Prof D Craig **2.O1 Organic Synthesis** **Lecture 5** 28.10.04

Alkylation of enones

The most thermodynamically acidic proton of an enone is at the γ-position, since abstraction of this leads to the most thermodynamically stable anion. This anion is stabilised by resonance, and has three potentially nucleophilic sites: the oxygen atom, and the α- and γ-positions. Kinetically-controlled (*i.e.* fastest) alkylation takes place at the α-position, giving an α-alkyl-β,γ-unsaturated ketone. This may then undergo a second α-alkylation, or isomerise to the thermodynamically more stable α-alkyl-α,β-unsaturated ketone. It's not surprising that mixtures of products are often formed in these reactions. The most kinetically acidic proton (*i.e.* removed fastest) is that at the α'-position. The resulting dianions are less thermodynamically stable (less conjugated) than those described above, and undergo alkylation reactions with electrophiles. *O*-Alkylation of dienolates may be observed, as with the saturated enolates discussed in Lecture 3. ***O*-Silylation** of dienolates gives **1,3-dienes** which are highly electron-rich, and are therefore effective in **Diels-Alder** reactions. Elsewhere in the course, Alan Armstrong will discuss the generation of enolates by dissolving metal reduction of enones.

Conjugate addition of carbanions

We saw in Lecture 2 that EWGs may render C=C double bonds electrophilic, and that this makes them susceptible to nucleophilic attack by species such as enolates. This is generally referred to as the Michael reaction. In this context, enolates may be regarded as stabilised anions (remember that unstabilised anions tend to add 1,2- to α,β-unsaturated carbonyl compounds, and stabilised anions add in a 1,4- fashion). These processes may be regarded as alkylation reactions of the enolate by the Michael acceptor. Sub-stoichimetric amounts base may be used for these transformations because the reactions are catalytic in base. The reactions are reversible, and in fact the use of stoichiometric amounts of base tends to promote the reverse reaction, and other side-reactions. Suitable bases are tertiary amines, and organic-soluble hydroxide species. One of the classical and most useful applications of the Michael reaction is...

The Robinson annelation

The word 'annelation' means ring-forming. In its simplest manifestation, the Robinson annelation involves the reaction of a saturated ketone in the presence of base with 3-buten-2-one, ('methyl vinyl ketone', MVK). There are problems, however:

(i) the reaction may not be regiospecific when unsymmetrical ketones are used;
(ii) MVK is very susceptible to polymerisation;
(iii) the reaction is reversible: obviously, this may reduce yields.

Some solutions to these problems are as follows.

1. **Improvement of regioselectivity by the use of enamines**. We saw earlier that enamines are regiodefined, stable enolate equivalents, and that they enter into Michael reactions with suitable electrophiles. This may be exploited in the Robinson annelation strategy.

2. **Prevention of reversibility by carbanion-stabilising groups**. As outlined above, an intermediate in the annelation sequence possesses a negative charge α- to the carbonyl group of the Michael acceptor. If this charge is stabilised by a second EWG, the reverse reaction is inhibited. Ideally the EWG should be removable from the final product: triethylsilyl fits the bill here.

Lecture 6: ***next Tuesday, 2 November*** *Carbanions stabilised by sulfur*