Aldol Condensation

Background

The aldol reaction is a key carbon-carbon bond forming reaction in organic chemistry. The product of the reaction is often a β -hydroxy aldehyde from which the reaction takes its name (aldehyde + alcohol = aldol). If the β -hydroxy aldehyde (or β -hydroxy ketone) goes on to eliminate a molecule of water, the reaction is known as an aldol condensation. The aldol reaction has been very important in the synthesis of various pharmaceuticals and natural products. When combined with a Michael reaction it is called a Robinson annulation, a key reaction used to make steroids. In biology, aldol-like reactions are used to form and breakdown sugars. Enzymes that perform reverse aldol reactions are known as aldolases and are involved in glycolysis.

Aldols can be catalyzed by either acid or base. In base, the aldehyde (or ketone) reactant forms an enolate. The enolate then reacts with another reactant molecule to form a β -hydroxy carbonyl product.



Under gentle conditions, the reaction can be stopped at the β -hydroxy carbonyl, but often the product goes on to eliminate and form an α - β unsaturated carbonyl compound. This is referred to as a condensation reaction because water is formed during the elimination.



The above reaction is known as an aldol self-condensation, meaning the enolate (nucleophile) and the carbonyl (electrophile) come from the same molecule – acetaldehyde. Mixed aldol condensations are also possible, but one has to be careful in choosing the two molecules for the reaction. If both are equally acidic (same ease of forming enolate) and equally reactive towards nucleophiles, then the result will be a mixture of products. In this experiment, acetophenone and *p*-anisaldehyde are used for the mixed aldol. Only acetophenone can form an enolate. Additionally, aldehydes react faster with nucleophiles because they are less sterically hindered, so *p*-anisaldehyde is the most likely electrophile. Taking advantage of these facts, we can obtain one product for the mixed aldol condensation.



Procedure

Reaction Setup

Place 3.0 mL of p-anisaldehyde and an equimolar amount of acetophenone in a 125 mL Erlenmeyer flask. Add 10 mL of 95% ethanol and stir with magnetic stir bar to dissolve the reactants. Next, add 7.5 mL of 2 M sodium hydroxide to the flask. **Caution** – solutions of strong bases are highly corrosive – keep away from the skin and eyes! Heat on a hot plate set to 60°C and continue stirring for 20 minutes.

Isolation and Purification

Cool the mixture in an ice bath and scatch the oil/water interface with glass stirring rod. It make take several minutes of scratching while cooling before crystals appear. Collect the crystals with vacuum filtration. Recrystallize the crude product from a 95% ethanol. Wash the resulting crystals with about 20 mL of cold 95% ethanol. Allow air to pass through the crystals for several minutes.

Characterization

Characterize the product by melting point and percent yield. The literature melting point of *trans-p*-anisalacetophenone is 77-78°C.

Chemicals: p-anisaldehyde, acetophenone, 95% ethanol, 2 M sodium hydroxide