Student-Designed Multistep Synthesis Projects in Organic Chemistry

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Abstract: The incorporation of research projects into undergraduate chemistry courses provides a perspective that is fundamentally unavailable in most laboratory experiences. While independent, multistep synthesis projects in organic chemistry have been reported previously, most efforts have been directed at relatively restricted, closely guided research plans with modest student participation in the experimental design. We have implemented a more open-ended synthesis project, limited principally by cost, safety and availability of materials. In the second semester of the sophomore organic sequence, students develop multiple drafts of a plan for a three-to-four-step synthesis. Subsequently, students obtain their own literature protocols for the individual steps. The synthesis is performed over three four-hour laboratory periods. The students conclude this project with a poster presentation of the results at the end of the semester. Evaluation of the students' work focuses not only on the successful synthesis of the target but also on planning, troubleshooting, purification, and spectral analysis.

Introduction

Synthesis projects in the undergraduate organic curriculum are attractive for a number of reasons. A transformation requiring a series of sequential reactions demands a higher level of skill and attention to detail from students than a single-step reaction. The ability to accomplish more complex goals, such as the synthesis of a compound with obvious applications, can make these projects attractive to students. Perhaps most importantly, independent synthesis projects can be used to introduce students to the way in which chemists practice science. Thus, a multistep synthesis project can act as a link between the classroom and the research laboratory.

For these reasons, synthesis projects are often a part of organic laboratory instruction [1–9]; however, students typically have little control over the development of the synthesis plan and, therefore, they miss out on a crucial phase of the research experience. In a typical organic laboratory project, an instructor may present students with a general scenario, such as a class of compounds that need to be synthesized because they have some potentially interesting application [1, 2, 8]. Students are then provided with general procedures for the preparation of these compounds. Although slight modifications may need to be made in order to prepare specific compounds, creative input and troubleshooting on the part of the students is often limited.

In order to make the connection between synthesis projects and the research endeavor more concrete, we have developed an approach that gives students more control over their experiments. In our laboratory curriculum, students choose their own target molecules, plan their own multistep syntheses, and troubleshoot their projects when synthetic steps are unsuccessful.

Discussion and Conclusions

In the second semester of the sophomore organic chemistry laboratory, we require all students to design a 3- or 4-step synthesis of a compound of their own choice. This project comprises approximately 25% of their laboratory grade. There are typically about 90 students enrolled in this course. The students work in pairs in a laboratory section with a maximum of 16 students; thus, there are usually 6 to 8 projects underway in each section. An organic chemistry faculty member often teaches 2 to 3 laboratory sections in the spring semester. While this laboratory sequence requires more attention from the instructor, we have not found it to be unusually difficult to monitor student progress.

Our projects are similar to others that require students to perform literature searches in order to obtain experimental procedures [3, 5–7]; however, our students must develop their own route for the multistep synthesis in addition to finding appropriate experimental protocols for each step in the primary literature. The only limitations that we impose on the student projects are: (1) The materials must be available in our stockroom. We only order compounds or reagents that would be used for some other purpose in the department. This limitation allows us to run this laboratory without costly expenditures. (2) The proposed procedures must be ones that can be performed safely by the students. We leave this decision up to the individual instructor. (3) The students must be able to characterize their products by traditional NMR, IR, and MS techniques. (4) Finally, for obvious reasons, the students are not allowed to synthesize controlled substances.

In this type of truly independent synthesis project, the planning stage takes on great importance (Figure 1). The amount of planning involved in this approach is considerable, and consequently, students must begin thinking about this project weeks in advance. While the independent syntheses occur in the sixth through eighth week of the semester, the students actually start planning their synthesis during the first week of laboratories. Thus, this project has replaced three laboratory experiments that had previously been one-step reactions, such as exploring the regiochemistry of electrophilic aromatic substitution.

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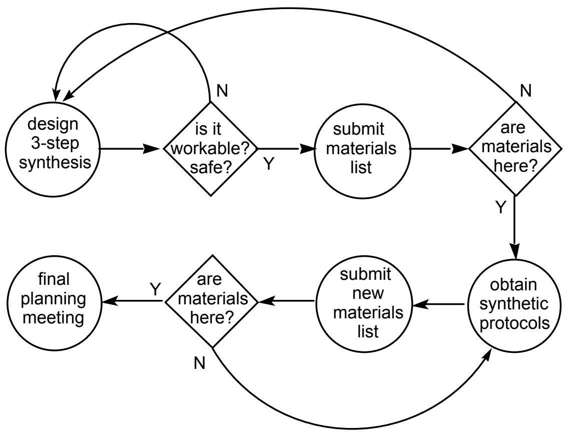

Figure 1. The planning stage of the independent synthesis project.

For each step:

a. Scale? (How much reactant? What size glassware?)
Encourage planning to eliminate waste

b. Safety considerations?

c. Indicator that reaction is done?
Follow reaction with TLC / GC?

d. Structural characterization of product?
Can the intermediates be characterized with NMR / IR?

e. Purification of products?
Distillation? Recrystallization? Chromatography? Extraction?

f. Special glassware, equipment or materials?
Constant temperature baths, Dean-Stark trap, UV lamp, etc.?

g. Does the reaction need to run outside of normal lab time?

Figure 2. Questions to be discussed at the planning meeting.

We have found that the key to success for implementing these types of projects involves substantial planning stages. By the second week of the semester, the students must submit a proposal for a three- or four-step synthesis. Students must then confer with their instructor to see that their synthesis has a chance of working, does not pose undue safety risks, and the starting material is available in our stockroom. Because each project involves a different set of reactions, each student must find synthesis protocols from the literature and adapt these procedures for their own experiments. Consequently, the laboratory instructor introduces the use of some standard library sources [10–12] and, by the third week of the semester, the students begin searching for experimental procedures. Because their proposed project may never have been carried out at our institution before, the students must also determine whether the starting materials are available. For the fourth week, the students submit a list of needed chemicals and glassware to the stockroom to check for availability. In addition, the students are also required to locate MSDS information on each of the chemicals needed and summarize the safety information (e.g. irritant, carcinogen, flammable) within a table of physical constants [13]. This planning process is done iteratively until the students have a synthesis for which they have literature procedures, does not propose safety risks, and involves available starting materials and reagents.

A final meeting with students before the start of the projects has proven beneficial in bolstering student preparedness (Figure 2). At this meeting, a number of issues are highlighted that students may not have thought of, such as the use of unusual equipment or the need to purify materials before proceeding. This meeting takes place instead of a laboratory experiment during the fifth week of the semester.

During the sixth, seventh, and eighth week of the semester, students carry out their proposed syntheses. In order to correctly identify their product, students have access to ^{1}H and ^{13}C NMR, GC–MS, IR, and UV spectroscopy. If the timing of reaction requires it, a student may attend another laboratory section to work up their reaction after consulting with the instructor. Each group is responsible for labeling and managing waste collection for their own project. Instead of turning in a full report for each experiment, the students turn in an experimental procedure in the style of the *Journal of Organic Chemistry* for each week.

Finally, all students present their results in a poster presentation that is attended by all students and faculty members involved. The students are provided with guidelines for preparing a poster (see Supporting Materials).

Another aspect that must be considered before implementing this approach for synthesis projects is the expectation of success. Instructors do not develop these experiments, so success is not guaranteed. In fact, students may find procedures that work on related compounds but not in their specific case. As a result, students are forced to independently problem solve when reactions do not work or when a mixture of products results. This approach provides additional opportunity to learn about a realistic aspect of research but can increase the level of frustration for the student. On the other hand, in a recent student survey, a majority of the students reported that this was their favorite laboratory exercise.

Despite the difficulty involved in planning and executing student-designed projects, a sampling of projects from one laboratory section in spring 2002 illustrates a variety of successful syntheses (Figure 3). These range from an approach in which three reactions were strung together to perform an overall transformation (I), to the execution of a classic acetoacetic ester synthesis inspired by a passage in the class textbook (II), to the synthesis of a medicinally important compound, salicylic acid (III).

Many students propose rather mundane three-step syntheses, while some students are very creative in their choice of projects. For example, a student in a previous year developed a unique asymmetric synthesis of an insect antifeedant compound. The biological activity of this compound had only been studied on the racemic mixture. This project developed into an undergraduate research effort that is now close to publication.

With the shift in emphasis to planning and troubleshooting to mimic a research project, the grading of these projects takes on a different character (Figure 4). Additional consideration is given to the quality of student effort in the experimental design, including a demonstration of having investigated primary and secondary literature sources [10, 11]. The students' grade also is dependent upon whether he or she obtained sufficient spectral data to analyze products and developed purification methods for mixtures obtained. Because these projects sometimes do not work, students are given credit for providing evidence of what the product of a reaction really was and also for revising their procedure in response to failure.

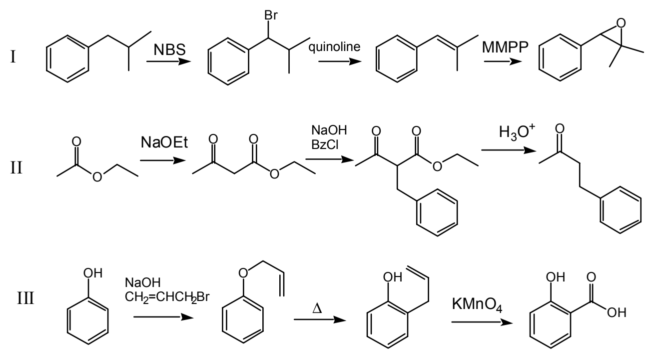

Figure 3. Examples of student-designed synthetic projects.

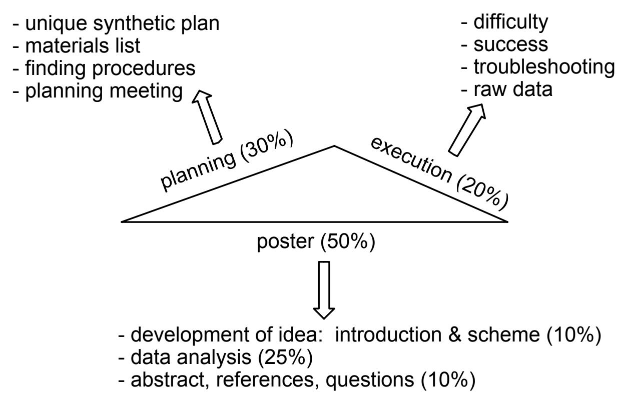

Figure 4. Grading the independent synthetic project.

	Structured synthesis lab	CSB/SJU synthesis project	Research project
overall goal	synthesis in context	accomplish 3 synthetic steps	gain insight into a problem
creativity	little student input	student input drives project	student influences project
practicality	limited by lab parameters	limited by materials	limited by facilities, funding
revision	usually not needed	key part of project	key part of project
literature	compounds' properties	source of procedures	procedures & insight
advising	instructor provides project	instructor provides feedback	advisor may provide idea
analysis	spectral data or mp	primarily via spectral data	primarily via spectral data
presentation	lab report to instructor	results communicated to peers	results communicated to peers

Figure 5. Significance of the synthetic project to understanding research.

The final poster then accounts for the remaining half of the project grade.

Independent synthesis projects, when practiced in this form, provide students with an experience that is a closer approximation to a research experience than a structured synthetic project (Figure 5). The key feature of this approach is allowing students to design and troubleshoot their own projects. The background work necessary to design a synthesis mirrors the type of planning that is integral to research, including the use of primary and secondary literature to work out experimental procedures; however, the design phase does require interactive work between the student and the instructor and should constitute a significant part of the student's project grade. Projects of this type help the students make the transition from being a laboratory student to being a researcher.

Supporting Materials. Poster Guidelines are available in a Zip file (http://dx.doi.org/10.1007/s00897020612a).

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