Chem 221b

Problem Set 8, Chapter 22

Due: April 11, 2005

Enols and Enolates

The Acetoacetic Ester Condensation (Claisen Condensation)

The base-mediated condensation of esters to form β-ketoesters has had an interesting history. Although the reaction often bears the name of Ludwig Claisen (1853-1930), who explored the scope of this reaction (1887) and related ones, he did not discover it. In 1863, Geuther discovered that sodium reacts with ethyl acetate to liberate hydrogen and generate a new compound $C_6H_9NaO_3$. Acidification of the sodium salt afforded "ethyl diacetic acid". The sodium compound reacted with alkyl halides to form a series of alkyl ethers. Consequently, Geuther formulated ethyl diacetic acid as having the the enolic structure $CH_3CH(OH)=CHCO_2C_2H_5$.

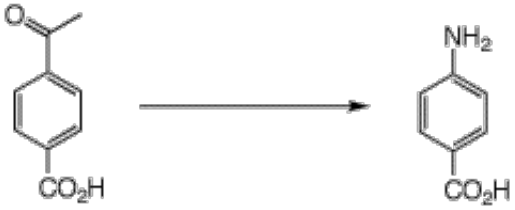
At about the same time, Frankland (of valence fame) and Duppa (1866) produced the same sodium salt by the same method. They proposed not only the formation of the the monosodium salt of ethyl acetate but also its disodium salt because they were able to isolate products of dialkylation on carbon. The formulation of Geuther's ethyl diacetic acid as a ketonic substance by Frankland led to acceptance of his views and a name change to acetoacetic ester. [You can see their paper here. Notice that they drew structures in the form of the then prevalent type theory. In this paper the Gay-Lussac method for determining the vapor density of a volatile compound was employed. A translation of Biot's description of the method and original diagrams of the apparatus are here.]

By 1877, Wislicenus demonstrated that there were no dianions in the process and that the dialkylation process was stepwise. In Claisen's 1887 paper he was able to show that sodium ethoxide and not sodium was the true condensing agent. Moreover, he claimed that the same sodio orthoester, $PhC(OCH_2Ph)(OCH_3)(ONa)$, was formed from benzyl benzoate and sodium methoxide or methyl benzoate and sodium benzylate. He proposed the following "mechanism", albeit from the "lasso school", for the formation of the sodium salt of acetoacetic ester.

Claisen found vindication in his mechanism because it explained why diethyl oxalate successfully condensed with ethyl butyrate but not with ethyl isobutyrate. Simply put, ethyl isobutyrate only had one hydrogen available and not the two minimally required by his mechanism. Dieckmann (1900) demonstrated that the problem was not that ethyl isobutyrate had only one hydrogen available but rather that the product formed with diethyl oxalate was formed reversibly. In subsequent papers, Claisen would expand the scope of these condensation reactions.

Nef (1897) suggested that Claisen's sodio orthoester could lose ethanol to form what we would call the enolate of ethyl acetate. This species could then react, in some unspecified way, with ethyl acetate to lead to the sodium salt of acetoacetic ester. On the other hand, Michael correctly pointed out that there was no evidence that Claisen's sodio orthoester even existed. Lapworth (1902) formulated the correct mechanism for the acetoacetic ester condensation. The controversy over whether acetoacetic ester existed in the keto or enol form led to the concept of tautomerism. In fact, acetoacetic acid exists in both forms. The tautomeric structures are readily seen in the ^{13}C NMR spectrum of acetoacetic ester. Knorr (1911) separated the enol and keto forms of acetoacetic ester. Source: J. B. Cohen, *Organic Chemistry* (1907)

1. Provide the conditions necessary to complete each of the following transformations. All reagents, solvents, and additional sources of carbon are available to you.

a) 

b) diethyl pimelate 

c) 

d) acetaldehyde 

e) diethyl adipate 

f) 

2. Capsaicin (**1**) is the hot, hot, hot in chili peppers. In spite of what the link claims, capsaicin is **not** an alkaloid.

a) Why?

A reasonable synthesis of capsaicin requires carboxylic acid **7**. Importantly, the double bond must be in the correct position in the chain and of the (*E*)-configuration, i.e., trans. Allylic alcohol **2** provides a convenient starting material.

b) How can **2** be prepared from isobutyraldehyde and acetylene?

One pathway to **7** is **2** --> **4** --> **5** --> **7**. The formation of bromide **4** occurs via an S_N1 reaction.

c) Illustrate the mechanism.

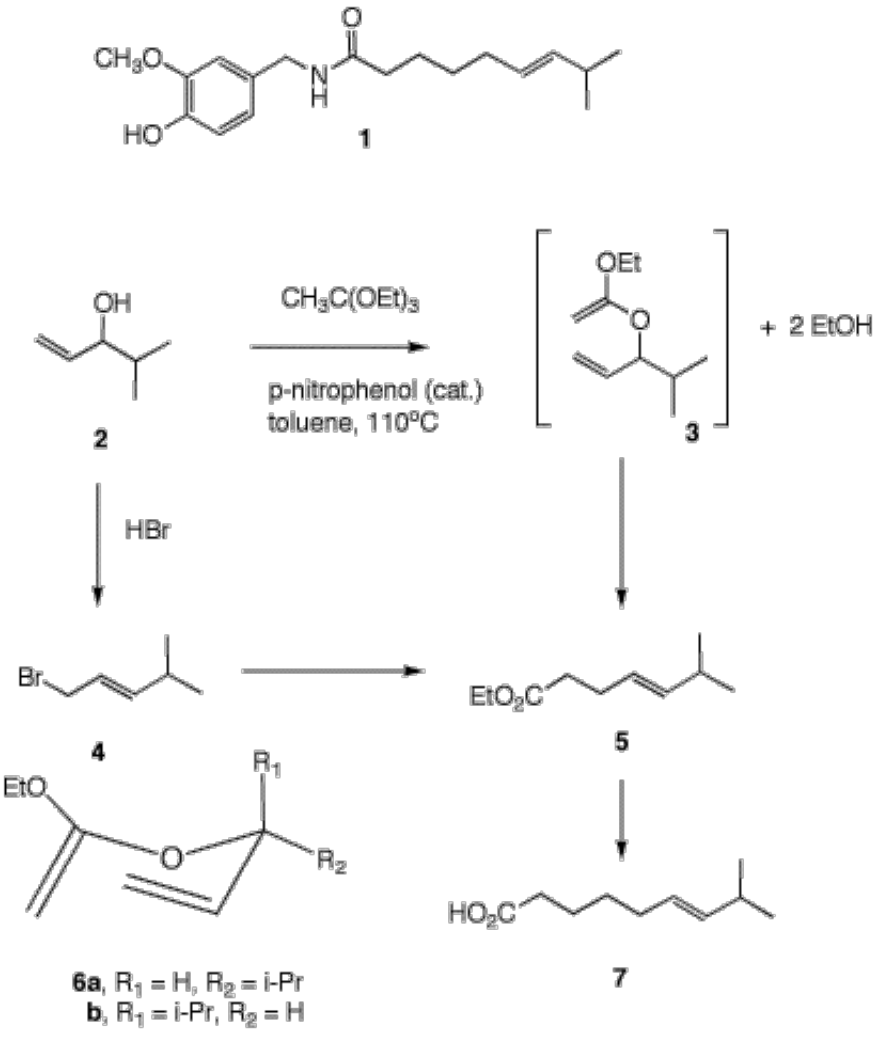
d) Why is little, if any, of the (*Z*)-bromide formed? [Hint: Compare the two allyl cations.]

e) Show how the malonic ester synthesis can be used for the conversion **4** --> **5**.

An alternative, **efficient** route from **2** --> **5** involves the reaction of allylic alcohol **2** with ethyl orthoformate in the presense of an acid catalyst in refluxing (boiling) toluene.

f) Would phenol be a weaker or stronger catalyst than p-nitrophenol? Explain and illustrate.

Intermediate **3** is formed along with ethanol. In large scale reactions, toluene is often distilled from the



reaction vessel?

g) Why?

h) Write an acid-catalyzed mechanism for the formation of **3** from **2**.

i) How do you know that formation of a cation from ethyl orthoacetate is more efficient than the formation of a cation from the allylic alcohol **2**? Draw them and explain. [Hint: Note that the reaction is efficient.]

Intermediate **3** forms ester **5** by rearrangement (Johnson-Claisen). A C-O single bond is broken as a C-C single bond is formed while two double bonds move.

j) Use three curved arrows on structure **3** to illustrate this process. [Note: One direction of arrow motion is preferable to the other. Explain.

The stereochemistry of this rearrangement, i.e., (*E*)- over (*Z*)-double bond, has been explained using conformational model **6**. The chairlike transition state resembles the ground state chair conformation of cyclohexane. Importantly, transition state **6** illustrates the importance of orbital overlap of the breaking, forming, and moving bonds while structure **3** does not.

k) Illustrate the overlap.

l) Of the transition states **6a** and **6b**, which one leads to ester **5**? Explain and illustrate.

m) What is the product of the other transition state?

n) Why is the transition state leading to the (*E*)-isomer preferred?

The malonic ester synthesis can be utilized again to homologate **5** --> **7** by the unit -CH_2CH_2-.

o) Illustrate the malonic ester synthesis.

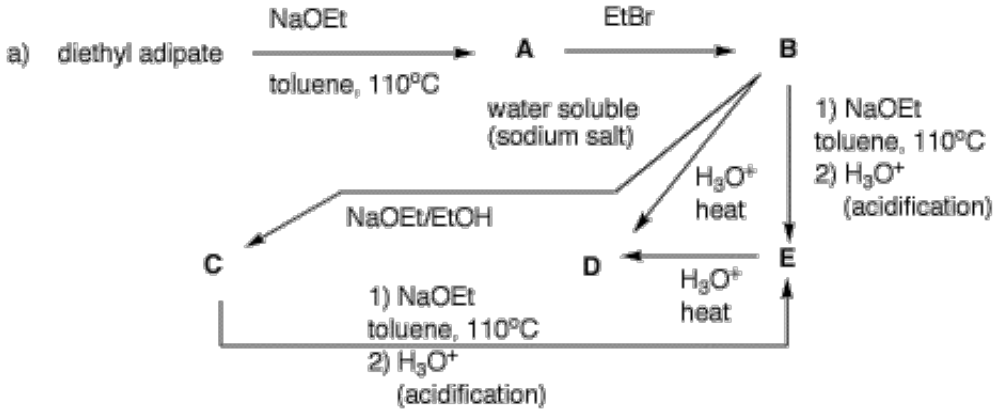
p) Prepare the benzylic amine from vanillin that is required for the synthesis of capsaicin.

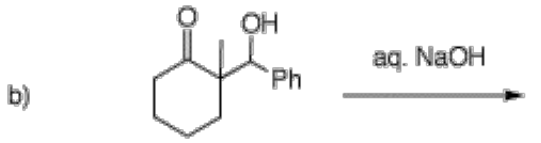
q) Synthesize capsaicin.

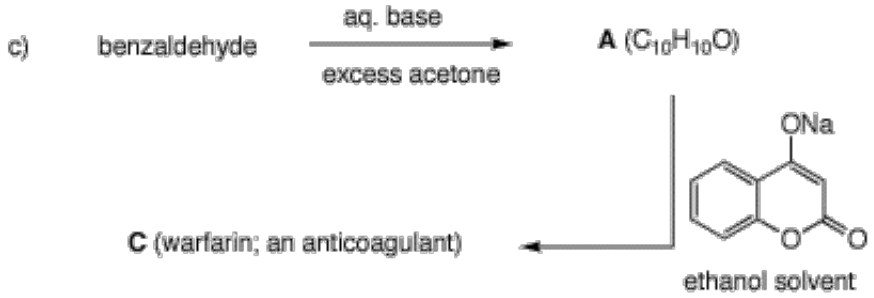
3. Ludwig Claisen not only developed the condensation reaction that bears his name but he also uncovered the original Claisen rearrangement. [Note: It is uncanny how eponomous reactions are always discovered or developed by the person with the same name. How come J. Doe didn't discover

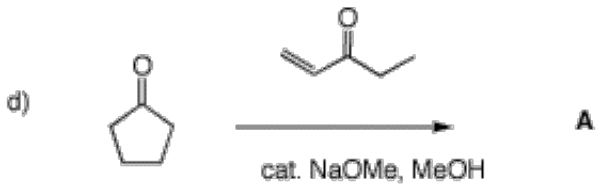
the Claisen rearrangement?] While investigating the reaction of the anion of acetoacetic ester with allyl bromide, he isolated two compounds of the same formula, $C_9H_{14}O_3$. Compound **A** was unaffected upon distillation and was found to be soluble in dilute aqueous NaOH. Compound **B** was insoluble in dilute NaOH; it rearranged to compound **A** upon distillation [i.e.; heat]. Aqueous acid hydrolysis of **A** afforded unsaturated ketone **C**, $C_6H_{10}O$. What are the structures **A-C**? Explain and illustrate their formation.

4. Provide the structures and mechanisms for formation of the lettered compounds in each of the problems below.





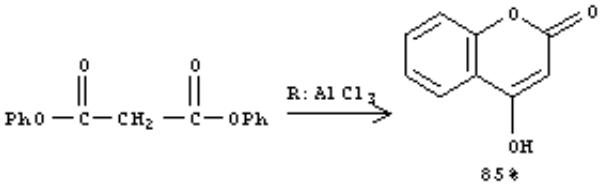




5. A search of the chemical literature revealed that the conjugate "acid" of the sodium salt in problem 4c

above can be prepared as shown on the right.

a) Show how the reactant can be prepared from malonic acid and phenol.
b) Provide a mechanism for the formation of the lactone. [Note: Although we have not seen examples of F-C reactions with esters, phenyl esters are more reactive than alkyl esters. Notice that the reaction is being conducted at temperatures well above what is necessary for standard acyl chloride F-C reactions.]
c) Draw a tautomeric form of the lactone.
d) Is aqueous NaOH suitable for forming the sodium salt of the lactone? Explain.



85%

NOTE: Classification: Cyclisation; FRIEDEL-CRAFTS ACYLATION; Isomerisation; Heterocycle formation; # Conditions: AlCl3; 180-185 deg 25mn, Reactants: 1, Reagents: 1, Steps: 1, Stages: 1