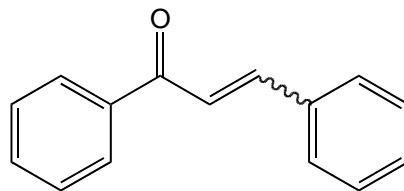


The Aldol Condensation

The aldol addition and condensation are among the most studied organic reactions. As carbon-carbon bond forming reactions, they are extremely important in synthesis. One application is in the preparation of chalcones (1,3-diaryl-2-propen-1-ones), many of which have antibacterial and antifungal activity.

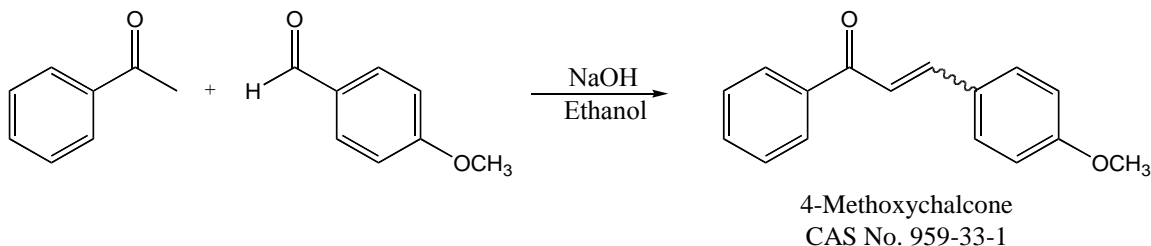


chalcone

Chalcone is a disubstituted alkene, which can exist as either the *cis* or *trans* isomer. The stereochemistry of a disubstituted alkene can usually be determined using $^1\text{H-NMR}$ by calculating the coupling constant (J) for one of the alkene hydrogens. Typically, *cis* alkenes have a J between 8 to 10 Hz, while *trans* alkenes have a J between 12 to 18 Hz. For a hydrogen that is split into a doublet, J can be calculated by taking the difference in the frequency of the two peaks (in ppm) and multiplying by the operating frequency of the NMR.

$$J \text{ (in Hz)} = [\delta(\text{peak 1}) - \delta(\text{peak 2})] \times (\text{operating frequency in MHz})$$

In this experiment, you will perform an aldol condensation of acetophenone with *p*-anisaldehyde to give 4-methoxychalcone. You will then analyze your substituted chalcone product using $^1\text{H-NMR}$ to determine the stereochemistry of the alkene.



Safety:

- 12M NaOH is very corrosive. **Handle with gloves!**

Required Reading:

Padiás:

Proton NMR Splitting (pp. 89 – 92)

Procedure:

CAUTION! 12M NaOH is very corrosive. Handle with gloves!

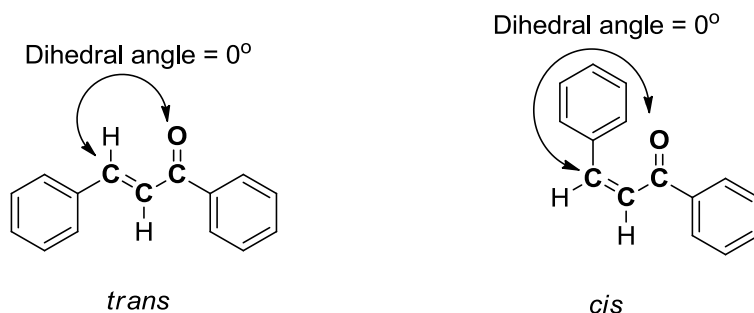
In a 5 mL conical vial with a spin vane, dissolve 136 mg of *p*-anisaldehyde in 1 mL of ethanol. Add 0.12 mL of acetophenone using a syringe and stir the mixture. Add 0.1 mL of 12M NaOH and stir the reaction for 5 minutes. ***IMPORTANT: Do not proceed to the next step unless you have a definite precipitate in your reaction vial. If you have no precipitate after 10 min of stirring, add another 0.1 mL of 12M NaOH.*** Transfer the contents of the vial into a small beaker containing 3 mL of ice water, rinsing the vial with an additional 3 mL of ice water. Collect the solid via vacuum filtration and wash with a small amount of ice water. Allow the vacuum to pull for at least 15 minutes to dry the product. In a 3-mL conical vial, recrystallize the product from about 1 mL of ethanol, and collect the solid via vacuum filtration. Determine the weight and melting point of your product, and obtain a ¹H-NMR spectrum.


Lab Report:

Calculate the percent yield (show the calculation) of your product. Compare your melting point to the literature value. Determine the coupling constant for one of the alkene hydrogen doublets of your ¹H-NMR (the most easily interpretable alkene resonance occurs at 7.8 ppm and Winthrop has a 300MHz NMR). Use the coupling constant to determine the stereochemistry of the alkene. Is this the result you expected?

Questions:

1. This particular experiment gives the condensation product, to the complete exclusion of the addition product. Explain why.
2. Find and draw the structure of *trans*-cinnamaldehyde, which is responsible for the characteristic fragrance and flavor of cinnamon. What is the coupling constant for the hydrogen on carbon-3 if the two peaks of the doublet occur at 7.412 and 7.416 ppm on a 400 MHz NMR? Is this value consistent with the structure?
3. Using Spartan, build models of *cis* and *trans*-chalcone. Determine the difference in the energies of formation between the two isomers:
 - a) For the each isomer, set the C=C-C=O dihedral angle to 0°, so that the molecules are drawn in the following conformations:



- b) Minimize the energy using the  button
- c) Calculate equilibrium geometry at the ground state using the semi-empirical/AM1 method.
- d) When the calculation is completed, select “Display” “Properties” and use “Energy” (not “Energy(aq)”) as the energy of formation for each molecule).

Using this energy difference as an approximation of the ΔG° , calculate the *trans/cis* ratio at equilibrium at 25 °C.