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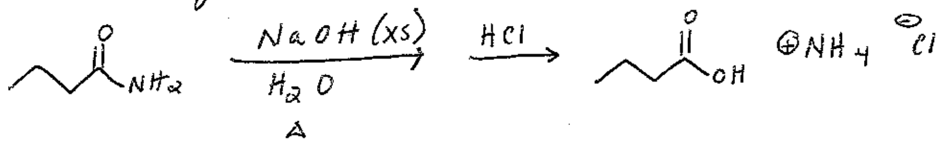
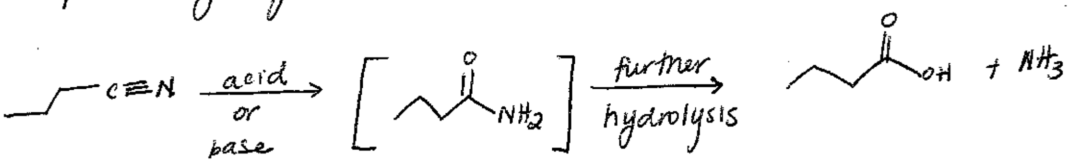
Recall: amide hydrolysis under alkaline conditions:



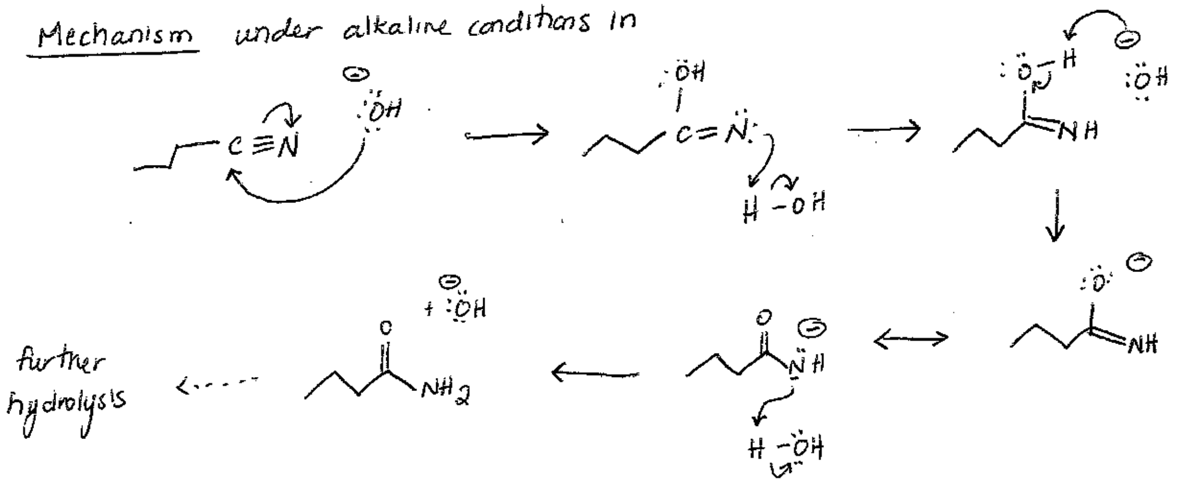
Nitrile Hydrolysis: require even harsher conditions

1) acidic or basic conditions
2) proceeds by way of amide intermediate



3) Nitrile is comparable to carbonyl as an electrophile (relatively unreactive)

Mechanism under alkaline conditions in



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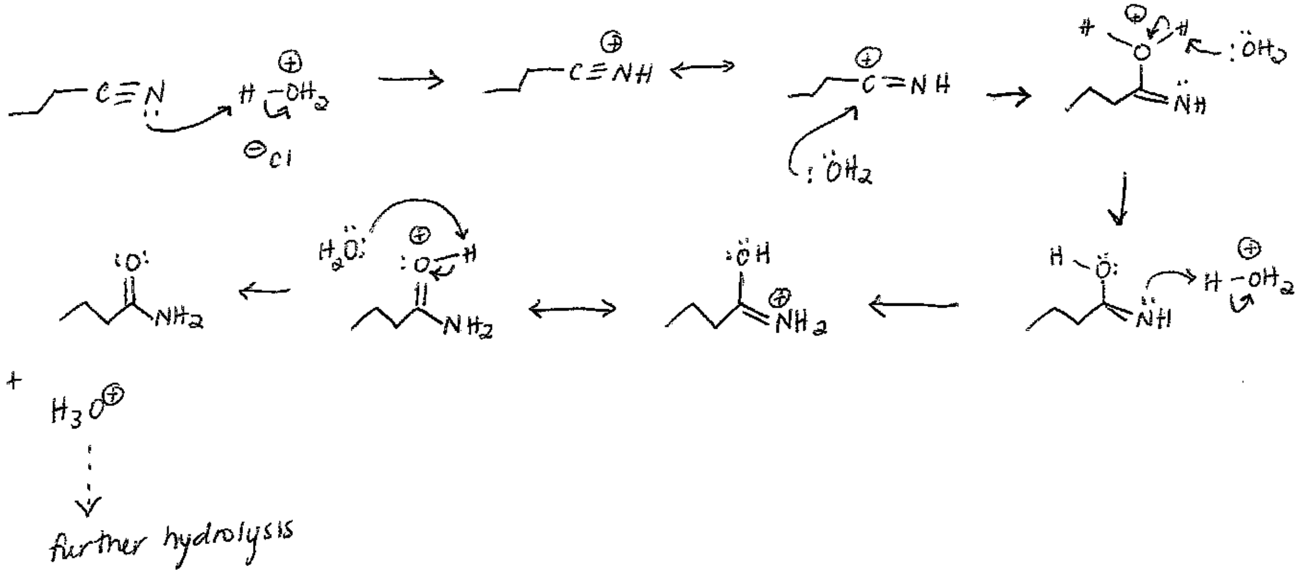
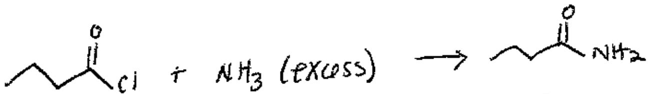
Mechanism under acidic conditions



Read 21.7 carefully!

Oxygen + Nitrogen Nucleophiles with acid chlorides or anhydrides.

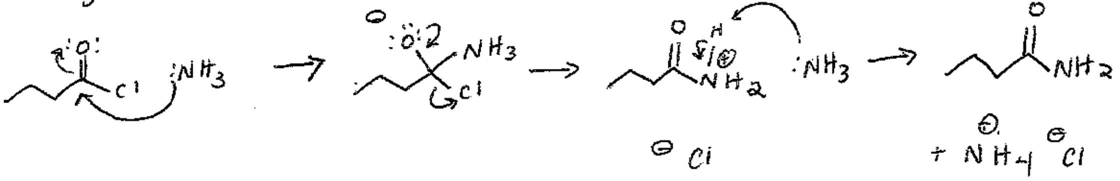
Synthetic Perspective: In contrast to amides, nitriles and esters, acid chlorides and anhydrides are highly reactive toward nucleophiles attack. Usually, one synthesizes such cmpds to use them in a subsequent rxn to generate ~~in~~ a more stable product.



($HCl + NH_3 \rightleftharpoons \overset{\oplus}{N}H_4 \; \overset{\ominus}{Cl}$)

pKa ~10

mechanism:



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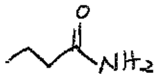
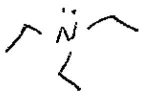
Question: which is more basic (& why)

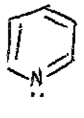
 vs. NH_3

amine protonation doesnt disturb resonance and is therefore more basic

* Use 2 equiv. of the amine! This is a waste of the amine! solution: use a cheap amine that cannot form a stable amide to function as base — neutralize HCl

common choices:

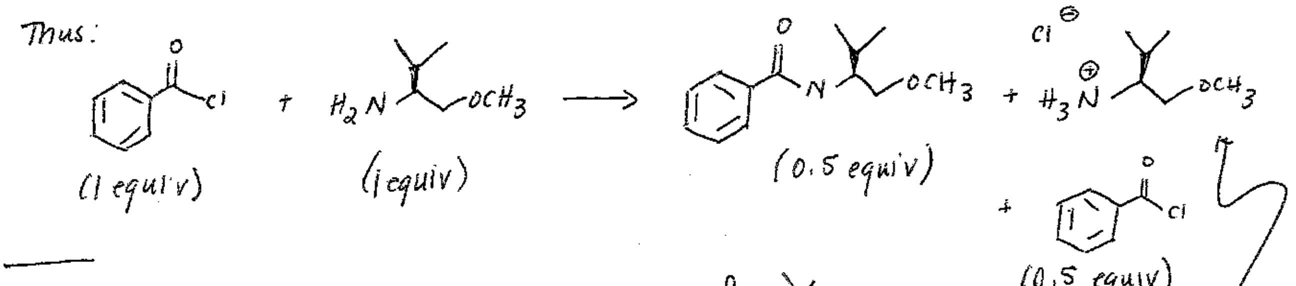

"Et_3N"

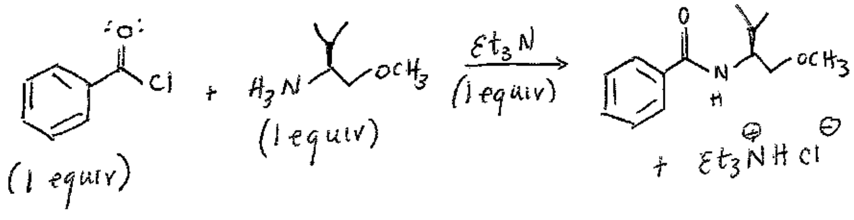

"pyridine"

"sacrificial amines"

Both 3° - no H to be lost (necessary to form amide)

Thus:





protonated amine is not reactive! No longer a nucleophile. Rxn is done!

Reactivity Perspective:

① $RCOCl$ more susceptible to nucleophilic attack than $RCONH_2$, $RCOOR'$
→ no resonance stabilization to be lost when TI (tetrahedral intermediate) forms (same for anhydride).

② TI breakdown is rapid when a good leaving group is ejected (same for anhydride)

see next page for example

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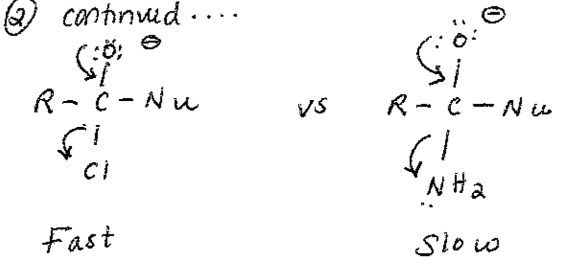
Reactivity Perspective:

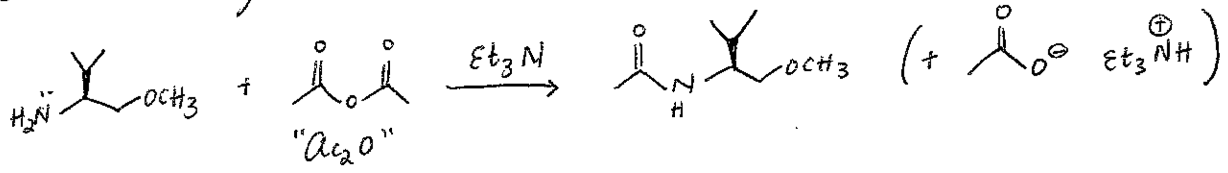
② continued ....



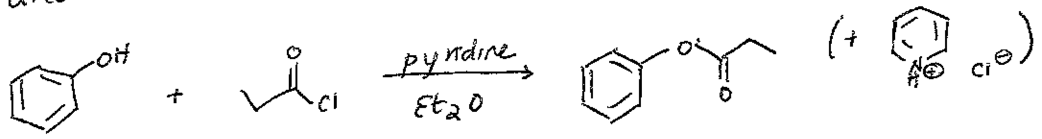
(same for anhydride)

Variations

① amine + anhydride → amide



② alcohol + acid chloride → ester



note: other method for ester synthesis are not applicable for phenols or 3 ° alcohols.

③ alcohol + TsCl → alkyl tosylate (Chem 345)