



Alkylation at the Alpha Position

Transcript

Instructor: Jessie Key

00:00:00:00 - 00:00:23:10

Instructor: Hello, again, Doctor Jessie Key here. In this slide show, you'll be exploring alkylation at the Alpha position and seeing how Regio chemistry can be controlled to give kinetic or thermodynamic products. Alkylation can be performed at the alpha position when an aldehyde ketone, ester or nitrile is treated first with LDA, lithium diisopropylamide, and then an alkyl halide is added.

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Instructor: 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 SN two substitution with the enolate acting as the nucleophile. Remember from organic one that with SN two reactions, steric hindrance is a concern.

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Instructor: So the alkyl halide should be either methyl or primary. When unsymmetrical ketones, like this two methyl cyclopentanone 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.

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Instructor: 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.

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Instructor: 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.

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Instructor: 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.

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Instructor: Alkylation at the alpha position is an interesting example of regioselectivity, which can be controlled by careful selection of the base and reaction temperature.