CHEM 222 section 01

LECTURE #21 Tues., Nov.13, 2007

Lecture topics & readings

Today's class
- finish rxns of benzene derivative: up to 15.10
  (not covering rest)

Before next class
- practice synthesis examples
- review Ch.10: organometallics

Next class
- continue rxns of carbonyl compounds (Ch.16-18)

15.7-8 More practical considerations & SYNTHESIS

Not all substituents have equal influence on reactivity / regiochem:

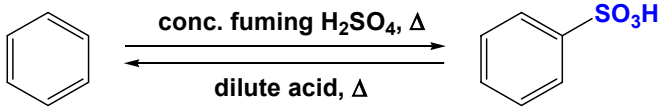
strong activators > weak activators >> deactivators

ortho-para directors >> meta directors

Choose your strategy carefully:

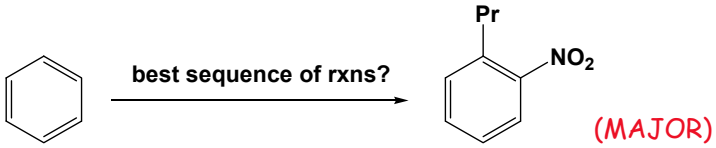
1. **Remember steric effects**
   - even 2C groups hinder substitution at ortho sites…
   - attach bulky group 1st ⇨ block ortho sites ⇨ clean para substitution
2. **Substituent modification *vs.* further ring substitution?**
   - pay attention to changes in group's activation/direction ability

A "blocking" trick: SULFONATION is reversible
- add on $-SO_3H$ to block a site ⇨ then remove it later



(see Problem 15.19)

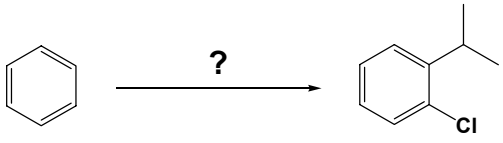
How could the following be synthesized from benzene?

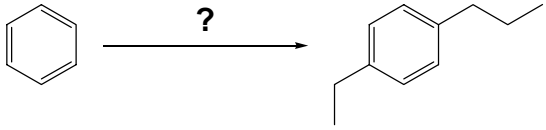


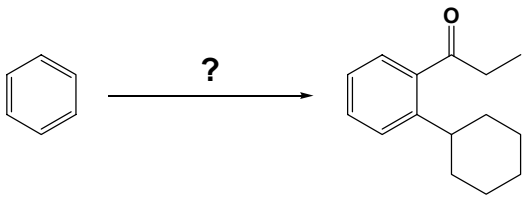
(MAJOR)

(3)

Provide a rxn sequence to make these as the major products…

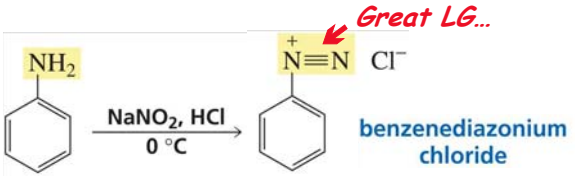






They don't all require "blocking". (answers next class)

15.9-10 Synthesis involving aryl diazonium salts

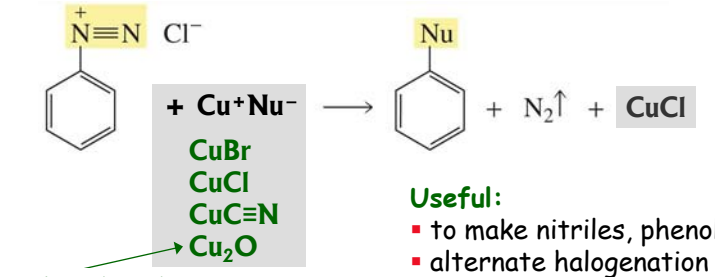


- Diazonium salts are unstable at T > 0°C.
- Alkyl diazonium salts are explosive!
- CH_2N_2 is useful = *diazomethane*

Mech. of rxn of 1° amines + nitrous acid: see 15.11

N_2(g) readily displaced by many Nu's (mechanism varies, not all understood)

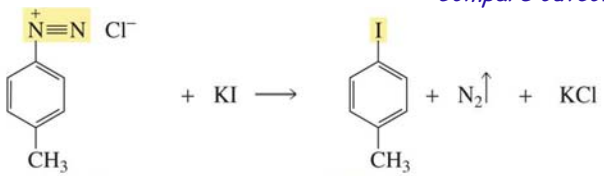
Sandmeyer rxns = copper(I) salt + diazonium salt:



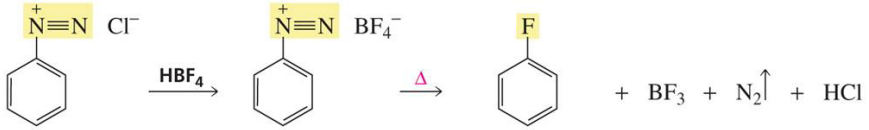
Useful:
- to make nitriles, phenols, halides…
- alternate halogenation route: if X_2/FeX_3 gives wrong regiochem…

Alternate iodination route:

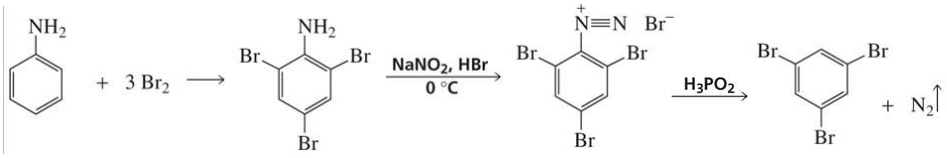
Compare outcome of our 1st approach: toluene + I_2/HNO_3



Fluorination route = Schiemann reaction:

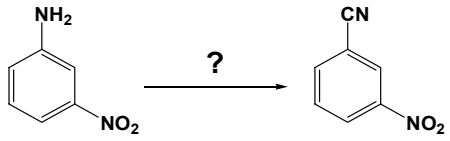


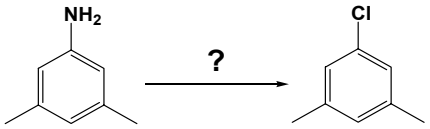
To remove an NH_2 group: convert to $-N^+\equiv N$ then replace with H using hypophosphorus acid



Provide a rxn sequence to make these as the major products…

(answers next class)





& how would you make the starting materials from benzene / aniline?

REACTIONS OF CARBONYL COMPOUNDS: Ch.16,17,18

Chapter Goals & hints

Understand the reactions of the most important functional group.

- Understand the electrophilic nature of the carbonyl carbon.
- Classify compounds as Class I or Class II & learn the significance: groups bonded to C=O displaceable or not displaceable?
- Learn the reactions of Class I and Class II carbonyl compounds.
- Learn to apply these rxns to synthesis & to see biological relevance.

Topics Outline: but not covered in text's order

Ch.16:	Nucleophilic acyl substitution Typical rxns of class I carbonyl compounds	except 16.12, 14, 18, 22
Ch.17:	Reactions of class II carbonyl compounds Reactions with common nucleophiles Carbon-carbon bond forming reactions	17.1-13 (all)
Ch.18:	Reactions at the α-carbon Enols & enolates, alkylation, condensations	18.1-16 (1^{st} $^2/_3$)

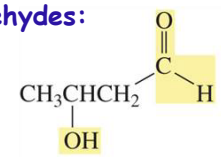
Carbonyl-derived functional groups = highest priority

Table 17.1 Summary of Functional Group Nomenclature

	Class	Suffix name	Prefix name
increasing priority	Carboxylic acid	-oic acid	Carboxy
	Ester	-oate	Alkoxycarbonyl
	Amide	-amide	Amido
	Nitrile	-nitrile	Cyano
	Aldehyde	-al	Oxo (=O)
	Aldehyde	-al	Formyl (CH=O)
	Ketone	-one	Oxo (=O)
	Alcohol	-ol	Hydroxy
	Amine	-amine	Amino
	Alkene	-ene	Alkenyl
	Alkyne	-yne	Alkynyl
	Alkane	-ane	Alkyl
	Ether	—	Alkoxy
	Alkyl halide	—	Halo

Carbonyl compounds: names & structures

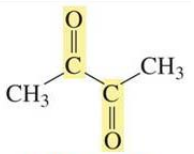
Aldehydes:



3-hydroxybutanal

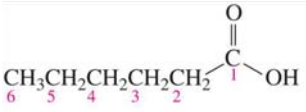
Ketones:

smelly feet & armpits...

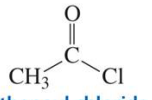


butanedione

Carboxylic acids:
e.g., hexanoic acid

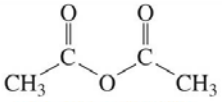


Acid halides:

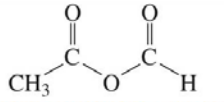


ethanoyl chloride
acetyl chloride

Acid anhydrides: 2 RCOOHs linked via loss of H_2O



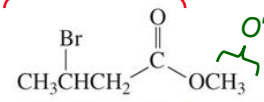
ethanoic anhydride
acetic anhydride
a symmetrical anhydride



ethanoic methanoic anhydride
acetic formic anhydride
a mixed anhydride

named 2nd, as if a carboxylate

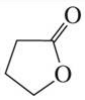
Esters:



methyl 3-bromobutanoate
methyl β-bromobutyrate

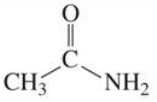
O's substituent named 1st as if a cation

Cyclic ester = lactone

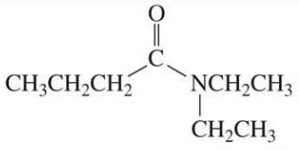


2-oxacyclopentanone
γ-butyrolactone

Amides:

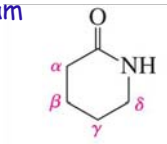


ethanamide
acetamide



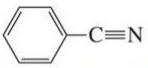
N,N-diethylbutanamide

Cyclic amide = lactam

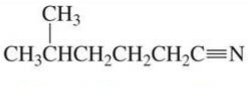


2-azacyclohexanone
δ-valerolactam

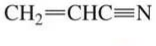
Nitriles:



benzenecarbonitrile
benzonitrile
phenyl cyanide



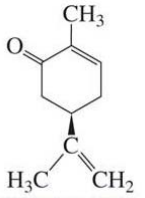
5-methylhexanenitrile
δ-methylcapronitrile
isohexyl cyanide



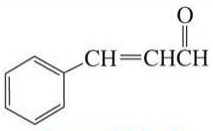
propenenitrile
acrylonitrile

(11)

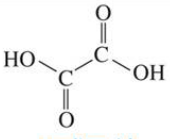
Carbonyl compounds are common in nature



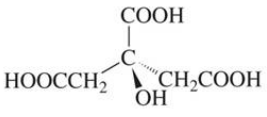
(*R*)-(–)-carvone
spearmint oil



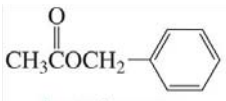
cinnamaldehyde
cinnamon flavoring



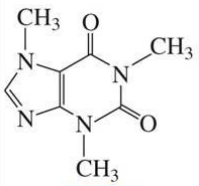
oxalic acid



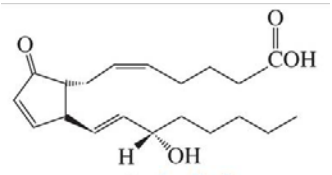
citric acid



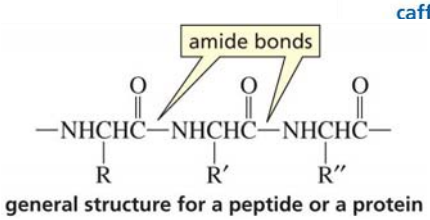
benzyl acetate
jasmine



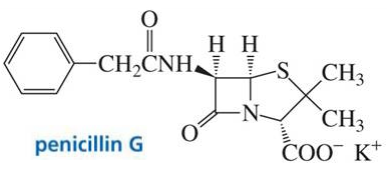
caffeine



prostaglandin A_2

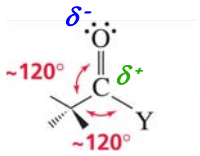


general structure for a peptide or a protein

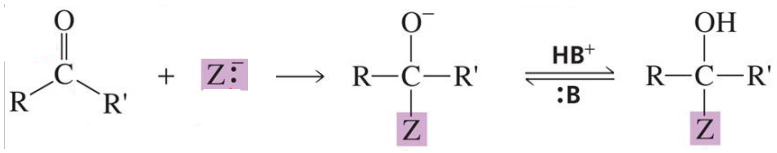


penicillin G

How aldehydes & ketones (Class II) react: (17.3) Nucleophilic addition



tetrahedral (Td) intermediate

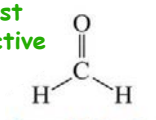


If Nu (Z) = relatively weak base
⇨Td int. can collapse to expel Z
⇨1st step reversible ($\rightleftharpoons$)

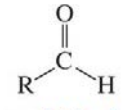
Nu (Z) has added to C=O bond (Nu addition product)

Relative reactivities: correlates with C=O bond polarity

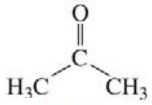
Most reactive



formaldehyde

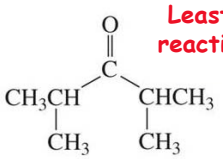


an aldehyde

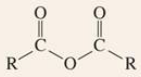
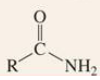


a ketone

Least reactive



Class I compounds: A group bonded to C=O can be displaced by a Nu

	Leaving group	Conj. Acid & its pK_a	
	Br^-	HBr	−9
	Cl^-	HCl	−7
			~3–5
	$^-OR'$	R'OH	~15–16
	^-OH	H_2O	15.7
	$^-NH_2$	NH_3	36

Easily displaced…
⇨very reactive to nucleophiles

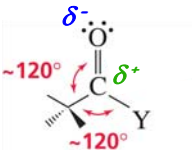
Can only be displaced if activated (*e.g.*, protonated…)

Class II carbonyl compounds: no displaceable groups bonded to C=O

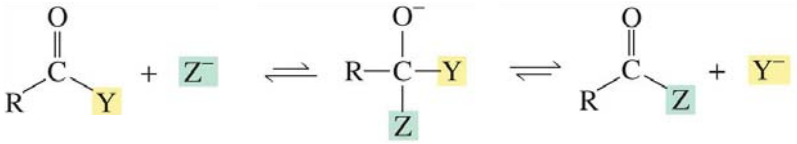
	H^-	H_2	~40
	R^-	RH	>60

Do not undergo substitution rxns.

How Class I carbonyl compounds react:
(16.5) Nucleophilic acyl substitution



Td int.



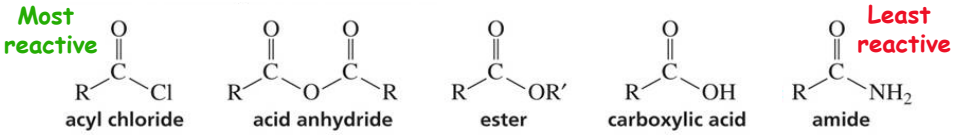
Because Y is a LG…

- Td int. can collapse to expel Y ⇨ substitution product

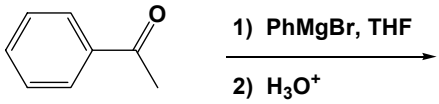
OR…

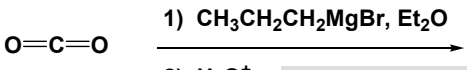
- Td int. can collapse to expel Z ⇨ back to reactants…

Relative reactivities: correlates with LG ability

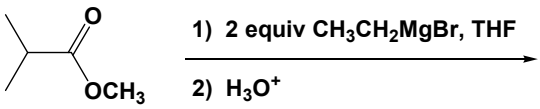


What would be the products of these reactions? (see 17.4)





Lab trick: *to test if your Grignard rgt has formed*
- *add drop of rxn mixture to dry ice*
- *then run TLC of residue: polarity RCOOH > RBr SM*



Ketones/aldehydes have more reactive C=O bonds than Class I carbonyls…