Organic Process Research & Development **2005**, *9,* 952–955

Safety Highlights

Safety Notables: Information from the Literature

This is the third annual literature overview on safety issues which are of interest to process chemists and engineers to appear in *Organic Process Research & Development*. As in the previous two years, 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 major industrial accidents. This paper 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 is to give a flavor of the issues facing other chemists and engineers and how they are solving these problems.

Chemical Reactivity Assessments in R&D

The open literature contains much guidance for chemical process hazard evaluations at the manufacturing and pilot-plant scale. Despite the observation that most incidents that occur at the lab scale (<25 L) have a lack of hazard analysis as a contributing factor, not many articles addressing this subject are found. David Leggett has seen fit to fill this void (*J. Hazard. Mater.* **2004**, *115*, 63) by describing a staged approach for chemical reactivity hazard evaluation and assessment applicable to an R&D environment. The article describes the use of a simple form designed to highlight potentially hazardous situations that could arise from the use and handling of chemicals during research. The form is constructed so that a potentially hazardous situation is immediately flagged and the user is directed towards a more formal review. The article contains extensive data tables which guide the reader through the process and gives one insight into the risks associated with a variety of reagents and reaction types. The author states the form is designed to be a self-audit for day-to-day use by lab personnel.

Learning from Experience

Through the use of real-life examples, chosen for their educational value, Trevor Kletz describes for the reader several process accidents and the actions needed to prevent them from occurring again (*J. Hazard. Mater.* **2004**, *115*, 1). The paper describes examples of a frequent, but unfortunate, way that many companies react after an accident. The author groups the examples into three general categories:

(1) those for which some investigators were too eager to recommend changes to instructions or better observation of them than to look for ways of removing the hazard or for changes in design that would make an accident less likely to happen;

(2) those for which some people fail to calculate the effects of changes or the time required for the changes to take place;

(3) those for which facts that were known in one industry or company may be unknown in another.

After describing the incidents the author challenges senior managers to dive deeply into accident reports and make sure their own organization is not making the same errors described in the article.

Safety Management System Failures

The U.S. Chemical Safety and Hazard Investigation Board (CSB) is charged with the key mission of determining the root causes of incidents, reporting their findings, and presenting recommendations to prevent similar incidents from occurring. In an article by Angela Blair of the CSB (*Process Safety Progr*. **2004**, *23*, 232), a review of the 21 completed case studies and incident investigations was given. Although the incidents came from a variety of industries, one trend emerged from these investigations; in every CSB investigation, management system failures were identified as at least causally related to the incident. The author goes on to outline many subcategories of system failures that were deemed to play a role in the incidents. Overall the data present a strong argument for improved safety management systems regardless of the scope or size of the enterprise. The areas for the broadest potential impact were identified.

Eight-Point Safety Program from Honeywell Process Solutions

Companies strive to be the Best-in-Class in a variety of areas, and safety is no exception. Bobby Stuart of Honeywell Process Solution (HPS) recently wrote an article outlining how his company has achieved some impressive results in the area of safety operations (*Chem. Eng.* **2005**, *April*, 63). The author describes the eight-point safety program at HPS and goes into detail about how each point is defined. The process involves these steps:

(1) Project Safety Assessment
(2) Data gathering and scope definition
(3) Defining the Safety Action Plan
(4) Management sign-off
(5) Kickoff and training
(6) Project execution
(7) Reward and recognition
(8) Project review and closeout (lessons learned)

Following these steps and instituting a culture of safety may not make you Best-in-Class, but it will certainly improve the safety operations of your organization.

The Effect of Process Pressures on Flashpoints and Flashpoint Estimation

A liquid's flashpoint, the temperature limit with respect to flammability, is a well-used value to both classify

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combustible liquids and for determining safe process temperatures. The flashpoint data are available in many books and on Material Safety Data Sheets (MSDSs), but such values are often expressed as constants. What is often overlooked is that these values are not constant and can vary significantly with pressure and other reaction parameters. In an article by Dehong Kong (*Chem. Eng.* **2004**, *December*, 50) the author outlines how to assess the effects of pressure on the flashpoint of combustible liquids. He states that the safety review process should include a review of the influence of pressure on flashpoints and that the flashpoint and the lower flammability limit should be determined under actual processing pressures. The author also goes through detailed descriptions of two incidents and gives advice on how to avoid similar events in one's own organization. The article also contains an interesting side bar titled "Does the MSDS give enough hazard data relevant to your operations?" Section 5 of an MSDS deals with the fire and explosion hazards of chemicals. The side bar recommends that when evaluating the fire and explosion hazards of a chemical, it is important not only to characterize the compound under normal conditions but under actual process conditions as well. Several remarks on how to run through this process are given.

A simple method for the estimations of flash points has been put forward by the group of Laurent Catoire in France (*J. Phys. Chem. Res. Data* **2004**, *33*, 1083). A flash point is the lowest temperature at which a liquid produces enough vapor in the air at atmospheric pressure to ignite in the presence of an ignition source. The article details the methods for estimating flash points that currently exist in the literature and describes the pros and cons of each method. The authors then outlined their new method and validated it with about 600 organic compounds, including polyfunctional compounds. The approach here is simple and accurate, and all of the parameters (well-known by chemists) are experimentally available or easily estimated. A second paper from the same authors outlined a similar approach to estimate the lower flammability limits of pure organic compounds (*Process Safety Progr.* **2005**, *24*, 130).

2-Nitrobenzoyl Chloride

Ortho-nitrated benzoyl chlorides are industrially important intermediates in the production of agrochemicals. Several incidents have been reported with this class of compounds in which violent explosions occurred due to thermal decomposition. Preliminary studies have been conducted by Maria Papadaki and her group on the thermal behavior and decomposition of 2-nitrobenzoyl chloride (*J. Hazard. Mater.* **2004**, *115*, 91). Their studies revealed that the decomposition reaction is strongly condition dependent with the heating rate of the sample playing a preponderant role in the course of the decomposition reaction. The key features of the reaction system that have been identified are reported.

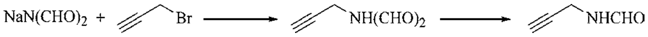
Safety Letters

Two letters have recently appeared in *Chem. Eng. News*. In the first letter a sudden violent decomposition occurred while transferring lithium 2,6-difluoroanilide (*Chem. Eng. News* **2005**, *February 28*, 8). The compound had been prepared from 2,6-difluoroaniline and *n*-butyllithium in diethyl ether. The authors offer cautionary advice against isolating any compounds containing both C−F and highly reactive metal−nonmetal bonds. For additional reading on this subject please see Peter Urben's comments in an earlier safety letter (*Chem. Eng. News* **1996**, *July 8*, 3).

A second letter describes an explosion during the preparation of 1,5-diamino-1*H*-tetrazole (*Chem. Eng. News* **2005**, *July 25*, 5). While following a published procedure (*Inorg. Chem.* **2005**, *44*, 4237) a sensitive and unexpected side product, 5-azidotetrazole, was formed. This undesired side product was in the ethanol extracts along with the desired compound. The author stated that if this procedure is repeated, the ethanol extracts should not be taken to dryness.

Preparations of *N*-Formylpropargylamine

In a paper from the process group at Merck on the synthesis of 5,6,7,8,-tetrahydro-1,8-naphthyridine fragments, the synthesis of *N*-formylpropargylamine was described (*J. Org. Chem.* **2004**, *69*, 8723).



In the references of the article, a description on how to safely handle *N*-formylpropargylamine was outlined. Neat *N*-formylpropargylamine is a crystalline solid that is not stable when heated above 170 °C. However, solutions of *N*-formylpropargylamine are safe to handle. Thermal characteristics of *N*-formylpropargylamine showed an exotherm of 3.5 cal/g that initiated at 170 °C followed immediately by a large decomposition exotherm of 311 cal/g that initiated at 215 °C. The heat release of the second exotherm was rapid and approached the shock sensitivity potential range. Caution when preparing these types of molecules should be taken.

Sodium Hydride Spills and Fires

Sodium hydride is an often-used base in synthetic organic chemistry labs and is usually purchased as a 60% suspension in mineral oil. Sodium hydride is a water-reactive, pyrophoric compound which has been a culprit in a fair share of industrial incidents and fires. An article from the process team at Eli Lilly and Company describes a recent incident with sodium hydride in a dispensing room (*Process Safety Progr.* **2005**, *24*, 86). The authors outline the steps put into place to improve the disposal and clean-up operations in the event of a sodium hydride spill and/or fire. Several materials, including the approved agent Methyl-X for smothering Class D fires, were examined for their smothering properties. The best material was determined to be damp fill sand. The sand was typical construction grade with a moisture content of 4−6%. A Detailed Action Plan to deal with these types of fires is given which was tested on a controlled spill of 500 g of sodium hydride. The application of the damp-sand-smothering technique to other metal fires is currently under investigation.

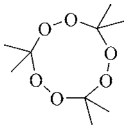
Glassware Cleaning

The exposure hazards associated with an industrial lab environment do not end when an experiment is complete.

The rinsing of laboratory glassware with acetone or other chemicals while cleaning the glassware represents a potential exposure concern. Workers at the Roche Colorado Corporation (RCC) have written a review of the various methods for cleaning laboratory glassware that are currently available (*Chem. Health Safety* **2005**, *May/June*, 30). The authors discuss the different types of ventilated sinks that are available and detail the engineering controls needed to be in place to limit the exposure to acetone vapors to the staff. The design, installation, and evaluation steps to place the ventilated sinks in the labs are described, and a significant drop in the concentration of airborne acetone was demonstrated.

Decomposition of Triacetone Triperoxide

The excessive heat of formation has been considered to be the key property of all explosives. However, a recent study from Ehud Keinan and co-workers has shown that this may not be the case for less-studied families of explosives (*J. Am. Chem. Soc.* **2005**, *127*, 1146). In the article the decomposition mechanism of triacetone triperoxide (TAPT) was studied along with those of several other analogues. TAPT is a very sensitive explosive with power close to that of TNT.

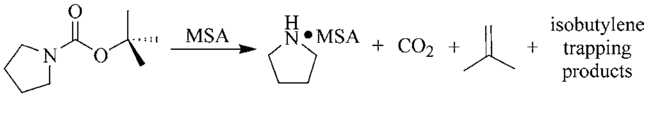


TAPT

Through the investigation, the explosion of TAPT was found not to be a thermochemically highly favored event. Its decomposition involves an entropy burst which is the result of the solid-state molecule rapidly going to one ozone molecule and three acetone molecules. The calculations used to identify the transition states, intermediates, and final products are given in very good detail. TAPT has been linked to several terrorist bombings in the past years (*Chem. Eng. News* **2005**, *January 24*, 35), and recently traces of TAPT were found in the apartment of a suspect in the July 7 bombings in London (*Chem. Eng. News* **2005**, *July 25*, 11). Without the commonly used nitro groups or metallic elements present in commonly used explosives, the detection of TAPT is very difficult. However, Ehud Keinan and co-workers have developed a tool which may help detect TAPT and other peroxide-based explosives in the future.

Environmentally Friendly BOC-deprotection

Dias *et al.* (*Org. Process Res. Dev.* **2005**, *9*, 39) characterized levels of isobutylene liberated during the methanesulfonic acid-catalyzed BOC-deprotection of *N*-BOC-pyrrolidine as a function of solvent. The reaction was chosen as a model compound for study.



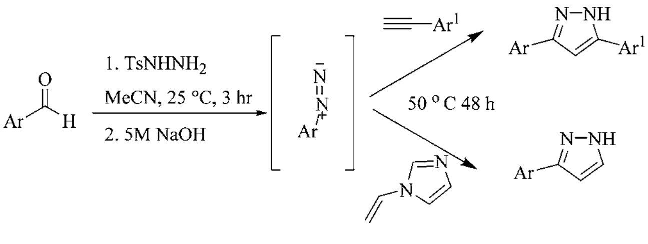
Solvents examined were THF, methanol, ethanol, 2-propanol, toluene, and dichloromethane. Isobutylene is a flammable volatile organic compound (VOC) with a boiling point of −6.9 °C and is regulated by the U.S. EPA. One full equivalent of isobutylene was released as an off-gas when THF was used as the BOC-deprotection solvent. Isobutylene emissions were reduced by 65−95% in other solvents. In alcohol solvents, the corresponding alkyl *tert*-butyl ethers are formed as byproducts of the reaction and remain in solution. In dichloromethane and toluene, oligomers of isobutylene can be formed under the reaction conditions and also remain in solution. These results provided the basis for developing an effective methanesulfonic acid/toluene scrubber for isobutylene that was successfully employed on pilot-plant scale.

Safer Borane−THF Solutions

A 1.0 M borane−THF solution stabilized with either 0.005 M 1,2,2,6,6,-pentamethyl-piperidine or 0.005 M *N*-isopropyl-*N*-methyl-*tert*-butylamine affords a safer and more stable reagent according to the manufacturer, Sigma-Aldrich, (Technical Bulletin, New, safer, amine-stabilized borane-tetrahydrofuran solutions for hydroboration and reduction, **2004**) as compared to 1.0 M borane−THF stabilized with 0.005 $NaBH_4$. Further, the safety advantage is achieved without sacrificing performance. For example, equal or better yield and selectivity was obtained for both racemic reduction of acetophenone and asymmetric reduction of acetophenone using R-Me-CBS-oxazaborolodine. The new amine-stabilized 1.0 M borane−THF solutions degrade more slowly and afford self-accelerating decomposition temperatures significantly greater than $NaBH_4$-stabilized 1.0 M borane−THF according to the technical bulletin.

Safer Alternative to Handling Diazo Compounds

Fulton, Aggarwal, and de Vicente (*Eur. J. Org. Chem.* **2005**, 147) developed a method to generate diazo compounds from tosylhydrazone salts, providing a safer alternative to directly handling diazo compounds. Their approach is based on the Bamford−Stevens reaction, which utilizes tosylhydrazone salts as diazo precursors. The authors have demonstrated the *in situ* method for a number of transformations including, but not limited to, Wittig olefination, sulfur ylide-mediated epoxidation, as well as aziridination and cyclopropanation chemistry. In some cases a phase transfer catalyst is employed. The synthesis of pyrazoles was demonstrated from the tosylhydrazone derivative generated from an aldehyde followed by coupling with the alkyne or alkene with good yields and excellent regioselectivity.



Although not specifically discussed in the paper the chemistry appears ideally suited for a continuous flow operation.

Process Intensification

Hessel, V. *et al.* (*Curr. Org. Chem* **2005**, *9*, 765) provides a current review of the application of microreactor technology specifically toward enabling process chemistry. The authors cover synthesis involving unstable intermediates and safe processing in hazardous and high-temperature regimes. An interesting safety benefit, noted by the authors, of operating in microstructured reactors is that explosions do not take place and is attributed to the wall effects that lead to radical chain termination rather than chain initiation and growth similar to the effect used in flame arrestors. Numerous chemical examples were shown to benefit by microreactor processing and are described with references therein. In a separate article, W. L. Luyben and D. C. Hendershot (*Ind. Eng. Chem. Res.* **2004**, *43*, 384) offer a good reminder regarding the need to understand process dynamics when processes are intensified. In their third example the authors compare a 20 m^3 semi-batch nitration process with a smaller-volume 0.5 m^3 CSTR reactor (continuous stirred tank reactor). In this example, the potential runaway hazard arises if nitric acid concentration within the reactor exceeds 15%. The author's primary point here is that, although there is a significantly reduced inventory of flammable and corrosive reaction mixture in the CSTR, the instrumentation and controls must work to ensure the process never overcharges nitric acid. The intensified CSTR design is more dependent on instrumentation and control system reliability, whereas the semi-batch design is inherently safer with respect to instrumentation (i.e. the total nitric acid charge does not exceed 15%). In general, full understanding of the inherent safety characteristics of both steady state and dynamic conditions is needed for the process to be safely intensified.

Before and after the Reactions

Back-to-back articles in *Chem. Eng.* this year addressed issues that occur before and sometimes after reactions are run in the pilot plants. In the first article Siddhartha Mukherjee walks the reader through the preparations needed for the initial start up of a process unit (*Chem. Eng.* **2005**, *January*, 36). The author offers advice on the precommissioning schedule, the precommissioning organization, and a check list for the plant inspection. In the second article, Natalie Kirk Moore and Brian Johnston discuss the temporary shutdown of a process plant (*Chem. Eng.* **2005**, *January*, 44). The authors outline the steps needed to protect plant assets from damage and allow for a smooth start up in the future.

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 including them in next year's review.

1. http://www.crhf.org.uk. The UK Chemical Reaction Hazard Forum contains over 120 examples of laboratory and chemical plant incidents that involve chemicals and processes that are not uncommon in the industry.
2. http://www.labsafety.org. The Laboratory Safety Institute (LSI) is a nonprofit, international educational organization for health, safety and environmental affairs.

Paul F. Vogt
Chemical Development,
Albany Molecular Research, Inc.
Albany, New York 12212, U.S.A.
E-mail: paul.vogt@albmolecular.com

David J. am Ende
Chemical Research & Development, Pfizer, Inc.
Groton, Connecticut 06340, U.S.A.
E-mail: david.j.amende@pfizer.com.

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