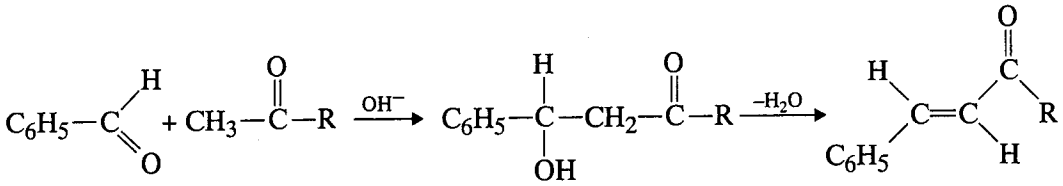
Experiment 35

The Aldol Condensation Reaction: Preparation of Benzalacetophenones (Chalcones)

Aldol condensation
Crystallization

Benzaldehyde reacts with a ketone in the presence of base to give α,β-unsaturated ketones. This reaction is an example of a crossed aldol condensation where the intermediate undergoes dehydration to produce the resonance-stabilized unsaturated ketone.

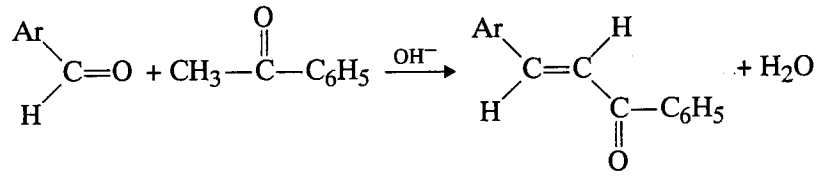


Intermediate

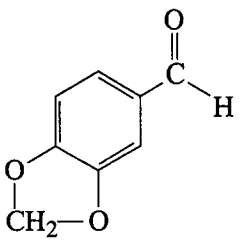
Crossed aldol condensations of this type proceed in high yield, because benzaldehyde cannot react with itself by an aldol condensation reaction because it has no α-hydrogen. Likewise, ketones do not react easily with themselves in aqueous base. Therefore, the only possibility is for a ketone to react with benzaldehyde.

In this experiment, procedures are given for preparing benzalacetophenones (chalcones). You should choose one of the substituted benzaldehydes and react it with the ketone acetophenone. All the products are solids that can be recrystallized easily.

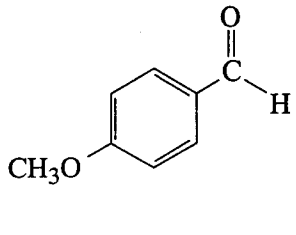
Benzalacetophenones (chalcones) are prepared by the reaction of a substituted benzaldehyde with acetophenone in aqueous base. Piperonaldehyde, *p*-anisaldehyde, and 3-nitrobenzaldehyde are used.



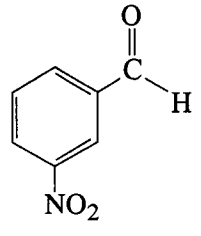
A benzaldehyde Acetophenone A benzalacetophenone *(trans)*



Piperonaldehyde



p-Anisaldehyde



3-Nitrobenzaldehyde

An optional molecular modeling exercise is provided in this experiment. We will examine the reactivity of the enolate ion of a ketone to see which atom, oxygen or carbon, is

more nucleophilic. The molecular modeling part of this experiment will help you to rationalize the experimental results of this experiment. It would be helpful to look at Experiment 17E, starting on page 187, in addition to the material given in this experiment.

REQUIRED READING

Review: Technique 4 Sections 4.3 and 4.7
Technique 5 Section 5.4

SPECIAL INSTRUCTIONS

Before beginning this experiment, select one of the substituted benzaldehydes. Alternatively, your instructor may assign a particular compound to you.

WASTE DISPOSAL

All filtrates should be poured into a waste container designated for nonhalogenated organic waste.

PROCEDURE

Running the Reaction. Choose one of three aldehydes for this experiment: piperonaldehyde (solid), 3-nitrobenzaldehyde (solid), or *p*-anisaldehyde (liquid). Place 0.150 g of piperonaldehyde (3,4-methylenedioxybenzaldehyde, $MW = 150.1$) or 0.151 g of 3-nitrobenzaldehyde ($MW = 151.1$) into a 5-mL conical vial. Alternatively, transfer 0.13 mL of *p*-anisaldehyde (4-methoxybenzaldehyde, $MW = 136.2$) to a *tared* conical vial and reweigh the vial to determine the weight of material transferred.

Add 0.12 mL of acetophenone ($MW = 120.2$, $d = 1.03$ g/mL) and 0.80 mL of 95% ethanol to the vial containing your choice of aldehyde. Place the conical vial into a 50-mL beaker. Stir the mixture with a microspatula to dissolve any solids present. You may need to warm the mixture on a hot plate to dissolve the solids. If this is necessary, then cool the solution to room temperature before proceeding with the next step.

Add 0.10 mL of sodium hydroxide solution[1] to the aldehyde/acetophenone mixture. Stir the mixture with your microspatula until it solidifies or until it becomes very cloudy (approximately 3 minutes).

Isolation of the Crude Product. Add 2 mL of ice water to the vial. If a solid is present at this point, stir the mixture with a spatula to break up the solid mass. If an oil is present, stir the mixture until the oil solidifies. Transfer the mixture to a small beaker with 3 mL of ice water. Stir the precipitate to break it up, and then collect the solid on a Hirsch funnel. Wash the product with cold water. Let the solid air-dry for about 30 minutes. Weigh the solid, and determine the percentage yield.

Crystallization of the Benzalacetophenone (Chalcone). Crystallize part of the chalcone using a Craig tube as follows:

3,4-methylenedioxychalcone (from piperonaldehyde). Crystallize a 0.040-g sample from about 0.5 mL of hot 95% ethanol; literature melting point is 122°C.

4-methoxychalcone (from p-anisaldehyde). Crystallize a 0.075-g sample from about 0.3 mL of hot 95% ethanol. Scratch the tube to induce crystallization while cooling; literature melting point is 74°C.

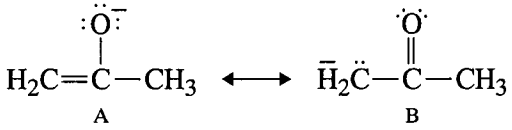
[1]The instructor should prepare this reagent in advance, in the ratio of 0.60 g of sodium hydroxide to 1 mL of water.

3-Nitrochalcone (from 3-nitrobenzaldehyde). Crystallize a 0.025-g sample from about 1 mL of hot methanol. Scratch the tube gently to induce crystallization while cooling; literature melting point is 146°C.

Laboratory Report. Determine the melting point of your purified product. At the option of the instructor, obtain the proton and/or carbon-13 NMR spectrum. Include a balanced equation for the reaction in your report. Submit the crude and purified samples to the instructor in labeled vials.

MOLECULAR MODELING (optional)

In this exercise we will examine the enolate ion of acetone and determine which atom, oxygen or carbon, is the more nucleophilic site. Two resonance structures can be drawn for the enolate ion of acetone, one with the negative charge on oxygen, structure **A,** and one with the negative charge on carbon, structure **B.**



The enolate ion is an **ambident nucleophile**—a nucleophile that has two possible nucleophilic sites. Resonance theory indicates that structure **A** should be the major contributing structure because the negative charge is better accommodated by oxygen, a more electronegative atom than carbon. However, the reactive site of this ion is carbon, not oxygen. Aldol condensations, brominations, and alkylations take place at carbon, not oxygen. In frontier molecular orbital terms (see the essay on page 174), the enolate ion is an electron pair donor, and we would expect the pair of electrons donated to be those in the highest occupied molecular orbital, the HOMO.

In the structure-building editor of your modeling program, build structure **A.** Be sure to delete an unfilled valence from oxygen and to place a −1 charge on the molecule. Request a geometry optimization at the AM1 semiempirical level. Also request the HOMO surface and maps of the HOMO and the electrostatic potential onto the electron density surface. Submit your selections for computation. Plot the HOMO on the screen. Where are the biggest lobes of the HOMO, on carbon or on oxygen? Now map the HOMO onto the electron density surface. The "hot spot," the place where the HOMO has the highest density at the point where it intersects the surface, will be bright blue. What do you conclude from this mapping? Finally, map the electrostatic potential onto the electron density. This shows the electron distribution in the molecule. Where is the overall electron density highest, on oxygen or on carbon?

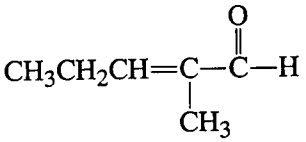
Finally, build structure **B** and calculate the same surfaces as requested for structure **A.** Do you obtain the same surfaces as for structure **A,** or are they different? What do you conclude? Include your results, along with your conclusions, in your report on this experiment.

QUESTIONS

1. Give a mechanism for the preparation of the appropriate benzalacetophenone using the aldehyde and ketone that you selected in this experiment.
2. Draw the structure of the *cis* and *trans* isomers of the compound that you prepared. Why did you obtain the *trans* isomer?

3. Using proton NMR, how could you experimentally determine that you have the *trans* isomer rather than the *cis* one?

4. Provide the starting materials needed to prepare the following compounds:

(a) 

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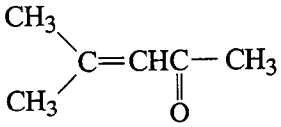
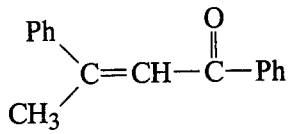
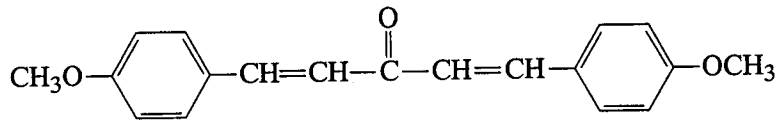
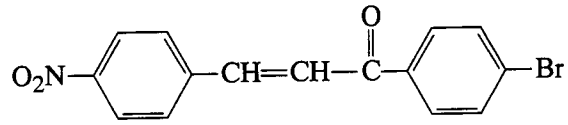
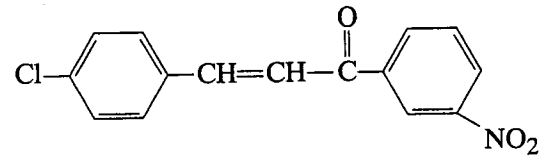
(b) 

(c) 

(d) 

(e) 

(f) 

5. Prepare the following compounds starting from benzaldehyde and the appropriate ketone. Provide reactions for preparing the ketones starting from aromatic hydrocarbon compounds (see Experiment 58).