

A Research Module for the Organic Chemistry Laboratory: Multistep Synthesis of a Fluorous Dye Molecule

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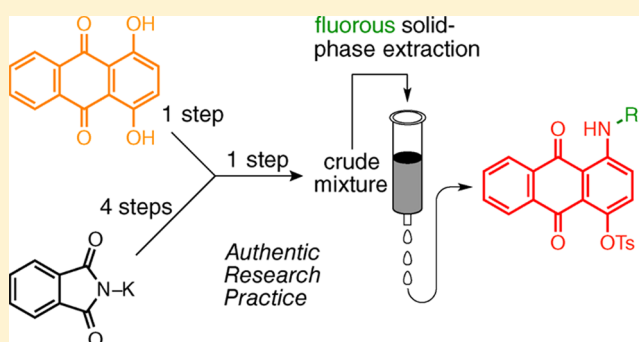
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S Supporting Information

ABSTRACT: A multi-session research-like module has been developed for use in the undergraduate organic teaching laboratory curriculum. Students are tasked with planning and executing the synthesis of a novel fluorous dye molecule and using it to explore a fluorous affinity chromatography separation technique, which is the first implementation of this technique in a teaching laboratory. Key elements of the project include gradually introducing students to the use of the chemical literature to facilitate their searching, as well as deliberate constraints designed to force them to think critically about reaction design and optimization in organic chemistry. The project also introduces students to some advanced laboratory practices such as Schlenk techniques, degassing of reaction mixtures, affinity chromatography, and microwave-assisted chemistry. This provides students a teaching laboratory experience that closely mirrors authentic synthetic organic chemistry practice in laboratories throughout the world.

KEYWORDS: Second-Year Undergraduate, Undergraduate Research, Laboratory Instruction, Organic Chemistry, Hands-On Learning/Manipulatives, Laboratory Equipment/Apparatus, Chromatography, Synthesis, Dyes/Pigments, Green Chemistry



Despite the great strides made in providing students with opportunities to engage and think about experiments they conduct in organic chemistry teaching laboratories,¹ change has been slow and not widespread. To date, many elegant examples of engaging, individual-inquiry laboratories have been reported.² Nevertheless, there still exists an urgent need to develop and share more of these experiences in order for the wider community to adopt experiments that approach authentic research laboratory practice.³ This report describes the development of an extended research-like module for a second-semester organic chemistry majors' laboratory course. The module was designed with the goal of making explicit connections between the students' experience in the project and authentic synthetic organic chemistry research.⁴ Many project-based laboratories are open-ended by allowing students to pick their targets (either novel or known compounds) and then develop synthetic plans based on previous literature.⁵ In this project, the targeted product itself was novel (but selected for students)⁶ and students were tasked with developing novel reaction conditions to synthesize that target.⁷

PROJECT DESCRIPTION

Context: Course Description

This project was developed for the second semester of a two-semester, two-credit introductory organic chemistry laboratory course sequence for chemistry and related majors; the project was first implemented in spring 2012 and successfully improved for spring 2013. The course is separate from the pre- or co-requisite organic lecture course and meets twice weekly for 3-h sessions, in sections each led by a graduate teaching assistant (TA). Typically, the student:TA ratio is less than 12:1, and the course consists of ~50–70% second-year students, with the remainder being composed primarily of third- and fourth-year students. Over the two years this project has been implemented, 40 students have participated. For many students, this project represents their first exposure to scientific research. The project could also be appropriate for an upper-division undergraduate organic laboratory course.

Research Module Development

In developing the research module, a primary goal was to introduce students to authentic organic chemistry practice—a goal to which student attention was explicitly drawn. This goal

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could be achieved by requiring students to find, adapt, and optimize procedures directly from the literature to develop and carry out a multistep synthesis. In so doing, a secondary goal of exposure to modern synthetic techniques, including microwave-accelerated synthesis and affinity chromatography, could be achieved. In particular, chromatography is an important part of the everyday life of synthetic organic chemists, but relatively little chromatography is carried out in organic teaching labs. Reasons for this omission may include the safety issues of packing and running columns with standard silica gel (inhalation hazard) in pressurized glassware (explosion hazard), as well as the cost of the silica gel and solvent disposal for single-use columns. The use of fluorous affinity chromatography with prepacked columns could make a chromatography process more feasible in teaching labs: the preparation issues are avoided, and the columns can be reused multiple times. Moreover, an understanding of affinity chromatography and noncovalent interactions is particularly relevant for students who go on to pursue work in biochemistry and areas of biology where it is a common technique.

Fluorous chemistry^{8,9} is a rapidly growing subfield of organic chemistry that has also gained attention in the context of green chemistry.¹⁰ This is due in part to the recyclability of many fluorous-tagged reagents and catalysts, as well as the fact that product isolation and purification using fluorous tags is greatly facilitated. The crux of the project reported herein was to synthesize a brightly colored molecule bearing a fluorous tag and then to use that product to explore fluorous solid-phase extraction (FSPE)¹¹ so that the separation process could be easily followed visually and understood conceptually. The project described is, to the best of our knowledge, the first reported implementation of fluorous synthesis and solid-phase extraction chemistry in the undergraduate organic teaching laboratory.¹²

In preliminary development, ways were sought to attach a fluorous tag to fluorescein derivatives; a recent fluorescein experiment from this *Journal* has already been successfully adopted in this course.¹³ After encountering difficulty early in the development phase for such a project, a fluorous aminoanthraquinone target was selected (Scheme 1). The rationale for this selection drew upon the precedent that compounds of type **1a** ($R = \text{CH}_2\text{R}_F$, $X = \text{F}$, where R_F is

perfluoroalkyl) are known to be useful molecules for visualizing fluorous separations,¹⁴ whereas aminoanthraquinones of type **1b** ($R = \text{alkyl or aryl}$, $X = \text{OTs}$) are known to be easily accessed from a readily available, inexpensive starting material (quinizarin, **2**).¹⁵

Once the target was selected, a route was devised that would require students to engage in multistep synthesis. After debate on how best to frame the experience for the students, it was ultimately decided to provide them with Scheme 2 in its entirety to facilitate their search for literature procedures to attempt directly or to modify to their needs.

Although explicitly told that they *could* deviate from the provided scheme if desired, students generally opted to follow the sequence shown. Several features of this route are noteworthy:

- all of the intermediates except the final product are known compounds, facilitating the literature search process;
- it combines familiar, textbook chemistry with challenging chemistry not typically found in traditional undergraduate laboratory or lecture;
- the literature procedures that are found as precedents for individual steps require modification for use in the teaching laboratories due to constraints of time, equipment, or reagent safety—requiring students to think critically about them and to come up with viable alternatives.

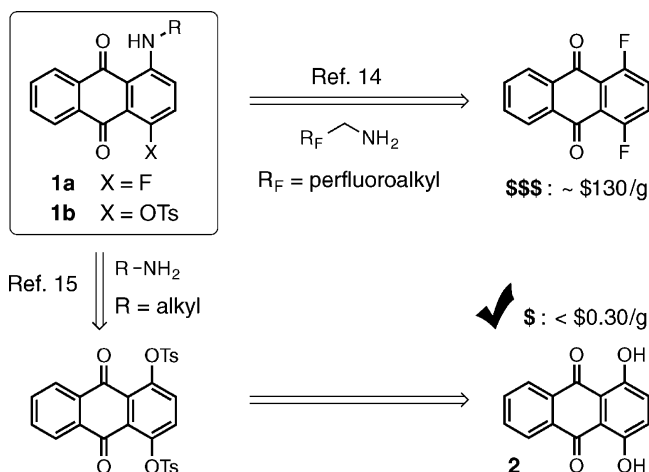
It was anticipated that such a project design would provide ample opportunity for students to develop their own chemistry and attempt to establish alternative reaction conditions for given transformations, while minimizing the time, logistical, and safety issues that typically accompany more open-ended projects.¹

Project Introduction and In-Class Preparation

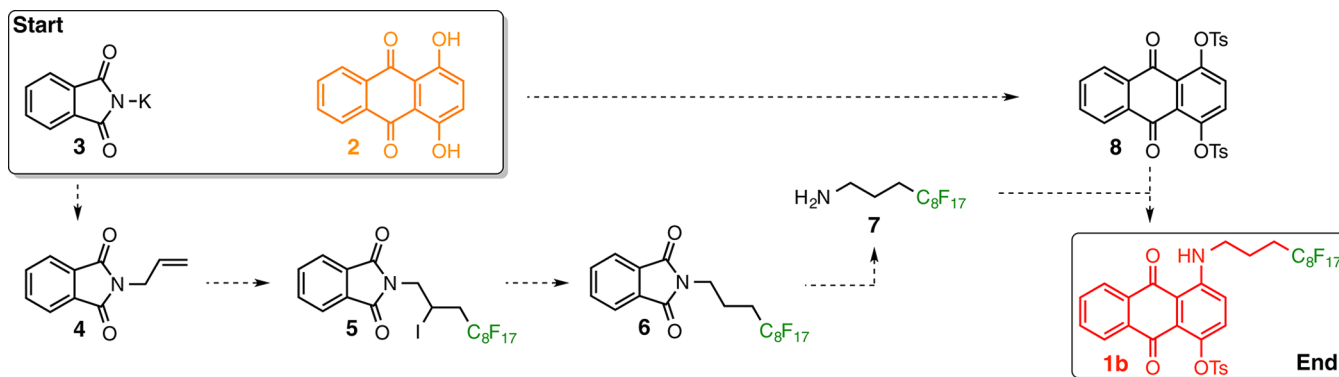
Early in the semester, students began using SciFinder Scholar,¹⁶ were introduced to the project, and were provided with Scheme 2. Students were told that they would, on an individual basis, have to submit a proposal before they began. The proposal would contain literature procedures for their reactions as well as their proposed modifications thereof (based on the rules below, *vide infra*). After several weeks of planning outside of class, students would be given six consecutive lab periods in which to carry out their individual synthesis. In the interim, students would continue to do typical laboratory experiments, as well as inquiry-based mini-projects^{2a,b} that served to prepare them for the capstone project. Additionally, students were given two lab periods interspersed through the early part of the semester to ease into the project and practice the literature search and independent work process prior to the dedicated block of project time.

Students were free to explore any chemistry that they had found as precedent, within the following constraints: (1) they would be allowed to leave reactions unattended or heating over extended time periods, if desired, *provided that they were properly labeled and that no reflux condenser was required* when the laboratory was unoccupied; (2) particular reactions that would require equipment that was unavailable to all students (a Parr hydrogenation bottle)¹⁷ and specific reagents (such as tBu_3SnH)¹⁸ were labeled off-limits; (3) their scale would be limited to a few attempts at the use of one gram of perfluorooctyl iodide in the conversion of **4** \rightarrow **5** in Scheme 2; and (4) their procedures would be vetted by the teaching

Scheme 1. Precedents for Synthesis of Aminoanthraquinone Dyes 1



Scheme 2. Basic Scaffold Provided to Students to Aid Their Literature Search



staff after an inspection for safety considerations. It was anticipated that these few rules would force students to be creative and to think critically about reaction design. At the same time, students would be able to experience a modicum of freedom and thus take ownership of their project.

Student Performance

Students were informed that another way that the project mirrors the typical practice of organic chemistry research is that the key intermediate, perfluorooctylpropyl amine **7**, is commercially available but at high cost. A small amount would be available to them if necessary to use on the final day of the project, so that they could still perform the final synthetic step and explore the FSPE technique. Rather than diminish their motivation or make them believe that this was an exercise in futility, this served to ease the pressure they felt that they *must* be able to make it to the end on their own in the time allotted (eight total lab periods). This is fortuitous, because, to date, the long-term objective of students' unaided synthesis of this compound has not been achieved.¹⁹ However, we strongly believe that the success of the project described herein is not contingent upon student synthesis of the final target, but, as in many graduate dissertations, the experience gained and growth undergone en route.

Lessons for Adoption Elsewhere

A secondary goal guiding module development was to produce a module that could be easily modified and adopted; this goal was part of the rationale to constrain the activity in such a way as to minimize the logistical issues perceived to be significant obstacles to the widespread adoption of project-based approaches. It is believed that, with a few modifications, this approach could be useful at other institutions.²⁰ For example, although students worked on the project individually, the project is also amenable for small groups of 2–3 students with division of the workload; groups working together would also allow a more systematic approach for the exploration of modified reaction conditions.

Easily modifiable background documents for various aspects of the project are available for adaptation. For example, if an instructor would simply like to demonstrate FSPE, many modifications of this project could be made to illustrate the technique using commercial reagents or shorter synthetic sequences. Although some of these compounds are relatively expensive,²¹ costs can be kept low by the use of small scales (≤ 50 mg) and grouping students. The targeting of strongly colored dye molecules means that only a small amount of product must be obtained to achieve a dramatic visual effect.

The current approach made heavy use of a laboratory microwave to give students practice with another modern, rapidly growing technique.²² Indeed, the microwave was another tool that students often thought to employ when dealing with the constraints of a traditional 3-h time block for a laboratory session. Fortunately, much of this chemistry was developed outside of the microwave and can also work well in departments without this equipment. If a microwave is available, a student to microwave ratio of about 6:1 is optimal to minimize bottlenecks in the sharing of this equipment resource. Although the microwave is equipped to handle multiple samples at a time, if students have proposed different conditions of time and temperature, this can result in a bottleneck.²³

HAZARDS

General laboratory safety procedures, including wearing appropriate personal protective equipment, must be followed at all times. All organic chemicals involved in these experiments are considered hazardous, and direct physical contact with them should be avoided. All experiments should be performed in a fume hood. Students were required to find the MSDS sheets of all reagents used and note particular hazards in their laboratory notebooks prior to use of the chemical. Use of AIBN (as in the conversion of **4** \rightarrow **5**) produces nitrogen gas during the course of the reaction, and therefore, precautions need to be taken for pressure build-up if this reagent is used under sealed vessel conditions.

CONCLUSION

A research module has been developed and successfully implemented in a second-semester introductory organic teaching laboratory for chemistry majors. Key features of the approach were an outlined route to a target that necessarily forced students to think critically about the procedures they planned to use to reach the targeted molecule and to propose modifications to known procedures. The module exposed students to modern chemistry through the use of microwaves and fluoros techniques, and engaged them in the process of organic chemistry as practiced in many laboratories across the world. While full details of the project evaluation and assessment will likely be reported upon additional data collection, the initial response to the project from the majority of students has been positive. Although some students resisted the extra work and others struggled with the frustration of "failed" experiments, students generally appreciated the chance to take ownership of their work, as well as the fact that this

represented a departure from “canned” experiments. This project or a slight modification thereof can be used to introduce students to authentic organic chemistry practice including modern synthetic techniques and should be easily adaptable to other settings.

■ ASSOCIATED CONTENT

■ Supporting Information

Notes to instructors, reagents list, background supporting documents for students, sample questions for assignments, quizzes, and tests. This material is available via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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(16) This may be the biggest logistical impasse for adoption of this approach at institutions that lack a subscription to this resource. However, by changing the focus from *finding* literature procedures to *optimizing* procedures (such as those in the Supporting Information), this project can still be used and be relatively open-ended for the students.

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(18) This rule was imposed due to the toxicity of alkyltin compounds and the often laborious workup steps required for removal of tin byproducts from such reactions.

(19) Specific details of student success rate on individual steps, as well as overall progress through the route, are provided to instructors in the Supporting Information.

(20) Information to facilitate this process is included in the Supporting Information.

(21) The 1,4-difluoroanthraquinone precursor (Scheme 1; prices quoted from Sigma Aldrich, October 2013) and the fluorous amines used in ref 14 were purchased for that study.

(22) The majors' teaching laboratory is equipped with a CEM MARS 5 microwave system. For more information and current microwave products, see: <http://www.cem.com> (accessed Dec 2013).

(23) Results from project evaluation surveys typically reflect this: students in larger sections are more likely to report that microwave sharing and logistics should be improved.