

Chemical laboratory incident, December 5, 2011, Lab Sciences Building
Release of Lachrymator Agent

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Description of the incident by the Principle Investigator (PI). In the evening of Dec. 5, 2011, a graduate student was carrying out a reaction that generally followed a known literature procedure that he had conducted twice before without incident in the eastern end of a fourth floor Laboratory Sciences Building laboratory. He was sonicating a stoppered reaction flask containing tetrahydrofuran (a flammable solvent), a large excess lithium dispersion (a pyrophoric alkali metal) and α,α' -dibromo-ortho-xylene (a potent irritant and lachrymator) in a sonicator that was sitting on a bench outside of a hood. A few minutes after the sonication had started, he heard the stopper blow out of the reaction vessel. This was followed by intense eye irritation due to volatilization of the lachrymator. At this point he did the right thing by contacting me about how to proceed. I briefly entered the lab to assess the situation and found the atmosphere to be intensely irritating to my eyes, clearly indicating that the lab could not be entered for remediation without a face mask and/or respirator. Because the faculty safety officer was there at the time I consulted with him, and we decided to immediately contact campus police, the director of our labs, and EHS. Campus police arrived fairly quickly, but there was no one from EHS on campus to respond. Campus police were given copies of the Material Safety Data Sheets (MSDS) of the chemical compounds involved. To prevent fumes from exiting the affected lab all door frames were taped to prevent exiting of the fumes. After some discussion with Campus police regarding potential fire hazard, and the unavailability of EHS personnel on site, Campus Police decided to sound a fire alarm and have the fire department on site until EHS personnel arrived, which took more than an hour. As a result of sounding the fire alarm, supply and exhaust air to the laboratories was shut down, thereby preventing the exhaust of the irritating fumes. The graduate student involved was also taken by Campus Police to the Barnes Hospital Emergency room,

and a Report of Injury and Illness was filled out and submitted the next day to department's executive director. When EHS finally arrived there was further discussion on how to proceed, and the first thing done was to restore ventilation. EHS ultimately decided to enter the room with protective clothing and self-contained breathing apparatus and to move the reaction flask to a hood and to coat areas that had been splashed with the reaction mixture with mineral oil to minimize the threat of further reaction. The next day, the atmosphere was clear of the lachrymator and the lab could be entered by my lab personnel. The oil wiped up and the remaining reagents in the reaction flask quenched and all waste properly disposed of.

Analysis of the incident by the PI. The student failed to appreciate the potential danger posed by the reagents and reactants and the exothermicity of the reaction, and failed to use common sense in performing the reaction. First, no reactions should be run outside of a hood, with the exception of those carried out by our automated DNA, PNA or peptide synthesis machines, or aqueous reactions involving non-toxic agents. Second, no reactions with the potential for gas evolution should be carried out without a pressure releasing and/or equalizing mechanism such as a vent, bubbler or drying tube, unless it is in a specifically designed pressure tube or apparatus. Third reactions with pyrophoric material should be carried out under a pressure equalizing inert gas system (nitrogen or argon). Fourth, potentially exothermic reactions should be carried out with a reflux condenser and in the presence of a cooling bath to moderate the reaction if necessary. The actual procedure (see below from *Synthesis* **2002**, No. 9, pg 1191) called for caution in large scale because of the exothermicity of the reaction ("exothermic formation" should have been written "exothermic reaction"), and called for the use of a reflux condenser. It also called for great care in handling any unreacted lithium at the end of the reaction. It would appear, however that this student did not adhere to general safe laboratory practices, or heed the warnings in the published experimental, in spite of them being clearly stated. The reaction should have thus been setup in the hood with a reflux condenser under nitrogen and the sonicator bath should have been moved to the hood.

Literature Experimental

5,6,11,12-Tetrahydrodibenzo[*a,e*]cyclooctadiene (7)

CAUTION: *Large scale reactions require special care due to the exothermic formation of the dibromide.*

α,α' -Dibromo-*o*-xylene (50 g, 189 mmol) was added at 0 °C to a suspension of Li sand (7.74 g, 1.1 mol) in anhyd THF (225 mL) in a 1 L round bottom flask, equipped with a reflux condenser. The mixture was degassed with argon at r.t., and then sonicated for 3–6 h. The reaction was complete once a blood red solution was observed in the flask, though unreacted Li was still present. The mixture was filtered, taking great care in handling Li, and then concentrated to a gummy solid. Purification using a short silica gel column with hexanes gave a white crystalline product (12.52 g, 63%) after solvent evaporation.

¹H NMR (CDCl₃): δ = 7.12 (s, 8 H), 3.18 (s, 8 H).¹⁴

Graduate student's description of the incident (English is not his native language).

On December 5th, I was working with a reaction of sonicating the Lithium powder with alpha,alpha'-Dibromo-o-xylene. This reaction should take 3-6 hours based on the literature report (Synthesis 2002, No. 9, 1191-1194). The product should be 5,6,11,12-Tetrahydrodibenzo[a,e]cyclooctadiene, which would be used for further synthesis. Around 3.2g of alpha,alpha'-Dibromo-o-xylene and around 3g of Lithium powder (washed with anhydrous THF) was added to a 50mL round bottom flask with a rubber stopper, together with around 25mL of anhydrous THF. That was the third time that I did this reaction and the previous two went well. After mixing the reagents and bubbling the nitrogen to the mixture, the flask was moved to the sonicator located in the east side of the room (LabSci 408) to see if the sonication was normal. I was planning to stop that several minutes later and leave the reaction in the hood and continue that the second day. After clamping the flask in the water bath of the sonicator, I went back to my desk to double check the procedure. At around 7:30, several minutes after sonicating, I heard the sound of the blow and I found that the stopper was blown out when I looked at the flask. I went close to the sonicator to check and I didn't see the fire either on the ground or in the water or in the flask. Due to the concern of the potential threat of fire and potential harm of the irritant chemical vapor, I asked my advisor for help for this chemical spill. My eyes turned bloody red due to the exposure to the irritant chemical vapor and I was transferred to the Barnes-Jewish Hospital afterwards.

Graduate student's statement about previous experience with the reaction and failure to take proper precautions.

The process was successfully performed twice without incident previously, which made me assume that the reaction was safe to carry out. Since the reaction was water sensitive, a rubber septa was used to prevent the air exchange, which turned out to be the cause of the spurting. I thought it would not be a problem to carry out this reaction since the flask is sealed, but the impact is that the vapor pressure of the solvent built up in the round bottom flask, which was a closed system, because the reaction was an exothermic heterogeneous reaction. I think that is the reason why the spill happened.

Student's recommendations on how to prevent a similar type of incident from occurring in the future

1. Every reaction should be done in the fume hood.
2. Read the procedure carefully and check the MSDS of all the reagents before use.
3. Be extremely careful when using alkali metals. Avoid contacting with air and water. For example, lithium powder in mineral oil should be washed in the flask under nitrogen or argon with anhydrous THF, which should be added with syringes. Due to the density difference, lithium would be on the surface of the THF and the THF on the bottom can be removed by syringes. The reaction needs to be done in the flask under nitrogen or argon, equipped with a reflux condenser. The extra lithium needs to be quenched with methylated spirits and 2-propanol in situ after the completion of the reaction. When the reaction between lithium and alcohol appears to have

finished, add methanol to ensure completion and leave overnight. The lithium derivatives need to be diluted and disposed of as aqueous miscible waste.

4. Never heat or do any reaction which is exothermic in a closed system. Instead, an ice cooling bath and a reflux condenser should be used for an exothermic reaction.
5. Learn about the standard procedures of dealing with all the reagents and processes.
6. Consult the advisor about the unfamiliar reactions beforehand.
7. Prepare everything that would be necessary for the possible hazards (e.g. sand, fire extinguisher).

Statement about future laboratory oversight by the PI. To avoid a similar incident in the future I have/will instruct students in the following common sense approach to risk assessment and minimizing risk of chemical reactions on a semiannual basis, and individually for all new research assistants and associates. This has been added to lab specific training, and was presented to three graduate students on the afternoon of Jan. 3, 2012. A review of hazard assessment and risk minimization will be repeated every 6 months and a record of who attended added to the lab safety Blue Book under lab specific training. Students have also been forwarded the link to the Chemical Safety Board site on Jan 3, 2012, to view the video on recent laboratory accidents (www.csb.gov) which will also be presented at group meeting. I also believe that the Chemistry Department should re-institute a chemical safety course that used to be given when I first started as an assistant professor here, but somehow was terminated a number of years ago and supplanted by the EHS training sessions which focus more on compliance issues. The original course covered such topics as explosive materials, electrical hazards, toxins, mutagens and carcinogens, lasers, air and water sensitive compounds, and provided students with an understanding and appreciation of hazards that they might encounter during PhD work in chemistry.

Guidance on minimizing risk and risk assessment provided by the PI.

1. Students have been/will be instructed to assume that all reactions are potentially dangerous and that all reactions should be carried out in a hood unless specifically approved by the research advisor or are carried out in automated synthesis machines.
2. Students have been/will be instructed that they should carefully read any published experimental write-up for cautionary statements with regard to the reactants and reagents and the experimental setup.
3. Students have been/will be instructed that they should also obtain the Material Safety Data Sheets and information from other sources on any reagents, reactants, and solvents that they are unfamiliar with to assess their reactivity and toxicity and then learn as much as they can on how to handle and dispose of such materials.
4. Students have been/will be instructed that their experimental setup should always take into account the air- and water-sensitivity of the reagents, gaseous products, and the potential exothermicity of the reaction. Students have been/will be taught to clamp a reaction flask high enough to enable heating mantles, oil baths, sonicators to be easily removed in the event of an exothermic reaction and to have an ice bath ready to cool the reaction if necessary. Students have been/will be instructed that all reactions should be open to the air; if air and water sensitive the reaction is to be

performed with a nitrogen bubbler; if only water sensitive the reaction can be performed with a drying tube. If the reaction is being specifically carried out under pressure, it must be done in an appropriate pressure tube or pressure reactor. Students have been/will be instructed that if a reaction is likely to produce a lot of gas, they should not use needles for venting, but rather a larger bore adapter, and if necessary gases should be scrubbed in the appropriate manner so as not to release any toxic or corrosive gases.

5. Students have been/will be instructed that a hood should not have any other reagents, reactants, or solvents in the hood, other than required for the reaction, as it could greatly aggravate or contribute to fire, explosion, and generally complicate dealing with a laboratory accident.
6. Students have been/will be instructed that if they are unfamiliar with a particular reagent/reactant/solvent and/or the appropriate techniques that they should look them up on the web and/or in books, and then consult with me to determine the best way to proceed.
7. Students have been/will be instructed that they should also plan on how to work up their reaction so as to minimize potential fire or toxicity hazards, and have a plan for destruction and/or disposal of hazardous products, or unreacted reagents.
8. Students have been/will be instructed that potentially dangerous reactions should be conducted on a small scale initially, and then carried out on a larger scale. In all cases, students must consult with me beforehand on how to carry out the reaction, and how to scale it up. Potentially dangerous reactions are those involving highly toxic or corrosive compounds, and/or pyrophoric materials.
9. Students have been/will be instructed that they should inform everyone else, including the PI, if they are carrying out a dangerous reaction, and make sure that someone will be present on that floor or preferably in the lab during the reaction. The student should also be wearing appropriate personal protective gear (lab coat, gloves, and shields) and use additional shields if necessary. The idea will always be that you cannot be too safe. Both the student carrying out the reaction, and the one that will be present should also know where the appropriate safety equipment is located prior to the start of the reaction, and what to do in the event of a fire or exposure to a toxic compound, and to contact 5-5555 in the event of an accident. Also pertinent information as to the reaction should be drawn on the hood glass, and reactants and reagents involved should be at the student's desk for easy access to emergency response personnel. In case of more dangerous reactions, a copy of the relevant information (MSDS, laboratory experimental, etc.) should be given to the PI and another student.
10. Students have been/will be instructed that they are not allowed to carry out potentially dangerous reactions in the evenings, night time or weekends when EHS is not readily available to respond to an emergency. Also dangerous reactions should not be carried out if no one else is present.
11. Students must clearly document in their notebooks any dangerous compounds and/or procedures, and clearly state how the compounds, reagents were handled, reactions carried out, and reactions worked up, and products disposed of.

Assessment of students' ability to assess and minimize risk. As part of weekly group meetings, students will be required to describe past and planned experiments and provide an assessment of the risk and how the risk was/will be minimized. Students will also be expected to discuss with me any reactions that involve potentially dangerous reactants, reagents, and provide literature documentation, Material Safety Data Sheets and procedures to be used for discussion and approval of a course of action.

Documentation of risk assessment training. Students will be required to attend laboratory specific training in which laboratory risk assessment and risk minimization are discussed and sign a sheet indicating that they participated in the meeting. The laboratory notebooks should also document the hazard assessment and procedures used, and if to be used routinely by one or more students, an SOP must be written up and added to the lab specific practice section.

Standard Operating Procedure (SOP) for reactions involving lithium metal in oil suspension.

Preface. Reactions involving alkali metals in oil suspension can be handled by a number of standard procedures depending on the particular metal, its density, the physical size of the metal pieces and reaction procedure and scale to be carried out. The hazard with alkali metals is that they will react vigorously with water and can spontaneously ignite. Finely powdered metals can also ignite in air when free of a protective mineral oil coating and oxide coating and thereby can ignite flammable solvents. Therefore these types of reactions must be carried out in a hood that is clear of other reactants, reagents, and solvents, with a double manifold connected to nitrogen and a vacuum source, and there should be a safety shower and class D fire extinguisher available in the lab. In addition, the research advisor should have been consulted on the reaction to be carried out and notified when it is to be carried out, and relevant literature and MSD sheets made available to him/her, as well as some other person that has to be present in the lab. The reaction should also be carried out during the day when EHS personnel are available to help deal with any accidents.

Procedure. In the case of lithium dispersion, the lithium is in the form of small particles in an oil suspension, which requires transfer to a tared reaction flask (generally a 2 neck round bottom flask + septa) via a powder addition funnel. Any small amounts of residual lithium dispersion on the funnel and spatula can be washed away with warm water to decompose the lithium. The funnel is then replaced with a septum and pump/filled with nitrogen through the septum with a needle via a double manifold. Alternatively, a vacuum adapter with a valve can be used in place of the septum and needle. The mineral oil can is then washed away with anhydrous THF or diethyl ether under an inert gas pressure. Please note: because pure lithium has a lower density (0.53 gm/cm^3) than THF (0.889 gm/cm^3) or diethyl ether (0.713 gm/cm^3), washing involves removing the solvent from the bottom. Hexane is often used to remove mineral oil from alkali metals, but may have too close a density (0.655 gm/cm^3) to lithium to be useful since the lithium particles will become denser if oxidized. A syringe is used to add the wash solvent, and either a syringe or cannula to remove the wash solvent. Transfer of the wash solvent by a cannula involves raising the cannula above the solvent level at which point some lithium could be transferred. As such, a syringe would afford greater control when removing the wash solvent, and would be preferred for small scale reactions. The wash solvent is transferred to another 2neck round bottom with septa under nitrogen with a needle vent. The combined wash solvents would then be treated dropwise with t-butanol under nitrogen bubbler pressure to quench any lithium present. When no further reaction is observed it would be followed by isopropanol, ethanol, methanol, and finally water, and then disposed of appropriately. If visible amounts of lithium had been transferred, a reflux condenser would be attached to the round bottom, and an ice bath would be ready, in the event of an exothermic reaction. Once the wash solvent is removed from the reaction flask, the reaction flask would be pumped/filled three times with nitrogen. The flask would then be reweighed to determine the amount of lithium present which will dictate the relative amounts of the other reagents according to stoichiometry and any requirement for excess lithium. In some cases it may not be necessary to wash away the mineral oil if it does not interfere with the reaction or the purification of the product. In this case the amount of lithium would be estimated from the % w/w listed. Following the weighing of the flask, the remainder of the reaction

apparatus can quickly assembled with oven dried components, consisting of a reflux condenser and vacuum adapter or septum/needle adapter to connect to the double manifold line. The reaction apparatus would then be immediately pump/filled three times with nitrogen. The reaction flask would be clamped high enough to allow removal of any required heating mantle, oil bath, sonicator, or other apparatus to be placed under the reaction flask, in the event that the flask needs to be cooled externally in the event of a highly exothermic reaction. The solvent and other reagents and reactants would then be added via syringe. When the reaction is complete, the final step is to separate the product mixture from any unreacted lithium, preferably, and in most cases, by quenching the lithium *in situ* with t-butanol, and other acohols as described above. If this is unfeasible due to the formation of lithium alkoxides which might react with the desired product, the reaction solution would be filtered from the lithium and lithium salts. This procedure would be carried out by replacing the condenser with a septum and needle supplying nitrogen gas, and the other septum or vacuum adapter with a medium frit air free filter tube (Chemglass AF-0544) attached to another two-neck round bottom flask fitted with a septum and needle vent (both ends of tube clamped). The reaction mixture would then be decanted under positive nitrogen pressure into the filter tube and filtered into the second round bottom flask. The receiving flask would be replaced by another round bottom, and any solid in the filter would be resuspended in fresh solvent or toluene and returned to the main flask and the residual lithium decomposed by adding t-butyl alcohol dropwise followed by a period of stirring under nitrogen as described above. When no further reaction is observed, then isopropanol would be added, followed successively by ethanol, then methanol, and finally water, giving time for each alcohol to react and until no further reaction is observed. A prepared ice bath would also be available in case the quenching reaction becomes too exothermic.

General cautionary/safety notes for this SOP: Once the mineral oil has been removed from lithium dispersion, it can ignite spontaneously in air if it has an unoxidized surface, as it might following a chemical reaction, so it is important to conduct all operations under nitrogen. Also the solvents generally used in such reactions or to wash the mineral oil away (diethyl ether, tetrahydrofuran) are very volatile and highly flammable. The entire reaction, work up and the quenching of the unreacted lithium in washes or in the reaction mixture must be performed in hood with the hood safety shield positioned in front of the apparatus. For larger scale reactions a second shield may be advisable. A dry-powder class D fire extinguisher should be accessible to extinguish any fires resulting from the accidental spillage of the washed lithium dispersion or unreacted lithium.

Extension of the lithium metal SOP to other reactions involving highly reactive heterogeneous reactions. The general procedures outlined in the SOP for reactions involving dispersed lithium in oil, can apply to a number of other reactions with highly reactive heterogeneous reactions, though the specific procedures will depend on the particular heterogeneous reagent, its density, particle size, reactivity, etc. Heterogeneous reagents that fit in this category are sodium and potassium metals, sodium hydride, calcium hydride, and their dispersions in oil, and lithium aluminum hydride. In most cases these reagents can be decomposed in situ and do not necessitate filtration. Most of these reagents are also used for drying solvents and specific procedures have been described in the literature and the web for setting up and decommissioning a solvent still.