

Reaction of Dimedone and Benzaldehyde: A Discovery-Based Lab for Second-Semester Organic Chemistry

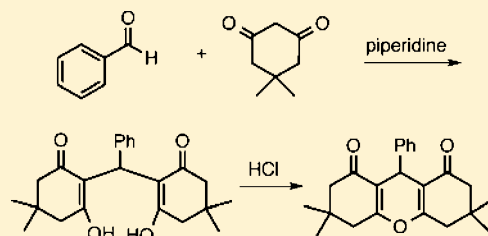
Anne M. Reeve*

Department of Chemistry and Biochemistry, Messiah College, Mechanicsburg, Pennsylvania 17055, United States

S Supporting Information

ABSTRACT: A simple, two-step synthesis of 9-phenylxanthene-1,8-dione from dimedone and benzaldehyde was developed for second-semester undergraduate organic chemistry. Both reactions afford crystalline solids in excellent yield by simply precipitating the product from solution. Reaction times are very short, and no specialized equipment, reagents, or purification techniques are needed. Multiple spectroscopic methods (IR and ^1H , ^{13}C , and DEPT NMR) are employed to solve the structures of the intermediate and final product, which are unknown to students. The products are not ones students would initially predict, but rather are derived from careful analysis of the spectroscopic data in conjunction with logical mechanistic steps. ^1H NMR peaks are well resolved, even at low field. Students have responded favorably over the five years this experiment has been used as a culminating experience in organic chemistry lab.

KEYWORDS: Second-Year Undergraduate, Organic Chemistry, Inquiry-Based/Discovery Learning, Aldehydes/Ketones, IR Spectroscopy, NMR Spectroscopy, Heterocycles, Laboratory Instruction, Hands-On Learning/Manipulatives



Critical thinking and data analysis skills should be developed throughout laboratory experiences in the undergraduate chemistry curriculum. However, all too often, students approach the laboratory as a series of cookbook directions to be followed uncritically with little true understanding of the underlying chemistry involved. One way to improve upon this situation is by incorporating discovery-based experiments involving unknowns into an organic chemistry laboratory. This approach requires that students thoughtfully engage with their own data to answer questions posed by the experiment.¹ Although numerous guided inquiry or discovery-based experiments are available in published lab texts² and in this *Journal*,³ there is a continuing need for additional interesting organic chemistry investigations. A simple, two-step reaction of dimedone and benzaldehyde yielding a xanthenedione final product provides an introduction to heterocyclic chemistry and occurs with excellent atom efficiency under relatively green conditions. This experiment, which has been used as a culminating experience in the organic laboratory for the past five years, incorporates comprehensive spectroscopic analysis of the reaction products, which are unknown to the students. Additionally, the mechanism reinforces the late second semester coverage of carbonyl condensation reactions.

The reaction of dimedone and various benzaldehyde derivatives has been used in the primary literature to synthesize xanthenedione derivatives (Scheme 1). 9-Aryl-1,8-xanthenediones such as **4** are of interest due to their variety of biological activities, including potential as antibacterials, antivirals, and anticancer agents,⁴ and their usefulness as laser dyes.⁵ Numerous reaction conditions have been employed for the synthesis of these heterocycles, from fairly simple solventless grinding⁶ to more complicated procedures using ionic liquids,⁷

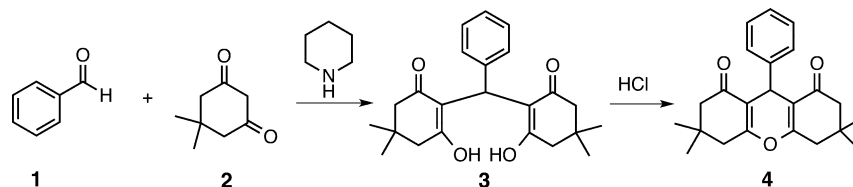
microwave irradiation,⁸ molecular iodine,⁹ and InCl_3 .¹⁰ The majority of the reported procedures yield **4** directly without isolating the interesting intermediate **3**, some require long reaction times, and many use expensive^{5,7} or hazardous^{5,9,10} reagents. The biological activity of many heterocycles, as well as the comparative lack of lab exercises focusing on them, makes this an appropriate area for development.

The reaction of dimedone **2** and benzaldehyde **1** appeared as a minilab in Lehman's¹¹ organic chemistry laboratory text. Minilabs are designed as time fillers: short, easy experiments that students could complete during down time in more involved procedures. The reaction is presented by Lehman as a cookbook procedure without clear goals or confirmation of product identities. The minilab has been completely recast as a comprehensive, question-driven, spectroscopy-intensive lab. This reaction sequence (Scheme 1) is appealing for a discovery-based lab because the products are not ones that would be initially predicted by students, but are derived from careful analysis of the spectroscopic data in conjunction with logical mechanistic steps. Furthermore, spectroscopic data indicate that compound **3** exists in the enol tautomer, something students do not expect. Last, the synthesis itself is technically easy and highly reliable on a miniscale or microscale, produces crystalline solids within a short reaction time, and poses no major hazards to personnel or the environment when conducted appropriately.

EXPERIMENTAL SECTION

Students work either individually or in pairs. One 3 h laboratory period is required to complete the synthesis.

Scheme 1. Reaction of Dimedone and Benzaldehyde



2,2'-(Phenylmethylene)bis-[3-hydroxy-5,5-dimethyl]-2-cyclohexen-1-one, 3

Benzaldehyde (2 mmol), dimedone (4.4 mmol), and piperidine (0.6 mmol) are dissolved in ethanol:water (8 mL of 1:1 (v:v)) in an Erlenmeyer flask (50 mL). The mixture is boiled gently for 5 min, and the product precipitates as a colorless solid. After cooling at 0 °C for 10 min, crystals are collected by vacuum filtration and washed with several portions (10 mL total volume) of ice cold ethanol:water (1:1 (v:v)), yielding 3 as a colorless crystalline solid. Students record IR and ^1H NMR spectra and are provided with ^{13}C and DEPT NMR spectra.

3,4,5,6,7,9-Hexahydro-3,3,6,6-tetramethyl-9-phenyl-1H-xanthen-1,8(2H)-dione, 4

Compound 3 (0.5–1.0 mmol) is dissolved in absolute ethanol (10 mL) in an Erlenmeyer flask (50 mL) with gentle heating. Water (2.5 mL) and HCl (6 M, 6 drops) are added, and the mixture is boiled gently for 5 min. After cooling, water is added dropwise until the mixture becomes cloudy, followed by cooling at 0 °C for 10 min. Crystals are collected by vacuum filtration and washed with several portions (10 mL total volume) of ice cold ethanol:water (1:1 (v:v)) to yield 4 as a colorless crystalline solid. Students record IR and ^1H NMR spectra and are provided with ^{13}C and DEPT NMR spectra.

HAZARDS

All of the organic materials and reagents used in this experiment pose the standard safety risks: flammability and irritation of the skin and respiratory tract. Piperidine causes burns to the skin and smells unpleasant. Gloves and chemical splash goggles must be worn for this experiment. The experiment should be conducted in a fume hood. The filtrate from the first reaction should be placed in a standard organic waste bottle. The filtrate from the second reaction can be disposed of down the drain after neutralization.

RESULTS AND DISCUSSION

A total of 235 students in a second semester of organic laboratory have completed this project over the past five years. A limiting feature of many otherwise interesting discovery-based projects is the difficulty or reliability of the organic synthesis itself. For the reaction of dimedone and benzaldehyde, the synthesis was not a stumbling block; both reactions ran very smoothly and were completed in less than 3 h total hands-on time. Student yields ranged from 40 to 99% (average 78%) for intermediate 3 and from 40 to 98% (average 69%) for xanthenedione 4. Experimental melting points were consistent with literature⁴ values. Students reported no particular problems or frustration with the synthesis itself.

The structure determination portion of the laboratory was appropriately challenging. Over 95% of students obtained the correct structure for both the intermediate 3 and the final product 4; representative IR and ^1H NMR spectra for 3 and 4 are in the Supporting Information. To help students realize that

3 exists in the enol tautomer, spectroscopic data for dimedone was provided along with a series of scaffolded questions that guided them through the interpretation. This exercise was designed to use a known compound to (a) show the spectroscopic evidence for the enol form of β -diketones and (b) introduce the DEPT spectrum, which further supported the predominant enol form and was helpful for making line assignments. Through this introduction, solving the structure of 3 became more accessible. One difficulty encountered by students was the unreliability of the integration of the enol hydrogen; under the conditions used, it often integrated quite low. A note about this in the scaffolded questions and a holistic interpretation of the integration and number of peaks in the NMR data led students to the symmetry in the dimedone portion of the molecule that was especially evident in low-field spectra (vide infra.) Occasionally, some students found the stoichiometry to be a stumbling block, but once they critically evaluated the integration of the dimedone portion vs the aromatic portion of the molecule, they discerned the 1:2 benzaldehyde:dimedone ratio. Most students approached the problem by using a logical mechanism in parallel with the spectroscopic evidence; that is, using the mechanism to derive a product that was consistent with the spectroscopic data. The acidity of active methylene groups was well covered in class, so they naturally used the enol or enolate form of dimedone to attack benzaldehyde as a first step. This problem solving strategy was part of the design goals for the experiment and was encouraged in the student handout. The mechanism included both aldol and Michael reactions, illustrating this important chemistry in an integrated pathway. For xanthenedione 4, both IR and ^1H NMR data showed that the enol hydrogen was lost and the ^{13}C NMR spectrum included an additional sp^2 carbon, again due to loss of the symmetry of the enol portion of the molecule. Logical mechanistic steps led to the final product.

One limitation encountered at many smaller institutions is the need for unknowns and reaction products to be structurally complex enough to provide an interpretation challenge for students, while simultaneously exhibiting sufficient resolution on low-field spectrometers. The NMR spectra of both 3 and 4 showed interesting differences between high-field and low-field spectrometers that could offer added value to the lab for institutions equipped with both instruments. In the ^1H NMR spectrum at 60 MHz, with the exception of the aromatic ring (AA'BB'C), all resonances for both compounds were singlets due to coincidental chemical shift overlap and presumably rapid equilibration of enol tautomers and ring conformations of 3 on the NMR time scale. The methylene and methyl groups of 3 were broadened, but still singlets. At high field, the aliphatic resonances were no longer chemical shift equivalent. At 400 MHz, the methyl groups of 3 were resolved into two singlets at 1.12 and 1.26 ppm and the methylene groups produced a second order multiplet, both of which could provide for an interesting discussion point about (pseudo)axial-equatorial chemical shift nonequivalence. For the xanthenedione final

product 4, the methylene groups were no longer in a symmetrical environment, so they had different chemical shifts, even at low field. Assignment was straightforward based on standard chemical shift trends. The methyl group resonances were narrow and separate due to the rigidity of the fused heterocycle. Students explained the difference in chemical shift of the methyl groups by making a model of the final product 4. From that, nearly all of them saw that the methyl groups were in different environments with respect to the aromatic ring and could not equilibrate through any form of conformational flexibility.

The pedagogical goals of this experiment involved detailed spectroscopic interpretation (including making line assignments) and use of the reaction mechanism as an adjunct to the spectroscopy. The pedagogical goals were assessed using the comprehensive assignment accompanying the lab. Students were required to explain their reasoning behind solving the structure, fully assign the spectra, and propose a reaction mechanism. The average score on this assignment over the past five years has consistently been $83 \pm 1\%$ ($n = 235$). Students reported that the assignment was challenging but doable. A student opinion survey conducted in the Spring 2013 showed that the lab was accomplishing its stated goals. Full survey data are included in the Supporting Information. Representative student comments included the following.

It allows students to use real data to determine structure rather than just looking everything up.

It was a lot of work, but it made me think of spectroscopy, mechanisms, and real data in a new way. It was like a real research experiment.

I think laboratories like the dimedone one are challenging but prepare me for the future. I also liked how it pulled in multiple techniques.

It certainly took the research aspect of organic chemistry to the next level (which is needed.)

In conclusion, the reaction of dimedone and benzaldehyde provided an interesting discovery-based lab experience for second-semester organic chemistry that emphasized spectroscopic interpretation. The synthesis was extremely reliable, yielding pure products by precipitation from the reaction mixture. While the products were not ones students would immediately predict, they are accessible from the spectroscopic data. Students have responded favorably to this lab over the past five years.

■ ASSOCIATED CONTENT

● Supporting Information

Notes for the instructor, student handout, and sample spectra. This material is available via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: areeve@messiah.edu.

Notes

The author declares no competing financial interest.

■ ACKNOWLEDGMENTS

The author wishes to acknowledge Roseann K. Sachs for helpful discussion and Franklin and Marshall College for providing high field NMR data.

■ REFERENCES

- (1) (a) Gaddis, B. A.; Schoffstall, A. M. Incorporating Guided-Inquiry Learning into the Organic Chemistry Laboratory. *J. Chem. Educ.* **2007**, *84*, 848–851. (b) Dunlap, N.; Martin, L. J. Discovery-Based Labs for Organic Chemistry: Overview and Effectiveness in Advances in Teaching Organic Chemistry. *ACS Symp. Ser.* **2012**, *1108*, 1–11.
- (2) Mohrig, J. R.; Hammond, C. N.; Schatz, P. F.; Morrill, T. C. *Modern Projects and Experiments in Organic Chemistry: Miniscale and Standard Taper Microscale*; W. H. Freeman and Company: New York, 2003.
- (3) For example: (a) Pelter, M. W.; Walker, N. M. A Discovery-Based Hydrochlorination of Carvone Utilizing a Guided-Inquiry Approach To Determine the Product Structure from ^{13}C NMR Spectra. *J. Chem. Educ.* **2012**, *89*, 1183–1185. (b) MacKay, J. A.; Wetzel, N. R. Exploring the Wittig Reaction: A Collaborative Guided-Inquiry Experiment for the Organic Chemistry Laboratory. *J. Chem. Educ.* **2014**, *91*, 722–725. (c) Sierra, M. G.; Pellegrinet, S. C.; Colombo, M. I.; Rúveda, E. A. An Exercise on Structure Elucidation Based on a Tricky Aldol Reaction. *J. Chem. Educ.* **2008**, *85*, 1094–1096. (d) Wieder, M. J.; Barrows, R. A Nitration Reaction Puzzle for the Organic Chemistry Laboratory. *J. Chem. Educ.* **2008**, *85*, 549–551. (e) Shadwick, S. R.; Mohan, R. S. The Discovery-Oriented Approach to Organic Chemistry. 2. Selectivity in Alcohol Oxidation. An Exercise in ^1H NMR Spectroscopy for Sophomore Organic Laboratories. *J. Chem. Educ.* **1999**, *76*, 1121–1122. (f) Krishnamurthy, H. G.; Jain, N.; Samby, K. Epoxide Chemistry: Guided Inquiry Experiment Emphasizing Structure Determination and Mechanism. *J. Chem. Educ.* **2000**, *77*, 511–513. (g) McElveen, S. R.; Gavardinas, K.; Stamberger, J. A.; Mohan, R. S. The Discovery-Oriented Approach to Organic Chemistry. 1. Nitration of Unknown Organic Compounds. An Exercise in ^1H NMR and ^{13}C NMR Spectroscopy for Sophomore Organic Laboratories. *J. Chem. Educ.* **1999**, *76*, 535–536. (h) Hammond, C. N.; Schatz, P. F.; Mohrig, J. A.; Davidson, T. A. Synthesis and Hydrogenation of Disubstituted Chalcones. A Guided-Inquiry Organic Chemistry Project. *J. Chem. Educ.* **2009**, *86*, 234–239. (i) Crouch, R. D.; Holden, M. S. An Organic Puzzle Using Meldrum's Acid. *J. Chem. Educ.* **2002**, *79*, 477–478. (j) Wink, D.; Angelo, N. G.; Henchey, L. K.; Waxman, A. J.; Canary, J. W.; Arora, P. S. Synthesis and Characterization of Aldol Condensation Products from Unknown Aldehydes and Ketones. *J. Chem. Educ.* **2007**, *84*, 1816–1818.
- (4) Ilangovan, A.; Muralidharan, S.; Sakthivel, P.; Malayappasamy, S.; Karuppusamy, S.; Kaushik, M. P. Simple and cost effective acid catalysts for efficient synthesis of 9-aryl-1,8-dioxooctahydroxanthene. *Tetrahedron Lett.* **2013**, *54*, 491–494.
- (5) Verma, G. K.; Raghuvanshi, K.; Verma, R. K.; Dwivedi, P.; Singh, M. S. An efficient one-pot solvent-free synthesis and photophysical properties of 9-aryl/alkyl-octahydroxanthene-1,8-diones. *Tetrahedron* **2011**, *67*, 3968–3704.
- (6) Jin, T.-S.; Zhang, J.-S.; Wang, A.-Q.; Li, T.-S. Solid-state condensation reactions between aldehydes and 5,5-dimethyl-1,3-cyclohexanedione by grinding at room temperature. *Synth. Commun.* **2005**, *35*, 2339–2345.
- (7) (a) Fang, D.; Yang, J.-M.; Liu, Z.-L. Eco-friendly synthesis of 1,8-dioxo-octahydroxanthenes catalyzed by ionic liquid in aqueous media. *J. Heterocycl. Chem.* **2011**, *48*, 468–472. (b) Makone, S.; Mahurkar, S. A Green Protocol for Efficient Synthesis of 1,8-Dioxo-Octahydroxanthenes Using Ionic Liquid. *Green Sustainable Chem.* **2013**, *3*, 27–32.
- (8) Kumar, D.; Sandhu, J. S. Efficient, solvent-free, microwave-enhanced condensation of 5,5-dimethyl-1,3-cyclohexanedione with aldehydes and imines using LiBr as inexpensive, mild catalyst. *Synth. Commun.* **2010**, *40*, 510–517.
- (9) Mulakayla, N.; Murthy, P. V. N. S.; Rambabu, D.; Aeluri, M.; Adepu, R.; Krishna, G. R.; Malla Reddy, C.; Prasad, K. R. S.; Chaitanya, M.; Kumar, C. S.; Basaveswara Rao, M. V.; Pal, M. Catalysis by molecular iodine: A rapid synthesis of 1,8-dioxo-octahydroxanthenes and their evaluation as potential anticancer agents. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2186–2191.

- (10) Tu, S.; Zhou, J.; Lu, Z.; Deng, X.; Shi, D.; Wang, S. Condensation of aromatic aldehydes with 5,5-dimethyl-1,3-cyclohexanedione without catalyst. *Synth. Commun.* **2002**, 32, 3063–3067.
- (11) Lehman, J. W. *Multiscale Operational Organic Chemistry: A Problem-Solving Approach to the Laboratory Course*; Prentice-Hall: Upper Saddle River, NJ, 2002; pp 504–505.