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Editorial

How Safe Are Your Reactions?

We recently had to reject a paper submitted to the journal on the grounds that the referee and I felt the process was unsafe. The chosen solvent for the chemistry was diisopropyl ether (DIPE), and there was no indication as to whether alternative solvents had been tried. Of all the ether solvents, DIPE would have been my last choice since it readily peroxidises. There is a long history of violent explosions involving peroxidised DIPE, with initiation of the explosion simply by disturbing a drum, unscrewing a bottle cap, or accidental impact.[1] The ether has two hydrogen atoms that are very susceptible to oxidation after a few hours exposure to air. Peroxidation is accelerated if the solvent is wet![2] Often these peroxygen compounds and their decomposition products, trimeric acetone peroxide, separate from solution, thus remaining in the vessel. Once the solvent has been removed by decantation, the dry, solid residue can easily explode.

Of course DIPE supplied in bulk or laboratory quantities is stabilised by the addition of phenolic compounds, other antioxidants, or even the presence of bases such as diethylenetriamine, triethylenetetramine, or tetraethylenepentamine. The problem is that the levels of stabiliser are usually below 50 ppm so that, once the container is opened, the stabiliser can be depleted. This is why most Material Safety Data Sheets (MSDS) recommend that containers, once opened, should be checked for peroxide content every 3 months or sooner if possible. The recommendation is that, if the container now contains peroxides, it should be disposed of in a safe manner. However, the MSDS may not indicate what the safe procedure is! The 6th edition of *Bretherick's Handbook of Reactive Chemical Hazards* gives references to procedures for safe disposal in a remote location by controlled explosion.

During any chemical reaction, and particularly during the work-up, where aqueous acid or base extractions may be involved, it is easy to remove the stabilisers. Many procedures then follow this with an evaporation to dryness (as did the submitted paper). This is a procedure you will find difficult to repeat, since you may have perished during the explosion resulting from the first evaporation.

An MSDS for DIPE states "Do not distill to dryness—leave at least 10% bottoms". It also states "containers of this material may be hazardous when empty" since they retain residues which may be peroxides.

Many chemical and pharmaceutical companies (including both companies I previously worked for) adhere to the principles of inherent safety propounded by Trevor Kletz and avoid using DIPE as a solvent; I strongly recommend this approach since there are many alternatives which should suffice. Ethers with a methyl group and/or a *tert*-alkyl group are usually the least susceptible to peroxidation, so that if an ethereal solvent must be used they are the preferred choice.

This final issue of *Organic Process Research & Development* in 2004 contains the annual safety supplement, Safety of Chemical Processes, and I thank David am Ende (Pfizer) and Paul Vogt (Albany Molecular) for their contributions to this feature. I must also thank Dave Lathbury (AstraZeneca) for suggesting the special issue on software and for his help in persuading authors to submit manuscripts.

The first special feature in 2005 will be on process analytical technology. If you would like to contribute to this feature, please contact me for more information at oprd@scientificupdate.co.uk.

Trevor Laird
Editor

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(1) *Bretherick's Handbook of Reactive Chemical Hazards*, 6th ed.; Urban, P. G., Ed.; Butterworth Heinemann: Oxford, 1999.
(2) Smallwood, I.; Arnold, E. *Solvent Recovery Handbook*; McGraw-Hill: London, 1993.

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