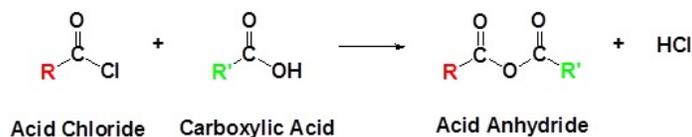


22.5: ACID ANHYDRIDE CHEMISTRY

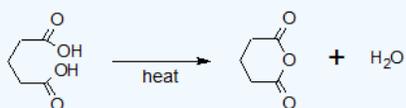
SYNTHESIS OF ACID ANHYDRIDES

Acid chlorides react with carboxylic acids to form anhydrides as shown in the reaction below.



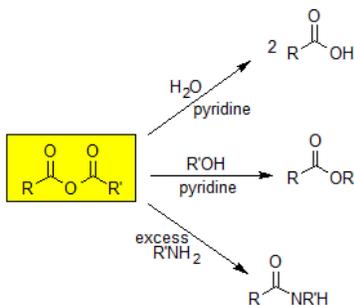
Some cyclic anhydrides can be synthesized from the corresponding dicarboxylic acid with gentle heating. The example below shows the reaction of glutaric acid to form a cyclic anhydride.

Example: Acid Anhydride Synthesis



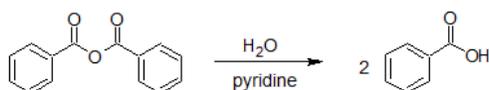
ACID ANHYDRIDE REACTIVITY

Acid anhydrides undergo hydrolysis and nucleophilic acyl substitution reactions.



ACID ANHYDRIDE HYDROLYSIS

Acid anhydrides readily hydrolyze to carboxylic acids. In many cases, this reaction is an unwanted side reaction and steps will be taken in the lab to keep the system "dry" (aka water free). The presence of pyridine facilitates proton transfers during the reaction. The hydrolysis reaction for benzoic anhydride is shown below.



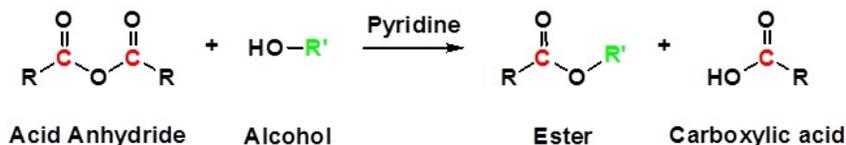
The mechanism is analogous to the mechanism for ester synthesis from acid anhydrides and is shown below in detail.

NUCLEOPHILIC ACYL SUBSTITUTION REACTIONS FROM ACID ANHYDRIDES

Carboxylic acid derivatives can be synthesized from acid anhydrides via the nucleophilic acyl substitution mechanism previously discussed.

ESTER SYNTHESIS

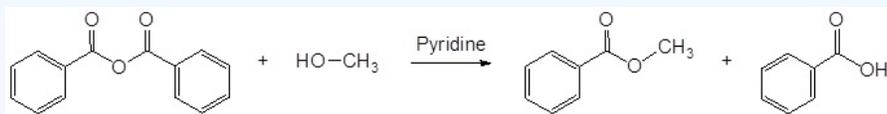
Acid anhydrides react with alcohols to produce esters as shown in the reaction below. The reactions of anhydrides frequently use pyridine as a solvent.



A carboxylic acid is also produced, but is not considered a synthetic product. The ester is considered the "product of interest".

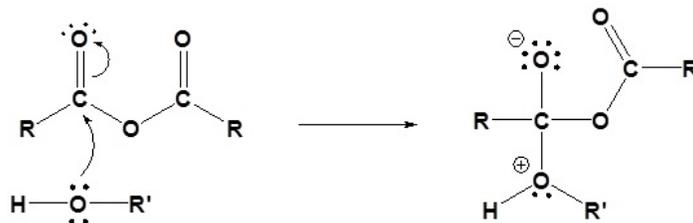
The synthesis of methyl benzoate from benzoic anhydride and methanol is shown in the example.

Example: Ester Synthesis

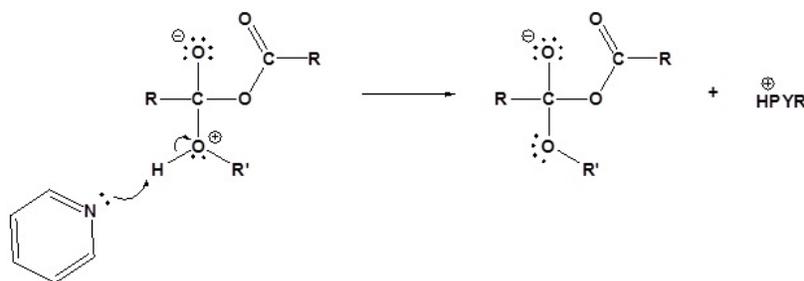


The mechanism follows the nucleophilic acyl substitution mechanism as previously discussed and reviewed below.

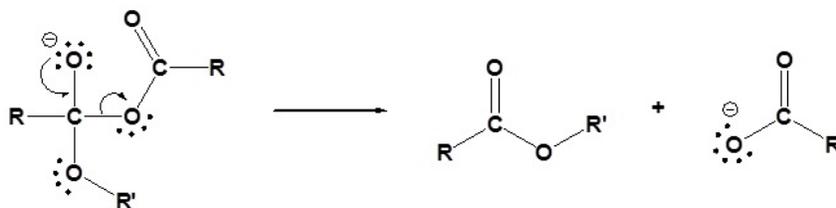
1) Nucleophilic Alcohol reacts with Electrophilic Carbonyl



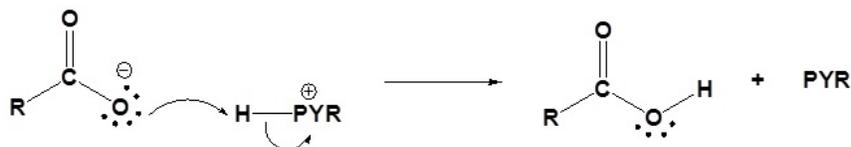
2) Deprotonation by pyridine



3) Leaving group removal

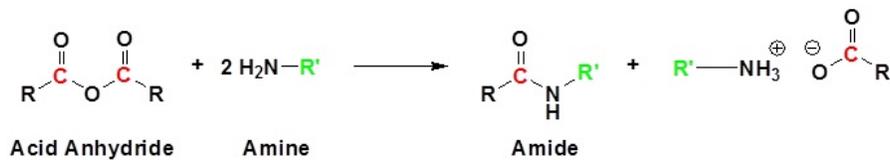


4) Protonation of the carboxylate

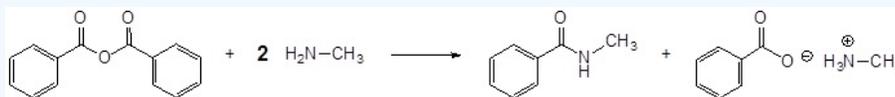


AMIDE SYNTHESIS

Acid Anhydrides react with amines to form amides. As seen with acid halide reactions, a second equivalent of the amine must be present for the reaction to proceed.

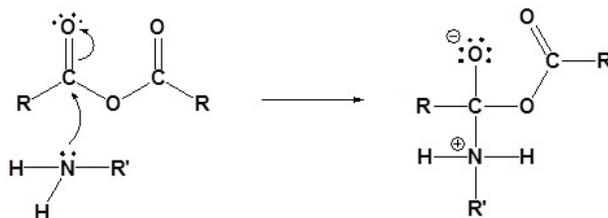


Example: Amide Synthesis

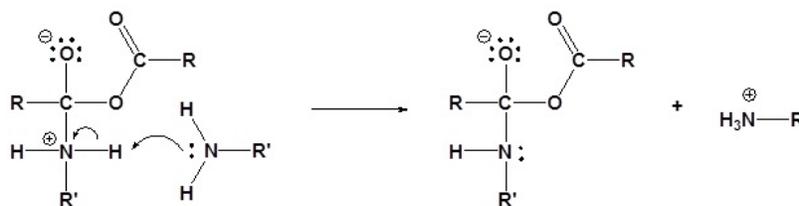


The mechanism for amide synthesis is analogous to the mechanism for ester formation. The only minor difference is that a second equivalent of the amine or ammonia is used instead of the pyridine.

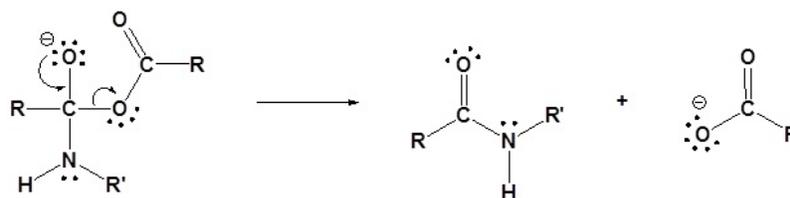
1) Nucleophilic Amine reacts with Electrophilic Carbonyl



2) Deprotonation by the amine

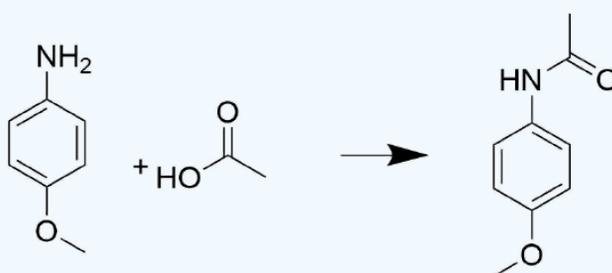


3) Leaving group removal

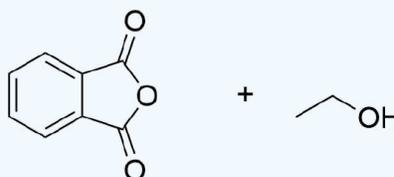


Exercise

6. Draw out the mechanism for the following reaction.

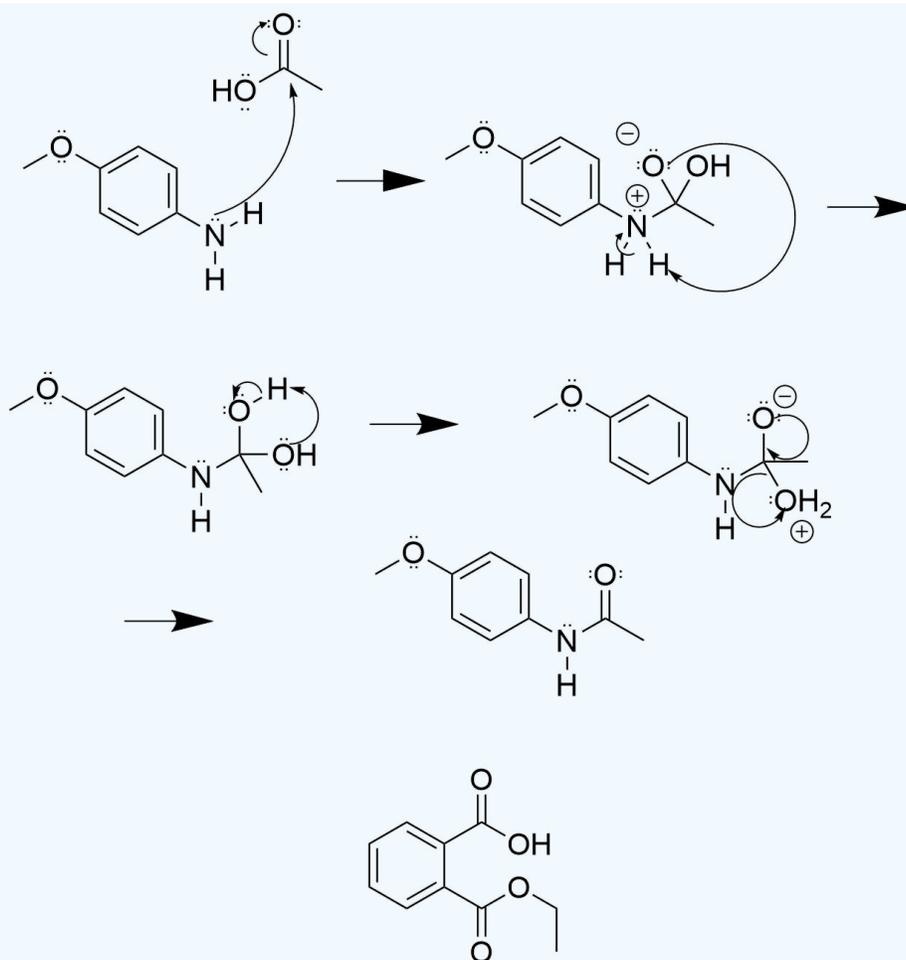


7. Draw the product of the reaction between these two molecules.



Answer

6.



CONTRIBUTORS AND ATTRIBUTIONS

- [Dr. Dietmar Kennepohl](#) FCIC (Professor of Chemistry, [Athabasca University](#))
- [Prof. Steven Farmer](#) ([Sonoma State University](#))

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