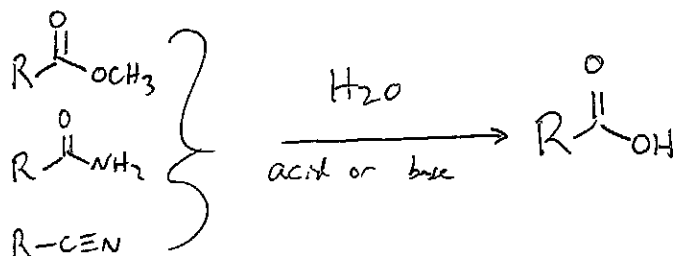


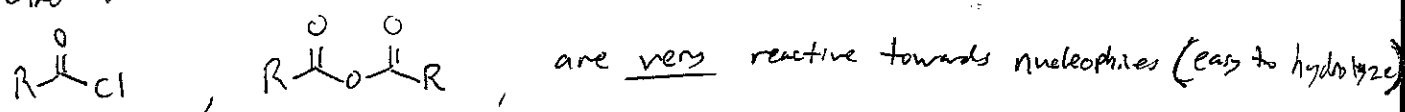
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Recall: Hydrolysis of Carboxylic Acid Derivatives



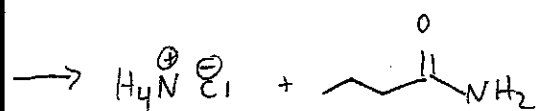
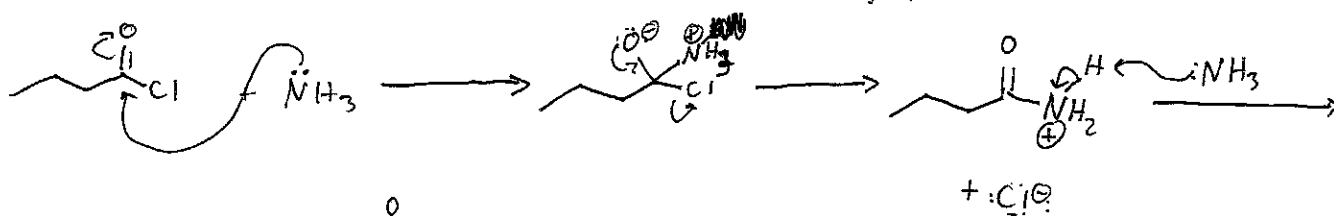
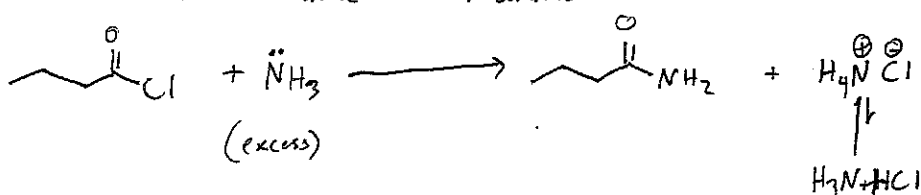
Other Derivatives:



We want to "harness" the reactivity of acid chlorides and anhydrides for the synthesis of esters and amides.

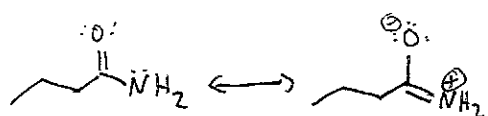
Ex:

Acid chloride + amine \rightarrow amide



Which is more basic? $\text{CH}_3\text{CH}_2\text{CH}_2\overset{\text{O}}{\parallel}{\text{C}}\text{NH}_2$ or NH_3 Why?

The amide has resonance delocalization, which is stabilizing.

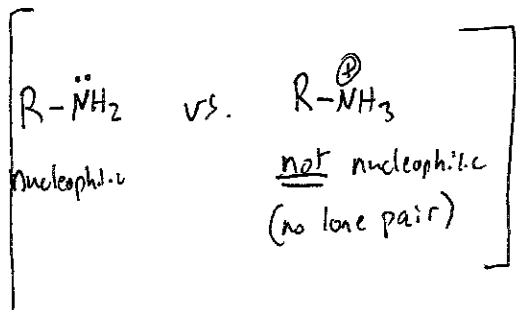
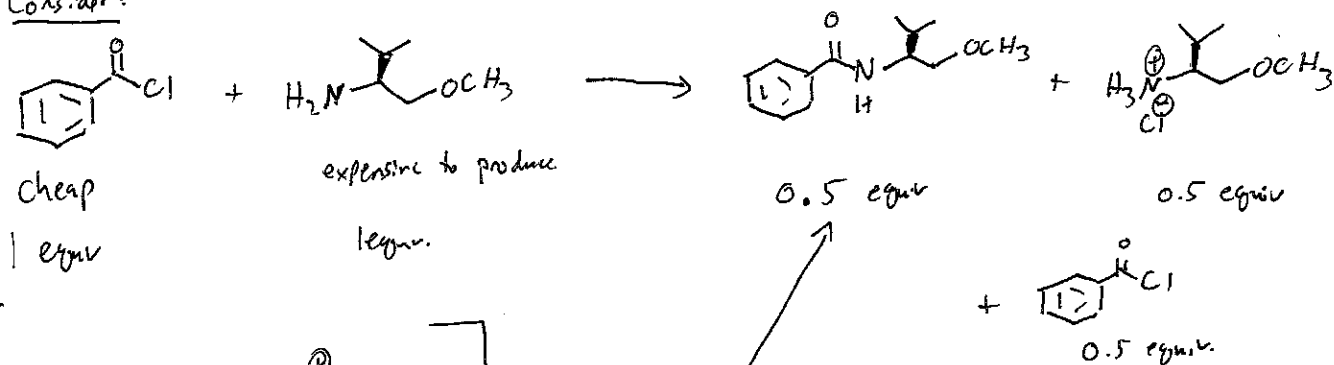


This resonance is lost when the nitrogen is protonated.

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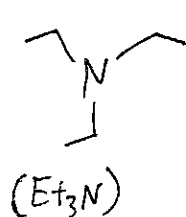
Final deprotonation means that 2 equiv. of NH_3 are required for each amide formed. This stoichiometric reality becomes problematic for "valuable" amines.

Consider:

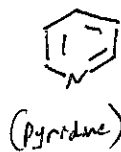


Maximum 50%
 yield! very wasteful.

Solution: we want to maximize amide formation w/ valuable amines via use of a "Sacrificial" amine (one that can't form an amide)

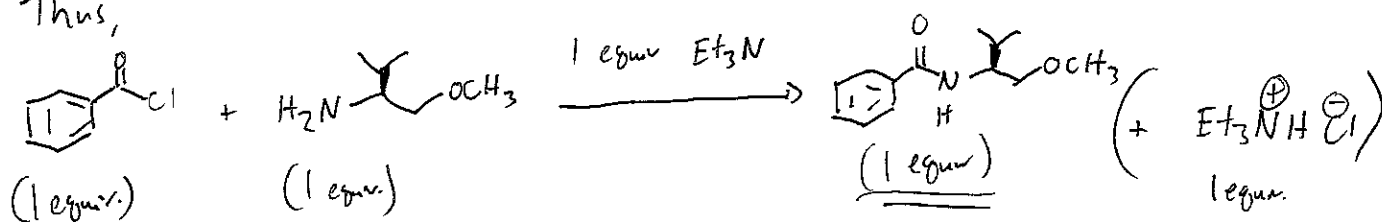


or



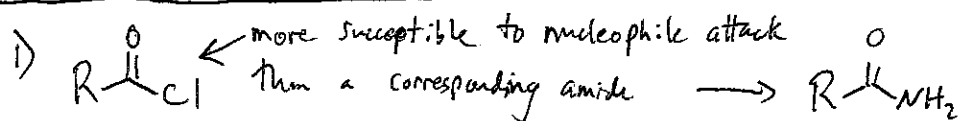
No N-H bond, so no stable amide can form. However, these are still basic, so they can serve that role in the mechanism.

Thus,



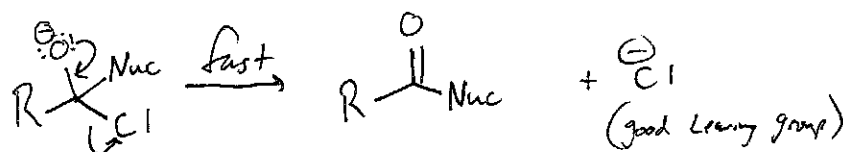
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Reactivity Patterns/Perspective:

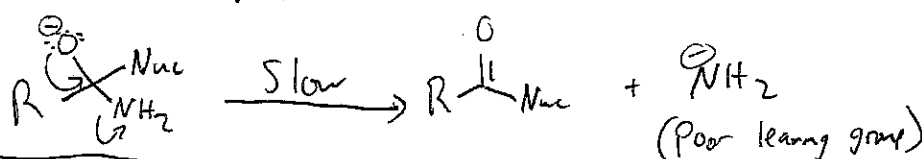


No resonance stabilization

2) TI breakdown:

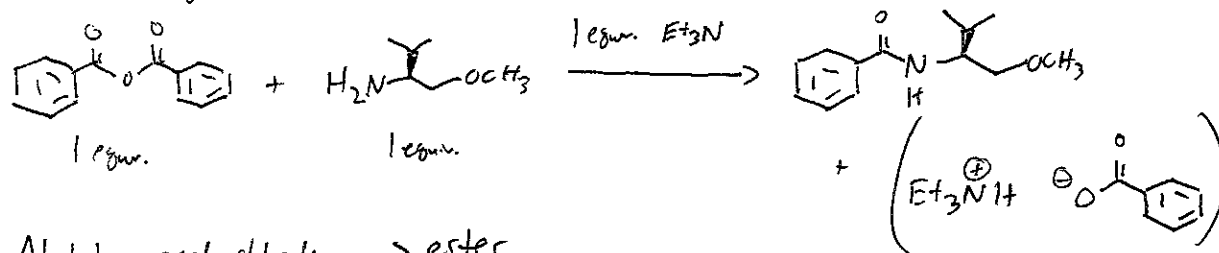


vs.

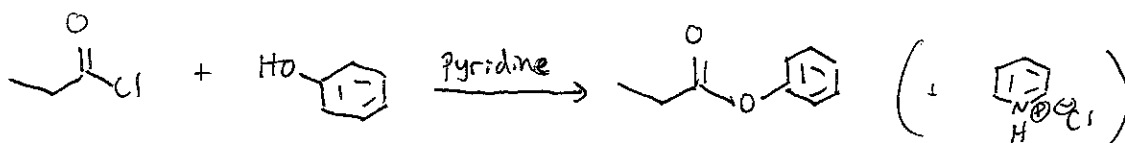


Variations:

1) Amine + anhydride \rightarrow amide



2) Alcohol + acid chloride \rightarrow ester



Note:

Acid-catalyzed esterification does not work for phenols ~~or 3°~~ (not nucleophilic enough)
 or 3° alcohols (competitive $S_N1/E1$)

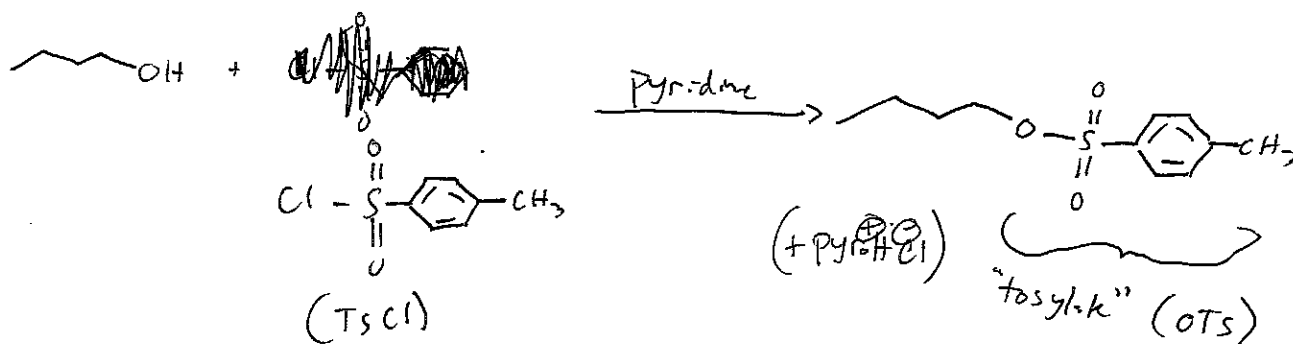
\therefore use acid chloride ^{method} instead.

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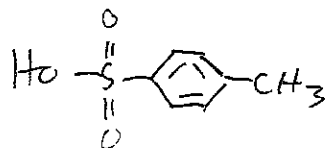
Recall/Reconsider (from Chem 343):

Formation of tosylates from alcohols to generate a good leaving group.

Ex:



Recognize TsCl as the acid chloride derivative of toluene sulfonic acid:



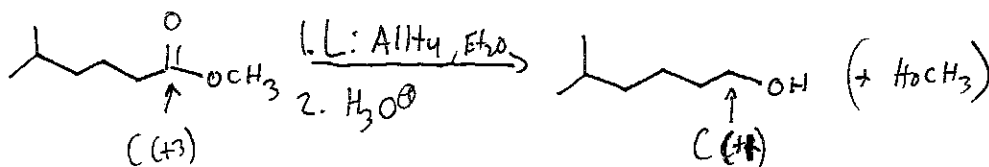
In all these reactions (hydrolysis, amide formation, ester formation), we retain the C(+3) oxidation state.

Now, we're going to discuss examples where the oxidation state does change:

Reduction of carboxylic acid derivatives:

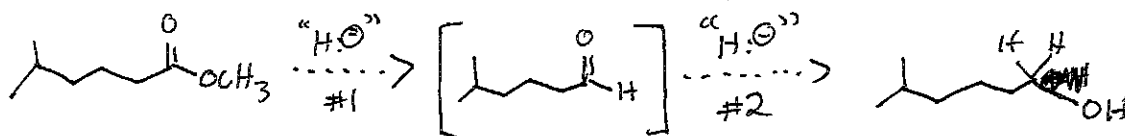
1) Ester \longrightarrow 1° alcohol, via LiAlH₄

Ex:



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Mechanism Overview: 2 equiv. " $\text{H}:\ominus$ " required for each molecule of ester.



Note: Impossible to "stop" at aldehyde stage. Why?

The ester is more stabilized by resonance than the aldehyde. So the ester is less electrophilic and attack on it is slower. So as soon as we generate any aldehyde, it is attacked preferentially.

Notes NaBH_4 (mild) does not reduce esters