PHA 6472: Organic Synthesis of Drug Molecules (3 Credits)

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Office:	P5-33, Medical Sciences Building
Office Hours:	By appointment
Prerequisites:	PHA 6447 (Drug Design I) or permission by the instructor
Required Text:	*Advanced Organic Chemistry. Part B: Reactions and Synthesis.* 5th Edition. Carey & Sundberg. *(chapter topics & recommended practice problems below)*
Class Time:	Tue. & Thurs. @ 8:00 – 10:00 am. (class will begin at 8:00 pm and typically last ~75 minutes; students have from 8:00 – 10:00 am to complete in-class examinations and must arrive on time)
Classroom:	COMM (HSC) C1-017
Additional Refs.:	a.) *Org. Lett.* **2005**, *7*, 3247-3250.
	b.) *Angew. Chem. Int. Ed.* **2000**, *39*, 44-122. (selected syntheses)
	c.) *J. Am. Chem. Soc.* **2006**, *128*, 6310-6311.
	d.) *J. Am. Chem. Soc.* **2016**, *138*, 7268-7271.
	e.) *Strategic Applications of Named Reactions in Organic Synthesis.* Kürti & Czakó.
	f.) Prof. Andrew Myers (Harvard) Chem 115 Handouts: https://faculty.chemistry.harvard.edu/myers/pages/chem-115-handouts

Course Description: This is a graduate-level synthetic medicinal chemistry course aimed at teaching advanced synthetic organic chemistry with an emphasis on learning modern reactions/reagents, reaction mechanisms, transition state models and retrosynthetic analysis as a tool for planning chemical syntheses of drug molecules. Chemical synthesis of drug molecules and other biologically active compounds will be presented from the literature.

Course Philosophy: The expectation is that each of you have mastered course materials presented in the two-semester undergraduate organic chemistry sequence (chemical bonding, functional group properties & chemical reactivity, stereochemistry, reaction mechanism/arrow formalism, multi-step synthesis, etc.). In addition, a prerequisite is that you have PHA 6447 (Drug Design I), which devoted seven lecture hours and one exam to both intermediate and introductory advanced organic chemistry concepts/topics. Students have also taken additional graduate-level (advanced) organic chemistry courses (e.g., CHM 5224: Basic Principles of Organic Chemistry) before this course. You will find that many of the basic C-C bond forming organic reactions (i.e., Diels-Alder, Aldol, Grignard, Cuprates) or functional group transformations (i.e., oxidations, reductions, alcohol to alkyl halide; carboxylic acid/derivative to amide) in this course have been presented in previous coursework; however, we will dive into many new intricacies of importance to modern synthetic chemistry in this course. For this reason, I advise that students review their undergraduate organic chemistry textbook and relevant PHA 6447 materials as the expectations are that you are proficient in that material.

To Be Successful In This Course: Memorizing transformations of reactions will NOT lead to a working knowledge of course materials/advanced organic chemistry, but rather, each student should aim to understand and be able to rationalize a detailed reaction mechanism for each reaction we discuss at the level discussed in class (and be able to push electrons using standard arrow formalism from prerequisite courses).

Rational electron flow (reaction mechanisms) should guide the reaction transformations and allow students to work through organic reactions. When students can work through reaction mechanisms (by drawing them out with pen and paper, several times) at a high proficiency, predicting products and proposing chemical syntheses of target structures is less of a problem. Think *"Orbital Alignment"* as you consider work through electron flow and mechanistic reaction pathways & transition states, which is important when considering stereochemical consequences of reactions.

Learning organic chemistry is an active experience that requires a significant amount of time. Students who work through problems actively (with pen on paper) do best. Students who simply review notes, do poorly. Be active in your studies – draw reaction mechanisms, solve problems suggested from your textbook, reference past exams/answer keys, create problems to self-test, test peer students and bring questions to me (before the relevant exam). Select handouts will be provided during lectures.

Details and clarity matter in this course and in a career involving chemistry research. All chemical structures should be drawn clearly for grading purposes. Review all of your answers before submitting in-class examinations. Structures drawn incorrectly will be marked wrong (examples of errors include the following: 1. drawing a methyl group instead of an ethyl group; 2. writing a methoxy group ortho on a benzene ring when it should be in the para position; 3. reactive intermediates/products of reactions drawn with incorrect stereochemistry, etc.; these are errors and credit cannot be given in these instances).

Students should anticipate devoting 6-9 hours outside of class each & every week to learning and mastering the material presented during lecture periods (semester is ~15 weeks; 90-135 hours total). The more time you spend drawing reaction mechanisms and transition state models from class notes, and solving suggested problems at the end of each chapter in the textbook, the better you can expect to perform in this course.

Course Objectives and Goals:

After the successful completing this course, students will be able to do the following:

1.) Develop an excellent working knowledge of advanced organic chemistry.
2.) Gain a significantly expanded knowledge base regarding modern chemical reactions, including transition states.
3.) Understanding chemical reactivity on a detailed mechanistic level.
4.) Be proficient in chemical synthesis strategies.
5.) Gain an increased vocabulary of named organic reactions.
6.) Use retrosynthetic analysis as a problem-solving tool for the synthesis of organic/drug molecules.
7.) Plan logical chemical syntheses of simple to complex drug molecules using retrosynthetic analysis.
8.) Understand the current chemical synthesis and medicinal chemistry literature.
9.) Understand the significant roles chemical synthesis plays in the development of drug molecules.

Student Evaluations: Students will be graded on four in-class exams. Note: Exams will be graded based on lecture content (not content that was presented in a different organic chemistry course, or based off information found in another source).

Exam 1:	25% (100 points)
Exam 2:	25% (100 points)
Exam 3:	25% (100 points)
Exam 4:	25% (100 points)
Total class points:	100% (400 points)

Course letter grades will be assigned according to the following percentage scale (out of 400 possible points): 100-91.5% (A), 91.4-89.5% (A-), 89.4-87.5 (B+), 87.4-81.5% (B), 81.4-79.5 (B-), 79.4-69.5 (C), 69.4-59.5 (D), <59.4 (E).

Required Text: *Advanced Organic Chemistry. Part B: Reactions and Synthesis.* 5th Edition. Carey & Sundberg.

Text Chapters and Suggested Problems (Literature References for Problems Included)

Ch 1: Alkylation of Enolates & Other Carbon Nucleophiles. *Problems: 1.2, 1.3, 1.8, 1.10.*
Ch 2: Reactions of Carbon Nucleophiles with Carbonyl Compounds. *Problems: 2.1, 2.2, 2.12, 2.14, 2.23.*
Ch 3: Functional Group Interconversion by Substitution, Including Protecting & Deprotection. *Problems: 3.1, 3.4, 3.15.*
Ch 4: Electrophilic Additions to Carbon-Carbon Multiple Bonds. *Problems: 4.1, 4.4, 4.12, 4.18.*
Ch 5: Reduction of C-C Multiple Bonds, Carbonyl Groups & Other FGs. *Problems: 5.1, 5.3, 5.4, 5.9, 5.11, 5.17.*
Ch 6: Concerted Cycloadditions, Unimolecular Rearrangements, and Thermal Eliminations. *Problems: 6.1, 6.3, 6.15, 6.19.*
Ch 7: Organometallic Compounds of Group I & II Metals. *Problems: 7.1, 7.8, 7.13, 7.15.*
Ch 8: Reactions Involving Transition Metals. *Problems: 8.1, 8.4, 8.7, 8.8, 8.14, 8.20.*
Ch 9: Carbon-Carbon Bond-Forming Reactions of Compounds of Boron, Silicon & Tin. *Problems: 9.1, 9.2, 9.15.*

Ch 10: Reactions Involving Carbocations, Carbenes & Radicals as Reactive Intermediates. *Problems:* *10.1, 10.2, 10.10.*
Ch 11: Aromatic Substitution Reactions. *Problems:* *11.1, 11.2, 11.3.*
Ch 12: Oxidations. *Problems:* *12.1, 12.2, 12.8, 12.10.*
Ch 13: Multistep Synthesis. *Problems:* *13.1, 13.2, 13.5, 13.8, 13.12.*

** Suggested problems are challenging and for practice – consult the literature references (at the back of the textbook) **

** Literature references for suggested problems are located at the end of Carey & Sundberg (5th ed.): p. 1271-1295 **

Course Schedule

Date: Room (Exam Dates Highlighted)

1/6:	C1-017	
1/11:	C1-017	
1/13:	C1-017	
1/18:	C1-017	
1/20:	C1-017	
1/25:	C1-017	
1/27:	**C1-017**	**Exam 1 (8:00 – 10:00 am)**
2/1:	C1-017	
2/3:	C1-017	
2/8:	C1-017	
2/10:	C1-017	
2/15:	C1-017	
2/17:	C1-017	
2/22:	**C1-017**	**Exam 2 (8:00 – 10:00 am)**
2/24:	C1-017	
3/1:	C1-017	
3/3:	C1-017	
3/8:	--	No Class (Spring Break)
3/10:	--	No Class (Spring Break)
3/15:	C1-017	
3/17:	C1-017	
3/22:	C1-017	
3/24:	C1-017	
3/29:	**C1-017**	**Exam 3 (8:00 – 10:00 am)**
3/31:	C1-017	
4/5:	C1-017	
4/7:	C1-017	
4/12:	C1-017	
4/14:	C1-017	
4/19:	C1-017	
4/21:	C1-017	"reading day"
4/26:	C1-017	final exam week; "no class"
4/28:	**C1-017**	**Exam 4 (8:00 – 10:00 am)**

Exams:

Students will have from 8:00 – 10:00 am to complete each in-class exam on the dates indicated on the course schedule. All exams will be closed-book exams and UF's Honor Code Policy will be upheld at all times.

Student Expectations:

Students are expected to arrive before class is scheduled to begin with cell phones turned off (not set to silent). No laptops are allowed in class, or any other electronic device that can be a distraction for other students. Students are expected to behave in a respectful, mature, courteous manner toward the instructor and fellow classmates at all times.

Attendance and Make-Up Exams:

Requirements for class attendance and make-up exams, assignments, and other work in this course are consistent with university policies that can be found at: https://catalog.ufl.edu/ugrad/current/regulations/info/attendance.aspx. No exam re-takes will be allowed in this course.

Miscellaneous:

Students are expected to complete exams with integrity, aligning with UF expectations. Academic dishonesty will not be tolerated. If a student commits academic dishonesty, the academic penalty will be a failing grade in the course. The UF policies and procedures on academic dishonesty will be followed. For University of Florida's honor code, see http://www.dso.ufl.edu/sccr/honorcodes/honorcode.php

Students with disabilities requesting classroom accommodations should first register with the Disability Resource Center (352-392-8565, www.dso.ufl.edu/drc/) by providing appropriate documentation. Once registered, students will receive an accommodation letter which must be presented to the instructor when requesting accommodation. Students with disabilities should follow this procedure as early as possible in the semester.

Information on current UF grading policies for assigning grade points. This may be achieved by including a link to the web page: https://catalog.ufl.edu/ugrad/current/regulations/info/grades.aspx.

Students are expected to provide feedback on the quality of instruction in this course based on 10 criteria. These evaluations are conducted online at https://evaluations.ufl.edu. Evaluations are typically open during the last two or three weeks of the semester, but students will be given specific times when they are open. Summary results of these assessments are available to students at https://evaluations.ufl.edu.

There are no Materials and Supplies Fees for this course. Contact info.: Counseling and Wellness Center: http://www.counseling.ufl.edu/cwc/ (392-1575); University Police (392-1111 or 9-1-1 for emergencies).