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Alpha Halogenation

Transcript

00:00:00:44 - 00:00:14:06
Dr.Jessie Key: Hello again, Dr. Jessie Key here. In this slide show, you'll be exploring alpha halogenation under both acidic and basic conditions and some of the interesting applications of alpha halogenation towards synthesis.

00:00:14:06 - 00:00:39:32
Dr.Jessie Key: Ketones and aldehydes are capable of undergoing halogenation at the alpha position under acidic conditions. In this example, ethanal is converted to 2-bromoethanal with the use of bromine under acidic aqueous conditions. Using this methodology, several different halogens can be installed, including bromine, chlorine and iodine however, fluorination is not common.

00:00:39:39 - 00:01:00:03
Dr.Jessie Key: Notice that the by-product of alpha halogenation is a hydrogen halide of the halogen used, a strong acid. This makes alpha halogenation autocatalytic as a strong acid by-product can catalyze the reaction. The mechanism for acid catalyzed alpha halogenation can be broken down into two parts.

00:01:00:03 - 00:01:19:37
Dr.Jessie Key: Part 1 – enol formation and Part 2 – halogenation. Let's walk through this mechanism together showing the alpha bromination of propan-2-one to 1-bromopropan-2-one. First, a proton transfer step occurs where the carbonyl oxygen lone pair abstracts a proton from the acid present.

00:01:19:37 - 00:01:37:35
Dr.Jessie Key: In this case, the hydronium ion. A second proton transfer then occurs where water is used as a base to remove the alpha proton. This moves the sigma bond electrons between alpha carbon and the hydrogen to form a new pi bond between the alpha carbon and the carbonyl carbon.

00:01:37:35 - 00:02:01:08
Dr.Jessie Key: The pi bond electrons of the carbonyl move up onto the carbonyl oxygen to give the enol intermediate. In the second part of the mechanism, halogenation, the enol

intermediate performs a nucleophilic attack from the alpha carbon onto the bromine. We can show this with curved arrow notation by bringing down a lone pair of electrons from the oxygen atom to reform the carbonyl pi bond.

00:02:01:08 - 00:02:30:04
Dr.Jessie Key: This causes the enol pi bond to attack one of the bromines of Br2, which breaks the bromine-bromine bond to eject off bromide as a leaving group. A final proton transfer occurs as water removes the extra proton on the carbonyl carbon to form a lone pair and remove the formal positive charge. When unsymmetrical ketones undergo alpha halogenation, there's a regiochemical preference for the halogenation at the more substituted alpha position.

00:02:30:04 - 00:03:14:55
Dr.Jessie Key: This can be seen in the following example where the unsymmetrical starting material, 2-methylpentan-3-one, can form two possible products, 2-bromo-2-methylpentan-3-one and 2-bromo-4-methylpentan-3-one The more substitute product, 2-bromo-2-methylpentan-3-one pentanthone, is the major product as its enol intermediate is more stable due to its greater substitution about the alkene bond. Alpha bromo ketones obtained from alpha halogenation can be used to generate alpha,beta-unsaturated ketones. E2 elimination can be performed using a variety of bases such as pyridine or potassium tert-butoxide.

00:03:14:56 - 00:03:44:04
Dr.Jessie Key: This example demonstrates the two step conversion of 2-methylcylohexanone to the alpha,beta-unsaturated ketone, 2-methylcyclohex-2-en-1-one. In the first step, alpha halogenation occurs at the more substute alpha position by using bromine under acidic aqueous conditions. The second step features E2 elimination by using pyridine base to give the more substituted alpha,beta-unsaturated ketone, 2-methylcyclohex-2-en-1-one.

00:03:46:68 - 00:04:23:55
Dr.Jessie Key: Alpha halogenation can also be performed under basic conditions, but suffers from difficult to control polyhalogenation whenever there's more than one alpha proton present. In this example, when 2,2-dimethylpentan-3-one undergoes alpha bromination, using hydroxide and bromine, both available alpha protons are replaced and the dihalogenated product 2,2-dibromo-4,4-dimethylpentan-3-one is formed. The mechanism for alpha halogenation under basic conditions first has proton transfer to form an enolate.

00:04:23:55 - 00:04:45:05
Dr.Jessie Key: This can be shown using curved arrow notation by starting an arrow at the lone pair of the base hydroxides oxygen. The alpha proton is removed and the sigma bond electrons are moved to form a new pi bond between alpha and carbonyl carbon. The carbonyl pi bond then moves to form a new lone pair on the carbonyl oxygen, which gives the enolate intermediate.

00:04:45:37 - 00:05:05:33
Dr.Jessie Key: In the second step, a nucleophilic attack occurs where the enolates oxygen lone pair moves down to reform the carbonyl pi bond. This allows the alkenyl pi bond to be used to perform the nucleophilic attack on the bromine, breaking the bromine-bromine bond. This generates the alpha halogenated product.

00:05:05:41 - 00:05:36:79
Dr.Jessie Key: Remember that if more than one alpha proton is present, this process will repeat uncontrollably in the presence of excess base and halogen. While uncontrollable polyhalogenation is generally undesirable, there's one helpful application of it known as the haloform reaction. Methyl ketones can be trihalogenated using excess halogen and hydroxide, then hydrolyzed to a carboxylic acid using aqueous acidic conditions.

00:05:36:79 - 00:06:05:30
Dr.Jessie Key: The haloform reaction is therefore a handy method to convert from methyl ketones to carboxylic acids. The mechanism for the haloform reaction is actually just a nucleophilic acyl substitution where the tribromomethyl group generated by polyhalgenation serves as the leaving group. The hydroxide nucleophile can perform nucleophilic attack at the carbonyl carbon, moving the carbonyl pi electrons up onto the carbonyl oxygen.

00:06:05:30 - 00:06:43:48
Dr.Jessie Key: When the tetrahedral alkoxide term, its lone pair comes back down to reform the carbonyl pi bond, the carbon-carbon bond between carbonyl and alpha carbon breaks and the tribromomethyl group is lost as a leaving group. Normally, carbon ions cannot serve as leaving groups, but in this case, the formal negative charge is stabilized enough by the electron withdrawing effects of the three attached halogens. Please note that the mechanism presented here is incomplete as under basic conditions, the carboxylic acid formed after loss of leaving group would be deprotonated by the strong base present, and therefore, a separate workup re-protonation would be required.

00:06:45:34 - 00:07:15:74
Dr.Jessie Key: In this video, you explored alpha halogenation under acidic conditions to give a mono-halogenate product via an enol intermediate, and you saw how this could be paired with a subsequent elimination to yield alpha,beta unsaturated ketones. As well, you saw that under basic conditions, polyhalogenation occurs via an enolate intermediate. When this reaction is performed with a methyl ketone, it can be paired with a subsequent nucleophilic acyl substitution to yield carboxylic acids.

00:07:15:74 - 00:07:19:26
Dr.Jessie Key: This is known as the Haloform reaction.