

# Heterocyclic Chemistry - Midterm

May 6<sup>th</sup>, 2008

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Department of Chemistry  
The Scripps Research Institute

Name: \_\_\_\_\_

Last 4 digits of your Social Security #: \_\_\_\_\_

This is an "open-notes" exam designed to last 2 hours that you have 4 hours to complete  
**Definition of "open notes"**: Only handwritten notes (from lectures and any other source), no copies allowed. Lecture summaries are the only handouts permitted during test.

**Please present ONLY your FINAL answers on these sheets**

Question 0 \_\_\_\_\_ < (5 points)

Question 1 \_\_\_\_\_ < (40 points)

Question 2 \_\_\_\_\_ < (40 points)

Question 3 \_\_\_\_\_ < (30 points)

Question 4 \_\_\_\_\_ < (40 points)

Question 5 \_\_\_\_\_ < (25 points)

Question 6 \_\_\_\_\_ < (30 points)

Question 7 \_\_\_\_\_ < (10 points)

Question 8 \_\_\_\_\_ < (20 points)

Question 9 \_\_\_\_\_ < (10 points)

Question 10 \_\_\_\_\_ < (25 points)

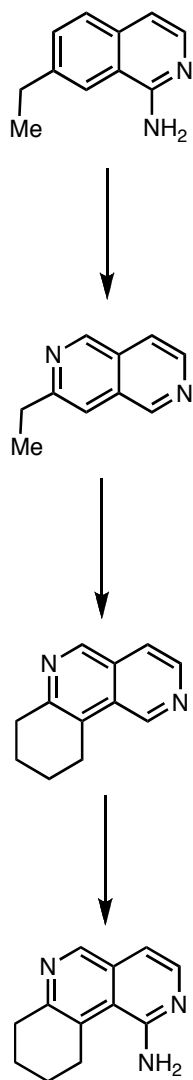
Question 11 \_\_\_\_\_ < (75 points)

Bonus Question \_\_\_\_\_ < (25 points)

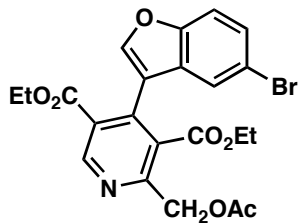
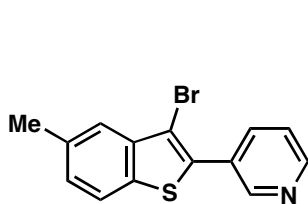
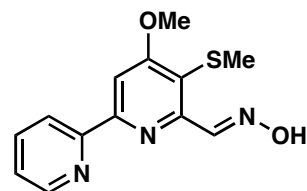
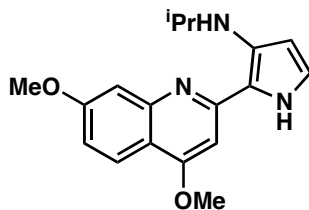
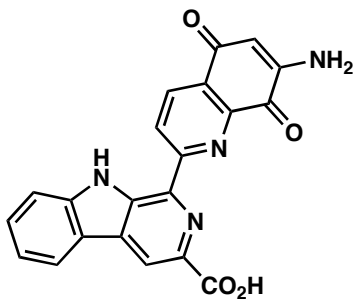
Total \_\_\_\_\_ out of 350 points

**Question 0 (5 points):** Why does the mixture of indole and 1,3,5-trinitrobenzene turn red?

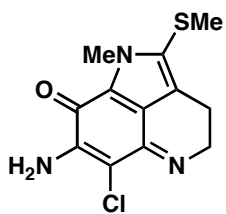
**Question 1 (40 points – 10 each).** Provide routes to intermediates of the following medicinal chemistry program evolution:



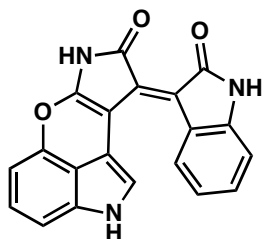
**Question 2 (40 points – 8 points each).** Below are five pyridine derived potential chemical leads. Your boss in a medicinal chemistry department wants to see your forward synthetic scheme for ALL FIVE in less than 15 minutes!



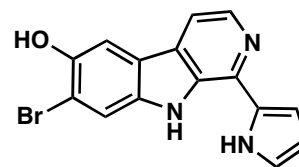
**Question 3 (30 points – 10 points each).** Propose total syntheses of the following natural products via aromatic heterocycles.



isobatzelline A

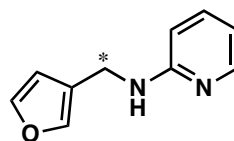
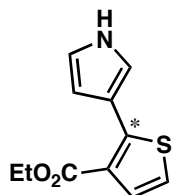
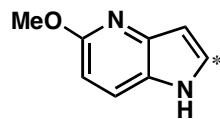
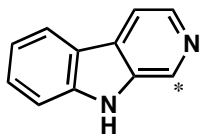


arcyroxindole A

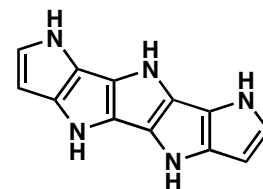
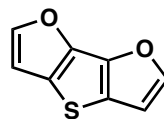
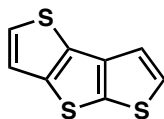
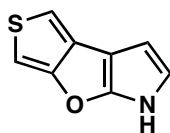
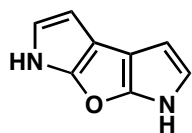


eudistomin A

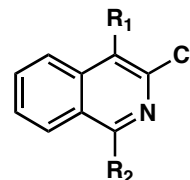
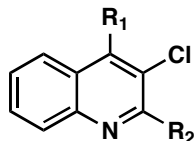
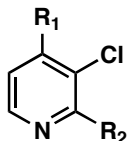
**Question 4 (40 points – 10 points each).** Propose how you would incorporate a  $^{14}\text{C}$  label at the specified position.



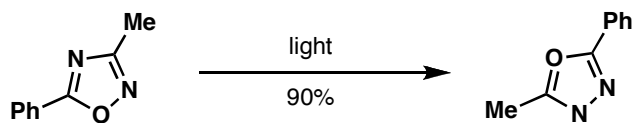
**Question 5 (25 points – 5 points each).** Derive syntheses of the five fused heterocycles:



**Question 6 (30 points).** Propose a strategy to access a variety of pyridines, quinolines, and isoquinolines with the following substitution patterns. Avoid transition metals and protecting groups. ( $R_1$ ,  $R_2$  = aryl or alkyl)

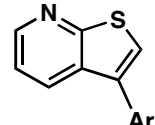
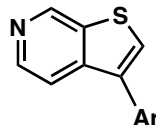
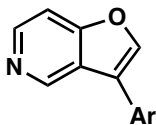
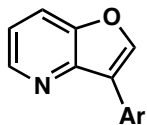


**Question 7 (10 points).** Provide a mechanism for the following reported conversion (J. Org. Chem. 2005, 70, 2322 - 2324).

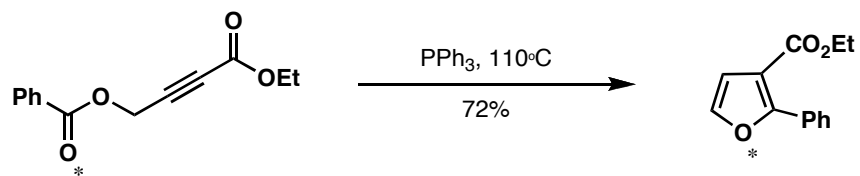




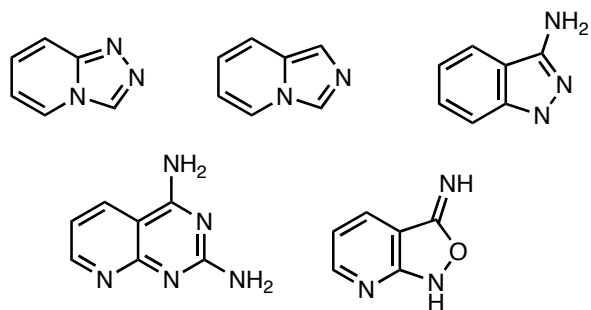
**Question 8 (20 points – 1 point each, 16 bonus).** Provide synthetic routes to the following aza-benzofurans and aza-benzothiophenes.



**Question 9 (10 points).** Provide a plausible mechanism for the following furan ring synthesis (J. Am. Chem. Soc. **2004**, *126*, 4118-4119).



**Question 10 (25 points – 5 points each).** As a prelude to the next half of the class, provide routes to the following heterocyclic systems we have not seen yet:



**Question 11 (75 points).** Deduce the structures of the following heterocycles (5 points each).

- a) ( $C_8H_6S$ ) Product from treatment of 3-bromobenzothiophene with *n*-BuLi.
- b) ( $C_{13}H_{13}NO$ ) Obtained upon treatment of 4-methylpyridine with  $BF_3 \cdot OEt_2$ , followed by LiTMP, followed by benzaldehyde.
- c) ( $C_{18}H_{17}NO$ ) Product of treatment of *N*-((trimethylsilyl)methyl)pyrrole with benzophenone and potassium *tert*-butoxide in refluxing THF.
- d) ( $C_5H_4BrN$ ) By reaction of pyridine with oleum and bromine at 130 °C.
- e) ( $C_6H_5NO_2$ ) Obtained by reaction of 3-methylpyridine with  $O_2$  and potassium *tert*-butoxide at room temperature in DMF.
- f) ( $C_7H_7ClINO$ ) The product when 2-chloro-3-iodopyridine is treated with LDA at -70 °C followed by acetaldehyde.
- g) ( $C_9H_6BrN$ ) Product when isoquinoline is treated with HCl followed by bromine in nitrobenzene at 80 °C. For bonus points, draw the true mechanism of this process.

- h) ( $C_4H_8N_2O_2$ ) Obtained upon treatment of pyrrole with excess hydroxylamine in ethanolic HCl.
- i) ( $C_6H_7NO$ ) Major product obtained from reaction of 2-acetylpyrrole with TFA at elevated temperatures.
- j) ( $C_{10}H_{12}O_2S$ ) Treatment of cyclohexanone with  $POCl_3/DMF$  followed by methyl 2-mercaptoacetate.
- k) ( $C_5H_5NO$ ) Obtained upon treatment of furfural with ammonia.
- l) ( $C_4H_3BrS$ ) Product from the treatment of 2,5-dibromothiophene with zinc in acetic acid.
- m) ( $C_5H_5ClS$ ) By reaction of thiophene with formaldehyde and HCl at 0 °C.
- n) ( $C_6H_6BrN$ ) Obtained when 2-bromopyridine is treated with LDA at -78 °C followed by MeI.
- o) ( $C_6H_6BrNO_2$ ) Product upon treatment of methyl 1*H*-pyrrole-2-carboxylate with bromine and pyridine.