8.8: ALKYLATION OF ENOLATE IONS

OBJECTIVES

After completing this section, you should be able to

1. write a general mechanism for the attack of an enolate anion on an alkyl halide.
2. write a reaction sequence to illustrate the preparation of carboxylic acids via the malonic ester synthesis.
3. identify the product formed, and all the intermediates, in a given malonic ester synthesis.
4. identify all of the compounds needed to prepare a given carboxylic acid by a malonic ester synthesis.
5. write a detailed mechanism for each of the steps involved in a malonic ester synthesis.
6. write a reaction sequence to illustrate the preparation of ketones through the acetoacetic ester synthesis.
7. identify the product formed, and all the intermediates, in a given acetoacetic ester synthesis.
8. identify all of the compounds needed to prepare a given ketone by an acetoacetic ester synthesis.
9. write a detailed mechanism for each of the steps involved in an acetoacetic ester synthesis.
10. identify the product or products formed when a given lactone, ester, nitrile or ketone is treated with lithium diisopropylamide followed by an alkyl halide.
11. identify the compounds needed to prepare a given α-substituted ketone, ester, lactone or nitrile by a method involving the alkylation of an enolate anion.

KEY TERMS

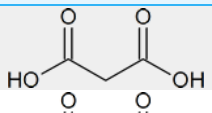
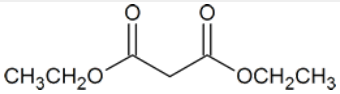
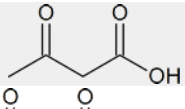
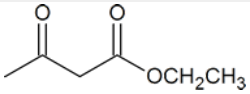
Make certain that you can define, and use in context, the key terms below.

- alkylation
- malonic ester synthesis

STUDY NOTES

The two syntheses discussed in this section provide routes to a wide variety of carboxylic acids and methyl ketones. You may wish to review the factors influencing S_N2 reactions (Section 11.3) in conjunction with this section.

You should try to memorize the structures of malonic ester and ethyl acetoacetate. The IUPAC names of these compounds are shown in the table below.

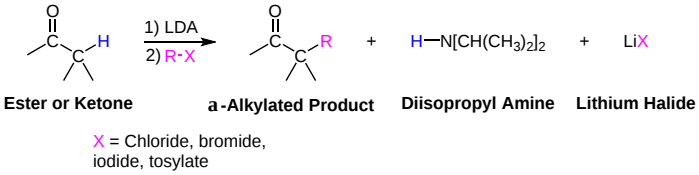
Structure	Common name	IUPAC name
	malonic acid	propanedioic acid
	malonic ester or diethyl malonate	diethyl propanedioate
	acetoacetic acid	3-oxobutanoic acid
	ethyl acetoacetate or acetoacetic ester	ethyl 3-oxobutanoate

ALKYLATION OF ENOLATES

Enolates can be alkylated in the alpha position through an S_N2 reaction with alkyl halides. During this reaction an α-hydrogen is replaced with an alkyl group and a new C-C bond is formed. The limitations of S_N2 reactions still apply. This includes preferring a good primary or secondary leaving group, X = chloride, bromide, iodide, tosylate. Tertiary leaving groups cannot be used in this reaction and typically give undesired E2 elimination products. A very strong base, such as LDA, is often used because of its ability to form the enolate completely. Removal of the carbonyl starting material from the reaction mixture makes it unavailable for nucleophilic addition by the enolate. Aldehydes are usually not directly alkylated because their enolates prefer to undergo the carbonyl condensation reactions discussed later in **Section 23.1**. In addition, the acidic hydrogen on carboxylic acids inhibits the formation of an enolate, and makes their direct alkylation

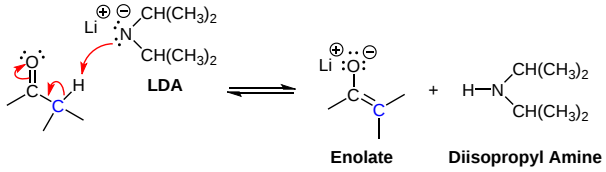
difficult. Esters, including lactones, and symmetrical ketones readily undergo direct alkylation. However, direct alkylations, like all enolate-based reactions, can form a racemic mixture if the alkylated α-carbon produced is chiral.

GENERAL REACTION

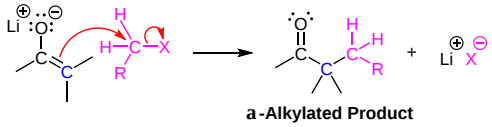


MECHANISM

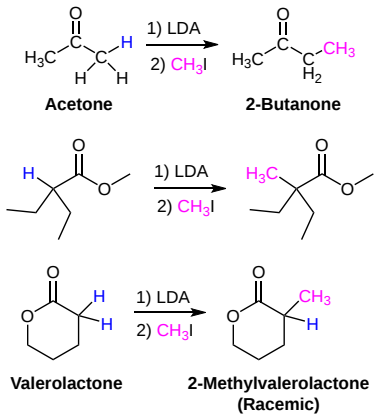
1) Enolate formation



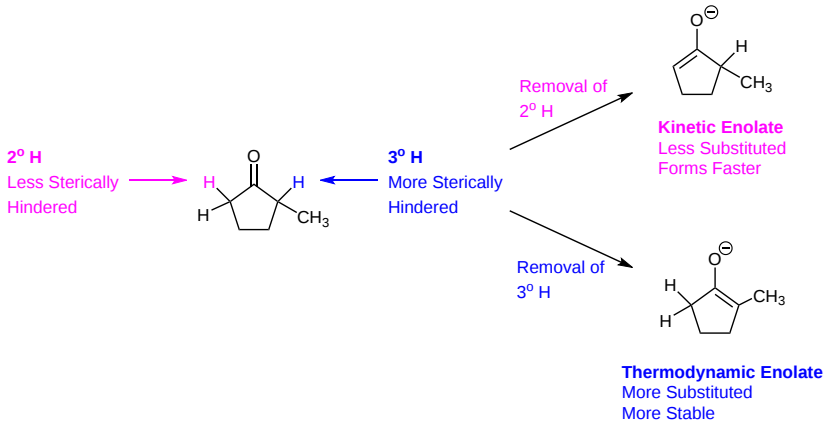
2) S_N2 attack



EXAMPLES



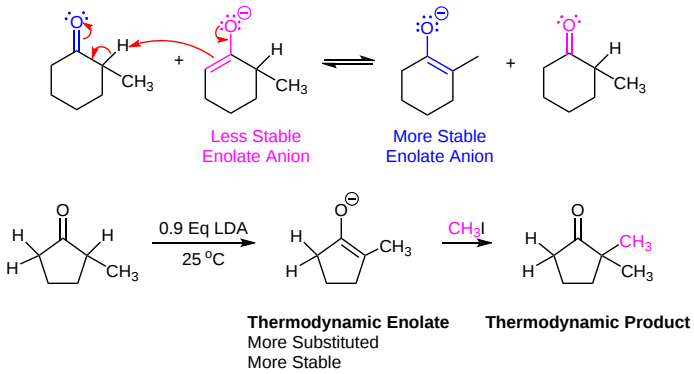
When an unsymmetrical ketone with two sets of non-equivalent α-hydrogens is treated with a base, two possible enolates can form. Regioselective enolate formation is possible under the proper conditions. The main determinant is whether the reaction is under kinetic control (rate) or thermodynamic control (equilibrium). Although a predominant product can be produced, a mixture of products is usually formed causing a reduction in product yield.



THERMODYNAMIC ENOLATES

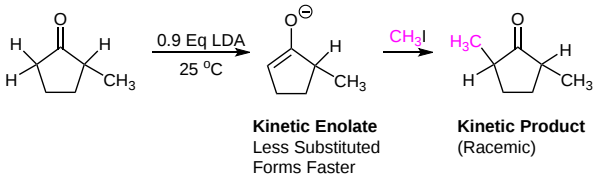
The thermodynamic enolate is formed when the more substituted α-hydrogen is removed. This leads to the more alkyl substituted, therefore the more stable, enolate to be formed. The presence of additional alkyl groups causes the formation of the thermodynamic enolate to be sterically hindered and kinetically slow, especially when a bulky base like LDA is used. Thermodynamic enolates are favored by conditions which allow for equilibration between the possible enolates. When the ketone starting material is not completely deprotonated, equilibrium between the possible enolates and the α-hydrogens of the ketone can occur. During equilibrium, interconversion between the enolates allows the lower energy of the thermodynamic enolate to dominate. Other conditions can also promote the formation of the thermodynamic enolate, such as higher reaction temperatures, or the use of a smaller less sterically hindered base such as sodium hydride (NaH). Weaker bases, such as sodium ethoxide, do not completely deprotonate the ketone starting material which also allows for enolate equilibrium to occur.

Example of enolate equilibration



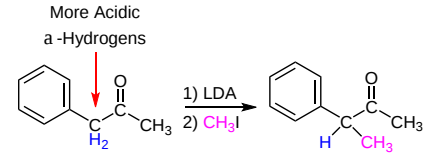
KINETIC ENOLATES

Kinetic enolates are favored under conditions which do not allow for equilibration between the enolates, such as the use of a strong bulky base, like LDA, in a molar equivalent to the ketone starting material. Kinetic enolates are formed when the less substituted α-hydrogen is deprotonated. Being less sterically hindered allows this α-hydrogen to be deprotonated faster even though it forms a less thermodynamically stable enolate. Using a molar equivalent of LDA completely converts the ketone starting material to an enolate, removing it from the reaction mixture and preventing equilibration between the possible enolates. Low reaction temperatures (-78 °C) prevent enolate equilibration and promote the formation of the kinetic enolate.



When and enolate of an asymmetric ketone is stabilized through additional resonance forms there is no competition between possible enolates despite kinetic or thermodynamics conditions. The resonance stabilized enolate will be preferentially alkylated to the point that formation of the alkylated products of other possible enolates will be minimal.

EXAMPLE

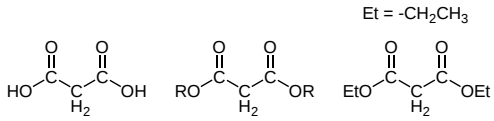


1-Phenyl-2-propanone **1-Methyl-1-phenyl-2-propanone (Racemic)**

MALONIC ESTER SYNTHESIS

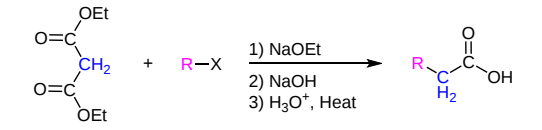
The malonic ester synthesis is a series of reactions which converts an alkyl halide to a carboxylic acid with two additional carbons. One important use of this synthesis pathway is that it allows for the creation of α-alkylated carboxylic acids which cannot be created by direct alkylation.

The starting material of this reaction is a malonic ester: a diester derivative of malonic acid. Diethyl propanedioate, also known as diethyl malonate, is the malonic ester most commonly used in pathway. Since it is a 1,3-dicarbonyl compound, diethyl malonate has relatively acidic α-hydrogens (pK_a = 12.6) and can be transformed to its enolate using sodium ethoxide as a base. Other alkoxide bases are not typically used given the possibility of a transesterification reaction.



Malonic Acid **Malonic Ester** **Diethyl Malonate**

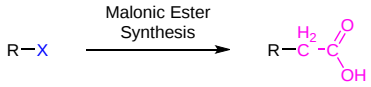
GENERAL REACTION



Diethyl malonate **Alkyl Halide** **a-Alkyl Carboxylic Acid**

PREDICTING THE PRODUCT OF A MALONIC ESTER SYNTHESIS

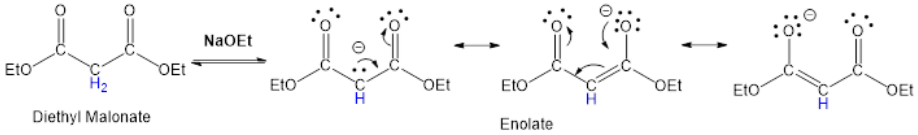
The product of a Malonic Ester Synthesis can be created by simply replacing the halogen on the alkyl halide with a $-CH_2CO_2H$ group.



MALONIC ESTER SYNTHESIS TAKES PLACE IN FOUR STEPS:

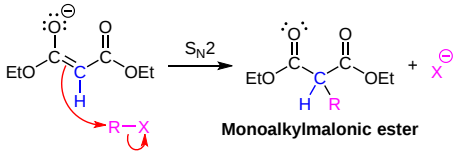
1) Enolate Formation

Reacting diethyl malonate with sodium ethoxide (NaOEt) forms a resonance-stabilized enolate.



2) Alkylation

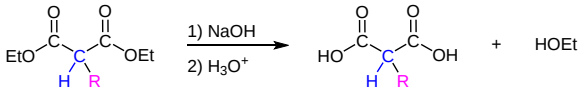
The enolate is alkylated via an S_N2 reaction to form an monoalkylmalonic ester.



Monoalkylmalonic ester

3) Ester hydrolysis and protonation

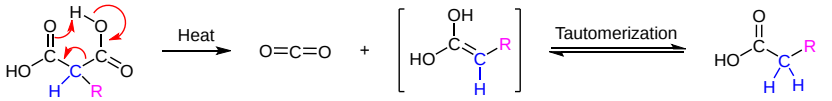
After alkylation, the diester undergoes hydrolysis with sodium hydroxide to form a dicarboxylate. Subsequent protonation with acid forms a monoalkyl malonic acid.



Monoalkyl Malonic Acid

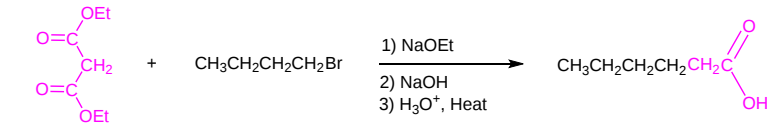
4) Decarboxylation & Tautomerization

Monoalkyl malonic acids decarboxylate when heated, forming an α-alkyl carboxylic acid and carbon dioxide (CO_2). Decarboxylation can only occur in compounds with a second carbonyl group two atoms away from carboxylic acid such as in malonic acids and β-keto acids. The mechanism occurs via a concerted mechanism involving a proton transfer between the carboxyl acid hydrogen and the nearby carbonyl group to form the enol of a carboxylic acid and CO_2. The enol undergoes tautomerization to form the carboxylic acid.



Carbon Dioxide **Carboxylic Acid Enol** **a-Alkylated Carboxylic acid**

EXAMPLE

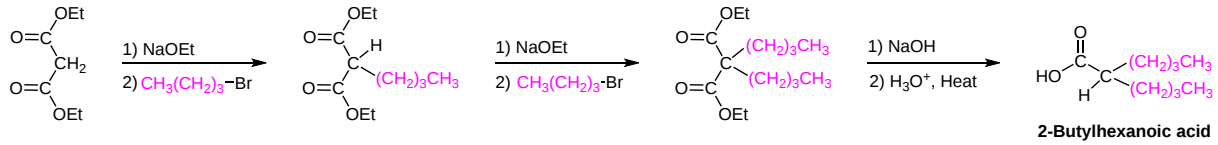


Diethyl malonate **1-Bromobutane** **Hexanoic Acid**

DIALKYLATION

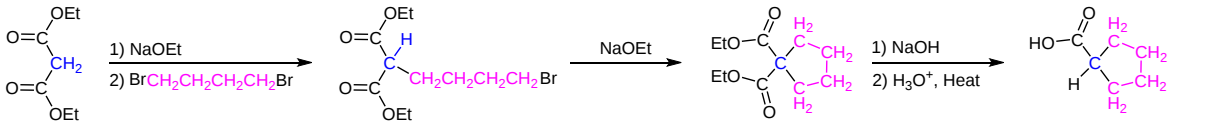
The presence of two α-hydrogens in malonic esters allows for a second alkylation to be performed prior to decarboxylation. This leads to dialkylated carboxylic acids. Due to the lack of stereochemical control inherent in enolate based reactions, if the two added alkyl groups are different, a racemic mixture of products will result.

EXAMPLES



2-Butylhexanoic acid

In a variation of the dialkylation reaction - if one molar equivalent of malonic ester is reacted with one molar equivalent of a dihaloalkane and two molar equivalents of sodium ethoxide, a cyclization reaction occurs. By changing the dihaloalkane, three, four, five, and six-membered rings can be created.

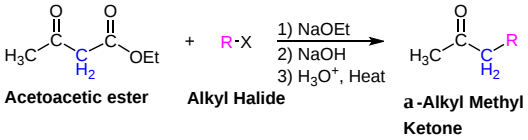


Cyclopentanecarboxylic acid

THE ACETOACETIC ESTER SYNTHESIS

The acetoacetic ester synthesis is a series of reactions which converts alkyl halides into a methyl ketone with three additional carbons. This reaction creates an α-substituted methyl ketone without side-products. The starting reagent for this pathway is ethyl 3-oxobutanoate, also called ethyl acetoacetate, or acetoacetic ester. Like other 1,3-dicarbonyl compounds, ethyl acetoacetate is more acidic than ordinary esters being almost completely converted to an enolate by sodium ethoxide.

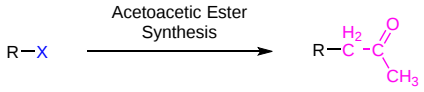
GENERAL REACTION



Acetoacetic ester **Alkyl Halide** **a-Alkyl Methyl Ketone**

PREDICTING THE PRODUCT OF AN ACETOACETIC ESTER SYNTHESIS

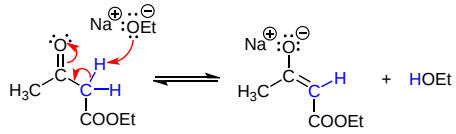
The product of a acetoacetic ester synthesis can be created by replacing halogen on the alkyl halide with a $-CH_2COCH_3$ group.



REACTION STEPS

1) Formation of the enolate

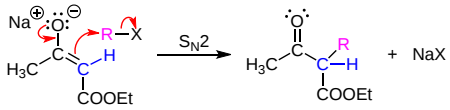
As previously described, the α-hydrogens of acetoacetic ester are rather acidic (pK_a = 10.7) allowing the enolate to be easily formed when sodium ethoxide is used as a base.



Acetoacetic ester **Sodioacetoacetic ester**

2) Alkylation via an S_N2 Reaction

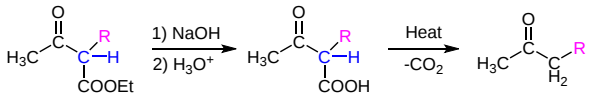
Subsequent reaction with an alkyl halide produces a monoalkylacetoacetic ester.



Monoalkylacetoacetic ester

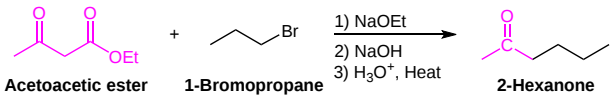
3) Ester hydrolysis and decarboxylation

Hydrolysis with NaOH followed by protonation produces an alkylated beta-ketoacid. β-ketoacids are easily decoboxylated to form an α-alkyl substituted methyl ketone and carbon dioxide (CO_2) using a similar mechanism as the malonic ester synthesis.



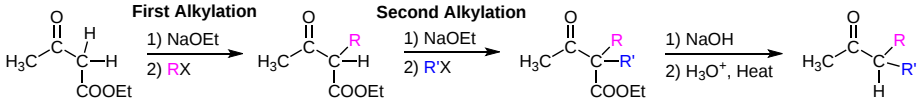
Monoalkyl b-ketoacid **Monoalkyl-methyl ketone**

EXAMPLES



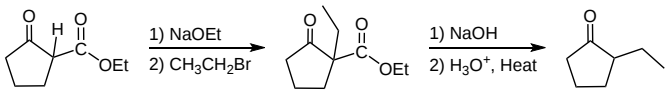
Acetoacetic ester **1-Bromopropane** **2-Hexanone**

Much like the malonic ester synthesis, a second alkyl group can added before the decarboxylation step.



The reaction steps of the acetoacetic ester synthesis can also be applied to other β-keto esters with acidic α-hydrogens. Because the α-hydrogens between the two carbonyls are the most acidic, they are preferentially deprotonated allowing for a single enolate to be formed. Even cyclic beta-keto esters can be alkylated and subsequently decarboxylated to give an α-alkylated cyclic ketone.

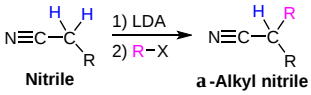
EXAMPLES



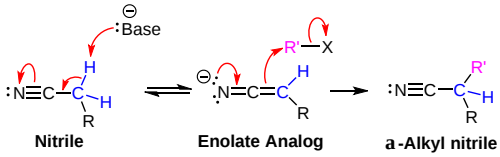
DIRECT ALKYLATION OF NITRILES

The presence of acidic α-hydrogens in nitriles gives them the ability to form an enolate equivalent which can be also be directly alkylated.

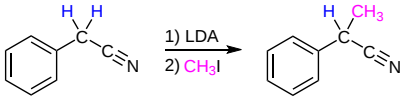
GENERAL REACTION



MECHANISM



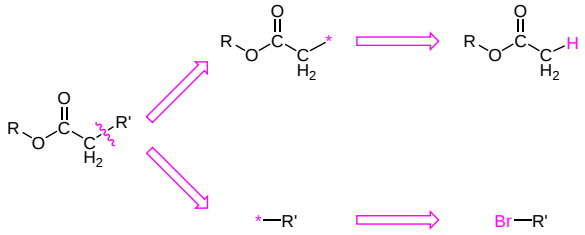
EXAMPLE



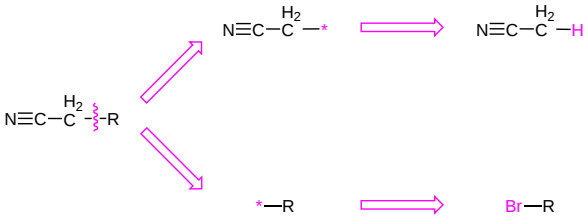
PLANNING A SYNTHESIS USING ENOLATE ALKYLATIONS

When planning a synthesis that could involve enolates, the key is to recognize the functionality which can form an enolate. During retrosynthetic analysis a C-C bond is broken between the α-carbon and the β-carbon away from this functionality. It is also important to be able to identify specific groups of atoms which indicate if a malonic ester or an acetoacetic ester synthesis can be used. Having multiple C-C bonds which can be broken allows for multiple synthetic pathways.

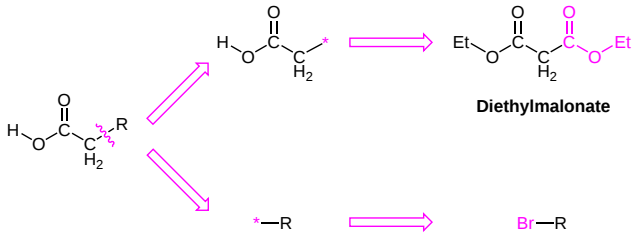
After retrosynthetically breaking the C-C bond, the fragment with the functionality will gain a hydrogen and the other fragment will gain a halogen. Sometimes the fragment with the functionality will become diethyl malonate or acetoacetic ester.

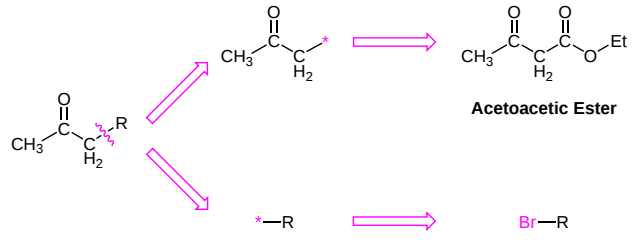


Direct Alkylation of an Ester



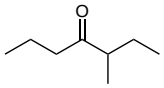
Direct Alkylation of a Nitrile



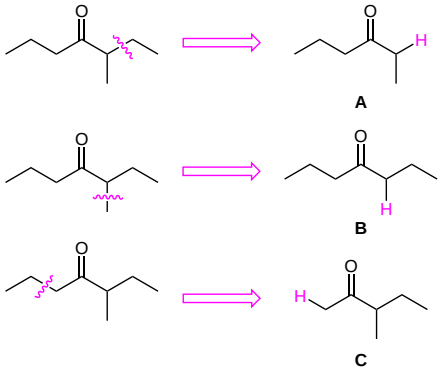


WORKED OUT EXAMPLE:

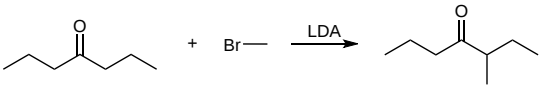
Plan a synthesis of the following molecule using an alkylation of an enolate. Consider multiple pathways and explain which is preferable.



The target molecule does not contain the appropriate fragments to utilize either the malonic ester or acetoacetic acid synthesis so direct alkylation of a ketone will likely be used. When analyzing this molecule, there are three α-β C-C bonds which could be cleaved to create a possible starting material. When looking at the possible starting materials, A and C are asymmetrical ketones and therefore can create multiple products during alkylation. B is a symmetrical ketone and should be the most likely to create the target molecule in high yield.



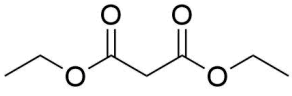
Possible Synthesis

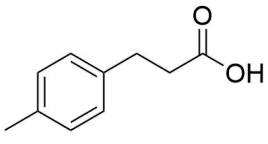


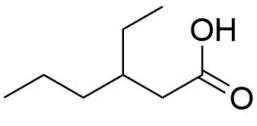
EXERCISES

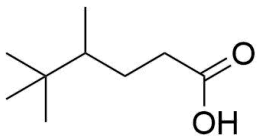
QUESTIONS

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



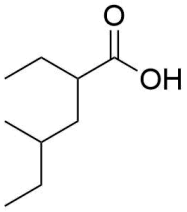
(a) 

(b) 

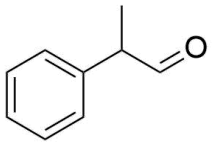
(c) 

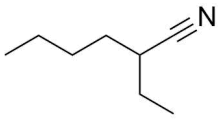
2) Why can't you prepare tri substituted acetic acids from a malonic ester?

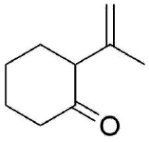
3) Propose a synthesis for the following molecule via a malonic ester.

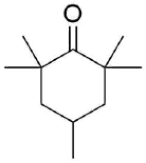


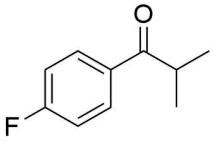
4) How might you prepare the following compounds from an alkylation reaction?

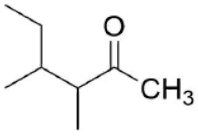
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

SOLUTIONS

1

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

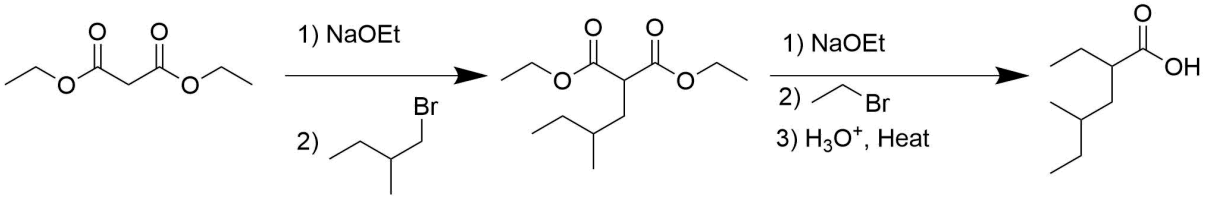
(b) 1) Malonic Ester, NaOEt, 2) 3-bromohexane, 3) Base, 4) Acid, Eat

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

2

Malonic esters only contain two acid protons.

3



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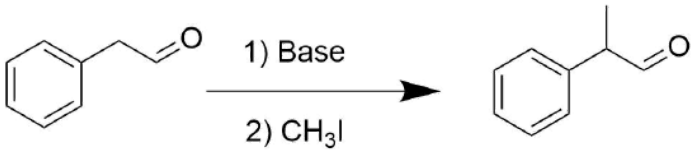
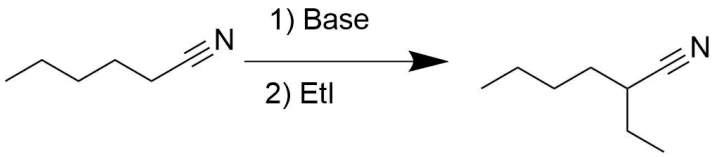


(a)



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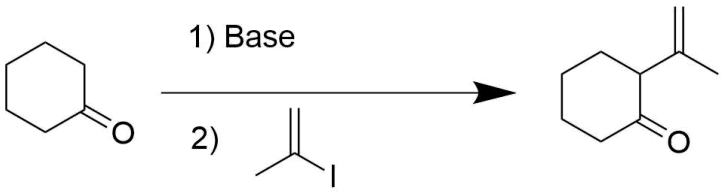

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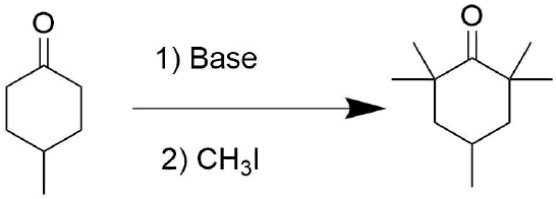

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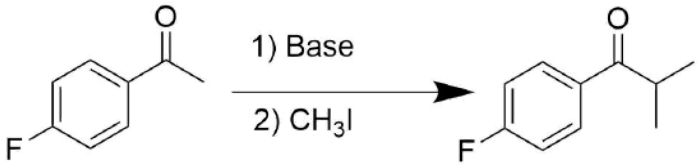
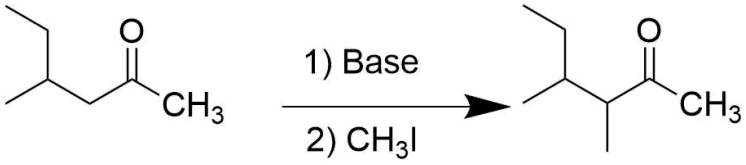


(e)



(f)