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Alkylation at the Alpha Position

Transcript

00:00:00:00 - 00:00:11:08
Dr.Jessie Key: Hello again, Dr. Jessie Key here. In this slide show, you'll be exploring alkylation at the alpha position and seeing how regiochemistry can be controlled to give kinetic or thermodynamic products.

00:00:11:08 - 00:00:44:39
Dr.Jessie Key: Alkylation can be performed at the alpha position when an aldehyde, ketone, ester or nitrile is treated first with LDA, (lithium diisopopyl amide) and then an alkyl halide is added. The LDA forms an enolate nucleophile in the first step, which can then perform nucleophilic attack on the electrophilic carbon of the alkyl halide to add the R group of the alkyl halide at the alpha position. If this reaction seems familiar, that's because it's just an SN2 substitution with the enolate acting as the nucleophile!

00:00:44:39 - 00:01:19:85
Dr.Jessie Key: Remember from organic one that with SN2 reactions, steric hindrance is a concern, so the alkyl halide should be either methyl or primary. When unsymmetrical ketones, like this 2-methylcylopentanone are used for alpha alkylation, there are two possible enolates which can form, the more substituted enolate, which is called the thermodynamic enolate and the less substituted enolate, which is called the kinetic enolate. You can better see the difference between these two possible enolates with an energy diagram.

00:01:19:85 - 00:01:51:91
Dr.Jessie Key: The thermodynamic enolate, shown here with the pink line, is more stable and lower energy due to having a more substituted enolate alkene stabilized by hyperconjugation. However, the thermodynamic enolate also has a higher activation energy due to the greater steric bulk at its alpha position hindering the proton transfer step of enolate formation. The kinetic enolate, shown here with the green line is less stable and higher energy due to having a less substituted enolate alkene.

00:01:51:91 - 00:02:22:19
Dr.Jessie Key: The kinetic enolate also has a lower activation energy due to the reduced steric hindrance at its alpha position, which facilitates the proton transfer step of the

enolate formation. You can favor the formation of one enolate over the other by careful choice of base and temperature. If a smaller strong base like sodium hydride is used at room temperature, the steric hindrance penalties are reduced, and there's energy to overcome the activation energy barrier.

00:02:22:19 - 00:02:43:62
Dr.Jessie Key: As a result, the thermodynamic product will be formed in majority. If a sterically hindered (bulky) base, like LDA is used at low temperature, the steric hindrance penalties are more severe and there's less energy to overcome the activation energy barrier. As a result, the kinetic product will be formed in majority.

00:02:44:22 - 00:02:54:30
Dr.Jessie Key: Alkylation at the alpha position is an interesting example of regioselectivity, which can be controlled by careful selection of the base and reaction temperature!