Reactions of Carbonyl Compounds

##### I. General Considerations

A. many reactions involve formation of tetrahedral intermediate followed by elimination:

 AN + DN



1. carbonyl - provides sink for electrons, accessible carbon, simultaneous bond forming/breaking

2. lone pairs must be antiperiplanar for group to leave tetrahedral intermediate, similar to acetal decomposition

3. acid/base and nucleophilic catalysis (Benzoin reaction)

##### B. Carbonyl is activated by electron withdrawing groups, deactivated by bulky groups



1. alkyl groups stabilize electronically

2. steric effect: alkyl groups are closer together after hybridization change: sp2 to sp3

C. Good nucleophiles readily add to carbonyl groups, may be reversible (second step)

D. Carbonyl must be activated by acid to react with weak nucleophiles like water



II. Hydration



Unfavorable for most carbonyl compounds

Reaction is fast when acid or base catalyzed, even if not favorable

##### III. addition of alcohol

###### A. acid or base forms hemiacetal, only acid the acetal

###### B. acetal is base stable

###### C. reversible with excess water

###### D. ketals normally only form with 1,2-diols

###### E. thioacetals also form, not readily reversible



IV. Addition/elimination of acid derivatives (sometimes acid or base catalyzed)



acyl transfer



V. hydrolysis of esters, page 380 in March, 7 of 8 mechanisms observed

 A. base hydrolysis of esters follows this mechanism: BAC2 (AN + DN)



no attack on R’

OH-, OR-, RNH2 attack carbonyl without catalysis

 B. acid catalyzed hydrolysis: AAC2 (Ah + AN + Dh + Ah + DN + Dh)



 O-acyl not O-ether cleavage

C. stable carbocations (tert-butyl or benzyl) favor AAL1 (Ah + DN + AN +Dh) carboyxlate leaves



D. bulky acyl group promotes AAC1 (Ah + DN + AN +Dh) as does concentrated acid with O-R bonds not easily cleaved



VI. Meerwein-Ponndorf-Verley reaction

 A. metal alkoxide transfer  H

 B. 6-member cyclic transition state

 C. Al is important in bringing together alkoxide and carbonyl

 D. equilibrium determined by reactivity of carbonyl

 E. driven by removal of propanone by distillation

VII. Cannizzaro Reaction

 A. disproportionation

 B. Rate = k[PhCHO]2[HO-]

 C. does not work with ketones: alkyl does not migrate

 D. metal coordinates oxygens like MPV reaction



VIII. amine addition



 A. at low pH water elimination is fast, amine group is protonated and amine addition is rate limiting

 B. at high pH, water elimination is slow and rate limiting and amine addition is faster.

 C. imine is more stable than enamine but tends to polymerize

 D. secondary amines can only form enamines

 E. R = OH, H, alkyl, NH2, NHCONH2, NHPh

IX. Grignard addition

 A. chelation important





evidence for radical reaction?

*side reactions*

B. Grignard with -H add hydride (analogous to MPV)



C. carbonyl with -H



X. Alkyl lithium reagents

 A. forms dimers and tetramers which affect steric demands

 B. Grignard and lithium reagents both follow Cram’s rule

XI. aldol condensations

1. base catalyzed – enolate formation

1. equilibrium favorable for aldehydes, note stereochemistry of transition state

2. not favorable for ketones, why doesn’t NaOH work for crossed aldol?



1. acid catalyzed – enol formation

1. favorable for aldehydes and ketones

2. tertiary alcohols dehydrate

1. crossed aldol – mixed aldehydes gives four possible products if both aldehydes have -H



XII. Claisen Condensation (why is there still starting ester in second step?)

A. alkoxide is not a good leaving group, assisted by CO double bond formation

B. equilibrium favors -keto enolate

C. neutralize to obtain product

D. Dieckmann - intramolecular condensation



XIII. Wittig reaction (phosphonium and ylid are stable salt)



XIV. phosgene and primary amine



XV. reductive amination



XVI. Mannich reaction p901 in March



XVII. Benzoin reaction (carbene catalysis)



XVIII. cyanogen bromide



XIX. Wolff rearrangement – migrating group retains configuration



XX. vinyl substitution

# A. bimolecular: addition/elimination, favored by electron withdrawing group



B. unimolecular: vinyl cation formation, unfavorable

1. facilitated by -aryl group, ArXC=CR2

2. occurs with very good leaving group such as OSO2CF3



Hofmann, Schmidt, Lossen, Curtius Rearrangement