Final Exam

Chem 3B, Fall 2018
Monday, December 10, 2018
3:00-6:00 pm

You have 180 minutes to complete this exam.

Please provide all answers in the space provided. Work drawn in the margins may not be picked up by the scanner and therefore will not be graded.

Point values are listed within each question. The exam is worth 350 points total.

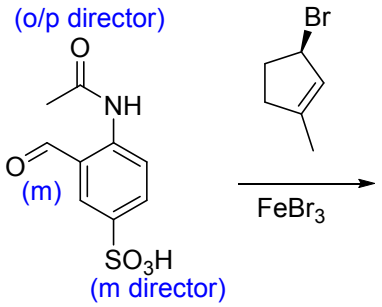
Partial Periodic Table

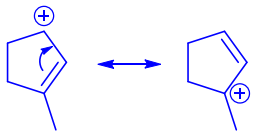
I	II	III	IV	V	VI	VII	VIII
H							He
Li	Be	B	C	N	O	F	Ne
Na	Mg	Al	Si	P	S	Cl	Ar
K	Ca	Ga	Ge	As	Se	Br	Kr
Rb	Sr	In	Sn	Sb	Te	I	Xe

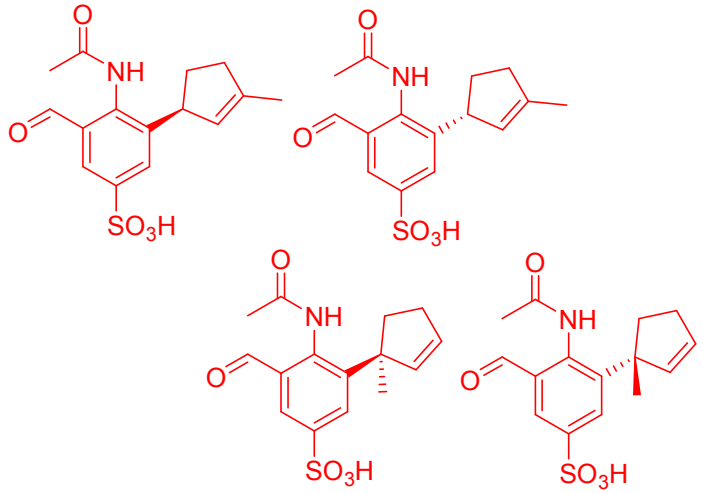
This Page is Scratch Paper

Please tear this cover page off at the start of the exam. It will not be collected, scanned, or graded, so make sure your answers are copied into the appropriate location on your exam.

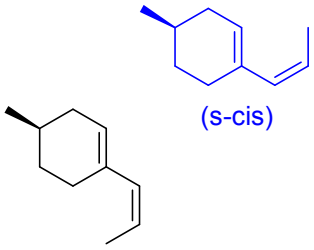
1. Predict the organic product(s) from the following reactions. Where relevant, show all stereoisomers. Pay particular attention to any information given in the product boxes. (2 x 15 = 30 pt)

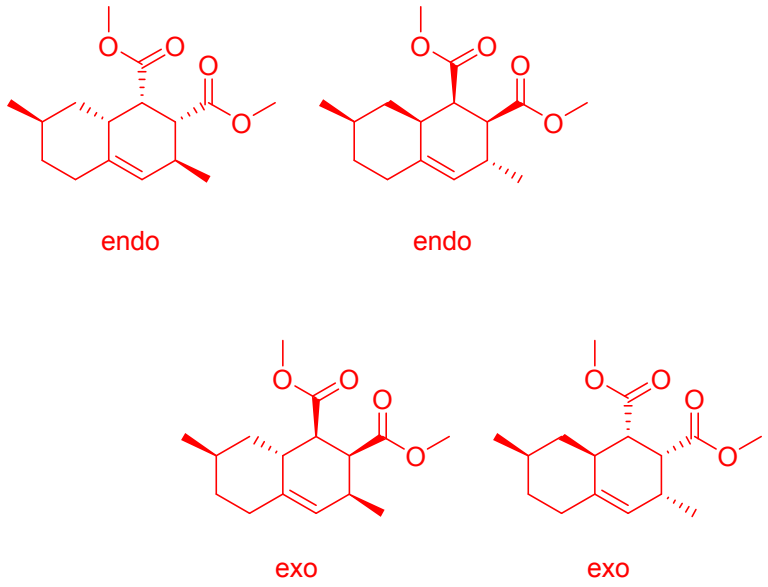






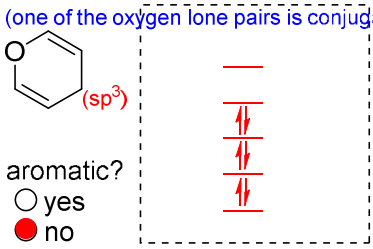
four isomeric EAS products (including stereochemistry)





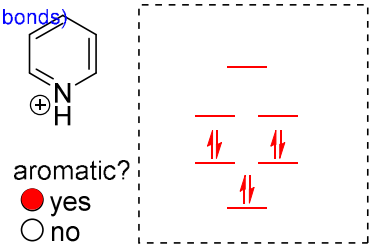
label each product "endo" or "exo"

2. Draw a π energy level diagram for each of the three molecules below. Fill in the electrons. Fill in a multiple choice bubble to state whether each one is aromatic or not. (20 pt)



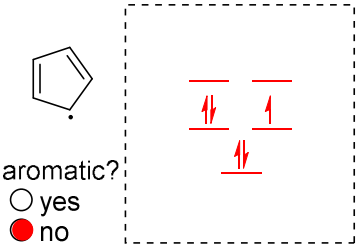
aromatic?
○ yes
● no

π MO energy level diagram, with electrons



aromatic?
● yes
○ no

π MO energy level diagram, with electrons

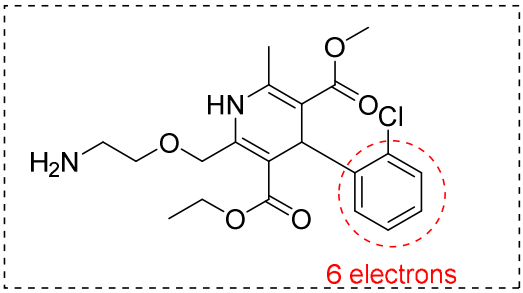


aromatic?
○ yes
● no

π MO energy level diagram, with electrons

3. Amlodipine (Norvasc) is a medication used to treat high blood pressure

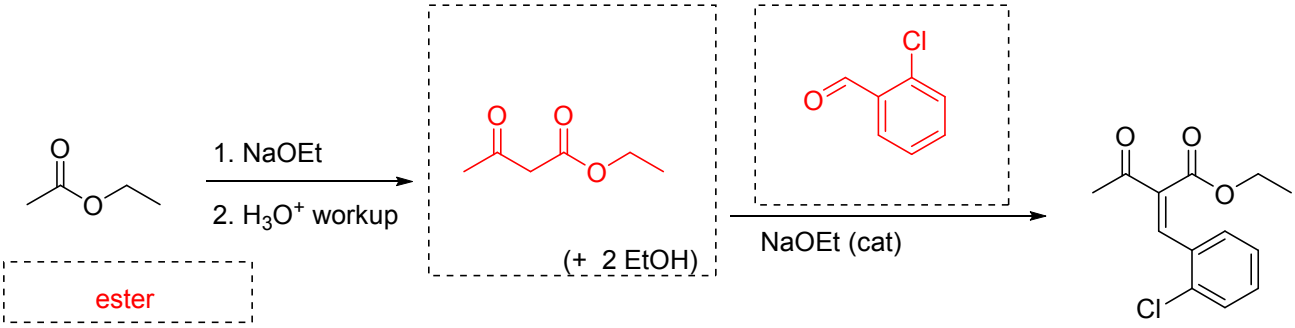
A. Circle the aromatic pi system(s) in the amlodipine structure. For each one, label it with how many electrons are counted toward Huckel's rules for that aromatic π system. (5 pt)



amlodipine

circle aromatic(s)
label # of aromatic electrons

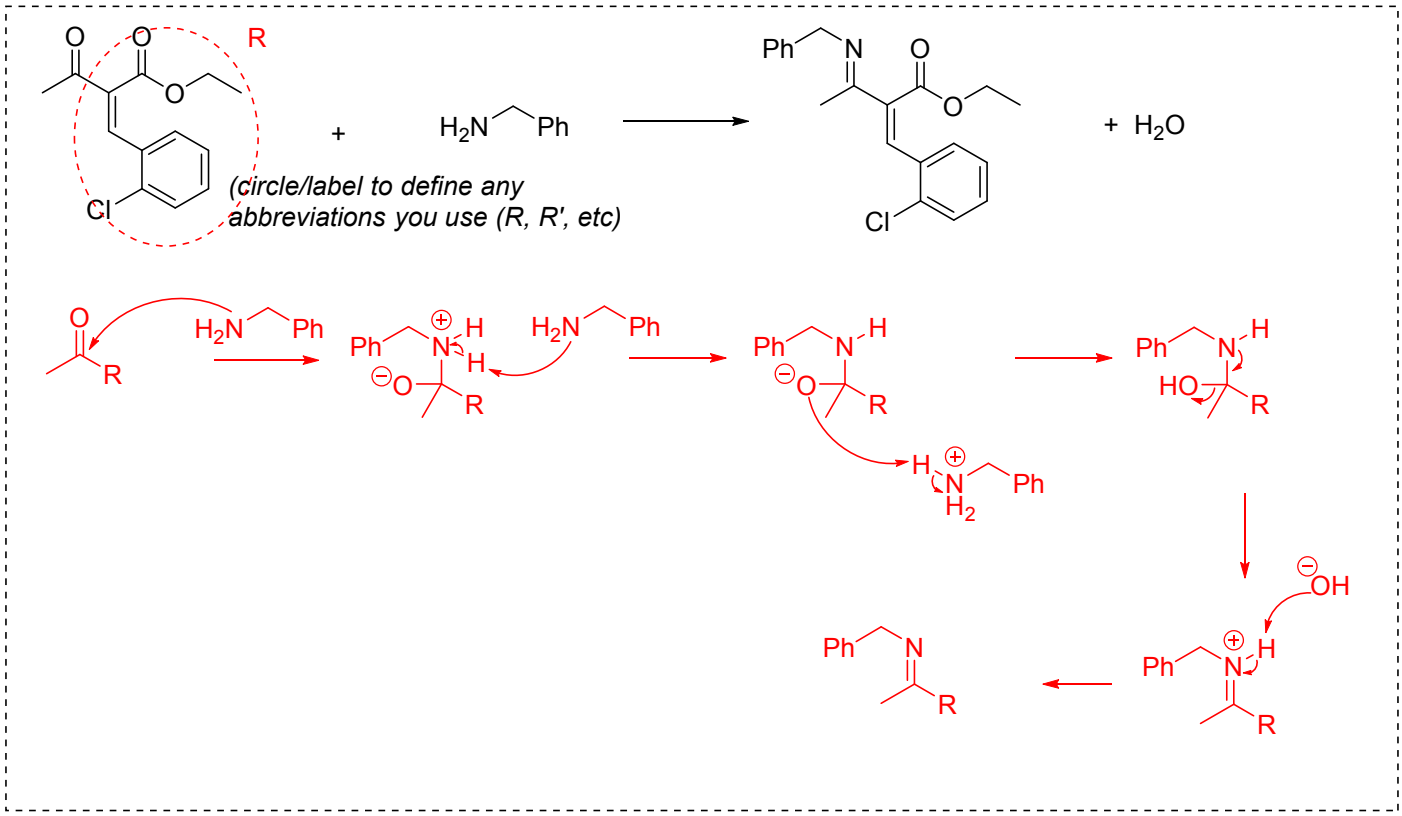
B. One possible synthesis of amlodipine starts with the reaction sequence below.[1] Name the reactive functional group in the starting material, then fill in the boxes in the multistep synthesis scheme (one structure per box). (15 pt)



ester

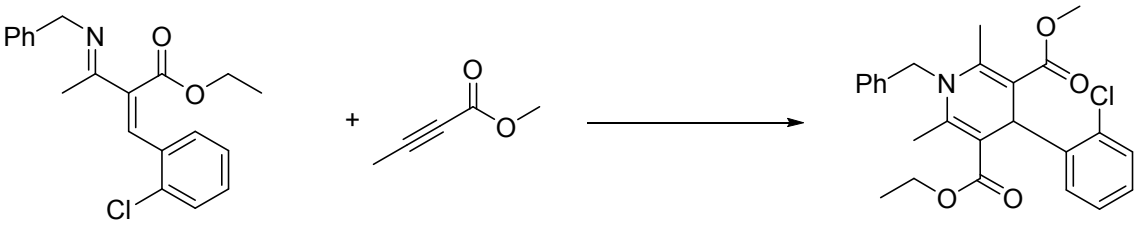
name of reactive functional group

C. Draw a curved arrow mechanism for the reaction below. (10 pt)



[1] Synthesis of Amlodipine Using Aza Diels-Alder Reaction *Bull. Korean Chem. Soc.* **2002**, 23(1), 143-144.

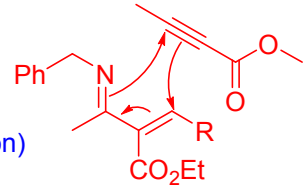
D. Draw two different curved arrow mechanisms for the reaction below, one **CONCERTED** and one **NOT CONCERTED**. Include the correct conformation and major resonance contributors of each reactant and intermediate. (15 pt)

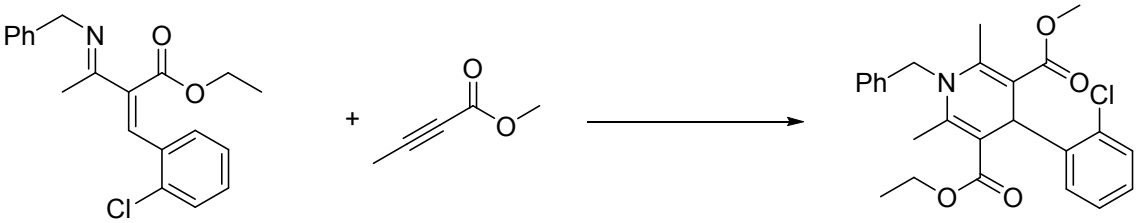


(circle/label to define any abbreviations you use)

CONCERTED mechansim

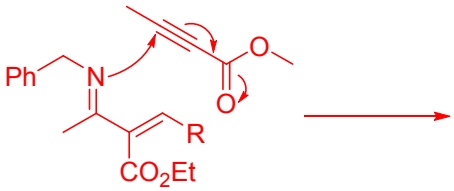
(rotated into s-cis conformation)

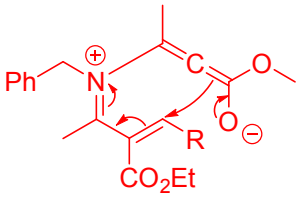




(circle/label to define any abbreviations you use)

NOT CONCERTED mechansim

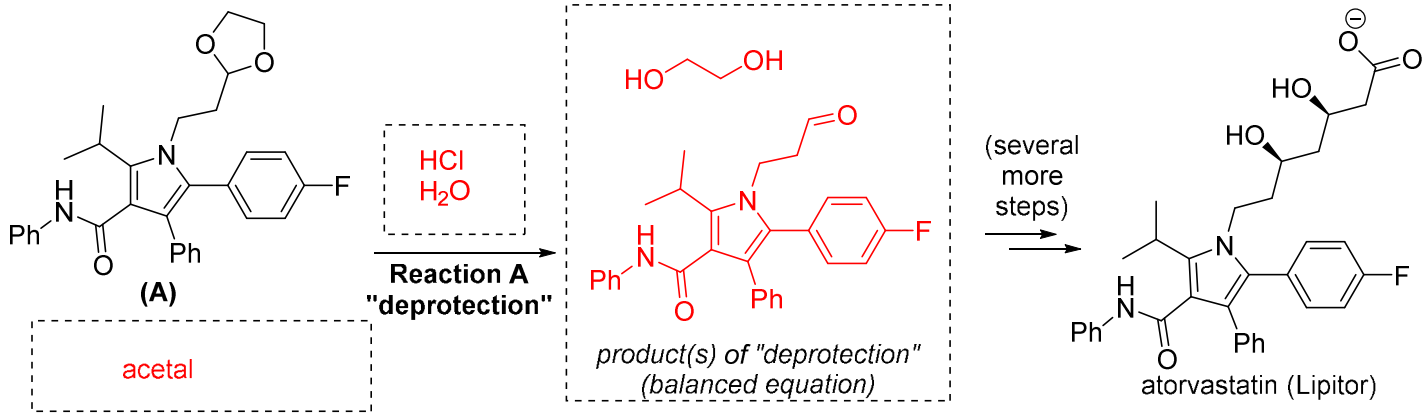




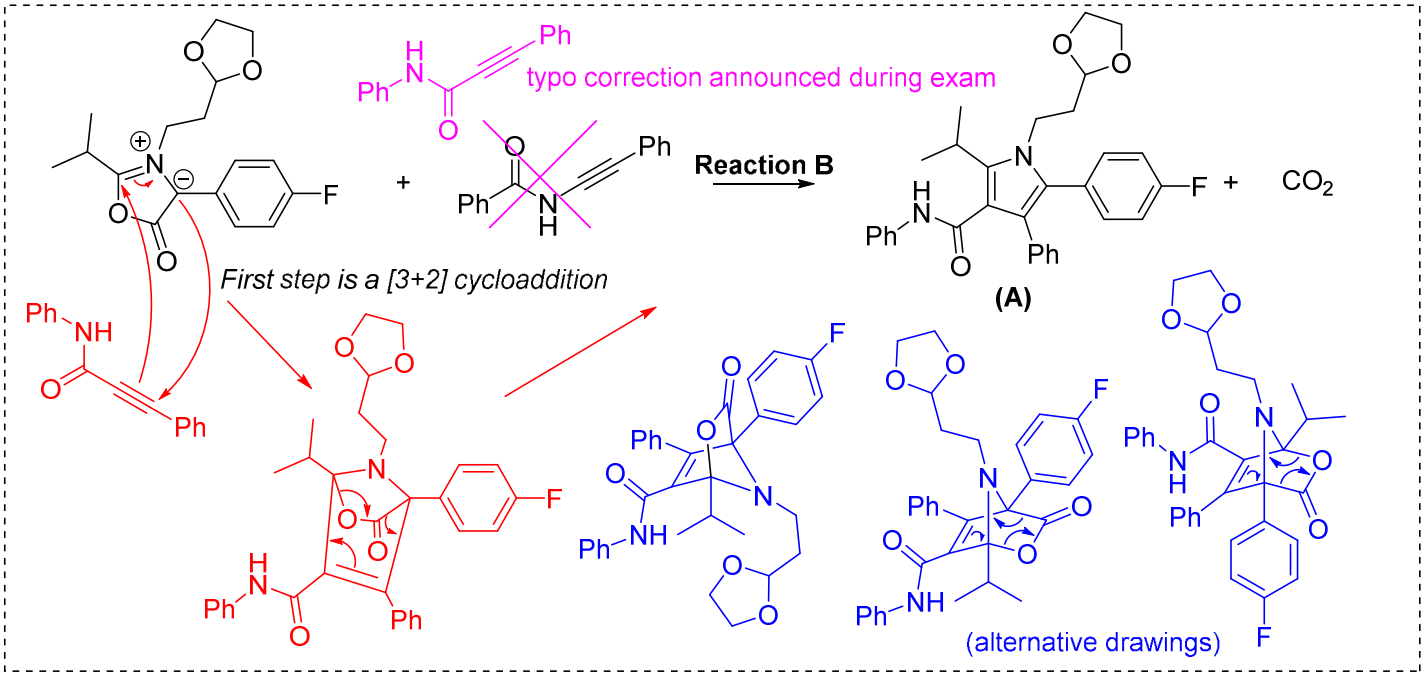
(in s-cis conformation during this step)

4. Atorvastatin (Lipitor) is a medication used to treat high blood pressure. This question examines several steps in a possible multistep synthesis of atorvastatin.[2]

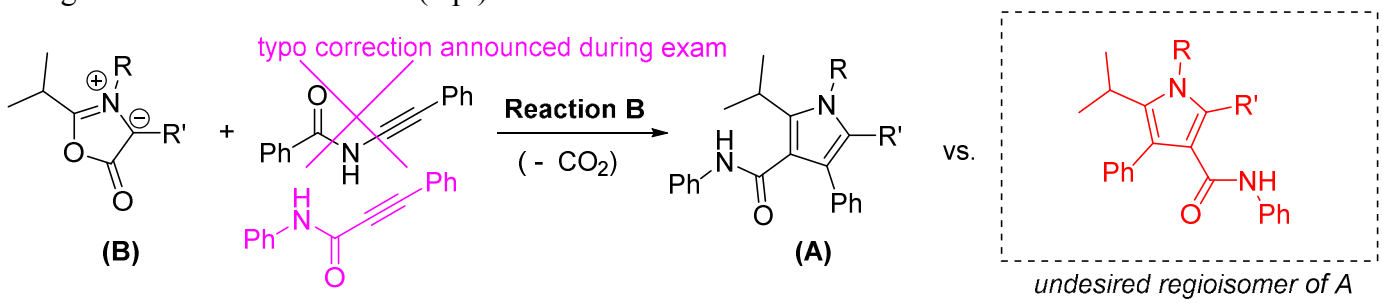
A. From starting material A, the next step in the multistep synthesis of atorvastatin (Reaction A) can be called a "deprotection". Name the reactive functional group, provide reaction conditions, and draw the resulting product(s). (15 pt)



B. Draw a curved arrow mechanism for Reaction B, using a [3+2] cycloaddition as the first step. (10 pt)

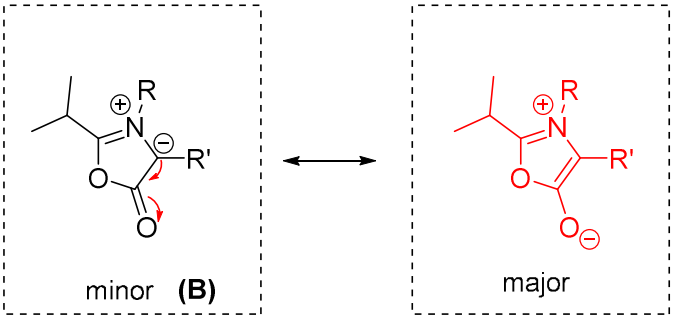


C. Researchers developing this reaction reported that Reaction B is very regioselective. Draw the undesired regioisomer (that they reported did NOT form due to high selectivity), using the abbreviations (R, R') given in the scheme below. (5 pt)



[2] The Discovery and Development of Atorvastatin, a Potent Novel Hypolipidemic Agent. *Prog. Med. Chem.* **2002**, 40, 1-22.

D. Structure B was drawn as a minor resonance contributor in Reaction B, to make the cycloaddition mechanism easier. Draw curved arrows and the major resonance contributor of B, and explain **two** different reasons that the resonance contributor you drew is more important. (10 pt)



(add curved arrows) *(draw structure)*

This is a more important resonance contributor because:

1. negative charge on more electroneg atom (O vs C)

2. this resonance contributor demonstrates aromaticity (two pi bonds and an oxygen lone pair = 6 electrons)

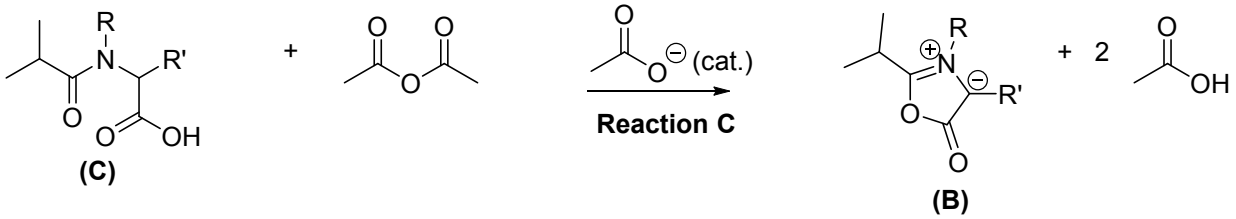
E. Fill in the four boxes with the names of the reactive functional groups in Reaction C, and draw a curved arrow mechanism. Make sure that the major resonance contributor of each intermediate is included in the mechanism. (20 pt for names) (10 pt for mechanism)

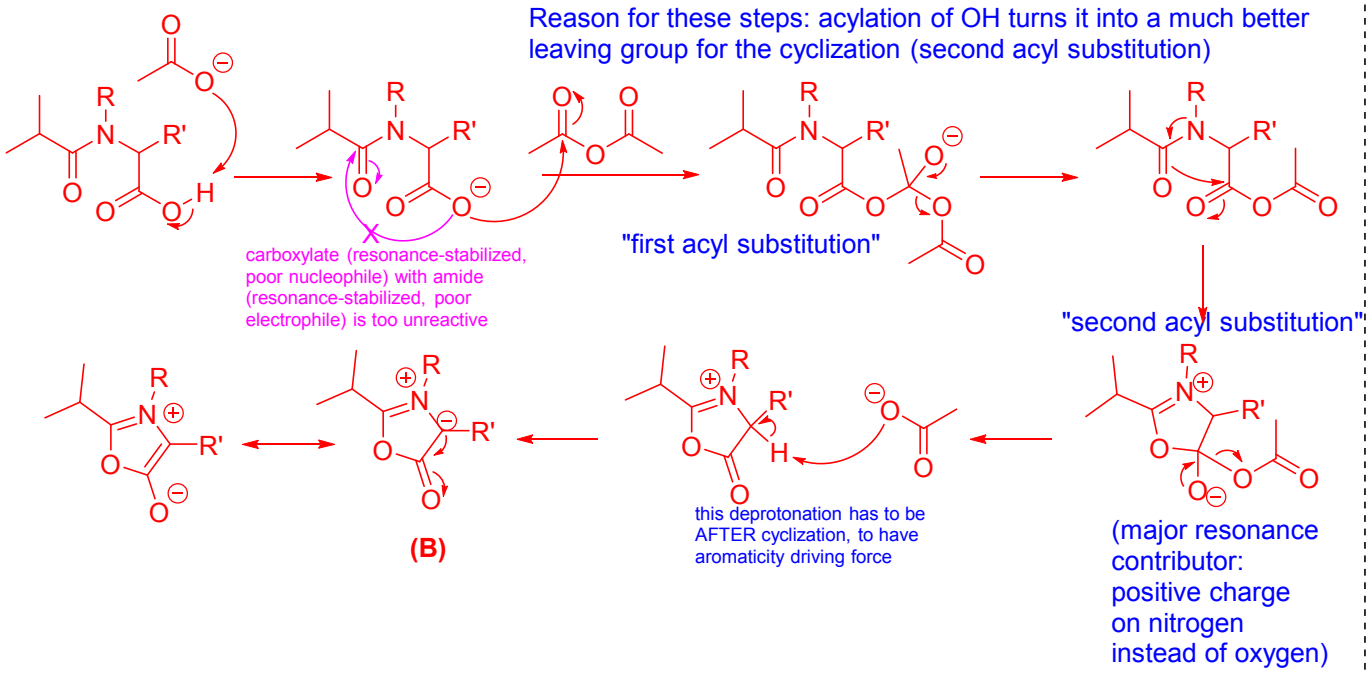
amide and carboxylic acid

(names of reactive functional groups)

anhydride

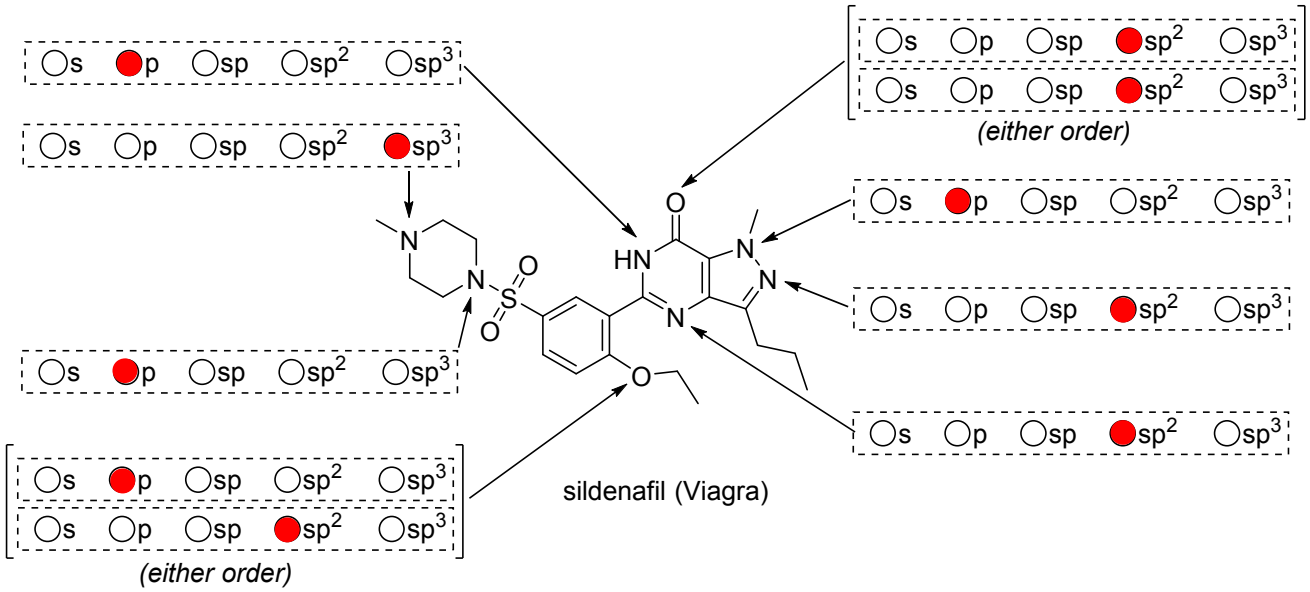
carboxylate





5. Sildenafil (Viagra) is a medication used to treat erectile dysfunction. The rest of the exam will examine many steps in the synthesis of sildenafil.[3]

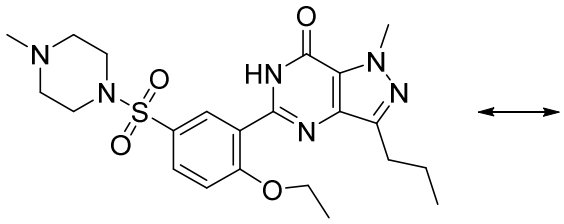
A. On the structure of sildenafil below, fill in one multiple-choice circle per row to indicate the hybridization of the orbital occupied by each pair of electrons. (10 pt)

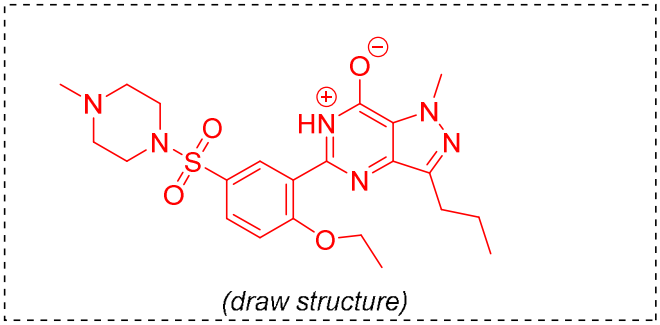


B. Sildenafil contains a **bicyclic heteroaromatic ring** system. (15 pt)

i. Draw curved arrows and the resulting resonance contributor which clearly demonstrate why this bicyclic ring system can be called "heteroaromatic".

ii. Explain classification of this resonance structure as "bicyclic heteroaromatic". Your answer must address multiple criteria (Huckel's rules) to earn full credit.





The resonance structure drawn can be labelled "bicyclic heteroaromatic" because:

"bicyclic" — contains two fused rings (two rings with shared atoms)

"hetero" — contains heteroatoms (nitrogens)

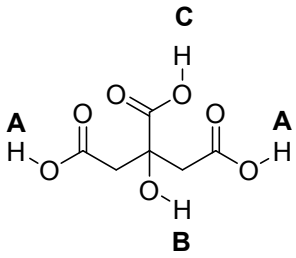
"aromatic" — cyclic, planar, conjugated pi system (all atoms in both rings are sp2 hybridized)

"4n+2" electrons (10 electrons in 4 pi bonds and one nitrogen lone pair)

[3] The Chemical Development of the Commercial Route to Sildenafil: A Case History. *Org. Process Res. Dev.* **2000**, *4*, 17−22. Synthesis of Commercial Phosphodiesterase(V) Inhibitors. *Organic Process Research & Development* **2005**, 9, 88-97

C. Sildenafil is formulated as the citrate salt (the product of an acid-base reaction with citric acid).

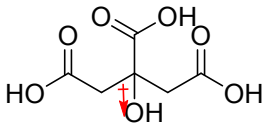
i. Fill in one bubble to state which site (A, B, or C) is the most acidic. Explain your choice by making comparisons to the other two sites. Use a picture and up to 5 words in each explanation. (10 pt)



citric acid

○ A ○ B ● C is the most acidic site in citric acid.

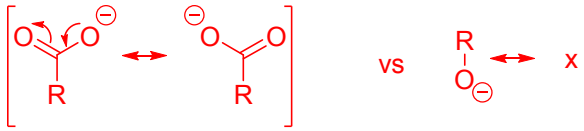
It is more acidic than A because:



inductive effect of adjacent oxygen

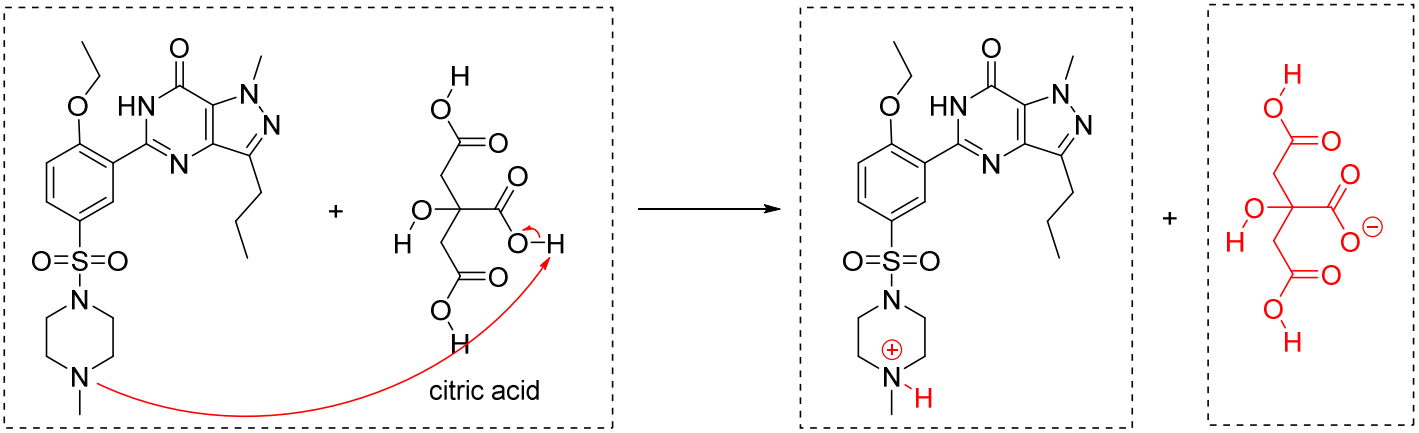
(picture and up to 5 words)

It is more acidic than C because: resonance



(picture and up to 5 words)

ii. Draw curved arrows and the resulting structures corresponding to the most stable favorable (stable) protonation state from the reaction of sildenafil with citric acid. (5 pt)



(add curved arrows for most favorable reaction)

conjugate acid of sildenafil
(add H and a charge to this structure)

citrate

iii. The pKa of citric acid is 3. Calculate the equilibrium constant for the acid-base reaction above. Write your answer in the small box. Show your work in the larger box. (5 pt)

10^7

calculated equilibrium constant

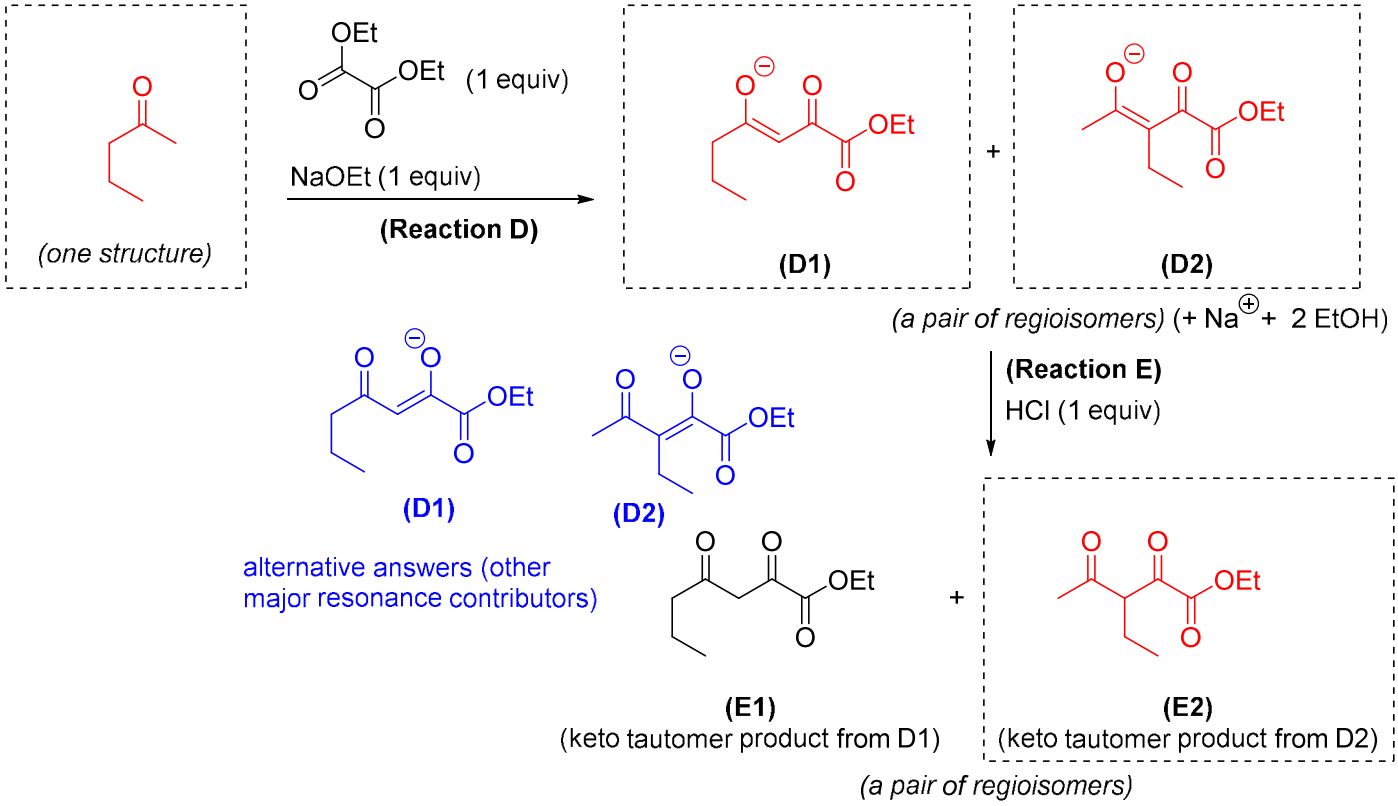
show work:

pKa = 10

$Keq = 10^{((conj\ acid)-(acid))} = 10^{((10)-(3))} = 10^7$

6. Sildenafil Multistep Synthesis, Part 1.

A. Fill in the missing structures (one structure per box) in the synthesis scheme for Reactions D and E, leading to a pair of regioisomeric products. (10 pt)



B. The ratio of regioisomers D1:D2 is different depending how long the reaction mixture is heated after all of the starting material is used up. Explain why the ratio changes over time. (5 pt)

Short reaction time: 89% D1 and 11% D2

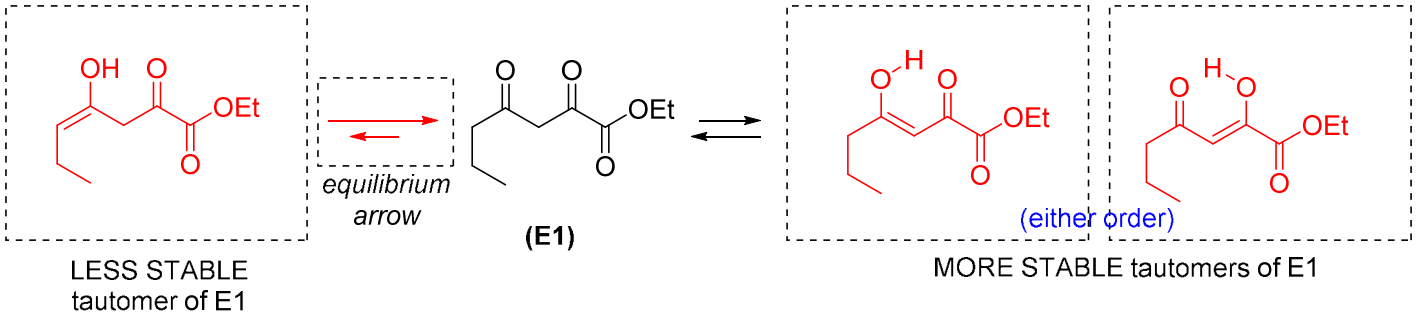
Long reaction time: 98% D1 and 2% D2

The ratio of D1:D2 changes over time because:

D1 and D2 are in equilibrium with each other because reaction D is reversible.

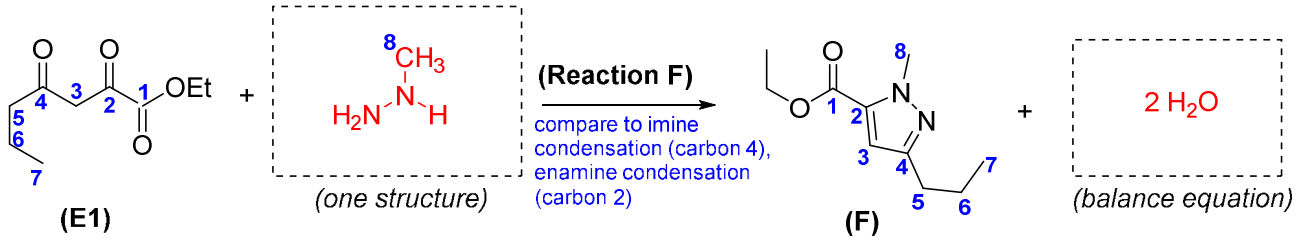
The ratio initially obtained (due to differences in rates of reaction) is not the same as the ratio after complete equilibration

C. Product E1 (from the reaction above) is isolated in equilibrium with several other tautomers. Draw the missing equilibrium arrow and tautomer structures. (10 pt)



D. The next step in the synthesis of sildenafil is the cyclization reaction below.

i. Fill in the boxes to balance Reaction F. (5 pt)

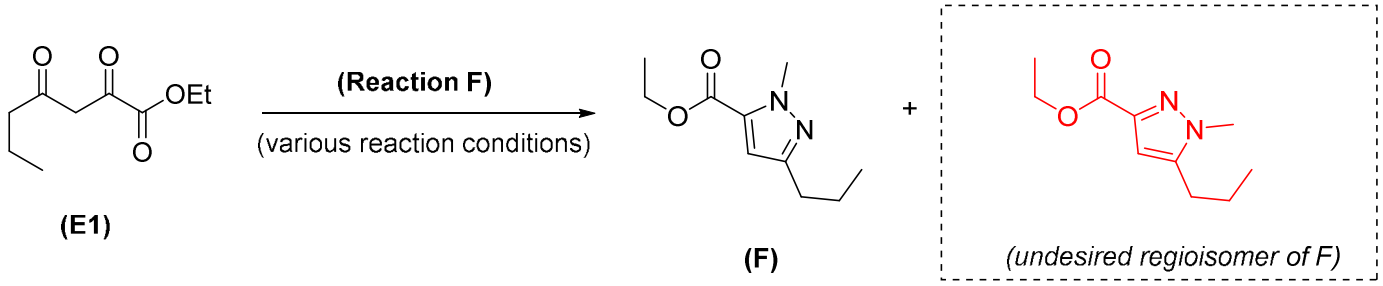


ii. What is the major driving force for Reaction F? (5 pt)

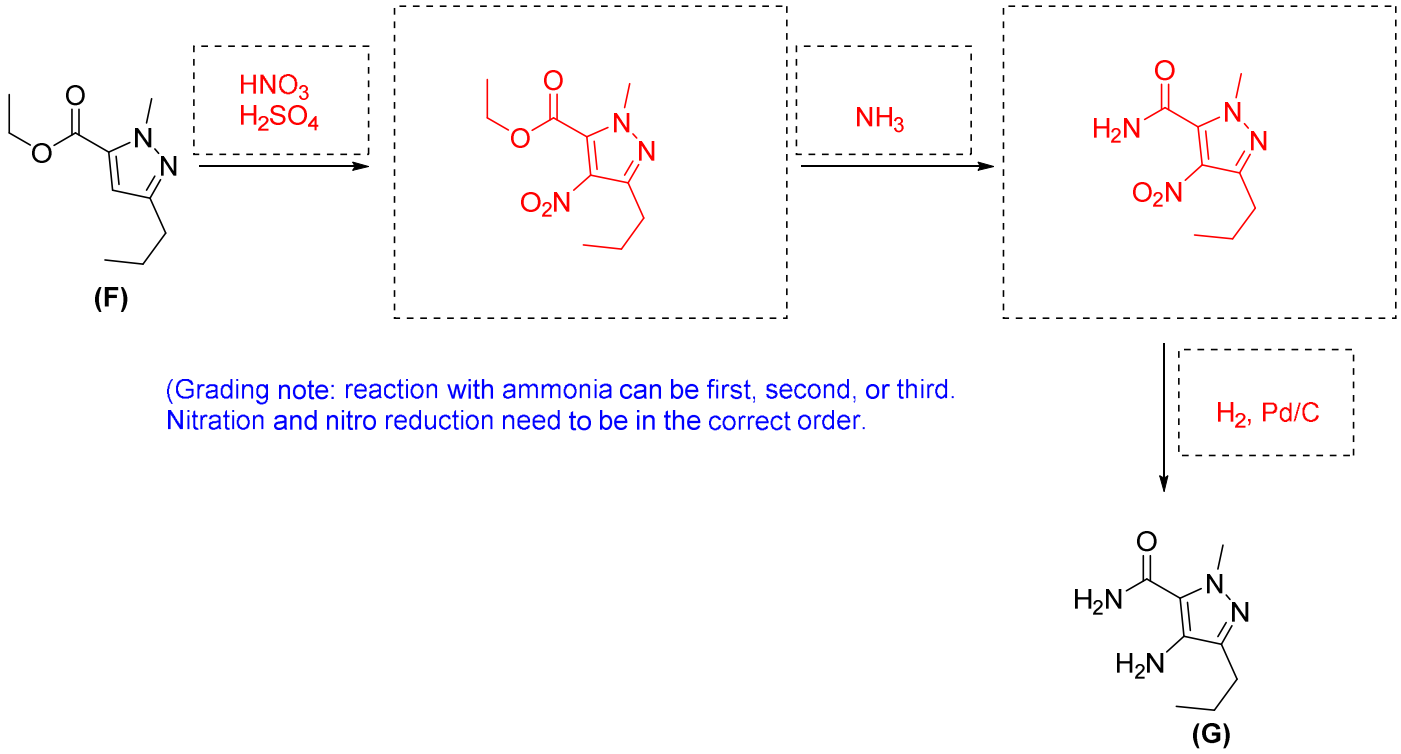
The major driving force for Reaction F is:
(5 words or less)

aromaticity
(Product F is aromatic)

iii. The reaction conditions for Reaction F have a significant effect of the regioselectivity of the reaction, so researchers spent a lot of effort optimizing the conditions (solvent, reaction time, etc). Draw the undesired regioisomer that they were trying to avoid. (5 pt)



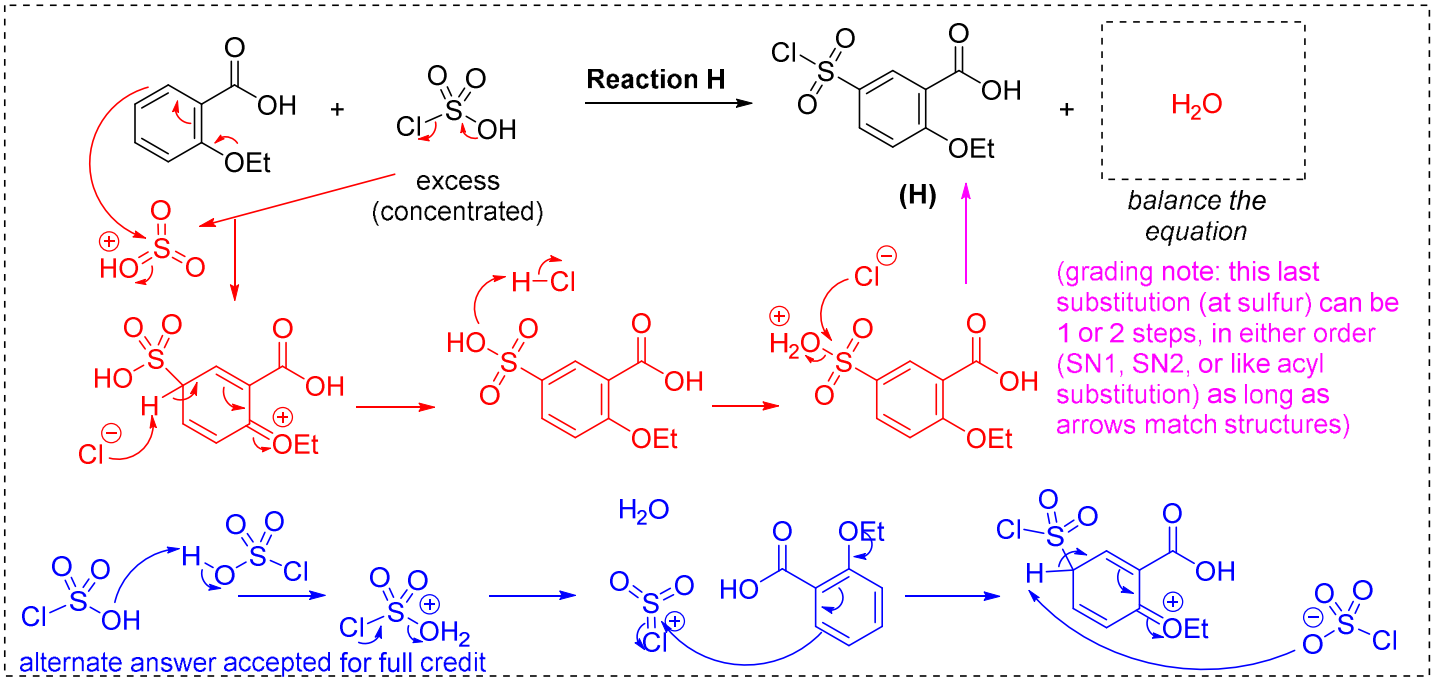
E. Fill in the boxes in the three-step synthesis of product G from starting material F. Assume that only one major product forms in each reaction. Do not combine multiple reaction steps in a single box (no numbered steps within a box). (15 pt)



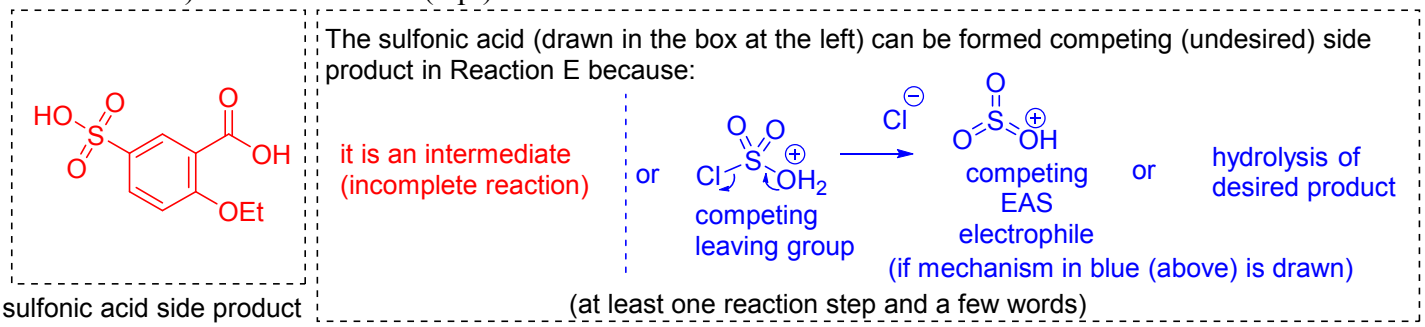
(Grading note: reaction with ammonia can be first, second, or third. Nitration and nitro reduction need to be in the correct order.

7. Sildenafil Multistep Synthesis, Part 2.

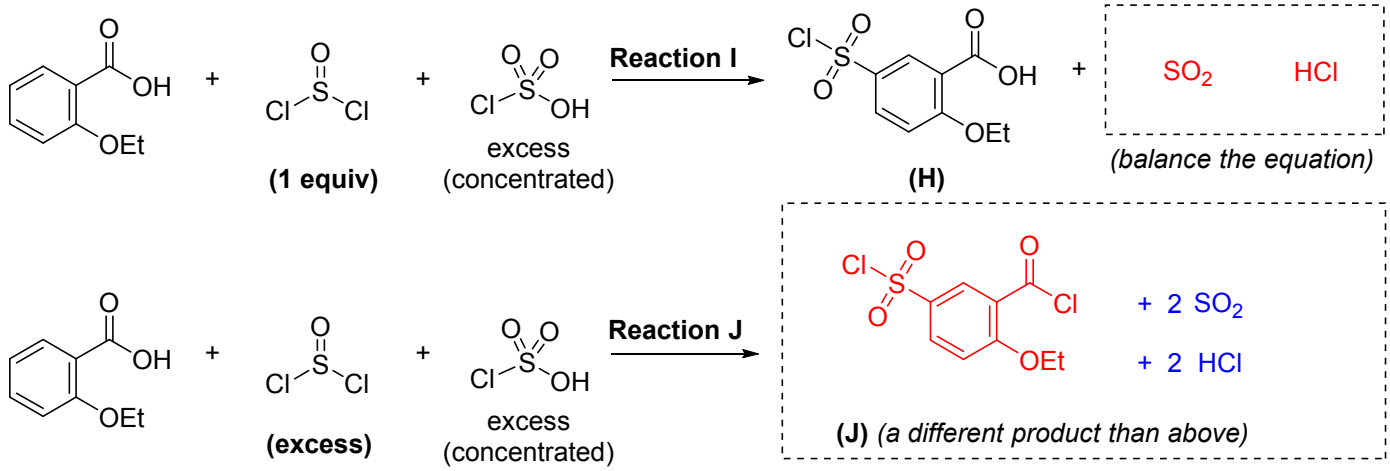
A. Balance the equation and draw a curved arrow mechanism **Reaction H**. Make sure that the major resonance contributor of each intermediate is included in the mechanism. (10 pt)



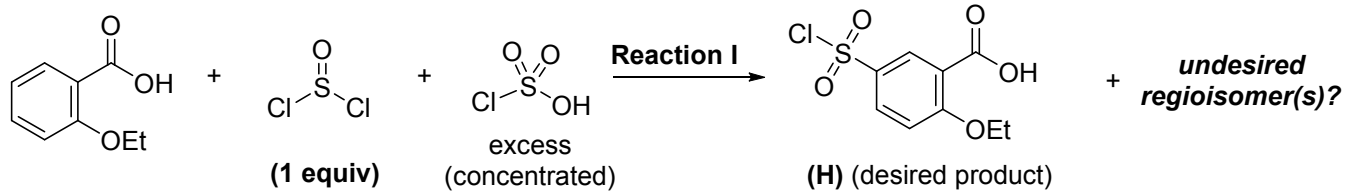
B. In Reaction H (above), a mixture of the desired product (H) and an undesired "sulfonic acid" side product is formed. Draw the undesired product and explain (using at least one reaction step and up to one sentence) how it can form. (5 pt)



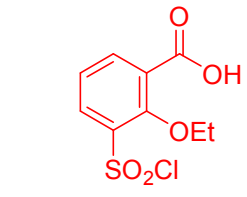
C. Researchers optimizing this reaction avoided the undesired side product by adding 1.0 equiv. of $SOCl_2$ to the reaction mixture. Balance the equation (Reaction I), and predict a different undesired side product (J) that could be formed if excess $SOCl_2$ was used instead (Reaction J). (10 pt)



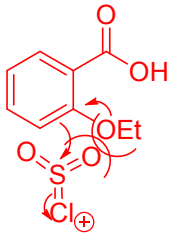
D. Even with the optimized reaction conditions (Reaction I), it is possible for undesired regioisomers of the product to form during the reaction. Draw two undesired regioisomers (based on the description below each box) and explain the selectivity. (10 pt)



an undesired regioisomer that is **MOST** likely to form



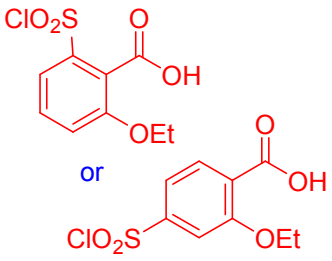
Less of this undesired regioisomer forms (than the desired product) because:



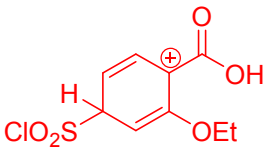
sterics
(electrophile and ethoxy group can have destabilizing steric interaction at the transition state, slowing down this reaction)

(drawing(s) and/or 10 words or less)

an undesired regioisomer that is **NOT** likely to form



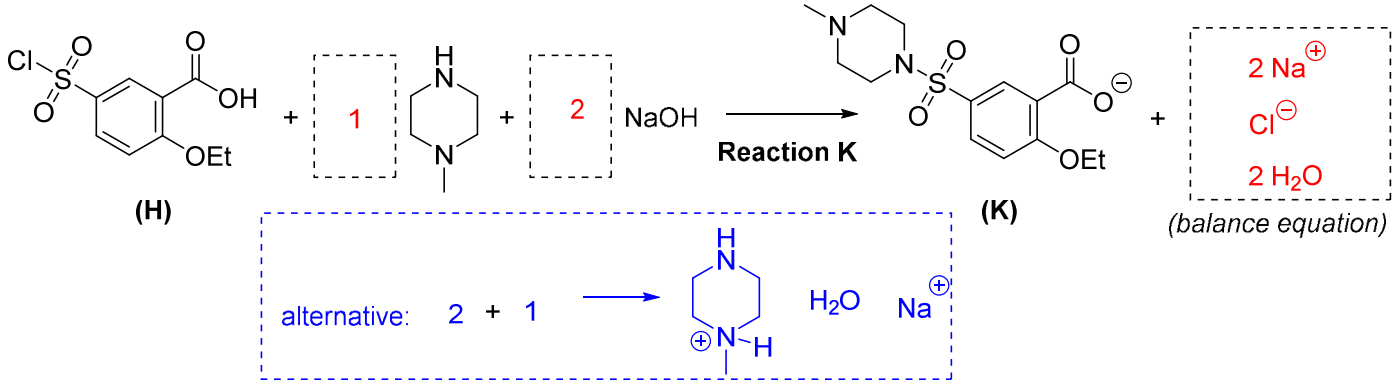
Less of this undesired regioisomer forms (than the desired product and regioisomer above) because:



Resonance directing effects
(ethoxy is ortho/para director, carboxylic acid is meta director)
(intermediate leading to this is higher energy because it does not have resonance stabilization from ethoxy oxygen

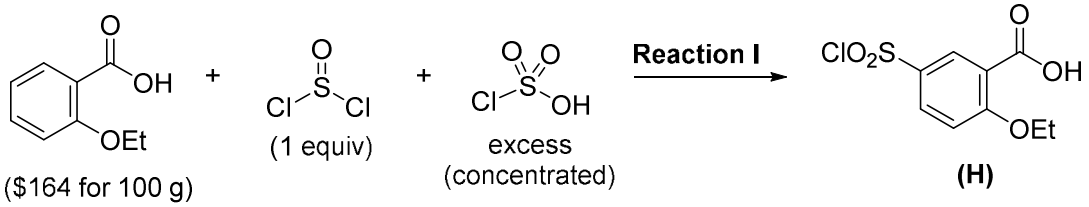
(drawing(s) and/or 10 words or less)

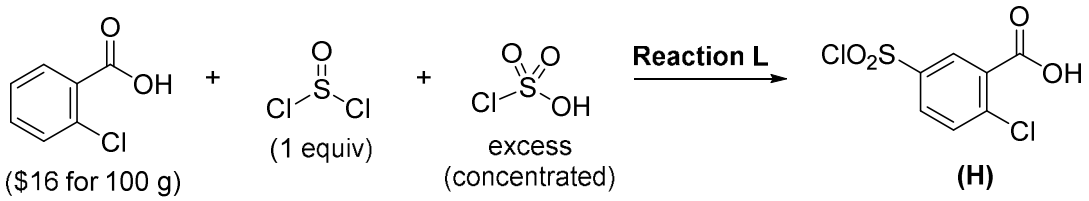
E. The next step in the synthesis of sildenafil is Reaction K. Balance the equation. (5 pt)



F. An alternative multistep synthesis of sildenafil that researchers explored started from a significantly less expensive starting material. Using the same reaction conditions, how would the rates of these two reactions compare? Explain your answer with drawings of the key intermediate(s) and 15 words or less. (5 pt)

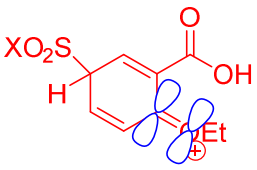
(same Reaction **I** as the previous two pages of the exam)



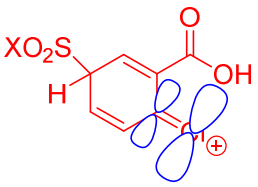


The rate of Reaction L will be: ○ **faster** than Reaction **I** ● **slower** than Reaction **I** ○ **same** as Reaction **I**

because:



(X = Cl or OH)

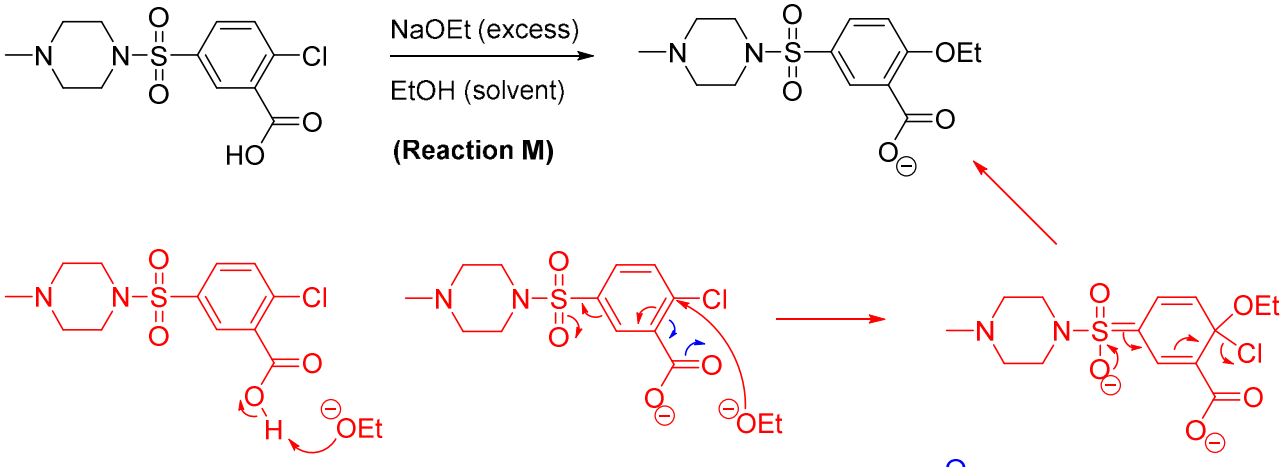


Cl is worse resonance electron donor than O due to orbital size mismatch

(Note: electronegativity of Ois higher (3.4) than electronegativity of Cl (3.2), so any explanation relying on electronegativity differemnces is incorrect because it would predict the opposite of the observed effect (Cl is deactivating, O is activating)

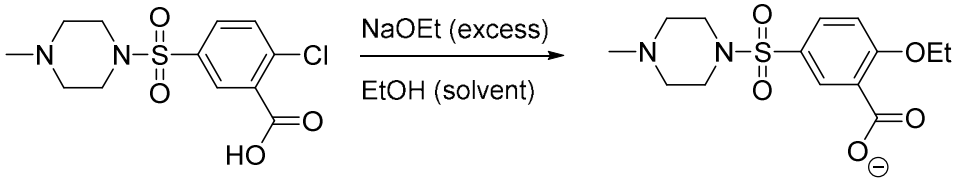
(drawings of key intermediate(s) and 15 words or less)

G. A later step in this alternative synthesis could be Reaction M. Draw a curved arrow mechanism. Make sure that the major resonance contributor of each intermediate is included in the mechanism. (10 pt)

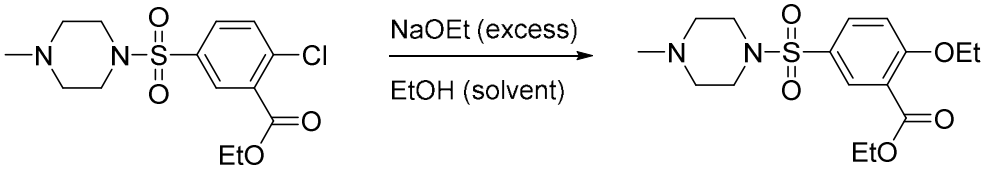


H. Using the same reaction conditions, how would the rates Reaction M and Reaction N compare? Explain your answer with drawings of the key intermediate(s) and 15 words or less. (5 pt)

(Reaction M)
(mechanism in previous question)

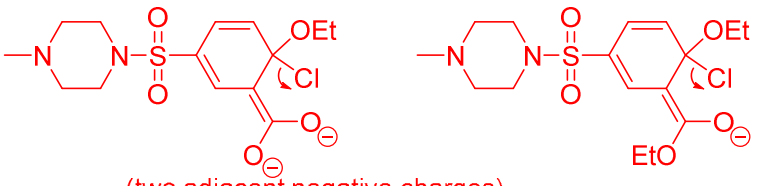


(Reaction N)



The rate of Reaction N will be: ● **faster** than Reaction M ○ **slower** than Reaction M ○ **same** as Reaction M

because:



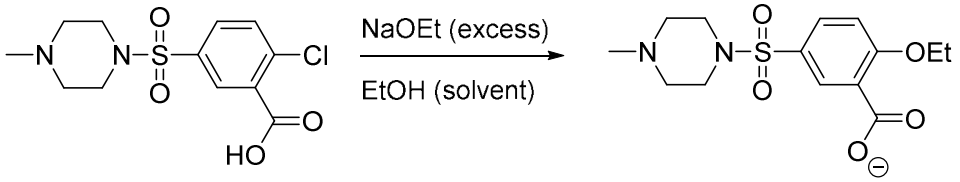
(two adjacent negative charges)

better resonance stabilization

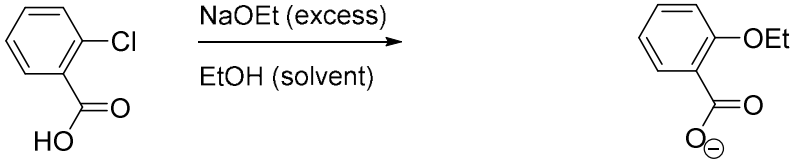
(drawings of key intermediate(s) and 15 words or less)

I. The reaction steps in the multistep synthesis could be carried out in a different order. Using the same reaction conditions, how would the rates Reaction M and Reaction O compare? Explain your answer with drawings of the key intermediate(s) and 15 words or less. (5 pt)

(Reaction M)
(mechanism in previous question)

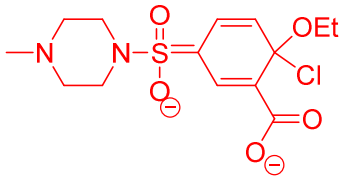


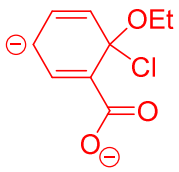
(Reaction O)



The rate of Reaction O will be: ○ **faster** than Reaction M ● **slower** than Reaction M ○ **same** as Reaction M

because:



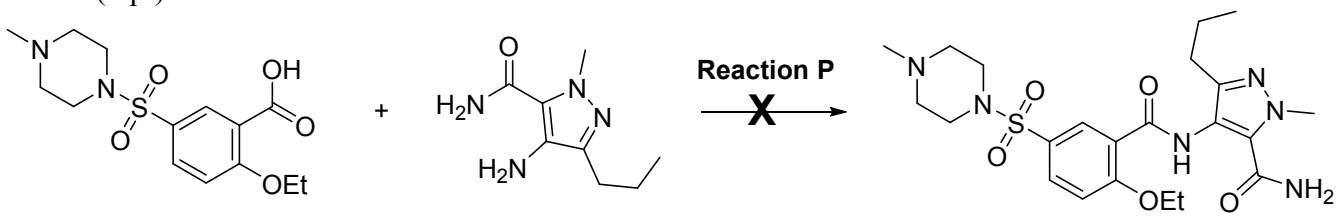


missing/worse resonance stabilization

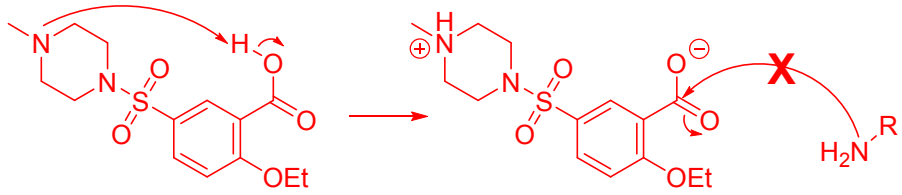
(drawings of key intermediate(s) and 15 words or less)

8. Sildenafil Multistep Synthesis, Part 3.

A. The next major desired intermediate in the synthesis of sildenafil is compound P, bringing together the compounds G and K that were synthesized in Question 6 and Question 7. Explain why Reaction P won't work. (5 pt)



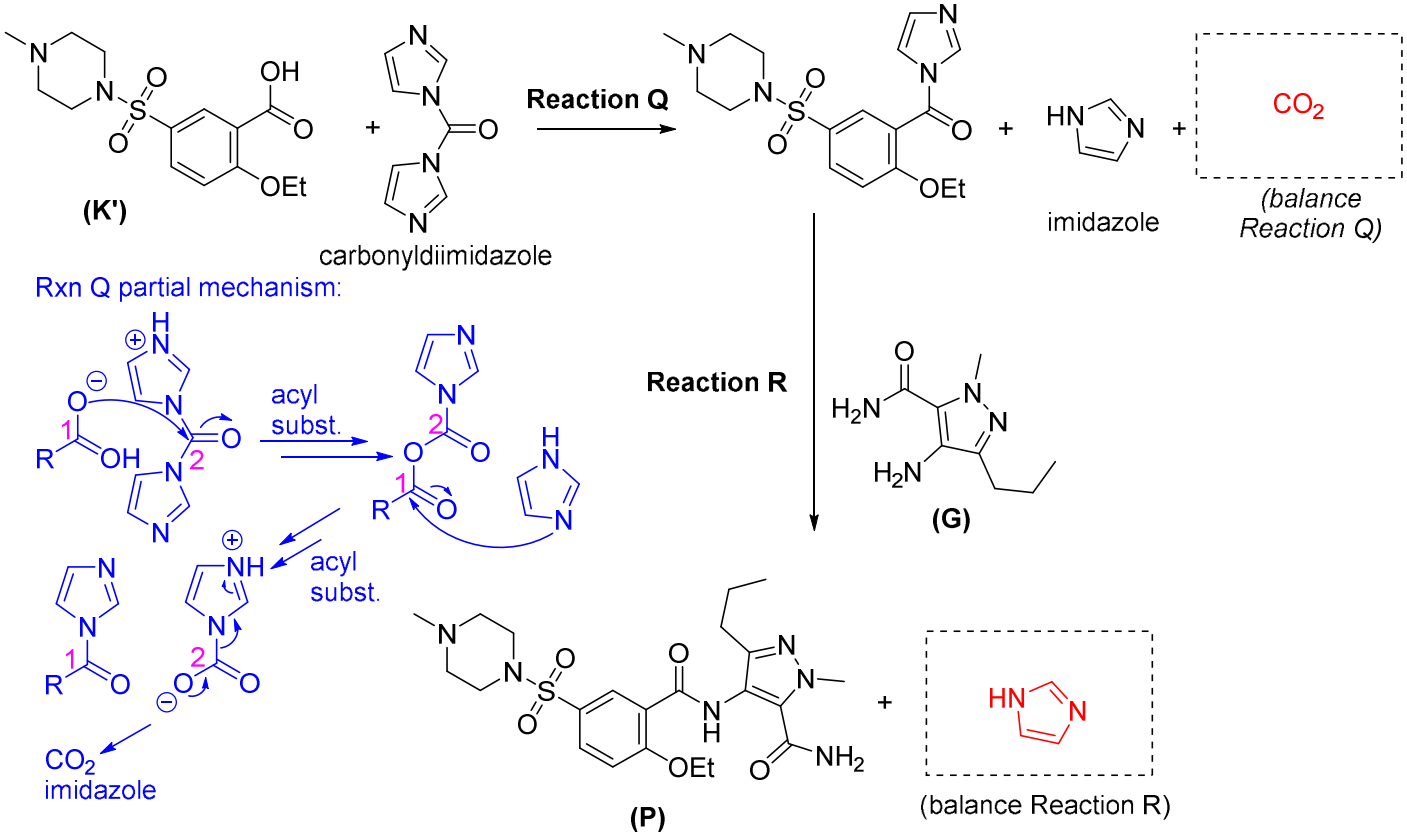
Reaction P won't work to make product P because:



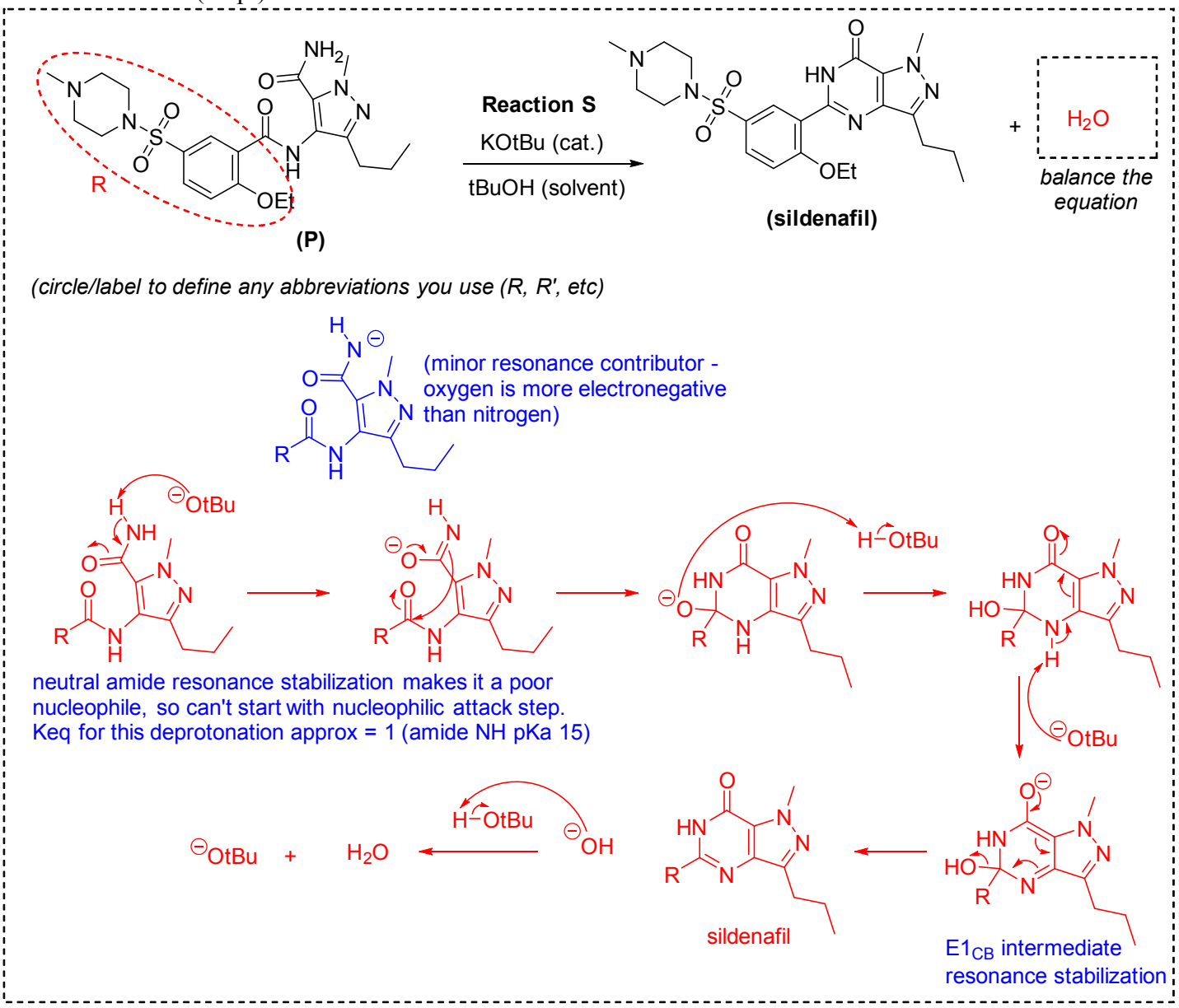
favorable carboxylic acid deprotonation would make carboxylate which is a poor electrophile

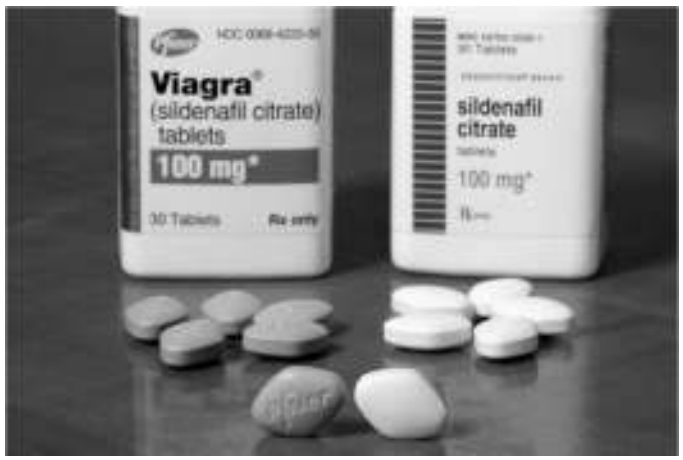
(at least reaction step drawing and up to one sentence)

B. To solve the problem above, Product P was made by a two-step synthesis sequence (Reactions Q and R), using the "coupling reagent" carbonyldiimidazole. Fill in the boxes to balance each reaction. (5 pt)



C. Balance the equation and draw a curved arrow mechanism for Reaction S, the final step in the synthesis of sildenafil. Make sure that the major resonance contributor of each intermediate is included in the mechanism. (10 pt)





(no questions on this page)

Congratulations on finishing Chem 3B!

Have a nice winter break.