

CHEM 330

Topics Discussed on Sept. 14

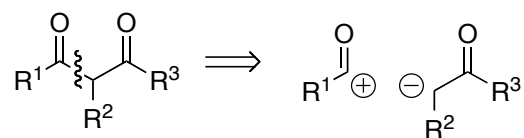
General guidelines for the assembly of molecular subunits:

1. Determine how heteroatomic functionalities affect the polarity of neighboring C atoms;
2. Disconnect a bond located between the heteroatoms
3. Identify synthons: whenever possible, rely on the natural polarity of C atoms;
4. Identify appropriate reagents that behave as carriers of the requisite synthons

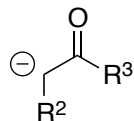
Guidelines for the assembly of 1,3-dioxygenated functionalities

The 1,3-dicarbonyl system ("type A" 1,3-dioxygenated structure):

Synthons required for the construction of a 1,3-dicarbonyl unit:



Carbonyl enolates as carriers of



Derivatives of carboxylic acids (acid chlorides, anhydrides, esters,...) as carriers of



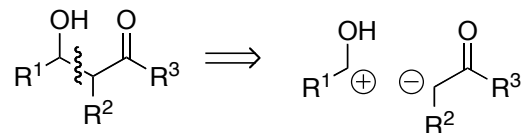
Free carboxylic acids (R-COOH) as inappropriate reagents for the conduct of the above reaction, due to facile deprotonation ($pK_a \approx 5$) under basic conditions and inability of carboxylates (R-COO⁻) to react with most nucleophiles

Acid chlorides and anhydrides as generally unsuitable reagents (with a few exceptions and for reasons to be addressed later) for the synthesis of 1,3-dicarbonyl systems

Esters and related species as ideal reagents for the above transformation

The 1,3-hydroxycarbonyl system ("type B" 1,3-dioxygenated structure):

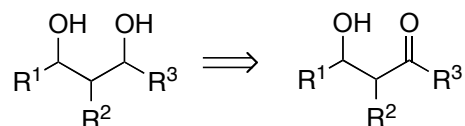
Synthons required for the construction of a 1,3-hydroxycarbonyl unit:



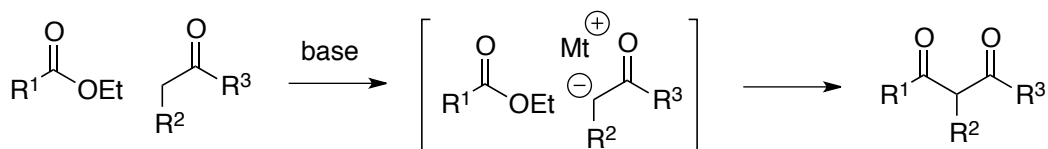
Aldehydes as carriers of



Construction of a 1,3-diol system ("type C" structure): a special case of 1,3-hydroxycarbonyl construction, because a C=O group may be reduced to an OH with appropriate hydride reagents:

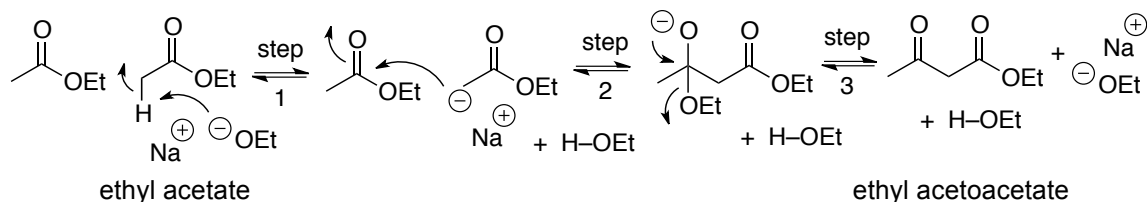


Formation of 1,3-dicarbonyl (=β-dicarbonyl) structures by reaction of carbonyl enolates with esters in the presence of a base: the Claisen condensation



Simplest possible case of the above reaction: the self-condensation (Claisen condensation) of ethyl acetate

Probable mechanism of the Claisen condensation of ethyl acetate mediated by EtONa:



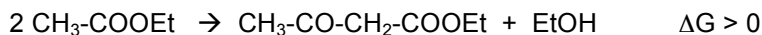
Principle: in the above chemical equation, EtONa is not consumed; i.e., it acts as a *catalyst* for the reaction.

Can we induce the above transformation by using only a small quantity (= a catalytic amount) of EtONa?

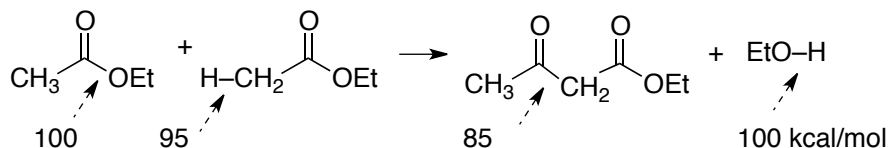
To address this question, one must determine (i) whether the overall reaction is thermodynamically feasible, and then (ii) analyze each step individually

(i) Is the reaction thermodynamically feasible (= what is its ΔG)?

The condensation of two molecules of ethyl acetate to form ethyl acetoacetate and ethanol as a thermodynamically unfavorable process



Because $\Delta G = \Delta H - T\Delta S$, and because the total number of molecules remains constant during the reaction (2 molecules are consumed and 2 are formed), ΔS will be small, and ΔG will be largely determined by ΔH (this is often the case for organic reactions). One can estimate ΔH from the dissociation energies (kcal/mol, values available from a table of BDE's) of bonds broken / formed during the transformation:



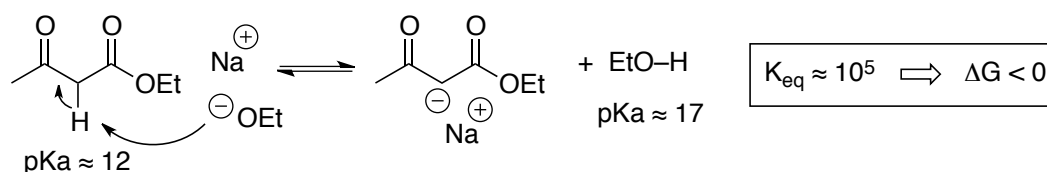
Bond breaking requires ca. 195 kcal/mol and bond forming releases ca. 185 kcal/mol, so, $\Delta H \approx + 10$ kcal/mol and $\Delta G > 0$. **The reaction is thermodynamically unfavorable!**

Active methylene: a CH_2 group with unusually acidic H's due to the presence of two flanking anion-stabilizing groups (e.g., two $\text{C}=\text{O}$'s in the product of the above reaction)

Active methylene compounds: molecules such as the product of the above reaction ("ethyl acetoacetate") that incorporate an active methylene

Acidity of the methylene protons of ethyl acetoacetate: $\text{pK}_a \approx 12$

Deprotonation of ethyl acetoacetate (more generally, of the 1,3-dicarbonyl product of a Claisen condensation) by EtONa :



Thermodynamically favorable nature of the above proton-transfer reaction

The above proton-transfer reaction as an event that in most cases barely compensates for the unfavorable character of the Claisen condensation

As a consequence of the above proton-transfer reaction, EtONa is *consumed* during the reaction. Therefore, one cannot induce the Claisen condensation with only a catalytic amount of EtONa , because the more acidic ethyl acetoacetate will convert all of the EtONa (the base) into EtOH : one thus needs at least one stoichiometric equivalent of EtONa to induce the transformation