Chemistry 2220
Organic Chemistry II
Fall Semester 2023
Dr. Rainer Glaser

TEST #3

Ch. 18: Reactions at the alpha-Carbon of Carbonyl Compounds. Enolization. Alpha-Halogenation of Carbonyls: base catalyzed, acid-catalyzed. Haloform reaction. Alpha-Halogenation of Carboxylic Acids and CA Halides: Access to alpha-hydroxy and alpha-amino carboxylic acids. Alpha-Alkylation of Ketones, Esters, 1,3-Dicarbonyls, beta-Keto Esters, Malonates. Enamines: Carbonyl alkylation, access to 1,3-dicarbonyls and gamma-keto esters.

Ch. 19: Condensation and Conjugate Addition Reactions of Carbonyl Compounds. Claisen and Dieckmann Condensations and Variants. Aldol Reaction and Variants. Conjugate Addition Reactions: Focus on Michael Additions and Variants. Robinson Annulation. Mannich Reaction.

Ch. 20 (in part): Amines. Synthesis of Aliphatic Amines (thru slide 29): Reduction of azides, Gabriel synthesis, reductive amination of carbonyls, syntheses via Hofmann and Curtius rearrangements, alkylation and acylation of amines.

Handout: Friday, Nov. 17, 2023, after class.
Due: Wednesday, Nov. 29, 2023, noon.

Name:

Question 1. Reactions at the alpha-Carbon of Carbonyls	35	
Question 2. Condensation Reactions	25	
Question 3. Conjugate Addition Reactions	15	
Question 4. Synthesis of Aliphatic Amines	25	
Total	100	

ALLOWED: Open book. Online resources.

NOT ALLOWED: Collaboration with others.

Question 1. Reactions at the alpha-Carbon of Carbonyls. (35 points)

(**a**) **Enolization and Introduction of a Deuterium Label**. The introduction of one deuterium into the alpha-position of propiophenone using NaOD in D_2O results in a _____ (1 p.) mixture of two enantiomers. Provide perspective drawings of the two deuterated isomers and label the chiral centers as "*R*" or "*S*". (14 points)

Propiophenone (1 p.)	Enantiomer #1 (2 p.)	Enantiomer #2 (2 p.)

Provide a detailed mechanism of the base-catalyzed labeling reaction, i.e., propiophenone and NaOD/D_2O. (4 p.)

Now consider the analogous but acid-catalyzed reaction, i.e., propiophenone and aq. DCl (which is equivalent to a small amount of HCl in D_2O solution). Provide a detailed mechanism. (4 p.)

(**b**) **Synthesis of Valine**. Alpha-halogenations of carbonyls and of carboxylic acids and their derivatives are important reactions. These halogenations are relevant because the alpha-halogenated compounds enable nucleophilic substitution of the alpha-halogen and, for example, one can synthesize alpha-amino acids via such a sequence. Suggest a synthesis of the amino acid valine from the appropriate carboxylic acid and initial alpha-bromination. Show reagents on top of the reaction arrows and show intermediates. Of course, the amino acid synthesized in this way would be a _____ (pure *R* enantiomer, pure *S* enantiomer, racemate, non-racemic mixture of enantiomers; 1 p.). (10 points)

Reaction diagram for the alpha-bromination of appropriate carboxylic acid <u>including</u> all relevant intermediates. (4 p.) IUPAC name of the substrate carboxylic acid. (1 p.)
Alpha-amino acid formation from alpha-brominated carboxylic acid. (3 points)
Of course, one needs ___ (1, 2, 3) ammonia molecules for each nucleophilic substitution of an alpha-brominated carboxylic acid because… (1 point)

What do you call an acid with an attitude?
A-mean-oh acid.

(c) Malonic Acid Synthesis of 4-Methylpentanoic acid, $(CH_3)_2CH\text{-}CH_2\text{-}CH_2\text{-}COOH$. This carboxylic acid would be needed, for example, for the synthesis of the alpha-amino acid leucine by the route discussed in (**b**). 4-Methylpentanoic acid can be made using the so-called "malonic acid synthesis", that is, the appropriate alkylation of diethyl malonate followed by base-catalyzed ester hydrolysis, and subsequent decarboxylation of the alkylated malonic acid. (11 p.)

<table>
<tr><td colspan="2">Draw the three important resonance forms of the enolate formed by deprotonation of diethyl malonate with NaOEt/EtOH. (3 p.)</td></tr>
<tr><td>Alkyl bromide substrate needed for the alkylation. (2 p.)</td><td>Product of monoalkylation of diethyl malonate. (1 p.)</td></tr>
<tr><td>Monoalkylation product after base-catalyzed ester hydrolysis. (1 p.)</td><td>Reagent needed to obtain the monoalkylated malonic acid. (1 p.)</td></tr>
<tr><td colspan="2">Draw the monoalkylated malonic acid properly oriented to undergo decarboxylation upon heating. Use curved arrows to explain how CO_2 is eliminated. (3 p.)</td></tr>
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Question 2. Condensation Reactions. (25 points)

(a) Let's review the mechanism of the **Claisen Condensation of ethyl propanoate**. Provide complete structures in your answers to the following questions. Show all atoms, show all bonds and lone pairs, and clearly show charges. You may use "CH_3" and "CH_2" for brevity. (12 points)

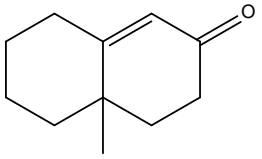
Ethyl propanoate. (1 p.)	Resonance forms of the enolate formed by reaction of ethyl propanoate with sodium ethoxide. Show resonance arrows. (3 p.)
Tetrahedral alkoxide intermediate formed by the addition of one ester enolate to one neutral ethyl propanoate. (2 p.)	Beta-keto ester product formed by ejection of _____ ion from the alkoxide intermediate. (2 p.)
Briefly explain why it is necessary to add aqueous mineral acid (i.e., aq. HCl) to the reaction mixture after the base-catalyzed CC coupling and before the recovery of the beta-keto ester product. (4 p.)	

(b) Let's review the mechanism of the NaOH catalyzed **Crossed Aldol Reaction between benzaldehyde and propiophenone**. Provide complete structures in your answers to the following questions. Show all atoms, show all bonds and lone pairs, and clearly show charges. You may use "CH_3" and "CH_2" for brevity. (13 points)

Benzaldehyde. (1 p.)	Propiophenone. (another 1 p.)
Resonance forms of the enolate formed by reaction of propiophenone with sodium hydroxide. Show resonance arrow. (3 p.)	
Intermediate beta-hydroxy carbonyl. (2 p.)	Alpha-beta unsat. carbonyl product. (2 p.)
The reaction is carried out by slowly adding propiophenone dropwise to a solution that contains benzaldehyde and NaOH. Briefly explain why the reaction is carried out in this way. An argument is needed about relative concentrations and their effect on product distribution. (4 p.)	

Question 3. Conjugate Addition Reactions. (15 points)

(a) Devise a synthesis of compound **A** shown **using a Michael addition** in the first step. Show all intermediates and specify required reagents for each step. (8 p.)



A

(b) A variant of the Robinson annulation **replaces methyl vinyl ketone with (*E*)-1,3-dichloro-2-butene** to avoid undesirable polymerization or condensation during the Michael addition. Outline the synthesis of compound **A** using (*E*)-1,3-dichloro-2-butene and show intermediates and specify required reagents for each step. (7 p.)

Question 4. Synthesis of Aliphatic Amines. (25 points)

(**a**) Show the reaction diagram for the reaction of cyclopentanone first with diethylamine and subsequently with $NaBH_3CN$. Draw complete structures of substrate and final product. Name the final product. This reaction is an example of a _____ of a ketone. (4 p.)

(**b**) Direct alkylation of ammonia and/or primary amines gives mixtures because of polyalkylation. It is better to alkylate an amine *indirectly* by way of *N*-acylation and subsequent reduction of the _____ (name of the functional group) to the amine. Describe a synthesis of *N*-ethylpropylamine using this strategy and include all reagents. (5 points)

(**c**) Primary amines can be synthesized by reduction of an alkyl azide. Draw the complete **Lewis-Kekulé structure of methyl azide** with the geometry that correctly reflects the hybridization angles at all N atoms. For each N atom, write down its hybridization. (3 points)

(d) The **Hofmann rearrangement** refers to the migration of an alkyl group R as a _____ (cation, radical, anion; 1 p.) in the formation of an isocyanate. This rearrangement is one step in the synthesis of a primary amine from a primary amide. Consider the formation of **propylamine** from the appropriate amide. Provide complete structures of the six species (all atoms, bonds, lone pairs, charges). Use curved arrows to show how the intermediate will undergo the Hofmann rearrangement. (8 points)

Substrate amide. (1 p.)	Brominated amide. (1 p.)	Intermediate that will undergo Hofmann rearrangement and curved arrows. (2 p.)
Isocyanate. (1 p.)	Carbamate. (1 p.)	Propylamine. (1 p.)

(**e**) The **Gabriel synthesis of isopropylamine** requires _____ (name of substrate), phthalimide, and KOH to form compound **A**. Reaction of **A** with _____ (name of reagent) and heating affords the product and compound **B**. (5 points, 1 p. each item)

Structure of Compound **A**.	Structure of **isopropylamine**.	Structure of Compound **B**.