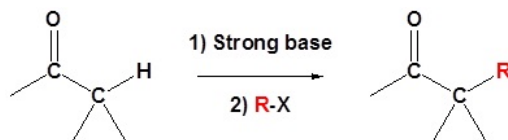


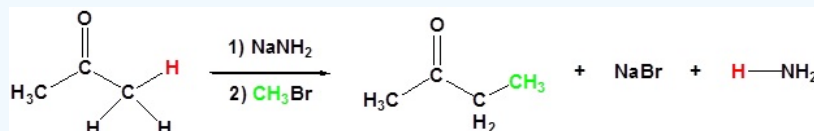
## 23.6: ALKYLATION OF THE ALPHA-CARBON VIA THE LDA PATHWAY

### ALPHA ALKYLATION

A strong base, such as lithium diisopropyl amide (LDA), sodium hydride, or sodium amide, creates the nucleophilic enolate ion which reacts with an alkyl halide suitable for the  $S_N2$  reactivity to form an alpha-alkylated product.



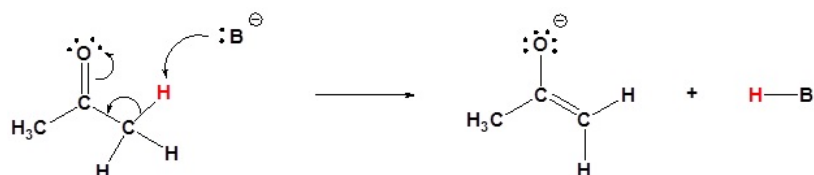
#### Example 1: Alpha Alkylation



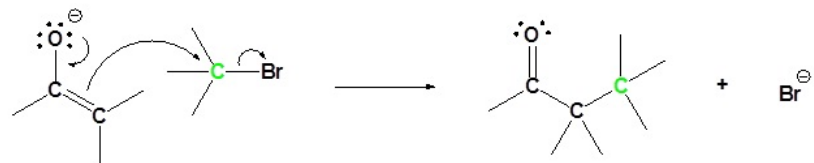
### MECHANISM

The mechanism begins with enolate formation. The resulting enolate is the nucleophile in an  $S_N2$  reaction with a suitable alkyl halide.

1) Enolate formation

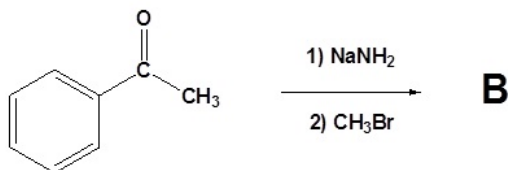
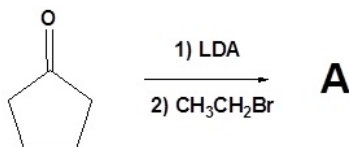


2)  $S_N2$  reaction

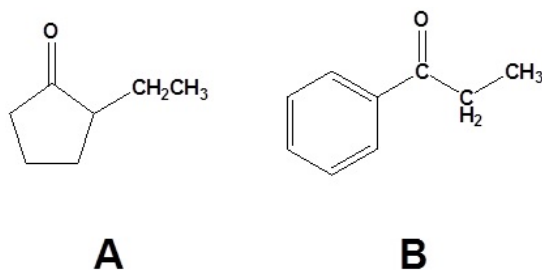


#### EXAMPLE QUESTION

Write the structure of the product for the following reactions.

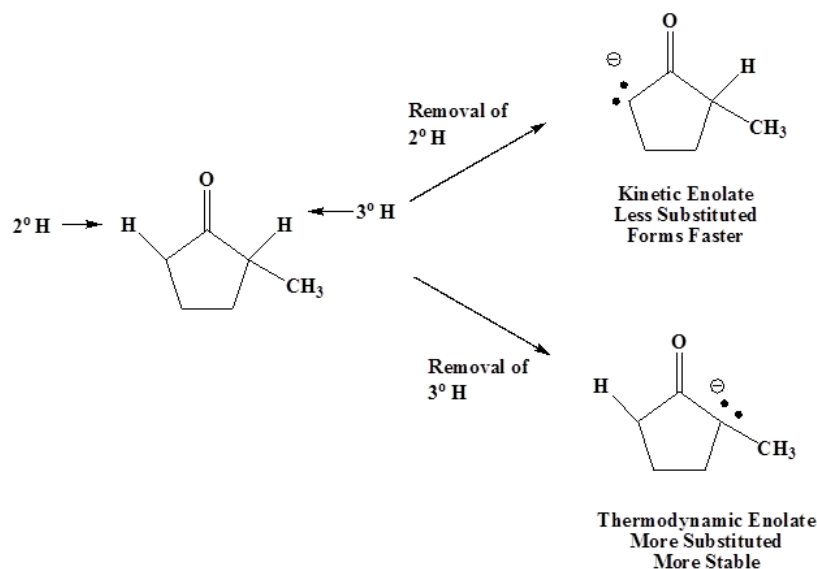


#### SOLUTION TO EXAMPLE QUESTION



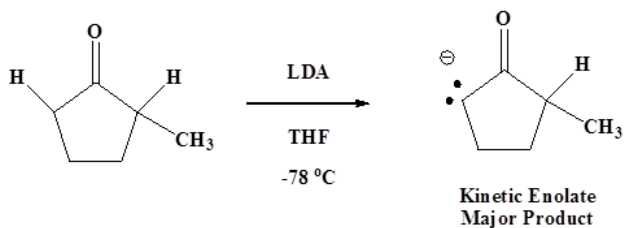
## ENOLATE OF UNSYMMETRICAL CARBONYL COMPOUNDS

Now let's consider what happens when an unsymmetrical carbonyl is treated with a base. In the case displayed below there are two possible enolates which can form. The removal of the 2° hydrogen forms the kinetic enolate and is formed faster because it is less substituted and thereby less sterically hindered. The removal of the 3° hydrogen forms the thermodynamic enolate which is more stable because it is more substituted.



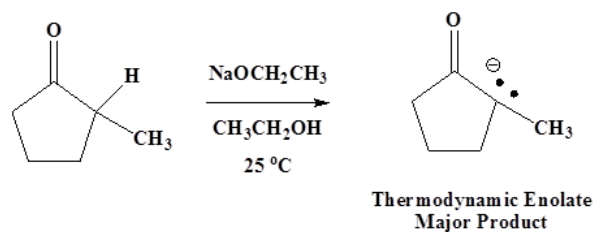
## KINETIC ENOLATES

Kinetic enolates are formed when a strong bulky base like LDA is used. The bulky base finds the 2° hydrogen less sterically hindered and preferably removes it. Low temperature are typically used when forming the kinetic enolate to prevent equilibration to the more stable thermodynamic enolate. Typically a temperature of -78 °C is used.



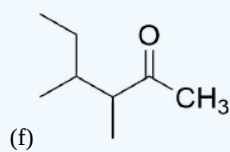
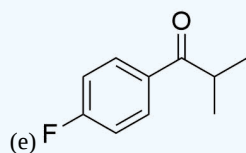
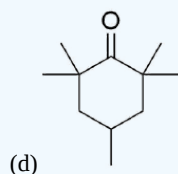
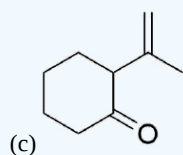
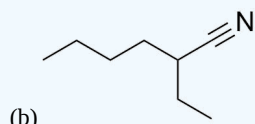
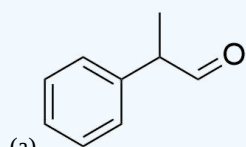
## THERMODYNAMIC ENOLATES

The thermodynamic enolate is favored by conditions which allow for equilibration. The thermodynamic enolate is usually formed by using a strong base at room temperature. At equilibrium the lower energy of the thermodynamic enolate is preferred, so that the more stable, more substituted enolate is formed.



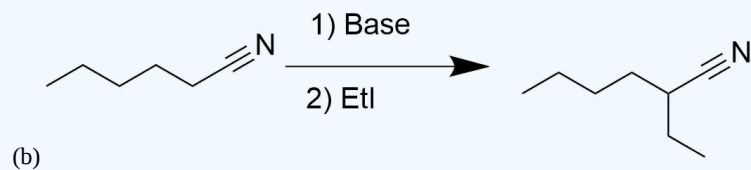
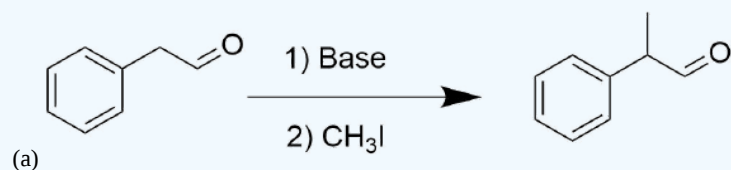
### Exercises

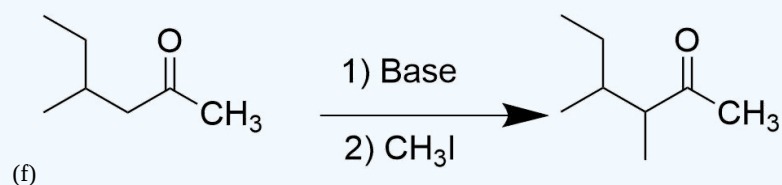
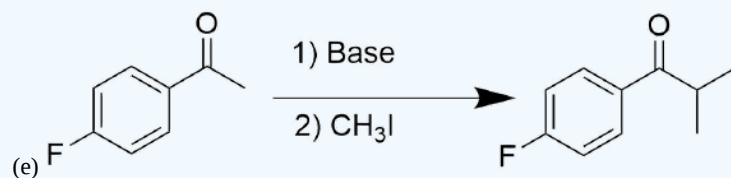
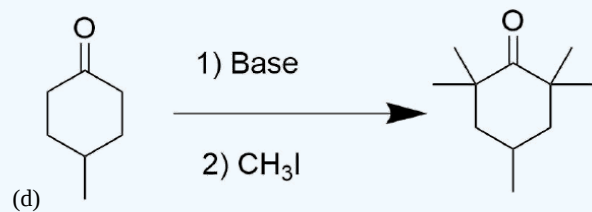
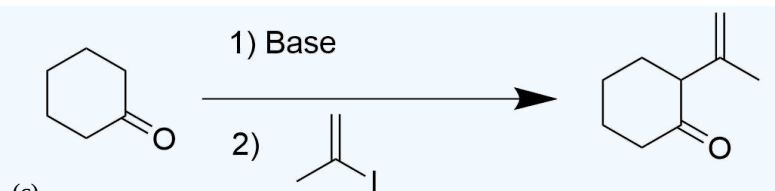
9. How might you prepare the following compounds from an alkylation reaction?



**Answer**

9.



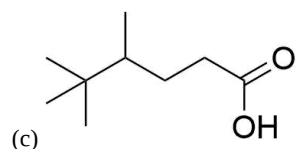
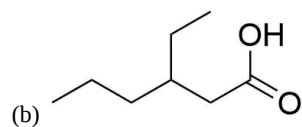
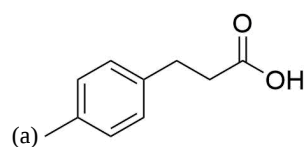
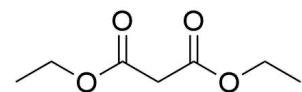


## EXERCISES

### QUESTIONS

#### Q22.7.1

Propose a synthesis for each of the following molecules from this malonic ester.

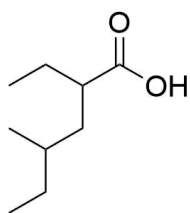


#### Q22.7.2

Why can't you prepare tri substituted acetic acids from a malonic ester?

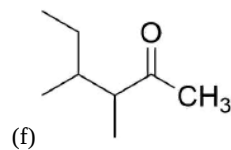
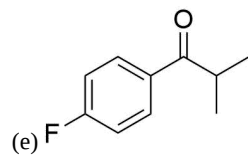
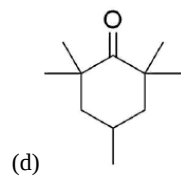
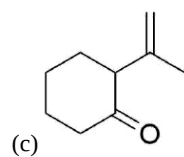
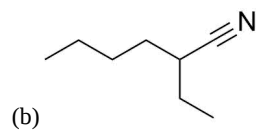
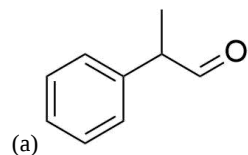
#### Q22.7.3

Propose a synthesis for the following molecule via a malonic ester.



#### Q22.7.4

How might you prepare the following compounds from an alkylation reaction?



#### SOLUTIONS

##### S22.7.1

(a) 1) Malonic Ester, NaOEt, 2) 4-Methylbenzyl Bromide, 3) Base, 4) Acid, Heat

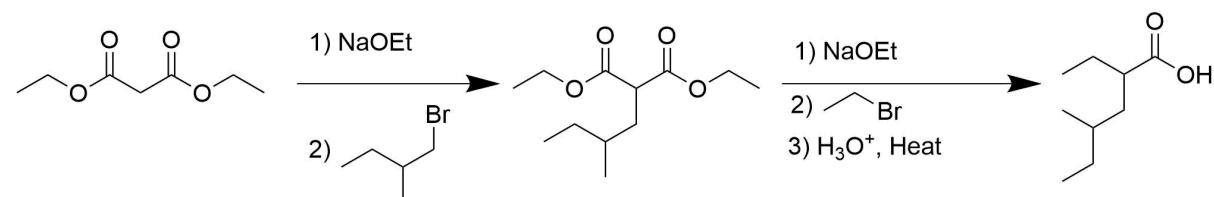
(b) 1) Malonic Ester, NaOEt, 2) 3-bromohexane, 3) Base, 4) Acid, Heat

(c) 1) Malonic Ester, NaOEt, 2) 1-Bromo-2,3,3-trimethylbutane, 3) Base, 4) Acid, Heat

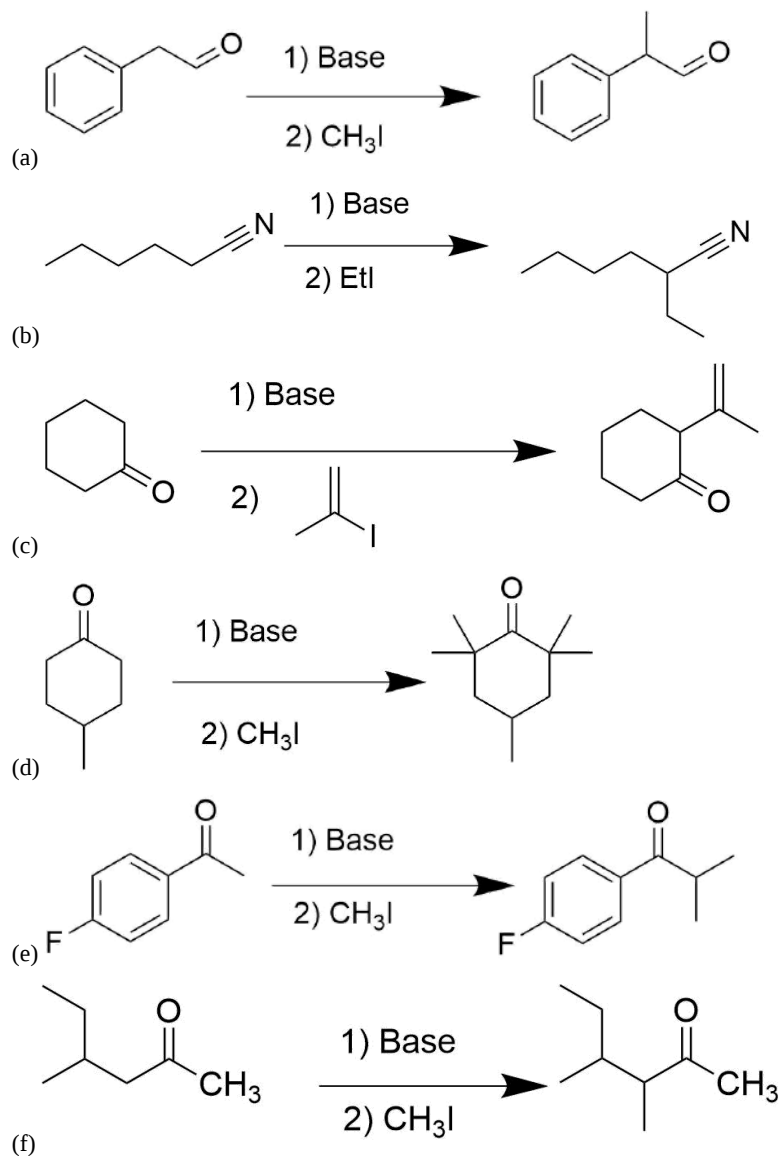
##### S22.7.2

Malonic esters only contain two acid protons.

##### S22.7.3



S22.7.4



## CONTRIBUTORS AND ATTRIBUTIONS

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, [Athabasca University](#))
- William Reusch, Professor Emeritus ([Michigan State U.](#)), [Virtual Textbook of Organic Chemistry](#)
- Prof. Steven Farmer ([Sonoma State University](#))

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