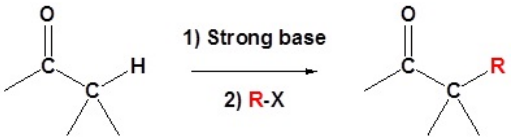
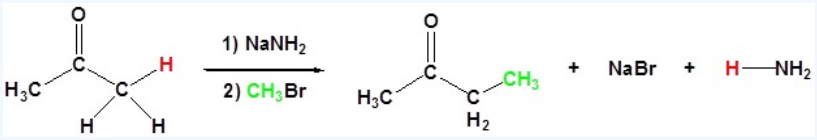
23.6: ALKYLATION OF THE ALPHA-CARBON VIA THE LDA PATHWAY

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.



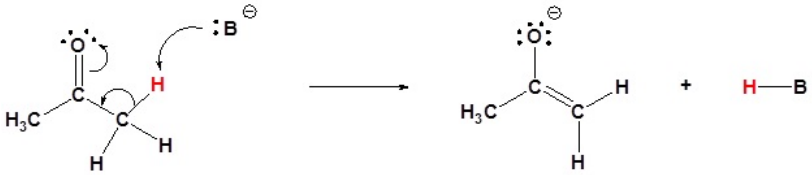
Example 1: Alpha Alkylation



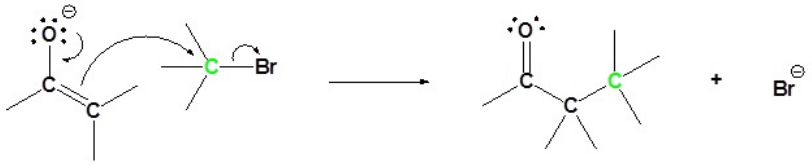
MECHANISM

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

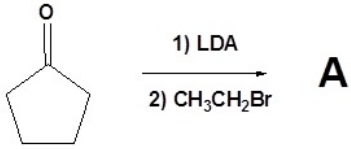


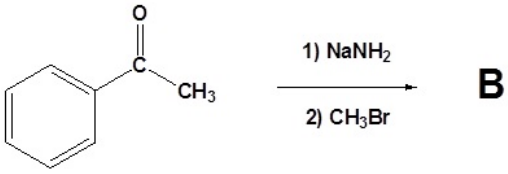
2) S_N2 reaction



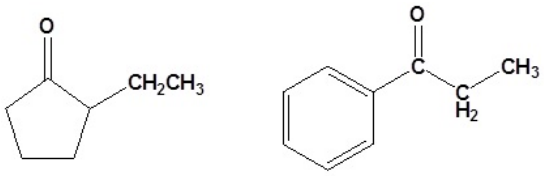
EXAMPLE QUESTION

Write the structure of the product for the following reactions.





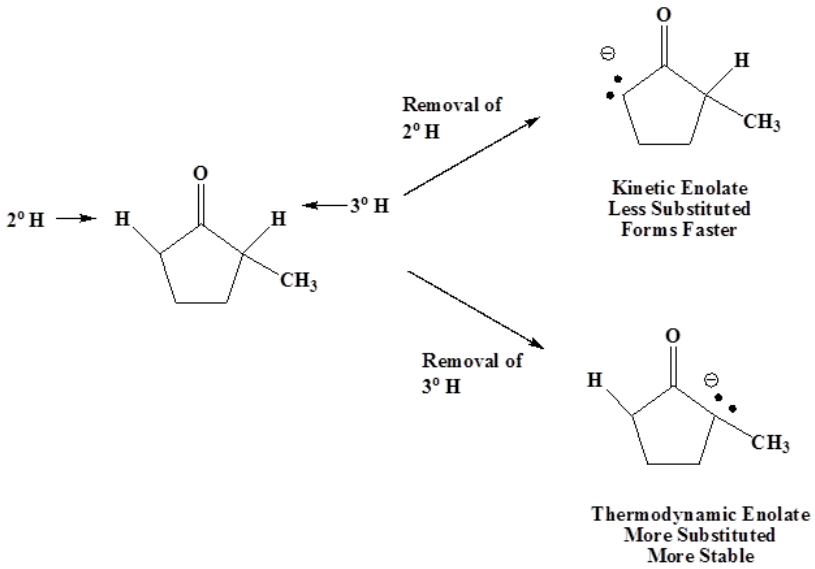
SOLUTION TO EXAMPLE QUESTION



A B

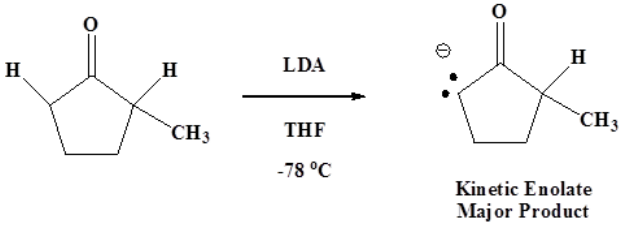
ENOLATE OF UNSYMMETRICAL CARBONYL COMPOUNDS

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 2o hydrogen forms the kinetic enolate and is formed faster because it is less substituted and thereby less sterically hindered. The removal of the 3o hydrogen forms the thermodynamic enolate which is more stable because it is more substituted.



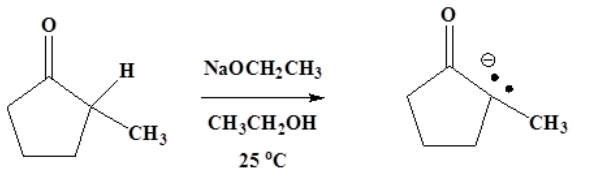
KINETIC ENOLATES

Kinetic enolates are formed when a strong bulky base like LDA is used. The bulky base finds the 2o hydrogen less sterically hindered and preferable 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 oC is used.



THERMODYNAMIC ENOLATES

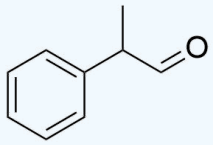
The thermodynamic enolate is favored by conditions which allow for equilibration. The thermodynamic enolate is usually formed by using a strong base at room temperature. At equilibrium the lower energy of the thermodynamic enolate is preferred, so that the more stable, more stubstituted enolate is formed.

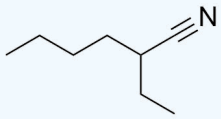


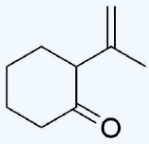
Thermodynamic Enolate
Major Product

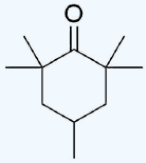
Exercises

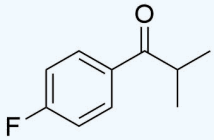
9. How might you prepare the following compounds from an alkylation reaction?

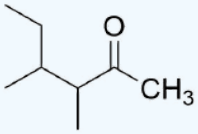
(a) 

(b) 

(c) 

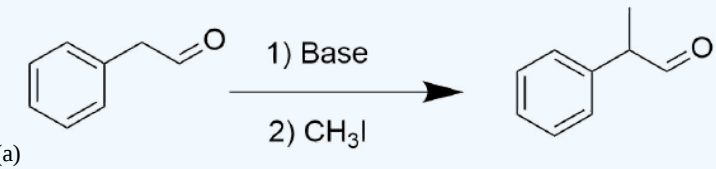
(d) 

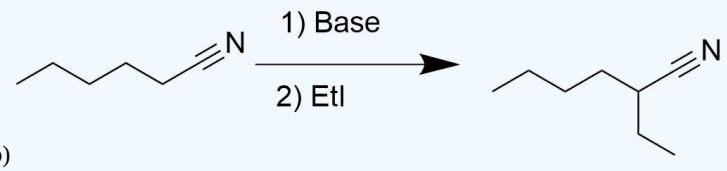
(e) 

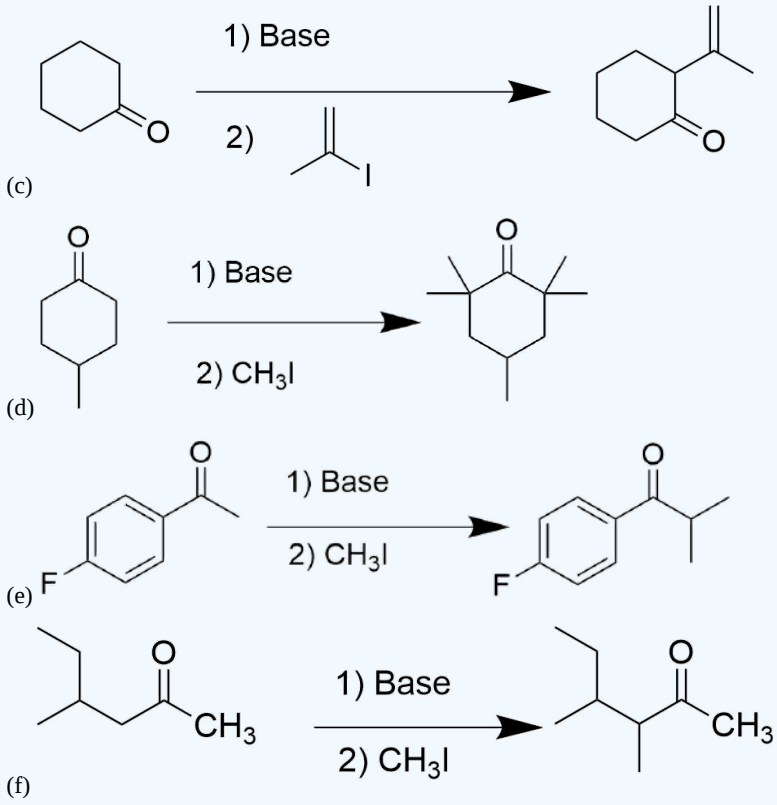
(f) 

Answer

9.

(a) 

(b) 

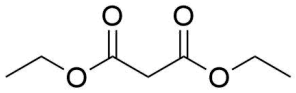


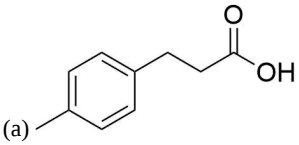
EXERCISES

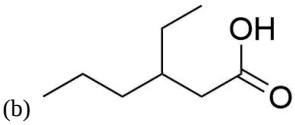
QUESTIONS

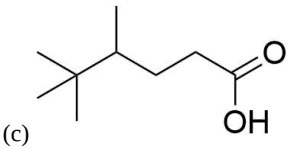
Q22.7.1

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







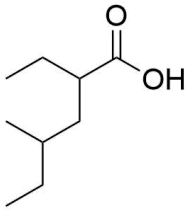


Q22.7.2

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

Q22.7.3

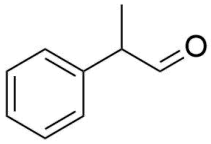
Propose a synthesis for the following molecule via a malonic ester.



Q22.7.4

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

(a)



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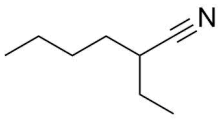

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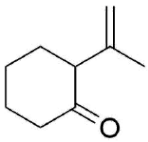

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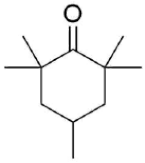

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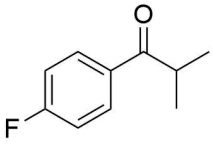

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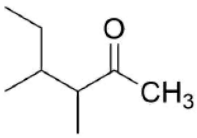


SOLUTIONS

S22.7.1

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

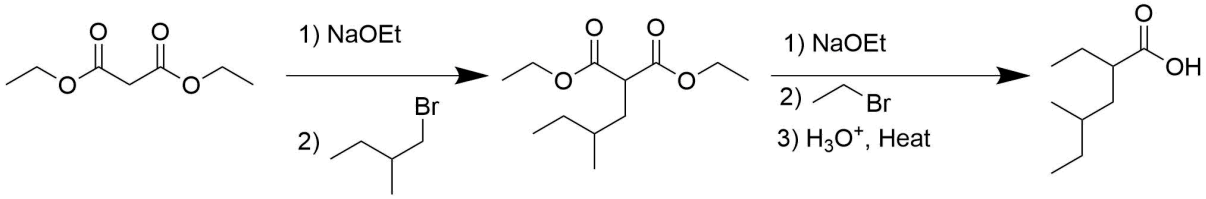
(b) 1) Malonic Ester, NaOEt, 2) 3-bromohexane, 3) Base, 4) Acid, Eat

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

S22.7.2

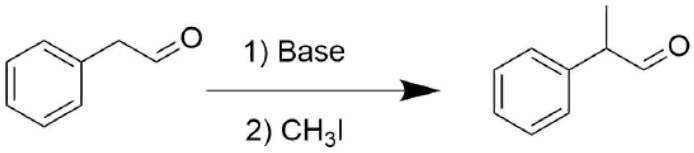
Malonic esters only contain two acid protons.

S22.7.3



S22.7.4

(a)



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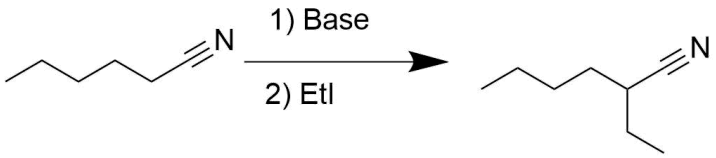

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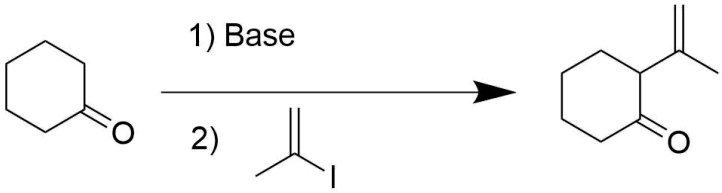

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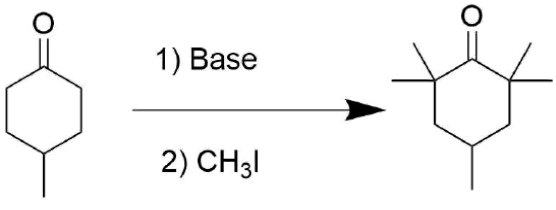

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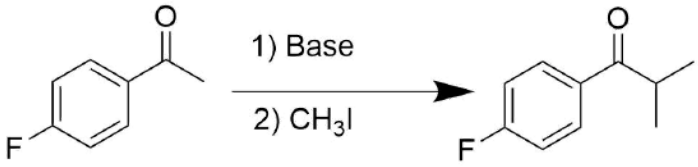

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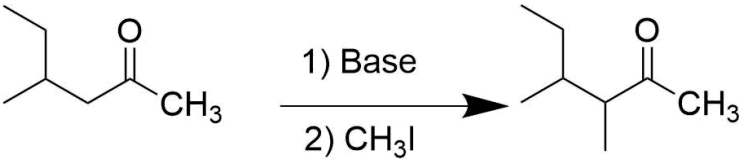

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