A classroom-based activity to teach students how to apply organic chemistry theory to design experiments

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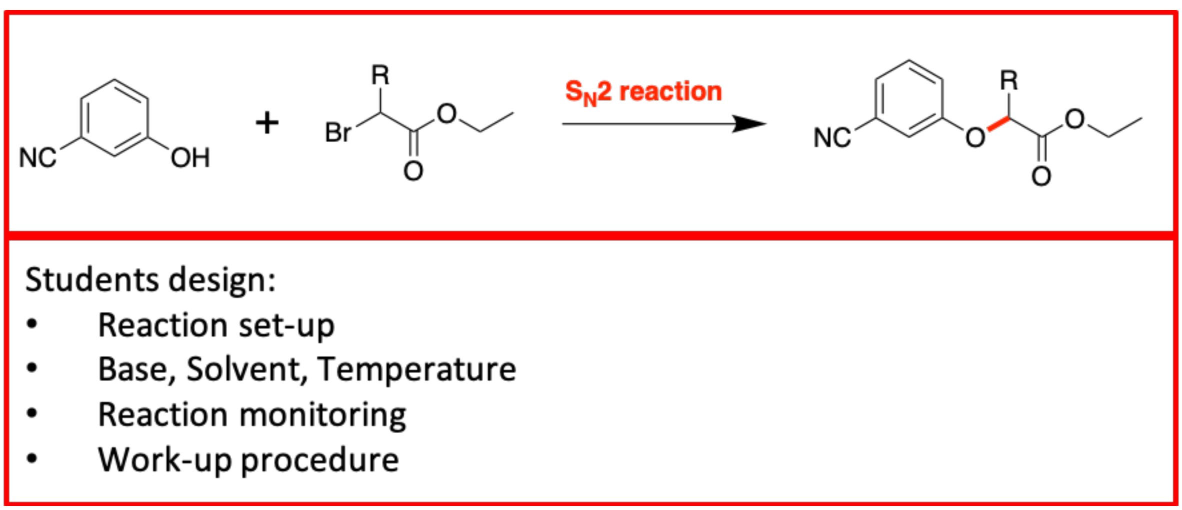
ABSTRACT

A core skill for practicing organic chemists is the ability to apply organic chemistry to design experiments. In this article we describe an activity to help students along the pathway towards developing into practicing organic chemists. The workshop teaches students how to use organic chemistry to design synthetic organic chemistry experiments by connecting theory to the choices of various reaction conditions which the students had to choose for their target molecules. Students who undertook this activity were able to design procedures yielding their target molecules and evidenced the development of experimental design skills.

GRAPHICAL ABSTRACT



KEYWORDS

Laboratory instruction, organic chemistry, undergraduate research

INTRODUCTION

The QAA chemistry benchmark statement, used to ensure UK chemistry degree are taught to the required standard, states that undergraduate chemistry degrees should *prepare students* *effectively for professional employment or research degrees in the chemical sciences* as one of the main aims of the degree.[1] Similarly, RSC accreditation stipulates that degrees should *provide effective preparation for professional employment or doctoral studies*.[2] ACS guidelines for bachelor level programs state that chemistry degrees should provide students with the *skills necessary to become successful scientific professionals*.[3] At a more detailed level, accreditation criteria highlight the importance of developing experimental design skills in undergraduate education through statements such as the *use the principles of […] experimental design*, *the ability to plan experimental procedures*, and *demonstrate a systematic understanding of fundamental physiochemical properties and an ability to apply that knowledge to the solution of theoretical and practical problems*.[3]

Hanson and Overton surveyed chemistry graduates to determine which skills they used in their current positions and which skills were well developed.[4] Amongst doctoral students, planning and designing experiments was the skill with the highest development deficit – that is, the skill which is most useful in their current position yet most underdeveloped in their undergraduate degree. This was also was the skill which they wished they had more opportunity to develop in their undergraduate studies. Raker and Towns investigated the types of problems that synthetic organic chemistry researchers solved in their work.[5, 6] They identified three types of problems; project level problems which involved the identification and selection of target molecules for synthesis, synthetic planning problems to design the synthesis of target molecules, and day-to-day problems such as ensuring reagents dissolve in solvents and purifying incomplete reactions.[5] Building on this, they proposed 7 attributes that organic chemistry problems at the undergraduate level should incorporate that reflects authentic practice of organic chemistry.[6] Bhattacharyyra and Bodner studied the way 1st and 3rd year organic chemistry graduate students thought about solving synthesis problems from a graduate course to understand how the transition from chemistry student to chemist occurs. 1st year organic chemistry graduate students thought of synthesis problems as mostly paper and pencil exercises.[7] They did not connect theory with practice and focused on grades. In comparison, 3rd year students could understand how these problems could be translated to problems they would solve in research and had developed more sophisticated problem-solving strategies. As 1st year students conducted their research studies, they became better at understanding how these synthesis problems have significance in real organic chemistry research.

At the undergraduate level, course-based undergraduate research experiences (CUREs) have been used to introduce students to authentic research activities in laboratory courses.[8-12] They have been shown to improve students scientific reasoning and critical thinking skills.[13-15] Recently, a redesigned organic chemistry course was developed by Cooper *et al.* to improve students' ability to apply models and scientific reasoning.[16] Efforts to develop experimental design skills have, understandably, largely occurred through laboratory curricula. Shaw *et al.* used a storyboarding approach to plan experiments, although the procedure was already given to students.[17] Seery *et al.* employed a scaffolding approach where students first perform an expository procedure then perform a similar inquiry-based experiment which requires more planning.[18] Szalay *et al.* developed a series of inquiry-based high school experiments requiring the application of fundamental chemical principles to design experiments.[19] Bouzidi and Gozzi introduced factorial experimental design to students through a Grignard experiment where students optimize conditions by changing multiple variables.[20] Slade *et al.* taught used a project where students had to adapt literature procedures to learn experimental design skills.[21] Coil *et al.* developed an course to teach experimental design skills in the classroom.[22] Previously, we developed a purification design experiment where students have to use their understanding of acid-base theory and solubility to purify a mixture of organic molecules.[23]

To be able to design a synthetic organic chemistry experiment, chemists must use their understanding of the chemical reaction taking place, chemical and physical properties of molecules, and understanding of practical techniques. Herein, we describe a workshop used to teach first year undergraduate students how to use organic chemistry theory from their studies to design the synthesis of an organic molecule.

WORKSHOP DESIGN AND DELIVERY

This three-hour workshop was designed for 1st year chemistry and medicinal chemistry students as part of their laboratory module in semester 2. At the time of this activity students have completed introductory organic experiments in the laboratory module with standard techniques such as reflux and liquid-liquid extraction, and have been taught acid/base theory, nucleophilic substitution and carbonyl chemistry in their theoretical modules which runs concurrently to the laboratory module.

The aim of the workshop was for students to learn how to use theory and an understanding of synthetic chemistry techniques to design an organic chemistry experiment. We wanted students to understand how a knowledge of organic mechanisms is applied to designing experiments over parameters such as the order in which to add reagents, the temperature of the reaction and potential for by-products, as well as other factors. This is so students are better prepared to undertake inquiry-based experiments and projects which are delivered in the 2nd and 3rd year which are also part of the development from student to practitioner.

In light of the research from Bhattacharyyra[7], and recommendations from Raker[6], we also wanted students to appreciate how this application of theory is part of research in organic chemistry. Therefore, we decided that students should design the synthesis of molecules that are being researched in our department for their potential as thrombosis inhibitors (figure 1). The overall format of the activity of workshop is as follows: researchers would introduce their project and reasons why they were interested in these target molecules; students would use the workshop to design the key step towards the synthesis of these targets; student submissions are submitted to the researchers who then run the experiments in the laboratory; the products are taken forward to make the biologically active molecules which are then tested in an assay to evaluate their inhibitory properties; students are given feedback on how well their experiments had worked and how their efforts had contributed to a real research project with the biological activity of the final molecules.

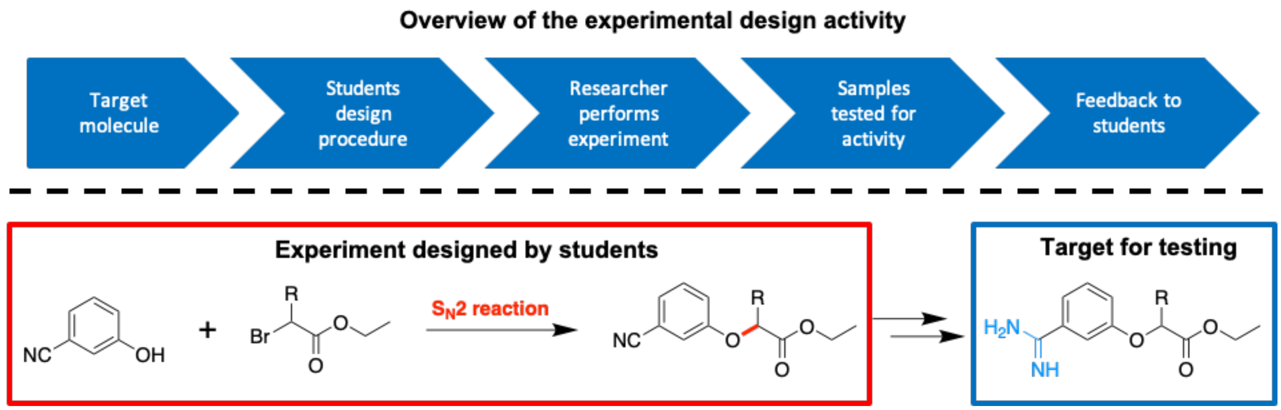


Figure 1: Overview of the experimental design activity and the reaction designed by students.

This experimental design activity has students directly engaged with synthetic planning and day to day problems. By designing an experiment for a real research project, students are given contextual information and can appreciate why solving this problem has a societal impact. The activity is open-ended because students can select reagents and conditions of their choosing which would feasibly synthesize their target molecules. This activity requires students to use their knowledge reaction terminology such as the S_N2 reaction to be able to solve this problem. As this activity was being delivered to 1st year undergraduates who had previously never solved this type of problem before, the workshop materials provided guidance so students could be challenged enough to learn new skills whilst not being 'lost' with how to solve this problem. Finally, to solve a problem of this nature students would have to refer to their lecture notes and search for reagent information (e.g. boiling points) to be able to design their experimental protocols.

As the year group were split into four cohorts who rotate between synthetic labs, physical chemistry labs and classroom-based activities, the workshop was delivered four times. In each workshop the students were given a slightly different target to work towards. Students were asked to work on this activity in groups of up to five. For this activity, each group had to complete and submit an experimental protocol sheet with their choice of base, solvent, reaction set-up, guidelines for monitoring their reaction by thin layer chromatography (TLC) and work-up procedure. For each parameter, students needed to also provide their reasoning. This was to encourage students to apply scientific reasoning for their choices rather than selecting them at random.

To aid their completion of the experimental protocol sheet, students worked through a handout which guided them through the activity. The first part of the activity required students to propose a curly arrow mechanism of the reaction. This was to ensure students understood that this reaction was proceeding through an S_N2 reaction, and therefore needed certain aspects of theory (e.g. the need for a base to generate a strong nucleophile) to be considered in the design of the experiment.

Students were given four possible bases to select from which were chosen so students would have to think about pK_a values and possible side reactions. Similarly, for solvents students were given a list to consider the type of solvent (non-polar/polar protic/polar aprotic), their boiling points if the reactions were to be heated, and their ability to solvate the reagents. To facilitate the thought process that a chemist would go through to choose these parameters, students completed tables to determine if a particular reagent or solvent should be used. This process eliminates many of the possible reagents but leaves more than one feasible base and solvent to choose from. This is to reflect the authentic nature of experimental design where there is not always one clear reagent which will work better than others. To finalize their choices, sometimes groups found additional reasons to choose between the final bases and solvents. For example, some groups researched the hazards of DMSO and DMF leading to them choosing the former. Whilst we directed students to choose between certain bases and solvents, sometimes students provided sound scientific reasoning for choosing other conditions. For example, we expected students to eliminate the possibility of using NaOH as a base due to competing S_N2 substitution and ester hydrolysis however, one group realized that mixing the phenol and base prior to the addition for the halide would eliminate the possibility of these side reactions so requested that their experiment was performed this way.

When an organic chemistry reaction is being performed it is important to monitor the reaction to check its progress and determine when the reaction is complete and ready to move onto the purification stage. Thin layer chromatography is the method that students had encountered in their synthetic labs. Students had to consider applying their knowledge of structural properties of organic molecules and thin layer chromatography to predict what the relative positions of the starting materials and products would be. Groups also had to provide instructions of how the researchers should proceed with the experiments (continue, heat or work-up) based on the potential appearance of

TLC plates at certain time points (1, 3 and 17 hours). This was to ensure students understood how to monitor a reaction make decisions through the course of a reaction.

To choose the temperature and reaction set-up of the experiment students mainly considered if their halides had primary or secondary substitution. If the halide was primary then many groups reasoned that the reaction would occur at room temperature, whereas those with secondary halides reasoned that the more hindered reaction center required heat. The main technique students were familiar with for heating reactions was heating under reflux. This meant students who chose either DMF or DMSO often selected high temperatures for these reactions. On the one hand this demonstrated that students understood that the temperature of a reflux reaction reflected the boiling point of the solvent, however in practice these temperatures were higher than needed and led to decomposition, such as dimethyl sulfide formation from DMSO. Therefore, from the 2nd year of running this workshop, we advised students who wished to reflux, that a temperature of 100 °C should not be exceeded.

The final part of the experimental protocol was to design a work-up procedure to separate the product from unreacted phenol (used in excess) and base. Here students would have to use their understanding of solubility and acid/base theory to determine if the components could dissolve in the organic and aqueous layer to construct a flow chart of the work-up process which would isolate the product.

At the end of the workshop instructors and researchers evaluated the submissions and planned the reactions to be performed in the laboratory. Where different groups had designed the same or similar conditions these were performed as a single experiment. This led to the number of experiments being performed as a manageable number. It was found that the student designs were successful in yielding enough product to be taken forward to the final targets for testing. Yields for students designed reactions ranged from 35-52%. These results were fed back to the students along with the biological activity of the final target molecules.

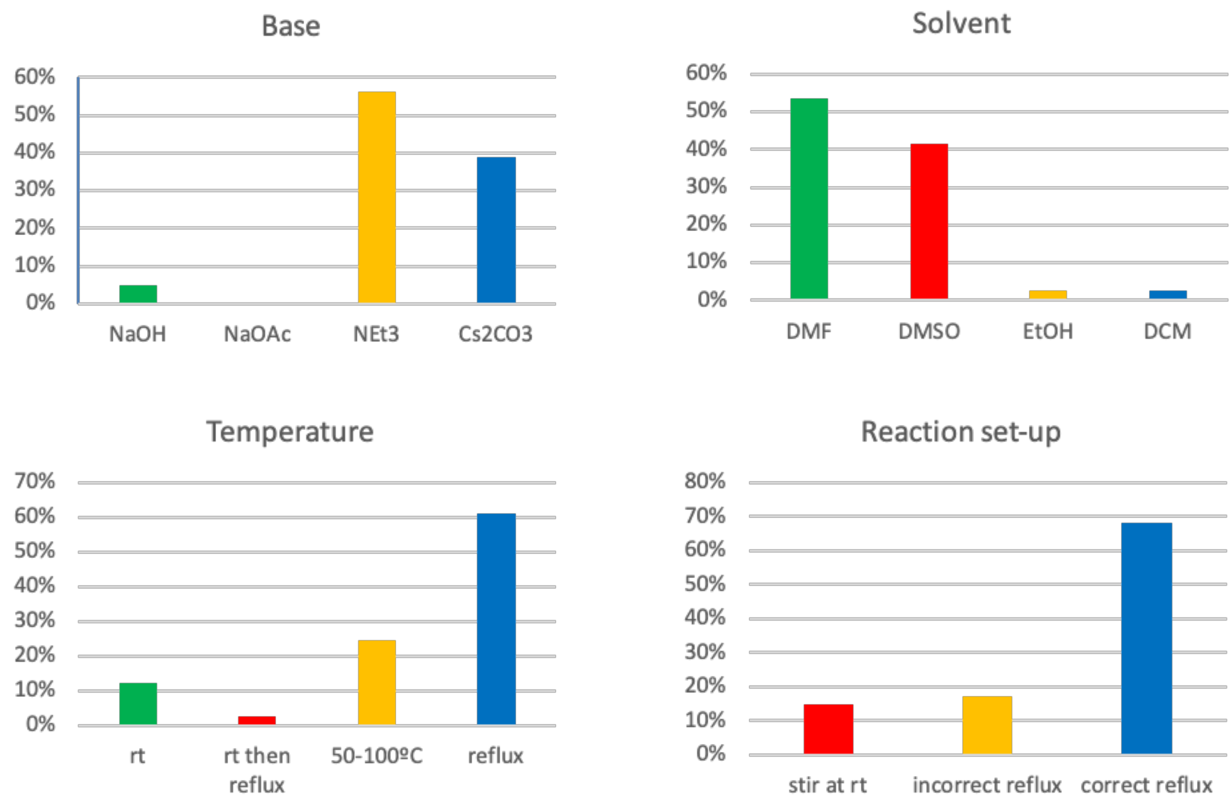


Figure 2: Summary of reaction parameters chosen by students.

STUDENT SUBMISSIONS

In 2018 and 2019 combined there were 41 experimental protocol submissions. We analyzed the protocols to determine what parameters students had chosen in their designs (figure 2). Triethylamine was the most popular base chosen by 56% of groups, followed by caesium carbonate at 39% and sodium hydroxide at 5%. No group chose sodium acetate which has a pK_a lower than that of phenol. The most common explanations for choosing the base was that it had a high pK_a. Some groups elaborated more and explained that this would ensure it could deprotonate phenol and would act as a nucleophile. For the solvent, 54% of groups chose DMF and 41% chose DMSO. This represents over 95% of submissions choosing a solvent that favors S_N2 reactions. The most common explanation by students for choosing their solvent was that it was polar aprotic. Some groups provided further explanation to say this meant the solvent would not solvate the nucleophile or participate in side reactions. Heating the reaction, either to a temperature ranging from 50-100 °C (24%) or to reflux

(64%) was the temperature most common temperature selected by groups designing a synthesis for secondary halides. Those reacting primary halides were more likely to select room temperature (12%) and one group selected room temperature then heating if the reaction had not occurred. Amongst the reasoning used to justify the temperature, increasing the rate of reaction was the most common reason following by further explanation by some of these groups to say that the reaction center is hindered. Those stirring at room temperature were most likely to explain that their reaction center was a primary halide. The percentage of different types reaction set-ups matched the proportion of students heating or stirring the reaction at room temperature. 17% of students heating their reactions provided an incorrect reflux set-up, usually with the water tubing the wrong way around.

When we analyzed the work-ups we found that only 7% of the designed work-ups would not have been viable for isolating the product from excess starting material (figure 3). All other submissions incorporated a base wash which would remove unreacted phenol. The remainder of work-up designs depended on the base that groups chose to use. Those that used triethylamine incorporated an acid wash either in the first or second step to remove the base from the organic layer. Those using caesium carbonate used either a water, base or acid wash as they reasoned the inorganic base would preferentially dissolve the in the aqueous layer.

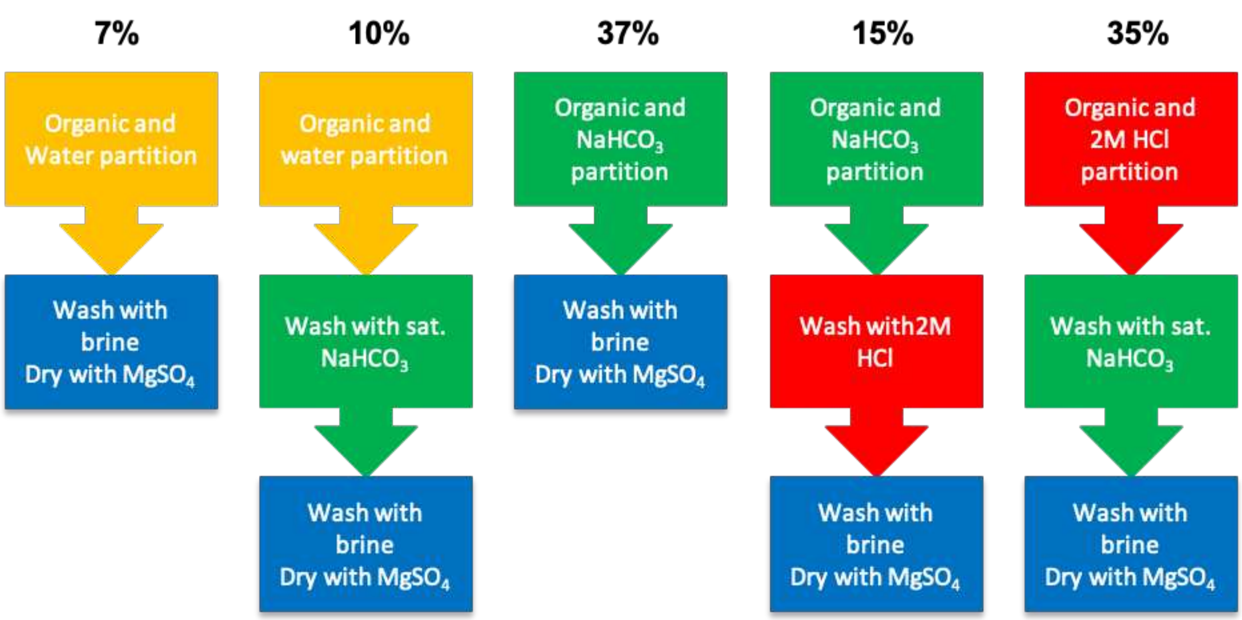


Figure 3: Summary of work-up protocols submitted by students.

EVALUATION OF SKILL DEVELOPMENT

To determine how this activity developed skills in experimental design students completed a self-assessment survey which we had designed previously to measure experimental design skills where they rated their knowledge, experience and confidence of particular skills.[24] This style of survey has also been used by others to measure the effect of practical skill development in laboratory courses.[25, 26] In our survey, students also rated their knowledge and confidence relating to their understanding of experimental parameters such as the properties of solvents, which were important for completing this activity. Ethical approval was obtained from the University of Leeds ethical approval board. The survey was completed by students at the start of the laboratory course (N = 306) and following this activity (N = 166) over two years of this workshop being administered. These results received represents over 50% of the students who took part in the activity. The pre and post survey means were calculated and shown to be statistically significant through t-tests ($p < 0.05$). Cohen's d values were calculated and the guidelines from Sawilosky were used to determine the effect size (table 1).[27]

For skills relating to setting up reactions and choosing their TLC parameters, medium effect sizes were seen for student's knowledge, experience and confidence. For designing a work-up the effect size was large for all three aspects of this skill. For understanding solvent properties, a small effect size was obtained. For understanding reactants properties and how TLC works, a medium effect was obtained. For liquid-liquid extraction there was a large effect was observed. Overall these results show that the activity was successful in improving students perceived skill development and understanding relating to experimental design.

Table 1. Results of the self-assessment of skills development survey.

Item		Pre-activity mean[a]	Post-activity mean[b]	Cohen's d	Effect
Choosing a suitable set-up of a reaction if this has not been given in a procedure.	Knowledge	3.07	3.53	0.51	Medium
	Experience	2.60	3.16	0.54	Medium
	Confidence	2.71	3.25	0.54	Medium
Choosing suitable parameters for monitoring reaction progress by thin layer chromatography (TLC)	Knowledge	2.71	3.06	0.71	Medium
	Experience	2.07	2.81	0.78	Medium
	Confidence	2.08	2.75	0.69	Medium
Designing a procedure to purify a mixture by liquid-liquid separation.	Knowledge	2.55	3.39	0.84	Large
	Experience	2.20	3.12	0.92	Large
	Confidence	2.27	3.06	0.79	Medium
Understanding how to use the properties of solvents to design experiments.	Knowledge	3.12	3.58	0.49	Small
	Confidence	2.87	3.25	0.39	Small
Understanding how to use the properties of reagents to design experiments.	Knowledge	3.02	3.62	0.64	Medium
	Confidence	2.80	3.43	0.66	Medium
Understanding the theory that underpins thin layer chromatography (TLC).	Knowledge	3.31	3.90	0.56	Medium
	Confidence	3.06	3.75	0.63	Medium
Understanding the theory that underpins liquid-liquid separation.	Knowledge	2.94	3.80	0.83	Large
	Confidence	2.75	3.64	0.85	Large

[a]N = 308.[b]N = 166

SUGGESTIONS FOR ADAPTING DELIVERY ELSEWHERE

The workshop was delivered by two of the authors (Mistry and Singh) who were familiar with the learning outcomes of the activity and experienced with teaching open-ended style laboratory activities. For an instructor, such as a Teaching Assistant, with less experience, the temptation with students struggling to get to the answer could be to tell the students what parameters to choose. Therefore, training may be necessary for those delivering this workshop to ensure the learning outcomes are met.

Whilst we included the laboratory synthesis and testing component by researchers for this activity, the learning outcomes would still be achieved without these components. This could be particularly advantageous where remote learning is required. Another advantage of the classroom-based nature of this activity is that it allows easy adoption in both laboratory and non-laboratory modules. For example, this activity could be used to a form of assessment for organic chemistry modules.

In reality, this type of reaction is more commonly performed in a sealed tube and/or with heating by microwave radiation. Our students had only had experience of heating experiments under reflux, hence this being the most popular choice. If students are familiar with sealed-tube reactions then this should be successful in producing the desired products should they choose this technique.

The activity could also be expanded to include students designs of further purification after work-up using column chromatography. These weren't included here because students are taught this technique in their second-year laboratory course.

CONCLUSION

In summary, we have designed an activity that helps students learn how to design experiments to synthesize organic molecules. Students were able use their knowledge to choose appropriate bases, solvents, reaction set-ups and purification procedures that yielded the desired products when tested experimentally. They were also able to contribute towards a real research project. We also evaluated the development of students' experimental design skills and understanding of reaction parameters, discovering that this activity was effective in improving students perceived skills.

ASSOCIATED CONTENT

The Supporting Information is available at https://pubs.acs.org.
Experimental design workshop handout (DOCX)
Experimental protocol form (DOCX)

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Notes

The authors declare no competing financial interest.

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