Organic Process Research & Development

Highlights from the Literature

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Safety Notables: Information from the Literature

This is the 10th annual literature overview on safety issues that 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 that 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 reveal how they are solving these problems.

CHEMICAL PROCESS SAFETY INCIDENTS: LEARNING FROM HISTORY

Design as a contributor to chemical process accidents was the subject of a paper by Kidam and Hurme (*J. Loss Prev. Process Ind.* **2012**, *25*, 655). The authors initially analyzed almost 300 major equipment-related accidents recorded in the Failure Knowledge Database (FKD). This analysis indicated that 79% of cases analyzed could be attributed to errors in the design phase. The paper then endeavored to pinpoint the time of occurrence of mistakes in a typical plant design project in order to further understand the major contributing factors. It was discovered that poor layout (17%), incomplete consideration of chemical reactivity or compatibility (16%), and poorly chosen process conditions (16%) were the most critical design errors. The authors also present a table mapping categories of the most common design errors (layout, process conditions, etc.) against phases of a typical design project (preliminary design, basic engineering, detailed engineering, etc.) and then assign values to each of the design error categories. This table is intended to help engineers focus on those design-error types that have been most commonly overlooked during earlier process plant designs.

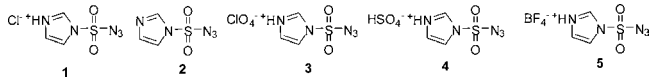
HANDLING HAZARDOUS CHEMICALS

Further contributions from William Luttrell have been published to help in the assessment of hazards associated with the handling of select organic compounds. The latest reviews appear in *J. Chem. Health Saf.* and provide a helpful supplement to material safety data sheets (MSDS), which should, of course, continue to be consulted before utilizing any new organic compound. This year's entries were vinyl chloride (*J. Chem. Health Saf.* **2012**, January/February, 30), xylene (*J. Chem. Health Saf.* **2012**, March/April, 34), toluene (*J. Chem. Health Saf.* **2012**, May/June, 34), and ethylene glycol (*J. Chem. Health Saf.* **2012**, September/October, 56).

David Leggett has authored two recent papers on Lab-HIRA (hazard identification and risk analysis for the chemical research laboratory). The first paper (*J. Chem. Health Saf.* **2012**, September/October, 9) describes how Lab-HIRA is used to assign a hazard severity levels to each reagent employed in a synthesis, to the overall synthesis itself, and to the reaction conditions employed. The procedure draws on 33 parameters, indicative of the hazardous properties of molecules and/or the operational conditions of the synthesis, to define the overall hazard potential. The second paper (*J. Chem. Health Saf.* **2012**, September/October, 25) outlines the procedure used to conduct a more formal risk analysis, which would follow the initial hazard identification assessment.

SAFER REAGENTS

Sensitivities of Imidazole-1-sulfonyl Azide Salts. A popular method to prepare organic azides involves the conversion of a primary amine to the desired azide by the action of a powerful diazo donor, most commonly a sulfonyl azide. Imidazole-1-sulfonyl azide hydrochloride (**1**) was previously developed and reported to be an inexpensive and shelf-stable diazo-transfer reagent that showed good efficacy (*Org. Lett.* **2007**, *9*, 3797). However, a follow-up note to this report was published, citing an explosion that occurred during the synthesis of this compound (*Org. Lett.* **2011**, *13*(9), 2514). As a result, Fischer et al. sought to quantify the sensitivity of **1**, the parent compound (**2**), and other salts (**3**–**5**) toward impact, friction, and



electrostatic discharge to provide a rational assessment of the relative safety of these compounds (*J. Org. Chem.* **2012**, *77*, 1760). The synthetic method for **2** and its salts (**1**,**3**-**5**) was presented, followed by data from thermal stability (DSC), impact sensitivity (BAM drophammer), friction sensitivity (BAM friction tester), and electrostatic discharge sensitivity testing (electric spark tester, ESD 2010 EN). This led to the conclusion that **2**, a neat liquid, should only be prepared and used in situ due to high sensitivity to impact and friction. The perchlorate ($HClO_4$) salt (**3**) was considered even more hazardous than the parent compound and "should not be prepared by those without expertise in handling energetic materials". Of particular interest was **1**, which showed sensitivity to impact and friction (not as sensitive as **2** or **3**) and must also be handled with caution. It was the opinion of the authors than the hydrogen sulfate (H_2SO_4; **4**) and tetrafluoroborate (HBF_4; **5**) salts are safer to manipulate, although they note that all usual precautions taken when handling energetic laboratory reagents should still be observed. These salts showed higher DSC decomposition temperatures and lower impact sensitivity when compared to **1**.

The authors also noted that the shelf-stability of each reagent is very important, especially if the reagents are to be kept in bulk. If not stored with dessication, **1** discolors and liquefies within a few weeks, producing brown oil that has the odor of hydrazoic acid. Hydrazoic acid is known to be explosive at room temperature and is also volatile (BP = 37 °C). **4** is less hygroscopic, although given a little over a year in storage (without desiccation), this salt also discolored and liquefied with the liberation of hydrazoic acid. Only **5** was unaffected by storage under ambient conditions for one year. The authors

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concluded **5** has the most favorable characteristics, but suggest **4** could be used if stored with the exclusion of moisture (if lower cost and ease of preparation is desired).

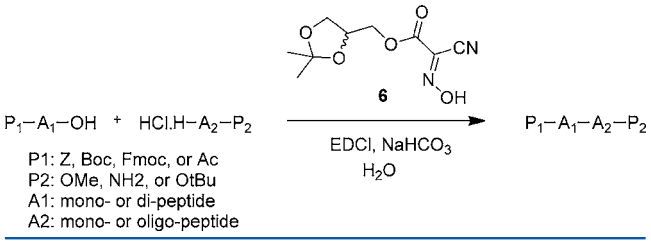
The authors concluded at the end of the paper that despite the advantages to **4** and **5**, none of the compounds was found to be completely insensitive, which would restrict transportation options and commercialization. They suggest that additives should be investigated to increase the shelf life of each compound.

Recently, benzotriazole-1-sulfonyl azide was presented as another effective diazo-transfer reagent (*J. Org. Chem.* **2010**, *75*(19), 6532). However, a follow-up note to this report was published by the authors in 2012 in which an explosion occurred with this solid following an acidic workup (using 6 N HCl). It was proposed that trace amounts of sodium azide could have been converted to highly explosive hydrazoic acid during that workup and that it was likely that this was responsible for the explosion. As sodium azide is used during the preparation of these imidazole-1-sulfonyl azide salts as well, an acidic workup would be expected to produce a similar result.

Extreme caution should be exercised when handling these diazo-transfer reagents (and any similar alternatives), treating them as potentially explosive compounds. Formation and use of the reagents in situ would minimize the potential for impact/friction sensitivity and would also provide an advantage due to dilution. Acidic workups should also be avoided due to the potential to form hydrazoic acid.

New Oxyma Derivative for Amide Bond Formations in Water. Wang and co-workers present a new derivative of Oxyma (2,2-dimethyl-1,3-dioxolan-4-yl)methyl 2-cyano-2-(hydroxyimino)-acetate, **6**) as a peptide-coupling additive for peptide-forming reactions in water (Scheme 1) (*Org. Lett.* **2012**, *14*(13), 3372).

Scheme 1

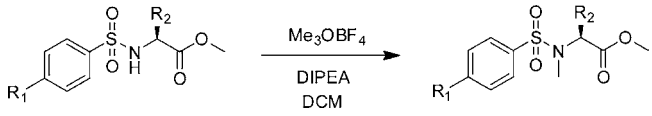


Oxyma (ethyl 2-cyano-2-(hydroxyimino)acetate) has been suggested to be less sensitive to shock and friction (explosivity) than traditional additives such as HOBt and HOAt, and as a result, it is thought to be a safer alternative (*Chem. Eur. J.* **2009**, *15*, 9394). This was based on a much broader DSC decomposition exotherm (despite a lower onset temperature), a smaller DSC decomposition energy, and a much lower decomposition pressure for Oxyma when compared to those of HOBt hydrate and HOAt. A comparison was not performed for shock or friction sensitivity. The authors expect that **6** would also be a safer alternative to HOBt and HOAt, although there is no shock/friction sensitivity or thermal stability data presented in the paper.

In addition, the authors state that this is the first reported example of a peptide-coupling additive used for the synthesis of oligopeptides in water, representing an improvement in green chemistry. The synthesis of **6** was presented (along with another Oxyma derivative), and the two derivatives were compared with Oxyma in a standard peptide-coupling reaction in water. The proposed derivative (**6**) was by far the most successful in that reaction, and afterwards those conditions were applied to the synthesis of a wide variety of dipeptides and tripeptides with partially protected α-amino acids to show effectiveness. Simple acidic and basic aqueous workup procedures were also shown to remove all reagents utilized in the reactions to give coupling products in high yield with high purity.

Trimethyloxonium Tetrafluoroborate as Replacement for Diazomethane for N-Methylations. De Marco et al. present the use of trimethyloxonium tetrafluoroborate in place of diazomethane for N-methylation reactions (Scheme 2)

Scheme 2



(*Tetrahedron* **2011**, *67*, 9708), which had previously been published by their research group (*J. Org. Chem.* **2003**, *68*, 7416). The rationale for the authors was the improvement in process safety, as diazomethane is known to be explosive and toxic, and this reagent also proved to be more efficient than diazomethane for less reactive substrates. The methodology was also extended to triethyloxonium tetrafluoroborate for N-ethylation to demonstrate validity.

DABSO as Replacement for Gaseous SO_2. Sulfur dioxide has many potential applications in organic synthesis, but the difficulty of handling a toxic gaseous reagent is a factor that limits its wider use, especially as the reaction scale increases. Woolven et al. (*Org. Lett.* **2011**, *13*(18), 4876) have introduced the combination of DABCO (1,4-diazabicyclo[2.2.2]-octane) and sulfur dioxide, making DABCO-bis(sulfur dioxide) (abbreviated as DABSO), as a bench-stable solid reagent that can function as a sulfur dioxide equivalent in a number of processes (Figure 1). The particular applications studied in this

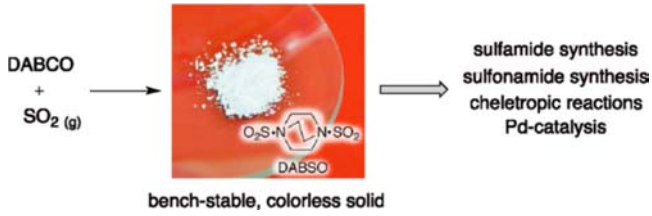


Figure 1. DABSO, formed from DABCO and sulfur dioxide, and some of its applications.

paper include the formation of sulfonamides, sulfamides, and sulfolenes. The authors suggest that this reagent could have a much wider use and continue to look for further application in their laboratory.

Alternative Bromination Conditions. Bromination of unsaturated C–C bonds has traditionally been performed by using molecular bromine as a reagent, mainly in chlorinated solvents and under harsh reaction conditions. Several dibromination methods have been developed recently using more environmentally benign bromination reagents, but these alternative protocols often use problematic substances or harsh conditions as well. For example, the use of NBS as a brominating agent usually leads to dibromination byproducts, requires the presence of inorganic bromide salts, and/or requires high

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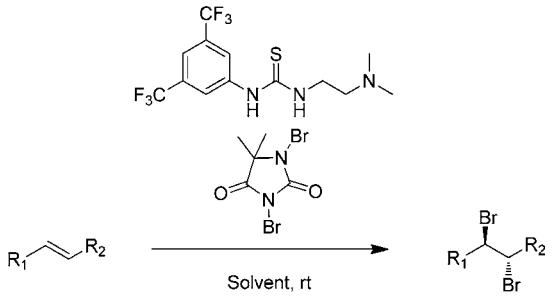
reaction temperatures. Hernández-Torres and co-workers present a dibromination technique (for unsaturated alkenes) that uses a solid, inexpensive bromine source (1,3-dibromo 5,5-dimethylhydantoin) with a thiourea catalyst at room temperature (Scheme 3) (*Org. Lett.* **2012**, *14*(7), 1858). The use of

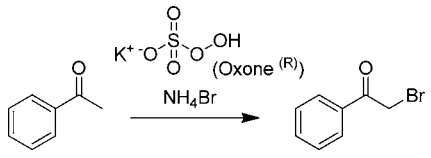
Scheme 3



a tertiary amine to enhance the reaction rate was studied, and yields were comparable in various solvents, including aqueous solvents. The procedure was extended to alkynes, aromatic rings, and dichlorination reactions (1,3-dichlorohydantoin derivative).

Similarly, the most commonly used reagents for α-bromination of ketones include molecular bromine, NBS, and cupric bromide. Though each provides good yields, each suffers from one or more disadvantages such as long reaction times, harsh reaction conditions, use of hazardous chemicals, and cumbersome workup procedures. Marcharla et al. present an efficient and environmentally safe method for the α-bromination of ketones using ammonium bromide and Oxone (Scheme 4)

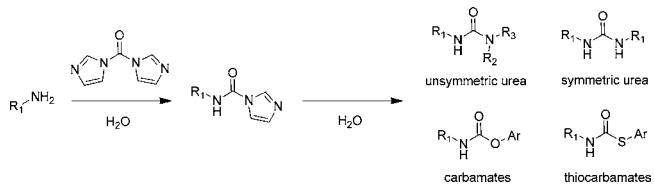
Scheme 4



(*Tetrahedron Lett.* **2012**, *53*, 191). The reaction proceeds at ambient temperature, but it should be noted that yields were low and reaction times long for some systems at this temperature. The authors reported the reactions proceed at reflux as well, but the thermal stability of Oxone should be further investigated if heating the system.

'Greener' Preparations of Urea and Carbamate Functional Groups. Urea and carbamate are important functional groups in many industries, and although a number of methodologies exist to synthesize these groups, 1,1′-carbonyldiimidazole (CDI) remains the most widely used reagent as many alternatives are highly toxic and create hazardous byproducts. CDI is relatively mild but is moisture sensitive and is known to react with water to evolve carbon dioxide (and yield 2 equiv of imidazole). As a result, organic solvents are typically used in reactions containing CDI, preferably under anhydrous conditions. Surprisingly, Padiya et al. report conditions in which the reaction of CDI with amines (eventually forming urea, carbamate, or thiocarbamate functional groups) occurs in water (Scheme 5) (*Org. Lett.* **2012**, *14*(11), 2814). The authors completed this transformation on a variety of primary and secondary amines at 0 °C with only a 20% excess of CDI. Each reaction is reported

Scheme 5

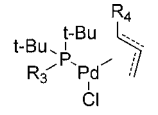


to go to completion within 10 min with water as a solvent, which is comparatively much faster than the reaction in organic systems. It should be noted that the authors also report a complete reaction of CDI with water at that temperature in only 10 min (in the absence of reagent).

Another "green" approach to CDI-mediated amide formations was presented by Verma and co-workers (*Tetrahedron Lett.* **2012**, *53*, 2373). This approach, which has also been used for Boc-protection of amines, has been reported to reduce the time for amidations from 2 to 4 h to 5 to 10 min without the use of any dry organic solvent (solvent-free) and nitrogen atmosphere. In contrast to the report above, these authors tried this reaction in water and reported that hydrolysis is dominant over the amide formation. However, they also reported that in the presence of catalytic imidazole hydrochloride (0.1 mol %) and a minimum amount of water, the amide formation was successful. The authors do suspect that the rate enhancements are likely attributed to the exothermic nature of the reactions (especially for the solvent-free conditions).

While neither of these articles may present directly scalable conditions for CDI-mediated amide formations, each suggests that these reactions may be performed in "greener" systems, thus enhancing the overall safety profile of the process.

Air-Stable Palladium Catalyst–Ligand Complexes.



11 different catalysts

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There are many reactions that require the complex of a catalyst and a ligand to be successful. In many protocols, the active catalyst is formed in situ by the addition of a palladium precursor to the ligand of choice. Typically, an excess of ligand is required (problematic if the ligand is expensive), and handling and storage can be an issue if the ligand is air sensitive or pyrophoric. Seechum and co-workers (Johnson Matthey Catalysis and Chiral Technologies) synthesized a series of Pd(R-allyl)LCl complexes, **7**, and evaluated them in Buchwald–Hartwig aminations, in addition to preliminary studies on the Suzuki coupling and α-arylation reactions (*J. Org. Chem.* **2011**, *76*, 7918). The comparison for each catalyst across the various reaction types is presented in the paper. The safety advantage from the use of these catalysts would be the reduction in hazards from the handling and storage, as the majority of the catalyst–ligand complexes were shown to be air stable.

Multikilogram-Scale Synthesis of a Chiral Cyclopropanol and an Investigation of the Safe Use of Lithium Acetylide–Ethylene Diamine Complex. Baxter and co-workers at Merck describe the multikilogram-scale synthesis of a chiral cyclopropanol ***ent*-8** and their work to enable the safe use of lithium acetylide–ethylene diamine complex **9** at 12.3 kg scale of **9** (Scheme 6) (*Org. Process Res. Dev.* **2012**, *15*, 87).

Although **9** is a relatively air stable, commercially available solid, its use on scale required extensive process safety work. The conversion in Scheme 6 required the use of a polar aprotic

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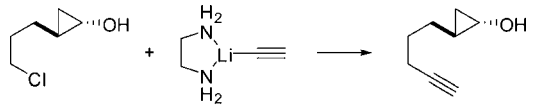
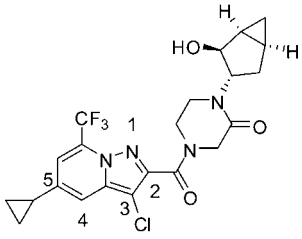
Scheme 6



9 rac-8

solvent (e.g., dimethyl sulfoxide (DMSO), *N*,*N*′-dimethylacetamide (DMAc), or *N*-methylpyrrolidinone (NMP)). The known thermal instability of polar aprotic solvents with strong bases was an immediate concern. Accelerating rate calorimetry (ARC) tests confirmed that DMSO was unsuitable for scale up due to the low decomposition onset, the large adiabatic temperature rise, and the very fast rates of decomposition. Additional solvent screening identified 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)pyrimidone (DMPU) as a better solvent from a safety perspective. In the original synthesis 2.1 equiv of **9** was required which led to the generation of a full equivalent of acetylene. The authors remind the reader of the very high flammability of acetylene which is classified as a Class 1 Group A solvent in the United Sates, a rating that is higher than those of hydrogen gas, ethylene oxide, and butadiene. Under the European Classification an IIC-rated plant is needed to handle significant quantities of acetylene. By using *n*-hexyllithium as a sacrificial base, they were able to greatly reduce the amount of acetylene generated, but ReactIR showed that acetylene was still being generated at a peak level of 7.2% in the headspace. This is at a level that requires the use of a properly rated plant (as described above). After the other process safety concerns were addressed, the chemistry above was scaled to provide 12.5 kg of **rac-8** in greater than 70% yield.

Ir C−H Activation and Other Catalysis Applied to a Complex Drug Candidate.



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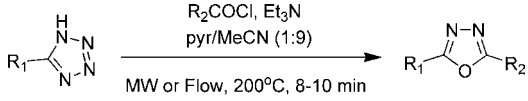
Davis and co-workers at GlaxoSmithKline demonstrate the use of a variety of transition metal catalysts to devise a safe route to several challenging structural motifs in a complex drug candidate, GSK 2585337A, **10** (*Top. Catal.* **2012**, *55*, 446). The original synthesis of the pyrazolopyridine used thermally unstable *O*-mesitylsulfonylhydroxylamine (MSH). They tried to substitute the more thermally stable hydroxylamine *O*-sulfonic acid (HOSA), but it did not provide the desired *N*-aminopyridinium. They were able to use CuI/$FSO_2CF_2CO_2Me$ to install a CF_3 group on the pyrazolopyridine core and IrOMe(COD)/bipyridine to activate the remote C5 position of the pyrazolopyridine to eliminate the need to use the hydroxylamine derivatives. By using the Ru (Hoveyda−Grubbs catalyst) to prepare a chiral aminocyclopentenone for oxysulfonium cyclopropanation, they were able to avoid the energetic intermediates inherent in the Simmons−Smith cyclopropanation and Curtius rearrangement. Through the prudent use of transition metal catalysts, the group demonstrated the ability to safely generate a diastereomerically complex molecule on kilogram scale without compromising safety.

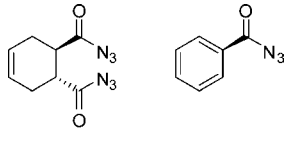
FLOW CHEMISTRY

High-Temperature Continuous Flow Synthesis of Oxadiazoles. The Huisgen reaction (Huisgen, R.; Sauer, J.; Sturm, H. J. *Angew. Chem.* **1958**, *70*, 272) synthesizes 1,3,4-oxadiazoles by reaction of 5-substituted-1*H*-tetrazoles with electrophiles (such as carboxylic acid anhydrides or acid chlorides). Tetrazole derivatives are high-energy compounds that are currently used as propellants and explosives. Due to the known thermal instability of the tetrazole nucleus, this method is not typically used on large scale. Reichart and Kappe describe a continuous flow application for this transformation via the Huisgen reaction (Scheme 7) (*Tetrahedron Lett.* **2012**, *53*, 952). The microreactor approach allows for only very small volumes of high-energy tetrazole to be thermally stressed at a time, drastically decreasing the severity of a potential decomposition reaction. Also, the use of a high-temperature/high-pressure flow regime allowed a drastic intensification of the reaction, leading to a reduction in reaction times to 5−10 min. Optimum reaction conditions were rapidly identified using microwave batch technology and were then translated to a continuous flow protocol. This represents yet another example of the safety benefit through the use of continuous flow technology.

Scheme 7



Acyl Azide Synthesis and Curtius Rearrangement in Microstructured Flow Chemistry Systems. Wille and coworkers at Sigma-Aldrich describe the use of a commercially available microstructured flow system and a newly designed automated extraction unit to safely generate 100-g quantities of acyl azides (*J. Flow Chem.* **2012**, *1*, 20). The automated extraction unit is able to accommodate flows of >10 mL/min and maintained the phase split in a given range (30−50 mL of organic phase) through the use of an impedance probe. Sometimes the acyl azides were so unstable that they were carried on to the next step (e.g., Curtius rearrangement) in flow. For example, the differential scanning calorimetry (DSC) test of a 1 M solution of diacyl azide **11** showed a decomposition onset below room temperature with a decomposition energy of 346 J/g. As a result, diacyl azide was driven to the diamine in flow. However, they found some of aryl azides to be stable enough to be sold commercially as 0.5 M solutions in *tert*-butyl methyl ether (TBME). For example, the DSC test of a 0.5 M solution of acyl azide **12** showed a decomposition energy of 187 J/g and the solution was shown to be stable by Radex at 75 °C for at least 8 h. With the commercially available glass microreactor and the automated extraction unit, they achieved a nonoptimized output of ∼30 g/h of **12** (80% yield, 96.0% purity by high performance liquid chromatography (HPLC)).



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DUST EXPLOSION HAZARDS

Collective Analysis of Pharmaceutical Dust Explosion Testing Data. As organic solids are handled in increasing scale, the need to characterize their dust explosion potential becomes of greater importance. Richter has summarized 240 safety reports of dust data of active pharmaceutical ingredients, pharmaceutical intermediates, and nutritional powders that have been collected by Abbott over the past 20 years (*Process Saf. Prog.* **2012**, *31*(2), 165). There are a number of other literature sources for dust explosion data of organic solids, "However, publicly available data for pharmaceutical powders is limited. Testing is expensive in terms of financial costs, laboratory time, and material costs, particularly in the case of active pharmaceutical ingredients (APIs) where material is precious and the amounts required for testing can represent a significant fraction of a given delivery in early phases of pharmaceutical development." Richter presents collective data for minimum ignition energy (MIE), minimum explosible concentration (MEC), minimum autoignition temperature-dust cloud (MAIT), and explosion severity testing. The data do not negate the need for dust testing specific materials, but there are many useful trends that can be seen in the data which can be useful in a multiuse facility. For example, almost half of the pharmaceutical samples (47%) had MIE's below 10 mJ, so using precautionary measures for this degree of hazard seem to be prudent for all pharmaceutical solids on scale. In general, the nutritional powders tend to be less hazardous than the APIs. Therefore, additional precautions may need to be implemented if APIs are to be manufactured in a plant that was designed for nutritional products. The collective data also allow design engineers to take into account the frequency of expected hazards when designing new plants.

PROCESS HAZARD ANALYSIS/PROCESS SAFETY MANAGEMENT

The Intersection of Process Safety and Corporate Responsibility. During the keynote address at the AIChE 2012 Spring Meeting and Global Congress on Process Safety, Michael Dolan of Exxon Mobil, called on the chemical process industries "to elevate process safety to a central role in our operations and a critical component of corporate social responsibility" (*Chem. Eng. Prog.* **2012**, *108*(6), 24). He reiterates that personnel safety incident rates (e.g., slips, trips, and falls) are not reliable indicators of our process safety performance. Since AIChE's founding in 1908, it has focused on engineering education and training. Dolan calls for us to continue our support of the Safety in Chemical Engineering Education program (SAChE), which works to integrate process safety into the entire chemical engineering curriculum. It needs to be more than just a single course, but rather a part of our core thought process. However, it does not end with colleges and universities. He lays out tough questions for various decision makers: design engineers, manufacturing engineers, process safety specialists, executives, and advocacy groups. Failure to take up this moral charge comes with great risks for our employees, the public, our profession, and our industry.

Over the last few decades, process safety management has evolved and matured considerably as a concept. Nonetheless, incidents continue to occur, often due to insufficient understanding of the urgency to identify best practices and drive process safety improvements within organizations. A paper by Mannan et al. of the Mary Kay O'Connor Process Safety Center of Texas A&M (*Process Saf. Environ.* **2012**, *90*, 91) addresses several of the critical challenges in implementing effective safety programs. Factors include a failure to learn from past incidents and to incorporate this experience into process designs, procedures, and training; failure to recognize leading indicators; increased complexity of process operations; and lack of communication. All of these factors are discussed in full, and the article provides an example on liquefied natural gas (LNG) industry safety to illustrate the importance of a science-based approach in mitigating unintended outcomes.

Dharmavaram and Klein of DuPont published a paper entitled "An Introduction to Assessing Process Hazards" (*Process Saf. Prog.* **2012**, September, 266). The article underscores the unfortunate fact that often an inadequate understanding of process hazards or a lack of basic hazard evaluation can directly lead to a poorly executed process hazard assessment (PHA), which in turn can be the genesis of adverse process incidents. The article emphasizes the value of carrying out an intrinsic hazard assessment (IHA), prior to undertaking the traditional PHA. It describes a systematic approach to execution of an IHA where the goal is to fully understand and document any process hazards. This differs from a PHA where the focus is on identifying relevant hazards, conducting a risk analysis, and implementing measures to mitigate the risk. The IHA evaluates a variety of physical and chemical properties then forms a composite hazard level score. This information is then employed to ensure a comprehensive PHA that uses multiple sources and types of data.

CHEMICAL ENGINEERING ASPECTS OF SCALE UP

Heat Transfer-Based Scale-Down of Chemical Reactions. In the pharmaceutical and fine chemicals industries, chemical engineers typically consider how to take a laboratory process and take it safely into a fixed equipment train (i.e., scale up). Davis and Viswanath of Eli Lilly present a new experimental paradigm in which the thought process is reversed—the plant process is scaled down into a similarly controlled lab reactor (*Org. Process Res. Dev.* **2012**, *15*, 1360). Their methodology simplifies many of the existing scale-up models and accurately predicts temperature profiles for both dose-controlled and nondose controlled reactions. They begin by thoroughly characterizing the heating and cooling behavior of both the plant reactor and lab reactor. They then constrain their lab equipment to mimic the behavior of the plant (e.g., maximum heat removal and maximum rate of temperature change). Besides accurate prediction of dosing curves and temperature profiles, the method has the advantage of accurately predicting impurity profiles that will be observed on-scale without needing to have an in depth knowledge of the kinetics of the system. They present their results for a scale up from a 0.5 to an 8 L reactor and from a 0.5 L reactor to an 8000 L reactor. They used a Mettler RTCal reactor and worked with Mettler to develop the Mettler iC Data Share module, which allows an Excel macro to input instrument values and then calculate and output the parameters for jacket control. However, their methodology is not limited to those laboratories which have access to a Mettler RTCal, since their method can be run on "any computer-controlled, physically well-characterized jacketed reactor that is capable of accurately measuring reaction and jacket temperatures and can react to rapid jacket set-point changes."

INHERENT SAFETY

An excellent article which reviews developments related to inherent process safety was published by Srinivasan of the

National University of Singapore (NUS) and Natarajan of the Institute of Chemical and Engineering Science (ICES) (*Process Saf. Environ.* **2012**, *90*, 389). The paper initially presents a summary of historical developments in inherent safety up to the year 2000 and then reviews the literature in the subsequent 11 years pertaining to developments in inherently safe design and the basic concepts of inherent safety. A total of 187 papers are classified into those which cover the following: material hazards, chemistry hazards, unit operation hazards, flow sheet and layout hazards, storage and transportation, and process control and human factors.

Mannan et al. of the Mary Kay O'Connor Process Safety Center of Texas A&M dedicates a paper (*Process Saf. Environ.* **2012**, *90*, 404) on an improved and inherently safe process for the N-oxidation of 3-picoline to Professor Trevor Kletz for his unique contributions to the field of process safety. It was demonstrated that conducting the N-oxidation under pressure and using 35% aqueous hydrogen peroxide as the oxidant at 110−125 °C rendered the process inherently safer, since hydrogen peroxide decomposition was insignificant and hence accumulation in the reactor was zero. This factor in turn eliminated any requirement to use excess peroxide to achieve full conversion, further improving safety.

■ TREVOR KLETZ

Related to the above article, Professor Trevor Kletz, one of the world's most foremost experts on process safety celebrated his 90th birthday in 2012, and numerous tributes have been paid to Trevor in the literature this year. Indeed the *Loss Prevention Bulletin* (*Loss Prev. Bull.* **2012**, October) has dedicated an entire issue as a birthday tribute issue to Trevor. Trevor has written numerous books on process safety, learning from accidents and inherently safe process design over his long and distinguished career, and we also add our congratulations to Trevor on the occasion of his birthday.

In sending Trevor these congratulations it seems only right that we should end this safety review with reference to an article by Trevor where he presents his thoughts on the history of process chemistry and his involvement in the development of that history, *J. Loss Prev. Process Ind.* **2012**, *25*, 763.

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