BIRLA INSTITUTE OF TECHNOLOGY & SCIENCE, PILANI

Second Semester 2021-2022

End-Semester Examination (CLOSED BOOK)

Course Name: Pharm. Process Chemistry **Course No: PHA G533**

Total Marks: 20 (scaled down to 10) **Date: 14-05-2022** **Duration: 75 minutes**

Instructions: a) All questions are compulsory; b) Use only blue/black pen; Maximum marks are mentioned in the square brackets; c) Handwriting should be legible; d) Give the answers for all sub-parts together in one place.

1) a) Briefly describe the evolution of process R&D in Germany and US (Max. 5 sentences each)? [**2**]

b) Where do pharmaceutical companies prefer to locate their process R&D sites and why (Max. 5 sentences)? [**2**]

c) Enlist 6 significant advancements/changes in process R&D that happened in the last 20-25 years. [**3**]

2) Answer the following regarding the synthesis of drug candidates in the process R&D departments.

a) Name the most commonly used 4 types of construction reactions. [**2**]

b) What types of heterocycles occur in drug candidates most commonly? [**2**]

c) Out of oxidation and reduction reactions which of these are commonly used and why? [**1.5**]

3) What are the three major objectives of the early development of the process for the API. [**1.5**]

4) Explain the role of solvation in solvent selection with the help of the example of crown ethers. [**2**]

5) Briefly describe *'Desk Screening'* during the initial process assessment. [**2**]

6) Briefly explain phi-factor and provide its formula [**2**]

BIRLA INSTITUTE OF TECHNOLOGY & SCIENCE, PILANI

Second Semester 2021-2022

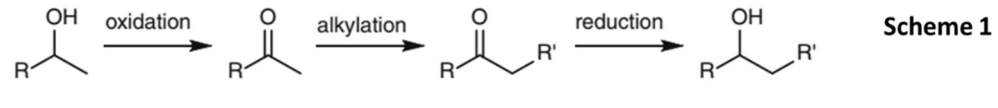
End-Semester Examination (OPEN BOOK)

Course Name: Pharm. Process Chemistry **Course No: PHA G533**

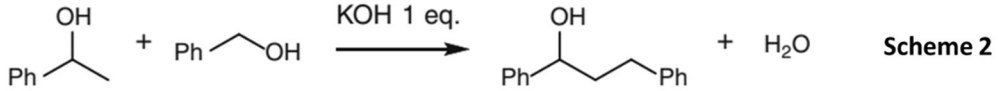
Total Marks: 25 **Date: 14-05-2022** **Duration: 105 minutes**

Instructions: a) All questions are compulsory; b) Use only blue/black pen; Maximum marks are mentioned in the square brackets; c) Handwriting should be legible; d) Give the answers for all sub-parts together in one place.

1) Generally, Scheme 1 is followed for the beta alkylation of alcohols where 90% yield is obtained at individual steps. Recently, researchers developed the process shown in Scheme 2 to achieve the same objective with 76% yield. a) Which of these do you think is more productive? Prove numerically b) Which of these is greener? Justify by the qualitative comparison of matrices of greenness. [2+2 = **4**]

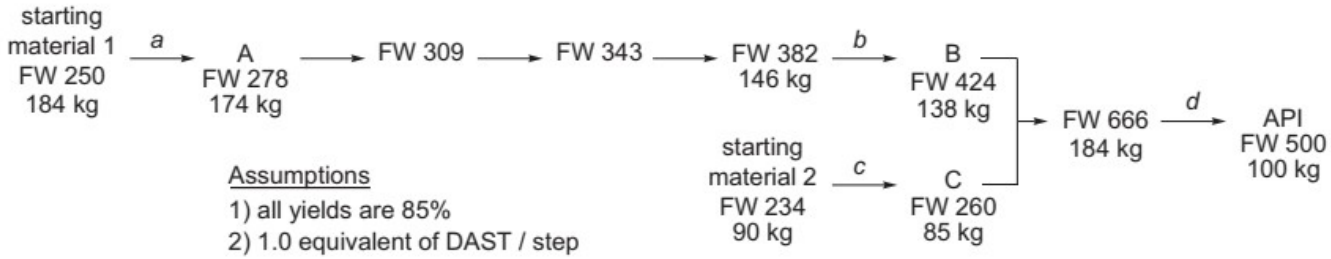


Scheme 1

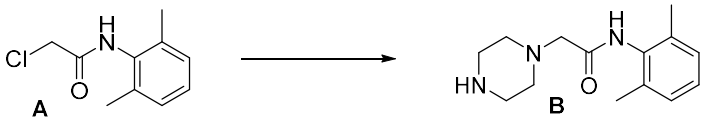


Scheme 2

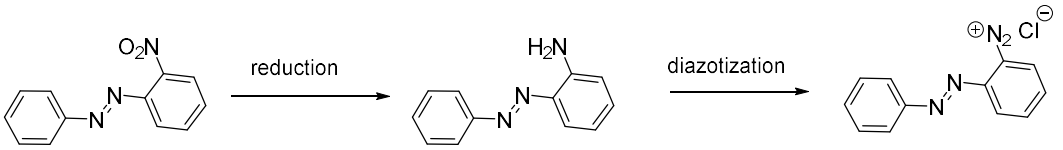
2) Cost of goods (CoG) is an important criterion for route selection. In the following hypothetical process, a very expensive fluorinating agent (diethylamino)sulfur trifluoride (DAST) can be positioned at four different stages (a,b,c,d). Explain with the help of calculations the best position for DAST to reduce CoG. [**5**]



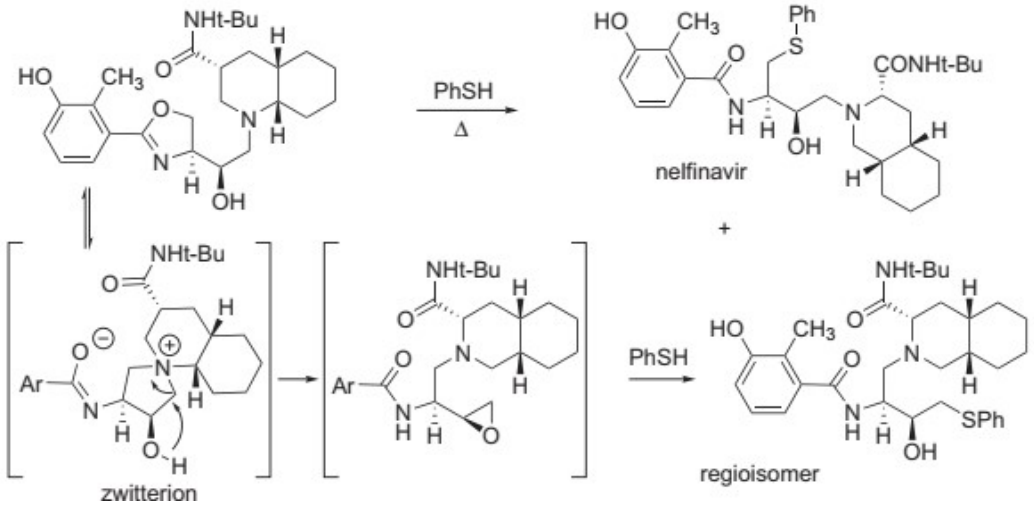
3) Researchers at Merck wanted to make intermediate **B** (pKa = 10) from **A** and piperazine. They found an impurity with a pKa of 8 and higher MW than **B**. a) Predict the structure of the impurity and how can you minimize its formation without using protection/deprotection? b) Explain, how you can separate impurity during the work-up? [3+2= **5**]



4) Following synthetic scheme is commonly performed at the discovery stage. As a process chemist, you are asked to optimize this process at a multi-Kg scale. a) Explain the safety associated risks in this scheme and how would you quantify them. b) What reagent would you prefer for the first step keeping in mind principle 1 of the Green Chemistry? Discuss its pros and cons. [2+3 = **5**]



5) In the synthesis of nelfinavir, a regioisomer was formed as an impurity. Based on knowledge of the mechanism explain what type of solvent would you select to reduce the regioisomer yield? [**2**]



6) A process control was developed to quantify the impurity **X** formed during the synthesis of a peptide using a coupling reaction between two amino acids. For every batch, compound **X** was isolated by crystallization, followed by drying and weighing. Comment on this process control, its suitability, and alternatives. [**3**]

7) A metalloenzyme is used to carry out the biotransformation of alcohol to a ketone. How would you quench this reaction without changing pH/temperature or adding an organic solvent? [**1**]