Loughborough University

CHEMISTRY IN DRUG DISCOVERY

21CMD213

Semester 1 2021/2022 (1a) Exam paper

This is a (1a) remote assessment examination, meaning you have **23 hours** in which to complete and submit this paper. How you manage your time within the 23-hour window is up to you, but we expect you should only need to spend approximately **2 hours** working on it. If you have extra time or rest breaks as part of a Reasonable Adjustment, you will need to add this to the amount of time you are expected to spend on the paper.

It is your responsibility to submit your work by the deadline for this examination. You must make sure you leave yourself enough time to do so.

It is also your responsibility to check that you have submitted the correct file.

Exam Help

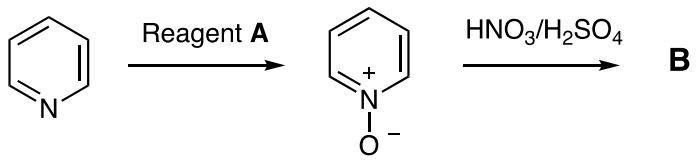
If you are experiencing difficulties in accessing or uploading files during the exam period you should contact the exam helpdesk. For urgent queries please call **01509 222900**. For other queries email examhelp@lboro.ac.uk

You may handwrite and/or word process your answers, as you see fit.

You may use any calculator (not just those on the University's approved list).

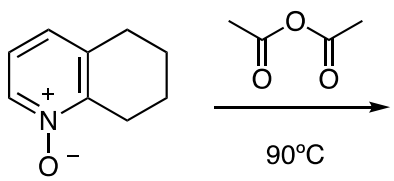
1. Answer **ALL** parts

a) In the scheme below, identify reagent **A** in the first step and product **B** in the second. Give reaction mechanisms for both steps. What happens when product **B** is treated with tripenylphoshine? [7 marks]



b) Give products formed in each of the reactions shown below. Provide a full mechanism to account for the course of the reaction in each case. Where appropriate, show the formation of the reactive species.

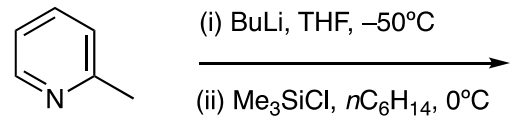
i)



[6 marks]

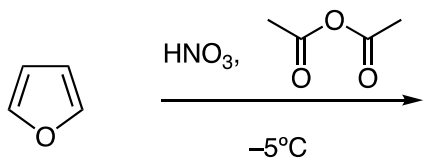
continued…

ii)



[5 marks]

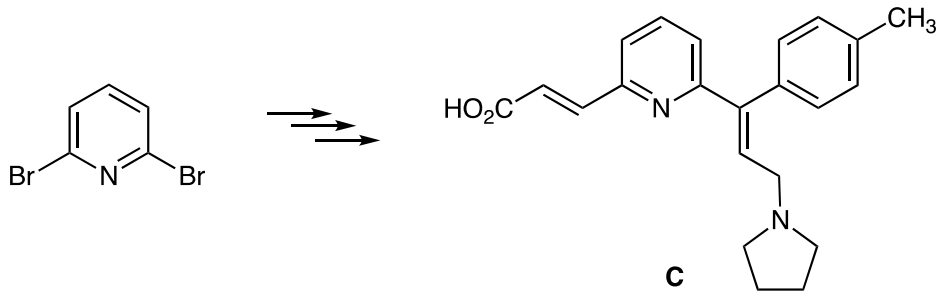
iii)



[7 marks]

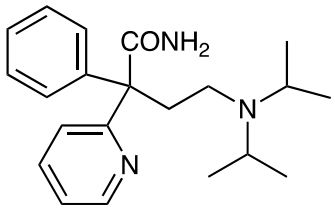
2. Answer **ALL** parts

a) Compound **C** below is a second-generation H1-receptor antagonist antihistamine and is used in the treatment of hay fever and other allergic reactions. Suggest the synthesis of **C** from 2,6-dibromopyridine shown in the scheme below. Explain in detail your choice of reagents, the order of reactions and the outcome of the reactions you have chosen. [15 marks]



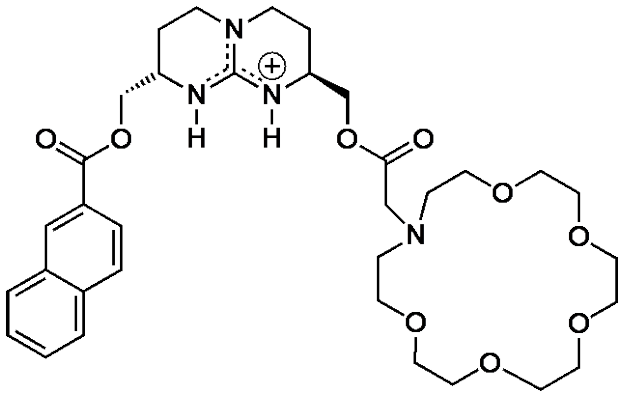
C

b) The compound below is an antiarrhythmic medication used in the treatment of ventricular tachycardia. Suggest a synthetic route to the compound below using any simple starting materials. Use retrosynthesis analysis to help with your answer. Explain the chemistry involved in each forward step. [10 marks]



3. Answer **ALL** parts

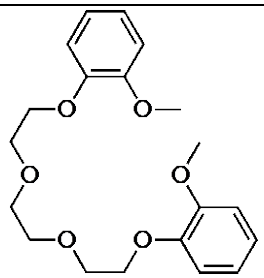
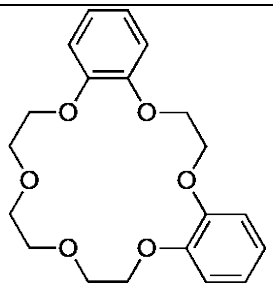
a) Below is the structure of a guanidinium-based molecular host designed to bind to the amino acid, L-phenylalanine.



i) Draw a plausible binding mode between the host and guest and describe the different types of non-covalent interactions involved in stabilising the host-guest complex. [8 marks]

ii) Describe two spectroscopic methods that could be used to determine the strength of the binding interaction between host and guest. [6 marks]

b) The binding between two polyether hosts and a K^+ ion gives the following changes in enthalpy and entropy at T=298 K.

Host	ΔH^o (kJ mol^{-1})	$T\Delta S^o$ (kJ mol^{-1})
 **D**	–9.5	3.1
 **E**	–33.0	5.8

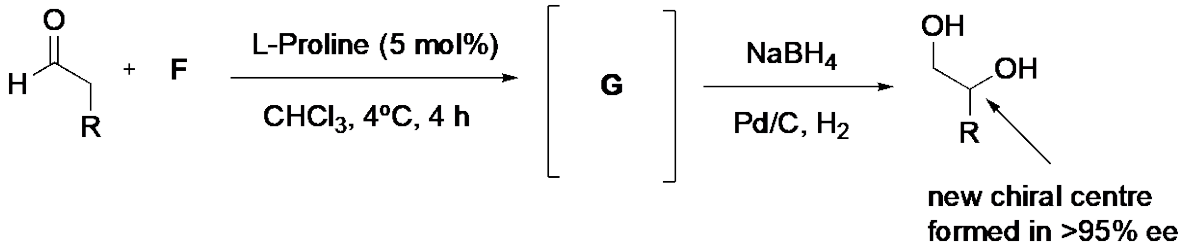
i) Use this data to calculate the association constant (log K_a) for the host-guest complexes. [4 marks]

ii) Explain the large variation in the host-guest binding strength. [4 marks]

iii) Propose a plausible structure of a host molecule with a higher affinity for K^+, which contains the same number of oxygen donor atoms as **D** and **E**. [3 marks]

4. Answer **ALL** parts

Proline has been utilised as an effective organocatalyst for the asymmetric α-functionalisation of aldehydes.



i) Using your knowledge of proline catalysed reactions describe a suitable R group on the aldehyde, the reagent (**F**) for the α-oxygenation reaction and draw the intermediate (**G**). [4 marks]

ii) Draw out and describe the catalytic cycle for this reaction. [6 marks]

iii) Rationalise the stereochemical outcome of the reaction. [12 marks]

iv) When the reaction was carried out in solvents other than $CHCl_3$ a competing reaction product was observed. Suggest a structure for this product and account for its formation. [3 marks]

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