Course Chem 345 Lecturer Gellman
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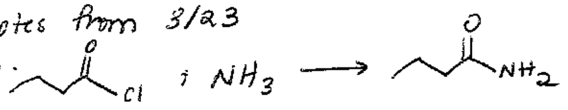
Reactions of Acid Chlorides with Oxygen and Nitrogen Nucleophiles

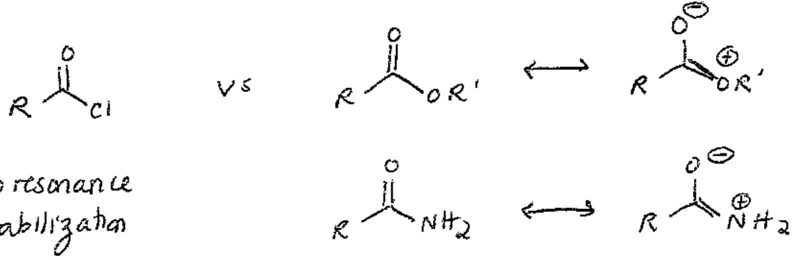
Notes from 3/23

①



consumes 2 equiv of NH_3 per molecule of amide formed.

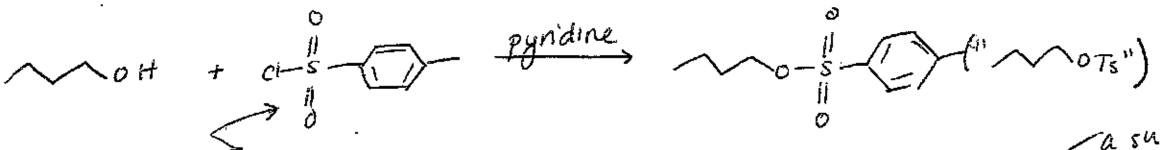
② acid chloride is more susceptible to nucleophilic attack than ester/amide



no resonance stabilization

resonance stabilization

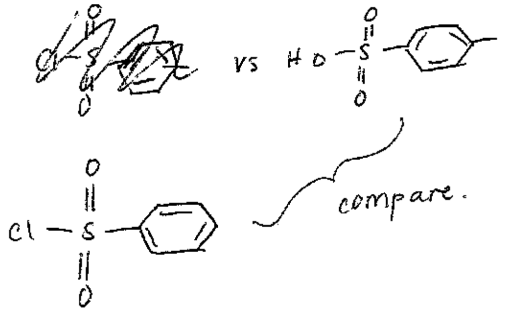
③ Alcohol + TsCl → alkyl tosylate (Chem 343)



This is another type of acid chloride.

-see text

a sulfonic acid



compare.

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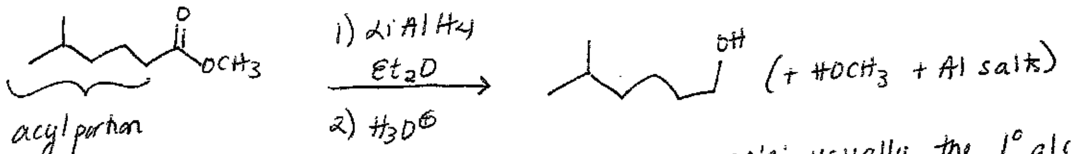
Reduction of Carboxylic acid Derivatives

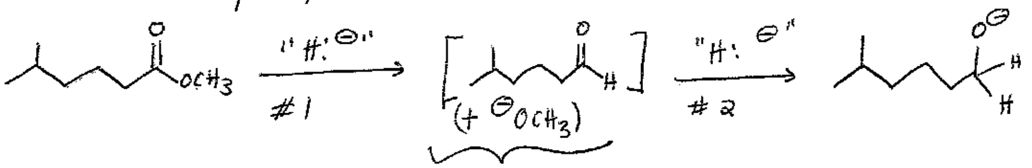
① Ester → 1° alcohol via $LiAlH_4$

ex:



note: usually the 1° alcohol derived from "acyl portion" is of most interest.

Note: 2 "$H^\ominus$" equiv per reduction event:

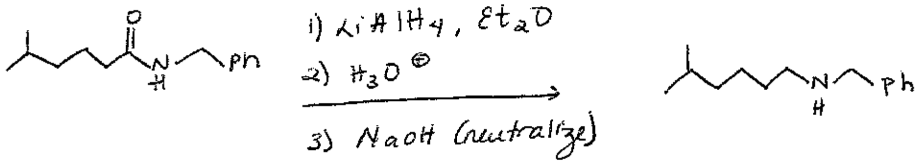


cannot isolate

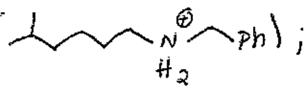
* The aldehyde <u>cannot</u> be isolated - more reactive than ester starting material

* Note: $NaBH_4$ does not effectively reduce esters

② Amide → amine via $LiAlH_4$



<u>note:</u> after Al complexes are destroyed w/ H_3O^+, amine is protonated

(); add base to generate neutral amine

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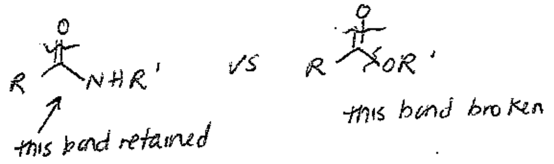
Contrast, ester vs. amide

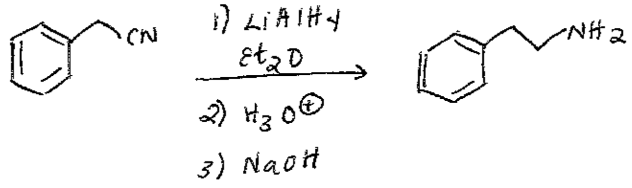


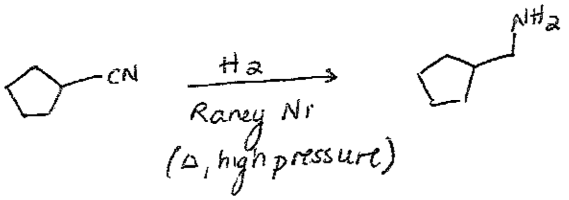
NaBH4 doesnt reduce amides

see text for further discussion

③ ~~Nitrile~~ Nitrile ⟶ 1° amine, via $LiAlH_4$ or catalytic hydrogenation.

ex:





* In all 3 cases (esters, amides, and nitriles), 2-stage reduction
overall: $C(+3) \longrightarrow C(+1)$

* Is it possible to stop at intermediate oxidation state [$C(+2)$]?
– Yes! must start w/ a highly reactive molecule: an acid chloride is more reactive than aldehyde (in contrast to esters, amides, nitriles which are less reactive than aldehydes)

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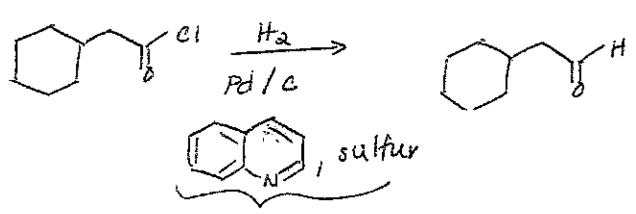
2 Methods (to stop at CG2) oxidation state)

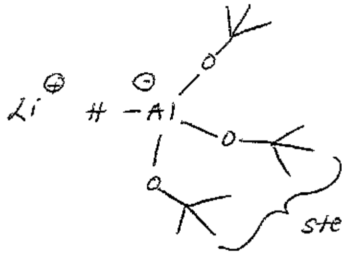
① Rosenmund reduction (H_2 + "poisoned catalyst")

ex:



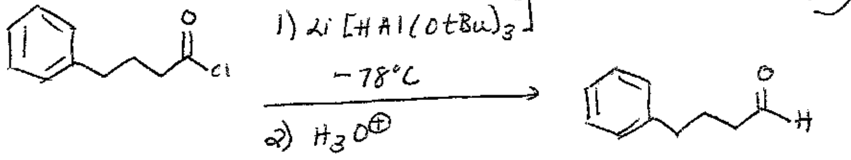
you can write poison

② Bulky Al hydride $Li[HAl(OtBu)_3]$



steric bulk reduces reactivity

Thus

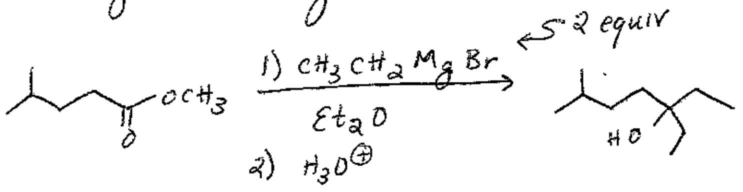


note: low temp: dry ice/acetone

Rxns of carboxylic acid derivatives w/ organometallic reagents

1) ester + Grignard or organolithium – double addition

ex:



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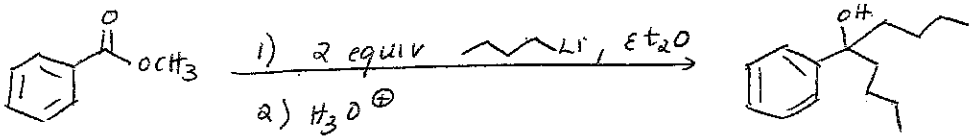
1) ester + Grignard or ~~organomet~~ organolithium → double ~~[illegible]~~ addition



Note: These rxns proceed via a ketone intermediate; however the ketone is more reactive than the ester
- so it is not possible to stop cleanly at ketone step.
- C(+3) → C(+1)