Naproxen – Lecture 2

Safety and environmental concerns in process chemistry

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Risk assessment

Hazards scale too

Video – importance of safety on process scale

Hazards and risk

- Hazards are features of the process that could cause harm if something went wrong:
  - Flammability of solvents
  - Toxicities of reagents
  - Reaction exotherms
  - Faulty equipment
  - Operator error
- The risk is determined by the likelihood that something will go wrong and the degree of harm it would cause

Mitigating risks 1

Here are some examples of hazards and approaches to mitigating the risks associated with them.

- Flammable solvents:
  - Use a less flammable solvent
  - Run the reaction at a lower temperature
  - Check the condenser is working before each reaction

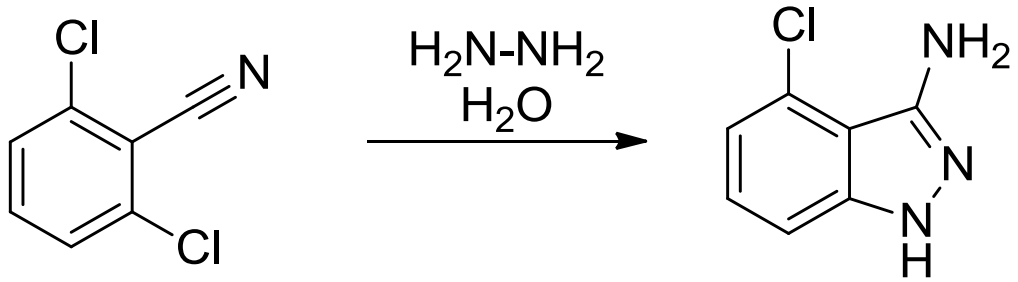
Mitigating risks 2

- Exothermic reactions:
  - Understand the thermodynamics of the process
  - Set safe operating temperatures and know what to do if the temperature begins to exceed the threshold
  - Have a contingency plan in the event of a run-away reaction

Worst case scenarios

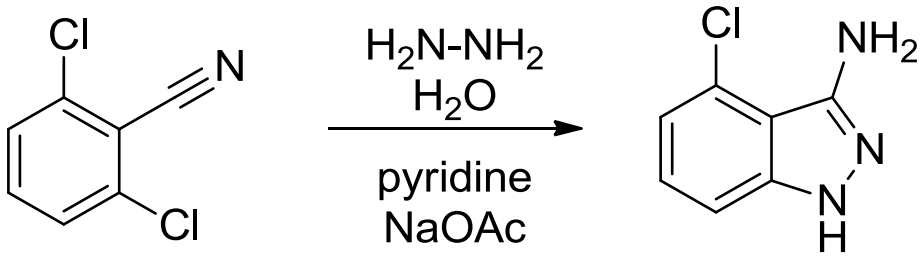
- Risk assessments should state clearly how to perform a procedure in a way that minimises the risks.
- It should also explain what to do if something goes wrong:
  - What if the cooling system fails
  - What if a pipe starts leaking when adding solvent
  - What if a worker inhales some of a reagent

Route design to minimise hazards 1



- This hydrazine condensation reaction has some serious hazards:
  - Hydrazine is toxic and highly flammable
  - Reaction is exothermic
  - Reaction produces HCl
  - Intermediate can react with HCl and then decompose exothermically at 70 °C

Route design to minimise hazards 2



- A thorough process safety review was conducted
- Adding base to the reaction was shown to prevent exotherm below 300 °C
- Many solvents and bases were screened to find the best combination: pyridine and sodium acetate
- Reaction proceeds quickly, so exposure of workers to hydrazine is minimised

Question and discussion

- There are risks involved in everyday activities too, but you are aware of the risks and minimise them without having to think about it.
- Make a list of the hazards involved in crossing the road and making a cup of tea. What actions do you take to minimise these risks?
- Discuss with the people next to you.

Answers 1

Making tea

- Hot water could cause burns: pour carefully and avoid skin contact. If you burn yourself then use whatever first aid is appropriate.
- Kettle could catch fire: look out for damage to the kettle, always fill above minimum water level. If kettle catches fire turn of the electricity and follow normal fire fighting procedures.
- Milk could be off: check milk before use. If not tea tastes sour, remake with fresh milk.

Answers 2

Crossing the road

- Could be hit by a car: look both ways, listen for engines, use pedestrian crossing if available. If an accident does occur, call for help and dial 999.

Green chemistry 1

Environmental impact of reactions must be considered in advance for several reasons:

- Ethical:
  - Accidental leakage of chemical waste can cause serious harm
  - Health of workers and the general public
  - Energy usage contributes to global warming
  - Chemical precursors often come from fossil fuels

Green chemistry 2

- Financial:
  - Disposal of hazardous waste is expensive
  - Energy costs of a process can be considerable

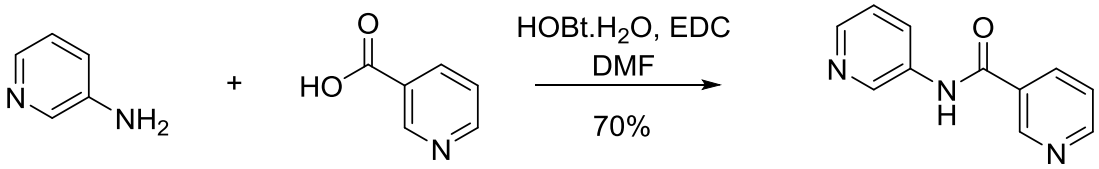
- Legal:
  - strict laws in place to protect the environment

Key considerations

- Reactions should be carried out efficiently
- Chlorinated solvents should be avoided
- Energy usage should be minimised
- Use renewably sourced materials where possible
- Synthetic routes should be as simple as possible
- Catalysis should be used wherever possible
- Reagents with severe hazards should be avoided

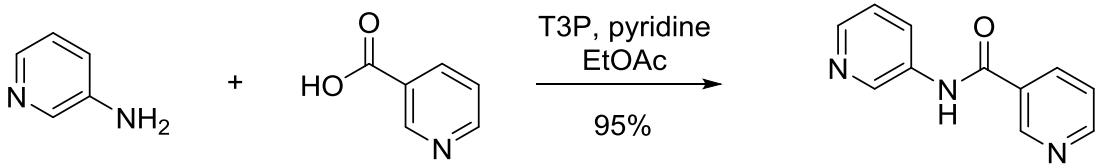
Discussion and questions

Below are two different procedures for carrying out an amide coupling. Which is greener and why?



purify by column chromatography

HOBt - explosive when dry, highly flammable; EDC - irritant; DMF - teratogenic, flammable, harmful



Purify by crystallisation

T3P - corrosive; pyridine- irritant, flammable; EtOAc - highly flammable, irritant

Answers

- The second route is greener.
- T3P is less hazardous than HOBt and EDC
- Ethyl acetate is a greener solvent than DMF
- Second route is higher yielding
- Better to recrystallise than column

Costs 1

2 categories

- **Variable costs** – change depending on the reactions you are carrying out:
  - Costs of raw materials
  - Heating and cooling of reaction vessels
  - Disposal of waste

Costs 2

- **Fixed costs** – don’t depend on which reactions are being carried out:
  - Building maintenance
  - Wages for plant workers
  - Insurance

Summary 1

- Risk assessment is critical on large scale
- The environmental impact of processes must be considered
- The costs of different synthetic routes must be considered

Summary 2

Before the workshop – Read about the steps you will have to optimise.

In the workshop you will be discussing different reaction conditions

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