Examination #5
“Carbon-Carbon Bond Forming Reactions, Sugars & Nucleic Acids”

The Final Learning Experience

Friday, May 5, 2000, 3:30 - 5:30

Your Name:

<table>
<thead>
<tr>
<th>Question</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Overview</td>
<td>40</td>
</tr>
<tr>
<td>2. Fancy Aldehydes &amp; Ketones &amp; Acids</td>
<td>30</td>
</tr>
<tr>
<td>3. Syntheses of Carbocycles</td>
<td>25</td>
</tr>
<tr>
<td>4. Aromatic Chemistry</td>
<td>20</td>
</tr>
<tr>
<td>5. Carbohydrates</td>
<td>55</td>
</tr>
<tr>
<td>6. DNA &amp; RNA Structure</td>
<td>30</td>
</tr>
<tr>
<td>7. Wittig Reaction (News #18)</td>
<td>40</td>
</tr>
<tr>
<td>Total</td>
<td>240</td>
</tr>
</tbody>
</table>
Question 1. Overview. (40 points)

There you are, you made it through the second semester of Organic Chemistry! While the first semester of organic chemistry basically was an introduction to bonding, stereochemistry and the chemistry of a few important functional groups, in the second semester of organic chemistry you learned how to change the carbon skeleton, the center issue of synthesis. Hence, carbon-carbon bond forming reactions are in the focal point of this final.

The chapter on carbanion chemistry contains many of the carbon-carbon bond forming reactions. One of the standard CC bond forming reactions is the aldol reaction. The aldol reaction of an aldehyde can lead to __________________________ by way of the aldol addition or it can go further and lead to _____________________ after condensation of _________. This reaction basically involves the nucleophilic addition of a carbanion to a carbonyl group. The Claisen reaction is analogous to the Aldol reaction in that it is a dimerization of sorts. The Claisen condensation of an ester leads to ______________________________. But there is a major mechanistic difference: While carbanions add to the carbonyl compound in the aldol reaction, the carbanion does a nucleophilic __________________________ reaction with the neutral ester. This reaction goes through a ________________ intermediate and the reactions mechanism is designated as _____. The Michael additions are the third big group of C-C bond formations involving carbanions. In a Michael addition a carbanion is added to an electron-______ alkene. This is an example of a nucleophilic addition to an alkene. You learned about electrophilic additions to alkenes in the first semester.

The nucleophilic substitution reaction of carboxylic acids and of their derivatives are nucleophilic substitutions at an unsaturated carbon-atom. Aside from these reactions, there also are many nucleophilic substitution reactions at saturated carbons that can be used in carbon-carbon bond forming reactions. A simple reaction of this type would be the nucleophilic substitution of chlorine in an alkyl chloride by cyanide ion. More complicated carbon nucleophiles of course also can be used and we will return to this chemistry below. These reactions involve alkylations of As & Ks and the alkylations of dicarbonyls. These kinds of reactions play an important role in the malonic acid synthesis
and the acetoacetic ester synthesis. All of these reactions form products that basically are fancy aldehydes, fancy ketones, fancy esters or acids, fancy alkenes or bigger molecules with several functionalities.

The “carbanion plus carbonyl approach” to carbon-carbon bonds may involve two types of carbanions: ________________ reagents and other organometallic reagents, on the one hand, and, on the other hand, the carbanions generated from carbon-_______ compounds, that is, compounds that contain ________________ H-atoms in the alpha-position to a carbonyl group.

Aside from the “carbanion plus carbonyl approach”, carbon-carbon bond formations also can be achieved by way of the Wittig reaction. Wittig reactions contains “carbanionic” carbons in the overall __________ (neutral, cationic, anionic) “ylides”. We will take a look at a few Wittig reactions in the last question.

Finally, aromatic chemistry was a big part of this course and we will review some of that chemistry again with a focus on carbon-carbon bond formation. Here we will try to make C-C bonds between a C-atom that is part of a benzene ring and another C-atom that is part of an aliphatic system. This kind of bond formation can be accomplished by way of a “nucleophilic aromatic substitution”. In this case a carbanion is generated and reacted with a benzene derivative that contains a very good nucleofug. Benzonitrile, for example can be readily obtained by nucleophilic aromatic substitution of the dinitrogen of benzene______________ ion by the nucleophile __________ which is employed as its __________ salt. This reaction is called the ______________ reaction. The Friedel-Crafts reactions are C-C bond formations of a different type. In the FC-alkylation, it is the benzene that serves as the __________ (electrophile, nucleophile) seeking to replace the halide of an alkyl halide with some help by a ______-acid. If one looks at this reaction from the perspective that something happens to the benzene, then one classifies this Friedel-Crafts alkylation reaction as an _______________ (electrophilic, nucleophilic) aromatic substitution where the electrophile is a ________________.

(40 points total, 2 points for each correct entry).
Question 2. Fancy Aldehydes & Ketones & Acids. (30 points)

(a) Beta-ketoesters undergo decarboxylation after hydrolysis and upon heating. This decarboxylation proceeds via a 6-membered ring transition state. For the beta-ketoacid shown, draw the conformation that contains the “6-membered ring” and draw “curved arrows” that indicate the electron flow in the decarboxylation. Also draw the products of the decarboxylation. (8 points)

(b) Draw the product obtained after hydrolysis and decarboxylation of the diester shown. Provide an acceptable IUPAC name of the product. (6 points)
(c) **Malonic Ester Synthesis.** The ethyl diester of malonic acid, EtOOC-CH₂-COOEt, is treated with sodium ethoxide followed by ethyl bromide. The product is treated with sodium ethoxide again and then again with ethyl bromide. Draw the product obtained after the twofold application of the NaOEt/EtBr sequence. Then draw the product that is obtained after hydrolysis and draw the final product obtained after heating. Name the final product. (8 points)

(d) **Acetoacetic Ester Synthesis.** The methyl ketone H₃C-CO-CH₂-CH₂-CH₃ can be prepared via an acetoacetic ester synthesis. Draw the structure of acetoacetic ester. Give reagents and product of the alkylation. Draw the structure of the product obtained after hydrolysis. Draw the structure after decarboxylation. Name the final product, the methyl ketone. (8 points)
**Question 3.** Synthesis of Carbocycles. (25 points)

**(a)** The Robinson annulation is a classic method for the synthesis of 6-membered rings. The Robinson annulation is a base-catalyzed tandem reaction and involves a _____________-reaction and an _____________-condensation. Draw the substrates used to prepare alpha,beta-unsaturated cyclohexene shown. Also draw the intermediate obtained by the first reaction of the sequence. (9 points)

![Diagram of Robinson annulation product]

**(b)** Suggest a synthesis of cyclohexanecarboxylic acid via a Diels-Alder reaction. Show substrates of the Diels-Alder reaction. Show the electron flow of the DAR using curved arrows. Suggest a method for the conversion of the product of the DAR into the cyclohexane derivative. (8 points)

**(c)** Suggest a synthesis of cyclopentanone by way of a Dieckmann condensation of an acyclic diester. Show the structures of the substrate diester and of the product of the Dieckmann condensation. Give conditions for the conversion of the beta-ketoester to the final product. (8 points)
**Question 4.** Aromatic Chemistry. (20 points)

(a) Draw the structure of the major product of this Friedel-Crafts reaction. (4 points)

\[ \text{C}_2\text{H}_5 \quad 1. \text{CH}_3\text{-CO-Cl} \quad 2. \text{AlCl}_3 \]

(b) Suggest a way to convert acetophenone, Ph-CO-Me, to ethyl benzene. (2 points).

(c) Suggest a synthesis of benzoic acid starting from toluene. Draw toluene, draw benzoic acid, and provide the reagent needed. (6 points)

(d) Suggest a synthesis of benzoic acid starting from aniline. Draw aniline. Provide the reagent needed for diazotization and provide the reagents needed for all subsequent transformations. (8 points)
Question 5. Carbohydrates. (55 points)

(a) Glycerinaldehyde is the smallest _________ (aldose, ketose). Draw the Fischer projection of D-glycerinaldehyde and also produce a perspective drawing of this same molecule. Mark the chiral carbon with a star. In the R/S-nomenclature, the absolute configuration of the chiral carbon is _____. (9 points)

(b) D-glycerinaldehyde is subjected to a chain elongation. This chain elongation involves a cyanohydrin formation, then a hydrolysis, and then a reduction with sodium amalgam. This chain elongation is referred to as the ____________________ synthesis. The cyanohydrin formation involves the reaction of the reagent ________ with the aldehyde function of the sugar. The hydrolysis of the cyanohydrin produces an ________________ acid which is then reduced to the aldose. The C1-carbon atom of D-glycerinaldehyde is converted into a chiral center in this chain elongation reaction and two products are formed. Draw the Fischer projections of these two products. For each of these products, mark whether it is D or L. These two products are ________________ (enantiomers, diastereoisomers). These two products also are referred to as ____________ (epimers, anomers) because they differ in the configuration of ____ (give number) chiral center(s). One of these products features a stereochemistry described as “erythro” and the other features a stereochemistry that is referred to as “threo”. Assign the correct label to the two products. (20 points, 6*2 for blanks, 8 for structures and labels.)
(c) D-glycerinaldehyde is treated with periodic acid, $\text{HIO}_4$. Show what products are formed in this reaction. When applied to a cyclic carbohydrate, the periodic acid cleavage provides information about the ______________ of the sugar. (6 points)

(d) The molecule shown is a __________ (mono, di, oligo, poly) saccharide. This sugar contains _____ (0, 1, 2) glucose molecule(s) and _____ (0, 1, 2) fructose molecule(s). Both rings are __________ (pyranoses, furanoses). The molecule ______ (is, is not) a reducing sugar. The molecule is ______ (alpha, beta) at the central anomeric carbon-atom. The stereochemistry of the hemiacetal is shown as ______ (alpha, beta) and interconversion _____ (is, is not) possible at that position. This sugar contains one ______ (1,4-, 1,6-, 4,6-) glycosidic bond. The trivial name of this sugar is __________ and this sugar is contained in ______________ (cellulose, amylose). (20 points)
**Question 6.** DNA & RNA Structure. (30 points)

(1, 2 p.) Label the C-atoms of the sugar moiety (e.g. assign the numbers 1’ to 5’ to the correct atoms).

(2, 2 p.) The sugar is a ___________ (pyranose, furanose).

(3, 2 p.) The fragment shown can be found in ______ (RNA, DNA).

(4, 2 p.) The sugar is _______________ (give the name of the free sugar).

(5, 2 p.) The anomeric carbon is ________ (alpha, beta).

(6, 2 p.) The fragment shown is a ___________ (nucleoside, nucleotide).

(7, 2 p.) Circle the alcohol function that would be used for another phosphate ester formation of the fragment shown would be incorporated into a single strand.

(8, 4 p.) The nucleobase in the fragment shown is ________________ or ____ (C, T, U, A, G) for short.

(9, 2 p.) This nucleobase is a ________________ (purine, pyrimidine) base.

(10, 2 p.) The name of the fragment shown is ____________________________________________.

(11, 2 p.) The fragment shown is abbreviated as ______________ (UMP, dUMP, AMP, dAMP, etc).

(12, 2 p.) In the Watson-Crick base pair, this nucleobase would H-bond with _____ (C, T, U, A, G).

(13, 2 p.) The Watson-Crick base pair involving the fragment shown contains _____ H-bonds.

(14, 2 p.) The hybridization of the N-atom involved in the N-glycosidic bond is ________.
**Question 7.** Wittig Reaction and Vitamin A. (40 points, News #18)

The newspaper article “NATURAL VITAMINS HAVE MORE ANTIOXIDANTS THAN MAN-MADE” featured vitamin A and beta-carotenes as important antioxidants. A good article to review some of the features of the Wittig reaction and of its important applications.

(a) In a Wittig reaction, a ______________ compound and an ylide react to form an ______________ (name of the class of compounds) and a phosphine ________. The ylide is formed by treatment of a phosphonium halide with a strong base. The phosphonium halide is generated by way of a ___________________ (nucleophilic, electrophilic) substitution reaction of an _______________ (name of the class of compounds) with a phosphine. (10 points)

(b) Suppose you convert benzyl bromide into an ylide using triphenylphosphine and NaOH as the base. Suppose further that you react this ylide with acetone. Draw both of the important resonance forms of the ylide (pay attention to formal charges), draw the structure of the oxaphosphetane formed by reaction with acetone, and draw the structure of the product of the Wittig reaction. Using “curved arrows” show how the oxaphosphetane is formed and how it is cleaved. (14 points)
(c) The phosphonium chloride shown can be deprotonated with sodium methoxide to form an ylide. Draw this ylide. This ylide can couple with an appropriate aldehyde X to obtain the vitamin A acetate shown. Draw the structure of the aldehyde X. (8 points)

(d) The ylide derived from the phosphonium chloride shown in (c) serves as the starting material for a synthesis of the beta-carotene shown below. The beta-carotene is constructed with two Wittig reactions between two molecules of the same ylide and one di-aldehyde. Indicate which two C=C bonds are formed in these two Wittig reactions and provide the structure of the required di-aldehyde. (8 points)