CatSci
BEYOND PROCESS CHEMISTRY

**Technical Piece**

# GUILTY BY-STANDERS: SOLVENTS IN SCALE-UP #2

*Not always as innocent as they are assumed*

## INTRODUCTION

Active Pharmaceutical Intermediates (APIs) are especially vulnerable to the formation of impurities derived from reactions with solvents or solvent components. This because APIs are typically densely functionalised small organic molecules bristling with activity which provides ample opportunity for them to react – even with solvents. As their complexity and molecular weight increases, the solubility of APIs or their immediate precursors tends to decrease, as does the degree of differentiation between them and any related impurities. Without recourse to chromatography, separating closely related structures with similar physical properties becomes a significant challenge, even more so when any impurities may need to be controlled to <0.1%.

## WHAT'S UP WITH SOLVENTS?

The primary purpose of a solvent is to solubilise materials, allowing reaction components to mix in the solution phase. It makes for a more reliable and robust process if all the key reaction components fully dissolve in a solvent; and for an even better one if either the product or by-products do not, such that they can be easily separated by crystallisation. These factors are especially important for scale-up.

Despite being otherwise potentially attractive, certain solvents are well known to be incompatible with certain materials or reaction classes which precludes their use. For example:

- protic solvents, such as water, alcohols and acids, will quench organo-metallic reactions
- esters and ketones will react with Grignard and organometallics reagents
- ketones may enolise under acidic or basic conditions (acetone self-condenses to mesityl oxide)
- aromatic solvents will undergo Friedel-Crafts reactions.

However, even allowing for the restrictions already noted, it is often over-looked that solvents should be inert. This is less often the case than might be supposed – and it is often during the scale-up of processes that this is revealed. The reasons for this may be due to the following factors:

- large-scale processes are usually much more concentrated than small-scale ones; if the substrate can react with any component to form an impurity, it will form more quickly and at higher levels due to increased concentration
- unit operations in large scale processes take much longer than in small scale ones, including heating and cooling cycles: this exposes the reaction components to longer periods of heating at higher concentrations, during which the solvent may also react; heating during distillations especially exacerbates the situation
- on small scale, despite the use of vastly higher solvent volumes, purification is often performed by chromatography which is very efficient at removing impurities: consequently, low level impurities from reactions with solvents may not be observed until chromatography is no longer used later in development for scale-up
- And lastly, as projects progress and manufacturing increases in scale, greater scrutiny is applied to product quality; this is especially true of APIs in the pharmaceutical industry, for which control of impurities is critical for patient safety: closer observation at this stage often reveals that the solvent has not been such an innocent by-stander.

It doesn't help of course that solvent is almost inevitably the largest single component in any given reaction.

## REACTION WITH SOLVENTS

Some reactions of solvents with intermediates or APIs are obvious. For example, if an ester is present in the molecule for which a different **alcohol** is used as the reaction solvent, partial or full trans-esterification might result under either acidic or basic conditions. This is easily avoided by choosing an alcoholic solvent consistent with the ester functionality; and less easily by ensuring no catalysing pH changes occur. However, even with a consistent alcoholic solvent, if traces of other alcohols are present as minor impurities (even within the solvent specification), an un-anticipated trans-esterification might still result.

Esters are often hydrolysed to form acids or their salts, so a degree of trans-esterification may not matter substantially (allowing for added analytical complexity). But **ester** solvents are prone to hydrolysis, especially ethyl acetate during pH changes on work-up (one reason why the more stable iPrOAc and nBuOAc esters are preferred on scale). If a bulk ester solvent suffers partial hydrolysis, both the alcohol and acetic acid are generated which may then result in trans-esterified and acetylated (M+42) impurities.

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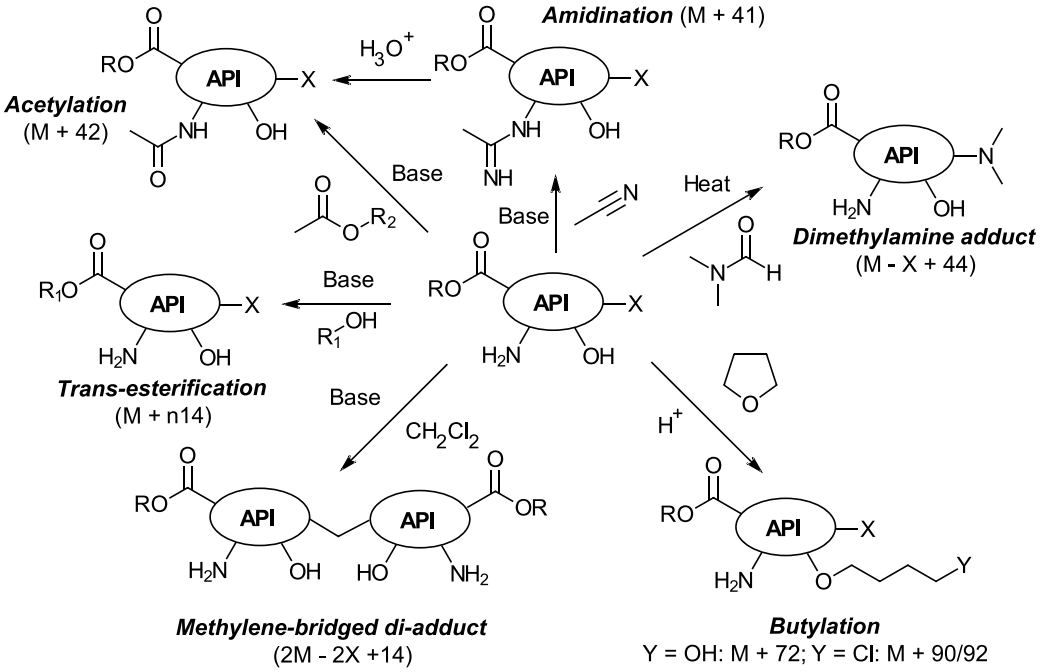


In a similar fashion, **acetonitrile** and other nitriles may also be hydrolysed under acidic or basic conditions, often on work-up, resulting in amidine by-products for example if nitrogen nucleophiles are present. Depending on their stability, hydrolysis may also result in acetylated impurities again (M+42).

Widely used **THF** is prone to ring-opening under highly acidic conditions which can result in capture of a butylated alcohol side chain (M+72), or the butyl chloride (M+91/93), often seen with acidic chloride sources. 2-Methyl THF and CPME are more robust, although like MTBE, they can be demethylated; however, these tend not to result in product-related impurities that are so troublesome to remove.

Chlorinated solvents, for which acetonitrile and THF have often substituted in recent years, were preferred for highly acidic reaction mixtures and reagents because they were stable to such conditions. They are now largely banned, with the exception of the still undesirable **dichloromethane**. Whilst robust to acidic conditions, under basic conditions it has been known to generate methylene bridged adducts (2M+14). Such impurities are often difficult to identify other than by mass spectra, because they often have similar LC retentions times and near identical NMR spectra to the parent molecule (the methylene bridge being easily over-looked). They also usually have poor solubilities, making them difficult to remove.

A last example is **DMF**, which is known to decompose on heating with temperature and time, generating low levels of $Me_2NH$ and CO. Intermediates and APIs with displaceable functionalities may react with the $Me_2NH$ to generate closely related amine impurities.

Reactions with solvents resulting in unexpected impurities may also occur due to the presence of materials that are expected in them, such as stabilisers like BHT or chloroform; and others which are not due to contamination. Of course, unexpected contamination may occur with any reactant or reagent, but quality assurance will be more critical with solvents because they form the bulk reaction medium.

## SUMMARY

Solvents may provide a source of impurities from both unexpected contaminants and minor components, but also from unexpected reactions directly with reaction components – they are often not the innocent by-standers they are wished or assumed to be. Close attention to solvents in both process development and analysis is required to avoid unpleasant surprises during the scale-up of APIs.

*Want to find out more?*
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