From the Lab to the Factory – Considerations for Synthetic Product Development

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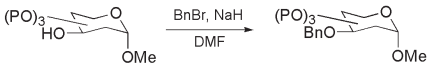
Introduction

When presenting their work, many synthetic chemists will comment on a synthesis being readily scalable. However, the product development scientist often makes drastic changes to the protocols when starting to make the process suitable for scale.[1] These changes can be due to a number of factors, but generally they fall under three main banners of safety, manufacturing considerations and environmental impact.

This article does not attempt to give an in-depth discussion of all of the factors that are considered in the development process. Rather, it attempts to highlight some of the issues that we have learned at NZP[2] through taking processes from laboratory through pilot plant and on to manufacturing scale. Naturally, many issues are specific to a given organization such that no chemist or engineer outside of that institution can design a process that takes these into account. However, there are some generic considerations for which a greater awareness at bench scale will flow through development and make for easier scale up.

Safety

Safety is (or should be) the foremost consideration when taking any process beyond bench scale. Inevitably, a chemist who has worked in a synthesis laboratory will have stories of fires, explosions, over pressurizations, and/or other incidents that have caused damage to equipment and/or people. These are accidents that occur on an operating scale from a few milliliters to, at most, a few liters. When tens, hundreds or thousands of litres of chemicals are involved the effects of an accident are potentially much worse as there is the potential to cause death and ruin factories; for businesses a major accident can be a company ending event.[3] The term *process safety* is very broad and the present discussion covers only those aspects that are relevant to the synthetic chemist - the engineering aspects of process safety are highly complex and likely of limited interest to the bench chemist. However, when an industrial chemist thinks of safety, both chemical and processing considerations do need to be taken into account. For instance: what chemicals are to be used and how are they best safely handled? What is happening to them in the reactor? What by-products are being formed? Is the reaction exothermic and, if so, can the equipment cope with this? How will the reaction be quenched and/or made safe? What will be in the waste streams? How will these be made safe and disposed of? How will an emergency be dealt with? While the answers to these questions could fill many pages and papers, an overview of the factors that must be taken into account when considering safety are illustrated by a suitable and appropriate example.



Scheme 1. Benzyl protection of a sugar

Benzyl protection of a hydroxyl group is a well used reaction, particularly in carbohydrate chemistry. This is usually carried out using benzyl bromide and sodium hydride with dimethylformamide (DMF) as a solvent (Scheme 1).[4] While this is a very useful and high yielding synthetic reaction, it is not optimal from a safety stand point. Benzyl bromide is a severe lachrymator and highly corrosive. DMF is a high boiling point solvent with significant handling issues. As a solvent it does not have concerning acute toxicity, but it does have chronic health issues. It targets the liver, kidney and central nervous system, and it is also a reproductive effector. The most concerning reagent in the benzylation mixture is sodium hydride. When used with DMF, NaH is especially prone to spontaneous ignition - to the extent that fires on scale up led to investigations into the optimal method of extinguishing them.[5]

The best way to consider such hazards such is to use the OSH mantra of *eliminate*, *isolate*, *minimize*, in that order. In the present example, sodium hydride is the reagent of greatest concern and should be replaced. Even a quick literature search provides a lengthy list of alternate reagents that have been used in this reaction.[4] A specific replacement used in collaboration by NZP and IRL Glycosyn was potassium hydroxide flakes. This triggered replacement of the DMF by acetonitrile which, while having a slightly heightened acute toxicity, is much easier to handle on scale and does not have the health concerns associated with DMF.

The last chemical to receive attention in the benzylation is benzyl bromide and this proved the most difficult to replace. Other benzyl halides such as the chloride are arguably less of a hazard than benzyl bromide, although anyone who has ever worked with them will attest to the fact that even the slightest exposure is very unpleasant. The removal of benzyl bromide from the reaction is possible only by re-designing the synthesis. If the molecule is being made as a starting block for further synthesis, particularly for an external customer, this may not be practical. An alternative is to include a quench at the end of the main reaction. The idea behind this is to convert any residual benzyl bromide (or for that matter any other hazardous reagent), into a less hazardous product thereby allowing safer handling of the final product mixture and the process wastes.

There has to be a limit to which the elimination of hazardous chemicals from a process can proceed. Was one to attempt to remove everything hazardous then there would

be no process left to work on. Thus *isolation* and *minimization* now take precedent. To isolate an operator from the chemical process requires engineering solutions that are not discussed here. The concept of minimization involves reducing to acceptable levels the impact of a chemical hazard on the operator; usually this is achieved by the use of personal protective equipment (PPE). Basic chemical safety often was not covered well in tertiary training courses, although the increased emphasis of occupational safety and health (OSH) standards is changing this. People working with chemicals need to know how to find the relevant safety and toxicity information to ensure their own safety and those in the environs, and this applies to laboratories as much as processing plants. Copies of material safety data sheets (MSDS) for all reagents are now required in all laboratories but people must know where they are kept and refer to them regularly. Where an MSDS sheet is not available for an intermediate or product expected from a given process then relevant assessment must be made prior to any experimentation commencing. The information must then be supplemented prior to any processing being undertaken, *e.g.* use of glove compatibility charts. It is well known that nitrile gloves generally offer more protection than latex but for some solvents latex is the better option. The Environmental Risk Management Authority of NZ (ERMA) website can be consulted for the hazardous substances and new organisms (HSNO) classifications for approved chemicals[6] while the OSH website contains information on the NZ workplace exposure standards.[7]

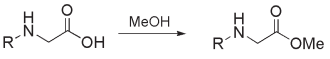
Finally, when discussing the safety of a process, thermodynamics considerations are important especially when exothermic reactions are involved. Calorimetry can provide much useful information although it must be applied to the process as a whole, including all reagent additions and quench reactions. Once this information is gathered it needs to be applied to the specific vessels in which the process is to be carried out. Each reactor has its own characteristic heat transfer properties and each heater/cooler unit has different capacity for dissipating changes in internal reaction temperature. This information will be used by a process engineer or technician to ensure that no more material is loaded into the system via header tanks or transfer vessels than the reaction system can cope safely with in the event of a catastrophic failure.

The present discussion is far from exhaustive and the reader is directed to the American Institute of Chemical Engineers quarterly journal *Process Safety Progress* as a valuable source of information.

Manufacturing considerations

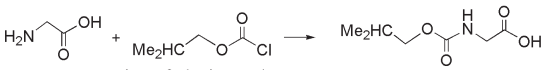
Manufacturing considerations cover issues specific to a given facility such as the equipment involved, and many can only be worked on in-house by people who know the equipment well. These can include the material the vessels and equipment are made from, the practicalities of loading and unloading the reactor, and how material is transferred around the plant. The synthetic chemist should consider scale up factors when designing a synthesis. Thus one should avoid reagents that cannot be used under certain circumstances, *e.g.* halogenated acids attack many grades of stainless steel while strongly basic hydroxide solutions etch glass.

Process-specific considerations must also be taken into account and these are best more fully investigated in the laboratory prior to moving into development. The critical points in a process must be identified and tested. For example, if an acidic product is being precipitated by adjustment to pH 3 what will happen if the pH is accidentally adjusted to pH 2.5, or pH 2 or pH 4? At what point in a process is the product sufficiently stable to be left overnight? When must operations be carried out within a specified time, temperature or other range? For example, if a process uses a glycine conjugate where, due to product solubility, the conjugate is taken up in methanol but recovered by precipitation from a less polar solvent, will the free glycine react with methanol and form its methyl ester (Scheme 2)? As methyl ester formation is temperature dependent its presence can be eliminated by temperature control. Were this not the case, other options such as converting the free acid into the sodium salt would need to be considered.



Scheme 2. Methylation of a glycine residue

While side reactions of the main product are often discussed in the literature, unwanted reactions between reagents are often overlooked. The formation of the glycine conjugate discussed above uses isobutyl (2-methyl-1-propyl) chloroformate in the conjugation step. This is because this compound is more stable and more user friendly than the more common laboratory reagent, ethyl chloroformate, including its added stability in water. Early conjugations employing ethyl chloroformate could result in quenching of the excess simply by washing with water. In contrast, isobutyl chloroformate persists through multiple water washings and goes on to react subsequently with amino acid forming a carbamate by-product (Scheme 3). To circumvent this, the carbamate either needs to be removed by purification or an alternate quench step included so as to ensure that there is no chloroformate remaining for reaction with the amino acid.



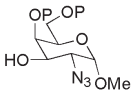
Scheme 3. Formation of glycine carbamate

Generally, optimization of a reaction is one of the quicker parts of the development process since much of the work is carried out in the research laboratory prior to transfer to the development chemist. However, product purification is usually a different story. For most synthetic chemists the focus is on how best to make a given compound. Purification is easy - pass it through a column. While flash chromatography is a very useful technique, it has significant problems as the scale increases. Industrially, a number of systems are available for large scale chromatography, many with pre-packed cartridges allowing for safer working systems. However, these add significantly to the cost. For fine chemicals, particularly those early in commercial life, this cost can be justified. For commodity products or chemicals for which there is significant price

competition, chromatography is simply too expensive. This often leads to a significant amount of development work on chemical purification.

The best place to start working on improving product purity is by examining the reaction itself. While reactions are often worked on in a laboratory to optimize yield, process development requires a trade off between what is economic in terms of reagents and purification. Thus, while precious metal-containing reagents may be fine for laboratory use thay are too expensive for commercial production. Other reagents, such as those containing tin oxides, are very difficult to remove from the product and may be prohibited when manufacture is for human end users. Side reactions, such as the chloroformate example discussed above, need to be identified so the process can be modified to eliminate them.

The techniques used to purify a given chemical will depend on the purity levels targeted. Many common laboratory techniques such as bi-phasic washings and crystallizations are far more effective than chemists often give them credit for. However, this requires that the product and its impurities have appropriate solubilities that allow for efficient separation in an economically small number of washings. It is often assumed that organic molecules, such as fully protected sugars, are insoluble in water, but this is not always the case and it should always be checked. Knowing the solubility of both the products and impurities can often lead to greatly simplified purification techniques. An example of this is an azide transfer reaction worked on by NZP and Glycosyn. The product **1** was a protected sugar with an azide at C-2, the major impurity was an organic amide formed during the reaction. In laboratory work this sugar had been purified by chromatography but attempts to crystallize it from a variety of solvents did not remove the amide impurity; the amide proved to be soluble in water while the sugar was not! This led to a purification protocol in which the sugar was precipitated from organic solvent by the addition of water allowing for recovery in greater than 99% purity.



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Environmental impact

Much of the discussion concerning the environmental impact of a process is covered when safety and manufacturing considerations are discussed. Despite this, it is always useful to look at a process from a purely environmental angle. Can the solvent volumes be reduced? Can any environmentally dangerous chemicals be replaced? What is going to happen to the waste streams and will they need treatment? How is the process going to be contained? What is going to be released? How are any gases produced going to be scrubbed, and how do we tell when the scrubber medium requires changing? How do we contain all chemicals in the event of fire? A spill? Another emergency situation? To answer these questions effectively requires engineered solutions that are specific to the given site and beyond the scope of this article.

Conclusion

When a process is given over to a development chemist for scale up there has often been much work done in the laboratory to optimize the product yield. However, this does not mean that the process is ready for scale up. The development chemist will often need to carry out extensive research and make significant changes to the laboratory process before it can be safely scaled for the equipment available at the particular facility. This brief discussion has covered some of the concerns of the development chemist when assessing a new process. While it provides a brief introduction to the area, examples of the scale up improvements made to synthetic pathways can be found in the ACS journal *Organic Process Research and Development*.

References & Notes

1. For examples see: Fuenfschilling, P.C.; Hoehn, P.; Mutz, J.-P. *Org. Process Res. Dev.* **2007**, *11*, 13-18; Saenz, J.: Mitchell, M.: Bahmanyar, S.; Stankovic, N. *et al*. *Org. Process Res. Dev*. **2007**, 30-38; Lee, H.W.; Ahn, J.B.; Kang, S.K.; Ahn, S.K.; Ha, D.C. *Org. Process Res. Dev*. **2007**, 190-199; Henegar, K.E.; Ball, C.T.; Horvath, C.M.; Maisto, K.D.; Mancini, S.E. *Org. Process Res. Dev*. **2007**, 346-353.
2. See: www.nzpsynthesis.com
3. For discussions of recent accidents in the US chemical industry, see: http://www.csb.gov. (accessed 7 May 2008).
4. Greene, T.W.; Wuts, P.G.M. *Protective groups in organic synthesis*, John Wiley & Sons: Davers MA, 3rd Edn. 1999.
5. Fluegeman, C.; Hilton, T.; Moder, K.P.; Stankovich, R. *Proc. Safety Prog*. **2005**, *24*, 86-90.
6. See: www.ermanz.govt.nz (accessed 7 May 2008).
7. See: www.osh.dol.govt.nz/order/catalogue/329.shtml (accessed 7 May 2008).