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One-Pot Synthesis of 7-Hydroxy-3-carboxycoumarin in Water

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Developing cleaner, safer, and environmentally friendly chemical processes is an important goal for chemists in both academia and industry (1). It is no longer acceptable to make products without being concerned about environmental pollution. Several strategies have been developed based on the idea that it is not only important what is produced but also how it is produced. To remove organic solvents from chemical processes, many old reactions have been revised and carried out in water (2), under solventless conditions (3), in supercritical fluids (4), in ionic liquids (5), in microemulsions (6), under high pressure (7), and by ultrasound (8) and microwaves (9). One-pot multicomponent processes¹ and one-pot consecutive processes² have been discovered that allow compounds to be prepared without having to isolate and purify the intermediates.

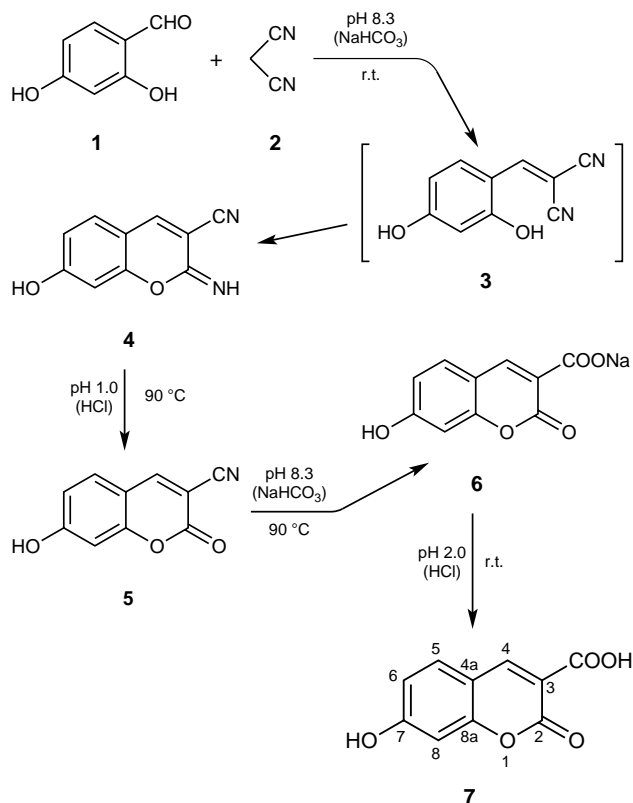
Water is a unique and extraordinary reaction medium and chemists have only recently begun to discover its benefits (2). In addition to practical advantages (abundant, cheap, nontoxic, nonflammable, nonexplosive), the aqueous medium is more convenient than organic solvents because (i) it can avoid protection of functional groups, such as OH and COOH, (ii) water-soluble compounds can be used directly without derivatization, (iii) the high heat capacity of water allows the reaction temperature to be easily controlled, and (iv) mineral salts, surfactants, and cyclodextrins can be used as additives. Two other important advantages of using water in organic synthesis are the possibility of controlling the pH of the reaction medium and isolating solid hydrophobic products by decanting or by filtering thereby avoiding the use of any organic solvent. Many Lewis acids work well in aqueous medium and recently we discovered that even AlCl₃, SnCl₄, and TiCl₄, recommended for use under anhydrous conditions, are excellent catalysts in aqueous medium (10). Many of the organic reactions carried out in aqueous media occur quickly, with high selectivity, and with excellent yield. Reactions previously thought impossible in water are today a reality.

Coumarin (2H-1-benzopyran-2-one) and its derivatives are widespread in nature (11). Owing to their importance in many fields of everyday life (12), such as pharmaceutical, cosmetic, perfume, and nutrition, their chemistry has been widely investigated and many natural and nonnatural coumarins have been synthesized. 3-Carboxycoumarins are a prominent target for study in the field of coumarins because the carboxylic acid group allows new functionalities to be easily prepared by introducing units of biological interest to increase the chemical activity of the compound, for example, units of cephalosporin (13), triazole (14), thiadiazine (14), thiadiazole (14), penicillin (15), and isourea (16). 3-Carboxycoumarins were recently prepared following the green

chemistry approach (17–19). The conjugative position of the hydroxy group in 7-hydroxy-3-carboxycoumarin, 7, facilitates the opening reaction of the lactone ring of this benzopyran system in the presence of bases, which allows glycosides to be prepared, aliphatic hydrocarbon chains to be introduced and oxocyclic rings to be built (20). The glycosylation of 7-hydroxy-4-methylcoumarin was recently proposed for an undergraduate organic chemistry laboratory class for fourth-year organic chemistry students (21).

Synthesis

This article describes the preparation of 7-hydroxy-3-carboxycoumarin, 7, starting from 2,4-dihydroxybenzaldehyde, 1, and malononitrile, 2, by one-pot consecutive reactions, carried out exclusively in water under heterogeneous conditions. The experiment consists of four fundamental steps (Scheme 1): (i) Knoevenagel reaction (1 + 2 → 3, aldol-like



Scheme 1. Reaction pathway to synthesize 7-hydroxy-3-carboxycoumarin, 7.

condensation) and the Pinner reaction ($3 \rightarrow 4$); (ii) acid-catalyzed hydrolysis of the imino functionality ($4 \rightarrow 5$); (iii) basic hydrolysis of cyano group ($5 \rightarrow 6$); and (iv) acid-base equilibrium ($6 \rightarrow 7$). The Knoevenagel condensation and the Pinner reaction were carried out in aqueous NaHCO_3 solution at room temperature and were completed in 1.5 h, while the hydrolysis of iminocyanide **4** required heating at 90°C for 1 h under acidic conditions. At this stage, the pH of the reaction medium was again changed to hydrolyze the cyanolactone **5** (pH 8.3; 2 h; 90°C). Acidification of the final solution at room temperature produced a 98% pure 7-hydroxy-3-carboxycoumarin, **7**, with 85% overall yield obtained by simple filtration.

The process can be stopped after completion of the first two reactions ($1 + 2 \rightarrow 3$ and $3 \rightarrow 4$, 1.5 h) or after the hydrolysis of iminocyanide **4** ($4 \rightarrow 5$) allowing the intermediate **4** or **5**, respectively, to be isolated with high yield and purity (> 95%) by simple vacuum filtration. These can be suitable stopping points for two or three lab periods; in this case the aqueous reaction mixture must be stored at room temperature and the subsequent reactions carried out the next day.

The one-pot synthesis can be monitored by TLC (aluminum sheets 5-cm \times 10-cm, silica gel 60 F254, ethyl acetate as eluent) at the three fundamental steps (Knoevenagel–Pinner reactions; acid hydrolysis at 90°C ; basic hydrolysis at 90°C and final acidification) displaying the starting material **1**, the cyanoimine **4**, the cyanocoumarin **5**, and the carboxycoumarin **7**, respectively, that have very distinct R_f values. TLC analysis is a powerful analytical tool that allows students to monitor the progress of their reactions.

All chemicals are commercially available from Aldrich Chemical Co. and the experiment can be carried out with standard laboratory equipment. Detailed experimental procedures, TLC analysis, IR and NMR spectra and their interpretation are provided in the Supplemental Material.^W To our knowledge no analogous experimental procedure has appeared in this *Journal* and the use of coumarins in a lab-experiment is rare (11a, 22).

Hazards

The experiment does not present any particular hazards but standard precautions should be used. The experiment should be carried out in a ventilated hood and gloves and safety glasses should always be used. Concentrated solutions of HCl may cause burns and contact with skin and eyes should be avoided. 2,4-Dihydroxybenzaldehyde, **1**, malononitrile, **2**, and the reaction products **4**, **5**, **6**, and **7** are skin, eye, and respiratory tract irritants and are toxic if ingested.

Results and Discussion

This experiment is suitable for an undergraduate-level organic chemistry lab course. Performing this type of synthesis the students may begin to appreciate two advantages of using an aqueous medium in organic synthesis, that is, being able to perform several reactions in sequence simply by changing the pH and isolating the desired product by filtration without using any organic solvent.

The students are introduced to:

1. A one-pot, multistep chemical operation in which it is possible to separate the intermediates.
2. An organic synthesis carried out without using organic solvents.
3. Interpreting IR and NMR spectra.
4. Investigating various organic functionalities.

This experiment encourages students to think in terms of reaction mechanisms; several examples of nucleophilic additions can be mentioned by the lab instructor (aldol condensation, alcoholysis of nitriles, hydrolysis of imines, and hydrolysis of nitriles). The experiment is particularly interesting if these topics are presented beforehand in the organic lecture.

Students performed this one-pot experiment in 7–8 h of lab work and obtained yields up to 75%. When the experiment included isolating intermediates **4** and **5**, the lab work took 10–11 h and the overall yields of intermediates from the initial malononitrile-aldehyde reaction were ca. 95 and 90%, respectively. The class work (lab instructor's explanation and discussion) required 4 h and included the interpretation and discussion of IR and NMR spectra.

Students were expected to characterize their final product and the intermediate products by melting points, interpret the IR and NMR spectra, and discuss the work in class.

Acknowledgments

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^WSupplemental Material

Instructions for the students, notes for the instructor, and interpretation of the TLC plates and IR, ^1H and ^{13}C NMR spectra are available in this issue of *JCE Online*.

Notes

1. A multicomponent process is a one-pot multistep chemical operation involving more than two starting reagents that react under defined reaction conditions to give the desired product.
2. A consecutive process is a one-pot multistep chemical operation in which it is necessary to change the experimental conditions or add reagents in order to promote the second, third, etc. reactions (see Wender, P. A. *Chem. Rev.* 1996, 96, 1–600).

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The structures of a number of the molecules discussed in this article are available in fully manipulable Chime format as JCE Featured Molecules in JCE Online (see page 912).

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