

Carbonyl Chemistry – Enolization

Primary Reading:

1. TJ Donohoe - Lecture notes on carbonyl chemistry.
2. Clayden, Greeves, Warren & Wothers, "Organic Chemistry", chapter 14

Additional Reading:

2. "Core Carbonyl Chemistry", John Jones, OUP Primer No 47.
3. "Mechanisms of organic reactions", H.Maskill, OUP Primer No 45.

Introduction

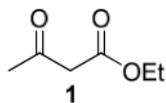
Nucleophilic attack at carbonyl compounds was covered in a previous tutorial. This tutorial aims to cover another major function of carbonyl compounds: enolisation and subsequent reaction. A proton α to a carbonyl centre is acidic (we can delocalise the charge on to the electronegative oxygen) and so that this C-H can be deprotonated and then further functionalised by reaction with an electrophile.

Make sure you cover the following topics:-

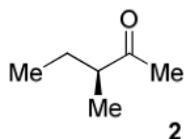
1. Keto - Enol tautomerism: structural effects on enol content. Base and acid catalysis. Factors contributing to the choice of which bases are used for particular reactions; reactivity of enols and enolates.
2. Simple reactions involving: enols and enolates: Halogenation (base and acid catalysed), deuteration, racemisation; enol ethers (compare with acetals) and enol esters.
3. Alkylation: stabilised and non-stabilised enolates; pK_a of substrate and choice of base. Acetoacetic ester and malonate synthesis. Simple ketone enolates. C versus O alkylation. Regioselectivity, formation of specific enolates, intramolecular alkylation leading to cyclisation.
4. Carbonyl condensations: enolisation followed by attack at C=O; aldol condensation and its reverse, α,β -unsaturated carbonyls, ester condensation both acyclic and cyclic (Claisen and Dieckmann). Crossed condensations, such as Aldol and Claisen type.
5. α,β -Unsaturated carbonyl compounds. Michael-type additions; 1,2 versus 1,4 addition. Hard versus soft arguments. Use of lithium/magnesium/copper reagents for 1,2 or 1,4 addition, etc.

DON'T FORGET ALL THE NORMAL CARBONYL REACTIONS.

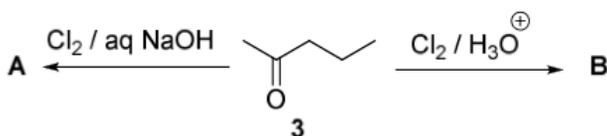
1a) Draw the species which contribute to the equilibria in aqueous propanone (acetone) at neutral pH. Why is there a greater proportion of enol tautomer present in similar equilibria for ethyl acetoacetate (EAA) **1**? below.



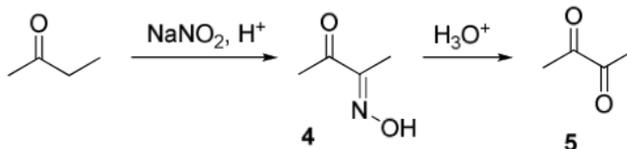
b) Explain and give mechanisms to illustrate why **2** is easily racemised under either aqueous acidic or basic conditions. If the reaction were carried out in D₂O instead of H₂O, what would the products of the reaction be?



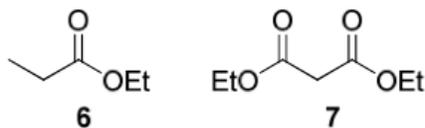
c) What are the products from the reaction of **3** under the conditions given below? Why do the products differ in acidic and basic conditions? Explain your answer.



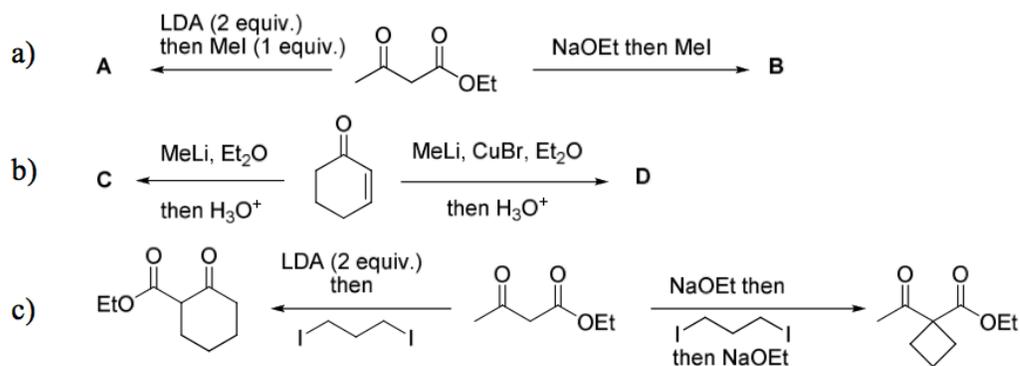
d) Give mechanisms for the formation of **4** from butanone and for the hydrolysis of **4** to **5**. Explain the regioselectivity shown for the formation of **4** from butanone.



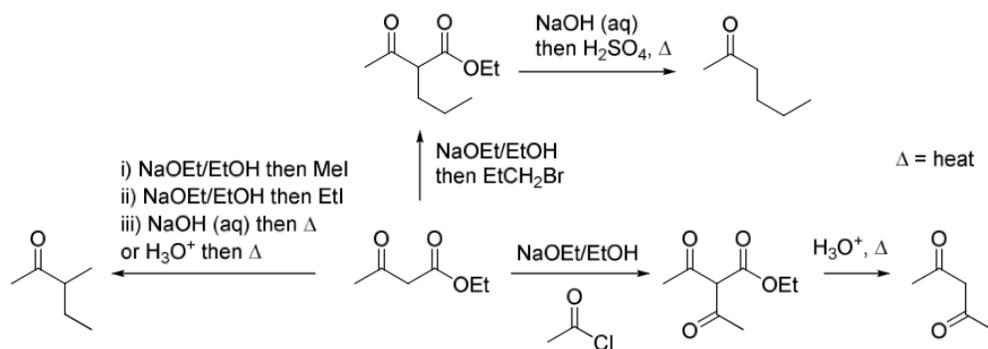
e) Explain why enolates derived from simple esters such as **6** are usually prepared with LDA (a strong, non-nucleophilic base) while those from β -dicarbonyl compounds such as **7** (diethyl malonate, DEM) can be prepared easily using NaOEt/EtOH.



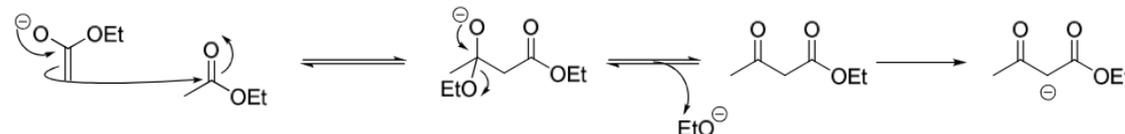
2. Predict the major products from these reactions; give mechanisms to show your reasoning. For part (a) consider the reaction going through either a mono-anion or di-anion; for part (b) consider Michael addition and the factors which determine 1,2 or 1,4 addition



3) Give mechanisms and reasoning for the following reactions.



4. Consider the Claisen ester condensation:



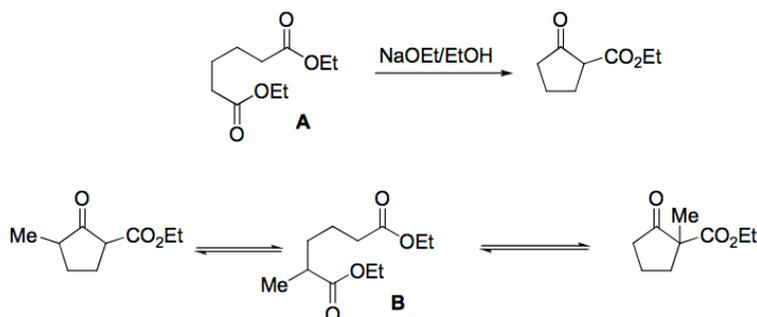
The reaction is reversible and success depends on removal of the products as a stable carbanion

a) Discuss the mechanism above carefully, explaining:

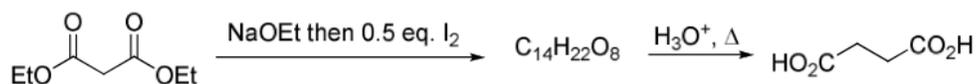
i) why sodium ethoxide, but not sodium hydroxide, is a suitable base catalyst;

ii) the importance of the relative pKa's of EAA (ca. 9), EtOH (ca. 16) and MeCOOEt (ca. 25).

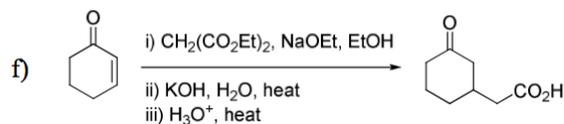
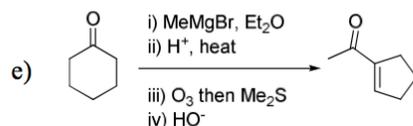
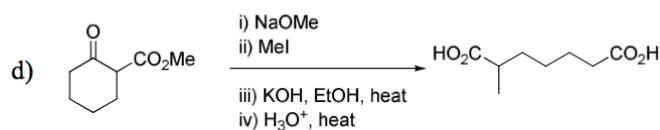
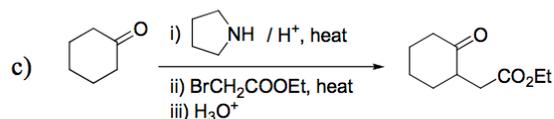
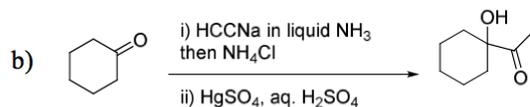
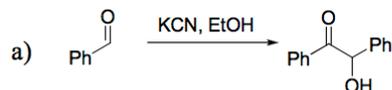
b) A undergoes an analogous intramolecular reaction (Dieckmann Condensation). There are two possible products when B is used under the same reaction conditions – draw mechanisms for their formation and interconversion.



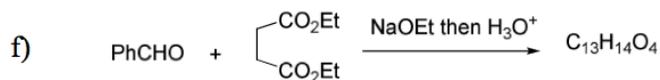
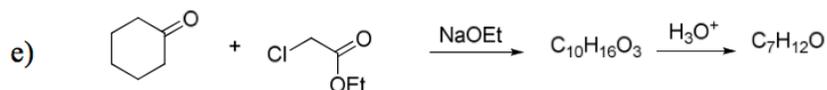
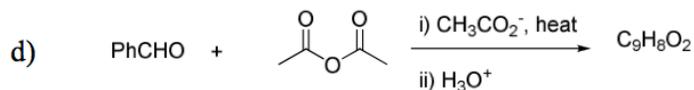
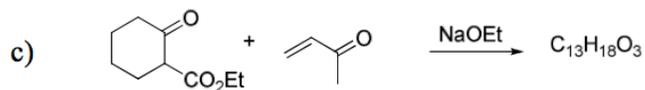
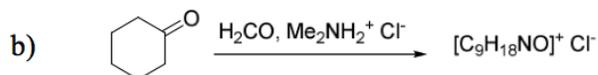
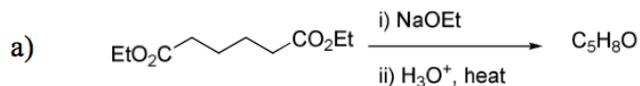
c) Give mechanisms for the following transformation.



5. Identify the probable intermediates in, and suggest possible mechanisms for all of the following transformations.



6. For all of the following give reaction mechanisms and indicate the structure of the products:



Now check your work: http://paton.chem.ox.ac.uk/teaching/files/Y1_Enolization_Notes.pdf