CHEM 330

Topics Discussed on Sept. 18

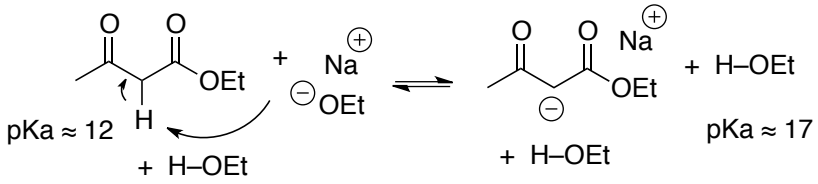
Principle: a Claisen condensation promoted by NaH/cat. EtOH takes place so that all steps but the final deprotonation of EtOH by NaH are reversible. Consequently, the system will tend to attain a thermodynamic energy minimum, and the product that forms will be the thermodynamically most favorable one. A reaction occurring under such conditions is said to proceed under **thermodynamic control**

Principle: mixing one equivalent of pure ethyl acetoacetate with excess pure ethanol in the presence of a catalytic amount of EtONa will induce a reverse Claisen condensation ("retro-Claisen"), resulting in conversion of the starting acetoacetate into two molecules of ethyl acetate (the thermodynamically more favorable state of the system):

$$CH_3\text{-}CO\text{-}CH_2\text{-}COOEt \;+\; EtOH \;\text{—[cat. } EtO^- \text{]—>}\; 2\; CH_3\text{-}COOEt \quad (\text{overall } \Delta G < 0)$$

Principle of microscopic reversibility: in each step of any given transformation, the forward and the reverse reactions occur along the same mechanistic pathway; i.e., by identical mechanisms operating in reverse

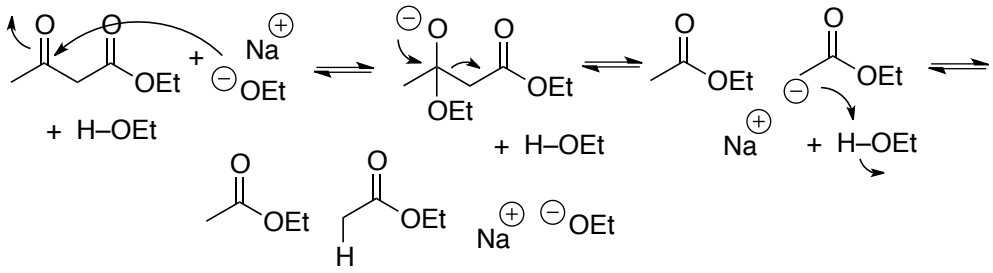
Example: a reverse Claisen condensation occurs as follows:



$K_{eq} \approx 10^5$ although the above equilibrium is shifted to the right, there will always be some residual free $EtO^{\ominus}$ and ethyl acetoacetate in the medium. Under the usual approximations (CHEM 203):

$$[CH_3COCH_2COOEt] \;=\; [EtO^{\ominus}] \approx \sqrt{10^{-5}} \approx 3 \cdot 10^{-3}$$

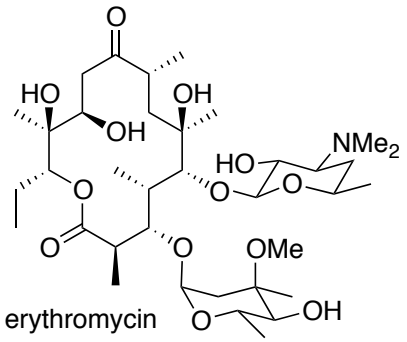
These residual concentrations of $EtO(^-)$ and CH_3COCH_2COOEt are sufficient to induce a slow, but inexorable, reverse reaction.



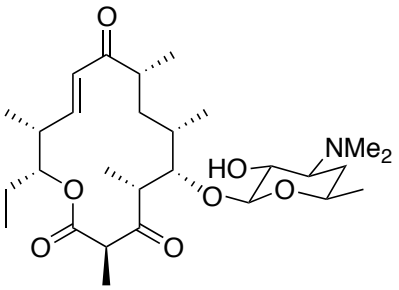
notice that the reversible reaction depends on proton exchanges among the various species: NaH removes all such protons and suppresses the retro-Claisen process

Lactones: cyclic esters

Macrolactone ("macrolide") antibiotics, e.g. erythromycin, narbomycin (structures below), etc. (notice the presence of type A, B and C 1,3-dioxygenated functionality):



erythromycin

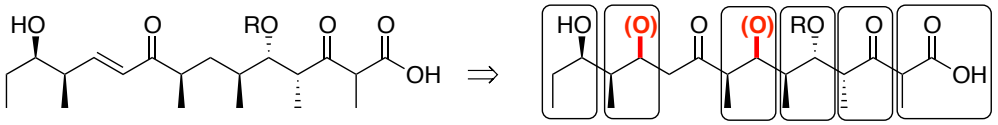


narbomycin

Importance of modified macrolides in modern antibiotics research

Narbomycin, erythromycin, etc., as substances composed of multiple propionic acid units (propionic acid = CH_3-CH_2-COOH), which are biogenetically merged through Claisen-type condensations, and therefore described as *polypropionate* natural products.

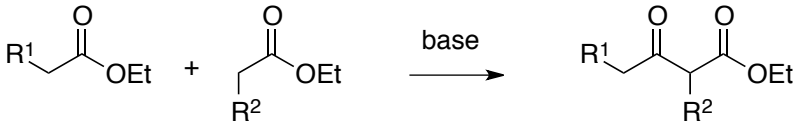
imagine opening the lactone ring of narbomycin: this leads to …



the open form of narbomycin (R = sugar residue)

Propionate subunits in the likely biosynthetic precursor of narbomycin: the red (O) groups (alcohol or carbonyl) are ultimately removed by the producing organism (*Streptomyces venezuelae*), which assembles the molecule by consecutive Claisen condensations.

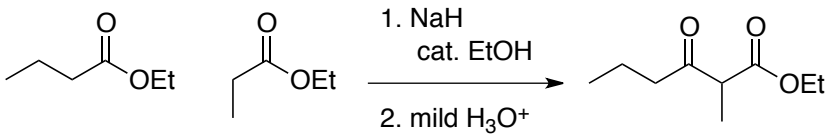
Desirability of Claisen condensations leading to the union of two different esters, e.g.:



Description of the above process as a cross-Claisen condensation

Formation of mixures of products upon attempted cross-condensation of two different — but similar — *enolizable* esters under conditions of thermodynamic control (reversible reactions induced, e.g., by NaH / cat. EtOH)

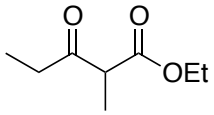
example: the attempted synthesis of **A** by cross-Claisen condensation of ethyl propionate with ethyl butyrate:



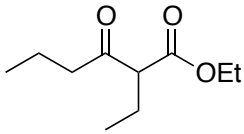
ethyl butyrate ethyl propionate

A: desired product (enolate of propionate added to intact butyrate)

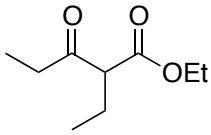
BUT: 3 other products are likely to form:



undesired product (enolate of propionate added to propionate)



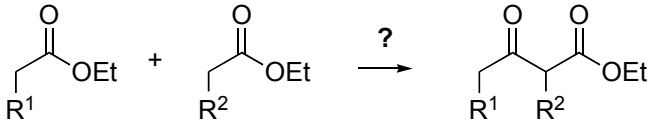
undesired product (enolate of butyrate added to butyrate)



undesired product (enolate of butyrate added to propionate)

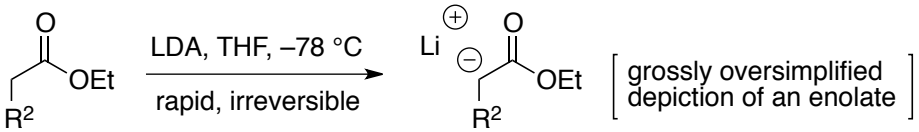
Principle: to achieve a selective cross-Claisen condensation of the type shown above, one cannot operate under conditions in which product distributions is determined by thermodynamic forces ("thermodynamic control" – as seen in the Claisen condensations discussed so far). Instead, one must operate under conditions in which no opportunity exists for thermodynamic equilibration of the initial product mixture (= no proton exchanges); i.e., under conditions of ***irreversibility***

General approach to the conduct of a kinetically controlled cross-Claisen condensation:

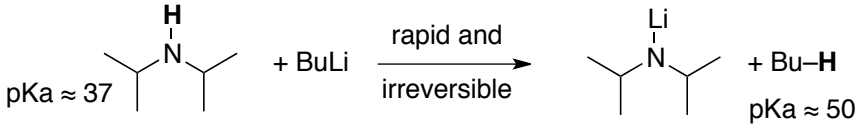


1. segregate the two esters

2. convert the "R^2" ester **rapidly, completely and irreversibly** (so it will not condense with itself) into the enolate, e.g, with LDA, in a solvent such as tetrahydrofuran (THF), at low temperature (–78 °C; Dry Ice / acetone bath) under N_2 or Ar atmosphere



Reminder: LDA (lithium diisopropylamide) is a strong, non-nucleophilic base prepared from diisopropylamine and BuLi (CHEM 213):



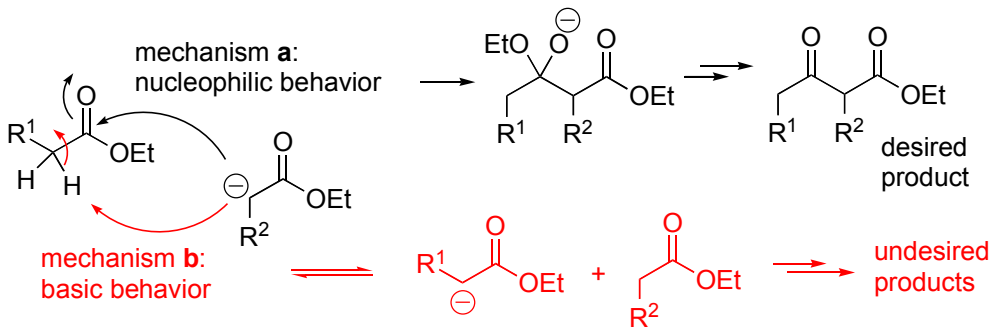
Rapid and irreversible deprotonation of enolizable esters, and carbonyl compounds in general, with LDA

3. cause the above enolate to react **rapidly, completely and irreversibly**, at low temperature, with the "R^1" component

4. the "R^1" component **must not be provided in the form of an ester**. Upon reaction, the ester would release EtO^-, which can reversibly deprotonate the "R^1" ester, thereby inducing undesired reactions. ErO^- can react with the initially formed 1,3-dicarbonyl product thus promoting the reverse reaction. These events would cause at least partial thermodynamic equilibration of the system, thus undermining our objective. Any EtOH that might form would also destroy the enoalte of "R^2+ ester

Moreover.....

Tendency of the preformed lithium enolate of, e.g., an ethyl ester, to react with a second enolizable ethyl ester both by addition to the C=O (nucleophilic behavior) and by proton transfer (basic behavior):



Comparable (not necessarily *equal*, but *similar*) rates of addition and proton transfer under such conditions, and consequent formation of mixtures of products.

Requirement for an "ester analog" in cross-Claisen condensations