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Safety Highlights

Safety Notables: Information from the Literature

Abstract:

This is the sixth annual literature overview on safety issues which are of interest to process chemists and engineers to appear in *Org. Process Res. Dev*. As in the previous 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 was 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 how these problems are being solved.

Special Issue on the Prevention of Explosions

A special issue of the *Journal of Loss Prevention in the Process Industries* which contained selected papers from the Twelfth International Colloquium on Dust Explosions, and the Seventh Colloquium on Gas, Vapor, Liquid and Hybrid Explosions was published in 2007 (*J. Loss Prev. Process Ind.* **2007**, *20*). The hope was that this issue would serve as a timely resource on the subject of industrial explosions and highlight the compelling need for research aimed at finding practical solutions to deal with the prevention and mitigation of industrial explosions. In one paper, the authors M. Sam Mannan, Harry West, and Patrick Berwanger walked through the lessons learned from recent incidents (*J. Loss Prev. Process Ind.* **2007**, *20*, 644). This paper focuses on three technical and engineering issues which, in the opinion of the authors, played a significant role in the causation of the incidents and the severity of consequences. The three issues are:

1. facility siting,
2. atmospheric venting, and
3. operator information systems.

Each of these issues is examined in detail, and real life examples are given to reinforce the importance of these factors. The authors provide a further reading section which is a good resource for additional information of this topic.

In a second article, a final footnote on the Flixborough disaster was presented by J.E.S. Venart (*J. Loss Prev. Process Ind.* **2007**, *20*, 621). This article goes through great detail to answer questions which still exist on the largest-ever peacetime explosion in the U.K. The author critically examines the findings of the original Court of Inquiry and applies modern computer modeling to add perspective on the incident. The article is an exceptional review of the incident and gives the reader food for thought on what actually happened that fateful day, and more importantly, what we should have learned.

Toxic Tips

William E. Luttrell has written reviews on organic molecules and the precautions which should be taken while working with these compounds. These molecular safety reviews appear in the *J. Chem. Health Saf.* and are a good addition to the MSDS which should be read prior to working with any new organic compound. Some examples of the compounds reviewed are: osmium tetroxide (*J. Chem. Health Saf.* **2007**, *September/October*, 40) and benzo(*a*)pyrene (*J. Chem. Health Saf.* **2007**, *November/December*, 21).

Inherently Safer Technology

Trevor Kletz in his book on plant design (*Plant Design for Safety*; Hemisphere Publishing Corporation: New York, **1991**) stated, “The essence of inherently safer approaches to plant design is the avoidance of hazards rather than their control by added-on protective equipment.” Trevor Kletz also proposed the five fundamental principles of inherent safety: minimization, substitution, attenuation, simplification, and limitation of effects. This year, as usual, many articles were published which discussed the principles of inherently safer design of chemical processes and process plants.

An excellent review of Inherent Safety and the advances that have been made in the past decade was written by David Moore *et al.* (*Process Saf. Progr.* **2008**, *27*(2), 115). The motivation for this review was the publication on the updated version of the classic reference by The Center for Chemical Process Safety (CCPS). The updated version includes lessons learned from the original publication in 1996 and hopes to build upon the wider acceptances of inherently safer design. The authors feel that the added examples and checklists in the book make this a very practical guide for anyone involved in process risk management and that the new edition should be part of your library (Bollinger, R. E. *Inherently Safer Chemical Processes: A Life Cycle Approach*; Wiley: New York, 1997; ISBN: 978-0-8169-0703-8). The same can be said for this well written article.

An article on the incorporation of inherent safety principles in process safety management was published by Amyotte *et al.* (*Process Saf. Progr.* **2007**, *26*(4), 333). Process safety management deals with the identification, understanding, and control of process hazards to prevent process-related injuries and incidents. Through the use of various inherent safety examples, both technical and from everyday life, the authors make a strong case that inherent safety is an integral component of effective process safety management. How to use and incorporate the inherent safety checklist of minimize, substitute, moderate, and simplify is described and is a very good qualitative reference tool to keep handy.

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The choice of the chemical process route is a key decision in the early stage of any project, and choosing an "inherently safer" route will help eliminate many hazards in the process. The earlier the parameters are examined to determine the inherently safer process, the better. Although there exists many indices to quantify the hazards and health and environmental impact of a chemical process, these available indices can be plagued by shortcomings. Recently, two new ones were introduced to give additional tools to the plant chemists and engineers. In the first, a consequence-based approach to the quantitative assessment of inherent safety was put forth by Alesandro Tugnoli *et al.* (*J. Am. Inst. Chem. Eng.* **2007**, *53*, 3171). The authors state that the availability of inherent safety drivers for early process design is a critical issue for the further development of the chemical and process industry. This new method developed allowed for the inclusion of hazards coming from auxiliary equipment that are often overlooked in conventional inherent safety assessment methods. In the second, Rajagopalan Srinivasan *et al.* (*Process Saf. Environ. Prot.* **2008**, *86*, 193) introduced a new metric called the Inherent-Benignness Indicator (IBI) for comparing process routes. Through the consideration of 15 different safety factors, the IBI is used to rank routes and determine the broad similarities and differences in the safety, health, and environmental footprints for the routes. The article walks the reader through the process of the IBI and gives case studies for manufacturing involving both acetic acid and methyl methacrylate.

Hazardous Reductions with Metal Hydrides

In a chemical safety alert (*Chem. Eng. News* **2008**, *86*(10), 6) the dangers associated with gases which may form during reductions with metal hydrides were discussed. The author, Dale Huber, outlines fires that have been caused by the production of silane gas during the synthesis of silicon nanoparticles on reduction of $SiCl_4$ by $LiAlH_4$ and gives references to other examples of silane and germane. The warning is expanded to include the attempts to reduce silicon, germanium, and tin halides with metal hydrides. The author advocates that these reactions should not be conducted without planning for the handling of the hazardous gases that may be generated, nor should they be published in the literature without mention of these hazardous byproducts.

In a related article, Robert Zalosh summarizes the nature of metal hydride fire incidents and reviews the appropriate fire suppression agents (*J. Loss Prev. Process Ind.* **2008**, *21*, 214). The standard fire suppression agents for these types of fires, Class D agents such as Met-L-X, are effective in initial fire extinguishment, but they do not cool the hydride during or after suppression and thus do not prevent reignition of the hydride during exposure to the air or during cleanup. The data presented suggest that it may be necessary to supplement Class D agents at large hydride fires with a separate application of liquid nitrogen or some other inert gas. The article goes through several recent incidents and gives tables of data on the effectiveness of several suppression agents.

Safety Is No Accident

The October 2007 issue of *Plant Eng.* was dedicated to safety in manufacturing plants. In one article, Randy Kates walks the readers through the process to lead a plant-wide safety program with commitment and planning (*Plant Eng.* **2007**, *October*, 29). He states that to improve the safety culture of an organization, the following should occur:

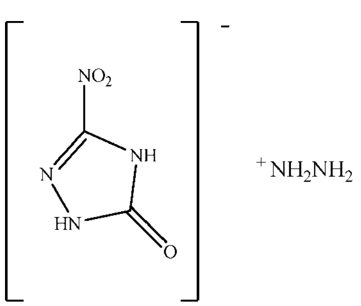
- The safety process must touch every person in the organization.
- Safety must be a permanent agenda item, discussed at the start of every meeting.
- Leaders must be held accountable for safety performance.
- Safety must be the operational fabric of the facility, not a separate function.
- Safety must be integral to every business activity.

Most importantly, it is highlighted that without involvement from every level of the organization, the implementation of a safety program will not be as successful as it could be when everyone is engaged.

In a second article, authored by Laura Brown, the issue of an aging workforce in the manufacturing industry is addressed (*Plant Eng.* **2007**, *October*, 45). It is noted that while the incidence of nonfatal occupational injuries across all industries was lower with older employees, the median days away from work due to an injury was much higher for older workers. This may be due to older workers being more experienced and cautious, thus fewer incidents, but that the recovery time for older workers who are involved in an incident may be longer. Some practical tips for improving the work environment are given which can benefit workers regardless of their ages.

Synthesis of Energetic Materials

Many readers of this review are looking for ways to lessen, or avoid all together, working with molecules that have hazardous thermal properties. However, scientists working to prepare novel propellants and explosives, such as Feng-qi Zhou and colleagues, deal with the dangers and rigors of working with thermally unstable compounds on a daily basis. The preparation and thermal characterization of high nitrogen containing compounds such as hydrazine 3-nitro-1,2,3-triazole-5-one complex (**1**) (*J. Hazard. Mater.* **2008**, *153*(1−2), 261) is outlined in good detail.



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Reading these types of papers gives a solid background on the preparation of thermally energetic compounds. Hopefully it can lead to insights into the proper amount of data required prior to synthesizing other potentially unstable targets on scale.

Organic Peroxide Hazard Ratings

Organic peroxides have been the culprit in many industrial accidents. Organic peroxides react violently and differently under various conditions such as shock, heat, external fire, and contamination. Yin-Shing Duh and colleagues assessed nine commercially available organic peroxides with differential scanning calorimetry (DSC), accelerating rate calorimetry (ARC), and vent sizing package 2 (VSP2), and an incompatibility rating was developed (*Process Saf. Progr.* **2008**, *27*(2), 89). The peroxides examined were cumene hydroperoxide (CHP), di-*tert*-butyl peroxide (DTBP), methyl-ethyl-ketone peroxide (MEKPO), *tert*-butyl hydroperoxide (TBHP), benzoyl peroxide (BPO), hydrogen peroxide, lauroyl peroxide (LPO), *tert*-butyl peroxybenzoate (TBPBZ), and dicumyl peroxide (DCPO). Each of the organic peroxides listed was tested for their onset temperatures, self-heat temperature and pressure rates, and heats of decomposition rates. Also, the adiabatic runaway characteristics for each were determined. Lastly, an incompatibility rating was devised for these peroxides and known impurities (6 N HCl and 6 N NaOH) found in process streams. The authors recommend that a contaminant be considered incompatible if the onset for thermal decomposition is lowered by at least 25 °C or the heat of decomposition is 25% greater. The paper also serves as a useful summary of the existing literature regarding these nine peroxides. An analogous study on the effects of acetone on MEKPO runaway reactions was also published in 2008 by Chi-Min Shu *et al.* (*J. Hazard. Mater.* **2008**, *153*, 1071).

Thermal Decomposition and Detection of Hydrogen Peroxide

Hydrogen peroxide (H_2O_2) is commonly used in a variety of industries. In the United States and New Zealand, there have been no less than seven accidents involving H_2O_2 in the past 4 years alone. Hydrogen peroxide-containing impurities, which can exist in a noncontrolled environment, have caused many of these explosions. In one accident in particular, the H_2O_2 was mixed with sulfuric acid which was believed to accelerate a catalytic decomposition of H_2O_2 and led to a runaway reaction and explosion. C.-M. Shu and co-workers investigated the thermal decomposition of hydrogen peroxide in the presence of sulfuric acid (*J. Therm. Anal. Calorim.* **2008**, *93*(1), 115). The authors, after thoroughly calculating the thermokinetic data, propose two different mechanisms of decomposition, depending on the concentration of sulfuric acid in the system.

The detection of hydrogen peroxide vapor is crucial in counterterrorism efforts as H_2O_2 has been used in explosive devices by terrorists in both England and Germany. The vapor monitoring of hydrogen peroxide is also an industrial health issue due to its widespread use and its inherent toxicity (OSHA PEL = 1 ppm). With these goals in mind, William Trogler and his co-researches at the University of California, San Diego, have developed a simple, inexpensive sensor that selectively detects hydrogen peroxide vapor (*J. Am. Chem. Soc.* **2008**, *130*, 3712; *Chem. Eng. News* **2008**, *86*(11), 10). Using metal phthalocyanines, the authors present a cheap, compact device that greatly improves upon the standard methods for H_2O_2 detection.

Industry-Wide Process Safety Metrics

Effective management controls are necessary for continuous improvement of process safety performance, but an industry-wide standardized set of metrics for measuring performance has not been implemented. The Center for Chemical Process Safety (CCPS) formed a committee to develop guidelines to serve as a global standard, and Overton and Berger have published the recommendations for leading and lagging process safety metrics (*Chem. Eng. Progr.* **2008**, *104*(5), 40). The metrics could be used to (1) drive continuous improvement by acting as an indicator of changes in performance, (2) perform benchmarking, and (3) prevent catastrophic events by serving as a leading indicator.

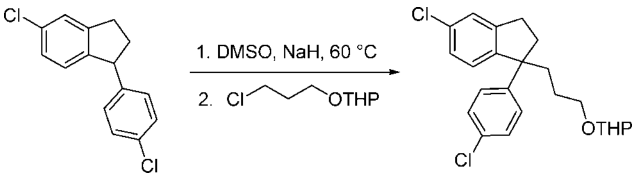
The definition of a process safety incident was developed through close collaboration between CCPS committee members, external stakeholders, and representatives from various trade associations. An incident is reportable as a process safety incident if it meets all of the following criteria:

(1) involves a chemical or chemical process,
(2) is above a minimum reporting threshold,
(3) occurs in a production, storage, distribution, utility, or pilot-plant location,
(4) is an acute release.

Each of the criteria listed above is discussed in detail, and a system to assign a severity ranking for various consequence categories is proposed. In addition, the CCPS recommends that companies implement and report three metrics including the total count of process safety incidents, the cumulative count of incidents normalized by man-hours, and the cumulative severity-weighted rate of process safety incidents. More information can be found at http://www.aiche.org/ccps/metrics/index.aspx.

Scale-Up of a Process Utilizing the Dimsylate Anion

The combination of strong base and DMSO can be a very unstable system, depending on processing conditions such as temperature and concentration. The hazards associated with NaH/DMSO have been extensively reported (*Bretherick's Handbook of Reactive Chemical Hazards*, 7th ed.; Urben, P. G., Ed.; Elsevier, Ltd.: Burlington, MA, 2007; p 380), and this combination is generally not employed for large-scale processes. Unfortunately, it is not always possible to completely avoid undesirable combinations such as this because suitable alternatives are not always available. Dahl and co-workers have reported that the alkylation of a phenylindane with an alkyl chloride, as shown below, was not successful with a variety of bases including *n*-BuLi, LDA, NaOMe, NaOEt, KO*t*-Bu, KHMDS (*Org. Process Res. Dev.* **2008**, *12*, 429).



The alkylation was successful with NaH in DMSO. Replacement of DMSO with NMP, THF, or DME was not successful. Therefore, process development efforts focused on diluting the mixture with THF in order to provide a boiling point barrier for removal of heat in the event of an uncontrolled exotherm. The researchers found that a 1:6 ratio of DMSO/

THF was optimal in order to achieve full alkylation. The safety profiles of the DMSO and DMSO/THF processes were studied and compared. When the reaction is performed in pure DMSO, the potential consequences could be devastating. In sharp contrast, the worst-case scenario for the DMSO/THF combination is loss of 30% of the THF under adiabatic conditions. The process was scaled to produce 5 kg of the desired API.

Essential Process Safety Data for Early Development Projects

The pharmaceutical industry is under increased pressures to compress timelines without using additional resources. In order to help meet this challenge, Julius Leonhardt and researchers from Bayer Schering Pharma AG have reported their worst-case strategy for early risk assessment of chemical projects on pilot-plant scale (*J. Loss Prev. Process Ind.* **2008**, *21*, 400). The worst-case assessment assumes three independent failures including full accumulation of reactants, loss of cooling, and loss of venting. The main risks are classified by systematically considering the thermal potential, gas evolution, hazardous material properties, and increased reactivity (explosive atmospheres, electrostatic charges, etc.). The authors recommend early involvement of safety experts and a properly regulated work-flow between the stakeholders in order to avoid safety-related delays. They hold a technology transfer meeting 2−3 weeks prior to the first pilot-plant batch, and the locked-in process is issued 1 week prior to the technology transfer meeting to ensure sufficient time for process safety testing. They begin with a “chemistry” only assessment that does not consider the scale-up equipment because it is typically not well defined early on. As the scale-up date approaches and the equipment is selected, an evaluation is performed to ensure the temperature and pressure design limits are not exceeded. Other considerations such as material compatibility are also assessed. Two case studies are discussed.

The review that safety experts undertake often involves the use of hazard assessment methods that have been published by academic laboratories and industrial safety professionals. These methods can range from simple analysis to fairly complex mathematical models. In a paper from Ulrich Fischer and coworkers from the Institute for Chemical Engineering in Zurich Switzerland, a variety of simple EH&S hazard assessment methods are compared that can be applied in early phases of chemical process design (*Process Saf. Environ. Prot.* **2008**, *86*, 77). The authors review various methods, compare and contrast the results they give, and apply them to six alternative routes of methyl methacrylate production.

In a third related article, a checklist for safer chemical batch reactions was published (*Chem. Eng.* **2008**, *115*(4), 61). The checklists are valuable as a guide for the design of a new process as well as being used to identify information gaps when an existing process undergoes a periodic review.

Transportation of Organic Solids on Dry Ice

Due to thermal instability, it is a common practice to ship samples of API and intermediates on dry ice. Wim Dermaut *et al.* at Janssen Pharmaceutica have reported an interesting safety hazard that can arise due to absorption of CO_2 at low temperature followed by desorption when the sample is warmed back to room temperature (*Org. Process Res. Dev.* **2008**, *12*, 130). On several occasions they noted pressure buildup in sample bottles that were shipped on dry ice, and in one occasion the lid was blown off. TGA studies confirmed that the organic solids absorbed CO_2 upon cooling and released it upon warming back to room temperature. Assumption of a worst-case scenario showed that the pressure in a sealed sample bottle could be as high as 220 bar for one of the samples tested. The authors suggest two mechanisms that could result in sealing of the sample bottle: overpressurization or different expansion coefficients of the lid, glass bottle, and sample material. They resorted to placing the samples in a hermetically sealed aluminum bag in order to avoid contact with the CO_2.

Interactive Optimization of Feed Rate to Minimize Thermal Accumulation

Reactions performed in semibatch mode present the opportunity to tune the safety profile of the process by controlling the rate of addition. Lamanna, Nilsson, and Reuse have reported a methodology for online control of process parameters using a real-time heat flow reaction calorimeter (*J. Therm. Anal. Calorim.* **2008**, *93*(1), 329). The dosing profile can be controlled such that the unreacted material is below a predetermined level. Another method is to run the process so that the instantaneous adiabatic temperature rise is at a stable, predetermined level. For either approach, at least one run with a constant dosing rate must be performed in order to determine the reaction enthalpy. The reaction of propionic anhydride with 1-butanol was used to demonstrate the approach.

Continuous Flow/Microreactors

Continuous flow processing has become more popular over the past few years due to precise temperature control and superior mixing. The low reaction volumes are advantageous from a process safety perspective and also allow for material-sparing process development which can be fully automated, allowing for 24 h/day operation if incorporated in an intelligent system. Finally, transfer of a continuous flow process from the laboratory to production scale is relatively easy because there is no need to reoptimize due to changes in thermal and mass transfer properties. The following is a sampling of the continuous flow literature that has appeared this year.

A short article from Sushma Davison of Britest explains how to decide between batch and continuous processes (*Chem. Eng.* **2008**, *July*, 42). The author suggests that it is necessary to identify the existing barriers to get the industry to even consider continuous processing instead of opting for the batch approach. Batch processing is seen as more flexible and thought to have less risk and shorter development timelines. However, continuous processing can offer substantial business and technical benefits, making it worth the effort of addressing the issue of unfamiliarity with operation and control. Britest recommends that process engineers look at the whole process design including both primary (API) and secondary (formulation) manufacturing processes. The primary objective of the whole manufacturing process is to produce a product that has the desired performance characteristics; therefore, it is critical to understand any processing that has an impact on the final product characteristics. A conceptual process model for deciding between batch or continuous modes is discussed.

Charlotte Wiles and Paul Watts from The University of Hull, Micro Reactor Group, in the U.K. have published a review that provides practical examples of the technology using a wide variety of synthetic transformations (*Eur. J. Org. Chem.* **2008**, *10*, 1655). The examples include single-phase reactions, biphasic reactions (gas−liquid, liquid−solid, catalytic membranes, immobilized enzyme), triphasic reactions, photochemistry, electrochemistry, removal of heavy metals, reaction screening, and continuous liquid−liquid extractions. For a second review on microreactor technology, see the report by Warmington and Challener which describes some of the continuous processes presented at recent Scientific Update events (*Spec. Chem. Mag.* **2008**, April, 40). For those wishing to see examples of continuous processing in pharma intermediates, readers are referred to a splendid article by Thomas LaPorte of Bristol-Myers Squibb Co. (*Curr. Opin. Drug Discovery Dev.* **2007**, *26*, 738 and the references cited therein).

Four Corning microreactors have been assessed for multiphase flow applications by Chevalier and co-workers (*Chim. Oggi* **2008**, *26*(2), 38). The Schotten−Baumann reaction showed significant improvement in conversion for one of the microreactors when compared to the batch process. Precipitation of polystyrene was used as a measurement of emulsification performance. Good control of particle size distribution was seen in one of the designs. The microreactors were tested with model reactions that produce a large amount of precipitates, $Fe(OH)_3$ and $Cu(OH)_2$, to determine the tendency to fouling and clogging of the channels. One of the microstructures was identified and developed as an efficient design for reactions that precipitate. Finally, one design for gas−liquid reactions is discussed.

The nucleophilic fluorinating agent DAST is widely used in the laboratory, but its use on large scale is limited because it can detonate at temperatures over 90 °C. Therefore, Gustafsson, Gilmour, and Seeberger developed a safe, scalable method that allows for the preparation of large quantities of fluorinated molecules by a deoxyfluorination method utilizing DAST in a microreactor (*Chem. Commun.* **2008**, *26*, 3022). The method allows for the conversion of a range of substrates including alcohols, lactols, aldehydes, and carboxylic acids. Dichloromethane was found to be the solvent of choice, and a 75 psi backpressure was used in order to allow for superheating to 70 °C in order to shorten the reaction times. The excess DAST and byproduct HF are quenched *in situ*. Steven Ley and co-workers have also reported on a fluorination method using DAST in a continuous flow microreactor (*Synlett* **2008**, *14*, 2111). They also chose dichloromethane as the solvent of choice, and used a 100 psi backpressure regulator to extend the temperature range up to 90 °C. They accomplished in-line purification using a glass column filled with equal amounts of calcium carbonate and silica gel. In addition to conversion of alcohols and aldehydes to the corresponding fluoride, clean transformation of two ketones to the corresponding difluoride was also achieved. The use of DAST as a cyclodehydration reagent to synthesize oxazolines from β-hydroxyamides was also demonstrated.

Seeberger *et al.* have also reported trimethylaluminum-mediated amide bond formation in a continuous flow microreactor (*Chem. Commun.* **2008**, *9*, 1100). Equimolar amounts of the amine, ester, and trimethylaluminum were mixed at 125 °C in THF for 2 min in a microreactor system. The release of gas due to the reaction of the amine with trimethylaluminum was not a problem, but substrates with acidic protons made the reaction more sensitive to high concentrations due to the pressure from the additional equivalent of methane gas. The crude reaction mixtures were continuously quenched with aqueous HCl by one of two methods. The authors report the synthesis of two pharmaceutically active substances to demonstrate the utility of the method.

The precise temperature control provided by microreactors enables researchers to fine-tune reaction conditions in order to maximize the yield of desired products and minimize impurities. Guangsheng Luo and researchers at Tsinghua University in Beijing have reported on improving the selectivity of temperature sensitive exothermic reactions (*Ind. Eng. Chem. Res.* **2008**, *47*, 4683). The reaction between cyclohexane carboxylic acid with oleum was used to demonstrate the principle. Conditions were found that allowed for good selectivity and conversion for the multiphase reaction. The selectivity was 99.6% at 65 °C for the flow process, while the selectivity dropped to 97% at 60 °C for a batch process. In addition to the relative insensitivity to temperature, the throughput for the flow process was 4 times higher than the batch process.

The rapid mixing provided by microreactors has been utilized for the efficient oxidation of sulfides to sulfoxides with H_2O_2 by Kirihara and co-workers (*Chem. Commun.* **2008**, *26*, 3040). The oxidation normally requires long reaction times in batch processing mode, and a significant amount of the sulfone overoxidation impurity is observed. The authors started with thioanisole as a model compound and studied its oxidation in a T-shaped micromixer. The solvent, reaction temperature, equivalents of H_2O_2, and residence time were investigated. The optimal conditions were found to be reaction in acetonitrile at 25 °C using 20 equiv of H_2O_2, and a residence time of 2.12 s to give 97% isolated yield of the desired sulfoxide and no sulfone. Several different sulfides were oxidized using the flow and batch methods, and the yields were higher for the flow method in each case.

Steven Ley and co-workers from the University of Cambridge and Jason Tierney from GlaxoSmithKline have reported a fully automated flow process for performing Curtius rearrangements with *in situ* trapping of the isocyanate rearrangement product (*Org. Biomol. Chem.* **2008**, *6*, 1577). Use of in-line polymer supported scavengers allows for isolation of the desired products without the need for laborious purification. An acetonitrile solution of triethylamine, the carboxylic acid, and the nucleophile was loaded into channel one, and an acetonitrile solution of diphenylphosphorylazide (DPPA) was loaded into channel two, and the two streams were combined in a simple T-mixing piece. After a residence time of 20−50 min at 120 °C in a convection flow coil (CFC) reactor, the resulting stream was purified by passage through a mixture of A-21 and A-15 scavengers. A wide range of products were obtained in good yield (>75%) and purity (>90%). Incorporation of a microwave device was used to obtain a Boc-protected amine, and substitution of triethylamine with 2,6-lutidine and substitution of the A-21 scavenger with PS-2,6-di-*tert*-butylpyridine resulted in efficient synthesis of an Fmoc-protected derivative. A further modification of the original process is also described to allow for the use of additional heterocyclic carboxylic acid building blocks. Finally, a protocol for the synthesis of mixed semicarbazide adducts using hydrazine-derived nucleophiles is discussed. In a second paper, the researchers from the University of Cambridge describe an immobilized azide source for the conversion of acid chlorides using Curtius chemistry (*Org. Biomol. Chem.* **2008**, *6*, 1587). A monolith was employed as the solid support in order to avoid large pressure drops or channeling that can be observed with gel-type resins or macroporous beads. The azide anions were immobilized onto ion-exchange resins to reduce the associated handling risks. The acyl azides were prepared by simply flowing an acetonitrile solution of the acid chlorides through the azide-exchange monolith. The stream was then fed through a drying column and then a CFC heated to 120 °C to promote rearrangement to the isocyanate. The isocyanates were collected in microwave vials containing various nucleophiles, sealed, and irradiated with microwaves at 100 °C for 10 min to obtain the desired products in good yields.

The generation and use of diazomethane is often avoided due its explosive nature. Recently, a continuous microscale system for the generation of diazomethane from Diazald and the subsequent *in situ* conversion of the diazomethane to the desired product was described by Annegret Stark *et al.* (*Green Chem.* **2008**, *10*, 41). The direct conversion of benzoic acid to benzoic acid methyl ester was studied extensively in the continuous system.

Kirschning and co-workers from the Institut für Organische Chemie have reported on Suzuki−Miyaura and Heck−Mizoroki reactions in flow-through mode using Najera's oxime-based palladacycle immobilized on poly(4-vinylpyridine) (*Synthesis* **2008**, *10*, 1589). First, Suzuki−Miyaura cross-coupling reactions were performed to test the catalytic activity of the precatalyst loaded onto a solid support. Several boronic acids gave good yields with *p*-bromoacetophenone as the coupling partner, but aryl bromides containing electron-donating substituents gave moderate yields of coupling products with phenylboronic acid. The sterically congested 2,6-dimethylbromobenzene gave a low yield when coupled with phenylboronic acid. 2-Bromothiazole, 3-bromothiophene, and 2-bromothiophenol were not suitable for achieving cross-coupling products under these continuous flow conditions. A small degree of reduced activity was observed after the fifth consecutive 24-h run, and no formation of palladium black was observed. Next, Heck−Mizoroki reactions were carried out at 110−120 °C in DMF with tributylamine. Aryl iodides gave satisfactory results, but aryl bromides gave only low to moderate yields of the coupling products. There was no loss of activity after 10 consecutive reactions, but some formation of palladium black was noted. Studies directed at understanding the nature of the catalyst species suggest that poly(4-vinylpyridine) may serve as a reservoir of a catalytically active palladium(0) which is released into solution.

Chemical Storage

Although a large number of resources are available to explain proper chemical storage, almost 25% of all chemical accidents stem from improper storage conditions. The authors of a recent paper argue that the available resources for proper storage of hazardous chemicals are helpful but provide insufficient information to completely mitigate storage risks (*J. Health Saf.* **2008**, *March/April*, 23). The take-home message is that there is no cookbook for chemical storage. Safe chemical storage cannot be reduced to a checklist or chart. The best approach for proper chemical storage is a process of several major steps that are specifically designed for the size and complexity of the inventory. The article explores the data gaps in the published storage information, examines the associated risks, and suggests methods to facilitate the continued removal of chemical storage risks.

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. For additional online resources, a comprehensive list of web-based resources on safety and environmental compliance was recently published (*Environ. Progr.* **2007**, *26*(4), 316). 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. EPA's Green Chemistry R&D: http://www.epa.gov/ORD/.
2. Center for Chemical Process Safety: http://www.aiche.org/ccps/.
3. AIHA Laboratory Health & Safety Committee: http://www2.umdnj.edu/eohessweb/aiha/accidents/index.htm.
4. The Laboratory Safety Institute: http://labsafety.org.
5. NOAA'S Chemical Reactivity Worksheet (click on "downloads" at): http://response.restoration.noaa.gov.
6. Safety videos from U.S. Chemical Safety & Hazard Investigation Board:http://www.youtube.com/profile?user=USCSB.

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