Acid Chlorides Reactions

Transcript

00:00:00:00 - 00:00:13:04
Dr.Jessie Key: Hello again, Dr. Jessie Key here. In this slide show, you'll be exploring the reactions of acid chlorides, which are arguably the most synthetically versatile of the carboxylic acid derivatives.

00:00:15:10 - 00:00:45:90
Dr.Jessie Key: One feature that makes acid chlorides so synthetically valuable is that they are the most reactive of the carboxylic acid derivatives. This facilitates their conversion into other groups. Acid chlorides can be converted into a variety of other functional groups, including carboxylic acids, esters, amides, primary alcohols, aldehydes, tertiary alcohols, and ketones.

00:00:45:90 - 00:01:11:06
Dr.Jessie Key: You'll be exploring the reactions to accomplish these conversions in the remainder of this video. Acid chlorides can undergo hydrolysis with water to give carboxylic acids by nucleophilic acyl substitution. Seen here, we have an example where ethanol chloride is undergoing hydrolysis to form ethanoic acid and hydrochloric acid.

00:01:11:30 - 00:01:33:01
Dr.Jessie Key: To avoid side reactions with other functional groups present, you'll often see the reaction conditions include the use of pyridine. Pyridine can remove the hydrochloric acid byproduct through formation of pyridinium chloride salt. Acid chlorides can undergo alcoholysis with primary alcohols to give ester products.

00:01:33:01 - 00:01:52:41
Dr.Jessie Key: Because of steric concerns, this reaction is limited to just primary alcohols. Seen here, we have ethanoyl chloride undergoing alcoholysis with ethanol to generate the ester ethyl ethanoate. Note the use of pyridine again to remove the hydrochloric acid by-product.

00:01:52:69 - 00:02:12:08

Dr.Jessie Key: We can also view the same reaction from the viewpoint of the alcohol. It is being acylated by reacting with the acid chloride to generate the ester. Acid chlorides can undergo aminolysis with primary amines to give secondary amides.

00:02:12:08 - 00:02:35:78
Dr.Jessie Key: Instead of using pyridine, two equivalents of the amine can be used. The first equivalent performs a nucleophilic attack of the nucleophilic acyl substitution, while the second equivalent reacts with the by-pduct hydrochloric acid to produce an ammonium chloride salt. Seen here, ethanol chloride is reacting with two molar equivalents of ethanamine to produce N-ethylethanamide.

00:02:35:78 - 00:02:54:32
Dr.Jessie Key: Aminolysis may also be performed with secondary amines to generate tertiary amides. Again, two equivalents of the amine are necessary. Shown here is the reaction of ethanoyl chloride with secondary amine and N-methylethanamine to generate the tertiary amide product N-ethyl-N-methylethanamide.

00:03:00:74 - 00:03:17:24
Dr.Jessie Key: Acid chlorides can undergo reduction with excess lithium aluminum hydride to generate primary alcohols. Water or hydronium is added in a subsequent workup step. Shown here, ethanoyl chloride is converted to ethanol by LAH reduction.

00:03:17:24 - 00:03:45:31
Dr.Jessie Key: Although this reaction goes through an aldehyde intermediate, it is almost impossible to stop at the aldehyde using lithium aluminum hydride. To effectively reduce to the aldehyde, a less reactive derivative of lithium aluminum hydride may be used lithium tri-tertbutoxy aluminum hydride - sometimes called LTBA. Acid chlorides can also undergo nucleophilic acyl substitution with organometallic reagents.

00:03:45:31 - 00:04:09:52
Dr.Jessie Key: Reaction with excess Grignard reagent generates tertiary alcohols where two new alkyl groups are added from the Grignard reagent. Water or hydronium ion workup is followed in a second step. The example shown here has ethanol and chloride reacting with excess ethylmagnesium bromide Grignard reagent, in ether, to give the tertiary alcohol 3-methylpentan-3-ol.

00:04:09:52 - 00:04:30:27
Dr.Jessie Key: Grignard reagents are too reactive to stop after a single substitution at the ketone intermediate. To accomplish this, a less reactive and more selective reagent must be used known as the Gilman reagent. The Gillman regent is a lithium dialkyl cuprate which reacts with acid chlorides, but not the resulting ketone.

00:04:30:27 - 00:04:57:49
Dr.Jessie Key: This is because the carbanionic character of the cuprate is lower due to the copper-carbon bond being less polarized. Shown here is an example with ethanoyl chloride reacting with lithium dimethyl cuprate to produce propan-2-one. To clearly show the

difference between Grignard and Gilman reagent, let's quickly look at the shared mechanism between the two.

00:04:57:77 - 00:05:32:01
Dr.Jessie Key: Both reagents will have their carbanions (shown here as R minus) perform a nucleophilic attack on the carbonyl carbon to generate the tetrahedral alkoxide intermediate. The lone pair from the alkoxide oxygen travels down to reform the carbon oxygen pi bond, which breaks the carbon chlorine sigma bond, moving those electrons onto the chlorine atom to eject it as the leaving group chloride. It is at this point where the Gilman reagent stops, a ketone where one alkyl group has been provided by the organometallic reagent.

00:05:32:60 - 00:05:57:72
Dr.Jessie Key: The Grignard is more reactive and continues further with a second nucleophilic attack by another equivalent of carbanion. A second tetrahedral alkoxide intermediate is generated, which then performs a proton transfer from the water or hydronium ion added in the workup step. This gives a tertiary alcohol product with two alkyl groups originating from the organometallic Grignard reagent.

00:05:58:52 - 00:06:11:00
Dr.Jessie Key: In this video, we saw the many different transformations that can be accomplished using acid chlorides. Is this versatility, which makes acid chlorides so valuable as synthetic intermediates.