Organic Chemistry II, 2002-2003

Organic Synthesis

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What is organic synthesis?

"The preparation of a desired organic compound from commercially available starting materials via some multi-step procedure."

Aims of the course

The purpose of this course of 14 lectures is to give you an understanding of the craft of organic synthesis according to the definition above. It's not an arbitrary definition - to be an effective synthetic chemist you have to able to deliver the product as well as plan and design the synthetic route. Synthesis is a multi-disciplinary part of organic chemistry: you need to have a thorough knowledge of what actually works (and if that information isn't available you need to be able to make an educated judgement as to whether your planned step will work or not), a good grasp of reaction mechanism (this will help you decide whether the desired transformation will occur if there are potentially competing reaction pathways), and an appreciation of strategy - when in a multi-stage synthesis you should carry out a particular transformation, and in what order you should assemble smaller sub-units of a relatively complex target molecule. At the end of the course, it is our intention that you will be able to look at an organic molecule, and

- recognise possible starting materials
- devise a strategy for the synthesis of the molecule
- propose a detailed synthetic route to the target compound

Accumulating all of this knowledge isn't just an academic exercise. It's extremely important commercially: the bulk of the chemical industry is based on organic synthesis, whether it be the production of medicines, insecticides, weed-killers, perfumes, dyes and even polymers. There is a certain amount of learning involved - for example, sodium borohydride reduces ketones, but (usually) not esters - but throughout the course we shall as far as possible try to explain the facts as they come your way, so that you don't feel that you're wading through a great swamp of seemingly unconnected pieces of information. Facts are important, but so are concepts, and an understanding of the reasons behind the observed chemical behaviour will help you rationalise unfamiliar reactions (and perhaps even invent some new ones): you can't possibly learn everything!

General considerations When designing a synthesis, the organic chemist is usually preoccupied with three main considerations:

(i) construction of the carbon framework
(ii) functional group interconversion
(iii) stereochemical control

(i) **Construction of the carbon framework**

This is obviously of key importance, and may be regarded as a strategy level consideration. We need to have a knowledge of carbon-carbon bond-forming reactions (single, double and triple bonds), and also to be able to identify which C-C bonds in the target molecule are suitable for making (you can buy C-C bonds, in the form of your starting material). The aldol and Diels-Alder reactions are examples of strategic C-C bond-forming transformations.

(ii) **Functional group interconversion (FGI)**

A chosen strategy may dictate the presence of a certain functional group in the molecule at a certain stage in the synthesis. This functional group may not be present in the product of the previous step, and we therefore need to be able to interconvert functional groups in readiness for the next stage of the synthesis. Thus FGI is more of a tactical consideration, but is dictated by the strategy being followed. FGIs include oxidation and reduction processes, hydrolysis reactions, use of protecting groups, in fact any transformation which turns one functionality into another, but leaves the basic carbon skeleton unchanged.

(iii) **Stereochemical control**

If a molecule contains one or more - let's say n - stereocentres (asymmetric centres), it's a near-certainty that only one of the 2^n possible stereoisomers is desired. We therefore need to be able to control the configuration of any new stereocentres which are formed during the course of our synthesis. Stereochemical considerations often influence decisions about strategy. Many of the factors influencing the stereochemical outcome of organic reactions may be understood by relatively simple concepts, and we'll meet some of these during the course.

C-C BOND FORMATION

Almost every synthesis you will ever plan will require the formation of one or more carbon-carbon bonds. There are usually many alternatives, so how do we decide which ones to make in our synthesis? We can't just take two carbon fragments and join them together. Since the target will almost invariably contain functional groups, we will find that in the important C-C bond-forming reactions...

either both of the carbon atoms to be joined bear FGs,
or one carbon atom bears a FG, and the other is directly adjacent to a FG.

Almost invariably, formation of a C-C bond implies the reaction of a nucleophilic carbon species with an electrophilic carbon species.

We can represent this idea by using the concepts of the disconnection, synthon and antithetical reaction: more on this in Lecture 2 (***FRIDAY, 4 October 10.00***).