Synthesis of an $\alpha,\beta$-Unsaturated Carboxylic Acid Derivative

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$\alpha,\beta$-Unsaturated carboxylic acids and their derivatives are widely distributed in nature. Some examples are presented in Figure 1.

Cynarin: An active principle found in artichoke

Benzyl Cinnamate: Found in Peru balsam. Is used in the perfume industry and as an artificial flavor. It is characterized by a sweet, balsamic fragrance.

Queen Substance: Produced in the mandibular gland of queen honey bees. Used to attract male bees for the purpose of mating. Also inhibits ovary development in worker bees.

Ferulic Acid

Oryzanol A: Found in rice bran and corn and barley oils. Has been examined for antiulcer effects.

Butyl tiglate: Found in the oil of Roman camomile.

Crocutin: One of the yellow red pigments isolated from saffron.

Figure 1. Some naturally occurring $\alpha,\beta$-unsaturated carboxylic acid derivatives.

One of the most versatile methods of synthesizing these compounds involves
constructing the double bond by condensing an enolate with an aldehyde or ketone (eq. 1).

\[
\begin{array}{c}
\text{R}^2\text{C}^\equiv\text{O}^\text{R}^1
\end{array} \quad \rightleftharpoons \quad \begin{array}{c}
\text{R}^2\text{C}^\equiv\text{O}^\text{R}^1 + \text{H}^\text{R}^1\text{C}^\text{O}^\text{X}
\end{array}
\]

(1)

\( X = \text{OR, NR}_2 \)

**Retrosynthesis of an \( \alpha,\beta \)-unsaturated carboxylic acid**

In general, the desired enolate cannot be generated directly from a carboxylic acid because of the presence of the more acidic carboxy proton (eq. 2).

\[
\begin{array}{c}
\text{H}^\text{R}^1\text{C}^\text{O} + \mathbb{B} \quad \rightarrow \quad \text{H}^\text{R}^1\text{C}^\text{O}^\text{2-} + \mathbb{B} \quad \rightarrow \quad \text{H}^\text{R}^1\text{C}^\text{O}^\text{2-}
\end{array}
\]

(2)

dianions are high energy intermediates

Therefore, carboxylic acid derivatives such as esters and amides are typically used. An acid anhydride can also be used as shown in equation 3.

\[
\begin{array}{c}
\text{Ph}^\text{H} + \text{Ac}_2\text{O} \quad \xrightarrow{\text{NaOAc}} \quad \text{H}_2\text{O} \quad \xrightarrow{>100^\circ\text{C}} \quad \text{Ph}^\text{H}\text{C}^\equiv\text{O}\text{OH}
\end{array}
\]

(3)

**A Perkin Reaction**

This reaction is known as the Perkin reaction after William Henry Perkin, who first reported on this procedure in 1868. Under Perkin conditions, only non-enolizable aldehydes and ketones can be used.

The inconvenience of always having to start with a carboxylic acid derivative can sometimes be circumvented by performing the reaction in the presence of a simple anhydride such as acetic anhydride (\( \text{Ac}_2\text{O} \)) and a base such as sodium acetate (\( \text{NaOAc} \)) or a tertiary amine. Under these conditions, an equilibrium is established between the symmetrical and unsymmetrical anhydride (eq.4).

\[
\begin{array}{c}
\text{R}^1\text{C}^\equiv\text{O}^\text{H} + \text{Ac}_2\text{O} \quad \rightleftharpoons \quad \text{R}^1\text{C}^\equiv\text{O}\text{C}^\equiv\text{O} + \text{HO}_2\text{C}
\end{array}
\]

(4)
In addition to protecting the carboxy group, the acyl group acts as an intramolecular trap for the alkoxide formed in the ensuing aldol type reaction (Scheme 1). The resulting acetoxyl group is now an excellent leaving group which aids with formation of the double bond.

![Chemical reaction diagram]

**Scheme 1**

Generating mixed anhydrides in situ and using these in the synthesis of $\alpha,\beta$-unsaturated carboxylic acids is an important extension of the Perkin reaction. Two examples of variations are shown in equations 5 and 6.

\[
\text{PhCH}_{2}\text{COH} + \text{PhH} + \text{COCHO} \xrightarrow{\text{NET}_3, \text{reflux}} \text{PhCH} = \text{CHCOH}^{\text{Ph}} \quad (5) \quad 83\%
\]

In equation 5 notice that the major product arises from enolization at the more acidic of
the two types of enolizable hydrogens found in the mixed anhydride. This is what one would expect under the thermodynamic conditions employed in these reactions.

\[
\text{Ac}_2\text{O}, \text{NaOAc} \quad \text{reflux} \quad \text{H}_2\text{O} \quad \text{reflux}
\]

\[
\begin{align*}
\text{N-acetylglycine} & + \text{H} & & \text{H} & & \text{H} \\
\text{Ar} & = \text{aromatic} & & \text{ring} & & \text{ring} \\
\text{H} & & \text{Ac}_2\text{O}, \text{NaOAc} & & \text{Ac}_2\text{O}, \text{NaOAc}, \text{ArCHO} & & \text{azlactone}
\end{align*}
\]

In the example shown in equation 6, the intermediate mixed anhydride would have three types of acidic hydrogens. Deprotonation of the amide N-H, the most acidic of the three, leads to a cyclic ester known as an azlactone. At this point in the reaction, only one pair of enolizable hydrogens remains. Enolization followed by reaction with the aldehyde leads to an alkoxide intermediate which is then trapped by acetic anhydride. Further enolization leads to the new double bond. Hydrolytic ring opening of these cyclic esters followed by catalytic hydrogenation provides an important synthetic route to natural and unnatural amino acids.

In this experiment you will be performing a modified Perkin reaction using the starting materials shown in equation 7. Your goal is to isolate and purify a product from this reaction and then determine the structure of this product from the spectral data supplied by your teaching assistant.

**Prelab Exercises:**

- Based on the above information, write a mechanism for the synthesis of the product shown in equation 6.
- Propose two reasonable products from the reaction outlined in equation 7.

\[
\text{Ph} \quad \text{H} \quad \text{H} \quad \text{NaOAc} \quad 100^\circ\text{C}
\]

**Prelab Checklist:** Include the structures and all relevant physical constants for the starting materials and solvents used in this reaction. Be sure to have the prelab exercises completed before coming to your discussion section.
Experimental Procedure

Attach a gas trap to the condenser as shown in the appendix.

Weigh approximately 1 mmol of benzaldehyde directly into a 5-mL long-neck round-bottom flask. Add an equimolar amount of 3-benzoylpropanoic acid and of sodium acetate. Introduce a stir bar and then stopper the flask with a cork. Take the reaction flask to the fume hood and add 0.5 mL of acetic anhydride using a syringe. Be sure to re-stopper the flask, and then take this mixture back to the lab bench and attach it to the gas trap using the connecting adaptor.

Chemical Safety Note: Acetic anhydride has a strong "acetic acid" odor and can be a lachrymator which is a substance whose vapors can make your eyes water. It is also an irritant and contact with skin should be avoided. If some gets on your skin, flush the effected area with water and have a colleague notify your teaching assistant.

While stirring, heat the reaction mixture using a sand bath and maintain the bath temperature between 95-105 °C for 1 hour.

Technique Tip: To help maintain the bath temperature, it is convenient to turn the control off as the desired temperature is being approached. When the temperature starts to decrease, turn the control back on until the temperature begins to rise again. A low setting on the control should allow you to reach the temperatures necessary for this reaction.

After 1 hour, remove the flask from the sand bath and let the mixture cool to room temperature. Add 1 mL of 80% ethanol to the mixture and stir thoroughly for 1 minute. Filter the contents of the flask through a Hirsch funnel and wash the solid once with 1 mL of ice-cold 80% ethanol and three times with 1 ml portions of hot water. Pull a vacuum on the filter flask to help dry the crude solid. Clean the Hirsch funnel for the next step.

Technique Tip: The hot water is most easily obtained by placing 10 mL of water in a 50 mL beaker and microwaving at 1000 W for 25 seconds. Be careful when removing the beaker from the microwave, it may be very hot!

Recrystallize the solid in 1-2 mL of absolute ethanol. Collect the final product on the Hirsch funnel and wash with 0.5 mL of ice-cold absolute ethanol. Determine the final weight and melting point of the product.

Supply this information to your TA who will then provide you with spectral data for 3-benzoylpropanoic acid and your product.

Clean-up: Place your product in the beaker labeled "Product for Recycling". Place the original filtrate and all washings in the container labeled "Non-Halogenated/Aqueous Organic Waste". Contaminated Pasteur pipettes, melting point capillaries, and used weigh paper should be disposed of in the white buckets labeled "Chemically Contaminated Material Only". Clogged syringe needles must be placed in the red container labeled "Syringe Needle Disposal".
Discussion

Interpret all spectra to the best of your ability. In your discussion include answers to the following questions.

1. Propose a mechanism for the formation of the product you isolated.

2. In the Perkin reaction shown in equation 3, a small amount of styrene, PhCH=CH₂ is formed. Propose a mechanism for the formation of this minor product. **Hint:** Examine the mechanism outlined in Scheme 1 and determine if there is some point where the reaction could partition.

3. Propose a mechanism for the reaction shown in equation 8. Note that the product has one ester group and one carboxylate function. Your mechanism needs to account for this finding. This reaction is known as the Stobbe condensation.

\[
\text{EtO} \quad \text{CO} \quad \text{OEt} \quad + \quad \text{Ph} \quad \text{CO} \quad \text{Ph} \quad \xrightarrow{\text{Me₃COK, Me₃COH (t-butanol) reflux}} \quad \text{Ph} \quad \text{C}=\text{C} \quad \text{Ph} \quad \text{OEt} \quad \text{(8)}
\]

4. Propose a synthesis of one of the a,b-unsaturated carboxylic acids shown in Figure 1. The only requirement is that the a,b-unsaturation be generated via enolate chemistry. Be sure to use appropriate protecting groups where necessary.