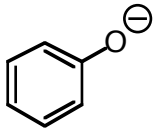
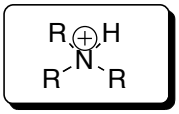
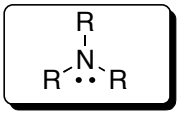
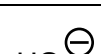
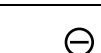
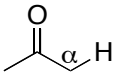
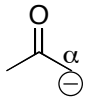
- Acids boil about 20º higher than same-weight alcohols
- First four acids are completely water soluble

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)

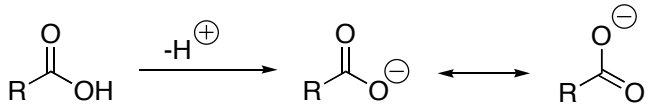
Class	Structure	Ka	Acid Strength	Base	Base Strength	
Strong Acids	H-Cl, H_2SO_4	10^2				**S**mell **A**wful!
Hydronium	H_3O^+, ROH^+ cationic	10^0		H_2O, HOR neutral		**H**umans
Carboxylic Acid		10^{-5}				**C**uz
Phenol		10^{-10}				**P**eople
Ammonium Ion (Charged)	 Charged, but only weakly acidic!	**10^{-12}**		 Neutral, but basic		**A**gainst
Water	HOH	10^{-16}				**W**orking
Alcohol	ROH	10^{-17}				**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

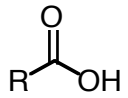
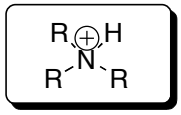
1. **Charge**
2. **Electronegativity**
3. **Resonance/Conjugation**
4. **Hybridization**
5. **Impact of Electron Donors/Withdrawers**
6. **Amines/Ammoniums**

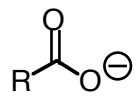
- **When comparing/ranking any two acids or bases, go through the above checklist to see which factors apply and might differentiate the two.**
- **When A neutral acid is involved, it's often best to draw the conjugate anionic bases, and to think from the anion stability side.**

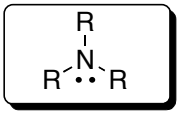
Acidity (20-4)

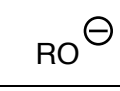


- Anion is stabilized by conjugation/resonance
- Charge dispersal
- Carboxylate is an anion, so is stabilized by electron withdrawing groups (increasing acidity) and destabilized by electron donating groups (decreasing acidity)

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



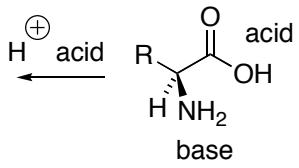


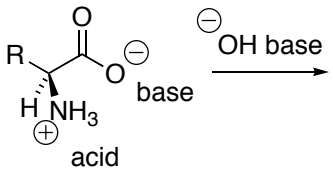


- Acids are a million times more acidic than average ammoniums (despite charge)
- Acids are trillions more acidic than alcohols

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. 

c. 

d. 

20.5 Carboxylate Salts

$RCO_2H + NaOH \rightarrow RCO_2Na + H_2O$ Produces weaker acid and base

- Easy to make
- Ionic → water soluble

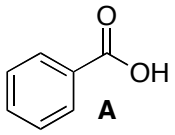
Acids are soluble in NaOH/water or $NaHCO_3/H_2O$

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

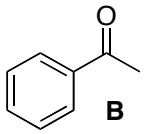
Purification Schemes for Acids from other Organics Based on Acidity

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: $RCO_2Na + HCl \rightarrow RCO_2H$
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

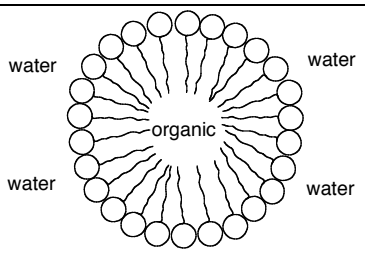
Soaps (not for test)

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

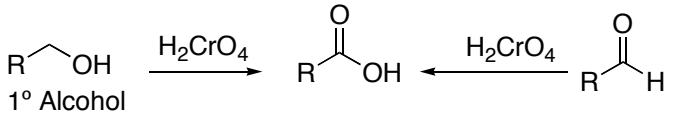
The hydrophobic hydrocarbon tails (strings) self-aggregate, while the ionic heads (circles) keep the microdroplet soluble in water. Organic materials can be dissolved inside the organic center, and carried through the water. Thus grease gets dissolved, and dirt protected by grease is freed.	

B. Synthesis of Carboxylic Acids

Synthesis of Carboxylic Acids

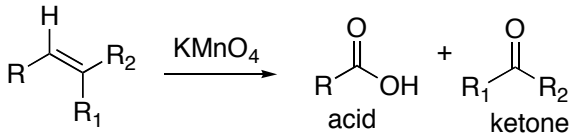
Review (20.8)

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



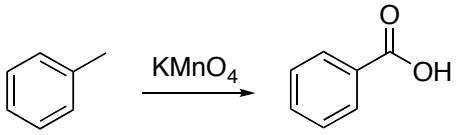
- No mechanism required for the reaction

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



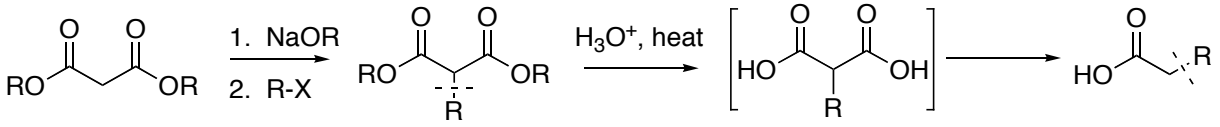
- No mechanism required for the reaction
- Where C=C begins, C=O ends. But where an attached H begins, an OH ends.
- RCH=CHR would give two acids; RCH=CH_2 would give an acid and carbonic acid (H_2CO_3), etc..

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.

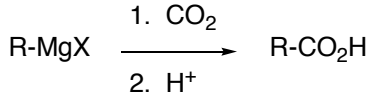
4. **From 1,3-Diesters: Via Hydrolysis/Decarboxylation**: (Chapter 22)

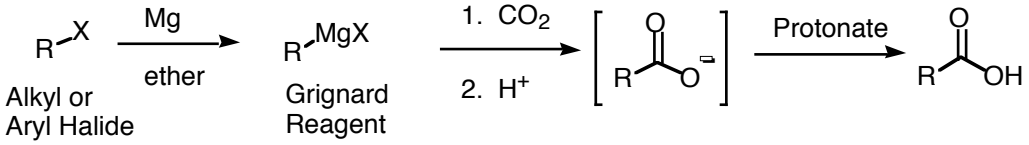


- Mechanism: Deprotation/Alkylation covered previously. The hydrolysis of the esters to acids will be required (see reaction 8b)

New Routes

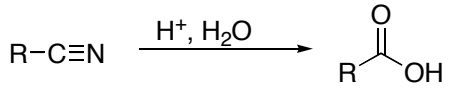
5. **From Grignard Reagents: Via Carboxylation**: (Section 20-8B)





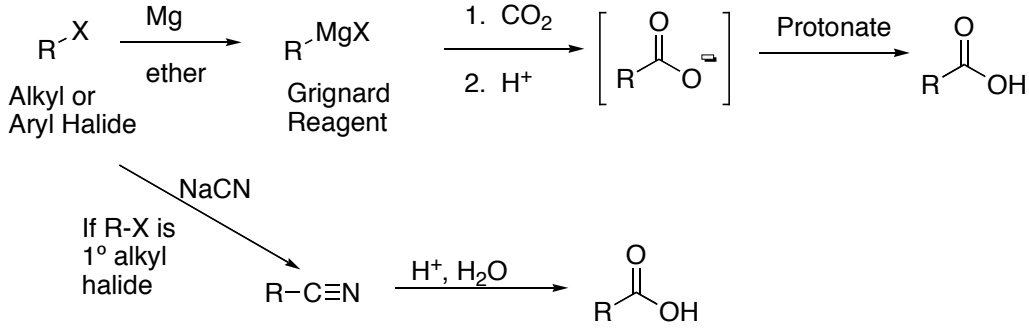
- Access: Alkyl or Aryl Acids
- Alkyl group can be 1º, 2º, or 3º
- Mechanism required. (From Grignard on.)

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



- Mechanism not required.

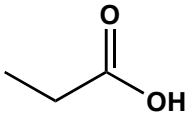
7. **From Halides: Either via Formation and Carboxylation of Grignards (Reaction 5) or via Formation and Hydrolysis of Nitriles (Reaction 6)**



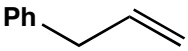
- Formation/Hydrolysis of Nitriles Requires a 1º Alkyl Halide to begin, since the formation of the nitrile proceeds via S_N2
- Reaction via the Grignard has no such limitation
- For 1º alkyl halides, the formation/hydrolysis of the nitrile is technically easier, since there is no need to handle air-sensitive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

Problems

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

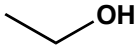
a. (C_3H_8O) $\xrightarrow{H_2CrO_4}$ 

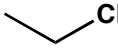
b. Bromobenzene $\xrightarrow[3.\ H_2CrO_4]{1.\ Mg;\ 2.\ epoxide;\ H_2O}$

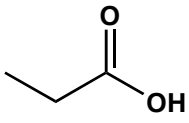
c. 

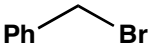
$\xrightarrow[2.\ H^+]{1.\ KMnO_4/NaOH/heat}$ (+ carbonic acid)

d. Benzene $\xrightarrow[FeBr_3]{Br_2}$ $\xrightarrow{Mg}$ $\xrightarrow[2.\ H^+]{1.\ CO_2}$

e. 

$\xrightarrow[2.]{1.}$ 

$\xrightarrow{H_3O^+}$ 

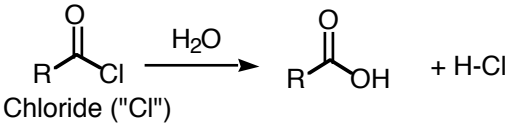
f. 

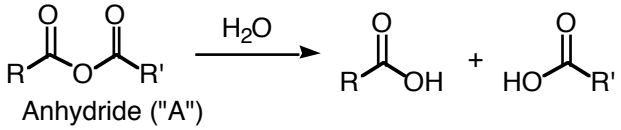
$\xrightarrow[2.\ H_3O^+]{1.\ NaCN}$

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**



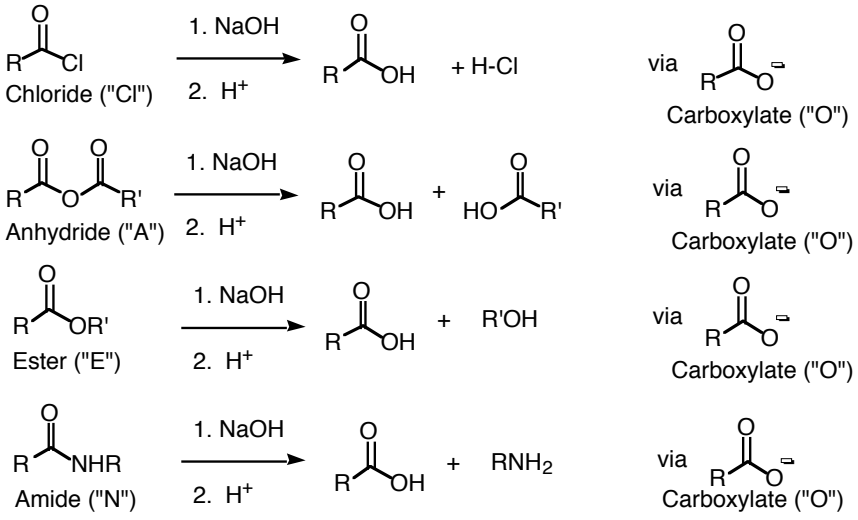


b) "Lateral" hydrolysis: From esters with water and acid catalysis (ACID WATER)

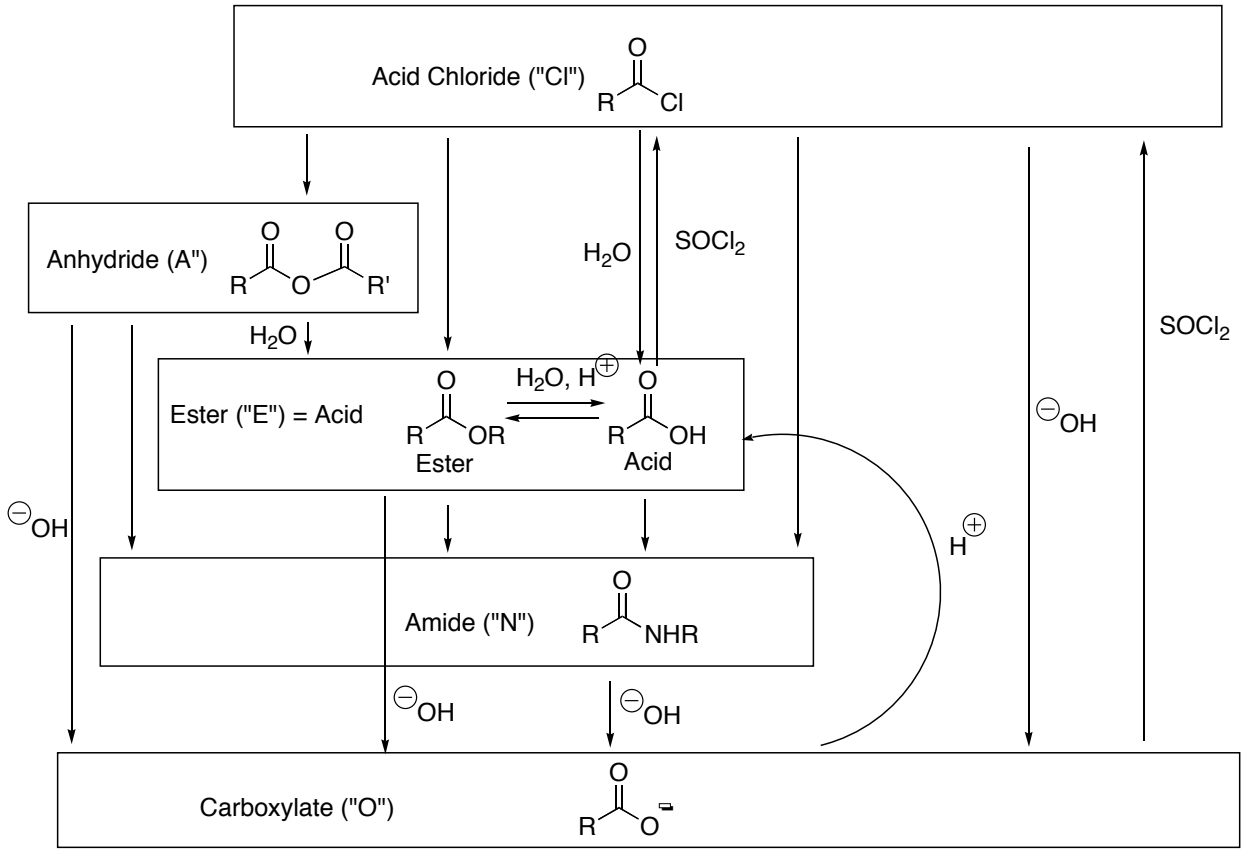
- **mechanism required: protonation-addition-deprotonation (to hemiacetal intermediate) followed by protonation-elimination-deprotonation (hemiacetal to acid)**
- These reactions are under equilibrium control. With excess water, you go to the acid. With removal of water and/or excess alcohol, the equilibrium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



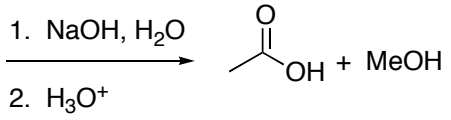
- "Cl-A-vE-N-O" Chlorides-Anhydrides-Esters (and Acids)-Amides-Carboxylates
- Any downhill step can be done directly
- Any "lateral" step (acid to ester or vice-versa) can be done with acid
- Any "uphill" sequence requires protonation or going up through the Acid Chloride, either directly (from an acid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

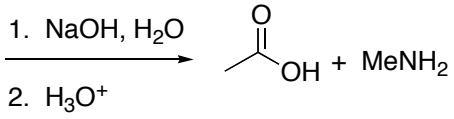
<u>"Cl-A-vE-N-O" applied to Hydrolysis</u>

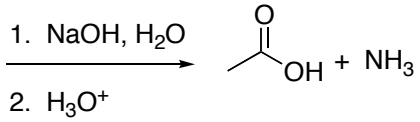
1. Chlorides and Anhydrides are "above" acids, so can be converted to acids by direct hydrolysis with neutral water
2. Esters are "lateral" to acids, so can be hydrolyzed to acids by acid-catalyzed hydrolysis
3. Chloride, anhydrides, esters, and amides can all be base-hydrolyzed (NaOH/water) to carboxylates.
   - 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

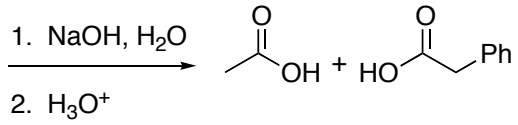
1. For the following problems, draw the starting materials that would give the indicated hydrolysis products.

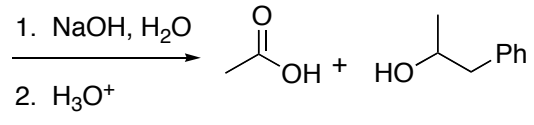
- Note: All of these are drawn as basic hydrolyses, but some could also be done using neutral water or acidic water. Mark which could proceed using neutral hydrolysis or acid-catalyzed hydrolysis in addition to via basic hydrolysis.







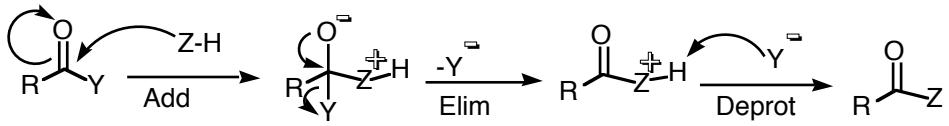




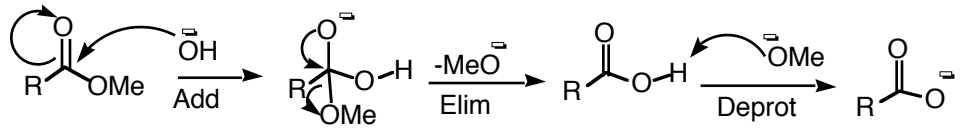
Mechanism: General Mechanism for Any "Downhill" Cl-A-vE-N-O Interconversions (8a, 8c, 11, 13, 15, 18):

All Proceed by Addition-Elimination-Deprotonation

General

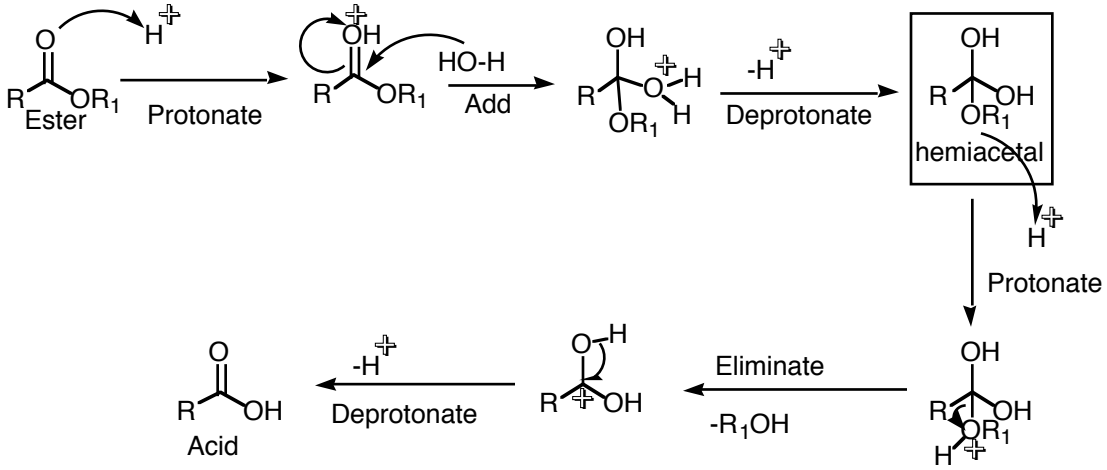


<u>Base Case</u>, Using Anionic Hydroxide: Slightly different because hydroxide nucleophile is anionic, not neutral; and product carboxylate is anionic, not neutral)

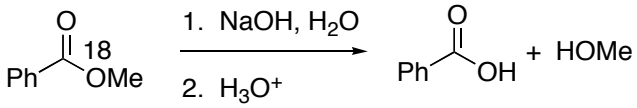


Acid-Catalyzed conversion from Ester to Acid (8b): (ACID WATER)

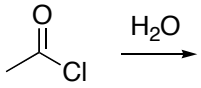
- **General Mechanism: protonation-addition-deprotonation (acid-catalyzed addition to a carbonyl to produce the tetrahedral hemiacetal intermediate) followed by protonation-elimination-deprotonation (acid catalyzed elimination)**

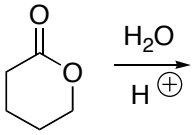


<u>Draw the Mechanisms for the following Hydrolyses</u>



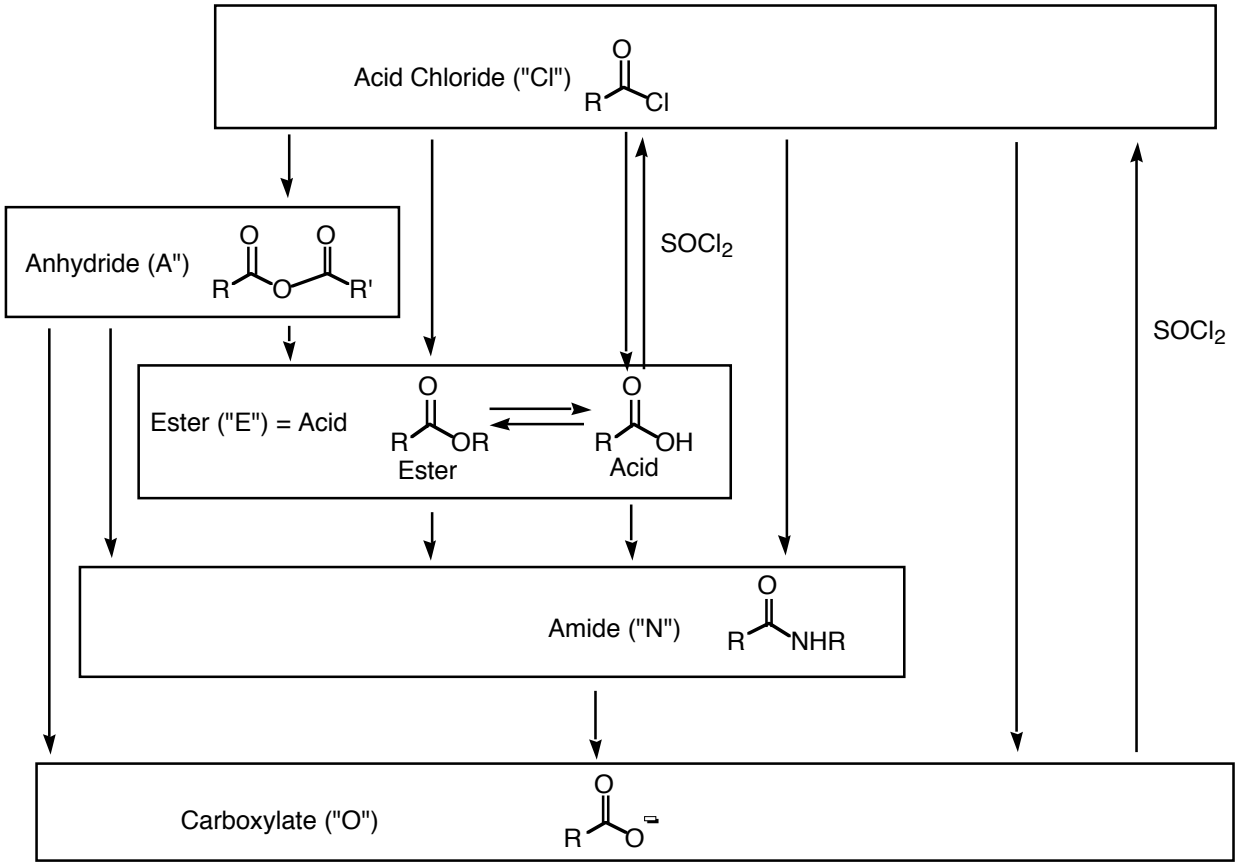
Where will the O^{18} label end up?





C. Reactions of Carboxylic Acids

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



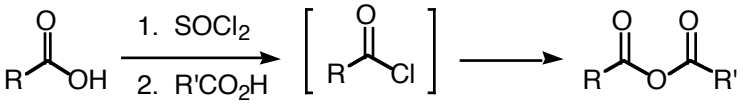
- "Cl-A-vE-N-O" Chlorides-Anhydrides-Esters (and Acids)-Amides-Carboxylates
- All can be interconverted by substitution procedures: 1, 2, or 3 steps
- Any downhill step can be done directly
- Any "lateral" step (acid to ester or vice-versa) can be done with acid
- Any "uphill" sequence requires going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

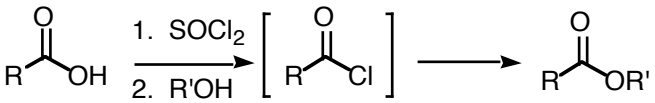
- Mechanism: Not Required
- Easy (but smelly) reaction.
  - Side products HCl and SO_2 are gases, so can just evaporate away leaving clean, useful product. So no workup is required, nice!
- Extremely useful because the acid chlorides are so reactive, and can be converted into esters, anhydrides, or amides.

11. **Indirect Conversion to Anhydrides**



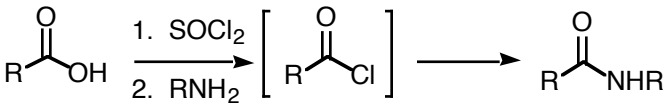
- mechanism required **for acid chloride to anhydride conversion: addition-elimination-deprotonation**
- Conversion of the acid chloride to the anhydride is a "downhill" reaction energetically.
- Conversion of the acid to the anhydride directly would be an "uphill" reaction
- Base often present to absorb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

13. **Indirect Conversion to Esters via Acid Chlorides**



- 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

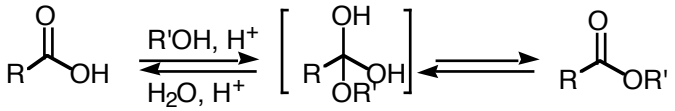
15. **Indirect Conversion to Amides**



- 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

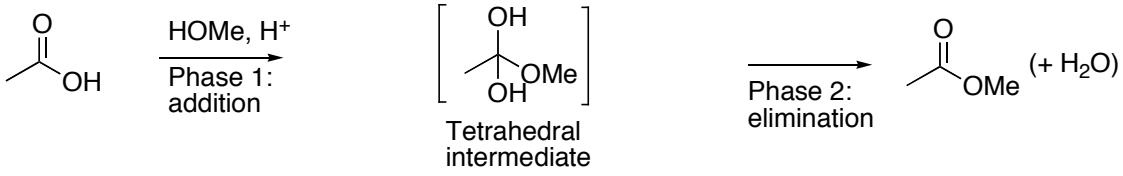
Condensation/Hydrolysis: Interconversions between Acids and Esters (20.10, 13, 21.7)

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

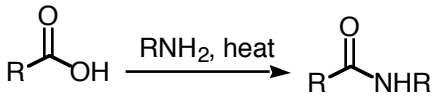


- **mechanism required: protonation-addition-deprotonation (to hemiacetal intermediate) followed by protonation-elimination-deprotonation (hemiacetal to ester)**
- These reactions are under equilibrium control.
  1. With excess water, you go to the acid.
  2. With removal of water and/or excess alcohol,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

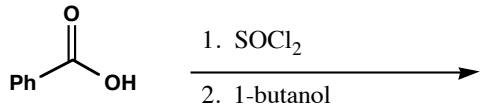


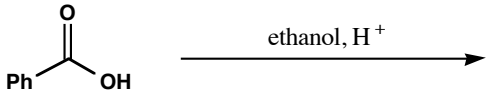
- **mechanism not required**
- This is a "downhill" reaction energetically, but is complicated and retarded by acid-base reactions. Normally the "indirect) conversion is more clean in the laboratory
- This reaction occurs routinely under biological conditions, in which enzymes catalyze the process rapidly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

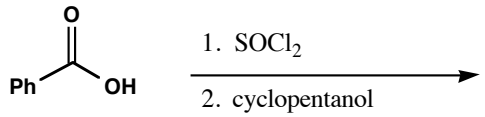
Problems

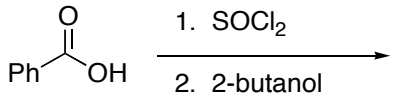
1. Synthesis of Acid derivatives. Draw the products for the following reactions.

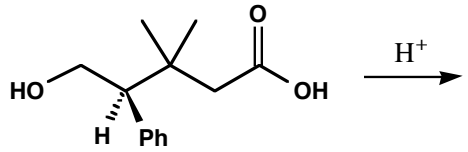
a. 

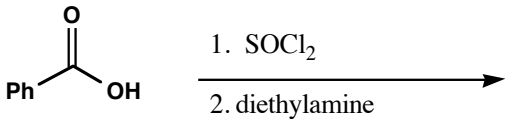
b. 

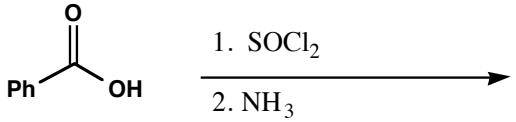
c. 

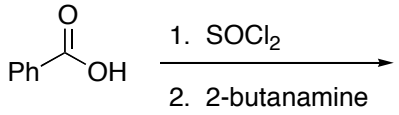
d. 

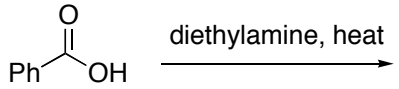
e. 

f. 

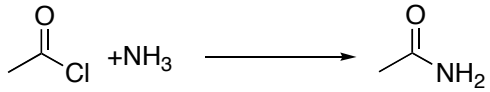
g. 

h. 

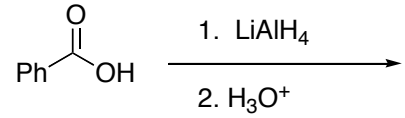
i. 

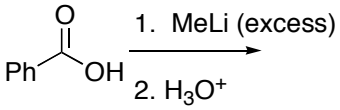
j. 

1. Draw the mechanism.

b. 

2. Draw the products for the following reactions.

a. 

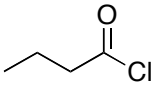
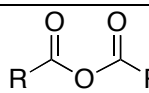
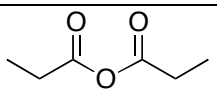
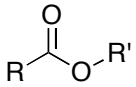
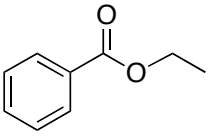
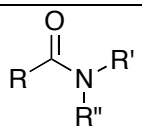
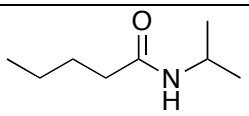
b. 

Ch. 21 Carboxylic Acid Derivatives: 

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

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	

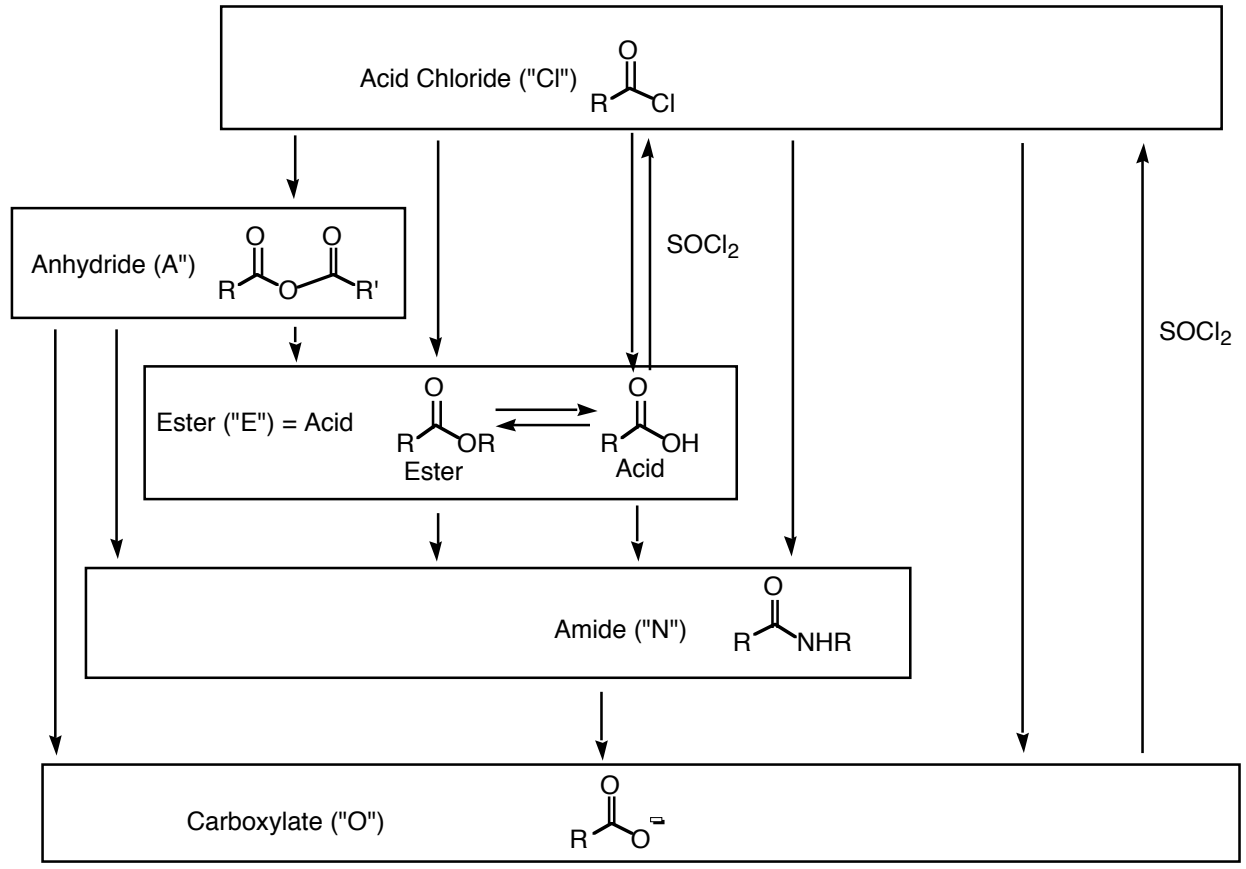
1. Draw the structures for the following esters.

a. propyl benzoate

b. methyl ethanoate

c. ethyl butanoate

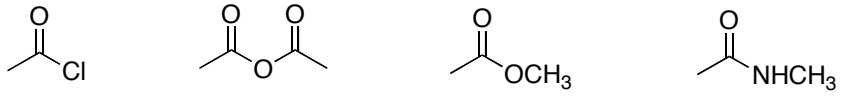
Interconversion of Acid Derivatives: Cl-A-vE-N-O



a. "Cl-A-vE-N-O" Chlorides-Anhydrides-Esters (and Acids)-Amides-Carboxylates
b. All can be interconverted by substitution procedures: 1, 2, or 3 steps
c. Any downhill step can be done directly
d. Any "lateral" step (acid to ester or vice-versa) can be done with acid
e. 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.)
f. 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)

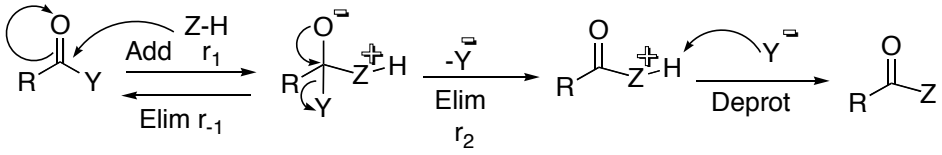
2. Rank the acidity of the following molecules, **1** being most acidic and **4** being least acidic.

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



Notes:

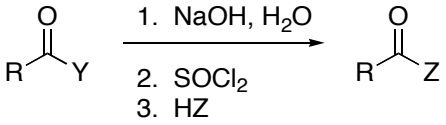
- Any "downhill" reaction can be done in one laboratory step
- Any "downhill" reaction involves a 3-step mechanism: addition-elimination-deprotonation



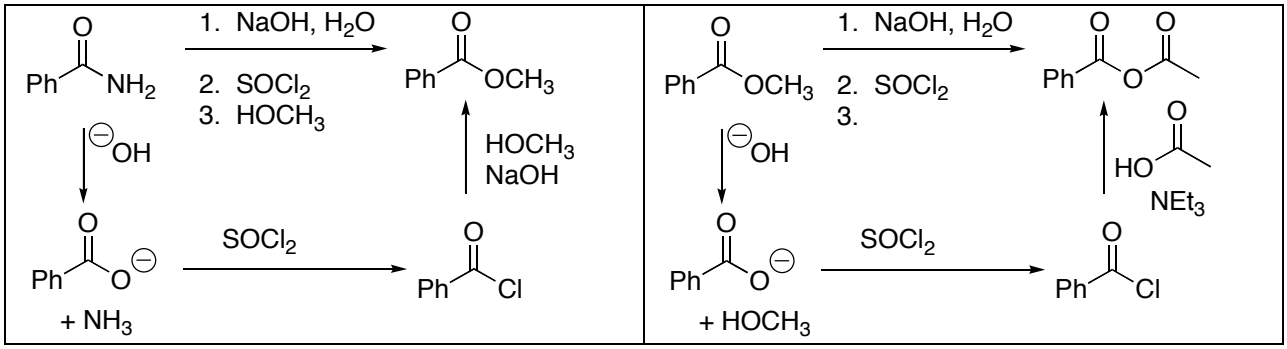
- The overall reactivity correlates the leaving ability of the $Y^{\ominus}$ for two reasons
  1. This affects the kinetic r_2/r_{-1} partion. If r_2 is slow, the addition is simply reversible
  2. The same factors that make $Y^{\ominus}$ a good leaving group also make the initial carbonyl more reactive 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 | Cl-A-vE-N-O |

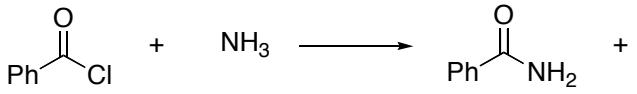
B. "Uphill" Reaction Sequences: 3-steps

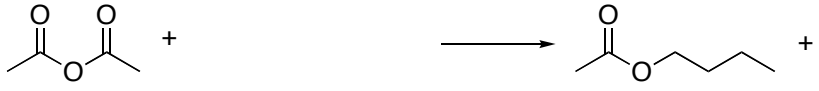


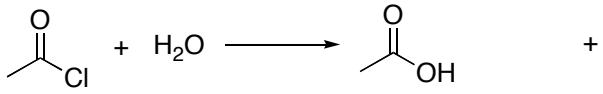
Ex:

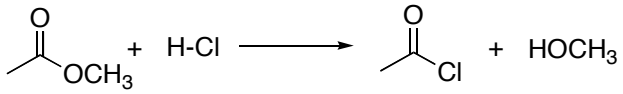


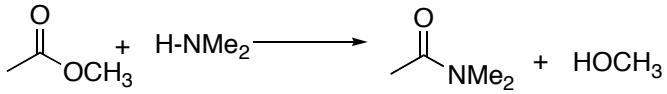
1. Which will proceed easily/directly? ("downhill"?) Add Appropriate Reactant(s) and Side Product. If it doesn't go directly, give indirect route.

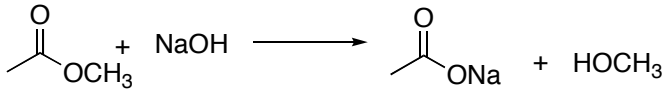
a. 

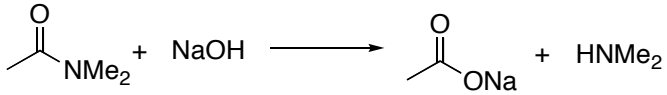
b. 

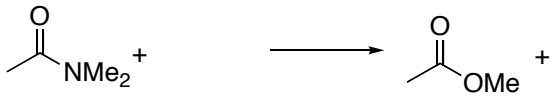
c. 

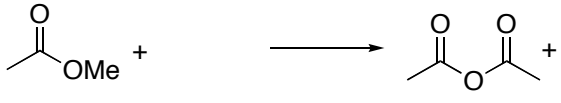
d. 

e. 

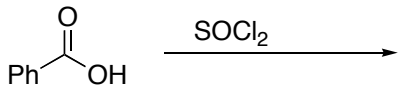
f. 

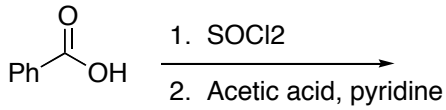
g. 

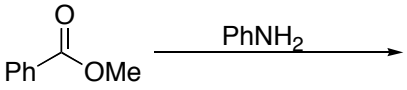
h. 

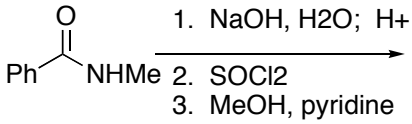
i. 

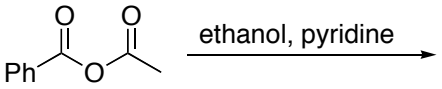
1. Provide products for the following transformations.

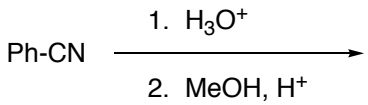
a. 

b. 

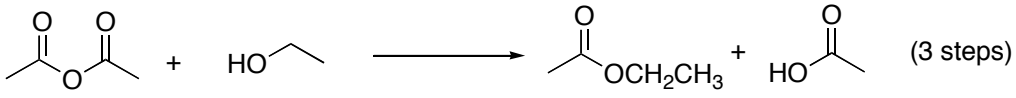
c. 

d. 

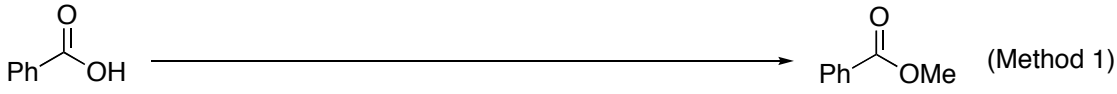
e. 

f. 

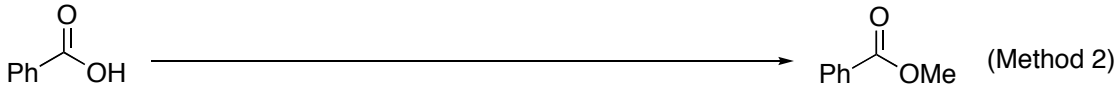
2. Draw the mechanism for the following reaction.



1. Provide reagents for the following transformations.

a. 

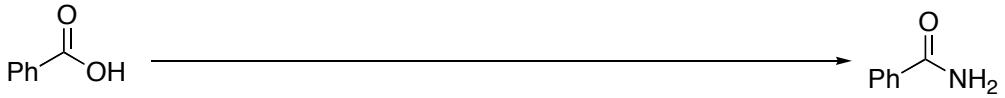
(Method 1)

b. 

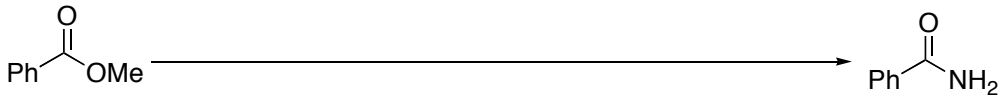
(Method 2)

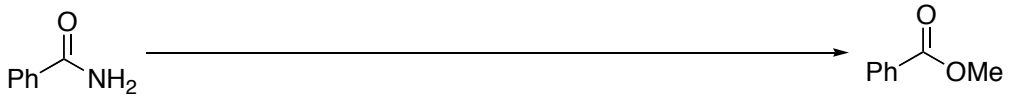
c. 

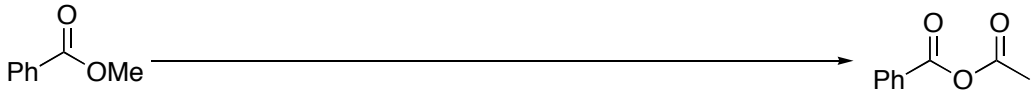
(Method 1)

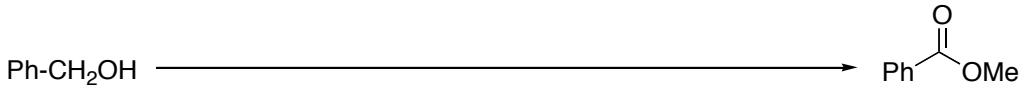
d. 

(Method 2)

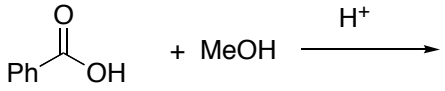
e. 

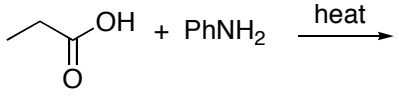
f. 

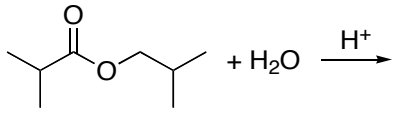
g. 

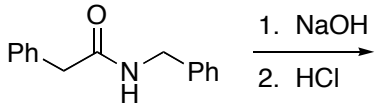
h. 

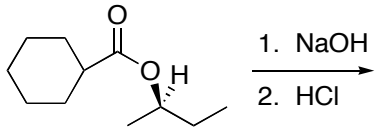
2. Provide products for the following condensation or hydrolysis transformations.

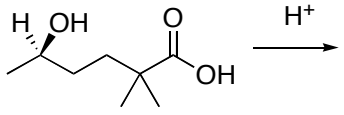
a. 

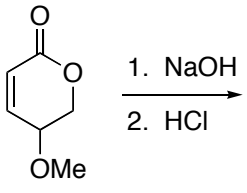
b. 

c. 

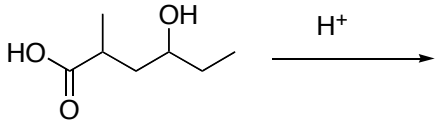
d. 

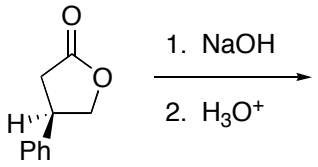
e. 

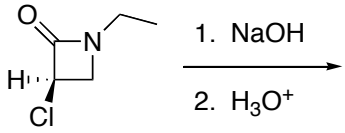
f. 

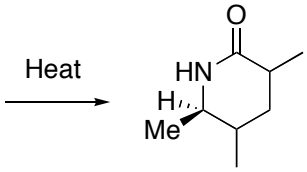
g. 

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

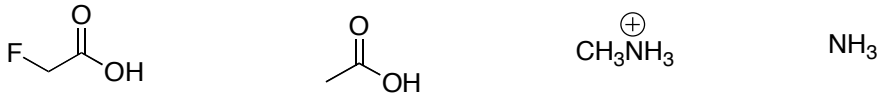
a. 

b. 

c. 

d. 

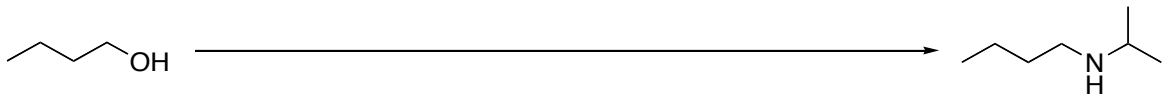
4. Rank the following as acids or bases.

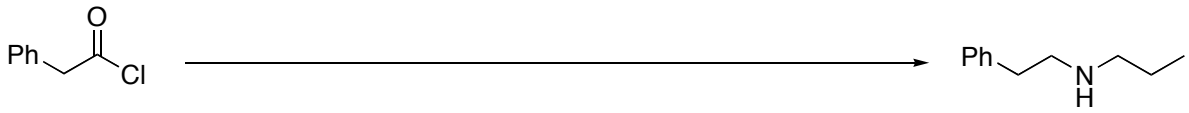
a. 

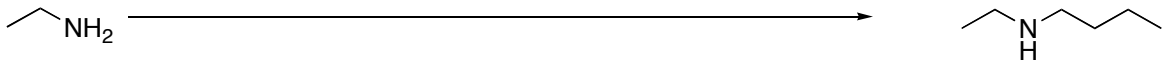
b. 

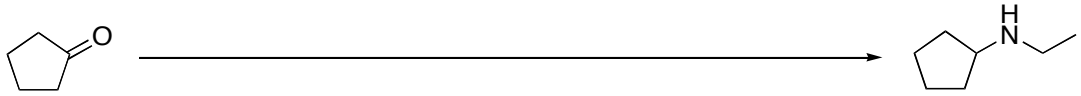
c. 

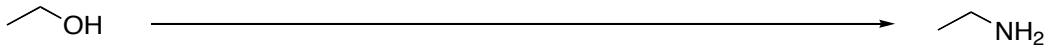
5. Provide reagents for the following transformations. There may be more than one solution.

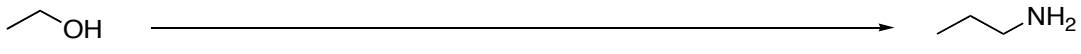
a. 

b. 

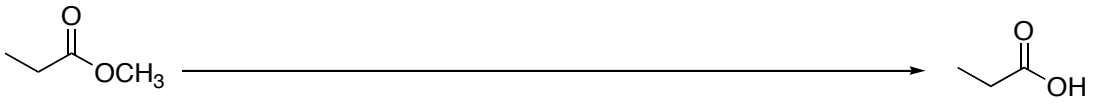
c. 

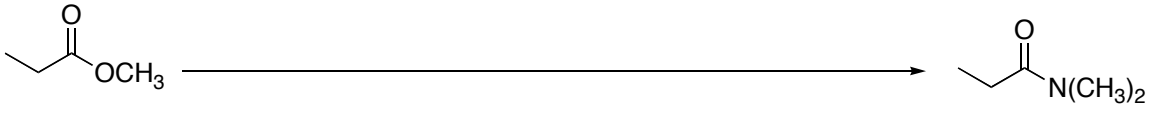
d. 

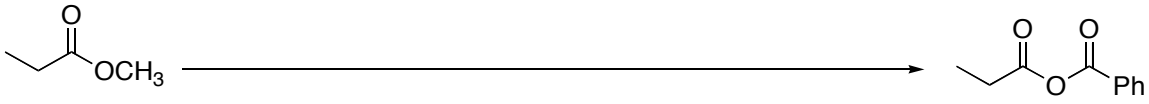
e. 

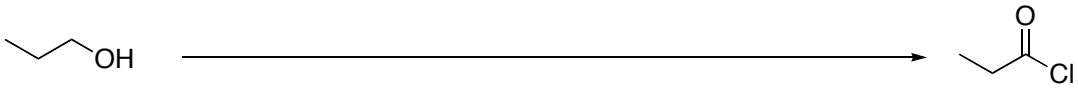
f. 

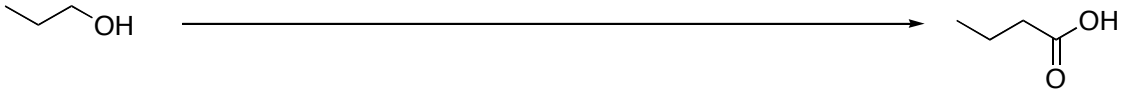
6. Provide reagents for the following transformations. There may be more than one solution.

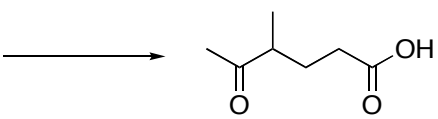
a. 

b. 

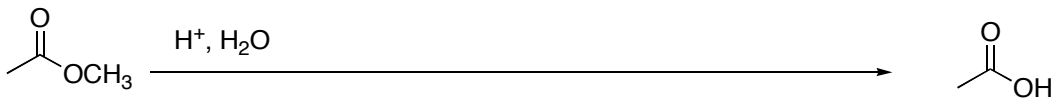
c. 

d. 

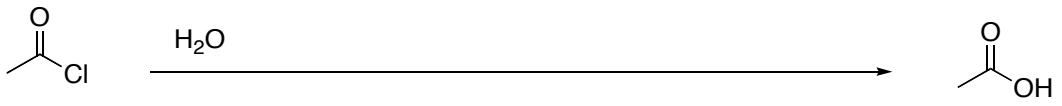
e. 

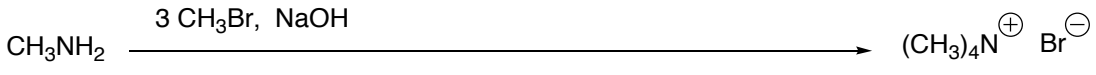
f. 

7. Provide mechanism for the following reactions.

a. 

b. 

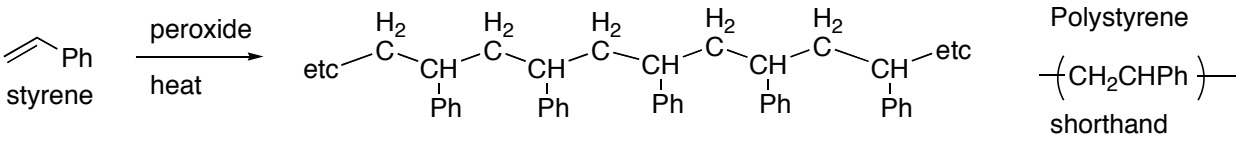
c. 

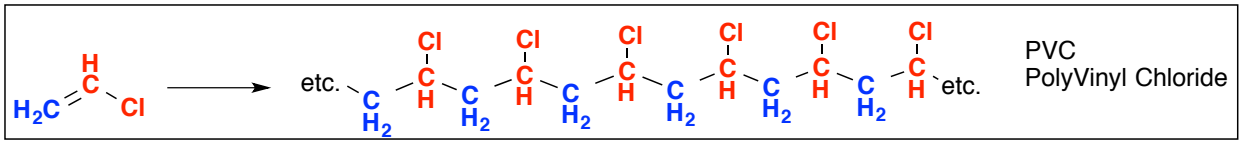
d. 

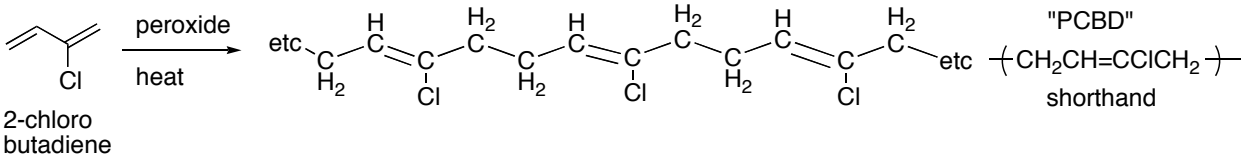
Polymers: Very large molecule composed of small repeating units (monomers) (8-16, ch26)

Two major classes of polymers:

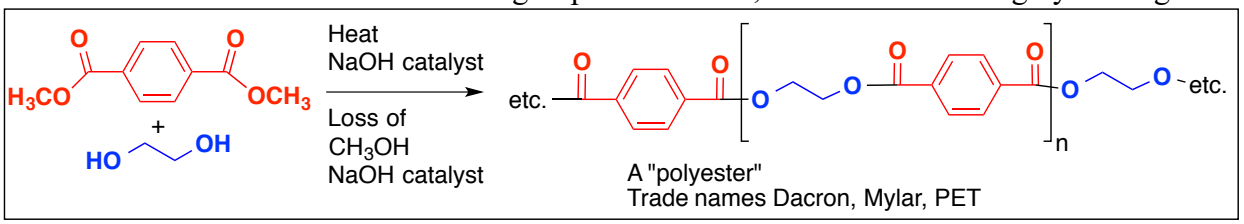
1. **Addition polymers**, made from alkenes and conjugated dienes:
   - All of the atoms in the original monomers are present in the polymers.
   - Additions can proceed via any of radical, cationic, anionic, or transition-metal mediated mechanism

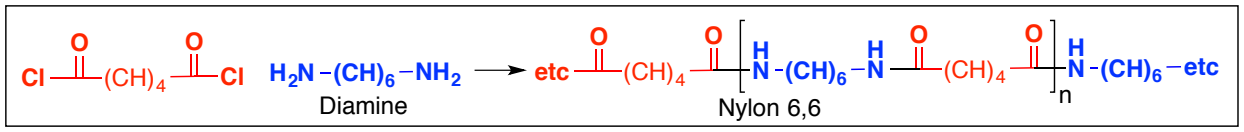






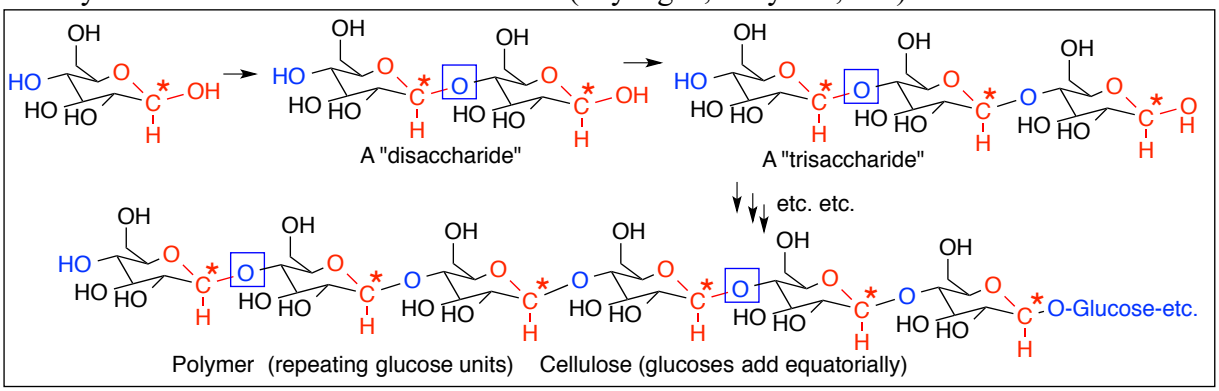
2. **Condensation polymers**,
   - Amides or Esters links connect units
   - Typically amines or alcohols reacting with carboxylic acids or ClAvENO variants
   - Polymerization is accompanied by extrusion of water if an acid is the precursor for the ester or amide
   - HCl, RCO_2H, or ROH may be produced if using RCOCl, anhydride, or an ester
   - Each unit needs a functional group at either end, so as to be able lengthy chain growth

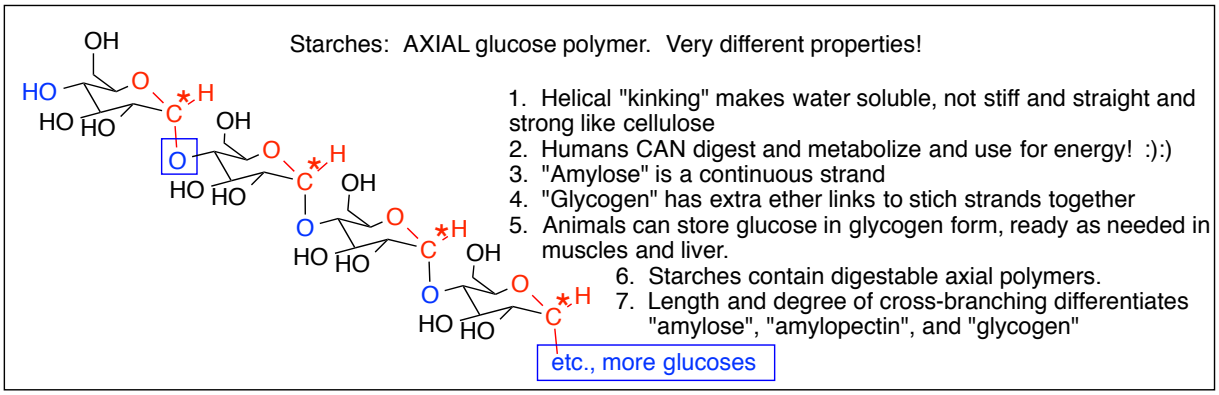




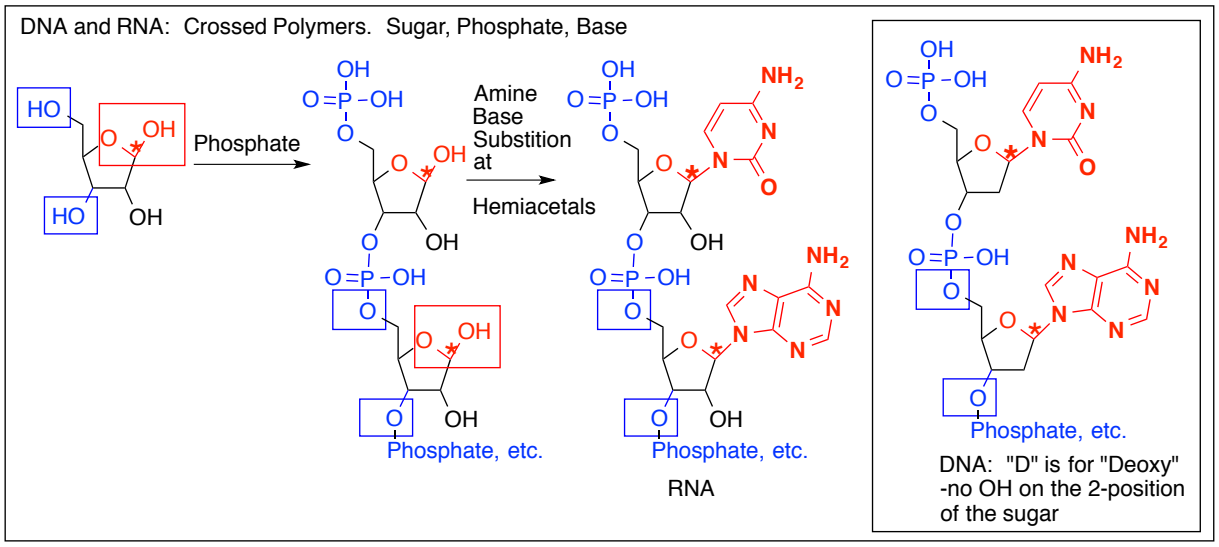
Major BioPolymers (All are Condensation Polymers)

1. Polysaccharides: Cellulose and Starches (Glycogen, Amylose, etc.)

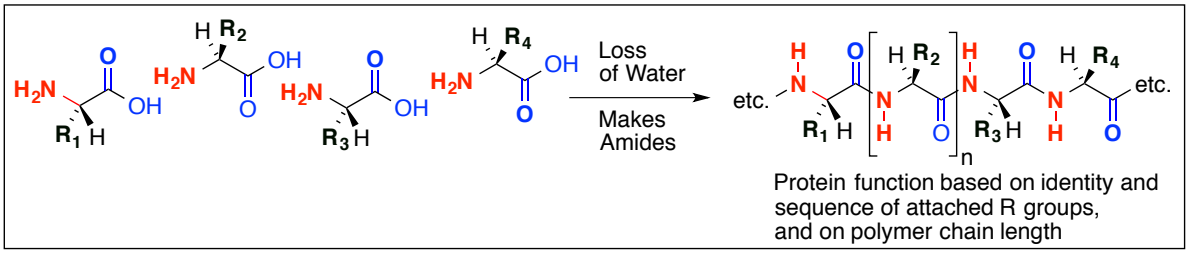




2. DNA + RNA



3. Proteins

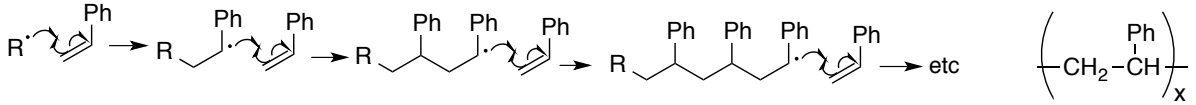


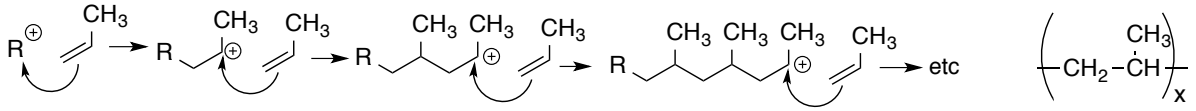
Addition Polymers from Alkenes and Conjugated Dienes

- Alkenes are common monomers for many common polymers
- Rubbers, plastics, piping, and all kinds of varying materials.
- Routinely named after the alkene, usually using it's common name
    - Polyethylene, polypropylene, polystyrene, polyisobutylene polyvinyl chloride (PVC)

- Addition polymerization: chain-growth by having monomer alkenes add onto the reactive end of a growing polymer
- Reactive end is usually a cation, radical, anion, or organometallic
- Something highly reactive
- Initiation: Getting it started by creation of a high reactive intermediate
- Termination: Some process to depopulate the cation or radical or whatever.

Examples of Radical or Cationic Chain Growth Mechanism:





Addition Polymers

- No change in atoms, you simply add all the atoms in the reactants together to make long polymer strings.

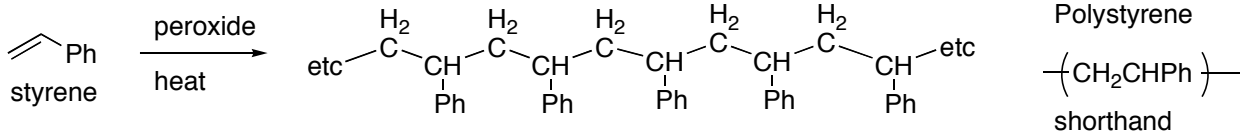
- The repeat unit in the polymer must have the same atoms as the monomer.
- Precursors: Alkenes or Conjugated Dienes

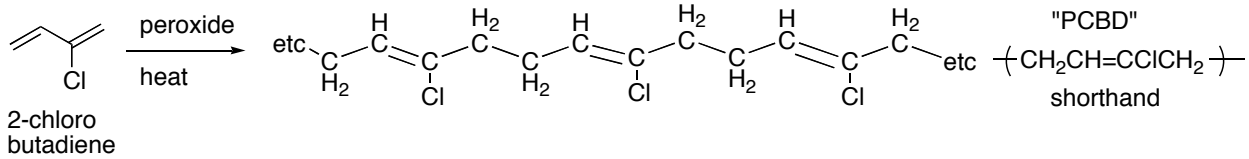
- Polymer has one fewer double bond than monomer: monoalkene → none; diene → one.

- For a conjugated diene, the two middle carbons end up double-bonded in the polymer
- Initiation/recognition: Usually radical/peroxides. Sometimes acid or Lewis acid catalyzed.

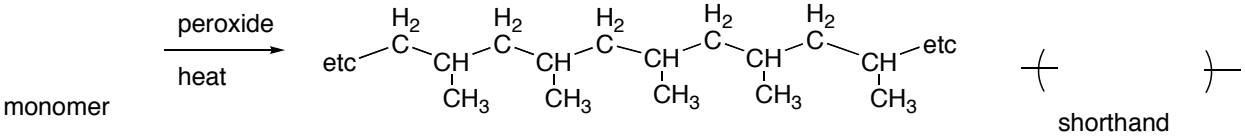
- Skills: Given monomer, draw polymer
- Skills: Given polymer, recognize monomer.
- Skills: Use and understand shorthand

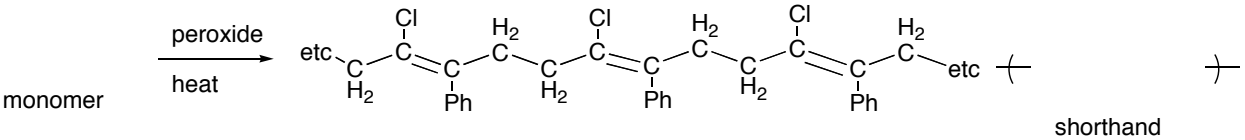
Ex: Mono-ene and diene polymers



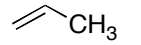


Problems: Draw the monomer and the shorthand version of polymer

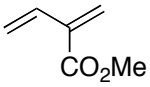




Draw the polymer from the following monomer, both shorthand and longstretch

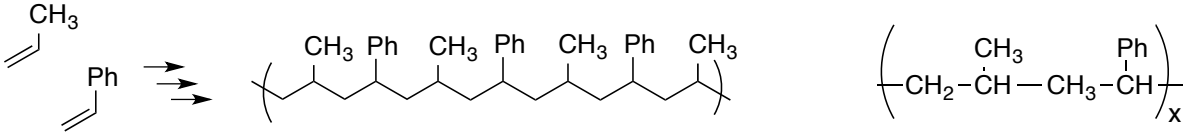


"propylene"



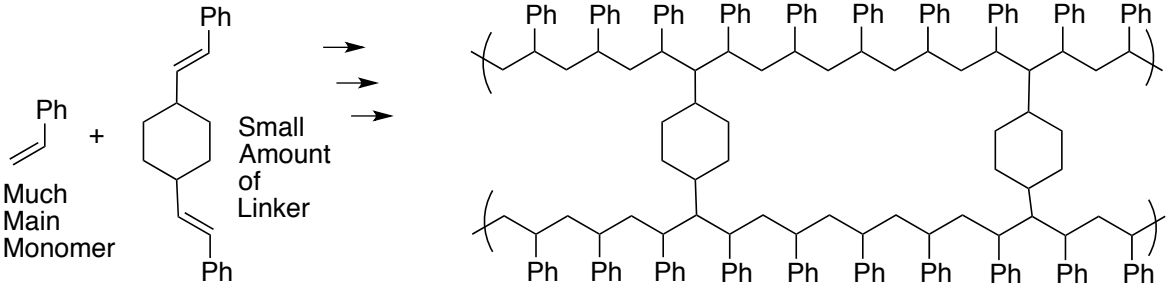
Mixed Polymers: When two different alkenes are used.

- Some will alternate consistently, others will be kind of random



Cross-linked Polymers: When two chains are linked together

- Use some variably small concentration of a molecule with two alkenes (or dienes) and some kind of tether/spacer
- Cross-linked chains are stronger and less flexible
- The ratio of main monomer to cross-linker dictates the frequency of ties.



Polymers and Physical Properties:

- Beyond scope here
- But lots of ways to manipulate length and degree of crosslinking
- Many laboratory ways to adjust practical factors such as strength and flexibility,