Methods for selective alkylation of ketones (continued from lecture 4...)

Alkylation of enones

The most thermodynamically acidic proton of an enone is at the □-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 □- and □-positions. Kinetically-controlled (i.e. fastest) alkylation takes place at the □-position, giving an □-alkyl-□,□-unsaturated ketone. This may then undergo a second □-alkylation, or isomerise to the thermodynamically more stable □-alkyl-□,□-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 □'-position. The resulting dianions are less thermodynamically stable (less conjugated) than those described above, and undergo alkylation reactions with electrophiles. Later 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 □,□-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. Catalytic base may be used for these transformations: 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 □- 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 fro the final product: triethylsilyl fits the bill here.

CARBANIONS STABILISED BY SECOND-ROW ELEMENTS

The nucleophilic carbon species we've looked at so far are organometallic reagents, ar enolates (and equivalents). The latter are of course carbanions stabilised by adjace heteroatom-containing □-systems. We're now going to look at carbanions in which negati charge is stabilised by an adjacent second-row element, e.g. silicon, phosphorus and sulfu The origin of the stabilisation is believed to be the overlap of the full orbital on the negati charge-bearing carbon atom with low-energy 3d orbitals on the heteroatom, allowing som delocalisation of the negative charge.

Sulfur-stabilised carbanions

Sulfur may be present in organic molecules in three different oxidation levels. If we consid a substance $R^1S(O)_nR^2$, when n = 0 it is a sulfide, or thioether; when n = 1, a sulfoxide; ar when n = 2, a sulfone. If R^1 is an alkyl group, R^2 is often an aromatic function, so that the is only one possible site of deprotonation i.e. on the alkyl group. The □-protons becom increasingly acidic on going from sulfide to sulfoxide to sulfone.

Sulfides

These need very strong base to effect □-deprotonation, typically t-BuLi. Slightly weak bases may be used when there are additional anion-stabilising groups (e.g. a double bonc The resulting carbanions may be alkylated by reaction with (usually) bromoalkanes, hydroxyalkylated by reaction with carbonyl compounds. The value of sulfides lies in the ready manipulation and/or removal after the C-C bond-forming reaction. They're easily mac by reaction of an appropriate sulfur nucleophile (e.g. thiophenoxide, PhS^-) with haloalkane. It's possible to have two sulfur atoms bonded to the same carbon atom, which case the □-protons are more acidic, e.g. in the case of 1,3-dithiane. Formation of th 2-lithio derivative and reaction with an electrophile gives a 2-substituted derivativ Hydrolysis then gives a carbonyl compound (aldehyde or ketone, depending on the numb of alkyl groups introduced). 1,3-Dithiane is thus the synthetic equivalent of the ^-CH synthon. 2-Substituted-1,3-dithianes may be synthesised from the reaction of an aldehyc with 1,3-propanedithiol in the presence of $BF_3.Et_2O$. Note that the alkylation reactior represent a reversal of the normal electrophilic nature of the carbonyl group. This revers process is generally referred to as **umpolung**.

Lecture 6: 10.00 Friday *Sulfoxides, sulfones, sulfur and phosphorus ylides*