Naproxen – Lecture 1

Project briefing and introduction to process chemistry

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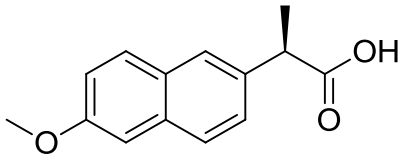
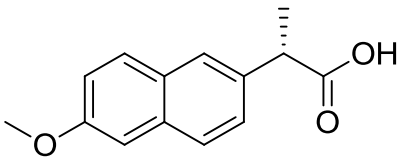
Brief

- You and your colleagues are a team of research and development chemists.
- You work for the process development section of a pharmaceutical company.
- Your teacher is your line manager.
- Our company produces (*S*)-naproxen, a non-steroidal anti-inflammatory drug.
- The (*S*)-enantiomer is active and (*R*) enantiomer is not.

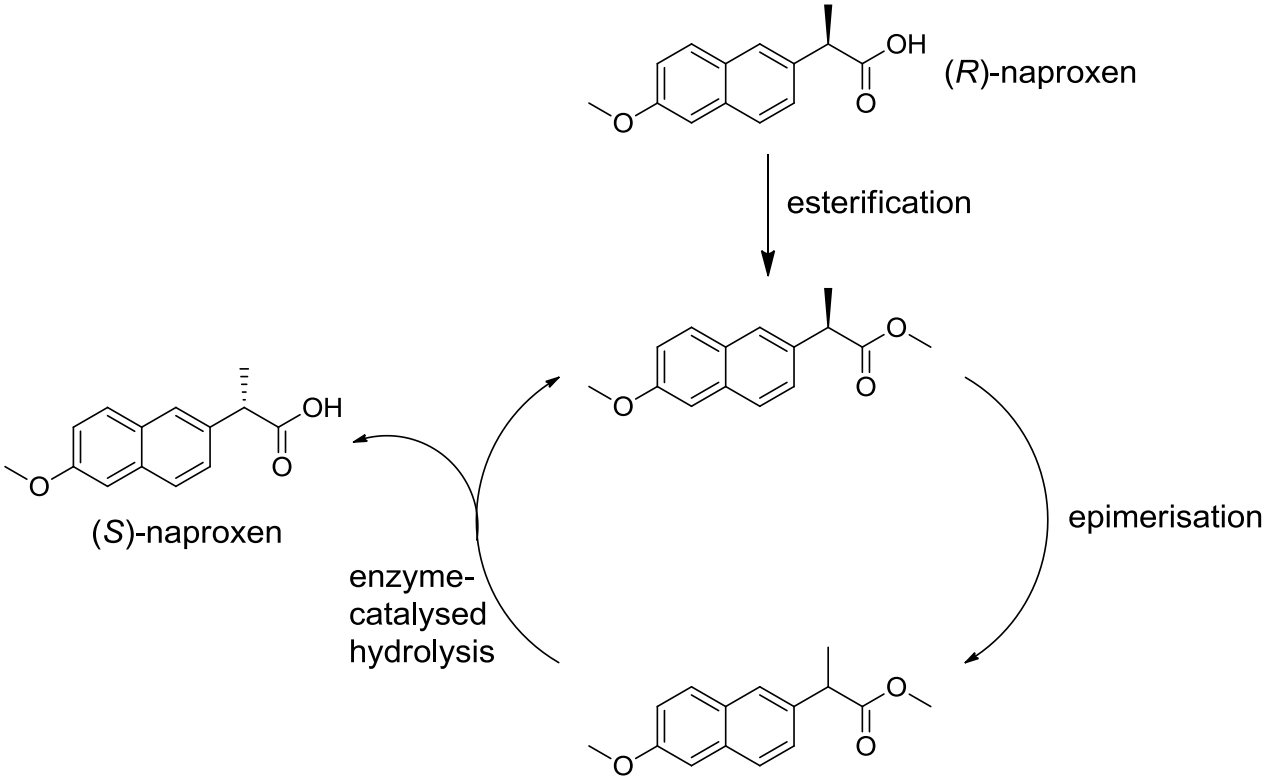


(*R*)-naproxen
inactive



(*S*)-naproxen
anti-inflammatory

Naproxen synthesis



Course overview

Week	Session	Length	Descriptions
1	Lecture 1	1 h	Introduction to the project. An introduction to the process chemistry examining the ways plant chemistry is different to lab chemistry
1	Workshop 1	1 h	Adapting laboratory scale reactions to pilot plant scale using the principles from lecture 1.
2	Lecture 2	1 h	Health and safety. Green chemistry considerations. Time and cost in process chemistry.
2	Workshop 2	1 h	Adapting laboratory scale reactions to pilot plant scale using the principles from lectures 1 and 2.
3 – 6	Laboratory work	Timetabled	Laboratory investigations to find the optimum conditions to recycle (*R*)-naproxen.
7	Group presentation	20 – 30 min	A group presentation to the manager and pilot plant team.
9 – 10	Written report due		Deadline for written report describing the project work and giving full experimental details for the lab work you carried out.

Assessment

- Project results 30%
- Laboratory report 40%
- Group presentation 20%
- Peer mark 10%

The key to good results is good team work, planning and communication

Meet Matt Tozer

- Matt Tozer is an industrial chemist

Process scale chemistry 1

Research labs

- Small scale (10 mg – 10 g)
- Make many different compounds
- Yields are unoptimised
- Expensive, inefficient or dangerous reagents can be used

Process scale chemistry 2

Chemical plants

- Large scale (tonnes)
- Only need to make one product
- Yields are highly optimised
- Processes must be safe, efficient and cost-effective

Efficient plant scale routes take a considerable amount of time and work to develop

Everything changes on scale

- Reactions can’t be done using giant round bottomed flasks, separating funnels and Buchner funnels.
- Glass and porcelain are too fragile.
- You can’t move reactors around.

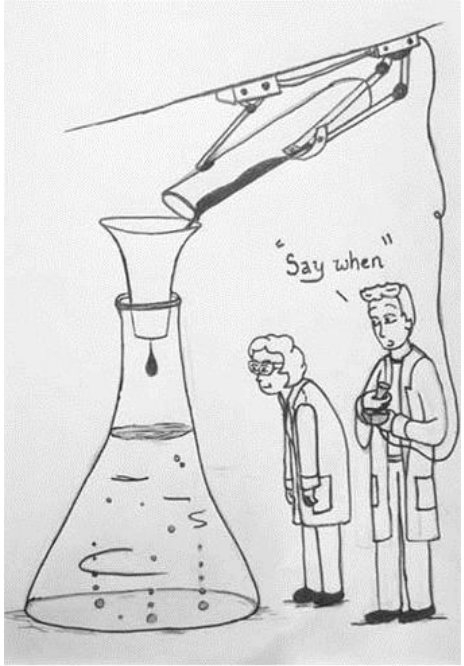


Image credit: Created by Ruth Narramore

Reaction vessels

Discovery scale

Image credit: photo by Martin McPhillie

Process research scale

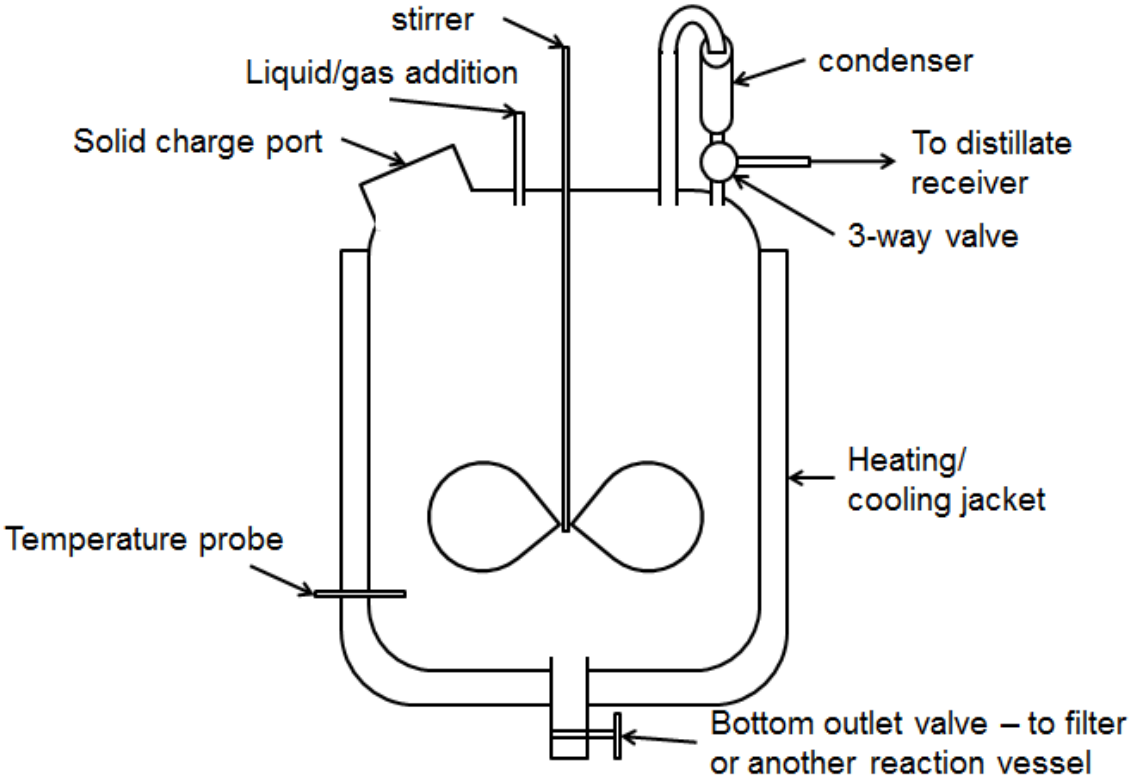
Image credit: Photo used with permission of John Blacker

Plant scale

Image credit: Released into public domain by Yuri Raysper

Plant vessel

Continuous stirred tank reactor



Addition of reagents

- Liquids added by pump, or residual vacuum
- Solids added through charge port
- Adding solids can be dangerous for workers
  - Powders could be inhaled
  - Could be splashed by liquids in vessel
- Specialist equipment needed to add air-sensitive or pyrophoric reagents

Heating and cooling

- Standard reactors: -15 – 140 °C
- Specialised vessels available for very cold or very hot reactions
- Heat transfer is slow – low surface area to volume ratio
- Because cooling is slow, exothermic reactions can “run away”

Work-up and transfer 1

Lab scale

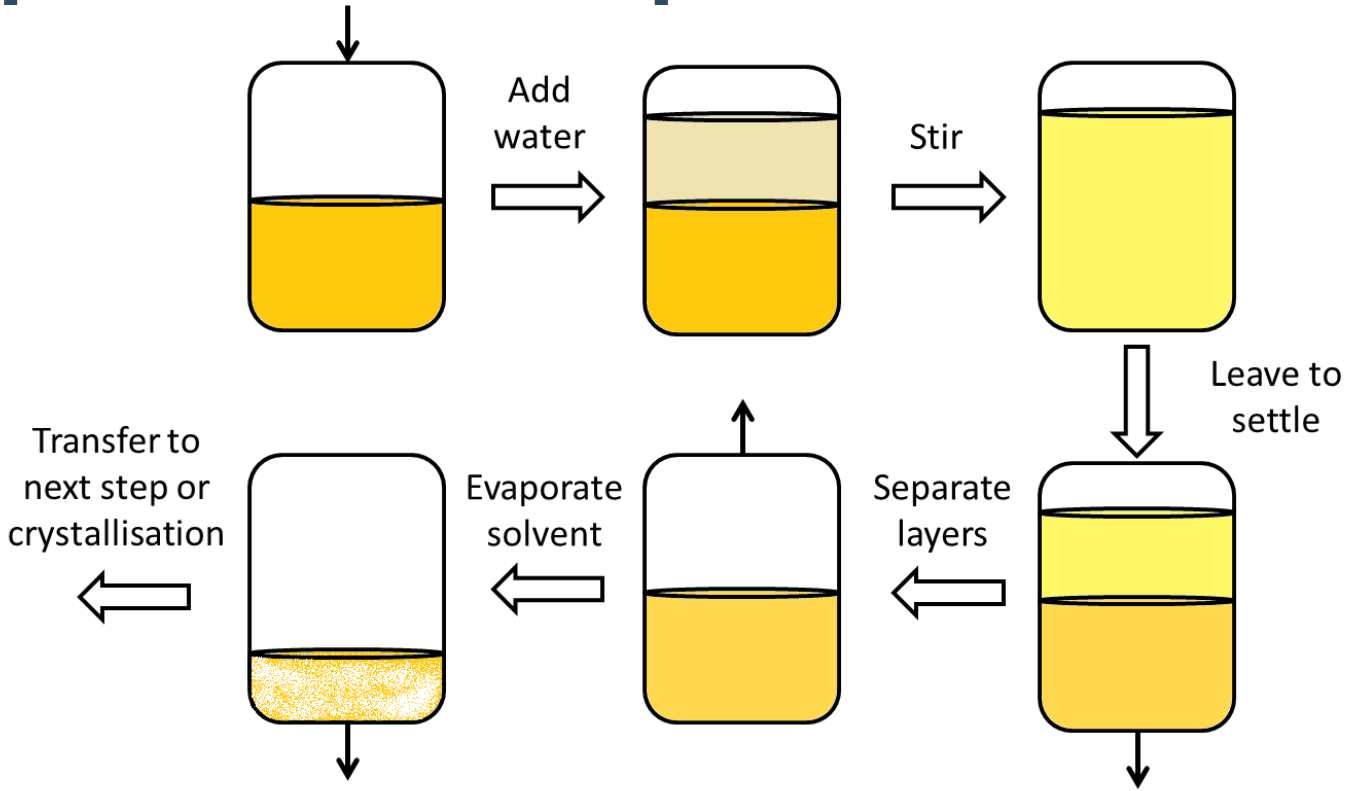
- Dilute/quench by addition of water
- Extract into organic solvent
- Dry over $MgSO_4$
- Concentrate using rotary evaporator
- Purify by recrystallisation

Work-up and transfer 2

Plant scale

- Dilute/quench by addition of water
- Extract into organic solvent
- Remove excess solvent by distillation
- Transfer slurry of product directly to next synthetic step
- Change solvent by distillation if necessary

Aqueous work-up



Purification

- Purification is usually saved for the last step in a synthetic route
- Reactions are optimised so that there are few impurities
- Most purifications are carried out by crystallisation.
- Filtration is carried out using specialist equipment and the product is dried in ovens
- Column chromatography can’t be done: too much solvent and silica is too dangerous.
- Distillation is possible for low MW oils.

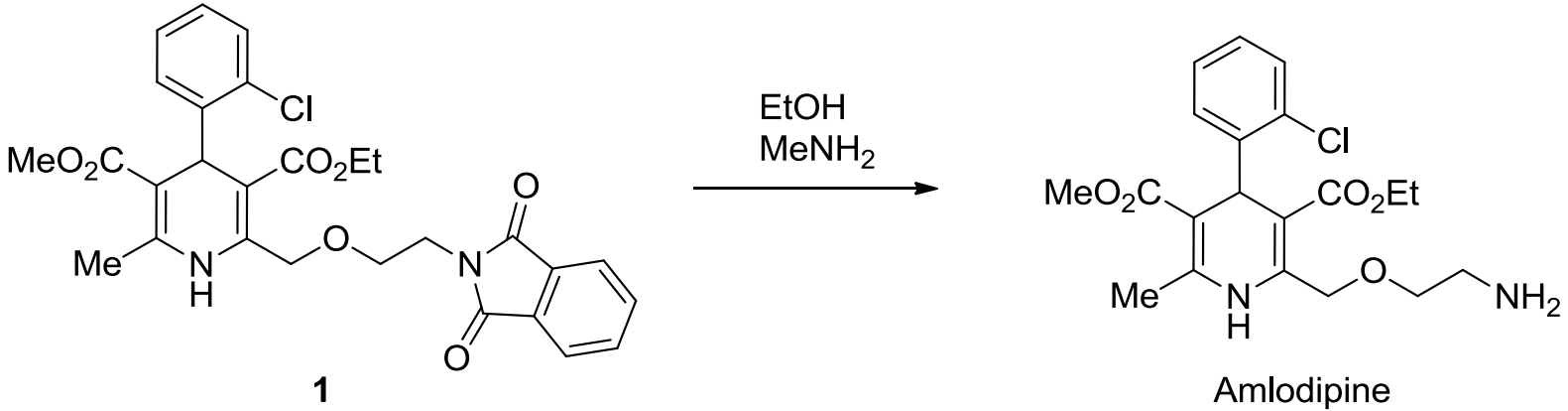
Questions and discussion

- Think about the lab techniques you've used in teaching labs.
- Which techniques would be easiest to use on a pilot plant?
- Are there any you couldn't use at all?
- Discuss your ideas with the people next to you.

Answers

- Easy: stirring, filtering, extraction, reflux, reactions under nitrogen, recrystallisation
- moderate: use of pyrophoric reagents and other particularly hazardous reagents, reactions at high pressure, cryogenic reactions
- Hard/impossible: rotary evaporation, column chromatography
- Any other suggestions?

Example process development



- Final step in the synthesis of blood pressure medication Amlodipine.
- First time in pilot plant yield was unexpectedly low.
- Distillation of $MeNH_2$ drives equilibrium back to starting material.

Improved route 1

Original pilot plant process

- Addition of EtOH and $MeNH_2$ to solution of intermediate 1
- Stirred until reaction complete
- Volume reduced by distillation
- Reaction quenched by addition of water
- Organic layers separated
- Concentrated to an oil
- Crystallisation and filtration

Improved route 2

New process solves this problem – No EtOH

- Add $MeNH_2$ to concentrated solution of intermediate 1
- Stirred until reaction complete
- Filter off product
- Crystallisation and filtration

Summary 1

- Large scale chemistry is carried out differently to lab chemistry
- Different techniques are used
- Reactions need to be planned in a lot more detail

Summary 2

Before the workshop – read the hand-out.

In the workshop you will be discussing the course outline and learning objectives

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