

Kaplan Orgo ①

* IUPAC naming $\Rightarrow$ alphabetical with groups not numerical

3-ethyl, 2-2-5 trimethyl NOT 2-2-5, trimethyl, 3-ethyl

$$K_a = \frac{[H^+][A^-]}{[HA]}$$

$$pK_a = -\log K_a$$

$pK_a < 0$ = strong acid

$pK_a > 0$ = strengthening base

nucleophiles $\Rightarrow$ tend to be good bases

L anions

L π bonds

L atom w/ lone pairs

L determined by 4 factors (nucleophilicity)

① charge $\Rightarrow$ goes $\uparrow$ w/ increasing e^- density

② electronegativity $\Rightarrow$ $\downarrow$ as EN $\uparrow$ because e^- not shared

③ steric hindrance $\Rightarrow$ bulkier molecules less nucleophilic

④ solvent $\Rightarrow$ protic solvents hinder nucleophilicity by protonating nucleophile or H-bonding

protic solvents

① carboxylic acids

② ammonia/amines

③ water/alcohols

Aprotic solvents

① DMF (dimethylformamide)

② DMSO (dimethylsulfoxide)

③ acetone

protic solvent + halogen $\Rightarrow$ nucleophilicity $I^- > Br^- > Cl^- > F^-$

aprotic solvent + halogen $\Rightarrow$ nucleophilicity $F^- > Cl^- > Br^- > I^-$

electrophiles $\Rightarrow$ tend to be good acids

L more $\oplus$ charge = greater electrophilicity $C^+ > C$

L ketones, alcohols, aldehydes, carboxylic acids

L anhydrides most reactive, then carboxylic acids & esters

leaving groups

L Best ones stabilize extra e^-

L weak bases

L conjugate bases of strong acids I^- , Br^- , Cl^-

L can be augmented by resonance

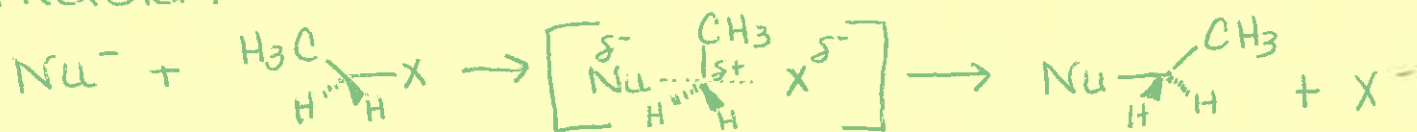
L leaving groups AND nucleophiles serve opposite purposes

L weaker base (leaving group) replaced by stronger base (nucleophile)

H $\Rightarrow$ never / rarely serves as leaving group

SN2 $\Rightarrow$ bimolecular, one step, rate = $k[\text{Nu}^-][\text{R-L}]$, concerted rxn

- ① nucleophile must be strong
 - ② substrate not sterically hindered
 - ③ less substituted the C, the more reactive it is in SN2
 - ④ inversion
- * No tertiary substrates

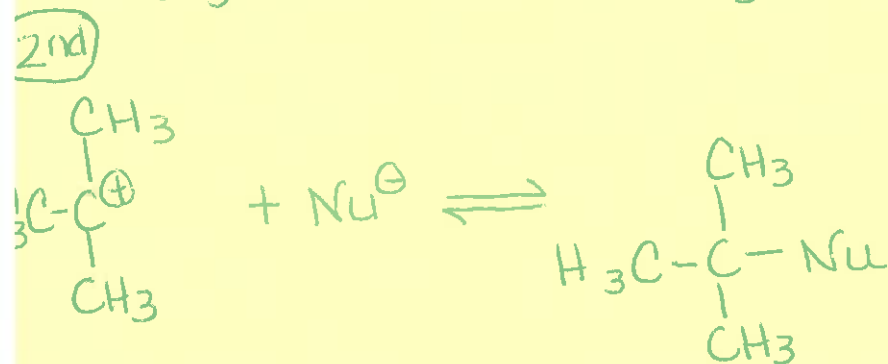
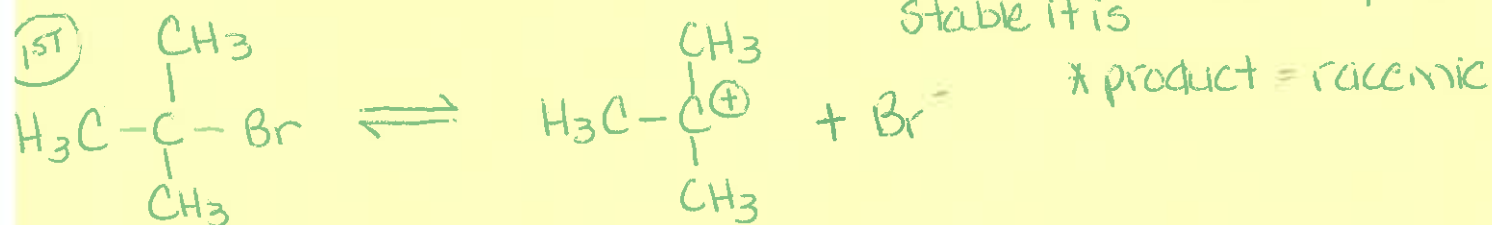


⑤ often alkyl halide, tosylate, mesylate

SN1 $\Rightarrow$ unimolecular, two steps, rate = $k[\text{R-L}]$

- ① 1st step = rate limiting
- ② leaving group leaves
- ③ carbocation created
- ④ nucleophile attacks

* rate depends only on $[\text{R-L}]$ of the substrate
 * more substituted C^+ , the more stable it is



Redox $\Rightarrow$ oxidation states of reactants change

oxidation = increasing the number of bonds to oxygen or other heteroatoms (NOT C or H)

reduction = increasing the number of bonds to H

oxidizing agent = element that accepts an e^- from another species (can be molecules accepting)

L gains e^- , reduced (reduces + charge)

$\text{L} = \text{O}_2, \text{O}_3$ or Cl_2

$\text{L} = \text{Mn}^{7+}$ in MnO_4^- , Cr^{6+} in CrO_4^{2-}

Often contain metals bonded to a large # of O atoms

Levels of oxidation

0 = alkanes

1 = CH, amines, alkyl halides

$\left\{ \begin{array}{l} 2 = \text{aldehyde, ketones, imines} \\ 3 = \text{COOH, anhydrides, esters, amides} \end{array} \right\}$
 $\left\{ \begin{array}{l} 4 = \text{four bonds to heteroatoms} \\ \text{CO}_2 \end{array} \right.$

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reducing agent = donates e^- to another atom or molecule

↳ Na, Mg, Al, Zn

↳ low EN

↳ low IE

↳ metal hydrides

↳ NaH, CaH_2 , LiAlH_4 , NaBH_4

↳ contain H^- ion

↳ often contain metals bonded to large # of hydrides

Bronsted-Lowry = proton

acids = proton donors

bases = proton acceptors

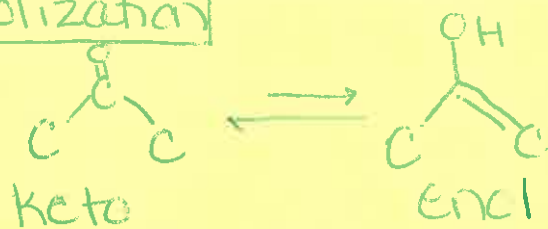
Lewis = electron

acids = electron acceptors ~ vacant orbitals

bases = electron donors ~ lone pairs, anions

* Ketones less likely to react than aldehydes due to steric hindrance

Enolization



tautomers $\Rightarrow$ differ only in placement of double bond
 $\downarrow$
 racemic mixture

* strong bases required

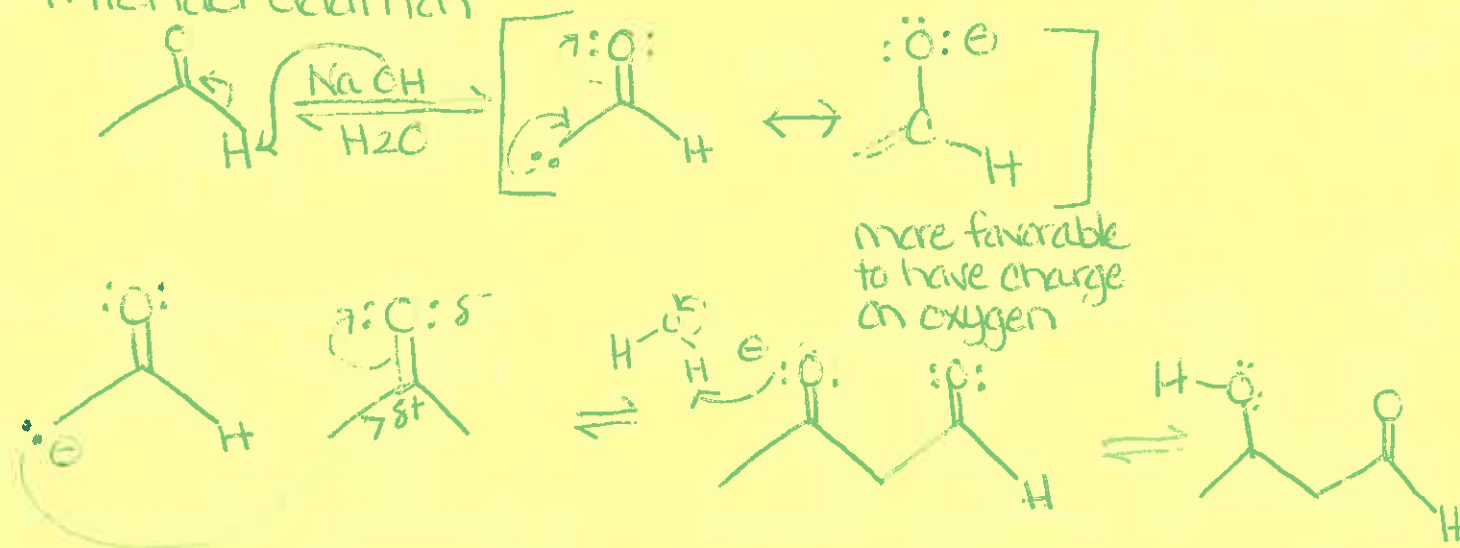
↳ CH_3^-

↳ LDA (lithium diisopropyl amide)

↳ KH (potassium hydride)

Aldol condensation $\Rightarrow$ type of enolization, α -racemization

↳ Michael addition

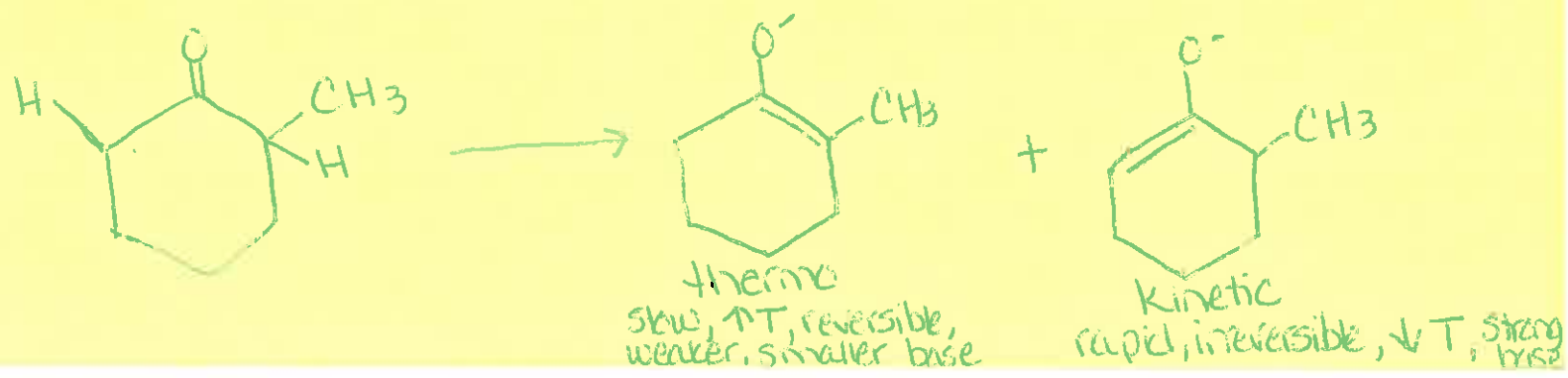


* equilibrium in enolates is dictated by kinetic and thermodynamic control of the reaction

↳ Kinetic formed more rapidly but less stable

↳ thermic formed more slowly and is more stable

↳ forms double bond with more substituted α -C



Imine v. Enamine



tautomers

enamine
(less favored)

imine
(more favored)

Aldol condensation

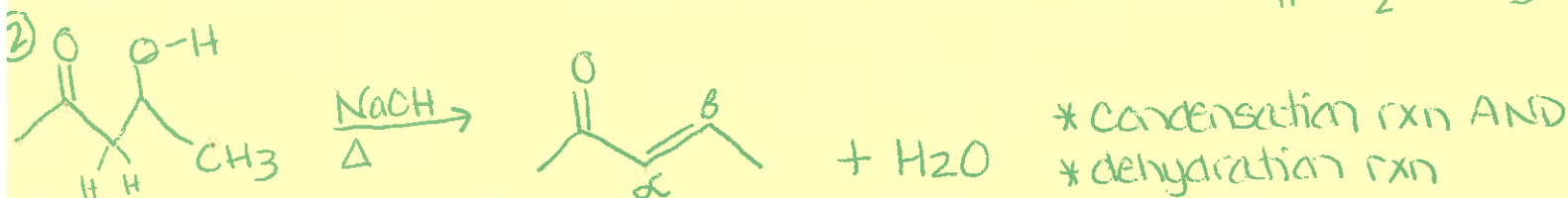
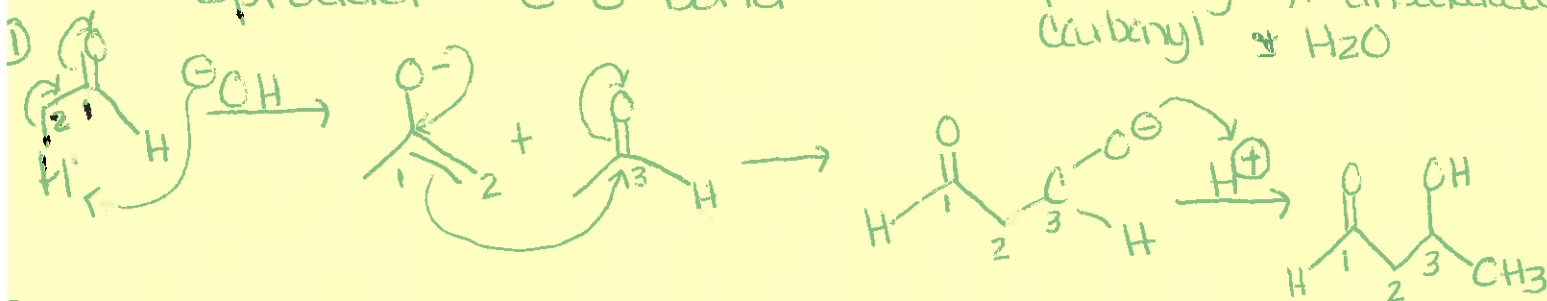
* aldehyde or ketone act as both electrophile & nucleophile

↳ electrophile = keto form

↳ nucleophile = enolate form

↳ product = C-C bond

* strong base + ↑ T, E1 or E2
producing α, β unsaturated
carbonyl + H₂O

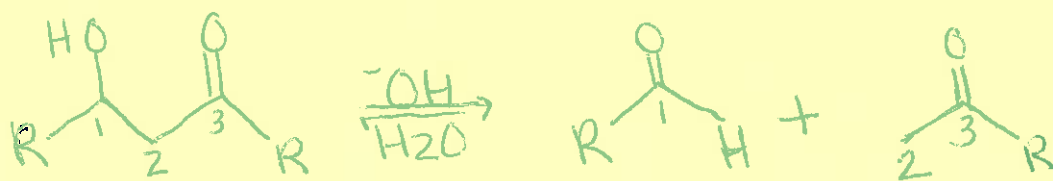


* condensation rxn AND
* dehydration rxn

retro-aldol ⇒ used to break bonds between α & β carbons

↳ aqueous base + heat

↳ stabilize intermediate



* H between two carbonyls = very acidic

CARBOXY - KAPLAN (4)

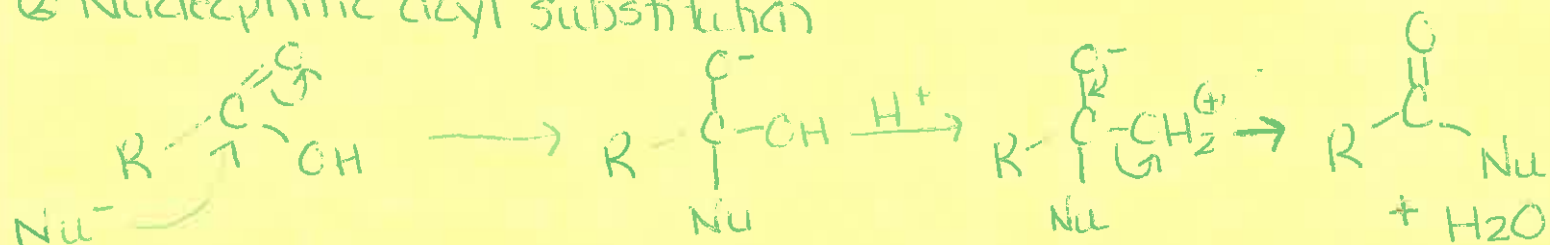
- * polar molecules
- * tend to form dimers
- * multiple H bonds $\uparrow$ boiling and melting points
- * β -dicarboxylic acids = 2 COOH separated by 1 C
LH on the carbon between = $\uparrow$ acidic

Synthesis

① Oxidation of aldehydes and ketones

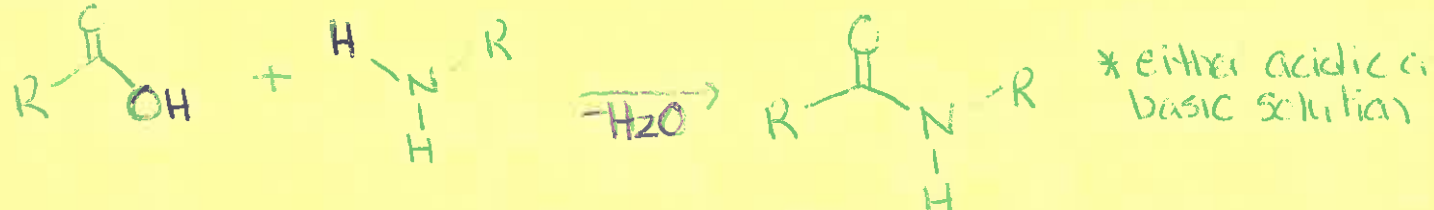
Usually $\text{Na}_2\text{Cr}_2\text{O}_7$, CrO_3 or KMnO_4

② Nucleophilic acyl substitution



Weak bases, conjugates of strong acids = good lvg groups

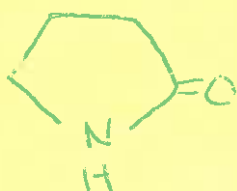
③ Amides



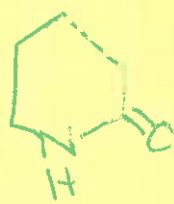
Cyclic amides = lactam



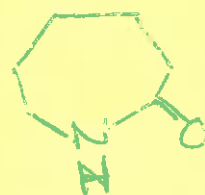
β -lactam



γ -lactam



δ -lactam

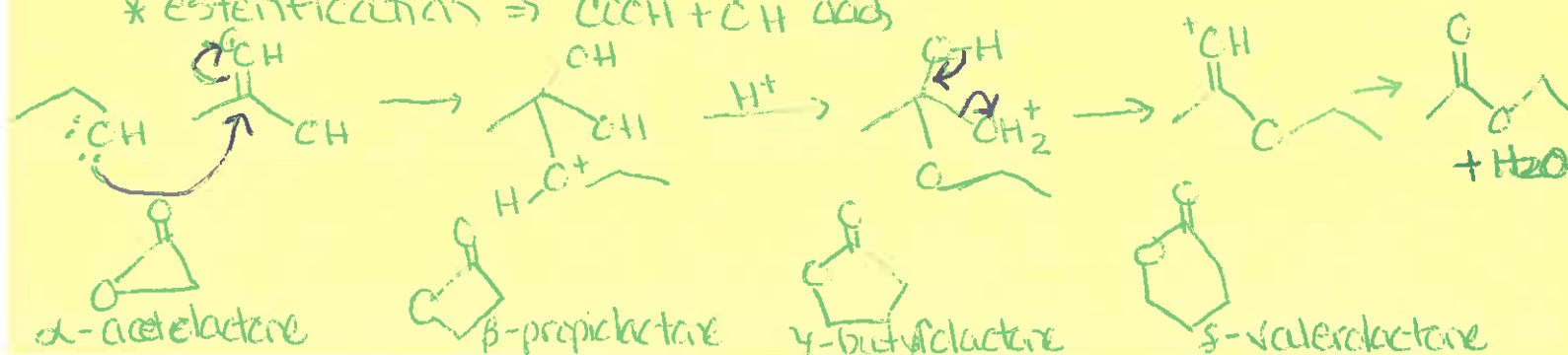


ϵ -lactam

④ Esters

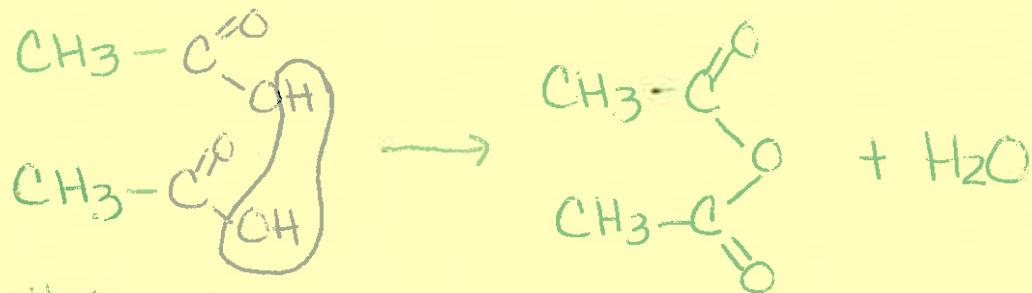
* hybrid between COOH + RCOR (ether)

* esterification $\Rightarrow$ $\text{COOH} + \text{CH}_3\text{OH}$ acids



5) anhydrides

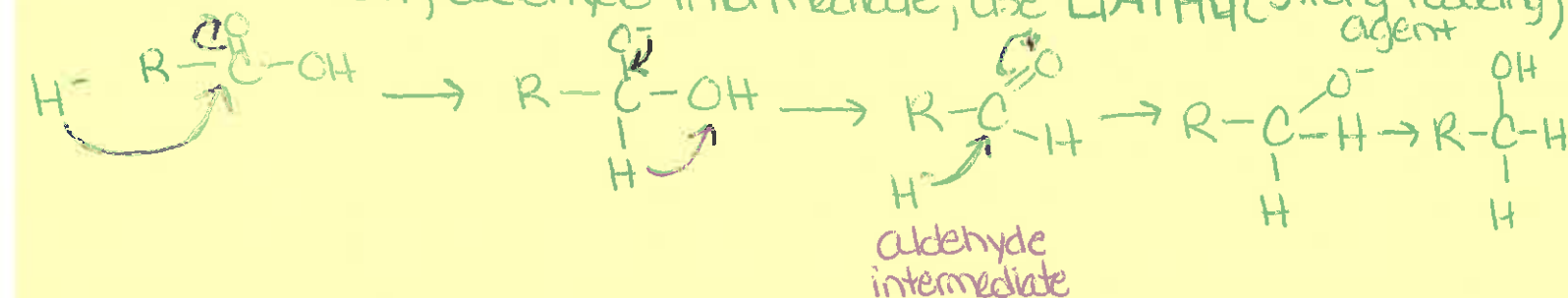
↳ condensation of 2 - COOH



* nucleophilic acyl substitution

6) reduction

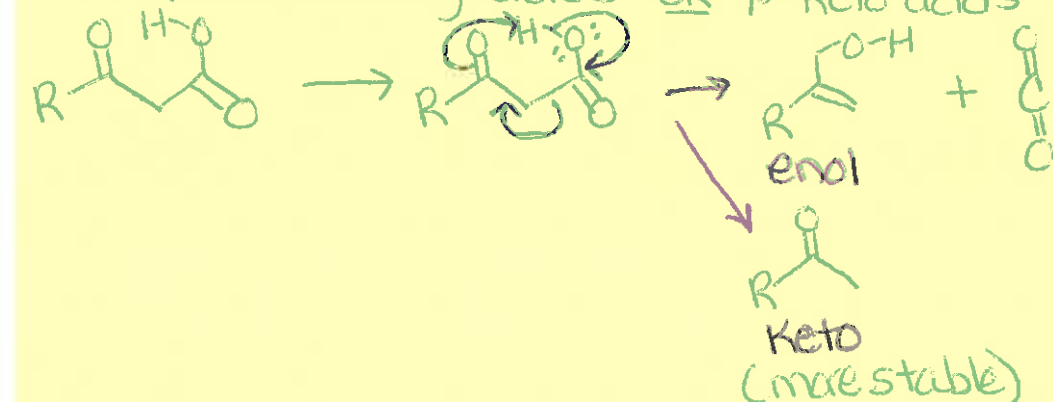
↳ COOH → OH; aldehyde intermediate, use LiAlH_4 (strong reducing agent)



7) decarboxylation

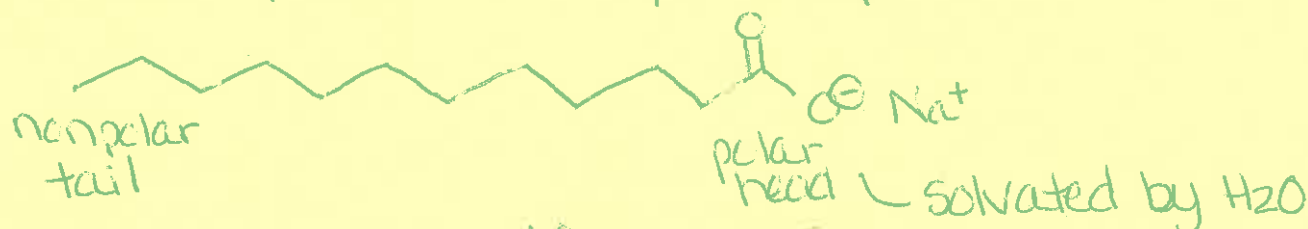
↳ loss of carboxyl group as CO_2

↳ 1,3 dicarboxy acids OR β -keto acids + HEAT



8) saponification

↳ long chain COOH + NaOH or KOH = salt
(fatty acid + lye = soap) ☺



in H_2O , arrange into micelles

↳ tails to center, heads to outer side

KAPLAN - Carboxy Derivs (5)

Amides

- * synthesized by COOH derivatives + NH_3 or amine
 - ↳ only 1° or 2° amines undergo this rxn
- * BP $\downarrow$ generally due to # of alkyl groups

Esters

- * synthesized via dehydration of COOH + OH derivatives
- * synthesized via anhydrides + OH 's

Anhydrides

- * condensation dimers of COOH
- * $\uparrow$ BP than COOH due to weight

Reactivity

Anhydrides > esters > amides
3- e^- withdrawing e^- withdrawing e^- donating

Steric Effects

↳ like $\text{S}_\text{N}2$ rxn, controls where a rxn occurs on molecule

Electronic Effects

- * induction $\Rightarrow$ distribution of charge across π bonds
- * conjugation $\Rightarrow$ presence of alternating single and multiple bonds
 - ↳ sp^2 or sp hybridized; leads e^- clouds above and below plane of molecule

Kaplan Orgo - Alcohols

* Capable of intermolecular H-bonding

* hydroxy H = weakly acidic

↳ ↑ melting point

↳ ↑ boiling point

↳ ↑ solubility in H₂O

↑ # OH ⇒ ↑ mp/bp

Oxidation rxns

1° → aldehydes by PCC ⇒ stops; lacks H₂O to hydrate the aldehyde

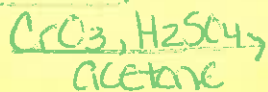
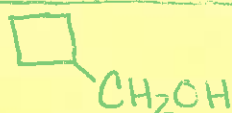
2° → ketones by PCC ⇒ or stronger oxidizing agent

3° → No bueno ☹

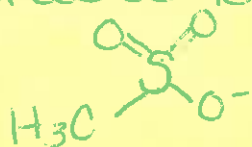
1° → CCOH by strong oxidizing agent; Na₂Cr₂O₇

2° → ketones by strong oxidizing agent; Na₂Cr₂O₇

Jones Oxidation → 1° to COOH, 2° to Ketones

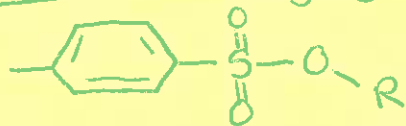


Mesylate → created to make OH a better leaving group



* also a good protecting group when we do NOT want OH to leave
prep: methylsulfonyl chloride + OH in base

Tosylate → -SO₃C₆H₄CH₃



* also good protecting group when we don't want OH to leave
prep: OH + p-toluenesulfonyl chloride

* aldehydes + ketones can be reacted with alcohol or diol to get acetals or ketals

1° Carbon

2° Carbon

+ 2-OR groups

+ 2-OR groups

Quinones → phenols + oxidizing agents

① electron acceptors in ETC

② phyloquinone = Vit K₁

③ menaquinone = Vit K₂

④ hydroxyquinone = medications

⑤ Ubiquinone = Co-enzyme Q; e⁻ carrier complexes I, II, III; lipid soluble

3° alcohols cannot be oxidized because they are already as oxidized as possible w/out breaking C-C bond

Ketones + Aldehydes

* lack of H-bond leads to $\downarrow$ BP

* good electrophiles

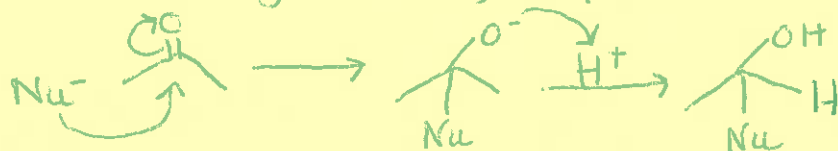
* aldehydes more reactive toward nucleophiles due to less steric hindrance

Carbonyl carbon = $\begin{array}{c} \text{O}^{\delta-} \\ \parallel \\ \text{C}^{\delta+} \end{array} \Rightarrow$ dipole moment; O = $\uparrow$ EN pulling e^- from C

Aldehydes $\Rightarrow$ created from 1° -OH by PCC; stronger oxidizing agent $\rightarrow$ COOH

Ketones $\Rightarrow$ created from 2° -OH by $\text{Na}_2\text{Cr}_2\text{O}_7$ or $\text{K}_2\text{Cr}_2\text{O}_7$ or CrO_3 or PCC; 2° -OH can't go too far; stops at ketone

Nucleophilic Add Rxn



Hydration $\Rightarrow$ ketones/aldehydes w/ $\text{H}_2\text{O} \rightarrow$ geminal diols

Acetals/Hemiacetals $\Rightarrow$ ketones/aldehydes + alcohols

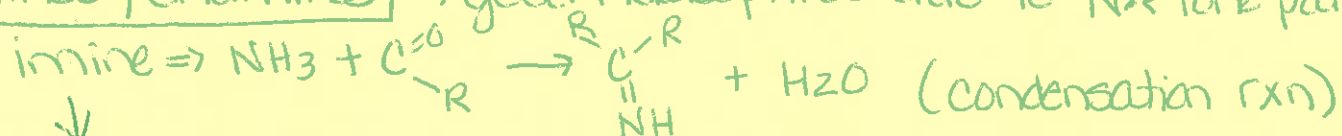
1 equivalent $\rightarrow$ hemi

2 equivalents $\rightarrow$ acetal/ketal via $\text{S}_\text{N}1$

$\hookrightarrow$ comparatively inert

$\hookrightarrow$ used as protecting groups

Imines/Enamines $\Rightarrow$ good nucleophiles due to N lone pair

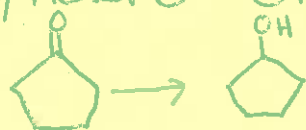


$\downarrow$
tautomerization = enamines

Cyanohydrins $\Rightarrow \text{HCN} + \text{ketone/aldehyde}$; stable compound

Aldehyde $\rightarrow \text{COOH}$ via $\text{KMnO}_4, \text{CrO}_3, \text{Ag}_2\text{O}, \text{H}_2\text{O}_2$

Aldehyde/ketone $\rightarrow \text{OH}$ via $\text{LiAlH}_4, \text{NaBH}_4$



hydride reagents

* Key points

① EN of oxygen on carbonyl C pull e^- away, charging it $\oplus$

orgo functional groups

$C=N$ imine

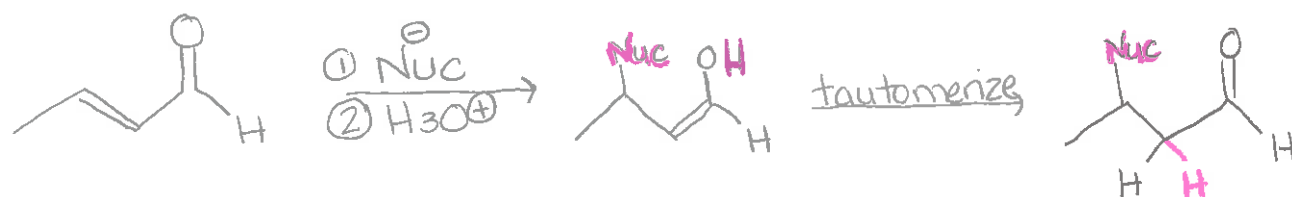
$C=C-N$ enamine } tautomers

$N-C=O$ amide

$O=C-O$ ester (-oate suffix)

$O=C-O-C=O$ anhydride

Michael Addition $\Rightarrow$ adds to β site



(1,4 addition)

Nucleophiles "Michael Donors"

