Topic 3 Summary Questions

1. **You are running the SN2 substitution below – a dipolar aprotic solvent is found to give maximum rate and yield – what would be a good choice and why?**

Answer: should ideally pick acetonitrile as the best option for this solvent class as most of the others have significant regulatory constraints (and are due to become more regulated in future) or other have issues due to, for example, waste treatment. NMP was also a popular choice until several years ago as it was less volatile than DMF or DMA, but has now been added to the REACH SVHC list (Substances of Very High Concern) (http://echa.europa.eu/candidate-list-table). DMSO may also be selected as it is not currently subject to regulatory constraints (at time of writing), however this has potential issues for an S_N2 reaction due to its ability to act as a nucleophile itself. Acetone could be considered as it is a popular medium for S_N2 reactions, but it is worth noting that it is not a dipolar aprotic solvent as was requested in the question.

2. **You have a reaction product in heptane – you can isolate by distilling the solvent off, or extracting into water and crystallising – which is the best option?**

Answer: The main issue with heptane is its environmental impact in water making the extraction and crystallisation option problematic, as you will be left with an aqueous waste stream contaminated with the solvent that will be difficult to treat following product isolation. Also, the distillation option would potentially allow the solvent to be recycled into the process BUT required purity of product may not allow simple distillation without a recrystallistation so this would need further investigation. Overall, any answer should consider the pros and cons of BOTH methods.

3. **The first route to Sildenafil citrate (Viagra™) used 1,350 Kg of dichloromethane/methylene chloride per Kg of product. Discuss the merits or otherwise of using this solvent in large volume production.**

The answer should state that the advantages of DCM are that it is cheap, readily available and also a good process solvent. The drawbacks, however should include:

- *Highly regulated solvent e.g. SED, WFD*
- *High volatility, difficult to reduce emissions to air*

- *Worker safety – may cause cancer*
- *Problematic disposal of waste solvent streams*

4. **Trifluorotoluene or 2-methyltetrahydrofuran have been suggested as replacements for methylene chloride. Discuss the relative merits of these solvents vs. methylene chloride.**

The answer should note that some data gaps with "new" solvents exist and should consider the parameters that solvents are typically assessed on – ideally with reference to one of the solvent guides presented in Topic 2. Trifluorotoluene – main advantage is lower volatility, however it is still an issue if aqueous streams are contaminated. 2-Me THF has a better environmental profile and is also manufactured from a renewable feedstock, however it has some process safety issues that need to be understood (e.g. peroxide formation).

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