Experiment 19 —

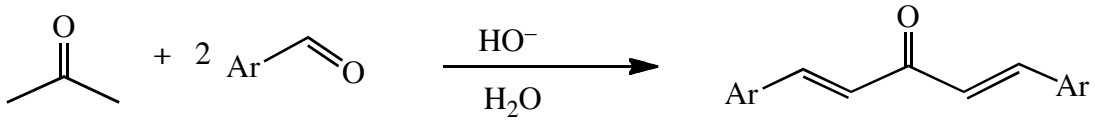
Aldol Condensation

Pre-lab preparation. (1) Write the *mechanism* of the base-catalyzed aldol condensation of acetone and a generalized aromatic aldehyde, Ar–CH=O to give the α,β-unsaturated product (i.e. the reaction at the top of the next page, but with a 1:1 ratio of ketone and aldehyde). Remember that dehydration in this case occurs under basic conditions, so it can't start with protonation of the hydroxyl group. Nor can it go via an E2 pathway. (2) Draw the structures of all the possible aldehyde and ketone reactants (*not* the 25 possible condensation products!). (3) The new CC double bonds of the condensation products are *E* rather than *Z*, as shown in the acetone example. Why? (4) What's the purpose of rinsing the crude product with dilute acetic acid, followed by ethanol? (5) What is the procedure for carrying out a single-solvent recrystallization? Write this out in detail.

The aldol condensation has historically been one of the favorite tools in the synthetic organic chemist's repertoire because of its versatility in forming new CC bonds. Since its discovery in the 1870s the aldol condensation has been use extensively in the synthesis of natural products and other complex molecules.

In a typical base-catalyzed aldol condensation an enolate ion attacks the carbonyl group of an aldehyde or ketone. This carbonyl *addition* produces a β-hydroxy carbonyl compound. In many cases the initially formed condensation product undergoes an "E1cB" dehydration to produce an α,β-unsaturated carbonyl compound as the final product. The dehydration is especially favorable if the new π-bond is conjugated at both ends.

In this lab, you will be doing a base-catalyzed 2:1 condensation of an aldehyde and a symmetrical ketone. Under your reaction conditions, the initial addition product will undergo dehydration to make the conjugated product. For example, the condensation of acetone and a generalized aromatic aldehyde would proceed as shown below.



Each group was to have been assigned a different aldehyde-ketone combination, but due to another accident in the stockroom, the bottles were mixed up. There's no time to analyze them, so we've just labelled them with code letters (ketones) and numbers (aldehydes). Each group will get a different letter-number combination. Do the condensation by following the general procedure below, make up an NMR sample, and when you get your spectrum you should be able to determine the identity of the aldehyde and ketone that you started with. Yes, you will get a 400-MHz ^{1}H NMR spectrum of *your very own product* this time!

We're fairly certain that the mystery ketones are acetone, cyclobutanone, cyclopentanone, cyclohexanone, and 4-methylcyclohexanone. The aldehydes are benzaldehyde, *p*-tolualdehyde, *p*-anisaldehyde, *trans*-cinnamaldehyde, and furfural. We'll put out a few of these for each lab section. We'll assign a code letter-number combination to each group during the pre-lab lecture.

Procedure. Combine *0.90 ml of aldehyde* (numbered unknown), *0.25 ml of ketone* (lettered unknown), 4 ml of 95% aq EtOH, and 3 ml of 2M aq NaOH. Stir the solution for 15 min (use a magnetic stir bar unless you need a work-out and want to do this by hand). If by this time solid precipitate has not started forming, or if precipitation is continuing slowly, heat the reaction mixture over a steam bath for another 10 - 15 min.

When precipitation appears to be complete, cool the mixture and isolate the solid. Rinse the product with about 5 ml of each of the following pre-chilled solvents: 95% EtOH, then 4% HOAc in EtOH, then 95% EtOH.

Now recrystallize your product. You'll need to find a suitable solvent or solvent mixture. You may want to try 95% aq EtOH and toluene (separately!) to start. Use about 20 mg of crude product and about 1/4 ml of solvent in a dispo test tube for each test. Remember, the point of a recrystallization is to purify the solid by getting it to go into solution, then come back out of solution in a way that creates clean, sparkling, beautiful crystals without all the dirt from the

reaction. If your product is very soluble in a solvent at room temp, is that a good recrystallization solvent? How about if it doesn't dissolve at room temp and doesn't dissolve upon heating? How about if it doesn't dissolve at room temp, but does dissolve upon heating? (If neither of these solvents works, rumor has it that the next one to try might be 9:1 EtOH/acetone.)

Once you've identified a viable solvent, recrystallize your entire batch of crude solid. Isolate and rinse the crystals in the usual way, press them between two pieces of filter paper to draw off most of the residual solvent, then put them on a watch glass and pop them into the oven (100°C) for 15 min to drive off the remaining traces of solvent.

Measure the mass of the purified product. The theoretical yield should be somewhere around 700 mg. Of course, you'll be able to determine your theoretical yield and % yield after you've determined the identity of your condensation product. Although we might benefit from running a TLC or measuring the mp, in the interest of expediency we're going to skip these and just get a ^{1}H NMR spectrum. The instructor or TA will help you make up an NMR sample. Label the tube with the initials of each group member.

Your report for this experiment will be completed outside of lab, after you get your NMR spectrum, and turned in at the beginning of the next lab period (the *last* regular lab period of the semester. boooooooo…). This should of course include the actual procedure you followed (e.g., volume(s) of solvent(s) you used for the crystallization, the appearance of the product, etc), as well as a discussion that includes a clear explanation of your structure determination based on the NMR. Also draw the aldehyde and ketone that you started with.

In your NMR spectrum you may see a small singlet at δ 7.26 for residual $CHCl_3$ in the $CDCl_3$ solvent, as well as a peak around δ 1.5 for water dissolved in the $CDCl_3$. There may be residual peaks for other things as well — Recrystallization solvent, perhaps? Unreacted starting material? Compounds from three labs ago that you forgot to clean out of the glassware? A good first step in analyzing an NMR spectrum is to mark all the signals that you can confidently assign to things like solvent and reactants. Then you can focus on the important signals.