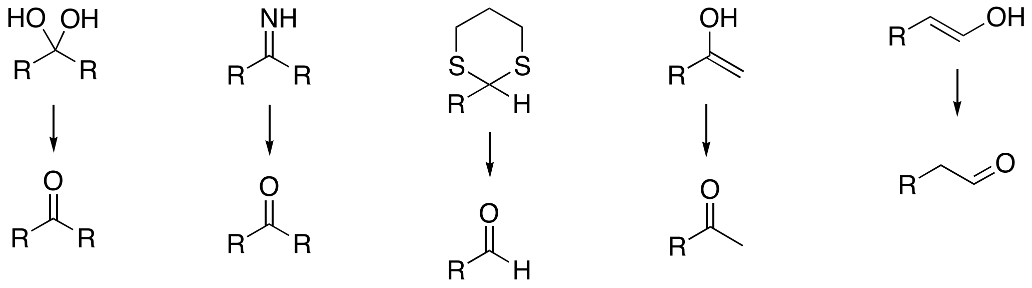
Note: Many groups can "hydrolyze" to carbonyls

- 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

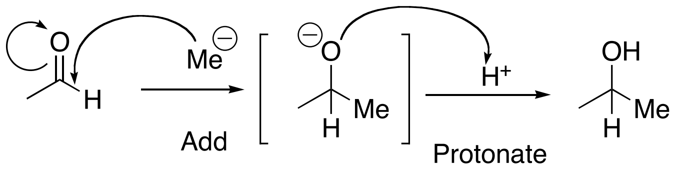


F. General Reactivity of Ketones and Aldehydes: Addition Reactions (Section 18.12)

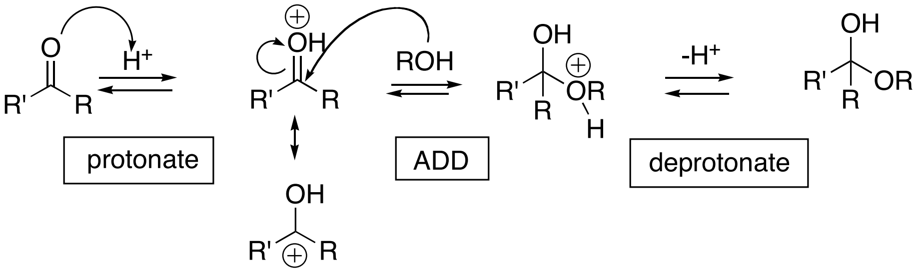
Key: Are reaction conditions anionic/basic or cationic/acidic (or perhaps buffered in between?)

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



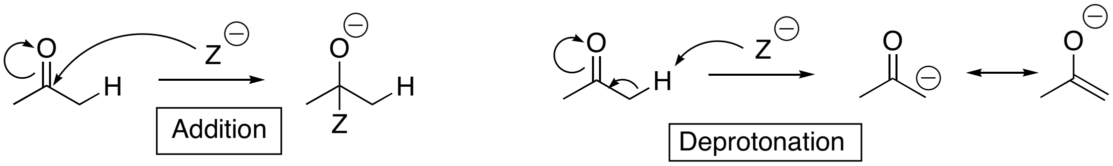
2. **Cationic Conditions** (acid is involved)
   a. General principles review for strongly anionic/basic conditions apply
      - Recipes that involve acid will be cationic
      - In a cationic mechanism, the first step will routinely involve protonation
      - In a cationic mechanism, the last step 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

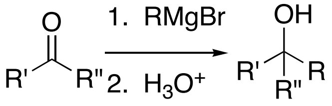
3. **Buffer Conditions** (both weak acid and weak base/nucleophile are present at same time)
   - RNH_2/H^+, KCN/HCN…
   - Reversibility again applies
   - Whether addition comes before protonation, or protonation precedes addition depends on the exact case

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

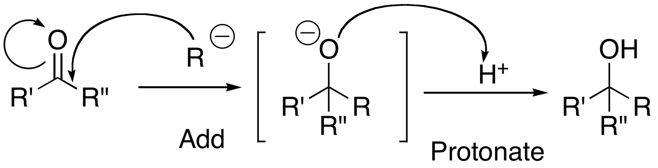


Addition of R⊖ (RMgBr) and H⊖ ($NaBH_4$, $LiAlH_4$) (Review, Section 18-12, Chapter 10)

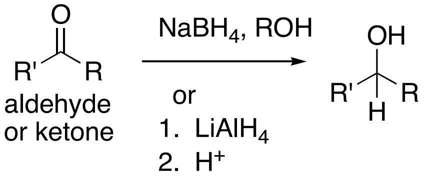
19



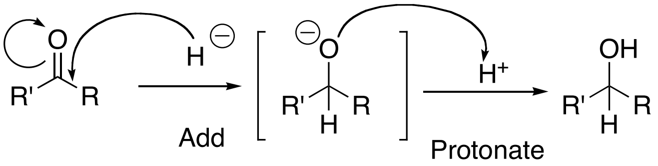
Grignard Addition of a Carbanion



20



Hydride addition.

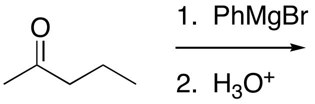


Note: For RMgBr and $LiAlH_4$, the basicity of the reagent is too strong to permit a proton source to be present at the same time. Thus the proton source must be added in a subsequent laboratory step. The $NaBH_4$ is weaker, both as a nucleophile but also as a base.

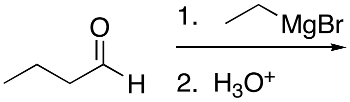
Draw products from the following reactions.

1º, 2º or 3º?

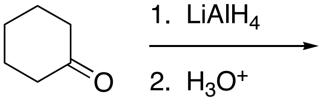
1



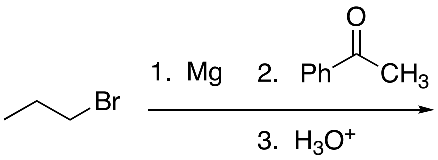
2



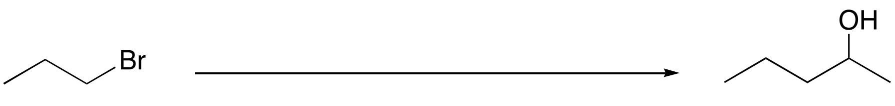
3



4

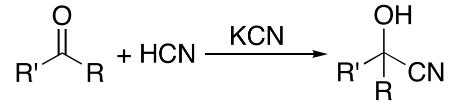


5



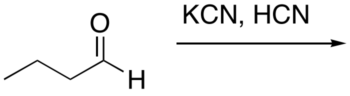
6. Draw the mechanism for reaction 1 above.

Addition of HCN to make "Cyanohydrins" (Section 18-15): Anionic Mechanism

21


HCN addition, anionic mech.

Draw the product and mechanism for the following:

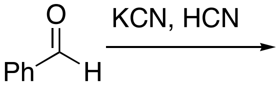


Mechanistic notes

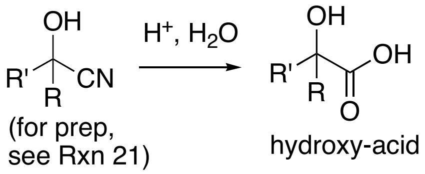
1. Addition first, protonation second
2. $^{\ominus}$CN is a good nucleophile, HCN a decent acid
3. KCN/HCN represents a **buffer situation**: weak base/weak acid, not obvious which dominates. But in this case the anion does and it proceeds via anionic mechanism.
4. $^{\ominus}$CN is actually used as 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.

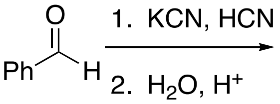

b.


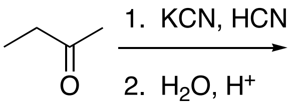
Key Support Reaction

29


- No Mech Responsibility
- Unique access to 2-hydroxyacids..
- Indirect provides the equivalent ("Synthon") for a $^{\ominus}$$CO_2H$ anion

Draw Products

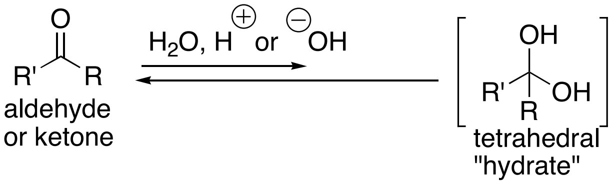
1.


2.


Reversible Addition of H_2O (H-OH) to Make Hydrates: Addition (and elimination) under Acidic or Basic Conditions (Section 18.14).

- 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

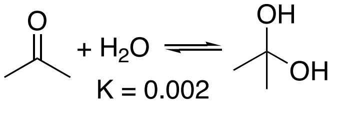
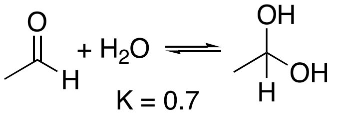
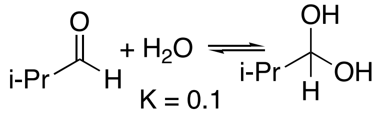
Mech Forward: Addition-Protonation. Nucleophile, anionic mechanism. Reversible.
Mech Reverse: Deprotonation-Elimination. Anionic mechanism. Reversible.

Cationic

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

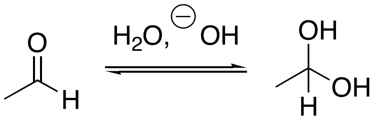
Notes:

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

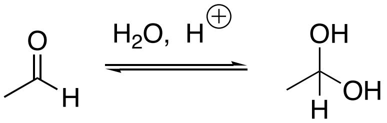
 K = 0.002	 K = 0.7	 K = 0.1

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 1° alcohols to carboxylic acids using H_2CrO_4 in water.

Draw the **ANIONIC addition** mechanism



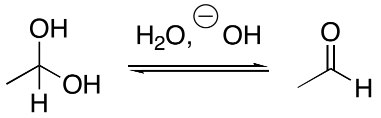
Draw the **CATIONIC addition** mechanism



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

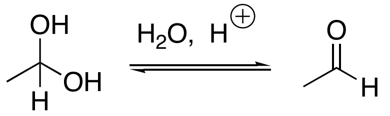
Draw the **ANIONIC elimination** mechanism

- Deprotonation precedes elimination
- E2-like



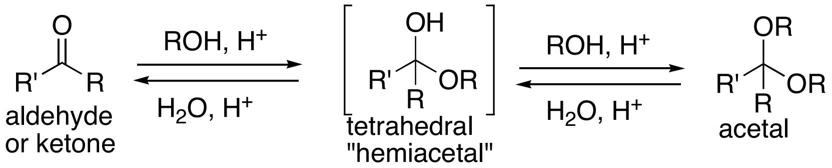
Draw the **CATIONIC elimination** mechanism

- Elimination precedes deprotonation
- E1-like



Reversible Reaction of ROH to Make Acetals via Hemiacetals. (Section 18.18, 19). Addition/Substitution under Acidic Conditions (Section 18.18, 19). 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.

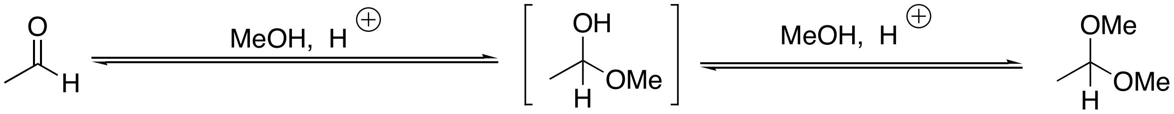
Notes:

- 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

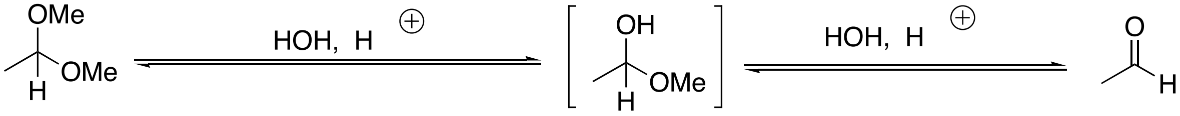
Notes:

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



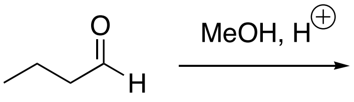
Draw the mechanism

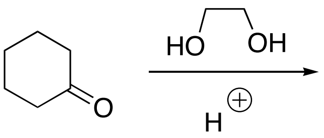


We have now seen three major acid-catalyzed reaction types in this chapter
1. Additions (protonate-**add**-deprotonate)
2. Eliminations (protonate-**eliminate**-deprotonate)
3. Substitutions (protonate-**eliminate-add**-deprotonate)

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

Draw the products for the following reactions

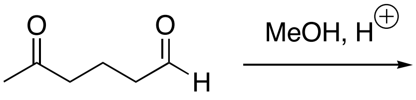
1 

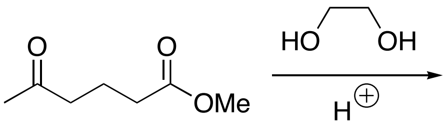
2 

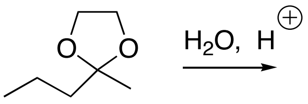
"Cyclic Acetal"

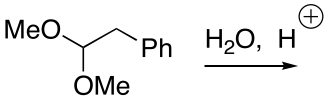
Key Synthetic Notes:

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 KETONES**
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 

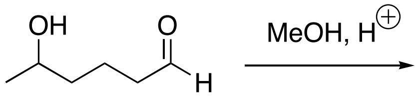
5 

6 

Equilibrium and Acetals

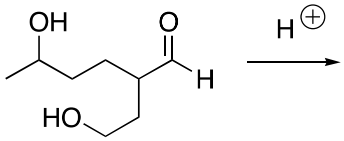
1. Normally favors the carbonyl, especially for ketones
2. Push to the acetal side by using excess alcohol
3. Push to carbonyl side by using excess water
4. **Equilibrium improves greatly for cyclic acetals.**
5. **Hemiacetals have a favorable equilibrium if and only if a 5- or 6-ring hemiacetal can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

7



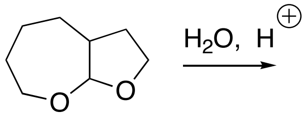
“Mixed Acetal”

8



“Cyclic Acetal”

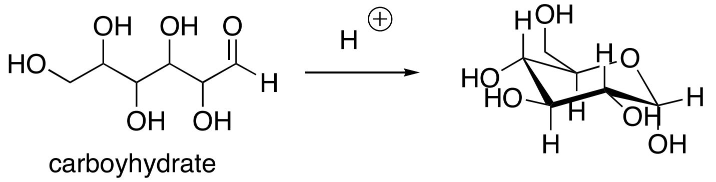
9



Hydrolysis Of cyclic acetal

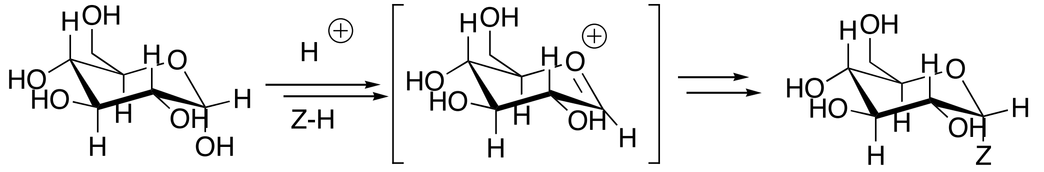
Hemiacetals, mixed acetals, and Sugar/Carbohydrate Chemistry (interest, not test)

10

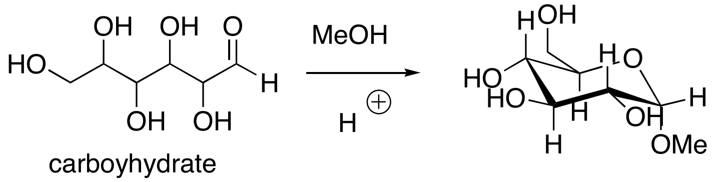


glucose

11



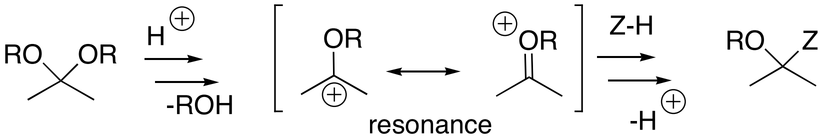
12



glucose mixed acetal

Notes:

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

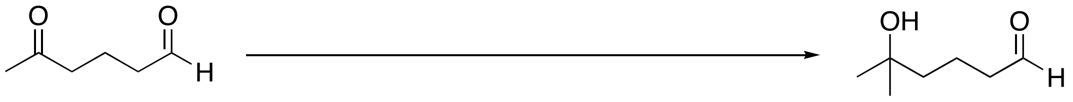


4. Carbohydrates exist as hemiacetals or acetals
5. Carbohydrates can polymerize or make complex derivatives via substitution at their acetal carbons

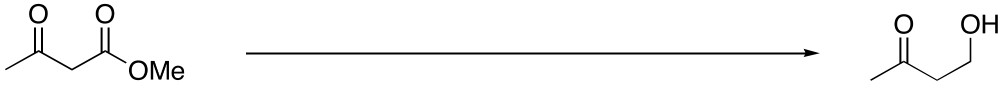
Acetals as Protecting Groups in Synthesis (Section 18-19)

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.

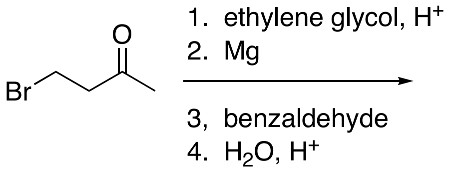
13



14

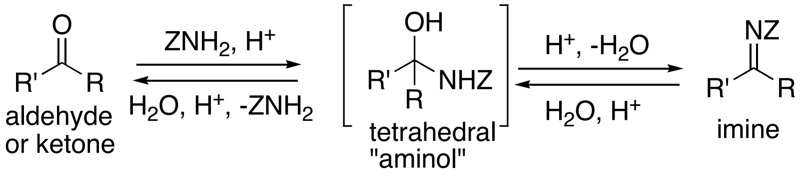


15



Addition of H_2N-Z Reagents (Sections 18-16,17)

25



18.16, 18.17

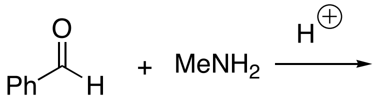
Cationic

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.

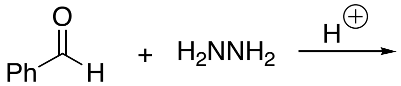
Mech Reverse: Protonation-Addition-deprotonation (aminol) Protonation-elimination- deprotonation (aldehyde or ketone). Reversible.

Notes:

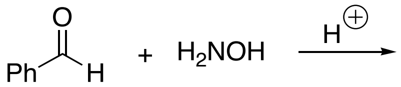
- "Z" can be a carbon, nitrogen, oxygen, or hydrogen atom/group.
- The "aminol" can't be isolated, it's only present at equilibrium.
- Equilibrium factors apply. Water drives to the carbonyl side; removal of water drives to the imine side.

1 

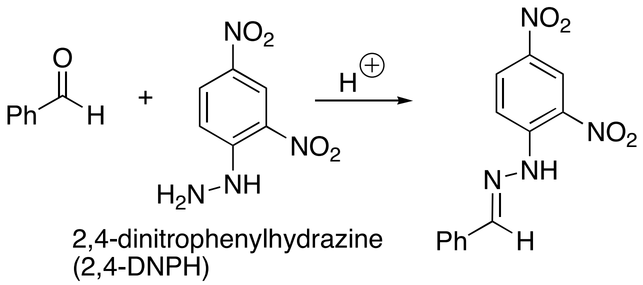
“Imine”
(Z = alkyl)

2 

Hydrazone
(Z = Nitrogen)

3 

Oxime
(Z = Oxygen)

4 

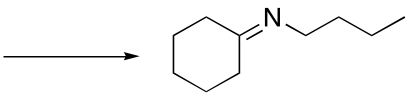
hydrazone

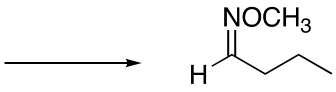
2,4-DNP derivative

2,4-DNP

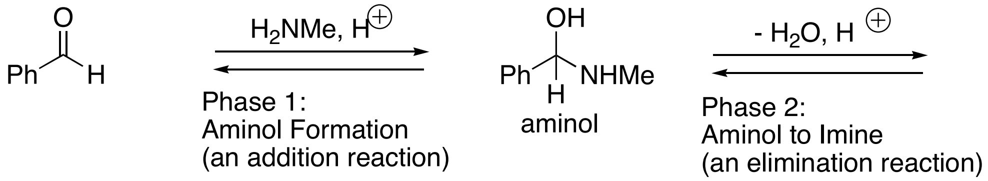
Notes:

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

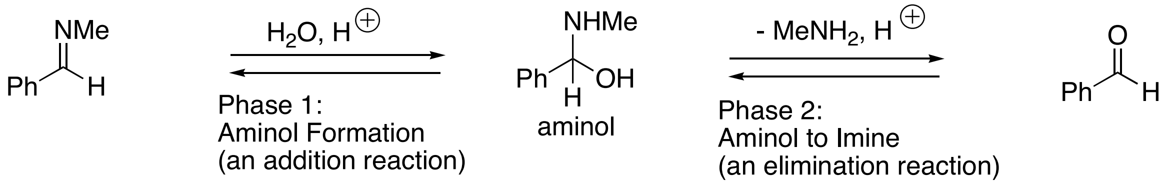
5 

6 

Draw the mechanism for the following:



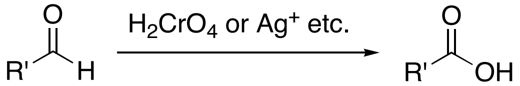
Draw the mechanism for the following:



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 $RNH_2 + 0.5 H^+ \rightarrow 0.5 RNH_2 + 0.5 RNH_3^+$ → a buffer system.
   c. In some cases, nucleophilic addition addition by the neutral but reactive amines (to give oxyanions) may actually precede protonation

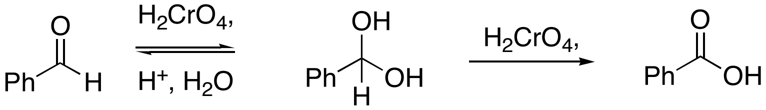
Oxidation of Aldehydes (Section 18.20)

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".

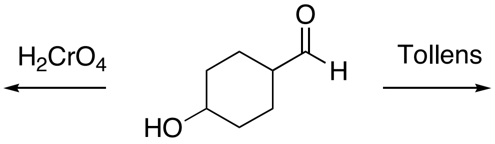
Review: Chromic Acid Oxidation proceeds in water via hydrate



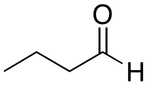
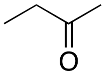
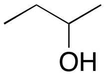
New: Ag^+ salts oxidize aldehydes in presence of alcohols, ketones

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

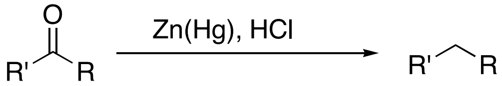
- A silver mirror forms



Chemical Tests

Class		DNP	Tollens	H_2CrO_4
Aldehydes				
Ketones				
Alcohols				

Deoxygenation of Ketones and Aldehydes (Section 18-21)

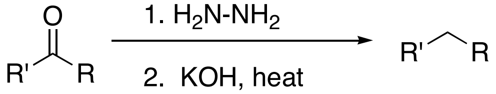
27


Acidic!
Works best for aromatic ketones.

18.21

Notes:

- Acidic conditions. Doesn't work well for molecules with acid-sensitive functionality.
- Works best for aromatic carbonyls. Saturated carbonyls are slower and less efficient.
- Acidic nature is complementary to the basic analog below.

28


Basic!

18.21

No Mech Responsibility

Notes:

- Basic conditions. Doesn't work well for molecules with base-sensitive functionality.

Basic nature is complementary to the acidic analog above.