CH270-15 Selective Organic Synthesis

20/21

Department
Chemistry
Level
Undergraduate Level 2
Module leader
Guy Clarkson
Credit value
15
Module duration
10 weeks
Assessment
20% coursework, 80% exam
Study location
University of Warwick main campus, Coventry

Description

Introductory description

N/A

Module web page

Module aims

This module builds on first year organic chemistry using your understanding of functional group reactivity to explore substituent effects on the electrophilic and nucleophilic substitution of aromatics. The introduction of heteroatoms into these systems provides a wealth of new chemistry and reactivity to be explored. Then transition metal catalysis for C-C bond forming will be examined as a counterpoint to earlier synthetic approaches.
The scope of the course then broadens to provide a range of synthetic chemistry to undertake many key functional group transformations. Reactions to form carbon-carbon single, double and triple bonds will be covered as well as their related oxidative cleavage. Oxidative and reductive reactions of carbon-heteroatom bonds will offer a complimentary picture of functional group manipulation. Many examples of regio- and stereoselectivity in these transformations will be highlighted. Finally, all this will be combined in the form of retrosynthetic analysis as a tool to develop your own strategies in organic synthesis.

Outline syllabus

This is an indicative module outline only to give an indication of the sort of topics that may be covered. Actual sessions held may differ.

Revision lectures on aromaticity
Aromaticity, aromatic ions and annulenes, orbital explanation of aromaticity, cyclobutadiene (distortion), cyclooctatetraene. Electrophilic substitution, o, m, and para, directing, activating and deactivating groups in benzene.

Further chemistry of benzene derivatives
Halogenation, Freidel Crafts acylation and alkylation, sulfonation, formylation, ipso substitution.
Sulfonation of naphthalene (kinetic verses thermodynamic), polyaromatics, C60
Electrophilic substitution reactions of disubstituted aromatics. Nucleophilic aromatic substitution, aryne formation.
Birch reduction, reduction of nitroaromatics, azo and diazonium salts and their transformations.

Deficient heterocycles
Pyridine, electrophilic substitution, nucleophilic substitution, pyridine-N-oxides, Chichibabin reaction. Electrophilic and Nucleophilic substitution of pyrimidines and quinolones. Synthesis of pyridines.

Excessive heterocycles
Pyrrole, substitution at N and C, furan, thiophene and reactions with electrophiles, cycloadditions
Imidazole, Indole, reations with electrophiles. Synthesis of pyrrole, furan, thiophenes and indole

Saturated heterocycles and carbohydrates
Synthesis of 3-6 membered oxygen and nitrogen saturated heterocycles (lactones and lactams).
Effect on rate of cyclisation of ring size (entropy and enthalpy). Synthesis of epoxides, aziridines and thiiranes, the bonding orbitals that form the ring
How ring strain dominates the reactivity of small rings (ring opening epoxides/penicillin
Acetonides/acetals as protective groups (synthesis and hydrolysis)

Organopalladium chemistry to make biaryl C-C bonds
Advantages/disadvantages compared to electrophilic aromatic substitution.
Pd(0) (electron rich) oxidative insertion into “electron poor” bonds via Pd complex.
Generation of the Pd(0) catalyst from Pd(OAc)2
Displacement of halide from complex by other organometallic coupling partner (Grignard organo zinc/tin/borate and how to make them
Reductive elimination to make C-C bond (or C-N with nitrogen nucleophiles).
Sonogashira coupling and Bergmann cyclisation
Generating aromatic systems from linear precursors

Making C–C bonds using Organometallics
Organometallic Reagents. Formation by deprotonation with strong bases, Grignard and alkyl lithium formation by oxidative insertion, halogen-metal exchange. Useful C–C bond formation by reacting organometallics with carbon dioxide, aldehydes/ketones, carboxylic acids, use of 1,3-dithianes.
Grignard Reagents. Synthesis by insertion. Reactions with formaldehyde, aldehydes and ketones,

esters, nitriles, addition to enones in absence/presence of Cu(I).
Organozinc Reagents. Reformatsky reaction.
Organocopper Reagents. Synthesis by transmetallationand their use in conjugate additions, SN2-displacements, epoxide openings and reactions with acid chlorides.

Making C–C bonds using enolates
Enolate formation using strong bases, C- vs O-alkylation, thermodynamic vs kinetic enolate formation, alkylation of enolate anions, crossed-aldol reactions, stereocontrolled aldols with E- and Z-lithium and boron enolates, Zimmerman-Traxler transition states. Alternatives to enolates: enamines and silyl enol ethers (Mukaiyama aldol). Use of enolates to make rings: Dieckmann reaction, Robinson annulation.

Making C=C bonds
Wittig reaction including: formation of phosphonium ylids, cycloaddition mechanism, reactivity comparison with sulfur ylids, E-alkenes from stabilised ylids, Z-alkenes using non-stabilised ylids. Alternatives to the Wittig reaction including (i) Horner-Wadsworth-Emmons reaction to make E-alkenes, use of Arbuzov reaction to make phosphonate esters; (ii) Peterson reactions under acidic and basic conditions, (iii) Julia reaction of sulfone anions. Use of elimination reactions to make alkenes including (i) dehydrations; (ii) pyrolytic syn-eliminations involving esters, N-oxides, sulfoxides and selenoxides; (iii) from 1,2-diols (Corey-Winter).

Making C≡ C bonds
Corey-Fuchs reaction.

Functionalisation of alkenes
Oxymercuration/reduction. Hydration by hydroboration including mechanism, stereochemical issues, improved regio- and chemoselectivity with 9-BBN. Synthesis of C–C and C–N bonds using organoboranes.

Oxidation
Oxidation of Allylic C-H Bonds
Using selenium dioxide and singlet oxygen.
Important Methods for the Oxidation of Alcohols
Jones oxidation, PCC including allylic transposition with tertiary allylic alcohols, manganese dioxide for selective oxidation of allylic/benzylic alcohols, Dess-Martin periodinane, DMSO based oxidations including Swern and Corey-Kim procedures. DMSO based oxidation of C–X bonds.

Oxidative cleavage of alkenes
Using $NaIO_4$ and cat. $OsO_4/NaIO_4$ (cf ozonolysis).

Reduction of C=O and C=N Bonds
Reduction of esters using lithium aluminium hydride and DIBAL, reduction of carboxylic acids using borane, use of sodium borohydride to reduce aldehydes/ketones, ‘exhaustive’ reduction of ketones to alkanes using (i) Clemmensen reduction, (ii) Wolff-Kishner, and (iii) dithioacetal

Reductive approaches to amine formation
Reduction of amides using $LiAlH_4$ and borane, use of azides to make amines, reduction of C=N bonds using sodium cyanoborohydride.
Reduction of C–X Bonds
Reduction of halides and pseudohalides with $LiAlH_4$, use of Appel reaction to prepare halides from

alcohols.

Learning outcomes

By the end of the module, students should be able to:

- Differentiate the ring substituents on benzene into activating and deactivating, and ortho/para or meta directing.
- Understand the role hetero atoms play in the chemistry of heteroaromatic systems.
- Describe the synthesis and chemistry of aliphatic heterocyclic compounds.
- Understand how & when to use organopalladium chemistry in biaryl and alkyne aryl synthesis.
- Develop a solid grounding of the mechanisms of a wide range of organic chemical reactions and transformations.
- Understand and apply a wide range of important chemical transformations of use in modern organic synthesis. As well as revision, further application of important organic reactions seen in year 1 and the exposure to a significant number of new reactions.
- Develop solutions to problems in organic chemistry using retrosynthetic analysis.
- Learn to use software packages to search the chemical literature using key words, structural and partial structural queries to find reaction conditions to guide retrosynthetic analysis of target organic molecules and source spectral data and physical properties.

Indicative reading list

1. Organic Chemistry J. Clayden, N. Greeves, S. Warren, OUP, 2012 2nd Edn [CGWW]. Further Reading

2. Mechanism in Organic Chemistry R. W. Alder, R. Baker, J. M. Brown Wiley, 1971. QD 1722.A5.

3. The search for organic reaction pathways P. Sykes Longman, 1972.

4. Advanced Organic Chemistry, J. March, 4th Edn., Wiley, 1992, QD 1722.M2.

5. Heterocyclic Chemistry, J. A. Joule, G. F. Smith, Reinhold.

6. Aromatic Chemistry, M. Sainsbury, Oxford University Press.

Research element

e.g. essay, dissertation, individual or group research, research skills activity, etc.

Subject specific skills

Problem solving
Teamwork
Organisation and time management

Transferable skills

Problem solving
Teamwork
Organisation and time management

Study

Study time

Type	Required
Lectures	30 sessions of 1 hour (20%)
Tutorials	4 sessions of 1 hour (3%)
Practical classes	2 sessions of 1 hour (1%)
Other activity	2 hours (1%)
Private study	112 hours (75%)
Total	150 hours

Private study description

Self-study 112 hrs in total.

Other activity description

Revision Sessions.

Costs

No further costs have been identified for this module.

Assessment

You do not need to pass all assessment components to pass the module.

Assessment group D1

	Weighting	Study time
Workshop reports	20%	
Two sequential workshop reports of 2-3 pages. Formative feedback of report 1 to be provided before 2nd report is submitted. 2nd report worth 20%		
Online Examination	80%	

Feedback on assessment

Oral and written feedback on tutorials from tutors (formative) and assessed workshops (formative and summative) from module leaders.
Cohort level examination feedback provided via Moodle following the Exam Board.

Past exam papers for CH270

Availability

Pre-requisites

To take this module, you must have passed:

- All of
  - CH161-30 Introduction to Organic Chemistry

Post-requisite modules

If you pass this module, you can take:

- CH3E9-15 Advanced Organic Chemistry and Laboratory
- CH3G3-30 Advanced Chemistry (Organic, Inorganic and Physical) Industrial Placement
- CH3F3-30 Advanced Chemistry (Organic, Inorganic and Physical)

Courses

This module is Core for:

- UCHA-4 Undergraduate Chemistry (with Intercalated Year) Variants
  - Year 2 of F101 Chemistry (with Intercalated Year)
  - Year 2 of F122 Chemistry with Medicinal Chemistry (with Intercalated Year)
- UCHA-3 Undergraduate Chemistry 3 Year Variants
  - Year 2 of F100 Chemistry
  - Year 2 of F100 Chemistry
  - Year 2 of F121 Chemistry with Medicinal Chemistry
- UCHA-F110 Undergraduate Master of Chemistry (with Industrial Placement)
  - Year 2 of F100 Chemistry
  - Year 2 of F110 MChem Chemistry (with Industrial Placement)
  - Year 2 of F112 MChem Chemistry with Medicinal Chemistry with Industrial Placement
- Year 2 of UCHA-F107 Undergraduate Master of Chemistry (with Intercalated Year)
- UCHA-F109 Undergraduate Master of Chemistry (with International Placement)
  - Year 2 of F109 MChem Chemistry (with International Placement)
  - Year 2 of F111 MChem Chemistry with Medicinal Chemistry (with International Placement)

- UCHA-4M Undergraduate Master of Chemistry Variants
    - Year 2 of F100 Chemistry
    - Year 2 of F105 Chemistry
    - Year 2 of F110 MChem Chemistry (with Industrial Placement)
    - Year 2 of F109 MChem Chemistry (with International Placement)
    - Year 2 of F125 MChem Chemistry with Medicinal Chemistry
- Year 2 of UCHA-F127 Undergraduate Master of Chemistry with Medicinal Chemistry(with Intercalated Year)