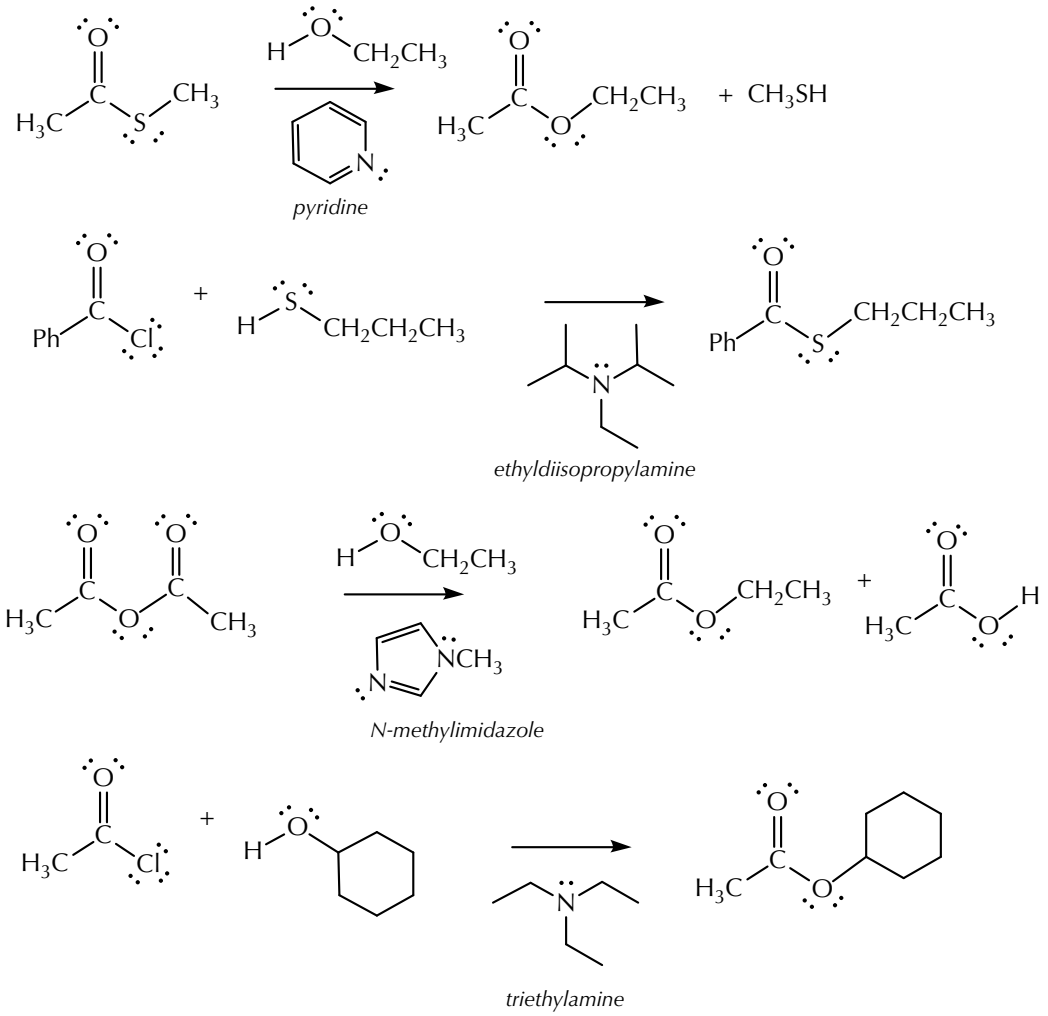
Figure 1324

Acylation under weak base conditions.



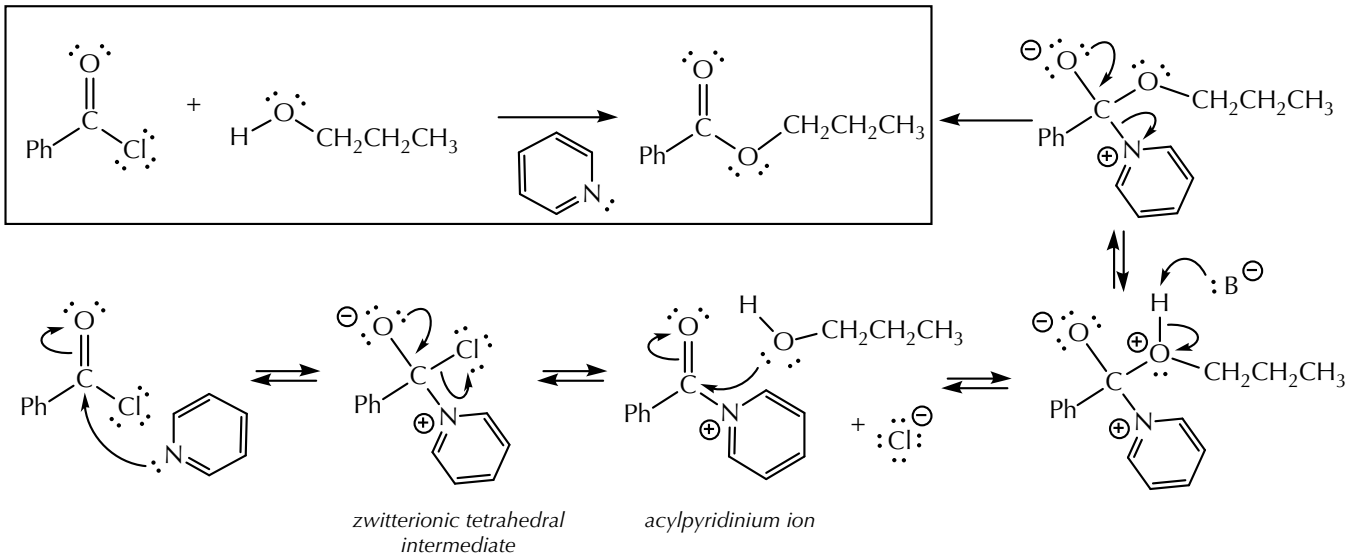
These are quite reasonable questions. The answer to the first two is yes. The answer to the third question is a matter of experimental reality: Chemical reactions are notoriously sensitive to reaction conditions, particularly when it comes to acid-base strength. In the real world of complex molecules built from diverse collections of functional groups, the ability to work in different acid-base domains (pK_a ranges) is an utter necessity.

In that light, the fact that this third category of reaction conditions is characterized as weak base may not be that surprising. The strong base conditions in Section B and the acid-catalyzed conditions in Section C might automatically suggest that weak base conditions were an inevitable domain for acylation reactions.

Figure 1324 is representative of the combination of reagents that characterizes this category of reaction conditions: an electrophile from among the more reactive acylating agents, a nucleophile that is an alcohol or a thiol, and an organic amine base with no NH bonds whose conjugate acid is in the pK_a 6–11 range.

Figure 1325A

Topics related to acylation reaction mechanisms under weak base conditions.



The presence of the amine base plays two roles in the reaction mechanism.

First, these bases are not strong enough to completely deprotonate alcohols or thiols, and so these are not equivalent to the strong base conditions where the conjugate bases of the nucleophile are formed. Second, the organic amine bases are themselves good nucleophiles—better nucleophiles, in fact, compared with the alcohols and thiols which are the intended nucleophiles for the acylation reactions. And this fact is the key feature of these acylation reaction mechanisms.

In combination with one of the strong acylating agents, the nucleophilic amines with no NH bonds undergo a fast acylation reaction that gives a cationic acyl intermediate, an acyl group with an even better leaving group than the one that it was attached to initially. If the amine had at least one NH bond, it would be readily deprotonated and result in the formation of an amide. But without an NH bond, the acylated nitrogen atom forms a cationic intermediate that is a powerfully reactive acylating agent because it carries a positively charged leaving group.

Figure 1325A shows the overall acylation transformation in the boxed equation, and then the mechanism below. Nucleophilic addition of the organic base (pyridine, in this case) creates a zwitterionic tetrahedral intermediate. The base has no proton to lose, and the carbonyl group can reform, in an elimination, by either ejecting the cationic nitrogen group to return to the starting material or ejecting the chloride ion. The exact partition between these pathways is unknown, but a respectable concentration of the acylpyridinium intermediate is formed.

The acylpyridinium intermediate is a more reactive acylating agent than the original acid halide, so much so that the neutral alcohol molecule is proposed to now be able to participate directly in the nucleophilic addition to the carbonyl group. The resulting tetrahedral intermediate has a net positive charge, bearing an acidic proton with a pK_a of about -2, and so its deprotonation reaction is readily accomplished by almost any Brønsted base in the reaction mixture. A second zitterionic intermediate results from the deprotonation reaction, and this intermediate can rapidly eliminate pyridine as its reforms the carbonyl group to give the acylation product.

Of note: In different books or on websites, depending on the author, you may see the elimination step precede the deprotonation step. In this text, we favor the idea that proton transfer reactions are fast and likely to be faster than any other processes.

Also of note: You may also see places where the deprotonation is shown as happening at the same time as the elimination reaction to reform the carbonyl group. This option is a blatantly bad idea, scientifically, because it is a mechanism that states explicitly that these two steps happen at the same time. It may seem convenient to combine the steps to save a little time and space, but a mechanism is the story you are telling about the timing of steps, and a drawing with simultaneous events is a mechanistic statement that the events are happening at the same time.

The summary for this set of reaction conditions is:

Heteroatom nucleophile:

Brønsted acids with pK_a values in the 10–20 range
(most common nucleophiles: alcohols, thiols)

Heteroatom on the acylating agent:

high to mid-range of reactivity
(most common acylating agents: acid halides, anhydrides, thioesters)

Weak base:

an organic base with no NH bonds, conjugate acid pK_a in the 6–11 range

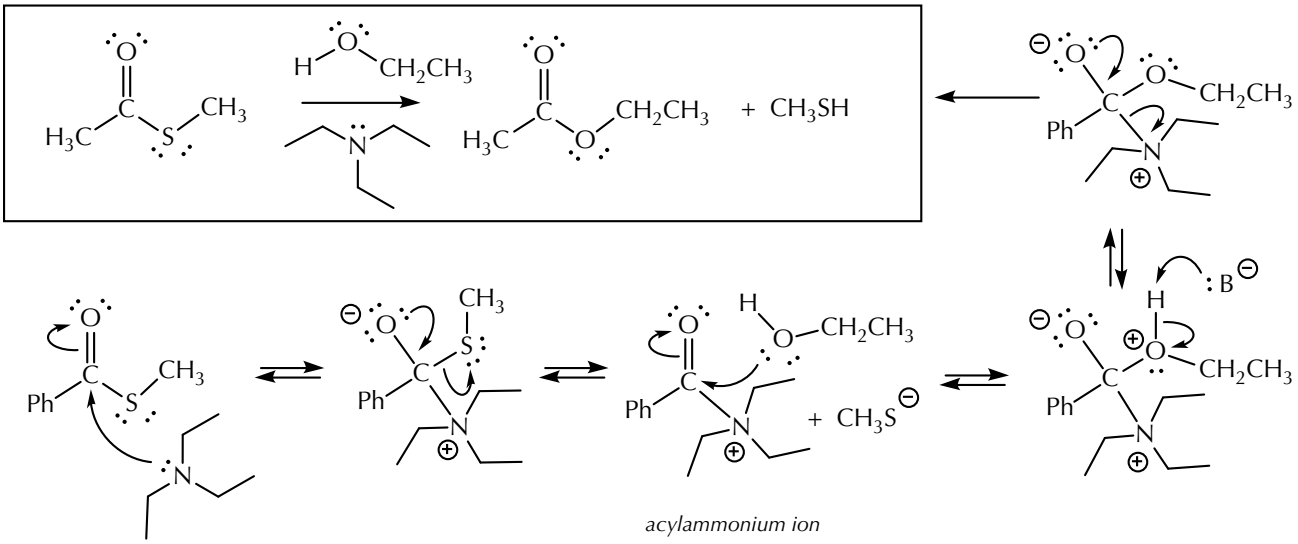
Mechanism: two sequential acylation reactions in five mechanistic steps

(1) nucleophilic addition of the base to the carbonyl group (zwitterionic intermediate)
(2) elimination of the heteroatom to leave a new, cationic acylating agent
(3) addition of the nucleophile to the carbonyl group of the cationic acylating agent
(4) deprotonation of the nucleophile
(5) elimination of the base

Figure 1325B illustrates a second example that satisfies the three criteria for acylation reactions under weak base reaction conditions.

Figure 1325B

Topics related to acylation reaction mechanisms under weak base conditions.

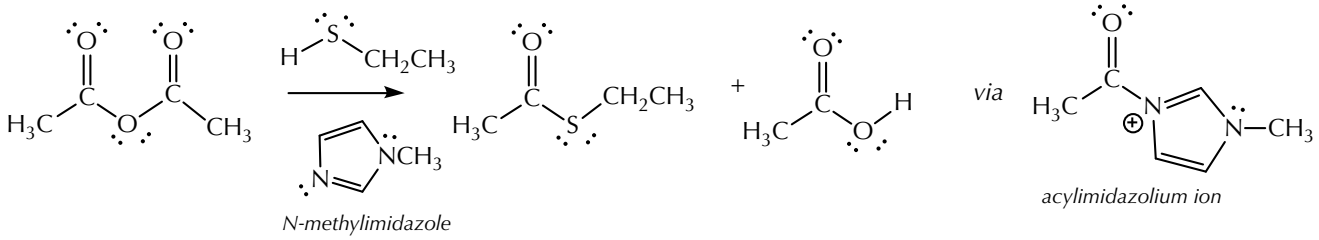


When the organic base is a tertiary amine, the cationic acylating agent is called an acylammonium ion. Take a moment to compare the details in this mechanism and the one drawn for the previous example, to see that they are identical, and to understand how the reaction conditions influence how the fundamental addition-elimination sequence is depicted. First the acylation of the organic base takes place. Then this new acylating agent is attacked by the neutral nucleophile because these bases are not strong enough to deprotonate it easily until it has become positively charged and lowered the pK_a value substantially.

The functional group in the imidazole ring is a structural analogy for an acid derivative (Figure 1325C). The nitrogen with the localized electron pair is about 100 times more basic than pyridine because there is delocalization that stabilizes a positive charge at that position from the other nitrogen atom. You can imagine the other significant resonance contributor for the structure of the acylimidazolium ion in which the nitrogen atom with the acyl group is uncharged and the nitrogen atom with the methyl group is then carrying the positive charge.

Figure 1325C

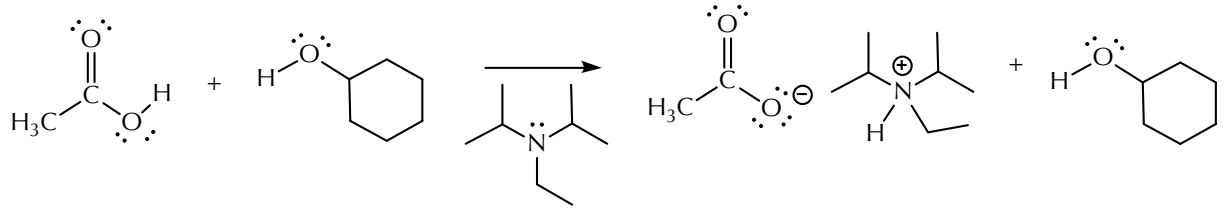
Topics related to acylation reaction mechanisms under weak base conditions.



Even under weak base conditions, the presence of a relatively stronger acid than the conjugate acid of the base would protonate the base and render it useless. Attempting to use a carboxylic acid as an acylating agent under base conditions is not likely to be successful (Figure 1325D).

Figure 1325D

Topics related to acylation reaction mechanisms under weak base conditions.



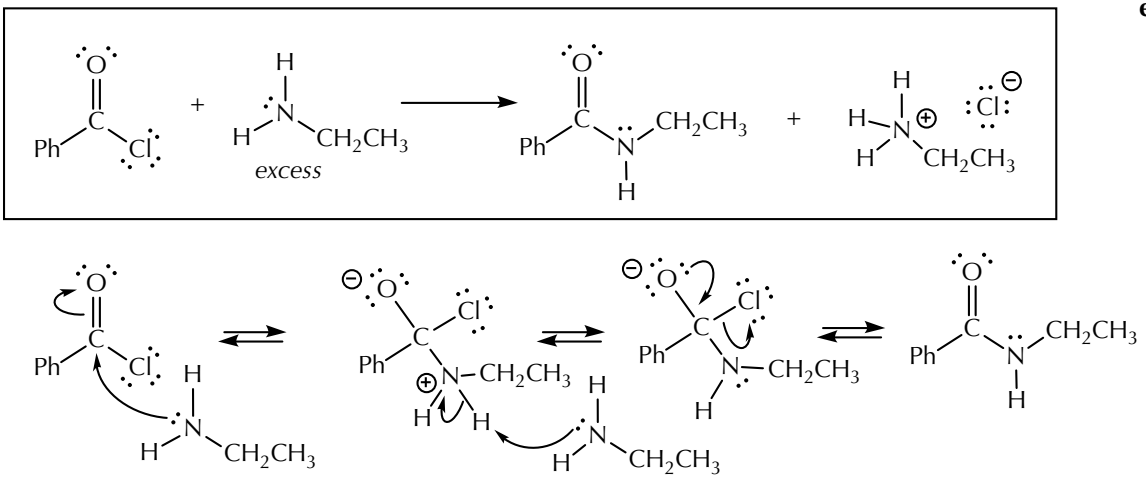
In the acylation reaction mechanisms shown so far in this section, organic bases (in particular, amines with no NH groups) are functioning as acylation catalysts. As detailed in Figures 1325A and 1325B, the amine (as a nucleophile) is acylated to give a new, short-lived cationic acylating agent in which the amine is released (as a leaving group) and available to be acylated again and continue the reaction cycle where it picks up and releases the acyl group. Amines with no NH groups are deliberately used for this purpose because a cationic nitrogen atom with an NH group would be readily deprotonated and would not function as an acylation catalyst. The nitrogen atom would simply end up being acylated. And this last sentence brings up the final set of acylation reactions under the weak base conditions: What do the mechanisms look like when amines bearing NH groups are the nucleophiles in acylation reactions that form amides?

Figures 1326A–1326C show the typical answer to the question posed in the previous paragraph. When the amine is not the limiting reagent and can be readily used in excess, the acylation mechanism is nearly the same as in the strong base cases. Simple amines bearing NH groups are commonly ammonia (NH_3), primary amines (RNH_2), or secondary amines (R_2NH).

Because amines are good nucleophiles, the reaction mechanisms begin exactly as in the other weak base examples: The nucleophilicity of the nitrogen atoms allows a direct addition to the carbonyl group to give a zwitterionic intermediate. In all the previous examples, no deprotonation of the cationic nitrogen atom was possible because there was no NH group. In the case of amines with an NH group, however, the rapid acid-base reaction can occur. Indeed, excess base is used precisely to enable this deprotonation

Figure 1326A

Acylation of amines: excess base.



reaction. Elimination of the original heteroatom from the resulting anionic intermediate is fast, resulting in the formation of the stable, neutral amide product.

In summary, the acylation reaction of amines using excess base is characterized by the following features:

Heteroatom nucleophile:

amines (and related aromatic compounds) with at least one N-H bond
(most common nucleophiles: ammonia: NH_3; 1° amines: RNH_2; 2° amines: R_2NH)

Heteroatom on the acylating agent:

any acylating agent except those with acidic protons, such as carboxylic acids, that would give an acid-base reaction

Mechanism: three steps

(1) nucleophilic addition of the amine to the carbonyl group (zwitterionic intermediate)
(2) deprotonation of the amine N-H bond
(3) elimination of the heteroatom leaving group

In Figure 1326B, as well as in 1326A, the leaving groups released from the acylating agent are not basic enough to deprotonate the conjugate acid of the amine, and so the ionic compounds (as shown in both equations) are the expected byproducts.

Figure 1326B

Acylation of amines: excess base.