Synthesis of 3-Carbethoxycoumarin, A Heterocyclic Compound


Introduction:
Cyclic organic compounds can be classified as either "carbocyclic", in which the ring systems contain all carbons, or "heterocyclic", in which the ring systems contain other ("hetero") atoms such as nitrogen, oxygen, sulfur, etc. in addition to carbon atoms. Many heterocycles have important pharmaceutical properties. The structures of two biologically important heterocycles are shown below.

A subclass of heterocyclic compounds are fused-ring heterocycles. These compounds contain a benzene ring fused to a heterocyclic ring. Some examples are shown below.

In this experiment, you will be synthesizing a fused-ring heterocycle, 3-carbethoxycoumarin, which is an example of a class of heterocyclic compounds called coumarins.

A very important coumarin compound is Warfarin, a powerful anticoagulant. In low doses, it is used as a blood thinner in humans with high blood pressure. At higher concentrations, Warfarin is used as a rodenticide. It is applied to corn or other grains to keep rats or mice away from the crops since the higher concentrations of ingested Warfarin cause the rodents to bleed internally. With rapid bodily fluid loss, the rodents move out of grain storage areas into the outdoors in search of water. Thus, they are less likely to die within the crop area. The “Warf” in Warfarin stands for Wisconsin Alumni Research Fund, which makes a bundle from the patent it holds on this compound.
The synthesis of the 3-carbethoxycoumarin heterocycle involves a transesterification followed by an aldol condensation reaction starting with salicylaldehyde and diethyl malonate. Esterification and aldol condensation reactions are described in your lecture textbook (e.g. McMurry).

The reaction calls for salicylaldehyde, diethyl malonate, piperidine and glacial acetic acid, which are all mixed in ethanol. The first step of this transformation to the product, 3-carbethoxycoumarin, is a transesterification. A transesterification is starting with one ester to make another ester (see scheme below). An aldol condensation involves the generation of an enolate, which serves as the nucleophile, to react with an aldehyde, the electrophile. A new carbon-carbon bond forms. A subsequent condensation leads to the final unsaturated ester product, 3-carbethoxycoumarin.

Scheme I. Transesterification and aldol condensation to synthesize 3-carbethoxycoumarin.

Base-catalyzed Transesterification:

![Base-catalyzed Transesterification Reaction](image)

Aldol Condensation:

![Aldol Condensation Reaction](image)

Prelab Exercises

1.) Why are the hydrogens on the alpha carbon of diethyl malonate acidic enough to be removed by the base piperidine? Consider the pKa of diethyl malonate and the conjugate base of diethyl malonate; draw all pertinent resonance structures.

2) What advantage(s) could there be for using piperidine rather than hydroxide as a base?

Cautions:

Piperidine is toxic, salicylaldehyde is a toxic irritant, and glacial acetic acid is a corrosive agent. Be careful when handling these chemicals.

Synthesis:
Place 1.1 mL salicylaldehyde and 1.7 mL diethyl malonate into a 25-mL round-bottom flask with a 1/2-inch magnetic stir bar. Add 4 mL ethanol, 20 drops piperidine, and 4 drops of glacial acetic acid. Connect the flask to a water condenser. Fill a plastic drying tube with Drierite (Common Shelf), using a glass wool plug at each end to hold the pellets in. Connect this drying tube to the top of the condenser using the glass/red rubber thermometer adapter from your kit. Reflux the solution for 2 hours using a heating mantle (no sand) and continuous stirring. Cool to room temperature slowly.

**Isolation and Purification:**

Once the solution has cooled slowly to room temperature, then cool in an ice bath. Stir the solution for 5 minutes in the ice bath after crystals first appear. Weigh two pieces of filter paper and note the weight in your notebook. Vacuum filter off the solid using a Büchner funnel with the two pieces of filter paper in it. Rinse out residual crystal from the flask with cold ethanol and add to solid in the funnel. Allow the crystals to dry until the next laboratory period.

Weigh the dry crystals on the filter paper and determine the percent yield and the melting point of the product. If the melting point is low, recrystallize from 95% ethanol.

**Analysis**

You may be instructed to analyze your final product by IR or NMR. Analyze your sample according to your Assignment sheet and prepare it as per the instructions on Sample Preparation in Lab Guide (inside back cover).

**Cleaning Up**

Dispose of all filtrates down the drain with lots of water.

**Final Report**

Be sure to include the mechanisms for the transesterification and aldol condensation reactions in your final report. Include the spectrum from the analysis method assigned with the structure and interpretation written directly on it.

**PostLab Questions**

1. What is the purpose of using the water condenser and drying tube?

2. A solution of 3-carbethoxycoumarin was refluxed in a solution of NaOH and water. What product(s) would you expect to form from the reaction?