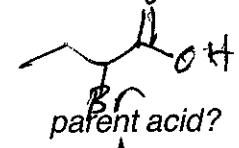


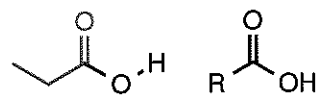
Chapter 21: Acid Derivatives

[Chapter 21 Sections: 21.6-21.12]

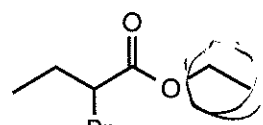
2-BROMOBUTANOIC ACID



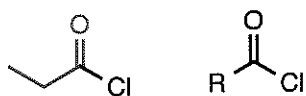
Nomenclature of Carboxylic Acid Derivatives



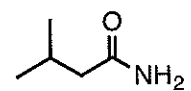
carboxylic acid propanoic acid



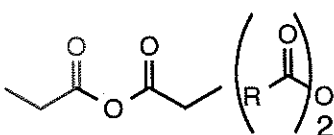
ETHYL 2-BROMOBUTANOATE



acid chloride propanoyl chloride

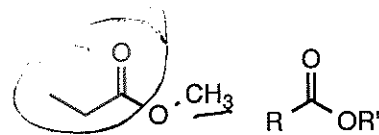


3-METHYLBUTANOIC ACID



acid anhydride propanoic anhydride

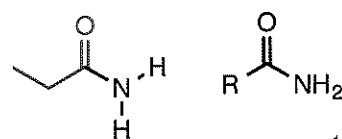
3-METHYLBUTANAMIDE



ester

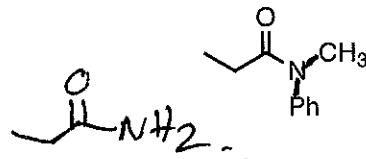
methyl propanoate

N,N-DIMETHYL 3-METHYLBUTANAMIDE



amide

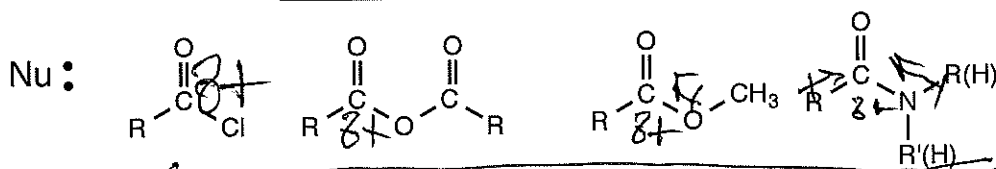
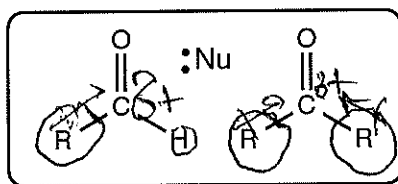
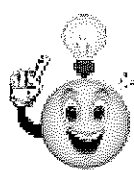
propanamide



N-METHYL, N-PHENYL PROPANAMIDE

Problems: 1-3

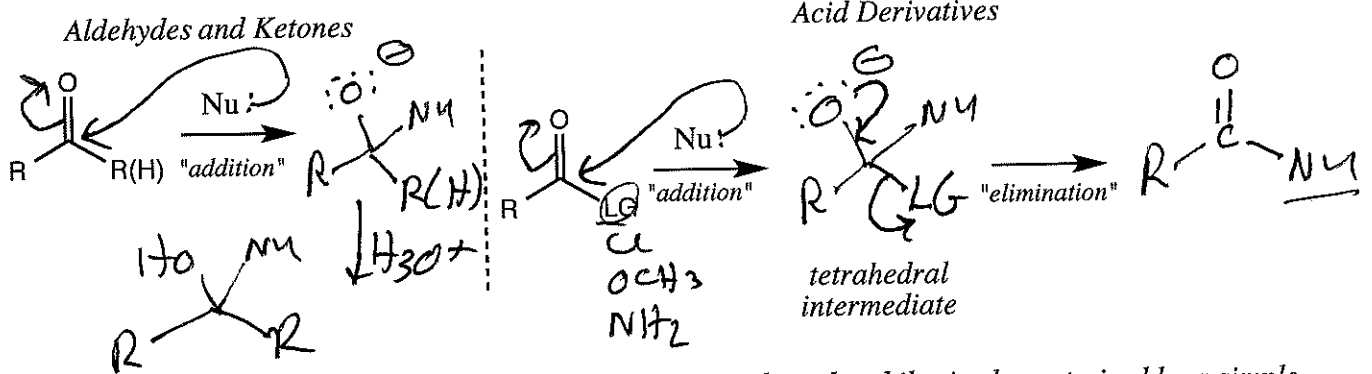
Relative Reactivity of the Acid Derivatives Towards Nucleophiles



← INCREASES = INCREASED REACTIVITY

- the relative reactivity of the acid chlorides towards nucleophilic addition is in line with the nature of the groups attached to the C=O
- electron withdrawing groups (i.e., Cl) enhance the partial positive charge on the carbon of the carbonyl group, increasing reactivity with nucleophiles
- electron donating groups dampen the partial positive charge on the carbon of the carbonyl group, decreasing reactivity with nucleophiles. The stronger the electron donation, the lesser the reactivity

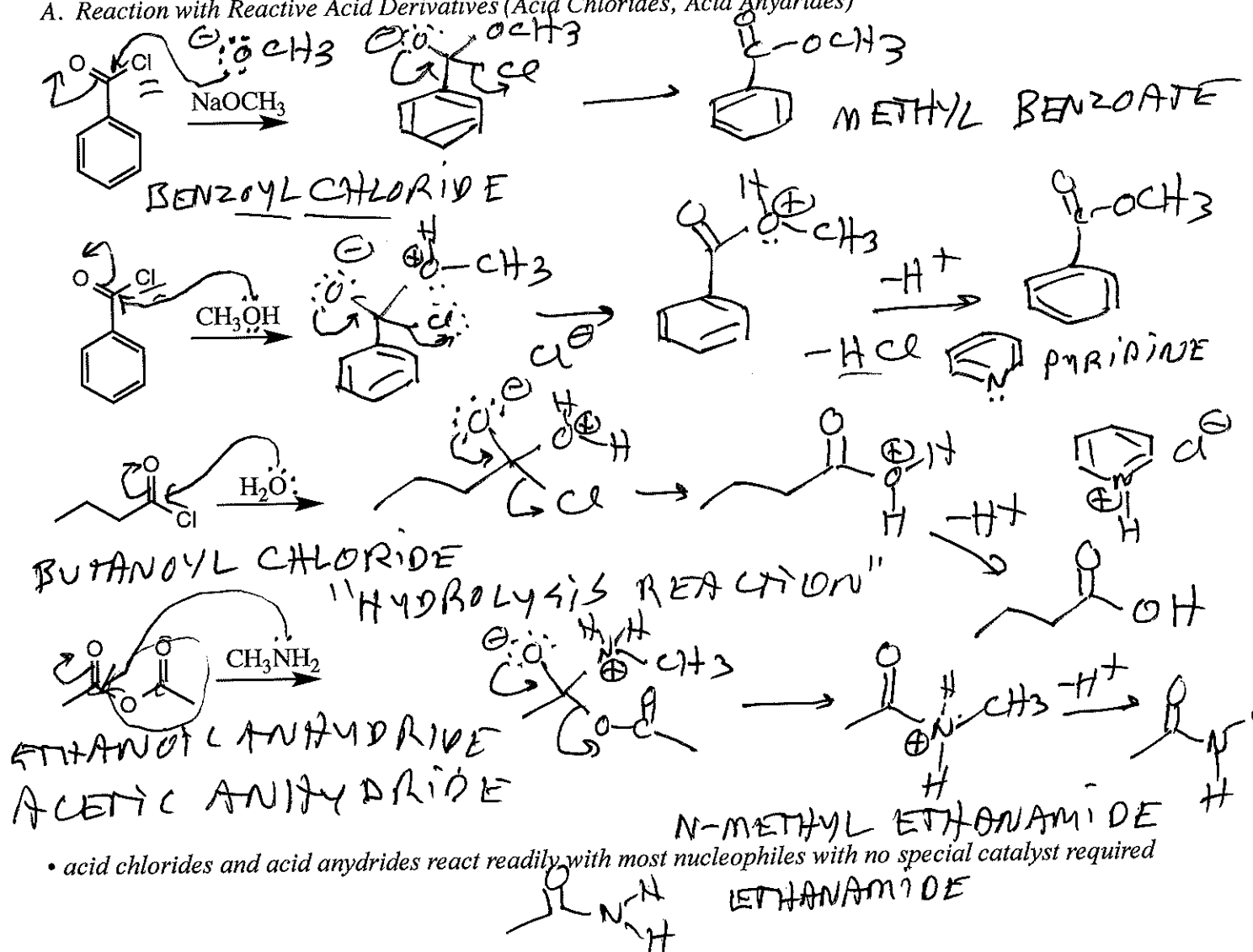
Defining the Difference in Reactivity Between the Carbonyl Groups of Aldehydes/Ketones and the Acid Derivatives



- the reaction of the C=O group of aldehydes and ketones with nucleophiles is characterized by a simple nucleophilic addition
- the reaction of the C=O group of the acid derivatives with nucleophiles is characterized by a two step process: addition of the nucleophile followed by elimination of the leaving group
- thus, the net result is a NUCLEOPHILIC SUBSTITUTION rather than an addition and is referred to as "nucleophilic acyl substitution"

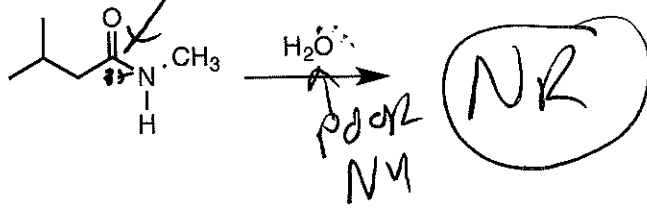
Mechanisms of Nucleophilic Substitution

A. Reaction with Reactive Acid Derivatives (Acid Chlorides, Acid Anhydrides)



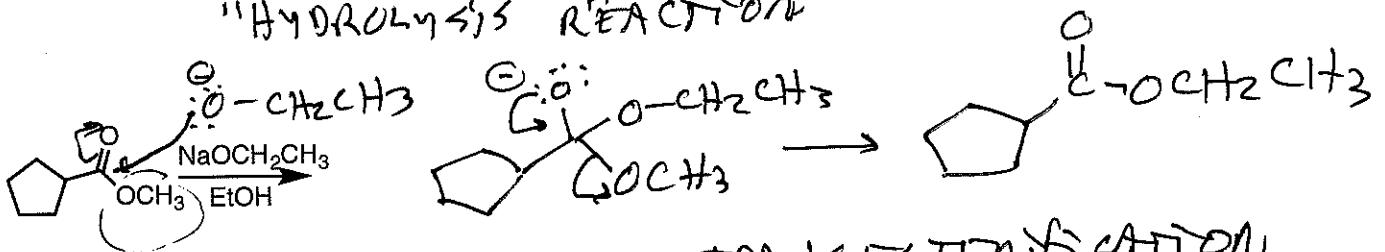
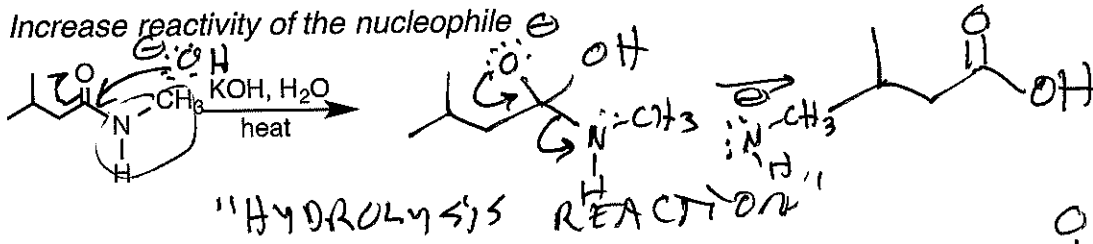
- acid chlorides and acid anhydrides react readily with most nucleophiles with no special catalyst required

B Reaction with Low Reactivity Acid Derivatives (Esters, Amides)

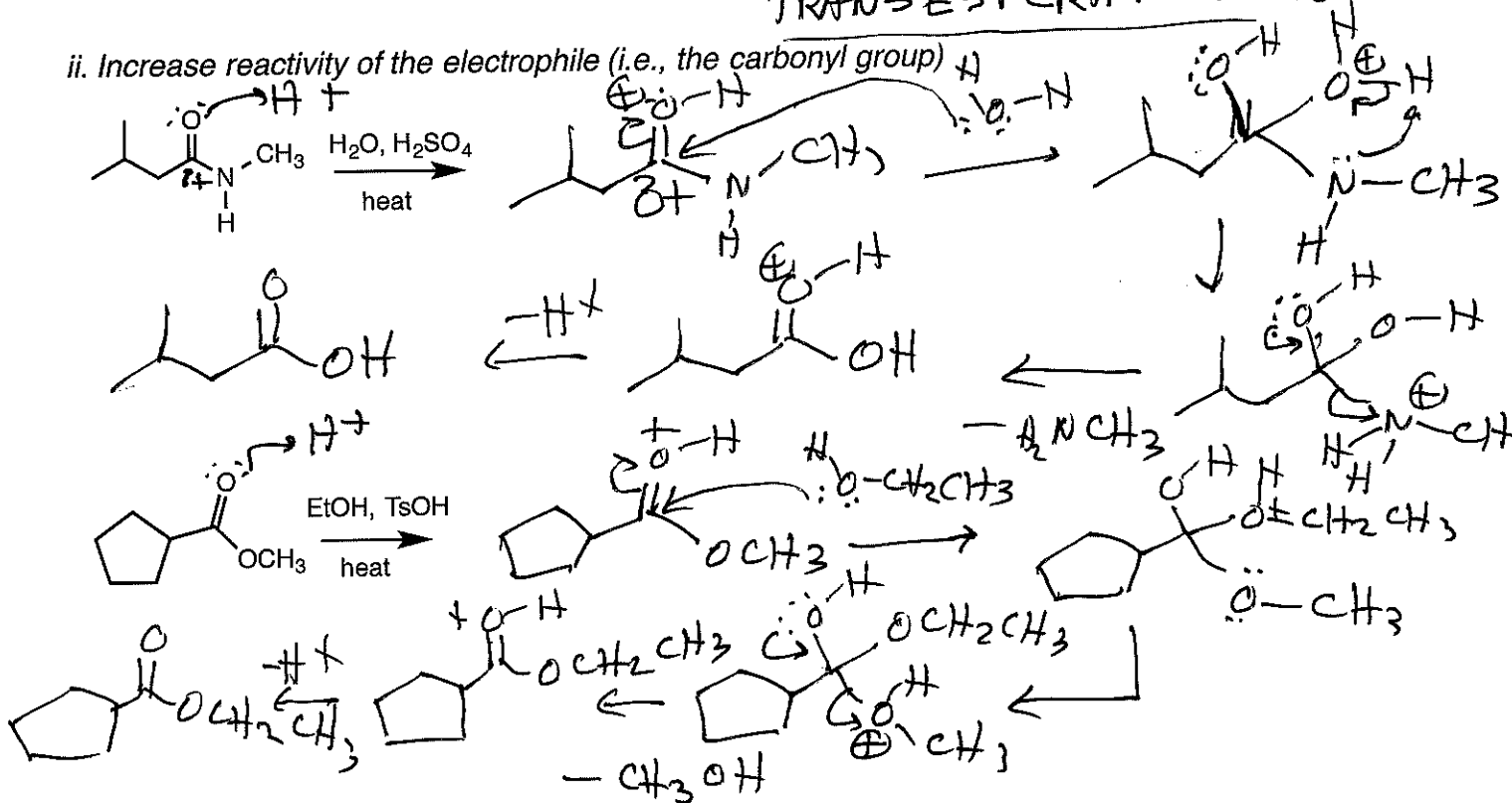


- esters and amides have much less reactive carbonyl groups than do acid chlorides and anhydrides
- therefore, to engage these acid derivatives in reactivity with nucleophiles, two strategies are possible

i. Increase reactivity of the nucleophile

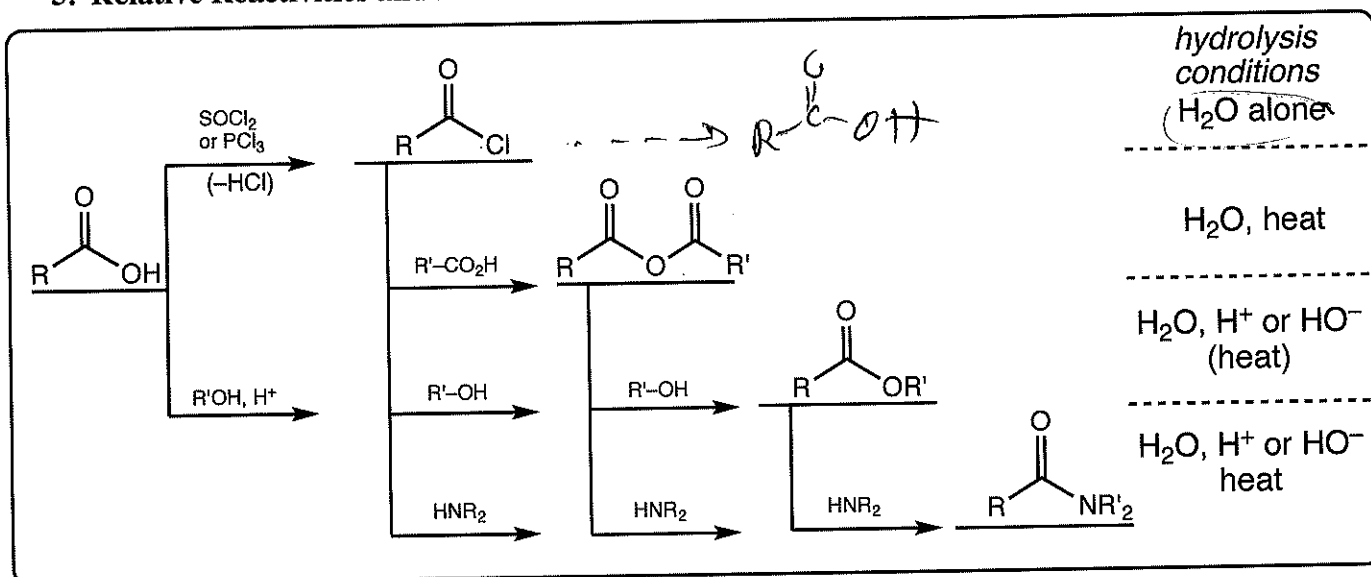


ii. Increase reactivity of the electrophile (i.e., the carbonyl group)



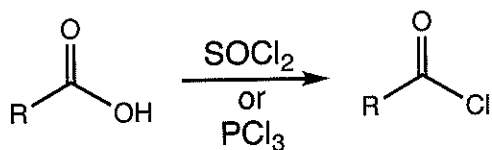
- the reactivity of amides is considerably less than that of esters. Heating the reaction is almost always necessary to engage amides in reactions, whereas esters will often react at room temperature (but always faster when heated)

5. Relative Reactivities and Interconversions of Acid Derivatives Summary Chart



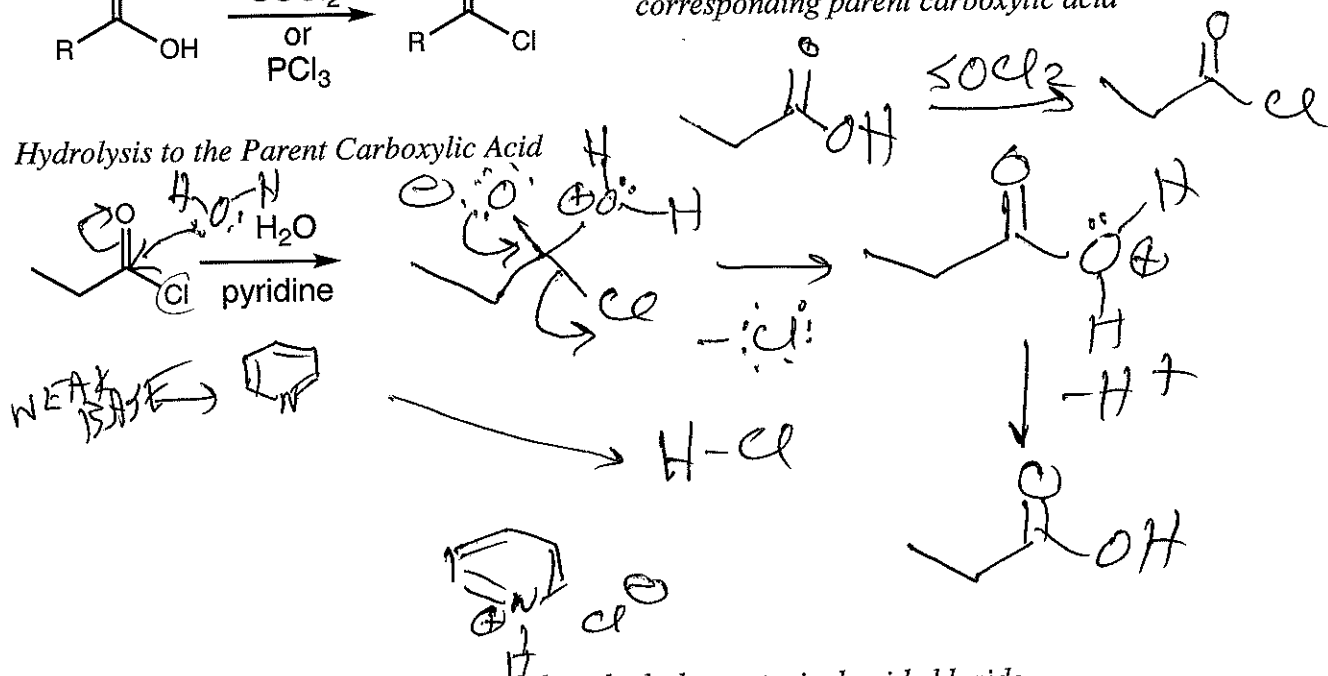
6. Acid Chlorides

A. Preparation



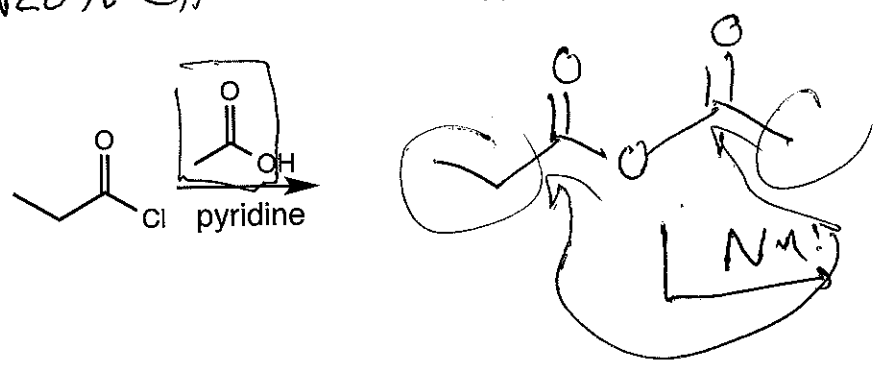
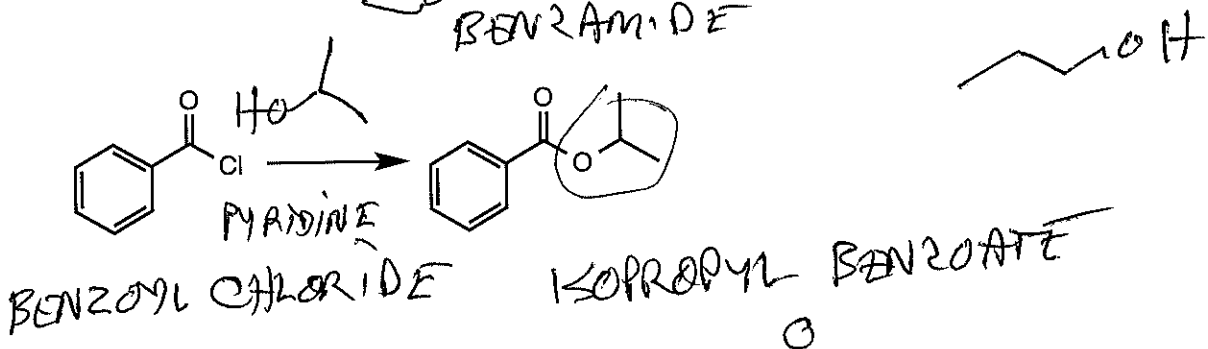
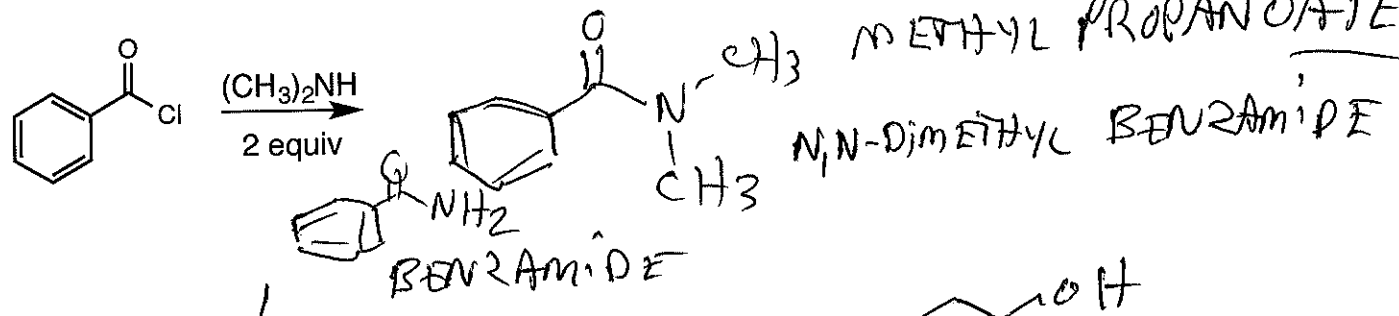
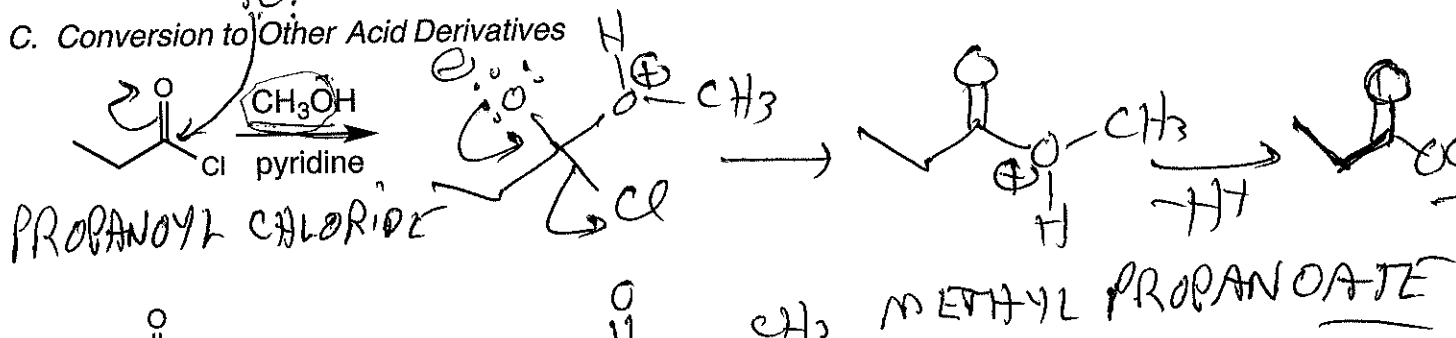
• acid chlorides may be synthesized **ONLY** from the corresponding parent carboxylic acid

B. Hydrolysis to the Parent Carboxylic Acid



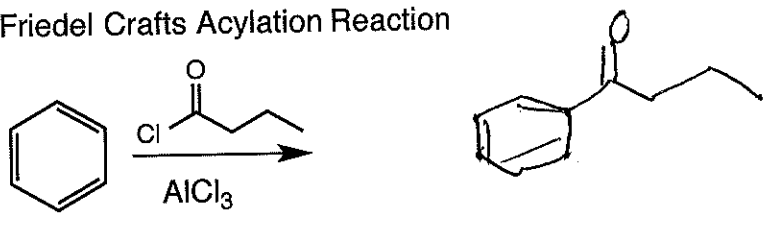
- water alone is a strong enough nucleophile to hydrolyze a typical acid chloride
- the rate of the reaction may be increased by using NaOH as nucleophile and/or heating the reaction
- a weak base like pyridine is often added to neutralize the HCl byproduct that is formed
- hydrolysis of acid chlorides is almost never a useful reaction, but more of a nuisance reaction

C. Conversion to Other Acid Derivatives



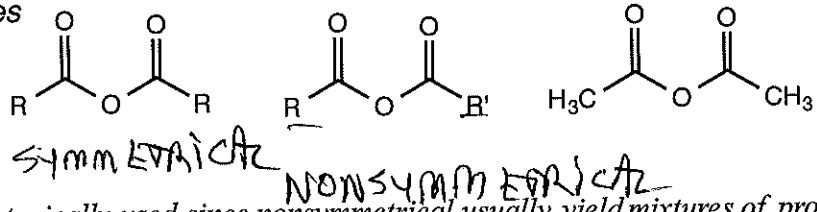
D. Some Other Useful Reactions

Friedel Crafts Acylation Reaction



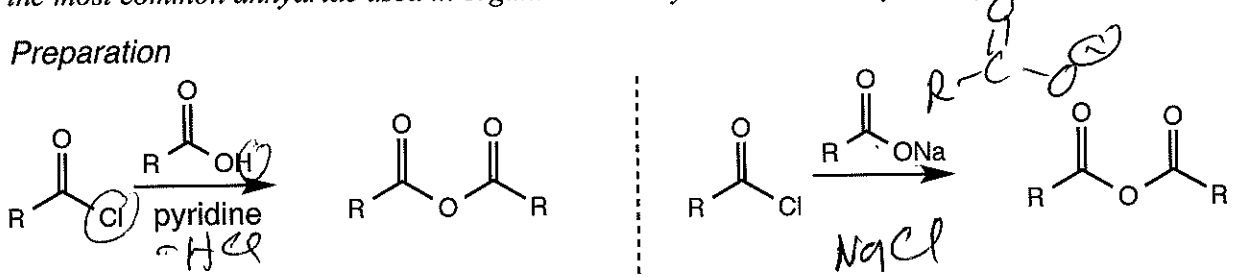
Acid Anhydrides

A. Types of Acid Anhydrides

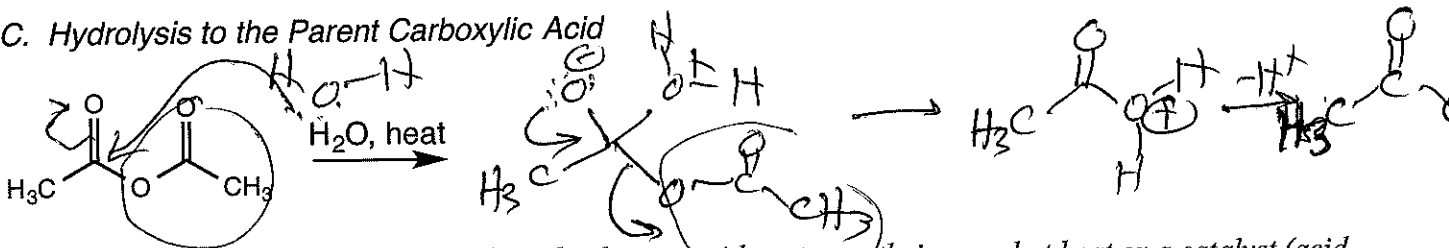


- symmetrical anhydrides are typically used since nonsymmetrical usually yield mixtures of products
- the most common anhydride used in organic chemistry is ethanoic anhydride (acetic anhydride)

B. Preparation

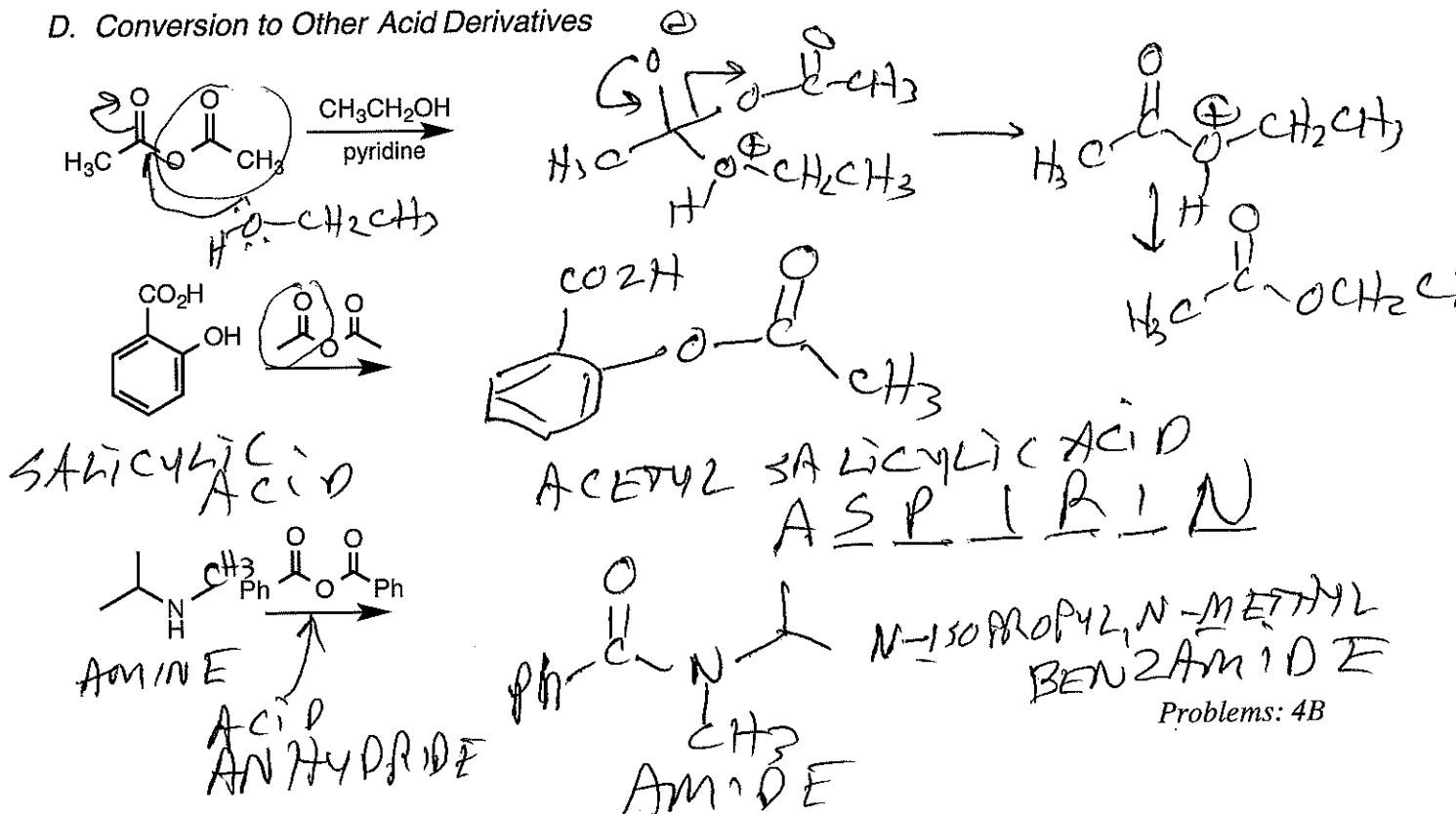


C. Hydrolysis to the Parent Carboxylic Acid

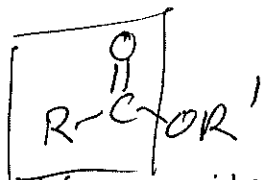


- acid anhydrides are reactive enough to slowly react with water on their own, but heat or a catalyst (acid or base) significantly increases the rate of the reaction
- hydrolysis of acid anhydrides is more of a nuisance reaction than a useful reaction

D. Conversion to Other Acid Derivatives

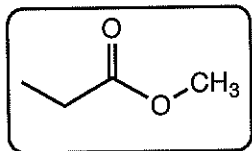
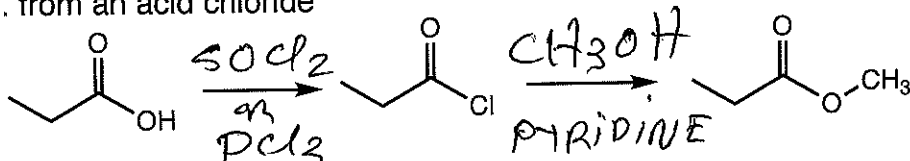


Esters $\text{RCO}_2\text{R}'$

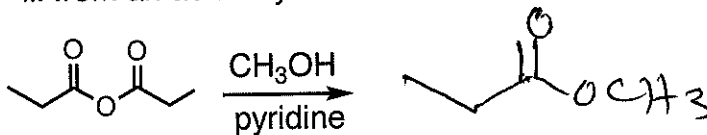


A. Preparation

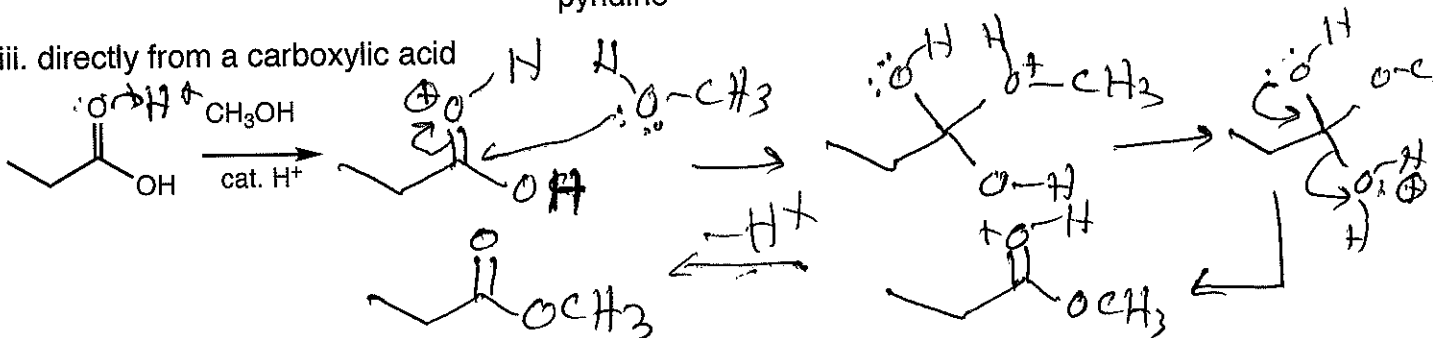
i. from an acid chloride



ii. from an acid anhydride

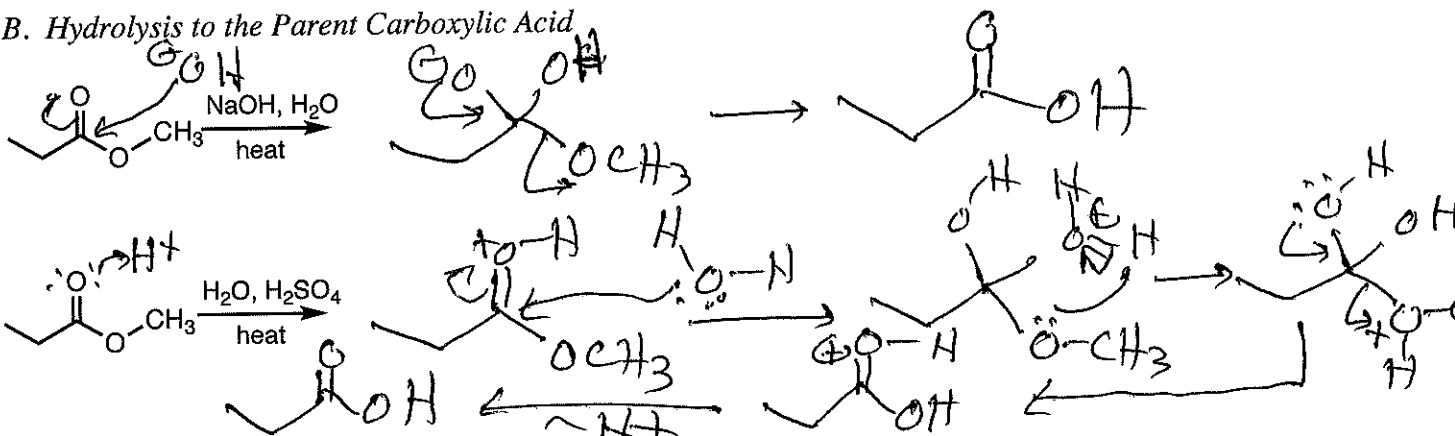


iii. directly from a carboxylic acid



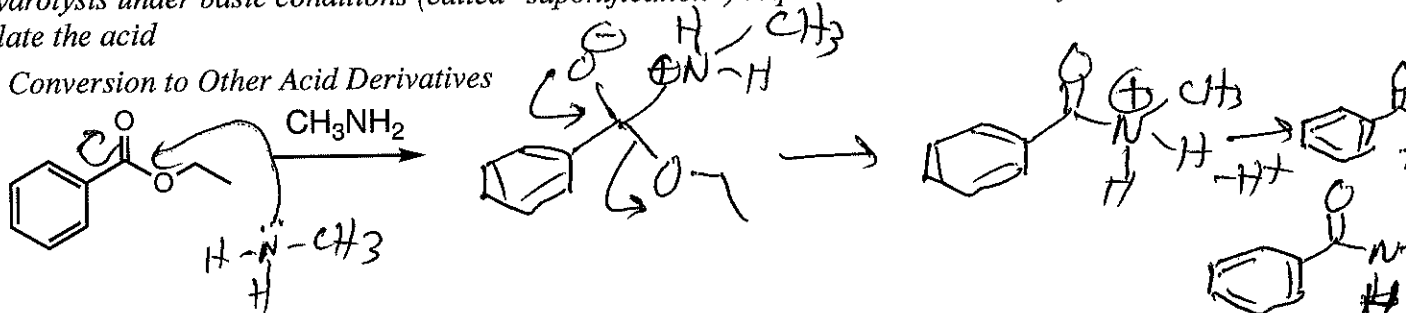
- formation of an ester directly from a carboxylic acid is called a "Fisher esterification"
- an acid catalyst is required since the carbonyl group of an acid is not reactive enough to react on its own
- the acid catalysts used are usually TsOH , H_2SO_4 or H_3PO_4

B. Hydrolysis to the Parent Carboxylic Acid

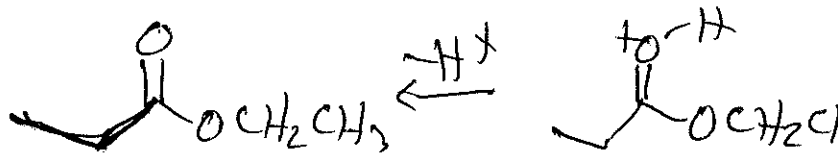


- the carbonyl group of esters is significantly less reactive than that of the anhydrides or acid chlorides
- hydrolysis of an ester requires acidic or basic catalysis and usually heat
- hydrolysis under basic conditions (called "saponification") requires neutralization of the reaction mixture to isolate the acid

C. Conversion to Other Acid Derivatives

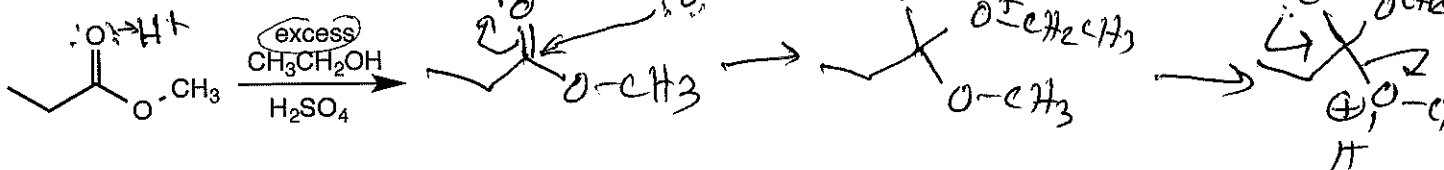


- formation of amides from esters is possible, but is not an often used reaction since the acid chlorides and anhydrides are more reactive starting compounds



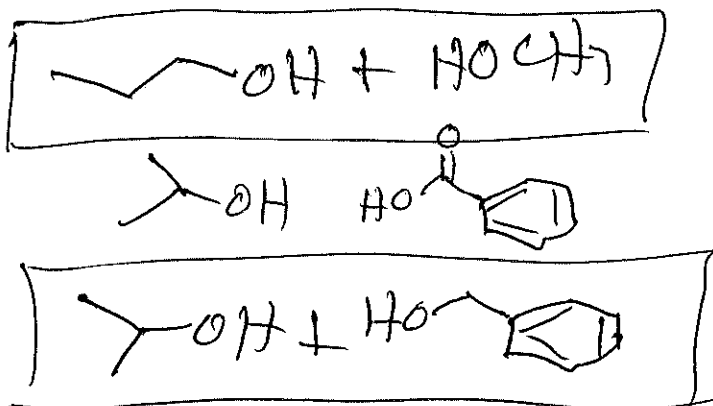
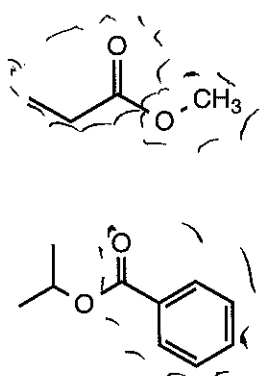
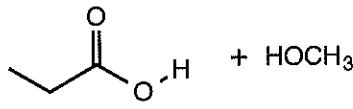
D. Some Other Useful Reactions

transesterification



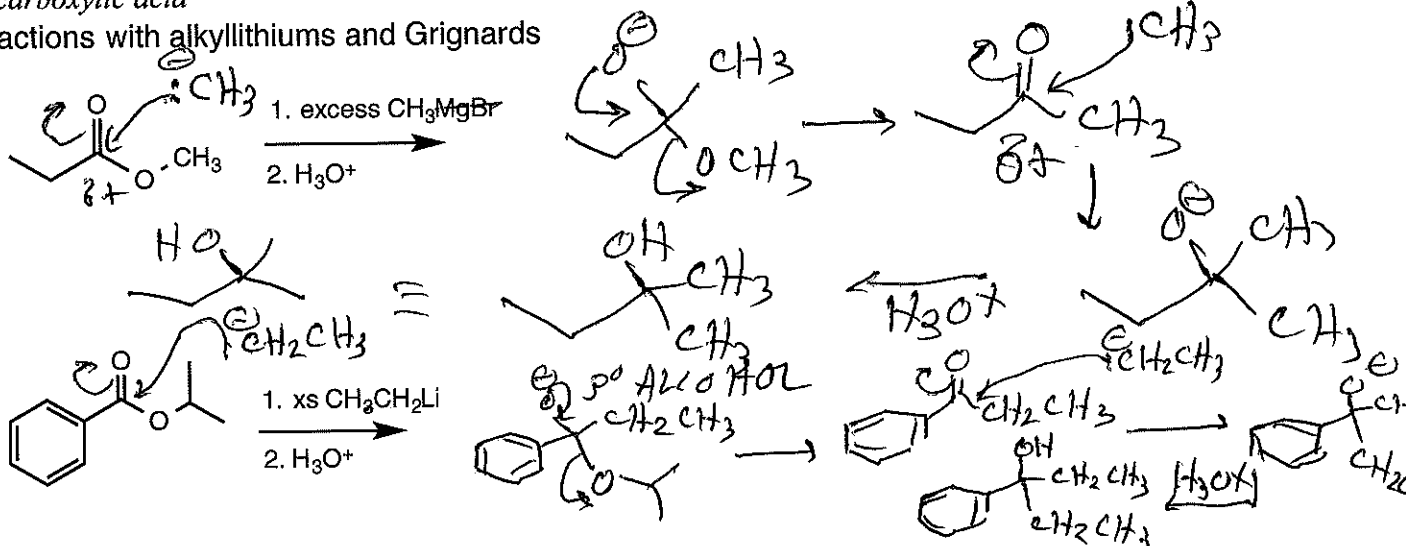
- conversion of one ester to another is readily achieved via acid catalysis in the presence of an excess of the new alcohol

reduction



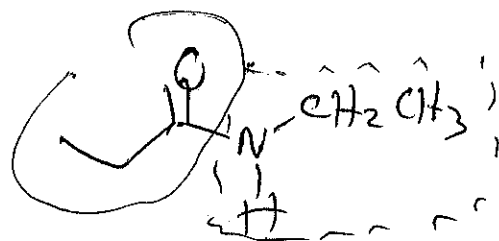
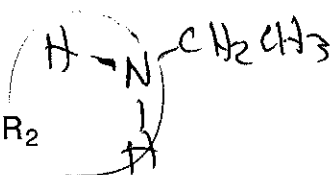
- reduction of esters takes place with the strong reducing agent $LiAlH_4$ ($NaBH_4$ is not strong enough)
- generally, two alcohol products result: one alcohol is that expected from reduction of the parent carboxylic acid, and the other alcohol the liberated alcohol used to form the ester from the carboxylic acid

reactions with alkylolithiums and Grignards



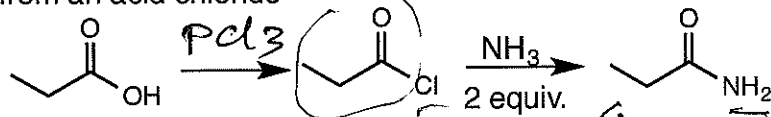
- the first addition of organometallic takes place in a typical nucleophilic substitution manner to eliminate the leaving group
- the carbonyl group of the product of the first addition, a ketone, is more reactive than the initial ester carbonyl and reacts faster with the organometallic in a second addition reaction
- thus, the net result is the addition of TWO equivalents of organometallic to the ester carbonyl and formation of a 3° alcohol

Amides



A. Preparation

from an acid chloride

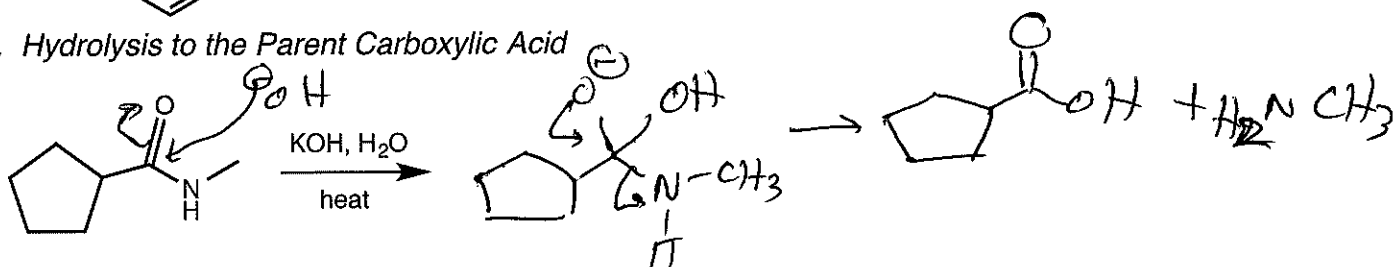


PROPANAMIDE

from an acid anhydride

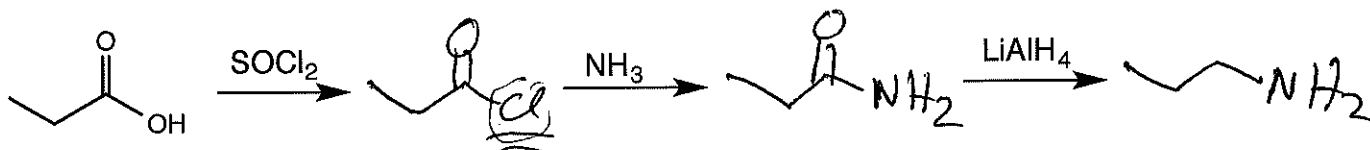
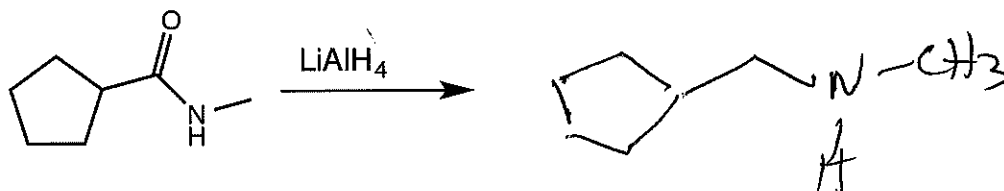


B. Hydrolysis to the Parent Carboxylic Acid



- the carbonyl of amides is the least reactive of the acid derivatives
- hydrolysis requires strongly acidic or basic conditions and heating

C. Some Other Useful Reactions



- reduction of amides leads to amines
- alkyl groups on the nitrogen remain intact during the reduction process