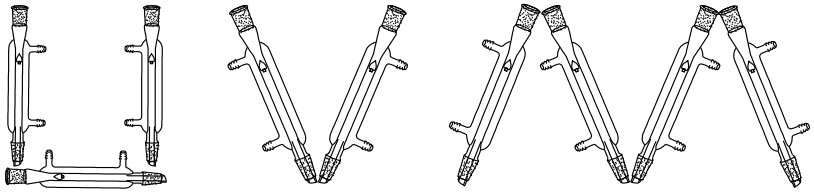

Advanced Organic Laboratory
Chemistry 146
Fall 2012

Instructor: Matthias Brewer 656-1042 Cook A316 Matthias.Brewer@uvm.edu
Teaching Assistant: Daniel Bercovici 656-0277 Cook A315 Daniel.Bercovici@uvm.edu
Lab Time: 1:00pm – 5:00pm T & Th, Cook A305
Instructor office hours: By appointment or for quick questions just stop by.
T.A. office hours: By appointment or for quick questions just stop by.
Website: www.uvm.edu/~mbrewer1

Texts: Blue lab notebook with page numbers; same as required for Chem. 35 (Bookstore item#: 77571)
No textbooks are required!

Books that will be useful:

Encyclopedia of Reagents for Organic Synthesis (EROS) [QD 77.E35 in reference section] This series includes: information about safety concerns; methods of preparation/purification; physical data; a survey of uses for each reagent. This should be consulted each time you handle a new reagent.
Spectrometric identification of organic compounds R.M. Silverstein, F.X. Webster *In Brewer's Office*
Organic Structural Spectroscopy J. Lambert, H. Shurvell, D. Lightner, R. Cooks *In Library*
High-Resolution NMR Techniques in Organic Chemistry T. Claridge *In Library*

Other books that may be useful:

Advanced Organic Chemistry, Part A, 4th ed. F.A. Carey and R.J. Sundberg ISBN: 0-306-46243-5
Advanced Organic Chemistry, Part B, 4th ed. F.A. Carey and R.J. Sundberg ISBN: 0-306-46245-1
The Art of Writing Reasonable Organic Reaction Mechanisms R.B. Grossman
Writing Reaction Mechanisms in Organic Chemistry A. Miller ISBN: 0-12-496711-6
Advanced Organic Chemistry, J. March, 4th or 5th edition ISBN: 0-471-58589-0
Stereochemistry of Organic Compounds, E.L. Eliel, S.H. Wilen ISBN: 0-471-01670-5

Course Purpose: I have designed this course to try to achieve several goals. The first, obviously, is to introduce you to some advanced laboratory techniques that are essential in modern synthetic organic chemistry. The second is to provide you with hands on experience with NMR, and to introduce you to more advanced NMR techniques and interpretation. Third, the experiments we preform will highlight some fundamental concepts in organic chemistry that you have likely seen in your course work. Unlike previous labs, many of the experiments that we do will be multi-step sequences in which the material you produce in one lab will be used in the next.

This course will address each of the following departmental learning goals for chemistry majors:

1. Students will demonstrate general knowledge in chemistry and will be able to apply chemical and physical principles in the solution of qualitative and quantitative chemical problems.
2. Students will understand the interplay of observational data, hypotheses, and hypothesis-driven experimentation through application of the scientific method.
3. Students will become proficient in chemical laboratory techniques and be able to apply these to practical and current problems in research.
4. Students will be able to read and critically evaluate the chemical and scientific literature.

5. The students will learn to present scientific data clearly and effectively through both written and verbal communication.

Grading: Lab report write-ups (85%); Work approach (5%); Other assignments (10%)
The majority of your grade (85%) will be based on the lab write-ups. These will be due one week from the completion of the lab work. This is an advanced lab and your write-ups should reflect this. The lab report will be comprised of several sections and separate handouts will demonstrate these to you in more depth. The following is a quick summary:

Prelab: The T.A. will verify that a prelab has been satisfactorily completed before any lab work will begin. If the prelab is not satisfactorily completed it will be assigned a grade of zero for its portion of the overall grade for this lab and the student will not begin labwork until the prelab is complete to the T.A.'s satisfaction. At a minimum the prelab must include: the date; a schematic drawing of the reaction to be done; a table showing the molecular weight, density (for liquids), number of moles, number of grams, and number of mL to be used for each substance; a list of potential hazards and precautions to be taken; a brief experimental procedure written in your own words that you will follow.

Observations and notes: A detailed description of what you actually did and what you observed. This should be in sufficient detail that anyone reading your notebook could repeat the reaction exactly as you did it. Examples of standard notes and observations include: the time something was added, how long it took to add it, how long materials were allowed to react, gas evolution, color change, precipitate formation, reproduction of TLC results including rf calculations, tare weights, weights or volumes of materials used, etc….

Post-lab write-up: This is where the majority of the grade will lie. This should be a formal (typed) detailed discussion of the experiment including a background discussion about the type of reaction preformed, a discussion of the mechanism (computer drawing software must be used to draw all chemical structures in the post-lab [drawing software can be downloaded for free from the UVM Chemistry Department website]), spectral interpretation (Proton **and** Carbon NMR **and** MS data), and an interpretation of the results. *For indicated experiments this must also include a detailed experimental procedure written in journal format including all spectral data.*

Assignment deadlines: Part of your assignment will be to gather NMR or GC/MS data for the compounds you prepare. You must turn these spectra into the T.A. on the assigned date or face a 1/3 grade deduction (i.e. A → A-). All assignments including post-lab write-ups must be handed in at the beginning of the lab period on the date they are due. Any assignment not handed in at the beginning of lab will be penalized by one letter grade if they are handed in by 1:00pm the following day (i.e. within 24 hrs of the deadline). If the assignment is handed in within the subsequent 24 hrs (i.e. within 48 hrs of the deadline) then the final grade will be penalized two letter grades. No assignment will be accepted after 48 hrs of the deadline.

Work Approach (5%): Work approach points will be assigned by the TA. These points should be considered something you have to earn, not something that is taken away as a punitive measure for making mistakes. How do you earn these points? Approach your laboratory work in a safe, effective and efficient manner while being a good class citizen. The actual yield of your product will not be considered, but your approach to safety in the laboratory as well as your cleanliness and ability to apply good chemistry practices in your work certainly will. People who leave class early rather than taking time to help tidy up communal laboratory space will find it difficult to earn these points, as will people who are careless in their work habits, use poor chemical practices, show unsafe behavior or use flawed laboratory techniques.

Other assignments (10%):
The following assignments will be worth a combined total of 10% of your final grade. Detailed instructions will be given at a later date:

1) *Chemical database searching*: Reaxsis provides electronic access to Beilstein organic chemistry database. SciFinder Scholar provides electronic access to Chemical Abstracts. These databases and their corresponding search engines are invaluable research tools for organic chemistry. You will be assigned a project that will introduce you to these tools.

2) *Graduate school search*: The goal here is to get you to think seriously about graduate school as a possible career path. You will be asked to identify at least 5 graduate programs that you would consider applying to, and to provide a quick summary of the research that interests you within those departments.

3) *Proposal to develop a green organic reaction*: Over the past several decades chemists have increasingly recognized the environmental impact of our discipline. Green chemistry is a blossoming field of study that aims to develop safe, practical and environmentally benign procedures to replace existing more hazardous reaction sequences. In this assignment you will be asked to provide a green method to make a certain compound. To determine the greenest approach to this synthesis you may of course consult the literature. We will then attempt to make the compound using one of the methods proposed.

4) *NMR spectrum interpretation exercise*: You will be given an NMR spectrum to interpret. The structure will be provided, but all coupling constants must be calculated and all peaks must be assigned to the correct proton on the structure.

Attendance: Due to the multi-step nature of the experiments to be preformed in this laboratory attendance is particularly important. If you miss a step you will not have the material available to you to perform the subsequent step. Therefore, any absence not prearranged with the instructor will result in a grade of zero for that particular multi-step sequence. This will have a major impact (>25%) on your final grade. *Religious Holidays: Students have the right to practice the religion of their choice. Each semester students should submit in writing to their instructors by the end of the second full week of classes their documented religious holiday schedule for the semester. Faculty must permit students who miss work for the purpose of religious observance to make up this work.*

Academic Conduct: Cheating or plagiarism will be considered grounds for failing the course. Cases of cheating or plagiarism may lead to further disciplinary actions including dismissal from the University according to the rules set forth in The University of Vermont's *Code of Academic Integrity*.

If you do not have a copy of the Aldrich Catalogue (i.e. Aldrich Handbook) request one at: http://www.sigmaaldrich.com/Brands/Aldrich.html
This is an invaluable free resource.

Schedule of Experiments

Sept. 4: Check in and introduction to course

Sept. 6: NMR training with Dr. Bruce Deker

Sept. 11: Reaction of methyl 4-formylbenzoate with $NaBH_4$ / GC/MS training

Sept. 13: Hetero-Diels-Alder Set up

Sept. 18: Work up Hetero-Diels-Alder reaction

Sept. 20: Set up diaza Claisen rearrangement

Sept. 25: Work up diaza Claisen rearrangement and optimize chromatography eluent by TLC (**NMR spectrum interpretation exercise due**)

Sept. 27: Purification of diaza Claisen rearrangement product by chromatography

Oct. 2: Synthesis of (4-nitrophenylethynyl)trimethylsilane *via* Pd catalyzed Sonogashira coupling

Oct. 4: Purification of (4-nitrophenylethynyl)trimethylsilane via chromatography **(Chemical database search assignment due)**

Oct. 9, 11, 16: Preparation of a 4-mer peptide by solid phase peptide synthesis, product purification and analysis by 2D NMR and MS^n-Mass Spec. and maybe a "fun lab".

Oct. 18: LDA titration/introduction to inert atmosphere techniques and TBS protection of 2-hydroxy

cyclohexanone

Oct. 23: Purification of the resulting α-silyloxy ketone via chromatography **(Green Ketone Synthesis Assignment First Draft Due)**

Oct. 25: Addition of lithiated ethyl diazoacetate to the ketone to give γ-silyloxy-β-hydroxy-α-diazoacetate

Oct. 30: Purification of γ-silyloxy-β-hydroxy-α-diazoacetate

Nov. 1st: Lewis acid mediated ring fragmentation of γ-silyloxy-β-hydroxy-α-diazoacetate and formation of a tricyclic nitrogen containing heterocycle via intramolecular azomethine ylide 1,3-dipolar cycloaddition and yield determination via NMR internal standard.

Nov. 6: Waste management presentation by ESF and tour of ESF facility **(Green Ketone Synthesis Assignment Final Draft Due)**

Nov. 8: Vacuum distillation (and maybe rocket propellant)

Nov. 13 and 15: Green Synthesis of ketone special project

Nov. 20 and 22: Preparation and consumption of *Meleagris gallopavo* (Happy Thanksgiving!)

Nov. 27: Green Synthesis of ketone special project **(Graduate school search Assignment Due)**

Nov. 29: Check out and Pizza party and possibly "build your own rockets" (if you are good).

Dec. 6^{h}: Final day to turn in last lab report.

Lab Report Due Dates and NMR / GCMS Responsibilities:

Lab Report 1:

Reaction of methyl 4-formylbenzoate with $NaBH_4$ / GC/MS training

Everyone gets her or his own NMR and GCMS by 9/18; Final lab report due 9/20 including full spectroscopic data write up in experimental section

Lab Report 2:

Hetero-Diels-Alder Setup and Work up Hetero-Diels-Alder reaction

Group A: NMR by 9/20; Group B: GCMS by 9/20; Final lab report due 9/27 including full spectroscopic data write up in experimental section

Lab Report 3:

Set up diaza Claisen rearrangement and work up diaza Claisen rearrangement and optimize chromatography eluent by TLC and Purification of diaza Claisen rearrangement product by chromatography

Group A: GCMS by 10/2; Group B: NMR by 10/2; Final lab report due 10/9

Lab Report 4:

Synthesis of (4-nitrophenylethynyl)trimethylsilane *via* Pd catalyzed Sonogashira coupling and Purification of (4-nitrophenylethynyl)trimethylsilane via chromatography

Group A: NMR by 10/9; Group B: GCMS by 10/9; Final lab report due 10/16 including full spectroscopic data write up in experimental section

Lab Report 5:

Preparation of a 4-mer peptide by solid phase peptide synthesis, product purification and analysis by 2D NMR and MS^n-Mass Spec.

No GCMS; Group B- Take NMR in DMSO-D_6 by 10/18; Final lab report due 10/25

Lab Report 6:

****Experiments run Oct. 18 → Oct. 30 will be combined into one lab report due on 11/8**

LDA titration / introduction to inert atmosphere techniques and TBS protection of 2-hydroxy cyclohexanone and purification of the resulting α-silyloxy ketone via chromatography

******Everyone gets her or his own GCMS and NMR before class on 10/25.******

Addition of lithiated ethyl diazoacetate to the ketone to give γ-silyloxy-β-hydroxy-α-diazoacetate and purification of γ-silyloxy-β-hydroxy-α-diazoacetate

Group A: NMR by 11/1, Group B: GCMS by 11/1

Lab Report 7:

******The experiment run Nov. 1 is due 11/13 and must include full spectroscopic data write up for each of the compounds prepared in the experimental section**

Lewis acid mediated ring fragmentation of γ-silyloxy-β-hydroxy-α-diazoacetate and formation of a tricyclic nitrogen containing heterocycle via intramolecular azomethine ylide 1,3-dipolar cycloaddition and yield determination via NMR internal standard. **Obviously everyone must take their own NMR and GCMS.**

Lab Report 8: **ESF tour on Nov. 6 and experiments run Nov. 8 → Nov. 27 will be combined into one lab report due on 12/6**

Waste management presentation by ESF and tour of ESF facility (provide a summary of the tour, and what you learned, in the write up).

Nov. 8: Vacuum distillation (and maybe rocket propellant) **Group A: GCMS by 11/13; Group B: NMR by 11/13**

Dec. 6th: Final day to turn in last lab report.