Expmt # 818: One-Pot Synthesis of 7-hydroxy-3-carboxycoumarin in Water


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Introduction:

Coumarin and its derivatives are widespread in nature. The relevance and importance of these substances are found in pharmaceuticals, cosmetics, and nutrition. Their chemistry has been researched in great detail and many natural and non-natural coumarins have been synthesized. The reaction of 2,4-dihydroxybenzaldehyde and malononitrile in the presence of sodium bicarbonate and hydrochloric acid, by way of the knoevenagel, pinner, and hydrolysis reactions produce 7-hydroxy-3-carboxycoumarin.

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\begin{align*}
\text{CHO} & \quad \text{CN} \\
\text{HO} & \quad \text{CN} \\
\text{HO} & \quad \text{COOH}
\end{align*}
\]

Cautions:

This particular reaction should be carried out under a well-ventilated hood, gloves and safety glasses should be worn at all times. Concentrated HCl may cause burns, and should be avoided from contact with the skin and eyes. 2,4-dihydroxybenzaldehyde, malononitrile, 7-hydroxy-3-carboxycoumarin and all the intermediates are skin, eye, and respiratory irritants.

Synthesis:

Under a well ventilated hood, place 1.38 g of finely powdered 2,4-dihydroxybenzaldehyde and 0.80 g of malononitrile into a 100 mL 2 neck round bottom
flask with a magnetic stirring bar. To this, add 50 mL of 0.05 M aqueous sodium bicarbonate solution. Vigorously stir this solution for 1.5 hours at room temperature under a reflux condenser.

After 1.5 hours, add 1.25 mL of concentrated hydrochloric acid and continue to stir this solution. Place this solution on a sand bath and heat at 90 °C for 1 hour with continuous stirring. After this 1 hour, cool the reaction to room temperature, 25 °C.

After cooling, add 20 mL of 1M aqueous sodium bicarbonate solution and place on a sand bath to be stirred at 90 °C for 2 hours. After 2 hours, cool this solution to room temperature. From this, the sodium salt of 7-hydroxy-3-carboxycoumarin is soluble in water.

This final solution obtained is a basic solution. Test with pH paper to ensure that this mixture is basic. Once confirmed, this basic mixture is to be acidified. Once cooled to room temperature, add concentrated hydrochloric acid dropwise to the solution while stirring at room temperature. Test the acidity of the solution after every drop or two until the pH of the solution reaches approximately 2 (red on litmus paper). Once the solution is acidified refrigerate it at 0-5 °C for at least one hour.

**Isolation and Purification:**

After refrigeration, a precipitated solid product forms as a dark orange color. Filter off the precipitated 7-hydroxy-3-carboxycoumarin from the aqueous medium by vacuum filtration using a Buchner funnel. Place the filtered product on a tared watch glass and let it dry in a well ventilated hood overnight.

Place the crude product in a 25 mL Erlenmeyer flask, and dissolve in a solution of 16 mL of hot distilled water, and 4 mL of hot acetic acid. Recrystallize the crude product
on a sand bath. After all the crude product goes into solution, allow the mixture to cool at room temperature and further cool in an ice bath. Filter off the solution by vacuum filtration and scrape the remaining crystals onto a tared watch glass allowing them to dry overnight. Record the weight of the final product after it is completely dry. The observed melting point of the final product is 244-251 °C.

**Clean-up:**

The filtrates from the crystallization and the recrystallization should be placed in the non-halogenated waste container. Watch glasses containing traces of 7-hydroxy-3-carboxycoumarin should be flushed with water and placed in the non-halogenated waste container.

**Analysis:**

The product from this reaction can be analyzed by NMR and IR spectroscopy. For $^1$H NMR the product will not dissolve in CDCl$_3$ so DMSO-solution should be used instead. For solid IR spectroscopy use potassium bromide as a background.

**Final Report:**

In the final report, write the name, structure and label all important peaks on each spectra obtained. Give yields, observed melting points of crude and recrystallized product. Include any problems that occurred during the reaction and how those problems could have attributed to potential product loss. Include your observations as the reaction occurred.