

9.3: CARBONYL CONDENSATIONS VERSUS ALPHA SUBSTITUTIONS

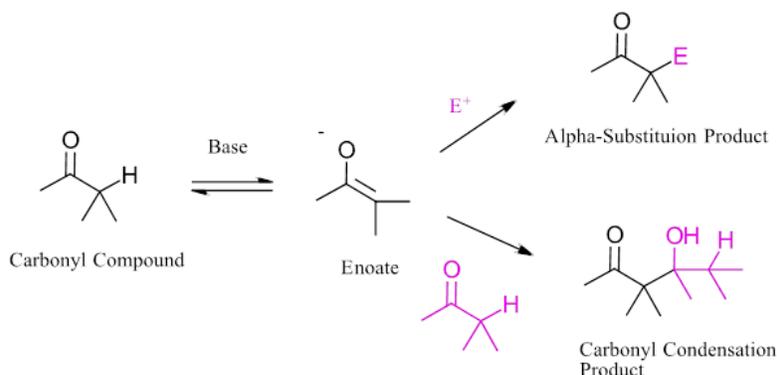
OBJECTIVES

After completing this section, you should be able to describe the difference between a carbonyl condensation reaction and an alpha-substitution reaction, and determine which of these two types of reaction is most likely to occur, given the appropriate experimental data.

STUDY NOTES

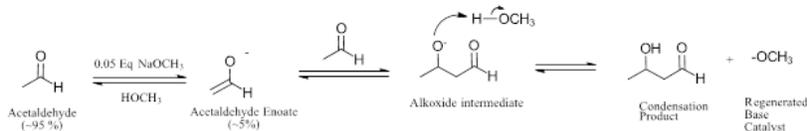
So far we have discussed three of the four general reactions of carbonyl compounds: nucleophilic additions of aldehydes and ketones (Chapter 19), nucleophilic acyl substitution reactions of carboxylic acid derivatives (Chapter 21) and alpha-substitution reactions (Chapter 22). The fourth general reaction, carbonyl condensation, is similar to the alpha-substitution reaction, so you need to appreciate how it differs from the other three and the conditions under which it occurs.

Carbonyl condensation and alpha-substitution reactions both involve the formation of a reactive enolate ion intermediate. How is it possible to generate an enolate ion for a alpha substitution reaction without a carbonyl condensation also occurring? What reaction conditions are required to cause one reaction and not the other?



In a carbonyl condensation a catalytic amount of base is used to generate only a small amount of the the enolate ion. Most of the carbonyl compound is unreacted and can react with the enolate. During the reaction the base catalyst is regenerated which can then produce more enolate ion and continue the cycle.

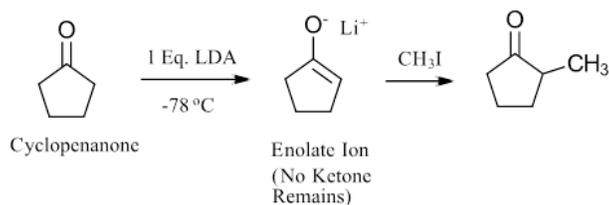
If acetaldehyde was reacted with 0.05 equivalents of sodium methoxide in a methanol solvent only a small amount (~5%) of the enolate would form. The majority of the acetaldehyde would be unchanged and capable of undergoing a condensation reaction with the enolate present. The alkoxide intermediate produced is protonated by methanol to the neutral condensation product and regenerates the methoxide base catalyst. Methoxide can then deprotonate a new acetaldehyde molecule to create another enolate allowing the reaction cycle to continue.



These steps are all reversible and it should be noted that reactants and products that are close in energy level can potentially undergo the reverse reaction if conditions change enough. While from a synthetic point of view in the laboratory this may mean increasing yields by driving the reaction to completion (e.g. adding heat, removing product), in biological systems it can have more drastic consequences. Indeed, depending on metabolic conditions, retro-aldol reactions (the reverse of aldol condensations, in which carbon-carbon bonds are broken) can occur.

In contrast, the alpha-substitution reaction is often more directional by design. To reduce unwanted competition from carbonyl condensation, the enolate ion intermediate is generated all at once with a full equivalent of strong base at low temperature. This effectively removes the carbonyl from the reactive mixture making it difficult for a carbonyl condensation to occur. The reactive enolate intermediate then is quickly quenched by rapid addition of the electrophile to complete the substitution reaction. As discussed in Section 22.7, for direct alkylation, strong bases like NaNH₂ and LDA were used to generate the enolate intermediate followed by addition of an alkylhalide.

An example is shown with the alpha-alkylation reaction of cyclopentanone. During this reaction, one equivalent of lithium diisopropylamide (LDA) is added to the reactant at $-78\text{ }^{\circ}\text{C}$ which completely converts cyclopentanone to the corresponding enolate ion. This leaves none of the ketone carbonyl remaining to undergo a condensation reaction. Methyl iodide is quickly added to react with enolate ion forming the alpha-alkylated product.



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