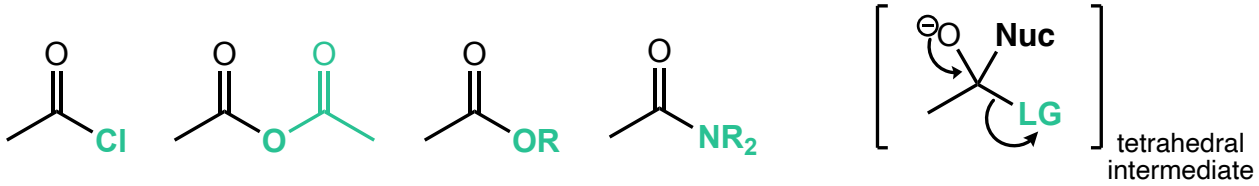
Substitution Reactions of Carboxylic Acids Worksheet Key

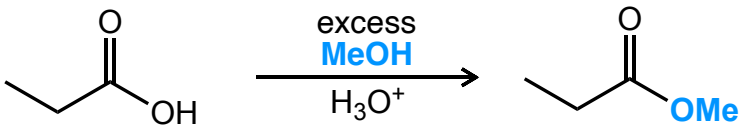
1. In your own words, **explain** why **aldehydes and ketones undergo addition chemistry** whereas **carboxylic acid derivatives undergo substitution chemistry**. It may be easiest to do this using generic structures of these functional groups.

Ketones and aldehydes do not contain leaving groups. Therefore, after the initial nucleophilic attack, the tetrahedral intermediate cannot reform the CO π bond. This results in an addition across the C=O π bond.

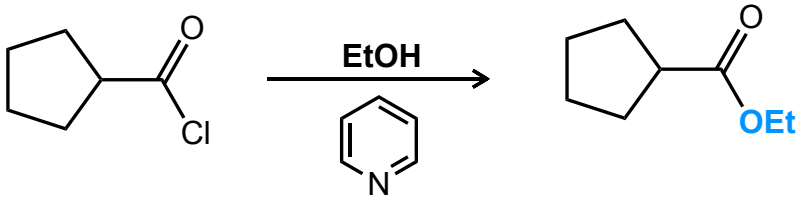
Carboxylic acid derivatives have a heteroatom attached and the **presence of a leaving group**. After the initial nucleophilic attack, the tetrahedral intermediate can collapse, expel the leaving group, and reform CO π bond. This results in carbonyl substitution.



2. **The product shown** for each reaction below is **incorrect**. **Explain why** and provide the **correct product** of each reaction.

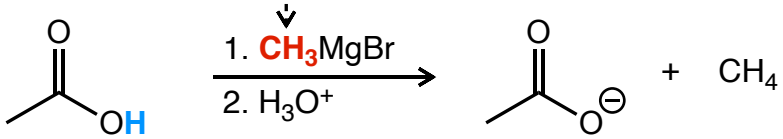


OH acts as a leaving group under acidic conditions, therefore reaction undergoes substitution to form an ester.



The proton in EtOH is removed, and the nucleophile overall is OEt, not OH.

(**strong base**, conjugate acid is CH_4, pK_a > 50)



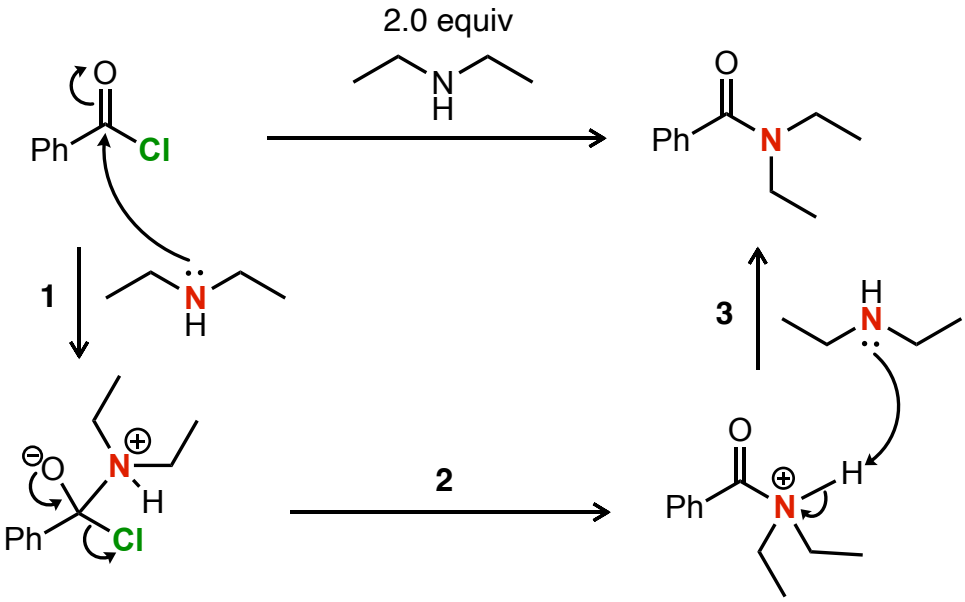
Carboxylic acids are too acidic and undergo rapid acid-base chemistry with Grignard reagents!

acid (pK_a ~ 5)

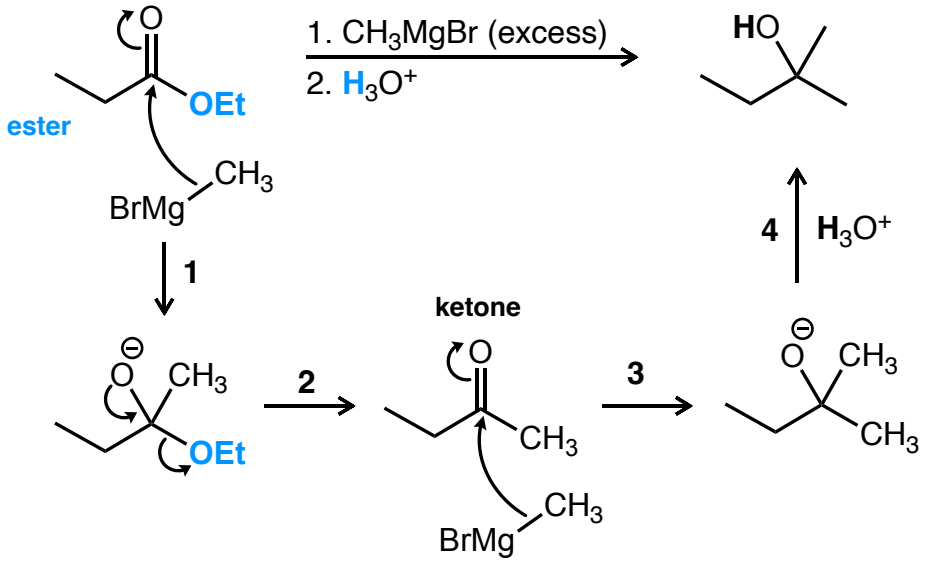
3. Reactions with acid chlorides and anhydrides generally require the use of an external base, like pyridine. Sometimes, the base used is just another equivalent of the nucleophile. With that in mind, **provide the curved-arrow mechanism** for the reaction below.

Generic mechanism:
1. Attack
2. Eliminate
3. Deprotonate

We need two equivalents of amine to have one serve as the nucleophile in step **1** and the other to serve as the base in step **3**.



4. **Draw a curved-arrow mechanism** for the reaction below, showing the reaction between an ester with excess Grignard reagent which forms 3º alcohols. Use your mechanism to explain why this is true, despite that we learned that esters undergo carbonyl substitution reactions rather than carbonyl addition reactions.



Steps **1** and **2**: Carbonyl substitution
Step **3** and **4**: Carbonyl addition

In **steps 1** and **2**, we see the addition and elimination mechanism associated with **carbonyl substiution**. However, the product of this carbonyl substitution reaction is a **ketone**, **which is more electrophilic than an ester.** Therefore, we see a **second reaction** - a **carbonyl addition** reaction between the ketone and the methyl Grignard reagent, then protonation to generate the 3º alcohol.

5. **Provide** the **missing starting material**, **reagent(s)**, or **major product** of each reaction below.