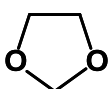


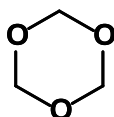
Mechanistic Assignment
CHEM 4000A – Medicinal Chemistry
Due at 12:00 noon on Friday, November 2, 2012

1. Formaldehyde is a gas which is not usually sold as a pure substance since it tends to react with itself. Even aqueous solutions of formaldehyde tend to contain primarily oligomers rather than monomers (formaldehyde molecules). An oligomer of formaldehyde has the structure shown for paraformaldehyde with a small value of n ; polymeric paraformaldehyde has large values of n (exact values vary between molecules in the sample).

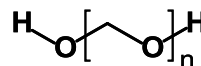
In one of the Friday problem sets, 1,3-dioxolane was used as a source of formaldehyde. Other common sources of formaldehyde include 1,3,5-trioxane and paraformaldehyde.



1,3-dioxolane



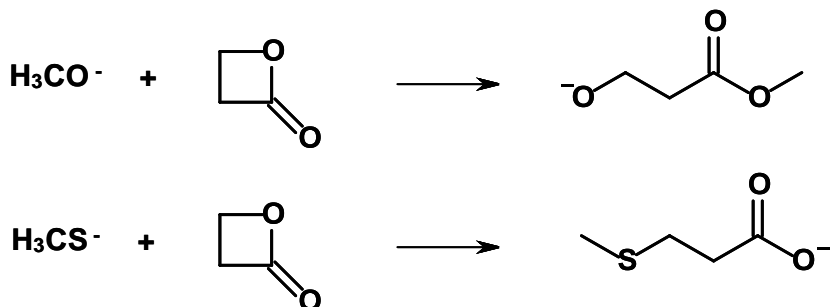
1,3,5-trioxane



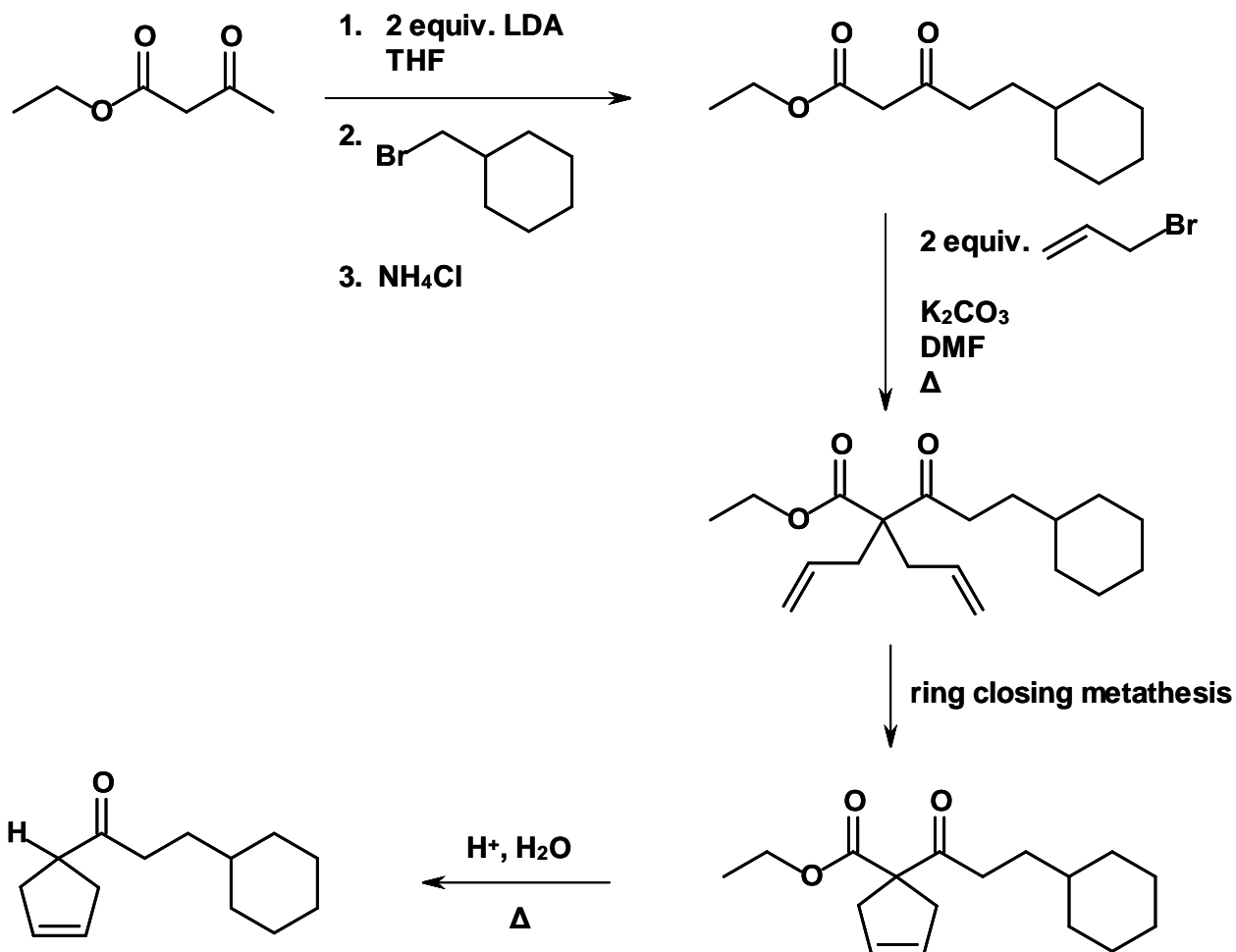
paraformaldehyde

- (a) Paraformaldehyde can be used to generate very pure formaldehyde for use in some biological labs. Heating paraformaldehyde gives formaldehyde gas in an equilibrium process.
- (i) Write a balanced chemical equation for the equilibrium between formaldehyde and paraformaldehyde. Instead of using the abbreviated form above, set $n=4$ and draw the whole molecule.
(n is usually much larger than 4, but nobody wants to draw the whole molecule with $n \gg 100!$)
- (ii) Why does this equilibrium favour paraformaldehyde at low temperatures but favour formaldehyde at high temperatures?
Hint: You may need to go back to concepts from CHEM 2000 and/or CHEM 2500...
- (b) Chemists tend to prefer 1,3,5-trioxane over paraformaldehyde for practical reasons. As a polymer, paraformaldehyde is fairly insoluble in most solvents whereas 1,3,5-trioxane dissolves in a variety of common organic solvents. Addition of a catalytic amount of acid to the solution is usually necessary.
- (i) Suggest a reasonable mechanism for the formation of 1,3,5-trioxane from formaldehyde.
You may assume that water is present.
- (ii) Suggest a reasonable mechanism for the formation of 1,3-dioxolane from 1,3,5-trioxane and 1,2-ethanediol in the presence of catalytic acid.
You may use H^+ as a generic acid. The solvent is 1,2-ethanediol.

2. Suggest a reasonable mechanism for each of the two reactions below, and explain the key difference(s) between them.



3. Consider the following sequence of reactions:



When the questions refer to step numbers, each arrow corresponds to a step in the synthesis.

(Step #1 therefore has three substeps; it's not just the "add LDA" part.)

- (a) (i) Suggest a reasonable mechanism for step #1. Clearly indicate when experimental conditions change (i.e. when a new reagent is added).
- (ii) With reference to your mechanism, explain why the β-ketoester reacts at the terminal carbon instead of the carbon between the two carbonyl groups.
- (b) (i) Suggest a reasonable mechanism for step #2.
- (ii) Why would K₂CO₃ have been used instead of NaOEt? Important factors to consider include acidity of the β-ketoester, strength of the bases and possible side reactions.
- (c) What is a "ring closing metathesis" reaction? Your answer should address the types of reactants involved, whether each is used in stoichiometric or catalytic amounts and a reasonable mechanism for step #3.
- Metathesis reactions are important enough that they merited a Nobel Prize.*
- (d) (i) Suggest a reasonable mechanism for step #4.
You may abbreviate non-reacting parts of the molecule as R, R', etc.
- (ii) Why would steps #3 and #4 have been done in this order rather than in reverse?