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Convenient Microscale Synthesis of a Coumarin Laser Dye Analog

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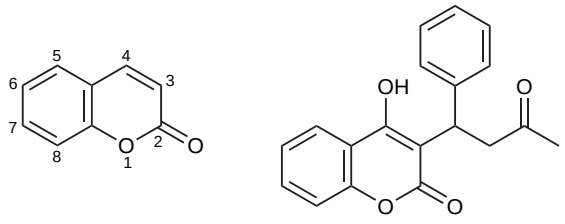
The undergraduate laboratory is a dynamic environment that is constantly adapting to satisfy the needs of both students and academia. Students require experiments that teach and reinforce essential concepts but also inspire them with chemistry that has memorable real-world applications *(1)*. Moreover, institutions are constantly devising methods to decrease waste, cost, and inherent hazards to students, while providing an enriching educational experience *(2)*.

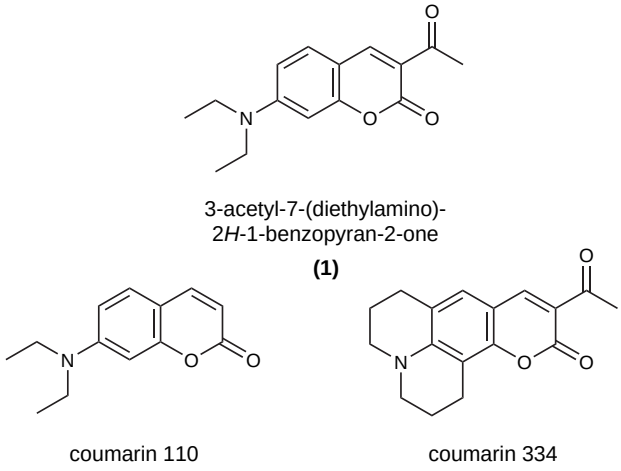
Coumarin (2*H*-1-benzopyran-2-one, Figure 1) and its derivatives constitute a fascinating class of organic substances that are of significance to everyday life. These versatile compounds are utilized industrially in areas such as cosmetics, food preservatives, insecticides, optical brightening agents, and fluorescent laser dyes *(3–7)*. Coumarins are also found abundantly in plants acting as growth regulators, fungistats, and bacteriostats *(4, 8)*. Many 4-hydroxycoumarin derivatives exhibit enzyme inhibition, antibiotic, and antithrombic activity and are therefore of medicinal interest *(6, 7, 9)*. The well-known coumarin derivative, warfarin (Figure 1), operates as an effective blood thinner and rat poison by antagonism of vitamin K 2,3-epoxide, preventing thrombin synthesis required for clotting *(10)*.



coumarin warfarin

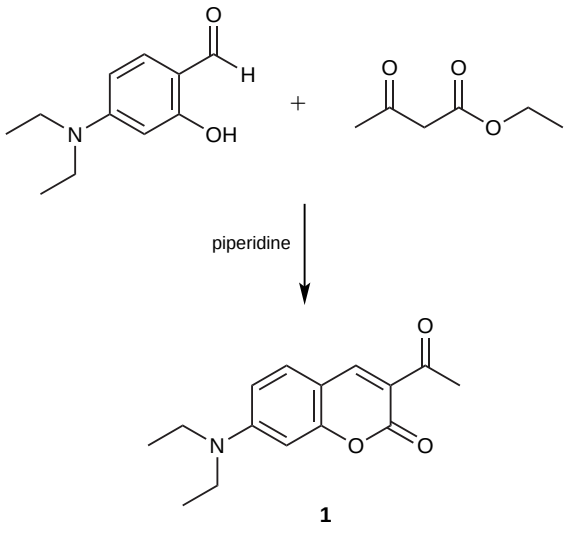
Figure 1. Structures of coumarin and warfarin.

Coumarins have been synthesized previously in this *Journal* by a Pechmann reaction *(11)*. Recently coumarins were also prepared via Knoevenagel condensations using solid base catalysis *(3)*, microwave irradiation *(4)*, and under aqueous conditions *(12)*. Other such reactions have been published in this *Journal (13–15)*. We wanted to develop an expeditious, mild Knoevenagel method to synthesize a fluorescent analog **1** of commercially available coumarin dyes (coumarins 110 and 334, Figure 2).[1] 7-(Diethylamino)coumarins are efficient laser dyes in the blue and green regions of the electromagnetic spectrum, with high quantum yields in most organic solvents *(16)*. Electron-donating dialkylamino groups enhance fluorescence while shifting the lasing region to longer wavelengths *(17)*. Synthesizing a laser dye analog quickly and efficiently under microscale conditions (Scheme I) would provide students ample time to assess the spectroscopic properties of **1**.



coumarin 110 coumarin 334

Figure 2. Structures of 3-acetyl-7-(diethylamino)-2*H*-1-benzopyran-2-one, coumarin 110, and coumarin 334.



Scheme I. Synthesis of 3-acetyl-7-(diethylamino)-2*H*-1-benzopyran-2-one, **1**.

Synthetic Overview

Ethyl acetoacetate (0.53 mL, 4.15 mmol) is added to 4-(diethylamino)salicylaldehyde (0.4 g, 2.07 mmol) in a 10-mL Erlenmeyer flask and a small stir bar introduced. Piperidine (3 drops) is added and the mixture stirred rapidly at room temperature until a viscous yellow–brown solution is formed (20–30 min). Absolute ethanol (5 mL) is then added causing a fine brown precipitate to form. The mixture is stirred and boiled gently until all the solid dissolves, then cooled to room temperature and in ice forming a bright yellow crystalline precipitate exhibiting blue fluorescence. This solid is collected using a Hirsch funnel and washed with cold absolute ethanol (1 × 5 mL). Recrystallization from absolute ethanol and thorough drying typically yields 0.24–0.32 g (45–60%):

mp 150–152 °C [lit. 151–153 °C *(18)*]

^{1}H NMR (200 MHz, $CDCl_3$, δ) : 1.23 (t, J = 7.2 Hz, 6H), 2.66 (s, 3H), 3.45 (q, J = 7.1 Hz, 4H), 6.45 (d, J_m = 2.2 Hz, 1H), 6.60 (dd, J_o = 9.0 Hz, J_m = 2.4 Hz, 1H), 7.38 (d, J_o = 8.9 Hz, 1H), 8.42 (s, 1H)

^{13}C NMR (400 MHz, $CDCl_3$, δ) : 12.5, 30.6, 45.2, 96.5, 108.1, 109.9, 116.1, 131.9, 147.8, 153.0, 158.7, 160.8, 195.6

IR ($CHCl_3$, cm^{-1}) : 1712.7 (C=O, lactone), 1663.9 (C=O, ketone)

Hazards

The experiment does not pose any significant hazards to students but standard undergraduate laboratory handling procedures should be followed. All work should be undertaken in a fumehood and gloves, laboratory coat, and goggles should be worn. All liquid reagents (absolute ethanol, ethyl acetoacetate, and piperidine) are flammable. Piperidine is a foul smelling liquid that is corrosive towards the eyes, skin, and respiratory system. 4-(Diethylamino)salicylaldehyde, ethyl acetoacetate, and 3-acetyl-7-(diethylamino)-2*H*-1-benzopyran-2-one are skin, eye, and respiratory irritants. All compounds encountered in this experiment are toxic if ingested. The coumarin product readily stains exposed skin.

Discussion

The synthesis and analysis of **1**, a fluorescent laser dye analog, stimulates students on many levels. An introduction to coumarin chemistry showcases an intriguing class of compounds with a diverse set of properties. The product synthesized is visually appealing and deviates from the common "white powders" that students are accustomed to making in an undergraduate laboratory.

The rapid, facile preparation allows plenty of opportunity for students to analyze the laser dye properties of **1**. Via UV–visible and fluorescence spectroscopy students can determine absorption and emission maxima for their product. This grants an opening to discuss spectroscopic concepts such as electronic energy states, spontaneous emission, and the relationship between absorption and fluorescence spectra *(19)*. Application of the Beer–Lambert law allows students to determine extinction coefficients for **1**. Students can then compare the properties of their laser dye analog with those of other coumarins and elucidate relationships between structure and spectroscopic properties *(16, 17)*.

The class can deduce and discuss the Knoevenagel condensation mechanism by sequentially incorporating well-known individual steps: deprotonation at the α-carbon in ethyl acetoacetate, aldol-like condensation, dehydration, and transesterification. To reinforce the mechanism students can be asked how they could generate alternative coumarins from various derivatives of ethyl acetate.

Compound **1** yields informative, clear ^{1}H NMR and IR spectra that can be used to confirm the product identity. The coumarin proton attached to C4 (atoms labeled in Figure 1) appears as a strongly deshielded singlet at δ 8.42 ppm. The proton NMR spectrum of 4-(diethylamino)salicylaldehyde can be distributed to students with the disappearance of aldehyde and phenol protons (δ 9.48 ppm and δ 11.63 ppm, respectively) indicative of reaction. The IR spectrum of **1** displays the absence of a hydroxyl absorption present in the phenol starting material and the appearance of two different carbonyl absorptions due to lactone and ketone functionalities.

Conclusion

The preparation and analysis of 3-acetyl-7-(diethylamino)-2*H*-1-benzopyran-2-one is appropriate within a mid-level undergraduate organic chemistry laboratory. The product can be synthesized, purified, and characterized within two hours with benefits of microscale reactivity being exemplified. Significantly, this procedure avoids lengthy heating under reflux or the use of a laboratory-grade microwave reactor *(4)*. The occasion to synthesize and assess spectroscopic characteristics of a laser dye analog promotes student enthusiasm and engenders a lasting impression of organic chemistry.

Acknowledgments

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[w]Supplemental Material

Instructions for the students, notes for the instructor, and spectroscopic information are available in this issue of *JCE Online*.

Note

1. Coumarins 110 and 334 are available from Sigma-Aldrich, catalog numbers 54,617-8 and 39,300-2, respectively.

Literature Cited

1. Stabile, R. G.; Dicks, A. P. *J. Chem. Educ.* **2003**, *80,* 313–315.
2. Li, E.; Barnett, S. M.; Ray, B. *J. Chem. Educ.* **2003**, *80,* 45–49.

3. Fringuelli, F.; Piermatti, O.; Pizzo, F. *J. Chem. Educ.* **2004,** *81,* 874–876.
4. (a) Bogdal, D. *J. Chem. Res. (S)* **1998,** 468–469. (b) Schoffstall, A. M.; Gaddis, B. A.; Druelinger, M. L. In *Microscale and Miniscale Organic Laboratory Experiments,* 2nd ed.; McGraw-Hill: New York, 2004; pp 441–445.
5. Sugino, T.; Tanaka, K. *Chem. Lett.* **2001,** 110–111.
6. Kumar, S.; Rao, V. C.; Rastogi, R. C. *Spectrochim. Acta*. **2001,** *57A,* 41–47.
7. Traven, V. F.; Vorobjeva, L. I.; Chibisova, T. A.; Carberry, E. A.; Beyer, N. J. *Can. J. Chem*. **1997,** *75,* 365–376.
8. Murray, R. D. H.; Méndez, J.; Brown, S. A. *The Natural Coumarins: Occurrence, Chemistry and Biochemistry;* Wiley: New York, 1982.
9. Traven, V. F.; Negrebetsky, V. V.; Vorobjeva, L. I.; Carberry, E. A. *Can. J. Chem*. **1997,** *75,* 377–383.
10. (a) O'Reilly, R. A.; Aggeler, P. M.; Leong, L. S. *J. Clin. Invest.* **1963**, *42*, 1542–1551. (b) Gringauz, A. In *Introduction to Medicinal Chemistry: How Drugs Act and Why;* Wiley: New York, 1997; pp 501–507.
11. Holden, M. S.; Crouch, R. D. *J. Chem. Educ.* **1998,** *75,* 1631.
12. Ramani, A.; Chanda, B. M.; Velu, S.; Sivasanker, S. *Green Chem.* **1999,** *1,* 163–165.
13. Rowland, A. T. *J. Chem. Educ.* **1995,** *72,* 548–549.
14. Kolb, K. E.; Field, K. W.; Schatz, P. F. *J. Chem. Educ*. **1990,** *67,* A304.
15. Kulp, S. S. *J. Chem. Educ*. **1988,** *65,* 742.
16. Giri, R.; Rathi, S. S.; Machwe, M. K.; Murti, V. V. S. *Spectrochim. Acta*. **1988,** *44A,* 805–807.
17. Reynolds, G. A.; Drexhage, K. H. *Opt. Commun.* **1975,** *13,* 222–225.
18. Czerney, P.; Hartmann, H. *J. Prakt. Chem*. **1982,** *324* (1), 21–28.
19. Hair, S. R. *J. Chem. Educ*. **1996,** *73,* A7–A9.