Recycling the undesired enantiomer of naproxen

A context/problem-based learning (C/PBL) resource

Workshop 2 – Answers

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Part 1

If you were a process chemist tasked with developing this reaction to use in a pilot plant why would you investigate alternatives to DMF, DCM and sodium hydride?

DMF is highly toxic and teratogenic. The risk of harming the plant workers if they are exposed is too high and it is very expensive and bad for the environment

DCM is bad from the environment, there are strict controls on the amount of chlorinated solvent you can dispose of, so it is very expensive to dispose of after the reaction.

Sodium hydride is air sensitive and flammable. If you can find a more stable base that will do the reaction as effectively that would be preferred. However, other strong bases may be just as hazardous, so some investigation is needed to determine what the best option is.

Which aspects of the reaction would you need to understand in more detail if you wanted to run it safely on a large scale?

Exotherms

Adding a reagent dropwise and checking the temperature doesn't exceed a specific temperature implies that the reaction is likely to present a high risk of thermal runaway.

Reactions like this can be done on scale, but a lot of work needs to be done in advance to test the limits of the system. Process chemists will need to carry out reactions to find out the limits of the system such as.

- What happens if you go 45 °C?
- Should you add at a constant rate, or do you need to slow down as you go along?
- What happens if you add it all at once?
- If adding it all at once would cause a serious accident, then what will you do to prevent that from happening?

In the second step you need to know exactly how much bromobutane to add and when, and know exactly what temperature and what rate of bromobutane addition might cause an exotherm. Understand what heating will do to the reaction.

Monitoring reaction completion

How do you tell if the formation of acetoacetate is complete: you can't see into the vessel to know if it's all dissolved. Can monitor volume of gas being produced, but this might not be precise enough. If you understand the process well enough you should know exactly when it will be dissolved without having to monitor it.

Taking a sample to check with litmus paper: opening a reaction to take out a sample is to be avoided instead work out in advance exactly how much time is needed for the pH to become neutral.

Work-up considerations

Can't dry with $MgSO_4$ – need to determine whether residual water will have a negative effect on the next step, can it be removed in any purification step?

Can't evaporate to dryness would need to transfer a concentrated solution to the next step

Distillation is possible, but requires specialist equipment.

Part 2

Students should realise that they cannot begin testing conditions for the enolisation and hydrolysis until they have made enough material in the proceeding steps and so plan for sufficient material to be made as early as possible in the project.

They should give a list of a few sets of conditions they want to try first for each of the steps that need optimising. They should then discuss how they will analyse their reactions efficiently so that they can refine their conditions.

They should decide which reactions they are each going to carry out during the first week and how they will decide which follow up reactions to do.