Alkylation of ketones i.e. the resulting carbanions are stabilised by one EWG (pKa 19-27).

Typically very strong bases are required to effect complete deprotonation of ketones. Again there is the issue of C- vs. O-alkylation, but with unsymmetrical ketones there is an additional question, that of regioselectivity of deprotonation. If the enolates formed by deprotonation of the two different kinds of α-proton are differently substituted, it is possible to achieve a fair degree of control by varying the reaction conditions:

- if the ketone is added to excess, hindered base in an aprotic solvent at low temperature, the less substituted, kinetic enolate is formed, by removal of the less hindered proton;
- if strong base is added to the ketone (often at r.t. or above), the more substituted (often), thermodynamic enolate is formed.

The ratio of these different enolates may be assessed by analysis of stable derivatives.

So far, we've identified several important issues concerning the formation and reactions of ketone enolates, namely those of C- vs. O-alkylation, and the regiochemistry of proton abstraction by the base. There's another problem - that of polyalkylation of the parent ketone. If the product of the alkylation reaction contains a further acidic hydrogen atom, then that may be abstracted by more base to give a second enolate, which then undergoes alkylation as before. There are various methods for getting round these problems.

Methods for selective alkylation

1. ***Direct regiocontrolled deprotonation*** *(followed by alkylation)*. This is the shortest and best route to regiochemically defined enolates and alkylated products. Of course, this requires a method for the regioselective formation of the desired enolate (see above).

2. ***Introduction of an activating substituent***. It's possible to monoalkylate a ketone by first attaching an EWG α- to the carbonyl function. This obviously provides additional stabilisation for the anion. One such activating group is the carboethoxy (ethoxycarbonyl) group, attached by reaction of the ketone enolate with diethyl carbonate. The product is a β-ketoester (remember?), and the activating group is removed by hydrolysis, followed by decarboxylation.

3. ***Specific enolates***. One useful strategy for the regiospecific generation and alkylation of enolates is by using as intermediates stable, isolable enol derivatives. Thus, the ketone is converted into a mixture of regioisomeric enolates which is then trapped, often by reaction with chlorotrimethylsilane (TMSCl). This gives a regioisomeric mixture of silyl enol ethers, which may be separated, e.g. by distillation (sometimes by chromatography). The enolate is regenerated by the action of methyllithium. The tetramethylsilane by-product is volatile, and therefore readily removed.

4. ***Enamines***. These may be regarded as the nitrogen analogues of enol derivatives. They're formed by reaction of a secondary amine with a carbonyl compound in the presence of an acid catalyst. Pyrrolidine, morpholine and piperidine (all trivial names!) are the most commonly used amines. Enamines are nucleophilic at the β-position. They react well with reactive alkylating agents (e.g. allyl bromide, benzyl bromide), giving mixtures of C- and N-alkylated products. Hydrolysis of the former then gives the alkylated parent ketone, and the secondary amine is regenerated. The unwanted *N*-alkylated derivatives are water soluble, but resistant to hydrolysis. Enones and acylating agents also react well. Enamines possess several attractive features:

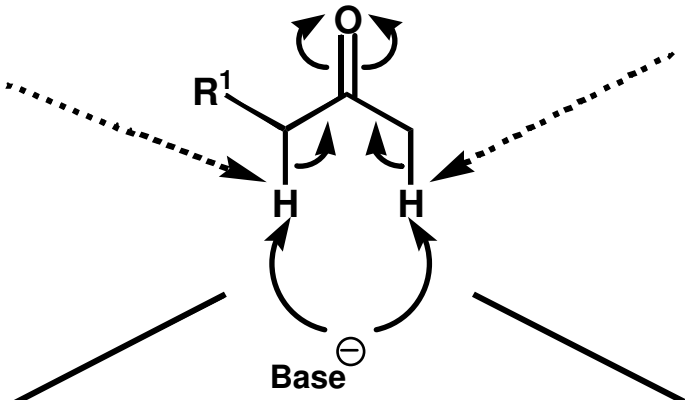
   (i) no base is used, so no self-condensation occurs;
   (ii) monoalkylation is usually observed: the intermediate alkylated enamines are unreactive towards further alkylation;
   (iii) alkylation in unsymmetrical ketones is regioselective: the major enamine is the less substituted one (steric inhibition of resonance).

Lecture 5: 09.00 Thursday 28th October *Enone alkylation, Robinson annelation; carbanions stabilised by second-row elements*

Kinetic and thermodynamic enolates

this α-proton is

- **more hindered**, and therefore
- removed **less quickly**:
- it is kinetically **less acidic**, but...



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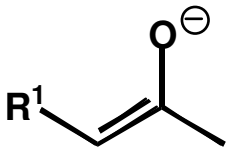
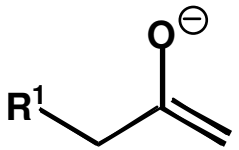


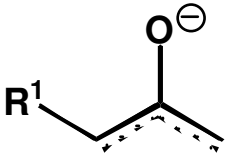


this enolate is

- **more substituted**, and therefore:
- **thermodynamically more stable**

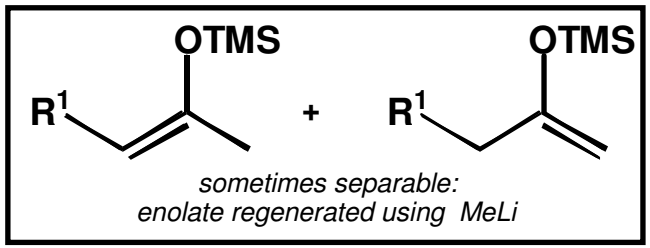
Formed by:
- addition of weak base to ketone, at
- relatively high temperatures

These are **equilibrating conditions**



i.e. a mixture

TMS–Cl



this enolate is

- **less substituted**, and therefore:
- **thermodynamically less stable**

Formed by:
- addition of ketone to strong base, at
- relatively low temperatures

These are **kinetic, non-equilibrating conditions**