Lesson VI.9. Nucleophilic Acyl Substitution of Acid Chlorides and Anhydrides

Lesson VI.9.1 Introduction to Nucleophilic Acyl Substitution

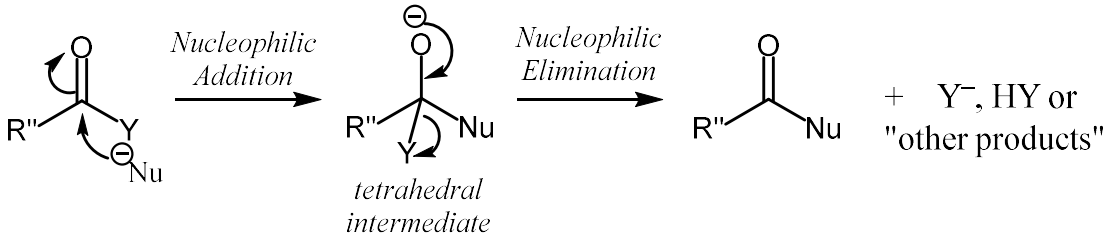
Unlike aldehydes and ketones, carboxylic acids and their derivatives (anhydrides, acid chlorides, amides and esters) undergo **nucleophilic acyl substitution**, sometimes abbreviated **S_NAc**. Nucleophilic acyl substitution is a two-step process:

1) Nucleophilic addition to the carbonyl carbon

2) Nucleophilic elimination of the best leaving group from what was the carbonyl carbon.

For the purposes of categorizing reactions as a way to help study them in this particular book, we will refer to the reactions that follow this pattern as being **Type B**.

Carbonyl Reaction Type B *NOT for aldehydes or ketones*



The net result is replacing the bond to Y with a new bond to a nucleophile component. The identity of Y, HY and "other products" in the figure above depend on the specific reaction and the starting functional group. The reason that ketones/aldehydes do not do nucleophilic acyl substitution it because in a ketone/aldehyde, the "Y" group is always CxHy or H. These are terrible leaving groups, and cannot even be protonated to become good leaving groups. Without any good leaving group, it is impossible for aldehydes or ketones to lead to a favorable nucleophilic elimination step. All of the other carbonyl functional groups we have introduced can undergo nucleophilic acyl substitution reactions, as we will see in the next group of lessons.

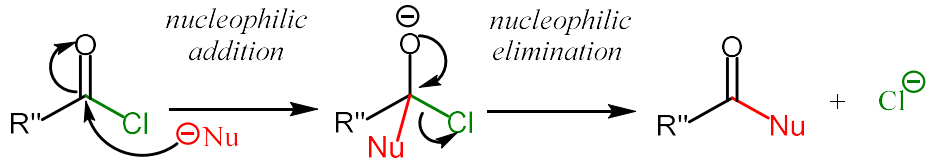
Lesson VI.9.2 Nucleophilic Acyl Substitution of Acid Chlorides.

As we saw in Lesson VI.4, acid chlorides are the most reactive carboxylic acid derivatives. The Cl of the acid chloride is an outstanding leaving group, so acid chlorides very readily undergo S_NAc reactions. Acid chlorides can be converted to anhydrides, esters, amides, and carboxylic acids through the general nucleophilic acyl substitution mechanism. If a neutral nucleophile is used it will need to be deprotonated to give a neutral product in the end, whereas no deprotonation is needed if you use a nucleophile that is already anionic:

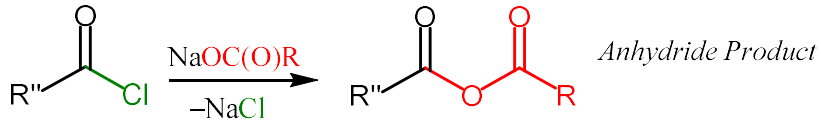
Anionic nucleophile (e.g. anions produced from NaOC(O)R, NaOH, NaOR, etc.)

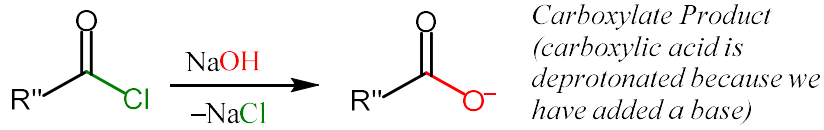
This is a nucleophilic acyl substitution (Type B), where step 1 is nucleophilic addition and step 2 is nucleophilic elimination:

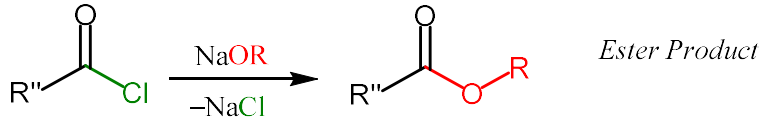
General Mechanism:



Specific Examples:

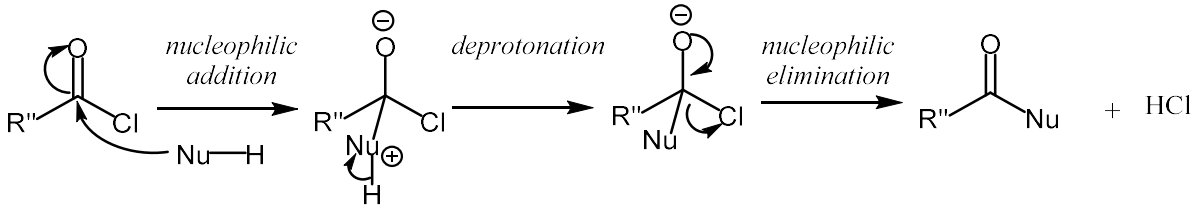




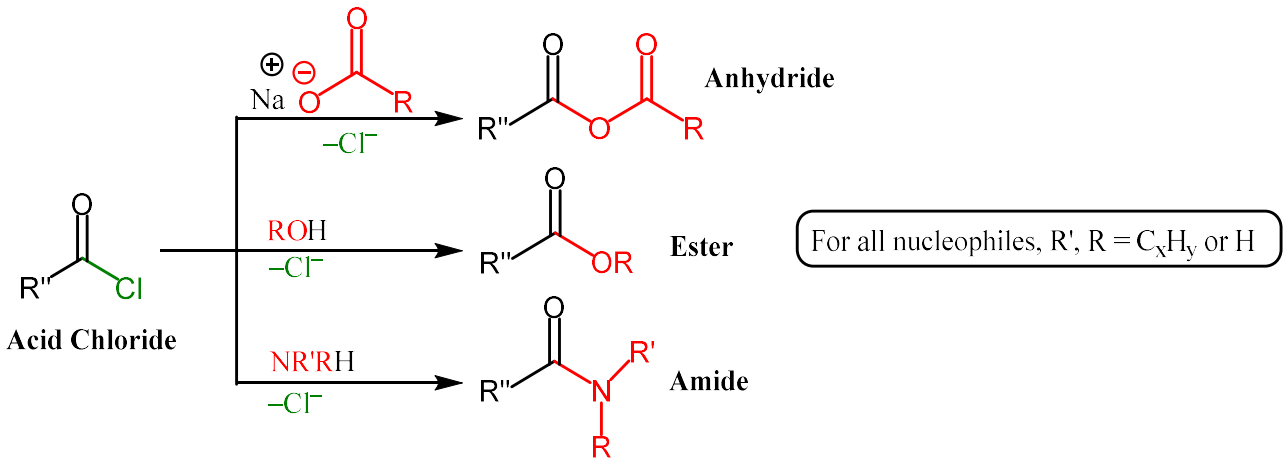


Neutral nucleophile (e.g. ROH, HNR_2, RNH_2, NH_3 or H_2O)

This mechanism generally requires the presence of base catalyst. If the NuH is itself a base (NuH = HNR_2, RNH_2 or NH_3), however, then we just use two equivalents of NuH (one to be the nucleophile, one to be the base). This mechanism consists of nucleophilic addition first as usual, but a deprotonation step is required before nucleophilic elimination can occur:

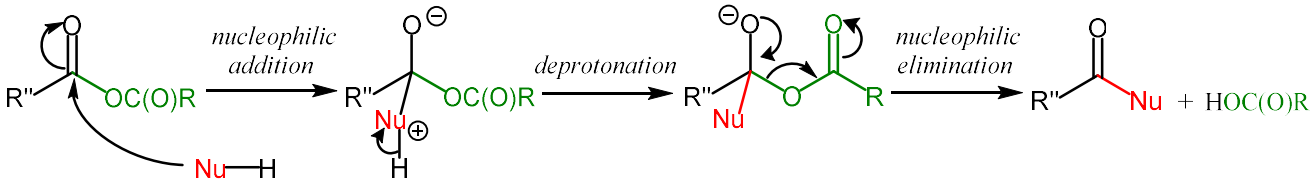


Some specific examples of S_NAC of acid chlorides with neutral nucleophiles are provided here:

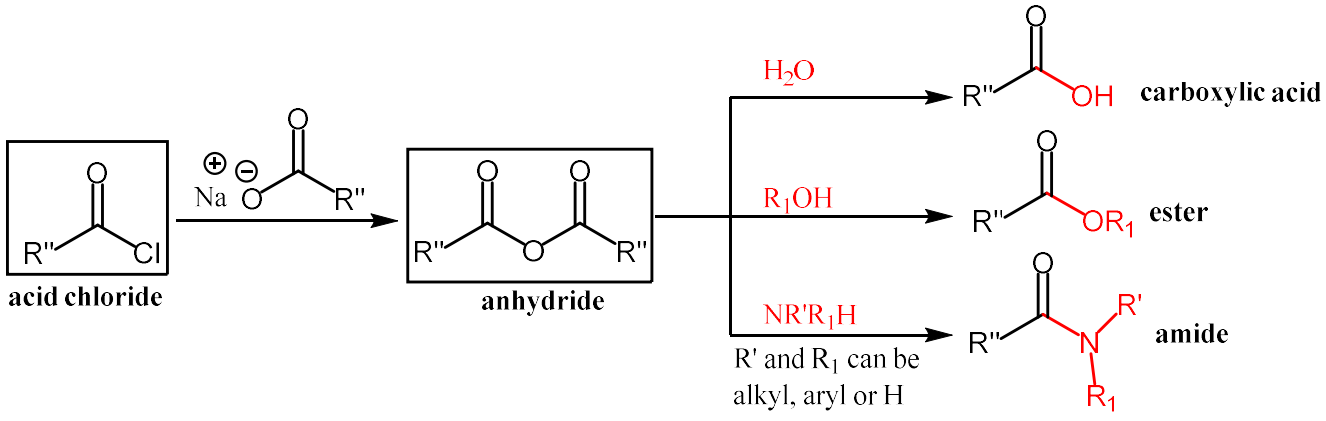


Lesson VI.9.3 Nucleophilic Acyl Substitution of Anhydrides

The second-most reactive carboxylic acid derivatives are acid anhydrides, and they can be converted to esters, amides and carboxylic acids. Anhydrides, however, cannot be converted to acid chlorides, since Cl^- is a better leaving group than $RC(O)O^-$. The general mechanism for the nucleophilic acyl substitution of anhydrides follows that we saw for acid chlorides with a neutral nucleophile:

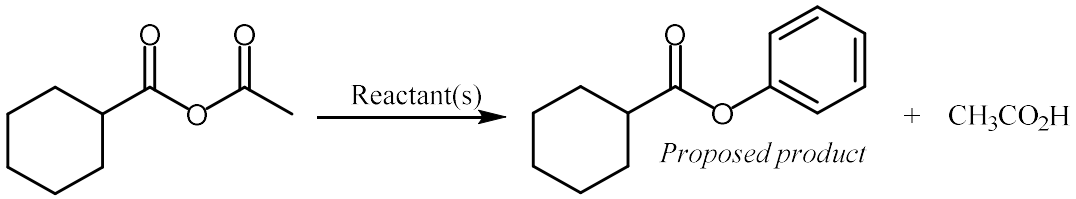


In these cases, Nu–H can be H_2O, ROH, a 1° amine, or a 2° amine. The following chart shows the nucleophilic acyl substitution reactions of anhydrides that give rise to carboxylic acids, esters, and amides.



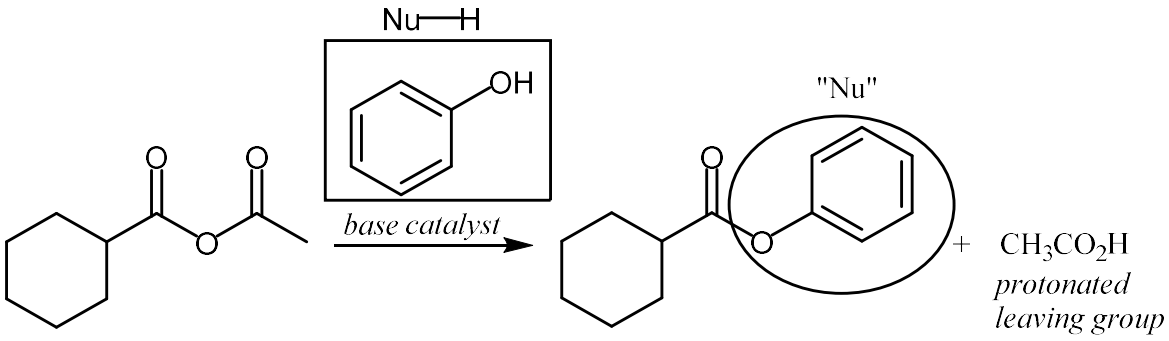
Example VI.9.1

Provide the missing reactant for the transformation shown. Would the proposed product be the major or minor product upon reaction of this acid anhydride with the missing reactant?

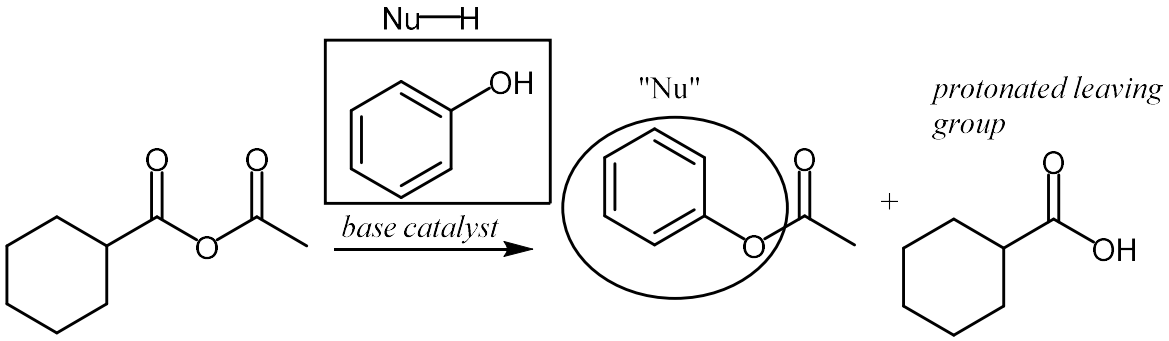


Solution VI.9.1

The above reaction is a nucleophilic acyl substitution where an anhydride is converted to an ester. If we circle the nucleophile in the reaction (as shown below) we can see it is a phenoxide (Ph—O^-), so the missing reactant (NuH) should be PhOH with catalytic base.

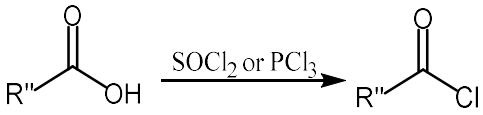


In this particular example, the two sides of the anhydride are different. One of the anhydride carbonyl carbons has a methyl substituent, whereas the other has a cyclohexyl substituent. Generally, we would predict that the nucleophile would attack the less hindered side. We would predict that the major product would result from nucleophilic attack on the acetate side and that the proposed product in the question would actually be the minor product:

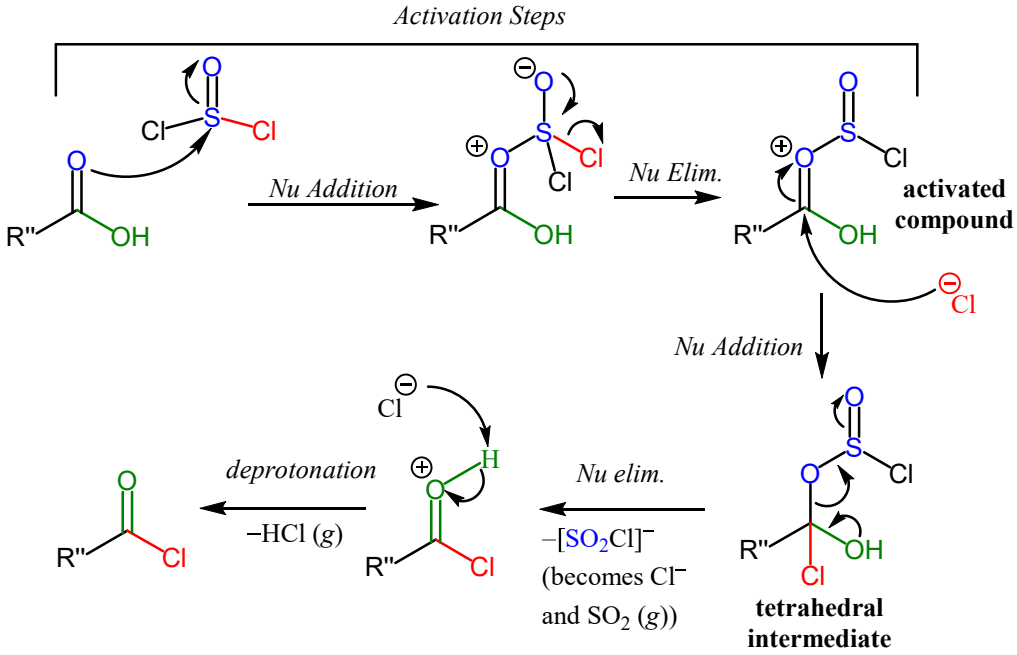


Lesson VI.10. S_NAc of Carboxylic Acids to form Acid Chlorides

Carboxylic acids react with phosphorus trichloride (PCl_3) or thionyl chloride ($SOCl_2$) to give acid chlorides. In these cases, the –OH is substituted for a –Cl:

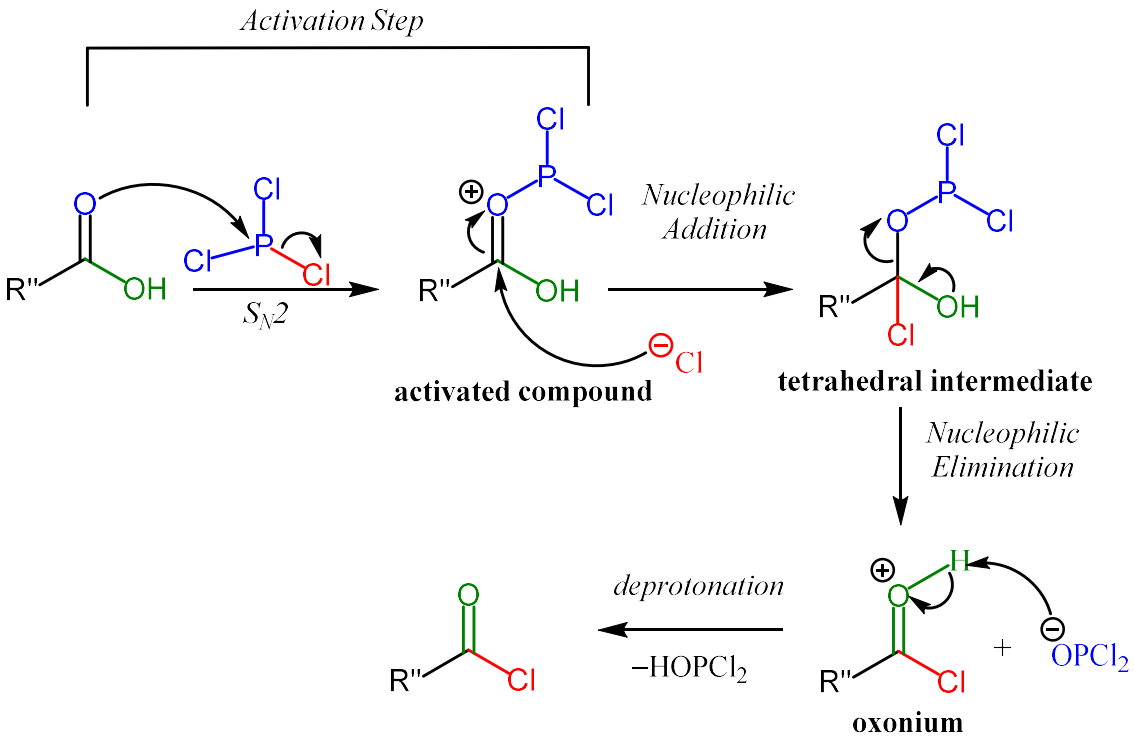


This nucleophilic acyl substitution is initiated by the reaction of the carbonyl oxygen with the sulfur of $SOCl_2$ or the phosphorus of the PCl_3, generating the chloride ion that will act as a nucleophile:



After initial activation, the usual steps of the S_NAc (Type B) reaction occur. The production of sulfur dioxide and HCl as side products makes the purification of this reaction rather easy, because both of these side products are gases that bubble out of the reaction vessel and can be collected. Sometimes pyridine is added to neutralize the HCl as it forms instead of letting it escape as a gas.

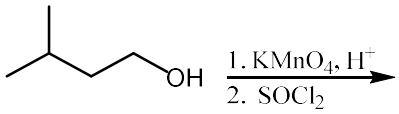
The reactions of carboxylic acids with PCl_3 proceed through a very similar mechanism to that observed for reaction with $SOCl_2$. The carbonyl O again acts as a nucleophile to activate it for nucleophilic acyl substitution:



In this case, the carbonyl O undergoes an S_N2 reaction with PCl_3 in the activation step, and then the nucleophilic acyl substitution takes place. Step 4 is needed to deprotonate the oxonium to yield a neutral product. A key difference from a practical standpoint is that the $HOPCl_2$ produced in step 4 is not a gas like the HCl/SO_2 byproducts of reaction with $SOCl_2$, which makes the purification steps harder.

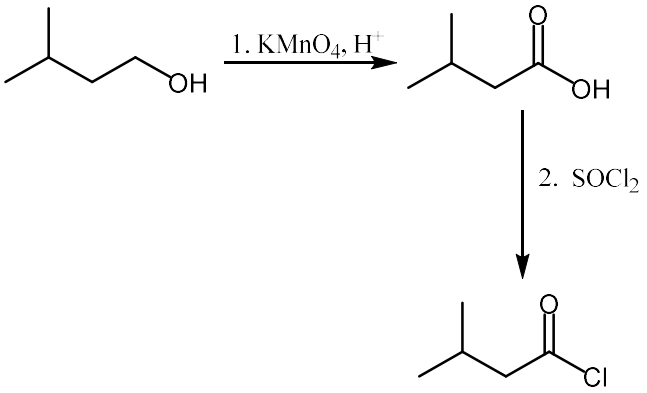
Example VI.10.1

Give the final product of the following two-step sequence:



Solution VI.10.1

The first reaction is an oxidation reaction with a strong oxidant ($KMnO_4$), which will produce a carboxylic acid from the given primary alcohol. The second reaction is a simple nucleophilic acyl substitution where the –OH will be substituted with –Cl

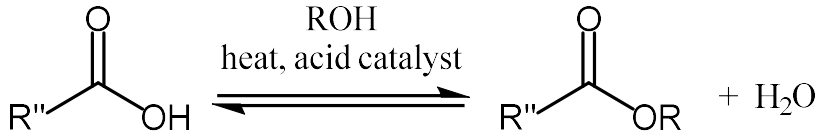

1. KMnO4, H+
OH
O
OH
2. SOCl2
O
Cl

Lesson VI.11. S_NAc Reaction of Oxygen Nucleophiles with Carboxylic Acids and Esters

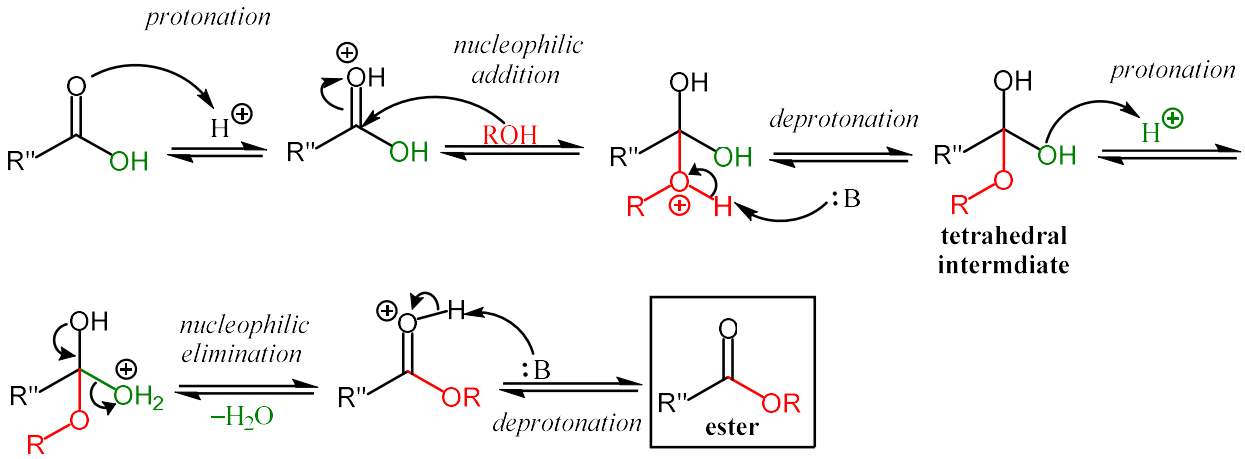
Lesson VI.11.1 Nucleophilic Acyl Substitution of Carboxylic Acids to form Esters

The new reactions in this Lesson are S_NAc (or Type B as described in Lesson VI.3) reactions in which we replace the leaving group with a group supplied by the nucleophile.

Carboxylic acids react with alcohols in the presence of an acid catalyst (such as H_2SO_4) and heat to produce esters (and water as a byproduct), this reaction is known as **Fischer Esterification**. The general reaction is the following:



The following figure shows a reasonable arrow-pushing mechanism for Fischer esterification:

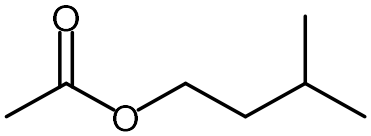


Although this mechanism looks complicated, you will see that the key steps are nucleophilic addition of the nucleophile and nucleophilic elimination, the usual nucleophilic acyl substitution steps. All of the other extra steps are just moving protons on and off as necessary.

Note that **each step of the reaction is reversible**. The ester product can react with the water and hydrolyze to give back the carboxylic acid, a useful reaction called **ester hydrolysis**. To ensure the production of the ester in high yields we will apply our knowledge of equilibrium processes in terms of LeChatelier's principle. Specifically, we can use a large excess of the alcohol reagent so that its consumption pushes the equilibrium towards ester formation. Alternatively, we can distill the water away as it forms, again to push the reaction towards ester formation.

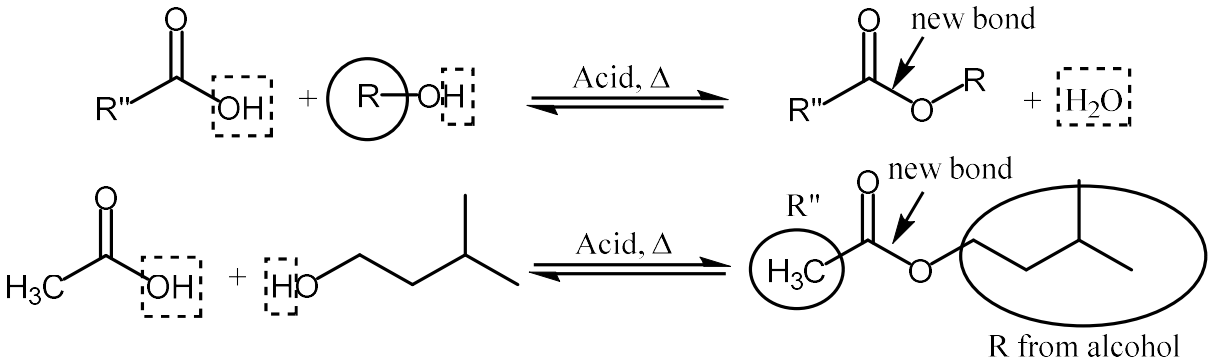
Example VI.11.1

Isoamyl acetate (structure below) is an ester found in banana oil and is responsible for the familiar banana aroma. Give the carboxylic acid and alcohol used in the formation of this ester.



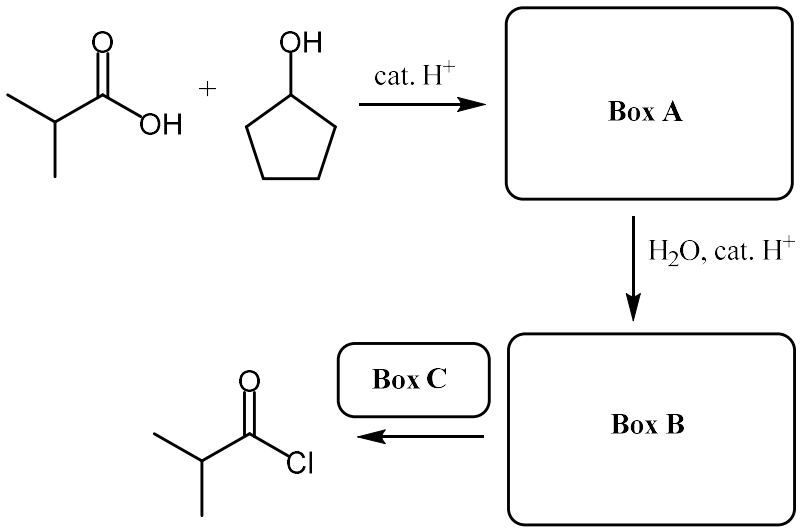
Solution VI.11.1

In order to find the reactants of this ester we put the general reaction and try to find both R" and R of the carboxylic acid and alcohol respectively. As the figure shows the carboxylic acid used is the acetic acid and isoamyl alcohol (3-methyl-1-butanol) is the alcohol used.



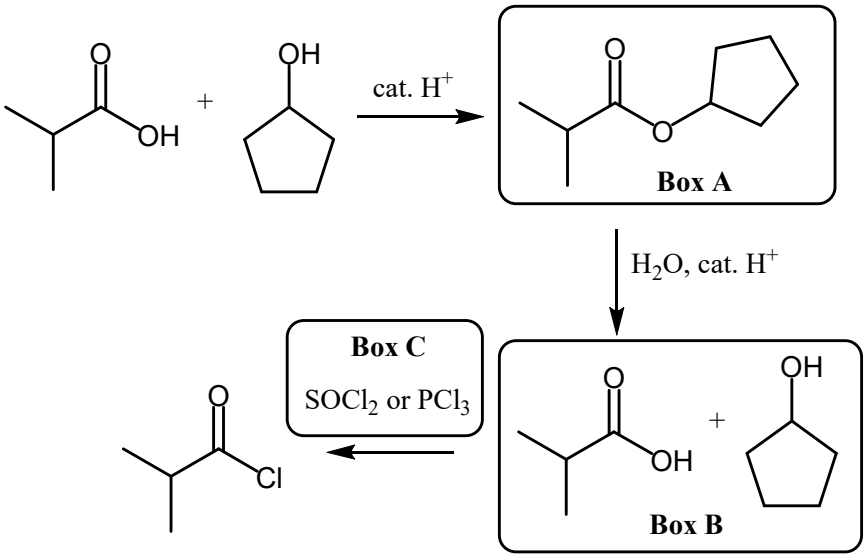
Example VI.11.2

Provide the missing reactants and products:



Solution VI.11.2

The product in Box A will be an ester, formed via Fischer Esterification. Reaction of the Ester with water/acid catalyst takes us back to the carboxylic acid in Box B. The missing reagents in Box C must facilitate conversion of the carboxylic acid into an acid chloride. Either $SOCl_2$ or PCl_3 will accomplish this. The completed scheme would be:



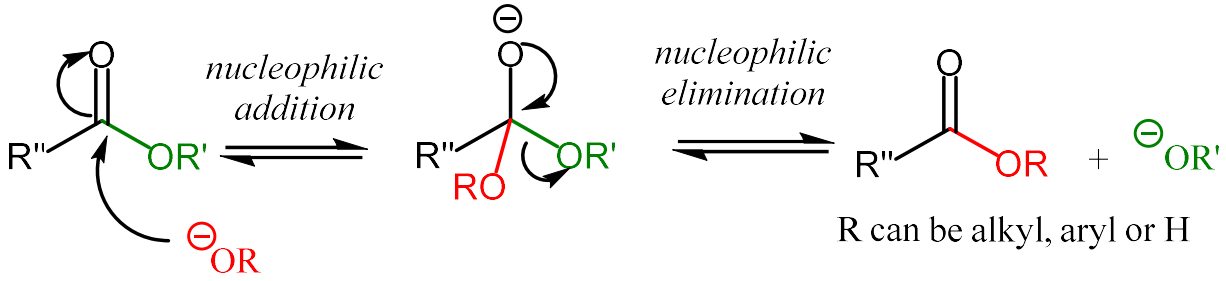
Lesson VI.11.2 Hydrolysis and Transesterification

Esters cannot be converted to acid chlorides or anhydrides because this would require nucleophilic elimination of RO^-, which is less stable (a worse leaving group) than Cl^- or $RC(O)O^-$. We have just seen that esters can, however, undergo acid-catalyzed hydrolysis (the reverse of Fischer Esterification). Esters can likewise be converted to other esters through **transesterification reactions**.

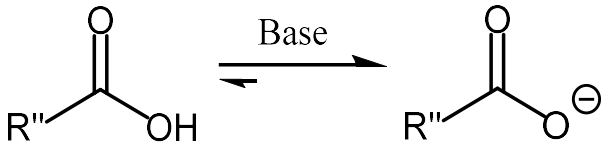
Like hydrolysis, the conversion of an ester into a different ester is a reversible reaction, which means that driving the equilibrium to favors the products can be achieved by applying LeChatelier's principle (e.g., adding more reactants, removing the products, etc.). Transesterification reactions follow two general mechanisms depending whether they are **base-catalyzed** or **acid-catalyzed** reactions.

Base-catalyzed transesterification/hydrolysis:

In this reaction, the base first deprotonates the nucleophile (not shown below). A standard S_NAc reaction follows:



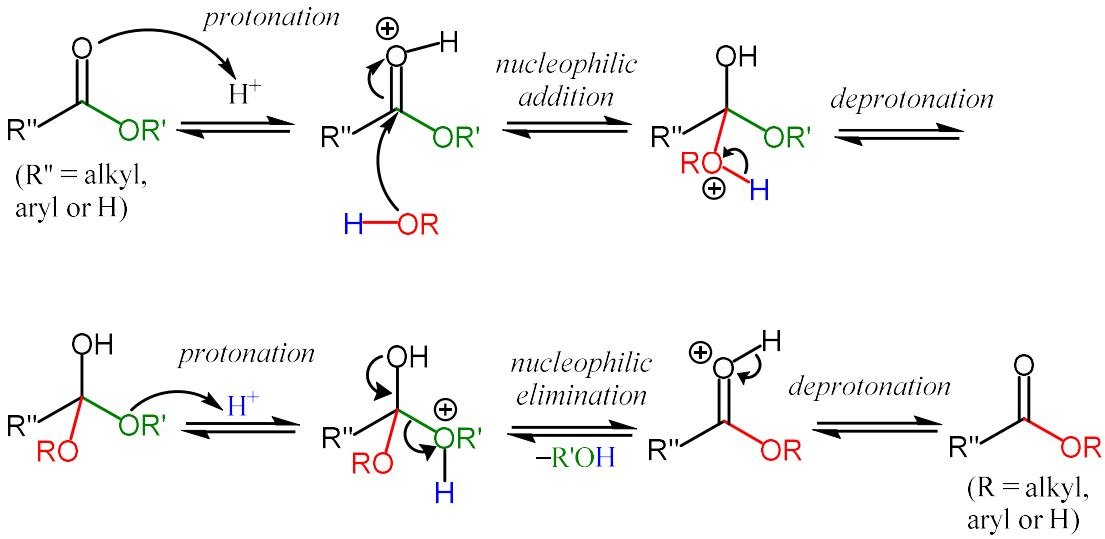
Note that if the initially-formed product is a carboxylic acid, it will be deprotonated in the basic reaction solution, so that a **carboxylate is the isolated product** when R = H:



With the strong bases typically used in these reactions, the equilibrium lies overwhelmingly to the right, producing the carboxylate as the major product.

Acid-catalyzed transesterification/hydrolysis:

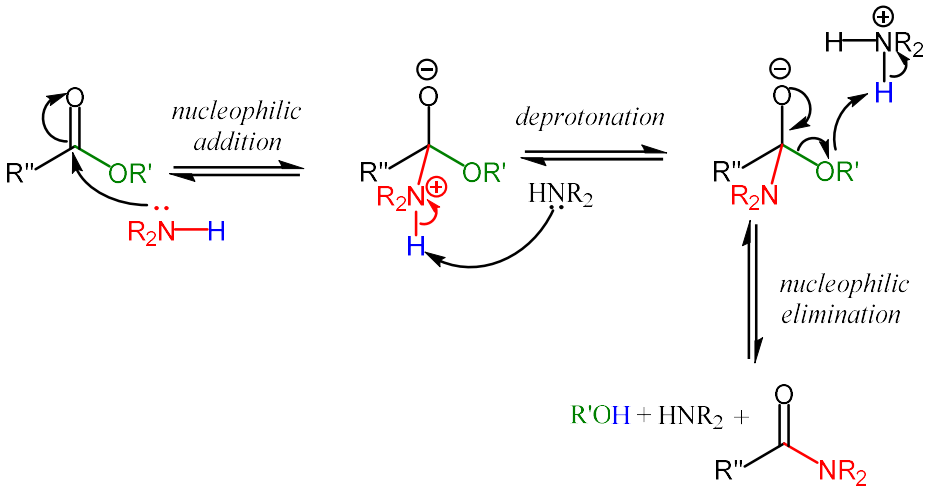
This reaction mechanism is essentially the same as that of Fischer Esterification, but starting with an ester instead of a carboxylic acid. The mechanism is shown below. Importantly, each step of the acid-catalyzed transesterification or acid-catalyzed hydrolysis is reversible. In order to drive the reaction in the forward direction, an excess of the nucleophile (ROH) is generally used.



Lesson VI.12. Amide Formation, Amide Hydrolysis and the Gabriel Synthesis

Lesson VI.12.1 Ammonolysis and Amidation

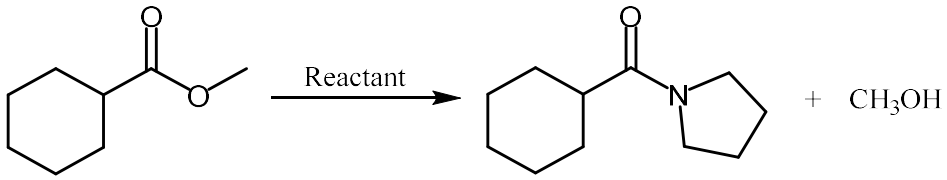
Esters can be converted to amides upon reaction with 1° amines, 2° amines, or NH_3 under base- or acid-catalyzed conditions via mechanisms similar to the transesterification mechanisms we saw in Lesson VI.11



When ammonia is used as the nucleophile, this reaction is called **ammonolysis**. When a 1° or 2° amine is used, this reaction is called **amidation**. These are all S_NAc (Type B) reactions.

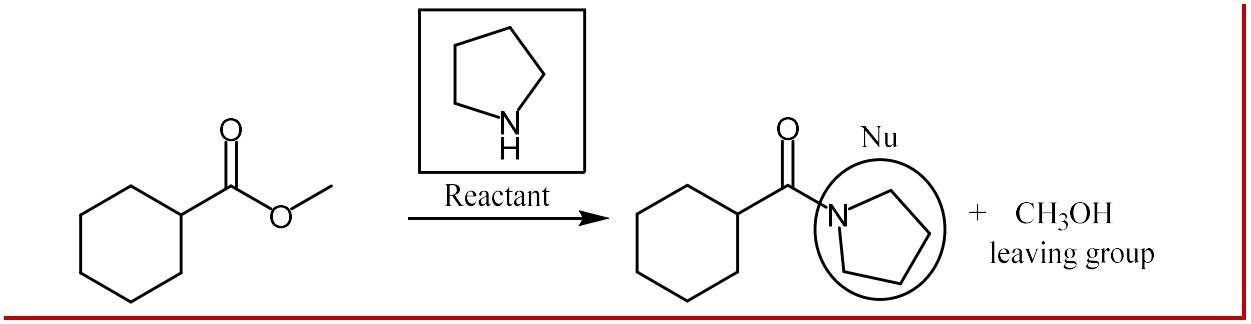
Example VI.12.1

Give the missing reactant in this nucleophilic acyl substitution



Solution VI.12.1

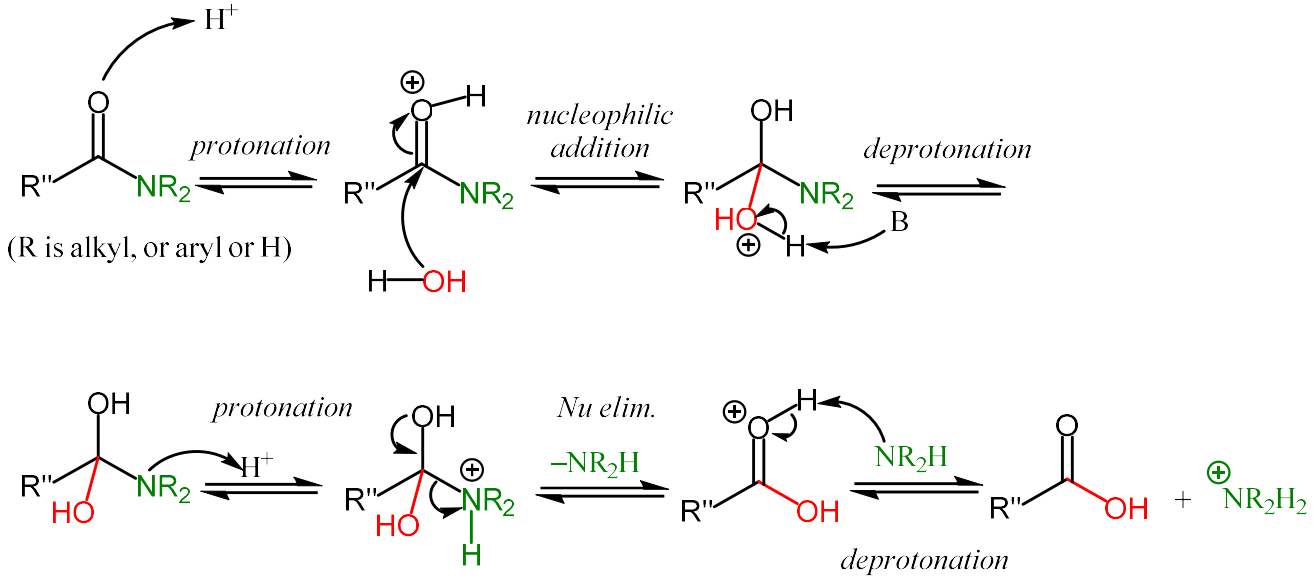
The above reaction is a nucleophilic acyl substitution where an ester is converted to an amide. If we circle the nucleophile in the reaction (as shown below) we can see it is a pyrrolidine anion so the missing reactant is NuH (amine)



VI.12.2 Amide Hydrolysis is a S_NAc Reaction

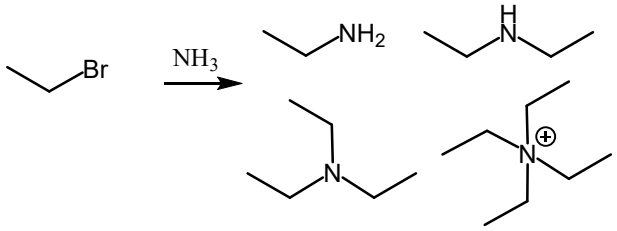
Amides are the least reactive of the carboxylic acid derivatives, and they can only undergo hydrolysis reactions to give carboxylic acids under harsh reaction conditions. Hydrolysis of amides can take place either in very strongly acidic conditions (e.g. addition of aqueous HI) or very strong basic conditions (e.g. addition of concentrated aqueous NaOH). Furthermore, the reactions require heating to higher temperatures than are used for hydrolysis of esters.

The general mechanism in either acidic or basic media is similar to the corresponding mechanism for ester hydrolysis (Lesson VI.11), with one exception: in an acidic medium, the amine (HNR_2) released by nucleophilic elimination is a sufficiently strong base that it will deprotonate the cationic oxygen in step 6, to afford the ammonium $[H_2NR_2]^+$.

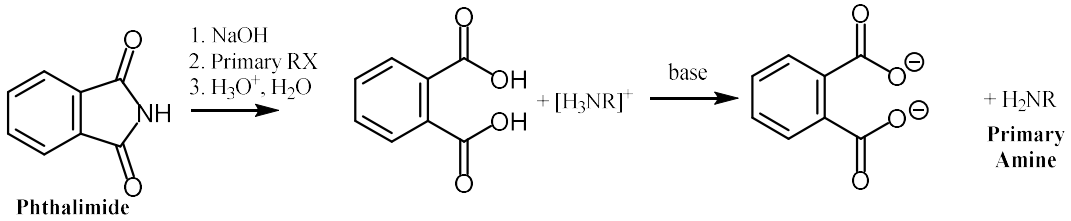


VI.12.3 Gabriel Synthesis

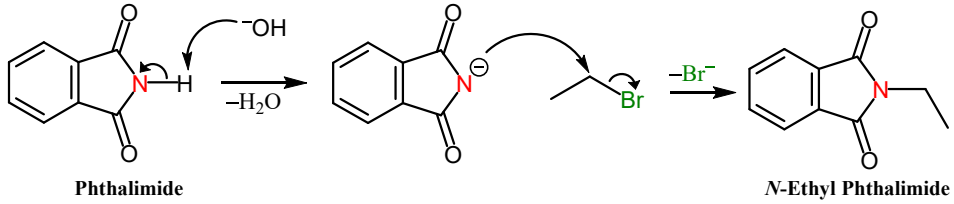
One very useful synthetic application that involves amide hydrolysis is the **Gabriel synthesis**. The Gabriel synthesis is an excellent way to make primary amines. If you try to make a primary amine by simple S_N2 reaction of a primary alkyl halide with ammonia, you will get some of the primary amine, but a variety of side products will also form:



The secondary and tertiary amines, in addition to the tetraethylammonium salt, can all form as well as the targeted primary amine because the initially-formed amines can add to the ethylbromide. The Gabriel synthesis uses a N that is between two carbonyl carbons, in a molecule called **phthalimide**, as a sort of protected N to which only one R group can add:



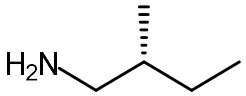
Note that if a base is added as a workup step the ammonium salt is converted to the target primary amine and the carboxylic acid is deprotonated to give the dicarboxylate. This makes separation easy, because the carboxylate is soluble in water, whereas the amine can be extracted into an organic solvent. The mechanism of steps 1 and 2 in the above scheme are a simple deprotonation to make the N into a good nucleophile, followed by an S_N2 reaction. These two steps are illustrated here for reaction with ethyl bromide:



The *N*-ethylphthalimide then undergoes amide hydrolysis to give the ethylammonium salt and the carboxylic acid.

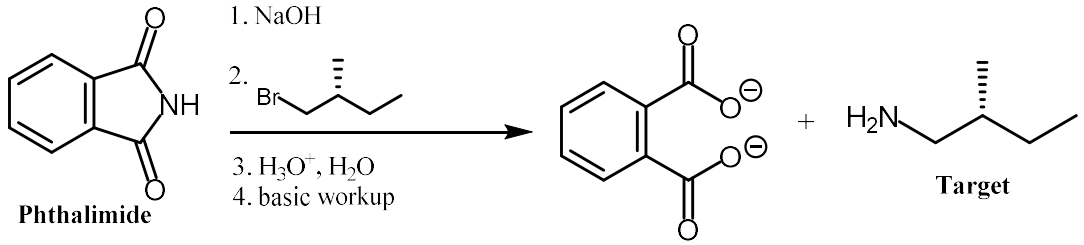
Example VI.12.2

Provide a reasonable synthetic route to prepare this target amine:



Solution VI.12.2

The target is a primary amine, so the Gabriel synthesis is a good choice for its synthesis. We will need phthalimide and the appropriate alkyl halide. In this case, we need (*R*)-1-bromo-2-methylbutane:



Phthalimide **Target**