Organic Process Research & Development

HIGHLIGHTS FROM THE LITERATURE

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Safety Notables: Information from the Literature

This is the ninth annual literature overview to appear in *Org. Process Res. Dev* on safety issues that are of interest to process chemists and engineers. As in the previous years, this review covers 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 how they are solving these problems.

■ TOXIC TIPS

William E. Luttrell continues to write reviews on organic molecules and the precautions that should be taken while working with these compounds. These molecular safety reviews appear in the *Journal of Chemical Health & Safety* (*J. Chem. Health Saf.*) and are a good addition to the MSDS which should be read prior to working with any new organic compound. Ethylene dichloride (*J. Chem. Health Saf.* **2010**, Sept/Oct, 29), ethylbenzene (*J. Chem. Health Saf.* **2011**, Jan/Feb, 41), butyraldehyde (*J. Chem. Health Saf.* **2011**, March/April, 27), benzene (*J. Chem. Health Saf.* **2011**, July/August, 32) were the more recent additions to this series.

■ EXPANSION OF A SOLVENT SELECTION GUIDE

Richard Henderson and his co-workers at GlaxoSmithKline (GSK) have published a solvent selection guide as part of GSK's award winning Eco-Design Toolkit. This Toolkit is a suite of web-based tools that provide clear practical information and guidance to scientists and engineers to enable them to move towards a more sustainable design and development of the chemical processes used in the manufacture of active pharmaceutical ingredients (APIs) (*Green Chem.* **2011**, *13*, 854). Solvents contribute a large environmental impact to the manufacture of APIs with millions of tons of solvents disposed of each year. This new solvent selection guide enables GSK scientists to objectively assess solvents for the chemical process they are attempting to run. The article breaks down the solvent selection process for chemists and engineers in chemical development, as expected, but also gives guidance for medicinal chemists and analytical chemists. This revised GSK solvent guide is an example of how GSK continuously strives to make choosing the sustainable option not only the right thing to do but also the easy thing to accomplish.

■ WORKPLACE SAFETY

OSHA celebrated its 40th anniversary this year, and since its inception, work-related deaths have dropped from 14,000 in 1970 to 4,400 in 2009. Clearly, progress has been made, but 4,400 deaths are still far too many. In an article by Vince McLeod, the topic of how to keep moving forward in improving working conditions and workplace safety (*Lab Manager* **2011**, June, 10) was discussed. The author walks the reader through the progress OSHA has made from being viewed as the 'enforcer' of rules and regulations to a provider of free information and open assistance to companies wishing to provide a safer work environment. Specifically, he outlines OSHA's Voluntary Protection Program (VPP) and how the VPP provides official recognition to businesses and work sites that have demonstrated outstanding efforts of both employees and employers in achieving exemplary health and safety.

■ 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 such as Christopher Badeen and colleagues, working to prepare novel propellants, explosives, and other energetic materials, deal with the dangers and rigors of working with thermally unstable compounds on a daily basis. In one such example, the thermal hazard assessment of the production of nitrobenzene (*J. Hazard. Mater.* **2011**, *188*, 52) is outlined in good detail. During the production of nitrobenzene by an adiabatic nitration process, the main byproducts are mono- and dinitrophenols as well as 2,4,6-trinitrophenol and 1,3-dinitrobenzene. The byproducts can become concentrated during the distillation step to remove high-boiling impurities. The work outlined in this article led to the conclusion that short-term exposure of nitrobenzene mixtures containing up to 20% dinitrobenzene to temperatures up to 208 °C should not pose a serious runaway reaction hazard.

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.

■ DUST EXPLOSION HAZARDS

Ebadat of Chilworth Technology presents an article (*J. Loss Prev. Process Ind.* **2010**, *23*, 907) discussing dust explosion hazard assessments, a subject of obvious importance in most chemical manufacturing. It describes a systematic approach to identifying and managing dust cloud explosion risks. The article also highlights that, according to the U.S. Chemical Safety Board (CSB), information to adequately assess dust explosion hazards is often not provided in the MSDSs.

■ LEARNING FROM HISTORY

The past year has seen a number of articles underlining the importance of learning from past incidents. Chosnek broaches the subject of corporate memory or more importantly, the loss of

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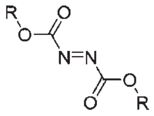
it in many instances when key staff members retire or leave an organization (*J. Loss Prev. Process Ind.* **2010**, *23*, 796). The paper advocates the creation of a system to form and maintain a corporate safety memory and describes how this can be implemented.

Abbasi et al. take the concept to a higher level, proposing the development of a new chemical process industry accident database to assist in past accident analysis (*J. Loss Prev. Process Ind.* **2010**, *24*, 426). The paper acknowledges the existence of a number of databases that already record past incidents including the Major Hazard Incident Data Service (MHIDAS), Major Accident Reporting System (MARS), and Failure and Accidents Technical Information Systems (FACTS). Some of these databases require an access fee or are not limited to chemical process industries. To address these drawbacks the authors have created a comprehensive open-source database to assist past accident analysis. The new resource is named PUPAD, is populated with 8000 accidents, and is viewed as a complementary resource to existing tools.

SAFER REAGENTS AND REAGENT HANDLING

Berger and Wehrstedt (members of the BAM Federal Institute for Materials Research and Testing, Division II.2 "Reactive Substances and Systems") present a wealth of data and expert analyses on the thermal stability and explosive properties of seven different azodicarboxylates [**1**] and two close relatives (*J. Loss Prev. Process Ind.* **2010**, *23*, 734). The most well-known member of this class, diethyl-azodicarboxylate (DEAD), is shock sensitive and thermally unstable to such an extent that the shipment of the pure reagent is prohibited in the United States. Since DEAD is shipped as a 40% solution in toluene, the authors tested that material as well. They tested the 10 materials by DSC, Deflagration test [C.2], Koenen test [E.1], Dutch pressure vessel test [E.2], Trauzl test [F.3], BAM Fallhammer [3(a)(ii)], and BAM Dewar test [H.4]. Perhaps one of the most interesting differences in the analogues was the large drop in severity in the Koenen test results upon addition of one carbon on the alkyl substituent going from DEAD to diisopropyl-diazocarboxylate (DIAD). Also noteworthy is the authors' statement that "based on the results of our experiments, the use of dichloromethane as a diluent for EDA [ethyldiazoacetate] poses a potential safety risk." Comprehensive DSC results are given at a variety of heating rates from 0.5 K/min to 40 K/min.



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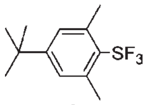
Pyrophoric reagents represent an important class of reactants in synthetic chemistry. An article by Quigley et al. discussing the safe handling and disposal of these materials in a laboratory setting provides a useful reference tool for any chemist working with pyrophoric liquids and solids (*J. Chem. Health Saf.* **2011**, Jan/Feb, 5).

As the importance of fluorinated compounds continues to grow in the pharmaceutical industry, new reagents continue to be proposed for the introduction of fluorine to complex organic molecules. Historically, the reagents have been toxic, difficult to handle, violently reactive with water, and thermally unstable with low onset temperatures and high decomposition energies. In recent years much progress has been made overcoming these shortcomings. Several articles were released within the last year about new fluorination reagents. One report is from Umemoto and co-workers that 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride (Fluolead) [**2**] is a thermally stable deoxofluorination reagent with high fluorinating capability and unusual resistance to aqueous hydrolysis (*J. Am. Chem. Soc.* **2010**, *132*, 18199). The authors studied at least 20 different aryl-substituted phenylsulfur trifluorides in an effort to use sterics and electronics to tune the reagents for desired traits. 4-*tert*-Butyl-2,6-dimethylphenylsulfur trifluoride [**2**] was the best fluorinating agent in terms of reactivity and stability. It is highly resistant to aqueous hydrolysis. Among the many clean conversions are nonenolizable carbonyls to CF_2 groups and carboxylic groups to CF_3 groups. DSC data and curves are given for 17 analogues in the Supporting Information of the *J. Am. Chem. Soc.* article.



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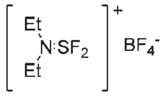
A second article by Bennett et al. (*Chem. Ind.* **2010**, 21) promotes the XtalFluor fluorination reagents [**3** and **4**] that were reported by Couturier in early 2010 (*J. Org. Chem* **2010**, *75*, 3401). The paper discusses the safety limitations of some of the more commonly used reagents for introducing fluorine into pharmaceuticals and underscores the potential utility of a safer deoxofluorination reagent.



3 - XtalFluor-E

4 - XtalFluor-M

A SAFE AND PRACTICAL PROCEDURE FOR DIFLUOROMETHYLATION

Sperry and Sutherland report on the difluoromethylation of methyl-4-hydroxy3-iodobenzoate at 7-kg scale (*Org. Process Res. Dev.* **2011**, *15*, 721). The most obvious source of difluorocarbene would be chlorodifluoromethane, a highly toxic gas. Of the alternatives, the authors chose sodium chlorodifluoroacetate (SCDA) due to its stability as a solid and availability in bulk. The use of an acetic acid derivative leads to the formation of CO_2 as a byproduct (1500 L of gas at 7-kg scale). An ARSST of the batch reaction showed an exothermic onset of 84 °C, dT/dt of 426 °C/min and dP/dt of 546 psi/min. Obviously the gas generation and large heat of reaction (−159 kJ/mol, ΔT_{ad} of 193 K) must be well controlled. Dosing a solution of SCDA (2.0−2.5 equiv) and starting phenol in DMF solution (3 vols) to a 95 °C suspension of potassium carbonate in DMF (2 vols) controlled the rate of gas generation and maintained a consistently high ratio of SCDA to phenol throughout the reaction (minimizing formation of di- and tri- adducts). RC1 calorimetry showed the reaction is almost dose controlled at 95 °C. TSu testing of the SCDA phenol solution showed that a very large exotherm and gas generation began at about 96 °C, but supported the storage of the feed stream at ambient temperature.

PROCESS HAZARD ANALYSIS

Two interesting papers related to Process Hazard Analysis (PHA) were published in the last year. One paper addressed the subject of oversights and omissions that can occur in PHA

(*Process Saf. Prog.* **2010**, September, 264). Examination of CSB investigations of incidents over a 10-year period revealed that in many cases either no PHA was conducted or lessons learned from similar incidents had not been incorporated into PHAs. The author provides a list of recommendations for improving PHAs and a useful section on potential future emerging issues identified during CSB investigations.

In the second paper related to PHA, Wincek argues for the implementation of a Conceptual Stage Hazard Review (CSHR) to formalize and document process safety reviews for early design stages (*Process Saf. Prog.* **2011**, September, 212). The paper explains that, since OSHA does not require this preliminary review, many processes are not formally subject to a process safety review until detailed designs are available. This delay can result in little time to make any fundamental process change needed to address hazards that are identified in a formal PHA. The article describes the CSHR and a parallel preliminary hazard analysis procedure aimed at tackling potential hazard issues during the development cycle.

■ DECIPHERING THE MSDS

The details of the fatal fire at UCLA involving *tert*-butyllithium were extensively described in numerous articles in 2009 (*Chem. Eng. News* **2009**, *87*, 29 and *Los Angles Times* **2009**, March, 1). Vince McLeod believes that a quick reading of the compound's Material Safety Data Sheet (MSDS) may have prevented this terrible loss (*Lab Manager* **2011**, January, 52). The purpose of an MSDS is to inform chemical users of the potential hazards encountered with a chemical's use. Since 1993, the American National Standard Institute has maintained the standard for preparing an MSDS. The article in *Lab Manager* takes the reader through each section of an MSDS in detail to make sure one is familiar with this complex document. McLeod states that, if you make the effort and get to know the layout and information contained in an MSDS, it will provide valuable information and be a reliable asset that you turn to in times of need.

■ COMPARISON OF TWO METHODS FOR SADT DETERMINATION

In recent years, there has been discussion in the literature about the validity of the heat accumulation storage test for packages of solids in excess of 8 L. Mallow, Michael-Schulz, and Wehrstedt have done full-scale testing of real packages by the US SADT test and compared the results to those from the test in a 500-mL Dewar (*J. Loss Prev. Process Ind.* **2010**, *23*, 740). Since the US SADT test is lengthy and must be done on full-scale packages, the authors chose three peroxides and 2,2′-azodi(isobutyronitrile) (AIBN) as representative materials. On the basis of their data the 500-mL Dewar correctly predicted the SADT for the seven packages they tested, and there "is a clear indication that the scale-up method described by the UN seems to be valid for at least 60 L even for solid organic peroxides and self-reactive substances." However, on the basis of their data the 500-mL Dewar sometimes had heat losses that were slightly greater than that determined from the US SADT test for the 20-kg package. Therefore, the upper limit for scale-up for the 500-mL Dewar needs to be reduced to some value between 5 and 20 kg.

■ SAFETY ISSUES WITH NANOMATERIALS

As nanomaterials progress through the development spectrum into manufacturing environments, the unique handling challenges of these materials will need to be well understood. A review of safety concerns in relation to nanomaterials is presented by Lavoie (*Process Saf. Prog.* **2010**, September, 182). The article summarizes pertinent literature references which may be useful to process engineers and chemists and discusses aspects of personal safety and environmental concerns.

■ INHERENTLY SAFER TECHNOLOGY

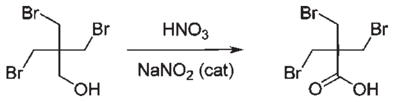
Trevor Kletz in his book on plant design (*Plant Design for Safety* Hemisphere Publishing Corporation: New York, 1991) stated, "The essence of inherently safer approaches to plant design is the avoidance of hazards rather than their control by added-on protective equipment." Kletz also proposed the five fundamental principles of inherent safety, minimization, substitution, attenuation, simplification, and limitation of effects. In 2010, a second edition of the book was published under the title *Process Plants: A Handbook for Inherently Safer Design*; CRC Press: Boca Raton, FL, U.S.A. and was coauthored by Paul Amyotte (for a review, see *Process Saf. Prog.* **2010**, *29*, 382). The key changes include updating with new developments from the past several years, addition of new examples of application of the fundamental principals of inherently safer design, and an emphasis of inherent safety in process safety management systems and ensuring an appropriate process-safety culture.

This year, as usual, many articles were published which discussed the principles of inherently safer technology (IST) or inherently safer design (ISD) of chemical processes and process plants.

In one example, the National Research Council (NRC) began exploring the application of inherently safer design for chemical manufacturing processes. The NRC case study will focus on an actual plant, the Bayer CropScience pesticide manufacturing facility in West Virginia (*Chem. Eng. News* **2011**, February 7, 9). This particular facility, which uses bulk quantities of methyl isocyanate had an explosion and fire in 2008 which led to the deaths of two employees (*Chem. Eng. News* **2011**, January 24, 7). Methyl isocyanate is the chemical that caused the tragic Bhopal toxic release in 1984 and has been phased out of use in most manufacturing processes through the world. Although methyl isocyanate was not involved in the Bayer CropScience incident, the proximity of the bulk storage tank to the exploding reactor was a cause of special concern. The NRC is moving forward with this study that will hopefully illuminate the use of inherently safer process assessments.

In a second example, Dennis Hendershot wrote a summary of IST and ISD with a very clear and focused definition of terms for the readers (*Process Saf. Prog.* **2010**, *29*, 389). The author states that ISD can be considered both at the overall process level as well as for each of the components that make up any process. He also walks the reader through a series of "myths" and common misconceptions of inherent safety and emphasized the need to implement ISD as early as possible in the research and development process prior to significant resources being expended in process or product development and before a plant has been built.

Scheme 1

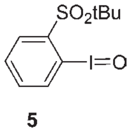


SAFE, SCALABLE NITRIC ACID OXIDATION

Bretherick's Handbook of Reactive Chemical Hazards has an extensive entry for nitric acid (35 pages of incidents in the 7th edition) and describes nitric acid as "the common chemical most frequently involved with reactive incidents." Nitric acid is a strong oxidant and is known for its propensity for thermal runaway reactions. Osato, Kabaki, and Shimizu report the development of a safe, scalable oxidation of 3-bromo-2,2-bis(bromomethyl)propanoic acid using a catalytic amount of $NaNO_2$ (*Org. Process Res. Dev.* **2011**, *15*, 581) [Scheme 1]. Preliminary study of the batch reaction (68% nitric acid at 90 °C) raised the following three concerns: (a) presence of an induction period, (b) two liquid phases, and (3) inability to control heat and gas evolution. In the next version of the process the starting alcohol was dissolved in acetic acid (1 vol) and dosed over 2 h into a 65 °C mixture of 68% nitric acid (8 equiv) and $NaNO_2$ (1 mol %). The heat of reaction was measured to be −216.0 kJ/mol (ΔT_{ad} = 113.8 K) with a maximum heat generation of 35 W after addition of 33% of the dose. After consideration of the mechanism of reaction, the dosing was paused after 10% of the charge to allow the concentration of NO_2 to build. The ΔT_{ad} at this point is only 11 K. After the consumption of the first 10% of the charge was confirmed by HPLC, the remainder of the charge was made over 3 h. The maximum heat curve for the modified process was fairly constant at about 8 W (maximum 10 W) with a much more constant gas evolution curve. The process was successfully carried out on 3000-L scale.

CHEMICAL SAFETY ALERT

Hupp and Nguyen of Northwestern University reported a reaction mixture detonation (*Chem. Eng. News* **2011**, January 10, 2). The chemical accident occurred while attempting to prepare 2-(*tert*-butylsulfonyl)iodosylbenzene [**5**]. The procedure was a modified version of known literature protocols (*J. Am. Chem. Soc.* **1999**, *121*, 7164 and *Organic Syntheses* Wiley: New York, 1973, Collect. Vol. 5, 660) with the main modification being the use of a higher concentration of H_2O_2/iodobenzene ratio while maintaining a similar H_2O_2 concentration. Although a theory is proposed, an exact cause of the explosion is not known. Until the cause can be ascertained, the authors strongly encourage researchers to consider using alternative, nonperoxide routes to 2-(tert-butylsulfonyl)iodosylbenzene and related compounds. More generally they recommend that aqueous H_2O_2 and acetic anhydride never be combined.



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FLASHPOINTS

Flash point is often employed to characterize the flammability of chemicals and to assist in determination of safe handling, processing, and storage practices. Rowley et al. published a paper proposing a method to allow determination of flash points for pure organic chemicals based on structural contributions (*Process Saf. Prog.* **2010**, December, 353). They authors indicate that if an accurate vapor pressure correlation or normal boiling point is known for an organic moiety, then flash point should be estimated using this source data. When both vapor pressure and boiling point are unknown, then a formula proposed by the authors can be utilized.

CONTINUOUS PROCESS FOR ALKENE OZONOLYSIS

Even though ozonolysis provides a useful method to selectively oxidize alkenes and alkynes to carbonyl compounds, it is often overlooked as a possibility due to the safety concerns with its implementation. Allian and co-workers (*Org. Process Res. Dev.* **2011**, *15*, 91) demonstrate that it can be used in organic process R&D to deliver kilograms of important research materials. They address the issues of (a) ozone toxicity, (b) thermal stability of the reactive intermediates, and (c) the exothermicity of the reaction. First, they estimated the heat of reaction of the ozone reaction and dimethyl sulfide (DMS) quench using the CBS-QB3 method in Gaussian 3. A subsequent calorimetry measurement of the ozone addition and the DMS quench (−381 kJ/mol, and −122 kJ/mol, respectively) in semi-batch mode agreed well with the computation estimate. In situ FTIR verified that the reaction was fast, was not limited by ozone mass transfer, and essentially consumed all the ozone added. These observations allowed them to use a standard lab reactor as a continuous stirred tank reactor to deliver 77 mmol of product per hour (300 g in four 12-h days). A continuous bubble reactor was constructed to scale up the synthesis to 770 mmol of product per hour (maintaining total amount of ozonide intermediate below 950 mmol at any instant), delivering 2.5 kg of material (four 9-h days). They also discuss the safety precautions that were implemented to ensure safe use of flammable solvents in the presence of air and emergency shutdown procedures.

INVESTIGATING EXOTHERMIC ACTIVITY

The release of chemicals from a phosgenation plant in the UK in 1991 was recently reviewed by Fishwick (*Loss Prev. Bull.* **2011**, February, 11). The article highlights the importance of investigating any atypical exothermic activity in a production batch in order to determine a likely root cause and underscores how a simple equipment malfunction (valve not functioning) can have catastrophic consequences. The paper references the original HSE investigation report.

DEVELOPMENT OF A SAFE AND PRACTICAL *N*-OXIDATION PROCEDURE

Alam and co-workers report the use of *m*-chloroperbenzoic acid (*m*-CPBA) in acetic acid to perform the *N*-oxidation of a pyrazolopyridine on 28-kg scale in 98% isolated yield (*Org. Process Res. Dev.* **2011**, *15*, 443). Solid *m*-CPBA is known to be shock-sensitive and potentially explosive, and even use of concentrated solutions of *m*-CPBA raises obvious safety concerns. Low solubility of the starting material and product required the use of acetic acid as the solvent at 55 °C. Since the reaction required 1.6 equiv of *m*-CPBA, a sodium bisulfate quench destroyed excess peroxides and prevented pressurization of waste drums. DSC, CRC, ARC, and ARSST were used to study the stability of the feed streams and reaction mixtures. CRC was used to study the heat of reaction and gas evolution (CO_2 and O_2 by TG/MS). The addition of room-temperature feed stock to the hot reaction helped to moderate the moderate heat of reaction of −87.1 kJ/mol.

DRUM PRESSURIZATION

Drum pressurization can represent a significant safety hazard, and unfortunately bulging drums are not uncommon. An article by Quigley et al. (*J. Chem. Health Saf.* **2010**, Sept/Oct, 24) discusses the major causes of overpressurized drums and highlights some mitigation strategies that minimize potential employee exposure or injury and environmental contamination.

TRIMETHYLSILYLDIAZOMETHANE: A SAFE NON-EXPLOSIVE, COST-EFFECTIVE, AND LESS TOXIC REAGENT FOR PHENOL DERIVATIZATION IN GC APPLICATIONS

Although diazomethane (DM) is known to be a gas that is highly explosive, toxic, and difficult to handle, it continues to be used for the quantitative, clean derivatization of phenols to methyl ethers before GC analysis. Luthe and co-workers investigated the use of trimethylsilyldiazomethane (TMS-DM) as a less hazardous reagent for *O*-methylation of phenols (*Environ. Int.* **2010**, *26*, 835). They first optimized the reaction conditions for TMS-DM with clean samples of phenolic metabolites of polychlorinated biphenyls. Since matrix effects can be critical in analytical chemistry they demonstrated the validity of the reaction conditions using a liver microsomal extract. The TMS-DM yields were equal or to or higher than those achieved with DM. The reaction times for TMS-DM were often longer than those of DM, but that is inconsequential since the DM derivatizations are usually left overnight. In addition to safety gains, TMS-DM is more cost-effective (up to 25% more cost-effective) than DM by their cost analysis that includes initial equipment, consumables, and labor costs.

PROCESS SAFETY AND THE HUMAN FACTOR

A number of papers were published in 2010 addressing the human element of process safety and the importance of not overlooking this key factor. Human error still appears to be a root cause in the majority of processing incidents.

In once such example, Hassan published a paper on effective plant safety management (*Chem. Eng.* **2011**, January, 50) that highlights three critical periods during a product's production life cycle where extra vigilance is crucial. The three phases were identified as the following:

1 Transition - where a company acquires a production plant. Many experienced staff members have likely departed the plant, and the new management is learning about plant operation.
2 Restructuring - where production slows down to mirror economic demand and sections of plant may be idle.
3 Routine - where plant operation becomes mundane and less experienced staff become involved. Experienced staff can relax and become less vigilant.

The author discusses a plan to implement in these situations that focuses on seven essential elements in order to reduce risk of a safety failure.

A SAFE AND PRACTICAL PROCEDURE FOR GLOBAL DEPROTECTION OF OLIGORIBONUCLEOTIDES

Zewge and co-workers report a safe and practical procedure for global deprotection of oligoribonucleotides using commercially available aqueous NH_4F (*J. Org. Chem.* **2010**, *75*, 5305). Typically, global deprotections of RNA 2′-*O*-TBS ethers is done with a large excess of highly hazardous $Et_3N\cdot3HF$. Thirteen different sets of reagents were screened. Deprotections using aqueous NH_4F in dimethylacetamide (1:1) or dimethylsulfoxide (3:1) were successful both in 96-well format and large-scale format (800 μmol). It is important to maintain the solvent ratios as stated above to ensure that both the fluoride salt and the RNA stay in solution. The conditions cleanly deprotected various sequences of 21-mers. Dinucleotides were examined by NMR and confirmed to proceed cleanly without phosphoryl group migration.

MINING THE WEB FOR SAFETY INFORMATION

Below is a list of web sites that we 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) OSHA www.osha.gov
(2) ACS Green Chemistry Institute www.acs.org/greenchemistry
(3) US Centers for Disease Control and Prevention (CDC) Workplace Safety & Health www.cdc.gov/Workplace/
(4) The Laboratory Safety Institute www.labsafetyinstitute.org
(5) Chemical Processing http://www.chemicalprocessing.com/experts/process_safety.html
(6) NIST WebBook http://www.webbook.nist.gov/chemistry
(7) Chemical Compatibility Chart http://rehs.rutgers.edu/pdf_files/Chemical_compatibility.html
(8) The Safety Library http://www.thesafetylibrary.com/lib/chemicalsafety/

Richard Barnhart

Process Safety Laboratory Pfizer Inc. Groton, Connecticut 06340, United States; E-mail: richard.barnhart@pfizer.com

Michael D. Ironside

Chemical Manufacturing and Development, Anacor Pharmaceuticals, Palo Alto, California 94303, United States; E-mail: mironside@anacor.com

Paul F. Vogt

Global Open Innovation Leader Momentive, Waterford, New York 12188, United States; E-mail: paul.vogt@momentive.com