Objectives

After completing this section, you should be able to

1. identify the two possible ways in which a given enolate anion could conceivably react with an electrophile.
2. write an equation to illustrate the haloform reaction.
3. identify the products formed from the reaction of a given methyl ketone with a halogen and excess base.
4. identify the methyl ketone, the reagents, or both, needed to obtain a specified carboxylic acid through a haloform reaction.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- haloform
- haloform reaction

Study Notes

Because the negative charge on an enolate ion is delocalized, there are two reactive sites and therefore two potential products. The $\alpha$-substituted product is much more common.

A "haloform" is any compound of the type CHX$_3$, where X = Cl, Br or I. Of these three compounds, chloroform is the most common.

The haloform reaction described in the reading is usually carried out with iodine. This reaction is called the "iodoform test," and is one of the reactions carried out in the laboratory as a simple qualitative test for methyl ketones.

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General Reaction of Enolates

The Ambident Character of Enolate Anions

Since the negative charge of an enolate anion is delocalized over the alpha-carbon and the oxygen, electrophiles may bond to either atom. Reactants having two or more reactive sites are called ambident, so this term is properly applied to enolate anions. Modestly electrophilic reactants such as alkyl halides are not sufficiently reactive to combine with neutral enol tautomers, but the increased nucleophilicity of the enolate anion conjugate base permits such reactions to take place.
Because alkylations are usually irreversible, their products should reflect the inherent (kinetic) reactivity of the different nucleophilic sites.

\[
R - X + \overset{\text{alkyl halide}}{\text{enolate anion}} \rightarrow \overset{\text{carbonyl compound}}{\text{carbonium ion}} + \overset{\text{alkyl halide}}{\text{alkylation}} + X^+ \]

If an alkyl halide undergoes an S\text{N}2 reaction at the carbon atom of an enolate anion the product is an alkylated aldehyde or ketone. On the other hand, if the S\text{N}2 reaction occurs at oxygen the product is an ether derivative of the enol tautomer; such compounds are stable in the absence of acid and may be isolated and characterized. These alkylations (shown above) are irreversible under the conditions normally used for S\text{N}2 reactions, so the product composition should provide a measure of the relative rates of substitution at carbon versus oxygen. It has been found that this competition is sensitive to a number of factors, including negative charge density, solvation, cation coordination and product stability.

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**The Haloform Reaction**

Methyl ketones typically undergo halogenation three times to give a trihalo ketone due to the increased reactivity of the halogenated product as discussed above. This trihalomethyl group is an effective leaving group due to the three electron withdrawing halogens and can be cleaved by a hydroxide anion to effect the haloform reaction. The product of this reaction is a carboxylate and a haloform molecule (CHCl\textsubscript{3}, CHBr\textsubscript{3}, CHI\textsubscript{3}). Overall the haloform reaction represents an effective method for the conversion of methyl ketones to carboxylic acids. Typically, this reaction is performed using iodine because the subsequent iodoform (CHI\textsubscript{3}) is a bright yellow precipitate which is easily filtered off.

**General reaction**

\[
\text{Methyl Ketone} + 3 X_2 \rightarrow \text{Trihalo Ketone} \rightarrow \text{Carboxylate} + \text{Haloform}
\]

**Example: The Haloform Reaction**

\[
\text{C}_6\text{H}_5\text{CH}_3 + \text{I}_2 \rightarrow \text{C}_6\text{H}_5\text{C} = \text{ONa} + \text{HCl}_3 + \text{Iodoform}
\]

**Mechanism**

1) Formation of the trihalo species

\[
\text{O} \quad \text{H} \quad \text{H} \quad \text{X} \\
\text{C} + 3 X_2 + \text{NaOH} \rightarrow \overset{\text{carbonyl compound}}{\text{carbonium ion}} + 3 \text{NaX} + 3 \text{H}_2\text{O}
\]
2) Nucleophilic attack on the carbonyl carbon

3) Removal of the leaving group

4) Deprotonation

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