Heterocyclic Chemistry - Midterm

May 4, 2006

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Department of Chemistry
The Scripps Research Institute

Name: _____

Last 4 digits of your Social Security #: _____

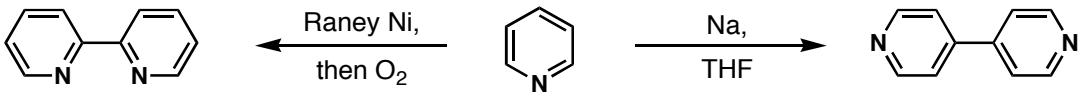
This is an "open-notes" exam designed to last 2 hours that you have 4 hours to complete
Definition of "open notes": Only handwritten notes (from lectures and any other source), no copies allowed. Lecture summaries are the only handouts permitted during test.

Please present ONLY your FINAL answers on these sheets

Question 1	**<**	**(10 points)**
Question 2	**<**	**(45 points)**
Question 3	**<**	**(10 points)**
Question 4	**<**	**(20 points)**
Question 5	**<**	**(15 points)**
Question 6	**<**	**(40 points)**
Question 7	**<**	**(10 points)**
Question 8	**<**	**(105 points)**
Question 9	**<**	**(15 points)**
Question 10	**<**	**(10 points)**
Question 11	**<**	**(20 points)**
Question 12	**<**	**(50 points)**
Bonus Question	**<**	**(25 points)**

Total _____ **out of 350 points**

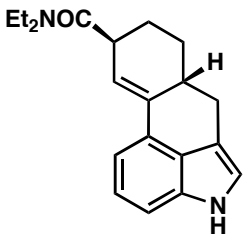
Question 1 (10 points). Bipyridyls can be synthesized by the dimerization of pyridine with either Raney nickel or sodium. Give a mechanism for this transformation and explain the difference in the regioselectivity of the two reagents.



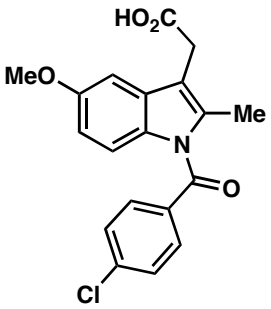
2,2' dimerization

4,4' dimerization

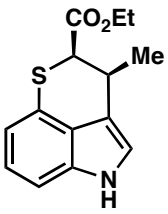
Question 2 (45 points). Provide practical synthetic routes to the following heterocycles (15 points each):



LSD

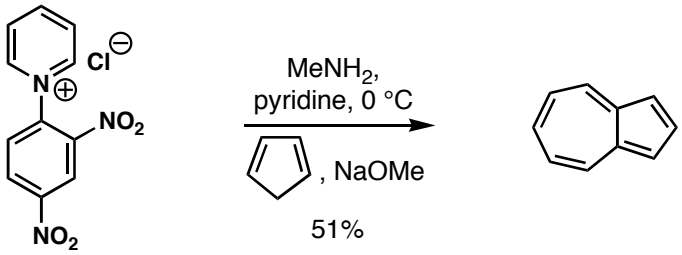


indomethacin



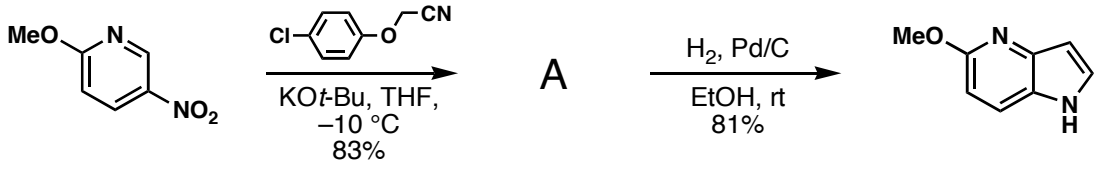
chuangxinmycin

Question 3 (10 points). Give a mechanism for the synthesis of azulene from the pyridinium salt shown.

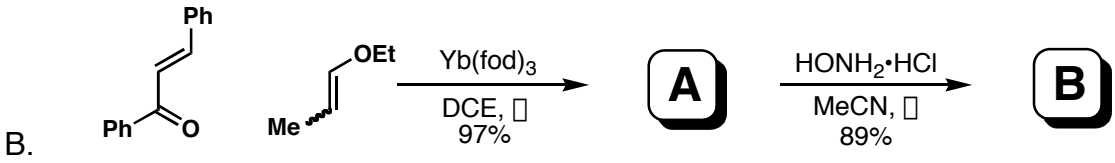


Question 4 (20 points). In the reactions shown below, identify the labeled intermediates and give reasonable mechanisms for their formation. (10 points each)

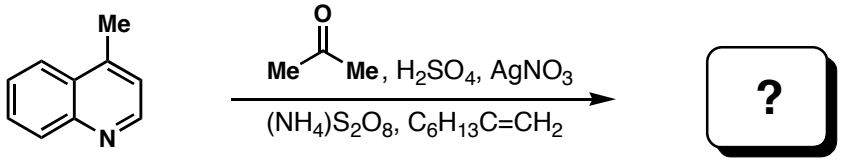
A.



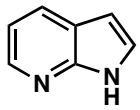
B.

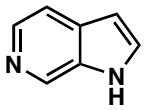


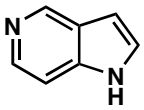
Question 5 (15 points). Electron deficient heterocycles react with nucleophilic radicals. Provide a mechanism and product for the following three component coupling. For full credit, label nucleophilic and electrophilic radical species and provide a name for this reaction. Note: Only organic intermediates need to be shown.

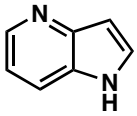


Question 6 (40 points). Derive syntheses of the four isomers of azaindole shown below. (10 points each)

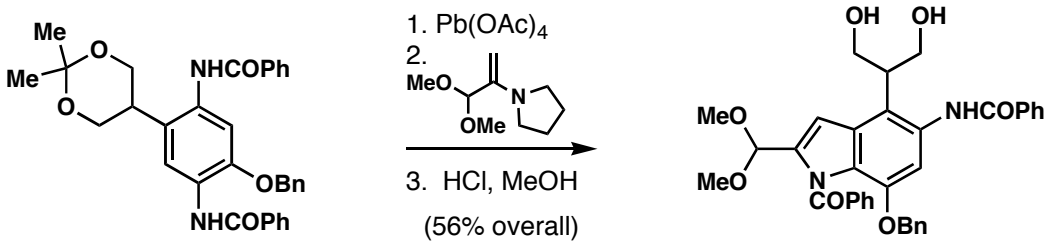




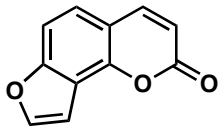




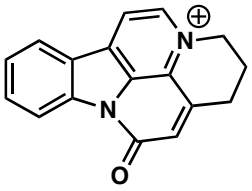
Question 7 (10 points). Using a variant of the Nenitzescu reaction, Boger and co-workers constructed the indole core of duocarmycin SA. Give a mechanism for this transformation.



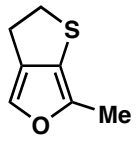
Question 8 (105 points). Propose total syntheses of the following products via aromatic heterocycles (15 points each).



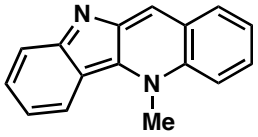
angelicin



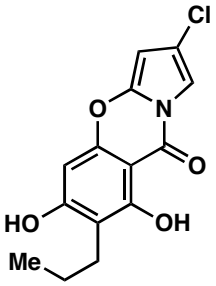
infractopicrine



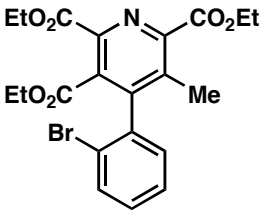
kahweofuran

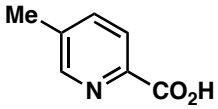


cryptolepine

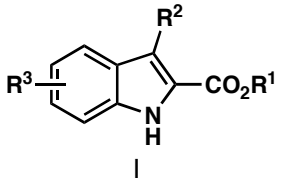


streptopyrrole



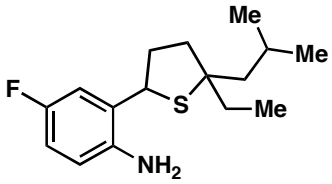


Question 9 (15 points): Design a route I wherein R^1, R^2, and R^3 all come from different building blocks.

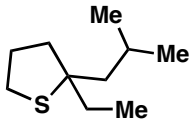


I

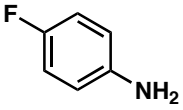
Question 10 (10 points): Chemists at a rival pharmaceutical company have indentified tetrahydrothiophene **A** as a hot target for the treatment of numerous pathologies. While building block **B** is readily available, their method for reaching **A** is tedious and expensive. Based on chemistry you have learned in this class, design a one-pot method for joining thiophene **B** with *p*-fluoroaniline and beat them to the market.



A



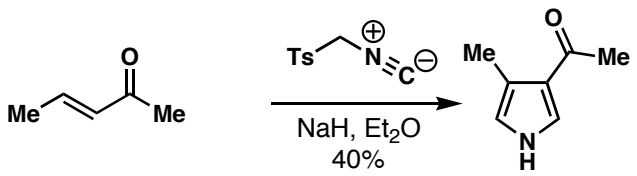
B



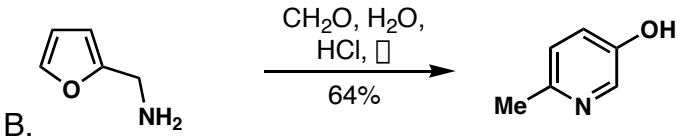
p-fluoroaniline

Question 11 (20 points). Give a mechanisms for the reactions shown below. (10 points each)

A.



B.



Question 12 (50 points). Deduce the structures of the following heterocycles (5 points each).

A. ($C_8H_8N_2$) Obtained upon treatment of 3-nitro-4-methylpyridine with vinyl magnesium bromide.

B. (C_9H_9N) Obtained by reacting *N*-acetyl-*o*-toluidine with sodium amide at 240 °C.

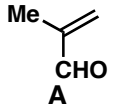
C. ($C_{12}H_{13}NO_2$) Obtained by reacting *p*-benzoquinone and ethyl 3-aminocrotonate in boiling acetone.

D. ($C_{11}H_{12}N_2O_3$) Formed upon condensation of 3-nitro-4-methyl-6-methoxypyridine with ethyl oxalate in the presence of potassium ethoxide, followed by hydrogenolysis.

E. ($C_{11}H_{16}O$) Formed upon treatment of 1-cyclohexyl pentane-1-4-dione with TsOH.

F. ($C_{13}H_{19}NSO_4$) Formed by treating a mixture of *t*-butyl acetoacetate, ethyl cyanoacetate, sulfur, and EtOH with morpholine.

G. ($C_{10}H_{11}NO_4$) Formed by mixing the dimethyl hydrazine of methacrylaldehyde (**A**) with dimethyl acetylene dicarboxylate.

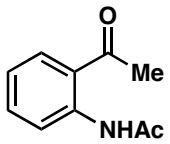


A

H. ($C_{11}H_{10}NCl$) Formed from 2,3-dimethylindole after treatment with KOH in chloroform.

I. ($C_{11}H_7NO_4$) Formed by treating isatin with 2-oxopropanoic acid and KOH at 95 °C.

J. ($C_{10}H_9NO$) Obtained as the major product from the treatment of *N*-(2-acetylphenyl)acetamide (**A**) with NaOH.



Bonus Question (25 points). Djerassi and co-workers reported the transformation of akuammiline to akuammicine in 1965. For extra credit towards the exam, please delineate a mechanism for this transformation.