This project is sponsored by AstraZeneca

A Process Development Project: The Synthesis of the Antiulcer Agent Esomeprazole

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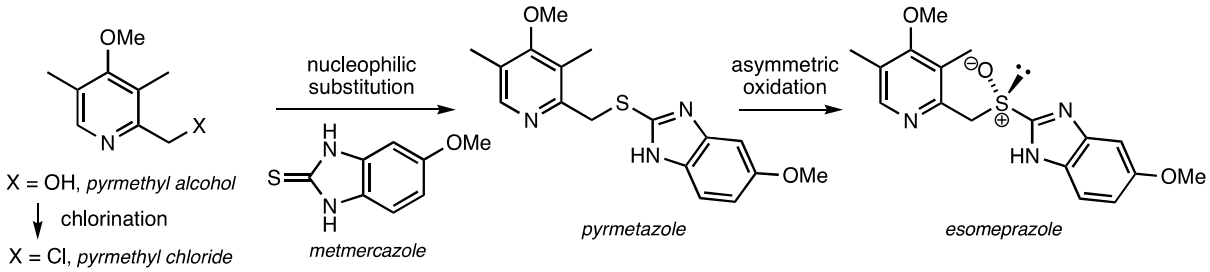
1. Aims

This project provides an introduction to the excitement and challenges of process development chemistry. You will learn some basic considerations of scale-up processes by preparing esomeprazole using a two-step reaction sequence. First, you will prepare pyrmetazole using a known chlorination/nucleophilic substitution process and then you will investigate the asymmetric oxidation of a sulfide group in pyrmetazole to form esomeprazole. You will work as part of a team to carry out a series of small-scale reactions, to investigate how the reaction conditions affect the efficiency and enantioselectivity of the oxidation, with the aim of developing an environmentally friendly synthesis.



2. Background Information

A Process Chemist Job Specification

Process chemists are responsible for identifying and developing new processes for the manufacture of chemical products. A process chemist implements process controls and test methods to assess the reliability and reproducibility of the production method. This includes scaling-up a research prototype (often devised in a medicinal chemistry laboratory) to pilot production (typically, to make a few kilograms to 200-300 kg of material) and then to full-scale manufacture. It is important that a safe method of production is developed, that meets all relevant legislation and safety regulations. In addition to development of scalable and robust processes, Process Chemists are responsible for production and delivery of active pharmaceutical ingredients (API) to support the activities of the wider project, for example, formulation and toxicological studies as well as phase 1, 2 and 3 clinical trials.

Esomeprazole – Biological Action and Synthesis

Esomeprazole (marketed as Nexium™) is an antiulcer drug developed by AstraZeneca. Antiulcer drugs are a class of drugs that are used to treat ulcers (sores or raw areas) in the stomach and upper part of the small intestine. The ulcers, sometimes called peptic ulcers, are caused by infection with a bacterium or by long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen. Esomeprazole acts as an antiulcer drug by selectively inhibiting an enzyme in the gut that is responsible for producing acid in the stomach (it is called a proton pump inhibitor). Its launch in 2000 was particularly noteworthy because it was the first enantiomerically pure proton pump inhibitor to enter the market.

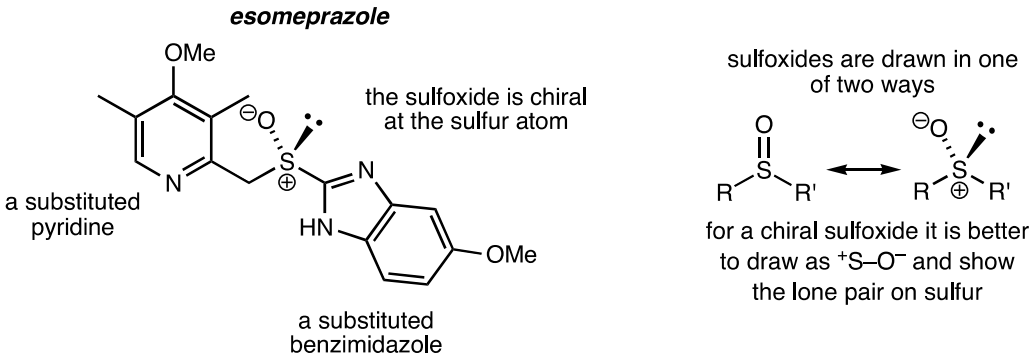
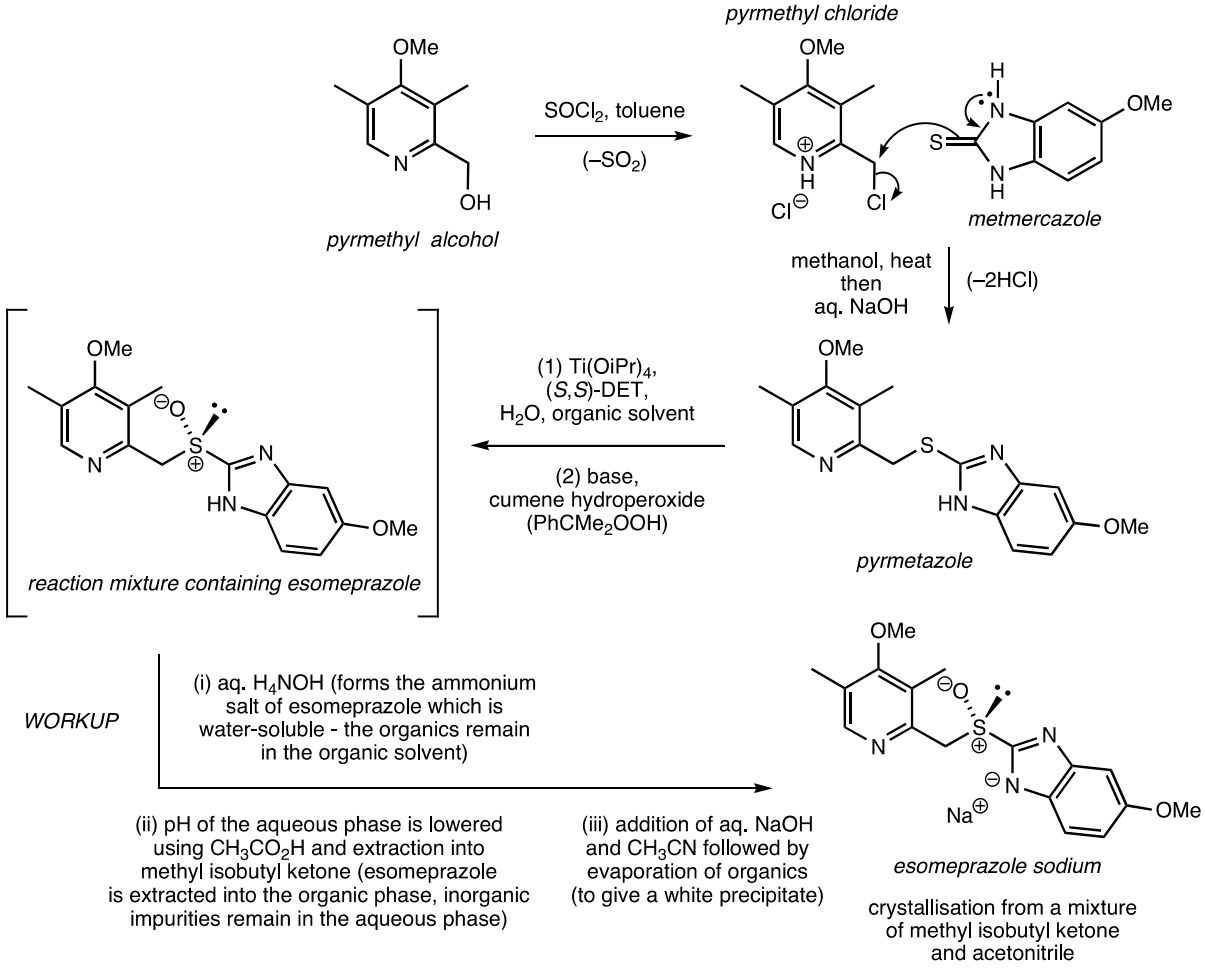


Figure 1. The structure of esomeprazole and the sulfoxide group

The synthesis of esomeprazole (developed by AstraZeneca) starts by chlorination of pyrmethyl alcohol using thionyl chloride ($SOCl_2$) in toluene as shown in Scheme 1. Pyrmethyl chloride is isolated (as the hydrochloride salt) and then heated with metmercazole in methanol, using aqueous sodium hydroxide as a base (to neutralise the HCl). On substitution, a sulfide called pyrmetazole is produced, typically in >90% yield, using an experimental procedure provided by AstraZeneca (the experimental details for this reaction are provided in Appendix 1).



Scheme 1. An overview of the synthesis of esomeprazole sodium

The key step in the synthesis is the asymmetric oxidation of the sulfide group in pyrmetazole. At the time, existing methods of asymmetric oxidation of sulfides provided unsuccessful, giving esomeprazole sodium in low yield and/or low enantioselectivity. Process chemists at AstraZeneca had to develop a new method of asymmetric oxidation of the sulfide, which was based on the conditions used for the Sharpless asymmetric epoxidation reaction (you should check the details of this reaction).

The method for oxidising the sulfide is divided into two steps:

In *step 1*, pyrmetazole is stirred with titanium tetraisopropoxide, $Ti(O^iPr)_4$, and (*S*,*S*)-diethyl tartrate in a mixture of water and an organic solvent. The reaction mechanism is not understood in detail but it is believed that a complex is formed between the sulfide group in pyrmetazole, $Ti(O^iPr)_4$ and the chiral tartrate, so that one face of the sulfide is shielded from oxidation.

In *step 2*, the sulfide is oxidised using cumene hydroperoxide ($PhCMe_2OOH$) in the presence of an amine base. The role of the base is unclear, although it is required to provide high levels of enantioselectivity.

The reaction mixture is then 'worked-up' using a three-step method (steps i-iii in Scheme 1), designed to remove organic and inorganic impurities by converting esomeprazole into esomeprazole sodium, a white crystalline solid that can be further purified by crystallisation. (The experimental details of the workup procedure are given in Appendix 3.) This project will focus on preparing and purifying esomeprazole using a 'cleaner' synthetic approach than is currently available, chiefly by exploring 'greener' solvents.

3. Practical Work

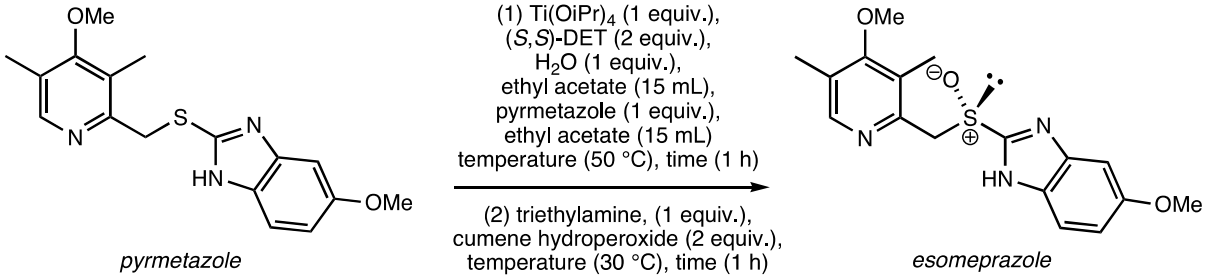
Optimising the reaction conditions

In the two-step oxidation of pyrmetazole (Scheme 1), a variety of experimental conditions can be changed, which could have an affect on the yield and/or enantiomeric excess of esomeprazole sodium. The medicinal chemistry group has provided you with the details of the oxidation conditions they used to prepare esomeprazole. As a team, you will determine the ratio of pyrmetazole:esomeprazole (using the ^1H NMR spectrum of the crude product) from the 'medicinal group reaction' and from variations of this reaction of your choosing (perhaps influenced by searching the chemical literature).

Each reaction must be assessed for hazards. This means that you must have noted the hazards (contained in Appendix 4 or to be retrieved from the chemical literature) and also describe any special containment techniques you are going to use in the reaction to ensure that the risks are minimised.

(a) The medicinal group reaction

The conditions of the reaction carried out by the medicinal group are outlined in Scheme 2 and the experimental details are given in Appendix 2. As detailed in Appendix 2, you should carry out this reaction starting with 0.25 g of pyrmetazole. You will use the results of this reaction as a starting point for optimising the synthesis of esomeprazole.



Scheme 2. The medicinal group reaction

(b) Analysis of esomeprazole

A number of methods could be used to assess the purity and enantiomeric excess (ee) of esomeprazole (e.g. chiral HPLC, optical rotation, NMR using a chiral shift reagent). As part of the experimental details in Appendices 1 and 2, the medicinal group have included the ^{1}H NMR spectroscopy data, which you can use for analysis of the crude reaction products (i.e. to determine the ratio of pyrmetazole : esomepazole). You will need to explore methods (e.g. preparative TLC, and/or column chromatography) to purify esomeprazole and then determine the ee using optical rotation and/or chiral HPLC.

As a group, you will also need to ensure that you do not mix up samples from different experiments – at the outset, you should consider a numbering system for experiments, samples and any analytical data.

(c) Variations of the medicinal group reaction

Possible variations to the medicinal group reaction are summarised in Figure 2 (if you would like to make any other variations, such as use of mixed solvents involving for example, ethylene carbonate, or the use of alternative oxidants, please check with a Coordinator first). There are many more variations than you will have time to complete and so, as a group, you need to decide which variations to investigate. To get meaningful comparisons, you need to choose a series of experiments where you change just one parameter at a time. For example, to investigate the influence of water, you need to change the number of equivalents of water in the reaction mixture, while keeping all the other reaction variables the same. The results of your experiments should help to guide you on new experiments to try. Because time is an issue, you will have to plan your experiments carefully and you will be asked to justify your decisions at the end of the project – *remember that you are aiming to develop conditions that offer greener credentials over the status quo*. (For each experiment, you should carry out a risk assessment using the hazards listed in Appendix 4/the template provided in Appendix 6 and use a maximum of 0.25 g of pyrmetazole). It is up to you to use your time in the laboratory as efficiently as possible – you are aiming for a number of high quality results (you may need to repeat experiments to check for reproducibility).

Equivalents of $Ti(O^iPr)_4$: (*S*,*S*)-DET *(med group = 1.0 : 2.0)*
0.2 : 2.0
0.5 : 2.0
2.0 : 4.0
1.0 : 1.0
5.0: 5.0

Equivalents of water *(med group = 1.0)*
0.25
0.50
0.75
2.00
5.00

Solvent for step 1 *(med group = EtOAc)*
tetrahydrofuran
toluene
methyl isobutyl ketone
2-methyltetrahydrofuran
propylene carbonate

Concentration of pyrmetazole in the organic solvent *(med group = 0.05 M in EtOAc)*
0.01
0.10
0.50
0.75

Time for step 1 (h) *(med group = 1)*
0.25
0.50
2.00
4.00

Temperature for step 1 (°C) *(med group = 50 °C)*
–10
0
10
30

Base for step 2 *(med group = triethylamine)*
diisopropylamine
N,*N*-diisopropylethylamine
1,8-diazabicyclo[5.4.0]undec-7-ene
4-dimethylaminopyridine
2,6-lutidine

Time for step 2 (h) *(med group = 1)*
0.25
0.50
1.50
2.00
4.00

Temperature for step 2 (°C) *(med group = 30 °C)*
–10
–5
0
5
10

Figure 2. Possible variations to the medicinal group reaction

4. Your Report

Individual project reports (written independently), up to a maximum of 4 sides of A4 (12-point font), must be handed in by the deadline advertised. Your report should be word-processed and it should be structured as follows. (You can add appendices e.g. giving representative & assigned spectra.)

(a) Introduction

Give the names of the students in your team and a bullet point list of the aims of the project.

(b) Summary of the optimisation work

(i) Briefly discuss your choice of reaction conditions and summarise your results in a table.
(ii) What are your conclusions about the optimum 'cleaner' reaction conditions?
(iii) Briefly discuss the advantages/disadvantages of analysing reaction products using NMR, optical rotation or chiral HPLC? Assign the ^{1}H NMR data provided for esomeprazole sodium (in Appendix 3). If you generated any other spectroscopic data, this should be fully assigned and included in your report.
(iv) Emphasise the green credentials of your optimised conditions.

(c) Scaling up the reaction

(i) For a subsequent investigation to scale-up the reaction, using your optimised conditions, give the full experimental details of a 10 g scale reaction.
(ii) You should calculate (showing your workings in an appendix) how much the solvents/reagents would cost (from the chemical supplier Sigma-Aldrich) to make a kilogram of esomeprazole from pyrmetazole.
(iii) You should discuss the safety implications of a large-scale process and provide advice on the following risk assessments (with regard to scaling-up your process to a pilot plant).

- The physical and chemical properties of the reactants, reagents, products and wastes (including impurities)
- The potential for substances in use to corrode the plant (a scaled up process may well be carried out in a container made of materials other than glass)
- The fire and explosion hazards
- The health hazards and personal protective equipment assessments
- The thermochemistry of both the desired and potential undesired reactions, in particular the rate of heat output (is a runaway exothermic reaction possible?)
- Environmental effects

(d) Future developments

If you had more time, what other variations to the med group reaction would you investigate, and why?

5. Poster

As part of the assessment you will produce a poster, as outlined in the guidelines provided. Each group A-C (of up to 3 students) will produce separate posters. To help you decide on the style/layout it is worth looking at the various posters dotted around the Department (some prize-winning posters, by PhD students, are displayed in the corridor). There are also a number of useful online resources that provide tips and guidelines for producing an outstanding poster.

6. Good Housekeeping and Risk Assessments

It is very important that you keep your work area (fumehoods and benches) clean and tidy at all times. Also, please ensure that the lockers are kept tidily and that any samples are clearly labelled. In the final week of the project, the lockers should be tidied/emptied of any samples – **if not, then marks will be deducted** (in the 'contribution to team-working and safety' category).
Prior to each experiment you must complete a risk assessment, signed off by a Coordinator (see Appendix 6). Please ensure that the appropriate risk assessment is displayed in the clear plastic wallet on the fumehood sash.

Appendix 1. Synthesis of Pyrmetazole

Pyrmethyl alcohol (4.4 g, 26.3 mmol) was dissolved in toluene (37.5 ml, water content 0.12 mg/ml), moistened with water (188 µl, 10.4 mmol) at room temperature. To the stirred solution, at 25-35 °C, thionyl chloride (4.67 g, 2.86 ml, 39.2 mmol) was added slowly over 1 h (typical flow rate of 0.095 ml/min) – beware of sudden increases in temperature (exotherms). You should follow the conversion of the reaction using thin layer chromatography – pyrmethyl alcohol has an R_f value of 0.2 in a 3:1 mixture of ethyl acetate:dichloromethane (a fast reaction is expected, typically 99% after complete addition of thionyl chloride; a white precipitate may form during the reaction). The mixture was evaporated (under reduced pressure; *CARE* – production of HCl gas) to give pyrmethyl chloride hydrochloride as a white solid (99%) (handle in a fumehood). Pyrmethyl chloride (1.78 g, 8 mmol) was dissolved in methanol (20 ml) and added to a suspension of metmercazole (1.44 g, 8 mmol) in methanol (10 ml). The solution was then heated to reflux for 4 h, after-which the methanol was evaporated to give a residue that was dissolved in ethyl acetate (60 ml). (If the residue does not dissolve completely then add a small quantity of methanol). The solution was then washed with sodium hydroxide (1 g of NaOH in 20 ml of water) using a separating funnel – a white precipitate may appear but this will dissolve during shaking. After removal of the aqueous layer, the organic layer was washed with water (20 ml), dried (using anhydrous $MgSO_4$), then evaporated (under reduced pressure) to give crude pyrmetazole as a thick oily syrup (>90%) (on standing in ethyl acetate, pyrmetazole may precipitate as a white solid); ^{1}H NMR ($CDCl_3$) δ 2.27 (3H, s), 2.31 (3H, s), 3.79 (3H, s), 3.82 (3H, s), 4.35 (2H, s), 6.82 (1H, d), 7.03 (1H, s), 7.41 (1H, d), 8.26 (1H, s); ^{13}C NMR ($CDCl_3$) 11.3 (CH_3), 13.4 (CH_3), 35.0 (CH_2), 55.8 (CH_3), 60.1 (CH_3), 111.0 (CH), 125.5 (C), 126.4 (C), 148.3 (CH), 150.5 (C), 155.7 (C), 155.9 (C), 165.0 (C).

Appendix 2. The Medicinal Group Synthesis of Esomeprazole

Water (0.014 ml, 0.76 mmol), (*S*,*S*)-diethyl tartrate (0.31 g, 1.52 mmol) and titanium tetraisopropoxide (0.22 g, 0.76 mmol) were added to a suspension of crude pyrmetazole (0.25 g, 0.76 mmol; very sticky!) in ethyl acetate (15 ml) at 50 °C under a nitrogen atmosphere (to give a red-orange solution). The mixture was stirred for 1 h at 50 °C, the temperature was then adjusted to 30 °C and subsequently triethylamine (0.077 g, 0.76 mmol) and cumene hydroperoxide (80% in cumene, 0.29 g, 1.52 mmol) were added – the solution turns to a golden yellow colour and darkens as the reaction proceeds. The progress of the oxidation can be followed using TLC – pyrmetazole has an R_f value of 0.25 in a 3:1 mixture of ethyl acetate:dichloromethane (look for the disappearance of cumene hydroperoxide, R_f = 0.85). After 1 h at 30 °C, the solution was cooled to room temperature and ethyl acetate (15 ml) and water (30 ml) was added. After shaking in a separating funnel, the two layers were allowed to settle (this may take a few minutes) and the organic layer was separated and then dried (using anhydrous $MgSO_4$). Evaporation of the organic layer (under reduced pressure – *note the hazards of cumene hydroperoxide* in Appendix 4) affords the crude product as an oily brown liquid. Analysis of the ^{1}H NMR spectrum (in CD_3SOCD_3 or $CDCl_3$) of the crude product is used to determine the ratio of pyrmetazole:esomeprazole. The ^{1}H NMR spectrum of esomeprazole in CD_3SOCD_3 shows characteristic peaks at approx. δ 4.65 and 4.75 (2H, 2 x d) ppm.

Appendix 3. Work-up Procedure for the Optimised Conditions (starting from 0.25 g of pyrmetazole) to give Esomeprazole Sodium *(please discuss with AFP before starting)*

To the reaction mixture was added ethyl acetate (15 ml) and it was then extracted with aq. ammonium hydroxide (12.5% NH_3 in water, 30 ml) – the layers may take a while to separate. The aqueous phase was adjusted to pH 7 (as indicated by litmus paper) using ethanoic acid and then methyl isobutyl ketone (5 ml) was added. The mixture was separated and the aqueous layer extracted with an additional portion of methyl isobutyl ketone (5 mL). To the combined organic layers were added an aqueous solution of sodium hydroxide (0.17 g of NaOH in 0.17 ml of water) and acetonitrile (40 ml) and the mixture stirred for 0.5 h. The solution was concentrated (under reduced pressure) during which time esomeprazole sodium gradually precipitated as an off-white crystalline solid; $[\alpha]_D^{20}$ = +30.5 (c 0.01 g/mL, H_2O); ^{1}H NMR (DMSO-d_6) δ 2.15 (3H, s), 2.20 (3H, s), 3.68 (3H, s), 3.71 (3H, s), 4.41 and 4.58 (2H, AB-system, 2 x *J* = 12.9 Hz), 6.56 (1H, dd, *J* = 8.5 and 2.4 Hz), 7.00 (1H, d, *J* = 2.4 Hz), 7.34 (1H, d, *J* = 8.5 Hz) and 8.30 (1H, s).

Appendix 4. Safety Assessment

Each reaction must be assessed for hazards. This means that you must have noted the hazards (contained in this document or to be retrieved from the chemical literature) and also describe any special containment techniques you are going to use in the reaction to ensure that the risks are minimised. Wear lab specs, gloves and a lab coat when handling chemicals and work in a ventilated fumehood.

Table 1: Physical and hazard data for starting materials, reagents and product

Name and Data	Hazards
Pyrmethyl alcohol **(4-methoxy-3,5-dimethylpyridin-2-yl)methanol** mw 167.21, mp. 56.5-60.5 °C	Harmful if swallowed.
Thionyl chloride mw 118.97, d 1.63 g/mL, bp. 79 °C	Reacts violently with water (liberates HCl). Poison. May be fatal if inhaled. Causes severe burns. May cause serious eye damage. For spills, do *not* use water, absorb in vermiculite or dry sand and deposit in a sealed container. For disposal of small amounts, in a fume hood, cover the thionyl chloride with excess solid sodium carbonate or calcium carbonate (add slowly, portionwise). When the reaction has subsided, very slowly add the mixture to a large beaker of cold water – allow to stand for 24 h. Test the pH of the solution and neutralise if necessary. Wash the solution into the drain. $SOCl_2 + Na_2CO_3 \rightarrow SO_2 + 2NaCl + CO_2$
Pyrmethyl chloride **(2-chloromethyl-4-methoxy-3,5-dimethylpyridine hydrochloride)** mw 222.11, mp.128-131 °C	Harmful if swallowed. Causes burns.
Metmercazole **(5-methoxybenzimidazolethiol)** mw 180.23 mp. 261-263 °C	Harmful if swallowed. Irritating to eyes, respiratory system and skin. Causes burns.
Titanium tetraisopropoxide **(titanium(IV) isopropoxide)** mw 284.22 d 0.96 g/mL mp 14-17 °C	Decomposes in the presence of moisture. Flammable. General irritant.
(2*S*,3*S*)-(-)-Diethyl D-tartrate mw 206.19, d 1.205 g/mL, bp 162 °C/19 mm Hg	Irritant. Avoid contact with skin/eyes
Cumene hydroperoxide Technical grade (80%; contains 20% cumene) d 1.03 g/mL	Combustible. Heat sensitive - heating about 150 °C may cause an explosion. Irritant. Strong oxidant. Toxic if swallowed. Harmful if inhaled or absorbed through the skin. Respiratory irritant.
Diisopropylamine mw 101.19, d 0.722 g/mL b.p. 84 °C	Flammable. May react violently with strong acids or oxidizers. Air sensitive. Harmful if swallowed, inhaled or absorbed through the skin.
Triethylamine mw 101.2 d 0.73 g/mL b.p. 89 °C	Extremely flammable. Readily forms explosive mixtures with air (has a low flash point, so keep away from sources of ignition). Corrosive – causes burns. Harmful by ingestion, inhalation and if absorbed through the skin.
***N*,*N*-Diisopropylethylamine (Hunig's base)** mw 129.24, d 0.742 g/mL b.p. 127 °C	Highly flammable. Corrosive – causes burns. Very destructive of mucous membranes.
1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) mw 152.24, d 1.018 g/mL b.p. 80-83 °C/0.6 mm Hg	Harmful if swallowed. Corrosive – causes burns. Lachrymator. Mist or vapour is very irritating if inhaled and in contact with the eyes.

4-Dimethylaminopyridine mw 122.17, d 0.984 g/mL b.p. 191 °C	Toxic in contact with the skin. Toxic if swallowed. Skin, eye and respiratory irritant.
2,6-Lutidine mw 107.15, d 0.92 g/mL b.p. 143-145 °C	Flammable. Protect from moisture. Harmful if swallowed. May be harmful if absorbed through the skin or inhaled. Irritant.
Pyrmetazole mw 329.42	May cause sensitisation by skin contact. Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
Esomeprazole sodium mw 367.4	May cause sensitisation by skin contact. Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

Table 2: Physical and hazard data for solvents

General irritant means a chemical that irritates the skin, the eyes and the respiratory system. Toxic by all routes indicates that toxic effects could be elicited via ingestion, skin absorption and by inhalation. **MEL** is the Maximum Exposure Limit and **OES** is the Occupational Exposure Standard; in both cases the lower the value the greater the potential hazard. Wear lab specs, gloves and a lab coat when handling chemicals and work in a ventilated fumehood (f/c).

Solvent	Hazard	Special instructions
Acetone	Highly flammable. Irritant. Liquid may cause permanent eye damage. **OES** 750 ppm	Remove from any sources of ignition
Acetonitrile	Highly flammable. Harmful by all routes. **OES** 40 ppm	Dispense and use only in f/c Bench rotary evaporators may be used only if the distillate is immediately transferred into solvent waste
Ammonia	Flammable. Harmful by all routes. Causes burns. **OES** 25 ppm	Handle only in f/c
Chloroform (deuterated chloroform)	Harmful if swallowed. **OES** 2 ppm. Possible risk of irreversible effects. Danger of serious damage to health with prolonged exposure	Always use in f/c Dispose of residues immediately into the chlorinated waste
Dichloromethane	Possible risk of irreversible effects. **MEL** 100 ppm	Dispose of solvent in chlorinated solvent waste
Diethyl ether	Extremely flammable. **OES** 400 ppm. May form explosive peroxides in air	Remove from any sources of ignition
Dimethylformamide	Flammable General irritant. **OES** 10 ppm. May be absorbed through the skin	
Dimethyl sulfoxide	Combustible. Irritant. A low hazard but absorbed through skin (substances dissolved in DMSO may be quickly absorbed)	
Ethanol	Highly flammable. **OES** 1000 ppm	Remove from any sources of ignition
Ethyl acetate	Highly flammable. **OES** 400 ppm	Remove from any sources of ignition
Light petroleum ether	Highly flammable. Toxic by inhalation and if swallowed. General irritant. **OES** 100 ppm	Remove from any sources of ignition

Methanol	Highly flammable. Toxic by inhalation and if swallowed. **OES** 200 ppm	Remove from any sources of ignition
Methyl isobutyl ketone	Highly flammable. Irritant. Toxic by swallowing. **OES** 50 ppm	Remove from any sources of ignition
2-Methyltetrahydrofuran	Highly flammable. **OES** not known. May form explosive peroxides. Irritating to eyes and respiratory system	Remove from any sources of ignition
Propylene carbonate	Low flammability. **OES** not known. Very irritating to eyes.	Remove from any sources of ignition
Tetrahydrofuran	Highly flammable. **OES** 100 ppm. May form explosive peroxides. Irritating to eyes and respiratory system	Remove from any sources of ignition
Toluene	Highly flammable. Toxic by inhalation, ingestion or by absorption through skin. **OES** 50 ppm	Remove from any sources of ignition

Appendix 5. General Safety Information

What to do in the event of a fire alarm

Evacuation from the Teaching Laboratory should be via the shortest possible route, including the main entrance, and not just the fire escape, to assemble in the designated area. Apparatus should be closed down safely; e.g. sources of heat should be turned off.

First aid

The Department maintains a Team of Certificated First-Aiders, any of whom should be summoned to a medical emergency. Their names are posted at all First Aid points, adjacent to telephones, on the safety notice board and on the web.

Personal accident form

A personal accident form (completed by a demonstrator, in triplicate) must be completed for all injuries.

Emergency showers

Showers are provided in laboratories for use in emergencies when clothing, or the person, is dangerously contaminated with chemical substances. If the shower is used, then the laboratory must be closed and the practical class discontinued until the aftermath has been dealt with.

Disposal of waste

Winchesters are labelled for the collection of the following categories of waste solvent: flammable, aqueous and halogenated. Always empty rotary evaporator collection flasks after use; do not leave the task to the next user who may not know the contents. All waste syringe parts, i.e. cartridges and needles from either disposable plastic or reusable glass syringes and waste scalpel blades, must be collected in designated yellow containers. Glass waste from laboratories must be collected in the designated grey bins provided in each work-room. Although some chemical contamination of glass waste is permissible, e.g. residual droplets in used Pasteur pipettes, the grey collection bins must not be used for bottles and jars, which still contain significant amounts of waste substances.

Appendix 6.

COSHH Risk Assessment

Name:	
Date:	
Experiment:	
Lab book page number:	
Reaction:	
	Hazard notes:
Starting materials and reagents: (include risk phrases)	
Solvents: (include risk phrases)	
Expected products and by-products:	
Procedure and protective equipment to be used:	
Work-up and purification:	
Waste disposal:	

_____ _____

(Project supervisor signature) (Date)