

Chapter 21. Addition of Soft Nucleophiles to Aldehydes and Ketones.

1. Nomenclature.
 - a) Aldehydes.
 - i) Systematic. Alkanal. Ethanal, hexanal, propenal.
 - ii) Trivial. Formaldehyde, acetaldehyde, acrolein, benzaldehyde.
 - b) Ketones.
 - i) Systematic. Alkanone. Propanone, 2-butanone, 5-hexen-3-one, 1-phenyl-1-ethanone. 3-Oxobutanoic acid.
 - ii) Trivial. Acetone, acetophenone, benzophenone.
2. Relative stability of aldehydes and ketones. Sterically and electronically, aldehydes more reactive.
3. Nucleophilic addition to aldehydes and ketones.
 - a) Under basic conditions, nucleophiles (usually anionic, except for amines) add to neutral carbonyl compounds. After the addition, the former carbonyl O is protonated to give the product.
 - i) Lone pair nucleophiles. HO^- , RO^- , $\text{RC}\equiv\text{C}^-$, $-\text{C}\equiv\text{N}$, H_3N , RNH_2 .
 - ii) Already talked about sigma bond nucleophiles.
 - b) Under acidic conditions, nucleophiles (always neutral) add to *protonated* carbonyl compounds. H_2O , ROH , H_3N , RNH_2 . After the addition, the nucleophilic atom is deprotonated to give the product.
4. Reversible nucleophilic addition to aldehydes and ketones.
 - a) Carbonyl + H_2O + (acid or base) \rightleftharpoons hydrate. *Slow in pure H_2O !* Equilibrium favors hydrate only for carbonyl compounds with electron-withdrawing groups on α -C's, e.g. Cl_3CCHO (chloral).
 - b) Carbonyl + ROH + (acid or base) \rightleftharpoons hemiacetal. *Slow in pure ROH !* Equilibrium favors hemiacetal only for carbonyl compounds with electron-withdrawing groups on α -C's, e.g. carbohydrates.
 - c) Carbonyl + $\text{HC}\equiv\text{N}$ + cat. base \rightleftharpoons cyanohydrin. Equilibrium favors product in aldehydes. Ketones are more iffy, but can buy acetone cyanohydrin. **Another way to make C-C bond!** E.g., almonds make mandelic acid from benzaldehyde in this way.
5. Nucleophilic addition followed by substitution. Acetal formation.
 - a) RCHO or R_2CO + $\text{R}'\text{OH}$ + cat. H^+ \rightleftharpoons $\text{RCH}(\text{OR}')_2$ or $\text{R}_2\text{C}(\text{OR}')_2$ + H_2O .
 - i) Proceeds through *hemiacetal*. Equilibrium toward acetal by removal of H_2O , pushed toward carbonyl by addition of H_2O .
 - ii) Most convenient with diols such as ethylene glycol. Entropy favors second reaction.
 - iii) Can be selective for aldehydes over ketones! Thermodynamically controlled.
 - iv) Does not work well for esters or acids!
 - b) Who cares?
 - i) Polysaccharides are made and broken down in this way. Glucose + 4-OH of glucose \rightarrow maltose $\rightarrow\rightarrow$ starch. Glucose + fructose (anomeric centers linked) \rightarrow sucrose.

- ii) Unlike carbonyl compounds, acetals are inert to bases and nucleophiles. So ketone or aldehyde can be converted to acetal, then reaction carried out on another functional group in molecule (e.g., carboxylic ester), then ketone or aldehyde freed up. E.g. ethyl 4-oxo-pentanoate to 5-hydroxy-2-pentanone.
6. Nucleophilic addition followed by dehydration.
- a) Carbonyl + RNH_2 or $\text{NH}_3 \rightleftharpoons$ imine (a N analog of a carbonyl compound) + H_2O .
- i) Nucleophilic addition to give a hemiaminal (carbinolamine) is followed by E1 elimination of H_2O (H^+ comes from N; O is protonated before it leaves).
- ii) Equilibrium favors imine for R = hydroxy, alkoxy, or amino groups. (Products called oximes, oxime ethers, or hydrazones.) When R = alkyl, equilibrium usually favors carbonyl, but can be pushed toward imine by removal of H_2O .
- iii) Fastest at near-neutral pH: acidic pH protonates starting material and slows first reaction, basic pH slows protonation of O in hemiaminal and prevents second reaction.
- b) Carbonyl + $\text{R}_2\text{NH} \rightleftharpoons$ enamine (a N analog of an enol) + H_2O .
- i) Nucleophilic addition to give a hemiaminal is followed by E1 elimination of H_2O (H^+ comes from C; O is protonated before it leaves).
- ii) Equilibrium usually favors carbonyl, but can be pushed toward enamine by removal of H_2O .
- c) Who cares?
- i) Imines (Schiff bases) are important biological intermediates. Enamines too (will see later).
- Retinal makes imine with lysine residue of rhodopsin.
 - Conversion of pyruvate to alanine catalyzed by pyridoxal (vitamin B_6).
- ii) Hydrazine N_2H_4 + carbonyl \rightarrow hydrazone. Hydrazone + KOH in DMSO \rightarrow alkane (Wolff-Kishner reduction).
7. Nucleophilic addition followed by elimination. Wittig reaction. **Another way to make C–C bond!**
- a) RCHO or $\text{R}_2\text{CO} + \text{Ph}_3\text{P}^+\text{-}\bar{\text{C}}\text{R}'_2 \rightarrow \text{RCH}=\text{CR}'_2$ or $\text{R}_2\text{C}=\text{CR}'_2$. By-product is $\text{Ph}_3\text{P}=\text{O}$.
- b) Mechanism. Via betaine. Questions about existence of betaine, but don't worry about it.
- c) $\text{Ph}_3\text{P} + \text{BrCHR}'_2 \rightarrow \text{Ph}_3\text{P}^+\text{-CHR}'_2 \text{Br}^- + \text{BuLi} \rightarrow \text{Ph}_3\text{P}^+\text{-}\bar{\text{C}}\text{R}'_2$. Thus half of an alkene can come from an alkyl bromide, and the other half from a ketone or aldehyde.
- d) Useful for making mono-, di-, and trisubstituted alkenes, but not for tetrasubstituted alkenes. Thus, $\text{RCH}=\text{CHR}' \Rightarrow \text{RCHO} + \text{BrCH}_2\text{R}'$ or $\text{RCH}_2\text{Br} + \text{R}'\text{CHO}$. And remember $\text{RBr} \Rightarrow \text{ROH}$!
- e) Better than addition of Grignard followed by dehydration, because dehydration follows Saytzeff's rule — thermodynamic ratio of products, more substituted favored — while Wittig reaction gives only one product.
8. Oxidation of aldehydes and ketones.
- a) Ketones to esters in Baeyer-Villiger reaction. $\text{RCOR} + m\text{CPBA} \rightarrow \text{RCO}_2\text{R}$ (ester). O atom inserts between carbonyl C and α -C.