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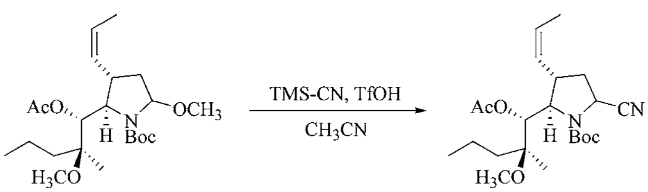
Safety Highlights

Safety Notables: Information from the Literature

This is the second annual literature overview on safety issues which are of interest to process chemists and engineers to appear in *Organic Process Research & Development*. This review will cover recent articles from the literature which address safety issues, common safety mistakes which seem to be repeated all too often, and a few major industrial accidents whose aftermath has impacted public perceptions and influenced the regulatory environment through enhancements to process safety standards. This contribution is not intended to be all-inclusive of the safety literature nor should the information presented be used to make decisions regarding safety without reading the full text of the appropriate article. The intent was to give a flavor of the issues facing other chemists and engineers and to note how they are solving these problems.

Nucleophilic Cyanide Additions

The use of NaCN and other cyanide anion equivalents are common in organic synthesis despite the potential for the generation of HCN gas. Steven Wittenberger and his team at Abbott (*Tetrahedron: Asymmetry* **2003**, *14*, 3541) recently used TMS cyanide in their preparation of a neuramidinase influenza inhibitor.



The Experimental Section for this transformation includes valuable information on the safe handling of TMS-CN. A detailed description of the protocols used is given along with references for further information. This should be must reading for anyone running or planning to run cyanide anion chemistry.

Learning from Flixborough

In 1974, an incident involving a caprolactam production plant (Nypro Limited) led to the death of over 25 people. A process for the air oxidation of cyclohexane to cyclohaxanone was being run when the release of an estimated 30 tons of cyclohexane as a vapor cloud occurred. The subsequent cloud ignited and caused the largest peace-time explosion in UK history. The fire and explosion resulted in 28 fatalities and 36 injuries (Crowl, D. A.; Louvar, J. F. *Chemical Process Safety*, 2nd ed., 2002). Two recent papers from a Taiwanese group led by Jenq-Renn Chen have discussed improved and inherently safer processes for the oxidation of cyclohexane. The autoxidation of liquid cyclohexane using pure oxygen was achieved with the addition of water (*Org Process Res. Dev.* **2004**, *8*, 252). The addition of water as a cosolvent allows the use of pure oxygen without forming the potentially explosive oxygen/cyclohexane mixtures in the reactor headspace. The added water forms an azeotrope with cyclohexane and its vapor and renders the vapor inflammable (*Process Saf. Prog.* **2004**, *23*, 72). For more information on the Flixborough accident and its aftermath please read the excellent review recently published by Dr. Venart of the University of New Brunswick (*Process Saf. Environ. Prot.* **2004**, *82(B2)*, 105).

Explosions with Sodium Azide in Chlorinated Solvents

Nucleophilic displacements carried out using sodium azide are common in organic synthesis. For safety, the choice of solvent should be selected carefully. Several explosions involving sodium azide with methylene chloride as solvent have been reported as Safety Letters (*Chem. Eng. News* April 19, 1993; *Chem. Eng. News* October 11, 1993; *Chem. Eng. News* December 22, 1986). It is believed that diazidomethane, which is unstable at high concentrations, is the culprit of these explosions (*J. Org. Chem.* **1990**, *55*, 2305). It is strongly urged that the use of any halogenated solvent or cosolvent be avoided when working with azides.

Chemical Reaction Hazard Identification and Evaluation

David Leggett's article presents a solid overview of the first steps process chemists and engineers should be taking when evaluating and identifying chemical reaction hazards. The article (*Process Saf. Prog.* **2004**, *23*, 21) is geared toward to small and medium-sized chemical manufacturing companies, but the ideas described are applicable to anyone involved in the scale-up of chemical processes. The author describes in detail 10 hazard information sources that are available for preliminary hazard evaluations. When these sources are utilized as a whole, they provide solid information on the risk potential of the proposed operation in a short period of time. Although nothing will replace the formal hazard assessment of a manufacturing process, this paper is an excellent guide for laying the groundwork for a safe process.

Flash Points and Flammability Limits

The process to measure the flash points of liquids was reviewed in an article by Vidal et al. from the Mary Kay O'Conner Process Safety Center (*Process Saf. Prog.* **2004**, *23*, 47). The authors discussed the various measurements that currently exist and point out potential pitfalls which may lead to erroneous estimations. The paper contends that a general mathematical model that is able to estimate the flash

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point temperature of liquid mixtures is needed. This model should be able to predict the flash point as a function of temperature, pressure, liquid compositions, and atmospheric compositions. Several recommendations to aid in the development of such a model are also outlined.

Best Practices in Incident Investigations

An article by Lisa Morrison (*J. Hazard. Mater.* **2004**, *111*, 161) summarizes the best practices in incident investigation in the chemical process industry. She gives examples from the industry and specifically from Nova Chemicals. Through her research, a list of what is needed to have a successful incident management system has been developed. The system must ensure the following:

1. that all incidents and near misses are reported,
2. that root causes are identified,
3. that recommendations from incident investigators identify appropriate preventative measures,
4. that these recommendations are resolved in a timely manner.

Details on how to achieve each of these points is given along with an excellent glossary of terms used in categorizing incidents.

Classifying Reaction Hazards

Two recent articles from the labs of William Rogers and M. Sam Mannan describe a new, simple classification scheme to characterize the thermal instability risks posed by reactive chemicals in a process (*J. Hazard. Mater.* **2003**, *104*, 255 and *Chem. Eng. Prog.* **2004**, *100*, 34). After reviewing the existing methods for reactive hazard evaluation and classifications, a new classification system is proposed. This new system is based on calorimetric data and the reactivity risk index that takes into account process conditions such as temperature, stored energy, concentration of energetic material, and contaminants. Real-life examples are described to demonstrate the usefulness of this new system.

Avoiding Safety Problems When Scaling Up

Mark Griffiths wrote an article giving his opinions on batch processing and how to avoid safety problem while transferring a reaction from the laboratory to the plant (*Chem. Eng. Prog.* **2003**, *99*, 20). Through a detailed case study, Mr. Griffiths describes several lessons that he has learned. These include the concept of right-to-left thinking—downstream-to-upstream and vice versa. In particular, the need for both the manufacturing team and the laboratory-and-development team to possess an in-depth understanding of the capabilities of the manufacturing facility. He argues that the time spent in developing this type of understanding at both ends of the operation is a worthwhile investment. He also adds a great rule of thumb for us all: processes rarely improve upon scale-up.

An Unforeseen Exothermic Mixture

In 1992, two drums erupted at Squibb in New Brunswick (*Chem. Eng. News* June 1, 1992 and *Process Saf. Prog.* **1994**, *13*, 153). A mixed distillate of thionyl chloride and EtOAc was stored in the drums used to ship the thionyl chloride. The logic was that if the drums were safe enough to contain $SOCl_2$, they should safely contain $SOCl_2$ diluted with EtOAc. There is an exothermic reaction when Zn(0), EtOAc, and $SOCl_2$ are combined; there is no reaction when any two of the three are together. The drum liners were probably cracked, exposing the galvanized metal to the distillate.

Removal of Hazardous Material from Piping

A Safety Bulletin from the U.S. Chemical Safety and Hazard Investigation Board describes the specific tasks that facilities should include in all work activities involving piping or equipment opening to ensure the complete removal of hazardous materials (http://www.csb.gov/safety_publications/docs/PipeOpeningBulletin.pdf). The article goes through the case history of a recent accident and the lessons learned. It also gives guidance on implementing plant-wide procedures for nonroutine work activities involving piping.

We Don't Know What We Don't Know

Other the past 10 years, efforts have been made to analyze reactive incident data and to look for patterns that may prevent similar incidents in the future (*J. Hazard. Mater.* **1987**, *14(2)*, 233; *Process Saf. Prog.* **1998**, *17(4)*, 259 and *J. Loss Prev. Process Ind.* **1999**, *12*, 79). In 2002, the U.S. Chemical Safety and Hazard Investigation Board released a report on 167 reactive chemical incidents that occurred between 1980 and 2001. In a paper by M. Sam Mannan, the data from this CSB report are mined, and conclusions are drawn as to what could have been done better and how to improve for the future (*J. Loss Prev. Process Ind.* **2004**, *17*, 261). Several screening tools were employed, and the pros and cons of the different approaches are given.

Turning Tragedy into Triumph

In the early morning of August 18, 1995, a fire broke out in FMC's Tonawanda, NY, plant warehouse where persulfates were stored. The incident led to several injuries as well as one fatality. In an article written by Douglas Lenz et al. the story of this incident and its aftermath is told (*Process Saf. Prog.* **2003**, *22*, 229). It is a very good account of the effort needed to make a product and company whole again after an incident.

Inherently Safer Design

The phrase "inherently safer design" coined by Trevor Kletz in the 1970s, is the simple concept that it is better to design processes that eliminate chemical plant hazards at the beginning than to engineer "add-on" technologies later to try and control them (*Chem. Ind.* **1978**, *9*, 124). Numerous papers on this topic seem to appear every year, and this review period is no exception. Dennis Hendershot's article, "A New Spin on Safety", gives a very good overview of the fundamentals of, and issues with, inherently safer design (*Chem. Proc.* **2004**, *May*, 16). In his section on design conflicts, he outlines how a process can be described as inherently safer if it eliminates or reduces one of its hazards. However, a majority of processes have multiple hazards, and a process that is inherently safer with respect to one hazard may or may not be inherently safer with respect to other hazards. The author contends that optimization efforts must focus on identifying the design that gives the best overall combination of desirable characteristics. In all likelihood, it will not maximize any single desirable characteristic of the process. Classical examples that expound upon this theme are given. Additional articles on the selection of inherently safer process routes (*Chem. Eng. Proc.* **2004**, *43(5)*, 641), on a hierarchical approach for the evaluation of chemical processes (*Trans. IChemE* **2003**, *81 (Part B)*, 430), on the real cost of process safety (*Trans. IChemE* **2003**, *81 (Part B)*, 406), and on a new graphical method for measuring inherent safety (*J. Hazard. Mater.* **2003**, *104*, 15) have also been published.

Effect of Iron on Thermal Decomposition of 50 wt % Aqueous Hydroxylamine Solutions

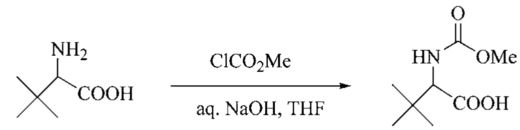
Cisneros, Rogers, and Mannan, of the Mary Kay O'Connor Process Safety Center (*J. Chem. Eng. Data* **2003**, *48*, 1164) present new findings on the effects of various forms of iron (Fe^{2+}, Fe^{3+}) on the thermal stability of 50 wt % hydroxylamine solutions. Rust was shown to cause heterogeneous iron catalysis of the decomposition of hydroxylamine but less violently than the homogeneous decomposition observed with Fe^{2+} and Fe^{3+} ions where 10 ppm is sufficient to trigger decomposition.

Safe Handling of Exothermic Reactions via Continuous Flow Reactors

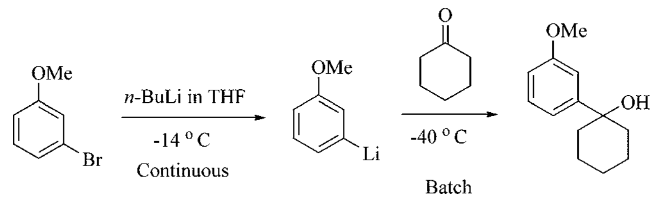
Continuous flow reactors, especially microreactors or small-volume reactors run in continuous mode, offer several advantages over batch processing. For fast exothermic reactions, continuous flow reactors offer enhanced heat transfer per unit volume of liquid, potentially enhanced mass transfer at the point the feeds mix, and enhanced safety via reduced inventory of reactive intermediates if the product is transferred immediately to a quench tank. In addition, reaction time may decrease if the process can be run more concentrated, and reproducibility and control may be improved. In the citations that follow are examples from recent literature where potentially hazardous chemistry was successfully operated in continuous flow reactors:

Helmut Pennemann et. al. (*Org. Process Res. Dev.* **2004**, *8*, 422) provide an excellent review of industrially relevant reactions that have been carried out in microflow devices. The authors show the dramatic reduction in processing time that is achieved in microflow as compared to batch processing, and many cases showed improved yields and selectivity.

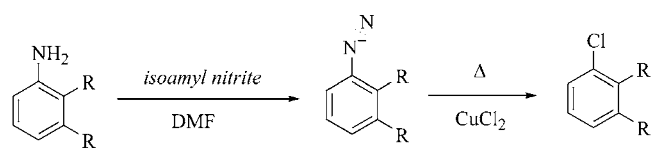
Zhang, Stefanick, and Villani (*Org. Process Res. Dev.* **2004**, *8*, 455) describe the application of microreactor technology as an efficient tool to enable the manufacture of kilogram quantities of pharmaceutically relevant intermediates. The authors provided results for the formation of methylcarbamates, a Newman–Kuart rearrangement, and a ring expansion via ethyl diazoacetate. For example, more than 83 g/h of *N*-methoxycarbonyl-L-*tert*-leucine were prepared using the CYTOS microreactor system for the exothermic addition of methyl chloroformate to *tert*-leucine. The yield obtained was 91% with a 7-min residence time.



In a separate study, the authors successfully achieved 54 g/h for the highly exothermic transmetalation of an aryl bromide with *n*-butyllithium and subsequent alkylation with cyclohexanone in 87% yield.



Fortt, Wootton, and de Mello (*Org. Process Res. Dev.* **2003**, *7*, 762) described the use of microfluidic reactors to incorporate mixing and quench on continuous microscale for the Sandmeyer reaction which goes through the thermally unstable diazonium salt.



Proctor and Warr describe their process to manufacture diazomethane (50–60 tons per year) in an integrated multistage continuous process (*Org. Process Res. Dev.* **2002**, *6*, 884) where diazomethane is immediately consumed to produce key intermediates for HIV protease inhibitor drugs. The maximum inventory of diazomethane never exceeds 80 g.

The use of static mixers in a continuous plug-flow reactor was advantageous for a two-phase highly exothermic Boc-protection of an amine (*Org. Process Res. Dev.* **2001**, *5*, 651) where efficient mixing and heat transfer were needed to afford high selectivity. The reactor was tubular fitted with Sulzer SMV mixing elements having a hold-up volume of 350 mL. In semi-batch mode undesired impurities (dimers of starting material) resulted from thermal gradients and local hot spots. The product selectivity was 99.9% via continuous versus 97% via semi-batch.

Anderson (*Org. Process Res. Dev.* **2001**, *5*, 613) provides an excellent practical guide to continuous processing and gives a wide range of examples of modes of continuous processing and discusses their respective advantages including plug flow, CSTR, electrochemical, microwave assisted, photochemical, and sonochemical flow technologies.

Hanns, Wurziger et al., (Merck Patent G.m.b.H., Germany PCT Int. Appl. (WO 2001-EP2302)) describe continuous reduction of aliphatic, aromatic, or heterocyclic compounds using DIBAL-H in hexane in a static mixer performed at room temperature affording increased safety and improved control of the reaction.

John Alsten (Pfizer, Inc) describes a continuous process (WO 2004074306) for the production of R−Rofleponide using perchloric acid as a reagent. Perchloric acid−steroid complexes were shown to be highly energetic (−3400 J/g), and it was shown that the process could be operated safely in a continuous flow system.

Mining the Web for Safety Information

The following is a list of web sites which the authors find useful for finding information on process safety and hazard analysis. If any readers have additions to this list, we would be most interested in seeing them and perhaps will include them in next year's review.

1. http://www.pub.acs.org/cen/safety/indes.html. The *Chem. Eng. News* website maintains a list of recent Safety Letters that have appeared.

2. http://www.epa.gov/IRIS/index.html. The Integrated Risk Information System (IRIS) is maintained by the EPA as a database for human health effects that may result from exposure to various substances found in the environment.

3. http://www.csb.gov. The official site of the U.S Chemical Safety and Hazard Investigation Board provides information on current and closed investigations of chemical accidents.

4. http://www.crhf.org.uk. The UK Chemical Reaction Hazards Forum publishes incidents (which are kept anonymous) in the chemical industry.

What the future holds no one can ever be sure, but if we keep learning from the past, hopefully the future will be a safer one.

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