

Chapter 12: Aldehydes and Ketones

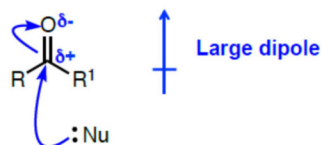
12.1 The Carbonyl Group: Structure and Reactivity

The Carbonyl Group:



Functional groups containing the carbonyl group:

Polarity of Carbonyl Compounds



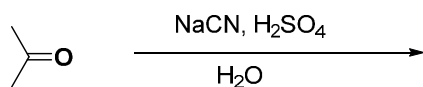
View from above and side:



b) Typical Reaction Scheme of a Nucleophilic Addition to C=O

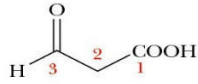
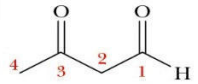
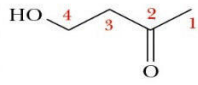
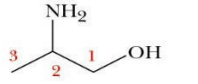
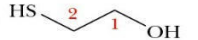
Two mechanistic steps:

1. Nucleophilic addition to the carbonyl group
2. Protonation of the resulting anion



12.2 Nomenclature of Aldehydes and Ketones

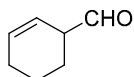
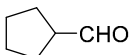
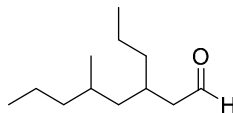
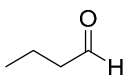
Functional group priorities with examples:

TABLE 12.1 Increasing Order of Precedence of Six Functional Groups				
Functional Group	Suffix	Prefix	Example of When the Functional Group Has Lower Priority	
Carboxyl	-oic acid	—		
Aldehyde	-al	oxo-	3-Oxopropanoic acid	
Ketone	-one	oxo-	3-Oxobutanal	
Alcohol	-ol	hydroxy-	4-Hydroxy-2-butanone	
Amino	-amine	amino-	2-Amino-1-propanol	
Sulfhydryl	-thiol	mercapto-	2-Mercaptoethanol	

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a) Aldehydes

1. Find parent chain containing CHO (and C=C or C≡C if present)
2. Replace the -e with -al
hexane →
hexene →
3. Number the chain beginning with the carbon of the CHO as #1
4. Include all substituents in the name
5. For -CHO as substituent, e.g. on a ring, use *carbaldehyde*

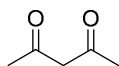
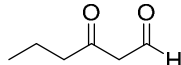
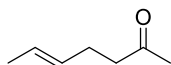
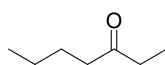


Common names:



b) Ketones

1. Find the parent chain containing the C=O
2. Replace -e with -one
3. Number the chain from the end closest to the C=O
4. Include all substituents in the name
5. For =O as substituent use oxo-



Common names:

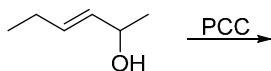
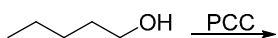
Acetone

Dicyclohexylketone

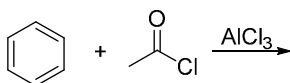
12.3 Synthesis of Aldehydes and Ketones

a) Oxidation of Alcohols

- Aldehydes are obtained by reacting 1° alcohols with PCC
- Ketones obtained by reacting 2° alcohols with PCC, CrO₃, or NaCr₂O₇

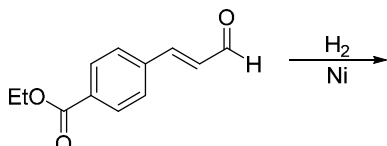
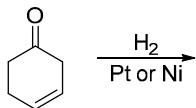
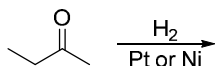


b) Friedel-Crafts Acylation



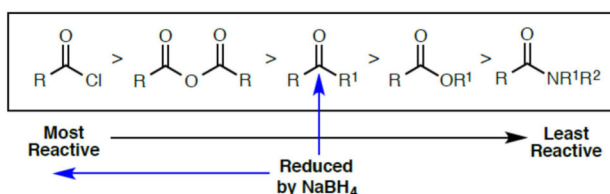
12.4 Catalytic Reduction of Carbonyl Compounds with H₂ (Hydrogenation)

Hydrogenation reduces aldehydes and ketones but not esters. Alkene or alkyne groups present are normally also reduced.



12.5 Reduction of Carbonyl Compounds with Hydride Reagents

Relative Reactivity of Carbonyl Compounds towards Nucleophilic Attack:

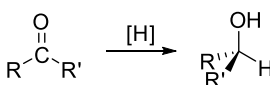
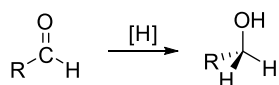


Reduction of **acid chlorides/anhydrides** to **alcohols** with **sodium borohydride**

Reduction of **esters** to **alcohols** using **lithium aluminium hydride**

Reduction of **amides** to **amines** using **lithium aluminium hydride**

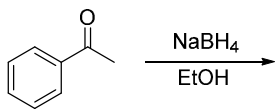
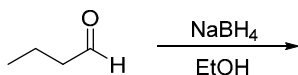
a) Reduction of Aldehydes and Ketones



Two common reductants that are employed in reducing carbonyl compounds are sodium borohydride (NaBH₄) and lithium aluminium hydride (LiAlH₄).

Sodium Borohydride as Reducing Agent for Ketones and Aldehydes

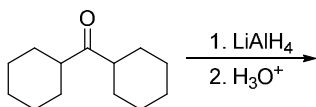
NaBH_4 is weak enough to be used in ethanol, a protic solvent, which can act directly as proton source for the resulting alkoxide.



Mechanism of a Sodium Borohydride Reduction in Ethanol:

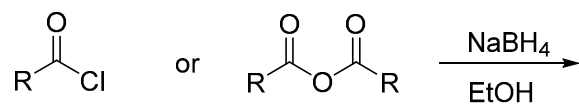
Lithium Aluminum Hydride as Reducing Agent

LiAlH_4 reacts violently with protic solvents by forming H_2 and must therefore be used in an inert solvent such as THF or diethyl ether. This requires an individual step to protonate the alkoxide (aqueous work up) which must be carried out very slowly.



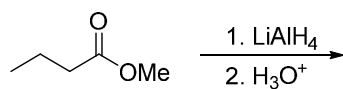
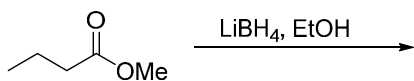
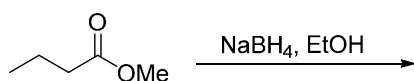
Mechanism:

b) Reduction of Acid Chlorides and Anhydrides to Alcohols: NaBH_4

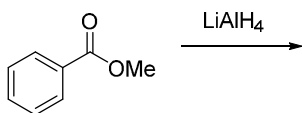


c) Reduction of Esters to Alcohols: LiBH_4 or LiAlH_4

Esters are not reduced by NaBH_4 , however, the slightly stronger reducing agent LiBH_4 is capable of reducing esters. LiAlH_4 will work as well but requires inert conditions and a second work-up step.



Mechanism of the Reduction of Esters to Alcohols with LiAlH_4 :



12.6 Grignard Reagents and Organolithium Compounds

Organometallic compounds have carbon-metal bonds which range from primarily ionic (e.g. Na^+ or K^+ salts), covalent with significant ionic character (organolithium and Grignard reagents) to primarily covalent (e.g. Cu , Hg , Tl).

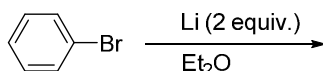
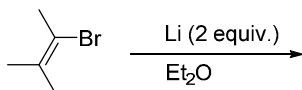
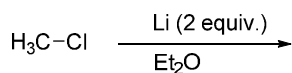
Sodium acetylides:

Organolithiums:

Grignard reagents:

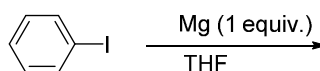
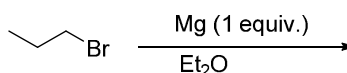
12.5.1 Synthesis of Organolithium Reagents

"Lithium-Halogen Exchange": 2 equivalents of Lithium are needed to generate one equivalent of the desired organolithium compound.



2.5.2 Synthesis of Grignard Reagents

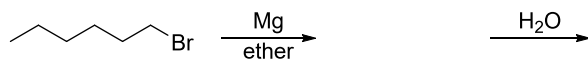
"Mg Insertion": Use of Mg turnings in an ether solvent results in a Mg insertion into the carbon-halide bond. Examples of ether solvents: Et_2O , THF, dioxane



b) Reactions of Grignard Reagents with Acidic Protons

Grignard reagents and organolithium compounds react with acids and electrophiles (HCl, H₂O, R-OH) by accepting H⁺ and forming hydrocarbons.

Reaction of Grignard reagent with water:



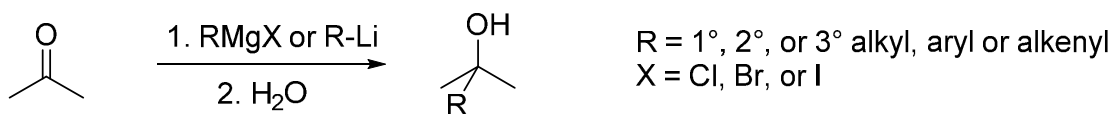
Reaction of organolithium reagent with ethanol:

Use of Grignard and organolithium reagents to prepare alkynyl organometallic reagents:

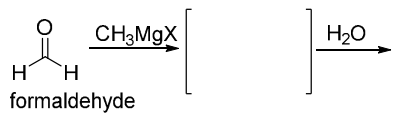
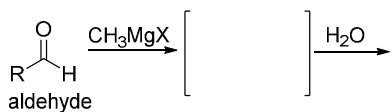
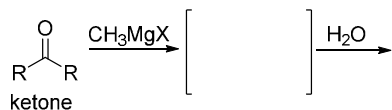
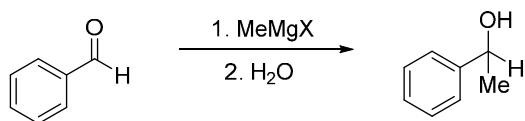
12.15

c) Reactions with Carbonyl Compounds

Grignard reagents (RMgX) and organolithium compounds are nucleophilic and attack the electrophilic carbon of carbonyl compounds:



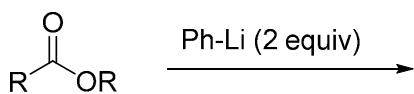
12.16

Aldehydes and ketones react once with Grignard reagents or organolithium reagents**Mechanism:**

12.17

Esters react twice with organometallic reagents

The ketone intermediate *cannot* be isolated when esters are used as starting materials because it is more reactive towards the nucleophile than the starting ester.

**Important:**

- The ketone will react with the organometallic species *more quickly* than the starting ester
- If only one equivalent of the organometallic reagent is present, the major product will be the alcohol (resulting from double addition) with about 50% of the starting material remaining.

12.18

d) Restrictions on the Synthesis and Use of Grignard Reagents

Grignard reagents cannot be prepared if the following functional groups are present:

- -OH, -NH, -SH, -COOH, terminal alkynes

- X and C=O are in the same molecule

12.19

12.7 Protecting Groups**a) for Alcohols: Silyl Protecting Groups**

TBS-Cl

TMS-Cl

TIPS-Cl

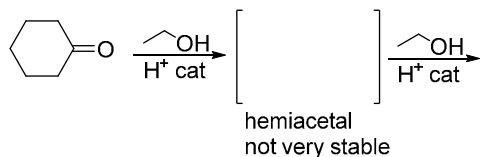
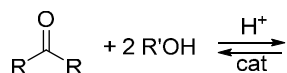
Preparation of a silyl ether:

Removal of silyl protecting groups:

12.20

b) for Aldehydes and Ketones**Acetals are Common Protecting Groups for Aldehydes and Ketones**

- Alcohols add to aldehydes and ketones to form hemiacetals, then acetals

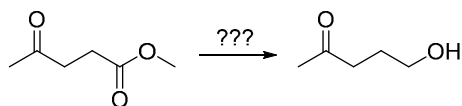


Acetal formation is reversible

- If H₂O is removed then acetal is favored
- If H₂O is added then C=O is favored

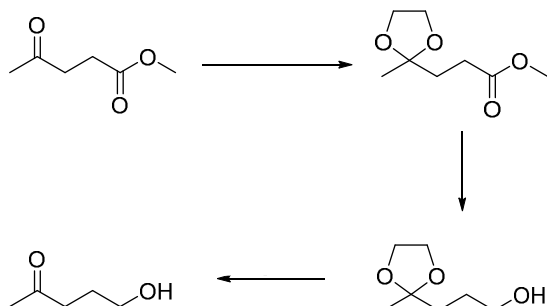
12.21

Exercise: How would you synthesize the following compound?



LiAlH₄ would reduce the ester but also the ketone.

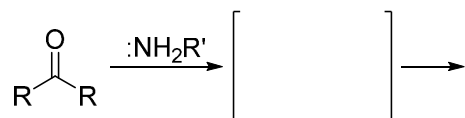
If the ketone is to be part of the product it needs to be protected.



12.22

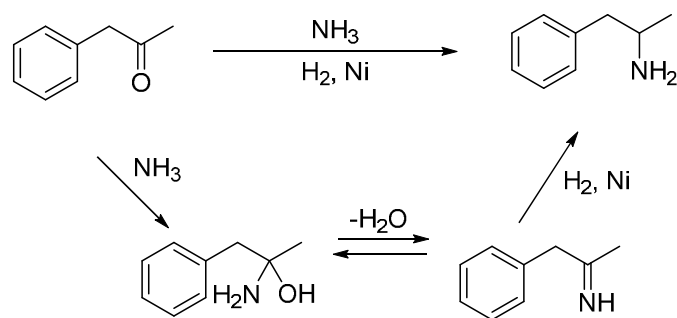
12.8 Reactions of Carbonyl Groups with Amines**a) Imine Formation**

A 1° amine adds to aldehyde or ketone to give an imine ($R_2C=NR$)



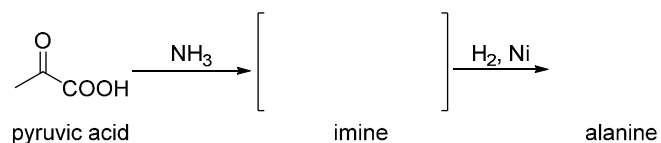
Common in biological pathways
Only works with ammonia and 1° amines

12.23

b) Reductive Amination of Aldehydes and Ketones

Ammonia and RNH_2 may be used to obtain 1° and 2° amines, respectively

12.24

c) Synthesis of an Amino Acid by Reductive Amination

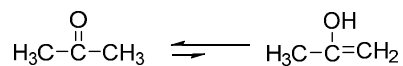
12.25

12.9 Keto-Enol Tautomerism

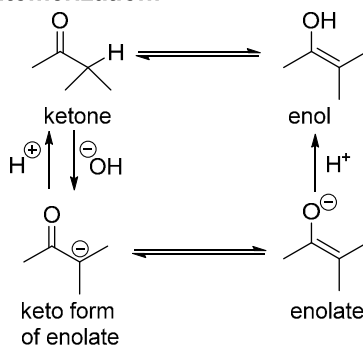
Tautomers are constitutional isomers readily interconvert. Tautomerism can occur with double bonds to O, S, or N if a protic α-hydrogen is present.

a) Keto and Enol Forms of Carbonyl Compounds

The keto form is more stable than the enol form:



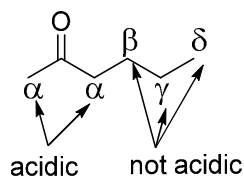
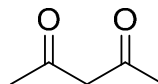
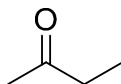
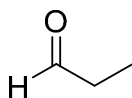
Equilibration of the keto-enol equilibrium can be catalyzed by acid or base. Tautomerism requires the presence of an acidic α-hydrogen.

Mechanism of base catalyzed tautomerization:

12.26

b) Acidity of α -Hydrogens in Carbonyl Compounds

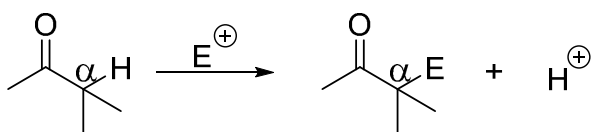
Which hydrogen atoms are acidic?

**Racemization at α -carbons:**

12.27

c) α -Halogenation

α -Halogenation is catalyzed both by acid and base since it involves an enol or enolate intermediate. Enols react with electrophiles Br_2 , Cl_2 , I_2 .

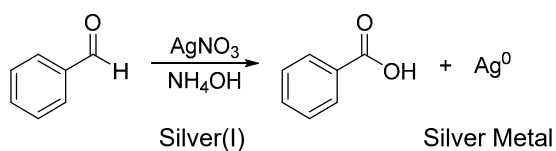


12.28

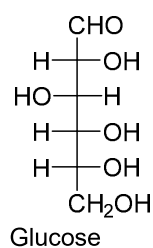
12.10 Oxidation of Aldehydes

CrO_3 or NaCr_2O_7 oxidizes aldehydes to carboxylic acids (see Chapter 8):

The Tollens' Reagent oxidizes only aldehydes.



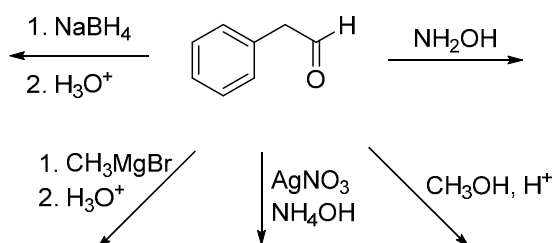
It is used in biological research as test for the presence of aldose sugars (e.g. glucose) which contain an aldehyde group in their open form.



12.29

12.11 Exercises

a) What is the product?



12.30

b) What is the product after each of these steps?

