

Safety Considerations and Proposed Workflow for Laboratory-Scale Chemical Synthesis by Ball Milling

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ABSTRACT: Chemical reactions that take place in a ball mill and in the absence of a bulk reaction solvent present different safety profiles to stirred solution reactions. Herein, we present and describe steps that a researcher may take to better ensure that they have considered some of the hazards and measures that emerge and minimize the risk to themselves and their colleagues.

KEYWORDS: ball milling, mechanochemistry, safety, laboratory scale

INTRODUCTION

Mechanochemistry enables activation of chemical bonds by the input of mechanical energy. In the example of ball milling, energy is imparted to reactive bonds through the high-energy impact of a ball bearing on to the sample.¹ In recent years, the use of electrically driven mills, rather than a manually driven mortar and pestle, has witnessed increased use for performing organic chemistry (Figure 1). Typically, for such an endeavor, either mixers or planetary mills are used. A planetary mill features the use of a vertical jar housed on a horizontal sun wheel. The jar is secured in such a way that when the sun wheel revolves, the secured jars move in a counter-directional manner. Within the jar are placed several ball bearings and the sample of interest. As the jar rotates, the balls grind around the outside, imparting shear forces to the sample before reaching a point in the revolution where they pull-off and impact on the sample on the opposite side. Mixer mills on the other hand house the jars in a horizontal position. Lateral displacement of the jars causes the balls and sample inside to traverse the length of the jar, resulting in high-energy impacts on each displacement. This method of inducing a reaction is very effective and does not require the use of a bulk reaction solvent: the motion and impact forces are sufficient to permit good mixing and promote reactivity. Indeed, there are several examples where ball-milled reactions proceed to completion in greatly reduced reaction times (likely as a consequence of their high effective concentration) and can lead to enhanced or altered selectivity and in some examples lead to products that are unobtainable by solution methods, as well as reduced sensitivity to air and moisture.² From a sustainable process perspective, minimizing solvent use or removing undesirable solvents is a very attractive prospect.³ Nevertheless, solvents are an age-old technology taught at the undergraduate level; their use is familiar to all chemists. From a safety perspective, solvents, in combination with stirring, offer a great tool for ensuring maximum uniformity/homogeneity of reaction mixtures and thermal heat dissipation as solvents can act as

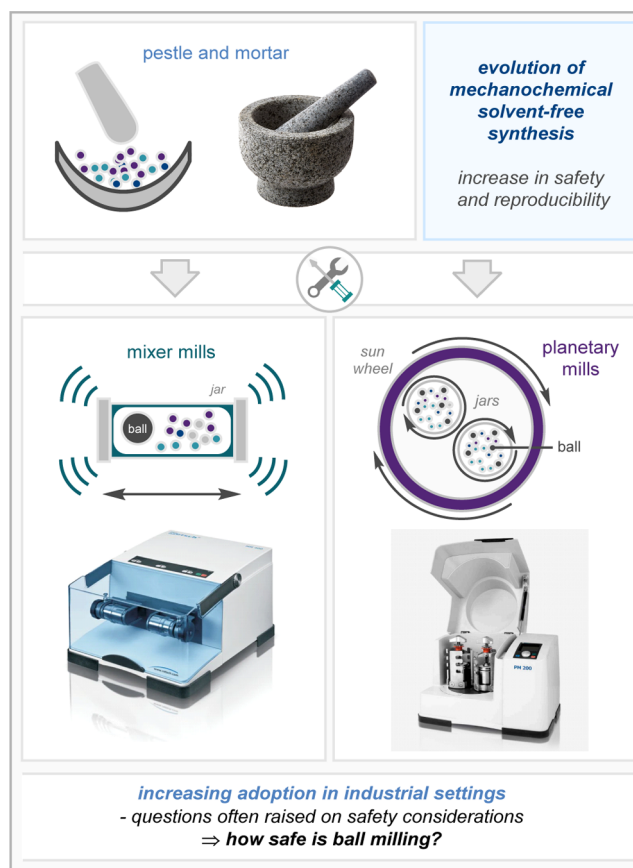


Figure 1. Mechanochemistry in synthesis.

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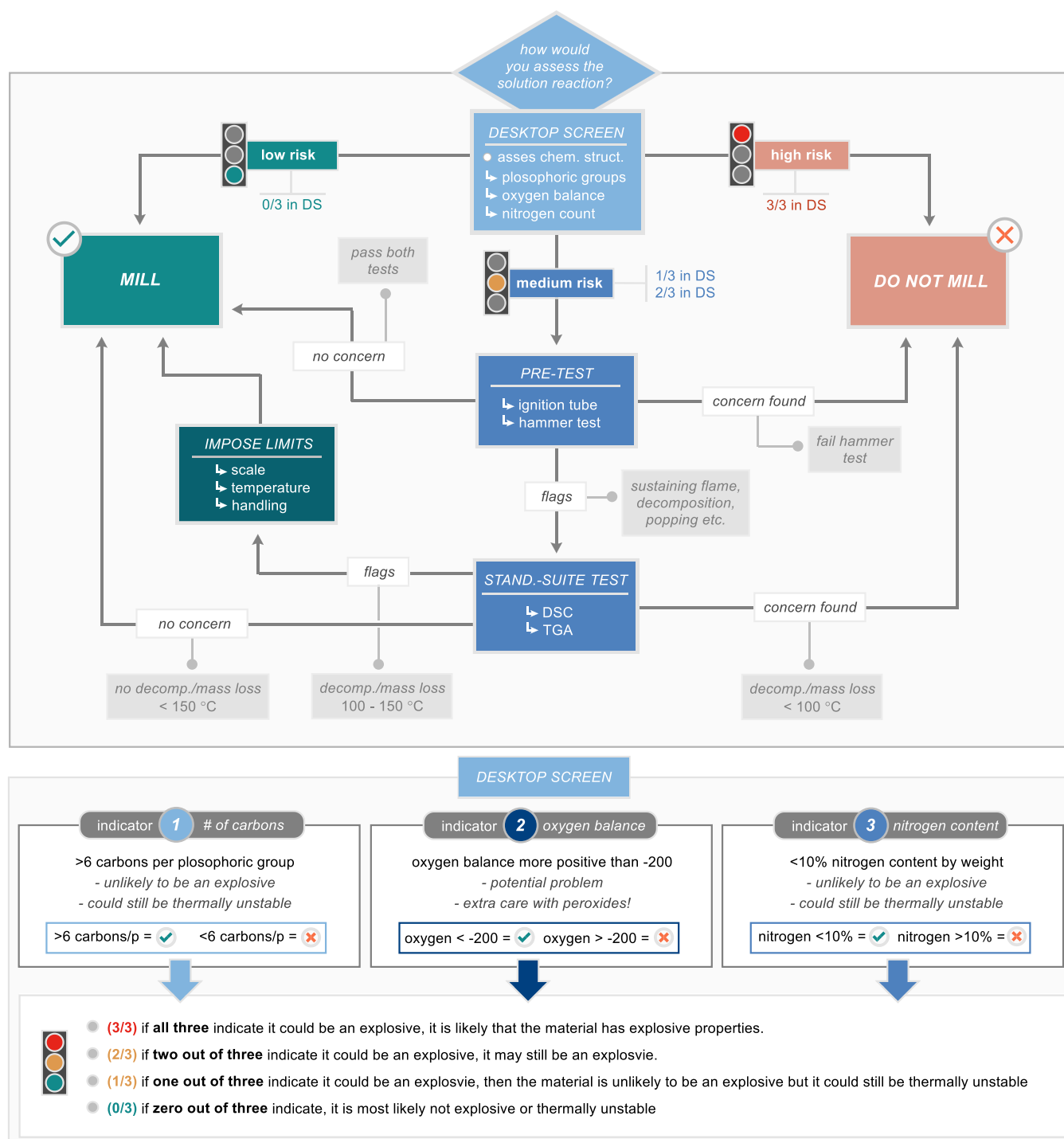


Figure 2. Proposed safety flow chart for implementation of ball milling for organic synthesis. DS = desktop screen, Chem. Struct. = chemical structure, Decomp. = decomposition, DSC = differential scanning calorimetry, and TGA = thermogravimetric analysis.

excellent heat sinks. Solvents are also essential for the purification of many compounds. However, solvents can present a flammable hazard as well as potential toxicological and environmental hazards, including their derivation from fossil fuels. When solvents are removed from the equation of a reaction, the safety profile changes. Moreover, when stirring is also removed, the homogeneity of the reaction profile will also change. For these reasons, the use of solvents has been a cornerstone of chemical synthesis of all types. Conducting reactions in the absence of a solvent needs a discussion about

reaction safety, which is further compounded if an alternative technology features the pulverization of solid materials using high-speed milling. As part of a broader program at Syngenta focusing on the reduction of solvent use in R&D departments,^{3c} we have compiled a safety protocol and a set of guidelines to facilitate the use of ball mills and present that herein. Guidance should be followed along with intuition from experienced researchers in synthetic chemistry. The aim of this paper is simply to share that workflow. The protocol was designed so that research chemists in organic chemistry labs

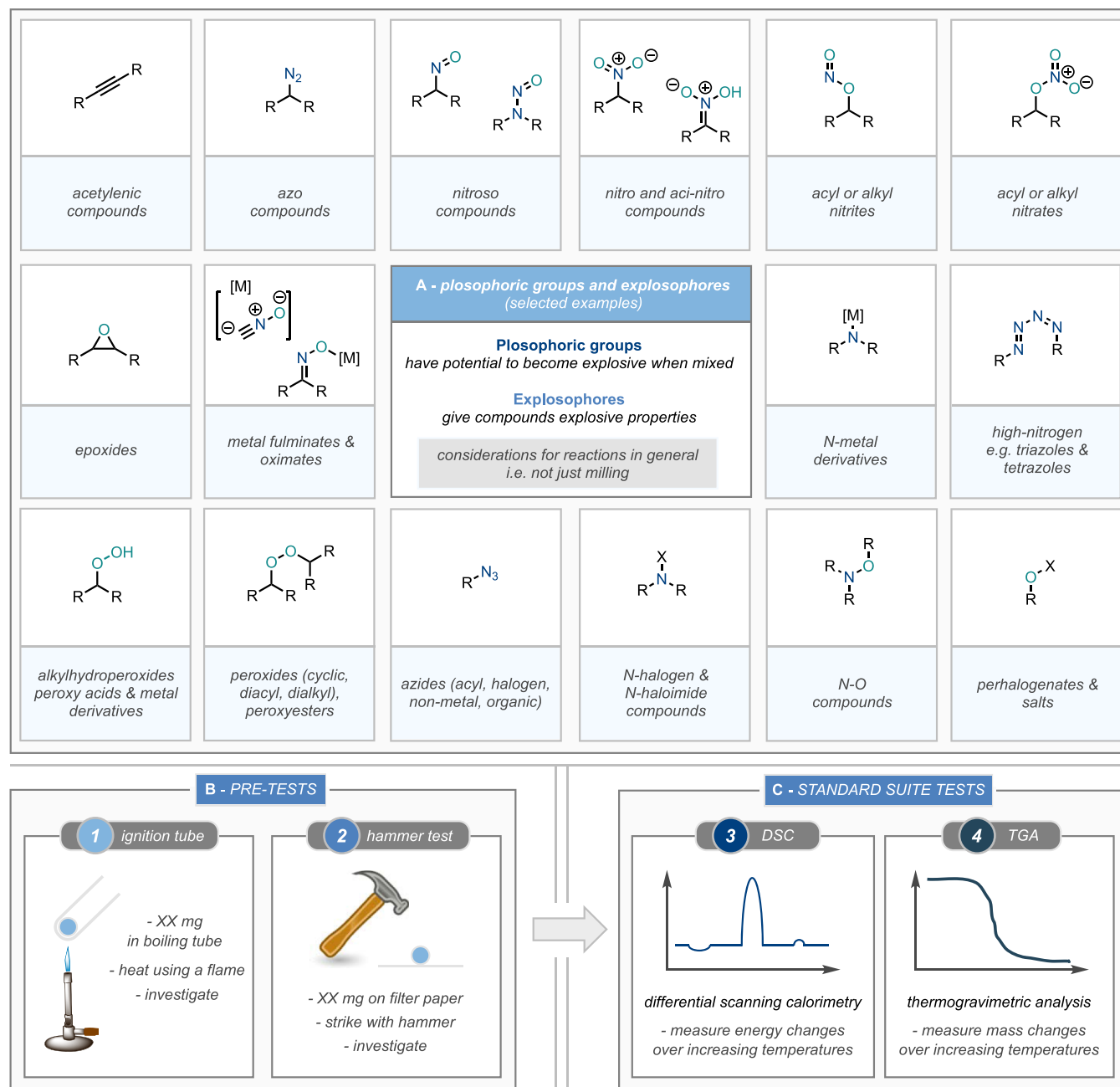


Figure 3. (Top) Overview of phosphoric groups and (bottom) graphical depiction or pre-tests.

(on scales typical with discovery research) can work largely independently from a more centralized safety team [up until a point that they will require differential scanning calorimetry (DSC) or thermogravimetric analysis (TGA)].

DISCUSSION

Safety Considerations of Milling Devices. Many of the commercially available mixer- and planetary-mill devices have inbuilt safety features. For example, a transparent plastic cover is used as a shield that closes over the top and front of the jars so that the jars are somewhat contained within a secondary enclosure. Milling devices are typically not pressure-rated, the jars are often not fully sealed, and as a consequence of this, any pressure buildup can be released during the milling process by the ends of the jar pushing apart from each other to vent. In our experience, we have seen this result in depositing the

reaction mixture on the inside of the plastic cover or the base of the mill. If a pressure buildup is anticipated, then slow release of the jar holder will also permit safe venting of any pressure buildup. Furthermore, the mills are typically fitted with a hard-wired trip, which prevents the mill from operating if the cover is open. With regard to noise generation, the perceived noise is lower in a fume cupboard (FC). A large part of the noise generated from a milled reaction is a direct reflection on the filling degree and ball mass loaded into the jar, as well as the materials for the manufacture of the milling jar and balls. A low loading of the sample relative to the free space volume of the jar will result in more direct impacts between the ball and jar and increased noise; this may also result in increased heat generation, where each impact imparts energy in the form of heat to the jar itself. In our experience, stainless-steel jars suffer from general wear-and-tear over time

and may be replaced by the user at their discretion. Acoustic chambers and noise cancellation setups might be useful at larger scales. Measurement of noise output from a standard R&D synthetic chemistry scale mill is typically in the range of 78 dB inside an open FC and 68 dB if the sash is closed. In operation within a closed FC, we believe that this is below the threshold to trigger additional safety measures (at least in the UK <https://www.hse.gov.uk/pubns/indg362.pdf>); however, further advice from local HSE may be required.

Flow Chart. Herein, we present some considerations, by way of a guide, for those interested in exploring the technique of ball milling. While there are many complexities of milling and solid-state chemistry, some of which are not well understood, we aim here to provide a simple safety framework for those wishing to investigate this promising sustainable technique. Our proposed safety flow chart for ball-milling reactions is presented in Figure 2 and at the laboratory scale focuses on the assessment of starting materials/reactants rather than whole reaction mixtures.

It is proposed that assessment of the reaction to be milled starts in much the same way as that of a good practice approach to a solution reaction, with a desktop screen (DS), where the researcher assesses the chemical structure of their proposed reaction including starting materials, products, and likely byproducts. Structures are screened for potential explosive properties or functional groups such as explosophores or phosphoric groups; many of these will be familiar to organic chemists, but a summary is provided in Figure 3 and reference footnotes.⁴ In total, compounds are assessed by three indicators: number of carbons per phosphoric group, oxygen balance, and nitrogen content (summarized in Figure 2 and reference footnotes). This type of screen allows researchers to determine if they are handling explosive substances prior to carrying out any experimental work and, hence, protect themselves and their co-workers accordingly.

Indicator 1: Number of Carbon Atoms per Phosphoric Group.⁴ The summary presented in Figure 3 provides a guide to the types of functional groups or intermediates that may be considered as phosphoric or explosophores. This is not an exhaustive list.⁴ While the presence of a single phosphoric group is unlikely to mean that the material is an explosive, it does indicate that the material has the potential to be thermally unstable. If there are more than six carbons per phosphoric group, it is unlikely to be explosive but could still be thermally unstable.^{4b,c}

Indicator 2: Oxygen Balance of the Material.⁵ If the oxygen balance is more positive than -200 , then there may exist a safety issue.⁵

Indicator 3: Nitrogen Content. If the total nitrogen content is less than 10% by weight for organic materials, it is unlikely to be explosive.⁶ Organic peroxides represent a special case to this where extra care needs to be taken.

If the results of this DS represent a “High Risk” (three out of three positive indicators), it is advised that milling is not commenced. If the results represent “Low Risk” (zero out of three indicators), then milling should commence with the standard milling device safety features in place. For any “Medium Risk” cases (one or two out of three positive indicators), we propose a short suite of follow-on tests designed to further assess sensitivity of reaction components with specific focus on impact and thermal degradation.

In some instances, because a molecule has either no oxygen atoms or no nitrogen atoms, it will be “ineligible” for oxygen

balance or nitrogen content calculation. In such cases, this would return a tick or a positive indicator but we propose instead that this should default to a negative indicator.

Pre-tests. Reminder: we propose that pre-tests are only performed on those components that received one or two out of three indicators from the DS. The following two pre-tests are proposed to minimize requirements for access to specialized equipment and “know-how”. If you have access to DSC and/or TGA tests, then you may prefer to bypass these tests and proceed straight to the standard suite tests; chemical intuition and experience may support your decision; ignition tube tests and hammer tests are routinely carried out at Syngenta, but local guidelines are followed on these tests.

Ignition Tube.⁷ An ignition tube test aims to crudely establish how a material will behave under high temperature conditions. To run an ignition tube test, 100–200 mg of the sample was placed into a boiling tube and heated in a flame (Figure 2). The outcomes of this test could be broadly classified as the following: melts and changes color; melts and changes color and goes pop; sustains a flame.⁷

Hammer Test.⁷ Most synthetic laboratories are unlikely to have the facilities for carrying out friction or impact sensitivity testing (such as a BAM Fall hammer or drop hammer apparatus); however, a hammer test is a crude but effective way of doing this. To run a hammer test, 100–200 mg of the sample component of interest was placed on a white filter paper in a FC; the filter paper was folded over so as to cover the sample. The filter paper containing the sample was struck with a hammer (a standard DIY hammer is sufficient, Figure 2).⁶ We look for a spark and listen for a loud report. Following the test, we inspect the white filter paper and look for evidence of ignition, burning or black marks, or smears or smudges.

Outcome from Pre-tests. Following investigations by pre-tests, if the sample had a clear ignition test (melted and changed color) and a clear hammer test (no spark, report, or black marks on the filter paper), then this material should be of no concern for milling. Decomposition in itself is not a concern for these tests but how it decomposes should be the key focus of the experimenter. If the hammer test returns a loud bang or flash, then the experimenter should stop processing this component and not mill. In all other cases, the materials should be further analyzed using standard suite tests.

Standard Suite Tests. Reminder: we propose that standard suite tests are only performed on those components that received one or two out of three indicators from the DS and then provided an unclear outcome from the ignition tube and hammer pre-tests. You may have proceeded straight here (bypassing the hammer and ignition pre-tests), if these techniques are readily available to you; chemical intuition and experience may support your decision.

Standard suite tests aim to better quantify the potential thermal instability and gas evolution of the component of interest using two key tools: DSC and TGA.

Differential Scanning Calorimetry Measurements. DSC is a thermoanalytical technique that monitors the difference in heat required to maintain a heating ramp on the sample of interest and a reference crucible. This technique can detect phase changes and decomposition events. A DSC trace was obtained for the component in question using a standard DSC safety measurement protocol.⁸ DSC traces can be relatively complex, but large exotherms indicate that a material is thermally unstable, as a “rough rule of thumb” subtracting 60 K from the left limit of the exotherm will give an

Compound	(1) Desktop Screen	(2) Pre-Test	(3) Standard-Suite	(4) Mill?
(A) TNT	Carbon/p: 2.33 Oxygen: -74 Nitrogen: 18.5%			NO
(B) Acetic Acid	Carbon/p: N/A Oxygen: -106.7 Nitrogen: N/A	Ignition: Pass Hammer: Pass		YES
(C) aminotetrazole	Carbon/p: 1 Oxygen: N/A Nitrogen: 82%			NO
(D) 2-nitrophenol	Carbon/p: 6 Oxygen: -132.3 Nitrogen: 10.1%	Ignition: flag (boiled with some darkening) 	DSC: left limit 250 °C TGA: not run	YES
(E) 4-nitrotoluene	Carbon/p: 7 Oxygen: -181.0 Nitrogen: 10.2%	Ignition: Pass Hammer: Pass	DSC: left limit 288 °C TGA: not run	YES

materials with no oxygen or nitrogen atoms are given a nominal 'cross' as part of the desktop screen for oxygen balance or nitrogen content.

Figure 4. Some worked examples of the proposed protocol.

indication of the safe upper temperature limit for research laboratory-scale operation.

Thermogravimetric Analysis. TGA is a thermoanalytical technique where the mass of the sample is monitored over the duration of an applied heating ramp. If the mass significantly changes, then this signifies thermal instability (or boiling/sublimation point) of the sample and identifies an upper limit to the temperature at which the reaction should be run. Is it possible that a gaseous byproduct has been lost from your sample as part of this heating process? Gas evolution will represent a pressure hazard inside the jar.

Outcome from Standard Suite Tests. On review of the DSC and TGA data, you are looking for the onset temperature of exothermic or mass loss processes. We assume that the milling conditions do not lead to bulk jar temperatures above 50 °C.⁹ If the left limit of the exotherm or mass loss occurs at >150 °C, proceed to milling; if it occurs at <100 °C, do not proceed to milling; and if it occurs between 100 and 150 °C, then proceed but consider “imposing limits” to your experiment (suggestions below).

Imposing Limits to Milled Reactions. Consideration of the following limitations to the milled reaction is recommended if the standard suite tests show decomposition and/or mass loss

in the range of >100 and <150 °C. In these cases, the risk of a safety-related failure can be limited by implementing some routine measures such as:

Scale. The scale of your process should be reduced. The exact scale could be directed by calculating the amount of possible gas that may be liberated in the event of thermal degradation of the component and comparing that to the size of the jar that will be used.

Temperature. In addition to the actual chemical reaction, many factors can affect the temperature in the jar, such as: ball size/mass, filling degree, volume ratios (of the ball, sample, and free volume), milling frequency, and reaction time. These factors are likely to be reaction-specific but should be taken into account as part of the risk assessment process.

Handling. For air-sensitive materials, the use of a glovebox is considered. As pressure could build up in the jar as a result of the generation of toxic/flammable gases, care should be exercised when opening the reactor jars, and this should be carried out in a FC while wearing appropriate PPE.

Worked Examples. In order to demonstrate the process, we include some worked examples summarized in Figure 4. Compound (a), trinitrotoluene, receives three negative indicators in the DS, one for 2.33 carbons for each phosphore

(three nitro group phosphores), one for an oxygen balance greater than -200 , and one for a nitrogen content greater than 10%. Compound (b), acetic acid, receives one positive indicator for having no phosphore, one negative indicator for having an oxygen balance greater than -200 , and one default negative indicator for “ineligibility” for the nitrogen content. Overall acetic acid scores one out of three for the DS; our chemical intuition would tell us that it should be safe; this is demonstrated by a clear hammer and ignition test. Notably these tests will be recorded locally and will not need to be repeated again for future reactions using this material. Compound (c), aminotetrazole, receives a negative indicator for having one carbon for its tetrazole phosphore, one default negative indicator for oxygen balance (no oxygens present), and one negative indicator for a nitrogen content of 82%! Compound (d), 2-nitrophenol, receives a negative for having six carbons to one phosphoric nitro group, one for having an oxygen balance greater than -200 , and a third negative for a nitrogen balance of 10.1%. Although 2-nitrophenol receives three negative indicators, both the carbons per phosphoric group and the nitrogen content are on the boundary of the set guidance and chemical intuition suggests that a single nitro group attached to an aromatic ring maybe safe. Proceeding to an ignition tube test demonstrated that this compound boils without a pop but does produce some darkening, raising a potential flag. Further investigation by a standard suite DSC test shows a melting transition with a peak at $47\text{ }^{\circ}\text{C}$ and then a decomposition peak with a left limit of $250\text{ }^{\circ}\text{C}$, signifying that this material is safe for milling. Compound (e), 4-nitrotoluene, receives a positive indicator for having seven carbons to one phosphoric nitro group, a negative indicator for having an oxygen balance greater than -200 , and a second negative indicator for a nitrogen balance of 10.2%. Pre-tests of this material both return acceptable outcomes, and DSC indicates a left limit of $288\text{ }^{\circ}\text{C}$, all signifying that it is safe to mill 4-nitrotoluene.

CONCLUSIONS

In conclusion, the technique of ball milling presents a reaction system where there is no bulk solvent and reagents, reactants, and products are subjected to high-impact forces. As a consequence, the safety profile associated with ball milling reactions requires reconsideration in order to effectively minimize hazards. The proposed safety flow chart specifically explores the hazards associated with impact and reduced thermal control and, we hope, serves as a useful framework for those interested in exploring this promising, sustainable technique. Much of the content that is presented here is likely to be already familiar to industrial researchers, but the order and decision points have been altered. Through collaboration between industry and academia, the presented safety flow chart is proposed and highlights the specific hazards associated with reactive ball milling at a laboratory scale. The presented protocol is in operation at Syngenta where access to DSC and TGA services is centralized to a core team of analytical experts. As noted, aspects such as toxicity and ecotoxicity of materials remain unchanged and practitioners should be mindful that particle size reduction can lead to the generation of pyrophoric materials, especially in the case of some reactive metals.¹⁰ Looking forward, we believe that mechanochemistry is a highly promising technology that can clearly complement and add value to the armory of techniques used for chemical synthesis; we anticipate that this provision of clear safety protocols would

elevate the field and speed up adoption by the fine chemical industry.

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Notes

The authors declare no competing financial interest.

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(5) (a) Determination of oxygen balance - The oxygen balance provides a measure of the oxygen available within the molecule for complete combustion. This indicator can only be used if there are oxygen atoms in the molecule. The explosive power (energy release) of the material is considered to be a maximum risk at equivalence, i.e. zero oxygen balance. A deficiency of oxygen will give a negative balance, whereas an excess of oxygen will give a positive balance. The oxygen balance is determined for the following chemical reaction: $C_xH_yO_z + x + y/4 - z/2 \bullet O_2 \rightarrow xCO_2 + y/2 \bullet H_2O$ and can be calculated from the following equation: Oxygen balance = $-1600(2x + y/2 - z)$ molecular weight where x, y and z refer to the number of carbon, hydrogen and oxygen atoms respectively in the molecule. Note: The molecular weight must include all atoms not just C, H and O. Most explosives have oxygen balances between -100 and +40. However, any material with an oxygen balance more positive than -200 should be treated with caution. (b) Recommendations on the Transport of Dangerous Goods Model Regulations – 22nd Revised Edition (Vol. I & II) ISBN: 9789211391886; (c) Recommendations on the Transport of Dangerous Goods: Manual of Tests and Criteria - Sixth Revised Edition, ISBN: 9789211391626

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(7) As a Reminder, Ignition tube and hammer-tests as described are only proposed for Reactions that were 1 or 2 out of 3 on the Initial desktop screen. Reactions with 3/3 positive Indicators should not typically undergo these tests, they are already discounted – however, we have made an exception in a worked example of 2-nitrophenol, where two Indicators are on the boundary, notably the ‘carbons per phosphore’ value. Is one of those close to the boundary. Ignition tube and hammer tests are always carried out within a fume cupboard with additional PPE, such as, leather gauntlets, apron and arm protectors as well as a face shield which is in addition to standard laboratory PPE, but there is also a degree of personal Responsibility, any chemist (or other person) who carries out such Investigations must accept that there is a Risk. If you need to go to this level of Investigation and you are not competent to carry this out then one should think very hard about even doing it.

(8) For an excellent guide on the use of DSC to assess thermal hazards see: Green, S. P.; Wheelhouse, K. M.; Payne, A. D.; Hallett, J. P.; Miller, P. W.; Bull, J. A. On the Use of Differential Scanning Calorimetry for Thermal Hazard Assessment of New Chemistry: Avoiding Explosive Mistakes. *Angew. Chem., Int. Ed.* **2020**, *59*, 15798–15802.

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