

Carbanions

We've looked at organometallic reagents as carbon nucleophiles. We'll now go on to examine fairly closely the use of carbanions as nucleophilic reactive species. As we said last week, these species are generated by deprotonation of the conjugate acid of the desired carbanionic species. Deprotonation may only occur if the proton to be removed is acidic to some extent, *i.e.* the resulting carbanion is stabilised. This stabilisation results from the presence of a suitable substituent on the carbon atom undergoing deprotonation, and may be a consequence of:

- (i) the inductive electron-withdrawing nature of the substituent; and/or
- (ii) the ability of the substituent to negative charge by resonance.

A league table of the pK_a values of a wide range of common carbon acids is given in March (4th edn.), p. 250-252. It's fair to say that the most important type of carbanion as far as organic synthesis is concerned is that derived from carbonyl compounds. Removal of the α -proton by a suitable base gives an enolate anion, more frequently referred to simply as an **enolate**.

Chemistry of enolates

Certain conditions have to be met in order to have a high concentration of our desired nucleophilic enolate present in the reaction medium. Both the solvent and the conjugate acid of the base must be weaker acids than the substrate to be deprotonated. Otherwise, given the reversibility of the deprotonation process, we would have incomplete deprotonation of the substrate, and there would be an appreciable concentration of the base in solution – remember that bases can also act as nucleophiles! For example, EtO^- is only useful as a base for those substrates which are substantially more acidic than EtOH ($pK_a \approx 18$). Also, the solvent must be a weaker acid than the conjugate acid of the base. These requirements may be expressed in terms of simple equilibria.

Typical bases These are: (i) alkoxides (usually with sodium as counter-cation, in alcohol solution, or as a suspension in Et_2O , benzene, or 1,2-dimethoxyethane (DME)) - potassium *t*-butoxide in *t*-BuOH or THF (commercially available) is a stronger base and a poorer nucleophile than most; (ii) alkali metals; (iii) alkali metal hydrides (NaH , KH); (iv) alkali metal amides (NaNH_2 , KNH_2). Particularly useful amides are those derived by deprotonation of secondary amines, namely lithium diisopropylamide (LDA; $i\text{-Pr}_2\text{NLi}$) and lithium hexamethyldisilazide (LHMDS; $\text{LiN}(\text{SiMe}_3)_2$). These are soluble in inert solvents such as THF, and are hindered, and therefore non-nucleophilic, strong bases ($i\text{-Pr}_2\text{NH}$ has a pK_a of around 37).

Typical solvents The rate of alkylation of enolates is very solvent dependent. We can divide the commonly used solvents into two distinct classes: (i) polar, aprotic solvents (DMF, DMSO, HMPA: sorry about all these abbreviations!); these are good cation solvators (δ^- oxygen atom), and poor anion solvators, and therefore leave a 'naked', reactive anion. Their high dielectric constant ensures good charge separation; (ii) weakly polar solvents (THF, DME); these are still able to coordinate cations (oxygen lone pairs), but charge separation is reduced because of the lower dielectric constant. There are also commonly-used additives (e.g. crown ethers [Chemistry Nobel Prize, 1987]), which enhance the nucleophilicity of anions by chelation of the cation.

Alkylation of relatively acidic compounds *i.e.* the resulting carbanions are stabilised by two EWGs ($pK_a \leq 15$).

Classic examples are diethyl malonate and ethyl acetoacetate (cf. first-year). These are the synthetic equivalents of respectively ethanoic acid anion and acetone anion, if alkylation is followed by hydrolysis and decarboxylation.

C- vs O-alkylation Enolate alkylation is often problematic because enolates are ambident nucleophiles, and may attack the alkylating agent via either the oxygen or α -carbon atoms. The ratio of the products of these processes can be difficult to control, and depends on several factors:

- (i) **solvent**: reactivity on oxygen may be attenuated if the negatively charged oxygen atom is hydrogen-bonded to solvent molecules. When this is the case, C-alkylation is favoured. Polar, aprotic solvents don't H-bond: O-alkylation results.
- (ii) **counter-cation**: small cations (e.g. Li^+) bind tightly to oxygen, promoting C-alkylation. Larger cations (K^+) favour O-alkylation. For 1,3-dicarbonyl substrates, the two oxygen atoms may chelate to the metal cation, resulting in exclusive C-alkylation.
- (iii) **alkylating agent**: for O-alkylation reagents with oxygen-derived leaving groups are usually used. For C-alkylation, iodides are used.

Adding this all together, the best conditions for C-alkylation would be the use of a lithium enolate in a protic solvent with an alkyl iodide as the alkylating agent.

Lecture 4: 09.00 Tuesday 26 October Unsymmetrical ketone alkylation

Prof A Armstrong Lectures 1 and 2: Tuesday 19 and Thursday 21 October, 09.00

We said in the lecture that by far the most commonly used type of stabilised carbanionic equivalent is an **enolate anion**, or simply **enolate**. They're generated by the action of a **non-nucleophilic** (usually) base on a ketone (it's difficult to generate aldehyde enolates because they're too powerful as electrophiles), or an ester, amide, etc. They're **ambident** nucleophiles: they can react on carbon or oxygen, but this usually may be controlled to give the desired C-alkylation (if we want to make C-C bonds, that is...).

