

Teaching & Learning Symposium 2007

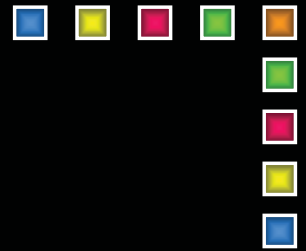
ICHO Training: Experiences & Insights

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Tue 11 Dec 2007



NUS High School of Mathematics and Science





● Introduction

● Some Perspectives

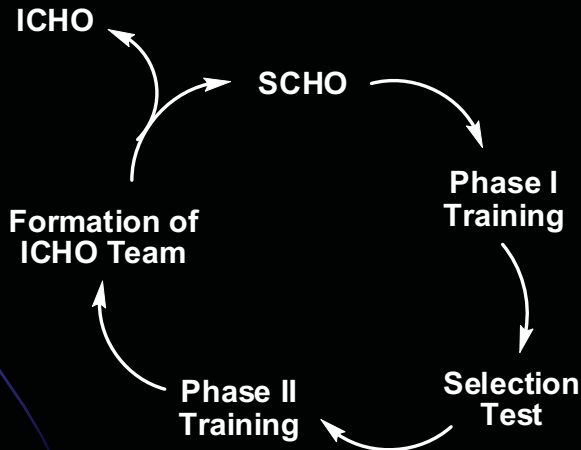
● Sample

● Q & A

Flow of Presentation

Introduction

- ICHO – what is it?
- Preparation the NUS way



Common Problems

- **No/ inadequate training on certain topics**
- **Wrong attitude (students and/or teachers)**
- **Started training too late**

How much should they know?

- ICHO syllabus!
- If the level is beyond the syllabus, Q will be guided adequately
- Knowledge of simple organic QA is assumed
- Knowledge of simple organic experimental set-up is assumed
 - reflux, recryst, extraction? TLC?

What I did...

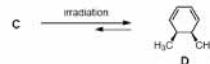
- Using past ICHO Q as a starting point to go through some of the more advanced topics
- Additional worksheets
- “Effective Learning – Journal Club Discussion”

Problem 14: Photochromic Ring Closure and Opening

1,3,5-Hexatriene is known to undergo light-induced cyclization to give 1,3-cyclohexadiene. The photochemical reaction is reversible and stereospecific. Thus, irradiation of (2*E*,4*Z*,6*E*)-octatriene (**A**) with UV-light gives cyclohexadiene (**B**). The choice of the wavelength of light depends on the absorption maximum of the compound to be irradiated, and the absorption maximum is related to the number of conjugated double bonds in a chain.



14-1 What is the chemical name of the starting triene (**C**) for the related reaction shown below?



A similar reaction mechanism is involved in the synthesis of biologically active molecules. For example, in the presence of sunlight, 7-dehydrocholesterol (**E**) undergoes an electrocyclic ring opening reaction to give provitamin D₃ (**F**), which can be further transformed through a [1,7]-hydrogen shift to yield vitamin D₃ (**G**).

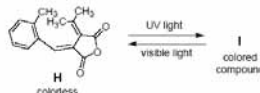


14-2 Of the two compounds 7-dehydrocholesterol (**E**) and vitamin D₃ (**G**), which would you expect to absorb light with the higher energy? (**E** or **G**)

14-3 What is the chemical structure of **F**?

This principle has been elaborated to develop photochromic materials. For example, irradiation of colorless compound **H** with UV light gives colored compound **I**. The color change is reversed upon exposure to visible light.

14-4 Give the structure of colored compound **I**.

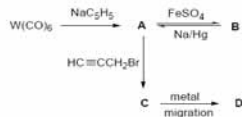


Problem 12: Metal Carbonyl Compounds

Carbon monoxide, as a two electron donor ligand, coordinates to transition metals to form metal carbonyl compounds. For example, iron forms the pentacarbonyl metal complex, $\text{Fe}(\text{CO})_5$. Nickel tetracarbonyl, $\text{Ni}(\text{CO})_4$, has been used for the purification of Ni metal in the Mond process. Electron counts of these metal carbonyl complexes show that they obey the 18-electron rule. Cobalt and manganese react with CO to form dinuclear complexes $\text{Co}_2(\text{CO})_8$ and $\text{Mn}_2(\text{CO})_{10}$, respectively. (Electronic configuration of Mn is $[\text{Ar}](3d)^5(4s)^2$) A metal-metal bond between the metal centers is considered essential in order for the compounds to obey the 18 electron rule. The cyclopentadienyl anion C_5H_5^- has also been widely used as a η^5 -ligand. For example, ferrocene (C_5H_5)₂Fe, a classical compound, obeys the 18 electron rule.

The reaction of $\text{W}(\text{CO})_6$ with sodium cyclopentadienide NaC_5H_5 yields an air sensitive compound **A**. Oxidation of **A** with FeSO_4 yields compound **B**. Compound **A** can also be prepared from the reaction of **B** with Na/Hg , a strong reducing agent. In the 1600-2300 cm^{-1} region of the IR spectrum, **A** shows absorption bands at 1744 and 1894 cm^{-1} and **B** absorption bands at 1904, and 2010 cm^{-1} . Compound **A** is a strong nucleophile and a good starting material for the synthesis of organometallic compounds containing metal-carbon bonds. The reaction of **A** with propargyl bromide ($\text{HC}\equiv\text{CCH}_2\text{Br}$) gives compound **C** containing a metal-carbon σ -bond. At room temperature compound **C** undergoes a transformation to yield compound **D**. The same chemical composition was found for compounds **C** and **D**. The chemical shifts (δ) of the CH_2 and CH resonances and coupling constants $J_{\text{H-H}}$ of propargyl bromide, **C** and **D** in the respective ^1H NMR spectra are listed in the following table.

^1H NMR	$\text{HC}\equiv\text{CCH}_2\text{Br}$	C	D
δ (CH_2)	3.86	1.90	4.16
δ (CH)	2.51	1.99	5.49
$J_{\text{H-H}}$ (Hz)	2.7	2.8	6.7



- 12-1 Explain the differences in the IR spectra of **A** and **B**.
- 12-2 Draw chemical structures for **A**, **B**, **C** and **D**.
- 12-3 The transformation of **C** to **D** involves a migration of the metal on the propargyl ligand. If $\text{DC}\equiv\text{CCH}_2\text{Br}$ is used for the synthesis of **C**, draw the structures of **C** and **D**.

What I did...

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ICHO Organic Chemistry Training 2006 – Exercise 1

This exercise is about literature appreciation and understanding. Please refer to the attached paper on "Spiroacetal Biosynthesis ..." by (Brett D. Schwartz et al. *Org. Lett.* 2005, 6, 1173.) and answer the following questions.

Question 1

One fine day, Charlie was reading the above paper to Grandpa Joe, Grandma Josephine, Grandpa George & Grandma Georgina. 4 of them made the following statement at the end of the day:

Grandpa Joe: Great work. Finally the exact pathway leading to (5) has been elucidated.

Grandma Josephine: Yes, and little did I realized that nature is able to selectively synthesized and used nine-carbon units from carbohydrates.

Grandpa George: How do chemists know which intermediates leads to (5) in this paper?

Grandma Georgina: That's simple. They did labeling studies using ^2H and GCMS. (11) & (18) were found to be the intermediate leading to (5)

Grandpa Joe: And the beauty is that nature is able to produce (5) in a stereoselective manner.

Comment on their statements.

Question 2

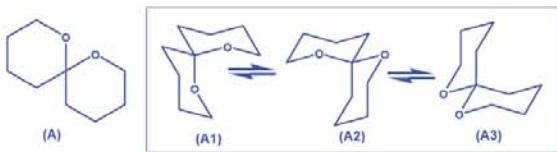
Refer to page 1174 second last line "...the spiroacetal 5 retained all four deuterium atoms ..." What does this tells you about the mechanism of the pathway leading to (5)?

Question 3

Using curve arrows, illustrate the mechanism of (13) to (5).

Question 4

An isomer of (5) has the following structure (A) and it has 3 conformations in equilibrium as follow:



ICHO Organic Chemistry Training 2006 – Exercise 5

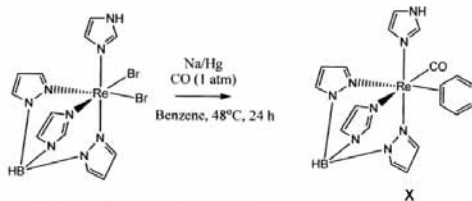
This exercise contains some Organometallic Chemistry based questions. Organometallic Chemistry is a hybrid field that requires knowledge from both organic and inorganic chemistry.

Question 1

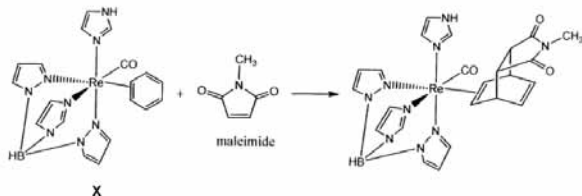
Besides the signals attributable to the protons of NH_3 ligands, the ^1H NMR spectrum of complex $[\text{Os}(\text{NH}_3)_2(\text{benzene})]^{2+}$ shows three sets of doublets in the aromatic region. Propose a detailed structure of the complex and briefly explain.

Question 2

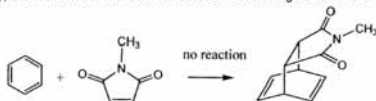
Harman from the University of Virginia reported the synthesis of a rhenium-benzene complex **X** as follow:



- (i) What is the function of Na/Hg in the reaction?
- (ii) What should be the structure of the complexed benzene? Explain your answer.
- (iii) In a later study, Harman demonstrated that the Re-benzene complex **X** could undergo Diels-Alder reaction with maleimide as follow:



On the contrary, it is well known that free benzene cannot undergo the same reaction.



Explain the result of Harman's study.

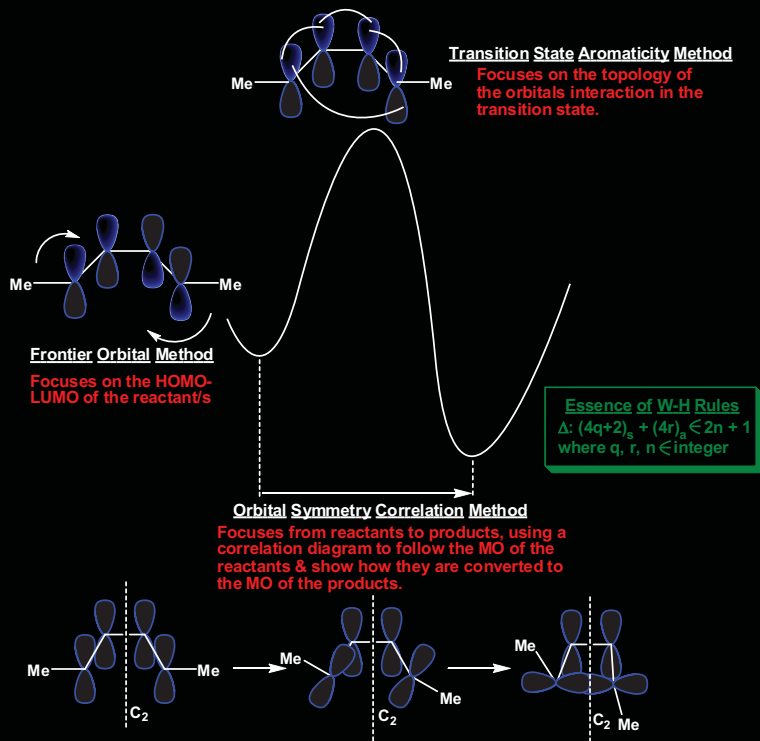
What I did...

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Effective Learning



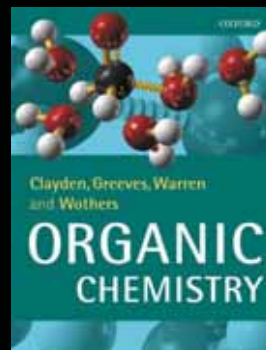
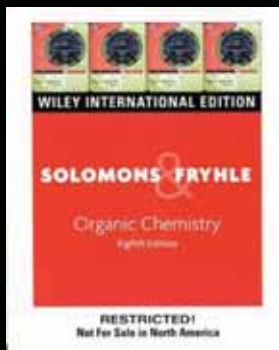
Pericyclic Reactions - A Story-telling Approach



R. B. Woodward et. al, *J. Am. Chem. Soc.* **1965**, 87, 395; K. Fukui, *Acc. Chem. Res.* **1971**, 4, 57.
 R. Hoffmann et. al, *J. Am. Chem. Soc.* **1965**, 87, 2046; R. Hoffmann et. al, *Acc. Chem. Res.* **1968**, 1, 17.
 M. J. S. Dewar, *Angew. Chem. Int. Ed. Engl.* **1971**, 10, 761; H. E. Zimmerman, *J. Am. Chem. Soc.* **1966**, 88, 1564.
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Suggestions

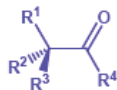
- Identify passionate students early (Mar/ Apr)
- Start training them early (May/ June) – frequency/ duration?
- Look at the big picture & examine the fundamentals
- Expose them to advance materials early
- Use past ICHO Q as a guide to the type of Q that might be asked!



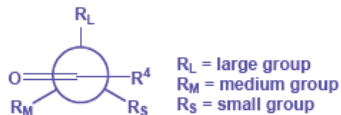
PROBLEM 8: Organic Chemistry Questions

(30 points)

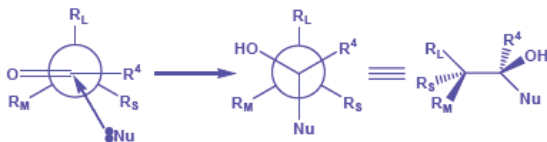
Felkin-Ahn model is being used to predict the stereochemical outcome of the nucleophilic addition of a nucleophile onto a carbonyl compound. The structure below shows a compound having a carbonyl group next to a chiral center.



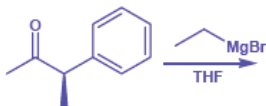
We normally classify the 3 groups using large, medium and small, depending on their size. After that, we arrange the resultant into the Newman project below, with the large group "orthogonal" to the carbonyl group.



The nucleophile will approach the molecule at an angle of 109° from the least hindered site as follow.



(8-a) Using the above information, predict the major product from the below reaction.



Problem 9

Please read the attached article "One-pot organocatalytic Domino Michael-Aldol and Intramolecular S_N2 Reactions. Asymmetric Synthesis of Highly Functionalized Epoxycyclohexanone Derivatives" by Mauro Marigo et. al. *J. Am. Chem. Soc.* **2006**, *128*, 5475 – 5479.

While they are hiking along the MacLehose trail at Sai Kung East Country Park, Tom and Jerry decide to discuss about the above mentioned article as it is related to their research interest. Their conversations are as follow:

Tom: I am wondering why the author chooses epoxycyclohexanone as the target to be synthesized.

Jerry: Well, one of the reasons is that it exhibits antifungal property. Another reason I can think of is that such compound serves as useful starting materials in organic synthesis.

Tom: Sounds fine to me. The reaction steps are beautiful, with compound 7a being used to protect the carbonyl group of compound 1 at the strategic instant.

Jerry: Yeah; however, the drawback is that the nature of R^1 affects the reaction significantly. In general, electron withdrawing groups give a much higher yield than electron donating groups.

(9-a) Comment on the above conversation.

Jerry: The article talked about "one-pot" reaction and strategy that is based on "atom economic principle". Why are such reaction/ strategy appealing?

Tom: Hmm...

(9-b) Can you help Tom?

Tom: Referring to scheme 2, how does compounds 7a and 1 leads to the first intermediate?

Jerry: Hmm, I am not so sure.

(9-c) Please help Jerry by illustrating the mechanism of the reaction.

Tom: Gosh! Did the article made a mistake? Shouldn't compound 2 attacks to the top of the first intermediate since there is favourable hydrogen bonding present in the top face? Hmm, I am wondering about the reaction mechanism of this reaction; seems complicated to me.

(9-d) What do you think?

Jerry: Well, I am not too sure about that since I haven't been touching organic chemistry for 2 years. However, one thing I know for sure. That is, AcONa is a stronger base than K_2CO_3 .

Tom: Fair enough. But how does compound 3 leads to compound 4?

Jerry: That's easy. AcONa deprotonates compound 3 at the α position bonded to the chlorine atom first. Following that, the nucleophilic α position then attacks the aldehyde via electrophilic addition.

(9-e) Comment on the above conversation.

Tom: From scheme 3, it shows that 4d(I) is more stable than 4d(II). To me, it doesn't make a difference.

(9-f) What do you think?

Tom: Oh yah, another beautiful thing about this article is that it doesn't matter what type of solvent we used for the reaction.

Jerry: Hmm, I doubt so. From theory, polar solvent should work the best. For example, MeCN should give the best yield and ee.

(9-g) What do you think?

Tom: There is something I am not clear about. If you take a look at Table 3, you will realize that there are 4 possible products, depending on the base and solvent system that you use. I am just curious how compounds 5a, 6 and 8 are obtained.

Jerry: All you have to do is to sit down and sketch out the mechanism using curve arrows!

(9-h) Can you help Tom by illustrating mechanisms leading to compounds 5a, 6 and 8?

Tom: Hmm ok but I'll leave that till later. Before we take a rest, I will like to check with you on the last part of the article under "Product Elaboration". What does the first statement of the first paragraph of the last page mean? How does the presence of ester functionality aids as a "superb handle"? In addition, why is product 11m obtained in the diastereoisomeric form as shown in figure 1? (in another words, how is it more stable than the rest of its diastereoisomers?)

Jerry: Hmm this question requires some thinking...

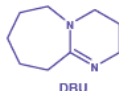
(9-i) Can you help Jerry so that they can go and take their well deserve break?

Off they proceeds to their well deserved break.

Problem 10

Please read the attached article "A Short Enantioselective Pathway for the Synthesis of the Anti-Influenza Neuramidase Inhibitor Oseltamivir from 1,3-Butadiene and Acrylic Acid" by Ying-Yeung Yeung et. al. *J. Am. Chem. Soc.* 2006, 128, 6310 – 6311.

- (10-a) Give 2 disadvantages of the industrial method of production Tamiflu.
- (10-b) Illustrate the mechanism of the reaction of 1,3-Butadiene with Acrylic Acid leading to compound 3. What is the role of compound 2?
- (10-c) Illustrate the mechanism of the reaction of compound 4 leading to compound 5.
- (10-d) Draw the most stable conformation of compound 5.
- (10-e) Why is there a need for compound 5 to be transformed into compound 6?
- (10-f) The structure of DBU is given below. What is the role of DBU in the transformation of compound 6 into compound 7?



- (10-g) Illustrate the mechanism of compound 8 leading to compound 9. (clue: 2 things happened also simultaneously)
- (10-h) Intuitively, illustrate the mechanism of compound 7 leading to compound 8. (clue: treat AIBN as a radical source)
- (10-i) Illustrate the mechanism of compound 9 leading to compound 10. Explain (*using electronic factor*) the stereochemistry of the 2 new chiral centers generated (i.e. why are they "trans" to one another instead of "cis"). Give the name of this mechanism.
- (10-j) Do you think the stereochemistry of the newly generated chiral centers of compound 12 can be explained using the same reasoning given for (10-f)? Why?

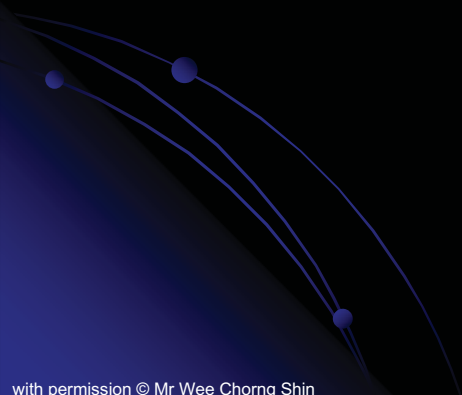
Conclusion

- Some of the strategies that I employed in ICHO training for the past 3 years were discussed.
- A couple of interesting questions being prepared for SCHO were discussed; the train of thoughts of how they were set were briefly mentioned.

Parting Shot

“It is difficult to say what is impossible, for the dream of yesterday is the hope of today and the reality of tomorrow.”

~R. H. Goddard~

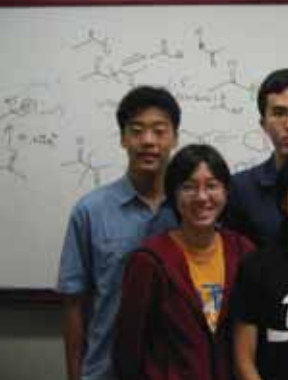
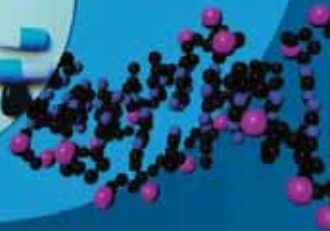


recommended for
'A' Level H3 Syllabus

Thinking Straight About

PHARMACEUTICAL CHEMISTRY

Wee Chong Shin
Yang Guorong Eugene
Chen Sin Hang
Lee Tian Xin
Chen Yeo Chuin Justin



Q & A

