Prof D Craig 2.O1 Organic Synthesis Lecture 2 12.10.04

In Lecture 1 a general statement was made: the formation of new C-C bonds involves the coupling of an electrophilic carbon species with a nucleophilic one. We'll now take a look at examples of these species which are used in synthesis.

ELECTROPHILIC CARBON SPECIES

1. ***Alkylating agents***. We can often make a prediction about what kind of reactivity a compound will have by looking at its polarisation. It's no surprise, then, that compounds which have a δ^+ charge on carbon are often good electrophiles, *e.g.* haloalkanes (especially bromo- and iodoalkanes) and epoxides. [Beware, though: alcohols have a δ^+ charge on the α-carbon, but are poor electrophiles in this sense because HO$^-$ is a poor leaving group.]

2. ***Carbonyl compounds***. The products of reactions of nucleophiles with aldehydes/ketones may react further by dehydration to give alkenes. Esters, anhydrides, acid chlorides and amides are all **acylating agents**, but have different reactivities; some of these differences are subtle, and may be exploited in organic synthesis.

3. ***Electrophilic alkenes***. You know that alkenes are normally nucleophilic. However, the presence of an EWG on one end of the C=C double bond polarises the π-electrons and renders one end of the double bond electrophilic. Carbonyl groups are typical EWGs in this context, but this now means that there are two places where a nucleophile could attack: (i) the carbonyl carbon atom (1,2-addition); (ii) the β-carbon atom (1,4-addition, or conjugate addition). These two modes of nucleophilic addition may compete with each other depending on the nature of the nucleophile, but in general, highly stabilised carbanions add 1,4-, and carbanions with little or no stabilisation add 1,2-. Other factors (steric factors, solvent, temperature, counter-cation) may also affect the regioselectivity.

NUCLEOPHILIC CARBON SPECIES

We can divide these nucleophilic carbon species into two classes: **organometallic species** (we'll look at Li, Mg, Cu), and **stabilised carbanions**. In general, organometallic species are formed by the reaction between the appropriate metal and haloalkane. Stabilised carbanions are generated by the action of a base on a compound having an acidic hydrogen atom – the conjugate acid of the desired carbanion.

Organometallic compounds

1. ***Organomagnesium reagents*** (Grignard reagents, after Professor Victor Grignard; he won the Nobel Prize in 1912). As you will remember from first year, these reagents are readily formed by reacting bromo- or iodoalkanes with magnesium metal in ethereal solvents. Diethyl ether and tetrahydrofuran are the most commonly employed solvents. The following carbon electrophiles react efficiently with Grignard reagents:

(i) aldehydes and ketones, to give alcohols
(ii) epoxides, to give alcohols: reaction usually takes place at the least hindered end of the epoxide;
(iii) esters, to give tertiary alcohols (addition of two equivalents of Grignard);
(iv) nitriles (cyano-substituted compounds), to give ketones (*cf.* first year)
(v) carbon dioxide, to give carboxylic acids (*cf.* first year).

Note the similarities between all these reactions: a δ^- carbon atom from the Grignard reagent is attacking nucleophilically a carbon atom rendered δ^+ by a neighbouring electronegative carbon atom (oxygen or nitrogen). Also, all these are examples of 1,2-addition (apart from the epoxide, perhaps). Reactions with haloalkanes are poor. With electrophilic double bonds substituted with a carbonyl group, remember from earlier that there are two possible sites of attack. In the absence of steric hindrance of the carbonyl carbon atom (particularly when the EWG is an aldehyde), Grignard reagents tend to add in a 1,2-fashion. For more sterically demanding electrophiles, 1,4-attack may compete significantly. If you want to ensure 1,4-attack, however, the presence of a catalytic amount of a Cu(I) salt works extremely well. We'll meet cuprates shortly.

2. ***Organolithium reagents*** These are readily prepared in an analogous fashion to the corresponding Grignard species, by reaction of a bromoalkane with two equivalents of lithium metal in an inert solvent, usually hexane. Many organolithiums (MeLi, n-BuLi, PhLi) are commercially available, usually in hexanes, or diethyl ether, or mixtures of these. Organolithiums tend to be more nucleophilic than Grignard reagents, so we often observe exclusive 1,2-attack when there's a choice. Otherwise, reactivity is similar to that of the Grignard reagents. You probably already know that *n*-BuLi is often used as a strong base (see later).

3. ***Organocopper reagents*** We saw above how the addition of Cu(I) salts to Grignard reagents changes their reactivity. The active ingredients in these processes are organocopper species. Best results are obtained if the **cuprate** is formed *in situ*, usually in diethyl ether, under anaerobic conditions. The mechanisms through which these species react are complex, and usually involve single electron-transfer (SET) processes. The big deal about organocopper reagents is their chemoselectivity towards electrophiles. They react well with:

(i) Halogen-substituted hydrocarbons, to give alkanes and alkenes;
(ii) Acid chlorides, to give ketones (contrast this with Grignard reagents);
(iii) Enones, to give β-substituted, saturated ketones (conjugate addition).
(iv) Epoxides and aziridines, to give alcohols and amines respectively

Note that ketones don't react with organocopper reagents (unlike Grignard reagents).

Lecture 3: 09.00, Thurs 14 October *Chemistry of enolates*