Experiment 41

Multistep Synthesis Project: Choosing and Completing a Synthetic Route

You have already done several multistep syntheses by this point in the semester, but for this project you will choose your own rather than following a predetermined lab procedure. This experience will be similar to doing graduate school research: your TA and the Lab Director will be able to offer you general advice on techniques, but the only information you'll have on the steps of your specific reactions will come from the literature. For this reason, you should be extremely attentive to your chosen literature procedure.

It's not absolutely crucial that you finish every step of your chosen synthesis. It's more important that you can discuss what you've accomplished so far, and what might have gone wrong or what you might have done differently. If you have to go back and repeat a step (or even start the entire project again from the beginning) then your grade won't necessarily suffer, so long as you provide a reasonable analysis. The NMR spectra you collect of your intermediates will help you to write this analysis and to determine how well each step of your synthesis has worked.

You can either choose one of the example projects given below, or select your own from the literature - the Journal of Chemical Education (available at pubs.acs.org) is a good place to look. Look for a synthesis that will take you around the allotted amount of time (six lab periods of three hours each); your choice may be rejected if it too long or too short. You can also pick a collection of short syntheses on a related theme – several examples are given below, like the "Liquid Crystals" or "Local Anesthetics" projects. If you do this, you should choose a set of syntheses that will add up to the allotted amount of time.

Be sure to check whether there is supporting information available for your source papers! This supporting information often contains a detailed procedure and sometimes even a lab experiment handout that was given to students.

If you choose your own project that is not listed in this experiment, there is a risk that the project will be rejected if the CU labs don't have the necessary equipment. If in doubt, ask first.

Only a single person from each lab section will be allowed to choose any particular project. For this reason, you should notify the lab director of your choice as early as possible to ensure you can do one of the projects that interest you the most. A tally of which projects are still available will be posted on the course website throughout the semester, on a page linked from the 3381 experiment schedule. Several other useful documents will also be available there, such as a template for materials requests and an example presentation and paper.

The projects give a wide range of possible yields. Scale the synthesis project up or down to aim for 400-800 mg of final product. If you're making multiple final products, then aim for 400-800 mg of each. You may also have to scale your glassware sizes up or down to compensate. For instance, if your paper calls for a 25 mL round-bottom flask but produces only 50 mg of final product, then you will probably have to use a 250 or 500 mL round-bottom flask if you scale your procedure up. In addition, some items of glassware (like conical vials) are designed for microscale use only. For instance, if the total volume of the reagents you will use for a step is greater than 5-10 mL and the procedure calls for a conical vial, you should use a round-bottom flask instead.

Experiment 41: Multistep Synthesis Project

Deliverables

For your project, you must complete all of the following steps. Due dates are given on the syllabus.

1. Write up a **materials request** describing which project you are choosing to do, and giving a list of materials and quantities you will need. The spreadsheet template that you must use is available on the course website. Download this document and edit it as needed, then email it as a spreadsheet to the Lab Director. You will have to list a CAS number and commercial source for each chemical you need – see further instructions in the spreadsheet. **Make sure you request every single item or reagent that you need**, because if you suddenly realize that you need something midway through your synthesis, there is no guarantee that it will arrive in time. It is a good idea to request 2-3 times as much of each compound as you expect to use, in case you need to repeat a step that has failed.
2. Write a **project proposal**, approximately one page long, detailing the synthesis or syntheses you intend to perform (including the synthesis drawn out in ChemDraw). This should also include mentions of any specialized equipment and what you intend to use it for. This will be due at the same time as the materials request, and must also be emailed to the lab director.
3. Type up a **prelab**, including all the normal parts of a prelab (hazards, mechanism, procedure, etc.). You might wish to plan in some fallback options – for instance, "Day 2: if intermediate NMR is clean and matches the literature NMR, perform the next step of the synthesis as follows. If not, perform column chromatography and recrystallize the intermediate." This is due at the start of the first lab period for this experiment.
4. While performing your synthesis, collect an **NMR spectrum** for the product of each step unless it is too reactive to isolate. For each compound you should collect at least a ^{1}H NMR, although you may wish to collect other spectra (^{13}C, 2D NMR, etc.). Compare each NMR to the literature spectra for your compounds, to help you analyze whether you synthesized your target product and how pure it is. If you have enough compound, you can also collect an IR and/or melting point. If you have a limited amount of intermediate, you can submit some for an NMR spectrum, then recover it back out of the tube, evaporate off the solvent, and carry it on to the next step of the synthesis. Some projects also specify the use of additional, specialized methods of characterization, such as DSC, PLM, MS, or UV-Vis. You should speak to the lab director about these.
5. Write a **paper** detailing the structure of your target compound, the steps you took to synthesize it, and the mechanism, percent yield, NMR, and descriptions of special apparatus (if any) for each step. You can also include a brief section on background information and relevance of the compound, and/or the methods you used to synthesize or characterize it. For instance, a synthesis featuring a palladium coupling reaction might have a section about the background and history of palladium coupling reactions. Each paper should include all of your relevant spectral data within the document, and all references must be cited in ACS format. An example paper is provided on the course website.
6. Create a 15-20 minute **presentation** about your synthesis project, to be given the week after the independent projects are finished. A computer with Powerpoint will be available, but you can bring your own computer and/or use different software if you prefer. An example of a satisfactory breakdown for this presentation is:
    a. 1-2 slides background information and relevance
    b. 1-2 slides procedure and reactions
    c. For each step of the synthesis: mechanism, percent yield, NMR, photos (if any) and descriptions of special apparatus (if any).
    d. Overall yield, satisfaction with lab, and possible improvements

    If you like, you can take photos of any unusual apparatus, solution appearances, etc. to put into the presentation. Make sure your chemical structures are legible; if you're using a background color other

than white, you might want to make your structures a different color, or use larger line widths for higher visibility.

7. Submit **electronic copies** of your presentation and your paper to the Lab Director, on the same day you submit the paper copy to your TA. The electronic version of the paper must be a single file – either PDF or docx – that contains all of the spectral data that you took of your compounds. This file should be named as "Section Number – Last Name"; for instance, "411 – Smith.pdf".

Potential Projects

Some possible project choices are listed below.

Name	References	Notes
Antidepressants	Perrine, D. M., Ross, J. T., Nervi, S. J., Zimmerman, R. H. *J. Chem. Educ.* **2000**, *77*, 1479-1480. Perrine, D. M., Sabanayagam, N. R., Reynolds, K. J. *J. Chem. Educ.* **1998**, *75*, 1266. More, J. D. *J. Chem. Educ.* **2008,** *85,* 1424-1425.	Aim to synthesize the compound from each paper. Do not ingest any of the compounds.
Artemisinin	Roth, R. J., Acton, N. *J. Chem. Educ.* **1991**, *68*, 612-613.	Perform photooxidation outdoors, in sunlight.
Azulene	Lemal, D. M., Goldman, G. D. *J. Chem. Educ.* **1988**, *65*, 923-925.	Perform first two steps on same day, to prevent dimerization of cyclopentadiene (step 2 will have to run in a hood after your lab period finishes – talk to lab staff). Lab staff will provide freshly-distilled THF for step 4 – be sure to request it the day before you need it. Monitor step 4 by using UV-Vis.
Betaine-30	Osterby, B. R., McKelvey, R. D. *J. Chem. Educ.* **1996**, *73*, 260-261.	Get a photo of betaine-30 dissolved in each of the solvents listed in the first paragraph of the paper.
Chrysanthemic Acid	Schatz, P. F. *J. Chem. Educ.* **1978**, *55*, 468-470.	You might not be able to finish the whole synthesis unless you do the first two reactions simultaneously, but get as far as you can.

Copper-Based Catalysis	Ison, E. A., Ison, A. *J. Chem. Educ.* **2012**, *89*, 1575-1577.	
Dyes	McCullagh, J. V., Daggett, K. A. *J. Chem. Educ.* **2007**, *84*, 1799-1802.	Aim to synthesize two or three of the dyes and characterize by UV-Vis.
10-Ethyl Flavin	Sichula, V. A. *J. Chem. Educ.* **2015**, *92*, 1539-1542.	You might not be able to finish the whole synthesis, but get as far as you can.
Fragrances	Miles, W. H., Connell, K. B. *J. Chem. Educ.* **2006**, *83*, 285-286.	Aim to synthesize methyl diantilis and at least two additional diantilis products. You can use other alcohols than the ones listed.
Insect Pheromones	Feist, P. L. *J. Chem. Educ.* **2008**, *85*, 1548-1549. De Jong, E. A., Feringa, B. L. *J. Chem. Educ.* **1991**, *68*, 71-72. Schwarz, M., Klun, J. A. *J. Chem. Educ.* **1986**, *63*, 1014-1015. Bartlett, P. A. et al. *J. Chem. Educ.* **1984**, *61*, 816-817. Cormier, R., Hoban, J. N. *J. Chem. Educ.* **1984**, *61*, 927-928.	Choose two or three of these pheromones to synthesize. If you use Method C from Schwartz, use DIC or EDCI instead of DCC (they are far safer and easier to remove from the product).
5-(2-Iodoethyl) salicylaldehyde	Ji, C., Peters, D. G. *J. Chem. Educ.* **2006**, *83*, 290-291.	Skip last step (conversion to thiol) due to toxicity and stench of product. Skip GC/MS characterization.
Ionic liquids	Dzyuba, S. V., Kollar, K. D., Sabnis, S .S. *J. Chem. Educ.* **2009**, *86*, 856-858. Mak, K. K. W., Siu, J., Lai, Y. M., Chan, P. *J. Chem. Educ.* **2006**, *83*, 943-945.	Aim to synthesize the ILs from both papers, and follow the Mannich reaction procedure from the second paper.

Liquid Crystals	Jensen, J., Grundy, S. C., Bretz, S. L., Hartley, C .S. *J. Chem. Educ.* **2011**, *88*, 1133-1136. Verbit, L. *J. Chem. Educ.* **1972**, *49*, 36-39.	Aim to synthesize at least two products from 1st paper, and cholesteryl benzoate from 2nd. Skip DSC analysis, but PLM will be available.
Local Anaesthetics	Demare, P., Regla, I. *J. Chem. Educ.* **2012**, *89*, 147-149. Reilly, T. J. *J. Chem. Educ.* **1999**, *76*, 1557.	Aim to synthesize either benzocaine or prilocaine from the first paper, and lidocaine from the second.
Organocatalysis	Wade, E. O., Walsh, K. E. *J. Chem. Educ.* **2011**, *88*, 1152-1154.	In addition to literature substrate, choose one other aldol reaction to enantioselectively catalyze. We don't have a chiral HPLC, so use polarimeter and/or chiral shift reagents to assess %ee.
Multistep Carbonyl Chemistry	Duff, D. B., Abbe, T. G., Goess, B. C. *J. Chem. Educ.* **2011**, *89*, 406-408.	
4-Nitro-1-ethynylbenzene	Goodwin, T. E., Hurst, E. M., Ross, A. S. *J. Chem. Educ.* **1999**, *76*, 74-75.	
Poly(phenylenevinylene)	Knoerzer, T. A., Balaich, G. J., Miller, H. A., Iacono, S. T. *J. Chem. Educ.* **2014**, *91*, 1976-1980.	Skip GC/MS and GPC characterizations. Step with butyllithium requires assistance/supervision from lab director, so provide notice when you are ready for this step.

Polymers	Weizman, H., Nielsen, C., Weizman, O. S., Nemat-Nasser, S. *J. Chem. Educ.* **2011**, *88*, 1137-1140. Mako, T., Levine, M. *J. Chem. Educ.* **2013**, *90*, 1376-1379. Carraher, C. E. *J. Chem. Educ.* **1978**, *55*, 51-52. Garner, C. M., Nething, M., Nguyen, P. *J. Chem. Educ.* **1997**, *74*, 95-96. Sanford, E. M., Hermann, H. L. *J. Chem. Educ.* **2000**, *77*, 1343-1344.	Choose at least two polymers to synthesize. Spin coater, DSC, GPC, and GC/MS are not accessible to students, so skip these steps. If synthesizing Nylon, use a three-necked flask with nitrogen fitting. If you use procedure from Weizman, use DIC or EDCI instead of DCC (they are far safer and easier to remove from the product).
Solid-Phase Peptide Synthesis	Kirin, S. I., Noor, F., Metzler-Nolte, N. *J. Chem. Educ.* **2007**, *84*, 108-111.	Choose one of the markers. Do not scale up this project to increase the yield. You will probably have to pause midway through the synthesis steps; follow the instructions for doing so. Submit samples for MS. NMR is not necessary since it's not very useful for this product.
Sunscreens	Stabile, R. G., Dicks, A. P. *J. Chem. Educ.* **2004**, *81*, 1488-1491.	Aim to synthesize compound listed in paper and at least one other homologue by using a different alkyl iodide. Characterize by UV-Vis.
Sweet and Bitter Compounds	Williams, B. D., Williams, B., Rodino, L. *J. Chem. Educ.* **2000**, *77*, 357-358. Mann, T. D., Mosher, J. D., Wood, W. F. *J. Chem. Educ.* **1992**, *69*, 668-669.	Do not ingest any of the products.
Terphenyl Derivatives	Colby Davie, E. A. *J. Chem. Educ.* **2015**, *92*, 1209-1213.	Start from the beginning of Lehman's synthesis (cited in this paper).