Organic Cumulative Exam
May 25, 2017

Answer only three of the five questions. No more than three question answers will be graded and any work not to be considered must be clearly marked as such. Clearly indicate which questions are to be graded on the front of your answer booklet.

1. (33 points) Jeon and Han recently published the following concise synthesis of (−)-flueggenine C using an intermolecular Rauhut-Currier reaction as a key step.  

   \[ \text{J. Am. Chem. Soc. 2017, 139, 6302.} \]

   \[
   \begin{align*}
   \text{condition(s)} & \quad \text{(a) NaH, THF} \\
   & \quad \text{0°C to rt} \\
   & \quad \text{(b) MeOH, rt} \\
   & \quad \text{52%}
   \end{align*}
   \]

   \[
   \begin{align*}
   \text{compound B} & \quad \text{(a) TBAF, CH\textsubscript{2}Cl\textsubscript{2}} \\
   & \quad \text{(b) Ac\textsubscript{2}O, DMAP} \\
   & \quad \text{Et\textsubscript{3}N, 74%}
   \end{align*}
   \]

   \[
   \begin{align*}
   \text{compound A} & \quad \text{DCC, THF} \\
   & \quad \text{90°C, 51%}
   \end{align*}
   \]

   \[
   \begin{align*}
   \text{compound C} & \quad \text{(a) MsCl, Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}} \\
   & \quad \text{(b) TFA, rt} \\
   & \quad \text{(c) K\textsubscript{2}CO\textsubscript{3}, THF} \\
   & \quad \text{rt, 62% (3 steps)}
   \end{align*}
   \]

   \[
   \begin{align*}
   \text{(-)-flueggenine C (5)}
   \end{align*}
   \]

(a) Please provide the reagents and exact conditions for the conversion of 1 into 2 and 2 into 3.

(b) Please provide the structures including stereochemistry for compounds A-C.

(c) Please provide a complete mechanism for the conversion of 3 into compound A.

(d) Please provide a complete mechanism for the conversion of C into compound 5.

(e) What is a Rauhut-Currier reaction?
2. Squaric acid (1) is an unusual vinylogous carboxylic acid of high acidity that is comparatively stable in spite of its small-ring structure.

(a) What is meant by the term *vinylogous carboxylic acid*? Account for the fact that both of the pK$_a$ values for squaric acid are significantly lower than that for a typical carboxylic acid and comment on the structure/character of dianion 3. *(6 points)*

(b) The original synthesis of squaric acid (1) is illustrated below. Provide mechanisms for the conversion of chlorotrifluoroethene (4) to cyclobutene 5 and further transformation of the latter to acid 1. *(10 points)*


(c) Chiral thiosquaramides were recently shown to be effective organocatalysts for the enantioselective conjugate addition of barbituric acids to nitroolefins. The reaction below is representative.


i. Suggest a synthesis of catalyst 6 from the diethyl ester of squaric acid. *(6 points)*

ii. Propose a mechanism for the reaction shown that accounts for the indicated dependence of enantiomeric excess on solvent. *(11 points)*
3. (33 points) The following transformation was recently reported en route to the
dimeric diterpenoid hispidanin A (9).


![Chemical structures and reactions](image)

(a) Provide a reasonable mechanism for the transformation of 1 into 2 and explain how
it rationalizes the stereochemical outcome.

(b) Using a 3-dimensional projection drawing of 2, explain how you would use 1-D
and/or 2-D NMR experiments to establish the stereochemistry.

(c) The authors used the following roadmap to make precursor 1. Provide appropriate
reagents/conditions for each step.

![Chemical structures](image)

(d) Tricycle 2 was converted to intermediate 8 and then to natural product hispidanin A
(9) through several steps. Provide a retrosynthesis of 8 to 2 showing the major
transformations needed, and show the second major fragment needed to complete
the synthesis of hispidanin A (9).
4. Pierce and coworkers recently described total syntheses of synoxazolidinones A and B, potent biofilm inhibitory compounds isolated from arctic ocean ascidians. The structure of synoxazolidinone A is shown below.


(a) *Structure Elucidation and Biosynthesis* (25 points)

i. Assign the protons in the attached $^1$H NMR spectrum of synoxazolidinone A. Use the atom labelling given and clearly mark solvent peaks.

ii. For full structure elucidation via 2D NMR experiments, do you think methanol-d4 is the best choice of NMR solvent?

iii. How can you assign the configuration at the double bond C6-C7?

iv. How can you determine the *relative* and the *absolute* configuration at C10 and C11? Name and describe briefly two techniques/experiments for each.

v. Draw a mechanism to show how oxazolidinone moieties can be formed biosynthetically.

(b) *Total Synthesis* (8 points)

i. Pierce et al. employed an imine acylation/enol addition strategy to generate the oxazolidinone heterocyclic core of the synoxazolidinones in five steps via iminium ion intermediates 2. What side-reactions must be avoided during the course of this elaboration?
5. (33 points)

(a) Proline is a competent catalyst for the dimerization of propionaldehyde. However, the trimerization of propionaldehyde is notably slower and less selective. What is the cause of this effect?


(b) The current popularity of photoredox catalysis and the earlier work of radical organocatalysis by MacMillan and coworkers is notable. What fundamental problem in reactivity did the radical organocatalysis work (and the later photoredox catalysis) attempt to solve? Were they successful? Explain.


(c) The MacMillan group has a catalysis discovery and research center paid for and created by Merck Pharmaceutical at Princeton. The endowment of the facility and personnel support nears half a billion dollars. Among the facility are multiple SYMYX robots which can autonomously run hundreds of reactions at a time to not only discover optimum reaction conditions, but ideal catalyst and reactant structures. Is there any room for any other lab or research to be competitive in the same area? Why or why not? Justify your answer.