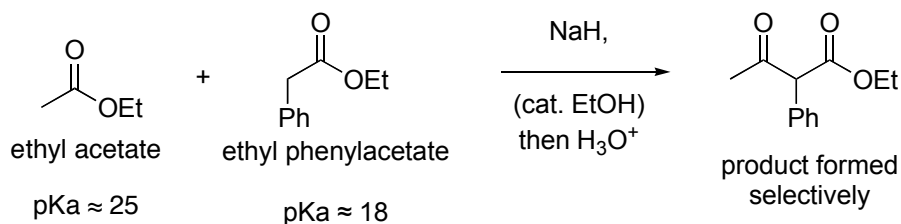


CHEM 330

Topics Discussed on Sept 23

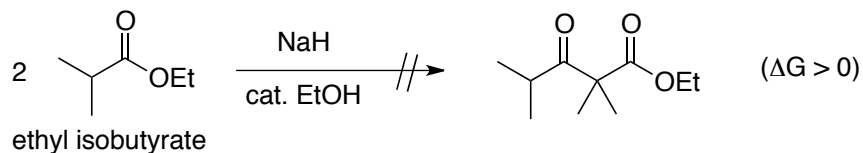
Special cases of successful cross-Claisen condensations occurring under conditions of reversible deprotonation:

Case b (less significant): condensation of a more acidic ester with a less acidic one, e.g.:

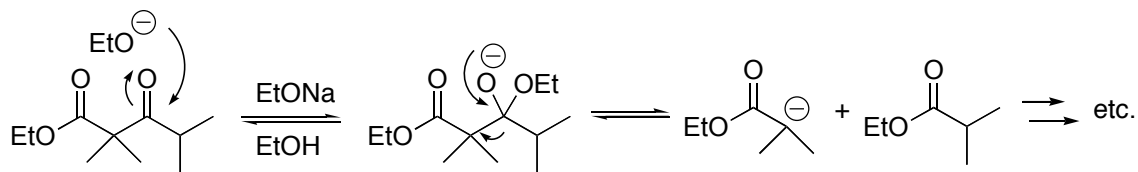


Case c (less significant still — at least as far as the condensation of two *independent* esters is concerned): cross condensation between 2 enolizable esters leading to only 1 kind of product capable of final deprotonation.

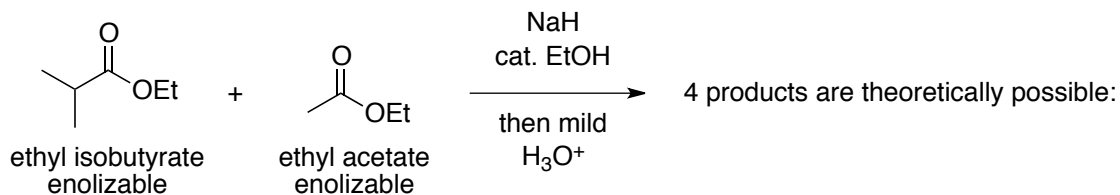
Reminder 1: a Claisen condensations carried out under conditions of reversibility, and leading to a product unable to undergo deprotonation, will fail because of unfavorable ΔG ; e.g.:

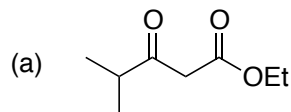


Reminder 2: the Claisen condensation reverts easily when a non-enolizable β -ketoester is exposed to e.g., $EtO^- / EtOH$:

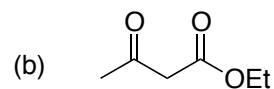


Example of **case c**: the reaction of ethyl propionate with ethyl isobutyrate:

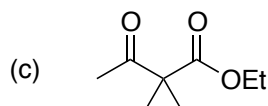




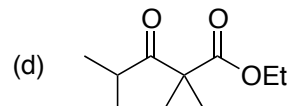
enolate of acetate has reacted with intact isobutyrate



acetate has reacted with itself



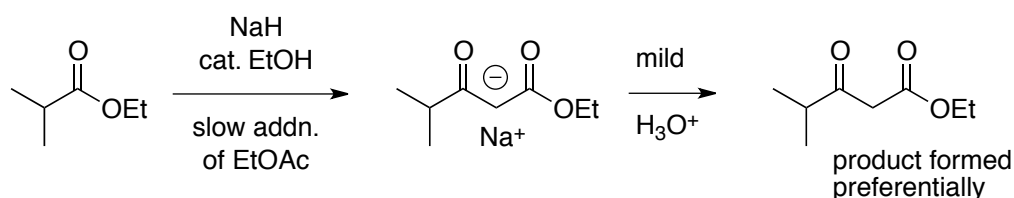
enolate of isobutyrate has reacted with intact acetate



isobutyrate has reacted with itself

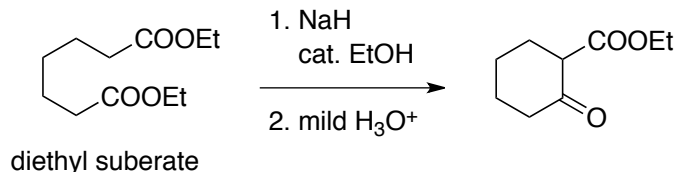
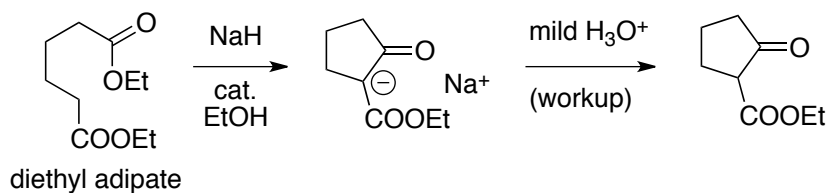
However

compounds (c) and (d) **do not form** under these conditions, because they cannot undergo the final deprotonation that drives the Claisen condensation toward the products. One may then obtain product (a) selectively by slow addition of ethyl acetate to a solution of ethyl isobutyrate containing NaH / cat. EtOH. Under these conditions, the instant concentration of ethyl acetate in the reaction mixture will be low, minimizing / suppressing the opportunity for self-condensation:



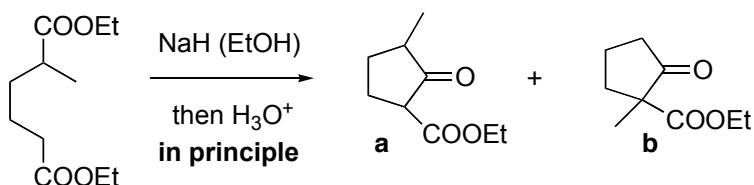
Significance of the above principle in the context of the intramolecular variant of the Claisen condensation, known as the Dieckmann reaction

examples of Dieckmann reactions



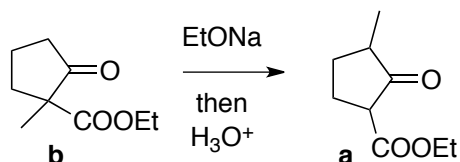
Dieckmann reactions are special cases of Claisen condensations; therefore they are governed by the same principles; e.g.:

- (i) In theory, the Dieckmann reaction of the diester shown below could lead either to product **a** or to product **b**:

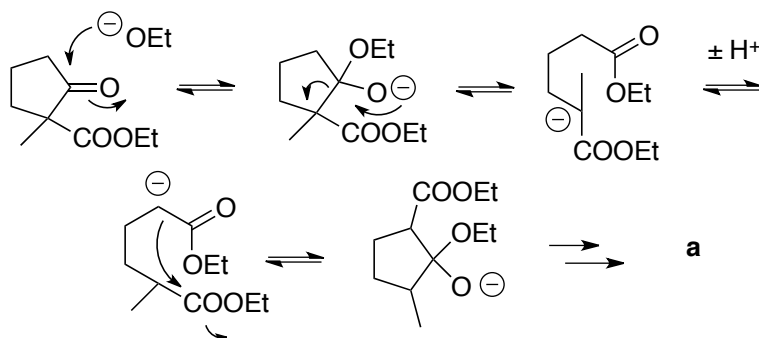


In fact, only **a** forms, because **a** is the only product that can undergo final deprotonation. Recall, it is this deprotonation that provides the thermodynamic driving force for the reaction.

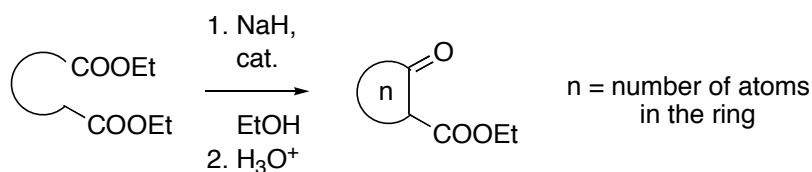
- (ii) If we were to make **b** independently and treat it with EtONa / EtOH, it would isomerize to **a**:



isomerization taking place through a retro-Dieckmann / Dieckmann sequence:



Scope of the Dieckmann reaction with respect to ring size of the product:



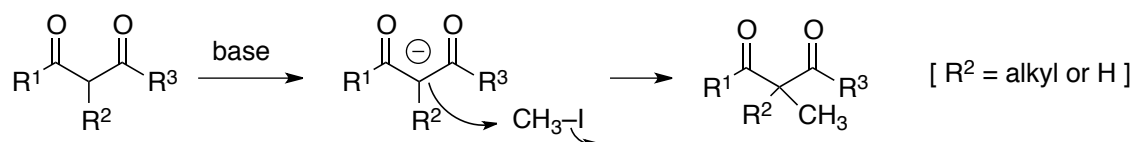
- $n = 3, 4$: the reaction fails because of ring strain.
- $n = 5, 6$: the reaction works well
- $n = 7$: the reaction is "ok"
- $n > 7$: the reaction fails because of unfavorable kinetics of the intramolecular process (slower) vs. the bimolecular one (faster). In part, this has to do with problematic conformational interactions that develop when the substrate attempts to "fold back" onto itself to form a ring. High dilution may promote ring formation in favorable cases.

note: in CHEM 330 we are only interested in Dieckmann reactions leading to the formation of 5/6 membered rings

The Dieckmann reaction as a valuable method for the creation of cyclic structures

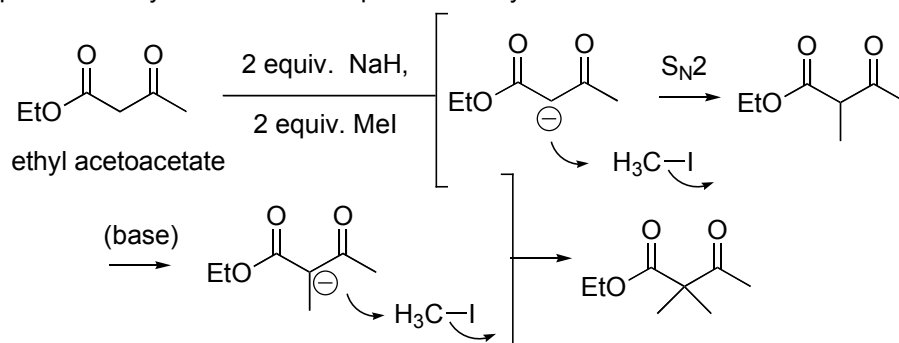
Technology for the assembly of substituted 1,3-dicarbonyl structures that are unavailable by Claisen-Dieckmann reactions carried out under conditions of thermodynamic control

Reminder: the enolate of a 1,3-dicarbonyl compound is fairly nucleophilic and it can react with appropriate alkyl halides leading to formation of new C–C bonds. Example:

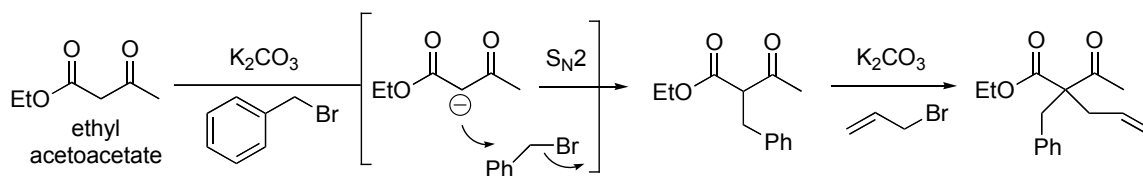


Mono- and di-alkylation of β -ketoesters, e.g. of ethyl acetoacetate, using bases such as NaH (or even K_2CO_3)

Example 1: bis-alkylation with two equiv of an alkyl halide



Example 2: mono- and-bis alkylation with distinct alkyl halides



Synthesis of cyclic compounds via β -ketoesters such as $\text{R-CO-CH}_2\text{-COOEt}$, e.g.:

