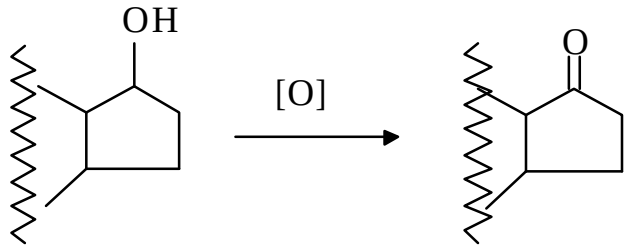
SCENARIO

You are a member of a synthetic organic chemistry research team at Syzygy Pharmaceuticals. Syzygy's scientists have discovered a new potential prescription drug, called X-37, to treat heart disease. They now need about 100 grams of X-37 for animal testing. If that is successful, the company will need a high-yield, low-cost synthesis for production runs of up to several kilograms.

A key step early in the 10-step synthesis is the oxidation of a secondary alcohol in a 5-membered ring to a ketone.



The original synthesis called for the reaction to be done with Jones reagent, a mixture of concentrated sulfuric acid and sodium dichromate. However, the yield was low and the isolation procedure tedious. Before major resources of the company are committed to a large-scale synthesis, the section head would like the chemists in the group to explore alternative reagents that may give an increased yield of product, with fewer disadvantages in the production method. The project was assigned to your group.

A search of the literature by one of your team revealed several possible mild oxidation agents. Both manganese dioxide and ruthenium tetroxide have been used to convert cyclopentanols to cyclopentanones in sensitive large molecules[1], but both have some environmental and commercial drawbacks which make them no more attractive than the chromium reagent. A potentially better reagent is sodium hypochlorite, NaOCl, which is commercially available as swimming pool chlorine, or in a somewhat weaker solution as household bleach. Your group decided to investigate this reagent further before making the first production run of X-37.

Because the starting materials for the production of X-37 are relatively expensive, your team will do the initial investigation using a model reaction, the oxidation of cyclopentanol to cyclopentanone. Once the best oxidizing agent is determined using this relatively inexpensive substrate, you can attempt the synthesis of X-37 with some confidence of success. The investigation protocol your group plans to follow is outlined on the next page. However, considerable planning remains to be done before the actual reactions are carried out.

EVALUATION OF A SYNTHESIS PROTOCOL

OXIDATION OF ALCOHOLS TO KETONES

PURPOSE: Two reagents that can be used to oxidize secondary alcohols to ketones are Jones reagent (Potassium or sodium dichromate in sulfuric acid) and sodium hypochlorite, NaOCl, in acetic acid[1]. The sodium hypochlorite can be used either as household bleach (5.5% w/w) or as "swimming pool chlorine". Which of these three reagents would you recommend for the oxidation of **1 mole** of cyclopentanol to cyclopentanone?

PROCEDURE: Devise a procedure to collect data on this question. Sample procedures are provided for Jones oxidation and for 12.5% hypochlorite (Note 5). You need to develop your own procedure for using household bleach.

Among the planning steps you need to consider are:

How many runs of each type of reaction will you attempt?
Is the protocol is clear, so you and your colleagues understand what to do at each step?
What scale will you use?
Do you need to scale up or down the reagent quantities listed in the sample procedure to fit a reasonable lab time and equipment available?
Is the exact quantity of each reagent specified for each step?
What will constitute a "successful" run? How will you know if it is successful?
Who will be responsible for each phase of the project, from planning to report?

TO COLLECT YOUR DATA: Perform each reaction type at least once, but multiple trials give more reliable results. Then compare data with your colleagues on your team.

TO WRITE THE REPORT: First, determine which person in your group is responsible for each part of the report. Will one person write and others review? Will each be responsible for a section? Who will do the statistics? the typing? the proofreading? Then write a report that **makes a recommendation** and **substantiates** that recommendation with your data. Follow the general format as outlined by your instructor at the beginning of the year. However, for this report, your discussion section should emphasize your answer to the original question and data that substantiates your answer, not proof of the product identity and things that went wrong. Some of the factors you should consider are:

yield
purity of product obtained
time needed for the reaction
ease of handling reagent
ease of workup of product
safety, toxicity and corrosiveness of materials involved
cost of reagents needed to perform the reaction
environmental cost
disposal costs (See Note 7)

SAMPLE PROCEDURE #1

use of Jones reagent[2]

SAFETY PRECAUTIONS: Safety goggles and gloves must be worn for all these operations.

In a beaker of suitable size were placed 50 mL water, 12.0 g (??mmol) of sodium dichromate dihydrate and 9.0 mL (??mmol) of concentrated sulfuric acid. The solution was stirred to make it homogeneous. In a 250 mL Erlenmeyer flask equipped with a magnetic stirrer were placed 50 mL of diethyl ether and 60 mmol (?? g) of cyclopentanol. This solution was placed in an ice bath and stirred while the Jones reagent was added through a dropping funnel into the flask at approximately 3 drops per second. The addition took about 10 min. The reaction mixture was allowed to stand for an additional 30 min, or overnight (Note 1).

The reaction mixture was poured into a separatory funnel. The lower aqueous layer was drawn off and saved for appropriate disposal, and the organic layer then shaken with 20 mL of 5% aqueous sodium bicarbonate solution. The sodium bicarbonate solution was drawn off and placed in a separate container. The ether solution was dried over anhydrous sodium sulfate and then the solution was decanted from the drying agent into a round-bottomed flask. The ether was removed by distillation, using a steam bath as a heat source, and collected for disposal The residue distilled at atmospheric pressure to give the ketone.

(Student will need to fill in data, yield, spectra, etc. A student who wants to use the gc must let the lab manager know at least 5 hr before it is needed--it needs to warm up.)

DISPOSAL PROCEDURES: What volume of each type of waste solution do you have? Don't forget to determine the appropriate disposal procedure for the sodium sulfate, too. What is the appropriate disposal procedure for each substance you have?[3] Highly dilute and dilutable aqueous solutions may go down the drain, but all organic solvents, **including wash acetone**, must be accounted for. How much would each procedure cost your company? (See Note 7 for a price list for disposal costs)

SAMPLE PROCEDURE #2

Use of 12.5% sodium hypochlorite[4]

SAFETY PRECAUTIONS: Safety goggles and gloves must be worn for all these operations.

In a 250 mL Erlenmeyer flask equipped with a thermometer and a magnetic stirrer were placed 10.0 g (?? mmol) of cyclopentanol and 25 mL of glacial acetic acid. The solution was chilled in an ice bath. In a dropping funnel were placed 90 mL of swimming pool chlorine (???brand, concentration ??% by weight. See Note 2). The hypochlorite solution was added dropwise with stirring to the alcohol solution at a rate that maintained the reaction temperature at 30-35 degrees. The entire addition took about 30-40 minutes. The reaction mixture was allowed to stand 30 minutes or overnight before isolation was continued.

Saturated sodium bisulfite solution was added, a few mL at a time, until all the excess sodium hypochlorite was destroyed, as shown by the clearing of the yellow color. (Note 3).

The reaction mixture was placed in a separatory funnel along with 75 mL of saturated sodium chloride solution and 50 mL ether. The funnel was shaken and the layers separated into different containers. The aqueous layer was returned to the funnel and shaken with an additional 50 mL of ether. The layers were again separated and the aqueous layer saved for appropriate disposal. The ether extracts were combined in the separatory funnel and washed with three separate 25 mL portions of 5% sodium carbonate solution (Note 4). The sodium bicarbonate washes were combined in a container for appropriate disposal. The ether solution was dried over anhydrous sodium sulfate and the solvent removed by distillation, using a steam bath as a heat source. The ether from the distillation was collected for appropriate disposal. The residue was distilled at atmospheric pressure to afford the product.

DISPOSAL PROCEDURES: What volume of each type of waste solution do you have? Don't forget to determine the appropriate disposal procedure for the sodium sulfate, too.[4] What is the appropriate disposal procedure for each solution? How much would each procedure cost your company? (See Note 7 for a listing of typical disposal costs)

EXTENSIONS: (Note 6) If there is time, and the equipment is available, consider the following variations.

Extension 1: Both of the lab procedures developed use diethyl ether as a major component of the reaction mixture, during the reaction itself and in the isolation of the product. From a manufacturing standpoint, however, ether is a very undesirable chemical to use. It is relatively expensive (as much as $20.00 per liter in lab quantities[5]), and is also extremely volatile and flammable. The volatility makes complete recovery for recycling difficult to do, and may produce problems for the company's air quality control measures. Flammability is always an issue in a manufacturing plant. Therefore, when a laboratory procedure is scaled up to production quantities, substitutes need to be found for diethyl ether.

A common substitute for diethyl ether as a solvent is methyl *t*-butyl ether (MTBE). It is readily available, and the cost ($11.00-13.00/liter[5]) is less than for diethyl ether. It has a boiling point of 55 degrees and a much higher flash point (-10 vs. -40 degrees). All of these attributes make it easier to handle.

Can MTBE be used for the recommended reaction instead of diethyl ether? It seems likely, but before committing your company to production, you will need to design and run some pilot reactions to answer this question. In addition, you need to compare the Material Safety Data Sheets (MSDS) for diethyl ether and MTBE, to assess the relative handling hazards for each solvent. MSDS information can be obtained through the stockroom or on line at this site, among others.

http://hazard.com/msds/index.html

Extension 2. Practical considerations will probably limit the students' initial experiments to the 5-10 gram range for raw materials. However, the initial question really concerns 1 mole or more of the desired product. Scaling up a reaction to large quantities often presents more problems to solve. Yields often change, and sometimes major changes in reaction conditions are needed.

Can the finally selected reaction really be used to make as much as one mole of cyclopentanol? Calculate the amount of materials needed. If your yield is less than 100%, don't forget to scale up even further to allow for the production of one mole of product in pure form. Carry out the reaction on the one mole scale, and report on the feasibility of this method for the production of large quantities of X-37.

Extension 3. In a manufacturing situation, after the "best" reagent for the transformation has been tentatively identified, thermochemical investigations are advisable prior to scaling the reaction to the one mole size. Typically, the heat of reaction is calculated for the reaction, and the maximum adiabatic temperature rise is calculated to determine "worst case" outcomes. In other words, If the reaction goes out of control when attempted on a large scale, how big a problem will it present in terms of potential fire or explosion hazard? In addition, Differential Scanning Calorimetry (DSC) testing is usually done on the reactants and products to determine if any of the reaction conditions could lead to runaway decomposition of any of the materials.

NOTES

Note 1. The reaction mixture forms an emulsion that separates slowly. For best results, allow the reaction mixture to stand overnight before proceeding with the isolation.

Note 2. This experiment was checked using Aquachem Liquid Chlorinizor®, 10% sodium hypochlorite by weight.

Note 3. Approximately 10 mL of saturated sodium bisulfite solution is needed.

Note 4. The reaction to produce carbon dioxide proceeds very vigorously, so separatory funnels should be vented frequently.

Note 5. Yields for the two reactions are similar, generally 30-60% with student glassware. Purity of product is comparable. However, both procedures have advantages and disadvantages from the procedural standpoint. Thus the students must exercise their own judgment and justify their recommendations with well-reasoned discussions of their data. In a trial run in the student laboratory, a number of students did not get complete conversion of the alcohol in any protocol followed. In addition, some found that for the hypochlorite reactions, extensive washing of the ether solution is necessary to remove all traces of the acetic acid.

Note 6. These extensions have been suggested by our industrial consultant, but have not been tried in our student laboratory because the format of the course does not lend itself to such extensive study of one reaction.

Note 7. To help the students calculate an estimated disposal cost, the following information is provided. These numbers are taken from the University of Wisconsin-Parkside price list for chemical disposal, and are based on a state-wide contract price. Individual corporations may have a less advantageous price structure. In addition, industrial chemical users may need to perform pre-treatments for final disposal which will add to the cost. For instance, in some instances, the chromium salts might need to be converted into a highly insoluble form before landfill disposal. Much depends on the company's handling procedures.

SUBSTANCE	**55-GAL DRUM**	**5 GAL LAB-PAK**
mixed organic solvents	$107.50	$1.55 /pound including container weight
chromium solution (corrosive mixture)	375.10	1.55/lb
mixed solid chemical waste	240.00	1.55/lb

REFERENCES

1. Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Vol 1, Wiley, New York, 1967.

2 Nimitz, J. S. *Experiments in Organic Chemistry*; Prentice-Hall, New Jersey, 1991; pp 263-269.

3. *Aldrich Catalog Handbook of Fine Chemicals*; Aldrich Chemical, Milwaukee, 1990; pp F16-F17.

4. Fessenden, R.; Fessenden, J. *Techniques and Experiments for Organic Chemistry;* Willard Grant, Boston, 1983; pp 188-197.

5. *Aldrich Catalog Handbook of Fine Chemicals*; Aldrich Chemical, Milwaukee, 1990.