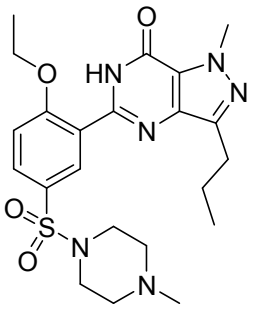
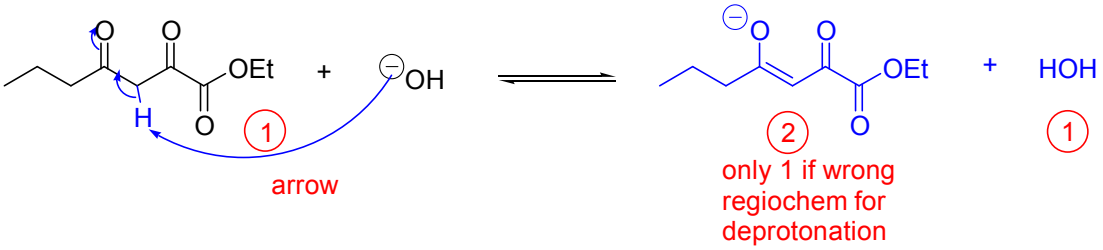
The first half of this exam focuses on the synthetic chemistry used to produce the pharmaceutical sildenafil citrate. Sildenafil is a potent and selective inhibitor of type 5 Phosphodiesterase (PDE 5). Inhibitors of PDE 5 increase cyclic guanosine monophosphate (cGMP) in smooth muscles, leading to smooth muscle relaxation and increased blood flow. While originally developed as a therapy for hypertension, sidenafil has gone on to be a blockbuster drug for Pfizer with World-wide sales in excess of $500 million USD/year for the treatment of erectile disfunction. It is marketed as Viagra. The structure of the drug is shown below.



Sidenafil (Viagra)

1.

a. The ketone shown is one of the first intermediates in Viagra synthesis. Draw the mechanism and product for the following reaction. **(4 points)**



b. Will the reaction favour the starting materials or the products? **(1 point)**

Products.

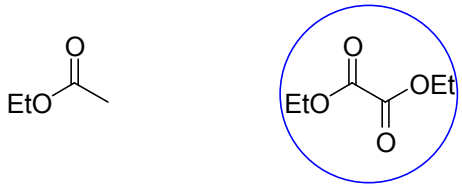
c. Justify your choice in **part b**. **(3 points)**

Either the 1) conjugate base of the carbonyl is doubly stabilized by the two carbonyl groups

or

2) the pKa of the b-dicarbonyl (pKa = 9) is lower than the pKa of water (pKa = 15.75)

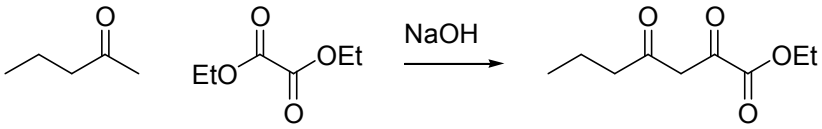
2. Attack of an ester carbonyl by an enolate is use to generate the ketone above. This question examines the relative reactivity of esters as electrophiles.
   a. Circle the most electrophilic molecule. **(2 points)**



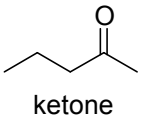
   b. Justify why this carbonyl is more electrophilic. **(2 points)**

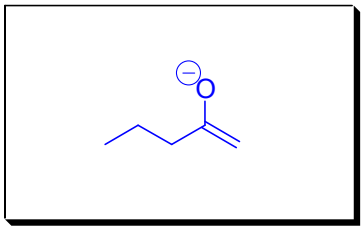
The additional ester functional group pulls e- density from the other ester carbonyl making it more reactive.

3. The reaction shown is a Claisen condensation from the synthesis of Viagra. The Claisen reaction is similar to the aldol reaction since an enolate attacks a carbonyl carbon. However in the Claisen reaction, the carbonyl is an ester, not an aldehyde or ketone.

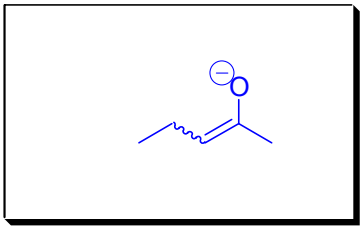


   a. Show the kinetic and thermodynamic enolates of the ketone. **(4 points)**





Kinetic enolate

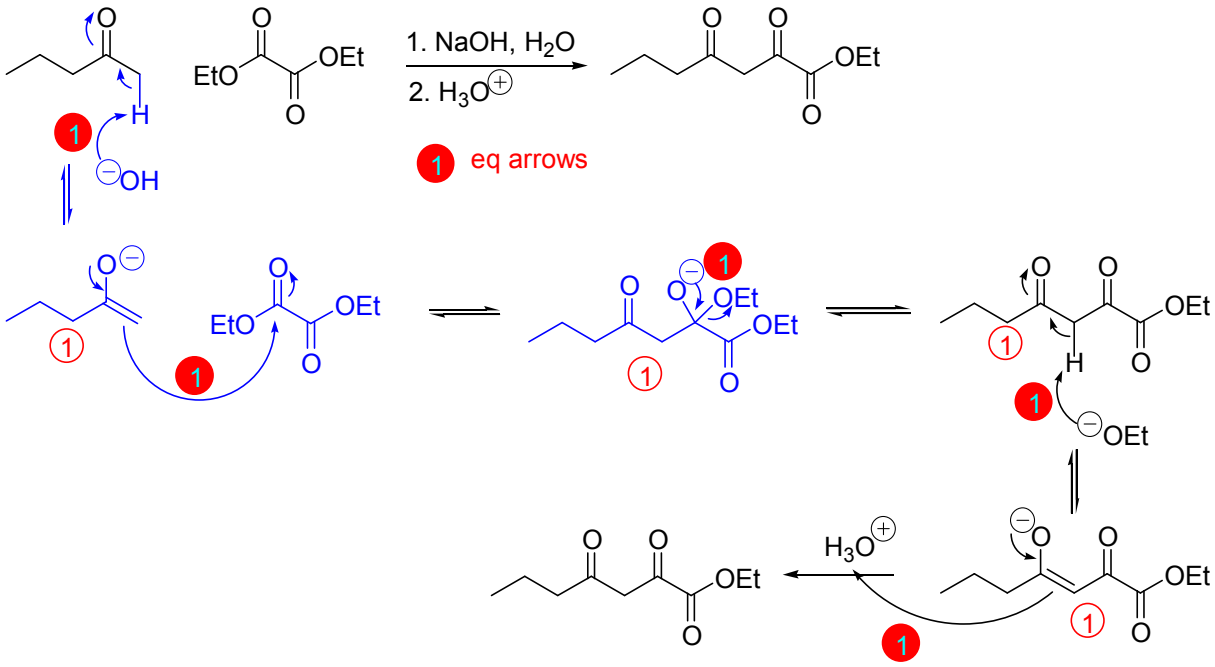


Thermodynamic enolate

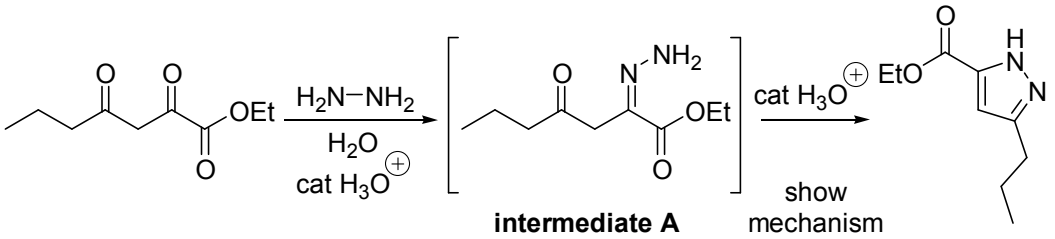
   b. Which enolate reacts with the carbonyl (diethyl oxalate) to produce the product. **(2 point)**

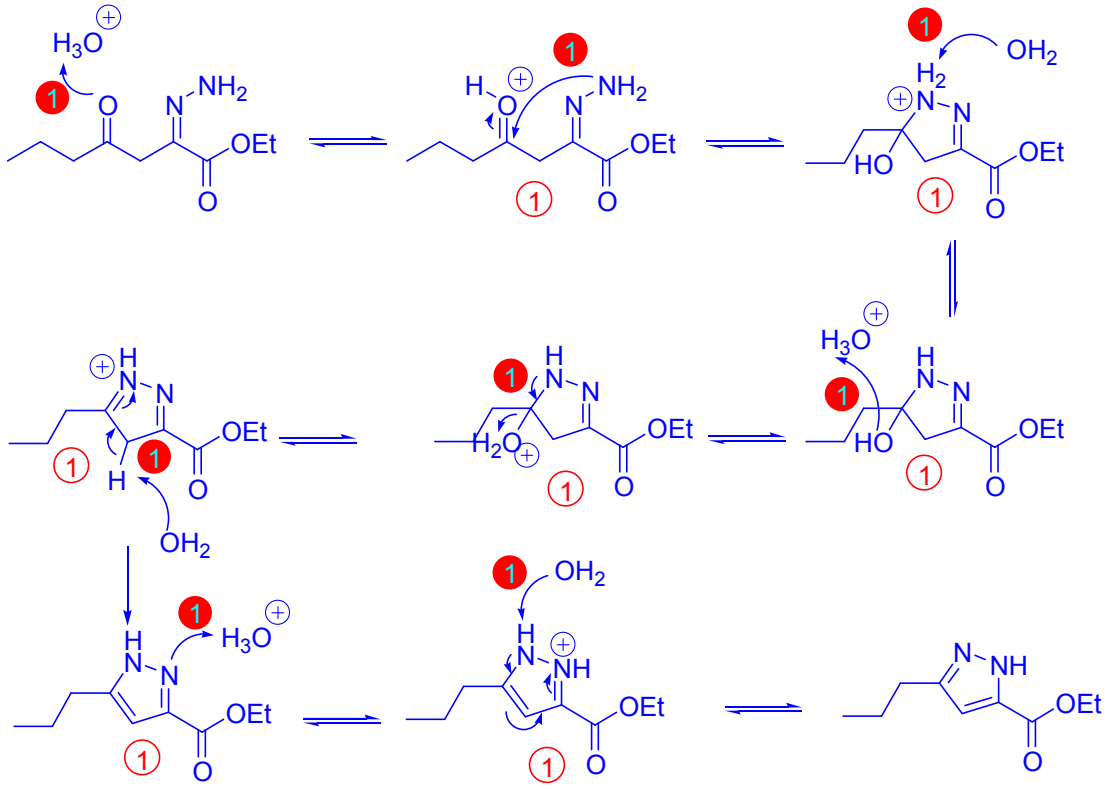
Kinetic

c. Provide a detailed reaction mechanism for this transformation. **(10 points)**



4. The next reaction in the sequence for formation of Viagra is the Knorr pyrazole synthesis. Intermediate A, shown below, is one possible intermediate in the formation of the pyrazole ring (a ring with 2 nitrogen atoms).
   a. Provide a detailed mechanism for the conversion of intermediate A into the product. **(15 points)**



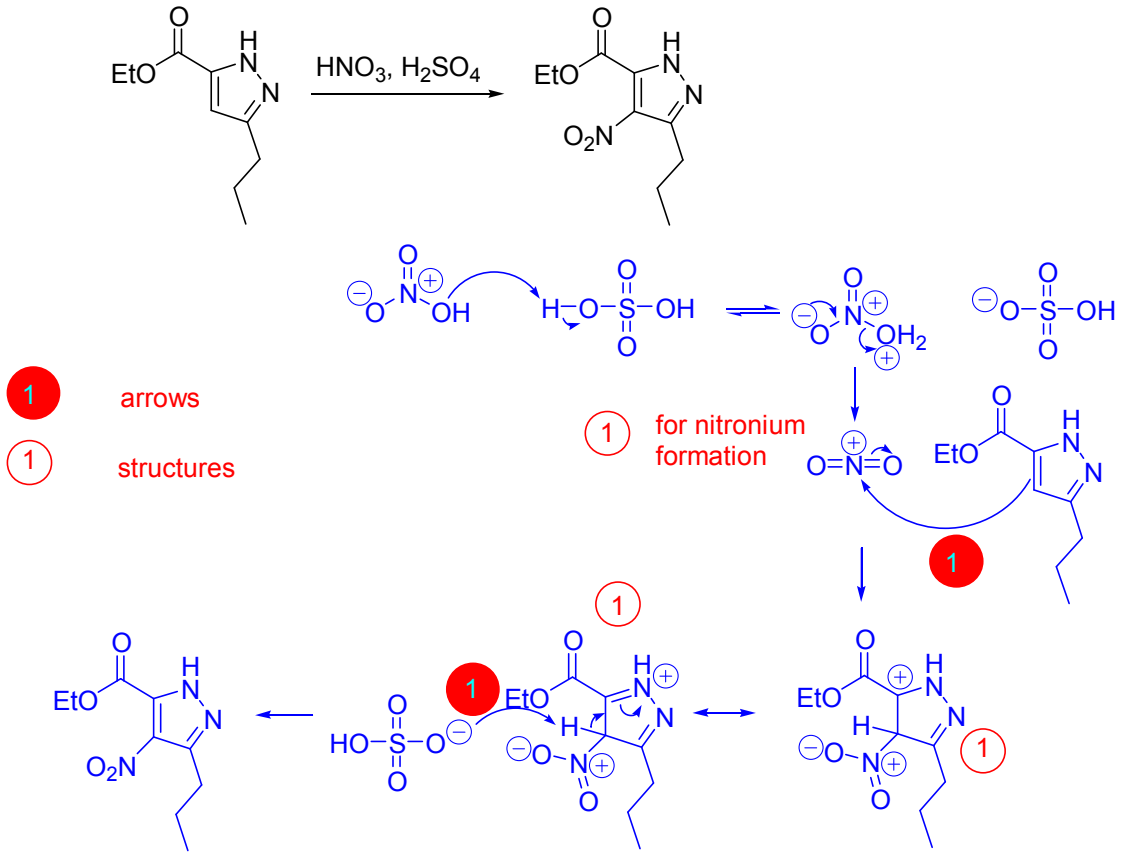


   b. Is the final product aromatic? Justify your answer. **(4 points)**

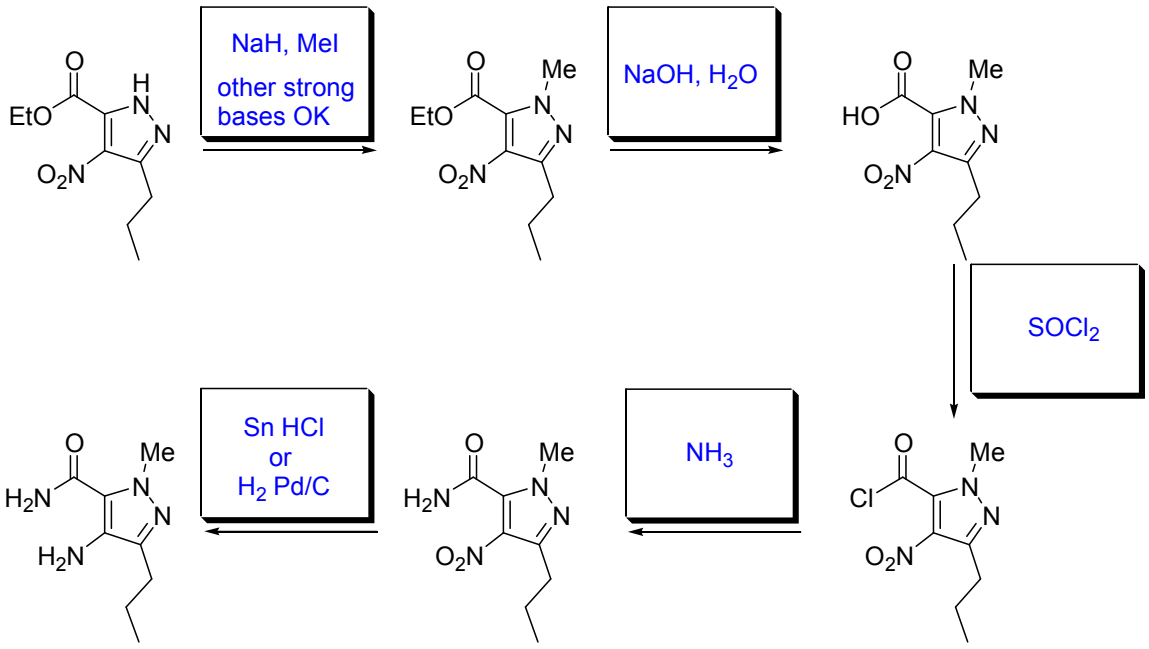
YES

1) Ring
2) P orbital on all atoms
3) 6 e- in P orbitals

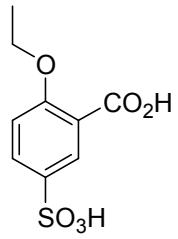
5. Provide the mechanism for the nitration reaction shown. **(5 points)**

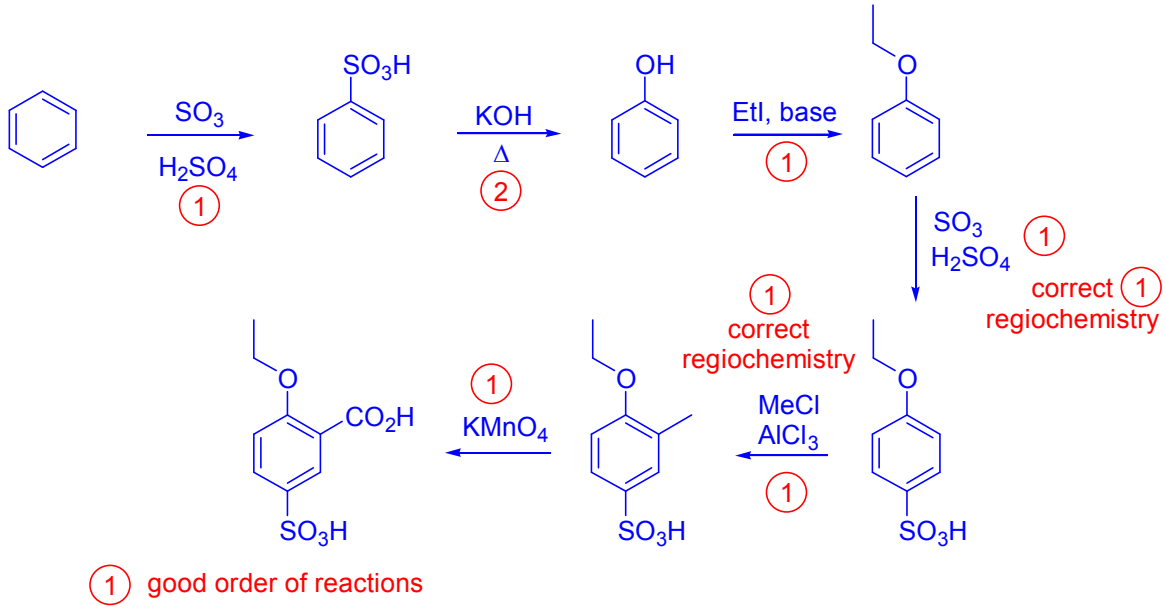


6. The nitration product is then converted into an amino amide in five steps. Provide the reagents. **(10 points)**



7. The next key reagent needed for Viagra synthesis is the trisubstituted aromatic ring shown. Provide a synthesis to make this compound form benzene. **(10 points)**





8. The chemists working on the process chemistry for the manufacture of Viagra performed the chemistry to produce the aromatic compound from question 7. They found the final product was a mixture of two regioisomers. In the aromatic region **regioisomer A** had three NMR signals each integrating for 1H: s at 8.69 ppm, d at 8.16 ppm, and d at 7.26 ppm. **Regioisomer B** also had three NMR signals each integrating for 1H: t at 7.77 ppm, d at 7.70 ppm, and d at 7.0 ppm.
   a. Which regioisomer is the correct product? **(2 points)**

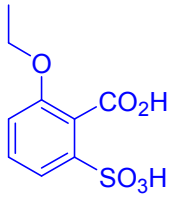
      Regioisomer A

   b. What NMR information confirms this? **(4 points)**

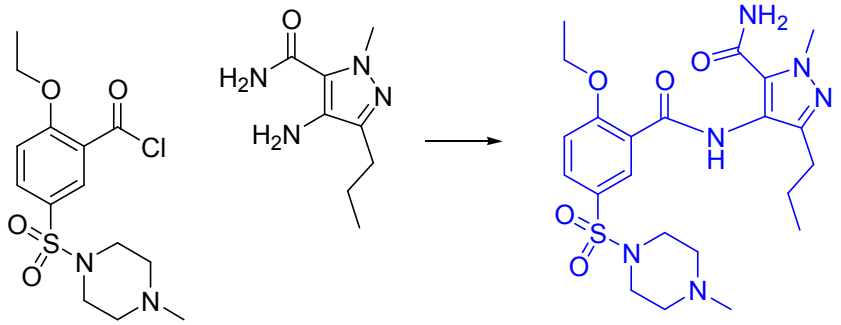
      The coupling found in Regioisomer A. The singlet see for regioisomer A indicates that there is an aromatic proton with both adjacent carbon atoms substituted. This can only occur in a 1,2,4-trisubstituted aromatic

   c. What is the aromatic substitution pattern of the other regiosiomer? **(2 points)**

      Regioisomer B is a 1,2,3-trisubituted aromatic.



9. The second last step in Viagra synthesis is shown.
   a. Provide the product for this reaction. **(4 points)**



   b. What is the name for the new type of functional group generated by this reaction? **(2 point)**

      Amide